Management of hyperlipidemia with statins in the older patient

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Abstract: Numerous randomized, double-blind, placebo-controlled studies and observational studies have demonstrated that statins decrease mortality and major cardiovascular events in older high-risk persons with hypercholesterolemia. The Heart Protection Study found that statins decreased mortality and major cardiovascular events in high-risk persons regardless of the initial level of serum lipids, age, or gender. The updated National Cholesterol Education Program (NCEP) III guidelines state that in very high-risk patients, a serum low-density lipoprotein (LDL) cholesterol level of <70 mg/dl is a reasonable clinical strategy, regardless of age. When a high-risk person has hypertriglyceridemia or low serum high-density lipoprotein cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL cholesterol-lowering drug. For moderately high-risk persons (2 or more risk factors and a 10-year risk for coronary heart disease of 10% to 20%), the serum LDL cholesterol should be decreased to <100 mg/dl. When LDL cholesterol-lowering drug therapy is used to treat high-risk persons or moderately high-risk persons, the serum LDL cholesterol should be decreased at least 30% to 40%.

Keywords: lipids, statins, lipid-lowering drugs, coronary heart disease, atherosclerotic vascular disease

Introduction

Numerous randomized, double-blind, placebo-controlled studies and observational studies have demonstrated that 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) reduce mortality and major cardiovascular events in high-risk older persons with hypercholesterolemia. The Heart Protection Study (HPS) showed that statins reduced mortality and major cardiovascular events in high-risk persons regardless of the initial level of serum lipids, age, or gender (HPS 2002). This paper will discuss the studies showing that statins decrease cardiovascular morbidity and mortality in high-risk older persons and discuss the updated National Cholesterol Education Program III (NCEP-III) guidelines for treatment of high-risk persons with lipid-lowering therapy.

Randomized, double-blind, placebo-controlled studies

In 4444 men and women with coronary heart disease (CHD) and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin 20 mg to 40 mg daily decreased serum total cholesterol by 25%, serum low-density lipoprotein (LDL) cholesterol by 35%, and serum triglycerides by 10%, and increased serum high-density lipoprotein (HDL) cholesterol by 8% (SSS 1994; Miettinen et al 1997; Pedersen et al 1998; Pedersen et al 2000). At 5.4-year median follow-up, compared with placebo, simvastatin significantly reduced all-cause mortality by 30%, CHD death by 42%, nonfatal myocardial infarction (MI) by 33%, major coronary events by 34%, cerebrovascular events by 30%, any atherosclerosis-related endpoint by

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34%, coronary revascularization by 37%, new or worsening angina pectoris by 26%, intermittent claudication by 38%, and arterial bruits by 30% (SSS 1994; Miettinen et al 1997; Pedersen et al 1998). Decreases in endpoint events were similar in older and younger men and women. The absolute risk reduction for both all-cause mortality and CHD mortality was approximately twice as great in persons 65 years of age and older as in those younger than 65 years of age (Miettinen et al 1997). At 7.4-year median follow-up, simvastatin significantly reduced all-cause mortality by 30% and CHD mortality by 38% (Pedersen et al 2000).

In the Cholesterol and Recurrent Events study involving pravastatin therapy for a period of 5 years in 4159 post-MI patients and serum total cholesterol levels <240 mg/dl and serum LDL cholesterol levels of 115 mg/dl to 174 mg/dl, compared with placebo, pravastatin 40 mg daily lowered serum total cholesterol by 20%, serum LDL cholesterol by 32%, and serum triglycerides by 14%, and raised serum HDL cholesterol by 5% (Sacks et al 1996; Lewis et al 1998). At 5-year median follow-up, compared with placebo, pravastatin significantly reduced CHD death or nonfatal MI by 24%, stroke by 31%, coronary artery bypass graft surgery by 26%, and coronary angioplasty by 23% (Sacks et al 1996). For every 1000 patients aged 65 to 75 years treated for 5 years with pravastatin, 225 cardiovascular hospitalizations would be prevented compared with prevention of 121 cardiovascular hospitalizations in 1000 younger patients (Lewis et al 1998).

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study randomized 9014 patients with a history of MI or unstable angina pectoris who had initial serum total cholesterol levels of 155 mg/dl to 271 mg/dl to pravastatin 40 mg daily or placebo (LIPID 1998, 2002). Compared with placebo, pravastatin lowered serum total cholesterol by 18%, serum LDL cholesterol by 25%, serum triglycerides by 11%, and raised serum HDL cholesterol by 5%. At 6.1-year follow-up, compared with placebo, pravastatin significantly lowered all-cause mortality by 22%, death from CHD or nonfatal MI by 24%, nonfatal MI by 29%, stroke by 19%, and coronary revascularization by 20% (LIPID 1998). Treatment of 1000 patients for 6 years with pravastatin prevented 30 deaths, 28 nonfatal MIs, 9 nonfatal strokes, 23 episodes of coronary artery bypass graft surgery, 20 episodes of coronary angioplasty, and 82 hospital admissions for unstable angina pectoris (LIPID 1998). The absolute benefits of therapy with pravastatin were greater in groups at higher absolute risk for a major coronary event such as persons aged 65 to 75 years, those with low serum HDL cholesterol levels, and those with a history of diabetes mellitus or smoking (LIPID 1998). At 8-year follow-up, pravastatin significantly lowered all-cause mortality by 18%, CHD death by 25%, and CHD death or nonfatal MI by 17% (LIPID 2002).

The HPS randomized 20 536 men and women with prior MI (8510 persons), other CHD (4876 persons), and no CHD (7150 persons) and a serum total cholesterol level of 135 mg/dl or higher to simvastatin 40 mg daily or to placebo (HPS 2002). Of the 7150 persons without CHD, 25% had cerebrovascular disease, 38% had peripheral arterial disease (PAD), 56% had diabetes mellitus, and 3% had only treated hypertension without atherosclerotic vascular disease or diabetes mellitus. Compared with placebo, simvastatin decreased serum LDL cholesterol by 39% (HPS 2002).

At 5-year follow-up, compared with placebo, simvastatin significantly lowered all-cause mortality by 13%, any cardiovascular death by 17%, major coronary events by 27%, any stroke by 25%, coronary or noncoronary revascularization by 24%, and any major cardiovascular event by 24% (HPS 2002). These significant decreases in mortality and in cardiovascular events occurred regardless of initial levels of serum lipids, age, or gender. First major cardiovascular event was significantly lowered by simvastatin by 24% in patients younger than 65 years, by 23% in patients aged 65 to 69 years, and by 18% in patients aged 70 to 80 years at study entry. Five years of simvastatin treatment prevented MI, stroke, and revascularization in 70 to 100 persons per 1000 treated patients.

In the HPS, 3500 patients had initial serum LDL cholesterol levels <100 mg/dl. Reduction of serum LDL cholesterol from 97 mg/dl to 65 mg/dl by simvastatin in these patients who would not be treated according to NCEP-III guidelines (NCEP 2001) caused a similar reduction in risk as did treating patients with higher serum LDL cholesterol levels. The HPS Investigators recommended treating persons at high risk for cardiovascular events with statins, regardless of the initial levels of serum lipids, age, or gender (HPS 2002).

The Prospective Study of Pravastatin in the Elderly at Risk study randomized 5804 men and women aged 70 to 82 years with a history of or risk factors for cardiovascular disease and a serum total cholesterol level of 154 mg/dl or higher to pravastatin 40 mg daily or placebo (Shepherd et al 2002). Compared with placebo, pravastatin lowered serum total cholesterol by 32% and serum triglycerides by 12%, and raised serum HDL cholesterol by 5%. At 3.2-year follow-up,

the primary endpoint of CHD death, nonfatal MI, or stroke was significantly reduced to 15% by pravastatin compared with placebo. CHD death or nonfatal MI was significantly lowered to 19% by pravastatin. Stroke risk was unaffected but pravastatin significantly lowered the risk for transient ischemic attack by 25%.

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study, 3086 patients with an acute coronary syndrome and a mean serum LDL cholesterol level of 124 mg/dl were randomized to atorvastatin 80 mg daily or to placebo 24 to 96 hours after hospitalization for 16 weeks (Schwartz et al 2001). At the end of the study, the serum LDL cholesterol increased 12% to 135 mg/dl in the placebo group and decreased 40% to 72 mg/dl in the atorvastatin group. At 16-week follow-up, compared with placebo, atorvastatin significantly lowered mortality, nonfatal MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization by 16% and stroke by 50%.

Sixty-nine older patients, mean age 75 years, with intermittent claudication due to peripheral arterial disease (PAD) and hypercholesterolemia were randomized to simvastatin 40 mg daily or to placebo (Aronow et al 2003). Compared with placebo, simvastatin significantly increased treadmill exercise time until the onset of intermittent claudication by 24% at 6 months after treatment and by 42% at 1 year after treatment.

In a study of 354 patients, mean age 68 years, with intermittent claudication due to PAD and hypercholesterolemia randomized to atorvastatin 80 mg daily or placebo, at 1-year follow-up, compared with placebo, atorvastatin 80 mg daily significantly improved pain-free treadmill walking distance by 40% and community-based physical activity (Mohler et al 2003). In another study of 86 patients, mean age 67 years, with intermittent claudication due to PAD and hypercholesterolemia, at 6-month follow-up, compared with placebo, simvastatin 40 mg daily significantly improved pain-free walking distance and total walking distance on a treadmill, significantly improved the mean ankle-brachial index at rest and after exercise, and significantly improved symptoms of claudication (Mondillo et al 2003).

In the Lipid Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes trial, 10 305 patients with hypertension and at least 3 other cardiovascular risk factors with no history of CHD and a mean serum LDL cholesterol of 133 mg/dl were randomized to atorvastatin 10 mg daily or to placebo (Sever et al 2003). At 3.3-year follow-up, the serum LDL cholesterol was 90 mg/dl in persons treated with atorvastatin. At 3.3-year follow-up, compared with placebo, atorvastatin significantly lowered the incidence of fatal CHD and nonfatal MI by 36%, fatal and nonfatal stroke by 27%, coronary events by 29%, and cardiovascular events and procedures by 21%.

In the Collaborative Atorvastatin Diabetes Study, 2838 patients with diabetes mellitus, no cardiovascular disease, and a serum LDL cholesterol <160 mg/dl were randomized to atorvastatin 10 mg daily or placebo (Calhoun et al 2004). At 3.9-year median follow-up, compared with placebo, atorvastatin significantly decreased time to first occurrence of acute CHD events, coronary revascularization, or stroke by 37%, acute coronary events by 36%, and stroke by 48%.

In the Reversal of Atherosclerosis with Aggressive Lipid Lowering study, intravascular ultrasound was used to measure progression of atherosclerosis in 502 patients with CHD randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily (Nissen et al 2004). The serum LDL cholesterol was lowered to 110 mg/dl in the pravastatin group and to 79 mg/dl in the atorvastatin group. At 18-month follow-up, compared with baseline values, patients treated with atorvastatin had no change in atheroma burden, whereas patients treated with pravastatin showed progression of coronary atherosclerosis.

In 4162 patients, mean age 58 ± 11 years, hospitalized for an acute coronary syndrome (29% with unstable angina pectoris and 71% with an acute MI), the median serum LDL cholesterol was 95 mg/dl in patients randomized to pravastatin 40 mg daily versus 62 mg/dl in patients randomized to atorvastatin 80 mg daily (Cannon et al 2004). At 2-year follow-up, the primary end point of death from any cause, MI, documented unstable angina pectoris requiring rehospitalization, coronary revascularization (performed at least 30 days after randomization), and stroke was 26.3% in the pravastatin group versus 22.4% in the atorvastatin group, a significant 16% reduction in favor of atorvastatin. Data from patients, mean age 61 years, also support early intensive therapy with simvastatin coupled with revascularization when appropriate after an acute coronary syndrome (de Lemos et al 2004).

In 10 001 patients, mean age 61 years, with stable CHD and a serum LDL cholesterol level <130 mg/dl, the effect of atorvastatin 10 mg daily versus 80 mg daily was investigated in a randomized, double-blind trial (LaRosa et al 2005). The mean serum LDL cholesterol levels were 77 mg/dl in patients

treated with atorvastatin 80 mg daily versus 101 mg/dl in patients treated with atorvastatin 10 mg daily. At 4.9-year median follow-up, the primary endpoint of a first major cardiovascular event was significantly reduced 22% by atorvastatin 80 mg daily.

A prospective meta-analysis of data from 90 056 participants in 14 randomized secondary prevention and primary prevention trials of statins was performed (CTT 2005). This meta-analysis showed that statin therapy can safely lower the 5-year incidence of major coronary events, coronary revascularization, and stroke by about one-fifth per 38.7 mg/dl reduction in serum LDL cholesterol, irrespective of the initial lipid profile or other presenting characteristics. The absolute benefit related chiefly to a person's absolute risk of such events and to the absolute reduction in serum LDL cholesterol achieved. These findings reinforce the need to give prolonged statin therapy with substantial serum LDL cholesterol reduction in all patients at high risk of any type of major vascular event.

This meta-analysis also showed that statins did not cause an increase in any site-specific cancer. The 5-year excess risk with statin use of rhabdomyolysis was 0.01%.

Observational studies

In an observational prospective study of 1410 patients, mean age 81 years, with prior MI and a serum LDL cholesterol of 125 mg/dL or higher, 48% of patients were treated with statins (Aronow and Ahn 2002a, 2002b; Aronow et al 2002a). At 3-year follow-up, compared with no treatment with statins, use of statins significantly decreased CHD death or nonfatal MI by 50% (Aronow and Ahn 2002a), stroke by 60% (Aronow et al 2002a) and heart failure by 48% (Aronow et al 2002b). Statins significantly decreased new coronary events in patients older than 90 years (12% of persons at entry) (Aronow and Ahn 2002a). Statins significantly reduced new stroke in patients aged 90 years and younger but not in patients older than 90 years (Aronow et al 2002a).

Lowering serum LDL cholesterol to <90 mg/dl was associated with a 20% incidence of new coronary events, whereas decreasing serum LDL cholesterol to 90–99 mg/dl was associated with a 48% incidence of new coronary events (Aronow and Ahn 2002a). The lower the serum LDL cholesterol in older persons treated with statins, the greater was the decrease in new coronary events (Aronow and Ahn 2002a). Decreasing serum LDL cholesterol to <90 mg/dl was associated with a 7% incidence of new stroke, whereas decreasing serum LDL cholesterol to 90–99 mg/dl was associated with a 16% incidence of new stroke (Aronow et al 2002a).The lower the serum LDL cholesterol in older patients treated with statins, the greater the decrease in new stroke (Aronow et al 2002a).

In an observational prospective study of 1410 patients, mean age 81 years, with prior MI and a serum LDL cholesterol level of 125 mg/dl or higher, patients treated with aspirin had a 52% significant decrease in new coronary events at 3-year follow-up (Aronow and Ahn 2002c). Patients treated with statins (49%) had a 54% significant decrease in coronary events independent of the use of aspirin.

In an observational prospective study of 529 patients, mean age 79 years, with prior MI, diabetes mellitus, and a serum LDL cholesterol of 125 mg/dl or higher, 53% of patients were treated with statins (Aronow et al 2002b). At 29-month follow-up, compared with no treatment with statins, use of statins significantly lowered CHD death or nonfatal MI by 37% and stroke by 47%.

In an observational prospective study of 660 patients, mean age 80 years, with symptomatic PAD and a serum LDL cholesterol of 125 mg/dl or higher, 48% of patients were treated with statins (Aronow and Ahn 2002d). At 39-month follow-up, compared with no treatment with statins, use of statins significantly reduced CHD death or nonfatal MI by 52% in patients with prior MI and by 59% in patients with no prior MI.

In a study of 551 patients with congestive heart failure and an abnormal left ventricular ejection fraction due to ischemic or nonischemic heart disease, 45% of the patients were treated with statins (Horwich et al 2004). At 1-year follow-up, the use of statins was associated with a significant 59% decrease in mortality.

In a study of 54 960 Medicare patients, mean age 79 years, with congestive heart failure and no contraindications to statins, use of statins (17% of group) significantly reduced 1-year mortality by 20% and 3-year mortality by 18% (Foody et al 2006). Statins also significantly reduced progression of valvular aortic stenosis in 180 patients, mean age 82 years (Aronow et al 2001), in 174 patients, mean age 68 years (Novaro et al 2001), and in 156 patients, mean age 77 years (Bellamy et al 2002).

In the ASTEROID trial, 349 patients, mean age 59 years, with coronary atherosclerosis treated with rosuvastatin which lowered the baseline serum LDL cholesterol from 130 mg/dl to 61 mg/dl and increased the baseline serum HDL cholesterol from 43 mg/dl to 49 mg/dl had intravascular ultrasound evaluations at baseline and after 24 months of therapy (Nissen et al 2006). At 2-year follow-up, patients

treated with rosuvastatin had significant regression of atherosclerosis for all 3 prespecified measures of disease burden.

Treatment guidelines

The NCEP-III guidelines recommended that the serum LDL cholesterol be decreased to <100 mg/dl in patients with CHD, other clinical forms of atherosclerotic vascular disease, diabetes mellitus, and with 2+ risk factors that conferred a 10-year risk for CHD greater than 20%, regardless of age (NCEP 2001). Patients with 2+ risk factors that conferred a 10-year risk for CHD of 10% to 20% were recommended to have their serum LDL cholesterol reduced to less than 130 mg/dl. These guidelines needed to be modified because of data published since these guidelines were recommended (Aronow 2004).

The updated NCEP III guidelines (Table 1) state that in very high-risk patients, a serum LDL cholesterol level of <70 mg/dl is a reasonable clinical strategy (Grundy et al 2004). When a high-risk person has hypertriglyceridemia or low serum HDL cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL cholesterol-lowering drug. For moderately high-risk persons (2 or more risk factors and a 10-year risk for CHD of 10% to 20%) the serum LDL cholesterol should be reduced to less than 100 mg/dl. When LDL cholesterol-lowering drug therapy is used to treat high-risk persons or moderately high-risk persons, the serum LDL cholesterol should be reduced at least 30% to 40%.

Table 1 Updated National Cholesterol Education Program III Guidelines for treating very high-risk and moderately high-risk persons with lipid-lowering therapy. Adapted from Grundy et al 2004

1. In very high-risk persons, a serum LDL cholesterol level of <70 mg/dl is a reasonable clinical strategy.
2. When a high-risk person has hypertriglyceridemia or low HDL cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL cholesterol-lowering drug.
3. For moderately high-risk persons (2 or more risk factors* and a 10-year risk for coronary heart disease of 10% to 20%), the serum LDL cholesterol should be lowered to <100 mg/dl.
4. When LDL cholesterol-lowering drug therapy is used to treat high-risk persons or moderately high-risk persons, the serum LDL cholesterol should be decreased at least 30% to 40%.

Note: *Risk factors include cigarette smoking, hypertension, or on antihypertensive medication, a serum HDL cholesterol <40 mg/dl, a family history of premature coronary heart disease, and age (men ≥45 years and women ≥55 years).
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Combination lipid-lowering drug therapy

In order, rosuvastatin, atorvastatin, and simvastatin are the 3 most potent statins in lowering serum LDL cholesterol (Jones et al 2003). If the serum LDL cholesterol cannot be lowered to goal level by a high dose of a potent statin, ezetimide, a bile acid sequestrant, or nicotinic acid should be added to the therapeutic regimen (Grundy et al 2004). Ezetimide is a cholesterol absorption inhibitor that inhibits dietary and biliary cholesterol absorption at the brush border of the small intestine and would be the author's choice to combine with a statin. Ezetimide is also marketed in combination with different doses of simvastatin as Vytorin. Unlike nicotinic acid, ezetimide and bile acid sequestrants do not increase the incidence of myopathy when combined with a statin.

If a high-risk person has hypertriglyceridemia or a low serum HDL cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL cholesterol-lowering drug. When serum triglycerides are ≥200 mg/dl, non-HDL cholesterol is a secondary target of therapy, with a goal 30 mg/dl higher than the recommended serum LDL cholesterol goal (Grundy et al 2004). If a fibrate is administered together with a statin, fenofibrate rather than gemfibrozil should be used since fenofibrate does not interfere with catabolism of statins and does not substantially increase the risk for clinical myopathy as does gemfibrozil (Prucksaritanont et al 2002).

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