

## Drug Treatment for Lipid Disorders

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Colestipol (Colestid <sup>®</sup> )	Interrupts bile acid reabsorption requiring bile acid synthesis from cholesterol.	2 scoops bid or tid (use bulk form). Begin with 1 scoop in the morning. 30 minutes before meal, increase to bid, then to 2 scoops bid.	Nonabsorbed with long-term safety established. LDL-C lowering 10%–15% (LRC-CPPT). <sup>1</sup>	Taste/texture, bloating, heartburn, constipation, drug interaction (avoidable by administration of drugs 1 hour before or 4 hours after) and TG increase.	Drug of choice for LDL-C lowering in children and in women with childbearing potential. Often used as second line drug with statins because it acts synergistically to induce LDL receptors. Do not use in patients with TGs >300 or those with GI motility disorders.
Colesevelam hydrochloride (WelChol <sup>®</sup> )	Interrupts bile acid reabsorption requiring bile acid synthesis from cholesterol.	Three 625-mg tablets bid (3.8 g total). 3 tablets with breakfast and 3 tablets with dinner.	Nonabsorbed with long-term safety established. LDL-C lowering 10%–15% (LRC-CPPT).	Taste/texture, bloating, heartburn, constipation, drug interaction (avoidable by administration of drugs 1 hour before or 4 hours after) and TG increase.	Drug of choice for LDL-C lowering in children and in women with childbearing potential. Often used as second line drug with statins because it acts synergistically to induce LDL receptors. Do not use in patients with TGs >300 or those with GI motility disorders.
Ezetimibe (Zetia <sup>®</sup> )	Selectively inhibits the intestinal absorption of cholesterol and related phytosterols.	10 mg qd.	Decreases the delivery of intestinal cholesterol to the liver, thereby reducing hepatic cholesterol stores and increases the clearance of cholesterol from the blood rather than inhibiting cholesterol synthesis. Reduces LDL-C by 18%, TG by 8%, and apolipoprotein B by 16%.	Well tolerated with few adverse reactions similar to placebo.	Can use in combination with statins; however, contraindicated in patients with active liver disease or elevated LFTs. When used in combination with statins, yields an additional LDL-C reduction of 12%, an increase in HDL-C of 3% and a TG reduction of 8%. Statin plus ezetimibe yield a total LDL-C reduction of 25.8%. Do not use in combination with resins, fibrates, or cyclosporine. May take at the same time as statin.
Ezetimibe and simvastatin (Vytorin <sup>®</sup> )	Combination of intestinal absorption blocker and statin. Both selectively inhibits the intestinal absorption of	Ezetimibe: 10 mg Simvastatin: 10, 20, 40, or 80 mg qhs.	Combination therapy fosters patient adherence with dosing. Synergistic benefits of both inhibition of intestinal cholesterol absorption by 54% and	Abnormal LFTs, myositis/myalgias.	Contraindicated in patients with active liver disease or elevated LFTs, pregnant patients, and nursing mothers. Do not use in combination with gemfibrozil, other fibrates, >1 g niacin amiodarone, or verapamil due

	cholesterol and partially inhibits HMG-CoA reductase.		statin LDL-C lowering of 45%–60% depending on dose.		to an increased risk of myopathy.
Gemfibrozil (Lopid <sup>®</sup> )	Reduces VLDL-C synthesis and induces lipoprotein lipase.	600 mg bid.	Best TG-reducing drugs, lowers 50% or more in many patients. Raises HDL-C 15%. Reduces CHD events by 24% in patients with low HDL-C, high TGs (Helsinki <sup>2</sup> , VA-HIT <sup>3</sup> ).	Nausea and skin rash.	Does not lower LDL-C reliably or LDL-C may increase in one third of patients. Used in combination therapy with statins cautiously due to increased incidence of myositis/myalgias. Alters statin metabolism and causes an increase in statin plasma concentration. Use with caution in patients with renal insufficiency and gallbladder disease.
Fenofibrate (Tricor <sup>®</sup> , Antara <sup>™</sup> , Lofibra <sup>™</sup> )	Reduces VLDL-C synthesis and induces lipoprotein lipase.	Tricor: 48, 145 mg/d Antara: 43, 87, 130 mg/d Lofibra: 54, 67, 134, 160, 200 mg/d.	Best TG-reducing drugs, lowers 50% or more in many patients. Raises HDL-C 15%. Reduces CHD in patients with low HDL-C, high TG (Helsinki, VA-HIT).	Nausea and skin rash.	Does not lower LDL-C reliably or LDL-C may increase in one third of patients. Used in combination therapy in combined hyperlipidemia. Need to use cautiously with statins, due to increased myositis/myalgias. Use with caution in patients with renal insufficiency and gallbladder disease. Use with repaglinide (Prandin <sup>®</sup> ) may cause prolonged severe hypoglycemia.
Atorvastatin (Lipitor <sup>®</sup> )	Partially inhibits HMG-CoA reductase, the rate-limiting step of cholesterol synthesis. This induces LDL receptor formation and removal of LDL-C from blood.	10–80 mg qd.	Well-studied for safety and efficacy in many trials. Lowers LDL-C 20%–60% depending on dose and drugs. Raises HDL-C 5%–10%; however, at higher doses (≥40 mg), can lower HDL-C. Lowers TG 15%–25%.	Abnormal LFTs, myositis/myalgias.	Drug of choice for elevated LDL-C based on safety and efficacy. Intensive lipid lowering with 80 mg of atorvastatin in patients with CHD provides significant benefit (percent reduction in CHD events) compared 10 mg. Liver function abnormalities less common than previously thought. The 6 statins have different metabolism allowing substitution if side effects occur. Used in combination with bile acid binding resins to synergistically lower LDL-C.

					Used in combination with niacin and fibrates in patients with combined hyperlipidemia. Use cautiously in patients on fibrates due to increased risk of myalgia/myositis.
Amlodipine and atorvastatin (Caduet®)		Amlodipine 10, 20, 40, or 80 mg Atorvastatin: 5 or 10 mg qd.	Combination therapy fosters patient adherence with dosing. Treats both lipid disorder and hypertension concomitantly using a statin and calcium channel blocker.	Edema, dizziness, headache, flushing, and palpitations.	Do not use in patients with congestive heart failure or severe aortic stenosis.
Fluvastatin (Lescol®, Lescol® XL)	Partially inhibits HMG-CoA reductase, the rate-limiting step of cholesterol synthesis. This induces LDL receptor formation and removal of LDL-C from blood.	Lescol: 20–40 mg qhs Lescol XL: 80 mg qhs	Well-studied for safety and efficacy in many trials. Lowers LDL-C 20%–30% depending on dose and drugs. Raises HDL-C 5%–10%. Lowers TG 15%–25%.	Abnormal LFTs, myositis/myalgias.	Drug of choice for elevated LDL-C based on safety and efficacy. Liver function abnormalities less common than previously thought. The 6 statins have different metabolism allowing substitution if side effects occur. Used in combination with bile acid binding resins to synergistically lower LDL-C. Used in combination with niacin and fibrates in patients with combined hyperlipidemia. Use cautiously in patients on fibrates due to increased risk of myalgia/myositis.
Niacin and lovastatin	Combination product of both extended release niacin (niaspan) and statin (lovastatin).	Niacin: 500 mg Lovastatin: 20 mg  Niacin: 2000 mg lovastatin: 40 mg qhs.	Combination therapy fosters patient adherence with dosing. Lowers LDL-C 30%–42%. Raises HDL-C 20%–30%. Reduces TG 32%–44%.	Flushing, nausea, glucose intolerance, gout, LFT abnormalities, and elevated uric acid levels. Myositis/myalgias.	Drug of choice for combined hyperlipidemia and for patients who require simplified dosing. May use a nonenteric coated aspirin taken 1 hour before evening dose along with a light snack to minimize flushing. Do not take with hot beverage.
Lovastatin (Mevacor®, Altoprev™)	Partially inhibits HMG-CoA reductase, the rate-limiting step of cholesterol synthesis. This	20–80 mg qhs.	Well-studied for safety and efficacy in many trials. Lowers LDL-C 20%–60% depending on dose and drugs. Raises HDL-C 10%. Lowers TG 15%–25%.	Abnormal LFTs myositis/myalgias.	Drug of choice for elevated LDL-C based on safety and efficacy. Liver function abnormalities less common than previously thought. The 6 statins have different metabolism allowing substitution if side effects occur. Used

	induces LDL receptor formation and removal of LDL-C from blood.		(4S <sup>4</sup> , WOSCOPS <sup>5</sup> , CARE <sup>6</sup> )		in combination with bile acid binding resins to synergistically lower LDL-C. Used in combination with niacin and fibrates in patients with combined hyperlipidemia. Use cautiously in patients on fibrates, due to increased risk of myalgia/myositis.
Pravastatin (Pravachol <sup>®</sup> )	Partially inhibits HMG-CoA reductase, the rate-limiting step of cholesterol synthesis. This induces LDL receptor formation and removal of LDL-C from blood.	10–40 mg qhs.	Well-studied for safety and efficacy in many trials. Lowers LDL-C 20%–40% depending on dose and drugs (28% decrease in LDL-C in the ALLHAT-LLT <sup>7</sup> trial). Raised HDL-C 10%. Lowers TG 15%–25%. (WOSCOPS, CARE). Reduces the risk of major CHD events by 19%–24%.	Abnormal LFTs, myositis/myalgias.	Drug of choice for elevated LDL-C based on safety and efficacy. Liver function abnormalities less common than previously thought. The 6 statins have different metabolism allowing substitution if side effects occur. Used in combination with bile acid binding resins to synergistically lower LDL-C. Used in combination with niacin and fibrates in patients with combined hyperlipidemia. Use cautiously in patients on fibrates, due to increased risk of myalgia/myositis.
Aspirin and pravastatin (Pravigard <sup>™</sup> PAC)		Aspirin: 81 or 325 mg Pravastatin: 20, 40, or 80 mg qhs.			
Rosuvastatin (Crestor <sup>®</sup> )	Partially inhibits HMG-CoA reductase, the rate-limiting step of cholesterol synthesis. This induces LDL receptor formation and removal of LDL-C from blood.	5–40 mg qhs.	Effective in lowering LDL-C 45%–63% depending on dose and drugs. Raises HDL-C 8%–14%. Lowers TG 10%–35% (STELLAR trial <sup>8</sup> ).	Abnormal LFTs, myositis/myalgias.	Newest of the 6 statins and therefore not as heavily studied in clinical trials to date; however, numerous industry trials having been conducted. Do not coadministered with warfarin or gemfibrozil. May be coadminister with fenofibrate and bile acid-binding resins to synergistically lower LDL-C.
Simvastatin (Zocor <sup>®</sup> )	Partially inhibits HMG-CoA reductase, the rate-limiting step of cholesterol synthesis. This	5–80 mg qhs.	Well-studied for safety and efficacy in many trials. Lowers LDL-C 20%–60% depending on dose and drugs. Raises HDL-C 10%. Lowers TG 15%–25% (4S).	Abnormal LFTs, myositis/myalgias.	Drug of choice for elevated LDL-C based on safety and efficacy. Liver function abnormalities less common than previously thought. The 6 statins have different metabolism allowing substitution if side effects occur. Used

	induces LDL receptor formation and removal of LDL-C from blood.				in combination with bile acid binding resins to synergistically lower LDL-C. Used in combination with niacin and fibrates in patients with combined hyperlipidemia. Use cautiously in patients on fibrates, due to increased risk of myalgia/myositis.
Niacin	Largely unknown. Reduces hepatic production of B-containing lipoproteins, increases HDL-C production.	500 mg to 1 g tid.	Lowers LDL-C and TG 10%–30%. Most effective drug at raising HDL-C (25%–35%). Long term efficacy studies (CDP <sup>9</sup> ).	Flushing, nausea, glucose intolerance, gout, LFT abnormalities, and elevated uric acid levels. May potentially increase homocysteine levels.	Drug of choice for combined hyperlipidemia and in patients with low HDL-C. Extended release preparations limit flushing and LFT abnormalities. OTC long-acting niacin preparations are not recommended as they increase the incidence of hepatotoxicity. Also lowers lipoprotein (a). Used in combination with statins or bile acid binding resins in combined hyperlipidemia. To minimize flushing, nonenteric coated aspirin can be taken 1 hour before evening dose along with a light snack. Do not take with hot beverages such as tea or coffee.
Niacin (Niaspan extended release <sup>®</sup> )	Largely unknown. Reduces hepatic production of B-containing lipoproteins, increases HDL-C production.	500 mg to 2 g qhs.	Lowers LDL-C and TG 10%–30%. Most effective drug at raising HDL-C (25%–35%). Long term efficacy studies (CDP).	Flushing, nausea, glucose intolerance, gout, LFT abnormalities, and elevated uric acid levels. May potentially increase homocysteine levels.	Drug of choice for combined hyperlipidemia and in patients with low HDL-C. Extended release preparations limit flushing and LFT abnormalities. Also lowers lipoprotein (a). Used in combination with statins or bile acid binding resins in combined hyperlipidemia. To minimize flushing, nonenteric coated aspirin can be taken 1 hour before evening dose along with a light snack. Do not take with hot beverages such as tea or coffee.
Omega-3 polyunsaturated fatty acids	Inhibits hepatic TG synthesis and augments	4 g/d (4 tablets).	Effective in controlling TG levels up to 45%. Raises HDL-C 13%.	Dyspepsia, nausea.	Can increase LDL-C in some patients with hypertriglyceridemia. May increase bleeding time; therefore, use

(Omacor <sup>®</sup> )	chylomicron TG clearance secondary to increased activity of lipoprotein lipase.				with caution in patients receiving anticoagulant therapy.
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ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; bid= twice daily; CARE= Cholesterol and Recurrent Events; CHD = coronary heart disease; GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; LRC-CPPT = Lipid Research Clinics Coronary Primary Prevention Trial; OTC = over the counter; qd = once daily; qhs = every night; STELLAR = Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin; TG = triglycerides; tid= three times daily; VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; VLDL = very-low-density lipoprotein cholesterol; WOSCOPS = West of Scotland Coronary Prevention Study

<sup>1</sup>Schucker B, Wittes JT, Cutler JA, et al. Change in physician perspective on cholesterol and heart disease. Results from two national surveys. *JAMA*. 1987;258(24):3521-3526.

<sup>2</sup>Levine GN, Keaney JF, Vita JA. Cholesterol reduction in cardiovascular disease. Clinical benefits and possible mechanisms. *N Engl J Med*. 1995;332(8):512-521.

<sup>3</sup>Rubins HB, Robins SJ. Conclusions from the VA-HIT study. *Am J Cardiol*. 2000;86(5):543-544.

<sup>4</sup>4S Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383-1389.

<sup>5</sup>Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333(20):1301-1307.

<sup>6</sup>Sacks FM, Rouleau JL, Moye LA, et al. Baseline characteristics in the Cholesterol and Recurrent Events (CARE) trial of secondary prevention in patients with average serum cholesterol levels. *Am J Cardiol*. 1995;75(8):621-623.

<sup>7</sup>The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288(23):2998-3007.

<sup>8</sup>Jones PH, Davidson MH, Stein EA, et al, for the STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol*. 2003;92(2):152-160.

<sup>9</sup>Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8(6):1245-1255.