Summary of the Role of Statins in the Treatment of Dyslipidemia

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Coronary heart disease (CHD) costs the United States more than $100 billion a year. Direct and indirect medical costs can be markedly reduced if clinicians use tools such as the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [NCEP ATP III]) guidelines to more accurately diagnose and treat patients at risk of CHD.

Underdiagnosis and Undertreatment
Currently, many at-risk patients are not being treated, either because the degree of their risk has not been adequately diagnosed, or physicians have failed to appropriately intensify therapy to lower CHD risk. For example, a large number of patients who had their first myocardial infarction (MI) were unaware they were at risk. Another important discovery is the role of inflammatory mechanisms in the development of CHD. Several investigators have shown that combining levels of inflammatory markers with low-density lipoprotein cholesterol (LDL-C) concentrations results in improved predictive models of future CHD risk than either risk factor alone.

Clinicians need to take a more active role in the assessment of CHD risk and the implementation of appropriate modes of therapy in at-risk patients. In addition, clinicians need to understand that lipid-lowering agents are safe and effective treatment options. A recent study by Fonarow and colleagues highlights the problem. These investigators found that a lipid-lowering agent was prescribed for only 31.7% of patients discharged from the hospital following an acute MI (n = 138,001). And, only 41.7% of patients with a history of hypercholesterolemia were discharged with a lipid-lowering agent.

The Metabolic Syndrome
Another group of patients being underdiagnosed and undertreated is that with relatively normal LDL-C concentrations (100 mg/dL to 129 mg/dL) but with other CHD risk factors such as the metabolic syndrome. Metabolic syndrome is defined as having three or more of the following five metabolic abnormalities:

- abdominal obesity,
- hypertriglyceridemia,
- low levels of high-density lipoprotein cholesterol,
- high blood pressure (or use of antihypertensive medication), and
- high fasting plasma glucose level (or use of medication).

Recent studies suggest that patients with the metabolic syndrome may benefit from statin therapy. A portion of the increased CHD risk seen in obese patients may be accounted for by risk factors associated with the metabolic syndrome. Although it is esti-

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imated that obesity alone accounts for 15% of the increase in risk of CHD, most of the additional risk that obese patients have appears to result from several metabolic syndrome factors (ie, insulin resistance and dyslipidemia), as well as other emerging risk factors that may be associated with obesity (proinflammatory state, prothrombotic state).8

Some authors have even suggested that a family history of the metabolic syndrome should be considered a risk factor. Kareinen and colleagues9 studied families with premature CHD and found a clustering of risk factors (ie, hyperinsulinemia, dyslipidemia, high fibrinogen level) in patients with premature CHD and asymptomatic family members meeting criteria for the metabolic syndrome. This study suggests that a family history of the metabolic syndrome or diabetes mellitus or both should be added as CHD risk factors.

Reducing Risk for Coronary Heart Disease

In patients with risk factors for CHD but normal LDL-C concentrations, it can be difficult to determine the most appropriate treatment. Evidence has shown that statin therapy can be beneficial for some of these patients.1011 One potential mechanism for this improvement is that statin therapy appears to modulate aspects of the inflammatory response involved in the development of atherosclerosis. Several investigators have documented that statin therapy may lower concentrations of inflammatory markers and reduce CHD risk.36

In a post hoc analysis of the Cholesterol and Recurrent Events (CARE) and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) studies, Sacks and colleagues12 found pravastatin sodium lowered relative risk in patients with diabetes with relatively low LDL-C levels (<125 mg/dL), but treatment had no significant effect in non-diabetic patients.

The CARE study was a double-blind trial of the use of pravastatin versus placebo for the secondary prevention of coronary events.10 The study included 4159 patients aged 21 to 75 years with a past history of MI and plasma total cholesterol levels of less than 240 mg/dL. Relative risk of the primary end point (fatal coronary event or a nonfatal myocardial infarction) was reduced 24% with pravastatin.

The LIPID study was a double-blind, randomized trial comparing the effects of pravastatin sodium, 40 mg daily, with those of a placebo in 9014 patients aged 31 to 75 years with a history of MI or hospitalization for unstable angina and a broad range of total cholesterol levels.11 Relative risk of death from CHD was reduced by 24%.

These two trials enlisted only people with CHD; however, even if patients with diabetes have no finding of heart disease, they are at equal risk with those who have CHD.

Similar results were observed in the Heart Protection Study,13 which found that statin treatment improved risk of CHD in patients with LDL-C levels of less than 115 mg/dL, but only if the patients were initially at high risk of CHD. Actually, there were more than 7000 patients with no prior CHD and nearly 4000 patients who had diabetes and no CHD. This powerful study of more than 20,000 patients demonstrated that reduction in an LDL-C level from 116 mg/dL in all patients reduces the risk of vascular disease by about 20%. The reduction of the LDL-C level from 116 mg/dL to 77 mg/dL in this study marks the first time we have data to support that LDL-C levels lower than 115 mg/dL improve cardiovascular risk in all patients.

Statins are emerging as the gold standard for reducing CHD risk. Rosuvastatin calcium is the next statin likely to be approved by the Food and Drug Administration. In clinical trials, rosuvastatin had a dose-dependent effect, resulting in a lowering of LDL-C concentrations of up to 65% in hypercholesterolemic patients.14 Rosuvastatin’s LDL-C lowering appears equal or superior to that of other statins. In a study by Davidson and colleagues15 comparing rosuvastatin and atorvastatin calcium, both agents were equally safe and effective in low- and medium-risk patients, but rosuvastatin had greater lipid-lowering effects in high-risk patients (patients with atherosclerosis or diabetes mellitus).15

The NCEP ATP III guidelines are an evidence-based approach to diagnosing and treating patients at risk of CHD. The guidelines provide easy-to-follow algorithms based on risk calculations that can be performed on personal computers or handheld PDAs.

Clinicians need to use these guidelines more often and understand the evidence on which they are based. This JAOA Supplement provides an excellent overview of the guidelines and the evidence used to develop and support them.

References


