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Hypolipidemics

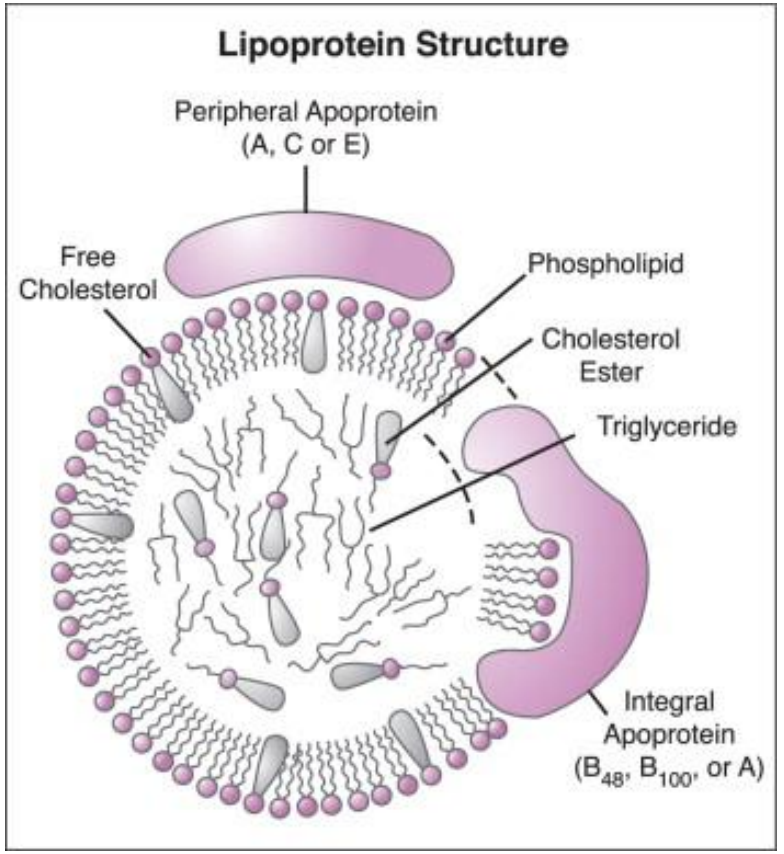
Pharmacology I
Spring Semester 2022
Department of Pharmacology and Toxicology
Faculty of Pharmacy MU

Lipids, lipoproteins

- Major lipids in plasma: fatty acids, triglycerides, cholesterol and phospholipids
- **Triglycerides** (triacylglycerols)
  - glycerol + three long-chain fatty acids
  - From dietary fat, synthesis in liver and other tissues
  - They are transported in chylomicrons → chylomicron remnants to the liver
  - Source of stored energy (lipolysis hydrolysis catalyzed by lipases)
- **Cholesterol**
  - Component of the cellular membranes
  - Precursor of steroid hormones, bile acids, vitamin D_3
  - In dietary fat or by synthesis (enzyme **HMG-CoA reductase** catalyses first step endogenous cholesterol biosynthesis)

Lipids, lipoproteins

- In plasma, lipids are transported in association with proteins:
  - Free fatty acids with albumin
  - In complexes as **lipoproteins**
- **Lipoproteins**
  - **Core – hydropfobic;** triacylglycerols, cholesterol ester
  - **Outer layer** from phospohlipids (outer hydrophilic part), cholesterol, apolipoproteins



Larry R. Engelking, Chapter 63 - Lipoprotein Complexes, Textbook of Veterinary Physiological Chemistry (Third Edition), Academic Press, 2015, ages 406-410, ISBN 9780123919090

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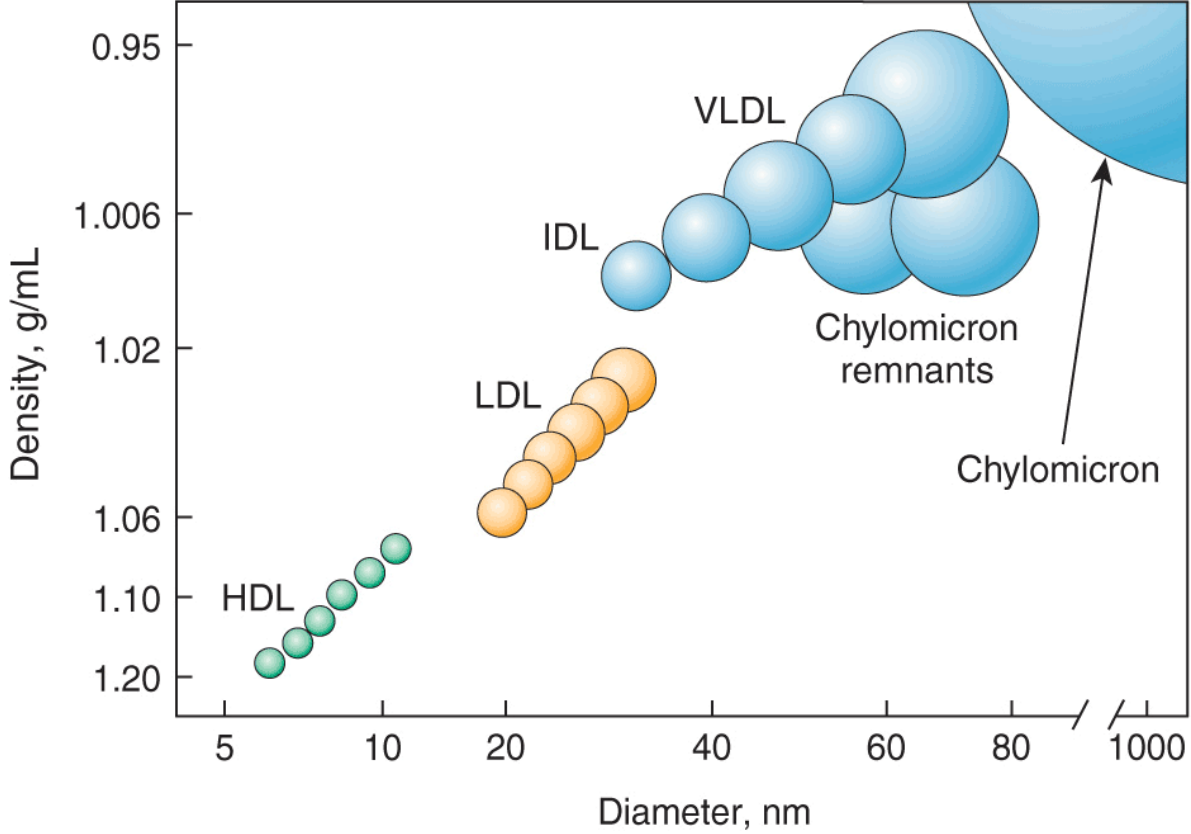
Lipids, lipoproteins

Apolipoproteins

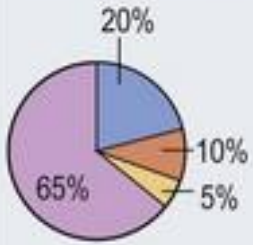
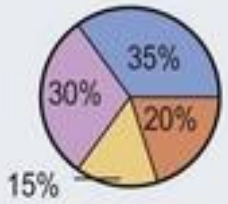
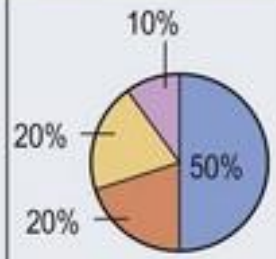
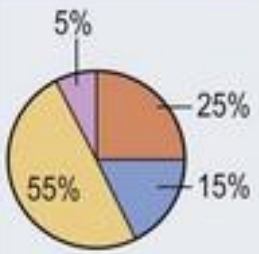
- Structural components of lipoproteins, enable binding to lipoprotein receptors (apoB-100 in LDL), cofactors for enzymes
- Classes: apoA, apoB, apoC etc.
- ApoB is an indicator of the amount of small atherogenic particles
- ApoA is an indicator of antiatherogenic particles
- ApoB/apoA-I is a predictor of cardiovascular risk
- Apolipoprotein(a) – lipoprotein(a) is an atypical lipoprotein that conteins molecules of apo(a)
- Apo(a) shares homology with plasminogen – atherogenic and thrombogenic effect

Lipoproteins



https://thoracickey.com/disorders-of-lipoprotein-metabolism/

Composition of lipoproteins

	chylomicrons	VLDL	IDL	LDL	HDL
triglyceride, cholesterol, phospholipid, protein					
apolipoproteins	C, B-48, E, A	B-100, C, E	B-100, E	B-100	A, C, E

https://basicmedicalkey.com/lipids-lipoproteins-and-cardiovascular-disease/

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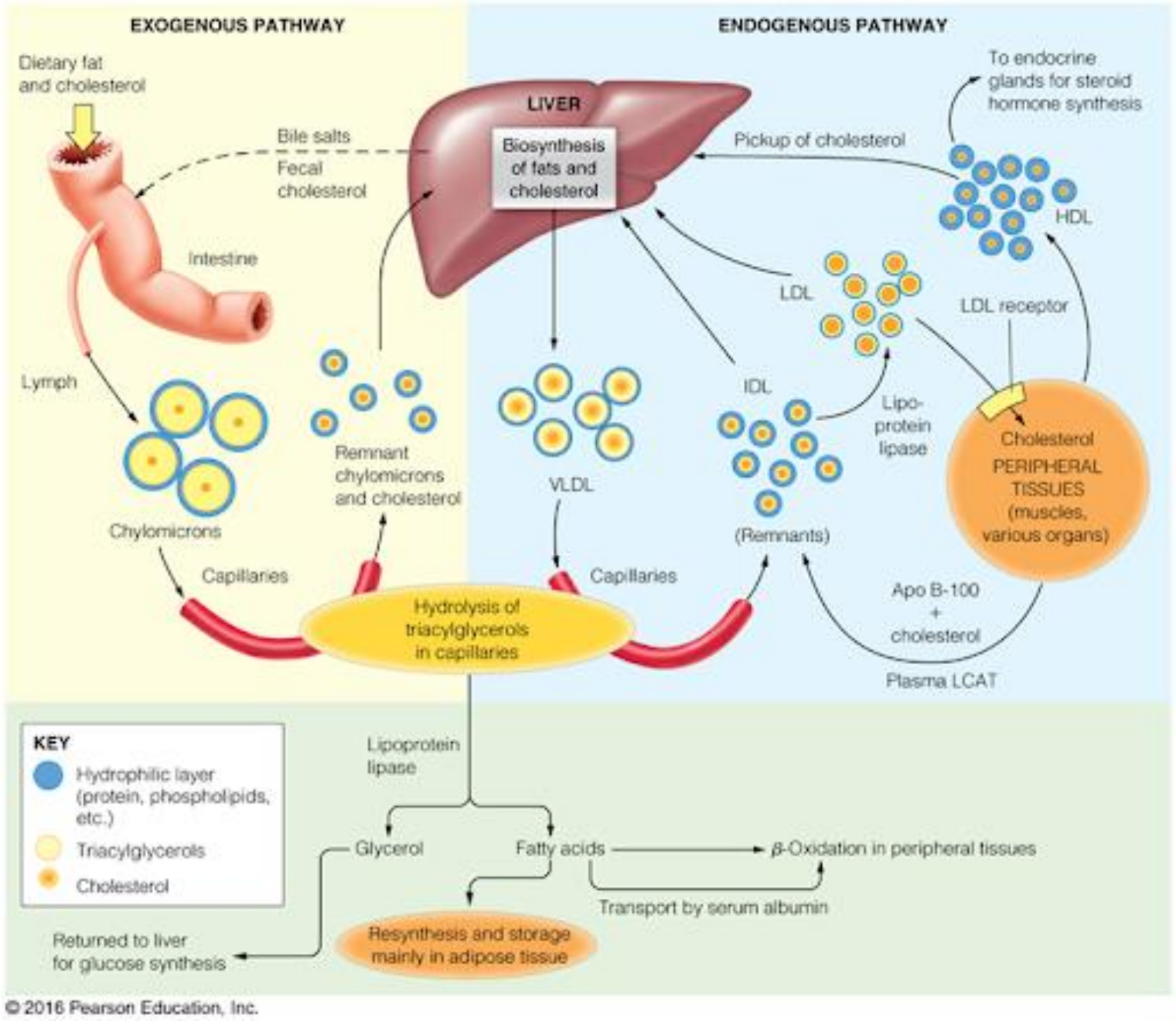
Lipoproteins

Classification od lipoproteins				
Lipoprotein	**Source**	**Density (g/ml)**	**Function**	**Risk of atherosclerosis**
Chylomicrons (CM)	Intestine	< 0.95	Transport of exogenous triglycerides	---- (CL remnants ↑↑)
VLDL	Liver	0.96 – 1.006	Transport of endogenous triglycerides	↑
IDL	Catabolism of VLDL	1.007 – 1.019	Precursor of LDL	↑↑↑
LDL	Catabolism of VLDL via IDL	1.02 – 1.063	Cholesterol transport	↑↑↑
HDL	Liver, intestine, catabolism of CM and VLDL	1.064 – 1.21	Reverse cholesterol transport	↓↓↓



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Dyslipidemia

- Medical condition of an abnormal level of blood lipids
- Results from increased synthesis or decreased catabolism of lipoprotein particles

- The clinical consequence of DLP is **atherosclerosis**
- Part of a condition called metabolic syndrom

  → co-occurence of cardiovascular risk factors as:

  atherogenic dyslipidemia (hypertriglyceridemia + reduced high-density lipoprotein cholesterol (HDL)), elevated fasting glucose, obesity and hypertension

Dyslipidemia

Classification:

(according to the European Atherosclerosis Society)

- The most common, simplified but for clinical practice sufficient

Isolated hypercholesterolemia

- ↑ concentration of total cholesterol (mainly the LDL-cholesterol fraction) at normal triglyceride levels

Combined hyperlipidemia

- concomitant ↑ in the concentration of total cholesterol and triglycerides

Isolated hypertriglyceridemia

- ↑ concentration of triglycerides at normal concentrations of total cholesterol

+ assessment of HDL-cholesterol concentration

Hypolipidemic treatment

- Agents reducing the concentration of lipid substances in the plasma
- One of the main approaches in primary and secondary **prevention of atherosclerotic cardiovascular diseases** (risk of ischemic stroke or myocardial infarction)
- Individualized approach (+ important **non-pharmacological** approach)
- Assessment of overall cardiovascular risk
- Approaches:
  - Reduction of LDL particle synthesis, increase of elimination
    - Lowering the amount of cholesterol for synthesis of atherogenic lipoproteins
    - Stimulation of LDL particle uptake
  - Increase of the concentration of HDL lipoproteins
  - Reduction of hypertriglyceridemia – activation of lipolysis

Agents used to affect dyslipidemia

Drugs that primarily lower cholesterol in LDL particles	**HMG-CoA reductase inhibition**	Statins
	Inhibition of the absorption of cholesterol from the small intestine	Ezetimibe
	Bile acid sequestrant	Colestyramine
	PCSK9 inhibitors	Alirocumab, evolocumab
Drugs that lower triglyceride levels and possibly increase the supply of HDL particles		Fibrates
Complex acting		Nicotinic acid

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Statins

- **HMG-CoA** (3-hydroxy-3-methylglutaryl coenzyme A) **reductase** competitive inhibitors
- Effect: lower LDL cholesterol → improve the prognosis of atherothrombotic events and cardiovascular mortality

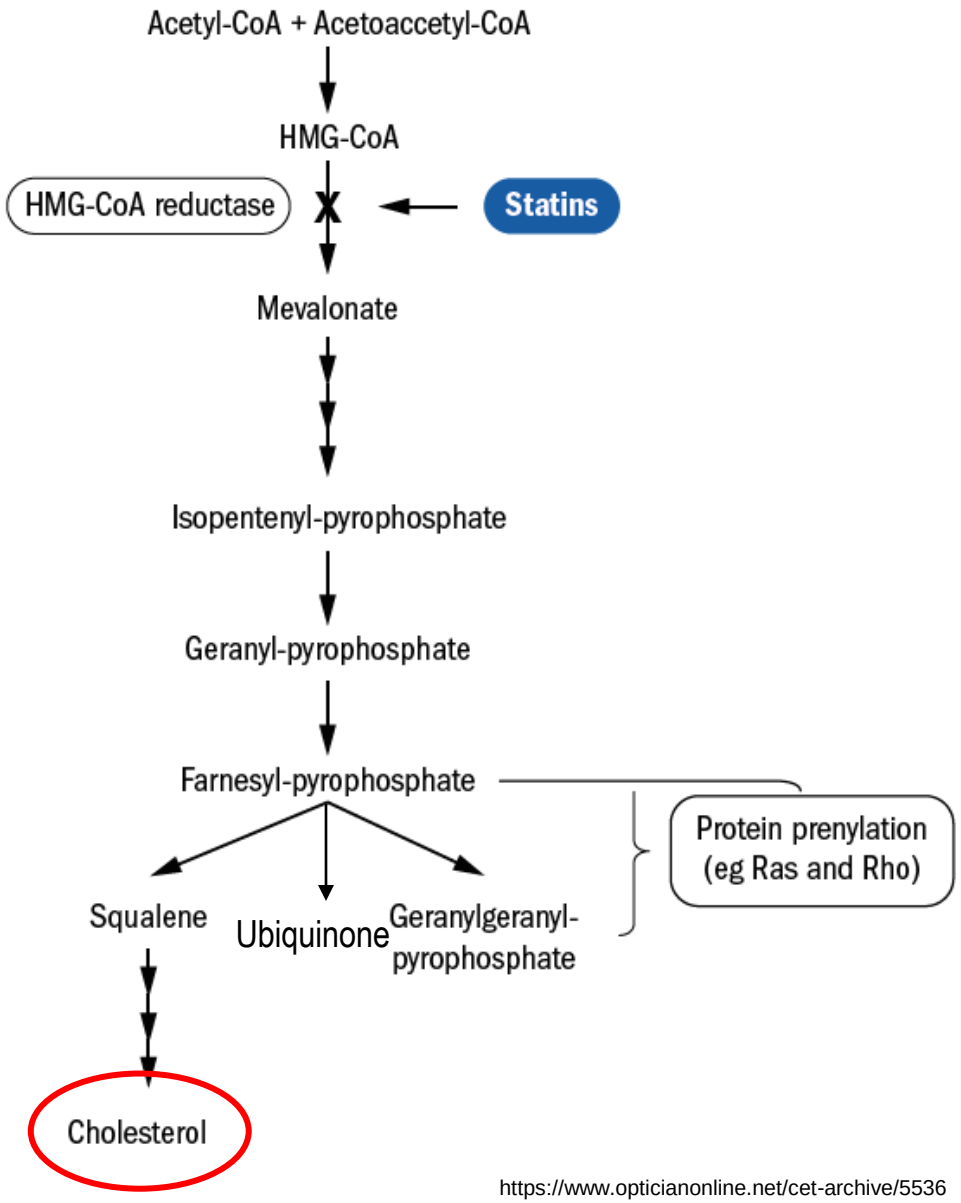
Statins

Mechanism of action:

- Competitive blocking of **HMG-CoA reductase** = rate-limiting enzyme in the cholesterol biosynthesis

→ ↓ cholesterole in hepatocytes → ↕ expression of LDL receptors, ↑ catabolism of LDL

→ ↓ concentration of VLDL (triglycerides-rich lipoproteins) → ↓ triglycerides (variable)



https://www.opticianonline.net/cet-archive/5536

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Statins

Pharmacokinetics

- **Lipophilic statins**
  - More susceptible to metabolism by the cytochrome P450 system – enterocytes + liver
  - Substrates of P-glycoprotein

  → ↓ absorption → ↓ bioavailability

  → ↑ risk of drug interactions
- **Hydrophilic statins**
  - Not significantly metabolized by cytochrome P450 enzymes

Statins

	Lipophilic			Hydrophilic
	Atorvastatin	**Simvastatin**	**Fluvastatin**	**Rosuvastatin**
Active metabolite	✓	✓	X	X
Prodrug	X	✓	X	X
Substrate of CYP3A4, P-gp.	✓	✓	X	X
Substrate of CYP2C9	X	X	✓	X (only to a limited extent)
Risk of drug interactions	intermediate	high	low	low
Bioavailability	≈ 15 %	< 5 %	≈ 20 %	≈ 20 %

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Statins – Drug interactions

- Simvastatin, atorvastatin are **substrates of CYP3A4** (biotransformation) and **P-glycoprotein** (efflux from enterocytes into the intestine, from hepatocytes into the bile etc.)

→ ↑ risk of drug interactions

- Strong (or moderate) inhibitors of CYP3A4/P-gp. encrease bioavaibility of that statins (clarithromycin, itraconazol, indinavir, ritonavir, amiodarone, verapamil etc.)

- Inhibition of the transporter OATP1B1 – fibrates, clarithromycin, rifampicin

(+ genetic polymorphism)

Statins

Simvastatin

- High affinity to the CYP4A3, P-gp. → low bioavaibility (< 5 %)
- Short $t_{1/2}$ (2–3 hours)
- Exposition to simvastatin depends on the activity of the transporter OATP1B1 (interindividual differences)

→ ↑ risk of adverse effects, drug interactions

Atorvastatin

- Higher bioavaibility, longer $t_{1/2}$ (14–16 hours)
- ↓ Dependence on the transporter OATP1B1
- ↓ Interindividual variability of the exposition to atorvastatin, ↓ risk of adverse effects

Statins

Fluvastatin

- Substrate of CYP2C9 – low potential of drug interactions
- Short $t_{1/2}$ (modified-release dosage)
- Very good tolerability

Rosuvastatin

- Hydrophilic – is not a substrate od CYP450 or P-gp.
- Long $t_{1/2}$
- High efficiency, good tolerability

Lovastatin

Pravastatin

(in the Czech Republic only in combination with fenofibrate, now not available on the market)

Statins – Adverse effects

- In general good tolerability
- **Myalgia** – muscle pain (without release of creatine kinase – CK)
- **Myopathy** – muscle pain with ↑ CK
  - fully reversible upon discontinuation of treatment or dose adjustment
- **Rhabdomyolysis**
  - Rare condition
  - Disruption of skeletal muscle integrity → release of intracellular muscle components including myoglobin into the bloodstream
  - Ranges from an asymptomatic illness to a life-threatening condition (extreme elevations in CK, electrolyte imbalances, acute renal failure etc.)
- **Asymptomatic elevation of liver enzymes**

Statin intolerance

- Any adverse event attributed to statin

  → Considered unacceptable by the patient (myalgia, myopathy)

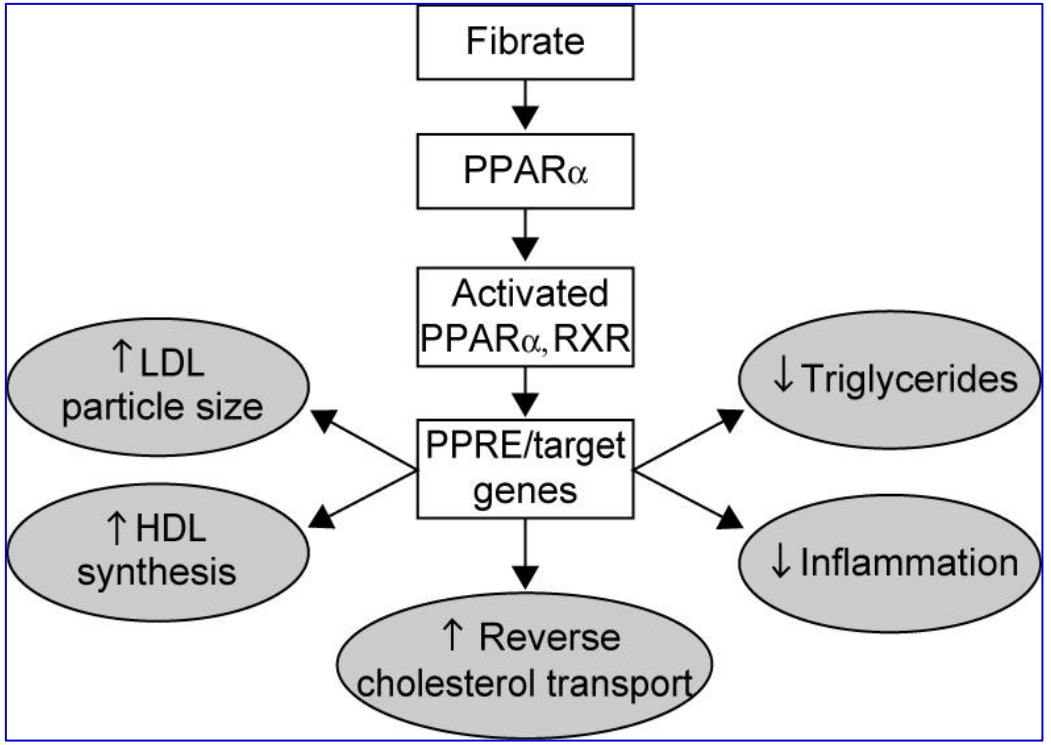
  → Some laboratory abnormalities

Fibrates

- Complex effects
- Mechanism of action:
  - Activation of **peroxisome proliferator-activated receptors** (**PPAR-alpha**)

    = Intracellular receptors – regulation of the transcription of several genes affecting lipid and lipoprotein metabolism
  - Activation of lipolysis → activation of lipoprotein lipase (+ stimulation of beta-oxidation of fatty acids)

    → **reduction of triglyceride levels**
  - Reverse cholesterol movement and stimulation of cellular fatty acid uptake
  - ↑ HDL levels



Goldenberg I, Benderly M, Goldbourt U. Update on the use of fibrates: focus on bezafibrate. Vascular Health and Risk Management. 2008 ;4(1):131-141.

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Fibrates

Indications:

- Severe **hypertriglyceridemia**
- **Mixed hyperlipidaemia** when statin therapy is contraindicated or not tolerated
- Additional therapy to statins used in mixed hyperlipidaemia in patients at high cardiovascular risk in whom neither triacylglycerols nor HDL cholesterol are adequately controlled

Adverse effects:

- Good tolerability
- Dyspepsia, elevated transaminase levels, slight increase in serum creatinine
- The risk of ↑ CK, myalgia and muscle damage increases in combination with statins

Contraindications: severe renal insufficiency

Drug interactions: warfarin (the risk of an increased anticoagulant effect), statins (↓ elimination of lipophilic statins)

Fibrates

Fenofibrate

- Proved reduction in triglyceride levels

Ciprofibrate

Bezafibrate

Gemfibrozil

Ezetimibe

- Inhibitor of the absorption of cholesterol from the small intestine

  → Blockage of Niemann-Pick C1-like 1 (NPC1L1) transport protein – allows cholesterol absorption

  - Located in the brush border of enterocytes in the proximal part of the intestine
  - Inhibits absorption of dietary cholesterol and cholesterol from enterohepatic cycle
  - NPC1L1 is located also in bile ducts – ↑ cholesterol levels in bile
- Effect: ↓ LDL-C levels
- In combination with statins – additive effect → potentiation of ↓ LDL-C levels

Ezetimibe

Indications:

- Primary hypercholesterolemia
- In combination with statins
- In monotherapy when statin administration is not appropriate or is not tolerated

Drug interactions:

- Risk of cholelithiasis in combination with fibrates
- No pharmacologically significant interactions have been reported

Adverse effects:

- Good tolerability
- No myalgia or myopathy
- In combination with statins does not increase their toxicity

Nicotinic acid (niacin)

- „the oldest“ hypolipidemic drug

Effects:

- The broadest spectrum of effects on blood lipid metabolism and lipoproteins
- ↓ VLDL → ↓ LDL concentrations, changes the profile of LDL subfractions towards larger and lower density particles
- ↑ HDL concentrations
- The only lipid therapy that ↓ lipoprotein(a) concentrations
- Non-lipid benefits – inhibits vascular inflammation (↓ ROS), reduces intravascular adhesion molecules

Nicotinic acid (niacin)

Mechanism of action:

- Activation of the anti-inflammatory G protein-coupled receptor GPR109A on the surface of adipocytes, monocytes, macrophages etc.

→ Inhibition of lipolysis in adipose tissue, reduced supply of free fatty acids, inhibition of hepatic enzyme diacylglycerol acyltransferase-2 → reduced TAG production, VLDL, LDL, ↓ uptake of HDL particles in the liver etc.

Nicotinic acid (niacin)

- Higher doses – daily dose of 2 000 mg
- Adverse effects:
  - Higher incidence, wider spectrum
  - Dose dependent (elimination by appropriate dosing and administration)
  - Flushing (caused by release of prostaglandin D2 and E2) → combination with specific antagonist for PGD2 receptor laropiprant (the combination is no longer registered)
  - Impaired liver function
  - Increased blood glucose levels
  - Hyperuricemia; dyspepsia

Inhibitors of PCSK9

- Monoclonal antibodies against PCSK9 convertase

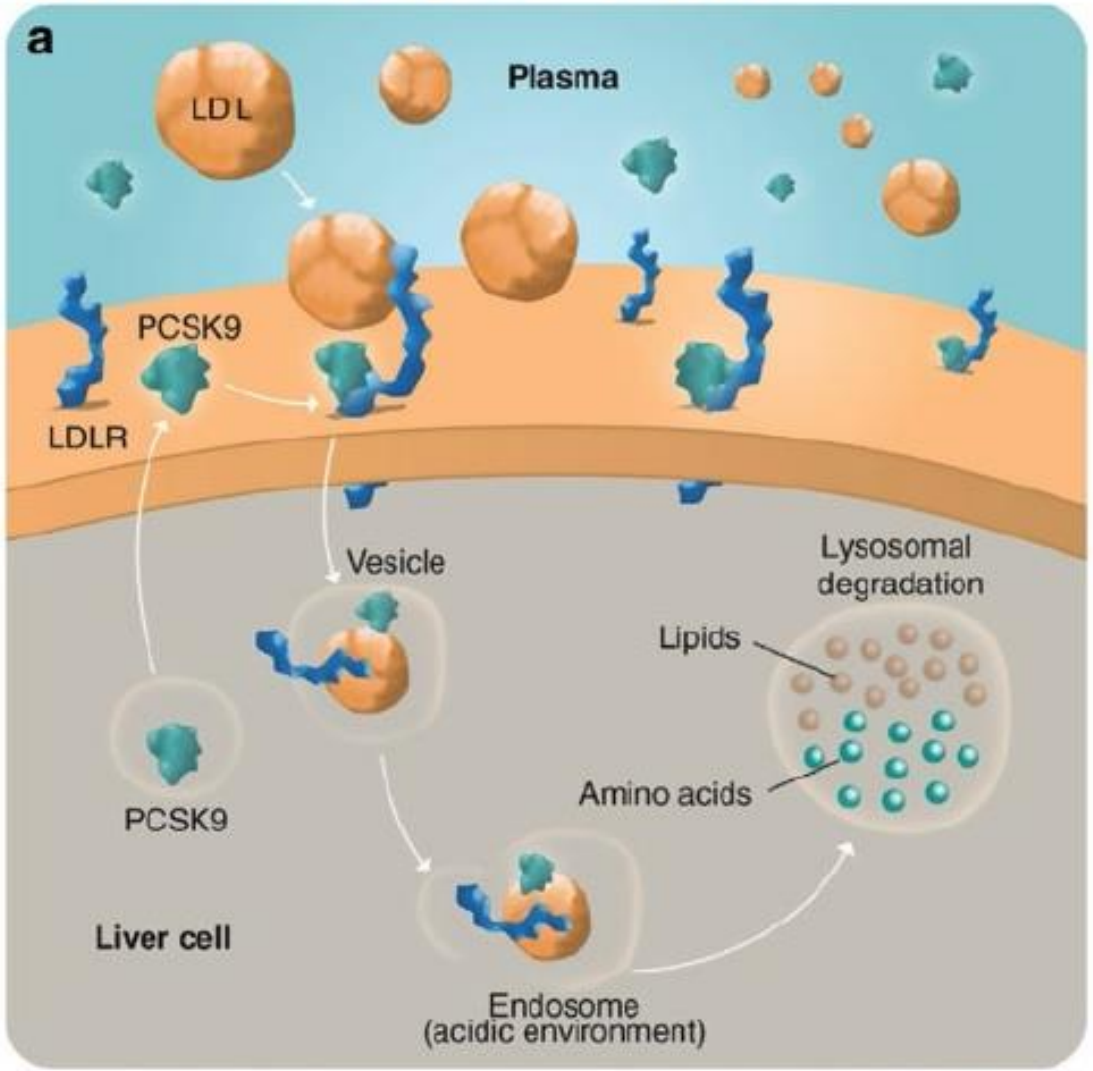
  (Proprotein **convertase** subtilisin/kexin9)
  - Role in the regulation of cholesterol transport into tissues and the degradation of LDL cholesterol
  - PCSK9 binds to LDL rp. on cellular surface → internalization of rp., prevention of recycling of LDL rp. – regulation of its amount

Principle: stimulation of LDL particle uptake by target tissues

Mechanism of action:

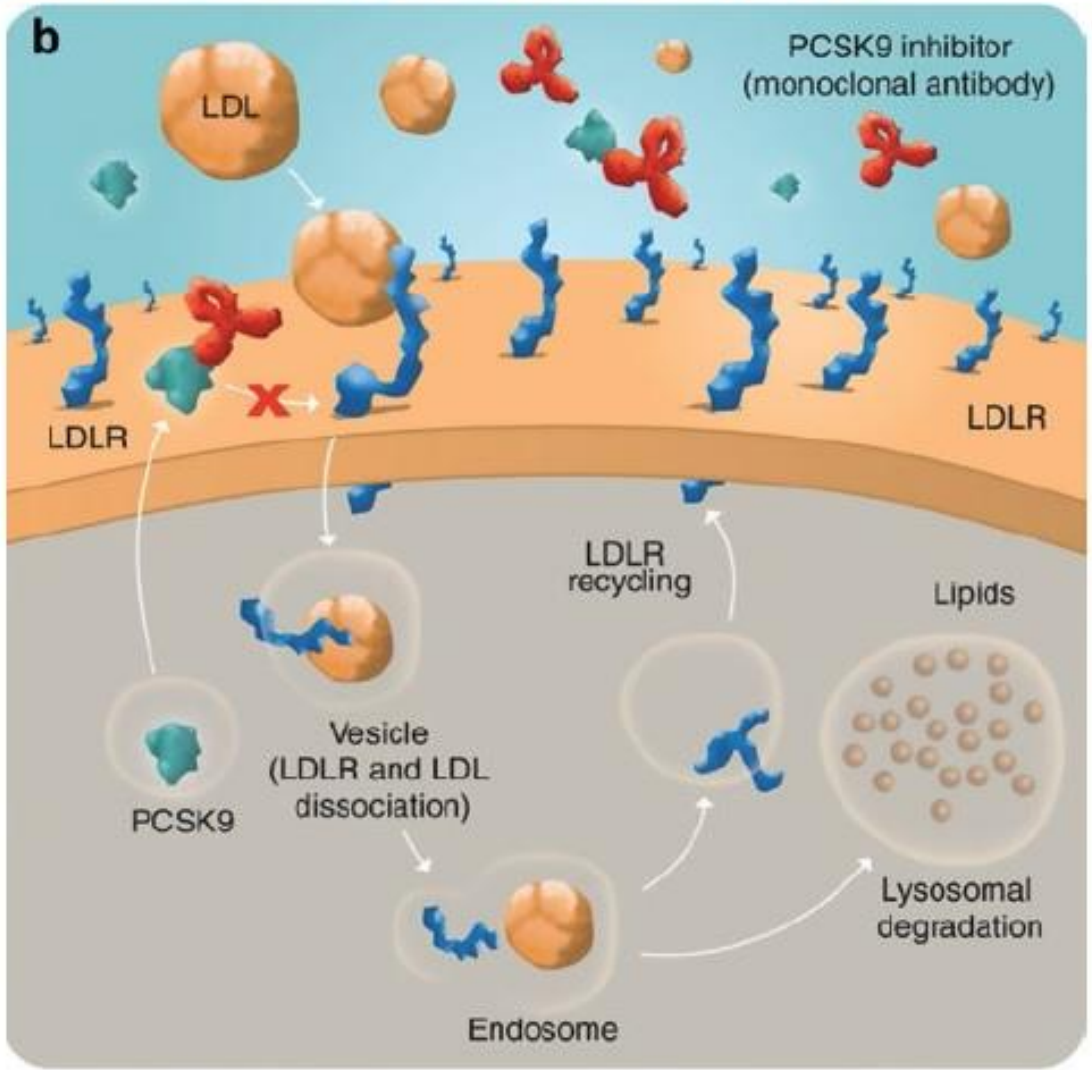
- Mab prevents binding of PCSK9 to LDL rp. and its subsequent degradation
  → ↑ amounts of LDL rp. → ↑ degradation of LDL particles
- Reduction of the amount of apo-B100

How does PCSK9 work?



a) Secreted PCSK9 binds to LDLR on the liver cell surface and mediates the lysosomal degradation of the complex formed by PCSK9 - LDLR - LDL.

How does Inhibitors work?



b) In the presence of a monoclonal antibody that binds to PCSK9, the PCSK9-mediated degradation of LDLR is inhibited, resulting in an increased uptake of LDL-cholesterol by LDLR as more LDLR are recycled at the cell surface.

Source: Krähenbühl S, et al. Unmet Needs in LDL-C Lowering: When Statins Won't Do! Drugs. 2016 Aug;76(12):1175-90

Inhibitors of PCSK9

- **Evolocumab**
- **Alirocumab**
- Both administrated as subcutaneous injection

→ each 2 weeks (alirocumab)/2–4 weeks (evolocumab)

- Bococizumab (not registered)

Indication: primarily familial hypercholesterolemia with insufficient response to other hypolipidemic treatments

A new PCSK9 antagonist from the siRNA family

- **Inclisiran** – "first-in-class" siRNA reducing LDL-C concentration (reg. 12/2020)
- siRNA = a small interfering RNA that regulates genetic expression through RNA interference
- Inhibits translation of the PCSK9 protein

Lopitamid

- Inhibitor of selective microsomal transfer protein (MTP) = intracellular protein that transfers lipids through biological membranes

Indication: homozygous form of familial hypercholesterolemia

- Homozygous form is a rare condition (LDL receptors are not synthesized or are non-functional → very high concentrations of LDL-cholesterol)

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Thank you for your attention