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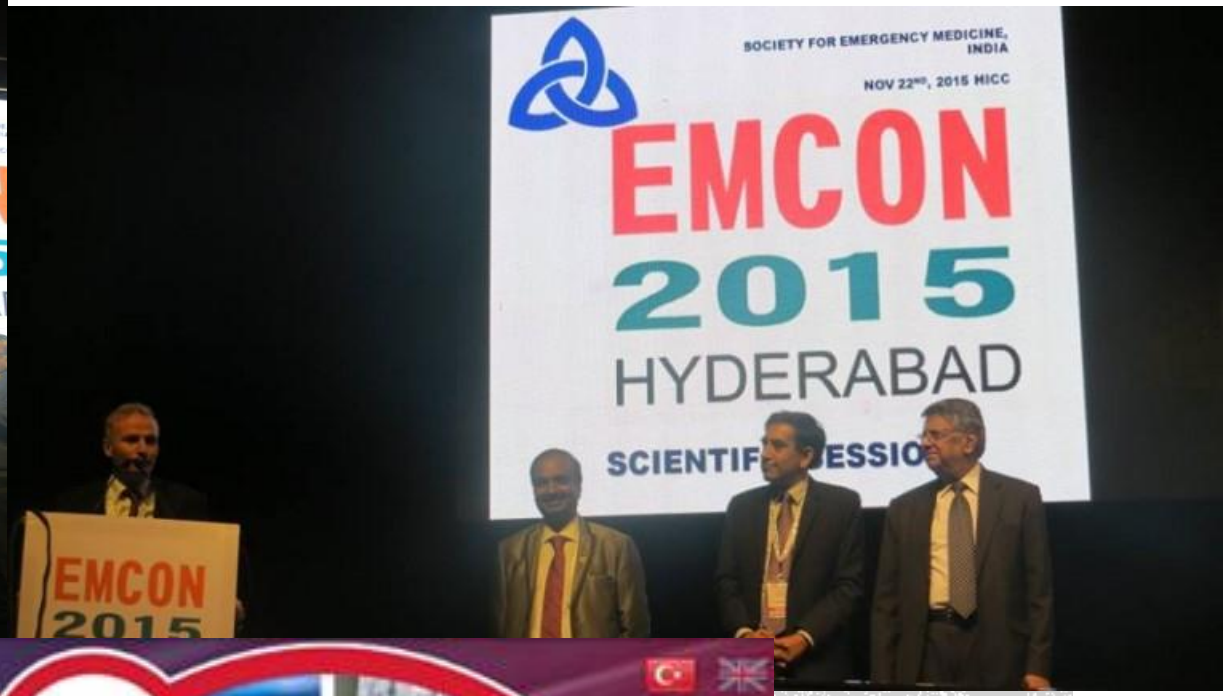
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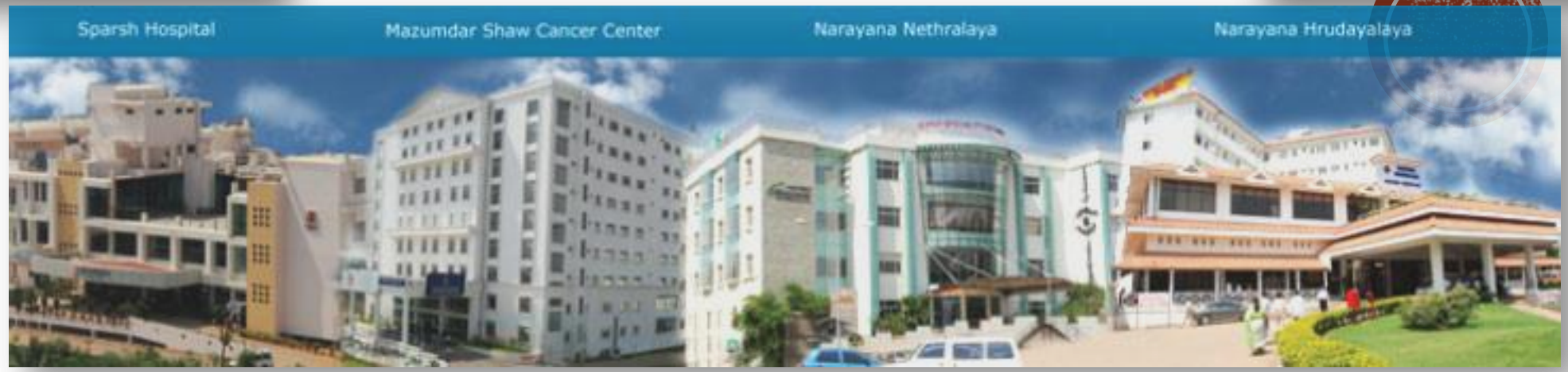
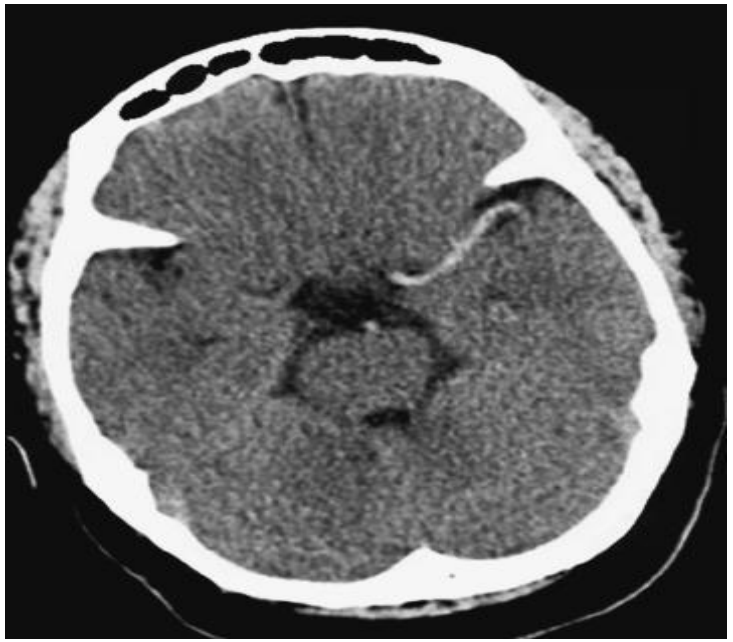
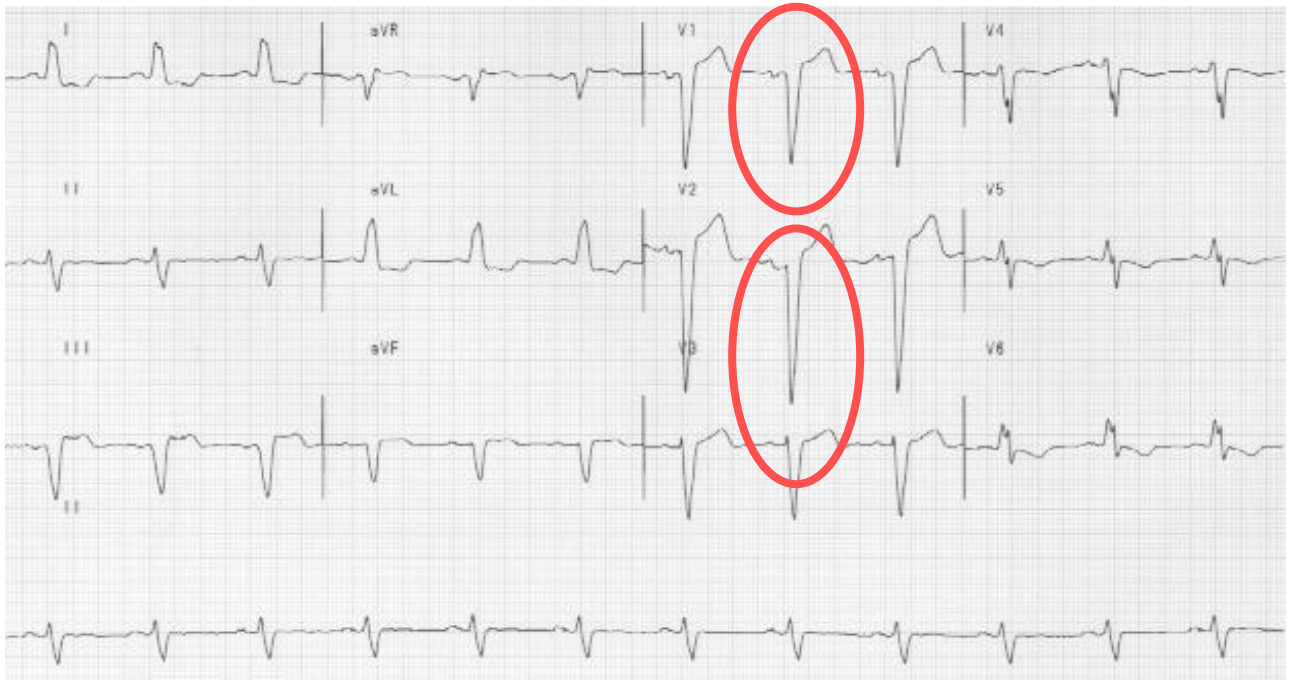
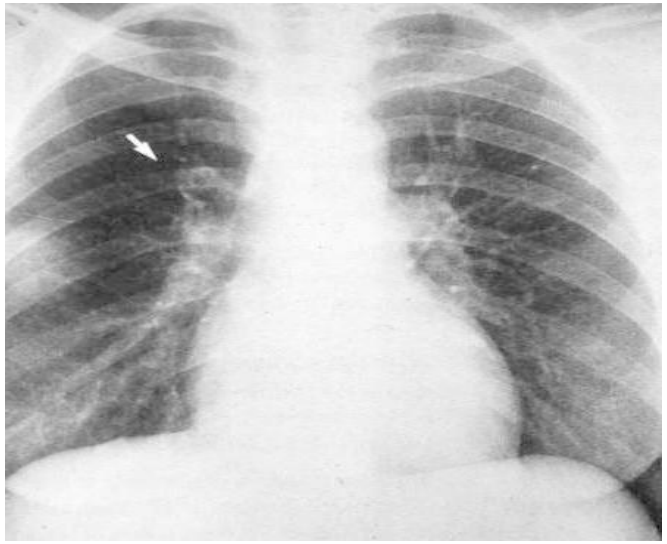
New Oral Anticoagulants in Clinical Practice

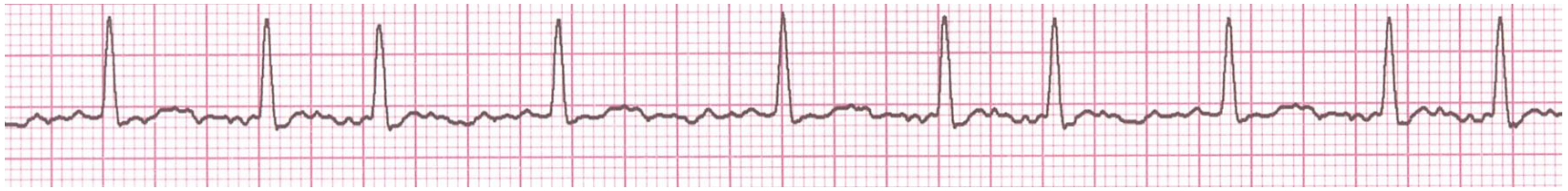
Dr. T. S. Srinath Kumar











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INTRODUCTION

- Oral anticoagulants or 'blood thinners' were proposed in 400 BC during the time of Hippocrates
- The first paper entitled 'Coumadin (warfarin) sodium – a new anticoagulant' was published in 1956

. Nicholson JH, Leavitt T Jr. Coumadin (warfarin) sodium – a new anticoagulant. *N. Engl. J. Med.* 255,491–501 (1956)

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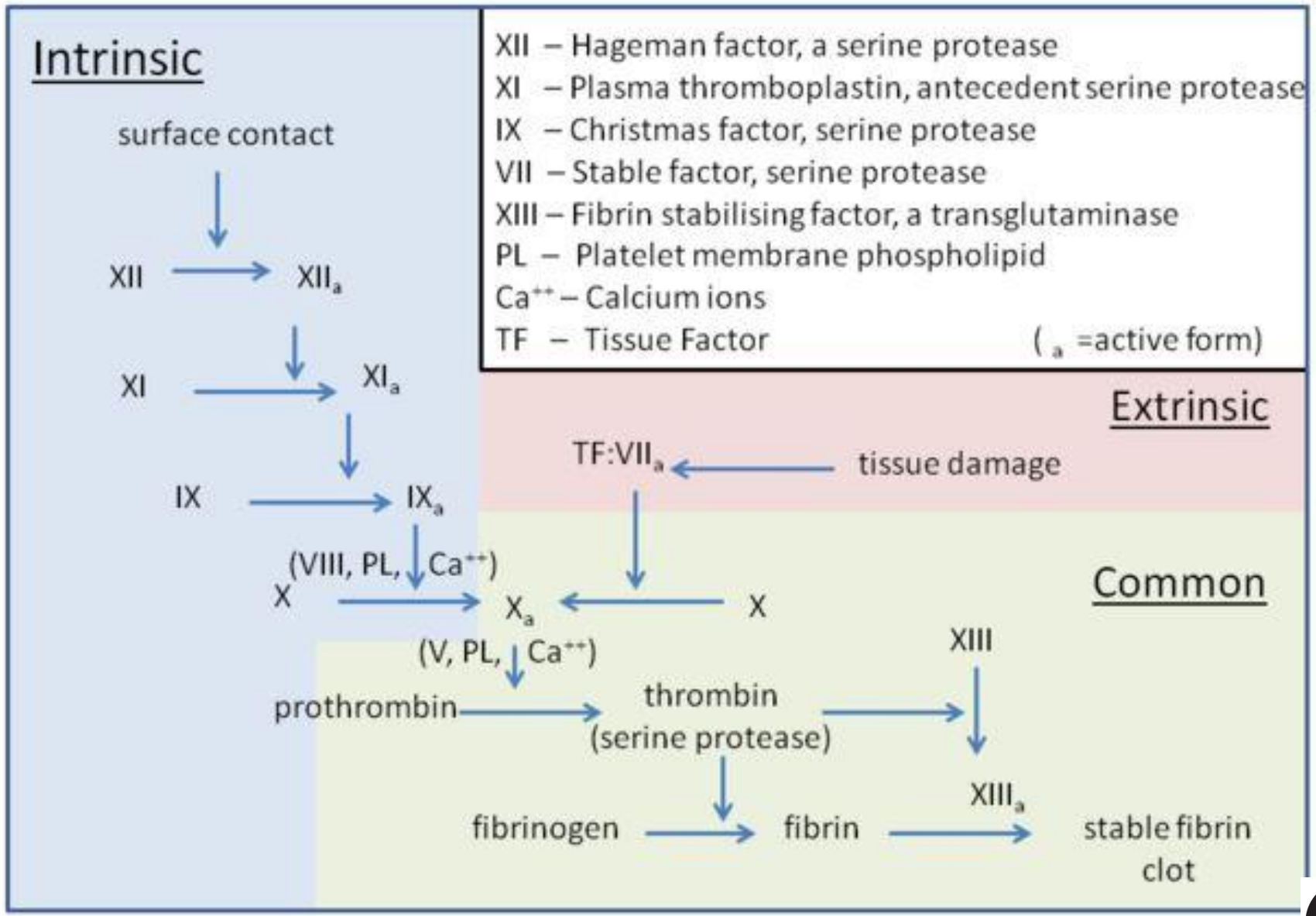
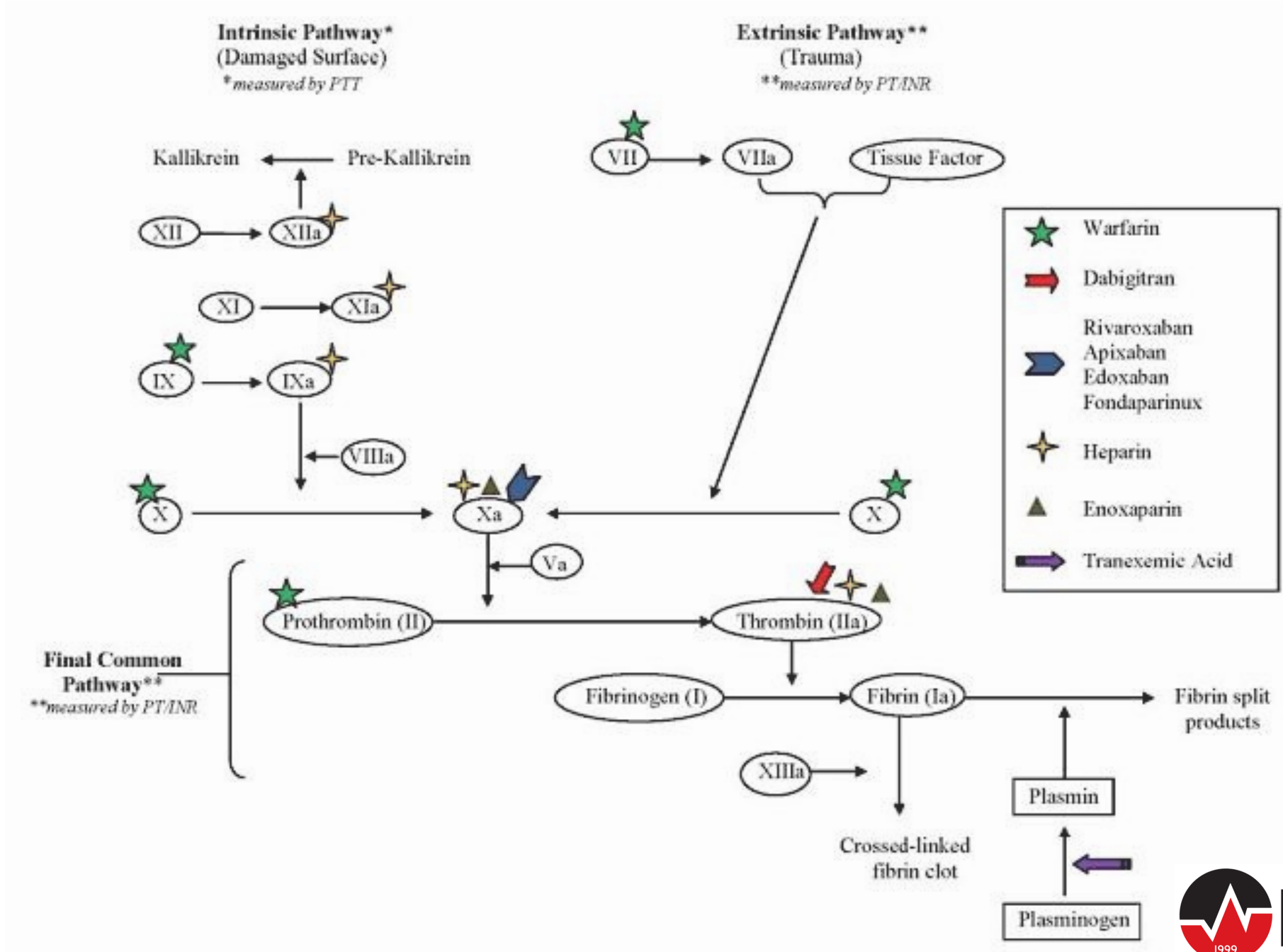
Coagulation Cascade and Site of Action of Various Anticoagulants

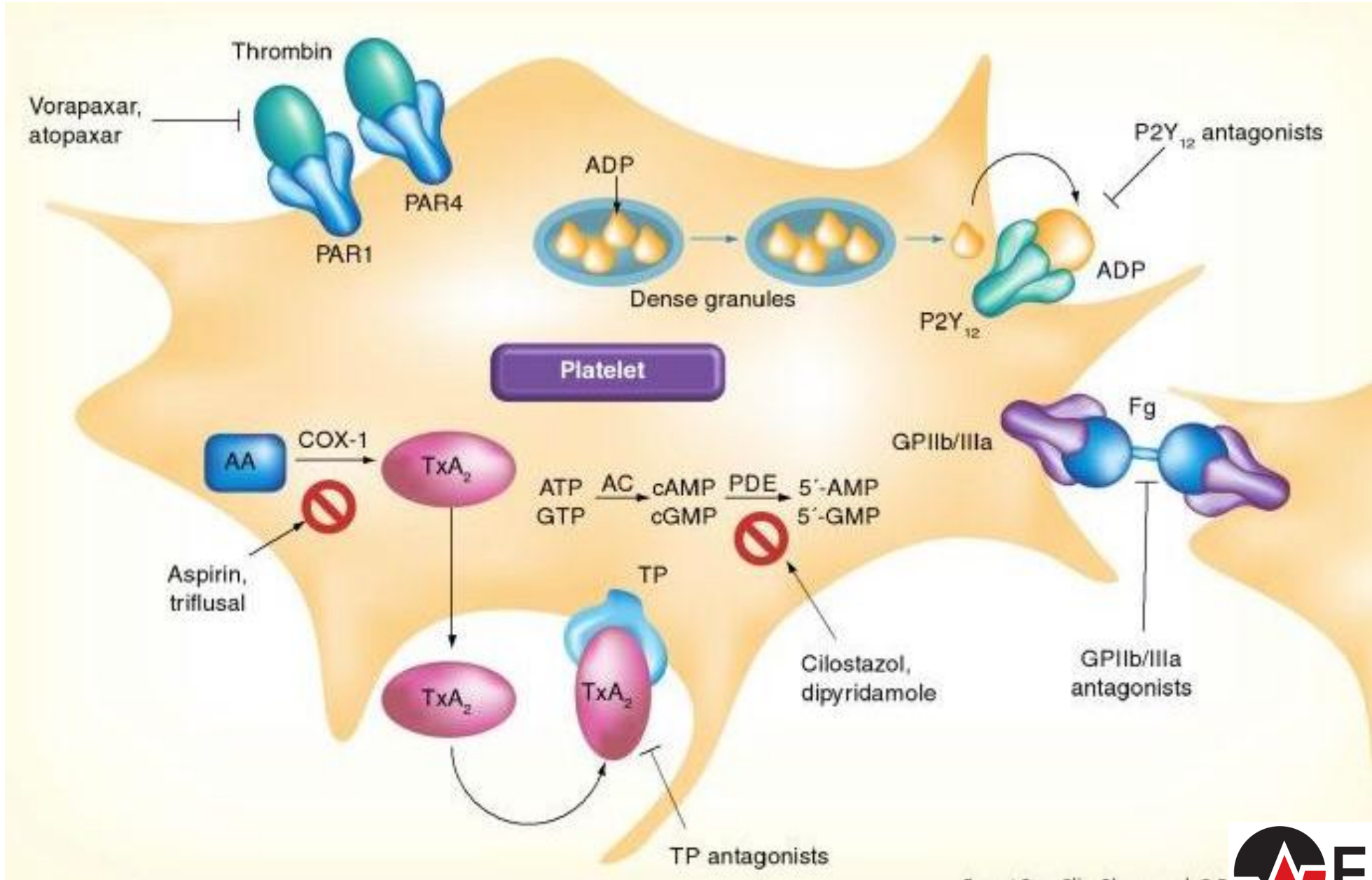
The three pathways that makeup the classical blood coagulation pathway



- Warfarin inhibits synthesis of factor II, VII, IX and X including protein C and S.
- Dabigatran inhibits the action of thrombin.
- Rivaroxaban, apixaban, edoxaban and fondaparinux block the effects of factor Xa.
- Enoxaparin binds to and accelerates the activity of antithrombin III, potentiating the inhibition of coagulation factors Xa and IIa.
- Enoxaparin prevents conversion of plasminogen to plasmin.

- Alteplase binds to fibrin using the fibronectin and kiringle2 domain.
- The protease portion then cleave the Arg/Val bond of plasminogen converting it to plasmin.
- Plasmin then degrades the fibrin matrix resulting in thrombolysis.


Intrinsic Pathway*
(Damaged Surface)
*measured by PTT
Extrinsic Pathway**
(Trauma)
**measured by PT/INR
Kallikrein
Pre-Kallikrein
XII
XIIa
XI
XIa
IX
IXa
VIIIa
VII
VIIa
Tissue Factor
X
Xa
X
Va
Prothrombin (II)
Thrombin (IIa)
Fibrinogen (I)
Fibrin (Ia)
Fibrin split products
XIIIa
Crossed-linked fibrin clot
Plasmin
Plasminogen
Final Common Pathway**
**measured by PT/INR
Warfarin
Dabigitran
Rivaroxaban
Apixaban
Edoxaban
Fondaparinux
Heparin
Enoxaparin
Tranexemic Acid


Thrombin
Vorapaxar,
atopaxar
PAR4
PAR1
ADP
Dense granules
P2Y12 antagonists
ADP
P2Y12
Platelet
Fg
GPIIb/IIIa
AA
COX-1
TxA2
ATP
GTP
AC
cAMP
cGMP
PDE
5´-AMP
5´-GMP
Aspirin,
triflusal
TP
TxA2
TxA2
Cilostazol,
dipyridamole
GPIIb/IIIa
antagonists
TP antagonists

PROBLEMS WITH WARFARIN

- Variable dose
- INR affected by diet, illness, etc
- Drug interactions can be problematic
- Narrow therapeutic index
  - BUT → its CHEAP !!
  - AND → INR is a good measure of compliance

THE IDEAL AGENT !!

- Once daily constant dose for all patients
- Predictable kinetics and anticoagulant effect
- No problematic drug interactions
- Several new agents
  - Dabigatran, Rivaroxaban, Apixaban

DABIGATRAN VS WARFARIN

- The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial of dabigatran in nonvalvular atrialfibrillation(NVAF) patients compared dabigatran to warfarin

- RE-MEDY trials compared dabigatran versus warfarin treatment of long-term VTE treatment, finding that dabigatran was significantly associated with lower rates of VTE

- The RE-COVER trial compared dabigatran versus warfarin for rates of recurrent VTE in patients who had already experienced a VTE. It concluded that dabigatran was non-inferior for preventing recurrent VTE and that there was no difference in major bleeding. The study also found that dabigatran was associated with less major and clinically relevant non-major bleeds.

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- The RE-NOVATE trial examined the difference in VTE post-total hip replacement (THR) between dabigatran 220 mg and 150 mg and enoxaparin. It was found that dabigatran in both doses was non-inferior to enoxaparin in regard to VTE prophylaxis and there was no difference in major bleeding.

- RE-MOBILIZE trial looked at dabigatran versus enoxaparin 30 mg BID for VTE prophylaxis after knee replacement, finding that dabigatran had inferior efficacy to enoxaparin and that both had similar bleeding rates.

RIVAROXABAN

- Bleeding risk was largely similar between warfarin and rivaroxaban; however, the ROCKET-AF study found that bleeding was less likely to be fatal with rivaroxaban and that there was less intracranial hemorrhage but more GI hemorrhage in patients taking rivaroxaban
- The rivaroxaban for thromboprophylaxis in acutely ill medical patients (MAGELLAN) trial the ten-day cohort, each group had a 2.7% odd of VTE, and rivaroxaban was non-inferior. In the longer 35-day cohort, rivaroxaban had less VTE (2.7 versus 5.7%), meeting the criteria for superiority. Rivaroxaban, found to be non-inferior to low molecular weight heparin, however, was associated with an increased risk of clinically relevant bleeding
- ANNEXA-4 trial (on-going) is in Phase 3B/4 and is examining the efficacy of Andexanet in reversing the anticoagulation effect of rivaroxaban, apixaban, and edoxaban.

CURRENT FDA INDICATIONS

	VTE prevention	VTE treatment	Non-Valvular AF	Mechanical heart valve
Apixaban (Eliquis®)	√ (hip + knee)	√	√	0
Dabigatran (Pradaxa®)	√ (hip)	√	√	0
Edoxaban (Savaysa®)	0	√	√	0
Rivaroxaban (Xarelto®)	√ (hip + knee)	√	√	0
Warfarin (Coumadin® or Jantoven)	√ (hip + knee)	√	√	√

WHY NOAC'S ???

Warfarin- High Maintenance

- Vitamin K
- Narrow therapeutic index
- Many drug interactions
- Delayed pharmacodynamics onset

NOAC's- More Predictable

- Not impacted by dietary Vitamin K
- More consistent pharmacokinetics
- Fewer drug interactions
- Relatively quick onset of action
- Not all require Heparin administration prior to use for VTE

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Interpretation of coagulation assays in patients treated with different NOACs

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12–24 h after ingestion	12–24 h after ingestion	12–24 h after ingestion[9]	16–24 h after ingestion
PT	Cannot be used	Cannot be used	Prolonged but no known relation with bleeding risk[5,9]	Prolonged: may indicate excess bleeding risk but local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	At trough: >2x ULN suggests excess bleeding risk	Cannot be used	Prolonged but no known relation with bleeding risk[9]	Cannot be used
dTT	At trough: >200 ng/ml or >65 s: excess bleeding risk	Cannot be used	Cannot be used[10]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	No data yet	Quantitative;[10] no data on threshold values for bleeding or thrombosis	Quantitative; no data on threshold values for bleeding or thrombosis
ECT	At trough: ≥3 × ULN: excess bleeding risk	Not affected	Not affected	Not affected

[a]No EMA approval yet. Needs update after finalization of SmPC.
Routine monitoring is not required. Assays need cautious interpretation for clinical use in special circumstances, as discussed in the text.
PT, prothrombin time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; INR, international normalized ratio; ULN, upper limit of normal.

CONTRAINDICATIONS

- Renal impairment
  - a reduced dose may be used in moderate renal impairment, depending on renal function, NOAC and indication
- Disorders of haemostasis
- Clinically significant active bleeding
- Prosthetic heart valve
- Liver disease
- Pregnant and breastfeeding women
- Children under 18 years

ADVERSE EFFECTS

	Dabigatran	Apixaban	Rivaroxaban
Common	bleeding anaemia nausea dyspepsia gastritis abdominal pain	bleeding anaemia dyspepsia GI bleeding	bleeding anaemia peripheral oedema itch, skin blisters muscle spasm
Infrequent	increased liver enzymes	thrombocytopenia increased liver enzymes	increased liver enzymes
Rare	allergic reactions	allergic reactions	allergic reactions

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MONITORING

Unlike warfarin:

- There is no need to routinely measure patient blood levels and make dose adjustments according to a 'therapeutic range'

However: Mass spectrometry is the gold standard for measuring DOAC concentrations

- NOACs are excreted renally. Renal function should be monitored:
  - At least annually
  - If the patients condition changes
- Patients should also be routinely assessed for signs of bleeding *and* for other bleeding risk factors (e.g. persistent hypotension; other medicines; platelet counts)

Agents for Reversal of Antithrombotics in ICH

Vit K antagonist

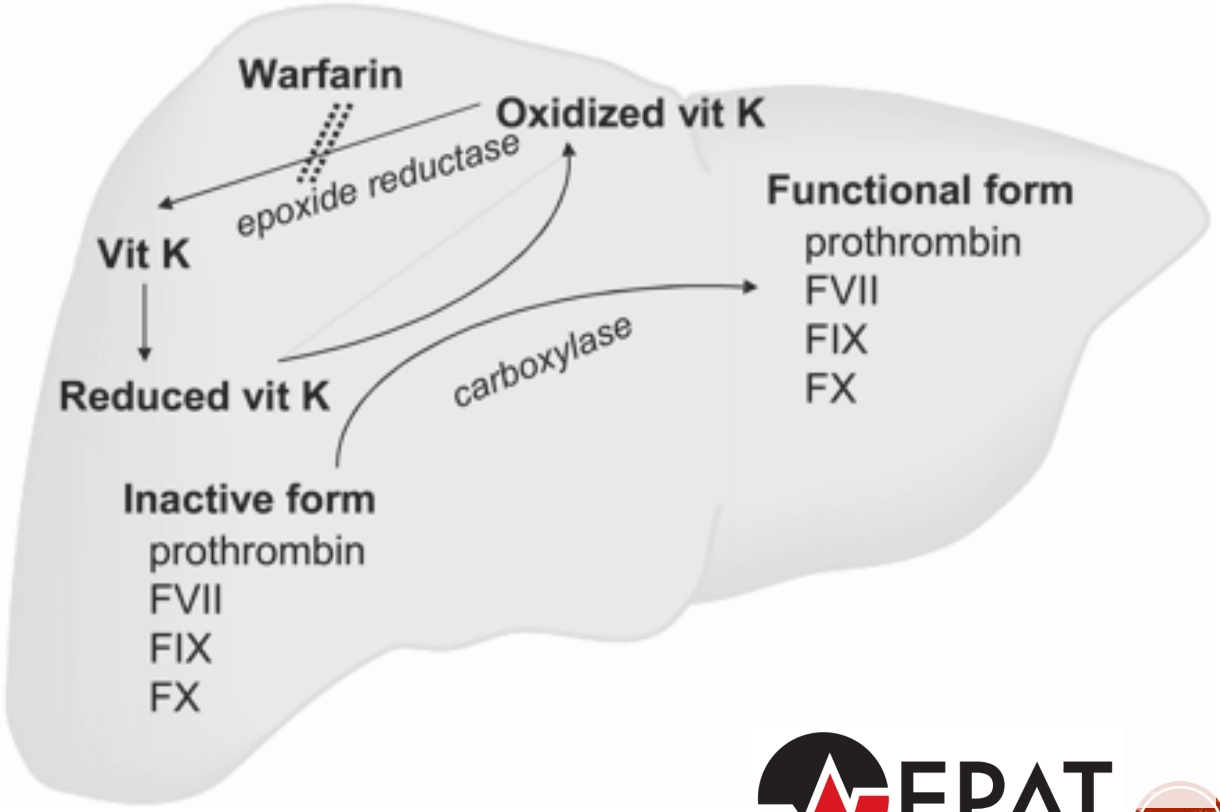
- If INR greater than or equal to 4 provide vitamin K 10mg IV and 3-4 factor Prothrombin Complex Concentrates(PCC) or fresh frozen plasma.

Direct factor Xa inhibitors

- Activated charcoal or 4 factor PCC.

Unfractionated heparin

- Protamine IV.



Pentasaccharides

- aPCC

Thrombolytic agents

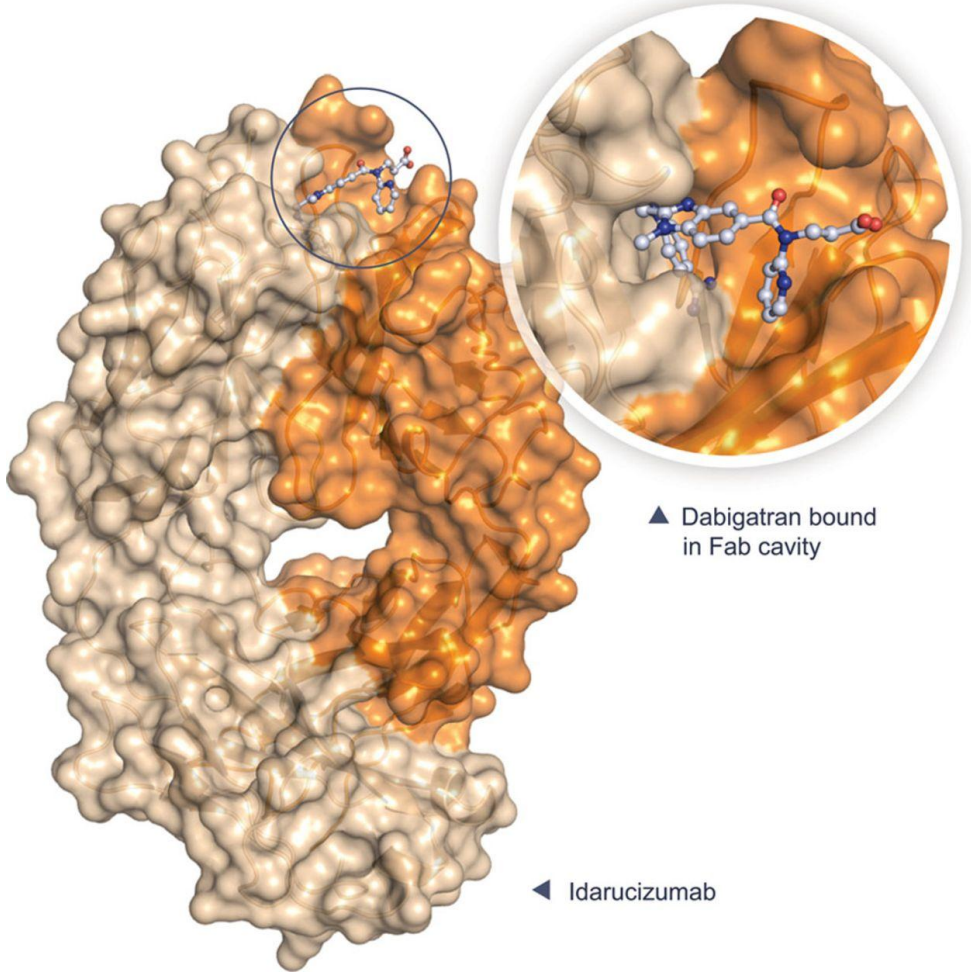
- Cryopercipitate 10units or antifibrinolytics.

Antiplatelet agents

- Desmopressin 0.4mcg or platelet transfusion during surgical procedures.

Idarucizumab

- Only works on dabigatran.
- It is a monoclonal antibody fragment.
- Binds with high affinity dabigatran.
- Rapidly reverses the coagulation effects.



Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

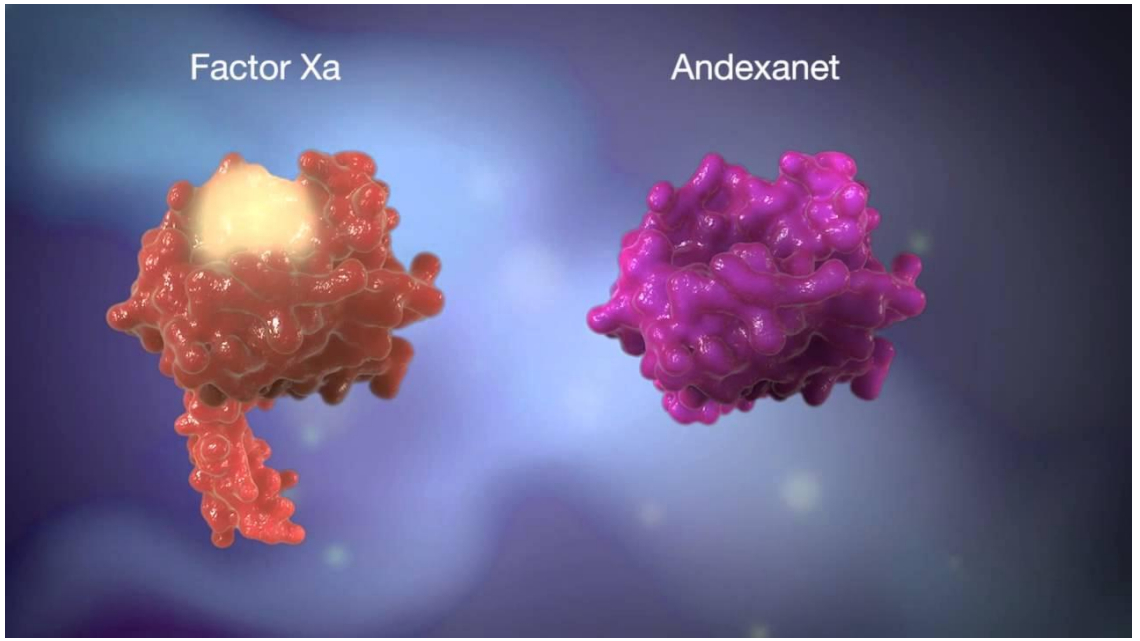
Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

N Engl J Med 2016; 375:1131-1141September 22, 2016DOI: 10.1056/NEJMoa1607887

Andexanet Alfa

- Acts as a target decoy for oral and injectable factor Xa inhibitors.
- Targets with high specificity.
- Reverses anticoagulant effect of :-

Oral direct	Injectable indirect
Apixaban	Enoxaparin
Edoxaban	Fondaparinox
Rivaroxaban	

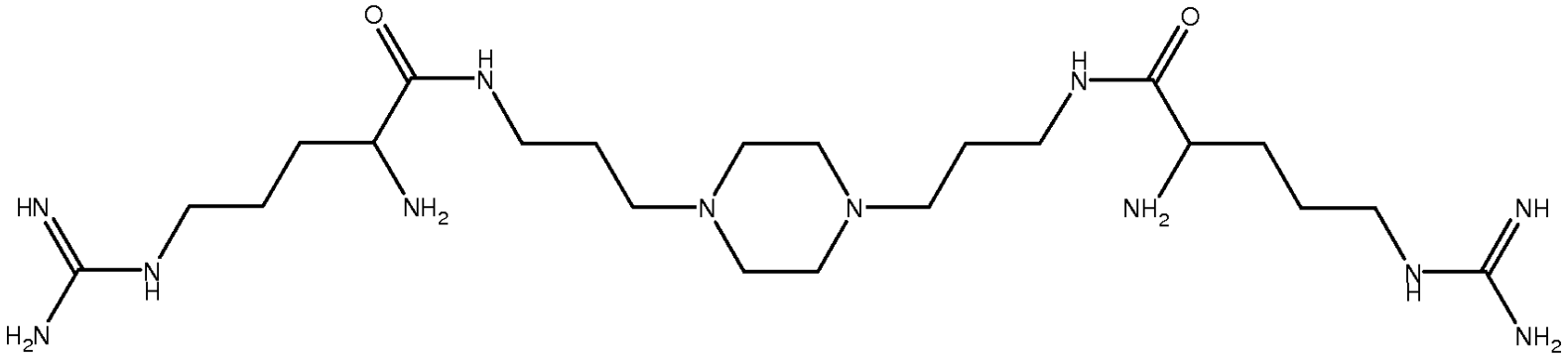


Aripazine

- It is a small synthetic molecule.

- Binds to
  - Oral factor Xa inhibitors and DTIs
  - UFH / LMWH

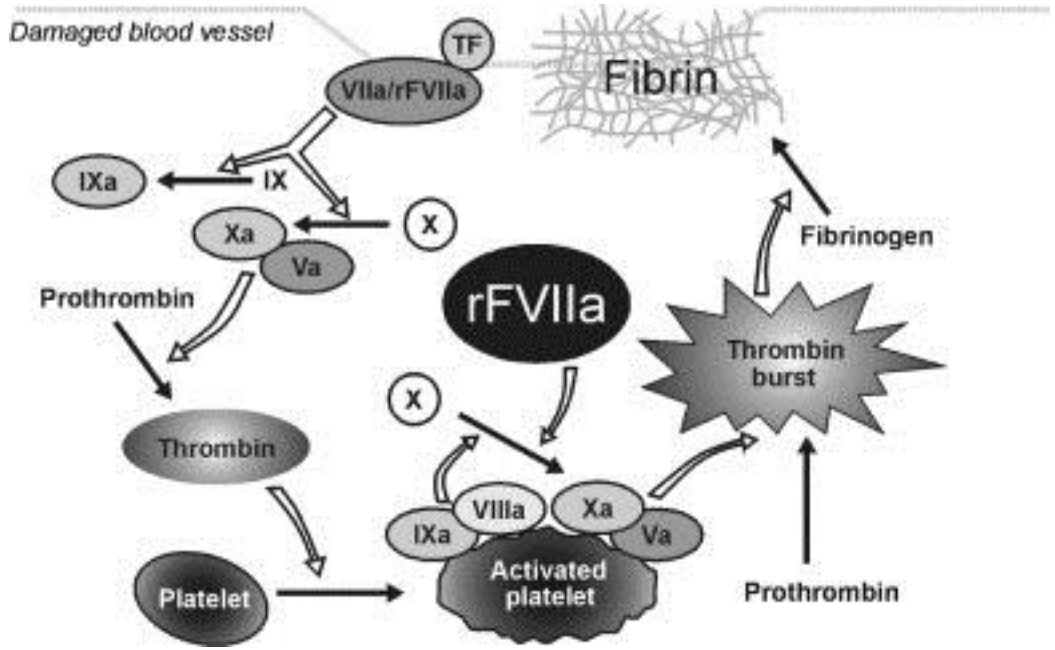
- Binds via non-covalent bonding and charge-chare interactions.



Reversal of oral factor Xa inhibitors by prothrombin complex concentrates: a re-appraisal. J Thromb Haemost. 2015 Jun;13 Suppl 1:S187-94. doi: 10.1111/jth.12949. PubMed PMID: 26149022.

Recombinant Human factor VIIa (rFVIIa)

- Activates the coagulation cascade via the extrinsic pathway.
- The dose required for reversal far exceeds the normal dosing of rFVIIa.
- This creates the possibility of thrombotic sequelae.
- It is not recommended for the treatment of target specific oral anticoagulant (TOSC) therapy.



Desmopressin

- A Synthetic analogue of vasopressin.
- Stimulates the release of von Willebrand Factor. (vWF)
- Increases the production of factor VIII.
- Risks of desmopressin use is low.
- Used in treatment of significant bleeding when taking Direct Oral Anticoagulants (DOAC).

Oral Activated Charcoal

- Its surface adsorbent properties allows for DOAC to be held back from absorption.
- Effective if given within two hours of ingestion for edoxaban and dabigatran.
- Within 8 hours for rivaroxaban.
- Within 6 hours for apixaban.

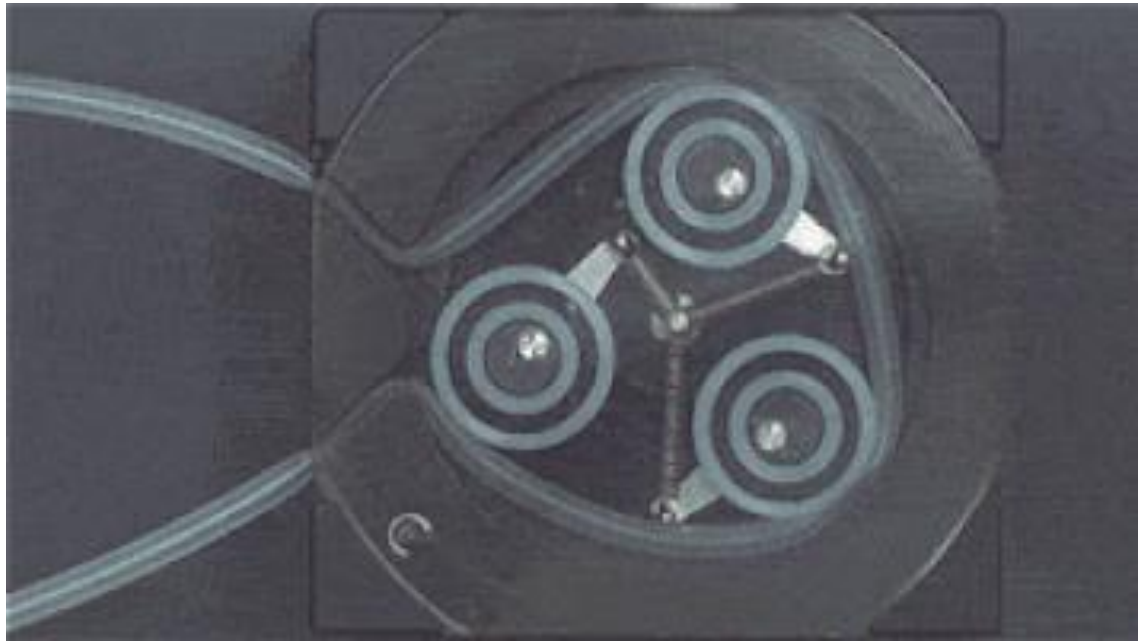
Hemodialysis

- Dabigatran is 80 – 85% excreted through kidney.

- This allows for haemodialysis to be a treatment option.

- Direct factor Xa oral inhibitors are protien bound and only 25 – 35% is excreted renally.

- Thus haemodialysis may not be a treatment option.



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