DRUGS AFFECTING COAGULATION, BLEEDING AND THROMBOSIS

Hemostasis is the arrest of the blood loss from damaged blood vessels. Three principal hemostatic are involved to prevent bleeding after injury.

(i) Adhesion and activation of platelets.
(ii) Formation of Blood clot
(iii) Vascular contraction

Thrombosis is the unwanted formation of a hemostatic plug or thrombus within the blood vessels or Heart.

It is important to distinguish between thrombi and emboli:

- ✓ A clot that adheres to a vessel wall is called a "**Thrombus**," whereas an intravascular clot that floats in the blood is termed an "**Embolus.**" Thus, a detached thrombus becomes an embolus. Both thrombi and emboli are dangerous, because they may occlude blood vessels and deprive tissues of oxygen and nutrients.
- ✓ Arterial thrombosis most often occurs in medium-sized vessels rendered thrombogenic by surface lesions on endothelial cells caused by atherosclerosis.
- ✓ Arterial thrombosis usually consists of a platelet- rich clot. In contrast, venous thrombosis is triggered by blood stasis or inappropriate activation of the coagulation cascade, commonly as a result of a defect in the normal hemostatic defense mechanisms. Venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets than are observed with arterial clots.

Blood clots are a multi-stage sequence that involves endothelial cells, the blood platelets, the coagulation cascade and the fibrinolytic system.

Clotting of blood involves basically three steps:

1. Activation of Prothrombin which is present in the plasma.
2. Conversion of prothrombin into thrombin in the presence of calcium and other factor.
3. Conversion of fibrinogen to fibrin (clot) by active thrombin.

Both the extrinsic and the intrinsic systems involve a cascade of enzyme reactions that sequentially transform various plasma factors (proenzymes) to their active (enzymatic) forms. They ultimately produce Factor Xa, which converts prothrombin (Factor II) to thrombin (Factor IIa,) Thrombin plays a key role in coagulation, because it is responsible for generation of fibrin, which is the GP that forms the meshlike matrix of the blood clot. If thrombin is not formed or if its function is impeded coagulation is inhibited.

COAGULANTS

These are substances which promote coagulation and are indicated in haemorrhagic states.

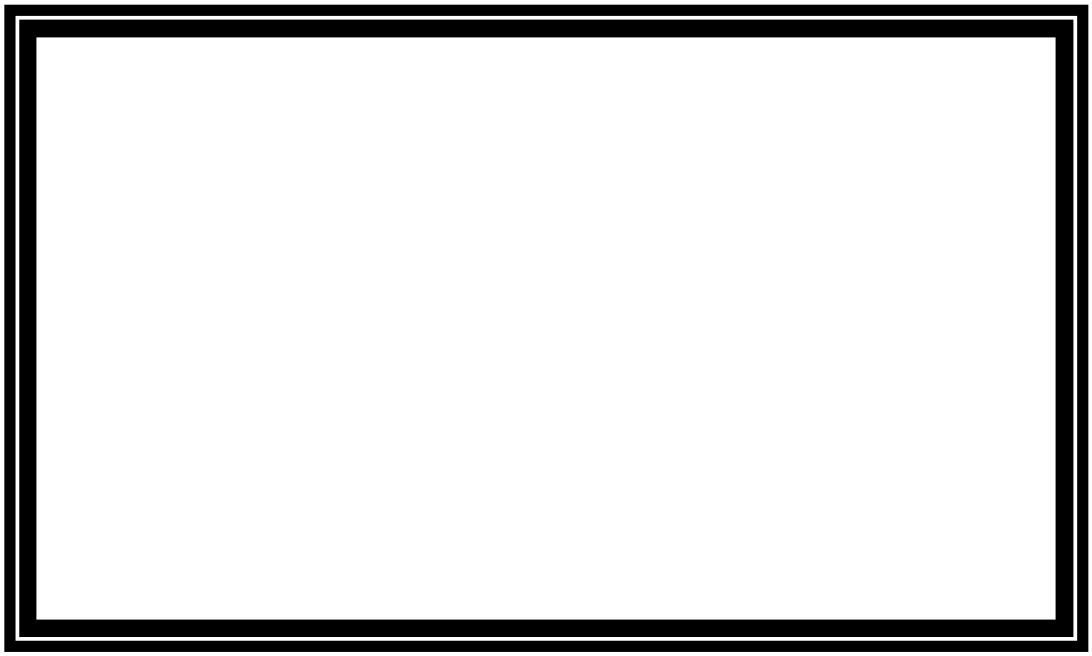
Fresh whole blood or plasma provides all the factors needed for coagulation and are the best therapy for deficiency of any clotting factor; also they act immediately. Other drugs usesd to restore haemostasis are:

1. Vitamin K
   K_1 (from plants, fat-soluble): Phytonadine (Phylloquinone)
   K3 (Synthetic)
   Fat soluble: Menadione, Acetamenaphthone
   Water soluble: Menadione sod. Bisulfate
   Menadione sod. Diphosphate
2. Miscellaneous
   Fibrinogen (human)
   Antihaemophilic factor

Desmopressin
Adrenochrome monosemicarbazone
Rutin, Ethamsylate

VITAMIN K

It is a fat-soluble dietary principal required for the synthesis of clotting factors.
It is essential for the formation of clotting factors II, VII, IX and X. These are all glycoproteins with several γ-carboxyglutamic acid (Gla) residues. The interaction of factors Xa and prothrombin (factor II) with Ca^{2+} and phospholipid. γ-Carboxylation occurs after the synthesis of the amino acid chain, and the carboxylase enzyme requires reduced vitamin K as a co-factor. Binding does not occur in the absence of γ-carboxylation. Similar considerations apply to the proteolytic activation of factor X by IXa and by VIIa.



Administration and pharmacokinetic aspects
Natural vitamin K_1 (**phytomenadione**) may be given orally or by injection. If given by mouth, it requires bile salts for absorption, and this occurs by a saturable energy-requiring process in the proximal small intestine. A synthetic preparation, **menadiol sodium phosphate**, is also available. It is water soluble and does not require bile salts for its absorption. This synthetic compound takes longer to act than phytomenadione. There is very little storage of vitamin K in the body. It is metabolised to more polar substances that are excreted in the urine and the bile.

Deficiency: deficiency of Vit. K occurs due to liver disease, obstructive jaundice, malabsorption, long-term antimicrobial therapy which alters intestinal flora. The most imp manifestation is bleeding tendency due to lowering of the levels of prothrombin and other clotting factors in blood. Haematuria is usually first to occur; other common sites of bleeding ate g.i.t., nose, and under the skin-ecchymoses.

USE:

(i) Dietary deficiency

(ii) Prolonged antimicrobial therapy

(iii) Obstructive jaundice or malabsorption syndrome

(iv) Liver disease

(v) New borns: all newborns have low levels of prothrombin and other clotting factors. Further decrease occurs in the next few days. The cause is both lower capacity to synthesize clotting factors as well as deficiency of vit.K. The defect is exaggerated in the premature infant.

(vi) Overdose of oral anticoagulants: Phytonadione is the preparation of choice, because it acts rapidly, dose depends on the everity of hypoprothrombinaemia and bleeding.
Severe: 10 mg i.m. followed by 5 mg 4 hourly; bleeding generally stops in 6-12 hrs, but normal levels of coagulation factors are restored only after 24 hrs.

TOXICITY

- ✓ Rapid i.v. injection of emulsified vit K produces flushing, breathlessness, a sense of constriction in the chest, fall in BP, few death are on record.

ANTOCOAGULANTS

- ✓ These are the drugs used to prevent clotting and thus prevent thrombosis.
- ✓ The anticoagulant drugs inhibit either the action of the coagulation factors (the thrombin inhibitors, such as *heparin* and *heparin*-related agents) or interfere with the synthesis of the coagulation factors (the vitamin K antagonists such as *warfarin*).

They classified into

1. **Used in vivo**
   - **A.** Parenteral anticoagulants: Heparin, Low molecular weight heparin, Heparinoids-Heparan sulfate, Danaparoid
   - **B.** Oral anticoagulants
     - (i) Coumarin derivatives: Bishydroxycoumarin, warfarin sod, Acenocoumarol, Ethylbiscoumacetate
     - (ii) Indandione derivative: Phenindione
2. **Used in vitro**
   - **A.** Heparin
   - **B.** Calcium complexing agents: Sodium citrate

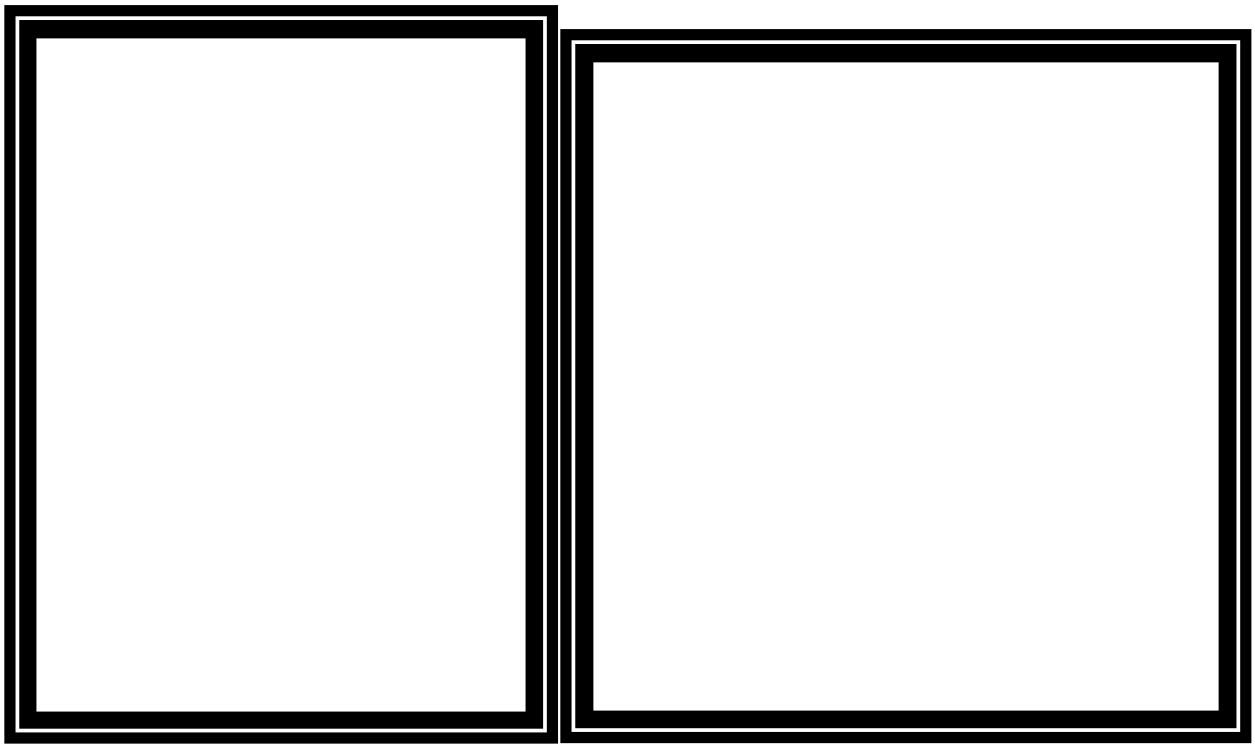
HEPARIN

- ✓ Heparin was discovered in 1916 by a second-year medical student at Johns Hopkins Hospital. He was attempting to extract thromboplastic (i.e. coagulant) substances from various tissues during a vacation project, but found instead a powerful anticoagulant activity. This was named heparin, because it was first extracted from liver.
- ✓ Heparin is a nonuniform mixture of straight chain mucoplysaccharides with MW 10,000 to 20,000. It contains polymers of two sulfated disaccharide units. It carries strong

electronegative charges and is the strongest organic acid present in the body. It occurs in mast cells as a much bigger molecular loosely bound to the granular protein. Thus, heparin is present in all tissues containing mast cells; richest sources are lung, liver and intestinal mucosa. Commercial preparations are extracted from beef lung or hog intestine and, because preparations differ in potency, assayed biologically against an agreed international standard: doses are specified in units of activity rather than of mass.

Mechanism of action:

- ✓ *Heparin* acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors.
- ✓ Antithrombin III is an α-globulin. It inhibits serine proteases, including several of the clotting factors, most importantly, thrombin (Factor IIa) and Factor Xa.
- ✓ In the absence of *heparin*, antithrombin III interacts very slowly with thrombin and Factor Xa.
- ✓ *Heparin* molecules bind to antithrombin III, inducing a conformational change that accelerates its rate of action about 1000-fold.
- ✓ *Heparin* also serves as a catalytic template for the interaction of antithrombin III and the activated coagulation factors.
- ✓ *Heparin* serves as a true catalyst, allowing antithrombin III to rapidly combine with and inhibit circulating thrombin and Factor Xa.
- ✓ In contrast, *LMWHs* complex with antithrombin III and inactivate Factor Xa but do not bind as avidly to thrombin. Indeed, *LMWHs* are less likely than *heparin* to activate resting platelets.



ADMINISTRATION AND PHARMACOKINETIC ASPECTS

- ✓ Heparin is not absorbed from the gut because of its charge and high molecular weight, and it is therefore given intravenously or subcutaneously (intramuscular injections would cause haematomas).
- ✓ Heparin acts immediately following intravenous administration, but the onset is delayed by up to 60 min when it is given subcutaneously. The elimination half-life is approximately 40-90 min.
- ✓ In urgent situations, it is therefore usual to start treatment with a bolus intravenous dose, followed by a constant-rate infusion.
- ✓ Low-molecular-weight heparins are given subcutaneously. T
- ✓ They have a longer elimination half-life than unfractionated heparin, and this is independent of dose (first-order kinetics), so the effects are more predictable and dosing less frequent (once or twice a day). LMWHs do not prolong the APTT.
- ✓ Unlike unfractionated heparin, the effect of a standard dose is sufficiently predictable that monitoring is not required routinely.
- ✓ **LMWHs are eliminated mainly by renal excretion, and unfractionated heparin is preferred in renal failure**, but with this exception LMWHs are at least as safe and effective as unfractionated heparin and are more convenient to use, because patients can be taught to inject themselves at home and there is generally no need for blood tests and dose adjustment.
- ✓ **Heparin should not be mixed with penicillin, tetracycline,hydrocortisone, or NA in the same syringe or infusion bottle. Heparinized blood is not suitable for blood counts.**

ADVERSE EFFECTS:

Despite early hopes of fewer side effects with *LMWHs*, complications have proven to be similar to those seen with *heparin.* However, exceptions are thromboembolic problems, which are less common.

a. **Bleeding complications:** The chief complication of *heparin* therapy is hemorrhage. Careful monitoring of the bleeding time is required to minimize this problem. Excessive bleeding may be managed by ceasing administration of the drug or by treating with *protamine sulfate*. When infused slowly, the latter combines ionically with *heparin* to form a stable, 1:1 inactive complex. It is very important that the dosage of *protamine sulfate* is carefully titrated (1 mg for every 100 units of *heparin* administered) because *protamine sulfate* is a weak anticoagulant, and excess amounts may trigger bleeding episodes or worsen bleeding potential.
b. **Hypersensitivity reactions:** *Heparin* preparations are obtained from porcine sources and, therefore, may be antigenic. Possible adverse reactions include chills, fever, urticaria, and anaphylactic shock.
c. **Thrombosis:** Chronic or intermittent administration of *heparin* can lead to a reduction in antithrombin III activity, thus decreasing the inactivation of coagulation factors and, thereby, increasing the risk of thrombosis. To minimize this risk, low-dose *heparin* therapy is typically used.

d. **Thrombocytopenia:** This condition, in which circulating blood contains an abnormally small number of platelets, is a common abnormality among hospital patients receiving *heparin*. *Heparin* therapy should be discontinued in patients that show severe thromboyctopenia. *Heparin* can be replaced by another anticoagulant, such as *dabigatran*, *lepirudin* or *argatroban*.
e. **Other:** *Heparin* may produce abnormal liver function tests, and osteoporosis has been observed in patients on long-term *heparin* therapy.
f. **Contraindications:** *Heparin* is contraindicated for patients who are hypersensitive to it; have bleeding disorders; are alcoholics; or are having or have had recent surgery of the brain, eye, or spinal cord.

CONTRAINDICATION

- ✓ Bleeding disorders, heparin induced thrombocytopenia.
- ✓ Severe hypertension (risk of cerebral hemorrhage), threatened abortion, piles, g.i.ulcers.
- ✓ Subacute bacterial endocarditis, large malignancies, tuberculosis
- ✓ Ocular and neurosurgery, Lumber puncture.
- ✓ Chronic alcoholics, Cirrhosis, renal failure
- ✓ Aspirin and other antiplatelet drugs should be used vary cautiously during heparin therapy.

Heparin antagonist: Protamine sulfate

- ✓ Strongly basic, low molecular weight protein obtained from the sperm of certain fish.
- ✓ It is a specific antagonist for heparin overdose
- ✓ It promptly neutralizes strongly acidic heparin weight by weight.1mg for 100 U heparin.
- ✓ In the absence of heparin it itself acts as a weak anticoagulant by interacting with platelet and fibrinogen.
- ✓ It is given I.V.
- ✓ Being basic it release histamine in the body and causes hypersensitivity reactions, sometimes flushing and breathing difficulties occurs.

Fondaparinux:

- ✓ It is a synthetic pentasaccharide that causes an antithrombin III- mediated selective inhibition of factor Xa.
- ✓ Neutralization of factor Xa interrupts the blood coagulation cascade leading ultimately to inhibition of thrombin formation.
- ✓ It is given SC once daily.
- ✓ Half-lilfe is 17-21 hrs which gets prolonged in renal impairment
- ✓ It is excreted unchanged in urine
- ✓ It is preferred for thromboprophylaxis of patient undergoing hip or knee surgery and for pulmonary embolism.

Hirudin:

- ✓ The anticoagulant from the medicinal leech, has been synthesized by recombinant DNA techniques.
- ✓ It is used as anticoagulant in the patients with heparin induced thrombocytopenia and associated thrombo-embolic disease.
- ✓ Also for prevention of ischemic complications associated with unstable angina.
- ✓ It is given prenatally

- ✓ ADR: hemorrhage, haematuria and increased transaminase.

Argatroban:

- ✓ It is a thrombin inhibitor,
- ✓ Used in patient with heparin induced thrombocytopenia
- ✓ Short duration of action
- ✓ Given by continued I.V. infusion

Danaparoid:

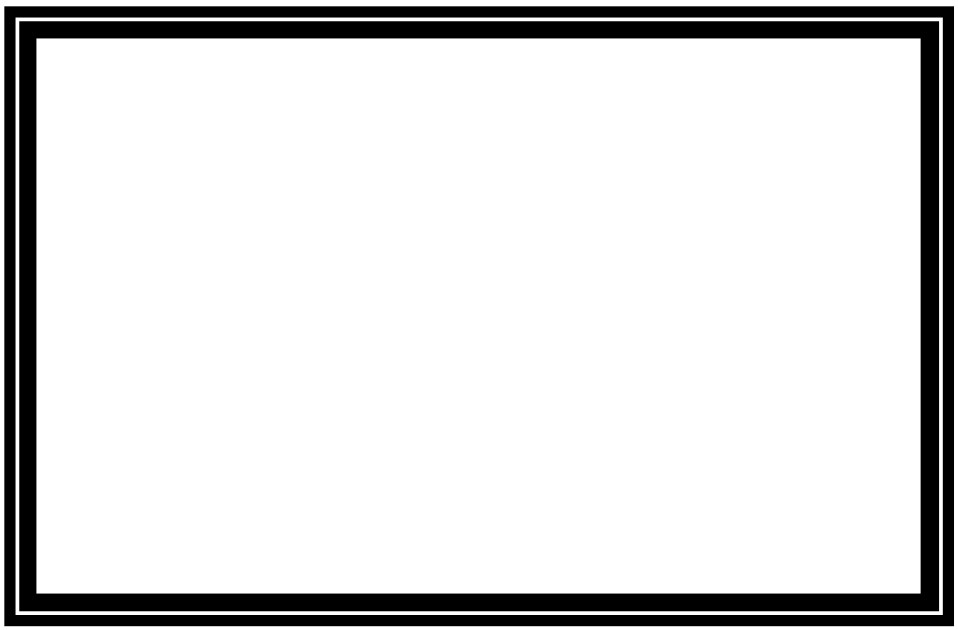
- ✓ Mixture of heparin like natural subatances (84% heparan sulfate+ 12% dermatan sulfate + 4% chondroitin sulfate) obtained from pig intestinal mucosa.
- ✓ It inhibits activation of factor Xa which inhibit thrombin generation.
- ✓ Used for prevetion of postoperative deep vein thrombosis following active hip replacement surgery
- ✓ For treatment of heparin induced thrombocytopenia
- ✓ Has longer elimination half-life of 24 hrs

ORAL ANTICOAGULANTS

- ✓ Oral anticoagulants were discovered as an indirect result of a change in agricultural policy in North America in the 1920s. Sweet clover was substituted for corn in cattle feed, and an epidemic of deaths of cattle from haemorrhage ensued.
- ✓ This turned out to be caused by bishydroxycoumarin in spoiled sweet clover, and it led to the discovery of warfarin (named for the Wisconsin Alumni Research Foundation).
- ✓ One of the first uses to which this was put was as a rat poison, but for more than 50 years it has been the standard anticoagulant for the treatment and prevention of thromboembolic disease.
- ✓ **Warfarin** is the most important oral anticoagulant; alternatives with a similar mechanism of action, for example **phenindione**, are now used only in rare patients who experience idiosyncratic adverse reactions to warfarin.
- ✓ Warfarin and other vitamin K antagonists require frequent blood tests to individualise dose, and are consequently inconvenient as well as having a low margin of safety

MECHANISM OF ACTION

- ✓ Vitamin K antagonists act only in vivo and have no effect on clotting if added to blood in vitro.
- ✓ They interfere with the post-translational γ-carboxylation of glutamic acid residues in clotting factors II, VII, IX and X.
- ✓ They do this by inhibiting *vitamin K epoxide reductase component 1* (VKORC1), thus inhibiting the reduction of vitamin K epoxide to its active hydroquinone form.
- ✓ Inhibition is competitive
- ✓ The effect of warfarin takes several days to develop because of the time taken for degradation of preformed carboxylated clotting factors.
- ✓ Onset of action thus depends on the elimination half-lives of the relevant factors. Factor VII, with a half-life of 6 h, is affected first, then IX, X and II, with half-lives of 24, 40 and 60 h, respectively.



PHARMACOKINETICS:

- ✓ *Warfarin* is rapidly absorbed after oral administration (100% bioavailability with little individual patient variation).
- ✓ Although food may delay absorption, it does not affect the extent of absorption of the drug.
- ✓ *Warfarin* is 99 percent bound to plasma albumin, which prevents its diffusion into the cerebrospinal fluid,
- ✓ urine, and breast milk.
- ✓ However, drugs that have a greater affinity for the albumin-binding site, such as sulfonamides, can displace the anticoagulant and lead to a transient, elevated activity.
- ✓ Drugs that affect *warfarin* binding to its plasma proteins can lead to drug interactions and variability in the therapeutic response to *warfarin*.
- ✓ *Warfarin* readily crosses the placental barrier.
- ✓ The mean half-life of *warfarin* is approximately 40 hours, but this value is highly variable among individuals. Prothrombin time, a measure of the extrinsic pathway, may be used to monitor *warfarin*
- ✓ therapy.
- ✓ The products of *warfarin* metabolism, catalyzed by the CYP450 system, are inactive. After conjugation to glucuronic acid, they are excreted in urine and feces.
- ✓ Agents that affect the metabolism of *warfarin* may alter its therapeutic effects.

THERAPEUTIC USES:

- ✓ *Warfarin* is used to prevent the progression or recurrence of acute deep vein thrombosis or pulmonary embolism after initial *heparin* treatment.
- ✓ It is also used for the prevention of venous thromboembolism during orthopedic or gynecologic surgery.
- ✓ Prophylactically, it is used in patients with acute myocardial infarction, prosthetic heart valves, and chronic atrial fibrillation.

ADVERSE EFFECTS:

- ✓ Bleeding as a result of extension of the desired pharmacological action is the most imp problem.
- ✓ Ecchymosis, Epistaxis, Hematuria, Bleeding, in the g.i.t
- ✓ Intracranial or other internal haemorrhages may be fatal.

FACTORS THAT POTENTIATE ORAL ANTICOAGULANTS

- ✓ Liver disease interferes with the synthesis of clotting factors; conditions in which there is a high metabolic rate, such as fever and thyrotoxicosis, increase the effect of anticoagulants by increasing degradation of clotting factors.
- ✓ Many drugs potentiate warfarin.
- ✓ **Agents that inhibit hepatic drug metabolism** Examples include cimetidine, imipramine, co-trimoxazole, chloramphenicol , ciprofloxacin, metronidazole, amiodarone and many antifungal azoles.
- ✓ **Drugs that inhibit platelet function** Non-steroidal anti-inflammatory drugs (NSAIDs) are particularly evident but some antibiotics incuding moxalactam and carbenicillin also alter platelet function. Aspirin increases the risk of bleeding if given during warfarin therapy, although this combination can be used safely with careful monitoring.
- ✓ **Drugs that displace warfarin from binding sites on plasma albumin** Some of the NSAIDs and chloral hydrate, for example, result in a transient increase in the concentration of free warfarin in plasma. This mechanism seldom causes clinically important effects, unless accompanied by an additional effect on warfarin metabolism.
- ✓ **Drugs that inhibit reduction of vitamin K** Such drugs include the cephalosporins.
- ✓ **Drugs that decrease the availability of vitamin K** Broad-spectrum antibiotics and some sulfonamides depress the intestinal flora, which normally synthesise vitamin K_2 (a form of vitamin K made by gut bacteria), but this has little effect unless there is a concurrent dietary deficiency.
- ✓ **Hyperthyroidism:** the clotting factor are degraded faster
- ✓ **Newborns:** have low levels of vit K and clotting factors

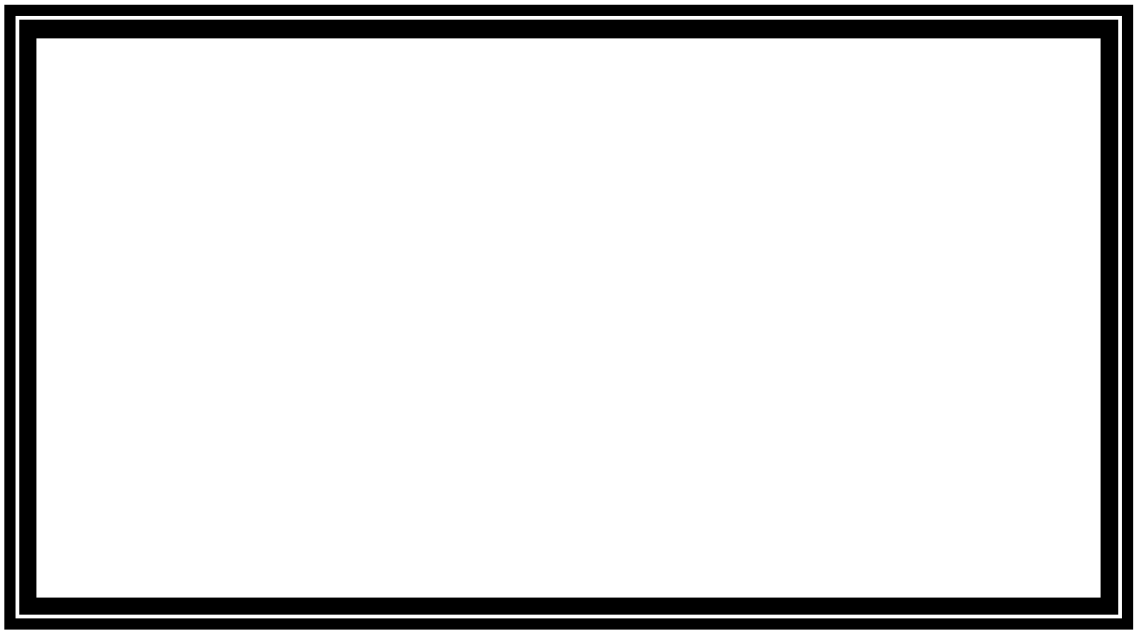
FACTORS THAT LESSEN THE EFFECT OF ORAL ANTICOAGULANTS

- ➢ **Physiological state/disease**
- ✓ There is a decreased response to warfarin in conditions (e.g. *pregnancy*) where there is increased coagulation factor synthesis.
- ✓ Similarly, the effect of oral anticoagulants is lessened in *hypothyroidism*, which is associated with reduced degradation of coagulation factors.
- ➢ **Drugs**
- ✓ Several drugs reduce the effectiveness of warfarin; this leads to increased doses being used to achieve the target INR.
- ✓ If the dose of warfarin is not reduced when the interacting drug is discontinued, this can result in over-anticoagulation and haemorrhage.

- ✓ **Drugs that induce hepatic P450 enzymes** Such induction will increase the degradation of warfarin (e.g. **rifampicin, carbamazepine , barbiturates, griseofulvin**).
- ✓ **Drugs that reduce absorption** Drugs that alter passage through the gastrointestinal tract, for example **colestyramine**, will affect absorption of warfarin.

USES OF ANTOCOAGULANTS

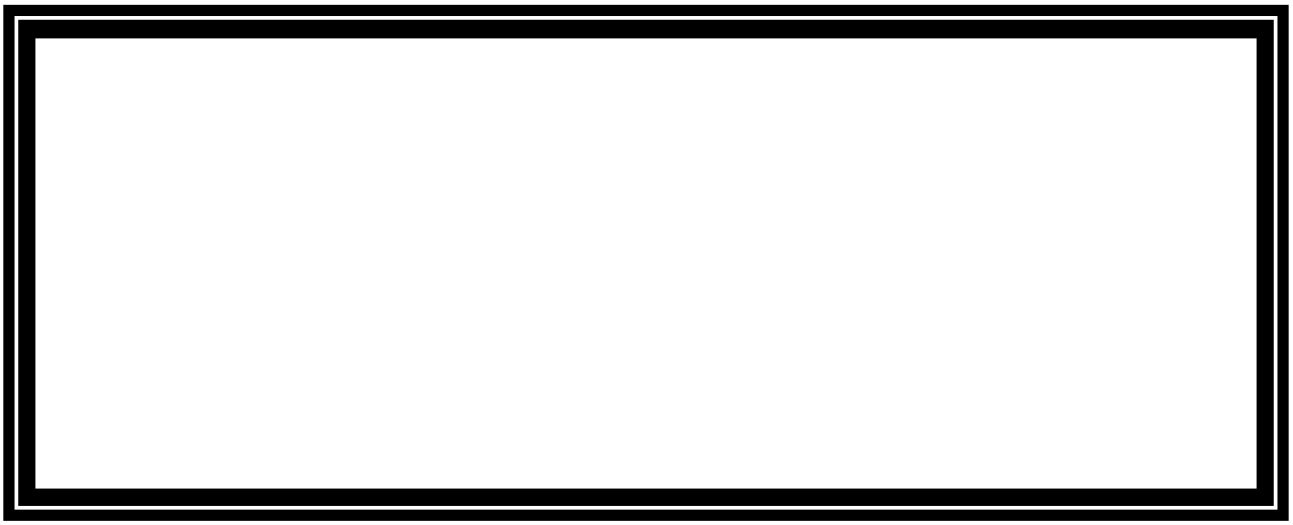
1. Deep vein thrombosis and pulmonary embolism
2. Myocardial infarction
3. Unstable angina
4. Rheumatic heart disease; Atrial fibrillation
5. Cerebrovascular disease
6. Vascular surgery, prosthetic heart valves, retinal vessels thrombosis, extracorporeal circulation, haemodialysis
7. Defibrination syndrome



FIBRINOLYTICS (THROMBOLYTICS)

- ✓ These are drugs used to lyse thrombi/clot to recanalize occulded blood vessels.
- ✓ They are curative rather than prophylactic; work by activating the natural fibrinolytic system.
- ✓ When the coagulation system is activated, the fibrinolytic system is also set in motion via several endogenous *plasminogen activators*, including tissue plasminogen activator (tPA), urokinase-type plasminogen activator, kallikrein and neutrophil elastase.
- ✓ Plasminogen is deposited on the fibrin strands within a thrombus.

- ✓ Plasminogen activators are serine proteases and are unstable in circulating blood. They diffuse into thrombus and cleave plasminogen, a zymogen present in plasma, to release plasmin
- ✓ Plasmin is trypsin-like, acting on Arg-Lys bonds, and thus digests not only fibrin but fibrinogen; factors II, V and VIII; and many other proteins.
- ✓ It is formed locally and acts on the fibrin meshwork, generating fibrin degradation products and lysing the clot.
- ✓ Its action is localised to the clot, because plasminogen activators are effective mainly on plasminogen adsorbed to fibrin.
- ✓ Any plasmin that escapes into the circulation is inactivated by plasmin inhibitors, including PAI-1, which protect us from digesting ourselves from within.



- ✓ *Streptokinase*, one of the first such agents to be approved, causes a systemic fibrinolytic state that can lead to bleeding problems.
- ✓ *Alteplase* acts more locally on the thrombotic fibrin to produce fibrinolysis.
- ✓ *Urokinase* is produced naturally in human kidneys and directly converts plasminogen into active plasmin.
- ✓ Clinical experience has shown nearly equal efficacy between *streptokinase* and *alteplase*.
- ✓ Fibrinolytic drugs may lyse both normal and pathologic thrombi.

COMMON CHARACTERISTICS OF THROMBOLYTIC AGENTS

Mechanism of action:

- ✓ All act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi
- ✓ Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age.
- ✓ Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis.
- ✓ Strategies to prevent this include administration of antiplatelet drugs, such as *aspirin*, or antithrombotics such as *heparin*.

Therapeutic uses:

- ✓ Originally used for the treatment of deep vein thrombosis and serious pulmonary embolism.
- ✓ Thrombolytic drugs are now being used less frequently for these conditions.
- ✓ Their tendency to cause bleeding has also blunted their use in treating acute myocardial infarction or peripheral arterial thrombosis.
- ✓ However, thrombolytic agents are helpful in restoring catheter and shunt function, by lysing clots causing occlusions.
- ✓ Thrombolytic agents are also used to dissolve clots that result in strokes.

Pharmacokinetics:

- ✓ For myocardial infarction, intracoronary delivery of the drugs is the most reliable in terms of achieving recanalization.
- ✓ However, cardiac catheterization may not be possible in the 2 to 6 hour "therapeutic window," beyond which significant myocardial salvage becomes less likely.
- ✓ Thus, thrombolytic agents are usually administered intravenously, because this route is rapid, is inexpensive, and does not have the risks of catheterization.

Adverse effects:

- ✓ The thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug.
- ✓ Thus, hemorrhage is a major side effect.
- ✓ These drugs are contraindicated in patients with healing wounds, pregnancy, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.
- ✓ Continued presence of thrombogenic stimuli may cause rethrombosis after lysis of the initial clot.

Alteplase

- ✓ *Alteplase* is a serine protease originally derived from cultured human melanoma cells. It is now obtained as a product of recombinant DNA technology.

Mechanism of action:

- ✓ *Alteplase* has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug.
- ✓ Thus, *alteplase* is said to be "fibrin selective," and, at low doses, it has the advantage of lysing
- ✓ only fibrin, without unwanted degradation of other proteins.

Therapeutic uses:

- ✓ *Alteplase* is approved for the treatment of myocardial infarction, massive pulmonary embolism, and acute ischemic stroke.
- ✓ *Alteplase* seems to be superior to *streptokinase* in dissolving older clots and, ultimately, may be approved for other applications.
- ✓ *Alteplase* administered within 3 hours of the onset of ischemic stroke significantly improves clinical outcome, that is, the patient's ability to perform activities of daily living.
- ✓ *Reteplase* is similar to *alteplase* and can be used as an alternative.

Pharmacokinetics:

- ✓ *Alteplase* has a very short half-life (5 to 30 minutes) and, therefore, is administered as a total dose equal to 0.9 mg/kg.
- ✓ Ten percent of the total dose is injected intravenously as a bolus and the remaining drug is administered over 60 minutes.

Adverse effects:

- ✓ Bleeding complications, including GI and cerebral hemorrhages, may occur.

STREPTOKINASE

Streptokinase is an extracellular protein purified from culture broths of Group C β-hemolytic streptococci.

Mechanism of action:

- ✓ *Streptokinase* has no enzymatic activity.
- ✓ Instead, it forms an active one-to-one complex with plasminogen.
- ✓ This enzymatically active complex converts uncomplexed plasminogen to the active enzyme plasmin.
- ✓ In addition to the hydrolysis of fibrin plugs, the complex also catalyzes the degradation of fibrinogen as well as clotting Factors V and VII.

Therapeutic uses:

- ✓ acute pulmonary embolism,
- ✓ deep vein thrombosis,
- ✓ acute myocardial infarction,
- ✓ arterial thrombosis, and
- ✓ occluded access shunts.

Pharmacokinetics:

- ✓ *Streptokinase* therapy is instituted within 4 hours of a myocardial infarction and is infused for 1 hour.
- ✓ Its halflife is less than half an hour.
- ✓ Thromboplastin time is monitored and maintained at two- to five fold the control value.
- ✓ On discontinuation of treatment, either *heparin* or oral anticoagulants may be administered.

Adverse effects:

1. **Bleeding disorders:**
   - ✓ Activation of circulating plasminogen by *streptokinase* leads to elevated levels of plasmin, which may precipitate bleeding by dissolving hemostatic plugs.
   - ✓ In the rare instance of life-threatening hemorrhage, *aminocaproic acid* may be administered.
2. **Hypersensitivity:**
   - ✓ *Streptokinase* is a foreign protein and is antigenic.
   - ✓ Rashes, fever, and, rarely, anaphylaxis occur.
   - ✓ Because most individuals have had a streptococcal infection sometime in their lives, circulating antibodies against *streptokinase* are likely to be present in most patients.
   - ✓ These antibodies can combine with *streptokinase* and neutralize its fibrinolytic properties.
   - ✓ Therefore, sufficient quantities of *streptokinase* must be administered to overwhelm the antibodies and provide a therapeutic concentration of plasmin.
   - ✓ Fever, allergic reactions, and therapeutic failure may be associated with the presence of antistreptococcal antibodies in the patient.
   - ✓ The incidence of allergic reactions is approximately 3 percent.

ANISTREPLASE (ANISOYLATED PLASMINOGEN STREPTOKINASE ACTIVATOR COMPLEX)(APSAC)

- ✓ *Anistreplase* is a preformed complex of *streptokinase* and plasminogen and is considered to be a prodrug.
- ✓ *Streptokinase* must be released, and only plasminogen will get converted to plasmin.

UROKINASE

- ✓ *Urokinase* is produced naturally in the body by the kidneys.
- ✓ Therapeutic *urokinase* is isolated from human kidney cells and has low antigenicity.

Mechanism of action:

- ✓ *Urokinase* directly cleaves the arginine-valine bond of plasminogen to yield active plasmin.

Therapeutic uses:

- ✓ *Urokinase* is only approved for lysis of pulmonary emboli.
- ✓ Off-label uses include treatment of acute myocardial infarction, arterial thromboembolism, coronary artery thrombosis, and deep venous thrombosis.

Pharmacokinetics:

- ✓ *Urokinase* has a short duration of action and is rapidly cleared by the liver (the kidney is only a minor pathway for elimination).
- ✓ Thus, the plasma half-life of *urokinase* is approximately 20 minutes.
- ✓ The half-life may be prolonged in patients with hepatic impairment.

Adverse effects:

- ✓ Bleeding is the most frequently reported side effect.
- ✓ Rare allergic or anaphylactic reactions have also been reported.

ANTIFIBRINOLYTIC

These are drugs which inhibit plasminogen activation and dissolution of clot.

EPSILON AMINO-CAPROIC ACID (EACA)

- ✓ It is an analogue of the amino acid lysine; combine with the lysine binding sites of plasminogen ans plasmin so that the latter is not able to bind to fibrin and lyse it.
- ✓ It is a specific antidote for fibrinolytic agents and has been used in many hyperplasminaemic states associated with excessive intravascular fibrinolysis resulting in bleeding, e.g.
    - Overdose of streptokinase/urokinase/alteplase
    - To prevent recurrence of subarachnoid and g.i. haemorrhage
    - Certain traumatic and surgical bleeding
    - Abruption placentae, PPH and certain cases of menorrhagia
- ✓ The usefulness of EACA in most of the above condition except in overdose of fibrinolytics.
- ✓ Rapid i.v. injection results in hypotesion, bradycardia, and may be arrhythmias.
- ✓ It should be used cautiously when renal function is impaired.
- ✓ Myopathy occurs rarely.

TRANEXAEMIC ACID

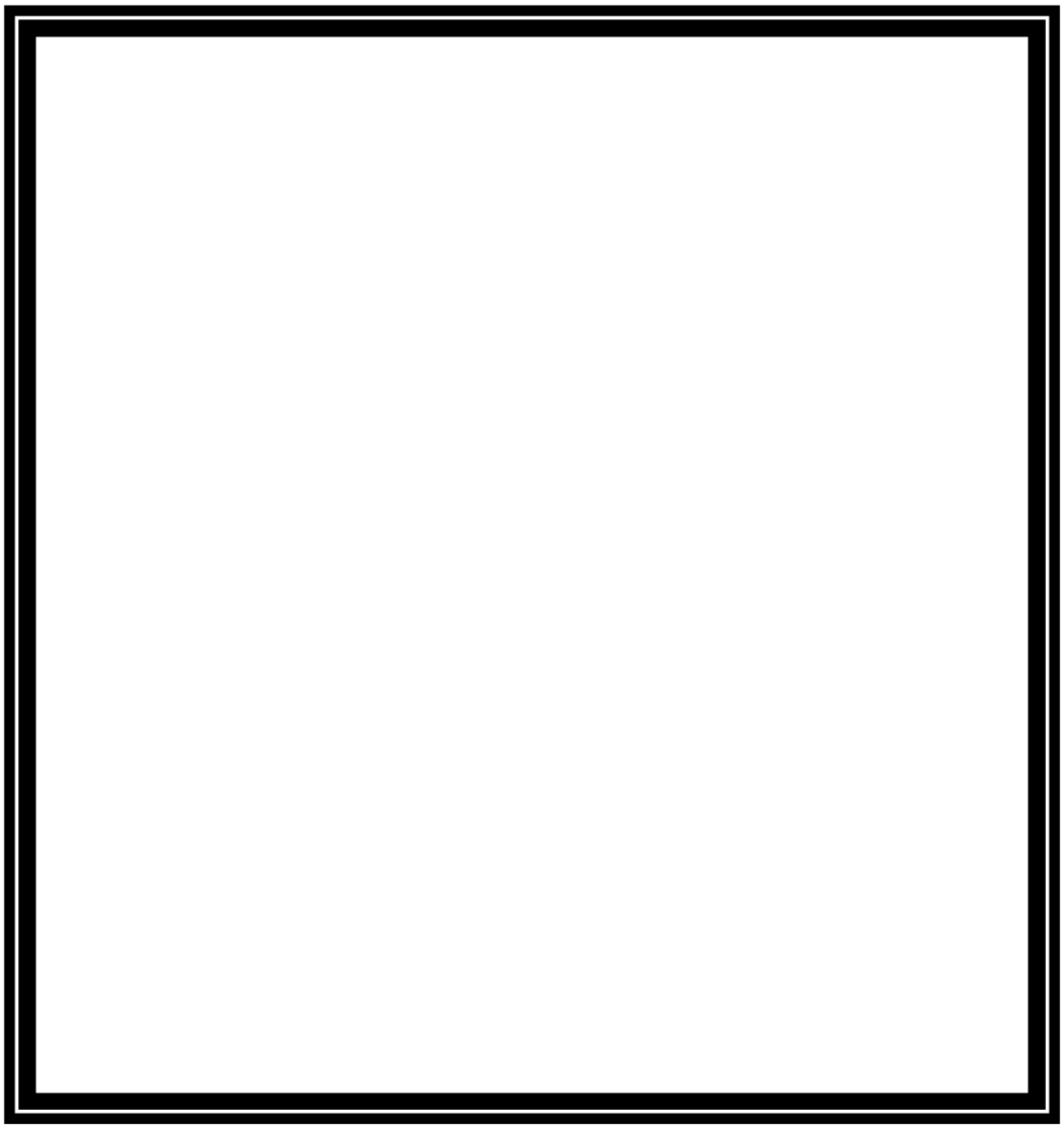
- ✓ Like EACA, it bid to the lysine binding site on plasminogen and prevents its combination with fibrin and is 7 times more potent.
- ✓ It has been used for prevention of excessive bleeding in:
    - Overdose of fibrinolytics
    - After cardio-pulmonary bypass surgery
    - After tonsillectomy, prostatic surgery, tooth extraction in haemophiliacs
    - Menorrhagia, specially due to IUCD.
    - Recurrent epistaxis, ocular trauma, bleeding peptic ulcer.
- ✓ Main side effects are nausea and diarrhea.
- ✓ Headache, giddiness and thrombophlebitis of injected vein are other adverse effects.

ANTIPLATELET DRUGS (ANTITHROMBOTIC DRUGS)

- ✓ These are drugs which interfere with platelet function and are useful in the prophylaxis of thromboembolic disorders.
- ✓ When platelets are activated, they undergo a sequence of reactions that are essential for haemostasis, important for the healing of damaged blood vessels, and play a part in inflammation. These reactions, several of which are redundant and several autocatalytic, include:

    - **Adhesion** following vascular damage via von Willebrand factor bridging between subendothelial macromolecules and glycoprotein [GP] Ib receptors on the platelet surface

- **Shape change** from smooth discs to spiny spheres with protruding pseudopodia
- **Secretion** of the granule contents including platelet agonists, such as ADP and 5-hydroxytryptamine, and coagulation factors and growth factors, such as platelet-derived growth factor
- **Biosynthesis of labile mediators** such as platelet-activating factor and thromboxane $(TX)A_2$
- **Aggregation**, which is promoted by various agonists, including collagen, thrombin, ADP, 5-hydroxytryptamine and TXA_2, acting on specific receptors on the platelet surface; activation by agonists leads to expression of GPIIb/IIIa receptors that bind fibrinogen, which links adjacent platelets to form aggregates
- **Exposure of acidic phospholipid** on the platelet surface, promoting thrombin formation and hence further platelet activation via thrombin receptors and fibrin formation via cleavage of fibrinogen.



- ✓ Various drugs act on different targets to interfere with platelet function.
- ✓ The clinically imp antiplatelet drugs are:
  - Aspirin
  - Dipyridamole
  - Ticlopidine
  - Clopidogrel
  - Abciximab

ASPIRIN

Mechanism of action:

- ✓ Stimulation of platelets by thrombin, collagen, and ADP results in activation of platelet membrane phospholipases that liberate arachidonic acid from membrane phospholipids.
- ✓ Arachidonic acid is fi rst converted to prostaglandin H_2 by COX-1.
- ✓ Prostaglandin H_2 is further metabolized to thromboxane A_2, which is released into plasma.
- ✓ Thromboxane A_2 produced by the aggregating platelets further promotes the clumping process that is essential for the rapid formation of a hemostatic plug.
- ✓ Aspirin inhibits thromboxane A_2 synthesis from arachidonic acid in platelets by irreversible acetylation of a serine, preventing arachidonate from binding to the active site, thus, inhibition of COX-1.
- ✓ This shifts the balance of chemical mediators to favor the antiaggregatory effects of prostacyclin, thereby impeding platelet aggregation.
- ✓ The inhibitory effect is rapid, apparently occurring in the portal circulation.
- ✓ The aspirin-induced suppression of thromboxane A_2 synthetase and the resulting suppression of platelet aggregation last for the life of the anucleate platelet, which is approximately 7 to 10 days.

PHARMACOKINETICS

- ✓ Complete inactivation of platelets occurs with 160 mg of aspirin given daily.
- ✓ The recommended dose of aspirin ranges from 50 to 325 mg, with side effects determining the dose chosen.
- ✓ Higher doses of aspirin increase drug-related toxicities as well as the probability that aspirin may also inhibit prostacyclin production.

- ✓ Formerly known as "baby aspirin," 81-mg aspirin is most commonly used in the United States.

USE

- ✓ Repeated administration of aspirin has a cumulative effect on the function of platelets.
- ✓ Aspirin is currently used in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent myocardial infarction, and to decrease mortality in pre- and post-myocardial infarct patients.
- ✓ Aspirin is frequently used in combination with other drugs having anticlotting properties, such as heparin or clopidogrel.

ADVERSE EFFECTS

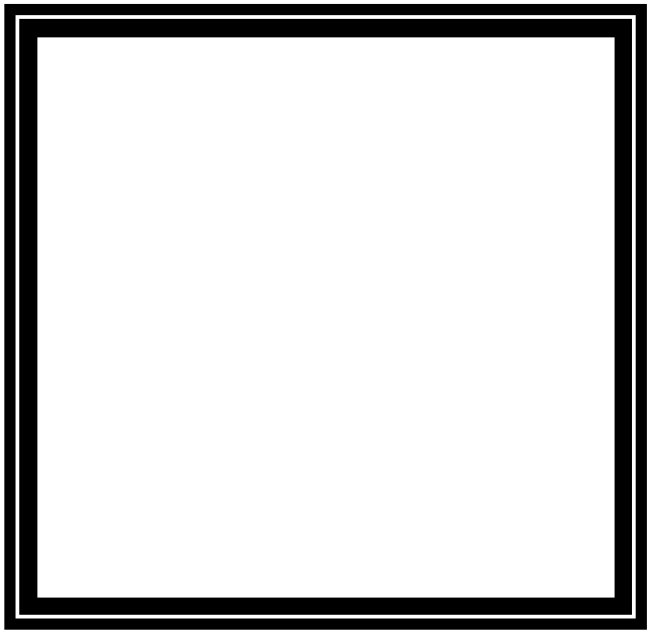
- ✓ Bleeding time is prolonged by aspirin treatment, causing complications that include an increased incidence of hemorrhagic stroke as well as gastrointestinal (GI) bleeding, especially at higher doses of the drug.

TICLOPIDINE, CLOPIDOGREL, AND PRASUGREL

- ✓ Ticlopidine, clopidogrel, and prasugrel are closely related thienopyridines that also block platelet aggregation, but by a mechanism diff erent from that of aspirin.

Mechanism of action:

- ✓ These drugs irreversibly 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.



Therapeutic use:

Although ticlopidine and clopidogrel are similar in both structure and mechanism of action, their therapeutic uses are different.

Ticlopidine

- ✓ It is approved for the prevention of transient ischemic attacks and strokes for patients with a prior cerebral thrombotic event.
- ✓ It is also used as adjunct therapy with aspirin following coronary stent implantation to decrease the incidence of stent thrombosis.

- ✓ However, due to its life-threatening hematologic adverse reactions, including neutropenia/agranulocytosis, **Thrombotic Thrombocytopenic Purpura** (TTP), and aplastic anemia, ticlopidine is generally reserved for patients who are intolerant to other therapies.

Clopidogrel

- ✓ It is approved for prevention of atherosclerotic events following recent myocardial infarction, stroke, and established peripheral arterial disease.
- ✓ It is also approved for prophylaxis of thrombotic events in acute coronary syndrome.
- ✓ Additionally, clopidogrel is used to prevent thrombotic events associated with percutaneous coronary intervention with or without coronary stent.
- ✓ Compared to ticlopidine, clopidogrel is the preferred agent in ischemic heart disease events, because there is more data to support use of clopidogrel in these cardiac patients.
- ✓ Furthermore, clopidogrel has a better overall side-effect profile, although TTP may also occur with this agent.

Prasugrel

- ✓ It is the newest ADP receptor antagonist.
- ✓ It is approved to decrease thrombotic cardiovascular events in patients with acute coronary syndrome.
- ✓ In clinical trials, prasugrel was more effective than clopidogrel in reducing cardiovascular death, nonfatal heart attack, and nonfatal stroke.

Pharmacokinetics:

- ✓ Food interferes with the absorption of ticlopidine but not with clopidogrel or prasugrel.
- ✓ After oral ingestion, all three of these drugs are extensively bound to plasma proteins.
- ✓ They undergo hepatic metabolism by the cytochrome P450 (CYP450) system to active metabolites.
- ✓ The maximum effect is achieved in 3 to 5 days, but when treatment is suspended, the platelet system requires time to recover.
- ✓ Elimination of the drugs and metabolites occurs by both the renal and fecal routes.
- ✓ Ticlopidine has a FDA black box warning due to the severe hematologic adverse reactions associated with its use.

ADVERSE EFFECTS:

- ✓ All three drugs can cause prolonged bleeding for which there is no antidote, but bleeding is more common with prasugrel.
- ✓ Serious adverse effects of **Ticlopidine** include neutropenia, TTP, and aplastic anemia requiring frequent blood monitoring, especially during the first 3 months of treatment.
- ✓ **Clopidogrel** causes fewer adverse reactions, and the incidence of neutropenia is lower.
- ✓ Clopidogrel has a black box warning for patients who are poor metabolizers.
- ✓ Clopidogrel is a prodrug, and its therapeutic efficacy relies entirely on its active metabolite.
- ✓ Genetic polymorphism of CYP450 2C19, that primarily biotransforms clopidogrel, leads to less active metabolite, variable pharmacokinetic properties and reduced clinical response in patients who are poor metabolizers. So called "**poor metabolizers**" of clopidogrel with acute coronary syndrome or who are undergoing percutaneous coronary intervention have been shown to have higher rates of cardiovascular events when treated

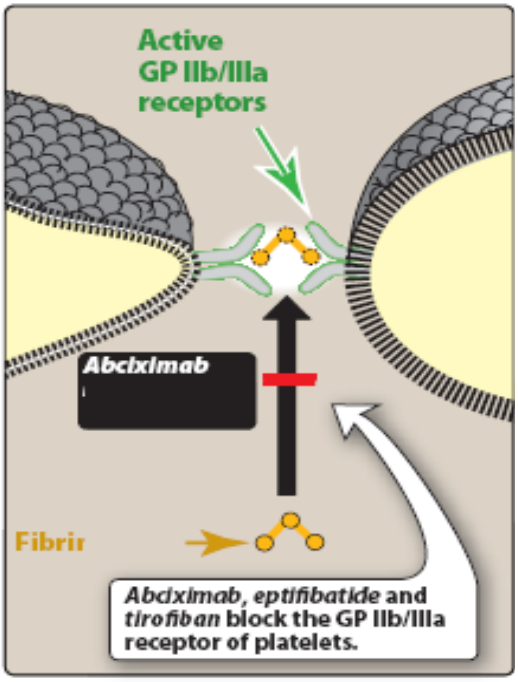
with standard doses of clopidogrel as compared to normal metabolizers. Tests are currently available to identify poor metabolizers,

- ✓ and it is recommended that other antiplatelets or different strategies be used.
- ✓ The major side effect of prasugrel is bleeding which can be fatal.
- ✓ **Prasugrel** has black box warnings for bleeding, stroke, and abrupt discontinuation in patients undergoing percutaneous coronary intervention.
- ✓ Because these drugs can inhibit CYP450, they may interfere with the metabolism of drugs such as phenytoin, warfarin, fl uvastatin, and tamoxifen if taken concomitantly.
- ✓ Indeed, phenytoin toxicity has been reported when taken with ticlopidine.

Abciximab

Mechanism of action

- ✓ The realization of the key role of the platelet GP IIb/IIIa receptor in stimulating platelet aggregation led to attempts to block this receptor on activated platelets.
- ✓ In turn, this directed the development of a chimeric monoclonal antibody, abciximab, which is composed of the constant regions of human immunoglobulin joined to the Fab fragments of a murine monoclonal antibody directed against the GP IIb/IIIa complex.
- ✓ By binding to GP IIb/IIIa, the antibody blocks the binding of fibrinogen and von Willebrand factor, and, consequently, aggregation does not occur.



Pharmacokinetics and Use:

- ✓ Abciximab is given intravenously along with either heparin or aspirin as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications.
- ✓ It is also approved for unresponsive unstable angina and for prophylactic use in myocardial infarction.
- ✓ After cessation of infusion, platelet function gradually returns to normal, with the antiplatelet effect persisting for 24 to 48 hours.

- ✓ The major adverse effect of abciximab therapy is the potential for bleeding, especially if the drug is used with anticoagulants or if the patient has a clinical hemorrhagic condition.
- ✓ Abciximab is expensive, limiting its use in some settings.

Eptifibatide and Tirofiban

- ✓ These two antiplatelet drugs act similarly to abciximab, namely, by blocking the GP IIb/IIIa receptor.
- ✓ Eptifibatide is a cyclic peptide that binds to GP IIb/IIIa at the site that interacts with the arginine-glycine-aspartic acid sequence of fi brinogen.
- ✓ Tirofiban is not a peptide, but it blocks the same site as eptifi batide.
- ✓ These compounds, like abciximab, can decrease the incidence of thrombotic complications associated with acute coronary syndromes.
- ✓ When intravenous (IV) infusion is stopped, these agents are rapidly cleared from the plasma, but their effect can persist for as long as 4 hours.
- ✓ **[Note: Only IV formulations are available, because oral preparations of these GP IIb/IIIa blockers are too toxic.]**
- ✓ Eptifibatide and its metabolites are excreted by the kidney.
- ✓ Tirofiban is excreted largely unchanged by the kidney and in feces.
- ✓ The major adverse effect of both drugs is bleeding.

Dipyridamole

- ✓ Dipyridamole, a coronary vasodilator, is used prophylactically to treat angina pectoris.
- ✓ It is usually given in combination with aspirin or warfarin.
- ✓ Dipyridamole increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase, resulting in decreased thromboxane A_2 synthesis.
- ✓ It may potentiate the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces.
- ✓ The meager data available suggest that dipyridamole makes only a marginal contribution to the antithrombotic action compare to that of aspirin.
- ✓ In combination with warfarin, however, dipyridamole is effective for inhibiting embolization from prosthetic heart valves.
- ✓ It has been described as “inappropriate” for use in the elderly as a sole agent due to adverse GI and orthostasis problems.

Cilostazol

- ✓ Cilostazol is an oral antiplatelet agent that also has vasodilating activity.
- ✓ It is FDA approved to reduce the symptoms of intermittent claudication.
- ✓ Non–FDA approved uses of cilostazol include the treatment of Buerger disease, vascular sclerosis complicating diabetes mellitus, and the improvement of symptoms in patients with chronic cerebral ischemia.
- ✓ Cilostazol is extensively metabolized in the liver, and the primary routes of elimination are via the urine and feces.
- ✓ Two of its metabolites are active.
- ✓ Cilostazol and its active metabolites inhibit phosphodiesterase type III, which prevents the degradation of cAMP, thereby increasing levels of cAMP in platelets and vascular tissues.

- ✓ The increase in cAMP levels in platelets and the vasculature prevents platelet aggregation and promotes vasodilation of blood vessels, respectively.
- ✓ Cilostazol favorably alters the lipid profile, by causing a decrease in plasma triglycerides and an increase in high-density lipoprotein cholesterol.
- ✓ Headache and GI side effects (diarrhea, abnormal stools, dyspepsia, and abdominal pain) are the most common adverse effects observed with cilostazol.
- ✓ Cilostazol and its metabolites are contraindicated in patients with congestive heart failure of any severity.
- ✓ It should be used cautiously in patients taking other phosphodiesterase III inhibitors and patients
- ✓ with a history of any cardiac disease.