Hyperlipidemia

Hyperlipidemia, **hyperlipoproteinemia**: Abnormally elevated level of lipid in blood, these lipids can adhere to the walls of the arteries and restrict blood flow which creates significant risk of heart attack and stroke. Plasma lipids include: cholesterols, triglycerides and phospholipids. Lipids are insoluble in plasma and are transported in protein capsule known as **LIPOPROTEIN**. **Cholesterol** plays the central role in the pathogenesis of **atherosclerosis.** It is the precursor molecule for the **formation of bile acids**, the **synthesis of steroid hormones**, and the **formation of cell membranes**. **TG** are an important source of **stored energy** in adipose tissue. **Phospholipids** are essential for cellular function and the transport of lipids in the circulation by forming a membrane bilayer of lipoproteins.

Types of lipoproteins:

1. Chylomicrons (TGs): → formed in GIT from dietary TG.

2. VLDL (TGs and cholesterol) → endogenously synthesized in liver. Degraded by LPL into free fatty acids (FFA) for storage in adipose tissue and for oxidation in tissues such as cardiac and skeletal muscle.

3. IDL (TGs, cholesterol); **and LDL (cholesterol)** → derived from VLDL hydrolysis by **lipoprotein lipase.** Normally, about 70% of LDL is removed from plasma by hepatocytes.

4. HDL (protective) →exert several anti-atherogenic effects. They participate in retrieval of cholesterol from the artery wall and inhibit the oxidation of atherogenic lipoproteins& removes cholesterol from tissues to be degraded in liver.

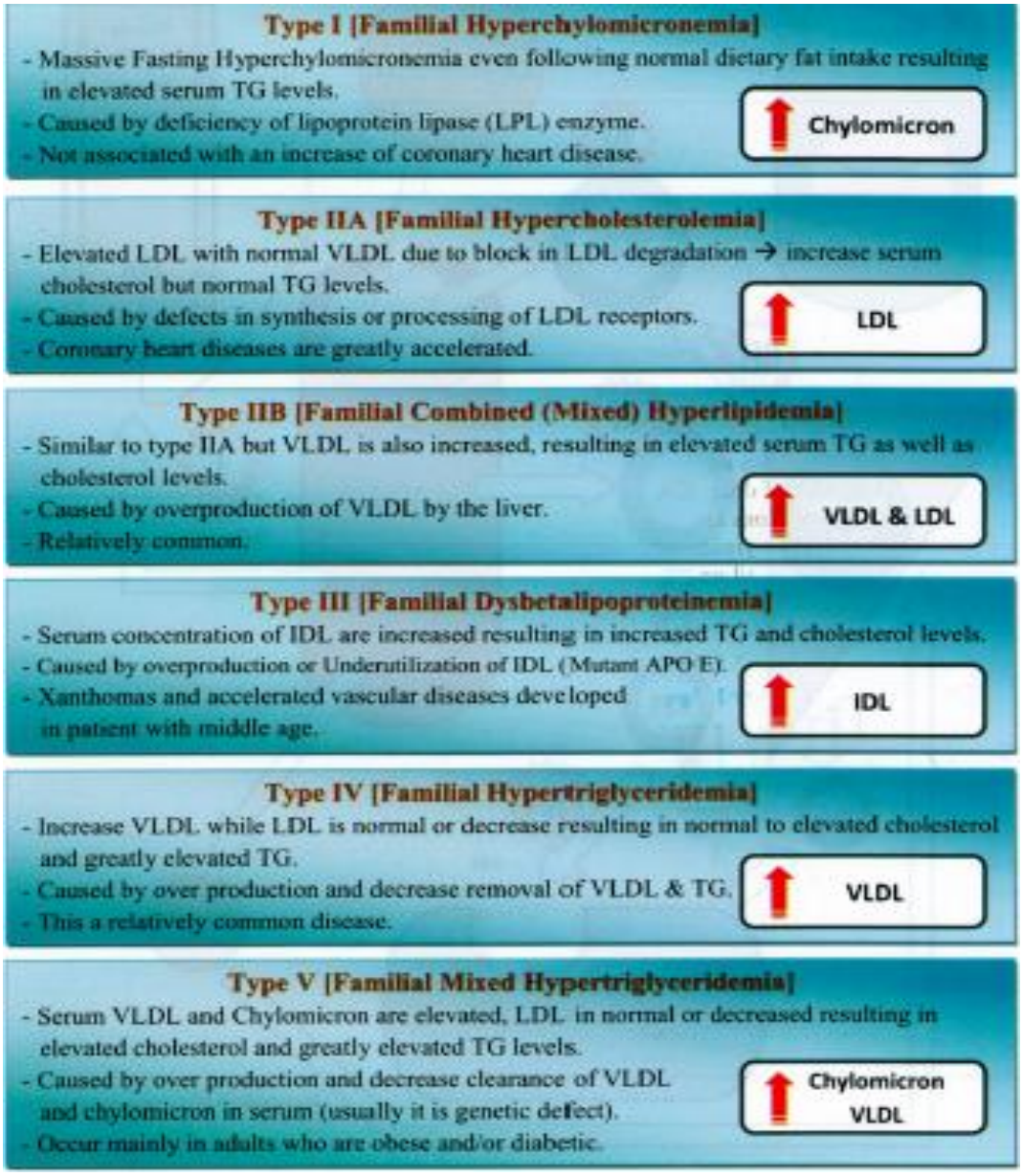
Lipid Metabolism (للأطلاع):

Lipids originate from two sources: endogenous lipids, synthesized in the liver, and exogenous lipids, ingested and processed in the intestine. Dietary cholesterol and triglycerides are packaged into chylomicrons in the intestine, before passing into the bloodstream via lymphatics. Chylomicrons are broken down by lipoprotein lipase (LPL) in the capillaries of muscle and adipose tissue to fatty acids, which then enter the cells. The chylomicron remnants, which have lost much of their triglyceride content, are taken up by the liver for disposal. The liver synthesizes triglycerides and cholesterol, and packages them as VLDLs before releasing them into the blood. When VLDLs (which consist mainly of triglyceride) reach muscle and adipose blood vessels, their

triglycerides are hydrolyzed by LPL to fatty acids. The fatty acids that are released are taken up by the surrounding muscle and adipose cells. During this process, the VLDLs become progressively denser and turn into LDLs. While most of the resulting LDLs are taken up by the liver for disposal, some circulate and distribute cholesterol to the rest of the body tissues. HDLs, which are also secreted from the liver and intestine, have the task of preventing lipid accumulation. They remove surplus cholesterol from tissues and transfer it to LDLs that return it to the liver.

Etiology of hyperlipidemias:

1- **Primary hyperlipidemia:** Up to 60% of the variability in cholesterol fasting lipids may be genetically determined. There are five primary inherited lipoprotein disorders which disturb lipid metabolism. These are:



2- **Secondary hyperlipidemia:** results from liver and biliary disease, obesity, hypothyroidism, diabetes, diet, alcohol excess, renal disease (nephrotic syndrome) and drugs (eg, progestins, thiazide diuretics, glucocorticoids, β blockers, protease inhibitors and cyclosporine).

CLINICAL PRESENTATION

Most patients are asymptomatic for many years. Symptomatic patients may complain of chest pain, palpitations, sweating, anxiety, shortness of breath, or abdominal pain. They may also experience difficulty with speech or movement or loss of consciousness. Depending on the lipoprotein abnormality, signs on physical examination may include cutaneous xanthomas, peripheral polyneuropathy, high blood pressure, and increased body mass index or waist size.

DIAGNOSIS

Diagnosis is typically based on medical history, physical examination and blood test done after overnight fasting. Measure plasma cholesterol, triglyceride, and HDL levels after a 12-hour fast because triglycerides may be elevated in nonfasting.

History and physical examination:

- Presence of cardiovascular risk factors or cardiovascular disease
- Family history of premature cardiovascular disease, hyperlipidemia, or diabetes mellitus
- Diabetes mellitus or glucose intolerance
- Central obesity
- High blood pressure
- Presence or absence of risk factors
- Presence or absence of kidney or liver disease, peripheral vascular disease, abdominal aortic aneurysm, cerebral vascular disease

- LDL-C < 100 mg/dL----------Optimal
  - 100-129 mg/dL ----------Near or above optimal
  - 130-159 mg/dL----------Borderline high
  - 160-189 mg/dL ----------High
  - > or = 190 mg/dL ----------Very high
- Total -C
  - <200 mg/dL---------- Desirable
  - 200-239 mg/dL----------Borderline high
  - > or= 240 mg/dL----------High
- TG-C:
  - <150 mg/dL----------Optimal
  - 150-199 mg/dL ----------Borderline high
  - 200-499 mg/dL ----------High
  - > or = 500 mg/dL ----------Very high
- HDL cholesterol:
  - <40 mg/dL ----------Low
  - >60 or = 60 mg/dL ---------- High

Management of hyperlipidemias

1. Any medical disorder that may be causing hyperlipidemia, e.g., diabetes, hypothyroidism, should be treated first.

2. Lifestyle Changes

- Weight reduction in the overweight patient can reduce LDL-C
- Smoking cessation
- Increasing physical activity should be a component of the treatment of any patient with high blood cholesterol. Regular physical exercise may reduce TG and VLDL-C levels, raise HDL-C levels slightly, promote weight loss or maintenance of desired weight, lower BP, and cause favorable changes in coronary blood flow.
- Dietary adjustment:

i. Reduce intake of saturated and trans-unsaturated fat to less than 7-10% of total energy
ii. Reduce the intake of cholesterol to less than 250 mg/day
iii. Replace sources of saturated fat and cholesterol with alternative foods such as low-fat dairy products and low glycemic index carbohydrates
iv. Reduce energy-dense foods such as fats and soft drinks, whilst increasing activity and exercise to achieve stable or negative energy balance (i.e., weight maintenance or weight loss)
v. Increase consumption of cardioprotective and nutrient dense foods such as vegetables, unrefined carbohydrates, fish, pulses, fruit etc.
vi. Adjust alcohol consumption, reducing intake if excessive or if associated with hypertension, hypertriglyceridemia or central obesity.
vii. Achieve additional benefits with supplementary intake of foods containing lipid-lowering nutrients such as dietary fiber and plant sterols.

3. **Lipid-lowering Therapy options**

Anti-hyperlipidemic drugs are mainly classified into five types they are:

1. HMG CoA REDUCTASE INHIBITORS: E.g.: Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin.

2. FIBRATES: E.g.: Fenofibrate, Gemfibrozil, Clofibrate.

3. Nicotinic acid: E.g: NIACIN.

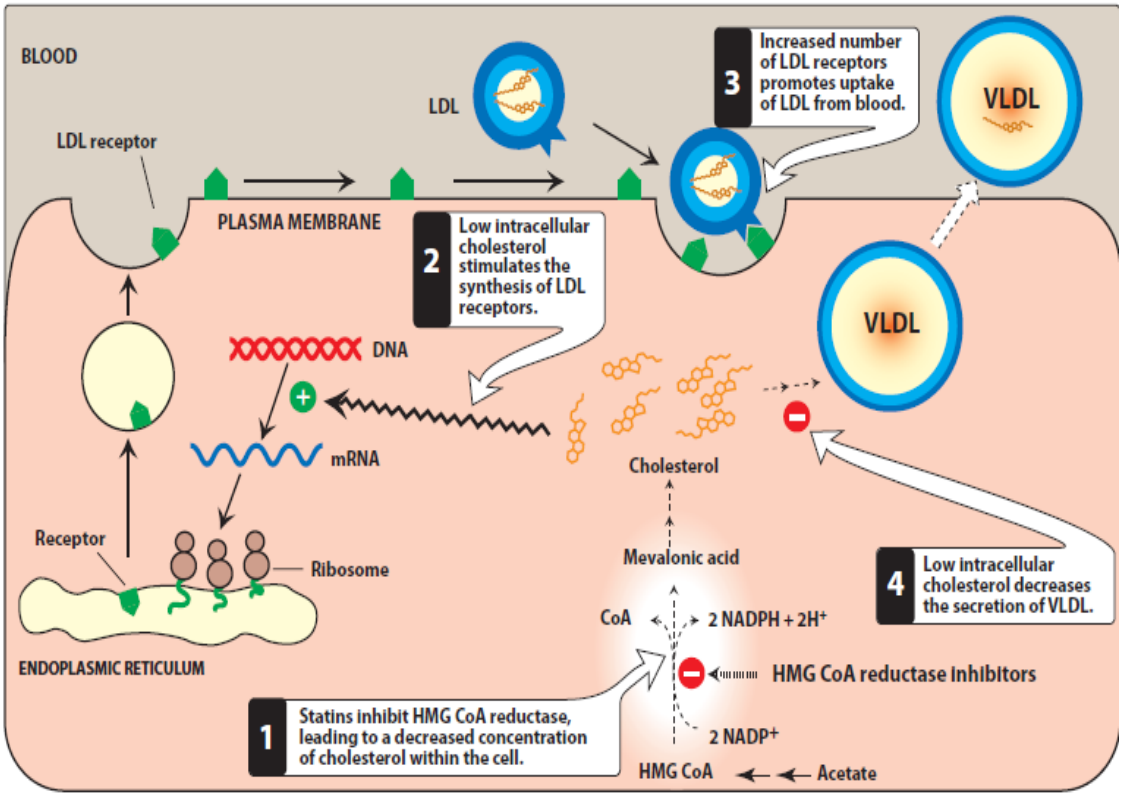
4. BILE ACID SEQUESTRANTS: E.g.: Colesevelam, Colestipol, Cholestyramine

5. CHOLESTEROL ABSORPTION INHIBITORS: E.g.: Ezetimibe.

H M G – COA Reductase Inhibitors (Statins): 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (commonly known as statins) lower elevated LDL-C, resulting in a substantial reduction in coronary events and death from CHD. They are considered first-line treatment for patients with elevated risk of CVD. Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity.

Mechanism of action

Lovastatin, simvastatin, pravastatin, atorvastatin, Fluvastatin, and rosuvastatin are competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol synthesis. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol. Depletion of intracellular cholesterol causes the cell to increase the number of cell surface LDL receptors that can bind and internalize circulating LDLs. Thus, plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL catabolism. Rosuvastatin, and atorvastatin are the most potent LDL cholesterol–lowering statins, followed by simvastatin, pravastatin, and then lovastatin and fluvastatin. The HMG CoA reductase inhibitors also decrease triglyceride levels and may increase HDL cholesterol levels in some patients.



Therapeutic uses: These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias. However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs. Combination therapy with a statin and a BAR is rational because the 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. 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 drug. The efficacy of many statins is greater if administered in the evening to coincide with the nighttime upturn in endogenous cholesterol biosynthesis; atorvastatin, and rosuvastatin with a longer half-life and more potent LDL-C lowering, may be administered without regard to time of day.

Adverse effects

1. Hepatotoxicity (increased serum transaminase).
2. Myopathy (increased creatine kinase) especially when combined with:
    - Other lipid lowering drugs: i) Fibrates. ii) Niacin.
    - Other drugs that are metabolized by 3A4 isoform of cytochrome P450 e.g.: erythromycin, cyclosporine, verapamil, ketoconazole. **Pravastatin** and Fluvastatin are the statins of choice to be given to a patient taking other drugs metabolized by cytochrome 3A4 system.
3. G.I.T upset.
4. Headache.

Note: liver transaminases and CK must be regularly measured during therapy with statins.

Drug interactions: Potentiate the action of oral anticoagulant and antidiabetic drugs (displacement from plasma protein binding sites).

Contraindications

1. Pregnancy & lactation.
2. Active liver diseases.

FIBRIC ACID DERIVATIVE (Fibrates): Fenofibrate and gemfibrozil are derivatives of fibric acid that lower serum triglycerides and increase HDL levels.

Mechanism of action:

The peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor family that regulates lipid metabolism. PPARs function as ligand-activated transcription factors. Upon binding to their natural ligands (fatty acids or eicosanoids) or antihyperlipidemic drugs, PPARs are activated. They then bind to peroxisome proliferator response elements, which ultimately leads to decreased triglyceride concentrations through increased expression of lipoprotein lipase and decreasing apolipoprotein (apo) CII concentration. Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels. Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AII.

Therapeutic uses: The fibrates are used in the treatment of hypertriglyceridemia. In patients who have TG levels >1,000 mg/dL and are at risk for developing pancreatitis, fibrates, + niacin, are the drugs of choice. Patients with familial dysbetalipoproteinemia and mixed hyperlipidemia, fibric acid derivatives are the drugs of choice.

Adverse effects:

The most common adverse effects are mild gastrointestinal (GI) disturbances. Because these drugs increase biliary cholesterol excretion, Gemfibrozil and probably fenofibrate enhance gallstone formation rarely. A myositis syndrome of myalgia, weakness, stiffness, malaise, and elevations in creatine kinase and aspartate aminotransferase may occur and may be more common in patients with renal insufficiency.

Drug interactions:

1. Increased risk of myopathy when combined with statins.
2. Displace drugs from plasma proteins (e.g., oral anticoagulants and oral hypoglycemic drugs).

Contraindications: Patients with impaired renal functions, pregnant or nursing women and preexisting gall bladder disease.

Niacin

Niacin (nicotinic acid) is a water-soluble B3 vitamin that can improve the levels of all serum lipids. Niacin inhibits the mobilization of free fatty acids from peripheral adipose

tissue to the liver, reduced synthesis and secretion of VLDL particles by the liver. Niacin also increases HDL by reducing its catabolism. The principal use of niacin is for mixed dyslipidemia or as a second-line agent in combination therapy for hypercholesterolemia. It is a first-line agent or alternative for treatment of hypertriglyceridemia and diabetic dyslipidemia. Cutaneous flushing and itching appear to be prostaglandin mediated and can be reduced by taking aspirin 325 mg shortly before niacin ingestion. Taking the niacin dose with meals and slowly titrating the dose upward may minimize these effects. GI intolerance is also a common problem. **Crystalline niacin** should be started at a low level (e.g., 250 mg in two or three divided doses daily) and slowly titrated as tolerated (e.g., daily doses increased by 250 mg every 3 to 7 days) to a maximum of 3,000 mg/day**, Sustained-release** (timed-release) dosage forms of niacin were developed to reduce the flushing side effects associated with crystalline niacin. E**xtended-release** dosage form of niacin, Niaspan is with pharmacokinetics intermediate between prompt- and sustained-release products. It has fewer dermatologic reactions and a low risk of hepatotoxicity. is available by prescription to treat elevated cholesterol and TG levels and appears to be better tolerated than either the crystalline or sustained-release forms. Laboratory abnormalities may include elevated liver function tests, hyperuricemia, and hyperglycemia. Niacin is contraindicated in patients with active liver disease, and it may exacerbate preexisting gout and diabetes. Combination with statins can produce large reductions in LDL and increases in HDL.

Bile Acid Resins

Cholestyramine, colestipol, and colesevelam are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine. The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration. This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile. Consequently, intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL-C. [Note: This increased uptake is mediated by an up-regulation of cell surface LDL receptors.] In addition, since bile acids are required for intestinal absorption of cholesterol, these resins decrease cholesterol absorption from the G.I.T. BARs are useful in treating primary hypercholesterolemia (familial hypercholesterolemia, familial combined dyslipidemia, and type IIa hyperlipoproteinemia). effectively lowers LDL-C when combining a drug that reduces

hepatocellular cholesterol biosynthesis (e.g., statins). Common GI complaints include constipation, bloating, epigastric fullness, nausea, and flatulence. They can be managed by increasing fluid intake, increasing dietary bulk, and using stool softeners. Other potential adverse effects include 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 more between the BARs and other drugs.

Cholesterol Absorption Inhibitors - Ezetimibe

Ezetimibe interferes with absorption of cholesterol from the brush border of the intestine, making it a good choice for adjunctive therapy. It is approved as monotherapy and for use with a statin. The dose is 10 mg once daily, given with or without food.

Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering. Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver. The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna and salmon. Approximately 4 g of marine-derived omega-3 PUFAs daily decreases serum triglyceride concentrations by 25% to 30%, with small increases in HDL-C. Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone. Omega-3 PUFAs can be considered as an adjunct to other lipid-lowering therapies for individuals with significantly elevated triglycerides (≥500 mg/dL). Although effective for triglyceride lowering, omega-3 PUFA supplementation has not been shown to reduce cardiovascular morbidity and mortality. The most common side effects of omega-3 PUFAs include GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste. Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelets. Myopathy occurs more frequently with lipid-lowering drug combinations.

Treatment Recommendations

Treatment of type I hyperlipoproteinemia is directed toward reduction of chylomicrons derived from dietary fat with the subsequent reduction in plasma triglycerides. Secondary causes of hypertriglyceridemia should be excluded, and, if present, the underlying disorder should be treated appropriately.

Primary hypercholesterolemia (familial hypercholesterolemia, familial combined dyslipidemia, and type IIa hyperlipoproteinemia) is treated with **BARs**, **statins**, **niacin**, or **ezetimibe**. Combined hyperlipoproteinemia (type IIb) may be treated with **statins**, **niacin**, or **gemfibrozil** to lower LDL-C without elevating VLDL and triglycerides. Niacin is the most effective agent and may be combined with a BAR. A BAR alone in this disorder may elevate VLDL and triglycerides, and their use as single agents for treating combined hyperlipoproteinemia should be avoided. Type III hyperlipoproteinemia may be treated with **fibrates** or **niacin**. Fish oil supplementation may be an alternative therapy. Type IV and V hyperlipoproteinemia requires stringent restriction of dietary fat intake. Drug therapy with **fibrates** or **niacin** is indicated if the response to diet alone is inadequate.

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 the lack of response prior to initiation of combination therapy. Screen carefully for contraindications and drug interactions with combined therapy, and consider the drug product monitoring. In general, a **statin** plus a **BAR** or **niacin** plus a **BAR** provides the greatest reduction in total and LDL cholesterol. Regimens intended to increase HDL levels should include either **gemfibrozil** or **niacin**, **statins** combined with either of these drugs may result in a greater incidence of hepatotoxicity or myositis.