# Overview of Lecture Series

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<th>When Things Go Wrong</th>
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<td>Heart Rate, Blood Pressure</td>
<td>Hypertension, Heart Failure, Arrhythmias</td>
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<th>Aetiology</th>
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<td>Treatment</td>
<td>Sympathoplegic Drugs, Diuretics, Vasodilators, Angiotensin Antagonists</td>
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<td>Prophylactic: Lipid lowering, Anti-coagulant, Anti-platelet drugs</td>
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<td>4. Heart Failure &amp; Cardiac Arrhythmias</td>
<td>Treatment</td>
<td>Heart Failure: Nitrites, Calcium Channel Blockers, Diuretics, Angiotensin Antagonists, β-Blockers, b-Receptor Agonist, Cardiac Glycosides</td>
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<td></td>
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Cardiovascular System & Its Diseases

Lecture #3 Myocardial Ischemia

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Cardiovascular System & Its Diseases:

Myocardial Ischemia

Overview

1. Pathophysiology
   - Stable Angina
   - Unstable Angina
   - Silent or Effort Ischemia
   - Variant Angina
   - Myocardial Infarction

2. Pharmacological Intervention
   - **Symptomatic**
     - Nitrates
     - Ca\(^{2+}\) Channel Blockers
     - \(\beta\)-Blockers
   - **Prophylactic**
     - Lipid Lowering Drugs
     - Anti-Coagulants
     - Fibrinolytic
     - Anti-platelet
Major Drug Groups

**Symptomatic**
Nitrates
Ca$^{2+}$ Channel Blockers
β-Blockers

**Prophylactic**

**Lipid Lowering Drugs**
1. Statins Inhibit cholesterol synthesis
2. Resins Block cholesterol reabsorption
3. Niacin Decreased VLDL secretion
4. Fibrates Lipoprotein lipase synthesis

**Anti-Coagulants**
1. Warfarin Vitamin K antagonist
2. Heparin Factor Xa & AT III

**Fibrinolytic**
1. Streptokinase Plasmin activation
2. Tissue Plasminogen Activators Endogenous

**Anti-platelet**
1. Aspirin / Ibuporfen TXA$_2$ inhibition
2. Ticlopidine / Clopidogrel Adenosine-R block
Myocardial Ischemia

Pathophysiology: What Is It?

Imbalance in Oxygen Supply & Demand

Arteriovenous Oxygen Difference is near maximum in coronary circulation. Therefore, redistribution of Regional Myocardial Flow is of major importance.
Pathophysiology: Symptoms

**Angina Pectoris:** (Chest Pain) Primary symptom associated with ischaemic heart disease. Caused by transient episodes of myocardial ischaemia. Pain is due to accumulation of metabolites in muscle tissue.

Affects 6.4 Million Americans

**Manifests in Different Forms:**

- **Stable Angina** (atherosclerotic block of coronary artery)
- **Unstable Angina** (rupture of atherosclerotic plaque)
- **Silent / Effort Ischemia** (Often induced by exercise)
- **Variant Angina** (focal/diffuse coronary vasospasm)
- **Myocardial Infarction** (Heart Attack, death of tissue)
Cardiovascular System & Its Diseases:

**Myocardial Ischemia**

**Pathophysiology: Aetiology**

- **Atherosclerosis:**
  - Deposition of Fatty Substances esp. cholesterol or fatty acids in arteries
  - Risks Factors include:
    - Hypertension
    - Hyperlipidemia
    - Obesity
    - Carbon Monooxide in Smoke
    - Sedentary life-style

- **Coronary Artery Spasm:**
  - Cause Unknown. May occur in patients with or without atherosclerosis
  - Risks Factors include:
    - Smoking
    - Stress
Cardiovascular System & Its Diseases:

Myocardial Ischemia

Pathophysiology: Arteriosclerosis & Plaques

Blood Vessel Damage

Plaque formation due to inflammation

Two Types Of Plaque

Endothelium-Smooth Muscle Interface
Ruptured lesion in endothelium

Narrowing of blood vessel lumen

FIGURE 22.10 Development of an atheromatous plaque. An injury to the endothelial lining allows LDL particles, monocytes, and platelets to enter the smooth muscle tissue. Inflammation at the injury site triggers the conversion of monocytes to macrophages, which scavenge the LDL particles and cholesterol to form enlarged foam cells (xanthoma cells). Smooth muscle cells, foam cells, platelets, and LDL particles form fibrous plaques. The plaques form in two ways: A, at the interface between the endothelium and the smooth muscle tissue, leaving an elevation in the repaired endothelium, or B, as an ulcerated, or ruptured lesion in the endothelium that protrudes into the lumen. Both types of plaque narrow the lumen and restrict blood flow.
Pharmacological Intervention: Possible Strategies

Cardiovascular System & Its Diseases:

Myocardial Ischemia

Several Possible Therapeutic Approaches:

1. Reduce Myocardial $O_2$ demand
2. Prophylactic Therapy
Pharmacological Intervention: Drug Types

Cardiovascular System & Its Diseases:

Myocardial Ischemia

Drug Types Currently Used

1. Nitrates
2. Ca\(^{2+}\) Channel Blockers
3. β-Blockers

Reduce BP
Venous Return
Force/Rate of Heart

Reduce O\(_2\) Demand and/or
Improve Coronary Flow

4. Lipid Lowering Drugs
5. Drugs Affecting Coagulation, Fibrinolysis & Platelet Aggregation

Targeted towards reducing plaque formation

Slower development of ischemia
Myocardial Ischemia

Symptomatic Intervention: Nitrates

- **Drugs:**
  - *Nitroglycerin* (synthesized 1846)
  - Isosorbide Nitrate

- **Indication:** Effort Angina
  - Variant Angina
  - Acute Coronary Syndrome

- **Mechanism:** Reduce venous return, cardiac size & diastolic myocardial oxygen consumption

- **Side-effects:** Orthostatic hypotension
  - Tachycardia
  - Headache
Symptomatic Intervention: \( \text{Ca}^{2+} \) Channel Blockers

- **Drugs:**
  - Verapamil
  - Nifedipine
  - Diltiazem

- **Indication:**
  - Effort Angina \((\text{prophylactic})\)
  - Variant Angina \((\text{prophylactic})\)

- **Mechanism:** Peripheral vasodilatation & Reduction of cardiac work

- **Toxicity:**
  - Orthostatic hypotension
  - AV Blockade
  - Edema
Cardiovascular System & Its Diseases:

Myocardial Ischemia

Symptomatic Intervention: β-Blockers

- **Drugs:** Propanolol

- **Indication:** Effort Angina (very important)
  - Variant Angina (no benefit)
  - Acute Coronary Syndrome (very important)

- **Mechanism:** Reduce blood pressure
  - Reduce cardiac work

- **Side-effects:** Orthostatic hypotension
  - Tachycardia
  - Headache
Cardiovascular System & Its Diseases:

Myocardial Ischemia

**Symptomatic Intervention:** Combination Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nitrates Alone</th>
<th>β Blockers or Calcium Blockers Alone</th>
<th>Combined Nitrate and β Blocker or Calcium Blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Reflex increase</td>
<td>Decrease</td>
<td>Decrease or no effect</td>
</tr>
<tr>
<td>Arterial pressure</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>End-diastolic pressure and fiber tension</td>
<td>Decrease</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Contractility</td>
<td>Reflex increase</td>
<td>Decrease</td>
<td>No effect or decrease</td>
</tr>
<tr>
<td>Ejection time</td>
<td>Reflex decrease</td>
<td>Increase</td>
<td>No effect</td>
</tr>
</tbody>
</table>

1 Undesirable effects (effects that increase myocardial oxygen requirement) are shown in *italics*; beneficial effects are shown in *bold*. 
Atherosclerosis: Deposition of Fatty Substances esp. cholesterol or fatty acids in arteries

Myocardial Ischemia

Prophylactic Intervention: Clinical Options

- Dietary changes to reduce cholesterol & lipids
- Cessation of Smoking
- Control of Blood Pressure
- Control of Diabetes
- Regular, moderate exercise
- *** Drugs to reduce plasma cholesterol ***
Cardiovascular System & Its Diseases:

**Myocardial Ischemia**

**Prophylactic Intervention:** Overview of Lipid Lowering Drugs

<table>
<thead>
<tr>
<th>GOAL</th>
<th>Prevent myocardial infarction and other atherosclerotic disorders such as stroke and peripheral vascular disease, prevent reinfarction (statins), and increase survival.</th>
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<tbody>
<tr>
<td>APPROACH</td>
<td>Prophylactic use to reduce formation of atherosclerotic plaque and subsequent narrowing of lumen in cardiac arteries.</td>
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</tbody>
</table>
**Cardiovascular System & Its Diseases:**

**Myocardial Ischemia**

**Prophylactic Intervention:** Sources Of Cholesterol

**2 Possibilities:**
- **Dietary** (gut) or
- **De Novo Synthesis** (liver)

**FIGURE 22-2** Total body balance of cholesterol, showing input by ingestion and liver synthesis, output by nonabsorption into feces, conversion into bile salts, delivery in bile salts to small intestine, partial reabsorption from bile, and delivery as lipoproteins into systemic circulation. Quantities shown are approximate daily amounts.
Cardiovascular System & Its Diseases:

Myocardial Ischemia

Prophylactic Intervention: *De Novo Synthesis Of Cholesterol* liver

**HMG-CoA**

Hydroxy-3-methyl-glutaryl-coenzyme-A
Cardiovascular System & Its Diseases:

Myocardial Ischemia

Prophylactic Intervention: Lipoprotein-transport system

**VLDL** transports cholesterol & triglycerides

**VLDL** deposited in adipose tissue & muscle

After lipolysis by lipoprotein lipase (LL)

Resultant **IDL** goes to hepatocytes or becomes **LDL**

**LDL**: low-density lipoprotein

**VLDL**: very low-density lipoprotein

**IDL**: intermediate-density-lipoprotein
Myocardial Ischemia

Prophylactic Intervention: Strategy For Lipid Lowering Drugs

1. Inhibition of Cholesterol Synthesis
   (HMG-CoA Reductase Inhibitors, e.g. Statins)

2. Prevention of Cholesterol Reabsorption
   (e.g. Resins)

3. Reduction of VLDL Secretion
   (e.g. Niacin)

4. Increased Synthesis of Lipoprotein Lipase
   (e.g. Fibrates)
Symptomatic Intervention: Inhibition of Cholesterol Synthesis

- **Drugs:** Statins (e.g. *lovastatin, atorvastatin*)

- **Mechanism:** Inhibit HMG-Co-A reductase that blocks the *de novo* synthesis of cholesterol

- **Side-effects:** May damage skeletal muscle or liver
  - Interference with myelination of infants
    (contraindicated in pregnancy)
Symptomatic Intervention: Preventing Cholesterol Reabsorption

- **Drugs:** Resins (e.g. * cholestyramine, colestipol)

- **Mechanism:** Non-absorbable macromolecules that bind cholesterol preventing reabsorption from gut

- **Side-effects:** Unpleasant gritty taste
  GI tract discomfort
  Interference of vitamin or drug absorption
Symptomatic Intervention: Reduction of VLDL Secretion

**Drugs:**  * Niacin (nicotinic acid, vitamin B₃)

**Mechanism:** Action not well understood though decrease in secretion of VLDL particles from liver

**Side-effects:** Occasional flush with itching reduced with aspirin. Rarely causes glucose intolerance
Cardiovascular System & Its Diseases:

Myocardial Ischemia

Symptomatic Intervention: Increased Synthesis of Lipoprotein Lipase

- **Drugs:** Fibrates (e.g. * gemfibrozil, fenofibrate*)

- **Mechanism:** Activate peroxisome proliferation-activated receptor-\(\alpha\) which increases lipoprotein lipase synthesis

- **Side-effects:** Nausea
  Skin Rash
  Occasional increase risk of gallstones
**Cardiovascular System & Its Diseases:**

**Myocardial Ischemia**

**Prophylactic Intervention:** *Drugs Affecting Plaque Formation*

<table>
<thead>
<tr>
<th>Therapeutic Overview</th>
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<tbody>
<tr>
<td><strong>Anticoagulation</strong></td>
<td>Arterial thrombosis</td>
</tr>
<tr>
<td>Heparin, coumarins</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathy</td>
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<tr>
<td></td>
<td>Cerebral emboli</td>
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<td></td>
<td>Hip surgery</td>
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<td></td>
<td>Vascular prostheses</td>
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<td></td>
<td>Heart valve disease</td>
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<td></td>
<td>Venous thromboembolism</td>
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<tr>
<td><strong>Fibrinolysis</strong></td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Streptokinase, urokinase, tissue plasminogen activator</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
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<tr>
<td><strong>Platelet Aggregation Inhibition</strong></td>
<td>Cerebrovascular accident, stroke</td>
</tr>
<tr>
<td>Aspirin</td>
<td>After coronary artery bypass surgery</td>
</tr>
<tr>
<td></td>
<td>Restenosis after angioplasty or thrombolysis</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Transient ischemic attack</td>
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3 Main Types:
Prophylactic Intervention: Strategies Of Drug Therapy

Cardiovascular System & Its Diseases:

Myocardial Ischemia

Inhibition of blood coagulation

Inhibition of platelet function

Stimulate lysis of pre-formed thrombus

FIGURE 23-1 Involvement of thrombin and platelets and their interaction in thrombosis.
Prophylactic Intervention: Inhibition Of Blood Coagulation

Drugs: * Warfarin and * Heparin

Mechanism: Blocks reactivation of Vitamin K epoxide Warfarin
Binds coagulation factor Xa and antithrombin III Heparin

Indications: Prevention & treatment of venous clotting
(especially deep vein thrombosis)

Side-effects: Teratogenic Warfarin, contraindicated during pregnancy
Bleeding Both
Prophylactic Intervention: Inhibition Of Blood Coagulation

**Warfarin** binds coagulation factors:

- II, VII, IX and X

**Heparin** binds:

- Coagulation factor Xa
- Antithrombin III

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*FIGURE 23-2*  A simplified model of thrombin generation. Reactions fall into four phases, which occur preferentially on surfaces. Activated platelets provide the surface for two of these phases; nonvascular tissue provides the surface for the extrinsic phase, and foreign surfaces such as glass and collagen activate the contact phase. In each, a multicomponent complex is assembled, comprising an enzyme, its substrate (a proenzyme), and a cofactor. This complex affects conversion of proenzyme to its active form at a rate thousands of times faster than that of the enzyme alone.
Cardiovascular System & Its Diseases:

Myocardial Ischemia

Prophylactic Intervention: Vitamin K Antagonists

Structural Similarity Amongst Vitamin K Dependent Proenzymes

Similarity Amongst Vitamin K & Its Antagonists
**Cardiovascular System & Its Diseases:**

**Myocardial Ischemia**

**Prophylactic Intervention:** Vitamin K Antagonists

Warfarin effects vary significantly amongst patients therefore effect is monitored with prothrombin time test.
Cardiovascular System & Its Diseases:

Myocardial Ischemia

Prophylactic Intervention: Heparin

- Heparin available in high molecular weight (HMW) and low molecular weight (LMW) form
  - HMW Heparin binds coagulation factor Xa and antithrombin III
    - Effect must be monitored
  - LMW heparins inhibit factor Xa but less effect on antithrombin III
    - Predictable response, not monitored
Cardiovascular System & Its Diseases:

Myocardial Ischemia

Prophylactic Intervention: Fibrinolytic Drugs

**Figure 34–3.** Schematic representation of the fibrinolytic system. Plasmin is the active fibrinolytic enzyme. Several clinically useful activators are shown on the left in bold. Anistreplase is a combination of streptokinase and the proactivator plasminogen. Aminocaproic acid (right) inhibits the activation of plasminogen to plasmin and is useful in some bleeding disorders.
Myocardial Ischemia

Prophylactic Intervention: Fibrinolytic Drugs

- **Drugs:** * Streptokinase bacterial culture & * Tissue Plasminogen Activators (tPA) recombinant

- **Mechanism:** Conversion of plasminogen to plasmin
  - Activation of plasminogen bound to fibrin

- **Indications:** Pulmonary embolism & Myocardial infarction

- **Side-effects:** Allergic response Streptokinae
  - Bleeding Both
Cardiovascular System & Its Diseases:
Myocardial Ischemia

Prophylactic Intervention: Anti-platelet Drugs

Collagen Wall activates platelets

1. Release of thromboxane A₂ (from arachidonic acid)
2. Secretion of adenosine diphosphate (ADP)

Thromboxane A₂ is potent aggregating agent & vasoconstrictor

Thromboxane A₂ & ADP stimulates appearance of fibrinogen binding sites on platelet membrane

(platelet aggregation)
Prophylactic Intervention: Cyclooxygenase inhibitors

- **Drugs:** *Aspirin* irreversible & *Ibuprofen* competitive

- **Mechanism:** Inhibits platelet cyclooxygenase blocking the synthesis of thromboxane $A_2$

- **Indications:** Transient ischemic attacks & Myocardial infarction

- **Side-effects:** Bleeding GI ulceration *aspirin*
Prophylactic Intervention: Adenosine receptor blockers

- **Drugs:** Ticlopidine & Clopidogrel

- **Mechanism:** Alternative to Aspirin;
  - Inhibits platelet response to secreted ADP at adenosine receptors

- **Indications:** Transient ischemic attacks & Myocardial infarction

- **Side-effects:** Bleeding, Skin rashes
**Major Drug Groups**

**Symptomatic**

Nitrates
Ca\(^{2+}\) Channel Blockers
\(\beta\)-Blockers

**Prophylactic**

**Lipid Lowering Drugs**
1. Statins  Inhibit cholesterol synthesis
2. Resins  Block cholesterol reabsorption
3. Niacin  Decreased VLDL secretion
4. Fibrates  Lipoprotein lipase synthesis

**Anti-Coagulants**
1. Warfarin  Vitamin K antagonist
2. Heparin  Factor Xa & AT III

**Fibrinolytic**
1. Streptokinase  Plasmin activation
2. Tissue Plasminogen Activators  Endogenous

**Anti-platelet**
1. Aspirin / Ibuporfen  TXA\(_2\) inhibition
2. Ticlopidine / Clopidogrel  Adenosine-R block
Mystery Case

ELEMENTARY, DR. WATSON...
Case Study

A 63-year-old man complains of sudden onset of numbness of his right hand plus a “funny feeling” on the right side of his face. This lasted for an hour but had resolved by the time he reached your office. On examination there are no neurological deficits and he looks well. The vital signs reveal BP 150/75 mmHg, pulse 110 beats/min and irregularly irregular, respiration 14/min and temperature of 37°C.

Has the patient had a stroke?

No; most probably, a transient ischemic attack Affecting the left middle cerebral artery
Cardiovascular System & Its Diseases:

Myocardial Ischemia

**Case Study**

*What could account for the episode of transient ischemia?*

**Occlusion by small embolus**

*Where did the embolus come from?*

**From inefficiently contracting left atrium**

He has atrial fibrillation
Myocardial Ischemia

Case Study

What is the most appropriate treatment for this patient?

Asymptomatic atrial fibrillation; prophylactic anticoagulant for life
Warfarin or Aspirin (though less effective)
Cardiovascular System & Its Diseases:

Myocardial Ischemia

What Have We Learned?

1. Different Types Of Ischemia

2. Different Types of Drug Therapy

   Symptomatic and/or Prophylactic