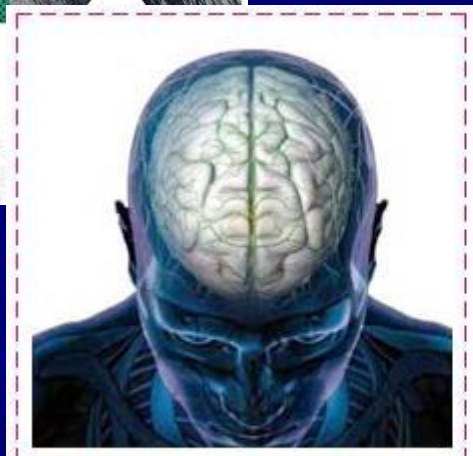
ZSMU Pharmacology Department

Lecture 2

SIDE EFFECTS OF DRUGS AFFECTING CARDIOVASCULAR SYSTEM


Memory Problems


Back Pain

Common side effects of cardiovascular drugs include:
changes in taste, **fatigue**, **sleep problems and muscle pain**.
Many patients also suffer from **cold-like symptoms** like **sore throat** and **coughing**, as well as **flu-like symptoms**, such as **nausea**, **vomiting** and **diarrhea**.

Patients might also experience **headaches**, **brain fog** and certain **sexual problems**.
More serious side effects include **jaundice**, **chest pain**, **kidney failure**, **fainting**, **changes** in **vision** or **heart rate**.

It is also possible for patients to experience an **allergic reaction** to their medication, which will produce symptoms like **swelling**, **rash** or **difficulty breathing**.

SIDE EFECTS OF CARDIAC GLYCOSIDES

Strophanthine, Corglycon, Digoxin, Digitoxin et al.

1. **GIT toxicity**: anorexia, nausea, vomiting, and diarrhea
2. Oliguria, in severe cases - Anuria
3. **Arrhythmias - due to Electrolyte Disturbances**:

□Ca2+, □K+, □ Mg2+

Ventricular ***Extrasystoles,*** **AV blockades**,
Atrial Tachycardia, Ventricular Tachycardia,
Ventricular Fibrillation.

4. **Neurological disturbances:** vertigo, disorientation, hallucinations, agitation, convulsions, visual disturbances (*Xanthopsia* – seeing of objects in yellow-green or grey-blue colours; blurred vision, photophobia, “rings” and “balls” before eyes).
5. **Gynecomastia.**

TREATMENT of OVERDOSE with CARDIAC GLYCOSIDEDS

- **Discontinuation of the drug, Gastric Lavage**
- **Activated charcoal**
- **Potassium - medications:**
  Potassium Chloride (KCl)
  Panangin, Asparcam
- **Complexones: Unithiol** (*Dimercaptol*)
  Sodium calcium edetate (*$CaNa_2$ EDTA*),
  Trilon B (*Sodium Edetate, Na edetate*)

- **Lidocaine or Phenytoin** for Ventricular arrhythmias
- **Atropine to treat AV blockade**
- **Specific Antibody Fragments for life threatening drug toxicity.**

• Side efects of Antiarrhythmic Drugs

Novocainamide (generic: Procainamide),

Rythmol (generic: Propafenone),

Tambocor (generic: Flecainide),

Norpace (generic: Disopyramide phosphate)

Cardiovascular: pain in the chest; arrhythmia, tachycardia or bradycardia, nosebleeds and palpitation, decrease in BP, chest pain or angina, heart failure, shock, heart block.

Respiratory: shortness of breath, sore throat

CNS: dizziness, shaking, trembling, blurred vision, fainting, walking unsteadily, pain in the muscles, paralysis

Sexual: gynecomastia, impotence.

Others: swelling in the face, tongue, lips, throat and the extremities, chills or fever, hunger or appetite loss, constipation, gaining weight.

CAST I and CAST II (1993-1994) –

Cardiac Arrhythmia Suppression Trial I and II

Encainide

Flecainide

Moricizine (*Ethacizine*)

successfully prevented ventricular ectopic beats in patients who had *Myocardial Infarction*.

However, continued therapy with either drug was associated with a 2-3-fold ↑ Death due to drug-induced Fatal Arrhythmias triggered by recurrent Myocardial Ischemia.

ADVERSE REACTIONS OF NITRATES

I. **Moderate**: headache, tinnitus (ear noise), flush, transient episodes of giddiness, weakness, tachycardia, nausea, vomiting.

II. **Severe**:

a) Sharp headache, giddiness, hypotension, syncope, collapse

b) Methemoglobinemia

III. **Dangerous** - *PARADOXICAL REACTIONS*:

a) Angina pectoris attack, myocardial ischemia with AMI and sudden death.

b) Sinus Bradycardia - in **4%** of patients after IV infusion due to *nervus vagus* activation and is controlled by IV *Atropine sulphate* administration.

Hypoxemia may stimulate the ***central vagal nuclei*** and

cold sweat, nausea, vomiting,

involuntary passage of urine and **feces**

may accompany **postural hypotension**.

Management: ***Head-low position*** to augment the venous return and **O_2 administration** may quickly correct the ***nitrite syncope***.

Tolerance to pharmacological actions of **nitrates** develops after repeated administration. **Cross tolerance** is common.

Tolerance to the antianginal action develops when the patient exposed to nitrate for all the 24 hours of the day and

is more common **with long-acting nitrates** such as

Forte-forms and **Transdermal preparations**.

Tolerance can be avoided by **omitting the night-time dose** of preparations.

During such nitrate-free periods, the patient should be covered by another antianginal drug, especially if he has severe angina.

Withdrawal Symptoms

Sudden stoppage of nitrates during chronic administration may precipitate severe angina due to ***coronary artery spasm***. Hence, such abrupt cessation should be avoided.

Risk factors of ADRs development:

- **Arterial Hypotonia**,
- **Increased Intracranial Pressure**,
- **Concomitant Administration** of other **hypotensive drugs**, especially ***vasodilators***,
- taking nitrates following the ingestion of
  alcohol beverages, **diuretics**,
  Sildenafil (***Viagra***),

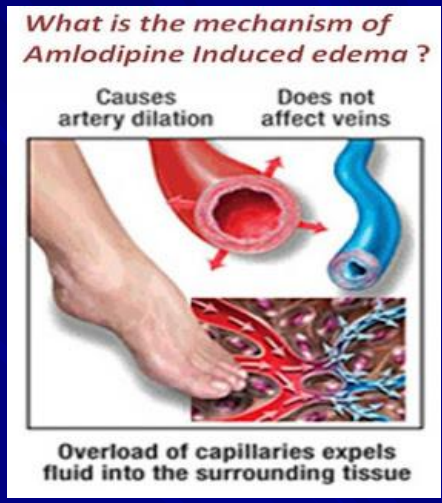
high air temperature (including ***bath***, ***sauna***, ***hot shower***).

PDE 5 inhibitors:
Sildenafil, Viagra, Sialis, Levitra -

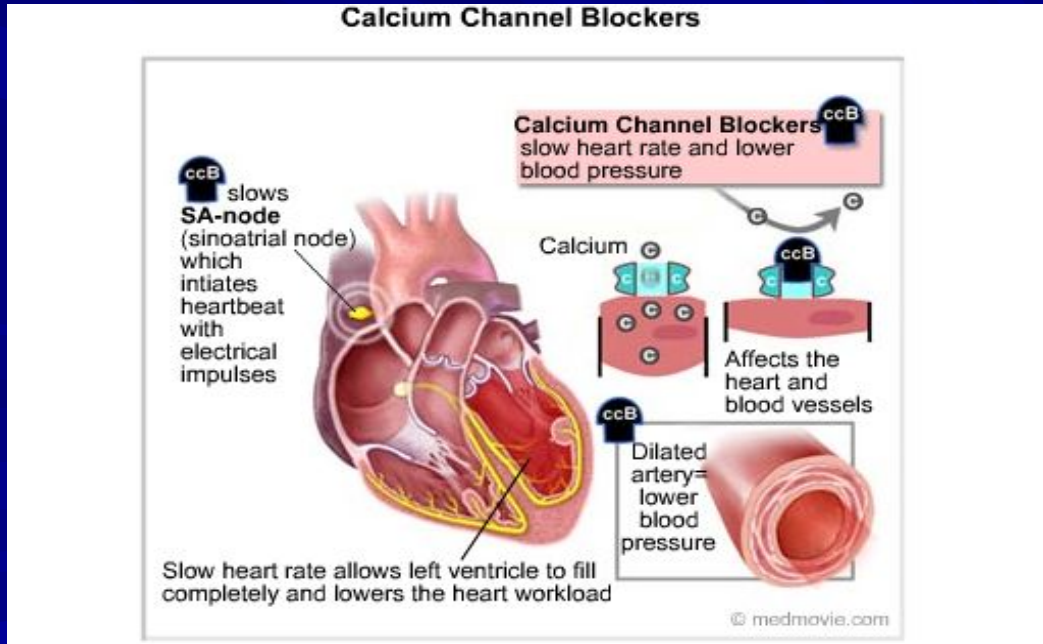
- selectively block PDE 5 responsible for destruction of cGMP => □ cGMP
- release NO in the corpora cavernosa => activation of guanylyl cyclase => □ cGMP synthesis => smooth muscle relaxation
- In healthy people:
  100 mg of Sildenafil =>↓BP by10 mm Hg
- After 0.5 mg Nitroglycerine => ↓BP by 5-10 mm Hg
- Sildenafil + Nitroglycerine => ↓BP by 25-51 mm Hg

Side Effects of Calcium Channel Antagonists

- Phenylalkylamines: Verapamil and Benzothiazepines: Diltiazem may cause Bradycardia to Heart Arrest – Asystole:
- Dihydropyridines – Nifedipine – Tachycardia



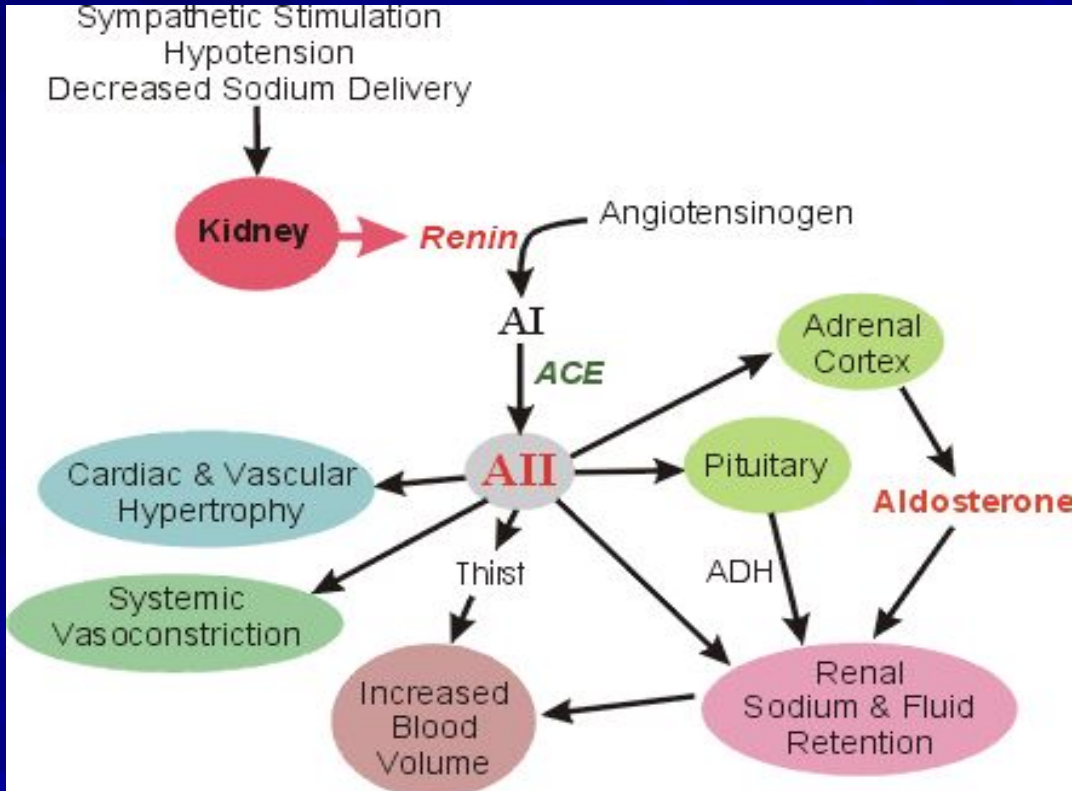
- AV blockades, ventricular arrhythmias
- Acute headache, dizziness, flushing,
- Nausea, Constipation,
- ↓ BP to **collapse**
- Peripheral edema – *tibial edemas*
- ↓ Heart Contraction,
- Pulmonary Edema



Side effects of ACE Inhibitors:

Captopril, Enalapril, Ramipril, Lisinopril

- Common SE: Cough, ↑ K^+ level, low BP, abnormal taste (metallic or salty taste), dizziness, drowsiness, rash, weakness.
- If one ACE inhibitor causes cough it is likely that the others will too.
- The most serious:
  - Kidney Failure,
  - Allergic Reactions,
  - ↓ Leucocytes,
  - Angioedema (swelling of tissues)



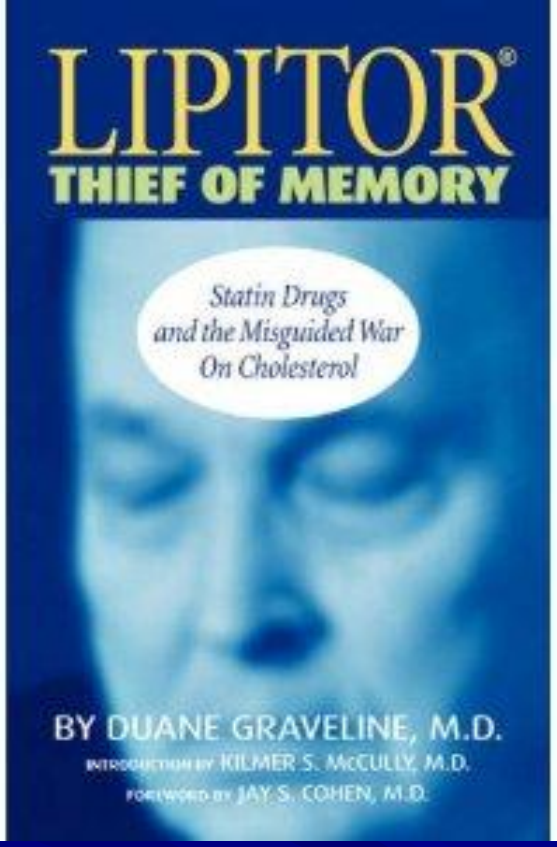
Side effects of beta-blockers

- Common: Fatigue, Cold hands, Upset stomach, Constipation, Diarrhea, Dizziness, Hyperlipidemia
- Less common: Shortness of breath, Trouble sleeping, Loss of sex drive, Impotence, Depression

- Beta blockers generally aren't used in people with asthma because of concerns that the medication may trigger severe asthma attacks.
- In people who have diabetes, beta blockers may block signs of low blood sugar, such as rapid heartbeat.

Side effects of Statins

- Atorvastatin (Lipitor)
- Pravastatin (Pravachol)
- Lovastatin (Mevacor)
- Simvastatin (Zocor)



- *other drugs which sound like super-hero names*

can cause: muscle aches, joint pains, impotence, lethargy, tinnitus, weight gain, cloudy urine, hopelessness, memory loss, rage beyond reason, personality change, getting old quickly.

Alzheimer's and Loss of Brain Function

- People with high cholesterol have better memory function and reduced DEMENTIA.
- Studies have shown that people with low cholesterol have a greater risk of Alzheimer's than those with high cholesterol.
- Dr. Duane Graveline wrote a book about what statins did to his memory, titled *Lipitor: Thief of Memory*.
- 6 months after Dr. Graveline started using Lipitor, he was diagnosed with Transient Global Amnesia.
- He was unable to formulate new memories and also had retrograde memory loss. Dr. Graveline started doing his own research on statin side effects. At present, Dr. Graveline has uncovered > 2,000 cases of transient global amnesia associated with the use of statins.

- **Pneumonia.** A recent study found that statin use increased the risk of pneumonia by a whopping 62% in elderly patients requiring hospitalization.

- **Cancer:** The Deadly Price of Using Statin Drugs.

After a thorough meta-analysis of studies on cancer and statin use, it was found that there was

an **inverse relationship** between **low cholesterol** levels and **cancer, i.e.** those people who were able to lower their cholesterol with statins were **at greater risk for developing cancer**.

- The statin drug **Vytorin** was taken off the market in **2008** after it was proven to have caused

  a whopping **64% increase in all types of cancer**.

- A recent study reported that among obese men, those who used a statin for 5 years or more had a whopping 80% greater risk of developing prostate cancer than those who did not use a statin drug.
- Other human studies have shown that statin drug use increases the risk of skin cancer and breast cancer.

A report based on the Framingham data (1993)

The relationship between total cholesterol level and all-cause mortality was positive (higher cholesterol level associated with higher mortality) at age 40 years, negative at age 80 years, and
negligible at ages 50-70 years.

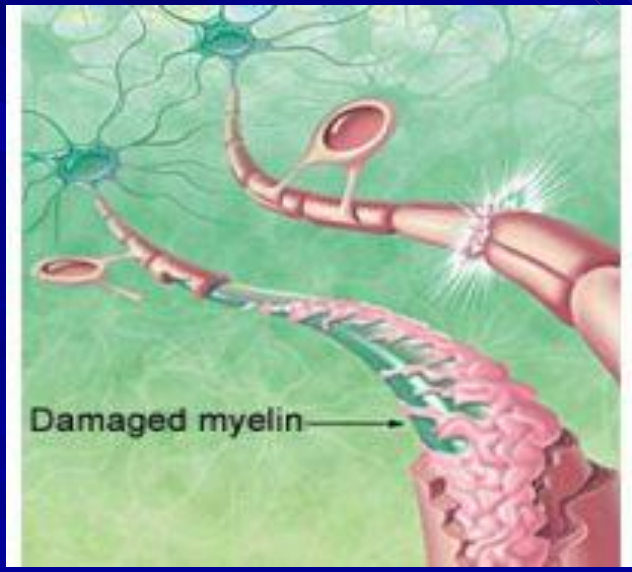
- The relationship with CHD mortality was positive at ages 40, 50, and 60 years but attenuated with age until the relationship was positive at age 70 years and negative at age 80 years.
- **Non-CHD mortality** was significantly **negatively** related to cholesterol level for ages
50 years and above.

- **Heart Failure** is a symptom of Co Q10 depletion, therefore it is very important that all statin users supplement with this vital nutrient (100-200 mg per day).
- A study done in the UK showed that patients at risk for heart failure benefited from having high cholesterol rather than low.
- Those patients who had low cholesterol were at a greater risk of dying from heart failure.
- Diabetes. A recent large-scale study done on postmenopausal women found that there was a whopping 48% increase in incidence of diabetes in women who took statins vs. women who did not take statins.
- A meta-analysis of studies has found that **statin use** is linked to an **increased risk** of **diabetes** in men and women of all **age groups**.

- “If you **deprive cholesterol** from the brain, then you directly affect the **machinery** that **triggers** the release of **neurotransmitters**.

- Neurotransmitters affect the **data-processing** and **memory functions**.
- In other words — how smart you are and how well you remember things.”

Cholesterol expert **Yeon Kyun Shin**



Mevacor (*Lovastatin*):

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for Hepatocellular Carcinoma (Liver Cancer) in males at drug exposures 2-7 times that of human exposure at 80 mg/day (doses in rats were 5, 30 and 180 mg/kg/day).

Pravachol (Pravastatin **)**:

Carcinogenesis, Mutagenesis, Impairment of Fertility.

In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of Hepatocellular Carcinomas in males at the highest dose (approximately 12 times the human dose of 80 mg)

ZOCOR® (Simvastatin):

In a 72-week carcinogenicity study, mice were administered daily doses of of 25, 100, and 400 mg/kg body weight, Liver Carcinomas were significantly increased in high-dose females and mid and high-dose males with a maximum incidence of 90% in males.

Drug treatment also significantly increased the incidence of

Lung Adenomas,
Liver Adenomas
Thyroid Follicular Adenomas

in mid- and high-dose males and females.

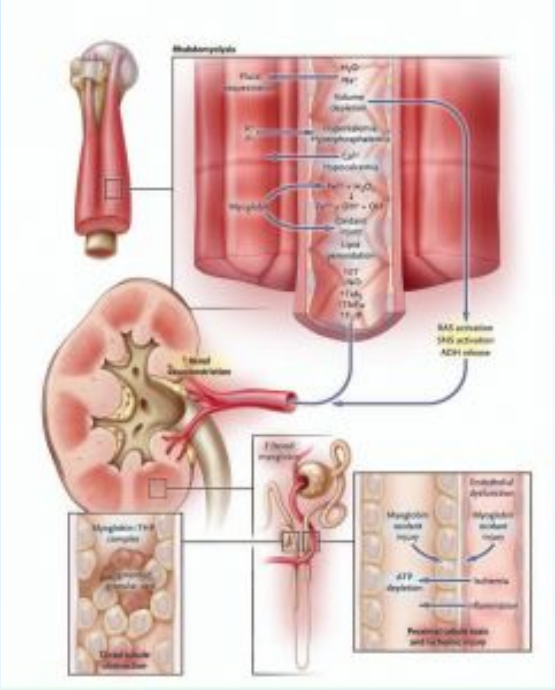
Liver Damage

A meta-analysis of studies shows that statins cause **Liver damage**, and sometimes **Liver failure**.

To protect the liver, all statin users should take a daily liver detox supplement, such as ***Liver Milk Thistle*** or ***Holy Thistle or Legalone***

Muscle pain and **weakness**, also known as ***Rhabdomyolysis***, is a common side effect of taking statins.

Most likely, this SE is due to **statin-induced depletion** of **Coenzyme Q10**, which is essential for proper muscle function.



Rhabdomyolysis can lead to **kidney injury**, **kidney failure**, and **death**.

Polyneuropathy is a nerve disease characterized by weakness, **tingling** and **pain** in the hands and feet, as well as **difficulty walking**.

Studies have shown that **Statin Use** is associated with an increased incidence of this condition.

Duration of statin use increases the risk of **polyneuropathy**, and the nerve damage is often **irreversible**.

Side Effects of Diuretics

Frequent urination, Arrhythmia,
Electrolyte abnormalities: K+, Na+, Mg2+, Ca2+;
Extreme tiredness or weakness, muscle cramps, blurred vision, lightheadedness, confusion, sweating, and restlessness.

Dehydration. Signs include dizziness, extreme thirst, excessive dryness of the mouth, decreased urine output, dark-colored urine, constipation.
FeverFever, sore throatFever, sore throat, cough, ringing in the ears, unusual bleeding or bruising, rapid and excessive weight loss.
Skin rash.
Loss of appetite, nausea, vomiting, muscle cramps.
Spironolactone can cause breast enlargement or tenderness in men and in women it can cause deepening of the voice, decreased hair growth, and irregular menstrual cycles.

- Apart from electrolyte disturbances such as K^+ depletion, hypercalcemia, hypokalemic and hypochloremic alkalosis,

THIAZIDES have few serious adverse reactions:

- Volume Depletion,
- Hyperglycemia,
- Hyperuricemia
- *Sulphonamide-like allergic reactions* such as dermatitis, thrombocytopenia and other blood dyscrasias.
- may precipitate renal failure or hepatic coma.

Treatment and Prevention of K^+ depletion:

K^+ can be supplemented (KCL, Panangin, Asparcam) and diet such as by increasing the intake of citrus fruit, potato, and black mulberry.

In some cases, K^+ -sparing diuretics may be necessary.

Side effects of Antiplatelet Drugs

Clopidogrel (Plavix), Ticlopidine (Ticlid)

Abciximab, Integrelin

- Thrombotic Thrombocytopenic Purpura :

small blood clots made of platelets form suddenly throughout the body, lowering the number of circulating blood cells.

This can cut off the blood supply to organs, especially the kidneys and brain.

Symptoms: fever, difficulty thinking clearly, and easy bruising.

- Neutropenia: an abnormally low number of leucocytes
- Agrunolocytosis: failure of the bone marrow to make enough leucocytes

Symptoms: fever, chills, sore throat and tiredness.

- Aplastic anemia: the bone marrow doesn't make enough new blood cells, which can lead to heart problems and even death.

Side effects of Direct Anticoagulants

Heparin, Fraxiparin, Enoxaparin

- Bleeding complications: bleeding gums, nosebleeds, coughing up blood, black, tarry, or bloody stools, blood in the urine
- Excessive bleeding may be managed by suspending the drug and treating with *Protamine sulfate.* Infused slowly, it combines with *heparin* to form a stable, inactive complex.
- Hypersensitivity reactions: chills, fever, urticaria, or anaphylactic shock are possible, since the *heparin* preparations are obtained from animal sources and may therefore be antigenic.
- Thrombocytopenia may occur after 8 days of therapy. In some patients, *heparin*-induced platelet aggregation is followed by the formation of antiplatelet antibodies.

Side Effects of Anticoagulants of Indirect Action
Warfarin, Neodicumarin , Phenylin, Syncumar

- Bleeding disorders.
- Minor bleeding may be treated by withdrawal of the drug and administration of oral *vitamin K*;
- Severe bleeding requires greater doses of the vitamin K given IV.
- Whole blood, Frozen plasma, Plasma concentrates of the blood factors may also be employed to arrest haemorrhaging.

Side Effects of Thrombolytic (*Fibrinolytic*) Drugs
Streptokinase, Urokinase, Streptodekase., Alteplase

- The main hazard of all agents is bleeding, including GI haemorrhage and stroke.
- Streptokinase can cause allergic reactions, low-grade fever, urticaria, rash, anaphylaxis and febrile reaction.
- Since *Streptokinase* is a bacterial antigen, it may result in rapid antibody formation

Streptokinase antibodies may be present as a result of prior streptococcal infections. Binding to such antibodies would neutralize streptokinase molecules.

- *Thrombolytics* should not be employed in the presence of acute inflammation, as it may encourage the spread of localized infection.

ANTIOXIDANT VITAMINS

- **HPS** (Heart Protection Study) (2001):

  Along with ↓Cardio-Vascular Events –

  Myocardial Infarctions, Strokes, Overall Mortality –

  in the group of *SIMVASTATIN,*

There ↓was Overall Mortality

In the group of *ANTIOXIDANT VITAMINS*:

Vitamins E, C and β-carotene – by **4%**,

the greatest increase – by **7% -**

in the group of cardio-vascular diseases.

Although these vitamin preparations have antioxidant properties, their therapeutical usefulness in preventing cardiovascular disease or cancer is not established.


Thank you for attention!