Preventing and Treating Venous Thrombosis in Oncology

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Learning Objectives

1. Interpret recent findings comparing safety and efficacy of "standard" anticoagulants with those of direct oral anticoagulants (DOACs)
2. Evaluate the risks and benefits of treatment of DOACs
3. Monitor and assess patient response to anticoagulant treatment

Financial Disclosure

Dr. Schwartz has nothing to disclose.

Clinical Issues: Cancer-Associated Thrombosis (CAT)

Prevention	• Identification of populations and patients at high risk • Determine strategy(s) for prevention • Assess safety and efficacy of prevention
Diagnosis	• Recognition of signs and symptoms of CAT • Evaluation of patient factors and treatment factors that contribute to risk for CAT • Diagnosis of thrombosis in the individual with cancer
Management	• Determine appropriate treatment strategy(s) for acute and chronic management of CAT (population vs. individual) • Management of recurrence CAT (population vs. individual) • Management of complications of anticoagulation therapy

Preventing and Treating VTE in Oncology

VTE = venous thromboembolism

Preventing and Treating VTE in Oncology

Case Scenario

- PL is a 67-year-old woman with lung cancer receiving carboplatin + pemetrexed + pembrolizumab. She is being seen in clinic today for follow-up prior to cycle 3.
  - She reports that she has been increasingly tired and short of breath
  - Decreased breath sounds on exam → pulmonary embolism, deep venous thrombosis

PMH

- Weight loss → decreased oral intake with diagnosis and following chemotherapy
- Atrial fibrillation (carvedilol)
- GERD (pantoprazole)

GERD = gastroesophageal reflux disorder; PMH = past medical history.

Risk Factors for Venous Thromboembolism in the Individual With Cancer

Cancer-Associated Thrombosis

- Cancer
  - Histology
  - Stage
  - Status
- Treatment(s)

Risk Factors for VTE (examples)

- Surgery
- Trauma
- Cardiac or respiratory failures
- Age
- Obesity
- Immobility
- Drugs (oral contraceptives)
- History
- Genetic predisposition

Timp JF, et al. *Blood* 2013; 1712-1723; Khorana AA, et al. *J Clin Oncol* 2006;24:484-90; Khorana AA, et al. *Cancer* 2013;119:648-55

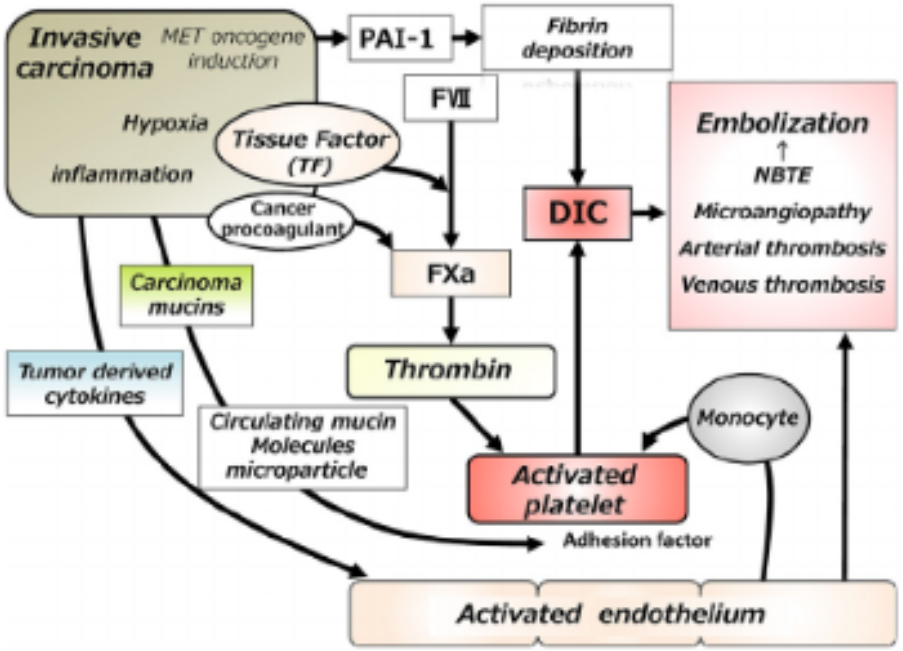
Relative VTE Risk for Cancer

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.

Active Cancer and Thrombosis



Mukai M, Oka T. *J Cardiol*. 2018;72:89-93

Treatment-Related Risk Factors: Medications

Examples:

- IMiDS (e.g., thalidomide, lenalidomide, pomalidomide) + dexamethasone
- Hormones (e.g., estrogens, progestins)
- SERMs (e.g., tamoxifen)
- VEGF inhibitors (e.g., bevacizumab)
- Erythropoietin (ESA)

IMIDs = immunomodulator drugs; SERM = selective estrogen receptor modulators; VEGF = vascular endothelial growth factor.

Risk Assessment Model → Prevention

Example: Multiple myeloma and IMiDs

Risk Factors	Recommended Approach
Individual risk factors • Obesity • Prior VTE • CVAD or pacemaker • Associated disease • Surgery • Use of erythropoietin • Blood clotting disorder	No risk factor: • Aspirin 81–325 mg PO daily 1 risk factor: • Aspirin 81–325 mg PO daily ≥ 2 risk factors: • LMWH (equivalent to enoxaparin 40 mg PO daily) • Warfarin (target INR 2-3)
Myeloma risk factors	
Myeloma therapy: IMiD in combination with HD dexamethasone, doxorubicin or multiagent chemotherapy	• LMWH (equivalent to enoxaparin 40 mg PO daily) • Warfarin (target INR 2-3)

HD = high dose; LMWH = low-molecular-weight heparin.

Palumbo A, et al. *Leukemia* 2008;22:414.

Khorana Predictive Model for Chemotherapy-Associated VTE

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

BMI = body mass index.

Khorana AA, et al. *Blood* 2008;111:4902-7. Khorana AA, et al. *Am J Hematol* 2012.

Predictive Model for Chemotherapy-Associated VTE

Total Score	Risk Category	Risk of Symptomatic VTE
0	Low	0.3–1.5%
1 or 2	Intermediate	1.8–4.8%
≥3	High	6.7–12.9%

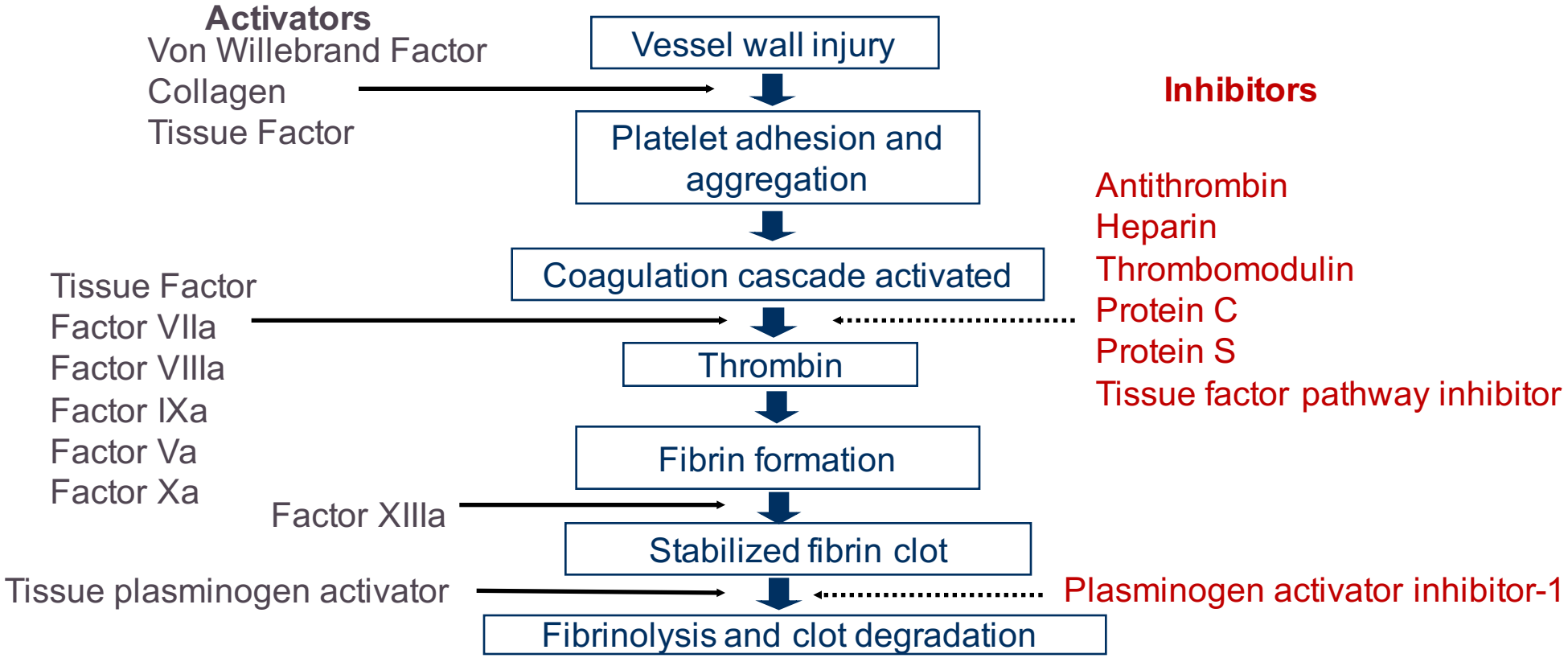
Khorana AA, et al. *Blood* 2008;111:4902-7. Khorana AA, et al. *Am J Hematol* 2012.

Management of an Individual With Cancer and VTE

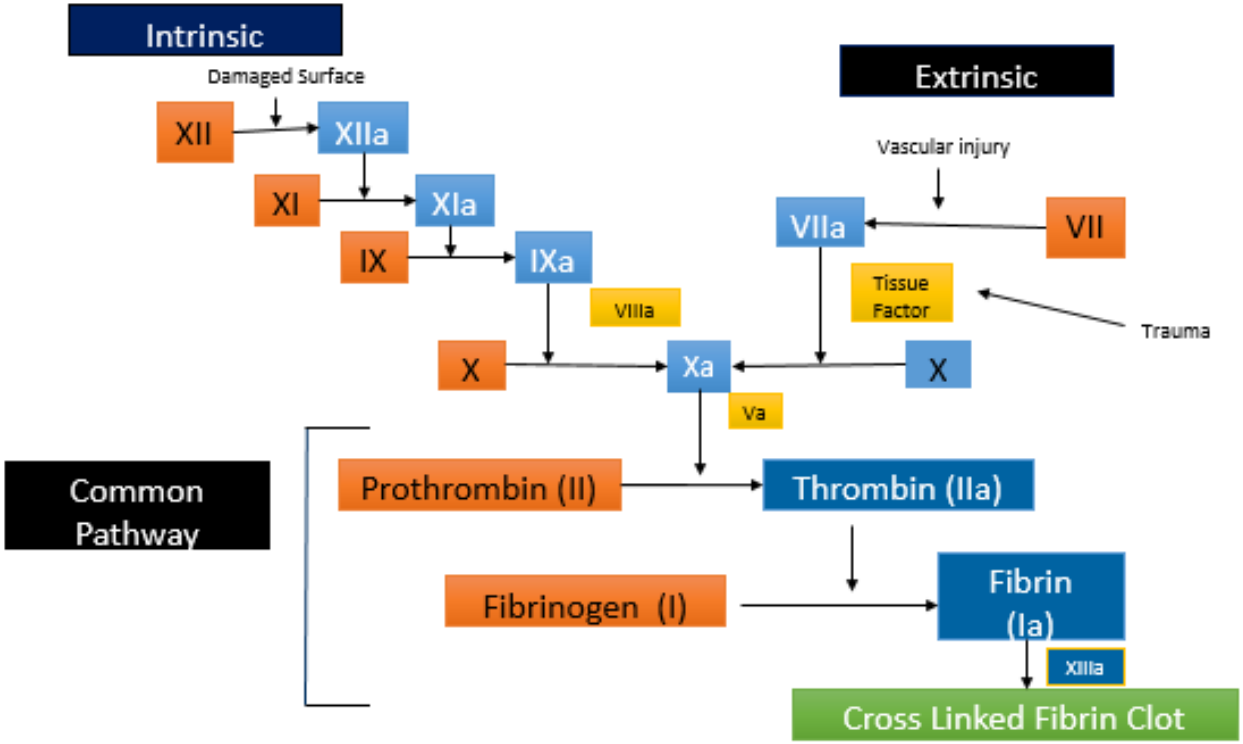
- Options for treatment (acute, chronic, during procedures)
- Considerations for treatment decision(s)
- Implementation strategies for anticoagulation
- Management strategies for patients with cancer on anticoagulation
- Discontinuation of treatment

Management Options for Venous Thromboembolism

Overview of Hemostasis



Coagulation Cascade



Natural Anticoagulants

- Protein C → Destroys factor V and factor VIII
- Protein S → Cofactor to protein C, free and bound
- TFPI
- Prostacyclin (PGI2) → 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.

Pharmacotherapy Options for Treatment of VTE

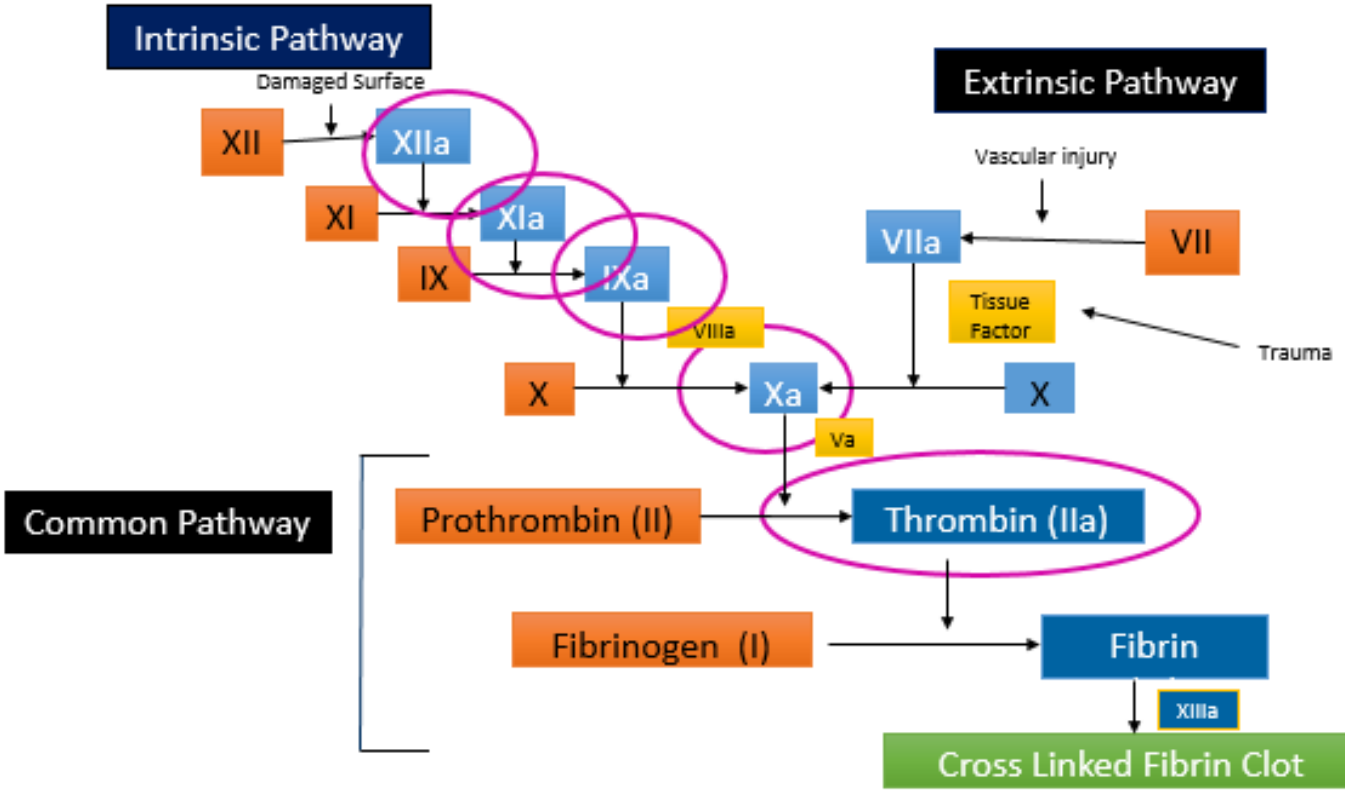
Heparin	Factor Xa Inhibitors	Vitamin K Antagonist	Direct Thrombin Inhibitors
UFH LMWH • Dalteparin • Enoxaparin	Apixaban (po) Betrixaban (po) Edoxaban (po) Fondaparinux (sc) Rivaroxaban (po)	Warfarin (po)	Dabigatran (po) Bivalent: • Hirudin (IV) • Bivalirudin (IV) • Desirudin • Lepirudin Univalent: •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

UFH = unfractionated heparin; IV = intravenously; po = orally; sc = subcutaneous.

Heparin

- Unfractionated heparin (UFH)
  - Highly sulfated mucopolysaccharide
  - UFH has a mean molecular weight 15,000 kDa (range from 3,000–30,000)
- Low-molecular-weight heparin (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)

Heparin: Targeting the Coagulation Cascade



Unfractionated Heparin

- Subcutaneously
  - VTE prophylaxis (low dose)
  - VTE treatment (rare)
- Intravenous infusion for VTE treatment (dose determined by aPTT)
- 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

Bleeding With UFH

- Discontinue heparin
  - Heparin serum half-life is ≈ 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

aPTT = activated partial thromboplastin times

Low-Molecular-Weight Heparin

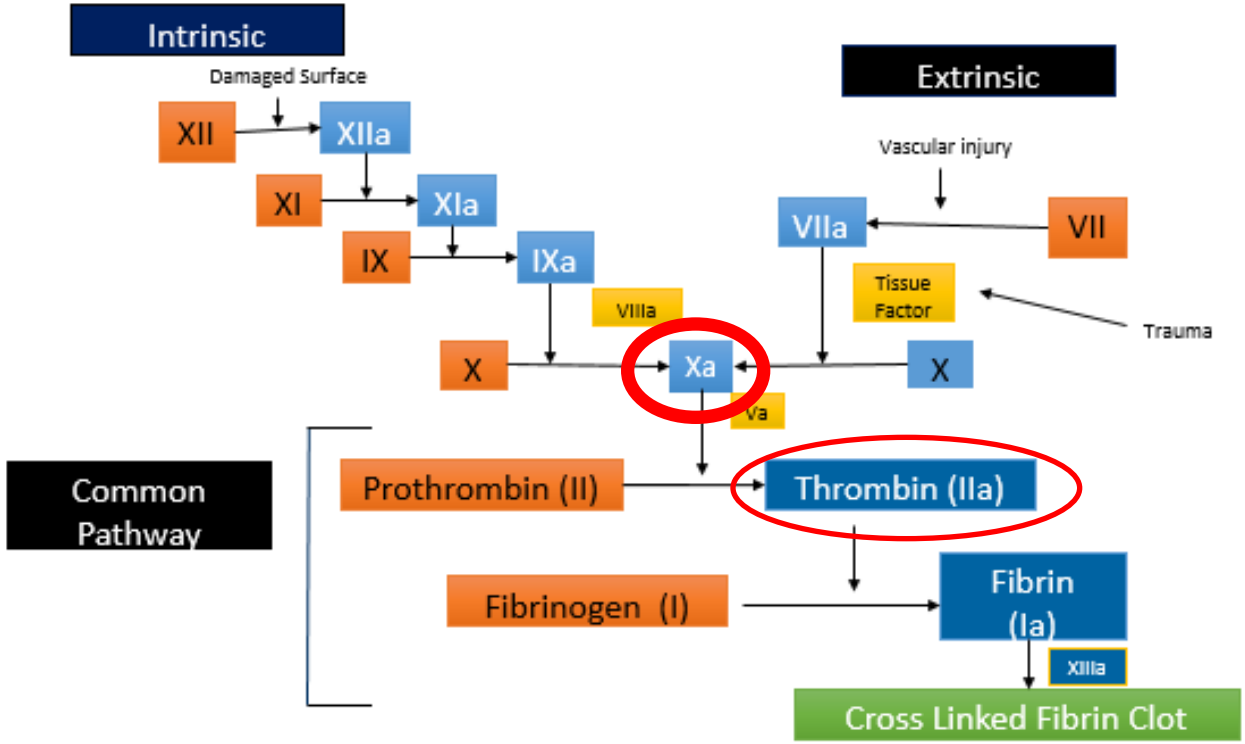
MOA

- 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 ≈ 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**

LMWH: anti-Factor Xa > anti-Factor IIa



Low-Molecular-Weight Heparin

Product	Thromboprophylaxis*	VTE Treatment*
Dalteparin	5000 units sc daily	200 units/kg sc daily
Enoxaparin	40 mg sc daily	1 mg/kg sc q12h or 1.5 mg/kg sc q24h

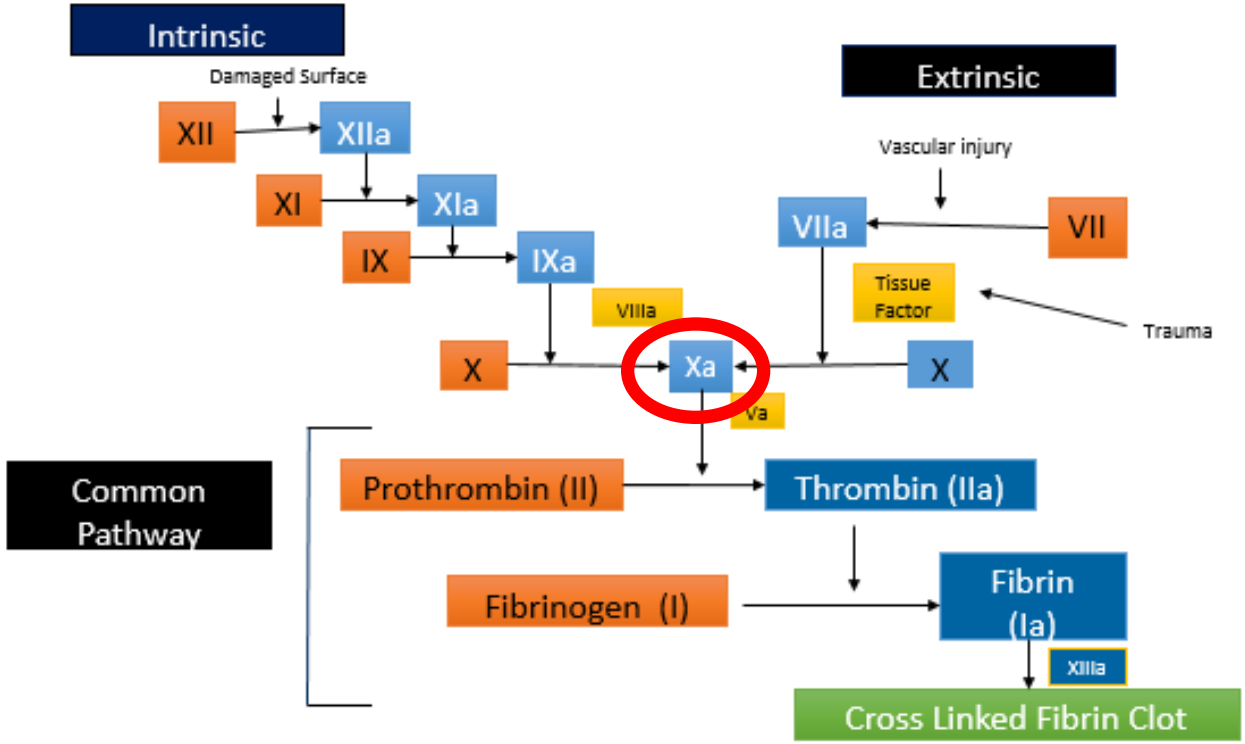
* Modifications may be required dependent on patient specific factors including obesity.

https://reference.medscape.com/drug/fragmin-dalteparin-342142; https://reference.medscape.com/drug/lovenox-enoxaparin-342174

Low-Molecular-Weight Heparin: Considerations

- Monitoring
  - LMWH has minimal effect on aPTT
  - Factor Xa monitoring 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
    - Absolute contraindication in recent or acute HIT
    - Relative contraindication in past history of HIT
  - Osteoporosis
  - Injection site reactions

LMWH: anti-Factor Xa > anti-Factor IIa



Target: Factor Xa

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
Betrixaban	Currently not indicated for treatment of VTE. Indication is for prophylaxis of VTE in adults hospitalized for an acute medical illness.

* 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.

https://reference.medscape.com/drug/arixtra-fondaparinux-342172; http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/XARELTO-pi.pdf; https://packageinserts.bms.com/pi/pi_eliquis.pdf; http://dsi.com/prescribing-information-portlet/getPIContent?productName=Savaysa&inline=true; https://reference.medscape.com/drug/bevyxxa-betrixaban-1000147

Parenteral Factor Xa Inhibitor: Fondaparinux

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

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

Fondaparinux: Comparing to Heparin

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 prophylaxis of DVT, treatment of acute DVT, treatment of acute PE
- 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.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021345s010lbl.pdf

Oral Factor Xa Inhibitors

- 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 in the US include:
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - Betrixaban

Oral Anticoagulants: Select 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	CYP3A4, P-gp	CYP3A4, 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 in Practice: Considerations

Advantages

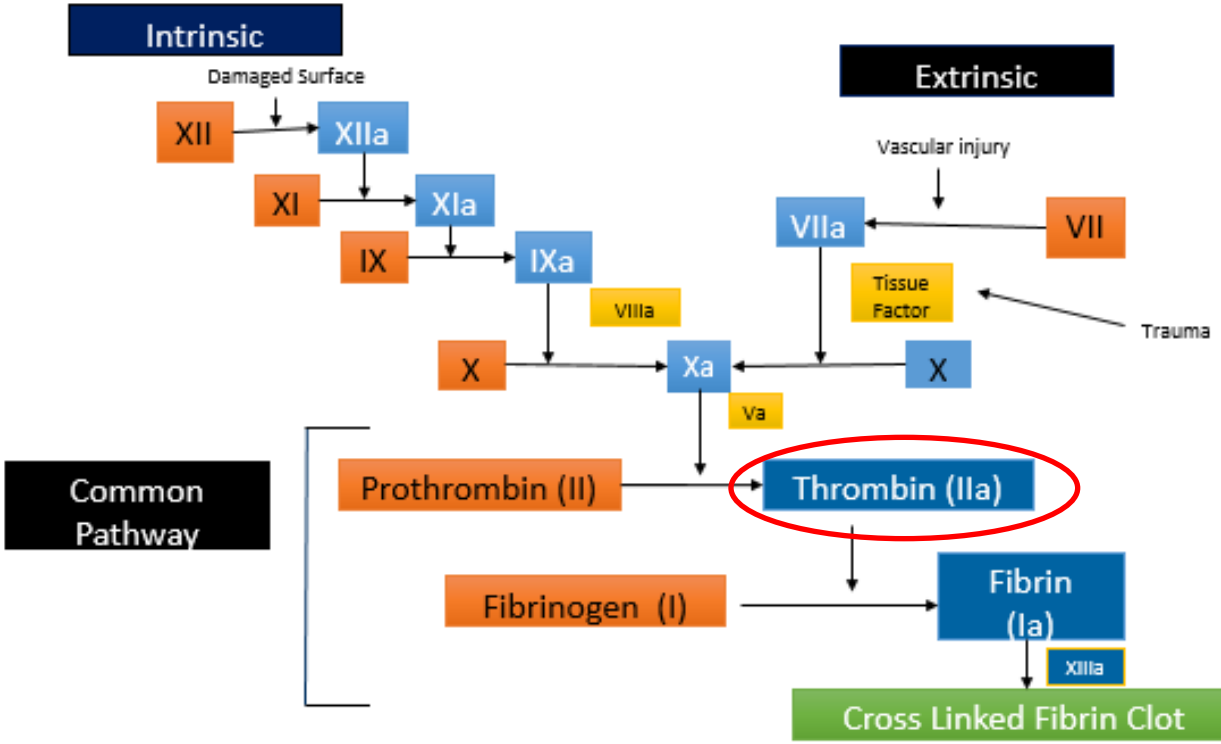
- Specificity
- No requirement for routine blood monitoring for dose adjustment
- Lack of cross-reactivity with HIT antibody
- Drug interactions (< warfarin)
- “Long” half-life

Disadvantages

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

Target: Thrombin (Factor IIa)

Management of VTE: Target for Therapy



Factor IIa Inhibitors

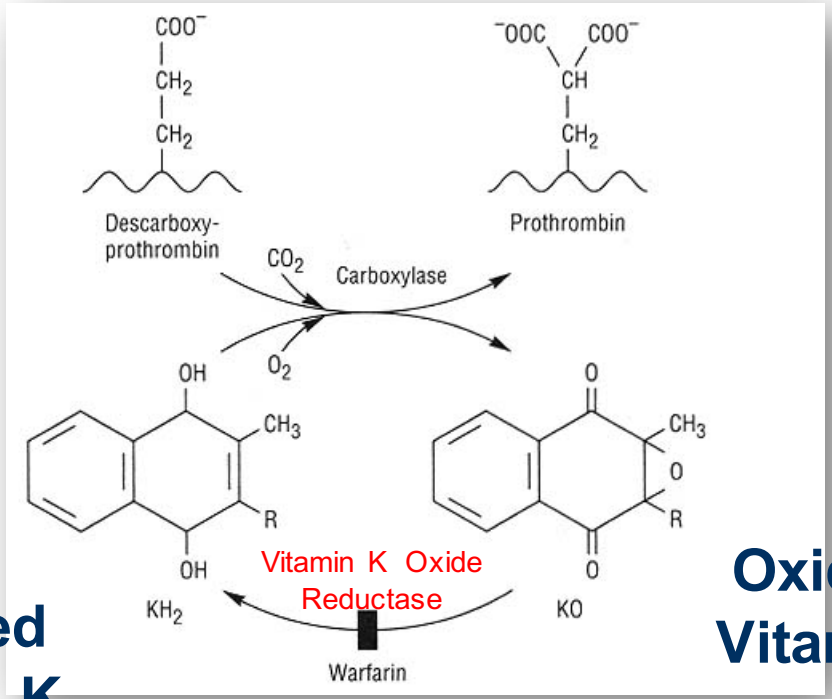
Agent	VTE Treatment*
Dabigatran	CrCL > 30 mL/min → 150 mg PO twice daily
	CrCl ≤ 30 mL/min or on dialysis → no recommendation
	Avoid in patients with CrCl < 50 mL/min with concomitant use of P-gp inhibitor
Hirudin	
Bivalirudin	Not indicated in VTE treatment
Desirudin	Not indicated in VTE treatment
Lepirudin	
Argatroban	Treatment of thrombosis in patient with HIT

* 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.

https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf; https://www.drugs.com/mmx/hirudin-recombinant.html; http://www.angiomax.com; https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021271s006lbl.pdf; https://reference.medscape.com/drug/refludan-lepirudin-342175; https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022485lbl.pdf

Vitamin K–Dependent Clotting Factors

Target: Vitamin K–Dependent Factors



Reduced Vitamin K

Oxidized Vitamin K

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

Warfarin: Inhibition of Coagulant Proteins

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

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

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 and clinical factors.

Case Scenario

- PL is a 67-year-old woman with lung cancer receiving carboplatin + pemetrexed + pembrolizumab. She is being seen in clinic today for follow-up prior to cycle 3.
  - She reports that she has been increasingly tired and short of breath.
  - Decreased breath sounds on exam → pulmonary embolism, deep venous thrombosis

PMH:

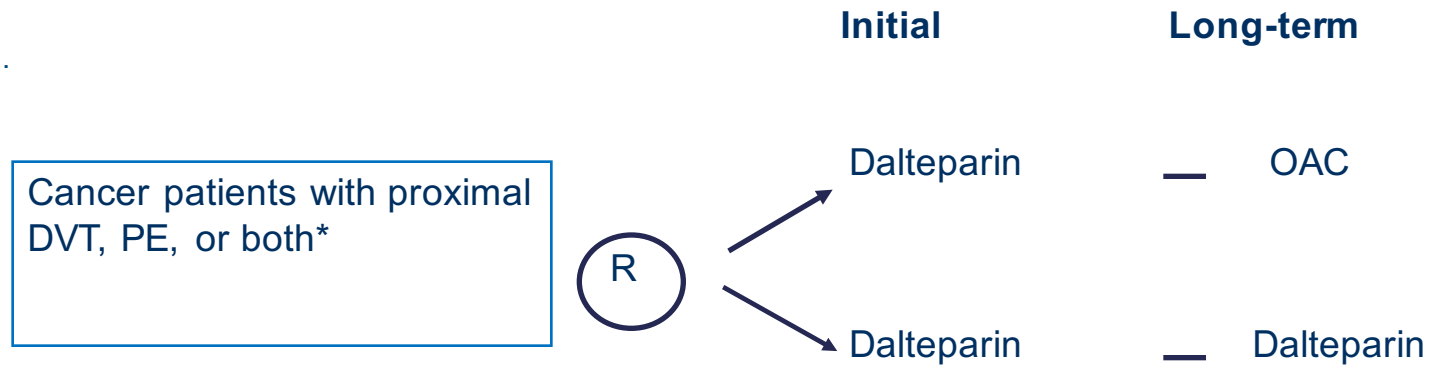
- Weight loss → decreased oral intake with diagnosis
- Atrial fibrillation (carvedilol)
- GERD (pantoprazole)

Evolution in the Management of VTE: Too Simply Stated

This does not mean to represent that older treatment options are no longer utilized.

Evolution in the Management of CAT: Too Simply Stated

Shifting From VKA → LMWH: CLOT Trial



***Objectively documented**

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

OAC = oral anticoagulant.

CLOT: Study Treatments

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	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)
Total VTE	**27**	**53**
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: CLOT Trial

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

SD = standard deviation

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

Bleeding Events in CLOT Trial

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

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

Treatment of Cancer-Associated VTE

Study (year)	Study Drug	Comparator	Follow-Up (months)	Recurrent VTE (%)		Major Bleeding (%)	
				Study Drug	Comparator	Study Drug	Comparator
CANTHANOX (2002)	Enoxaparin	LMWH + warfarin	3	2.8	6.7	7	16
CLOT (2003)	Dalteparin		6	8	15.8	5.6	3.6
ONCENOX (2006)	Enoxaparin		7	6.9 (BID) 6.2 (QD)	10	6.5 (BID) 11.2 (QD)	2.9
LITE (2006)	Tinzaparin	UFH + warfarin	3	7	16	7	7
CATCH (2015)	Tinzaparin	LMWH + warfarin	6	7.2	10.5	2.1	2.4

Imberti D, et al. *Expert Opinion Pharmacotherapy* 2018;19:1177.

Evolution in the Management of CAT: Too Simply Stated

Treatment of VTE: **Subgroup Analysis** of Individuals With Cancer in VTE Trials

Study (year)	Study Drug	Comparator	Recurrent VTE % (N)		Major Bleeding % (N)	
			Study Drug	Comparator	Study Drug	Comparator
EINSTEIN (2014)	Rivaroxaban	LMWH + warfarin	2.6 (6/232)	4 (8/198)	2.6 (6/232)	4.1 (8/196)
AMPLIFY (2015)	Apixaban		3.7 (3/81)	6.4 (5/78)	2.3 (2/87)	5 (4/80)
RECOVER (2015)	Dabigatran		5.6 (10/173)	7.4 (12/162)	3.8 (6/159)	4.6 (7/152)
Hokusai-VTE (2016)	Edoxaban		3.7 (4/109)	7.1 (7/99)	4.6 (5/109)	3 (3/99)

Imberti D, et al. Expert Opinion Pharmacotherapy 2018;19:1177. EINSTEIN; Mh P, et al. Lancet Heamatology 2014;e37. AMPLIFY: Agnelli Ge, et al. J Throm Haemost 2015:2187. RECOVER: Schulman S, et al. Throm Haemost 2015:150. Hokusai VTE: Raskob GE, et al. Lancet Haematol 2016: 2379.

Hokusai VTE: Edoxaban vs LMWH for Cancer-Associated VTE

Methods

- Open-label, noninferiority trial
- Individuals with cancer who had an acute symptomatic or incidental VTE
- Treatments
  - LMWH x 5 days → Edoxaban 60 mg po daily*
  - LMWH (dalteparin)
- Duration of treatment: at least 6 months and up to 12 months
- Outcomes
  - Primary: composite of recurrent VTE or major bleeding during the 12 months post randomization

* Edoxaban dose adjusted for patients with CrCl 30 – 50 mL/min, body weight ≤ 60 kg, or receiving concomitant treatment with potent P-glycoprotein inhibitor

Hokusai VTE: Edoxaban for Cancer-Associated VTE

Characteristic	Edoxaban (n=522)	Dalteparin (n=524)
PE ± DVT	62.8%	62.8%
DVT only	37.2%	37.2%
Incidental DVT or PE	32%	32%
Metastatic disease	52.5%	53.4%
Cancer treatment within 4 week	71.6%	73.1%
Risk factors for bleeding	82.4%	81.6%

Raskob GE, et al. *N Eng J Med* 2018;378:615.

Hokusai VTE: Edoxaban vs LMWH for Cancer-Associated VTE

Outcome Measure Definitions:

- **Recurrent venous thromboembolism** was defined as symptomatic new DVT or PE, incidental new DVT or PE involving segmental or more proximal pulmonary arteries, or fatal PE or unexplained death for which PE could not be ruled out as cause.
- **Major bleeding** was defined as overt bleeding that was associated with decrease in Hgb of 2 g/dL or more, led to transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death.
- **Clinically relevant non major bleeding (CRNMB)** was defined as overt bleeding that did not meet criteria for major bleeding but was associated with the use of medical intervention, contact of the physician, interruption of the assigned treatment, discomfort, or impairment of activities of daily living.

Hokusai VTE: Edoxaban for Cancer-Associated VTE

Outcome	Edoxaban (n=522)	Dalteparin (n=524)	Hazard Ratio (95% CI)	P Value
Recurrent VTE or major bleeding	**67%**	**71%**	**0.97 (0.7 – 1.36)**	**0.006 (noninferiority) 0.87 (superiority)**
Recurrent VTE	7.9%	11.3%	0.71 (0.48 – 1.06)	
Major bleed	6.9%	4.0%	1.77 (1.03-3.04)	0.04
Major or clinically relevant non major bleeding	14.6%	11.1%	1.38 (0.98-1.94)	

Raskob GE, et al. *N Eng J Med* 2018;378:615.

SELECT-D Trial: Rivaroxaban vs LMWH with Cancer-Associated Venous Thromboembolism

Methods

- Multicenter, randomized, open-label, pilot trial in United Kingdom
- Individuals with active cancer who had a symptomatic PE, incidental PE or symptomatic lower extremity proximal DVT

Treatments

- LMWH arm: dalteparin 200 IU/kg daily x 1 month then 150 IU/kg daily for months 2-6
- Rivaroxaban 15 mg PO BID x 21 days then 20 mg PO daily for 6 months.

- Duration of treatment: 6 months

Outcomes

- Primary: VTE recurrence over 6 months

SELECT-D Trial: Rivaroxaban vs LMWH with Cancer-Associated Venous Thromboembolism

Thrombosis	Dalteparin (n=203)	Rivaroxaban (n=203)
VTE recurrence	9%	4%
PE	4.5%	2%

Bleeding Events	Dalteparin (n=203)	Rivaroxaban (n=203)
Major bleeding	3%	5.4%
Clinical relevant non major bleed (CRNMB)	3.4%	12.3%

Young AM, et al. *J Clin Oncol* 2018;36:2017.

DOAC vs LMWH for CAT

- Systematic review and meta-analysis including observational trials and randomized controlled clinical trials (RCT)
  - 426 articles → 25 full text review → 13 (qualitative) + 2 (quantitative)
  - Meta-analysis of 2 RCT
- Results:
  - DOACs had lower 6 month recurrent VTE compared to LMWH
  - DOACS had higher major bleeding when compared to LMWH
  - DOACs associated with higher clinically relevant non major bleeds

DOAC = direct oral anticoagulants

Li A, et al. Thrombosis Res 2018.

Ongoing Trials: DOACs vs LMWH in CAT

TRIALS	Sample Size	DOAC	Comparator	Treatment Duration
CARAVAGGIO	1126	Apixaban	LMWH	6 months
CASTA-DIVA	200	Rivaroxaban	LMWH	3 months
CONKO-11	450	Rivaroxaban	LMWH	3 months
ADAM-VTE	300	Apixaban	LMWH	6 months

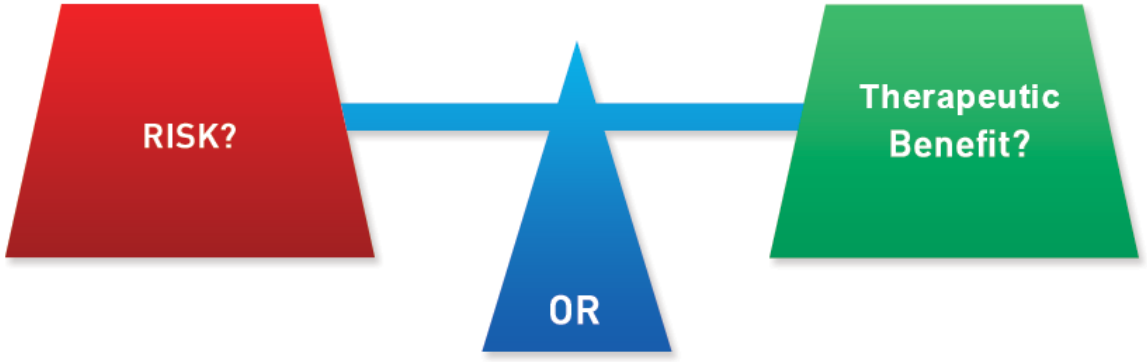
Verso M, et al. Thromb Res 2018; S168,

NCCN Guidelines Cautions: Apixaban, Edoxaban, Rivaroxaban

- Associated with urinary and intestinal tract bleeding→ caution in patients with urinary or GI lesions, pathology or instrumentation
- Use with caution in compromised renal function
- Use with caution in compromised liver function
- Evaluate drug-drug interaction prior to therapy, and throughout therapy
- Patient identification of chronic anticoagulation
- Assessment of patient adherence prior to therapy, and throughout therapy

Anticoagulation at Extremes of Body Weight

The optimal anticoagulant agent and dosing strategy for patients at extremes of body weight.



McCaughan G, et al. Expert Review Hematol 2018; 11:817-28. Kido K, et al. Annal Pharmacotherapy 2018

Management of an Individual With Cancer and VTE

- Options for treatment (acute, chronic, during procedures)
- Considerations for treatment decision(s)
- Implementation strategies for anticoagulation
- Management strategies for patients with cancer on anticoagulation
- Discontinuation of treatment

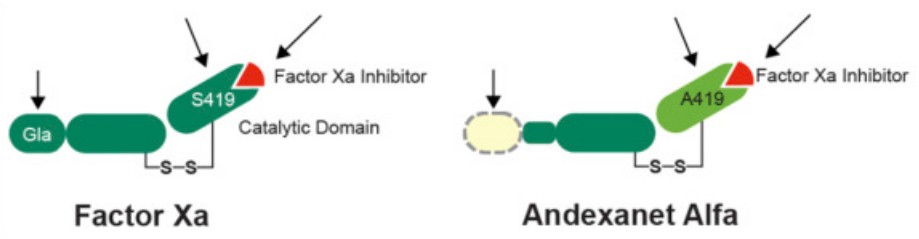
Reversal of Anticoagulant Activity: Establishing an Approach Prior to Necessity

- The ability to reverse an anticoagulant should be considered when selecting an approach to treatment of VTE in the individual with cancer.
- Clinical situations to consider:
  - Bleeding
  - Urgent / emergent invasive procedure (e.g., surgery)
  - Thrombocytopenia
- Reversal agents (e.g., agent specific)
- Management considerations beyond reversal agents
  - Reversal protocols are associated with risk of thromboembolism
  - Reversal vs holding anticoagulation

Reversal of Anticoagulation

Anticoagulant	Reversal Agent
Unfractionated heparin	Protamine
Low-molecular-weight heparin	Protamine
Warfarin	Vitamin K
Dabigatran	Idarucizumab
Rivaroxaban	Andexanet alfa
Apixaban	

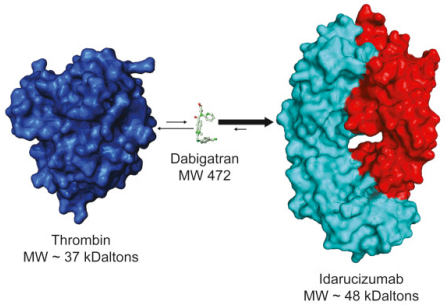
Andexanet Alfa



- Recombinant modified human factor Xa decoy protein
- Developed as a specific reversal agent for direct and indirect Factor Xa inhibitor
- Evaluation in patients with acute major bleed within 18 hours after administration of a Factor Xa inhibitor→ 79% effective hemostasis[1]
- Current indication:
  - Patients treated with rivaroxaban and apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

1. Connolly SJ, et al. N Engl J Med 2016; 375 (12): 1131.

Idarucizumab



- Humanized monoclonal antibody fragment that binds dabigatran and its metabolites → neutralizing anticoagulant effect.
- Multicenter, prospective, open-label study in patients who had uncontrolled bleeding or were about to undergo an urgent procedure.
  - Median maximum percentage reversal was 100%
  - Median time to cessation of bleeding in evaluable patients was 2.5 hr
  - Thrombotic events post reversal

Pollack CV, et al. *N Engl J Med* 2017; 377:431.

Additional Resources

- Udayachalerm S, et al. The reversal of bleeding caused by new oral anticoagulants (NOACs): A systemic review and meta-analysis. *Clin Appl Throm Hemo* 2018;1-10.
- NCCN Guidelines
- Institutional guidelines

When to Consider No Active Treatment

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

Contradictions to Anticoagulation Treatment

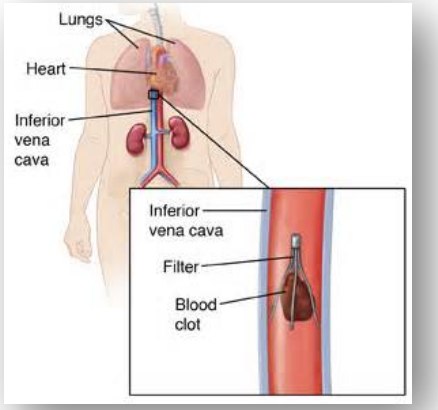
- ABSOLUTE (NCCN Guidelines 2018)
  - Recent CNS bleed, hemorrhagic CNS metastases
  - Active bleeding (major): more than 2 units transfused in 24 hr

Contradictions to Anticoagulation Treatment

RELATIVE Contraindications (NCCN Guidelines 2018)

- Chronic, clinically significant measurable bleeding > 48 hr
- Thrombocytopenia (platelets < 50K/mcL)
- Severe platelet dysfunction
- Recent major operation at high risk of bleeding
- Underlying hemorrhagic coagulopathy
- High risk for falls
- Neuraxial anesthesia/lumbar puncture
- Interventional spine and pain procedures
- CNS metastases
- Long-term antiplatelet therapy

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.

Recommendations: LMWH for Individuals with Chemotherapy-Induced Thrombocytopenia

Platelet Count	Dose Adjustment	Dose of Enoxaparin	Alternative Once Daily Regimen
> 50K	Full dose enoxaparin	1 mg/kg Q12H	1.5 mg/kg Q24H
25 – 50K	Half-dose enoxaparin	0.5 mg/kg Q12H	-
< 25K	Temporarily hold enoxaparin (restart based on platelet and clinical assessment)		

Mantha S, et al. J Thromb Thrombolysis 2017; NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease version 2.2018.

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.

NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease version 1.2018.
Streiff MB. J Thromb Thrombolysis 2015;39:353-366. Piran S, et al. Thromb Res 2018:S172.

Predictor of Recurrent VTE in Malignancy

Purpose

- Association of tissue factor (TF), clinical risk factors, and other biomarkers measured at the time of initial VTE with recurrent VTE in the CATCH trial.

Results

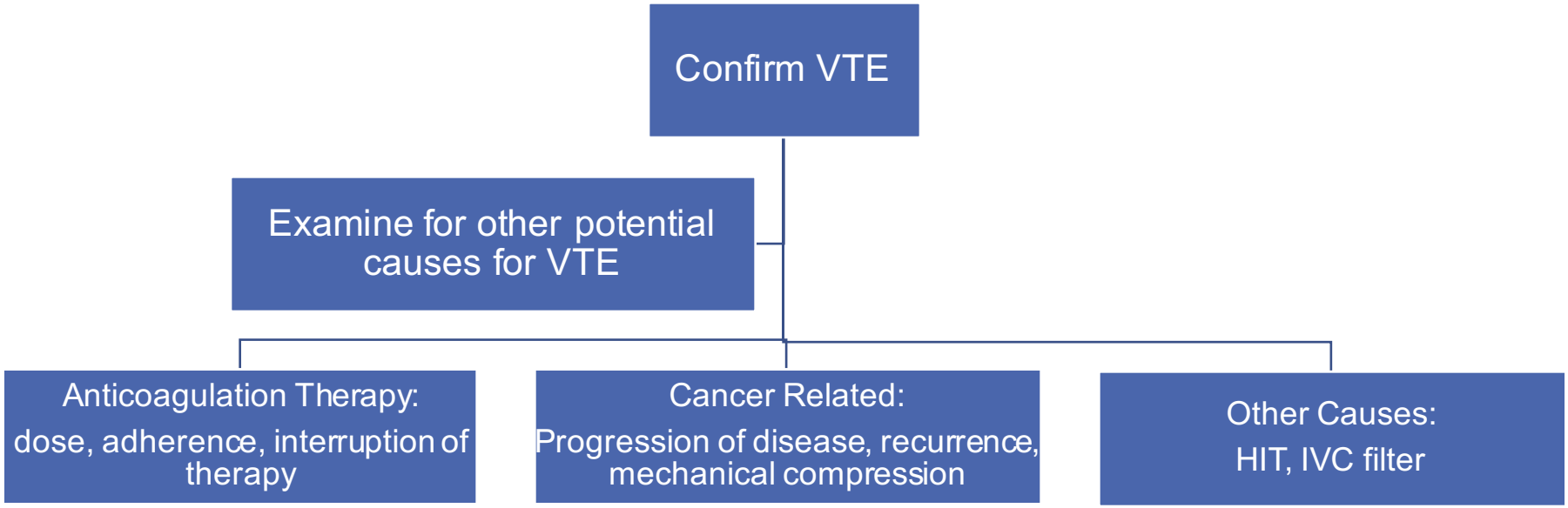
- Patients with the highest TF had the greater VTE recurrence
- Other significant variables include venous compression from mass and hepatobiliary cancer.

CATCH trial: Comparison of Acute Treatments in Cancer Hemostasis Trial

Risk Factors for Recurrent Venous Thromboembolism

- Younger patients (< 65 years)
- PE
- Cancer
  - Site (brain, lung, ovarian cancer, pancreatic cancer, myeloproliferative disorder, myelodysplastic disorder)
  - Stage
  - Time since diagnosis (< 3 months)
  - Histology

Management of Recurrent Cancer-Associated Thrombosis (on anticoagulant therapy)



Piran S, et al. *Thromb Res* 2018:S172

Potential Strategies for Optimizing Therapy With Recurrent VTE While on Anticoagulation

LMWH

- Optimize dose
- Dose-guided by peak antiXa level

Warfarin

- If INR within therapeutic range consider switch to alternative drug therapy
- If subtherapeutic INR consider overlap with LMWH until INR therapeutics

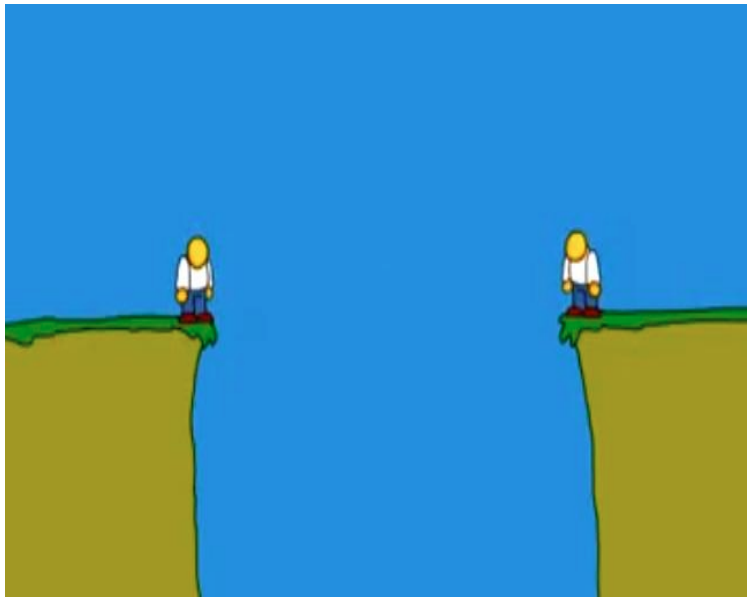
Factor Xa Inhibitors*

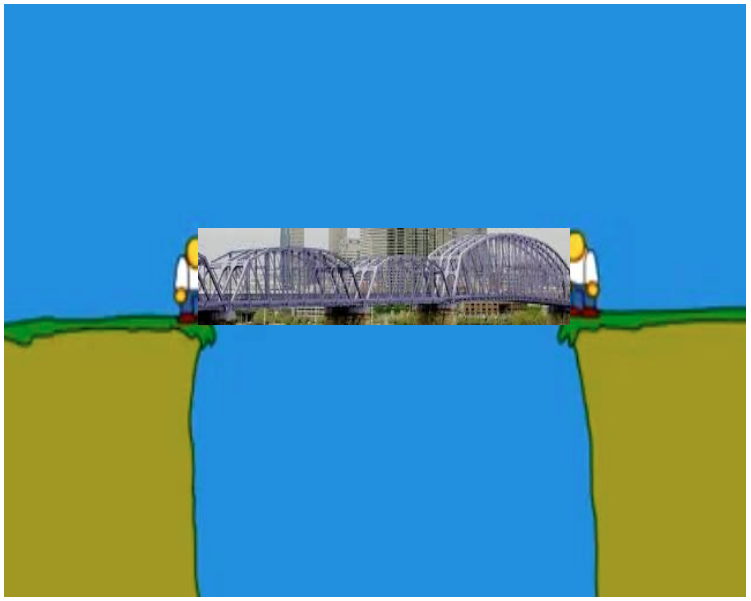
- Consider alternative drug therapy

* Not addressed in the recommendations provided in the reference.

Adapted from Piran S, et al. Thromb Res 2018:S172,

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





Bridging Strategies

- Strategies are determined by patient factors, current anticoagulation and reason for bridging.

Example: Apixaban Management in Periprocedural Setting (NCCN)

Patient Characteristics	Terminal Elimination Half-life	Stop Apixaban Before Procedure	
		LOW BLEEDING RISK	HIGH BLEEDING RISK
Male 18–45 years	10–15 hour	40–60 hour	60–90 hour
Female or elderly male	14–16 hour	56–64 hour	84–96 hour
Pt with CrCl 15–50 mL/min	17–18 hour	68–72 hour	102–108 hour

NCCN Clinical Practice Guidelines in Oncology: Cancer-Associated Venous Thromboembolic Disease version 2.2018.

Evaluation of Bleeding Risk With Procedure

Bleeding Risk Category	Surgery or Procedure (abbreviated list)
Very high	• Neurosurgical procedure • Urologic surgery • Cardiac surgery
High	• Renal or hepatic biopsy • Major orthopedic surgery • Head and neck cancer • Major intra-abdominal surgery
Low	• Arthroscopy • Bronchoscopy • Removal of central venous catheter
Very low	• Minor dermatologic procedure • Cataract removal

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

Minimizing the Risk of VTE: Prophylaxis

- Issue: Risk of VTE
  - The duration of hospitalization may be shorter than the duration of VTE prophylaxis evaluated in clinical trial
  - VTE events may occur post hospitalization
- Strategies: Extend prophylaxis
  - LMWH
  - Oral Factor Xa inhibitors

Betrixaban

- APEX (Acute Medically Ill VTE Prevention with Extended Duration Betrixaban)

Cohort	Treatment	Efficacy * (%)	Major Bleeding (%)	Major and CRBM (%)
1	Betrixaban (n= 2311) Enoxaparin + placebo (n=2310)	6.9 8.5	0.6 0.7	3.1 1.9
2	Betrixaban (n=3402) Enoxaparin + placebo (n=3387)	5.6 7.1	0.7 0.6	3.2 1.7
3	Betrixaban (n=3716) Enoxaparin + placebo (n=3716)	5.3 7.0	0.7 0.6	3.1 1.6

*Efficacy included symptomatic DVT, asymptomatic proximal DVT, symptomatic PE, fatal PE/VTE-related death

Cohen AT, et al. *N Engl J Med* 2016;375:534

Heparin-Induced Thrombocytopenia (HIT)

Characterized

- ↓ platelet count of > 50% from baseline prior to heparin
- Hypercoagulability
- 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
- Consider 4 extremity duplex US to identify subclinical DVT

Greinacher A. *N Engl J Med* 2015;373:252-61.

HIT Pre-Test Probability Score Assessment

Suspicion of HIT based on the 4 T's:

- Thrombocytopenia (0 → 2)
- Timing of onset of platelet fall (days of heparin therapy) (0 → 2)
- Thrombosis or other sequelae (0 → 2)
- Other causes of platelet fall (0 → 2)

Total HIT Pre-test Probability Score

- Low probability (0 → 3)
- Moderate (4 or 5)
- High (6 → 8)

Heparin-Induced Thrombocytopenia

Treatment

- Discontinue all heparin
- Start or continue DTI or fondaparinux
  - Discontinue after at least 5 -7 days and when INR in target range
- Consider starting warfarin when platelets return to baseline (> 150K)
  - NOTE: avoid warfarin with acute HIT
- Duration of treatment:
  - HIT without thrombosis: minimum of 4 weeks (if no serious bleeding)
  - HIT with thrombosis: minimum of 4 months as indicated for thrombotic event

Considerations for Choice of Anticoagulation in the Individual With Cancer-Associated Thrombosis 2018

Evidence

- Efficacy (prevention of VTE)
- Bleeding complications

Patient Considerations

- Cancer (type, status, treatment plan)
- Organ function (e.g., kidney)
- Drug interactions
- Ability to neutralize
- Convenience
- Cost

Direct Oral Anticoagulation in Cancer-Associated Thrombosis

Benefit

- Oral administration
- Low risk of major bleeding
- Less drug-drug interactions compared with VKA

Concerns

- Cost
- Use in patients with active GI bleeding
- Use in patients with “extremes of weight” (50 kg or > 150 kg)

VKA = vitamin K antagonists

SMARTIE

This has been a SMARTIE presentation.

SMARTIE participants, you can now go to smartie2018.com or visit the SMARTIE booth to answer the post-session questions for this presentation.

If you would like more information about this program, please ask a conference staff member or visit the SMARTIE booth.