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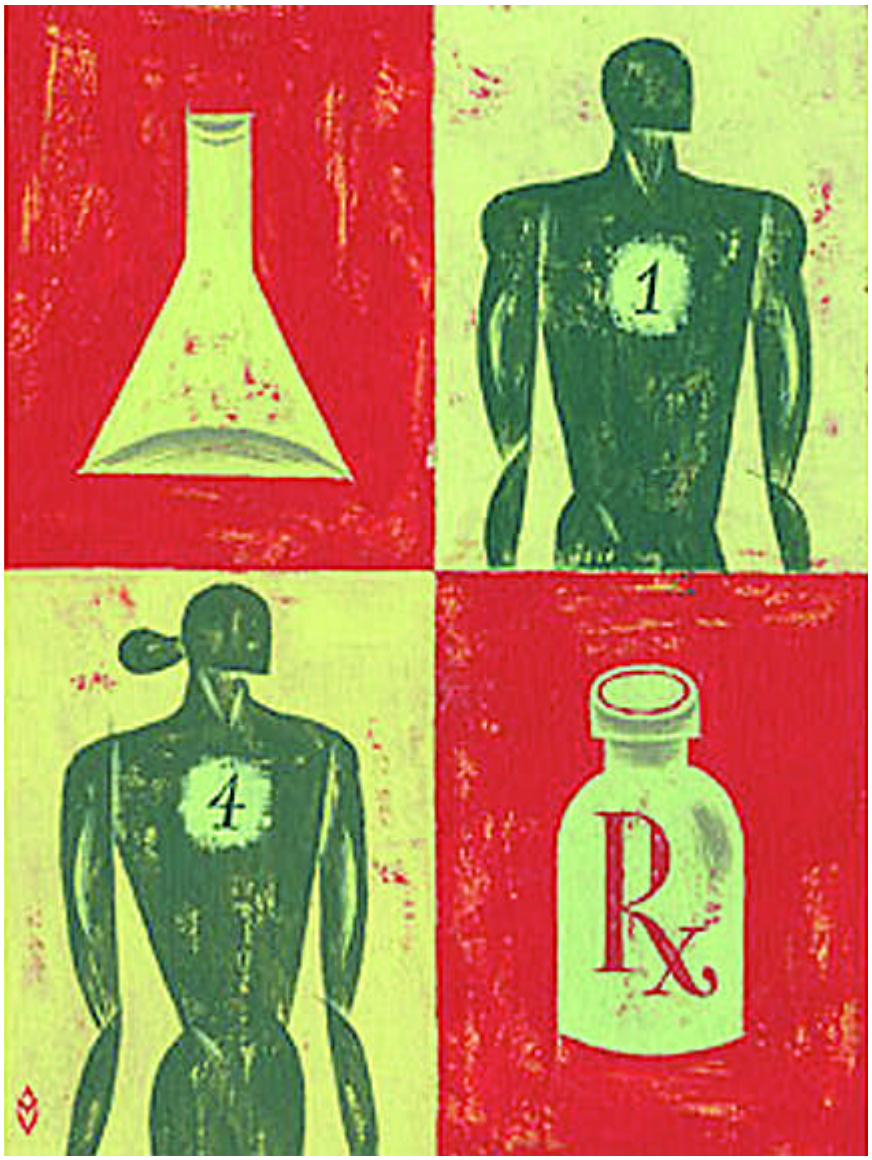

Treatment Options for Hypercholesterolemia: Scientific Review

UC Davis Center for Health Services Research in Primary Care
June 2004

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About the Foundation

The **California HealthCare Foundation**, based in Oakland, is an independent philanthropy committed to improving California's health care delivery and financing systems. Additional copies of this report and other publications can be obtained by visiting **www.chcf.org**.

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Contents

Overview of the Prescription Drug Information Project

As prescription drug benefits shrink because of annual spending caps, increased copayments, limited formularies, or combinations of these scenarios, out-of-pocket expenses for prescription drugs are increasing. Consumers are faced with choices and potential clinical tradeoffs concerning their medications.

The Prescription Drug Information Project (PDIP) is a collaborative venture between the University of California (UC), with UC Davis as the lead site, and the California HealthCare Foundation. The goal of the PDIP is to support clinicians and patients in California in their day-to-day decisions about which drugs to prescribe or take. The governing principle is that accurate, understandable information on effectiveness, side effects, and costs will help clinicians and patients to select the best drug or treatment at the best price.

The PDIP focuses on drugs that are currently promoted directly to the public. The United States has witnessed a steep increase in direct-to-consumer (DTC) advertising of prescription drugs, from $791 million in 1997 to nearly $2.5 billion in 2001.[1] Fewer than 40 DTC drugs account for most of these expenditures. Many physicians, managed care organizations, and health policy analysts believe that DTC advertisements provide incomplete or inaccurate information to consumers, which nonetheless contribute to increased consumer demand for DTC drugs. Furthermore, there is widespread concern that consumer demand translates into inappropriate and unnecessary prescribing of DTC drugs. On the other hand, proponents of DTC advertising argue that advertisements raise awareness of undertreated conditions and encourage more dialog between patients and physicians. Still, proponents and critics agree that making accurate information accessible to both consumers and clinicians is never a bad thing.

To this end, the PDIP has two components: information retrieval and dissemination. The information retrieval process is led by UC Davis, whereas the dissemination campaign is coordinated by the California HealthCare Foundation (CHCF). In the first round of information retrieval, the project focuses on treatments for gastroesophageal reflux disease, hypercholesterolemia, and osteoarthritis. In a subsequent phase, treatments for depression, allergic rhinitis, and asthma will be undertaken.

To develop an appropriate evidence base for the planned informational campaign, two approaches are utilized. The first uses publicly available drug class reviews produced by the Drug Effectiveness Review Project (DERP). These systematic literature reviews are conducted by Evidence-based Practice Centers (EPC) with oversight and coordination from the Oregon EPC. To date, the DERP has prepared nine such reports on topics ranging from skeletal muscle relaxants to estrogen preparations. The three reports that are the most relevant to the first round of information retrieval are entitled:

- Drug Class Report on Proton Pump Inhibitors (updated April 2003);
- Drug Class Report on HMG-CoA Reductase Inhibitors (Statins) (updated July 2003); and
- Drug Class Report on Cyclooxygenase-2 (COX-2) Inhibitors and Nonsteroidal Anti-inflammatory Drugs (NSAIDs) (updated May 2003).

To address treatment alternatives not covered by the DERP reports, teams of pharmacists and physicians at UC Davis prepared supplemental reports on treatment options for each of the three target conditions: gastroesophageal reflux disease (GERD), hypercholesterolemia, and osteoarthritis. Each UC Davis writing team consisted of one academic pharmacist and one physician-specialist. The teams were instructed to compose a concise, evidence-based synopsis of the treatment options for a particular condition, including pharmacologic and nonpharmacologic options. They were also asked to provide information on the costs of drug therapy, focusing on average wholesale and Medicare cash prices. The teams consisted of John Siepler, Pharm.D., and Walter Trudeau, M.D. (GERD); Robert Mowers, Pharm.D., and Thomas Balsbaugh, M.D. (hypercholesterolemia); and Robert Mowers, Pharm.D., and Gurtej Cheema, M.D. (osteoarthritis).

The UC Davis reports were reviewed by two outside national experts and then reviewed by a formal expert panel (Scientific Advisory Committee) comprised of seven distinguished faculty from five UC health sciences campuses. All experts submitted conflict-of-interest disclosure statements that are on file at UC Davis. The reports were revised based on input from the Scientific Advisory Committee. Formal deliberations by the Committee, including their assessment of the validity of key findings, are available elsewhere (CHCF Interim Report, 12/12/2003).

I. Introduction to Treatment Options for Hypercholesterolemia

This monograph reviews the current treatment modalities for dyslipidemia and provides information about treatment efficacy, side effects, safety, and cost. The monograph should be used in conjunction with the report on 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase inhibitors from the Drug Effectiveness Review Project (DERP), which has been charged by the state of Oregon to review and compare certain classes of drugs in an unbiased fashion. Several health care delivery systems (state and national) are using this process to help in the selection of their formulary medications.

Coronary heart disease (CHD) remains the leading cause of mortality and morbidity in the United States.[2,3] Epidemiologic studies such as the Framingham study and the National Health and Nutrition Examination Survey (NHANES 1988–1994) demonstrate that the risk of developing CHD is directly related to the levels of total and low-density lipoprotein (LDL) cholesterol in the blood.[4, 5] It has been estimated that for every 1% increase in blood cholesterol level, there is a 2% increase in the incidence of CHD. In addition, for every 1% decrease in high-density lipoprotein (HDL) cholesterol level, there is a 2% to 3% increase in the incidence of CHD.[6] In the National Cholesterol Education Program's (NCEP) Third Report on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III), LDL cholesterol is still the primary target; however, HDL cholesterol is defined as a secondary treatment goal in patients with hypertriglyceridemia.[7] Non-HDL cholesterol, which is the sum of LDL and very low-density lipoprotein (VLDL) cholesterol, is calculated by subtracting HDL cholesterol from total cholesterol. The ATP III guidelines also identify patients with the metabolic syndrome or low HDL cholesterol levels as candidates for therapy. Table 1 shows the LDL cholesterol goals and cutpoints for therapeutic lifestyle changes and drug therapy in different risk categories, according to ATP III guidelines.[7]

CHD risk equivalents comprise other clinical forms of atherosclerotic disease (e.g., peripheral arterial disease; abdominal aortic aneurysm; and symptomatic, carotid artery disease), diabetes, and risk factors that confer a 10-year risk of more than 20% for CHD. Risk factors used to calculate Framingham risk scores include LDL cholesterol level, cigarette smoking, hyper-

tension (blood pressure greater than or equal to 140/90 mm Hg or use of any antihypertensive medication), low HDL cholesterol level (less than 40 mg/dL), family history of premature CHD (CHD in male first-degree relatives younger than 55 years or in female first-degree relatives younger than 65 years), and age (men: 45 years or older; women: 55 years or older). The ATP III guidelines provide a risk assessment tool for calculating the 10-year risk of CHD; this calculator is available at http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof.

II. Therapeutic Management

Nondrug Treatments

Therapeutic Lifestyle Changes

Therapeutic lifestyle changes can have a substantial effect on dyslipidemia. Epidemiologic studies have shown that physically active persons have a lower risk of CHD than do sedentary persons. This reduced risk is multifactorial, but is probably mediated by an improved lipid profile. In a prospective trial of exercise for sedentary, overweight persons, exercise had widespread beneficial effects on the lipoprotein profile.[8]

Improvements were related to the frequency and duration of activity and not to improvement in fitness or weight loss. A consensus statement by the Centers for Disease Control and Prevention and the American College of Sports Medicine recommends 30 minutes of moderate-intensity physical activity on most (preferably all) days of the week.[9] Dietary therapy is also an important part of a successful therapeutic lifestyle change. If a patient is able to maintain a weight reduction diet and exercise program for 1 year, HDL cholesterol levels could increase by 13%.[10] Exercise training programs (e.g., brisk walking or jogging for 15 to 20 miles per week) are effective in raising HDL cholesterol levels by 2 to 8 mg/dL and lowering triglyceride levels by 5 to 38 mg/dL. Exercise training seldom lowers total and LDL cholesterol levels.[11]

Practitioners should emphasize the benefits and importance of eating a healthy diet that is low in saturated fats, trans fatty acids, and cholesterol; increasing the amount of soluble fiber in the diet (10 to 25 g/day); losing weight; and increasing physical activity. Many studies have reported the beneficial effects on lipids by omega-3 fatty acids and plant stanols.[12,13] A meta-analysis of 41 trials showed that the intake of 2 g/day of stanols or sterols reduced LDL cholesterol levels by 10%.[14,15] Indeed, eating foods that are low in saturated fat and cholesterol and high in stanols or sterols can reduce LDL cholesterol levels by 20%.[14] A higher intake of unsaturated fat can decrease LDL cholesterol levels and increase HDL cholesterol levels in patients with the metabolic syndrome. In another meta-analysis, every gram increase in soluble fiber reduced LDL cholesterol levels by an average of 2.2 mg/dL.[16]

Providers should actively work with patients for 6 months to effect therapeutic lifestyle changes. Patients who cannot reach these goals in this time period should be considered for lipid-lowering pharmacotherapy.

Pharmacotherapy

Common medications used to treat hypercholesterolemia include HMG-CoA reductase inhibitors (statins), bile acid sequestrants, niacin, and cholesterol absorption inhibitors. DERP has reported on statins. The purpose of the following section is to review the DERP findings and provide a summary of other pharmacologic treatments for hypercholesterolemia. With the recent Food and Drug Administration (FDA) approval of rosuvastatin (Crestor®), we will also briefly comment on the role of rosuvastatin.

HMG-CoA Reductase Inhibitors (Statins)

All statins lower cholesterol in a dose-dependent manner, but the effect is not linear. Increasing the dose for 10 mg to 20 mg will produce a larger percent reduction in cholesterol then increasing the dose from 20 mg to 30mg.[17] We agree with the findings of DERP that all statins in equipotent doses are effective in reducing LDL cholesterol levels by up to 40%. In fact, there is evidence that atorvastatin, lovastatin, and simvastatin can achieve reductions of 40% to 49%.[18] Early data for rosuvastatin suggest that rosuvastatin can achieve reductions in LDL cholesterol levels of 40% at a 5-mg dose, and up to 50% at a 10-mg dose.[19] If a patient requires a reduction of more than 50%, atorvastatin or rosuvastatin are the only statins likely to be effective. Table 2 compares the lipid-lowering effects of statins and other medications.

DERP has concluded that there is good evidence of improved cardiac outcomes with lovastatin, pravastatin, and simvastatin. Only pravastatin and simvastatin have been shown in controlled trials to reduce all-cause mortality among patients with and without known cardiovascular disease, an important finding because all-cause mortality automatically accounts for the most important benefits and risks of treatment. Previously, there were no data to suggest that atorvastatin would improve cardiac outcomes. However, recent results from the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) support this conclusion.[20] The improved cardiovascular outcomes for these four medications in this drug class suggest that a class effect may exist. Fluvastatin has only been shown to decrease atherosclerotic progression, and not improve cardiovascular outcomes. No cardiovascular outcome data have been published for rosuvastatin. There is no evidence to support differences in cardiovascular outcomes among the various statins because of the lack of good-quality comparison studies. Clinicians who are skeptical of the class effect may choose to only use lovastatin, pravastatin, simvastatin, or atorvastatin. Pravastatin and fluvastatin, which are associated with few drug-drug interactions, may be the drugs of choice in patients taking other drugs that are metabolized by the liver (cytochrome P-450 3A4 pathway).

The association between the degree of cholesterol lowering and a reduction in cardiac risk is an important clinical question in statin therapy. Previous trials do not provide an answer; most titrated the statin to a fixed dose. There are a number of ongoing trials that will directly compare the cardiac benefits of higher and lower doses of statins. If there is a marked difference in outcome from a greater degree of cholesterol lowering, the conclusions of this manuscript may no longer be valid.

Finally, we agree with the DERP findings that there is insufficient evidence that the currently marketed statins differ in liver toxicity and myotoxicity at equipotent doses. Of note, there is

concern that higher doses of rosuvastatin (greater than 40 mg) may cause hepatotoxicity. Because rosuvastatin was recently approved by the FDA, more data will be needed to determine if rosuvastatin is more or less likely to cause liver toxicity or myotoxicity. In addition to myotoxicity, up to 5% of patients who take statins may complain of myalgias.[21] Still, despite the frequency of this complaint, statins have the lowest discontinuation rate of any class of lipid-lowering agent.[22]

Cholesterol Absorption Inhibitors

Despite the wide acceptance and use of statins, many patients do not achieve the cholesterol goals outlined in the ATP III guidelines for reasons such as poor compliance, failure to increase the statin dose, or a need to lower LDL cholesterol levels to a level that available statins cannot achieve. Sometimes patients require combination therapy. Ezetimibe (Zetia®) is a new class of medication approved by the FDA to treat hypercholesterolemia. It has been shown, either as monotherapy or in combination with a statin, to reduce total and LDL cholesterol levels and to raise HDL cholesterol levels slightly. As a single agent, ezetimibe lowers LDL cholesterol levels by 18%.[23] When used in combination with simvastatin, atorvastatin, lovastatin, or pravastatin, there is a further decrease of 10% to 15% as compared with statin therapy alone.[24-27] Thus far, there have been no published studies of the effects of ezetimibe, either alone or in addition to a statin, on cardiovascular morbidity and mortality. The final role that ezetimibe will play in the treatment of hypercholesterolemia will await the results of these studies. In the mean time, ezetimibe is an option for patients who are unable to take a statin or for whom statin monotherapy is not effective. Patients receiving combination ezetimibe and statin therapy may be at a slightly higher risk of hepatotoxicity, and therefore their liver function tests should be monitored closely.

Niacin

Niacin, a B-complex vitamin, is one of the most effective and least expensive medications used to treat hypercholesterolemia. It is believed to lower cholesterol levels by inhibiting triglyceride synthesis, which in turn reduces hepatic VLDL production and thus lowers LDL cholesterol levels. Niacin also promotes the clearance of chylomicrons, VLDL, and triglycerides. Niacin raises HDL cholesterol levels by decreasing the catabolism of apolipoprotein AI. In the Coronary Drug Project, niacin was shown to decrease the incidence of myocardial infarction, but not overall mortality.[28] However, at 15 years, 9 years after termination of the trial, overall mortality was lower in the niacin group than in the placebo group.[29] Thus, niacin may have long-term benefits on mortality, which were not evident during the formal period of the Coronary Drug Project.

Despite its therapeutic benefits, niacin's usefulness is limited by its side effects. The immediate-release formulation commonly causes flushing, itching, and headaches. These adverse effects, which appear to be the result of prostaglandin-mediated vasodilation, may be reduced by taking 325 mg of aspirin shortly before the niacin dose or by taking niacin with meals. The vasodilation seems to be related to the rising plasma concentrations of niacin. Patients can take their immediate-release niacin with fatty meals, thereby delaying and prolonging niacin absorption. Unfortunately, this strategy may subvert a low-fat diet. Sustained-release niacin products may minimize these adverse effects, although some sustained-release formulations have been associated with a higher rate of hepatitis. A general strategy to reduce side effects is to start at a low dose of niacin and titrate up slowly. An extended-release form of niacin has recently become available (Niaspan®) that may not have the same risks of niacin-induced hepatitis and that may be better tolerated by patients. As yet, there are no data to suggest that extended-release formulations are

superior to immediate-release formulations (at the same total daily dose) in lowering LDL cholesterol and triglyceride levels or raising HDL cholesterol levels. Patients can initially take 500 mg of Niaspan at bedtime, often with aspirin to reduce flushing, and subsequently increase the Niaspan dose at monthly intervals. In a study in which 517 patients were given Niaspan monotherapy in doses of up to 3 g for up to 96 weeks,[30] LDL cholesterol levels decreased markedly, by 18% at week 48 and 20% at week 96. There were also large elevations in HDL cholesterol levels (26% at week 48; 28% at week 96) and modest decreases in total cholesterol levels (12% at week 48; 13% at week 96), as well as a decrease in the ratio of total to HDL cholesterol of about 30%. The use of niacin in patients with diabetes has been discouraged because high doses can worsen glycemic control. However, Niaspan has been shown to be effective in lowering LDL cholesterol levels and raising HDL cholesterol levels, while only worsening glucose control in a small number of patients.[31,32] Still, diabetic patients taking Niaspan should be monitored for the development of niacin-related glucose intolerance. There are no published studies evaluating the effects of Niaspan (alone or in combination with a statin) on cardiovascular morbidity and mortality.

Bile Acid Sequestrants

Cholestyramine, colestipol, and colesevelam (WelChol®) are bile acid sequestrants. Owing to their modest effects on cholesterol levels, these agents are delegated as adjuncts to statins or niacin. Cholestyramine and colestipol are suspended in liquids, usually juices or applesauce. These agents are difficult to take as they cause bloating, belching, constipation, gas, heartburn, and nausea. Further, they are associated with drug interactions (mainly by interfering with drug absorption) and may raise triglyceride levels. The newest bile acid sequestrant is colesevelam. Colesevelam is administered as six or seven 625-mg tablets daily in one or two doses and is effective in lowering LDL cholesterol levels as monotherapy or in combination with statins.[33-35] In a 24-week trial, colesevelam at 4.5 g/day lowered total cholesterol levels by 9% to 18% and LDL cholesterol levels by 20%.[36] Studies evaluating the effects of colesevelam, either alone or in addition to a statin, on cardiovascular morbidity and mortality have not been published.

III. Clinical Conclusions

THERAPEUTIC LIFESTYLE CHANGES MAY BE USED on a trial basis for 6 months for patients with hyperlipidemia, with active monitoring and assistance by physicians. Medications are frequently required to achieve target LDL cholesterol levels. The initial choice for medication therapy is a statin. Statins are generally better tolerated than most other medications and have the most evidence supporting improved cardiac outcomes. Target levels for LDL cholesterol are established by the ATP III guidelines; the choice of statin depends on the degree of reduction needed. Any statin can be used to reduce cholesterol levels by up to 40%. This choice can be made by cost or formulary coverage (Table 3). As more companies manufacture generic lovastatin, we anticipate the costs to decrease rapidly. Only atorvastatin and rosuvastatin have been shown to reduce LDL cholesterol levels by more than 50%. No one statin has been found to have superior safety or tolerability. Patients should be re-evaluated after the first 6 weeks of therapy. Consider increasing the statin up to the maximum dose until the LDL cholesterol goal is reached. If the patient fails to reach the ATP III goal, a bile acid sequestrant or niacin can be added.

IV. Appendices

Table 1. LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Cholesterol		
	Goal	Level At Which to Initiate Therapeutic Lifestyle Changes	Level At Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100–129 mg/dL: drug optional)
≥2 Risk Factors (10 year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10%–20%: ≥130 mg/dL10-year risk <10%: 160 mg/dL
0–1 Risk Factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: drug optional)

*Reproduced from the ATP III Guidelines.[7]

ATP III = Adult Treatment Panel III; CHD = coronary heart disease; LDL = low-density lipoprotein.

Table 2. Effects of Various Drugs on Blood Lipid Levels

	Effect on:				
Drug (Generic)	**Daily Dose**	**Total Cholesterol**	**LDL Cholesterol**	**HDL Cholesterol**	**Triglycerides**
Advicor (niacin/lovastatin)	20 mg lovastatin combined with 500, 750, or 1000 mg of slow-release niacin	b 18% – 29%	b 24% – 41%	q 9% – 13%	b 10% – 25%
Crestor (rosuvastatin)	5 – 40 mg	b 33% – 46%	b 7% – 63%	q 8% – 14%	b 10% – 35%
Lescol (fluvastatin)	20 – 80 mg	b 17% – 27%	b 22% – 36%	q 3 – 9%	b 12% – 23%
Lescol XL (fluvastatin XL)	80 mg	b 25%	b 33% – 35%	q 7% – 11%	b 19% – 25%
Lipitor (atorvastatin)	10 – 80 mg	b 25% – 45%	b 35% – 60%	q 5% – 9%	b 19% – 37%
Mevacor (as generic lovastatin)	10 – 80 mg	b 16% – 34%	b 21% – 42%	q 2% – 9%	b 6% –7%
Niaspan (niacin)	2000 mg	b 12%	b 17%	q 26%	b 35%
Pravachol (pravastatin)	10 – 80 mg	b 16% – 27%	b 22% – 37%	q 2% – 12 %	b 11% – 24%
WelChol (colesevelam)	4.5 g	b 10%	b 18%	q 3%	Small variable changes
Zetia (ezetimibe)	10 mg	13%	18%	q 1%	8%
Zocor (simvastatin)	5 – 80 mg	b 19% – 36%	b 26% – 47%	q 8% – 16%	b 12% – 33

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 3: Cost Comparision of Antihypercholesterolemia Agents

Drug Category		Drug Name	Brand Name	Dose Range per Day	AWP Cost Range for 30-Day Supply		AWP Cost for 30-Day Average Daily Dosage	
		HMG Co-A Inhibitors (Statins)			**Brand***	**Generic***	**Brand**	**Generic**
✚	✚	Atorvastatin	(Lipitor®)	10 mg – 80 mg	$70 - $104	N/A	$$	N/A
✚	✚	Fluvastatin	(Lescol®)	20 mg – 80 mg	$48 - $67	N/A	$$	N/A
✚	■	Lovastatin	(Mevacor®)	10 mg - 80mg	$59 - $317	$28 - $80	$$$	$$
✚	✚	Pravastatin	(Pravachol®)	10 mg – 80 mg	$75 - $75	N/A	$$$	N/A
✚	✚	Rosuvastatin	(Crestor®)	5 mg – 40 mg	$79 - $79	N/A	$$	N/A
✚	✚	Simvastatin	(Zocor®)	5 mg – 80 mg	$56 - $131	N/A	$$$	N/A
		Cholesterol Absorption Inhibitors						
✚	✚	Ezetimibe	(Zetia®)	10 mg	$68 - $68	N/A	$$	N/A
		Bile Acid Sequestrants						
✚	■	Cholestyramine Bulk Powder	(Questran®)	4.0 g – 24.0 g	$28 - $171	$16 - $96	$$$$	$$$
✚	■	Colestipol Granules	(Colestid®)	5.0 g – 30.0 g	$27 - $162	N/A	$$$	N/A
✚	■	Colesevelam	(WelChol®)	3.75 g – 4.375 g	$152 - $178	N/A	$$$$	N/A
		Micellaneous						
●	●	Niacin (Immediate release)		3.0 g – 8.0 g	N/A	$5 - $14**	N/A	$
✚	■	Niaspan® (slow release)		1.0 g –3.0 g	$61 - $333	$6 - $19	$$$$	$

* Discounted AWP cost reflects brand discount of AWP - 5% and generic AWP - 30%. 30-day drug supply based on minimum and maximum dosage ranges. Pricing reference dated 12/31/03, pricing results may vary due to use of different strengths/cost to achieve dosage.

** OTC Pricing is retail-based

● = Drug is non-prescription item, may not be covered by health plans

■ = Available as Brand and Generic, Generic will have lower copay with Brand copay dependent on Plan Formulary

✚ = Brand, copay varies by Plan

$ = Less than $60.00

$$ = Between $60.00 and $119.99

$$$ = Between $120.00 and $179.99

$$$$ = More than $180.00

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