

# Anticoagulants

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Medicinal Chemistry

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27 March 2008

# Outline

- General Overview of Anticoagulants
- Overview of Blood Coagulation
- Anticoagulant Drugs
- History of Anticoagulant Drugs
- Use of Anticoagulants Today, Prevention
- Future Outlook



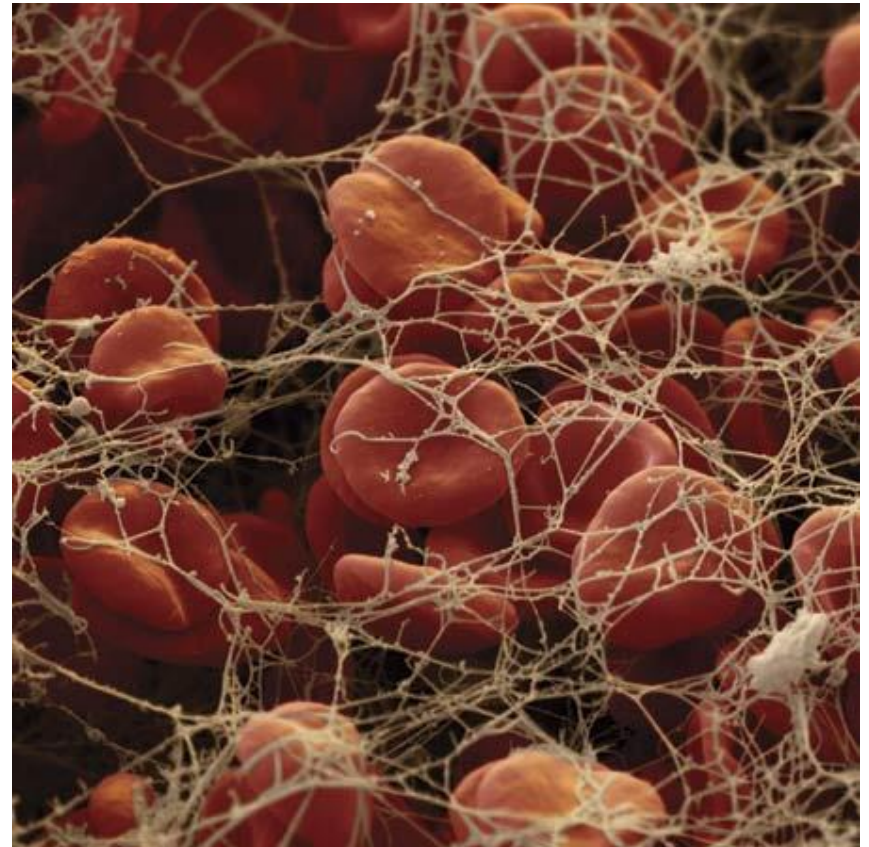
# Anticoagulants – General Overview

- Drugs that help prevent the clotting (coagulation) of blood
- Coagulation will occur instantaneously once a blood vessel has been severed
- Blood begins to solidify to prevent excessive blood loss and to prevent invasive substances from entering the bloodstream

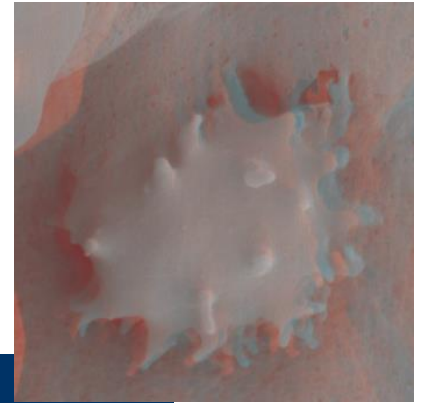


# A Blood Clot

- Consists of platelets meshed into fibrin
- A web-like accumulation of strands with RBCs
- There are two major facets of the clotting mechanism – the platelets, and the thrombin system



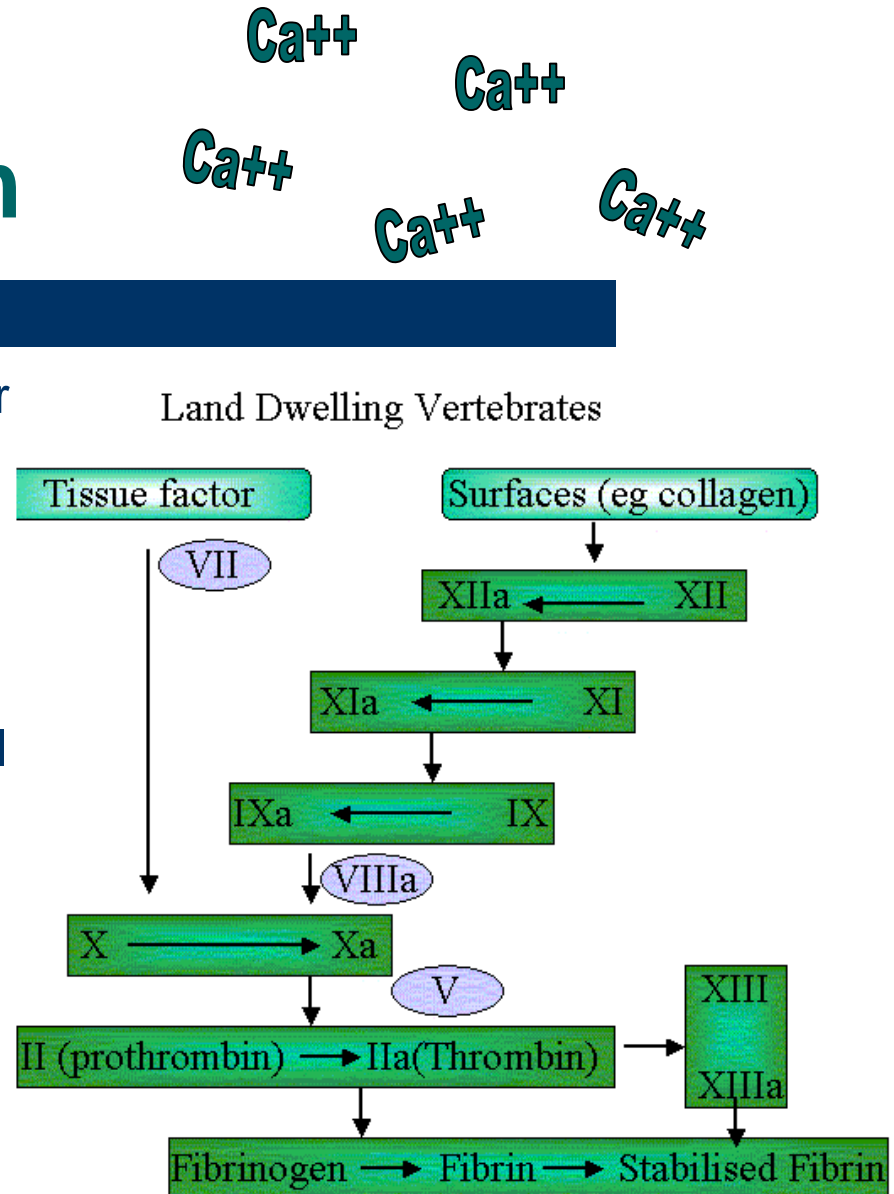
# Platelets



- Tiny cellular elements, made in the bone marrow, that travel in the bloodstream waiting for a bleeding problem to develop
- When bleeding occurs, chemical reactions change the surface of the platelet to make it activated and become “sticky”
- These activated platelets begin adhering to the wall of the blood vessel at the site of bleeding

# Thrombin System

- Calcium ions must be present for the thrombin system to begin
- The thrombin system consists of several blood proteins that activate when bleeding occurs
- The activated clotting proteins engage in a cascade of chemical reactions that finally produce a substance called fibrin
- Fibrin strands stick to the exposed vessel wall, clumping together and forming a web-like complex of strands
- Red blood cells become caught up in the web, causing a clot



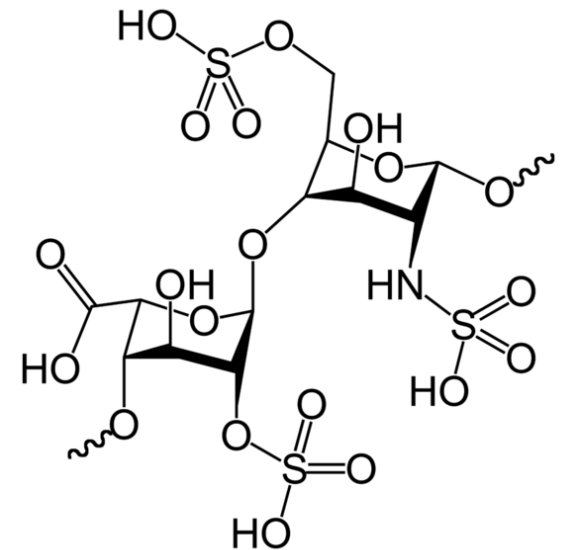
# Coagulation Factors

Factor	Name
I	Fibrinogen
II	Prothrombin
III	Tissue Factor or thromboplastin
IV	Ca <sup>++</sup>
V	Proaccelerin
VII	Proconvertin
VIII	Antihemophilic A factor
IX	Antihemophilic B factor or Christmas factor

Factor	Name
X	Stuart or Stuart-Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor, contact factor
XIII	Fibrin stabilizing factor Prekallikrein factor High-molecular-weight kininogen

# Heparin

- Heparin is a naturally-occurring anticoagulant produced by basophils and mast cells to prevent formation and extension of blood clots
- Heparin does not disintegrate clots that have already formed. It permits the body's natural clot lysis mechanisms, i.e. fibrinolysis, to work normally to break down previously formed clots
- As the thrombokinase is released, it neutralizes the action of heparin to allow clotting to occur





# Anticoagulant Use

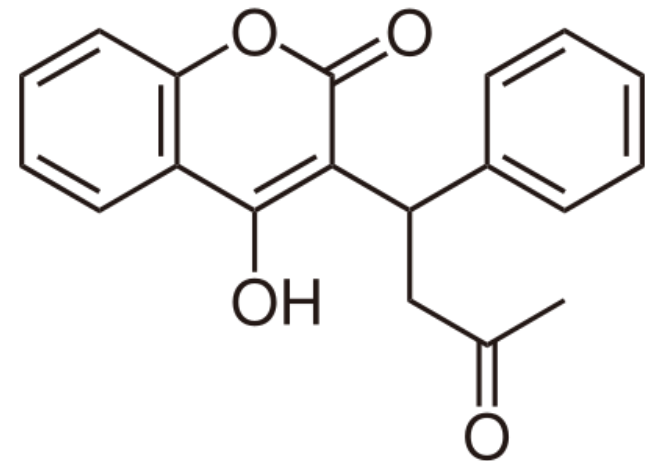
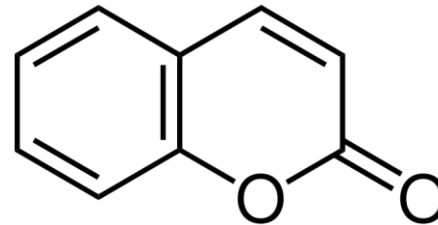
- Anticoagulant drugs help prevent the development of harmful clots in the blood vessels by lessening the blood's ability to cluster together
- The function of these drugs is often misunderstood because they are sometimes referred to as blood thinners; they do not in fact thin the blood
- These drugs will not dissolve clots that already have formed, but it will stop an existing clot from becoming worse and prevent future clots

# Anticoagulant Drugs

- Heparin and warfarin are the two traditional anticoagulants
- Anticoagulants are used for acute coronary syndromes, deep-vein thrombosis (DVT), pulmonary embolism (PE), and heart surgery
- Thrombus - A blood clot that forms abnormally within the blood vessels
- Embolus - When a blood clot becomes dislodged from the vessel wall and travels through the bloodstream
- It is also given to certain people at risk for forming blood clots, such as those with artificial heart valves or who have atrial fibrillation (AF)

# Warfarin

- Warfarin is an oral medication
- It is a synthetic derivative of coumarin, a chemical found naturally in many plants -- it decreases blood coagulation by interfering with vitamin K metabolism
- It stops the blood from clotting within the blood vessels and is used to stop existing clots from getting bigger (as in DVT) and to stop parts of clots breaking off and forming emboli (as in PE)



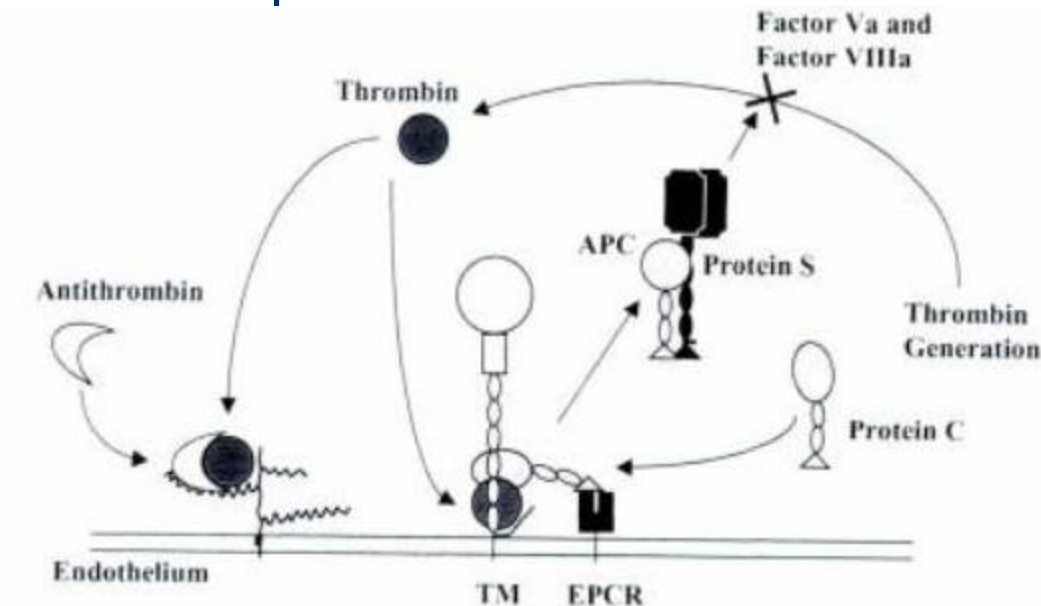
# Warfarin



- The most common side effects of warfarin are bleeding and bruising
- The bleeding can be in the form of prolonged bleeding from cuts; bleeding that does not stop by itself
- Treatment is monitored by regular blood testing using the International Normalized Ratio (INR), which is a measure of how much longer it takes the blood to clot when oral anticoagulant drug is used

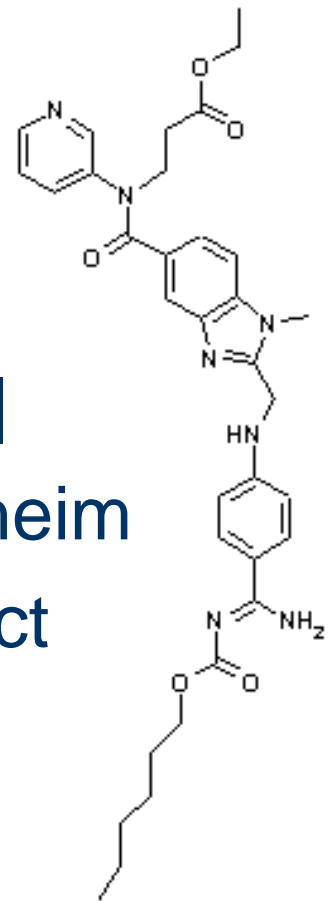
# Warfarin

- Warfarin inhibits the effective synthesis of biologically active forms of the vitamin K-dependent clotting factors: II, VII, IX and X, as well as the regulatory factors protein C, protein S and protein Z



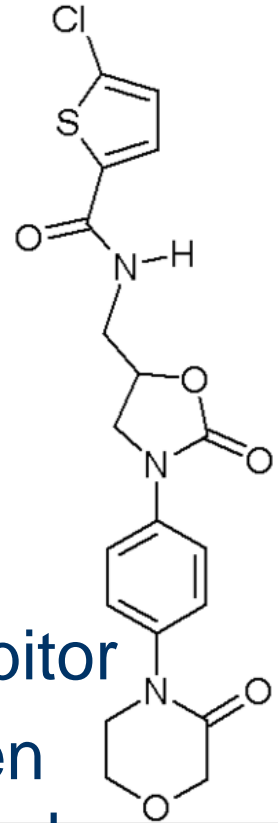
# Dabigatran etexilate

- It was developed by Boehringer Ingelheim
- Dabigatran etexilate is a new oral direct thrombin inhibitor and the prodrug of dabigatran
- Dabigatran is a small molecule that reversibly inhibits both free and clot-bound thrombin by binding to exosite 1 and/or the active site of thrombin

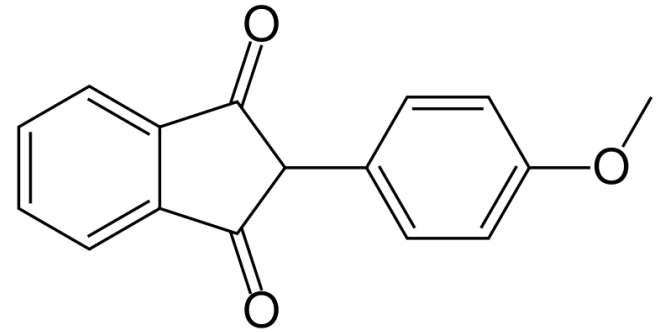


# Rivaroxaban

- Developed by Bayer
- Rivaroxaban is an orally available, small-molecule, active site-directed factor Xa inhibitor
- There are no significant interactions between food, antacids, digoxin, aspirin, naproxen and rivaroxaban have been noted suggesting that dose adjustment of rivaroxaban would not be required when these agents are concurrently administered



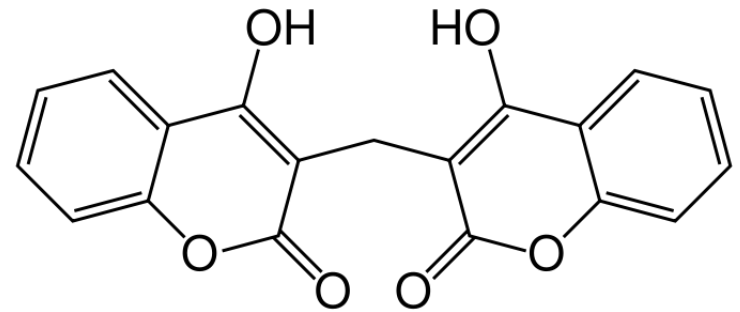
# Anisindione



- Anisindione (brand name Miradon) is a synthetic oral anticoagulant and an indanedione derivative
- Reduces the prothrombin activity of the blood
- It prevents the formation of active procoagulation factors II, VII, IX, and X, as well as the anticoagulant proteins C and S, in the liver by inhibiting the vitamin K–mediated gamma-carboxylation of precursor proteins



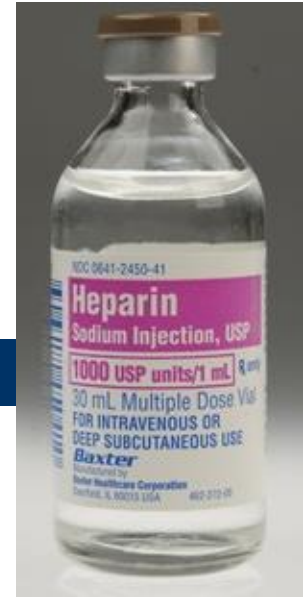
# Dicumarol



- It is a potent oral anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent clotting factors (prothrombin and factors VII, IX and X) in the liver; it is starting to largely replace warfarin
- Dicumarol is produced naturally by conversion of nontoxic coumarin in moldy sweet clover hay, lespepeza hay or sweet vernal hay
- It is used especially in preventing and treating thromboembolic disease
- Formerly called bishydroxycoumarin

# Heparin

- Heparin is given by injection or drip into a vein (intravenously) or by injection under the skin (subcutaneously) for treatment and prevention
- It is derived from porcine intestinal mucosa, standardized for anticoagulant activity
- Heparin works by inhibiting the three major clotting factors (thrombin, thromboplastin, and prothrombin)
- It slows the process of thromboplastin synthesis, decelerates the conversion of prothrombin to thrombin, and inhibits the effects of thrombin on fibrinogen, blocking its conversion to fibrin
- The agent also causes an increase in the number of negatively charged ions in the vascular wall, which helps prevent the formation of intravascular clots.



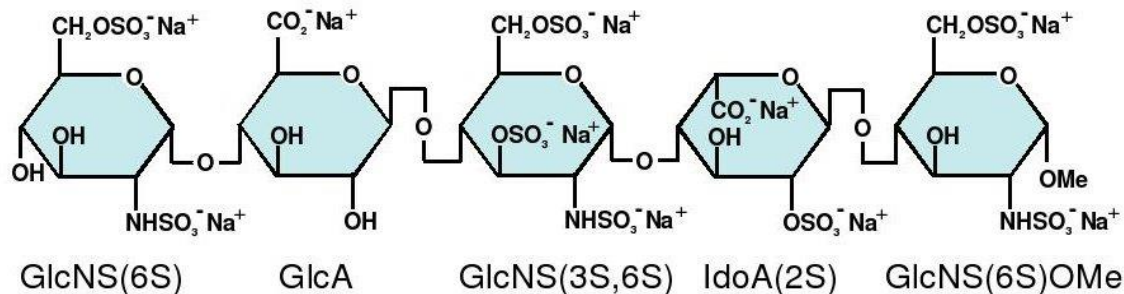
# Low-molecular weight heparin

- Low-molecular weight heparin is gradually replacing heparin for treatment of most patients with venous thromboembolism and acute coronary syndromes because it has more convenient and cost-effective
- It has similar results to heparin
- Administered by subcutaneous injection
- LOVENOX® is an example



# 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



# History of Anticoagulants

- In 1960, DW Barritt and SC Jordan performed the first randomized trial showing the efficacy of anticoagulant therapy in the treatment of venous thromboembolism. Since then, important therapeutic advances have been made in the treatment of deep venous thrombosis and pulmonary embolism.

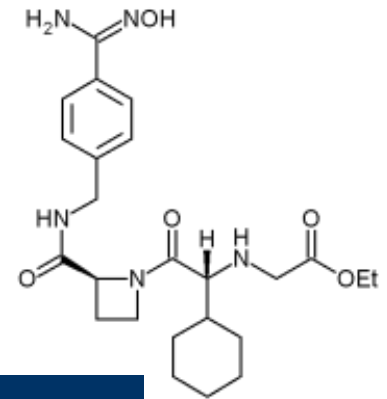
# History of Anticoagulants



- 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



# History of Anticoagulants



- Ximelagatran was the first oral direct thrombin inhibitor and had proven efficacy for prevention and treatment of VTE, stroke prevention with AF and recurrent coronary events after acute myocardial infarction
- It was initially approved for short-term VTE prevention in patients undergoing orthopedic surgery in Europe
- It was withdrawn by AstraZeneca in 2006 due to lab works confirming significant damage to the liver

# The future for anticoagulants

- Limitations of warfarin have fostered a great interest in the development of novel anticoagulants for oral use to potentially replace warfarin
- The design of specific inhibitors against molecular targets that play a pivotal role in the coagulation cascade are in development

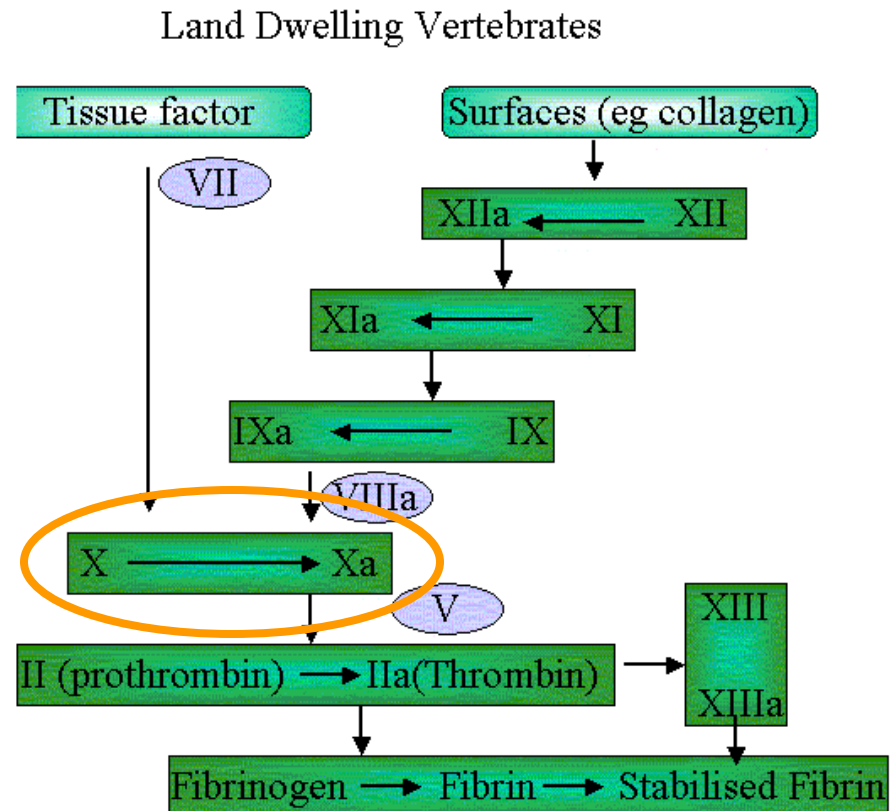


# The future for anticoagulants

- 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

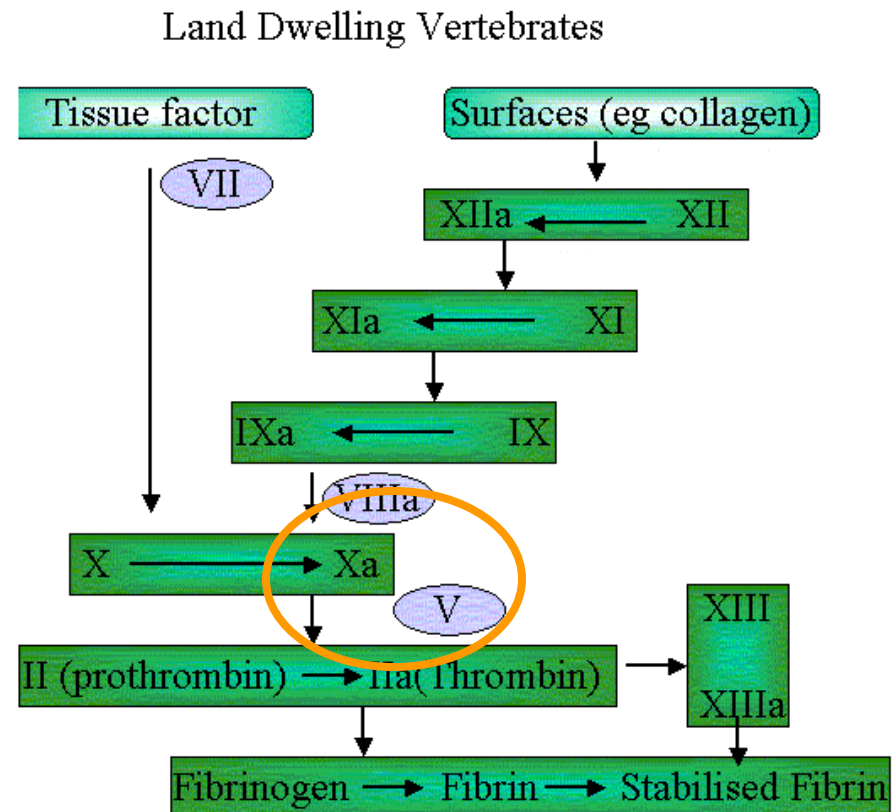
# The future for anticoagulants

- Factor Xa 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



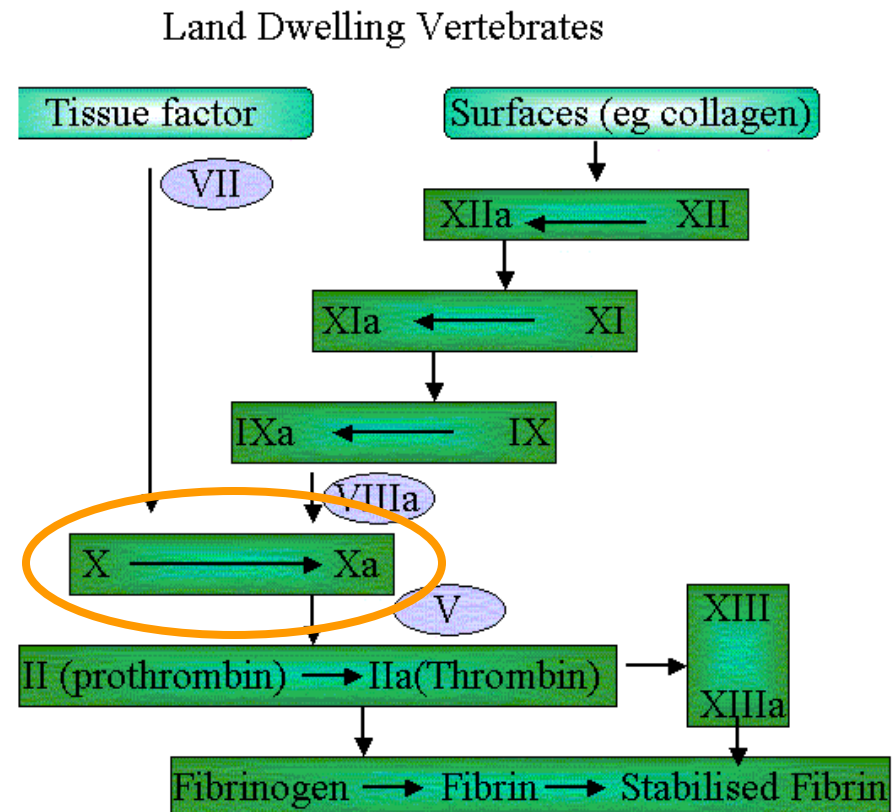
# The future for anticoagulants

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



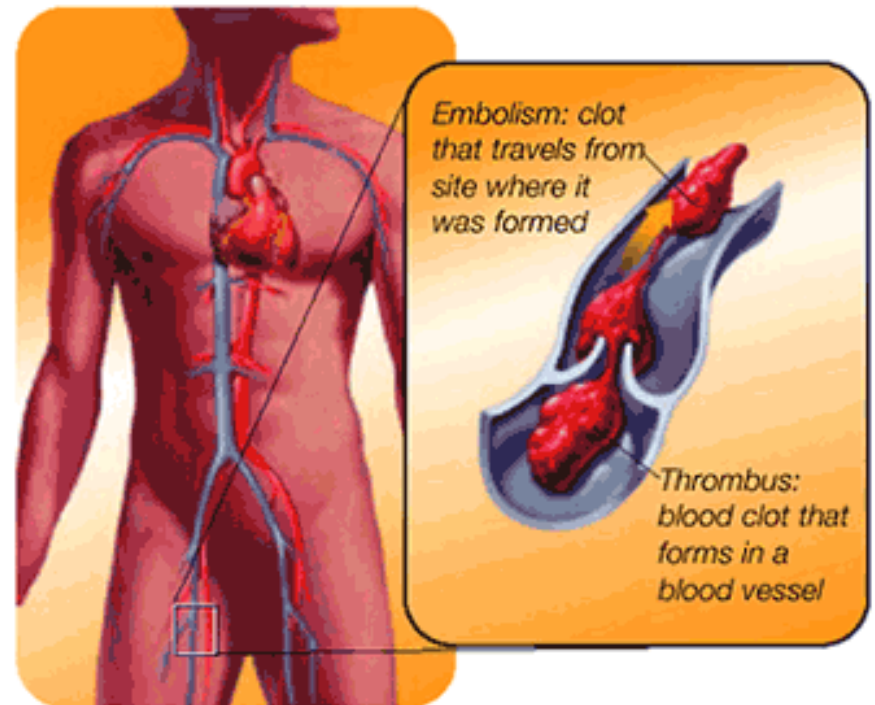
# The future for anticoagulants

- It is hypothesized that anticoagulants targeting factor Xa might be more effective than those targeting coagulation factors located lower down in the cascade, such as thrombin



# The future for anticoagulants

- This concept has been partially proved when the first indirect factor Xa inhibitor, fondaparinux, received FDA approval for the prevention and treatment of VTE.



# References

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