PHARMACOLOGY

Lectures 9,10:
Drugs for Hyperlipidemia

OBJECTIVES:

By the end of those 2 lectures the student will be able to:

- Define hyperlipidemia vs normal lipid levels
- Discuss the non-pharmacological treatment of hyperlipidemia
- Classify lipid lowering agents targeting exogenous & endogenous pathways
- Expand on the pharmacology of drugs related to each group
- Hint on adjuvant drugs that can help in lipid lowering

Before studying this lecture, we advise you to study biochemistry lectures of cholesterol metabolism & lipoproteins

PHARMACOLOGY 435

Abbreviations:
C = cholesterol
CM = cylomicrons
LPL= lipoprotein lipase enzyme

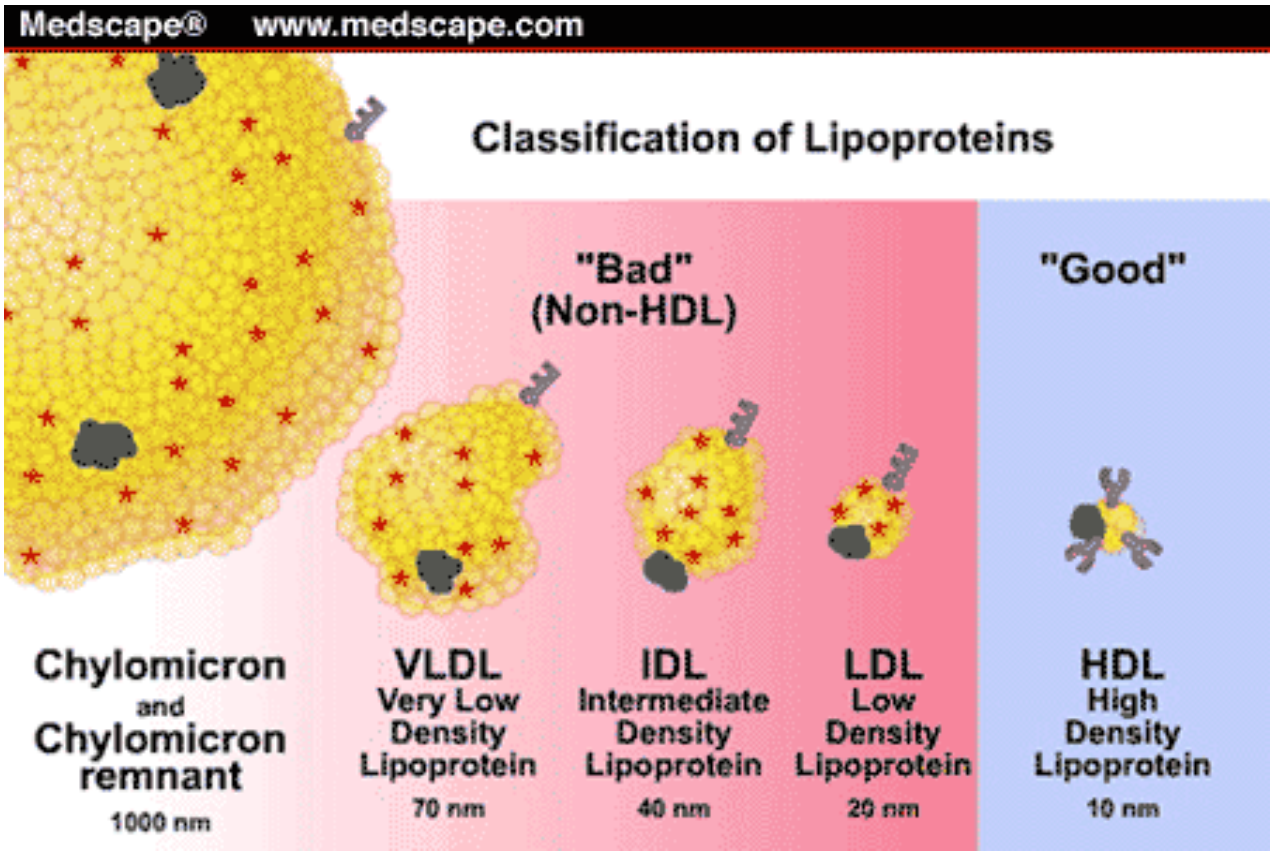
- Important.
- Extra notes.

Introduction to lipids

Origin of lipids

e.g. **Cholesterol (C) & Triglycerides (TG)**

- **endogenous lipids: de novo synthesized in the liver**
- **exogenous lipids: ingested and processed in the intestine (dietary)**



Lipid profile blood tests: detected in serum after a 12-hour fast.

Lipid	Normal Lipid levels
Cholesterol	< 200 mg/dl
Triglycerides	< 220 mg/dl
LDL	< 130 mg/dl (Bad C)
HDL	> 50 mg/dl (Good C, non-atherogenic)

Introduction to Hyperlipidemia

Hyperlipidemia is the most common form of dyslipidemia,
It denotes abnormally increased levels of any or all LIPIDS and/or LIPOPROTEINS [LP] in blood.
Hyperlipidemia is a major cause of atherosclerosis which may lead to CAD and ischemic cerebrovascular disease.

Types of hyperlipidemia :

1- Familial Hyperlipoproteinemia

Which caused by elevated level of one lipid or lipoproteins as the following :

Lipoproteinemia	↑LP	↑Lipids	Risk
Type I	CM	TGs	-
Type IIa	LDL	C	↑
Type IIb	VLDL & LDL	TG & C	↑
Type III	IDL	TGs & C	↑
Type IV	VLDL	TGs	↑
Type V	VLDL & CM	TGs & C	_

2- Secondary hyperlipidemia

Risk factors:

smoking (reduced levels of HDL, cytotoxic effects on the endothelium, increased oxidation of lipoproteins, and stimulation of thrombogenesis)

family history of CVD, Hypertension, obesity, inactivity / lack of exercise, alcohol intake (increases TGs)

DM (increased generation of VLDL and free fatty acids presented to the liver)

Therapeutic strategies for treatment of hyperlipidemia

1-Therapeutic lifestyle changes :

1. **Healthy diet**; optimal Quantitative & Qualitative fat content:
- Diet has <30% of calories as fat, <7% as saturated fat and <200mg cholesterol/day
- Avoid trans-fatty acids & acute increase in C intake
- Use vegetable oils rich in unsaturated fatty acids: oleic acid, linoleic acid & linolenic acids. Diet should also contain **plant stanols** (which interfere with the formation of micellar* cholesterol) & soluble fibers

* **Micelles** are lipid molecules that arrange themselves in a spherical form in aqueous solutions.

- Eat food high in antioxidants vitamins

2. **Regular exercise**
3. **Cessation of hazards habits**; smoking, alcohol, …etc
4. **Losing weight**

Can achieve a fall in LDL-C of 8-15% … but long-term compliance is a problem. Only recommended for patients with non-familial low grade hyperlipidemia

2-Antihyperlipidemic agents :

According to **the mechanism of action**	According to **the site of action**
1- Inhibits cholesterol absorption in the intestine: **Ezetimibe** 2-Sequester bile acids in the intestine: **Exchange resins (AKA bile acid sequestrants)** 3- Inhibits de novo synthesis of cholesterol by Inhibition of HMG CoA reductase (key enzyme for cholesterol synthesis) **Statins (1st drug choice)** 4- Alter relative levels of different plasma LPs **Fibrates, Nicotinic acids**	I-Agents targeting exogenous cholesterol • **Ezetimibe** • bile acid sequestrants: **Colestipol** & **cholestyramine** II-Agents targeting endogenous cholesterol • **Statins** • **Fibrates** • **Nicotinic acid** Adjuvant agents • **Omega-3-Fatty Acids** • **Stanols**

I- agents targeting exogenous pathways

1. BILE ACID SEQUESTRANTS (Are polymeric anion exchange resins)

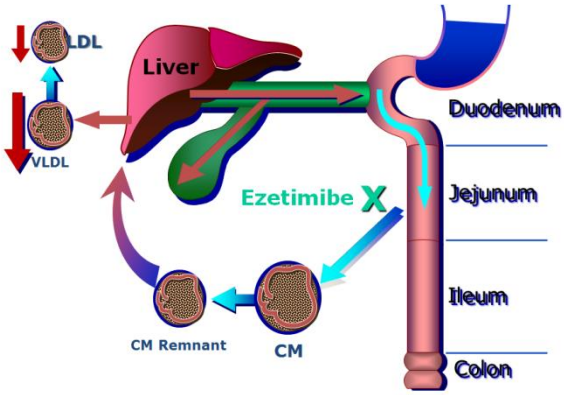
	Cholestyramine	Colesevelam	Colestipol
Overview	• Moderately effective, with excellent safety record • Large MW polymers • can raise triglycerides modestly • Decrease levels of plasma LDL by decreasing intracellular cholesterol concentration. • The concentration of HDL-c is unchanged.		
Mechanism of action	1. Bind to bile acids and bile salts in the small intestine 2. They form resin/bile acid complex which is excreted in the feces (↑10 fold), thus lowering the bile acid concentration. 3. By doing so, they prevent enterohepatic cycling of bile acids 4. This obligates the liver to synthesize replacement bile acids, causing hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile. 5. Consequently, intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol- containing LDL particles (by an up-regulation of cell surface LDL receptors), **leading to a fall in plasma LDL-C.**		
Indication	• **Excellent choice for people who cannot tolerate other types of drugs**		
ADRs	• **They are clinically safe as they are not systemically absorbed** • ↑ GIT bloating, diarrhea, constipation, dyspepsia, abdominal discomfort • ↓ absorption of fat soluble vitamins (A, D, E, K)		
Contra-indications	• Complete Biliary obstruction (because bile is not secreted into the intestine, and thus resins would be of no use) • Chronic constipation • Severe hypertriglyceridemia (TG >400 mg/dL), because the bile acid binding resins can raise triglycerides modestly (about 5%) and thus cannot be used if the triglycerides are elevated.		
Interactions	• ↓ absorption of some drugs : Statins, Ezetimibe, Chlorothiazides, Digoxin, Warfarin. Therefore, these drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after taking resins. • **Colesevelam** hasn't been shown to interfere with other drugs **(best choice for patient on multiple drug regimens)**		

I- agents targeting exogenous pathways (cont.)

1. Inhibition of Cholesterol Absorption in the Intestine by **Selective C Transporter Inhibitors;** Ezetimibe

2. Sequester Bile Acids in Intestine by Sequestrants**:** Colestipol & Cholestyramine

2. Ezetimibe

Mechanism of action	**Selectively inhibits absorption of dietary and biliary cholesterol** in the small intestine, leading to a Decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and lowers LDL by reducing its precursor (VLDL) *** This mechanism is distinct from that of statins, which inhibits de novo synthesis of LDL principally in the liver.** 
Pharmacological action	↓LDL 20%, ↓ TG 8% , ↑ HDL 1-4% no effect on steroids, lipid-soluble vitamins, bile acid. (unlike resins)
Pharmaco-kinetics	Absorbed & conjugated in intestine to active **glucuronide** (> potent) -Reaches peak blood level in 12–14 hours -Its half-life is 22 hours -Undergoes enterohepatic circulation (prolong action of drug) -80% of the drug is excreted in **feces** N.B. Drug level will ↑ if with **statins** & ↓ if with **cholystyramine**
Indications	As Monotherapy: Primary **prevention** of low risk of CHD. (if LDL is very high, statins should be used. Ezetimibe isn't used alone except in modest ↑of LDL) As Combination Therapy; it's safe With: (**statins**; synergistic In moderate/severe ↑ LDL) Or (If must ↓ statin dose because of side effects) Or (With other lipid lowering drugs As **fibrates** **).**
ADRs & Interactions	Not common: • **GIT disturbance** (the main symptoms for most of antihyperlipidemics) • headache, fatigue, arthralgia and myalgia. • Seldom reversible impairment of hepatic function

II-Agents targeting endogenous cholesterol

Statins (HMG-Co A Reductase Inhibitors)

	Simvastatin	Lovastatin	Atorvastatin	Pravastatin	Rosuvastatin

Overview

- the most effective & best-tolerated agents for treating hyperlipidemia
- first-line drugs when **LDL-lowering** drugs are indicated
- they cause modest decrease in plasma TG and slight ↑ in HDL-C)

- ↓LDL 18-55%
- ↑ HDL 5-10%
- ↓ TG & VLDL 10-30%

Mechanism of action :

1. **potent competitive inhibitors of HMG-CoA reductase, which catalyzes a rate-limiting step in de novo hepatic cholesterol synthesis. Thus, HMG-Co A is not converted to mevalonic acid, reducing cholesterol. And Because C is required for the synthesis of VLDL (the precursor of LDL-C), production of VLDL & LDL will decrease.**
2. **The liver compensates for this decrease in cholesterol by ↑ the number of LDL receptors on the surface of hepatocytes (upregulation of LDL- R), This results in ↑ removal of LDL from the blood and lowering of serum LDL- C levels.**

Advantages

Pleiotropic effects of statins (Beyond cholesterol lowering):

- improvement of endothelial function,
- increased nitric oxide bioavailability & antioxidant properties,
- inhibition of inflammatory & thrombogenic responses,
- stabilization of atherosclerotic plaques
- Furthermore, statins have beneficial extrahepatic effects on the immune system, CNS, and bone.

indication

❖ Monotherapy :

Primary Prevention :

1- Patients with hyperlipidemia and with other risks for ischemic insults.

2. **Type IIa Hyperlipoprotinemia**. If there is no control, combine (bile acid sequestrants / ezetimibe, niacin,..) to decrease **cholesterol** .

Secondary Prevention :

In all ischemic insults : [stroke, ACSs up to AMI, …..etc.]

So given from 1st day of ischemic attack (stabilize plaques)

❖ Combination therapy

1. Mixed dyslipidemias; Added to fibrates or niacin if necessary.
   (because the use of a statin alone may be insufficient for the treatment of mixed dyslipidemia, which is characterized by low levels of HDL-C and elevated levels of TG with or without ↑ LDL-C.)
2. In diabetics and patients with insulin resistance [metabolic syndrome]. Because these patients will possess small dense LDL (severely atherogenic) with evident endothelial dysfunction & increased thrombotic profile. (due to its **Pleiotropic effects)**

statins (cont.)

Pharmaco-kinetics

- Most statins have a **high first-pass** clearance by the liver
- Greater than 95% of most of these drugs are **bound to plasma proteins** with **short half-life**
- Drug-drug interactions involve specific interactions with the cytochrome **P-450** drug metabolizing system, especially **CYP3A4**
- All statins are taken orally at bedtime because hepatic cholesterol synthesis is maximal between midnight and 2:00 a.m. , **except atorvastatin** taken at any time because of its long half-life (14 hours)

ADVERSE EFFECTS

- **Common**: Headache , myalgia, fatigue, GI intolerance, and flu-like symptoms
- **Hepatotoxicity**, raised concentrations of liver enzymes (serum aminotransferases)
- **Teratogenicity**, statins should be avoided during pregnancy

❖ Myopathy:

- Muscle aches, or weakness associated with an elevation of creatine kinase (CK) released from muscles, are the best indicator of statin-induced myopathy.
- Failure to recognize myopathy and to discontinue drug therapy can lead to rhabdomyolysis (the destruction of striated muscle cells), myoglobinuria, and acute renal necrosis.

lab investigations

It is important to check CK & liver enzymes regularly upon administration of statins.

1. ↑ Creatine kinase activity (index of muscle injury) :
Measured only if myalgia or myositis develops. if CK increases 3-5 folds, we decrease statin doses / omit combination with fibrates…..
2. ↑Serum aminotransaminase, can progress to evident hepatotoxicity. So lab investigations are recommended every 6 month. if levels increase up to 3 folds at any time, statin must be stopped then dose adjusted.

Inter-actions

❖ Statins **potentiate** the action of oral **anticoagulant** and **anti-diabetic** drugs (by displacement from plasma protein binding sites (activation))

❖ Drugs that increase the risk of statin-induced myopathy include:

- Other antihyperlipidemics (fibrates)
- Drugs metabolized by 3A4 isoform of cytochrome P450: erythromycin, verapamil, cyclosporin, ketoconazole.

Pravastatin and fluvastatin are the statins of choice in patients taking other drugs metabolized by cytochrome 3A4 system.

Main ADRs & contraindication:

II-Agents targeting endogenous cholesterol

Niacin (Nicotinic Acid):

Definition

- Water soluble B-complex vitamin with multiple actions
- **most effective** medication for **increasing HDL** cholesterol levels and it has positive effects on the complete lipid profile

Mechanism

- In adipose tissue: it binds to adipose nicotinic acid receptors, this will lead to decrease in free fatty acids mobilization from adipocyte to the liver resulting in ↓ TG and thus ↓ VLDL synthesis
- In liver: Niacin (Nicotinic acid) inhibits hepatocyte diacylglycerol acyltransferase-2 (a key enzyme for TG synthesis) → it decrease VLDL production (by decreasing TG synthesis & esterification)
- In plasma : it increase LPL activity that increase clearance of VLDL & chylomicron
- Niacin also promotes hepatic apoA-I production and slows hepatic clearance of apoA-I and HDL (most favorable effect)

Pharmaco-logical Actions

- Effect on VLDL : ↓ VLDL by :

1- ↓ synthesis in liver
2- increased clearance in plasma
3-↓ mobilization of free fatty acids from adipose tissue

- Effect on LDL : ↓ LDL due to reduction in its precursor (VLDL)
- Effect on HDL : induces a **large** increase in HDL-C (The catabolism of HDL can be inhibited by nicotinic acid through a mechanism that is largely unknown)

Indications

- Monotherapy or in combination with fibrate, resin or statin
- **Niacin exerts greatest beneficial effects on wide range of lipoprotein abnormalities:**

• Type IIA hypercholestrolemia - Type IIB hypercholesterolemia & any combined hyperlipidemia
• Patient with hypertriglyceridemia & low HDL-C.
• Hyperchylomicronemia.
• mixed dyslipidemia

Adverse effects

- Most common: Sensation of warmth & cutaneous flushing (prostaglandin-induced vasodilation) → (can be avoided by low dose of **Aspirin** half-an-hour before the use of niacin, because it blocks prostaglandin).
  N.B Slow release formulations→ ↓incidence of flushing
- Pruritus, rash, dry skin
- **GIT disturbance:** Dyspepsia: nausea, vomiting, reactivation of peptic ulcer (↓ if taken after meal).
- **High dose:**

• Reversible ↑ liver enzymes → hepatotoxicity.
• Impairment of glucose tolerance → Hyperglycemia in diabetes patients (don't give to diabetes patient).
• ↑ uric acid. (thus contraindicated in patients with gout)

Contra-indications

Gout – Peptic ulcer – Hepatotoxicity – Diabetes mellitus

II-Agents targeting endogenous cholesterol

Fibrates	They are Peroxisome proliferator activator receptor [PPARa] Agonists, which are a class of intracellular receptors that modulate fat metabolism.		
Mechanism	They increase gene transcription for **lipoprotein lipase (LPL)** leading to increased catabolism of TG in VLDL and chylomicrons		
Drugs	**Clofibrate**	**Fenofibrate**	**Gemfibrozil**
Pharmacological action	• ↑ LPL activity → increases clearance of VLDL & chylomicron in plasma • ↑ HDL (by increasing the production of the apoprotein components of HDL) • ↑ LDL-C uptake by the liver (↓ LDL in plasma) • ↓ **TG .** due to ↓ VLDL • ↑FFA uptake by the liver • ↓ Vascular inflammation • Improve glucose tolerance • ↑ excretion of hepatic C in bile, thus endogenous hepatic C synthesis may be decreased.		
Indications	1st-line defense for: • Mixed dyslipidemia (i.e. raised serum TG and C) • Patients with low HDL and high risk of atheromatous disease (often **type 2 diabetic patients)** • Patients with severe resistant dyslipidemia (combination with other lipid lowering drugs).		
Adverse effects	• **GIT** (indigestion, abdominal pain, diarrhea) • Rash, urticaria, hair loss • **Myositis** : can occur resulting in weakness and tenderness of muscles, Myalagia, Myositis, Rhabdomyolysis ➔Acute renal failure ➔ Occurs: -In alcoholics, -If combined with **statins** (each –ve metabolism of other) -In impaired renal function • **Gallstones**: fibrates, especially Clofibrate increases C content of bile, predisposes to gallstones**, and its use is therefore limited to patients who have cholecystectomy**		
Contraindications	• Pregnant or nursing women (cause teratogenicity, but not as severe as statin) • Renal impairment. • Gall-bladder disease. • In alcoholics		
Interactions	- increase risk of myopathy when combined with statins . (↓ **metabolism of statins ➔ toxicity ➔ myalgia, myositis) . Give lower doses** - Displace drug from plasma proteins. e.g. oral anticoagulants (**warfarin ↑ bleeding tendency ➔ anticoagulant dose must be adjusted)** and oral hypoglycemic drugs)		

Combinations & adjuvants

Antihyperlipedemic combinations:

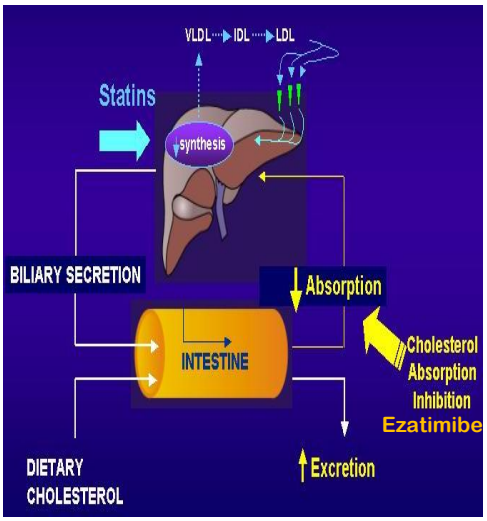
Indications:

1. **Severe hypertriglycerdemia or severe hypercholesterolemia**
2. **To take lower doses of each drug**
3. **High LDL or VLDL not normalized with a single drug** (failure of monotherapy)

Resins: decreases the absorption of statins and ezetimibe, Therefore, these drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after taking resins.

Statins & Fibrates

- **Contraindicated (in full dose) because the incidence of myopathy may increase**
- **So, use not more than ¼ maximum dose of statin and use pravastatin (Pravastatin and fluvastatin are the statins of choice in patients taking other drugs metabolized by cytochrome 3A4 system)**



Statin & ezetimibe (synergistic combination)
- Statin blocks synthesis of endogenous cholesterol while ezetimibe blocks exogenous cholesterol

Adjuvants in Hyperlipidemia

The adjuvant	**Omega -3-FA** (found in fish oils containing highly unsaturated FA)	**β---Sitosterol** (found in plants with structure similar to cholesterol)
Mechanism of action and Pharmacological Effect	• ↓ enzymes involved in TG synthesis . • ↑ beta-oxidation of FFA Lead to decreases TG . • ↓ platelet function • Prolongation of bleeding time • Reduction of plasma fibrinogen • Anti -inflammatory effects it gives Some vascular protection	They work by mimicking cholesterol and competing with it for dietary & biliary Absorption, thereby ↓ LDL levels up to 10%
Indication	**Adjunctive treatment of very high TGs**	Given as food supplement before meal in **Hypercholesterolemia**

Summary

Drug Class	Agents	Effects (% change)	Side Effects
HMG CoA reductase inhibitors	Lovastatin Pravastatin	↓LDL (18-55), ↑ HDL (5-15) ↓ Triglycerides (7-30)	Myopathy, increased liver enzymes (hepatotoxicity)
Cholesterol absorption inhibitor	Ezetimibe	↓ LDL(14-18), ↑ HDL (1-3) ↓Triglyceride (2)	Headache, GI distress
Nicotinic Acid (Niacin)		↓LDL (15-30), ↑ HDL (15-35) ↓ Triglyceride (20-50)	Flushing (+aspirin) Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity
Fibric Acids	Gemfibrozil Fenofibrate	↓LDL (5-20), ↑HDL (10-20) ↓Triglyceride (20-50)	Dyspepsia, gallstones, myopathy
Bile Acid sequestrants (Resins)	Cholestyramine	↓ LDL no change in HDL(slight increase) ↑ Triglyceride	GI distress, constipation, decreased absorption of other drugs

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reductase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	↑
Cholesterol absorption inhibitor	↓	↑	↓

Figure 23.12
Characteristics of antihyperlipidemic drug families. HDL = high-density lipoprotein; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein.

THANK YOU FOR CHECKING OUR WORK

435 PHARMACOLOGY TEAM

Quiz

لولوه الصغير
شادن العمران
لمى الزامل
كوثر الموسى
ديمه الراجحي
جواهر الحربي
دلال الحزيمي
رنيم الدبيخي
نورة الصومالي
منيرة السلولي

شماء السعد
رهف بن عبّاد
سارة الخليفة
ساره المطوع
فاطمة الدين
آية غانم
أسرار باطرفي
نوف العبدالكريم
وضحى العتيبي
ريما الحيدان

عبدالرحمن السياري
أحمد اليحيى
خالد الزهراني
عبدالله الجنيدل
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