Lipid-lowering therapy in older persons

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Abstract

Numerous randomized, double-blind, placebo-controlled studies and observational studies have shown that statins reduce mortality and major cardiovascular events in older high-risk persons with hypercholesterolemia. The Heart Protection Study showed that statins reduced 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 III guidelines state that in very high-risk persons, a serum low-density lipoprotein (LDL) cholesterol level of < 70 mg/dl (1.8 mmol/l) is a reasonable clinical strategy for moderately high-risk persons (2 or more risk factors and a 10-year risk for coronary artery disease of 10% to 20%), and the serum LDL cholesterol should be reduced to < 100 mg/dl (2.6 mmol/l). 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 by at least 30% to 40%. The serum LDL cholesterol should be decreased to less than 160 mg/dl in persons at low risk for cardiovascular disease. Addition of other lipid-lowering drugs to statin therapy has not been demonstrated to further reduce cardiovascular events and mortality.

Key words: lipids, statins, lipid-lowering drugs, atherosclerotic vascular disease, low-density lipoprotein cholesterol.

Introduction

Numerous studies have demonstrated that a high serum total cholesterol or low-density lipoprotein (LDL) cholesterol is a risk factor for new or recurrent coronary events in men and in women [1–6]. Among patients 65 years of age and older with prior myocardial infarction in the Framingham Heart Study, serum total cholesterol was significantly related to death from coronary heart disease (CHD) and to all-cause mortality [2]. At 40-month follow-up of 664 elderly men and at 48-month follow-up of 1,488 elderly women, an increment of 10 mg/dl of serum total cholesterol was associated with a 1.12 increase in the relative risk of new coronary events in both men and in women [5].

Hypercholesterolemia was a risk factor for stroke and for peripheral arterial disease (PAD) in 1,834 elderly persons [7]. An increased serum LDL cholesterol was also a risk factor for atherosclerotic vascular disease and for dementia with and without atherosclerotic vascular disease in elderly patients [8]. However, serum total cholesterol was not a risk factor for stroke in older persons in the Framingham Study [9].

A low serum high-density lipoprotein (HDL) cholesterol level is a risk factor for new coronary events in men and in women [1, 5, 6, 10–12]. At 40-month follow-up of 664 elderly men and at 48-month follow-up of 1,488 elderly women, a decrement of 10 mg/dl of serum HDL cholesterol increased the relative risk of new coronary events 1.70 times in men and 1.95 times in women [5].

A low serum HDL cholesterol is a risk factor for stroke [7, 13] and for PAD in men and in women [7, 14–16]. In 1,834 elderly men and women, there was a 1.36 times greater probability of having stroke and a 1.24 times greater probability of having PAD for a decrement of 10 mg/dl of serum HDL cholesterol after controlling for other prognostic variables [7]. A decreased serum HDL cholesterol was also a risk factor for atherosclerotic vascular disease and for dementia with and without atherosclerotic vascular disease in elderly persons [8]. However, low serum HDL cholesterol was not a risk factor for stroke in older persons in the Framingham Study [9]. Hypertriglyceridemia is a risk factor for new coronary events in elderly women but not in elderly men [1, 6].

Persons aged 65 years and older have a higher prevalence of cardiovascular morbidity and mortality than persons younger than 65 years [17]. According to the American Heart Association statistics in 2004, 84% of cardiovascular deaths, 83% of CHD deaths, and 88% of stroke deaths occurred in persons aged 65 years and older [17]. Since elderly persons are at greater risk for cardiovascular morbidity and mortality than younger persons, they need to have their modifiable risk factors such as dyslipidemia intensively treated. This article will discuss the evidence-based studies supporting the treatment of dyslipidemia in the elderly to reduce cardiovascular morbidity and mortality.

Randomized, double-blind studies

The strongest and most consistent evidence relating cholesterol lowering to cardiovascular event reduction in the elderly derives from secondary prevention studies. In 4,444 men and women (of whom 1,021 were 65 to 70 years of age at study entry) with CHD and hypercholesterolemia in the Scandinavian Simvastatin Survival Study (4S), compared with placebo, simvastatin 20 mg to 40 mg daily reduced serum total cholesterol by 25%, serum LDL cholesterol by 35%, and serum triglycerides by 10%, and increased serum HDL cholesterol by 8% [18–21]. At 5.4-year median follow-up of persons aged 65 to 70 years at study entry, compared with placebo, simvastatin significantly reduced all-cause mortality by 34%, CHD death by 43%, nonfatal myocardial infarction by 33%, major coronary events by 34%, cerebrovascular events by 30%, any atherosclerosis-related endpoint by 34%, new or worsening angina pectoris by 26%, intermittent claudication by 38%, and arterial bruits by 30% [18–20]. Reductions 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 [19]. At 7.4-year median follow-up, simvastatin reduced all-cause mortality by 30% and CHD mortality by 38% [21].

In the Cholesterol and Recurrent Events (CARE) study involving pravastatin treatment for a period of 5 years in post-myocardial infarction patients and serum total cholesterol levels less than 240 mg/dl (6.2 mmol/l) and serum LDL cholesterol levels of 115 to 174 mg/dl (3.0 to 4.5 mmol/l), compared with placebo, pravastatin 40 mg daily reduced serum total cholesterol by 20%, serum LDL cholesterol by 32%, and serum triglycerides by 14%, and increased serum HDL cholesterol by 5% [22, 23]. At 5-year median follow-up of 1,283 patients aged 65 to 74 years at study entry, compared with placebo, pravastatin significantly reduced major coronary events by 32%, CHD death by 45%, CHD death or nonfatal myocardial infarction by 39%, stroke by 40%, and coronary revascularization by 32% [23]. For every 1,000 persons 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 1,000 younger persons [23].

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study randomized 9,014 persons with a history of myocardial infarction or unstable angina pectoris who had initial serum total cholesterol levels of 155 to 271 mg/dl (4.0 to 7.0 mmol/l) to pravastatin 40 mg daily or placebo [24, 25]. Compared with placebo, pravastatin reduced serum total cholesterol by 18%, serum LDL cholesterol by 25%, and serum triglycerides by 11%, and increased serum HDL cholesterol by 5% [24, 25]. At 8-year follow-up of 3,514 persons aged 65 to 75 years at study entry, compared with placebo, pravastatin significantly reduced all-cause mortality by 21%, death from CHD by 24%, fatal and nonfatal myocardial infarction by 26%, death from cardiovascular disease by 26%, need for coronary artery bypass graft surgery by 26%, and need for coronary angioplasty by 34% [25]. Treatment of 1,000 persons for 6 years with pravastatin prevented 30 deaths, 28 nonfatal myocardial infarctions, 9 nonfatal strokes, 23 episodes of coronary artery bypass surgery, 20 episodes of coronary angioplasty, and 82 hospital admissions for unstable angina [24]. The absolute benefits of

treatment 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 [25].

The Heart Protection Study randomized 20,536 men and women (5,806 of whom were aged 70 to 80 years) with prior myocardial infarction (8,510 persons), other CHD (4,876 persons), and no CHD (7,150 persons) and a serum total cholesterol level of 135 mg/dl (3.5 mmol/l) or higher to simvastatin 40 mg daily or to placebo [26]. Of the 7,150 persons without CHD, 25% had cerebrovascular disease, 38% had PAD, 56% had diabetes mellitus, and 3% had only treated hypertension without atherosclerotic vascular disease or diabetes mellitus. At 5-year follow-up, compared to placebo, simvastatin significantly reduced 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% [26]. These significant reductions in mortality and in cardiovascular events occurred regardless of initial levels of serum lipids, age, or gender. First major cardiovascular event was significantly decreased by simvastatin by 24% in persons younger than 65 years, by 23% in persons aged 65 to 69 years, and by 18% in persons aged 70 to 80 years at study entry [26]. Five years of simvastatin treatment prevented myocardial infarction, stroke, and revascularization in 70 to 100 persons per 1,000 treated persons [26].

In the Heart Protection Study, 3,500 persons had initial serum LDL cholesterol levels less than 100 mg/dl (2.6 mmol/l). Decrease of serum LDL cholesterol from 97 mg/dl to 65 mg/dl (2.5 to 1.7 mmol/l) by simvastatin in these persons who would not be treated according to National Cholesterol Education Program (NCEP) III guidelines [27] caused a similar decrease in risk, as did treating patients with higher serum LDL cholesterol levels [26]. The Heart Protection Study Investigators recommended treating persons at high risk for cardiovascular events with statins, regardless of the initial levels of serum lipids, age, or gender [26].

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study randomized 5,804 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 (4.0 mmol/l) or higher to pravastatin 40 mg daily or placebo [28]. Compared with placebo, pravastatin reduced serum total cholesterol by 32% and serum triglycerides by 12%, and increased serum HDL cholesterol by 5%. At 3.2-year follow-up, the primary endpoint of CHD death, nonfatal myocardial infarction, or stroke was significantly decreased 15% by pravastatin compared with placebo [28]. Coronary heart disease death or nonfatal MI was significantly reduced by 19% by pravastatin [28]. Stroke risk was unaffected but pravastatin significantly reduced the risk for transient ischemic attack by 25% [28]. Risk reduction on pravastatin therapy was unrelated to baseline serum LDL cholesterol but showed a significant interaction with baseline serum HDL cholesterol [29].

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, 3,086 persons, mean age 65 years, with an acute coronary syndrome and a mean serum LDL cholesterol level of 124 mg/dl (3.2 mmol/l), were randomized to atorvastatin 80 mg daily or placebo 24 to 96 h after hospitalization for 16 weeks [30]. At the end of the study, the serum LDL cholesterol increased by 12% to 135 mg/dl (3.5 mmol/l) in the placebo group and decreased by 40% to 72 mg/dl (1.9 mmol/l) in the atorvastatin group. At 16-week follow-up, compared with placebo, atorvastatin significantly reduced death, nonfatal myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization by 16% and stroke by 50% [30].

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention (VA-HIT) Trial randomized 2,351 men, mean age 64 years (77% older than 60 years of age), with CHD, a mean serum total cholesterol of 175 mg/dl (4.5 mmol/l), a mean serum LDL cholesterol level of 112 mg/dl (2.9 mmol/l), a mean serum HDL cholesterol level of 32 mg/dl (0.8 mmol/l), and mean serum triglycerides of 161 mg/dl (4.2 mmol/l) to gemfibrozil or placebo [31]. Gemfibrozil reduced serum total cholesterol by 4%, did not change serum LDL cholesterol, reduced serum triglycerides by 31%, and increased serum HDL cholesterol by 6%. At 5.1-year median follow-up, compared with placebo, gemfibrozil significantly reduced coronary death or nonfatal myocardial infarction by 22% and coronary death, nonfatal myocardial infarction, or stroke by 24% [31]. These data suggest that gemfibrozil may be useful in reducing the incidence of coronary events in persons with CHD whose primary lipid abnormality is a low serum HDL cholesterol level.

Sixty-nine elderly patients, mean age 75 years, with intermittent claudication due to PAD and hypercholesterolemia were randomized to simvastatin 40 mg daily or placebo [32]. 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 [32].

In a study of 354 persons, 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 [33]. In another study of 86 persons, 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 [34].

In the Lipid Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes (ASCOT-LLA) trial, 10,305 persons (6,570 aged 61 to 79 years) 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 (3.4 mmol/l) were randomized to atorvastatin 10 mg daily or to placebo [35]. At 3.3-year follow-up, the serum LDL cholesterol was 90 mg/dl (2.3 mmol/l) in persons treated with atorvastatin. At 3.3-year follow-up, compared with placebo, atorvastatin significantly reduced the incidence of fatal CHD and nonfatal myocardial infarction by 34% in persons aged 60 years and younger and by 36% in persons older than 60 years [35]. Atorvastatin also significantly reduced fatal and nonfatal stroke by 27% [35].

In the Reversal of Atherosclerosis With Aggressive Lipid Lowering (REVERSAL) study, intravascular ultrasound was used to measure progression of atherosclerosis in 502 persons, mean age 57 years, with CHD, randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily [36]. The serum LDL cholesterol was reduced to 110 mg/dl (2.8 mmol/l) in the pravastatin group and to 79 mg/dl (2.0 mmol/l) 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 [36].

In 4,162 patients, mean age 58 ±11 years, hospitalized for an acute coronary syndrome (29% with unstable angina pectoris and 71% with an acute myocardial infarction) (PROVE IT-TIMI 22), the median serum LDL cholesterol was 95 mg/dl (2.5 mmol/l) in patients randomized to pravastatin 40 mg daily versus 62 mg/dl (1.6 mmol/l) in patients randomized to atorvastatin 80 mg daily [37]. At 2-year follow-up, the primary end point of death from any cause, myocardial infarction, 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 [37].

In the Collaborative Atorvastatin Diabetes Study, 2,838 patients (62% older than 60 years) with diabetes mellitus, no cardiovascular disease, and a serum LDL cholesterol less than 160 mg/dl (4.14 mmol/l) were randomized to atorvastatin 10 mg daily or placebo [38]. At 3.9-year median follow-up, compared with placebo, atorvastatin significantly reduced time to first occurrence of acute CHD events, coronary revascularization, or stroke by 37%, acute coronary events by 36%, and stroke by 48% [38].

In the Treating to New Targets (TNT) study of 10,001 patients, mean age 61 years, with stable CHD and a serum LDL cholesterol level less than 130 mg/dl (3.36 mmol/l), the effect of atorvastatin 10 mg daily versus 80 mg daily was investigated in a randomized, double-blind trial [39]. The mean serum LDL cholesterol levels were 77 mg/dl (1.99 mmol/l) in patients treated with atorvastatin 80 mg daily versus 101 mg/dl (2.61 mmol/l) 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 by 22% by atorvastatin 80 mg daily [39].

In the Study Assessing Goals in the Elderly (SAGE), 893 ambulatory CAD patients aged 65 to 85 years with at least 1 episode of myocardial ischemia lasting at least 3 min during 48-hour ambulatory electrocardiographic screening were randomized to atorvastatin 80 mg daily or to pravastatin 40 mg daily and followed for 12 months [40]. Total duration of myocardial ischemia detected by 48-hour ambulatory electrocardiograms at month 3 and at month 12 after randomization was significantly reduced by both atorvastatin and pravastatin, with no significant difference between the 2 treatment groups. Compared with pravastatin, atorvastatin significantly reduced serum LDL cholesterol levels, insignificantly reduced major acute cardiovascular events by 22%, and significantly reduced all-cause mortality by 67% [40].

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, 4,731 patients, mean age 63 years, who had a stroke or transient ischemic attack within 1 to 6 months prior to study entry, a serum LDL cholesterol of 100 to 190 mg/dl (2.58 to 4.91 mmol/l), and no CHD, were randomized to atorvastatin 80 mg daily or placebo [41]. The mean LDL cholesterol was 73 mg/dl (1.89 mmol/l) in patients on atorvastatin and 129 mg/dl (3.33 mmol/l) in patients on placebo. At 4.9-year median follow-up, atorvastatin significantly reduced the incidence of new stroke by 16% and of major cardiovascular events by 20% [41].

In the Justification for the Use of Statins in Prevention: an Intervention Trial evaluating Rosuvastatin (JUPITER), 17,082 apparently healthy persons, median age 66 years, with a serum LDL cholesterol of less than 130 mg/dl (3.36 mmol/l) and high-sensitivity C-reactive protein levels of 2.0 mg/l or higher, were randomized to rosuvastatin 20 mg daily or placebo [42]. At 1.9-year median follow-up, rosuvastatin significantly reduced serum LDL cholesterol levels by 50%, high-sensitivity C-reactive protein levels by 37%, and the primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina pectoris, or death from cardiovascular causes by 44% [42].

A meta-analysis was performed in 14 randomized trials of statins in 18,686 diabetics, mean age 63 years (1,466 with type 1 diabetes and 17,220 with type 2 diabetes) [43]. After 5 years, 42 fewer diabetics (95% CI: 30 to 55) had major cardiovascular events per 1,000 randomized to statins [43].

A meta-analysis was performed in 26 randomized trials of statins in 170,000 persons [44]. The reduction in major cardiovascular events per 1.0 mmol/l reduction in serum LDL cholesterol was 22% (95% CI: 18% to 25%) in persons aged 65 years and younger, 22% (95% CI: 17% to 26%) in persons aged 66 to 75 years, and 16% (95% CI: 3% to 27%) in persons older than 75 years [44].

A meta-analysis was also performed in 9 randomized trials of statins for secondary prevention in 19,569 patients aged 65 to 82 years [45]. Over 5 years, statins reduced all-cause mortality by 22% (95% CI: 11% to 35%), CHD mortality by 30% (95% CI: 17% to 47%), nonfatal myocardial infarction by 26% (95% CI: 11% to 40%), need for revascularization by 30% (95% CI: 17% to 47%), and stroke by 25% (95% CI: 6% to 44%). The estimated number needed to treat to save 1 life was 28 [45].

In 5,518 type 2 diabetics, mean age 62 years, treated with simvastatin, patients were randomized to receive either masked fenofibrate or placebo [46]. At 4.7-year mean follow-up, the combination of fenofibrate plus simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin plus placebo [46].

In 9,795 type 2 diabetics aged 50 to 75 years (2,131 with cardiovascular disease), patients were randomized to treatment with fenofibrate or placebo [47]. At 5-year follow-up, the primary outcome of coronary events was not reduced by fenofibrate [47].

A study was performed in 15,067 patients at high cardiovascular risk who were randomized to atorvastatin plus the cholesteryl ester transfer protein (CETP) inhibitor torcetrapib or to atorvastatin alone [48]. Torcetrapib increased serum HDL cholesterol by 72% and reduced serum LDL cholesterol by 25%. At 1-year follow-up, the trial was stopped because torcetrapib increased cardiovascular events by 25% ($p = 0.001$) and increased all-cause mortality by 58% ($p = 0.006$) [48].

A study was performed in 15,871 patients with a recent acute coronary syndrome who were randomized to the CETP inhibitor dalcetrapib or placebo [49]. Over the course of the study, dalcetrapib increased serum HDL cholesterol by 31% to 40% and had a minimal effect on serum LDL cholesterol levels. At 31-month median follow-up, dalcetrapib insignificantly increased the primary outcome of CHD death, nonfatal myocardial infarction, ischemic stroke, unstable angina, or cardiac arrest with resuscitation by 4% [49].

Among 3,414 patients, mean age 64 years, with atherosclerotic cardiovascular disease and low serum HDL cholesterol levels treated with simvastatin plus ezetimibe if needed to maintain the serum LDL cholesterol less than 70 mg/dl (1.81 mmol/l), at 36-month follow-up, patients randomized to niacin had improvements in serum HDL cholesterol and triglyceride levels but no clinical improvement compared to patients randomized to placebo [50]. In this study, patients treated with niacin had a 67% increase in ischemic stroke or stroke of uncertain origin ($p = 0.09$) [50].

At the American College of Cardiology Meeting on March 9, 2013, Dr. Jane Armitage presented data from the Heart Protection study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study. In this study, 25,673 high-risk patients were randomized to treatment with simvastatin or simvastatin/ezetimibe plus extended-release niacin plus the anti-flushing agent laropiprant or to treatment with simvastatin or simvastatin/ezetimibe. At 3.9-year follow-up, compared to treatment with simvastatin or simvastatin/ezetimibe, addition of niacin did not reduce the primary outcome of major vascular events but increased there were 31 serious adverse events per 1,000 niacin-treated patients. Excess diabetic complications were increased by 3.7% ($p < 0.0001$). Excess new diabetes was increased by 1.8% ($p < 0.0001$). Excess infection was increased by 1.4% ($p < 0.0001$). Excess gastrointestinal complications were increased by 1% ($p < 0.0001$). Excess bleeding (gastrointestinal and intracranial) was increased by 0.7% ($p < 0.0002$).

Observational studies

In all of the observational prospective studies performed by this author, the attitude of the different physicians toward treating hypercholesterolemia in high-risk older persons determined whether statins were prescribed. In an observa-

tional prospective study of 488 men and 922 women, mean age 81 years, with prior myocardial infarction and a serum LDL cholesterol of 125 mg/dl (3.2 mmol/l) or higher, 48% of persons were treated with statins [51–53]. At 3-year follow-up, compared to no treatment with statins, use of statins significantly reduced CHD death or nonfatal myocardial infarction by 50% [51], stroke by 60% [52], and heart failure by 48% [53]. Statins significantly reduced new coronary events in persons older than 90 years (12% of persons at entry) [51]. Statins significantly reduced new stroke in persons aged 90 years and younger but not in persons older than 90 years [52].

Reducing serum LDL cholesterol to less than 90 mg/dl (2.3 mmol/l) was associated with a 20% incidence of new coronary events, whereas reducing serum LDL cholesterol to 90 to 99 mg/dl (2.3 to 2.6 mmol/l) was associated with a 48% incidence of new coronary events [51]. The lower the serum LDL cholesterol in elderly persons treated with statins, the greater was the reduction in new coronary events [51]. Decreasing serum LDL cholesterol to less than 90 mg/dl (2.3 mmol/l) was associated with a 7% incidence of new stroke, whereas decreasing serum LDL cholesterol to 90 to 99 mg/dl (2.3 to 2.6 mmol/l) was associated with a 16% incidence of new stroke [52]. The lower the serum LDL cholesterol in elderly persons treated with statins, the greater was the decrease in new stroke [52].

In an observational prospective study of 1,410 elderly persons, mean age 81 years, with prior myocardial infarction and a serum LDL cholesterol level of 125 mg/dl (3.2 mmol/l) or higher, patients treated with aspirin had a 52% significant decrease in new coronary events at 3-year follow-up [54]. Elderly persons treated with statins (49% of the persons) had a 54% significant decrease in new coronary events independent of the use of aspirin [54].

In an observational prospective study of 171 men and 358 women, mean age 79 years, with prior myocardial infarction, diabetes mellitus, and a serum LDL cholesterol of 125 mg/dl (3.2 mmol/l) or higher, 53% of persons were treated with statins [55]. At 29-month follow-up, compared with no treatment with statins, use of statins significantly reduced in elderly persons CHD death or nonfatal myocardial infarction by 37% and stroke by 47% [55].

In an observational prospective study of 264 men and 396 women, mean age 80 years, with symptomatic PAD and a serum LDL cholesterol of 125 mg/dl (3.2 mmol/l) or higher, 48% of persons were treated with statins [56]. At 39-month follow-up, compared with no treatment with statins, use of statins significantly reduced CHD death or nonfatal myocardial infarction by 52% in elderly persons with prior myocardial infarction and by 59% in persons with no prior myocardial infarction [56].

In a study of 551 persons with congestive heart failure and an abnormal left ventricular ejection fraction due to ischemic or nonischemic heart disease, 45% of the persons were treated with statins [57]. At 1-year follow-up, the use of statins was associated with a significant 59% reduction in mortality [57].

In a study of 180 persons, mean age 82 years, with mild valvular aortic stenosis, 62 persons (34%) were treated with statins [58]. At 33-month follow-up, use of statins was associated with a significant decrease in the progression of aortic stenosis [58].

In a study of 174 persons, mean age 68 years, with mild-moderate aortic stenosis, 57 persons (33%) were treated with statins [59]. At 21-month follow-up, persons treated with statins had reduced progression of aortic stenosis [59]. In a community-based study of 156 persons, mean age 77 years, with aortic stenosis, 38 persons (24%) were treated with statins [60]. At 3.7-year follow-up, persons treated with statins had slower progression of aortic stenosis [60].

These observational data were confirmed by 1 prospective trial using rosuvastatin [61]. However, 2 prospective trials (1 using atorvastatin and 1 using simvastatin plus ezetimibe) did not confirm these data [62, 63]. It is unlikely that statins will affect a heavily calcified valve with severe aortic stenosis. However, patients with aortic stenosis often have associated cardiovascular disease such as CHD, other atherosclerotic vascular disease, or diabetes mellitus, which will benefit from treatment with statins.

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 [64]. At 1-year follow-up, the use of statins was associated with a significant 59% decrease in mortality [64]. In 54,960 Medicare patients, mean age 79 years, hospitalized for heart failure, use of statins caused a significant 20% reduction in 1-year mortality and a significant 18% reduction in 3-year mortality [65]. However, a double-blind, placebo-controlled study in 4,574 patients with heart failure and abnormal or normal left ventricular ejection fraction showed at 3.9-year median follow-up that rosuvastatin 10 mg daily did not affect clinical outcomes [66].

In a prospective, open-label blinded end-points trial of 507 patients with CHD in the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) trial, ro-

suvastatin 40 mg daily for 2 years reduced serum LDL cholesterol by 53% from 130 to 61 mg/dl (3.36 to 1.58 mmol/l), increased serum HDL cholesterol by 15% from 43 to 49 mg/dl (1.11 to 1.27 mmol/l), and reduced serum triglycerides by 20% from 152 to 121 mg/dl (3.93 to 3.13 mmol/l) [67]. Intravascular ultrasound showed at 2-year follow-up significant regression of atherosclerosis for all 3 prespecified intravascular ultrasound measures of disease burden [67]. The ASTEROID trial also showed at 2-year follow-up that rosuvastatin therapy to reduce the serum LDL cholesterol level to less than 70 mg/dl (1.81 mmol/l) produced regression of CHD by reducing percent diameter stenosis and improving minimum lumen diameter as measured by quantitative coronary angiography [68].

Evaluable intravascular ultrasound evaluations were made at baseline and at 8-12 month follow-up in 252 patients with an acute coronary syndrome randomized to statin therapy with pitavastatin 4 mg daily or atorvastatin 20 mg daily in an open-label, prospective study with blind end point evaluation [69]. Significant regression of coronary plaque volume occurred in both treatment groups with no significant difference between the 2 statins [69].

The use of lipid-lowering drugs in 27 of 78 patients with CAD and life-threatening ventricular arrhythmias treated with an implantable cardioverter-defibrillator (ICD) was associated with a significant decrease in recurrence of life-threatening ventricular arrhythmias from 57% to 22% [70]. The use of lipid-lowering drugs in 83 of 362 patients with CHD treated with an ICD for ventricular tachycardia/ventricular fibrillation significantly reduced recurrence of ventricular tachycardia/ventricular fibrillation by 60% [71]. The use of statins in 154 of 281 patients with CHD and ventricular arrhythmias treated with an ICD was associated with a significant decrease in recurrence of ventricular arrhythmias from 50% to 30% [72].

Statins significantly reduced death or ventricular tachycardia or ventricular fibrillation by 35% in patients with an ICD in the Multicenter Automatic Defibrillator Implantation trial (MADIT)-II [73]. The use of statins in 402 of 965 patients, mean age 70 years, treated with an ICD, was significantly associated with a 42% reduction in all-cause mortality [74]. The use of statins in 121 of 209 patients, mean age 72 years, with heart failure treated with combined cardiac resynchronization-I CD therapy was associated with a significant 54% reduction in appropriate ICD shocks and with a significant 95% reduction in mortality [75]. The use of statins in 58% of 209 patients, mean age 72 years, with heart failure treated with combined cardiac resynchronization-I CD therapy and in 49% of 320 patients, mean age 71 years, with heart failure treated with an ICD reduced appropriate ICD shocks by 65% ($p < 0.0001$) and reduced time to mortality by 82% ($p < 0.0001$) [76]. At 1,243 days follow-up of 549 patients, mean age 74 years, with heart failure treated with an ICD, use of statins reduced appropriate ICD shocks by 46% ($p = 0.002$), inappropriate ICD shocks by 48% ($p = 0.025$), and time to all-cause mortality by 68% ($p = 0.0009$) [77]. In the MADIT-Cardiac Resynchronization Therapy trial, 499 of 821 patients (61%), mean age 63 years, with nonischemic cardiomyopathy were statin users [78]. At 4-year follow-up, the cumulative probability of fast ventricular tachycardia/ventricular fibrillation or death was reduced from 19% in nonstatin users to 11% for statin users ($p = 0.006$) [78]. Randomized clinical trials need to be performed to confirm the validity of these studies [70–78].

In 100 patients undergoing noncardiac vascular surgery, the incidence of cardiac death, nonfatal myocardial infarction, stroke, or unstable angina at 6-month follow-up was lower in 50 patients treated with atorvastatin than in 50 patients treated with placebo (8% vs. 26%, respectively, $p = 0.031$) [79]. Of 510 patients who survived abdominal aortic aneurysm (AAA) surgery beyond 30 days and followed for a median of 4.7 years, 154 (30%) were treated with statins [80]. In this study, statins significantly reduced all-cause mortality by 60% ($p < 0.001$) [80].

In 160 patients who died during hospitalization after undergoing major noncardiac vascular surgery and in 320 controls, statin therapy was significantly less common in patients who died (8%) than in controls (25%) ($p < 0.001$) [81]. Perioperative cardiovascular complications of death, myocardial infarction, myocardial ischemia, congestive heart failure, or ventricular tachyarrhythmias occurring after major noncardiac vascular surgery were significantly lower in patients treated with statins (9.9% of 526 hospitalizations in patients treated with statins and in 16.5% of 637 hospitalizations in patients not treated with statins; $p = 0.001$) [82]. In a study of 577 patients, mean age 74 years, undergoing carotid endarterectomy (300 patients), lower extremity revascularization (179 patients), or AAA repair (98 patients), stepwise Cox regression analysis showed that use of statins was a significant independent predictor of reduced perioperative myocardial infarction or death during 2-year follow-up by 57% ($p < 0.0001$) [83]. In a study of 408 diabetics, mean age 66 years, with ischemic stroke and of 404 age-matched and gender-matched diabetics without ischemic stroke, the serum LDL cholesterol level was significantly higher in diabetics with ischemic stroke ($p < 0.001$) [84].

Of 130 patients, mean age 67 years with an AAA not treated surgically, 58% of patients were treated with statins [85]. The sizes of the AAAs were 4.6 cm at baseline and 4.5 cm at 23-month follow-up in patients treated with statins (p not significant) and 4.5 cm at baseline and 5.3 cm at 24-month follow-up in patients not treated with statins ($p < 0.001$). Four of 75 patients (5%) treated with statins died at 45-month follow-up, and 9 of 55 patients (16%) not treated with statins died at 44-month follow-up ($p < 0.05$) [85].

Of 449 patients, mean age 72 years, with severe carotid arterial disease who did not undergo revascularization, 298 (66%) were treated with statins [86]. Follow-up was 26 months in patients treated with statins and 21 months in patients not treated with statins. Stepwise Cox regression analysis showed that use of statins reduced the time to development of new stroke or new myocardial infarction or death by 87% ($p < 0.0001$) [86]. Randomized clinical trials need to be performed to confirm the validity of these studies [79–86].

Statins exert effects on endothelial function, oxidative stress, and inflammation in patients with arterial hypertension and normal cholesterol levels [87]. The role of statins in hypertension is discussed elsewhere [88, 89]. The optimal blood pressure goal in patients with diabetes mellitus or chronic kidney disease is discussed elsewhere [90].

Treatment with atorvastatin reduces the concentration of interleukin-6 and of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) after 2 months of therapy in patients with dilated cardiomyopathy [91]. The effect of atorvastatin on reducing the concentration of interleukin-6 and of NT-proBNP is weaker in patients with dilated cardiomyopathy and coexistent atrial fibrillation than in patients with dilated cardiomyopathy without atrial fibrillation [92]. Dilated cardiomyopathy patients most likely to benefit from statin therapy are likely to be in New York Heart Association class II or III and should have normal or increased levels of lipids [93].

In 197,551 patients, the beneficial effect of statins in preventing the development of renal dysfunction appears to be independent of their lipid-lowering effect [94]. Statin therapy significantly modifies the lipid profile in chronic kidney disease patients not on dialysis therapy [95]. Current evidence from clinical trials on the clinical potential of statins in dialyzed patients is limited [96].

Three hundred and five patients, mean age 74 years, were not treated with statins during the first year of being seen in an academic cardiology practice but were subsequently treated with statins [97]. Mean follow-up was 65 months before statin use and 66 months after statin use. Statin use reduced the incidence of myocardial infarction from 10% to 4% ($p < 0.01$), the incidence of percutaneous coronary intervention from 22% to 13% ($p < 0.01$), and the incidence of coronary artery bypass graft surgery from 18% to 7% ($p < 0.001$) [97].

In 357 patients with CHD followed in an academic cardiology practice, the use of statins in a 2-year treatment period prior to 2002 was 40% and increased in a 2-year period during 2005–2008 to 90% [98]. The increased use of statins, β-blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in these patients with CHD in the later period was associated with a decrease in myocardial infarction or cerebrovascular events or coronary interventions from 29.1% to 9.2% ($p < 0.001$) [98].

In 183 patients, mean age 71 years, with CHD followed in an academic cardiology practice who had at least 2 coronary angiographies at least 1 year apart, the mean follow-up between coronary angiographies was 58 months [99]. The mean serum LDL cholesterol was 94 mg/dl in patients with progressive CHD and 81 mg/dl in patients with nonprogressive CHD ($p = 0.09$) [99].

Underutilization of lipid-lowering drugs

Despite the efficacy of statins in reducing cardiovascular morbidity and mortality, these drugs have been underutilized in elderly persons [100–102]. In 335 persons, mean age 81 years, with prior myocardial infarction and a serum LDL cholesterol greater than 125 mg/dl (3.2 mmol/l) admitted from a hospital to a nursing home, 17 persons (5%) were being treated with a lipid-lowering drug [100]. In this study, the attitude of the different physicians toward treating hypercholesterolemia in high-risk older persons determined whether statins were prescribed. In elderly persons living in the community, mean age 80 years, with an increased serum LDL cholesterol followed at the Mount Sinai Medical Center Geriatrics Clinic, 80 of 159 elderly persons (50%) with prior myocardial infarction, 28 of 65 persons (43%) with a prior stroke, and 19 of 46 persons (41%) with PAD were being treated with lipid-lowering drugs [101]. Of 23,013 patients with an acute myocardial infarction, 24% were receiving a statin at hospital discharge [102]. In this study, 15.5% of 8,452 persons aged 80 years and older with an acute myocardial infarction were receiving a statin at hospital discharge [102].

However, a systematic educational program has been demonstrated to improve utilization of lipid-lowering drugs in elderly persons [103, 104]. In persons, mean age 70 years, seen at a university hospital with CHD and dyslipidemia, 58 of 112 persons (52%) were treated with lipid-lowering drugs prior to a systematic educational program

and 152 of 173 persons (88%) after a systematic educational program [103]. In persons with hypercholesterolemia, mean age 77 years, seen in an academic nursing home, use of a systematic educational program significantly improved the use of lipid-lowering drugs in persons with CHD from 29% to 70% in 63 persons, in persons with PAD from 28% to 79% in 19 persons, in persons with stroke from 24% to 64% in 44 persons, and in persons with diabetes mellitus from 26% to 67% in 52 persons [104].

Treatment guidelines

Lifestyle measures are important in the treatment of dyslipidemia. The person should achieve and maintain a desirable weight. The diet should be low in cholesterol (less than 200 mg daily). Less than 30% of total caloric intake should be fatty acids. Saturated fatty acids should comprise less than 7% of total calories, polyunsaturated acids up to 10% of total calories, and monounsaturated fatty acids 10% to 15% of total calories. The diet should also be high in fiber and high in fruits and vegetables. There is no strong evidence to support any dietary supplements. A more liberalized diet is warranted in elderly persons prone to malnutrition. Moderate intensity exercise is recommended for 30 to 60 min daily. Smoking should be stopped, hypertension treated, and diabetes controlled.

The NCEP III guidelines recommend that the serum LDL cholesterol be reduced to less than 100 mg/dl (2.6 mmol/l) in persons with CHD, other clinical forms of atherosclerotic vascular disease, diabetes mellitus, and with 2+ risk factors that confer a 10-year risk for CHD greater than 20%, regardless of age [27]. Elderly persons with 2+ risk factors that confer a 10-year risk for CHD of 10% to 20% should have their serum LDL cholesterol reduced to less than 130 mg/dl (3.4 mmol/l) [27]. These guidelines needed to be modified because of data published since these guidelines were recommended [105].

The updated NCEP III guidelines (Table I) state that in very high-risk persons, a serum LDL cholesterol level of less than 70 mg/dl (1.8 mmol/l) is a reasonable clinical strategy [106]. 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 (2.6 mmol/l) [106]. 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 by at least 30% to 40% [106]. The author concurs with these updated guidelines [106]. The author would not treat elderly persons with life-threatening illness causing limited life expectancy or advanced dementia with lipid-lowering therapy. The 2013 American College of Cardiology/American Heart Association lipid guidelines recommend high-dose statin therapy (40–80 mg of atorvastatin or 20–40 mg of rosuvastatin daily) in men and women aged 75 years and younger with clinical atherosclerotic cardiovascular disease and moderate-dose or high-dose statin therapy in patients older than 75 years for secondary prevention and high-dose statin therapy for primary prevention in persons aged 21 years and older with a serum LDL cholesterol of 190 mg/dl (4.91 mmol/l or higher) unless contraindicated [107]. These guidelines recommend moderate-dose statins for primary prevention in diabetics aged 40–75 years with a serum LDL cholesterol between 70–189 mg/dl (1.81–4.89 mmol/l), high-dose statins for primary prevention in diabetics with a 10-year risk of developing atherosclerotic cardiovascular disease of 7.5% or higher, and clinical judgment for use of statins in diabetics younger than 40 years, older than 75 years, or with a serum LDL cholesterol < 70 mg/dl (1.81 mmol/l) [107]. Men and women aged 40 to 75 years without diabetes mellitus and with a serum LDL cholesterol between 70–189 mg/dl (1.81–4.89 mmol/l) should be treated for primary prevention if their 10-year risk of atherosclerotic cardiovascular disease is 7.5% or higher with moderate-dose to high-dose statin therapy and if their 10-year risk of atherosclerotic cardiovascular disease is 5.0% to 7.4% with moderate-dose statins [107].

Addition of other lipid-lowering drugs to statin therapy has not been demonstrated to further reduce cardiovascular events and mortality. The American Diabetes Association 2013 guidelines state that diabetics at high risk for cardiovascular events should have their serum LDL cholesterol reduced to less than 70 mg/dl with statins [108]. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dl. Combination therapy of a statin with either a fibrate or

Table I. Updated National Cholesterol Education Program III guidelines for treating very high-risk and moderately high-risk elderly persons (adapted from [106])

In very high-risk persons, a serum LDL cholesterol level of less than 70 mg/dl is a reasonable clinical strategy.
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 by at least 30% to 40%.

LDL – low-density lipoprotein, CHD – coronary heart disease, HDL – high-density lipoprotein.

niacin has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not recommended [108]. Hypertriglyceridemia should be treated with dietary and lifestyle changes. Severe hypertriglyceridemia should be treated with drug therapy to reduce the risk of acute pancreatitis.

Significance of updated guidelines to elderly

American Heart Association statistics show that persons aged 65 years and older have a higher prevalence of cardiovascular morbidity and mortality than persons younger than 65 years [17]. American Heart Association statistics also show that hypercholesterolemia is present in 60% of American men and in 77% of American women aged 65–74 years [17]. Many studies have also demonstrated a greater absolute risk in cardiovascular events in older persons than in younger persons treated for hypercholesterolemia [19, 23, 26]. On the basis of the data reviewed in this paper, the author strongly recommended updating the NCEP III guidelines [105] and strongly supports the updated guidelines [106]. However, implementing the revised guidelines will require treating millions of elderly Americans with intensive lipid-lowering therapy who are not being treated now.

Framingham risk scoring should be used in elderly persons as in middle-aged persons. Elderly persons with CHD, other clinical forms of atherosclerotic vascular disease, diabetes mellitus, and two or more risk factors conferring a 10-year risk for CHD greater than 20% should be treated with intensive lipid-lowering therapy, regardless of age, gender, or serum lipids levels. Studies need to be performed to investigate whether elderly persons with subclinical atherosclerosis should be treated with lipid-lowering therapy.

Adverse effects

Asymptomatic increases in concentrations of liver transaminases are recorded with all statins but are not clearly associated with an increased risk of liver disease [109]. In the Heart Protection Study, a greater than 4 times increase in alanine aminotransferase occurred in 43 of 10,269 patients (0.42%) treated with simvastatin 40 mg daily and in 32 of 10,267 patients (0.31%) treated with placebo [26]. Study treatment was stopped because of myopathy in 0.5% of patients treated with simvastatin and in 0.5% of patients treated with placebo. Rhabdomyolysis occurred in 5 patients (0.05%) treated with simvastatin and in 3 patients (0.03%) treated with placebo [26]. Drug interactions with statins are discussed elsewhere [109, 110].

Future research

Studies need to be performed to investigate whether elderly persons with subclinical atherosclerosis should be treated with statins. Studies should be performed to investigate whether combination therapy with a bile acid sequestrant plus a statin will reduce cardiovascular events and mortality more than a statin alone. New lipid-lowering drugs need to be investigated to determine whether, when added to statin therapy, there will be a further reduction in cardiovascular events and mortality. Although a low serum HDL cholesterol level is a potent risk factor for cardiovascular events, numerous drugs that raise serum HDL cholesterol have not been found to reduce cardiovascular events. The data clearly show that one cannot rely on drugs causing improvement in serum lipids only. Favorable cardiovascular outcomes must be achieved before using these drugs in clinical practice. Future research should also investigate how low the serum LDL cholesterol should be decreased in elderly high-risk persons and the role of potent drugs which raise serum HDL cholesterol in the treatment of high-risk elderly persons with dyslipidemia.

Conclusions

Elderly persons have a higher prevalence of cardiovascular morbidity and mortality than younger persons. Numerous randomized, double-blind, placebo-controlled studies and observational studies have shown that statins reduce mortality and major cardiovascular events in elderly high-risk persons with hypercholesterolemia. The Heart Protection Study showed that statins reduced mortality and major cardiovascular events in elderly high-risk persons regardless of the initial level of serum lipids, age, or gender. The updated National Cholesterol Education program III guidelines state that in very high-risk persons, a serum LDL cholesterol level of < 70 mg/dl (1.8 mmol/l) is a reasonable clinical strategy. 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 < 100 mg/dl (2.6 mmol/l). 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 by at least 30% to 40%. All elderly persons with diabetes mellitus should be treated with lipid-lowering therapy. Future research should investigate how low the serum LDL cholesterol should be decreased in elderly high-risk persons and the role of potent drugs which raise HDL cholesterol in the treatment of high-risk elderly persons with dyslipidemia. Studies need to be performed to investigate whether elderly persons with subclini-

cal atherosclerosis should be treated with statins. Studies should also be performed to investigate whether combination therapy with a bile acid sequestrant plus a statin will reduce cardiovascular events and mortality more than a statin alone.

Conflict of interest

The authors declare no conflict of interest.

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