

## Unit 7: Drugs for Coagulative Disorders

Topic: Coagulative Disorders

Steps in Hemostasis:

**Hemostasis** – this is the proper formation of the blood clot and at the same time, it is also considered as the breakdown of the blood clot. Because other than producing blood clot, it is very important for the blood clot to be dissolved.

1. Vascular Phase
2. Platelet Phase
3. Coagulation Phase
4. Clot formation
5. Fibrinolysis

**Anticoagulant** – two most common example of anticoagulant is warfarin and heparin

### Hemostasis

- Hemostasis is a complex process involving multiple steps and many clotting factors.
- Hemostasis is the balance between clot formation and clot breakdown
- It is very important that our blood should form blood clots in order to stop bleeding or excessive blood loss
- E.g., when you had tissue injury, then there was hemorrhage therefore your blood will produce blood clot in order to stop bleeding but at the same time, those blood clot must be dissolved or broken down because if not, it can clog or block your blood vessel that can result to many medical problems
- It should be treated quickly if there's an abnormality into what we known as hemostasis
- Hemostasis occurs when blood is present outside of the body or blood vessel. It is the innate response of our body to stop bleeding and blood loss

### Events in Hemostasis

The main thing that will occur for us to have hemostatic process in our body is **tissue injury**. Because first thing that will happen for your blood to initiate hemostasis, there should be a blood vessel injury first for the hemostatic response to be triggered

#### I. Vascular phase

- Cutting or damaging blood vessels leads to vascular spasm that produces a **vasoconstriction** which will slow or even stop blood flow.
- Vascular phase happens as a response to blood vessel injury. This response lasts for at least 30 minutes and it is localized only to the damaged area meaning not all your blood vessels constricts when undergoing vascular phase, but only the blood vessel that is found in the damaged area.
- Stimuli for blood formation could be endothelial injury, if there is presence of foreign matter in the blood, or when there is blood flow abnormality. These are the different things that initiate this process

#### II. Platelet phase

- Also known as **platelet adhesion**

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- In larger blood vessels, **platelets begin to stick** to the surfaces of endothelial cells.
- Aggregation of platelets leads to the formation of a platelet plug.
- Platelets adhere to injury site and aggregate to form temporary plug

Why are they called as temporary plug?

- Because similar with vasoconstriction, they can also help stop the bleeding when fibrin (medical term) or blood clot is not yet produced.

### III. Coagulation phase

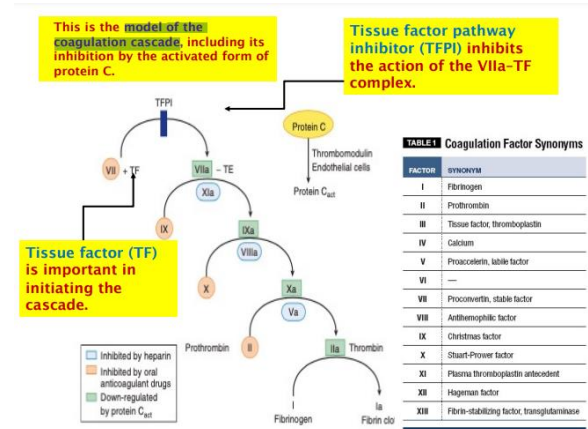
- Also known as **coagulation cascade**
- This specific process begins **30 seconds to several minutes** after phase 1 and phase has commence
- This process depends in the presence of blood or different clotting factors in our blood
- The overall process involves the formation of the insoluble protein Fibrin from the plasma protein Fibrinogen through the action of the enzyme Thrombin. **Fibrin** forms a network of fibers which traps blood cells and platelets forming a **thrombus or clot**.

**Fibrin** is the medical term for blood clot. The origin of fibrin is the fibrinogen, the enzyme that is responsible for the conversion of fibrinogen to fibrin is **thrombin**.

**NOTE:** this process is the time when our body is now producing scab or in tagalog “langib”

### Two pathways leading to the formation of the thrombus:

- Extrinsic pathway
- Intrinsic pathway



This is the model of the coagulation cascade, including its inhibition by the activated form of protein C.

Tissue factor pathway inhibitor (TFPI) inhibits the action of the VIIa–TF complex.

Tissue factor (TF) is important in initiating the cascade.

| Factor | Synonym                          |
|--------|----------------------------------|
| I      | Fibrinogen                       |
| II     | Prothrombin                      |
| III    | Tissue factor, thromboplastin    |
| IV     | Calcium                          |
| V      | Proaccelerin, labile factor      |
| VI     | -                                |
| VII    | Proconvertin, stable factor      |
| VIII   | Antihemophilic fact              |
| IX     | Christmas factor                 |
| X      | Stuart-Prower factor             |
| XI     | Plasma thromboplastin antecedent |

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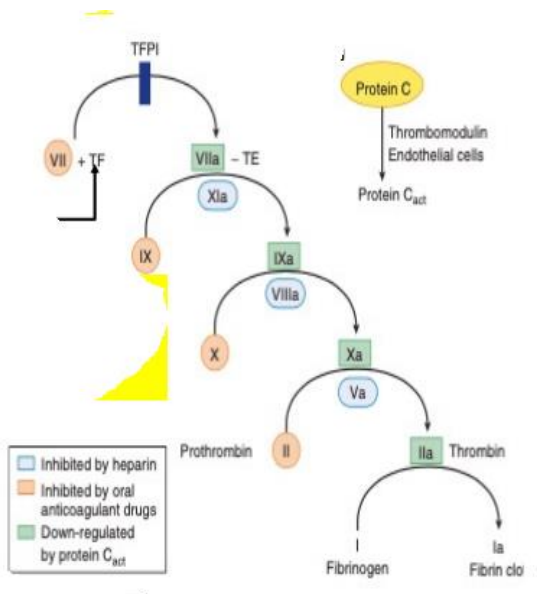
|      |                                                |
|------|------------------------------------------------|
| XII  | Hageman factor                                 |
| XIII | Fibrin-stabilizing factor,<br>transglutaminase |

**NOTE:** most of clotting factor are protein with the exemption of clotting **factor IV**, rather it is a calcium which is a mineral

Calcium have effect in your body:

- it is able to produce contraction of the smooth muscle
- it is a primary mineral in the bone in the form of hydroxyapatite or calcium phosphate
- and in the blood, it is one of the clotting factors

Our clotting factors are synthesized from the liver so if the patient has liver damage definitely they will have a problem with clotting factors because in the first place, our liver is the primary organ in which clotting factors are synthesized.



Note: the meaning of a is active form

The first clotting factor that will take effect under the coagulation cascade is clotting factor VII that will bind to TF (Tissue Factor) to be converted to its activated form which is inhibited by TFPI (Tissue Factor Pathway Inhibitor).

When clotting factor VII is activated, this can activate clotting factor XI. Clotting factor XIa or activated clotting XI, will now initiate the conversion of clotting factor IX to its activated form.

**NOTE:** Christmas factor deficiency or clotting factor IX deficiency is one of the most common type of hemophilia (deficiency of clotting factor). Hemophilia B is called as Christmas disease

When clotting factor IX is activated, it will now activate clotting factor VIII

**NOTE:** clotting factor VIII deficiency is called hemophilia A which is also called as classic hemophilia. It is called as classic hemophilia because it is the most common form of deficiency of clotting factor

Activated clotting factor VIII, will now convert clotting factor X to its activated form.

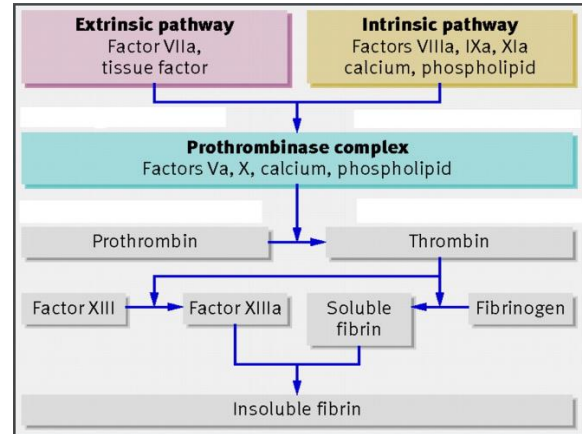
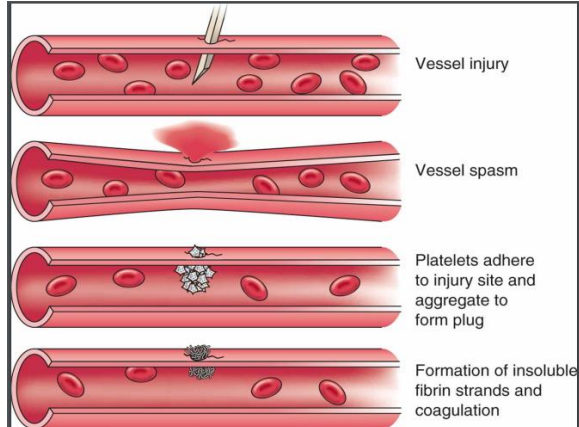
When clotting factor X is activated it will now activate the clotting factor V.

Activated clotting factor V will convert clotting factor II (Prothrombin) to its activated form (Thrombin)

Thrombin now will convert clotting factor I (Fibrinogen) to its activated form (Fibrin)

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## Review:

**Extrinsic pathway**

- Initiated with material **outside of the blood**.
- E.g., external trauma, injury or damage that causes blood to escape from the blood vessels
- Very rapid process; Smaller clots

**Intrinsic pathway**

- Initiated by trauma inside the blood vessel
- Initiated by the **blood coming in contact with exposed collagen** in the blood vessel wall
- Slower; Larger clots
- Much more dangerous specially when they produce large clots inside the body that can lead to blockage and will result to medical problem (e.g., myocardial ischemia)

**IV. Clot Retraction**

- After 2 or 3 days, the clot begins to contract. Platelets in the clot contain **contractile proteins**.
- Clot retraction is the shrinking of blood clot over a number of days. Therefore, the edges of the blood vessel wall at the point of injury are slowly brought together again to repair the damage that occur
- These proteins pull the edges of the wound together and **reduces the chance of further hemorrhage**. This activity also assists the repair processes.

**NOTE:** don't remove the scab when clot retraction is still not happening. Until the proteins are still not contracted, don't attempt to remove it for the wound to close totally. Also, during the wound healing process, we have nerve signals in our spinal cord that skin is being stimulated. Since the brain is interpreting it as the skin being stimulated during clot retraction, the brain perceives those signals as itchy. These nerves are also sensitive to chemical like histamine which releases in response to an injury therefore the affected area will begin

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now to tingle or to itch that explains why when the wound is healing, it started to itch.

**V. Fibrinolysis**

- Dissolution of the clot.
- The breakdown of the clot is due to the production of a powerful proteolytic enzyme **Plasmin**.

**Plasmin** is the enzyme that dissolves the fibrin

- Removing a blood clot is essential to restoring normal circulation.
- \*This step completes the hemostasis

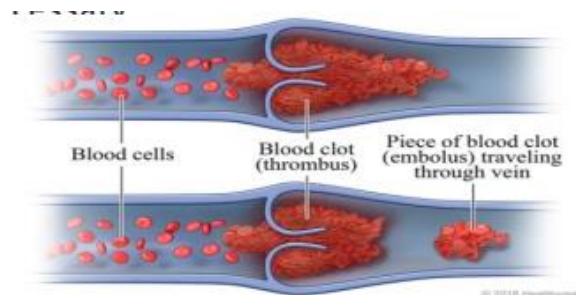
**Two major examples of blood clot:**

**Thrombus** – is the stationary blood clot

**Embolus** – is what we called traveling blood clot

**What are the forms of Blood Clot?**

- Once a **stationary clot** forms (thrombus), it often grows larger as more fibrin is added.
- Pieces of the clot may break off and travel in the blood stream to possibly lodge elsewhere.
- A **traveling clot** is known as an embolus
- When clots or emboli form, drug therapy becomes necessary.



Why is drug therapy being necessary specially if you experience embolism?

- Because these embolus is possible to lodge in different parts of your blood vessel. Possible it can clog the vein of your artery into your heart or it can cause blockage to your periphery that may cause deep vein thrombosis or if it causes blockage to your pulmonary artery, it can cause pulmonary embolism or if it blocked coronary artery, you can have coronary artery disease resulting to acute myocardial ischemia that may lead to angina pectoris

**Thrombophilia**

- Too much blood clot
- It can cause embolism
- A condition in which blood **can form clots too easily**. Blood clots can be very serious and need to be treated quickly.

**Risk Factors:**

1. Acquired after surgery
2. trauma
3. medical disease and medication use
4. or prolonged periods of decreased movement, such as during international flights or hospitalizations.
5. It also has genetic predisposition

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**Types of Thrombophilia**

- **Antiphospholipid Antibody Syndrome (APLS)**
  - **autoimmune disease** in which the body produces antibodies against certain blood proteins
  - protein C is responsible to control proper production of blood clot however if you have APLS, there is an antibody that destroys this protein that can result to excessive blood clot because you're losing proper control to regulate production of clotting factors
- **Factor V Leiden**
  - Abnormal coagulant protein that **does not deactivate when it should**. It is the **most common** inherited thrombophilia.
  - This condition increases the patient's risk of producing blood clot
- **Prothrombin Gene Mutation**
  - The body produces **too much prothrombin**, a coagulant protein that is also called Factor II.
  - Therefore, there are too much thrombin production resulting to increased conversion fibrinogen to fibrin causing excessive blood clot

Prothrombin activates thrombin so that it can convert fibrinogen into fibrin

- **Protein C, D and ATII Deficiency**
  - People with these **inherited deficiency** disorders do not produce enough of these proteins.

**Health Problems associated to Thrombophilia:**

- **Deep Vein Thrombosis**
  - You developed formation of stationary blood clot
  - form within deep veins, usually in the legs or pelvis but sometimes in the arms. Symptoms can include swelling or pain in the legs.
- **Pulmonary Embolism**
  - A DVT that breaks off and travels to the lungs is called a pulmonary embolism. A clot that becomes lodged in a lung artery can cause lung damage, organ damage or death.
- **Arterial Thrombosis**
  - A blood clot that forms in an artery is called an arterial thrombosis. Arterial clots that break apart can damage any of several different organs.
  - When arterial thrombosis blocked coronary artery it will result to acute myocardial ischemia
  - When it is totally blocked and there is no oxygen that's being delivered to your cardiac muscle, it is now called as acute myocardial infarction

**Hemophilia**

- can result to excessive bleeding
- most common manifestation of hemophilia is epistaxis meaning there is nose bleeding, or there is stain of blood in your stool or urine. Also those patient who are

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experiencing hemophilia are easy to have bruises

- A consequence of a **deficiency in plasma coagulation factors**
- A rare disorder in which your blood doesn't clot normally because it lacks sufficient blood-clotting proteins (clotting factors).

2 actions of Von Willebrand factor:

1. it is one of the responsible to activate clotting factor 8
2. it binds to platelet to help the platelet to aggregate with each other to produce temporary plug or platelet plug to stop bleeding

### Types:

#### 1. Hemophilia A

- **factor VIII (FVIII) deficiency** or classic hemophilia
- factor VIII is also known as anti-hemophilic factor
- Hemophilia occurs in approximately 1 in 5,000 live births. Hemophilia A is 4x as common as hemophilia B while more than half of patients with hemophilia A have the severe form of hemophilia.

#### 2. Hemophilia B

- **factor IX (FIX) deficiency** or Christmas disease
- factor IX is also known as Christmas factor

Factor IX is named after Stephen Christmas. Stephen Christmas is the very first patient that is diagnosed with hemophilia B

#### 3. Von Willebrand disease

- genetic disorder caused by missing or defective Von Willebrand factor, a clotting protein. VWF binds factor VIII, a key clotting protein, and platelets in blood vessel walls, which help form a platelet plug during the clotting process

|              |                                                                                                                                                                                |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Type 1 VWD   | <ul style="list-style-type: none"> <li>- most common type</li> <li>- 60%-80% of patients suffer from type 1</li> <li>- Only have deficiency of VWF</li> </ul>                  |
| Type 2 VWD   | <ul style="list-style-type: none"> <li>- 15%-30% of patients suffer from type 2</li> <li>- Produce VW Factor but does not function the way it should</li> </ul>                |
| Type 3 VWD   | <ul style="list-style-type: none"> <li>- 5%-10% of patients.</li> <li>- Total absence of VWF</li> <li>- Patient are not capable to synthesize the VWF in their body</li> </ul> |
| Acquired VWD | <ul style="list-style-type: none"> <li>- results after a diagnosis of an autoimmune disease,</li> </ul>                                                                        |

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|  |                                                                                                                   |
|--|-------------------------------------------------------------------------------------------------------------------|
|  | such as lupus, or from heart disease or some types of cancer. It can also occur after taking certain medications. |
|--|-------------------------------------------------------------------------------------------------------------------|

4. Appropriate laboratory tests
  - Platelet count
  - evaluation of a peripheral blood sample
  - APTT (activated partial thromboplastin time) test
  - PT-INR (prothrombin time – international normalize ratio) test
  - Coagulation time test

Common manifestation of hemophilia:  
excessive bleeding resulting to epistaxis  
(nose bleed)

### What are the diagnosis for coagulative disorders?

1. Clinical assessment,
2. Pertinent history, and family history (e.g., Von Willebrand Disease is an example of coagulative disorder that is cause by genetic changes that are almost always inherited; it is passed down from the parent to their offspring)
3. Medical history and intake of medicine

The intake of medicine is also being asked by the clinician for them to conclude if the drug causes the problem because there are certain example of drugs that can cause this disorder

Examples:

- anti-infectives such as antibiotic, or certain antiviral drugs
- also anticoagulant, those drugs that can affect bleeding disorder or bleeding property of the body
- also, those blood coagulation factors
- hormones such as estrogens
- hemostatic agents

### Screening Test

- a. **Coagulation time test or the clotting time test** - measurement of the **intrinsic power of the blood** to convert fibrinogen to fibrin (blood clot)
  - This measures your blood's ability to form blood clot and how long it takes for it to clot
  - Testing can help the doctor assess the risk of patient of having excessive bleeding or developing clots that we called as thrombosis that can form somewhere else in their blood vessels

2 ways to perform clotting time test:

1. Test tube method
  - 2 ml of the blood is being collected to the patient. In 20 minutes, that specific blood sample is being observed. Suppose to be in 20 minutes, a clot should be formed however, if the blood sample didn't produce blood clot, meaning the patient have deficiency of clotting factors or they have problem in coagulation that's called as hemophilia

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- But when the blood clot is formed in less than 5 minutes, therefore the patient have excessive blood clotting factors which is called as thrombophilia
- are added. (A normal range is around **21 to 35 seconds.**)
- APTT is use if the patient is taking heparin

## 2. Using capillary tube

b. **Prothrombin time test (PT-INR)**

- measures **how quickly your blood clots.**
- aka pro time test or PT test, INR
- INR of 1.1 or below is considered normal. An INR range of 2.0 to 3.0 is generally an effective therapeutic range for people taking warfarin
- Therefore, the PT-INR is a useful laboratory test in order for the clinician to monitor the effect of warfarin to the patient. Less than PT-INR of 2.0 to 3.0 means the warfarin could be ineffective but greater than that specific volume means the warfarin is already causing toxicity

Prothrombin is a protein that is produced by our liver that helps our blood to produce fibrin (blood clot)

When we bleed, a series of chemicals (those clotting factors) will be activated. So, the blood clot will be formed in order to stop bleeding.

c. **APTT test**

- Activated Partial Thromboplastin time
- **Helps evaluate a person's ability to appropriately form blood clots.** It measures the number of seconds it takes for a clot to form in a sample of blood after substances (reagents)

**Drugs for Coagulative Disorders:**

2 main problems with regards to coagulation:

Hemophilia – when you're deficient in clotting factor which results to bleeding

Thrombophilia – when you produce excessive clotting factor, the blood is fast to clot

**Anticlotting drugs:**

- Are used in the treatment and prevention of thrombophilia (e.g., myocardial infarction, acute coronary syndrome, atrial fibrillation, ischemic stroke, and deep vein thrombosis)

**I. Anticoagulant**

- Two most common example of an anticoagulant are heparin and warfarin
- used to prevent the formation of clots

**II. Antiplatelets**

- used to inhibit platelet aggregation
- example is aspirin

platelets are important to homeostasis because they are the one who are first to response, or until there are no fibrin that is being produced, for the bleeding to stop

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**III. Thrombolytics**

- Used to dissolve such life-threatening clots
- Anticoagulants and antiplatelets only prevents the further enlargement of the blood clot
- The only drugs that can dissolve clots are thrombolytics
- Main MOA: they stimulate the conversion of plasminogen to plasmin. Plasmin is a proteolytic enzyme that dissolves fibrin

- ✓ Prevent thrombi from forming or growing larger

**Drugs that facilitate clotting**

- These are the example of drugs that are used to manage hemophilia which leads to excessive bleeding

**Hemostatics**

- used to speed clot formation, or to limit bleeding from a surgical site.
- The most common example is tranexamic acid

**Anticoagulants**

- Anticoagulants prevent the formation and enlargement of clots.
- Only used to prevent further enlargement but when it comes to dissolving the clot, it is not capable to do that.
- Examples: warfarin (coumadin), heparin & LMWH (low molecular weight heparin)

**Actions:**

- ✓ Inhibit certain clotting factors
- ✓ Lengthen clotting time

**Difference of Warfarin and Heparin**

|                  | <b>WARFARIN</b>                                                                                                                                                                                                                                | <b>HEPARIN</b>                                                                                                                                                                                                                                           |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemistry</b> | Obtained from natural sources particularly from <b>plant</b> source. The phytochemical to which it was isolated is from coumarin                                                                                                               | Obtained from animals, particularly in sulfated glycosaminoglycan.<br><br>Sulfated glycosaminoglycan is a group of compounds occurring mainly in <b>connective tissue</b> of certain animals. They are complex polysaccharide which contains amino group |
| <b>MOA</b>       | Inhibits vitamin K synthesis<br><br>It also capable to directly inhibit clotting factors such as clotting factor 1972<br><br>*1972 is a mnemonic for us to remember the clotting factors that is inhibited by warfarin<br><br>1972 is clotting | Activates antithrombin III                                                                                                                                                                                                                               |

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|                     |                                                                                                                        |                                                                                                                                                                                                                            |  |                 |                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                     | factor 10, 9, 7 and 2                                                                                                  |                                                                                                                                                                                                                            |  |                 | are pregnant and to those who are planning to get pregnant                                                                                                                                                 | which there is a decreased platelet in your body                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Route</b>        | Oral or IV                                                                                                             | IV or SC<br>IM is contraindicated = hematoma (bruising)<br><br>*it is not given orally because it is unstable when given thru oral route of administration. It is only given thru parenteral route but thru IV and SC only |  | <b>Antidote</b> | Vitamin K<br><br>The main rationale of using vitamin k for the treatment of warfarin toxicity is physiologic antagonism. Why is that? Because warfarin is an anticoagulant while vitamin k is procoagulant | Protamine SO2 (sulfate)<br><br>Why is that? Heparin is highly acidic and it can be neutralized by basic molecule (common example is protamine sulfate)<br><br>Protamine sulfate is carefully titrated 1 mg for every 100 units of heparin administered<br><br>The type of interaction that happens between heparin and protamine sulfate is chemical antagonism. Chemical antagonism in the sense of neutralization |
| <b>Monitoring</b>   | PT-INR hemo                                                                                                            | APTT                                                                                                                                                                                                                       |  |                 |                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Target</b>       | INR 2-3                                                                                                                | 1.5-2.5x control                                                                                                                                                                                                           |  |                 |                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Uses</b>         | Prophylactic for acute MI, prevention of progression or recurrence of acute deep-vein thrombosis or pulmonary embolism | prevention of venous thrombosis, treatment of pulmonary embolism and acute myocardial infarction                                                                                                                           |  |                 |                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Side effects</b> | Bleeding, teratogenic (causes damage to the developing fetus)<br><br>*Contraindicated for patients that                | Bleeding, allergy (since it is obtained from animal sources), thrombocytopenia<br><br>*thrombocytopenia is a condition in                                                                                                  |  |                 |                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                     |

As additional: The action of warfarin can be reverse by vitamin k but the recovery requires the synthesis of new normal clotting factor. Therefore, it is very slow to take

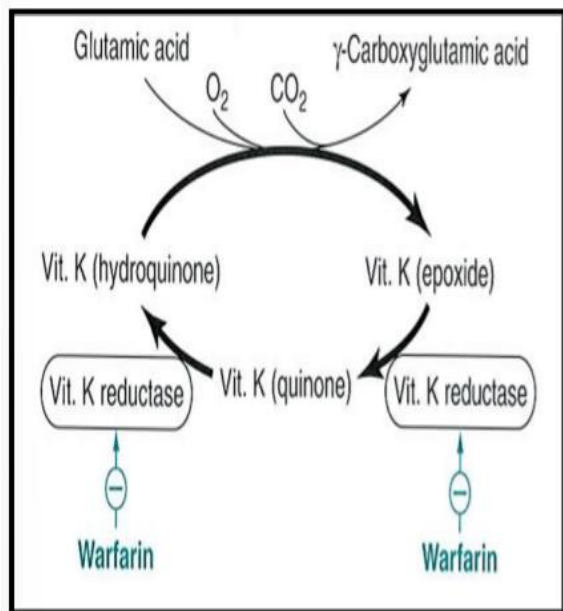
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effect, it takes 6-20 hours for the improvement to be seen in the patient that had warfarin toxicity.

More rapid reversal can be achieved by transfusion with fresh or frozen plasma that contains normal clotting factor. (this is for emergency cases)

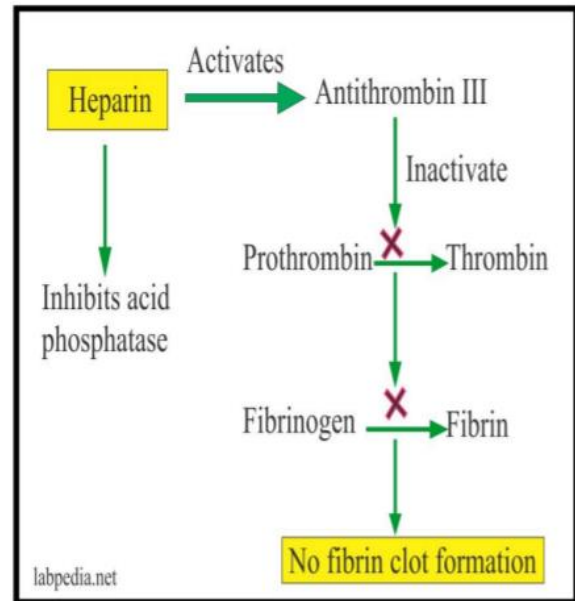
\*yes, vitamin k is an antidote but the effect is slow

**Mechanism of Action of Warfarin**

Warfarin is capable to inhibit vitamin K, it is capable to inhibit vitamin K reductase. Vitamin K reductase is the one that converts Vitamin K (epoxide) to Vitamin K (quinone) and it is also capable to convert Vitamin K (quinone) to Vitamin K (hydroquinone) for it to be active form.

\*Why do we need to inhibit vitamin k? because vitamin k is a procoagulant vitamin meaning it is capable to promote coagulation. Therefore, in order for warfarin to prevent coagulation, it directly inhibits

vitamin k therefore producing anticoagulant effect also it is capable to inhibit clotting factor 1972

**Mechanism of Action of Heparin**

Heparin activates antithrombin III.

\*what is antithrombin III and why does it need to be activated by heparin? Antithrombin III is an example of substance that can inactivate prothrombin or it prevents the conversion of prothrombin to thrombin. Thrombin is the one responsible for conversion of fibrinogen to fibrin. So by activating antithrombin III, there is no fibrin clot formation.

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**Vitamin K**

Other name(s): antihemorrhagic factor

In nature, there are 3 types of existing vitamin k:

- Phylloquinone or phytonadione (vitamin K-1)
- Menaquinone (vitamin K-2), methylphytyl naphthoquinone, phytonadione.
- Menadiol, menadione (vitamin K-3)

A **procoagulant** used as **antidote for Warfarin toxicity**. Foods high in Vitamin K (must be avoided during Warfarin Therapy):

- ✓ Green leafy vegetables
- ✓ Milk and milk products
- ✓ Some cereals
- ✓ Orange juice
- ✓ Cauliflower
- ✓ Cucumbers

**Anticoagulants (LMWH)****Low molecular weight heparin****Examples:**

1. Enoxaparin (Lovenox)
2. Tinzaparin (Fragmin)
3. Dalteparin (Innohep)

\*Why are they called as low molecular weight? Because they contain fraction of heparin that have molecular weight of 2000 to 6000. Because the MW of heparin ranges from 15,000 to 20,000

**Indications:**

anticoagulants of choice for treating pregnant women with prosthetic heart valves or venous thromboembolism

main reason for that is that they don't cross placental barrier therefore, they do not cause damage to developing fetus since they have low lipid solubility, therefore they can't enter the placental barrier that protects the developing fetus

**Advantages when compare to heparin:**

- ✓ Do not require intense monitoring
- ✓ Longer half-life than heparin
- ✓ With less bleeding

**Anticoagulants (Direct Thrombin Inhibitors)****1. Lepirudin (Refludan)**

- Polypeptide that is closely related to hirudin

**Hirudin** – is a type of substance that is isolated from hirudo medicinalis or medicinal leech (linta). There is only certain leech that can produce anticoagulant effect

- effective in the treatment of HIT (heparin-induced thrombocytopenia)

thrombocytopenia is when your blood platelet count is low

- CI: streptokinase or alteplase because it can cause excessive bleeding

Streptokinase is a thrombolytic or fibrinolytic meaning it is capable to dissolve the existing blood clot

- Desirudin, Bivalirudin

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**2. Argatroban**

- directly inhibits thrombin
- prophylactic for the treatment of thrombosis in patients with HIT

**3. Fondaparinux (Arixtra)**

- first in a new class of pentasaccharide anticoagulants that is purely synthetic
- prophylaxis of deep-vein thrombosis

**4. Dabigatran**

- Is the only direct thrombin inhibitor that is orally active therefore it is given through **oral route** of administration

**Adverse effects of Anticoagulants:**

Most common and potentially serious adverse effect is bleeding.

**Signs:**

- ✓ Bruising (hematoma)
- ✓ bleeding gums
- ✓ nosebleed
- ✓ blood in urine or stool

they have more predictable anticoagulant response than heparin because they do not bind to plasma protein and are not neutralized by platelet factor number 4

**Platelets**

- also known as our thrombocytes
- they are important in homeostasis
- platelet aggregation contributes to the clotting process and very important in clots that formed in the arterial circulation. However, platelets also appear to play central role in pathologic coronary and cerebral artery occlusions
- platelet aggregation is triggered by a variety of endogenous mediator (e.g., adenosine diphosphate, prostaglandin, and thromboxane). Whereby example of substances that inhibit platelet aggregation are cAMP (cyclic adenosine monophosphate) and PGI<sub>2</sub> (prostacyclin)
- another example of substance that are capable to promote platelet aggregation are thrombin and fibrin
- thrombocytosis, this is the example of condition where the number of platelets is too high. The opposite of thrombocytosis is thrombocytopenia where there is deficiency of platelets

**Antiplatelets**

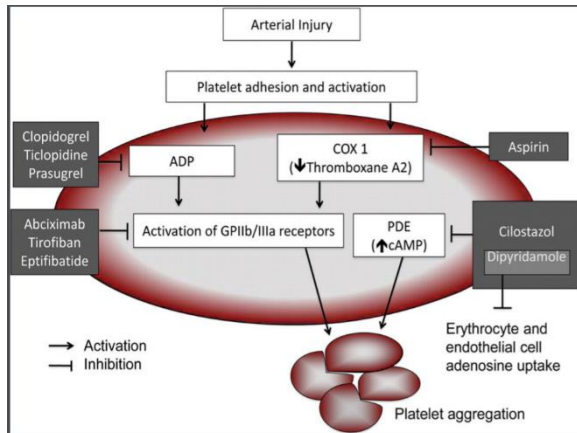
Antiplatelet agents prolong bleeding time by interfering with platelet aggregation.

**Four primary subclasses:**

1. aspirin
2. adenosine diphosphate (ADP) receptor blockers
3. glycoprotein IIb/IIIa receptor blockers
4. PDE inhibitors

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Why are they used as antiplatelet?



As we all know, aspirin is an example of COX (cyclooxygenase) inhibitor. It inhibits the conversion of arachidonic acid to thromboxane because thromboxane promotes platelet aggregation. Therefore, by blocking the aspirin (COX enzyme), therefore thromboxane will decrease resulting to decreased platelet aggregation.

Main action of cilostazol which is an example of phosphodiesterase inhibitor. PDE is an example of enzyme which inactivates cAMP which inhibits platelet aggregation. So therefore, cilostazol produces antiplatelet action by means of increasing cAMP by inhibiting its metabolism, by inhibiting the enzyme PDE

For dipyridamole, it is an example of inhibitor of erythrocyte and endothelial cell adenosine uptake. Adenosine can promote platelet aggregation

Another example is those drugs that blocks adenosine receptor. Its uptake and its receptors must be block. Dipyridamole is the one that blocks the uptake those that blocks the receptor are clopidogrel, ticlopidine, and prasugrel

With regards to those drugs that inhibits the activation of glycoprotein IIb and IIIa

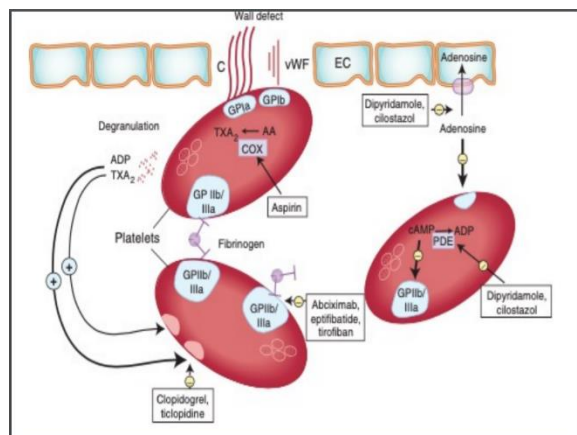
receptor, they are abciximab, tirofiban, and eptifibatide

**REMEMBER:** substance that promotes platelet aggregation are adenosine diphosphate, prostaglandin, thromboxane, thrombin, and fibrin. Whereby the inhibitor of platelet aggregation is cAMP, and PGI<sub>2</sub>. This is the main reason why COX 2 selective inhibitor like celecoxib and rofecoxib are prone to develop cardiovascular thrombotic event.

Why do they have that adverse event?

- Because since they are COX 2 inhibitor, they inhibit COX 2 enzyme that particularly increases the concentration of PGI<sub>2</sub> (prostacyclin) in the body. PGI<sub>2</sub> prevents the platelet to aggregate with each other. When PGI<sub>2</sub> is inhibited by means or COX 2 blocker such as rofecoxib, valdecoxib, or those drugs that end with -coxib, it results to decrease PGI<sub>2</sub> in the blood.
- Therefore, if there is no (or decreased) PGI<sub>2</sub> in the blood, it will now cause clumping and it results to constricted blood vessels which results to cardiovascular thrombotic event

## Unit 7: Drugs for Coagulative Disorders



This illustration shows the platelet membrane functions or how promotion and inhibition of platelet in the blood.

Platelet membrane receptors include glycoprotein Ia receptor which binds to collagen and also glycoprotein Ib receptor which binds to von Willebrand factor. Glycoprotein IIb and IIIa binds to fibrinogen and other macromolecules.

Antiplatelet are the following: PGI<sub>2</sub> that are release from endothelium and also aggregating substance are release from degranulating platelet that includes adenosine diphosphate, thromboxane a<sub>2</sub>, and as well as serotonin

### Aspirin (Acetylsalicylic acid)

**MOA:** irreversible inhibitor of COX

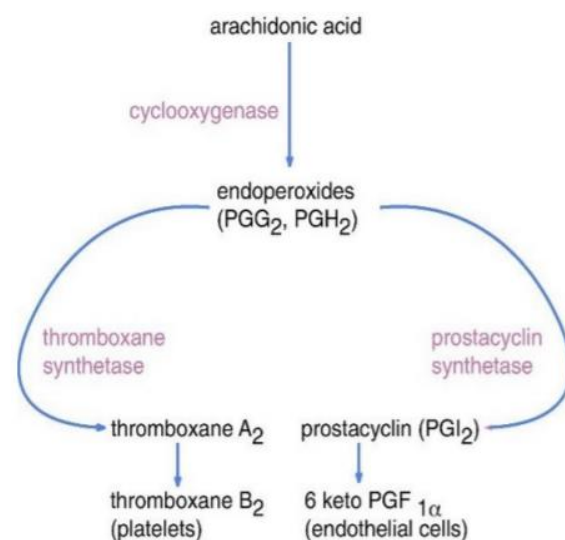
**Indications:** Prophylactic for transient cerebral ischemia and to reduce the incidence of recurrent Myocardial Infarction

**REMEMBER:** aspirin is not only an antiplatelet. Different dosages or dosage strength of our aspirin can provide different pharmacological action

Example:

- at 0.25-0.5 g, it is an analgesic and an antipyretic
- 3-4 grams of aspirin is used for anti-inflammatory, for rheumatic fever, or rheumatoid arthritis

**Dose:** 100 to 325 mg is used as an antiplatelet drug



### Adverse effects:

1. increased incidence of hemorrhagic stroke
2. gastrointestinal bleeding

why does it cause gastrointestinal bleeding?

- Because in the first place, it is a non-selective COX inhibitor. It blocks both COX 1 and as well as COX 2
- If COX 1, which is a cytoprotectant which means it produces mucosal barrier in the stomach, if blocked it can't produce cytoprotectant leading to damage in the linings of the stomach wall resulting to gastrointestinal bleeding
- 3. Toxicity in aspirin leads to salicylism = most common

## Unit 7: Drugs for Coagulative Disorders

manifestation of salicylism is tinnitus  
(buzzing sound in the ear)

**Contraindication:**

Anticoagulants (e.g., warfarin and heparin) –  
increase bleeding

Ibuprofen – antagonize platelet inhibition

Thrombocytopenic purpura (TTP) – it is an  
example of an immune disorder in which the  
blood doesn't clot normally. This condition  
is now more commonly known as immune  
thrombocytopenia (ITP)

Aplastic anemia – deficiency of all blood  
cells, that includes the RBC, WBC, and  
platelets

**ADP (adenosine diphosphate) Receptor Blockers**

**MOA:** Irreversibly inhibit the binding of  
ADP to its receptors on platelets

**Also known as:** thienopyridines

**Examples:**

- Clopidogrel (Plavix)
- Ticlopidine (Ticlid)
- Prasugrel (Effient)

Clopidogrel, prasugrel, and other ticlopidine  
are converted in the liver to active  
metabolites that irreversibly inhibit  
adenosine diphosphate receptor and thereby  
preventing adenosine diphosphate mediated  
platelet aggregation. They need to be  
converted to their active metabolites in the  
liver in order to be effective

- **Clopidogrel** is the preferred agent in  
**ischemic heart disease events**
- Clopidogrel is safer than ticlopidine

Because with regards to their adverse effect,  
it is very minimal such as nausea, vomiting,  
diarrhea, and toxicity causes hemorrhage

- Ticlopidine causes:  
neutropenia/agranulocytosis,  
thrombotic **thrombocytopenic  
purpura (TTP)**, and aplastic anemia

**Glycoprotein IIa and IIb Blockers**

Why do we need to block glycoprotein  
receptors? Because glycoprotein IIa and IIb  
receptors are example of receptors in which  
fibrinogen and other molecules bind. It can  
promote platelet aggregation

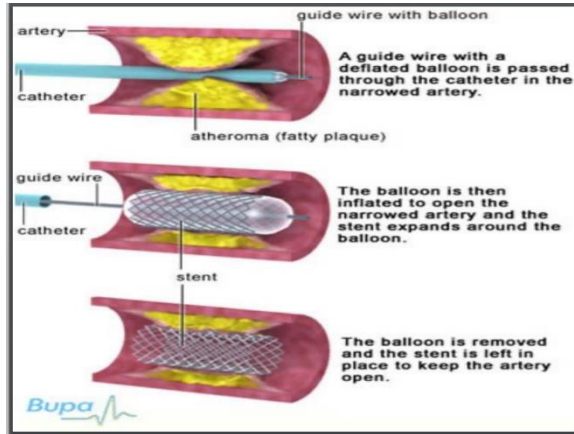
**Abciximab**

- The most common drug under this  
classification
- Chimeric monoclonal antibody
- Given IV along with heparin or ASA  
as an adjunct for patients undergoing  
angioplasty

NOTE: heparin and other anticoagulant  
should NOT be combined with aspirin  
because it is known to develop hemorrhage  
or bleeding. Clinicians will only be choosing  
if anticoagulants or antiplatelets will be used

- S/E: bleeding

## Unit 7: Drugs for Coagulative Disorders



Angioplasty is a medical procedure in which there is an insertion of deflated balloon and when that balloon is in the site where there is an atherosclerosis, the balloon is then inflated to open the narrowed artery and the stent expands around the balloon. The balloon is removed and the stent is left in place to keep the artery open.

### PDE (Phosphodiesterase) Inhibitor

Why are they used as an antiplatelet? Because PDE is the enzyme that inactivates cAMP. To increase the platelet aggregation, the cAMP should be inactivated

### Dipyridamole

Dipyridamole and newer cilostazole appear to provide PDE inhibiting effect

**REMEMBER:** they have dual MOA. First is they prolonging platelet inhibiting action of intracellular cAMP by inhibiting its metabolism. Second is that they can also inhibit the uptake of adenosine by the endothelial and erythrocytes

- It is also a coronary vasodilator
- usually given in combination with aspirin or warfarin; it is ineffective when used alone.
- S/E: Coronary steal phenomenon

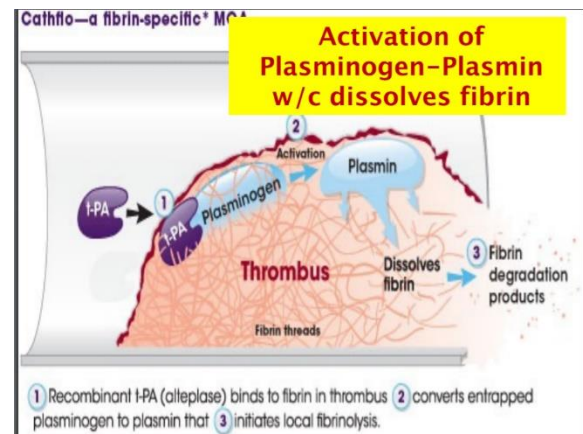
Coronary steal phenomena is a term given to blood being stolen from one region of the coronary tree by another

### Thrombolytics

**Thrombolytics** are used to dissolve existing clots. Prescribed for disorders in which a clot has already formed, including the ff:

1. Acute MI
2. Pulmonary embolism
3. Cerebrovascular accident (CVA)
4. DVT
4. Arterial or Coronary thrombosis

Thrombolytics are sometimes called as fibrinolytics or plasminogen activator because its main MOA is on how they can dissolve the existing blood clot is by activating the plasminogen



Main MOA: they activate plasminogen to become plasmin. Plasmin is the proteolytic enzyme that is capable to dissolve the fibrin

## Unit 7: Drugs for Coagulative Disorders

**Three examples of thrombolytic group:**

- **Streptokinase (streptase)**
  - Example of drug that is isolated from a microorganism
  - Protein from streptococci
  - This streptokinase is obtained from bacterial culture although not itself an enzyme. Streptokinase forms a complex within endogenous plasminogen. The plasminogen in this complex undergoes conformational changes that allows it to rapidly convert plasminogen into plasmin
  - S/E: allergy, bleeding

Most serious manifestation of toxicity of streptokinase is cerebral hemorrhage

- **Tissue Plasminogen Activator**
  - Alteplase (activase), Reteplase (Retavase)
  - Derived from cultured human melanoma cells
  - More selective than streptokinase
  - S/E: bleeding
- **Anistreplase**
  - Anisoylated plasminogen streptokinase activator complex
  - A prodrug meaning it must be converted to its active metabolite upon metabolism
  - S/E: bleeding

Drugs for hemophilia

### Hemostatics

**Hemostatics** are used to promote the formation of clots.

#### 1. Aminocaproic & tranexamic acid (hemostan)

- Synthetic
- MOA: Inhibit plasminogen activation
- Potential side effect of treatment is intravascular thrombosis

Added information:

- pharmacists and other non-pharmacy personnel must extra careful when dispensing tranexamic acid (hemostan) because it is an example of a SALAD medication. It's look-a-like drug is alaxan fr capsule.
- Tranexamic acid is now used for cosmetic products because it has skin-whitening effect or it make the skin more radiant. That is why it is now present in soaps, lotions, creams

#### 2. Aprotinin

- Stops bleeding by blocking plasmin
- It can inhibit streptokinase

**Indication:**

- Approved for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass surgery.

At high doses (greater than 200 IU per mL), it can inhibit kallikrein. Kallikrein can promote bradykinin and also causing the production of plasmin

When low doses (greater than 50 IU per mL) it inhibits the plasmin

Unit 7: Drugs for Coagulative Disorders

3. **Desmopressin acetate**

- The vasopressin V2 receptor agonist **desmopressin acetate increases the plasma concentration of von Willebrand factor and factor VIII.**
- It is used to prepare patients with mild hemophilia A or von Willebrand disease for elective surgery.