



## Non-CME Webinar Series

designed with the trainee in mind

*first Tuesday of the month*

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# Anticoagulation and Pain Procedures

Tuesday, October 5, 2021

7-8:30 pm ET



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# Hemostasis

- Vascular spasm:
  - Endothelial damage
  - Endothelin, myogenic mechanism, nociceptor mechanism
- Platelet plug formation:
  - VWF (Gp1b), collagen exposure, TF
  - Platelet degranulation: ADP, TXA2
- Coagulation
- Clot retraction and repair
- Fibrinolysis



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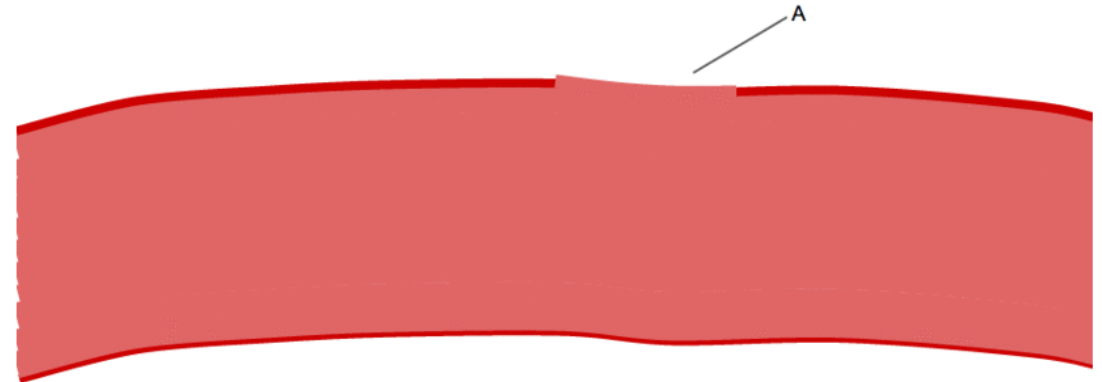
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## Platelet plug formation

- VWF (Gp1b), collagen exposure, TF
- Changes on morphology of platelets.
- Degranulation: ADP, TXA2





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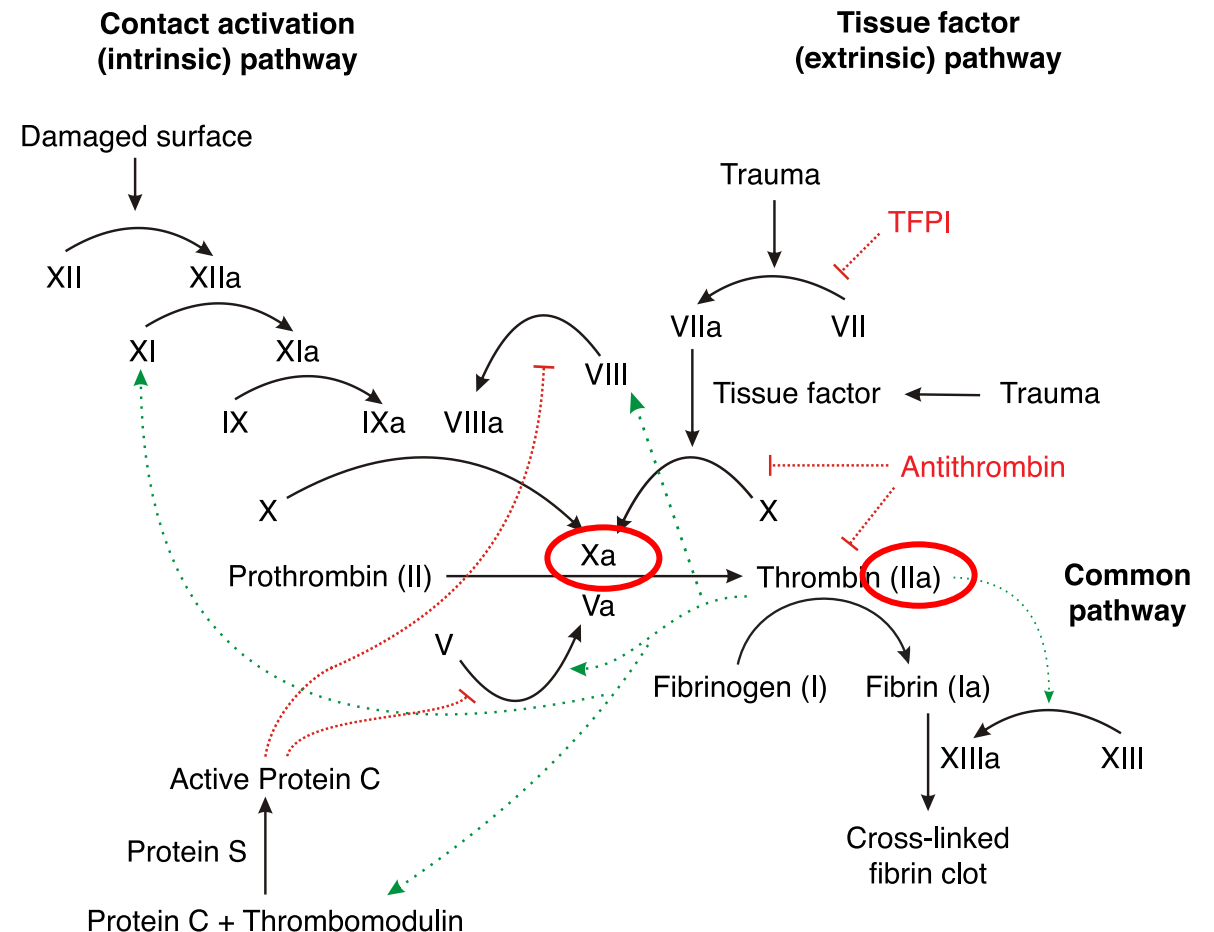
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# Coagulation

- Coagulation factors: Liver Px (except factor VIII).
- Extrinsic and intrinsic pathway
- Initiation: TF exposure -> VII activation -> X activation -> Thrombin
- Amplification: Enhancement of production of thrombin. Factor V
- Propagation: Fibrinogen to fibrin
- Stabilization: fibrin stabilizing factor XIII, crosslink fibrin polymers (mesh)





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# PHARMACOLOGY





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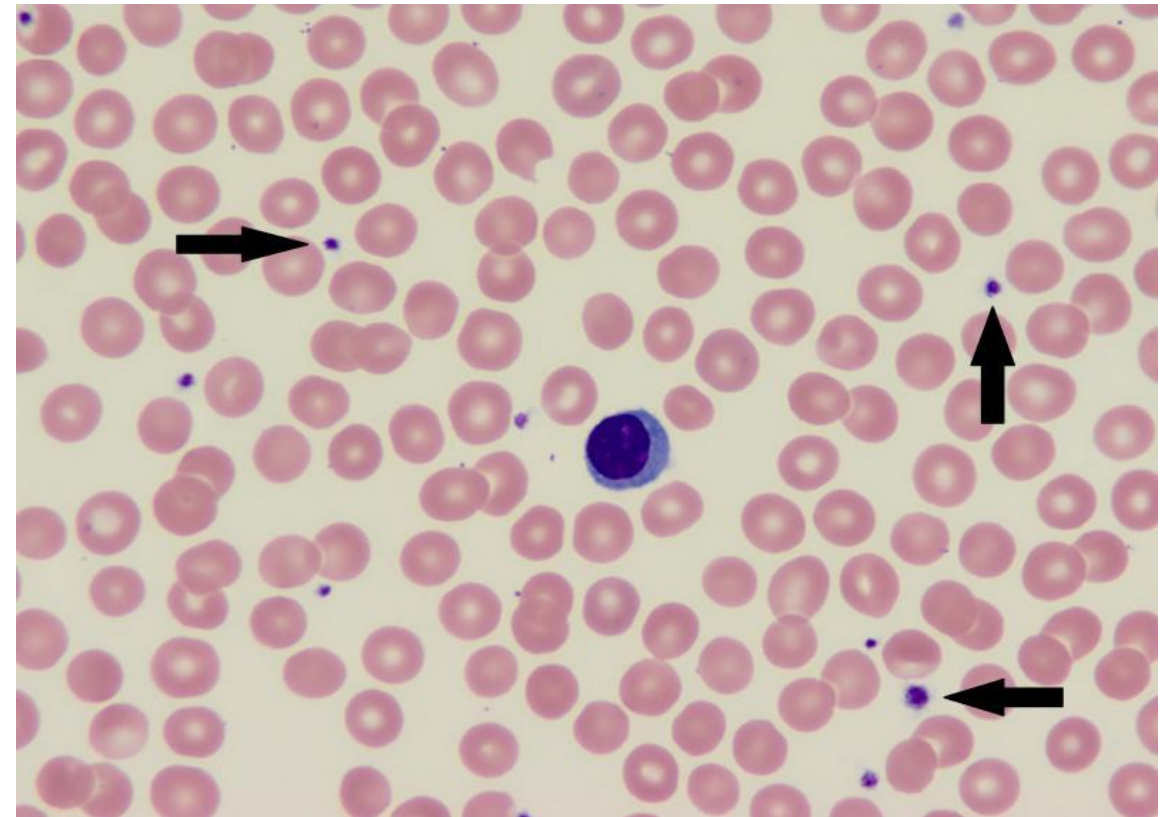
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## Platelet inhibitors

- Megakaryocytes
- Normal Platelet count: 150-350k
- Half life 7-10 days
- Platelet pool replaced 10% per day





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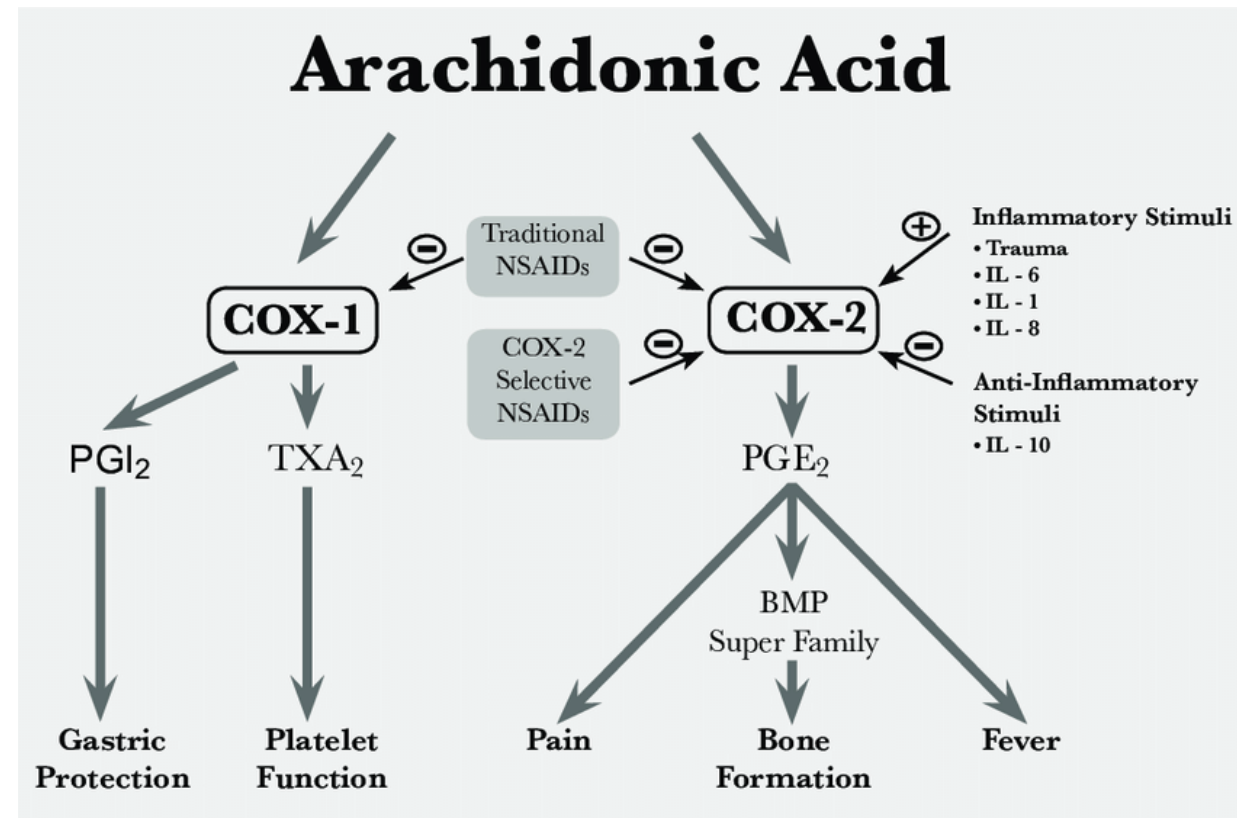
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## NSAIDS

- Inhibit prostaglandins production by blocking the cyclooxygenase (COX)
- COX1: Constitutive, (stomach, renal) – PGI<sub>2</sub> Prostacyclin, Thromboxane A<sub>2</sub>
- COX2: Inducible secondary to inflammation.
- Aspirin irreversible, others reversible binding (clearance dependent)
- Selective COX 2 do not affect platelet function (no need to stop).



van der Heide, H.J.L., Koorevaar, R.C.T., Lemmens, J.A.M. *et al.* Rofecoxib inhibits heterotopic ossification after total hip arthroplasty. *Arch Orthop Trauma Surg* **127**, 557–561 (2007).



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**TABLE 2.** Half-lives of Commonly Administered Non-ASA NSAIDs

Agent	Half-life, h	Discontinuation Time 5 Half-lives, h	Recommended Discontinuation Time, d
Diclofenac <sup>119</sup>	1–2	5–10	1
Etodolac <sup>120</sup>	6–8	30–40	2
Ibuprofen <sup>121</sup>	2–4	10–20	1
Indomethacin <sup>122</sup>	5–10	25–50	2
Ketorolac <sup>123</sup>	5–6	25–30	1
Meloxicam <sup>124</sup>	15–20	75–100	4
Nabumetone <sup>125</sup>	22–30	110–150	6
Naproxen <sup>126</sup>	12–17	60–85	4
Oxaprozin <sup>127</sup>	40–60	200–240	10
Piroxicam <sup>128</sup>	45–50	225–250	10





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# Aspirin

- Has 170-fold greater affinity for COX-1 over COX-2
- Irreversibly inactivates COX-1: acetylation of the amino acid serine
- Inactivates COX-1 and blocks Thromboxane A<sub>2</sub> production for the life span of a platelet
- 1 hour after ingestion: greater than 90% reduction in thromboxane levels
- Also inactivates COX-1 in mature megakaryocytes on bone marrow (2 days)
- Single dose of 100 mg suppresses COX activity by 95% (increases with repeated dosing)
- Primary prophylaxis: Use in absence of established cardiovascular disease.
- Secondary prophylaxis: In the presence of overt cardiovascular disease or conditions conferring particular risk (e.g., diabetes).
- When used for secondary prophylaxis: reduce risk of stroke and myocardial infarction 25% to 30%.
- Discontinuation: platelet rebound phenomenon (prothrombotic state) increased thromboxane, enhancement of thrombus stability, improvement in fibrin cross-link networks, and decreased fibrinolysis



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## ADP Receptor (P2Y12) Inhibitors

- **Clopidogrel (Plavix):**
  - Prodrug, irreversible binding
  - Max platelet inhibition 60%
  - 50% recovery after 3 days and 100% after one week.
  - Susceptible to genetic polymorphisms (ineffective in up to 30% population)
- **Ticlopidine (Ticlid):**
  - Antagonize ADP at the receptor irreversibly
  - Aplastic anemia
- **Prasugrel (Effient):**
  - Prodrug, higher irreversible activity (80%) compared to clopidogrel
- **Ticagrelor (Brilinta):**
  - Rapid onset (2-4 hours peak after intake)
  - Has the highest antithrombotic activity >90%
  - Reversible



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# Phosphodiesterase Inhibitors

- Platelets express 3 PDE isoenzymes: PDE-2, PDE-3, and PDE-5
- Dipyridamole:
  - PDE-3 inhibitor
  - Increase cAMP
  - Often combined with ASA
  - Blocks Thromboxane synthase (Decreases platelet aggregation with vasodilation)
- Cilostazol
  - PDE-5 inhibitor
  - Increase cGMP
  - Treat lower extremity vascular claudication
  - Could be used on clopidogrel low responders



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# Glycoprotein GPIIb/IIIa Inhibitors

- Very potent. May induce thrombocytopenia
- Abciximab: monoclonal antibody directed against the GFPIIb/IIIa receptor.
  - Inhibits over 80% of ADP induced platelet aggregation and thrombin generation.
  - Given via IV administration.
- Eptifibatide: inhibitor of the fibrinogen binding site on the GPIIb receptor.
- Tirofiban

**HOT TOPICS**


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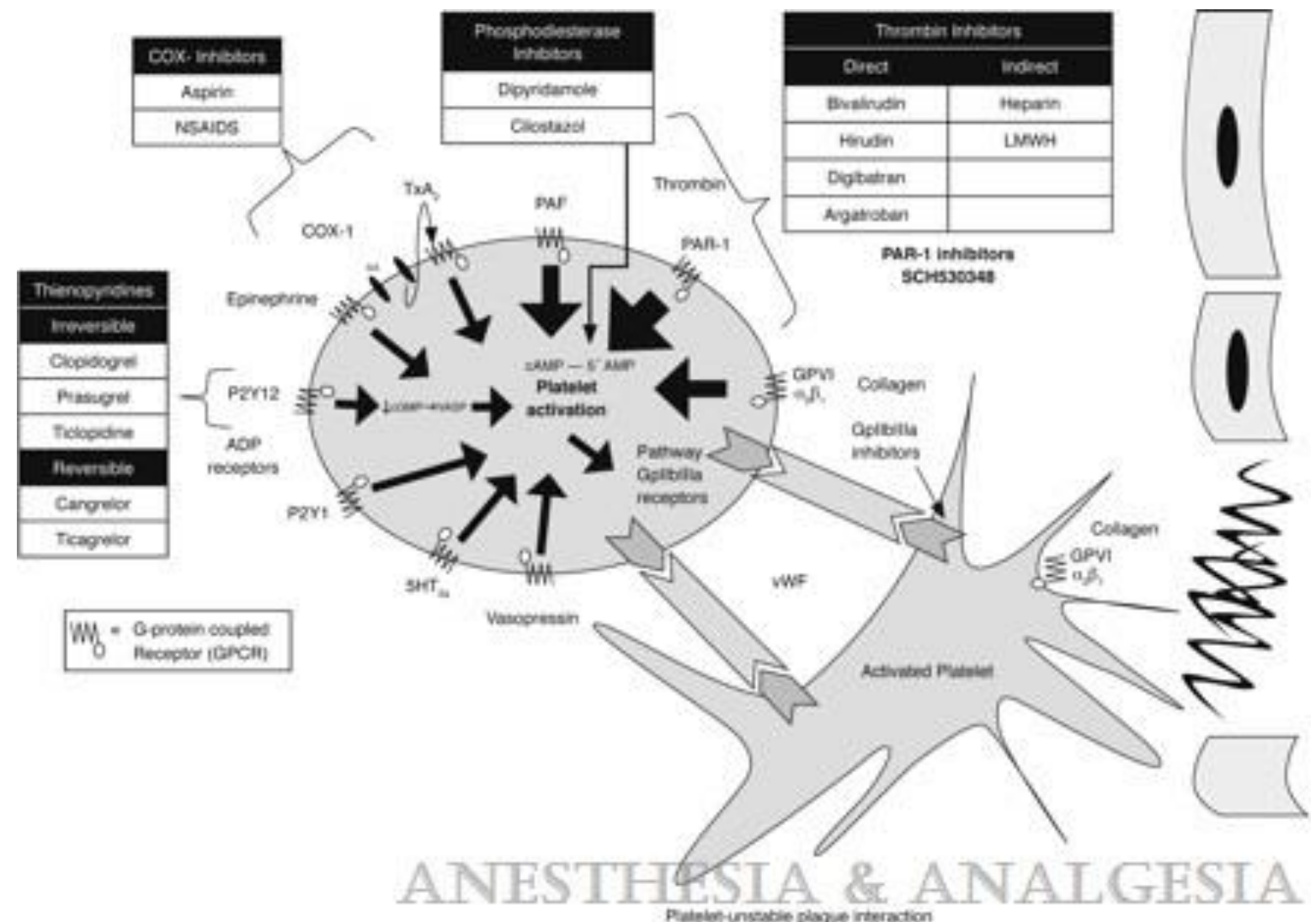
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Hall, Richard; Mazer, C. David  
Anesthesia & Analgesia 112(2):292-318,  
February 2011.



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# ANTICOAGULANTS



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# Warfarin

- Inhibits the  $\gamma$ -carboxylation of vitamin K–dependent coagulation factors (II, VII, IX, and X) and proteins C and S.
- Factor VII (6–8 hours), IX (20–24 hours), X (20–42 hours), II (48–120 hours).
- Protein C is anticoagulant. Can be pro-coagulant the first hours.
- Difficult to titrate: narrow therapeutic index, CYP2C9 metabolism.
- Thromboplastin time (PT), used to titrate dose.
- International Normalized Ratio INR (0.8-1.1). Full effect > 4 days.
- Clotting factors concentration >40% adequate for hemostasis.



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# Heparin

- Unfractionated heparin inactivates thrombin (factor IIa) and factor Xa by enhancing antithrombin III activity
- Anticoagulant effect of IV heparin is immediate, whereas subcutaneous heparin takes 1 hour.
- IV Heparin has a half-life of 1.5 to 2 hours, LMWH 3-6hours
- Reversal: Protamine
- Monitoring:
  - IV via PTT (Therapeutic anticoagulation: PTT is 1.5 to 2.5 times).
  - LMWH via anti-factor Xa activity level (CKD, <50Kg or >80Kg)





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# Direct Factor Xa Inhibitors

- NOACs (Novel Oral Anticoagulants)
  - Don't require serial monitoring.
  - Safer (shorter  $\frac{1}{2}$  life than warfarin)
- Apixaban (Eliquis) and rivaroxaban (Xarelto)
  - Reversed by Andexanet alfa or recombinant factor Xa
  - Can be monitored with the anti-factor Xa assay
- Fondaparinux (ArixtraR)
  - 100% bioavailable
  - Once/day dosing



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# Direct thrombin inhibitors

- Inhibition of IIa, independently of antithrombin III.
- Dabigatran (PradaxaR), Argatroban (Acova™), Bivalirudin (Angiomax R), Lepirudin (RefludanR), Desirudin (IPRIVASKR), and Hirudin
- Dabigatran
  - Used to prevention of stroke in A-fib patients
  - May be better than enoxaparin for VTE prophylaxis
  - PTT is prolonged but no linear relationship
  - Dialysis would reduce concentration
  - Reversal Praxbind (idarucizumab)



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# Thrombolytic Agents

- Conversion of plasminogen and thrombin to plasmin. “Clot busters”
- Recombinant tissue-type plasminogen activator (tPA), streptokinase, urokinase, tenecteplase, and reteplase
- Disrupt the fibrin mesh.



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# Herbal and supplements

- Garlic: Platelet aggregation inhibition
- Ginkgo Biloba: Antagonize platelet activating factor (PAF) and collagen
- Ginseng: Reduce effect of Warfarin
- Vitamin E >400 IU daily
- Fish oil