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Treatment of Hypercholesterolemia

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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 high-risk patients with hypercholesterolemia. The Heart Protection Study showed that statins reduced mortality and major cardiovascular events in high-risk patients 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/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%), the serum LDL cholesterol should be reduced 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 reduced 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 found to further reduce cardiovascular events and mortality.

Keywords: Lipids; Statins; Lipid-lowering drugs; Low-density liporotein cholesterol; High-density lipoprotein cholesterol; Triglycerides

A systematic review using PubMed showed that numerous studies have shown 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]. At 40-month follow-up of 664 elderly men and at 48-month follow-up of 1,488 elderly women, an increase 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 is also a risk factor for stroke and for peripheral arterial disease (PAD) [7]. An increased serum LDL cholesterol is also a risk factor for atherosclerotic vascular disease and for dementia with and without atherosclerotic vascular disease [8].

A low serum high-density lipoprotein (HDL) cholesterol is a risk factor for new coronary events in men and in women [1,5,6,9-11]. 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 also a risk factor for stroke [7,12] and for PAD [7,13-15]. 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 decrease of 10 mg/dl of serum HDL cholesterol after controlling for other prognostic variables [7]. Decreased serum HDL cholesterol was also a risk factor for atherosclerotic vascular disease and for dementia with and without atherosclerotic vascular disease [8]. Hypertriglyceridemia is a risk factor for new coronary events in women but not in men [1,6].

Persons aged 65 years and older have a higher prevalence of cardiovascular morbidity and mortality than persons younger than 65 years [16]. Since older 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.

Randomized, Double-Blind, Studies

The strongest and most consistent evidence relating cholesterol lowering to cardiovascular event reduction comes from secondary prevention studies. In 4,444 men and women with coronary artery disease (CAD) 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 low-density lipoprotein (LDL) cholesterol by 35%, and serum triglycerides by 10%, and increased serum high-density lipoprotein (HDL) cholesterol by 8% [17-20]. At 5.4-year median follow-up, compared with placebo, simvastatin significantly reduced all-cause mortality by 34%, CAD death by 43%, nonfatal myocardial infarction (MI) by 33%, major coronary events by 34%, cerebrovascular events by 30%, any atherosclerosis-related endpoint by 34%, new or worsening angina by 26%, intermittent claudication by 38%, and arterial bruits by 30% [17-19]. Reductions in endpoint events were similar in older and younger men and women. The absolute risk reduction for both all-cause mortality and CAD mortality was approximately twice as great in persons 65 years of age and older as in those younger than 65 years [18]. At 7.4-year median follow-up, simvastatin reduced all-cause mortality by 30% and CAD mortality by 38% [20].

In the Cholesterol and Recurrent Events (CARE) study involving pravastatin treatment for a period of 5 years in post-MI patients and serum total cholesterol levels less than 240 mg/dL and serum LDL cholesterol levels of 115 to 174 mg/dL, compared with placebo, pravastatin 40 mg daily decreased serum total cholesterol by 20%, serum LDL cholesterol by 32%, and serum triglycerides by 14%, and increased serum HDL cholesterol by 5% [21,22]. 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%, CAD death by 45%, CAD death or nonfatal myocardial infarction

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by 39%, stroke by 40%, and coronary revascularization by 32% [22]. For every 1,000 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 1,000 younger patients [22].

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study randomized 9,014 patients with a history of MI or unstable angina who had initial serum total cholesterol levels of 155 to 271 mg/dL to pravastatin 40 mg daily or placebo [23,24]. Compared with placebo, pravastatin lowered serum total cholesterol by 18%, serum LDL cholesterol by 25%, serum triglycerides by 11%, and increased serum HDL cholesterol by 5%. At 8-year follow-up of 3,514 patients aged 65 to 75 years at study entry, compared with placebo, pravastatin significantly lowered all-cause mortality by 21%, death from CAD by 24%, fatal and nonfatal MI by 26%, death from cardiovascular disease by 26%, need for coronary artery bypass graft surgery by 26%, and need for coronary angioplasty by 34% [24]. Treatment of 1,000 patients for 6 years with pravastatin prevented 30 deaths, 28 nonfatal MIs, 9 nonfatal strokes, 23 episodes of coronary artery bypass surgery, 20 episodes of coronary angioplasty, and 82 hospital admissions for unstable angina [23]. The absolute benefits of treatment with pravastatin were greater in groups at higher absolute risk for a major coronary event such as patients aged 65 to 75 years, those with low serum HDL cholesterol levels, and those with a history of diabetes mellitus or smoking [24].

The Heart Protection Study randomized 20,536 men and women with prior MI (8,510 patients), other CAD (4,876 patients), and no CAD (7,150 patients) and a serum total cholesterol level of 135 mg/dL or higher to simvastatin 40 mg daily or to placebo [25]. Of the 7,150 patients without CAD, 25% had cerebrovascular disease, 38% had PAD, 56% had diabetes, and 3% had only treated hypertension without atherosclerotic vascular disease or diabetes. At 5-year follow-up, compared to 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% [25]. These significant reductions in mortality and in cardiovascular events occurred regardless of initial levels of serum lipids, age, or gender. Five years of simvastatin treatment prevented MI, stroke, and revascularization in 70 to 100 patients per 1,000 treated patients [25].

In the Heart Protection Study, 3,500 patients had initial serum LDL cholesterol levels less than 100 mg/dL. Decrease of serum LDL cholesterol from 97 mg/dL to 65 mg/dL by simvastatin in these patients who would not be treated according to National Cholesterol Education Program (NCEP) III guidelines [26] caused a similar decrease in risk as did treating patients with higher serum LDL cholesterol levels [25]. The Heart Protection Study Investigators recommended treating patients at high risk for cardiovascular events with statins, regardless of the initial levels of serum lipids, age, or gender [25].

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study randomized 5,804 men and women 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 [27]. Compared with placebo, pravastatin lowered 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 CAD death, nonfatal MI, or stroke was significantly reduced 15% by pravastatin compared with placebo [27]. CAD death or nonfatal MI was significantly reduced 19% by pravastatin [27]. Risk reduction on pravastatin therapy was unrelated to baseline serum LDL cholesterol but showed a significant interaction with baseline serum HDL cholesterol [28].

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, 3,086 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 placebo 24 to 96 hours after hospitalization for 16 weeks [29]. 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 reduced death, nonfatal MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization by 16% and stroke by 50% [29].

Sixty-nine patients with intermittent claudication due to PAD and hypercholesterolemia were randomized to simvastatin 40 mg daily or placebo [30]. 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 [30].

In a study of 354 patients 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 [31]. In another study of 86 patients 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 [32].

In the Lipid Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes (ASCOT-LLA) trial, 10, 305 patients with hypertension and at least 3 other cardiovascular risk factors with no history of CAD and a mean serum LDL cholesterol of 133 mg/dL were randomized to atorvastatin 10 mg daily or to placebo [33]. At 3.3- year follow-up, the serum LDL cholesterol was 90 mg/dL in patients treated with atorvastatin. At 3.3-year follow-up, compared with placebo, atorvastatin significantly lowered the incidence of fatal CAD and nonfatal MI by 34% in patients aged 60 years and younger and by 36% in patients older than 60 years [33]. Atorvastatin also significantly decreased fatal and nonfatal stroke by 27% [33].

In the Reversal of Atherosclerosis With Aggressive Lipid Lowering (REVERSAL) study, intravascular ultrasound was used to measure progression of atherosclerosis in 502 patients with CAD randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily [34]. The serum LDL cholesterol was reduced 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 had progression of coronary atherosclerosis [34].

In 4,162 patients hospitalized for an acute coronary syndrome (29% with unstable angina 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 [35]. At 2-year follow-up, the primary end point of death from any cause, MI, documented unstable angina 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% decrease in favor of atorvastatin [35].

In the Collaborative Atorvastatin Diabetes Study, 2, 838 patients with diabetes, no cardiovascular disease, and serum LDL cholesterol less than 160 mg/dL were randomized to atorvastatin 10 mg daily or placebo [36]. At 3.9-year median follow-up, compared with placebo, atorvastatin significantly decreased time to first occurrence of acute CAD events, coronary revascularization, or stroke by 37%, acute coronary events by 36%, and stroke by 48% [36].

In the Treating to New Targets (TNT) study of 10, 001 patients with stable CAD and a serum LDL cholesterol level less than 130 mg/dL, the effect of atorvastatin 10 mg daily versus 80 mg daily was investigated in a randomized, double-blind trial [37]. 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 the primary endpoint of a first major cardiovascular event was significantly lowered 22% by atorvastatin 80 mg daily [37].

In the Study Assessing Goals in the Elderly (SAGE), 893 ambulatory CAD patients with at least 1 episode of myocardial ischemia lasting at least 3 minutes during 48-hour ambulatory electrocardiographic screening were randomized to atorvastatin 80 mg daily or to pravastatin 40 mg daily and followed for 12 months [38]. Total duration of myocardial ischemia detected by 48-hour ambulatory electrocardiograms at month 3 and at month 12 after randomization was significantly decreased by both atorvastatin and pravastatin with no significant difference between the 2 treatment groups. Compared with pravastatin, atorvastatin significantly lowered serum LDL cholesterol levels, insignificantly decreased major acute cardiovascular events by 22%, and significantly reduced all-cause mortality by 67% [38].

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, 4,731 patients who had a stroke or transient ischemic attack within 1 to 6 months prior to study entry, serum LDL cholesterol of 100 to 190 mg/dL, and no CAD were randomized to atorvastatin 80 mg daily or placebo. [39] The mean LDL cholesterol was 73 mg/dL in patients on atorvastatin and 129 mg/dL in patients on placebo. At 4.9-year median follow-up, atorvastatin significantly lowered the incidence of new stroke by 16% and of major cardiovascular events by 20% [39].

In the Justification for the Use of Statins in Prevention : an Intervention Trial evaluating Rosuvastatin (JUPITER), 17,082 apparently healthy individuals with a serum LDL cholesterol of less than 130 mg/dL and high-sensitivity C-reactive protein levels of 2.0 mg/L or higher were randomized to rosuvastatin 20 mg daily or placebo [40]. At 1.9-year median follow-up, rosuvastatin significantly decreased serum LDL cholesterol levels by 50%, high-sensitivity C-reactive protein levels by 37%, and the primary end point of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes by 44% [40].

A meta-analysis was performed in 14 randomized trials of statins in 18,686 diabetics [41]. After 5 years, 42 fewer diabetics had major cardiovascular events per 1,000 randomized to statins [41].

A meta-analysis was performed in 26 randomized trials of statins in 170, 000 individuals [42]. The reduction in major cardiovascular events per 1.0 mmol/L reduction in serum LDL cholesterol was 22% in persons aged 65 years and younger, 22% in persons aged 66 to 75 years, and 16% in persons older than 75 years [42].

A meta-analysis was also performed in 9 randomized trials of statins for secondary prevention in 19, 569 patients [43]. Over 5 years, statins lowered all-cause mortality, CAD mortality 30%, nonfatal MI 26%, need for revascularization 30%, and stroke 25%. The estimated number needed to treat to save 1 life was 28 [43].

In 5,518 type 2 diabetics treated with simvastatin, patients were randomized to receive either masked fenofibrate or placebo [44]. At 4.7-year mean follow-up, the combination of fenofibrate plus simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke compared with simvastatin plus placebo [44].

In 9,795 type 2 diabetics, patients were randomized to treatment with fenofibrate or placebo [45]. At 5-year follow-up, the primary outcome of coronary events was not lowered by fenofibrate [45].

A study was performed in 15,067 patients at high cardiovascular risk who were randomized to atorvastatin plus the cholesteryl ester transfer protein (CETP) inhibtor torcetrapib or to atorvastatin alone [46] Torcetrapib increased serum HDL cholesterol 72% and decreased serum LDL cholesterol 25%. At 1-year follow-up, the trial was stopped because torcetrapib significantly increased cardiovascular events 25% and significantly increased all-cause mortality 58% [46].

A study was performed in 15,871 patients with a recent acute coronary syndrome who were randomized to the CTEP inhibitor dalcetrapib or placebo [47]. 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 CAD death, nonfatal MI, ischemic stroke, unstable angina pectoris, or cardiac arrest with resuscitation by 4% [47].

Among 3,414 patients 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, 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 [48]. In this study, patients treated with niacin had a 67% nonsignificant increase in ischemic stroke or stroke of uncertain origin [48].

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 laropriprant 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 decrease the primary outcome of major vascular events but increased 31 serious adverse events per 1,000 niacin-treated patients.

Observational Studies

In an observational prospective study of 488 men and 922 women with prior MI and a serum LDL cholesterol of 125 mg/dL or higher, 48% of persons were treated with statins [49-51]. At 3-year follow-up, compared to no treatment with statins, use of statins significantly reduced CAD death or nonfatal MI by 50%,[49] stroke by 60%,[50] and heart failure by 48% [51].

The lower the serum LDL cholesterol in patients treated with statins, the greater was the reduction in new coronary events [49]. The

lower the serum LDL cholesterol in patients treated with statins, the greater was the reduction in new stroke [50].

In an observational prospective study of 1,410 patients with prior MI and serum LDL cholesterol level of 125 mg/dL or higher, patients treated with aspirin had a 52% significant reduction in new coronary events at 3-year follow-up [52]. Patients treated with statins (49% of the patients) had a 54% significant reduction in new coronary events independent of the use of aspirin [52].

In an observational prospective study of 171 men and 358 women with prior MI, diabetes, and a serum LDL cholesterol of 125 mg/dL or higher, 53% of patients were treated with statins [53]. At 29-month follow-up, compared with no treatment with statins, use of statins significantly decreased CAD death or nonfatal MI by 37% and stroke by 47% [53].

In an observational prospective study of 264 men and 396 women with symptomatic PAD and a serum LDL cholesterol of 125 mg/dL or higher, 48% of patients were treated with statins [54]. At 39-month follow-up, compared with no treatment with statins, use of statins significantly reduced CAD death or nonfatal MI by 52% in patients with prior MI and by 59% in patients with no prior MI [54].

In a study of 551 patients with heart failure and an abnormal left ventricular ejection fraction due to ischemic or nonischemic heart disease, 45% of the patients were treated with statins [55]. At 1-year follow-up, the use of statins was associated with a significant 59% lower mortality [55].

In a study of 180 patients with mild valvular aortic stenosis, 62 patients (34%) were treated with statins [56]. At 33-month follow-up, use of statins was associated with a significant reduction in progression of aortic stenosis [56].

In a study of 174 patients with mild to moderate aortic stenosis, 57 patients (33%) were treated with statins [57]. At 21-month follow-up, patients treated with statins had less progression of aortic stenosis [57]. In a community-based study of 156 patients with aortic stenosis, 38 patients (24%) were treated with statins.[58]At 3.7-year follow-up, patients treated with statins had slower progression of aortic stenosis [58].

These observational data were confirmed by 1 prospective trial using rosuvastatin [59]. However, 2 prospective trials (1 using atorvastatin and 1 using simvastatin plus ezetimibe) did not confirm these data [60,61]. 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 CAD, other atherosclerotic vascular disease, or diabetes, which will benefit from treatment with statins.

In a study of 551 patients with heart failure and an abnormal left ventricular ejection fraction due to ischemic or nonischemic heart disease, 45% of the patients were treated with statins [55]. At 1-year follow-up, use of statins was associated with a significant 59% lowering of mortality [55]. In 54, 960 Medicare patients hospitalized for heart failure, use of statins caused a significant 20% lowering of 1-year mortality and a significant 18% lowering of 3-year mortality [62]. 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 [63].

In a prospective, open-label blinded end-points trial of 507 patients with CAD in the Effect of Rosuvastatin on Intravascular Ultrasound –Derived Coronary Atheroma Burden (ASTEROID) trial, rosuvastatin 40 mg daily for 2 years lowered serum LDL cholesterol 53%, increased serum HDL cholesterol 15%, and reduced serum triglycerides 20% [64]. Intravascular ultrasound showed at 2-year follow-up significant regression of atherosclerosis for all 3 prespecified intravascular ultrasound measures of disease burden [64]. 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 caused regression of CAD by decreasing percent diameter stenosis and improving minimum lumen diameter as measured by quantitative coronary angiography [65].

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 [66]. Significant regression of coronary plaque volume occurred in both treatment groups with no significant difference between the 2 statins.

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 lowering of recurrence of life-threatening ventricular arrhythmias from 57% to 22% [67]. The use of lipid-lowering drugs in 83 of 362 patients with CAD treated with an ICD for ventricular tachycardia/ventricular fibrillation significantly lowered recurrence of ventricular tachycardia/ventricular fibrillation by 60% [68]. The use of statins in 154 of 281 patients with CAD and ventricular arrhythmias treated with an ICD was associated with a significant lowering of recurrence of ventricular arrhythmias from 50% to 30% [69].

Statins significantly decreased death or ventricular tachycardia or ventricular fibrillation by 35% in patients with an ICD in the Multicenter Automatic Defibrillator Implantation trial (MADIT)-II [70]. The use of statins in 402 of 965 patients treated with an ICD was significantly associated with a 42% lowering of all-cause mortality [71]. The use of statins in 121 of 209 patients 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% lowering of mortality [72]. The use of statins in 58% of 209 patients with heart failure treated with combined cardiac resynchronization-I CD therapy, in 49% of 320 patients with heart failure treated with an ICD significantly reduced appropriate ICD shocks 65%, and significantly reduced time to mortality 82% [73]. At 1,243 days follow-up of 549 patients with heart failure treated with an ICD, use of statins significantly decreased appropriate ICD shocks 46%, inappropriate ICD shocks 48%, and time to all-cause mortality 68% [74]. In the MADIT-Cardiac Resynchronization Therapy trial, 499 of 821 patients (61%) with nonischemic cardiomyopathy were treated with statins [75]. At 4-year follow-up, the cumulative probability of fast ventricular tachycardia/ventricular fibrillation or death was significantly lowered from 19% in nonstatin users to 11% for statin users [75].

In 100 patients undergoing noncardiac vascular surgery, the incidence of cardiac death, nonfatal MI, stroke, or unstable angina pectoris at 6-month follow-up was significantly less in 50 patients treated with atorvastatin than in 50 patients treated with placebo (8% versus 26%, respectively) [76]. 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 [77]. In this study, statins significantly reduced all-cause mortality by 60% [77].

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%) [78]. Perioperative cardiovascular complications of death, MI, myocardial ischemia, 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 [79]. In a study of 577 patients 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 MI or death during 2-year follow-up by 57% [80].

Of 130 patients with an AAA not treated surgically, 58% of patients were treated with statins [81]. 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 and 4.5 cm at baseline and 5.3 cm at 24-month follow-up in patients not treated with statins. 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 [81].

Of 449 patients with severe carotid arterial disease who did not undergo revascularization, 298 (66%) were treated with statins [82]. 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 significantly reduced the time to development of new stroke or new MI or death by 87% [82].

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 [83]. Three hundred and five patients were not treated with statins during the first year of being seen in an academic cardiology practice but were subsequently treated with statins [84]. Mean follow-up was 65 months before statin use and 66 months after statin use. Statin use significantly lowered the incidence of MI from 10% to 4%, the incidence of percutaneous coronary intervention from 22% to 13%, and the incidence of coronary artery bypass graft surgery from 18% to 7% [84].

Underutilization of Lipid-Lowering Drugs

Despite the efficacy of statins in decreasing cardiovascular morbidity and mortality, these drugs have been underutilized [85-87]. In 335 patients with prior MI and a serum LDL cholesterol greater than 125 mg/dL admitted from a hospital to a nursing home, 17 patients (5%) were being treated with a lipid-lowering drug.[86] In persons living in the community with an increased serum LDL cholesterol followed at the Mount Sinai Medical Center Geriatrics Clinic, 80 of 159 patients (50%) with prior MI, 28 of 65 patients (43%) with prior stroke, and 19 of 46 patients (41%) with PAD were being treated with lipid-lowering drugs [86]. Of 23,013 patients with an acute MI 24% were receiving a statin at hospital discharge. [88]

However, a systematic educational program has been shown to improve utilization of lipid-lowering drugs [88,89]. In patients seen at a university hospital with CAD and dyslipidemia, 58 of 112 patients (52%) were treated with lipid-lowering drugs prior to a systematic educational program and 152 of 173 patients (88%) after a systematic educational program [88]. In patients with hypercholesterolemia seen in an academic nursing home, use of a systematic educational program significantly improved tuse of lipid-lowering drugs in patients with CAD from 29% to 70% in 63 patients, in patients with PAD from 28% to 79% in 19 patients, in patients with stroke from 24% to 64% in 44 patients, and in diabetics from 26% to 67% in 52 patients [89].

Treatment Guidelines

Lifestyle measures are important in treating dyslipidemia. The patient 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. Moderate intensity exercise is recommended for 30 to 60 minutes daily. Smoking should be stopped, hypertension treated, and diabetes controlled.

The NCEP III guidelines recommended that the serum LDL cholesterol be lowered to less than 100 mg/dL in patients with CAD, other clinical forms of atherosclerotic vascular disease, diabetes, and with 2+ risk factors that confer a 10-year risk for CAD greater than 20%, regardless of age [26]. Patients with 2+ risk factors that confer a 10-year risk for CAD of 10% to 20% should have their serum LDL cholesterol lowered to less than 130 mg/dL [26]. These guidelines needed to be modified because of data published since these guidelines were recommended [90].

The updated NECP III guidelines recommend that in very high-risk patients, a serum LDL cholesterol level of less than 70 mg/dL is a reasonable clinical strategy [91]. For moderately high-risk patients (2 or more risk factors and a 10-year risk for CAD of 10% to 20%), the serum LDL cholesterol should be lowered to less than 100 mg/dL [91]. When LDL cholesterol-lowering drug therapy is used to treat high-risk or moderately high-risk patients, the serum LDL cholesterol should be reduced at least 30% to 40% [91]. Patients without cardiovascular disease with 0 to 1 risk factors should have a serum LDL cholesterol of less than 160 mg/DL. The author concurs with these updated guidelines. The author would not treat patients with life-threatening illness causing limited life expectancy or advanced dementia with lipid-lowering therapy. The NECP IV guidelines should soon be published.

Addition of other lipid-lowering drugs to statin therapy has not been shown to further lower 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 [92]. Lower-risk diabetics should have their serum LDL cholesterol lowered to less than 100 mg/dL. Combination therapy of a statin with either a fibrate or niacin has not been demonstrated to provide additional cardiovascular benefit above statin therapy alone and is not recommended [92]. Hypertriglyceridemia should be treated with dietary and lifestyle changes. Severe hypertriglyceridemia should be treated with drug therapy to reduce the risk of acute pancreatitis.

Adverse Effects

Asymptomatic increases in concentrations of liver transaminases occur with all statins but are not associated with an increased risk of liver disease [93]. 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 [25]. 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 [25]. Drug interactions with statins are discussed elsewhere [93].

Conclusions

Numerous randomized, double-blind, placebo-controlled studies and observational studies have demonstrated that statins reduce mortality and major cardiovascular events in patients with hypercholesterolemia. The Heart Protection Study showed that statins reduced mortality and major cardiovascular events in high-risk patients 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 patients, a serum LDL cholesterol level of <70 mg/dL is a reasonable clinical strategy. For moderately high-risk patients (2 or more risk factors and a 10-year risk for CAD of 10% to 20%), the serum LDL cholesterol should be lowered to <100 mg/dL. When LDL cholesterol-lowering drug therapy is used to treat high-risk or moderately high-risk patients, the serum LDL cholesterol should be lowered at least 30% to 40%. Patients without cardiovascular disease with 0 to 1 risk factors should have serum LDL cholesterol of less than 160 mg/DL. All diabetics should be treated with statins. Addition of other lipid-lowering drugs to statin therapy has not been shown to further lower cardiovascular events and mortality. Future research should investigate how low the serum LDL cholesterol should be lowered in high-risk persons, newer drugs that lower serum LDL cholesterol, and the role of newer potent drugs, which increase serum HDL cholesterol in the treatment of high-risk persons with dyslipidemia.

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