Medical Device Thrombosis

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Introduction

- Blood contacting medical devices are widely used to treat cardiovascular diseases
- Thrombus formation is a common cause of failure of these devices
- Thrombi on these devices are composed of platelet aggregates and fibrin
- Antiplatelet agents and anticoagulants are often used for prevention or treatment

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What is the first step in thrombus formation on a medical device?

1. Contact activation
2. Platelet adhesion
3. Protein adsorption
4. Complement activation

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How should medical device thrombosis be treated?

1. Vitamin K antagonist
2. Dabigatran
3. Fondaparinux
4. Thrombolysis

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Goal of this presentation

How do these devices initiate clotting and how can this be minimized or prevented?

- Examine interfaces between blood and device
- Review the pathogenesis of clotting of these devices: role of the intrinsic pathway of coagulation
- Methods for prevention of thrombosis:
  - (Surface modifications to render biomaterials less thrombogenic)
  - Administration of systemic antithrombotic agents
- Explain why some anticoagulants are better than others for prevention of thrombosis on blood contacting medical devices

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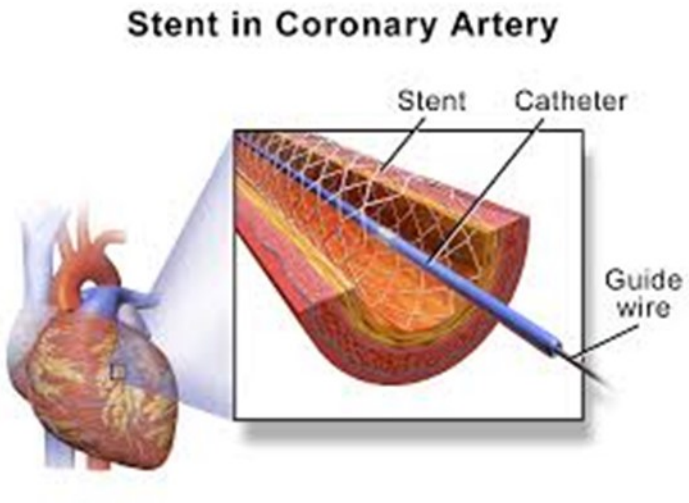
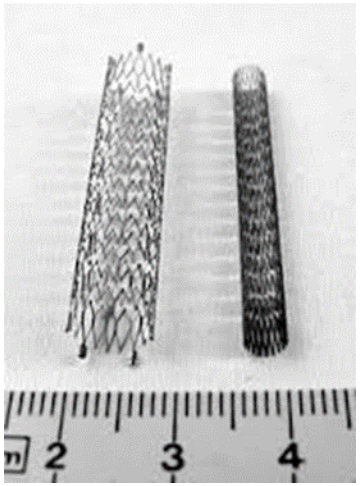
Medical devices: Stents

- Metal or plastic tube inserted into the lumen of a vessel to keep it open
- Bare metal, drug eluting or bioresorbable stent





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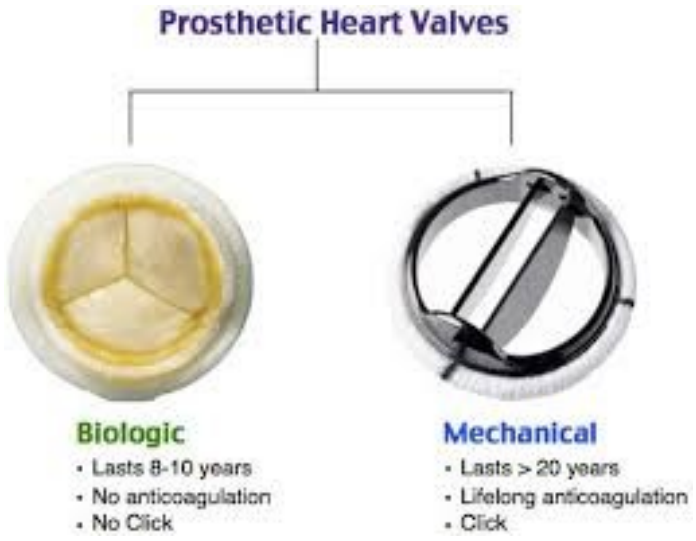
Medical devices: mechanical heart valves

- Prosthetics designed to replicate the function of the natural valves of the heart
- Modern mechanical valves can last indefinitely, but require lifelong treatment with anticoagulants



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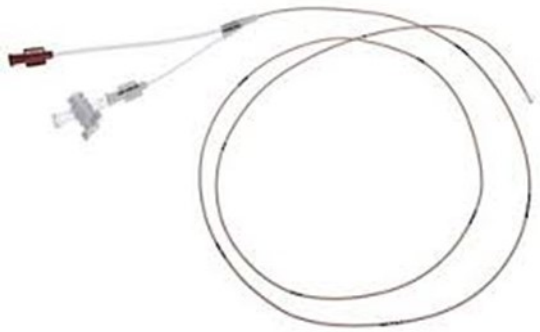
Medical devices: Catheters

- Thin tube inserted into the lumen of a vessel to administer fluids/drugs, to provide access by surgical instruments etc



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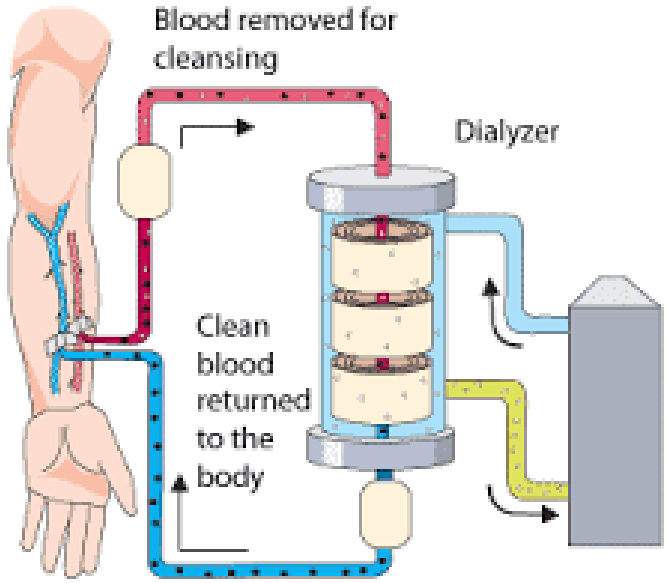
Medical devices: Haemodialysis

- Purification of blood when kidneys are not working normally



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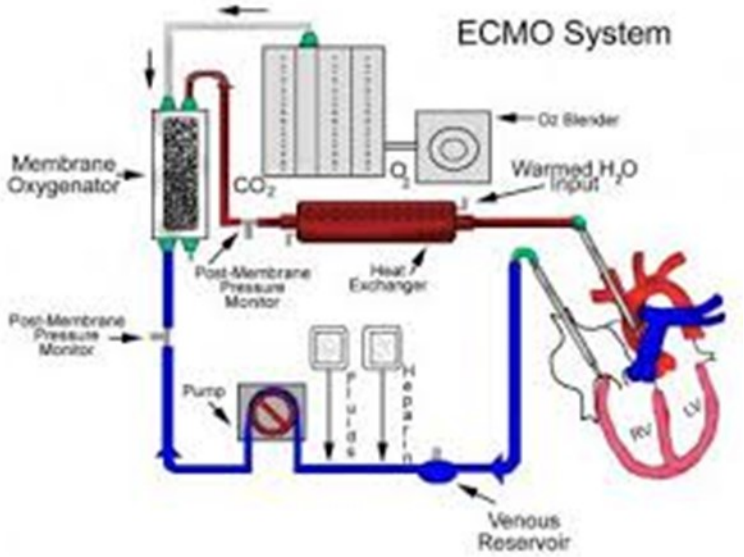
Medical devices: ECMO

- Extracorporeal Membrane Oxygenation
- Provides cardiac and respiratory support to persons whose hearts and lungs are unable to privde an adequate amount of gas exchange to sustain life



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Medical devices

- Material of device comes into contact with blood
- Blood coagulation system may be activated
- Risk of thrombus formation on the device
  - Improper functioning of device
  - Occlusion of the vessel

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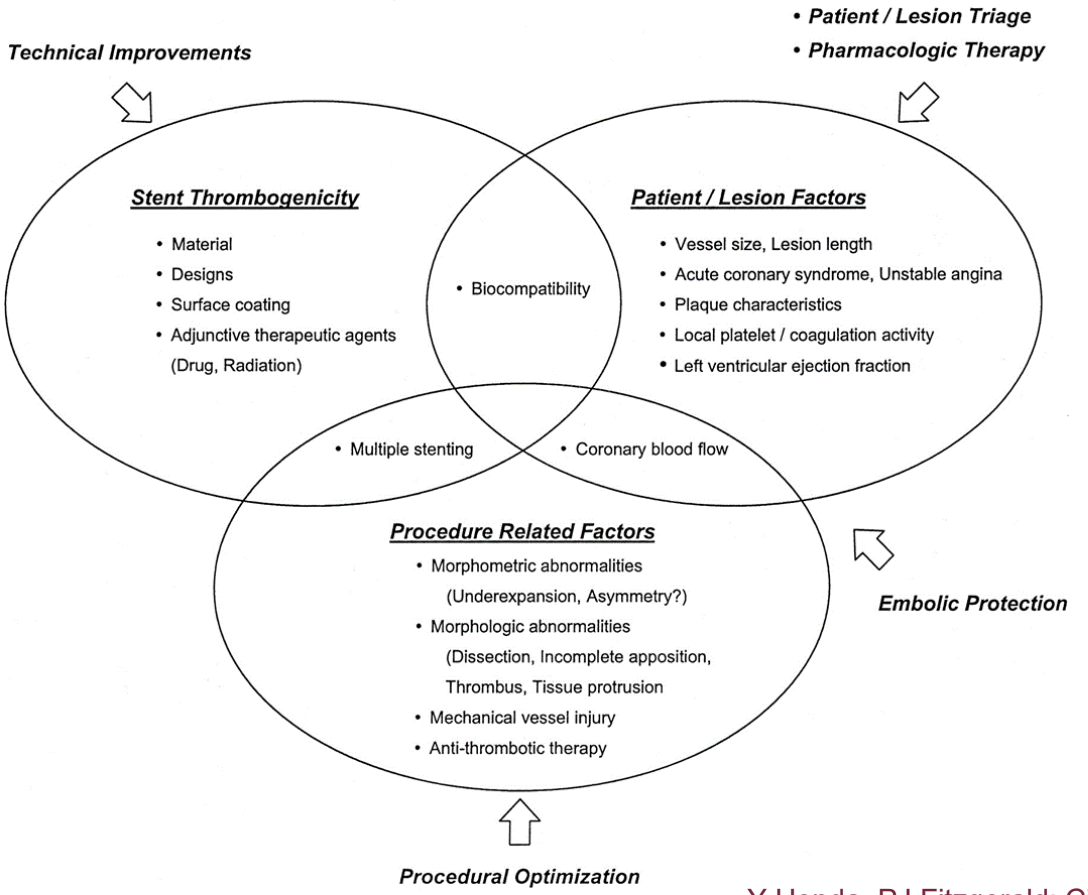
Medical device thrombosis: is it a problem?

- 650-700,000 stents are implanted every year in the USA
- Stent thrombosis occurs in ‘only’ 1-2% of patients
- Adverse effects are myocardial infarction or death in >70% of these patients

Multiple risk factors involved in the development of stent thrombosis

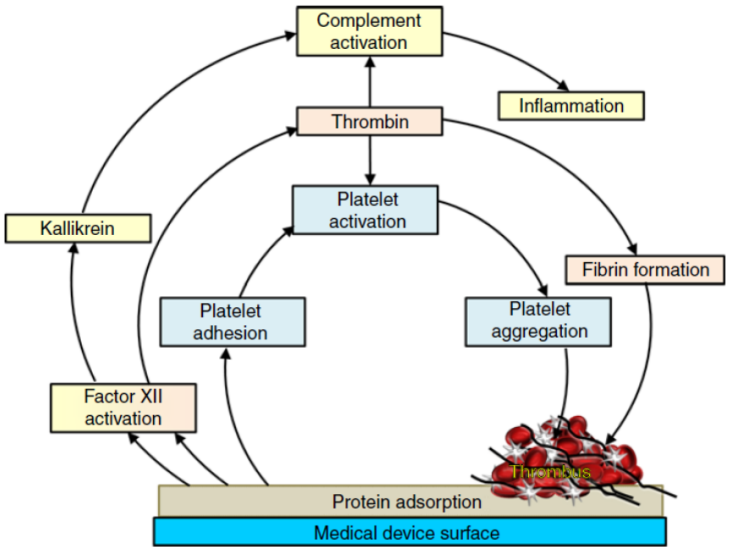


Y Honda, PJ Fitzgerald; Circulation 2003;108:2-5 | 13

How do medical devices lead to thrombosis?

Series of interconnected processes:

- Protein adsorption
- Adhesion of platelets, leukocytes and red blood cells
- Thrombin generation
- Complement activation



Yau et al. Blood 2015;118:6667

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Protein adsorption

- Initiating event: protein layer modulates subsequent reactions
- Dynamics of adsorption are related to chemical and physical properties of the surface and the proteins
- Adsorbed proteins form a surface monolayer with a thickness of 2-10 nm
- Protein concentration on the surface can be 1000-fold higher than in plasma
- Surface absorption is a reversible process and changes over time: the Vroman effect

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The Vroman effect

- Proteins adsorb to a surface in a specific order
- First, highest mobility proteins are bound
- These are later replaced by fibrinogen and finally by high molecular weight kininogen
- In the absence of flow: albumin; globulin; fibrinogen; fibronectin; factor XII and HK

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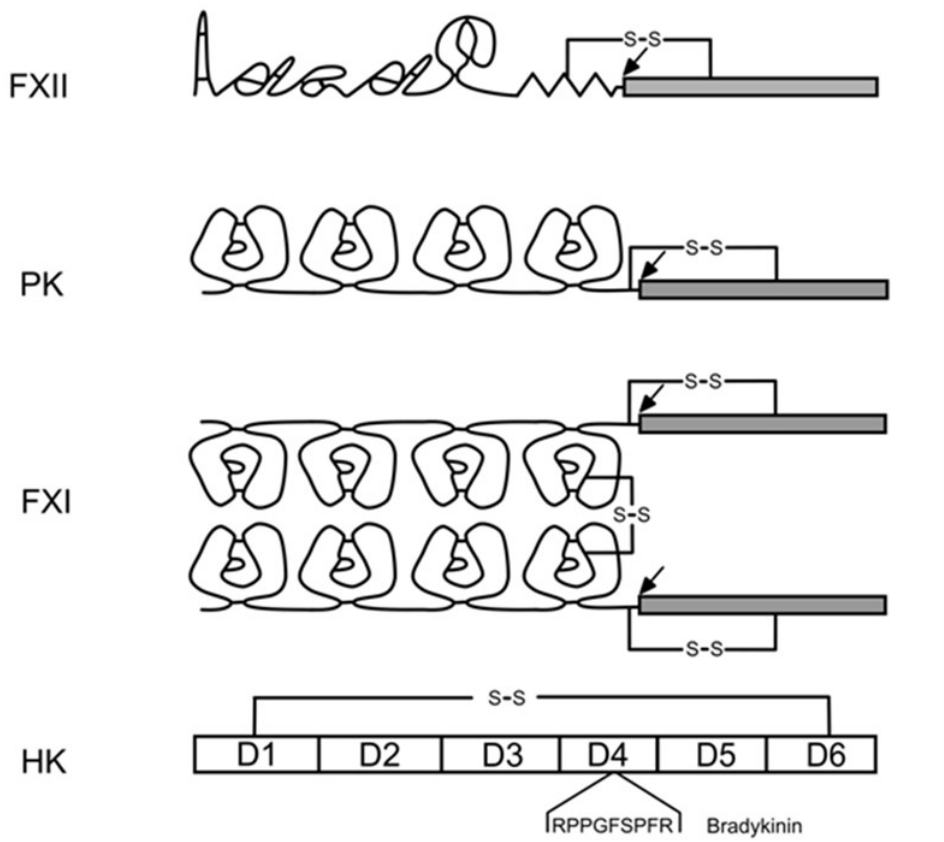
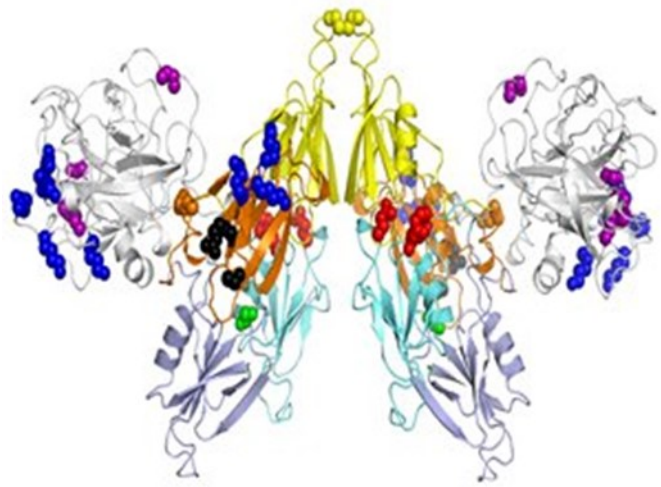
Fibrinogen adsorption

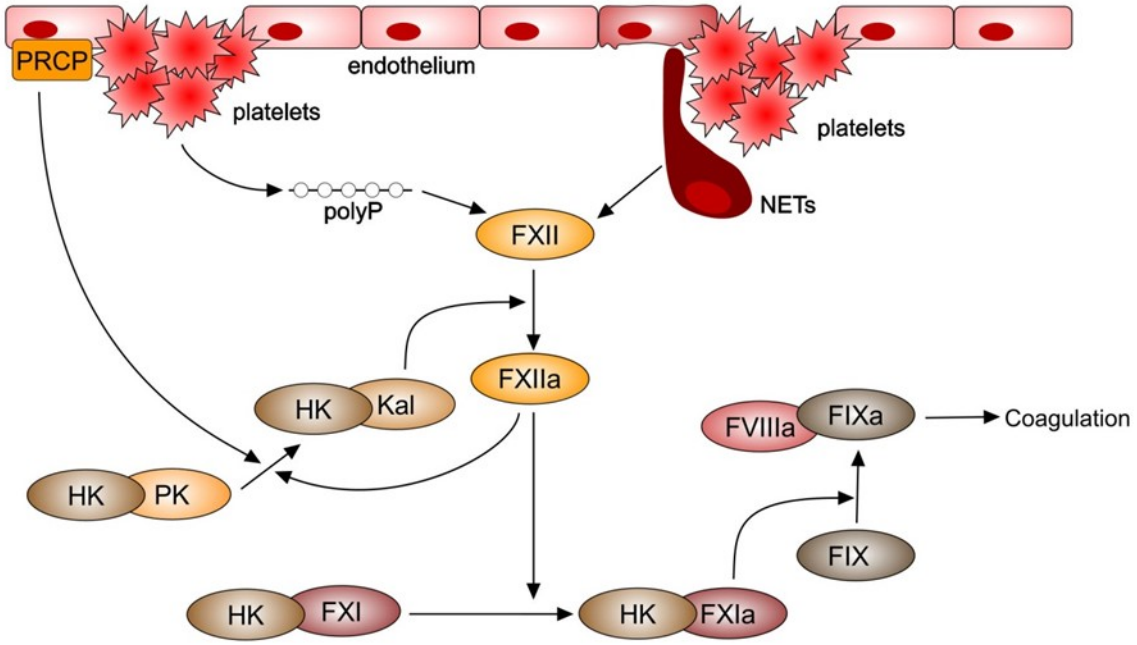
- Responsible for platelet adhesion via GPIIbIIIa
- Even in quiescent state of platelets, GPIIbIIIa can bind to fibrinogen adsorbed to artificial surfaces
- Adsorbed platelets become activated and release agonists such as thromboxane A2 and ADP thereby amplifying adhesion, activation and aggregation
- Leukocytes (neutrophils) adhere to adsorbed fibrinogen via CD11b/CD18
- Adherent platelets promote leukocyte adhesion via P-selectin on platelets and P-selectin glycoprotein ligand-1 on the leukocyte
- These processes are followed by red blood cell adhesion

The contact system





Contact system



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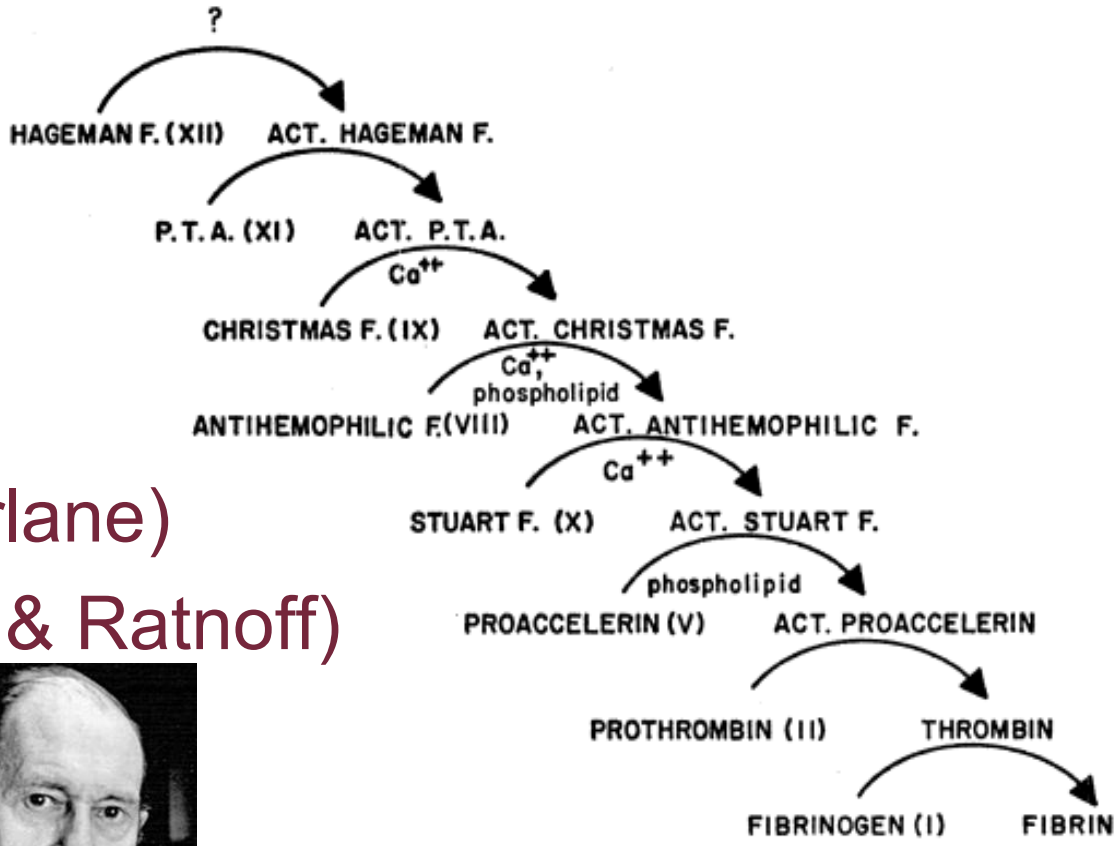
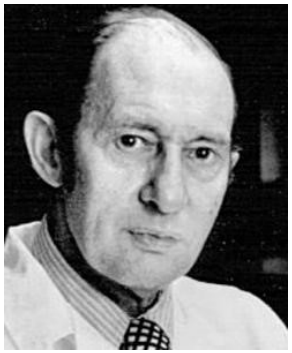
Coagulation is a cascade system (1964)



- Cascade (McFarlane)
- Waterfall (Davie & Ratnoff)



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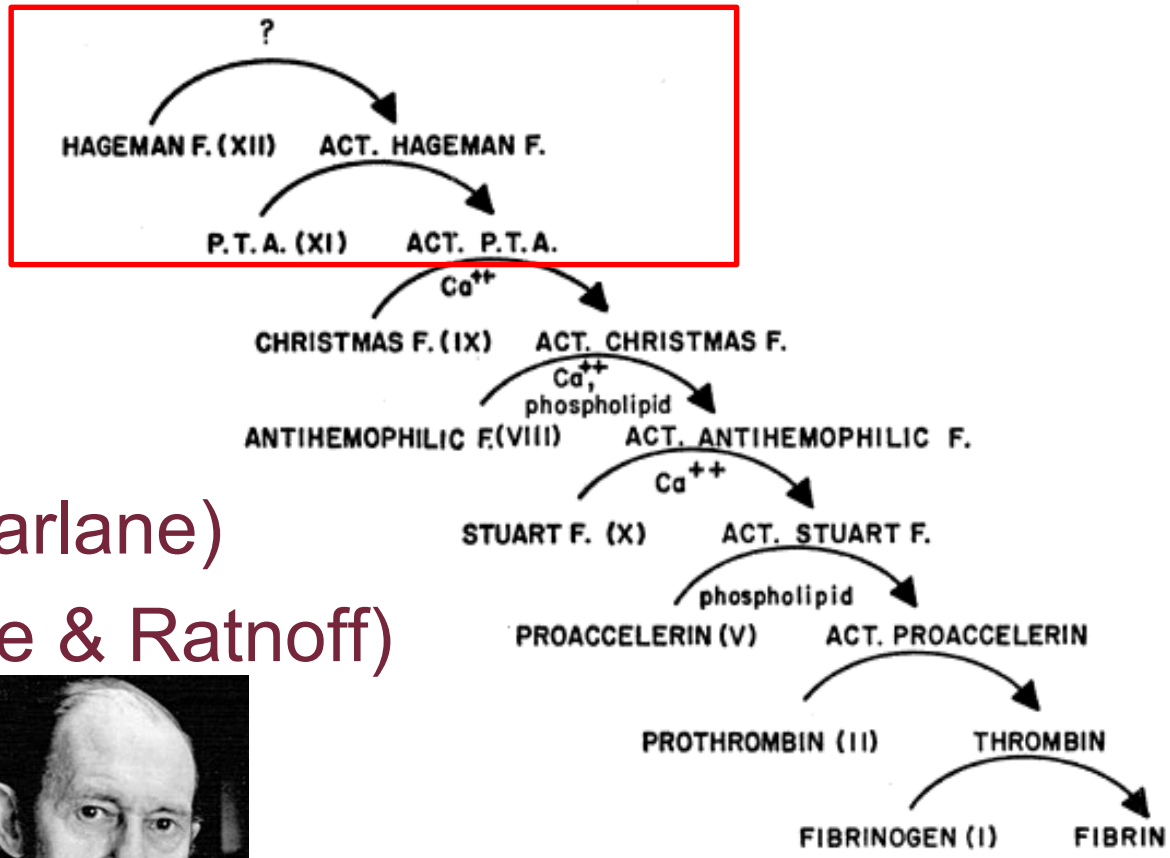

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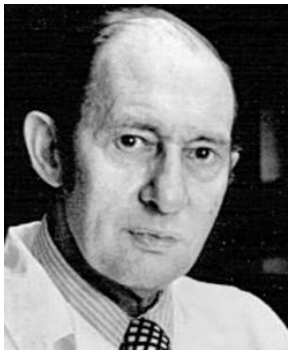

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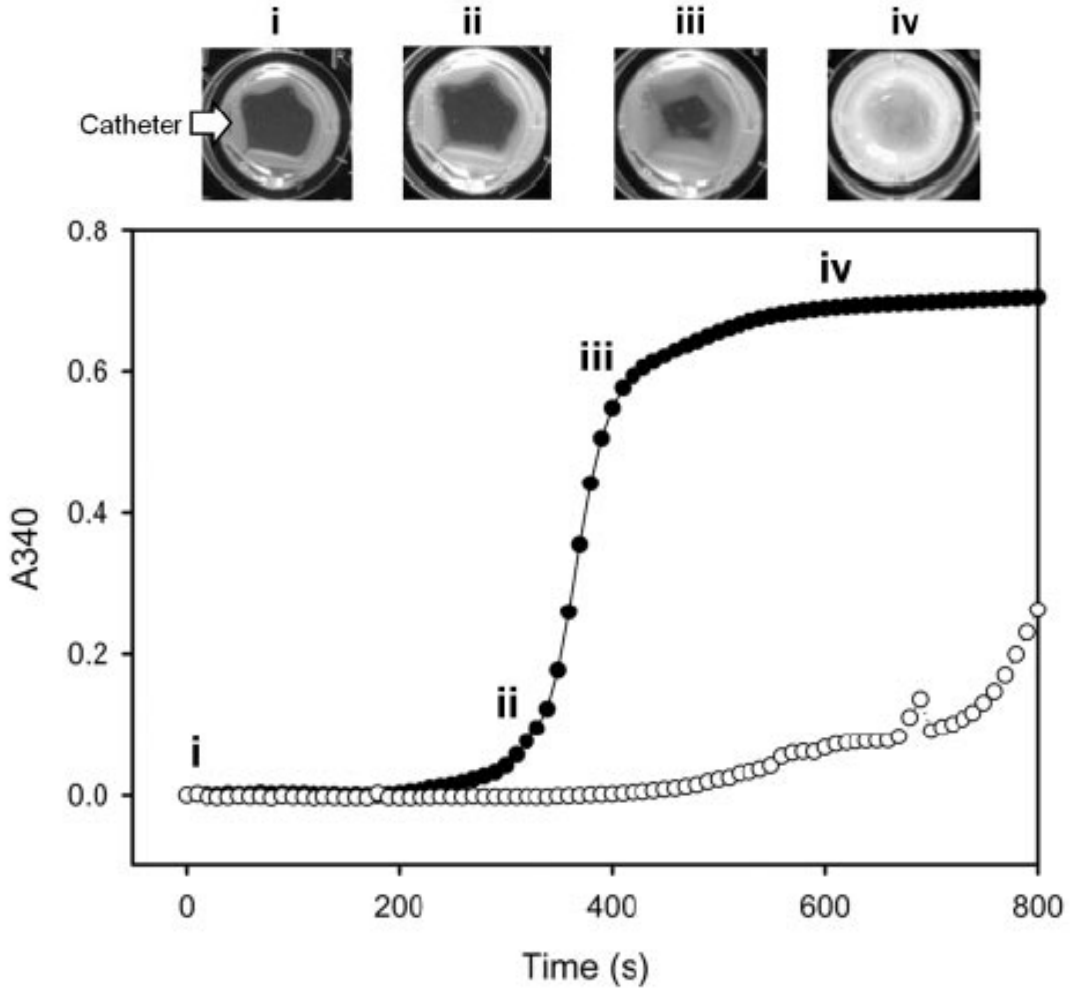
Activation of the contact system

- Assembly on negatively charged surfaces
- Glass/kaolin/elagic acid for the APTT
- Polyphosphates/RNA/DNA/NETs/misfolded proteins

Catheter-induced clotting in platelet-poor plasma



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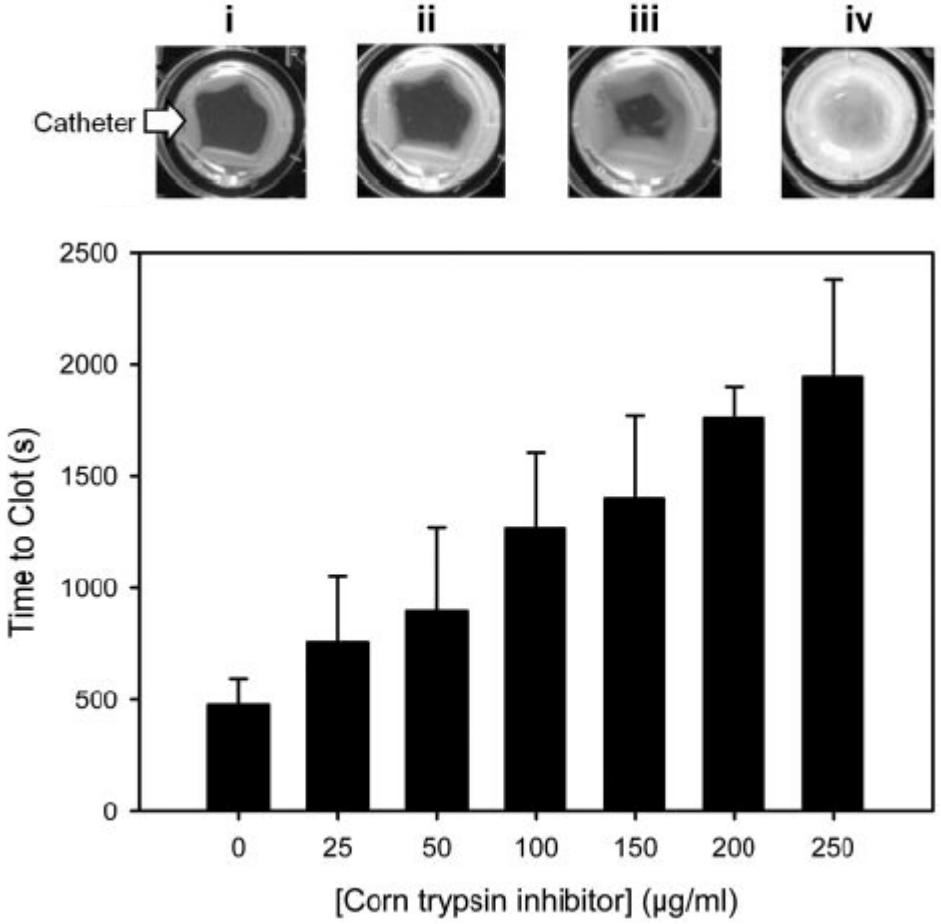
Inhibition of the contact system delays catheter occlusion in vitro



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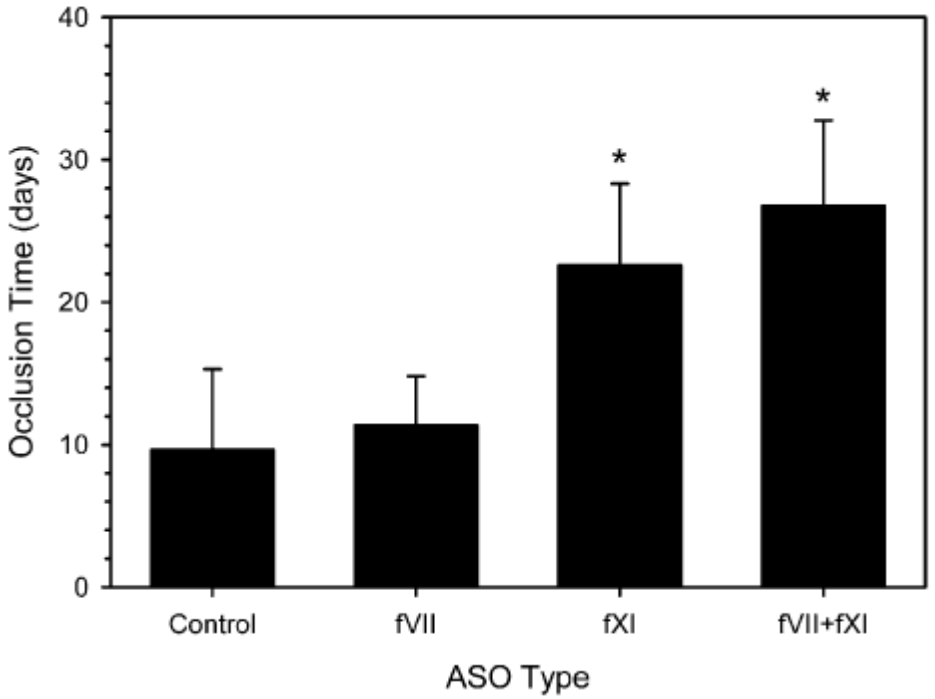
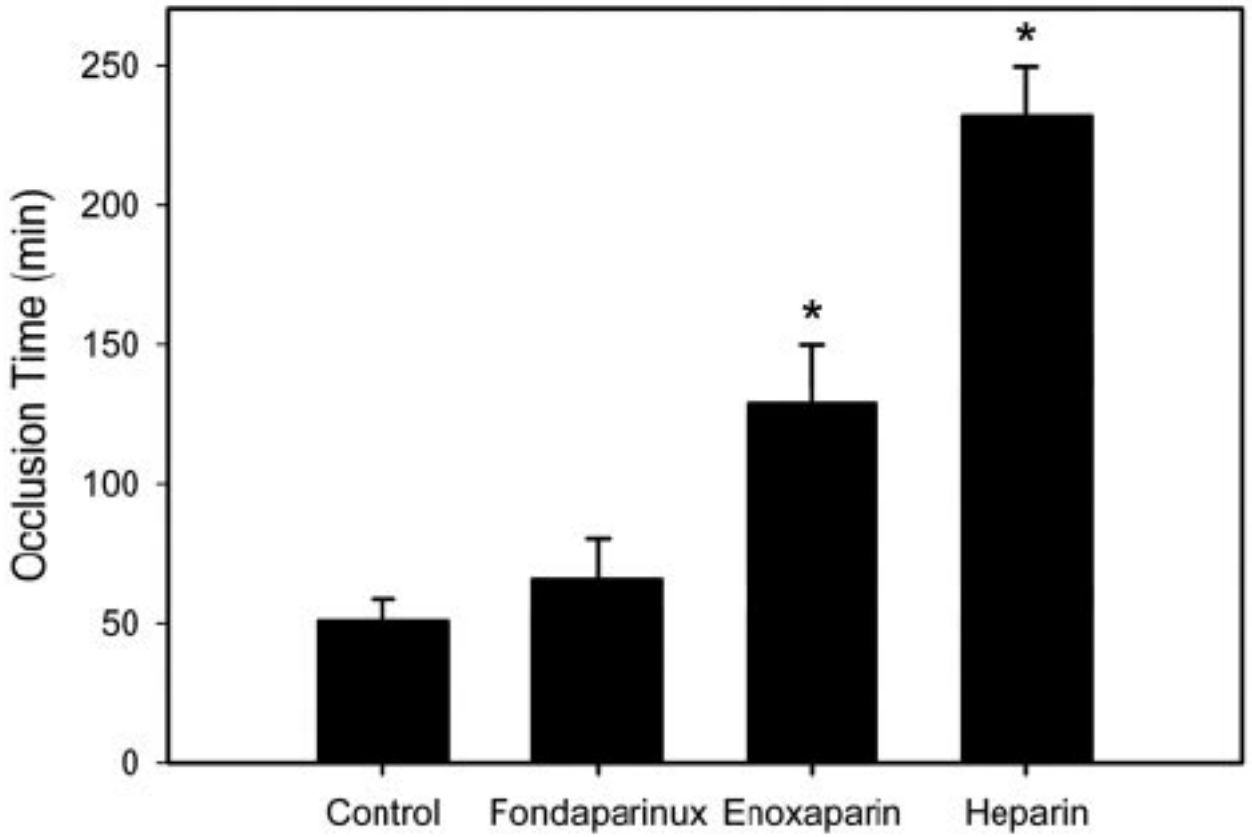
Inhibition of the contact system delays catheter occlusion in vivo (rabbits)



Effect of heparin on catheter occlusion in rabbits



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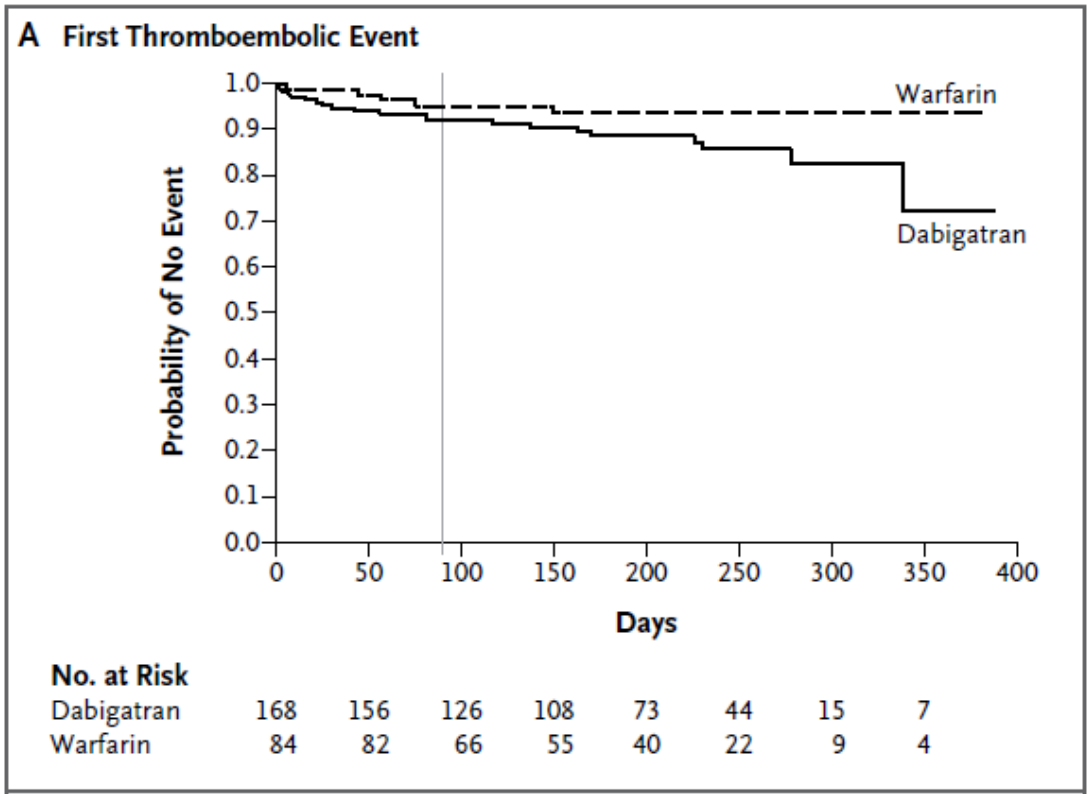
Dabigatran vs warfarin in patients with mechanical heart valves



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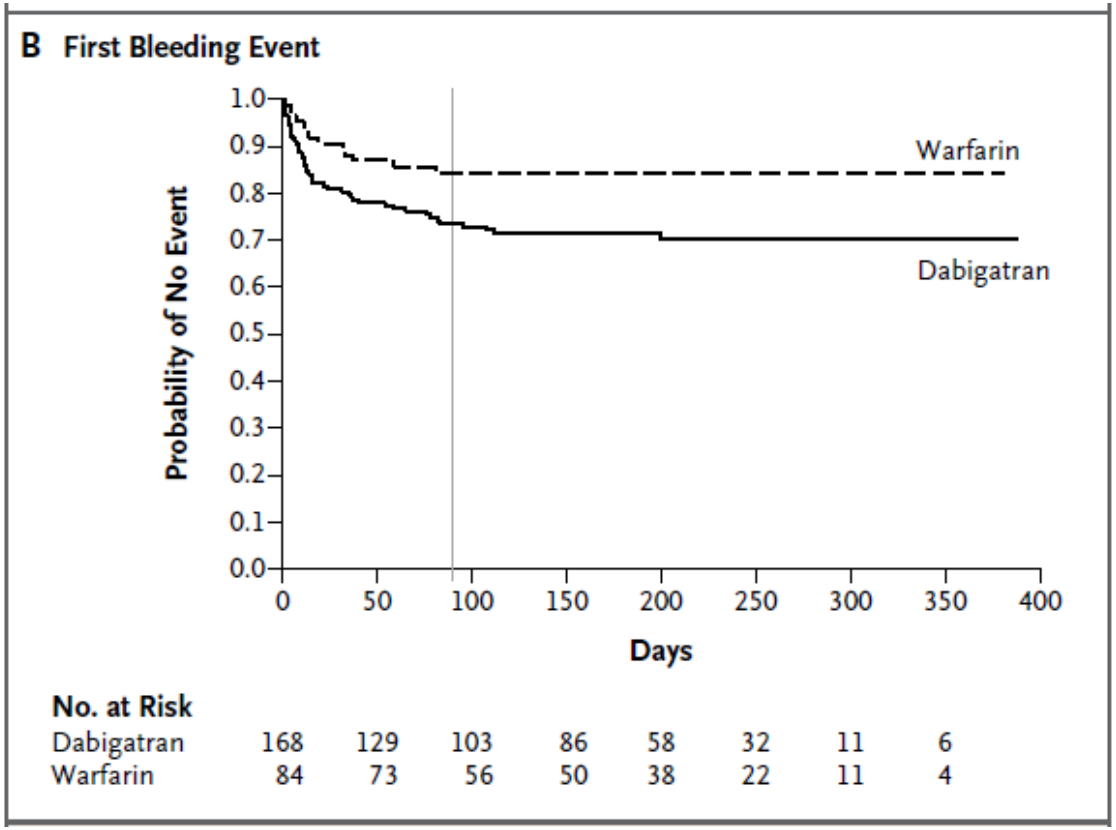
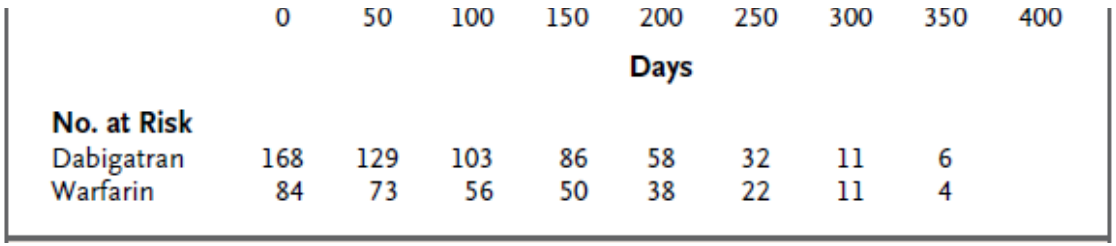


Dabigatran vs warfarin in patients with mechanical heart valves

B First Bleeding Event

In conclusion, the results of our phase 2 study indicate that at the doses tested, dabigatran was not as effective as warfarin for the prevention of thromboembolic complications in patients with mechanical heart valves and was associated with an increased risk of bleeding. These results might be explained by the relative inability of dabigatran to suppress activation of coagulation that occurs when blood is exposed to the artificial surfaces of the valve prosthesis. The use of dabigatran has no positive value and was associated with excess risk in patients with mechanical heart valves.



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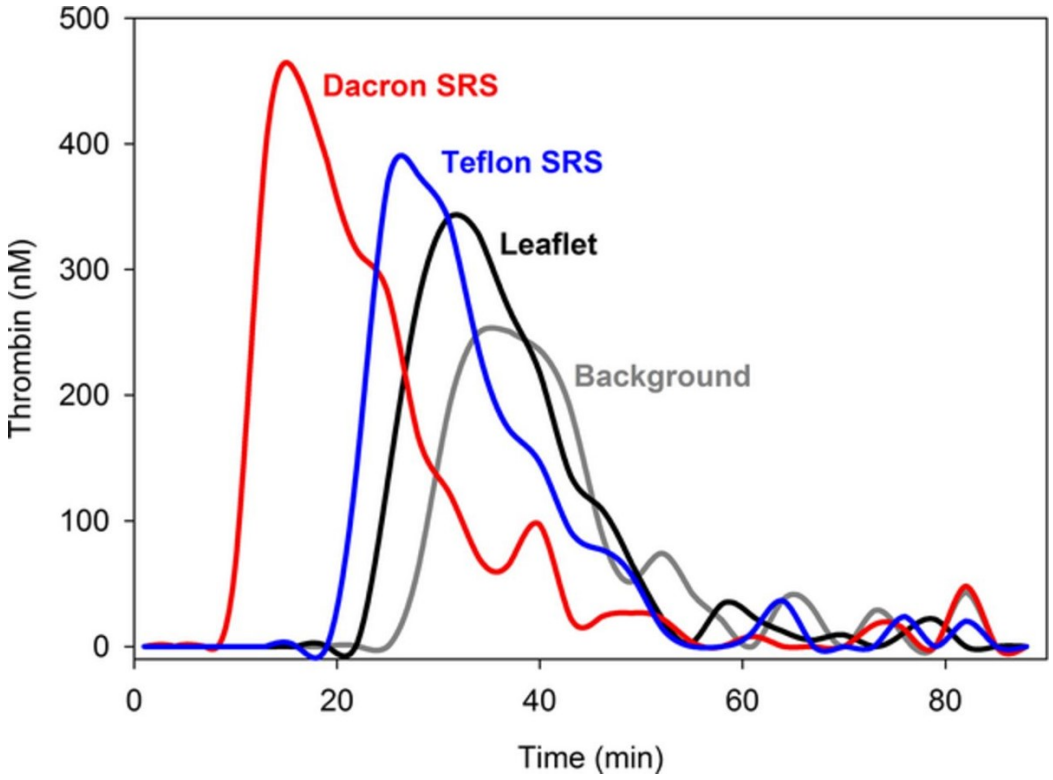
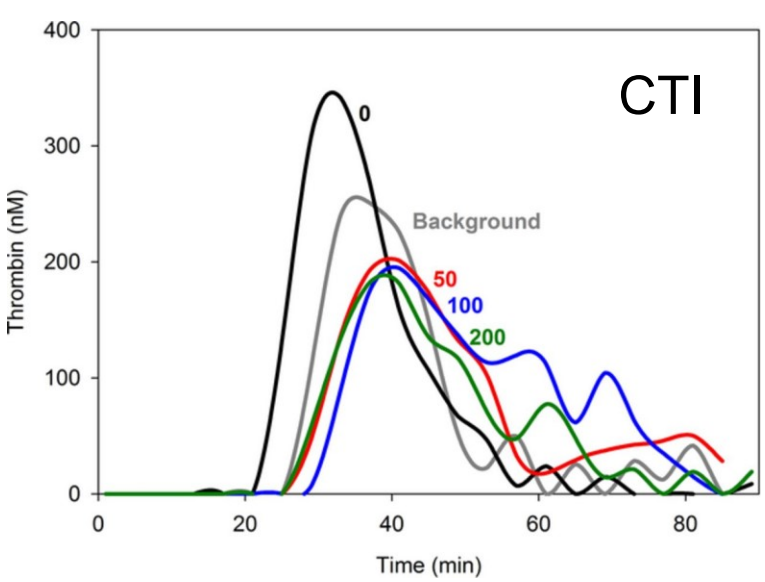
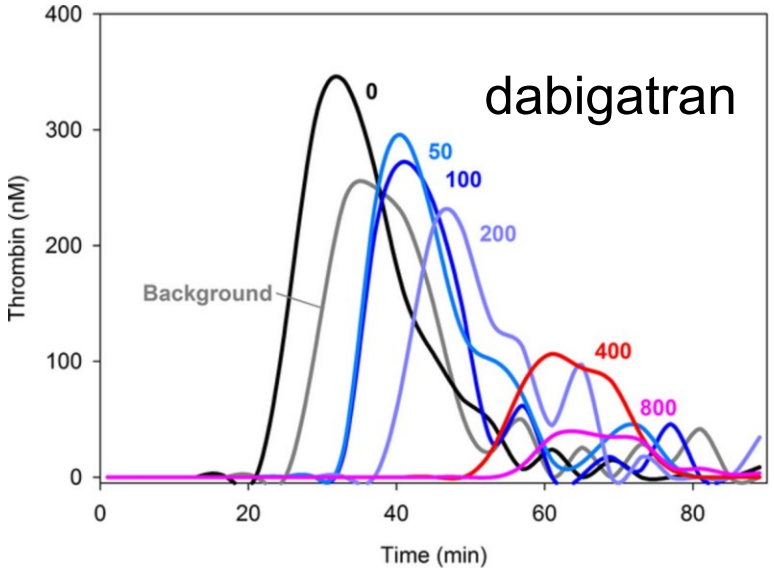
FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves

Thrombin generation on leaflets and sewing ring segments of mechanical heart valves



Inhibition of thrombin generation on valve leaflets





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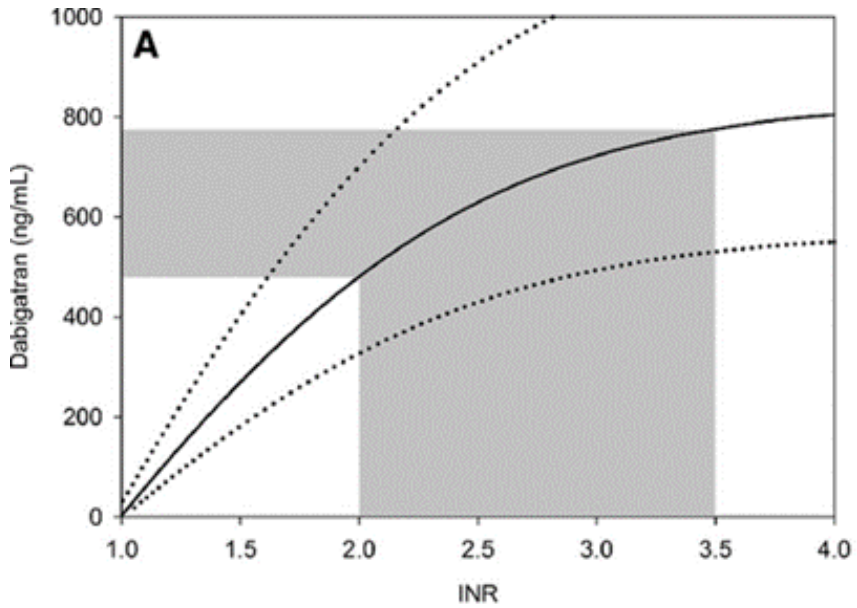

Dose-equivalency plot predicts a more than doubling of the maximum dabigatran dose in patients to achieve the same effect as VKA

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What is the first step in thrombus formation on a medical device?

1. Contact activation
2. Platelet adhesion
3. Protein adsorption
4. Complement activation

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How should medical device thrombosis be treated?

1. Vitamin K antagonist
2. Dabigatran
3. Fondaparinux
4. Thrombolysis

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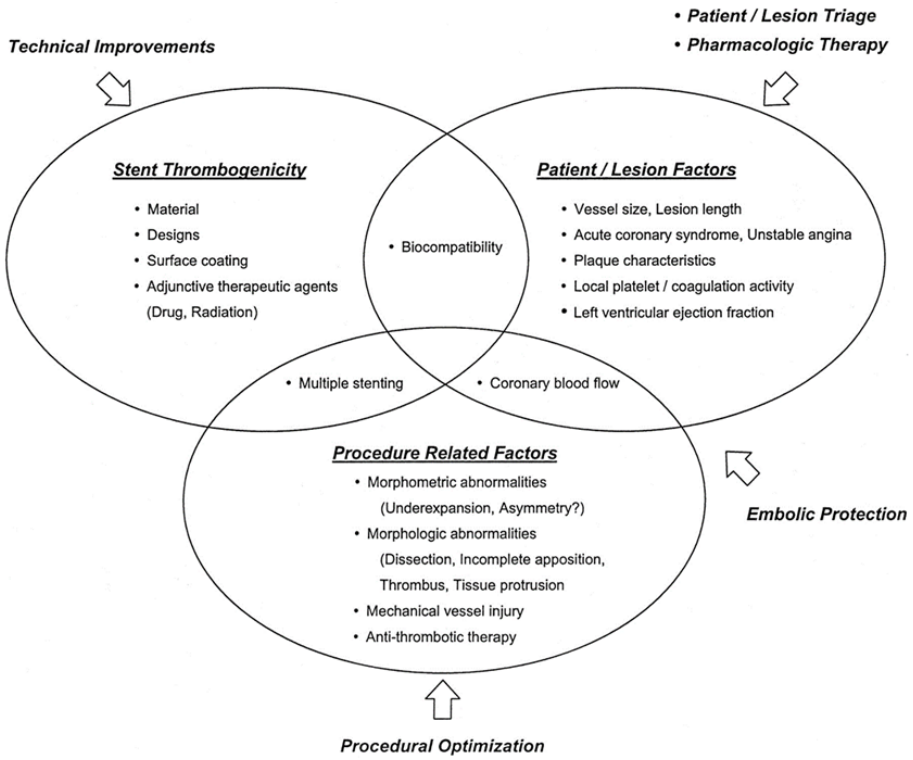
Treatment of medical device associated thrombosis

- Currently: heparin/vitamin K antagonist therapy
- In the (near) future: contact factor inhibition

Future elimination of thrombus formation by medical devices?

- Increased understanding of processes involved in protein deposition and subsequent activation of platelets and coagulation on artificial surfaces: novel biomaterials resistant to protein and cell deposition
- Advances in materials science: development of natural counterparts thereby obviating the need for systemic antithrombotic therapy



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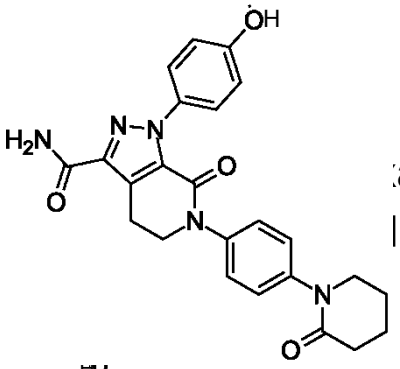
THANK YOU FOR YOUR ATTENTION

Direct Oral Anticoagulants (DOACs)

Xa inhibitors



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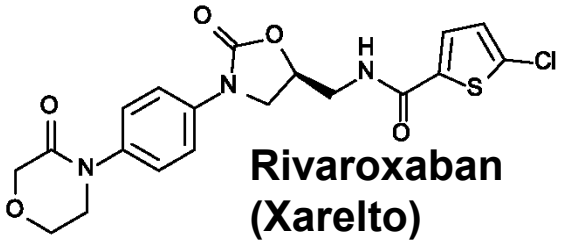
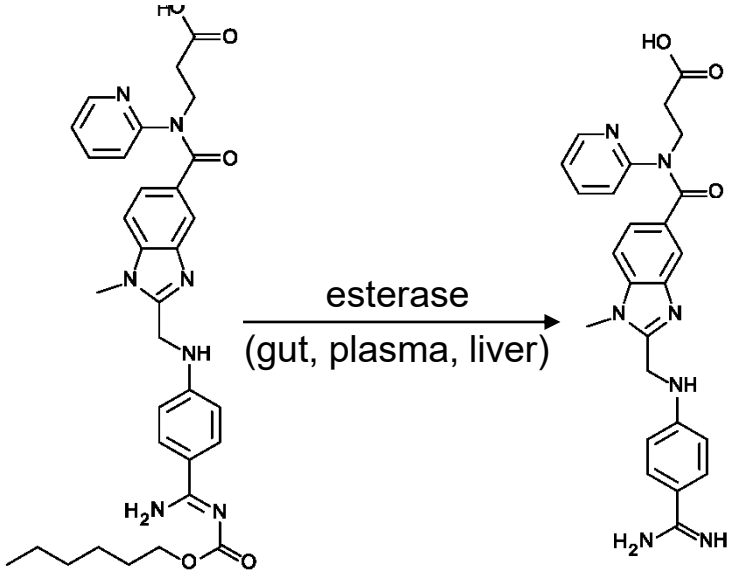


Rivaroxaban (Xarelto)

IIa inhibitor



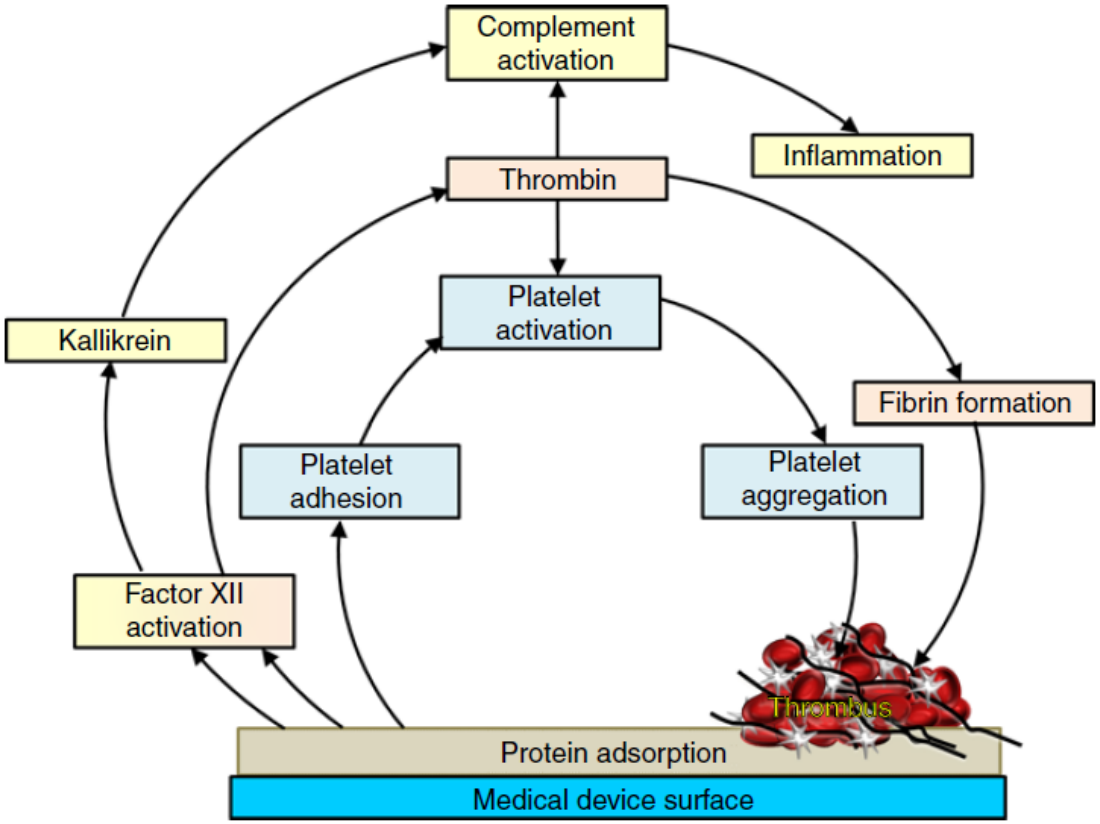
Dabigatran-etexilate (Pradaxa)

Dabigatran

DOACs

- competitive and reversible inhibitors
- bind to active site of Xa or IIa

Medical device associated thrombosis



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