


Efficacy of statin treatment based on cardiovascular outcomes in elderly patients: a standard meta-analysis and Bayesian network analysis

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Abstract

Objective: Statins have been shown to be beneficial for the prevention of cardiovascular events. In elderly individuals, the efficacy of statins remains controversial and the comparative effect of statins has not been assessed.

Methods: MEDLINE, Embase, and the Cochrane Central database were searched for randomized controlled trials that assessed statins in older patients.

Results: Seventeen trials were analyzed. When used for secondary prevention, statins were associated with reduced risk of cardiovascular events, all-cause mortality, cardiovascular mortality, revascularization, and stroke. When used for primary prevention, statins reduced the risk of myocardial infarction and revascularization, but did not significantly affect other outcomes. A modest difference between pharmaceutical statin products was found, and high-quality evidence indicated that intensive atorvastatin had the greatest benefits for secondary prevention.

Conclusions: In secondary prevention, evidence strongly suggests that statins are associated with a reduction in the risk of all-cause mortality, cardiovascular events, cardiovascular mortality, and revascularization. However, differences in the effects of various statins do not appear to have significant effects on therapy in secondary prevention for the elderly.

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Keywords

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Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide.¹ Dysfunction of lipid metabolism and elevated serum levels of low-density lipoprotein cholesterol (LDL-C) are major risk factors for atherosclerotic cardiovascular diseases (ASCVDs).^{2,3} Statins are the most widely used lipid-lowering therapy in the world, and they are the first-line therapy for dyslipidemia. Statin therapy has been shown to be very beneficial for primary and secondary prevention of CVD.^{4,5} The 2013 guidelines of the American College of Cardiology and American Heart Association (ACC/AHA) recommend the use of statins for adults to reduce the rate of cardiovascular adverse events.⁶ With society's increasing life expectancy, more than 80% of the occurrence of CVD and/or cardiac deaths occur in older individuals (aged 65 years and older),⁷ therefore, prevention and reduction of CVD has become increasingly crucial in this population.⁸ Based on current guidelines, statin use is recommended for nearly all patients between the ages of 65 and 75 years, especially for secondary prevention of CVD.⁹

Despite these guidelines, large-scale, randomized, controlled trials of statins in older patients are limited because of age-related changes in pharmacokinetics and pharmacodynamics in this population.¹⁰ Several studies have combined and analyzed previous trials. For example, Teng et al.¹¹ performed a meta-analysis that demonstrated a role for statins in the primary prevention of cardiovascular adverse events in the elderly from a risk-benefit perspective. However, the

evidence quality levels and recommendations were not assessed. A recent study included an analysis of the efficacy of statins and non-statins in the elderly. This study supported the use of statins for secondary prevention of CVD in older patients based on high-certainty evidence.¹² However, this study did not compare various statins or provide a final ranking of the different statin drugs. In addition, there were relatively few head-to-head trials assessing the effectiveness of various statins, which is an increasing concern for the elderly. Therefore, it is imperative to synthesize the current information regarding statins and conduct a quantitative evaluation of treatment with different statins in patients aged 65 years and older.

The current study comprises a standard meta-analysis and Bayesian network analysis, and it aims to summarize the present evidence for statin use in primary and secondary prevention of CVD in older individuals (≥ 65 years) with or without CVD. Estimation of the clinical outcomes and results of several different statins may help clinicians to provide more detailed, quantitative information to develop best practice guidelines for the rational use of statins in older patients.

Methods

This study was performed in accordance with the Cochrane Collaboration guidelines, and it is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension (PRISMA) statement for systematic reviews incorporating network meta-analyses for

health care interventions.^{13,14} All analyses were based on previous published studies, and thus, no ethics approval or patient consent was required.

Search strategy

The relevant RCTs published from January 1995 to July 2019 were identified from MEDLINE, Embase, and the Cochrane Central database. The search was restricted to trials in humans that were published in English language journals. The main search terms used to maximize the search sensitivity and specificity were as follows: statin, hydroxymethylglutaryl-CoA, pravastatin, simvastatin, atorvastatin, rosuvastatin, fluvastatin, lovastatin, cerivastatin, randomized controlled trials (RCTs), clinical trial, randomized, and cardiovascular disease.

Inclusion and exclusion criteria

Inclusion criteria (PICO) for the network analysis were as follows: (1) Patient/population: elderly patients (age ≥ 65 years or mean age > 70 years) were included in the statin or control group of the study; (2) Intervention/exposure and comparison/control: studies comparing any single statin at any dose with either a control (placebo/usual care) or another type of statin; (3) Outcome: the primary endpoint was cardiovascular events (including myocardial infarction, stroke, cardiovascular death, and revascularization), and secondary endpoints were all-cause mortality, cardiovascular mortality, myocardial infarction, need for revascularization, or stroke; and (4) Study design: RCTs. Exclusion criteria were as follows: (1) Overlapping and repetitive data; (2) review articles, single case reports, and noncomparable studies; (3) the number of elderly patients for comparison was less than 100; and (4) follow-up period of less than 6 months.

Study selection

In this study, two reviewers (CN Zhai and K Hou) independently screened the titles and abstracts from the articles against the eligibility criteria. The full text of the studies that potentially met the inclusion criteria was inspected to determine the final included studies. Disagreements regarding the inclusion of a study were resolved by consensus and arbitration by a third author (HL Cong).

Data extraction

The data from all included articles were extracted independently by two investigators (CN Zhai and K Hou). The data included the study title, publication date, authors, number of patients, types of statin, drug dose, duration of follow-up, and outcome. Network plots were used to describe the network geometry.¹⁵ The corresponding authors of the included studies were contacted to obtain any required information that was missing. The total extracted data were verified by a third investigator (HL Cong).

Assessment of methodological quality and evidence synthesis

The methodological quality and the risk of bias for each included article was independently assessed by two authors (CN Zhai and R Li) following the Cochrane Handbook for Systematic Reviews of Interventions 5.3.¹⁶ Disagreements were resolved by discussion, and the corresponding author (HL Cong) was the adjudicator when no consensus could be achieved. The evidence grade was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group guidelines. As recommended by the GRADE working group, the lowest evidence quality for any of the outcomes was used to rate the overall

evidence quality. The evidence quality is graded using GRADE Pro version 3.6 software (McMaster University, 2015 [developed by Evidence Prime, Inc.], available from grade.pro.org). The strengths of the recommendations are reported based on the quality of the evidence.

Statistical analysis

Data analysis was conducted using RevMan software, version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and STATA 15.0 software (StataCorp, College Station, TX, USA). The odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate dichotomous outcomes. The inverse variance and Mantel–Haenszel techniques were used to combine the separate statistics. Heterogeneity was investigated using the Q statistic, and P values <0.05 were regarded as statistically significant. To control for the risk of random type I or II error because of the sparse data and repetitive testing of accumulating data, and to assess the reliability and conclusiveness of the present evidence, trial sequential analysis (TSA) of any statin versus placebo/usual care was conducted on each clinical outcome with at least two trials. A default type I error of 5% and type II error of 20% was used. TSA was performed using TSA software, version 0.9 beta.¹⁷ Bayesian network meta-analysis (NMA) was conducted using the aggregate data drug information system (ADDIS) v1.16.5 (van Valkenhoef, University of Groningen, the Netherlands). Outcomes were combined using the random effects model.¹⁸ For all estimates, convergence was achieved at 50,000 iterations and autocorrelation was checked and confirmed. Markov chain Monte Carlo (MCMC) modeling was conducted to estimate the relative ranking probability of each treatment group.¹⁹ For each clinical outcome, we estimated the probability of each treatment included in the network

to be the best among all treatments using the surface under the cumulative ranking curve (SUCRA).²⁰ Because the directly and indirectly compared results in any network were available, incoherence analyses (defined as the statistical disagreement between two evidence types) were conducted using the Node Split method.²¹ In addition, to assess the robustness of outcome findings, sensitivity analyses were conducted by excluding studies with unique populations (i.e., diabetic mellitus, heart failure) and studies with a high risk of bias. Publication bias was statistically evaluated using Begg funnel plots and Egger bias test using STATA 15.0 software (StataCorp). The above methods were used to statistically measure the degree of funnel plot asymmetry.^{22,23}

Results

Search of the published literature

There were 2167 articles that were identified during the initial electronic search. After the abstracts were screened, most articles were excluded because they had no relevance to this analysis. In total, 1373 articles failed to meet the eligibility criteria and another 65 articles were removed because of unusable data, a small number cases, or a very short follow-up period. Seventeen studies satisfied the eligibility criteria (Figure 1).

Characteristics and methodological quality of the included studies

Seventeen RCTs, which included 41,924 patients, examined the effect of various statins in older individuals (age ≥ 65 years), with or without CVD, were included in the present NMA.^{24–40} Participants' clinical characteristics are summarized in Table 1. The methodological quality of included studies is shown in Figure 1. Judgements about risk-bias items are presented as

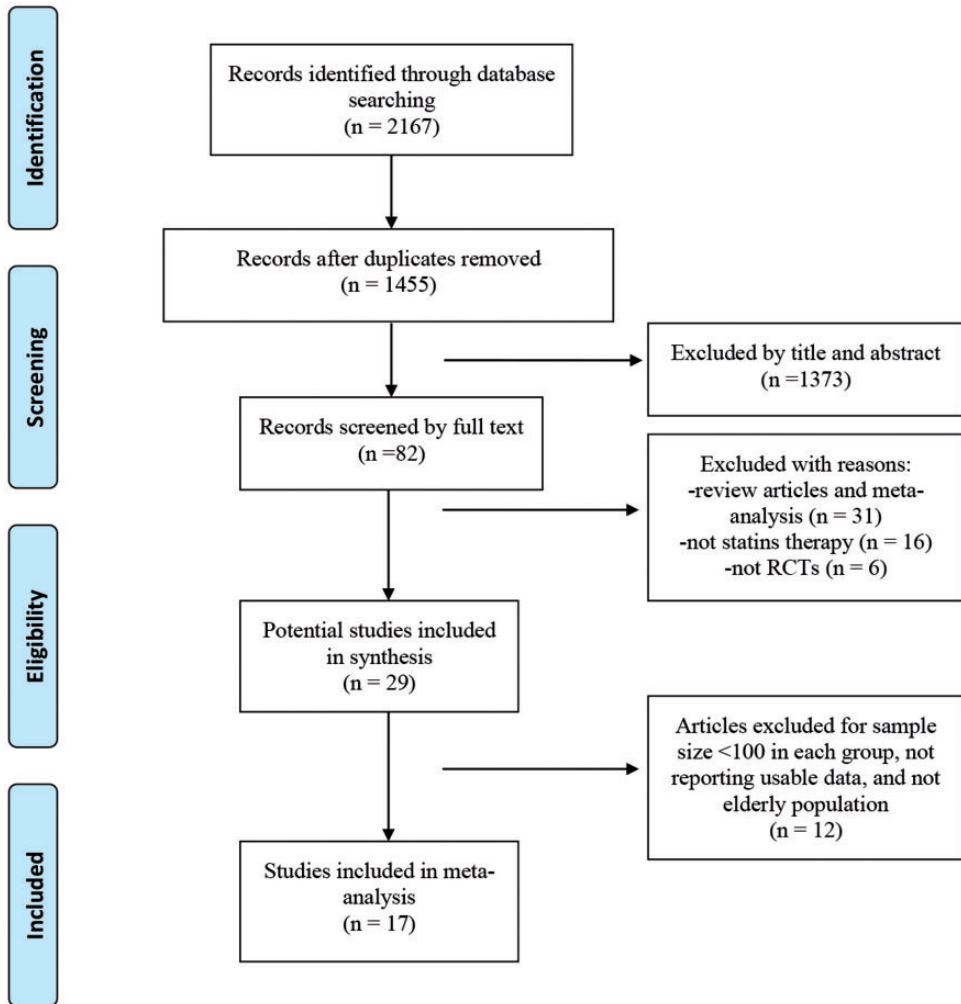


Figure 1. Search strategy based on the PRISMA statement. PRISMA, Preferred Reporting Items for Systematic Reviews.

percentages across all included RCTs in Figure 2. In the summary criterion, two trials (12%) were estimated as having a high risk of bias, one trial (6%) as moderate risk, and 14 trials (82%) as low risk (Figure 3).

Five statins were included in these trials. Atorvastatin was studied in six trials (6754 patients),^{30,32–34,36,37} pravastatin in six trials (7626 patients),^{25,27,29,30,38,39} rosuvastatin in two trials (5392 patients),^{31,40}

fluvastatin in two trials (503 patients),^{25,27} and simvastatin in three trials (3687 patients).^{23,31,34} Based on dose intensity defined by the 2013 ACC/AHA guidelines,⁴¹ four trials^{30,32–34} used statins at a high-intensity dose (atorvastatin, 80 mg/day), 12 trials^{24–29,31,35–38,40} used moderate-intensity dose (atorvastatin, 10 mg/day; pravastatin, 40 to 80 mg/day; simvastatin, 20 to 40 mg/day; rosuvastatin, 5 to 10 mg/day; Fluvastatin, 40 to 80 mg/day),

Table 1. Characteristics of the included randomized controlled trials.

Study (year)	Patient status/condition	No. of elderly patients	Treatment Comparisons (mg/day)	Outcome measure	Follow-up, years	Age range, years	Male sex (%)	Hyper-tension (%)	Diabetes (%)	Current smokers (%)
4S ^a (1997)	CHD	1021	Simvastatin 20 mg vs. placebo	All-cause mortality, cardiovascular events, Cardiovascular mortality, MI, revascularization	5.4	65–70	NA	NA	NA	NA
CARE ^a (1998)	CHD	1283	Pravastatin 40 mg vs. placebo	cardiovascular events, cardiovascular mortality, MI, revascularization, stroke	5	65–75	81.4	46.1	18.5	11.5
FLARE ^a (1999)	CHD	366	Fluvastatin 80 mg vs. placebo	All-cause mortality, cardiovascular mortality, MI	0.8	65–80	77	38	9	16
LIPID ^a (2001)	CHD	3514	Pravastatin 40 mg vs. placebo	All-cause mortality, cardiovascular mortality, MI, revascularization, stroke	5	65–75	80	45	10	6
LIPS ^a (2002)	CHD	623	Fluvastatin 80 mg vs. placebo	All-cause mortality, cardiovascular mortality, MI, revascularization, stroke	3.9	65–80	78	43	15	15
PROSPER ^{a, b} (2002)	Older patients with/without CVD	5804	Pravastatin 40 mg vs. placebo	All-cause mortality, cardiovascular events, stroke	3.2	70–82	48.3	61.9	10.8	26.8
HPS ^b (2003)	T1DM and T2DM	2592	Simvastatin 40 mg vs. placebo	cardiovascular events,	4.8	65–80	75.3	NA	100	NA
CARDS ^b (2006)	T2DM	1129	Atorvastatin 10 mg vs. placebo	cardiovascular events, cardiovascular mortality, MI, revascularization, stroke	3.9	65–77	52.5	NA	100	15.6

(continued)

Table 1. Continued.

Study (year)	Patient status/condition	No. of elderly patients	Treatment Comparisons (mg/day)	Outcome measure	Follow-up, years	Age range, years	Male, sex (%)	Hyper-tension (%)	Diabetes (%)	Current smokers (%)
SAGE ^a (2007)	CVD	893	Atorvastatin 80 mg vs. pravastatin 40 mg	All-cause mortality, cardiovascular events, MI, revascularization, stroke	1	65–85	70	64.4	23.2	6.2
CORONA ^a (2007)	IHD, HF	5011	Rosuvastatin 10 mg vs. placebo	All-cause mortality, cardiovascular events, MI, revascularization, stroke	2.7	NA	76.5	43.4	29.5	8.6
IDEAL ^a (2009)	MI	3759	Atorvastatin 80 mg vs. simvastatin 20–40 mg	All-cause mortality, cardiovascular mortality	4.8	65–80	76.4	NA	NA	NA
ALLIANCE ^a (2009)	CVD	1001	Atorvastatin 80 mg vs. usual care	All-cause mortality, cardiovascular events, MI, revascularization, stroke	4.5	65–78	80.7	NA	21.7	10.9
SPARCL ^a (2009)	Stroke or TIA	2249	Atorvastatin 80 mg vs. placebo	All-cause mortality, cardiovascular events, revascularization, stroke	3.5	≥65	56	NA	17.5	11.5
JUPITER ^b (2010)	Older patients without CVD	5695	Rosuvastatin 10 mg vs. placebo	All-cause mortality, cardiovascular events, MI, revascularization, stroke	1.9	NA	48.5	65.6	NA	NA
ASCOT-LLA ^b (2011)	Older patients with without CVD	4445	Atorvastatin 10 mg vs. placebo	All-cause mortality, cardiovascular events, MI, stroke	3.3	≥65	80.4	26.7	100	23.7

(continued)

Table 1. Continued.

Study (year)	Patient status/condition	No. of elderly patients	Treatment Comparisons (mg/day)	Outcome measure	Follow-up, years	Age range, years	Male sex (%)	Hyper-tension (%)	Diabetes (%)	Current smokers (%)
MEGA ^b (2011)	Older patients with hyperlipidemia	1814	Pravastatin 10–20 mg vs. usual care	All-cause mortality, cardiovascular events, stroke	5	≥65	48.1	21	52	14
ALLHAT-LLT ^b (2017)	Older patients with hypertension	2867	Pravastatin 40 mg vs. placebo	All-cause mortality, cardiovascular events, cardiovascular mortality, MI, stroke	4.6	≥65	50.6	100	51.1	22.3

Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IHD, ischemic heart disease; HF, heart failure; TIA, transient ischemic attack.

^asecondary prevention, ^bprimary prevention.

and one trial³⁹ used a low-intensity dose (pravastatin, 10 to 20 mg/day). In addition, two trials compared atorvastatin to simvastatin or pravastatin. The mean (standard deviation; SD) of the follow-up duration was 3.7 years (range, 0.8–5.4 years), and at least eight trials^{24,25,27,32,33,35,38,39} had a long follow-up period of 4.5 years.

Clinical outcomes of the standard meta-analysis and Bayesian network analysis

Figure 4 shows the network geometry for all clinical outcomes in this study. The results of the standard meta-analyses are shown in Table 1. Figure 5 shows the estimates of secondary prevention outcomes of any statin against control group outcomes from the standard meta-analysis, in addition to the estimate of each statin against the control group from the network analysis, with the corresponding ranking probability (SUCRA) and quality levels of evidence (GRADE). Bayesian network analysis estimates of clinical outcomes for each comparison between various statins and control groups.

Cardiovascular events

Thirteen trials^{24,25,29,31,33–40} included 34,911 elderly patients and compared the risk of cardiovascular events between any statin and the control group (placebo/usual care). For secondary prevention in older patients with ASCVD, six trials^{24,25,29,31,33,34} that included 13,130 patients indicated that statins were associated with a 28% relative reduction in cardiovascular events (OR: 0.72, 95% CI: 0.61–0.84; GRADE: high). For primary prevention in the elderly, seven trials (21,781 patients in total)^{29,35–40} identified a similar risk of cardiovascular events between patients on statins and the control group (OR: 0.88, 95% CI: 0.72–1.06; GRADE: moderate). Based on the

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
4S 1997	?	?	-	-	?	+	?
ALLHAT-LLT 2017	+	+	-	-	+	+	+
ALLIANCE 2009	+	?	-	+	+	+	?
ASCOT-LLA 2011	+	+	+	+	+	+	-
CARDS 2006	+	+	+	+	+	+	?
CARE 1998	+	+	+	+	+	+	-
CORONA 2007	+	+	+	+	+	+	+
FLARE 1999	+	+	+	+	+	+	+
HPS 2003	+	+	+	+	+	+	-
IDEAL 2009	+	+	-	+	+	+	+
JUPITER 2010	+	+	+	+	+	+	-
LIPID 2001	+	+	-	+	+	+	+
LIPS 2002	+	+	+	+	+	+	-
MEGA 2011	+	+	-	+	+	+	-
PROSPER 2002	+	+	+	+	+	+	-
SAGE 2007	+	+	+	+	+	+	+
SPARCL 2009	+	+	+	+	+	+	-

+ Low risk of bias
 - High risk of bias
 ? Unclear risk of bias

Figure 2. Methodological quality of included trials. This risk-of-bias tool incorporates an assessment of randomization (sequence generation and allocation concealment), blinding (participants, personnel, and outcome assessors), completeness of outcome data, selection of outcomes reported, and other sources of bias. The items were scored with “yes,” “no,” or “unsure.”

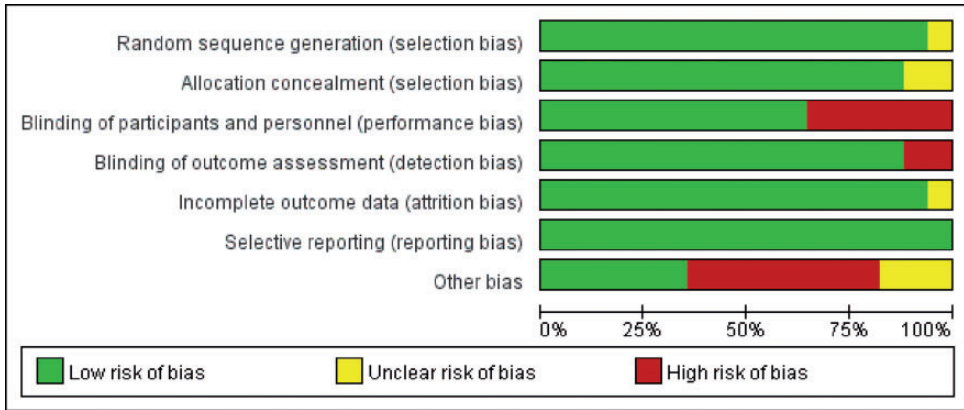


Figure 3. Risk of bias. Each risk-of-bias item is presented as percentages across all included trials, which indicate the proportion of different levels of risk of bias for each item.

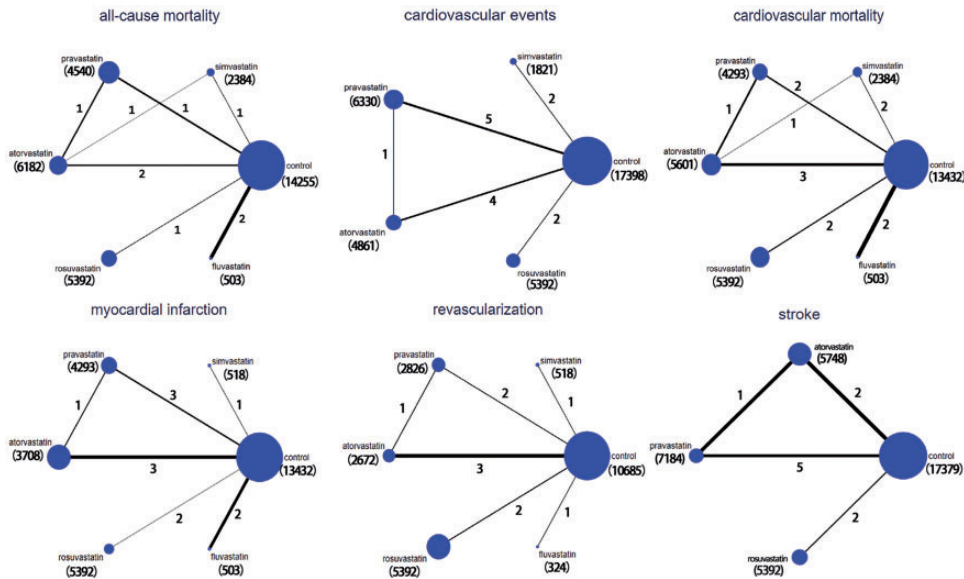


Figure 4. Network plots of evidence for overall clinical outcomes. **Line:** Direct comparison between two linked drugs (statins/control). Each line links a statin regimen that have been directly compared in studies, while the thickness of the line is proportional to the precision of each direct estimate. The number of trials per comparison is reported next to each line. **Circle:** Statin types/control for trial comparisons. The width of each circle is proportional to the number of studies included. In addition, the number of patients included in each treatment (statins/control) is reported in the bracket below the statin/control name.

Bayesian NMA comparing different statins for secondary prevention (Figure 5), high-quality evidence indicated that 80 mg of atorvastatin had the highest probability of

having the greatest benefit for preventing cardiovascular events (three trials^{30,31,33} including 4141 patients; OR: 0.68, 95% CI: 0.49–0.92; SUCRA, 77%). This was

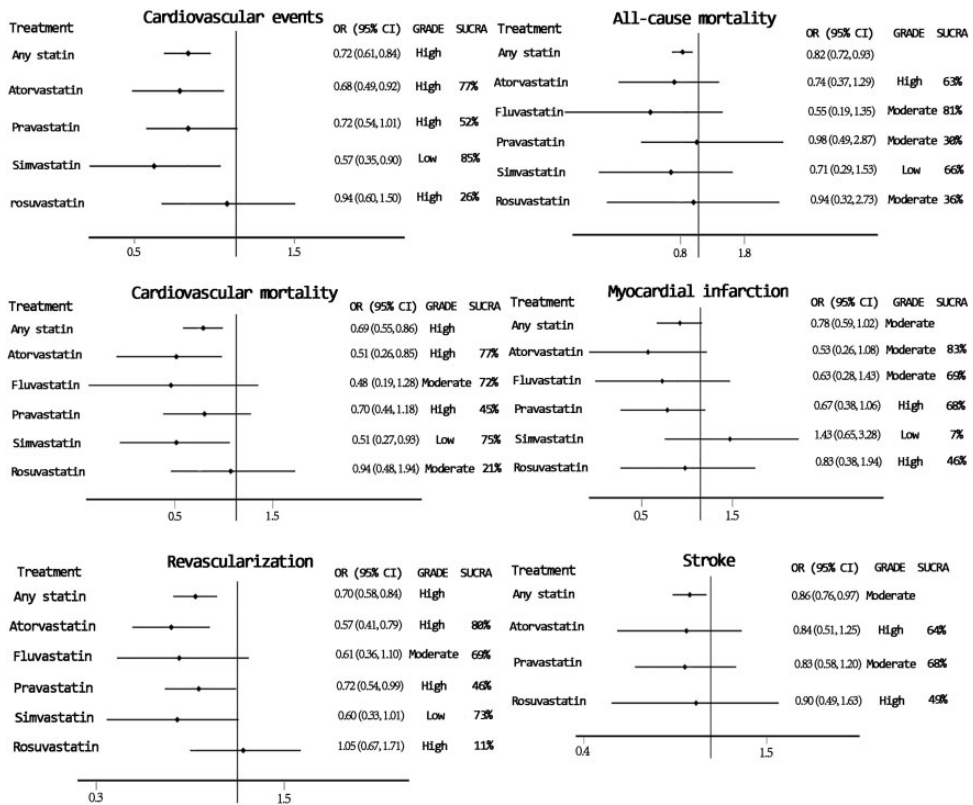


Figure 5. Forest plot of the meta-analysis estimate for each statin compared with the control group, and of each statin against control within the networks for clinical outcomes in secondary prevention with at least two trials compared with the corresponding ranking probability (SUCRA) and quality of evidence (GRADE) for each statin regimen for each outcome. SUCRA, surface under the cumulative ranking curve; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

followed by 40 mg of pravastatin (three trials^{25,29,30} including 4739 patients; OR: 0.72, 95% CI: 0.54–1.01; SUCRA, 52%) and 10 mg of rosuvastatin (one trial³¹ including 5011 patients; OR: 0.94, 95% CI: 0.60–1.50; SUCRA, 26%). Low-quality evidence indicated that 20/40 mg of simvastatin (one trial²⁴ including 1021 patients; OR: 0.57, 95% CI: 0.35–0.90; SUCRA, 85%) was associated with a reduction in cardiovascular events.

All-cause mortality

Eleven trials^{24,26–28,31,33,34,37–40} that included 28,606 older patients compared any statin with a control group and addressed all-cause mortality. In the standard meta-analyses for secondary prevention, statins were associated with an 18% relative reduction in all-cause mortality (seven trials^{24,26–28,31,33,34} including 13,785 patients; OR: 0.82, 95% CI: 0.72–0.93; GRADE: high). For the primary

prevention subgroup, four trials (14,821 patients in total)³⁷⁻⁴⁰ found that statins had no statistically significant effect on all-cause mortality compared with the control group (OR: 0.94, 95% CI: 0.76-1.16; GRADE: low). When comparing different statins for secondary prevention, low-quality evidence indicated that 80 mg of fluvastatin (two trials^{26,28} including 989 patients; OR: 0.55, 95% CI: 0.19-1.35; SUCRA, 81%), 20/40 mg of simvastatin (two trials^{24,32} including 4780 patients; OR: 0.71, 95% CI: 0.29-1.53; SUCRA, 66%), and 80 mg of atorvastatin (four trials^{30,32-34} including 7900 patients; OR: 0.74, 95% CI: 0.37-1.29; GRADE: high; SUCRA: 63%) were associated with reductions in the risk of all-cause mortality.

Cardiovascular mortality

Eleven trials^{24-28,31,33,36-38,40} included 26,955 older patients and compared the risk of cardiovascular mortality between any statin and the control group. In the standard meta-analyses for secondary prevention, seven trials^{24-28,31,33} comprising 12,819 patients indicated that statins were associated with a 31% relative reduction in cardiovascular mortality (OR: 0.69, 95% CI: 0.55-0.86; GRADE: high). For primary prevention, four trials^{36-38,40} (14,136 patients) were included, which reported that statins did not have a significant effect on cardiovascular mortality compared with the control group (OR: 1.00, 95% CI: 0.81-1.24; GRADE: low). When comparing different statins for secondary prevention, high-quality evidence indicated that 80 mg of atorvastatin caused a significant 49% relative risk reduction (three trials^{30,32,33} including 5,651 patients; OR: 0.51, 95% CI: 0.26-0.85; SUCRA: 77%). Low-quality evidence showed that 20/40 mg of simvastatin caused a 49% risk reduction (two trials^{24,32} including 4,780 patients; OR: 0.51, 95% CI: 0.27-0.93;

SUCRA: 77%) in cardiovascular mortality, followed by 80 mg of fluvastatin (two trials^{26,28} including 989 patients; OR: 0.48, 95% CI: 0.19-1.28; GRADE: low; SUCRA: 72%), and 40 mg of pravastatin (three trials^{25,27,30} including 5,688 patients; OR: 0.70, 95% CI: 0.44-1.18; GRADE: high; SUCRA, 45%).

Myocardial infarction

In the standard meta-analyses, 11 trials^{24-28,31,33,36-38,40} included 26,955 older patients and compared the risk of myocardial infarction between any statin and control group. For secondary prevention, seven trials^{24-28,31,33} comprising 12,819 patients detected no significant difference between patients on statins and controls (OR: 0.78, 95% CI: 0.59-1.02; GRADE: moderate). For primary prevention, four trials^{36-38,40} (14,136 patients in total) identified that statins were associated with a significant reduction in the incidence of myocardial infarction (OR: 0.61, 95% CI: 0.50-0.73; GRADE: high). Low to moderate-quality evidence indicated that there was no statistically significant difference in the incidence of myocardial infarction in patients taking atorvastatin (two trials^{30,33} including 4445 patients; OR: 0.54, 95% CI: 0.21-1.10; GRADE: moderate; SUCRA: 73%), rosuvastatin (one trial⁴⁰ including 5695 patients; OR: 0.54, 95% CI: 0.17-1.69; GRADE: low; SUCRA: 68%), or pravastatin (one trial³⁸ including 2867 patients; OR: 0.71, 95% CI: 0.22-2.15; GRADE: low; SUCRA: 48%) compared with controls.

Revascularization

Nine trials^{24,25,27,28,31,33,34,36,40} included 21,526 elderly patients and compared patients who were taking any statin compared with control patients to address revascularization. For secondary prevention, seven trials,^{24,25,27,28,31,33,34} comprising

14,702 patients indicated that statins were associated with a 30% relative reduction in revascularization (OR: 0.70, 95% CI: 0.58–0.84; GRADE: high). For primary prevention, two trials^{36,40} (6,824 patients), found that the risk of revascularization was reduced in the statin compared with the control group (OR: 0.49, 95% CI: 0.32–0.76; GRADE: low). When comparing different statins for secondary prevention, high-quality evidence indicated that 80 mg of atorvastatin had the highest probability of having the greatest benefit for revascularization (three trials^{30,33,34} including 3,250 patients; OR: 0.57, 95% CI: 0.41–0.79; SUCRA: 80%), followed by 20/40 mg of simvastatin (one trial²⁴ including 1021 patients; OR: 0.60, 95% CI: 0.33–1.01; SUCRA: 73%), 80 mg of fluvastatin (one trial²⁸ including 623 patients; OR: 0.61, 95% CI: 0.36–1.10; SUCRA: 69%), and 40 mg of pravastatin (three trials^{25,27,30} including 5,688 patients; OR: 0.72, 95% CI: 0.54–0.99; SUCRA: 46%). However, because of the low-quality of evidence and small number of trials, reliable results regarding the use of different statins for primary prevention could not be estimated.

Stroke

Eleven trials^{25,27,29,31,33,34,36–40} included 34,812 older patients and compared the risk of stroke between any statin and the control group. For secondary prevention, six trials^{25,27,29,31,33,34} (15,623 patients) indicated that statins were associated with a 24% relative reduction in stroke (OR: 0.86, 95% CI: 0.76–0.97; GRADE: high). For primary prevention, six trials^{29,36–40} (19,189 patients) identified that the risk of stroke was similar between patients on statins and controls (OR: 0.78, 95% CI: 0.60–1.00; GRADE: moderate). There were no statistically significant differences in secondary prevention when comparing pravastatin (four trials^{25,27,29,30} including

8,253 patients; OR: 0.83, 95% CI: 0.58–1.20; GRADE: high; SUCRA: 68%), atorvastatin (three trials^{30,33,34} including 4,141 patients; OR: 0.84, 95% CI: 0.51–1.25; GRADE: moderate; SUCRA: 64%), and rosuvastatin (one trial³¹ including 5,011 patients; OR: 0.90, 95% CI: 0.49–1.63; GRADE: high; SUCRA: 49%) with the control group.

Trial sequential analysis

The trial sequential analysis results are shown in Figures 6 and 7. For secondary prevention (Figure 6) of cardiovascular events, all-cause mortality, cardiovascular mortality, and revascularization, the TSA comparing any statins with the control group showed that the cumulative z-curve crossed the conventional boundary ($P=0.05$) as well as the trial sequential monitoring boundary and never regressed. When random error is excluded, evidence indicating that statins reduced the risk of these outcomes was reliable. However, for myocardial infarction, the cumulative z-curve failed to cross the conventional boundary and trial sequential boundary, indicating that the risk of random type II error (information deficit 15,967) could not be excluded. The cumulative z-curve for stroke also did not cross the trial sequential boundary, and thus, random type I error could not be excluded (information deficit 11,370). For primary prevention of cardiovascular events, all-cause mortality, cardiovascular mortality, and stroke, the TSA indicated that the cumulative z-curve failed to cross the conventional boundary and the trial sequential boundary (Figure 7). Revascularization data indicated that the z-curve also did not cross the trial sequential boundary, and thus, random type I error could not be excluded. The cumulative z-curve crossed the conventional and trial sequential boundary for myocardial

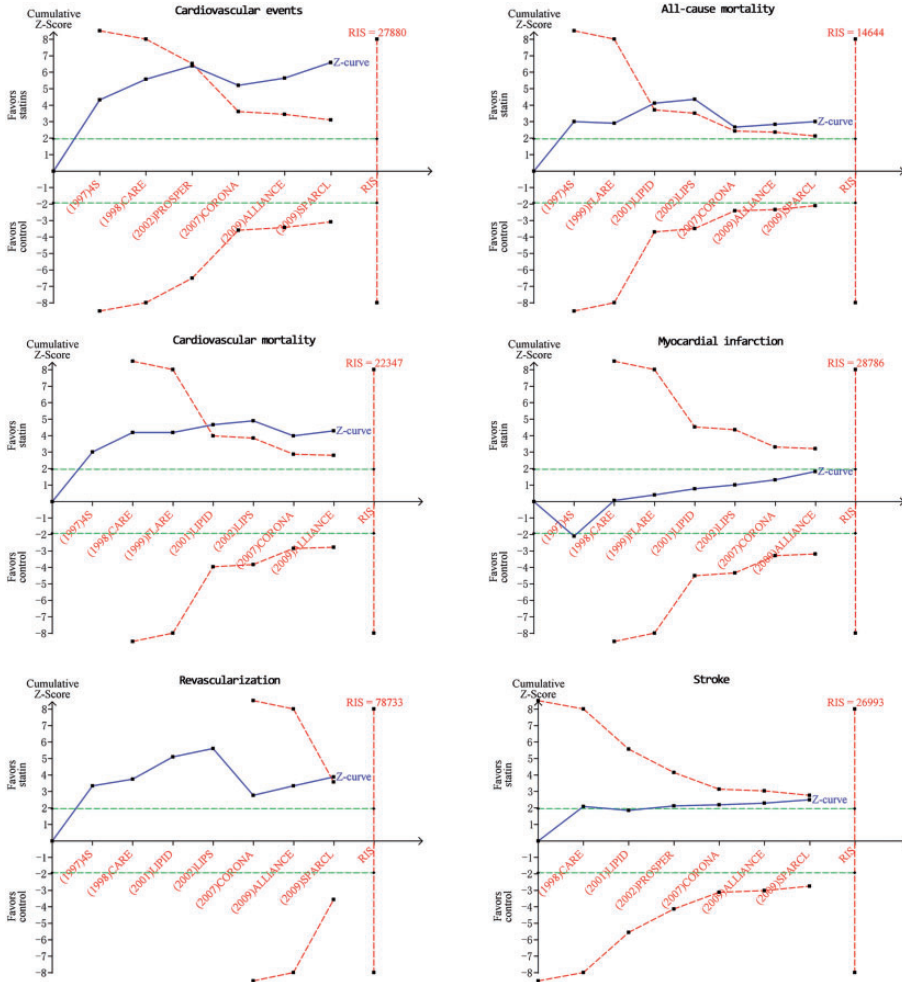


Figure 6. Results of the trial sequential analysis (TSA) of the risks of clinical outcomes for older patients in secondary prevention. TSA provided a termination criterion for clinical trials by estimating the required information size (RIS). **Red dotted line:** TSA boundary curve. **Green dotted line:** The conventional boundary curve. **Blue line:** The cumulative z-curve of the meta-analysis. **Abscissa:** The cumulated sample sizes of included trials in meta-analysis. The accumulated Z-curve passed through the conventional boundary curve and also across the TSA boundary curve, indicating a positive and reliable conclusion has been reached before reaching the expected amount of information size (including cardiovascular events, all-cause mortality, cardiovascular mortality, and revascularization).

infarction, indicating that the risk of random type I error could be excluded.

Additional analyses

In the standard meta-analysis, publication bias tests were performed for all endpoints

of included RCTs. Some significant publication biases were shown for cardiovascular events and stroke via the Begg rank-correlation method (stroke, $P=0.03$) and the Egger weighted-regression method (cardiovascular events, $P=0.04$; stroke, $P=0.01$) (Table 2). To explore the sources

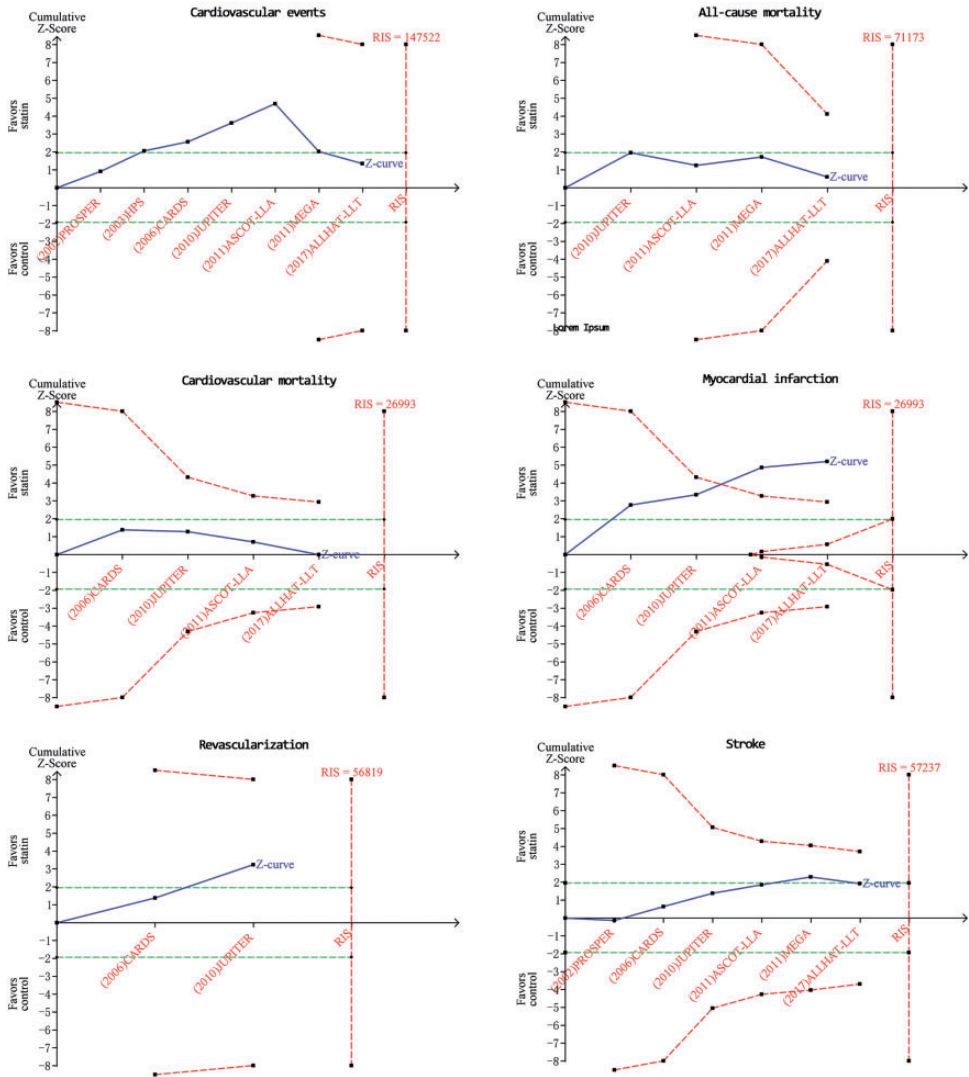


Figure 7. Trial sequential analysis (TSA) of the risks of clinical outcomes for the older patients in primary prevention.

of heterogeneity, a sensitivity analysis was conducted, as described below. For each clinical outcome, subgroup analyses by statin treatment dose (studies investigating statins at low- versus medium- versus high-intensity dose) were performed. These analyses estimated results that only included trials that were classified as having a low

risk of bias, as well as those that excluded individuals with diabetes mellitus and heart failure. After excluding studies with a high bias risk, there was a statistically significant difference in the reduction of stroke (OR: 0.72, 95% CI: 0.54–0.95) in primary prevention and for myocardial infarction (OR: 0.73, 95% CI: 0.63–0.84) in secondary

Table 2. Publication bias assessment of this meta-analysis.

Clinical outcomes	Egger test		Begg test	
	t-value	p	t-value	p
All-cause mortality	-1.62	N.S.	1.56	N.S.
Cardiovascular mortality	-1.62	N.S.	0.78	N.S.
Cardiovascular events	-2.27	0.04	1.77	N.S.
Myocardial infarction	-1.32	N.S.	1.40	N.S.
Revascularization	-2.09	N.S.	1.98	N.S.
Stroke	-3.05	0.01	2.13	0.03

N.S., not significant.

prevention. Other results of sensitivity analyses were similar to those of the overall analysis and did not show significant differences compared with the main analyses.

Discussion

Over the past 10 years, the prevalence of dyslipidemia has increased dramatically.⁴² Recent evidence indicates that a high lipid level is closely related to ASCVD and that dyslipidemia is the critical independent risk factor for ASCVD.⁴³ ASCVD is the leading cause of death in the elderly.⁴⁴ Therefore, actively and effectively reducing a deleterious lipid level is of great significance for prolonging the life span in the elderly. Statin therapy is an important strategy for reducing lipid levels, and prevention of cardiovascular adverse events by statins has been demonstrated for primary and secondary prevention of cardiovascular disease.^{45,46} However, because of the particularity of the older population, comorbidities and adverse effects might render research results difficult to interpret, and the elderly are usually excluded from pre-marketing clinical trials.⁴⁷ Thus, the therapeutic benefits of preventive medicine in the elderly are not well established. The present study summarized and quantified the current RCTs in the elderly (≥ 65 years) as well as in a subgroup of the elderly population. Assessment

of the evidence quality and recommendations were concurrently conducted and the clinical benefits of several various statins were compared.

The overall meta-analysis of all clinical outcomes in the current study showed that the elderly could significantly benefit from statin therapy. Subgroup analysis exploring differences between primary and secondary prevention indicated that statin therapy was more beneficial for secondary prevention. Statins can significantly reduce the risk of mortality, cardiovascular events, and revascularization, and the level of evidence was higher for secondary prevention compared with primary prevention. However, subgroup analysis revealed differences in the risk of myocardial infarction and stroke. Reducing the risk of stroke was better reflected in secondary prevention, although there was no statistically significant reduction for myocardial infarction. However, a reductive trend was observed for myocardial infarction.

For the first time, a TSA was used to calculate the sample size. The included studies were identified based on the different publication years and adjusted for random errors. This analysis counterbalanced the lack of sample size estimation in the standard meta-analysis.⁴⁸ The TSA analysis revealed that most clinical endpoints suggest that statin treatment can

significantly reduce cardiovascular adverse outcomes in older patients when used for secondary prevention of cardiovascular disease. The possibility of a false negative could not be excluded as the reason for the only negative result (myocardial infarction). The sensitivity analysis, which excluded studies with a high risk of bias, also supported this result. The lack of a positive result for myocardial infarction might be associated with variances in the types of myocardial infarction that were assessed, and in the overall physical condition of the patient population.^{49,50} In addition, a false positive that may not be excluded when assessing the stroke risk might be related to the different types of stroke that were assessed, such as cardiogenic stroke and hemorrhagic stroke. These issues have not been explained in depth in previous clinical trials. A recent study indicated that statin therapy in post-stroke patients increased the risk of hemorrhagic stroke; however, when weighing the benefits and potential harms, statins had an overall beneficial effect in patients with a history of stroke.⁵¹ Therefore, the risk of stroke for elderly patients who are taking statins needs to be studied further.

Even if the treatment effects of various statins appear to be similar, there could be differences in other critical dimensions such as the pharmacokinetic properties. Different statins show different susceptibilities to changes in metabolism that are associated with differences in various isoenzymes of the liver cytochrome CYP450 family. Accurate data comparing the relative effectiveness of different statins were not sufficient and the results were unclear, especially in older individuals. However, the effectiveness of statin therapy for secondary prevention of cardiovascular disease was nearly indisputable.^{52,53} For example, the SAGE trial demonstrated that intensive atorvastatin (80 mg/day) therapy was associated with reductions in cardiovascular

adverse events and mortality compared with moderate pravastatin therapy (40 mg/day).³⁰ The IDEAL study showed that the magnitude of the effect in favor of intensive atorvastatin was higher in younger patients compared with elderly patients, although no significant interactions between age and treatment were found.³² Additionally, a recent study conducted a network analysis to compare the benefits and harms of various statins in patients with ischemic strokes or transient ischemic attacks, and the authors concluded that differences in the effects among statins had potential therapeutic equivalence.⁵⁴ Similarly, the Bayesian network analysis in this study found no significant differences among different statins for secondary prevention in the elderly. The only difference may be that intensive atorvastatin treatment (80 mg) might be more effective compared with other statins for reducing the rate of cardiovascular events, cardiovascular mortality, and revascularization compared with the control group. In addition, although this study did not assess the degree of LDL-cholesterol (LDL-C) reduction, it is reasonable to assume that LDL-C reduction by atorvastatin significantly exceeded the effect that was observed by studies that evaluated simvastatin, pravastatin, or fluvastatin. Clinicians need to be aware that some drugs can inhibit CYP3A4 (e.g., erythromycin, antiretrovirals), leading to an increase in the plasma atorvastatin level, which is a risk factor for increased morbidity, rhabdomyolysis, and muscular toxicity.

With the recommendation of the 2016 European Society of Cardiology/European Society of arteriosclerosis (ESC/EAS) guidelines, the status of statins as the cornerstone of lipid-lowering drugs is still unshakable, especially for high-risk individuals and secondary prevention of ASCVD.⁵⁵ The present study strongly supports this and the recommendation could be

extrapolated to the elderly population. Analysis in the current study seems to support the feasibility of giving priority to a particular statin that is more beneficial for elderly high-risk groups, better tolerated, and more effective at reducing recurrent cardiovascular disease, especially cardiovascular events, cardiovascular mortality, and revascularization. However, the quality of the evidence for the benefits of statins for primary prevention in the elderly is less certain. We considered that the degree of treatment effects on prognosis is strongly associated with the degree of pre-existing cardiovascular risk and the starting point of statin treatment. The late prognosis might be more beneficial in elderly patients with elevated cholesterol levels, especially for those patients whose statin treatment for primary prevention was started early. Therefore, it is more reasonable to recommend initiation of statin therapy based on individual risk stratification.⁵⁵ In addition, large-scale, high-quality randomized controlled trials examining statins for the primary prevention of cardiovascular disease and the prevention and treatment of specific diseases, including stroke, are needed. The strengths of the current study include the implementation of a trial sequential analysis methodology, which added certainty to previous findings because it controlled for the risk of false-positive and false-negative results in the meta-analysis as a result of sparse data and the repetitive analyses of data. This study further assessed outcomes using the GRADE system; thus, the evidence can be considered to be conclusive. Overall, this meta-analysis will help physicians and older patients choose the appropriate statin regimen, and it provides suggestions for future trials in the elderly population.

Despite the above strengths, there are limitations to this study. First, because of the small number of included studies and unavailable data, subgroup analysis could

not be performed on types of comorbidities and the degree of LDL-cholesterol reduction. Second, to some extent, clinical heterogeneity cannot be resolved completely, such as different ethnicities, past drug regimens, complex physical differences among the elderly, and clinical experience. Third, individual studies with varied methodological quality and potential language bias were more likely to give rise to various types of bias. Fourth, the safety of statins for the elderly needs to be independently evaluated.

Conclusion

Evidence strongly suggests that statins are associated with a reduction in the risk of all-cause mortality, cardiovascular events, cardiovascular mortality, and revascularization for older patients when used for secondary prevention. However, the overall evidence level for primary prevention is low. Differences in the effects among statins have potential therapeutic equivalence for secondary prevention in the elderly. Further studies are needed to ascertain the benefits of statins for primary prevention and to conduct a cost-effectiveness analysis.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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