

Secondary thrombophilic states and drug induced thrombophilia

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

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

- | Category | 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% |

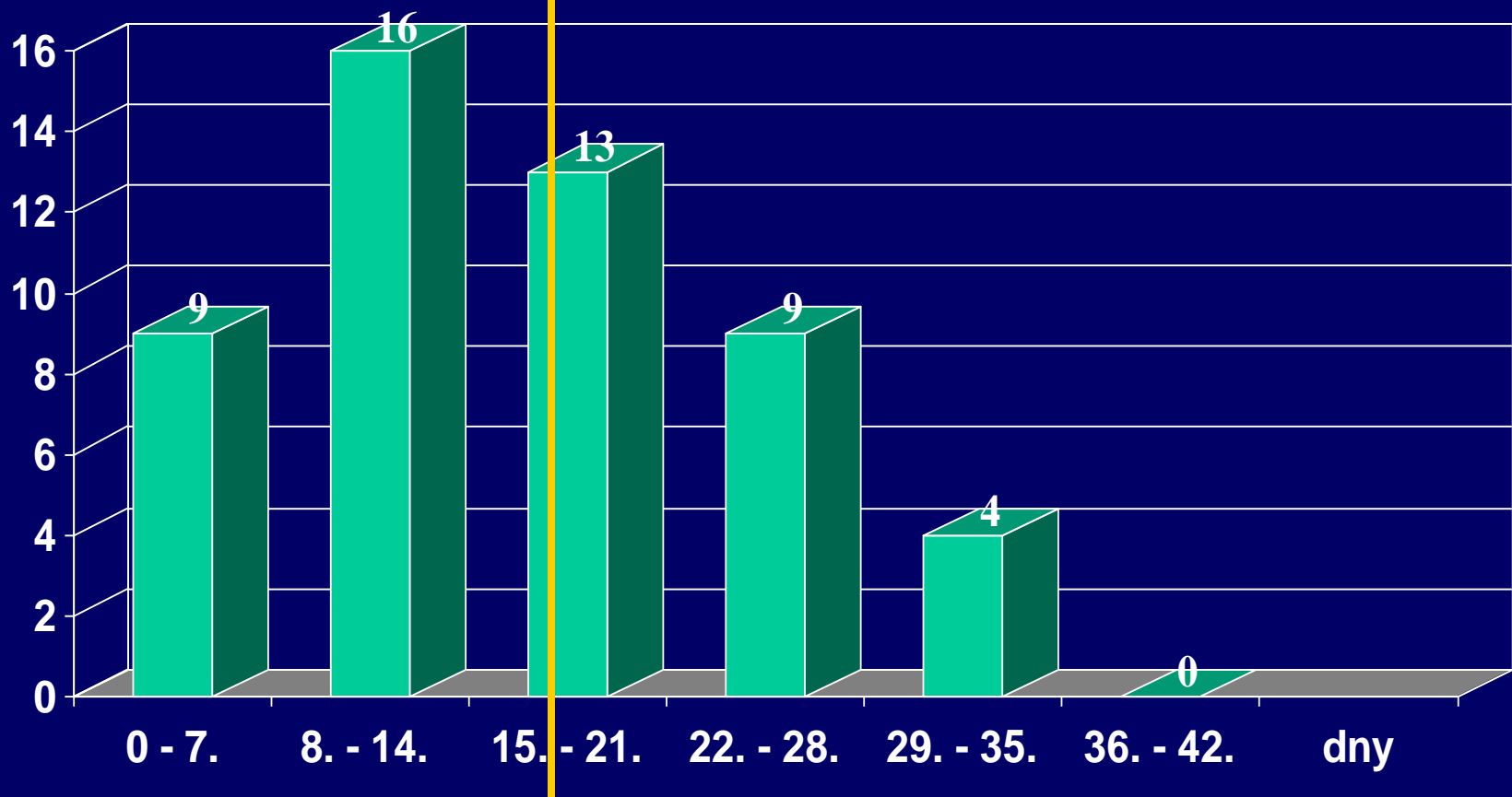
The classification of risk profile

- **Low risk**
 - Non-complicated surgery lasting <30 min in a patient aged < 40 years
- **Intermediate risk**
 - Surgery in a patient 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 circumstances)
- **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, anti-IIa, anti-Xa
 - Hip fracture LMWH
 - Polytrauma LMWH
 - Acute posttraumatic paralysis LMWH

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



Pregnancy:

↓ PS

↑ Fbg, FVII, FVIII, vWF

OC:

↑ Fbg, FVII, FVIII, vWF

↓ PS, AT III

Stress:

↑ Fbg, FVII, FVIII, vWF

↑ tPA

↓ α 2AP, PIg

Inflammation

- ↑ Fbg, FVII, FVIII, vWF
- ↑ α 1AT, PAI-1, tPA, α 2MG, Plg

Sepsis

- Damage of endothelium
- Activation of monocytes, granulocytes, expression of TF
- Activation of platelets
- DIC
 - ↓ fibrinogen, procoagulation factors and inhibitors of coagulation
 - ↓ platelets

Acq. thrombophilia

- Defect of inhibitors (AT, PC, PS, APCR)
- Elevation of FVIII, fibrinogen
- Elevation of PAI - 1
- Hyperhomocysteinemia

Antiphospholipid antibodies

- heterogenous auto-antibodies against proteins bound to negatively charged phospholipids on cell membranes

Antiphospholipid antibodies - mechanism

- inhibition:
 - release of prostacyclin from the endothelium
 - protein C activation
 - fibrinolysis activation by complex prekallikrein+FXII
- stimulation:
 - activation of platelets
 - activation of FX on platelet surface
- other effects outside haemostasis

Antiphospholipid syndrome clinical criteria

Thrombosis:

- venous or arterial
- proven only histologically
- but not superficial thrombophlebitis

Antiphospholipid syndrome clinical criteria

Pregnancy disorders:

- three or more subsequent spontaneous abortions before the 10th week of gestation (excluding other causes)
- one or more deaths of morphologically normal fetus (documented by sonography or direct examination) after week 10 of gestation
- one or more premature births (34 weeks and earlier) of a healthy newborn in severe pre-eclampsia or severe placental insufficiency

Antiphospholipid syndrome laboratory criteria

- anticardiolipin antibodies (ACLA):
 - IgG and/or IgM > 40 U/ml or > 99. percentil)
- anti- β -glycoprotein I antibodies:
- IgG and/or IgM > 99. percentil
- are present 12 weeks or more weeks apart
- it is examined by a standardized ELISA

Antiphospholipid syndrome laboratory criteria

Lupus anticoagulans:

- are present 12 weeks or more weeks apart
- evidence of prolongation of the screening test (aPTT, PT)
- there is no correction by norma plasma
- shortening after addition of excess of phospholipids

Antiphospholipid syndrome - diagnosis

- presence of at least one criterion:
 - laboratory
 - clinical
- the symptom has a maximum distance of 5 years from laboratory criteria

Types of APS and management

- **Type I (venous)** – LMWH, UFH, W
- **Type II (arterial)** – LMWH, LD UFH, ASA, W
- **Type III (CNS, retinal)** – LMWH, ASA, W,
- **Type IV (combination)** – LMWH, LD UFH, W
- **Type V (abortions)** – LMWH, ASA
- **Type VI (no clinical criteria)**
 - in pregnancy (ASA, LD W)
 - in situations at risk for thrombosis (LMWH, LD UFH)

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[®]) - oligosaccharid 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%:**

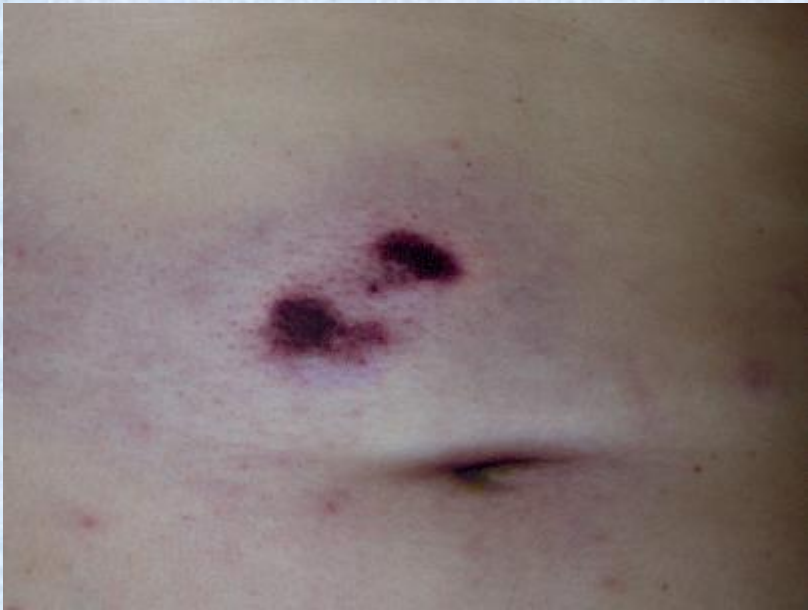
- Internal a gyneacological:
 - UFH > 4 days
- after surgery:
 - * LMWH > 4 days

- **> 1%:**

- After surgery:
 - UFH > 4 days

Platelets' count assay à
2-3 days
treatment day 4-14

Skin necrosis



- heparin induced



- coumarine induced

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

Drug induced thrombophilia - mechanisms

Endothelial Damage

Mechanical injury to endothelium

5-FU, contrast media

Apoptosis of endothelial cells

VEGF antagonists

Induction of hypersensitivity reaction

Drug-eluting stents

Proteolysis of endothelial cell contact

Tissue plasminogen activator

Expression of pro-inflammatory mediators

Cis-platinum

Expression of tissue factor

Rapamycin

Decreased expression of anticoagulation mediators

COX-2 inhibitors

Expression of pro-coagulation mediators

Thalidomide, sildenafil

Platelets

Increased platelet adhesion

Tissue plasminogen activator

Aggregation of platelets

Erythropoietin, nanoparticles

Increased platelet reactivity

Ciclosporin

Autoantibodies against platelet factors

Heparin

Red Blood Cells

Phosphatidylserine exposure

Phenylhydrazine

White Blood Cells

Increased adhesion molecules

All-trans retinoic acid, interferon- α

Coagulation System

Increased coagulation factors

Hormone replacement therapy

Antiphospholipid antibodies

IVIG

Decreased anticoagulation factors

L-asparaginase, sildenafil

Decreased fibrinolysis

Corticosteroids, erythropoietin

Blood Flow

Vasoconstriction

SSRIs, ephedra

Blood stasis

IVIG, erythropoietin