Haemostasis II

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LECTURES IN THIS SECTION

1. Trombophilias - Prof. Kvasnička

2. Haemostasis I - platelet dysfunctions
Prof. Kvasnička

3. Coagulopaties - MD Konířová

4. Haemostasis II - plasmatic coagulation MD Loužil

Etiology

- vessel wall
- platelets (thrombocytopenia, -pathy)
- clotting cascade –coagulation factors, fibrin formation

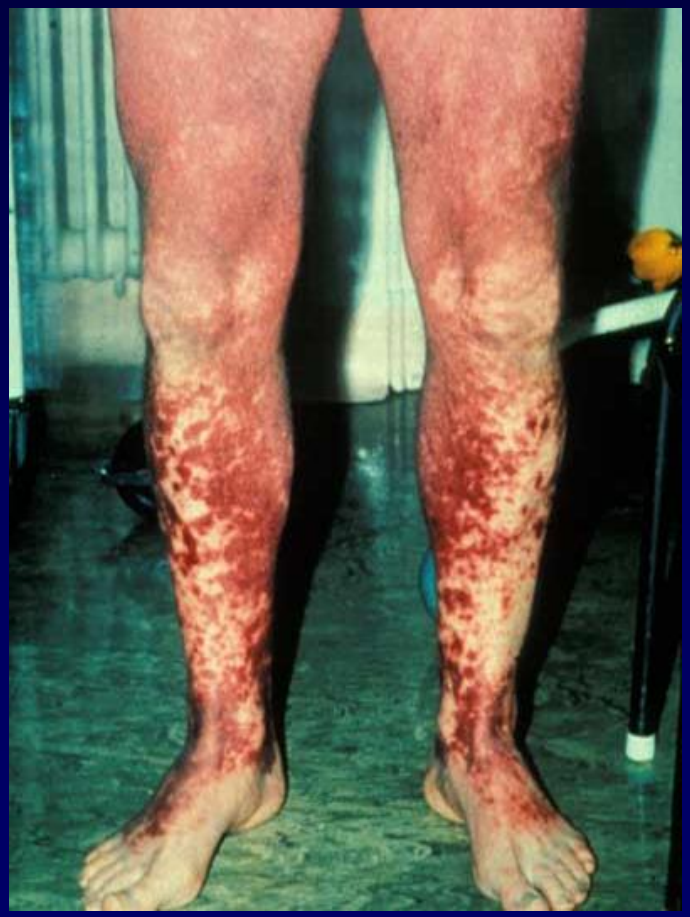
- Inherited versus aquired disorders

Investigation of patient with anamnesis of bleeding or patological results

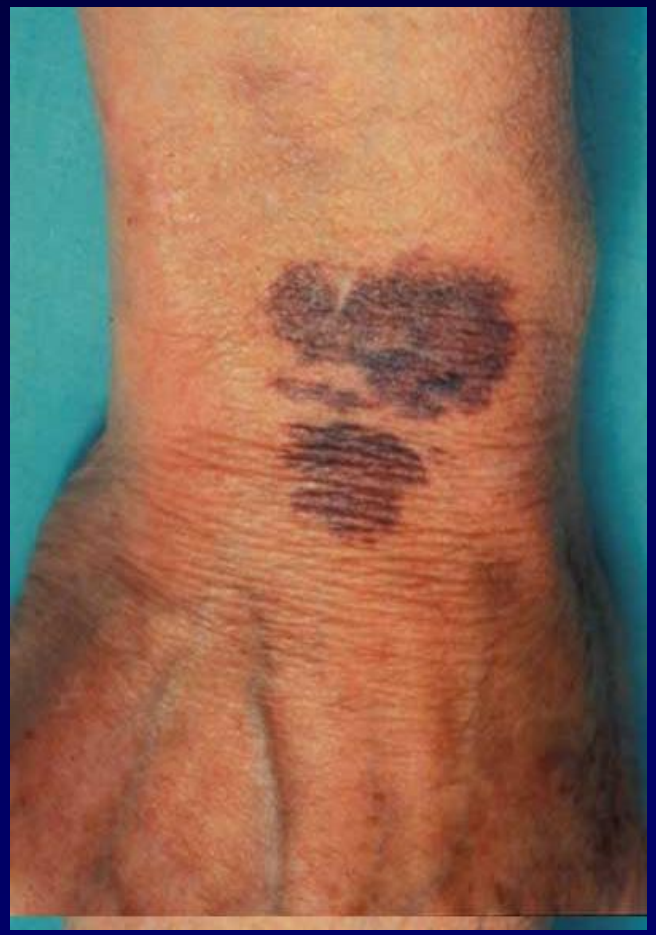
- Important personal history
  - Spontaneous bleedings
  - Bleedings after surgery, trauma, delivery, menstruation bleeding, tooth extraction
- Family history
- Physical investigation
  - Bleeding symptoms, hepato event. splenomegaly, lymph nodes

Physical investigation - skin

Henoch-Schönleinova purpura



Senile purpura



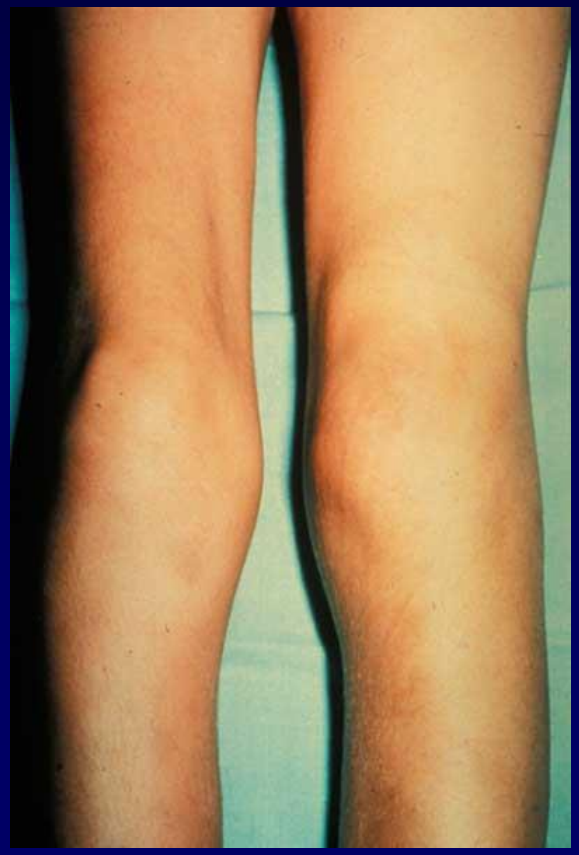
Physical investigation

- **Gynaecological bleeding**
- **GIT bleeding**
- **Oral cavity**
- **Haematuria**

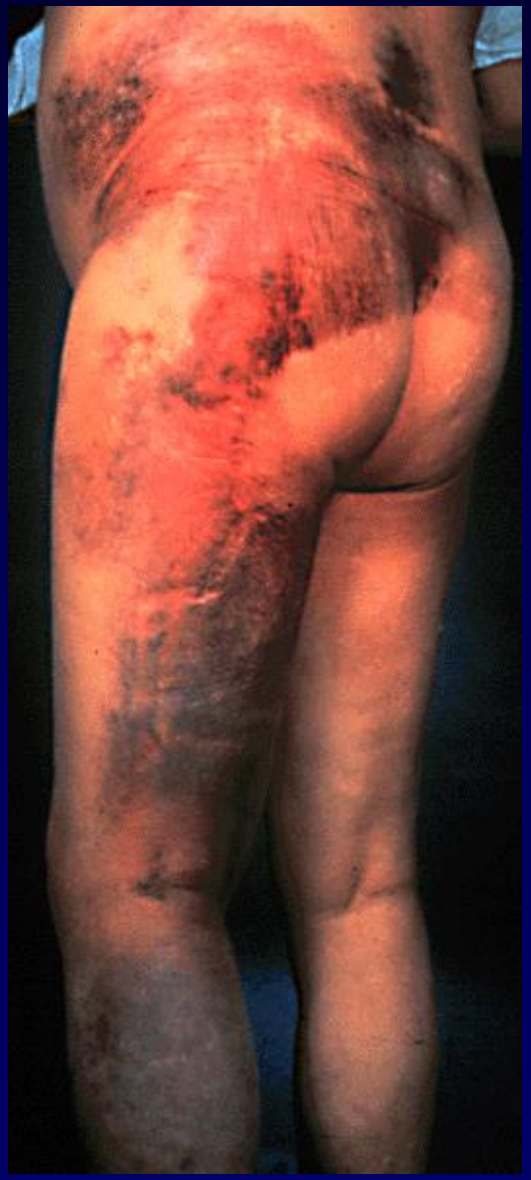
Epistaxis

Bleeding disorders with factor deficiency

Haemartros in haemophilia A

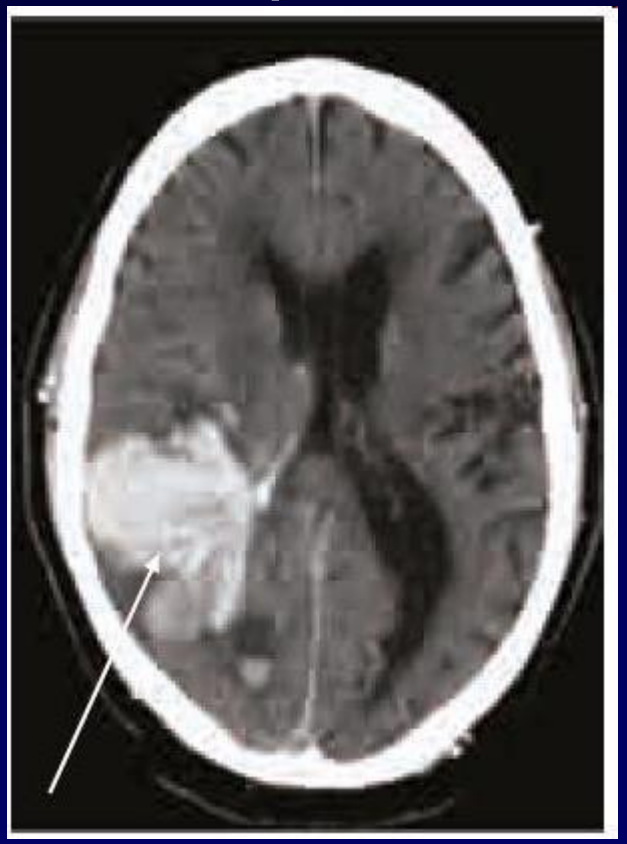


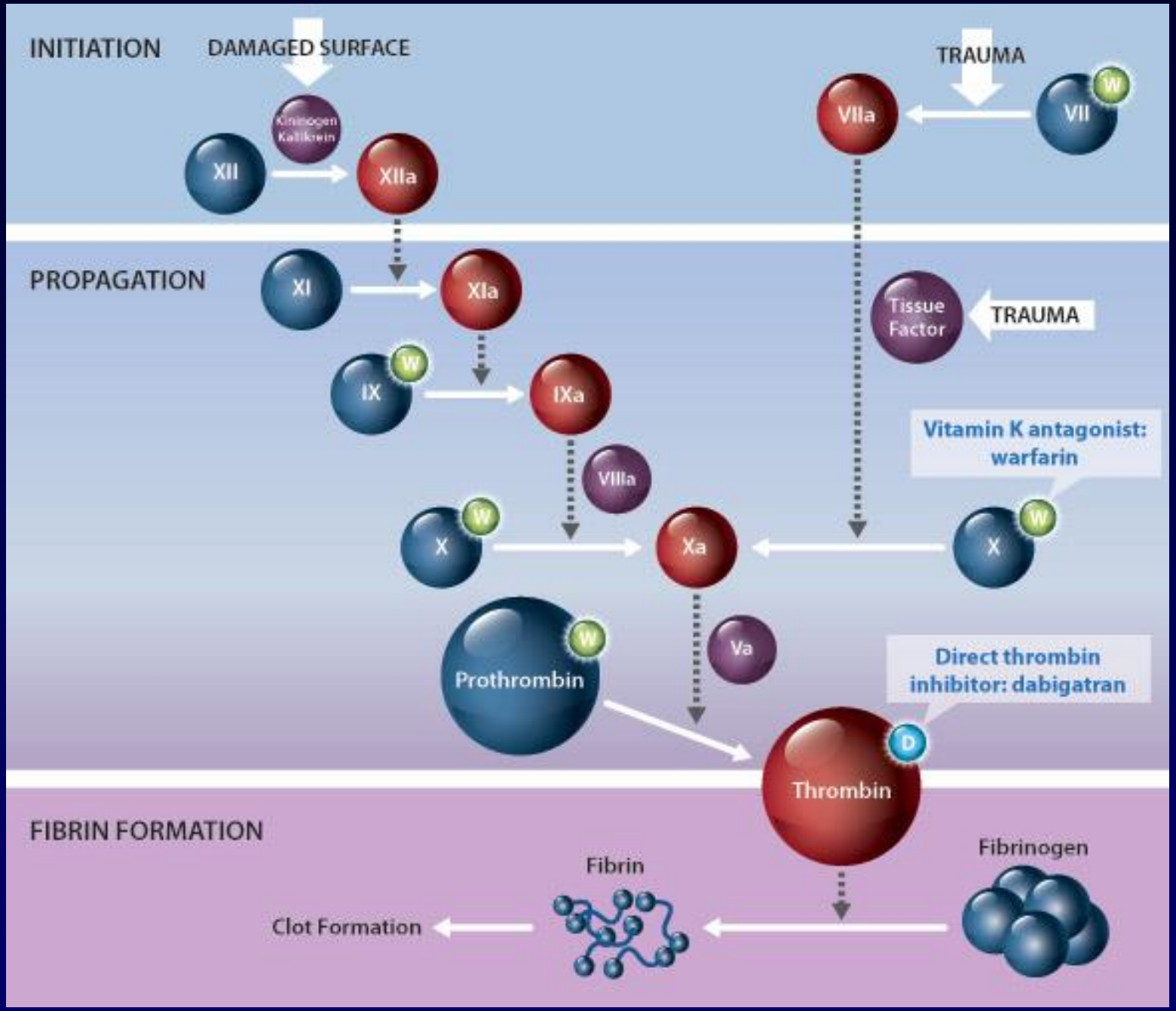
Ekchymosis – aquired inhibitor of F VIII



CNS bleeding

- Neurological symptoms
- severe haemophilia A or warfarin overdose




INITIATION
DAMAGED SURFACE
Kininogen
Kallikrein
XII
XIIa
TRAUMA
VIIa
VII
W
PROPAGATION
XI
XIa
Tissue Factor
TRAUMA
IX
W
IXa
Vitamin K antagonist: warfarin
VIIIa
X
W
Xa
X
W
Prothrombin
W
Va
Direct thrombin inhibitor: dabigatran
D
Thrombin
FIBRIN FORMATION
Fibrinogen
Fibrin
Clot Formation

Groups of coagulation factors:

(I, V, VIII, XIII)

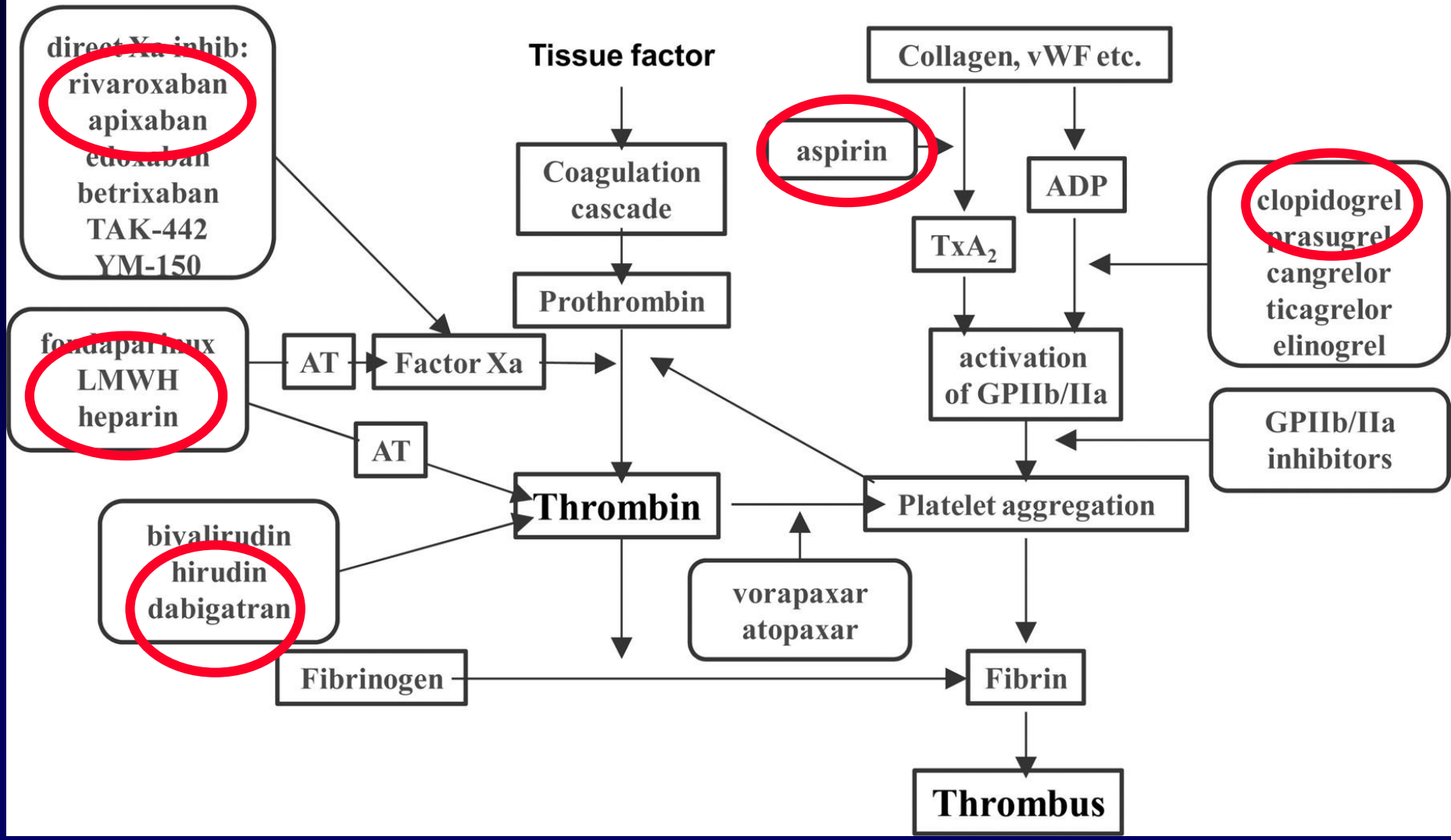
consumed in clotting process, increasing in imflamation, V and VIII increasing in pregnancy

(II, VII, IX, X)

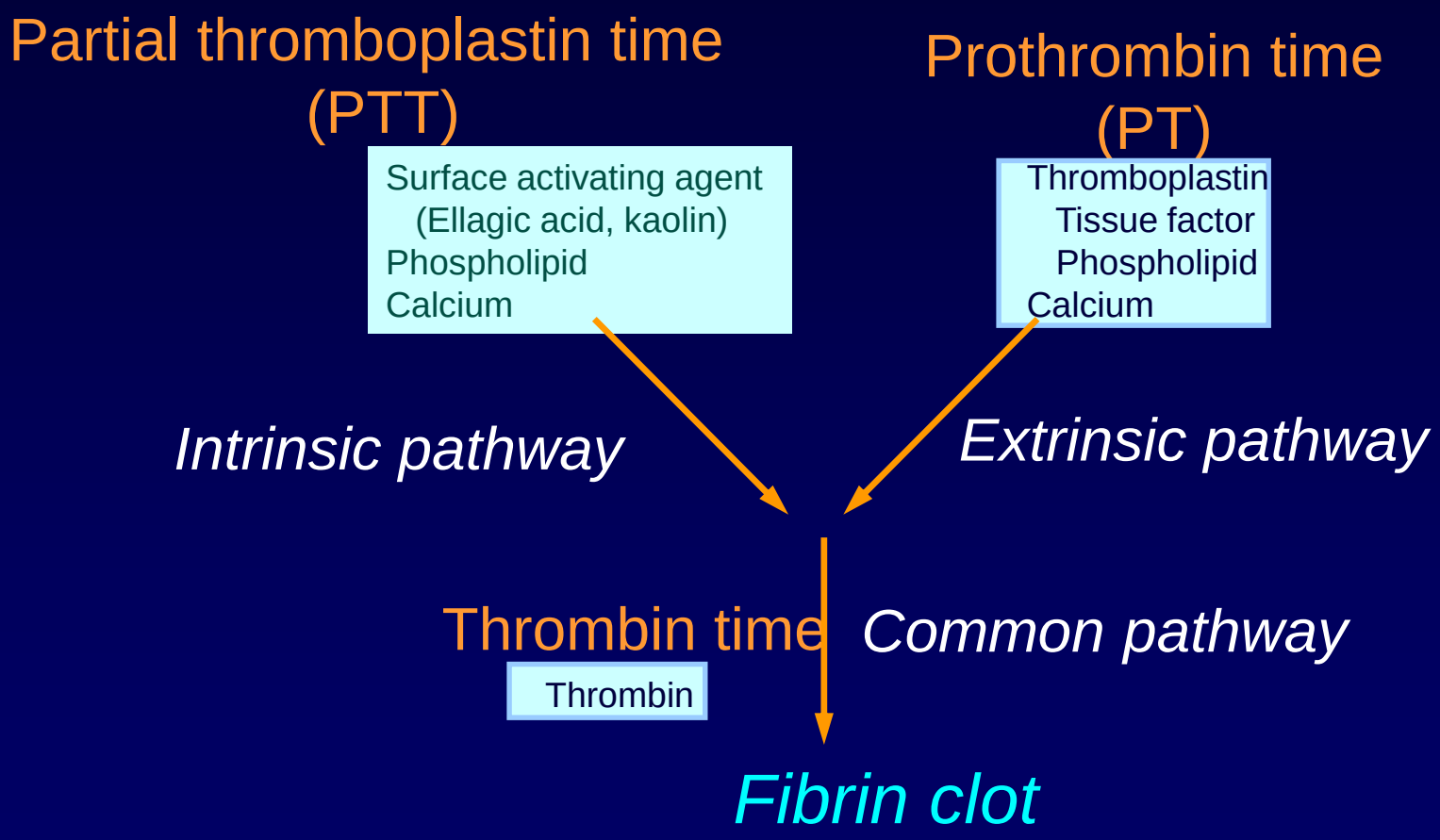
consumed in clotting process, dependent on vitamin K, inhibited with warfarin

contact phase (XI, XII, Prekallikrein-Fletchers, HMWK-Fitzgerald)
not consumed in clotting process

Targets of Antithrombotic Agents



Laboratory evaluation of coagulation process



Laboratory results

Thrombocytes	150-350 x 10^9/l
APTT	28-40 sec
PT (INR)	10-15 sec, 0.8-1.2
TT	<18 sec
Fbg	2-4g/l
FDP	negative
D-dimers	0-180
ATIII	70-140%
PFA 100 epinefrin	84-160s
PFA 100 ADP	68-121s
Consumption of prothrombin	>40s
Bleeding time	3-5 min
TEG	Bed side test

How many is needed

- Tooth extraction : simple ≥ $30x10^{9}/l$, complicated ≥ $50x10^{9}/l$
- Small surgery: ≥ $50x10^{9}/l$
- Big surgery: ≥ $70x10^{9}/l$
- Neurosurgery: ≥ $100x10^{9}/l$
- Spontaneous delivery: ≥ $50x10^{9}/l$
- C-section + epidural anestesia : ≥ $70x10^{9}/l$
- Needle biopsy: ≥ $50x10^{9}/l$
- Bronchoscopy, endoscopy: ≥ $50x10^{9}/l$
- CVC: ≥ $30x10^{9}/l$ – depends on skills and localization
- Patient can be released from hospital: ≥ $10\text{-}20x10^{9}/l$

Case

- Patient 38 y.
- Brain hemmorhage
- BC normal
- increased APTT – 162 s (normal 28-40s)
- PT, TT, Fbg, DD, ATIII normal
- factor VIII levels 0,6% (normal 80-160%)
- Mixing test - corection aphter adding normal plazma

Haemophilia A a B

Haemophilia A	Haemophilia B
Deficient factor	
Factor VIII	Factor IX
Inheritance	
X-bind recessive	X-bind recessive
Incidence	
1/10,000 men	1/50,000 men

Severity of desease — According to factor level

<1% - severe – spontaneous bleeding

1-5% - moderate – bleeding by small injuries

over 5% - mild – bleeding by surgeries or trauma

Haemophilia A

Clinical manifestation (hemophilia A & B inrecocnizable)

Haemarthrosis (most common)
- **mostly knees > elbows > ankles**

Bleeding in soft tissues (for example muscles, CAVE compartment sy– m. iliopsoas)
- **Muscular atrophy**
- **Shortened tendons**

Other sites of bleeding
- **Urinary tract**
- **CNS (may be life-threatening; start treatment befor the result of CT)**
- **Prolonged bleeding after surgery or dental extractions**

Haemophilia A a B

- Most serious complication of treatment – ibhibitor against FVIII – more common against FVIII (medical but also economical problem) – the only threatment rFVIIa or aPCC)
- - occures mainly in childhood, it can disappear spontaneously or with treatment - ITI (Bonn, Malmö protocol)
- - 10-15% patients, mainly with severe haemophilia A

- *Other complications* – HIV infection, Hepatitis B and C

- 1 IU FVIII/kg raises level - 2%
- 1 IU F IX/kg raises level - 1%

Substitution of F VIII and IX in patients with severe haemophilia

2 types of situations

1. **Spontaneous bleeding – mostly joints – dose dependent on the type od joint and its localisation**

Target doses and maintenance doses

100% target dose – CNS bleeding, retroperitoneum, retropharynx

Antifibrinolytics – epistaxis, tooth extraction, GIT bleeding

1. **Planned and acute surgeries**

Big surgery, ortopedic surgery – target dose 100%, maintenance dose 50%

Tooth extraction – target dose 80%, antifibrinolytics - continues 6-8 days after extraction

Treatment

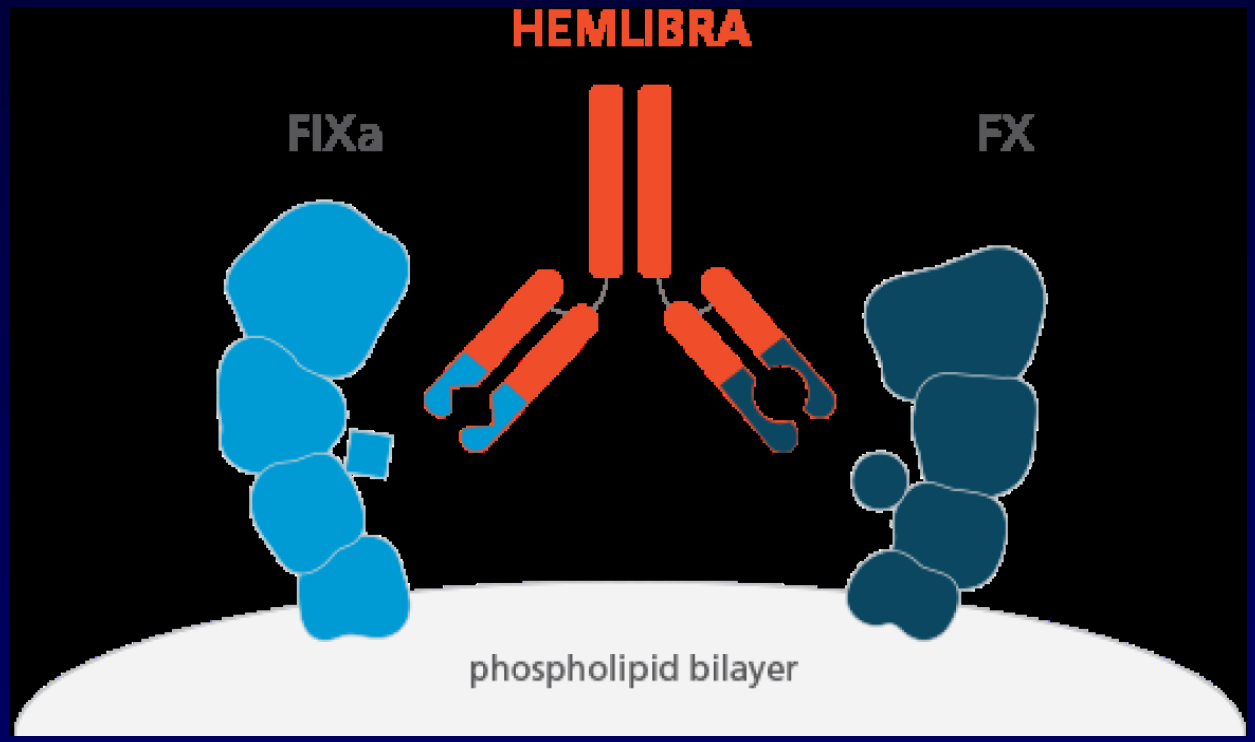
- plazmatic vs. recombinant factors (incidence of inhibitor similar)

- plazmatic preparates – from plasma donors – still small risk of transfering infection

- recombinant preparates – produced by rekombinant technology

- - extended halflife products (conection with albumin, Fc fragment, PEG)
- - new drugs – emicizumab (Hemlibra) (bivalent antibody binds aktivovated FIX and FX) – haemophilia A with inhibitor, haemofilie A without inhibitor, s.c., halflife 1 month
- - concizumab (anti TFPI), s.c., halflife 1-7 days, same indication as emicizumab, but also haemophilia B with inhibitor
- - gene therapy – individual cases – mainly haemophilia B

Emicizumab



von Willebrand disease

von Willebrand factor

- originated in endothelia and megakaryocytes, further multimers creation
- Carrier of f VIII
- Anchoring platelets to subendothelium
- Bridging between platelets

Inheritance - autosomal dominant (type 1,2)

- autosomal reccessive (type 3)

Incidence - 1/10,000

Bleeding character – skin, mucosa, very variable according to disease type

vWD Types

Type I – partial quantitative deficit of vWF

Type II- qualitative defect of vWF

2A impared activity of vWF interaction with platelets (missing high-molecular multimers)

2B enhanced afinity of vWF to platelets GPIIb

2M impared activity of vWF interaction with platelets (present high-molecular multimers)

2N impaired afinity of vWF to f VIII

Type III complete deficit of vWF

Laboratory results in different subtypes of vW disease

Test	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3
VWF:Ag	↓	N or ↓	N or ↓	N or ↓	N	0
VWF:RCo	↓	↓↓↓	↓ ou ↓↓	↓↓	N	0
Agglut high dose low dose	 N or ↓ 0	 ↓↓↓ 0	 N ++	 decreased 0	 N 0	 0 0
F VIII	N or ↓	N or ↓	N or ↓	N or ↓	↓↓	↓↓↓
Multimers	N	IMW & HMW absent	HMW absent	N or ↓	N	0
VWF:CB	↓	↓↓	↓↓	N or ↓	N	0

Treatment of vW disease

- DDAVP – demopresin, possible to give as intranasal sprey
- - vWD type 2B contrindication
- Substitution therapy: Plazmatic concentrates of vWF/FVIII
- - CAVE misdiagnosis of mild haemophilia A and vWD type Normandy (investigation of binding vWFtoFVIII)
- Antifibrinolytics
- Estogenes – in women – menstruation bleeding

Aquired inhibitor of FVIII (in persons without haemophilia)

- Incidence 1/1 000 000 people – 22% mortality
- Mostly persons more than 60 years old, but young patients also pissible (women after delivery)
- in 38% patients spontaneous remision
- 50% idiopathic
- Clinical symptoms: skin, mucosal and intramuscular bleeding, GIT, urogenital bleeding and CNS
- Dg: mixing tests without corection, low FVIII, specific inhibitor of F VIII
- Treatment: 1. underlying disorder, 2. therapy of bleeding (rFVII, pFVIII, aPCC) + antifibrinolytics, 3. combined imunosupression – mostly CS+cyclophosphamide; event. Replacement of CFA with CSA; IVIG; imunoadsorbtion
- rearly aquired inhibitor of vWF, possible other coagulation factors, very often secondary to other disease

Question 1
What is the most common cause of prolongation of APTT in asymtomatic patient?

1. Heamophilia A

2. Deficiency of F XII or LA

3. Aquired haemophilia

4. DIC

Laboratory results in TTP

Leuko 7x10e9/l

Hb 68g/l

Schisto 8 promile

Trombo 12x10e9/l

LDH 10,2 ukat/l

Bili 22,6 mmol/l

ADAMTS 13 aktivita <2%

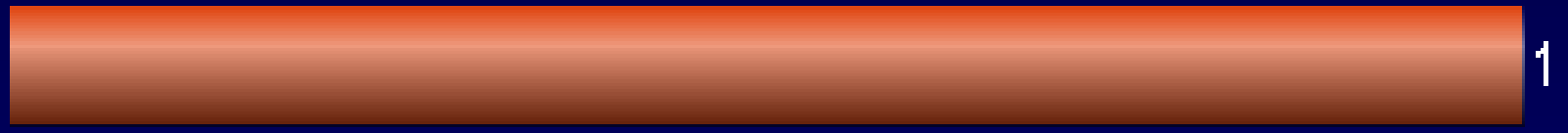
Amount of inhibitor 130,9 U/ml

Coagulation results in normal values

Question 2
What kind of disease has this laboratory results?

1. DIC

2. Aquired inhibitor



3. TTP

4. Wrong blood sample

Trombotic trombocytopenic purpura

Trombotic mikroangiopathy caused by deficiency of metaoproteinase vWF (ADAMTS 13) and occurence of high molecular weight multimers vWF, wich activates and agregates thrombocytes

Incidence 2-7/ 1 000 000 people

Much more common aquired form

Symptoms: pentade of symproms - thrombocytopenia, MAHA, neurological symtoms, fever, renal insuficiency– full expressed only in 40% patients, anemia a thrombocytopenia always

Important to begin treatment immediately - TPE (when not available FFP) + immunossupresion (cortikosteroids), when bad response or relaps – Mabthera (anti CD 20)

Question 3
What is stil the biggest comlication of heamophilia patients treatment?

1. HIV infection

2. Hepatitis B

3. Hepatitis C

4. Inhibitor

Question 4
What you wouldn‘t see in heamophilia patient?

1. Spontanneous bleeding in joints

2. Joint deformities mainly in older patients

3. Epistaxis and strong menstruation

4. Positivity of hepatitis C – PCR or antibodies, mainly in older patients

Rare deficiencies of other coagulation factors

1. Dysfibrinogenemia a hypofibrinogenemia
2. Congenital deficiency of FVII
3. Congenital deficiency of FXI – haemophilia C
4. Congenital deficiency of FXIII
5. Congenital combined deficiency of coagulation factors