Treatment of thromboembolic disease

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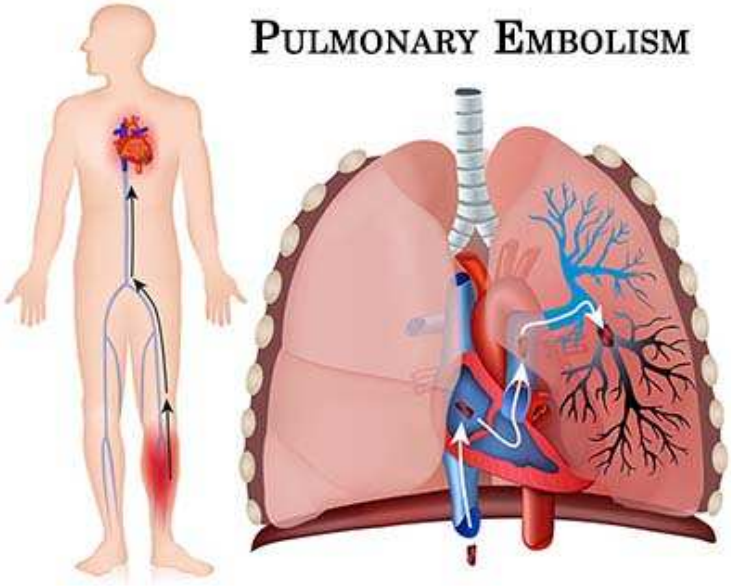
TEN – Thromboembolic disease

- **Presence of thrombus** within venous system causing obstruction
  - Complication - pulmonary embolism potentially fatal

- **Risk of thrombus leads**
  - Posttrombotického syndrómu
  - Thromboembolic pulmonary hypertension

TEN – Thromboembolic disease (2)

- **Clinical pathology layout**
  - flebothrombosis
  - Pulmonary embolism (50 % patients with flebothrombosis)
  - Statistically 3rd most common cause of death
  - *Superficial phlebitis*
    - NSAID
    - heparinoids



Source of embolism

- **Secondary** with known cause of origin

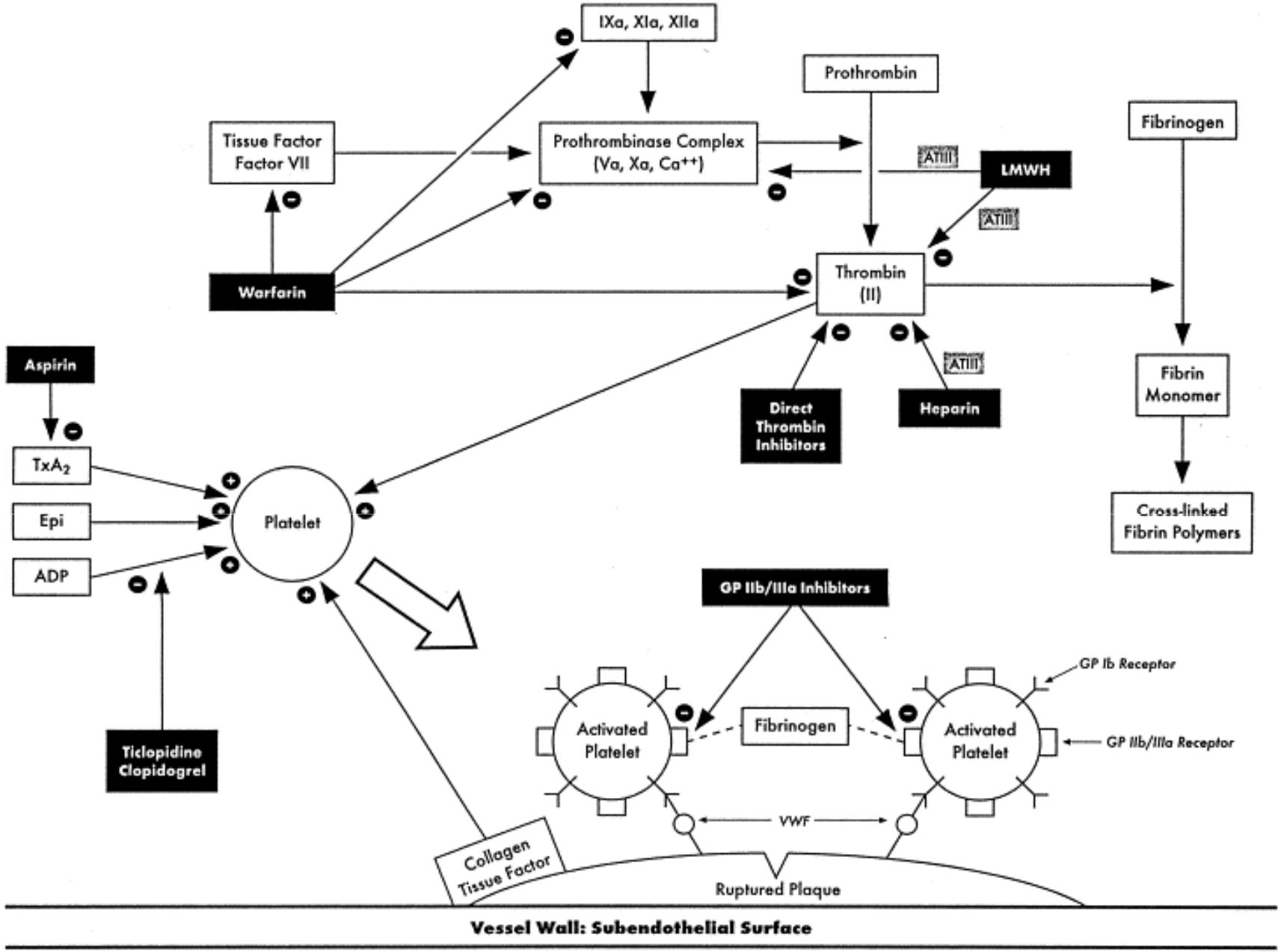
- **Primary** idiopathic
  - 30 – 50 % of cases
  - Oncology screening with detection of possible malignancy
  - Hereditary thrombophillic status

Incidence of thrombosis

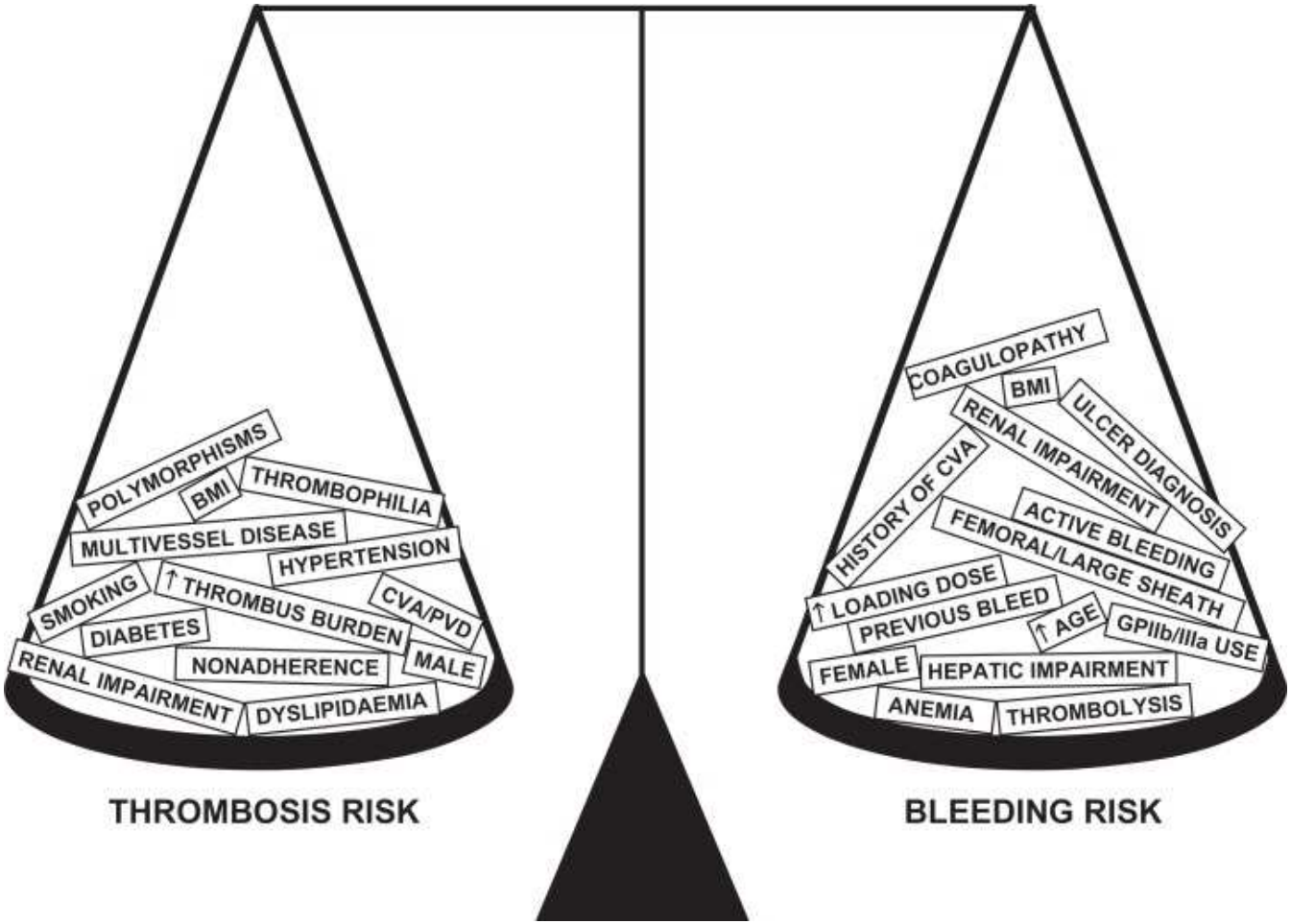
PATIENTS IN RISK GROUP	INCIDENCE (%)
Long time immobility in bed	10 – 20
Abdominal surgery	15 – 40
Stroke	20 – 50
Neurosurgery	15 – 40
Fractures of limbs	20 – 70
Large orthopedic surgery (hip, knee replacement)	40 – 80
Trauma	40 – 70
Critically ill patients on ICU	10 – 80
Spinal cord injury	60 - 80

Thromboembolic disease and Virchow trias

- Change in laminar blood flow
  - turbulence
  - Blood stasis
- Change in coagulation blood properties
  - Shift of ballance towards hypercoagulation
- Damaged vessel wall


IXa, XIa, XIIa
Prothrombin
Fibrinogen
Tissue Factor
Factor VII
Prothrombinase Complex
(Va, Xa, Ca++)
ATIII
LMWH
ATIII
Warfarin
Thrombin
(II)
Aspirin
ATIII
Fibrin
Monomer
Direct
Thrombin
Inhibitors
Heparin
TxA2
Epi
ADP
Platelet
Cross-linked
Fibrin Polymers
GP IIb/IIIa Inhibitors
GP Ib Receptor
Activated
Platelet
Fibrinogen
Activated
Platelet
GP IIb/IIIa Receptor
Ticlopidine
Clopidogrel
VWF
Collagen
Tissue Factor
Ruptured Plaque
Vessel Wall: Subendothelial Surface

What is the goal of the treatment of thromboembolic disease ?



Risk factors

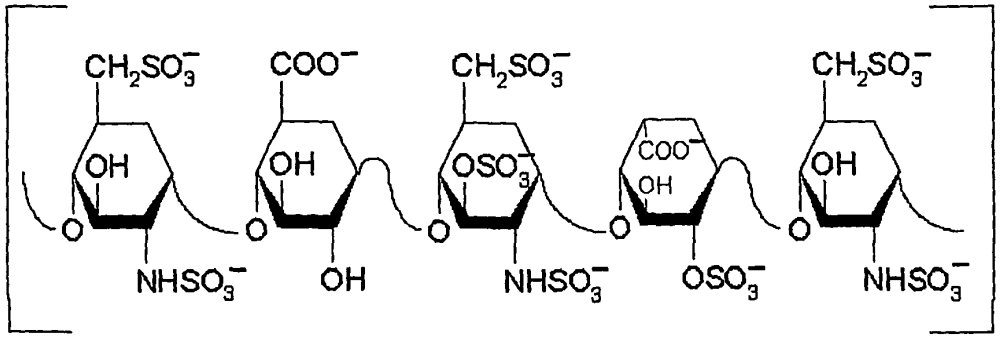
Congenital thrombofilia	**Insufficiency of anticoagulation factors (AT-III, protein C, proteín S), presence of antiphospholipid antibodies (L.antikoagulans). F-V Leiden mutation, Prothrombin mutation (20210 G-A), hyperhomocysteinemia,**
Thrombophilia – acquired	**Malignancy,** sepsis, Myeloproliferative diseases, nefrotick syndrom, IBD, age (40 years), positive anamnesis, immobility and trauma, serious internal condition (CHF, stroke), autoimmune diseases (lupus a nd „lupus-like“), gravidity, anatomic abnormalities in venous system, obesity
Circumstances contributing on thromboembolic disease	Travelling and dehydration, trauma coupled with fixation, pharmacotherapy (staroids, HRT, birth-control pills), smoking

Therapeutic groups

- **„indirect“ anticoagulants**
  - heparin, LMWH a pentasacharides
  - Vitamin K antagonists (coumarines)
- **„direct“ anticoagulants**
  - NOACs, hirudin
- thrombolysis

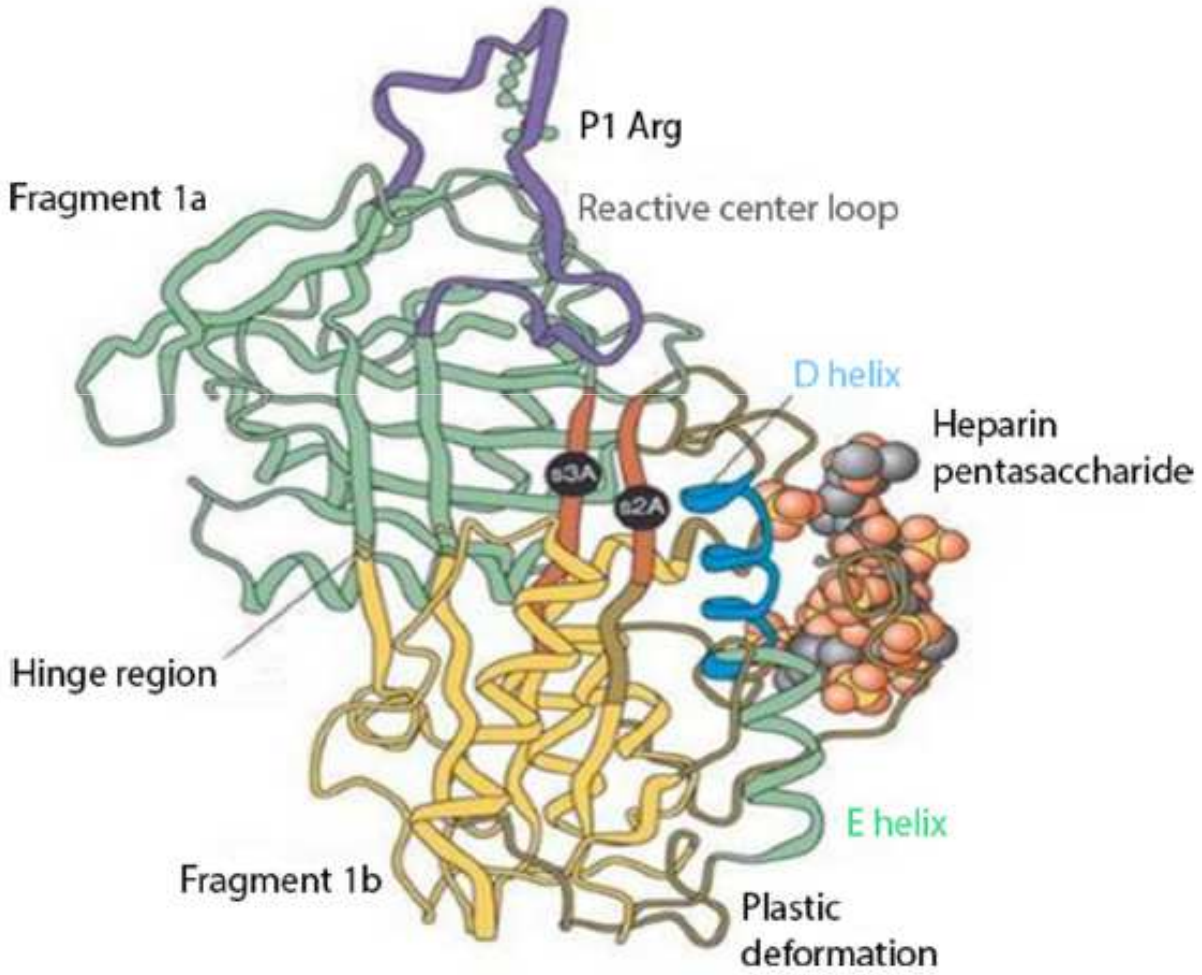
Heparin structure

- mukopolysacharide with **variable** chain leght (**5-30 000 Da**)
- Anticoagulant and pleiotropic activity
  - Antiinflamnatory
  - Cytostatic
  - immunomodulatory



Heparin

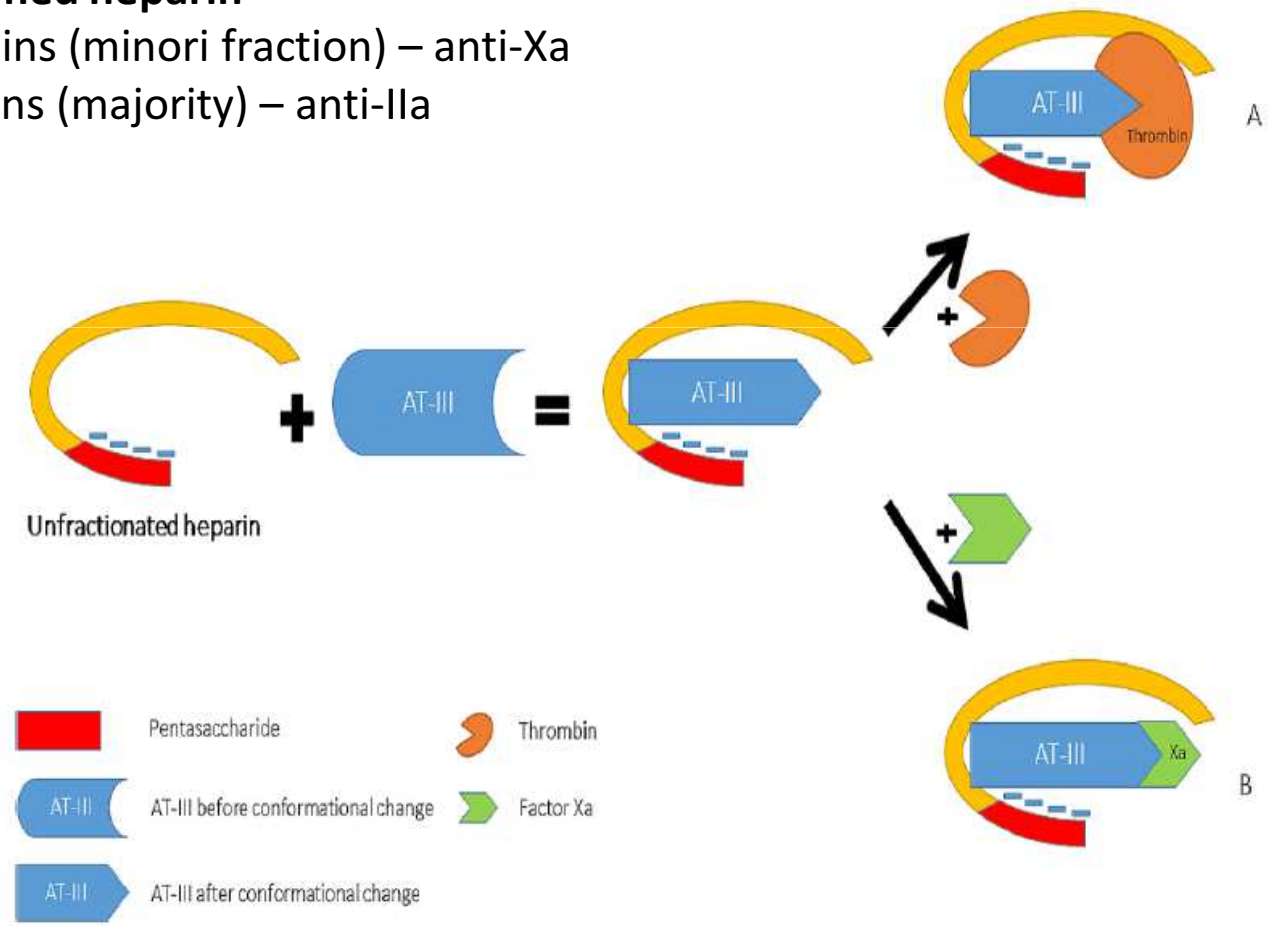
Heparin – mechanism of action



Quaranta et al. (2015), The physiologic and therapeutic role of heparin in implantation and placentation. PeerJ 3:e691; DOI 10.7717/peerj.691

Heparin – mechanism of action (2) – variable according mixture of chains

Unfractioned heparin
Short chains (minori fraction) – anti-Xa
Long chains (majority) – anti-IIa



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Heparin - advantages

- Rapid onset of action (i.v. administration)
- Relativelly cheap
- Available in patiens with severe kidney insufficiency

- **Antidote** available
  - Protamine suplhate 1mg: 100 IU Heparin

Heparin - cons

- Non-linear pharmacokinetics (**distribution and elimination**) – narrow therapeutic range

- Daily monitoring of anticoagulation activity (**aPTT**)
- Heparin resistance (**acute phase proteins**)
- Only in i.v. infusion (!!! i.m. and s.c. !!!!)

Heparin – cons (2)

- Riziko hyperkoagulácie po vysadení
  - Neschopnosť väzby heparinu na **trombin viazaný fibrínom**

- Aktivita priamo viazaná na prítomnosť **AT-III**
  - Deficiencia AT-III (1-5 %)
  - Substutúcia rekombinantného AT-III a monitorácia

Monitoring of anticoagulation activity

- aPTT – **activated partial tromboplastin time**
  - Interval 1,5 – 2,5x against control specimen
  - First value 12 hrs after i.v. heparin
  - Extracorporeal methods, cathetrisation methods, dialysis (**ACT-activated coagulation time**)

- dosing
  - Bolus **5000 – 10000 IU**
  - i.v. continual infusion **400 IU/kg**

Heparin - adverse effects

- Bleeding
- **Thrombocytopenia**
- Osteopenia and osteoporosis
- allergy

Heparin induced thrombocytopenia (HIT)

- **HIT-1**
  - Manifestation 1st -2nd day of treatment in 10 % of patients
  - Mild thrombocyte decrease
  - Relativelly benign and temporary
  - **Heparin treatment termination not necessary**
- **HIT-2**
  - Manifestation 4th–5th day of treatment in 0,5-5 % liečených
  - Immunologically mediated (IgG AB agains **heparin-PF4**)
  - Endotel and Thrombocytes activation
  - Life-threatening **thrombosis and DIC**
  - **Immediate heparin discontinuation**

Heparin-induced thrombocytopenia (HIT)

- Check platelet count before heparin starts
- Monitoring of platelet count dynamics

- **Heparin stop** indicated with platelet count below 50 % of initial value (**HIT-2**)

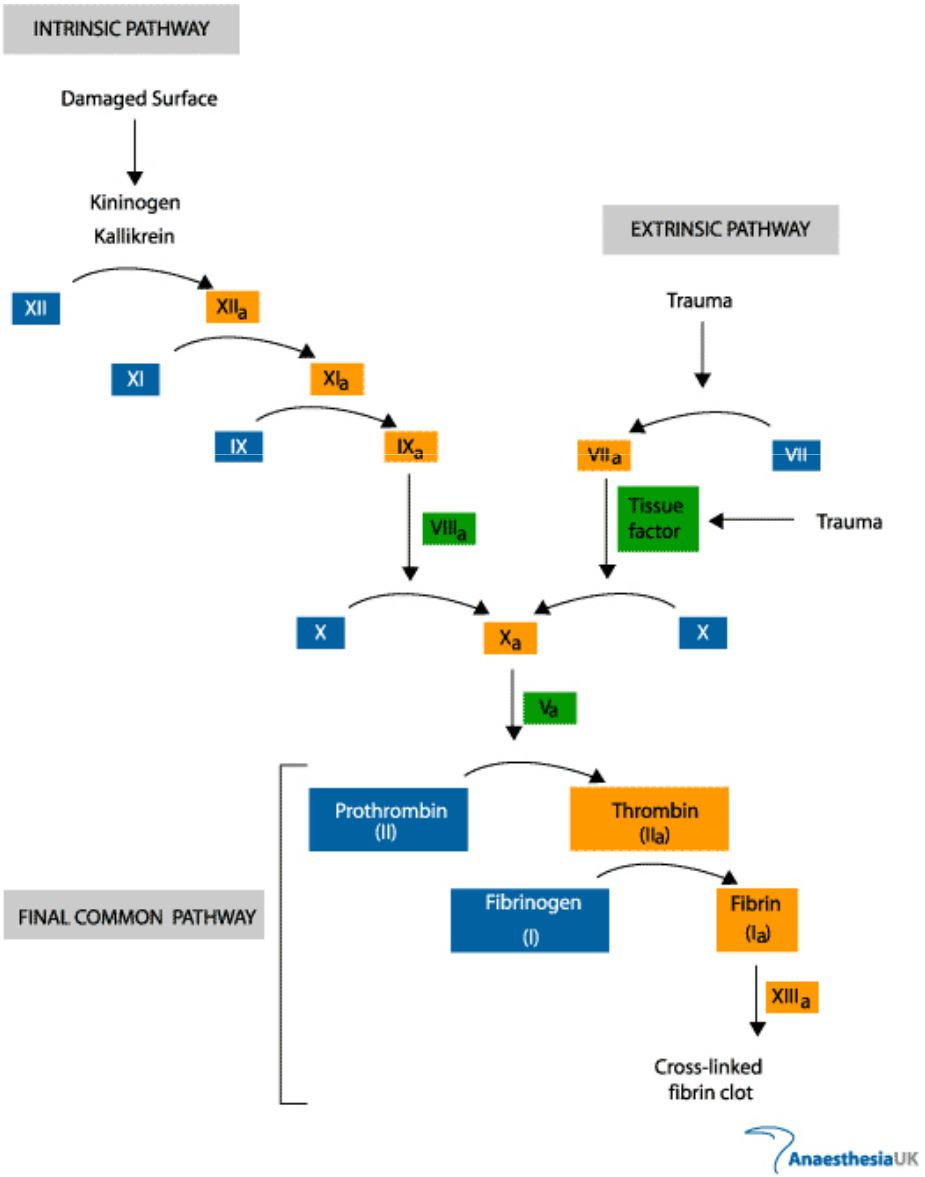
- Fondaparinux, lepirudin, ~~LMWH, warfarin~~

Heparin neutralisation with protamin-sulphate

- Protamin dose calculation
  - Heparin halflife **1-2 hrs**
  - Heparin dose estimation to neutralize
  - (**cumulative dose in past 3-6 hrs**)

- i.v. **protamin-sulphate** (non-registered)
- **1 mg = 100 IU heparin**

Low molecular weight heparin



Basic differences between UF-heparin and LMWH

- **Native heparin chain depolymerisation**
  - 15 sacharide units
- **Improved parameters**
  - ↓ plasma protein binding
  - ↓ thrombocyte and endotel binding
  - Predictable anticoagulant activity
  - Possible **s.c.** administration (1-2x/day)
  - **Dosing according patients weight**
  - **Self-administration injectors**

Structure of LMWH and it`s impact on FD

- Mixture of various chain leght heparins (average n=15)
- ↓ molecular weight (5000 Da)

- **Anti-Xa activity**
  - Most common chain leght (n=5)
- **Anti-IIa activity**
  - Most common chain leght (n=18)

Anticoagulation activity monitoring via Anti-Xa method

- **MAJOR ELIMINATION ORGAN - KIDNEYS**
  - Anti-Xa not necessary if no kidney damage present

- Anti-Xa control indicated
  - gravidity
  - Renal insufficicency
  - Obese and asthenic patients

- **anti-Xa** control after **3 days of treatment**
- 2-4 hrs after s.c. dose

LMWH PK parameters

LMWH	weight (Da)	ANTI-Xa /ANTI-IIa ratio	F (s.c.) (%)	HALFLIFE (hod)
Enoxaparine	4200	10:1	100	7
Bemiparine	3600	8:1	96	6
Nadroparine	4600	4:1	88	4
Dalteparine	5000	3:1	90	5

ADVANTAGE IN FK PARAMETERS, BUT ABSENT ANTIDOTE .

FONDAPARINUX

- **PENTASACHARIDE** with predictable anticoagulant activity
- Anti-Xa activity mediated via high AT-III selectivity (300:1)
- **Prolonged effect**
- Complete resorption after s.c. administration
  2,5 mg, 7,5 mg
- AC activity monitoring not necessary
- Absent risk of HIT, absent antidote

Oral anticoagulants

- ***Warfarin* (antivitamin K)**

- ***Dabigatran (inhibitor IIa)***
- ***Rivaroxaban (inhibitor Xa)***
- ***Apixaban (Inhibitor Xa)***

- ***Edoxaban (inhibitor Xa)***

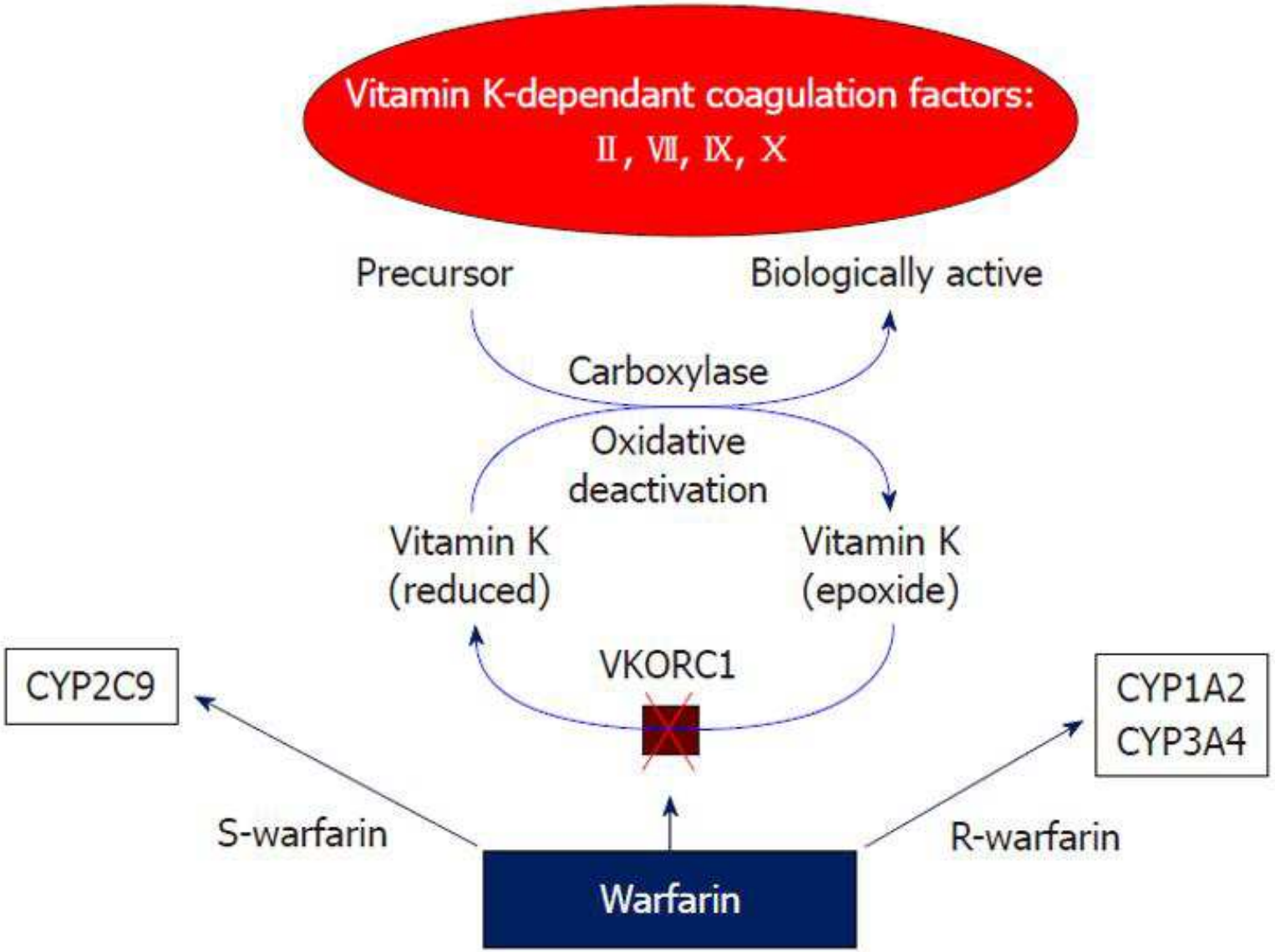
VITAMIN K

- SOURCE
  - Food (20 %)
  - Intestinal flora (80 %)

- insufficiency
  - Cholestasis
  - Treatment of broad-spectre ATB
    - (β-lactam 2nd and higher generation)

WARFARIN – FEATURES (1)

- Coagulation factors systhesis inhibitor
  - ANTIVITAMIN K ?
  - VITAMIN K ANTAGONIST
  - No effect on blood viscosity



***S*-warfarin 4x more potent than *R*-warfarin – PK interactions**

WARFARIN – FEATURES (2)

- **Good p.o. bioavailability**
- High plasma protein binding (**albumin**) **(99 % resorbed fraction)**
- Extensive liver metabolism
- **Enterohepatal recirculation**

- **<u>Delayed onset of action</u> (heparin necessary)**

Treatment initiantion and monitoration

- 5-10 mg in single dose
- When ? (morning, noon ?)
- Risk of **paradox hypercoagulation**

$$\text{INR} = \frac{\text{PATIENT PT}}{\text{STANDARD PT}}$$

WARFARIN AND POSSIBLE COMPLICATIONS

- **bleeding**
  - Rectum, GIT (stomach, bowel)
  - Intracranial bleeding

- Skin **coumarine necrosis**
- Blood panel abnormalities
- hepatotoxicity
- Increased fracture risk

WARFARIN AND DRUG INTERACTIONS

NONE …

CLINICALLY RELEVANT INR PARAMETER EXERTION

- Slow-down coumarine metabolism in liver
- Speed-up coumarine liver metabolism

- Enterohepatal recirculation block
- FC drug interactions at distribution level

- **FD drug interaction**

NOACs

- **advantages**
  - Linear FC and FD parameters
  - Predictable anticoagulant activity
  - Monitoration not necessary
  - Absent clinically relevant drug interactions
  - Low risk of genetic resistance

  - Safe and more effective

NOACs

- **disadvantages**
  - Antidote absent (except dabigatran)
  - Higher rate of GIT bleeding*
  - expensive

DABIGATRAN (PRADAXA)

- ester **dabigatran etexilat** (substrate p-gp)
- Hydrolysis via plasma esterase enzymes without P450 CYP effect
- DVT treatment:
  - 5 days LMWH + dabigatran
- **Profylaktic dose 220 mg , 150 mg once a day**

DABIGATRAN (PRADAXA)

- **Direct thrombin inhibitor (IIa)**
  - Free fraction
  - Fibrin coupled

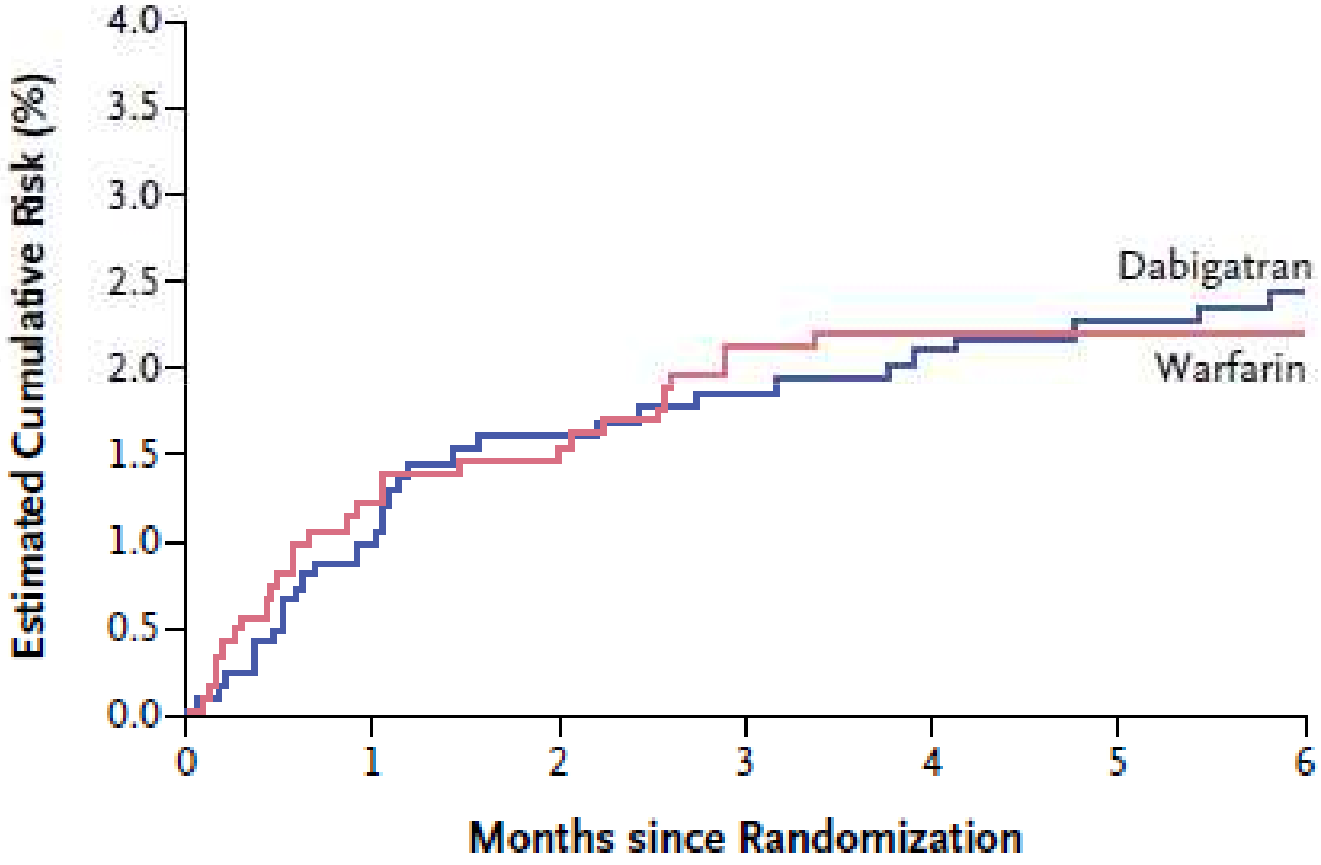
- Inhibition of secondary **thrombin-mediated** thrombocyte aggregation

- **<u>DABIGATRAN ETEXILATE (PRADAXA)</u>**
  - Bioavailability **3-7 %**
  - **Clinically relevant drug interactions on absorption level**
  - **P-GP inhibition**
  - Amiodarone cardioversion

RE-COVER účinnosť a bezpečnosť

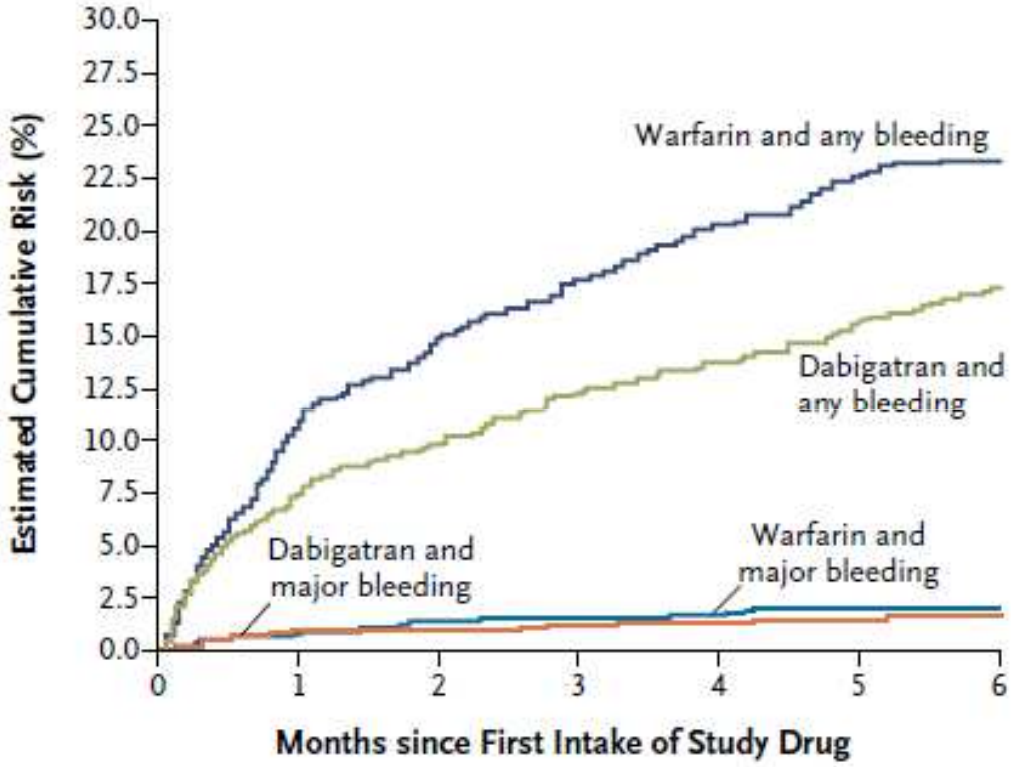
Outcome	Dabigatran (N=1274)	Warfarin (N=1265)	Hazard Ratio (95% CI)*
Efficacy analysis†			
Primary end point of venous thromboembolism or related death — no. of subjects (%)			
During the study period	30 (2.4)	27 (2.1)	1.10 (0.65–1.84)
During the study period plus an additional 30-day follow-up‡	34 (2.7)	32 (2.5)	1.05 (0.65–1.70)
Secondary end point — no. of subjects (%)			
Symptomatic deep-vein thrombosis	16 (1.3)	18 (1.4)	0.87 (0.44–1.71)
Symptomatic nonfatal pulmonary embolism	13 (1.0)	7 (0.6)	1.85 (0.74–4.64)
Death related to venous thromboembolism	1 (0.1)	3 (0.2)	0.33 (0.03–3.15)
All deaths	21 (1.6)	21 (1.7)	0.98 (0.53–1.79)
Safety analysis§			
Major bleeding event — no. of subjects (%)	20 (1.6)	24 (1.9)	0.82 (0.45–1.48)
Fatal event — no. of events	1	1	
Bleeding into critical organ — no. of events	1	9	
Intracranial	0	3	
Hemarthrosis	1	5	
Hemoptysis	0	1	
Event resulting in fall in hemoglobin level or need for blood transfusions — no. of subjects (%)¶	20 (1.6)	18 (1.4)	
Major or clinically relevant nonmajor bleeding event — no. of subjects (%)	71 (5.6)	111 (8.8)	0.63 (0.47–0.84)
Any bleeding event — no. of subjects (%)	205 (16.1)	277 (21.9)	0.71 (0.59–0.85)

RE-COVER efficacy – DVT risk in 6 months



No. at Risk							
Dabigatran	1274	1238	1221	1203	1192	1181	1024
Warfarin	1265	1215	1204	1194	1187	1174	998

RE-COVER bleeding



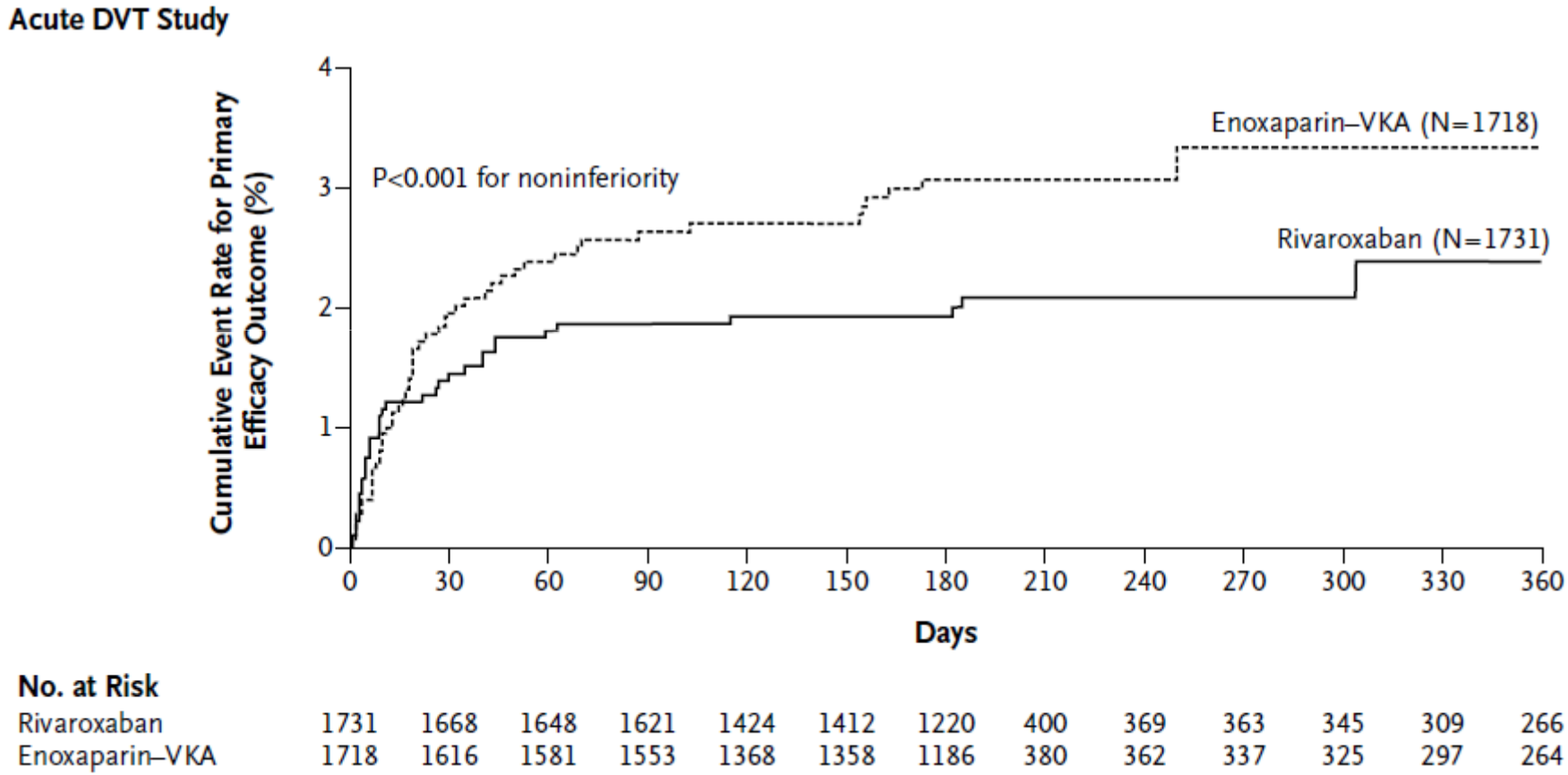
No. at Risk							
Dabigatran and major bleeding	1273	1194	1153	1124	1105	1080	884
Warfarin and major bleeding	1266	1178	1146	1128	1110	1093	859
Dabigatran and any bleeding	1273	1117	1055	1002	971	931	747
Warfarin and any bleeding	1266	1064	993	950	909	870	692

RIVAROXABAN (XARELTO)

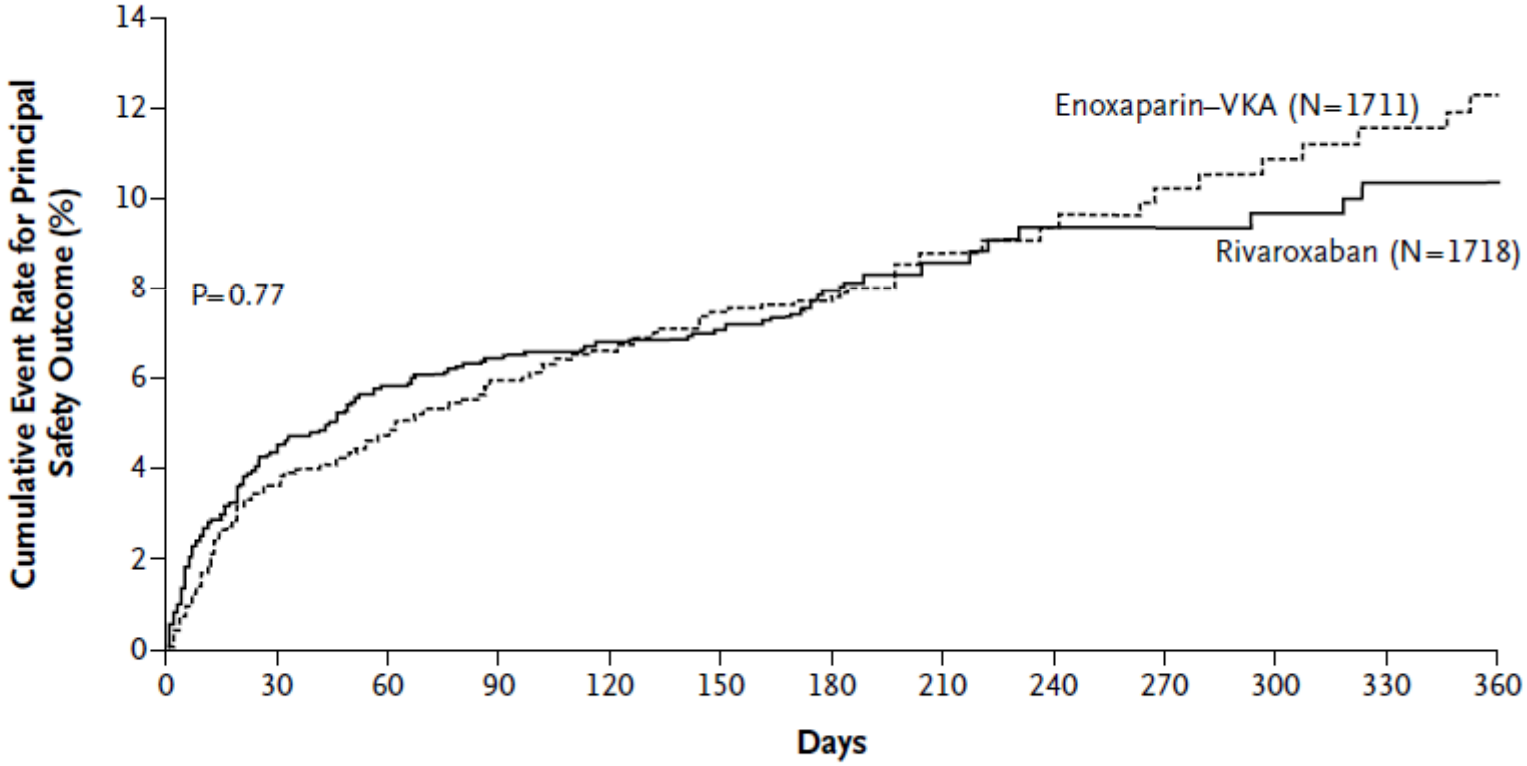
- Direct fXa inhibitor
- Predictable anticoagulation activity

- **Prevention and treatment** of DVT a PE
  - 15 mg 2x day (3 weeks)
  - 20 mg 1x day maintenance dose

EINSTEIN TRIAL
rivaroxaban vs enoxaparin (warfarin)



EINSTEIN TRIAL
rivaroxaban vs enoxaparin (warfarin) - safety



No. at Risk

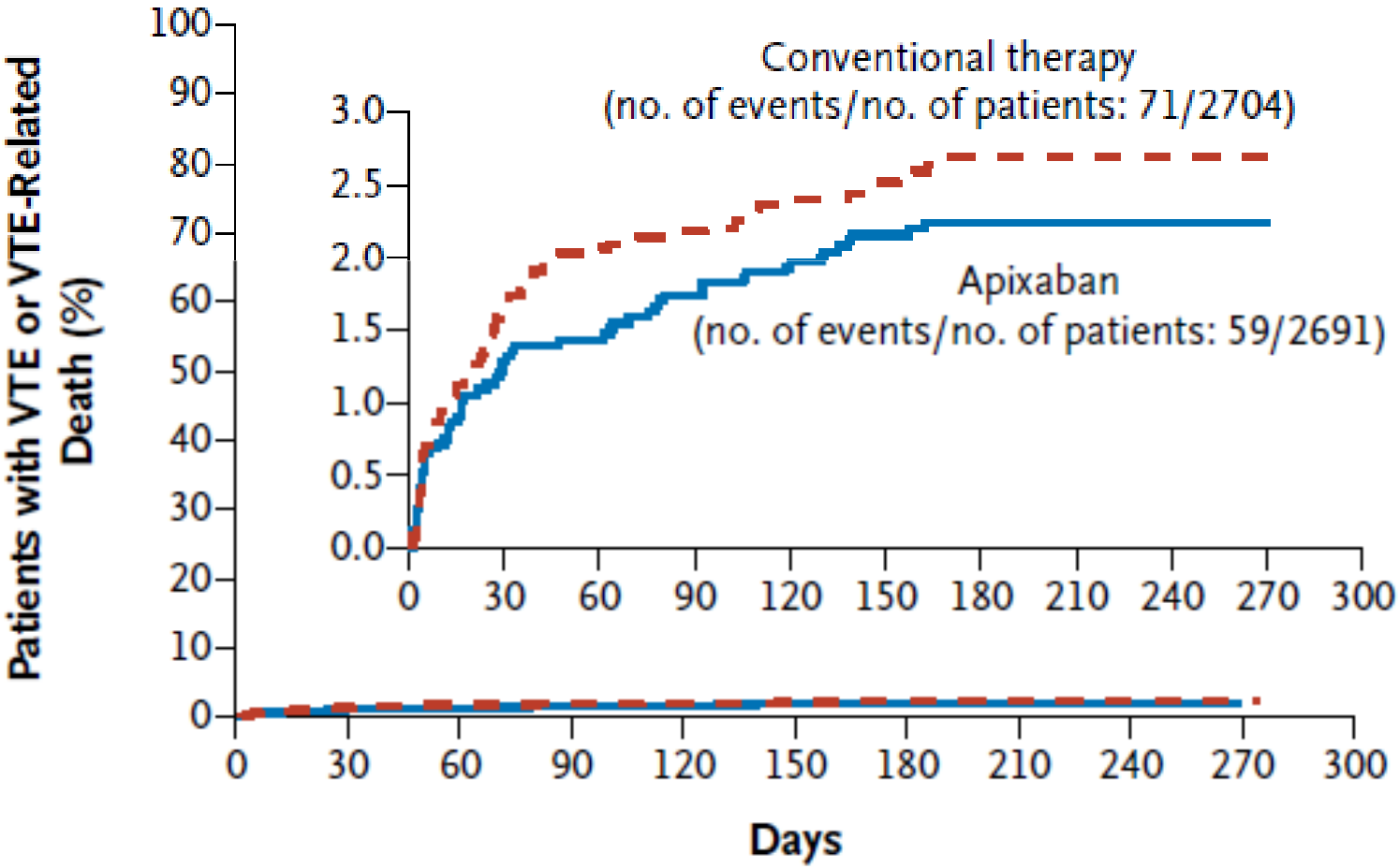
Rivaroxaban	1718	1585	1538	1382	1317	1297	715	355	338	304	278	265	140
Enoxaparin–VKA	1711	1554	1503	1340	1263	1238	619	338	321	287	268	249	118

APIXABAN (ELIQUIS)

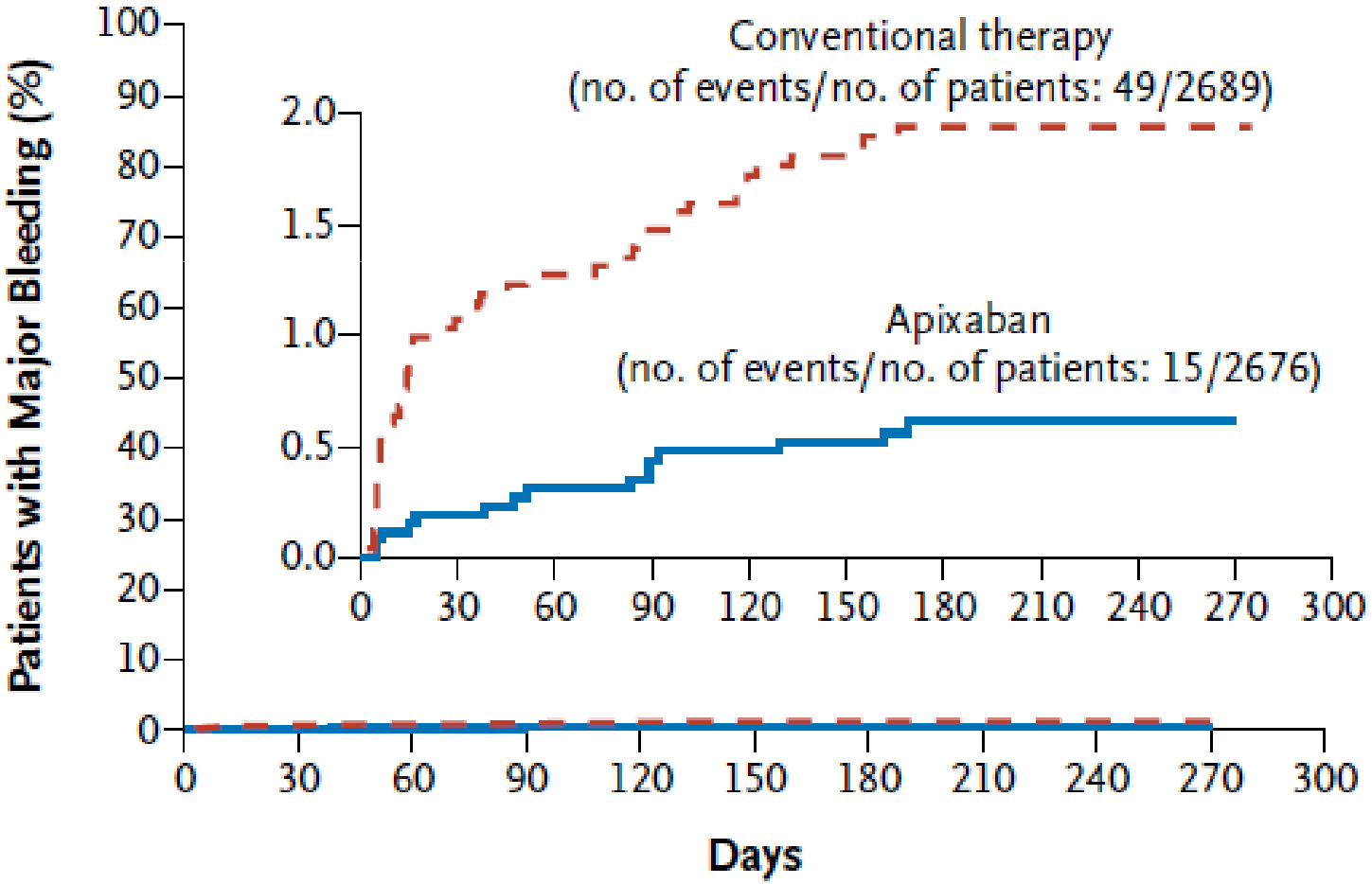
- Direct fXa inhibitor
  - Free and bound fraction
  - Loading 10 mg 2x day (7 days)
  - Maintenance dose 5 mg 2x day

- *age, body weight, serum creatinine level above 133 umol/L

AMPLIFY apixaban – efficacy



APMLIFY apixaban – safety



PK FEATURES

	dabigatran	rivaroxaban	apixaban
Cieľová štruktúra	IIa(trombin)	Xa	Xa
Cmax	0,5-2,0	2,0-4,0	3,0-4,0
Interakčný potenciál	P-gp	P-gp a CYP3A4	P-gp a CYP3A4
Polčas	14-17	9-13	12-15
Podiel renálnej eliminácie [%]	80	33	27

Thank you

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