Prevention and Treatment of Coronary Heart Disease
Who Benefits?
John C. LaRosa, MD

Abstract—Coronary heart disease (CHD) remains a leading cause of morbidity and mortality in the United States, despite our better understanding of the pathobiology of atherosclerosis, our knowledge of risk factors, the widespread availability of inexpensive cholesterol screening, and the availability of effective and well-tolerated cholesterol-lowering agents. Advances in these areas have created controversies regarding who should be screened and treated for primary or secondary prevention of coronary events. The advent of the statin class of lipid-lowering agents represented a major advance, because they are much more effective and better tolerated than previous agents. There is general agreement that patients with hypercholesterolemia and established CHD require treatment for secondary prevention of recurrent coronary events. Primary prevention is controversial in all patient groups except those with diabetes, because their risk of developing CHD is dramatically increased. Postmenopausal women and the elderly are undertreated, whereas young adults may be underdiagnosed and undertreated. Several ongoing trials may resolve the controversies about which patient groups will benefit from different prevention and treatment strategies. (Circulation. 2001;104:1688-1692.)

Key Words: coronary disease ■ lipids ■ population ■ statins

The causal role of elevated serum cholesterol levels in the pathogenesis of atherosclerosis and its clinical sequelae is well established. The advent of HMG-CoA reductase inhibitors, or statins, was a major advance in lipid-lowering therapy that revolutionized the treatment of atherosclerosis. Significant reductions in mortality and morbidity from cardiovascular disease are among the clinical benefits of statin therapy established in large-scale, randomized, controlled primary and secondary prevention trials.1–5 Moreover, a meta-analysis of randomized controlled trials indicated that the reduction in LDL cholesterol achieved with statin therapy decreases the risk of coronary heart disease (CHD) and all-cause mortality to a similar extent in both men and women and in elderly and middle-aged persons.6 Because statins are effective and safe, they are now the most widely prescribed class of lipid-lowering agents. This article provides recommendations for screening and treatment of specific patient groups with hypercholesterolemia.

Women
The risk of CHD, which is the leading cause of death and a significant cause of morbidity in women, increases with age >50 years.7 Although CHD risk factors are well established, risk-factor management in women is poor. For example, the Heart and Estrogen/progestin Replacement Study (HERS)8 reported that fewer than 10% of enrolled women with documented CHD had baseline LDL-cholesterol levels below the 2.59 mmol/L (100 mg/dL) goal established by the National Cholesterol Education Program (NCEP), despite widespread agreement that women with established CHD need lipid-lowering treatment (Table 1).7 In addition, aggressive risk-factor management and lifestyle changes (eg, smoking cessation, increased physical activity, maintaining a healthy weight, consumption of a diet low in saturated fat and high in fruits and vegetables) are strategies to be used in all women to help prevent CHD and/or lower the probability of a cardiovascular event.

The rationale for estrogen replacement therapy in women with CHD is less well founded. Its initial justification in postmenopausal women was because of its favorable effects on serum lipid concentrations, but these effects account for only approximately one third of the putative clinical benefits.9–11 Other potential cardioprotective effects of estrogen include its direct effects on arterial reactivity and atherogenesis.10,12,13 Estrogen improves endothelium-dependent vasodilation and markers of fibrinolysis and vascular inflammation, and it inhibits the response of blood vessels to injury and the subsequent development of atherosclerosis.

Numerous observational studies have reported lower CHD rates in postmenopausal women receiving estrogen than in those who did not.9,14–16 The strongest association was in postmenopausal women with CHD: estrogen users had 35% to 80% fewer recurrent events than nonusers.11,16–21 HERS,8,22 a prospective, randomized, controlled trial that included nearly 3000 women with documented CHD, however, did not show a reduction in the number of CHD events in postmenopausal women with established coronary disease after 4.1 years of hormone replacement therapy, despite an...
11% reduction in LDL-cholesterol and a 10% increase in HDL-cholesterol levels. In addition to providing no overall cardiovascular benefit, hormone replacement therapy was associated with a 3-fold increase in the risk of thromboembolic events compared with placebo treatment.\textsuperscript{22,23} Moreover, the Estrogen Replacement and Atherosclerosis study\textsuperscript{24} found no angiographic evidence that estrogen or hormone replacement therapy affects the progression of atherosclerosis in women with coronary disease. Hormone replacement therapy also had no significant effect on stroke risk in HERS.\textsuperscript{25} Within the overall null effect of hormone replacement therapy in HERS, there was an interesting trend with respect to risk: in the first year, there was a 50% increase in cardiovascular events, but in years 3 to 5, the risk of CHD was reduced in women who received hormone replacement therapy.\textsuperscript{22} Healthy women assigned to hormone replacement therapy in the Women’s Health Initiative\textsuperscript{26} also experienced a small increase in cardiovascular events in the first 2 years that is lessening with continued treatment.

Statins are more effective than estrogen\textsuperscript{27} or hormone replacement therapy\textsuperscript{28} in lowering plasma LDL-cholesterol concentrations in postmenopausal women with hypercholesterolemia or coronary artery disease. Combining estrogen or hormone replacement therapy with a statin somewhat improved the reduction in LDL cholesterol observed with statin therapy alone, enhanced the increase in HDL cholesterol, and obliterated estrogen-induced triglyceride changes.\textsuperscript{28} Whether this combination improves the benefit on coronary events over statins alone is unknown.

### Patients With Diabetes

The prevalence of diabetes in patients with established CHD is 2- to 3-fold higher than in the general population.\textsuperscript{29} Not only are patients with diabetes at increased risk for CHD,\textsuperscript{30} but their prognosis after developing CHD, including survival, is also worse than that in nondiabetic patients.\textsuperscript{31-33} The American Heart Association recommends a target LDL-cholesterol level of <3.36 mmol/L (<130 mg/dL) for primary prevention of cardiovascular disease in patients with diabetes.\textsuperscript{34} Because prognosis is worse in patients with diabetes, some experts support more aggressive treatment to achieve target LDL-cholesterol levels of <2.59 mmol/L (<100 mg/dL), irrespective of evidence of CHD (Table 1).\textsuperscript{29,34}

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>With CHD</th>
<th>Without CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>Treat</td>
<td>To be determined†</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>Elderly</td>
<td>Treat</td>
<td>Treat†</td>
</tr>
<tr>
<td>Young adults</td>
<td>Treat</td>
<td>Depends on risk level</td>
</tr>
</tbody>
</table>

*Treatment includes lifestyle modifications (smoking cessation, weight control, American Heart Association step diets, exercise) and/or pharmacological therapy with a statin to achieve target LDL-cholesterol level. Risk-factor modification in all patients with hypercholesterolemia is important for preventing or lowering risk of CHD events.

†In the United States, approximately two thirds of people >65 years old are women.

Patients with diabetes benefit greatly from lifestyle changes, including weight loss, increased levels of physical activity, and dietary modifications. In addition, many patients with diabetes and dyslipidemia will require lowering of LDL cholesterol. The Diabetes Atherosclerosis Intervention Study demonstrated that correction of lipoprotein abnormalities is associated with a reduction in the angiographic progression of coronary artery disease in patients with type 2 diabetes.\textsuperscript{35} Subgroup analyses of the Scandinavian Simvastatin Survival Study (4S)\textsuperscript{36-37} and Cholesterol and Recurrent Events (CARE)\textsuperscript{38} trials showed that changes in serum lipid levels are similar in patients with and without diabetes who were treated with a statin and that the risk of recurrent CHD events and revascularizations was significantly reduced in diabetic subjects. In the 4S subgroup analyses, these findings were also demonstrated in subjects with impaired fasting glucose levels and subclinical diabetes.\textsuperscript{37}

Neither the 4S nor the CARE trial, however, was designed specifically to assess statin therapy in patients with diabetes. The first trial to prospectively evaluate statin treatment in a sizable cohort of patients with diabetes (nearly 6000) is the MRC/BHF Heart Protection Study.\textsuperscript{39} With a follow-up period of ≥5 years, study completion is not expected until 2002.

### The Elderly

The elderly are the fastest-growing segment of the US population. CHD is the leading cause of morbidity and mortality in the elderly; its incidence and prevalence peak in persons >65 years old, and most coronary events occur in this segment of the population.\textsuperscript{40} Despite these statistics and recommendations stating that age alone should not exclude persons from treatment,\textsuperscript{39} elderly patients with hypercholesterolemia are underdiagnosed and undertreated.\textsuperscript{41,42}

Estimates from the CARE study indicate that the number of preventable cardiovascular events and hospitalizations for cardiovascular disease after 5 years of statin treatment are greater in the elderly than in all patients or in younger patients with previous myocardial infarction and average cholesterol levels (207/1000 and 225/1000 patients versus 150/1000 and 130/1000 patients, respectively).\textsuperscript{43}

### TABLE 1. Treatment Recommendations for Patient Groups With Hypercholesterolemia*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>With CHD</th>
<th>Without CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young adults</td>
<td>Treat</td>
<td>To be determined†</td>
</tr>
<tr>
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<td>Treat</td>
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</tbody>
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*Treatment includes lifestyle modifications (smoking cessation, weight control, American Heart Association step diets, exercise) and/or pharmacological therapy with a statin to achieve target LDL-cholesterol level. Risk-factor modification in all patients with hypercholesterolemia is important for preventing or lowering risk of CHD events.

†In the United States, approximately two thirds of people >65 years old are women.

### TABLE 2. Estimated Number of Preventable Cardiovascular Events per 1000 Patients With Average Cholesterol Levels Treated for 5 Years With a Statin

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients</th>
<th>Patients ≥60 Years Old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal CHD</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Clinical nonfatal myocardial infarction</td>
<td>26</td>
<td>52</td>
</tr>
<tr>
<td>Revascularization procedures†</td>
<td>62</td>
<td>52</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>Other cardiovascular event</td>
<td>38</td>
<td>57</td>
</tr>
<tr>
<td>Subtotal</td>
<td>150</td>
<td>207</td>
</tr>
<tr>
<td>Cardiovascular hospitalizations†</td>
<td>121</td>
<td>225</td>
</tr>
</tbody>
</table>

Adapted from data in Sacks et al\textsuperscript{3} and Lewis et al.\textsuperscript{43}

†Patient groups for cardiovascular hospitalizations are younger patients and patients <65 to 75 years old.

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121/1000 patients, respectively; Table 2).43 Given the prevalence and significance of CHD in the elderly and that lowering of LDL cholesterol with a statin provides the same benefit as or greater benefit than in younger persons with CHD,5,43,44 statin treatment in the elderly with established CHD is strongly recommended (Table 1).40

Cholesterol-lowering therapy as primary prevention in the elderly, however, is more controversial. Although elderly individuals without CHD are not well represented in most studies, the reduction in risk of events with statin therapy in patients >65 years old has been shown to be similar to that in younger patients.2,4 In addition to favorable responses to statin treatment, several lines of evidence support extrapolation of treatment recommendations to the elderly: the pathobiological process is the same; epidemiological data indicate that high cholesterol levels confer a high attributable risk in the elderly; and angiographic trials show that advanced disease in older subjects responds to cholesterol lowering and risk reduction.40

In addition, the elderly have the greatest burden of silent atherosclerosis as well as overall atherosclerotic burden.45 Even elderly people with normal (that is, average) cholesterol levels have a sizable disease risk. With age, the serum cholesterol level needed to achieve a given level of atherosclerotic plaque burden becomes progressively lower as a result of plaque accumulation over many years.40 Moreover, a large number of cardiac deaths prevented in primary and secondary prevention trials with cholesterol-lowering therapy occurred in the elderly. As a result, although the predictive value of serum cholesterol levels lessens with age, they still contribute to coronary disease, and elevated levels can be used to predict coronary risk as noted below.46,47

Some confusion about the value of cholesterol lowering in the elderly relates to variations in risk assessment from expressions of relative, absolute, and attributable risk.45,48 Relative risk assessments are lower in the elderly because of competing mortalities and cumulative disease effects. Absolute risk (number of events within a specified time period) is high in the elderly, as is attributable risk (excess risk in those with a defined high cholesterol). Because of their high attributable and absolute risk, statin treatment in the elderly can be expected to prevent a greater number of acute coronary events than it will in younger patients—a premise confirmed in clinical trials of statin therapy.1–3

Young Adults

The most unsettled issues surrounding screening for and treatment of hypercholesterolemia are with young adults. The strong correlation between cholesterol levels in young adults and coronary disease later in life is well established: a single elevated cholesterol level in a man in his early 20s is predictive of coronary risk 40 years later.49 Nonetheless, a large number of cardiac deaths prevented in primary and secondary prevention trials with cholesterol-lowering therapy occurred in the elderly. As a result, although the predictive value of serum cholesterol levels lessens with age, they still contribute to coronary disease, and elevated levels can be used to predict coronary risk as noted below.46,47

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Several recent studies provide convincing evidence of the need to modify or control risk factors in asymptomatic adolescents and young adults to prevent or delay the development of clinical atherosclerosis. In children as young as 11 years old who had cholesterol levels within the normal range, changes in the arterial wall indicative of the atherosclerotic process were observed, and arterial distensibility lessened with higher cholesterol levels.52 An autopsy study of persons 15 to 34 years old, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, found that low HDL-cholesterol and high non–HDL-cholesterol levels, as well as smoking, were associated with more extensive fatty streaks and raised lesions.53 VLDL- and LDL-cholesterol levels were positively associated, and HDL-cholesterol levels negatively associated, with fatty streaks and raised lesions. Another autopsy study of persons 2 to 39 years old, the Bogalusa Heart Study,54 demonstrated that the extent of fatty streaks and fibrous plaques in the aorta and coronary arteries increased with age and the number of risk factors present (elevations in body mass index, systolic blood pressure, serum LDL cholesterol, serum triglycerides) and that smoking increased the percentage of intimal surface having fatty streaks or fibrous plaques.

It is unlikely that clinical trials enrolling exclusively young adults will be conducted, because they have a low rate of clinical heart disease. Many of the ongoing statin clinical trials, however, have a lower age for inclusion than previous trials. Evidence from primary prevention clinical trials, moreover, indicates that risk-factor modification and statin treatment can prevent coronary events in middle-aged adults.2,4,6

This is particularly remarkable given that their atherosclerosis is likely to be well established, although not yet symptomatic.

Conclusions

CHD remains a leading cause of morbidity and mortality in the United States despite our better understanding of the pathobiology of atherosclerosis, our knowledge of risk factors, the widespread availability of inexpensive cholesterol screening, and the availability of effective and well tolerated cholesterol-lowering agents. Advances in these areas have heightened controversies regarding the appropriate selection of candidates for treatment.

Diet remains an important part of the management of lipid disorders, but, primarily for cultural reasons, its overall effectiveness is modest. The advent of the statin class of lipid-lowering agents represented a revolutionary advance in the treatment of lipid disorders. These agents are much more effective in lowering LDL cholesterol than previous classes of lipid-lowering agents, and they are well tolerated.

There is general agreement that patients with hypercholesterolemia and established CHD require treatment for secondary prevention of recurrent coronary events. Risk-factor management and lifestyle modifications are part of any treatment plan. Treatment with a statin probably will be necessary, however, in most patients to achieve the target LDL-cholesterol levels established by the NCEP guidelines. Screening for lipid levels and primary prevention remain controversial in young adults and, to a lesser extent, in postmenopausal women and the elderly. Notwithstanding,
both postmenopausal women and the elderly are undertreated with respect to risk-factor management and cholesterol-lowering therapy.

The role of estrogen or hormone replacement therapy as lipid-lowering and/or cardioprotective therapy in postmenopausal women has not been clearly established and should not be used in place of more established cholesterol-lowering therapy, including statins. Given the high atherosclerotic burden in elderly patients, the high attributable risk associated with elevated (and normal) cholesterol, and the demonstrated benefits of statin treatment in reducing major cardiovascular events, including stroke, screening and primary prevention with a statin in the elderly are reasonable recommendations to substantially reduce morbidity and healthcare costs. Even though young adults pose the greatest difficulty with respect to recommendations, mounting evidence of the onset of atherosclerotic lesions in early childhood, even in children with normal cholesterol levels, suggests that it is reasonable to extrapolate the beneficial effect of statins on coronary events in middle-aged adults to longer-term risk in younger adults. Thus, screening, risk-factor management, and promoting a healthy lifestyle in young adults are, at a minimum, reasonable measures to prevent the development of symptomatic atherosclerosis and future coronary events. Several ongoing treatment trials for atherosclerosis may further elucidate the role of therapy in different patient groups and resolve the controversies regarding how to promote, in the most date the role of therapy in different patient groups and resolve going treatment trials for atherosclerosis may further eluci-

References


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