

Efficacy and Safety of Statin Monotherapy in Older Adults: A Meta-Analysis

Caroline G. P. Roberts,¹ Eliseo Guallar,² and Annabelle Rodriguez¹

¹Division of Endocrinology, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

²Department of Epidemiology, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland.

Background. Statin therapy significantly reduces cardiovascular events. Older patients, however, are less likely to be prescribed statins than younger patients due to concern over lack of indication, lower predictive value of cholesterol levels, and increased risk of adverse events. To determine the effect of statins on all-cause mortality and on major cardiovascular events, including stroke, we performed a meta-analysis of statin trials that included older adult participants.

Methods. Mortality, cardiovascular events, and adverse event outcomes were extracted from published randomized, placebo-controlled clinical trials of persons aged 60 years and older.

Results. Data on 51,351 patients were evaluated. Statins reduced all-cause mortality by 15% (95% confidence interval, 7%–22%), coronary heart disease (CHD) death by 23% (15%–29%), fatal or nonfatal myocardial infarction (MI) by 26% (22%–30%), and fatal or nonfatal stroke by 24% (10%–35%). The relative risk of cancer comparing statins to placebo was 1.06 (0.95–1.18). Adverse event data were not consistently reported.

Conclusions. Statin therapy significantly reduced all-cause and CHD mortality, as well as risk of stroke and MI. Statin therapy should be offered to older patients at high risk of atherosclerotic disease events.

THE risk of coronary heart disease (CHD) increases progressively with greater total cholesterol levels (1), but the predictive value of cholesterol levels in older individuals is less robust than in younger individuals (2). The possibility of a lower benefit, the lack of a perceived indication (3), and concerns about the increased risk of adverse events (AE) (4) likely contribute to the observation that statins are prescribed less often in older patients (3,5,6). Because cardiovascular event rates increase as people age beyond 65 years (7), this attitude may translate into a suboptimal use of statins for population prevention strategies.

Older adults derive benefit from many other cardiovascular preventive and therapeutic interventions, including antihypertensive therapies (8), coronary artery bypass grafting (9), and percutaneous coronary intervention (10). For statins, post hoc analyses of randomized controlled trials have demonstrated effective reductions of CHD mortality (11–13), all-cause mortality (11,13), and composite cardiovascular events in elderly persons (11,13). Additionally, the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a randomized controlled trial specifically designed to evaluate statin therapy in the elderly population showed that statin therapy reduced composite coronary events and CHD death but not all-cause mortality or stroke (14). In a recent meta-analysis of randomized controlled trials, statin monotherapy was effective in reducing CHD death and major vascular events in participants 65 years and older (15). This reduction was significant and similar in magnitude to the effect of statins in younger persons. However, all-cause mortality, stroke risk reduction, and AE rates were not specifically reported for the older individuals. Thus, the purpose of this meta-

analysis was to provide a detailed assessment of the efficacy and safety of statins on clinical outcomes in older adults.

METHODS

We performed a PubMed search designed to identify randomized controlled trials of atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, and lovastatin using a validated algorithm for identifying randomized controlled trials in PubMed (16). The search period was from 1966 through 2005.

Prespecified inclusion criteria were: (i) double-blinded, randomized comparison of statin versus placebo; (ii) average age of study participants ≥ 60 years or presence of subgroup analyses limited to participants ≥ 60 years of age; (iii) duration of the randomized portion of the study at least 1 year, with at least 50% of the randomized participants completing 1 year of treatment; (iv) report of total mortality or clinical cardiovascular endpoints and/or AE outcomes; and (v) study population not composed of end-stage renal disease patients. We excluded studies of cerivastatin as this statin is no longer on the market.

Data Abstraction and Quality Assessment

Two investigators (CGPR and AR) independently reviewed the titles, abstracts, and text of retrieved articles to evaluate eligibility criteria and to extract study data. Disagreements were resolved by consensus. We attempted to contact corresponding authors for cardiovascular event outcomes that were not reported in the selected publications.

Study Outcomes

The cardiovascular outcomes analyzed were all-cause mortality, CHD mortality, fatal and nonfatal MI, and fatal

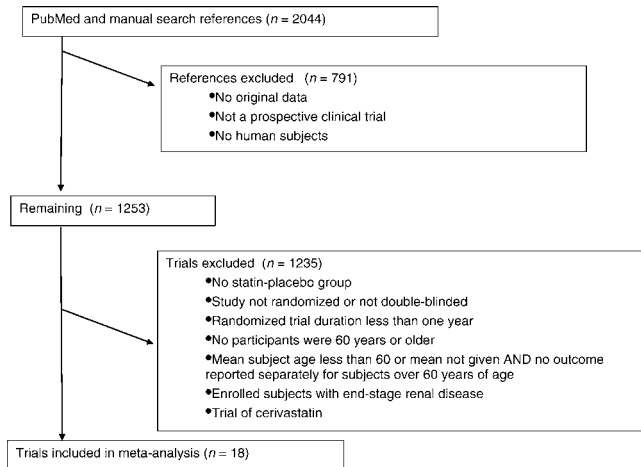


Figure 1. Schema of PubMed literature search. A total of 2044 articles were identified based on a selection of keywords. Eighteen publications were deemed acceptable for the meta-analysis based on prespecified criteria.

and nonfatal stroke. As the stroke rate in persons 65 years and older was reported separately in the Heart Protection Study (HPS) (17), these values were used rather than the stroke rate for the entire HPS study population. The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) reported fatal and nonfatal MI rate in persons > 60 years old, thus these values were used in our analysis, whereas other outcomes from this trial were from all individuals (18). Event rates were evaluated for the five trials and trial subanalyses that included only persons 65 years old and older and that reported cardiovascular outcomes (11–14). The time of divergence of cumulative cardiovascular events of statin and placebo groups was collected. Specific AE included cancer incidence, incidence of creatine kinase (CK) > 10 times the upper limit of normal, incidence of hepatic transaminase levels > 3 times the upper limit of normal, and incidence of persons withdrawing from the trial due to an AE. Other AE were grouped by organ system.

Statistical Analyses

All analyses were performed by intention-to-treat. Relative risks (RRs) and 95% confidence intervals (CIs) comparing statin versus placebo were calculated for each study. Pooled RRs were computed using an inverse variance weighted random effects model. Between-study heterogeneity was quantified by the chi-square statistic. Statistical analyses were performed with Stata 9 (StataCorp LP, College Station, TX), and p values < .05 were considered significant.

RESULTS

Figure 1 summarizes the trial selection process. Table 1 shows the characteristics of the 18 trials included in our analysis (11–14,17–31). The total number of participants was 51,351 with 4961 total deaths. Persons in 13 trials ($N = 41,702$) had a mean age < 70 years, and in 3 trials ($N = 6041$) a mean age \geq 70 years. The mean age was not

available for two trials ($N = 3608$). Twenty-eight percent of individuals were women. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial subgroup analysis of 997 women participants met our criteria for inclusion in the meta-analysis, whereas the results of the overall trial did not. Of the nine trials that reported race, 94% of 17,471 participants were white.

Of the 51,351 participants in the 18 trials, 31,633 (62%) were aged 60 years or older (11–14,17–19,22–26,28,31). The age of 4111 participants (8%) could not be determined as this information was not reported (20,21,27,29,30); however, these trials were included because the mean age was 60 years or older. Of the 31,633 older participants, 11,859 (37%) were enrolled in trials that either specifically and exclusively enrolled persons 65 years old or older or reported subanalyses for persons 65 years old or older (11–14,19,24).

Most trials targeted populations at high risk for CHD events, requiring a history of confirmed coronary artery disease, the presence of Adult Treatment Panel (ATP) III CHD risk equivalents, or the presence of ATP III risk factors such as early family history of CHD, smoking, or hypertension. Only two studies (19,26) excluded persons with CHD.

All-Cause Mortality

There were 4961 deaths of 49,210 participants in the 14 trials that reported all-cause mortality. The statin group showed a significant 15% reduction in all-cause mortality in older adult (RR = 0.85, 95% CI, 0.78–0.93; $p = .001$) (Figure 2). There was no statistically significant heterogeneity between the 14 trials (p for heterogeneity = .14). Of the 10,433 participants 65 years old or older in four trials reporting all-cause mortality, 654 events occurred in the statin group, and 769 events occurred in the placebo group (RR = 0.83, 95% CI, 0.70–0.99; $p = .04$; p heterogeneity = .09) (11,12,14,22).

Four trials reported time-to-event data for all-cause mortality (11,12,20,31). The two trials that specifically reported these data separately for participants 65 years old or older showed a separation of cumulative events at 1 year (11) and between 2 and 3 years (12). The other two trials with a mean participant age of 60 years or older showed separations in events at 3 months (20) and at 1 year (31).

Cardiovascular Outcomes

A total of 2152 CHD deaths occurred in 36,729 individuals in the nine studies that reported CHD death. Nine hundred forty-three CHD deaths were in statin-treated participants, and 1209 were in placebo-treated participants. The reduction in CHD deaths due to statin therapy was 23% (RR = 0.77, 95% CI, 0.71–0.85; $p < .001$) (Figure 3), with no statistically significant heterogeneity between trials (p for heterogeneity = .40). Of the 11,622 participants 65 years old or older in four trials reporting CHD death in this age group, 335 deaths occurred in the statin group and 472 occurred in the placebo group (RR = 0.71, 95% CI, 0.61–0.82; $p < .01$; p for heterogeneity = .3) (11–14).

The findings were very similar for MI risk. There were 3962 fatal and nonfatal MI in the 44,541 participants

Table 1. Characteristics of Trials Included in the Meta Analysis

Study Name or First Author, Year (Ref)	Countries	Population	Cholesterol Inclusion Criteria (mg/dL)	Percent Men	Percent White	Statin	Avg Follow-Up, y	N	Average Age	Age Range, y
Santinga et al., 1994 (19)*	United States	Medical clinic	LDL-C > 165 for men, > 170 for women; Trig < 250	33	75	Pravastatin	1.8	141	71	64-90
ACAPS, 1994 (20)	United States	Asymptomatic carotid artery	LDL-C 130-159 with any risk factors, or 160-189 with up to one risk factor; Trig ≤ 400	52	92	Lovastatin	3	919	61	40-79
Oxford Cholesterol Study, 1994 (21)	United Kingdom	CAD or CAD risk factors	Total C ≥ 136	85	NR	Simvastatin	3.4 [†]	621	63	40-75
PLAC-I, 1995 (22)	Canada, United States	Undergoing coronary angiography	LDL-C ≥ 130, < 190; Trig ≤ 350	78	88	Pravastatin	2.3	94	NR	65-75
PLAC-II, 1995 (23)	United States	CAD	Male age 50-54 y, LDL-C 140-185; Male age ≥ 55, LDL-C 150-182; Female age 50-54 y, LDL-C 148-152; Female age ≥ 55, 151-189; Trig < 350	85	NR	Pravastatin	3	151	63	50-75
Chan, 1996 (24)*	Taiwan	Hypertension and lipid clinic	Total C ≥ 250; Trig < 399	49	NR	Pravastatin	1	96	77	≥ 65
4S Elderly, 1997 (11)	Nordic countries	CAD	Total C ≥ 212-309; Trig ≤ 221	76	NR	Simvastatin	5.4	1021	67	65-70
CARE elderly subanalysis, 1998 (13)	Canada, United States	CAD	Total C < 240; LDL-C 115-174; Trig < 350	82	94	Pravastatin	5 [†]	1283	69	65-75
SCAT, 2000 (25)	Canada	CAD	Total C ≥ 159-240; HDL-C < 85	89	NR	Simvastatin	4	460	61	≥ 30
AFCAPS/TexCAPS Women's subanalysis, 2001 (26)	United States	No evidence of CAD, low HDL	Total Chol 180-264; LDL-C 130-190; HDL-C ≤ 47; Trig ≤ 400	0	89	Lovastatin	5.2	997	63	55-73 y
LIPID elderly subanalysis, 2001 (12)	Australia, New Zealand	CAD	Total C 155-270; Trig < 445	80	NR	Pravastatin	6	3514	NR	65-75
FLORIDA, 2002 (27)	The Netherlands	CAD	Total C ≤ 252; Trig ≤ 399	83	99	Fluvastatin	1	540	61	30-87
HPS, 2002 (17,28)	United Kingdom	CAD, other arterial disease or DM; HTN (subset of patients)	Total C ≥ 135, ≤ 270	75	NR	Simvastatin	5	20,536	64	40-80
LIPS, 2002 (29)	Europe, Canada, Brazil	Successful percutaneous intervention	Total C 135-270; Trig < 400	84	NR	Fluvastatin	3.9	1677	60	18-80
PROSPER, 2002 (14)*	Scotland, Ireland, The Netherlands	Vascular disease or smoking, HTN or DM	Total C 155-349, Trig < 532	48	NR	Pravastatin	3.2	5804	75	70-82
ASCOT-LLA, 2003 (18)	Nordic countries, United Kingdom, Ireland	Hypertension	Total C ≤ 252; Trig ≤ 445	81	95	Atorvastatin	3.3 [†]	10,305	63	40-79
Mohler et al., 2003 (30)	United States	Peripheral artery disease	LDL-C ≤ 160	77	94	Atorvastatin	1	354	68	≥ 25
CARDS, 2004 (31)	United Kingdom, Ireland	Type 2 DM	LDL-C ≤ 160; Trig < 600	68	94	Atorvastatin	4 [†]	2838	62	40-75

Notes: *Study specifically and exclusively enrolled elderly participants only.
[†]Median.

C = cholesterol; NR = not recorded; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; Trig = triglycerides; CAD = coronary artery disease; HTN = hypertension; DM = diabetes mellitus; ACAPS = Asymptomatic Carotid Artery Progression Study; PLAC = Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; CARE = Cholesterol and Recurrent Events; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; FLORIDA = Fluvastatin On Risk Diminishing after Acute Myocardial Infarction; HPS = Heart Protection Study; LIPS = Lescol Intervention Prevention Study; PROSPER = Pravastatin in elderly individuals at risk of vascular disease; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study.

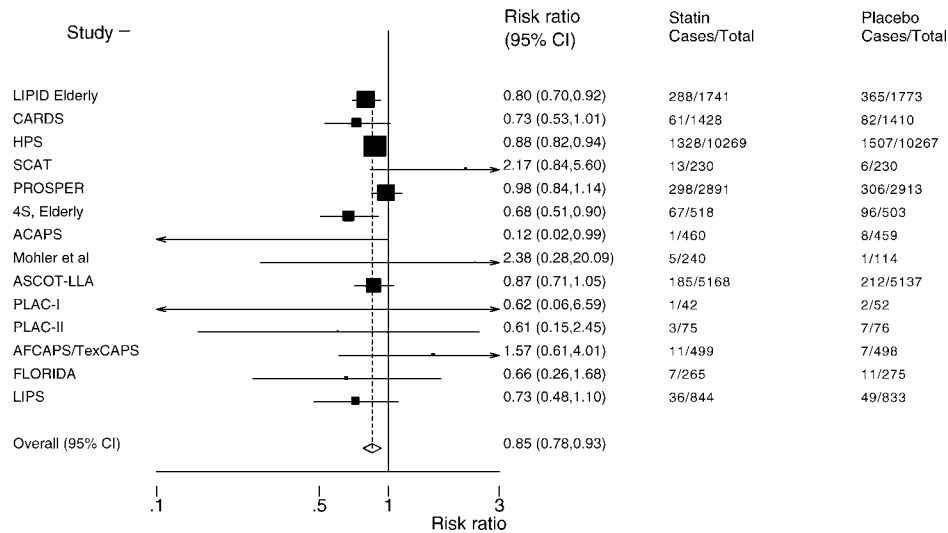


Figure 2. Risk ratio for all-cause mortality from 14 studies.

enrolled in the 13 trials that reported this outcome. The risk of MI was significantly reduced in statin-treated compared to placebo-treated participants (RR = 0.74, 95% CI, 0.70–0.78; $p < .001$) (Figure 4). There was no statistically significant heterogeneity (p heterogeneity = .49). In the five trials reporting fatal and nonfatal MI rates in participants 65 years old and older, 651 events occurred in 5832 statin-treated participants, and 853 events occurred in 5884 placebo-treated participants (RR = 0.75, 95% CI, 0.67–0.84; $p < .01$; p for heterogeneity = .25) (11–14,22).

Time-to-event data for fatal and nonfatal MI were reported in four trials (12,14,18,20), and two additional trials reported these data for participants 65 years old and older (12,32). The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial elderly subgroup analysis (12) and the pooled analysis of Pravastatin Limitation of

Atherosclerosis in the Coronary arteries (PLAC-I and PLAC-II) (32) showed separation in the cumulative fatal and nonfatal MI events at < 1 year in participants 65 years old and older. The PROSPER trial showed a separation in events at < 1 year (14). The three trials with participants with a mean age of 60 years or older reported a separation in events of ≤ 1 year (18,20,29).

All trials reporting fatal and nonfatal stroke outcomes enrolled persons with CHD or at high risk for CHD. There were a total of 1531 strokes reported in 37,265 participants in 11 trials. The rate of fatal and nonfatal stroke was reduced by 24% in statin-treated participants (RR = 0.76, 95% CI, 0.65–0.90; $p = .001$; p for heterogeneity = .10) (Figure 5). Of the 21,392 participants 65 years old and older for whom data on stroke are reported, 1237 suffered a stroke, 548 in the statin group and 689 in the placebo group (RR = 0.81,

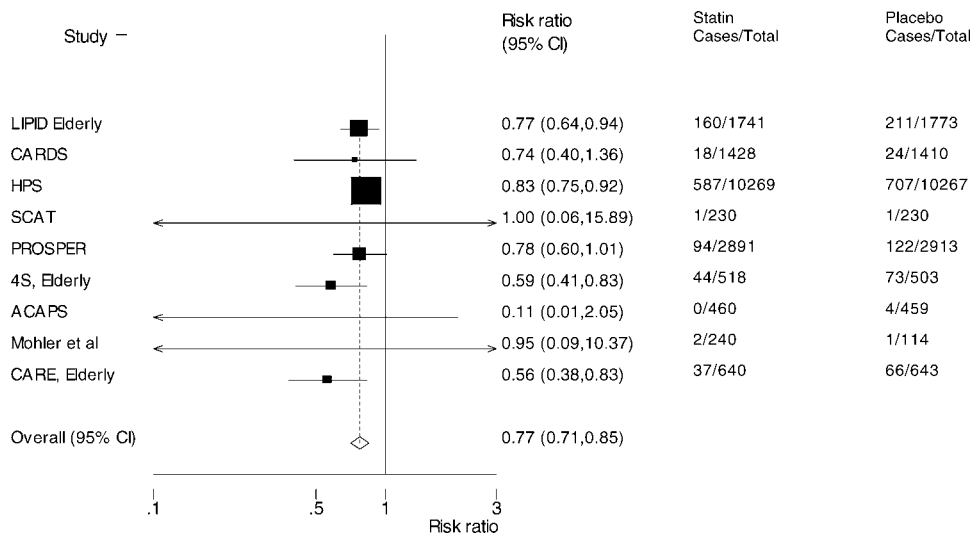


Figure 3. Risk ratio for coronary heart disease (CHD) death from nine studies.

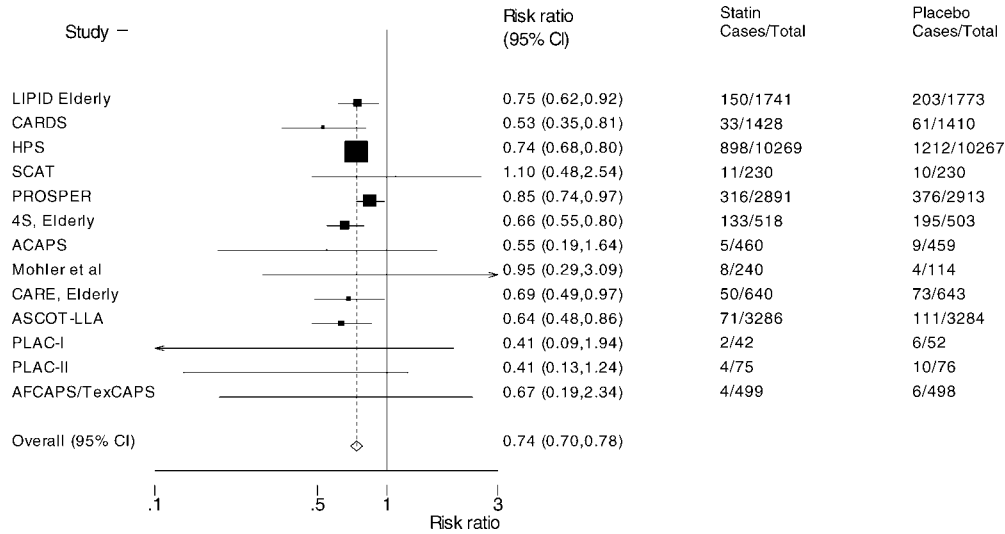


Figure 4. Risk ratio for fatal and nonfatal myocardial infarction (MI) from 13 studies.

95% CI, 0.66–1.00; $p = .05$; p for heterogeneity = .05) (12–14,22,28). Only the HPS reported rates for hemorrhagic and ischemic stroke separately. While ischemic strokes were statistically significantly reduced in the statin-treated group (RR = 0.70, 95% CI, 0.60–0.81), the small number of hemorrhagic strokes resulted in a wide CI (RR = 0.95, 95% CI, 0.65–1.40) (28).

Cancer

There were 3215 cases of cancer reported in nine publications including 47,152 participants. The RR of cancer in the statin-treated participants was 6% greater than in the placebo groups (RR = 1.06, 95% CI, 0.95–1.18; $p = .28$; p heterogeneity = .11) (Figure 6). However, in the three trials reporting cancer rates in persons 65 years old and

older, there were 636 cancers in 5150 statin-treated participants, and 553 cancers in 5189 placebo-treated participants (RR = 1.16, 95% CI, 1.01–1.22; $p = .04$; p for heterogeneity = .25) (11,12,14).

Adverse Events

Adverse event reporting in the trials varied greatly and therefore was deemed unsuitable for quantitative meta-analysis. Several trials in this article were included because they reported AE data even though they did not report cardiovascular event data (19,21,24). Musculoskeletal symptoms and CK and hepatic transaminase abnormalities were the most commonly reported AE. There were no differences in the rates of transaminase elevations > 3 times the upper limit of normal or CK elevations > 10 times the

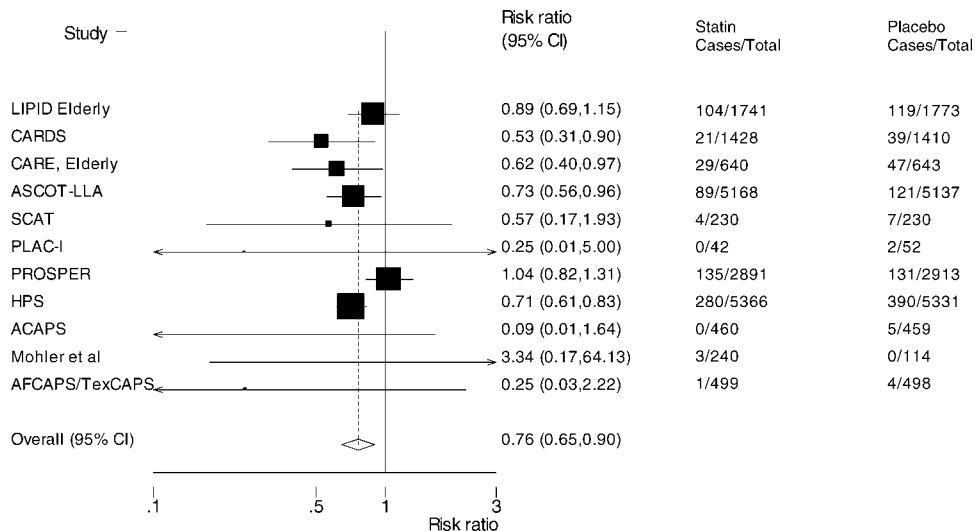


Figure 5. Risk ratio for fatal and nonfatal stroke from 11 studies.

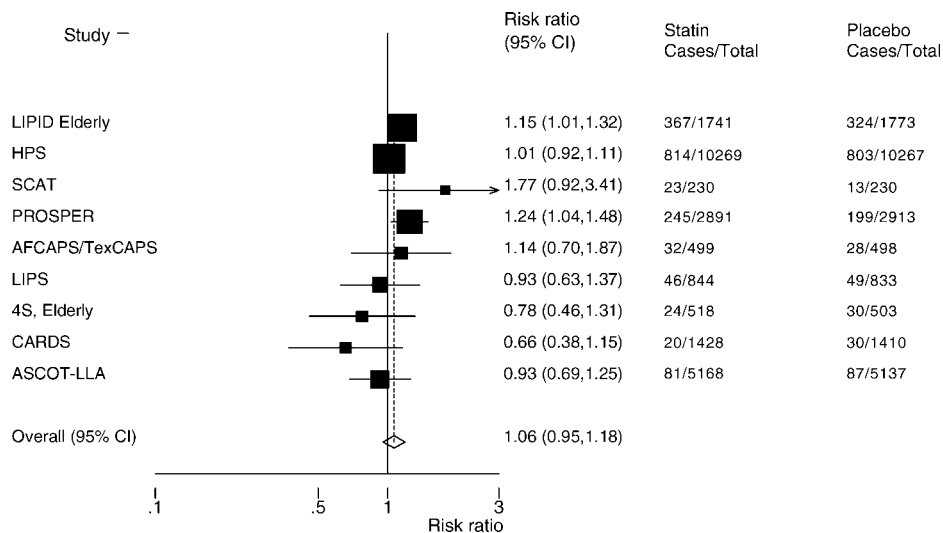


Figure 6. Risk ratio for cancer from nine studies.

upper limit of normal. The rate of study discontinuation due to an AE was the same in statin- and placebo-treated groups.

There were significantly more complaints of musculoskeletal and gastrointestinal symptoms in the statin-treated group than in the placebo-treated group ($p < .01$ for both) (Table 2). The absolute difference in musculoskeletal AE between the two groups was 1.3%. It was not possible in this analysis to determine the number of discontinuations of study drug due to musculoskeletal complaints, as the data was not reported consistently in the trials. The high incidence of gastrointestinal symptoms (40%–49%) is due to one publication in which there were more gastrointestinal complaints than participants in each group as each complaint was counted as a separate event (21). When evaluating only those events that were considered possible adverse drug reactions from the same publication, the incidence of gastrointestinal complaints was 20% in both the statin- and placebo-treated groups.

DISCUSSION

Our meta-analysis found that statin therapy is effective in reducing all-cause mortality and cardiovascular outcomes,

including MI, CHD death, and stroke, in older adults. Individual trials and subgroup analyses examining older persons have shown variable ability of statins to reduce mortality as well as individual or composite cardiovascular events. PROSPER, which to date is the only published trial of statins that specifically targeted older participants, did not demonstrate a reduction in all-cause mortality or stroke (14). The benefit of statins in older adults is clinically important not only for the reduction of fatal events, but also for the reduction of nonfatal events that contribute to morbidity and loss of independence.

Lack of perceived indication has been identified as an obstacle to statin treatment of older patients (3). Observational studies showing no correlation between cholesterol levels and CHD (33,34) or all-cause mortality (35) in older individuals have challenged the utility of screening and treating high cholesterol in this group. However, other studies have shown increased risk of CHD in older persons with higher cholesterol levels (1,36–39). Other observational studies linking low cholesterol with higher death rates in the elderly population have caused further skepticism of the safety of statin therapy (40); however, lower cholesterol

Table 2. Adverse Events

Adverse Events	Statin			Placebo			Number of Trials Reporting Event	Chi-Square Value	<i>p</i> Value
	Events	Total (<i>N</i>)	Percent	Events	Total (<i>N</i>)	Percent			
Musculoskeletal	4596	16,884	27	4309	16,666	26	7	8	< .01
Gastrointestinal	1129	2296	49	833	2076	40	4	37	< .01
Dermatologic	103	2663	4	115	2487	5	4	1.8	NS
Pulmonary	1091	12,517	9	1092	12,295	9	4	0.2	NS
Genitourinary, renal	316	2248	14	293	2028	14	3	0.1	NS
Hepatic	62	1741	4	67	1773	4	1	0.1	NS
Ophthalmologic	15	555	3	4	303	1	3	1.7	NS
Transaminase > 3 × ULN	87	16,863	0.5	70	16,631	0.4	7	1.6	NS
CK > 10 × ULN	14	15,973	0.1	20	15,973	0.1	6	1.1	NS
Withdrawal from study due to adverse event	961	14,238	6.7	951	13,865	6.9	8	0.1	NS

Notes: NS = not significant; ULN = upper limit of normal; CK = creatine kinase.

levels may be explained at least in part by declining cholesterol levels due to comorbid illness (41).

Limited life expectancy of older adults and elderly patients may inhibit providers from prescribing statins to their patients (42). However, the time-to-event data reported in our trials showed a consistent divergence in the placebo- and statin-treated groups in the rates of fatal and nonfatal MI at < 1 year in participants 65 years old and older as well as in participants with a mean age of 60 years or older. Time to all-cause mortality events was not as consistent; however, the longest time to separation of events between the treatment and placebo groups was < 3 years.

The PROSPER trial showed a significant increased incidence of cancer in the statin group (14); however, a meta-analysis of other statin trials by the PROSPER authors showed no increase in cancer risk. Two recently published meta-analyses of statin trials also showed no increased cancer risk in the statin-treated participants, including a subset of participants 70 years old and older (15,43). Although the cancer rates in the overall group are not significantly different between the statin- and placebo-treated groups, the rates in the group aged 65 years and older are significantly greater in the statin group. This estimate, however, was based only on three trials. Notably, the trials included in our analysis have a maximum average follow-up time of 5.4 years. Given that many individuals are treated with statins for decades, this duration of time may not be adequate to fully assess cancer risk. More uniform reporting of cancer outcomes and longer follow-up periods are needed to firmly establish the role of statins on cancer development, particularly in older adults (44).

Geriatric care providers may be reluctant to use statins in older patients due to concerns of increased risk of AE (4,40). Our meta-analysis showed that rates of hepatic transaminase and CK elevations were not increased in the statin-treated older adults, a finding that may allay provider concerns about serious AE. However, the criteria for reporting transaminase and CK elevations in most trials were > 3 and > 10 times the upper limits of normal, respectively, thresholds that may be higher than generally applied in clinical practice. Musculoskeletal and gastrointestinal complaints were more common in statin-treated participants. Although it was not possible to assess the clinical severity of these symptoms in the current analysis, the rates of study drug discontinuation due to AE was no different between the statin- and placebo-treated groups. Our AE evaluation was limited by the diverse reporting formats of individual trials. We attempted to overcome this problem by considering AE according to organ system; however, fewer than half of the trials reported complaints that fit into organ system categories.

Data on primary prevention of cardiovascular events with statins in the elderly population is scarce. Most of the trials included in our analysis enrolled persons with known CHD or ATP III CHD risk equivalents, ensuring a high number of cardiovascular events. There were not enough trials to determine the benefit of statin therapy for primary prevention in older adults. Whereas the PROSPER trial showed no statistically significant difference between the primary

and secondary prevention subgroups, the primary prevention subgroup considered alone was not significantly protected from cardiovascular events (14). The AFCAPS/TexCAPS trial enrolled persons with low high-density lipoprotein (HDL) as the only CHD risk factor, and excluded participants with established CHD (26). Subclinical cardiovascular disease was a strong predictor of cardiovascular events in older participants of the Cardiovascular Health Study (45).

An important limitation of our meta-analysis is the relatively small number of trials included in the analysis of each outcome. We attempted to contact the corresponding author of each of the 18 included trials for additional outcomes data. In some cases, additional data were provided; in other cases, our request was refused or we did not receive a reply.

The mean age cutoff of 60 years was chosen to include a maximum number of trials with predominantly older participants. While nearly two-thirds of participants were 60 years old or older, the inclusion of data from persons younger than 60 years may have affected our results by causing an over- or underestimation of the effect of statins if the younger participants benefit significantly more or less than older participants, respectively. However, subanalyses of older participants in several large trials showed equivalent risk reduction in older compared to younger participants, with greater absolute risk reduction in the older subgroups because of overall high event rates (11–13). Thus, we feel it is unlikely that inclusion of some participants younger than 60 years greatly influenced our findings. In persons 65 years old and older our meta-analysis found statins to be effective in reducing all-cause mortality, CHD death, and fatal and nonfatal MI. Stroke rates in this age group were not significantly reduced on statin-therapy, but with data from more trials, it appears to have the potential to reach significance.

Older adults enrolled in clinical trials may not be representative of the general population of all older adults, potentially limiting the application of our findings to broader categories of older adult patients. Comorbid conditions and the burden of multiple other medications in older adult patients may be of concern to providers (46), but these data were not reported for study participants. Women made up just 27% of participants, and non-whites were poorly represented. Observational studies of very elderly persons (≥ 85 years old) with high cholesterol do not show an increased risk of CHD death (47). As only 12% of participants included in our meta-analysis were older than 70 years, we were not able to confirm that the risk reduction afforded by statins persists into the 9th decade of life. It was not possible to examine differences in event rates among women, non-whites, and very elderly persons as part of our analysis.

Older adults are at particularly high risk of cardiovascular mortality and morbidity. While clinicians should be aware that statins may increase clinical musculoskeletal and gastrointestinal symptoms in older adults, statins unquestionably reduce the risk of cardiovascular events in older adults and are indicated in older adult patients with mild to moderately elevated cholesterol levels. The inconsistent

findings regarding statin therapy and cancer risk demand more prospective clinical trials in older adults.

ACKNOWLEDGMENTS

Dr. Rodriguez receives grant support from the National Institutes of Health and from Titan Pharmaceuticals. She also receives honoraria payment from Sanofi Aventis and Abbott Laboratories.

CORRESPONDENCE

Address correspondence to Annabelle Rodriguez, MD, Johns Hopkins Bayview Medical Center, 5200 Eastern Avenue, Mason F. Lord, Center Tower, Suite 4300, Baltimore, MD 21224. E-mail: arodrig5@jhmi.edu

REFERENCES

- Lloyd-Jones DM, Wilson PW, Larson MG, et al. Lifetime risk of coronary heart disease by cholesterol levels at selected ages. *Arch Intern Med*. 2003;163:1966–1972.
- 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;272:1335–1340.
- Cournot M, Cambou JP, Quentzel S, Danchin N. Key factors associated with the under-prescription of statin in elderly coronary heart disease patients: results from the ELIAGE and ELICOUR surveys. *Int J Cardiol*. 2006;111:12–18.
- Golomb BA. Implications of statin adverse effects in the elderly. *Expert Opin Drug Saf*. 2004;4:389–397.
- Ramsay SE, Morris RW, Papacosta O, Lennon LT, Thomas MC, Whincup PH. Secondary prevention of coronary heart disease in older British men: extent of inequalities before and after implementation of the National Service Framework. *J Public Health (Oxf)*. 2005;27:338–343.
- Rasmussen JN, Gislason GH, Abilstrom SZ, et al. Statin use after acute myocardial infarction: a nationwide study in Denmark. *Br J Pharmacol*. 2005;60:150–158.
- Arnold AM, Psaty BM, Kuller LH, et al. Incidence of cardiovascular disease in older Americans: the Cardiovascular Health Study. *J Am Geriatr Soc*. 2005;53:211–218.
- MacMahon S, Rodgers A. The effects of blood pressure reduction in older patients: an overview of five randomized controlled trials in elderly hypertensives. *Clin Exp Hypertens*. 1993;15:967–978.
- O'Keefe JH Jr, Sutton MB, McCallister BD, et al. Coronary angioplasty versus bypass surgery in patients >70 years old matched for ventricular function. *J Am Coll Cardiol*. 1994;24:425–430.
- Chauhan MS, Kuntz RE, Ho KL, et al. Coronary artery stenting in the aged. *J Am Coll Cardiol*. 2001;37:856–862.
- Miettinen TA, Pyörälä K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris. *Circulation*. 1997;96:4211–4218.
- 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;134:931–940.
- 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;129:681–689.
- Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet*. 2002;360:1623–1630.
- Cholesterol Treatment Trialists Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants. *Lancet*. 2005;366:1267–1278.
- Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *Int J Epidemiol*. 2002;31:150–153.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomized placebo-controlled trial. *Lancet*. 2002;360:7–22.
- Sever PS, Dahlöf B, Poulter NR, et al. 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*. 2003;361:1149–1158.
- Santinga JT, Rosman HS, Rubenfire M, et al. Efficacy and safety of pravastatin in the long-term treatment of elderly patients with hypercholesterolemia. *Am J Med*. 1994;96:509–515.
- Furberg CD, Adams HP, Applegate WB, et al. Coronary heart disease/myocardial infarction: effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation*. 1994;90:1679–1687.
- Keech A, Collins R, MacMahon S, et al. Three-year follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality trial. *Eur Heart J*. 1994;15:255–269.
- Pitt B, Mancini GBJ, Ellis SG, Rosman HS, Park JS, McGovern ME, for the PLAC-I Investigators. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol*. 1995;26:1133–1139.
- Crouse JR III, Byington RP, Bond MG, et al. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *Am J Cardiol*. 1995;75:455–459.
- Chan P, Tomlinson B, Lee-CB, Pan WH, Lee YS. Beneficial effects of pravastatin on fasting hyperinsulinemia in elderly hypertensive hypercholesterolemic subjects. *Hypertension*. 1996;28:647–651.
- Teo KK, Burton JR, Buller CE, et al. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis. *Circulation*. 2000;102:1748–1754.
- Clearfield M, Downs JR, Weis S, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): efficacy and tolerability of long-term treatment with lovastatin in women. *J Womens Health Gend Based Med*. 2001;10:971–981.
- Liem AH, van Boven AJ, Veeger NJGM, et al. Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. *Eur Heart J*. 2002;23:1931–1937.
- Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004;363:757–767.
- Serruys PWJC, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention. *JAMA*. 2002;287:3215–3222.
- Mohler ER, Hiatt WR, Creager MA, for the Study Investigators. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation*. 2003;108:1481–1486.
- 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 randomized placebo-controlled trial. *Lancet*. 2004;364:685–696.
- Furberg CD, Pitt B, Byington RP, Park JS, McGovern ME. Reduction in coronary events during treatment with pravastatin. *Am J Cardiol*. 1995;76:60C–63C.
- Kronmal RA, Cain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age. A report based on the Framingham data. *Arch Intern Med*. 1993;153:1065–1073.
- Simons LA, Simons J, Friedlander Y, McCallum J. Cholesterol and other lipids predict coronary heart disease and ischaemic stroke in the elderly, but only in those below 70 years. *Atherosclerosis*. 2001;159:201–208.
- Fried L, Kronmal RA, Newman AB, et al. Risk factors for 5-year mortality in elderly: the Cardiovascular Health Study. *JAMA*. 1998;279:585–592.

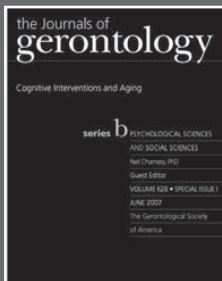
36. Barrett-Connor E, Suarez L, Khaw KT, Criqui MH, Wingard DL. Ischemic heart disease risk factors after age 50. *J Chronic Dis*. 1984; 37:903-908.
37. Benfante R, Reed D. Is elevated serum cholesterol a risk factor for coronary heart disease in the elderly? *JAMA*. 1990;263:393-396.
38. Frost PH, Davis 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;84:2381-2388.
39. 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;126:753-760.
40. Wilson MM. Cholesterol and the aged: ... and the beat goes on. *J Gerontol A Biol Sci Med Sci*. 2005;60A:600-602.
41. Volpato S, Leveille SG, Corti MC, Harris TB, Guralnik JM. The value of serum albumin and high-density lipoprotein cholesterol in defining mortality risk in older persons with low serum cholesterol. *J Am Geriatr Soc*. 2001;49:1142-1147.
42. Lewis S. Statin therapy in the elderly: observational and randomized controlled trials support event reduction. *Am J Geriatr Cardiol*. 2004; 13:10-16.
43. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. *JAMA*. 2006;295:74-80.
44. Guallar E, Goodman SN. Statins and cancer: a case of meta-uncertainty. *Am J Med*. 2001;110:738-740.
45. Kuller LH, Arnold AM, Psaty BM, et al. 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. *Arch Intern Med*. 2006;166: 71-78.
46. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005; 294:716-724.
47. Weverling-Rijnsburger AWE, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RGJ. Total cholesterol and risk of mortality in the oldest old. *Lancet*. 1997;250:1119-1123.

Received June 19, 2006

Accepted October 26, 2006

Decision Editor: Luigi Ferrucci, MD, PhD

Just Released!



Available through
GSA's online store
at www.geron.org.

"Cognitive Interventions and Aging"

A special issue of *The Journal of Gerontology: Psychological Sciences*

Inside:

Developing Context and Background Underlying Cognitive Intervention/Training Studies in Older Populations Jeffrey W. Elias and Molly V. Wagster

Should One Use Medications in Combination With Cognitive Training? If So, Which Ones? Jerome Yesavage, Jennifer Hoblyn, Leah Friedman, Martin Mumenthaler, Bret Schneider, and Ruth O'Hara

The Impact of Speed of Processing Training on Cognitive and Everyday Functions Karlene Ball, Jerri D. Edwards, and Lesley A. Ross

The Neural Correlates of an Expanded Functional Field of View Paige E. Scalf, Stanley J. Colcombe, Jason S. McCarley, Kirk I. Erickson, Maritza Alvarado, Jenny S. Kim, Ruchika P. Wadhwa, and Arthur F. Kramer

Improving Cognitive Function in Older Adults: Nontraditional Approaches Denise C. Park, Angela H. Gutches, Michelle L. Meade, and Elizabeth A. L. Stine-Morrow

Training and Maintaining Memory Abilities in Healthy Older Adults: Traditional and Novel Approaches George W. Rebok, Michelle C. Carlson, and Jessica B. S. Langbaum

An Engagement Model of Cognitive Optimization Through Adulthood Elizabeth A. L. Stine-Morrow, Jeanine M. Parisi, Daniel G. Morrow, Jennifer Greene, and Denise C. Park

Do Self-Monitoring Interventions Improve Older Adult Learning? John Dunlosky, Elena Cavallini, Heather Roth, Christy L. McGuire, Tomaso Vecchi, and Christopher Hertzog

Training Older Adults To Use New Technology Jamye M. Hickman, Wendy A. Rogers, and Arthur D. Fisk

A Multilevel Modeling Approach to Examining Individual Differences in Skill Acquisition for a Computer-Based Task Sankaran N. Nair, Sara J. Czaja, and Joseph Sharit