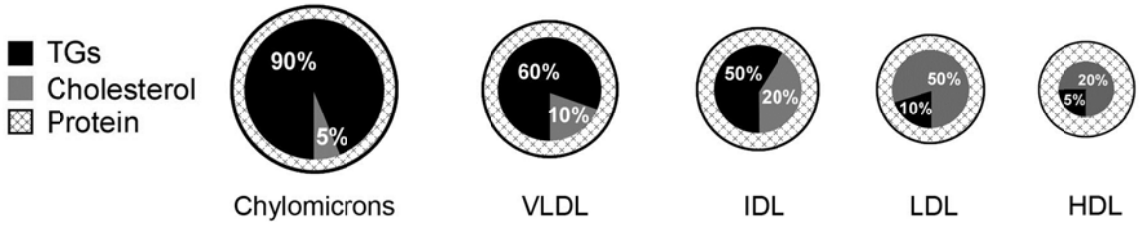
# Chapter 6

# Pharmacology Of The Blood

## Part 1: Hyperlipidemia and drugs that lower plasma lipids

### Basic information

- **Lipoproteins** consist of a hydrophobic lipid core (TGs or cholesterol) surrounded by a hydrophilic coat of phospholipids and proteins (apoproteins), which render them miscible in aqueous plasma.
- There are **5** classes of lipoproteins depending on their relative proportion of the core lipids, type of apoprotein, size, and density:



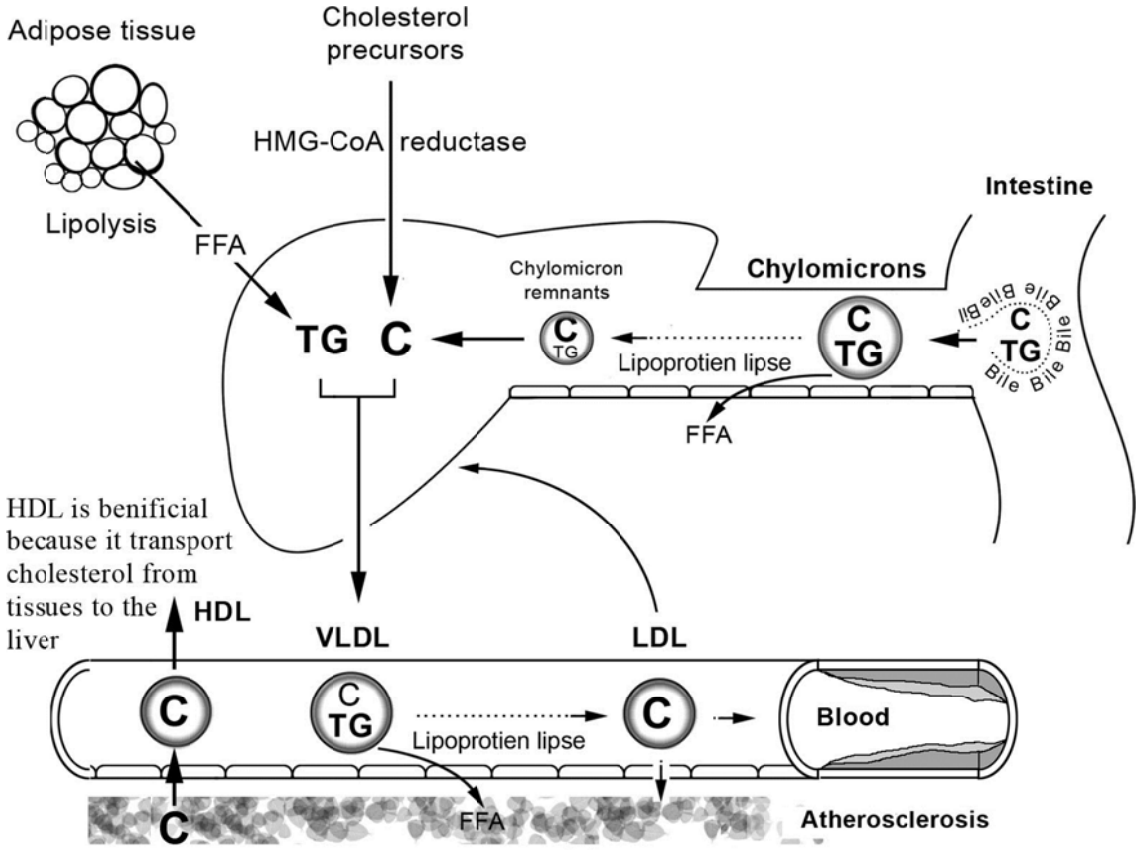

- The **intestine** is the main *source* of lipid precursors. The **liver** is the main site of *synthesis* of lipoproteins. The **adipose tissue** is the main site of *storage* of TGs. Fat cells don't synthesize any lipoproteins.

### Lipoprotein metabolism

- **In the exogenous pathway**, absorbed cholesterol and TGs are transported in plasma as **chylomicrons**. On the vascular endothelium, the core TGs is hydrolyzed by a surface-bound *lipoprotein lipase* into FFA which enter the tissue and utilized. The chylomicrons **remnants** (containing mainly cholesterol) pass to the liver where cholesterol is stored, oxidized to bile acids, or secreted in the bile. Alternatively, it may enter the synthesis of **VLDL**.
- **In the endogenous pathway**, cholesterol and newly synthesized TGs are assembled as **VLDL** and delivered to the blood where TGs core is hydrolyzed by

*lipoprotein lipase* into FFA as described above. The smaller VLDL particles having less TGs and more cholesterol are now termed **LDL**. Cholesterol in the LDL may be: (1) utilized by the tissues; (2) returns again to the liver; (3) deposited subintimal in blood vessels and cause **atherosclerosis**.

- When cells **die**, cholesterol in their plasma membranes is returned to the liver as plasma **HDL** particles. HDL functions as scavenger lipoproteins.




## Classification of hyperlipidemia

- **Primary (familial; hereditary) hyperlipidemia:** is genetically determined.

| Class | Increased lipoprotein | Synonym |
|---|---|---|
| **Type I** | ↑ chylomicrons | Familial chylomicronemia |
| **Type IIa** | ↑ LDL | Familial hypercholesterolemia |
| **IIb** | ↑ LDL and VLDL | Familial combined hyperlipidemia |
| **Type III** | ↑ IDL | Familial dysbetalipoproteinemia |
| **Type IV** | ↑ VLDL | Familial hypertriglyceridemia |
| **Type V** | ↑ VLDL and chylomicrons | Familial mixed hyperlipedemia |

- **Secondary (acquired) hyperlipidemia:**
  - Hypercholesterolemia: hypothyroidism, nephrotic syndrome, and drugs.
  - Hypertriglyceridemia: DM, alcohol, gout, chronic renal failure.

## LIPID LOWERING DRUGS

### Classification of drugs

- **Inhibitors of intestinal cholesterol absorption:**
  - Bile acid binding resins: cholestyramine, colestipol
  - Ezetimibe
- **Activators of plasma lipoprotein lipase:** fibric acid derivatives
- **HMG-CoA reductase inhibitors:** statins.
- **Inhibitors of hepatic lipid production:** nicotinic acid, acipimox
- **Other drugs:** d-thyroxin, neomycin, and probucol

**Drug therapy is indicated in:**

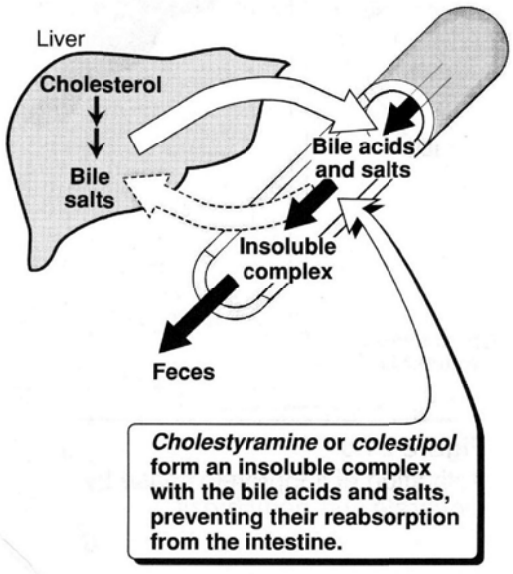
Failure of non-drug therapy.

Primary (hereditary) hyperlipidemia.

## Cholestyramine and colestipol

### Mechanism of action

They form **complexes** with bile acids in the intestine and ↓ enterohepatic absorption of bile salts and ↓ absorption of cholesterol.




### Therapeutic uses

- Hypercholesterolemia **(type IIa):** Bile acid sequestrants are effective in reducing plasma cholesterol (10%–20%) in patients with some normal LDL receptors.
- Diarrhea due to bile acid malabsorption.
- Pruritus due to obstructive jaundice.

### Adverse effects

- GIT upset (the most common): nausea, vomiting and **steatorrhea** (due to ↓ fat absorption).
- ↓ absorption of fat-soluble vitamins.
- ↓ absorption of anionic drugs e.g. digitalis and warfarin.

## Ezetimibe

### Mechansism of action

Ezetimibe is a selective inhibitor of intestinal cholesterol absorption. It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in the bile.

**Therapeutic uses**

Hypercholesterolemia: ezetimibe is synergistic with HMG-CoA reductase inhibitors, producing decrease of 25% in LDL cholesterol.

**Adverse effects**

Reversible hepatic dysfunction: liver function tests should be done at regular intervals.

## HMG-CoA reductase inhibitors (Statins)

**(Lovastatin, Pravastatin, Mevastatin, Atorvastatin)**

**Mechanism of action**

Competitive **inhibition of hydroxy-methyl-glutaryl coenzyme-A** (HMG-CoA) **reductase** → ↓ **cholesterol synthesis** and ↑ hepatic uptake of LDL.

**N.B.**

Statins should be taken at night as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life.

**Therapeutic uses**

- Hypercholesterolemia **(type II).**
- With other drugs for combined hyperlipidemia**.**

**Adverse effects**

**H** : **Hepatic dysfunction** leading to elevation of serum transaminases. Therapy should be stopped if liver enzymes rise > 3-folds the upper normal value.

**M** : **Myopathy, myositis** and **rhabdomyolysis** in both **skeletal** and **cardiac** muscle leading to ↑ of *creatine phosphokinase (CPK)* enzyme.

**G** : **GIT upsets:** nausea, vomiting, anorexia (the most common).

**Co-A** : **Cataract** (lenticular **O**pacity) in middle-**A**ged individuals.

**Reductase** : **R**enal dysfunction (especially with lovastatin).

## Fibric acid derivatives (Fibrates)

**(Clofibrate, Fenofibrate, Bezafibrate, Gemfibrozil)**

**Mechanism of action**

Fibrates act on **nuclear receptors** called *peroxisome proliferator activated receptors-α (PPAR-α)* leading to ↑ synthesis of **lipoprotein lipase** → ↑ peripheral catabolism of **VLDL** and **chylomicrons (TGs).**

**Therapeutic uses:**

- Hypertriglyceridemia **(types IIb, III, IV and V).**
- Fenofibrate has **antidiuretic action** in individuals with mild to moderate diabetes insipidus.

### Adverse effects

- **GIT upsets:** nausea, vomiting (the most common).
- Increase formation of **cholesterol gallstones**.
- **Hepatic dysfunction** and elevation of serum transaminases.
- Fibrates increase the **risk of myopathy** if used in combination with **statins**.
- Skin **rash** and dermatologic reactions.

## Nicotinic acid (Niacin; vitamin B3)

### Mechanism of action

- Niacin (but not nicotinamide) **inhibits lipolysis** in adipose tissue and inhibits **fatty acid synthesis** by the liver → ↓ hepatic **VLDL** and **LDL** synthesis.
- This is distinct from the role of niacin as a vitamin, in which it is converted to nicotinamide and is used for the biosynthesis of the cofactors NAD and NADP.

### Therapeutic uses

In combination with other drugs for **all types** of hyperlipidemia (**except type I** which is mainly treated by diet control).

### Adverse effects

- **Skin flushing** and **burning** sensation (the most common). It is harmless effect mediated by PGs and histamine release and can be diminished by taking aspirin 30 minutes before taking nicotinic acid.
- Gastric irritation (the drug should be avoided in peptic ulcer).
- Hyperglycemia, hyperuricemia, and reversible increase in serum transaminases.

### Summary

| | Effect on LDL | Effect on HDL | Effect on TGs |
|---|---|---|---|
| **Bile acid-binding resins** | ↓↓↓ | ↑ | ---- |
| **Reductase inhibitors** | ↓↓↓ | ↑ | ↓ |
| **Fibrates** | ↓ | ↑ | ↓↓↓ |
| **Niacin** | ↓ | ↑↑↑ | ↓↓ |

### Treatment with drug combinations

| | |
|---|---|
| **Hypercholesterolemia** | Cholestyramine + Reductase inhibitors |
| **Hypertriglyceridemia** | Niacin + Fibrates |
| **Familial combined hyperlipidemia** | Cholestyramine + Fibrates.<br>Cholestyramine + Niacin.<br>Statins + Fibrates *(this combination may ↑ risk of myopathy).* |