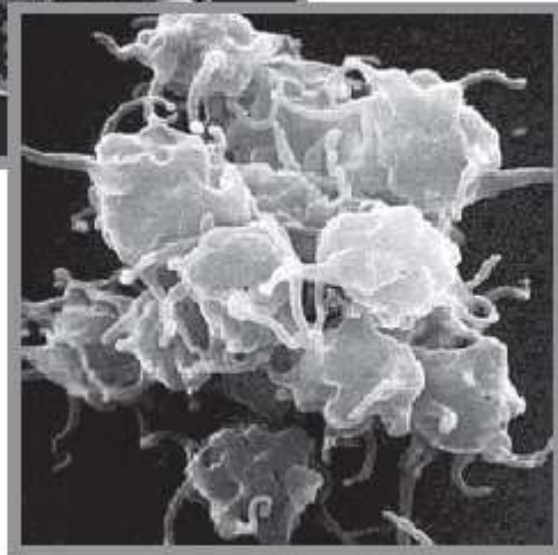
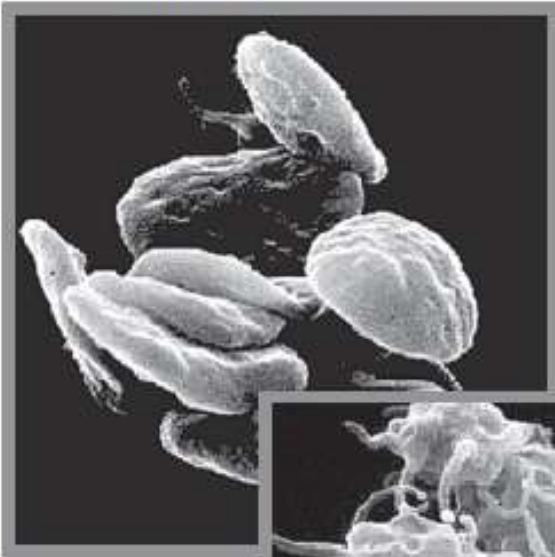


Resting platelet



Activated platelet

Scanning electron micrograph of platelets

Coagulant and anticoagulant

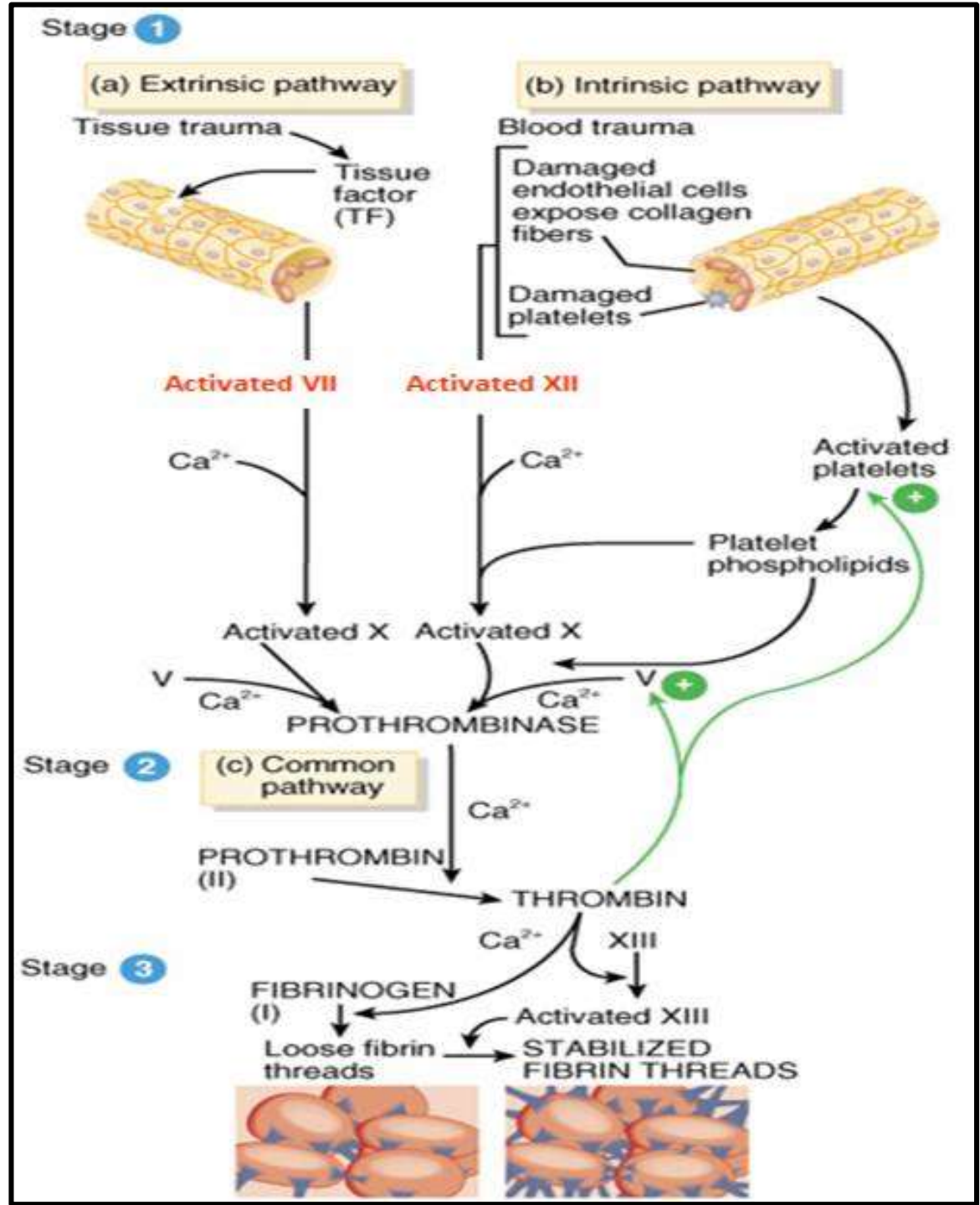
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Coagulants

Coagulant

- Haemostasis (arrest of blood loss) and blood coagulation involve complex interactions between the injured vessel wall, platelets and coagulation factors.

Mechanisms of blood coagulation



Coagulants

Vitamin K	K1 (from plants fat-soluble):	Phytonadione (Phylloquinone)
	K3 (synthetic)	
	—Fat-soluble:	Menadione, Acetomenaphthone
	—Water-soluble:	Menadione sod. Bisulfite, Menadione, sod. Diphosphate
Miscellaneous	Fibrinogen (human), Antihæmophilic factor, Desmopressin, Adrenochrome monosemicarbazone, Rutin, Ethamsylate	

Vitamin K

- Vit. K is a fat-soluble dietary principle required for the synthesis of clotting factors.
- **Daily requirement:** Vit. K₂ produced by colonic bacteria and 3–10 µg/day external source may be sufficient. The total requirement of Vit. K for an adult has been estimated to be 50–100 µg/day.

tamin K

These factors are inactivated by *heparin-antithrombin* complex.

Synthesis of these factors is inhibited by *coumarins*

Intrinsic pathway

XII → XIIIa

XI (+) → XIa

IX (+) → IXa

X (+) → Xa

Prothrombin (II) (+) → Thrombin (IIa)

Fibrinogen (+) → Fibrin

Extrinsic pathway

VII → VIIa

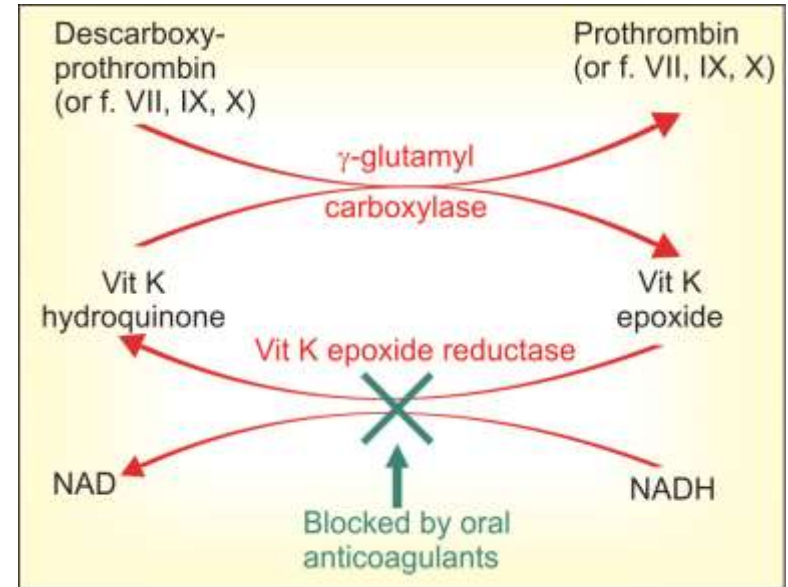
VIIa (+) → X

X (+) → Xa

Vit. K

Inactive form

Functional form



Vit. K

Vitamin K

Action:

Vit K acts as a cofactor at a late stage in the synthesis by liver of coagulation proteins - prothrombin, factors VII, IX and X.

Use: The only use of vit K is in prophylaxis and treatment of bleeding due to deficiency of clotting factors.

Coagulants

Plasma fractions

- Deficiencies in plasma coagulation factors can cause bleeding.
- **Factor VIII deficiency (classic hemophilia or hemophilia A) and factor IX deficiency (Christmas disease, or hemophilia B)** account for most of the heritable coagulation defects. Concentrated plasma fractions and recombinant protein preparations are available for the treatment of these deficiencies.

Coagulants

Desmopressin acetate

- Desmopressin (DDAVP) stimulates the release of *von Willebrand factor (vWF)* from the **Weibel–Palade bodies** of **endothelial cells**, thereby increasing the levels of vWF (as well as coagulant factor VIII) 3 to 5-fold.
- It also used to promote the release of von *Willebrand factor* in patients with **coagulation disorders** such as *von Willebrand* disease, **mild hemophilia A** and **thrombocytopenia**.

Coagulants

Cryoprecipitate

- Cryoprecipitate is a plasma protein fraction obtainable from whole blood. It is used to treat deficiencies or qualitative abnormalities of fibrinogen.
- It may also be used for patients with factor VIII deficiency and von Willebrand disease

Anticoagulants

Anticoagulants

<u>Used</u> <u>in vivo</u>	Parenteral anticoagulants	Indirect thrombin inhibitors: Heparin, Low molecular weight heparins, Fondaparinux, Danaparoid
		Direct thrombin inhibitors: Lepirudin, Bivalirudin, Argatroban
	Oral anticoagulants	Coumarin derivatives: Bishydroxycoumarin (dicumarol), Warfarin sod, Acenocoumarol (Nicoumalone), Ethylbiscoumacetate
		Indandione derivative: Phenindione
		Direct factor Xa inhibitors: Rivaroxaban
		Oral direct thrombin inhibitor: Dabigatran etexilate

Anticoagulants

<u>Used in vitro</u>	Heparin	150 U to prevent clotting of 100 ml blood.
	Calcium complexing agents: Sodium citrate	1.65 g for 350 ml of blood (used to keep blood in the fluid state for transfusion)
	Sodium oxalate	10 mg for 1 ml blood (used in blood taken for investigations)
	Sodium edetate	2 mg for 1 ml blood (used in blood taken for investigations)

Blood clotting factors and drugs that affect them

Component or Factor	Common Synonym	Target for the Action of:
I	Fibrinogen	
II	Prothrombin	Heparin, dabigatran (IIa); warfarin (synthesis)
III	Tissue thromboplastin	
IV	Calcium	
V	Proaccelerin	
VII	Proconvertin	Warfarin (synthesis)
VIII	Antihemophilic factor (AHF)	
IX	Christmas factor, plasma thromboplastin component (PTC)	Warfarin (synthesis)
X	Stuart-Prower factor	Heparin, rivaroxaban, apixaban, edoxaban (Xa); warfarin (synthesis)
XI	Plasma thromboplastin antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Proteins C and S		Warfarin (synthesis)
Plasminogen		Thrombolytic enzymes, aminocaproic acid

Anticoagulant

- The anticoagulant drugs inhibit either the action of the coagulation factors (heparin) or interfere with the synthesis of the coagulation factors (warfarin).
- Heparin or Unfractionated heparin (UFH) is a heterogeneous mixture of sulfated mucopolysaccharides with MW 10,000 to 20,000 g/mol. Its biologic activity is dependent upon the endogenous anticoagulant **antithrombin**.

Anticoagulant

- The shorter-chain, low-molecular-weight (LMW) fractions of heparin (**enoxaparin, dalteparin, and tinzaparin**) inhibit activated factor X but have less effect on thrombin than the high-molecular-weight (HMW) species.
- **Monitoring of Heparin Effect:** Close monitoring of the activated partial thromboplastin time (aPTT or PTT) is necessary in patients receiving UFH. Levels of UFH may also be determined by protamine titration (therapeutic levels 0.2–0.4 unit/mL) or anti-Xa units (therapeutic levels 0.3–0.7 unit/mL).

Anticoagulant

- **Toxicity:** Bleeding, loss of hair and reversible alopecia, heparin-Induced thrombocytopenia.
- **Contraindications:** Heparin should be avoided in patients who have recently had surgery of the brain, spinal cord, or eye; and in patients who are undergoing lumbar puncture or regional anesthetic block.
- **Reversal of Heparin Action:** **Protamine** antagonize the heparin. Intravenous injection of protamine neutralises heparin weight for weight, i.e. 1 mg is needed for every 100 U of heparin.

Use of anticoagulant

- The aim of using anticoagulants is to prevent thrombus extension and embolic complications by reducing the rate of fibrin formation.
 - *Deep vein thrombosis and pulmonary embolism*
 - *Myocardial infarction*
 - *Unstable angina*
 - *Rheumatic heart disease; Atrial fibrillation*
 - *Cerebrovascular disease*
 - *Vascular surgery, prosthetic heart valves, retinal vessel thrombosis, extracorporeal circulation, haemodialysis*
 - *Defibrination syndrome*

Direct factor Xa inhibitors

- **Rivaroxaban:** It is an orally active direct inhibitor of activated factor Xa which has become available for prophylaxis and treatment of Deep Vein Thrombosis (DVT).

Oral direct thrombin inhibitor

- **Dabigatran etexilate:** It is a **prodrug** which after oral administration is rapidly hydrolysed to dabigatran, a direct thrombin inhibitor. Dabigatran reversibly blocks the catalytic site of thrombin and produces a rapid anticoagulant action.

FIBRINOLYTICS

(Thrombolytics)

Thrombolytics

Streptokinase, Urokinase, Alteplase (rt-PA), Reteplase

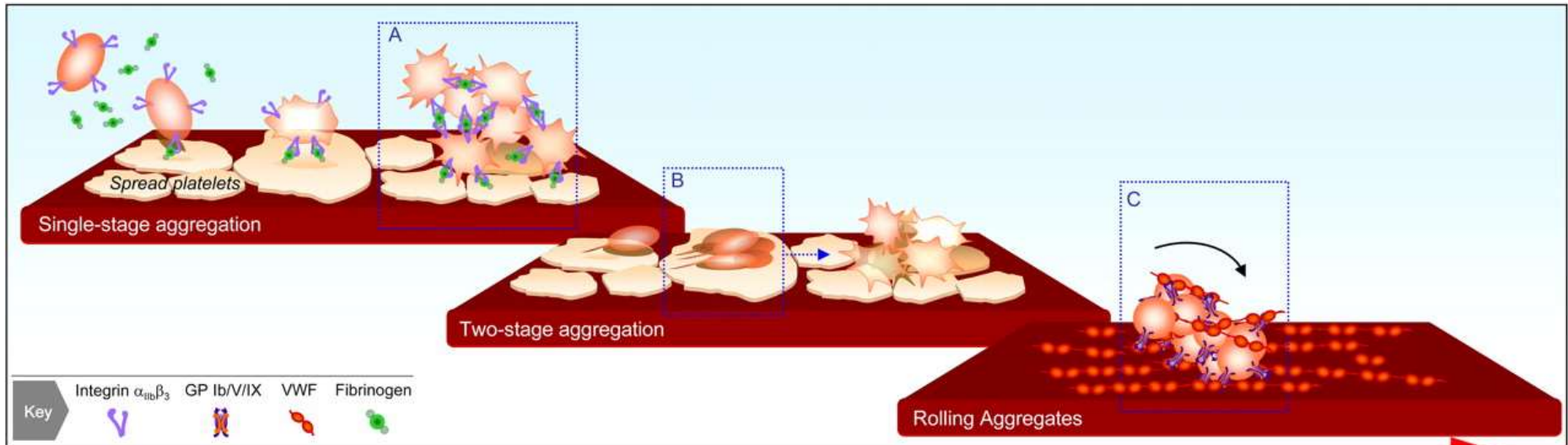
Tenecteplase:

- These are drugs used to lyse thrombi/clot to recanalize occluded blood vessels (mainly coronary artery).
- **Streptokinase** is a protein synthesized by *Streptococci* that combines with the proactivator plasminogen.
- **Urokinase** is a human enzyme synthesized by the kidney that directly converts plasminogen to active plasmin.

Thrombolytics

Streptokinase, Urokinase, Alteplase (rt-PA), Reteplase
Tenecteplase:

- **Uses of fibrinolytics:**
- Administration of fibrinolytic drugs by the i.v. route is indicated in cases of **pulmonary embolism with hemodynamic instability, severe deep venous thrombosis** such as the **superior vena caval syndrome**, and **ascending thrombophlebitis** of the iliofemoral vein with **severe lower extremity edema**.
- These drugs are also given intra-arterially, especially for peripheral vascular disease.



Characteristic Features:	A	B	C
Adhesion Receptor	Integrin $\alpha_{IIb}\beta_3$	Integrin $\alpha_{IIb}\beta_3$, GP Ib/V/IX	GP Ib/V/IX
Activation-dependent	Yes	Yes	No
Tether formation	No	Yes	Yes
Ligand	Fibrinogen	VWF, Fibrinogen, Fibronectin	VWF
Platelet Morphology	Sphere and filopodia	Discoid	Smooth Spherical

Platelet aggregation inhibitors

Image source: Jackson SP. The growing complexity of platelet aggregation. Blood. 2007;109(12):5087-95.

Platelet aggregation inhibitors

Aspirin:

- Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation.
- The platelet aggregation inhibitors described below inhibit cyclooxygenase-1 (COX-1) or block GP IIb/IIIa or ADP receptors, thereby interfering with the signals that promote platelet aggregation.
- **Use:** Aspirin is used in the prophylactic treatment of transient cerebral ischemia.

Platelet aggregation inhibitors

Ticlopidine, clopidogrel, prasugrel, and ticagrelor:

- These drugs inhibit the binding of ADP to its receptors on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other. Ticagrelor binds to the P2Y₁₂ ADP receptor in a reversible manner.
- **Use:** **Clopidogrel** is approved for prevention of atherosclerotic events in patients with a recent MI or stroke and for prophylaxis of thrombotic events in acute coronary syndromes.

Platelet aggregation inhibitors

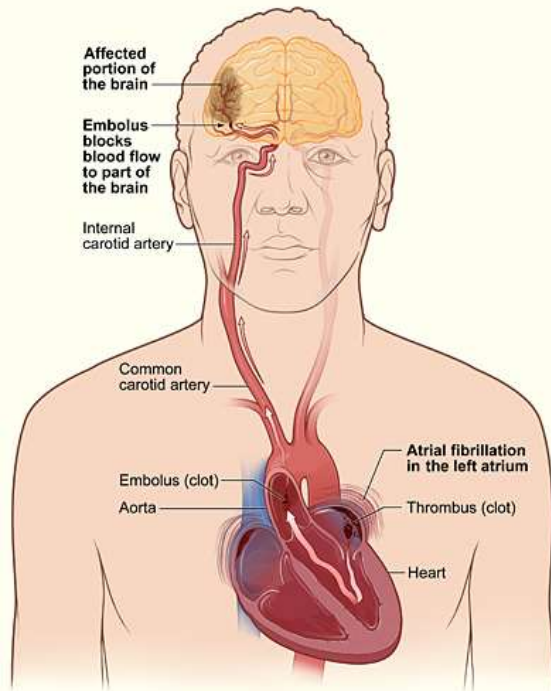
Ticlopidine, clopidogrel, prasugrel, and ticagrelor:

- **Use:** **Ticlopidine** is indicated for the prevention of transient ischemic attacks and strokes in patients with a prior cerebral thrombotic event. It is generally reserved for patients who are intolerant to other therapies.
- **Prasugrel** is approved to decrease thrombotic cardiovascular events in patients with acute coronary syndromes.
- **Ticagrelor** is approved for the prevention of arterial thromboembolism in patients with unstable angina and acute MI.

Platelet aggregation inhibitors

Abciximab, eptifibatide, and tirofiban:

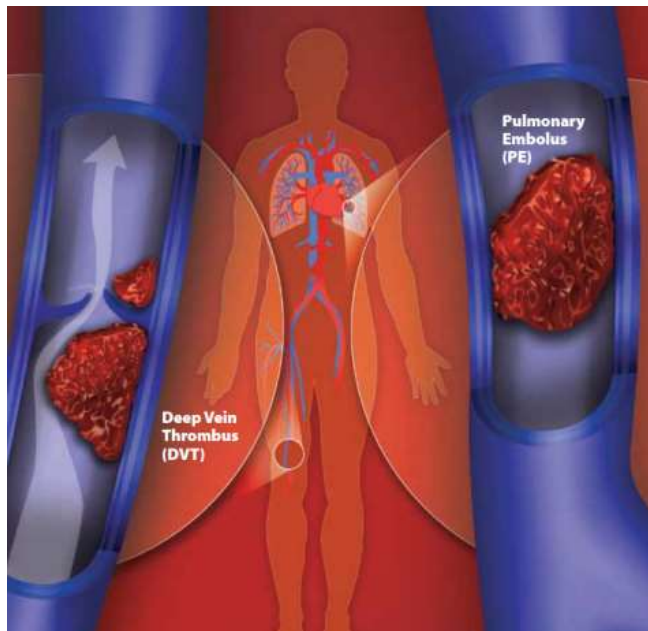
- A chimeric monoclonal antibody, abciximab, eptifibatide inhibits the glycoprotein IIb/IIIa receptor complex.
- **Use:** These agents are given intravenously, along with heparin and aspirin, as an adjunct to percutaneous coronary intervention (PCI) for the prevention of cardiac ischemic complications.



**March:
Blood Clot
Awareness Month**

*Get the stats and facts to
help spread awareness about
this silent killer.*

Find out more <http://BloodClotRecovery.net>



Thank you