ABSTRACT

Cardiovascular disease is a leading cause of death in men and women. Hypercholesterolemia is a major risk factor for coronary heart disease. Both primary and secondary prevention trials have documented a cardioprotective effect of lipid-lowering therapy. However, the results of these trials have not been fully implemented in clinical practice. Three secondary prevention and 2 primary prevention clinical trials evaluating the effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) on morbidity and mortality are reviewed briefly. Although both secondary and primary prevention trials demonstrated cardioprotective benefits in men and women, prescribing lipid-lowering agents even in patients with documented coronary artery disease (CAD) is low—39%, as reported in a recent study. A survey of primary-care physician practices has demonstrated that only 38% overall of patients receiving lipid-lowering therapy were achieving target low-density lipoprotein (LDL) levels. In fact, only 18% of the patients with documented CAD in this study had achieved goal levels. Another cross-sectional study showed that diabetic patients, a particularly high-risk group for cardiovascular events, were 20% less likely to receive lipid-lowering agents than those patients without diabetes. Multivariate analysis of a national sample of patients with documented CAD revealed the most important predictors for a patient to receive a lipid-lowering prescription were younger age and documentation of LDL levels. Because lowering LDL cholesterol levels has been shown to reduce cardiovascular mortality, physicians must improve the lipid management currently observed in clinical practice.

The prevalence of cardiovascular disease (CVD) is staggering. In the United States more than 60 million people suffer from 1 or more forms of CVD, including hypertension, coronary heart disease (CHD), and stroke. This equates to 1 in 5 men and women having some form of CVD. Research has demonstrated that hypercholesterolemia is a major risk factor for CHD. Fortunately, clinical trials have shown that pharmacological agents that decrease low-density lipoprotein cholesterol (LDL-C) reduce the risk of CVD. Reductions in the risk of CHD and all-cause mortality have been observed in men and women who received 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). Therefore, the practice of evidence-based medicine dictates that men as well as women should be aggressively treated to achieve clinical management of high blood cholesterol. This paper presents clinical evidence for cholesterol-
lowering therapy in women and describes the lack of appropriate lipid management currently observed in clinical practice.

**Leading Causes of Death**

Cardiovascular disease was the cause of approximately 1 million deaths (40.6% of all deaths) in 1998. During the late 1970s and 1980s more men than women died of CVD each year; however, in the mid 1980s nearly one-half million women died of CVD annually (Figure 1). In 1998, heart disease ranked as the number 1 cause of death of women in the United States, accounting for 503,927 total deaths. In that same year, 259,467 women died from all forms of cancer combined. Lung cancer was the cause of death in 64,475 women, and breast cancer claimed the lives of more than 40,000 women—a figure representing a small fraction of deaths as compared to the one-half million women who died of CVD in 1998. Yet recent data demonstrate that women feel they are at greater risk of dying from breast cancer than from CVD.

Cardiovascular disease is a serious cause of morbidity and mortality in men and women. However, women who survive an initial cardiovascular event are more likely to die from subsequent CVD than are men. Within 1 year post myocardial infarction (MI), 38% of women die as compared to 25% of men. Recurrent MI trends are just as dismal during the first 6 years after a recognized heart attack: 35% for women and 18% for men.

**Landmark Primary and Secondary Prevention Statin Trials**

A few years ago, hormone replacement therapy (HRT) was considered cardioprotective in postmenopausal women. However, results of the Heart and Estrogen/progestin Replacement Study (HERS) did not reveal a protective effect. The HERS study was a randomized, blinded, placebo-controlled study evaluating the use of HRT as a secondary prevention of CHD in 2763 women. No differences were observed between the active-treatment or placebo-treatment groups in the occurrence of nonfatal MI or CHD death, coronary revascularization, unstable angina, congestive heart failure (CHF), resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. During the first year of the clinical trial there were more cardiovascular events in the group receiving hormonal replacement than in the placebo-treatment group. Therefore, the use of HRT is not recommended for secondary prevention of CHD because there is no overall cardiovascular benefit and there is a pattern of early increased risk of CHD events with HRT.

Several clinical trials utilizing statin therapy as primary or secondary prevention have demonstrated beneficial effects on lipid profiles and survival. To date, 5 randomized, controlled, clinical trials have evaluated the effect of statin therapy to reduce LDL-C and the risk of cardiovascular events. Of these studies, the Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events (CARE), and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) were secondary prevention studies conducted in patients with CHD at baseline. The remaining trials, West of Scotland Coronary Prevention Study (WOSCOPS) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) were primary prevention studies.

The 4S study evaluated 4444 hyperlipidemic subjects with a history of MI or angina, 19% of whom...
were women. Therapy with 20 mg of simvastatin per day was associated with a 30% reduction in total mortality (the primary outcome measure) as compared to placebo ($P = .0003$). This was the first trial to demonstrate a beneficial effect in women. Women receiving simvastatin therapy experienced a 34% reduction in major coronary events (coronary death, nonfatal definite or probable MI, silent MI, or resuscitated cardiac arrest) as compared to those women treated with placebo ($P < .001$). During subgroup analysis, no significant interaction between a patient’s gender and type of treatment was observed for the primary or secondary endpoints. Overall, patients receiving simvastatin experienced the following mean changes from baseline in serum lipid concentrations: 25% reduction in total cholesterol, 35% reduction in LDL-C, 8% increase in high-density lipoprotein cholesterol (HDL-C), and 10% reduction in triglycerides.

The CARE study evaluated the effect of 40 mg of pravastatin per day in 4159 patients (14% of whom were women) with CHD and average cholesterol levels. The primary endpoint was death from CHD or a symptomatic nonfatal MI. Overall, pravastatin therapy was associated with a 24% lower incidence of the primary endpoint as compared to placebo ($P = .003$). In women the effect was even more dramatic: a 46% reduction in cardiovascular death or myocardial infarction ($P = .001$). Similarly, patients who were 60 years or older and treated with pravastatin experienced a 27% risk reduction in the primary endpoint as compared to those patients who received a placebo ($P < .001$). Reductions in total cholesterol by 20%, LDL-C by 28%, and triglycerides by 14% as well as an increase in HDL-C of 5% were associated with pravastatin therapy.

Death from CHD was the primary endpoint in the third secondary prevention study, LIPID. In this trial, 9014 patients with a history of MI or unstable angina and average cholesterol were randomized to receive 40 mg of pravastatin per day or a placebo. Pravastatin therapy was associated with a 24% reduction in risk of death from CHD and a 22% reduction in overall mortality as compared to placebo ($P < .001$). Reductions in total cholesterol by 20%, LDL-C by 28%, and triglycerides by 14% as well as an increase in HDL-C of 5% were associated with pravastatin therapy.

The WOSCOPS primary prevention study enrolled 6595 men with hypercholesterolemia and no CHD. The men treated with 40 mg of pravastatin per day experienced a 31% reduction in the combined primary endpoint of nonfatal MI and death from CHD as compared to those men who received placebo ($P < .001$). Pravastatin therapy lowered plasma cholesterol by 20%, LDL-C by 26%, and triglycerides by 12%, but it raised HDL-C by 5%.

The AFCAPS/TexCAPS trial evaluated 5608 men (age 45 years to 73 years) and 997 women (age 55 years to 73 years) who did not have CHD and had an average serum LDL-C level and a low HDL level. Daily administration of 20 mg to 40 mg of lovastatin was associated with a 37% lower incidence of primary endpoint of fatal or nonfatal MI, unstable angina, or sudden cardiac death as compared to placebo ($P < .001$). Although no statistically significant difference in the primary outcome measure between men and women was observed, the relative risk reduction with lovastatin therapy as compared to placebo was 46% in women and 37% in men. Subjects treated with

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**Figure 2. Patients on Nondrug and Drug Therapy Who Reached Target LDL-C Levels:** The Lipid Treatment Assessment Project (L-TAP)^^14^ Adapted from Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med.* 2000;160(4):459-467, with permission from the American Medical Association.
Lovastatin experienced an 18% reduction in total cholesterol, 25% reduction in LDL-C, 15% reduction in triglyceride, and a 6% increase in HDL-C. These changes in lipid parameters were similar in men and women.

**RESULTS OF CLINICAL PRACTICE**

Clearly, the use of statins has shown a positive impact on the lipid profile and CVD events in both primary and secondary prevention studies involving both men and women. Other beneficial effects of statin administration include plaque stabilization, restoration of endothelial function, and reduction in inflammation and C-reactive protein levels. The results of clinical trials, coupled with educational efforts sponsored by the American Heart Association, and guidelines published by the National Cholesterol Education Program (NCEP), should be reflected as a positive impact on patient care in clinical practice.\(^3\)\(^-\)\(^{13}\)

Three recent studies have evaluated the treatment of hyperlipidemia in clinical practice involving both primary-care physicians and cardiologists.\(^{14}\)\(^-\)\(^{16}\)

Achievement of the NCEP LDL-C goals was assessed in the Lipid Treatment Assessment Project (L-TAP),\(^{14}\) which enrolled 4888 dyslipidemic patients (50% were women) and represented 606 primary-care physicians. Patients, all of whom received the same lipid-lowering therapy for at least 3 months, were categorized into 3 risk groups: low risk with fewer than 2 risk factors and no evidence of CHD (23.4%); high risk with 2 or more risk factors and no evidence of CHD (46.7%); established CHD with a previous MI, bypass surgery, or angioplasty (29.9%). The L-TAP study was conducted from 1996 to 1997 when NCEP's Adult Treatment Panel (ATP) II guidelines were in place. Almost all primary-care physicians (95%) included in this survey indicated they followed NCEP guidelines in practice. Target levels of LDL-C were achieved by 38% of the patients, with the highest success rate in the low-risk group (68%) and the lowest success rate in the established CHD group (18%), as shown in Figure 2.

A second study determined the frequency of lipid level documentation and prescription of lipid-lowering therapy in ambulatory-care patients with documented coronary artery disease (CAD).\(^{15}\) A retrospective chart audit of 48 586 patients with CAD (mean age of 68) treated in 140 practices nationwide

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**Figure 3. Percentage of Patients on Lipid-Lowering Agents by Age\(^{15}\)**

![Chart showing percentage of patients on lipid-lowering agents by age]


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<thead>
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<th>Table. Predictors of Lipid-Lowering Therapy(^{15})</th>
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<td><strong>OR</strong></td>
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<td>Age (years)*</td>
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*Compared to patients aged 55-64
†Compared to the South

OR = odds ratio; CI = confidence interval; LDL = low-density lipoprotein; MI = myocardial infarction; CABG = coronary artery bypass grafting.

was recently conducted. Cardiology-only practices represented 80% of these sites, and about one third of these patients (36%) were women. Concurrent medical conditions included hypertension (43%), diabetes mellitus (18%), MI (29%), and coronary artery bypass graft (CABG, 29%). Surprisingly, only 66% of these patients had documented total cholesterol levels, and 44% had documented LDL-C levels within 1 year of their last visit. One fourth of the patients were at LDL-C goal of <100 mg/dL. Overall, only 39% of patients were prescribed lipid-lowering agents. In patients less than age 65, men appeared to be more aggressively treated than women. After age 65, men and women were undertreated (Figure 3). Statins were prescribed in 84% of patients, followed by fibric acid in 13%, niacin in 8%, and bile resins in 3%. Two thirds of the patients receiving statin therapy were being treated with a starting dose, which may help to explain why so few patients were at goal. No relationship between LDL-C and the percentage of patients at a starting dose of a statin or the mean dose of statin prescribed was observed. The predictors of lipid-lowering prescription are shown in the Table. Compared with patients aged 55 years to 64 years, patients 65 years or older were significantly less likely to receive therapy. Patients with documented LDL-C were 4 times more likely to receive such prescriptions.

Another chart audit of 49,721 patients with CAD (37% women) analyzed pharmacologic lipid management in association with age and diabetes status. Medical practices analyzed included cardiology (56%), multiple specialty (22%), internal medicine (12%), family medicine (4%), and other (5%). Patients with diabetes were significantly more likely to be younger; to have hypertension, CABG, coronary angioplasty, CHF, lower HDL-C, lower LDL-C, or higher triglycerides; and were less likely to have received pharmacologic therapy for dyslipidemia (P <.01). Surprisingly, given the high incidence of concurrent risk factors, diabetic patients were 20% less likely to receive lipid-lowering agents than those patients without the disease. Similar to previous analyses, older patients were significantly less likely to be treated with lipid medications as compared to younger patients.

**DISCUSSION**

Cardiovascular disease is the number 1 cause of death of women in the United States and represents a serious public health issue. Clinical trial evidence supports the use of lipid-lowering therapy in the primary and secondary prevention of CVD in both men and women. Unfortunately, recent analyses of clinical practice suggest that 82% of patients treated with hyperlipidemia therapy are not reaching the ATP II LDL-C goal of ≤100 mg/dL. Particularly unsettling is information suggesting that patients with CAD and with concurrent diabetes are 20% less likely to receive lipid-lowering therapy than are nondiabetic patients with CAD. Overall, patients who do not undergo lipid-level testing, as well as those who are age 65 years and older, are less likely to be treated.

Such unsatisfactory statistics are not likely to improve when the more stringent ATP III LDL-C goals of <100 mg/dL are considered. Studies estimate that 36 million Americans are now candidates for lipid-lowering therapy. It is critically important for health care providers to recognize that patients overall are not being treated to LDL-C goals and are not receiving the maximal morbidity and mortality benefits from lipid-lowering treatment demonstrated by multiple clinical trials. The barriers to optimal care must be studied and eliminated. An emphasis on LDL testing and aggressive treatment of the older patients and diabetic patients will translate into a reduction in cardiovascular events.

**REFERENCES**


