HYPERLIPIDEMIA

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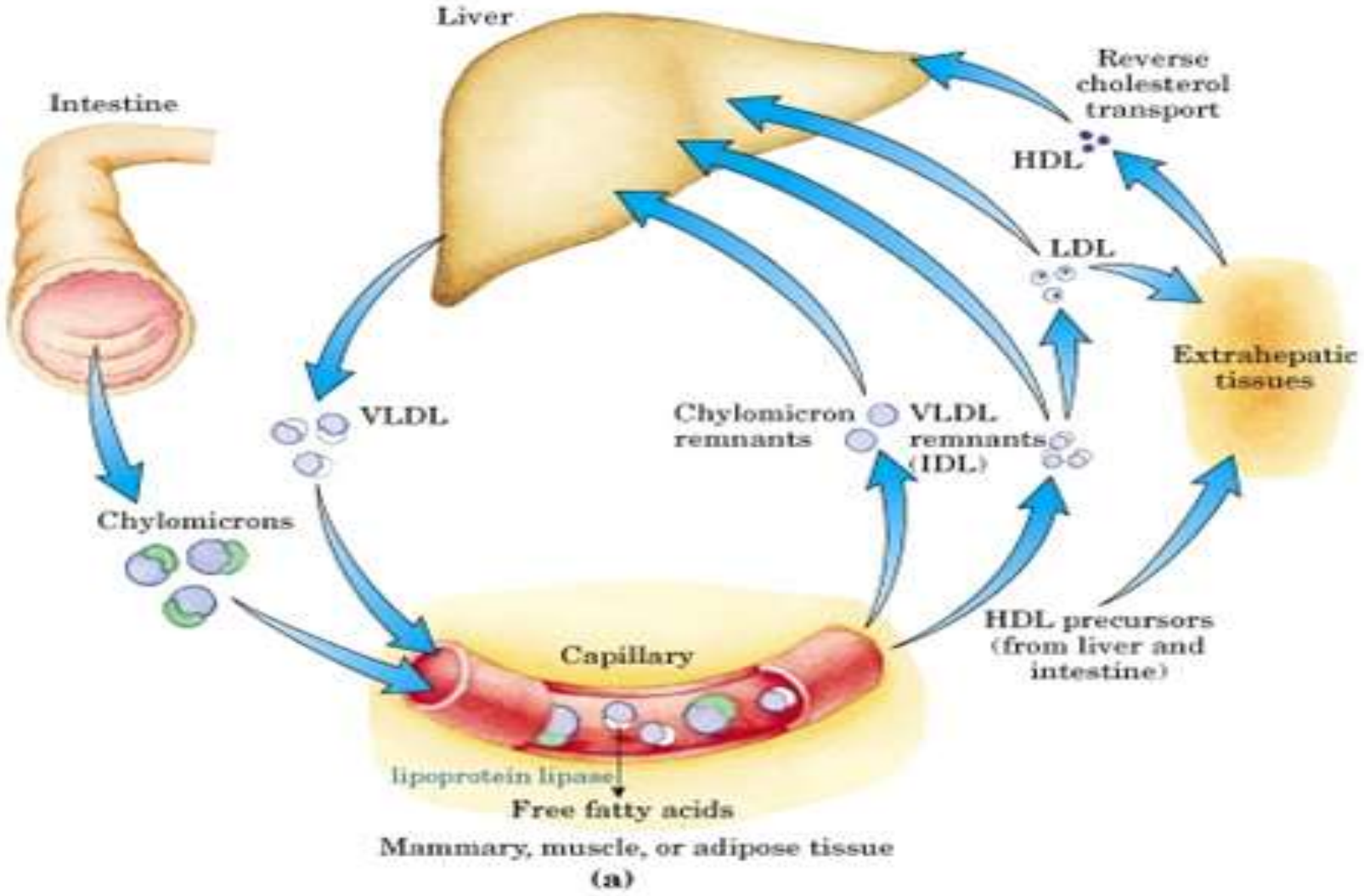
DEFINITION

- Dyslipidemia is defined as **elevated** total cholesterol, LDL cholesterol, or triglycerides; a **low** HDL cholesterol; or a **combination** of these abnormalities.
- Hyperlipoproteinemia describes an increased concentration of the **lipoprotein macromolecules** that transport lipids in the plasma.
- Abnormalities of plasma lipids can result in a *predisposition to coronary, cerebrovascular, and peripheral vascular arterial disease.*

Lipoprotein Cycle:



PATHOPHYSIOLOGY

Pathophysiology:

- Lipids are transported in the bloodstream as **complexes** of lipid and proteins known as lipoproteins.
- Atherosclerosis can result from ***injury to endothelium*** accompanied with or mediated by ***oxidation; infection or immunity; or a combination of those***.
- **Oxidized** LDL provokes an **inflammatory response** mediated by a number of chemoattractants and cytokines.

Pathophysiology

- **Repeated** injury and repair within an atherosclerotic plaque eventually lead to a ***fibrous cap*** protecting the underlying core of lipids, collagen, calcium, and inflammatory cells such as T lymphocytes. **Maintenance** of the fibrous plaque is critical to **prevent plaque rupture** and *subsequent coronary thrombosis*.

Types:

- Dyslipidemia can be primary (Genetic or familial) or secondary to a medication.
- Primary disorders are classified into **six categories**.
- The types and corresponding lipoprotein **elevations** include the following:
- *I (chylomicrons), IIa (LDL), IIb (LDL + very low density lipoprotein, or VLDL), III (intermediate-density lipoprotein), IV (VLDL), and V (VLDL + chylomicrons).*

Secondary:

- Medications like:
  - *progestins, thiazide diuretics, glucocorticoids, β-blockers, isotretinoin, protease inhibitors, cyclosporine, mirtazapine, sirolimus.*

Underlying Etiology:

- The primary defect in familial hypercholesterolemia is the *inability to bind LDL to the LDL receptor* (LDL-R) or, *rarely, a defect of internalizing the LDL-R* complex into the cell after normal binding.
- This leads to **lack of LDL degradation** by cells and unregulated **biosynthesis of cholesterol**, with total cholesterol and LDL cholesterol (LDL-C) **being inversely proportional** to the deficit in LDL-Rs.

TABLE 9-2 Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals[a]

Age

Men: ≥45 years

Women: ≥55 years or premature menopause without estrogen-replacement therapy

Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative)

Cigarette smoking

Hypertension (≥140/90 mm Hg or on antihypertensive medication)

Low HDL cholesterol (<40 mg/dL)[b]

CLINICAL PRESENTATION

Type I & II:

- Familial **hypercholesterolemia** is characterized by a **selective elevation in LDL** and *deposition of LDL-derived cholesterol in tendons (xanthomas) and arteries (atheromas).*
- Familial **lipoprotein lipase deficiency** is characterized by a **massive accumulation of chylomicrons** and a corresponding ***increase*** in **plasma triglycerides** .

Presentation:

- Presenting manifestations include *repeated attacks of pancreatitis and abdominal pain*, *eruptive cutaneous xanthomatosis, and hepatosplenomegaly beginning in childhood.*
- Symptom **severity** is **proportional** to *dietary fat intake, and consequently to the elevation of chylomicrons.* Accelerated **atherosclerosis** is **not associated** with this disease.

Type III:

- Patients with familial type III hyperlipoproteinemia develop the following clinical features **after age 20:**
  - Xanthoma striata palmaris (yellow discolorations of the palmar and digital creases);
  - Tuberous or tuberoeruptive xanthomas (bulbous cutaneous xanthomas); and
  - Severe atherosclerosis involving the coronary arteries, internal carotids, and abdominal aorta.

Type IV:

- It's common and occurs in adults, primarily in patients who are ***obese, diabetic, and hyperuricemic*** and ***do not have xanthomas***. It may be **secondary** to **alcohol** ingestion and can be aggravated by *stress, progestins, oral contraceptives, thiazides, or β-blockers.*

Type V :

- Type V is characterized by ***abdominal pain, pancreatitis, eruptive xanthomas, and peripheral polyneuropathy***. These patients are commonly **obese, hyperuricemic, and diabetic**; *alcohol intake, exogenous estrogens, and renal insufficiency* tend to be **exacerbating** factors. The risk of atherosclerosis is **increased** with this disorder.

DIAGNOSIS

Tests:

- A fasting lipoprotein profile including total cholesterol, LDL, HDL, and triglycerides should be measured in all adults 20 years of age or older at least once every 5 years.
- Measurement of plasma cholesterol , triglyceride, and HDL levels after a 12-hour or longer fast is **important**, because triglycerides may be **elevated in nonfasted** individuals; **total cholesterol** is only **modestly** affected by fasting.

Diagnostic Parameters:

- **Two determinations**, **1 to 8 weeks apart**, with the patient on a **stable diet and weight**, and in the **absence** of acute illness, are recommended to minimize variability and to obtain a reliable **baseline**.
- If the total cholesterol is **>200 mg/dL**, a **second** determination is recommended, and if the values are **more than 30 mg/dL** apart, the average of **three values should be used.**

TABLE 9-1 Classification of Total, LDL, and HDL Cholesterol and Triglycerides

Total cholesterol	
<200 mg/dL	Desirable
200–239 mg/dL	Borderline high
≥240 mg/dL	High
LDL cholesterol	
<100 mg/dL	Optimal
100–129 mg/dL	Near or above optimal
130–159 mg/dL	Borderline high
160–189 mg/dL	High
≥190 mg/dL	Very high
HDL cholesterol	
<40 mg/dL	Low
≥60 mg/dL	High
Triglycerides	
<150 mg/dL	Normal
150–199 mg/dL	Borderline high
200–499 mg/dL	High
≥500 mg/dL	Very high

Diagnostic Parameters:

- After a lipid abnormality is confirmed, major components of the evaluation are the **history** (including age, gender, and, if female, menstrual and estrogen replacement status), **physical examination, and laboratory investigations.**

Assessment:

- A complete history and physical examination should assess :
  - (1) Presence or absence of *cardiovascular risk factors or definite cardiovascular disease in the individual*;
  - (2) **Family history** of **premature** cardiovascular disease or lipid disorders;

Assessment:

- (3) Presence or absence of **secondary** causes of hyperlipidemia, including **concurrent medications**; and
- (4) Presence or absence of *xanthomas, abdominal pain, or history of pancreatitis, renal or liver disease, peripheral vascular disease, abdominal aortic aneurysm, or cerebral vascular disease (carotid bruits, stroke, or transient ischemic attack).*

Risk Factors:

- *Diabetes mellitus is regarded as a CHD risk **equivalent**.*

  That is, the presence of diabetes in patients without known CHD is associated with the same level of risk as patients without diabetes but having confirmed CHD.

Further Investigations:

- Lipoprotein electrophoresis is useful to determine which class of lipoproteins is affected; if needed.
- If the triglyceride levels are <400 mg/dL and neither type III hyperlipidemia nor chylomicrons are detected by electrophoresis, then one can calculate VLDL and LDL concentrations:
  - VLDL = triglycerides ÷ 5;
  - LDL = total cholesterol – (VLDL + HDL).
- Initial testing uses total cholesterol for case finding, but subsequent management decisions should be based on LDL.

HDL:

- Because total cholesterol is composed of cholesterol derived from ***LDL, VLDL, and HDL***, determination of HDL is useful when total plasma cholesterol is elevated.
- HDL may be ***elevated by moderate alcohol ingestion*** (fewer than two drinks per day), ***physical exercise, smoking cessation, weight loss, oral contraceptives, phenytoin, and terbutaline***.
- HDL may be **lowered** by *smoking, obesity, a sedentary lifestyle, and drugs such as β-blockers.*

DESIRED OUTCOME

- The goals of treatment are to **lower total and LDL cholesterol** in order to **reduce the risk** of first or recurrent events such as myocardial infarction, angina, heart failure, ischemic stroke, or other forms of peripheral arterial disease such as carotid stenosis or abdominal aortic aneurysm.

TREATMENT

TABLE 9-3 LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLCs) and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate TLCs (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 (optional goal: <70)	≥100	≥100 (<100: consider drug options)[a]
Moderately high risk: 2+ risk factors (10-year risk 10–20%)	<130	≥130	≥130 (100–129: consider drug options)
Moderate risk: 2+ risk factors (10-year risk <10%)	<130	≥130	≥160
Lower risk: 0–1 risk factor[b]	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

Nonpharmacologic Therapy

Life Style Modifications:

- Therapeutic lifestyle changes are begun on the first visit and include ***dietary therapy, weight reduction, and increased physical activity***.
- Inducing a weight loss of **10% should be discussed** with patients who are overweight.
- In general, physical activity of **moderate intensity 30 minutes a day for most** days of the week should be encouraged.

Life Style Modifications:

- All patients should be counseled to stop smoking and to control hypertension.
- The objectives of dietary therapy are to progressively decrease the intake of total fat, saturated fat, and cholesterol and to achieve a desirable body weight.

Dietary Alternatives:

- Excessive dietary intake of cholesterol and saturated fatty acids leads to decreased hepatic clearance of LDL and deposition of LDL and oxidized LDL in peripheral tissues.
- Increased intake of soluble fiber in the form of oat bran, and whole grain and such; can result in useful adjunctive reductions in total and LDL cholesterol (5% to 20%).

Dietary Alternatives:

- In epidemiologic studies, ingestion of ***large amounts of cold-water oily fish was associated with a reduction in CHD risk***.
- Fish oil supplementation has a *fairly large effect in reducing triglycerides and VLDL cholesterol*, but it ***either has no effect on total and LDL cholesterol or may cause elevations in these fractions***. Other actions of fish oil may account for any cardioprotective effects.

Efficacy:

- If all recommended dietary changes were instituted, the estimated average reduction in LDL would range from 20% to 30%.

PHARMACOLOGIC THERAPY

TABLE 9-5 Effects of Drug Therapy on Lipids and Lipoproteins

Drug	Mechanism of Action	Effects on Lipids	Effects on Lipoproteins
Cholestyramine, colestipol, colesevelam	↑ LDL catabolism ↓ Cholesterol absorption	↓ Cholesterol	↓ LDL ↑ VLDL
Niacin	↓ LDL and VLDL synthesis	↓ Triglyceride ↓ Cholesterol	↓ VLDL, ↓ LDL, ↑ HDL
Gemfibrozil, fenofibrate, clofibrate	↑ VLDL clearance ↓ VLDL synthesis	↓ Triglyceride ↓ Cholesterol	↓ VLDL, ↓ LDL, ↑ HDL
Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin	↑ LDL catabolism ↓ LDL synthesis	↓ Cholesterol	↓ LDL
Ezetimibe	Blocks cholesterol absorption across the intestinal border	↓ Cholesterol	↓ LDL

TABLE 9-6 Lipoprotein Phenotype and Recommended Drug Treatment

Lipoprotein Type	Drug of Choice	Combination Therapy
I	Not indicated	–
IIa	Statins	Niacin or BARs
	Cholestyramine or colestipol	Statins or niacin
	Niacin	Statins or BARs
		Ezetimibe
IIb	Statins	BARs, fibrates, or niacin
	Fibrates	Statins or niacin or BARs[a]
	Niacin	Statins or fibrates
		Ezetimibe
III	Fibrates	Statins or niacin
	Niacin	Statins or fibrates
		Ezetimibe
IV	Fibrates	Niacin
	Niacin	Fibrates
V	Fibrates	Niacin
	Niacin	Fish oils

Dosages of Selected Lipid-Modulating Drugs

Drug	Initial Dosage	Usual Dosage	Maximal Dosage	Comment
Cholestyramine	4 g before main meal	4 g BID before heaviest meals	8 g BID before heaviest meals	May prescribe 24 g/d, but few patients can tolerate.
Colestipol	5 g of powder or 2 g of tablets every day before main meal	5 g of powder or 4 g of tablets BID before heaviest meals	10 g of powder or 8 g of tablets BID before heaviest meals	May prescribe 30 g of powder per day, but few patients can tolerate.
Colesevelam	6 × 0.63-g tablets/d	Same	7 × 0.63-g tablets/d	Less bulk is associated with less gastrointestinal intolerance.
Niaspan	500 mg QHS	1,000–2,000 mg QHS	2,000 mg QHS	Increase dose by 500 mg daily every 4 weeks.
Atorvastatin	10–40 mg every day	10–40 mg every day	80 mg every day	Administer any time of day.
Fluvastatin	20–40 mg QHS	20–40 mg QHS	40 mg BID 80 mg XL every day	Modified-release form (XL) has similar efficacy but has less bioavailability (and less risk of adverse effects).
Lovastatin	20 mg with dinner	20–40 mg with dinner	40 mg BID	Administration with food increases bioavailability. BID dosing provides greater LDL-C–lowering efficacy than every day.
Pitavastatin	1–2 mg every day	1–2 mg every day	4 mg every day	Administer any time of the day with or without food.
Pravastatin	10–40 mg every day	10–40 mg every day	80 mg every day	Administer with food to reduce dyspepsia.
Rosuvastatin	10–20 mg every day	10–20 mg every day	40 mg every day	Administer any time of the day.
Simvastatin	20–40 mg every PM	20–40 mg every PM	80 mg every PM[b]	Administer with food to reduce dyspepsia.
Gemfibrozil	600 mg BID	Same	Same	
Fenofibrate[a]	67–201 mg every day	Same	201 mg every day	

[a] Multiple formulations are available and doses do vary.

[b] Restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. For more information regarding simvastatin, please see http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm.

BID, twice daily; LDL-C, low-density lipoprotein cholesterol; QHS, every evening at bedtime.

HMG-CoA Reductase Inhibitors

- **Agents: (Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin)**
- Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, interrupting the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol biosynthesis.
- **Reduced** synthesis of LDL and **enhanced** catabolism of LDL mediated through **LDL-Rs** appear to be the principal mechanisms for lipid-lowering effects.

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*

Specific statins and doses are noted in bold that were evaluated in RCTs (17,18,46-48,64-67,69-78) included in CQ1, CQ2 and the CTT 2010 meta-analysis included in CQ3 (20). All of these RCTs demonstrated a reduction in major cardiovascular events. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*.

*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 (47).

‡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.

bid indicates twice daily; FDA, Food and Drug Administration; IDEAL, Incremental Decrease through Aggressive Lipid Lowering study; LDL–C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.

Formulation, dosing, and common adverse effects of lipid-lowering drugs

Lipid-Lowering Drug	Dosage Forms	Usual Adult Maintenance Dose Range	Adverse Effects
Statins			
Atorvastatin	10, 20, 40, 80 mg tablets	10 to 80 mg once daily (at any time of day	Most frequent side effects are constipation, abdominal pain, diarrhea, dyspepsia, and nausea. Statins should be discontinued promptly if serum transaminase levels (liver function tests) rise to 3 times upper limit of normal, or if patient develops signs or symptoms of myopathy.
Fluvastatin	20, 40 mg capsules; 80 mg extended-release tablets	20–40 mg/day as a single dose (evening) or 40 mg twice daily; 80 mg once daily (evening)	
Lovastatin	10, 20, 40 mg tablets	10 to 80 mg/day as a single dose (with evening meal) or divided twice daily with food	Approximate equivalent doses of HMG-CoA reductase inhibitors are: atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40 mg, pravastatin 40 mg, simvastatin 20 mg, and rosuvastatin 5 mg.
Lovastatin ER	20, 30, 60 mg tablets	20 to 60 mg/day as a single dose	
Pravastatin	10, 20, 40, 80 mg tablets	10 to 80 mg/day as a single dose at bedtime	
Rosuvastatin	5, 10, 20, 40 mg tablets	5–40 mg/day (at any time of day). 40 mg reserved for those who don't achieve LDL cholesterol goal on 20 mg	
Simvastatin	5, 10, 20, 40, 80 mg tablets	5–80 mg/day as a single dose in the evening, or divided	

Efficacy:

- When used as **monotherapy**, statins are ***the most potent total and LDL cholesterol-lowering agents*** and among the **best tolerated**. Total and LDL cholesterol are reduced in a ***dose-related fashion by 30% or more*** when added to ***dietary*** therapy.

Combinations:

- Combination therapy with a **statin and BAR** is rational because numbers **of LDL-Rs are increased**, leading to **greater degradation of LDL cholesterol**; intracellular **synthesis** of cholesterol is inhibited; and **enterohepatic** recycling of bile acids is **interrupted**.

Combinations:

- Combination therapy with a statin and ezetimibe is also rational because ezetimibe inhibits **cholesterol absorption** across the gut border and adds **12% to 20% further reduction** when combined with a statin or other drugs.

Adverse Reactions:

- **Constipation** occurs in fewer than 10% of patients taking statins. Other adverse effects include **elevated serum aminotransferase levels** (primarily alanine aminotransferase), elevated **creatine kinase** levels, **myopathy, and rarely rhabdomyolysis.**

Bile Acid Resins (BARs):

- Agents: **(Cholestyramine, Colestipol, Colesevelam)**
- The primary action of BARs is to **bind bile acids** in the **intestinal** lumen, with a concurrent interruption of **enterohepatic circulation** of bile acids, which decreases the bile acid pool size and **stimulates hepatic synthesis of bile acids from cholesterol**.

MOA:

- **Depletion** of the hepatic pool of cholesterol results in an **increase in cholesterol biosynthesis** and an increase in the number of **LDL-Rs on the hepatocyte** membrane, which stimulates an enhanced rate of **catabolism** from plasma and lowers LDL levels.
- The increase in hepatic cholesterol biosynthesis may be paralleled by **increased hepatic VLDL production**, and, consequently, BARs may **aggravate hypertriglyceridemia** in patients with **combined** hyperlipidemia.

Indications & SE:

- BARs are useful in treating **primary hypercholesterolemia** (familial hypercholesterolemia, familial combined hyperlipidemia, type IIa hyperlipoproteinemia).
- GI complaints of *constipation, bloating, epigastric fullness, nausea, and flatulence* are most commonly reported. These adverse effects can be **managed by increasing fluid intake**, modifying the diet to **increase bulk, and using stool softeners**.

Administration:

- The gritty texture and bulk may be **minimized by mixing the powder with orange drink or juice.**
- Colestipol may have **better palatability** than cholestyramine because it is **odorless and tasteless**. Tablet forms should help improve **adherence** with this form of therapy.

Adverse effects:

- Impaired absorption of fat-soluble vitamins A, D, E, and K; hypernatremia and hyperchloremia; GI obstruction; and reduced bioavailability of acidic drugs such as *warfarin, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, loperamide, and possibly iron*.
- Drug interactions may be avoided by **alternating administration times with an interval of 6 hours or greater** between the BAR and other drugs.

Niacin

- **Niacin** (nicotinic acid) reduces the hepatic synthesis of VLDL, which in turn leads to a ***reduction in the synthesis of LDL.***
- Niacin also **increases HDL** by reducing its catabolism.
- The principal use of niacin is **for mixed hyperlipidemia** or as a ***second-line agent in combination therapy for hypercholesterolemia***.
- It is a ***first-line agent*** *or alternative for the treatment of* ***hypertriglyceridemia and diabetic dyslipidemia***.

Adverse Reactions:

- Niacin has many common adverse drug reactions; most of the symptoms and biochemical abnormalities seen ***do not require discontinuation of therapy.***
- Cutaneous flushing and itching appear to be ***prostaglandin mediated*** and can be **reduced** by taking *aspirin 325 mg shortly before niacin ingestion.*

Adverse Reactions:

- Taking the niacin dose **with meals** and slowly titrating the dose upward may **minimize** these effects. Concomitant ***alcohol and hot drinks may magnify the flushing and pruritus from niacin***, and they should ***be avoided at the time of ingestion***. GI intolerance is also a common problem.
- Potentially important laboratory abnormalities occurring with niacin therapy include *elevated liver function tests, hyperuricemia, and hyperglycemia.*

Adverse Reactions:

- ***Niacin-associated hepatitis*** is more common with ***sustained-release preparations***, and their use should be **restricted** to patients **intolerant** of regular-release products.
- Niacin is **contraindicated** in patients with **active liver disease**, and it may **exacerbate** preexisting **gout and diabetes**.
- Nicotinamide should **not** be used in the treatment of hyperlipidemia because it **does not effectively lower cholesterol or triglyceride levels.**

Fibric Acids

- **Agents: (Gemfibrozil, Fenofibrate, Clofibrate)**
- Fibrate **monotherapy** is effective in **reducing VLDL**, but a reciprocal **rise in LDL may occur** and total **cholesterol** values may remain relatively **unchanged**.
- Plasma HDL concentrations **may rise 10% to 15%** or more with fibrates.

Efficacy:

- Gemfibrozil **reduces** the synthesis of **VLDL** and, to a lesser extent, **apolipoprotein B** with a concurrent **increase** in the rate of **removal of triglyceride-rich lipoproteins** from plasma.
- Clofibrate is **less effective** than gemfibrozil or niacin in reducing VLDL production.

Adverse Reactions:

- GI complaints , rash, dizziness, and transient elevations in transaminase levels and alkaline phosphatase, respectively.
- Clofibrate and, less commonly, gemfibrozil may enhance the formation of **gallstones**.

Adverse Reactions:

- A myositis syndrome of **myalgia**, **weakness, stiffness, malaise**, and **elevations in CK and AST** may occur and seems to be more common in patients with ***renal insufficiency.***
- **Fibrates** may **potentiate** the effects of **oral anticoagulants**, and the INR should be **monitored very closely** with this combination.

Ezetimibe

- **Ezetimibe** interferes with the **absorption** of cholesterol from the brush border of the intestine, a novel mechanism that makes it a good choice for **adjunctive therapy**. It is approved as both **monotherapy and for use with a statin**. The dose is **10 mg once** daily, given **with or without** food. When used alone, it results in an approximate **18% reduction in LDL cholesterol**. When added to a statin, ezetimibe lowers LDL by about an **additional 12% to 20%.**

Uses & SE:

- A combination product containing ezetimibe 10 mg and simvastatin 10, 20, 40, or 80 mg is available.
- Ezetimibe is well tolerated; approximately 4% of patients experience **GI upset**.
- Because cardiovascular outcomes with ezetimibe have **not been evaluated,** it should be reserved for *patients unable to tolerate statin therapy or those who do not achieve satisfactory lipid lowering with a statin alone*.

Fish Oil Supplementation

- Diets high in omega-3 polyunsaturated fatty acids (from fish oil), *reduce cholesterol, triglycerides, LDL, and VLDL and may elevate HDL cholesterol.*
- Fish oil supplementation may be most **useful in patients with hypertriglyceridemia**, but its role in treatment is **not well defined.**

Uses & SE:

- **Lovaza (omega-3-acid ethyl esters)** is a prescription form of concentrated fish oil EPA 465 mg and DEA 375 mg.
- The daily dose is 4 g/day, which can be taken as four 1-g capsules once daily or two 1-g capsules twice daily. This product lowers ***triglycerides by 14% to 30% and raises HDL by about 10%.***
- Complications of fish oil supplementation such as ***thrombocytopenia and bleeding disorders have been noted, especially with high doses*** (EPA, 15 to 30 g/day).

Combination Drug Therapy

- Combination therapy may be considered **after adequate trials of monotherapy** and for patients documented to be **adherent** to the prescribed regimen.
- **Two or three** lipoprotein profiles **at 6-week intervals** should confirm **lack of response** prior to initiation of combination therapy.

Monitoring & Efficacy:

- Contraindications to and drug interactions with combined therapy should **be screened carefully**, and the **extra cost** of drug **product and monitoring** should be **considered**.
- In general, a **statin** plus a **BAR** or **niacin** plus a **BAR** provide the **greatest reduction** in total and LDL cholesterol.

Monitoring & Efficacy:

- Regimens intended to **increase** HDL levels should include either **gemfibrozil** or **niacin**, bearing in mind that **statins** combined **with either** of these drugs may result in a **greater incidence of hepatotoxicity or myositis.**
- Familial combined hyperlipidemia may ***respond better to a fibrate and a statin*** than to a **fibrate and a BAR**.

Treatment Of Hypertriglyceridemia:

- Lipoprotein pattern types I, III, IV, and V are associated with **hypertriglyceridemia**, and these primary lipoprotein disorders should be **excluded prior to implementing therapy.**
- A family history **positive for CHD is important** in identifying patients at risk for **premature atherosclerosis**.
- If a patient with CHD has elevated triglycerides, the associated abnormality is ***probably a contributing factor to CHD and should be treated.***

Treatment Of Hypertriglyceridemia:

- High serum triglycerides should be treated by achieving **desirable body weight**, consumption of **a low saturated fat and cholesterol diet, regular exercise, smoking cessation, and restriction of alcohol** .
- Secondary therapeutic target in persons with high triglycerides is the sum of LDL and VLDL (termed *non-HDL* [total cholesterol – HDL]).

Considerations:

- The goal for non-HDL with high serum **triglycerides is set at 30 mg/d**L higher than that for LDL on the premise that **a VLDL level of 30 mg/dL or less is normal.**
- Drug therapy with **niacin** should be considered in patients with **borderline- high triglycerides <u>but</u>** with *accompanying risk factors of established CHD, family history of premature CHD, concomitant LDL elevation or low HDL, and genetic forms of hypertriglyceridemia associated with CHD.*

Considerations:

- Niacin may be used **cautiously** in persons with **diabetes** ; it can cause a slight increase in glucose and no change in hemoglobin A1C. Alternative therapies include **gemfibrozil, statins**, and **fish oil**.
- The goal of therapy is to **lower triglycerides and VLDL** particles that may be **atherogenic**, **increase HDL, and reduce LDL.**

Considerations:

- Very high triglycerides are associated with **pancreatitis** and other adverse consequences. Management includes *dietary fat restriction (10% to 20% of calories as fat), weight loss, alcohol restriction, and treatment of coexisting disorders* (e.g., diabetes).
- Drug therapy includes **gemfibrozil, niacin**, and higher-potency statins (**atorvastatin, rosuvastatin**, and **simvastatin**).

TREATMENT OF LOW HDL CHOLESTEROL

- Low HDL cholesterol is a **strong independent risk predictor of CHD**. In low HDL, the primary target remains **LDL**, but treatment *emphasis shifts to weight reduction, increased physical activity, smoking cessation, and to* ***fibrates*** *and* ***niacin*** *if drug therapy is required*.

TREATMENT OF DIABETIC DYSLIPIDEMIA

- It's characterized by **hypertriglyceridemia**, **low HDL, and minimally elevated LDL.** Small, dense LDL (pattern B) in diabetes is **more atherogenic** than larger, more buoyant forms of LDL (pattern A).
- Diabetes is a CHD risk equivalent, and the primary target is to **lower the LDL to <100 mg/dL**. When LDL is >130 mg/dL, most patients *require simultaneous therapeutic lifestyle changes and drug therapy.*

Treatment:

- When LDL is between 100 and 129 mg/dL, *intensifying glycemic control, adding drugs* for atherogenic dyslipidemia (**fibrates, niacin**), and *intensifying LDL-lowering therapy* are options. **Statins** are considered by many to be the **drugs of choice** because the primary target is LDL.