

Key Concepts and Complications: Managing Cancer-Associated Thrombosis

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Disclosures

- Consultant for BMS/Pfizer x1

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Objectives:

- **Define** deep vein thrombosis (DVT) or pulmonary embolism (PE) based on location, acuity, and severity.
- **Implement** an appropriate intervention for treatment.
- **Identify risk factors** for venous thromboembolism (VTE) and recurrence and **understand rationale for duration** of anticoagulation.

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Defining the Clot - Location

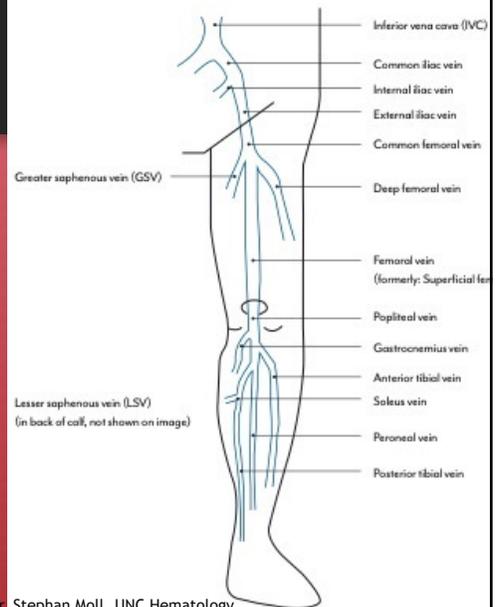
- A venous clot can be **superficial** (superficial thrombophlebitis) or **deep** (DVT).
- A DVT can be **proximal** (popliteal vein and above) or **distal** (below the popliteal vein).
- In general, treatment duration and/or dosing is different depending on these factors. There is somewhat less variation in the case of cancer-associated thrombosis, as we will discuss.

This and other helpful material can be found at clotconnect.org

Illustrations courtesy of Dr. Stephan Moll, UNC Hematology

Superficial Veins

Deep Veins



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Defining the Clot - Acute vs Chronic

- Venous Doppler can usually differentiate between **acute** and **chronic** features for DVT.
- It is less straightforward to determine the chronicity of PE, particularly if incidentally found.
- In general, the appearance on imaging should be considered in conjunction with the patient history.
- If questions arise, call radiology for clarification!

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Pulmonary Embolism - Definitions

- **Low-risk:** No evidence of right heart strain.
- **Submassive:** evidence of right heart strain, without hemodynamic instability.
- **Massive:** Hemodynamic instability, generally hypotension/shock.
- To categorize - often will obtain troponin values and/or echocardiogram. Positive troponin, RV dilation, RA dilation are all indications of RH strain. Can also see RH strain on CT scan.¹

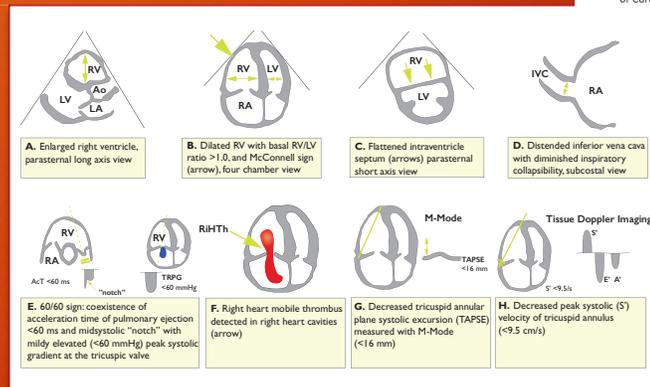


Figure 3 Graphic representation of transthoracic echocardiographic parameters in the assessment of right ventricular pressure overload. A' = peak late diastolic (during atrial contraction) velocity of tricuspid annulus by tissue Doppler imaging; AcT = right ventricular outflow Doppler acceleration time; Ao = aorta; E' = peak early diastolic velocity of tricuspid annulus by tissue Doppler imaging; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; RA = right atrium; RHTh = right heart thrombus (or thrombi); RV = right ventricle/ventricular; S' = peak systolic velocity of tricuspid annulus by tissue Doppler imaging; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid valve peak systolic gradient.

Figure from ESC, citation 1

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Case:

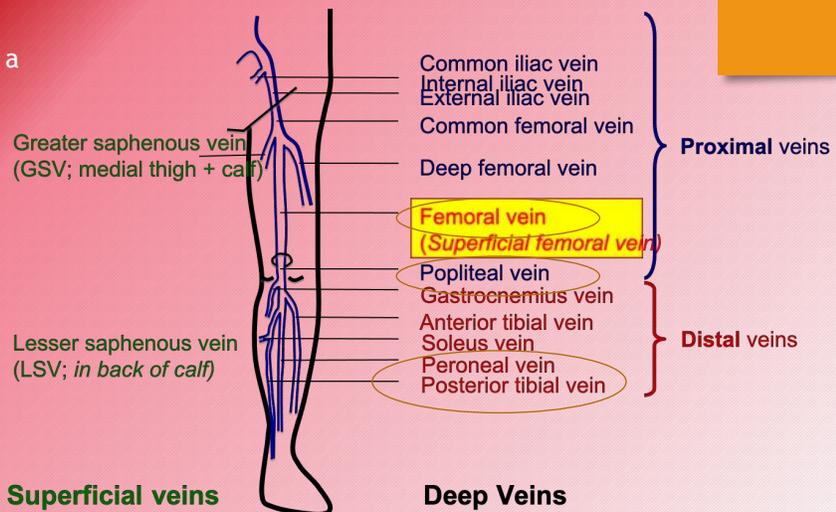
- 45 yo female with metastatic breast cancer and new left lower extremity swelling and pain.
- Sent for lower extremity Doppler ultrasound:
 - Acute obstruction of the left lower extremity femoral vein at mid thigh, distal thigh, popliteal vein, posterior tibial vein 1/2, and peroneal vein.
 - No evidence of DVT in the RLE.



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Step 1: Define the clot.

- Is this a proximal DVT or a distal DVT?
- Is it acute or chronic?



Illustrations courtesy of Dr. Stephan Moll, UNC Hematology

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Step 2: Assess Risk Factors

There are many risk factors with variable relevance.

Cancer patients are more likely to be impacted by some of these risks due to illness and treatment - i.e. infections, blood transfusions, trauma (surgery), etc.

Additionally, cancer itself is a risk factor for VTE.¹

Table 3. Predisposing factors for venous thromboembolism (data modified from Rogers et al.²⁴ and Anderson and Spencer²⁵)

Strong risk factors (OR > 10)
Fracture of lower limb
Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
Hip or knee replacement
Major trauma
Myocardial infarction (within previous 3 months)
Previous VTE
Spinal cord injury
Moderate risk factors (OR 2–9)
Arthroscopic knee surgery
Autoimmune diseases
Blood transfusion
Central venous lines
Intravenous catheters and leads
Chemotherapy
Congestive heart failure or respiratory failure
Erythropoiesis-stimulating agents
Hormonal replacement therapy (depends on formulation)
In vitro fertilization
Oral contraceptive therapy
Post-partum period
Infection (specifically pneumonia, urinary tract infection, and HIV)
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Paralytic stroke
Superficial vein thrombosis
Thrombophilia
Weak risk factors (OR < 2)
Bed rest >3 days
Diabetes mellitus
Arterial hypertension
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy
Varicose veins

VTE = Venous thromboembolism; OR = Odds ratio; VTE = venous thromboembolism.

Table - from ESC, citation 1



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Step 2: Assess Risk Factors

- This patient is receiving chemotherapy.
- She was recently admitted (2 weeks ago) for 3 days for neutropenic fever, no source identified.
- She has not had a recent blood transfusion and she has not had surgery in 6 months.
- **Risk factors for VTE:**
 - 1) Active malignancy (metastatic breast cancer)
 - 2) Recent hospitalization/immobility
 - 3) Recent infection
 - 4) Receiving Chemotherapy
- **Risk factors for bleeding:** None.

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Step 3: Treatment Do they have contraindications to anticoagulation?²

Absolute contraindications

Active bleeding (major)
 Indwelling neuraxial catheters
 Neuraxial anesthesia/lumbar puncture
 Interventional spine and pain procedures

Relative contraindications

Chronic, clinically significant measurable bleeding >48 hours
Thrombocytopenia (platelet count <30,000–50,000/ μ L or clinical judgment)
 Underlying hemorrhagic coagulopathy (eg, abnormal PT or aPTT excluding a lupus inhibitor/anticoagulant) or known bleeding disorder in the absence of replacement therapy (eg, hemophilia, von Willebrand disease)
 Severe platelet dysfunction
Recent major operation at high risk for bleeding
High risk for falls (head trauma)
CNS metastases
 Long-term antiplatelet therapy



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Step 3: Treatment - Drug Choice^{2,3}



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DOACS: Preferred for patients without gastric or gastroesophageal lesions

Apixaban (category 1): 10mg PO q12h x 7 days, then 5mg PO q12h
 Edoxaban (category 1): Initial LMWH or UFH x5 days, then edoxaban 60mg PO daily (dose adjust for renal function)
 Rivaroxaban: 15mg PO q12h x 21 days, then 20mg daily.

LMWH: Preferred for patients with gastric or gastroesophageal lesions

Dalteparin (category 1): 200 units/kg SC daily x 30 days, then 150 units/kg daily
 Enoxaparin: 1mg/kg SC q12h

If above not appropriate/available:

Dabigatran: initial LMWH or UFH x5 days, then dabigatran 150mg PO q12h

American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer



Short-term treatment for patients with active cancer (initial 3-6 months). RECOMMENDATION 23. For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH (conditional recommendation, low certainty in the evidence of effects ⊕⊕○○).

Other options

Fondaparinux
 UFH
 Warfarin

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Considerations for specific anticoagulants²:

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<p style="text-align: center;">DOACS:</p> <p>Stage IV/V CKD: CrCl <30ml/min</p> <p>Active/clinically significant liver disease</p> <p>Strong inhibitors/inducers of CYP3A4, P-gp</p>	<p style="text-align: center;">LMWH:</p> <p>CKD: Consider alternative for CrCl <30ml/min</p> <p>History of HIT</p>	<p style="text-align: center;">UFH History of HIT</p> <p style="text-align: center;">Fondaparinux CKD: CrCl <30, caution with CrCl 30-50</p> <p style="text-align: center;">Warfarin Concomitant inhibitors and inducers of CYP2C9, 1A2, 3A4</p>
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Step 4: Treatment Duration²

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For most DVT/PE:

- At least 3 months

OR

- As long as active cancer
- Specifically for non-catheter-associated, recommendation is indefinite anticoagulation while cancer is active, undergoing treatment, or risk factors persist.

It can be difficult to determine when “active cancer” ends during early survivorship/surveillance. Shared decision making is helpful in determining plans for this interval.

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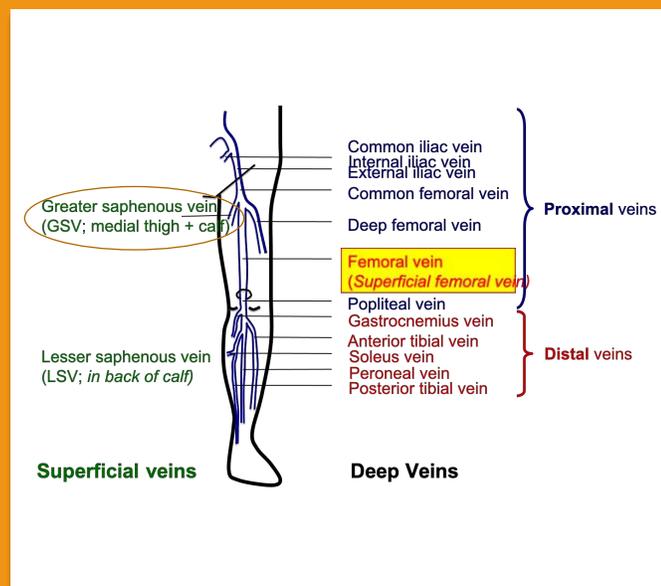
Case 2:

- 60 year old male with rectal cancer and new erythematous, tender area with palpable cord along the medial thigh
- Sent for Doppler which demonstrate:
 - *Acute superficial vein thrombosis involving the great saphenous vein, 4cm from the saphenofemoral junction.*

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Step 1: Define the clot

- Is the clot **superficial** or **deep**?
- Is it **acute** or **chronic**?



Illustrations courtesy of Dr. Stephan Moll, UNC Hematology

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Step 2: Assess risk factors

- This patient is receiving chemotherapy, has not recently been hospitalized, has not had recent surgery, but has a BMI of 40. He has a family history of PE in his father.
- His risk factors:
 - 1) Active malignancy (rectal cancer)
 - 2) Obesity (BMI 40)
 - 3) Family history of VTE
 - 4) Receiving chemotherapy

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Step 2: Assess Risk Factors - Bleeding

- This patient has rectal cancer and has a history of GI bleeding.
- He is not on any antiplatelet medications.
- He has normal platelets.
- He has normal renal function, CrCl 65ml/min

Risks for bleeding:

- 1) GI malignancy with history of GI bleeding

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Step 3: Treatment - Choice of Drug

- Recall - NCCN Guidelines caution against use of DOACs with GI malignancies
- However... Caravaggio trial demonstrates similar bleeding risks for apixaban and dalteparin, including in GI malignancies.⁴

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Guy Meyer, M.D., Andres Muñoz, M.D., Menno V. Huisman, M.D., Jean M. Connors, M.D., Alexander Cohen, M.D., Rupert Bauersachs, M.D., Benjamin Brenner, M.D., Adam Torbicki, M.D., Maria R. Suevo, M.D., Catherine Lambert, M.D., Gualberto Gussoni, M.D., Mauro Campanini, M.D., Andrea Fontanella, M.D., Giorgio Vescovo, M.D., and Melina Verso, M.D., for the Caravaggio Investigators*

	Dalteparin	Apixaban
Recurrent VTE	46/579 (7.9%)	32/576 (5.6%)
Major Bleeding	23/579 (4.0%)	22/576 (3.8%)
Major GI Bleeding	10/579 (1.7%)	11/576 (1.9%)

gether, these findings may expand the proportion of patients with both cancer and venous thromboembolism who would be eligible for treatment with apixaban, including patients with gastrointestinal cancer. On the basis of these

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Step 4: Treatment Duration²

NCCN Guideline:
Anticoagulation at least 6 weeks IF:²
 - SVT >5cm
 - SVT extends above knee

Anticoagulation for at least 3mo IF
 - SVT within 3cm of SFJ

Consider repeat ultrasound in 7-10 days if SVT <5cm or below knee. Consider anticoagulation if progressing.

The duration of treatment in this patient should be a *minimum* of 6 weeks because his SVT extends above the knee but is 4cm from the SFJ.

While the NCCN guidelines do not mandate longer-term anticoagulation for this patient, his risk of recurrence and/or VTE is likely significant while he continues to have active malignancy.

This situation warrants discussion regarding risks and benefits of anticoagulation considering both his episode of VTE/recurrence risk and his bleeding risks.



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Case 3:

- 67 yo female with diffuse large B-cell lymphoma receiving chemotherapy who presents with shortness of breath and pleuritic pain.
- Troponin negative, D-dimer 4,980
- Chest CTA:
 - *Acute pulmonary emboli involving bilateral lower lobe segmental and subsegmental pulmonary arteries. No CT evidence of right heart strain.*

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Step 1: Define the clot

- Acute pulmonary embolism, Low-Risk
 - This episode was acute, with new sudden-onset symptoms.
 - Her PE would be considered low-risk because:
 - No evidence of right heart strain on CTA
 - Negative troponin

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Step 2: Assess Risk Factors

- This patient has DLBCL but is not obese (BMI 24), has no personal or family history of VTE, is not on hormone therapy.
 - Her risks:
 - 1) Active malignancy (DLBCL)
 - 2) Receiving chemotherapy
- Risk factors for bleeding:
- 1) Thrombocytopenia associated with chemotherapy cycles

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Step 3: Treatment - Choice of Drug

- Treatment for this episode would be the same as with proximal DVT, as discussed above.
- However -
 - This patient is receiving cytotoxic chemotherapy.
 - On review of records, her platelets decline to 20-70 range with each cycle of chemotherapy.

How do you manage her anticoagulation in the setting of recurrent thrombocytopenia?

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Management of Anticoagulation with Chemotherapy-Induced Thrombocytopenia²:

- If high risk (i.e. within 1mo of VTE event, or history of recurrent VTE), consider transfusing to 50k or in rare cases, IVC filter.
- For patients lower risk for recurrence, consider dose-reduction/holding anticoagulation as follows:

Enoxaparin Dose Modification in the Setting of Thrombocytopenia			
Platelet Count	Dose Adjustment	Suggested Dose of Enoxaparin	Alternative Once-Daily Dosing Regimen
>50,000/ μ L	Full-dose enoxaparin	1 mg/kg twice daily	1.5 mg/kg daily
25,000–50,000/ μ L	Half-dose enoxaparin	0.5 mg/kg twice daily	—
<25,000/ μ L	Temporarily hold enoxaparin		

• Note: NCCN currently does not recommend use of DOACs below a platelet count of 50,000/ μ L as there is limited published experience using DOACs in this situation.



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isth These recommendations are generally consistent with ISTH Guidelines, 2018.⁶

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Step 4: Duration of Treatment

- Same as Case 4.
- Review here the ASH and ASCO Guidelines^{3,5}:

Recommendation 4.3. Anticoagulation with LMWH, DOACs, or VKAs beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. Anticoagulation beyond 6 months needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak to moderate).

Long-term treatment (>6 months) for patients with active cancer and VTE. RECOMMENDATION 32. For patients with active cancer and VTE, the ASH guideline panel *suggests* long-term anticoagulation for secondary prophylaxis (>6 months) rather than short-term treatment alone (3-6 months) (conditional recommendation, low certainty in the evidence of effects ⊕⊕○○).

RECOMMENDATION 33. For patients with active cancer and VTE receiving long-term anticoagulation for secondary prophylaxis, the ASH guideline panel *suggests* continuing indefinite anticoagulation over stopping after completion of a definitive period of anticoagulation (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

ASCO recommends continued anticoagulation in those with higher-risk disease such as those with metastatic disease or receiving chemotherapy.



ASH guidelines recommend continued anticoagulation in patients with active cancer.



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Case 5:

- 75 year old male with metastatic lung cancer who presents with newly diagnosed left upper lobe and left lower lobe segmental pulmonary emboli incidentally found on monitoring CT.
- Last prior CT was 3 months ago and no emboli were present
- He is asymptomatic.

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Step 1: Define the clot

- CTA with PE, no evidence of right heart strain
- Troponin was not performed
- No echo
- Given no symptoms, incidentally found, and no CT evidence of right heart strain, this would be considered a **low-risk PE**.

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Step 2: Assess Risk Factors

- Patient is 72 years old with a BMI of 23. Non-smoker. No family history of DVT. Has been receiving chemotherapy. Has a port which has been present for 1 year without issues. No recent travel. Last hospitalization for pneumonia 6mo ago.
- Risk factors:
 - 1) Active malignancy (metastatic lung cancer)
 - 2) Receiving chemotherapy

Risk factors for bleeding: 1) Age

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Step 3: Treatment - Choice of Drug and Step 4: Duration of Therapy

- We have reviewed drug options - DOAC, LMWH... but...
- For incidentally found VTE, do you treat at all?^{3,5}



RECOMMENDATION 26. For patients with cancer and incidental (unsuspected) pulmonary embolism (PE), the ASH guideline panel *suggests* short-term anticoagulation treatment rather than observation (conditional recommendation, very low certainty in the evidence of effects ⊕○○○).

Recommendation 4.7. Incidental PE and deep vein thrombosis should be treated in the same manner as symptomatic VTE, given their similar clinical outcomes compared with patients with cancer with symptomatic events (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

ASCO

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Case 6:

- 55 year old female with uterine cancer presents with three days of worsening left upper arm swelling, pain, and tenderness. She has a PICC line in the left arm.

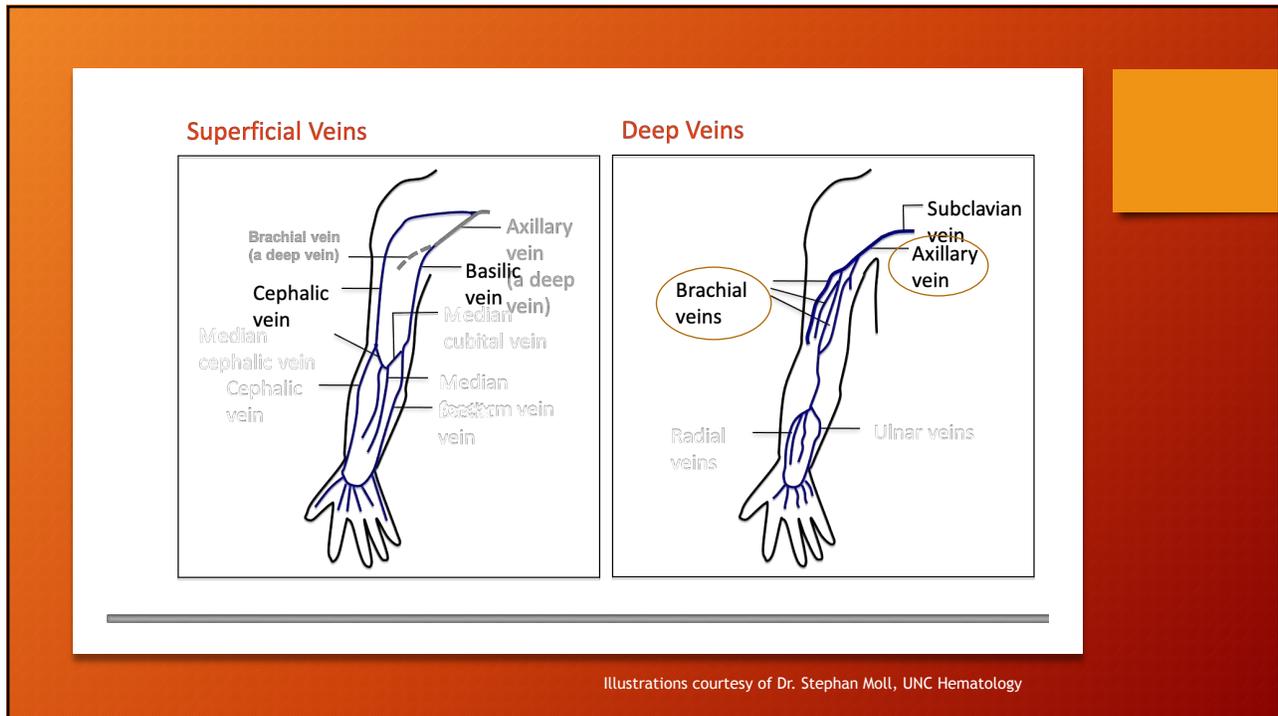
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Step 1: Define the clot

- Venous Dopplers are obtained and confirm thrombosis:
- *Acute obstruction in the left brachial vein, axillary vein. Other veins fully compressible.*

Is this a **deep** or **superficial vein thrombosis**?

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Step 2: Assess the risk factors

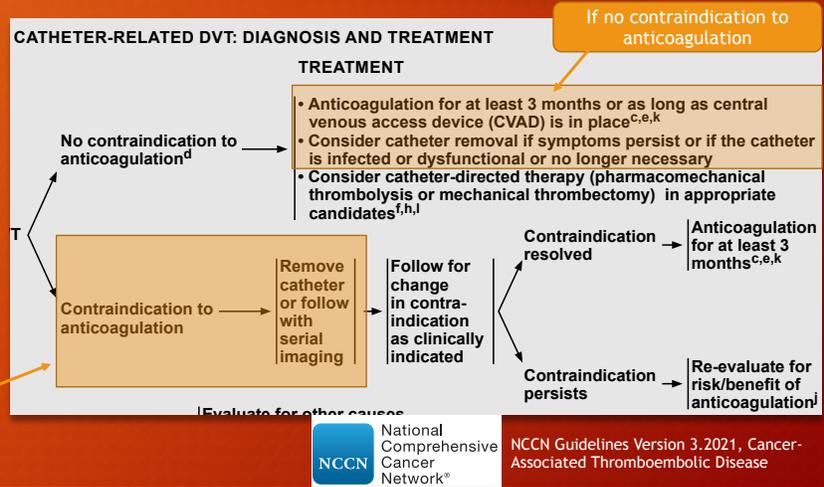
- This patient has been receiving chemotherapy for her uterine cancer. She had surgery 3 weeks ago as an outpatient. Her BMI is 32. She is not on any hormone therapy. She has not recently traveled. She has not recently traveled. She has no family history of VTE. She has not been on any recent hormone therapies.
- Risk Factors for VTE:
 - 1) Active malignancy (uterine cancer)
 - 2) Chemotherapy
 - 3) Recent surgery
 - 4) Obesity
 - 5) PICC line

Risk factors for bleeding: None.

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Step 3 & 4: Treatment and Duration²

- Choice of drug - as reviewed, DOAC or LMWH would be recommended.
- With this patient, what is the appropriate management of the PICC line?



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Take-home points:

Steps in managing newly diagnosed DVT include:

- 1) Define the clot
- 2) Assess risks
- 3) Determine treatment
- 4) Determine duration

Anticoagulation with DOAC or LMWH is preferred. Either is usually appropriate.^{2,3}

Renal function is a critical consideration in choice of anticoagulant.²

Cost is also an important factor. For DOACs, copay cards are widely available.

For most acute DVT/PE in patients with active malignancy, recommendation is indefinite anticoagulation until no active malignancy/not receiving chemotherapy.^{3,5}

Incidentally found DVT/PE should be treated in patients with active malignancy.^{3,5}

Anticoagulation must be managed closely in patients with chemotherapy-induced thrombocytopenia.²

Line-associated DVT can often be managed without removing CVAD.²

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UNC DVT Walk-In Program

- Rapid follow-up for patients with newly diagnosed DVT.
- Ensure anticoagulation is started, appropriate, affordable, and that patient receives education.
- Located at UNC Eastowne
 - 100 Eastowne Drive, Chapel Hill, NC
- Can place referral within the UNC system.
- Hope to expand to accept referrals outside UNC in 2022.



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Citations

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