Lecture 9: Pharmacological influence of cardio-vascular system disorders

Topics:
1. Cardiac glycosides and drugs for chronic heart failure
2. Antiarrhythmic drugs
3. Lipid-regulating drugs
4. Antianginal and other anti-ischemic drugs
5. Antihypertensive drugs
6. Pharmacological Treatment of Heart Failure

1. Cardiac glycosides and drugs for chronic heart failure

Classification:
1.1. Cardiac glycosides
- short and rapid onset action:
  - Digoxin,
  - rare used: Lanatoside C, Ouabain (Strophanthin G), Methyldigoxin, Acetyldigoxin, Deslanoside
- long and slow onset action: Digitoxin.

1.2. Other positive inotropic agents
- phosphodiesterase inhibitors:
  - bipyridines: Milrinone, Amrinone (Inamrinone),
  - imidazoles: Enoximone
- calcium-sensitising agents:
  - benzimidazoles: Levosimendan, Pimobendan,
- stimulants of beta-adrenergic receptors:
  - beta1-adrenergic agonists: Dobutamine, Prenalterol
  - beta1,beta2-adrenergic agonists: Isoproterenol (Isoprenaline)
  - dopamine and alpha,beta-adrenergic agonists: Dopamine
- glucagon (pancreatic hormone)
- non-selective inhibitors of phosphodiesterase: Theophylline, Caffeine.

1.1. Cardiac glycosides

Sources
The major cardiac glycosides were obtained from the foxglove, Digitalis purpurea, Scrofulariaceae for digitoxin (Digitalis formerly discovered by Nativelle). The digoxin, acetyldigoxin, the lanatoside C and deslanoside were obtained from woolly foxglove, Digitalis lanata, Scrofulariaceae. Strophanthin (ouabain) was obtained from various Strophanthus, Apocynaceae.

Some toads glands of the skin produce bufadienolides, similar to cardenolides. Based on highly sensitive immunochemical techniques it was demonstrated that ouabain is synthesized by the adrenal glands and perhaps by the brain in humans and other mammals. Ouabain is released as an endocrine and paracrine agent in certain circumstances, such as high salt intake and heart failure. In congestive heart failure, plasma concentrations of ouabain are positively correlated with the severity of the deficiency. There are chemical and physiological reasons to question whether ouabain is indeed synthesized in patients with heart failure, progression of the disease continues to the point of requiring treatment with exogenous glycosides are an insufficient supply of endogenous and the development of tolerance or another alternate? Meanwhile, it seems surprising that one can have more than one endogenous ligand for the receptor. This case may demonstrate convergent evolution in plants, frogs and mammals.

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Structure of cardiac glycosides:
- a steroid nucleus containing an unsaturated lactone ring at the C17 position, and one or more glycosidic (sugar) residues at C3:
  - unsaturated lactone ring is essential for pharmacodynamic properties
  - steroid nucleus explains endocrine effects
  - glycosidic (sugar) residues are essential for pharmacokinetic properties (absorption, half-life and metabolism) and for specificity of action, are bound by steroid nucleus through a very reactive hydroxil group which is necessary for the activity.

Mechanism of action of cardiac glycosides
- inhibition of Na+/K+-ATPase (membrane-bound transporter called sodium pump) from the membrane of myocardial cells and other excitable cells (neurons, smooth muscle);
- activation of voltage-dependent calcium channels;
- increasing the release of calcium from the sarcoplasmic reticulum.

The pharmacodynamic effects of cardiac glycosides
A. The cardiac effects
- Mechanical effects: the positive inotropic effects; tonotropes positive effects.
- The electrical effects:
  1. direct electrical effects:
     - to the top: a short extension of the action potential, followed by reduction thereof, especially during the plateau reduction of the action potential is determined, probably by increasing the potassium conductance (which is produced by the increase in intracellular calcium) → an action similar to that produced by stimulation of cardiac M2 receptors (negative chronotropic effect and the negative dromotropic effect);
  2. the indirect electrical effects:
     - therapeutic doses: parasympathomimetic effects - the negative chronotropic effect (slower pace), the negative dromotropic effect (slowed conduction), but the effect bathmotropic positive;
     - toxic doses: the sympathomimetic effects - the atrioventricular extrasystoles, atrial and ventricular fibrillation.
B. Extracardiac effects:
- weak diuretic effects;
- modulatory effect on blood pressure.

Pharmacokinetics
- absorption after oral administration: Lanatoside C - very low; Digoxin - 50%; Digitoxin - 90%; strophanthin G is only administered intravenously; concomitant administration of Digoxin with antibacterial agents (e.g., erythromycin) → toxic effects by increasing the bioavailability; administration concomitant cholestyramine or antacids determines the decrease of absorption of Digoxin;

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o distribution: liver, kidney, skeletal muscle, only 1% accumulates at heart;
o plasma protein binding: strophanthin G is not connected; Lanatoside C - the small proportion; Digoxin - 50%; Digitoxin - the high proportion;
o hepatic metabolism: Digoxin - 10%; Digitoxin - 90%;
o digitalis to slow-acting and long-term, after oral administration, enterohepatic circulation;
o elimination: in the kidney → Digoxin - 90%; Digitoxin - 10%;
o digitalis exhibit the phenomenon of accumulation: after the last dose, the effect persists → very little, strophanthin G and C Lanatoside; 6 to 7 days, Digoxin, 14 days for Digitoxin.

Indications:
- heart failure, especially associated with atrial fibrillation or with tachycardia;
- chronic atrial fibrillation, atrial flutter.

Adverse reactions:
- **cardiac effects** (are based on an ion imbalance: hypokalemia, hypomagnesemia, hypercalcemia):
  - in therapeutic doses: the early late depolarization, the bigeminy, sinus bradycardia, atrioventricular extrasystoles, tachycardias (atrial or ventricular) conduction disorders (atrioventricular block, the lengthening of the PR on ECG or block type II or III);
  - in toxic doses → atrial tachycardia with block, ventricular tachycardia, ventricular fibrillation;
- **digestive effects**: anorexia, nausea, vomiting, abdominal pain, diarrhea due to prokinetic effect (by direct action, but also by stimulation of the area postrema of the fourth ventricle - "trigger area");
- **renal effects**: oliguria, anuria;
- **endocrine effects**: gynecomastia, amenorrhea-galactorrhea syndrome;
- **adverse effects in the CNS** (more rarely):
  - sedation, headache, dizziness, disorientation,
  - visual disturbances with a yellow hallow around objects, bright wavy lines, aberrations of color perception, hallucinations,
  - agitation and convulsions are occasionally reported.

Contraindications
- bradycardia, ventricular tachycardia, atrioventricular block;
- hepatic or renal impairment;
- myocarditis;
- pericarditis;
- mitral stenosis;
- association with drugs:
  - Erythromycin (by destroying the intestinal flora, erythromycin increase digoxin bioavailability by reducing the catabolism normally performed by the intestinal flora);
  - drugs that reduce absorption: cholestyramine, antacids;
  - drugs that determine negative inotropic effects: β-adrenergic blockers and calcium channel blockers;
  - drugs that determine hyperkliemia: ACE inhibitors, potassium-sparing diuretics;
  - drugs that determine hypokalemia: thiazide diuretics (potentiate digitalis effects);
  - drugs that decrease renal elimination: Amiodarone, Propafenone;
  - compounds with calcium (hypercalcemia potentiate digitalis effects).

If overdose of digoxin, the antidote is represented by the specific anti-digoxin (Fab fragments).
1.2. Other positive inotropic agents

1.2.1. Phosphodiesterase inhibitors: Milrinone, Inamrinone (previous name Amrinone), Enoximone

Chemical structure:
- bipyridines: Milrinone, Inamrinone (previous name Amrinone),
- imidazoles: Enoximone

Mechanism of action:
- inhibits phosphodiesterase 3 isoforms (PDE3) in cardiac and vascular muscle
- increased calcium influx during the action potential
- inhibition of ATP-ase Na⁺ / K⁺.

Pharmacodynamic effects:
- positive inotropic activity by direct stimulation of myocardial contractility, with minimal chronotropic activity;
- vasodilatory activity arterial and venous dilation with a consequent fall in systemic and pulmonary vascular resistances, and left and right heart filling pressures and an increase in renal blood flow and glomerular filtration.

Pharmacokinetics: intravenous administration. Milrinone has a shorter half-life than Inamrinone and is less likely to cause thrombocytopenia. Metabolism: hepatic, elimination: renal (40% unchanged).

Indication: acute congestive heart failure (short-term treatment)

Contraindications: severe valvular heart disease,

Adverse effects: atrial and ventricular arrhythmias, hypotension, thrombocytopenia, reversible hepatotoxicity, nephrotoxicity, reducing the sense of taste and olfactory sensitivity

Precautions: dosage adjustments may be necessary in patients with hepatic impairment or with severe renal impairment.

Milrinone is the agent of choice among currently available PDE inhibitors for short-term, parenteral inotropic support.

1.2.2. Calcium-sensitising agents: Levosimendan, Pimobendan

Levosimendan and Pimobendan are novel calcium-sensitising agents (= agents that produce inotropic effect by stabilizing the calcium–troponin C complex and facilitate myocardial cross-bridging).

Chemical structure: benzimidazoles.

Mechanism of action:
- sensitise myofibrils to Ca2+, binds to troponin-C in cardiomyocytes, reduce the Ca2+ sensitivity of contractile proteins in vascular smooth muscle;
- inhibition of PDE3 (low for Levosimendan compared to Pimobendan);
- for Levosimendan also opening of ATP-sensitive K+ channels.

Pharmacodynamic effects:
- inotropic positive effect and enhances cardiac output;
- vasodilation of peripheral arteries and venules, reduces systemic vascular resistance and lowers pulmonary capillary wedge pressure;
- anti-inflammatory effect.

These drug don’t influence myocardial oxygen consumption.

Indication: acute congestive heart failure

Adverse effects: hypotension, dose-related increase in heart rate, headache.
2. Antiarrhythmic drugs

Vaughan-Williams Classification of Antiarrhythmic Drugs:

2.1. Class 1 (Sodium Channel-Blocking Drugs)
2.1.1. Subgroup 1A: Quinidine, Procainamide, Disopyramide, Ajmaline; Aprindine
2.1.2. Subgroup 1B: Lidocaine; Phenytoin; Mexyletin; Tocainide
2.1.3. Subgroup 1C: Propafenone; Flecainide; Encaainide; Lorcanide; Indecainide; Moricizine; Cibenzoline

2.2. Class 2 (Beta-Adrenoceptor–Blocking Drugs): Propranolol; Metoprolol; Nadolol; Atenolol; Esmolol; Acebutolol; Sotalol (cu mecanism adițional de clasă a III-a);

2.3. Class 3 (Drugs That Prolong Effective Refractory Period by Prolonging Action Potential): Amiodarone; Bretylium; Sotalol, Ibutilide; Dofetilide; Clofilium; Pranolium;

2.4. Class 4 (Calcium Channel–Blocking Drugs): Verapamil; Diltiazem;

2.5. Class 5 (other antiarrhythmic agents): Adenozine; Magnezium sulphate; Cardiac glycosides.

For antiarrhythmic drugs: a drug concentration that is therapeutic (antiarrhythmic) under the initial circumstances of treatment may become "proarrhythmic" (arrhythmogenic) during fast heart rates (more development of block), acidosis (slower recovery from block for most drugs), hyperkalemia, or ischemia.

CLASS 1 (SODIUM CHANNEL-BLOCKING DRUGS)
Subgroup 1A: Quinidine, Procainamide, Disopyramide, Ajmaline; Aprindine
Antiarrhythmics subgroup IA are called "quinidine" group; the lengthening of the QT interval.

Mechanism of action:
- block voltage - dependent sodium channel (they combine with fast sodium channels open and in their inactive state and thereby inhibit recovery after repolarization in a time- and voltage-dependent manner which is associated with subsequent dissociation of the drug from the sodium channels) are effective to inhibit ectopic arrhythmias.
- Quinidine also blocks potassium channels; it is a weak alpha blocker and has anticholinergic effects.
- Procainamide also blocks potassium channels; it is a weak alpha blocker.

Electrophysiological effects:
- moderate phase 0 depression
- prolong the action potential duration by blocking outward potassium current
- prolong refractoriness
- slows the upstroke of the action potential, slows atrio-ventricular and intraventricular conduction and prolongs the QRS duration of the ECG (increase QT interval)
- increase of ectopic automaticity (tertiary centers);
- depress myocardial contractility negative inotropic effect.

Indications:
- atrial tachiarhythrias (=supraventricular arrhythmias): atrial fibrillation, atrial flutter
- ventricular arrhythmias: ventricular tachycardia, ventricular ectopic activity
- Quinidine has also antimalarial effects, alpha-adreneric blocking effect and atropine-like effect.
Adverse effects:
- risk of arrhythmias (due to increase of ectopic automaticity);
- Quinidine iv administration determines hypotension and sinus tachycardia (due to alpha-adrenergic blocking effects and atropine-like effects);
- Quinidine cardiac toxicity:
  - torsades de pointes due to the prolongation of QT interval; this may evolve to ventricular fibrillation;
  - atrioventricular block, syncope, asystole;
  - depression of myocardial contractility (can aggravate heart failure);
- Quinidine digestive symptoms (in 1/3 to 1/2 of patients): diarrhea (may induce hypokaliemia which potentiate torsades de points), nausea, and vomiting;
- Quinidine intoxication = cinconism (blurred vision, dizziness, headache, tinnitus, psychosis);
- Procainamide: antinuclear antibodies (to 1/2 of patients), systemic eritematosus lupus (to 1/5 of patients).

Subgroup 1b: Lidocaine (Lignocaine); Phenytoin; Mexiletine; Tocainide
Antiarrhythmics subgroup IB are "lidocaine" group; shortening of the QT interval.
Mechanism of action: voltage - dependent sodium channel blockade (they act on sodium inactivated channels) → suppression of ectopic automatism
Electrophysiological effects:
- shorten the action potential duration
- negligible effect on repolarization, on QT interval, on atrio-ventricular conduction (but in ischemic myocardium reduce conduction of impulses) and on myocardial contractility
- minimal effect on phase 0 upstroke
- shorten refractoriness
- reduction of ectopic automaticity (tertiary centers).
Indications:
- ventricular arrhythmias: ventricular tachycardia, ventricular ectopic activity
  - Lidocaine i.v. is drug of choice for ventricular arrhythmias.
  - Phenytoin i.v. is drug of choice for tachyarrhythmias due to digoxin intoxication.
  - Mexiletine is a Lidocaine-like drug with oral administration.
Adverse effects of Lidocaine:
- fairly toxicity on CNS system: drowsiness, confusion, convulsions – in high doses;
- hypotension.
Lidocaine is one of the least cardiotoxic antiarrhythmics.

Subgroup 1c: Encainide; Flecaïnide; Lorcaïnide; Propafenone; Indencaïnide; Moricizine; Cibenzoline
Antiarrhythmics subgroup IC doesn’t change the QT interval.
Mechanism of action: voltage - dependent sodium channel blockade (on open state)
  - Flecaïnide, Propafenone → also blocks potassium channels.
Electrophysiological effects:
- no effects on the action potential duration, on QT interval, on repolarization
- depression of phase 0 of the action potential
- slows atrio-ventricular conduction
- prolong refractoriness
• depress myocardial contractility → negative inotropic effect
• reduction of ectopic automaticity (tertiary centers)

**Indications:**
• ventricular arrhythmias: ventricular tachycardia, ventricular fibrillation
• atrial arrhythmias (= supraventricular arrhythmias): atrial fibrillation, atrial flutter refractory to other treatments.

**Adverse effects:**
• proarrhythmic effects risk: atrioventricular block, fascicular blocks;
• left ventricular failure.

2.2. **CLASS 2 (BETA-ADRENOCEPTOR-BLOCKING DRUGS):** Propranolol; Metoprolol; Nadolol; Atenolol; Esmolol; Acebutolol; Sotalol (with additional mechanism of class 3);

**Electrophysiological effects:**
• shorten the action potential duration;
• slows atrio-ventricular conduction
• no effects on QT interval
• depress myocardial contractility → negative inotropic effect
• reduction of the automatism of the sinus node
• prolong refractoriness
• reduction of ectopic automaticity (tertiary centers).

**Indications:**
• atrial tachyarrhythmias: sinus tachycardia, prevention of paroxysmal supraventricular tachycardia;
• ventricular arrhythmias: premature ventricular contractions, prevention of ventricular fibrillation.

2.3. **CLASS 3 (DRUGS THAT SLOW THE OUTWARD POTASSIUM CURRENT):** Amiodarone; Dronedarone; Bretylium; Sotalol, Ibutilide; Dofetilide; Clofilium; Pranolium; Vernakalant.

**Mechanism of action:** potassium channel blockade and sodium channel fast voltage-dependent (inactive during repolarization).
• Amiodarone: also block beta receptors, has calcium channel blocking actions and has antithyroid action.
  ○ Amiodarone has properties of all four classes because is a K+, Na+, Ca2+ channel blocker and noncompetitive α and β-blocker.

**Electrophysiological effects:**
• prolong the action potential duration
• slows sino-atrial automatism and atrio-ventricular conduction; no effect on intraventricular conduction
• prolongs the QRS duration on the ECG (increase QT interval)
• no effect on myocardial contractility
• reduction of ectopic automaticity (tertiary centers).
• prolong refractoriness
• prolong repolarization

**Pharmacokinetics:**
• can be administered iv or oral (food enhance absorption),

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onset of action: 2 days – 2 weeks even with loading.
- it is stored in many tissues (cumulation phenomenon) → explain the adverse effects.
- leaves body very slow; very long half-life (25-60 days).

**Indications:**
- Amiodarone → ventricular and atrial arrhythmias refractory to other treatments (e.g., paroxysmal supraventricular tachycardia, paroxysmal tachycardia ventricular, atrial fibrillation, atrial flutter)
  - Amiodarone is the most effective drug for maintenance of sinus rhythm in patients with atrial fibrillation and for decreasing risk of ventricular tachyarrrhythmias.
- Bretylium → used iv in life-threatening ventricular tachycardia and fibrillation;
- Ibutilide → used iv for acute conversion of atrial flutter/fibrillation to sinus rhythm.

**Advantages of Amiodarone:**
- Low incidence of pro-arrhythmogenic effects;
- Has little effect on contractility and is one of the best drugs to use in heart failure;
- It improves mortality in nonischemic cardiomyopathy patients at risk of sudden death, possible advantageous after myocardial infarction.

**Adverse effects:**
- Amiodarone:
  - In acute administration:
    - atrio-ventricular block;
    - hypotension;
  - In chronic administration:
    - Dose-independent adverse effects:
      - interstitial pulmonary fibrosis (can be rapidly progressive and fatal);
      - thyroid dysfunction: hypo or hyper (because Amiodarone contains iodine and thus may interfere with iodine uptake),
      - toxicity in pregnancy and breastfeeding
    - Dose-dependent adverse effects:
      - corneal microdeposits and optic neuropathy (optic neuritis may progress to blindness),
      - photosensitivity (skin deposits result in a photodermatitis and a gray-blue skin discoloration in sun-exposed areas),
      - hepatotoxicity (transaminases increased at doses higher than 600mg/day),
      - sinus bradicardia, proarrythmogenic effect;
      - CNS (tremor, ataxia, dizziness).
  - raise levels of Digoxin, Warfarin, Diltiazem, Cyclosporin, Quinidine, Procainamide, Phenytoin.
- hypotension → Bretylium;
- adverse effects of β - blockers → Sotalol.

2.4. **CLASS 4 (CALCULUM CHANNEL–BLOCKING DRUGS):** Verapamil; Diltiazem; 

**Mechanism of action:** calcium channel type L blockade

**Electrophysiological effects:**
- shorten the action potential duration;
- no effects on QT interval
• reduction of the automatism of the sinus node
• slows atrio-ventricular conduction; no effect on intraventricular conduction
• depress myocardial contractility → negative inotropic effect
• prolong refractoriness
• no influence on ectopic automaticity (tertiary centers).

**Indications:**
• atrial arrhythmias (= supraventricular arrhythmias): atrial fibrillation, atrial flutter
  o Verapamil is drug of choice for paroxysmal supraventricular tachycardia

2.5. CLASS 5 (OTHER ANTIARRHYTHMIC AGENTS): Adenozine; Magnezium sulphate; Cardiac glycosides

**Adenozine**
• It is a nucleoside that occurs naturally in the body (half life is 10-15 seconds).
  • **Mechanism of action:** agonist on purinergic receptors
    o from heart: negative chronotrope and dromotrope effects;
    o from vessels: vasodilation.
  • **Indications:** drug of choice for paroxysmal supraventricular arrhythmias (conversion to sinus rhythm).
  • **Adverse effects:** dyspneea, chest pain, headache, flushing.

**Magnezium sulphate**
• **Indications:** drug of choice for torsades de points and digoxin-induced arrhythmias.
• **Adverse effects:** bradycardia, headache, flushing.

3. Lipid-regulating drugs

**Classification**

3.1. Cholesterol absorption inhibitors:
3.1.1. Bile acid sequestrants: Cholestyramine and colestipol;
3.1.2. Inhibitors of intestinal absorption of cholesterol and plant sterols: Ezetimibe.

3.2. Inhibitors of cholesterol biosynthesis:
3.2.1. HMG-CoA reductase inhibitors (statins): Lovastatin, Simvastatin, Fluvastatin, Pravastatin, Atorvastatin, Rosuvastatin, Losuvasstatin, Cerivastatin, Mevastatin, Pitavastatin;
3.2.2. fibrates: Clofibrate, Fenofibrate, Bezafibrate, Gemfibrozil, Ciprofibrate, Tocofibrate, Pirifibrate, Simfibrate;
3.2.3. niacin group: niacin (nicotinic acid), Nicotinamide, Xantinol nicotinate, Acipimox.
3. Other substances: Probucol; Omega-3-acid ethyl esters; Neomicine; estrogens; Dextrotiroxine.

1. Cholesterol absorption inhibitors
1.1. Bile acid sequestrants: Cholestyramine and colestipol
Cholestyramine and colestipol are anion-exchange resin, capable of binding to a number of drugs in the GI tract and may delay or reduce their absorption.
  • **Mechanism of action:** inhibits cholesterol absorption because releases chloride ions and adsorbs bile acids in the intestine → forming a nonabsorbable complex that is excreted along
with unchanged resin in the feces. Cholestyramine must be taken in 2 or 3 times daily with meals, setting resins bile salts taken between meals have no effect.

**Pharmacodynamic effects:**
- partial removal of bile acids from the enterohepatic circulation;
- decrease in plasma total cholesterol and low-density lipoprotein (LDL) concentrations;
- moderate increases in plasma triglyceride concentrations, due to moderate increases in very low-density lipoprotein (VLDL) concentrations
- modest increase (less than 10%) in the high-density lipoprotein (HDL)-cholesterol fraction in patients with type II hyperlipoproteinemia

**Pharmacokinetics:** are not absorbed from gastro-intestinal tract, are not metabolised by digestive enzymes.

**Indications:**
- primary hypercholesterolemia as adjunct to dietary therapy to decrease elevated serum total and LDL-cholesterol concentrations (hyperlipidemia type IIa and IIb);
- pruritus associated with partial cholestasis;
- cardiac glycoside toxicity as adjunct in the treatment (to reduce initial absorption of the glycoside).

**Adverse effects:**
- gastro-intestinal effects: constipation (most frequent), abdominal discomfort and/or pain, abdominal distention, bloating, flatulence, nausea, vomiting, anorexia, heartburn, biliary colic, steatorrhea, indigestion
- dose-related increases in serum triglyceride concentrations.

**Contraindications:**
- association with cardiac glycosides, thiazide diuretics, Warfarin, Tetracycline, Vancomycin, Tiroxine, fer salts, Folic acid, Phenylbutasone, Acethylsalicylic acid.
- pregnancy.

1.2. Ezetimibe

**Pharmacodynamic effects:** cholesterol and plant sterols absorption inhibitor

This results in decreased delivery of intestinal cholesterol to the liver, which causes a reduction in hepatic cholesterol stores, a compensatory increase in hepatic uptake of cholesterol from systemic circulation, and consequently, an increase in systemic clearance of cholesterol. Ezetimibe does not appear to inhibit the absorption of triglycerides, fatty acids, bile acids, progesterone, ethyl estradiol.

**Pharmacokinetics:** More than 90 % of Ezetimibe is absorbed systemically. Ezetimibe is rapidly and extensively metabolized in the small intestine and liver to a pharmacologically active metabolite. Ezetimibe is excreted mainly in feces, less in urine.

**Indications:** hypercholesterolemia in association with statins

Ezetimibe is adjunct to dietary therapy in the treatment of primary hypercholesterolemia and mixed dyslipidemia, homozygous familial hypercholesterolemia, homozygous familial sitosterolemia.

Ezetimibe/Simvastatin combination therapy is useful for the management of primary hypercholesterolemia or mixed dyslipidemia in adults.

**Adverse effects:**
- elevations in serum aminotransferase (transaminase) concentrations
- elevations of serum creatine kinase
- diarrhea, abdominal pain, fatigue.

**Contraindications:** active liver disease, pregnant or nursing women.
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2.1. Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins):

Lovastatin, Simvastatin, Fluvastatin, Pravastatin, Atorvastatin, Rosuvastatin, Losartan, Cerivastatin, Mevastatin, Pitavastatin.

**Mechanism of action:** Inhibit HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonic acid, an early precursor of cholesterol.

**Pharmacodynamic effects:**
- antilipemic action → decrease elevated cholesterol concentrations
  - reduce serum concentrations of low-density lipoprotein (LDL)-cholesterol.
  - reduce serum concentrations of very low-density lipoprotein (VLDL)-cholesterol.
  - reduce serum concentrations of apolipoprotein B (apo B).
  - moderate decrease in serum concentrations of triglycerides
  - slight increase in HDL-cholesterol concentrations
- antiatherogenic effects (slow the progression of and/or induce regression of atherosclerotic lesions)
- anti-inflammatory activity

**Pharmacokinetics:**
- rapidly absorbed following oral administration
- food reduce the systemic bioavailability of lovastatin, fluvastatin, pravastatin, atorvastatin
- evening administration of atorvastatin and pravastatin was associated with a decrease in peak plasma concentrations and areas under the plasma-concentration time curve
- undergo extensive first-pass metabolism in the liver
- metabolized: principally in the liver (lovastatin, simvastatin, atorvastatin and rosuvastatin have active metabolites, while the principal metabolites of fluvastatin and pravastatin are pharmacologically inactive); Lovastatin and simvastatin are inactive lactone prodrugs.
- half-lives: long for atorvastatin and rosuvastatin (14 and 19 hours, respectively), the other statins have relatively short half-lives (between 0.5-3 hours)
- elimination: in urine and feces.

**Indications:**
- dyslipidemias: primary hypercholesterolemia and mixed dyslipidemia, homozygous familial hypercholesterolemia, primary dysbetalipoproteinemia, and/or hypertriglyceridemia
- coronary heart disease for the prevention of cardiovascular events

**Adverse effects:**
- gastro-intestinal tract effects: diarrhea, abdominal pain, flatulence, anorexia, nausea
- hepatotoxicity (dose dependent increases in serum aminotransferase concentrations);
- myopathy and/or rhabdomyolysis - after higher dosages of statins or after concomitant use of statins and macrolide antibiotics, Cyclosporine, niacin, fibric acid derivatives, certain antifungal azoles (i.e., itraconazole, ketoconazole), alcohol
- skin rash, pruritus;
- CNS effects: headache, asthenia, fatigue, dizziness

**Contraindications:**
- active liver disease
- pregnant or lactating women, women of childbearing age
- children

2.2. Fibrates (fibric acid derivatives): Clofibrate, Fenofibrate, Bezaftinate, Gemfibrozil, Ciprofibrate, Tocofibrate, Pirifibrate, Simfibrate.

**Mechanism of action:**
- stimulation of activity of lipoprotein-lipase;
- inhibition of hepatic synthesis of VLDL.
Pharmacodynamic effects:
- antilipemic effects → decrease elevated triglyceride and cholesterol concentrations
  - decreases serum concentrations of:
    - total cholesterol,
    - low-density lipoprotein (LDL)-cholesterol,
    - apolipoprotein B (apo B),
    - very low-density lipoprotein (VLDL)-cholesterol,
    - triglycerides,
  - increases serum concentrations of:
    - high-density lipoprotein (HDL)-cholesterol,
    - apolipoprotein A-I (apo A-I),
    - apolipoprotein A-II (apo A-II).
- antiatherogenic effects
- decreases platelet adhesiveness.
Fenofibrate has been shown to reduce serum uric acid concentrations.
Pharmacokinetics:
- rapidly and completely absorbed from the GI tract
- high percentage is protein bound (mainly albumin)
- metabolized: in the liver
- excreted: mainly in urine.
Indications:
- primary hypercholesterolemia and mixed dyslipidemia
- hypertriglyceridemia
- coronary heart disease for the prevention of cardiovascular events
Adverse effects:
- gastro-intestinal tract effects: epigastric pain or dyspepsia
- hepatotoxicity (increases in serum aminotransferase concentrations)
- slight decreases in hemoglobin, hematocrit and in leukocyte count
- cholelithiasis (due to increase cholesterol excretion in bile)
- myositis, myopathy, and/or rhabdomyolysis
Contraindications:
- hepatic impairment, including primary biliary cirrhosis
- severe renal impairment;
- preexisting gallbladder disease
- pregnant or lactating women,
- children
- alcohol.

2.3. Niacin group: niacin (nicotinic acid), Nicotinamide, Xantinol nicotinate, Acipimox.
Niacin and niacinamide are water-soluble, B complex vitamins.
Mechanism of action: partial inhibition of free fatty acid release from adipose tissue, a decreased delivery of free fatty acids to the liver, and a decrease in triglyceride synthesis and VLDL-triglyceride transport.
Pharmacodynamic effects:
- antilipemic action → reductions in cholesterol and triglyceride concentrations
  - reduce serum concentrations of low-density lipoprotein (LDL)-cholesterol and and very-low-density lipoprotein (VLDL)-cholesterol,
  - reduce in serum concentrations of triglycerides
  - increase in HDL-cholesterol concentrations
- antiatherogenic effects
- cutaneous vasodilation
- activates the fibrinolytic system

**Indications:**
- dyslipidemias: hypercholesterolemia and/or hypertriglyceridemia, type V hyperlipoproteinemia
- coronary heart disease for the prevention of cardiovascular events
- pellagra

Niacin in combination with:
- a bile acid sequestrant, is used as an adjunct to dietary therapy to decrease elevated serum total and LDL-cholesterol concentrations,
- lovastatin is used in the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia
- an HMG-CoA reductase inhibitor is considered drug of choice for hypercholesterolemia in adults with increased LDL-cholesterol.

**Adverse effects:**
- gastro-intestinal tract effects: diarrhea, nausea, vomiting, abdominal pain, dyspepsia, anorexia
- flushing, pruritus, headache
- hepatotoxicity (dose dependent increases in serum aminotransferase concentrations)
- elevation in blood glucose concentrations
- elevation in blood uric acid concentrations

**Contraindications:**
- active liver disease
- pregnant or lactating women,
- gout
- active peptic ulcer disease
- arterial bleeding

**Acipimox** has lower frequency of adverse effects, but it is less efficient as antilipemic drug.

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### 3. Other antilipemic drugs

#### 3.1. Probucol

Probucol is used to lower levels of cholesterol from blood.

**Pharmacodynamic effects:**
- antilipemic action → reductions in cholesterol concentrations
  - reduce serum concentrations of low-density lipoprotein (LDL)-cholesterol and and high-density lipoprotein (HDL)-cholesterol,
  - does not influence serum concentrations of triglycerides
- antioxidant effects (reduce oxidation of fatty acids)

**Pharmacokinetics:** Probucol remains in the body few months after stopping the treatment

**Indications:** pure hypercholesterolemia

**Adverse effects:**
- gastro-intestinal tract effects: nausea, abdominal pain
- allergic reactions
- QT prolongation with risk of arrhythmias

**Contraindications:**
- pregnant or lactating women,
- children.
3.2. **Omega-3-acid ethyl esters**

Omega-3 fatty acids (n-3 fatty acids) are long-chain, polyunsaturated fatty acids (PUFAs), that are obtained mainly from marine sources such as fatty fish.

**Mechanism of action:**
- inhibit diacylglycerol O-acyltransferase
- increase peroxisomal b-oxidation

**Pharmacodynamic effects:**
- antilipemic action  reductions in triglyceride concentrations
  - reduce in serum concentrations of triglycerides
  - reduce serum concentrations of very-low-density lipoprotein (VLDL)-cholesterol.

**Indications:**
- hypertriglyceridemia
- coronary heart disease for the prevention of cardiovascular events

**Adverse effects:**
- hepatotoxicity (increases in serum aminotransferase concentrations)
- increases in LDL-cholesterol concentrations
- prolongation of bleeding time

3.3. **Neomicine** reduces serum concentrations of LDL-cholesterol.

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4. **Antianginal and other anti-ischemic drugs**

4.1. **Anginal attacks:** Nitroglycerin (sublingual), Amyl nitrite (inhalatory)

4.2. **Maintenance treatment:**

- **Basic treatment**
  - Nitrates: Nitroglycerine, Isosorbide mononitrate (ISMN), Isosorbide dinitrate (ISDN), Penta erythroid tetrarnitrate (PETN)
  - compounds with similar action to nitrates: Nicorandil, Molsidomin;
  - β-adrenergic blockers;
  - α,β-adrenergic blockers: Labetalol
  - Ca²⁺-channel blockers: Verapamil; Diltiazem; Nifedipine; Amlodipine; Felodipine; Isradipine, Nicardipine, Nisoldipine;
  - metabolic modulators (partial inhibitors of the fatty acid oxidation pathway in myocardium or pFOX inhibitors): Trimetazidine, Ranolazine,
  - selective I₅ sodium channel blockers: Ivabradine,

- **Adjunct treatment**
  - antiplatelet drugs: Acetylsalicilic acid (75-325 mg/day); Clopidogrel, Ticlopidine; Abciximab, Eptifibatide; Dipiridamol;
  - lipid-lowering drugs;
  - ACE-inhibitor drugs;
  - other coronarodilatators:
    - Carbocromen; Methylcromone;
    - Amiodarone.
Trimetazidine and Ranolazine
Are metabolic modulators.

Mechanisms of action:
- shift myocardial metabolism from free fatty acid oxidation to glucose metabolism, resulting in reduced myocardial O2 consumption.
- block non-selective voltage-dependent sodium channel;
- reduce the production of free radicals;
- reduce the level of the Cu-Zn superoxide dismutase.

Pharmacodynamic effects:
- reduction of fatty acid oxidation;
- increase in the oxidation of glucose;
- reduced myocardial O2 consumption.

Indications:
- prophylaxis of angina pectoris;
- the symptomatic treatment of vertigo, Meniere’s syndrome;
- corio-retinal vascular disease.

Adverse effects (rarely, <1%): epigastric pain, nausea, pruritus, headache.

Ivabradine

Mechanisms of action:
- selective and specific inhibitor of the cardiac pacemaker If current of sodium channel in the sino-atrial node (it inhibits the If current in a dose-dependant manner).

Pharmacodynamic effects:
- decrease heart rate
- decrease myocardial oxygen demand at rest and during exercise.

Indications:
- symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who have a contra-indication or intolerance to β-blockers.

5. Antihypertensive drugs

5.1. Drugs for maintenance treatment of hypertension
- diuretics
  - thiazide diuretics (sulfonamide diuretics):
    - thiazides: Hydrochlorothiazide, Chlorothiazide, Methylcloethiazide, Polythiazide, Hydroflumethiazide, Bendroflumethiazide, Cyclopentiazide, Benzhthiazide
    - analogues of thiazides: Indapamide, Chlorthalidone, Quinethazone, Metolazone, Clopamide, Xipamide
  - loop diuretics:
    - sulfonamide loop diuretics: Furosemide and its analogues (Bumetanide, Piretaniade), Torsemide
  - K+ sparing diuretics:
    - physiologically antagonists (direct acting): Amiloride, Triamterene
    - aldosterone antagonists (mineralocorticoid receptor antagonists):

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- nonselective on steroidal hormone receptors: Spironolactone, Prorenone
- selective on aldosterone receptors: Eplerenone
- carbonic anhydrase inhibitors: Acetazolamide

- calcium channels blockers
  - Action on Calcium channels from blood vessels and heart: Nifedipine, Amlodipine, Nitrendipine, Nicardipine; Verapamil; Diltiazem
  - Specific action on Calcium channels from blood vessels: Felodipine, Isradipine, Nisoldipine, Lacidipine, Lercanidipine, Nimodipine

- Angiotensin and renin-angiotensin-aldosteron system inhibition
  - angiotensin receptors blockers (= ARB, selective antagonists on angiotensin AT1 receptors from vessels): Valsartan, Losartan, Candesartan, Telmisartan, Irbesartan, Eprosartan.
  - angiotensin converting enzyme inhibitors (ACEI): Captopril; Enalapril, Ramipril, Quinapril, Perindopril, Lisinopril, Benazepril; Fosinopril; Moexipril, Spirapril, Trandolapril, Cilazapril, Alacepril, Altiopril, Fentiapril, Pivalopril, Zofenopril, Delapril, Imidapril.

- Substances blocking sympathetic system activity
  - Antagonists on beta receptors

<table>
<thead>
<tr>
<th>WITHOUT sympathetic intrinsic activity (SIA)</th>
<th>with SIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>semiselective block β1, β2 – adrenergic receptors</td>
<td>Propranolol, Timolol, Sotalol, Nadolol, Bupranolol</td>
</tr>
<tr>
<td>selective β1 – adrenergic receptors blockers</td>
<td>Metoprolol, Atenolol, Bisoprolol, Esmolol, Betaxolol, Nebivolol</td>
</tr>
</tbody>
</table>

- Antagonists on alpha receptors: Phenoxybenzamine, Prazosin, Terazosin, Doxazosin, Indoramin
- block α1 presynaptic receptors and stimulate α2 postsynaptic adrenergic receptors: Urapidil
- centrally acting sympatholytic agents
  - Acting mainly on CNS:
    - Selective agonists on I1 imidazoline receptors: Moxonidine, Rilmenidine
    - Agonists on α2 presinaptic adrenergic receptors and I1 imidazoline receptors: Clonidine
    - Other mecanism of action: Methyldopa, Guanabenz, Guanfacine
  - Acting on CNS and peripherally: Reserpine
    - Acting mainly peripherally: Guanetidine, Guanadrel, Bethanidine, Debrisoquin

- direct acting vasodilatation drugs: Hydralazine, Minoxidil, Diazoxide
- 5-HT1C and 5HT2 antagonists: Ketanserin
5.2. Drugs for treatment of hypertensive emergencies

- **parenteral agents for hypertensive emergencies:**
  - Furosemide (action onset in 15 minutes);
  - Nitroglycerine (action onset in 2-5 minutes, duration 5-10 minutes);
  - Propranolol (action onset in 1-2 minutes);
  - Enalapril (action onset in 15 minutes, duration 6 hours);
  - Labetalol (action onset in 5 minutes, duration 4-8 hours);
  - Esmolol (action onset in 5-30 minutes, duration 30 minutes);
  - Nicardipine (action onset in 15-30 minutes, duration 40 minutes);
  - Sodium nitroprusside (action onset in seconds, duration 3-5 minutes);
  - Diazoxide (action onset in 1-5 minutes);
  - Fentolamine (action onset in 1-2 minutes);
  - Ketanserine (action onset in 10 minutes);
  - Fenoldopam (action onset in 4 minutes, duration 8-10 minutes);
  - Urapidil (action onset in 10-20 minutes, duration 4-6 h);
  - Other drugs: Hydralazine (action onset in 10-20 minutes, duration 4-6 hours); Trimetaphan (action starts in 1-5 minutes, duration 10 minutes), Clonidine, Methyldopa, Reserpine;

- **oral agents for hypertensive emergencies:**
  - Furosemide;
  - Nitroglycerin (action onset in 5 minutes, duration 5-10 minutes) – also sublingual;
  - Captopril (action onset in 15-30 minutes, duration 4-6 h) – also sublingual;
  - Nifedipine (action onset in 5-15 minutes, duration 3-6 h);
  - Losartan (action onset in 60 minutes, duration 12-24 h);
  - Labetalol (action onset in 30-120 minutes, duration 6-12 h);
  - Clonidine (action onset in 30-60 minutes, duration 6-8 h).

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6. Pharmacological Treatment of Heart Failure

**Heart failure** is viewed as a consequence of disordered circulatory dynamics and pathologic cardiac remodeling.

**Chronic heart failure (CHF)** is typically a chronic illness during which episodic, acute decompensation may occur. Chronic heart failure is a pathological state characterized by abnormal cardiac function which is responsible for the failure of heart to pump blood in the body.

**Acute heart failure (AHF)** is characterized by low arterial pressure (cardiogenic shock) and dyspnoea (pulmonary edema).

6.1. Pharmacological therapy for CHF

6.1.1. Vasodilator drugs:

- **angiotensin converting enzyme inhibitors (ACEI)** \(\rightarrow\) drugs of choice
  - sulphhydryle: Captopril;
  - dicarboxilate: Enalapril, Ramipril, Quinapril, Perindopril, Lisinopril, Benazepril;
  - phosphonate: Fosinopril;
  - miscellaneous: Trandolapril, Cilazapril;

- **angiotensin II receptor antagonists** \(\rightarrow\) for patients who not tolerate ACEI
  - selective on AT1 receptors from vessels: Valsartan, Losartan, Candesartan, Telmisartan, Irbesartan, Eprosartan;
- beta-adrenoceptor antagonists → under specialist care
  - beta1-adrenergic antagonists: Metoprolol, Bisoprolol
  - alpha, beta-adrenergic antagonists: Carvedilol

- direct acting vasodilators:
  - nitrates: Nitroglycerine, Isosorbide dinitrate, Isosorbide mononitrate, Nitroprusside
  - arteriolar vasodilator: Hydralazine

- vasopressin receptor antagonists:
  - V1, V2-receptor antagonist: Conivaptan,
  - V2-receptor antagonist: Tolvaptan, Lixivaptan, Satavaptan

6.1.2. Diuretic agents → essential for symptomatic treatment
- loop diuretics
- thiazide diuretics
- K+ sparing diuretics

6.1.3. Positive inotropic agents
- cardiac glycosides

6.2. Pharmacological therapy for AHF: positive inotropic agents
- phosphodiesterase inhibitors:
  - bipyridines: Milrinone, Amrinone,
  - imidazoles: Enoximone

- calcium-sensitising agents:
  - benzimidazoles: Levosimendan, Pimobendan,

- beta1-adrenergic agonists: Dobutamine, Prenalterol
- beta1, beta2-adrenergic agonists: Isoproterenol
- dopamine and alpha, beta-adrenergic agonists: Dopamine
- Glucagon (pancreatic hormone).