SYSTEMATIC REVIEW AND META-ANALYSIS

Efficacy and safety of statin therapy in hypertensive elderly patients without dyslipidemia: a systematic review and meta-analysis

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ABSTRACT

Background: The role of statins for primary cardiovascular prevention in older adults with hypertension but without established cardiovascular disease remains uncertain. This systematic review and meta-analysis evaluated the effectiveness and safety of statin therapy in this population.

Methods: PubMed, Scopus, Web of Science, Cochrane CENTRAL, and Google Scholar were searched for English-language studies published between 2005 and 2025. Eligible studies included adults aged ≥60 years with hypertension and no established cardiovascular disease who received statin therapy compared with no statin, placebo, or usual care. Randomized controlled trials and observational studies were included. Hazard ratios were used as the primary effect measure for time-to-event outcomes, while risk ratios from crude event counts were analyzed separately. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool or the Newcastle-Ottawa Scale, and certainty of evidence was evaluated using GRADE.

Results: Four studies involving 17,173 participants were included, of whom 16,709 contributed to cardiovascular outcome analyses. Statin therapy was associated with lower risks of major adverse cardiovascular events (HR 0.78, 95% CI 0.69-0.88), myocardial infarction (HR 0.64, 95% CI 0.48-0.87), and stroke (HR 0.78, 95% CI 0.63-0.97), with no detectable heterogeneity for these outcomes. No significant association was observed with cardiovascular mortality (HR 0.92, 95% CI 0.71-1.19). The pooled random-effects estimate for all-cause mortality was also not statistically significant (HR 0.86, 95% CI 0.70-1.06); the randomized estimate was null (HR 0.98, 95% CI 0.77-1.23), whereas the observational estimate showed lower mortality (HR 0.79, 95% CI 0.68-0.93). Safety data were limited but showed no clear increase in muscle symptoms, marked transaminase elevation, serious adverse events, or new-onset diabetes; no cases of rhabdomyolysis were reported. The certainty of evidence was low for non-fatal cardiovascular outcomes and very low for mortality and safety outcomes.

Conclusion: Statin therapy was associated with fewer major cardiovascular events, myocardial infarctions, and strokes among older adults with hypertension without established cardiovascular disease, based on one post-hoc randomized subgroup analysis and one observational cohort. However, evidence for mortality

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benefit remains uncertain: the randomized estimate for all-cause mortality was null, and the apparent reduction came from the observational study alone. Mean baseline LDL cholesterol was 133-138 mg/dl, so the findings should not be generalized to strictly normolipidemic patients or to low-dose statin therapy.

Keywords: Statins, hypertension, older adults, cardiovascular disease, stroke, mortality, systematic review, meta-analysis.

Introduction

Cardiovascular disease remains a major cause of morbidity and mortality in older adults, with hypertension further increasing cardiovascular risk. Statins are well established for reducing LDL-C and preventing cardiovascular events, but their role in primary prevention among older adults, particularly those without marked dyslipidemia or established cardiovascular disease, remains less certain [1,2]. Current recommendations therefore highlight overall cardiovascular risk, age, comorbidity, life expectancy, and potential treatment-related harms when considering statin therapy in this population [3,4].

Evidence generally supports a reduction in major vascular events with statin therapy in older adults, although the strength of evidence becomes less certain with advancing age, including primary prevention [5,6]. Individual trials have also reported inconsistent findings. PROSPER reduced coronary events but did not significantly reduce stroke or all-cause mortality, while the older-adult analysis of ALLHAT-LLT found no significant cardiovascular or mortality benefit with pravastatin [7,8]. The question is relevant in older patients with hypertension whose cholesterol levels are not elevated. ASCOT-LLA showed that low-dose atorvastatin reduced coronary and stroke events in hypertensive patients with average or below-average cholesterol levels [9]. Similar benefits were observed in primary-prevention populations in JUPITER and HOPE-3, although these studies were not specifically restricted to older hypertensive adults without dyslipidemia [10,11]. Thus, the applicability of these findings to this more narrowly defined population remains uncertain.

The US Preventive Services Task Force supports statin use for primary prevention in selected adults aged 40-75 years with cardiovascular risk factors but considers the evidence insufficient to determine the balance of benefits and harms when statin therapy is initiated in adults aged 76 years or older without established cardiovascular disease [4]. This uncertainty is clinically important because older adults have a higher baseline risk of cardiovascular events but also a greater likelihood of multimorbidity, polypharmacy, treatment intolerance, and competing risks. Moreover, the evidence base has often combined participants with different lipid profiles and cardiovascular risk characteristics, making it difficult to determine whether the observed benefits apply specifically to older hypertensive adults without dyslipidemia.

This systematic review and meta-analysis therefore aimed to evaluate the available evidence on the cardiovascular benefits, mortality outcomes, and safety of statin therapy in older adults with hypertension and without established cardiovascular disease, with more focus on patients without conventional dyslipidemic indications for treatment.

Methods

Protocol, registration, and reporting

This systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12]. The protocol was registered prospectively with PROSPERO, the international prospective register of systematic reviews, on 7 August 2025 under registration number CRD420251121460.

Eligibility criteria

Studies were eligible if they enrolled adults aged 60 years or over with hypertension who were free of established cardiovascular disease, and if they compared the initiation of statin therapy with no statin therapy, placebo, or antihypertensive therapy alone. Participants were required to have no indication for lipid-lowering therapy under the guidelines in force at the time the study was conducted. Eligible designs were randomized controlled trials, cohort studies, and case-control studies. Eligible studies reported at least one of the following outcomes: major adverse cardiovascular events, myocardial infarction, stroke, hospitalization for a cardiovascular cause, cardiovascular mortality, all-cause mortality, or adverse effects of statin therapy. Reports were restricted to those published in English between 2005 and 2025. Studies were excluded if participants were under 60 years, if statins were given for another indication such as secondary prevention or diabetes, or if participants had established cardiovascular disease or dyslipidemia requiring treatment. Case reports, animal studies, preclinical and *in vitro* studies, non-English reports, reports published before 2005, reports with data insufficient for extraction or with methodology that could not be determined, and duplicate publications of the same study population were also excluded. Where a study population was reported more than once, the report with the longest follow-up and the most complete outcome data was retained.

Deviation from the registered protocol. Three of the four included studies did not meet the eligibility criteria as originally registered (the baseline lipid profile, age, and cardiovascular history of each study are given in Section 3.2) and were retained under an amendment to the registered protocol .

Normal Lipid Profile Thresholds: In accordance with our protocol, normal lipid levels were defined as Total Cholesterol <200 mg/dl, LDL-C <100 mg/dl, HDL-C >40 mg/dl (men) or >50 mg/dl (women), and Triglycerides <150 mg/dl.

PROSPERO Registration: The systematic review protocol was registered on August 7, 2025 (Registration ID:CRD420251121460). No post-registration amendments were required.

Rationale for Study Selection: While our primary focus targets elderly hypertensive patients without dyslipidemia, certain studies (e.g., post-hoc and mechanistic trials) were retained to evaluate secondary objectives, specifically the pleiotropic effects of statins (such as anti-inflammatory properties, endothelial improvement, and attenuation of vascular/atrial remodeling) and to address evidence gaps in underrepresented older cohorts.

Information sources and search strategy

A comprehensive search was performed in the Cochrane Central Register of Controlled Trials, PubMed, and Scopus. Web of Science and Google Scholar were searched in addition, in order to identify relevant studies that the primary databases might have missed. Searches covered the period from 2005 to 2025 and were limited to reports published in English. Medical Subject Headings were combined with free-text terms. The search string was as follows:

("low-dosestatins"OR"simvastatin"OR"atorvastatin" OR "pravastatin" OR "hydroxymethylglutaryl-CoA reductase inhibitors") AND ("elderly" OR "older adults" OR "aged") AND ("hypertension" OR "high blood pressure") AND ("cardiovascular events" OR "major adverse cardiovascular events" OR "MACE" OR "myocardial infarction" OR "stroke" OR "all-cause mortality" OR "adverse effects")

The reference lists of all reports assessed at full text were screened for additional eligible studies.

Study selection

Records retrieved from all sources were imported into reference management software and deduplicated. Titles and abstracts were screened by three reviewers, with each record assessed independently by two of them. The full texts of records passing that stage were assessed independently by two reviewers against the eligibility criteria. Disagreements at either stage were resolved by discussion, and by a third reviewer where discussion did not produce consensus. The numbers of records at each stage of selection are reported in Section 3.1.

Data extraction

Two reviewers extracted data independently onto a standardized extraction form that had been piloted on two reports before use. Extracted variables included study design, year of publication, country and setting, trial registration and funding, recruitment period and duration of follow-up, participant demographics, baseline blood pressure and lipid concentrations, comorbidity, concomitant medication, statin agent and daily dose, comparator, and every reported outcome together with its definition and method of ascertainment. Data were recorded exactly as published, without conversion or rounding at the point of extraction. Where a study reported adverse event frequencies as percentages without absolute numbers, counts were obtained by applying the reported percentage to the denominator of the relevant arm and rounding to the nearest whole number; such counts are approximate to within one event. Where a study reported an effect estimate with a confidence interval but no standard error, the standard error was recovered from the confidence limits on the logarithmic scale.

Risk-of-bias assessment

Two reviewers assessed the risk of bias independently, resolving disagreements by consensus and by a third reviewer where consensus was not reached. Randomized studies were assessed with the Cochrane Risk of Bias 2 tool across its five domains, applied at the level of the individual outcome rather than the study, as the tool requires. Cohort and case-control studies were assessed with the Newcastle-Ottawa Scale, awarding up to four stars for selection, two for comparability and three for outcome ascertainment. Total scores of 7-9 were regarded as good, 4-6 as fair and 0-3 as poor; this banding is conventional rather than prescribed by the scale itself, and is stated here so that readers may apply a different one if they prefer. The Newcastle-Ottawa Scale reflects confounding only through its two comparability stars.

Effect measures

Hazard ratios (HRs) formed the primary effect measure wherever the contributing studies reported time-to-event estimates, and the adjusted estimate was used in preference to the crude one where both were available. Risk ratios (RRs) calculated from crude event counts were reported as a secondary measure. Hazard ratios and RRs s were never combined within a single pooled estimate. Absolute effects were obtained by applying the pooled RR to the median control-group risk across the contributing studies, and are expressed per 1000 participants with the corresponding number needed to treat.

Certainty of the evidence

The certainty of the evidence for each outcome was assessed by two reviewers independently using the GRADE approach, with disagreements resolved by discussion. Randomized evidence began at high certainty and observational evidence at low certainty. Ratings were considered for reduction based on risk of bias, inconsistency, indirectness, imprecision, and publication bias, and for upgrading on grounds of large effect, dose-response relationship, or probable confounding that would reduce an observed effect.

Statistical analysis

All analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria). Inverse-variance pooling, the DerSimonian-Laird and restricted maximum likelihood estimators of between-study variance, the Hartung-Knapp adjustment, and the associated heterogeneity statistics were implemented directly rather than taken from a package and were validated against closed-form results before use. The validation suite confirms that a standard error is correctly recovered from a reported confidence interval, that a RRs and its standard error are correctly calculated from a two-by-two table, that two identical studies pool to themselves with Cochran's Q and I-squared both zero, that inverse-variance weights are proportional to the reciprocal of the variance, that Cochran's Q matches its closed form, and that a continuity correction of 0.5 is applied correctly to a zero cell. All pooled estimates reported in

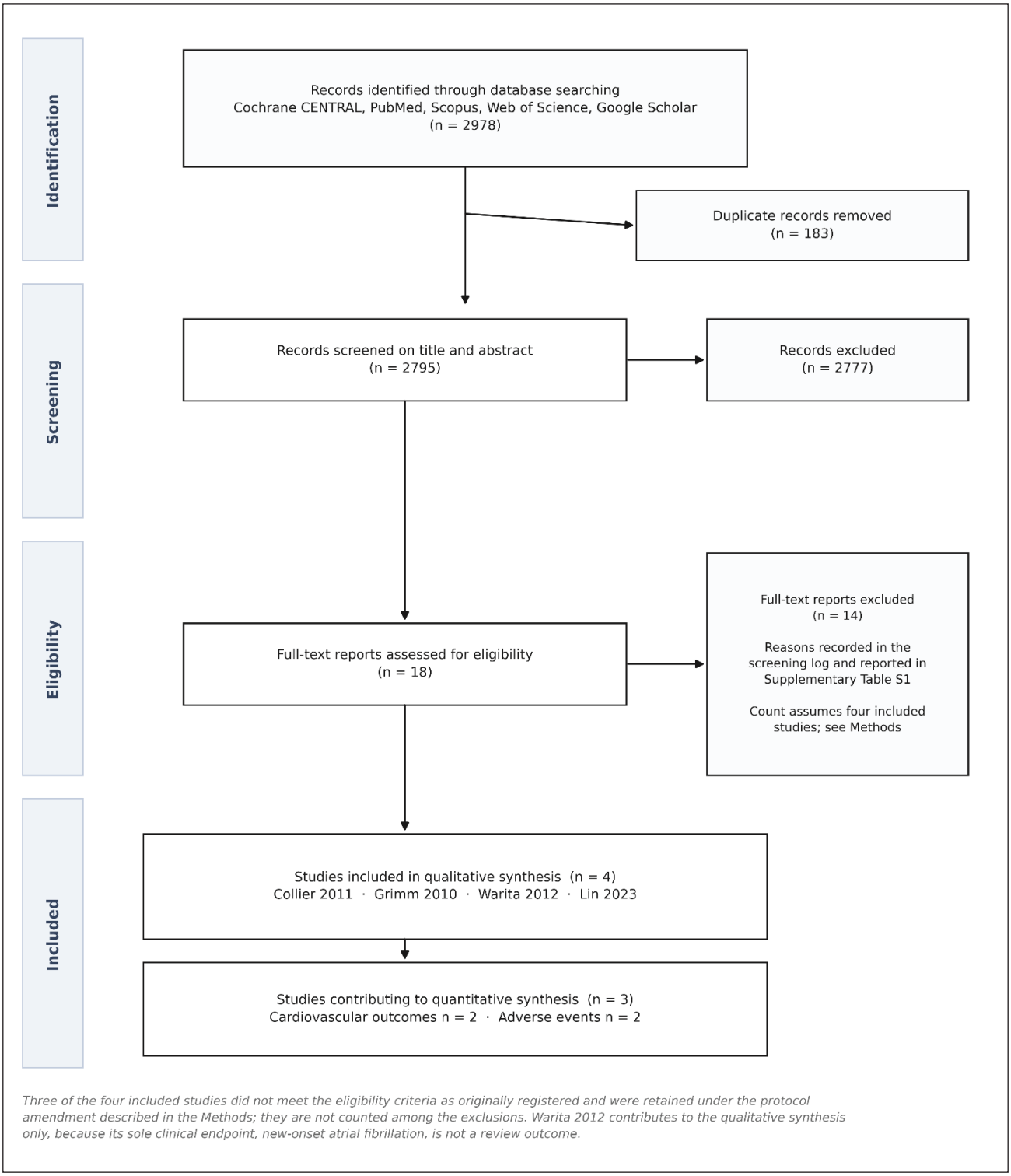


Figure 1. *Flow of information through the review, following the PRISMA 2020 statement.*

this paper are random-effects estimates obtained with the DerSimonian-Laird estimator of between-study variance and Wald-type 95% confidence intervals on the log scale, and a common-effect estimate is reported only where stated.

Results

Study selection

The searches of PubMed, Scopus, Web of Science, Cochrane CENTRAL, and Google Scholar, supplemented by citation screening, involved the records summarized in Figure 1. The database searches identified 2,978 records. After removal of 183 duplicates, 2,795 records were screened by title and abstract, and 2,777 were excluded. Eighteen full-text reports were assessed against the eligibility criteria, and 14 were excluded, with reasons listed in Supplementary Table S1, leaving four studies in the review. Three of the four did not meet the eligibility criteria as originally registered (Section 2.2).

Characteristics of the included studies

The four reports together included 17,173 participants, of whom 16,709 contributed to the meta-analysis of cardiovascular outcomes. Their design, setting, population, intervention, and duration are set out in Table 1. Two reports described randomized trials and two described cohort studies. Recruitment covered 1998 to 2015 and publication 2010 to 2023. Follow-up ranged from 6 weeks in the shortest study to a median of 4.8 years in the longest, a difference that bears directly on which outcomes each study could plausibly capture. Collier et al. [13] reported a post-hoc analysis of the Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial restricted to the 4445 participants aged 65 years and over. All had treated hypertension and at least three additional cardiovascular risk factors, none had a history of coronary heart disease, and entry required a non-fasting total cholesterol concentration of 251 mg/dl or less. Participants received atorvastatin 10 mg daily or matching placebo for a median of 3.3 years, and the trial was stopped early on the recommendation of its data safety monitoring board. This is the only included study in which both the population and the statin dose correspond to the review question as originally framed.

Lin et al. [14] assembled 2761 new statin users and 9503 propensity-score matched non-users aged 65 years and over, all free of any recorded history of cardiovascular disease, from a hospital database linked to national claims and death registries in Taiwan. Hypertension was present in 71.6% of users and 66.2% of non-users, so the cohort is not confined to hypertensive patients. Ninety-six per cent of statin users received moderate-intensity therapy while only 4% received low-intensity therapy, and the low-intensity subgroup was not reported separately. Median follow-up was 4.8 years.

Warita and colleagues [15] followed 220 Japanese patients aged 65 years and over who had hypertension with left ventricular hypertrophy and preserved ejection fraction, allocating 110 to pitavastatin 1-2 mg daily and 110 to no statin according to whether national guidelines indicated lipid-lowering treatment. Grimm and colleagues [16] randomized 244 treated hypertensive adults to amlodipine with or without atorvastatin 20 mg for 6 weeks; the mean age was 56 years, and the endpoints were attainment of blood pressure and low-density lipoprotein cholesterol goals rather than clinical events.

Table 2 presents the baseline characteristics by treatment group. Mean age ranged from 55.5 years in the comparator arm of Grimm and colleagues [16] to 75 years in both groups of Warita et al. [15]. Baseline low-density lipoprotein cholesterol ranged from 127.4 mg/dl to 146 mg/dl across the intervention groups. The mean baseline lipid profile did not satisfy every threshold reported in the protocol definition of a normal lipid profile, and the discrepancy was largest in Warita et al. [15], where the statin group began treatment at 146 mg/dl against 103 mg/dl in the comparator group, a difference of 43 mg/dl that reflects the clinical indication on which allocation was based.

Table 1. *Characteristics of the included studies.*

Study, year	Country	Design	Population	Intervention	Comparator	N, statin/control	Follow-up
Collier, 2011 [13]	Europe	Post-hoc analysis of a randomized double-blind trial (ASCOT-LLA)	Aged 65 years and over, treated hypertension, at least three additional cardiovascular risk factors, no coronary heart disease, total cholesterol 251 mg/dl or less	Atorvastatin 10 mg daily	Placebo	2189 / 2256	Median 3.3 years
Lin, 2023 [14]	Taiwan	Retrospective cohort, propensity-score matched 1:4	Aged 65 years and over, no history of cardiovascular disease; hypertension in 71.6% of users and 66.2% of non-users	New statin use; 96% moderate intensity, 4% low intensity	Matched non-users	2761 / 9503	Median 4.8 years
Warita, 2012 [15]	Japan	Prospective cohort, allocation by clinical indication	Aged 65 years and over, hypertension with left ventricular hypertrophy and preserved ejection fraction	Pitavastatin 1-2 mg daily	No statin	110 / 110	Median 23 months
Grimm, 2010 [16]	United States	Randomized double-blind, double-dummy trial (TOGETHER)	Treated hypertensive adults aged 21 years and over with at least two additional risk factors; mean age 56 years	Amlodipine 5-10 mg with atorvastatin 20 mg	Amlodipine 5-10 mg with placebo	122 / 122	6 weeks

ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial; Lipid-Lowering Arm; N, number of participants (statin/control). Study references are given in square brackets.

Table 2. *Baseline characteristics of participants by study and treatment group.*

Study and group	n	Age, years	Female, %	SBP / DBP, mmHg	TC, mg/dl	LDL-C, mg/dl	HDL-C, mg/dl	TG, mg/dl	Diabetes, %	Prior CVD, %
Collier et al., atorvastatin [13]	2189	71.1 (4.1)	18.7	168.2 / 92.3	210.9 (30.8)	132.8 (28.0)	51.6 (14.4)	135.9 (68.7)	26.0	13.0
Collier et al., placebo [13]	2256	71.1 (4.0)	20.6	168.2 / 92.2	211.8 (30.4)	134.2 (28.2)	51.3 (13.6)	136.1 (64.9)	27.5	14.1
Lin et al., statin users [14]	2761	71.9 (5.9)	63.9	NR	NR	138.1 (26.2)	NR	NR	30.8	0
Lin et al., non-users [14]	9503	71.8 (5.8)	63.7	NR	NR	131.1 (25.3)	NR	NR	30.0	0
Warita et al. [15], pitavastatin	110	75 (5)	57.3	132 / 78	NR	146 (14)	52 (15)	NR	12.7	16.4
Warita et al., no statin [15]	110	75 (5)	46.4	133 / 79	NR	103 (16)	53 (10)	NR	13.6	13.6
Grimm et al., combination [16]	122	56.5	53.3	132.3 / 81.0	209.5 (29.7)	127.4 (21.7)	54.7 (17.5)	140.4 (99.5)	0	0
Grimm et al., amlodipine alone [16]	122	55.5	45.9	132.9 / 81.9	214.0 (30.7)	131.5 (24.7)	55.5 (16.1)	137.6 (80.9)	0	0

CVD, Cardiovascular disease; DBP, Diastolic blood pressure; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; NR, Not reported; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglycerides. Values are mean (standard deviation) or percentage unless stated otherwise.

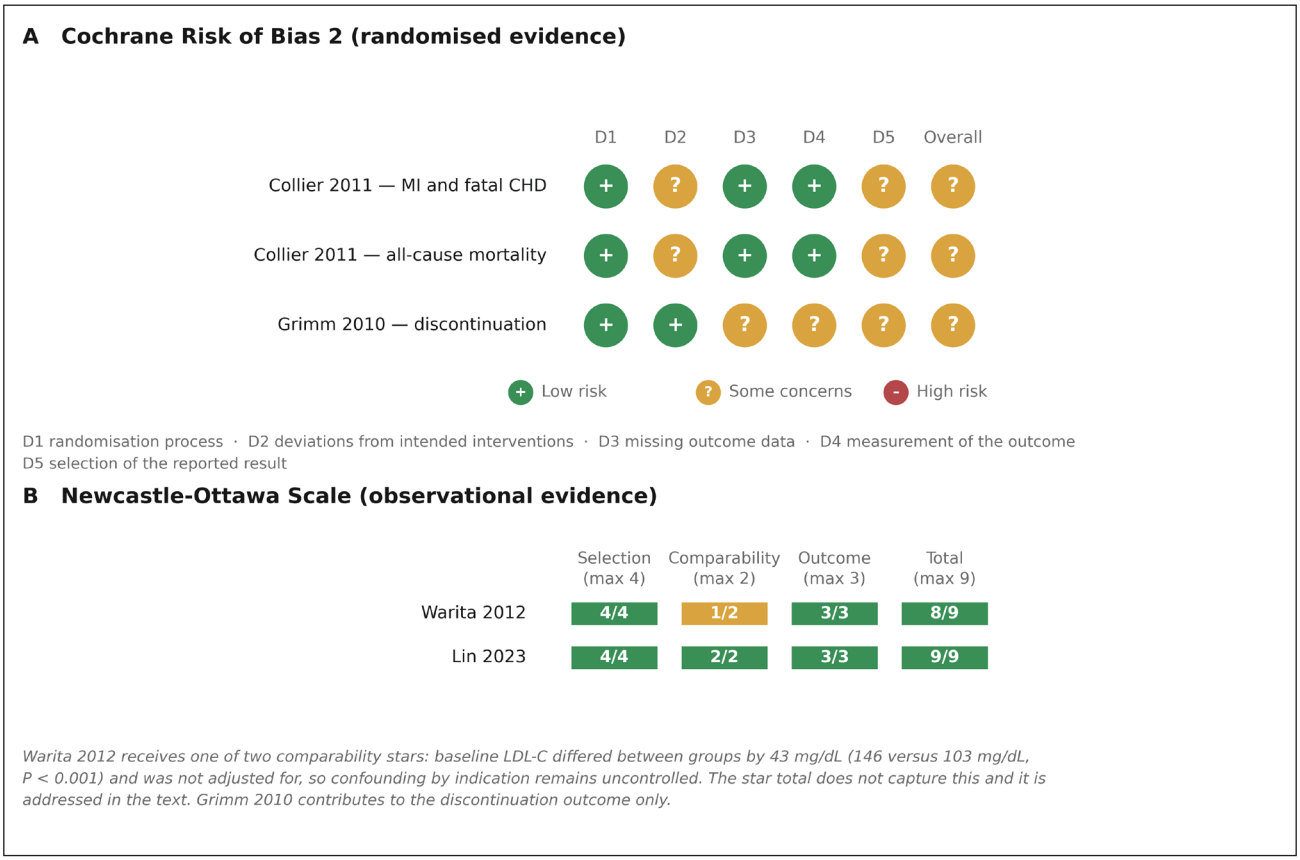


Figure 2. *Risk of bias. Section A, Cochrane Risk of Bias 2 judgements for the randomized evidence, assessed per outcome. Section B, Newcastle-Ottawa Scale domain scores for the observational evidence.*

Risk of bias in the included studies

Risk-of-bias assessments are presented in Figure 2. The two randomized studies were assessed with the Cochrane Risk of Bias 2 tool at the level of the individual outcome, and the two cohort studies with the Newcastle-Ottawa Scale. For Collier and colleagues [13], the randomization process was found to be at low risk because allocation was centrally concealed within a double-blind parent trial and the two groups within the stratum aged 65 years and over were closely balanced across every reported baseline variable. Missing outcome data were negligible, with follow-up information unavailable for 42 of 4445 participants and vital status unavailable for 6, and

outcome measurement was judged at low risk because endpoints were adjudicated by a blinded committee. Twenty percent of older participants allocated to atorvastatin discontinued treatment and 12.1% of those allocated to placebo received open-label statins, which biases the intention-to-treat estimate towards the null; the authors themselves note that the observed effect is therefore likely to understate the true one. The age-stratified comparison was also clearly post-hoc, although all eight parent-trial endpoints were reported for both strata, which limits the scope for selective reporting. For Grimm and colleagues [16], randomization and adherence to the intended interventions were judged at low risk, but the 6-week duration, the absence of a pre-specified adverse event endpoint and the small number of events produced some concerns in the remaining three domains, and an overall judgement of some concerns for the single outcome to which the study contributes.

On the Newcastle-Ottawa Scale, Lin and colleagues [15] scored 9 of 9. Exposure was ascertained from prescription records, outcomes through validated claims algorithms and a national death registry, and follow-up was essentially complete. Both comparability stars were awarded because the propensity score balanced age, sex, smoking, diabetes, and baseline low-density lipoprotein cholesterol category, while a marginal structural model additionally controlled for time-varying cholesterol. Warita and colleagues [15] scored 8 of 9, losing one comparability star. That single lost star understates the problem. Allocation in that study was determined by whether the treating physician

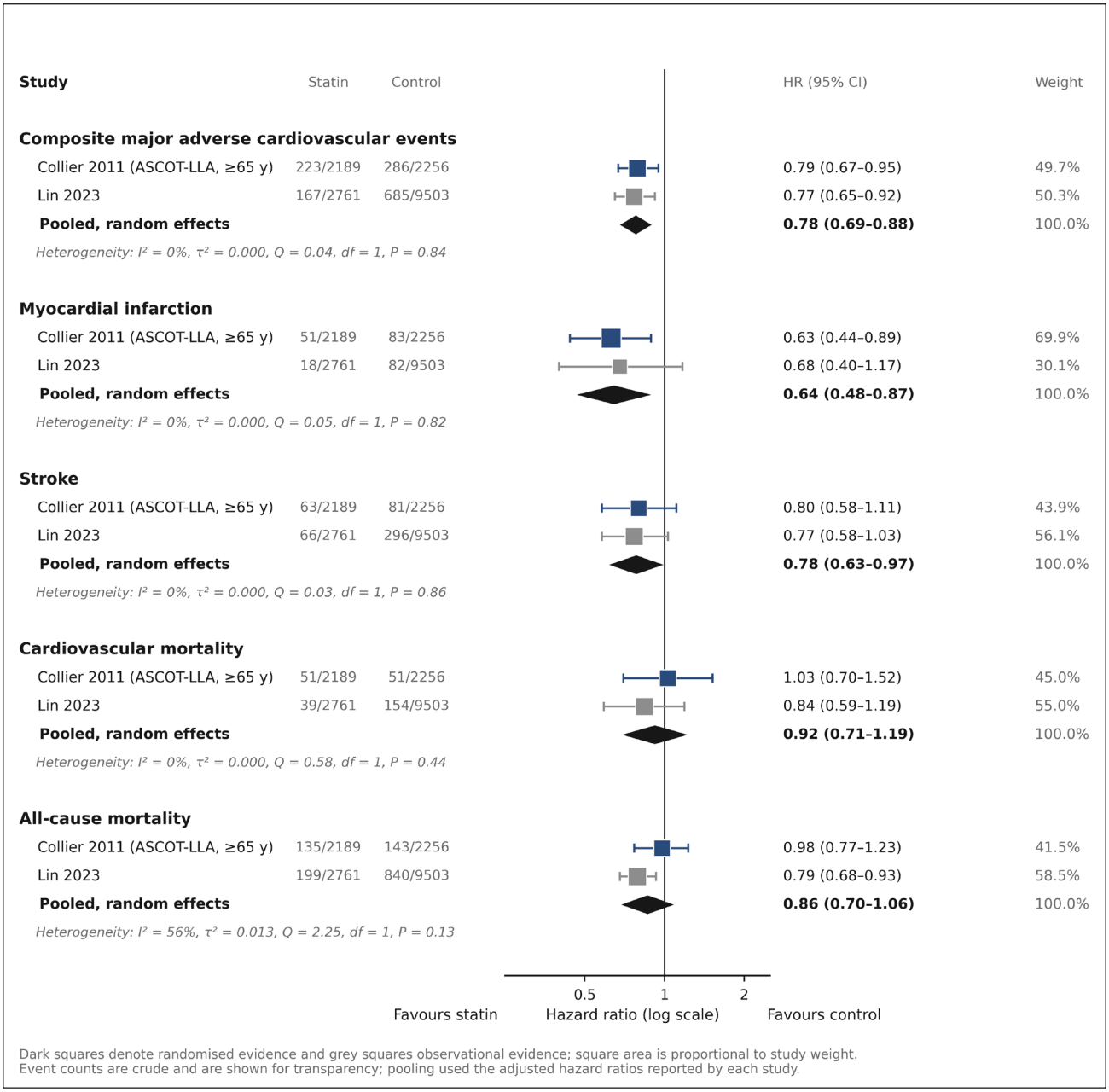


Figure 3. *Forest plot of pooled hazard ratios for cardiovascular outcomes.*

Table 3. *Pooled effect estimates for all outcomes amenable to quantitative synthesis.*

Outcome	Studies	Participants	Events, statin/ control	Pooled HR (95% CI)	Pooled RR (95% CI)	I^2, %	*p* value
Composite major adverse cardiovascular events	2	16,709	390 / 971	0.78 (0.69-0.88)	0.82 (0.73-0.92)	0	<0.001
Myocardial infarction	2	16,709	69 / 165	0.64 (0.48-0.87)	0.67 (0.50-0.89)	0	0.003
Stroke	2	16,709	129 / 377	0.78 (0.63-0.97)	0.78 (0.64-0.96)	0	0.026
Cardiovascular mortality	2	16,709	90 / 205	0.92 (0.71-1.19)	0.94 (0.73-1.22)	0	0.53
All-cause mortality	2	16,709	334 / 983	0.86 (0.70-1.06)	0.87 (0.74-1.03)	56	0.17
Discontinuation due to adverse events	2	4689	81 / 68	Not applicable	1.90 (0.34-10.48)	46	0.46

CI, Confidence interval; HR, Hazard ratio; RR, Risk ratio. I^2 and *p* values refer to the hazard-ratio analysis for the cardiovascular and mortality outcomes and to the risk-ratio analysis for discontinuation due to adverse events; *p* values are from Wald tests.

judged a statin to be indicated, the resulting groups differed in baseline low-density lipoprotein cholesterol by 43 mg/dl, and the multivariable model did not adjust for it.

Effect of statin therapy on cardiovascular outcomes

Pooled estimates for the five cardiovascular outcomes are shown in Figure 3 and summarized in Table 3. HRs formed the primary analysis because both contributing studies reported time-to-event estimates; RRs calculated from crude event counts are reported alongside them as a secondary analysis. Randomized and observational evidence are displayed separately within each outcome in Figure 3, and the pooled estimate combining them should be read with the caution set out in Section 3.5.

Composite major adverse cardiovascular events

Statin therapy reduced the composite endpoint. Collier et al. [13] recorded 223 events among 2189 participants allocated to atorvastatin against 286 among 2256 allocated to placebo, giving an HR of 0.79 (95% CI 0.67-0.95). Lin et al. [14] recorded 167 events among 2761 statin users against 685 among 9503 non-users, giving an adjusted HR of 0.77 (95% CI 0.65-0.92). The two estimates and the pooled HR were almost identical was 0.78 (95% CI 0.69-0.88, $p < 0.001$) with no noticeable heterogeneity ($I^2 = 0\%$, $\tau 2 = 0.000$, Q = 0.04, df = 1, $p = 0.84$). The corresponding RR from crude counts was 0.82 (95% CI 0.73-0.92). Applied to a control risk of 99 events per 1000 participants, this represents 18 fewer events per 1000 (95% CI 27 fewer to 8 fewer), or one event avoided for every 56 patients treated over 3-5years.

Myocardial infarction

The reduction in myocardial infarction was the largest of any outcome examined. Collier et al. [13] recorded 51 events against 83 in the placebo group (hazard ratio 0.63, 95% CI 0.44-0.89) and Lin et al. [14] found 18 against 82 (adjusted hazard ratio 0.68, 95% CI 0.40-1.17). The pooled HRs was 0.64 (95% CI 0.48-0.87, $p = 0.003$), again without heterogeneity ($I^2 = 0\%$, Q = 0.05, df = 1, $p = 0.82$). The pooled RR was 0.67 (95% CI 0.50-0.89), equivalent to 8 fewer infarctions per 1000 participants (95% CI 11 fewer to 3 fewer) against a control risk of 23 per 1000. The randomized estimate carried 69.9% of the weight, so this result rests mainly on trial evidence.

Stroke

Neither study found a statistically significant effect on stroke in isolation, but the pooled estimate reached conventional significance. Collier et al. [13] reported 63 fatal and non-fatal strokes against 81 (hazard ratio 0.80, 95% CI 0.58-1.11) and Lin et al. [14] reported 66 ischemic strokes against 296 (adjusted hazard ratio 0.77, 95% CI 0.58-1.03). Pooling gave an HR of 0.78 (95% CI 0.63-0.97, $p = 0.026$) with $I^2 = 0\%$ (Q = 0.03, df = 1, $p = 0.86$), and a RR of 0.78 (95% CI 0.64-0.96). The absolute difference was 7 fewer strokes per 1000.

Cardiovascular mortality

No effect on cardiovascular mortality was detected. Collier et al. [13] reported 51 cardiovascular deaths in each group (hazard ratio 1.03, 95% CI 0.70-1.52) and Lin et al. [14] reported 39 against 154 (adjusted hazard ratio 0.84, 95% CI 0.59-1.19). The pooled HR was 0.92 (95% CI 0.71- 1.19, $p = 0.53$) with $I^2 = 0\%$ (Q = 0.58, df = 1, $p = 0.44$). The confidence interval spans a 29% relative reduction and a 19% relative increase, so the data are compatible with a clinically valuable benefit and with a modest harm.

All-cause mortality

All-cause mortality was the only outcome at which the two studies diverged. Collier et al. [13] found no difference, with 135 deaths against 143 (hazard ratio 0.98, 95% CI 0.77-1.23), whereas Lin et al. [14] estimated a reduction, with 199 against 840 (adjusted hazard ratio 0.79, 95% CI 0.68-0.93). Heterogeneity was moderate ($I^2 = 56\%$, $\tau 2 = 0.013$, Q = 2.25, df = 1, $p = 0.13$). Under the pre-specified random-effects model, the pooled HR was 0.86 (95% CI 0.70-1.06, $p = 0.17$), whereas a common-effect model gave 0.84 (95% CI 0.74-0.96, $p = 0.011$). The two models therefore disagree on statistical significance.

HR, Hazard ratio; CI, Confidence interval. Dark squares denote the randomized study, and grey squares the observational study; horizontal lines are 95% CIs and diamonds are pooled random-effects (DerSimonian-

Laird) estimates. Event counts are crude and shown for transparency; pooling used the hazard ratios reported by each study (adjusted estimates where available).

Heterogeneity, sensitivity analyses and small-study effects

Statistical heterogeneity was absent for four of the five cardiovascular outcomes, with $I^2 = 0\%$ and Cochran Q well below its degrees of freedom in each case (Table 3). This concordance is good, but it should not be over-interpreted. With only two studies contributing to each outcome, Q has a single degree of freedom, and the test has very low power, so $I^2 = 0\%$ indicates that heterogeneity could not be detected rather than that it is absent. Publication bias was not assessed. The protocol specified funnel plots and Egger's regression test, both of which require at least ten contributing studies to have adequate power, and no outcome in this review approached that threshold. The possibility of small-study effects and of selective reporting within the available literature therefore cannot be excluded and remains a limitation of the synthesis. Because each pooled estimate combines a post-hoc subgroup of one randomized trial with an adjusted estimate from one observational cohort, the design-specific estimates are shown separately in Figure 3. For composite cardiovascular events, myocardial infarction and stroke, the randomized and observational HRs were similar (0.79 and 0.77, 0.63 and 0.68, and 0.80 and 0.77, respectively), whereas for all-cause mortality they differed (0.98 and 0.79).

Safety and tolerability

Safety findings are shown in Figure 4. Only one outcome, discontinuation of treatment because of an adverse event, was reported by more than one study. Collier et al. [13] recorded 77 discontinuations among 2189 participants receiving atorvastatin against 68 among 2256 receiving placebo (risk ratio 1.17, 95% CI 0.85-1.61), while Grimm et al. [16] recorded 4 among 122 against none among 122, requiring a continuity correction (risk ratio 9.00, 95% CI 0.49-165.38). The pooled random-effects estimate was 1.90 (95% CI 0.34-10.48, $I^2 = 46\%$). This pooled value carries little information. It combines a 6-week trial of atorvastatin 20 mg with a 3-year trial of atorvastatin 10 mg, and its width is driven entirely by the zero cell in the smaller study. The estimate from Collier and colleagues [13] alone, which is both larger and longer, provides a more dependable indication that discontinuation for adverse events was not substantially increased.

The remaining safety outcomes in the Collier et al. [13] study alone are presented without pooling. Muscle symptoms were no more frequent with atorvastatin than with placebo, with myalgia of any grade in 2.6% against 3.3% (risk ratio 0.79, 95% CI 0.56-1.12), and no

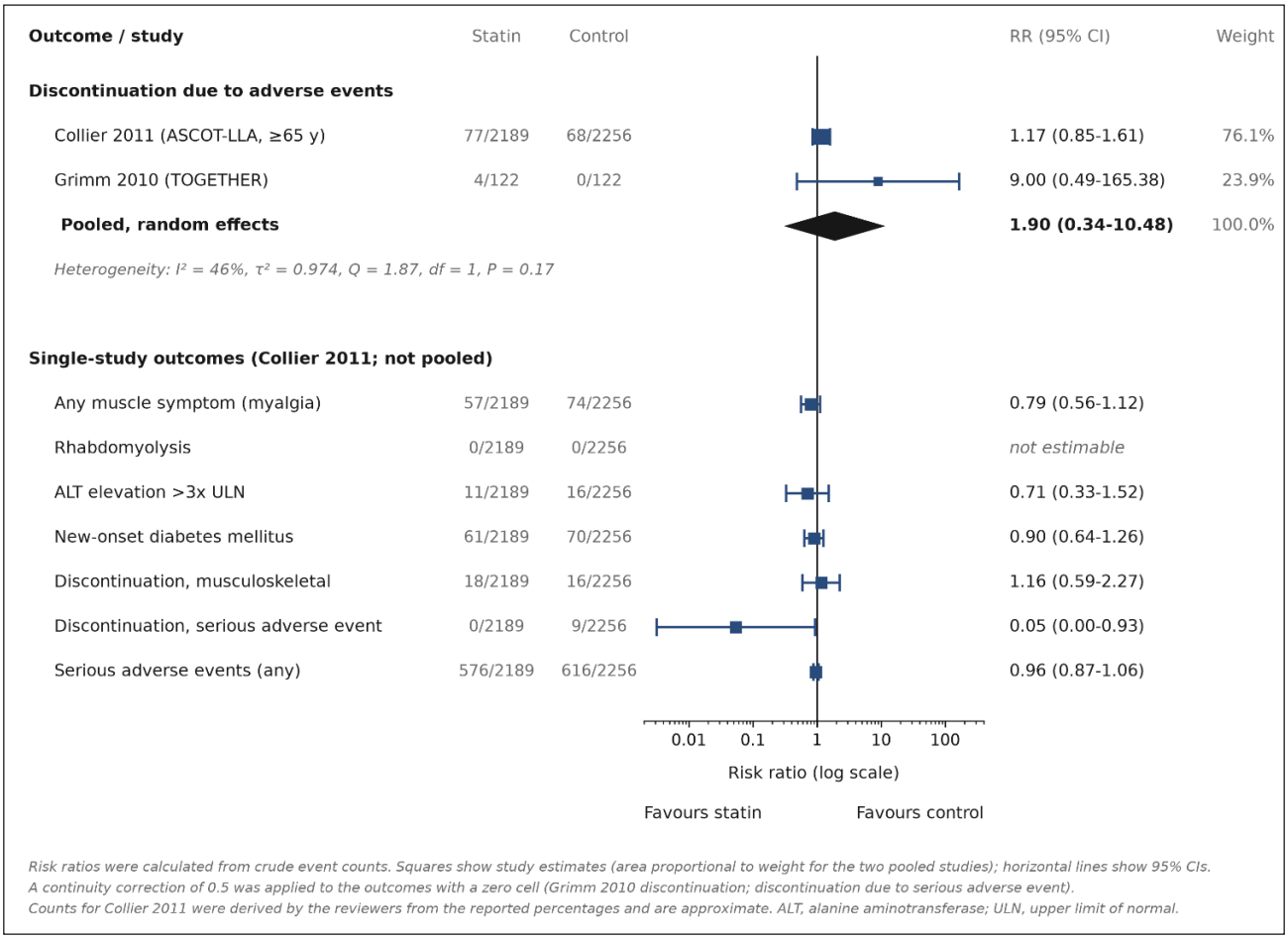


Figure 4. *Forest plot of adverse event outcomes.*

case of rhabdomyolysis occurred in either group among participants aged 65 years and over. Transaminase elevation exceeding three times the upper limit of normal occurred in 0.5% versus 0.7% (risk ratio 0.71, 95% CI 0.33-1.52). New-onset diabetes mellitus occurred in 2.8% versus 3.1% (risk ratio 0.90, 95% CI 0.64-1.26), and discontinuation attributed to musculoskeletal or connective tissue disorders in 0.8% versus 0.7% (risk ratio 1.16, 95% CI 0.59-2.27). Serious adverse events of any kind were reported by 26.3% of the atorvastatin group and 27.3% of the placebo group (risk ratio 0.96, 95% CI 0.87-1.06). No participant allocated to atorvastatin discontinued because of a serious adverse event, compared with nine allocated to placebo; the resulting RRs of 0.05 (95% CI 0.00-0.93) rests on a zero cell.

The upper part shows the single outcome reported by more than one study. The lower part shows outcomes available from Collier et al. [13] alone, presented individually and not pooled. Risk ratios were calculated from crude event counts. A continuity correction of 0.5 was applied to Grimm et al. [16] (zero events in the comparator arm). Counts for Collier et al. [13] were derived from reported percentages and are approximate.

Other findings

Two studies reported findings that could not enter any pooled analysis. Warita et al. [15] examined new-onset atrial fibrillation, an endpoint outside the outcomes specified for this review. During follow-up (median 23 months), atrial fibrillation developed in 5 of 110 patients receiving pitavastatin and in 15 of 110 not receiving a statin, giving a univariate HR of 0.32 (95% CI 0.12-0.88, $p = 0.027$). In a multivariable Cox model, statin use remained an independent predictor (odds ratio 0.182, 95% CI 0.062-0.529, $p = 0.002$) as did coronary artery disease and baseline left atrial peak strain. The authors also reported regression of left ventricular mass index and improvement in left atrial function in the treated group. These findings are consistent with a pleiotropic effect of statins on atrial remodeling, but the study cannot support a causal reading: patients received pitavastatin because guidelines specified lipid-lowering treatment, their baseline low-density lipoprotein cholesterol was 43 mg/dl higher than that of the comparison group, and this difference was not adjusted for. No myocardial infarction, stroke, or death was reported. Grimm et al. [16] reported surrogate endpoints only. At 6 weeks, 67.8% of participants receiving amlodipine with atorvastatin attained the combined blood pressure and low-density lipoprotein cholesterol goal against 9.6% receiving amlodipine alone (odds ratio 19.0, 95% CI 9.1-39.6, $p < 0.001$; risk difference 58.2% points, 95% CI 48.1-68.4). Systolic blood pressure at week 6 was 3.3 mmHg lower in the combination group ($p = 0.02$). No cardiovascular event was recorded. The study contributes to this review only through its adverse event data.

Certainty of the evidence

Certainty of evidence was evaluated using the GRADE framework for each outcome (Table 4). Overall, no outcome exceeded low-certainty evidence, as all were downgraded for serious risk of bias and indirectness. Risk of bias was considered serious because the randomized evidence was derived from a post-hoc subgroup analysis with treatment discontinuation and crossover to open-label statin therapy. In addition, although the observational study was methodologically robust, residual confounding could not be excluded. Indirectness was also a major concern because neither study directly reflected the review population of elderly hypertensive patients with normal lipid levels. Baseline LDL cholesterol concentrations were above the protocol-defined threshold in both studies (133 mg/dl in Collier et al. [13] and 138 mg/dl in Lin et al. [14]). Furthermore, 96% of statin users in the Lin et al. [14] cohort received moderate-intensity rather than low-intensity statins, and only approximately 70% of its participants were hypertensive. Thus, the available evidence addresses a related, but not identical, clinical question. Cardiovascular mortality was further downgraded for imprecision because its confidence interval included both potentially meaningful benefit and modest harm. All-cause mortality was additionally downgraded for inconsistency, given moderate heterogeneity ($I^2 = 56\%$) and differing results between random-effects and common-effect models. Single-study safety outcomes were also downgraded for imprecision. Publication bias could not be formally assessed because of the limited number of studies.

Summary of main findings

Among 16,709 participants from one randomized subgroup analysis and one matched cohort study, statin therapy was associated with fewer composite cardiovascular events (hazard ratio 0.78, 95% CI 0.69-0.88), fewer myocardial infarctions (0.64, 95% CI 0.48-0.87), and fewer strokes (0.78, 95% CI 0.63-0.97), with no detectable heterogeneity for any of the three. No effect was shown on cardiovascular mortality (0.92, 95% CI 0.71-1.19), and the position on all-cause mortality depended on the model chosen (random effects 0.86, 95% CI 0.70-1.06; common effect 0.84, 95% CI 0.74-0.96) and on study design (randomized 0.98, 95% CI 0.77-1.23; observational 0.79, 95% CI 0.68-0.93). Adverse events, including muscle symptoms, transaminase elevation and new-onset diabetes, were no more frequent with statin therapy than without it in the one study that reported them, and no case of rhabdomyolysis occurred. Certainty in these estimates is low for the non-fatal outcomes and very low for the mortality and safety outcomes, constrained principally by the small number of contributing studies and by the distance between the populations studied and the population the review set out to describe.

Discussion

The cardiovascular analyses included 16,709 adults aged 65 years and older without established cardiovascular disease, of whom about three-quarters had hypertension (all participants in the randomized study and 66.2% to 71.6% of those in the cohort study). Statin therapy was associated with lower risks of composite cardiovascular events, myocardial infarction, and stroke, with no clear

reduction in cardiovascular or all-cause mortality. The benefit was therefore mainly evident for non-fatal cardiovascular outcomes. The magnitude of the associations was consistent with larger randomized syntheses in older adults, although the certainty of evidence was low for non-fatal outcomes and very low for mortality and safety outcomes. Findings from randomized and observational evidence are distinguished below, particularly for mortality.

Comparison with randomized evidence

The reduction in cardiovascular events was consistent with previous randomized evidence. The Cholesterol Treatment Trialists' Collaboration reported a rate ratio of 0.79 per 1.0 mmol/l reduction in LDL cholesterol across 28 trials, while Teng et al. [17] reported a relative risk of 0.82 for composite major adverse cardiovascular events in randomized primary-prevention trials of patients aged 65 years and older, and Gencer et al. [18] reported 0.74 per 1.0 mmol/l reduction among those aged 75 years and older [17-19]. Our estimate of 0.78 therefore falls within the range of established evidence. The reduction in myocardial infarction was somewhat larger, although this may partly reflect the substantial contribution of ASCOT-LLA, which was stopped early for benefit and may consequently have overestimated treatment effects [9,13]. The pooled reduction in stroke was also consistent with larger meta-analyses [17-19], despite the lack of significant findings in either contributing study individually. This contrasts with PROSPER, which found no reduction in stroke, possibly because its relatively short follow-up limited the ability to detect a longer-term effect [7]. ALLHAT-LLT provides an important comparison because its population closely resembled that of the present review. It found no significant benefit of pravastatin among older hypertensive adults, but substantial crossover between treatment groups resulted in limited separation in LDL cholesterol [8]. Similar treatment discontinuation and crossover occurred in the trial included in our review [13]. Such treatment dilution would tend to bias estimates toward the null and may explain differences between individual trials and the broader randomized evidence.

Observational evidence and mortality

The most important uncertainty concerns mortality. Observational studies have generally reported larger reductions in mortality than randomized trials. Awad et al. [20] reported lower all-cause mortality, cardiovascular mortality, and stroke among statin users aged 65 years and older, although the certainty of evidence was very low. In contrast, a meta-analysis of randomized primary-prevention trials in adults aged 65 years and older did not show a significant reduction in all-cause mortality [17]. The present review reproduced this discrepancy: the randomized study showed essentially no association with all-cause mortality, whereas the observational study revealed a reduction [13,14]. For cardiovascular mortality, neither design-specific estimate excluded the null (randomized HR 1.03, 95% CI 0.70-1.52; observational HR 0.84, 95% CI 0.59-1.19), whereas for all-cause mortality the randomized estimate was HR 0.98 (95% CI 0.77-1.23) and the observational estimate was HR 0.79 (95% CI 0.68-0.93). The pooled random-effects estimate was not statistically significant, while the common-effect model produced a significant result. This difference highlights the uncertainty surrounding the mortality finding and cautions against interpreting the common-effect estimate in isolation. Residual confounding may be an explanation as statin users may differ from non-users in functional status, frailty, healthcare engagement, and life expectancy,

Table 4. *GRADE summary of findings. Statin therapy compared with no statin therapy in elderly hypertensive patients without established cardiovascular disease.*

Outcome	Participants (studies)	Relative effect (95% CI)	Assumed risk, control, per 1000	Absolute difference, per 1000 (95% CI)	Reasons for downgrading	Certainty
Composite major adverse cardiovascular events	16,709 (2)	0.78 (0.69-0.88)	99	-18 (-27 to -8)	Risk of bias, indirectness	Low
Myocardial infarction	16,709 (2)	0.64 (0.48-0.87)	23	-8 (-11 to -3)	Risk of bias, indirectness	Low
Stroke	16,709 (2)	0.78 (0.63-0.97)	34	-7 (-12 to -1)	Risk of bias, indirectness	Low
Cardiovascular mortality	16,709 (2)	0.92 (0.71-1.19)	19	-1 (-5 to +4)	Risk of bias, indirectness, imprecision	Very low
All-cause mortality	16,709 (2)	0.86 (0.70-1.06)	76	-10 (-20 to +2)	Risk of bias, indirectness, inconsistency	Very low
Any muscle symptom	4445 (1)	0.79 (0.56-1.12)	33	-7 (-14 to +4)	Risk of bias, indirectness, imprecision	Very low
Transaminase elevation above three times the upper limit of normal	4445 (1)	0.71 (0.33-1.52)	7	-2 (-5 to +4)	Risk of bias, indirectness, imprecision	Very low

CI, Confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, Hazard ratio; RR, Risk ratio. Relative effects are HRs for the cardiovascular and mortality outcomes and RRs for the muscle symptom and transaminase outcomes. Absolute differences per 1000 were calculated by applying the pooled RR to the assumed control risk (the median control-group risk across contributing studies for pooled outcomes, and the observed control-group risk for single-study outcomes).

even after propensity-score adjustment [14]. The wider observational literature is also inconsistent, with some studies reporting no mortality benefit and others showing substantial reductions [21,22]. The agreement between randomized and observational estimates for non-fatal cardiovascular outcomes was much closer, increasing confidence in these findings.

Statins in patients without marked dyslipidemia

The findings also support the view that cardiovascular benefit from statins does not necessarily depend on elevated baseline cholesterol. JUPITER showed a reduction in cardiovascular events among older participants with LDL cholesterol below 130 mg/dl and elevated hs-CRP, while ASCOT-LLA reported benefit in hypertensive patients with average or below-average cholesterol [9,10]. Evidence from HOPE-3 and more analyses combining older participants from HOPE-3 and JUPITER further supports the effectiveness of statins in primary prevention populations not selected for hypercholesterolemia [11,23]. However, these findings should not be interpreted as direct evidence in strictly normolipidemic patients. The results should therefore not be generalized to all older adults with hypertension and normal lipid levels. No study contributing to the present review specifically enrolled participants according to a biochemical definition of normolipidemia; baseline LDL cholesterol was approximately 133-138 mg/dl, and only a small proportion of patients in the observational cohort had LDL cholesterol below 100 mg/dl [13,14].

Low-dose therapy, safety, and additional findings

Evidence supporting low-dose statin therapy is available, although studies rarely combined low-dose treatment with inclusion of patients having unremarkable cholesterol levels. The MEGA trial showed cardiovascular benefit with pravastatin 10-20 mg daily, while atorvastatin 10 mg produced a comparable effect in hypertensive patients in ASCOT-LLA [9,24]. The main evidence gap is therefore not the effectiveness of low-dose statins itself, but the lack of trials specifically evaluating low-dose therapy in older hypertensive adults without dyslipidemia. Safety findings were generally reassuring. Rates of myalgia, marked transaminase elevation, and serious adverse events were not increased with statin therapy and were broadly consistent with previous evidence in older adults [17]. No rhabdomyolysis occurred in the available data. However, the absence of a significant increase in new-onset diabetes in this small synthesis should not be interpreted as evidence that the risk does not exist. The larger meta-analysis by Sattar et al. [25] showed some increase in incident diabetes with statin therapy, with approximately one additional case for every 255 patients treated for 4 years. The limited sample size of the present review was insufficient to reliably detect an effect of this magnitude. Estimates for treatment discontinuation because of adverse events were also imprecise because of the small number of contributing studies. Additional findings, including a possible reduction in atrial fibrillation with pitavastatin, are hypothesis-generating rather than confirmatory because of non-randomized treatment allocation, baseline differences between groups, and the fact that atrial fibrillation was not a prespecified outcome [15]. Similarly, the short-term evidence on combined amlodipine and atorvastatin treatment provides information on target attainment and tolerability but does not establish effects on cardiovascular events [16]. Ongoing randomized evidence in the oldest age group, such as the PREVENTABLE trial of atorvastatin 40 mg versus placebo in adults aged 75 years and older without cardiovascular disease [26], may clarify the balance of benefit and harm at older ages, although it tests a higher-intensity regimen and will not by itself answer the low-dose question. Overall, the available evidence supports a reduction in non-fatal cardiovascular events with statin therapy in older hypertensive adults without established cardiovascular disease, while the effects on mortality and the specific role of low-dose treatment in strictly normolipidemic patients remain uncertain.

Strengths and limitations

A major strength of this review is its methodological transparency. Protocol amendments and their rationale were reported explicitly, derived estimates were identified, and randomized and observational estimates were displayed separately for every outcome. Risk of bias was assessed at the individual outcome level, while the limitations of the Newcastle-Ottawa Scale, including its ability to assess confounding by indication, were considered in the narrative assessment. Analyses that could not provide meaningful estimates because of insufficient studies were not reported as definitive findings. Several limitations, however, affect the interpretation of the results. Most importantly, the included populations do not match the review question as originally framed: no study enrolled participants according to a biochemical definition of normolipidemia; mean baseline LDL cholesterol was 133 and 138 mg/dl in the two studies contributing cardiovascular outcomes, about three quarters of the pooled participants had hypertension, and three of the four included studies did not meet the eligibility criteria as originally registered. The results should therefore not be generalized to all older adults with hypertension and normal lipid levels. In addition, each pooled estimate combines one post-hoc randomized subgroup analysis with one observational cohort, and the two designs should be interpreted separately, particularly for mortality. Only two studies contributed to each cardiovascular outcome, limiting reliable estimation of between-study variance and preventing calculation of prediction intervals. Therefore, an I^2 of zero should be interpreted as undetectable rather than absent heterogeneity. Outcome definitions also differed between studies, mainly for stroke, which was defined more broadly in one study than the other. Publication and small-study bias could not be adequately assessed because fewer than 10 studies were available for any outcome. The search was also restricted to English-language publications from 2005 to 2025, which may

have resulted in the exclusion of relevant evidence. Finally, safety outcomes were reported by only one trial and were presented as percentages rather than raw event counts; the reviewers therefore had to reconstruct event numbers, making these estimates approximate.

Conclusion

In adults aged 65 years and older without diagnosed cardiovascular disease, most of whom had hypertension, statin therapy was associated with lower risks of composite cardiovascular events, myocardial infarction, and stroke. These effects were consistent with findings from larger studies of older adults, and the randomized and observational estimates agreed for non-fatal outcomes. However, no clear benefit was observed for cardiovascular mortality. The randomized estimate for all-cause mortality was null (HR 0.98, 95% CI 0.77-1.23), and the apparent reduction was limited to observational evidence (HR 0.79, 95% CI 0.68-0.93) and was sensitive to the statistical model used. This finding should therefore be interpreted cautiously because of the potential for residual confounding and healthy-user effects. Statin therapy appeared generally well tolerated, with no clear increase in muscle symptoms, transaminase elevation, or serious adverse events, and no cases of rhabdomyolysis were reported. However, the certainty of evidence was low for non-fatal cardiovascular outcomes and very low for mortality and safety outcomes. The findings should not be generalized to all older adults with hypertension and normal lipid levels, because the included populations had mean baseline LDL cholesterol of 133 to 138 mg/dl and no study enrolled participants on the basis of a normal lipid profile.

Conflict of interest

The authors declare that they have no competing interests.

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Consent for publication

Not applicable.

Availability of data and materials

All data used in this systematic review were derived from published studies cited in the manuscript. The extracted and analyzed data are available from the corresponding author upon reasonable request.

Ethical approval

Not required because this study used data from previously published studies and did not involve individual-level participant recruitment.

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Supplementary content (if any) is available online.

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