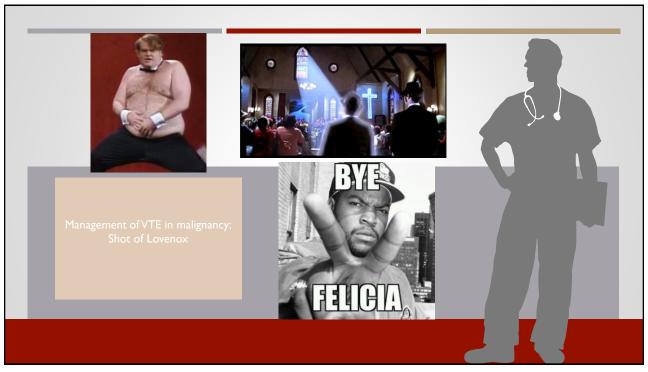


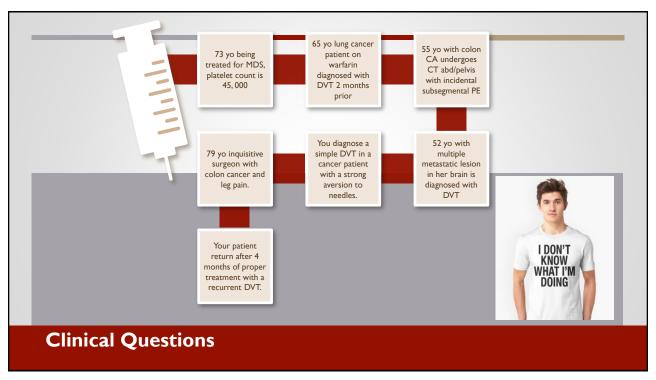
# VENOUS THROMBOEMBOLISM (VTE) IN THE SETTING OF CANCER: CLINICAL CONUNDRUMS

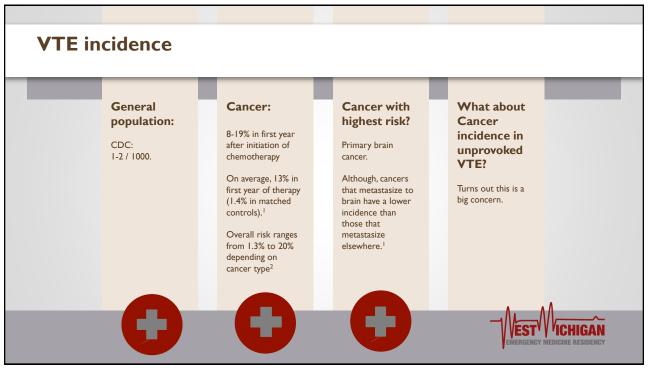
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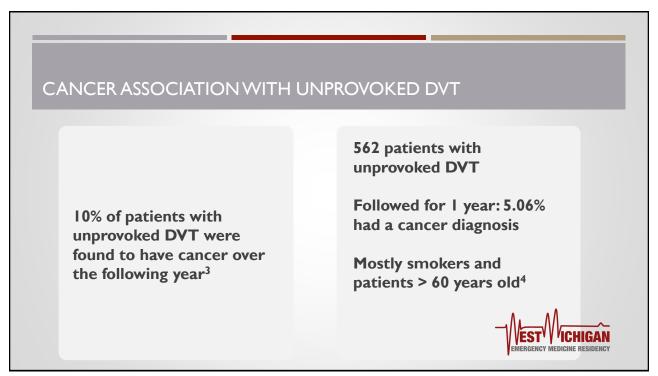
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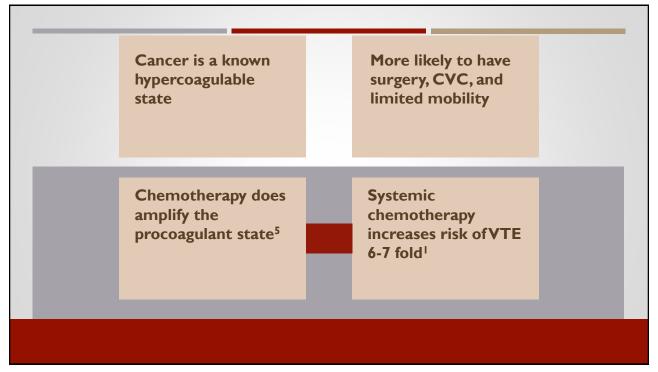
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### MAKING THE DIAGNOSIS

- Diagnosis will be made doppler
  - If clinical exam still suspicious with negative doppler, repeat exam is recommended in I-2 weeks
  - Explicitly describe this in the discharge instructions
- D-Dimer?



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Active cancer Freatment or palliation within 6 months	No 0	Yes +1			
Bedridden recently >3 days or major surgery within 12 weeks	No 0	Yes +1	II IST DON'T		
Calf swelling >3 cm compared to the other leg Measured 10 cm below tibial tuberosity	No 0	Yes +1	JUST DON'T  Clinical signs and symptoms of DVT	No 0	Yes +3
Collateral (nonvaricose) superficial veins present	No 0	Yes +1	PE is #1 diagnosis OR equally likely	No 0	Yes +3
Entire leg swollen	No 0	Yes +1	Heart rate > 100	No 0	Yes +1.5
Localized tenderness along the deep venous system	No 0	Yes +1	Immobilization at least 3 days OR surgery in the previous 4 weeks	No 0	Yes +1.5
Pitting edema, confined to symptomatic leg	No 0	Yes +1	Previous, objectively diagnosed PE or DVT	No 0	Yes +1.5
			Hemoptysis	No 0	Yes +1
Paralysis, paresis, or recent plaster immobilization of the lower extremity	No 0	Yes +1	Malignancy w/ treatment within 6 months or palliative	No 0	Yes +1
Previously documented DVT	No 0	Yes +1		_1/\/	M
Alternative diagnosis to DVT as likely or more	No 0	Yes -2		VEST <sup>V</sup> EMERGENCY	V VICHIGAN MEDICINE RESIDENCY



- A word about D-Dimer
  - 2 main assays
    - D-dimer units (DDU)
    - Fibrin equivalent units (FEU)
  - All major studies used d-Dimers measure in FEU
  - FEUs are age x 10 ug/L
  - DDUs are age x 5ug/L<sup>7</sup>



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### **TREATMENT**

- Noncancer patients:
  - Low molecular weight heparin (LMWH) for 5-10 days followed by warfarin
  - Direct oral anticoagulants (DOACs)
- Cancer patients:
  - LMWH for 6 months
  - Full Dose for I month and 75% dose for next 5 months.
  - American College of Chest Physicians recommends continuing while cancer is active<sup>8</sup>



### SO, THAT'S A NO ON WARFARIN?

- Multiple factors lead to decreased efficacy
  - Higher recurrence
  - Multiple drug interactions with chemo
  - Possible liver involvement with malignancy
  - Malnutrition
  - Difficulty in maintaining an INR
  - Higher incidence of major bleeding
  - Acceptable alternative for long-term therapy if LMWH is not available/feasible<sup>9,10</sup>



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### TREATMENT – DIRECT ORAL ANTICOAGULANTS

- Clinical trials comparing these to warfarin were non-inferiority studies
- Only 2-9% were cancer patients
- Subsequent meta analysis suggested that DOACs may be more efficacious than warfarin; no direct comparisons have been done.<sup>8</sup>



### TREATMENT - DOACS

- Multiple guidelines
  - "There are insufficient data to suggest that direct oral anticoagulants would be appropriate for treatment of cancer associated VTE."<sup>8,10</sup>
- Contraindications
  - In addition to normal contraindications, keep in mind renal function, age, weight, etc.



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### RASKOB ET.AL: EDOXABAN VS. LMWH - 201811

- Edoxaban
  - Recurrent VTE: 7.9%
  - Major Bleeding 6.9%

- LMWH
  - Recurrent VTE: 11.3%
  - Major Bleeding 4.0%



### TREATMENT OF INCIDENTAL PE – NONCANCER PATIENTS

#### Goy et al. in 2015

- Review of 2213 patients with a diagnosis of subsegmental PE
- Showed that whether or not anticoagulation was given, there were no recurrent PEs, yet 5% of anticoagulated patients developed life-threatening bleeding<sup>12</sup>

### The 2018 ACEP Clinical Policy on Acute Venous Thromboembolic Disease:

Withholding anticoagulation in patients with subsegmental PE a Level C recommendation and states: "Given the lack of evidence, anticoagulation treatment decisions for patients with subsegmental PE without associated DVT should be guided by individual patient risk profiles and preferences [Consensus recommendation]."

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### TREATMENT OF INCIDENTAL VTE IN MALIGNANCY

- Similar rate of recurrent VTE and mortality for those found to have incidental/asymptomatic VTE vs. symptomatic VTE
- Therefore, treat all VTE<sup>8,10</sup>



### ANTICOAGULATION IN THE CANCER PATIENT

### The decisions seems simple

VTE = Treat

## We must appreciate the bleeding risk in the cancer patient

- 4.7% recurrent DVT
- 8.9% bleeding event
- · 4.6% major bleeding event
- In the first 3 months of anticoagulation, 1.4% had fatal recurrence of PE
- 1.9% died of a fatal bleed<sup>13</sup>





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### CONTRAINDICATIONS TO ANTICOAGULATION – INTRACRANIAL LESIONS

- Intracranial hemorrhage occurred in 20-50% of patients with brain metastasis
- No significant difference in occurrence between those receiving LMWH and match controls not on anticoagulation<sup>14</sup>
- Guidelines:
  - Relative contraindication by American Society of Clinical Oncology<sup>15</sup>
  - Absolute contraindication by National Comprehensive Cancer Network<sup>16</sup>



### CONTRAINDICATIONS TO ANTICOAGULATION -**THROMBOCYTOPENIA**

- Less than 50,000/uL is a relative contraindication
  - Transfuse up to 50,000/uL and then treat
- Between 25,000-50,000/uL
  - Consider 50% dose of LMWH
- Under 20,000/uL
  - No anticoagulation 10



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Table 4. Contraindications and Other Considerations to Withhold Therapeutic Anticoagulant Therapy in Patients With Cancer and VTE\*

Contraindication/Consideration

#### Absolute contraindications†

Active major, serious, or potentially life-threatening bleeding not reversible with medical or surgical intervention, including but not limited to any active bleeding in a critical site (ie, intracranial, pericardial, retroperitoneal, intraocular, intra-articular, intraspinal) Severe, uncontrolled malignant hypertension

Severe, uncompensated coagulopathy (eg, liver failure) Severe platelet dysfunction or inherited bleeding disorder Persistent, severe thrombocytopenia (< 20,000/μL) Surgery or invasive procedure, including but not limited to lumbar puncture, spinal anesthesia, and epidural catheter placement

### Relative contraindications‡ Intracraria Ctive, longoing, bleeding.

Active peptic or other GI ulceration at high risk of bleeding Active but non-life-threatening bleeding (eg, trace hematuria) Intracranial or CNS bleeding within past 4 weeks

Major surgery or serious bleeding within past 2 weeks Persis Sevene uncontrolled malignant

### Patients hyper tension is of uncertain benefit Patient receiving end-of-life/hospice care

Very limited life expectancy with no palliative or symptom reduction

Asymptomatic thrombosis with concomitant high risk of serious

Patient characteristics and values

### \*CNS lesions, Gl-ulcerations, active but non-life threatening, CNS bleeding within 4 weeks, and Major surgery within 2 weeks.

Abbreviation: VTE, venous thromboembolism.
\*These criteria are specific for therapeutic doses of anticoagulation and Insea claims alle specime for imperiod consequence of anticoagulation and should not be applied to prophylactic doses of anticoagulation. †Absolute contraindications are situations in which anticoagulation should not be administered because the risk of harm associated with bleeding is likely to exceed the potential benefit from anticoagulation. \*Relative contraindications are situations in which anticoagulation may be administered if the risk of recurrent or progressive thrombosis is estimated to evocat the risk of bleeding.

xceed the risk of bleeding.

Contraindications to anticoagulation in cancer patients with VTE<sup>10</sup>

Severe coagulopathy (liver failure)

Severe, thrombocytopenia/platelet dysfunction

Surgery or invasive procedure, including LP, epidural catheters, etc

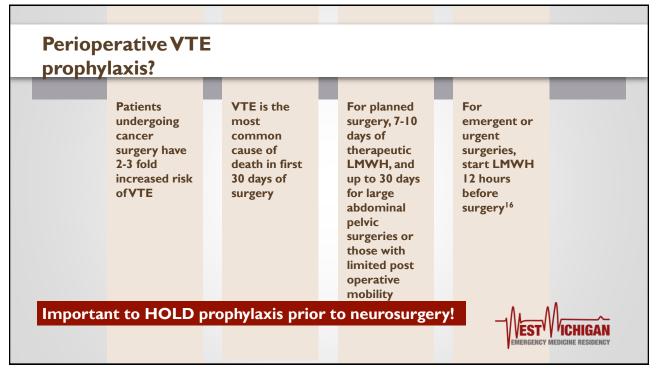


### PATIENTS IN WHOM ANTICOAGULATION HAS UNCERTAIN BENEFIT:

- End of life or Hospice care
- Very limited life expectancy with no palliative or symptom reduction benefit
- Asymptomatic VTE with high risk of bleeding



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### VTE PROPHYLAXIS IN HIGH RISK PATIENTS

- High-grade glioma has high incidence of VTE (12-30%)<sup>17</sup>
  - PRODIGE trial:
    - 99 patients treated with LMWH: 5.1% major bleeds, 9.1% thrombotic events
    - 87 patients received placebo: 1.2% major bleeds, 14.9% thrombotic events
  - Prophylaxis is not generally recommended<sup>18</sup>



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### EMPIRIC THERAPEUTIC ANTICOAGULATION

- Mostly an outpatient question
- Khorana score utilized by oncology team
- Certain cancer/chemo combinations have extremely high risk<sup>19</sup>
  - Eg. Multiple Myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone have extremely high risk.
  - High grade glioma: extremely high risk

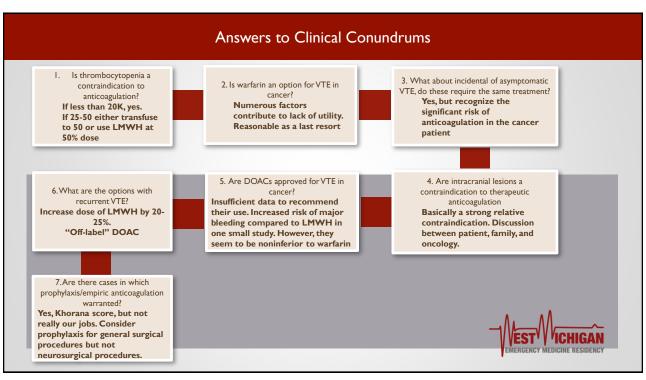


### **RECURRENT VTE**

- Incidence
  - 3-4 time risk of recurrent VTE while on therapy compared to those without cancer
  - 10-17% in first 6 months for those on warfarin therapy
  - 6-9% in first 6 month for those on LMWH therapy<sup>20</sup>
- Treatment
  - Consider increasing dose of LMWH by 20-25%
  - IVC filters: Should be avoided except for those with absolute contraindication to anticoagulation
- I year mortality = 50% in this situation<sup>21</sup>



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### REFERENCES

- I. Khorana AA, Dalal M, Lin J, et al. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer
  patients undergoing chemotherapy in the United States. Cancer. 2013;119(3):648-55.
- 2.Horsted F, West, J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systemic review and meta-analysis. PLoS Med. 2012;9:1-19.
- 3. Carrier M, Le Gal G, Wells PS, et al. Systemic review: the Trousseau syndrome revisited: should we screen extensively for cancer in patients with venous thromboembolism? Ann Intern Med. 2008;149:323-333.
- 4. Delluc A, lanotto JC, Tromeur C, et al. Real-world incidence of cancer following a first unprovoked venous thrombosis: Results from the EPIGETBO study. Thromb Res. 2018;164:79-84.
- 5. Lee AYY. Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. J Clin Oncol. 2006;24:104-1498
- 6. Geersing GJ, Zuithoff NPA, Kearon C, et al. Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta-analysis. BMJ. 2014;348:g1340
- 7.Wolf SJ, Hahn SA, Nentwish LM, et al. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the
  emergency department with suspected acute venous thromboembolic disease. Ann Emerg Med. 2018;71(5):59-101.



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### **REFERENCES**

- 8. Kearon C, Kahn SR, Giancarlo A, et al. Antithrombotic therapy for venous thromboembolic disease. Chest. 2008;133:454S-545S.
- 9. Nene RV, Coyne CJ. Management of cancer-associated venous thromboembolism in the emergency department. Ann Emerg Med. 2017;69(6):768-776.
- 10. Lyman GH, Khorana AA, Kederer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31:2189-2204.
- I1. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med. 2018;378(7):615-624.
- 12. Goy J, et al. Sub-segmental pulmonary embolism in three academic teaching hospitals:a review of management and outcomes
- 13. Farge D, Trujillo-Santos J, Debourdeau P, et al. Fatal events in cancer patients recieveing anticoagulant therapy for venous thromboembolism. Medicine. 2015;94(32):e1235.
- 14. Donato J, Campigotto F, Uhlmann EJ, et al. Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin: a matched cohort study. Blood. 2015;126:494-499.
- 15. 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. J Clin Oncol. 2015;33:654-656.



### **REFERENCES**

- 16. Streiff MB, Holmstrom B, Ashrani A, et al. Cancer-associated venous thromboembolic disease, version 1.2015: featured updates to the NCCN guidelines. J Natl Compr Cancer Netw. 2015;33:654-656.
- 17. Perry JR. Thromboembolic disease in patients with high-grade glioma. Neuro Oncol. 2012;14:iv73-iv80.
- 18. Perry JR, Julian JA, Laperriere NJ, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low molecular (LMWH) thromboprophylaxis in patients with newly diagnosed malignant glioma. J Thromb Haemost. 2010;8:1959-1965.
- 19. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapyassociated thrombosis. Blood. 2008;111:4902-4907.
- 20. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Cancer. 2002;100:3484-3488.
- 21. Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am | Med. 2006;119:1062-1072.