Treatment of ischemic heart disease (IHD)

Metabolic syndrome (Syndrome X)
- Fasting hyperglycemia
- High blood pressure
- Central obesity
- Decreased HDL cholesterol;
- Elevated triglycerides

Ischemic heart disease
- Heart problems caused by narrowed heart arteries → decreased blood and oxygen supply
- Also called coronary artery disease and coronary heart disease
- Ischemia often causes chest pain or discomfort known as angina pectoris

Etiology
- Fixed partial obstruction of an artery or arteries due to atheroma or other pathological processes
- Inappropriate arterial vasospasm
- A thrombus
- Severe mocardial ischemia → infarction (death of cardiac cells)

Pathophysiological process
- Hemodynamic abnormalities
- Neurohormonal activation – progression of heart failure
  - Renin – angiotensin – aldosterone system
  - Sympathetic nervous system
  - Natriuretic peptides: NEP-inhibitor
  - Arginine vasopressin – Endothelin
  - Cytokines

Classification of Hyperlipoproteinemias

<table>
<thead>
<tr>
<th>Type</th>
<th>Lipoproteins</th>
<th>Elevations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (rare)</td>
<td>chylomicrons</td>
<td>TG ↑–C</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>C ↓</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL, VLDL</td>
<td>C ↑–C</td>
</tr>
<tr>
<td>III (rare)</td>
<td>IDL, VLDL</td>
<td>C/TG ↓</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>TG ↑–C</td>
</tr>
<tr>
<td>V (rare)</td>
<td>chylomicrons, VLDL</td>
<td>➔</td>
</tr>
</tbody>
</table>

C = cholesterol, TG = triglycerides, LDL = low-density lipoprotein, VLDL = very-low-density lipoprotein, IDL = intermediate-density lipoprotein.
Risk Factors

- Family history of coronary artery disease, diabetes, high blood pressure or atherosclerosis
- Smoking
- Poor nutrition, especially too much fat in the diet
- Previous heart attack or stroke
- Overweight
- Hypertension
- Elevated cholesterol and/or low level of HDL (high-density lipoprotein)
- Type A personality

Symptoms

- Myocardial infarction (MI), the most important form of IHD, in which the duration and severity of ischemia is sufficient to cause death of heart muscle
- Angina pectoris, in which the ischemia is less severe and does not cause death of cardiac muscle
- Chronic IHD with heart failure
- Sudden cardiac death

Symptoms

- Temporary damage and pain (ischemia)
- Loss of muscle activity (acute heart failure)
- Permanent heart muscle damage, heart muscle does not grow back (acute myocardial infarction /infarct).
- Long term loss of heart muscle activity (chronic heart failure)
- Cardiac arrhythmias: irregular heartbeat which can be fatal. Most death is due to arrhythmias, usually tachyarrhythmias.
- Other structural damage to the heart including damaged heart valves, actual perforation of the heart and a thin walled fibrous floppy heart

Angina pectoris

- The main symptom of coronary artery disease
- It occurs when the oxygen supply to the myocardium is insufficient for its needs

Angina pectoris

- It is characterized by a sudden, severe pressing, substernal pain radiating to the left arm or neck or back or stomach
- The onset of chest pain is connected with the exercise and is diminished by its end
- The pain can be stopped by nitrates
Types of angina

- Stable (caused by fixed coronary stenosis)
- Unstable
- Variant (called Printzmetal’s angina)

Unstable angina

- Occurs suddenly at rest or with limited physical activity and increases in frequency and severity; often occurs prior to myocardial infarction
- Diseases that cause unstable angina:
  - Coronary arteriosclerosis
  - Transient platelet aggregation and coronary thrombosis
  - Coronary artery spasm
  - Coronary vasoconstriction following adrenergic stimulation
  - Accumulation of potent vasoconstrictors at sites of endothelial injury

Variant angina

- Chest pain at rest
- Pain at the same time of day (early morning)
- ST segment elevation during chest pain
- Chest pain accompanied by ventricular arrhythmias
- Nitrates relieves chest pain and elevation of ST segment

Other causes of chest pain

- Pneumonia
- Pericarditis
- Pulmonary embolism
- Rib fractures
- Nerve compression
- Shingles
- Esophageal spasm and reflux
- Gallbladder attack

ANTIANGINAL DRUGS

- Improve perfusion of the myocardium
- Reduce metabolic demand of myocardium

ANTIANGINAL DRUGS

- Organic nitrates
- Calcium antagonists
- β-adrenergic blockers
- Anticoagulants
  - Trimetazidine
ORGANIC NITRATES

MECHANISM OF ACTION
- They are thought to relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide (NO)
- It activates guanylate cyclase and increases the cGMP
- Elevated cGMP leads to dephosphorylation of the myosin light chains, resulting in vascular smooth muscle relaxation

ORGANIC NITRATES

TOLERANCE
- Repeated administration of these drugs results in diminished relaxation of smooth muscle
- Tolerance to the antianginal effect develops rapidly
- It can be overcome by provision of nitric-free interval (10-12 hours)

ORGANIC NITRATES

EFFECTS ON CARDIOVASCULAR SYSTEM
- Reduction of cardiac oxygen consumption secondary to reduced cardiac pre- and after-load
- Redistribution of coronary flow towards ischaemic areas via collaterals
- Relief of coronary spasm

ORGANIC NITRATES

ADVERSE EFFECTS
- HEADACHE
- FACIAL FLUSHING
- POSTURAL HYPOTENSION
- TACHYCARDIA

Organic nitrates

- ON dilate
  - Veins
  - Arteries
  - Arterioles
  - Other smooth muscles

Organic nitrates

- Nitroglycerin
- Erythritol tetranitrate
- Isosorbide dinitrate
- Isosorbide mononitrate
- Pentaerythritol tetranitrate
Nitroglycerin
- Sublingual
- Sustained release formulation
- Ointment
- Transdermal system

Sublingual nitroglycerin
- At the first sign of an attack
- 5 to 10 minutes before an activity which might cause chest pain
- 3 sprays or 3 tablets during 15 minutes!!!
- Call 911!!!

BETA-ADRENOCEPTOR ANTAGONISTS
- Decrease exertionally-induced increases in heart rate
- Decrease systolic blood pressure (if hypertension is present)
- Decrease cardiac contractile activity
- As a result → reduce oxygen demand (blockade of sympathetic cardiac stimuli)

BETA -ADRENOCEPTOR ANTAGONISTS
- reduce the frequency and severity of angina attacks
- increase exercise duration and tolerance (with nitrates)
- can be used in stable and unstable angina, also in myocardial infarction
- they are contraindicated in variant angina (increase coronary spasm)

BETA -ADRENOCEPTOR ANTAGONISTS
- Metoprolol, Acebutolol, Atenolol → reduce heart responses and myocardiac contractile activity without affecting bronchial smooth muscle (cardioselective)

BETA -ADRENOCEPTOR ANTAGONISTS
- UNWANTED EFFECTS
  - Bradycardia
  - Hypotension
  - Block impulse conduction in the heart
  - Headache/dizziness
  - Weakening
  - Spasm of smooth muscle
  - Male sexual disfunction
  - Insomnia
### BETA-ADRENORECEPTOR ANTAGONISTS
- Acebutolol
- Alprenolol
- Atenolol
- Metoprolol
- Oxprenolol
- Pindolol
- Propranolol
- Sotalol

### CALCIUM ANTAGONISTS
- Inhibit the entrance of calcium through calcium L-type channels into cardiac and smooth muscle cells of the coronary and systemic arteries.
- This leads to decreasing in smooth muscle tone and vascular resistance.

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### CALCIUM ANTAGONISTS
- Reduce venous pressure (preload).
- Reduce arteriolar pressure (afterload).
- Reduce myocardial oxygen consumption.

### CALCIUM ANTAGONISTS
- There are three chemical classes:
  - Dihydropyridines
    - Nifedipine, Nicardipine, Felodipine, Amlodipine
  - Phenylalkylamines
    - Verapamil, Bepridil
  - Dibenzazepine
    - Diltiazem

### CALCIUM ANTAGONISTS
- Effects of phenethylalkylamines and dibenzazepines:
  - Cause arterial dilatation, reducing blood pressure (reduced after-load).
  - Dilate also coronary vessels.
  - Impaire atrioventricular conduction and reduce contractility.

### CALCIUM ANTAGONISTS
- Clinical uses:
  - Antidysrhythmic therapy (Verapamil) esp. atrial tachycardia.
  - Antianginal effect (Amlodipine, Diltiazem) – stable angina following exercise or stress, alone or in combination with other antianginal drugs.
  - Antihypertension therapy (Amlodipine).
CALCIUM ANTAGONISTS

Unwanted effects of nifedipine:
- Hypotension
- Dizziness
- Flushing
- Skin rash
- Peripheral edema
- Tachycardia

Unwanted effects of verapamil/diltiazem:
- Bradycardia
- Hypotension
- Congestive heart failure
- Heart block
- Skin rash
- Constipation

Variant angina

- Coronary vasospasm
  - Nitrates
  - Nifedipine
  - Verapamil
  - Diltiazem

Acute Myocardial Infarction

- Syndrome associated with severe irreversible regional myocardial ischemia.
- Treatment:
  - Early palliative treatment of AMI
  - Limitation of death of heart cells
  - Treatment of effects of ischemia
  - Non-pharmacologic interventions in AMI
  - Treatment of syndromes related to AMI

Early palliative treatment

- Morphine
- Oxygen
- Nitroglycerin (sublingually)
- Aspirin

Limitation of death of heart cells

- Thrombolytics – administered as soon as possible
  - Tissue plasminogen activator
  - Streptokinase
  - Heparin
  - Aspirin
- Nitrates – reduce preload and chest pain

Complications of MI

<table>
<thead>
<tr>
<th>Complications type</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>Angina, reinfarction, infarct extension</td>
</tr>
<tr>
<td>Mechanical</td>
<td>Heart failure, cardiogenic shock, mitral valve dysfunction, aneurysms, cardiac rupture</td>
</tr>
<tr>
<td>Arrhythmic</td>
<td>Atrial or ventricular arrhythmias, sinus or atrioventricular node dysfunction</td>
</tr>
<tr>
<td>Embolic</td>
<td>Central nervous system or peripheral embolization</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Pericarditis</td>
</tr>
</tbody>
</table>
### Treatment of effects of ischemia

- **Anti-arrhythmic agents**
  - Lidocaine (life-threatening VF)
  - Procainamide (VT)
  - Atropine (supression of overactivity of Purkinje fibres)
- **Aspirin and beta-receptor antagonists**
  - Improve long-term survival
- **Sympathomimetics (cardiogenic shock)**
  - NE
  - Dopamine
  - Dobutamine

### Mechanisms of action of anti-anginal drugs

- **Reduction of heart rate**
  - Beta-blockers
- **Reduction of preload**
  - Nitrates
- **Reduction of afterload**
  - Calcium antagonists – Vasodilators (Nitrates)
- **Coronary artery vasodilation**
  - Nitrates, Calcium antagonists
- **Reduction of contractility**
  - Beta-blockers, Calcium antagonists

### Non-pharmacologic interventions in AMI

- PTCA
- Stents
- Coronary artery bypass grafts

### Combination therapy

- Nitrates + beta-blockers
- CCB + beta-blockers
- CCB + nitrates
- CCB + beta-blockers + nitrates

### Platelet in IHD

- Platelets, which circulate in the blood, promote clot formation (thrombosis) when a blood vessel is injured. However, when platelets collect on atheromas in an artery’s walls, the resulting clot can narrow or block the artery and result in a heart attack

### Anti-Platelet Drugs in Therapy of IHD

- These drugs prevent platelets from clumping and blood clots from forming.
- They also reduce the risk of a heart attack.
- They are used to treat people who have stable or unstable angina or who have had a heart attack.
Anti-Platelet Drug

- ACETYL SALICYLIC ACID
- Clopidogrel
- TICLOPIDINE
- DIPYRIDAMOLE
- Eptifibatide
- Tirofiban
- ABCIXIMAB

Cholesterol

- **HDL** - High density Lipoproteins
  Since the fat is depleted from the circulation it has been proven that HDL can protect people from heart disease and is therefore considered as a GOOD cholesterol.

- **LDL** - Low Density Lipoproteins
  Increased amount of LDL can accumulate in the inner walls of arteries and clog them up and therefore it is considered as a BAD cholesterol.

**STATINS**

- Lovastatin
- Simvastatin
- Fluvastatin
- Atorvastatin
- Pravastatin
- Cerivastatin
- Rosuvastatin

**STATINS**

- Reduce plasma LDL-cholesterol concentration - it is the main biochemical effect
- Reduce plasma triglyceride level
- Increase plasma HDL-cholesterol concentration
STATINS – other actions
- Improved endothelial function
- Reduced vascular inflammation
- Reduced platelet aggregability
- Increased neovascularisation of ischaemic tissue
- Increased circulating endothelial progenitor cells
- Stabilisation of atherosclerosis plaque
- Antithrombotic actions
- Enhanced fibrinolysis
- Immune suppression

STATINS – clinical uses
- Primary prevention of arterial disease in patients from group of high risk
- Secondary prevention of myocardial infarction and stroke
- Familial hypercholesterolaemia

STATINS – adverse effects
- Gastrointestinal disturbance
- Increased plasma concentration of transaminase
- Myopathia and rhabdomyolysis (in patients suffer from renal insufficiency)

STATINS – contraindications
- Liver failure
- Renal insufficiency
- Myopathy and rhabdomyolysis
- Pregnancy and nursing mothers
- Children and teen-agers

FIBRATES
- Clofibrate
- Fenofibrate
- Gemfibrozil

FIBRATES
- Ligands for the DNA transcription regulator peroxisomal proliferator-activated receptor \(\alpha\) (PPAR\(\alpha\)), which regulates gene transcription (liver!)
**FIBRATES**

- Cause a decrease in plasma triacylglycerol (TG) levels by stimulating lipoprotein lipase activity, which hydrolyzing TG
- Increase HDL-cholesterol
- Modest reduction LDL-cholesterol

**FIBRATES – other actions**

- Reduce plasma fibrinogen
- Improve glucose tolerance
- Inhibit vascular smooth muscle inflammation

**FIBRATES – clinical uses**

- Treatment of hypertriglyceridemia
- Type III hyperlipoproteinemia (TG elevated)

**FIBRATES – adverse effects**

- Gastrointestinal disturbances
- Myositis (renal dysfunction)
- Predispose to gallstones

**FIBRATES – contraindications**

- Sever hepatic dysfunction
- Renal dysfunction
- Gall bladder disease
- Pregnant and lactating women

**BILE ACID BINDING RESINS**

- Colestipol
- Cholestyramine
BILE ACID BINDING RESINS

- Nonabsorbable anion exchange resins
- Sequester bile acids in the intestine
- Decreased absorption of exogenous cholesterol
- Increased metabolism of endogenous cholesterol

BILE ACID BINDING RESINS

- Lower plasma cholesterol
- Increase triglyceride

BILE ACID BINDING RESINS

CLINICAL USES

- Treating some kinds of hyperlipidemias (IIa, IIb)
- In patients with biliary obstruction

BILE ACID BINDING RESINS

UNWANTED EFFECTS

- Gastrointestinal symptoms (abdominal pain, nausea, constipation or diarrhoea)
- Reduced absorption of folic acid and ascorbic acid
- Impaired absorption of fat-soluble vitamins (A,D,E,K)
- Interfere with the intestinal absorption of many drugs (tetracycline, digoxin, aspirin)

BILE ACID BINDING RESINS

ADVERSE EFFECTS

- Cutaneous flushing
- Palpitation
- Gastrointestinal disturbances
- Impaired glucose tolerance
- Hyperuricemia

NIACIN (NICOTINIC ACID)

- Inhibits lipolysis in adipose tissue
- Decreases in liver triacylglycerol synthesis
- Reduces LDL concentration
- Increases HDL level
NIACIN (NICOTINIC ACID)

- Therapeutic uses – hypertriglyceridemia (+ elevated LDL or low HDL)
- Adverse effects – flushing, dyspepsia

Ezetimibe (Ezetrol)

- Inhibits the absorption of cholesterol in the intestine
- Used in combination with statins or fibrates
- ↓ LDL, TG, apoB, total cholesterol
- ↑ HDL

Ezetimibe - indications

- Primary hypercholesterolemia and mixed dyslipidemia
- homozygous familial hypercholesterolemia
- homozygous familial sitosterolemia

Ezetimibe

- Contraindications
  - Hypersensitivity
  - Active liver disease or persistent increases in serum aminotransferase (transaminase) concentrations (with statins)
- Side effects:
  - Back pain, arthralgia, diarrhea, sinusitis, abdominal pain, myalgia, chest pain and dizziness.

Probucol

- Reduces plasma cholesterol concentrations (LDL, HDL)
- Variable effect on serum triglyceride concentrations

Probucol

- Lowers serum cholesterol by increasing the fractional rate of low-density lipoprotein (LDL) catabolism
- May inhibit early stages of cholesterol biosynthesis
- May slightly inhibit dietary cholesterol absorption
- May inhibit the oxidation and tissue deposition of LDL cholesterol
Probucol

- Recommended for use as an adjunct to dietary measures in patients with primary hypercholesterolemia (type IIa hyperlipoproteinemia) and a significant risk of coronary artery disease, who have not responded to diet or other measures alone
- Prevention of restenosis after reperfusion and revascularisation procedures

Probucol

- GI side effects
- Prolongs the QT interval and has been associated with cardiac arrhythmias