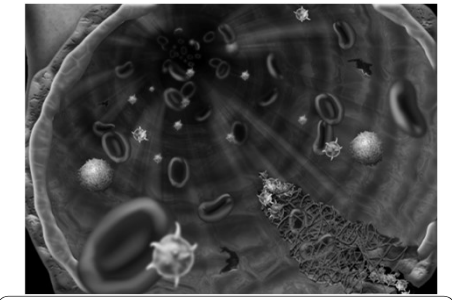
Drugs affecting clotting and hemopoiesis



MUDr. Alena Máchalová

Hemostasis

Hemostasis is the arrest of blood loss from damaged vessels and is essential to life

mechanisms playing part in hemostasis are
- vasoconstriction
- blood coagulation (coagulation factors)
- thrombocytes adhesion and activation

hemostasis is consisting of 3 phases:
vascular
platelet
coagulation

→ continuing with fibrinolysis (to prevent coagulation which is not necessary in following parts of the vessel)

Required for the proper functioning of HAEMOSTASIS processes

CORRECT BLOOD FLOW (no stagnation of blood)

INTACT BLOOD-VESSEL WALL (preserved endothelium and sufficient production of all its mediators)

BALANCED REGULATION of coag. and anticoag. processes

DYSFUNCTION → **PATHOLOGY**

Bleeding conditions
Hypercoagulation states

Congenital disorders
Acquired disorders

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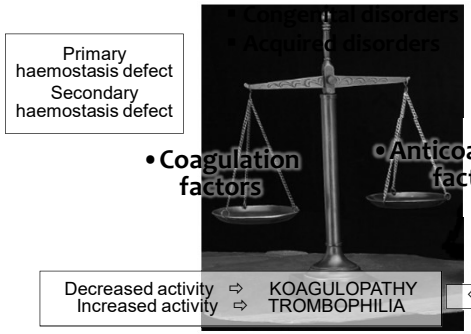

Primary haemostasis defect
Secondary haemostasis defect

Fibrinolysis defect
Lack of anticoagulant factors

Decreased activity ⇨ KOAGULOPATHY
Increased activity ⇨ TROMBOPHILIA

⇦ Decreased activity

venous thrombosis
arterial thrombosis

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Drugs affecting clotting

−

Anticoagulants

Thrombolytics

Antiplatelet drugs

Drugs improving deformability of ery

+

Antifibrinolytics

Hemostatics

Blood products

Coagulation cascade

- the coagulation factors except VIII, V a TF are present in blood in the form of inactive precursors (zymogens)

- f. V and VIII are not enzymes

- TF – high affinity membrane receptor for f VII

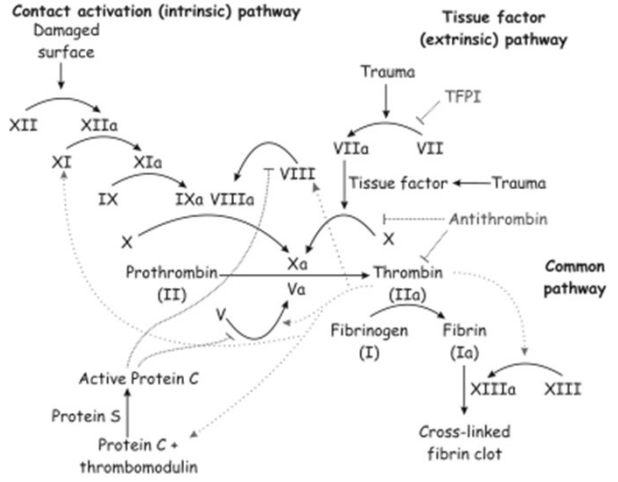
- cascade must be regulated by inhibitors, AT III

-coagulation is working as an amplifier –
  - why? .... evolutionary advantage

Coagulation cascade

- there are two classical pathways of coagulation –
  - *contact activation pathway* (formerly known as the intrinsic pathway, because all the components are present in blood), it is activated when blood comes into contact with artificial surface

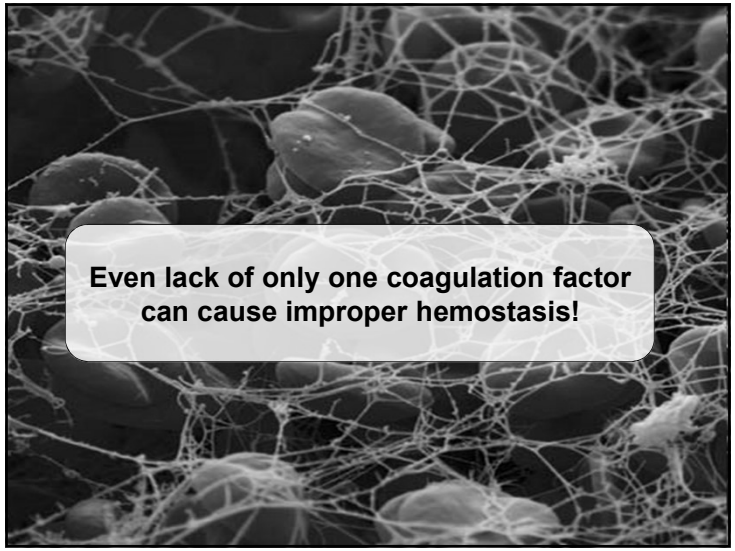
  - *tissue factor pathway* (formerly known as the extrinsic pathway), this is the more important, primary pathway, which is initiated by contact with „tissue factor“, it is also much quicker



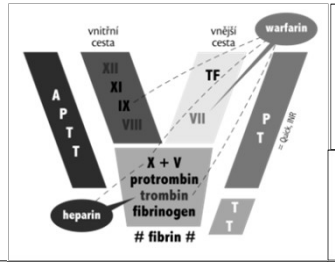
- **1 – fibrinogen**
- **2 – prothrombin**
- **3 – tissue thromboplastin**
- **4 – Ca ions**
- **5 – proakcelerin**
- **7 – prokonvertin**
- **8 – antihemofilic factor – von Willebrand faktor**
- **9 – Christmas factor**
- **10 – Stuart-Prover factor**
- **11 – PTA**
- **12 – Hageman faktor**
- **13 – fibrin stabilising factor**
- **14 – protein C**

Coagulation cascade

- Endothelium –
  - Covered by heparansulphate
  - Active particiopant of coagulation – synthesis of vWF, tissue factor, PAI (in response to angiotensin IV)
  - Limitation of hemostasis – PGI2, NO, ADP (platelets inhibition), tPA, thrombomodulin



Laboratory evaluation of haemocoagulation



PROTHROMBIN TIME (PT):
Quick test (14s)
INR (0,8-1,2) 80-120%
is used to evaluate the extrinsic pathway of coagulation activation

TROMBIN TIME (TT):
(11-19s)
is used to evaluate the common pathway in the activation of coagulation

ACTIVATED PARTIAL THROMBOPLASTIN TIME (aPTT)
(26-50s)
It is used to evaluate the **intrinsic** pathway of coagulation activation.

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Anticoagulants

- do not work against old thrombuses
- influencing ATIII or synthesis of coag. factors
- monitoring of therapy is necessary
- **Indications:**
  - **Deep venous thrombosis**
  - **Lung embolisation**
  - **Arterial embolisation**
  - **Prevention of arterial emboli in patients with heart valve failure, atrial fibrilation and acute myocardial infarction**

Direct

- heparin and its derivates, pentasaccharides, gatrans, xabans

Indirect

- „oral antikoagulants“

Přímá antikoagulancia

1. Antithrombine activators (= inhibitors of IIa and Xa)
Heparin UFH
LMWH (incl. sulodexide)
Heparinoids
Pentasaccharides

2. Direct thrombin inhibitors (IIa)
gatrans

3. Factor Xa inhibitors
xabans

} NOACs = novel oral anticoagulants alias DOACs

Direct anticoagulants HEPARIN

- i.v. or s.c. anticoagulants, used also in vitro to coat inside surface of test tubes, dialysis machines etc.
- its molecule has the biggest negative charge of all biomolecules
- it was discovered in 1916 by a second-year medical student, who was attempting to extract some coagulant substances from various tissues during a vacation project, instead he found a powerful anticoagulant
- interesting fact: it is present even in bodies of invertebratae, who are lacking coagulation system similar to ours

Direct anticoagulants HEPARIN

- physiologic function is not known, maybe antibacterial protection in wound
- released together with histamin, maybe to prevent forming of thrombus in dilated vessels
- produced by mastocytes and basophiles and released mostly in liver (hepar), lungs and gut
- commercial preparates are extracted from beef lung or pig intestine
- its doses are specified in units of activity, not in mass

Direct anticoagulants HEPARIN a its derivates

How does it work?

- anticoagulation activity of heparin depends on presence of ATIII, which is irreversible inhibitor of thrombin activity as well as some other coagulation factors (e.g. factor Xa)
- heparin cca 1000x accelerates and helps interactions of ATIII (exposing its active site for quick interaction with proteases)

The effect of heparin depends on the presence of antithrombin III ⇨ is recommended to monitor its level during prolonged treatment.

Direct anticoagulants HEPARIN

- in vitro elongation of APTT - activated parcial thromboplastin time – 25-39s, → therapy control
-
- decreasing adhesivity and count of thrombocytes (↓ PGF-I), anticoagulant, antithrombotic, antifibrinolytic, antiinflammatory, antilipidemic activity
-
- efficient in vitro and in vivo in contrast with peroral anticoagulants

Direct anticoagulants HEPARIN

- It is administered intravenously, in bolus 3 times a day or by continuous infusion (non-standard bioavailability after i.m. and s.c. administration - still sometimes given s.c. as part of miniheparinization)
- It remains in circulation for a short time (it binds to endothelial cells and macrophages and acute phase proteins)
- It does not cross the placenta or into breast milk
- Biotransformation occurs in the liver ⇨ inactive product
- Renal excretion
- Elimination half-life is proportional to the dose administered

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Direct anticoagulants HEPARIN

Indication:

- Deep vein thrombosis (DVT) and pulmonary embolism (PE): treatment and prophylaxis
- Acute coronary syndromes
- Percutaneous coronary intervention (PCI)
- Thromboembolic disorders
- Arterial embolization: treatment and prophylaxis (atrial fibrillation)
- Vascular and cardiac surgery
- Extracorporeal circulation (hemodialysis, hemofiltration, and cardiopulmonary bypass during cardiac surgery)
- Arterial and venous catheters, pulmonary artery catheters (heparin flushes)
- Diagnostic and therapeutic interventional radiologic procedures

Direct anticoagulants HEPARIN

KI: bleeding
condition after big surgery
malign hypertension
trombocytopenia
abortus imminens

Protamine sulfate = specific antagonist
- basic protein with afinity to negative charged heparin → complex
- overdose treatment 1mg/100u of heparin

AE: bleeding – GIT, urinary system and adrenal glands
•trombocytopenia
•hypersensitivity

Direct anticoagulants Low-molecular-weight heparins

• heparin fragments

Nadroparin (Fraxiparin), enoxaparin (Clexane), dalteparin (Fragmin), parnaparin, reviparin, certoparin…

• mol. weight cca 2 - 9 kDa (heparin 15 - 20)

• s.c. application

• lower risk of adverse effects, less frequent dosing

• patients are able to give injections themselves at home

Direct anticoagulants Low-molecular-weight heparins

• increase ATIII activity against IIa and **Xa** (early phase of coagulation)

• halflife is doubled when compared to heparin (cca 200 mins), much better bioavailability

• they do not prolong APTT, however monitoring is not required, because they are eliminated by 1st. order kinetics

• eliminated by liver, monitoring of thrombocytes

FOR COMPLEMENTARY ANTICOAGULANT THERAPY

1. **Antithrombine activators**

sulodexide (soft capsules, inj.sol.)

Mixture of
80 % - „medium" molecular weight heparin
20 % - glykosaminoglykan dermatan

MoA
is complex, due to the effect of both components
- Anticoagulant, antiplatelet, mild fibrinolytic
- Lipolytic effect due to activation of lipoprotein lipase
- Protective and reparatory effects on endothelium
- Improving the rheological properties of blood

I: DVT, ischaemic heart disease, critical limb ischaemia (CLI), microcirculatory disorders in diabetic, scerebral artery occlusion.

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Direct anticoagulants Heparinoids

• polysulphur esters of sacharids e.g. Heparansulfate, dermatansulphate or mixture danaparoid
• obtained from animal intestinal mucous membrane
• they are mostly used locally on skin (thrombophlebitis, injuries)
• we can use them to substitute heparin in HIT

Direct anticoagulants Sulphonated pentasacharid

• fondaparinux (Arixtra), indraparinux
- (named for Asterix a Obelix) indirectly anti-Xa, deep venous thrombosis, pulmonal embolisation, s.c. admin.

Direct anticoagulants Thrombin inhibitors

Antithrombin III - congenital deficiency

Hirudin
• polypeptide present in leech saliva (Hirudo medicinalis)
• reacts directly with thrombin without ATIII
lepirudin, desirudin, bivalirudin – parenteral administration

Argatroban – hepatic metabolism, suitable in kidney failure, HIT

Direct anticoagulants Thrombin inhibitors - GATRANS

Gatrany - dabigatran (RMP Pradaxa), ximelagatran (pro-drug) → melagatran (withdrawn)

- oral anticoagulant therapy without monitoring (high correlation between plasmatic levels and effect)

• MoA - They inhibit not only **fibrin-bound** thrombin but also **free** thrombin ⇨ inhibit thrombin-induced platelet aggregation

- P-gp substrate ⇨ DDI (careful with verapamil)
- CAVE
  - gastritis, oesofagitis, GER
  - GFR 30-50ml/min
  - over 75 let

- Beedinn complications (enterorrhagia, hematuria, melena)
- GIT bleeding ⇨ USE GASTROPROTECTIVES

Direct anticoagulants Thrombin inhibitors - GATRANS

ANTIDOTE
• **idarucizumab** Praxbind® 10ml/2,5g

= humanized monoclonal antibody fragment that binds specifically to dabigatran with very high affinity and immediately neutralizes its anticoagulant effect.

•The binding affinity of idarucizumab for dabigatran is approximately 300 times higher than the affinity of dabigatran for thrombin.

I:
- Withdrawal of the anticoagulant effect of dabigatran during life-threatening or uncontrolled bleeding or during urgent surgery
- Intravenous administration (two consecutive infusions or bolus injections, giving a total of 5 g of idarucizumab)

The use of RMP is limited by its price

Direct anticoagulants Xa inhibitors

Xabans
- **direct Xa inhibition (both pathways)**
- **no effect on platelets or thrombin**
- **oral administration (once a day), rapid onset of action**

Rivaroxaban (RMP Xarelto)
Apixaban
Betrixaban

For parenteral admin. otamixaban, in ČR not registered

Direct anticoagulants Xa inhibitors

CI: liver insuff. (esp. rivaroxaban)

AE
- bleeding
- dizziness, headache, stomach pain, elevated bilirubin
- Rare – serious skin reactions SJS/TEN*, icterus

• Interactions with strong CYP3A4 and P-glp inhibitors

ANTIDOTE andexanet alfa AndexXa®
•Higher affinity for the FXa inhibitor than natural FXa (decoy receptor)

* Stevens-Johnson syndrome / toxic epidermal necrolysis

aripazine / ciraparantag/PER977 (Perosphere, USA)

A small, synthetic, water-soluble molecule that binds by non-covalent hydrogen **bonding to FXa inhibitors as well as FIIa.**

In phase II of the clinical trial.

„Universal“ NOAC ANTIDOTE (gatrans, xabans)

But also LMWH and UFH

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GATRANS or XABANS ??

• … state of the patient vs expected effects …

An increased incidence of GIT bleeding has been reported

Hepatal insufficiency is a contraindication for xabans (especially rivaroxaban)

Renal insuficience

rivaroxaban is not recommended in patients with clearance of creatinine < 15 ml/min

dabigatran is not recommended in patients with clearance of creatinine < 30 ml/min

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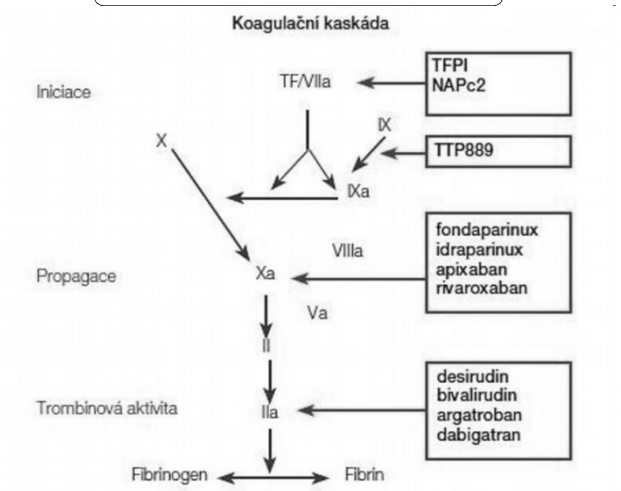
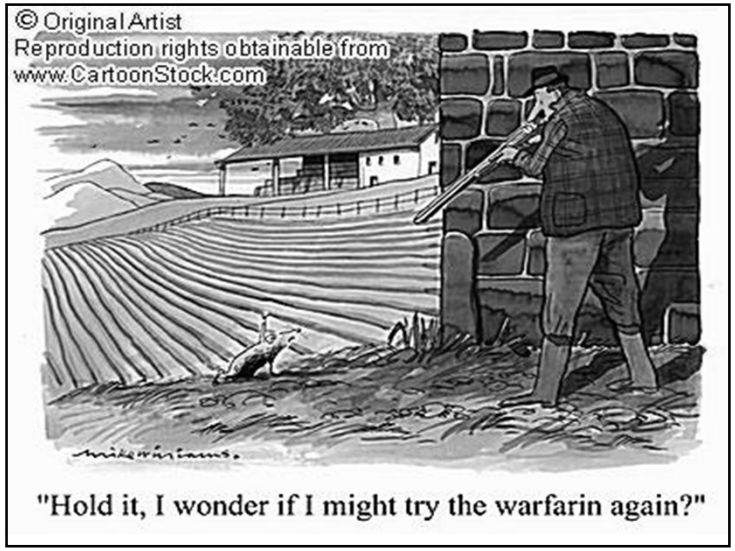
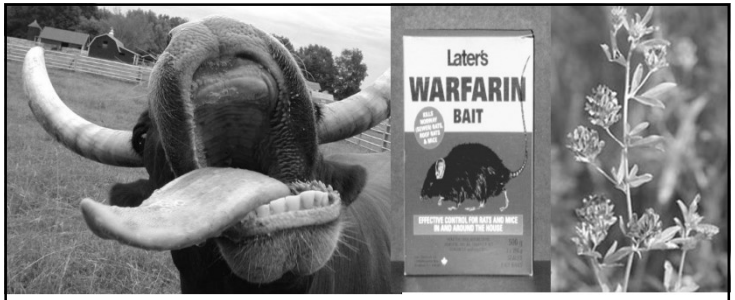
ADVANTAGES OF NOACs/DOACs	DISADVANTAGES OF NOACs/DOACs
Rapid onset of action	Dose reduction in renal insufficiency
Absence of interactions with food Only few potent drug interactions	Limited availability of laboratory tests to check the effectiveness of therapy
Wide therapeutic window, fixed dose in adults	Potential for overuse (patients with VTE are treated for a long time, even at low risk of relapse)
No need of monitoring	They have a short half-life, so there is a risk of a rapid decrease in the anticoagulant effect if the dose is left out
Patient comfort (oral administration)	

New anticoagulants





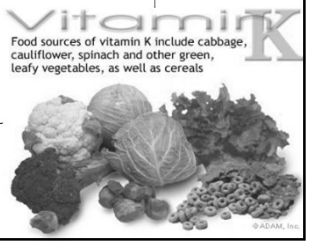


Indirect anticoagulants

Indirect anticoagulants

- structural similarity with vitamin K
- kompetitive antagonists of vitamin K
  - vit K is essencial for posttranslational carboxylation in clotting factors II (prothrombin), VII, IX, X, protein C and protein S
  - inducing synthesis of structuraly incomplete coag. factors

• only in vivo
• delayed effect



Indirect anticoagulants

• binding to plasma protein (up to 99%)
• metabolised in liver (CYP450), excretion – bile, urine
• monitoring by measuring the INR – (international normalised ratio)
  healthy preson INR 0.8-1.2
  with warfarin INR 2-3

• AE: - haemorrhage in skin, GIT, kidneys, brain
  - rarely necrose of small intestine or skin or soft parts of the body

Warfarin embryopathy:
nasal hypoplasia
chondrodysplasia punctata
CNS abnormity
mikrocephalia
blindness

• KI: - gastrointestinal ulceration
  - trombocytopenia
  - malign hypertension
  - pregnancy (teratogenic, bleeding), breast-feeding

Indirect anticoagulants

• I: prevention of trombembolic diseases
  deep venous trombosis
  lung embolism
• anticoagulant effect can be supressed by
  administering dose of vit K 20-40mg iv

Warfarin
• p.o. or i.v. aplikation
• D: starting doses 5-15mg
  long-term doses 5-7 mg

Dikumarol
Etylbiskumacetát
Fenprokumon

Indirect anticoagulants

• High variability in dosing
  • according to some published papers 0,5 – 50 mg/day!

• genetic influences
  • CYP 2C9 activity (need to reduce doses down to 60%) – in Caucasian population 10 – 20% of people

  • mutation of C1 subunit epoxid-reductase (enzyme directly influenced by warfarin) – need to reduce dosing - in Caucasian population 14 - 37% of people

• the therapy must be often customized according to diet, co-morbidities
• there are tables to help physicians

Indirect anticoagulants

Warfarin – many interactions (plasma binding, CYP metabolisation)

– mostly ↑ risk of bleeding (sometimes induction of biotransformation – St. John´s wort, phenobarbital, rifampicin)

- alcohol !!!, allopurinol, anabolic steroids, several ATB and chemotherapeutics, disulfiram, thyroid hormones…

- Cardiology drugs – ASA, heparin, chinidin, amiodaron…

PHARMACOGENETICS of WARFARIN THERAPY

Gene CYP2C9 encodes an enzyme by which warfarin is metabolised. Polymorphism affects the pharmacokinetics and the amount of DRD

Gene VKORC1 encodes the C1 subunit of the transmembrane protein "vitamin K epoxide reductase system" = VKOR.

Patients with variant alleles need lower doses of WARFARIN to maintain the same INR (2-3 times)

Up to 20% of the population belong to the high-risk group of carriers of the VKORC1 AA or VKORC1 GA polymorphism and at the same time at least one CYP2C9 mutation (2 *, 3 *)

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CPIC - Clinical Pharmacogenetics Implementation Consortium recommends using the pharmacogenetic algorithm at http://www.warfarindosing.org - a dosing table predicting the optimal dose of warfarin with respect to other factors.

recommended by CPIC and modified from FDA materials

VKORC1	*CYP2C9*					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

• The ranges are derived from many published clinical (pharmacogenetic) studies

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Warfarin - drug interactions

Tabulka 2. Klinicky signifikantní interakce jednotlivých lékových skupin s warfarinem (upraveno d

Míra interakce	Antibiotika	Kardiovaskulární léky	Analgetika	CNS
Potenciace				
Vysoká	Ciprofloxacin Kotrimoxazol Erytromycin Flukonazol Isoniazid Metronidazol Mikonazol	Amiodaron Klofibrát Fenofibrát Propafenon	Phenylbutazone Piroxikam	Alkol Citalo Sertr
Pravděpodobná	Amoxicillin/klavulanát Azithromycin Klarithromycin Levofloxacin Ritonavir Tetracyklin	Acetylsalicylová kyselina Fluvastatin Simvastatin	Acetaminophen Tramadol Celecoxib	Disul Phen Fluvo
Inhibice				
Vysoká	Griseofulvin Nafcillin Ribavirin Rifampin	Cholestyramin		Barbi Karba
Pravděpodobná	Ritonavir	Bosentan	Azathioprin	

Interní medicína pro praxi | 2011; 13(11) | www.internimedicina.cz

• Adapted from Moravec, Terapie warfarinem a režimová opatření – mýty a fakta. Interní medicína pro praxi. 2011; 13(11)

Warfarin - drug interactions

lékových skupin s warfarinem (upraveno dle 13)

skulární léky	Analgetika	CNS léky	GIT léky	Jiné
on t on	Phenylbutazone Piroxikam	Alkohol Citalopram Sertralin	Cimetidine Omeprazol	Anabolické steroidy
cylová kyselina n tin	Acetaminophen Tramadol Celecoxib	Disulfiram Phenytoin Fluvoxamine		Fluorouracil Tamoxifen Levamisole Paclitaxel
ramin		Barbituráty Karbamazepin		Merkaptopurin
	Azathioprin			Vakcína chřipky

ernimedicina.cz

- Adapted from Moravec, Terapie warfarinem a režimová opatření – mýty a fakta. Interní medicína pro praxi. 2011; 13(11)

OTHER FACTORS AFFECTING INR

Decrease of INR

- Reduced metabolism
- Uremia
- Higher intake of food containing a lot of vitamin

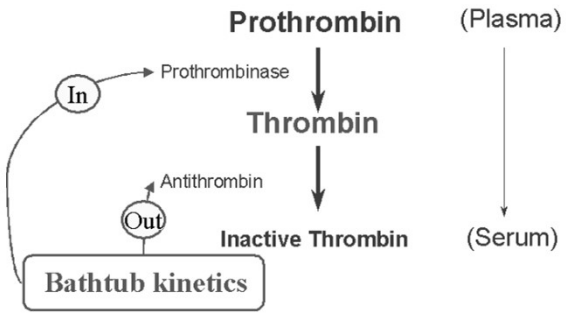
RISK of treatment ineffectiveness and thrombus formation

Increase of INR

- Increased metabolism (thyrotoxicosis, fever, infection)
- Malaabsorption states with vitamin K deficiency
- Hepatal insuficiency
- ATB therapy and suppression of intestinal microflora

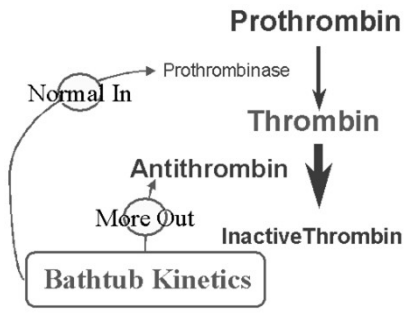
RISK of bleeding

Normal Situation



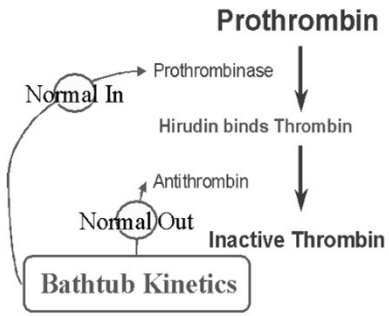
The dynamics of thrombin appearance and disappearance are like the filling of a bathtub without a stopper from a large bucket (the bucket size is the amount of prothrombin, prothrombinase activity determines how fast it is poured in, and the drain size is the action of antithrombin)

Heparin



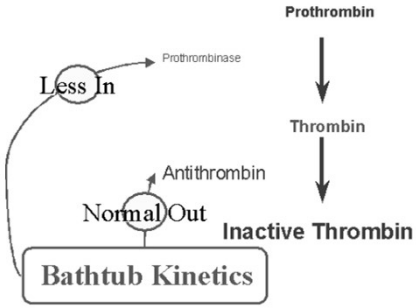
Heparin makes antithrombin a much more potent thrombin inhibitor, it works on the drain side. Thrombin comes in normally but goes out much faster. The result is less thrombin.

Hirudin



Hirudin binds directly to thrombin, so the IN- and OUT velocities remain unchanged but thrombin itself is inhibited.

Oral Anticoagulation

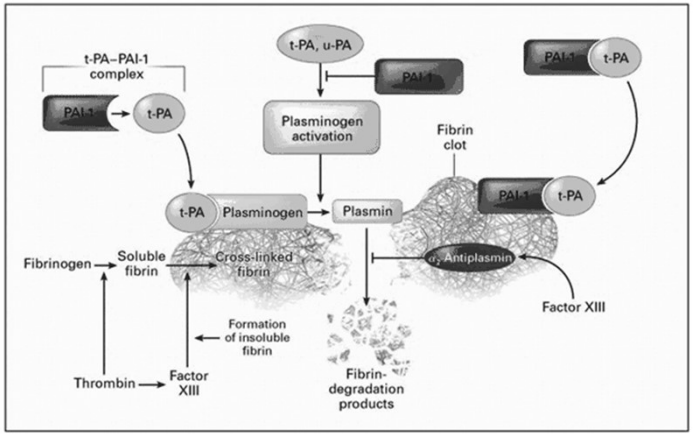


Lack of vitamin K or drugs that prevent its functioning (vitamin K antagonists) make that several clotting factors including prothrombin, are not formed normally. However, thrombin decay remains normal, or: less in and normal out.

Fibrinolysis

- via FXII, at the same time with coagulation steps leading to removal of the thrombus – fibrinolysis are taken
- the most important factor is plasmin, it is found in inactive form in plasma and it is incorporated into thrombus bound to fibrin
- to prevent early thrombus dissolution it contains also α2-antiplasmin, which is inhibitor of plasmin, and is nearly completely inhibiting it
- plasmin activation is possible via two main plasmin activators - t-PA (tissue PA) produced by endotelium and u-PA (urokinase like PA) produced by fibroblasts, epitelium, pneumocytes, placent cells etc.)

Fibrinolysis



Fibrinolysis

- the main role of t-PA is regulation of iv thrombi, u-PA participates in proteolytic processes like tissue remodelation, tumor invasion, fertilisation or embryogenesis
- urokinase is u-PA metabolit – enzym found in urine with preservated aktivation ability
- fibrinolysis aktivation is under controle of plasminogen activator inhibitor PAI 1-3 and protein nexin

Fibrinolysis

- fibrinolysis is influenced by fibrin – on its surface complex t-PA + plasminogen + fibrin is formed, activated plasmin is immediately inhibited by α2-antiplasmin
- lysis occurs when t-PA is released from endotelium upwards from wound (reaction to slowing-down of the blood flow)
- this release of t-PA activates small amount of plasmin, which alterates the structure of fibrin and enlarge fibrin surface, thus enabeling the activation of more of plasminogen
- this way activation overbalance inhibition and lysis accelerates

Fibrinolysis

- ε-aminokapronic or tranexamic acid, binds to fibrinogen and prevent its adsorption on fibrin → antidote, haemophilic patients
- fibrinolysis is depending on PA/PAI ratio, which is under influence of many external factors:
  - exercise, stress, fear, anger, smoking
  - ↑↑ level of PAI is in the morning, at the same time t-PA is ↓↓

  => the highest incidence of AMI

Fibrinolytika (trombolytika)

Fibrinolytics (thrombolytics) are plazminogen activators (PA).

Ideal thrombolytic drug should be administered i.v. and should cause selective thrombolysis in the thrombus without converting plasminogen into plasmin

Fibrinolytics
- I. generation
- II. generation

I. generation

Non-selective → systemic activation of plasmin

- **streptokinase**
- **urokinase**

II. generation

Binding to fibrin → fibrinolysis targeted on the thrombus

- **t-PA**
- **anistreplase**
- **saruplase**

Fibrinolytics (thrombolytics)

Clinical use:

Severe lung embolisation
Deep venous thrombosis
Arterial oclusion

Acute myocardial infartion therapy

Unwanted effects:

Bleeding

Fibrinolytics (thrombolytics)

Contraindications

Absolute

Active bleeding from intracranial or chest trauma

Bleeding from tumor or from vascular abnormality

Relative

Hypertension

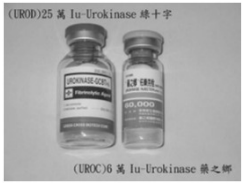
Other risks of bleeding

Fibrinolytics (thrombolytics) non-selective streptokinase

- **nonenzymatic protein isolated from β-hemolytic streptococcus**
- **indirectly causes activation of plasminogen**
- **parenteral administration → lysis of ACUTE thrombi**
- **it is cheap, but antigenous,– prev. bolus hydrocortisoni 100 mg i.v., do not give again in 1 year after the previous usage**
- **I: - very good drug for recanalisation after IM infusion + AcSal**
  - **~~RMP Streptase~~**

Fibrinolytics (thrombolytics) nonselective urokinase

- **origin is human urine, metabolic product of u-PA**
- **direct plasminogen activator**
- **not antigenous**
- **weaker than streptokinase, ↓ AE, ~~RMP Rheotromb~~**



Fibrinolytics (thrombolytics) selective t-PA (alteplase)

- **high afinity to fibrin**
- **concentrations used in therapy are 1000x higher than physiologic, short t1/2 = risk of reoclusion**

- **alteplase RMP Actilyse –** recombinant, single-chain t-PA
- **duteplase** - double-chain tPA
- **reteplase** – similar but has a longer elimination half- life allowing bolus administration, simpler structure = only peptid domain of tPA
- **tenecteplase (TMK-tPA), RMP Metalyse** – bolus administration, 80x higher selectivity than alteplase

Fibrinolytics (thrombolytics) selective anistreplase ASPAC

- **= acetylated streptokinase – plasminogen activator complex**
- **inactive form, binding to fibrin → deacetylation → activation**
- **activated anistreplase is quickly eliminated from circulation by α2- antiplasmin → ↓ AE**
- **very good effect in AMI**
- **antigenous**

Fibrinolytics (thrombolytics) selective Saruplase (rscu–PA)

- **similar to urokinase, but high afinity to fibrin**
- **possible combination of saruplase with t-PA for reperfusion of coronary arteries**

Defibrinants ankrod, batroxobin

- **snake toxins, degradating fibrinogen to fibrin → consumption, thrombolytic action**
- **used more often as anticoagulant than trombolytics**

- **Ankrod (ancrodum)** is purificated defibrinant protease from snake **Ankistrodon rhodostoma (Calloselasma rhodostoma) –** ***Malayan pit viper*****,** which is used as fibrinogenolytic and anticoagulant.

•**Batroxobin** is serin protease from snake **Bothrops atrox –** ***Common lancehead*****,** which is decreasing plasma level of fibrinogen, plasminogen and α2 –antiplasmin. It has similar effects as ankrod.

Alfimepraze

- **enzyme obtained by recombinant technology**
- **it is derivate of metaloproietinase called fibrolase obtained from malayan pit viper**
- **specific MoA: direct degradation of fibrin**
- **advantage – very short t1/2 in systemic circulation**
- **currently in clilnical testing**

Antifibrinolytics

- **inhibit plasmin from binding to fibrin**
- additive drugs used when substituting loss of coagulation factors to stop bleeding during/after surgery (e.g. tonsilectomy, prostatectomy)
- menorrhagia
- dental surgery in heamophilic patients (extraction)
- AE: nausea, KI: DIC

- ~~**ε-aminokapronic acid (EACA)**~~
- **tranexamic acid -** renaissance - reduce blood loss during trauma bleeding (accidents, accidents)
- ***p*-aminometylbenzoic acid (PAMBA)** renal elimination

•**aprotinin –** inhibits proteolytic enzymes (trypsin, chymotrypsin and plasmin) – for fibrinolytic drugs overdose, pancreatitis, patient at risk of major blood loss during heart or liver surgery

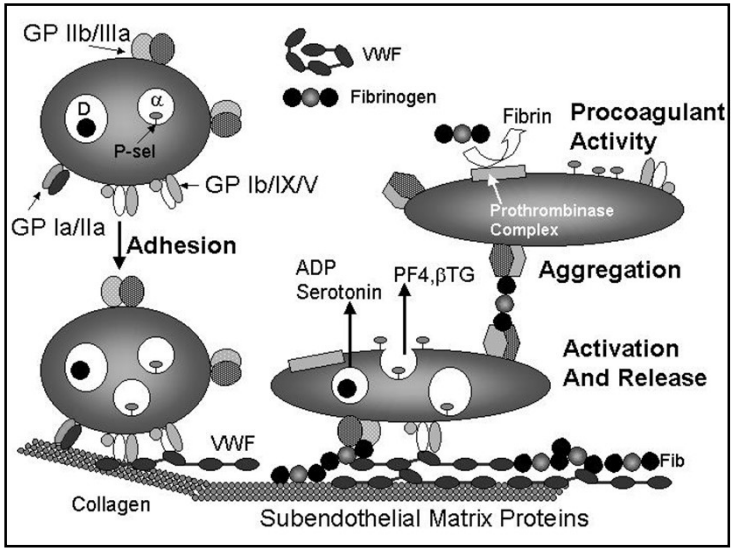
Agregation

- platelets adhesion to vasal subendotel via collagen, basal membrane, Ib receptors and vWF (which is cast loose from complex with FVIII during coagulation)

- start of many complex reactions, shape changes, release of many substances → support adhesion, lysozym (antibacterial), vasoconstriction, PF4 – binds ATIII – prevents early inhibition of coagulation, atracts leukocytes etc.

- aggregation is promoted by various agonists including colagen, thrombin, ADP and TXA acting on specific receptor on the platelet surface, activation leads to expresion of IIIb/IIa receptors which binds fibrinogen and links platelets together (aggregation)

- forming clot is at the same time signal for surrounding tissues to start works on its cleaning away = fibrinolysis (release of t-PA)



Antiplatelet drugs (Antiagregants)

• **inhibition of agregation, specific <u>profylaxion of arterial thrombose, secundar prevention of AMI</u>**

• **antiplatelet therapy after AMI needs to be started as soon as possible (for the best results not later than 1 hour after first symptoms)**

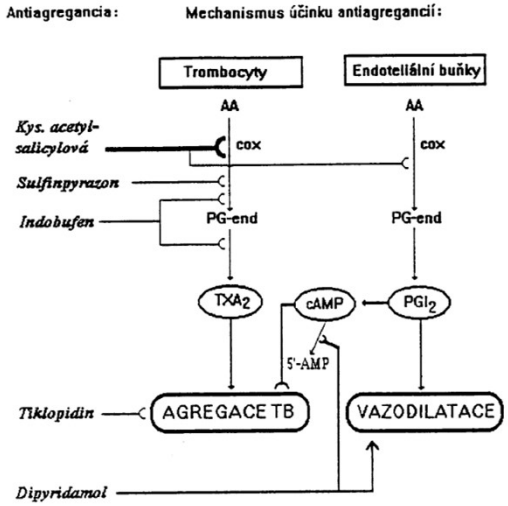
• **usually used in combination with heparin to ensure proper perfusion and infarction size reduction**

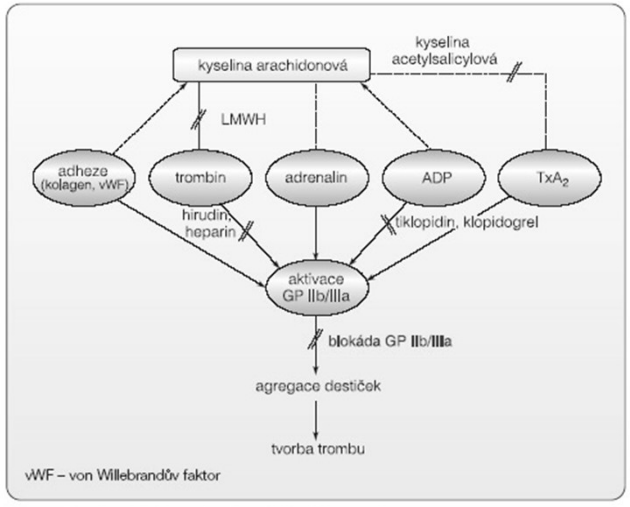
• **there are other drugs with antiplatelet activity, but these are not used in this indication : hydrochlorochin, klofibrate, indometacin, fenylbutazon, some of prostaglandins and neurotropics**

Antiplatelet drugs (Antiagregants)

How do they work?

1. **Inhibition of thromboxan A2 syntese - inhibition of COX**
   ASA, indobufen, sulfinpyrazon
2. **Inhibition of thromboxan A2 syntese via increasing cAMP level in thrombocyte**
   - **inhibition of fosfodiesterase – dipyridamol, pentoxifylin**
   - **stimulation of adenylatcyklase – prostacyklin and analogs**
3. **Inhibition of fibrinogen cross-bridging among thrombocytes**
   - **inhibition of ADP $P2Y_{12}$ receptor in thrombocyte membrane - ticlopidin, clopidogrel, prasugrel, ticagrelor**
   - **inhibition of fibrinogen receptor in thrombocyte membrane (IIb/IIIa) – tirofiban, lamifiban, monoclonal antibodies – abciximab)**





Obr. 3 Aktivační kaskáda vedoucí ke shlukování destiček.

Antiplatelet drugs (Antiagregants)

Indications:

- ischemic cerebrovaskular diseases
- ischemic heart disease
  - periferal arteries disesases
  - to reduce thrombogenous effect of synthetic materials

Antiplatelet drugs acetylsalicylic acid

- deacetylates and irreversibly inhibits COX
- COX: in thrombocytes → TXA2 (agregation)
  in endotel cells → PGI2 (antiagregation and vasodilatation)
  ⇒ we want to block TXA2
- Thrombocytes unlike endotel cells are not able to syntetise COX = selective inhibiton of COX in thrombocytes (persistence 7-10 days)
- Effect depends on dose (high doses block also endotel COX)

Antiplatelet drugs acetylsalicylic acid

- Low doses of AcSal can reduce risk of AMI and sudden death in patients with angina pectoris down to 50%
- Also other NSAID (ibuprofen, naproxen) have antiagregant effect, but this effect is not irreversible
  - **<u>AMI – first-aid treatment immediately administer 500mg ASA</u>**

Antiplatelet drugs acetylsalicylic acid

- D: usually 50-100mg per day
- there is no laboratory test to monitore effectivity of therapy – only clinical symptoms
- No antidote available, in case of need it is possible to administer hemostyptics, antifibrinolytics or thrombocytes

Antiplatelet drugs acetylsalicylic acid

- Indication:
  - AIM, instable AP
  - Prevention of AIM (also combined with warfarin)
  - Ischemic brain stroke
  - After PTCA, by-pass
- Disadvanatges:
  - AE – about 20% of pacients
  - Rezistance to ASA 10-20% of pacients

Antiplatelet drugs (Antiagregants)

Other NSAIDs with antiaggregant properties – but reversible

Sulfinpyrazon
- NSAID, competitive inhibitor of COX
- inhibing adhesion of thrombocytes and releasing of several substances
- elonging persistance of platelets in circulation
- Indobufen – short effect, expensive
- Picotamide

Antiplatelet drugs – pentoxifylin

•improves deformability of erythrocytes

•decreasing level of fibrinogen and blood viscosity, thus improving microcirculation, antiinflamatory ef.

Antiplatelet drugs – dipyridamol

• coronary vasodilatant, phosphodiesterase inhibitor

• decreasing adhesivity of platelets to damaged endotel
↑ cAMP in platelets → ↓ TXA2
• used in combination with aspirin, warfarin

Antiagregancia – cilostazol

• vasodilatant, phosphodiesterase inhibitor

• in limb ischemia, claudication

Antiplatelet drugs – tienopyridines

• **block receptor P2Y12 for ADP** (activates receptors on surface of thrombocytes → this is where fibrinogen binds)

• onset is slow (several days) and lasts 7-10 days
• NU: hemorrhage, diarrhea and leucopenia

1. Ticlopidin (RMP Ticlid)
2. Clopidogrel
   - better effect, less AE
   - convenient combination with ASA after PCI with stent implantation RMP Plavix, Clopidogrel…
   - Fix combination with ASA RMP Duoplavin, Duocover
3. Prasugrel – 3.generation RMP Efient

Antiplatelet drugs – non tienopyridines

REVERSIBLE

Ticagrelor
Adm. 2x a day According to clinical studies has a better reduction in CV events than after the combination of clopidogrel + ASA administration

Cangrelor
Rapid onset of action in minutes (for continuous infusion only)

Biological half-life is only 3 minutes ⇨ full platelet function is restored within 1 hour of stopping the infusion

Antiplatelet drugs

GP IIb/IIIa Rc antagonists

- **they are supposed to block all pathways of platelet activation since they all converge on activation of GP IIb/IIIa receptor**
  1. eptifibatide – small peptide, i.v. adm., short effect

  2. tirofiban, lamifiban – similar structure to ligands for GP IIb/IIIa receptor, i.v. adm. effect lasts 2-4 hours

  3. abciximab – monoclonal antibody fragment directed against the receptor, only for high-risk patients, immunogenous

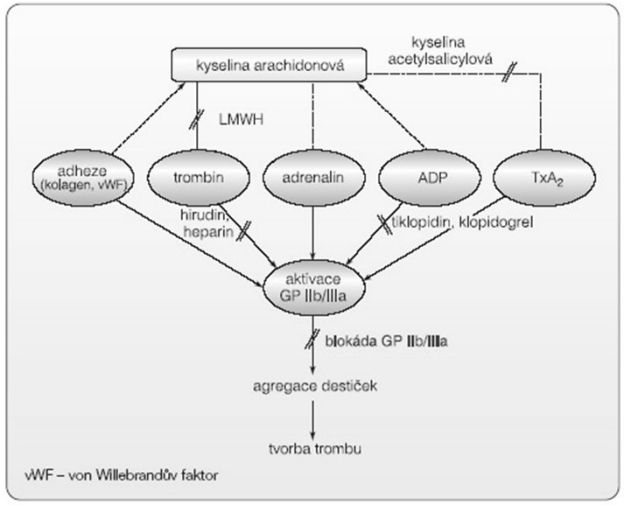
oral active inhibitors – sibrafiban, roxifiban, lefradafiban… – did not pass clinical trials

Antagonisté IIb/IIIa Rc

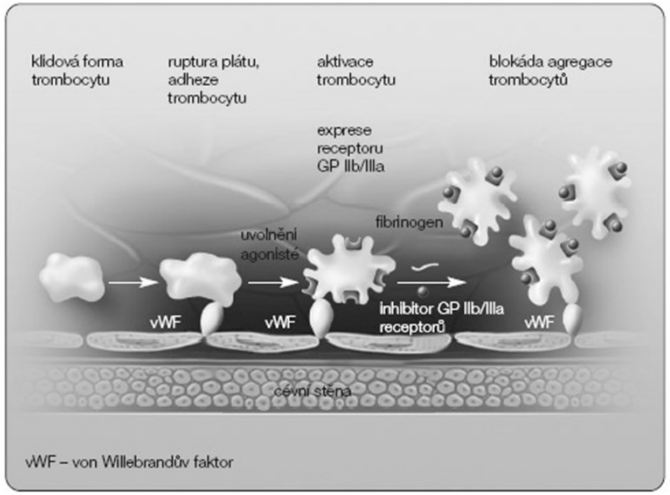
In clinical practise ve have currently available these intravenous drugs: abciximab (ReoPro), tirofiban (Aggrastat) a eptifibatid (Integrilin)

Disadvantage is high price

In our conditions we consider IIb/IIIa blockers indicated in:
- PCI with thrombus in coronar arthery confirmed by angiography
- high-risk patient (with positive troponin, diabetics)
- in intervention on degeneratively changed aortocoronar bypass



Obr. 3 Aktivační kaskáda vedoucí ke shlukování destiček.



Obr. 4 Mechanismus účinku inhibitorů receptorů GP IIb/IIIa.

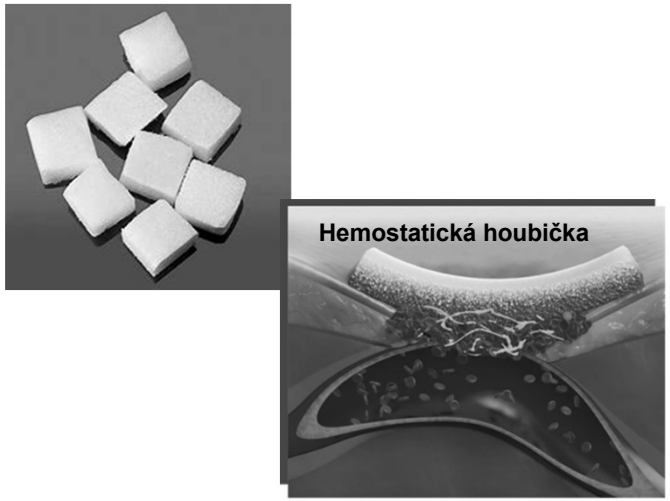
Hemostatics

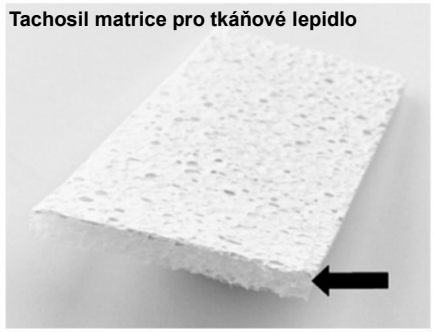
- **Used to control and stop bleeding in injured patients or after surgery or in diseases causing excessive bleeding.**

- **gelatine**
- **gelatine sponge**
- **colagen**
- **etamsylate**
- **vasopresine derivates**

- **frozen blood plasma, human fibrinogen, thrombin, coagulation factors (Novo VII)**

Topical hemostatic		Commercial name
Passive or Mechanical Agents	Gelatins	Surgifoam®, Gelfoam®, Gelfilm®, Gelita-spon®, Geli putty®
	Collagen	Instat®, Helitene®, Helistat®
	Cellulose-based products: oxidized regenerated cellulose	Surgicel Original®, Surgicel Nu-Knit®, Oxycel®, Surgicel Fibrillar®, Interceed®, Gelitacel®
	Cellulose-based products: oxidized cellulose	ActCel®, Gelitacel®
	Polyssacharide hemospheres	Arista™AH
	Adhesives	BioGlue®
Active Agents	Topical thrombin	Thrombin-JMI®, Evithrom®, Recothrom®
	Fibrin sealants	Tisseel®, Evicel®, Crosseal™
Flowable agents	Porcine gelatin + thrombin Bovine collagen + thrombin	Surgiflo®, Floseal®





Hemostatics

Etamsylate (RMP Dicynon):
antihemorrhagic and angioprotective effect
no influence on coagulation factors or fibrinolysis
stimulates trombopoiesis
increase PGI2 synthesis

Vasopresine derivates:
terlipresin → lypresin, ~~ornipresin~~
strong vasoconstriction, decrease of blood flow in splanchnic area (decrease in portal pressure)

note. desmopresin is used in treatment of diabetes insipidus (longer t1/2 than vasopresin) and nykturia in children and adults