# Hypolipidemics

This study material is recommended specifically for practical courses from Pharmacology II for students of general medicine and stomatology. These brief notes could be used to prepare for the lesson and as a base for own notes during courses. Addititonal explanations and information are given in single lessons.

# Plasma lipoproteins

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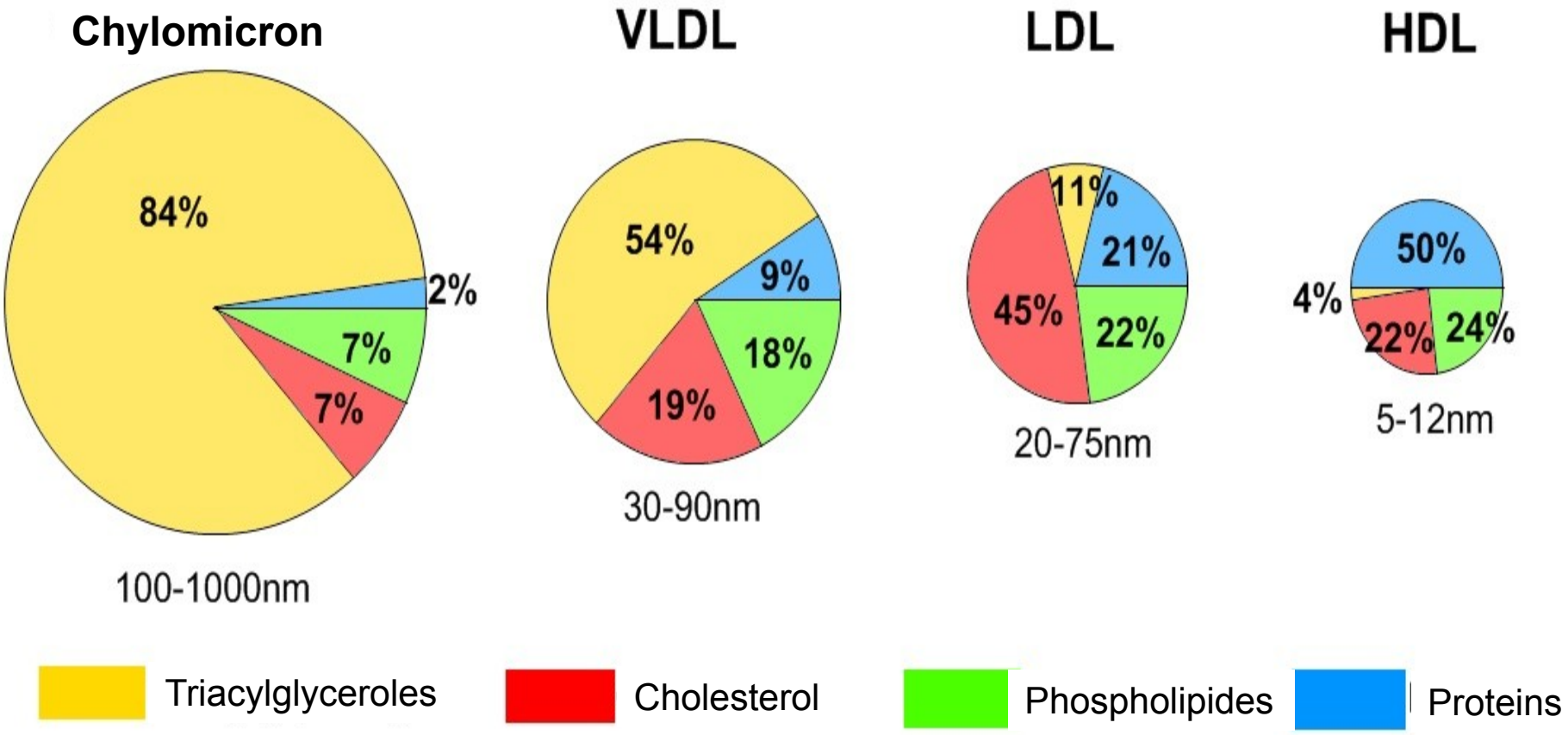
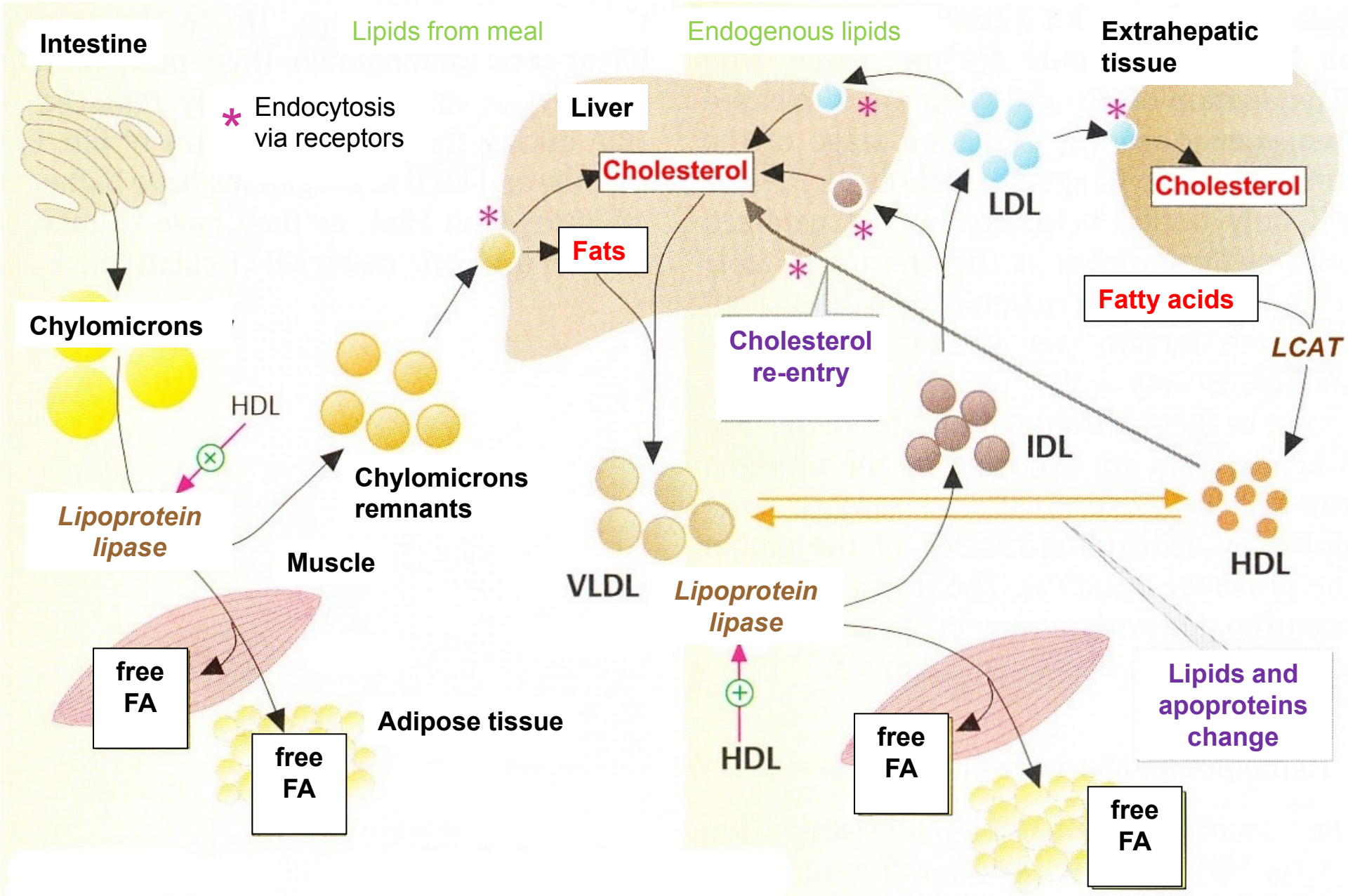
# Composition of lipoproteins



# Lipoprotein metabolism



# Dyslipidemia

- change of cholesterol levels and/or TAG and/or HDL cholesterol
  - serum sampling after 10 hours after last meal

- **Tot-Ch / HDL-Ch ratio= atherogenic index**
  - ideal apo-B / apo-A1
  - optimum < 5
  - (< 4 in persons with ↑ CVS risk)

- **↑ ↑ cardiovascular risk**
  -

# LIPID PLASMA LEVELS (mmol. $l^{-1}$)

| | normal | low | intermediate | very high risk |
|---|---|---|---|---|
| TC | < 5. 2 | 5. 2 - 6. 5 | 6. 5 - 7. 8 | > 7. 8 |
| TG | < 2. 3 | 2, 0 - 2. 5 | 2. 5 - 4. 6 | > 4. 6 |
| LDL | < 4. 1 | 4. 0 - 5. 0 | 5. 0 – 5. 5 | > 5. 5 |
| HDL f | > 1. 2 | | < 1. 0 | < 0. 8 |
| HDL m | > 1. 4 | | < 1. 2 | < 1. 0 |
| $\frac{\text{HDL}}{\text{LDL}}$ | $\geq$ 0. 25 | 0. 2 – 0. 25 | < 0. 2 | << 0. 2 |

# Dyslipidemia

- **primary**
- **secondary** (caused by other disease)
  - 
  - 
  - 
  - 

# Hyperlipoproteinemia classification

| Type | ↑ lipoprotein | ↑ lipid | Classification | Relation to IHD |
|---|---|---|---|---|
| I | chylomicrons | TG | LPL deficiency→ ***Familiar hypertriacylglycerolemia*** | none |
| IIa | LDL | Cholesterol | defekt LDL-receptoru → ***Familiar hypercholesterolemia*** | ↑ |
| IIb | LDL + VLDL | Cholosterol + TG | ***Familiar / combined hyperlipoproteinemia*** | ↑ |
| III | β-VLDL | Cholosterol + TG | ***Familiar dysbetalipoproteinemia*** | ↑ |
| IV | VLDL | TG | ***Familiar hypertriacylglycerolemia*** | ↑ |
| V | VLDL + chylomikrony | TG | ***Mixed hypertriacylglycerolemia*** | ↑ ? |

# HYPOLIPIDEMICS

**Purpose of administration:**

- myocardial infacrtion prevention
- prevention of other complications (ictus, peripheral vessels ischaemic disease)

**Main effect:**

- prophylaxis of atherosclerotic plaques formation = vessel diameter reduction

**Hyperlipidemia risk factors:**

- ✓ CH and lipid‘s high blood levels (from diet, synt. *de novo*)
- ✓ increased BP
- ✓ tobacco smoking
- ✓ obesity, diabetes mellitus
- ✓ sedentary lifestyle

# Regime precautions

- quit smoking, regular physical activity, diet adjustment
  - weight reduction, decrease of fats in diet (mainly animal) and increase of fibre intake

# Dyslipidemia pharmacotherapy

## 1. Plasma cholesterol decrease

- decrease intestinal (re)absorption of bile acids/cholesterole
  - **RESINS, EZETIMIB**
- inhibits cholesterol and VLDL synthesis
  - **STATINS, NICOTINIC ACID**
- increase cholesterol clearence
  - **PROBUCOL**

## 2. Plasma TAG decrease

- inflence on VLDL synthesis
  - **NIKOTINIC ACID**
- influence on plasma lipoprotein conversion
  - **FIBRATES**

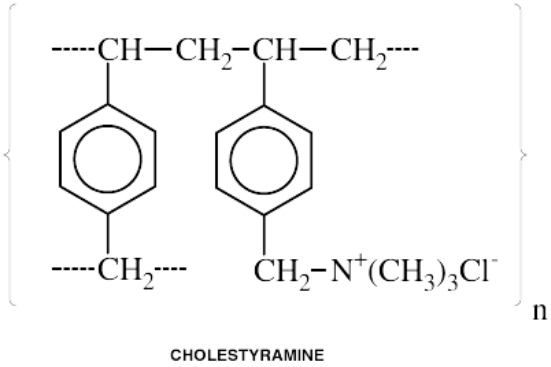
# 1. Drugs ↓ plasma CH

a. decreasing intesrinal bile acid/CH reabsorption
   - **RESINS**
   - **EZETIMIB**

b. inhibit synthesis of CH and VLDL
   - **STATINS**
   - **NIKOTINIC ACID**

c. increase of CH clearence
   - **PROBUCOL**

# RESINS




CHOLESTYRAMINE

## *colestyramine, colestipol, colesevelam*

- synthetic resins, binds to **bile acids** in intestine
  - 1g binds 100 mg of bile ac.

  → ***decrease of bile acid re-entry to liver***

  → increase of bile acids synthesis from CH (activation of 7-α-hydroxylasis)

  → increase of liver LDL uptake **(up-regulation of LDL-receptor)**

  → cholesterol tissue mobilization and uptake from plasma to liver
- combination with …

# RESINS

**PK: are not absorbed (1 mil. D)**, not biotransformed

→

**AE:** common and complicating therapy (mainly adherence to therapy)

- constipation, flatulence, vit. K malabsorption; dry, peeling skin
- ↑ **TAG, ALP, transaminases**
- **<u>interactions</u> with co-administered drugs - ↓ bioavailability**
  - 1 hour before or 4 hours after resins
- colesevelam lowest incidence of AE

cab be also used in **bile duct obstruction** to reduce the amount of bile acids

# EZETIMIB

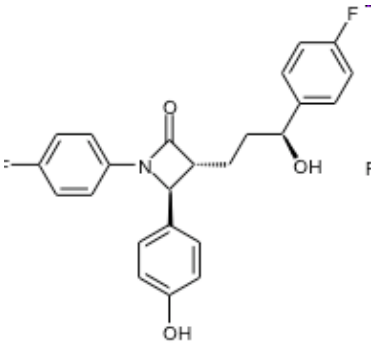
- **<u>intestinal absorption inhibitor</u>** of all sterols (fyto- and cholesterol) block of transport protein*→ decrease cholesterol availability
- **main effect: decrease of LDL**
- **synergistic effect with statins** (when co-administered– LDL reduction up to 25%)

**PK:** p.o. fast absorption, conjugated to active glucuronide

- enterohepatal recirculation- long $T_{1/2}$ (22 hrs), 80 % eliminated in bile

**AE:** cephalgia, GIT dyscomfort

- should not be combined with resins



Ezetimib

*Niemann Pick C1 Like 1 (NPC1L1)

# STATINS

- ***simvastatin, lovastatin, fluvastatin, pravastatin***
- ***atorvastatin, rosuvastatin*** *(long acting)*

**MofA:**

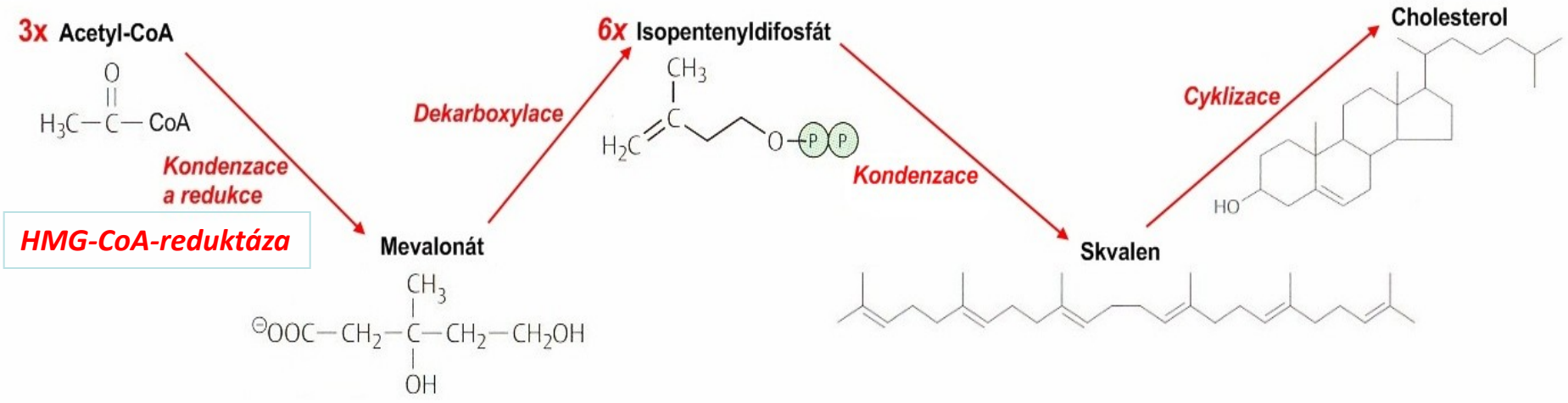
- ↓ cholesterol in hepatocytes

→ ↑ **LDL-receptors synthesis** in liver (LDL receptor up-regulation)

→ ↑ **cholesterol liver uptake**

→ ↑ **LDL clearence**

# Cholesterol synthesis



# STATINS

**PK:** lova- a simvastatin prodrugs

- 30 % intestinal absorption
- significant **first pass effect**
  - CYP3A4 and 2C9 biotransformation
  - CYP3A4 inhibition (e.g. ketoconazole, macrolides, fibrates…) → cumulation and sign of toxicity
  - simvastatin only CYP3A4 metabolism –↑ risk of interactions!
- concentrated in liver
- bile excretion; pravastatin also kidney elimination

# STATINS

**I:** hypercholesterolemia with ↑**LDL** (in monotherapy decrease upt o 40%)

- in combination with resins – **LDL decrease up to 60 %**

- **pleiotropic (extralipid) effects of statines:**
  -
  -
  -

**CI:** gravidity, lactation, children (limited knowledge), hepatopathy

# STATINs

**AE: liver impairment:** ↑ of transaminases and creatine kinases (should be monitored)

**skeletal muscles myositis** (0,5% incidence) can lead tok **rhabdomyolysis and renal failure** *(most often after combination of simvastatin + gemfibrozil; generaly after combinations with fibrates and CYP3A4 inhibitors)*

- **<u>interactions!!</u>**

# Statins‘ drug-drug interactions

| CYP 450 | effect | drugs |
|---|---|---|
| **inhibition 3A4** | ↑ statin plasma level | cyclophosphamide, codein cyclosporine, diazepam, keto-conazole, nifedipine, vera-pamil, lidocain, grapefruit juice |
| induction 3A4 | ↓ statin plasma level | barbiturates, carbamazepine, phenytoin, rifampicine, primidone . . . |
| inhibition 2C9 | ↑ statin plasma level | amiodarone, cimetidine, fluoxetine, isoniazide, ketoconazole, metronidazole . . . |
| induction 2C9 | ↓ statin plasma level | barbiturates, carbamazepine, phenytoin, rifampicine . . . |

# NICOTINIC ACID (niacin)

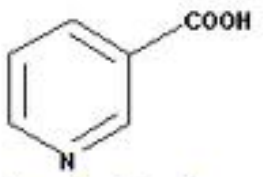
- **derivatives*: acipimox, xantinol nicotinate***

**MofA: decrease TAG synthesis (up to 60 %)** – *not fully described*

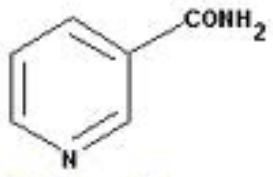
- ↓ VLDL from liver → follow –up by **LDL**,
- necessary ↑↑ doses than in vitamine supplementation

**PK:** water soluble, p.o. readily absorbed, liver metabolism, renal excretion

**I: all types of dyslipoproteinemia** (decrease of TAG level upt ot 60% and CH up to15-30%)



Kyselina nikotinová



Nikotinamid

# NICOTINIC ACID (niacin)

**AE:** typical is **rash phenomenon**

**flushing** (most evident on face and neck - PGD2 release)

- **pruritus** (decreased by ASA administration)
- hyperurikemia (KI gout), GIT disturbances, hyperglycaemia, glycosuria

- *reg. only in **combination with laropiprant** ($PGD_2$ rec.antagonist - blocks rash phenomenon!!!)*

# PROBUCOL

**MofA:** leads to production of **structurally different LDL**

→ **faster elimination** from circulation in comparison to normal LDL

- **antioxidant** – prevents productionof oxidized LDL and thus prevents **foam cells** formation
- ↓ HDL!
- sdecrease LDL-cholesterol up to 15 – 20 %

**PK:** low peroral biolavailability

high liposolubility → elimination in weeks after drug discontinuation

**AE:** GIT disturbances(diarrhoea etc.) headache, vertigo

# 2. Plasma TAG ↓ agents

a. influencing sythesis of VLDL
   - **NICOTINIC ACID**

b. influencing plas,a lipoprotein conversion
   - **FIBRATES**

- physiological plasma levels TAG – 2 mmol/l (1,7)
- ↑↑ **conc.** TAG **– risk of pancreatitis**
- **medium**↑ conc. of TAG in combination with **HDL plasma level beneath 1 mmol/l** – **high risk of atherosclerosis**
- **mild**↑ TAG **- diet + ω3 PUFA**

# FIBRATES

## *fenofibrate, ciprofibrate, bezafibrate*
*(gemfibrozil, clofibrate)*

**MofA:** *PPAR-α* rec. agonists* – **inhibit liver VLDL production and↑ VLDL katabolism** (↑ LPL activity)

- ↓ circulating VLDL (TG) up to 35 % → ↓ total and LDL-cholesterol
- mild ↑ **HDL** (decrease TAG releases the HDL binding capacity for chol. esters)

**I:**

- instead of **familiar hypertriglyceridemia** (type I – LPL deficiency)

**PK:** good intestinal absorption, ↑protein binding., **enterohepatal recirc.** renal excretion

**peroxisome proliferator-activated receptors*

# FIBRATES

**AE:** nausea, vomiting, risk of cholelithiasis (↑CH in bile), myalgia, tiredness

- **dangerous myositis** up to **rhabdomyolysis**, **dysrhytmias** – *↑↑↑risk with statines!*
- ***clofibrate-*** *chronic toxicity* ***(cholelithiasis, ↑ overal mortality)***

**CI:** hepatopathy, ↓ renal functions

# OTHER AGENTS WITH HYPOLIPIDEMIC ACTIVITY

- **ABSORBABLE**
  - esential phosholipides
  - vitamines C and E
  - magnesium
  - heparinoids

- **UNABSORBABLE:**
  - neomycine
  - plant sterols – sitosterol, sitostatol
  - activated charcoal
  - dietary fibre