Anticoagulants

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Anticoagulant drugs

- used for the prevention and treatment of arterial and venous thromboembolism

- Thrombosis –thrombus formation within the circulation

Types of anticoagulants

- heparinoids
  - unfractionated heparin (UFH)
  - low-molecular- weight heparin (LMWH)
  - Fondaparinux
- vitamin K antagonists (VKA) — warfarin,
- new oral agents — dabigatran, rivaroxaban, apixaban

Heparin

Mechanism of action

Unfractionated Heparin (UFH)

- Inhibits Thrombin (IIa), IXa, Xa, XIa and XIIa
- Therapeutic action: Xa, thrombin

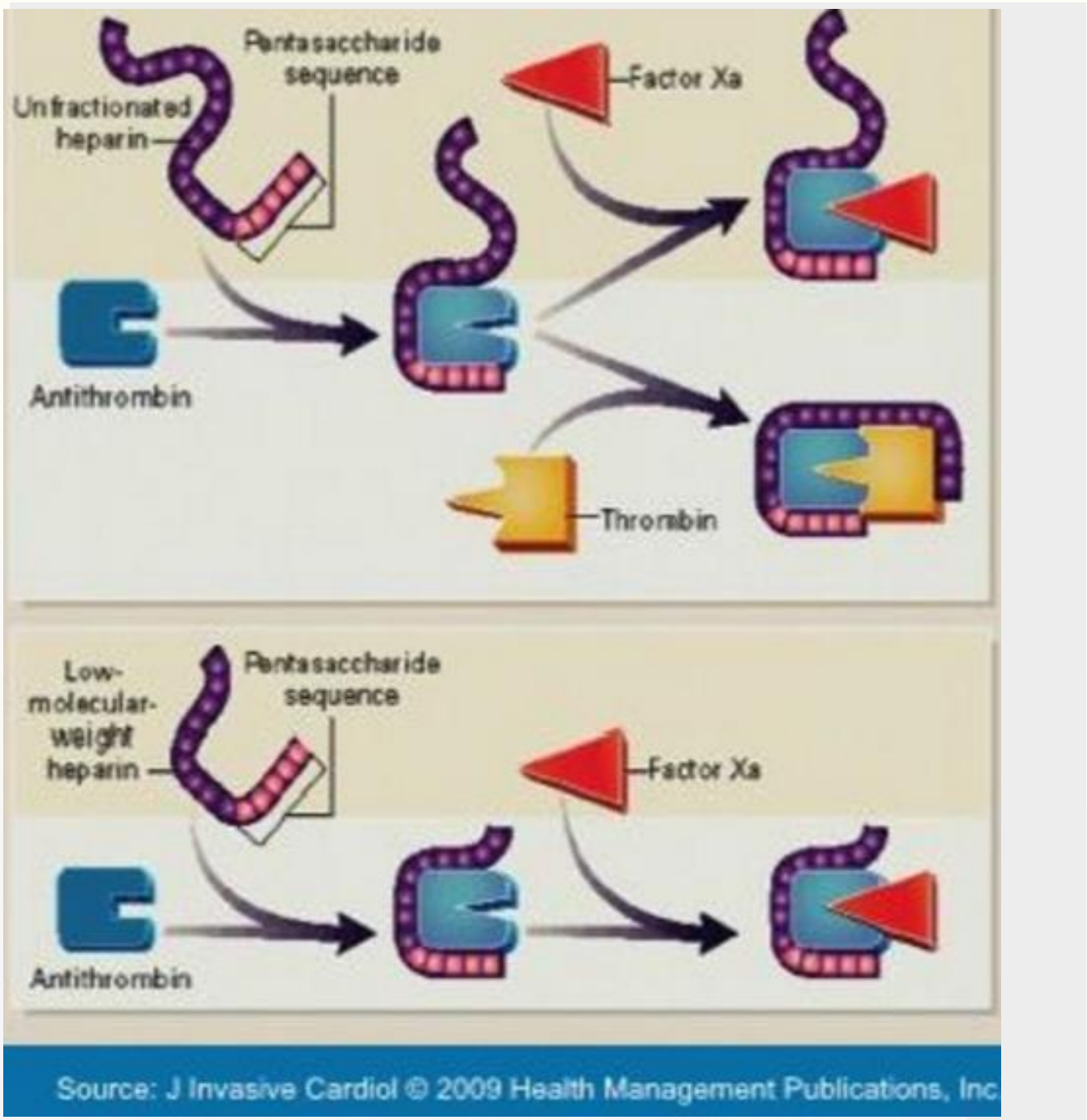
Potentiates the action of anthrombin 111

Low Molecular Weight Heparin (LMWH)

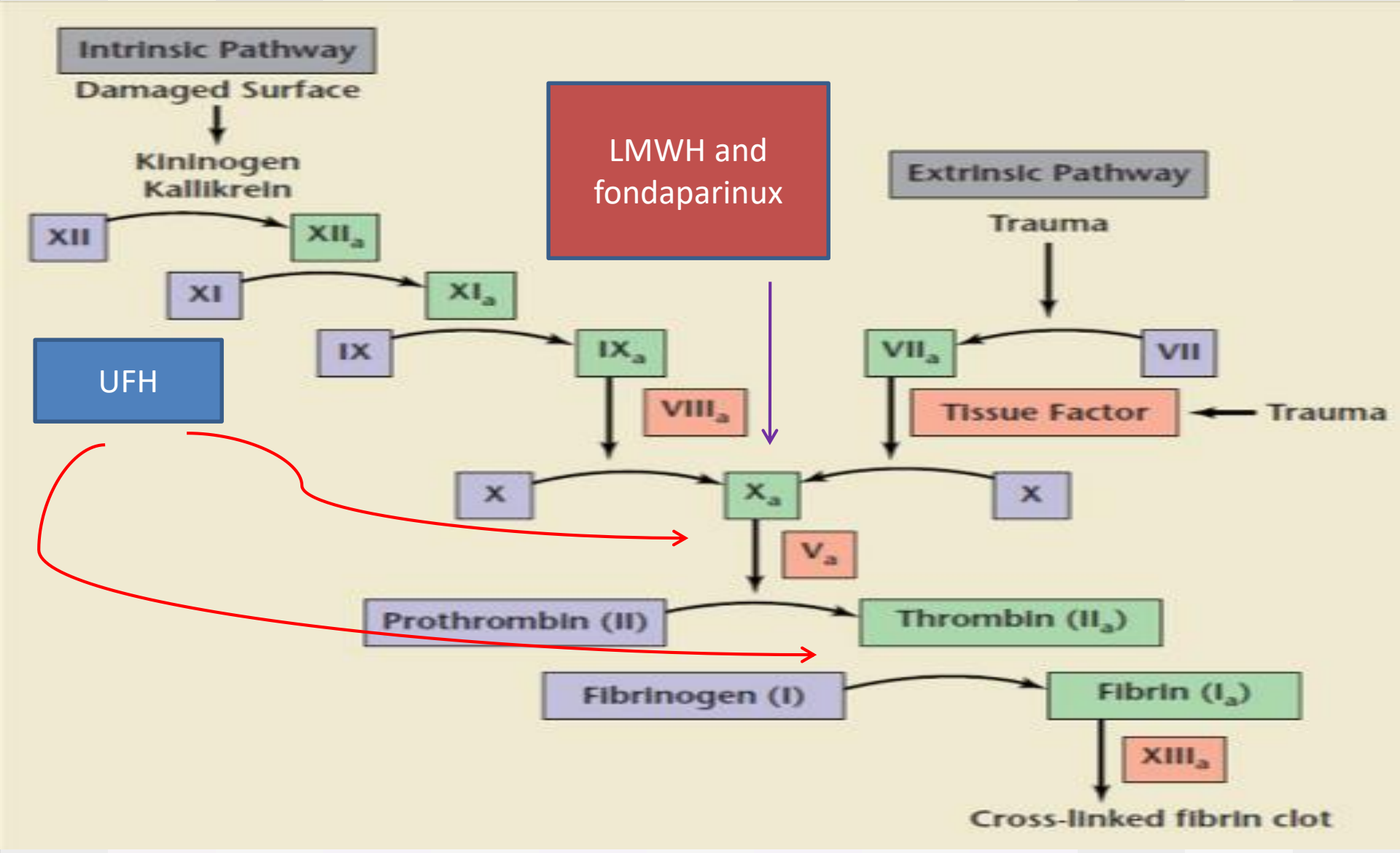
- Predominantly inhibit factor Xa

Fondaparinux

- Purely inhibits factor Xa


Pentasaccharide sequence
Unfractionated heparin
Factor Xa
Antithrombin
Thrombin
Low-molecular-weight heparin
Pentasaccharide sequence
Factor Xa
Antithrombin
Source: J Invasive Cardiol © 2009 Health Management Publications, Inc

Mechanism of action



Unfractionated heparin

- 1st anticoagulant discovered
- consists of a series of glycosaminoglycan chains and is processed from animal intestinal mucosa
- anticoagulant effect mainly by potentiating the action of the physiological anticoagulant antithrombin ten thousand-fold
- unpredictable pharmacokinetics and a short elimination half-life

Unfractionated heparin

- Adverse effects

-bleeding

-allergy

-heparin-induced thrombocytopenia (HIT)

-osteopenia (long term use)

- monitoring of heparin -using the activated partial thromboplastin time (target -2-3 times of normal APTT)
- Dosing of UFH requires a bolus dose for initiation of an UFH infusion.

Low molecular weight heparin

- produced by depolymerization of UFH chains to produce a shorter glycosaminoglycan chain.
- more predictable pharmacokinetics, a longer half-life
- monitoring is required only in patients with renal failure and those at extremes of body weight, and is performed using anti-Xa concentration

UFH vs LMWH.

UFH	LMWH
intravenous (IV) infusion or subcutaneous (SC) injection	easier mode of administration (SC injection) than UFH.
Unpredictable pharmacokinetics	more predictable pharmacokinetics
short elimination half-life	longer half-life
Needs infusion followed by bolus	Bolus doses
potentiating the action of the physiological anticoagulant antithrombin	binds to antithrombin but has a greater inhibitory effect on factor Xa.
SE- heparin-induced thrombocytopenia (HIT) and osteopenia	Less compared to UFH
No dose adjustment in RF	Reduce dose in RF
Need monitoring in all	Monitoring only special circumstances
Monitoring - apTT	Factor Xa levels
Reverse anticoagulant effect - protamine sulphate	Only partially reversed by protamine

fondaparinux

- is a synthetic form of the heparin pentasaccharide molecule
- Anti Xa activity
- Indications similar to other types
- However more benefit in MI
- Costly
- Long half life- single daily dose (LMWH is given bd)

Indications of heparin

- Prevention of thrombosis of peripheral catheters
- Prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE),
- Treatment of cardiac ischaemia and critical ischaemia of the lower limb

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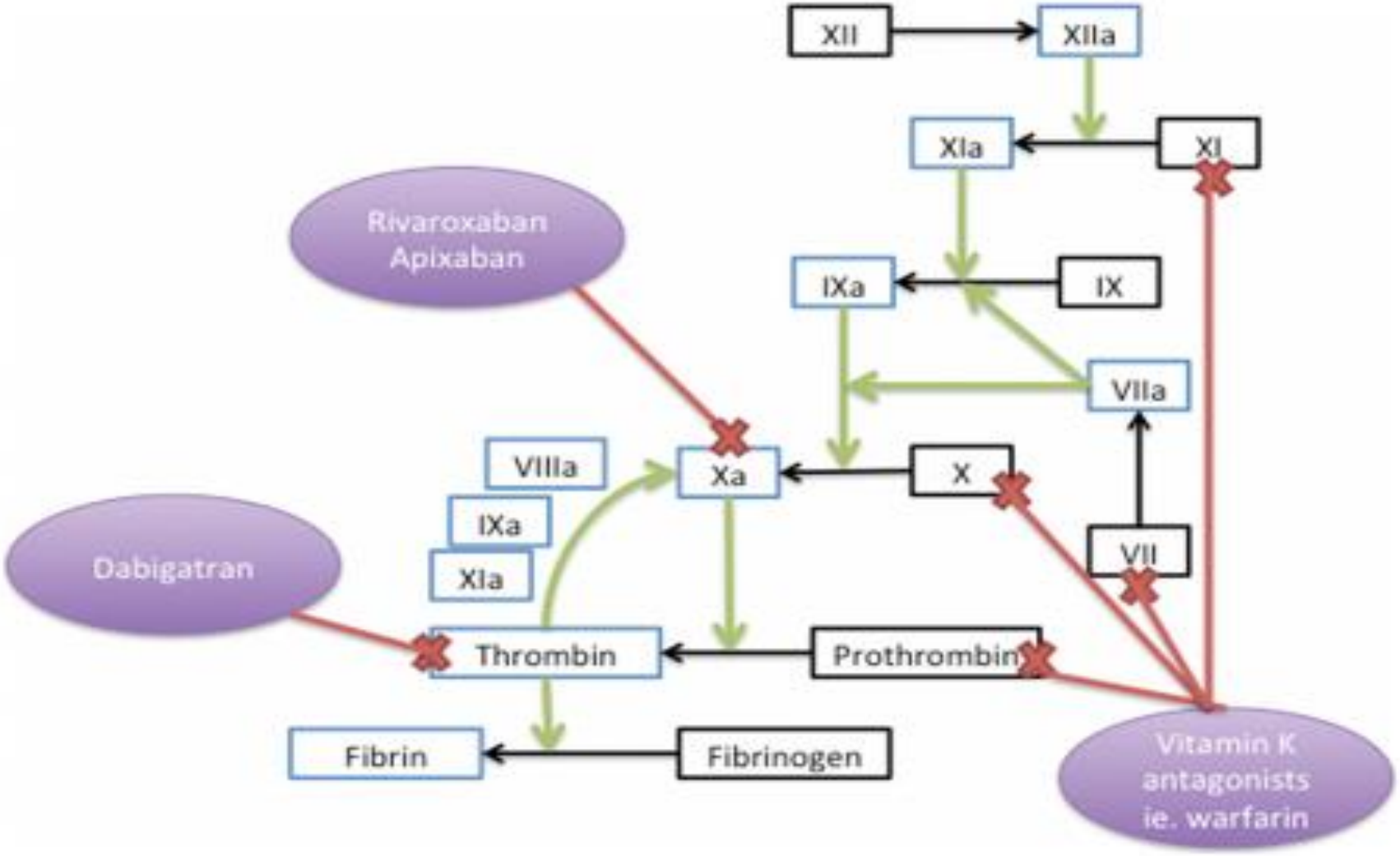
Warfarin

- **Mode of action**

warfarin prevents gamma carboxylation of vitamin K-dependent clotting factors (II, VII, IX and X), producing an anticoagulant effect

takes several days to have full anticoagulant effect.


XII
XIIa
XIa
XI
Rivaroxaban
Apixaban
IXa
IX
VIIa
VIIIa
IXa
XIa
Xa
X
VII
Dabigatran
Thrombin
Prothrombin
Fibrin
Fibrinogen
Vitamin K
antagonists
ie. warfarin

Warfarin

- Monitoring –Prothombin time
- Contraindicated in T1 of pregnancy (Is continued on heparin)- warfarin embrayopathy/fetal warfarin syndrome
- Dosing and initiation –patient dependant
- Acute thrombosis -----initiate warfarin with heparin
- Why?

the initial reduction proteins C & S by warfarin may lead to an enhanced prothrombotic effect.

- Initiating high doses –not benificial

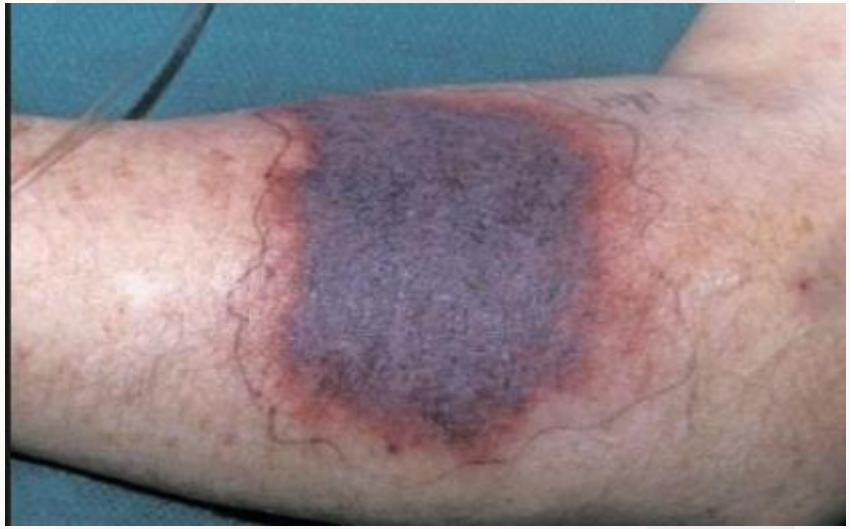
INR targets with warfarin and indicatiosns

Indication	Target INR
Pulmonary embolism	2.5
Proximal deep vein thrombosis	
Calf vein thrombosis	
Non-rheumatic atrial fibrillation ($CHADS_2$ score >1)	
Mural thrombus	
Cardiomyopathy	
Mechanical prosthetic aortic heart valve	
Bioprosthetic valve	
Mechanical prosthetic mitral heart valve	3.5
Recurrent venous thrombosis on warfarin therapy	

Adverse events

- Hemorrhage
- Necrosis of skin
- Systemic atheroemboli and cholesterol microemboli
- Vascular disorders: vasculitis
- Hepatobiliary disorders
- Gastrointestinal disorders: nausea, vomiting, diarrhea, taste perversion, abdominal pain, flatulence, bloating

Skin necrosis



Contraindications

- Hemorrhagic tendencies
- Recent major surgery
- Threatened abortion, eclampsia, and preeclampsia
- Unsupervised patients with conditions associated with potential high level of non-compliance
- Hypersensitivity
- Malignant hypertension

Drug interactions

- CYP450 isozymes involved in the metabolism of Warfarin
- Drugs that inhibit these enzymes increase risk of bleeding
- Drugs that activate these enzymes reduce the anticoagulant effect
- What are the drugs interacting with warfarin?

Some common drug interactions

Medscape® www.medscape.com

Pharmacodynamic interactions	Mechanism
ASA/NSAIDs	Antiplatelet, gastrointestinal injury
Clopidogrel/Ticlopidine	Antiplatelet
Tramadol	INR elevation (unclear mechanism)[33]
Levothyroxine	Increased catabolism of clotting factors
Vitamin K-containing food/supplements	INR depression (circumvent warfarin mechanism of action)

Clinical case

- A 56 year old female on warfarin for non valvular AF presents with lethargy and found to be pale. She has a history of tarry stools for five days . Her INR is 3.5
- What is the next step in management ?

Reversal of anticoagulation

- Life threatening bleeds - dried prothrombin complex (prothrombin complex concentrate; PCC) contains factors II, VII, IX and X in combination with IV. Vitamin K

FFP if PCC not available

- non-major bleeding -discontinuation of warfarin or a decrease in dosage and/or administration of vitamin K will usually suffice