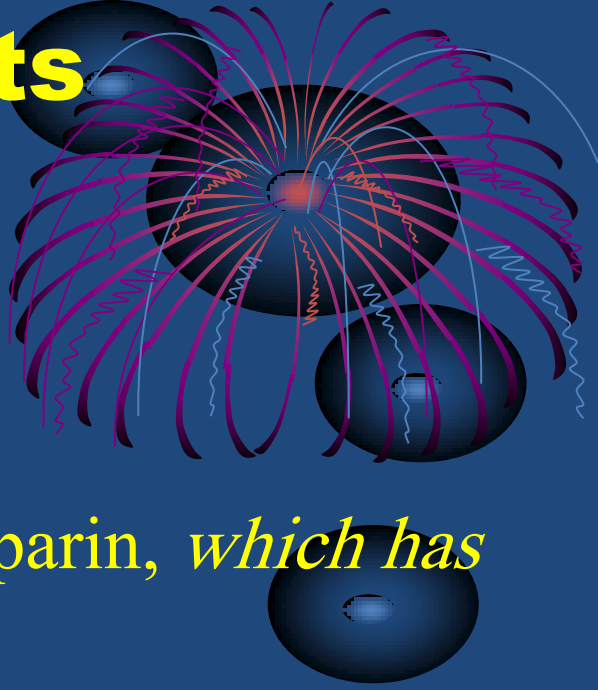
Drugs used to reduce clotting

Drug Class	Prototype	Action	Effect
1. Anticoagulant			
Parenteral			
	Heparin	Inactivation of clotting factors	Prevent DVT
Oral	**Warfarin**	Decrease synthesis of clotting factors	Prevent DVT
2. Antiplatelet	**Aspirin**	Decrease platelet aggregation	Prevent arterial thrombosis
3. Thrombolytic	**Streptokinase**	Fibinolysis	Breakdown of thrombi

I. Anticoagulants

1. Heparin



Structure

Mucopolysaccharide

Metabolism

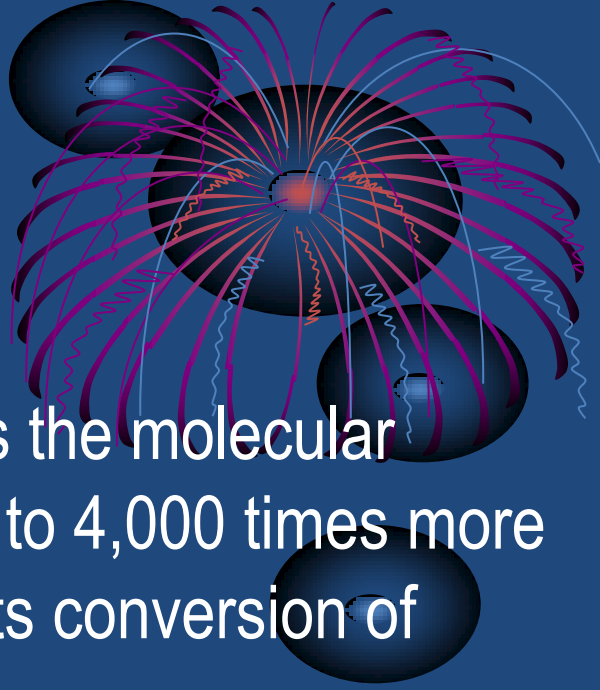
Partially in the liver by heparinase to uroheparin, *which has only slight antithrombin activity.*

20-50 % is excreted unchanged.

{The heparin polysaccharide chain is degraded in the gastric acid} administered IV or SC.

Heparin should not be given IM {danger of hematoma formation}.

Unfractionated heparin (UFH)



Mol weight:

3000-30000

Mechanism of action:

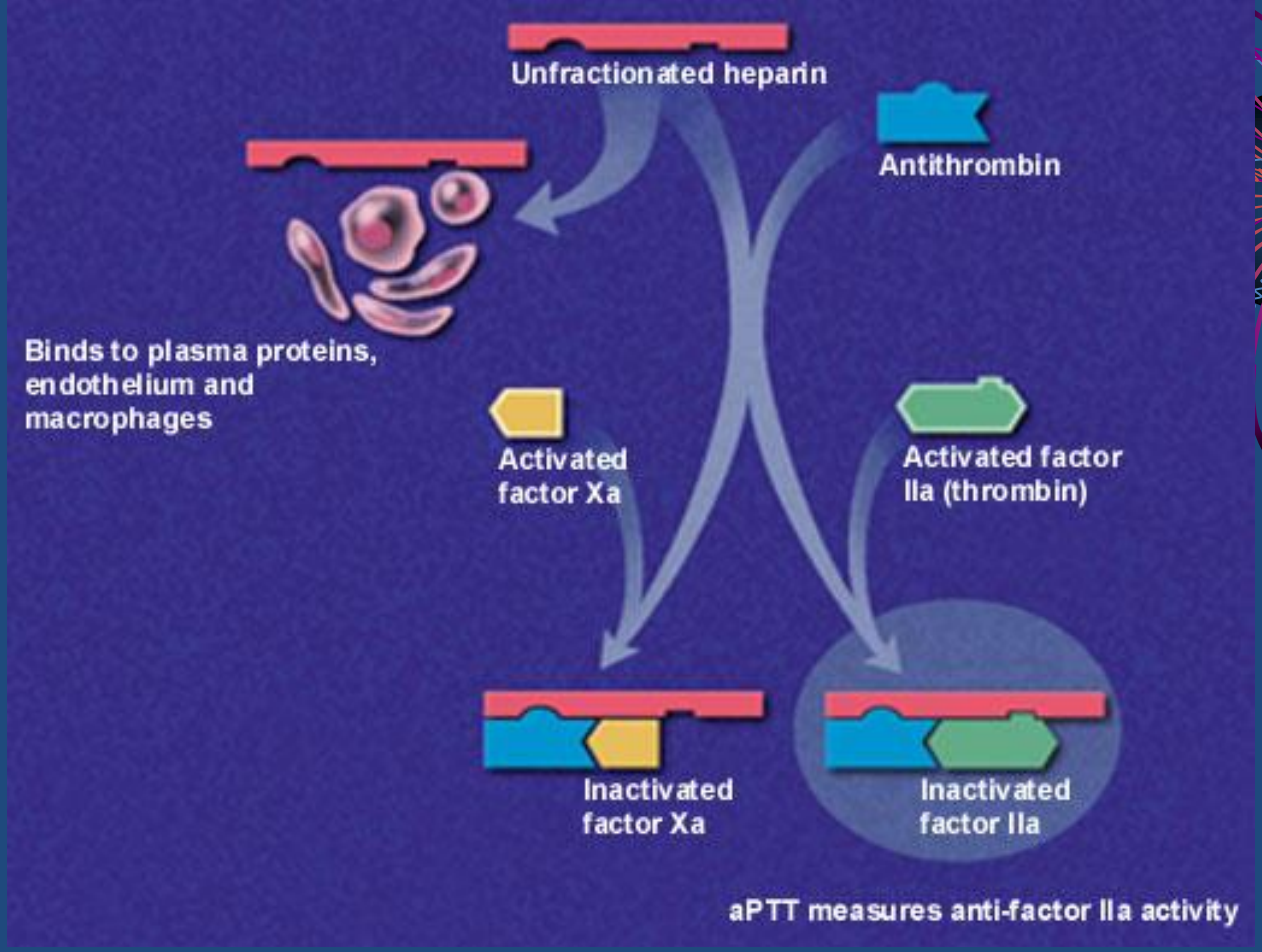
•*Primarily:* interaction with antithrombin III: alters the molecular configuration of antithrombin III, making it 1,000 to 4,000 times more potent as an inhibitor of thrombin formation: limits conversion of fibrinogen to fibrin: prolongs aPTT

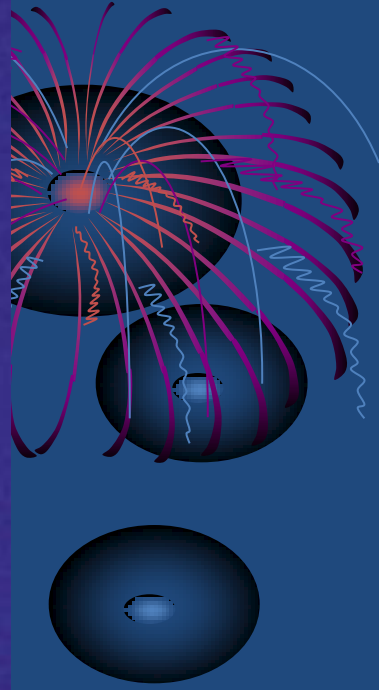
•*Also* inhibits the effects of factor Xa on the coagulation cascade & limits platelet aggregation.

Half-life:

IV: 1 hr

SC: 3 hrs.





UFH inactivate factor IIa through formation of a tertiary complex *(unlike LMWH).*

UFH binds more to plasma proteins, endothelium and macrophages: reduced bioavailability & greater patient variability to a given dose.

UFH inactivates factors IIa and Xa & affects the aPTT (measure of anti-factor IIa activity).

Dosing options.

Preoperative: 5,000U 2 hours before surgery.

{The single preoperative dose seems to be as effective as multiple preoperative doses}.

Postoperative: 8 to 12 hrs after surgery & every 8 to 12 hrs until the patient is fully ambulatory.

Antidote:

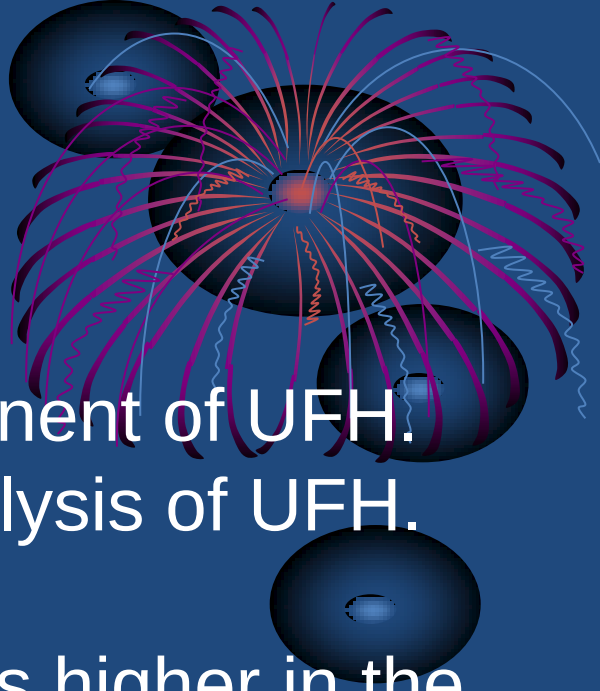
Protamine sulphate

Monitor:

aPTT

Use in pregnancy: {does not cross the placenta} safe

Low-Molecular-Weight Heparin



•Molecular weight

1000-10000 Da.

•Produced by

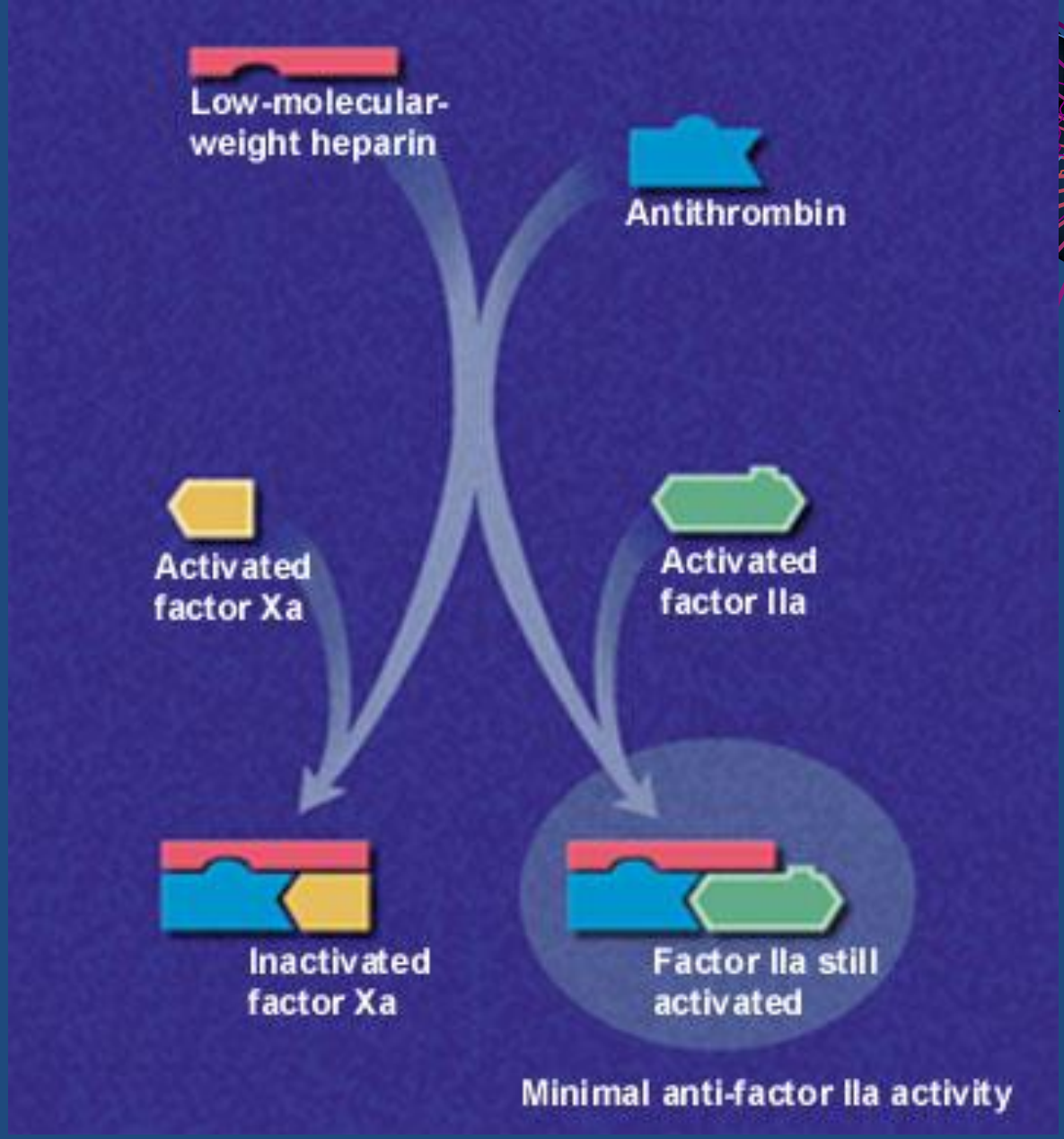
concentrating the low molecular component of UFH.

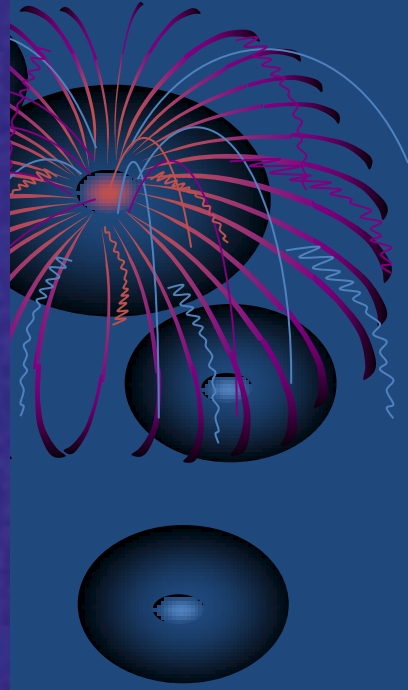
Enzymatic or chemical controlled hydrolysis of UFH.

•The mechanism of action

Primarily by inhibiting factor Xa, which is higher in the coagulation cascade than antithrombin: LMWH is more efficient than UFH.

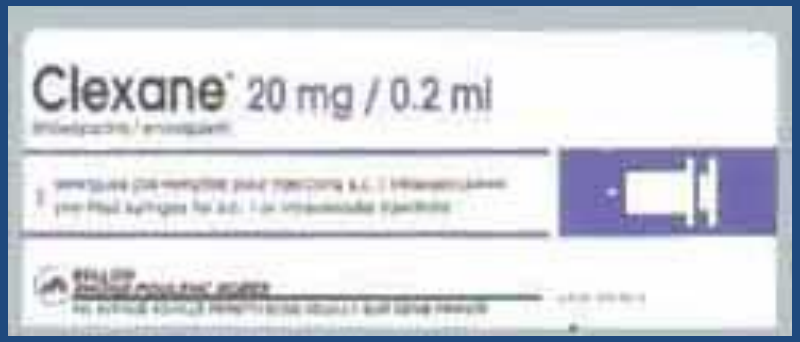
{the molecular configuration of antithrombin III is not altered by LMWH} thrombin conversion is minimally inhibited and aPTT is not appreciably affected.





LMWH inhibits factor Xa and minimally affects factor IIa; thus aPTT is not used to measure its anticoagulant activity.

Generic	Trade	Manufacturer	Mol Wt
Enoxaparin	Lovenex, Clexane	Rhone-Poulence-Rorer	4500
Tinzaparin	Logiparine	Novo	4850
Dalteparin	Fragmin	Kabi	6370



Half-life:

4 hrs, by any route: longer dosing interval.

Bioavailability

More consistent than that of UFH: dosing is based on lean body mass & Less thrombocytopenia.

Use in pregnancy:

Does not cross the placenta: safe.

Dosing options.

Prophylaxis: Once a day

Therapy: Twice-daily.

Enoxaparin is an LMWH

Moderate risk: 20 mg/d

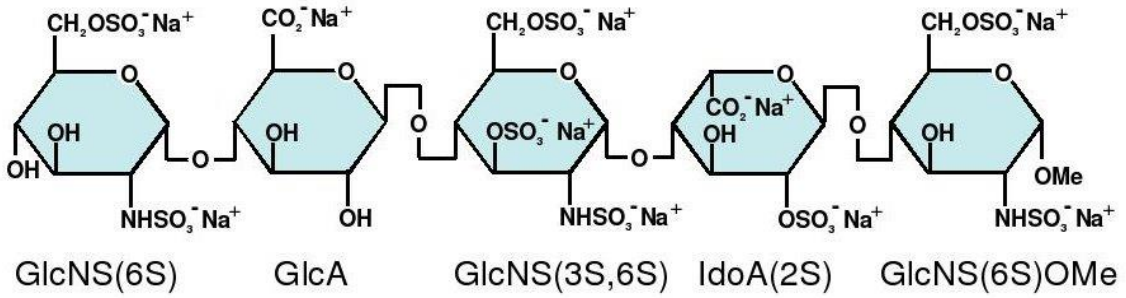
High risk: 40 mg/d.

•Advantage

Decreased need for monitoring

Fondaparinux

- Fondaparinux is given via injection once daily
- It is licensed for initial treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for venous thromboembolism prevention in patients undergoing surgery for hip fracture or hip/knee replacement



Hirudin

- Medicinal leeches:
  - Used since ancient times to relieve body of “bad humors”
    - Egyptians, Greeks
  - Reached peak popularity in mid-19th century

Hirudo medicinalis

- 1884: John Haycraft in Birmingham demonstrated that medicinal leeches, *Hirudo medicinalis*, secrete a substance that prevents blood from clotting

- 1904: Substance named hirudin

- 1957: Markwardt isolated the active anticoagulant substance, determined it to be a polypeptide 65 AAs long which inhibited thrombin

- Estimated to require 50,000 leeches annually for diagnostics and treatment
- 1986: DNA isolated and cloned
- Today recombinant hirudin is made in yeast cells
  - Lepirudin, desirudin, bivalirudin

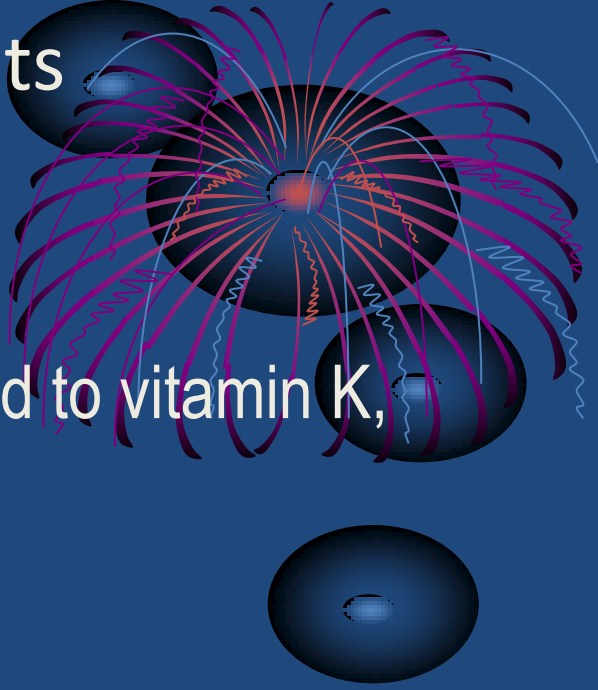
History of Anticoagulants

- Warfarin has been the drug of choice for the prevention and treatment of arterial and venous thrombotic disorders for more than 40 years
- It was initially marketed as a pesticide against rats and mice, and is still popular for this purpose

Vitamin K antagonists

- The vitamin K anatagonists or coumarins were first isolated by Karl Paul Link at the University of Wisconsin in the 1930s. The observation that cows bled to death after eating mouldy clover had led Link ’ s team to isolate the anticoagulant factor from the contaminated clover. Link later developed a synthetic coumarin derivative. This was patented by the Wisconsin Alumni Research Foundation who named it warfarin as a contraction of the organization ’ s acronym, WARF, and the word coumarin. The use of coumarins became widespread in the 1940s

2. Oral anticoagulants



- Coumarins - warfarin, dicumarol

Structure:

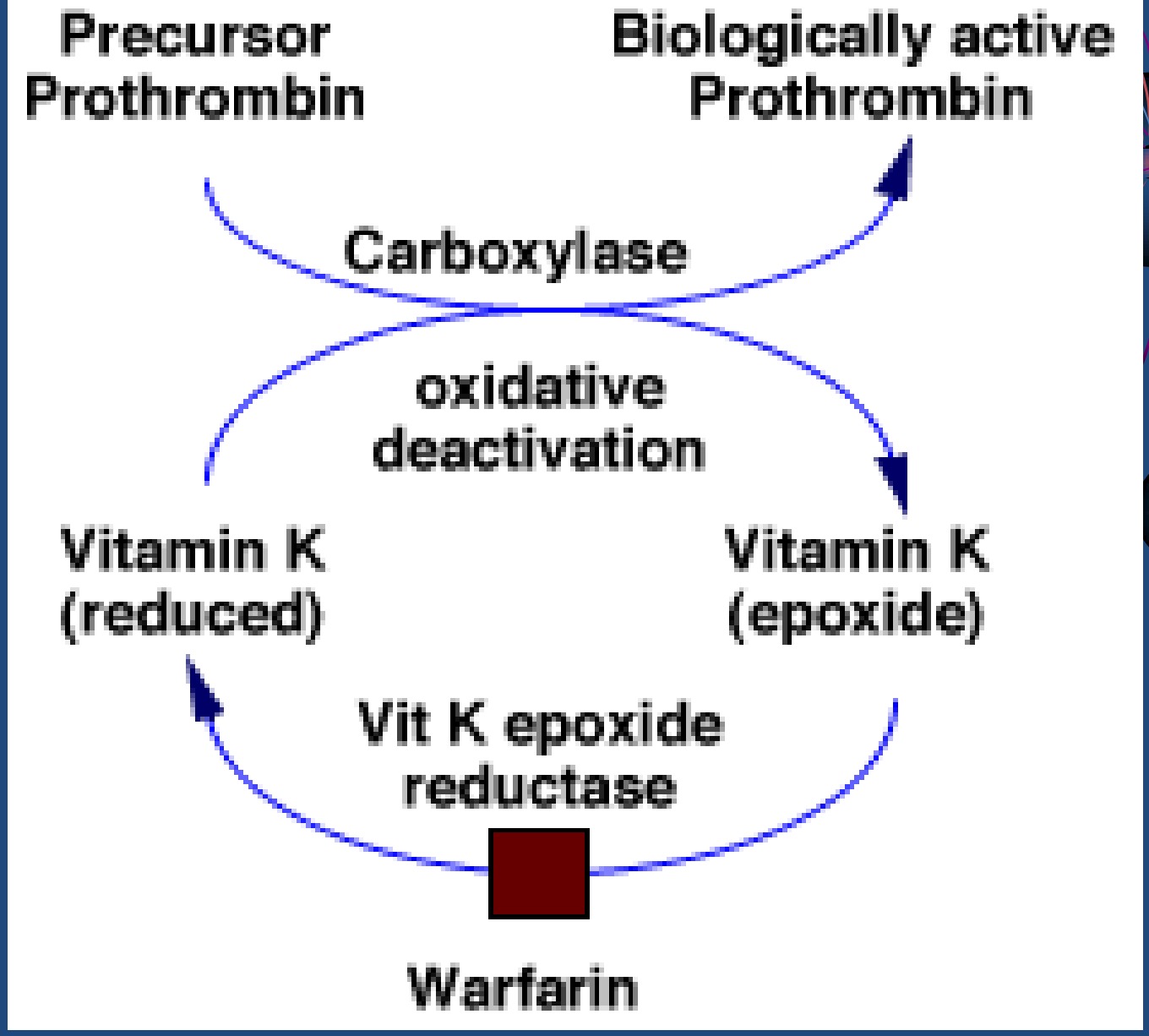
small, lipid-soluble molecules, Structurally related to vitamin K, isolated from clover leaves

Mechanism:

- Inhibits production of active clotting factors
- blocks the Vitamin K-dependent glutamate carboxylation of precursor clotting factors e.g. FII, VII, IX , X

Metabolism:

- Absorption: rapid
- Binds to albumin
- Clearance is slow: 36 hrs
- Delayed onset: 8-12 hr {T1/2 of clotting factors in plasma}



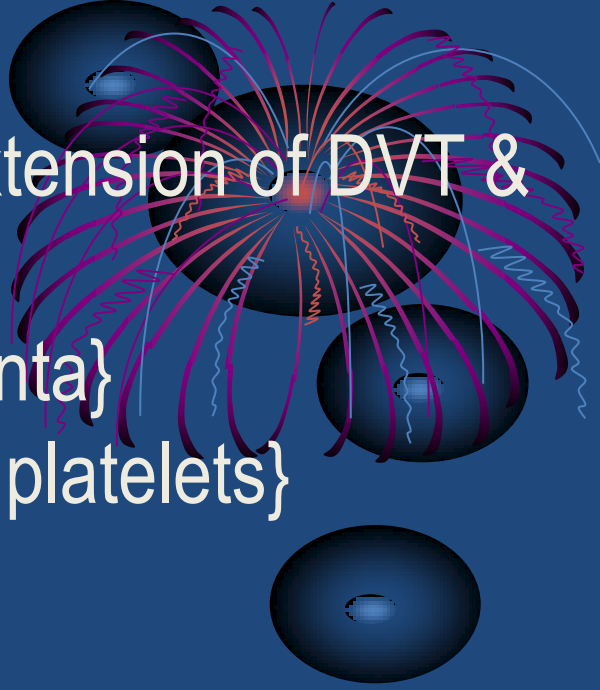
blocks the Vitamin K-dependent glutamate carboxylation of precursor clotting factors

Use:

To prevent the formation, recurrence or extension of DVT & PE

Not used in pregnant women {cross placenta}

Not used for arterial thrombi {No effect on platelets}



Toxicity:

bleeding

birth defects

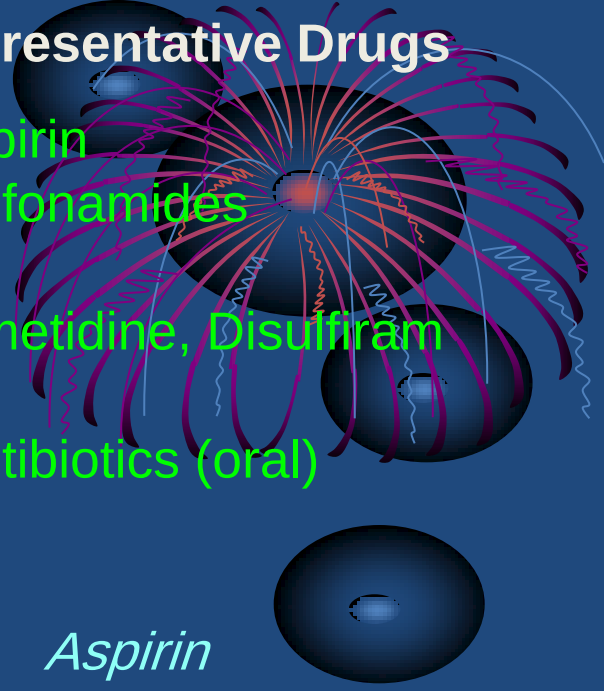
Overdose:

Reversed by vitamin K infusion

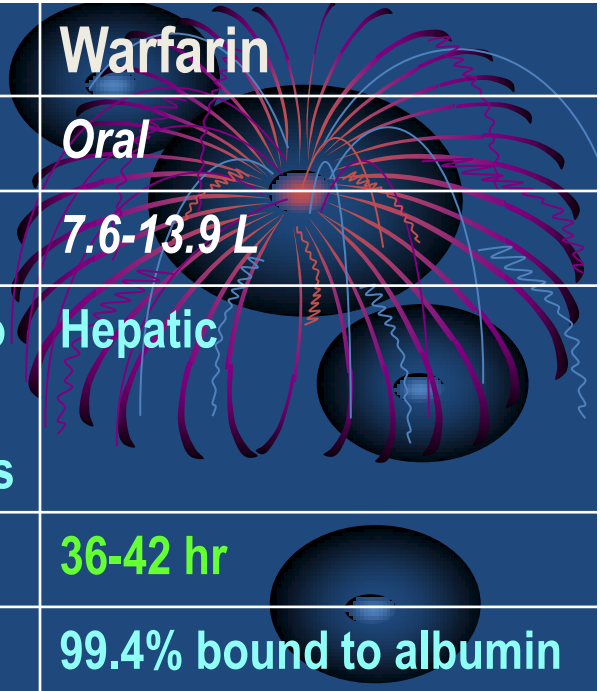
Recovery needs synthesis of new clotting factors

Warfarin tablets, 5, 3 and 1mg

Category	Mechanism	Representative Drugs
Drugs that Increase Warfarin Activity	Decrease binding to Albumin	Aspirin Sulfonamides
	Inhibit Degradation	Cimetidine, Disulfiram
	Decrease synthesis of Clotting Factors	Antibiotics (oral)
Drugs that promote bleeding	*Inhibition of platelets*	*Aspirin*
	Inhibition of clotting Factors	*Heparin Antimetabolites*
Drugs that decrease Warfarin activity	Induction of metabolizing Enzymes	Barbiturates Phenytoin
	Promote clotting factor Synthesis	Vitamin K
	Reduced absorption	Cholestyramine Colestipol

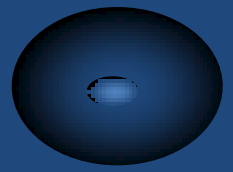


	Heparin	Warfarin
Absorption	*Parentral only*	*Oral*
Vol of distribution	*Plasma vol (0.07 L/kg)*	*7.6-13.9 L*
Metabolism/Clearance	Hepatic metabolism & uptake by reticulo endothelial system Also by thrombin & other clotting factors	Hepatic
Elimination t1/2	50-90 min	36-42 hr
Protein binding	Bound to antithrombin III & other serine proteases	99.4% bound to albumin
Plasma concentration (therapeutic)	0.2-0.4 U/ml	1.5 mg/L
Side effects	Bleeding Thrmbocytopenia Osteoporosis	Bleeding Skin necrosis Drug interactions
Treatment of bleeding	•Mild: Slow or stop infusion •Severe: Protamine 1 mg/100 u of estimated heparin remaining in body	•Mild: hold 1-2 doses, observe, restart at lower dose •Severe: Vit K or fresh frozen plasma



II. Antiplatelet Drugs

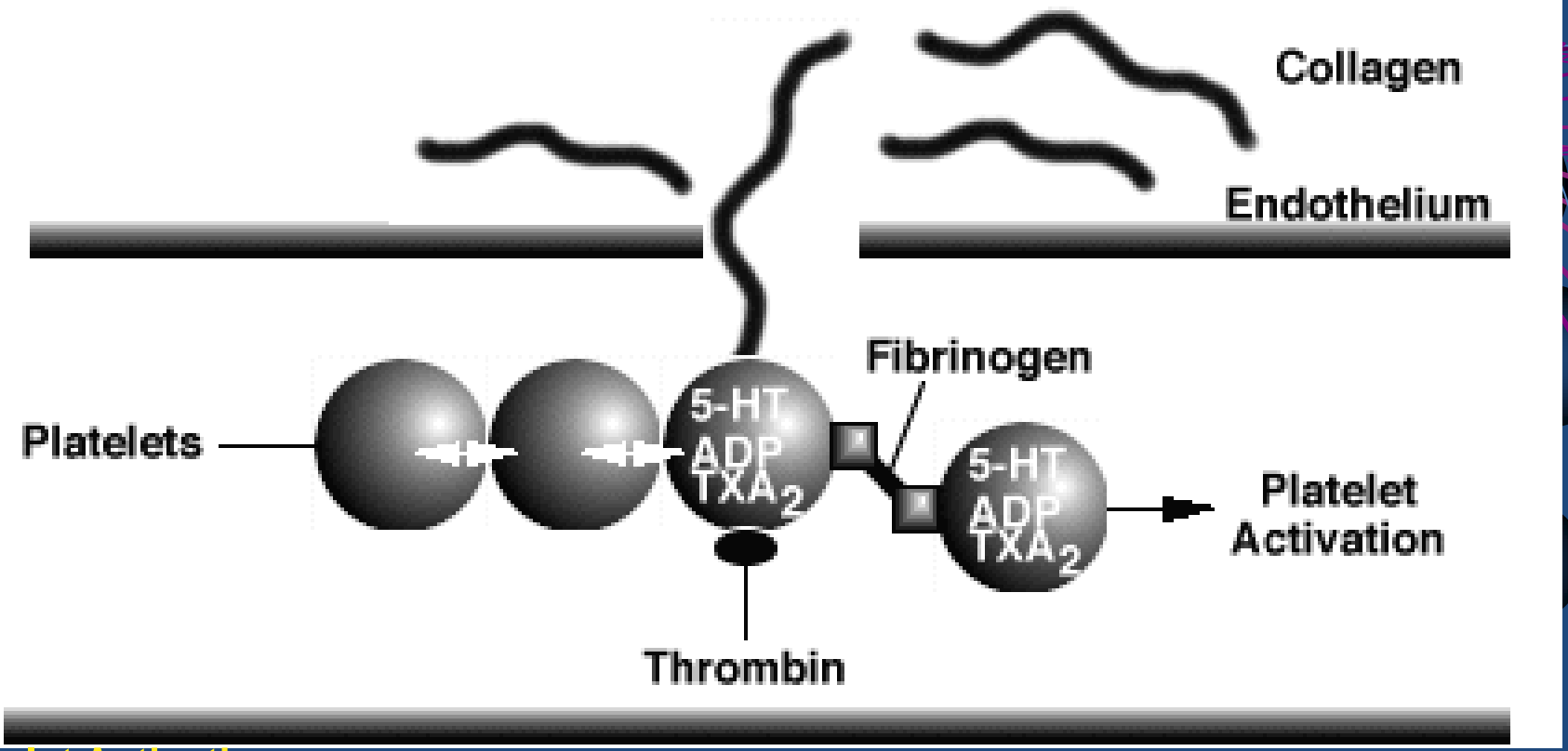
Activation and aggregation of platelets is a major component of thrombosis especially in arteries



Targets for platelet inhibitory drugs:

(a) inhibition of prostaglandin metabolism through inhibition of cyclooxygenase (aspirin)

(b) inhibition of ADP-induced platelet aggregation (ticlopidine) , (clopidogrel)

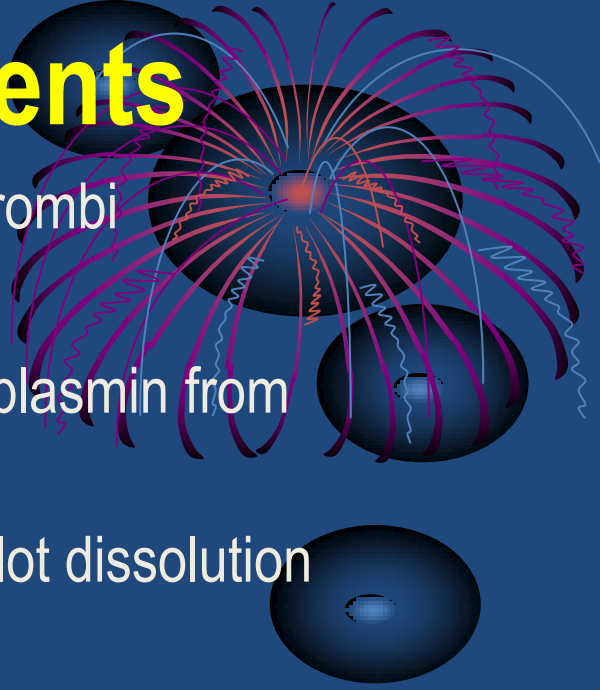


Platelet Activation:

- **Endothelial damage** of vessel: exposes collagen
- **Activated platelets** release ADP, serotonin (5-HT)& thromboxane A2 (TXA2-) from arachidonic acid: platelet aggregation by causing the appearance of binding sites for fibrinogen on platelet membrane
- **Fibrinogen** is involved: platelet to platelet adhesion (aggregation)
- **Thrombin** causes further platelet activation by releasing platelet ADP & stimulating PG synthesis

prostacyclin (PGI2) - synthesized within vessel walls inhibits thrombogenesis by increasing platelet cAMP. Nitric oxide (NO) - released by endothelium - increases cAMP

III. Thrombolytic Agents



Agents which reduce the formation of arterial platelet thrombi

Mechanism:

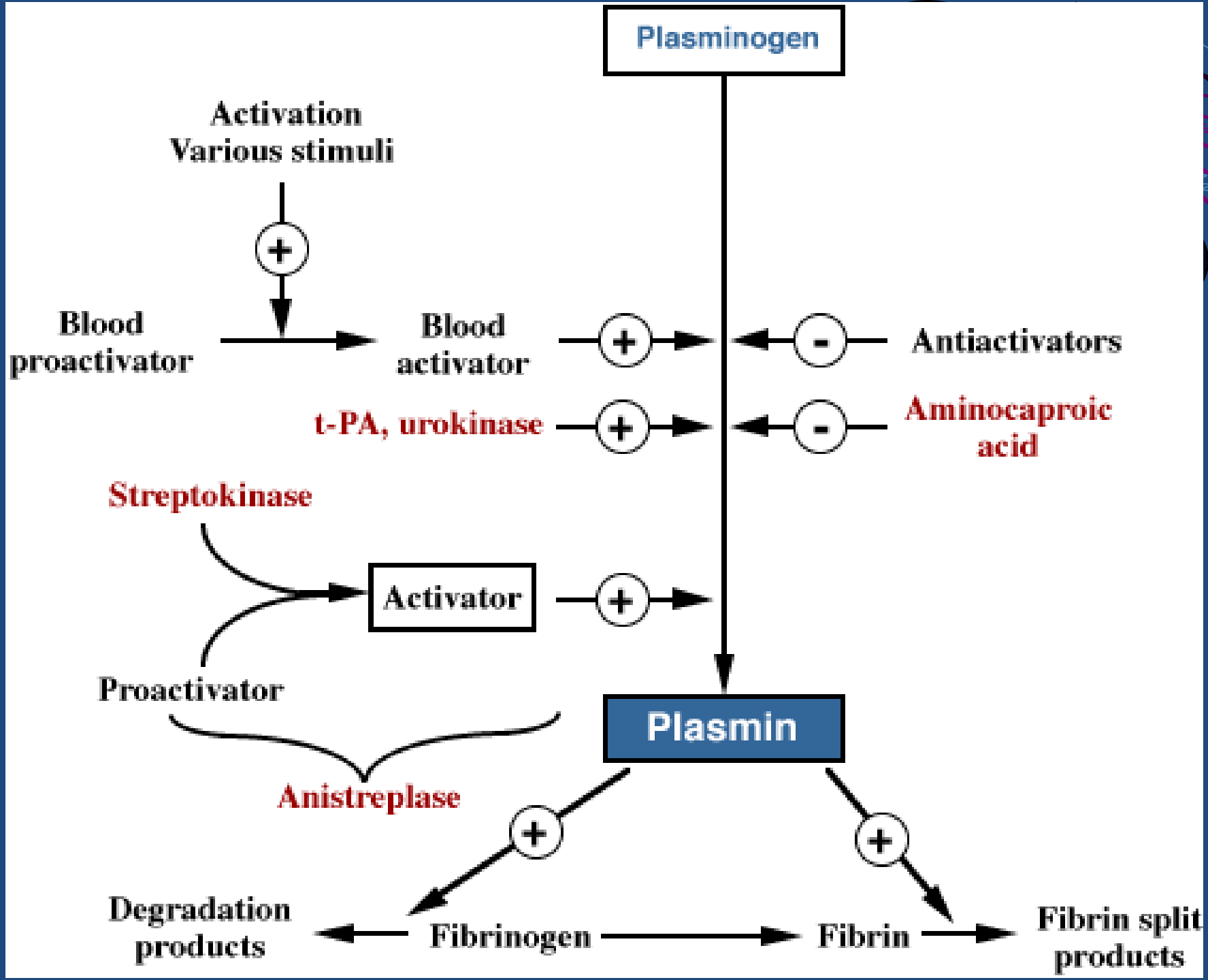
- Rapid lysis of thrombi by catalyzing the formation of plasmin from plasminogen
- Endogenous plasmin breaks down fibrin promoting clot dissolution

Use:

- Emergency treatment of coronary artery thrombosís in M.I.
- IV or intracoronary injection
- DVT: rapid recanalization of occluded vessels

Toxicity:

- Bleeding (intracranial, G.I.)
- Allergic reactions (i.e. streptokinase)


Plasminogen
Activation
Various stimuli
+
Blood
proactivator
Blood
activator
+
-
Antiactivators
t-PA, urokinase
+
-
Aminocaproic
acid
Streptokinase
Activator
+
Proactivator
Plasmin
Anistreplase
+
+
Degradation
products
Fibrinogen
Fibrin
Fibrin split
products

Streptokinase:

Purified from bacteria

Continuous use: immune reaction

Forms a complex with plasminogen & catalyzes it: rapid conversion to plasmin

Urokinase:

From cultured human kidney cells

No immune response

Directly converts plasminogen to plasmin

tPA:

Produced by recombinant techniques

No immune reaction - EXPENSIVE

Promotes conversion of plasminogen (that is found to fibrin) to plasmin

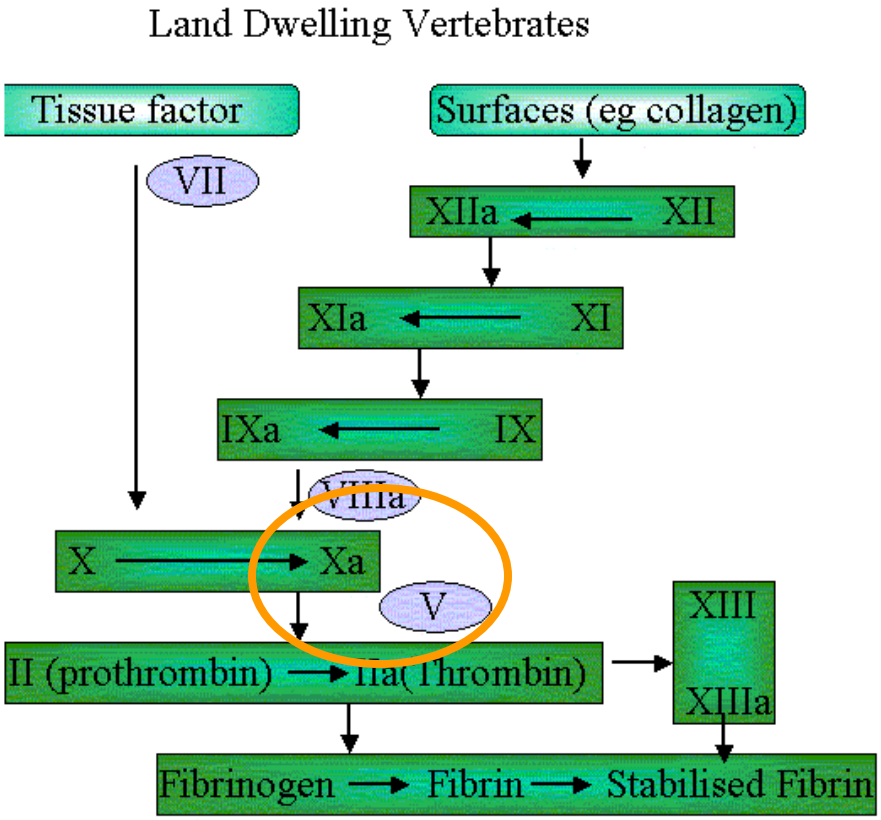
In theory, selective for formed clots

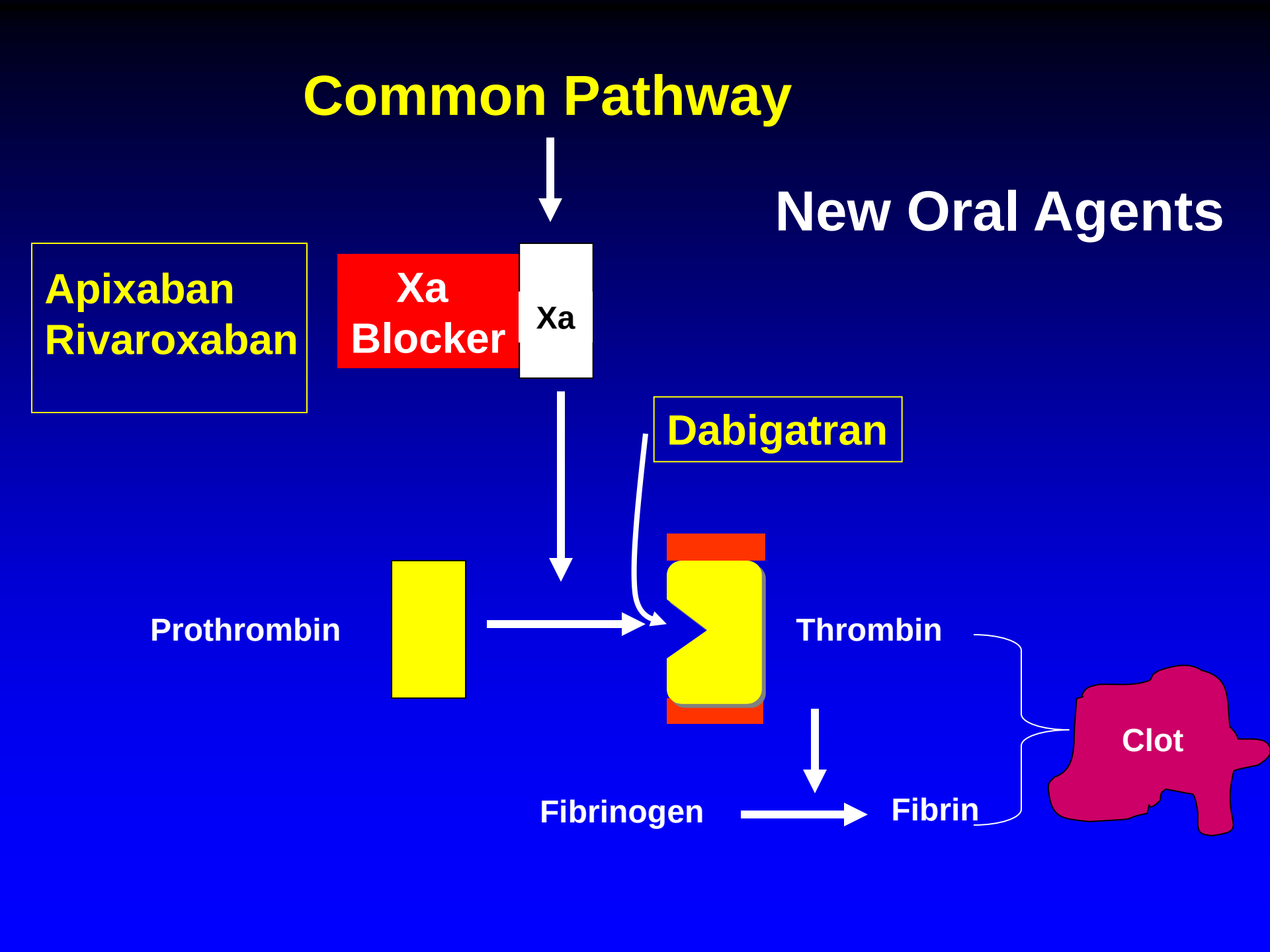
The future for anticoagulants

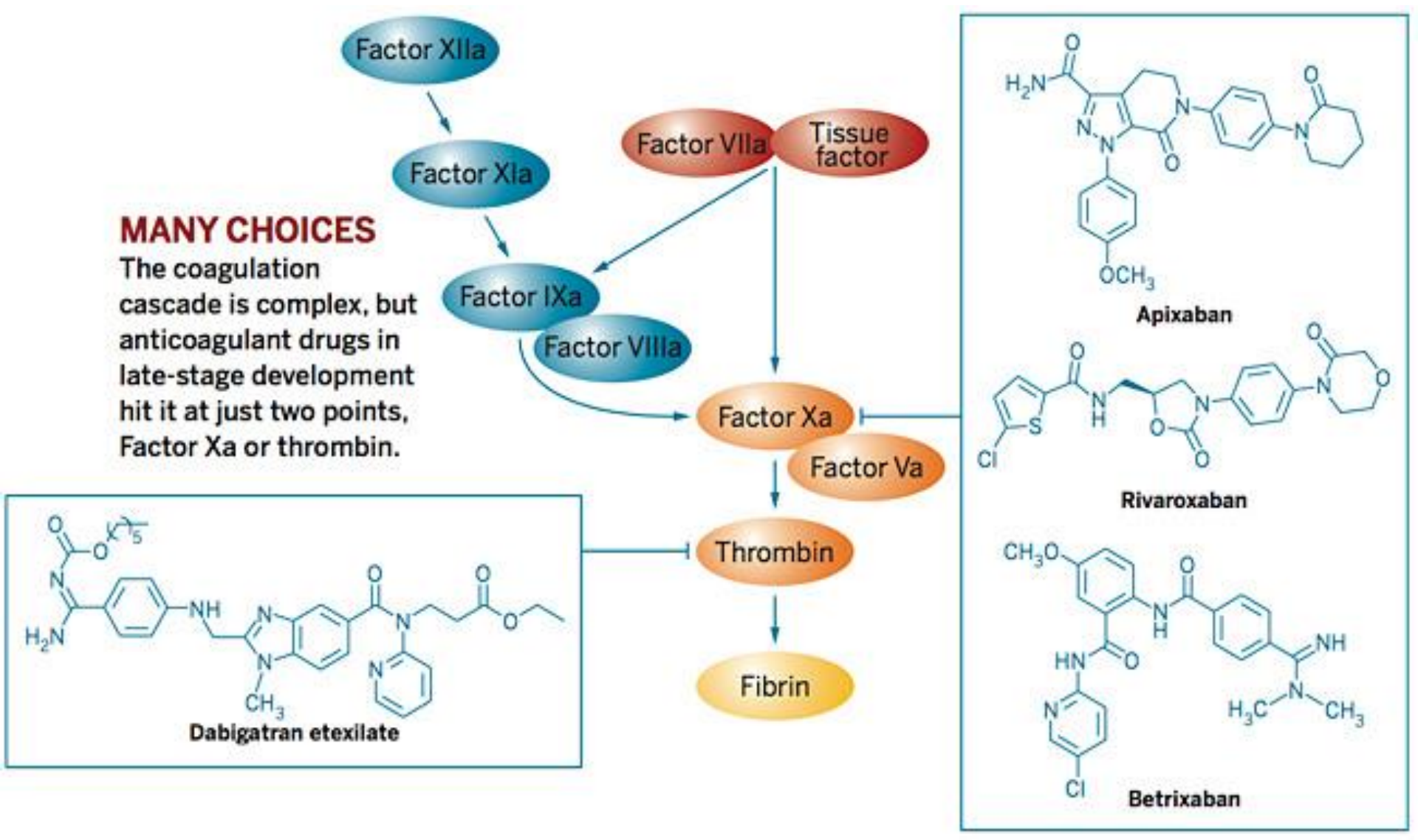
- Molecular targets are factor IIa (thrombin) and factor Xa
- The two candidate compounds, one direct thrombin inhibitor (dabigatran etexilate) and one direct factor Xa inhibitor (rivaroxaban) are hoping to be approved as new oral anticoagulants in the near future

The future for anticoagulants

- Factor Xa also regulates thrombin generation via binding to factor Va followed by activation of prothrombin to thrombin




Common Pathway
New Oral Agents
Apixaban
Rivaroxaban
Xa Blocker
Xa
Dabigatran
Prothrombin
Thrombin
Fibrinogen
Fibrin
Clot


Factor XIIa
Factor XIa
Factor VIIa
Tissue factor
MANY CHOICES
The coagulation cascade is complex, but anticoagulant drugs in late-stage development hit it at just two points, Factor Xa or thrombin.
Factor IXa
Factor VIIIa
Factor Xa
Factor Va
Thrombin
Fibrin
Dabigatran etexilate
Apixaban
Rivaroxaban
Betrixaban

Ideal Anticoagulant

Disadvantage of Warfarin	Ideal Anticoagulant
Slow onset of action **Need for Injectable agent**	Fast onset of action, allowing for acute treatment of VTE and use post-procedures
Slow resolution of action	Fast resolution of action, allowing for use pre-procedures
Regular blood monitoring	No routine blood monitoring
Many drug interactions	No drug interactions
Interactions with diet	No interactions with diet
Wide range of therapeutic doses	Narrow-ranged, fixed doses
Unpredictable dose-response	Predictable dose-response
Teratogenicity	Safe in pregnancy
Slow reversibility via vitamin K	Immediate reversibility

DABIGATRAN ETEXILATE (Pradaxa®, Boeringher-Ingelheim)

PHARMACOLOGY:

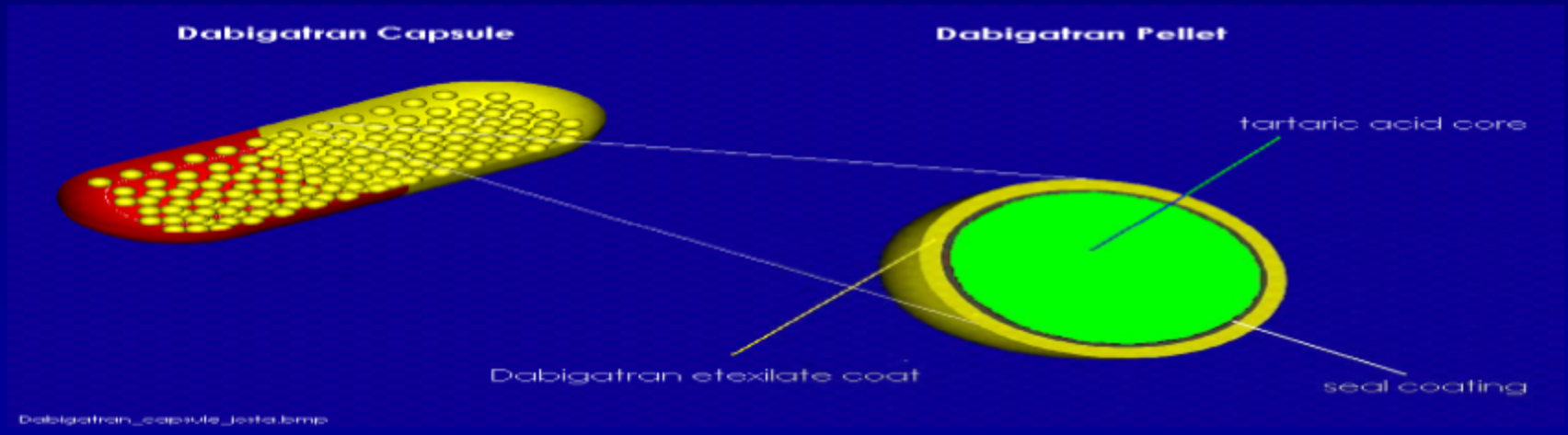
- Prodrug, converted to the active dabigatran moiety by hydrolysis via nonspecific esterases.
- Dabigatran is a reversible and selective direct thrombin inhibitor.
- Dabigatran inhibits human thrombin and thrombin-induced platelet aggregation.
- Dabigatran inhibits both clot-bound and fluid-phase thrombin.

FDA indication (Approved October 2010):

- Dabigatran is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Dabigatran: Ensuring Appropriate Use
Capsule Stability

- Dabigatran exetilate requires an acid environment for absorption
- Capsules contain multiple drug pellets
- Each pellet has a tartaric acid core (coated with drug) that creates an aci microenvironment to improve dissolution and absorption independent o gastric pH



DO NOT CRUSH, CHEW OR BREAK CAPSULES

Dabigatran: Ensuring Appropriate Use
Capsule Stability

- Once bottle is opened, contents must be used within 30 days
  - Cap on bottle contains dessicant to reduce moisture and avoid degradation

Comparison of Oral Anticoagulants

Characteristic	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Site of action	Vitamin K antagonist	Direct thrombin inhibitor (IIa)	Factor Xa inhibitor	Factor Xa inhibitor
Maximum time to onset	2–5 days	2 hours	2.5–4 hours	3 hours
Half-life	2–5 days	14–17 hours	5–9 hours in healthy patients; 9–12 hours in elderly patients	8–15 hours
Drug interactions	Acetaminophen; aspirin; NSAIDs; anti-infectives; SSRIs; phenytoin; multiple other drugs (and diet)	P-gp inducers (eg, rifampin); dronedarone; ketoconazole; aspirin; NSAIDs; clopidogrel	Strong inhibitors and inducers of CYP3A4 and P-gp; aspirin; NSAIDs; clopidogrel	Aspirin; clopidogrel; potentially, strong inhibitors and inducers of CYP3A4 and P-gp

NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors (antidepressants); P-gp = P-glycoprotein

Potential Advantages of New Oral Anticoagulants

- Oral administration
- Rapid onset of action
  - Eliminates 2 AC regimen
- Predictable effect with fixed or weight-based dosing
  - No monitoring
- Less food/drug interactions
- Short half- life
  - Ease of reversal/ no bridging
- More convenient
  - Potentially leading to greater use
- More cost effective
  - No routine monitoring
  - Fewer ADEs requiring ER visits and hospitalizations
- Possible superior efficacy
- Possible superior safety

The Future for Warfarin?

- Warfarin will not disappear!
- Use will continue in many circumstances, including:
  - Mechanical heart valves and other un-studied indications
  - Patients who ‘fail’ therapy on a new AC
  - A monitored drug may be preferred for patients with:
    - Compliance issues
    - Drug interaction issues
    - Changing/ poor renal or hepatic function (dialysis?)
  - There may be initial resistance to new agents
    - Especially to convert over a stable warfarin patient

Foods With Anticoagulant Properties

Last Updated: Jan 10, 2014 | By Jill Corleone

Photo Caption Garlic has anticoagulant properties. Photo Credit Blue Jean Images/Digital Vision/Getty Images

Overview

The American Heart Association defines an anticoagulant as a medication that prevents blood from clotting. Anticoagulants are given to people who are at risk for blood clo people with artificial heart valves, ar people with atrial fibrillation. Comm anticoagulants include Coumadin a heparin. According to Nutrition411, some foods and supplements have anticoagulant properties and can affect blood clotting. If you are taking anticoagulants, you should avoid these foods unless a doctor says otherwise.

Ginger

Photo Caption Sliced ginger root Photo Credit grafvision/iStock/Getty Images

Ginger is the underground stem of the Zingiber plant. It has been used for its medicinal properties in Asian cultures for thousands of years. Ginger is most commonly recommended as an aid for stomach upset like nausea and vomiting. According to the University of Maryland Medical Center, preliminary studies show ginger may help prevent blood from clotting. They go on to say that it is too early to make firm recommendations to heart patients, but these affects may help protect against blood vessel blockage that can lead to heart attack and stroke.

Garlic

Photo Caption Garlic bulbs in bowl Photo Credit denphumi/iStock/Getty Images

Garlic is another food that has been used for its medicinal purposes for thousands of years. The University of Maryland Medical Center says garlic is recommended to help prevent heart disease. In addition to decreasing bad cholesterol and increasing good cholesterol, garlic helps prevent platelet aggregation, also known as blood clotting. According to the University of Maryland Medical Center, allicin appears to be the chemical property in garlic with the anticoagulant powers.

Vitamin E

Photo Caption Cut mango Photo Credit Adam Korzeniewski/iStock/Getty Images

Vitamin E is a fat-soluble vitamin naturally found in some foods. There are many health claims related to vitamin E, most notably its antioxidant and anti-inflammatory properties. According to the Office of Dietary Supplements, vitamin E has been shown to prevent or delay the onset of coronary heart disease by preventing the formation of blood clots. Food sources of vitamin E include almonds, wheat germ, sunflower seeds, peanuts, safflower oil, spinach and mangoes.

Fish Oil

Photo Caption Fresh tuna steaks Photo Credit Jack Puccio/iStock/Getty Images

Fatty fish like salmon, tuna, and halibut contain an essential fatty acid called omega 3 fatty acid. Recently, studies have shown that omega 3 fatty acids reduce the risk of heart disease, says the University of Maryland Medical Center. The American Heart Association recommends eating fish twice a week for heart health. In addition to lowering triglyceride levels and blood pressure, omega 3 fatty acids in fish contain anticoagulant properties that slow down the development of blood clots to help prevent and treat atherosclerosis.