Lipid-reducing Drugs; Is There a Difference?

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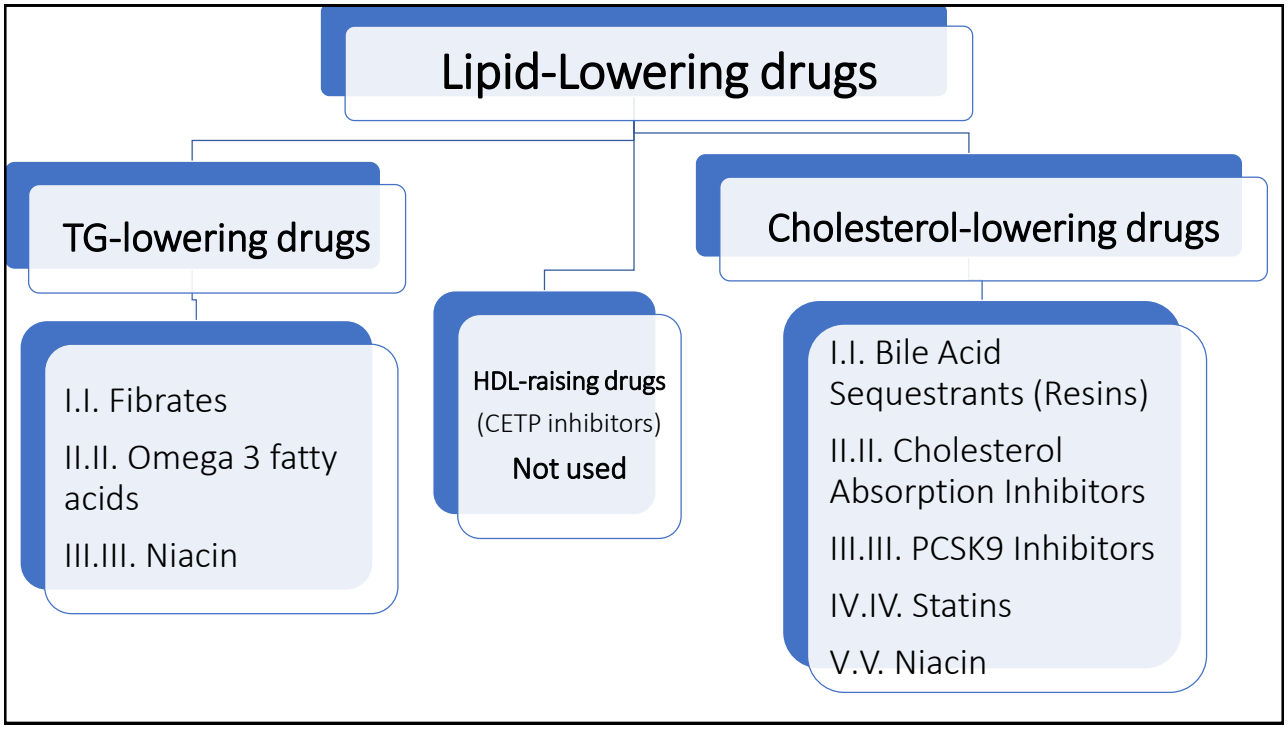
Is There a Difference?

- Lipid lowering drugs encompass a wide spectrum of various families of drugs.
- Each family has its unique properties that are quite different from those of other families.
- Differences are found in the target of action (LDL vs. triglycerides), mode of action, efficacy, tolerability, side effects, drug interactions, even monthly price.
- Even within the same family, we can find obvious differences between different representatives.

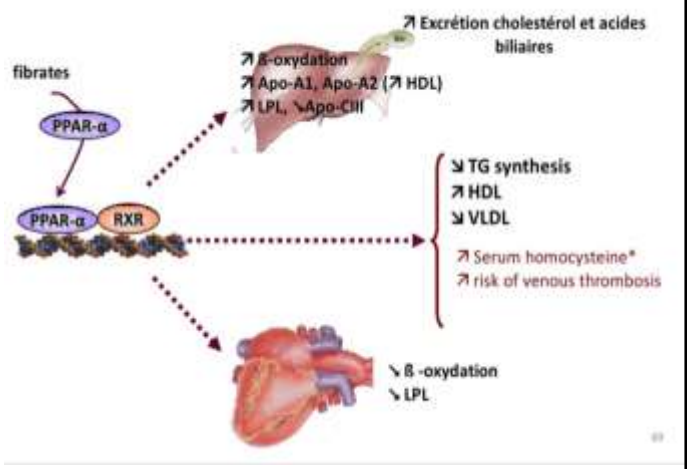


1. Triglyceride-Lowering Drugs

Fibrates

Fibrates (& Omega 3 FAs): Mechanism of Action

- Agonists of peroxisome proliferator-activated receptor-α (PPAR- α).
- Regulate gene expression, acting via transcription factors →
  - ↑ peripheral lipolysis (**lowering TGs**).
  - ↑ hepatic synthesis of apoA1 & apoA2 (**raising HDL**),



Side Effects (Common to all Fibrates)

- Commonest:

1. Gastrointestinal disturbance (< 5%), skin rashes (2%).
2. Myopathy, liver enzyme elevations, and cholelithiasis (esp. with statin combinations) (more with gemfibrozil).

- Less common:

1. Small increases in the incidence of pancreatitis, venous thromboembolism.
2. Rise in serum creatinine and homocysteine.

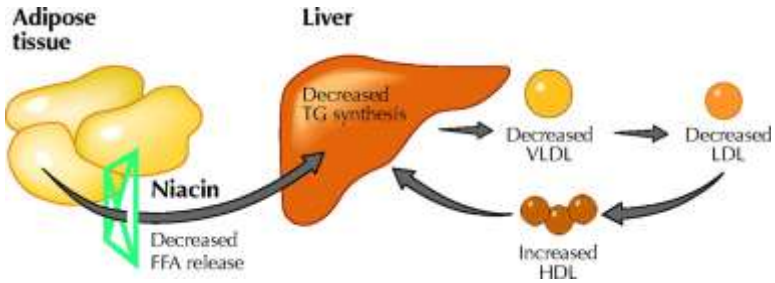
Are all Fibrates the Same?

- Examples: Gemfibrozil, Bezafibrate, Fenofibrate.
- Gemfibrozil: 31% TG reduction, but too many drug interactions (inhibitor of CYP3 A4 hepatic microsomal pathway).
- Bezafibrate: also a PPAR γ agonist, tends to control blood sugar. However, no major long-term outcome trials with clear results.
- ***Fenofibrate***: 30-60% decrease in TG, less drug interactions than gemfibrozil. ***Only one recommended by name by ESC guidelines***.

Nicotinic Acid (Niacin)

Niacin: Mechanism of Action

- Has key action sites in both *liver* and *adipose tissue*.
- *In adipose tissue* (via action on lipase): ↓ mobilization of FFAs from adipose tissues to liver → ↓ substrate for hepatic lipoprotein synthesis.
- *In the liver*: inhibits diacylglycerol acyltransferase-2 (DGAT-2), resulting in ↓ TG synthesis & ↓ secretion of VLDL particles from the liver → consequent ↓ IDL and LDL particles.
- Raises HDL-C by stimulating apoA1 production *in the liver*.

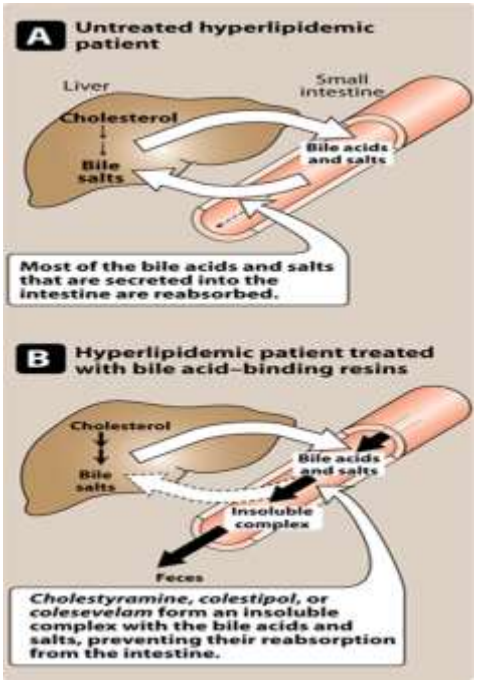


2. Cholesterol-Lowering Drugs

I. Bile Acid Sequestrants (Resins)

Bile Acid Sequestrants (Resins): Mechanism of Action

Bind bile acids in intestine→ prevent absorption of bile acid into the enterohepatic circulation→ bile depletion → liver synthesizes more from hepatic stores of cholesterol →compensatory increase in hepatic LDLR activity → ↓LDL-C levels in blood.



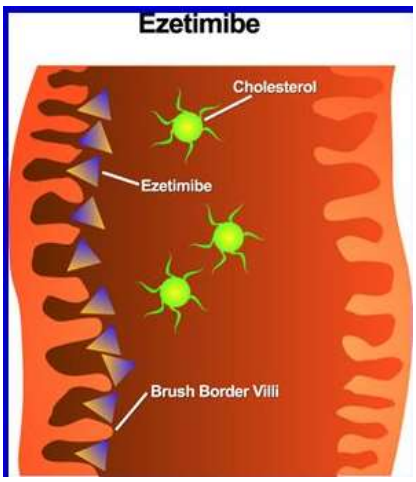
Are all Bile Acid Sequestrants the Same?

- Examples: cholestyramine, colestipol, recently *colesevelam*.
- Colesevelam:
  - ✓newer formulation, better tolerated than cholestyramine
  - ✓fewer drug interactions, can be taken with statins and other drugs.

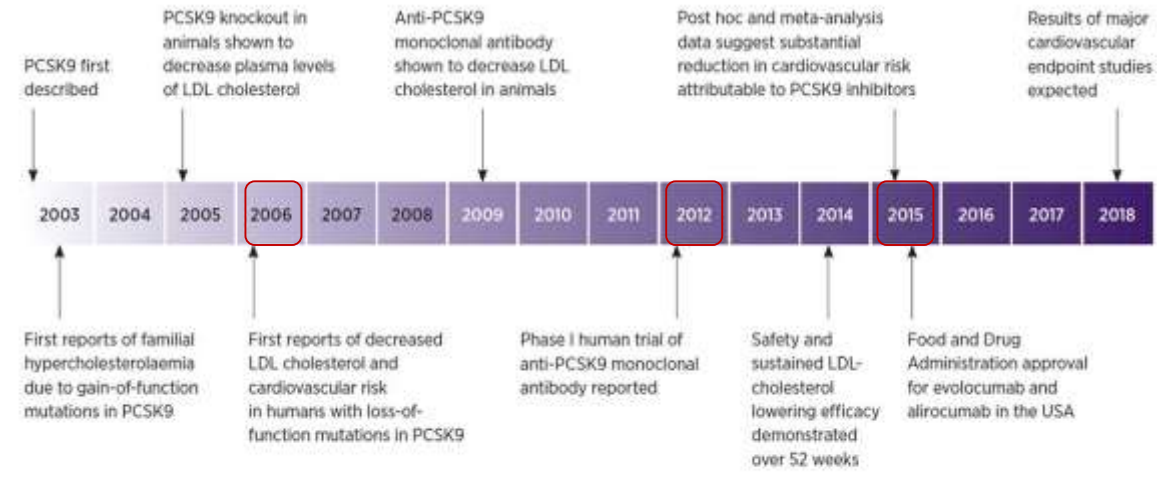
II. Cholesterol Absorption Inhibitors

Cholesterol Absorption Inhibitors: Mechanism of Action

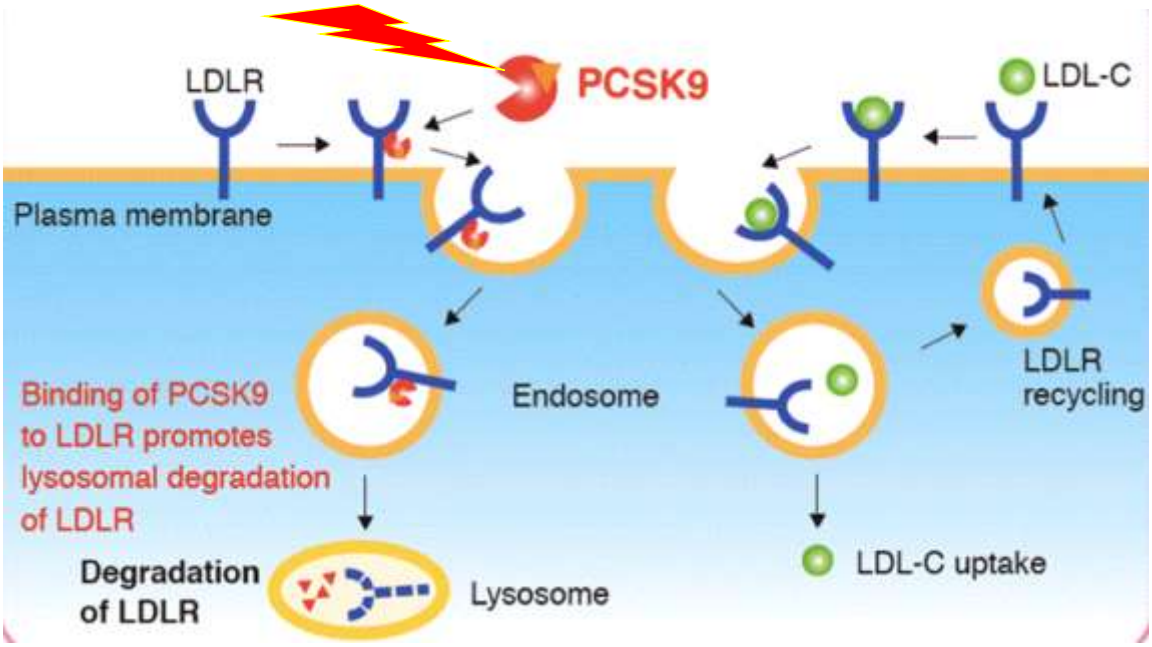
- **Ezetimibe:** inhibits cholesterol absorption at the level of the brush border of the intestine by interacting with the Niemann-Pick C1-like protein 1 (NPC1L1), without affecting absorption of fat-soluble nutrients.



III. PCSK9 Inhibitors



LDL low-density lipoprotein



PCSK9 Inhibitors: Mechanism of Action

- PCSK9 is a protein involved in the control of the LDLR. Higher levels of this protein in plasma → promote (upon binding) the LDLR lysosomal catabolism → ↓ LDLR expression → ↑ plasma LDL-C concentration.
- Lower levels of PCSK9 → ↓ plasma LDL-C levels.

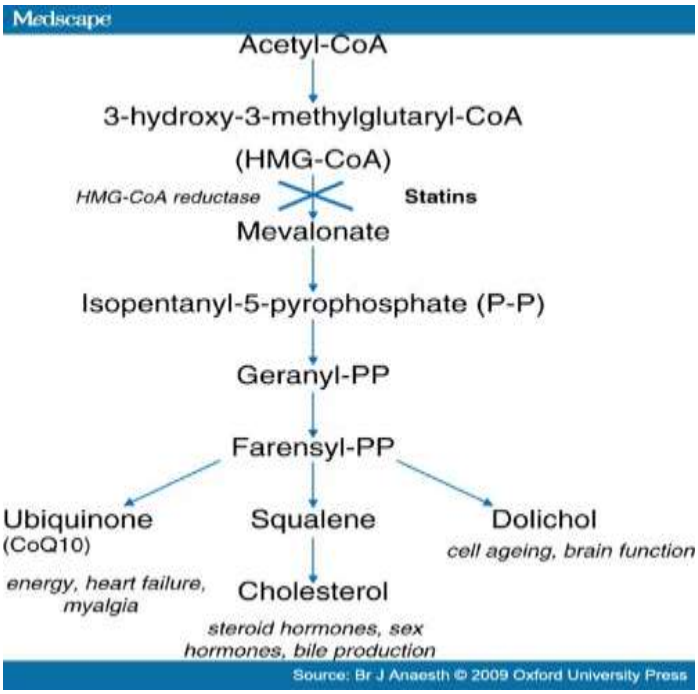
- Therapeutic strategies have been developed mainly using **monoclonal antibodies** (Mabs) that target this protein → reduce LDL-C levels by ≈60%.
- No major effects are reported on HDL-C or plasma TGs.

IV. Statins

1. Statins

Mechanism of action:

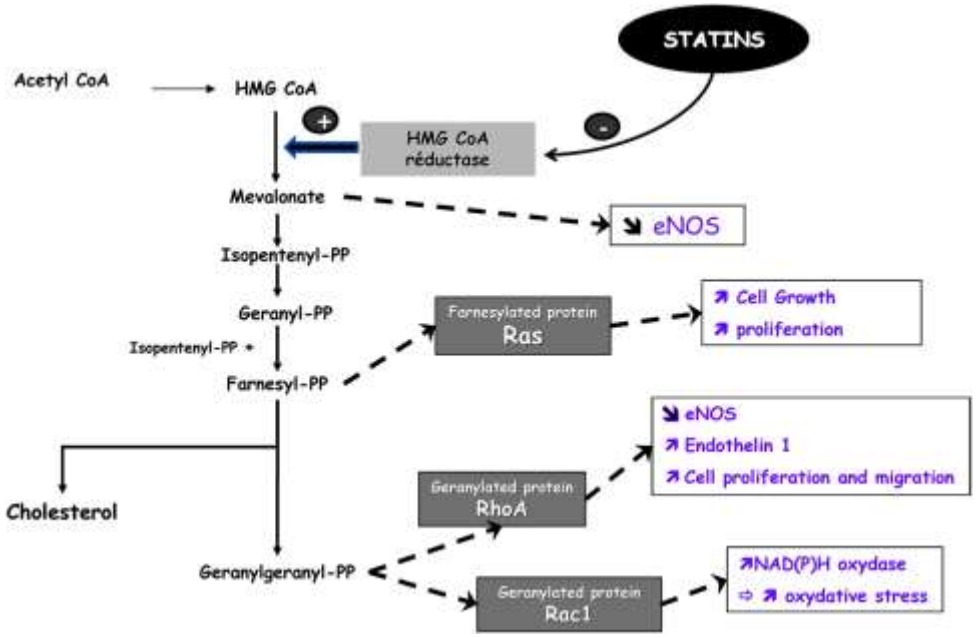
- Competitively inhibit HMG-CoA reductase activity → ↓ cholesterol synthesis in the liver.



Statins: "Pleiotropic Effects"

Pleiotropic = non-lipid effects:

- Improve endothelial function
- Stabilize platelets
- ↓ fibrinogen
- ↓ CRP, anti-inflammatory (inhibit atherogenesis)



Side Effects (all statins with varying degrees)

- **Myalgia** (without CK elevation): (5–10% of patients)
- **Myopathy (CK elevation)**: incidence is low (< 1/10,000)
- ALT & AST elevations (0.5–2.0%)
- Type II DM: incidence may increase with statins
- Minor effects: GI disturbances, headache, fatigue, pruritis
- Contraindicated in pregnancy (FDA Category X)

Cholesterol-lowering Drugs.. Quick Comparison

Quick Comparison..

	Cholesterol Absorption Inhibitors	Bile Acid Sequestrants	Niacin (Nicotinic acid)	PCSK9 Inhibitors	Statins
Mechanism of Action	↓ Cholesterol absorption at intestinal brush border	Bind bile→ ↓bile absorption→ liver uses more cholesterol for bile synthesis	↓ FFA mobilization of from adipose tissues to liver → ↓ hepatic TG synthesis→↓ VLDL, IDL, LDL, & ↑HDL	Monoclonal abs targeting PCSK9 (protein responsible for LDL receptor degradation)→ ↑ LDL receptors	Inhibit HMG CoA reductase (key enzyme in cholesterol synthesis) + "pleiotropic effects"
Examples	Ezetimibe	Cholestyramine, Colestipol, Colesevelam	Niacin	Alirocumab Evolocumab	Simva, Atorva, Lova, Prava, Fluva, Rosuva, Pitava
Group "Star"	Ezetimibe	Colesevelam	Niacin	Alirocumab Evolocumab	Rosuvastatin, Atorvastatin
Efficacy (LDL reduction)	15-20%	18-25%	15-18%	50-70%	Variable 20-60%
Administration	Oral, daily	Oral, daily	Oral, daily	**SC, q 2 weeks**	Oral, daily

Quick Comparison.. (contd)

	Cholesterol Absorption Inhibitors	Bile Acid Sequestrants	Niacin	PCSK9 Inhibitors	Statins
Side Effects	Minimal	GI adverse effects (marked)	Flushing, Pruritis Hepatotoxicity, GI discomfort Glucose intolerance Hyperuricaemia	Itching at injection site Flu-like symptoms Neurocognitive effects (rare)	Myalgia, myopathy Liver enzyme elevation GI symptoms
Drug Interactions	None	Many ↓ absorption of fat-soluble vitamins	-----	Absent	Variable Present
Side effects limit use?	No	**Yes**	**Yes**	No	Sometimes
Price	++	+	+	+++++	+++
Effect on HDL?	No effect	May ↓	↑↑	No effect	Variable, Modest ↑
Guideline recommendations	**II A** (statin intolerance or goal not reached with statins)	**II A** (statin intolerance) **II B** (goal not reached with statins)	---	**II B** (statin intolerance or goal not reached with statins)	**I A**

Are All Statins the Same?

Statins: History

- First isolated from Penicllium citrinum mould (1972).
- Compactin (Mevastatin): 1st to be studied in man.
- Lovastatin (from Aspergillus terreus): 1st to be approved for use in humans.
- Pravastatin, Simvastatin: chemically modified derivatives.
- Pitavastatin, Fluvastatin, Atorvastatin, Rosuvastatin: synthetic products.

Are all Statins the Same?

- Statins differ in their absorption, bioavailability, plasma protein binding, excretion and solubility.
- Lovastatin and simvastatin are prodrugs, whereas the other available statins are administered in their active form.
- Simvastatin, atorvastatin and lovastatin undergo *significant hepatic metabolism via cytochrome P450 isoenzymes* (CYPs), whereas pravastatin, fluvastatin, rosuvastatin and pitavastatin DO NOT.

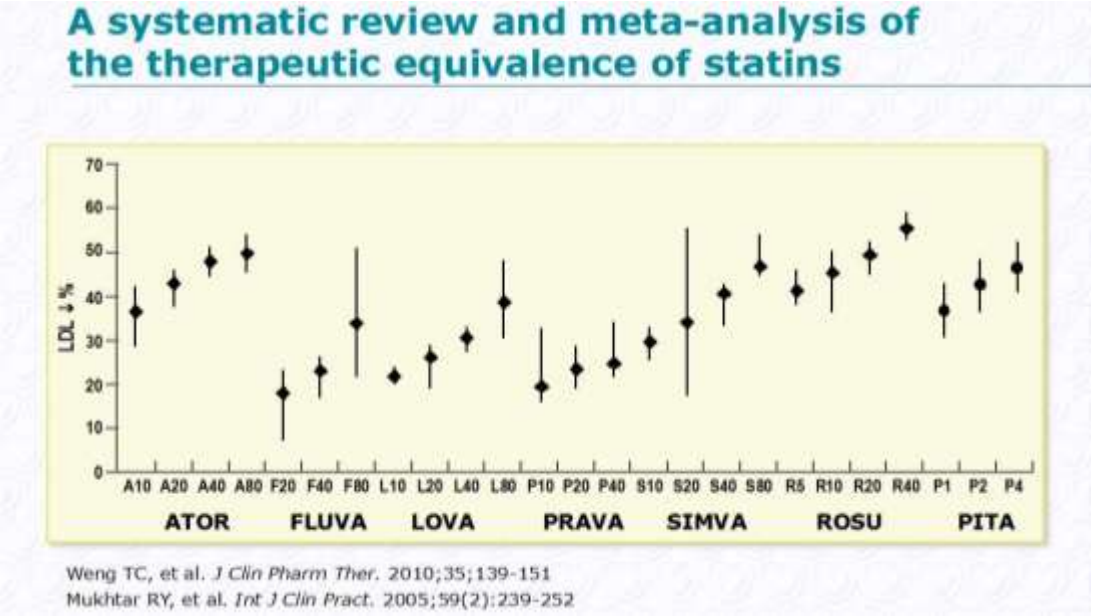
Same Interactions?

- Drugs that inhibit the CYP 450 3A4 microsomal pathway for metabolism→ ↑ risk of myositis & CK elevation with statins that use this pathway.
- Examples: **gemfibrozil**, **amiodarone**, **verapamil**, **diltiazem**, **ranolazine**, azole antifungals, erythromycin, cimetidine, methotrexate, cyclosporins.
- Combinations of statins with **fibrates** may enhance the risk for myopathy. Risk is highest for **gemfibrozil** (better avoided).

Statin Metabolism via Cytochrome P 450 Isoenzymes

	Metabolized via CYP3A4	Not metabolized via CYP3A4
Examples	Simvastatin Atorvastatin Lovastatin	Pravastatin Fluvastatin Rosuvastatin Pitavastatin
Interaction with CYP 450 3A4 inhibitors	Yes	No
Risk of myositis & CK elevation	More	less
Myopathy risk with fibrates	More	less

Same Efficacy (LDL)?



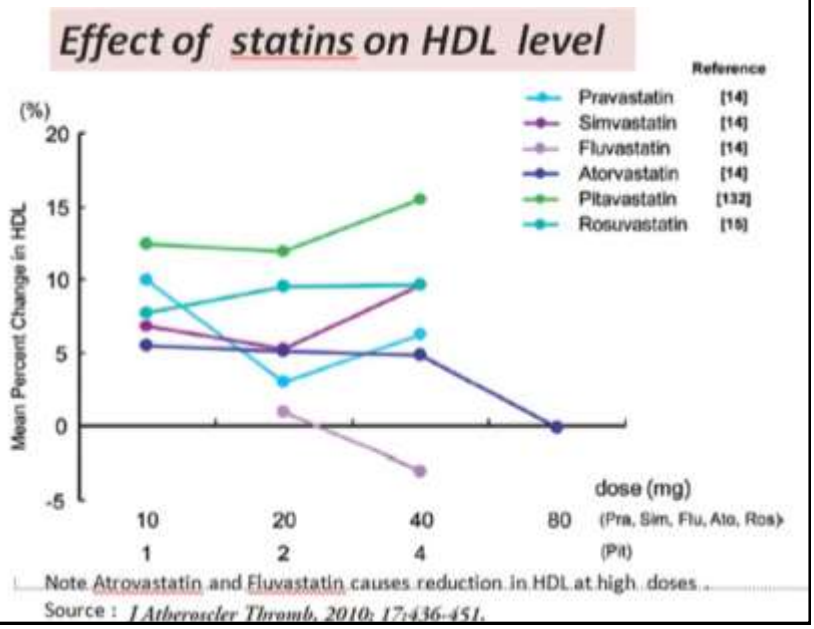
Intensity of Statin Therapy (American Guidelines)

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Same Efficacy (HDL)?



Guideline Recommendations with Different Groups

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Pharmacological treatment of hypercholesterolaemia

Recommendations	Class	Level
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

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European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272
Atherosclerosis 253 (2016) 281-344-d oi:10.1016/j.atherosclerosis.2016.08.018

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Drug treatments of hypertriglyceridaemia

Recommendations	Class	Level
Drug treatment should be considered in high-risk patients with TG >2.3 mmol/L (200 mg/dL).	IIa	B
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	IIb	B
In high-risk patients with TG >2.3 mmol/L (200 mg/dL) despite statin treatment, fenofibrate may be considered in combination with statins.	IIb	C

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Efficacy of drug combinations for the management of mixed dyslipidaemias

A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided.
If TG are not controlled by statins or fibrates, prescription of n-3 fatty acids may be considered to decrease TG further, and these combinations are safe and well tolerated.

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Drug treatments of low high-density lipoprotein-cholesterol is considered

Recommendations	Class	Level
Statins and fibrates raise HDL-C with similar magnitude and these drugs may be considered.	IIb	B
The efficacy of fibrates to increase HDL-C may be attenuated in people with type 2 diabetes.	IIb	B

NB. CETP inhibitors were NOT mentioned in recommendations.


Thank you.