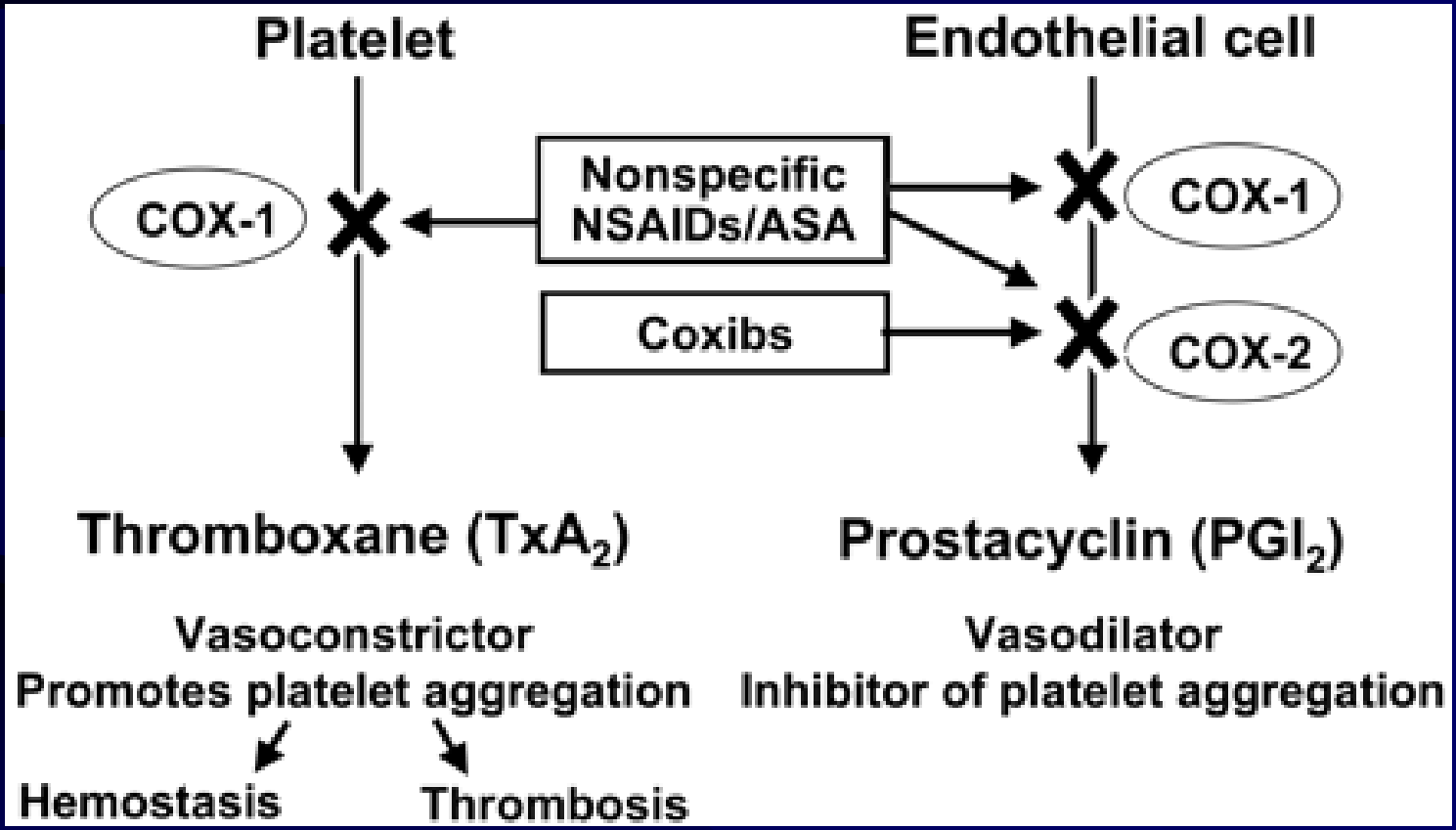
Anticoagulation therapy

J.Chlumský

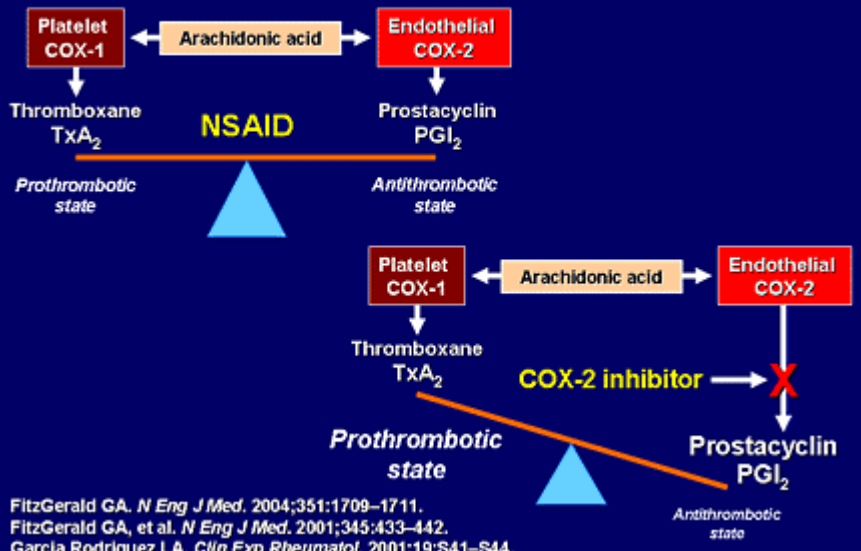
1.Antithrombotic therapy = ASA, ticlodipin, clopidogrel

2.Thrombolytic therapy = streptokinase, TPA

3.Antikoagulation therapy =heparin, warfarin

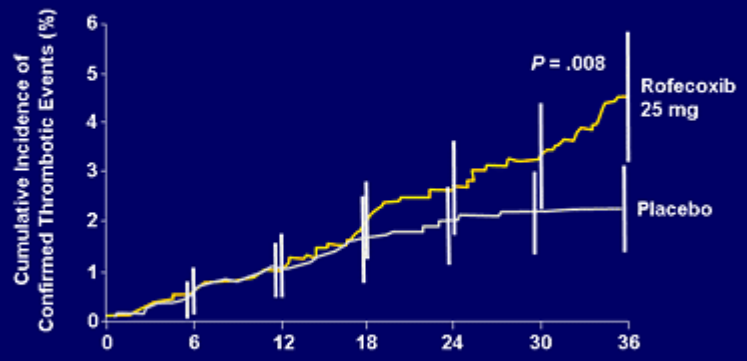

Platelet
Endothelial cell
COX-1
Nonspecific
NSAIDs/ASA
COX-1
Coxibs
COX-2
Thromboxane (TxA_2)
Prostacyclin (PGI_2)
Vasoconstrictor
Promotes platelet aggregation
Vasodilator
Inhibitor of platelet aggregation
Hemostasis
Thrombosis

Mechanism-Based FitzGerald Hypothesis



FitzGerald GA. *N Eng J Med.* 2004;351:1709–1711.
FitzGerald GA, et al. *N Eng J Med.* 2001;345:433–442.
Garcia Rodriguez LA. *Clin Exp Rheumatol.* 2001;19:S41–S44.

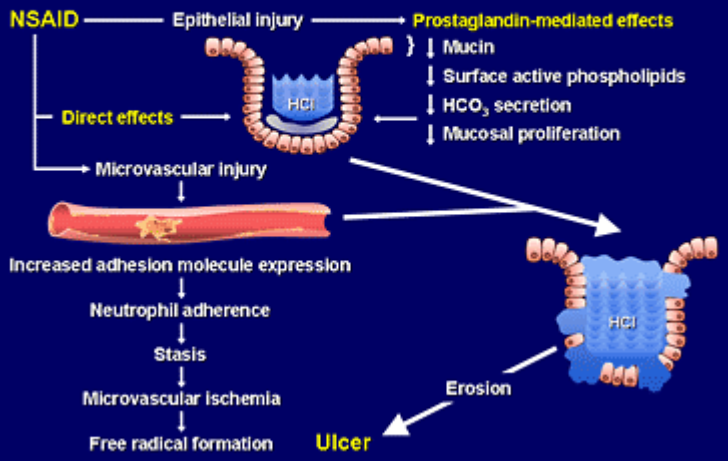
APPROVe Trial: Confirmed Thrombotic Cardiovascular Events Over Time



Patients at Risk:							
Rofecoxib	n =	1287	1129	1057	939	938	896	727
Naproxen	n =	1299	1195	1156	1079	1042	1001	835

Bresalier RS, et al. *N Engl J Med.* 2005;352:1092–1102.

Mechanisms of NSAID-Related Ulcer Formation



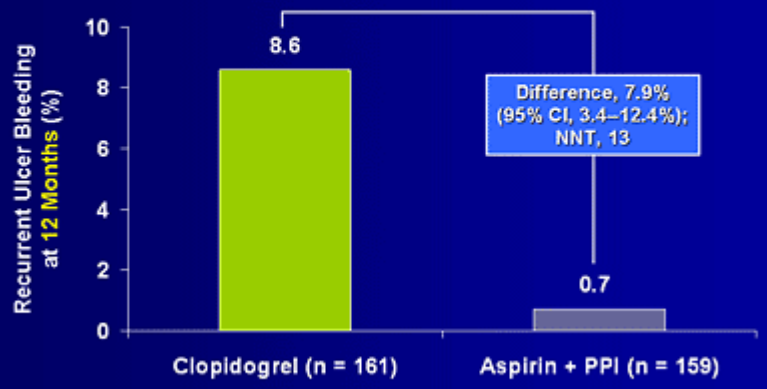
Scheiman JM. *Gastroenterol Clin North Am.* 1996;25:279–298.

Aspirin and NSAIDs: A Common and Potentially Dangerous Combination

Treatment Regimen	Increased Incidence of GI Events Over General Population	95% CI
Low-dose aspirin	2.6	2.2–2.9
Low-dose aspirin + NSAIDs	5.6	4.4–7.0

National cohort study in Denmark of 27,694 people on aspirin 100–150 mg qd.
CI=confidence interval.
Sørensen HT, et al. *Am J Gastroenterol.* 2000;95:2218–2224.

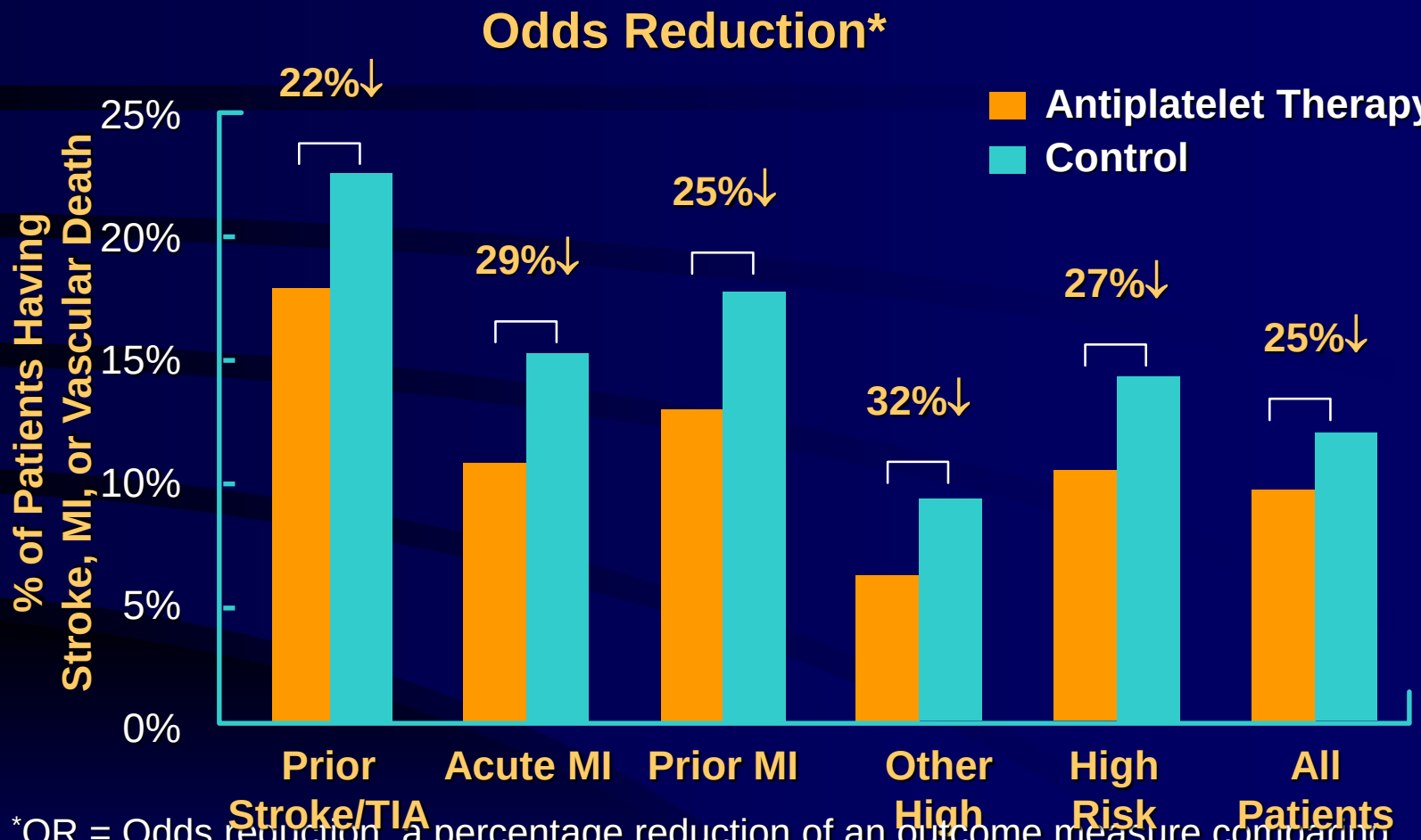
Clopidogrel vs Aspirin + Esomeprazole to Prevent Recurrent Ulcer Bleeding in Low-Dose Aspirin Users



Double-blind, randomized trial of clopidogrel 75 mg qd + placebo bid vs aspirin 80 mg qd + esomeprazole 20 mg bid for 12-months after ulcer healing and *H pylori* eradication.
Chan FK, et al. *N Engl J Med.* 2005;352:238–244.

Antiplatelet Trialists' Collaboration

Efficacy in Prevention of Ischemic Events

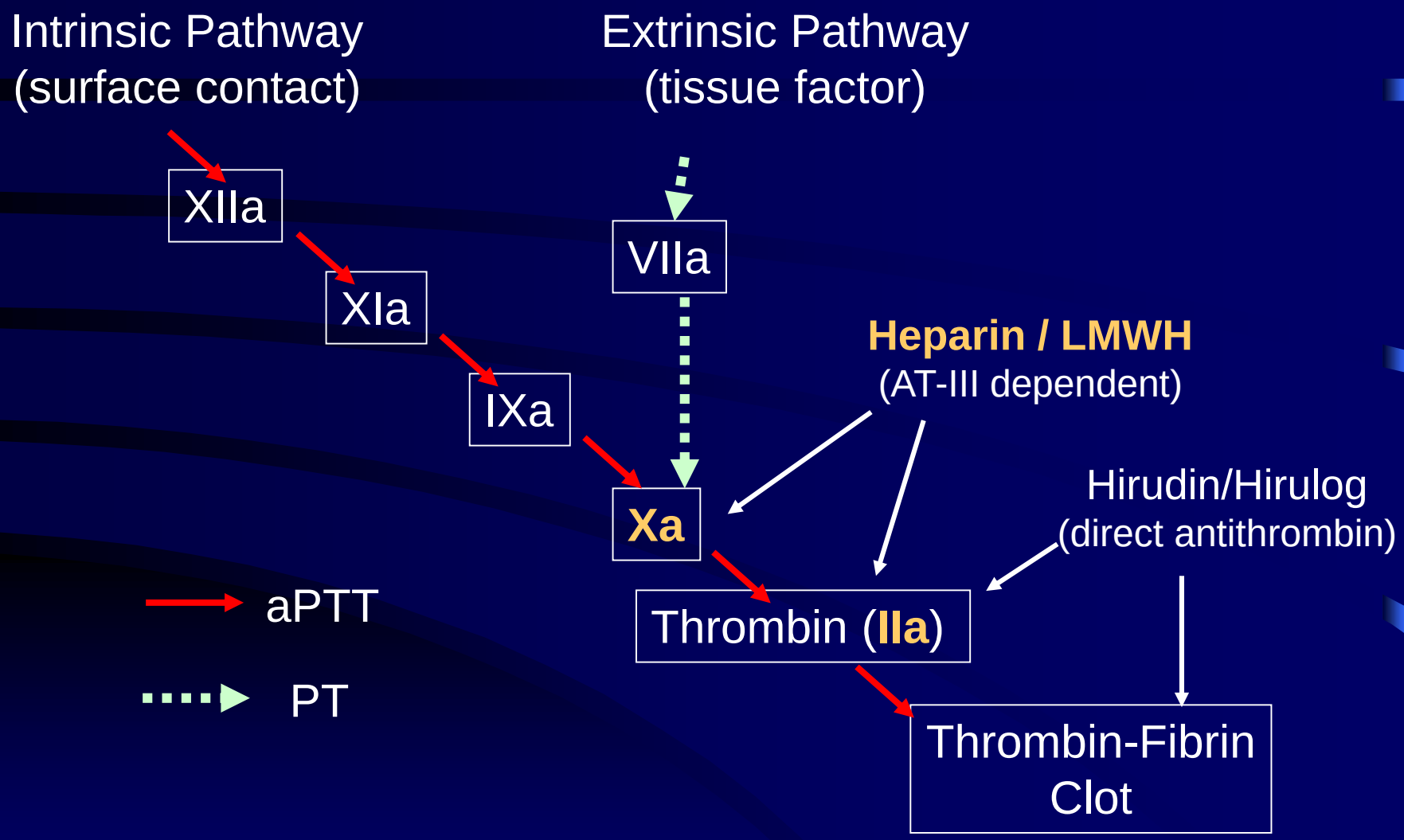


*OR = Odds reduction, a percentage reduction of an outcome measure comparing treatment to control group. Antiplatelet Trialists' Collaboration. *BMJ*. 1994;308:81–106.

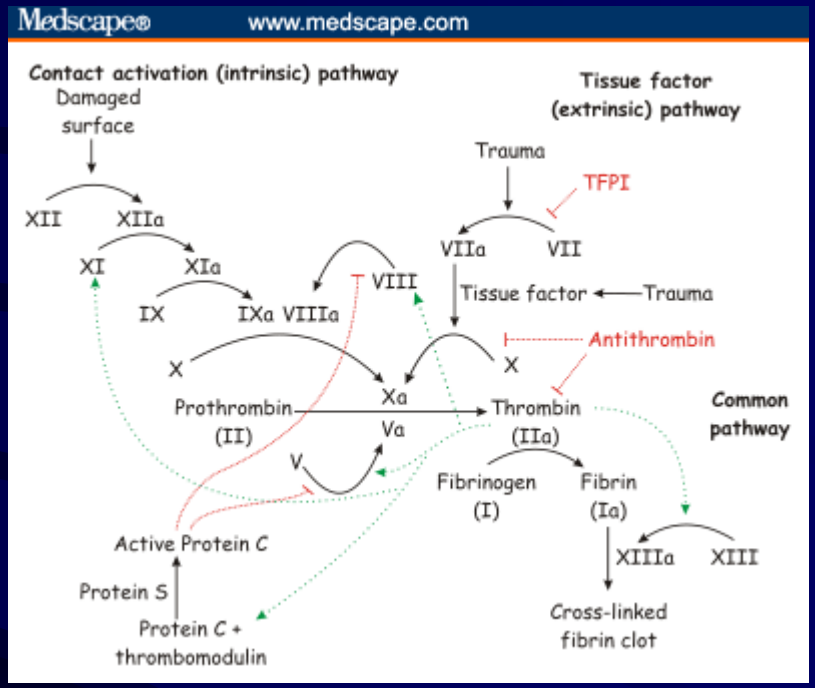
ASA – 7 days,
indobufen- 12 h

ticlopidin - neutropenia
clopidogrel - resistence
prasugrel

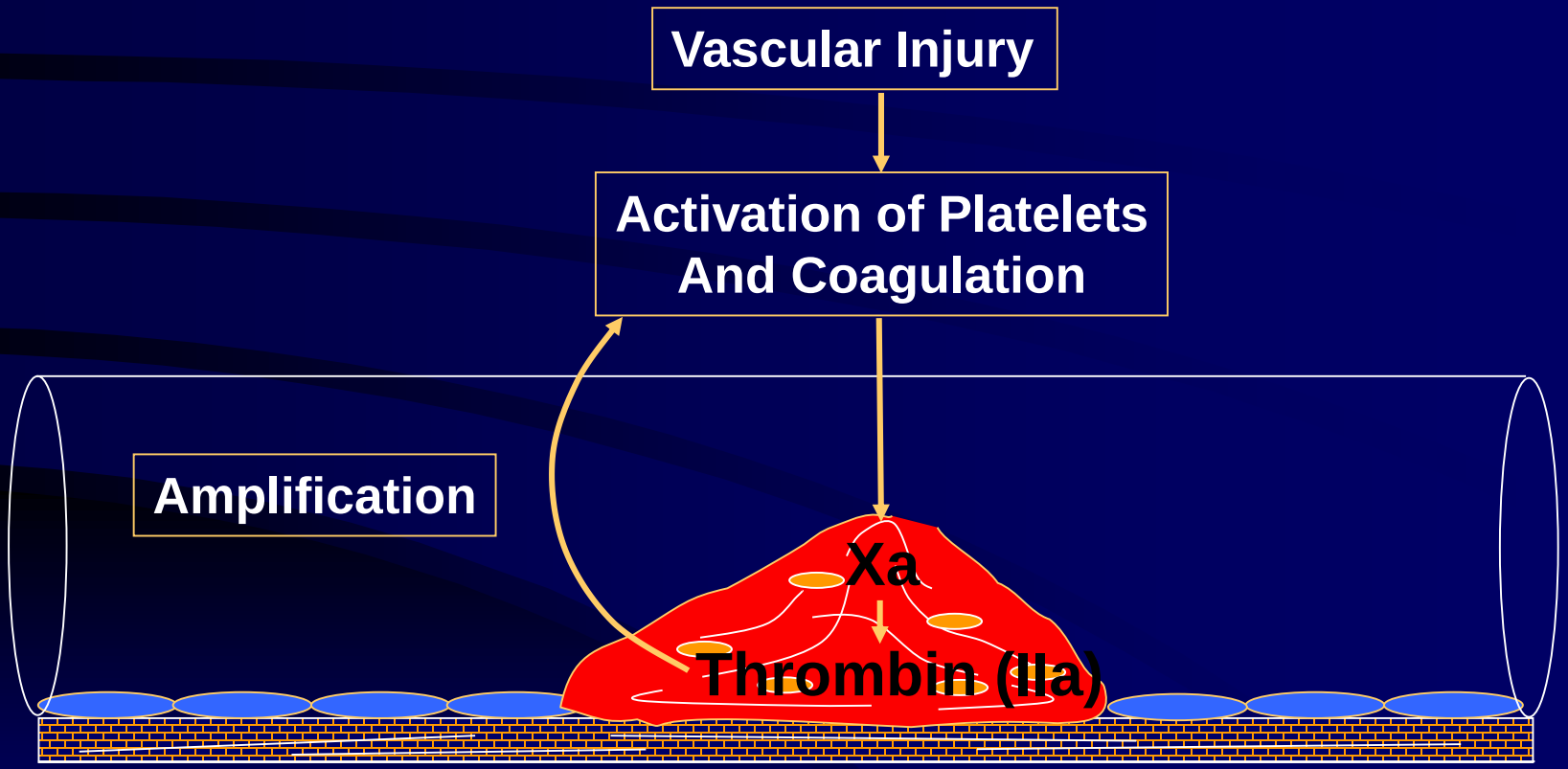
Coagulation Cascade



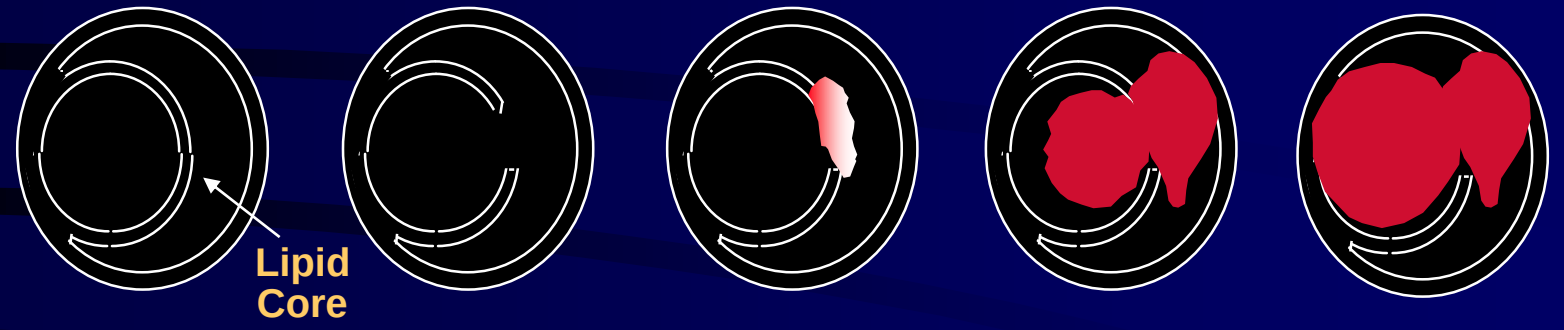
Courtesy of VTI


Medscape®
www.medscape.com
Contact activation (intrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
VIII
X
Prothrombin (II)
Xa
Va
V
Active Protein C
Protein S
Protein C + thrombomodulin
Tissue factor (extrinsic) pathway
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
Antithrombin
X
Thrombin (IIa)
Common pathway
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked fibrin clot

The Procoagulant State in Thrombolysis



Role of Platelets in Thrombus Formation in Acute Ischemic Events



Vessel wall injury → Plaque rupture → Exposure of subendothelial collagen and other platelet-adhering ligands

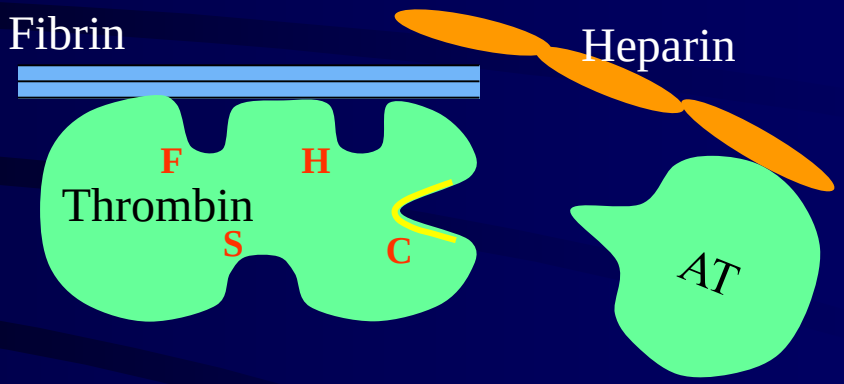
MI

Stroke

Vascular Death

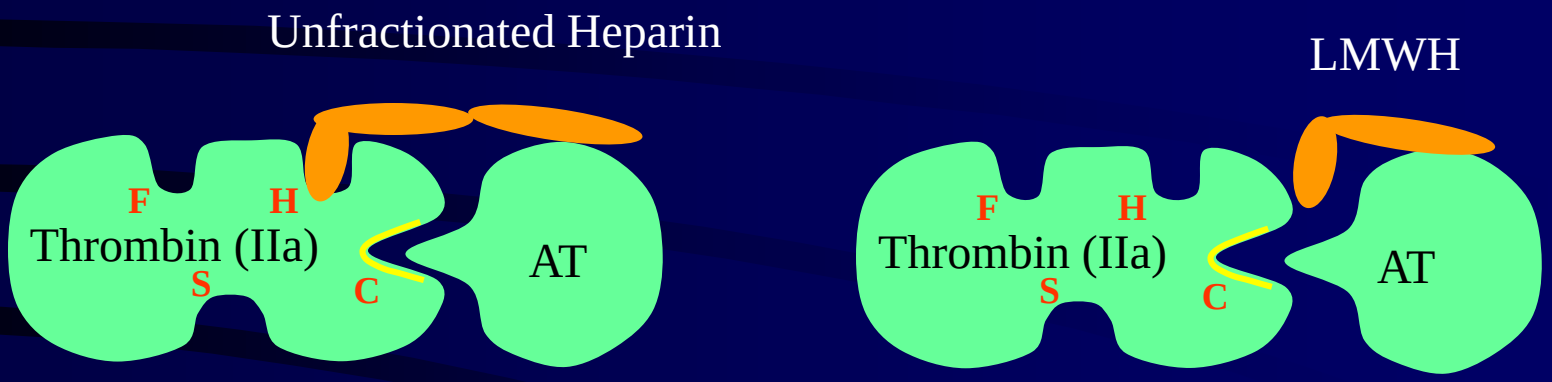
Schafer AI. *Am J Med*. 1996;101:199–209.

Inactivation of Thrombin by Heparin-AT Complexes



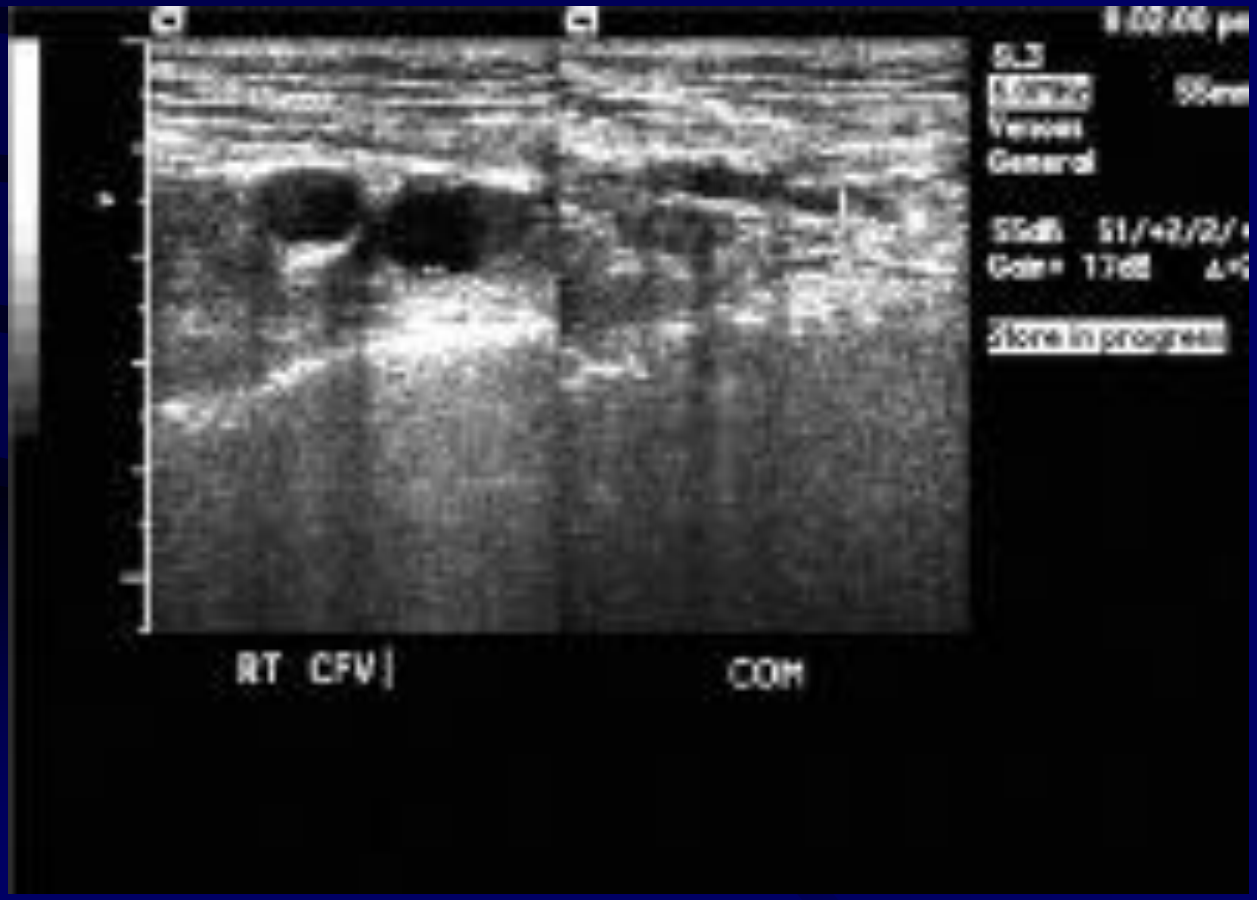
When thrombin binds to fibrin, it becomes resistant to inactivation by heparin.

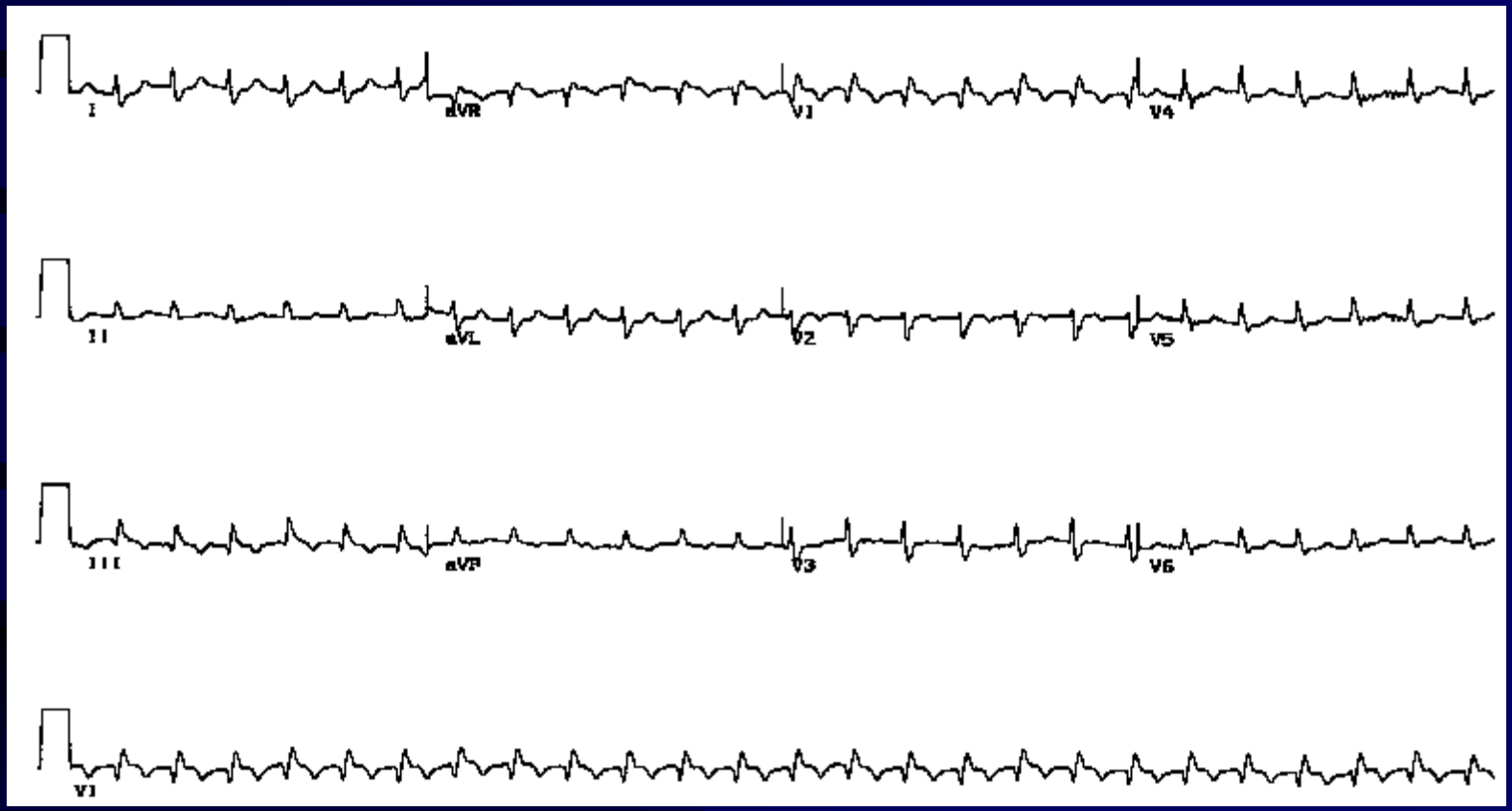
Differential inhibitory activity against factor Xa and IIa activity

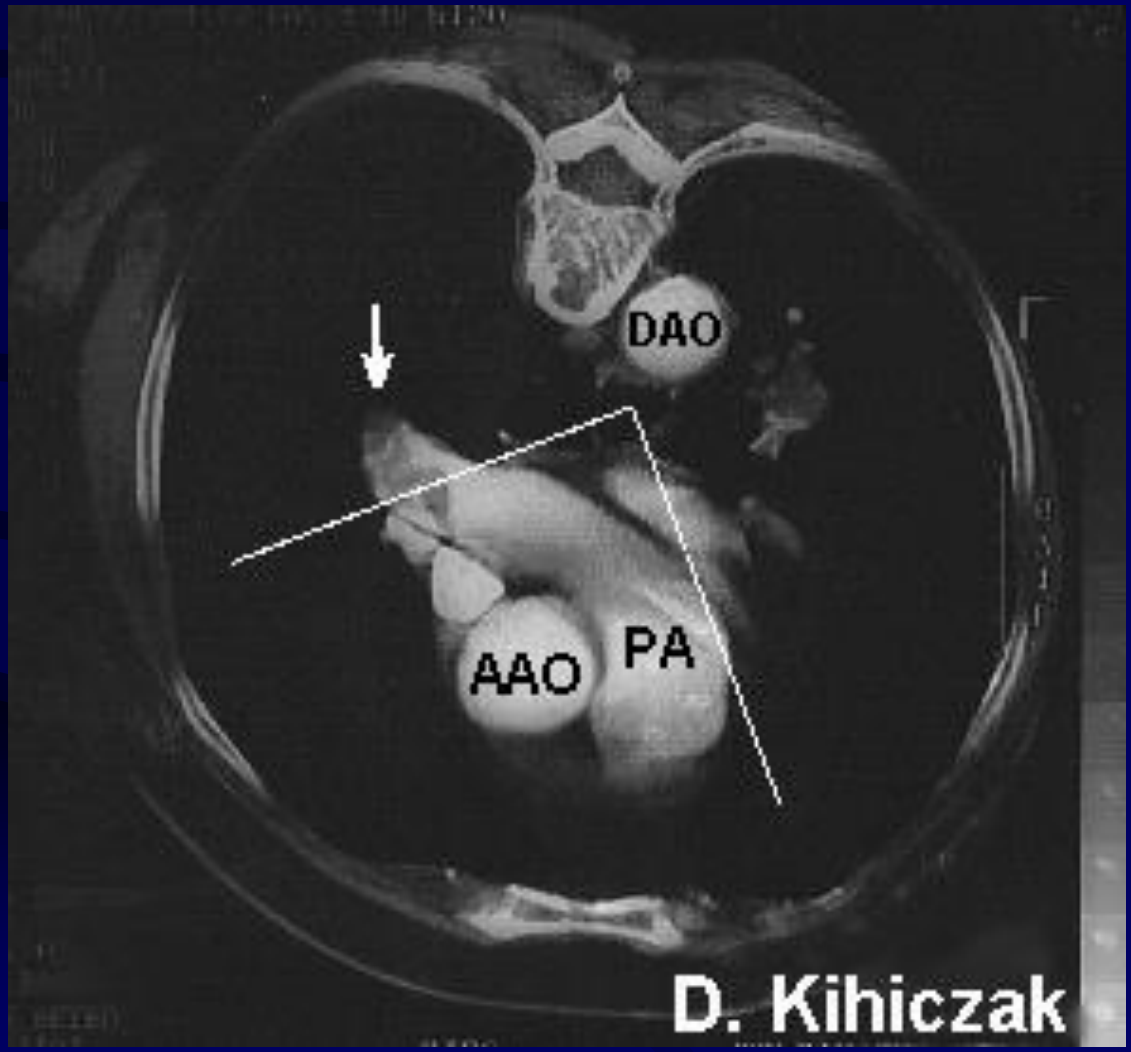


By binding to AT, most UH and LMWH can inhibit Xa activity. Fewer than half the chains of LMWH are of sufficient length to also bind factor IIa, therefore has decreased anti-IIa activity.

DUS

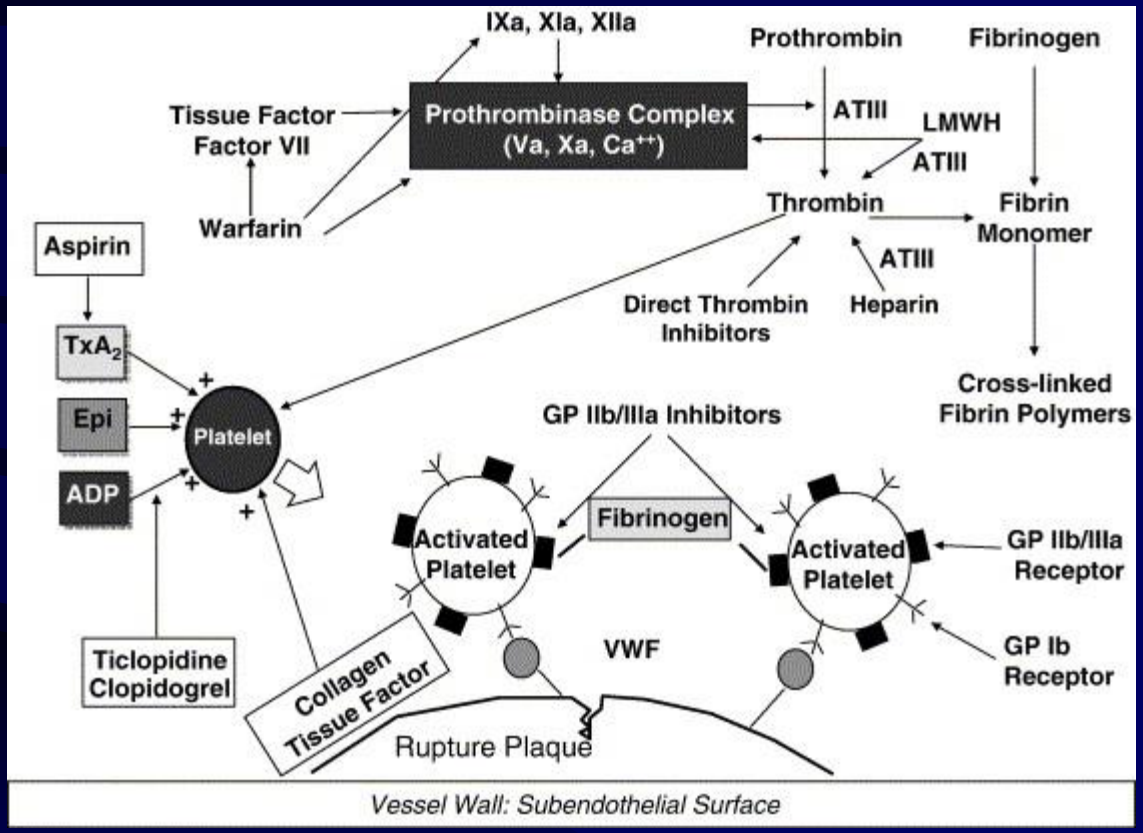



I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1


DAO
AAO
PA
D. Kihiczak

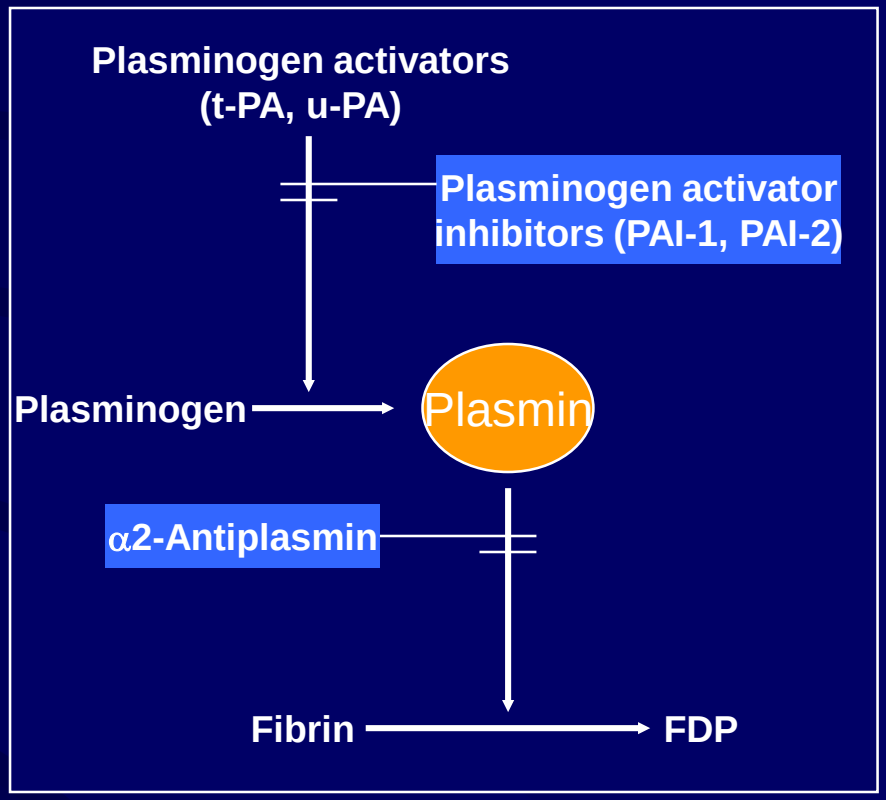
anticoagulation therapy

DVT after surgery	3 m
DVT, PE	6 m
DVT+ tumor, protein C or S deficiency	6-18 m
DVT + AT III def., homozygot aPC,	Long live


IXa, XIa, XIIa
Prothrombin
Fibrinogen
Tissue Factor
Factor VII
Prothrombinase Complex
(Va, Xa, Ca++)
ATIII
LMWH
ATIII
Warfarin
Thrombin
Fibrin
Monomer
Aspirin
ATIII
Direct Thrombin
Inhibitors
Heparin
TxA2
Epi
ADP
Platelet
GP IIb/IIIa Inhibitors
Cross-linked
Fibrin Polymers
Activated
Platelet
Fibrinogen
Activated
Platelet
GP IIb/IIIa
Receptor
Ticlopidine
Clopidogrel
Collagen
Tissue Factor
VWF
GP Ib
Receptor
Rupture Plaque
Vessel Wall: Subendothelial Surface

Physiologic Fibrinolytic System (plasmin - key to fibrinolysis)

- **Plasminogen**
  - synthesized in the liver
  - circulates in high concentrations
  - significant homology with LP(a)
- **Plasminogen Activator**
  - t-Pa and u-PA released by endothelium
  - converts plaminogen to plasmin
  - fibrin surface facilitates fibrinolysis by providing the binding site for the formation of plasminogen-tPA complex
  - free floating t-PA has low activity
- **Fibrinolytic Inhibitor**
  - PAI-1 is the main inhibitor of tPA & uPA



Thrombolytic therapy

Streptokinase: 250 000 j bolus
and 1 250 000 j /l h
or 100 000 j/ h 24-48 h

tPA: 15 mg bolus, 50 mg l h,
35 mg l h

Indication

IM
pulmonary embolism

local – leg embolism or trombosis