Eisele Amanda (Orcid ID: 0000-0002-9791-169X)
Seystahl Katharina (Orcid ID: 0000-0002-4072-5669)

Accepted Article

Venous thromboembolic events in glioblastoma patients: an epidemiological study

Amanda Eisele[1], Katharina Seystahl[1], Elisabeth J. Rushing[2], Patrick Roth[1], Emilie Le Rhun[1,3], Michael Weller[1], Dorothee Gramatzki[1]

[1]Department of Neurology, Clinical Neuroscience Center, University Hospital and University of Zurich, Zurich, Switzerland;

[2]Department of Neuropathology, University Hospital Zurich, Zurich, Switzerland;

[3]Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland

Correspondence: Dorothee Gramatzki, MD, Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, CH-8091 Zürich, e-mail: dorothee.gramatzki@usz.ch, Telephone +41 44 255 5511, Fax +41 44 255 4507. ORCID ID: 0000-0002-9054-5498.

Total word count: 5242 (including title page, references, and structured abstract)

Introduction, Method, Results and Discussion: 3344 (3500).

References: 41 (50).

Abstract: 242 (250).

Supplementary Material: Table S1, Table S2

Running title: VTE in glioblastoma.

Keywords: anticoagulation, bleeding, epidemiology, glioblastoma, VTE

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ene.15404

This article is protected by copyright. All rights reserved.

Accepted Article

Author contributions:

Study conception and design: DG, ELR, MW.

Material preparation, data collection and analysis: DG, AE, KS, ELR, ER, PR.

Writing the first draft of the manuscript: AE, DG, MW.

Approval of the final manuscript: all authors.

Acknowledgements:

The authors would like to thank the patients and their families for making this study possible and acknowledge the contributions of the multidisciplinary teams taking care of glioblastoma patients in the Canton of Zurich, Switzerland.

Funding:

This work was supported by a grant from the Krebsliga Zurich to MW and DG (KLS-3110-02-2013), a grant from the Betty and David Koetser Foundation for Brain Research of the University of Zurich, Switzerland (F-86001-60-01) and a personal grant ("Filling the gap") of the University of Zurich, Switzerland to DG, a personal grant ("Filling the gap") of the University of Zurich, Switzerland and of the "Walter und Gertrud Siegenthaler Foundation" to KS.

Conflict of interest statement:

KS has received honoraria for board participation from Roche.

ELR has received personal fees from AbbVie, Adastra, Bayer, LEO Pharma, Seagen and Tocagen.

PR has received honoraria for lectures or advisory board participation from Bristol-Myers Squibb, Covagen, Debiopharm, Merck Sharp and Dohme, Novocure, QED, Roche and Virometix and research support from Merck Sharp, Dohme and Novocure.

MW has received research grants from Abbvie, Adastra, Apogenix, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure and Quercis, and honoraria for lectures or advisory board participation or consulting from Abbvie, Adastra, Bristol Meyer Squibb (BMS), Celgene, Medac, Merck, Sharp & Dohme (MSD), Merck (EMD), Nerviano Medical Sciences, Novartis, Orbus, Philogen, Roche, Tocagen and yMabs.

All remaining authors declare that they have no conflict of interest.

Accepted Article

Accepted Article

Abstract

Background: Venous thromboembolic events (VTE) are a major complication in cancer patients, and therefore, also in brain cancer patients, anticoagulants are considered appropriate in the treatment of VTE.

Methods: Frequency, risk factors and treatment of VTE, as well as associated complications were assessed in a population-based cohort of glioblastoma patients in the Canton of Zurich, Switzerland. Correlations between clinical data with survival were retrospectively analyzed using the log rank test and Cox regression models.

Results: Four hundred fourteen glioblastoma patients with isocitrate dehydrogenase (IDH) wildtype status were identified. VTE were documented in 65 patients (15.7%). Median time from tumor diagnosis to the occurrence of VTE was 1.8 months, and 27 patients were diagnosed with VTE postoperatively (within 35 days) (42.2%). History of prior VTE was more common in patients who developed VTE than in those who did not (p=0.004). Bevacizumab treatment at any time during the disease course was not associated with occurrence of VTE (p=0.593). Most patients with VTE (N=61, 93.8%) were treated with therapeutic anticoagulation. Complications occurred in 14 patients (23.0%), mainly intracranial hemorrhages (N=7, 11.5%). Overall survival did not differ between patients diagnosed with VTE and those who had no VTE (p=0.139). Tumor progression was the major reason for death (N=283, 90.7%), and only 3 patients (1.0%) died associated with acute VTE.

Conclusions: VTE occurred early in the disease course, suggesting that the implementation of primary venous thromboembolism prophylaxis during first-line chemoradiotherapy could be explored in a randomized setting.

Introduction

Patients diagnosed with primary brain tumors have a high risk for venous thromboembolic events (VTE), reported in a range of 14% to 32% [1-6]. The incidence of VTE is high throughout the course of disease [2], but seems to peak in the first 6 months after diagnosis [7]. Recurrent VTE may be seen in a third of patients diagnosed with glioblastoma [3].

Risk factors for VTE in brain tumor patients include immobility, higher age, obesity, comorbidities, history of VTE, subtotal tumor resection, glioblastoma histology, and recurrent disease [8, 9]. Bevacizumab appears not to increase the risk of VTE in glioblastoma patients [8, 10-12]. The association of blood group with VTE in glioma patients has been discussed controversially. While B blood group was found to be predictive for VTE in a cohort of 139 glioblastoma patients [13], this was not confirmed in a prospective study of patients diagnosed with glioma, including glioblastoma [7]. Elevated factor VIII levels [7] and low platelets or high leukocytes [14] have been reported to increase the risk of VTE in glioblastoma patients. Moreover, podoplanin expression by primary brain tumors induces platelet aggregation and is associated with increased risk of VTE [15].

Recommendations for prophylaxis and treatment of VTE in patients diagnosed with primary brain tumors are based largely on extrapolation from patients with other tumors and consensus [8, 16]. Primary venous thromboembolism prophylaxis in the ambulatory setting is not recommended but should be considered for hospitalized patients [17]. Low-molecular weight heparin (LMWH) should be chosen as the first-line venous thromboembolism prophylaxis and initiated within 24 hours after brain surgery [8, 18]. A single prospective randomized study (PRODIGE trial) on primary prophylaxis with LMWH for VTE in patients with primary brain tumors, including glioblastoma

Accepted Article

Accepted Article

noticed a trend towards reduced VTE, but the trial was stopped prematurely [19]. Prophylactic anticoagulant use is associated with increased risk of bleeding in glioblastoma patients [19-21].

Therapeutic doses of LMWH are recommended for the treatment of VTE. Direct oral anticoagulants (DOAC) should not be routinely used in glioblastoma patients, given the lack of data from clinical trials in this population. The duration of therapeutic anticoagulation for treatment of VTE should be at least 6 months.

In an analysis of three randomized trials including patients with newly diagnosed glioblastoma, therapeutic anticoagulation initiated between the start of concomitant temozolomide with radiotherapy and the start of maintenance temozolomide therapy was associated with inferior survival [22]. It is unclear whether VTE in these patients contributed to inferior survival. No association with survival was observed in patients treated with prophylactic doses of anticoagulants or with antiplatelet agents [22].

VTE are associated with inferior survival in cancer patients [23]. It has remained unclear whether there is an association between VTE and survival in glioblastoma patients. Anticoagulants have been speculated to improve survival in cancer patients, not only by preventing VTE, but also because of direct anticancer effects [24-28]. Data from two Cochrane reviews on cancer patients do not suggest a mortality benefit from oral or parenteral anticoagulation, respectively, while the risk for bleeding is likely increased [29, 30].

The association of VTE, anticoagulant use and its complications with survival in glioblastoma patients on a population-based level remains unclear. Here we performed a retrospective study of VTE in 414 patients with IDH-wildtype glioblastoma, who were diagnosed over a ten-year timeframe in the Canton of Zurich, Switzerland.

Accepted Article

Patients and Methods

Patient identification

All patients, 18 years or older, who resided in the Canton of Zürich, Switzerland, and were diagnosed with glioblastoma between 2005 and 2014, were included in a glioblastoma cancer registry in the Canton of Zurich, Switzerland. Patient identification data were provided by the Cancer Registry of the Cantons Zurich and Zug. Epidemiological data on this patient cohort were published previously [31, 32]. For the present analysis, we excluded all patients who lacked molecular data on the IDH mutation status based on the 2021 World Health Organization (WHO) classification [33].

Disease characteristics

All tumors in the glioblastoma cancer registry had been classified according to the WHO 2007 criteria [34] in the local pathology departments, and in a second step were classified by IDH mutation status based on the WHO 2021 classification [33]. The O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation status was determined by methylation-specific PCR. IDH mutation status was assessed using IDH1-R132H immunohistochemistry. According to WHO 2021 criteria, IDH1-R132H-negative glioblastomas in patients 55 years or older at diagnosis (N=296) could be regarded as IDH-wildtype tumors without any additional sequencing [33]. In cases with available tissue (N=66), IDH1-R132H-negative tumors in patients younger than 55 years were subjected to *IDH1* and *IDH2* sequence analyses. In 52 patients younger than 55 years, the IDH mutation status was obtained by immunohistochemistry only. Extent of resection was determined by early postoperative magnetic resonance imaging (MRI) or, if no MRI was available, by cranial computed tomography (CT).

Macroscopic (gross) total resection was defined by the absence of contrast enhancement. Clinical and treatment data were extracted from medical records. History of cancer was defined by any cancer diagnosis, independent of histology or WHO grade. A history of intracranial bleeding or stroke was defined by any listed event in a medical report prior to the diagnosis of glioblastoma.

Statistical analyses

Demographic, clinical, molecular tumor marker and co-medication data were analyzed by descriptive statistics. The Chi-square test was performed for analysis of nominal variables, and the Mann-Whitney U test was used for the comparison of quantitative variables between groups. OS was calculated from primary surgery for glioblastoma to death or last follow-up. Patients were censored at last follow-up. Kaplan-Meier curves were used to estimate OS, and differences were analyzed using the log-rank test. Cox proportional hazards regression models were used for multivariate analyses to test the association of clinical and molecular markers, including the occurrence of VTE, with survival. A time-dependent term of VTE considering the time of tumor diagnosis to VTE was included where indicated. All statistical analyses were performed using IBM SPSS, Version 27 (IBM Corporation, Armonk, NY), and a p value of 0.05 was set as statistically significant.

Ethics

This study was approved by the Ethics Committee of the Canton of Zurich (KEK-ZH-Nr. 2009-0135/1; KEK-ZH-Nr. 2015-0437).

Data availability statement

Accepted Article

Coded data not provided in the article will be made available upon request of other qualified investigators for purposes of replicating results.

Accepted Article

Results

Patient characteristics

A total of 414 patients diagnosed with IDH-wildtype glioblastoma in the Canton of Zurich, Switzerland, were included in this study. Median follow-up of surviving patients was 10.1 months (95% CI 5.2-13.2), assessed from the time of diagnosis. Patient characteristics are summarized in Table 1. VTE were documented in 65 patients (15.7%) during the course of disease. In the cohort of patients diagnosed with VTE (VTE-cohort), 45 patients (69.2%) were male, compared to 216 male patients (61.9%) in the cohort of glioblastoma patients who were not diagnosed with VTE (p=0.260). KPS, extent of resection, *MGMT* promoter methylation status, as well as first-line treatment did not differ between these two cohorts. Exposure to bevacizumab at any time was not associated with an increased risk of VTE. History of intracranial hemorrhage or cerebrovascular stroke was similar in both groups whereas history of VTE was seen more often in the VTE cohort (N=6, 9.2%) than in the control cohort (N=8, 2.3%; p=0.004; Table 1).

Characterization of the VTE cohort

Patient characteristics at time of VTE diagnosis are summarized in Table 2. Median time from tumor diagnosis to VTE was 1.8 months. At the time of VTE diagnosis, patients commonly had a reduced performance status. Most patients were on steroids (N=39, 60.9%) and were overweight with a BMI greater than 25 kg/m^2 (N=28, 63.6%). The majority of VTE were observed within 35 days after initial surgery (N=27, 42.2%). During first-line treatment, an additional 18 patients (28.1%) were diagnosed with VTE. A swimmer plot depicting the occurrence of VTE for each patient of the VTE cohort over the time of the course of the disease is shown in Figure 1. In patients experiencing

Accepted Article

Accepted Article

VTE later in the course of disease, essentially all occurred during phases of tumor-specific treatment rather than in treatment-free intervals.

Perioperative prophylaxis for VTE could be confirmed in 32 patients (82.1%) while 7 patients (17.9%) had no documented prophylaxis in the medical records; data were missing in 26 patients. Bevacizumab co-medication at time of VTE diagnosis was noted in 10 patients (15.6%). Approximately half of the patients diagnosed with VTE had pulmonary embolism (N=36, 56.3%). Out of the patients with pulmonary embolism, 7 patients (10.9%) were diagnosed with concomitant deep vein thrombosis. At the time of VTE diagnosis, 53 patients (82.8%) were symptomatic and 45 patients (70.3%) reported their symptoms to the clinician. In 11 patients (17.2%), the clinician first noted the symptoms leading to the VTE diagnosis, while the patients themselves were not aware of them (Table S1). All 7 patients diagnosed with both pulmonary embolism and deep vein thrombosis had a CT scan of the chest, as well as an ultrasound examination or a CT venography of the legs. Two patients were diagnosed with pulmonary embolism based exclusively on their clinical symptoms and died immediately. Patients with isolated deep vein thrombosis, who had no desaturation or chest pain, did not undergo a chest CT scan (Table S1).

At the time of VTE diagnosis, 12 patients (19.7%) were on prophylactic anticoagulation (Table 2). Almost all patients (N=61, 93.8%) received therapeutic anticoagulation for the treatment of VTE. Only 2 patients were given prophylactic anticoagulation (3.1%). Another 2 patients died immediately from VTE (3.1%) before anticoagulation could be initiated. Therapeutic anticoagulation was achieved mostly with LMWH (N=29, 47.5%), followed by vitamin K antagonists (N=26, 42.6%). The latter were combined with inferior vena cava filters in 5 patients (8.2%), mostly to postpone full anticoagulation for a few days in freshly operated patients. Median time of therapeutic anticoagulation was 4.6 months for all patients with implemented anticoagulation after VTE (N=60).

Twenty-nine patients underwent therapeutic anticoagulation until death with a median duration of therapeutic anticoagulation of 2.1 months. The remaining 31 patients (N=1 patient with missing data on duration of anticoagulation) received therapeutic anticoagulation for a median of 6.4 months (Table 2).

Fourteen of 61 patients (23.0%), who received therapeutic anticoagulation, suffered from complications (Table 2), including intracranial hemorrhage (N=7, 11.5%; in N=5 symptomatic), subdural hematoma (N=2, 3.3%), anal bleeding (N=2, 3.3%) and oral hemorrhage (N=1.6%). One of these 14 patients died due to intracranial bleeding. Therapeutic anticoagulation had to be stopped in 10 patients, while 3 patients were able to continue the treatment. Out of the 14 patients with complications under therapeutic anticoagulation, 6 patients (42.9%) were on LMWH, 5 patients (35.7%) on vitamin K antagonists (combined with a vena cava filter in one patient), 2 patients on a DOAC, and one patient on unfractionated heparin (Table 2). In most patients (N=60) the VTE had no impact on the treatment schedule (92.3%), while in 5 patients (76.9%) chemotherapy or bevacizumab, respectively, were delayed or stopped.

Four patients in the VTE cohort had a second VTE. Two patients were on therapeutic anticoagulation at the time of the second VTE with a median time to the occurrence of the second VTE of 6.4 months. Two other patients were not anticoagulated (median time between the VTE events was 12.4 months.

Survival data

Median OS for the whole cohort was 12.1 months (95% CI 11.0-13.3). Median overall survival for patients diagnosed with VTE was 14.2 months (95% CI 10.8-17.5) compared to 11.0 months (95% CI 10.7-13.1) for patients without VTE (Table S2). Kaplan Meier survival curves stratified according to the diagnosis of VTE are shown in

Accepted Article

Figure 2. Survival in patients diagnosed with VTE compared to those patients who were not was similar (p=0.139) (Table S2, Figure 2).

Most patients died of tumor progression (90.7%) (Table 3). In patients in an end-of-life setting with a main focus on palliative and supportive care, death as a result of neurological decline over time was assumed to be because of tumor progression. Sudden and unexpected death was observed in 5 patients (1.6%). Out of these 5 patients, one patient had a VTE around 2 months before his death and was treated with a vena cava filter. Another 4 patients (1.3%), died of intracranial hemorrhage. One of these patients was on prophylactic anticoagulation at the time of death, none was on therapeutic anticoagulation. One patient, who was on prophylactic anticoagulation, died of an extensive bleeding in the gluteal muscle. Sixteen patients (5.1%) died from other reasons, mainly systemic infections (N=8, 50%), and there were two lethal accidents (12.5%). In patients who had VTE during the course of disease, 3 patients (6.4%) died associated with acute VTE, presumably cardiopulmonary failure based on the clinical presentation (Table 3).

VTE were not associated with risk of death in univariable Cox regression analysis (p=0.14, HR=0.80, 95% CI 0.60-1.07). Multivariable Cox regression analysis confirmed known prognostic or predictive markers in glioblastoma, including age, KPS, extent of resection, MGMT promoter methylation status or first-line treatment. In contrast, the diagnosis of VTE at any time during the course of disease again was not associated with increased risk for death (HR 0.86, 95% CI 0.60-1.25, p=0.435) (Table 4). In addition, we included a time-dependent covariable for the time of tumor diagnosis to time of VTE in this Cox regression for risk of death (p=0.007, HR 16.4, 95% CI 2.15-124.81), however, it was confirmed that VTE were not associated with risk of death in this adjusted model (p=0.12, HR 0.79, 95% CI 0.59-1.06).

Accepted Article

Discussion

This study was performed to explore the incidence of VTE, a major complication in cancer patients, and the association with survival in glioblastoma patients on a population level. In the present IDH-wildtype glioblastoma cohort, 65 patients (15.7%) were diagnosed with VTE during the course of disease (Table 1). Several reports, mainly single center studies, describe an incidence of VTE between 14.5% and 32.3% in glioma cohorts [3, 4, 35, 36] (Table 5). Differences in the incidence of VTE in these studies can probably be explained by the retrospective nature and the lack of standardized screening for VTE, especially in asymptomatic patients. Higher VTE incidences, compared to glioblastoma patients, were reported in other cohorts, including patients with WHO grade 2 and 3 astrocytoma [35, 36]. The concept of an increased risk for VTE in IDH-mutant gliomas remains controversial. While Diaz and colleagues postulated an increased risk for VTE in patients with IDH-mutant tumors [35], this finding was not confirmed in a subsequent study [36]. Unruh and colleagues described a higher frequency of intratumoral microthrombi in IDH1/2-wildtype tumors, independent of histological grade [6]. The authors suggested that mutant *IDH1/2* has potent antithrombotic activity within gliomas as well as in the peripheral circulation, probably because mutant *IDH1/2* initiates *F3* promoter hypermethylation resulting in a relative lack of tissue factor-containing microparticles (TF-MP) [37]. In addition, the IDH1/2 metabolite D-2-hydroxyglutarate (D-2-HG) has been discussed to have antiplatelet activity based on calcium-dependent inhibition of human platelet aggregation and clotting.

Our data indicate that the risk of VTE is already high early in the disease course with a median time to VTE of 1.8 months (Table 2). In our cohort, many patients were diagnosed with VTE in the first 35 days after neurosurgical intervention. This is in line

Accepted Article

with the recommendation that patients with cancer, including patients diagnosed with brain tumor and brain metastasis should receive perioperative VTE prophylaxis [16]. In addition, a large retrospective analysis confirmed craniotomy for brain tumors to be an independent risk factor for VTE compared to craniotomy for other reasons, including ischemic stroke or bleedings [38]. Among brain tumor patients, the risk of VTE in patients diagnosed with glioblastoma is reportedly higher than the risk in those diagnosed with meningioma [39]. As a mechanism a systemic procoagulative state has been reported more frequently in glioblastoma patients compared to meningioma patients [40]. Additionally, in our dataset the phase of initial treatment appears to place patients at risk, suggesting that prophylactic anticoagulation might be useful specifically during the early disease trajectory.

Conversely, it seems counterintuitive to assume that the risk of VTE decreases during the course of disease, since several risk factors such as steroid use, immobility, possible increase of BMI, and tumor burden should be more prevalent in later disease stages. Thus, it is also conceivable that the apparently lower rate of VTE in later disease stages reflects less stringent follow-up or follow-up at less experienced sites.

In our study, history of VTE was significantly associated with the incidence of VTE after diagnosis of glioblastoma (Table 1). Patients who developed VTE were characterized by increased BMI (≥25 kg/m^2, 63.6%), reduced KPS (<70%, 56.5%) and co-medication with steroids (60.9%) (Table 2), which are known risk factors for VTE in brain tumor patients [8, 9]. Our study does not allow for drawing conclusions regarding causality of risk factors for VTE. Although we found decreased platelet levels at time of VTE diagnosis in 21.7% of our patients, it remains unclear whether this represents an independent risk factor for VTE in glioblastoma patients. A negative association of VTE and platelet count at time of diagnosis in primary brain tumors has been described [14].

Accepted Article

Bevacizumab appears not to be associated with an increased risk of VTE in randomized clinical trials on glioblastoma patients [8, 10-12]. On a population-based level, we confirm that bevacizumab treatment at any time during the course of disease was not associated with VTE (Table 1).

Although VTE have been linked to inferior survival in cancer patients in general [23], such a negative association between VTE in glioblastoma patients and survival was not seen in our cohort (Table S2, Table 3, Figure 2). We even noticed a trend towards superior survival in glioblastoma patients with VTE, almost all of which received full anticoagulation. As patients in our study were diagnosed between 2005 and 2014 and the first DOAC (rivaroxaban) for the treatment of VTE was approved in Switzerland in 2012, these anticoagulants are underrepresented for VTE treatment in our cohort. A recent study showed a satisfactory safety profile of DOAC compared to LMWH in glioblastoma patients with pulmonary embolism and the advantages of avoiding injections, less need of monitoring and fewer interactions nowadays might favor their use in clinical practice [41]. The complication rate of all patients receiving DOAC for VTE treatment was high in our study (50%; Table 2), but due to the very limited number of patients in this cohort comparisons with the complication rate under LMWH or vitamin K antagonists cannot be made. The complication rate among patients receiving LMWH (20.7%) or vitamin K antagonists (19.0%) were similar.

These population-based data appear to be at odds with observations on the significance of VTE in clinical trial populations. No association with survival was observed in patients treated with prophylactic doses of anticoagulants or with antiplatelet agents in a retrospective analysis of three randomized clinical trials in glioblastoma patients [22]. In this dataset, therapeutic anticoagulation initiated between the start of concomitant temozolomide with radiotherapy and maintenance temozolomide was associated with inferior survival. Although 3 patients (6.4%) with

VTE in our study died in association with an acute thromboembolic event, VTE were not a major cause of death (Table 3).

The main limitations of this study include the retrospective nature of data collection, including missing data on steroid administration over time and treatment intensity, as well as the lack of data on *IDH* mutation status by sequencing in some patients younger than 55 years, and on *MGMT* promoter methylation status. Based on the retrospective nature of this study, the prevalence of VTE, notably in later disease stages, as well as the prevalence of prescription or intensity of VTE prophylaxis may be underestimated. Although VTE were identified in 15.7% of glioblastoma patients on this population-based level, VTE were not associated with death. Therefore, our data do not support the implementation of primary venous thromboembolism prophylaxis in glioblastoma patients without further data from controlled studies. However, VTE occurred early in the course of disease, suggesting that the implementation of primary venous thromboembolism prophylaxis using a safe and well tolerated agent could be explored during first-line chemoradiotherapy in a randomized setting.

Accepted Article

References

[1]. Muster V, Gary T. Incidence, Therapy, and Bleeding Risk-Cancer- Associated Thrombosis in Patients with Glioblastoma. *Cancers (Basel)*. 2020 **12**.

[2]. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. *Cancer*. 2000 **89:** 640-646.

[3]. Edwin NC, Khoury MN, Sohal D, McCrae KR, Ahluwalia MS, Khorana AA. Recurrent venous thromboembolism in glioblastoma. *Thromb Res*. 2016 **137:** 184-188.

[4]. Yust-Katz S, Mandel JJ, Wu J*, et al.* Venous thromboembolism (VTE) and glioblastoma. *J Neurooncol*. 2015 **124:** 87-94.

[5]. Taillibert S, Taillandier L, Le Rhun E. Venous thrombosis in patients with high-grade glioma. *Curr Opin Oncol*. 2015 **27:** 516-521.

[6]. Unruh D, Schwarze SR, Khoury L*, et al.* Mutant IDH1 and thrombosis in gliomas. *Acta Neuropathol*. 2016 **132:** 917-930.

[7]. 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:** 299-305.

[8]. Roth P, Pace A, Le Rhun E*, et al.* Neurological and vascular complications of primary and secondary brain tumours: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow-up. *Ann Oncol*. 2021 **32:** 171-182.

[9]. Jo JT, Schiff D, Perry JR. Thrombosis in brain tumors. *Semin Thromb Hemost*. 2014 **40:** 325-331.

[10]. Chinot OL, Wick W, Mason W*, et al.* Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014 **370:** 709-722.

[11]. Gilbert MR, Sulman EP, Mehta MP. Bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014 **370:** 2048-2049.

Accepted Article

Accepted Article

[12]. Wick W, Gorlia T, Bendszus M*, et al.* Lomustine and Bevacizumab in Progressive Glioblastoma. *N Engl J Med*. 2017 **377:** 1954-1963.

[13]. Heenkenda MK, Malmstrom A, Lysiak M*, et al.* Assessment of genetic and non-genetic risk factors for venous thromboembolism in glioblastoma - The predictive significance of B blood group. *Thromb Res*. 2019 **183:** 136-142.

[14]. Thaler J, Ay C, Kaider A*, et al.* Biomarkers predictive of venous thromboembolism in patients with newly diagnosed high-grade gliomas. *Neuro Oncol*. 2014 **16:** 1645-1651.

[15]. Riedl J, Preusser M, Nazari PM*, et al.* Podoplanin expression in primary brain tumors induces platelet aggregation and increases risk of venous thromboembolism. *Blood*. 2017 **129:** 1831-1839.

[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:** 496-520.

[17]. Lyman GH, Bohlke K, Khorana AA*, et al.* Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014. *J Clin Oncol*. 2015 **33:** 654-656.

[18]. Agnelli G, Piovella F, Buoncristiani P*, et al.* Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med*. 1998 **339:** 80-85.

[19]. 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:** 1959-1965.

[20]. Perry SL, Bohlin C, Reardon DA*, et al.* Tinzaparin prophylaxis against venous thromboembolic complications in brain tumor patients. *J Neurooncol*. 2009 **95:** 129-134.

Accepted Article

[21]. Robins HI, O'Neill A, Gilbert M*, et al.* Effect of dalteparin and radiation on survival and thromboembolic events in glioblastoma multiforme: a phase II ECOG trial. *Cancer Chemother Pharmacol*. 2008 **62:** 227-233.

[22]. Le Rhun E, Genbrugge E, Stupp R*, et al.* Associations of anticoagulant use with outcome in newly diagnosed glioblastoma. *Eur J Cancer*. 2018 **101:** 95-104.

[23]. Kuderer NM, Ortel TL, Francis CW. Impact of venous thromboembolism and anticoagulation on cancer and cancer survival. *J Clin Oncol*. 2009 **27:** 4902-4911.

[24]. Mousa SA, Petersen LJ. Anti-cancer properties of low-molecular-weight heparin: preclinical evidence. *Thromb Haemost*. 2009 **102:** 258-267.

[25]. Mousa SA, Mohamed S. Inhibition of endothelial cell tube formation by the low molecular weight heparin, tinzaparin, is mediated by tissue factor pathway inhibitor. *Thromb Haemost*. 2004 **92:** 627-633.

[26]. Collen A, Smorenburg SM, Peters E*, et al.* Unfractionated and low molecular weight heparin affect fibrin structure and angiogenesis in vitro. *Cancer Res*. 2000 **60:** 6196-6200.

[27]. Takeuchi A, Yamamoto Y, Munesue S*, et al.* Low molecular weight heparin suppresses receptor for advanced glycation end products-mediated expression of malignant phenotype in human fibrosarcoma cells. *Cancer Sci*. 2013 **104:** 740-749.

[28]. Balzarotti M, Fontana F, Marras C*, et al.* In vitro study of low molecular weight heparin effect on cell growth and cell invasion in primary cell cultures of high-grade gliomas. *Oncol Res*. 2006 **16:** 245-250.

[29]. Kahale LA, Hakoum MB, Tsolakian IG*, et al.* Oral anticoagulation in people with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database Syst Rev*. 2017 **12:** CD006466.

[30]. Akl EA, Kahale LA, Hakoum MB*, et al.* Parenteral anticoagulation in ambulatory patients with cancer. *Cochrane Database Syst Rev*. 2017 **9:** Cd006652.

[31]. Gramatzki D, Roth P, Rushing E*, et al.* Bevacizumab may improve quality of life, but not overall survival in glioblastoma: an epidemiological study. *Annals of Oncology*. 2018 **29:** 1431-1436.

[32]. Gramatzki D, Dehler S, Rushing EJ*, et al.* Glioblastoma in the Canton of Zurich, Switzerland revisited: 2005 to 2009. *Cancer*. 2016 **122:** 2206-2215.

[33]. Louis DN, Perry A, Wesseling P*, et al.* The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021 **23:** 1231-1251.

[34]. Louis DN, Ohgaki H, Wiestler OD*, et al.* The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*. 2007 **114:** 97-109.

[35]. 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:** e1063-e1069.

[36]. Mandel JJ, Youssef M, Yust-Katz S*, et al.* IDH mutation status and the development of venous thromboembolism in astrocytoma patients. *J Neurol Sci*. 2021 **427:** 117538.

[37]. Turcan S, Rohle D, Goenka A*, et al.* IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature*. 2012 **483:** 479-483.

[38]. Kimmell KT, Jahromi BS. Clinical factors associated with venous thromboembolism risk in patients undergoing craniotomy. *J Neurosurg*. 2015 **122:** 1004-1011.

[39]. Fluss R, Kobets AJ, Inocencio JF*, et al.* The incidence of venous thromboembolism following surgical resection of intracranial and intraspinal meningioma. A systematic review and retrospective study. *Clinical Neurology and Neurosurgery*. 2021 **201:** 106460.

[40]. Yerrabothala S, Gourley BL, Ford JC*, et al.* Systemic coagulation is activated in patients with meningioma and glioblastoma. *J Neurooncol*. 2021 **155:** 173-180.

[41]. Dubinski D, Won SY, Voss M*, et al.* Direct oral anticoagulants vs. low-molecular-weight heparin for pulmonary embolism in patients with glioblastoma. *Neurosurg Rev*. 2022 **45:** 451-457.

Accepted Article

Accepted Article

Figure 1. Swimmer plot depicting the occurrence of venous thromboembolic events for each patient.

Each bar of the Y-axis represents one individual patient of the venous thromboembolic events (VTE) cohort (N = 65). The X-axis represents time in months since hospitalization for initial surgery. The red diamonds represent the VTE. The blue square represents the date of first operation. Yellow dots represent dates of tumor progression. Green triangles represent any further operation other than the initial surgery. Bars represent the duration of hospitalization for first operation (blue), treatment-free periods (grey), the duration of initial radiotherapy plus/ minus concomitant temozolomide (orange), the duration of maintenance temozolomide (bright green), the duration of initial therapy other than temozolomide (dark green) or the duration of any other treatment at time of progression (yellow).

Figure 2. Venous thromboembolic events and survival.

Kaplan Meier survival curves are shown for glioblastoma patients diagnosed with (blue line) or without (red line) venous thromboembolic events. The log rank test was used for comparison.

Tables

Table 1. Patient characteristics at baseline.

	Non-VTE cohort N=349 (84.3%)	VTE cohort N=65 (15.7%)	P value
Age†, years			
Median	63.0	59.7	0.065
Range	18-90	37-83	
Sex, N			
Male	216 (61.9%)	45 (69.2%)	0.260
Female	133 (38.1%)	20 (30.8%)	
KPS†, N			
90-100%	54 (15.6%)	6 (9.2%)	0.299
70-80%	203 (58.7%)	44 (67.7%)	
< 70%	89 (25.7%)	15 (23.1%)	
No data	3 (-)	-	
Extent of surgical resection†, N			
Gross total resection (≥99%)	114 (32.8%)	31 (47.7%)	0.125
Incomplete resection (<99%)	155 (44.5%)	21 (32.3%)	
Biopsy	78 (22.4%)	13 (20.0%)	
Autopsy	1 (0.3%)	-	
No data	1 (-)	-	
MGMT promoter methylation status, N			
Methylated	111 (45.7%)	16 (34.8%)	0.172
Unmethylated	132 (54.3%)	30 (65.2%)	
No data	106 (-)	19 (-)	
First-line therapy, N			
Radiotherapy plus TMZ	170 (49.7%)	38 (58.5%)	0.336
Radiotherapy alone	68 (19.9%)	13 (20.0%)	
Chemotherapy alone	26 (7.6%)	1 (1.5%)	
Others‡	22 (6.4%)	5 (7.7%)	
No therapy	56 (16.4%)	8 (12.3%)	
No data	7 (-)	-	
Bevacizumab at any time during the disease, N			
Yes	123 (36.5%)	26 (40.0%)	0.593
No	214 (63.5%)	39 (60.0%)	
No data	12 (-)	-	
History of cancer, N			
Yes	52 (15.0%)	8 (12.3%)	0.574
No	295 (85.0%)	57 (87.7%)	
No data	2 (-)	-	
History of intracranial bleeding, N			
Yes	6 (1.7%)	0 (0%)	0.287
No	343 (98.3%)	65 (100%)	
History of cerebrovascular stroke, N			
Yes	9 (2.6%)	2 (3.1%)	0.819
No	340 (97.4%)	63 (96.9%)	
History of VTE, N			

Accepted Article

Yes No	8 (2.3%) 341 (97.7%)	6 (9.2%) 59 (90.8%)	0.004
Analyzed time-frame 2005-2009 2010-2014	 141 (40.4%) 208 (59.6%)	 30 (46.2%) 35 (53.8%)	 0.387

N, number of patients; IDH, isocitrate dehydrogenase; KPS, Karnofsky performance status; MGMT, O^6-methylguanine DNA methyltransferase; RT, radiotherapy; TMZ, temozolomide; VTE, venous thromboembolic event; †, at time of diagnosis; ‡, mainly experimental drugs in clinical trials or bevacizumab.

Accepted Article

Table 2. Patient characteristics at time of VTE.

VTE cohort, N=65	N (%)
Type of VTE	
Deep vein thrombosis	26 (40.6%)
Pulmonary embolism	29 (45.3%)
Sinus vein thrombosis	2 (3.1%)
Deep vein thrombosis plus pulmonary embolism	7 (10.9%)
No data	1 (-)
KPS	
90-100%	10 (16.1%)
70-80%	17 (27.4%)
< 70%	35 (56.5%)
No data	3 (-)
Steroids	
Yes	39 (60.9%)
No	25 (39.1%)
No data	1 (-)
BMI, kg/m^2	
Underweight <18.5 kg/m^2	1 (2.3%)
Normal weight ≥18.5 to 24.9 kg/m^2	15 (34.1%)
Overweight ≥25 to 29.9 kg/m^2	11 (25.0%)
Obesity ≥30 kg/m^2	17 (38.6%)
No data	21 (-)
Platelets, G/l	
Normal level	47 (78.3%)
Decreased level (CTCAE ≥ grade 1)	13 (21.7%)
No data	5 (-)
Tumor status	
Prior to first recurrence	48 (75.0%)
After first recurrence	16 (25.0%)
No data	1 (-)
Disease phase	
Postoperatively (≤35 days)	27 (42.2%)
First-line treatment	18 (28.1%)
Second-line treatment	7 (10.9%)
Third-line treatment	5 (7.8%)
No tumor specific treatment (>35 days)	7 (10.9%)
No data	1 (-)
Co-treatments	
Radiotherapy, concomitant TMZ	9 (14.1%)
Maintenance TMZ	5 (7.8%)
Chemotherapy alone	2 (3.1%)
Radiotherapy alone	3 (4.7%)
Immune checkpoint inhibitor alone	1 (1.6%)
Bevacizumab alone	7 (10.9%)
Radiotherapy plus bevacizumab	2 (3.1%)
Chemotherapy plus bevacizumab	1 (1.6%)
No treatment	34 (53.1%)
No data	1 (-)

Accepted Article

Antiplatelet treatment / anticoagulation at the time of VTE	
Antiplatelet treatment	3 (4.9%)
Prophylactic anticoagulation	10 (16.4%)
Therapeutic anticoagulation	0 (0.0%)
Antiplatelet treatment plus prophylactic anticoagulation	2 (3.3%)
No treatment	46 (75.4%)
No data	4 (-)
Treatment of VTE	
Prophylactic anticoagulation	2 (3.1%)
LMWH	2 (3.1%)
Therapeutic anticoagulation	61 (93.8%)
LMWH	29 (47.5%)†
DOAC	4 (6.6%)†
Vitamin K antagonist	21 (34.4%)†
Unfractionated heparin	2 (3.3%)†
Vena cava filter / vitamin K antagonist	5 (8.2%)†
No treatment	2 (3.1%) (died immediately of VTE)
Complications from therapeutic anticoagulation for VTE	
Intracranial hemorrhage	7 (11.5%)
CTCAE grade 2	3 (4.9%)
CTCAE grade 3	4 (6.6%)
Subdural hematoma, CTCAE grade 2	2 (3.3%)
Oral hemorrhage, CTCAE grade 1	1 (1.6%)
Anal bleeding	2 (3.3%)
CTCAE grade 2	1 (1.6%)
CTCAE grade 3	1 (1.6%)
Epistaxis, CTCAE grade 2	1 (1.6%)
Gastrointestinal hemorrhage, CTCAE grade 3	1 (1.6%)
No complication	47 (77.0%)
Complications from what kind of therapeutic anticoagulation for VTE (percentage of N=14 patients with complications, or percentage of the number of patients under the respective treatment)	
LMWH (N=19)	6 (42.9%, 20.7%)
DOAC (N=4)	2 (14.3%, 50.0%)
Vitamin K antagonist (N=21)	4 (28.6%, 19.0%)
Unfractionated heparin (N=2)	1 (7.1%, 50.0%)
Vena cava filter / vitamin K antagonist (N=5)	1 (7.1%, 20.0%)
Time from tumor diagnosis to VTE	
Median (SD; range), months	1.8 (13.3; 0.0-78.0)
Duration of anticoagulation after VTE	
Median (SD; range), months	
All VTE patients with anticoagulation (N=60)	4.6 (8.4; 0.1-58.4)
Patients who had anticoagulation until death (N=29)	2.1 (4.0; 0.1-16.9)
Patients who stopped anticoagulation for other reasons (N=31)	6.4 (10.6; 0.7-58.4)

Accepted Article

Reason for stopping anticoagulation after VTE (percentage of N=61 patients with anticoagulation)	
Death	29 (47.5%)
Complication	10 (16.4%)
Decision of the physician	14 (22.9%)
Unknown	8 (13.1%)
Recurrent VTE under anticoagulation (percentage of N=61 patients with anticoagulation)	
Failure rate	2 (3.3%)
Median time to treatment failure (months, 95% CI)	12.4 (12.3-12.6)

BMI, body mass index; CI, confidence interval, N, number of patients; RT, radiotherapy; SD, standard deviation; TMZ, temozolomide; VTE, venous thromboembolic event; †, percentages calculated for the group of patients who received therapeutic anticoagulation (N=61).

Accepted Article

Table 3. Reason for death.

	All patients N=414	Non-VTE cohort N=349	VTE cohort N=65
Reason for death			
Tumor progression	283 (90.7%)	246 (92.8%)	37 (78.7%)
Bleeding	5 (1.6%)	4 (1.5%)	1 (2.1%)
intracranial	4 (1.3%)	3 (1.1%)	1 (2.1%)
gluteal muscle	1 (0.3%)	1 (0.4%)	0
Thromboembolic event (assumed cardiopulmonary failure)	3 (1.0%)	0	3 (6.4%)
Sudden unexpected death of unknown reason	5 (1.6%)	4 (1.5%)	1 (2.1%)
Other†	16 (5.1%)	11 (6.7%)	5 (10.6%)
Alive / lost of follow up	51 (-)	41 (-)	10 (-)
No data	51 (-)	43 (-)	8 (-)

†, accident (N=2), suicide (N=1), gastrointestinal disease (N=1), hyperglycemia (N=1), infection (N=8), intraoperative complication (N=1), liver disease (N=1), myocard infarction (N=1); VTE, venous thromboembolic event.

Accepted Article

Table 4. Multivariate analysis with regards to death (Cox regression).

	N	HR (95% CI)	P value
Age†			
> 65 years	120	1	ref
≤ 65 years	163	0.64 (0.47-0.88)	0.006
Sex			
Male	185	1	ref
Female	98	1.16 (0.88-1.53)	0.296
KPS†			
< 70%	68	2.00 (1.44-2.78)	<0.001
70-80%	171	1	ref
90-100%	44	0.64 (0.43-0.94)	0.022
Extent of resection†			
Biopsy	49	1	ref
Incomplete	123	0.43 (0.29-0.62)	<0.001
Gross total (≥ 99%)	111	0.27 (0.18-0.40)	<0.001
MGMT promoter methylation status			
Unmethylated	161	1	ref
Methylated	122	0.57 (0.43-0.75)	<0.001
Postsurgical therapy			
No therapy	34	1	ref
RT alone	52	0.40 (0.24-0.64)	<0.001
CT alone	23	0.30 (0.16-0.55)	<0.001
RT plus TMZ	156	0.19 (0.12-0.30)	<0.001
Others‡	18	0.16 (0.85-0.31)	<0.001
VTE during the course of disease			
Yes	46	0.86 (0.60-1.25)	0.435
No	237	1	ref

RT, radiotherapy; CT, chemotherapy; TMZ, temozolomide; CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolic event; †, at time of diagnosis; ‡, mainly experimental drugs in clinical trials, or bevacizumab.

Accepted Article

Table 5. Review of the literature (selected papers).

	Propective / retrospective study	Single- / multicenter study	Included patients (N)	Screening	Follow-up	Patients diagnosed with VTE, N (%)	Treatment, N (%)
Our study, 2021	Retrospective	Multicenter (Canton of Zurich, Switzerland)	IDH wildtype glioblastoma (414)	VTE during the course of disease	10.1 months	65 (15.7)	Prophylactic anticoagulation LMWH 2 (3.1) Therapeutic anticoagulation LMWH 29 (47.5) DOAC (4 (6.6) Vitamin K antagonist 21 (34.4) Unfractionated heparin 2 (3.3) IVC filter / vitamin K antagonist 5 (8.2) None 2 (3.1)
Mandel et al., 2021	Retrospective	Single center (MD Andersen, Texas)	Astrocytoma (IDH-mutant or IDH-wildtype status) (282)	VTE during the course of disease	-	all tumors: 52 (18.4%) all grades, IDH wildtype: 45 (19.3) all grades IDH mutant: 7 (14.3)	Vitamin K antagonist 4 (7.7) IVC filter / vitamin K antagonist 2 (3.8) IVC filter alone 9 (17.3) IVC filter / DOAC 1 (1.9%) LMWH 29 (55.8) IVC filter / LMWH 3 (5.8) DOAC 2 (3.8) Other 2 83.8)
Diaz et al., 2020	Prospectively collected data; retrospectively analyzed	Single center (University of Virginia)	Glioma WHO grade 2 (147) WHO grade 3 (109) WHO grade 4 (334)	VTE during the course of disease	17.9 months	WHO grade 2: 12 (8.2) WHO grade 3: 10 (9.2) WHO grade 4: 103 (30.8) all grades, IDH wildtype: 102 (26.5) all grades IDH mutant: 18 (8.7)	-
Le Rhun et al., 2018	Prospective studies; retrospectively analyzed	Multicenter	Glioblastoma (IDH-mutant or IDH-wildtype status) (1273)	Anticoagulant exposure at time from i) randomization to start combined radio-chemotherapy, or ii) from combined radio-	-	i) 1 out of 1273 (0.1) ii) 22 out of 1017 (2.2)	new VTEs except one were treated with therapeutic anticoagulation

Accepted Article

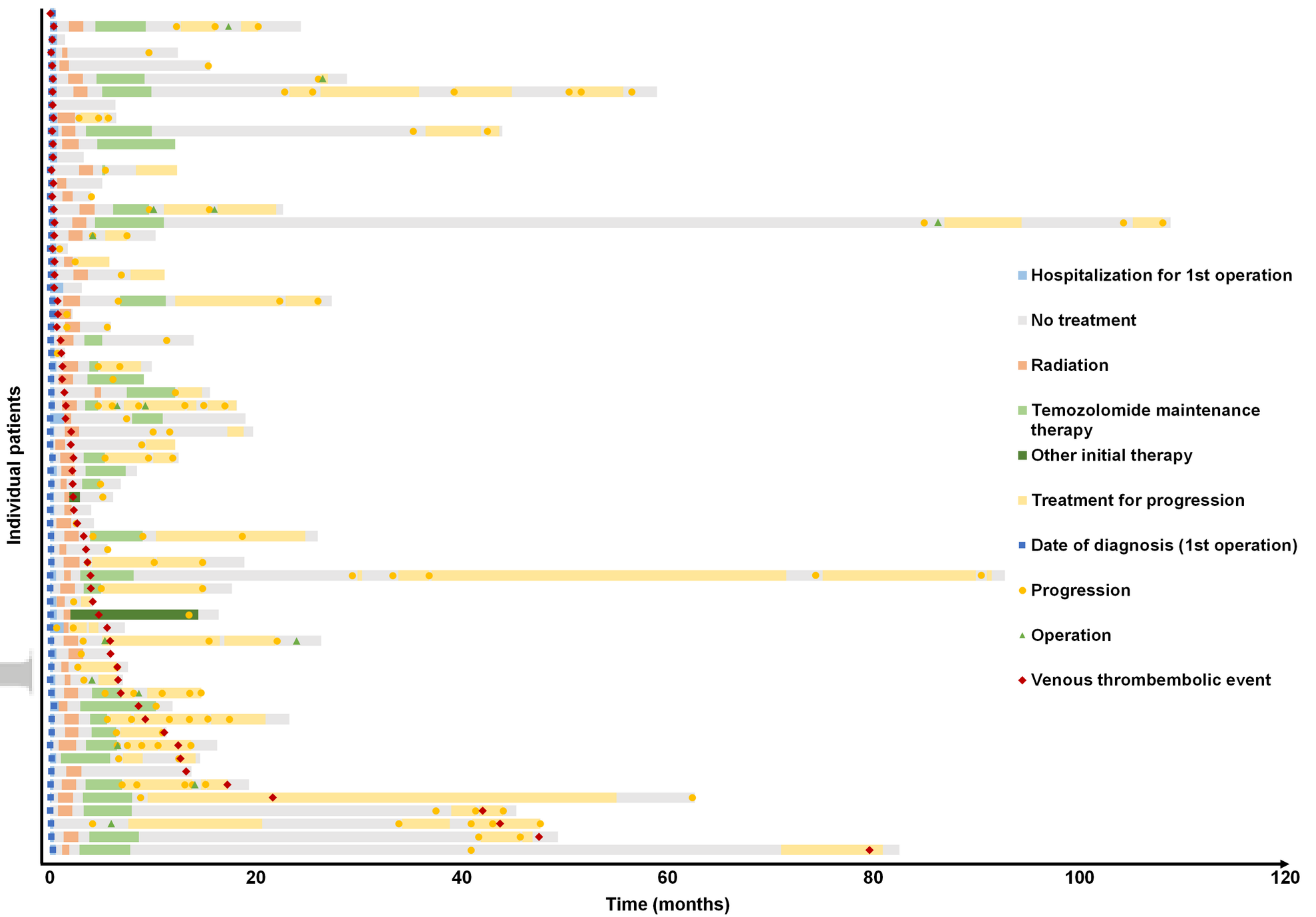
				chemotherapy to start of temozolomide maintenance			
Edwin et al., 2016	Retrospective	Single center (Cleveland)	Glioblastoma (450)	VTE during the course of disease	Minimum of 6-months follow-up	145 (32.2)	IVC filter alone 39 (26.9) IVC filter with AC 21 (14.5) Anticoagulation alone 54 (37.2) LMWH 36 (24.8) Warfarin 15 (10.3) Heparin 2 (1.4) DOAC 1 (0.7) None 31 (21.4
Yust-Katz et al., 2015	Retrospective	Single center (MD Anderson)	Glioblastoma (440)	VTE after starting adjuvant chemotherapy	Minimum of 6-months follow-up	64 (14.5)	Anticoagulation alone 36 Coumadin 8 LMWH 28 IVC filter 2 IVC / anticoagulation 21 Unknown 3 None 2

DOAC, direct oral anticoagulants; IDH, isocitrate dehydrogenase; IVC, inferior vena cava; LMWH, low molecular weight heparin; VTE, venous thromboembolic event.

Accepted Article

Accepted Article

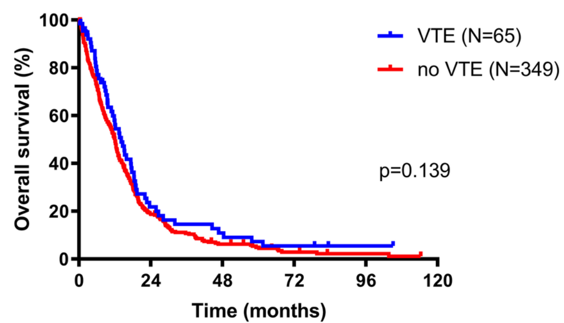
Figure 1



ENE_15404_EJN_VTE_Figure1.tif

Accepted Article

Figure 2



ENE_15404_EJN_VTE_Figure2.tif

MANAGE-**PD**

Tool for Making Informed Decisions to **Aid Timely Management of Parkinson's Disease**

MANAGE-PD allows you to:

- Identify PD patients inadequately controlled on oral medications
- Determine which patients with PD may be adequately controlled on their current treatment regimen or may require changes to their treatment regimen

Scan the QR code to access to the web

Click here to access to the web

MANAGE-PD is an AbbVie Inc. registered Medical Device. It is a collaborative research and development effort between AbbVie Medical Affairs and Health Economics and Outcomes, the Parkinson's Foundation and an international panel of Movement Disorder Specialists.

©2022 AbbVie Inc. All rights reserved. The Parkinson's Foundation logo is the sole property of the Parkinson's Foundation used with written permission. Any use of the Parkinson's Foundation name or logo without Foundation permission is prohibited. All content in https://www.managepd.eu/ is intended only for informational use by healthcare professionals and is not offered as or intended to be medical advice for any particular patient. This information is not intended for patients. Only a healthcare professional exercising independent clinical judgement can make decisions regarding appropriate patient care and treatment options considering the unique characteristics of each patient.

PD: Parkinson´s Disease

Parkinson's Foundation

Veeva Code: ABBV-AA-00335-FM Approved: January 2022

abbvie