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SYSTEMATIC REVIEW

Statins for Primary Prevention of Cardiovascular Disease in Elderly Patients: Systematic Review and Meta-Analysis

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Abstract

Background Statins have been shown to be beneficial in primary and secondary prevention settings; however, their role in the elderly remains a clinical conundrum, given that age-related factors could alter the risk–benefit ratio of statin treatment. This study aimed to critically evaluate the efficacy and safety of statins for primary prevention of cardiovascular disease (CVD) in the elderly.

Methods We systematically reviewed randomized controlled trials comparing any statins with placebo or usual care for primary prevention of CVD in subjects aged ≥65 years. Relative risks (RRs) using a random effects model were calculated and sensitivity analyses were performed to assess the robustness of findings.

Results Eight studies ($n = 25{,}952$) were included in the meta-analysis. Statins significantly reduced the risks of composite major adverse cardiovascular events (RR 0.82, 95 % CI 0.74–0.92), nonfatal myocardial infarction [MI] (0.75, 0.59–0.94) and total MI (0.74, 0.61–0.90). Treatment effects of statins were statistically insignificant in fatal MI (0.43, 0.09–2.01), stroke (fatal: 0.76, 0.24–2.45; nonfatal: 0.76, 0.53–1.11; total: 0.85, 0.68–1.06) and all-cause mortality (0.96, 0.88–1.04). Significant differences were not observed in myalgia (0.88, 0.69–1.13), elevation of hepatic transaminases (0.98, 0.71–1.34), new–onset diabetes (1.07, 0.77–1.48), serious adverse events (1.00, 0.97–1.04) and discontinuation due to adverse events (1.10, 0.85–1.42). The occurrence of myopathy, rhabdomyolysis and cognitive impairment was largely unreported in the included trials.

Conclusions From a risk–benefit perspective, there is a role of statins for the primary prevention of major adverse cardiovascular events in elderly patients. Further studies are needed to ascertain the benefits of statins on fatal MI, stroke and all-cause mortality.

Key Points

Benefits of statins for primary prevention of cardiovascular disease are less well-established in the elderly.

This study revealed that statin therapy was associated with significant risk reduction in composite major adverse cardiovascular events, nonfatal myocardial infarction (MI) and total MI.

No significant differences in the adverse risk profiles were observed.

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1 Background

Cardiovascular disease (CVD) is the leading cause of mortality worldwide [1]. Elevated serum levels of total and low-density lipoprotein cholesterol (LDL-C) are associated with increased risk for CVD [2]. Statins, one of the most widely used classes of drugs globally [3, 4], are important first-line drugs for dyslipidemia. Clinical data have shown that statins are beneficial in reducing the risks of cardiovascular adverse events and mortality in adults with and without established CVD [5–10]. This forms the basis of the 2013 guidelines of the American College of Cardiology and American Heart Association (ACC/AHA), which recommend the use of statins for individuals at an elevated absolute risk for CVD [11]. A chart review of 22,646 elderly subjects aged 85 years and beyond showed that of those who received a statin (24 %), more than half used it for primary prevention [12]. The prevalence of statin use for primary prevention is likely to increase given that advanced age is a risk factor for CVD. It is estimated that 97 % of elderly individuals aged between 65 and 75 years would meet the criteria for statin treatment according to the 2013 ACC/AHA guidelines [13].

The elderly population has a high prevalence of chronic diseases and is the largest user of prescription medications [14]. However, prescribing in the elderly presents unique challenges due to age-related changes in their pharmacokinetics and pharmacodynamics [15]. Premarketing clinical trials often exclude older people in view of comorbidities and adverse effects that could cause difficulty in interpreting study results. Therefore, the benefits of treatment in the elderly, especially in preventive medicine, are less well-established [16]. In CVD, it has been observed that the relative risks (RRs) for coronary artery disease and stroke associated with elevated serum cholesterol decrease after the age of 65 years [17]. Given the age-related physiologic changes, the balance of the potential risks and probable benefits of statins need to be re-weighed when we decide whether or not statins should be started, or continued, in the elderly. Recent data found statins to be cost-effective for primary prevention in people aged ≥75 years. However, the caveat was that even a small increase in geriatric-specific adverse effects from statins, specifically 10–30 % increased risk of functional limitation or mild cognitive impairment, could offset the cardiovascular benefit [18]. Therefore, this systematic review aimed to critically evaluate the efficacy and safety of statins for primary prevention of CVD in the elderly.

2 Methods

We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [19] in reporting the results of this systematic review.

2.1 Search Strategy

We searched the PubMed database for systematic reviews on statins for the prevention of cardiovascular events published from 1 March 2009 to 31 August 2014. We elected to conduct the search over a period from 2009 to 2014 based on the guide from the Agency for Healthcare Research and Quality (AHRQ), which recommends that a search for synthesized literature over the last 5 years is sufficient if the interventions are well-established and have been the focus of recent research activity [20]. Given that PubMed and EMBASE (European-focused database) searches restricted to the English language have been found to return similar results [21], we chose to search PubMed. The initial literature search was part of a larger systematic review to identify randomized controlled trials (RCTs) that studied statins in primary prevention or primary and secondary prevention settings. An update search was conducted in August 2014 using the PubMed and Cochrane Library databases to identify additional RCTs of statins in the primary prevention of CVD for the period elapsed since the latest search date in the published systematic review. The search was conducted based on combinations of the following terms: 'hydroxymethylglutaryl-CoA reductase inhibitors', 'anticholesteremic agent', 'atorvastatin', 'fluvastatin', 'lovastatin', 'pravastatin', 'rosuvastatin', 'simvastatin', 'cardiovascular diseases', 'coronary disease', 'myocardial infarction', 'cerebrovascular disorder' and 'stroke'. The search was restricted to trials in humans that were published in English. The search strategy is described in the electronic supplementary material. The Cochrane Collaboration's sensitivity and precision-maximizing strategy was adopted [22], and cross-checking of bibliographies from other published review articles was also conducted to supplement the electronic searches.

2.2 Inclusion and Exclusion Criteria

Studies that met the following criteria were included in the final review and meta-analysis:

- comprised a cohort of participants aged ≥65 years and without established CVD;

- participants were randomized to a statin (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin) or placebo (or usual care);
- reported at least one of the following outcomes: major adverse cardiovascular events [MACEs] (myocardial infarction [MI], stroke, coronary revascularization, cardiac sudden death, angina), all-cause mortality, elevation in hepatic transaminases (defined as >3× upper normal limit [UNL], elevation in creatine kinase [CK] (defined as >10× UNL), myalgia (muscle weakness, stiffness or pain), myopathy (myalgia associated with >10× UNL of CK levels), rhabdomyolysis, serious adverse events, tolerability (discontinuation due to adverse events), incidence of new–onset diabetes and cognitive impairment.

Trials that included participants younger than 65 years of age were excluded if they did not report results stratified by age.

2.3 Study Selection

Three reviewers (MT, LL, YJ) screened titles and abstracts against predefined study inclusion criteria. Full-text articles were independently screened by two reviewers (MT, LL) for eligibility. Any disagreements were resolved by consensus.

2.4 Data Collection and Risk of Bias Assessment

Data on patient characteristics, study design, duration of follow-up, statin regimen (agent and dose), outcomes, and funding sources were extracted by one reviewer (LL) using a structured form. The entries were then verified by a second reviewer (MT) for accuracy. The quality of the included studies was assessed using the Cochrane Risk of Bias Tool [23], with due consideration of six domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data and selective reporting. We also considered sponsorship bias. Judgment on the risk of bias was made for each domain based on three categories: high risk, low risk and unclear risk of bias.

2.5 Data Analysis

Meta-analyses of outcomes were performed using a random effects model in STATA software, version 13 (StataCorp LP, College Station, TX, USA). Summary effects were reported as RRs with corresponding 95 % confidence intervals (CI). Statistical heterogeneity between trials was evaluated using the Chi square test at a significance level of $p < 0.1$ and I^2 statistic. Trial data were considered to be heterogeneous when the I^2 statistic was >50 %. Where significant heterogeneity was present, sensitivity analyses were performed to investigate study designs or study level characteristics as possible sources of heterogeneity.

3 Results

3.1 Description of Studies

The initial search yielded 1549 systematic reviews, of which 12 unique systematic reviews were considered relevant. These 12 systematic reviews comprised seven studies evaluating statins for primary prevention only [9, 24–28] and five studies evaluating statins in both primary and secondary settings [5, 29–32]. Fifty-nine RCTs were extracted from these studies, while the updated search for recent RCTs retrieved 387 records. After applying our study inclusion criteria, a total of eight trials [33–40] were eligible for our meta-analysis. Two trials focused on elderly subjects, and six trials comprised subgroup analyses of elderly subjects. The study selection process is shown in Fig. 1.

3.2 Study Population

Overall, 25,952 subjects were included in our analyses, of whom 12,974 (49.9 %) were allocated to statin therapy and 12,978 (50.1 %) were allocated to control (placebo or usual care). The studies were predominantly conducted in Western populations, with only one trial in an Asian population. The mean age of subjects was 72.7 years (range 69–75.5 years), and the mean follow-up was 3.5 years (range 1–5 years). The proportion of patients with diabetes and hypertension was 51.2 and 56.8 %, respectively. While one trial (JUPITER) excluded diabetic patients at entry, subjects in three trials (ASCOT–LLA, CARDS and HPS) all had diabetes, while all subjects in the ALLHAT–LLT trial had hypertension. Twenty-two percent of patients were current smokers or had a history of smoking, and average baseline LDL-C level (weighted) across studies was 3.73 mmol/L. Characteristics of the included studies are presented in Table 1.

3.3 Risk of Bias Assessment

The overall methodological quality of included trials was moderate. Trials were judged as having a low risk of bias in most domains (Fig. 2a, b). Two trials [33, 39] were open-labeled while the rest were double-blinded, and six trials were sponsored by industry.

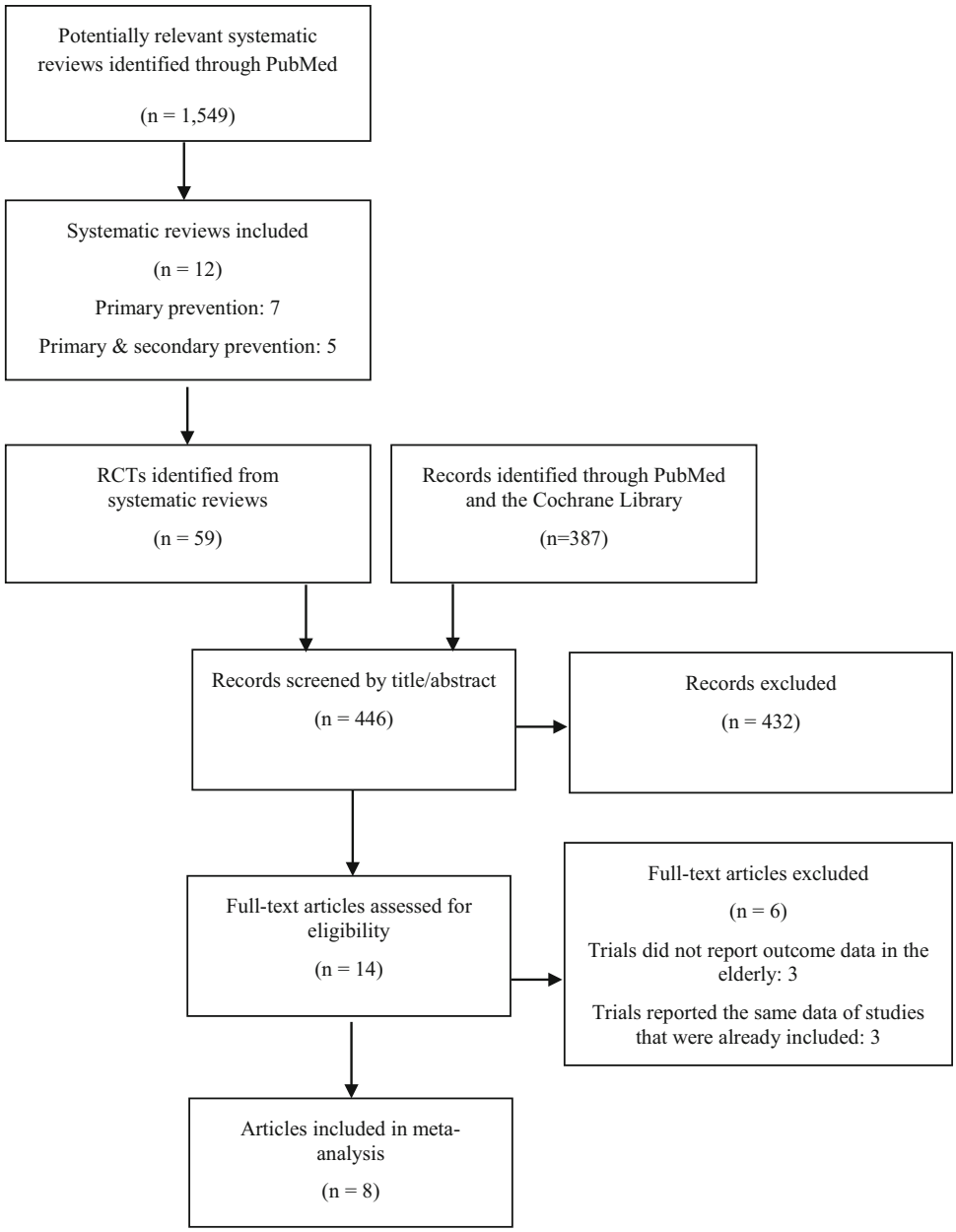


Fig. 1 Study selection process. *RCTs* randomized controlled trials

3.4 Effects of Statins

3.4.1 Major Adverse Cardiovascular Events

Of the 18,914 elderly subjects included in seven trials, 2347 MACEs occurred during the follow-up. Statin treatment was associated with a significant reduction in the incidence of MACEs (RR 0.82, 95 % CI 0.74–0.92). Significant heterogeneity was observed in this analysis ($I^2 = 71.5$ %, $p = 0.002$) (Fig. 3). However, the results were robust to sensitivity analyses performed by restricting the analysis to studies conducted in the Western population (RR 0.83, 95 % CI 0.74–0.93), and double-blinded studies (RR 0.82, 95 % CI 0.76–0.89).

3.4.2 Myocardial Infarction

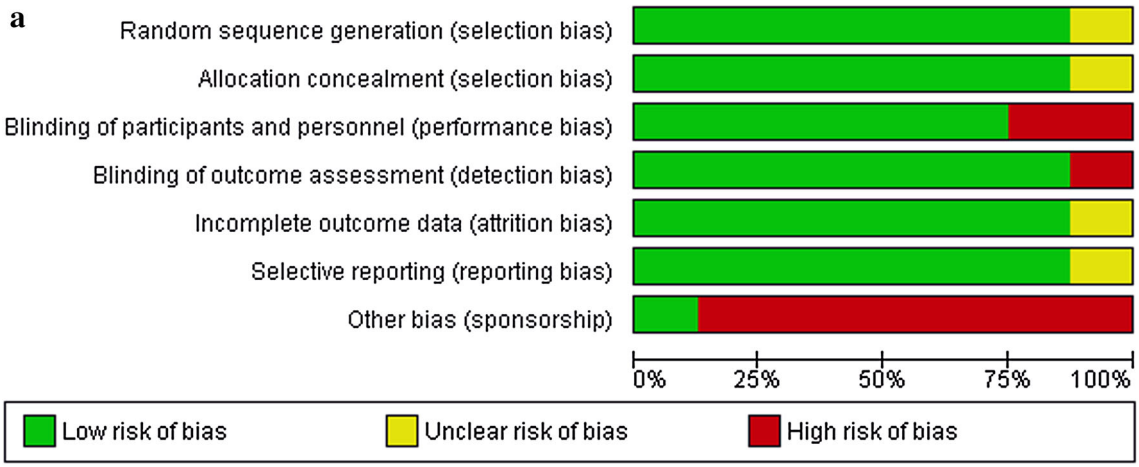
Data were available on a total of 869 MI events among 20,317 subjects in five trials. No significant difference was detected between statins and control in fatal MI (RR 0.43, 95 % CI 0.09–2.01). Statins significantly prevented non-fatal MI and total MI with RRs of 0.75 (95 % CI 0.59–0.94) and 0.74 (95 % CI 0.61–0.90), respectively. Heterogeneity was observed for the analysis of fatal MI

Table 1 Characteristics of included trials

Study	Country	Year of publication	Mean follow-up, years	No. of subjects (statin/control)	Mean age, years (range)	Women (%)	Statin and dose	Diabetes (%)	HTN (%)	Smoking (%)	Mean baseline lipid levels (mmol/l)			
											TC	LDL-C	HDL-C	TG
ALLHAT–LLT [33]	US, Puerto Rico, US Virgin Islands and Camada	2002	4.8	5809 (2913/2896)	72 (65–111)	47.8	Pravastatin 40 mg/day	38.3	100	41.3	5.77	3.75	1.24	3.84
ASCOT–LLA [34]	UK, Sweden, Norway, Denmark, Finland, Ireland	2011	3.3	4445 (2189/2256)	NA	19.6	Atorvastatin 10 mg/day	100	26.7	23.7	5.48	3.44	1.33	1.73
Bruckert et al. [35]	France, Italy, Spain, Belgium and Israel	2003	1	1229 (607/622)	75.5 (69–92)	74.9	Fluvastatin XL 80 mg/day	7	55.9	16.2	7.28	5.18	1.36	1.53
CARDS [36]	UK and Ireland	2006	3.9[a]	1129 (572/557)	69 (65–77)	31.4	Atorvastatin 10 mg/day	100	NR	15.6	5.3	3.06	1.44	1.53
HPS [37]	UK	2003	4.8	2592 (1303/1289)	NA	24.7	Simvastatin 40 mg/day	100	NR	NR	NR	NR	NR	NR
JUPITER [38]	North America, South America, Europe and Africa	2010	1.9	5695 (2878/2817)	74 (70–97)	51.6	Rosuvastatin 20 mg/day	0	65.6	8.4	NR	NR	NR	NR
MEGA [39]	Japan	2011	5	1814 (927/887)	NA	51.9	Pravastatin 10–20 mg/day	52	21	14	NR	NR	NR	NR
PROSPER [40]	Scotland, Ireland and The Netherlands	2002	3.2	3239 (1585/1654)	75 (70–82)	58.5	Pravastatin 40 mg/day	12.2	71.6	33	5.69	3.78	1.31	1.52

ALLHAT–LLT Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial–Lipid-Lowering trial component, *ASCOT–LLA* Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm, *CARDS* Collaborative Atorvastatin Diabetes Study, *HPS* Heart Protection Study, *JUPITER* Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin, *MEGA* Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese, *PROSPER* Prospective Study of Pravastatin in the Elderly Evaluating Rosuvastatin, *NR* not reported, *HTN* hypertension, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *NA* not available

[a] Median follow-up



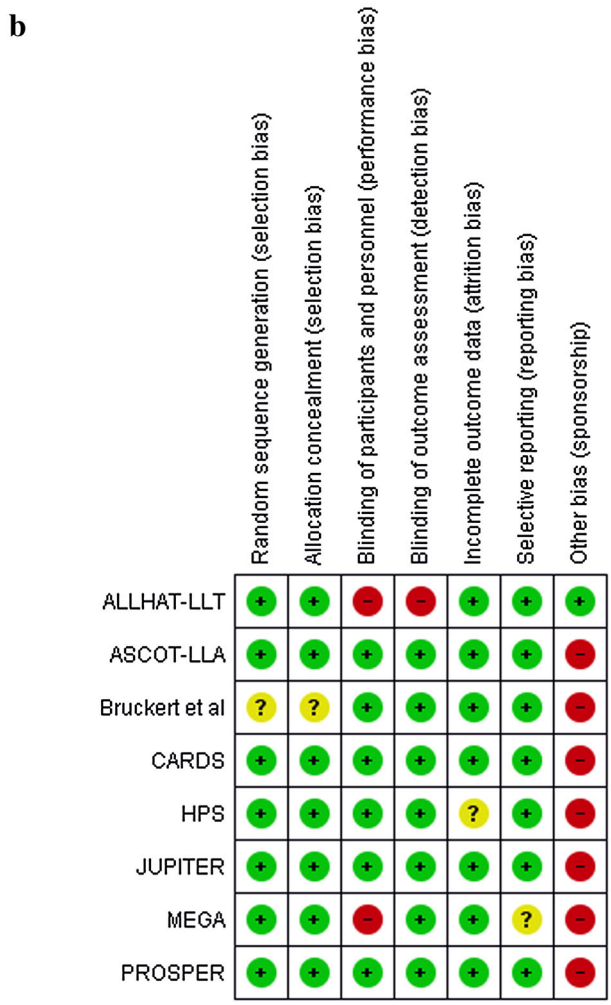


Fig. 2 Risk of **a** bias graph and **b** bias summary: review authors' judgments about each risk of bias item presented as percentages across all included studies

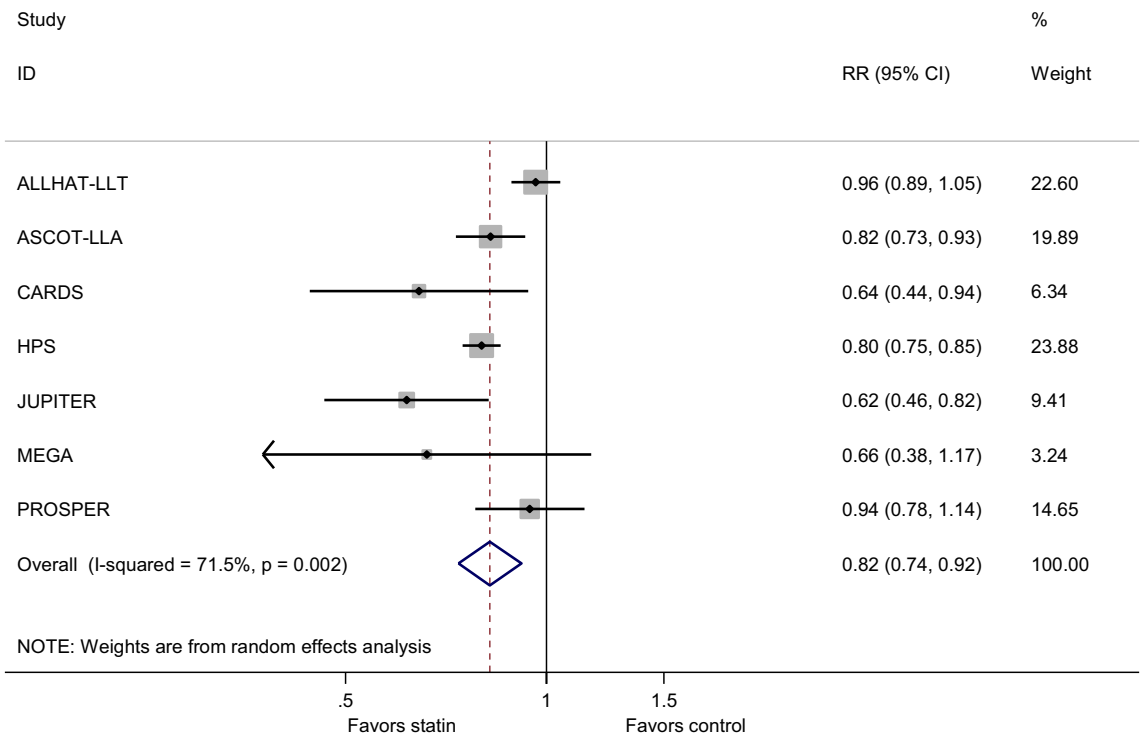


Fig. 3 Relative risk of major adverse cardiovascular events. *RR* relative risk, *CI* confidence interval

(I^2 76.6 %, $p = 0.039$), which could be attributed to the small number of studies (Fig. 4).

3.4.3 Stroke

Data were available on a total of 684 stroke events among 21,800 subjects in six trials. Statins did not significantly reduce the risk of fatal stroke (RR 0.76, 95 % CI 0.24–2.45), nonfatal stroke (RR 0.76, 95 % CI 0.53–1.11) and total stroke (RR 0.85, 95 % CI 0.68–1.06). Significant heterogeneity in the results was not observed (Fig. 5).

3.4.4 All-Cause Mortality

During the mean follow-up of 3.5 years, there were a total of 986 (8.5 %) deaths among 11,631 patients receiving a statin, and 1040 (8.9 %) deaths among 11,729 patients on control. Statins were not significantly different than control in preventing all-cause mortality (RR 0.96, 95 % CI 0.88–1.04). No evidence of heterogeneity was observed ($I^2 = 0$ %, $p = 0.521$) (Fig. 6).

3.4.5 Safety and Tolerability

Insufficient outcome data were available to perform meta-analysis on myopathy, rhabdomyolysis and cognitive impairment. These outcomes were reported in one trial [38, 40], and were not significantly different between statins and control. When compared the incidence of adverse events, the absolute percentage of patients in statins versus control were 0.831 versus 0.827 % for elevation of hepatic transaminases, 1.28 versus 1.54 % for myalgia, 2.82 versus 2.64 % for new–onset diabetes, and 22.91 versus 22.93 % for serious adverse events. The differences were not statistically significant (Fig. 7). In terms of discontinuation due to adverse events, statins were also not significantly different from control (RR 1.10, 95 % CI 0.85–1.42) (Fig. 8).

4 Discussion

Our analysis included a total of 25,952 elderly participants with specified cardiovascular risks but no established CVD. We found that statins significantly reduced the risk of MACEs by 18 %, nonfatal MI by 25 %, and total MI by 26 %, over a mean treatment period of 3.5 years. Statin therapy was associated with a nonsignificant risk reduction in fatal MI, stroke (fatal, nonfatal and total) and all-cause mortality. In terms of safety, there were no statistically detectable differences between statins and control in myalgia, elevation of hepatic transaminases, new–onset

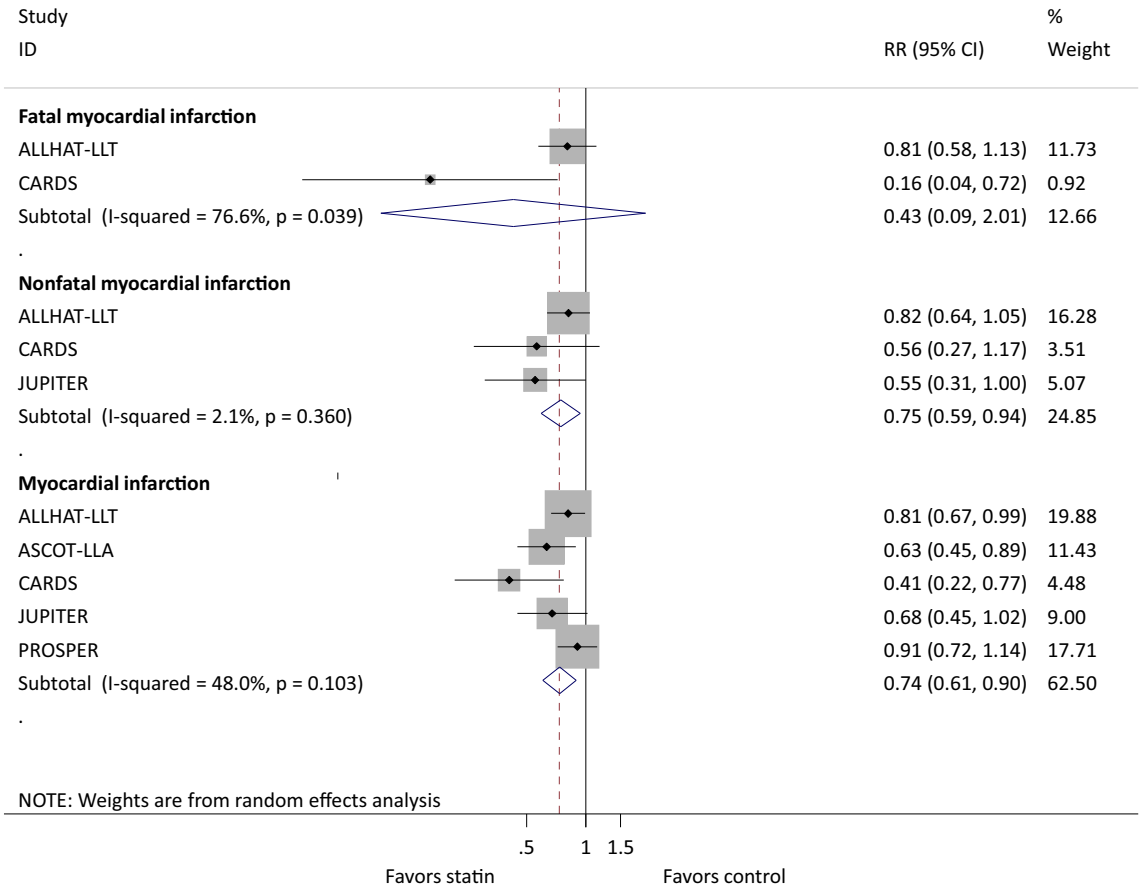
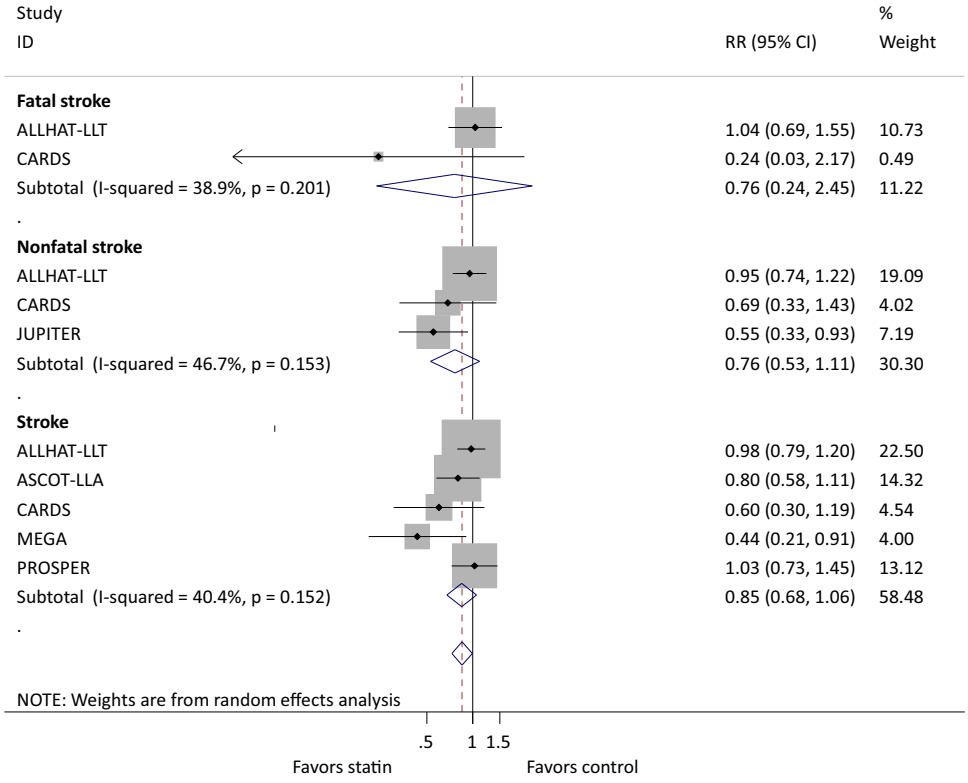


Fig. 4 Relative risk of myocardial infarction. *RR* relative risk, *CI* confidence interval

diabetes, serious adverse events and discontinuation due to adverse events. The occurrence of myopathy, rhabdomyolysis and cognitive impairment was either uncommon or not reported.

Our findings were generally consistent with published meta-analyses of statins for primary prevention [8–10, 25, 28, 41], which favored the use of statins. The meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration showed a similar trend. The risk of major vascular events for the age group >65 years receiving statins was 0.81 (0.77–0.86) [7]. Our findings of the statin effects on stroke contradicted some of the earlier analyses [8, 9]. In the Cochrane review that included 18 RCTs evaluating 56,934 participants without previous coronary heart disease (CHD) [9], the RR for statins versus control in stroke was 0.78 (95 % CI 0.68–0.89). Apart from the fact that the Cochrane review evaluated statin therapy in the general population of patients, the association between serum cholesterol levels and stroke incidence has been controversial. Strokes can be either hemorrhagic or ischemic; additionally, there are different stroke subtypes such as subarachnoid and atherothrombotic. As a result, the association between serum cholesterol and stroke is more complex when compared with MI which is usually due to atherothrombosis [42].

Our study differed from the earlier meta-analysis of statin trials in the elderly [41] as we included data on a wide range of treatment outcomes, including adverse events. Given that elderly individuals are more prone to adverse effects of medications due to age-related factors, it is prudent to weigh the benefits relative to harms of statin therapy. We also analysed the incidence of nonfatal events for MI and stroke. Nonfatal cardiovascular adverse outcomes are debilitating, and substantially reduce the quality of life in the elderly. By analysing only the total MI or total stroke, the true benefits of statin therapy on nonfatal cardiovascular outcomes may be underestimated. In our analysis, statins did not significantly reduce the risk of fatal and nonfatal stroke. These results differed from the published study, which reported a significant reduction of stroke by 24 %. Notably, we included data from ALLHAT–LLT [33] (the largest non-industry-funded trial of statin published to date) in our analysis for stroke.



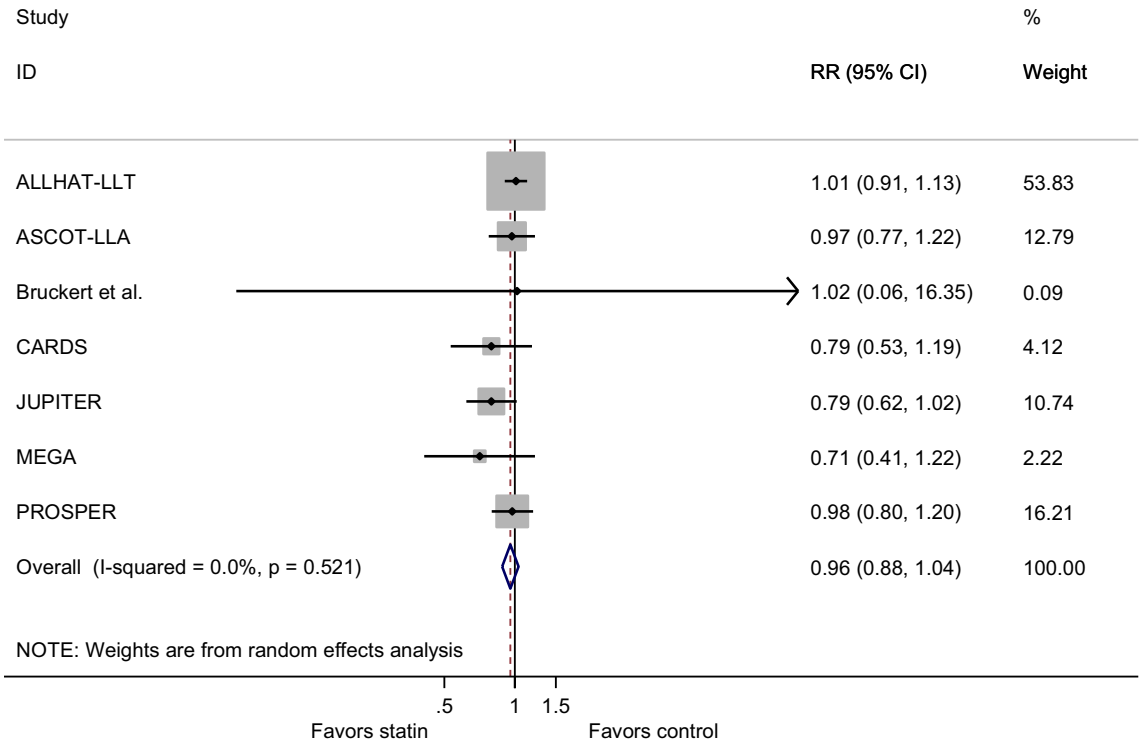


Fig. 5 Relative risk of stroke. *RR* relative risk, *CI* confidence interval

Fig. 6 Relative risk of all-cause mortality. *RR* relative risk, *CI* confidence interval

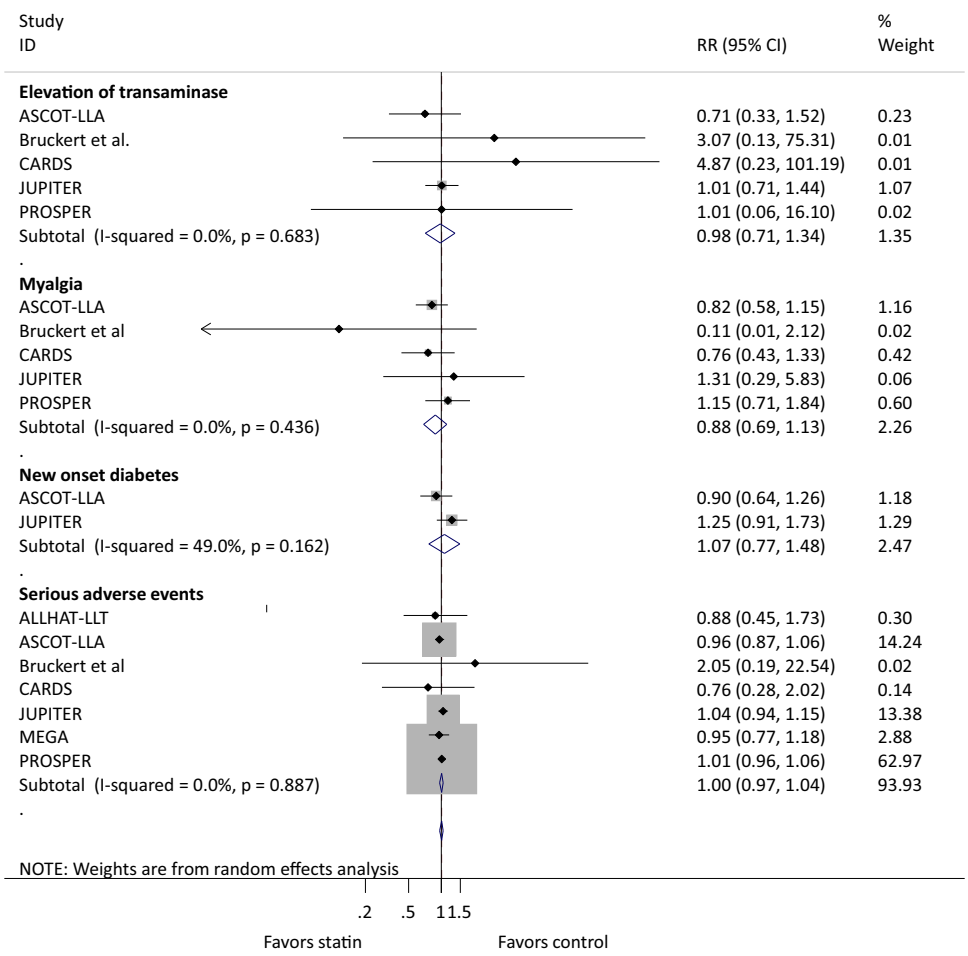


Fig. 7 Relative risk of adverse events. *RR* relative risk, *CI* confidence interval

In our analysis, statin therapy was not associated with any detectable differences in myalgia and hepatic transaminase elevation. Myopathy and rhabdomyolysis were infrequent in the included studies, even though muscle-related side effects are the common causes that limit the use of statins in clinical practice. A possible reason could be that patients are stringently selected and closely monitored in clinical trials. Therefore, the rates of adverse events are expected to be lower when compared with the real-world. According to a systematic review of cohort studies, RCTs, voluntary notifications to national regulatory authorities, and published case reports, the incidence of rhabdomyolysis in patients taking statins was estimated as three per 100,000 person-years, and myopathy was 11 per 100,000 person-years [43]. The incidence of clinically important liver disease attributable to statins was rare, although statins have been reported to cause significant increased hepatic transaminase elevation [31, 43]. Earlier studies have found that adverse events correlated to statin doses [31, 44] and differed among different statins [45]. Atorvastatin, simvastatin and lovastatin, metabolized by cytochrome P450 (CYP) 3A4, were associated with a higher incidence of muscle diseases when compared with fluvastatin (primarily metabolized by CYP2A9) and pravastatin (not metabolized by the CYP450 system) [46]. Older individuals commonly receive multiple medications and are more prone to drug interactions. Given the unique characteristics of this patient population, clinicians should carefully consider the dose and type of statins in their prescriptions.

A significant impact of statin therapy on new–onset diabetes was not detected; however, it is noteworthy that our results were based on only two trials. A recent meta-analysis showed that statin therapy was associated with a 9 % increased risk for diabetes [47], with the authors concluding that the risk was low when compared with the beneficial effects of statins. Among the many potential adverse effects of statins, cognitive impairment is one that has received much attention. In 2014, the US FDA issued warnings about the risk of cognitive impairment associated with statin use [48]; however, a meta-analysis of 25 RCTs involving 29,012 participants did not show any significant

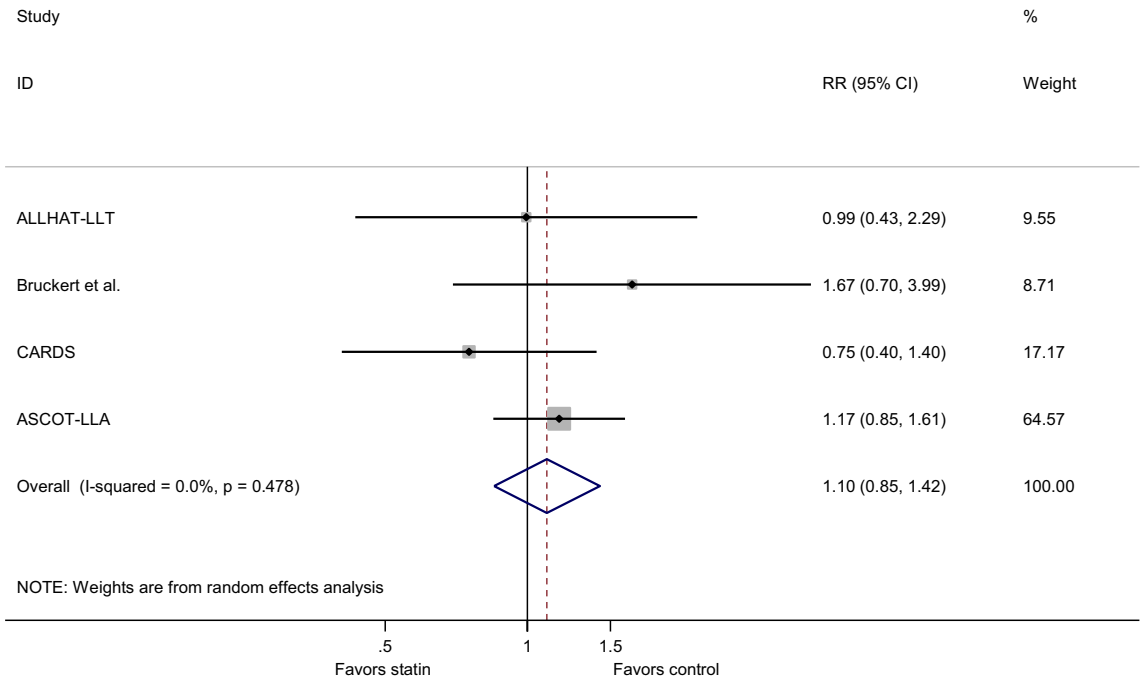


Fig. 8 Relative risk of discontinuation due to adverse events. *RR* relative risk, *CI* confidence interval

adverse effects of statins on all cognitive tests, in either cognitively intact individuals or individuals with Alzheimer's disease [49].

Our study has some potential limitations that should be considered. First, as in all systematic reviews and meta-analyses, our results relied on the number and quality of the included trials. While six of the included trials were double-blinded, two trials were open-labeled. Therefore, we carried out sensitivity analyses to investigate the impact of performance and detention bias on the consistency of the results. Second, data were largely not derived from trials that were designed specifically to capture statin effect in older subjects. Only two trials were designed to study older subjects. Third, there may be study heterogeneity as the elderly participants in the included trials had different risk levels and on different statins. Finally, the limited follow-up period of the included trials may underestimate the incidence of adverse events and the incidence of benefits. Despite these limitations, our study provided comprehensive insights into the benefits and risks of statin therapy among older individuals without established CVD. Given that the validity of a systematic review depends on whether the search retrieved appropriate literature, we aimed to identify a large number of relevant studies from published systematic reviews that might have contained data on the elderly. To our knowledge, our study can be considered the first meta-analysis to examine both efficacy and adverse events, including a wide range of possible outcomes of statin therapy in older people. The present findings are useful to support informed clinical and policy decisions about the use of statins for the primary prevention of cardiovascular events.

5 Conclusions

In this meta-analysis of eight RCTs, statin therapy significantly reduced the incidence of MACEs, nonfatal MI and total MI. No significant differences in adverse risk profiles were observed between the statin treatment group and the control group. From a risk–benefit perspective, there is no compelling reason to preclude prescribing statins in elderly patients. However, the unique characteristics of this population warrant clinicians to consider factors such as expected life expectancy and the lag time to observe a beneficial effect or adverse event when initiating statin therapy in elderly individuals. Further studies are needed to ascertain the benefits of statins in stroke and all-cause mortality for primary prevention in the elderly.

Compliance with Ethical Standards

Funding This study was not supported by any grants or organizations.

Conflicts of interest Monica Teng, Liang Lin, Ying Jiao Zhao, Ai Leng Khoo, Barry R. Davis, Quek Wei Yong, Tiong Cheng Yeo and Boon Peng Lim declare that they have no conflicts of personal interest.

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