# Drugs Used in Thromboembolic Disease II

| Drug | MOA | Administration | Uses | Side Effects | Notes |
|---|---|---|---|---|---|
| **Warfarin** | -Vitamin K epoxide reductase **inhibitor**: prevents reduction of the inactive vitamin K epoxide back to its active hydroquinone form<br>-Act in the **liver**, not in the circulation: block the ɣ-carboxylation (a final synthetic step that transforms a precursor into various factors: prothrombin, VII, IX, X and proteins C and S → become biologically **inactive)**<br>*Time to maximal effect depends on factor degradation half-lives in the circulation **(VII=6, IX=24, X= 40 and II=60 hrs)** | -Given orally<br>-Treatment is initiated with small doses of 5-10mg, not large loading doses<br>-Response monitored by Prothrombin Time (**PT**)<br>→International Normalized Ratio (INR)= Patient PT/ Mean of normal PT for the lab<br><br>***Drug-drug interactions**: some drugs and other conditions increase (PT) of warfarin and some decrease it (**refer to slide 11**) | -Anticoagulant: in arterial and venous thrombosis<br><br>*Warfarin resistance is seen in cancer patients | *Toxicity:<br>Bleeding<br>-Teratogenicity → contraindicated in pregnancy<br>-Cutaneous necrosis, infarction of breast, fatty tissues, intestine and extremities → due to inhibition of Protein C and S, **especially** in patients genetically deficient in them<br><br>*Reversal of Action (to **counteract** toxicity):<br>-Vitamin K<br>-Fresh-frozen plasma<br>-Prothrombin complex concentrates<br>-Recombinant factor VII | -Structure similar to Vit. K<br>-Underprescribed: due to fear of toxicity<br>-100% bioavailability, peaks after one hour<br>-99% bound to plasma proteins → small volume of distribution and long half-life(36hr).<br>-Does not cross BBB, but crosses the placenta<br>-Hydroxylated in the liver<br>-Present in two enantiomorphs<br>-Action starts after about 48 hrs → after elimination of most of the factors in the circulation → **So, do not increase the dose** |
| **Fibrinolytic Agents** | | | | | |
| **Fibrinolytic Agents (General View)** | -Rapidly lyse thrombi by catalyzing the formation of Plasmin from Plasminogen | | *Indications<br>-Pulmonary embolism with hemodynamic instability<br>-Deep venous thrombosis<br>-Ascending thrombophlebitis<br>-Acute myocardial infarction | | -Create a generalized lytic state<br>*Aspirin (Antiplatelet) is required<br>***Indications apply to fibrinolytic drugs below** |
| **Streptokinsae** | -Binds to plasminogen in plasma to activate it → **plasmin → dissolves fibrin clot** | -Early administration is important (after diagnosis) | -Fibrinolytic agent (thrombolytic): in arterial and venous thrombosis | *Highly antigenic:<br>-Can cause allergic reactions<br>-Can result in inactivation of the drug | -Protein synthesized by Streptococcus<br>- Not specific to fibrin → causes bleeding everywhere |

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| **Urokinase** | -Directly converts plasminogen into plasmin | | -Fibrinolytic agent (thrombolytic): in arterial and venous thrombosis | *Not antigenic | -A human enzyme synthesized by the kidneys<br>-Expensive |
| **Anistreplase (ASPAC)** | -Deacylated at fibrin surface → Active complex released<br>(More active and selective) | | -Fibrinolytic agent (thrombolytic): in arterial and venous thrombosis | | -**ASPAC**: Anisoylated Plasminogen Streptokinase Activator Complex<br>-Long action, t½ → 6h<br>-Fibrinolytic agents create a generalized lytic state |
| **(t-PA)** **Ateplase**<br>**Reteplase**<br>**Tenecte -plase** | -Bind to fibrin and activate plasminogen at the fibrin surface<br>-**Specific** action within the thrombus → **avoids** systemic activation<br>-Action less affected by age of thrombus | Given by infusion over 1-3 hours | -Fibrinolytic agent (thrombolytic): in arterial and venous thrombosis | | **-t-PA:** Tissue-type Plasminogen Activators<br>-Synthesized by the endothelial cells, also recombinant DNA tech<br>-Short action t½ = 8 min<br>-Very Expensive |
| **Antiplatelet Drugs** | | | | | |
| **Aspirin** | -Inhibits thromboxane A2(TXA2) synthesis by irreversibly acetylating (COX-1) → inhibits platelet activation | Dose: 80 – 325 mg | -Used in arterial disease | | - Platelets do not have DNA so aspirin causes permanent inhibition of platelets' COX<br>-half-life 7-10 days |
| **Ticlopidine**<br>**Clopidogrel**<br>**Prasugrel** | Irreversibly block P2Y12 (an ADP receptor on the platelet surface) | | - Useful in TIAs, completed stroke, unstable angina and after placement of coronary stents<br>-Useful for patients who cannot tolerate aspirin | - Can cause leukopenia, GI irritation and skin rash | |

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| **Cangrelor**<br>**Ticagrelor** | Reversible inhibitors of P2Y12 (ADP inhibitors) | | -Used in arterial disease | | |
| **Abciximab (Monoclonal Antibody)**<br>**Eptifibatide (Synthetic peptide)**<br>**Tirofiban** | All inhibit the final common pathway of platelet aggregation by blocking fibrinogen and von Willebrand factor (vWF) from binding to activated glycoprotein (GP) IIb/IIIa | | -Used in arterial disease | | |
| **SCH530348**<br>**E5555** | Inhibit thrombin mediated platelet activation by targeting protease-activated receptor-1 (PAR-1), the major thrombin receptor on platelets | | -Used in arterial disease | | |
| **Dipyridamole**<br>**Cilostazole** | inhibit adenosine uptake and phosphodiesterase enzyme →↑c AMP in platelets and elsewhere | | -Used in arterial disease<br>-Also work as vasodilators | | |
| **Dazoxiben** | Inhibits TX synthetase enzyme | | -Used in arterial disease | | |
| **Sulotroban** | Inhibits TXA2 receptor | | -Used in arterial disease | | |
| **Anagrelide** | Reduces platelet production by decreasing megakaryocyte maturation | | -Used in arterial disease | | |
| **Lipid Lowering Agents** | Reduce activity of platelets indirectly by reducing viscosity of plasma | | -Used in arterial disease | | |

# Drugs Used in Thromboembolic Disease II

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|---|---|---|---|---|---|
| **Hemostatic Agents** | | | | | |
| **Whole Blood** | | | To restore hemostasis and stop the bleeding | | |
| **Fresh Frozen-Plasma** | | | | | |
| **Plasma Fraction** | | | | | |
| **Vitamin K** | | | | | |
| **Absorbable Gelatin Foam or Film** | | Used as physical agents to cover the wounds | To restore hemostasis and stop the bleeding | | |
| **Oxidized Cellulose** | | | | | |
| **Thrombin (Powder)** | | | | | |
| **Plasmin Inhibitors** | | | | | |
| **α2 Antiplasmin (Physiological)** | | | To prevent adverse consequences arising from **plasmin** overactivity | | |
| **Aprotinin (Bovine parotid gland)** | | | | | |
| **Aminocaproic Acid** | | | | | |
| **Tranexamic Acid** | | | | | |

# Platelet Adhesion and Aggregation

| Platelet Adhesion and Aggregation | |
|---|---|
| **GPIa/IIa & GPIb** | Platelet receptors →bind to collagen and von Willebrand factor (vWF), causing platelets to adhere to the subendothelium of a damaged vessel |
| **P2Y1 & P2Y12** | Receptors for ADP → when stimulated by agonists, these receptors activate the fibrinogen-binding protein GPIIb/IIIa and (COX-1) to promote platelet aggregation and secretion. |
| **PAR1 & PAR4** | Protease-activated receptors → respond to thrombin (IIa) |
| **Thromboxane A2** | The major product of COX-1 involved in platelet activation |
| **Prostaglandin I2** | Synthesized by endothelial cells, inhibits platelet activation |

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