

Lipid Management in the Geriatric Patient

Ajith P. Nair, MD, Bruce Darrow, MD, PhD*

KEYWORDS

- Geriatric • Elderly • Cholesterol • Lipids
- Statins • Fibrates • Niacin • Ezetimibe

In the United States, the proportion of the population older than 65 years will increase from 12.4% in 2000 to 19.6% in 2030, and the number of persons older than 80 years will increase from approximately 9.3 million in 2000 to an estimated 19.5 million in 2030.¹ As the population ages, the number of persons at risk for adverse cardiovascular events will increase. Although octogenarians represent only 5% of the United States population, they account for 20% of all hospitalizations for myocardial infarctions (MI) and 30% of all MI-related hospital deaths.² Prevention of cardiovascular disease and modification of risk factors in the elderly population thus demands significant attention. Paradoxically, despite their increased risk of cardiac events, elderly patients are less likely to receive appropriate therapy.³ Reluctance in treating geriatric patients classically stems from concerns regarding the ultimate benefits of therapy when weighed against the side effects. In a Canadian study of 396,077 patients older than 66 years who had a history of cardiovascular disease or diabetes, only 19.1% were treated with statins. Furthermore, the adjusted probabilities of statin prescription declined with increasing cardiovascular risk; rates were 37.7%, 26.7%, and 23.4%, respectively, in low-, intermediate-, and high- risk patients between the ages of 66 and 74 years.⁴ Although the relative risk reduction (RRR) of cholesterol-lowering therapy may be equivalent among the young and old, the absolute magnitude of risk reduction (ARR), or number of cardiovascular events prevented, is greater in elderly patients.⁵ Treatment for dyslipidemia therefore is indicated in elderly patients and should include consideration of high-dose therapy as well as combination therapy for maximum risk reduction.^{6,7}

CHOLESTEROL PROFILES AND CARDIOVASCULAR RISK IN ELDERLY PATIENTS

Although some studies failed to detect an association between high serum cholesterol levels and cardiovascular risk in elderly patients,^{8,9} other prospective studies reported a significant correlation between coronary heart disease (CHD) mortality and both total cholesterol and low-density lipoprotein (LDL) cholesterol levels.^{10,11} In the studies that

Cardiovascular Institute, Mount Sinai Medical Center, One Gustave L. Levy Place, NY 10029, USA

* Corresponding author.

E-mail address: bruce.darrow@mountsinai.org (B. Darrow).

Endocrinol Metab Clin N Am 38 (2009) 185–206

doi:10.1016/j.ecl.2008.11.003

0889-8529/08/\$ – see front matter © 2009 Elsevier Inc. All rights reserved.

endo.theclinics.com

found an association between lower cholesterol levels and increased cardiovascular mortality,^{12,13} there may be an element of reverse epidemiology.¹⁴ Chronic illnesses, including end-stage renal and liver diseases and cancer, often are associated with poor nutritional status, low cholesterol profiles, and higher overall mortality rates. Congestive heart failure, often caused by CHD, can lead to debilitation and lower cholesterol levels. Death results from cardiovascular causes, thus eliminating the beneficial association between low cholesterol levels and cardiovascular mortality. After adjusting for overall nutritional status by using other measures including albumin and ferritin, total cholesterol and LDL cholesterol have, in fact, been demonstrated to have the same correlation to cardiovascular risk as seen in younger patients.

Cholesterol profiles vary with increasing age, and declines in total cholesterol and LDL cholesterol have been noted after reaching a plateau between the ages of 50 and 60 years in men and 60 and 70 years in women.^{15,16} In cross-sectional studies this decline may be caused by depletion of individuals who have higher cholesterol levels because of earlier cardiovascular-related mortality. In prospective studies in the elderly, this decline in cholesterol may be secondary to decreasing weight.¹⁷ LDL cholesterol increases more rapidly in men than in women after the age of 20. By age 55 to 60 years, however women may have concentrations that exceed those in men because of an accelerated increase after menopause. High-density lipoprotein (HDL) cholesterol decreases in men after puberty and remains lower than in women at all age groups.¹⁸ In the Systolic Hypertension in the Elderly Program (4763 persons; mean age, 72 years), the mean baseline total cholesterol level was 236 mg/dL, the mean HDL cholesterol level was 54 mg/dL; and the LDL cholesterol level averaged 154 mg/dL.¹¹ Over a follow-up of 4.5 years, higher baseline total, non-HDL, and LDL cholesterol levels and the ratios of total cholesterol, non-HDL cholesterol, and LDL cholesterol to HDL cholesterol were associated with a 30% to 35% higher rate of CHD events. Likewise, Framingham data established that a 1% increase in total cholesterol produced a 2% increase in the incidence of CHD, and this relation has been demonstrated to apply to persons age 60 to 70 years.¹⁹

Other studies have demonstrated that there is a U-shaped relationship between cholesterol and total mortality in the elderly. In a study of 4066 elderly patients, persons with the lowest total cholesterol levels (≤ 160 mg/dL) had the highest rate of death from coronary artery disease (CAD), whereas those who had elevated total cholesterol levels seemed to have a lower risk for death from CHD.¹⁰ After adjustment for markers of poor health (eg, low serum iron and albumin levels), elevated total cholesterol remained predictive of increased CHD death. It is unclear whether chronic illness has a direct pathophysiologic effect (eg, through procoagulant and proinflammatory mediators) on CHD or if a lifelong burden of atherosclerotic disease and its consequences, such as congestive heart failure, results in frailty and subsequent low cholesterol levels at the terminal stages of life. Other markers, such as apolipoprotein A1, have been shown to be prognostic markers for ischemic heart disease but may not improve prediction significantly over HDL cholesterol.²⁰

TREATMENT OF ELDERLY PATIENTS WHO HAVE DYSLIPIDEMIA

Data supporting the use of statins for the prevention of cardiovascular events in the elderly stem from the results of several subgroup analyses of large, randomized trials. Despite the potential for error in subgroup analysis,^{21,22} data provided by these studies have been consistent in demonstrating the benefit of lipid-lowering therapy in the elderly.

Multiple trials have demonstrated that the benefits of statin therapy for secondary prevention of cardiac events in elderly patients are equivalent to or greater than the

benefits in younger patients.²³ Based on this finding, the National Cholesterol Education Program (NCEP) issued an update to the Adult Treatment Panel III (ATP III) guidelines recommending that elderly patients (> 65 years) at higher risk receive lipid-lowering therapy.²⁴ Although other lipid-lowering therapies also have proven beneficial in elderly patients, treatment with 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) have demonstrated efficacy in both the secondary and primary prevention of cardiovascular events in elderly patients.

Secondary Prevention of Coronary Heart Disease in Elderly Patients

Subgroup analyses of the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) trial, the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, and the Heart Protection Study (HPS) have demonstrated that the benefits of statins in elderly patients are equivalent to or greater than the benefits seen in the overall study cohorts (**Table 1**).

Scandinavian simvastatin survival study

The 4S trial randomly assigned 4444 patients between the ages of 35 and 70 years who had moderate hypercholesterolemia and a history of MI or angina pectoris to simvastatin or placebo. Treatment with simvastatin resulted in a 30% reduction in the risk of death from all causes ($P < .0003$) and a 42% reduction in CHD death ($P < .0001$) over a median follow-up period of 5.4 years.²⁵ Patients enrolled in this trial had total serum cholesterol levels between 213 and 309 mg/dL and initially were assigned randomly to simvastatin, 20 mg/d, or placebo. The simvastatin dose was increased to 40 mg/d in patients whose total cholesterol remained above 201 mg/dL.

The trial included 1021 patients older than 65 years at study enrollment. In post hoc analysis, patients were divided into two groups, 65 years of age or older (mean age, 67 years) and younger than 65 years (mean age, 56 years).²⁶ The changes observed in each of the subpopulations were similar at 6 weeks and remained stable over the entire study period. All-cause mortality was significantly reduced in the patients in the simvastatin group aged 65 years or older, with a relative risk (RR) of 0.66 (95% confidence interval [CI], 0.48–0.90; $P < .009$). This 34% RRR was greater than the 28% RRR in patients younger than 65 years (RR, 0.72; 95% CI, 0.57–0.91; $P < .007$). The RR for CHD mortality in the simvastatin group was reduced equivalently by 43% in patients aged 65 years and older and by 42% in patients younger than 65 years. Despite similarities in RRR, the ARR in the group aged 65 years and older was more than twice that in group under 65 years of age for both all-cause and CHD mortality because of the substantial increase in the all-cause mortality rates among patients more than 65 years old (number needed to treat [NNT], 16 for patients age 65 years or older, versus 40 for patients younger than 65 years).

Heart protection study

The HPS randomly allocated 20,536 United Kingdom adults (age 65–79 years) who had a history of coronary disease, other occlusive arterial disease, diabetes, or high-risk hypertension to simvastatin, 40 mg/d, or placebo over an average 5-year treatment period.²⁷ The study's primary outcomes were overall mortality and fatal or nonfatal vascular events. The average compliance with simvastatin was 85%, and the average non-study statin use in the placebo arm was 17%. Approximately 28% of patients studied were age 70 years and older. Monotherapy with simvastatin, 40 mg/d, reduced LDL cholesterol by approximately 58 mg/dL from a mean of 131 mg/dL at baseline. All-cause mortality was significantly reduced by 1.8% in the 10,269 patients in the simvastatin group versus the 10,267 patients in the placebo

Study	Patients	Statin	End Point	Duration	Description	Results ^a
4S ²⁶	4444 total; 1021 were age ≥ 65 years at the start of study; post hoc assessment of trial	Simvastatin, 20 mg or 40 mg, versus placebo	All-cause mortality, cardiovascular mortality	5.4 years	Patients had total cholesterol levels between 213 and 309 mg/dL and triglyceride levels ≤ 2.5 mmol/L	Simvastatin produced a 34% RRR in all-cause mortality (<i>P</i> = .009) and 43% RRR in CHD mortality (<i>P</i> = .003). There was a greater ARR in elderly patients (NNT, 15 versus 67)
Heart Protection Study ²⁷	20,536 adults in the United Kingdom; 28% age > 70 years	Simvastatin, 40 mg, versus placebo	Overall mortality and fatal/nonfatal vascular events	5 years	Subgroup analysis; mean LDL 131.4 mg/dL at baseline	There was an ARR of 9.2% and a RRR of 28% for major vascular events (NNT, 11)
CARE trial ³¹	4159 US and Canadian patients who had average cholesterol levels (≤ 240 mg/dL); 1283 age 65–75 years	Pravastatin, 40 mg, versus placebo	Coronary death, recurrent MI, need for revascularization, stroke	5 years	Subset analysis of the CARE trial: patients who had baseline cholesterol levels of 155–271 mg/dL	Pravachol treatment led to a 32% RRR (NNT, 11) in major coronary events
LIPID trial ³³	9014 patients post-MI or who had unstable angina from 87 centers in New Zealand and Australia; 3514 age 65–75 years	Pravastatin, 40 mg, versus placebo	All-cause mortality, CHD death and non-fatal MI, stroke	6 years	Subgroup analysis; baseline cholesterol levels 155–271 mg/dL	RRR in mortality by 21%, death from CHD by 24%, CHD death or nonfatal MI by 22%, and MI by 26%; stroke reduction NS
Prospective Pravastatin Pooling Project ³⁴	Pooled analysis of 19,768 patients from the WOSCOPS, CARE, and LIPID trials; 4843 age 65–75 years	Pravastatin versus placebo	Coronary death or nonfatal MI	5–6 years	Baseline cholesterol levels between 177–297 mg/dL, LDL-C between 125–212 mg/dL	RRR in primary end point of 26%

Abbreviations: 4S, Scandinavian simvastatin survival study; ARR, absolute risk reduction; CARE, cholesterol and recurrent events trial; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; LIPID, long-term intervention with pravastatin in ischemic disease study group; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction; WOSCOPS, west of Scotland coronary prevention study.

^a All reductions are statistically significant (*P* < .05).

group because of a significant reduction in the coronary death rate. Overall, therapy with simvastatin, 40 mg/d, led to a 25% reduction in the rates of MI, stroke, and revascularization. After adjusting for the rate of non-adherence in the treatment group and for statin use in the placebo group, statin use was estimated to reduce the rates of these events by about a third.

Among all patients, major vascular events occurred in 19.8% in the simvastatin group versus 25.2% in the placebo group ($P = .002$).²⁸ In older patients, the respective rates for major vascular events in the simvastatin versus placebo groups were 20.9% versus 27.2% in patients between the ages of 65 and 70 years and 23.6% versus 28.7% in patients older than 70 years (NNT, 16 and 20, respectively). The stroke rate also was reduced in elderly patients.²⁹ Over 5 years, in the patients between the ages of 65 and 70 years, strokes occurred in 4.5% of the patients allocated to simvastatin and in 6.3% of those allocated to placebo (NNT, 56). In patients older than 70 years, the rate of stroke was 5.8% in the simvastatin group versus 8.2% in the placebo group (NNT, 42).

Side effects from simvastatin were minimal. The rates of new primary cancer were similar in the simvastatin and placebo groups (7.9% versus 7.8%; RR, 1.0; 95% CI, 0.91–1.11). There was no significant difference in cancer deaths. Furthermore, there was no significant difference between the groups in treatment cessation because of elevated liver enzymes. Unexplained muscle pain or weakness was reported by similar percentages in each group (32.9% of the simvastatin-allocated versus 33.2% of the placebo-allocated participants).

Cholesterol and recurrent events trial

The CARE trial randomly assigned 4159 patients recruited from 80 United States and Canadian medical centers who had a history of MI and plasma total cholesterol levels less than 240 mg/dL to pravastatin, 40 mg/d, or placebo.³⁰ Over a mean follow-up of 5 years, pravastatin led to a 24% ($P = .003$) reduction in the risk for coronary death or recurrent MI, a 26% ($P = .005$) reduction in the need for coronary bypass surgery, a 23% ($P = .01$) reduction in the need for coronary angioplasty, and a 31% reduction ($P = .01$) in the frequency of strokes. A subset analysis of 1283 patients age 65 to 75 years demonstrated greater RRR and ARR in major coronary events and stroke.³¹ Major coronary events occurred in 28.1% of patients in the placebo arm and in 19.7% of patients in the pravastatin arm, leading to an RRR of 32% and a NNT of 11 to prevent a major coronary event. In older patients in the pravastatin group, coronary death decreased from 7.3% to 4.5% (NNT, 33), and the incidence of stroke decreased from 7.3% to 4.4% (absolute reduction, 2.9%; 95% CI, 0.3–4.5%; NNT, 33).

Long-term intervention with pravastatin in ischemic disease trial

A similar subgroup analysis from the LIPID trial, which randomly assigned 9014 patients age 31 to 75 years who had previous MI or unstable angina and baseline plasma cholesterol levels of 155 to 271 mg/dL to pravastatin, 40 mg/d, or placebo, was consistent with the results previously described.³² In this trial, patients were followed for a 6-year period, and the prespecified primary outcome was death from CHD. Secondary outcomes included death from any cause, death from CHD or nonfatal MI, nonhemorrhagic stroke, coronary revascularization, and duration of hospital stay. Of the total number of enrolled patients, 3514 patients between the ages of 65 and 75 years were selected. Compared to younger patients in the placebo arm, older patients had significant differences (all $P < .001$) in the rates of death (20.6% versus 9.8%), MI (11.4% versus 9.5%), unstable angina (26.7% versus 23.2%), and stroke (6.7% versus 3.1%).³³ Older patients randomly assigned to pravastatin had lower

rates of overall mortality (16.5% versus 20.6%; $P = .003$; NNT, 22) and CHD or nonfatal MI (15.5% versus 19.7%; $P = .002$; NNT, 21). The authors concluded that for every 1000 elderly patients treated over 6 years, pravastatin prevented 45 deaths, 33 MIs, 32 unstable angina events, 34 coronary revascularization procedures, and 133 major cardiovascular events, compared with 22 deaths and 107 major cardiovascular events per 1000 younger patients.

Pooled pravastatin trials

In pooled analysis of three trials using pravastatin, 40 mg/d, a total of 19,768 patients were evaluated via a prospectively defined protocol initiated after the start of each of the three individual trials.³⁴ These trials were the West of Scotland Coronary Prevention Study (WOSCOPS)³⁵ and the CARE³⁰ and LIPID³² studies reviewed previously. The primary end points of coronary death or nonfatal MI were reduced significantly in younger (age < 65 years) and older (age \geq 65 years) patients. Among the 4843 patients age 65 to 75 years, the RRR in the primary end point was 26% (95% CI, 14%–35%; $P < .001$). The RRR in older patients did not differ from that seen in younger patients (21% RRR in patients aged 55–64 years and 32% RRR in patients aged < 55 years).

The CARE and LIPID studies excluded patients over 75 years of age, the 4S trial included only those less than 70 years old, and the HPS included persons younger than 80 years. Subgroup analysis of the aforementioned trials included only patients age 65 to 75 years. In the Intermountain Heart Collaborative Study, 7220 consecutive patients who had angiographically defined CAD (stenosis \geq 70%) were followed after hospital discharge, and therapy with statins was associated with significant mortality reduction across all age groups.³⁶ Overall mortality over a mean follow-up period of 3.3 ± 1.8 years was 16%. Mortality rates in patients age 80 years and older was 29.5% among patients not taking statins versus 8.5% among those taking statins (hazard ratio [HR] 0.50; $P = .036$; NNT, 5). In patients age 65 to 79 years, the rates were 18.7% without statins versus 6.0% with statins (HR 0.56; $P < .001$; NNT = 8); in those younger than 65 years the rates were 8.9% versus 3.1% (HR 0.70; $P = .097$; NNT, 18). Elderly patients were less likely than younger patients to receive statins (19.8% of patients age 80 years and older, 21.1% of patients age 65–79 years, 28% among patients < 65 years; $P < .0001$). Despite the limitations of a single-center, observational study with potential confounders, this study nonetheless demonstrated similar RRRs in elderly patients, especially those age 80 years or older.

In a meta-analysis of nine secondary interventional prevention trials with statins that included a total of 19,569 patients ranging in age from 65 to 82 years, all-cause mortality was 15.6% with statins compared with 18.7% with placebo (NNT, 30). The 5-year relative risk reduction was 22% (RR, 0.78; 95% CI, 0.65–0.89). CHD mortality was reduced by 30% (RR, 0.70; 95% CI, 0.53–0.83), nonfatal MI by 26% (RR, 0.74; 95% CI, 0.60–0.89), and stroke by 25% (RR, 0.75; CI 0.56–0.94).³⁷

Primary Prevention of Coronary Heart Disease in Elderly Patients

In patients who do not have a previous history of cardiovascular events, modification of risk factors for cardiovascular disease is essential, especially in patients at higher risk. The primary prevention of cardiovascular events in elderly patients also has been demonstrated through subgroup analysis of several large-scale statin trials and prospective cohort studies (**Table 2**).

Air force/Texas coronary atherosclerosis prevention study

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was the first large-scale study to evaluate the effects of a statin on the primary

Table 2
Primary prevention trials using statins in the elderly

Study	Patients	Statin	End Point	Duration	Description	Results ^a
AFCAPS/ TexCAPS ³⁸	6605 patients; 1416 age > 65 years	Lovastatin, 40 mg, versus placebo	Fatal/nonfatal MI, unstable angina, sudden cardiac death	5.2 years	Subgroup analysis; baseline triglyceride level was 221 mg/dL; mean LDL-C level was 150 mg/dL	37% RRR in primary end point apparent in men > 57 years and women > 62 years
CARDS ⁴⁰	2838 type 2 diabetic patients with LDL < 160 mg/dL and the presence of one other CVD risk factor; 1129 age 65–75 years	Atorvastatin, 10 mg, versus placebo	Acute CHD events, revascularization and strokes	3.9 years	Post hoc analysis comparing 1129 patients age 65–75 years with 1079 patients age < 65 years	ARR of 3.9% in older patients versus 2.7% in younger patients
Cardiovascular Health Study ⁴¹	5201 patients age > 65 years at study entry	General statin use	MI, stroke, CAD-related death	7.3 years	Cohort study	Statin use associated with decrease in CV events (HR, 0.44) and all-cause mortality (HR, 0.56)
PROSPER ^{b,42}	5804 men and women age 70–82 years with a history of or at risk for vascular disease; cholesterol levels 154–351 mg/dL	Pravachol, 40 mg, versus placebo	Primary outcome was combined end point of definite or suspected death from CHD, nonfatal MI, or fatal or nonfatal stroke	3.2 years	Randomized, placebo-controlled trial in elderly patients	Pravastatin reduced the risk of the primary end point by 15%; risk of CHD death was 24% lower; no difference in all-cause mortality; increase in new cancer diagnosis by 25%

Abbreviations: AFCAPS/TexCAPS, air force/Texas coronary atherosclerosis prevention study; ARR, absolute risk reduction; CAD, coronary artery disease; CARDS, collaborative atorvastatin diabetes study; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HR, hazards ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PROSPER, pravastatin in elderly individuals at risk of vascular disease; RRR, relative risk reduction.

^a All reductions are statistically significant ($P < .05$).

^b The PROSPER trial evaluated secondary prevention in patients who had vascular disease and primary prevention of events in those at risk for vascular disease.

prevention of cardiovascular events.³⁸ When compared with placebo, treatment with lovastatin (20 mg–40 mg) produced a 37% reduction ($P = .001$) in the risk for a first acute major coronary event (defined as fatal or nonfatal MI, unstable angina, or sudden cardiac death) over an average follow-up of 5.2 years. The event rate in the lovastatin group was 7 per 1000 patient years versus 11 per 1000 patient years in the placebo group. Of the 6605 patients studied, 1416 patients were older than 65 years. The event rate in the older cohort of patients was higher, and the RRR with lovastatin was similar in both men and women older than the median age.

Collaborative atorvastatin diabetes study

The Collaborative Atorvastatin Diabetes Study evaluated the use of atorvastatin, 10 mg/d, for the primary prevention of acute CHD events, coronary revascularization, and strokes in patients age 40 to 75 years who had type 2 diabetes, LDL cholesterol concentrations of less than 160 mg/dL, and one other risk factor for CVD (hypertension, retinopathy, microalbuminuria, macroalbuminuria, or active smoking).³⁹ A total of 2838 patients were enrolled in the randomized trial. A separate post hoc analysis compared 1129 patients age 65 to 75 years with 1709 younger patients.⁴⁰ The ARR in a first major cardiovascular event in older patients was 3.9% (38% RRR; $P = .001$; NNT, 21) versus 2.7% in younger patients (37% RRR; $P = .017$; NNT 33). There was no significant difference in ARR between the two groups ($P = .546$). There was no significant decrease in all-cause mortality in either group.

Cardiovascular health study

The Cardiovascular Health Study (CHS) was a prospective cohort study of risk factors for cardiovascular disease in men and women age 65 years and older at entry. Data from the CHS demonstrated the benefits of statins in the primary prevention of cardiovascular events. The CHS cohort consisted of 5201 patients. After the exclusion of patients who had a previous history of cardiovascular events and patients who did not receive cholesterol-lowering medications, 1914 subjects were evaluated.⁴¹ During a follow-up period of 7.3 years, there were 382 cardiovascular events that included MIs, strokes, and CAD-related death, and there were 362 total deaths.⁴¹ When compared with patients who did not use cholesterol-lowering agents, statin use was associated with decreased risk of cardiovascular events (multivariate HR, 0.44; 95% CI, 0.27–0.71) and all-cause mortality (HR, 0.56; 95% CI, 0.36–0.88). A subgroup of patients older than 74 years also demonstrated a benefit from statin use.

Pravastatin in elderly individuals at risk of vascular disease trial

The largest trial designed to evaluate the benefit of statin therapy in exclusively elderly patients was the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial. Unlike the aforementioned studies, the PROSPER trial evaluated the benefit of pravastatin in the primary prevention of CHD events and cerebrovascular events in elderly patients at risk for developing vascular disease and the secondary prevention of these events in elderly patients who had existing vascular disease.⁴² The trial randomly assigned 5804 men ($n = 2804$) and women ($n = 3000$) age 70 to 82 years with cholesterol levels ranging from 154 mg/dL to 351 mg/dL to pravastatin, 40 mg/d ($n = 2891$) or placebo ($n = 2913$). All patients had risk factors for or a history of vascular disease. The primary end point was a composite of coronary death, nonfatal MI, and fatal or nonfatal stroke. Treatment with pravastatin lowered LDL cholesterol levels by 34%. Over an average follow-up period of 3.2 years, the incidence of the primary end point in the pravastatin group was 14.1%, versus 16.2% in the placebo group (NNT, 48; HR, 0.85; 95% CI, 0.74–0.97; $P = .014$). The incidence of CHD death and nonfatal MI also was reduced from 12.2% to 10.1% (HR, 0.81; CI, 0.69–0.94; $P = .006$). The risk

of stroke was unaffected, although the 4.5% overall rate in the group was half the expected rate, thus decreasing the power to detect a difference. Despite a tendency toward greater benefit in patients who had a history of vascular disease, the RRR was similar in the primary and secondary arms of the trial.

Of note, there was a significant increase in the risk of new cancers in the treatment group (HR, 1.25; CI, 1.04–1.51; $P = .020$), which the authors concluded may have been a chance finding, given the results of meta-analysis that have failed to draw similar conclusions.⁴³ A meta-analysis including the 4S, CARE, LIPID, WOSCOPS, and AFCAPS trials evaluated the risk for cancer and determined that there was no difference in absolute risk for cancer between patients randomly assigned to statins and those taking the placebo. The estimated differences were 0.0% for all nonfatal cancers (95% CI, –0.8% to –0.8%) and –0.1% for all fatal cancers (95% CI, –0.7% to 0.4%).⁴³ Likewise, the PROSPER trial investigators conducted a meta-analysis of trials lasting more than 3 years and using pravastatin (WOSCOPS, CARE, LIPID, and PROSPER).⁴² The investigators found that the risk for cancer with pravastatin was not significantly higher than with placebo (HR, 1.06; 95% CI, 0.96–1.17).

Intensive Lipid Therapy in the Elderly

The benefit of intensive statin therapy in patients at high risk for vascular events has been proved in several trials.^{44–46} The apprehension about treating elderly patients with intensive statin therapy stems from concern regarding side effects and a question whether the benefit is similar to that in younger patients. Despite these concerns, analysis of several trials has supported the use of intensive statin therapy in high-risk elderly patients (**Table 3**).⁶

Myocardial ischemia reduction with acute cholesterol lowering trial

The Myocardial Ischemia Reduction with Acute Cholesterol Lowering trial randomly assigned 3086 patients to atorvastatin, 80 mg, or placebo between 24 and 96 hours after hospital admission for an acute coronary syndrome (ACS).⁴⁴ The primary end point was a combination of death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia requiring hospitalization. Atorvastatin was continued for 16 weeks, and treatment led to a reduction in LDL cholesterol from 124 mg/dL to 72 mg/dL. There was 15% RRR in the primary end point with atorvastatin and a greater than 50% reduction in the incidence of stroke.⁴⁷ In post hoc analysis, there was a 14% decrease in the primary end point among older patients, which was less than the 22% seen in younger patients ($P = .11$).⁴⁸ Both primary and secondary end points occurred more often in the elderly patients, however. The primary end point occurred in 12.4% and 21.7% of the younger and older placebo populations, respectively. Therefore, the ARR was similar in younger (2.9%) and older patients (2.25%). Older patients discontinued statin therapy more often than younger patients (5.3% versus 3.5%, respectively), and serious adverse events occurred in 1.2% of elderly patients.

Pravastatin or atorvastatin evaluation and infection therapy—thrombolysis in myocardial infarction 22 trial

The efficacy of pravastatin, 40 mg/d, versus atorvastatin, 80 mg/d, in preventing adverse CHD outcomes in patients presenting with ACS was evaluated in the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) trial.⁴⁵ Patients were assigned randomly to therapy within 10 days of presentation, and the primary end point was a composite of death from any cause, MI, unstable angina requiring hospitalization, revascularization at least 30 days after randomization, and stroke. Treatment with pravastatin reduced the mean LDL cholesterol level from 106 mg/dL to 95 mg/dL, whereas atorvastatin

Study	Patients	Statins	Endo Point	Duration	Description	Results ^a
MIRACL trial ⁴⁸	3086 patients who had ACS	Atorvastatin, 80 mg, versus placebo	Combined death, nonfatal acute MI, cardiac arrest with resuscitation, recurrent myocardial ischemia	16 weeks	Patients randomly assigned within 24–96 hours of ACS admission	ARR similar in old and young patients; 14% reduction in primary end point in older patients versus 22% in younger patients
PROVE-IT TIMI 22 trial ⁴⁹	4162 patients who had ACS; 624 age > 70 years	Atorvastatin, 80 mg, versus pravastatin 40 mg	Death, MI, and unstable angina	6 months	Substudy analysis; patients randomly assigned to therapy within 10 days of ACS presentation	Older patients with LDL < 70 mg/dL had an ARR of 8% and RRR of 40% compared with 2.3% and 26%, respectively, in younger patients
TNT trial ⁵⁰	10,001 patients who had stable CHD; 3809 age > 65 years	Atorvastatin, 80 mg, versus atorvastatin, 10 mg	CHD death, nonfatal MI, resuscitated cardiac arrest, stroke	4.9 years	Subgroup analysis	ARR of 2.3% and RRR of 19% in the high-intensity arm; NNT 34 in older patients versus 26 in younger patients
SAGE trial ⁵¹	893 patients age 65–85 years who had a history of CAD	Atorvastatin, 80 mg, versus pravastatin, 40 mg	Primary end point was absolute change in duration of ischemia as assessed by 48-hour ambulatory ECG; secondary MACE end points	12 months	Prospective, randomized, double-blind trial in older patients	Pravastatin and atorvastatin reduced the total duration of myocardial ischemia equally; 77% reduction in all-cause mortality with high-dose atorvastatin versus pravastatin

Abbreviations: ACS, acute coronary syndrome; ARR, absolute risk reduction; CAD, coronary artery disease; CHD, Coronary heart disease; MACE, major adverse cardiovascular events; MI, myocardial infarction; MIRACL, myocardial ischemia reduction with acute cholesterol lowering trial; NNT, number needed to treat; PROVE-IT, pravastatin or atorvastatin evaluation and infection therapy; RRR, relative risk reduction; SAGE, study assessing goals in the elderly; TNT, treating to new targets.

^a All reductions are statistically significant ($P < .05$).

reduced the mean LDL cholesterol level from 106 mg/dL to 62 mg/dL. The RRR in the primary end point was 15% with atorvastatin; this benefit was noted at 30 days and persisted through 6 months. Among the 4162 patients enrolled, 624 patients older than 70 years were identified in a subsequent substudy and were compared with younger patients using a composite end point of death, MI and unstable angina.⁴⁹ Older patients who reached the LDL cholesterol goal of less than 70 mg/dL had an 8% ARR (NNT, 12) and a 40% RRR ($P = .008$) for major CHD events; younger patients had an ARR of 2.3% (NNT, 40) and a RRR of 26% ($P = .013$).

Treating to new targets study

Secondary analysis of the Treating to New Targets (TNT) study demonstrated that more aggressive reduction in LDL cholesterol in older patients led to a reduction in major cardiovascular events without significant adverse side effects.^{46,50} Of the 10,001 patients enrolled in the trial who had stable CHD and LDL cholesterol levels below 130 mg/dL, 3809 were older than 65 years. Patients were assigned randomly to atorvastatin, 10 mg/d or 80 mg/d, and were evaluated over a median 4.9 years. The primary outcome was the time to first occurrence of a major cardiovascular event (death caused by CHD, nonfatal MI, resuscitated cardiac arrest, or stroke).

The mean age of the older cohort was 69.9 years. After 12 weeks of therapy, the LDL cholesterol level was 72 mg/dL in patients assigned to atorvastatin, 80 mg/d, versus 97 mg/dL in those receiving 10 mg/d. There was a negligible increase in HDL cholesterol in both groups. Elderly patients assigned to the higher dose experienced a 2.3% ARR in the primary end point (12.6% versus 10.3%; $P = .032$) and a 19% RRR. This ARR in the primary end point was similar to that in patients less than 65 years old (2.3%; HR, 0.76; CI, 0.64–0.90; $P = .001$). Despite the increase in the rate of strokes in the elderly, there was no difference in stroke rates between high-dose and low-dose atorvastatin.

The study assessing goals in the elderly trial

The Study Assessing Goals in the Elderly (SAGE) trial was a 12-month, prospective, multicenter, randomized, double-blind trial that evaluated the effects of intensive versus moderate lipid-lowering therapy in older patients who had CHD.⁵¹ Like the PROSPER trial, the SAGE trial was designed to evaluate high-intensity lipid therapy in an exclusively elderly population. A total of 893 patients age 65 to 85 years who had a history of CAD and more than one episode of myocardial ischemia that lasted longer than 3 minutes during ambulatory ECG were assigned randomly to atorvastatin, 80 mg/d, or pravastatin, 40 mg/d. The primary end point was absolute change from baseline in total duration of ischemia as assessed by 48-hour ambulatory ECG. Ischemia was defined as an ST-segment depression of 1 mm or more below the baseline in more than two leads and lasting for more than 1 minute. The ischemic burden was defined as the depression amplitude multiplied by the duration of ischemia. Major cardiovascular events were defined as cardiovascular death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization procedures, fatal and nonfatal stroke, and hospitalization for unstable angina.

Baseline LDL cholesterol levels were between 100 mg/dL and 250 mg/dL. The average patient age was 72.4 ± 5.1 years in the atorvastatin group and 72.6 ± 5.2 years in the pravastatin group. At 12 months, atorvastatin produced greater decreases than pravastatin in mean LDL cholesterol level (55.4% versus 32.4%; $P < .001$), triglycerides (26.3% versus 7.0%; $P < .001$), and apolipoprotein B (44.8% versus 24.5%; $P < .001$). Pravastatin, however, did lead to a greater increase in HDL cholesterol than atorvastatin (7.6% versus 5.0%; $P = .009$).

Both pravastatin and atorvastatin reduced the total duration of myocardial ischemia at 12 months (both, $P < .001$). The mean ischemia time was reduced by 42.7 minutes, from 113.5 minutes to 70.8 minutes, in the atorvastatin group ($P < .001$) and by 45.6 minutes, from 124.3 to 78.7 minutes, in the pravastatin group ($P < .001$). There was a trend toward fewer major adverse cardiovascular events and a 77% reduction in all-cause mortality in the group taking atorvastatin 80-mg/d group relative to pravastatin, 40 mg/d, over 12 months (1.3% versus 4.0%; $P = .014$).

Rosuvastatin

There are limited studies on the use of rosuvastatin in the elderly. The Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin study was a 6-week randomized, open-label trial comparing the effects of rosuvastatin, atorvastatin, simvastatin, and pravastatin on lipid profiles in patients who had hypercholesterolemia.⁵² In a subgroup analysis of patients older than 65 years (mean age, 71 years), rosuvastatin, 10 mg, decreased LDL cholesterol levels by a mean of 52 mg/dL (27%) from a mean baseline of 190 mg/dL.

The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial evaluated the benefits of statin therapy in elderly patients who had heart failure. Of the trials discussed previously, only the PROSPER trial⁴² and the HPS²⁹ included patients who had left ventricular dysfunction, and both these trials excluded patients who had severe systolic dysfunction. Previous retrospective analysis had demonstrated mortality benefit with statin use in elderly patients who had heart failure.^{53,54} The CORONA trial sought to evaluate this potential benefit in a randomized, prospective fashion. A total of 5011 patients older than 60 years (mean age, 73 years) who had New York Heart Association class II, III, or IV heart failure who were receiving optimal medical therapy were assigned randomly to receive rosuvastatin, 10 mg/d, or placebo.⁵⁵ Patients were followed for a median duration of 32.8 months. The primary composite outcome was death from cardiovascular causes, nonfatal MI, or nonfatal stroke. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalizations. The average ejection fraction was $31 \pm 7\%$ in both groups. Despite significant reductions in LDL cholesterol levels from 137 mg/dL to 76 mg/dL (43.8%; $P < .001$) and C-reactive protein, there was no significant difference in the primary end point, death, coronary outcomes, or death from coronary causes. In prespecified secondary analysis, there was a 19% reduction in hospitalizations among patients receiving rosuvastatin (2193 in the rosuvastatin group versus 2694 in the placebo group; $P < .001$). There was no difference in creatinine kinase elevations, muscle-related symptoms, or elevated aminotransferases in the rosuvastatin group. The results of the CORONA trial bring into question the benefit of statins in elderly patients who have ischemic heart failure. The lack of benefit has been postulated to result from other coexisting conditions that may not be affected by statins or from a significant portion of deaths caused by scar-associated sudden cardiac death.⁵⁶

Despite the lack of published data regarding reduction in clinic events, rosuvastatin has demonstrated benefit in delaying the progression of atherosclerosis, as measured by carotid intima media thickness, in patients who have subclinical atherosclerosis and low Framingham risk.⁵⁷ In higher-risk patients, many of whom had previous MIs, rosuvastatin promoted atherosclerotic plaque reduction as assessed by intravascular ultrasound and quantitative coronary angiography.^{58,59} Data from the Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin trial,⁶⁰ which was halted early, probably will demonstrate the benefits

of rosuvastatin in decreasing major adverse cardiovascular events, and the potential benefits in elderly patients remain to be seen.

Adverse Effects from Statins

Despite the relative safety of statins, the risks of side effects in the elderly may be increased because of polypharmacy.⁶ In a study of elderly patients presenting to a Canadian emergency room, the average number of prescribed medications was 4.2 per patient, and 10.6% of 283 visits were attributed to adverse drug-related events.⁶¹ In the United States, a survey of non-institutionalized adults demonstrated that 40% of persons older than 65 years of age used five or more medications, and 12% used 10 or more medications.⁶² Despite the potential for adverse effects, streamlining therapies to those with demonstrated clinical benefit may maximize outcomes and limit the potential for adverse side effects.

Data from the aforementioned trials note that side effects from statin use are equivalent, or at times higher, than in younger patients. Adverse effects from statins are more common with high doses and when combined with gemfibrozil. In the subgroup analysis of the PROVE-IT trial, the side-effect profiles were similar between elderly and younger patients receiving high-dose atorvastatin therapy. Liver function elevations occurred in 2.3% of older and 2.2% of younger patients, and creatinine phosphokinase elevations occurred in 1.1% versus 1.3%.⁴⁹ The TNT and SAGE trials noted an increased number of treatment-related adverse events, however. In the TNT subgroup study, an increased number of withdrawals and side effects were noted in older patients who were receiving atorvastatin, 80 mg/d, versus 10 mg/d, and this increased rate was similar to the rates observed in the 4S trial substudy.⁵⁰ Adverse events occurred in 8.3% of patients receiving higher doses versus 5.2% of those receiving lower doses, and the withdrawal rate was 4.4% in the high-dose group versus 2.2% in the low-dose group. There also was a slightly greater incidence of elevation in the liver function values (1.2% versus 0.2%) in the high-intensity group, but no difference in myalgias or muscle toxicity was observed. The SAGE trial also noted more frequent elevations in liver function tests (4.3% versus 0.2%; $P < .001$) in the atorvastatin, 80 mg, group versus the pravastatin, 40 mg, group. Myalgias were similar in both groups (3.1% with atorvastatin versus 2.7% with pravastatin; $P = .70$), and there were no cases of rhabdomyolysis.⁵¹ In the "Z phase" (Zocor, chronic phase) of the A to Z trial, 2265 patients who experienced ACS and received simvastatin, 80 mg/d, after a 1-month period of receiving 40 mg/d were compared with 2232 ACS patients who received placebo for 4 months followed by simvastatin, 20 mg/d.⁶³ The primary end point, which was a composite of cardiovascular death, nonfatal MI, readmission for ACS, and stroke, was not achieved. Therapy with high-dose simvastatin increased myopathy, with nine patients (0.4%) experiencing creatinine phosphokinase elevations more than 10 times the upper limit of normal and three patients developing overt rhabdomyolysis.

Awareness of the potential for adverse side effects with statins is important. Patients experiencing such effects can be switched to other statins that are metabolized differently. Lipophilic statins include lovastatin, simvastatin, atorvastatin, and fluvastatin. The first three drugs are metabolized by the cytochrome p450 3A4 enzyme for conversion to water-soluble metabolites. Hydrophilic statins include pravastatin and rosuvastatin, and like fluvastatin, are not metabolized by the cytochrome p450 3A4 system and thus are less likely to have interactions with substances that inhibit this pathway (including amiodarone, diltiazem, verapamil, high intake of grapefruit juice, azole fungals, cyclosporine, and macrolides).⁶ Moreover, gemfibrozil has the potential to increase side effects from all statins except fluvastatin (Lescol), increasing serum

levels to sixfold by blocking the glucuronidation pathway. Fortunately fenofibrate does not block this pathway and does not increase statin levels. Thus, substituting fenofibrate and using statins that are not metabolized by the cytochrome P450 3A4 isoenzyme system such as fluvastatin, pravastatin, and rosuvastatin may limit drug interactions.

Although there have been reports of an association between statin use and dementia in the elderly,⁶⁴ data on this risk are equivocal. Initial studies suggested decreased risk for dementia with the use of statins.^{65,66} Subsequent contradictory reports suggested that statins provide no therapeutic benefit in preventing dementia.⁶⁷ Retrospective analysis and flaws in study design have been suggested as reasons for these discrepant conclusions.⁶⁸ Although clinical evidence is lacking, laboratory data suggest a decrease in beta-amyloid generation and cerebral deposition through cholesterol lowering.⁶⁹ Preliminary studies suggest that atorvastatin might be of clinical benefit in the treatment of Alzheimer's disease;⁷⁰ larger, prospective studies on this subject are warranted to offer more definitive conclusions. Likewise, conflicting data exist on an association between statin use and age-related macular degeneration.^{71,72} Although the use of statins has been linked to advanced neurovascular age-related macular degeneration, confounding factors may play a role, and no definitive conclusions can be made regarding the role of statins in age-related macular degeneration.⁷³

Other Lipid-Lowering Therapies and Combination Therapy

Although the benefits of statin use in geriatric patients are well established, little has been published describing the efficacy and safety of use of non-statin therapies (**Table 4**).

Ezetimibe: efficacy and safety

Ezetimibe is indicated for the reduction of LDL cholesterol, either as monotherapy or in combination with statins. The Effect of Combination Ezetimibe and High-Dose Simvastatin versus Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia trial focused attention on the absence of data regarding the efficacy of simvastatin, 80 mg, plus ezetimibe, 10 mg, in improving carotid intima media thickness versus simvastatin alone, although LDL cholesterol levels were significantly lower in the combination group (141 mg/dL versus 193 mg/dL).⁷⁴ Although this study had design flaws that may have precluded beneficial effects of the combination being observed, the most appropriate use of ezetimibe may be either in combination with statin therapy in patients who cannot reach LDL cholesterol goals on statin monotherapy or in patients who cannot tolerate statins.

A pooled analysis of 1861 patients showed that in patients over age 65 years the addition of ezetimibe made no significant difference in the incidence of serious side effects after 12 weeks of therapy, although discontinuation for possible side effects was greater in the small population of patients over age 75 years.⁷⁵ Substantially more patients taking ezetimibe-plus-statin therapy in this meta-analysis were at or below target LDL cholesterol levels, irrespective of age. The product-prescribing supplement for both ezetimibe and combination ezetimibe/simvastatin (Vytorin) noted no increase in adverse events in geriatric patients in the trials reviewed for Food and Drug Administration (FDA) approval.

Fibrates: efficacy and safety

Fibrates, including gemfibrozil and fenofibrate, are indicated for monotherapy or for adjunctive therapy for treatment of dyslipidemias, particularly in patients who have hypertriglyceridemia and/or low HDL cholesterol. Few data, however, support the

Drug	Suggested Use	Side Effects
Ezetimibe	Combined use with high-dose statins for goal LDL reduction or with low statin doses to minimize side effects	No increase in side effects with use in elderly
Fibrates (gemfibrozil, fenofibrate)	Monotherapy or combination therapy in patients who have hypertriglyceridemia and/or low HDL; limited study of their benefits in geriatric patients	Increased risk for rhabdomyolysis with combined use of gemfibrozil and statins; gemfibrozil also decreases warfarin metabolism
Niacin	Monotherapy or combination therapy for elevated LDL, hypertriglyceridemia, and low HDL	Flushing (less common with sustained-release formulation), worsening glycemic control in diabetics; no increase in side effects among geriatric patients
Omega-3 fatty acids	Combined with statins; outcomes data limited in geriatric patients	No serious side effects

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

efficacy of these medications in patients over age 65 years. Many of the largest randomized trials of fibrate limited or disallowed the enrollment of geriatric patients: the maximum age was 72 years in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial,⁷⁶ 74 years in the Bezafibrate Infarction Prevention Trial,^{77,78} and 55 years in the Helsinki Heart Study.⁷⁹

The Fenofibrate Intervention and Event Lowering in Diabetes study investigated the use of fenofibrate versus placebo in 9795 patients who had diabetes and reported a small decrease in the overall number of total cardiovascular events in the fenofibrate group. Patients between age 65 and 75 years composed about 40% of the study population,⁸⁰ but in subgroup analysis these patients did not have any significant benefit from fibrate treatment.⁸¹ The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, still in progress, has a maximum age of 79 years and may help clarify the benefit of fenofibrate in geriatric patients.⁸²

Fibrate therapy is associated with a low incidence of several potential side effects, including increased rash, gastrointestinal complaints, increased serum creatinine level, muscle aches, rhabdomyolysis, liver function abnormalities, and deep vein thrombosis.^{83–85} An increase in adverse events has been noted with gemfibrozil in patients who concurrently are using statins or who have renal insufficiency, and thus caution should be used in geriatric patients who fall into these categories.^{85,86} A significant increase in serum creatinine during fibric acid therapy should prompt lowering the dose by one half to one third; and with a glomerular filtration rate less than 30 mL/min/1.73 m² body surface area, the fenofibrate dose should be 48 mg/d rather than 145 mg/d. It is not clear that incidence of adverse effects of fibrate monotherapy is otherwise increased in geriatric patients. There are isolated reports of increased

prothrombin time in two geriatric patients^{87,88} and one non-geriatric patient⁸⁹ taking stable doses of warfarin after starting fibrate therapy.

Niacin: efficacy and safety

Niacin, or nicotinic acid, also is indicated as either monotherapy or adjunctive therapy for treatment of elevated LDL cholesterol, hypertriglyceridemia, and/or low HDL cholesterol. The largest outcome trial, the Coronary Drug Project, showed reduced incidence of MI and a mortality benefit for niacin compared with placebo, but enrollment was restricted to patients age 35 to 64 years. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2 trial compared carotid intima media thickness in 167 patients (mean age, 67 years) receiving moderate-dose statin therapy and randomly assigned to 1 g niacin or placebo and found a significant benefit in the niacin group. Adverse cardiac events were fewer in the niacin group; the study was not powered to detect a significant effect on clinical events.⁹⁰

Niacin has been associated with flushing, as well as gastrointestinal side effects and rare hepatotoxicity.⁸³ Flushing is less common with sustained-release niacin (eg, Slo-Niacin) than with immediate-release niacin, but hepatotoxicity at higher doses is greater. In addition to the side effects, concerns about worsening glycemic control in diabetics have limited use of this medication, but a recent review of the subject concluded that this risk may be limited.⁹¹ The product-prescribing supplement for extended-release niacin (Niaspan) noted no increase in adverse events in geriatric patients in the trials reviewed for FDA approval.

Omega-3 fatty acids: efficacy and safety

Omega-3 fatty acids are dietary supplements and thus are not regulated by the FDA, with the exception of a proprietary formulation (Lovaza) indicated for treatment of patients who have hypertriglyceridemia. They have little effect on the serum levels of LDL cholesterol and HDL cholesterol⁹² and thus may be most effective when combined with statins; this combination seems to be both safe and effective.^{93,94} The Gruppo Italiano per lo Studio della Sporavvivenza nell'Infarto Miocardico-Prevenzione study demonstrated a decrease in sudden cardiac death after MI among patients receiving n-3 polyunsaturated fatty acid (850–882 mg eicosapentaenoic acid and docosahexaenoic acid).^{95,96} Data on the benefits in of omega-3 fatty acid therapy in geriatric patients are lacking, however.

The safety of omega-3 fatty acid supplements has been demonstrated in geriatric patients, particularly in studies investigating their effects on the progression of dementia.⁹⁷ Despite the antiplatelet effects, there does not seem to be a significant clinical risk of bleeding, even when with omega-3 fatty acid therapy is added to other antithrombotic agents.^{92,98}

SUMMARY

Despite the proven benefits of lipid-lowering therapy in elderly patients, the agents are underused in this population. A retrospective cohort study of 34,501 persons older than 65 years noted that the persistence of statin therapy in older patients declines over time, and nonwhite race, lower income, older age, depression, dementia, and occurrence of CHD events after starting treatment were independent risk factors for the discontinuation of therapy.⁹⁹ Nonetheless, increased awareness of the importance of risk-factor modification in the elderly has led to earlier treatment of dyslipidemia. After the publication of the NCEP ATP III guidelines, the use of statins in the elderly increased,¹⁰⁰ and it is hoped that this change will translate into clinical benefit. Multiple primary and secondary trials have demonstrated that the benefits of statins in geriatric

patients are equivalent to or greater than the benefits in younger patients because there is the same RRR in older persons and a greater ARR. Although side effects may be slightly increased with high-dose statin therapy, careful vigilance in monitoring drug interactions and limiting polypharmacy can reduce these effects. In patients who do not meet LDL cholesterol targets or who have concomitant hypertriglyceridemia or low HDL cholesterol, combination therapy with non-statin agents can be considered. Considering the burden of atherosclerotic disease in the geriatric population, modification of risk factors is essential. Anti-lipid therapy plays a vital role in reducing cardiovascular events and should be considered in most geriatric patients when applicable.

REFERENCES

1. US Census Bureau. State and national population projections. Available at: <http://www.census.gov/population/www/projections/popproj.html>. Accessed June 2, 2008.
2. Williams MA, Fleg JL, Ades PA, et al. Secondary prevention of coronary heart disease in the elderly (with emphasis on patients > or =75 years of age): an American Heart Association scientific statement from The Council on Clinical Cardiology Subcommittee on Exercise, Cardiac Rehabilitation, And Prevention. *Circulation* 2002;105(14):1735–43.
3. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. *JAMA* 2004;291(15):1864–70.
4. Malenka DJ, Baron JA. Cholesterol and coronary heart disease. The importance of patient-specific attributable risk. *Arch Intern Med* 1988;148(10):2247–52.
5. Grundy SM, Cleeman JI, Rifkind BM, et al. Cholesterol lowering in the elderly population. Coordinating Committee of the National Cholesterol Education Program. *Arch Intern Med* 1999;159(15):1670–8.
6. Maroo BP, Lavie CJ, Milani RV. Efficacy and safety of intensive statin therapy in the elderly. *Am J Geriatr Cardiol* 2008;17(2):92–100.
7. Shepherd J. Monotherapy vs combination therapy for dyslipidemia in the elderly. *Am J Geriatr Cardiol* 2008;17(2):108–13.
8. Kronmal RA, Cain KC, Ye Z, et al. Total serum cholesterol levels and mortality risk as a function of age. A report based on the Framingham data. *Arch Intern Med* 1993;153(9):1065–73.
9. Krumholz HM, Seeman TE, Merrill SS, et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA* 1994;272(17):1335–40.
10. Corti MC, Guralnik JM, Salive ME, et al. Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. *Ann Intern Med* 1997;126(10):753–60.
11. Frost PH, Davis BR, Burlando AJ, et al. Serum lipids and incidence of coronary heart disease. Findings from the Systolic Hypertension in the Elderly Program (SHEP). *Circulation* 1996;94(10):2381–8.
12. Onder G, Landi F, Volpato S, et al. Serum cholesterol levels and in-hospital mortality in the elderly. *Am J Med* 2003;115(4):265–71.
13. Schatz IJ, Masaki K, Yano K, et al. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet* 2001;358(9279):351–5.
14. Kalantar-Zadeh K, Block G, Horwich T, et al. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 2004;43(8):1439–44.

15. Tiyyagura SR, Smith DA. Standard lipid profile. *Clin Lab Med* 2006;26(4):707–32.
16. Kreisberg RA, Kasim S. Cholesterol metabolism and aging. *Am J Med* 1987;82(1B):54–60.
17. Ferrara A, Barrett-Connor E, Shan J. Total, LDL, and HDL cholesterol decrease with age in older men and women. The Rancho Bernardo Study 1984–1994. *Circulation* 1997;96(1):37–43.
18. Choi BG, Vilahur G, Viles-Gonzalez JF, et al. The role of high-density lipoprotein cholesterol in atherothrombosis. *Mt Sinai J Med* 2006;73(4):690–701.
19. Castelli WP, Wilson PW, Levy D, et al. Cardiovascular risk factors in the elderly. *Am J Cardiol* 1989;63(16):12H–9H.
20. Flornvall G, Basu S, Larsson A. Apolipoprotein A1 is a stronger prognostic marker than are HDL and LDL cholesterol for cardiovascular disease and mortality in elderly men. *J Gerontol A Biol Sci Med Sci* 2006;61(12):1262–6.
21. Lagakos SW. The challenge of subgroup analyses—reporting without distorting. *N Engl J Med* 2006;354(16):1667–9.
22. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine—reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007;357(21):2189–94.
23. Dornbrook-Lavender KA, Roth MT, Pieper JA. Secondary prevention of coronary heart disease in the elderly. *Ann Pharmacother* 2003;37(12):1867–76.
24. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002;106(25):3143–421.
25. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344(8934):1383–9.
26. Miettinen TA, Pyorala K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1997;96(12):4211–8.
27. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360(9326):7–22.
28. Farmer JA, Gotto AM Jr. The Heart protection study: expanding the boundaries for high-risk coronary disease prevention. *Am J Cardiol* 2003;92(1A):3i–9i.
29. Collins R, Armitage J, Parish S, et al. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004;363(9411):757–67.
30. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events trial investigators. *N Engl J Med* 1996;335(14):1001–9.
31. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med* 1998;129(9):681–9.
32. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study group. *N Engl J Med* 1998;339(19):1349–57.
33. Hunt D, Young P, Simes J, et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or

- exceed those seen in younger patients: results from the LIPID trial. *Ann Intern Med* 2001;134(10):931–40.
34. Sacks FM, Tonkin AM, Shepherd J, et al. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. *Circulation* 2000;102(16):1893–900.
 35. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333(20):1301–7.
 36. Allen Maycock CA, Muhlestein JB, Horne BD, et al. Statin therapy is associated with reduced mortality across all age groups of individuals with significant coronary disease, including very elderly patients. *J Am Coll Cardiol* 2002;40(10):1777–85.
 37. Afilalo J, Duque G, Steele R, et al. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. *J Am Coll Cardiol* 2008;51(1):37–45.
 38. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279(20):1615–22.
 39. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364(9435):685–96.
 40. Neil HA, DeMicco DA, Luo D, et al. Analysis of efficacy and safety in patients aged 65–75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetes Care* 2006;29(11):2378–84.
 41. Lemaitre RN, Psaty BM, Heckbert SR, et al. Therapy with hydroxymethylglutaryl coenzyme a reductase inhibitors (statins) and associated risk of incident cardiovascular events in older adults: evidence from the Cardiovascular Health Study. *Arch Intern Med* 2002;162(12):1395–400.
 42. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360(9346):1623–30.
 43. Bjerre LM, LeLorier J. Do statins cause cancer? A meta-analysis of large randomized clinical trials. *Am J Med* 2001;110(9):716–23.
 44. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285(13):1711–8.
 45. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350(15):1495–504.
 46. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352(14):1425–35.
 47. Waters DD, Schwartz GG, Olsson AG, et al. Effects of atorvastatin on stroke in patients with unstable angina or non-Q-wave myocardial infarction: a Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) substudy. *Circulation* 2002;106(13):1690–5.
 48. Olsson AG, Schwartz GG, Szarek M, et al. Effects of high-dose atorvastatin in patients > or = 65 years of age with acute coronary syndrome (from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering [MIRACL] study). *Am J Cardiol* 2007;99(5):632–5.
 49. Ray KK, Bach RG, Cannon CP, et al. Benefits of achieving the NCEP optional LDL-C goal among elderly patients with ACS. *Eur Heart J* 2006;27(19):2310–6.

50. Wenger NK, Lewis SJ, Herrington DM, et al. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. *Ann Intern Med* 2007;147(1):1–9.
51. Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation* 2007;115(6):700–7.
52. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003;92(2):152–60.
53. Foody JM, Shah R, Galusha D, et al. Statins and mortality among elderly patients hospitalized with heart failure. *Circulation* 2006;113(8):1086–92.
54. Ray JG, Gong Y, Sykora K, et al. Statin use and survival outcomes in elderly patients with heart failure. *Arch Intern Med* 2005;165(1):62–7.
55. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;357(22):2248–61.
56. Masoudi FA. Statins for ischemic systolic heart failure. *N Engl J Med* 2007;357(22):2301–4.
57. Crouse JR 3rd, Raichlen JS, Riley WA, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR trial. *JAMA* 2007;297(12):1344–53.
58. Ballantyne CM, Raichlen JS, Nicholls SJ, et al. Effect of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography. A study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. *Circulation* 2008;117:2458–66.
59. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006;295(13):1556–65.
60. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation* 2003;108(19):2292–7.
61. Hohl CM, Dankoff J, Colacone A, et al. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. *Ann Emerg Med* 2001;38(6):666–71.
62. Kaufman DW, Kelly JP, Rosenberg L, et al. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA* 2002;287(3):337–44.
63. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;292(11):1307–16.
64. Bernick C, Katz R, Smith NL, et al. Statins and cognitive function in the elderly: the Cardiovascular Health Study. *Neurology* 2005;65(9):1388–94.
65. Jick H, Zornberg GL, Jick SS, et al. Statins and the risk of dementia. *Lancet* 2000;356(9242):1627–31.
66. Rockwood K, Kirkland S, Hogan DB, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Arch Neurol* 2002;59(2):223–7.
67. Zandi PP, Sparks DL, Khachaturian AS, et al. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County study. *Arch Gen Psychiatry* 2005;62(2):217–24.

68. Li G, Higdon R, Kukull WA, et al. Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. *Neurology* 2004;63(9):1624–8.
69. Simons M, Keller P, De Strooper B, et al. Cholesterol depletion inhibits the generation of beta-amyloid in hippocampal neurons. *Proc Natl Acad Sci U S A* 1998; 95(11):6460–4.
70. Sparks DL, Sabbagh MN, Connor DJ, et al. Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. *Arch Neurol* 2005;62(5):753–7.
71. Klein R, Knudtson MD, Klein BE. Statin use and the five-year incidence and progression of age-related macular degeneration. *Am J Ophthalmol* 2007; 144(1):1–6.
72. McGwin G Jr, Modjarrad K, Hall TA, et al. 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors and the presence of age-related macular degeneration in the Cardiovascular Health Study. *Arch Ophthalmol* 2006;124(1):33–7.
73. Cukras CA, Agron E, SanGiovanni JP, et al. The use of statins and the development of AMD in AREDS [abstract 3772]. Association for Research in Vision and Ophthalmology 2008 Annual Meeting. Ft Lauderdale, FL; 2008.
74. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;358(14):1431–43.
75. Lipka L, Sager P, Strony J, et al. Efficacy and safety of coadministration of ezetimibe and statins in elderly patients with primary hypercholesterolaemia. *Drugs Aging* 2004;21(15):1025–32.
76. Rubins HB, Robins SJ, Iwane MK, et al. Rationale and design of the Department of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (HIT) for secondary prevention of coronary artery disease in men with low high-density lipoprotein cholesterol and desirable low-density lipoprotein cholesterol. *Am J Cardiol* 1993;71(1):45–52.
77. Goldbourt U, Behar S, Reicher-Reiss H, et al. Rationale and design of a secondary prevention trial of increasing serum high-density lipoprotein cholesterol and reducing triglycerides in patients with clinically manifest atherosclerotic heart disease (the Bezafibrate Infarction Prevention Trial). *Am J Cardiol* 1993; 71(11):909–15.
78. The Coronary Primary Prevention trial: design and implementation: the Lipid Research Clinics Program. *J Chronic Dis* 1979;32(9–10):609–31.
79. Manttari M, Elo O, Frick MH, et al. The Helsinki Heart Study: basic design and randomization procedure. *Eur Heart J* 1987;8(Suppl 1):1–29.
80. Scott R, Best J, Forster P, et al. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: baseline characteristics and short-term effects of fenofibrate [ISRCTN64783481]. *Cardiovasc Diabetol* 2005;4:13–22.
81. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366(9500):1849–61.
82. Buse JB, Bigger JT, Byington RP, et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. *Am J Cardiol* 2007;99(12A):21i–33i.
83. Birjmohun RS, Hutten BA, Kastelein JJ, et al. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2005;45(2):185–97.
84. Davidson MH, Armani A, McKenney JM, et al. Safety considerations with fibrate therapy. *Am J Cardiol* 2007;99(6A):3C–18C.
85. Holoshitz N, Alsheikh-Ali AA, Karas RH. Relative safety of gemfibrozil and fenofibrate in the absence of concomitant cerivastatin use. *Am J Cardiol* 2008; 101(1):95–7.

86. Guay DR. Micronized fenofibrate: a new fibric acid hypolipidemic agent. *Ann Pharmacother* 1999;33(10):1083–103.
87. Rindone JP, Keng HC. Gemfibrozil-warfarin drug interaction resulting in profound hypoprothrombinemia. *Chest* 1998;114(2):641–2.
88. Aldridge MA, Ito MK. Fenofibrate and warfarin interaction. *Pharmacotherapy* 2001;21(7):886–9.
89. Ahmad S. Gemfibrozil interaction with warfarin sodium (Coumadin). *Chest* 1990; 98(4):1041–2.
90. Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 2004; 110(23):3512–7.
91. Goldberg RB, Jacobson TA. Effects of niacin on glucose control in patients with dyslipidemia. *Mayo Clin Proc* 2008;83(4):470–8.
92. Bays HE. Safety considerations with omega-3 fatty acid therapy. *Am J Cardiol* 2007;99(6A):35C–43C.
93. Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther* 2007;29(7):1354–67.
94. Nambi V, Ballantyne CM. Combination therapy with statins and omega-3 fatty acids. *Am J Cardiol* 2006;98(4A):34i–8i.
95. Gruppo Italiano per lo Studio della Sporavvivenza nell'Infarto Miocardico - Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354:447–55.
96. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sporavvivenza nell'Infarto Miocardico (GISSI)-prevenzione. *Circulation* 2002;105:1897–903.
97. Freund-Levi Y, Eriksson-Jonhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegaAD study: a randomized double-blind trial. *Arch Neurol* 2006;63(10):1402–8.
98. Harris WS. Expert opinion: omega-3 fatty acids and bleeding-cause for concern? *Am J Cardiol* 2007;99(6A):44C–6C.
99. Benner JS, Glynn RJ, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002;288(4):455–61.
100. Nichols GA, Nag S, Chan W. Intensity of lipid-lowering therapy and low-density lipoprotein cholesterol goal attainment among the elderly before and after the 2004 National Cholesterol Education Program Adult Treatment Panel III update. *Am Heart J* 2007;154(3):554–60.