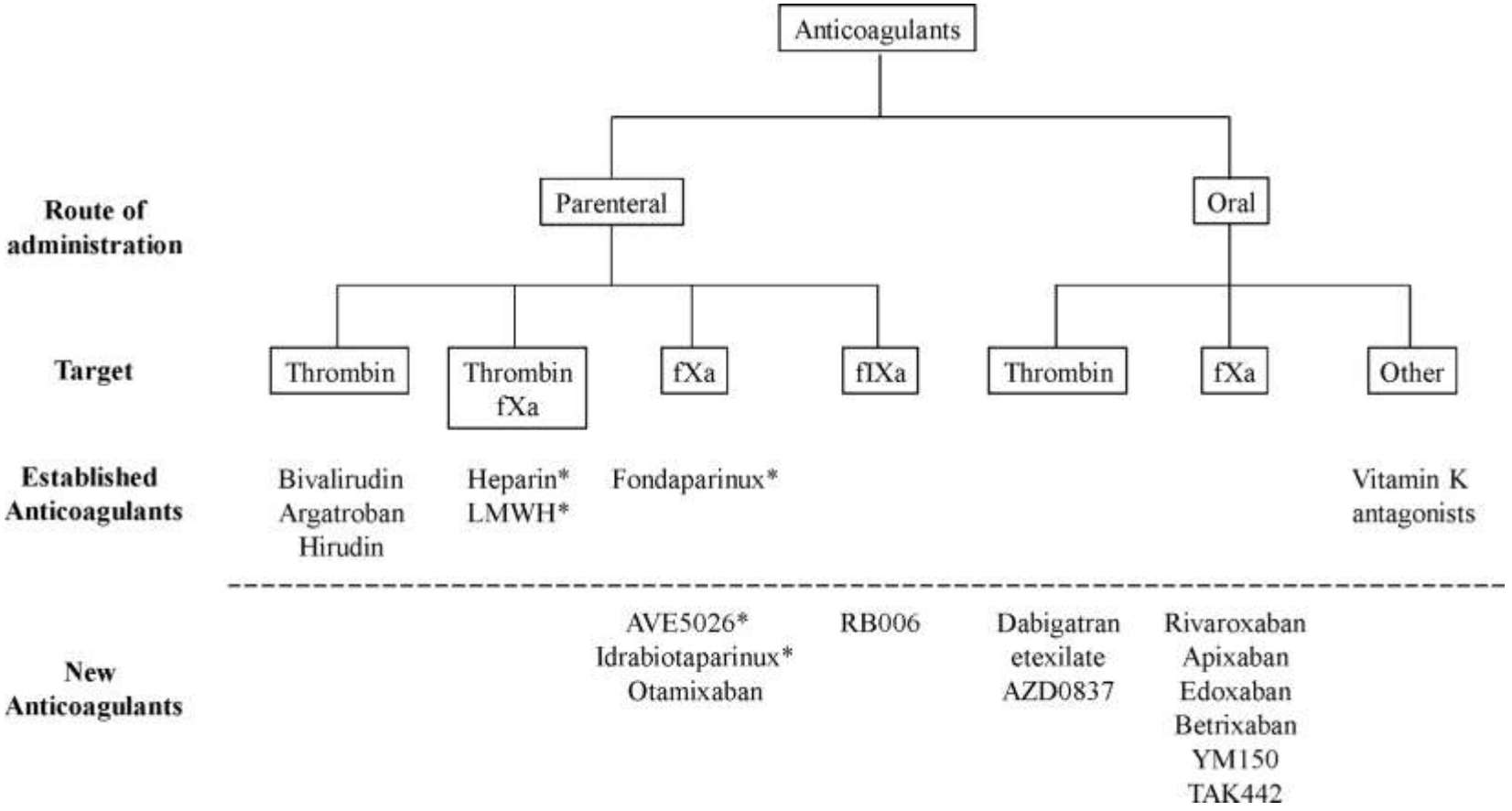
Antikoagulandid, nende toimemehhanismid ja määramine

TIIT SALUM

ELMÜ suvekool 2013

Figure. Classification of established anticoagulants and new anticoagulants that were recently licensed for use or are in advanced stages of clinical development. fIXa indicates factor IXa. *Indirectly inhibit coagulation by interacting with antithrombin. †...



Eikelboom J, Weitz J. Circulation 2010;121:1523-1532

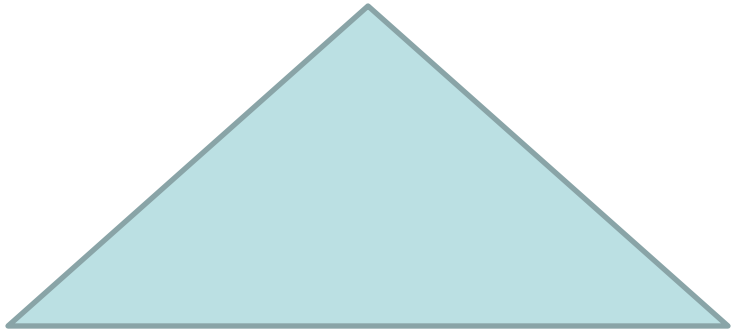
Hüübimismehhanism

Antikoagulantide toime hüübimisele

Määramismeetodid

HÜPERKOAGULATSIOON

Kasvajad, sepsis, trombofiilia

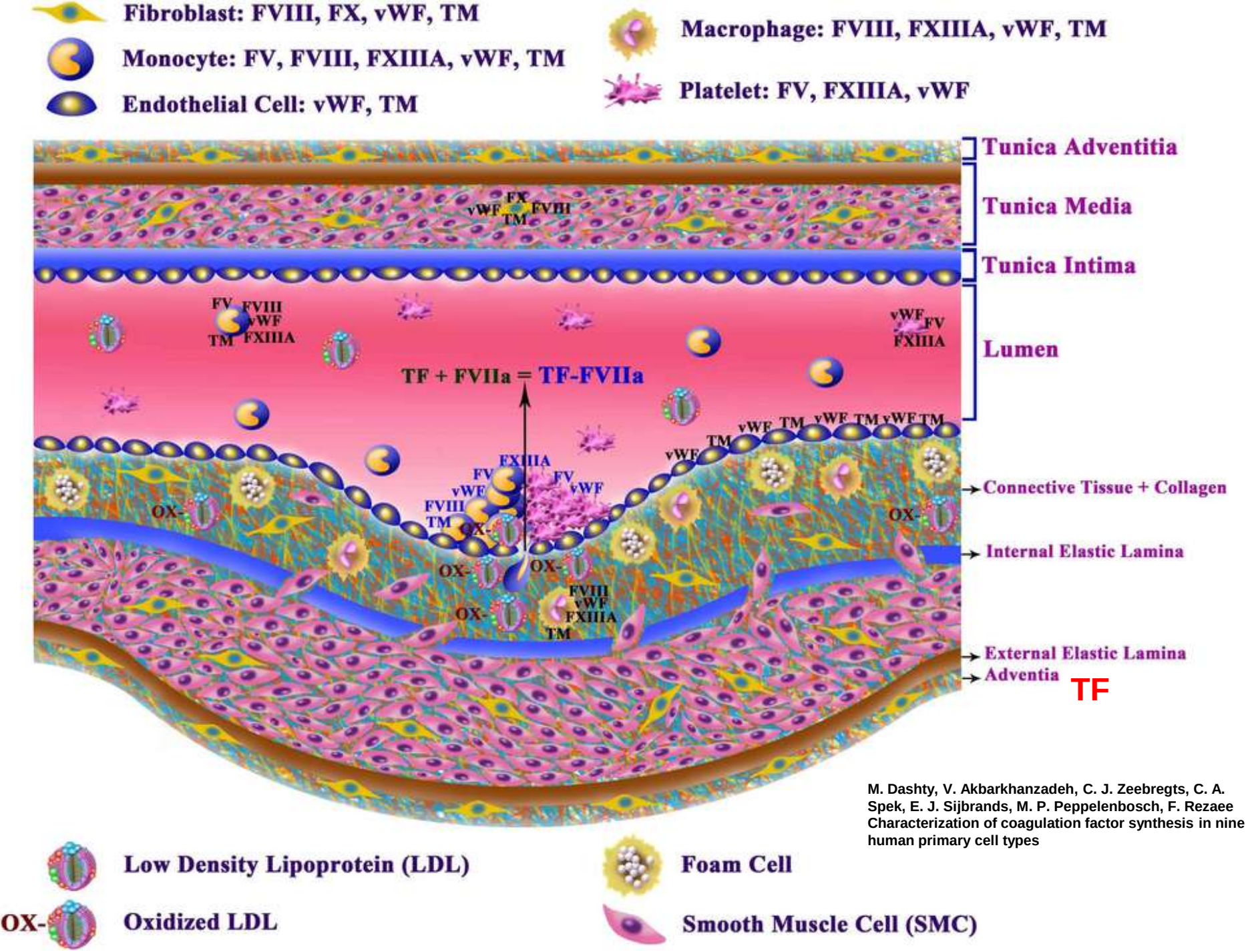


VERESOONE SEINA KAHJUSTUS

Trauma, ateroskleroos

STAAS

Südame töö häired, liikumatus, rasedus, rasvtõbi



M. Dashty, V. Akbarkhanzadeh, C. J. Zeebregts, C. A. Spek, E. J. Sijbrands, M. P. Peppelenbosch, F. Rezaee
Characterization of coagulation factor synthesis in nine human primary cell types

HÜPERKOAGULATSIOON - Trombofiilia:

Kaasasündinud:

Factor V Leiden (aPCR)
Füsioloogiliste antikoagulantide häired – AT III, PC, PS, FXIII mutats., düsfibrinogeneemia

Omandatud:

Antifosfolipiid sündroom – PC inhib., FIIa teke

Hüperlipideemia (oxLDL) – PLT aktivatsioon

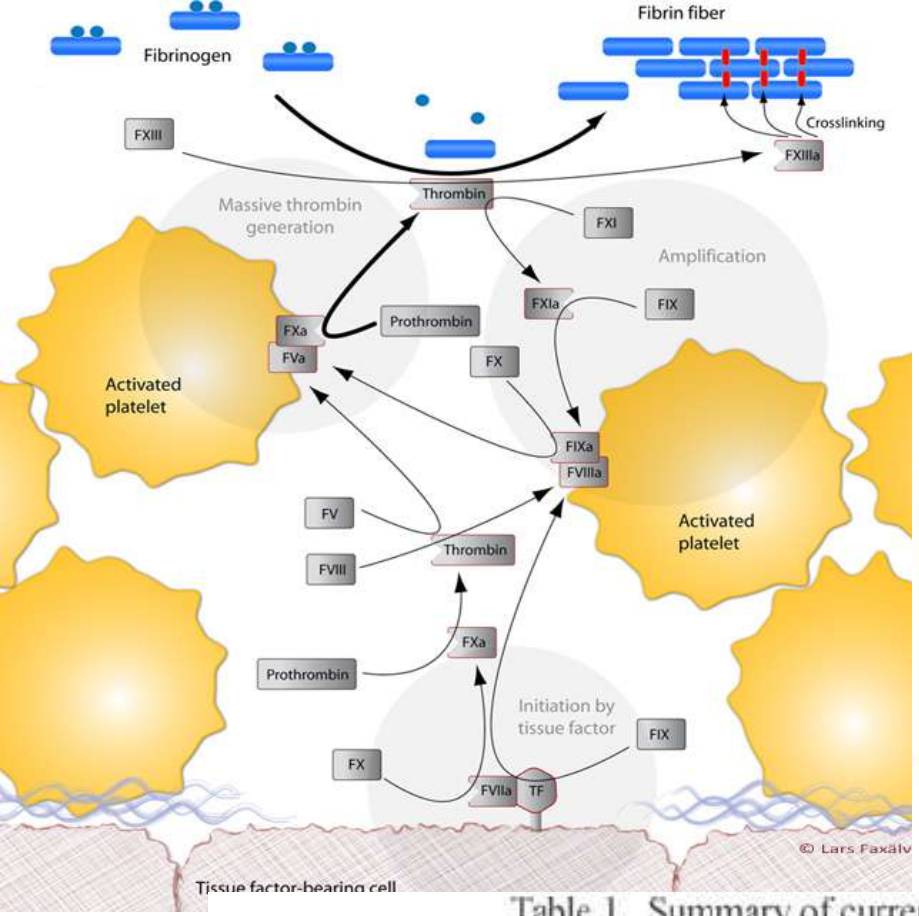
Homotsüsteiini tõus (metab. häire, B6, foolhappe, B12 defitsiit) – endoteeli kahjustus, oxLDL teke, trombomoduliini aktiivsuse langus, TF laadne toime hüübimisele

Suitsetamine – oxLDL teke, NO langus, veresoonte ahenemine

ATEROSKLEROOS – naastu makrofaagid on olulised TF allikad

HÜÜBIMISMEHHANISM

1. Kaskaad
2. Cell based



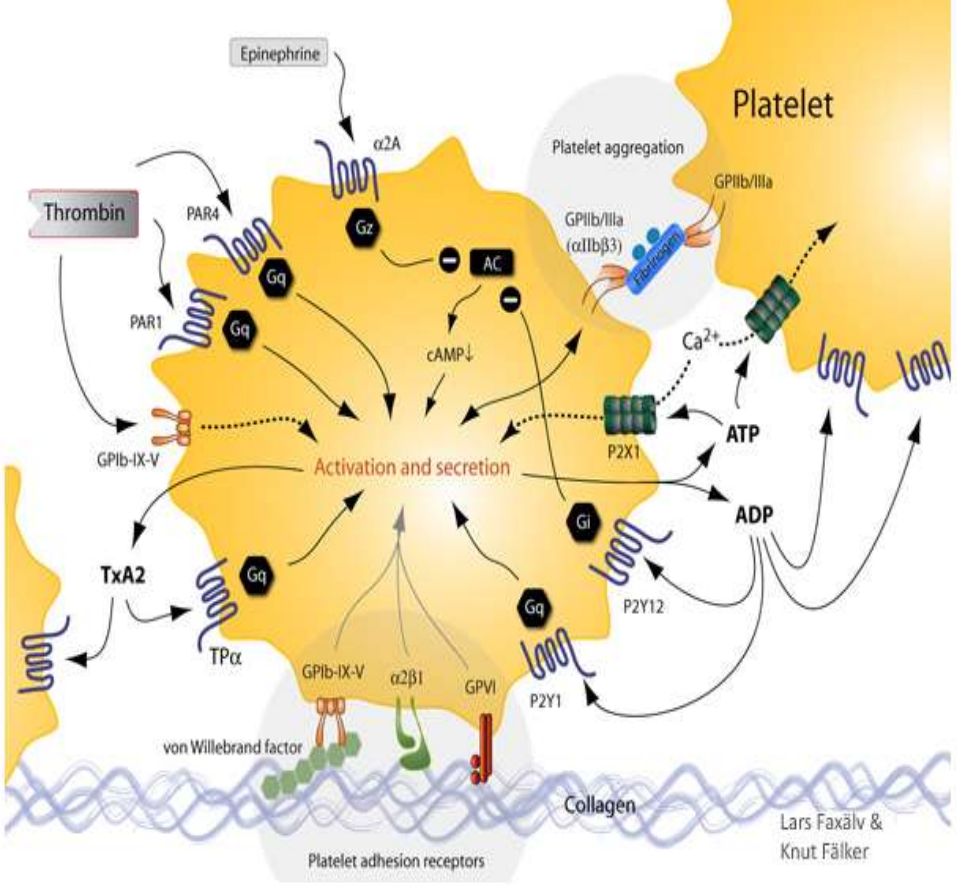
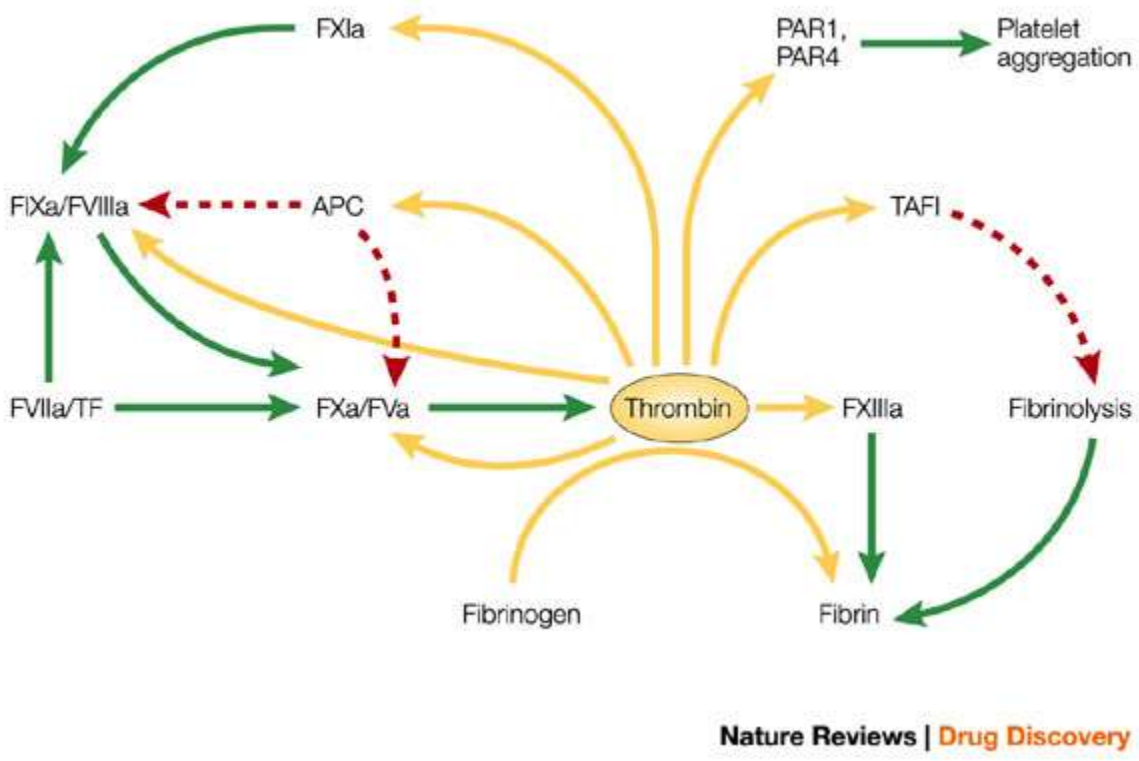


Table 1. Summary of current cell-based model of coagulation

Coagulation phases			
Initiation	Amplification	Propagation	Termination
Vascular endothelium and circulating blood cells are disturbed; Interaction of plasma-derived activated factor VII with tissue factor	Thrombin activates platelets, cofactors V and VIII and factor XI on the surface of platelets	Production of large amounts of thrombin, the formation of a stable buffer at the site of injury and interruption of blood loss	Process of coagulation is restricted to prevent thrombotic occlusion of the intact areas of vessels

Trombiini tähtsus hüübimise regulatsioonis:

1. Fibrinogeen – fibriin
2. FV ja FVIII aktivatsioon
3. FXIII aktivatsioon
4. PLT aktivatsioon
5. Trombomoduliiniga koos PC aktivatsioon



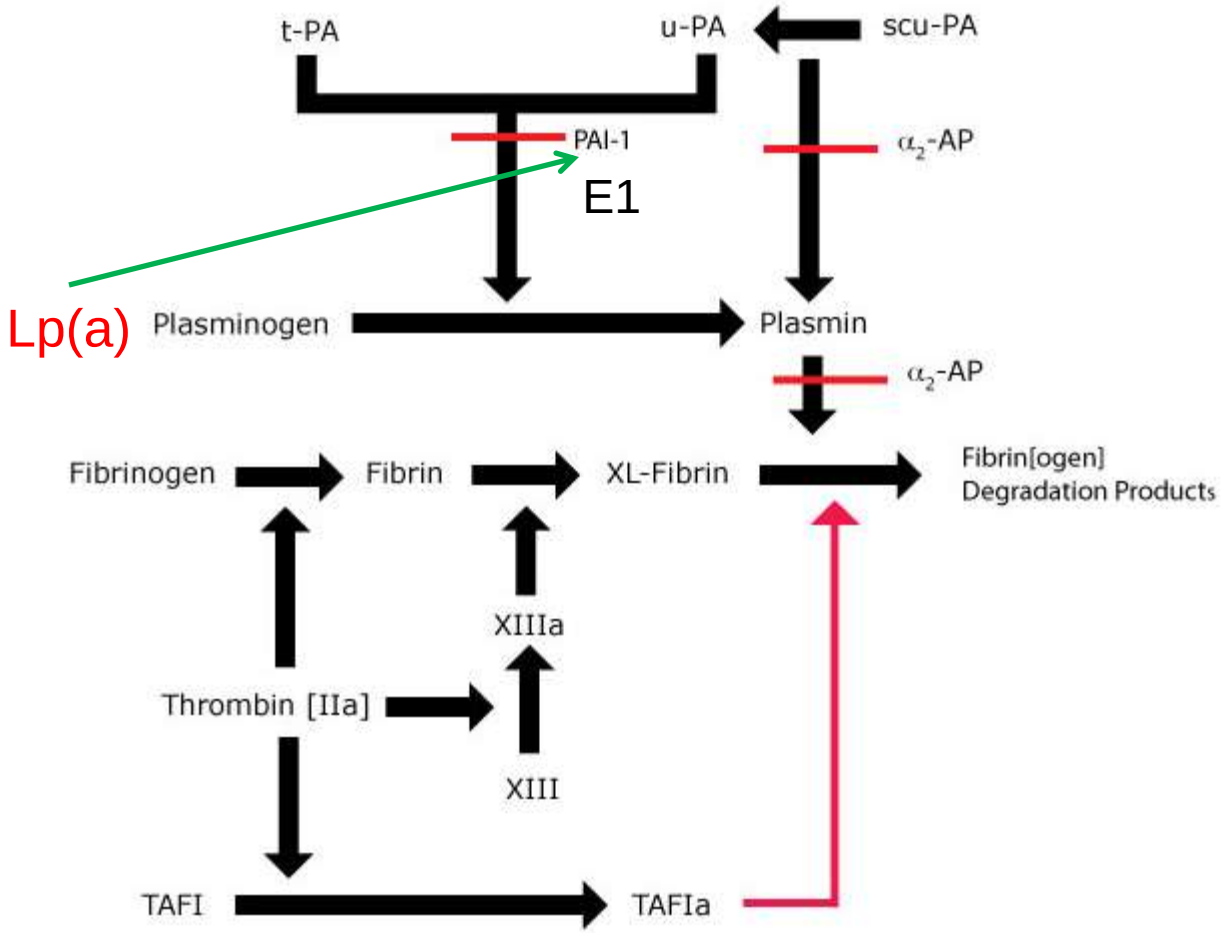
Füsioloogilised antikoagulandid

Seriinproteaaside inhibiitorid

1.Serpin C1 (ATIII) (VIIa+TF; IXa; Xa; XIa; XIIa; trombiin; kallikreiin)
2.Heparin (basofiilid, nuumrakud) koos ATIII

Aktiveeritud koagulatsioonifaktorite neutraliseerijad:
1.Trombomoduliin (trombiin)
2.PC (serpin A5); PS – Va; VIIIa
3.TFPI (TF inhib)

FIBRINOLÜÜS



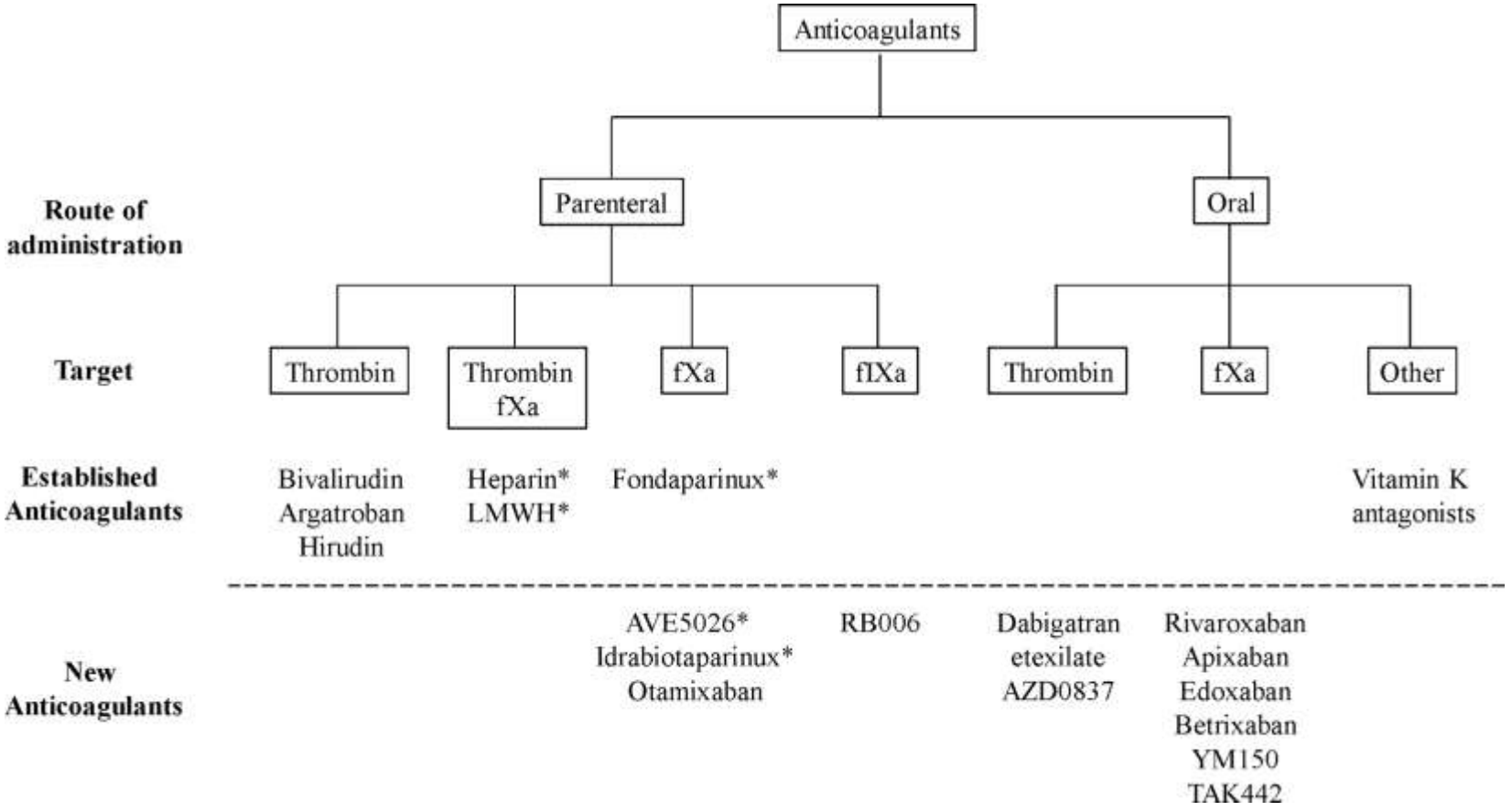
	Venoosne tromb		Arteriaalne tromb
Congenital:	Antithrombin, protein C (protein S) deficiency APC resistance Plasminogen deficiency t-PA decrease or PAI increase	*Congenital:*	Homocystinuria Lpa increase (Protein S deficiency) (APC resistance)
Acquired:	Bed immobilization Trauma Surgery Pregnancy and/or puerperium Oral contraceptives Stasis Cancers Antiblastic i.v. drugs Indwelling catheters APA syndrome	*Acquired:*	Athero-arteriosclerosis Diabetes Oral contraceptives and smoking Polycythemia and other hyperviscosity conditions Thrombocytosis Hypertension Paroxysmal nocturnal hemoglobinuria Sickle cell anemia APA syndrome

Antikoagulantide toime hüübimisele

ANTIKOAGULANDID

1.Varfariin
2.Hepariinid
3.Otsesed FXa inhibiitorid (xabans)
4.Otsesed trombiini inhibiitorid
5.FIXa inhibiitorid

Figure. Classification of established anticoagulants and new anticoagulants that were recently licensed for use or are in advanced stages of clinical development. fIXa indicates factor IXa. *Indirectly inhibit coagulation by interacting with antithrombin. †...



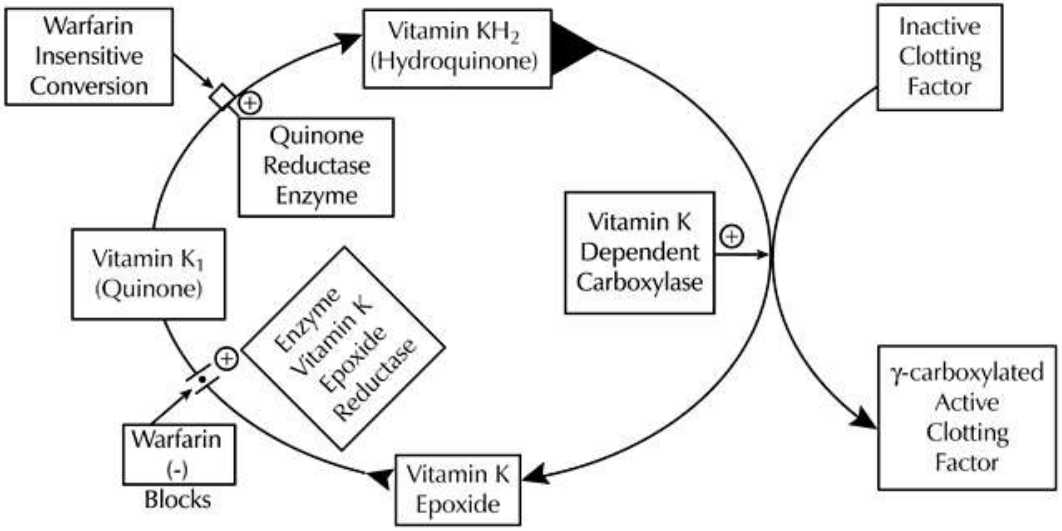
Eikelboom J, Weitz J. Circulation 2010;121:1523-1532

Varfariin toimib vitamiin K-st sõltuvatele hüübefaktoritele (II, VII, IX,X); PC; PS

Vitamiin K on kofaktoriks Glu karboksüülimisel. Tekkinud Gla + Ca^{2+} on vajalik koagulatsiooni faktorite seostumiseks PLT fosfolipiididega

PT aja pikenemine

Toimemehhanism



Vitamin K cycle. Warfarin blocks the conversion of vitamin K epoxide to vitamin C.

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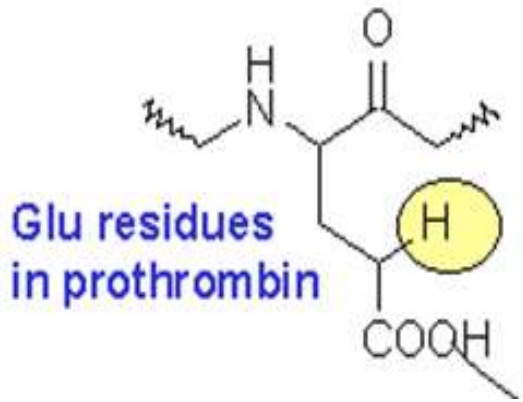
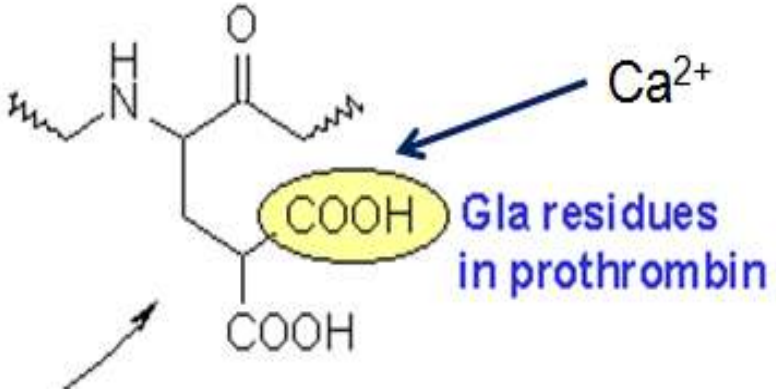
Glu karboksüülimine
Ca seostumine
Ca seostumine PLT fosfolipiididega
Protrombiin trombiin

II, VII, IX, X, PC, PS





HEPARIINID – kaudse Xa toimega (ATIII); FIIa

1. UFH
2. LMWH
3. Hepariini derivaadid

1/3 hepariinist seostub ATIII-ga (Serpin C1)
Suurte dooside puhul toimub seostumine ka HCII-ga (Serpin D1)

Hepariin/AT kompleks inhibeerib:

F IIa (ka Va;VIIIa); Xa ; IXa; XIa; XIIa; TF (LMWH mitte)

Võrreldes LMWH-ga, UFH seostub rohkem plasmavalkudega, endoteeliga, makrofaagidega, seega biosaadavus väheneb ja doosi variaabelsus on suur.

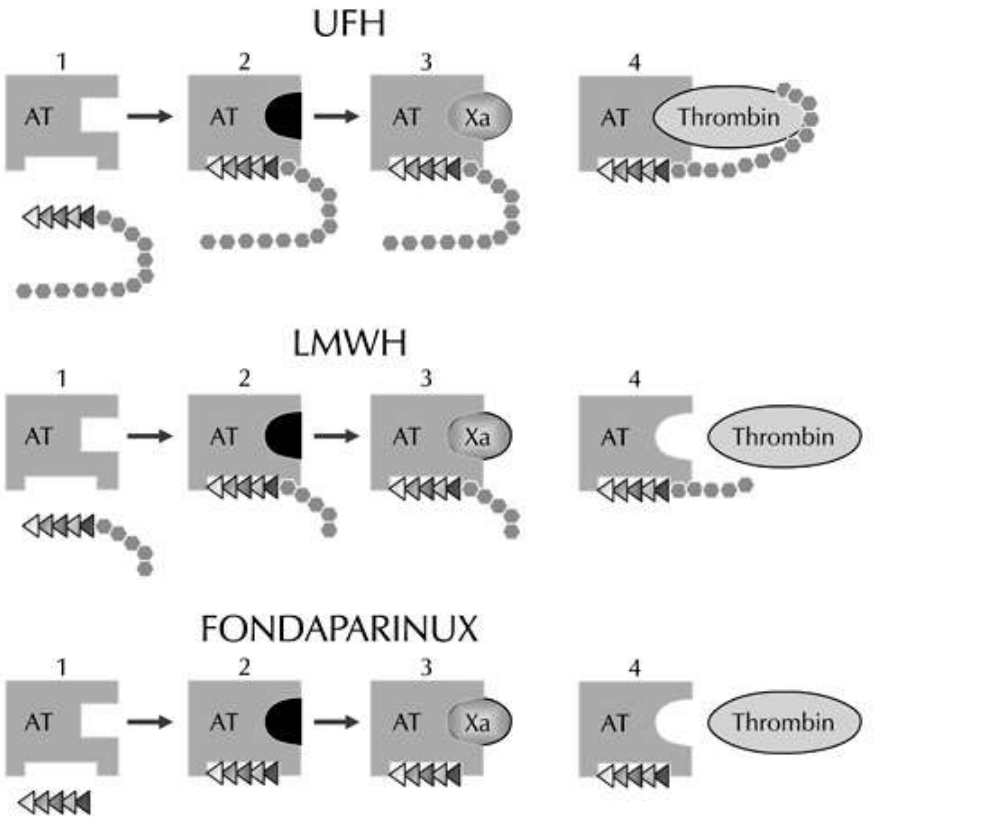


Figure 11-1. Mechanism of action of UFH, LMWH, and fondaparinux. Abbreviations: UFH = unfractionated heparin; LMWH = low molecular weight heparin; AT = antithrombin; Xa = activated factor X.

CD

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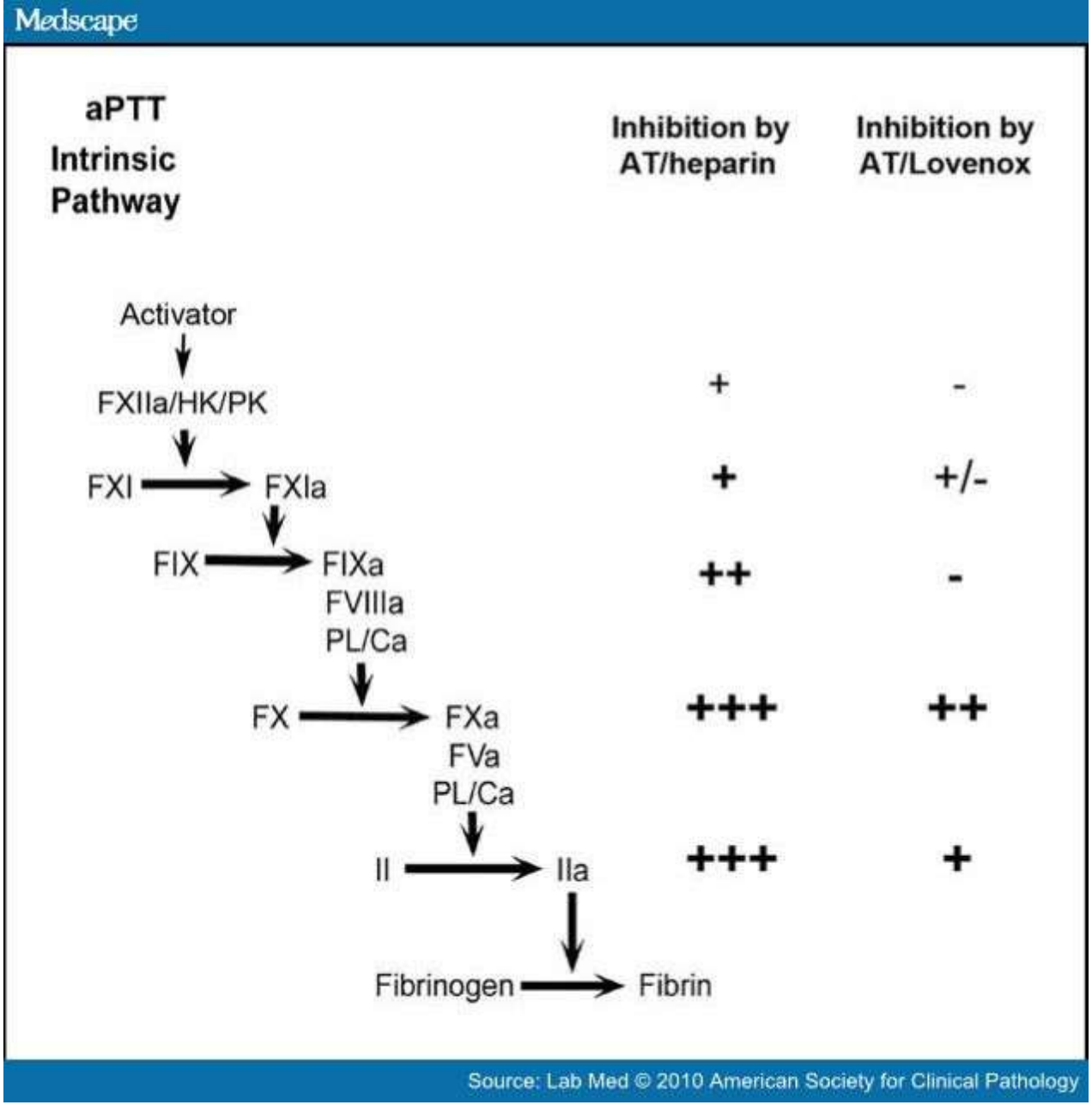
NB! Seostudes trombiiniga inhibeeritakse fibriini teket aga ka trombiini poolt FV ja FVIII aktivatsiooni

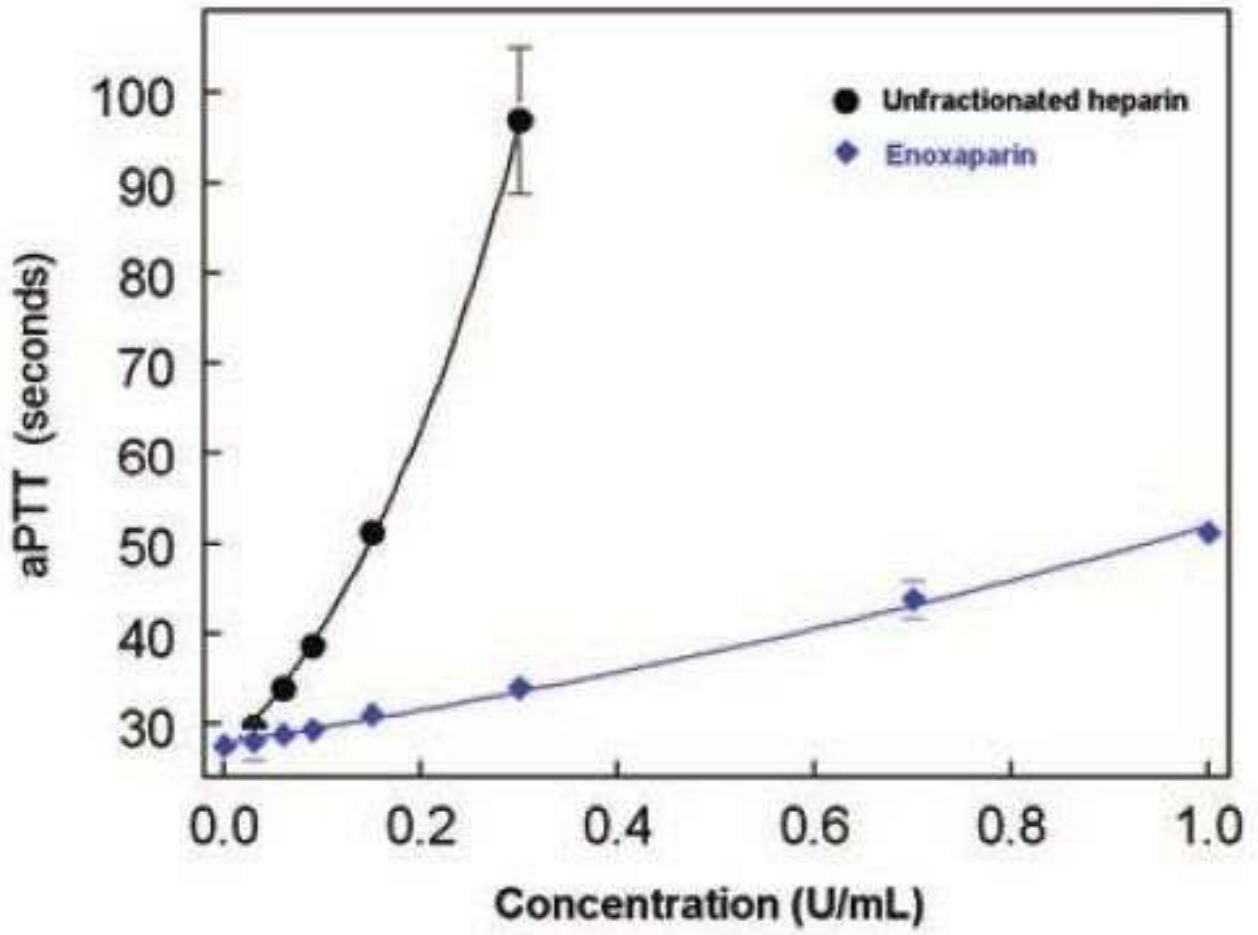
Low-Molecular-Weight Heparins

Anti-Factor Xa : Anti - Factor IIa Ratios

Agent	Trade	Xa:IIa	Mol Wt (d)
Enosaparin	Lovenox	3.8 : 1	4,200
Dalteparin	Fragmin	2.7 : 1	6,000
Ardeparin	Normiflo	1.9 : 1	6,000
Nadroparin		3.6 : 1	4,500
Reviparin		3.5 : 1	4,000
Tinzaparin		1.9 : 1	4,500


Medscape
aPTT
Intrinsic
Pathway
Inhibition by
AT/heparin
Inhibition by
AT/Lovenox
Activator
FXIIa/HK/PK
+
-
FXI
FXIa
+
+/-
FIX
FIXa
FVIIIa
PL/Ca
++
-
FX
FXa
FVa
PL/Ca
+++
++
II
IIa
+++
+
Fibrinogen
Fibrin
Source: Lab Med © 2010 American Society for Clinical Pathology

Medscape



Advantages of LMWH over UH

- No need for laboratory monitoring
  - when given on a weight-adjusted basis, the LMWH anticoagulant response is predictable and reproducible
- Higher bioavailability - 90% vs 30%
- Longer plasma half-life
  - 4 to 6 hours vs 0.5 to 1 hour
  - renal (slower) vs hepatic clearance

Otsesed FXa toimega (xabans)

New Oral Xa Inhibitors

Rivaroxaban

Apixaban

Betrixaban

Edoxaban

TAK-442

PD0348292

LY517717

YM150

Trombiini vastased ained

Trombiinile otseselt toimivad ravimid:

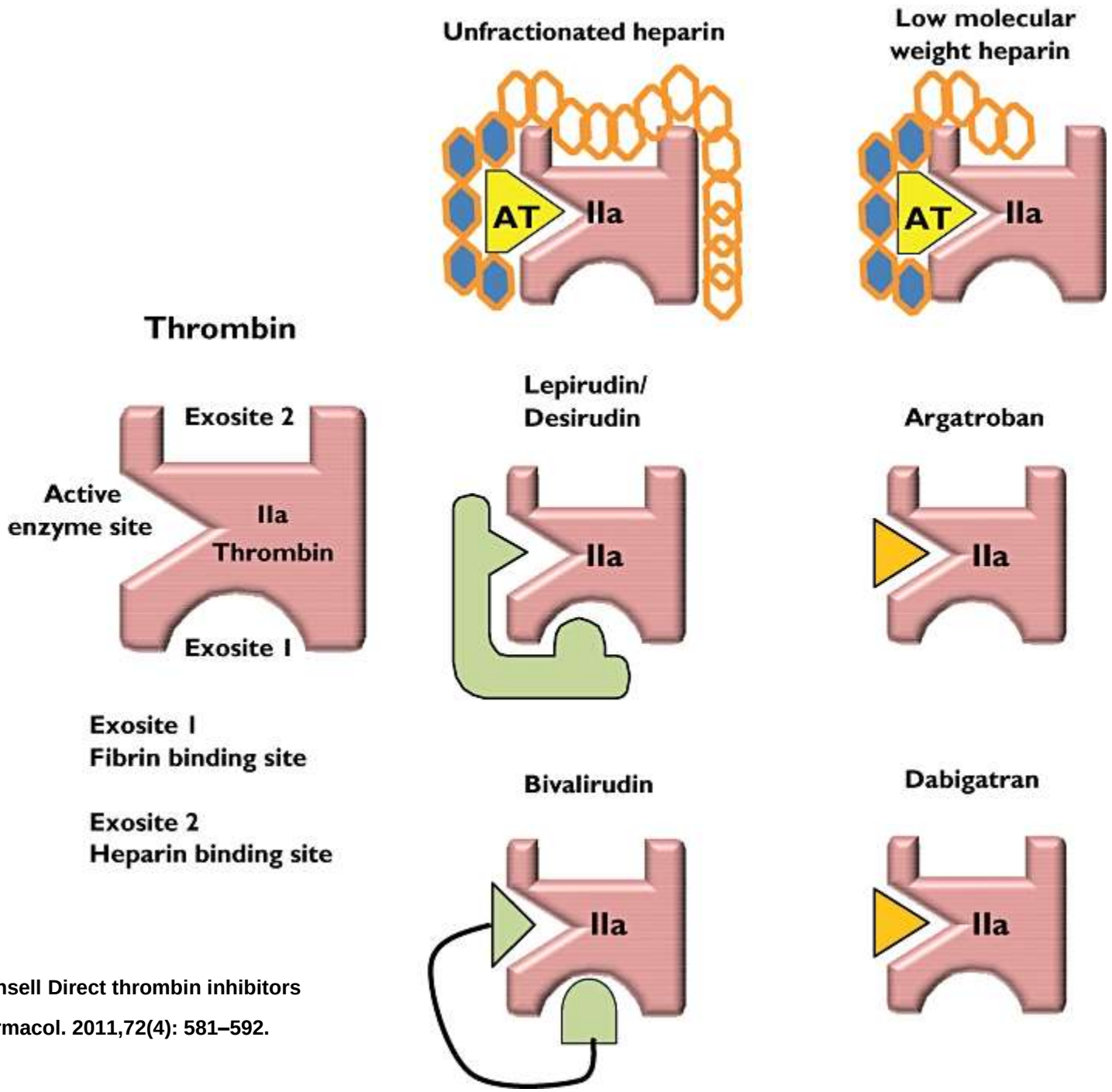
Bivalentsed

Hirudin (lepirudin)
bivalirudin

Univalentsed

argatroban
dabigatran,

NB! Pidurdub fibriini moodustumine ja faktorite XIII, V ja VIII aktivatsioon (V ja VIII kiirendavad trombiini moodustumist)



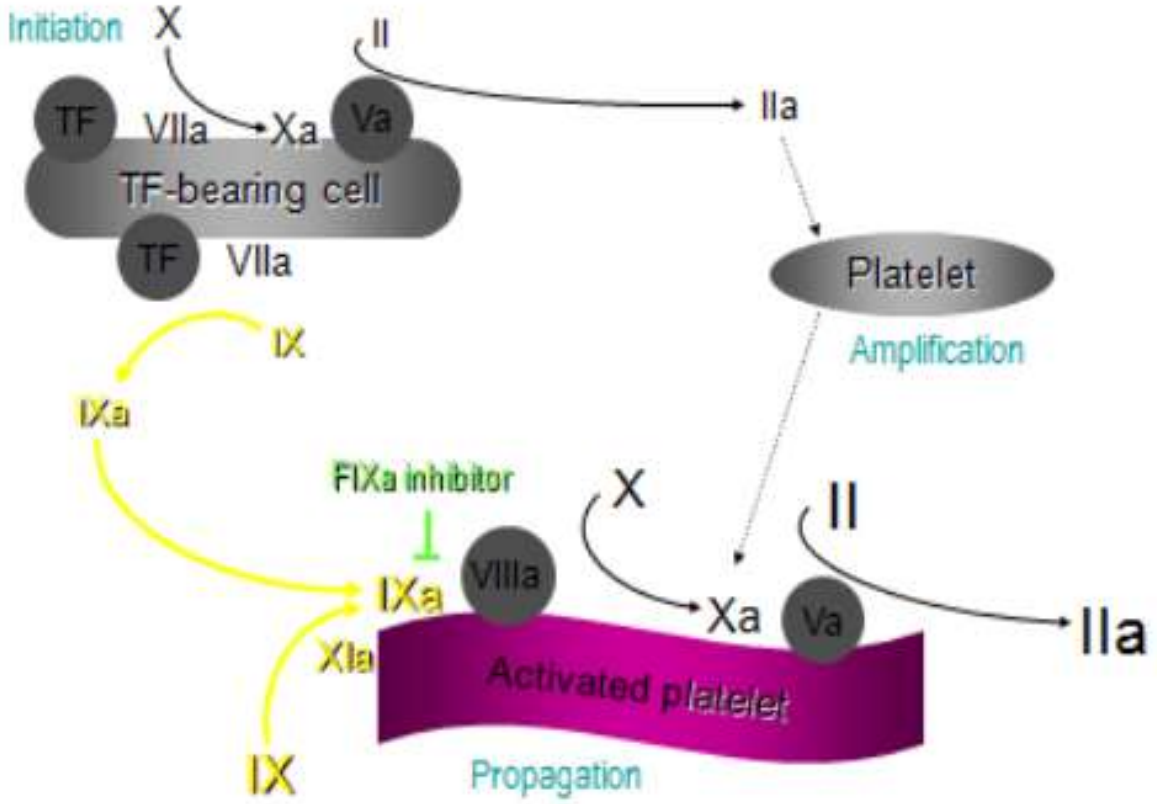
C J Lee, JE Ansell Direct thrombin inhibitors

Br J Clin Pharmacol. 2011,72(4): 581–592.

Rationale for Targeting Factor IXa

- FVIIIa/FIXa activation of FX is the rate limiting step in thrombin generation
  - FIX knockout mice lack occlusive clot formation following vascular injury due to insufficient generation of thrombin to form platelet aggregates.
- FIXa concentration is lower than Xa and thrombin, making high levels of target inhibition more readily achievable
- High Factor IX levels are associated with increase in ACS and venous thromboembolism
  - Transgenic mice overexpressing FIXa have a shorter lifespan and develop arterial thrombosis and myocardial fibrosis with vascular distribution patterns similar to those of ischemic cardiomyopathy in humans
- Hemophilia B Carriers-Reduced CHD Mortality
- Foreign materials (eg. catheters and guidewires) lead directly to FIX activation

Rationale for Targeting FIXa



Monroe DM. Arterioscler Thromb Vasc Biol 2002;22:1381-1389.

Indications for anticoagulant treatment

- Deep Vein Thrombosis
- Pulmonary Embolism
- Myocardial Infarction
- Unstable Angina
- Rheumatic Heart Diseases; Atrial Fibrillation
- Cerebrovascular Diseases
- Defibrination Syndrome
- Vascular Surgery, Prosthetic Heart Valves, Retinal Vessel Thrombosis,
- Extracorporeal Circulation, Haemodialysis

Määramismeetodid

PT test

Välise tee ja ühise tee test (tromboplastiin - TF, fosfolipiid, Ca^{2+}
Varfariinravi kontrolliks (II, VII, X, fibrinogeen, TF)

Varfariin toimib vitamiin K-st sõltuvatele hüübefaktoritele (II, VII, IX,X); PC; PS

aPTT test

sisemise ja ühise tee test (osaline tromboplastiin - Fosfolipiid (kefaliin) – PLT fosfolip. asendaja, pinna-aktivaator (kaoliin, silica) – FXII aktiveerimine, Ca^{2+}

HMWK, Kallikreiin, XII, XI, IX, VIII, X, V, II, fibrinogeen

UFH määramiseks

Kui FVIII; fibrinogeen tõusnud, vajalik anti-Xa määramine (ka ACT)

Activated Clotting Time [ACT] – point-of-care testimiseks

Kontaktaktivats (FXII)

UFH

Monitoring of LMWH

- Unnecessary in majority of patients
- May be useful in specific instances
  - renal insufficiency (creatinine >2.0 mg/dl)
  - obese patients with altered drug pK
  - major bleeding risk factors
- aPTT not useful - low anti-IIa activity
- anti-factor Xa assay is more appropriate, but not widely available

LMWH määramine

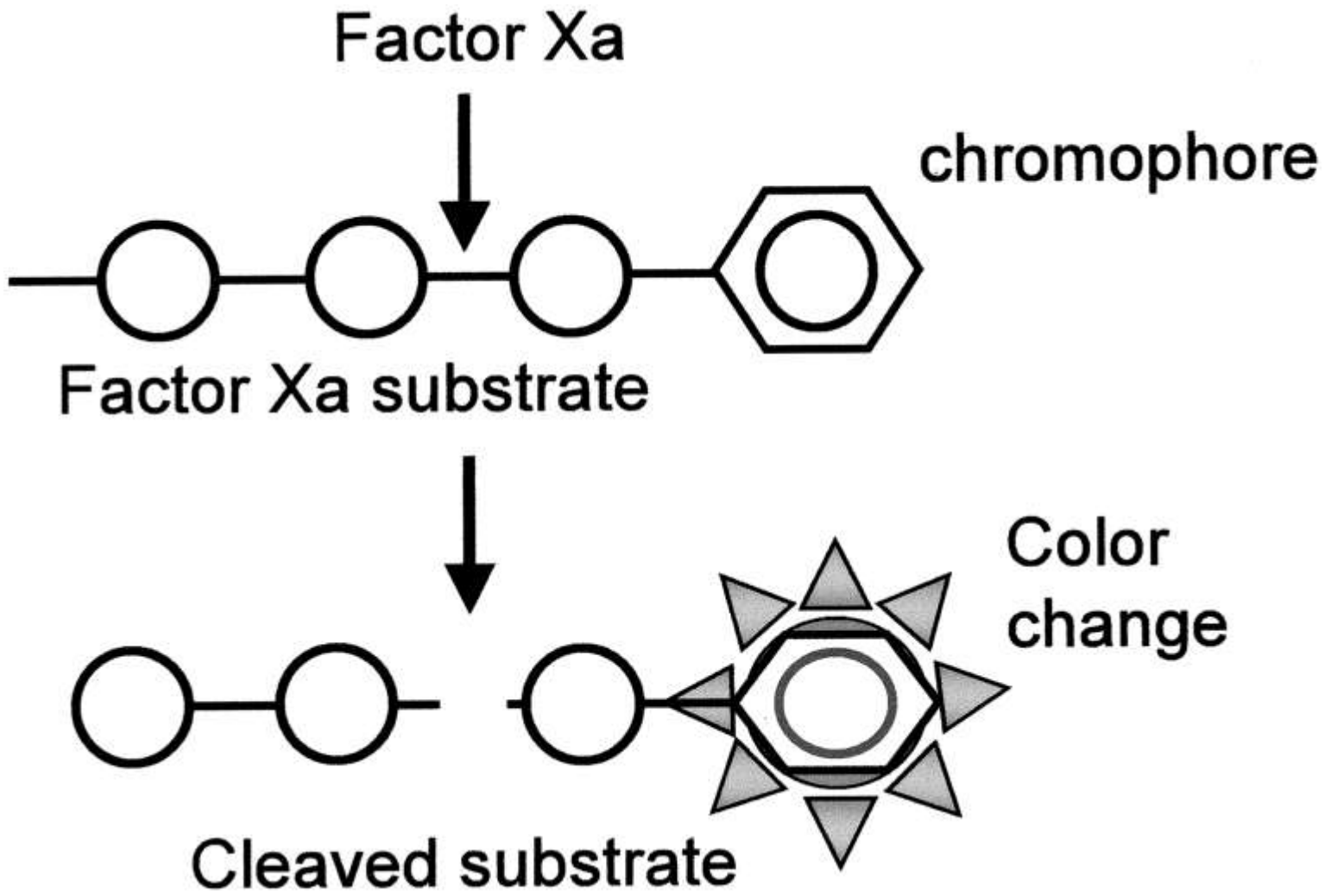
Kromogeenne FXa uuring, (4h peale sc injektsiooni)

aPTT ei sobi (LMWH ei toimi FII ja FIX)

Ei ole mõjutatud teistest koagulatsioonifaktoritest, vit.K mõjutavatest antikoagulantidest,

NB! Used to monitor warfarin in the presence of a lupus anticoagulant, hirudin or argatroban (which prolong the PT and increase the INR), because warfarin decreases factor X (also factors II, VII, IX), and the chromogenic assay has no interference from lupus anticoagulant, hirudin or argatroban

Figure 3. Factor Xa heparin assay.



Bates S M , and Weitz J I Circulation 2005;112:e53-e60

Otsesed trombiini inhibiitorid

Testimine:

1. Hemoclot (diluted thrombin time)
2. Ecarin clotting time, chromogenic assay, ROTEM
3. aPTT (lineaarsus, erinevad ravimid, reagendid)
4. TT – on tundlik kuid ei ole korrelatsiooni doosiga

Ecarin (prothrombin activator) clotting time involves the addition of small amounts to Ecarin to plasma and measuring the time to clot formation i.e. the conversion of fibrinogen to fibrin. Meizothrombin is generated by the Ecarin and cleavage at the Arg323 bond is the rate-limiting step in its formation. In the presence of hirudin, meizothrombin is inhibited and so clot formation is prolonged.