Antithrombotic therapy

Thrombophilia – clinical criteria

- trhombosis in younger age:
  - venous under age 45 years
  - arterial under age 35 years
- recurrence of thrombosis
- atypic localization of thrombosis
- positive family history of VT
- repeated fetal loss

Acquired risk factors of thrombosis

- **Specific risk factors**
- Aging
- Long-lasting immobilization
- History of thromboembolism
- Overweight
- Varicosity
- Heart failure
- Stroke
- Hip & leg fractures
- Infections of colon
- Nefrotic syndrome
- Oestrogens
- Malignancy

Risk factors of DVT - thrombofilias

- **hereditary:**
  - **factor V Leiden**
  - **protrombin 20210A**
  - **↓ antitrombin III**
  - **↓ protein C**
  - **↓ protein S**
  - **dysfibrinogenemia**
- **mixed etiology:**
  - **factor VIII >150%**
  - **↑ fibrinogen**
  - **↑ homocystein**
- **acquired:**
  - **antiphospholipid syndrome**

Hereditary thrombotic states

	Prevalence (%)		Rel. Risk of DVT
prothrombotic factor	DVT	Normal population	
FV Leiden heterozygot	**20**	**5**	**6.0**
FII20210A	**6.2**	**2-3**	**3.0**
PS def.	2.2	0.2	2-10
PC def.	2.1	0.3	5-10
ATIII def.	1.1	0,2	50
dysfibrinogenemia	0.8	?	?
Elevation of FVIII*	20	11	3.0
Hyperfibrinogenemia*	15	8	2.0
Hyperhomocysteinemia*+	10	5	2.0

***** *Mixed etiology* **+** *dietetic influences*

Coopera a Krawczacka

Factor Va

- cofactor of FXa
- cofactor of aPC for degradatio of FVIIIa
- by aPC is cleaved at site:
  - Arg 506
  - Arg 306
  - Arg 679

Faktor V – mutation
(chromosome no 1)

- **Leiden** **Arg 506G ln**
- Cambridge Arg 306 Thr
- Hong Kong
  - 1 Arg 485 Lys
  - 2 Arg 306 Gly
- HR2 haplotype His 199 Arg

Faktor V Leiden
(G1691A » Arg506Gln)

In Caucasian population:

- All population 5%
- DVT without selection 20%
- DVT clinical thrombophilia 40%

Seligsohn U., N Engl J Med, 2001

Factor V Leiden
(heterozygots)

DVT risk is increased:		**5-6x**
• **homozygotes**		**50-100x**
• in pregnancy		5-15x
• + OC III. generation	20x	(OC only 3-4x)
• + HRT	15x	(HRT OC only 2-4x)

Mutation of prothrombin 20210A (20210 G →A)

- missence mutation in non-translated part of gene
- **DVT risk is incerased 3x**
- ↑ plasma level of FII
- 2-3 % in all population
- 6 % DVT without selection
- 7-18 % DVT and positive family history of DVT

Protrombin - G20210A

(heterozygotes)

DVT risk is increased: **3x**

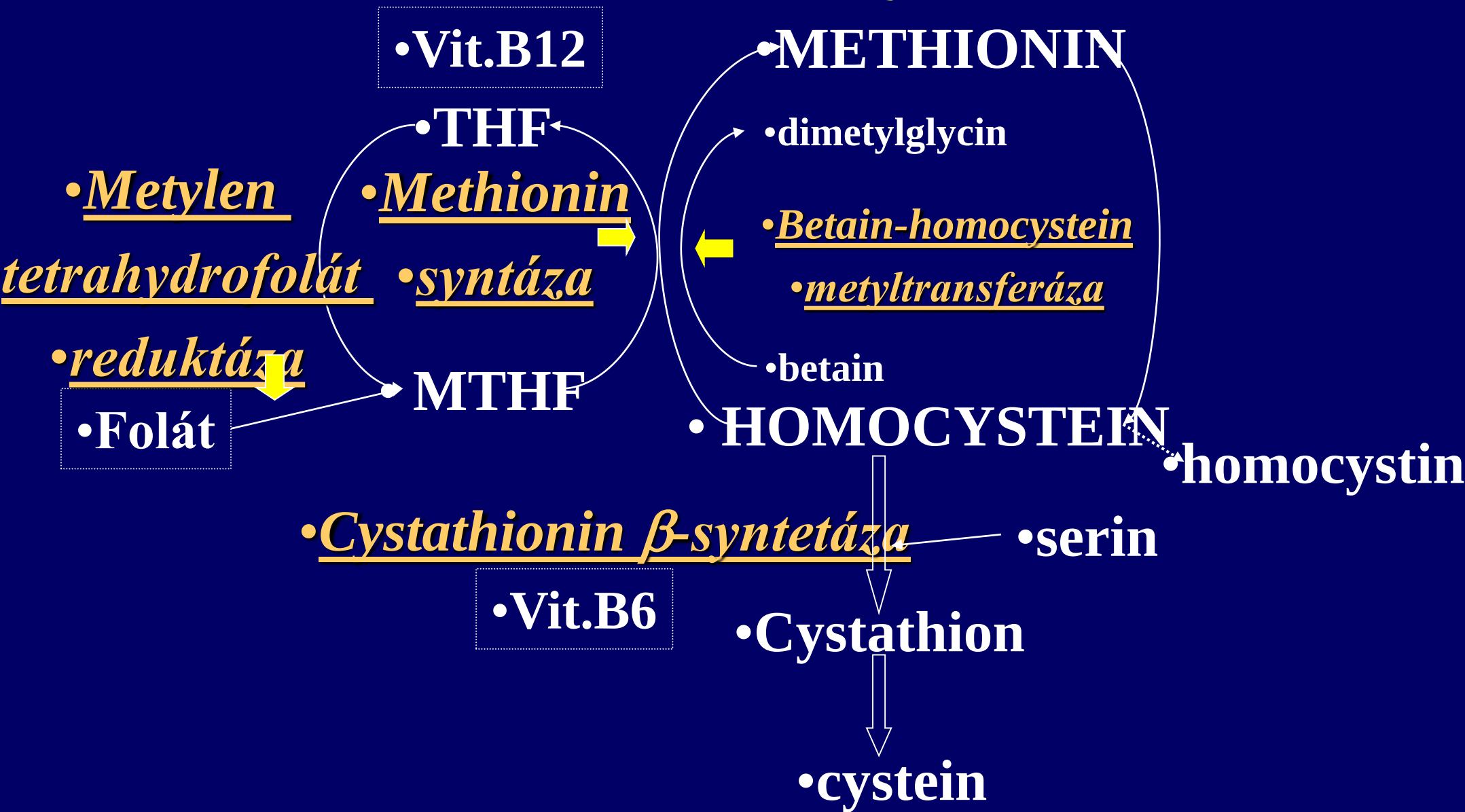
- **homozygotes:**
  1/3 without DVT **1/3 spont. DVT** **1/3 sec. DVT**

- **Heterozygotes with FVL** **50-100x**

- in pregnancy 10x
  heterozygotes with FVL 100x

- + OC III. generation 3-16x (OC only 3-4x)
- + OC + smoker: risk of VT of CNS: 150x

Metabolis of homocysteine



Mild hyperhomocysteinemia

- **15-30 μmol/l**

  - 5% of all population

  -10-20 % of DVT

  - 2 x ↑ risk of DVT, AT

  - folate deficiency is in 5 -15 % of population

- polymorfism C677T in gene for MTHFR

  - TT: 10-15% - T/C: 40-45% - C/C: 50-55%

  - TT: 1/4-1/3 has mild hyperhomocysteinemia

- Treatment:
  - Folate: 0.5 mg
  - B12: 0.4 mg
  - B6: 3-10 mg

Antithrombotic therapy

- prevention of thrombus formation
- prevention of thrombus progression
- thrombus dissolution
- prevention of rethrombosis
- prevention of secondary changes

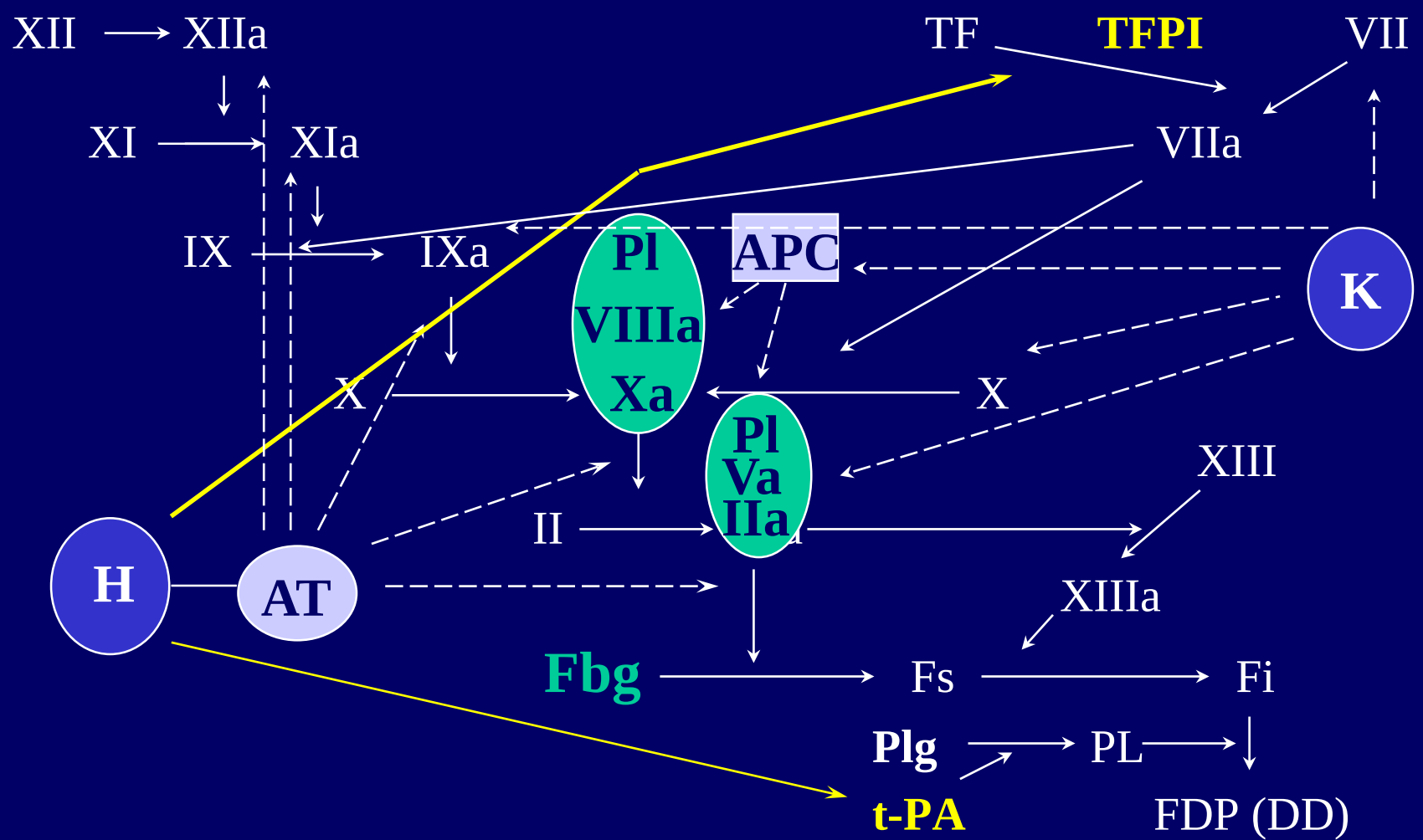
Actual requirements for antithrombotics:

- simple administration (oral, no laboratory monitoring, no diet restrictions, no concomittant therapy restrictions)
- safe therapy (without bleeding, without adverse events)
- inexpensive

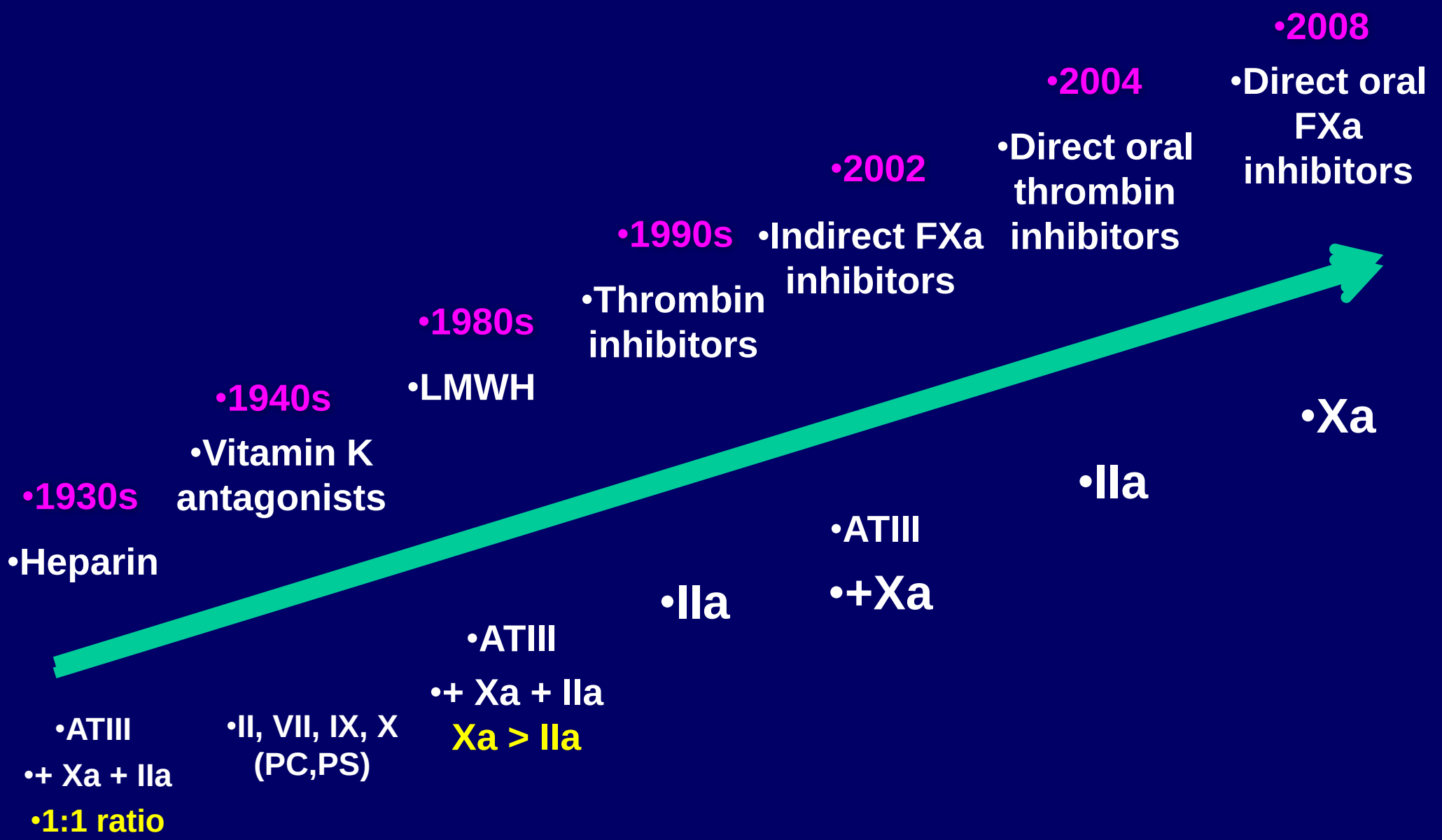
Antithrombotic therapy

- **anticoagulant (anti-IIa):**
  - ***indirect thrombin inhibitors (antithrombin-mediated): heparin, LMWH***
  - ***coumarins – reduce levels of vitamin-K dependent factors: warfarin***
  - ***direct thrombin inhibitors: hirudin, dabigatran***
- **antithrombotic (anti-Xa):**
  - ***indirect factor Xa inhibiotris: LMWH, pentasacharides***
  - ***direct factor Xa inhibotors: xabans (rivaro-, api-, edoxaban)***
- **antiaggregation (antiplatelet):**
  - ***ASA***
  - ***clopidogrel, prasugrel, ticagrelor, cangrelor, etc.***
  - ***GP IIb/IIIa inhibitors***
- **thrombolytic:** ***rt-PA***
- **substitution:** ***AT, PC***

Coagulation cascade and antithrombotic therapy



Antithrombotics development



Indication for anticoagulant therapy - heparins, coumarins

- venous thrombosis and embolism
- atrial fibrillation
- heart valve replacement
- artificial surfaces – HD, extracorporeal circulation
- antiphospholipid syndrome
- DIC

Risk of VTE in surgery

Cathegory	Pelvic	Proximal	Fatal PE
High (large orthopedic surgery, urologic surgery (age >40), history of VTE, extensive pelvic & abdominal surgery for malignancy)	**40-80%**	**10-30%**	**1-5%**
Intermediate (common surgery & age >40 & duration > 30 minutes, surgery & contraceptives, urgent sectio Cesarea)	**10-40%**	**2-10%**	**0,1-0,8%**
Low (small surgery, young patient, no risk factors)	**< 10%**	**<1%**	**<0,01%**

The classification of risk profile

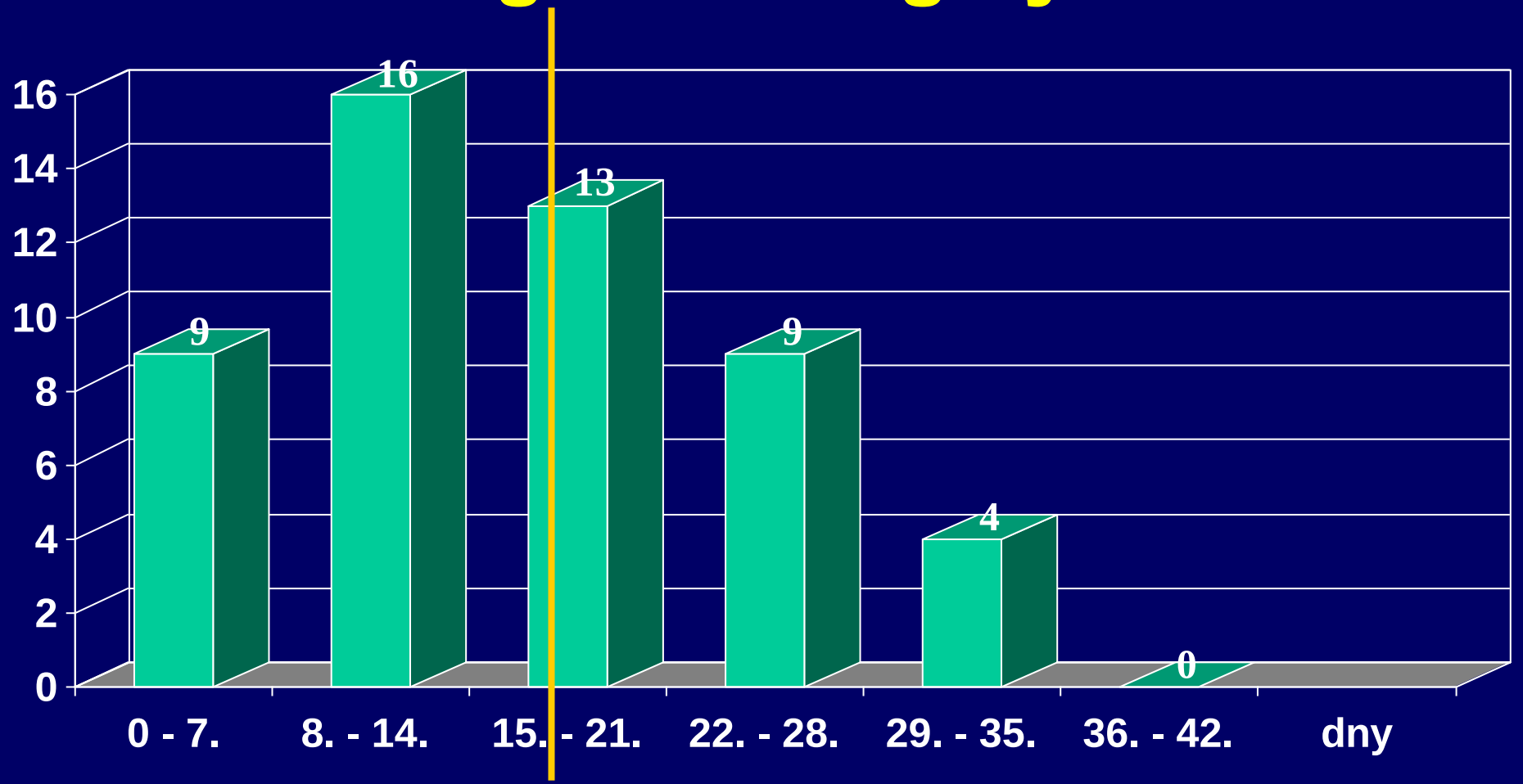
- Low risk
- Non-complicated surgery lasting <30 min in a patient aged < 40 years
- Intermediate risk
- Surgery in a patinet aged 40-60 years without any risk factor
- Larger surgery in a patient aged > 40 years without any risk factor
- Small surgery in patients with risk factor/s
- High risk
- Larger surgery in a patient aged >60 years without risk factors
- Larger surgery in patient aged 40-60 years with risk factor/s
- The highest risk
- Large surgery in a patient aged >40 years with history of VTE and/or recent malignancy
- Hypercoagulable states, polytrauma, heroic surgery

Indication of antithrombotic prevention according to the risk

- **Low risk** – bandage (other according to the circumstancies)
- **Intermediate risk**
  - (common & chest surgery, gynecological surgery)
  - LMWH, LD UH
- **High risk**

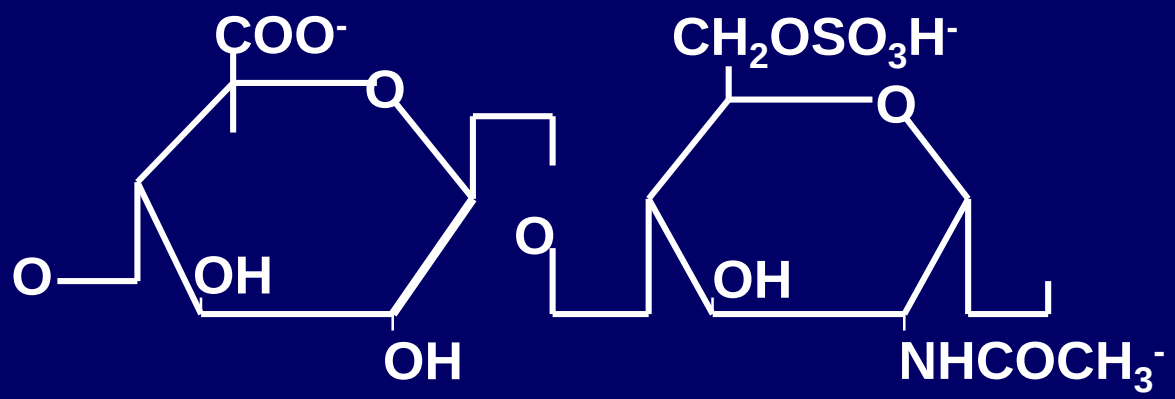
• Elective total hip replacement	LMWH, anti-IIa, anti-Xa
• Elective knee replacement	LMWH, amti-Iia, anti-Xa
• Hip fracture	LMWH
• Polytrauma	LMWH
• Acute posttraumatic paralysis	LMWH

Occurence of postoperative VTE depending on time interval after high risk surgery



GLYCOSAMINOGLYCAN

HEPARIN



GLUCURONIC ACID
IDURONIC ACID

N-ACETYL-D-GLUCOSAMINE-
6-O-SULPHATE

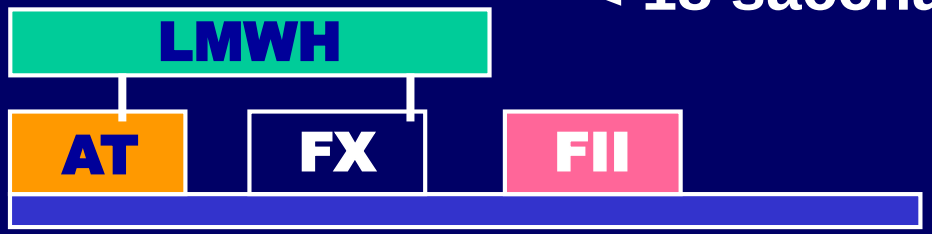
Heparin function

- **Antithrombin-mediated:**
  - reversible binding to AT
  - potentiates binding of AT to FIIa a FXa (inactivation):
    - heparin binding to FXa is not necessary
    - heparin binding to FIIa is necessary

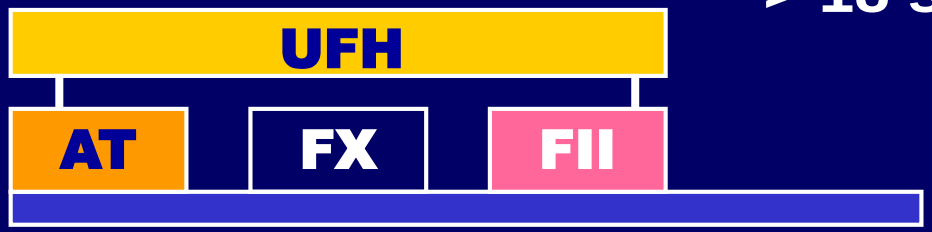
- **Releases TFPI into circulation** (tissue factor pathway inhibitor)
- **Stimulates t-PA release**
- **Binds also to cellular surfaces:**
  - Platelets : DF 4
  - Endothelium
  - Leukocytes

Mechanisms of effect of UH a LMWH

< 18 saccharide units



> 18 saccharide units



Dosing and monitoring of heparin treatment

VTE treatment:

- **bolus 80 U/kg**
- **18 U/kg/hour continual IV infusion**
- **↑aPTT:**
  - **prolonged aPTT 1.5-2.5 R (2-3x)**
  - anti-IIa: 0.2-0.4 U/ml
  - anti-Xa: 0.35-0.7 U/ml
- **↑ TT, normal reptilase time**

VTE prophylaxis:

- **5000 U 2-3 times/day SC**

Heparin treatment monitoring

ACT (Activated Clotting Time)

- Activation of coagulation by contact surfaces, e.g. kaolin
- Whole blood: „bed side“ test
- Thoracic surgery in extracorporeal circulation
- Normal range: 120 - 180 s
- Therapeutic range: 300 - 600 s

Low Molecular Weight Heparins

Generic name	Trade name	anti-Xa / anti-IIa
Nadroparin	**Fraxiparine**	3.0
Dalteparin	**Fragmin**	2.0
Enoxaparin	**Clexane**	3.3
Bemiparin	**Zibor**	8.0
Parnaparin		4.0
Tinzaparin		1.8
Certoparin		4.2

Monitoring and dosing of LMWH treatment

VTE therapy:

- **100 U anti-Xa/kg twice daily SC**
  - **except for Zibor (115 U anti-Xa/kg once daily SC)**
- **routine monitoring not required**
- **anti-Xa** (blood collected 3-4 hours after SC application):
  - **0.5 – 1.0 U/ml**
  - **anti-Xa monitoring:**
    - **renal insufficiency**
    - **body weight > 100 kg or < 50 kg**
    - **pregnancy**
    - **high risk of bleeding**
- only borderline prolonged aPTT at therapeutic dosing

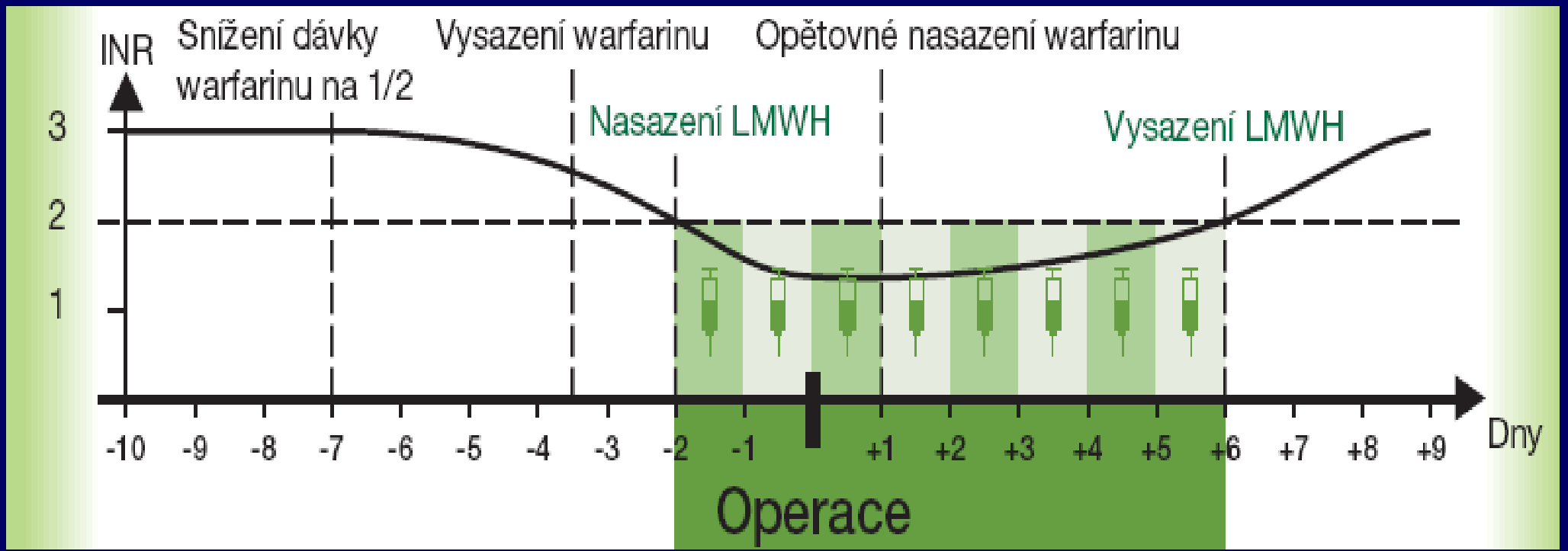
Monitoring and dosing of LMWH prophylaxis

VTE prophylaxis:

- **2000 – 5000 U anti-Xa SC once daily**
- **routine monitoring not required**
- **anti-Xa** (blood draw 3-4 hours after SC application):
  0.2 – 0.4 U/ml
- **specific dosing for each LMWH**

→DOSING ACCORDING TO SmPC!

LMWH as a „bridging“ therapy



Indirect FXa inhibitors

- **Pentasacharides (fondaparinux)** – prefered over UFH
- **Dosing 7,5 mg once daily SC**
  (5 mg in patients < 50 kg and 10 mg > 100 kg)
- **Contraindications:**
  - CKD with CrCl < 30 ml/min.
  - bacterial endocarditis

GlaxoSmithKline: Prescribing information, Arixtra (fondaparinux sodium) injection. Available at http://us.gsk.com/products/assets/us_arixtra.pdf (accessed October 26, 2012

Coumarins – warfarin

- Coumarins therapy usually follows after initial treatment with heparins – overlap required for at least 5 following days
- Dosing individual – 1.5–12.5 mg/day
- Specific laboratory monitoring: **INR 2.0–3.0**
- Significant drug and diet interactions
- Monitoring every 4 – 6 weeks

Schulman S, Parpia S, Stewart C, Rudd-Scott L, Julian JA, Levine M. Warfarin dose assessment every 4 weeks versus every 12 weeks in patients with stable international normalized ratios: a randomized trial, Ann Intern Med 2011;155:653-9, W201-3

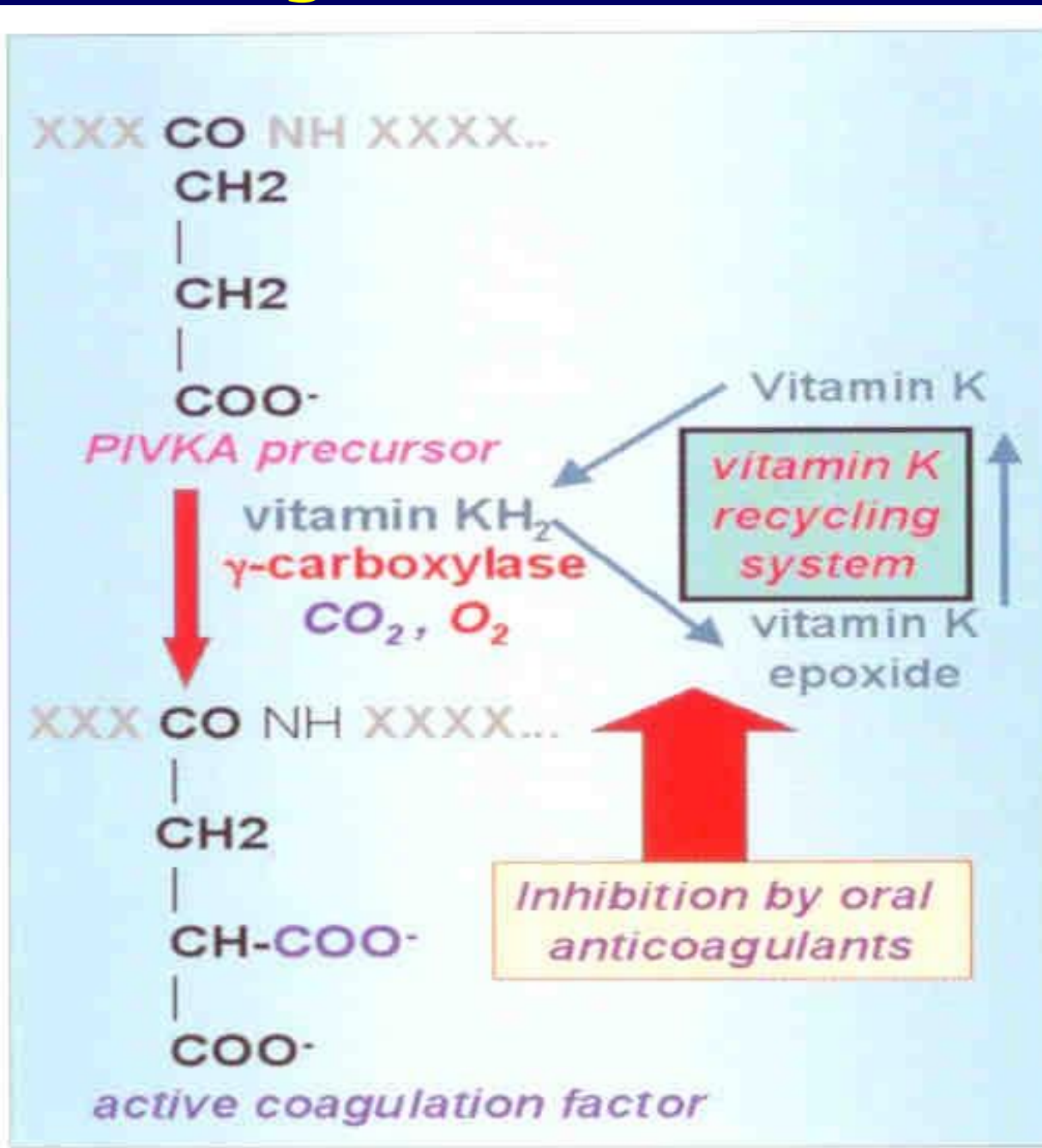
Schwarz UI, Ritchie MD, Bradford Y, et al: Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med 2008;358(10):999-1008

Vitamin K dependent coagulation factors

- FII, FVII, FIX, FX

- glutamic acid carboxylation
- necessary for phospholipids binding through Ca bridges

- coagulation factors are produced but they are not coagulation active - PIVKA forms (Protein Induced by Vitamin K Absence / Antagonist)



Coumarins

generics	*half-life*
ethylbiscumacetate (*Pelentan*)	2 hours
warfarin (*Warfarin*)	72 hours
phenprocoumon (*Marcoumar*)	160 hours

Coumarin therapy monitoring

Prothrombin time (PT):

- ***therapeutic range:***

  2.0 – 3.0 INR (international normalized ratio)

- ***„normal range“ :***

  0.8 – 1.2 INR

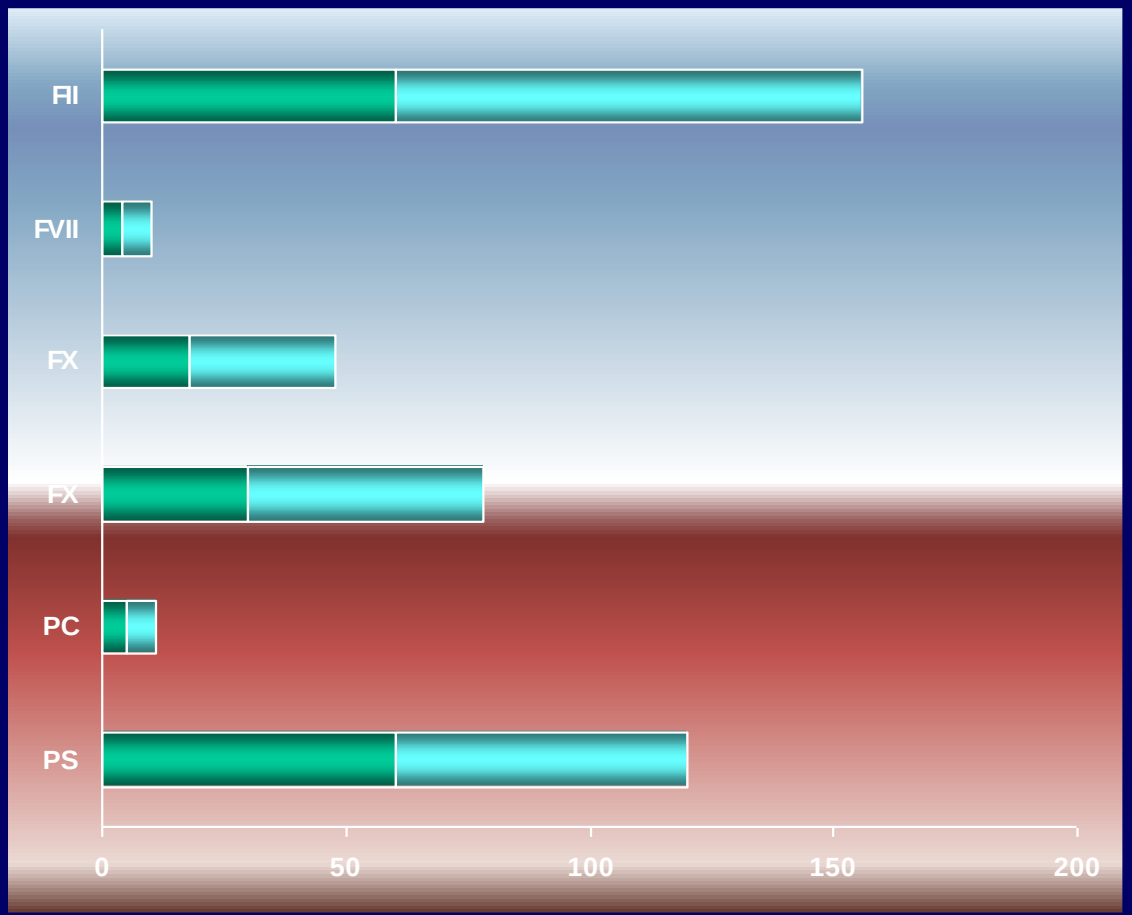
$$\left| \frac{t_{pac.}}{t_{norm.}} \right|^{ISI}$$ **(international sensitivity index)**

Bleeding on warfarin

Trial	*N*	*INR*	*risk %*
Hull (82)	96	3.0-4.05	22.4
		2.0-2.5	4.3
Turpie (88)	210	2.5-4.0	13.9
		2.0-2.5	5.9
Saour (90)	247	7.4-10.8	42.4
		1.9-3.6	21.3
Altmann (91)	99	3.0-4.5	24.0
		2.0-2.9	6.0

Halftime of factors influenced by coumarines (hours)

- **FII** 60 - 96
- FVII 4 - 6
- FIX 18 - 30
- **FX** 30 - 48
- PC 5 - 6
- PS 60

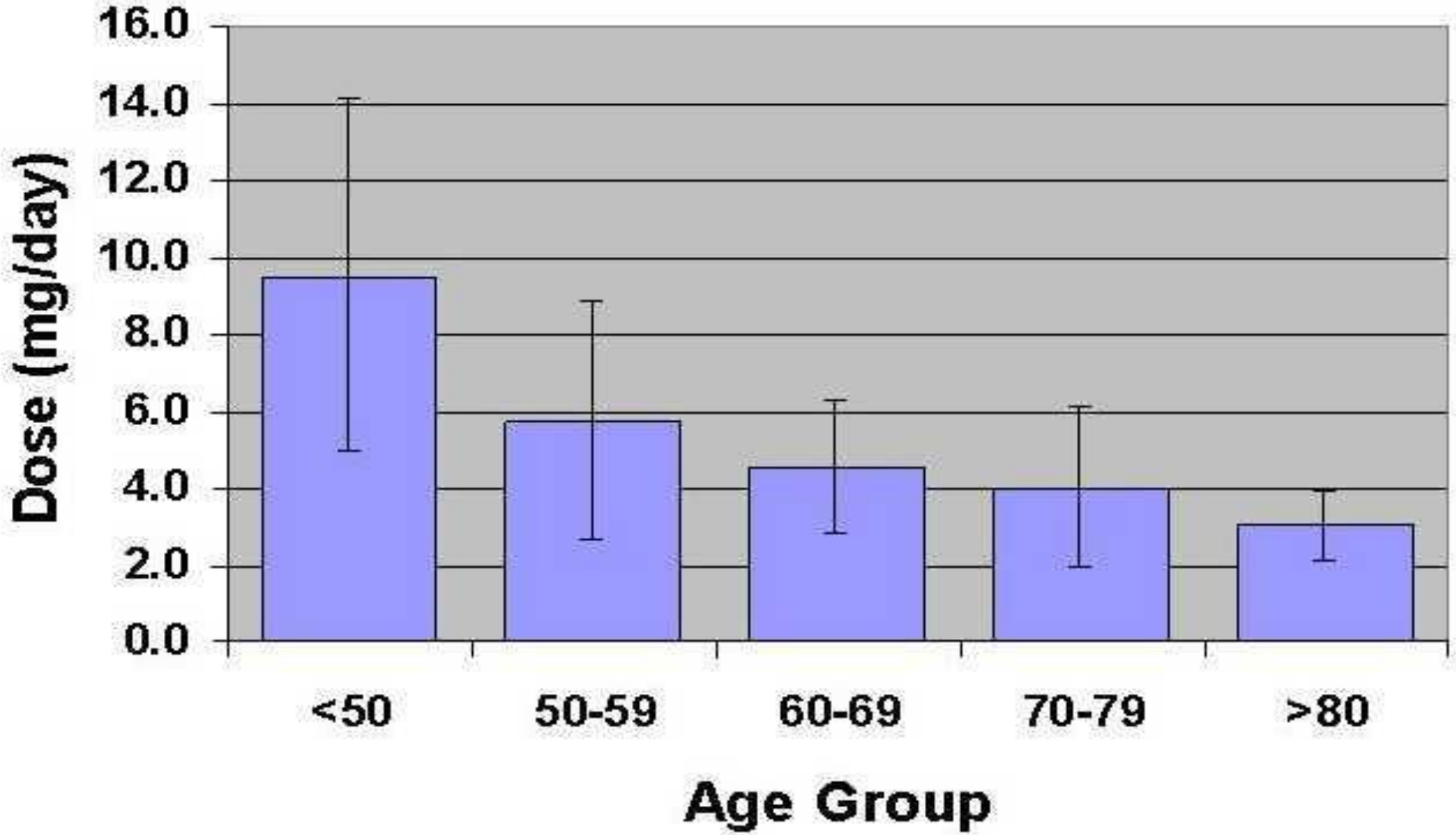


Warfarin dosing

- **Warfarin 5 mg daily (7,5 mg on Day 1)**
- PT monitoring from Day 3
- overlap with LMWH for min. 4-5 days, not only until PT 2-3 INR:
  - from Day 2 decreasing FVII, PC
  - from Day 3 decreasing FII, FIX, FX, PS
  - risk: **rethrombosis,** coumarin necrosis
- multiple drug interactions!!!
- influence of vit. K from diet (grean leaves, herbal tea…)
- diferences in metabolism:
  - doses from 1.5 mg daily up to over 15 mg daily

Warfarin Dose Requirements

- **100 Sunnybrook Anticoagulation Clinic Patients**



DVT treatment duration

depends on risk of recurrence, which is higher in the following circumstances:

- Male
- Elderly
- Higher BMI
- Neurological impairment (limb paresis)
- Malignancy
- Antiphospholipide syndrome
- IndiopaticVTE
- Positive family history
- Trombophilia (inhibitors defficiency, trombophilic gene mutations)
- Persistent D-dimer elevation
- Permanent inferior vena cava filter

DVT provoked by a transient risk – 3 months, otherwise „long-term“ treatment

Duration of coumarin therapy

- Distal or provoked thrombosis – *3 months*
- Proximal thrombosis – *6 months*
- Complicated thrombosis (PE) – *6–12 months*
- Hypercoagulable state:
  - severe (ATIII, homozyg. FVL, double heterozyg. FVL a PT)
    - *long lasting (life long)*
  - FVL, PT20210A polymorphism
    - *after the first episode of VTE standard duration of therapy*
- Critical situation management – *transient targeted*

Higher sensitivity to warfarin

Propeptid FIX mutation

Ala (GCC) -10Thr(ACC) - *Chu et al., 1996*

Ala (GCC) -10Val (GTC) - *Oldeburg et al., 1997*

Cytochrome P450 polymorphism

cytochrom P450(2C9), P450(3A4)

cytochrom P450(1A2), P450(3A4)

VKORC1 mutation

Interactions of coumarines with drugs & food

- Potentiation of warfarin effect (NSA)
- Lowering of warfarin effect (barbiturates, broccoli)
- Influence on absorption (antacides)
- Influence on vit K production (antibiotics)
- Potentiation of bleeding risk (ASA)

- (Extreme) wide range of daily dose:
  - 5 – 7.5 mg usually
  - 1.5 mg / low – 15 mg / high metabolizer

Quantity of vit K in selected foodstuffs (ug/100g)

- Broccoli 270
- Celery 300
- Cabbage 817
- Dill 400
- Cauliflower 300
- Chives 380
- Parsley 700
- Spinach 500
- Kale 1540
- Olive oil 400
- Soya oil 542
- Sunflower oil 10
- Green tea 712
- Chicken meat 300

Complications of warfarin therapy

- **Bleeding** (overdose, mutation of propeptide of FIX, polymorphisms of cytochrome P450)

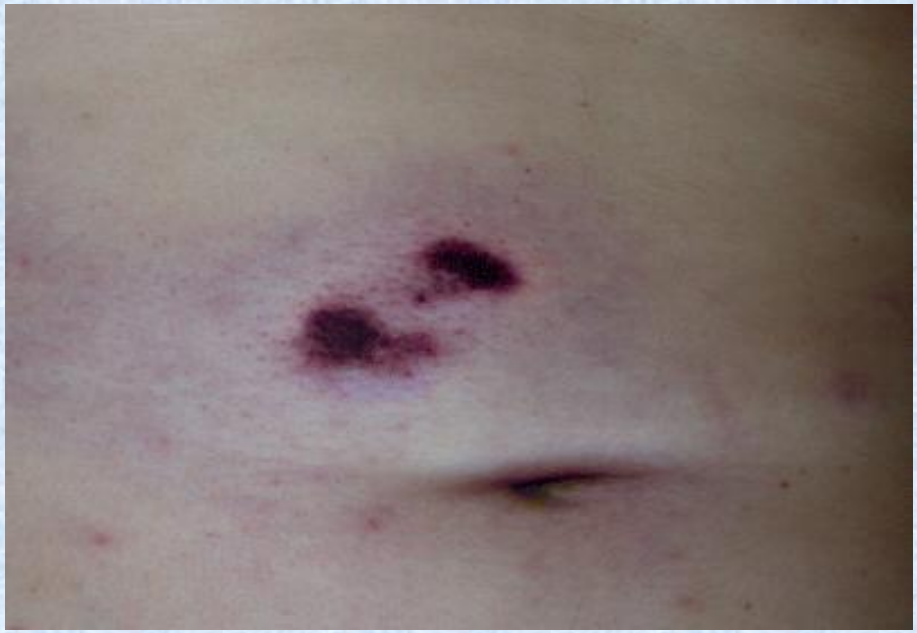
  Bleeding up to 7%, fatal 0.5%

- **Coumarine skin necrosis**

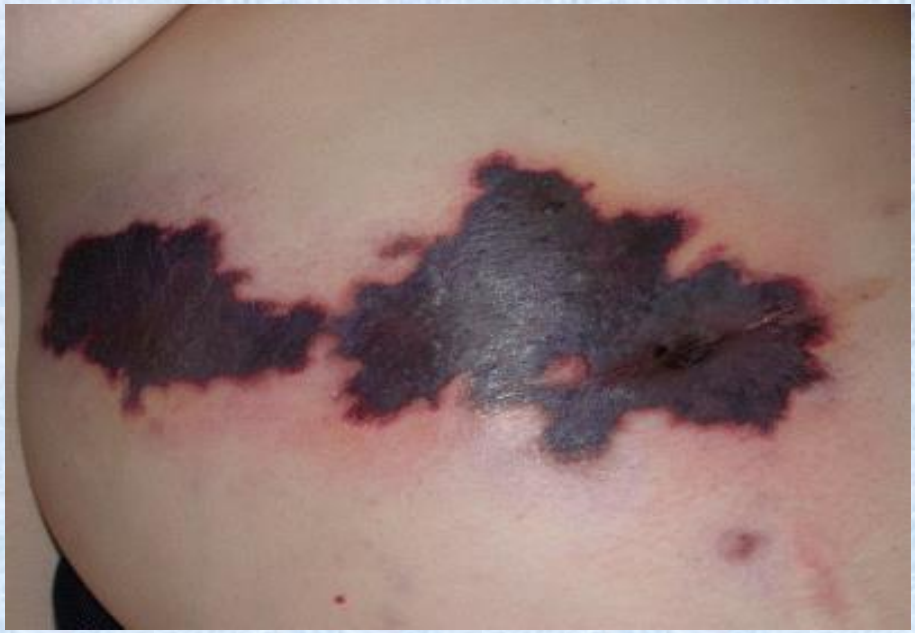
- **Failure of therapy** (resistance, neoplasma)

- **Teratogenic effect** (mainly from 6th to 12th week of pregnancy)

Skin necrosis



- **heparin induced**



- **coumarine induced**

**Bichler A.J. et al: Hypersensitivity reactions to anticoagulant drugs: diagnosis and managment option. Allergy 2006: 61: 1432-1440*

Which values of INR are acceptable?

Clinical situation	**target INR**
Minor bleeding & high risk of VTE	2-2.1
Major bleeding & intermediate risk of VTE	1.5
Life threating bleeding & low risk of VTE	1.0

Schulman S, NEJM 2003

Possibilities of INR correction

- Lowering or ommiting of warfarin dose
- Application of prothrombin complex factors (FFP, PCC, APCC)
- Administration of K vitamine

Recommended management of coumarin overdose

- **INR 3.0 - 5.0** dose reduction/delay until INR < 3.0
- **INR 5.0 - 9.0** dose delay until INR < 3.0
  - High risk of bleeding: oral vitamin K 1-5 mg (drops)
- **INR > 9.0** dose delay and oral vitamin K 2-5 mg
  - High risk of bleeding: oral or IV vitamin K 5-10 mg
- **major bleeding or emergency surgery:**
  - prothrombin complex concentrate (PCC) 25-50 U/kg
    - full effect lasts only 6 hours (halftime of FVII)
  - IV vitamin K 5-10 mg (allways to be applicated together with substitution – PCC)

Heparin induced thrombocytopenia - HIT

Etiology:

- complex heparin-PF4 + antibody stimulates platelet Fc receptor
  - Induce platelets aggregation
  - Venous and arterial thrombosis in ~ 50% patients with HIT
- day 4 - 10 after onset of heparin treatment
- decline of platelet count more than 50%

Scoring system of HIT diagnosis:4 T´s

Lo et al: JTH 2006; 4: 759-765

	2 points	1 point	0 points
Thr-penia; plt count	> 50% nadir >20 x10^9/l	30–50% nadir 10–19 x10^9/l	< 30% nadir < 10 x10^9/l
Timing	5–10D; ≤1D (H 30D before)	5–10D ? plt; >14D; ≤1D (H 30 – 100D)	≤4D
Thrombosis	New, skin necrosis	progression, recurrence, non-necrotic skin lesion	none
Thr-penia; other reason	none	possible	yes

- > 3 points ⇒ laboratory examination, discontinuation of UFH or LMWH
- 4-5 point - moderate, 6-8 points – high suspicion of HIT

HIT: diagnosis

- **Clinical + laboratory**:
  - Decline of plt count (thrombosis, skin necrosis)
  - HIPA:
    - Aggregation of healthy platelets + patient‘ s PPP + heparin
    - Low (50%) sensitivity, almost 100% specificity
  - ELISA:
    - complex heparin - PF4 antibodies
    - High sensitivity, low specificity
  - Release of 14*C-serotonine
    - the highest sensitivity and specificity

HIT: treatment

- Cross-reactivity between UFH and LMWH:

- argatroban – IIa inhibitor (1C)
- bivalirudin – IIa inhibitor (2C)

- danaparoid – heparinoid with predominant FXa inhibition (1B)

- Fondaparinux (Arixtra®) - oligosacharid with FXa inhibition (2C)

- Warfarin after normalization of plt count> 150

- If no thrombosis – **prophylactic dosage for 30 days**

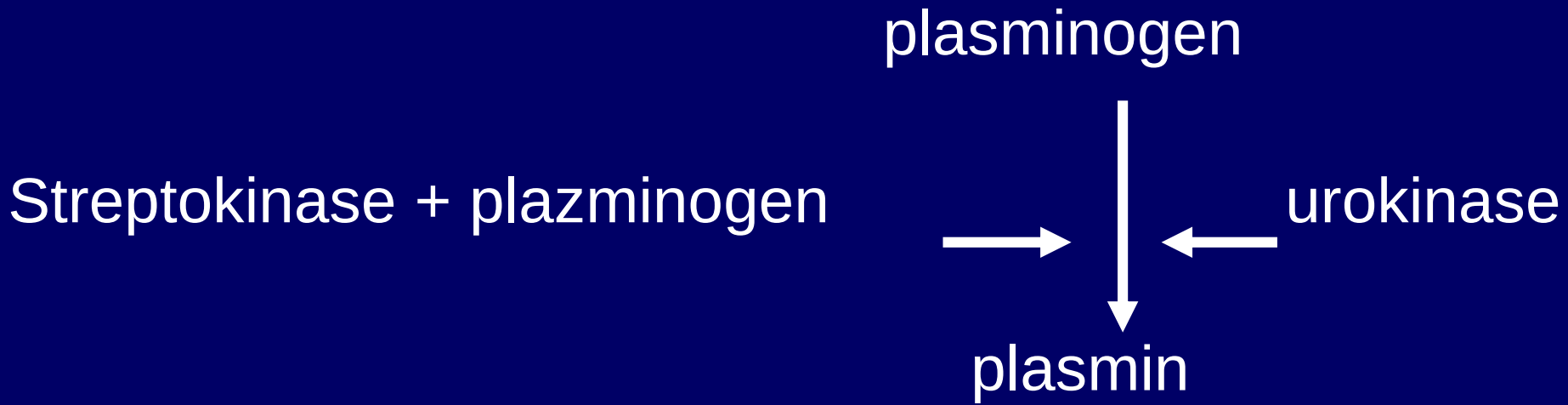
HIT – platelets‘ count according to the risk

- **< 0,1%:**
  - < 4 days
  - internal and gyneacological indication:
    - LMWH for > 4 days
- **0,1 – 1%:**
  - Internal a gyneacological:
    - UFH > 4 days
  - after surgery:
    - * LMWH > 4 days
- **> 1%:**
  - After surgery:
    - UFH > 4 days

Platelets‘ count assay á 2-3 days treatment day 4-14

Thrombolytic therapy

- streptokinase (*Streptase, Kabikinase, Awelyzin*)
- urokinase (*Ukidan)*, prourokináza (scu-PA)



  - **monitoring: TT 30-90 s**
- **r-tPA (*Actilyse*)**
  - binds to fibrin and activates plasminogen
  - rtPA 100 mg via 2-hour i.v. infusion
  - no monitoring (fibrinogen)

Substitution therapy with coagulation inhibitors

(direct measurment of functional activity)

Antithrombin (Antithrombin III)

1 unit increases AT level by 1 - 1.5 %

- hereditary defficiency:
  - perioperative prophylaxis, in pregnancy LMWH/UFH prophylaxis
  - VTE treatment together with LMWH/UFH
- acquired defficiency with AT levels < 50 %
  - sepsis
  - VTE

Protein C (Ceprotin, Xigris)

- inherited homozygous defficiency with purpura fulminans
- or severe acquired defficiency – meningococcal sepsis

Direct thrombin inhibitors (not AT III-mediated)

- hirudin
- recombinant - lepirudin *(Refludan)*
- synthetic - argatroban – *(Novastan)*
  - **dabigatran – oral *(Pradaxa)***

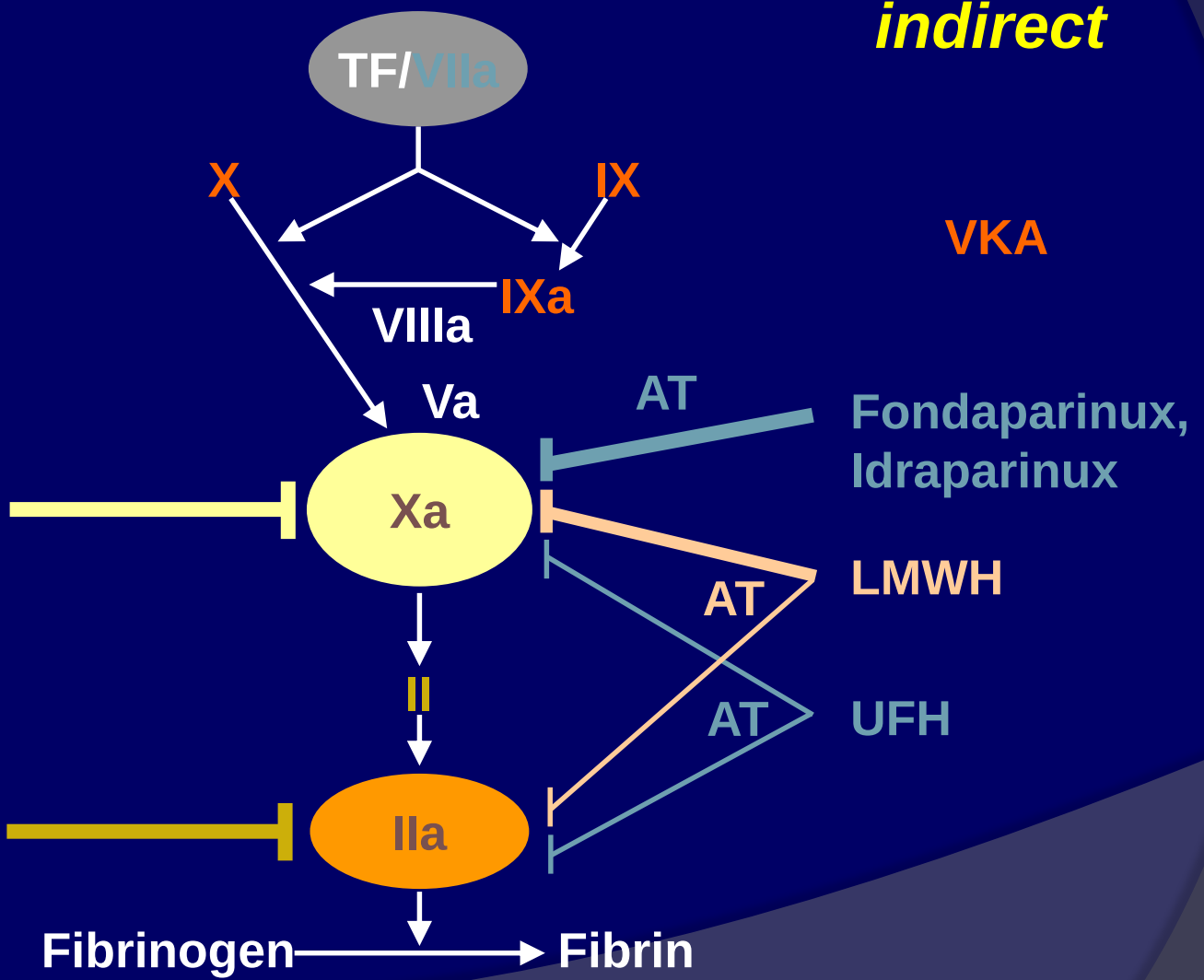
monitoring:

- **Hemoclot**
- **aPTT**
- **Ecarin clotting time (ECT):** ecarin cleaves FII to FIIa indepently from Ca and phospholipids

Factor Xa inhibitors

- **indirect**
  - **antithrombin-mediated**
  - **synthetic pentasacharides**
  - **fondaparinux** (***Arixtra***)
  - **idraparinux** – prolonged action (once per week SC)
- **direct (xabans)**
  - **NOT antithrombin-mediated**
  - **rivaroxaban** (***Xarelto***)
  - **apixaban** (***Eliquis***)
  - edoxaban (***Lixiana, Savaysa***)
- **monitoring: anti-Xa**

Targets for antithrombotic drugs



Weitze et al, 2005; Weitz et al, 2008

Direct inhibitors of factor IIa and Xa

	PT (INR)	aPTT	fibrinogen	TT	monitoring
dabigatran PRADAXA®	⇧	⇧ ⇧	could be influenced	⇧⇧⇧	Anti-IIa (μg/l)
rivaroxaban XALERTO® apixaban ELIQUIS®	⇧⇧	⇧	not influenced	not influenced	Anti-Xa (μg/l)

***** plasma half-life:
- **dabigatran** 12-17 h
- **rivaroxaban** 5-11 h
- **apixaban** 8-15 h

***** renal elimination:
- 80%
- 1/3
- ¼

* daily dose
- 220 – 300 mg
- 10 - 30 mg
- 5 - 10 mg

Novel Oral Anticoagulants (NOAC)

	Pradaxa (dabigatran etexilate)	Xarelto (rivaroxaban)	Eliquis (apixaban)
Mechanism of action	Thrombin inhibitor	FXa inhibitor	Inhibitor Xa
Doses	2x150 mg (red. 110)	prev. 10, th 20 mg	2 x 2,5/5 mg
Bioavailability	6,5%	80-100%	aprox. 50%
Prodrug	Yes	No	No
t1/2	12–14 hours	9–13 hours	aprox. 12 hours
Tmax	0,5–2 hours	2–4 hours	3–4 hours
Possible interactions	Strong P-gp inhibitors	Strong CYP3A4/P-gp inhibitors	Strong CYP3A4/P-gp inhibitors
Plasmatic proteins binding	34-35%	92–95%	87%
Elimination	80% renal	33% renal	27% renal

Bauer KA. J Thromb Haemost 2011; 9 Suppl 1:12-9; SPC Pradaxa 02/2012; SPC Xarelto ; SPC Apixaban

Monitoring of NOAC: usually not necessary

- **Pradaxa:** roughly aPTT, TT, plasma level - test „Pradaxa anti-IIa“:

	2x150 mg daily	220 mg 1x daily	
– Peak:	175 (117-275) μg/l	71 (35-162) μg/l	(percentil 25-75)
– Nadir:	91 (61-143) μg/l	22 (13-36) μg/l	(percentil 25-75)

- **Xarelto:** really roughly PT, plasma level of anti-Xa:

	20 mg 1x daily	10 mg 1x daily
– Peak:	215 (22-535) μg/l	125 (91-195) μg/l
– Nadir:	32 (6-239) μg/l	9 (1-38) μg/l

- **Eliquis:** really roughly PT, plasma level of anti-Xa:

	2x5 mg daily	2x2.5 mg daily
– Peak:	128 μg/l (CV 10%)	62 μg/l (CV 37%)
– Nadir	50 μg/l (CV 20%)	21 μg/l (CV 17%)

Bleeding in patients treated by direct IIa / Xa inhibitors

- to stop therapy – $t_{1/2}$: 5-17 h
- specific antidotes – now only for dabigatran, single dose of Prax-bind
  - Anti-direct Xa inhibitor: only in studies
- drug elimination:
  - activated carbon
  - haemodialysis (not rivaroxaban – binding on plasma proteins)
  - haemoperfusion
  - plasmapheresis (fondaparinux, dabigatran)
- nespecific hemostyptic therapy:
  - aPCC (activated prothrombin complex concentrate)
    - Content: FII, FVIIa, FIX, FX
  - rFVIIa
  - antifibrinolytics

Antidotes for anticoagulant therapy

- **Heparin, LMWH:**
  - Protamine (1 mg / 100 U UFH)
    - Binds to heparins
    - Not sufficient neutralization after SC aplication of LMWH
- **Warfarin:**
  - vitamin K (2-5 mg)
  - prothrombin complex concentrates (PCC)
    - FII, VII, IX, X
  - FFP
- **Factor IIa and Xa inhibitors:**
  - specific antidotes ongoing clinical trials, only Prax-binde for use
  - PCC, rFVIIa
  - dialysis (only dabigatran)

Surgical interventions

- Embolectomy – massive PE, possibly documented by angiography
- 20% operative mortality (before1985 32 %)

Stein PD, Alnas M, Beemath A, Patel NR: Outcome of pulmonary embolectomy. Am J Cardiol 2007;99(3)

- vena cava filters

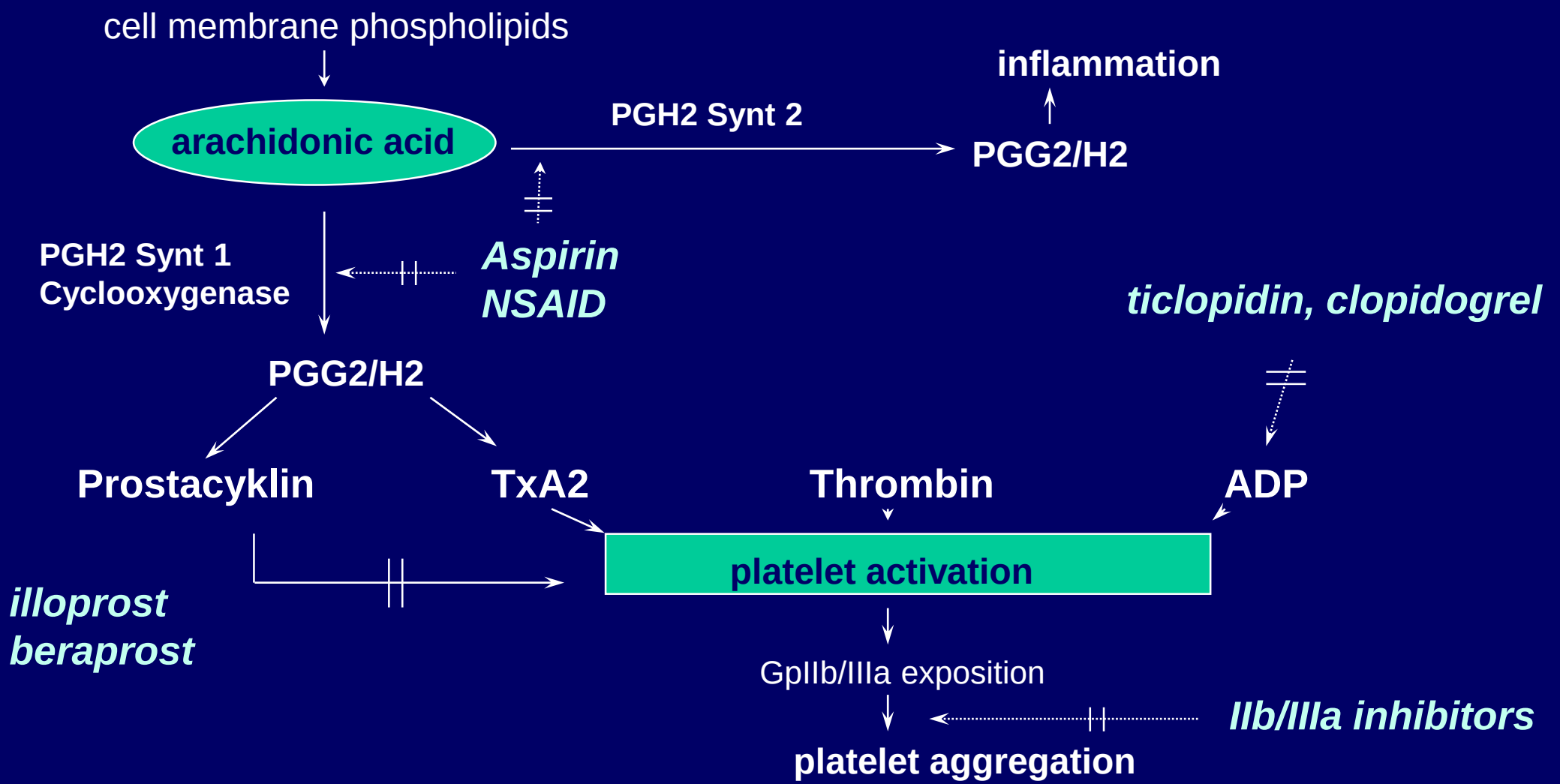
indicated when contraindication to anticoagulant therapy, complications of anticoagulant therapy, recurrent VTE despite adjusted anticoagulant therapy and prior to pulmonary embolectomy

AMERICAN COLLEGE OF CHEST PHYSICIANS

ACCP guidelines

- 9th edition (2012)

Platelet activation pathways



Acetylsalicylic acid

- Irreversible serin acetylation 529 AA in COX-1
- → decreased production of:
  - platelet activator thromboxane (TX)A2
  - its metabolite thromboxane TXB2 in serum
  - 11-dehydro-thromboxane B2 in urine
    - aprox. 30% is of non-platelet origin
- 150-fold less afinity to COX-2:
  - serin 516 acetylation
  - 10% of circulating platelets contain COX-2
    - possible origin of TXA2

COX-1 inhibition

~ acetylsalicylic acid (ASA):
  ~ Anopyrin, Godasal, Acylpyrin, Aspirin
  ~ 100 (200) mg daily
  ~ effective during the whole life span of platelets
  ~ must be stopped 5-10 days before surgery

~ other non-steroidal anti-inflammatory drugs (NSAIDs):
  • indobufen (*Ibustrin*)
    - 200 mg twice daily
    - reversible effect 12-24 hours
    - no evidence for clinical benefit

Thienopyridines

- **Irreversible block of ADP receptors P2Y12:**
  - **disulphide bonds formation between the drug and receptor cysteine**
  - **acts in megacaryopoiesis phase – must be stopped 5-10 days before surgery**
- **Prodrug:**
  - **the active form is produced by liver cytochrome P450**
    - **Affected also by other drugs**
    - **CYP2C19*1, slower metabolism with alleles *2, *3**
    - **CYP3A4**
    - **CYP1A2**
    - **CYP3A5:**
- **Inhibition:**
  - **CYP2B6**
- **Higher variability in effect on platelets than ASA**

Thienopyridines

~ **Ticlopidin (ApoTic) - agranulocytosis**

  ~ 250 mg twice daily

~ **Clopidogrel (Plavix, Trombex) : oral**

  ~ **75 mg daily**

~ **Prasugrel (Efient) : oral**

Direct drugs, not prodrugs, effect less variable:

~ **Ticagrelor (Brilique):** oral

~ Cangrelor: i.v.

~ Elinogrel: oral or i.v.

PAR antagonists – voraxapar, atopaxar

Antiaggregation therapy monitoring- ASA

Clinical:

- relapse of MI, stroke, chronic limb ischemia

Laboratory – definition (?) of efficacy-resistence:

- **ADP-induced platelet aggregation** 10 μmol/l in PRP:
  - ***max. aggregation < 70%***
- **ARA-induced platelet aggregation** 0,5 mg/ml in PRP:
  - ***max. aggregation < 20%***
- **Cathionic propyl gallate aggregation** in PRP:
  - decreased slope of aggregation curve < aprox. 50%/min.
  - time to 50% of maximum aggregation > aprox. 100 sec.
- **PFA-100:**
  - prolonged closure time with Col/Epi above upper limit of normal
  - ↓ metabolite: **thromboxane-β2** in serum (11-dehydro in urine)

Antiaggregation therapy monitoring- clopidogrel

ADP-induced platelet aggregation 5 or 20 μmol/l in PRP:

- ***decrease by 10-30% of absolute value compared to the value before treatment***

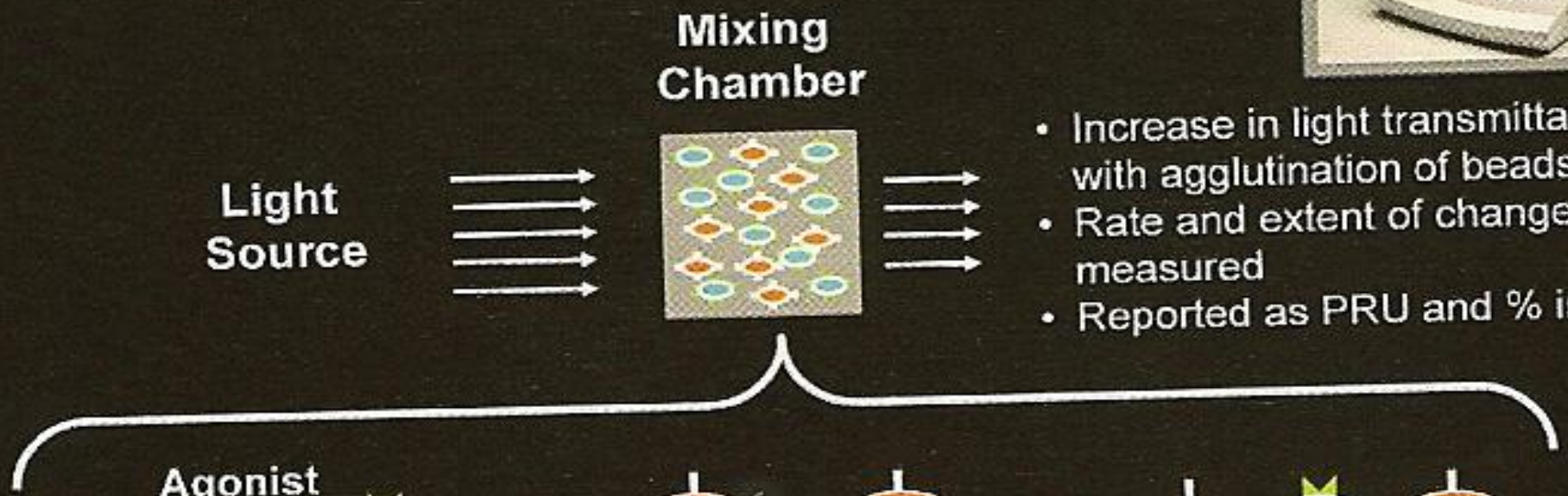
VASP-P:

- phosphorylation of vasodilator (PGE1) stimulated phosphoprotein
- stimulation of P2Y12 receptor blocks VASP phosphorylation
- evaluation of VASP phosphorylation after addition of ADP, following previous PGE1 stimulation
- if P2Y12 is blocked by clopidogrel, addition of ADP will not reduce VASP phosphorylation
- effective therapy – **phosphorylation after addtion of ADP will not be reduced** < ***50%***

Antiaggregation therapy monitoring - whole blood aggregation Multiplate®

- impedance aggregometry
- whole blood
- induction of aggregation
  - ARA (ASPI test) - monitoring: ASA
  - ADP clopidogrel
  - ADP+PGE1 clopidogrel
  - thrombin (TRAP test) IIb/IIIa inh.

VerifyNow POC Assay Mimics Optical Aggregometry



- Increase in light transmittance with agglutination of beads
- Rate and extent of change measured
- Reported as PRU and % inhibition

POC = point of care. PRU = platelet reaction unit.

Gp IIb/IIIA inhibitors monitoring

~ ***monoclonal antibodies, peptides and small molecules***

- **Platelet aggregation in whole blood – impedance method Multiplate®:**
  - TRAP test:< 30 U

- **VerifyNow Assay®:**
  - Platelet Aggregation Units (PAU)
  - abciximab (ReoPro®)
    - 0-44 PAU - > 80% inhibice
    - 0-13 PAU - > 95% inhibice
  - eptifibitide (Integrilin®)
    - 0-31 PAU - > 80% inhibice
    - 0-10 PAU - > 95% inhibice

Summary

- At the present time standard monitoring and dose adjustment of antiaggregation therapy is not recommended.

- Recommended only in clinical trials.