



Anticoagulants





Anticoagulants

Did You Know?

That major bleeding occurs in about 6.5% of patients on anticoagulants..

That's 1 patient in 15 and commonly, GI Bleeding.

That 1% is fatal bleeding such as intracranial hemorrhage.

Anticoagulants

Did You Know?

Because of the narrow therapeutic window, anticoagulants such as warfarin and heparin frequently results in bleeding that can be **life threatening..**





Anticoagulants

Did You Know?

They are sometimes referred to as **blood thinners**; they **do not** in fact thin the blood.

These drugs will **not** dissolve clots that already have formed.

They permit the body's natural process, **fibrinolysis**, to work to break down previously formed clots.



Anticoagulants

Did You Know?

Coagulation will begin **instantaneously** once a blood vessel has been severed.

Anticoagulants

How are clots formed?



Anticoagulants- Platelets

When bleeding occurs, platelets releases thromboxane that activate the platelet and become **“sticky”**

These activated platelets begin adhering to the wall of the blood vessel at the site of bleeding



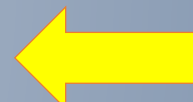
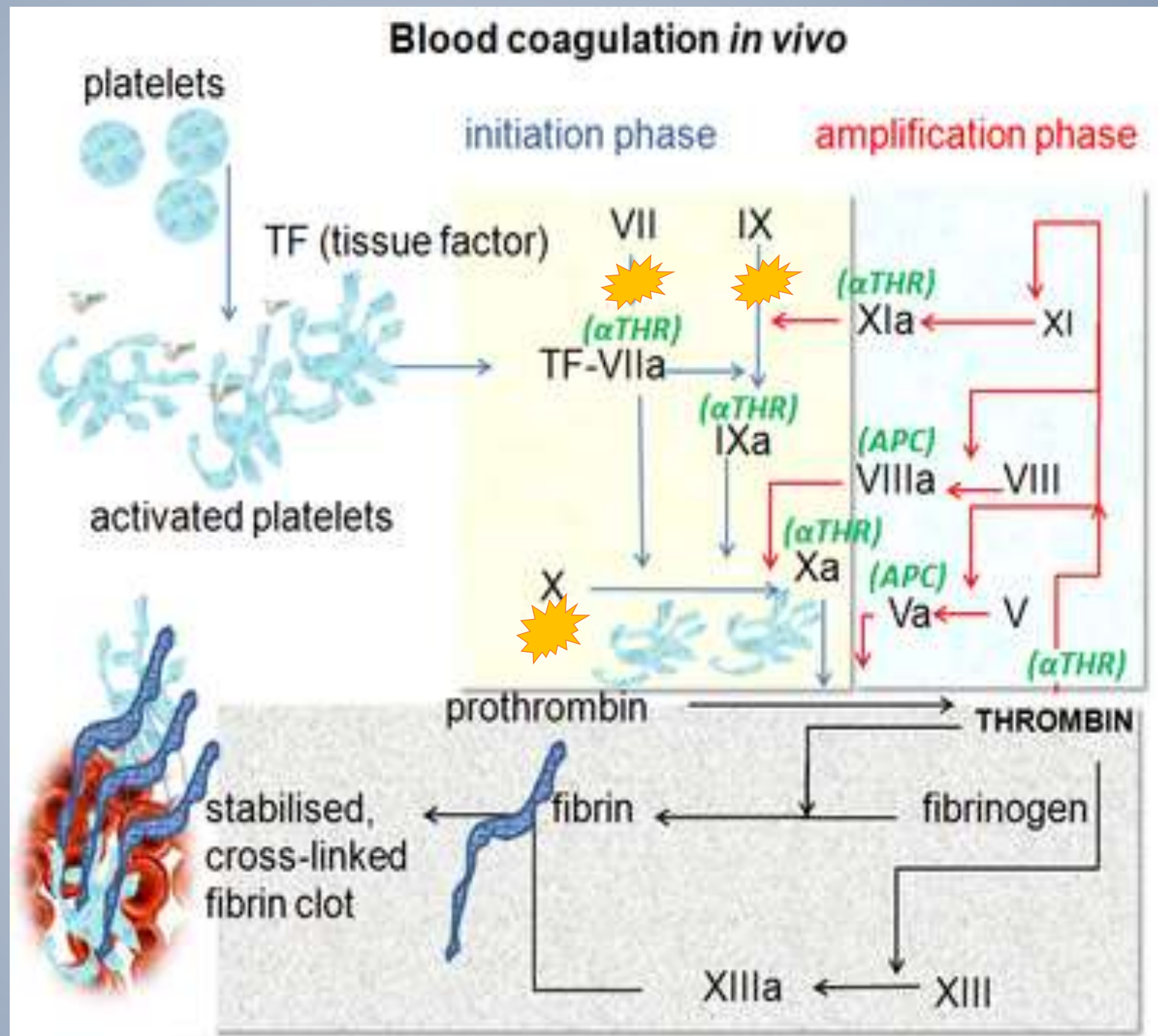
Anticoagulants

Fibrinogen is converted to **Fibrin** by **Thrombin**.

Fibrin strands stick to the exposed vessel wall, clumping together and forming a web-like complex of strands and red blood cells become caught up in the web,

Causing a Clot







Anticoagulation classes

Antiplatelet

Aspirin, Clopidogrel, ASA/dipyridamole

Vitamin K antagonist

Coumadin, warfarin

Thrombin inhibitors

Heparin, LMWH, Pradaxa

Xa factor inhibitors

Xarelto, Eliquis, Arixtra, Savaysa



Signs and Symptoms of Bleeding

- ✓ **Red or brown urine**
- ✓ **Black or bloody stool**
- ✓ **Vomiting of blood or material that looks like coffee grounds**
- ✓ **Bruising that develops without an injury**
- ✓ **Severe headache or stomach pain**
- ✓ **Joint pain, discomfort or swelling, especially after an injury**



Signs and Symptoms of Bleeding

- ✓ **Dizziness or weakness**
- ✓ **Bleeding from the gums**
- ✓ **Swelling or pain at an injection site**
- ✓ **Diarrhea, vomiting or inability to eat for more than 24 hours**
- ✓ **Fever**

Anticoagulants

Anticoagulants are used for;

- **Acute coronary syndromes,**
- **Deep-vein thrombosis (DVT),**
- **Pulmonary embolism (PE),**
- **Heart surgery.**
- **Atrial Fib**
- **Patients with artificial heart valves.**





Anticoagulants

Question

Who can tell me approximately when anticoagulants were first used to treat patients?

- 1 – 25 years ago**
- 2 - 85 years ago**
- 3 - 2,500 years ago**

Anticoagulants

A cattle disease in the Midwest in the **1920s** causing bleeding was traced to spoiled **sweet clover** the cattle was eating.

This substance was extracted and identified as **coumarin** at the University of Wisconsin.

This led to the development of dicoumarol in 1941 and rat poison in **1954** – Coumadin, warfarin.



Anticoagulants

Coumadin, warfarin





Anticoagulants

DID YOU KNOW?

There are **803** known **Drug** interactions with **Coumadin, warfarin**

Of that number, **208** are considered **MAJOR!**



Anticoagulants - Coumadin

Warfarin, the only drug listed in this category.

It is an oral anticoagulant that inhibits **Vitamin K**

Vitamin K is an activator of coagulating **factors II, VII, IX and X.**

Regular blood monitoring (international normalized ratio-INR) is done to check for effectiveness and safety.



Key interactions in the older patient
involve Coumadin, warfarin

INCREASE the EFFECT of Warfarin - Bleeding

Warfarin with NSAIDS

Warfarin and Sulfa Drugs

Warfarin and Macrolides

Warfarin and Quinolones

Warfarin and Amiodarone

Warfarin and Vitamin E



Key interactions in the older patient
involve Coumadin, warfarin

DECREASE the effect of Coumadin, warfarin

Anticonvulsants

Carbamazepine – Tegretol

Phenytoin – Dilantin (+/-)

Phenobarbital

Warfarin interactions in Older Patients

Typical Food interactions with Warfarin, Raw and Boiled Green Vegetables with HIGH Vitamin K Levels

Kale

Spinach

Turnip greens

Parsley

Mustard greens

Avocado

Brussel Sprouts

Broccoli

Romaine Lettuce

Chard

Green Tea

Grapefruit*

*** (decreases ability to metabolize Coumadin)**





Reversing an Anticoagulant

HASHTI

Hold the dose

Antidote

Support treatment (fluids)

Hemostatic measures (surgical)

Transfusion

Investigate (source)

Reversing Coumadin

1 - Vitamin K

Takes 4-24 hours for results

2 - Fresh Frozen Plasma

Fluid overload & transfusion related acute lung injury

3 - Prothrombin Complex Concentrate

Extremely rapid – 30min



Dosing Adjustments in a NON-Bleeding Patient

COUMADIN				
TARGET INR 2.0-3.0				
INR < 2.0	INR 3.1-3.5	INR 3.6-4.0	INR 4.1-8.9	INR > 9.0
		Hold 0-1 dose	Hold 0-2 doses	Hold 2 doses
Increase 10-15%	Decrease 0-10%	Decrease 10-15%	Decrease 10-15%	Decrease 15-20%
			Possible Vit K 2.5mg	Plus Vit K 2.5-5mg
Repeat INR within 1 week	Repeat INR within 2 weeks	Repeat INR within 1 week	Repeat INR in 2 DAYS	Repeat INR the NEXT day



Anticoagulants

Thrombin Inhibitors



Anticoagulants

In 1916, a pharmacologist at Johns Hopkins discovers **HEPARIN**

Heparin from the Greek word **HEPAR** meaning liver.

The liver produces **Fibrinogen and Prothrombin.**



Anticoagulants

Heparin was delayed until **1930** until a water soluble preparation was developed.

Later heparin was chemically altered by fractionation.

Leading to low-molecular-weight heparins such as enoxaparin, **“LOVENOX”**



Anticoagulants - Heparins

Heparin is an injectable anticoagulant that inhibits **thrombin** and factor **Xa**, factors necessary in the final stages of blood clotting cascade.

There are two types of heparins:

high molecular weight heparins

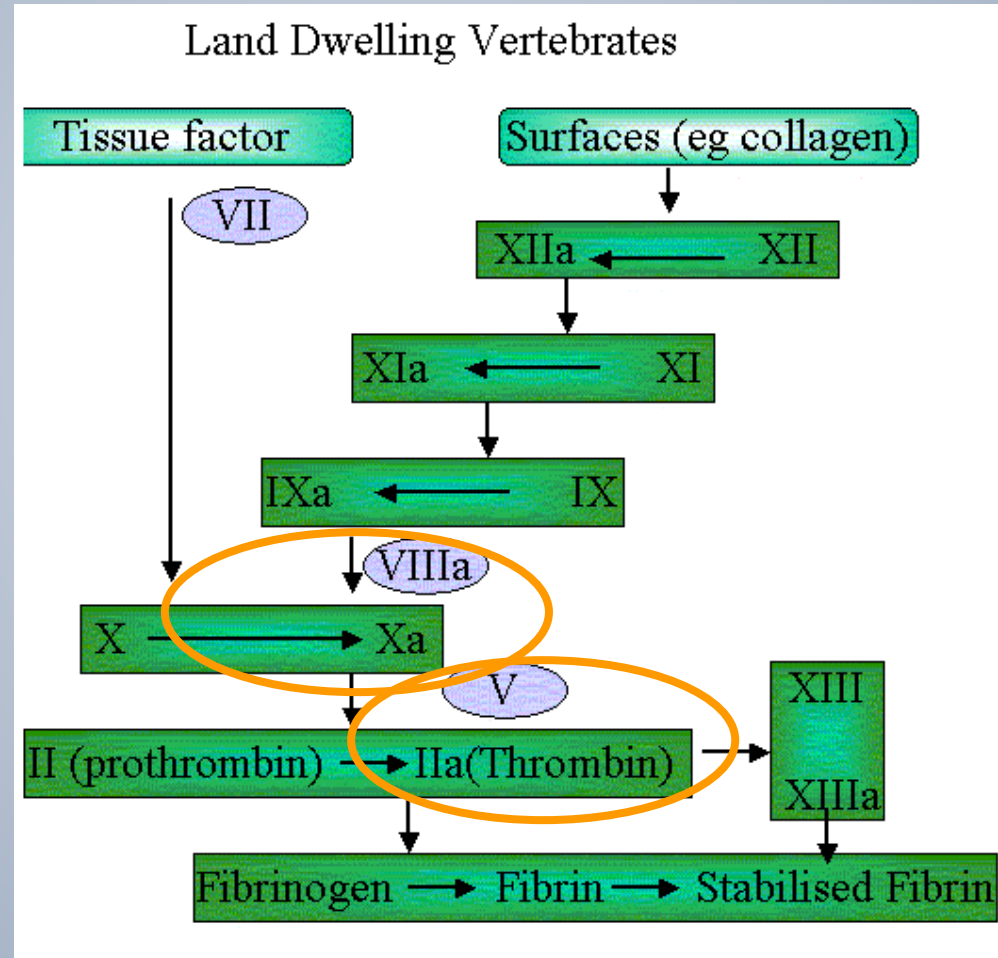
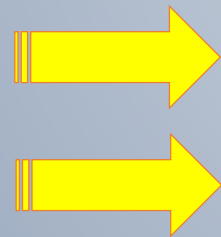
High molecular weight heparins require blood monitoring to check the **activated partial thromboplastin time – aPTT to measure the "intrinsic pathway"** .

low molecular weight heparins. (Lovenox)

Low molecular weight heparins give a better anticoagulant response and **do not** need routine blood monitoring and for the most part is replacing Heparin therapy.



Anticoagulants



Anticoagulants

Thrombin Inhibitors

Heparin Sodium (*heparin*)

Heparin Lock Flush (*heparin flush*)

Lovenox (*enoxaparin*)

Fragmin (*dalteparin*)

Innohep (*tinaparin*)

Pradaxa (*dabigatran*)





Reversing Thrombin inhibitors

Heparin

Short half-life, lasts up to 3 hours, **Protamine** reverses heparin, 1mg/100U heparin Adm in the last 4 hrs. **CAUTION**, 0.2% show anaphylaxis, with a **30% mortality rate**.

Lovenox

1mg **protamine** for every 1 mg enoxaparin if <8Hr.

Pradaxa

Adm **Praxbind**, Approved by FDA IN 2015, works in minutes with almost an immediate response.

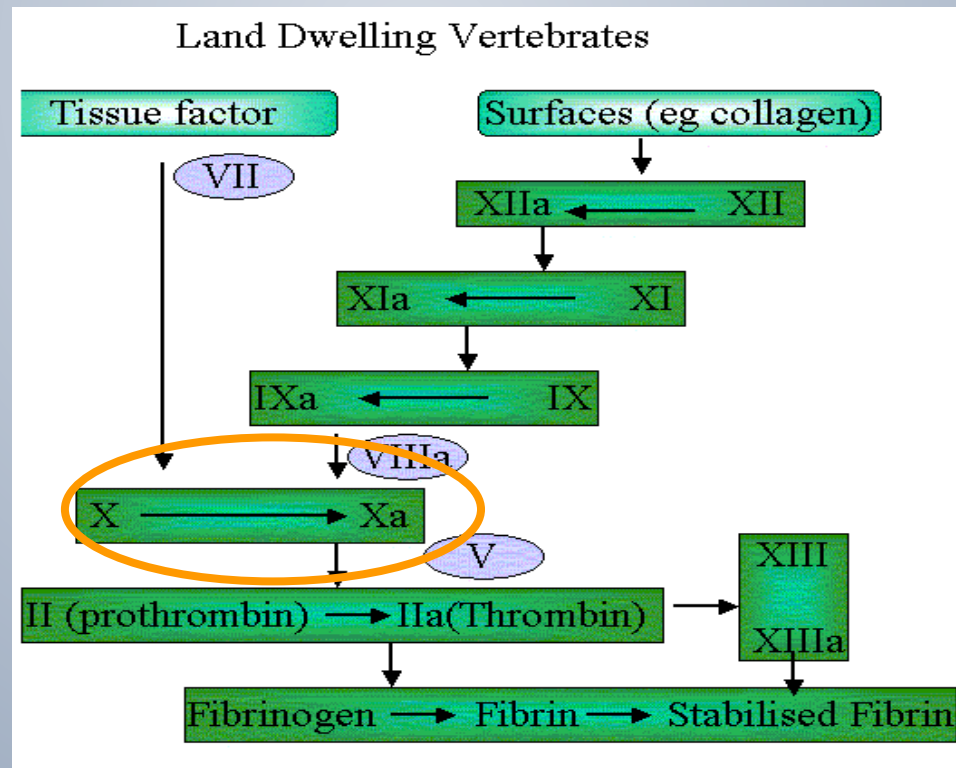
Anticoagulants

Xa Factor Inhibitors



Anticoagulants

Factor Xa is an attractive target for the design of new oral anticoagulants because of the unique role factor Xa plays in the coagulation cascade as a connection between the extrinsic and intrinsic pathways



Anticoagulants

Factor Xa Inhibitors

Arixtra (*fondaparinux*)

Xarelto (*rivaroxaban*)

Eliquis (*apixaban*)

Savaysa (*edoxaban*)



Factor Xa Inhibitors

- It's less of a risk with the new medications. And since they wear off faster than warfarin, bleeding problems may not be as serious when they happen.
- No real reversing agents yet, but have a short half-life .
- You don't need as many routine [blood](#) tests.
- No **Vitamin K** issues and vegetables
- Minimal dose adjustments
- Here are some drugs that don't mix well, but not nearly as many as with warfarin.



Factor Xa Inhibitors

Medications to watch with **Xa** factor Inhibitors

- Amiodarone – CrCl <80, Increase effect
- Azithromycin – CrCl <80, Increased Effect
- Coreg – CrCl <80, Increased Effect
- Cipro – CrCl <80, Increased Effect
- Dilantin & Pb – **Decreased** Effect
- Diltiazem – CrCl < 80. Increased effect
- NSAIDS – Increased Effect
- SSRIs and SNRI – Increased Effect
- Tegretol – **Decreased** Effect
- Trazodone – Increased effect



Factor Xa Inhibitors

When not to switch to a Xa factor inhibitor?

- Epidural/Spinal Hematoma Risk
- Stay on warfarin if you have kidney failure or if you have mechanical heart valves
- Monitor for CrCl <80





Reversing Factor Xa Inhibitors

Arixtra, Xarelto, Elikvis, Savaysa

FEIBATM (aPCC): clotting factors II, IX, and X and activated factor VII

Kcentra (PCC) clotting factors II, VII, IX and X

Andexanet Alfa reverses Elikvis and Xarelto within 3-5 minutes. *In Phase III Trials now....*



Factor Xa Inhibitors

QUESTION?

Should we change the patients on Coumadin, warfarin to the new **Xa** Factor inhibitors?

If the patient is on warfarin, they are stable, and don't have bleeding problems, and labs are not an issue there's generally not a compelling reason to switch."



Thank You