GLIOMA - VENOUS THROMBOEMBOLISM
GLIOMA - VTE
GLIOMA - VTE

First principles, Clarice. Simplicity. Read Marcus Aurelius. Of each particular thing ask: what is it in itself? What is its nature? What does he do, this man you seek?

by Hannibal Lecter • played by Anthony Hopkins

The Silence of the Lambs
The two string problem

- Substantial risk for developing VTE
- Concern antithrombotic agents can precipitate hemorrhage
The goal of the exercise was to tie the two strings together.
The two string problem

VTE is common in high-grade gliomas.
   Why?
   When?
   High risk patients?
   Treatments?

What to do with VTE?
   Prevention.
   Treatment.
   Vs
   Bleeding risk
Epidemiology

• Estimates of the incidence of **VTE** consistently show increased relative risk among patients with cancer compared with the general population.
  – Better dx tools.
  – Better survival
  – New treatments

Lee et al. Blood 2013, 122:2310-17
Epidemiology

- VTE increased in GBM.
- Prospective studies of GBM, the observed incidence of symptomatic VTE ranges from 17 to 26%.
- These patients had twice the risk of mortality compared with other patients.

Perry JR. Neuro Oncol. 2012 Sep;14 Suppl 4:iv73-80
Mechanism of VTE development in Gliomas

Coagulation system is continually activated in GBM!

When?

• Risk persists throughout the clinical course
  – Postoperative period following craniotomy.
  – During intensive chemotherapy.

Marras LC et al. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. Cancer 2000 1;89(3):640-6
# Risk factors

## Patient Factors
- Age (>75 y).
- Prior VTE.
- Leg paresis.
- Prolonged immobility.
- Multiple medical comorbidities.
- Obesity.
- ABO type (A, AB).

## Glioma- factors
- Tumor grade (high)
- Intraluminal thrombosis.
- Recurrent disease
- Tumor size (>5 cm)
- Postoperative residual disease

## Treatment-factors
- Long operative time (>4h)
- Postoperative period.
- Chemotherapy
- Anti-VEGF treatment
- Hormonal therapy
- Venous access device

---

High risk patients
### Patient characteristics

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Site of cancer</th>
<th>Pre-chemotherapy platelet count ≥350,000/mm$^3$</th>
<th>Pre-chemotherapy leukocyte count &gt;11,000/mm$^3$</th>
<th>Body mass index ≥35 kg/m$^2$</th>
<th>High-risk score ≥ 3; Intermediate-risk score = 1–2; Low-risk score = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Very high risk (brain, stomach, pancreas)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>High risk (lung, lymphoma, gynecologic, bladder, testicular)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Hemoglobin level &lt;10 g/dl or use of red cell growth factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Pre-chemotherapy leukocyte count &gt;11,000/mm$^3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Body mass index ≥35 kg/m$^2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Rates of VTE according to scores from the risk model in the derivation and validation cohorts.
Venous thromboembolism (VTE) and glioblastoma

Shlomit Yust-Katz1,2 · Jacob J. Mandel3 · Jimin Wu5 · Ying Yuan5 · Courtney Webre4 · Tushar A. Pawar6 · Harshad S. Lhadha6 · Mark R. Gilbert6 · Terri S. Armstrong6,7

Received: 29 October 2014/Accepted: 6 May 2015/Published online: 19 May 2015
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Table 4 Applying the Khorana scale for the study population

<table>
<thead>
<tr>
<th>VTE</th>
<th>Khorana scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
</tr>
</tbody>
</table>

Sensitivity = 63/(64) = 98 %, specificity = 21/(376) = 5.6 %, VTE venous thromboembolism
Background: VTE is a common complication in HGG; however, its incidence remain uncertain. KS is the only validated predictive model to gauge cancer patient’s cancer risk for developing VTE. Methods: The aim of this study is to analyze the incidence of VTE and KS in ambulatory patients (pts) with HGG receiving chemotherapy. We performed a retrospective review in 10 hospitals of the Cancer and Thrombosis Working Group of the Spanish Society of Medical Oncology (SEOM). A total of 469 consecutive patients from January 2008 through December 2011 were included in the analysis. Results: VTE was identified in 13.6% of pts. Median age: 60.5 (range 19-85). Type of glioma (GB/AA/O): 348/82/27. Previous VTE: 5 (1%). Previous arterial thromboembolism: 28 (5.9%). Type of first VTE: 84.3% pulmonary embolism (PE) and 15.7% others (deep vein trombosis (DVT) and superficial vein trombosis (SVT)). KS (Table 1). No difference was observed between VTE+ and VTE- groups in accordance with epidemiologic, concomitant treatment or oncological treatment (surgery, chemotherapy, antiangiogenetics or surgery). Conclusions: The high incidence of VTE observed in this study is consistent with prior reports. We remark the high incidence of PE in the
Biomarkers predictive of venous thromboembolism in patients with newly diagnosed high-grade gliomas

Johannes Thaler, Cihan Ay, Alexandra Kaider, Eva-Maria Reitter, Johanna Haselböck, Christine Mannhalter, Christoph Zielinski, Christine Marosi, and Ingrid Pabinger

Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Austria (J.T., C.A., E-M.R., J.H., I.P.); Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna General Hospital, Vienna, Austria (J.T., C.A., E-M.R., C.Z., C.M.A.I., J.H., I.P.); Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria (C.M.A.I.); Clinical Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria (C.Z., C.M.A.I.); Center for Medical Statistics, Informatics and Intelligent Systems, Section for Clinical Biometrics, Medical University of Vienna, Vienna, Austria (A.K.)

Corresponding Author: Ingrid Pabinger, MD, Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Waehringer Guertel 18–20, A-1090 Vienna, Austria. (ingrid.pabinger@meduniwien.ac.at).

Variable

Hemoglobin (per 1 g/L increase)
Leukocyte count (per doubling)
Platelet count (per $50 \times 10^9$/L increase)
Soluble P-selectin (per doubling)
Peak thrombin generation (per 50 nM increase)
Prothrombin fragment 1 + 2 (per doubling)
Fibrinogen (per 50 µg/mL increase)
Factor VIII activity (per 20% increase)
D-dimer (per doubling)
C-reactive protein (per doubling)
Factor V Leiden mutation

Risk assessment model 1

Risk assessment model 2
Bevacizumab

Associated with an increased risk of:

1° VTE
2° Bleeding into the primary tumor
Figure 2. Relative Risk (RR) of Venous Thromboembolism Associated With Bevacizumab vs Control

The RR of venous thromboembolism (combination of all-grade and high-grade venous thromboembolism if data for all-grade venous thromboembolism were not available) was calculated using a fixed-effects model. The size of the squares is directly proportional to the amount of data in each trial.

Nalluri et al. JAMA 2008;300: 2277-2285
# Bevacizumab- VTE

**AVAglio: AEs of Special Interest for BEV**

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>RT/TMZ/PL (n=447)</th>
<th></th>
<th>RT/TMZ/BEV (n=464)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
<td>All grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td><strong>Bleeding:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cerebral haemorrhage</td>
<td>2.2</td>
<td>0.7</td>
<td>2.6</td>
<td>1.5</td>
</tr>
<tr>
<td>mucocutaneous bleeding</td>
<td>8.9</td>
<td>–</td>
<td>26.7</td>
<td>0.4</td>
</tr>
<tr>
<td>other</td>
<td>8.1</td>
<td>0.4</td>
<td>11.6</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Wound-healing complications</strong></td>
<td>2.2</td>
<td>0.7</td>
<td>3.7</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Arterial thromboembolic events</strong></td>
<td>1.6</td>
<td>1.3</td>
<td>5.0</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Venous thromboembolic events</strong></td>
<td>9.6</td>
<td>8.1</td>
<td>7.8</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>13.0</td>
<td>2.0</td>
<td>37.5</td>
<td>10.3</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>4.0</td>
<td>–</td>
<td>14.0</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>GI perforation (including GI fistula/abscess)</strong></td>
<td>0.2</td>
<td>0.2</td>
<td>1.7</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Abscesses and fistulae</strong></td>
<td>0.4</td>
<td>0.4</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Congestive heart failure</strong></td>
<td>0.2</td>
<td>–</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Posterior reversible encephalopathy syndrome</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
### Bevacizumab - VTE

#### RTOG 0825: Treatment-Related Toxicities

<table>
<thead>
<tr>
<th>Category</th>
<th>During chemoradiation plus BEV or PL</th>
<th>During adjuvant treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td></td>
<td>PL (n=300)</td>
<td>BEV (n=303)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>4 (1.3)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (1.7)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>22 (7.3)</td>
<td>24 (8.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17 (5.7)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (2.7)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>1 (0.3)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.3)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td><strong>Thromboembolic disease</strong></td>
<td>3 (1.0)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Visceral perforation</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>
• Bleeding is a frequent complication of bevacizumab.

• Most cases involve low-grade mucocutaneous hemorrhages that can be managed easily and that rarely lead to treatment discontinuation.

• A major concern of bevacizumab in brain tumors is the risk of ICHs.

• In clinical trials, rates of ICH are relatively low in GBM patients treated with bevacizumab 0-4%.

Friedman et al. JCO 2009;27:4733-4740
### Bevacizumab- Hemorrhage

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<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Bevacizumab- Hemorrhage

• Presence of signs of recent hemorrhage within the tumor mass, the implications for treatment with bevacizumab should be evaluated carefully.
At present, in the vast majority of clinical trials with bevacizumab:

• Therapeutic anticoagulation is not considered a contraindication, and it is not an exclusion criterion.

TO-DO LIST

NOTHING
Prevention of VTE in cancer patients

**DURATION OF PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM WITH ENOXAPARIN AFTER SURGERY FOR CANCER**

DAVID BERGOVIST, M.D., PH.D., GIACARLO AGNELLI, M.D., ALEXANDER T. COHEN, M.D., AMIRAM ELDOR, M.D., PAUL E. NILSSON, M.D., PH.D., ANNE LE MOIGNE-AMIRAN, M.S., AND FLAVIA DIETRICH-NETO, M.D., FOR THE ENOXACAN II INVESTIGATORS.

**ABSTRACT**

**Background** Abdominal surgery for cancer carries a high risk of venous thromboembolism, but the optimal duration of postoperative thromboprophylaxis is one month after orthopedic surgery significantly reduces the frequency of deep-vein thrombosis, as compared with low-molecular-weight heparin given only during the first postoperative week. **Table 2**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Total no. of patients</th>
<th>Total no. of cancer patients</th>
<th>Intervention</th>
<th>CAT in placebo, n/N (%)</th>
<th>CAT in thromboprophylaxis, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDENOX22</td>
<td>579</td>
<td>72</td>
<td>Enoxaparin 40 mg daily</td>
<td>8/41 (19.5)</td>
<td>3/31 (9.7)</td>
</tr>
<tr>
<td>PREVEN23</td>
<td>3,706</td>
<td>137</td>
<td>Dalteparin 5,000 IU daily</td>
<td>6/72 (8.3)</td>
<td>2/65 (3.1)</td>
</tr>
<tr>
<td>ARTEMIS74</td>
<td>644</td>
<td>98</td>
<td>Fondaparinux 2.5 mg daily</td>
<td>2/51 (3.9)</td>
<td>8/47 (17.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CAT, cancer-associated thrombosis; no., number.
Prevention of VTE

"Apparently they’re better than The Cure."

<table>
<thead>
<tr>
<th>Guía</th>
<th>Pacientes sin factores de riesgo de ETV</th>
<th>Pacientes con factores de riesgo de ETV</th>
<th>Factores de riesgo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESMO 2011*</td>
<td>No / Nivel 2C</td>
<td>Considerar tromboprofilaxis / Nivel 2c</td>
<td>No definidos</td>
</tr>
<tr>
<td>NCCN 2013*</td>
<td>No / Nivel de evidencia no definido</td>
<td>Considerar tromboprofilaxis / Nivel de evidencia no definido</td>
<td>Khorana ≥ 3</td>
</tr>
<tr>
<td>ISTH 2013?</td>
<td>No / Nivel 1B</td>
<td>Considerar tromboprofilaxis en dos situaciones clínicas</td>
<td>Pacientes con cáncer de páncreas localmente avanzado o metastásico</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1) Pacientes con cáncer de páncreas localmente avanzado o metastásico en tratamiento con quimioterapia y con bajo riesgo de sangrado. Nivel 1B</td>
<td>Pacientes con cáncer de pulmón localmente avanzado o metastásico</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Pacientes con cáncer de pulmón localmente avanzado o metastásico en tratamiento con quimioterapia y con bajo riesgo de sangrado. Nivel 2B</td>
<td></td>
</tr>
<tr>
<td>ACCP 2012?</td>
<td>No / Nivel 2B</td>
<td>Considerar si bajo riesgo de sangrado / Nivel 2B</td>
<td>ETV previa, inmovilización, tratamiento hormonal, inhibidores de la angiogénesis, talidomida y lenalidomida</td>
</tr>
<tr>
<td>ASCO 2013?</td>
<td>No / Nivel de evidencia no definido</td>
<td>Considerar tromboprofilaxis en pacientes altamente seleccionados</td>
<td>No definidos</td>
</tr>
</tbody>
</table>

Tabla 5: Profilaxis del paciente ambulatorio en tratamiento con quimioterapia según las diferentes guías.
Prevention of VTE in glioma patients
Evaluating the risk of bleeding

- Frequency of symptomatic bleeding into gliomas averages 2 to 4% in the absence of antithrombotic therapy.

Prevention of VTE in gliomas

- Patients who have an active malignancy with an acute medical illness or reduced mobility should receive pharmacologic thromboprophylaxis in the absence of contraindications.
Addition of enoxaparin starting the day after surgery:

- Significantly reduces clinically manifest VTE
- Despite an increase in major bleeding events.
- Further studies are needed to delineate the types of patients with an increase of VTE risk and risk/benefits ratio of physical and pharmacological treatments in the perioperative period.
Prevention of VTE in gliomas

- Outside of the perioperative period and hospitalization:
- Long-term prophylactic anticoagulation is not recommended due to a lack of available data in the literature.

Trial was terminated prematurely because of the unavailability of placebo.
**PRODIGE:** a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma

J. R. PERRY, * J. A. JULIAN, † N. J. LAPERRIERE, ‡ W. GEERTS, § G. AGNELLI, ¶ L. R. ROGERS, **
M. G. MALKIN, †† R. SAWAYA, †‡‡ R. BAKER, §§ A. FALANGA, †¶ S. PARPIA, † T. FINCH† and
M. N. LEVINE**

*Division of Neurology, Sunnybrook Health Science Centre, Toronto; †Ontario Clinical Oncology Group and Department of Oncology, McMaster University, Hamilton; ‡Department of Radiation Oncology, Princess Margaret Hospital, University Health Network, Toronto; §Thromboembolism Program, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; ¶Internal and Vascular Medicine-Stroke Unit, University of Perugia, Perugia, Italy; **Department of Neurology, Neurological Institute, University Hospitals, Case Medical Centre, Cleveland, Ohio; ††Department of Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin; †‡‡Department of Neurosurgery, University of Texas MD Anderson Cancer Center, Houston, Texas, USA; §§Hematology Department, Royal Perth Hospital, Perth, Australia; †¶Division of Immunohematology and Transfusion Medicine, Department of Oncology/Hematology, Ospedali Riuniti di Bergamo, Bergamo, Italy; and **Department of Oncology, McMaster University and Juravinski Cancer Centre, Hamilton, Ontario, Canada

---

**Table 3** Details of patients with major bleeding events*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day</th>
<th>Episode</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>1</td>
<td>Fell at home.</td>
<td>Surgical evacuation.</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Epidural hematoma</td>
<td>Drug stopped. PE on Day 83.</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>Intratumoral bleed, Fatal</td>
<td>Death.</td>
</tr>
<tr>
<td></td>
<td>187</td>
<td>Asymptomatic epidural hematoma</td>
<td>Drained.</td>
</tr>
<tr>
<td></td>
<td>245</td>
<td>Intratumoral bleed</td>
<td>Died of disease progression 5 days later.</td>
</tr>
<tr>
<td></td>
<td>220</td>
<td>New seizures, subdural hematoma</td>
<td>DVT 3 weeks later.</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>Drained. Remains alive.</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; DVT, deep vein thrombosis. *All on study drug at time of the event.
PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma


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Conclusions: Trends suggesting reduced VTE and increased intracranial bleeding were seen in the LMWH thromboprophylaxis group. The role of long-term anticoagulant thromboprophylaxis in patients with brain tumors remains uncertain.
## Prevention of VTE in gliomas

### Dalteparina

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### Tinzaparina

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### Effect of dalteparin and radiation on survival and thromboembolic events in glioblastoma multiforme: a phase II ECOG trial

H. Ian Robins · Anne O’Neill · Mark Gilbert · Mark Olsen · Ronald Sapiente · Brian Berkey · Minesh Mehta

Received: 23 March 2007 / Accepted: 4 September 2007 / Published online: 20 September 2007
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### Tinzaparin prophylaxis against venous thromboembolic complications in brain tumor patients

Stephanie L. Perry · Cindy Bohlin · David A. Reardon · Annick Desjardins · Allan H. Friedman · Henry S. Friedman · James J. Vredenburgh

Received: 10 February 2009 / Accepted: 22 April 2009 / Published online: 5 May 2009
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Prevention of VTE in gliomas

Taken together and reflected against the background of other human cancers, clinical trials for VTE prophylaxis are urgently needed.
Prevention of VTE in gliomas

• Role of the oral factor X blocker **apixaban**.

• Controlled, triple-blind, multinational phase III study randomizes pts. in a 1:1 fashion to receive either postop prophylactic anticoagulation with apixaban (2.5mg b.i.d) or placebo over a 12-month-period in addition to the international first line standard therapy.

• The primary endpoint is overall survival.
Treatment of VTE
Treatment of VTE

Hannibal Lecter Social Chart
Treatment of VTE

- Inferior vena cava (IVC) filters

Treatment of VTE

- Anticoagulation is now generally preferred because:
  - the incidence of complications with IVC filters is much higher than originally thought.
  - Risk of hemorrhage secondary to anticoagulation is not as high as originally feared.
Treatment of VTE

• Anticoagulation should be avoided in:
  – Presence of prior intracranial bleeding.
  – Preexisting bleeding diathesis (e.g., platelet count \(<50,000/\text{microL}\)).
  – Coagulopathy.
  – Should be used with caution in those determined to be at high risk for bleeding after the use of anticoagulants.
Treatment of VTE

LMWH as the sole treatment

Overall, CLOT trial, included 34 patients with primary CNS malignancy.
Treatment of VTE

Duration of anticoagulation:

• Remains controversial.
• Minimum of 6 months is commonly recommended.
Direct oral anticoagulants (DOAs)

- Safety profile of direct oral anticoagulants is unknown in patients with brain tumors.
  - Trials excluded patients with cancer or included only a small number
- No antidotes exist.
- Potential drug interaction with chemotherapy and antiepileptic agents
- Guidelines do not recommend DOAs in cancer patients.
Management of VTE during bevacizumab administration

• Bevacizumab should be stopped and an appropriate therapy with LMWH prescribed.
• Bevacizumab can be **resumed** after the start of anticoagulant therapy.
• Should be **discontinued** in cases of grade 4 VTE or recurrent VTEs refractory to anticoagulant treatment

Summary

• No standardized approach.
• GBM patients not be anticoagulated, except in the postoperative period.
• Anticoagulation in all patients with brain tumors and VTE – except those that have a high rate of intracranial hemorrhage.
• LMW Heparin for anticoagulation.
• Clinical trials for VTE in GBM are urgently needed.

Many challenges remain.
Thanks for your attention!

Imaginative solution

Breaking the rules!