

Venous Thromboembolism: An Ounce of Prevention is Worth a Pound of Cure

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Objectives

- Review the importance of VTE prevention
- Discuss alternative for VTE prophylaxis
- Overview the management of VTE

Case Presentation – Part 1

- A 62 year-old man is admitted to the hospital with fever and pneumonia
- His past medical history is only notable for hypertension
- He has no known drug allergies
- Only medication on admission is atenolol
- Family history is unremarkable
- He does not smoke or drink alcohol

Case Presentation – Part 1

- Physical examination T 101.5°F, HR 90, BP 130/60, O₂ sat 93%; decreased breath sounds at the right base
- Laboratory studies reveal WBC 15,400; the remainder of the CBC, coags, and chemistries are within normal limits
- A chest radiograph reveals lobar pneumonia in the right lower lobe

Case Presentation – Part 1

- After cultures of sputum, blood, and urine are obtained he is started on ceftriaxone and doxycycline
- His atenolol is continued

Case Presentation – Part 1

- On the morning of hospital day 3 he is afebrile and feeling better overall
- A decision is made to convert the antibiotic regimen to oral moxifloxacin and discharge the patient the next day

Case Presentation – Part 1

- In the late morning of hospital day 3 he complains of left calf pain and swelling
- An ultrasound of the lower extremities is obtained and reveals thrombus extending into the superficial femoral vein (part of the deep venous system)
- Diagnosis: deep venous thrombosis

Venous Thromboembolism (VTE)

- Rate in acutely ill medical patients estimated to be 5 to 15%
- Cause of 5 to 10% of deaths in hospitalized patients
 - Often cited as the most common potentially preventable cause of death

Use of Prophylaxis

- ENDORSE study is a multinational study examining the use of VTE prophylaxis in the acute hospital care setting
- American College of Chest Physicians (ACCP) Guidelines used to determine who should have received prophylaxis
- N=68,183

Cohen AT et al. Lancet 2008;371:387-94

Use of Prophylaxis

Patient Type	<u>Prophylaxis</u> Total Patients	Percent given Prophylaxis
Surgical	<u>11,613</u> 19,842	58.5%
Medical	<u>6,119</u> 15,487	39.5%

Cohen AT et al. Lancet 2008;371:387-94

Effect of Prophylaxis on VTE

- Several large studies indicate that appropriate prophylaxis can reduce the incidence of VTE by about one-half
 - Mismetti P et al. *Thromb Haemost* 2000;83:14-19
- One study in the MICU setting showed appropriate prophylaxis was associated with a 55% reduction in the odds of death
 - Lentine KL et al. *Am J Med* 2005;118:1373-1380

Guidelines for Risk Assessment

- Every patient admitted to the hospital should be assessed for the risk of venous thromboembolism
- Patients who are judged to be at sufficiently high risk should be treated with mechanical or pharmacologic prophylaxis

Virchow's Triad

- Stasis
- Vessel Injury
- Hypercoagulability

Virchow's Triad – Stasis, Vessel Injury, Hypercoagulability

- Surgery, trauma, immobility, paresis
- Increasing age
- Pregnancy and postpartum
- Heart or respiratory failure
- Obesity

Virchow's Triad – Stasis, Vessel Injury, Hypercoagulability

- Previous deep vein thrombosis
- Smoking
- Varicose veins
- Central venous catheterization

Virchow's Triad – Stasis, Vessel Injury, Hypercoagulability

- Increasing age
- Acute medical illness
- Inherited or acquired thrombophilia
- Malignancy or cancer therapy
- Inflammatory bowel disease
- Nephrotic syndrome
- Estrogen therapy

ACCP Recommendations for VTE Prophylaxis – Medical Patients

Acutely ill medical patients with CHF, severe respiratory disease, or who are confined to bed and have additional risk factors such as active cancer, prior VTE, sepsis, acute neurologic disease should receive pharmacologic prophylaxis or if anticoagulants contraindicated should receive prophylaxis with GCS or IPC

NICS Venous Thromboembolism Risk Assessment Form Version 1 2007

1. Treating doctor to determine highest medical or surgical risk category
 2. Check contraindications, tick recommended prophylaxis
 3. Record drugs and orders for GCS/IPC* in medication chart
 4. Print name, sign and date on completion

AFFIX PATIENT LABEL

Risk category	Medical risk factors	Tick	Recommended prophylaxis	Tick
HIGH	Ischaemic stroke		Low Dose Unfractionated Heparin or	
	History of DVT/PE			
	Decompensated heart failure		Low Molecular Weight Heparin OR	
	Active cancer			
	Acute on chronic lung disease		If heparin contraindicated Graduated Compression Stockings &/or Intermittent Pneumatic Compression	
	Acute on chronic inflammatory disease			
Age > 60 years Unless otherwise well and ambulant and no other risk factors		No prophylaxis recommended		
LOW	None of the above			
HIGH	Surgical risk factors	Tick	Recommended prophylaxis Low Molecular Weight Heparin or	
	Orthopaedic surgery of pelvis, hp or lower limb			
	Multiple trauma		Fondaparinux (orthopaedic cases only) AND	
	Major trauma			
	Major surgery* and age > 60 yrs		Graduated Compression Stockings &/or Intermittent Pneumatic Compression	
Major surgery and age 40-60 yrs with medical risk factors				
MODERATE	Major surgery and age 40-60 yrs without medical risk factors		Low Dose Unfractionated Heparin OR	
	Major surgery age 16-40 yrs with medical risk factors			
	Minor surgery and age > 60 yrs		Low Molecular Weight Heparin	
	Minor surgery and age 40-60 yrs with medical risk factors			
LOW	Major surgery and age 16-40 yrs without medical risk factors		Graduated Compression Stockings (optional)	
	Minor surgery and age 16-40 yrs with medical risk factors			
	Minor surgery and age 16-60 yrs without medical risk factors			
If contraindicated for chemoprophylaxis or mechanical prophylaxis, indicate reasons below:				
	Chemoprophylaxis contraindications	Tick	Mechanical prophylaxis contraindications	Tick
	Active bleeding		Severe peripheral disease	
	High risk of bleeding (e.g. Haemophilia, Thrombocytopenia, Active peptic ulcer)		Severe peripheral neuropathy	
	Adverse reaction to unfractionated heparin or low molecular weight heparin		Severe lower limb oedema	
	On therapeutic anticoagulation		Extreme leg deformity	
	Other		Recent skin graft	
			Severe dermatitis	
			Other	
If no prophylaxis required, indicate reason:				
If prophylaxis required, all drugs and orders for GCS/IPC* must be written on the Patient Medication Chart				
Doctor's Name (PRINT):			Position:	
Doctor's Signature:			Date:	

* GCS - graduated compression stockings /IPC - intermittent pneumatic compression. * Major surgery refers to any intra-abdominal surgery and all other operations >45 mins.

SAMPLE NICS Venous Thromboembolism Risk Assessment Form

All hospitals should have a form which assesses the risk of venous thromboembolism (VTE) in admitted patients and allows the treating doctor to come to a decision about the appropriate treatment for every patient admitted to hospital. The prophylaxis decision should include consideration of the patient's age, nature of the operative procedure or medical condition and the presence of identified risk factors. For each patient admitted, a decision about the type of prophylaxis required by the patient should be made and noted in the medical record. This should include 'nil required' where applicable. It is important that this sample risk assessment form above is adapted by each hospital in order to meet compliance with policies on venous thromboembolism prophylaxis in each hospital.

This sample risk assessment form was developed by the National Institute of Clinical Studies (NICS), an affiliate of the National Health and Medical Research Council (NHMRC), in collaboration with the VTE Prevention Advisory Group. It includes best practice thromboprophylaxis recommendations that are based on Prevention of Venous Thromboembolism: Best Practice Guidelines for Australia and New Zealand, 3rd Edition, August 2005, RCM Australia.

For more information on the NICS VTE Prevention Program, go to www.nics.gov.au and follow the links to "Program" and "Venous Thromboembolism Prevention". © Copyright NHMRC 2007 www.nhmrc.gov.au/nics

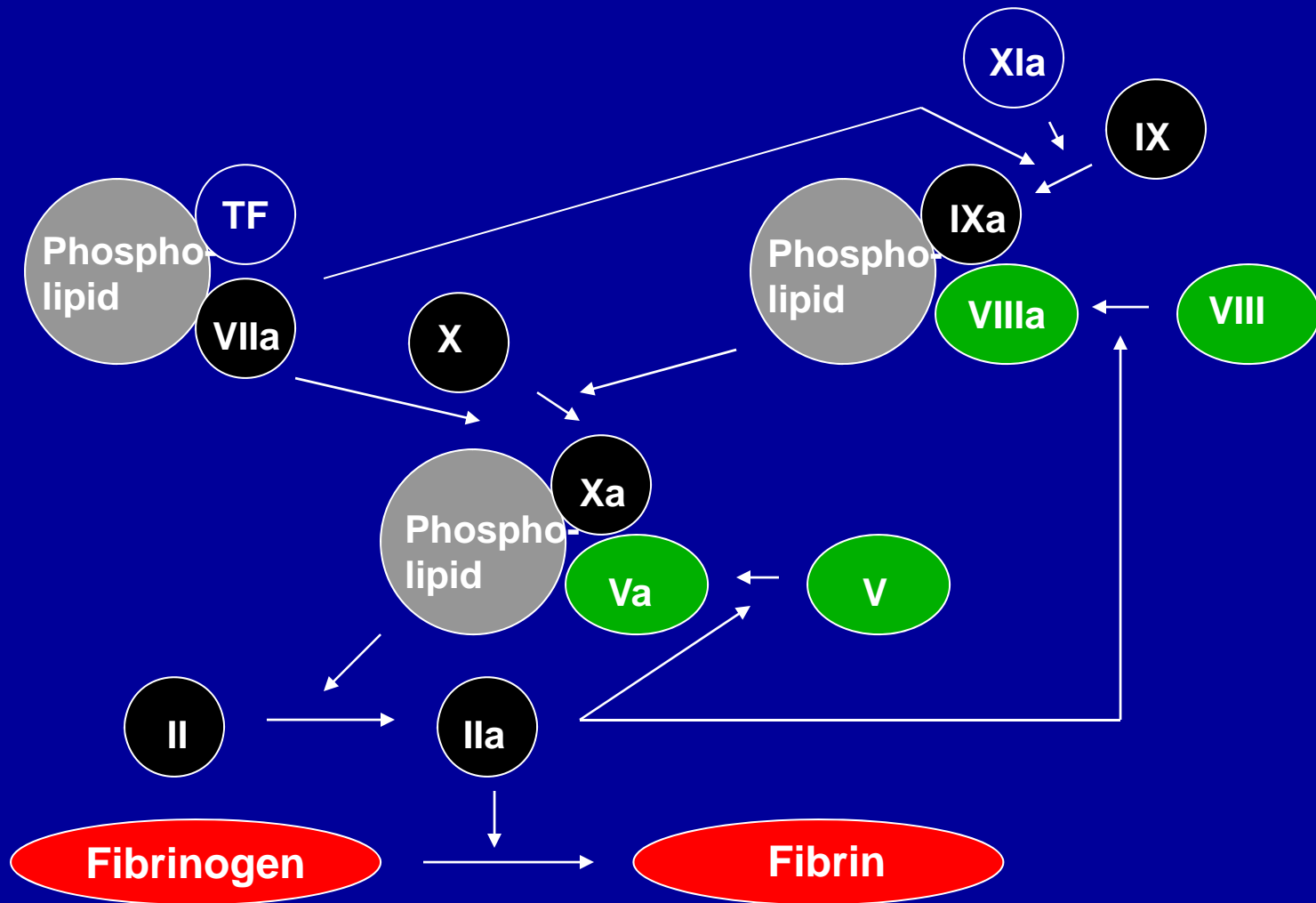
Prophylactic Strategies

- Graduated compression stockings (GCS)
- Intermittent pneumatic compression (IPC)
- Aspirin
- Vitamin K antagonists (warfarin)
- Unfractionated heparin (UFH)
- Low molecular weight heparins (LMWH)
- Fondaparinux

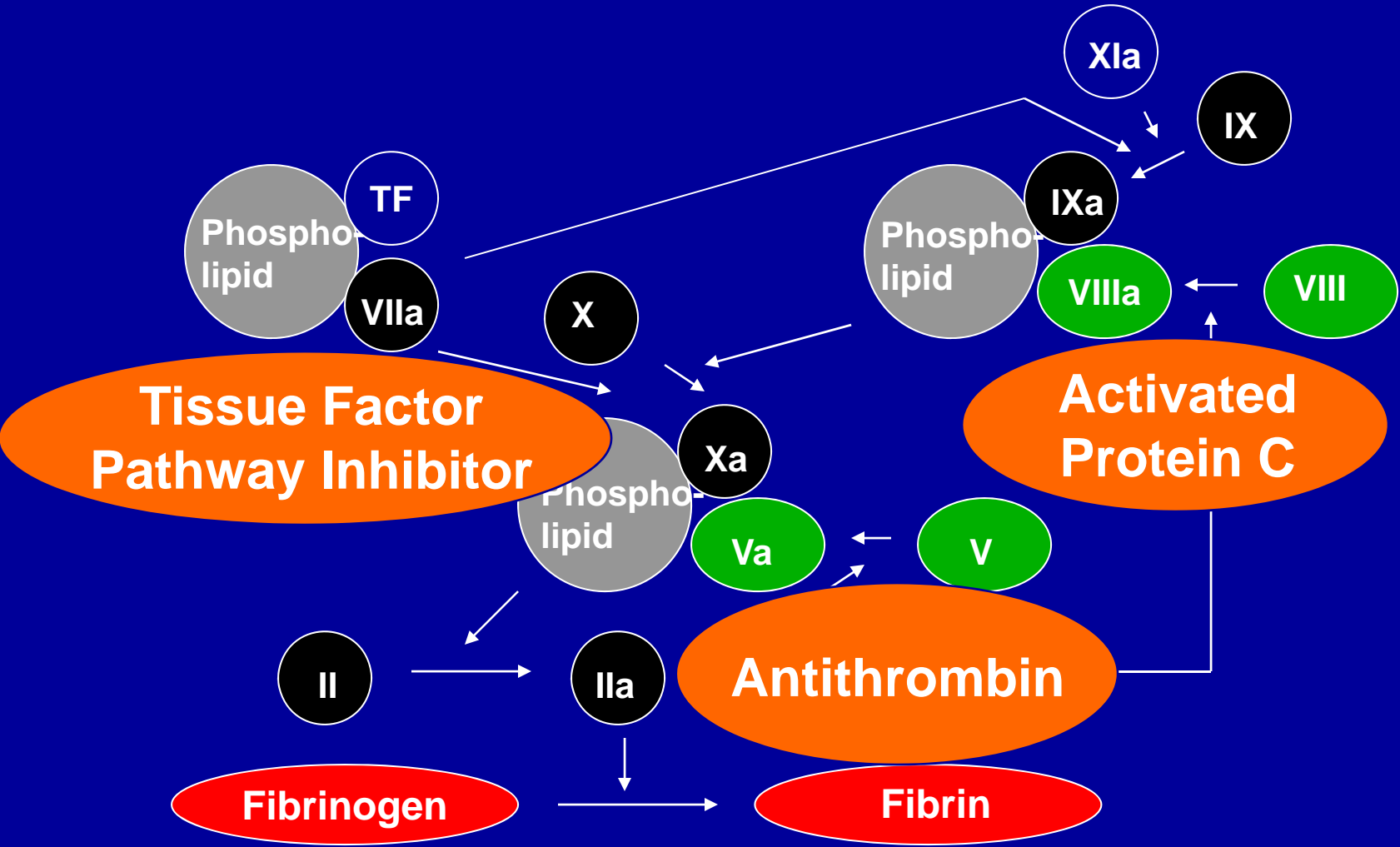
Pharmacologic Options for VTE Prophylaxis

Drug	Dose
Unfractionated heparin	5000 units sc q8 or 12h
LMWH Enoxaparin Dalteparin	40 mg sc once daily 5000 units sc once daily
Fondaparinux	2.5 mg sc once daily

The Coagulation Cascade



Natural Anticoagulant Pathways



Pharmacologic Anticoagulation

- Activate natural anticoagulants
 - Activators of antithrombin
- Inhibit pro-coagulants directly
 - Direct thrombin inhibitors
- Decrease the level of clotting factors
 - Vitamin K antagonists

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Activating Antithrombin

- Unfractionated heparin
- Low molecular weight heparin
- Fondaparinux

Unfractionated Heparin

- Glycosaminoglycan comprised of D-glucosamine and iduronic acid
- Molecular weight of 5,000 to 30,000
- Markedly increases the ability of antithrombin to inactivate thrombin (ternary complex) and factor Xa
- PTT commonly used for monitoring

Unfractionated Heparin

- Rapid onset of action
- Even with algorithms for dosing, titration required to achieve therapeutic levels
- Fully reversible
 - 1 mg protamine sulfate/100 units heparin
- Highest incidence of heparin - associated thrombocytopenia

Low Molecular Weight Heparin

- Prepared from unfractionated heparin by chemical or enzymatic depolymerization
- Molecular weight 1,000 to 10,000 provides reproducible absorption
- Less inhibition of thrombin relative to factor Xa, dependent on preparation
- Anti-factor Xa levels used for monitoring

Low Molecular Weight Heparins

- Relatively rapid onset of action (~2 hrs)
- Once or twice daily administration
- Partially reversible
 - 1 mg protamine sulfate/1 mg enoxaparin
- Superior to warfarin in setting of cancer
- Incidence of heparin-induced thrombocytopenia probably less than UFH

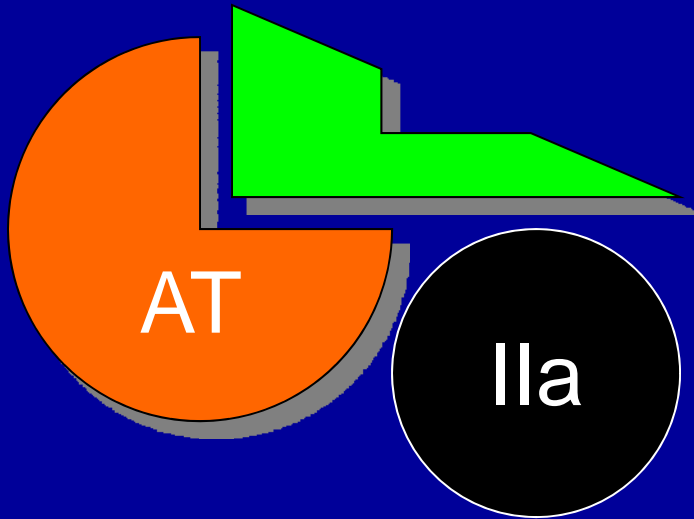
Fondaparinux

- Pentasaccharide similar to the antithrombin binding site of heparin
- Molecular weight of 1728
- Exclusive inhibition of factor Xa
- Relatively rapid onset of action (~2 hrs)
- Once daily administration

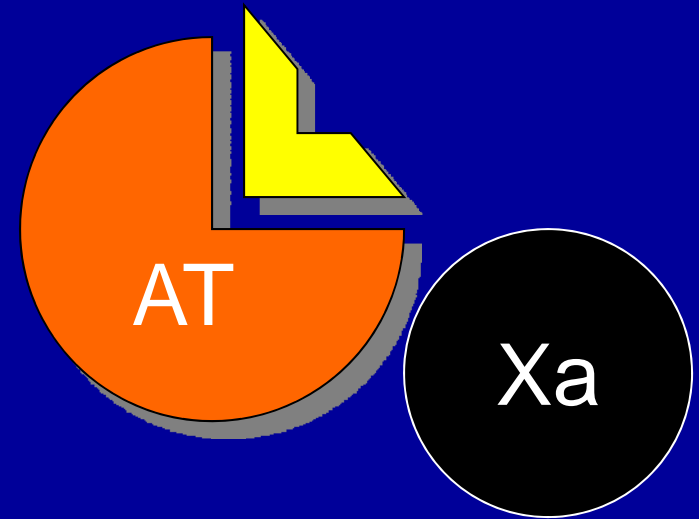
Fondaparinux

- Renal excretion
- Anti-factor Xa levels used for monitoring, if necessary
- Not reversible with protamine sulfate
- One case report of heparin-induced thrombocytopenia (controversial)
 - Warkentin TE, Maurer BT, Aster RH. N Engl J Med 2007;356:2653-5.

Mechanism of Action



Enhancement of AT activity for thrombin by UFH requires direct contact with thrombin



Enhancement of AT activity by fondaparinux for Xa is independent of contact with Xa

Case Presentation – Part 2

- In the afternoon of hospital day 3 he receives enoxaparin 120 mg sc and that evening he receives warfarin 10 mg p.o. (height is 178 cm, weight is 82 kg)
- He is discharged the next morning on moxifloxacin, atenolol, enoxaparin 120 mg daily and warfarin 5 mg daily with outpatient follow-up in 4 days

Case Presentation – Part 2

- When seen 4 days later in follow-up he notes that he has been compliant with his medications but now he seems to have more pain and swelling in his left leg
- An ultrasound is obtained and reveals extension of clot toward the inguinal region

Case Presentation – Part 2

- Laboratory studies obtained on day 5 of enoxaparin reveal platelets of $132,000/\mu\text{L}$
- On the day of hospital discharge the platelet count was $338,000/\mu\text{L}$
- Diagnosis: heparin-induced thrombocytopenia-thrombosis syndrome

Principles of Therapy of HIT

- Rapid discontinuation of heparin or LMWH once the diagnosis is suspected
 - Clinical suspicion outweighs laboratory data
- Institution of an effective anticoagulant that will not exacerbate thrombosis
- Transition to a regimen for extended duration anticoagulation as appropriate

HITTS is a Medical Emergency

- Heparin-induced thrombocytopenia-thrombosis syndrome is associated with loss of limbs and with loss of life
- Effective therapy should be instituted as soon as possible based upon clinical suspicion rather than laboratory testing

Warfarin and HIT

- Use of warfarin alone without a bridging agent rapidly drops the protein C anticoagulant level and is associated with venous limb gangrene and skin necrosis syndromes



Therapeutic Alternatives for HIT

- Direct thrombin inhibitors
- Use of fondaparinux is off-label and is currently controversial pending additional clinical trial data

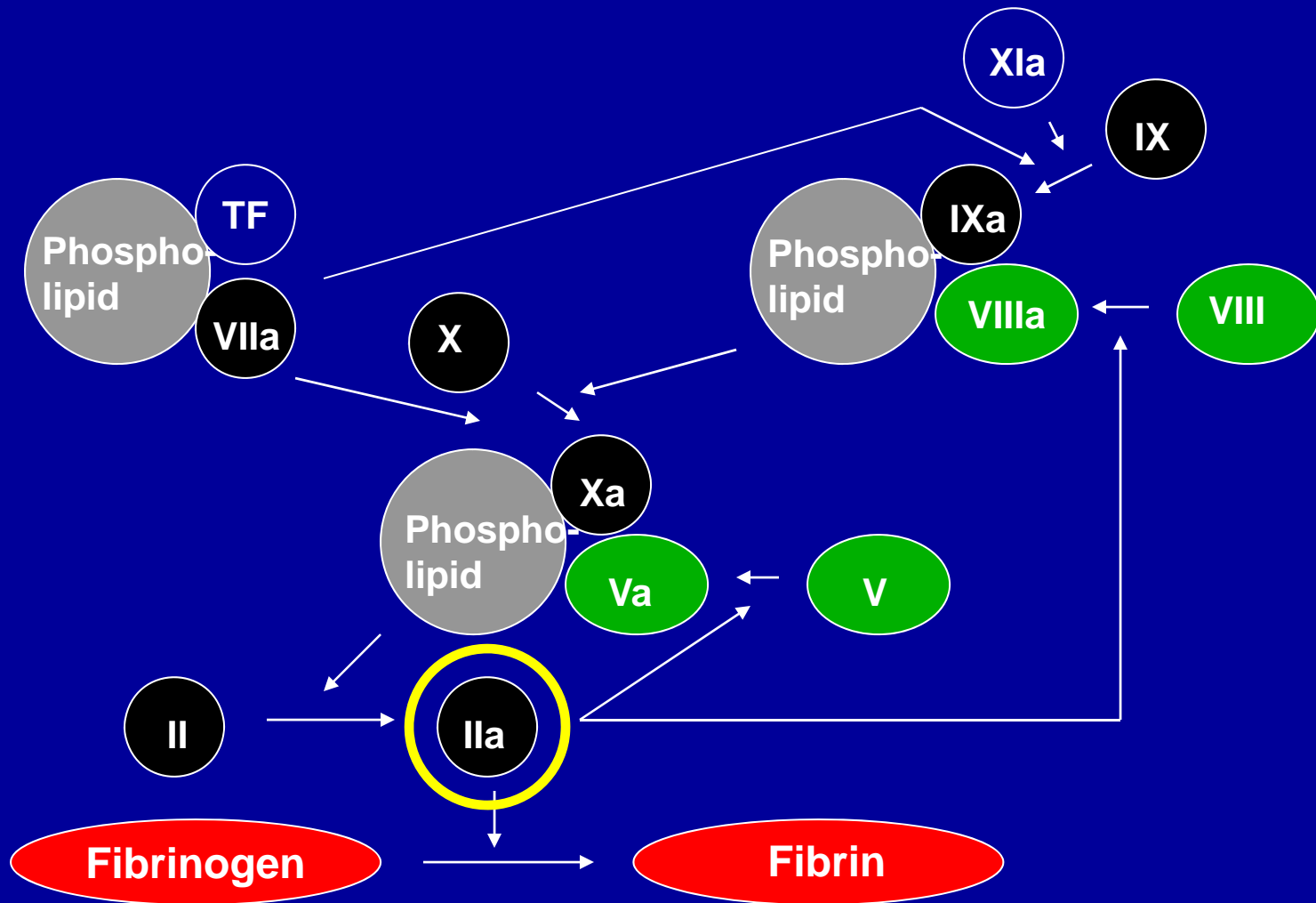
Pharmacologic Anticoagulation

- Activate natural anticoagulants
 - Activators of antithrombin
- Inhibit pro-coagulants directly
 - Direct thrombin inhibitors
- Decrease the level of clotting factors
 - Vitamin K antagonists

Inhibiting Clotting Factors Directly

- Lepirudin
- Bivalirudin
- Argatroban
- Novel agents in development

The Coagulation Cascade



Lepirudin

- Recombinant hirudin
- Direct thrombin inhibitor
- Renal clearance
- Half-life is 80 minutes with normal kidneys
- Administer by continuous infusion titrating PTT to 1.5 to 2.5 times baseline
- No reversal agent available

Bivalirudin

- Synthetic 20 amino acid peptide
- Direct thrombin inhibitor that is gradually itself inactivated by thrombin
- Clearance is by combination of renal mechanisms and proteolytic cleavage
- Half-life is 25 minutes with normal kidneys
- Labeled for use in patients with unstable angina undergoing angioplasty

Argatroban

- Small molecule (L-arginine-derivative)
- Direct thrombin inhibitor
- Hepatic clearance
- Half-life is 40 minutes with normal liver
- Administer by continuous infusion titrating PTT to 1.5 to 2.5 times baseline
- Causes notable increase in PT/INR
- No reversal agent available

Select Oral Anticoagulants Currently in Development

- Direct Thrombin Inhibitor
 - Dabigatran
- Direct Factor Xa Inhibitors
 - Rivaroxaban, Apixiban

Case Presentation – Part 3

- The patient is hospitalized and is anticoagulated with lepirudin
- Warfarin is held until the platelet count returns to baseline and is then restarted
- When the INR off of lepirudin is 2.3 the patient is discharged to home on warfarin 5 mg daily with graduated compression stockings

Case Presentation – Part 3

- He continues on warfarin 5 mg daily and regularly wears his compression stockings
- His leg pain and swelling gradually improve over the next two weeks and he resumes his usual activities
- Warfarin is continued for a total of three months and then discontinued
- One year later he is doing well

Pharmacologic Anticoagulation

- Activate natural anticoagulants
 - Activators of antithrombin
- Inhibit pro-coagulants directly
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- Decrease the level of clotting factors
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Decreasing Clotting Factors

- Vitamin K antagonists
 - Warfarin
 - Dicumarol and others (outside United States)

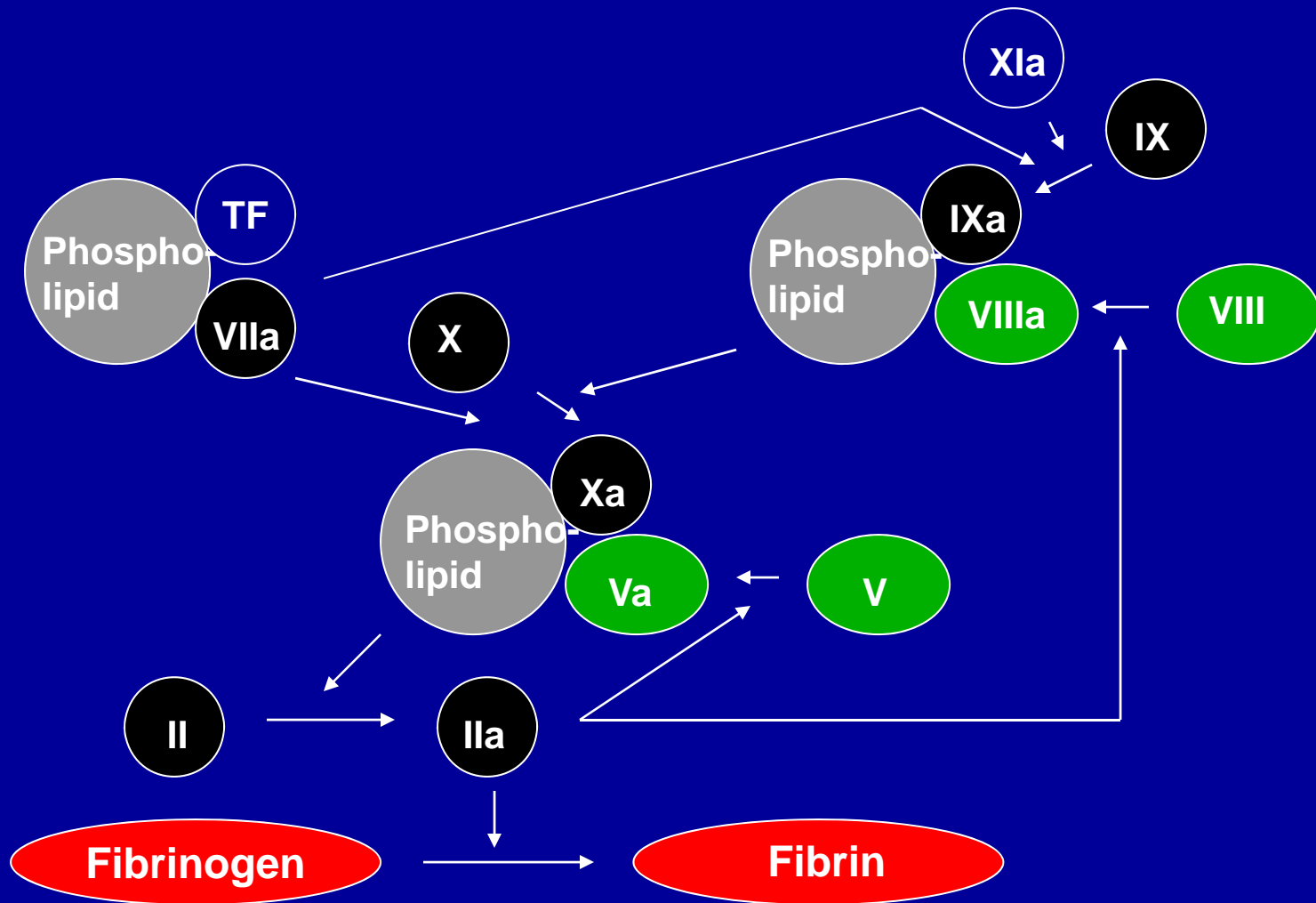
Warfarin

- Product of veterinary research on the etiology of hemorrhagic disease of cattle
- Karl Link and colleagues at the Wisconsin Alumni Research Foundation identified dicumarol as the responsible compound
- Subsequently developed as rodenticide and as a pharmaceutical for humans

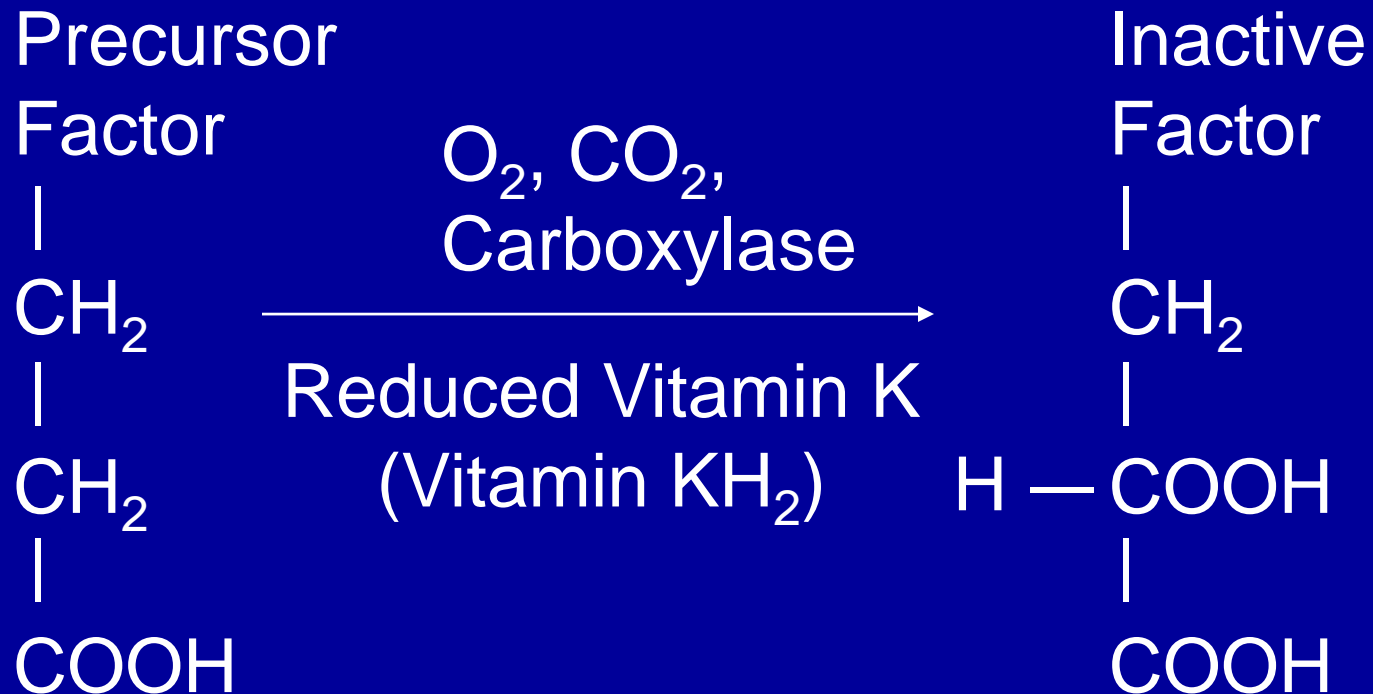
Role of Vitamin K

- Coagulation factors II, VII, IX, X, as well as Protein C and Protein S all require gamma-carboxylation for function
- Allows clotting proteins to bind calcium and coordinate with phospholipid surfaces upon which coagulation occurs

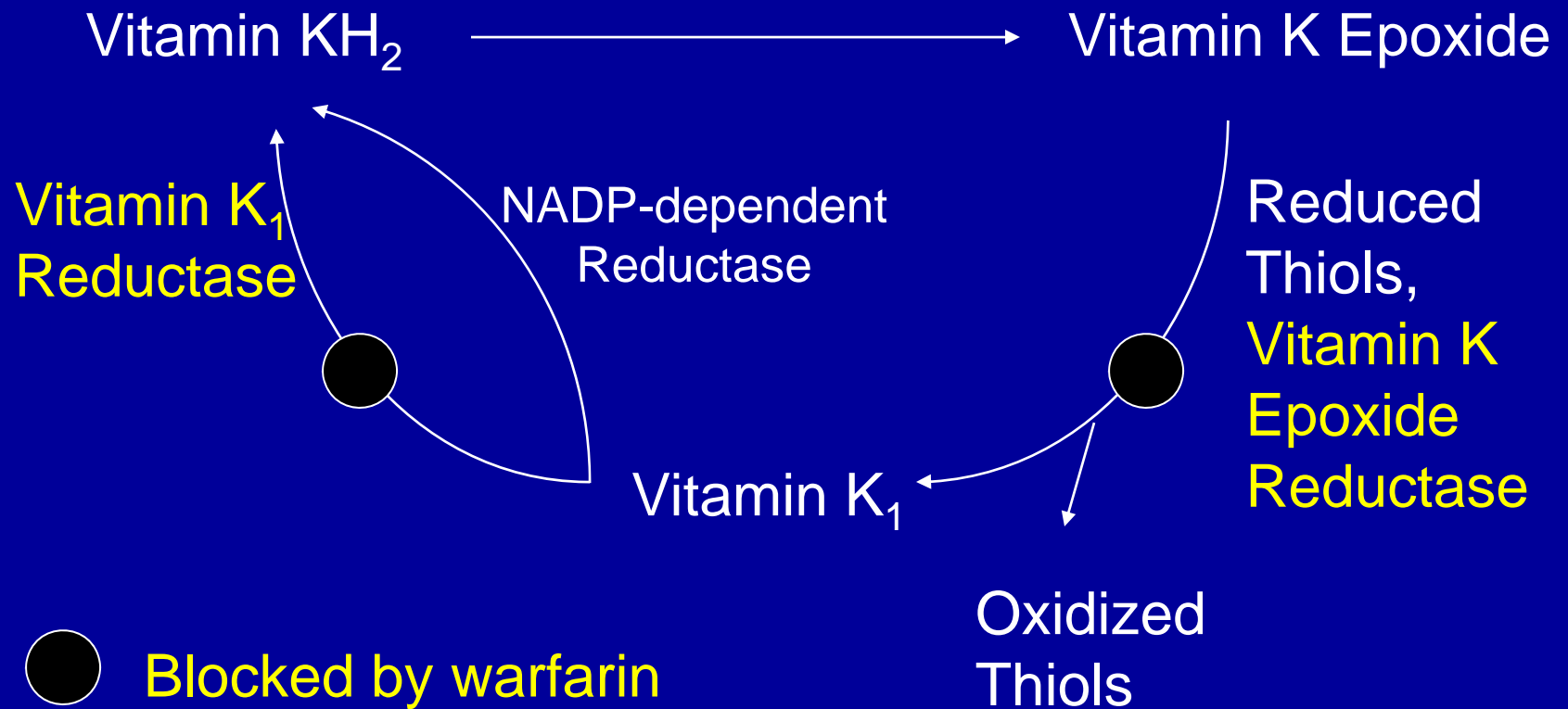
The Coagulation Cascade



Gamma-Carboxylation



Vitamin K



Half-Lives of Vitamin K-Dependent Coagulation Proteins

Protein	Half-Life (hours)
Factor II	72
Factor VII	4-6
Factor IX	24
Factor X	36
Protein C	8
Protein S	30

Initial Effect of Warfarin

- Factor VII and IX levels decrease rapidly, increasing the INR
- Antithrombotic effect is mainly due to decreased factors II and X
- Rationale for overlapping warfarin and another systemic anticoagulant for 4 to 5 days in the setting of thrombosis

Intensity of Anticoagulation

- In the absence of evidence based upon therapeutic response, the appropriate intensity of warfarin anticoagulation for all patients (including those with lupus anticoagulants/antiphospholipid abs) is an INR of 2 to 2.5
 - Segal JB, Streiff MB, Hofmann LV, et al. Ann Intern Med 2007;146:211-22.

Duration of Anticoagulation

- For patients with transient risk factors only 3 months of anticoagulation suffices
- Patients with unprovoked venous thromboembolism, repeat thrombosis, and/or inherited risk factors may benefit from extended duration anticoagulation
 - Kearon et al. N Engl J Med 2003;349:631-9
 - Ridker et al. N Engl J Med 2003;348:1425-34

Summary

- Every patient admitted to the hospital should receive appropriate prophylaxis against venous thromboembolism
- Outpatient management of venous thromboembolism is possible with appropriate follow-up

Summary

- Heparin-induced thrombocytopenia is primarily a clinical diagnosis and should be treated aggressively

NATF Programs

- ✧ Free NATF Membership
- ✧ eThrombosis: NATF's Online Journal
- ✧ eForum: NATF's Online Conversation
- ✧ NATF-Sponsored Medical Grand Rounds
- ✧ NATF Traveling Fellowship for Scientists and Health Professionals (MD, DO, PhD, PharmD, RPh, NP, RN, PA)
- ✧ Thrombosis Summit 2009, *September 26, 2009, Boston, MA*
- ✧ Proactive Thrombosis Prevention Forum, *April 10, 2009, Boston MA*

More Information at www.NATFonline.org

