Agents used in hyperlipidemia

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What is hyperlipidemia?

- hyperlipidemia = hyperlipoproteinemia
- hyperlipemia = ↑ triglycerids

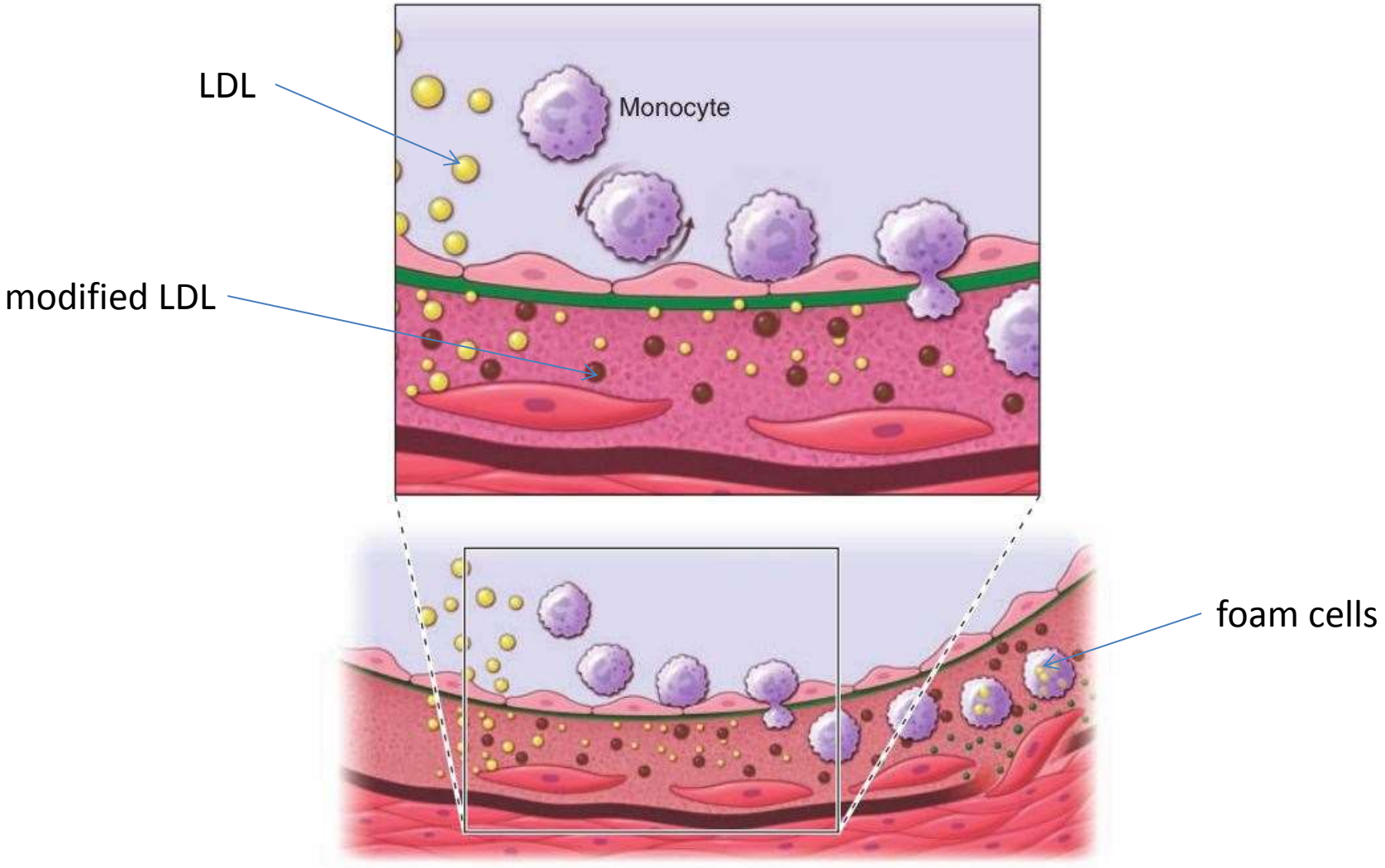
- primary hyperlipoproteinemias
  - genetic background e.g.
    - primary chylomicronemia - deficiency of LPL or its cofactor, apo C-II (recessive)
    - familial hypercholesterolemia – defects of LDL receptors
- secondary hyperlipoproteinemias
  - underlying disease e.g.
    - diabetes, alcohol, hypothyroidism, drugs (corticosteroids, protease inhibitors) etc.

Clinical significance of hyperlipidemias

- **atherosclerosis**
  - leading cause of death
  - lipid transport **into** the artery wall
    - apo B-100: LDL, IDL, VLDL, Lp(a)
  - retrieval of cholesterol **from** the artery wall
    - HDL
    - also inhibit oxidation lipoproteins
  - cellular components
    - foam cells, cholesteryl ester filled smooth muscle cells
    - accumulation of : foam cells, collagen, fibrin, calcium
  - slow occlusion / **rupture and quick occlusion**

- **acute pancreatitis**
  - in marked hyperlipemia (triglycerides above 7.9 mmol/L (700 mg/dL))

Atheroma development



Clinical significance of lipid lowering drugs

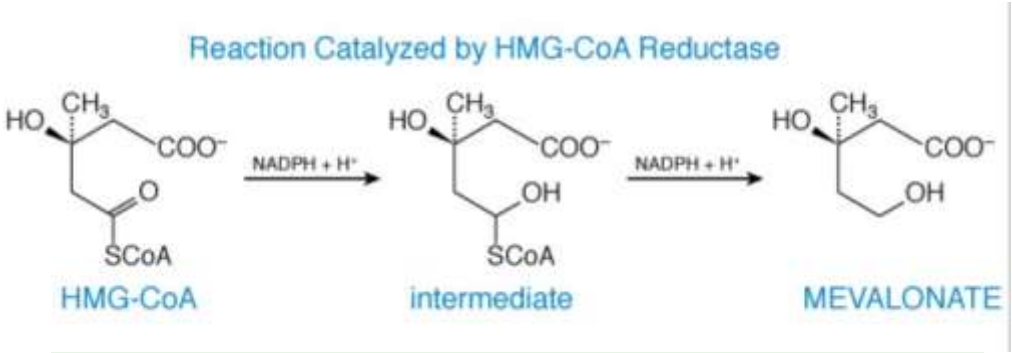
- increased risk of atherosclerosis
  - ↑ conc. of: cholesterol (total/LDL) / triglycerides
  - ↓ conc. of HDL-C

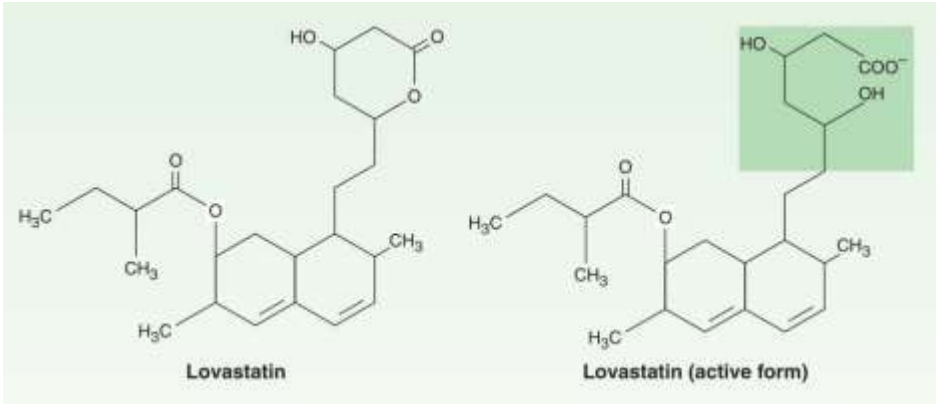
- atheroma development is dynamic
  - reversible (improvement) during aggressive lipid-lowering therapy
  - but not only atheromas - ↓ **mortality**

Classification of antihyperlipidemics

- **HMG-CoA reductase inhibitors (statins)**
  - 3-hydroxy-3-methylglutaryl–coenzyme A
  - lovastatin, atorvastatin, fluvastatin, pravastatin ...
- **bile acid-binding resins**
  - colestipol, cholestyramine, colesevelam
- **niacin (nicotinic acid)**
  - *but not niacinamide*
- **fibric acid derivatives (fibrates)**
  - gemfibrozil, fenofibrate, bezafibrate
- **cholesterol absorption inhibitors**
  - ezetimibe

HMG-CoA reductase inhibitors (statins)





- lovastatin, simvastatin – prodrugs (hydrolysis)
- pravastatin, atorvastatin, fluvastatin, rosuvastatin – active

Mechanism of action of statins

- **↓ cholesterol synthesis**
  - ↑ expression of the LDL receptor gene + ↓ degradation of LDL receptors
  - ↑ number of LDL receptors
  - ↑ removal of LDL from the blood
  - ↓ LDL-C
- ↑ removal of LDL precursors
  - VLDL remnants and IDL (enriched in apoE)
- ↓ hepatic VLDL production

Beneficial clinical effects of statins

- **lipid levels**
  - ↓ triglyceride
  - ↓ LDL-C (≈20-55% - highest efficacy: rosuvastatin / atorvastatin)
    - dose and drug dependent
    - effect in almost all patients with high LDL-C levels
      - except homozygous familial hypercholesterolemia
  - HDL-C
    - few studies in patients with low HDL-C
      - maybe differences among statins
    - if normal HDL-C → small increase
- non-lipid roles ? – not firmly established
  - improved endothelial function (NO)
  - improved plaque stability ?
  - anti-inflammatory role (↓ CRP)
  - lipoprotein oxidation ↓
  - ↓ venous thromboembolic events (rosuvastatin vs. placebo – 43%)

Pharmacokinetics of statins

- prodrugs
  - lovastatin and simvastatin
- significant first pass → low oral bioavailability
  - uptake (OATP1B1) → biliary excretion
  - metabolism (CYP3A4) – mostly somewhat active
  - potential for **drug-drug interactions**
    - CYP3A4 ↓: e.g. erythromycin, cyclosporine, ketoconazole, HIV protease inhibitors, tacrolimus, nefazodone, *fibrates*, paroxetine, venlafaxine
- half-life
  - mostly: 1-4 hours
  - **longer: atorvastatin and rosuvastatin** (14-20 hours)
    - contribution to greater cholesterol-lowering efficacy ?

Adverse effects of statins

- **hepatotoxicity**
  - ↑ serum aminotransferase – monitor
  - more severe hepatic toxicity – discontinue
- **myopathy**
  - minor ↑ creatine kinase
  - rarely marked ↑ creatine kinase
    - generalized discomfort muscle pain, tenderness, weakness
  - check baseline CK
    - but myopathy can occur without ↑ CK
- pregnancy
  - do not use
  - also in nursing mothers and children

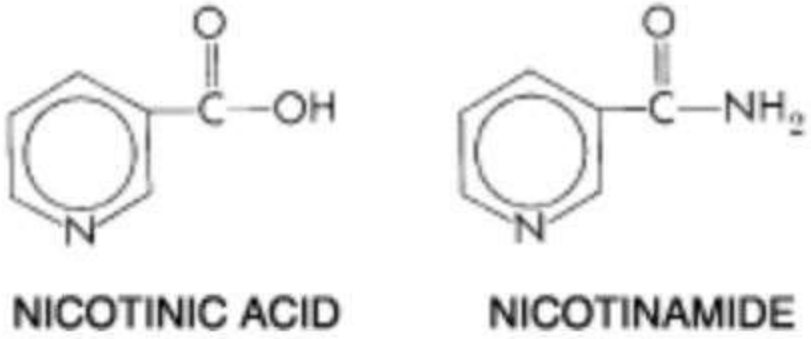
Bile acid-binding resins

- **colestipol, cholestyramine**, colesevelam
  - cationic exchange resins (not absorbed)
- bind bile acids – prevent reabsorption
  - normal: bile acids reabsorbed → negative feedback
  - resins prevent negative feedback → hepatic bile-acid synthesis ↑ → hepatic cholesterol ↓ → LDL receptors ↑
  - hepatic triglyceride synthesis ↑
    - avoid in hypertriglyceridemia

Bile acid-binding resins

- uses
  - primary hypercholesterolemia
    - may ↑ VLDL → combination
  - cholestasis, bile salt accumulation
    - pruritus ↓
  - digitalis intoxication
    - bind digoxin
- adverse effects
  - constipation, bloating
  - steatorrhea
  - gallstones ?
  - vitamin K malabsorption – see anticoagulants
  - impaired drug absorption
    - e.g. digoxin, thiazides, pravastatin, fluvastatin, ezetimibe

Niacin (nicotinic acid)



- vitamin B_3 (both)
- but only niacin affects lipid levels
- for hypolipidemic effects larger doses (2-6 g/day)
- ↑ **HDL-C**, ↓ triglycerides, ↓ LDL , ↓ ***Lp (a)***
- side effects limit its usefulness

Mechanism of action of niacin

- inhibits VLDL secretion in the liver
  - in adipose: ↓ intracellular (hormon-sensitive) lipase
  - ↓ flux of free fatty acids to the liver
  - ↓ hepatic triglyceride synthesis
  - ↓ VLDL production → ↓ LDL levels
- HDL-C levels ↑
  - synthesis is not enhanced
  - fractional clearance of apoA-I in HDL is reduced

Clinical use of niacin

- HDL ↑ (most effective) / Lp (a) ↓ (the only effective)
- hypercholesterolemia
  - heterozygous familial + other
  - in **combination** (resin / statin)
- severe mixed lipemia
  - TG ↓↓ (+ marine omega-3 fatty acids)
- maybe also useful
  - combined hyperlipidemia
  - dysbetalipoproteinemia

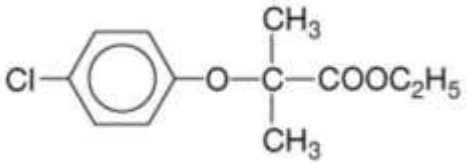
Adverse effects of niacin

- *cutaneous flushing*
  - maybe prevented by NSAIDs
  - tolerance
- nausea, abdominal discomfort
- pruritus
- **hepatotoxicity** – monitoring!
- hyperuricemia

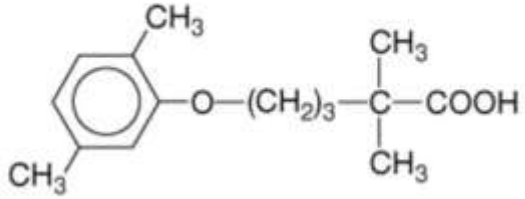
Fibric acid derivatives (fibrates)

- clofibrate – first but
  - – ↑ mortality
- gemfibrozil
  - – ↓ fatal and nonfatal cardiac events
  - – ≈ mortality
- fenofibrate
- bezafibrate

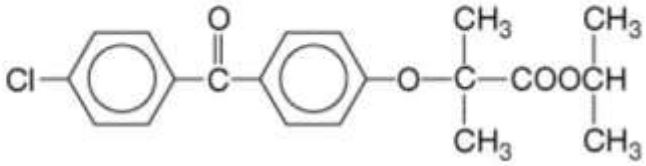
CLOFIBRATE



GEMFIBROZIL



FENOFIBRATE



Mechanism of action of fibrates

- **not completely clear**
- binding to PPAR-α → alt. gene transcription
  - ↑ LPL synthesis → ↑ clearance of TG-rich lipoprot
  - ↓ expression of apoC-III →↑ VLDL clearance
  - ↑ apoA-I and apoA-II expression →↑ HDL (fenofibrate > gemfibrozil)
- potential antithrombotic effects ?
  - ↓ coagulation
  - ↑ fibrinolysis

Clinical use of fibrates

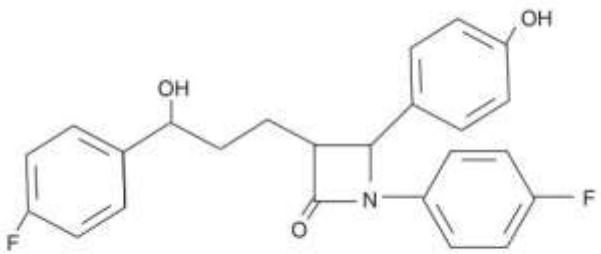
- hypertriglyceridemias (VLDL)
  - also useful: HIV protease inhibitor induced hypertriglyceridemia
- dysbetalipoproteinemia
  - in which VLDL, chylomicron remnants ↑ / LDL ↓
- in combination
  - bile-acid binding resins
  - fenofibrate + rosuvastatin
    - if both LDL and VLDL ↑
    - CAVE! - liver and muscle toxicity

Adverse effects of fibrates

- myopathy
  - ↑ risk with HMG-CoA reductase inhibitors (choose fenofibrate if necessary)
- cholesterol gallstones
- interaction with coumarin anticoagulants

Cholesterol absorption inhibitors (ezetimibe)

- mechanism of action
  - ↓ intestinal absorption of
    - cholesterol and phytosterols
  - ↓ NPC1L1 transport protein
  - ↓ cholesterol content of chylomicrons
- primary use
  - adjunctive therapy with statins
    - as compensatory ↑ in cholesterol synthesis
    - LDL-C ↓ greater but clinical cv benefits controversial



Ezetimibe

Cholesterol absorption inhibitors (ezetimibe)

- pharmacokinetics
  - glucuronidated in the intestinal epithelium
  - enterohepatic recirculation
  - **bile-acid sequestrants: absorption ↓**
- adverse effects
  - rare hypersensitivity
  - safety in **pregnancy** is **not** proven
    - and see **combination products** (ezetimibe + statin)

General comments

- diet
- diet + drugs (maybe combinations)

- avoid in
  - pregnant / likely to become pregnant
  - lactating

- may need to adjust doses of coumarine anticoagulants

- rarely indicated in children

- temporary suspension of statins in severe illness