

**CME ARTICLE**

## Assessing the Value and Affordability of Cholesterol Reduction in the Managed Care Setting

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**A**therosclerosis is a disorder that manifests itself in various vascular beds—brain, heart, and legs. In terms of morbidity and mortality, few diseases rival the socioeconomic burden produced by atherosclerosis. Ischemic stroke, myocardial infarction (MI), and peripheral arterial disease (PAD) are three common manifestations resulting from atherosclerosis.<sup>1</sup> Approximately 60 million Americans suffer from one of these manifestations of atherosclerosis, and 40% of these patients have more than two coexisting conditions (Figure 1).<sup>1</sup> Four million Americans suffer from cerebral ischemia, and 150,000 die from this condition each year (Figure 2).<sup>2</sup> Stroke is the leading cause of long-term disability in the United States.<sup>3,4</sup> PAD affects approximately eight million Americans.<sup>2,4</sup> The mortality rate among these men and women is 4% per year.<sup>5,6</sup> This accounts for 7,760,000 deaths over a 10-year period.<sup>2,4</sup>

Myocardial infarction is the leading cause of death in the United States. Of the 13 million Americans with coronary artery disease (CAD), 1.5 million suffer an acute myocardial infarction (AMI) each year (Figure 2).<sup>2</sup> Approximately 300,000 AMI patients die before reaching the hospital, and another 200,000 die within

the first month after the AMI.<sup>3,4</sup> The majority of patients who die from AMI do so within 24 hours of admission to the hospital.<sup>3,4</sup> Advances in treatment have reduced the death rate from AMI by 30% since 1983. Today 13.5 million Americans have survived an AMI or episodes of unstable angina pectoris.<sup>3,4</sup>

### Costs of Cardiovascular Disease Treatment

The cost of atherosclerotic disease to individuals and society is substantial. Men with CAD lose an average of 13 years from their life expectancy while women lose 12 years. Because CAD can produce a diverse clinical presentation, the true individual and societal costs of treating CAD are difficult to determine. The total of both direct and indirect costs of care for atherosclerotic disease likely exceeds \$90 billion annually (Table 1). According to the 1998 Heart and Stroke Statistics, the direct cost for treating myocardial infarction was \$51.1 billion.<sup>5</sup> Direct costs were comprised of the following: institutional care (\$39.3 billion), physician and other professional visits (\$7.5 billion), medications (\$2.9 billion), and home healthcare and other medical goods (\$1.4 billion). The indirect cost resulting from loss of productivity due to morbidity and mortality associated with myocardial infarction was \$44.5 billion.<sup>5</sup>

Unfortunately, AMI patients are at increased risk for a recurrent MI (23% for men and 31% for women) and stroke (9% for men and 18% for women).<sup>2</sup> Similarly,

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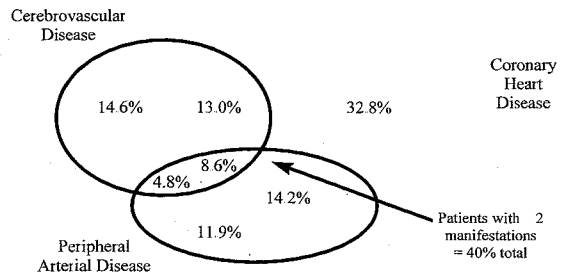
patients with cerebrovascular disease are at greater risk of developing CAD (20%) or recurrent stroke (29%) within 10 years of the initial event.<sup>6</sup> While the subsequent development of atherosclerotic complications in patients with stroke or AMI is generally recognized, clinicians may fail to appreciate that PAD is a strong marker for underlying cerebrovascular and cardiovascular disease. In fact, the 10-year mortality rate of 40% to 50% observed in patients with PAD is due to the occurrence of myocardial infarction or stroke.<sup>7</sup>

**Pathophysiology**

Atherosclerosis is derived from the Greek words "athero" and "sclerosis" that refer to the two major components of the plaque-like vascular lesions. Athero is derived from the Greek word for gruel, which is similar to the necrotic debris found at the base of most plaques. Sclerosis comes from the Greek word for hard, which corresponds to the fibrotic cap of the lesion. Recently, we have witnessed an increase in knowledge of atherosclerotic disease. In 1985, the Nobel Prize in physiology was awarded to Brown and Goldstein for discovering the low-density lipoprotein (LDL) receptor and elucidating its involvement in the atherosclerotic process.<sup>4</sup> Today, we understand many of the various roles that lipids, endothelium, macrophages, inflammatory mediators, plaque rupture, and thrombosis play in atherosclerosis.<sup>8</sup>

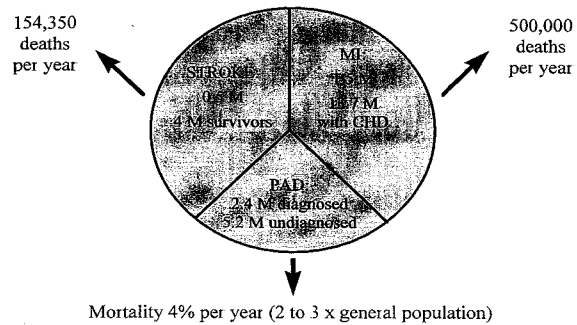
The first visually apparent atherosclerotic lesion is the fatty streak, which is observed as yellow stripes running parallel to the vessel axis. As the atherosclerotic lesion progresses, a necrotic core composed of extracellular lipid and cellular debris develops near the base of the lesion adjacent to the internal elastic lamina. A fibrous cap composed of collagen and smooth muscle covers the lesion. The lesion may ulcerate, contain hemorrhage within it, or have thrombosis superficial to the thrombogenic base. These advanced lesions are referred to as vulnerable lesions. Factors contributing to thrombosis of vulnerable lesions in-

**Figure 1.** Cardiovascular Disease: Comorbidity of Atherosclerotic Conditions



Aronow WS, Ahn C. *Am J Cardiol* 1994;74:64-65.

**Figure 2.** Epidemiology of Cardiovascular Disease in the United States



American Heart Association. 1997 Heart & Stroke Statistics Update; Dormandy et al. *J Cardiovascular Surg* 1989;30:50-57.

**Table 1.** Economic Impact of Myocardial Infarction

<b>Direct Cost: \$47.5 billion</b>
- Hospital/nursing home: \$36.7 billion
- Physician/other professionals: \$6.8 billion
- Drugs: \$2.7 billion
- Home health/other medical durables: \$1.3 billion
<b>Indirect Cost: \$43.4 billion</b>
- Lost productivity due to morbidity: \$6.4 billion
- Lost productivity due to mortality: \$37.0 billion
<b>Total Cost: \$90.9 billion</b>

clude the rheology of blood flow, the thrombosis-stimulating substrate that is exposed to flowing blood, and systemic factors in blood, especially a high LDL-C, increased catecholamines, and diabetes mellitus.

### Cardiovascular Risk Factors

Patients with documented CAD are 12 times more likely to die from CAD if they have elevated LDL-C concentrations than those people with normal levels of LDL-C.<sup>9</sup> Unfortunately, only one in four patients who needs treatment for elevated cholesterol receives such treatment.<sup>9</sup> Furthermore, the risk of acute recurrences of atherosclerotic events is directly proportional to age. The number of Americans over 65 years of age is expected to increase from 34.2 million in 1995 to 60.8 million in 2020. Therefore, secondary prevention in atherosclerotic arterial disease is important in controlling the overall cost of care for atherosclerosis, especially in the elderly. Therapeutic approaches should be directed towards recognizing atherosclerosis as a generalized disease process, regardless of the site of its initial manifestations. Preventive measures for one atherosclerotic condition should prevent overt manifestations of atherosclerotic disease elsewhere.

### Cholesterol Reduction

Since LDL-C levels correlate directly with the probability of future coronary events in patients with known CAD, the National Heart, Lung, and Blood Institute's National Cholesterol Education Program (NCEP) defines target LDL-C levels to enable clinicians to direct and monitor cholesterol-reducing therapy.<sup>10</sup> For primary prevention in patients with less than two coronary risk factors, the target LDL-C is  $\leq 160$  mg/dL, whereas in patients with more than two coronary risk factors the target LDL-C is  $\leq 130$  mg/dL. For secondary prevention, the target LDL-C is 100 mg/dL. Since HDL cholesterol affords protection against CAD, NCEP guidelines list HDL cholesterol values below 35

mg/dL as a positive risk factor for CAD, whereas HDL cholesterol values above 60 mg/dL are considered as a negative risk factor for CAD. Adherence to NCEP treatment guidelines can have a favorable medicoeconomic impact if one considers that for every 10% reduction in LDL-C there is a 20% reduction in the incidence of CAD-related complications.<sup>11</sup>

Dietary modifications and increased physical activity reduce cholesterol and help curb overeating. Unfortunately, a substantial number of patients are unable to adhere to recommended dietary modifications and do not achieve target reductions in their cholesterol levels. Patients with familial hypercholesterolemia and those with severely elevated LDL-C levels must be treated with cholesterol-lowering medications, despite compliance to dietary modification. Drug therapy is indicated if correction of secondary causes of hypercholesterolemia and implementation of lifestyle modifications fail to achieve target LDL-C levels within a six-month period.

The NCEP guidelines classify lipid-lowering drugs as follows: bile acid sequestrants, nicotinic acid, HMG-CoA reductase inhibitors, and other agents. Choices for first-line therapy are nicotinic acid and bile acid sequestrants and the HMG-CoA reductase inhibitors. Estrogen replacement therapy (ERT) is considered as adjunctive therapy in postmenopausal women. Table 2 provides important information regarding cholesterol-lowering agents. The choice of agent should be based on treatment goals, individual efficacy, side effects, and cost and compliance considerations. Bile sequestrants are nonsystemic agents; however, poor palatability and bothersome side effects limit compliance. Nicotinic acid is an affordable and inexpensive alternative to bile sequestrants, but frequent, dose-limiting side effects make this agent less than ideal. HMG-CoA reductase inhibitors are more expensive than the other lipid-lowering agents, but these agents con-

**Table 2.** Comparison of Lipid-Lowering Agents

Agent	% LDL Reduction	% HDL Increase	% Triglyceride Reduction	Contraindications	Major Side Effects	Usual Daily Dose
Bile Acid Sequestrants	15 to 30	3 to 5	no change	Triglycerides >200 to 500 mg/dL	Gastrointestinal complaints, poor palatability	Colestipol 5 to 20 g Cholestyramine 4 to 16 g
Nicotinic Acid	10 to 25	15 to 35	20 to 50	Chronic liver diseases, diabetes, gout, ulcers	Flushing, hyperglycemia, hyperuricemia, gastritis, hepatotoxicity	Crystalline 1.5 to 3 g Sustained release 1 to 2 g
HMG-CoA	24 to 40	5 to 15	10 to 24	Active or chronic liver disease, concurrent use of fibrates or nicotinic acid	Elevated serum transaminases, rhabdomyolysis	Lovastatin 10 to 80 mg Pravastatin 10 to 40 mg Simvastatin 5 to 40 mg Fluvastatin 20 to 40 mg Atorvastatin 10 to 20 mg Cerivastatin 0.3 mg
Gemfibrozil	no change	10 to 15	20 to 50	Liver or biliary disease, renal failure	Gastrointestinal complaints, biliary disorders	Gemfibrozil 600 to 1200 mg
Estrogens	15	15	10 increase	Estrogen-dependent cancers, thrombotic disorders, migraine	Weight gain, hypertension	Conjugated estrogens 0.625 mg

sistently provide effective LDL-C lowering with minimal side effects and convenient once-daily dosing. Most clinicians view the HMG-CoA reductase inhibitors as drugs of choice for LDL-C reduction.<sup>12</sup>

Recent studies with HMG-CoA reductase inhibitors have documented reductions in CAD-related morbidity and mortality in large numbers of patients with varying comorbidities. The West of Scotland Coronary Prevention Study (WOSCOPS) was a 5-year prospective trial comparing pravastatin 40 mg daily with placebo in 6,595 men (age 45 to 64 years) with hypercholesterolemia

(plasma cholesterol  $272 \pm 23$  mg%) and no CAD-related hospitalizations within the previous 12 months or a prior history of myocardial infarction.<sup>13</sup> Pravastatin reduced LDL-cholesterol by 26%. When compared with placebo, pravastatin was associated with a 31% reduction in the risk for nonfatal myocardial infarction, a 33% reduction in deaths that were definitely related or suspected to be related to CAD, and a 32% reduction in all deaths related to some form of cardiovascular disease.<sup>13</sup>

The Scandinavian Simvastatin Survival Study (4S) was a 5-year prospective trial comparing simvastatin 10 mg to 40

mg daily with placebo in 4444 patients (age 35 to 70 years) with hypercholesterolemia and preexisting CAD. Simvastatin reduced LDL-C by 35%. When compared with placebo, simvastatin reduced all-cause mortality by 30%, CAD-related deaths fell by 42%, and there was a 34% reduction in cardiovascular events and complications. The 4S trial was the first study to show a benefit from cholesterol reduction in women and older patients. In the 4S trial, simvastatin reduced the frequency of major coronary events by 35% in women when compared with placebo.<sup>14</sup> In patients 65 years of age or older, simvastatin reduced all-cause mortality by 34%, coronary mortality by 43%, and the need for coronary revascularization by 41% when compared with placebo. Patients with diabetes mellitus also benefited from cholesterol reduction with simvastatin in the 4S trial. In these patients, simvastatin reduced coronary mortality by 54% and nonfatal myocardial infarctions by 32% when compared with placebo.

The Cholesterol and Recurrent Events (CARE) Trial evaluated the effects of lipid-lowering therapy in patients with CAD and normal or mildly elevated LDL-C.<sup>15</sup> In this 5-year study, 4159 men and women 21 to 75 years of age with a history of AMI, a total cholesterol of <240 mg/dL and LDL-C values in the range of 115 mg/dL to 174 mg/dL<sup>15</sup> received pravastatin (40 mg/d) or placebo. Pravastatin produced a 28% reduction in LDL-C and a 5% increase in HDL-C. Treatment with pravastatin led to a 26% and a 22% decrease in the need for bypass surgery and angioplasty, respectively ( $P < 0.001$ ). Pravastatin use reduced the incidence of nonfatal MI, fatal MI, and stroke by 24%, 37%, and 31%, respectively ( $P < 0.003$ ). Elderly patients and females experienced the greatest benefit (ie, a 46% reduction in coronary events) from pravastatin in the CARE Trial.<sup>15</sup> The study's authors concluded that the CARE Trial provides strong support for use of cholesterol-lowering therapy in elderly patients and females.<sup>15</sup>

### Economic Benefits of Cholesterol Reduction

In 1992, the aggregate cost of CAD in the United States per year for medical treatment and lost wages was between \$50 billion and \$100 billion.<sup>11</sup> Wittels and colleagues estimated the 5-year costs, in 1986 US dollars, of treating CAD events to be: \$51,211 for acute myocardial infarction, \$24,980 for angina pectoris, \$40,581 for unstable angina pectoris, \$9,078 for sudden death, and \$19,697 for nonsudden death.<sup>16</sup> The investigators also calculated the 5-year costs of major CAD-related interventions to be \$32,465 for CABG and \$26,916 for angioplasty.<sup>16</sup> Therapy with HMG-CoA reductase inhibitors can lower overall healthcare costs in patients with CAD by decreasing the use of more expensive services. The results of 4S indicate that simvastatin treatment in 100 CAD patients, over a 6-year period, could prevent 4 to 9 expected coronary deaths, 7 of 21 nonfatal myocardial infarctions, and 6 of 19 expected CABG surgeries and coronary angioplasty procedures. Pederson and colleagues analyzed hospital admissions data from the 4S trial to evaluate the impact of simvastatin on healthcare resource use and to perform a cost-minimization analysis.<sup>17</sup> In the placebo group ( $n = 2223$ ), there were 1905 hospitalizations (average duration, 7.9 days) for acute cardiovascular events or coronary revascularization procedures among 937 patients. In the simvastatin group ( $n = 2221$ ), however, there were 3 such hospitalizations (average duration, 7.1 days) among 720 patients (all differences,  $P < 0.0001$ ). The corresponding number of hospitalizations was 15,089 and 9951 in the two groups, respectively (34% reduction,  $P < 0.0001$ ). The expected reduction in hospitalization costs over the 5.4-year period of the trial would be \$3,872 per patient. These savings in hospitalization costs reduce the effective cost of simvastatin by 88% to \$0.28 per day. Data from 4S show the cost of treating acute exacerbations of CAD outweighs the cost of secondary prevention.

A commonly asked pharmacoeconomic question is what patient population receives the greatest benefit for every dollar spent on cholesterol-lowering therapy? In 1990, Wittels reported that for primary prevention, the cost per year of life saved ranges from \$45,000 to \$65,000 for simvastatin to \$100,000 to \$200,000 for cholestyramine.<sup>18</sup> In the WOSCOPS, the net benefit of taking pravastatin (40 mg daily for 5 years) for primary prevention was a 2.2% reduction in myocardial infarction and death from CAD and a 0.7% reduction in death from all cardiovascular causes.<sup>14</sup> Based on these findings, to prevent one myocardial infarction or CAD-related death, you must treat 45 patients with hypercholesterolemia for 5 years. Likewise, you must treat 143 patients to prevent one death from cardiovascular causes. If the monthly cost of pravastatin therapy in the retail market is \$100 (ie, \$6,000/5 years), approximately \$270,000 must be spent to prevent one myocardial infarction or CAD-related death; and \$858,000 would be spent to prevent one death from cardiovascular causes.

The cost-effectiveness ratios for primary prevention are higher and vary widely depending on age, gender, and number of risk factors for CAD. Cost-effectiveness analysis of cholesterol-lowering therapy shows that primary prevention of CAD is most cost effective, in terms of cost per year of life saved, in the following patients: (1) those with high pretreatment serum cholesterol levels; (2) young individuals; and (3) men. When treatment is targeted to men (35 to 65 years of age) with the above factors and pretreatment cholesterol levels above 190 mg/dL, the cost per year of life saved (YOLS) is reduced by 17% to 29%. In a 55- to 64-year-old man with a cholesterol level  $\geq 300$  mg/dL, the cost-effectiveness ratio ranges from \$20,200/YOLS for three CAD risk factors to \$78,300/YOLS for no CAD risk factors.<sup>19</sup> Treatment of men aged 45 to 54 costs twice as much as treatment at age 55 to 64.<sup>19</sup> Cost-effectiveness ratios for primary prevention

in women range from \$40,000/YOLS for a total cholesterol at or higher than 300 mg/dL and multiple risk factors to more than \$1,000,000/YOLS for younger women without risk factors.<sup>19</sup>

Hsu and colleagues found that the most favorable cost-effectiveness ratios for HMG-CoA reductase inhibitor therapy are with high-risk CAD patients.<sup>16</sup> Therefore, in high-risk CAD patients, the cost per year of life saved with HMG-CoA reductase inhibitor therapy may be lower than that observed for primary prevention.<sup>10,11,16</sup> In support of this observation, the Pravastatin Limitation of Atherosclerosis in Coronary Arteries and the Pravastatin, Lipids, and Atherosclerosis in the Carotids Trials showed that monotherapy with pravastatin was cost effective in patients with preexisting CAD.<sup>20,21</sup> Pravastatin therapy costs \$19,082 per YOLS for patients with CAD and one risk factor, \$14,022 for CAD plus two risk factors, and \$10,630 for CAD and three risk factors.

#### Formulary Considerations

The recent interest in lowering serum cholesterol concentrations has led to the vigorous promotion of numerous cholesterol-lowering agents. Therefore, the multiplicity of available HMG-CoA reductase inhibitors and the limited financial resources that can be allocated to the prevention and treatment of CAD make it necessary to ensure the objective evaluation, selection, and use of HMG-CoA reductase inhibitors. A primary consideration in the selection of a cholesterol-lowering agent is the drug's ability to reduce LDL-C to levels that favorably alter morbidity and mortality in patients with CAD. Results from the WOSCOPS, 4S, and CARE show that a 25% to 35% reduction in LDL-C is both feasible and beneficial.<sup>13-15</sup> The benefits of this level of reduction in LDL-C are seen within the first 18 months of therapy and are fully realized within 5 years.

The cost of cholesterol-lowering drug therapy is sensitive to the cost of the agents. One interesting strategy is to determine the mean cost of drug per

dose per day to achieve a target reduction in LDL-C. Table 3 estimates the annual average wholesale price of therapy (US dollars) to achieve targeted reductions in LDL-C with an HMG-CoA reductase inhibitor.

**Table 3.** Estimated Cost per Year of Therapy to Reduce LDL-C (US Dollars)

Drug	Strength	LDL-C Reduction	Annual Wholesale Price
Atorvastatin	10 mg	39%	\$666.00
Cerivastatin	0.3 mg	30%	\$482.00
Fluvastatin	40 mg	24%	\$497.00
Lovastatin	40 mg	32%	\$1,478.00
Pravastatin	20 mg	32%	\$753.00
Simvastatin	10 mg	33%	\$740.00

**Conclusions**

Treatment with HMG-CoA reductase inhibitors plus lifestyle modifications can have a very beneficial impact on morbidity and mortality associated with CAD. Unfortunately, only 25% of eligible patients receive treatment for their hypercholesterolemia. Therefore, clinicians have an obligation to inform patients about the value of cholesterol-lowering therapy and about the importance of complying with the medical therapy for the treatment of hypercholesterolemia. Since hospital and nursing home expenses represent the largest portion of the costs of treating CAD, lipid-lowering programs provide an opportunity for managed care organizations to improve the health of their populations, while at the same time reducing the cost of care. Although numerous studies have proven the efficacy of HMG-CoA reductase inhibitors, tolerability and affordability will determine the ultimate value of these agents.

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