Lipid and Nonlipid Benefits of Statins

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The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) provides an evidence-based approach to the diagnosis of dyslipidemia and the management of low-density lipoprotein cholesterol (LDL-C). This article provides a brief overview of the ATP III therapeutic approach (therapeutic lifestyle changes alone or in combination with a pharmacologic agent) in which the patient's level of risk for coronary heart disease guides the intensity of intervention to lower LDL-C concentrations. Because statins have been found to effectively help patients reach ATP III target LDL-C levels to reduce their risk of coronary events, they tend to be the treatment of choice when initial therapy with therapeutic lifestyle changes alone fails to achieve the target level. Discussion includes a summary of the beneficial properties of statins beyond lipid lowering.

According to the ATP III guidelines, the primary target guiding treatment of patients with lipid disorders who are at risk for coronary heart disease (CHD) is the lowering of low-density lipoprotein cholesterol (LDL-C) concentrations. An LDL-C level of less than 100 mg/dL is considered optimal. In addition to lipid concentrations, the guidelines emphasize risk assessment and primary prevention in persons with multiple risk factors for CHD.

Assessment of Risk for Coronary Heart Disease Presence of Clinical Atherosclerotic Disease

According to the ATP III guidelines, a complete lipoprotein profile should be followed by identification of the presence of clinical atherosclerotic disease. Clinical CHD and CHD equivalent (defined as asymptomatic carotid artery disease, peripheral arterial disease, or abdominal aneurysm) confer a high risk for CHD (CHD risk equivalent). Established CHD confers a greater than 20% 10-year risk for future CHD events, as determined by use of the Framingham scoring system.

In persons without CHD or signs of atherosclerosis, risk assessment is a two-step process. Initially, the number of risk factors other than LDL-C level, including age, total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels, is tabulated, followed by a 10-year risk assessment using the Framingham scoring system. In addition, assessment of risk should also include obesity, physical inactivity, and atherogenic diet, all important lifestyle risk factors.

Multiple Risk Factors

Major multiple (two or more) risk factors for CHD include age (men $\geq 44$ years; women $\geq 55$ years); hypertension ($\geq 140/90$ mm Hg); low HDL-C level ($<40$ mg/dL); family history of premature CHD; and cigarette smoking. The ATP III guidelines stratify individuals with multiple risk factors as having a greater than 20%, a 10% to 20%, and less than a 10% risk for myocardial infarction (MI) plus CHD-related death. Individuals who have a greater than 20% risk are assigned to the CHD risk equivalent category.

Zero to One Risk Factor

Almost all individuals who have zero to one risk factor have a 10-year risk of less than 10%, obviating the need for assessment of 10-year risk.

Treatment Goals of the ATP III Guidelines

The ATP III guidelines recommend an LDL-C goal of less than 100 mg/dL and initiating TLC changes in all individuals whose LDL-C levels equal or exceed 100 mg/dL. Treatment with TLC should include improved diet, a weight reduction program, and an exercise program. Failure of TLC may result in the need for the addition of pharmacologic treatment, and patients at higher risk levels (CHD, CHD equivalents, and 10-year risk $\geq 10\%$) may benefit from early initiation of drug therapy.

Several pharmacologic treatment options are available, including 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors.
(statins), fibrates, niacin, and bile acid sequestrants (Table 1). The characteristics of the underlying lipid abnormality may influence the initial choice of therapy.

Risk assessment will influence the intensity of treatment and help clinicians identify which patients have an increased likelihood of benefiting from early initiation of drug therapy (Table 2).

Although the intensity of treatment is guided by the risk assessment methodology described previously, there may be some populations with lower levels of calculated 10-year risk that may benefit from early initiation of more intensive pharmacotherapy. Treatment is based largely on baseline LDL-C concentration, but the ATP III guidelines acknowledge that physician discretion is important and that each patient is unique and should be treated accordingly.

Discretion on the part of clinicians should also take into account populations that may be more susceptible to CHD.

**Middle-aged Men**—As expected, middle-aged men (35 to 65 years old) have a high prevalence of the major risk factors and are predisposed to abdominal obesity and the metabolic syndrome. (See section on “Patients With Diabetes.”) Middle-aged men with a relatively high risk for CHD should be given intensive LDL-lowering therapy.

**Middle-aged Women**—In middle-aged women (45 to 65 years old), the onset of CHD is generally delayed 10 to 15 years compared with that in men, with most CHD occurring after age 65 years. Older persons (men aged >64 years; women aged >74 years) with CHD and CHD risk equivalents may benefit from statin therapy.

In the recent Heart Protection Study (HPS), a secondary prevention trial, patients older than 70 years had a significant benefit from simvastatin, 40 mg once daily (23.6% event rate at 5 years) compared with the control group (28.7% event rate). This would be an absolute risk reduction of 5.1% with a number needed to treat (NNT) of 19. Basically, it would be necessary to treat 19 patients for 5 years to save one vascular event.

If the same information from this study is used for patients younger than 65 years, the NNT would be the same (NNT = 19). Thus, both age groups received the same benefit from simvastatin therapy in the HPS. If one looks at the benefit of treating women in the HPS, women received significant benefit from the use of 40 mg daily. Women in the control group had an event rate of 17.7% over the course of the study, and those in the treatment group had a 14.4% event rate.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>ATP III* Guidelines: Treatment Options</th>
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<tr>
<td>Lipid and Lipoprotein Effects</td>
<td>Low-Density Lipoprotein Cholesterol Level</td>
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<tr>
<td>HMG CoA reductase inhibitors (statins)</td>
<td>Decreased 18% to 55%</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Decreased 15% to 30%</td>
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<tr>
<td>Nicotinic acid</td>
<td>Decreased 5% to 25%</td>
</tr>
<tr>
<td>Fibric acid</td>
<td>Decreased 5% to 20%</td>
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†HMG CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adult Treatment Panel III* Guidelines: Low-Density Lipoprotein Cholesterol (LDL-C) Concentrations</th>
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<tr>
<td>Risk Category</td>
<td>LDL-C Goal at Which to Initiate TLC†</td>
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<tr>
<td>Coronary heart disease (CHD) or CHD Risk Equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL</td>
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<tr>
<td>Two or more risk factors (10-year risk ≤20%)</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Zero to one risk factor</td>
<td>&lt;160 mg/dL</td>
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†TLC indicates therapeutic lifestyle changes.
rate. The NNT would then be 96. If one were to treat 96 women with simvastatin for 5 years (study course duration), simvas-tatin therapy would prevent one vas-cular event.

The question of primary prevention use of statins in the elderly (age > 60 years) has only recently been addressed in the large Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) trial with atorvastatin calcium, 10 mg daily.4 The use of atorva-statin in this group of patients revealed a significant reduction in nonfatal and fatal MI and CHD. Women in this study did not show a a significant benefit from ator-vasstatin; however, the study comprised only 1072 patients, which may have been too small a number to show significance in 3.3 years. The data safety monitoring board stopped the study because of the highly significant benefit of atorvastatin in reducing mortality.

In summary, the use of statins in primary and secondary prevention in the elderly is worthwhile. The use of statins in women as secondary preven- tion is beneficial, but the benefit of the use of statins in women for primary preven- tion is unclear at this time. It is impor-tant to remember that the event rate in the group receiving placebo in the HPS secondary prevention trial was 27% and the event rate in the group receiving placebo in the primary prevention ASCOT trial was 3%. This is a huge dif-ference in patient events; however, even in the ASCOT trial (3% placebo event rate), there was still a significant reduc- tion in CHD events with atorvastatin.3,4

**Patients With Diabetes and the Metabolic Syndrome**—The ATP III guidelines reclassifies diabetes from a CHD risk factor to a CHD risk equiva-lent, meaning patients with diabetes have a 10-year risk for a major coronary event equal to that of a patient with established CHD (≥20%). Patients with type 2 dia-betes mellitus not only are more likely than patients without diabetes to have CHD develop,5 but they also have a higher mortality rate following an MI.56 Other risk factors for CHD that are highly concordant with type 2 diabetes include abdominal obesity, hypertriglyceridemia, low HDL-C level, and hypertension, which are a cluster of lipid and nonlipid risk factors referred to as the metabolic syndrome.7

Lipid goals for patients with type 2 diabetes are the same as those in patients with established CHD or CHD equiva-lents. Because of the complexity of dia-betes and associated comorbidities, other secondary goals of therapy are neces-sary. Similarly, for patients with the metabolic syndrome, there are two main treatment goals.

The first goal is to reduce the con-tribution of underlying causes such as obesity and physical inactivity. Interven-tion with activation of the muscu-loskeletal system through aerobic exercise may have wide-ranging beneficial effects, consistent with osteopathic medicine’s tenet of the central role of the muscu-loskeletal system and the body’s innate abilities for self-healing. The second goal is to treat the patient for lipid and nonlipid risk factors.

For patients with the metabolic syn-drome, the combination of TLC and pharmacologic treatment is the most effective method.8-17

**Specific Racial and Ethnic Groups**—The ATP III does not modify general recom-mendations for specific racial and ethnic groups such as African Ameri-cans, Hispanics, Native Americans, Asian and Pacific Islanders, and South Asians because of lack of evidence.

**Emerging Risk Factors**

Lipoprotein(a), homocysteine, pro-thrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease are emerging risk factors. Although these factors are not directly involved in calculating 10-year CHD risk and their pres-ence does not modify LDL-C goals, they may influence the intensity of treatment used to reach target levels.

**Efficacy of Statins in the Treatment of Patients With Hypercholesterolemia**

Treatment of all patients should include TLC. However, it may be difficult to achieve LDL-C goals with TLC alone, especially in patients at high risk for CHD. Better results have been demonstrated when treatment includes drug therapy versus TLC alone.8-18 Of the pharma-coologic treatment options available, statins tend to be the treatment of choice.

In a recently reported landmark pri mary prevention trial (ASCOT) that was stopped by the data safety monitoring board at 3.3 years,4 fixed-dose atorva-statin calcium, 10 mg (without titration), was found in a hypertensive population of 19,342 patients to reduce fatal and non-fatal stroke (89 in atorvastatin-treated group vs 121 in the placebo group; event rate ratio, 0.73 [95% CI 0.56-0.96], P = .024); total cardiovascular events (389 vs 486, 0.79 [CI 0.69-0.90], P = .0005), and total coronary events (178 vs 247, 0.71 [CI 0.59-0.86], P = .0005).

To date, the ASCOT had the lowest reported placebo event rate (3% in this large population). It also brings into question whether dosage titration is neces-sary or statins have effects beyond the LDL-C number. Five of the seven large trials, including the ASCOT, have not titrated the statin dosage: the HPS (fixed-dose simvastatin, 40 mg/d);7 and the Cholesterol and Recurrent Events (CARE) study,9 the West of Scotland Coronary Prevention Study (WOSCOPS),10 and the Long-Term Interven-tion with Pravastatin in Ischaemic Disease (LIPID) study11 (fixed-dose pravastatin sodium, 40 mg/d).

For the busy physician who is inter-ested primarily in preventing cardio-vascular events, is it necessary to reach an LDL-C goal or use the dosage of drugs in the study that was proven to reduce clinical events? Only time and research will give the answer to this complex ques-tion. Currently, the ATP III recommends the goal approach.4

Davidson and associates,12 in 2002, reported that only 12% of patients with type IIA or type IIB hypercholesterolemia randomly assigned to receive placebo once daily for 12 weeks achieved their treatment goal. In contrast, 80% of patients receiving a statin (5 mg or 10 mg of rosuvastatin calcium or 10 mg of ator-vasatin calcium) reached their choles-terol goals.12

Because statins are the most effec-tive drug in lowering LDL-C levels, they are usually considered first-line therapy. Clinicians should choose the appropriate statin and dose based on an individual’s risk factors (Figure).
Cholesterol-Independent Actions of Statins

Increasing evidence confirms the pivotal role of oxidized LDL (oxLDL) in the pathogenesis of atherosclerosis from endothelial dysfunction to plaque destabilization and therefore emphasizes the importance of lowering the LDL-C level as central to the strategy of both primary and secondary prevention of cardiovascular death or morbidity.

It is well known that high levels of oxLDL cause local leukocyte recruitment into the vessel wall as an early step in atherogenesis, and it is largely explained by the increased expression of endothelial leukocyte adhesion molecules. Transcriptional activation of adhesion molecules is sensitive to the intracellular redox status and of major importance in the development of atherosclerosis. In concert with the increase in free radicals and infiltration of cholesterol into macrophages, there is increased production of cytokines that are known to destabilize atherosclerotic plaques.

Statins inhibit HMG CoA reductase and consequently lower LDL-C concentrations. Experimental and clinical data indicate that statins may also have beneficial effects on the vascular system independent of cholesterol lowering. That is, the cellular antioxidative properties of
Statins leading to decreased oxidative stress and restoration of nitrous oxide bioactivity may be of special relevance to vascular functioning.

These additional effects of statins include decreased inflammation, hypertrophy, and blood clotting, and increased reendothelialization. The exact mechanism is unclear but likely involves the ability to block the synthesis of lipid attachments to intracellular signaling molecules that are dependent on HMG CoA reductase. Further, statins have recently been shown to have beneficial effects in Alzheimer’s disease, ischemic stroke, and osteoporosis.

The multifunctional aspects of statins may explain the results from the HPS. The HPS found statins to be beneficial in reducing CHD risk regardless of baseline LDL-C concentrations in high-risk patients (known coronary disease, other occlusive arterial disease, or diabetes) with a major vascular (first major coronary event, stroke, or revascularization) placebo event rate of 25.2%. Investigators found that high-risk patients with low to normal LDL-C levels benefited from statin therapy as much as those patients with higher concentrations. Patients (N = 3500) entering the study with an LDL-C level of less than 97 mg/dL received the same benefit from simvastatin as those with high LDL-C levels.

Statin therapy resulted in an 18% reduction in coronary mortality rate, a 38% reduction in the incidence of first nonfatal MI, and a 27% reduction in the incidence of nonfatal MI or coronary death. Investigators determined these benefits to be independent of other cardioprotective modes of treatment such as aspirin, β-blockers, and angiotensin-converting enzyme inhibitors. All-cause mortality was significantly reduced (128 [12.9%] deaths among 10,269 patients allocated to receive simvastatin versus 1507 [14.7%] among 10,267 allocated to receive placebo; P = .0003). This is an absolute risk reduction of 1.8% in approximately 5 years. Thus, one would need to give simvastatin, 40 mg, to 55 people for 5 years to prevent one death (NNT = 55).

Statins and Inflammation

Adult Treatment Panel III acknowledges that C-reactive protein (CRP), a marker of inflammation, is an emerging risk factor for CHD. Ridker and colleagues recently reported the results of an 8-year study analyzing the predictive value of both CRP and LDL-C levels in relation to cardiovascular events in women. In this cohort of 27,939 women followed up for a mean of 8 years, 77% and 46% of women who had a coronary event had LDL-C levels of less than 160 mg/dL and less than 130 mg/dL, respectively. The investigators conclude that CRP is a stronger predictor of future cardiovascular events than LDL-C, though taking both biological markers into account results in superior risk detection than either measure alone.

C-reactive protein has potential as another marker of CHD risk and may be a future target of therapy. However, the ATP III guidelines do not recommend routine measurement of inflammatory markers for the purpose of modifying LDL-C goals in primary prevention.

Statins may exert anti-inflammatory actions that reduce the development of atherosclerosis. In atherosclerotic mice (deficient in apo E), statins decreased the inflammatory response and reduced atherosclerosis beyond reductions attributable to plasma cholesterol lowering. In humans, statins reduce CRP.

Statins and Blood Clotting

Another coronary risk factor that may be influenced by statins is blood clotting. In a small study, Undas and colleagues observed that treatment with simvastatin (20 mg/d for 3 months) in patients with advanced coronary disease (n = 17) reduced blood clotting. Furthermore, statin therapy decreased rates of prothrombin activation, factor Va generation, fibrinogen cleavage, and factor XIII activation, and increased the rate of factor Va inactivation.

Statins and Reendothelialization

Statins also appear to strengthen collagen in plaques in vessels and promote reendothelialization to secure both plaque stability and prevent rupture. In primate studies, statin therapy (pravastatin or simvastatin) in monkeys fed an atherogenic diet was found to reduce inflammation and plaque vulnerability. In addition, atherosclerotic lesions in the treated monkeys were notably different, showing reduced macrophage content as well as less vascular cell adhesion molecule-1, interleukin-1β, and tissue factor expression. Furthermore, lesions had higher concentrations of smooth muscle cells and collagen. All these changes were independent of cholesterol lowering, because dietary cholesterol was adjusted to equalize plasma cholesterol concentrations among groups.

Vascular remodeling by statins has also been seen in humans. Corti and colleagues examined magnetic resonance images of either or both aortic and carotid atherosclerotic plaques in patients with asymptomatic hypercholesterolemia (n = 18). After 12 months of treatment with simvastatin, significant reductions in vessel wall thickness and area, without changes in lumen area, were observed. The authors speculated that statins induce vascular remodeling, which reduces atherosclerotic lesions without altering the lumen.

Similar results have been seen by Zhao and colleagues, who examined magnetic resonance images of 32 carotid arteries in 16 patients with coronary artery disease and found that the patients receiving intensive lipid-lowering therapy (niacin, 2.5 g/d, plus lovastatin, 40 mg/d, plus colestipol, 20 g/d; n = 8) had slight improvements in plaque strength as measured by increased fibrous and calcium deposits and lower lipid content within their plaques.

The mechanism of action for reendothelialization remains unclear, but a recently reported animal study suggested that statins may mobilize bone marrow–derived endothelial progenitor cells to promote tissue neovascularization to help reendothelialization. Taken as a whole, the decreased inflammation, increased plaque strength, and decreased hypertrophy may all contribute to reduced risk in coronary events independent of lipid concentrations. The net result is a more stable atherosclerotic lesion that is less susceptible to rupture.

Comment

The ATP III guidelines provide the framework for improved outcomes in the treatment of patients with dyslipidemia. To date, statins are the most effective agents in helping patients achieve their lipid goals. Statins are safe, effective, and appear to reduce CHD risk by
both lipid- and nonlipid-dependent actions. Furthermore, statins are effective in a wide range of patients. As Clearfield states in the previous article, there is a large body of evidence supporting the beneficial role of statins in the reduction of risk for CHD.

As we continue to develop newer statin medications, statin use will likely continue to rise. These agents aid patients reaching ATP III targets to safely and effectively reduce their risk of coronary events.

References


