Antiagregating agents and anticoagulants
Causes of arterial thrombosis

a) Unstable atherosclerotic plaque (crucial factor for arterial thrombosis)

b) Endothelial dysfunction (more frequent - women middle age)

c) Generalised hypercoagulation

• For arterial thrombosis is decisive activation of thrombocyte homeostasis
Pathophysiology of acute coronary syndromes

Soft plaque → plaque disruption → occlusive thrombus

perfusion decrease → ischemia → necrosis
Venous thrombosis

a) Blood velocity decreased
   • (coagulation factors activation)

b) endothelial dysfunction

c) generalized hypercoagulation

• For venous thrombosis is decisive secondary homeostasis activation
Antiplatelet therapy
TROMBOCYTE

normal

activation
ADHESION - stabilization phase
binding through fibronectin, collagen, laminin and vWF

subendothelial space

-**Fn**
-**Col**
-**Lam**
-**vWF**

- $\alpha_5\beta_1$
- $\alpha_2\beta_1$
- $\alpha_6\beta_1$

GPIb-V-IX

trombocyte
THROMBOCYTE ADHESION
ANTIPLATELET AGENTS

1) ADHESION BLOCKADE
   - GP Ib/IIa, vWF antagonists (clinical trials)

2) ACTIVATION BLOCKADE
   - inhibition - TXA$_2$., ADP, serotonine., thrombin activation
     (inhib. COX, TXA$_2$ recept., ticlopidin, clopidogrel)

3) PLATELET STABILISATION (↑cyclic nukleotides)
   - cAMP (dipiridamol) or cGMP (NO donors)

4) ANTI-AGGREGATION (GP lib/IIla inhibition)
   - peptides (abciximab, eptifibatid),
   - fibans 1st. generation (tirofiban), 2. generation
Thromboxane activation inhibitors

a) Cyclooxygenase inhibition (COX₁):
   - irreversible inhibition: ASA
   - reversible inhibition: indobufen, NSA, sulfinpyrazone

b) Tromboxane syntase inhibition:
   dazoxibene, ozagrel

c) TXA₂ receptor antagonists: ridogrel, nidrogrrel
ACETYLSALICYLIC ACID
(ASPIRIN, ASA)

• irreversible acetylation COX$_1$ (up to 7 days)
• pharmacoeconomy highly effective
• optimal dose 100 - 350 mg (75-2000 mg)
• 10 - 20% population ASA resistant

**indication:** acute coronary ischemia (IM, unstable angina)
secondary prevention (after IM, stroke, TIA, peripheral occlusion, arterial intervention)
primary prevention – high risk patients
hypertension a diabetes
ASA mechanism of action

Phospholipase - PLA2

arachidonic acid

ASA
indobufen

COX-1

PGG2/PGH2

COX-2

COX-2 inhib.

trombocyte
endothel

activated
endothel

TXA2

PGE2

PGF2a

PGI2
ASA - CV MORTALITY AND MORBIDITY (IM, STROKE) (ANTIPLATELET TRIALIST COLLABORATION)

ANTIPLATELET AGAINST CONTROL

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>EVENTS</th>
<th>COHORT</th>
<th>RRR ± SD</th>
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<tbody>
<tr>
<td>3 primary prev.</td>
<td>1176</td>
<td>27210</td>
<td>12 ± 6 %</td>
</tr>
<tr>
<td>20 cerebral</td>
<td>1916</td>
<td>9530</td>
<td>24 ± 5 %</td>
</tr>
<tr>
<td>11 MI</td>
<td>2270</td>
<td>15529</td>
<td>24 ± 4 %</td>
</tr>
<tr>
<td>11 AMI</td>
<td>2783</td>
<td>18126</td>
<td>26 ± 4 %</td>
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<tr>
<td>12 AP</td>
<td>398</td>
<td>3450</td>
<td>39 ± 9 %</td>
</tr>
<tr>
<td>20 CABG/PTCA</td>
<td>245</td>
<td>3057</td>
<td>33 ± 13 %</td>
</tr>
<tr>
<td>28 peripheral</td>
<td>444</td>
<td>3864</td>
<td>25 ± 10 %</td>
</tr>
<tr>
<td>51 DVT</td>
<td>67</td>
<td>4771</td>
<td>42 ± 19 %</td>
</tr>
<tr>
<td>30 others</td>
<td>283</td>
<td>3948</td>
<td>44 ± 10 %</td>
</tr>
<tr>
<td>189 total</td>
<td>9789</td>
<td>90297</td>
<td>25 ± 2 %</td>
</tr>
</tbody>
</table>

Br Med J 1994
RESISTANCE TO ASA

- antiaggregation effect decreased
- multifactorial etiology
- higher incidence of thrombotic events
- 5% non-responders
- 20% semi-responders
Competitive COX-1 inhibitors

indobufen, sulfinpyrazon,...

• Comparable effect to ASA not proven
• Not recommended for therapy
Thienopyridinines

- Ticlopidin (1. generation)
- Clopidogrel (2. generation)
- Prasugrel (3. generation)
ADP activation inhibitors (thienopyridines)

- Irreversible block ADP activation
- More effective than ASA,
- Potenciación of ASA

Ticlopidine – slow onset, agranulocytoses.

Clopidogrel – faster onset, leukopenia rare
   potenciación of fibrinolysis

- Indikations: acute coronary sy, sec. prevention., PTCA
- Very high price in comparison with ASA
TICLOPIDIDINE

• thienopyrididine derivative, slow onset, full effect after 8-11 days
• Inhibition of ADP platelet activation (induced by collagen, adrenaline)
• irreversible effect for thrombocyte life span (effect disappears after 10-14 days)
• dose 2x250 mg
• In most countries not used
TICLOPIDIDINE

**Indication:** allergy or bad tolerance ASA
CV events during ASA treatment
PTCA, PTA (4 weeks)

**Adverse events:**

- GIT dyscomforth (with meal)
- Neutropenia 0,5-1,0%
  (check blood count WBC!)
CLOPIDOGREL

• irreversible blockade platelet activation (and aggregation) mediated by ADP
• faster onset
• safer (rare neutropenia)
• dosage: 75 mg daily, first dose 300 mg, effect after 4-6 h., steady state after 3-7 d
CLOPIDOGREL

Effect - potentiation by ASA

indications:

• acute coronary syndrome (up to 6-12 m after attack),
• coronary interventions (PTCA + stent, prim. PTCA)
• secondary prevention of atherosclerosis (not very effective)

• PTCA – Percutaneous Transluminal Coronary Angioplasty
CV mortality (MI/stroke) changes after treatment with clopidogrel

N: 12 562
ASA - clopidogrel combination - potentiation

PRASUGREL
thienopyridin

- irreversible block P2Y12 receptors
- Pro-drug metabolic activation
- resistance rare
- oral, onset of activity during 30 min
- faster onset
PRASUGREL
thienopyridin

indications:

• acute coronary syndrome
• coronary interventions (PTCA + stent, prim. PTCA)
• secondary prevention of atherosclerosis
• (not very effective)
Clopidogrel against prasugrel in mortality (12 months) -

CV+, IM, stroke

Clopidogrel: 12.1%
Prasugrel: 9.9%

Bleeding

Clopidogrel: 1.8%
Prasugrel: 2.4%

NNT = 46
NNH = 167

↓ o 19%
TICAGRELOR

- non-thienopyridine - P2Y$_{12}$ receptor block
- reversible receptor inhibition
- peroral, quick onset (1-2 h)
- safer, but short acting
- very promising for subacute treatment
Comparison of ADP receptor inhibitors acute CV events

- CURRENT klopigogrel 75 vs 150 mg: 15%*
- TRITON prasugrel: 19%*
- PLATO ticagrelor: 16%*
Mechanism of action
GP IIb/IIIa antagonists
GP IIb/IIIa antagonists

- acute coronary syndrome, including interventions
  (most effective)

- economy – more expensive (app. 1000 US $)

- peptides: abciximab (REOPRO) - antibodies
  eptifibatide (INTEGRILIN) - cyclic peptide

- nonpeptide (fibans)
  1. generation: parenteral - tirofibane (AGGRASTAT)
      peroral (orbo-, xemilo-, sibrafiban,...)
  2. generation: higher affinity to receptors, other effects
      (roxi-, cromo-, frada-, lefradafiban)
Abciximab (ReoPro)
- Monoclonal antibody – combination of 2 fragments
- Specific binding to IIb/IIIa receptor
- Long lasting effect (fading for 14 days)
- High affinity to receptors

Optimal effect for prevention and treatment of thrombotic complications after coronary interventions

High price
IIb/IIIa peptide antagonists

eptifibatid

small peptides

Imitate aminoacid sequentiation of fibrinogene chain (arginin-glycin-aspartin)

Shorter effect in comparison with abciximab

eptifibatid (cyclic heptapeptide)

Main indication – acute coronary events (nonQ-MI) high risk patients
Non-peptide GP IIb/IIIa antagonists

Tirofibane – synthetic nucleoside analogue

- Injections
- Quick onset of action
- Short acting - effect 4 – 8 hours
- Derived from Viper venom

Indications – non-stabile angina, PTCA
IIb/IIIa receptor antagonists clinical use

- PTCA – Percutaneous Transluminal Coronary Angioplasty
  - Acute coronary syndrom, mainly MI

- PTCA with thrombotic complications (local)

- Pharmacological treatment of non-Q MI

- Pharmacological treatment of AMI
NEW ANTIPLATELET AGENTS

TRIFLUSAL (inhibition platelet COX), similar to ASA, better tolerability

RIDOGREL (combination - block TXA₂ receptor and synthesis.), better than ASA (AMI)

TROMBOSTATIN (oligopeptide, blocking thrombocyte thrombin receptor PAR-1, bradykinine degradating product),

ANAGRELID - nonspecific inhibition of platelet activation (ADP, thrombin, collagen),
for acute coronary syndrome only, trombocytemia
Rational use of antiplatelet therapy

- **Ischemic hearth disease** – acute form only (i.e. MI) ASA, clopidogrel, eptifibatide, tirofiban (ticlopidine)
- **Secondary prevention** atherosclerosis after MI, stroke, TIA ASA, clopidogrel, event. ticlopidine)
- **stable AP, silent ischemia, peripheral ischemia** ASA, clopidogrel, event. ticlopidine
- **Primary prevention** of high risk patients – ASA
- **After revascularisation interventions** (stent) - ASA, clopidogrel, ticlopidine, abciximab, event. eptifibatid or tirofiban
- **Atrial fibrilation** (when anticoagulants are contraindicated) – ASA
ANTICOAGULANTS
Secondary homeostasis

eritrocytes

trappping
ANTICOAGULANTS
mechanism of action

1. Thrombin inhibitors –
   - **direct** (hirudines, ximelagatran, gatroban, efegatran)
   - **indirect** (heparines, LMWH)

2. Factor Xa inhibitors – **direct** (xabans)
   - **indirect** (heparine, LMWH, pentasacharids - fondaparinux)

3. vitamin K dependent factors inhibition (**vitamine K antagonists**)
The coagulation system is divided into an internal and an external system. Key components include:

- **Fibrinogen** → **Fibrin** → **Fibrin net**
- **Prothrombin** → **Trombin**
- **XIIa** → **IXa**
- **VIIa/TF**
- **Xa**
- **XIa**

**Anticoagulation** involves:
- Heparines, pentasacharides
- Plazmin

**Other Components**:
- Thrombomodulin
- Hirudins
- Ximelagatran
THROMBIN INHIBITORS

a) indirect (heparine, LMWH)
   - no inhibition for thrombin bind to fibrin or f.Xa

b) direct (hirudines, competitive and noncompetitive inhibitors)
   - strong antithrombotic effect
AT III

LMWH, UFH
ATIII mediated blockade of catalytic site for heparine activation

MELAGATRAN
Reversible blockade of catalytic site

DIRECT TROMBIN INHIBITORS

THROMBIN

INDIRECT TROMBIN INHIBITORS

TROMBIN

AT III

Catalytic site

HIRUDINE
reversible blockade of fibrine catalytic and binding site
HEPARINE - UFH

- Sulphonyl-mucopolysaccharide
- Continuous infusion necessary (sc. application uncertain)
- Dosage prediction questionable (binding, variable pharmacokinetic)
- Inability to inactivate thrombin bind to fibrin
- Neutralised by platelet factor 4
- Induced trombocytopenie (HIT), bleeding
- Average effective dose 30 thousands IU 24h
- Neutralised by protamin sulfate
- Replaced in most indications by LMWH
Mechanism of action

AT III

UFH

THROMBON

Fibrinogen binding site

catalytic site for f. Xa a thrombin

UFH, LMWH

AT III

f.Xa

UFH, LMWH

PENTASACHARIDS
Heparine fractionisation

heparin (UFH) → pentasacharids → LMWH
LOW MOLECULAR WEIGHT HEPARINS (LMWH)

- Heparin depolymerisation (15 sacharides units)
- Higher inhibition of fXa and lower thrombin
- Inability to inhibit thrombin bind to fibrin
- Longer effect
- Predictable effekt
- Good s.c. resorption
- Lower incidence of trombocytopenie (HIT)
- Incomplete neutralization by protamine
# Low molecular weight heparins (LMWH)

<table>
<thead>
<tr>
<th>Heparin</th>
<th>mol. weight</th>
<th>anti-Xa/anti-IIa</th>
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<tbody>
<tr>
<td>UFH heparin</td>
<td>12 – 15 000</td>
<td>1,0</td>
</tr>
<tr>
<td>dalteparin</td>
<td>6 000</td>
<td>2,7</td>
</tr>
<tr>
<td>enoxaparin</td>
<td>4 200</td>
<td>3,8</td>
</tr>
<tr>
<td>nadroparin</td>
<td>4 500</td>
<td>3,6</td>
</tr>
<tr>
<td>parnaparin</td>
<td>5 000</td>
<td>3,7</td>
</tr>
<tr>
<td>reviparin</td>
<td>4 000</td>
<td>3,5</td>
</tr>
<tr>
<td>tinzaparin</td>
<td>6 000</td>
<td>1,9</td>
</tr>
</tbody>
</table>
PENTASACHARIDES - f.Xa INHIBITORS

- selective factor Xa block, analog from pentasacharid sequence of heparinu, activate ATIII
- advantages: easy dosing, longer effect, predictable effect
- disadvantage: no antidote known

- fondaparinux:
  - prevention and treatment of perioperative TED and AKS
  - better prophylaxisthan LMWH in DVT
  - registered and reimbursed
  - indaparinux: application 1x weekly
Hirudin, bivalirudin, lepirudin, desirudin

- **direct trombin inhibitors**
- reversible blockade of the catalytic and binding side of fibrin
- proteins, parenteral application
- shorter effect (30-150 min)
- **indication:** heparin induced trombocytopenia - HIT
  (antibodies vs. compl. heparin and PF4)

- rarely used
Gatrans
direct thrombin inhibitors
**DABIGATRAN**
*(Pradaxa)*

- **Direct binding to thrombin catalytic center** without AT

- **thrombin inhibition**
  (free and even bind to fibrin)
DABIGATRAN

- **Direct reversible thrombin inhibition**
- **peroral**
- **Quick onset (max. effect after 1 hour)**
- **Long lasting effect (2x daily)**

- **Indication:** prevention and treatment TE comparable to LMWH
- **For stroke prevention better than warfarin**
DABIGATRAN

Antagonist

idarucizumab

- humanized antibody fragment (Fab)
- direct binding to dabigatran
- immediate effect
XIMELAGATRAN

- oral prodrug with conversion to melagatran
- excellent resorption and bioavailability
- reversible inhibitor of trombin
- 2x daily, without monitoring need
- lower variability compared to warfarin
  - (less interactions)
- **Indication**: prevention and FT treatment, long-term anticoagulation in TED prevention
Xabans
– direct inhibition of f. Xa

rivaroxaban, apixaban, otamixaban, edoxaban, …
RIVAROXABAN (Xarelto)

• Reversible inhibition of f. Xa (even bind to fibrin)

• Direct effect without AT

• Strong inhibition of thrombin activation, but not thrombin activity
RIVAROXABAN

- peroral
- $t_{1/2}$ 6-9 hours, 1-2x daily
- Small variability in response
- Prevention of TE after orthopedic operations, atrial fibrillation, DVT treatment
- Comparable to enoxaparine
APIXABAN

direct factor Xa inhibition
Peroral and injections
Standard effect, no monitoring

$t_{1/2}$ 8-12 hours, 1-2x daily

Low risk of interactions
APIXABAN

For prevention of TE after orthopedic operations – better than enoxaparine

For prevention of stroke during atrial fibrillation better than ASA and warfarin
vitamin K  warfarin
Vitamin K antagonist- WARFARIN

- Synthesis inhibition of „vitamin K dependent“ factors – defect factors synthesis
- good bioavailability, plasma protein binding
- Significant interindividual variability
- interaction with food and other drugs,
- Laboratory monitoring the INR is essential
- First stage of treatment procoagulation effect
warfarin

KUMATOX - jed na potkany a myši
CYP2C9 Polymorphism

- via CYP2C9 metabolism 15-20% of drugs
  - ASA and NSAIDs, warfarin, sulphonamides, phenitoin, barbiturates,
  - activation of AT₁rec. blockers (sartanes)
- > 30 types of polymorphism: slow, medium and quick metabolism
- Impact of CYP2C9*2 (10-20% population) CYP2C9*3 (6-9% population) – slow metabol.
- significanz slow down degradation of warfarin (5-27x ↓ clearence), ↑ risc of bleeding
Drug interactions of warfarin

CYP 2C9

- substrate: warfarin, sartans, NSAID, PAD
- inhibitors: amiodaron, klopidogrel, fluvastatin, NSAID
- inductors: herbs

Warfarin x amiodaron, fluvastatin, COXI
Narrow therapeutic window for warfarin

Risk of bleeding

INR < 2.0 - INR > 4.0

Risk of thrombembolisme
Warfarin indications

Prevention of embolism

- Atrial fibrialtion
- Valvular prosthesis
- Chronic thromboembolis
- Pulnomal artery embolism
- Trombofilic disiease
Warfarin contraindications

- Coagulopathy,
- High risk of bleeding -
  - Gastric ulcer
  - Crohn disease,
  - High hypertension
  - gravidity
Bleeding during warfarin treatment

WARFARIN

- Stop treatment
- vitamin $K_1$ p.o. (1-10 mg), event. i.v.
- Fresh frozen plasma i.v.
- Prothromplex – human coagulation factors – II (prothrombin), VII, IX, X - ??
Arterial trombosis treatment - fibrinolysis activation
FIBRINOLYSIS SCHEME

Tissue-type (t-PA)
Urokinase type (u-PA)

plasminogen

plasmin

fibrin degradation products

FIBRIN

Plasmin inhibitors

pI-1
pI-2
pI-3

Plasminogen activators

Inhibitors

α₂-antiplasmin
α₂-makroglobulin

Fibrin degradation products
Advantages and disadvantages of essential fibrinolytics

**streptokinase:** effective, cost effective, antigenic, hypotension

**r-tPA (tissue plasminogen activator):** quick and very effective, nonantigenic, selective short term effect, very expensive

**antistreplase:** quick effect (bolus), long lasting (APSAC) antigenic, average price

**urokinase:** effective, bolus, neantigenic, expensive
ANTI-PLATELET TREATMENT POSSIBILITIES

1) adhesion inhibitors: monoclonal antibodies versus vWF and platelet rec. GPII\A

2) activation inhibitors: 
   a) tromboxan activation blockers:
      COX blockers (ASA, indobufen)
      TX rec. inhibitors (ridogrel)
      tromboxan-synthasis inhibitor (dazoxiben)
   b) ADP rec. blockers: tiklopidin, klopidogrel
   c) serotonin rec. blockers: naftidrofuryl, ketanserin
   d) trombin rec. blocker: inhibitory trombin
   e) multipotent platelet rec. blockers: (anagrelid)

3) aggregation inhibitors: GPIIb/IIa rec. antag. (abciximab, integrilin,
   epitifibatid, II. generation: roxifiban, lotrafiban, fradafiban)

4) platelet stabilisation: via cAMP (dipyridamol) or cGPM (NO donors)