



UNIVERSITY *of*
DEBRECEN

DRUGS USED IN DISORDERS OF COAGULATION

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Reasons of thrombosis

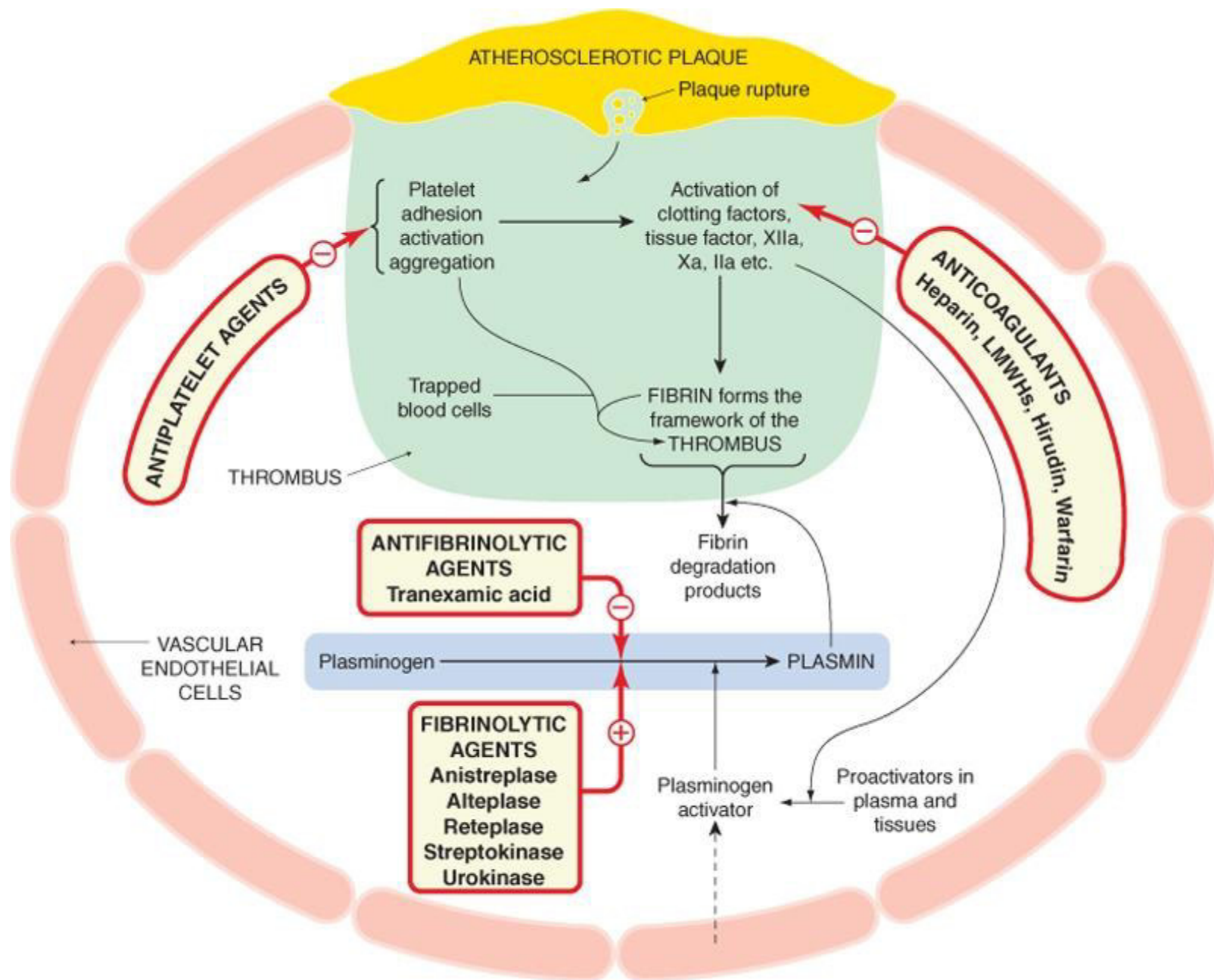
Damage of vessel wall	most frequently rupture of atherosclerotic plaque
Altered blood flow	e.g. atrial fibrillation
Abnormal coagulability	e.g. pregnancy, contraceptive drugs

Arterial thrombosis

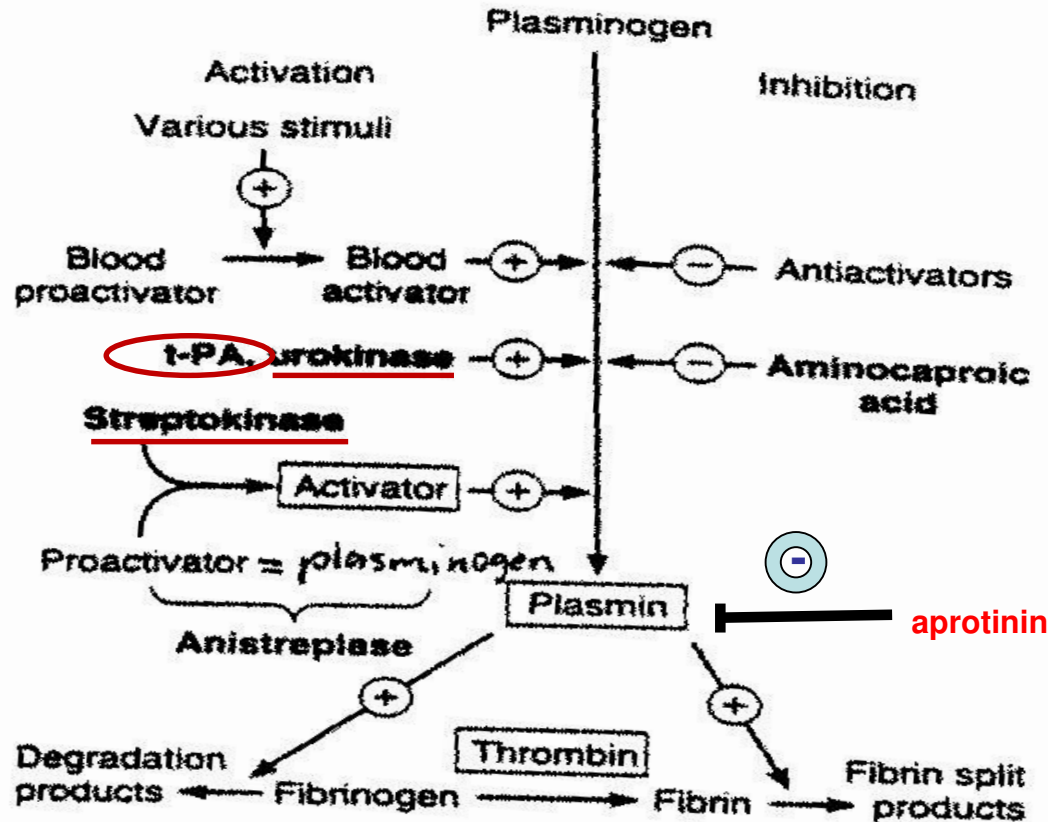
platelet-rich (white) thrombi therapy: **antiplatelet and fibrinolytic drugs**

Venous thrombosis

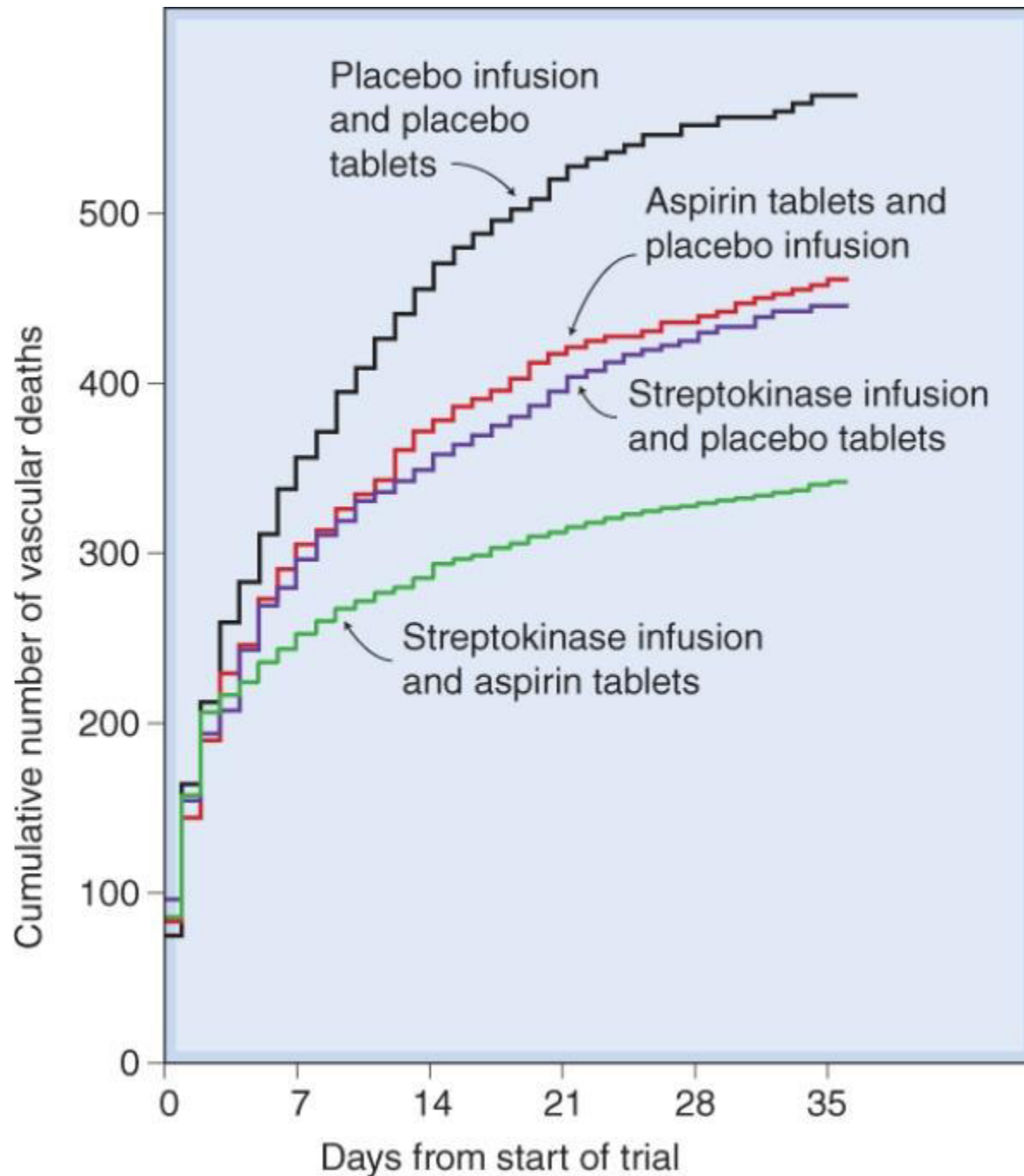
red thrombi therapy: **anticoagulants**



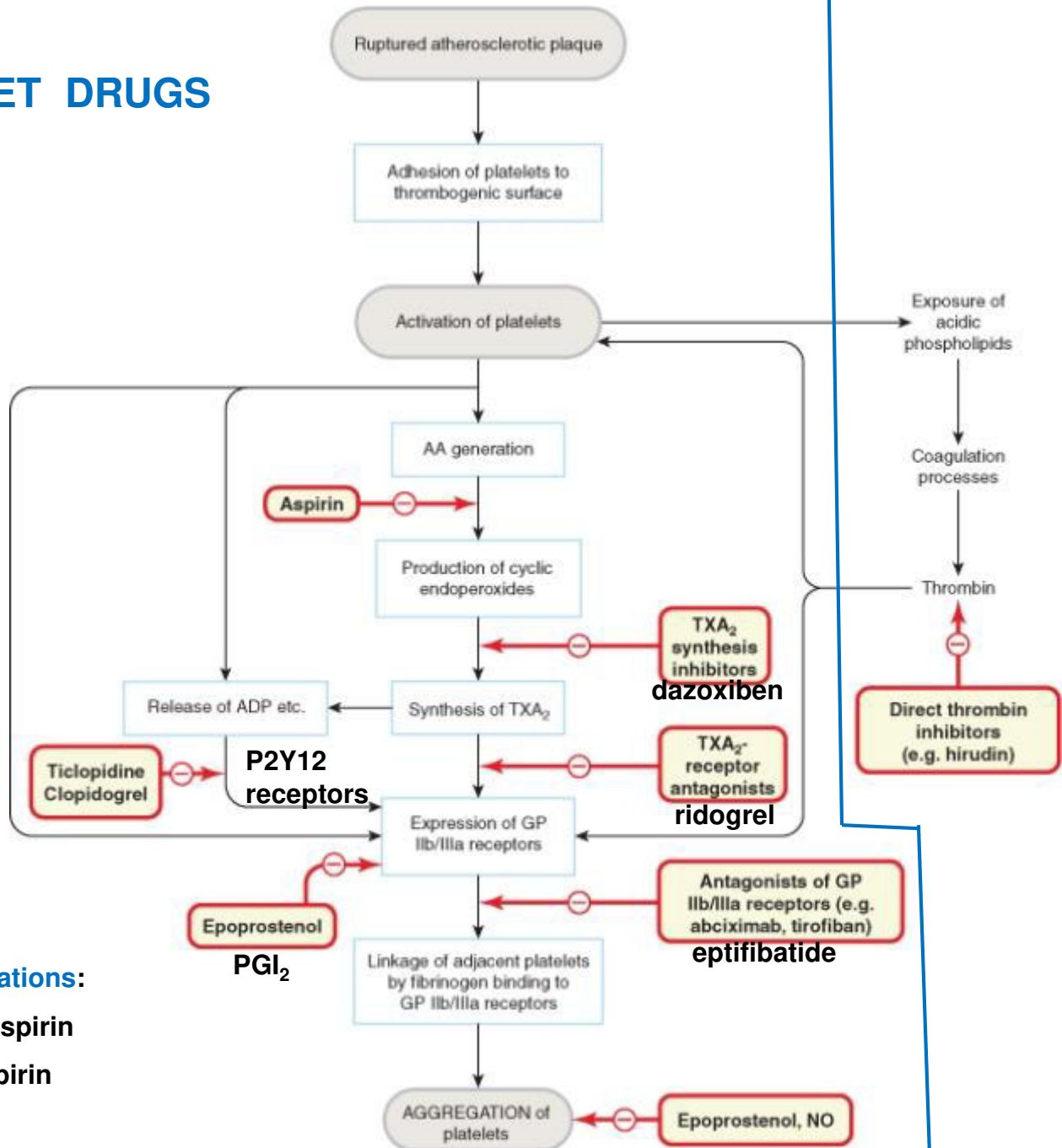
Fibrinolytic and antifibrinolytic drugs



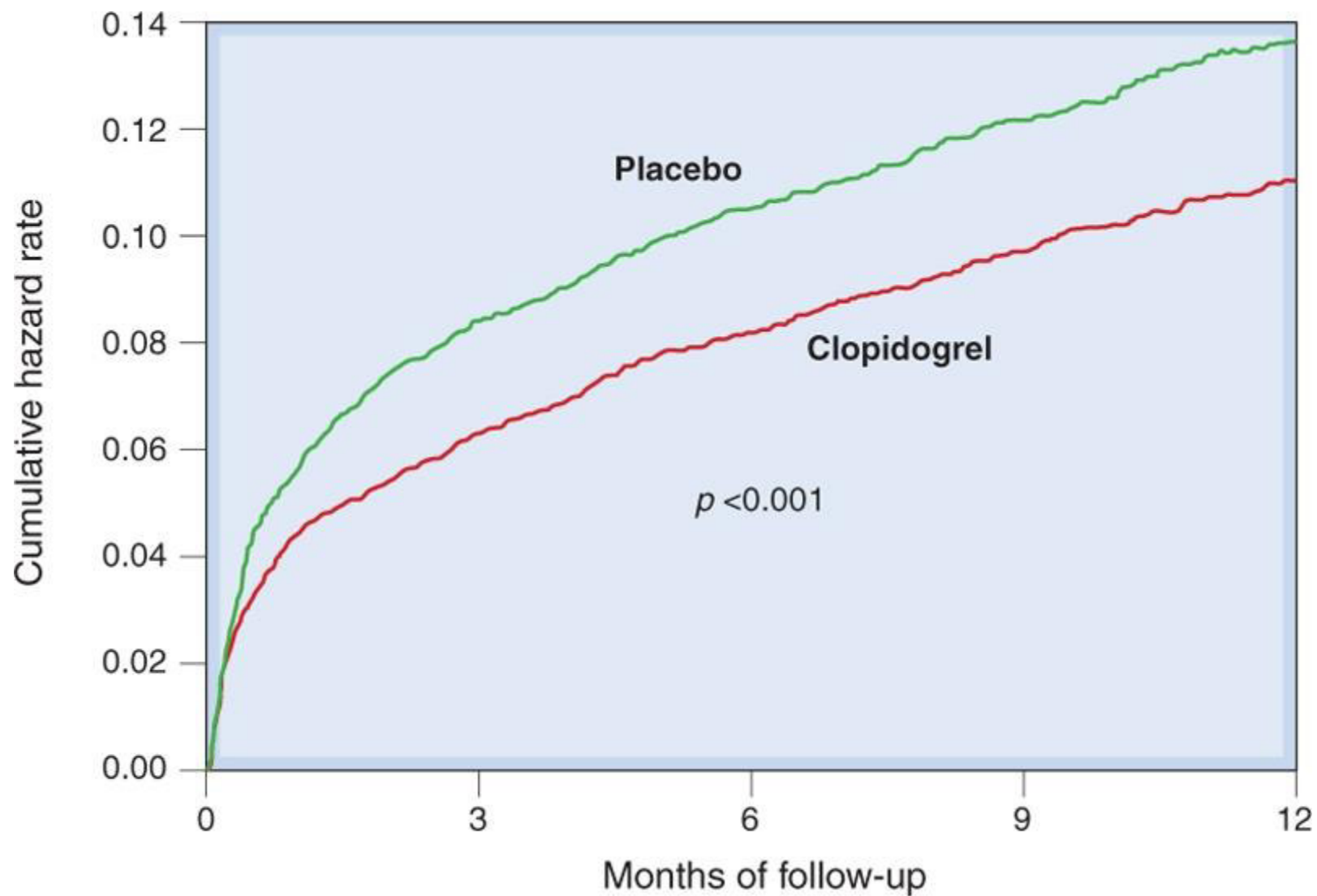
Clinical use: AML or stroke in the first hours



ANTIPLATELET DRUGS

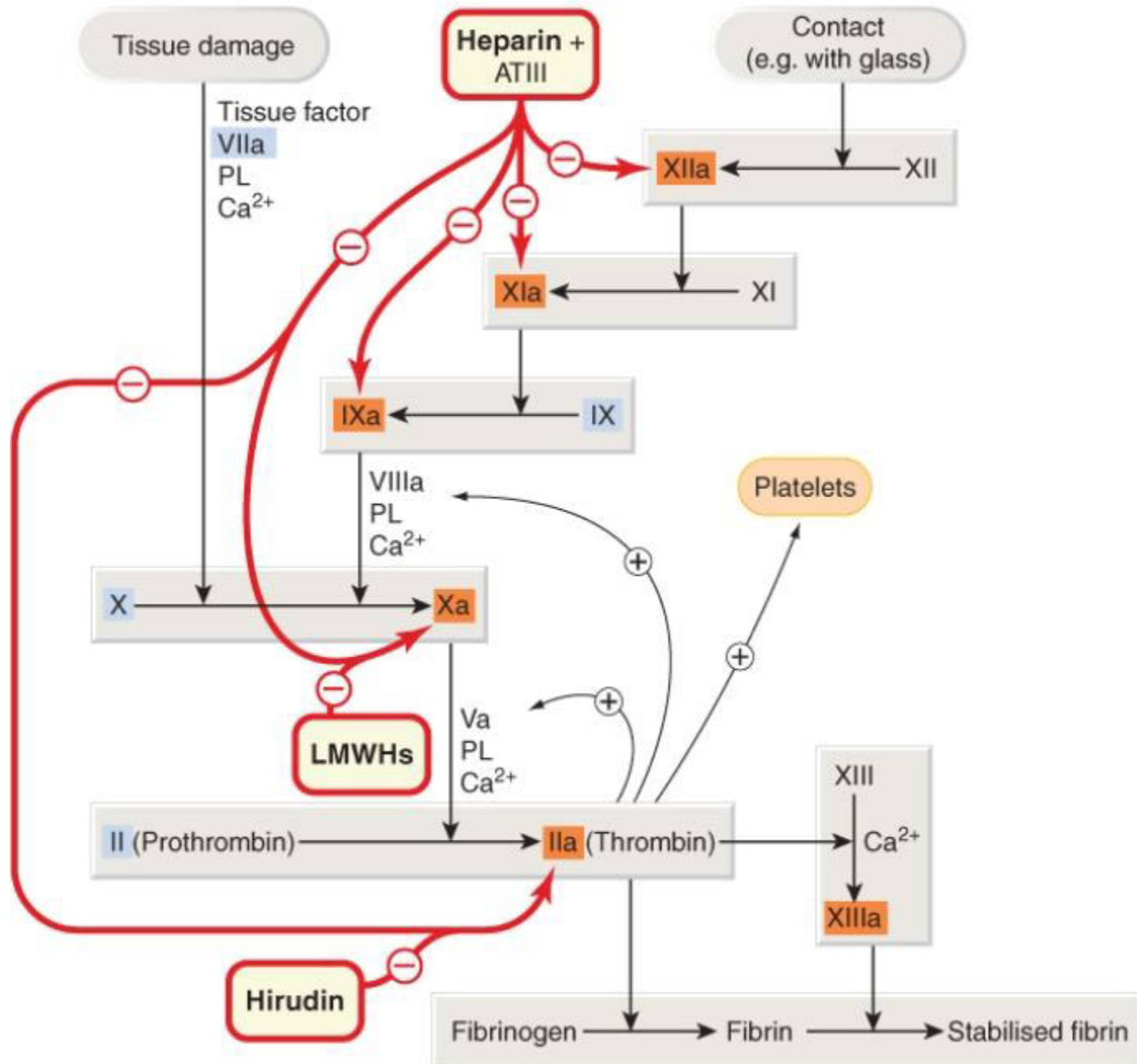


Additive combinations:
dipyridamole + aspirin
clopidogrel + aspirin

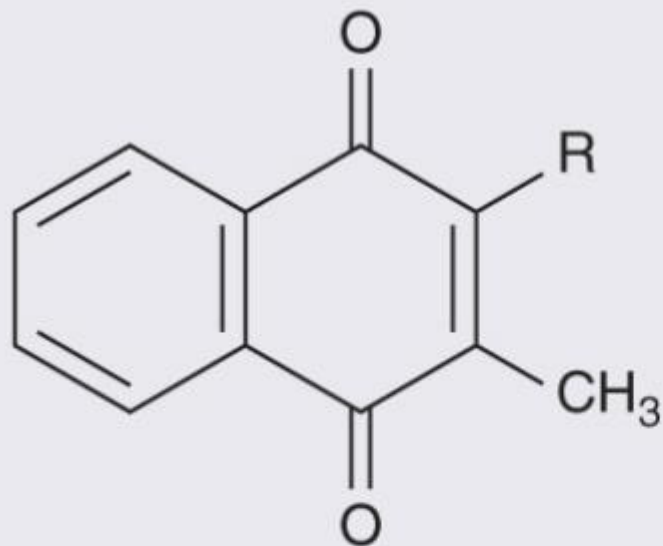


Extrinsic pathway

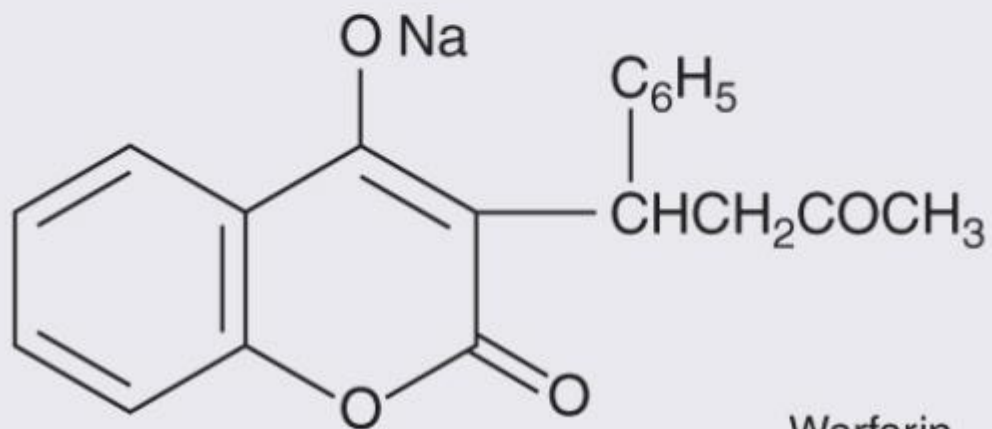
Intrinsic pathway



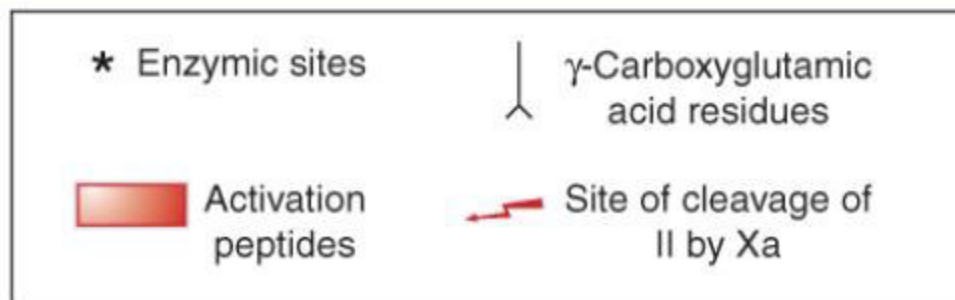
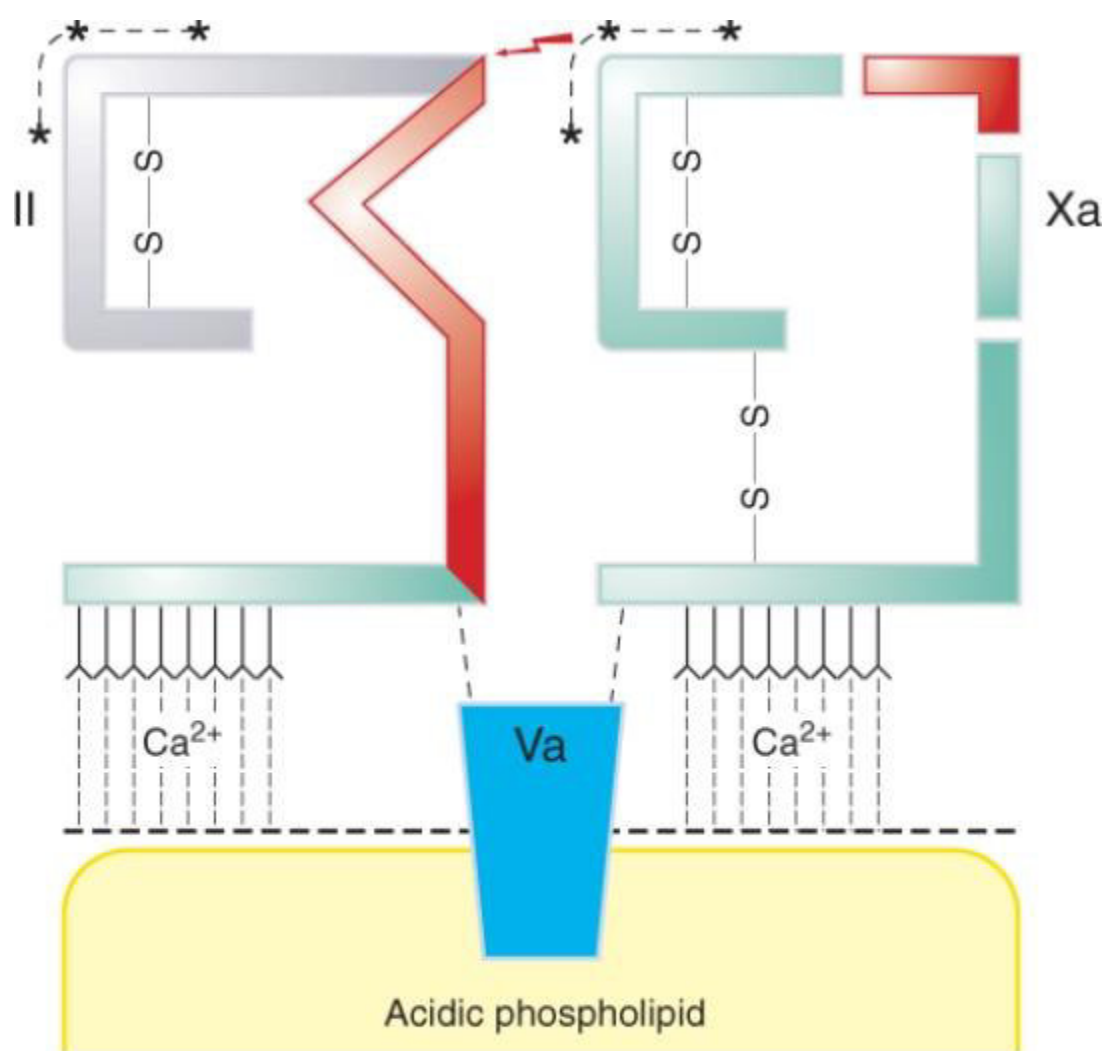




Vitamin K
(natural vitamin)



Warfarin
(vitamin K antagonist)



$O_2 + CO_2 + \text{Glutamic acid residues}$
(in II, VII, IX, X)

$\gamma\text{-Carboxyglutamic acid residues}$
(in II, VII, IX, X)

Vitamin K reduced form
(hydroquinone)

Vitamin K oxidised form
(epoxide)

Vitamin K
reductase

Vitamin K
(quinone)

Vitamin K
reductase

Warfarin

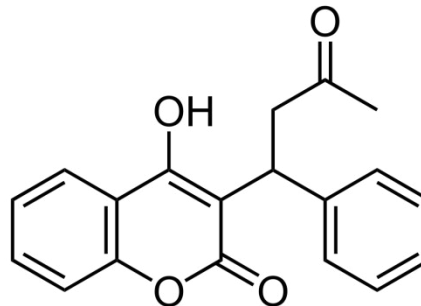


WARFARIN/acenokumarol

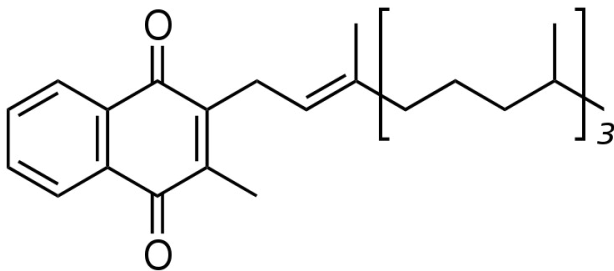
Active ingredient of Syncumar is the acenokumarol
p.o. anticoagulant for long-term therapy.

Clinical indication: deep vein thrombosis, pulmonary edema,
cardiac arrhythmia with high risk for stroke, artificial grafts

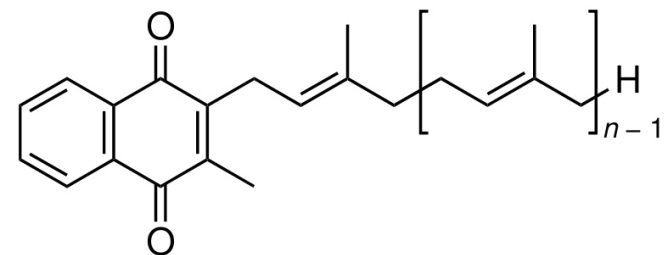
Vitamin K antagonist



warfarin



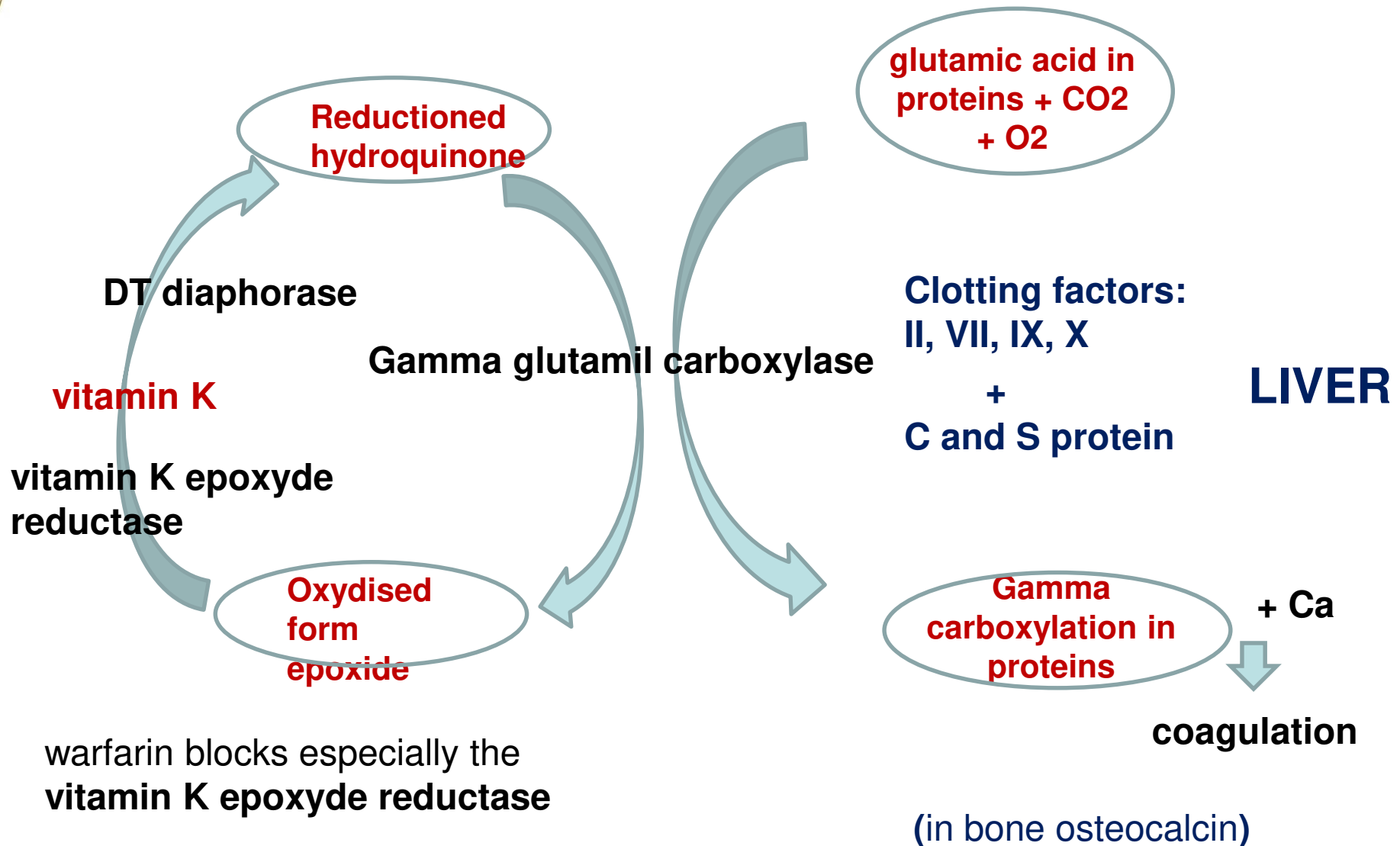
vitamin K1 (plants)



vitamin K2 (intestinal bacteria)



Mode of action of WARFARIN





Effect of WARFARIN

30-50 % reduction in synthesis of vitamin K-dependent clotting factors in the liver the left fraction has less effectiveness because of the lack of a decarboxylation (10-40 % of the normal value)



Prolonged bleeding time – individual doses based on the monitorization of the INR

There is NO effect on the previously synthesized carboxylated proteins



**Several days are required for onset!!
Long duration of action**

**T_{1/2} of clotting factors influence the onset:
VII 6h < IX 24 h < X 36 h < II 50 h (protrombin)**



Pharmacodynamic interactions of WARFARIN

vitamin K reduces effects of warfarin

➤ 250 ug/day K vitamin reduces effect significantly in practice

➤ 100 ug/day  INR=0.2 reduction

➤ Too low K vitamin intake is NOT good !

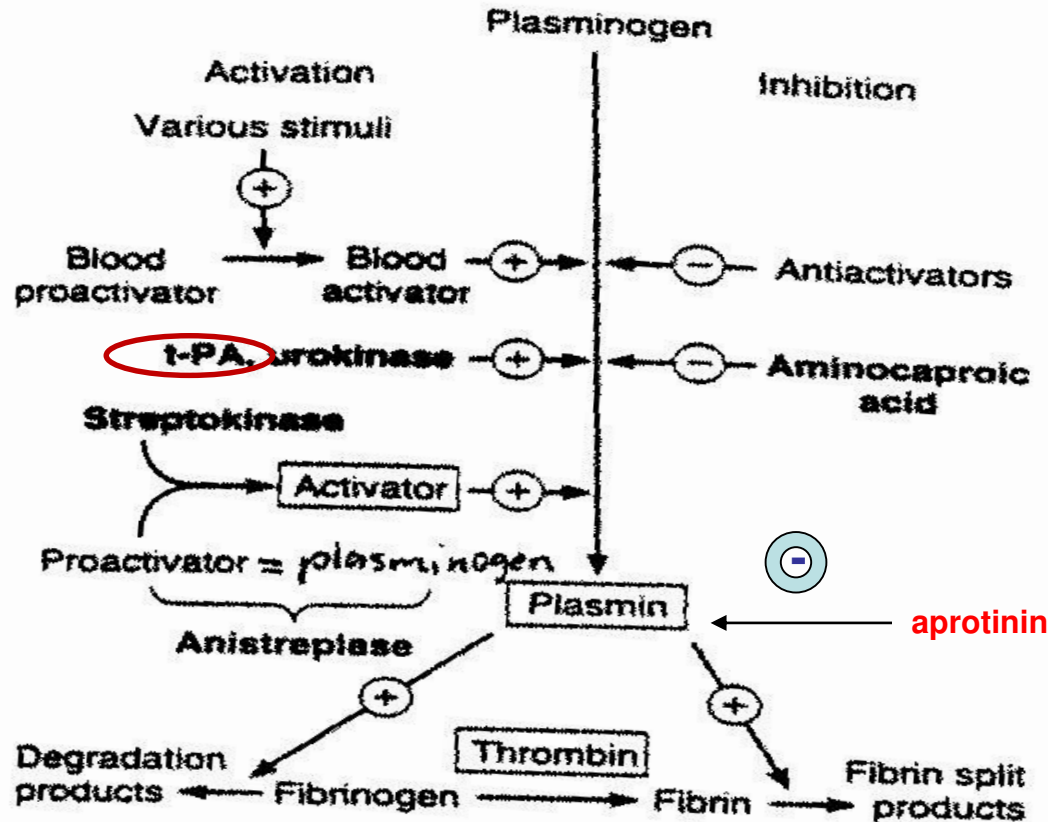


➤ Relative high amplitudes in changes
of the absorbed amount of the K
vitamin

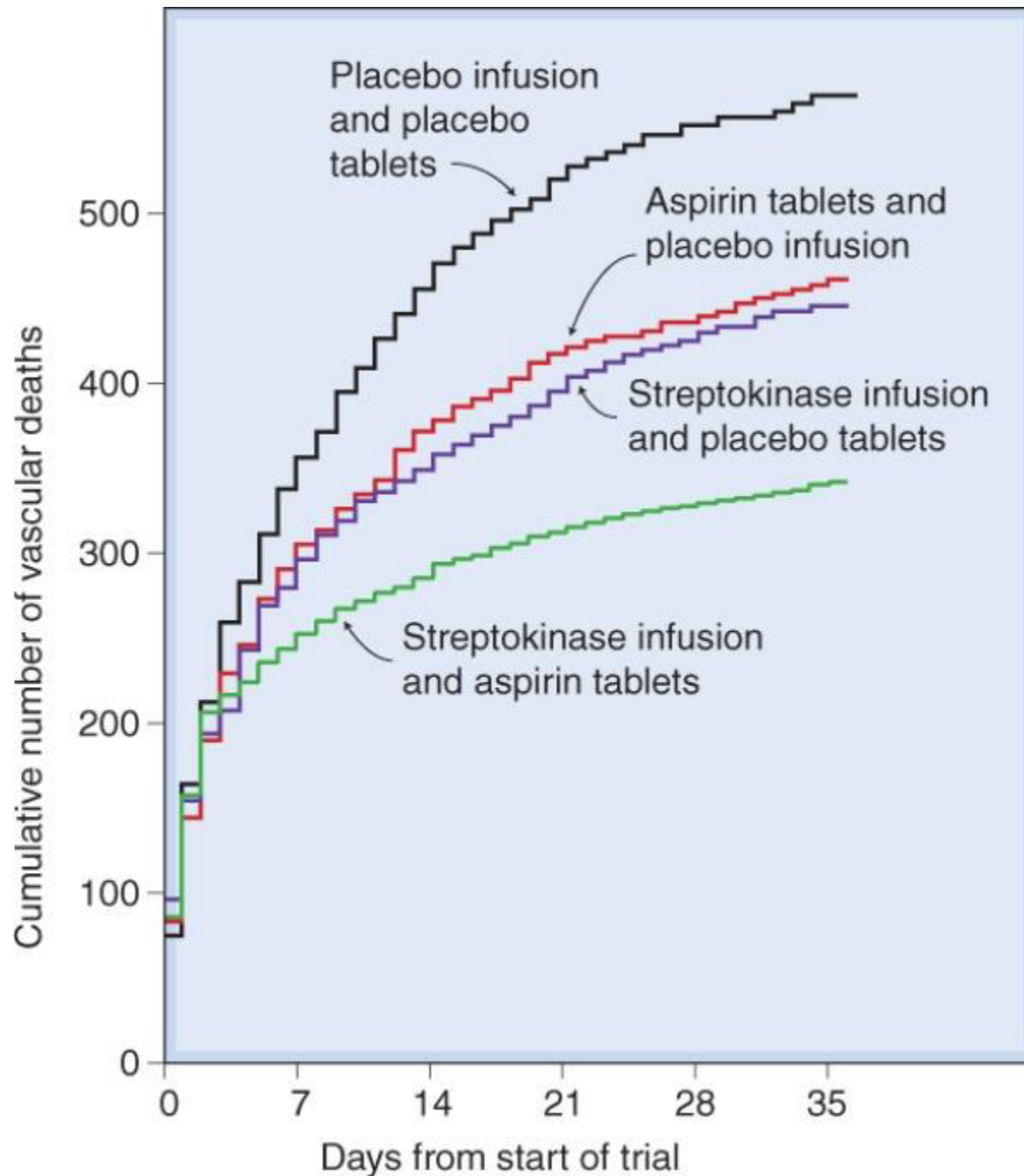


Higher risk for trombosis

Fibrinolytic and antifibrinolytic drugs



Clinical use: AMI or stroke in the first hours



ANTICOAGULANTS

Oral:

Proprietary names	formule	International name	quantity
Syncumar	tablet	acenocoumarol	2 mg
SP54	dragée	pentosanpolysulfate natrium	25 mg

Parenteral:

Heparin	inj.	heparin natrium	5000 UI/ml
Heparibene Na	inj.	heparin Na	5000, 25000 UI/amp
Heparin-Ca	inj.	heparin calcium	25000 UI/ml
Heparibene Ca	inj.	heparin Ca	5000, 20000 UI/amp.

Low molecular weight (LMW) heparins:

Clexane	inj.	enoxaparine	Mw:cc.4500 D
Fragmin	inj.	dalteparine Na	Mw:cc.5700 D
Fraxiparine	inj.	nadroparine Ca	Mw:cc.4500 D
Sandoparin	inj.	sandoparine Na	Mw:cc.5000-7000 D

Others:

AntitrombinIII alfa	inj.	antitrombin III	500, 1000 UI
AntitrombinIII Immuno	inj.	.	250, 500, 1000 UI

Comparing heparin and coumarin-derivatives

	HEPARIN	Coumarin-derivatives
Chemistry	Mwt: HMW 6000-20000 LWH negatively charged water soluble 1 mg >120 IU	Mwt: acenocoumarol: 353 lipophilic
Pharmacokinetics absorption distribution elimination	orally→ NOT absorbed im→ hematoma only iv or sc only in the plasma ! does NOT cross the PLACENTA kidney, liver fast dose-dependent T1/2 iv a few hours	well absorbed orally strong protein binding ! crosses the placenta CONTRAINDICATE in PREGNANCY slow T1/2 10-40 h
Pharmacodynamics	enhances the effect of ANTITROMBIN III	inhibitsb the K vitamin- dependent synthesis of protrombin (F II) and the Factors VII, IX, X
onset duration of action	immediate short	slow long

	HEPARIN	Coumarin-derivatives
Laboratory control	(clotting time) PTT	prothrombin -level
ADVERSE EFFECTS	B L E E D I N G	
	thrombocytopenia alopecia osteoporosis	damage to the fetus (bones) CONTRAINDICATED in PREGNANCY ! skin necrosis interactions with many other drugs
ANTIDOTE	1 mg protamine sulfate / 100 IU heparin	Vitamin K ₁ (KONAKION) plasma , blood protrombin concentratum

Anticoagulants

	in vitro	in vivo
Ca⁺⁺ bindings: fluoride, oxalate, EDTA	+	
heparin	+	+
Coumarin-derivatives: warfarin (SYNCUMAR)		+

INTERACTIONS OF COUMARIN ANTICOAGULANTS

PHARMACOKINETIC

DISPLACEMENT FROM SERUM ALBUMINS

↑
Phenylbutazone
Sulfinpyrazone

INHIBITION OF METABOLISM (= elimination)

↑
Phenylbutazone
Sulfinpyrazone
Metronidazole
Trimethoprim - Sulfamethoxazole

↑
Amiodarone
Disulfiram
Cimetidine

ENZYME - INDUCTION

↓
Barbiturates
Rifampin

INHIBITION OF ABSORPTION

↓
Cholestyramine

PHARMACODYNAMIC

INHIBITION OF PLATELET FUNCTION

↑
Phenylbutazone
Sulfinpyrazone
Aspirin

OTHER

↑
Heparin
3rd generation cephalosporins
Some diuretics (Spironolactone chlorthalidone)
↓
Vitamin K

↑
risk of bleeding is increasing

↓
or decreasing

Many interactions with vitamin K-rich food !!



Vitamin K containing foods

consumable/admissible

low vitamin K containing



- Meat, fish
- Cereals
- Bread and bagels
- pasta
- potatoe
- Rise
- Milk, diary

< 60 %



➤ Daily requirement of
vitamin K is 80 ug/day (US)

if only enourmous amounts
increases warfarin requirement

common vitamin K containing



butter, oil, olive oil
carrot, mushroom, asparagus
grean bean and pea, cucumber
apple, orange
celery, omion, cumin
parsley, dill



60-199 %



High vitamin K containing foods

>200 % of the daily requirement of vitamin K

Limited consume is needed:



- | | | | |
|----------------------------|-------|-------------------------------|-------|
| ➤ Eggs, liver | | ➤ Green-grocery oils | |
| ➤ soya | | ➤ Rude parsley | 600 % |
| ➤ lettuce | | ➤ green of the mustard boiled | |
| ➤ Spinach boiled or fresh | 560 % | or fresh | |
| ➤ mangold boiled or fresh | 360 % | ➤ Turnip cabbage | 530 % |
| ➤ broccoli boiled or fresh | | ➤ raspberry, strawberry | |
| ➤ cabbage | | ➤ tomato | |
| ➤ Chinase cabbage | | ➤ pepper | |
| ➤ Cale boiled or fresh | 660 % | | |

Max. once daily - ½ cup

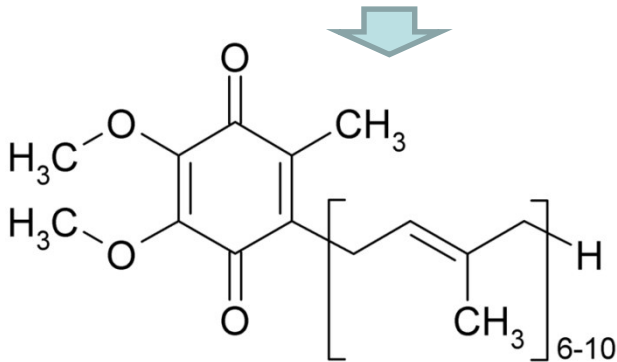
Coenzim Q10 – warfarin interactions

Coenzim Q10 - ubiquinon

In the majority of cells, its chemical structures is similar to vitamin K.

Tyrosin+fenilalanin+mevalonic acid

main effect: mitochondrium electron transport



other effects: fluidity of the membranes,
controlling of apoptosis

100 mg Coenzim Q10 reduces of the effect of the warfarin by 30-17 %



Coenzim Q10 in foods

Deficiency is common despite we are able to synthesize:

Studied in 1550 humans < 32 % of population had normal values

- aging
- Statin therapy – HMG –CoA reductase (hydroxyl-metil-glutaril-CoA) inhibition

symptoms: fatigue, muscle weakness, myopathy, headache, migrén

Th: 1-3 mg/kg/day in deficiency (most common 3x100 mg)



Coenzim Q10 – ubiquinone: dietary supplement < 1200 mg/day is safety

Foods:

- meat
- fish
- vegetables
- fruits



variable effects of warfarin

DIRECT TROMBIN INHIBITORS

e.g. in heparin induced thrombocytopenia (HIT)

hirudin (from medicinal leech) and its analogues:

By renal excretion:

- **bivalirudin and hirudin large molecules - irreversible**
- **lepirudin is the recombinant form of hirudin- short T_{1/2}**

By hepatic elimination:

- **argatroban small molecule – advantage in renal insufficiency**

NO ANTIDOTE !!! aPTT monitoring

Antibody formation !

ORAL DIRECT TROMBIN INHIBITORS

To prevent venous thromboembolism in patients with hip and knee replacement surgery

ximelagatran - hepatotoxicity- it was withdrawn

dabigatran for oral use !!!

its efficacy and safety is equivalent to LMWH

No routine monitoring is required

Direct inhibitors of factor Xa

apixaban (Eliquis)

rivaroxiban (**XARELTO**) *per os !!!*

oxazolidinon származék

Clinical use:

deep vein thrombosis, prevention of pulmonary edema,

atrial fibrillation to prevent stroke , systemic embolism

to prevent tromboembolism in orthopaedic surgery

Efficacy and safety are similar to LMWH

No routine monitoring is required

Toxicity:

Risk of intestinal haemorrhage is similar to warfarin therapy, however it increases in elderly especially in patient older than 75 years.

New directions

Vaccination is under investigation:

1. Vaccination against thromboxan A₂ (TxA₂)
2. Vaccination against coagulation factor XI:

Coagulation factor XI serves as a signal amplifier in the intrinsic coagulation pathway. Blockade of FXI by mAbs or small-molecule inhibitors inhibits thrombosis without causing severe bleeding, which is an inherent risk of currently available antithrombotic agents.