

## Clinical Implications of Recent Cholesterol Lowering Trials for the Secondary Prevention of Coronary Heart Disease

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### **Abstract**

Coronary risk factors, including hypercholesterolemia, contribute substantially to the development and clinical expression of atherosclerosis. Of all patients, those with established coronary heart disease benefit the most from risk factor modification (secondary prevention). Over the past 2 decades, 18 of 19 angiographic cholesterol lowering trials have demonstrated slowing of the progression of coronary or carotid atherosclerosis. Three important trials completed in the last 2 years have clarified the clinical benefit that can be derived from cholesterol lowering. All three also demonstrate findings that support the National Cholesterol Education Program (NCEP) guidelines. These are the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) trial, and the Post-Coronary Artery Bypass Graft (Post-CABG) trial. The 4S and CARE trials demonstrated 24% to 40% reductions in total and cardiovascular mortality and morbidity, less need for coronary revascularization procedures, and fewer hospitalizations. Coronary disease patients with a total cholesterol level of >200 mg/dL or low-density lipoprotein cholesterol (LDL-C) levels of >125 mg/dL showed clear benefit from simvastatin or pravastatin. This benefit appeared to be independent of age, gender, other risk factors, and other medications. The Post-CABG trial demonstrated less arte-



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riographic disease progression in patients undergoing aggressive versus moderate cholesterol reduction. Recent advances in our understanding of coronary atherosclerosis pathophysiology suggest that cholesterol lowering reduces cardiovascular events through improvements in endothelial function, reductions in oxidized LDL-C and reductions in plaque inflammation. These factors result in less atherosclerosis progression and more plaque stability. Unfortunately, only about 25% of coronary heart disease patients are currently on cholesterol lowering drugs. The same treatment gap exists for other risk factor modifications. These data suggest an important opportunity exists to improve the care of coronary disease patients.

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**C**oronary heart disease is both highly prevalent and preventable. Currently in the United States, more than 10 million people have symptomatic coronary artery disease. The consequences are more than 1.5 million myocardial infarctions, 500,000 deaths, and a total economic burden of \$128 billion annually. Asymptomatic coronary artery disease is even more prevalent. Autopsy studies of trauma victims have demonstrated the presence of histological coronary atherosclerosis in 50% to 75% of young men, with high-grade stenoses in 5% to 10%. By age 90, more than 70% of individuals have high-grade stenoses.<sup>1</sup>

Considerable epidemiologic and experimental evidence suggests that hypercholesterolemia plays an important role in the genesis of coronary and other atherosclerosis.<sup>2-5</sup> Following early identification of the presence of cholesterol in atheroma, Anitschkow observed that atherosclerotic lesions could be induced in susceptible animals through high

saturated fat and cholesterol diets, and that lesions regressed when low fat and cholesterol diets were resumed.<sup>6</sup> The landmark Framingham Heart Study, initiated in 1948, followed more than 5,000 men and women who were initially without cardiovascular disease. This study originated the concept of coronary risk factors, demonstrating a prospective relationship among the factors of increased age, male gender, hypercholesterolemia, cigarette smoking, hypertension, diabetes, physical inactivity, obesity and coronary heart disease risk.<sup>7</sup> The Seven Countries Study<sup>8</sup> and the Multiple Risk Factor Intervention Trial (MULTI-FIT)<sup>9</sup> found continuous, graded relationships between serum cholesterol and coronary heart disease risk, although societies appear to lie on different cholesterol-risk curves. Approximately 90% of the regional variation in coronary atherosclerosis can be attributed to variations in cholesterol, cigarette smoking, and ingestion of antioxidants. The presence of established

coronary heart disease increases the risk of a subsequent event approximately six-fold, irrespective of cholesterol level.

The strongest evidence that total cholesterol and low-density lipoprotein cholesterol (LDL-C) are causally related to the development of coronary heart disease is derived from randomized, controlled primary (initially healthy) and secondary (established disease) prevention clinical trials. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)<sup>10</sup> and the Helsinki Heart Study<sup>11</sup> found 19% to 34% reductions in cardiovascular events in hypercholesterolemic men treated with cholestyramine and

THE 19 RANDOMIZED, CONTROLLED ANGIOGRAPHIC TRIALS	
<b>ACAPS</b>	(Asymptomatic Carotid Artery Progression Study, 1994)
<b>BECAIT</b>	(Bezafibrate Coronary Atherosclerosis Intervention Trial, 1996)
<b>CCAIT</b>	(Canadian Coronary Atherosclerosis Intervention Trial, 1994)
<b>CLAS</b>	(Cholesterol Lowering Atherosclerosis Study, 1987)
<b>FATS</b>	(Familial Atherosclerosis Treatment Study, 1990)
<b>HARP</b>	(Harvard Atherosclerosis Reversibility Project, 1994)
<b>Heidelberg</b>	(1992)
<b>KAPS</b>	(Kuopio Atherosclerosis Prevention Study, 1995)
<b>LHT</b>	(Lifestyle Heart Trial, 1990)
<b>MAAS</b>	(Multicentre Anti-Atheroma Study, 1994)
<b>MARS</b>	(Monitored Atherosclerosis Regression Study, 1993)
<b>NHBLI</b>	(National Heart, Blood, and Lung Institute Type II Coronary Intervention Study, 1984)
<b>PLAC I</b>	(Pravastatin Limitation of Atherosclerosis in the Coronary Arteries, 1995)
<b>PLAC II</b>	(Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries, 1995)
<b>POSCH</b>	(Program on the Surgical Control of the Hyperlipidemia, 1990)
<b>REGRESS</b>	(Regression Growth Evaluation Statin Study, 1995)
<b>SCOR</b>	(Specialized Center of Research Intervention Trial, 1990)
<b>SCRIP</b>	(Stanford Coronary Risk Intervention Project, 1994)
<b>STARS</b>	(St. Thomas Atherosclerosis Regression Study, 1992)

gemfibrozil, respectively. Although no changes in overall mortality were observed in these and other early trials employing modest cholesterol reductions, a meta-analysis suggested that mortality could be reduced with sufficient cholesterol lowering.

More recently, the West of Scotland Coronary Prevention Study (WOSCOPS)<sup>12</sup> found a 31% reduction in coronary heart disease mortality plus nonfatal myocardial infarction in hypercholesterolemic men who were randomized to pravastatin. Angiographic and clinical event secondary prevention trials have reinforced these observations and have found that the largest benefit from cholesterol lowering appears to be for those with established coronary heart disease.

### Angiographic Trials

During the past 2 decades, 19 randomized, controlled trials [see sidebar, page S84] have investigated whether cholesterol lowering was associated with reduced rates of angiographic or ultrasonic progression of coronary or carotid atherosclerosis, respectively.<sup>13-17</sup> Cholesterol reduction in these trials was achieved by widely differing regimens including low-fat diet, exercise, single or multiple drugs, and partial ileal bypass surgery. With time, trials more commonly employed HMG-CoA reductase inhibitors reflecting their widespread clinical use, good efficacy, and high patient compliance rates.<sup>18</sup> Trials ranged from 1 to 10 years in duration and enrolled anywhere between 43 to 838 patients. All but one of the trials demonstrated that patients receiving lipid-lowering agents were more likely than those in control groups to evidence less disease progression, more stability of existing lesions, fewer new lesions, and/or more disease regression. The lone exception, the HARP study, was undertaken in patients with the lowest cholesterol.<sup>19</sup>

Absolute differences in coronary luminal dimensions between treatment and control groups were found to be small but significant; on average this

represented a 50% to 75% reduction in disease progression. A few trials demonstrated an average minimal reduction in percent diameter stenosis on the order of 1% to 5%, suggesting disease regression. Overall, changes in disease progression tended to correlate with LDL-C lowering; disease regression was associated with high-density lipoprotein cholesterol (HDL-C) raising. A consistent observation in these angiographic trials was that there was a substantial reduction in cardiovascular events (a mean of 48%) despite modest, although statistically significant, decreases in disease progression. This was unexpected since the trials were not powered to demonstrate changes in events. Moreover, cardiovascular events appeared to decrease within *months* of starting treatment, despite the fact that 1 to 2 years are needed to demonstrate anatomic changes. Patients with angiographic disease progression had a significantly increased incidence of cardiovascular events. This association supported the developing concept of plaque "stabilization" brought about by cholesterol lowering. These preliminary findings set the stage for three large trials: the Scandinavian Simvastatin Survival Study (4S),<sup>20</sup> the Cholesterol and Recurrent Events (CARE) trial<sup>21</sup> and the Post-Coronary Artery Bypass Graft (Post-CABG) trial.<sup>22</sup> The first two focused on secondary prevention of cardiovascular events and the last examined aggressive versus moderate cholesterol reduction.

### The Scandinavian Simvastatin Survival Study

Although earlier event and angiographic secondary prevention trials had demonstrated reductions in cardiovascular events, cholesterol lowering had not been clearly shown to reduce all-cause mortality. This hypothesis was directly addressed in the 4S study, which was designed with all-cause mortality as its primary endpoint.<sup>20,23-25</sup> A total of 4444 men (81%) and women, ages 35 to 70 years with prior myocardial in-

farctions (79%) and/or angina were randomized to receive simvastatin or placebo. Initial cholesterol levels were 213 mg/dL to 310 mg/dL and triglycerides were <200 mg/dL. Simvastatin was administered at 20 mg/day or 40 mg/day with the intent to lower cholesterol below 200 mg/dL. Twenty-five percent of the subjects were smokers and 5% were diabetic. Over the 5.4-year median follow-up period, simvastatin lowered mean cholesterol from 260 mg/dL to 189 mg/dL (-25%). A 30% reduction in all-cause mortality was observed (182 vs. 256 deaths,  $P = 0.0003$ ). Significant reductions were also observed in myocardial infarctions, in the need for coronary angioplasty or bypass surgery, in strokes or transient ischemic attacks, and hospitalizations (Table 1). No increases in noncardiovascular morbidity or mortality were observed and no neuropsychiatric adverse effects were experienced. The frequency of adverse events was the same in both the placebo and treatment groups (5.8% and 5.7%, respectively), and the same number of patients discontinued placebo and simvastatin (13% and 10%, respectively).

Benefit was generally demonstrated in all subgroups. Although all-cause mortality was not reduced in women, probably due to the smaller subgroup size, total cardiovascular events were reduced to the same extent in both genders. As in the primary prevention WOSCOPS trial, a reduction in cardiovascular events was observed within 1 year in the treatment group. Benefit was observed irrespective of other risk fac-

tors, including age, hypertension, cigarette smoking history, and diabetes, and concomitant medications (including aspirin, beta-blockers, and calcium channel inhibitors). The risk of major cardiovascular events was reduced to the same extent at all initial cholesterol levels. Although hypertriglyceridemic patients were excluded (>200 mg/dL), patients with high triglyceride levels appeared to derive more benefit. The 4S trial was designed to assess the effects of lowering cholesterol below a threshold of 200 mg/dL. Within this model, there appeared to be little correlation between decrease in mortality and the amount of cholesterol reduction. A weak correlation was observed between decrease in mortality and LDL-C lowering, and a strong correlation was found with apolipoprotein-B lowering. The question of how much cholesterol lowering is ideal was better addressed in the Post-CABG study.

Hospitalizations for acute cardiovascular events or coronary revascularizations were reduced from 1905 in the placebo group (average duration 7.9 days) to 1403 in the simvastatin group (average duration 7.1 days). The corresponding number of hospital days was 15,089 and 9951, respectively (-34%). In the United States, the resulting reduction in hospitalization costs over the 5.4-year trial would reduce the effective cost of simvastatin 88% to \$0.28 per day. Table 2 compares the cost effectiveness of several healthcare measures in terms of cost per year of life saved. Generally, measures costing less than \$50,000 to \$60,000 per year of life saved are considered to be cost effective. In comparison, primary prevention is less cost effective, with substantial variations, depending on whether individuals are high- or low-risk. Higher risk individuals derive more benefit from risk factor modification, which is therefore more cost effective.

### The Cholesterol and Recurrent Events Study

In contrast to the patients studied in the 4S study, the majority of coronary

**Table 1.** Summary Results of the Scandinavian Simvastatin Survival Study

Result	Simvastatin	Placebo
Total cholesterol	189	260
Total mortality	182	256
Myocardial infarction	380	553
PTCA or CABG	252	383
Stroke or TIA	66	103
Unstable angina	295	331
Hospital days	9951	15,089

heart disease patients in the US have "borderline" elevated cholesterol levels (mean 225 mg/dL). This has led to an incorrect impression that these patients would not benefit from cholesterol lowering. This is cited as a frequent reason why modification is not undertaken. The CARE study, which tracked 4159 patients (3583 men), used pravastatin 40 mg/day, and was designed to determine the value of cholesterol lowering in patients who had had a previous myocardial infarction (mean 10 months prior), total cholesterol levels of <240 mg/dL, and triglycerides of <400 mg/dL.<sup>21</sup> Mean lipid values for the group studied were total cholesterol levels of 209 mg/dL, LDL-C levels of 139 mg/dL, HDL-C levels of 39 mg/dL, and triglycerides of 155 mg/dL. This mean cholesterol is almost equal to the American average (208 mg/dL). Pravastatin was shown to reduce total cholesterol by 20% and LDL-C levels by 32%. Over the 5 years of the trial, the primary endpoint—CHD mortality plus nonfatal myocardial infarction—was reduced from 274 in the control group to 212 in the pravastatin group (-24%, *P* = 0.003). As in the 4S study, strokes, unstable angina, and the need for coronary angioplasties or bypass surgeries were also reduced (13% to 31%).

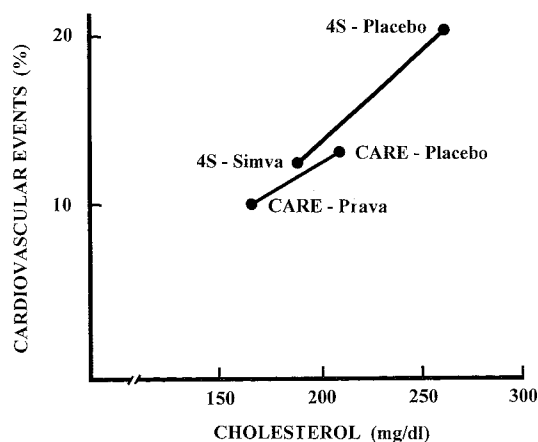
Benefit from cholesterol lowering was observed in all subgroups except those with initial LDL-C of <125 mg/dL. An important, but not statistically significant finding, was that more reduction in the primary endpoint was observed in women (-46%) than in men (-20%). The presence of age (60 or more years), hypertension, diabetes mellitus, cigarette smoking, and prior coronary revascularization were not associated with diminished effect. Although there was equal benefit in the groups with initial cholesterol above and below the mean (209 mg/dL), the 851 patient group with initial LDL-C levels of <125 mg/dL appeared not to benefit. Unlike the results of the 4S study, less reduction in cardiovascular endpoints was observed in those with higher initial

**Table 2.** Cost Effectiveness of Medical and Hygienic Measures (Per Year of Life Saved)

Measure	Cost (\$)
Water chlorination	4,000
Cholesterol reduction (secondary prevention)	10,000
Pneumococcal vaccination	12,000
Hepatitis vaccination	20,000
Thrombolytic therapy	20,000
Blood pressure reduction	30,000
Breast cancer screening	40,000
Renal dialysis	40,000
Automobile air bags	40,000
Estrogen replacement	40,000
Coronary bypass surgery	50,000
Neonatal intensive care	50,000
TPA vs. streptokinase	60,000
Home radon testing	140,000
EPA mandate	600,000

triglycerides. The CARE study results extend the important observations of the 4S study to the majority of coronary heart disease patients in the United States. Taken together, the 4S and CARE studies demonstrate a continuous reduction in cardiovascular events with cholesterol lowering from 260 mg/dL to 157 mg/dL (Figure 1).

**Figure 1.** Major Cardiovascular Event Rates in the 4S and CARE Studies Show a Continuous Decline in Cholesterol Lowering with Simvastatin and Pravastatin



### The Post-CABG Trial

Although the 4S and CARE studies demonstrated clear benefits in secondary prevention populations over a wide range of initial cholesterol levels, they were not intended to assess the benefit afforded by different degrees of cholesterol lowering. Moreover, as noted above, analysis of the 4S data was not consistent in demonstrating a benefit proportional to the change in lipoprotein fractions. The Post-CABG trial was designed to address this issue. Predominately an angiographic trial, it compared disease progression in 1,351 patients (92% men) who had undergone prior bypass surgery in a 2x2 factorial design trial of moderate versus aggressive cholesterol lowering and low-dose warfarin versus placebo administration.<sup>22</sup> The moderate cholesterol lowering group received 4 mg of lovastatin daily, resulting in a mean LDL-C of 135 mg/dL. The aggressive cholesterol lowering group received a mean of 84 mg of lovastatin daily, resulting in a mean LDL-C of 95 mg/dL. Preliminary data suggest that by composite angiographic index, the aggressive cholesterol lowering group had less bypass graft disease progression than the moderate treatment group over 4 years. No benefit was observed in the low-dose warfarin group. An 18% reduction in cardiovascular events ( $P = 0.09$ ) was observed in the aggressive cholesterol reduction group and significant reductions (-29%) were observed in need for additional coronary revascularization procedures. This was the first trial to document an additional benefit for an aggressive treatment program designed to meet the National Cholesterol Education Program (NCEP) recommendations for lowering LDL-C to <100 mg/dL in patients with established coronary heart disease.<sup>26</sup>

### Pathophysiology

Advances in our understanding of the pathophysiology of coronary atherosclerosis have explained many of the findings in these key studies.<sup>27-32</sup> In broad terms, coronary atherosclerosis is

an initially slow process of intimal lipid, monocyte and T-lymphocyte accumulation, which leads to the migration and proliferation of smooth muscle cells and elaboration of collagen and matrix in the subintimal layer. In its more advanced stages, this process is punctuated by acute episodes of plaque rupture, thrombosis, and vessel reorganization, which underlie the clinical syndromes of unstable angina and acute myocardial infarction. Beginning in the first few decades of life, coronary heart disease remains asymptomatic until significant lumen compromise develops or sudden occlusion occurs. In the former circumstance, stable exertional angina may be the presenting symptom, although this occurs in only 26% of men and 47% of women.<sup>33</sup> Unstable angina, urgent need for coronary revascularization, acute myocardial infarction, and sudden death together make up the majority of initial presenting symptoms. Important early pathophysiologic processes include endothelial dysfunction caused by coronary risk factors, mechanical trauma, infections (possibly chlamydia, cytomegalovirus and herpes viruses), and autoimmune processes, and the progressive modification of LDL, predominantly by oxidation. Once atherosclerotic plaques develop, the combined factors of local plaque inflammation, dissolution of internal plaque collagen, and vasomotion lead to plaque disruption, with ensuing partial or complete vessel thrombosis. Cholesterol lowering has been shown to slow the progression of coronary atherosclerosis and reduce plaque rupture, which leads to the occurrence of cardiovascular events.

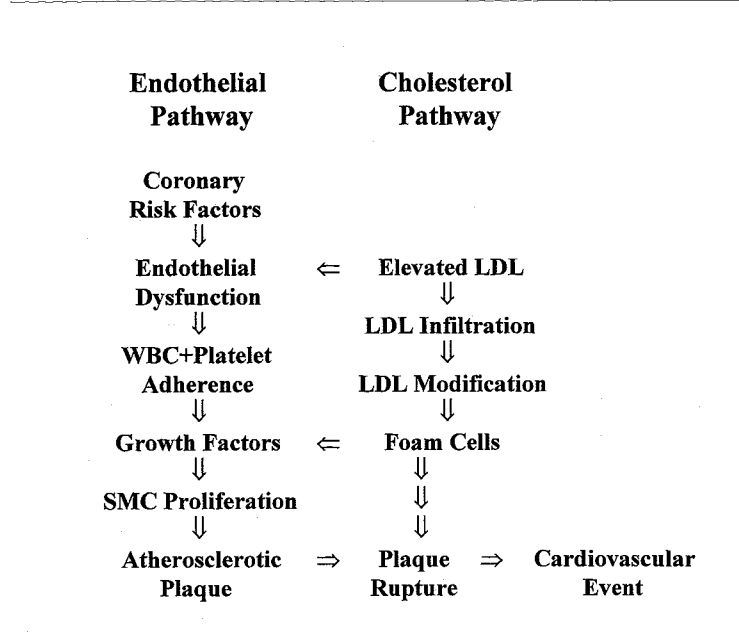
Two parallel processes play important roles in the initiation of atherosclerosis: endothelial dysfunction and lipid accumulation and modification (Figure 2). The endothelium is the monocellular lining of blood vessels and is the largest endocrine, paracrine, and autocrine organ in the body. It controls vasoregulation (vasodilation and vasoconstriction), vessel growth, aggregation of platelets, adhesion of monocytes,

and fibrinolysis. Normal endothelium prevents the development of atherosclerosis. All coronary risk factors, including hypercholesterolemia, produce endothelial dysfunction. The mechanism appears to be through increased production of oxygen-free radicals which combine with and deactivate nitric oxide and other vasoprotective molecules. This results in increased platelet aggregation, monocyte adhesion, vasoconstriction, and decreased fibrinolysis, all of which are important factors in the development of atherosclerosis and plaque rupture. Antioxidant vitamins may help prevent the development of atherosclerosis by reducing the degradation of nitric oxide.

Cholesterol deposition (predominantly from LDL-C) and modification is the second major process initiating atherosclerosis. Initially, LDL-C passes through the endothelial barrier by a process called transcytosis. This process is accelerated by increases in serum LDL-C and decreases in HDL-C. In addition to being a source for reverse cholesterol transport back to the liver, HDL-C also exerts an antioxidant effect. With time, intimal LDL-C undergoes progressive modification through oxidation, glycosylation, and acetylation. Macrophages, endothelial cells, and smooth muscle cells are the likely sources of LDL-C oxidation. Minimally modified LDL-C is a potent inhibitor of endothelial function. Maximally modified LDL-C is recognized as foreign material by macrophages and taken up via their scavenger receptors, creating metabolically active foam cells. These add to a number of growth factors which induce smooth muscle cell migration, proliferation, and matrix generation, leading to the formation of complex atheroma.

Cardiovascular events occur when "vulnerable" atheroma rupture. Incomplete luminal thrombosis may produce unstable angina and/or rapid progression of stenosis severity. Complete thrombosis may produce myocardial infarction if inadequate collateralization is present.

**Figure 2.** Current Concepts on the Development of Atherosclerosis



Vulnerable plaques tend to be eccentric and have large, coalescent lipid pools, thin fibrous caps, and reduced internal plaque collagen. With vasoactivity or fluctuating blood pressure, these cholesterol "abscesses" often rupture at the intersection of the atheroma and the more normal vessel wall. High concentrations of T-lymphocytes, foam cells and cytokines have been identified in the region of plaque rupture, suggesting an inflammatory mechanism. Through the elaboration of interferon-gamma, T-lymphocytes may suppress smooth muscle cell proliferation and induce foam cells to digest internal plaque collagen through the secretion of metalloproteinases. These are major factors in plaque instability. The effectiveness of aspirin in secondary prevention may be, in part, due to its anti-inflammatory properties.

Cholesterol reduction stabilizes plaques by decreasing plaque inflammation and foam cell number and activity and by increasing plaque collagen. Clinically, only modest degrees of regression have been observed with cho-

lesterol lowering, although chronic anorexia and starvation are associated with a dramatic reduction in coronary atherosclerosis at autopsy. Cholesterol reduction also lessens endothelial dysfunction, thereby reducing the vasoactivity that is thought to be an important factor in plaque rupture. Improved endothelial function is also associated with increased intrinsic fibrinolysis (tPA: PAI-1). Six studies have demonstrated improved coronary or brachial artery vasoactivity with cholesterol reduction in healthy and atherosclerotic subjects, supporting the linkage of risk factor modification through changes in endothelial function. Endothelium-dependent vasoactivity appears to improve with reduction of cholesterol to levels between 150 mg/dL and 170 mg/dL.<sup>34</sup> This is similar to the observations of the clinical event trials.

#### Clinical Recommendations

Recent clinical angiographic and event trials and studies of vascular biology have demonstrated a remarkable concordance of data showing improvements in endothelium-dependent vasoactivity, slowing of atherosclerosis progression, and reduction in cardiovascular morbidity and mortality with aggressive cholesterol reduction. There appears to be continuous benefit from reducing an elevated cholesterol level to approximately 160 mg/dL and/or an elevated LDL-C to below 100 mg/dL. These findings are consistent with the NCEP recommendations to initiate a low fat and cholesterol diet in coronary heart disease patients with LDL-C levels of >100 mg/dL and add a pharmacologic agent for those with LDL-C of >130 mg/dL with the intent of lowering LDL-C to <100 mg/dL.<sup>26</sup> For patients with coronary heart disease, this strategy is very cost effective compared with other widely accepted treatments.

Unfortunately, surveys have shown that 75% of coronary heart disease patients are currently receiving no cholesterol lowering therapy.<sup>35</sup> Numerous reasons are given for this treatment gap,

including high drug costs and side effects, guideline complexities, questionable benefit in patients with "borderline" cholesterol, prolonged use of diets alone ("dietary holding pattern"), nonacceptance of the cholesterol hypothesis, and confusion over who should manage lipids. This treatment gap extends to almost all other aspects of medical management, and represents one of the largest problems in the management of coronary heart and other chronic diseases. Currently, only one American out of two with coronary heart disease is on aspirin or receives an aspirin within two days of the diagnosis of acute myocardial infarction.<sup>36</sup> Only 28% of smoking patients hospitalized for acute myocardial infarction are counseled to stop smoking.<sup>37</sup> Similar data exist for other cardiovascular drugs and risk factors. Efforts directed at the secondary prevention of coronary heart disease, including cholesterol lowering, represent highly cost- and clinically-effective means for reducing the burden of this prevalent illness.

#### ... REFERENCES ...

1. Joseph A, Ackerman D, Talley D, et al. Manifestations of coronary atherosclerosis in young trauma victims: An autopsy study *J Am Coll Cardiol* 1993;22:459-469.
2. Miller M, Vogel R. *The Practice of Coronary Disease Prevention*. Williams and Wilkins, Baltimore, MD; 1996:1-294.
3. Rossouw J, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. *N Engl J Med* 1990;323:1112-1119.
4. LaRosa JC, Cleeman JI. Cholesterol lowering as a treatment for established coronary heart disease. *Circulation* 1992;85:1229-1235.
5. Stamler J, Stamler R, Brown WV, et al. Serum cholesterol: Doing the right thing. *Circulation* 1993;88:1954-1960.
6. Anitschkow N. Experimental atherosclerosis in animals. In: Cowdry EV, ed. *Arteriosclerosis: A Study of the Problem*. Macmillan, New York, NY; 1933:271-322.
7. Anderson M, Castelli WP, Levy D. Cholesterol and mortality: 30 years of follow-up from the Framingham Study. *JAMA* 1987; 257:2176-2180.



8. Keys A, Arararis C, Blackburn H, et al. Epidemiological studies related to coronary heart disease: Characteristics of men aged 40-59 in seven countries. *Acta Med Scand* 1967;180(Suppl 460):1-392.
9. Debusk RF, Houston-Miller N, Superko R, et al. A case-management system for coronary risk factor modification after acute myocardial infarction. *Ann Intern Med* 1994; 120:721-729.
10. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention (LRC-CPPT) Trial results II: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 1984;251:365-374.
11. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237-1245.
12. Shepherd J, Cobbe S, Ford I, et al, for the West of Scotland Coronary Prevention Study (WOSCOPS) Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-1307.
13. Brown BG, Zhao XQ, Sacco DE, Albers JJ. Lipid lowering and plaque regression—new insights into prevention of plaque disruption and clinical events in coronary disease. *Circulation* 1993;87:1781-1791.
14. Phillips NR, Waters D, Havel RJ. Plasma lipoproteins and progression of coronary artery disease evaluated by angiography and clinical events. *Circulation* 1993; 88:2762-2770.
15. Waters D, Craven TE, Lesperance J. Prognostic significance of coronary atherosclerosis. *Circulation* 1993;87:1067-1075.
16. Brown BG, Maher VMG. Reversal of coronary heart disease by lipid-lowering therapy. Observations and pathological mechanisms. *Circulation* 1994;89:2928-2933.
17. Gotto AM. Lipid lowering, regression and coronary events: A review of the Interdisciplinary Council on Lipids and Cardiovascular Risk Intervention, seventh council meeting. *Circulation* 1995;92:646-656.
18. Byington RP, Jukema JW, Salonen JT, et al. Reduction in cardiovascular events during pravastatin therapy. Pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. *Circulation* 1995;92:2419-25.
19. Sacks FM, Pasternak RC, Gibson CM, Rosner B, Stone PH. The Harvard Atherosclerosis Reversibility Project (HARP) group: Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolemic patients. *Lancet* 1994;344:1182-1186.
20. Pedersen TR, Kjekshus J, Berg K, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389.
21. Sacks FM, Pfeffer MA, Moye LA, et al, and the Cholesterol and Recurrent Events (CARE) Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335: 1001-1009.
22. The Post Coronary Artery Bypass Graft (Post-CABG) Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anti-coagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med* 1997;336:153-162.
23. Kjekshus J, Pedersen TR. Reducing the risk of coronary events: Evidence from the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol* 1995;76:64C-68C.
24. Scandinavian Simvastatin Survival Study Group. Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1995;345:1274-1275.
25. Pedersen TR, Kjekshus J, Olsson AG, et al. Cholesterol lowering and the use of healthcare resources. Results of the Scandinavian Simvastatin Survival Study. *Circulation* 1996;93:1796-1802.
26. Grundy SM, Chait A, Clark LT, et al, for the Expert Panel on Detection, Evaluation, and Management of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP). *JAMA* 1993;269:3015-3023.
27. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary arteriography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988; 78:1157-1166.
28. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: Modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 1989;320:915-924.
29. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease. *N Engl J Med* 1992;326:242-250.
30. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992;326:310-318.
31. Libby P. Molecular basis of the acute coronary syndromes. *Circulation* 1995;91: 2844-2850.
32. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;92: 657-671.

33. Kannel WB, Abbott RD. Incidence and prognosis of myocardial infarction in women: The Framingham Heart Study. In: Eaker ED, Packard B, Wenger NK, Clarkson TB, Tyroler HA, eds. *Coronary Heart Disease in Women*. Bethesda, MD: National Heart Lung and Blood Institute, 1987.
34. Vogel RA, Corretti MC, Plotnick GP. Changes in flow-mediated brachial artery vasoactivity with lowering of desirable cholesterol levels in healthy, middle-aged men. *Am J Cardiol* 1996;77:37-40.
35. Cohen MV, Byrne M-J, Levine B, et al. Low rate of treatment of hypercholesterolemia by cardiologists in patients with suspected or proven coronary artery disease. *Circulation* 1991;83:1294-1304.
36. Krumholtz HM, Radford MJ, Ellerbeck EF, et al. Aspirin in the treatment of acute myocardial infarction in elderly Medicare beneficiaries: Patterns of use and outcomes. *Circulation* 1995;92:2841-2847.
37. Ellerbeck EF, Jencks SF, Radford MJ, et al. Quality of care for Medicare patients with acute myocardial infarction: A four-state pilot study from the Cooperative Cardiovascular Project. *JAMA* 1995;273:1509-1514.