

# Management of Venous Thromboembolism for Patients With Hematologic Malignancies

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# Learning Objectives

1. Describe the various factors associated with elevated VTE risk in cancer patients
2. Discuss indications and contraindications for cancer-associated VTE prophylaxis and therapy
3. Review available anticoagulation treatment modalities and devices
4. Monitor and assess patient response to anticoagulation treatment
5. Comment on the effective use of emergency antidotes and reversal agents

VTE = venous thromboembolism.

# Financial Disclosure

Dr. Schwartz has nothing to disclose.

# Definitions for Today's Discussion

- Venous thromboembolism (VTE)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- Management of VTE
  - Acute phase: first 5–10 days
  - Short term: 3–6 months
  - Long term: beyond 3–6 months
- Hemostasis: The complex process of maintaining the integrity of the circulatory system following damage to blood vessels
  - Hemostatic clots: localized to the vessel wall
  - Thrombotic clots: impairment of blood flow

# Overview of Hemostasis

## Activators

Von Willebrand Factor  
Collagen  
Tissue Factor

Vessel wall injury

Platelet adhesion and aggregation

Coagulation cascade activated

Thrombin

Fibrin formation

Stabilized fibrin clot

Fibrinolysis and clot degradation

Tissue Factor  
Factor VIIa  
Factor VIIIa  
Factor IXa  
Factor Va  
Factor Xa

Factor XIIIa

Tissue plasminogen activator

## Inhibitors

Antithrombin  
Heparin  
Thrombomodulin  
Protein C  
Protein S

Tissue factor pathway inhibitor

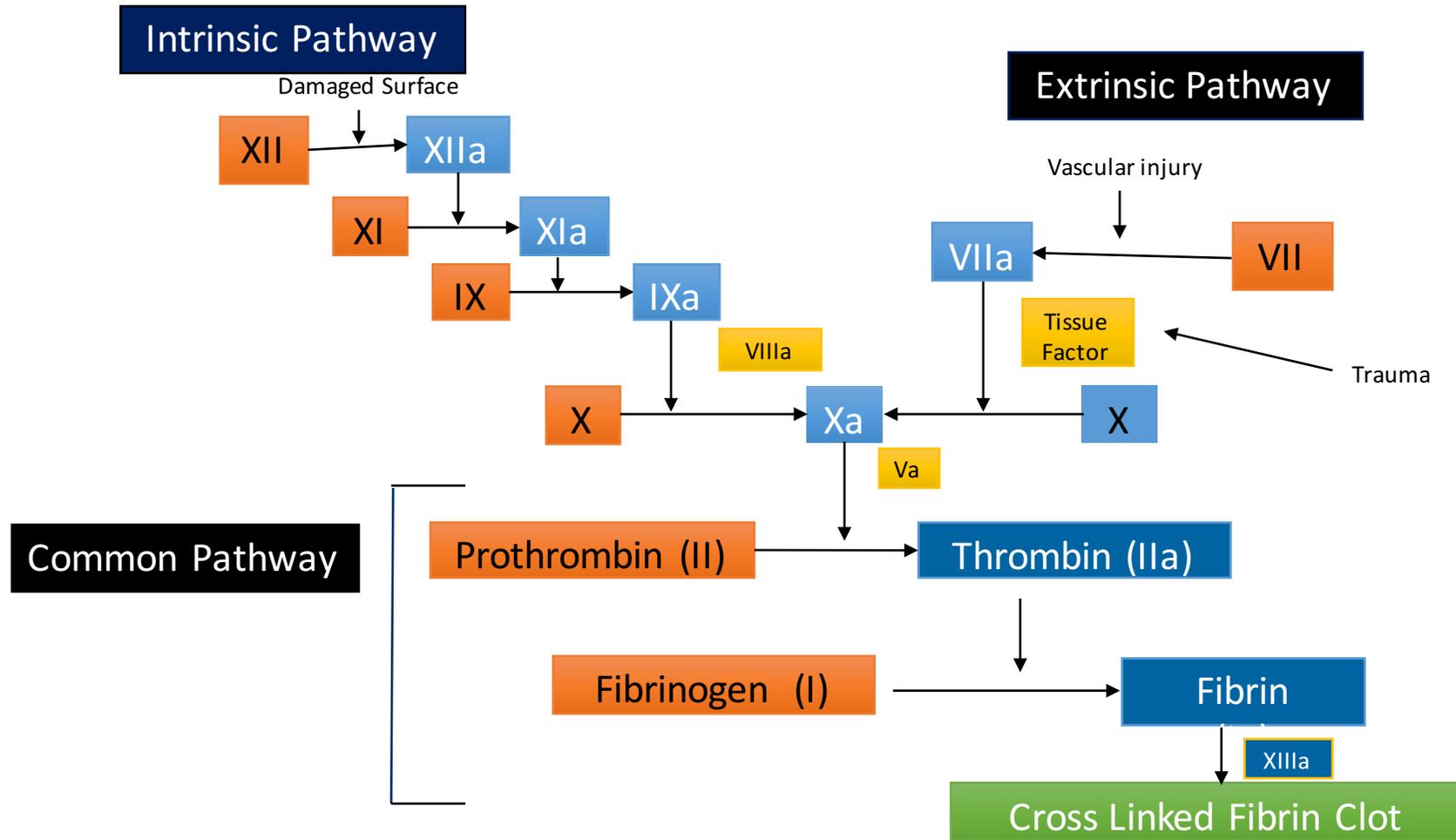
Plasminogen activator inhibitor-1

# Natural Anticoagulants

- Protein C → Destroys factor V and factor VIII
- Protein S → Cofactor to protein C, free and bound
- TFPI
- Prostacyclin (PGI<sub>2</sub>) → inhibits platelet aggregation
- Antithrombin III → neutralizes thrombin
  - Binds to natural heparin found on surface of normal endothelial cells
  - Inhibits Factor Xa, IXa, and TF bound with VIIa
- tPA → Converts plasminogen to plasmin, which acts on fibrinogen or fibrin to form FDP (or D dimers)

TFPI = tissue factor pathway inhibitor; tPA = tissue plasminogen activator.

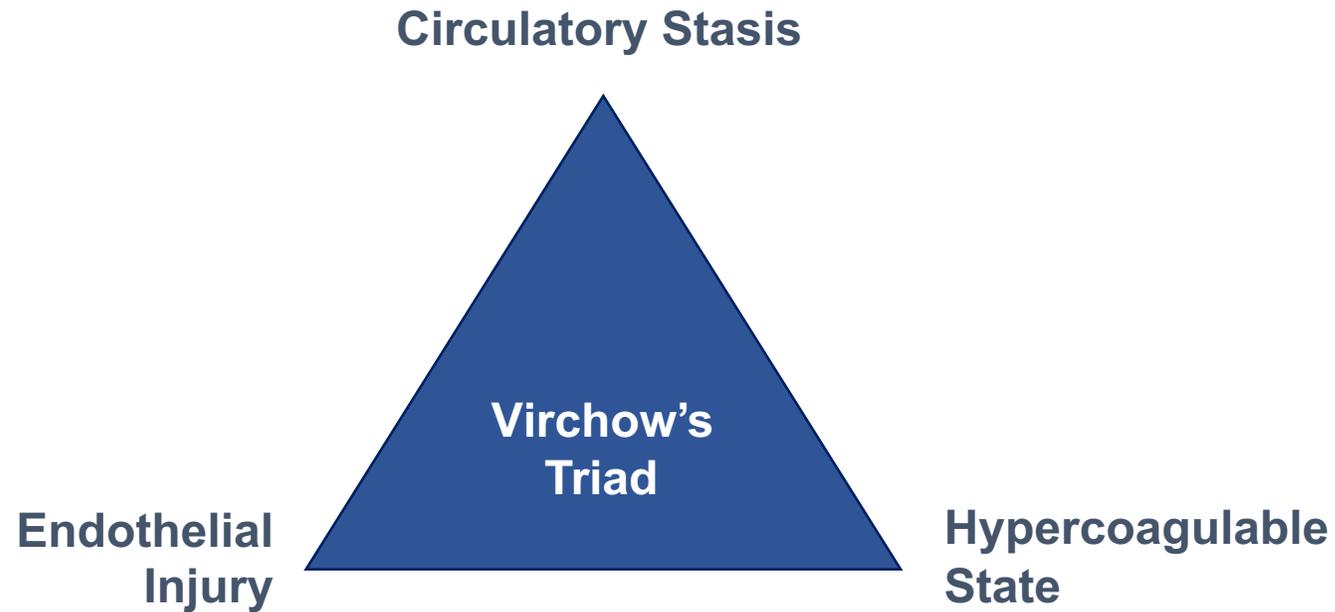
# Coagulation Cascade



# Nomenclature

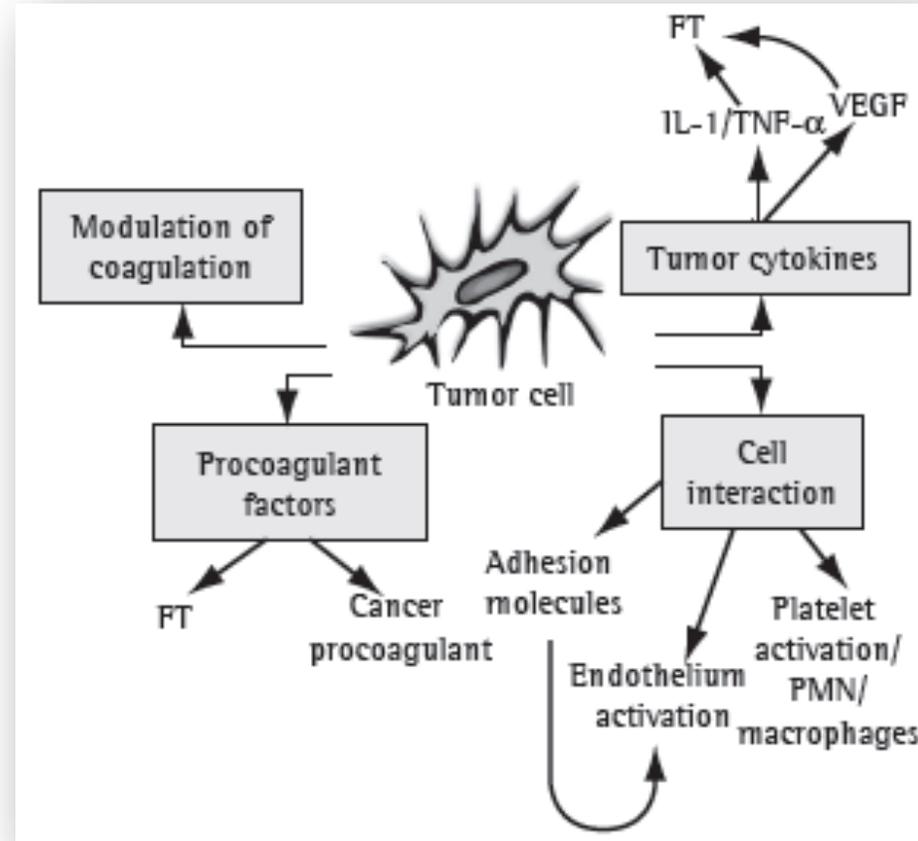
- Heparin
  - UFH: Unfractionated heparin
  - LMWH: Low molecular weight heparin
- Oral Anticoagulants
  - NOACs: Novel/new oral anticoagulants
  - DOACs: Direct oral anticoagulants
  - TSOACs: Target-specific oral anticoagulant

# Thrombosis in Cancer: Etiology



Lip GY et al. *Lancet Oncol* 2002;3:27-34.

# Active Cancer and Thrombosis



FT = tissue factor; IL = interleukin; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor

[http://www.scielo.br/img/revistas/jbpneu/v34n5/en\\_a11fig01.gif](http://www.scielo.br/img/revistas/jbpneu/v34n5/en_a11fig01.gif).

# Relative VTE Risk for Cancer

Origin	RR	95% CI
Head and neck	0.29	0.20–0.40
Breast	0.44	0.40–0.48
Prostate	0.98	0.93–1.04
Lung	1.13	1.07–1.19
Colon	1.36	1.29–1.44
Stomach	1.49	1.33–1.68
Lymphoma	1.80	1.65–1.96
Pancreas	2.05	1.87–2.24
Leukemia	2.18	2.01–2.37
Brain	2.37	2.04–2.74
Uterus	3.34	2.97–3.87

CI = confidence interval; RR = relative risk.

Rocha AT, et al. *Vasc Health Risk Manag* 2007;3:533-53.

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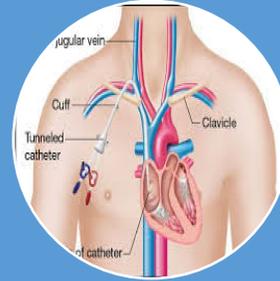
# Risk for VTE



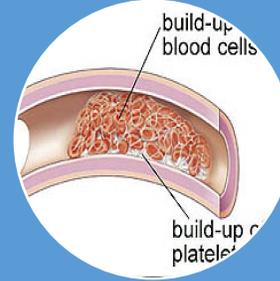
Age



History



Vascular  
Stasis



Hypercoagulable  
States



Medications



# Potential Risk Factors in the Individual with Cancer

## Patient-Related

- Age
- Obesity
- History of VTE
- Hypercoagulable conditions
- Comorbidities

## Cancer-Related

- Malignancy
- Extrinsic vascular compression due to cancer and/or lymphadenopathy
- Pathology of disease (e.g., adenocarcinoma)
- Extent of disease (e.g., metastatic cancer)

## Treatment-Related

- Surgery
- Chemotherapy
- Endocrine therapy
- Antiangiogenesis agents
- CVAD
- Medications for symptoms (e.g., ESA)

CVAD = central venous access devices; ESA = erythropoiesis-stimulating agent.  
Khorana AA, et al. *J Clin Oncol* 2006;24:484-90; Khorana AA, et al. *Cancer* 2013;119:648-55.

# Predictive Model for Chemotherapy-Associated VTE

Total Score	Risk Category	Risk of Symptomatic VTE
0	Low	0.8%–3%
1 or 2	Intermediate	1.8%–8.4%
≥3	High	7.1%–41%

Khorana AA, et al. *Blood* 2008;111:4902-7.

# Predictive Model for Chemotherapy-Associated VTE

Patient Characteristics	Risk Score
Site of primary cancer	
• Very high risk (stomach, pancreas)	2
• High risk (lung, lymphoma, gyn, bladder, testicular)	1
Pre-chemotherapy platelet $>350 \times 10^9/ L$	1
Hemoglobin $<10$ g/dL or ESA use	1
Pre-chemotherapy leukocyte count $>11 \times 10^9/ L$	1
BMI $\geq 35$ kg/m <sup>2</sup>	1

BMI = body mass index.

Khorana AA, et al. *Blood* 2008;111:4902-7.

# Clinical Issues and Thrombosis

## Prevention

- Identification of populations and patients at high risk
- Determine strategy(s) for prevention

## Diagnosis

- Recognition of signs and symptoms
- Evaluation of patient and treatment factors
- Diagnosis of thrombosis

## Management

- Acute management
- Chronic management
- Prevention

# DVT

- **Symptoms**

- Swelling, pain, warmth, or erythema of unilateral extremity
- Heaviness in extremity
- Unexplained persistent calf cramping
- Swelling in face, neck, or supraclavicular space
- Catheter dysfunction (if catheter is present)

- **Signs**

- Dilation of superficial veins and a palpable cord
- Homan's sign

- **Diagnostic studies**

- Duplex venous ultrasonography
- Contrast-enhanced CT (indirect CT venography)
- MRI
- Standard venography
- Serum D-dimer (note: elevated in malignancy)

CT = computed tomography; MRI = magnetic resonance imaging.

# Superficial Vein Thrombosis

- Diagnosis primarily on basis of clinical symptoms
  - Tenderness
  - Erythema
  - Indurated cord associated with superficial vein
- Negative ultrasound for DVT

# Clinical Presentation of PE

- **Symptoms**

- Cough
- Chest pain and/or tightness
- Back pain
- Shortness of breath
- Dyspnea on exertion
- Palpitations
- Hemoptysis
- Dizziness
- Syncope

- **Signs**

- Tachypnea
- Tachycardia
- Diaphoresis
- Distention of neck veins
- Cyanosis
- Hypotension
- Radiographic evidence of DVT

# PE

- CTA
- VQ lung scan
- Pulmonary angiography

CTA = computed tomography angiography; VQ = ventilation/perfusion.

# Assessment of Risk for VTE

- Assessment tools for VTE
  - Role of D-dimer testing
  - Role of probability assessment
    - Wells model
    - Geneva model
  - Clinical decision support tools
    - PERC

PERC = Pulmonary Embolism Rule Out Criteria

# Wells Criteria: Clinical DVT Model

Clinical Characteristic	Score
Active cancer	1
Paralysis, paresis, or recent plaster cast immobilization of lower extremity	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than the asymptomatic side	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

Score of 1 or 2 points indicates moderate risk of DVT; score of 3 or higher indicates a high risk of DVT.

Wells PS, et al. *N Engl J Med* 2003;349:1227-35.

# Wells Criteria: Clinical PE Model

Clinical Characteristic	Score
Active cancer	1
Surgery or bedridden for 3 days or more during the past 4 weeks	1.5
History of DVT or PE	1.5
Hemoptysis	1
Heart rate >100 beats/minute	1.5
PE judged to be the most likely diagnosis	3
Clinical signs and symptoms compatible with deep venous thrombosis	3

Score of 2–6 points indicates an intermediate probability of PE

Score > 6 indicates a high probability of PE

Streiff MB, et al. *J Thromb Thrombolysis* 2016;41:32-67.

# Assessment of Risk for VTE (in Cancer?)

- Assessment tools for VTE
  - Role of D-dimer testing
  - Role of probability assessment:
    - Wells model
    - Geneva model
  - Clinical decision support tools
    - PERC

“ ...in various clinically important subgroups, such as patients with cancer, the validity of the Wells rule is questioned...”  
Geersing GJ, et al. *BMJ* 2014;348:g1340.

# Predictive Model for Chemotherapy-Associated VTE

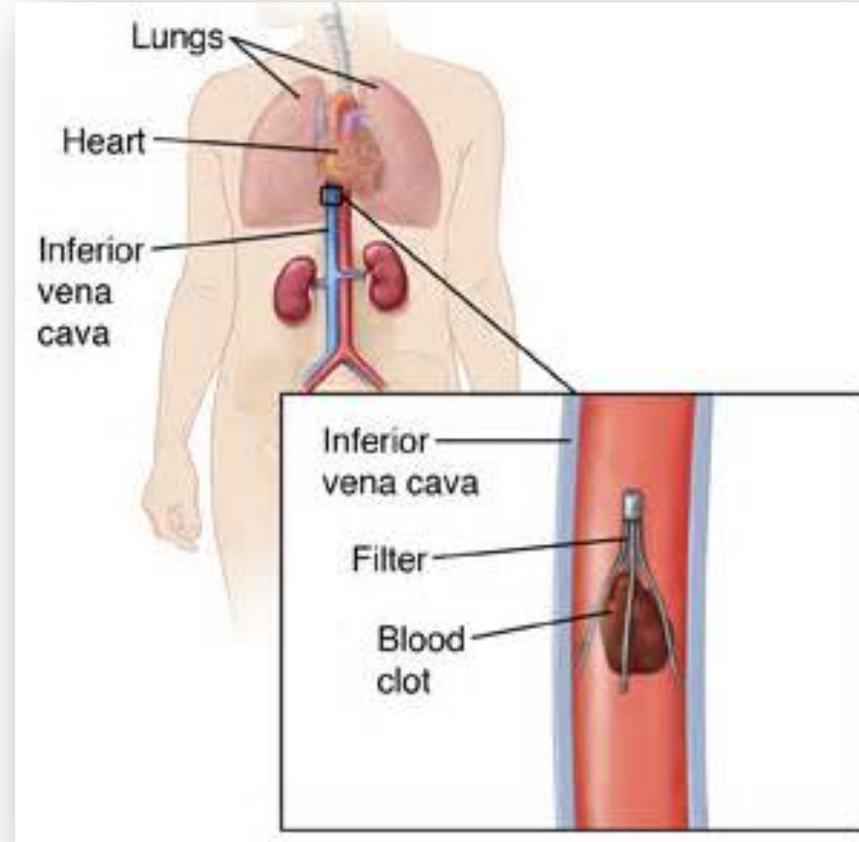
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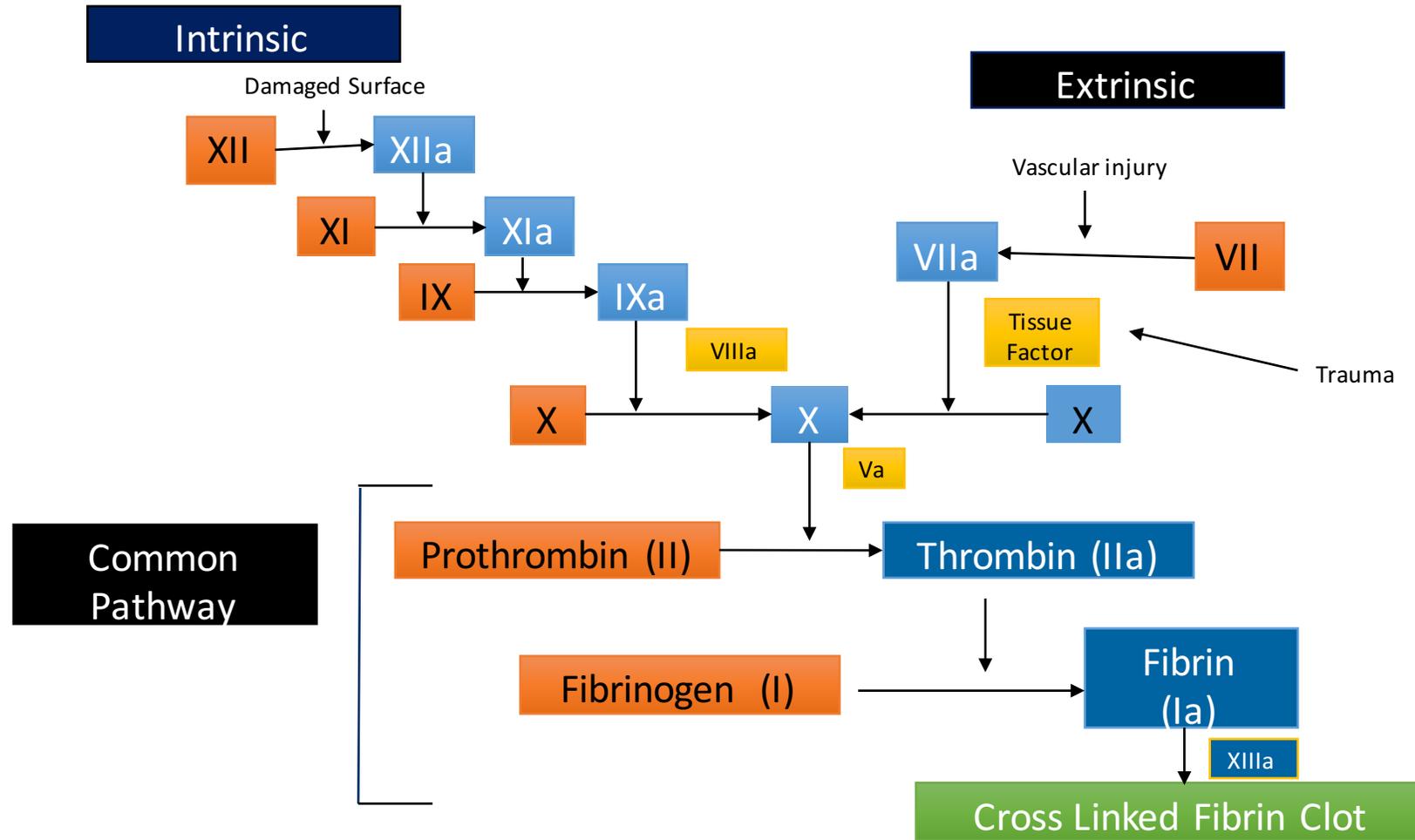
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# Management Options for Venous Thromboembolism

# Physical Barriers: Filter



# Target: Coagulation Cascade



# Target: Development of Factors

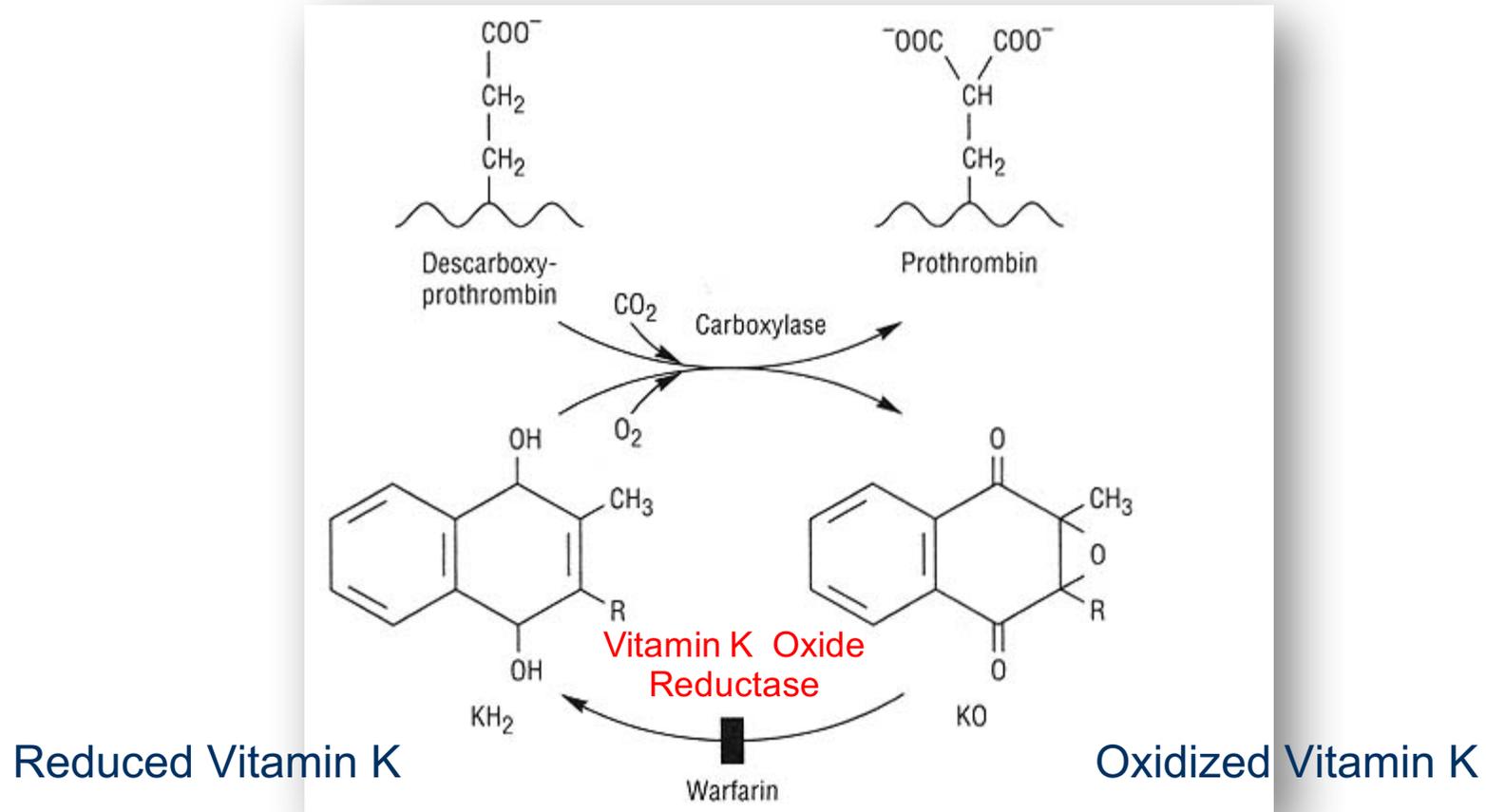


Image courtesy of Open Source Clinical Toxicology Curriculum. <http://curriculum.toxicology.wikispaces.net/2.2.7.5.1+Anticoagulant>

# Pharmacotherapy Options for Treatment of VTE

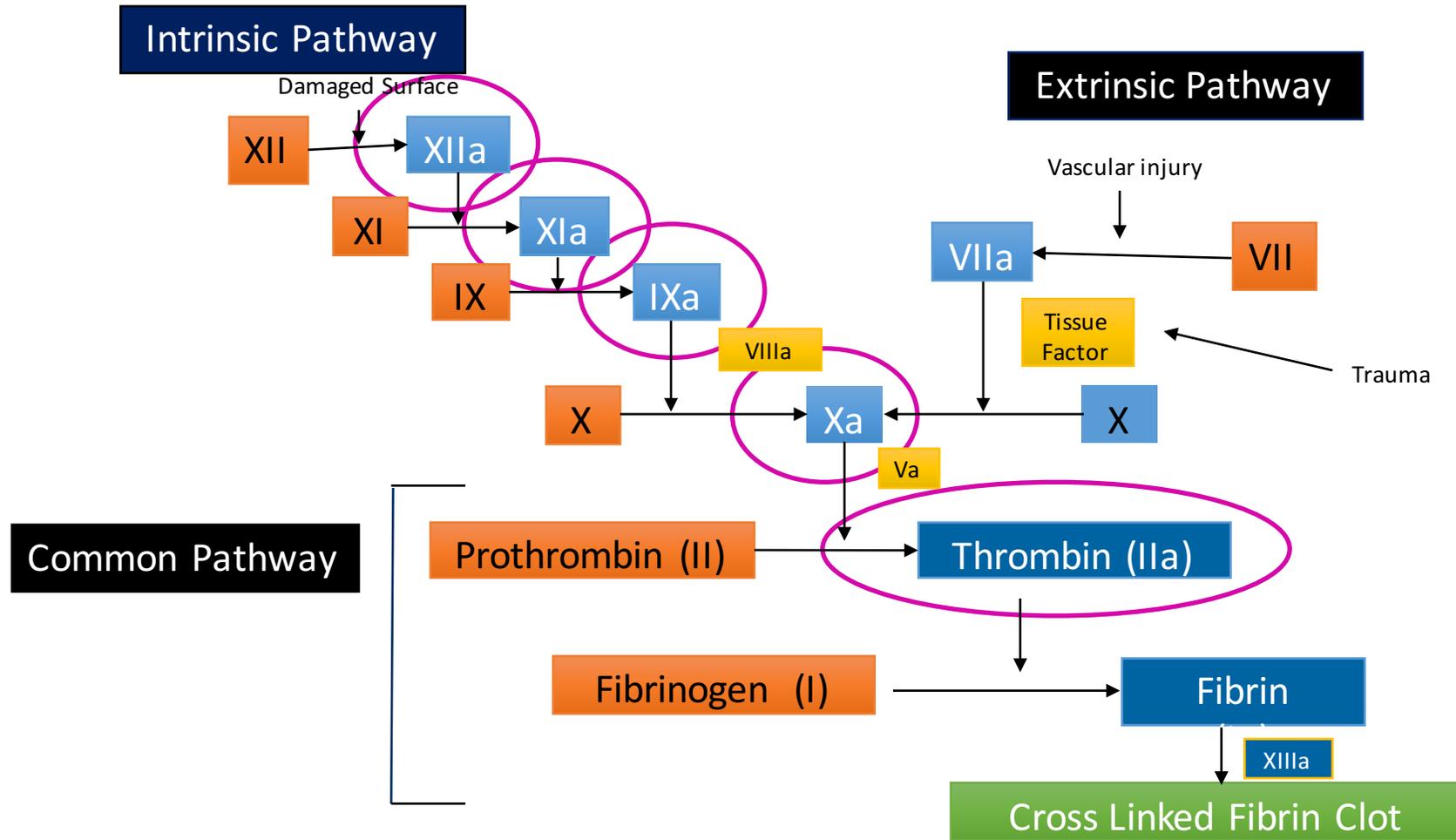
Heparin	Factor Xa Inhibitors	Vitamin K Antagonist	Direct Thrombin Inhibitors
UFH	Apixaban (po) Edoxaban (po)	Warfarin (po)	Dabigatran (po)
LMWH • Dalteparin • Enoxaparin	Fondaparinux (sc) Rivaroxaban (po)		Bivalent: • Hirudin (IV) • Bivalirudin (IV) • Desirudin • Lepirudin  Univalent: • Argatroban (IV)

IV = intravenously; po = orally; sc = subcutaneous.

# Heparin

- UFH
  - Highly sulfated mucopolysaccharide
  - UFH has a mean molecular weight 15,000 kDa (range from 3,000–30,000)
- LMWH
  - Derived from UFH by chemical or enzymatic depolymerization
    - About one-third of the size of UFH
    - Prepared using different methods of depolymerization and therefore differ (not interchangeable on a unit-to-unit basis)

# Coagulation Cascade



# UFH

- Administration
  - Subcutaneously
    - VTE prophylaxis (low dose)
    - VTE treatment (rare)
  - Intravenous infusion for VTE treatment (dose determined by aPTT)
- Dosing
  - Initial dosing for VTE is weight based
    - Heparin 80 units/kg bolus followed by 18 units/kg per hour
  - Dose adjustment to target aPTT
    - Target aPTT of 2–2.5x control

aPTT = activated partial thromboplastin times.

NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease version 1.2016.

# UFH (cont)

- Adverse effects
  - Bleeding
  - HIT
    - Type I: Not antibody mediated
    - Type II: Antibody mediated (0.1%–0.2%)
  - Osteoporosis (UFH 20K units for >6 months)
  - Skin reactions → necrosis (rare)

HIT = heparin-induced thrombocytopenia.  
Kearon C, et al. C. 2012;141:419s-494s.

# Heparin-Induced Thrombocytopenia

- Characterized
  - ↓ platelet count of > 50% from baseline prior to heparin
  - Hypercoaguability
  - Heparin-dependent platelet activating IgG antibodies
- Onset
  - Onset 5 – 10 days after start of heparin
  - Delayed onset HIT: after cessation of heparin
  - Autoimmune HIT: absence of heparin
- Assessment
  - Platelet count
  - Platelet factor 4-heparin antibody test
- Treatment
  - Discontinuation of all heparin
  - Initiation of alternative anticoagulation (avoid warfarin with acute HIT)

# Bleeding With UFH

- Discontinue heparin
  - Heparin serum half-life is  $\approx$  60–90 minutes
- Transfusion
- Supportive care
- Reversal of anticoagulant effect: Protamine sulfate
  - Dosing is determined by the timing and dose of heparin
  - Maximal tolerated dose of protamine is 50 mg
  - aPTT should be used to assess effects of neutralization
  - Adverse effects are common: hypotension, bradycardia

# Role of UFH in Management of VTE in Patients With Hematology Malignancy?

- High bleeding risk ← Short half-life
- Weight
  - BMI >40 kg/m<sup>2</sup>
  - <50 kg
- Renal dysfunction
  - Renal dysfunction (CrCl <30 mL/min)
  - Unstable renal function

CrCl = creatinine clearance.

# Heparin

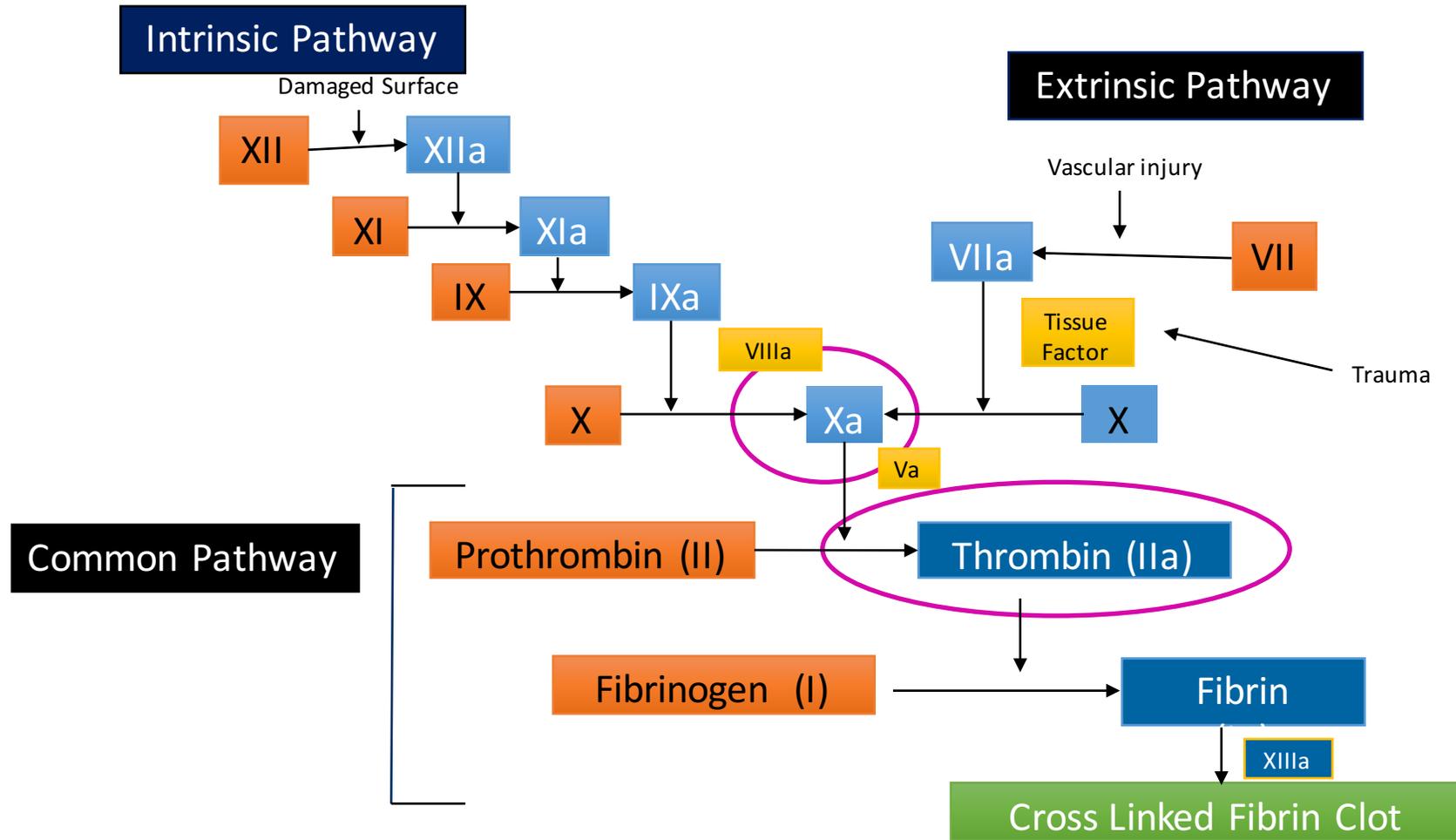
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  - About one-third of the size of UFH
  - Prepared using different methods of depolymerization and therefore differ (not interchangeable on a unit-to-unit basis)

# Coagulation Cascade



# LMWH

- MOA
  - Pentasaccharide sequence of heparin binds to antithrombin (AT) increasing interaction of antithrombin and Factor Xa
  - Less inhibitory activity against thrombin (Factor IIa) compared with UFH
- Pharmacokinetics
  - Peak anti-Factor Xa activity  $\approx$  3–4-hour post-sc dose
  - Half-life is 3–6 hours after sc dosing
  - >90% bioavailability after sc dosing
  - Clearance is not dependent on dose
  - **Elimination is predominantly renal**

CrCl = creatinine clearance.

NIH. US National Library of Medicine. DailyMed. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=bd794164-0cad-4ca3-9f62-ae9118f6e4a2>

# LMWH (cont)

Product	Thromboprophylaxis*	VTE Treatment*
Dalteparin	5000 units sc daily	200 units/kg sc daily
Enoxaparin	40 mg sc daily	1 mg/kg sc Q12H

\* Modifications may be required dependent on patient specific factors.

NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease version 1.2016.

# LMWH (cont)

- Monitoring
  - LMWH has minimal effect on aPTT
  - Factor Xa activity is used in **select** situations (e.g., pregnancy, obesity, renal dysfunction, children)
- Reversal of anticoagulation
  - Partially reversed with protamine (approximately 60%)
- Adverse effects
  - Bleeding
  - HIT
  - Osteoporosis
  - Injection site reactions

# LMWH: Interpretation of Anti-Xa Levels

## Target Ranges for Treatment VTE

LMWH	Frequency of Administration	Target Range (4 hr post dose) Anti-Xa units/mL
Enoxaparin	Twice-daily dosing	0.6–1.0
Enoxaparin	Once-daily dosing	>1.0
Dalteparin	Once-daily dosing	1.05

# LMWH: Clinical Considerations

- Role in patients with renal insufficiency ( $Cl_{cr} < 30$  mL/min)
  - Obese (BMI >30)
  - Weight <50 kg
  - Elderly >70 years
  - Neutralizing LMWH → incomplete anti-Xa neutralization of LMWH by protamine
- 
- Out-of-pocket cost for patients
  - Self-administration of sc injections
  - Tolerance to LMWH
  - Social support

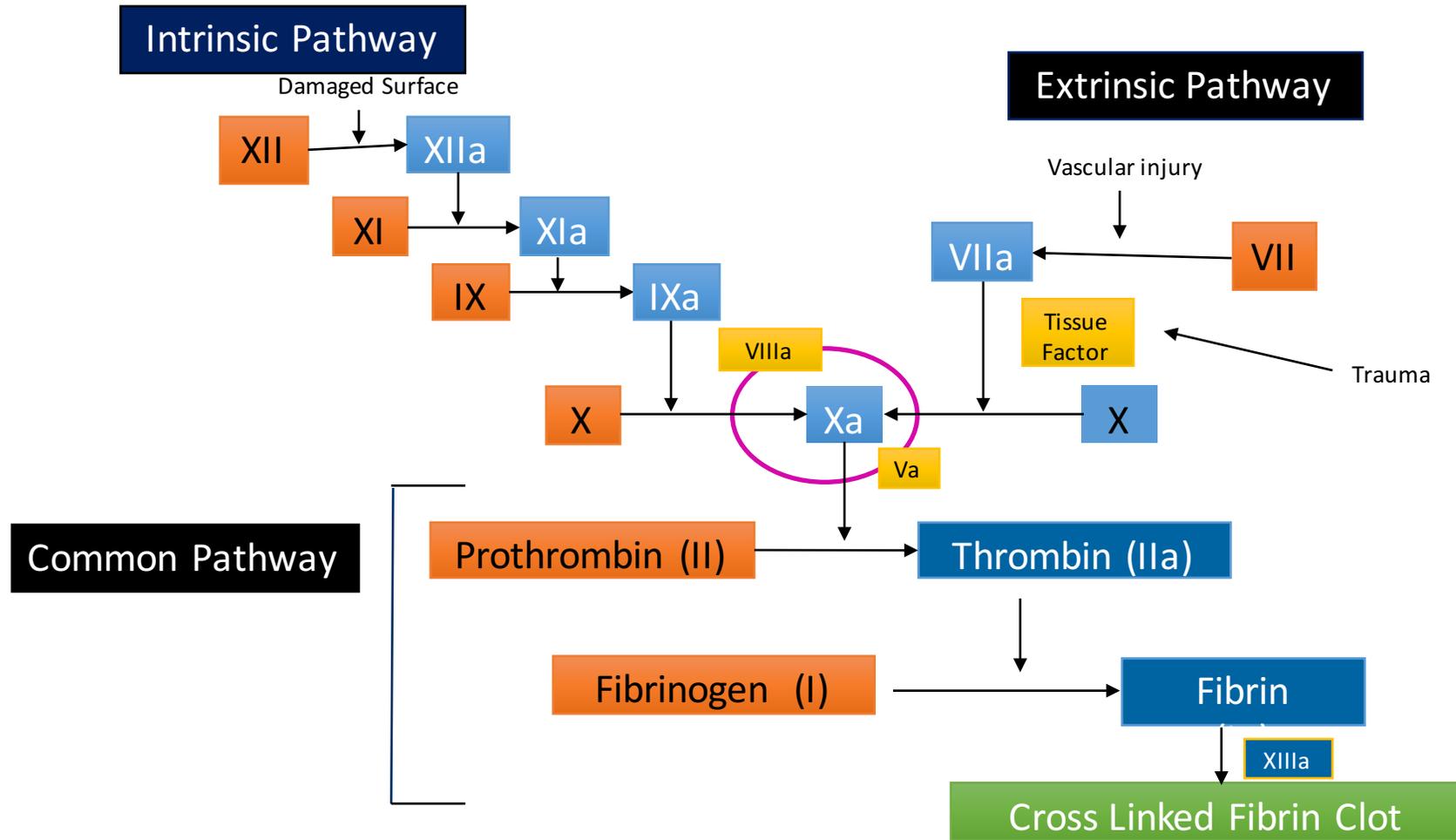
# Pharmacotherapy Options for Treatment of VTE

Heparin	Factor Xa Inhibitors	Vitamin K antagonist	Direct Thrombin Inhibitors
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# Target: Factor Xa



# Coagulation Cascade



# Factor Xa Inhibitors

Agent	VTE Treatment*
Fondaparinux	<50 kg: 5 mg sc daily 50–100 kg: 7.5 mg sc daily >100 kg: 10 mg sc daily
Rivaroxaban	15 mg po twice daily for 21 days, followed by 20 mg po once daily
Apixaban	10 mg po twice daily for 7 days, 5 mg po twice daily
Edoxaban	60 mg po daily

\* The doses listed are per package labeling, and do not reflect dose modifications required for select situations such as organ dysfunction, extreme body weights, or drug interactions.

# Fondaparinux

- Synthetic analog of the pentasaccharide sequence found within heparin chains
- Mechanism
  - Inhibitor of Factor Xa
  - No effect on thrombin
- Pharmacokinetics
  - 100% bioavailability (sc administration)
  - Peak levels occur 2–3-hour post-sc administration
  - Renal elimination
  - Half-life is  $\approx$  17-21 hours (normal renal function)

Nutescu EA, et al. *J Thromb Thrombolysis* 2016;42:296-311.

# Heparin and Heparin Derivatives

Feature	Heparin (UFH)	LMWH	Fondaparinux
Source	Biological	Biological	Synthetic
Molecular weight	15,000 Da	5,000 Da	1,500 Da
Target	XIIa, IXa, XIa, Xa, IIa	Xa > IIa	Xa
Bioavailability (sc)	30%	90%	100%
Half-life	1 hour	4 hours	17 hours
Monitoring test	aPTT, anti-Factor Xa	Anti-Factor Xa	Anti-Factor Xa
Renal excretion	No	YES	YES
Antidote	Protamine	Protamine	None
Incidence of HIT	<5%	<1%	Unreported

Nutescu EA, et al. *J Thromb Thrombolysis* 2016;42:296-311.

# Fondaparinux

- Approved for DVT, PE prophylaxis, and treatment
- May be used in patients with history of HIT
- Treatment dosing is weight-based, per package labeling:

Patient Weight	Dose Regimen
<50 kg	5 mg sc daily
50–100 kg	7.5 mg sc daily
>100 kg	10 mg sc daily

- Dose for postsurgical prophylaxis and also for bridge therapy is 2.5 mg sc once daily.

# Fondaparinux (cont)

- Disadvantages
  - Long half-life (advantage in some situations)
  - Role in patients with renal insufficiency (CrCl <30 mL/min)
  - No proven method for neutralizing LMWH
- Clinical considerations
  - Out-of-pocket costs
  - Willingness to self-administer sc injection
  - Intolerance to LMWH
  - Adherence
  - Support at home

# DOAC: Factor Xa

- Competitive, selective potent direct Factor Xa inhibitors
- Reversible binding to the active site of free-floating Factor Xa and Factor Xa within the clot
- Current products
  - Rivaroxaban
  - Apixaban
  - Edoxaban

# Oral Anticoagulants: Target Factor Xa

	Rivaroxaban	Apixaban	Edoxaban
Target	Xa	Xa	Xa
Prodrug	-	-	-
Bioavailability	80%	50%	62%
Peak effect	2-4 hours	1-3 hours	1-2 hours
Half-life	5-9 hours	9-14 hours	10-14 hours
Renal elimination	33%	25%	35%–50%
Protein binding	90%	87%	55%
Dialyzable	No	No	Possible
P'kinetic interactions	Cyp 3A4, P-gp	Cyp 3A4, P-gp	P-gp
Antidote	No	No	No
Laboratory	PT, Anti-Xa	Anti-Xa	Anti-Xa

Nutescu EA, et al. *J Thromb Thrombolysis* 2016;42:296-311.

# Factor Xa Inhibitors

## Advantages

- Specificity
- No requirement for routine blood monitoring for dose adjustment
- Lack of cross-reactivity with HIT antibody
- Drug interactions (< warfarin)
- “Long” half-life

## Disadvantages

- Dosing in renal insufficiency
- Dosing in obesity
- Reversal agent available
- “Long” half-life
- Patients with cancer were underrepresented in phase III trials

# Pharmacotherapy Options for Treatment of VTE

Heparin	Factor Xa Inhibitors	Vitamin K antagonist	Direct Thrombin Inhibitors
UFH	Apixaban (po) Edoxaban (po)	Warfarin (po)	Dabigatran (po)
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# Target: Thrombin



# Direct Thrombin Inhibitors

Agent	Dose	Dose Adjustment
Lepirudin <sup>1</sup>	0.1 mg/kg/hour IV infusion	Renal
Argatroban <sup>2</sup>	2 µg/kg/minute IV infusion	Hepatic
Bivalirudin <sup>3</sup>	0.15–0.2 mg/kg/hour IV infusion	Renal
Desirudin <sup>4</sup>	15 mg sc Q12H for prophylaxis	Renal
Dabigatran <sup>5</sup>	150 mg po twice daily	Renal

1. Bayer. Refludan (lepirudin) prescribing information. <http://medlibrary.org/lib/rx/meds/refludan/>

2. Novartis. Argatroban (argatroban) prescribing information. <http://labeling.pfizer.com/ShowLabeling.aspx?id=1212>

3. The Medicines Company. Angiomax (bivalirudin) prescribing information. [http://www.angiomax.com/downloads/ANG\\_USPI.pdf](http://www.angiomax.com/downloads/ANG_USPI.pdf)

4. Marathon Pharmaceuticals. Iprivask (desirudin) prescribing information. <http://medlibrary.org/lib/rx/meds/iprivask-2/>

5. Boehringer Ingelheim. Pradaxa (dabigatran) prescribing information. <http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf>

# Direct Thrombin Inhibitors (cont)

- Dabigatran etexilate (prodrug) → Dabigatran (active drug)
- Competitive inhibitor that reversibly binds to both clot and free thrombin
- Inhibition of thrombin-induced platelet aggregation

# DOAC: Direct Thrombin Inhibitor Dabigatran

	Dabigatran
Prodrug	Yes
Absorption	Requires acidic environment
Bioavailability	6.5% (pH dependent)
Time to peak effect	1.5–3 hours
Half-life	12–17 hours
Dosing frequency	Twice daily
Metabolism	Conjugated
Elimination	Renal (80%) Biliary (20%)

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# Oral Anticoagulants: Target Factor Xa

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa	Xa	Xa	Xa
Prodrug	Yes	-	-	-
Bioavailability	6.5% (pH dependent)	80%	50%	62%
Peak Effect	1.5–3 hours	2–4 hours	1–3 hours	1–2 hours
Half-life	12–17 hours	5–9 hours	9–14 hours	10–14 hours
Renal elimination	80%	33%	25%	35-50%
Protein binding	35%	90%	87%	55%
Dialyzable	Yes	No	No	Possible
P'kinetic interactions	P-gp	Cyp 3A4, P-gp	Cyp 3A4, P-gp	P-gp
Antidote	Idarucizumab	No	No	No
Laboratory	aPTT, TT, ECT	PT, Anti-Xa	Anti-Xa	Anti-Xa

Nutescu EA, et al. *J Thromb Thrombolysis* 2016;42:296-311.

# DOAC: Coagulation Assays

Anticoagulant	PT/INR	TT	ECT	aPTT	HEPTEST
Dabigatran	↑	↑	↑	↑	-
Rivaroxaban	↑	-	-	↑	↑
Apixaban	↑	-	-	↑	↑

ECT = ecarin clotting time; INR = international normalized ratio; PT = prothrombin time; TT = thrombin time.

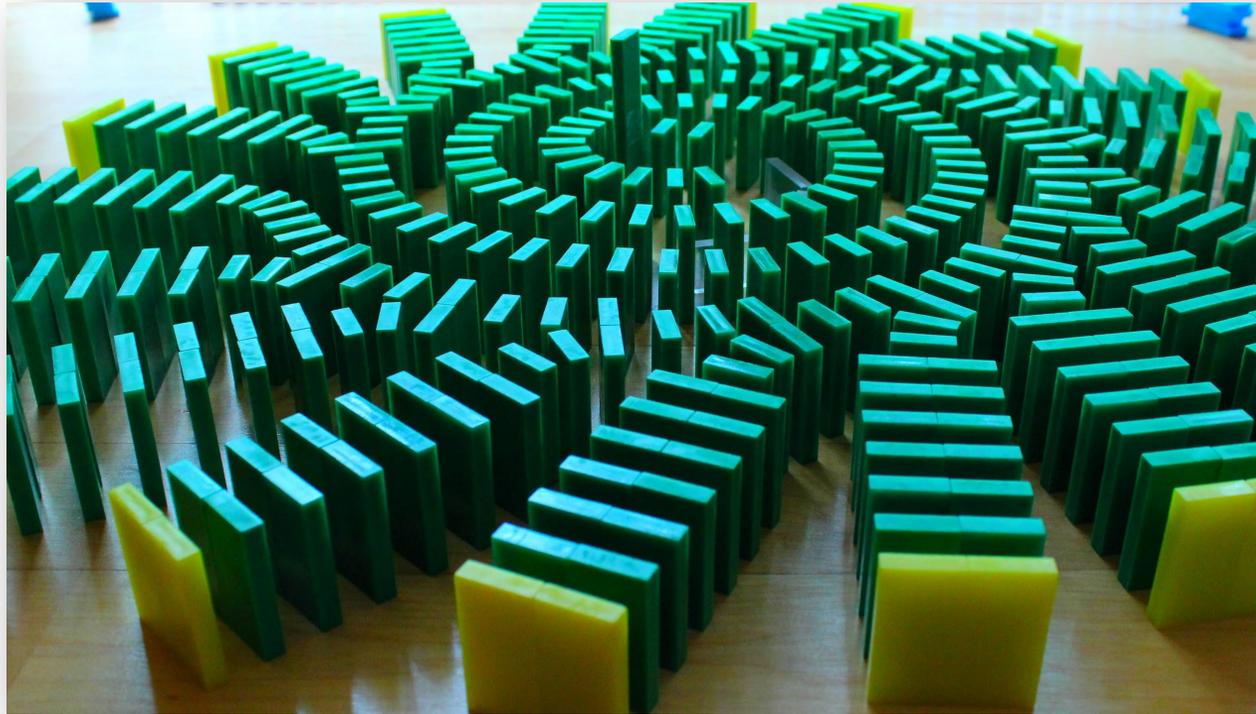
Miyares MA, et al. *Am J Health-Syst Pharm* 2012;69:1473-84.

# Old Oral Anticoagulant

# Target: Vitamin K



# Target: Vitamin K-Dependent Factors



# Vitamin K Antagonists

- Mechanism of action
  - Inhibition of vitamin K epoxide/reductase
  - Interferes with cyclic conversion of vitamin K and vitamin K epoxide
  - Impairs carboxylation of vitamin K–dependent clotting factors
  - Inhibits carboxylation of regulatory anticoagulation proteins C, S, and Z
- Examples of vitamin K antagonists (VKA)
  - Warfarin
  - Acenocoumarol

# Warfarin: Mechanism of Action

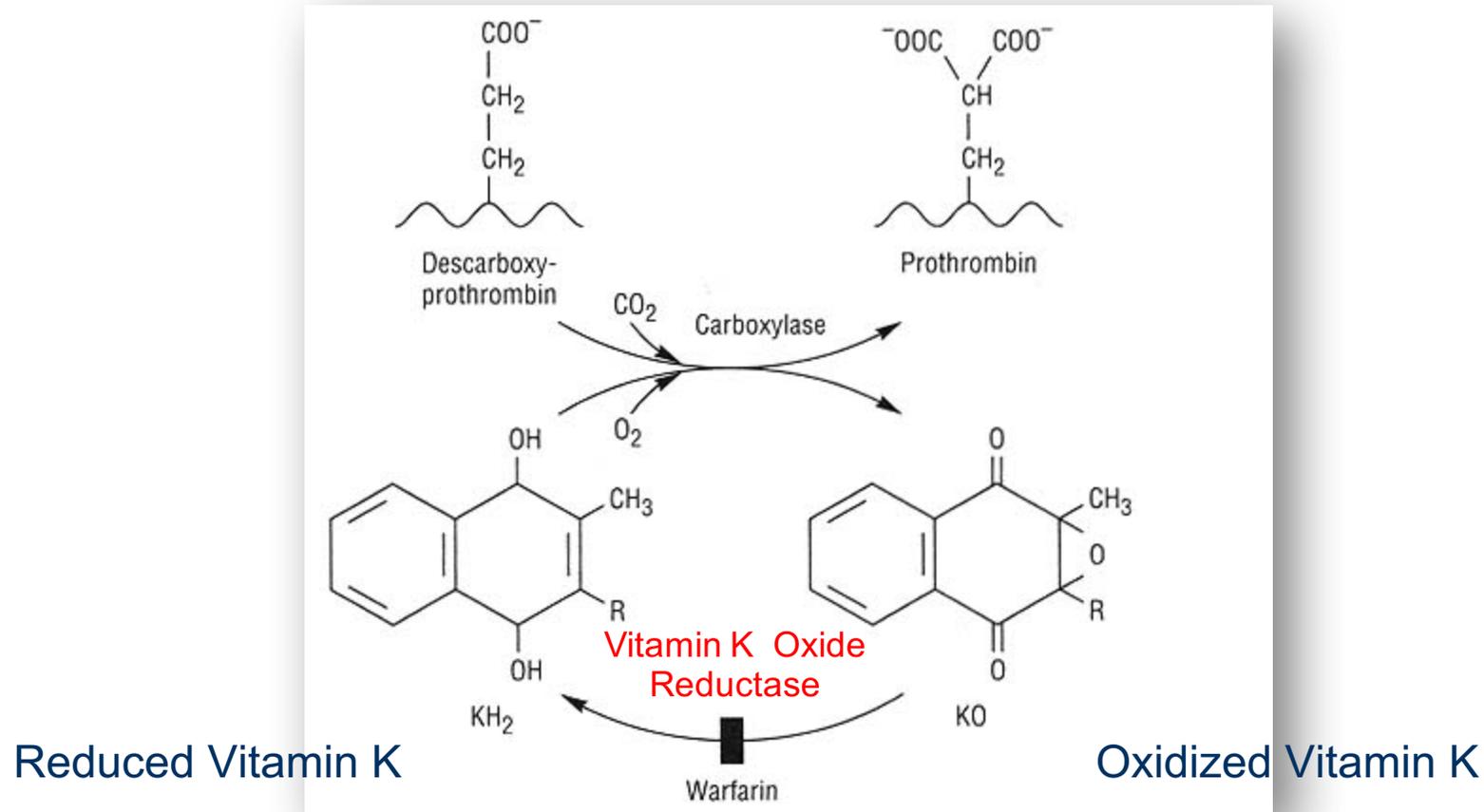


Image courtesy of Open Source Clinical Toxicology Curriculum. <http://curriculum.toxicology.wikispaces.net/2.2.7.5.1+Anticoagulant>

# Warfarin: Mechanism of Action

Protein	Half-life (hours)
<b>Coagulation factor</b>	
Factor II	42–72
Factor VII	4–6
Factor IX	21–30
Factor X	27–48
<b>Regulatory anticoagulant proteins</b>	
Protein C	8
Protein S	60
Protein Z	40–45

Nutescu EA, et al. *J Thromb Thrombolysis* 2016;42:296-311

# Overview of Hemostasis

## Activators

Von Willebrand Factor  
Collagen  
Tissue Factor

Vessel wall Injury

Platelet adhesion and aggregation

Coagulation cascade activated

Tissue Factor  
Factor VIIa  
Factor VIIIa  
Factor IXa  
Factor Va  
Factor Xa

Thrombin

Fibrin formation

Factor XIIIa

Stabilized fibrin clot

Tissue plasminogen activator

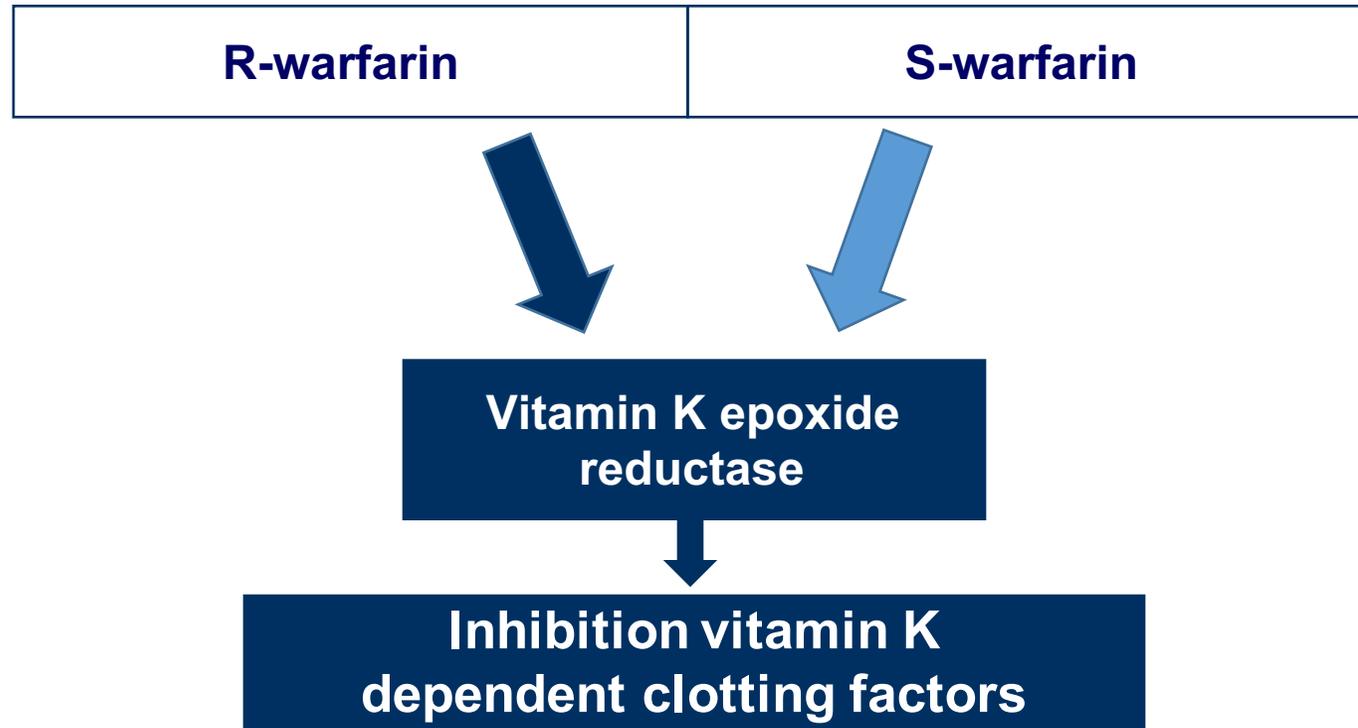
Fibrinolysis and clot degradation

## Inhibitors

Antithrombin  
Heparin  
Thrombomodulin  
Protein C  
Protein S  
Tissue factor pathway inhibitor

Plasminogen activator inhibitor-1

# Warfarin Is a Racemic Mixture



# Warfarin: Initiating Therapy

- Routine use of pharmacogenetic testing is not recommended
- Initially administered concomitantly with UFH, LMWH, or fondaparinux for at least 5 days and INR of 2 or more is achieved
- Vitamin K antagonists should not be initiated prior to heparin therapy
- Dose of initiation is determined by patient specific factors
- Frequency of monitoring INR during titration of dose is determined by patient-specific factors

# Warfarin: Initiating Therapy (cont)

- Baseline INR should be obtained prior to beginning warfarin
- Identify patients at risk for an increased baseline INR
  - Patients with lupus like anticoagulant
  - Malnourished
  - Chronic diarrhea
  - Liver disease

# Warfarin: Maintenance Dose

- Response to warfarin fluctuates over time
- Strategies required to determine changes in warfarin dose during treatment include:
  - INR monitoring
  - Changes in bleeding risk
  - Changes in factors that influence warfarin effect
- It is essential to establish a partnership in providing care
  - Health care team
  - Patient
  - Caregivers

# Warfarin: Factors That May Affect INR

- Diarrhea
- Nausea (decrease po intake)
- Vomiting
- Diet (nutritional supplements)
  - Cranberry
  - Grapefruit juice
- Alcohol
  - Chronic
  - Acute
- Thyroid function
- Liver function
- Medication change
- Diet changes
- Nonadherence
- Activity

# Warfarin: Drug Interactions

- Proposed mechanism
  - Impact on clotting factor synthesis
  - Impact on clotting factor catabolism
  - Impact on metabolism of warfarin
  - Absorption of warfarin and vitamin K
  - Production of vitamin K by gut flora
  - Additive anticoagulation effects

Wittkowsky AK. *Semin Vasc Med* 2003;3:221-30.

# Warfarin

- Pharmacodynamic effect
  - Caution when combining warfarin with drugs that may increase bleeding.
    - Aspirin → Decrease platelet function
    - Clopidogrel → Decrease platelet function
    - Nonsteroidal anti-inflammatory agents → Gastrointestinal irritation
    - Drugs that decrease platelet number (e.g., cytotoxic chemotherapy)

# Warfarin (cont)

- Pharmacodynamic effect
  - As warfarin targets vitamin K–dependent clotting factors, the amount of vitamin K in diet impacts effect
    - Diet plays a significant role in drug efficacy
    - Patients do NOT have to avoid vitamin K rich foods
      - Consistency is essential
      - Communication in changes are also important
    - Examples of food high in vitamin K
      - Leafy green vegetables
      - Liver
      - Green tea

# Warfarin: Monitoring of Therapy

- The INR target range is determined based on patient factors and indications
- A common target INR range used in patients being treated for VTE is 2.0–3.0
  - INR below 1.5 is not protective
  - INR 3.0–4.0 is not dangerous in most cases, but is higher than necessary
- Management strategy of patients with INR above target range are based on:
  - INR (absolute level and evolution)
  - Bleeding and/or risk for bleeding
  - Access to monitoring

Nutescu EA, et al. *J Thromb Thrombolysis* 2016;42:296-311.

# Management Consideration for Individuals With Hematologic Malignancies with VTE

# Contraindication to Anticoagulation Therapy

## Absolute

- Recent CNS bleed, or intracranial or spinal lesion at high risk for bleed
- Active bleeding (major): More than 2 units transfused in 24 hours

## Relative

- Chronic, clinically significant measurable bleeding >48 hours
- Thrombocytopenia (platelets <50 K/ $\mu$ L)
- Severe platelet dysfunction
- Recent major operation at high risk of bleeding
- Underlying hemorrhagic coagulopathy
- High risk for falls (head trauma)
- Neural anesthesia/lumbar puncture
- Interventional spine and pain procedures

CNS = central nervous system.

NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease version 1.2016.

# Minimizing the Risk of VTE: Prophylaxis

- At-risk populations to consider prophylaxis
  - Hospitalized patients
    - Adult medical and surgical patients
    - Diagnosis of cancer (clinical suspicion of cancer)
  - Ambulatory cancer patients
    - Surgical oncology patients: high-risk abdominal or pelvic cancer surgery patients
    - Myeloma receiving thalidomide, lenalidomide, or pomalidomide

# Therapy of VTE

- Evidence-based guidelines
  - VTE: Chest guidelines
  - VTE in cancer: NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease, version 1.2016
  - VTE in cancer: ASCO Clinical Practice Guideline. Lyman GE, et al. *J Clin Oncol* 2013;31. (Update 2015)
- Guidance documents
  - Streiff MB, et al. *J Thromb Thrombolysis* 2016;41:32-67
  - Becattinia C, et al. *J Am Coll Cardiol* 2016;67:1941-55.

NCCN = National Comprehensive Cancer Center.

# Pharmacologic Treatment of VTE in a Patient With Cancer

- Immediate treatment with one of the following for a minimum of 5–7 days
  - LMWH
  - UFH
  - Fondaparinux
- Chronic therapy is required
  - LMWH
  - Warfarin (requires initial treatment with parenteral anticoagulant)

# Therapeutic Anticoagulation for VTE in Cancer

- Acute management
  - LMWH
  - Fondaparinux
  - UFH
    - IV load, then continuous infusion with dose adjusted to target aPTT
    - SC

DOACs are not recommended at this time

# Therapeutic Anticoagulation for VTE

- Acute management
  - LMWH
  - Factor Xa inhibitors
    - Fondaparinux
    - Rivaroxaban
    - Apixaban
    - Edoxaban (+ parenteral anticoagulation)
  - UFH
  - Dabigatran (+ parenteral anticoagulation)

Becattini C, et al. *J Am Coll Cardiol* 2016;67:1941-55; Bertoletti L, et al. *Pharmacol Res* 2016.

# Therapeutic Anticoagulation for VTE in Cancer

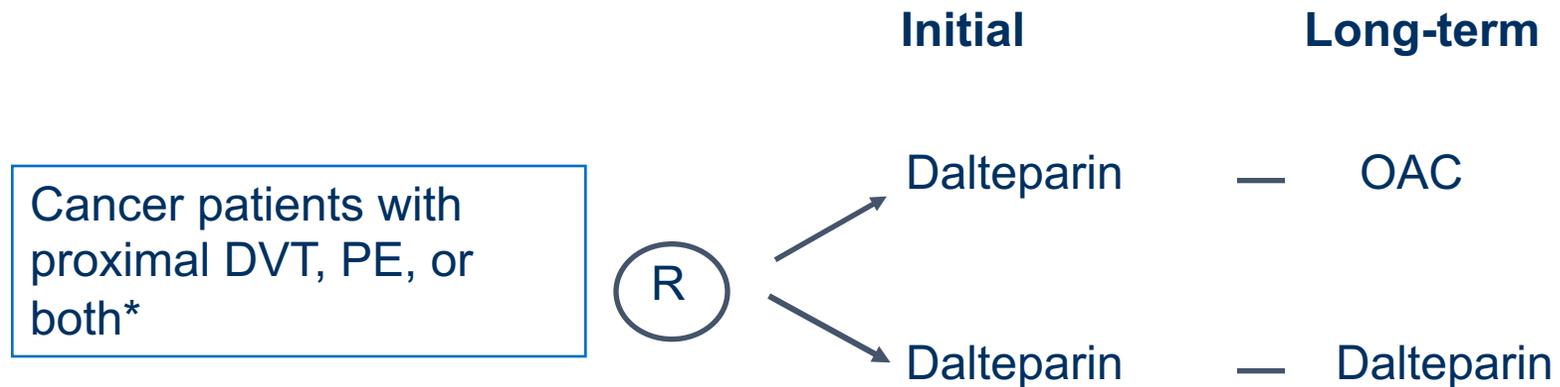
- Chronic management
  - LMWH as monotherapy
  - Warfarin (target INR 2-3)

**DOACs are not recommended at this time**

NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease version 1.2016. Lyman GH, et al. *J Clin Oncol* 2013;31:1-17.

# CLOT Trial

- Multicenter, open-label, randomized study (N = 676)



**\*Objectively documented**

OAC = oral anticoagulant.

Lee AY, et al. *N Engl J Med* 2003;349:146-53.

# CLOT: Study Treatments

	Initial treatment (5–7 days)	Long-term therapy (6 months)
OAC	Dalteparin 200 U/kg sc once daily	Warfarin or acenocoumarol (target INR 2.5)
LMWH	Dalteparin 200 U/kg sc once daily	Month 1: Dalteparin 200 U/kg Month 2–6: 75%–80% of full dose

Lee AY, et al. *N Engl J Med* 2003;349:146-53.

# CLOT: Primary Endpoint Recurrent VTE

	Dalteparin (n = 336)	OAC (n = 336)
<b>Total VTE</b>	<b>27</b>	<b>53</b>
DVT	14	37
Nonfatal PE	8	9
Fatal PE	5	7

Lee AY, et al. *N Engl J Med* 2003;349:146-53.

# Time in Target INR Range: OAC Group in CLOT Trial

INR	Mean Proportion of Total Treatment Time <sup>1</sup>	Mean Proportion of Total Treatment Time <sup>2</sup>
>3.0	24%	24%
<b>2.0–3.0</b>	<b>46%</b>	<b>50%</b>
<2.0	30%	25%
Mean INR (SD)	2.5 (0.74)	

SD = standard deviation.

<sup>1</sup>Lee AY, et al. *N Engl J Med* 2003;349:146-53; <sup>2</sup>Hutten BA, et al. *J Clin Oncol* 2000;18:3078-83.

# Bleeding Events in CLOT Trial

	Dalteparin (n = 338)	OAC (n = 335)	<i>P</i> value
Major bleed	19 (5.6%)	12 (3.6%)	.27
Any bleed	46 (13.6%)	62 (18.5%)	.09

Lee AY, et al. *N Engl J Med* 2003;349:146-53.

# CLOT Summary

- Efficacy
  - Dalteparin reduced recurrence of VTE by 52% compared with OAC ( $P = .002$ )
  - Dalteparin was effective in preventing recurrent DVT/PE over the 6-month study period
- Bleeding
  - Dalteparin was associated with a lower 6-month incidence of any bleeding compared with OAC
  - Major bleeding with dalteparin was similar to OAC

# Therapeutic Anticoagulation for VTE in Cancer

- Chronic management
  - LMWH as monotherapy
  - Warfarin (target INR 2–3)

DOACs are not recommended at this time

NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease version 1.2016.

# Therapeutic Anticoagulation for VTE in Cancer

- Duration of chronic management
  - Minimum of 3 months
  - Noncatheter-associated DVT or PE → Indefinite anticoagulation while cancer is active, under treatment, or if risk factors for recurrence persists
  - Catheter-associated thrombosis → Continue anticoagulation as long as catheter is in place
- Providers should continue to discuss with patients the risks/benefits of anticoagulation to determine the appropriate duration of therapy

# Therapeutic Anticoagulation for VTE

- Chronic management
  - LMWH as monotherapy
  - Warfarin (target INR 2–3)
  - DOAC

Becattini C, et al. *J Am Coll Cardiol* 2016;67:1941-55.

# Guidelines vs. Clinical Practice

- Retrospective analysis of MarketScan database for adult patients with **newly diagnosed cancer**
- Findings
  - Warfarin most utilized anticoagulant for outpatient treatment VTE
  - Initiation with LMWH → Oral anticoagulant
  - Increased use of DOACs

# When to Consider No Active Treatment

- Patient refusal
- No therapeutic advantage
- No palliative benefit
- Unreasonable burden of anticoagulation treatment

# When to Consider Filter\* Placement

- Absolute contraindication to therapeutic anticoagulation
- Failure of anticoagulation
- Patient nonadherent with prescribed anticoagulation
- Baseline cardiac or pulmonary dysfunction severe enough to make any new or recurrent PE life threatening
- Patient with documented multiple PE and chronic pulmonary hypertension

\*Retrievable filters are strongly preferred.

# Complications of IVC Filters

- Access site thrombosis
- DVT
- Filter migration/embolization
- Filter misplacement (outside target zone)
- Filter strut fracture
- Guidewire entrapment
- IVC thrombosis
- IVC penetration
- PE
- Inability to remove retrievable filter

IVC = inferior vena cava.

Streiff MB, et al. *J Thromb Thrombolysis* 2016;41:32-67.

# What Is the Role of Thrombolytic Agents for VTE?

- Thrombolytic agents may reduce PTS by promoting clot lysis and reduce venous outflow obstruction and venous valvular damage
- Higher rates of complete clot lysis compared with conventional anticoagulation for catheter-directed thrombolysis
- Patients that may benefit from thrombolytic therapy if eligible:
  - Iliofemoral DVT
  - Symptom duration of <14 days
  - Good functional status
  - Life expectancy of  $\geq 1$  year
  - Low bleeding risk

PTS = post-thrombotic syndrome.  
Kearon C, et al. *Chest* 2012;141:e419S-94S.

# Contraindications to Thrombolysis

## Absolute

- History of hemorrhagic stroke
- Intracranial tumor
- Ischemic stroke (3 months)
- History of major trauma, surgery, or head injury (3 week)
- Low platelet (<100K)
- Active bleeding
- Bleeding diathesis

## Relative

- Age >75 years
- Pregnancy
- First week postpartum
- Noncompressible puncture site
- Traumatic resuscitation
- Refractory hypertension
- Advanced liver disease
- Infective endocarditis
- Recent gastrointestinal bleed (3 months)
- Life expectancy  $\leq 1$  year

# Options for an Individual Who Has an Extension of VTE During Therapy?

- Anticoagulation “failure” is defined as an extension of DVT or a new VTE while on therapeutic anticoagulation therapy
- Treatment decision(s) depend on:
  - Site of extension (e.g., new PE on anticoagulation)
  - Potential for HIT
  - Assessment of anticoagulation therapy
    - Patient adherence
    - Agent
    - Dose
    - Regimen

# Options for an Individual Who Has a Recurrence of VTE Despite Anticoagulation Therapy?

- Anticoagulation “failure” is defined as an extension of DVT or a new VTE while on therapeutic anticoagulation therapy
- Patients with potent situational risk factor for thrombosis are at low risk for recurrence, while patients suffering unprovoked events are high risk for recurrence.

# Options for an Individual Who Has a Recurrence of VTE Despite Anticoagulation Therapy?

Ottawa Prediction Rule for Recurrent VTE in Cancer

Risk Factor	Points
Female	+1
Lung cancer	+1
Prior VTE	+1
Breast cancer	-1
Low stage (TNM stage I)	-2

Low risk < 0 points; Intermediate risk = 0 points; High risk  $\geq$  1 point

# Options for an Individual Who Has a Recurrence of VTE Despite Anticoagulation Therapy?

## Strategies for optimizing care

- Assess adherence to therapy
- Identify clinical additions associated with anticoagulation failure:
  - Cancer
  - Antiphospholipid syndrome
  - HIT
  - Vascular compression syndromes
- Consider
  - Warfarin → Increase goal of INR
  - LMWH → Assess Factor Xa and/or escalated dose
  - Alternative agents

# What Is the Best Strategy for Reversing Anticoagulation?

- Reversal recommendations for specific agents are provided in the NCCN Guidelines to facilitate care in the event of a life-threatening bleed or emergent surgery
- Familiarize yourself with availability of these products and the mechanism to order for patient care

# Reversal of Anticoagulation

Anticoagulant	Antidote
Heparin	Protamine
LMWH	Protamine
Warfarin	Phytonadione (Vitamin K1)
Dabigatran	Idarucizumab

NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease version 1.2016.  
Huisman MV, et al. *Amer J Med* 2016;129:S89-S96.

# How Do You Manage a Patient Who Has a Planned Procedure?

- Consider the risk of bleeding for the procedure
- Consider the risk of thrombosis in the individual patient
- Recommendation for management outlined in the NCCN Guidelines
- Procedures may include:
  - Surgery
  - Bone marrow biopsy
  - Dental procedures
  - Lumbar puncture

# Discussion

## **VENOUS THROMBOEMBOLISM**

SANDRA E. KURTIN, RN, MS AOCN, ANP-C      This is entitled the Management of Venous Thromboembolism for Patients with Hematological Malignancies. Please join me in welcoming our speaker, Dr. Rowena Schwartz, who is an associate professor of Pharmacy at the University of Cincinnati.

DR. SCHWARTZ    Coagulation and cancer is a fascinating topic. It's a broad topic. When we talk about different issues in oncology, we usually talk about treatment of disease or treatment of a complication of a disease. And lately, in the last couple years, we talk about comorbidities in patients. When we talk about VTE in cancer patients, we're hitting all three; we're talking about being caused by the cancer, being caused by the treatment, and the fact that many people come in with the risk of VTE and having VTE. It's a broad topic.

This is a major topic. One of the things that we're going to do is go over some of the basics, and I want to take that opportunity to talk about nuances that are important in oncology and in cancer.

The key thing when we talk about these issues is I want you to think about what you see in your patients because one of the things that is very clear is that how we manage patients with thrombosis is evolving. We are learning much more about the etiology and how we can treat. I want you to think of those things so at the end, instead of asking me questions, I would open it up so we can have some discussion.

Here's our learning objectives for the day, and that is, we're going to really talk about the risk factors for VTE in this population, talk a little bit about prophylaxis, going to focus on treatment. We're going to talk about the options that are available and how those options for VTE fit in the treatment of VTE related to malignancy. One of the key things that you're going notice is what we're going to talk about is not necessarily what you see in your practice. I think that's important to understand how we monitor response and then talk about some of the anecdotes. The key thing here is that what I say is probably not going to hit the depth of what you want to know in practice, so I did a lot of references that are reviews -- so use those reviews. If you have a topic you want to know, go and get that paper because that's probably the best information.

The other thing I did is I learned a lot on the guidelines that are available, so instead of taking things from what I think is my idea of what practice should be, I went to what experts' ideas of what practice should be. So those are available as well.

I have nothing to disclose at this time. If you look at what we're going to talk about, as I mentioned we're going to focus on VTE, mainly deep vein thrombosis and PE. The key thing is that does not even begin to scratch all the types of VTE that you can see in patients with malignancy. The NCCN guidelines on VTE do a nice job of looking at subsets of types of thrombosis and the things that you need to consider for those different subsets.

The other thing that you'll see more in the literature now is a talk about the timing, and that's really changing. We often talk about acute management of VTE

as being that first 5 to 7 days, that historically we used a parenteral anticoagulant. That's a little changing now with some of the treatment options for VTE. Maybe not in malignancy, but for the sake of this discussion, acute management will be that time.

And then if you look at short term, some people call it chronic, but short term is 3 to 6 months. And the issue that becomes a challenge in patients with malignancy is the long-term treatment, and that's beyond the 6 months. When I used to work in an anticoagulation clinic in an oncology center, one of our biggest things was people wanted to do that 3 to 6 months and didn't think of the long-term risk of our patients. More and more of our patients have chronic cancer, so when they have VTE, their risk for VTE is a chronic disease just like their cancer is. And that really has changed how we used to look at treatment of VTE and, say, someone who had lung cancer that did not have the longevity that we see now.

Let's just go right into hemostasis, which I think you guys are pretty well aware of. This is a simplistic picture I put together many years ago and it goes over some of the processes that we see. I use it for a couple of key reasons; one is, this is a good way to talk about the natural inhibitors of clotting. One of the things that we're going to talk about when we mention warfarin is, we're going to talk about its effect on some of these natural anticoagulants, protein C and protein S. If you go through this process, it's what you remember with the cell cycle, clotting cascade, and every other diagram in school that you didn't want to

learn because all you wanted to know is how you treat this; that's what this diagram is.

You can see if we go up here, we have vessel wall injury. When the vessel wall is injured you get initial vasoconstriction, then you get aggregation of platelets because of this release of the natural activators with Von Willebrand factor. With that, the platelets then granulate and ADP, thromboxane A2 is released, and this causes the formation of this clot. You get adhesion, and then from this clot you get the cascade of the coagulation cascade. And we'll talk a little bit more about that, both the intrinsic and the extrinsic.

From that you get thrombin formation, which then causes fibrin formation, and then you get stabilization of the clot. And this should be a review for most of you. These are some of the natural anticoagulants, and I show this as a slide to remind you of these proteins, C and S, and then talk about antithrombin III to remember that these are natural anticoagulants because the drugs we use impact these anticoagulants.

This is the diagram that I think everyone enjoys looking at. The only one I like better is the cell cycle, and if you gave me the cell cycle, I would be quite excited. If you look at this -- and I think you're all very familiar with it -- a couple key things here. You can see that this tissue factor, which is actually factor III, when it's released with an injury to that vessel that starts the extrinsic pathway. The extrinsic pathway is also called tissue factor pathway. It's a really rapidly acting response, and it forms a relatively small clot.

With damage to the surface, you get the extrinsic. Intrinsic pathway develops that bigger, more solid clot, and then you go to the common pathway where you get prothrombin made to thrombin, fibrinogen to fibrin, and then you get the formation of the clot. This is one of the main targets of our therapies, and so this cascade we'll see again and again and again.

If you look at some of the nomenclature that you'll have within your slides, I just wanted to mention UFH stands for unfractionated heparin, low-molecular weight heparin you all know. But I wanted to talk about the naming that is out there now and some of the controversy about the new oral anticoagulants. So when I say "new oral anticoagulants," it depends on when you started practice. For me, they're brand new oral anticoagulants. For some of you, you're like, "They were out for 10 years before I was born." This is really one of the reasons why people don't like to call them NOACs because they're not new or novel anymore because they have been developed and are being used.

Another terminology that you may see is this direct because these are the agents that work directly on these factors versus some of our older agents like heparin and warfarin. They have an indirect effect on coagulation, where these new agents are more targeted. That's target; you're going to see targets here too. It's truly an oncology talk because we're talking targets.

And then the other thing is that there was big controversy, and I just gave you the reference where they talk about what the naming should be. I'm not going to refer to them as direct or new; what I'm going to refer to them as is by their mechanism of action because I think that's important for understanding. I

learned that lesson when I did antiemetics. It's important to know how drugs are grouped together, so if you try one and you want to try a different one, you want to know the different mechanism of action.

This is the other obligatory slide that you have to have in a talk about thrombosis and that's Virchow's triad. Virchow is a Prussian physician who is attributed to having determined this triad; that's actually not true. What he did determine is the factors that are important to take a thrombosis to an embolism. He was very enthralled by why that occurred and he identified those factors. He's the father of cellular pathology and he's attributed with this triad, but what he did is identify -- just like we need to identify -- those factors in patients that play a role in identifying problems.

That's going to be one of my key things I'm going to say to you today. There is not enough understanding of specific cancers, specific treatments, and specific populations to know how we should modify our treatment today. So one of the things that you can do in practice is when you see something, identify it and look at it and evaluate it because that's the only way that we learn further. I give that to you as a challenge.

If you look at the three factors I think you're all very well aware of: stasis, hypercoagulable, and endothelial injury. This is a slide that talks about why cancer has an increased risk of coagulopathy, and the key thing here is that this slide makes it sound like cancer, increased risk. And the reality of it is pancreatic cancer is not glioma, is not lung cancer, is not breast cancer. When you look at increased risk, the path of physiology of the increased risk of clots in patients

with cancer is determined somewhat by the cancer itself. So it's really important that we simplify things a lot, but probably too much. This is a great thing to say that there are cytokines that are important and there are procoagulants, but the reality is, we really need to learn more about those cancers and what causes it and specific types of cancer. In fact, it's not even just cancer, it's also in the histology of those cancers.

This is taken from a study that was published in 2007, and it was a retrospective analysis of outpatient medical patients to see what their risk of clots were and it was in inpatients, hospitalized patients. You can see, first of all, a couple key things; it's from the early 2000s, which I think was just yesterday, but others of you may not, so it was just a few years ago in my mind. But the key thing is this does not separate the risk based on the cancer, based on the patient population, based on what treatment they were receiving.

This is not to give you the absolute risk, this is to give you an idea of what patient populations are at high risk. If you look at this, I bet most of you would pick out the ones that you see that you think of were a high risk. Working in an anticoagulation center, I saw pancreatic cancer, I saw colon cancer, and I saw something no one ever told me I would see, and I saw glioma. Those are patients I saw that were at very high risk. And you can see if you pick those out.

For this, we're going to focus a little bit on hematologic. One of the ways that we will do it is if you look here you can look at lymphoma. The key thing with lymphoma is, lymphoma is not lymphoma is not lymphoma. This increased risk is with high-grade lymphoma, which is a very small population of what we see. And

the increased leukemia risk is actually with APML; again, a very small population of what we see. These numbers give you a nice idea, but when you watch and practice, you'll identify those patients that are at risk.

Disease separated from treatment is a little difficult, and if you look back over time, how we treat lymphoma today is not how we treated lymphoma 10 years ago, so you can see that that is changing. And that's one of the things I would encourage you, as new treatments are coming onto the market and the plethora of new agents, it's important to look at what the risks are with these patients as we're using them.

This is risk factors for VTE. I was new at Cincinnati, I had some time, I decided to do a creative slide, probably not as good as I thought it was at the time. These are some of the risk factors that you see for VTE. And you can pick these out. Age is one. History of VTE, certainly a high risk factor; vascular stasis, now this is just general VTE; hypercoagulable state; and medication. If we take that and we take it to the individual with cancer, you can kind of separate it into three big buckets; one is in patient-related factors, one is in cancer-related factors, and one is in treatment-related factors. And if you look at these, you can see that one population you cannot define what their risk factor is and it really has to be individualized.

When I look at these, a couple things I want to bring out -- there are patient-related factors that are modifiable, such as smoking and alcohol and increased exercise. I'm not up here preaching about them, I don't smoke, I don't drink a lot, and I used to exercise. So it's really hard for me to preach that, but it's

really important to realize that there are modifiable factors and that these are factors that in our population of individuals with cancer, perhaps we should be doing a better job at talking to them about the risk of VTE and what they can do to modify that risk. If you look at cancer-related, we already talked about malignancy. If you look, adeno is increased for squamous cell and that makes sense because a lot of adenocarcinoma are mucin producing.

But the other issue that's really important, and becomes an issue when you talk about treatment, is the volume of disease. Advanced disease is very different than localized disease. One of the reasons I say that, when you're making a treatment decision and you're thinking of how aggressive you're going to be, someone who has advanced disease that is maybe getting worse, you may be more aggressive than someone who has disease that you're treating and it's going to go away. It's really important to look at where patients are in their treatments and how they're responding.

In terms of treatment-related surgery, surgery, surgery; chemotherapy, we don't know which ones, but chemotherapy; endocrine therapies, especially estrogen-specific therapies are a risk factor; central venous access devices; and then antiangiogenic agents, and we'll talk about these a little bit later.

There are predictive models to try to determine for a patient receiving chemotherapy in the ambulatory setting, what their risk is of having VTE. These are the characteristics that have been looked at, and if you can look at this, it does not hit many of the patients that you see, correct? But you can see that if you have a score of greater than three, you have a high risk; 7 to 41%. This is

well done work, defining risk, but it doesn't hit all the patients that we see. So this is my ask that there is a lot of potential, to look at the patients you see that have VTE to contribute to this literature. And I'm saying you should contribute to the literature, not me. I just want to make that clear.

Let's go to the clinical issues. If you look at the clinical issues, the key things we can talk about are who do we prevent, who do we do primary prevention? And that's an area that I don't think that we've done well with yet. And then once we diagnose, who do we treat, and then how long do we treat, and how do we manage those patients?

Let's start with just some of the symptoms. This is stuff that is second nature to you, so I'm not going to spend a whole lot of time on it. You can look at the signs and symptoms; you'll recognize most of them. A couple key things I wanted to bring out here from practice is face swelling, catheter dysfunction; these are two key things to look at, if there's catheter-related thrombosis. The issue is that a fibrin clot does not make it a VTE. If you have a clot in the catheter, it does not necessarily make it a VTE. But these are high-risk factors, and when you see them, a potential evaluation for VTE.

When you look at DVT, the thing that I would say in practice is the most challenging -- I was just telling somebody, I had just started at the University of Cincinnati, and so my credentialing and stuff is just going through. They let me shadow somebody finally this week, and so I went into a clinic and saw patients; I don't think that they were used to somebody being that excited to see a patient before. But I went in and one of the fellows was talking about a patient who had

leg swelling and he said, you know, “But he’s had leg swelling before because he’s getting immunotherapy, so it’s no big deal.” One of the biggest challenges with VTE symptom identification is that they overlap so much with what we see in disease -- and I’ve seen this with pain as well. When you have it and you evaluate it and it’s negative, you tend to walk away from it and think, “I did it once.” But the reality of it is you can’t just do it once and it’s a hard decision, how often do you do it? You look at guidelines, it says do it, if it comes back negative, go back, evaluate it again, but that’s it. But you and I both know that it’s not a week that you’re seeing a patient, you’re seeing them over years.

One of the big challenges that we see with actual diagnosis is getting in this field that we know with a patient. If a patient has leg swelling, they’re really at risk for a clot because of the whole issue of compression. It may be that when you do the initial evaluation, it’s fine, but down the line it may need to be evaluated again.

The other thing is that when you talk about pain and warmth, patients that are on pain medications, patients that are taking nonsteroids or acetaminophen because of symptoms they’re having with chemotherapy, patients on steroids for their antiemetic, you may be masking some of these signs that you normally see. I think one of the key things here is being very aware of the signs, and I think we need to identify risk factor identification for certain populations.

I did want to mention superficial vein thrombosis for a couple key reasons; one, these usually have a negative ultrasound when you do it for DVT, but they can be very uncomfortable for patients, so these are patients that we often do

use things like warmth and nonsteroids. But it depends on where that thrombosis is if there is a risk for subsequent DVT. It's not like a superficial vein thrombosis should not be treated. You need to look at the location to make a good determination if anticoagulation is required. And the NCCN guidelines in one of their many algorithms does talk about what patients you should consider anticoagulation for, even with a superficial vein thrombosis.

Presentations of PE -- again, something that you probably all recognize. And the key thing I'm going to say with this is that when you look at the presentation of PE, if you think DVT is hard to recognize in a patient population, PE is really hard to recognize. If you look at these symptoms: I've had a chronic cough for the last 6 weeks, and I did ask my husband if I should be evaluated. He's a nurse, he told me and quit being such a hypochondriac. But I think about it a lot, so I do exercise, I don't think I have a high risk. But if you look at all of these types of symptoms, they're really challenging. And where this is a real problem [is] as an outpatient because it's not us recognizing the risk, it's teaching patients and their families that they need to call in with these symptoms.

Looking at the evaluation, CTA is what's recommended, V/Q scan be used, and where a pulmonary angiogram is probably used is only when they're going to do thrombolytic extraction or therapy.

Assessment for risk for VTE. One of the real hot topics in the general medicine literature about thrombosis is the use of tests to help identify when patients have symptoms if they should be evacuated. I'll just start off by saying that the use of such tests could be very helpful so that we don't have to keep re-

evaluating the same way when people come back negative. The problem with this, and I'll just say this up front to give you the bottom line, is that this is not data that has been looked at in the cancer population and so when you read this, realize that the subset of oncology patients doesn't fit so nicely in it.

There's a number of different strategies that have been used; use of D-dimer, and we'll talk about that in a minute; the use of probability assessment, the Wells model is what I have in my handout and what I will show you; as well as clinical decision support tools, like the Pulmonary Embolism Rule-Out Criteria.

This is the Wells criteria looking at clinical DVT model. And you can see that active cancer is in it, and you can see that if you look at it closely, you can see a score of one or two indicates moderate risk, score of three or higher are at risk for DVT. This is the model that was used for PE, and you can see active cancer increased risk. But when they did an evaluation of this, looking at it for oncology patients, or patients with cancer, in the blue it says, "In various clinically important subgroups, such as patients with cancer, the validity of the Wells rule is questioned." So these criteria really are not as helpful.

That being said, the question of D-dimer comes up. D-dimer is really being looked at as a way to determine if there is a risk of clot, but in cancer patients, D-dimer is often elevated because of the inflammation and may not be very helpful. I have seen D-dimer be used in patients, and it's usually in patients who have active cancer treated, have had a clot, and the determination when they are disease free if there is a recurrence of the clot when there is a clinical sign or symptom. What does that say to you? That D-dimer is not, at this time, great

criteria to use. But I wanted to mention it because you're seeing it a lot in the literature about VTE. And this went back to what we talked about already.

Management options for VTE. If you look at management options, go to the first. One of the first ways that we can do management is to just decrease the risk of a DVT going to the lung and doing an IVC filter is a strategy. I wanted to take a minute to talk about this because, in practice, I think it's one of the things that is used a little freely and there's dangers associated with it. When you do an IVC filter, it does not decrease the risk of VTE. It decreases the risk of a PE, but it actually can make VTE worse because you're putting a foreign substance in the IVC filter.

When you put an IVC filter in, you have a period of time when you can retrieve them, if it's a retrievable time, and if you can't retrieve them, patients can have them forever, and that can be somewhat of a problem. IVC filters have a place in therapy, but there are risks associated with them.

What we look at is how we can manipulate the anticoagulation cascade, and that's going to be one of our big targets. And the other way is how we can manipulate the development of those facts. I'm going to tell you a story here. My first job, I was at the University of Pittsburgh and they asked me to teach a chemotherapy course and I did all these great overheads that'll date me. And when I did these overheads, they had all these diagrams on them; I loved them. Afterwards, the instructor took me on the side and said, "You need to cut those structures." So now I've learned to put them in to appease myself, so don't worry about them, just know that this is for me.

Let's look at what we have in terms of options. We have heparin, factor Xa inhibitors, vitamin K antagonists, and direct thrombin inhibitors, and that's how I want you to think of them. And because of time, we're going to go through these relatively fast because I think they're drugs most of you know relatively well. Heparin -- we have unfractionated heparin and we have low-molecular weight heparin. It binds, it activates antithrombin III, and heparin then binds thrombin. Heparin's a big molecule, binds thrombin and antithrombin III. Unfractionated heparin are smaller molecules, does not bind like thrombin, it binds antithrombins III. Why am I telling you this? Because the mechanism of action of heparin is that it binds antithrombin and thrombin, it, therefore, has effect on thrombin, factor X, factor Xa, and a number of other clotting factors, not as much; so when you look at heparin, unfractionated heparin, factor IX, and thrombin.

Low-molecular weight heparin, because it's smaller, does not have that effect on thrombin; it has it mainly on factor Xa. When we monitor the effects from heparin, we use aPTT because that's basically a measurement of the intrinsic and common pathways and it measures thrombin. But low-molecular weight heparin, because it doesn't have as much of an effect on thrombin, aPTT is not as helpful. So that's why low-molecular weight heparin is a heparin, but a smaller molecule.

Administration -- you probably all know this. The key thing with heparin to realize is that it's fast onset, fast working. When you have a patient that's symptomatic, it is something that will work almost immediately. Because of its short half-life, when you stop it, it stops. In a hematologic patient who has high

risk of bleeding, it is something that you can shut off relatively fast. It is also a great option for someone who has to be anticoagulated up until doing a procedure almost to the minute because you can shut it off and do the procedure. And you can sit there and think a day, 2 days off anticoagulation before a big procedure, not a big risk. I have a friend who had a procedure and had secondary thrombosis during the day and a half she was off of anticoagulation because it was a relatively aggressive procedure. So it's really important to realize that heparin has really some nice opportunities.

If you look at the side effects; bleeding, I think you can all tell me about the bleeding you see with heparin. So let's talk about some of the other things, and that is HIT and osteoporosis. HIT we're going to talk about in a second; there's two types, it's the media type that's probably not really HIT, and there's the autoimmune HIT, and I will mention it briefly and give you some good references.

Osteoporosis -- we always said you only saw osteoporosis if you used heparin for a long term. In oncology patients, we use heparin for long term, so osteoporosis is certainly a risk that we need to consider in patients that are on prolonged anticoagulation with heparin.

Heparin-induced thrombocytopenia -- we know that heparin can bind platelet factor 4 and that platelet factor 4 in heparin form and antibody -- again, an immunologic response to it -- and causes HIT, which is both thrombosis and thrombocytopenia. When you get that antibody formed, it actually causes both platelet activation that causes the thrombosis, as well as an increase in clearance of platelets, and that's the thrombocytopenia.

HIT can occur within 4 to 7 days of starting heparin. But think of our patients that have cancer; they have seen heparin so many times before that you can see HIT almost immediately in a patient who has received heparin in the past. So HIT should be something that you would consider if someone has a decrease in platelets of greater than 50% if they've been on heparin for a little while or if they have had it in the past. The treatment, discontinuation of all heparin and then initiation of a different agent. You don't want to use warfarin in the initial management of HIT, and we'll talk about that in a minute.

Bleeding with heparin -- that's there and it's also in the NCCN guidelines, so just want to remind you that when you talk about reversal, it depends on when the heparin was given, how much was given. There's not a set dose, so I would never ask that question, how much protamine do you give? It depends very much on what the dose was of heparin that you gave.

Management -- these are some of the issues with heparin to consider. The key thing is this is where you use it with patients that don't fit into the low-molecular weight heparin use.

Low-molecular weight heparin -- we talked a little bit about it already. Its main effect is on thrombin and factor Xa, more factor Xa than thrombin. It's a smaller molecule, more predictable. You give it subcutaneously, it has good effects. The key risk with this is that it's renally eliminated. And this is an issue not only in those patients that have renal dysfunction, but in patients whose renal function is changing. So patients who have been on low-molecular weight

heparin need to be moved off if they are having changing of their renal function because the anticoagulation effect may change.

Here are the two products that are commercially available and the dose for both thromboprophylaxis, as well as VTE. For enoxaparin, you can see it's twice a day dosing. Many of you will have seen that after a patient's been on twice a day for a month for the initial treatment, that you will often change to a once a day dosing for convenience.

Monitoring -- I think we've hit most of these things. Factor Xa can be used to monitor, but it's not a good way to monitor for anticoagulation effect. Where it's used is in patients that are high risk of clotting or bleeding. So when you have patients that are obese and you're giving a huge dose and you're worried that you're overdosing because you're basing on weight, you may use a factor Xa level to get an idea that you're in a range that is safe. Same thing with renal dysfunction, same thing with pediatric patients and pregnancy.

These are the factor A levels, and I just gave you the ones that are looked at. This is 4 hours post-dose. You'll read a lot about getting a trough effect for our post-dose is one of the best times that you can get it and that you can see when they're within range.

Clinical considerations -- where the real benefit of this agent comes is that when we talk about the use, it's been shown to be beneficial. The problem that comes is people don't want to inject themselves. I ran the anticoagulation clinic for 5 years, and the doc I worked with who is wonderful would say, "Low-molecular weight heparin, low-molecular weight heparin." And people would say,

“No, no.” So not taking low-molecular weight heparin and giving that to them and taking something that’s not as good that they will take, well, that’s the treatment option that you sometimes have to make a decision.

Factor Xa inhibitors -- the key thing about these factor Xa inhibitors is that the use in oncology has been limited. The target is factor Xa. These are the agents; fondaparinux subcutaneously, the other three oral. Fondaparinux data in oncology, the other three not necessarily in oncology. Saying that knowing that you’ll probably see them used, it’s important to at least talk about some of the issues with them. Fondaparinux, the good thing with it is that you can do it once a day; it has a long half-life. The bad thing with it, you can use it once a day, it has a long half-life. That means, if you’re bridging somebody, it’s a real problem. There was a real big push for fondaparinux when it first came out because of pricing. Now that pricing differential makes it maybe not as good, the great thing about fondaparinux to put in your head is that you have a very low risk of HIT. So with a patient that has a risk of HIT, this is an agent to consider.

This is to show you I have a lot of these diagrams that compare them because I think they’re really helpful, and you can see the three agents compared because I like tables.

Dosing is based on weight, and the dosing is different for different indications. Let’s talk about the direct oral anticoagulants that inhibit factor Xa. These are direct; they have a direct effect on factor Xa. They are not indirect like heparin and like low-molecular weight heparin. They are more consistent in their efficacy and that is why they have really taken over in many clinical situations

except, perhaps, oncology. These are the three agents compared; they are all not used in the same way. A couple key factors to look at is the bioavailability is different. Rivaroxaban you need to take with food. If you look at renal elimination, you can see there's some differences and the drug interaction. There's a number of drug interactions, not your warfarin drug interactions, but certainly drug interactions.

These are advantages and disadvantages that I think we've mentioned. And then let's go to the direct thrombin inhibitors. This effect is mainly on thrombin, so aPTT will be affected. These are the agents. In this case, these are the IV and this is the oral. If you look at dabigatran, it in itself is not an anticoagulant, it needs to be converted to its active agent. And one of the big things about dabigatran that's of importance is that it's poorly bioavailable, how it's packaged; it needs an acidic environment to be absorbed, it needs to be absorbed and then it's converted to an active agent. One of the key things in how it's formulated is that it's on these pallets, and if you open them and break them, you get increased bioavailability. Here's the bioavailability -- 6.5%. When you chew or crush it, it goes up to 75% and your effect is the anticoagulation. So be aware of that because it's an important consideration in this drug.

You can see there's renal elimination, again, a drug that's difficult to use in a patient with renal insufficiency. And this just looks at all of the DOACs together to give you an idea of some of the differences.

An old oral anticoagulant -- that's what I named it -- and this is warfarin. And I'm not going to go over it too much except for some key factors I want to

point out. This explains how it works, and this is my favorite part. This is your precursor to your clotting factors, this is your clotting factors. In order to get your clotting factors, you get a carboxylation and you require reduced vitamin K. So you give the reduced vitamin K, it's utilized, and then you get oxidized vitamin K, and you recycle this so it can keep happening. Warfarin blocks the recycling of that vitamin K so you can't make clotting factors. When you use warfarin, again, it's not a direct effect. It does it like the other ones, it doesn't break down the clot, it just decreases the formation of clotting factors so you decrease the propagation of the clot. And how long it takes to work depends on how much clotting factor that you have. That's one of the key points; when you take away warfarin, you've already blocked that for a while, so you'll still see effect.

The key thing I always want to talk about is that it blocks not only these clotting factors, but it also blocks regulatory anticoagulant proteins. Remember from this picture? These are your procoagulants, and if you block that, what you get is clotting by blocking the formation of proteins C and S when you start the drug, so you never start warfarin without using something else to block that initial increased risk of thrombosis. That's why you don't start warfarin and then later add something else on or just continue the warfarin; it's really important to realize that risk. Some of you remember the purple toe syndrome that you used to see, that people used to report with warfarin? A lot of it is because of that clotting.

Warfarin is a racemic mixture; S warfarin is more effective, more active. The key reason I show you this is because the R-enantiomer and the S-enantiomer are broken down differently and, therefore, there are differences in

drug interactions and also in genomic metabolism of warfarin. And this just talks about some of the initiation.

Because I have about 5 minutes, what I'm going to do -- because we went through all the drugs -- I think the warfarin things, I'm going to keep some key things I want as we go through. The key thing I want to make sure I emphasize is when you start warfarin, you always get an INR -- always, always. To assume you know what someone's ability to clot is by looking at them, to assume it's 1, can be overdosing in this patient population. Patients that have bad eating habits, people that have lost a lot of weight, people with diarrhea, often will have a high INR, so a baseline INR is essential.

Responses to warfarin fluctuate over time, so don't get confident that you can just give a dose and it will work, and you all know that we monitor INR. But a key factor is anything that will change the dose needs to be communicated, and the only way to do that is not to wait until you call them, but to make sure they call you; so developing a relationship with that patient or family member or caregiver to make sure they call you. The worst thing that ever happened to me in my career is a patient who I saw in clinic for warfarin made a dose adjustment, he then went to his physician's appointment and he got put on ketoconazole and dexamethasone, which increases it. My note was already in the chart for the first time in my life, before that note was in the chart, had no way of knowing that, and if that patient hadn't called, I never would have known and he would have been toxic. So it's really important to make sure the patient and the caregiver, the key people that coordinate.

I want to get to management considerations, contraindications. Contraindications can be absolute or relative. They can be permanent or they may be changing, so these contraindications may change over time. Someone who couldn't get anticoagulation may be able to get it with other changes.

Prophylaxis -- the at-risk population that we know are people that are not ambulatory and that has been historically patients in the hospital. But as we move patients out of the hospital, I think we need to look at those patients that are not ambulatory that are recovering post-surgery and the potential benefit of using prolonged anticoagulation. Right now, the recommendations are people that have pelvic or ovarian high-risk abdominal surgeries. The other high risks that we know in oncology are patients with myeloma receiving the immunomodulating agents with dexamethasone and/or chemotherapy.

Therapy of VTE -- the guidelines that are published by ASCO, NCCN, as well as that by the CHEST, are good documents. There are also some guidance documents that I've put here that will give you some nice indications of the people that don't fit the normal guidelines.

VTE with cancer -- we treat them. The recommendation right now is that we treat them with either low-molecular weight heparin, unfractionated heparin, or fondaparinux and then consider chronic therapy with low-molecular weight heparin or warfarin. That's the recommendation today. What you won't see up here is those direct oral anticoagulants.

If you look at acute management, they're not recommended; that's what I just said. If you look at acute management of VTE that is not cancer, so this

doesn't say cancer on it, you can see there are a number of other options that are used. If you're working with people that deal with VTE that don't know your cancer population, they may recommend use of some of these new agents. But, at this time the studies that look -- and there's great studies -- in fact, this review on this page does a nice job of looking at all these newer anticoagulants and looking at the data. About 2 to 7% of the population were cancer population, so that's why at this time, even though I think there probably is a role, we don't know what that role is.

Chronic management, low-molecular weight heparin or warfarin, and the direct oral anticoagulants are not recommended. This is the clot study. I will go to the bottom line. It showed that low-molecular weight heparin used long term is better than using a vitamin K antagonist, such as warfarin.

A couple key things that I want to make sure that we talk about -- duration of treatment. When we talk about duration of treatment we usually talk 3 to 6 months. The duration of the cancer is the duration of the treatment in a patient with a VTE related to the cancer. It is one of the most challenging things to talk to a patient about because a patient wants to know, "How long am I going be on this?" And to say, "I don't know," when you say 6 months and their disease comes back, then you have to say, "Longer than 6 months." So they're on anticoagulation while they have the disease, and I think that's really challenging to talk about.

Catheter-associated thrombus -- as long as they have the catheter in place, and a minimum of 3 months.

Chronic -- this was a market scan database analysis for newly diagnosed cancer and they found that warfarin was still the most commonly used anticoagulation, not low-molecular weight heparin despite the data. Is anybody here surprised about that? I'm not. Yell out, what would be the reason that you think people still -- there you go. And so one of the big reasons is cost, what's the second reason people don't like to use low-molecular heparins? Sticking themselves and -- I have a friend who's second clot with cancer, and she was on low-molecular weight heparin and couldn't wait to get to back on warfarin. I don't think that's a phrase I've ever said, "Can't wait to get back on warfarin."

So even though the guidelines are there, people are tending still to go with warfarin because of those social issues that are very important. And the other thing is there is an increased use of the direct oral anticoagulants even though the data is not there in studies. Even though they're not in guidelines, definitely people are starting to use those factor Xa inhibitors, as well as direct thrombin inhibitors.

When not to consider active treatment? I put this up because I'm sure many of you people see patients end of life, and one of the big questions is, do you take this off? You take off anticoagulation when you're not going to increase problems associated from taking it off. If you have someone with a clot in their leg and it's painful, taking away anticoagulation makes the clot bigger and more painful. So taking away anticoagulation may be good at end of life, but it may not be. And so considering that is really something important when you're looking at a patient and taking off for palliation reasons.

When to place filter -- I think we've talked a little about this. This is the risk associated from filters. Really important if you can to use retrievable filters, that's where you would go.

Thrombotic agents for VTE are becoming en vogue again. You used to think of it when we used these agents systemically; now with catheter-directed, less of a risk. And so there are some indications that are beneficial with these agents, so I put that in. And, again, those are in NCCN, and here's your risks.

Those people who have a clot despite what you think is good anticoagulation. The first issue is to evaluate if you are having good anticoagulation and to look and see if they're taking their drugs, if they're taking them how they're supposed to be doing it, and then optimizing the dose and then to switch to another agent if needed.

These are the reversal agents. I recommend that instead of memorizing reversal agents, you use the NCCN guidelines because they put not only the risk but also the relative risk of bleeding with how you do reversal. And any of you who work with warfarin know that an INR of 4 is not great, an INR of 10 scares you to death, but if you're not bleeding with an INR of 10 and the INR is coming down, that's a whole different risk factor for reversal. And when you reverse somebody with warfarin what you're seeing, unfortunately, is that you're going to have long-term effective reversal.

**[END]**