NCEP Drug Treatment

The information contained in this document is taken directly from the National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III) that is published by the National Institutes of Health – National Heart, Lung and Blood Institute.

Major Classes of Drugs Available Affecting Lipoprotein Metabolism

- HMG CoA reductase inhibitors—lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin
- Bile acid sequestrants—cholestyramine, colestipol, colesevelam
- Nicotinic acid—crystalline, timed-release preparations, Niaspan®
- Fibric acid derivatives (fibrates)—gemfibrozil, fenofibrate, clofibrate
- Estrogen replacement
- Omega-3 fatty acids

Major Uses and Lipid/ Lipoprotien Effects of Each Drug Class

Drug Class	Major Use	Lipid/ Lipoprotein Effects
HMG CoA reductase inhibitors (statins)	To lower LDL cholesterol	LDL ↓ 18-55% HDL ↑ 5-15% TG ↓ 7-30%
Bile acid sequestrants	To lower LDL cholesterol	LDL ↓ 15-30% HDL ↑ 3-5% TG No effect or increase
Nicotinic acid	Useful in most lipid and lipoprotein abnormalities	LDL ↓ 5-25% HDL ↑ 15-35% TG ↓ 20-50%
Fibric acids	Hypertriglyceridemia; Atherogenic dyslipidemia	LDL ↓ 5-20% (in nonhypertriglyceridemic persons); may be increased in hypertriglyceridemic persons HDL ↑ 10-35% (more in severe hypertriglyceridemia) TG ↓ 20-50%

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Daily and Maximum Dosages of Each Drug Class

Drug Class	Agent	Daily Doses	Maximum Daily Dose	Available Preparations
HMG CoA reductase inhibitors (statins)	Lovastatin	20-80 mg	80 mg	10, 20, 40 mg tablets
	Pravastatin	20-40 mg	40 mg	10, 20, 40 mg tablets
	Simvastatin	20-80 mg	80 mg	5, 10, 20, 40, 80 mg tablets
	Fluvastatin	20-80 mg	80 mg	20, 40 mg capsules, 80 mg XL tablets
	Atorvastatin	10-80 mg	80 mg	10, 20, 40, 80 mg tablets
	Cerivastatin*	0.4-0.8 mg		
Bile acid sequestrants	Cholestyramine	4-16 g	24g	9g packets (4g drug) 378g bulk 5g packets (4g drug) 210 g bulk
	Colestipol	5-20 g	30 g	5g packets (5g drug) 450 g bulk
	Colesevelam	2.6-3.8 g	4.4 g	625 mg tablets
Nicotinic acid	Immediate release (crystalline)	1.5-3 g	4.5 g	Many OTC preparations by various manufacturers for both crystalline and sustained-release nicotinic acid. The extended release preparation (Niaspan®)is a prescription drug.
	Sustained release	1-2 g	2 g	
	Extended release (Niaspan®)	1-2 g	2 g	
Fibric acids	Gemfibrozil	600 mg	1200 mg	600 mg tablets
	Fenofibrate	200 mg	200 mg	67 and 200 mg tablets
	Clofibrate	1000 mg	2000 mg	500 mg capsules

*Cerivstatin was withdrawn from the market by the manufacturer in August 2001.

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Efficacy, Safety, Side Effects and Contraindications of Each Drug Class

Drug Class	Efficacy	Safety	Side Effects	Contraindications
HMG CoA reductase inhibitors (statins)	Reduce risk for CHD and stroke	Side effects minimal in clinical trials	Myopathy Increased liver transaminases	**Absolute**: ▪ active or chronic liver disease **Relative**: ▪ concomitant use of cyclosporine, macrolide antibiotics, various anti-fungal agents and cytochrome P-450 inhibitors (fibrates and nicotinic acid should be used with caution)
Bile acid sequestrants	Clinical trial evidence of CHD risk reduction	Clinical trial evidence of lack of systemic toxicity; GI side effects common	Upper and lower gastrointestinal complaints common. Decreased absorption of other drugs	**Absolute**: ▪ Dysbetalipoproteinemia ▪ Triglycerides >400 mg/dL **Relative**: ▪ Triglycerides > 200 mg/dL
Nicotinic acid	Clinical trial evidence of CHD risk reduction	Serious long-term side effects rare in crystalline form; serious hepatotoxicity may be more common with sustained-release form	Flushing Hyperglycemia Hyperurecemia (or gout) Upper GI distress Hepatotoxicity	**Absolute**: ▪ Chronic liver disease ▪ Severe gout **Relative**: ▪ Diabetes ▪ Hyperurecemia ▪ Peptic ulcer disease
Fibric acids	Clinical trials indicate a moderate reduction in CHD risk	Serious side effects seemingly do not occur in the long term, although early studies suggested an increase in non-CHD mortality	Dyspepsia Various upper GI complaints Gallstones Myopathy	**Absolute**: ▪ Severe renal disease ▪ Severe hepatic disease

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Evidence Statements for Each Drug Class

Drug Class	Evidence Statements
HMG CoA reductase inhibitors (statins)	HMG CoA reductase inhibitors (statins) are powerful LDL-lowering drugs (A1). Statin therapy reduces risk for acute coronary syndromes, coronary procedures, and other coronary outcomes in both primary and secondary prevention (A1). It also reduces risk for stroke in secondary prevention (A1). Treatment with statins is generally safe, although rarely persons experience myopathy (D1). Myopathy is more likely in persons with complex medical problems or in those who are taking multiple medications (D1).
Bile acid sequestrants	Bile acid sequestrants produce moderate reductions in LDL cholesterol (A1). Sequestrant therapy reduces risk for CHD (A1). They are additive in LDL-cholesterol lowering in combination with other cholesterol-lowering drugs (C1). They lack systemic toxicity (A1).
Nicotinic acid	Nicotinic acid effectively modifies atherogenic dyslipidemia by reducing TGRLP, raising HDL cholesterol, and transforming small LDL into normal-sized LDL (C1). Among lipid-lowering agents, nicotinic acid is the most effective HDL-raising drug (C1). Nicotinic acid usually causes a moderate reduction in LDL-cholesterol levels (C1), and it is the most effective drug for reducing Lp(a) levels (C1). Nicotinic acid therapy is commonly accompanied by a variety of side effects, including flushing and itching of the skin, gastrointestinal distress, glucose intolerance, hepatotoxicity, hyperuricemia, and other rarer side effects (C1). Hepatotoxicity is more common with sustained-release preparations (D1). Nicotinic acid therapy produces a moderate reduction in CHD risk, either when used alone or in combination with other lipid-lowering drugs (A2, B2).
Fibric acids	Fibrates are effective for modifying atherogenic dyslipidemia, and particularly for lowering serum triglycerides (C1). They produce moderate elevations of HDL cholesterol (C1). Fibrates also are effective for treatment of dysbetalipoproteinemia (elevated beta-VLDL) (C1). They also can produce some lowering of LDL, the degree of which may vary among different fibrate preparations (C1). Fibrates also can be combined with LDL-lowering drugs in treatment of combined hyperlipidemia to improve the lipoprotein profile, although there is no clinical-trial evidence of efficacy for CHD risk reduction with combined drug therapy (C1, D1). Fibrate therapy moderately reduces risk for CHD (A2, B1). It may also reduce risk for stroke in secondary prevention (A2). Evidence for an increase in total mortality due to an increased non-CHD mortality, observed in the first large primary prevention trial with clofibrate, has not been substantiated in subsequent primary or secondary prevention trials with other fibrates (gemfibrozil or bezafibrate) (A2, B1). Nonetheless, fibrates have the potential to produce some side effects. Fibrate therapy alone carries an increased risk for cholesterol gallstones (A2), and the combination of fibrate and statin imparts an increased risk for myopathy (B2).

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Recommendations for Each Drug Class

Drug Class	Recommendations
HMG CoA reductase inhibitors (statins)	Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals
Bile acid sequestrants	Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL cholesterol, for younger persons with elevated LDL cholesterol, for women with elevated LDL cholesterol who are considering pregnancy, for persons needing only modest reductions in LDL cholesterol to achieve target goals, and for combination therapy with statins in persons with very high LDL-cholesterol levels.
Nicotinic acid	Nicotinic acid should be considered as a therapeutic option for higher-risk persons with atherogenic dyslipidemia. It should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a substantial increase in LDL-cholesterol levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL-cholesterol levels. Nicotinic acid should be used with caution in persons with active liver disease, recent peptic ulcer, hyperuricemia and gout, and type 2 diabetes. High doses of nicotinic acid (>3 g per day) generally should be avoided in persons with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia.
Fibric acids	Fibrates can be recommended for persons with very high triglycerides to reduce risk for acute pancreatitis. They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-VLDL). Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia. They also should be considered in combination with statin therapy in persons who have elevated LDL cholesterol and atherogenic dyslipidemia.

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Omega-3 fatty acids

The n-3 fatty acids (linolenic acid, DHA, and EPA) have two potential uses. In higher doses, DHA and EPA lower serum triglycerides by reducing hepatic secretion of triglyceride-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. They are available in capsules of fish oil, and doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia.

Recent clinical trials also suggest that relatively high intakes of n-3 fatty acids (1–2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce risk for major coronary events in persons with established CHD. Although this usage falls outside the realm of "cholesterol management," the ATP III panel recognizes that n-3 fatty acids can be a therapeutic option in secondary prevention. The n-3 fatty acids are recommended only as an option because the strength of the clinical trial evidence is moderate at present. The n-3 fatty acids can be derived from either foods (n-3 rich vegetable oils or fatty fish) or from fish-oil supplements. In the view of the ATP III panel, more definitive clinical trials are required before relatively high intakes of n-3 fatty acids (1–2 g/day) can be strongly recommended for either primary or secondary prevention.

Hormone replacement therapy (HRT)

Risk for CHD is increased in postmenopausal women whether the menopause is natural, surgical, or premature (Kannel et al., 1976; Rosenberg et al., 1981; Colditz et al., 1987). Loss of estrogen has been proposed as a cause for increased risk. This putative mechanism was strengthened by results of numerous case-control and epidemiological studies which suggested that either estrogen alone, or in combination with progestin, reduces risk for CHD in primary and secondary prevention. However, benefit of estrogen replacement was not confirmed in a secondary prevention trial, the Heart and Estrogen/progestin Replacement Study (HERS) (Hulley et al., 1998). A subsequent angiographic study also revealed no apparent benefit from HRT (Herrington et al., 2000).

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Baseline measurements

Prior to initiating drug therapy, baseline lipid and lipoprotein measurements that will be used to follow the drug's efficacy and safety should be documented. Except for acute hospitalization, the initial lipoprotein profile upon which treatment decisions are based should be the average of two measurements done one to four weeks apart while the patient is consistently following a low-fat diet. Baseline measurements also include liver function tests (i.e., ALT or AST), CK and appropriate medical history.

Monitoring Parameters & Follow Up Schedule For Each Drug Class

Drug Class	Monitoring Parameters	Follow Up Schedule
HMG CoA reductase inhibitors (statins)	Muscle soreness, tenderness or pain	Evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each follow up visit. Obtain a CK when persons have muscle soreness, tenderness, or pain.
	ALT, AST	Evaluate ALT/AST initially, approximately 12 weeks after starting, then annually or more frequently if indicated.
Bile acid sequestrants	Indigestion, bloating, constipation, abdominal pain, flatulence, nausea	Evaluate symptoms initially, and at each follow up visit. Also check time of administration with other drugs.
Nicotinic acid	Flushing, itching, tingling, headache, nausea, gas, heartburn, fatigue, rash	Evaluate symptoms initially, and at each follow up visit.
	Peptic ulcer	Evaluate symptoms initially, then as needed.
	Fasting blood sugar (FBS) and uric acid	Obtain an FBS and uric acid initially, 6–8 weeks after starting therapy, then annually or more frequently if indicated to monitor for hyperglycemia and hyperuricemia.
	ALT and AST	Obtain an ALT/AST initially, 6–8 weeks after reaching a daily dose of 1,500 mg, 6–8 weeks after reaching the maximum daily dose, then annually or more frequently if indicated.
Fibric acids	Abdominal pain, dyspepsia, headache, drowsiness	Evaluate symptoms initially, and at each follow-up visit.
	Cholelithiasis	Evaluate history and symptoms initially, and then as needed.