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THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

Venous Thromboembolism in Lymphoma: Risk Stratification, Prophylaxis, and Treatment

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Disclosure

- I have no relevant financial disclosures
- I am an employee of the University of Chicago
- I will be discussing off-label uses of medications
- I serve on an ABIM Task Force membership
  - ABIM exam content is confidential and will not be presented
  - No ABIM questions will be disclosed or discussed in this presentation
  - Any questions I created for this talk will not be used for ABIM exams
  - My talk is unrelated to ABIM educational products

Objectives

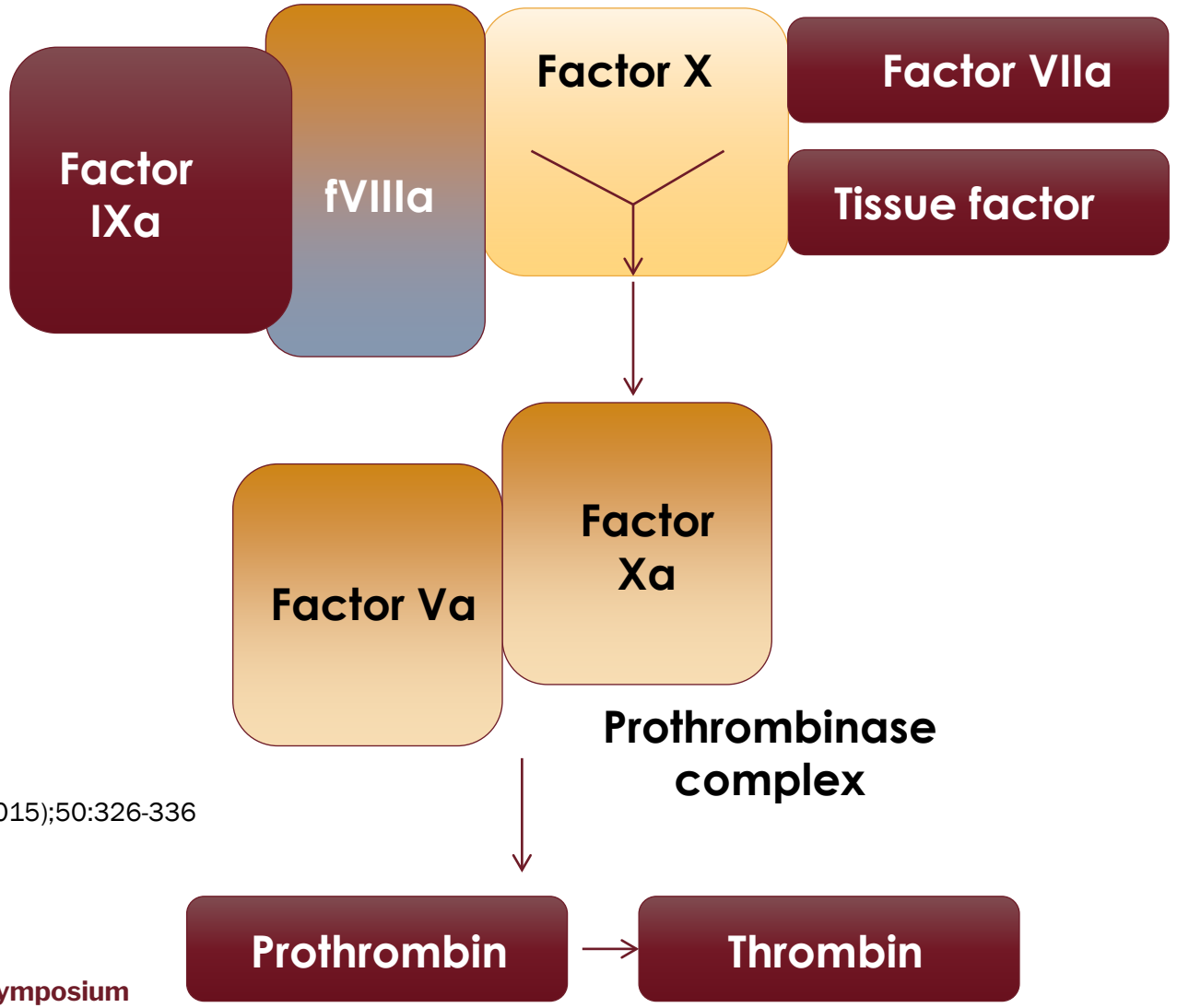
- Review anticoagulants and their targets
- Discuss general VTE management approaches
- Introduce VTE risk stratification scoring systems for cancer patients
- Determine when to provide VTE prophylaxis for lymphoma and cancer patients
- Discuss VTE treatment for lymphoma and cancer patients

Hemostatic balance is the goal of anti-thrombotic therapy

Hemostasis= physiologic coagulation

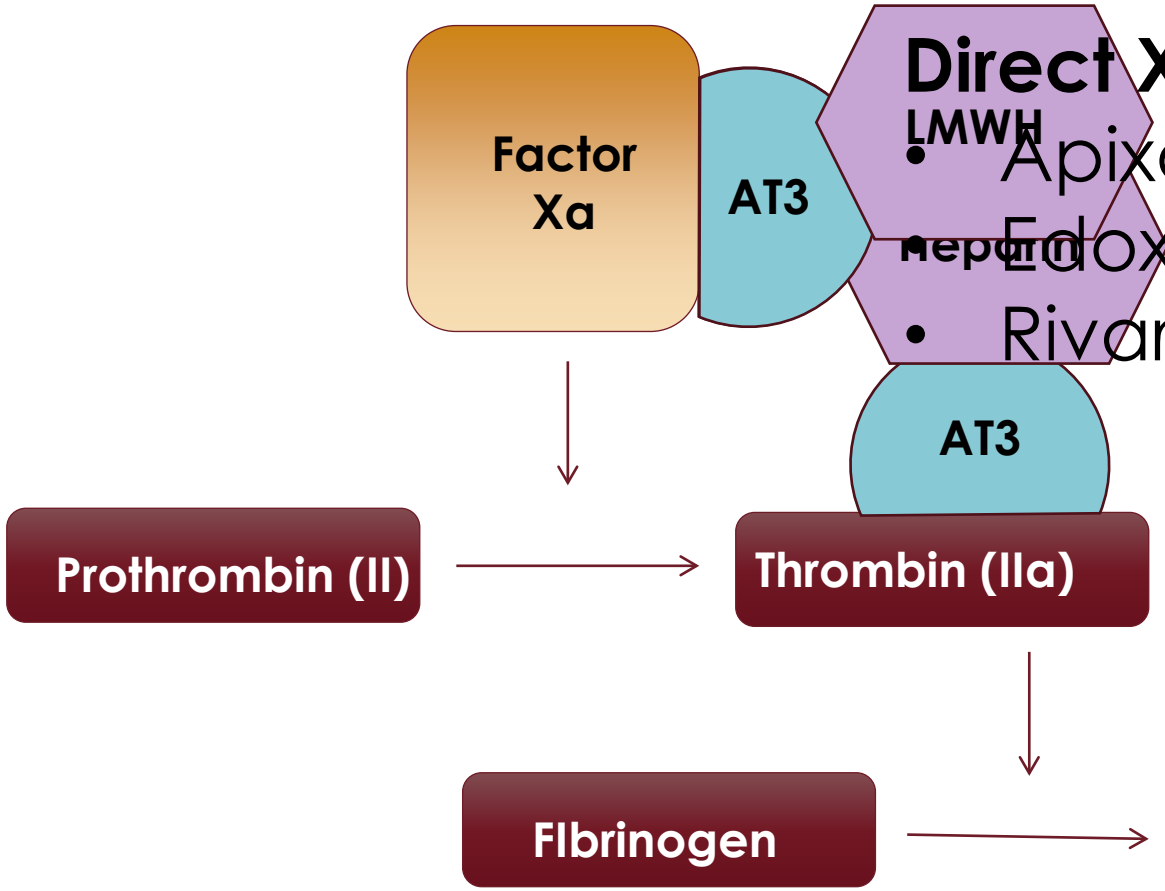
Bleeding **Thrombosis**

Hemostasis requires activation of the clotting cascade



Adapted from Smith SA et al.Crit Rev Biochem Mol Biol (2015);50:326-336

Anticoagulants target key clotting factors



Direct Xa Inhibitors

- Apixaban
- Edoxaban
- Rivaroxaban

Warfarin decreases

- **Factor II**
- **Factor VII**
- **Factor IX**
- **Factor X**

Direct Thrombin Inhibitors

- Dabigatran (PO)
- Argatroban (IV)
- Bivalirudin (IV)

Key trials of direct oral anticoagulants (non-cancer patients)

Dabigatran

RE-COVER (NEJM 2009)
RE-COVER II (Circulation 2014)

Rivaroxaban

EINSTEIN-DVT (NEJM 2010)
EINSTINE- PE (NEJM 2012)
EINSTEIN-CHOICE (NEJM 2017)

Apixaban

AMPLIFY (NEJM 2013)
AMPLIFY-EXT (NEJM 2013)

Edoxaban

HOKASAI-VTE (NEJM 2013)

Direct oral anticoagulants are safe and effective

- **DOACs were non-inferior to warfarin for efficacy**
- **DOACs have similar to less bleeding than warfarin**
  - Dabigatran has similar major bleeding
  - Rivaroxaban had less CNS bleeding
  - Apixaban had less overall bleeding
- **DOACs are approved for VTE treatment**
  - Favored over warfarin if CrCl and liver ok
  - Renal dysfunction impacts choices
  - Cost and insurance issues
  - Patient concern over short follow-up of data

Shared decision making for non-cancer VTE patients

- Warfarin
  - Cost
  - Experience
  - Once daily dosing but must bridge
  - Can use with renal/liver dysfunction
  - Able to monitor
- Dabigatran
  - Approved and available reversal agent (Idarucizumab)
  - No need to monitor but should bridge
- Rivaroxaban
  - Once daily dosing after 3 weeks
  - Low dose extension data
  - No need to monitor
  - Approved reversing agent andexanet
- Apixaban
  - Decreased bleeding risk for all groups
  - No need to monitor
  - Low dose extension data
  - Approved reversing agent andexanet

Duration of therapy depends on associated risk factors

- Surgery
- Pregnancy/estrogen
- Long plane flights > 8 (or 6? Or 4?) hours
- Prolonged immobility
- Fractures
- Medications (ex: lenalidomide)
- Cancer
- MPD/Jak2 mutation
- PNH
- Antiphospholipid antibody syndrome

Identifying thrombotic risk factors associated with cancers

- **Assess thrombotic risk for individual cancer patients**
  - Very high risk tumors: gastric and pancreatic cancer
  - Lymphoma is a high risk malignancy

- **Determine when cancer patients should receive VTE prophylaxis**
  - ➢Outpatients
  - Inpatients
  - Immunomodulatory drugs

- **Choose appropriate anticoagulants for cancer associated VTE**

Khorana Risk Score for outpatients

- Prospective observational study of 2701 cancer outpatients
- Risk model validated in an independent cohort of 1365 patients
- Five predictive variables assigned point values

Factor	Points assigned
Site of cancer	2 (very high risk) or 1 (high risk)
Platelet > 350 x $10E^9$/L	1
Hemoglobin < 10 g/mL or ESA use	1
WBC > 11 x 10^9/L	1
BMI > 35 kg/m^2	1

Low risk	High risk	Very high risk
Breast	Lymphoma	Gastric
Colorectal	Lung	Pancreas
Head and neck	Gynecologic	
	Bladder	
	GU excluding prostate	

Khorana A et al. Blood (2008); 111 (10); 4902-4907

Rates of VTE by Khorana Socre

Development of Khorana risk score[1]

Risk category	Rate of VTE (derivation)	Rate of VTE (validation)
Low risk (0)	0.8%	0.3%
Intermediate risk (1-2)	1.8%	2%
High risk (≥3)	7.1%	6.7%

VTE risk of patients on chemotherapy[2]

Risk category	Rate of VTE at 6 months
0	1.5%
1	3.8%
2	9.6%
3	17.7%

[1]Khorana A et al. Blood (2008); 111 (10); 4902-4907
[2]Ay C et al. Blood (2010); 116 (24); 5377-5382

Bleeding event definitions

- **Major bleeding event-** acute clinically overt event and
  - Hgb drop ≥ 2g/dL
  - Transfusion of ≥ 2 units PRBC
  - Bleeding into a critical site or organ or join
  - Fatal bleeding
- **Clinically relevant non- major bleeding event**
  - Any bleeding affecting hemodynamics
  - Any bleeding leading to hospitalization
  - Subcutaneous hematoma larger than 25 cm^2 (>100 cm^2 if traumatic)
  - Intramuscular hematoma without compartment syndrome
  - Epistaxis lasting > 5 min, repetitive, or requires intervention
  - Macroscopic hematuria that was spontaneous or lasted >24 hours after procedure
  - Macroscopic GI bleeding (includes rectal bleeding if more than spots on toilet paper)
  - Hemoptysis (more than a few speckles in sputum and unrelated to PE)
  - Any bleeding with clinical consequences (need for medical intervention, need for unscheduled physician contact including telephone call, temporary cessation of study drug, or associated with pain or impairment of ADLs)
- **Minor bleeding events- neither MB or CRNMB**

Agnelli G etl al.Apixaban for extended treatment of VTE.NEJM (2013); 368:699-708

Efficacy of prophylaxis for cancer patients undergoing chemotherapy

AVERT[1]

	Apixaban	Placebo	P value
VTE (%)	4.2	10.2	<0.001
DVT	2.4	4.4	
PE	1.7	5.8	
Major bleeding	3.5	1.8	0.046
CRNB	7.3	5.5	

CASSINI[2]

	Rivaroxaban	Placebo	HR
Primary efficacy composite	6.0	8.8	0.66 (0.4-1.09)
Symptomatic event	3.6	4.5	
Asymptomatic event	2.1	4.3	
VTE related death	0.2	0.7	
Major bleeding	2.0	1.0	1.96 (0.59-6.49)
CRNB	2.7	2.0	1.34 (0.75-3.17)

[1]Carrier M et al. N Eng J Med (2019); 380(8):711-719.
[2]Khorana AA et al. N Engl J Med (2019); 380(8):720-728
2019 ASCO Guidelines (Key NS et al, J Clin Oncol (2020); 38(5):496

ASH 2021 Recommendations of VTE prophylaxis[1]

Scenario	Recommendations
Hospitalized medical patients with cancer	• Pharmacologic prophylaxis (LWMH rather than UFH) • Discontinue at discharge
Patients with cancer undergoing surgery	• Mechanical prophylaxis if bleeding risk is high • Otherwise mechanical and pharmacologic prophylaxis LMWH or fondaparinux rather than UFH • No recommendations on use of VKA or DOACs • For major abdominal/pelvic surgery continue after discharge
Primary prophylaxis in cancer patients receiving chemotherapy	• Low risk of thrombosis: no prophylaxis • Intermediate risk of thrombosis: DOAC but not parenteral • High risk of thrombosis: DOAC but not parenteral
Primary prophylaxis for central lines	• No parenteral or oral prophylaxis

[1]Lyman GH et al. ASH 2021 Guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv (2021).

ThroLy risk model for lymphoma patients

	Score
Previous VTE/MI/CVA	2
ECOG 2-4/reduced mobility	1
BMI > 30 kg/m^2	2
Extranodal disease	1
Mediastinal disease	2
ANC < 1 x 10^9/L	1
Hemoglobin < 10 gm/dL	1

Risk category	Points
Low risk	0-1
Intermediate risk	2-3
High risk	>3

Antic D et al.Am J Hematol (2016); 91(10):1014-1019

ThroLy risk model applied to DLBCL

	VTE (%)	P value
ThroLy low risk	8.4	0.014
ThroLy Intermediate risk	12.4	
ThroLy High risk	22.3	
Modified ThroLy low risk (<3)	10.1	0.038
Modified ThroLy high risk (≥3)	17.2	

Abdel-Razeq et al.Clin Appl Thromb Hemost (2021); 27:1-6.

VTE Prophylaxis Summary

- Cancer is strong pro-thrombotic risk factor
- Consider VTE prophylaxis for cancer patients hospitalized for acute medical illnesses
- Use post-operative VTE prophylaxis for patients undergoing surgery
  - Till discharge or up to 7-10 days
  - Consider 4 weeks for abdominal and pelvic surgeries
- Consider VTE prophylaxis for Khorana Score $\geq$2 patient undergoing chemotherapy
- The Khorana risk score is less able to identify VTE risk groups in lymphoma patients
- Lymphoma specific VTE risk scores, such as ThroLY, have been developed
- It is unclear how best to use VTE risk scores for patients with lymphoma

Treatment of patients with cancer associated VTE

Clinical questions to answer when evaluating patients

1. Where are the tumor masses located?
   - Anatomic provoking factors
   - Anticoagulant bleeding risks
2. What is the bleeding risk of the patient?
3. Is the cancer curable (ex: lymphoma)?
4. Does the patient have adequate renal and liver function?
5. Is the patient taking medications that interact with anticoagulants?

Low molecular weight heparin is superior to warfarin for VTE treatment

CLOT Trial

	Dalteparin	Warfarin	P value
DVT	4.2%	11%	
Non fatal PE	2.4%	2.7%	
Fatal PE	1.5%	2.1%	
Any VTE	8.1%	15.9%	0.002
Major bleeding	6%	4%	0.27
Any bleeding	14%	19%	0.09

Lee AYY eta l. N Engl J Med (2003); 349: 146-153.

HOKUSAI VTE Cancer (Edoxaban vs Dalteparin)

	Edoxaban	Dalteparin
Recurrent VTE or major bleed	**12.8 %**	**13.5 % (P=0.005 non-inf)**
Recurrent VTE	7.9	11.3 (P >0.05)
Recurrent DVT	3.6	6.7
Recurrent PE	5.2	5.3
CRNMB	14.6	11.1
Major bleed and CRNMB	**18.6**	**13.9 (1.03-1.89)**
Death from any cause	39.5	36.6
EFS	55.0	56.5

	Edoxaban	Dalteparin
VTE + MB + CRNMB	26.5	25.2

Raskob GE et al. N Engl J Med (2018); 378(7): 615

ADAM VTE: Apixaban versus Dalteparin

	Apixaban	Dalteparin	P value
Major bleed (primary)	0	1.4%	0.138
CRNMB (secondary)	6.2	4.2	
MB+ CRNMB	6.2%	6.3%	
VTE (secondary)	0.7%	6.3%	0.0281
Arterial thrombosis	0.7%	0.7%	
Mortality	16%	11%	

McBane et al. J Thromb Haemost (2020); 18(2):411-421.

Caravaggio: Apixaban versus Dalteparin

Primary outcomes

	Apixaban	Dalteparin	P value
Recurrent VTE	5.6%	7.9%	<0.001 noninferiority 0.09 for superiority
Recurrent DVT	2.3%	2.6%	
Recurrent PE	3.3%	5.5%	
Fatal PE	0.7%	0.5%	
Major bleeding	3.8%	4.0%	0.60
Major GI bleeding	1.9%	1.7%	
Major non GI bleeding	1.9%	2.2%	

Agneli G et al.N Engl J Med; 382(17):1599.

Caravaggio: Apixaban versus Dalteparin

Secondary outcomes

	Apixaban	Dalteparin	HR
Recurrent VTE or major bleeding (composite)	8.9%	11.4%	0.70 (0.45-1.07)
CRNMB	9.0%	6.0%	1.42 (0.88-2.30)
Major or CRNMB	12.2%	9.7%	1.16 (0.77-1.75)
Death from any cause	23.4%	26.4%	0.82 (0.62-1.09)
Event free survival[1]	73.3%	68.6%)	1.36 (1.05-1.76)

[1]Event free survival = absence of recurrent VTE, major bleed, or death

Agneli G et al.N Engl J Med; 382(17):1599.

SELECT-D pilot study: Rivaroxaban versus Dalteparin

	Rivaroxaban	Dalteparin
Recurrent VTE	3.9%	8.9%
Lower extremity DVT	1.5%	3.4%
PE	2.0%	4.4%
Other	1.0%	1.0%
Major bleeding	5.4%	3.0%
CRNMB	12.3%	3.4%

Young AM et al.J Clin Oncol (2018);36(20):2017-2023

DOACs compare favorably to dalteparin

- DOACs are as effective to more effective than dalteparin
- DOAC bleeding risks are similar to increased compared to daleparin
- Increased DOAC associated bleeding is seen with GI and GU malignancies
- DOACs are useful when patients prefer oral medications
- Important to note that
  - Azole antifungals interact metabolically with DOACs
  - DOACs are hepatically and renally cleared
  - DOAC absorption occurs in stomach and proximal small bowel

Management of DOAC bleeding complications

Minor bleeding	Moderate bleeding	Severe bleeding
Consider d/c of DOAC	Stop DOAC	Stop DOAC
Local measures	Local measures	Local measures
	IVF	IVF
	PRBC support PRN	PRBC support
		ICU monitoring
		Consider reversal

Anticoagulant	Reversal options
Dabigatran	Charcoal Dialysis 4F PCC **Idarucizumab**
Apixaban and rivaroxaban	4F PCC **Andexanet**

Adapted and modified from Deborah M. Siegal et al. Blood 2014;123:1152-1158

Matching reversing agents to specific DOACs

- **Andexanet**[1,2]
  - Recombinant modified and inactivated factor Xa
  - Binds to direct oral anti-Xa inhibitors
  - Approved for reversal of life threatening bleeds due to apixaban and rivaroxaban
  - Off protocol for other anti-Xa inhibitors

- **Idarucizumab**[3]
  - Monoclonal fragment which binds dabigatran
  - Binding is 350x that of thrombin
  - Approved for life threatening bleeding, bleeding into critical organ, reversal prior to emergent procedures

[1]ANNEXA-4 Connolly SJ et al.N Engl J Med (2016);375:1131

[2]ANNEXA-4 Connolly Sj et al.N Engl J Med (2019);380:1326

[3]RE-VERSE AD: Pollack CV et al.N Engl J Med (2015); 373: 511-52

Summary

- Cancer is a known thrombotic risk factor
- Lymphoma is considered a high risk malignancy
- The Khorana risk score can identify patients at higher VTE risk associated with chemotherapy
- Several VTE risk scores have been developed for lymphoma (ex: ThroLy)
- Currently unclear how to apply VTE risk scores to lymphoma patients
- DOACs can be considered for prophylaxis of Khorana risk $\geq$ 2 patients
- DOACs and LMWH are preferred over warfarin for cancer associated VTE treatment
- DOACs are preferred to LMWH for treatment due to convenience
- Lymphoma is not necessarily an indefinite thrombotic risk factor (curable)

Audience response question

A 65 year old man presents for evaluation of diffuse large B cell lymphoma. Workup reveals stage 3 disease without bulky mediastinal involvement. ECOG = 1. Laboratory evaluation demonstrates WBC 8.9 x 10^9/L, HGB 9.5 g/mL, and PLT 325 x 10^9/L. His CrCL is 73 mL/min. His BMI is 27 kg/m^2. A portacath is placed and he is scheduled to initiate therapy with R-CHOP. He is referred to you for VTE prophylaxis recommendations. You estimate that his bleeding risk is low. Based on his Khorana score you recommend

(A) Observation
(B) Apixaban 2.5mg BID
(C) Rivaroxaban 10mg daily
(D) Enoxaparin 40mg sc daily
(E) Warfarin INR goal 2-3