Special Report: The Efficacy and Safety of Statins in the Elderly

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Executive Summary

Background
HMG-CoA reductase inhibitors (statins) are the most widely prescribed class of medications for hypercholesterolemia. They have been shown to be efficacious in reducing adverse cardiovascular events in numerous large clinical trials. These trials, however, have generally targeted middle-aged men, resulting in under-representation of the elderly population (i.e., older than 65 years). It is not certain whether results from statin trials in younger age groups can be extrapolated to the elderly population. In addition, the comparative efficacy of statins in elderly subpopulations (e.g., very old, primary vs. secondary prevention, etc.) is not known.

Objective
This Special Report will review the evidence from clinical trials that evaluates the use of statins in the elderly age group, primarily regarding the initiation of statins in elderly patients who are not currently taking antilipidemic therapy. The beneficial effect of statins on cardiovascular outcomes, and the potential benefit on other non-cardiovascular outcomes, will be weighed against the adverse event profile for these medications in the elderly in order to determine the overall benefit/risk ratio for this class of medications.

Methods
MEDLINE® was searched (via PubMed) using the terms "statins," "HMG-CoA Reductase," "elderly," and "aged" from 1980 through September 2006, limited to English-language articles on human subjects. In addition, a separate search was conducted for adverse events using the key words "statins," "HMG-CoA Reductase Inhibitors," "elderly," "adverse events," and "complications." Electronic searches were supplemented with the "related articles" function on PubMed for key studies, and with a hand-search of bibliographies from recent review articles and clinical studies.

Studies were selected for inclusion in this Special Report that met the following criteria: full-length, randomized controlled trials published in peer-reviewed journal in the English language; included a population of elderly patients (older than 65 years), or reported outcomes separately for the elderly subgroup; compared statin use with placebo control, or usual care control; and, reported on cardiovascular outcomes. Meta-analyses were also included if they analyzed clinical trials that met the preceding inclusion criteria, included a subgroup analysis based on age, and used patient-level data for analysis. For adverse events, the article selection criteria was the same except that the study design could also include cohort studies that included at least 100 patients, and/or case series that included at least 100 patients.

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Results

One clinical trial specifically included a population of elderly patients (PROSPER), and 3 other clinical trials (CARE, LIPID, 4S) provided "extended" subgroup analyses of the elderly population, consisting of a separate peer-reviewed publication reporting on the elderly subgroup. These 4 trials provided the bulk of evidence for this Special Report on the cardiovascular benefits of statins in the elderly. These clinical trials primarily included patients with existing coronary heart disease (secondary prevention), except for the PROSPER trial, which included patients with existing coronary disease as well as patients without coronary disease (primary prevention).

All 4 of the clinical trials reported that statins were efficacious in reducing adverse cardiovascular events. These studies reported a 20–40% relative risk reduction for coronary heart disease (CHD) death, and similar improvements in the rates of myocardial infarction (MI). There was a less consistent effect reported for stroke, with only 1 study (CARE) reporting a statistically significant decrease. All 4 of these studies also showed consistent benefits on a variety of composite cardiovascular endpoints.

The PROSPER trial, the only trial of an elderly population, also reported outcomes for statin usage in both secondary and primary prevention. The reduction in relative risk of coronary events was substantially greater for usage in secondary prevention (0.76; 95% CI: 0.60–0.92) than in primary prevention (0.94; 95% CI: 0.75–1.12).

Three of the studies (CARE, LIPID, 4S) compared cardiovascular outcomes in the elderly with those in the non-elderly population. These trials addressed secondary prevention only. In general, the benefits for the elderly population were at least as great, or greater, than the non-elderly population. The relative risk reduction (RRR) was approximately equal or slightly higher for the elderly population, and the absolute risk reduction (ARR) was greater for the elderly population across the majority of outcomes. Four other clinical trials that reported "simple" subgroup analyses corroborate these findings, with similar RRRs reported for the elderly and non-elderly populations.

An individual patient-level meta-analysis of 14 clinical trials, including over 34,000 elderly patients, reported a subgroup analysis of elderly vs. non-elderly participants. The authors of this study reported the RRR per 1.0 mmol/L reduction in cholesterol. Overall the RRR and ARR for the main outcomes were similar to that found in the individual studies included in this assessment. The conclusions of this meta-analysis differed in that that the relative risk reduction was statistically less for elderly vs. non-elderly patients (0.29 vs. 0.36, $p<0.01$), while the ARR was not statistically different between the 2 groups (2.4% vs. 2.4%, p=NS).

Evidence on outcomes other than cardiovascular endpoints is lacking. Similarly, the data on adverse events are not robust. Adverse event data are derived from the clinical trials and 3 additional cohort studies. The clinical trials do not report increased rates of adverse events for patients treated with statins compared with placebo. One study reported an increase in the incidence of cancer associated with statin use, but results on cancer incidence from the other trials are mixed. The cohort studies provide limited data on the rates of adverse events and are not adequate for determining the absolute rates of events for the elderly population.

Conclusions

The benefits of statins in reducing cardiovascular events extend to the elderly population. The relative benefit of statin treatment in this population is likely to be similar to that for younger patients, while the absolute benefit is likely to be greater due to the increased rate of cardiovascular events in this population.

There are several limitations to these conclusions. The available evidence primarily refers to secondary prevention of coronary events. There is very little evidence for the effectiveness of statins when used for primary prevention in elderly patients, and the available evidence suggests that the relative (and even more so, absolute) risk reduction from statins is smaller when used for

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primary prevention. Also the available evidence does not represent the entire spectrum of age in "elderly" patients. These trials do not include the "old" old, enrolling few patients older than 75 years and virtually no patients older than 80 years. As a result, the comparisons made between the elderly and non-elderly populations are made within relatively narrow ranges of age.

The data on adverse events from statins in the elderly population are not robust. While the frequency of serious adverse events is low, it is not possible to estimate the rates of adverse events with any precision. Also, there is a lack of data on the potential non-cardiovascular benefits of these agents. These factors contribute to considerable uncertainty regarding the overall benefit/risk ratio of these agents. Future research is needed on these areas of uncertainty in order to better define the overall benefit/risk ratio for these agents in the elderly.

Contents

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Objectives

The overall objective of this Special Report is to review the evidence on the efficacy and safety of HMG-CoA reductase inhibitor medications (statins) in elderly patients. In doing this, the Report will attempt to provide an estimate of the overall benefit/risk ratio for these medications in elderly patients, considering both multiple potential benefits and adverse events. Recognizing that the "elderly" population is very heterogeneous, and that there is a wide age range within the population defined as elderly, the Report will attempt to look at several age subgroups within the elderly: 65–69 years; 70–80 years; and older than 80 years.

Statins are the most widely prescribed lipid-lowering medications and their benefit in reducing adverse cardiovascular events has been well-documented. However, the evidence for benefit in elderly patients is less robust. Epidemiologic evidence has questioned whether the association between cholesterol and heart disease in the elderly population is as strong as the association in the middle-aged population, for which most of the clinical trial evidence is available. The adverse effect profile may also differ in elderly patients, with rates of adverse effects expected to be higher for elderly patients. This may also have an impact on the risk/benefit ratio.

This Report will review the available clinical trial evidence on the use of statins in the elderly. This review will include both trials that specifically targeted elderly patients for enrollment, as well as trials that enrolled a broader age range and included subgroup analyses based on age. Evidence on both secondary and primary prevention will be sought. Evidence on the adverse effects of statins will be examined both in the clinical trial data and in other sources of published data. These will include cohort studies, case series, case-control studies, and registry data.

Background

HMG-CoA Reductase Inhibitors (Statins)

There are currently 6 different statins approved by the U.S. Food and Drug Administration (FDA) for marketing in the U.S. These are atorvastatin, lovastatin, pravastatin, fluvastatin, simvastatin, and rosuvastatin. A seventh statin, cerivastatin, was previously available but later removed from the market due to a higher incidence of myopathy compared to other statins.

Statins inhibit the synthesis of cholesterol in the liver by blocking a key enzyme (HMG CoA reductase) early in the cholesterol biosynthesis cascade. This results in reduced formation of cholesterol, particularly low-density lipoproteins (LDL). Total cholesterol is reduced by 20–50% depending on the specific agent and the dose. LDL cholesterol is reduced by 30–60% depending on the agent and the dose.

The most common adverse effects of statins include myopathy and liver toxicity. Myopathy is uncommon, but may lead to potentially fatal rhabdomyolysis. An FDA advisory paper on the safety of statins (Pasternak et al. 2002) estimated that severe myopathy occurs at a rate of 0.08% with lovastatin and simvastatin. Fatal rhabdomyolysis was extremely rare, occurring at a rate of less than one death per million prescriptions for statins. Markedly higher rates for cerivastatin were noted by the FDA, leading to withdrawal of this drug from the market. There was no evidence that any of the statins remaining on the market had different rates of severe myopathy and/or fatal rhabdomyolysis.

An FDA advisory paper concluded that the risk of severe myopathy was increased for very old patients (>80 years old), especially among women, but comparative rates of myopathy were not reported according to age (Pasternak et al. 2002). Other factors that increased the risk for myopathy were small body frame, frailty, multisystem disease, multiple medications, use in the perioperative period, ingestion of large amounts of grapefruit juice, and numerous individual medications that may interact with statins.

Liver toxicity, as evidenced by abnormalities in liver enzyme function occurs in 0.5–2.0% of patients and is dose-dependent (Pasternak et al. 2002). However, these laboratory abnormalities are unlikely to lead to serious clinical adverse events. Progression to liver failure is very rare, and some experts do not believe that it occurs at all (Pasternak et al. 2002).

Statin Treatment in the Elderly

Large statin trials have established benefits of these agents in prevention of cardiovascular disease (Table 1). In at least 17 large clinical trials, statins have been shown effective for both primary and secondary prevention. These

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Table 1. Overview of Randomized, Controlled Trials of Statins for Primary or Secondary Prevention of CHD

			Baseline Age Demographics					Risk Factors/Comorbidities (%)								
Clinical Trial Name	Patient Population	Study Arms	Mean Age	Age Range	% >65 yrs	% >70 yrs	% >80 yrs	Diabetes	HTN	Smoking	Family CHD	Low HDL	Prior CHD	Angina	Study Duration (Mean f/u)	Results by Age Subgroup?
AFCAPS/TexCAPS (n=6,605) (Downs et al. 1998)	Primary Prevention Study: Men/women without clinically evident atherosclerotic CV disease; average cholesterol levels	Lovastatin 20–40 mg Placebo	58	45–73	22	—	—	3	22	13	16	35	—	—	5.2 years	No
ALERT (n=6,605) (Hodaas et al. 2003)	Renal transplant patients	Fluvastatin 40 mg Placebo	50	30–75	—	—	—	19	75	18	11	—	15	—	5.1 years	No
ALLHAT-LLT (n=10,355) (ALLHAT 2002)	Older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor	Pravastatin 40 mg Usual care	66	≥55	—	—	—	35	10	13	14	—	—	—	4.8 years	Yes
ASCOT-LLA (n=10,305) (Sever et al. 2003)	Hypertension patients with average or lower than average cholesterol levels	Atorvastatin 10 mg Placebo	63	40–79	64[1]	—	—	25	—	33	—	—	—	—	3.3 years (Trial termed early)	Yes No
CARDS (n=2,838) (Colhoun et al. 2004)	Primary Prevention Study: Men/women with type 2 diabetes (without high LDL)	Atorvastatin 10 mg Placebo	62	40–75	62[1]	12	—	—	—	—	—	—	—	—	3.9 years (Trial termed early)	No No
CARE (n=4,159) (Sacks et al. 1996)	Secondary Prevention Study: Men/women with coronary disease, who have average cholesterol levels	Pravastatin 40 mg Placebo	59	21–75	—	—	-	15	43	21	—	—	—	—	5.0 years	Yes

[1] % patients >60 yrs; % >65 yrs not reported

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Table 1. Overview of Randomized, Controlled Trials of Statins for Primary or Secondary Prevention of CHD (cont'd)

			Baseline Age Demographics					Risk Factors/Comorbidities (%)								
Clinical Trial Name	Patient Population	Study Arms	Mean Age	Age Range	% >65 yrs	% >70 yrs	% >80 yrs	Diabetes	HTN	Smoking	Family CHD	Low HDL	Prior CHD	Angina	Study Duration (Mean f/u)	Results by Age Subgroup?
HPS (n=20,536) (Heart Protection Study Collaborative Group 2002)	Men/women with history of CVD, diabetes or noncoronary vascular disease	Simvastatin 40 mg Placebo	63	40–80	—	28	—	19	41	14	—	—	41	—	5 years	Yes
LIPID (n=9,014) (LIPID Study Group 1998)	Men/women with prior MI or unstable angina	Pravastatin 40 mg Placebo	63	31–75	—	—	—	12	—	—	—	—	—	—	6.1 years	Yes
PREVEND IT (n=1,439) (Asselbergs et al. 2004)	Average risk, persistent, microalbuminuria	Pravastatin 40 mg Placebo Fosinopril 20 mg Placebo	58	28–75	—	—	—	3	—	40	—	—	3	—	3.8 years	
PROSPER (n=5,804) (Shepherd et al. 2002)	Men/women age 70 or over with history of CAD or risk factors	Pravastatin 40mg Placebo	75	70–82	0	100	—	11	62	27	—	—	14	26	3.2 years	
4S (n=4,444) (4S Group 1994)	Men/women with history of CHD	Simvastatin 40 mg Placebo	59	35–70	521	—	—	5	26	26	—	—	—	21	5.4 years	Yes
Riegger et al. 1999 (n=365)	Men/women with history of CAD	Fluvastatin 40 mg twice daily Placebo	60	40–70	—	—	—	5	29	9	—	—	36	—	52 weeks	No
WOSCOPS (n=6,595) (Shepherd et al. 1995)	Middle-aged men with hypercholesteremia and no history of MI	Pravastatin 40 mg Placebo	55	45–64	—	—	—	1	16	44	—	—	—	—	4.9 years	No

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Table 1. Overview of Randomized, Controlled Trials of Statins for Primary or Secondary Prevention of CHD (cont'd)

			Baseline Age Demographics					Risk Factors/Comorbidities (%)								
Clinical Trial Name	Patient Population	Study Arms	Mean Age	Age Range	% >65 yrs	% >70 yrs	% >80 yrs	Diabetes	HTN	Smoking	Family CHD	Low HDL	Prior CHD	Angina	Study Duration (Mean f/u)	Results by Age Subgroup?
Cannon et al. 2004 (n=4,162)	Hospitalized men/women following recent acute coronary syndrome; intensive statin vs. standard statin regimen (non-inferiority study)	Pravastatin 40 mg Atorvastatin 80 mg	58	—	—	—	—	18	50	37	—	—	18	—	2 years (18–36 months)	
A to Z (n=4,497) (de Lemos et al. 2004)	Early initiation of statins following acute coronary syndrome event	Simvastatin 40 mg for 1 month, then 80 mg Placebo for 4 months, then simvastatin 20 mg	61	52–79	—	—	—	24	50	41	22	—	—	—	721 days	Yes – based on Kaplan Meier
FLORIDA (n=540) (Liem et al. 2002)	Men/women following MI; early initiation of statin therapy	Fluvastatin 80 mg Placebo	60	30–87	—	—	—	—	—	—	—	—	12	—	1 year (362 days)	No
MIRACL (n=3,086) (Schwartz et al. 2001)	Men/women with unstable angina or non-Q-wave acute MI. Early initiation of statin therapy	Atorvastatin 80 mg Placebo	65	—	—	—	—	23	55	28	—	—	—	—	16 weeks	No

Abbreviations:
CAD coronary artery disease
CHD coronary heart disease
CV cardiovascular
HTN hypertension
LDL low density lipoprotein
MI myocardial infarction

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trials have treated patients across a wide range of lipid levels, including patients with hyperlipidemia, normal lipid levels and coronary artery disease, and patients with low HDL. The relative risk reduction has been fairly consistent in the statin trials, with a 20–40% decrease in adverse cardiovascular events (Figure 1).

Enrollment in the statin trials has mainly targeted middle-aged men, with the vast majority of patients in these trials between the ages of 40 and 70 years. It may be problematic to extrapolate the results of trials in younger patients to older patients. The lifespan for elderly patients is less, decreasing the potential for long-term benefit as with younger patients.

The association between plasma cholesterol and adverse cardiovascular events is less strong for elderly patients. As a result, it has been hypothesized that the relative benefit from statin treatment may be less than that observed in younger patients. However, epidemiologic evidence has not been consistent on this question. Some studies have shown a less-strong association in elderly patients (Kronmal et al. 1993; Krumholz et al. 1994), while others have shown similar associations in older and younger groups (Benfante and Reed 1990; Rubin et al. 1990; Howard et al. 1997).

It has been proposed that the discrepancy in these epidemiologic factors arises from the presence of confounding variables, such as comorbidities and frailty. In one cohort study of 4,066 persons followed for 5 years (Corti et al. 1997), the authors demonstrated that controlling for comorbidities and frailty led to a consistent relative risk for all age groups.

On the other hand, the absolute risk of adverse cardiovascular events increases with age, indicating a potentially larger absolute risk reduction over a given period of time for elderly patients. This is demonstrated by the stratified analysis from the LIPID trial (LIPID Study Group 1998), in which the relative risk for cardiovascular outcomes was stratified by age (Table 2).

There is also some evidence from non-clinical trial data that the absolute benefit from statin treatment may be greater in elderly patients. In a cohort study of 7,221 patients with documented coronary artery disease (CAD), both the relative risk reduction (RRR) and the absolute risk reduction (ARR) were higher for older age groups (Allen Maycock et al. 2002). There were large differences in the ARR, compared to more modest differences in the RRR (Table 3).

Determining the net benefit of statin treatment requires consideration of multiple beneficial effects and potential adverse effects of these agents. The main benefit of statins is a reduction in adverse cardiovascular events. The cardiovascular benefits of statins have been well-established in prior clinical trials.

However, there are other non-cardiovascular benefits that may result from statin use, and which are not as well-characterized as are the effects on cardiovascular outcomes. Some of these secondary benefits may be the result of reducing cholesterol deposition in blood vessels and other organs. Examples of these potential benefits include a decrease in the incidence of dementia, which may be mediated through improved blood flow to the CNS, and a decrease in age-related eye diseases.

In a nested case-control study from the U.K. (Jick et al. 2000), patients between the ages of 50–89 with clinically diagnosed dementia or Alzheimer's disease were compared with non-demented patients on statin use. Patients with untreated hyperlipidemia did not have a significantly reduced risk of dementia (odds ratio [OR] 0.71; 95% CI: 0.45–1.14), while patients treated with statin had a 71% reduction in the incidence of dementia (OR 0.29; 95% CI: 0.13–0.63, p=0.002). In a study of 5,092 elderly participants from one county in Utah (Zandi et al. 2005), the authors found a significant inverse association between statin use and dementia on cross-sectional analysis (OR 0.44; 95% CI: 0.17–0.94). However, over a follow-up of 3 years, statin use at baseline did not predict a lower future incidence of dementia. These findings led the authors to conclude that statins may be less commonly prescribed for patients with dementia rather than that they have a protective effect on the development of dementia.

Age-related eye diseases, such as macular degeneration and/or cataracts, may also be affected by treatment with statins. In the Beaver Dam Study (Klein et al. 2006), a large longitudinal study of risk factors for age-related eye diseases, statins were associated with a lower incidence of nuclear cataracts. The cumulative incidence of cataracts over 5 years was 12.2% in participants using statins and 17.2% in participants not using statins (OR 0.55; 95% CI: 0.36–0.84).

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Figure 1. Comparison of Relative Risk Reduction (RRR) in Major Statin Trials
(Reproduced from NCEP ATP III report: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf, page II-41)

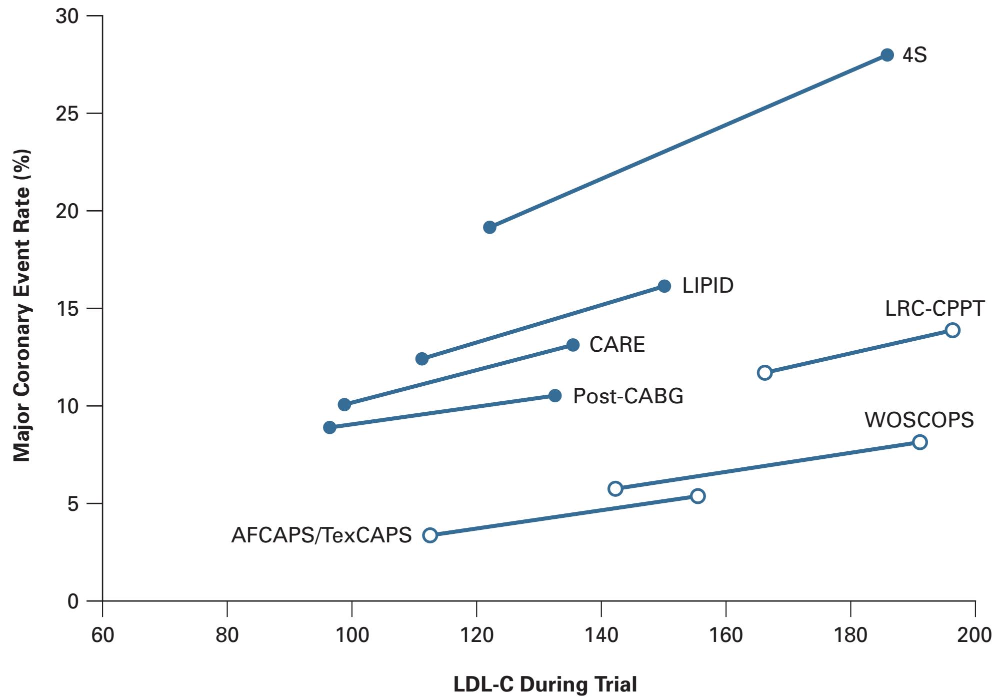

Table 2. Relative Risks for Cardiovascular Events Stratified by Age (LIPID 1998)

	Age Group			
Outcome Measure	<55	55–64	65–69	≥70
Coronary heart disease death	1.00	1.68	2.63	3.97
Cardiovascular death	1.00	1.79	2.94	4.41
Death from any cause	1.00	1.99	3.34	4.44
Stroke	1.00	2.14	4.19	4.36
Myocardial Infarction (MI)	1.00	1.02	1.27	1.50
Coronary heart disease death or non-fatal MI	1.00	1.23	1.79	2.31
Coronary artery bypass graft (CABG) surgery	1.00	1.15	1.20	0.91
Percutaneous transluminal coronary angioplasty	1.00	0.85	0.66	0.57

Table 3. ARR and RRR in Patients with CAD Treated with Statins (from Allen Maycock et al. 2002)

Age	ARR	RRR
<65 years	5.8%	0.70
65–79 years	12.7%	0.56
≥80 years	21%	0.50

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Other potential effects of statins may be unrelated to the lipid-lowering effect. These types of benefits may include the anti-inflammatory effects of statins, improvement in endothelial cell function, and/or effects on platelet function. These potential benefits are often referred to as the "pleiotropic effects" of statins, and mainly refer to the effect of statins on physiologic parameters such as platelet or endothelial function.

There is evidence that statins may be underutilized in the elderly population compared to younger patients (Massing et al. 2001). In an observational study of 49,721 patients with documented coronary artery disease (CAD), there was an inverse relationship between the rates of prescriptions for statins. Approximately 50% of patients 45–54 years of age were prescribed statins. There was a steady decline in the rate of statin use for older age groups, decreasing to approximately 15% in patients older than 85 years.

The reasons for the lower use of statins in the elderly are not well understood. Possible reasons for this pattern are: 1) Lack of evidence for benefit in elderly patients due to exclusion of elderly patients from the major statin trials; 2) perception among physicians that benefit is less due to shorter overall life expectancy; 3) perception among physicians that the risk of statins outweighs the benefits in elderly patients.

Another contributing factor may be that guidelines on statin use in the elderly are not as explicit as those for non-elderly patients. The FDA advisory paper (Pasternak et al. 2002) stated that while statins are not contraindicated in the elderly, "As a rule, statin therapy should be employed more cautiously in older patients, particularly older thin or frail women." Guidelines from the National Cholesterol Education Program (National Cholesterol Education Program 2002) do not separately address recommendations for lipid-lowering therapy in the elderly population. However, these guidelines do state that patients should not be denied lipid-lowering therapy based solely on age.

Methods

Search Methods

Relevant studies were identified in a variety of ways. The major statin trials were identified through review of recent statin review articles, including hand-search of the bibliographies of these studies. A literature search was also performed through MEDLINE® (via PubMed) using the terms "statins," "HMG-CoA Reductase," "elderly," and "aged" from 1980 through September 2006, limited to English-language articles on human subjects. Electronic search was supplemented with the "related articles" function on PubMed for key studies, and with a hand-search of bibliographies from recent review articles and clinical studies. In addition, a separate search was conducted for adverse events using the key words "statins," "HMG-CoA Reductase Inhibitors," "elderly," "adverse events," and "complications." This search was also supplemented by hand search of relevant bibliographies and using the "related articles" function on PubMed.

Study Selection

Studies that met the following inclusion criteria were selected for inclusion in this review:

- Full-length articles published in the peer-reviewed literature
- Randomized, controlled trials that compared treatment with one of the currently available statin medications with placebo control or usual care control group.
- Reported on cardiovascular outcomes
- Included a population of elderly patients (>65 years of age), or reported separate results for the subgroup of elderly patients, or included a subgroup analysis of elderly vs. non-elderly patients for one or more cardiovascular outcomes

For articles on adverse events, studies that met the following criteria were included in the review:

- Full-length articles published in the peer-reviewed literature
- Study design was one of the following:
  - Randomized, controlled trials that compared treatment with one of the currently available statin medications with placebo control or usual care control group, or
  - Cohort study with greater than 100 patients, or
  - Case series with greater than 100 patients
- Reported on adverse events associated with statin treatment

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- Included a population of elderly patients (>65 years of age), or reported separate results for the subgroup of elderly patients, or included a subgroup analysis of elderly vs. non-elderly patients for one or more adverse events

Medical Advisory Panel Review

This Special Report was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on November 2, 2006. In order to maintain the timeliness of the scientific information in this Special Report, literature searches were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Special Report.

Problem Formulation

Patient Indications

The relevant patient population for this review will be elderly patients in whom statin therapy is indicated. Indications for statin therapy will be derived from current available guidelines, most prominently the Third Report of the National Cholesterol Education Program (NCEP) on the Evaluation, Detection and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (National Cholesterol Education Program 2002).

The definition of "elderly" for this Report will be age 65 years and older. Recognizing that this definition represents a wide range of ages that may represent distinct populations in terms of risks and benefits, evidence will be sought that specifically addresses statin us in the following age groups:

- 65–69 years of age
- 70–80 years of age
- >80 years of age

Evidence will also be included, when available, on the comparative efficacy of statins in other subpopulations of the elderly, such as primary vs. secondary prevention, men vs. women, comparisons of specific statin medications, etc.

Technologies to be Compared

The primary comparison for use of statins will be compared to no statin use. The optimal comparison group in trials of statins will therefore be a placebo control.

Statins may also be compared to alternative cholesterol-lowering strategies. These may include nonpharmacologic strategies such as diet and exercise. There are a number of classes of alternative pharmacologic agents, including bile acid sequestrants, nicotinic acids, fibric acids, and ezetimibe.

Health Outcomes

Health outcomes of statin use include beneficial effects of the drugs and adverse effects associated with their use. The overall benefit/risk ratio of statin use in the elderly is the goal of this Report, and will require consideration of the balance of the beneficial and adverse outcomes associated with statin use.

The beneficial effects include the main intended effect of statin use on reducing atherosclerotic vascular disease, as well as secondary beneficial effects that may result. For the purposes of this Report, evidence on the following beneficial health outcomes will be sought:

- Overall mortality
- Cardiovascular mortality
- Non-fatal adverse cardiovascular events
  - MI
  - Stroke
  - Revascularization procedures
  - Hospitalizations for unstable angina
- Incidence and/or progression of dementia
- Incidence of cataracts

Statins may have a variety of other beneficial effects on physiologic parameters (pleiotropic effects). These include beneficial effects on inflammation, endothelial function, platelet function, thrombosis, and anti-oxidant effects. Since these measures represent primarily pathophysiologic effects of statins, they are by definition intermediate outcomes, and will not be included as health outcomes for the purposes of this Report.

Adverse effects of statins include the following:

- Myopathy
- Liver toxicity
- Incidence of cancer
- Other adverse events

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Specific Assessment Question

In elderly patients with indications for statin use, what is the evidence on the efficacy and safety of these agents, compared to no statin use?

Review of Evidence

A total of 12 studies were identified that met the inclusion criteria for this review. Data from 4 large clinical trials provides the bulk of the evidence on the cardiovascular benefits of statins in the elderly population. One of these 4 trials (Shepherd et al. 2002, hereafter referred to as "PROSPER") was conceived and implemented specifically to evaluate the efficacy of statins in an elderly population. For the remaining 3 clinical trials (Sacks et al. 1996, LIPID Study Group 1998, and 4S Group 1994, hereafter referred to as "CARE," "LIPID," and "4S," respectively), a separate article analyzing results in an elderly subgroup was published for each (Lewis et al. 1998, Hunt et al. 2001, and Miettinen et al. 1997, respectively) thus providing a detailed and comprehensive analysis of outcomes in the elderly subgroup. These analyses will be referred to as "extended" subgroup analyses. In 4 other statin trials, there is relevant evidence from a "simple" subgroup analysis, in which the relative risk reduction for one or more of the main outcome measures was compared between younger and older age groups. Additionally, a large patient-level meta-analysis (Cholesterol Treatment Trialists' Collaborators 2005) is included that provides a subgroup analysis by age across 14 separate statin trials. Finally, 3 cohort studies were identified that reported relevant information on adverse events.

Beneficial Outcomes (Reduction in Cardiovascular Events)

PROSPER Trial. The PROSPER trial (Table 4) enrolled 5,804 elderly persons aged 70–82 years with a prior history of vascular disease or risk factors for vascular disease and without cognitive impairment. The trial included a run-in period in which compliance was assessed, and 18% (1,252/7,056) of participants were excluded from randomization for under- or overutilization of medication. Participants were randomized to pravastatin or placebo and assessed every 3 months over a mean follow-up of 3.2 years.

The primary outcome of this trial was a composite end-point of cardiovascular death, non-fatal MI, and fatal and non-fatal stroke. Other endpoints included the individual measures of cardiovascular and cerebrovascular events. Non-cardiovascular endpoints included an assessment of change in cognitive function and disability over the course of the study. This study was rated as "good" by formal quality assessment (Appendix Table A).

Results of PROSPER are summarized in Tables 5 and 6. There was a significant reduction in the rate of the primary endpoint for the pravastatin group (14.1% vs. 16.2%, p=0.014). This represented a RRR of 15%, an ARR of 2.1%, and a number-needed-to-treat of 48 over a 3-year period to prevent one cardiovascular event.

For the secondary outcomes, there were some measures that showed significant group differences, but the majority did not. There was a significant decrease in the composite outcome of all cardiac events for the pravastatin group vs. the control group (15.7 vs. 18.0, HR 0.85; 95% CI: 0.75–0.97, p=0.012). For the individual outcome measures, significant reductions for the statin group vs. placebo were found for coronary heart disease or non-fatal MI (10.1% vs. 12.2%, HR 0.81; 95% CI: 0.69–0.94, p<0.006), transient ischemic attack (2.7% vs. 3.5%, HR 0.75; 95% CI: 0.55–1.0, p=0.05), and deaths from coronary heart disease (3.3% vs. 4.2%, HR 0.76; 95% CI: 0.58–0.99, p=0.043).

Outcome measures that did not show significant group differences were stroke (fatal, non-fatal, and total), non-fatal MI, revascularization, peripheral artery surgery, hospitalizations for heart failure, and deaths from vascular causes, nonvascular causes, cancer, and trauma or suicide. The rate of cognitive decline was similar in both groups. Finally, all-cause mortality was similar in the pravastatin and control groups (10.3% vs. 10.5%, HR 0.97; 95% CI: 0.83–1.14, p=NS).

Prespecified subgroup analyses included a breakdown by pre-existing vascular disease, gender, LDL level, HDL level, smoking, hypertension, and diabetes. Significantly greater risk reductions were found for the subgroups of low HDL level vs. high HDL level (HR 0.64; 95% CI: 0.52–0.80 vs. HR 1.09; 95% CI: 0.84–1.41, p=0.007), and for patients without diabetes vs. patients with diabetes (HR 0.79; 95% CI: 0.69–0.91 vs. HR 1.27; 95% CI: 0.90–1.80, p=0.02).

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There also appeared to be a trend toward a differential effect for gender and pre-existing coronary heart disease (secondary prevention), but these relative risk differences did not reach statistical significance. For the primary outcome measure, the relative rate reduction was greater in men (0.77; CI: 0.65–0.92) than in women (0.96; CI: 0.79–1.18). There was also a more pronounced reduction in relative risk for secondary prevention (0.78; 95% CI: 0.66–0.93) than for primary prevention (0.94; 95% CI: 0.77–1.15).

The 3 other studies in Tables 4–6 represent subgroup analyses from larger statin trials (CARE, LIPID, and 4S). These 3 “extended” subgroup analyses were reported in separate publications, thus allowing more detailed analysis of the elderly subgroup than is available from “simple” subgroup analyses performed as part of the analysis for the entire group. All 3 of these trials evaluated secondary prevention, i.e., enrolled patients with prior coronary heart disease.

CARE Trial. The CARE trial was intended to evaluate secondary prevention with pravastatin in patients with “average” cholesterol levels. The larger trial included 4,159 participants with an age range of 21–75 years, history of previous MI, total cholesterol levels less than 240 mg/dL, and LDL levels between 115-174 mg/dL. Patients were randomized to pravastatin 40 mg or placebo and followed for an average of 5 years.

The CARE subgroup analysis (Lewis et al. 1998) (Table 4) included patients who were 65–75 years old at the time of randomization (n=1,283). The mean age for this population was 69 years. The primary endpoint of the trial was coronary heart disease death or non-fatal MI. Secondary endpoints included the composite outcome of major coronary events (coronary heart disease death, non-fatal MI, bypass, or angioplasty) and individual measures of adverse cardiovascular events, such as MI, stroke, etc. This study was rated as “good” by formal quality assessment (Appendix Table A).

Results demonstrated a benefit for the pravastatin group across most of the outcome measures reported (Tables 5 and 6). There was a 6.7% absolute risk reduction and a 39% relative risk reduction in the primary outcome measure for the pravastatin group, translating to a number needed to treat (NNT) of 15 over a period of 5 years. There were also significant reductions in the rates of MI, stroke, and bypass or angioplasty.

LIPID Trial. The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial enrolled 9,014 patients between the ages of 31–75 years of age with a history of CAD and total cholesterol levels between 155–271 mg/dL. The patients were randomized to pravastatin 40 mg per day or placebo and followed for a mean of 6 years. The primary outcome of this trial was death from coronary disease. Secondary outcome measures included death from any cause, death from cardiovascular disease, death from coronary heart disease or non-fatal MI, total stroke, non-hemorrhagic stroke, revascularization, and hospitalizations.

The subgroup analysis from the LIPID trial (Hunt et al. 2001) included 3,514 patients between the ages of 65–75, with a mean age of 70 (Table 4). This study was rated “good” by formal quality assessment (Appendix Table A).

Results of the LIPD subgroup analysis showed a benefit for the elderly subgroup across all major endpoints (Tables 5 and 6). This included death from any cause, death from cardiovascular causes, and individual measures of adverse cardiovascular events.

4S Trial. The Scandinavian Simvastatin Survival Study (4S) enrolled 4,444 patients 35–70 years of age with a history of CAD and total cholesterol levels between 213–309 mg/dL. Patients were randomized to simvastatin 20 mg per day or placebo, with an increase in simvastatin dose to 40 mg per day if total cholesterol remained greater than 200; median follow-up was 5.4 years. The primary endpoint was all-cause mortality, with other endpoints including major coronary events (CHD deaths, non-fatal MI, or survivors of cardiac arrest), any CHD-related event, any atherosclerotic-related event, and revascularization procedures.

The subgroup analysis of the 4S study (Meittinen et al. 1997) included 1,021 patients between the ages of 65–70 (Table 4). This study was rated “good” by formal quality assessment (Appendix Table A).

Results of this analysis revealed a benefit for the elderly population in all outcomes measured, including all-cause mortality (Tables 5 and 6). There was a relatively large absolute

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Table 4. Statins in the Elderly (Full-length Articles): Study Demographics

Clinical Trial Name	Study Arms	n	Mean Age	Age Range	% male	% female	Diabetes	Smoking	HTN	Prior MI	Prior Angina	Prior Stroke	Prior Vascular Disease[a]	Previous Revasc	Claudication	LDL Baseline	Study Duration (Mean f/u)
PROSPER (Shepherd et al. 2002)	Total	5,804	75	70–82	48	52	11	27	62	14	26	11	44	—	—	147 mg/dL	3.2 years
Elderly men/women age 70 or over with history of	Pravastatin 40 mg	2,891															
CAD or risk factors	Placebo	2,913															
CARE (Lewis et al. 1998)	Total	1,283	69	65–75	81	19	19	12	48	60	23	11	—	55	—	115–174 mg/dL	5 years
Elderly men/women age 65 and over with	Pravastatin 40 mg	640															
CAD, MI, and average cholesterol	Placebo	643															
LIPID (Hunt et al. 2001)	Total	3,514	70	65–75	80	20	10	6	45	60	40	6	—	40	14	129–169 mg/dL	6 years
Elderly men/women with CAD	Pravastatin 40 mg	1,741															
	Placebo	1,773															
4S (Meittinen et al. 1997)	Total	1,021	67	65–75	76	24	6	18	29	68	18	—	—	6	8	213–309 mg/dL	5.4 years
Elderly men/women with previous MI or active,	Simvastatin 20 mg	518															
stable angina	Placebo	503															

[a] Stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction, peripheral arterial disease surgery, or amputation for vascular disease more than 6 months before study entry.

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Table 5. Statins in the Elderly (full-length articles): Results of Individual Endpoints

	Death														
	All cause			Cardiac			Nonfatal MI			Non-fatal Stroke			CABG or PTCA		
Study	Treatment	Placebo	p-value RRR ARR NNT	Treatment	Placebo	p-value RRR ARR NNT	Treatment	Placebo	P-value RRR ARR NNT	Treatment	Placebo	p-value RRR ARR NNT	Treatment	Placebo	p-value RRR ARR NNT
PROSPER	10.3%	10.5%	p=0.74* — — —	3.3%	4.2%	p=0.043 21% 0.9% 111	7.7%	8.7%	p=0.10*	4.0%	4.1%	p=0.85*	1.3%	1.6%	p=0.36*
CARE (subgroup analysis)	—	—	—	5.8%	10.3%	p=0.004 44% 4.5% 22	6.4%	8.9%	p=0.09*	4.5%	7.3%	p=0.03 38% 2.8% 36	11.4% p=0.01	16.2%	p=0.01 30% 4.8% 21
LIPID (subgroup analysis)	16.5	20.6%	p=0.003 20% 4.1% 24	9.2%	11.9%	p=0.009 22% 2.7% 37	8.6%†	11.4%†	p=0.005 74% 3.3% 30				—	—	—
4S (subgroup analysis)	12.9%	19.1%	p=0.009 32% 6.2% 16	8.5%	14.5%	p=0.003 41% 6% 17	17.2%	24.3%	p=0.004 29% 7.1% 14	—	—	—	9.9%	15.9%	p=0.003 38% 6% 17

* Not significant. Note: Study was not powered to detect difference in endpoint.
† Includes fatal and nonfatal MI; Nonfatal MI alone not reported in trial.
CABG: coronary artery bypass graft
PTCA: percutaneous transluminal coronary angioplasty
Shaded results indicate a primary endpoint of the pivotal trial

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Table 6. Statins in the Elderly (full-length articles): Results of Composite Cardiovascular/CHD Endpoints Results

	CHD Death Nonfatal MI Fatal Stroke or Nonfatal Stroke			CHD Death or Nonfatal MI			Fatal or Nonfatal MI (Total MI)			Fatal or Nonfatal Stroke (Total Stroke)		
	Treatment	Placebo	p-value RRR ARR NNT	Treatment	Placebo	p-value RRR ARR NNT	Treatment	Placebo	p-value RRR ARR NNT	Treatment	Placebo	p-value RRR ARR NNT
PROSPER[1]	14.1%	16.2%	p=0.014 13% 2% 50	10.1%	12.2%	p=0.006 17% 2% 50	7.8%	11.4%	p=0.03	4.7%	4.5%	p=0.81*
CARE[2] (subgroup analysis)				10.8%	17.3%	p=0.001 38% 7% 15						
LIPID[3] (subgroup analysis)				15.5%	19.7%	p=0.001 21% 4% 25	8.6%	11.4%	p=0.005 25% 3% 33	6.0%	6.7%	p>0.2* — — —
4S[4] (subgroup analysis)				23.6%	33.4%	p<0.001 29% 10% 10						

* Not significant. Note: Study was not powered to detect difference in endpoint.
Shaded results indicate a primary endpoint of the pivotal trial

reduction in all-cause mortality for this trial of 6.2%, and the absolute risk reduction for other outcomes ranged from 6.0–14.5% (Tables 3 and 4). The relative risk reductions for this population ranged from 33–43% across all outcome measures reported.

Other Beneficial Outcomes. There are limited data from the included studies on the effect of statins on noncardiovascular outcomes. Only one study, PROSPER, specifically included outcome measures designed to evaluate dementia. This study evaluated cognitive decline over time by a number of measures, including the mini-mental status exam, activities of daily living, and a number of standardized cognitive tasks. Cognitive function showed a similar decline in both the pravastatin and placebo groups, with no significant differences noted on any of the outcome measures used.

None of the studies reviewed for this Report included any outcome measures related to the incidence of age-related eye diseases. There were no other noncardiovascular beneficial outcomes reported in these included trials.

Comparison of Benefits in Elderly and Non-Elderly Age Groups. The CARE, LIPID, and 4S trials provided direct comparison of outcomes for elderly patients compared to non-elderly patients. The data from these 3 comparisons provide the most direct evidence on the relative benefits of statin use in older vs. younger patients (Table 7). The "simple" subgroup analyses from an additional four trials (ALLHAT, A to Z, ASCOT-LLA, HPS), as well as the subgroup analysis from the patient-level meta-analysis (Cholesterol Treatment Trialists' Collaborators 2005), provide additional evidence on this question.

In the CARE trial, the elderly population showed greater benefit across nearly all outcome measures compared to the non-elderly population (Table 7), both in the RRR and the ARR. The only outcome measure that did not follow this pattern was unstable angina, in which the benefit was greater for the non-elderly population.

In the LIPID trial, the relative risk was generally similar for elderly and non-elderly patients, but the absolute risk was higher in the elderly group for nearly all outcomes, resulting in lower NNTs for the elderly group.

In the 4S trial, the comparison of younger and older age groups followed a pattern similar to that in the LIPID trial. The relative risk reduction was similar for the primary outcome, and similar or slightly higher in the elderly subgroup for the secondary outcomes. The absolute risk reduction was greater for the elderly population across all outcomes, except for revascularization procedures.

An additional 4 large statin trials (ALLHAT, A to Z, ASCOT-LLA, HPS) contained "simple" subgroup analyses, in which the RRR for the primary outcome was compared among elderly and non-elderly subgroups. For each of these subgroup analyses, the RRR for the primary outcome did not differ significantly between elderly and non-elderly patients (Table 8).

The HPS trial performed a subgroup analysis in 3 age groups, older than 70 years, 65–69 years, and younger than 65 years. For major cardiovascular events, the RRR was slightly lower for the over-70 group (RR 0.79; 95% CI: 0.71–0.89), compared to the 65–69 group (RR 0.74; 95% CI: 0.66–0.84) and the younger than 65 groups (RR 0.74; 95% CI 0.70–0.82). The RRR in all of these subgroups was statistically significant, but the difference between the relative risks among subgroups was not significantly different.

An additional publication from the HPS trial evaluated a number of other outcomes by age subgroups (HPS study group 2005). This analysis, which also evaluated 3 subgroups of age (>70 years, 65-69 years and <65 years), demonstrated that the RRR for all-cause mortality, vascular deaths, and first vascular events were similar for all age subgroups. The RRR was statistically significant in each age strata, with RRR ranging from 12% to 26% for these outcomes. In contrast, there was a non-statistically significant reduction seen in non-vascular deaths, with no difference in the RRR by age.

The ALLHAT trial did not find significant reductions in their primary endpoint of all-cause mortality for either the elderly or non-elderly subgroup. This trial also performed subgroup analysis by age for one of the secondary outcomes, CHD death plus non-fatal MI. For this endpoint, the RRR for the elderly population (0.94; 95% CI: 0.80–1.12) was lower than that for the non-elderly population (0.83-1.06), but neither reached statistical significance. This trial also included a subgroup analysis by age

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Table 7. Direct Comparisons of Benefits in Elderly and Non-Elderly Patients

Outcome	ARR (%)		RRR (%)		NNT	
	>65 yrs	<65 yrs	>65 yrs	<65 yrs	>65 yrs	<65 yrs
CARE Trial						
CAD death or non-fatal MI	6.7	1.5	39	13	15	67
Fatal or non-fatal MI	3.8	2.0	33	21	26	50
CABG or PTCA	5.2	5.0	32	25	19	20
Unstable angina	-1.2	3.8	-8	21	-83	26
Congestive heart failure	3.2	-0.3	23	-6	31	-333
Stroke	2.9	0.4	40	20	34	250
Major coronary event	9.0	4.9	32	19	11	20
LIPID Trial						
CAD death or non-fatal MI	4.7	3.2	22	25	21	31
CAD death	2.9	1.4	24	24	35	71
Death from any cause	4.5	2.2	21	24	22	46
Fatal or non-fatal MI	3.3	2.8	26	31	30	36
Stroke	1.3	0.6	12	26	79	170
Unstable angina	3.2	2.8	11	12	31	36
CABG	2.5	2.6	26	19	40	39
PTCA	.9	1.2	34	12	112	85
4S Trial						
Major cardiac events	9.8	8.3	34	34	10	12
CAD death	6.0	2.8	43	42	17	36
Death from any cause	6.2	2.5	34	28	16	40
Non-fatal MI	7.1	6.6	33	33	14	15
Any CHD-related event	13.3	8.9	34	25	8	11
Any atherosclerotic event	14.5	8.9	33	24	7	11
Revascularization	6.0	5.8	41	35	17	17

ARR absolute risk reduction
CABG coronary artery bypass graft
CAD coronary artery disease
CHD coronary heart disease
MI myocardial infarction
NNT number needed to treat
PTCA percutaneous transluminal coronary angioplasty
RRR relative risk reduction

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Table 8. Other Studies Reporting Results in Elderly Subgroup ("simple" subgroup analyses)

Clinical Trial	Patient Population	Type of Prevention	Study Duration (Mean f/u)	Subgroups by Age	Relative Risk for Primary Outcome
ALLHAT-LLT (n=10,355)	Older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional coronary heart disease risk factor	Primary and secondary prevention	4.8 years	>65 years	1.01 (0.89–1.15)
				55-64 years	0.93 (0.74–1.16)
ASCOT-LLA (n=10,305)	Hypertension patients with average or lower than average cholesterol levels	Primary prevention	3.3 years	>60 years	0.64 (0.47–0.86)
				<60 years	0.66 (0.41–1.06
A to Z (n=4,497)	Early initiation of statins following acute coronary syndrome event.	Secondary prevention	2 years	>65 years	0.90 (0.73–1.18)
				<65 years	0.87 (0.70–1.12)
HPS (n=20,536)	Patients with history of cardiovascular disease, diabetes or non-coronary vascular disease	Secondary prevention	5 years	>70 years	0.79 (0.71–0.89)
				65-69 years	0.74 (0.66–0.84)
				<65 years	0.74 (0.70–0.82)

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Table 9. Adverse Events

Study	Group	Total AEs	Serious AEs	Drug-related AEs	Myalgias/ Myopathy	Rhabdomyolysis	Liver Toxicity	Cancer
Clinical Trials								
PROSPER 2002	Pravastatin	NR	56% (1,608/2,891)	NR	1.2% (36/2,891)	0	0.03% (1/2,891)[1]	8.5%* (245/2,891)
	Placebo	NR	55% (1,604/2,913)	NR	1.1% (32/2,913)	0	0.03% (1/2,913)[1]	6.8% (199/2,913)
CARE	Pravastatin	NR	NR	NR	NR	NR	NR	
	Placebo	NR	NR	NR	NR	NR	NR	
LIPID	Pravastatin	1,437[2] 1,741 pts	NR	NR	13.3 (231/1,741)	NR	NR	21.1 (367/1,741)
	Placebo	1,472[2] 1,773 pts	NR	NR	13.9 (241/1,773)	NR	NR	18.3 (324/1,773)
4S	Simvastatin	88.4% (458/518)	57.5% (298/518)	0.4%[3] (2/518)	NR	NR	1.5%[1] (8/518)	4.6% (24/518)
	Placebo	92.6% (466/503)	68.6% (345/503)	0.4%[3] (2/503)	NR	NR	1.6%[1] (8/503)	6.3% (32/503)
Cohort Studies								
Horiuchi 2004	Simvastatin ("low-dose")	NR	NR	3.2% (316/9,860)	0.8% (79/9,860)	NR	1.0% (99/9,860)	NR
Mellies 1993	Pravastatin 20 mg	NR	NR	17% (9/53)	6% (3/53)	NR	6%[4] (3/53)	NR
	Pravastatin 40 mg	NR	NR	11% (5/44)	0 (0/44)	NR	0[4] (0/44)	NR
D'Agostino 1992	Lovastatin 20–80 mg/day	112[2] 144 pts	NR	NR	13.2% (19/144)	NR	NR	NR

* Significant difference compared to placebo at $p<0.05$
1 Defined as transaminases three times the upper limit of normal or greater
2 Total number of adverse events, rates per-patient NR
3 Serious, adverse events related to drug
4 Defined as discontinuation of medication due to elevated liver enzymes

for one of the secondary outcomes, CHD death plus nonfatal MI. For this outcome, the RRR for the elderly patients (RR 0.94; 95% CI: 0.80–1.12) was somewhat less than for the non-elderly population (RR 0.83; 95% CI: 0.65–1.06), but this RRR did not reach statistical significance for either subgroup and the difference in the relative risks was not statistically significant.

The ASCOT-LLA trial was the only primary prevention trial that reported a subgroup analysis based on age. For this trial, the RRR was essentially the same for patients older than 60 years of age (RR 0.64; 95% CI: 0.47–0.86) and for patients younger than 60 years (RR 0.66; 95% CI: 0.41–1.06). The RRR reached statistical significance for the older subgroup but not for the younger subgroup.

The A to Z trial reported a subgroup analysis for patients older than 65 years of age compared to patients younger than 65 years. The RRR for this analysis was essentially the same in both the elderly (RR 0.90; 95%CI: 0.73–1.18) and the non-elderly subgroups (RR 0.87; 95% CI: 0.70–1.12). For both subgroups, the RRR did not reach statistical significance.

An individual patient-level meta-analysis of 90,056 patients from 14 large statin trials was published in 2005 (Cholesterol Treatment Trialists' Collaborators 2005). This included approximately 34,982 patients who were older than 65 years at the start of the trial and approximately 7,304 patients older than 75 years at the start of the trial. This analysis included all of the elderly patients contained in the present Special Report from the 8 trials containing any type of subgroup analysis by age, as well as participants from 6 additional statin trials that did not report any subgroup analysis by age. The authors of this study reported their outcomes in a slightly different manner, indexing the reduction in cardiovascular events to the reduction in LDL levels, as the RRR per 1.0 mmol/L reduction in LDL.

The authors of this meta-analysis examined 2 composite outcomes (major coronary events and major vascular events) in 3 subgroups of age, ≤65 years, >65 years, and >75 years. For major coronary events, the relative risk was slightly lower in the ≤65 years age group (RR 0.74, 95% CI: 0.69–0.79) compared to the >65 years group (RR 0.81, 95% CI: 0.76–0.88) and the >75 years group (RR 0.82, 95% CI 0.70–0.96). The relative risk for the ≤65 years age group was significantly different from the older age groups at p=0.01. The absolute decrease in major coronary events did not differ for the ≤65 years group (2.4%) compared to the >65 years group (2.4%) and the >75 years group (2.2%). For major vascular events, the RR for the ≤65 years age group was 0.78 (95% CI: 0.75-0.81) compared with a RR of 0.81 (95% CI: 0.77–0.86) for the >65 years age group and 0.82 (95% CI: 0.72–0.93) for the >75 years group. The difference between these relative risks was not significant.

This meta-analysis also examined the benefits of statin use by length of time on the medications. This analysis is important for the elderly population since they are likely to be treated for shorter periods of time due to a lower life expectancy. The authors concluded that a significant benefit was evident by 1 year of treatment. This benefit increased over the subsequent years up to 5 years of treatment.

Adverse Events

Data on adverse events were reported by 3 of the 4 clinical trials included in this Report (PROSPER, LIPID, 4S). The fourth clinical trial, CARE, did not contain any data on adverse events for the elderly subpopulation. An additional 3 cohort studies were identified that met the inclusion criteria for adverse events (Horiuchi et al. 2004; Mellies et al. 1993; D'Agostino et al. 1992). Results from these studies are summarized in Table 9.

In the clinical trials, the overall rates of adverse events, defined as either total adverse events or serious adverse events, were not higher for the statin group compared to placebo groups. In the PROSPER trial, the overall rates of adverse events were similar between groups, with one or more serious adverse events reported by 56% of patients in the pravastatin group and 55% in the placebo group. The LIPID trial reported a total of 1,437 adverse events in 1,741 patients for the pravastatin group, compared with 1,472 adverse events in 1,773 patients in the placebo group. In the 4S trial, serious adverse events were reported in 57.5% of patients in the simvastatin group compared with 68.6% in the placebo group. In the 3 cohort studies, the rates of drug-related adverse events ranged from 3.2–17%.

Myalgias and/or myopathy were reported by 2 of the clinical trials (PROSPER, LIPID). In both

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trials, the rate of patient-reported symptoms of myalgia was similar between the statin and control groups (1.2% vs. 1.1% in PROSPER; 13.3% vs. 13.9% in LIPID), and there were no reported cases of rhabdomyolysis in either group. In the cohort studies, symptomatic myalgias were reported by 0.8–13.2% of patients.

Abnormal liver function enzymes (transaminases greater than 3 times normal) were reported by 2 clinical trials, PROSPER and 4S, with similar rates reported for the statin and placebo groups. Abnormalities in liver function enzymes were reported by 2 of the cohort studies (Horiuchi et al. 2004; Mellies et al. 1993), with rates of 1% and 3% respectively.

The incidence of new cancers (excluding non-melanoma skin cancers) was reported by 3 trials (PROSPER, LIPID, 4S). In PROSPER, the overall incidence of cancer was higher in the pravastatin group compared to the control group. There were a total of 245 cancers among 2,891 persons in the pravastatin group and 199 cancers among 2,913 persons in the control group (HR 1.25; 95% CI: 1.05–1.51, p=0.02). When examined by specific type of cancer, there was a significant increase for gastrointestinal cancer (HR 1.46; 95% CI: 1.00–2.13, p=0.05), but not for other types of cancer.

In the LIPID trial, the incidence of cancer in the elderly subpopulation was slightly higher for the pravastatin group compared to placebo, but this difference did not quite reach statistical significance (RR 1.14; 95% CI: 0.98–1.32). In contrast, for the non-elderly population the risk of cancer was slightly lower for the pravastatin group, but this difference again did not quite reach statistical significance (RR 0.87; 95% CI: 0.73–1.02). In the 4S trial, there were more cancers reported in the placebo group compared to the simvastatin group (6.3% vs. 4.6%) but this difference also did not reach statistical significance.

Discussion

Evidence on the cardiovascular benefits of statins in the elderly is derived primarily from one large randomized controlled trial that is restricted to the elderly population (PROSPER), and extended subgroup analyses on the elderly population from 3 other large statin trials (CARE, LIPID, 4S).

The evidence from these 4 trials demonstrates that statin therapy in the elderly population results in reduced rates of adverse cardiovascular outcomes. The benefit in the elderly population is likely to be at least as great as the benefit in the non-elderly population. In the 3 studies that provide direct comparisons between elderly and non-elderly patients, the absolute risk reduction and the number-needed-to-treat are consistently higher for the elderly subgroup. This pattern is true for all outcomes except for revascularization procedures. The lack of benefit seen for reduction in revascularization procedures may result from decisions to treat the elderly less aggressively with invasive procedures compared to the non-elderly population.

In the studies providing direct comparisons, the relative risk reduction is approximately the same, or slightly higher, for the elderly population compared to the non-elderly population. In 2 of the 3 reports (LIPID, 4S), the RRR was roughly equivalent between groups, while in the third report (CARE) the RRR was greater for the elderly population across the majority of reported outcomes. As with the ARR, the RRR for revascularization procedures was not greater for the elderly population.

The individual patient-level meta-analysis, which included the data from all of the trials included in this review, in addition to 6 other studies that provided patient-level data, corroborates the conclusion that there is a significant reduction in cardiovascular outcomes for the elderly population. Overall the RRR and ARR for the main outcomes were similar to that found in the individual studies included in this assessment. The conclusions of this meta-analysis differed in that the relative risk reduction was statistically less for elderly vs. non-elderly patients (0.29 vs. 0.36, p<0.01), while the ARR was not statistically different between the 2 groups (2.4% vs. 2.4%, p=NS).

There are several caveats to these conclusions, however. First, the only trial that specifically evaluated the elderly population, PROSPER, reported somewhat less benefit compared to the other trials. Both the RRR (15%) and the ARR (2.1%) for the primary outcome in this trial were relatively small compared to the other trials. In addition, the majority of secondary outcome measures did not show significant differences in PROSPER.

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Second, the entire range of the "elderly" population is not well represented by these data. There is very little data for patients over 75 years of age, and essentially no data for patients 80 years old or greater. As a result of the lack of patients greater than 75 years old, the comparisons made between the elderly and non-elderly populations are made within a relatively narrow range of ages.

Third, the evidence from these trials refers to the initiation of statin therapy, as opposed to the continuation of statin therapy in elderly patients who are already on treatment. However, it is likely that the data on initiation of therapy is generalizable to the continuation of therapy. Also, this evidence mainly supports the use of statins for secondary prevention in the elderly, and there is very limited evidence from these trials on the benefits for primary prevention. The PROSPER trial included both patients with prior CAD (secondary prevention) and patients with only risk factors for CAD (primary prevention). There were 2,565 patients with prior CAD and 3,239 patients without prior CAD. On subgroup analysis, the reduction in relative risk of coronary events was substantially greater for usage in secondary prevention (0.78; 95% CI: 0.66–0.93) than in primary prevention (0.94; 95% CI: 0.77–1.15).

The other three trials that reported extended subgroup analyses were all secondary prevention trials and all these trials supported significant benefits for the elderly population. Evidence from the simple subgroup analyses were also primarily for secondary prevention. One simple subgroup analysis was from a primary prevention trial (ASCOT-LLA) and in this trial, the relative risk reduction was essentially the same.

The available evidence on adverse events in the elderly population is derived from the PROSPER study, 2 of the 3 extended subgroup analyses, and an additional 3 small cohort studies. In the clinical trials included in this review that reported adverse events, rates of adverse events were similar between the statin and the placebo groups. Myopathy and rhabdomyolysis, perhaps the most serious complications of statin therapy, may be more common in the elderly, however the available evidence included in this review is not sufficient to determine whether this is true. The incidence of serious myopathies and rhabdomyolysis is exceedingly low across the entire population of patients treated with statins. Therefore, small to modest increases in the rates of these complications for elderly patients will still mean that the absolute risk of these events is quite small.

The data on whether statin therapy in the elderly is associated with higher rates of cancer is not definitive. Although numerous meta-analyses have demonstrated a lack of increased cancer risk in the overall populations of the statin trials, the same cannot be said for the elderly population. The PROSPER trial reported a statistically significant 25% increase in the rate of all cancers (excluding non-melanoma skin cancers) for the pravastatin group. The LIPID trial reported an approximately 14% increase in the incidence of cancer for the statin group, a difference that approached but did not reach statistical significance (RR 1.14; 95% CI: 0.98–1.32). Interestingly, this trial reported a decrease in cancer incidence of a similar magnitude for the non-elderly population (RR 0.87; 95% CI: 0.73–1.02) resulting in no difference in cancer incidence between the statin and placebo groups across the entire population. The 4S trial subgroup analysis did not report an increased risk of cancer for the statin group.

There are few data available from clinical trials to evaluate the non-cardiovascular benefits of statins. The PROSPER trial evaluated the rate of cognitive decline, and found that statin use was not associated with an improvement in the rate of cognitive decline. There were no other non-cardiovascular benefits included among the outcome measures in the 4 trials included in this Report.

Because of the lack of robust data on adverse events and non-cardiovascular benefits, it is not possible to determine the overall benefit/risk ratio of these agents. While the cardiovascular benefits are likely to be the primary determinant of decisions to use these agents, there may be clinical situations where risks of adverse events or other potential non-cardiovascular benefits may be important considerations in whether to use a statin. Better evidence on these outcomes would be helpful to clinicians who may need to make decisions based on a more precise estimate of the overall benefit/risk ratio for these medications.

The balance sheet for beneficial and adverse outcomes (Table 10) attempts to give the best possible overview of the benefits and risks of

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statins in elderly patients. This table reiterates the cardiovascular benefits of statins for the elderly, which are at least as large, or larger, than the benefits in the non-elderly population. However, there is considerable uncertainty regarding the non-cardiovascular benefits of statins, and the rates of adverse events, in the elderly population, limiting the overall conclusions that can be made.

Despite the lack of good data on the rates of adverse events, it is extremely unlikely that any small to moderate increase in the rates of adverse events, such as might be reasonably expected in the elderly population, will outweigh the cardiovascular benefits. Therefore, there are no compelling reasons to withhold statin therapy in the elderly population, especially for secondary prevention.

One factor that may limit the benefits of statins for the elderly population is a lower life expectancy. For elderly patients with very short life expectancies, the absolute benefit of statin therapy is reduced. The length of treatment in the available studies is 3–7 years. The majority of elderly patients without a terminal disease will, in fact, have life-expectancies exceeding 5–7 years and therefore will benefit from statin therapy. The individual patient-level meta-analysis reported benefit by length of time treated and concluded that a significant benefit could be detected after 1 year of treatment.

The results of this Special Report suggest that the lower rate of statin prescriptions in elderly patients represents underuse of these agents. Underuse may result from the perception that the benefit of statin therapy is less in the elderly and that adverse effects are substantially greater. These assumptions, however, are not supported by the data. Health plans might consider educational programs intended to increase the use of statins for secondary prevention in elderly populations.

Table 10. Balance Sheet: Statin Use in the Elderly

	Elderly	Non-Elderly	No Statin Use
All-cause mortality	↓	↓	—
Cardiovascular			
Coronary heart disease death	↓↓(↓)	↓↓	—
Composite cardiovascular events	↓↓(↓)	↓↓	—
Myocardial infarction	↓↓	↓↓	—
Stroke	↓(?)	↓(?)	—
Revascularization procedures	↓(?)	↓↓	—
Non-cardiovascular			
Dementia/Alzheimer's	(?)	NA (?)	—
Cataracts	(?)	NA (?)	—
Macular degeneration	(?)	NA (?)	—
Adverse events			
Myopathy/rhabdomyolysis	↑(↑)	↑	—
Liver toxicity	↑(?)	↑(?)	—
Cancer incidence	↑(?)	—	—
Other adverse events	(?)	(?)	—

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References

Allen Maycock CA, Muhlestein JB, Horne BD et al. (2002). 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*, 40:1777-1785.

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. (2002). Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*, 288:2998-3007.

Arntz HR, Agrawal R, Wunderlich W et al. (2000). Beneficial effects of pravastatin (+/-colestyramine/niacin) initiated immediately after a coronary event (the randomized Lipid-Coronary Artery Disease [L-CAD] Study). *Am J Cardiol,* 86:1293-8.

Asselbergs FW, Diercks GFH, Hillege HL et al., for the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators. (2004). Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminemia. *Circulation,* 110:2809-16.

Benfante R, Reed D. (1990). Is elevated serum cholesterol level a risk factor for coronary heart disease in the elderly? *JAMA*, 263:393-396.

Cannon CP, Braunwald E, McCabe C et al. (2004). Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*, 350:1495-504.

Cholesterol Treatment Trialists' Collaborators. (2005). Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet*, 366:1267-1278.

Colhoun HM, Betteridge DJ, Durrington PN et al. (2004). Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study (CARDS): multicentre randomized placebo-controlled trial. *Lancet*, 685-96.

Corti MC, Guralnik JM, Salive ME et al. (1997). Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. *Ann Intern Med*, 126:753-760.

D'Agostino RB, Kannel WB, Stepanians MN et al. (1992). Efficacy and tolerability of lovastatin in elderly hypercholesterolemic patients. *Clin Ther*, 14:68-76.

de Lemos JA, Blazing MA, Wiviott SD et al. (2004). Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes. Phase Z of the A to Z trial. *JAMA*, 292:1307-16.

Downs JR, Clearfield, M, Weis S et al. (1998). Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. *JAMA*, 279:1615-22.

Heart Protection Study Collaborative Group. (2002). MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo controlled trial. *Lancet,* 360:7-22.

Heart Protection Study Collaborative Group. (2005). The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: a randomized placebo-controlled trial. *BMC Medicine*, 3;6:1-21.

Hodaas H, Fellstrom B, Jardine AG et al. (2003). Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomized, placebo-controlled trial. *Lancet*, 361:2024-31.

Horiuchi H, Kita T, Mabuchi H et al. (2004). Primary cardiovascular events and serum lipid levels in elderly Japanese with hypercholesterolemia undergoing 6-year simvastatin treatment: a subanalysis of the Japan lipid intervention trial. *J Am Geriatr Soc*, 52:1981-1987.

Howard G, Manolio TA, Burke GL et al. (1997). Does the association of risk factors and atherosclerosis change with age? *Stroke*, 28:1693-1701.

Hunt D, Young P, Simes J et al. (2001). 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*, 134:931-40.

Jick H, Zornberg GI, Jick SS et al. (2000). Statins and the risk of dementia. *Lancet*, 356:1627-1631.

Klein BE, Klein R, Lee KE et al. (2006). Statin use and incident nuclear cataract. *JAMA*, 295:2752-2758.

Kronmal RA, Cain KC, Ye A et al. (1993). Total serum cholesterol levels and mortality risk as a function of age. *Arch Intern Med*, 153:1065-1073.

Krumholz HM, Seeman TE, Merrill SS et al. (1994). Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA*, 272:1335-1340.

Lansberg PJ, Mitchel YB, Shapiro D et al. (1995). Long-term efficacy and tolerability of simvastatin in a large cohort of elderly hypercholesterolemic patients. *Atherosclerosis*, 116:153-162.

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Lewis SJ, Moye LA, Sacks FM et al. (1998). 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*, 129:681-9.

Liem AH, van Boven AJ, Veeger NJ et al., for the FLuvastatin On Risk Diminishment after Acute myocardial infarction study group. (2002). Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. *Eur Heart J*, 23:1931-7.

LIPID Study Group. (1998). 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,* 339:1349-57.

Massing MW, Sueta C, Chowdhury M et al. (2001). Lipid management among coronary artery disease patients with diabetes mellitus of advanced age. *Am J Cardiol*, 87:646-649.

Mellies MJ, DeVault AR, Kassler-Taub K et al. (1993). Pravastatin experience in elderly and non-elderly patients. *Atherosclerosis*, 101:97-110.

Miettinen TA, Pyorala K, Olsson AG et al. (1997). Cholesterol-lowering in women and elderly patients with myocardial infarction and angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). *Circulation,* 96:4211-8.

National Cholesterol Education Program. (2002). Third report of the National Cholesterol Education Program (NCEP) on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. NIH publication No. 02-5215, http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf, accessed 10/3/06.

Pasternak RC, Grundy SM, Smith SC et al. (2002). ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. *J Am Coll Cardiol,* 40:567-571.

Riegger G, Abletshauser C, Ludwig M et al. (1999). The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment. *Atherosclerosis,* 144:263-70.

Rubin SM, Sidney S, Black DM et al. (1990). High blood cholesterol in elderly men and the excess risk for coronary heart disease. *Ann Intern Med*, 113:916-920.

Sacks FM, Pfeffer MA, Moye LA et al. (1996). The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*, 335:1001-9.

Scandinavian Simvastatin Survival Study Group. (1994). Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet*, 334:1383-9.

Schwartz GG, Olsson AG, Ezekowitz MD et al. (2001). Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL Study: a randomized controlled trial. *JAMA*, 285:1711-8.

Sever PS, Dahlof B, Poulter NR et al. (2003). Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower than average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid lowering arm (ASCOT-LLA): a multicentre randomized controlled trial. *Lancet,* 361:1149-58.

Shepherd J, Biauw GJ, Murphy MB et al. (2002). Pravastatin in elderly individuals of vascular disease (PROSPER): a randomized controlled trial. *Lancet*, 360:1623-30.

Shepherd J, Cobbe SM, Ford I et al. (1995). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med,* 333:1301-7.

Thompson PD, Clarkson P, Karas RH. (2003). Statin-associated myopathy. *JAMA*, 289:1681-1690.

Zandi PP, Sparks DL, Khachaturian AS et al. (2005). Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch Gen Psychiatry*, 62:217-224.

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Appendix

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Table A. Quality Assessment for Clinical Trials

Study/yr	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Comparable Intervention(s)	Comparable Measurements	Appropriate Analysis of Outcomes	OVERALL QUALITY LEVEL
PROSPER 2002	YES	YES (?) 86% of follow-up visits completed, same in each group	YES	YES	YES All comparisons of outcomes done with ITT	GOOD
CARE	YES	YES (?) 92% adherence with follow-up visits in statin group, 86% in placebo	YES	YES	YES All comparisons of outcomes done with ITT	GOOD
LIPID	YES	YES (?)	YES	YES	YES All comparisons of outcomes done with ITT	GOOD
4S	YES	YES (?)	YES	YES	YES All comparisons of outcomes done with ITT	GOOD

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