PHARM.D • YEAR 3

Medicinal Chemistry

CHAPTER 7.4

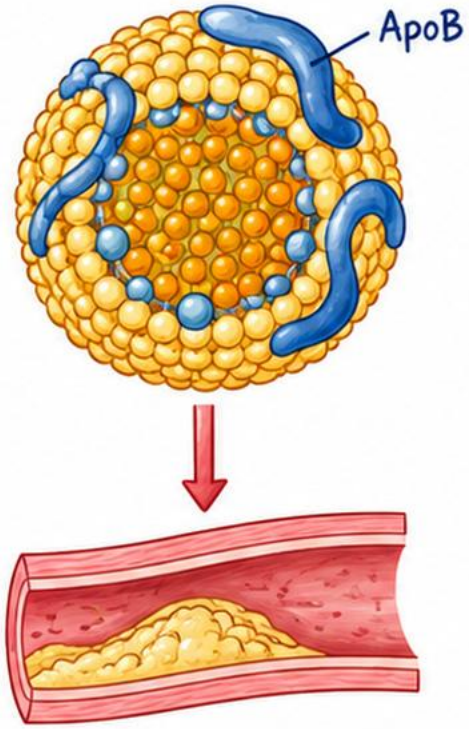
Antihyperlipidemic Agents



PPT CHAPTER COVER

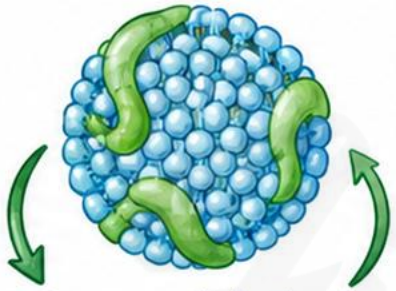
Dyslipidaemia: what the targets mean

LDL
(atherogenic)

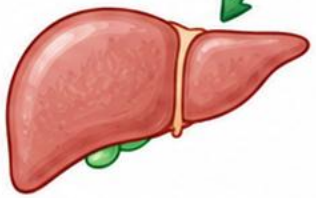


Contributes to atherosclerotic plaque formation

HDL
(protective role)



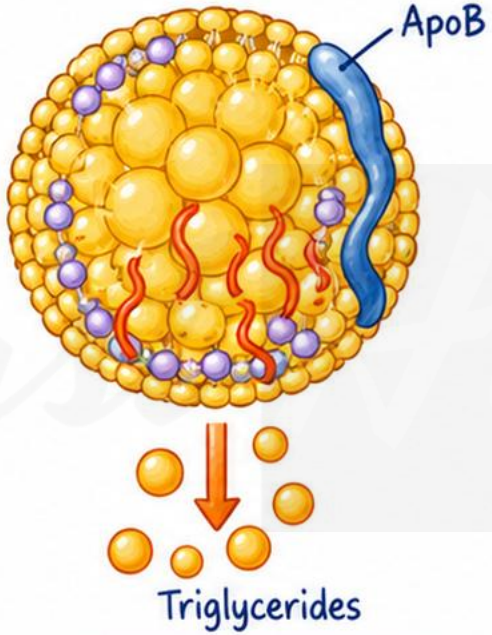
Reverse cholesterol transport



Participates in reverse cholesterol transport

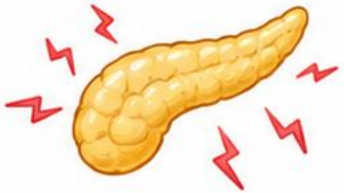
Does not simply sweep intact LDL particles out of blood.

VLDL
(triglyceride-rich)



Triglycerides

Very high triglycerides can increase pancreatitis risk.



What dyslipidaemia includes

- Dyslipidaemia includes elevated LDL cholesterol, elevated triglycerides and other adverse lipoprotein patterns.

Risk and mechanisms

- ApoB-containing particles contribute to atherosclerotic plaque formation.

HDL function

- HDL participates in reverse cholesterol transport; it does not simply sweep intact LDL particles out of blood.

High triglycerides

- Very high triglycerides can increase pancreatitis risk.

Drug selection

- Drug selection depends on the lipid abnormality and overall cardiovascular risk.
- Medicinal chemistry explains how statins, fibrates and bile-acid resins engage different targets.

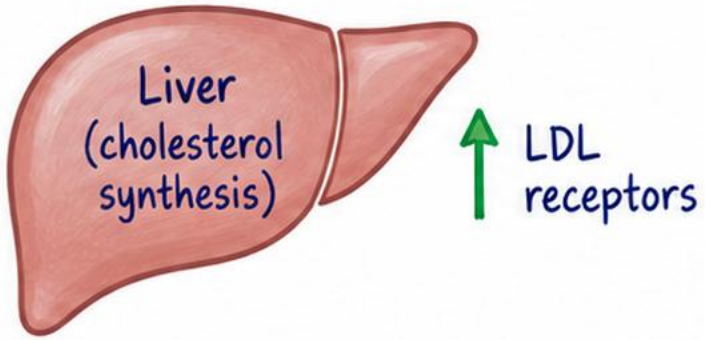
Important note

- A source brand list should not be treated as an individualized treatment plan.

Lipid-lowering classes: three main targets

Statins

- Inhibit HMG-CoA reductase, decreasing hepatic cholesterol synthesis.
- Increase LDL-receptor-mediated clearance.
- Mainly lower LDL.



Fibrates

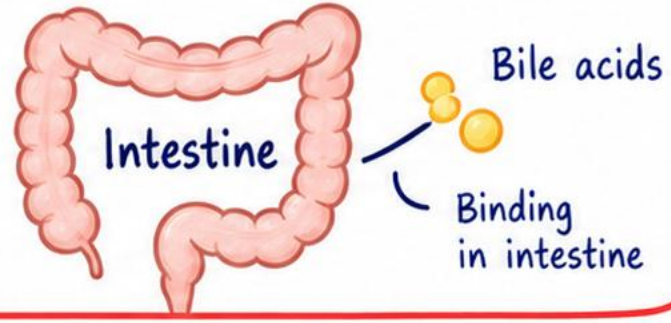
- Activate PPAR-alpha, changing lipid-metabolism gene expression.
- Usually lower triglycerides.



PPAR-alpha
(changes lipid-metabolism gene expression)

Bile-acid sequestrants

- Remain in the intestine and bind bile acids.
- Hepatic bile-acid replacement can increase LDL receptors.
- Lower LDL but may raise triglycerides.
- Resins may raise triglycerides, so they are not general treatments for hypertriglyceridaemia.



Modern table entries such as ezetimibe do not change these core chemical families.

Clofibrate: phenoxyisobutyrate ester

Identity and structure

- Clofibrate is ethyl 2-(4-chlorophenoxy)-2-methylpropanoate, a phenoxyisobutyrate ester.
- The para-chloro phenoxy group and ester-to-acid relationship are the central medicinal-chemistry anchors.

Metabolism

- Ester hydrolysis produces clofibric acid, the pharmacologically relevant acid form.

Mechanism of action

- Fibrate activity is associated with PPAR-alpha activation and altered triglyceride-rich lipoprotein metabolism.

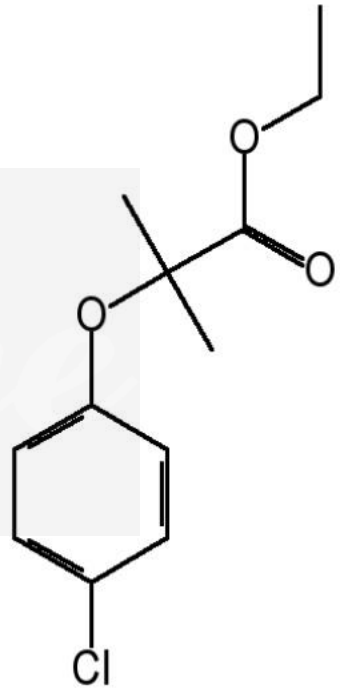
Clinical status

- Clofibrate is mainly a historical teaching example rather than a preferred contemporary lipid medicine.

Limitations

- Gallstones, gastrointestinal effects and adverse outcome concerns limit its role.

Parent/free form: $C_{12}H_{15}ClO_3$



Verified molecular structure

Fibrate SAR and disposition.

Scaffold

Aryloxyisobutyric-acid region is useful for classical fibrates; aromatic substitutions affect lipophilicity and receptor interactions.

Acidic group

Influences binding and disposition.

Clofibrate ester —Hydrolysis→ Clofibric acid

Renal function and interactions

Affect exposure and individual-drug selection.

Muscle and hepatic toxicity

Important cautions, especially with interacting lipid-lowering medicines.

Gallstones

A recognized fibrate concern.

Individual fibrates differ in evidence, kinetics and safety.

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