MODELE CELLULAIRE DE LA COAGULATION

Martial Hamon, MD, FESC
University Hospital of Caen

Disclosure Statement

Affiliation/Financial Relationship

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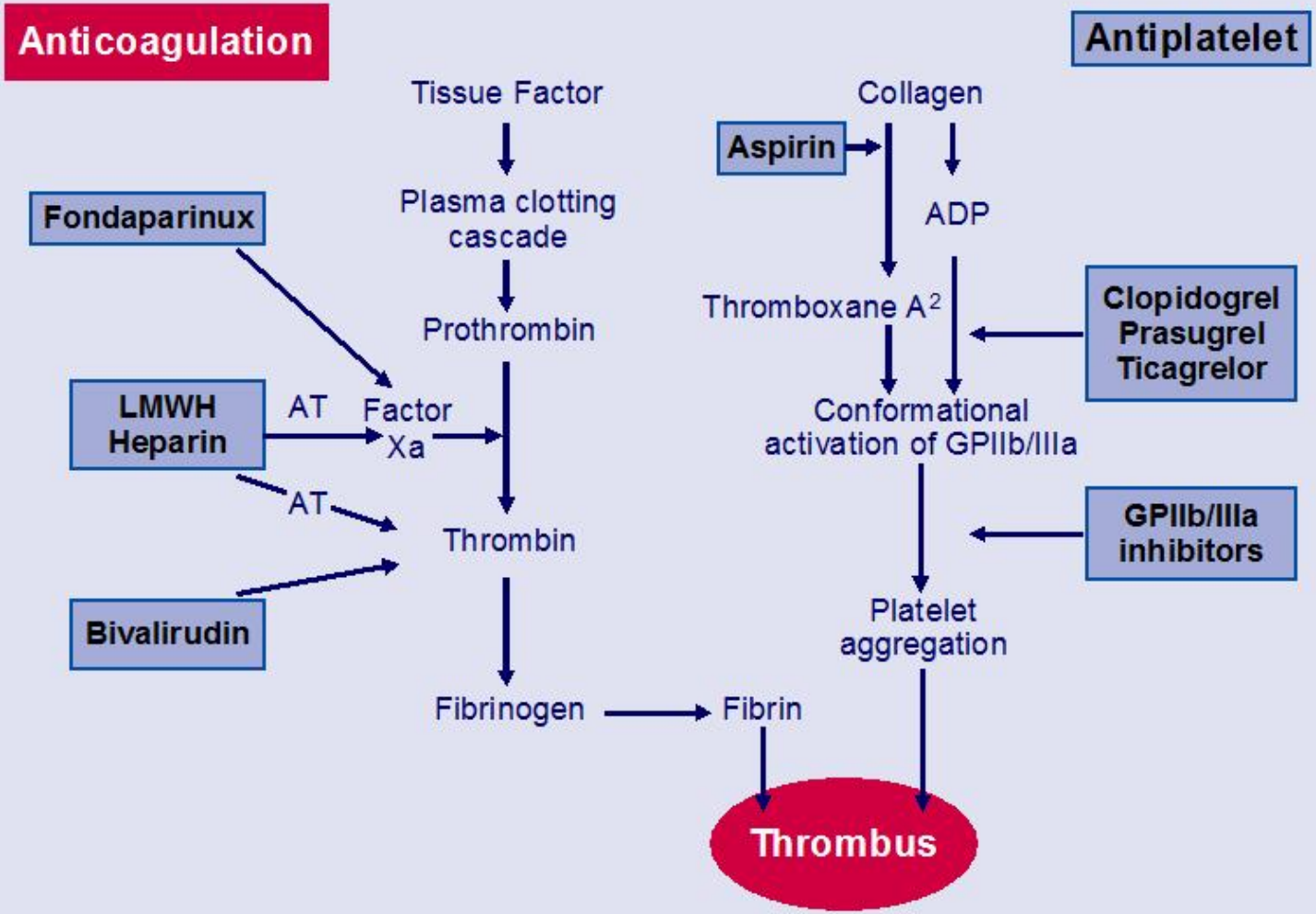
  GlaxoSmithKline, Lilly, The Medicines Company.

- **Consulting Fees/Honoraria:**

  Terumo, The Medicines Company, Biotronik, Cordis, Medtronic.

Targets for antithrombics



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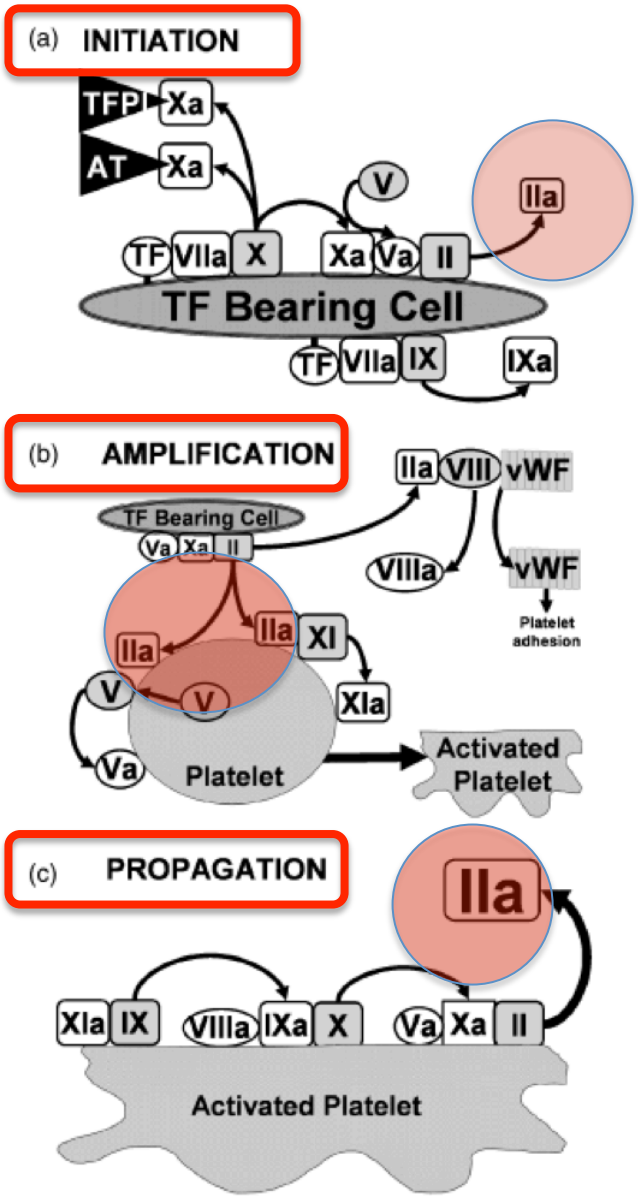
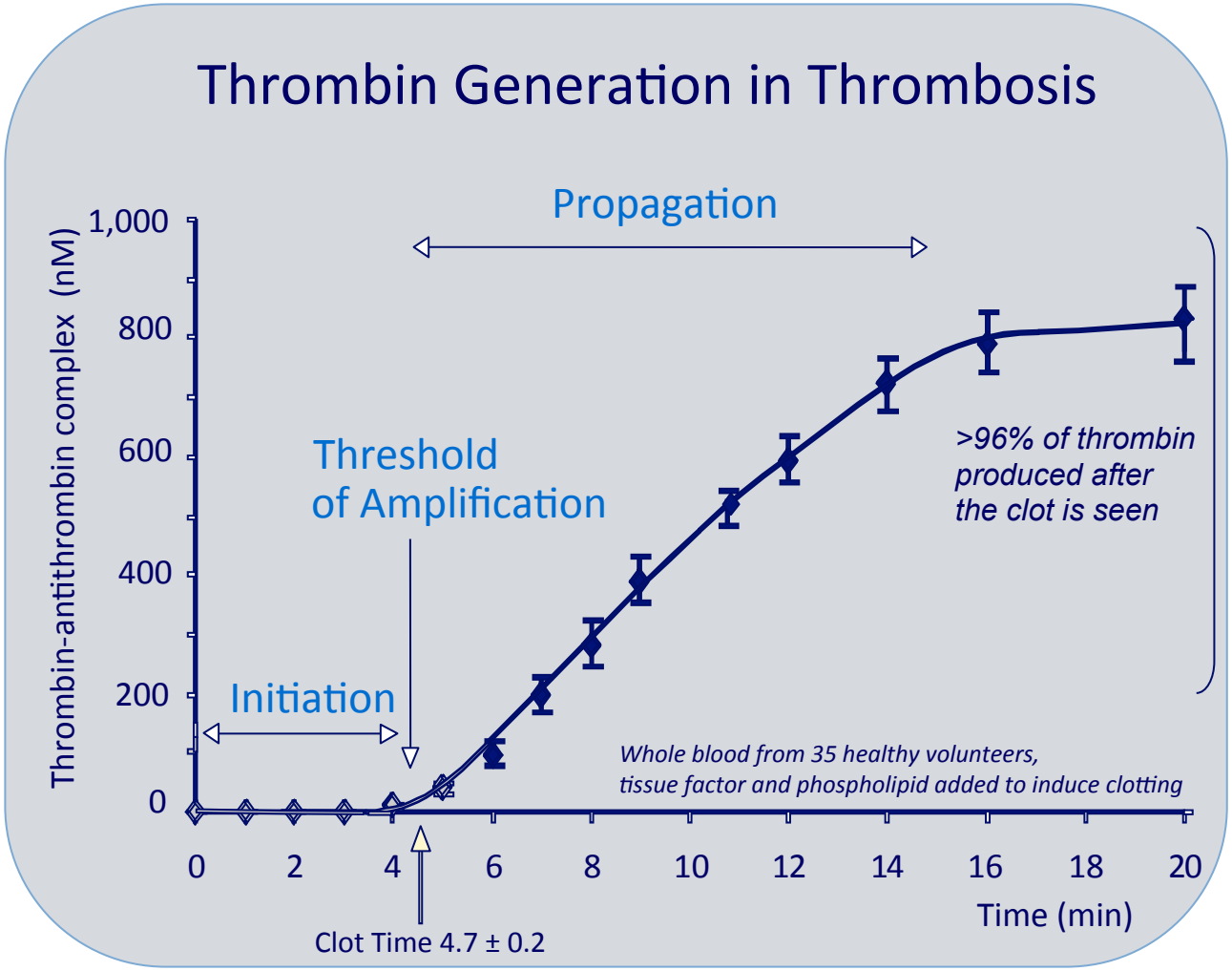
Cell Model of Coagulation-Thrombosis



Hoffman et al *Thromb Haemost*. 2001

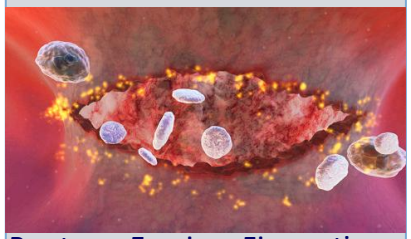
Becker R. *Am Heart J*. 2005

Central Role of Thrombin in Thrombosis



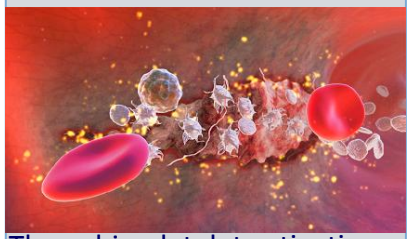
Adapted from Mann K et al. *Arterioscler Thromb Vasc Biol*. 2003
Coughlin S et al. *Thromb Haem.* 2001

1.Initiation: Tissue factor



Rupture, Erosion, Fissuration

2.Amplification: Platelets



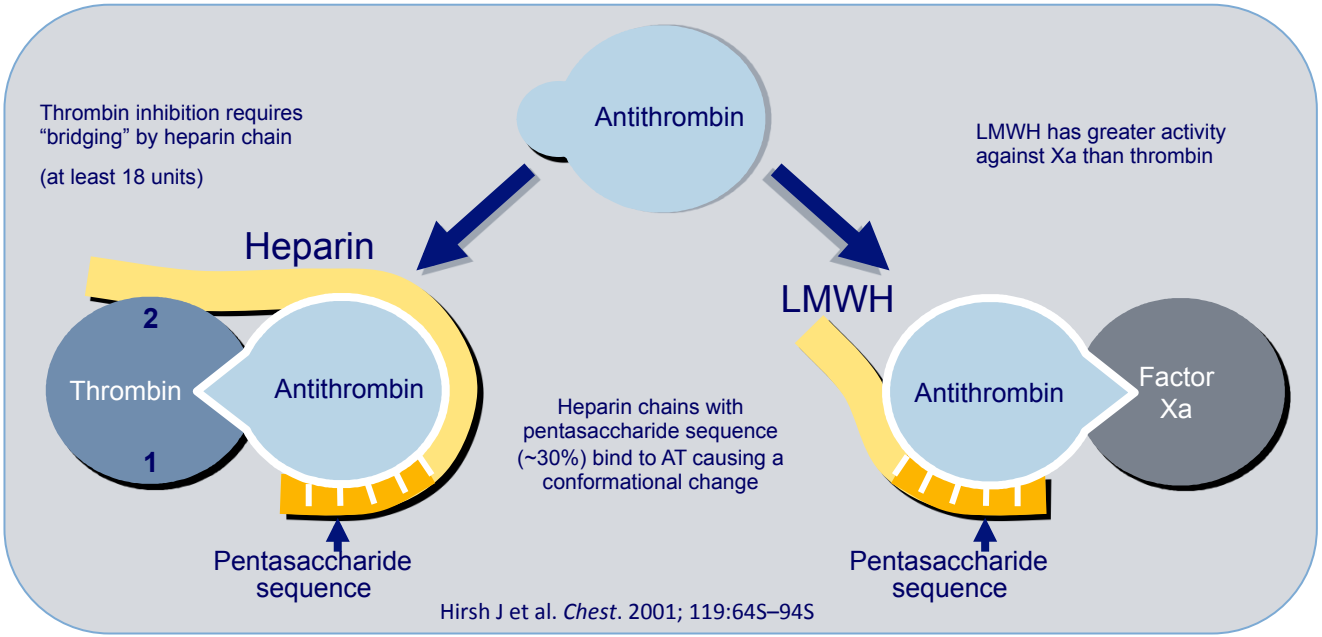
Thrombin platelet activation

3.Propagation

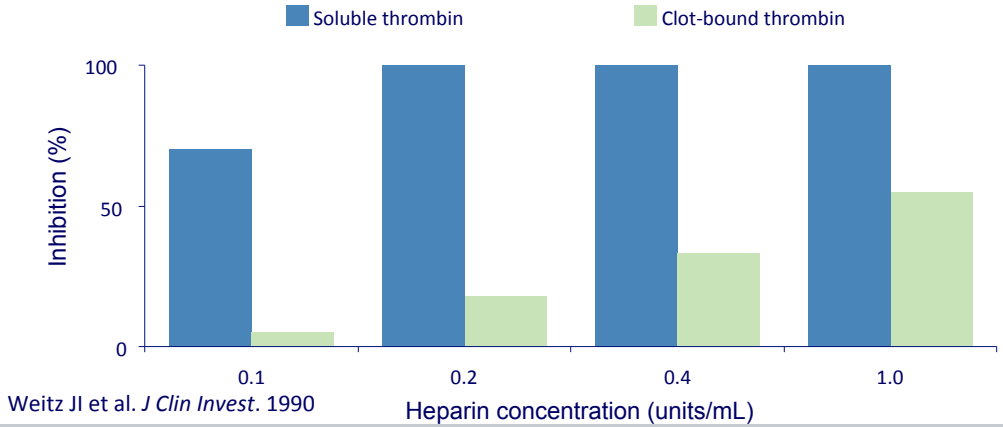
Massive thrombin production

Hoffman et al *Thromb Haemost*. 2001
Becker R. *Am Heart J*. 2005

Heparin/LMWH: mechanism of action



Hirsh J et al. *Chest*. 2001; 119:64S–94S



Weitz JI et al. *J Clin Invest*. 1990

Heparin Limitations

- Unpredictable anticoagulant response
- Narrow therapeutic window
- Limited activity in the presence of platelet-rich clot
- Procoagulant effect (Heparin-induced platelet activation)
- Heparin-induced thrombocytopenia (Heparin-PF4 Ab)

Hirsh J et al. *Chest*. 1995; Weitz JI et al. *Circulation*. 2002; Hirsh J et al. *Chest*. 1998; Sobel M et al. *J Vasc Surg*. 2001; Anand SX et al. *Am J Cardiol*. 2007.

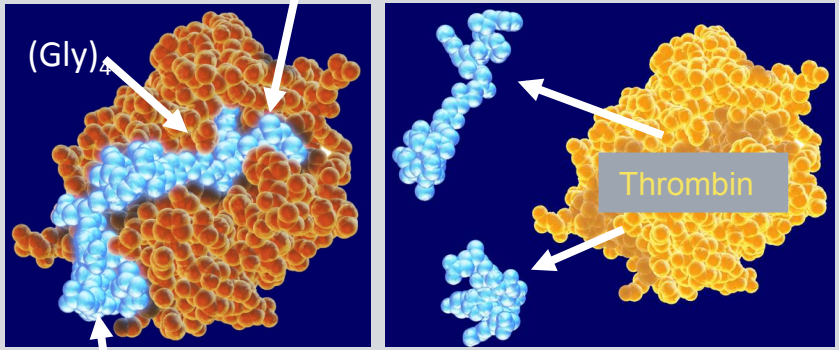
Bivalirudin mechanism of action

Direct and reversible binding to thrombin

Bivalirudin binds to active site and substrate recognition site of thrombin

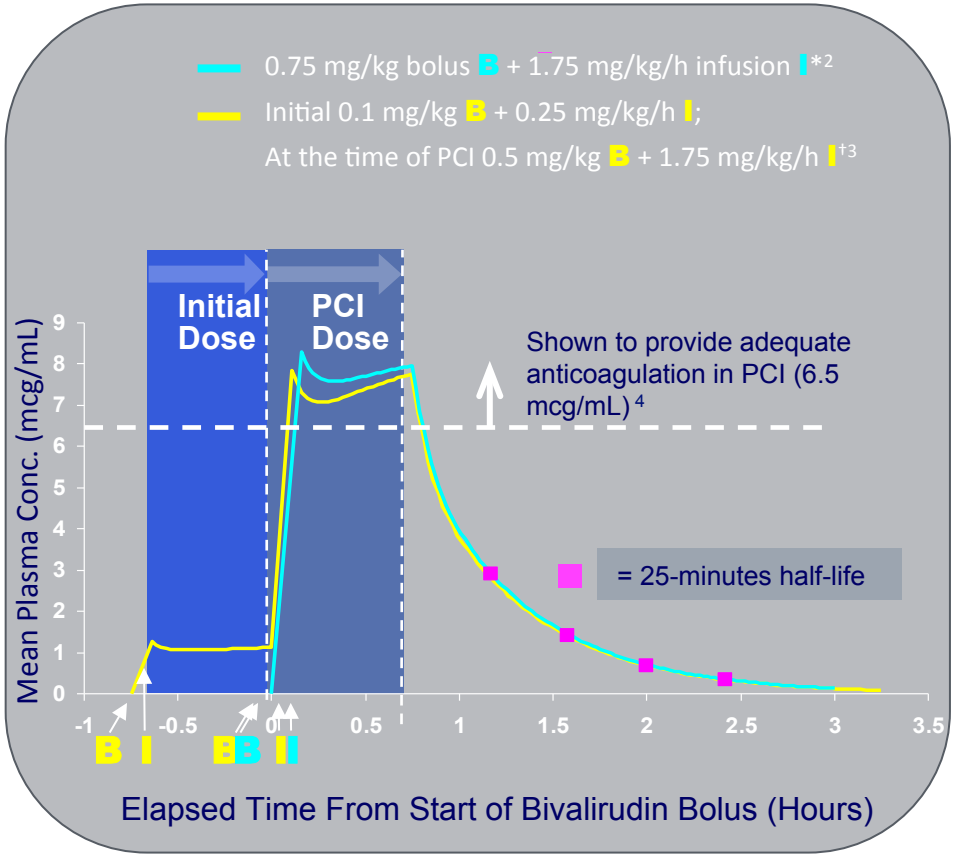
Bivalirudin slowly cleaved allowing thrombin to resume its hemostatic function

D-Phe-Pro-Arg-Pro
(active-site-binding portion)



C-terminal dodecapeptide
(Substrate recognition:
Exosite 1-binding portion)

Bivalirudin: predictable pharmacology



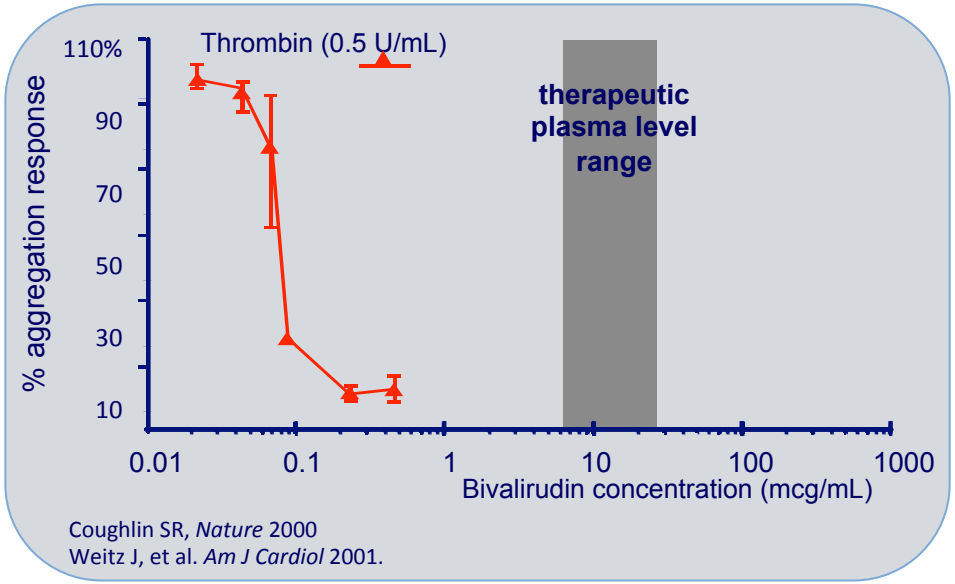
† Dose used in the ACUITY trial. PCI dose derived from phase 2 dose ranging study used in REPLACE-1 & 2.

Maraganore J et al Biochemistry 1990;30:7095-101

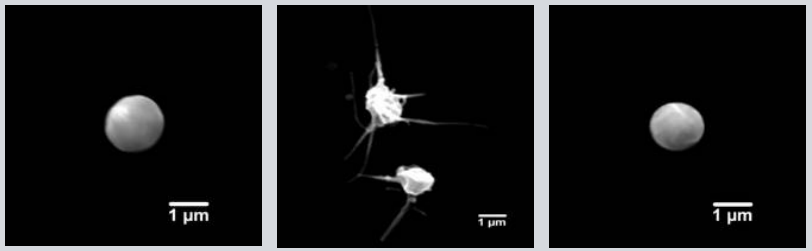
[2]Lincoff AM et al. *JAMA* 2003; 289: 853-863. [3]Stone G et al. *Am Heart J*. 2004;148:764-75. [4]Topol E, et al. *Circulation* 1993; 87:1622.

Bivalirudin: Platelet inhibition via thrombin

Thrombin is the most potent platelet agonist known



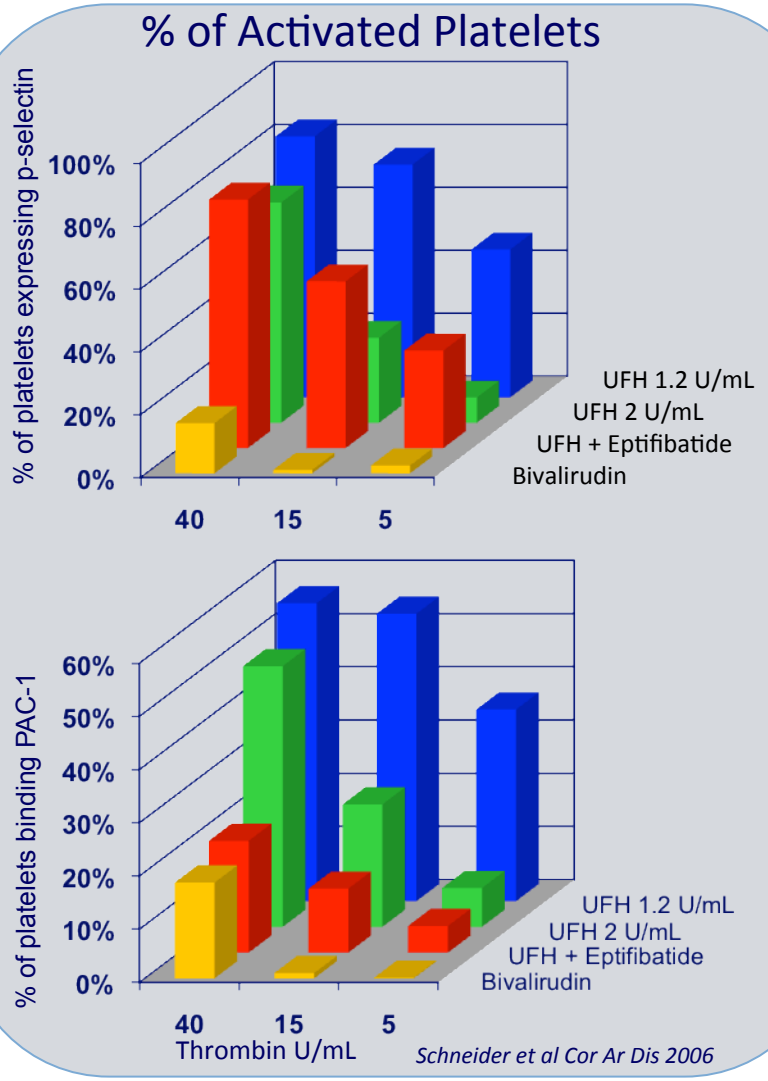
Coughlin SR, *Nature* 2000
Weitz J, et al. *Am J Cardiol* 2001.



Control platelets | **Platelets treated with UFH** | Platelets treated with Bivalirudin

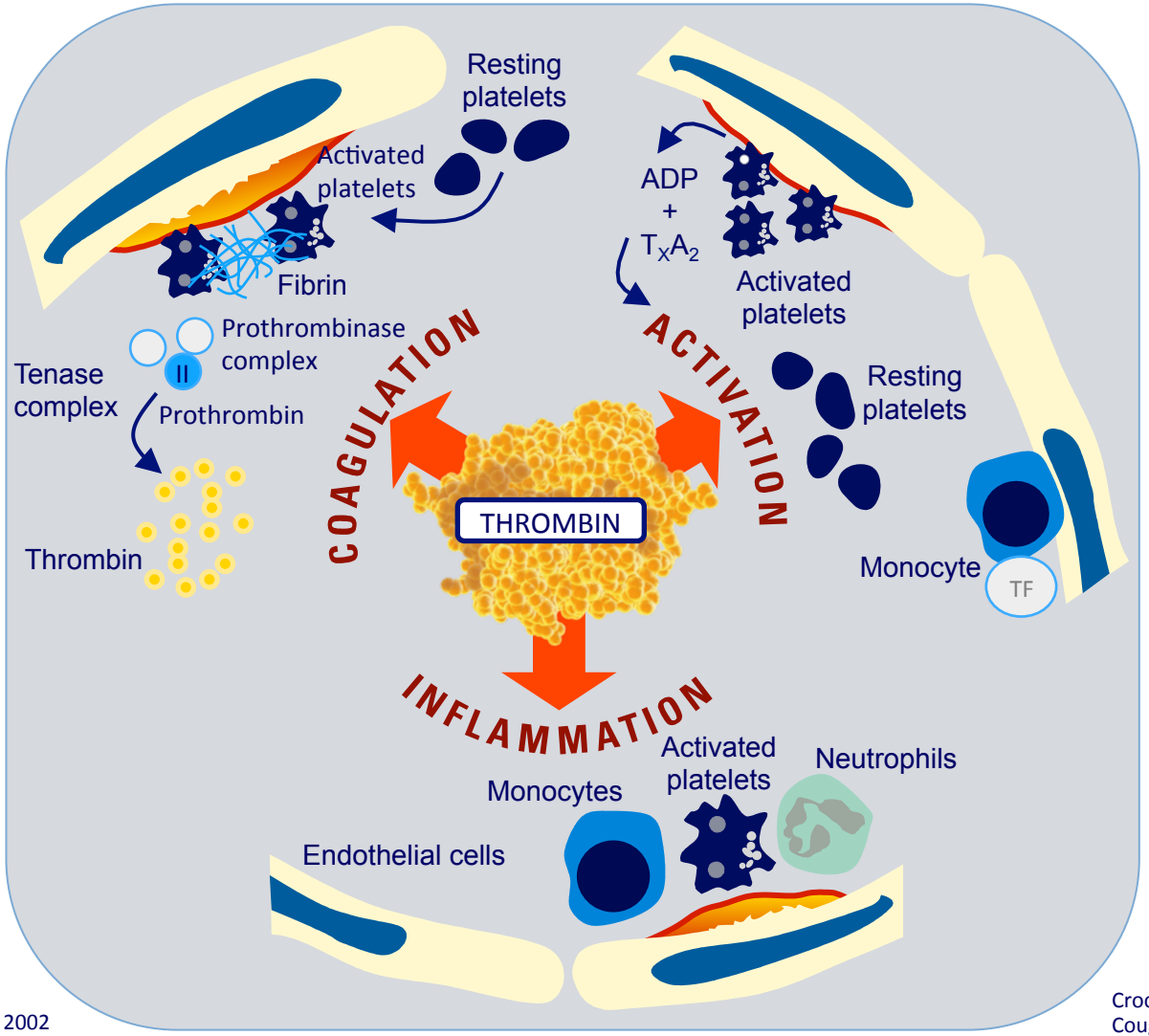
Platelets from healthy volunteers treated with 30 min bivalirudin (12µg/mL) or 0.1 to 1.0 U/mL of heparin

Anand SX et al. Am J Cardiol. 2007



Schneider et al Cor Ar Dis 2006

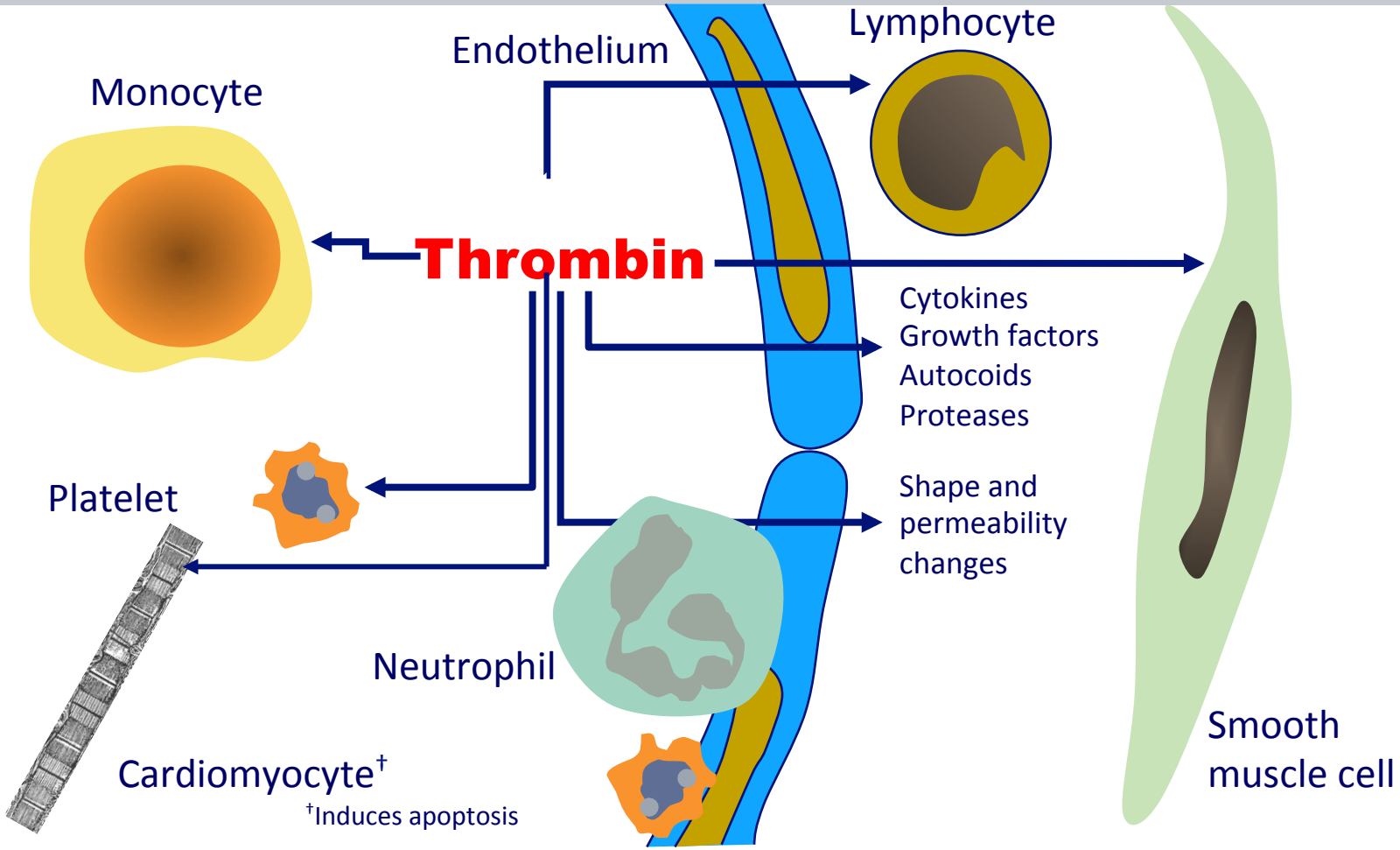
The critical roles of thrombin



Mann KG. *Chest.* 2003
Monroe DM et al. *ATVBiol.* 2002

Croce K et al. *Curr Opin Hematol.* 2007
Coughlin SR. *Nature.* 200

Thrombin: effects beyond clotting



Adapted from Coughlin SR, *Nature* 2000; 407: 258-264 Mirabet M. J *Mol Cell Cardiol* 2005; 39:277-83