الادوية الخافضة للشحوم

Antihyperlipidemic Agent

يعتبر نمط الحياة الصحي أول خط دفاع ضد ارتفاع الكوليسترول في الدم . غير أنه أحياناً لا يكفي النظام الغذائي والتمارين الرياضية. وقد تحتاج كذلك إلى تناول أدوية للكوليسترول للمساعدة على ما يلي :

- **الحد من نسبة كوليسترول البروتين الدهني منخفض الكثافة LDL**، وهو الكوليسترول "الضار" الذي يزيد من خطر الإصابة بأمراض القلب
- **الحد من الدهون الثلاثية**، وهو نوع من الدهون في الدم يزيد أيضًا من خطر الإصابة بأمراض القلب
- **زيادة نسبة كوليسترول البروتين الدهني مرتفع الكثافة HDL**، وهو الكوليسترول "النافع" الذي يقي من أمراض القلب

Lipoprotein levels

The optimal level for LDL cholesterol is < 100 mg/dL.

It is considered high when it is **≧ 160 mg/dL**.

HDL cholesterol should ideally be < 40 mg/dL.

It is considered high if it is **> 60 mg/dL.**

Total cholesterol should be < 200 mg/dL.

It is considered high if it is **> 240 mg/dL.**

Goals for Lipids

- LDL
  - < 100 →Optimal
  - 100-129 → Near optimal
  - 130-159 → Borderline
  - 160-189→ High
  - ≥ 190 → Very High
- Total Cholesterol
  - < 200 → Desirable
  - 200-239 → Borderline
  - ≥240 → High
- HDL
  - < 40 → Low
  - ≥ 60 → High
- Serum Triglycerides
  - < 150 → normal
  - 150-199 → Borderline
  - 200-499 → High
  - ≥ 500 → Very High

The story of lipids

- Chylomicrons transport fats from the intestinal mucosa to the liver
- In the liver, the chylomicrons release triglycerides and some cholesterol and become low-density lipoproteins (LDL).
- LDL then carries fat and cholesterol to the body's cells.
- High-density lipoproteins (HDL) carry fat and cholesterol back to the liver for excretion.

- When oxidized LDL cholesterol gets high, atheroma formation in the walls of arteries occurs, which causes atherosclerosis.
- HDL cholesterol is able to go and remove cholesterol from the atheroma.
- Atherogenic cholesterol → LDL, VLDL,IDL

Dyslipidemia and Related Diseases

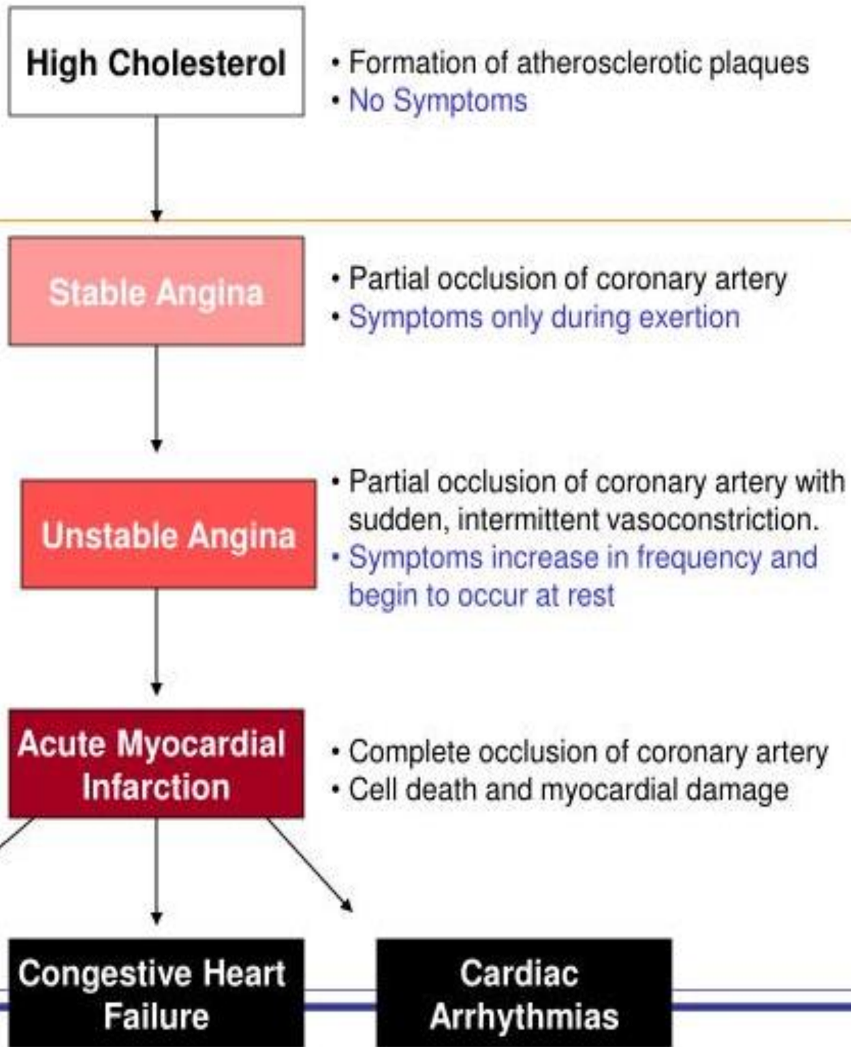
Dyslipidemia **is a general term used to describe high levels of LDL cholesterol (LDL-C) or triglycerides, or low levels of HDL cholesterol (HDL-C).**

Dyslipidemias are major contributors to atherosclerosis and atherosclerosis-related conditions, such as coronary heart disease (CHD), ischemic cerebrovascular disease, and peripheral vascular disease.

Genetic disorders and life-style may contribute to the dyslipidemias.

Therapy for dyslipidemias is based on the blood levels of LDL-C, HDL-C, and triglycerides (found mainly in VLDL cholesterol)

TYPICAL PROGRESSION OF EVENTS IN CLASSIC ANGINA PECTORIS



• Consequences of damage to the heart

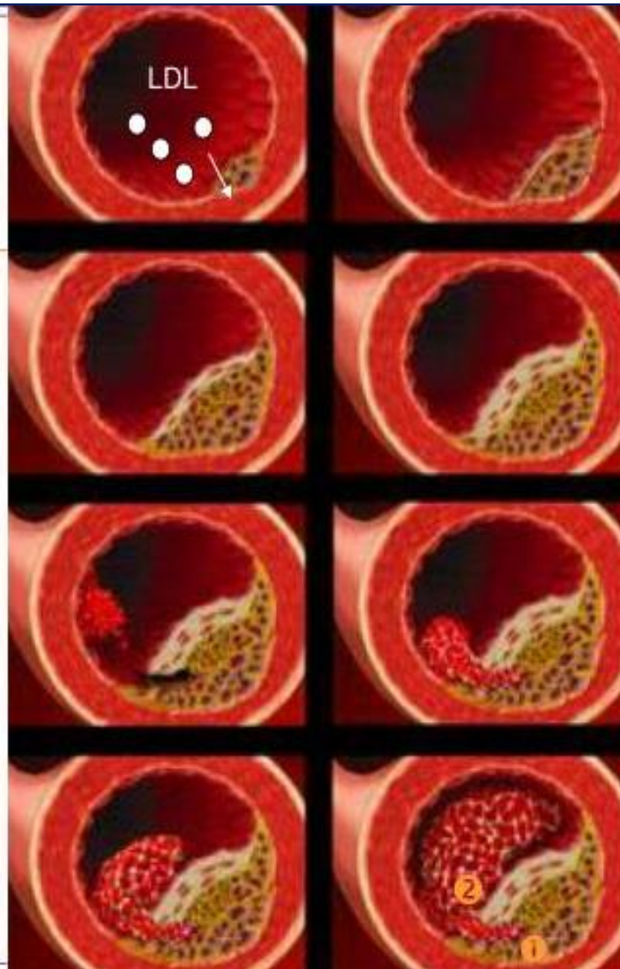
ATHEROSCLEROSIS

LDL from the blood penetrates the arterial walls and accumulates in smooth muscle cells in the form of cholesterol esters.

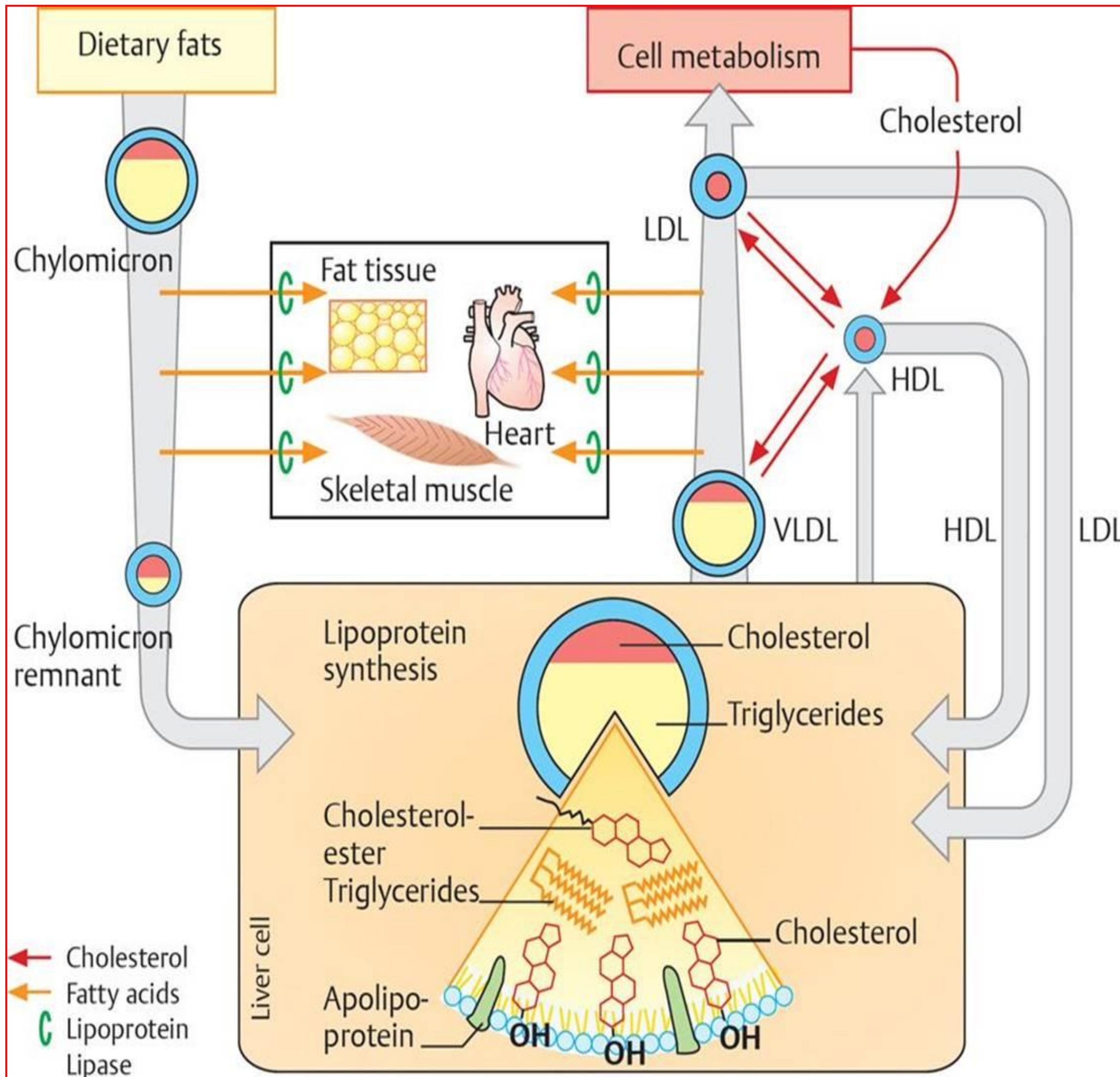
These smooth muscle cells along with activated macrophages are transformed into lipid-filled foam cells.

These foam cells shear off with constant blood flow and pull of parts of the vessel walls along with them, exposing underlying tissue

The end result is a plaque with a center consisting of ❶ cholesterol deposits and cell components and ❷ a "cap" consisting of aggregated platelets and fibrin.



Lipoprotein metabolism.



Enterocytes release absorbed lipids in the form of triglyceride-rich chylomicrons. These are acted upon by lipoprotein lipases in endothelial cells, producing fatty acids, which are stored in tissues. The remnants of chylomicrons are transported to liver cells, where they are a source of dietary cholesterol. The liver uses this and hepatically produced cholesterol to synthesize very-low-density lipoproteins (VLDLs) and bile acids. VLDLs are released into the blood and supply tissues with fatty acids. The low-density lipoprotein (LDL) remnants either return to the liver or supply cells with cholesterol. (HDL, high-density lipoprotein.)

Antihyperlipidemic Therapy

- **Initial therapy is to institute lifestyle changes,**
- including **reduction of dietary intake of cholesterol and saturated fats**
- **increased intake of soluble fiber and plant sterols**.
- In addition, **weight management and increased physical activity should be initiated.**
- **If these are insufficient to lower LDL-C to the desired level, drug therapy is indicated.**

The National Cholesterol Education Program has established guidelines for initiation of drug therapy in dyslipidemias based on the **blood levels of the lipoproteins after an overnight fast**. The presence of other major risk factors, such as **cigarette smoking**, **hypertension,** low **HDL-C (< 40 mg/dL),** family history of **premature CHD,** and **age**, determine the level to which cholesterol should be lowered

Antihyperlipidemic Drugs

Antihyperlipidemic drugs are used to **hyperlipidemias** or **hyperlipoproteinemias** and conditions characterized by elevated plasma levels of cholesterol or triglycerides, for example**, type 2 diabetes, metabolic syndrome**, and **hypertriglyceridemia.** Diabetics usually have high triglycerides, moderate elevations of total cholesterol and LDL-C, and low HDL-C.

Metabolic syndrome

Metabolic syndrome is a combination of medical disorders that increases the risk of developing atherosclerotic disease, for example, coronary heart disease, peripheral vascular disease, and stroke. It also increases the risk of developing type 2 diabetes. Its etiology is unknown, but weight, advancing age, lifestyle factors, and genetics are all known to be involved. Signs of metabolic syndrome include fasting hyperglycemia, hypertension, abdominal obesity, high levels of triglycerides, and low levels of HDL-C. Treatment primarily involves weight management and increasing exercise, then drug management for hypertension, diabetes, and to correct lipid levels as appropriate.

تصنيف خافضات الشحوم :

تصنف حسب آلية التاثير الى عدة مجموعات :

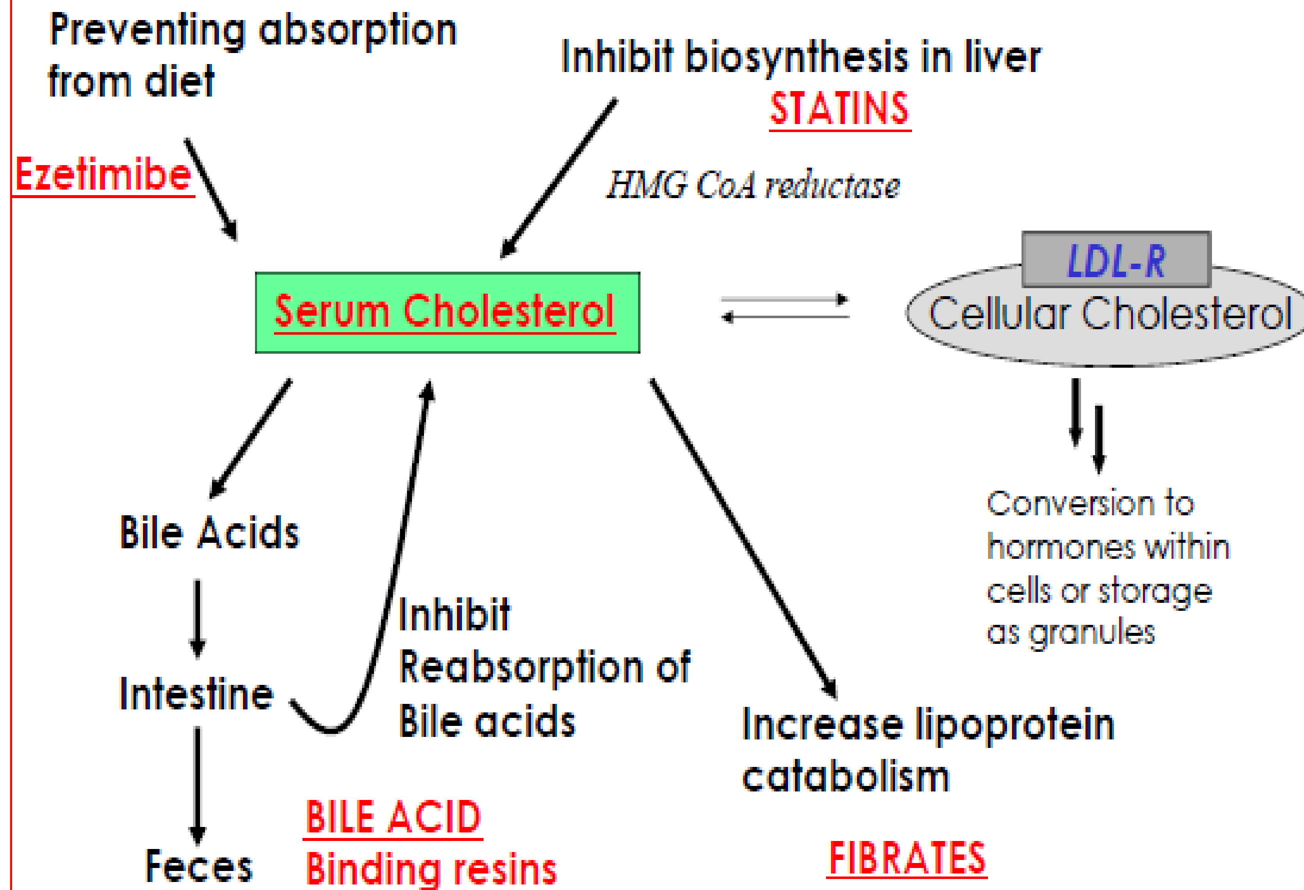
١ – **مجموعة الفيبرات :** تزيد من تحطم الليبوبروتين

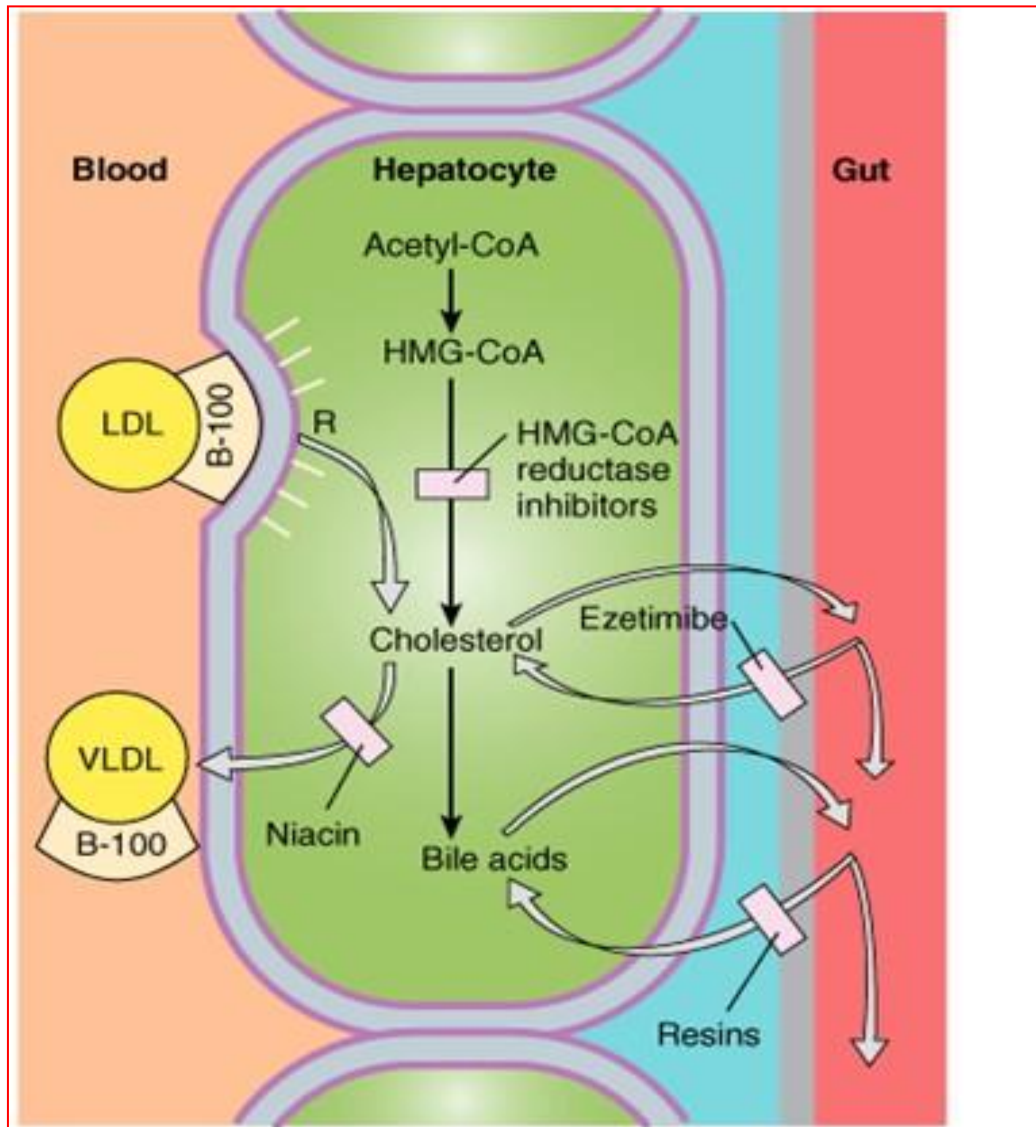
٢ – **مجموعة الستاتينات :** تمنع الاصطناع الحيوي للكولسترول في الكبد

٣ – **الراتنجيات الرابطة للحموض الصفراوية :** تمنع اعادة امتصاص الحموض الصفراوية

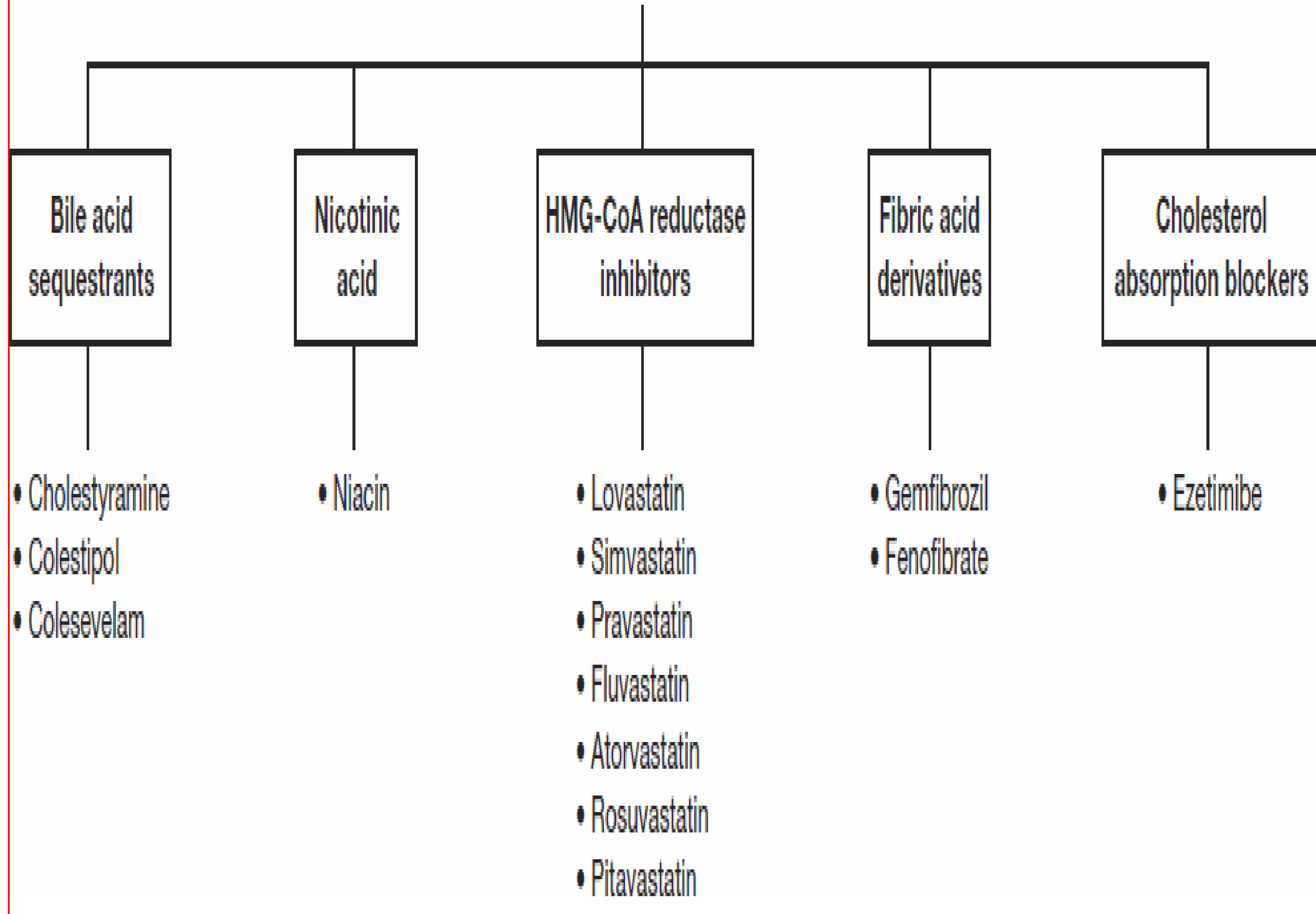
٤ – **ايزيتيميب :** يمنع امتصاص الكولسترول من الغذاء

٥ – **متفرقات**


Strategy for Controlling Hyperlipidemia
Preventing absorption from diet
Ezetimibe
Inhibit biosynthesis in liver
STATINS
HMG CoA reductase
LDL-R
Serum Cholesterol
Cellular Cholesterol
Conversion to hormones within cells or storage as granules
Bile Acids
Intestine
Feces
Inhibit Reabsorption of Bile acids
BILE ACID
Binding resins
Increase lipoprotein catabolism
FIBRATES



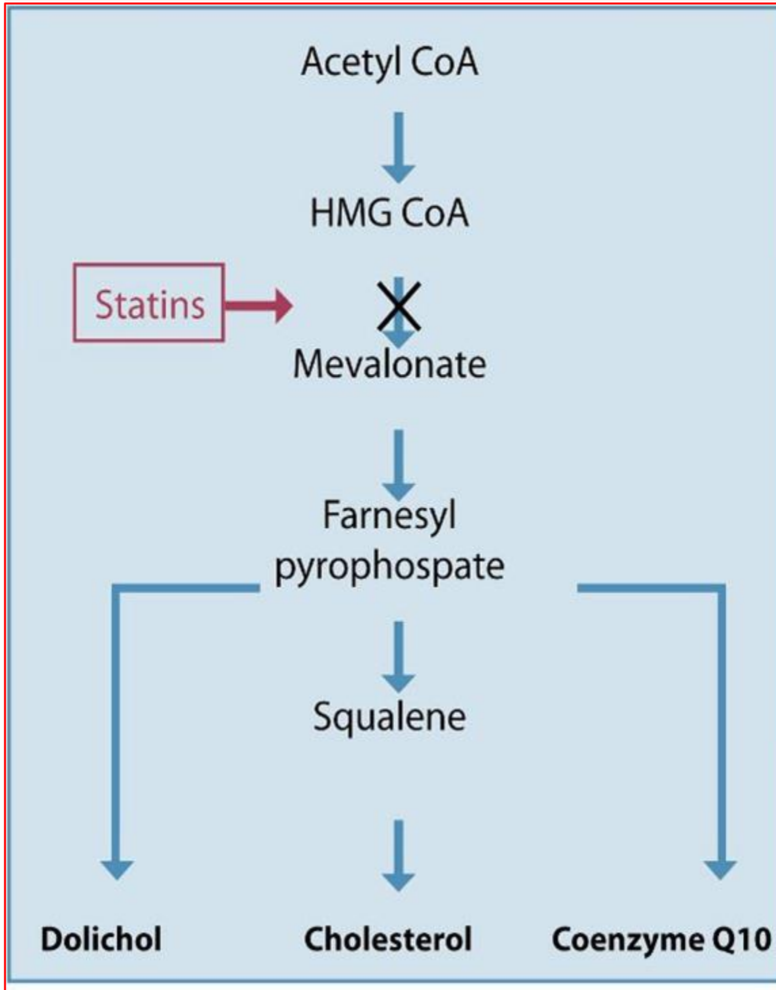
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology,*



Antihyperlipidemics
Bile acid sequestrants
Nicotinic acid
HMG-CoA reductase inhibitors
Fibric acid derivatives
Cholesterol absorption blockers
• Cholestyramine
• Colestipol
• Colesevelam
• Niacin
• Lovastatin
• Simvastatin
• Pravastatin
• Fluvastatin
• Atorvastatin
• Rosuvastatin
• Pitavastatin
• Gemfibrozil
• Fenofibrate
• Ezetimibe

STATINS الستاتينات

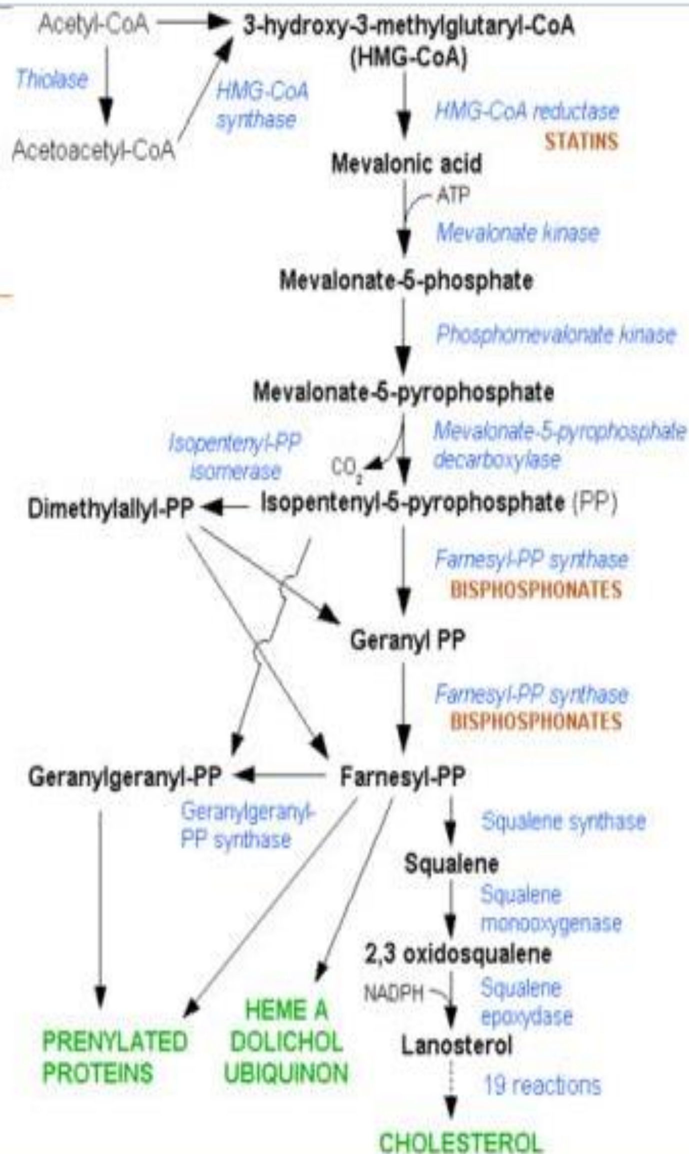
(HMG-COA Reductase Inhibitors)



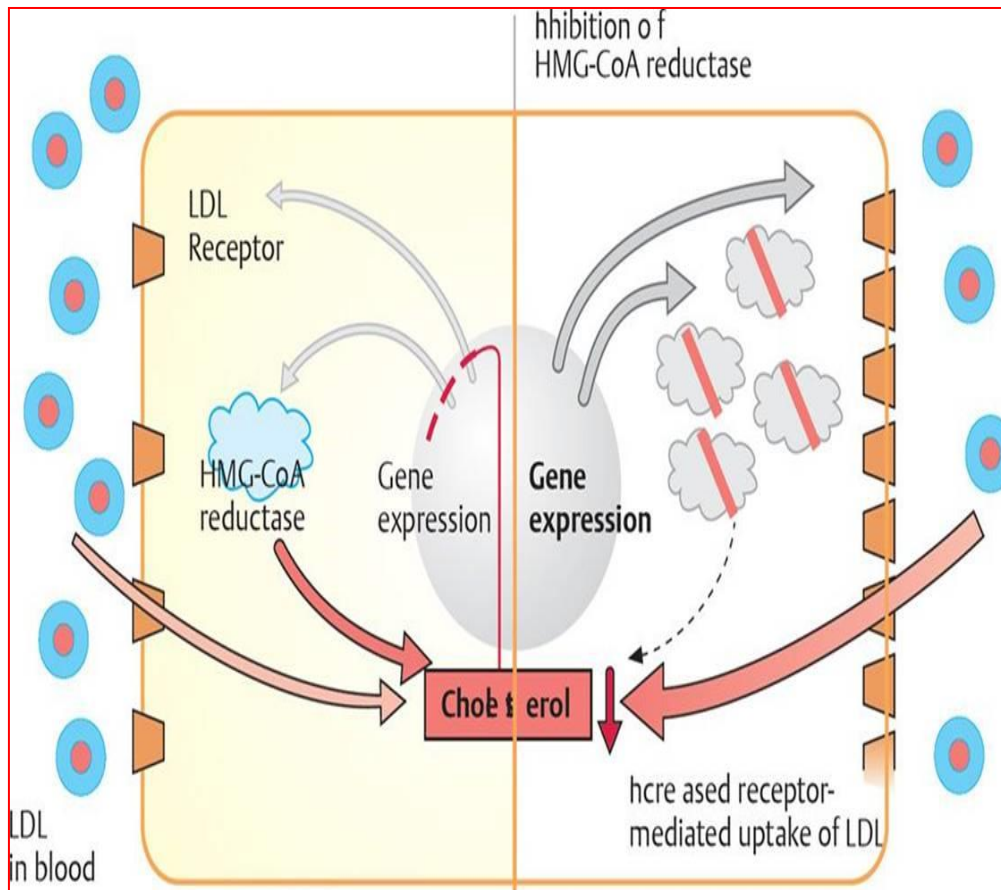
ادوية هذه المجموعة تثبط انزيم HMG-COA Reductase المسؤول عن تحويل HMG-COA الى الميفالونات في طريق التصنيع الحيوي للكولسترول و بذلك تخفض تركيز الكولسترول .

Statins

The statins (3-hydroxy-3-methylglutaryl [HMG]−coenzyme A [CoA] inhibitors) have become the most widely prescribed drugs for lowering plasma cholesterol levels.

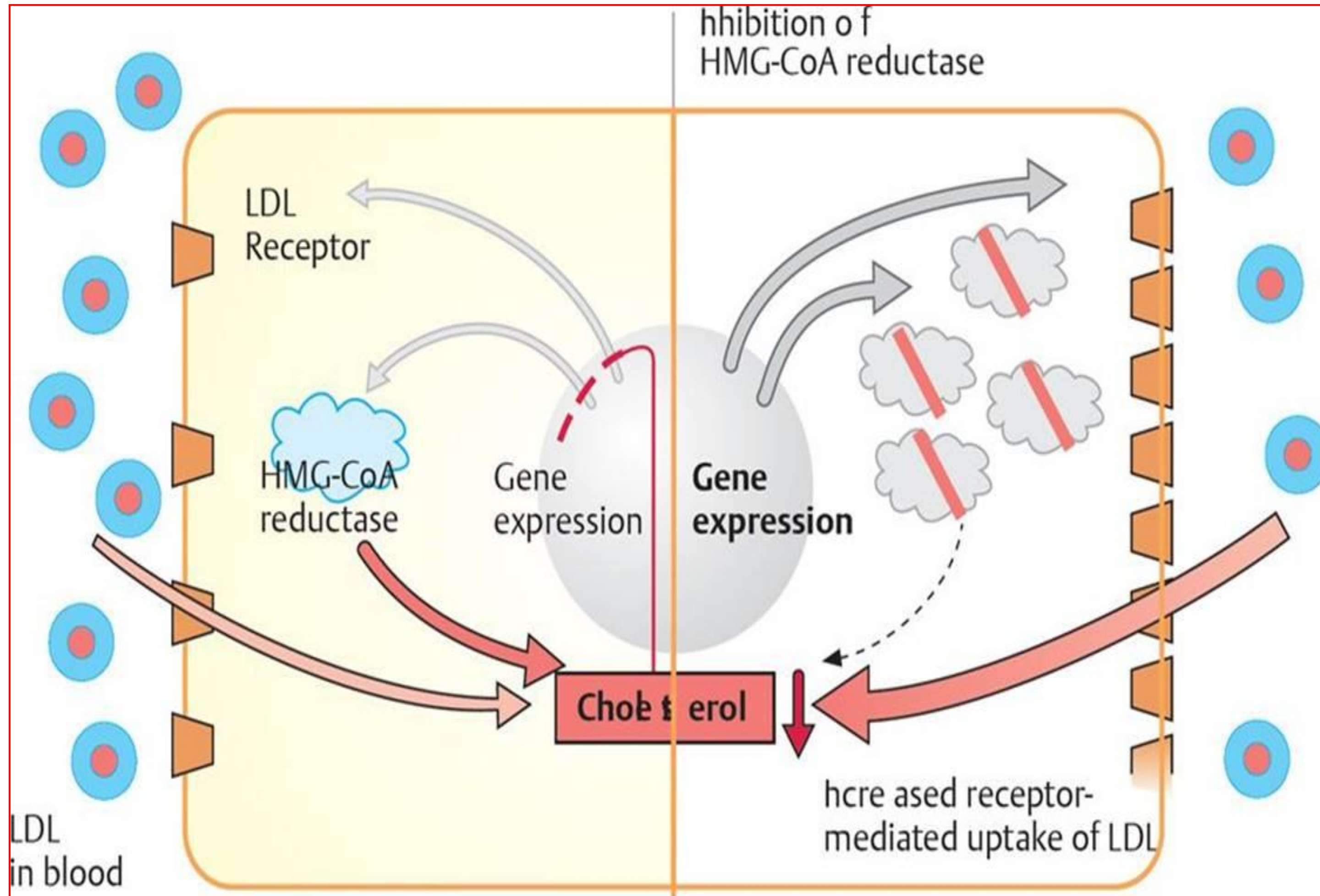


Acetyl-CoA
3-hydroxy-3-methylglutaryl-CoA
(HMG-CoA)
Thiolase
HMG-CoA
synthase
Acetoacetyl-CoA
HMG-CoA reductase
STATINS
Mevalonic acid
ATP
Mevalonate kinase
Mevalonate-5-phosphate
Phosphomevalonate kinase
Mevalonate-5-pyrophosphate
Isopentenyl-PP
isomerase
CO_2
Mevalonate-5-pyrophosphate
decarboxylase
Dimethylallyl-PP
Isopentenyl-5-pyrophosphate (PP)
Farnesyl-PP synthase
BISPHOSPHONATES
Geranyl PP
Farnesyl-PP synthase
BISPHOSPHONATES
Geranylgeranyl-PP
Farnesyl-PP
Geranylgeranyl-
PP synthase
Squalene synthase
Squalene
Squalene
monooxygenase
2,3 oxidosqualene
NADPH
Squalene
epoxydase
Lanosterol
19 reactions
PRENYLATED
PROTEINS
HEME A
DOLICHOL
UBIQUINON
CHOLESTEROL



Mechanism of action.
The major mechanism of these agents is to competitively inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis This causes significant reductions in LDL-C by causing an increased expression of LDL receptors on hepatocytes and increased removal of LDL from the blood Statins also reduce blood triglyceride levels.

In the presence of HMG-CoA reductase inhibitors, hepatocytes increase the production of LDL-receptor proteins. This allows LDL uptake from the blood to increase to provide the liver with its only source of cholesterol


hhibition o f
HMG-CoA reductase
LDL
Receptor
HMG-CoA
reductase
Gene
expression
Gene
expression
erol
hcre ased receptor-
mediated uptake of LDL
LDL
in blood

Low systemic availability

3-Hydroxy-3-methyl-
glutaryl-CoA

HMG-CoA
Reductase

Mevalonate

Cholesterol

Bio-
activation

Active form

Extraction
of lipophilic
lactone

Active
uptake of
anion

Oral
administration

Lovastatin

Fluvastatin

Effects

– **Lowers LDL and triglyceride levels**

– **Increases HDL levels**

Uses

– **First-line treatment for hypercholesterolemia**

– **Used prophylactically to prevent adverse vascular events in patients with diabetes mellitus or cardiovascular disease**

High vs Medium Intensity Statins

High: (Lowers LDL-C by greater than 50%).

1. Atorvastatin (40-80 mg)
2. Rosuvastatin (20-40 mg)

Medium: (Lower LDL-C by 30 to 50%).

1. Atorvastatin (10-20 mg)
2. Rosuvastatin (5-10 mg)
3. Simvastatin (20-40mg)
4. Pravastatin (40-80mg)
5. Lovastatin (40 mg)
6. Fluvastatin (40 mg PO BID)
7. Pitavastatin (2-4 mg)

Statin	Half-Life	Suggested Time of Administration
Lovastatin (Mevacor)	1.1-1.7 hours	Night
Simvastatin (Zocor)	3 hours	Night
Fluvastatin (Lescol)	IR: <3 hours ER: 9 hours	Night
Pitavastatin (Livalo)	12 hours	Anytime
Atorvastatin (Lipitor)	Parent Drug: 14 hours Metabolites: 20-30 hours	Anytime
Rosuvastatin (Crestor)	19 hours	Anytime
Pravastatin (Pravachol)	77 hours	Anytime

فئة الدواء	الفوائد	الآثار الجانبية المحتملة
أتورفاستاتين فلوفاستاتين لوفاستاتين بيتافاستاتين برافاستاتين روزوفاستاتين سيمفاستاتين	تقليل كوليسترول البروتين الدهني منخفض الكثافة والدهون الثلاثية، مع زيادة كوليسترول البروتين الدهني مرتفع الكثافة قليلاً	ألم العضلات، وزيادة مستويات السكر في الدم، والإمساك، والغثيان، والإسهال، وألم المعدة، والتقلصات، وارتفاع إنزيمات الكبد

Statin Benefit Groups

1. Clinical evidence of ASCVD
2. LDL-C >190 mg/dL
3. Age 40–75 years with diabetes and an LDL-C 70–189 mg/dL
4. Age 40–75 years without diabetes, an LDL-C 70–189 mg/dL, and an estimated 10-year risk of ASCVD >7.5% (10-year risk of ASCVD based on Pooled Cohort Equations available at my.americanheart.org/cvriskcalculator)

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Side effects

These include gastrointestinal (GI) upset in < 10% of patients, muscle weakness in combination with fibrates, and altered liver enzymes.

Contraindications

– Liver disease

Drug Interactions

The HMG-CoA reductase inhibitors increase warfarin levels so prothrombin times (expressed as International Normalized Ratio should be monitored.

Accumulation and effect of HMG-CoA reductase inhibitors in the liver.

The HMG-CoA reductase inhibitors mimic the normal enzyme substrate, which renders it unavailable for cholesterol synthesis in the liver. These drugs accumulate in the liver, as they have a high rate of presystemic elimination. This accumulation is advantageous because it concentrates the actions of these drugs where they are needed. The liver maintains its requirement for cholesterol by the uptake of LDL from the blood, thus lowering plasma cholesterol levels.

Rhabdomyolysis

Rhabdomyolysis is the rapid breakdown of skeletal muscle due to injury to muscle tissue. The muscle breakdown product, myoglobin, is harmful to the kidney and can precipitate acute kidney failure. Signs and symptoms include **pain, tenderness, and swelling of the affected muscle**, as well as nausea, vomiting, confusion, arrhythmias, coma, anuria, and later disseminated intravascular coagulation (DIC). This is a rare complication of treatment with statins and fibrates.

Bile Acid Sequestrants Cholestyramine and Colestipol

Mechanism of action

These agents are insoluble resins that are not absorbed by the body, but that bind bile acids in the gut, thus preventing bile acids from being absorbed. This necessitates an increase in the hepatic conversion of cholesterol to bile acids, thereby reducing the cholesterol available through the enterohepatic circulation for production of plasma lipids. They also lower LDL and plasma cholesterol. illustrates the effect of cholesterol-lowering drugs like cholestyramine on cholesterol metabolism in the liver.

الراتنجيات الرابطة للحموض الصفراوية راتنج الكوليستيرامين

Cholestyramine Resin

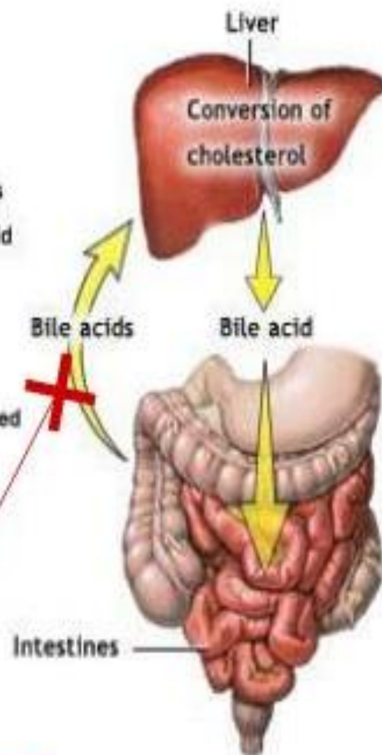
بعد تناول هذا المركب عن طريق الفم فان الراتنج يبقى في السبيل الهضمي ثم يحدث تبادل بين شوارد الكلورايد من جهة و الحموض الصفراوية في المعي الدقيق و هذا يؤدي الى الاقلال من اعادة امتصاص الحموض الصفراوية مما يؤدي الى استقلاب الكولسترول في الكبد الى حموض صفراوية .

هذا الراتنج لا يرتبط مع الادوية المعتدلة او الاملاح الامينية و لكن الادوية الحمضية بشكلها المتشرد يمكن ان ترتبط .

كوليستيرامين هو الاختيار في ارتفاع شحوم الدم من النمطType IIa و ذلك مع الحمية الغذائية

الكولسترامين كوليسفيلام كوليستيبول	تقليل كوليسترول البروتين الدهني منخفض الكثافة، مع احتمال زيادة كوليسترول البروتين الدهني مرتفع الكثافة قليلاً	الإمساك، والانتفاخ، والغثيان، والغازات، وحرقة المعدة

DRUGS USED TO TREAT HYPERLIPIDEMIA: CHOLESTEROL



- Liver normally converts cholesterol into bile acid
- Bile acids move into intestines
- Most bile acid is returned to liver
- Result = Higher blood cholesterol levels

BINDING RESINS

- **BILE ACID-BINDING RESINS:** (colestipol cholestyramine, colesevelam; all begin with chol- or col-)
  - REDUCE LDL (CHOLESTEROL), used for isolated increase in LDL
  - Level of VLDL may increase in patients with hypertriglyceridemia
  - Large hydrophobic resins taken orally that bind to bile acids in the intestine and prevent bile acid re-absorption (usually 95% re-absorbed)
  - Cholesterol is required for bile acid synthesis in the liver
  - Reduced bile acid concentrations in the liver results in greater conversion of cholesterol to bile acids and lower liver cholesterol levels
  - Lower cholesterol results in an up-regulation of the number of LDL receptors on liver cells which increases cholesterol uptake from the blood

Pharmacokinetics

Given orally, these drugs bind with bile acids in the intestine and produce an insoluble complex that is excreted in the feces

Effects

– Decreases LDL levels

– May increase triglycerides, or they may remain unchanged

– Increases HDL levels

Uses

These agents are used alone for the treatment of hypercholesterolemia in patients 11 to 20 years of age. However, they are most often used as secondary agents if statin therapy does not reach its desired goal.

Side effects

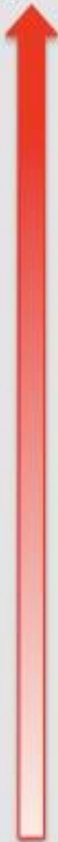
– Nausea, constipation, steatorrhea (the presence of excess fat in feces), and deficiency of fat-soluble vitamins (A, D, E, K)

Note: Compliance may be a problem due to the unpleasant taste of the drug.

Drug interactions

These agents may interfere with the absorption of other drugs given concurrently (e.g., warfarin); therefore, drugs should be taken ~1 to 2 hours before or several hours after taking bile acid sequestrants.

↑ triglycerides

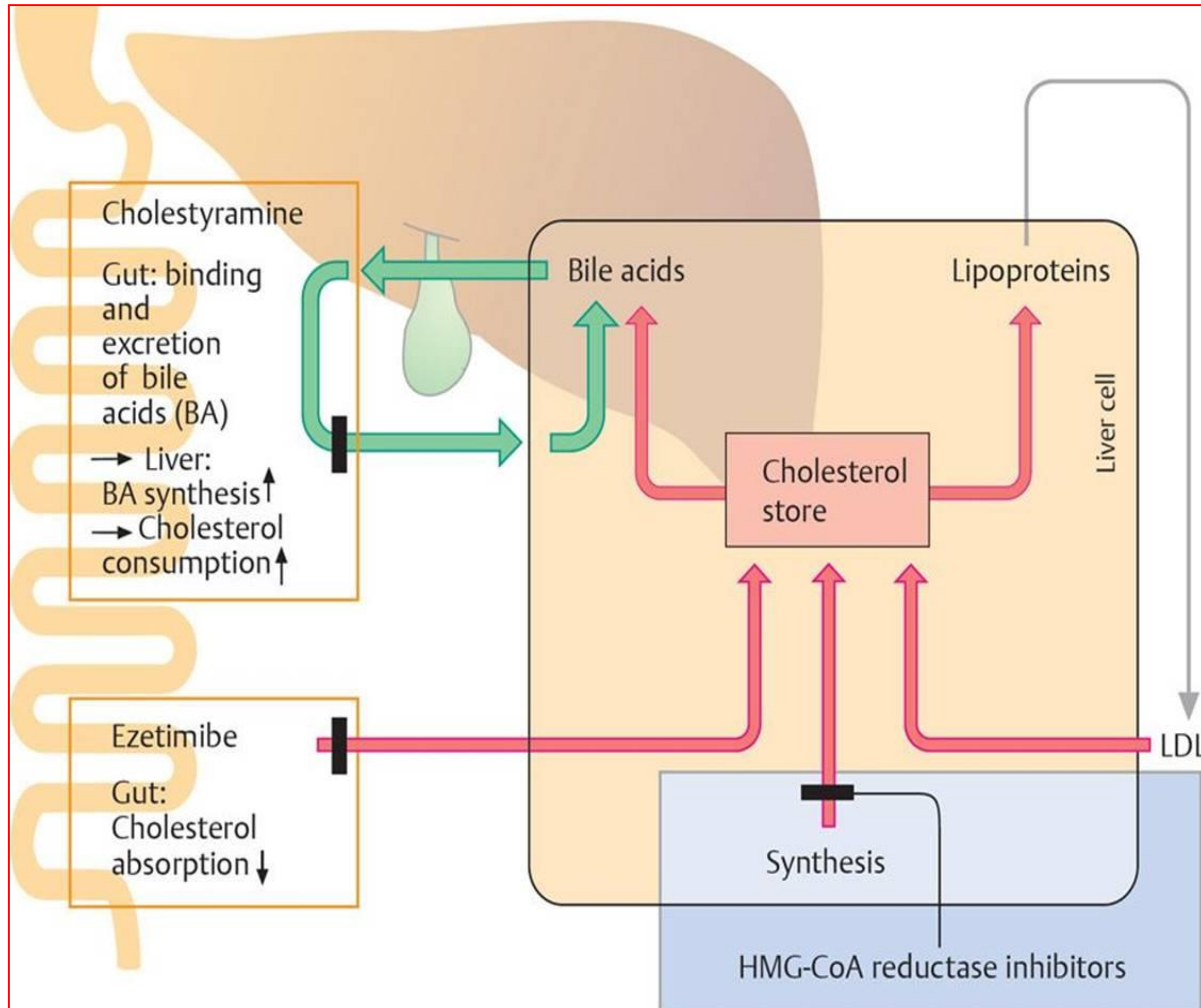


- **Chylomicrons:** Rich in triglycerides (TG). Transport TG from GIT to tissues.
- **VLDL**: Rich in triglycerides. Produced in liver (from NEFAs liberated by fat breakdown) and transport TG from liver to tissues.
- **LDL:** Richer in cholesterol – produced from VLDL. Transport cholesterol to tissues. Taken up by LDL-receptors.
- **HDL**: Rich in cholesterol. Produced in liver and intestine. Transport cholesterol from tissues to liver.

↑ cholesterol

Cholesterol metabolism in liver cell and cholesterol-lowering drugs

Cholesterol-lowering drugs may act in the gut to reduce the absorption of dietary cholesterol, they may inhibit cholesterol synthesis in the liver, or they may act to increase the consumption of cholesterol.



Ezetimibe

Mechanism of action

Ezetimibe inhibits cholesterol absorption in the small intestine.

مثبط امتصاص الكوليسترول **إزيتمايب**	تقليل كوليسترول البروتين الدهني منخفض الكثافة؛ تقليل الدهون الثلاثية قليلاً، مع زيادة كوليسترول البروتين الدهني مرتفع الكثافة قليلاً	ألم المعدة، والإسهال، والإرهاق، وتقرح العضلات؛ يجب تجنبه أثناء فترة الحمل والرضاعة

Effects

– Lowers LDL-C levels by ~18%

Uses

It is used primarily as adjunctive therapy with statins.

Side effects

– May increase the hepatotoxicity and myopathy of statins

المزج بين أدوية تثبيط امتصاص الكوليسترول والأدوية الخافِضة للكوليسترول إزيتمايب- سيمفاستاتين	تقليل كوليسترول البروتين الدهني منخفض الكثافة والدهون الثلاثية، وزيادة كوليسترول البروتين الدهني مرتفع الكثافة	ألم المعدة، والإرهاق، والغازات، والإمساك، وألم البطن، والتقلصات، وتقرح العضلات، والألم، والضعف

Nicotinic Acid (Niacin)

Mechanisms of action

– Inhibition of hepatocyte diacylglycerol acyltransferase-2, a key enzyme for triacylglycerol synthesis, decreasing secretion of VLDL and LDL-C
– Decreased hepatic catabolism of apolipoprotein A-I increases the half-life and concentrations of HDL-C.
– Niacin also reduces vascular inflammatory genes involved in atherosclerosis.

Effects

– Decreases levels of LDL and triglycerides
– Increases HDL levels

Uses

Niacin is used to treat hypertriglyceridemias and hypercholesterolemia. It is especially useful in patients with both hypertriglyceridemia and low HDL-C levels.

Note: Nicotinamide is not effective in lowering lipids, although it acts interchangeably with nicotinic acid as a vitamin

Side effects

– Cutaneous flushing, burning, and itching are common, as is GI irritation, nausea, and vomiting. The niacin flush results from the stimulation of prostaglandins D_2 and E_2 from subcutaneous Langerhans cells by a G protein–coupled niacin receptor.

– Activation of peptic ulcers, abnormal elevation of liver enzyme levels, hyperglycemia, and hyperuricemia occur infrequently.

Contraindications

– Chronic liver disease

– Gout

– May be inappropriate for use in peptic ulcer disease, hyperuricemia, and diabetes

النياسين	تقليل كوليسترول البروتين الدهني منخفض الكثافة والدهون الثلاثية، وزيادة كوليسترول البروتين الدهني مرتفع الكثافة	هبات ساخنة بالوجه والعنق، والحكة، واضطراب المعدة، وزيادة السكر في الدم

DRUGS USED FOR THE TREATMENT OF HYPERTRIGLYCERIDEMIA

- Niacin
  - Clinical use
    - Hypertriglyceridemia
    - Familial hypersholesterolemia (in combination with cholesterol-lowering drugs)
    - Mixed (multi-factorial) hyperlipidemias
  - Adverse effects
    - Flushing (cutaneous vasodilation and sensation of warmth) – prostaglandin-related effect
    - Increase gastric acid secretion – may be taken with antacids or inhibitors of gastric acid secretion – is contraindicated in patients with peptic ulcer
    - Impairment of glucose tolerance – is contraindicated in patients with insulin resistance
    - Hepatotxicity
    - Hyperuricemia – may precipitate gout

مجموعة الفيبرات : Fibrate

- كيميائيا هي مشتقات Fibric acid
- هذه الادوية تنشط اكسدة الحموض الدسمة β-oxidation في الميتاكوندريا
- لذلك تستعمل في خفض مستويات الحموض الدسمة و الشحوم الثلاثية في البلاسما
- هي عوامل خافضة للشحوم تستعمل بشكل واسع في معالجة الاشكال المختلفة من ارتفاع الشحوم و الكولسترول
- تمتص بسرعة مع الوجبات
- ترتبط مع البروتين بنسبة ٩٩%
- عمر النصف يتراوح من ١ ساعة (جيمفيبروزيل) الى ٢٠ ساعة (فينوفيبرات)
- تتوزع بشكل واسع
- تطرح عن طريق البول ٩٠% بشكل مقترنات غلوكورونية

DRUGS USED FOR THE TREATMENT OF HYPERTRIGLYCERIDEMIA

- Fibric acid derivatives: Gemfibrozil, Fenofibrate
  - Mechanism of action
    - Ligands of nuclear receptor, peroxisome proliferator-activated receptor-alpha (PPAR-α)
    - Increase expression of LPL, increase lipolysis of triglycerides
    - Intracellular lipolysis in adipose tissue is decreased
    - LDL levels may increase, especially in patients with mixed hyperlipidemias
  - Clinical use
    - Hypertriglyceridemia
  - Adverse effects
    - May promote cholesterol gallstones
    - Myopathy
    - Liver toxicity

الجيل الأول :
كلوفيبرات Clofibrate

الكلوفيبرات هو الدواء المفضل في علاج النوع الثالث من ارتفاع الليبوبروتين typ III hyperlipoproteinemia و يمكن ان يكون مفيد في typ IIb و typ IV و لكنه غير فعال في typ I و typ IIa

الكلوفيبرات يمكن ان يخفض التراكيز الدموية للشحوم الثلاثية و الكولسترول و لكن تاثيره اكبر على الشحوم الثلاثية

Type	Major Lipids
I	Increased chylomicrons and increased triglycerides. Uncommon.
IIA	Increased low-density lipoprotein (LDL) and increased cholesterol.
IIB	Increased very low-density lipoprotein (VLDL), increased LDL, increased cholesterol and triglycerides. Very common.
III	Moderately increased cholesterol and triglycerides. Uncommon.
IV	Increased VLDL and markedly increased triglycerides. Very common.
V	Increased chylomicrons, VLDL, and triglycerides. Uncommon.

الجيل الثاني :
فينوفيبرات Fenofibrate

يخفض الشحوم الثلاثية و الكولسترول

جيمفيبروزيل Gemfibrozil

يخفض تركيز VLDL و ينشط اطراحها من البلاسما له تاثير ضعيف على الكولسترول و لكنه يسبب ارتفاع مستوى HDL

فينوفايبرات جمفبروزيل	تقليل الدهون الثلاثية؛ تقليل كوليسترول البروتين الدهني منخفض الكثافة إلى حد ما، وزيادة كوليسترول البروتين الدهني مرتفع الكثافة	الغثيان، وألم المعدة، والم العضلات

Fibrates

Gemfibrozil and Clofibrate

Mechanism of action

These drugs lower VLDLs and plasma triglycerides by stimulating lipoprotein lipase. They also lower cholesterol by inhibiting its synthesis and enhancing excretion in the bile.

Effects

– Decreases LDL and triglyceride levels
– Increases HDL levels

Uses

– Hypertriglyceridemia and hypercholesterolemia

Side effects

Side effects include GI disturbances (nausea, diarrhea, and cramps), muscle weakness, and rash. Long-term use may increase the incidence of thromboembolism, angina, arrhythmias, or gallstones

Contraindications

– Pregnancy
– Impaired renal or hepatic function

Drug interactions

These agents displace acidic drugs (e.g., warfarin and phenytoin) from plasma proteins; thus a reduced dose of anticoagulant (or other drug) is required.

عوامل اخرى خافضة للشحوم :

LDL Oxidation Inhibitor (بروبوكول Probucol)

عند الانسان يسبب انخفاض مستويات الكولسترول في الكبد و البلاسما عن طريق زيادة تقويض LDL و يمكن ان يمنع اصطناع الكولسترول و لكنه لا يؤثر على الشحوم الثلاثية في البلاسما
ينقص LDL و بشكل اقل HDL (الآلية غير معروفة تماما و لكن انخفاض HDL يمكن ان تعزى الى قدرة البروبوكول في منع اصطناع Apoprotein AI البروتين الرئيسي في HDL)

Drugs for Treatment of Hyperlipidemia

	LDL	HDL	Triglycerides
Diet change	↓10%–15%	Variable increase	↓10%–20%
Statins	↓20%–60%	↑10%–15%	↓10%–20%
Bile acids resins	↓15%–30%	↑3%–5%	No change or mild increase
Fibrates	↓5%–20% or increase	↑10%–35%	↓40%–50%
Ezetimibe	↓18%–22%	↑1%–3%	↓8%–12%
Niacin	↓15%–30%	↑20%–30%	↓20%–50%

Medications for Hyperlipidemia

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
Cholesterol absorption inhibitor	Ezetimibe	↓ LDL(14-18), ↑ HDL (1-3) ↓Triglyceride (2)	Headache, GI distress
Nicotinic Acid		↓LDL (15-30), **↑ HDL (15-35)** **↓ Triglyceride (20-50)**	Flushing, Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity
Fibric Acids	Gemfibrozil Fenofibrate	↓LDL (5-20), ↑HDL (10-20) **↓Triglyceride (20-50)**	Dyspepsia, gallstones, myopathy
Bile Acid sequestrants	Cholestyramine	↓ LDL ↑ HDL No change in triglycerides	GI distress, constipation, decreased absorption of other drugs

DRUGS USED FOR TREATING HYPERLIPIDEMIA

HYPERTRIGLYCERIDEMIA:

- Niacin
- Fibric acid derivatives

HYPERCHOLESTOLEMIA:

- Bile-acid binding resins
- Statins
- Ezetimibe
- Combination therapy (e.g., ezetimibe + a statin drug)

FYI: LIPITOR (generic name atorvastatin) = a statin drug

Fredrickson classification of Hyperlipidemias

Hyperlipoproteinemia	Synonyms	Problems	Labs description	Treatment
Type I	*Buerger-Gruetz syndrome, Primary hyperlipoproteinaemia, or Familial hyperchylomicronemia*	Decreased lipoprotein lipase (LPL) or altered ApoC2	Elevated Chylomicrons	Diet Control
Type IIa	*Polygenic hypercholesterolaemia* or Familial hypercholesterolemia	LDL receptor deficiency	Elevated LDL only	Bile Acid Sequestrants, Statins, Niacin
Type IIb	Combined hyperlipidemia	Decreased LDL receptor and Increased ApoB	Elevated LDL and VLDL and Triglycerides	Statins, Niacin, Gemfibrozil
Type III	*Familial Dysbetalipoproteinemia*	Defect in ApoE synthesis	Increased IDL	Drug of choice: Gemfibrozil
Type IV	*Endogenous Hyperlipemia*	Increased VLDL production and Decreased elimination	Increased VLDL	Drug of choice: Niacin
Type V	*Familial Hypertriglyceridemia*	Increased VLDL production and Decreased LPL	Increased VLDL and Chylomicrons	Niacin, Gemfibrozil

Dug	Mechanism of action	Adverse drug reaction	Effect on lipids
HMG-CoA reductase inhibitors: Lovastatin (10-80 mg) simvastatin (5-40 mg) atorvastatin (10-80 mg) rosuvastatin (5-20 mg)	Decrease cholesterol synthesis by inhibition of HMG-CoA reductase	Rise serum transaminases level, muscle tenderness, myopathy (rare)	Decrease LDL, increase HDL, decrease TG
Bile acid sequestrants: Cholestyramine(4-16 mg) colestipol (5-30 mg)	Decease bile acid absorption, increase LDL receptors on hepatocytes	Unpalatable, flatulence,	Decrease LDL, increase HDL, TG not affected
Fibric acid derivatives: Gemfibrozil (1200 mg) benzafibrate (600 mg) fenofibrate (200 mg)	Increase lipoprotein lipase activity, decrease release of fatty acid from adipose tissue	Skin rash, eosinophilia, impotency	Decrease LDL, increase HDL, decrease TG
Nicotinic acid (2-6 gm)	Decrease production of VLDL	Flushing, heat, itching	Decrease LDL, increase HDL, decrease TG

Summary of Lipid-Lowering Drugs and Their Impact on ASCVD Risk

Drug Type	Dosage	ASCVD Risk Reduction[a]	Comments	Key Contraindications
Statins	See **TABLE 1**	—	Initial drugs of choice for ASCVD risk reduction; high intensity for high-risk patients	Active liver disease, including persistently elevated hepatic transaminase levels
Bile-acid sequestrants: Cholestyramine Colestipol Colesevelam	 4-8 g po bid 5-15 g po bid 3 × 3.75 g po bid	Limited	Initial studies used bile-acid sequestrants alone; trial data outdated	History of bowel obstruction; serum TG >500 mg/dL or hypertriglyceridemia-induced pancreatitis
Niacin	500-3,000 mg po daily	Limited	May be used for hypertriglyceridemia	Active liver disease, including persistently elevated hepatic transaminase levels; active peptic ulcer disease
Fibrates: Fenofibrate Gemfibrozil	 135 mg (range 120-200 mg) po daily 600 mg po bid	No	Indicated for hypertriglyceridemia; gemfibrozil should not be used in combination with most statins	Severe renal dysfunction; active liver disease; gallbladder disease
Ezetimibe	10 mg po daily	Yes	Data for risk reduction with statins	Statin contraindications apply with concomitant ezetimibe
PCSK9 inhibitors: Alirocumab Evolocumab	 75-150 mg SC q2w; 300 mg SC q4w 140 mg SC q2w; 420 mg SC q4w	Yes	Both agents have outcome data demonstrating risk reduction with statins; evolocumab indicated for HoFH	Known hypersensitivity to agent
Icosapent ethyl	2 × 1 g po bid with food	Yes	Data for risk reduction with statins in high-risk patients with TG >150 mg/dL	Known hypersensitivity to agent
Bempedoic acid	180 mg po daily	No data	Outcomes trial in progress	No contraindications; use with caution with hyperuricemia and/or risk of or history of tendon rupture
Inclisiran	300 mg SC q6mo	No data	Investigational	Not yet established
Evinacumab	15 mg/kg IV q4w	No data	Investigational	Not yet established

[a] In combination with statins.
ASCVD: atherosclerotic cardiovascular disease; HoFH: homozygous familial hypercholesterolemia; PCSK9: proprotein convertase subtilisin/kexin type 9; TG: triglycerides.

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme responsible for degradation of LDL-C receptors in hepatocytes. LDL receptors are responsible for removing LDL-C from the blood. Greater PCSK9 activity leads to fewer LDL receptors and higher plasma LDL-C levels. The first drugs to target PCSK9 were the monoclonal antibodies (Mabs) **alirocumab and evolocumab**, which bind to and inhibit PCSK9 (PCSK9 inhibitors). These drugs have similar therapeutic profiles, producing a 45% to 60% reduction in LDL-C when used alone or in combination with statins. Both drugs are given SC at 2- or 4-week intervals. The most common adverse effect of these drugs is injection-site reactions. Since both **alirocumab and evolocumab** are fully human Mabs, immunologic responses, including allergic reactions and the development of antidrug neutralizing antibodies, are rare

Both PCSK9 inhibitors have been evaluated in combination with statin therapy in morbidity and mortality studies**. Evolocumab** was studied in 27,564 patients with established CVD and a baseline LDL-C of 70 mg/dL or greater on maximally tolerated statin. **Evolocumab** produced a significant relative RR of 15% for CVEs. This occurred primarily because of reductions in myocardial infarction (MI), stroke, and coronary revascularization; there was not a decrease in CV death**. Alirocumab** was studied in 18,924 patients with a recent hospital admission for ACS who had a baseline LDL-C of 70 mg/dL or greater on maximally tolerated statin. Similar to **evolocumab, alirocumab** produced a significant relative RR of 15% for CVEs.

The benefit of **alirocumab** was due to a decrease in MI and stroke, but not CV death. The results of these trials support the addition of PCSK9 inhibitors to statins in patients not achieving LDL-C levels below 70 mg/dL, but data in patients not taking a statin are lacking. Cost-effectiveness concerns continue to limit PCSK9 inhibitor therapy. Although manufacturers recently reduced the cost of these drugs by 60% to approximately $5,800 per year, insurance barriers remain, including unaffordable copayments for some patients

Icosapent Ethyl

Prescription omega-3 fatty acids (eicosapentaenoic acid [EPA] and/or docosahexaenoic acid [DHA]) are indicated to treat severe hypertriglyceridemia (TG levels of 500 mg/dL or higher). A number of trials investigating various formulations of omega-3 fatty acids demonstrated inconsistent effects on ASCVD risk. These results were most likely related to the use of low doses of omega-3 fatty acids, differences in baseline ASCVD risk in study subjects, and possibly the use of products containing both EPA and DHA. However, a prescription EPA-only omega-3 fatty acid (**icosapent ethyl**) has been found to significantly reduce ASCVD risk in patients with established CVD or DM who had at least one other CV risk factor, elevated TG (>135 mg/dL-499 mg/dL), and an LDL-C level between 41 g/dL and 100 mg/dL on statin therapy.

The Reduction of Cardiovascular Events with **Icosapent Ethyl**-Intervention Trial (REDUCE-IT), which enrolled more than 8,000 subjects and lasted nearly 5 years, demonstrated that patients receiving icosapent ethyl (2 g bid with food) were 25% less likely than placebo patients ($P < .001$) to experience CV death, nonfatal MI, stroke, coronary revascularization, or unstable angina. Safety issues with icosapent ethyl included increased risk of atrial fibrillation (AF; 5.3% vs. 3.9%; $P = .003$), greater risk of hospitalization for AF (3.1% vs. 2.1%; $P = .004$), and higher—though nonsignificant—risk of serious bleeding events (2.6% vs. 2.1%; $P = .06$). Icosapent ethyl's benefit in reducing ASCVD risk was unexpected given the previously inconsistent effect of these drugs and the premature discontinuation of a similar mortality study using a high-dose combination (EPA and DHA) prescription omega-3 fatty acid.

The specific mechanism of **icosapent ethyl** in CV risk reduction is unknown but most likely results from the use of an EPA-only omega-3 fatty acid. Based on the findings from REDUCE-IT, the FDA recently approved icosapent ethyl for use in patients taking maximally tolerated statin therapy with baseline TG of 150 mg/dL or higher who have established CVD or DM and two or more additional ASCVD risk factors

Bempedoic Acid

This oral nonstatin agent reduces LDL-C **by inhibiting ATP-citrate lyase,** an enzyme in the cholesterol biosynthesis pathway, upstream from the site where statins reduce cholesterol synthesis. **Bempedoic acid**, a prodrug, requires coenzyme A activation by very-long-chain acyl-CoA synthetase-1. This activity occurs solely in the liver and not in the muscle, potentially limiting musculoskeletal complaints. Bempedoic acid does not have substantial effects on lipid fractions other than LDL-C. This agent was approved in early 2020 as an adjunct to diet and maximally tolerated statin therapy in the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established ASCVD who require additional LDL-C–lowering

Bempedoic acid is available as a single dosage of 180 mg daily and as a fixed-dose combination with ezetimibe 10 mg daily

It is metabolized primarily in the liver via glucuronidation. Although less than 5% of the drug is cleared unchanged, few data exist on patients with severe renal disease (creatinine clearance <30 mL/minute), and there are no data on patients with end-stage renal disease or on hemodialysis. **Bempedoic acid** is a weak inhibitor of the organic anion transport-2 membrane transporter, which is the most likely mechanism for the increases in serum creatinine and uric acid that can occur during therapy. The drug should be used cautiously in patients with gout. Rare instances of tendon rupture have been reported, but the mechanism and risk factors are unknown

Owing to its metabolism by uridine glucuronosyltransferase, **bempedoic** acid is associated with an approximately twofold increase in blood levels of simvastatin and pravastatin. Maximal dosages of simvastatin and pravastatin with bempedoic acid are 20 mg daily and 40 mg daily, respectively.

Bempedoic acid has been found to decrease LDL-C by approximately 18% in patients with ASCVD or HeFH who are on maximally tolerated statin therapy.[19] In patients with statin intolerance, bempedoic acid was found to **decrease LDL-C by 21% (17%-25%) when used alone and by 28% (22%-34%) when used in combination with ezetimibe**

Currently, no outcomes data are available for bempedoic acid, but an outcomes trial is in progress in patients with statin intolerance (only low-intensity statin therapy allowed) who are at very high risk for or have established ASCVD.

Inclisiran

Inclisiran is a small interfering RNA (siRNA) agent that inhibits production of the PCSK9 protein in hepatocytes. **Inclisiran** was previously known as **ALN-PCS**, an siRNA conjugated with triantennary *N*-acetylgalactosamine (GalNAc) carbohydrates. This compound was relatively unstable and had to be given IV. The addition of another GalNAc carbohydrate to ALN-PCS improved its stability, allowing the compound (ALN-PCSsc) to be administered by SC injection. The addition of the GalNAc carbohydrate was also clinically important, as it has specific affinity for binding to asialoglycoprotein receptors in the liver. This leads to specific uptake and binding of inclisiran in the liver, with no activity in peripheral tissues.

Inclisiran is a double-stranded RNA molecule that, after uptake in the hepatocyte, binds to a multiprotein complex known as *RNA-induced silencing complex* (RISC). This RISC combines with messenger RNA (mRNA) specific to PCSK9, which induces activation of an enzyme that promotes degradation of the mRNA-RISC complex. The mRNA is degraded, but the active siRNA within the RISC remains active, producing a long-lasting silencing of mRNA targeting PCSK9. Because of its unique mechanism of action, inclisiran reduces intracellular PCSK9 synthesis and has a prolonged duration of action

ANGPTL3 Inhibitor

Angiopoietin-like protein 3 (ANGPTL3) is a hepatically secreted protein that inhibits lipoprotein and endothelial lipase, resulting in decreased levels of TG-rich lipoprotein and HDL-C. Inhibition of ANGPTL3 reduces LDL-C levels through an unknown mechanism.

Evinacumab, an Mab that inhibits ANGPTL3, was studied in 65 patients with homozygous familial hypercholesterolemia (HoFH). Patients had to have genetic mutations in LDL receptors, PCSK9, or apoB with a baseline untreated TC greater than 500 mg/dL and a TG level less than 300 mg/dL.

In addition, patients had to be older than age 12 years with an LDL-C greater than 70 mg/dL on maximally tolerated lipid-lowering therapy. Patients were randomized 2:1 to evinacumab 15 mg/kg IV or placebo every 4 weeks for 24 weeks. Evinacumab decreased LDL-C by 49% ± 8% at 24 weeks. LDL-C was decreased by 50% or greater in 56% of evinacumab patients compared with 4.5% of placebo patients. Genetic mutations in the LDL receptor did not appear to affect response to evinacumab. The overall rate of adverse reactions was less with evinacumab than with placebo, but more serious adverse reactions occurred with evinacumab (4.5%) than with placebo (0%). Evinacumab's unique mechanism of action appears to be independent of LDL-receptor function, which may be particularly valuable in patients with HoFH

Conclusion

Statins remain the agents of choice for the treatment of dyslipidemia in patients who have or are at substantial risk for established coronary heart disease.

Despite statin use, the risk of adverse CVEs persists. The use of other types of lipid-lowering drugs (e.g., **ezetimibe, PCSK9 inhibitors, icosapent ethyl**) **in combination with statins** has been shown to further reduce CV risk.

Lipid-lowering drugs with novel mechanisms of action are being evaluated for their ability to further reduce CV risk.