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SYSTEMATIC REVIEW

The Safety and Tolerability of Statin Therapy in Primary Prevention in Older Adults: A Systematic Review and Meta-analysis

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Abstract

Purpose The use of statins in the primary prevention of cardiovascular disease (CVD) is increasing in older adults. Nonetheless, good clinical evidence for the safety and tolerability of statins in this population is limited.

Objective We aimed to evaluate the safety and tolerability of statins in older adults without overt CVD, focusing on statin-related muscle symptoms.

Methods Double-blinded randomised controlled trials (RCTs) of statins published before January 2012 were identified from a Cochrane review updated to 2012. Trials published between January 2012 and July 2018 were identified through the CENTRAL, MEDLINE and EMBASE databases. Eligible trials were limited to those including individuals aged ≥ 65 years without overt CVD, who were followed for at least 1 year. Trials had to have reported at least one of the outcomes of interest. Pooled relative risk (RR) estimates and 95% confidence intervals (CIs) were calculated using random-effects models.

Results We identified 11 trials, including 18,192 participants (mean age 73.7 years; 43% females). Compared with placebo, statins neither increased the risks of muscle-related symptoms (RR 1.01; 95% CI 0.90–1.12), total adverse events (AEs) and serious AEs nor led to more total permanent treatment discontinuations and discontinuations due to AEs or specifically due to muscle-related symptoms. No evidence of heterogeneity was observed in any of these outcomes.

Conclusions This meta-analysis of RCTs found no excess incidence of muscle-related symptoms, total AEs, serious AEs and treatment discontinuations attributable to statin treatment compared with placebo among older adults without CVD.

1 Introduction

Use of statins for the secondary prevention of cardiovascular disease (CVD) in older adults, defined as individuals aged ≥ 65 years, has been well-acknowledged and is supported by a strong body of evidence [1]. However, for primary prevention with statins, recommendations in clinical guidelines from different countries are inconsistent in adults aged 65–75 years and are generally lacking in those aged ≥ 75 years, who have been largely underrepresented in clinical trials [2, 3]. Despite this, statin prescriptions for primary prevention in older adults have markedly increased over the past decade, because of their higher disease burden and poorer outcomes following a first cardiovascular event [4–6]. The widespread use of statins in this subpopulation has raised great concerns about potential statin-related risks, upon which the clinical trial evidence is weak and limited [7].

Compared with younger adults, older adults seem to be more susceptible and less resilient to statin-related adverse events (AEs) and drug–drug interactions because of decreased physiologic reserve, multiple morbidities and polypharmacy [8, 9]. Statin-associated muscle symptoms (SAMS) are the most commonly reported AEs in clinical practice, occurring in approximately 7–29% of statin users and contributing to ≤ 75% of treatment discontinuations of statins within 2 years of treatment initiation [10]. The clinical presentation of SAMS is highly heterogeneous

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Key Points

This meta-analysis of randomised controlled trials systematically evaluated the safety and tolerability of statins in older adults without overt cardiovascular disease (CVD).

This meta-analysis found no significant difference in muscle-related symptoms, any adverse event and any serious adverse event between statin and placebo groups in older adults without CVD.

This meta-analysis found no excess incidence of total treatment discontinuations and adverse event-related treatment discontinuations of statins relative to placebo in older adults without CVD.

and mainly characterised by muscle pain or aches (myalgia), muscle weakness, stiffness and cramp, with normal or slightly elevated creatine kinase (CK) concentrations [10]. For older adults, SAMS may substantially affect their independence and quality of life by exacerbating physical deconditioning and frailty [11]. Two rare and severe forms of SAMS—myopathy (defined as muscle symptoms with CK > 10 × the upper limit of normal [ULN]) and rhabdomyolysis (defined as muscle symptoms with CK > 40 × ULN when accompanied with renal impairment and/or myoglobinuria) are devastating and potentially life threatening [10]. In real-world populations, it was estimated that myopathy and rhabdomyolysis occur in 5 and 1.6 patients per 100,000 person-years, respectively [12].

The high incidence and prevalence of SAMS and other statin-related AEs were mainly observed in non-randomised scenarios, including observational studies, patient registries and routine clinical settings [13]. However, given the lack of a comparator in these contexts, any relation between reported AEs and statin use can only be seen as associative. In contrast, results yielded using data from randomised controlled trials (RCTs) that enable the establishment of causal relations should provide more reliable evidence of actual statin-attributable AEs. Therefore, we conducted a systematic review and meta-analysis of RCTs to comprehensively evaluate the safety and tolerability of statins versus placebo in primary prevention in older adults, focusing on the risk of SAMS. We also assessed the incidence of total AEs, serious AEs (SAEs), and permanent treatment discontinuations between statin and placebo groups, as these outcomes present the general safety and tolerability profiles of a treatment.

2 Methods

2.1 Systematic Review Registration

The study protocol was previously registered (PROSPERO: CRD42017058436) and published [14]. This systematic review and meta-analysis was reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method [15].

2.2 Data Sources and Study Selection

We selected eligible trials published before January 2012 from the reference list of a published Cochrane systematic review (updated to 2012) of RCTs of statins including adults without established CVD [16]. A new search using the CENTRAL, MEDLINE and EMBASE databases was conducted to identify eligible trials published between January 2012 and July 2018. The full search strategy was outlined in our protocol [14]. No language restrictions were applied. We also manually searched relevant reviews and the reference lists of eligible articles to supplement the electronic search. Two reviewers (ZZ and LA) independently screened the titles and abstracts of articles against the selection criteria. The full text of articles that potentially met the eligibility criteria were retrieved. Discrepancies were resolved by discussion with a third reviewer (MN).

2.3 Selection Criteria

We included studies that met the following criteria: double-blind RCTs of statins versus placebo with at least 1 year of follow-up and reporting at least one outcome of interest (defined in Sect. 2.4) in (subgroup of) participants aged ≥ 65 years without overt CVD.

We also excluded studies that (1) targeted participants with certain pre-existing conditions, including cancer, hypothyroidism, acute infection, chronic kidney disease, HIV infection, post-transplantation, or any other acute illness that may increase the risk of AEs [17]; (2) studied cerivastatin, which was withdrawn from the market in 2001; or (3) studied a combination of statins with any other lipid-lowering medication as the study treatment.

2.4 Outcomes

The primary outcome was adverse muscle symptoms, including myalgia, muscle weakness, stiffness, tenderness and cramp (myopathy and rhabdomyolysis were not included) [10].

Other outcomes included myopathy, rhabdomyolysis, any AE (refers to the AEs recorded in the original trial; we did

not exclude adverse muscle symptoms, myopathy and rhabdomyolysis if these outcomes were counted as AEs in the original trial), any SAE (defined as adverse experiences that were considered serious, including life threatening, causing death or a permanent disability or incapacity and resulting in or prolonging hospitalisation) [18], permanent treatment discontinuation of statins or placebo for any reason, AEs or adverse muscle symptoms.

2.5 Data Extraction and Quality Assessment

Two reviewers (ZZ, LA) independently extracted data using a predefined, standardised data extraction sheet. When trial outcome data were published in a form that corresponded to our age eligibility criteria (age ≥ 65 years), we extracted them directly from the publication in aggregate form. If no subgroup data were provided for those aged > 65 years, we requested individual patient data from the corresponding authors and/or pharmaceutical sponsors of the original trial and performed the appropriate analysis for that age group. We assessed the risk of bias of included trials using Cochrane's risk of bias tool (RevMan version 5.3.5, The Cochrane Collaboration) [19]. We assessed the overall risk of bias for each trial based on the judgement of each domain as high, low or unclear risk and rated it by the highest risk assigned across individual domains. We used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to rate the quality of evidence for each outcome across all the trials as very low, low, moderate or high, and created a 'summary of findings' table (Supplementary Table 1) [20]. More details can be found in our published protocol [14].

2.6 Data Synthesis and Analysis

To account for a between-study variation in the effect sizes of an outcome, we employed the DerSimonian and Laird random-effects models to perform meta-analyses of outcomes (except for myopathy and rhabdomyolysis) [21]. Results of the analyses were presented as relative risks (RRs) with 95% confidence intervals (CIs). We provided a narrative statement for myopathy and rhabdomyolysis as most included trials reported zero events of these two outcomes in both arms.

Between-study heterogeneity was assessed using the I^2 statistic [22]. I^2 values of 0–40%, 30–60%, 50–90% and 75–100% correspond to negligible, moderate, substantial and considerable heterogeneity, respectively [21]. Subgroup analyses were conducted for the primary outcome based on prespecified factors, including follow-up duration (< 3 years, ≥ 3 years), the dose intensity of statins (standard, intensive, multiple) [23] and the solubility of statins (hydrophilic, lipophilic). As only nine trials reported the primary outcome, we were unable to assess publication bias using funnel plots and Egger's regression test as planned [24]. A leave-one-out sensitivity analysis was conducted by iteratively removing one study at a time to assess the impact of every single study. Meta-regression was not conducted to minimise the risk of false positives [25].

All the analyses were conducted using R (version R-3.5.1). All tests were 2-tailed. A p value < 0.05 was considered statistically significant.

3 Results

3.1 Trials Retrieved and Study Characteristics

The trial selection flowchart is presented in Fig. 1. Of 9751 citations identified initially by our new established search, 71 articles were retrieved for full review and two publications from one trial (HOPE-3 [Heart Outcomes Prevention Evaluation-3] [26]) met our eligibility criteria in the database search. However, this trial had a wider age range criterion and was later excluded because we could not obtain separate data for older adults [27]. Ten RCTs selected from the Cochrane review and one from the manual search were included in the final analyses, with a total of 18,192 subjects included (mean age 73.7 years; 43% females; median follow-up 3.0 years).

The characteristics of the included RCTs are summarised in Table 1. Trials conducted by Bruckert et al. [30] and Chan et al. [31] exclusively enrolled older adults without overt CVD. Data from three trials were derived from the post-hoc analyses of the primary trials [32–34]. Data from four trials were extracted from individual patient data [35–38]. Data from the PROSPER trial [39] were obtained from the meta-analysis by Teng et al. [40] and data from the ASCAPS-TexCAPS trial [41] were from the meta-analysis by Iwere et al. [42].

3.2 Risk of Bias and Quality of Evidence

Results of the risk-of-bias assessment are presented in Fig. 2. In terms of the rating of methodological quality items across all included trials, half of the trials were rated as having an unclear risk of bias for random sequence generation and allocation concealment. Most of the trials were rated as having an unclear or high risk of 'other bias' because they were funded by pharmaceutical companies. For the remaining items, most of the included trials were rated as having a low risk of bias. In terms of the methodological quality for each individual trial, eight trials (ASCAPS-TexCAPS [41], PROSPER [39], CARDS [34], PREVEND IT [37], ASPEN [38], Bone et al. [36], METEOR [35] and ASCOT-LLA [32, 43]) were rated as having an unclear risk of bias, and three

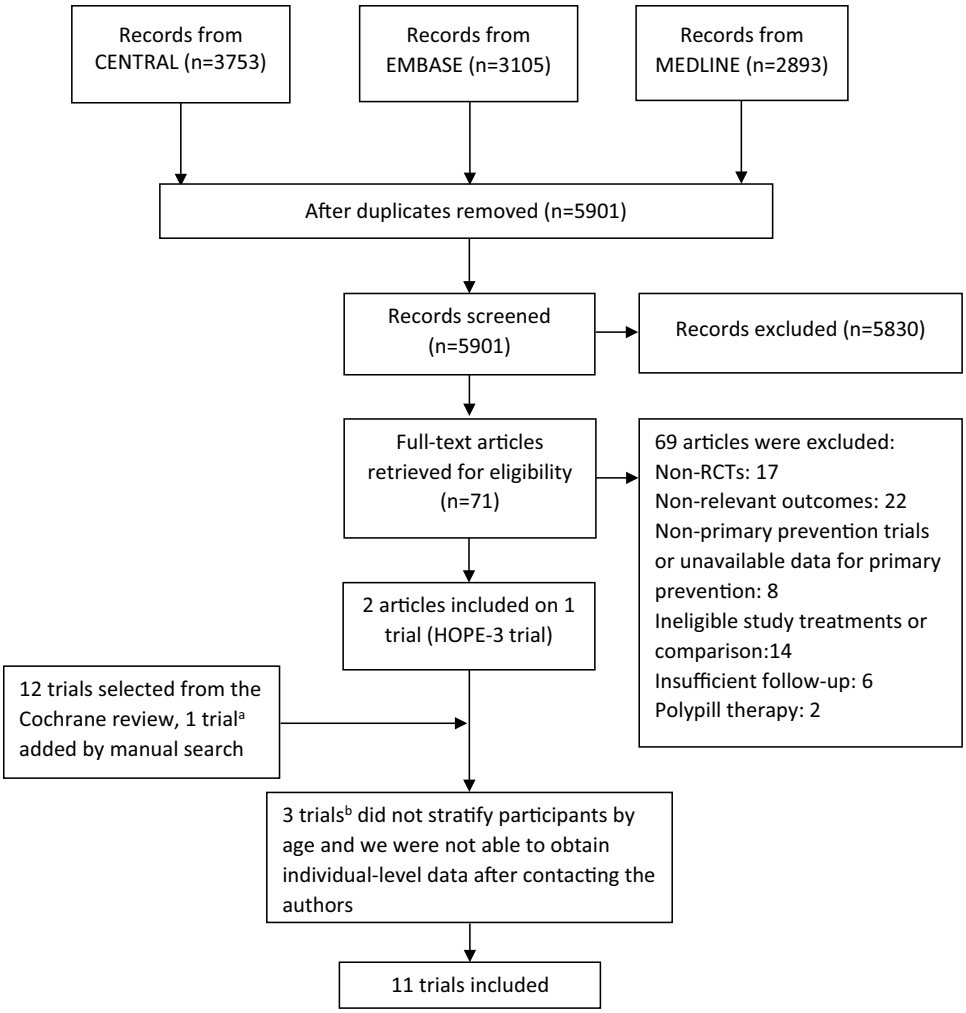


Fig. 1 Study selection process. *RCT* randomised controlled trial. [a]Trial by Bruckert et al. [30]. [b]MRC/BHF (Medical Research Council/British Heart Foundation) Heart Protection study [28], HOPE-3 (Heart Outcomes Prevention Evaluation-3) trial [26] and ACAPS (Asymptomatic Carotid Artery Plaque Study) trial [29]

trials (Chan et al. [31], Bruckert et al. [30] and JUPITER [33, 44]) were rated as having a high risk of bias.

The quality of evidence applied for each outcome was summarised in the 'summary of findings' table according to the GRADE approach (Supplementary Table 1). The quality of evidence on adverse muscle symptoms, AEs, SAEs and permanent treatment discontinuations due to AEs and muscle-related symptoms was rated moderate and that on myopathy, rhabdomyolysis and total permanent discontinuations was rated low.

3.3 Adverse Muscle Symptoms

Nine trials with 7.7% (642/8346) of participants in the statin group versus 7.5% (622/8287) of participants in the placebo group reported adverse muscle symptoms. There was no significant difference in the risk of adverse muscle symptoms between the two groups (RR 1.01; 95% CI 0.90–1.12; $p=0.50$; $I^2=1.1\%$) (Fig. 3).

3.4 Myopathy and Rhabdomyolysis

Seven trials with 0.06% (4/6724) of participants treated with statins versus 0.05% (3/6655) treated with placebo reported myopathy. Of seven trials with available data on rhabdomyolysis, only one case (1/7691) was recorded in the statin group; none (0/7617) were recorded in the placebo group.

3.5 Adverse Events and Serious Adverse Events

Six trials with 34.3% (581/1694) of participants treated with statins versus 30.0% (468/1560) treated with placebo reported AEs. Seven trials with 28.0% (2238/7989) of participants treated with statins versus 28.5% (2270/7958) treated with placebo reported SAEs. The risks of both AEs (six trials; RR 0.99; 95% CI 0.95–1.04; $p=0.95$; $I^2=0.0\%$) and SAEs (RR 1.01; 95% CI 0.97–1.05; $p=0.89$; $I^2=0.0\%$) did not differ significantly between statin and placebo (Fig. 4).

Table 1 Baseline characteristics and outcomes reported of the included trials

Study, country	Patients (*n*) (statin/PL)	Mean age (range), years	Median follow-up, years	Female (%)	Statins (dose)	Dosage intensity	Baseline LDL-C (mmol/L)	Run-in (weeks)	Stop early	Outcome reported
Chan et al. [31], China	96 (48/48)	77 (≥65)	1.0	51	Pravastatin[a] 15 mg/day	Standard	5.27	Dietary (12)	No	MS, AE, TPD, PD-AE, PD-MS
ASCAPS-TexCAPS [41], USA	1416 (715/701)	NR (65–75)	5.2	25	Lovastatin[b] 20–40 mg/day	Standard	4.06	Dietary (12), PL (2)	Yes	MY
PROSPER [39], Scotland, Ireland, the Netherlands	3239 (1585/1654)	75 (70–82)	3.3	59	Pravastatin[a] 40 mg/day	Standard	3.80	PL (4)	No	MS, MY, RB, SAE
Bruckert et al. [30], France, Italy, Spain, Belgium, Israel	1229 (607/622)	76 (69–92)	1.0	75	Fluvastatin XL[b] 80 mg/day	Standard	5.17	None	Yes	MS, MY, AE, SAE, TPD, PD-AE, PD-MS
PREVEND IT [37], The Netherlands	143 (78/65)	70 (65–76)	3.8 (mean)	27	Pravastatin[a] 40 mg/day	Standard	4.30	None	No	TPD, PD-AE
CARDS [34], UK, Ireland	1129 (572/557)	69 (65–77)	3.9	31	Atorvastatin[b] 10 mg/day	Standard	3.06	PL (6)	Yes	MS, MY, RB, AE, SAE, PD-AE
ASPEN [38], 14 countries	590[c] (309/281)	69 (65–78)	4.0	34	Atorvastatin[b] 10 mg/day	Standard	2.98	PL (6)	No	MS, MY, RB, AE, PD, PD-AE, PD-MS
Bone et al. [36], USA	129 (100/29)	69 (65–78)	1.0	100	Atorvastatin[b] 10–80 mg/day	Multiple	3.4–4.9	None	No	MS, RB, AE, SAE, PD, PD-AE, PD-MS
METEOR [35], USA, Europe	81 (58/23)	NR (65–74)	1.8	77	Rosuvastatin[a] 40 mg/day	Intensive	3.99	None	No	MS, MY, RB, AE, SAE, PD, PD-AE, PD-MS
JUPITER [33, 44], 26 countries	5695 (2878/2817)	74[d] (70–97)	1.9	52	Rosuvastatin[a] 20 mg/day	Intensive	2.80	PL (4)	Yes	MS, MY, RB, SAE
ASCOT-LLA [32, 43], UK, Sweden, Norway, Denmark, Finland, Ireland	4445 (2189/2256)	71 (≥65)	3.3	20	Atorvastatin[b] 10 mg/day	Standard	3.44	None	Yes	MS, RB, SAE, PD-AE, PD-MS

AE adverse event, *ASCAPS-TexCAPS* Air Force/Texas Coronary Atherosclerosis Prevention Study, *ASCOT-LLA* Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm, *ASPEN* The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus, *CARDS* Collaborative Atorvastatin Diabetes Study, *JUPITER* Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin, *LDL-C* low-density lipoprotein cholesterol, *METEOR* Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin, *MS* muscle-related symptoms, *MY* myopathy, *NR* not reported, *PD-AE* permanent discontinuation due to AEs, *PD-MS* permanent discontinuation due to muscle-related symptoms, *PL* placebo, *PREVEND IT* Prevention of Renal and Vascular Endstage Disease Intervention Trial, *PROSPER* Pravastatin in Elderly Individuals at Risk of Vascular Disease, *RB* rhabdomyolysis, *SAE* serious adverse event, *TPD* total permanent discontinuation

[a]Hydrophilic

[b]Lipophilic

[c]Patients with a history of angina were excluded

[d]Median

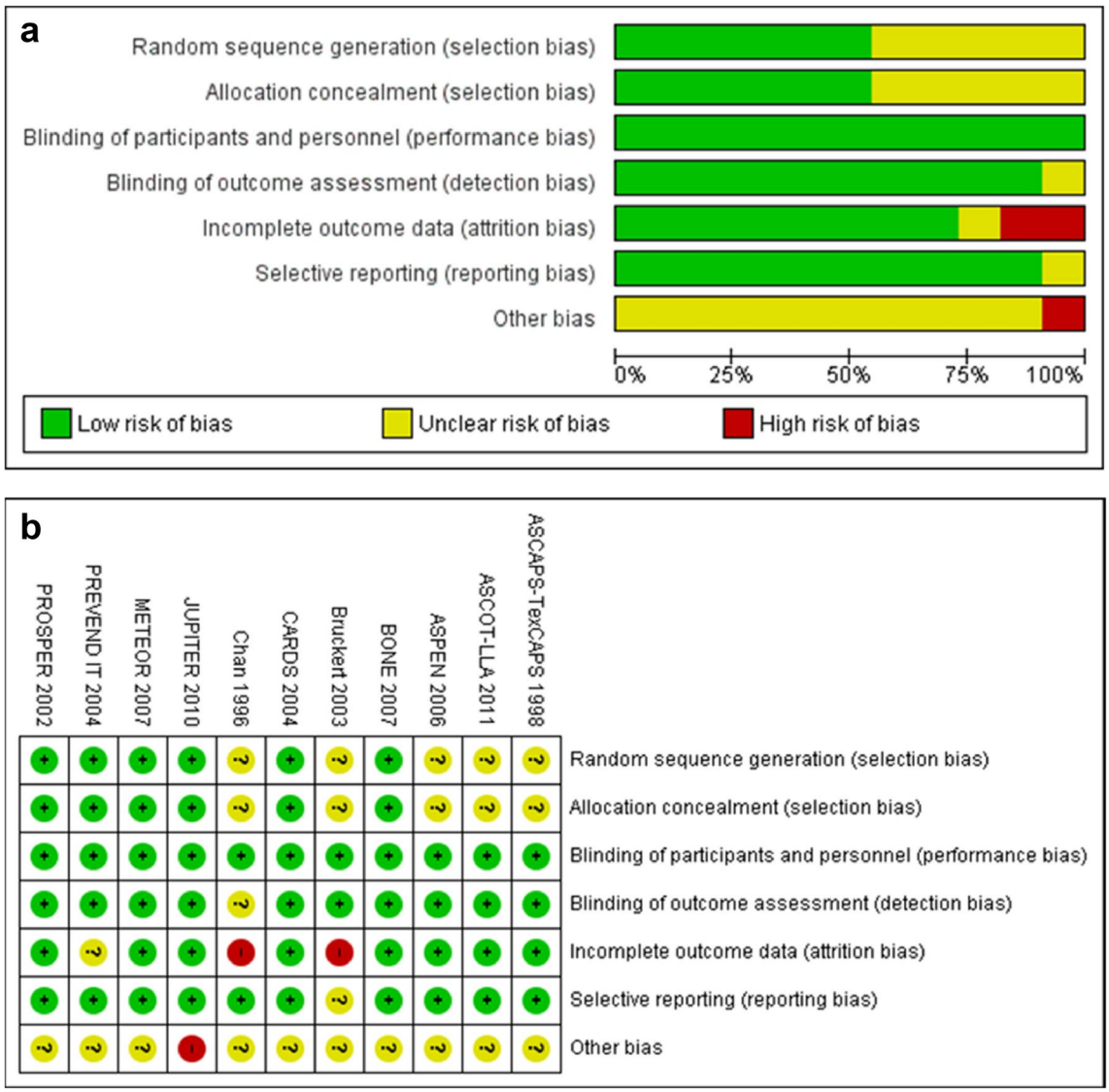


Fig. 2 Risk of bias (**a**) summary and (**b**) graph: review author's judgements about each methodological quality item presented as percentages across **a** all included trials and **b** for each included trial

3.6 Permanent Treatment Discontinuation

No significant differences between statins and placebo were observed in the incidence of total permanent treatment discontinuations (six trials; RR 0.99; 95% CI 0.81–1.22; $p = 0.81$; $I^2 = 0.0\%$) or permanent treatment discontinuations due to AEs (eight trials; RR 1.05; 95% CI 0.83–1.33; $p = 0.59$; $I^2 = 0.0\%$) and due to adverse muscle symptoms (six trials; RR 1.17; 95% CI 0.64–2.14; $p = 0.75$; $I^2 = 0.0\%$) (Fig. 4).

3.7 Subgroup Analyses

The results of subgroup analyses suggested that our primary result was consistent regardless of the solubility and dosing of statins assigned and the follow-up duration of trials (Supplementary Figs. 1, 2, 3).

3.8 Sensitivity Analysis

The results yielded by the leave-one-out sensitivity analysis were consistent with the primary result, indicating that our primary finding was not driven by any single study (Supplementary Fig. 4).

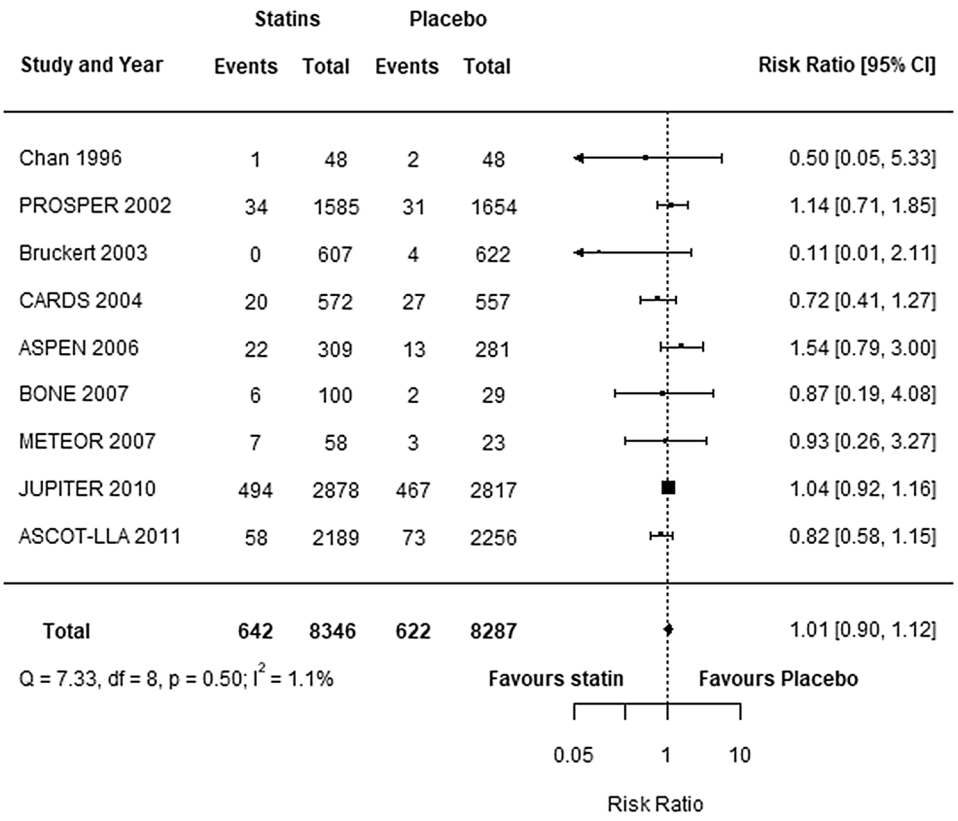


Fig. 3 Relative risks (95% confidence intervals) of adverse muscle symptoms between the statin and placebo groups. *CI* confidence interval

4 Discussion

4.1 Principal Findings

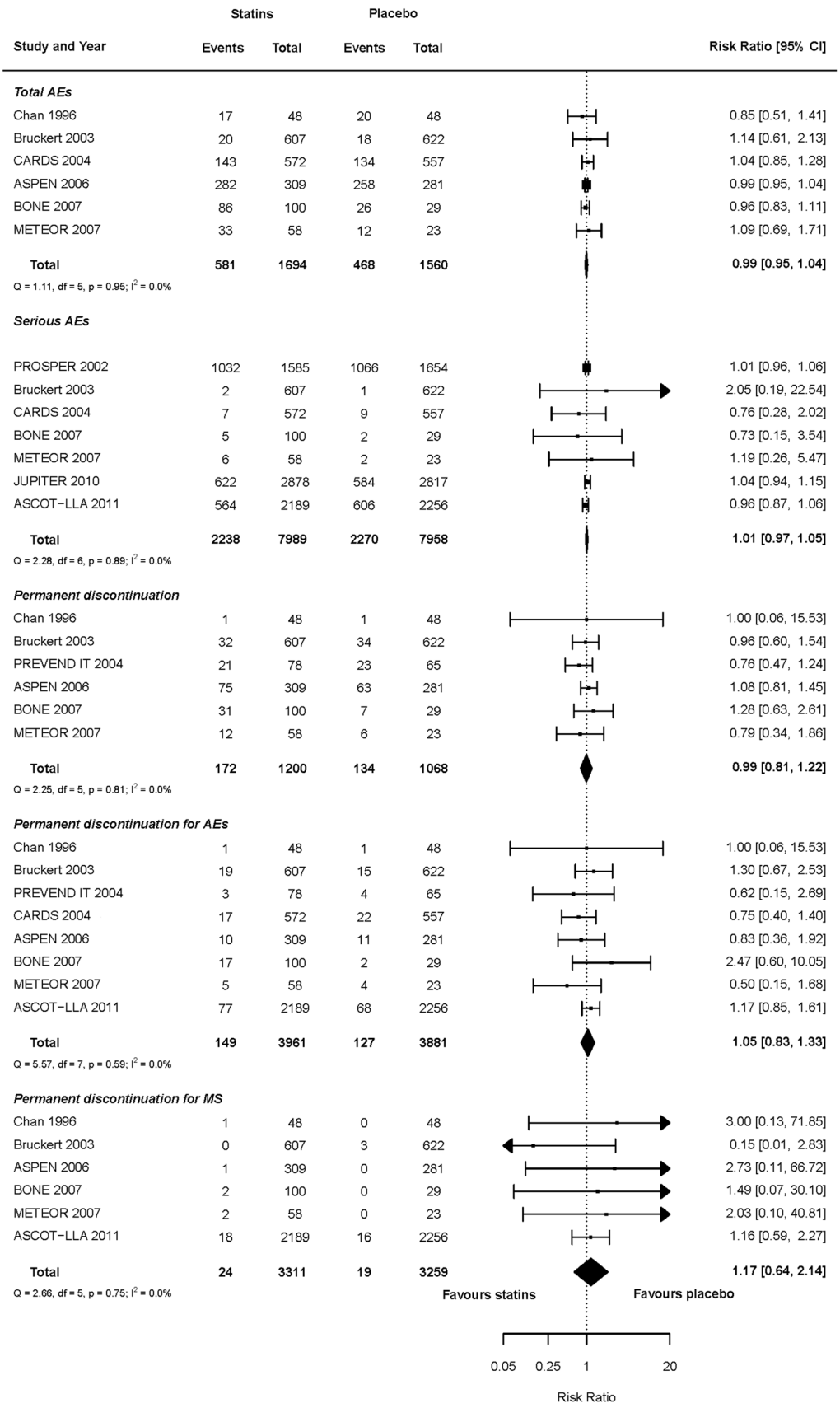
In this meta-analysis of 11 RCTs, we found no evidence of an excess incidence of adverse muscle symptoms, AEs and SAEs attributable to statins compared with placebo in older adults without overt CVD. For myopathy and rhabdomyolysis, incidence rates were extremely low in both statin and placebo groups. Additionally, the incidence of total permanent discontinuations and of permanent discontinuations due to AEs or adverse muscle symptoms were not significantly different between statin and placebo groups. Our study findings supplement the current evidence base regarding the safety and tolerability of statin use in older adults in the primary prevention setting.

We did not evaluate the risk of other purported statin-related AEs such as diabetes and haemorrhagic stroke, as they may only emerge after long-term statin exposure in large numbers of patients [45]. In a cohort study of 22,340 older adults, 45% discontinued statins within 1 year of treatment initiation [46]. It therefore seems likely that participants may be more concerned about the more immediate side effects of statins such as SAMS.

4.2 Comparison with Other Studies and Possible Explanations

Prior to our study, Teng et al. [40] conducted a meta-analysis using published data from statin trials and found no increased risk of myalgias, SAEs and AE-related treatment discontinuations associated with statin use versus placebo/usual care in older adults without CVD. Our study updated their study findings by adding new data from four clinical trials, applying stringent selection criteria and looking into additional clinically relevant safety-related outcomes. Another meta-analysis of RCTs of older adults with and without CVD history [42] also showed no significant difference in the risks of muscle-related symptoms and AE-related treatment discontinuations between statin and placebo/usual care groups.

Our study findings were consistent with previous meta-analyses of RCTs, but they do not concur with the high prevalence of SAMS and other statin-related AEs observed in routine clinical settings. In the absence of a comparator group in real-world scenarios, it is possible that a patient and their health providers may misattribute symptoms to statins if that patient is taking a statin. Evidence for this was seen in a large cohort study in a routine care setting, in which > 90% of statin users who were rechallenged after


Statins
Placebo
Study and Year
Events
Total
Events
Total
Risk Ratio [95% CI]
Total AEs
Chan 1996 17 48 20 48 0.85 [0.51, 1.41]
Bruckert 2003 20 607 18 622 1.14 [0.61, 2.13]
CARDS 2004 143 572 134 557 1.04 [0.85, 1.28]
ASPEN 2006 282 309 258 281 0.99 [0.95, 1.04]
BONE 2007 86 100 26 29 0.96 [0.83, 1.11]
METEOR 2007 33 58 12 23 1.09 [0.69, 1.71]
Total 581 1694 468 1560 0.99 [0.95, 1.04]
Q = 1.11, df = 5, p = 0.95; I² = 0.0%
Serious AEs
PROSPER 2002 1032 1585 1066 1654 1.01 [0.96, 1.06]
Bruckert 2003 2 607 1 622 2.05 [0.19, 22.54]
CARDS 2004 7 572 9 557 0.76 [0.28, 2.02]
BONE 2007 5 100 2 29 0.73 [0.15, 3.54]
METEOR 2007 6 58 2 23 1.19 [0.26, 5.47]
JUPITER 2010 622 2878 584 2817 1.04 [0.94, 1.15]
ASCOT−LLA 2011 564 2189 606 2256 0.96 [0.87, 1.06]
Total 2238 7989 2270 7958 1.01 [0.97, 1.05]
Q = 2.28, df = 6, p = 0.89; I² = 0.0%
Permanent discontinuation
Chan 1996 1 48 1 48 1.00 [0.06, 15.53]
Bruckert 2003 32 607 34 622 0.96 [0.60, 1.54]
PREVEND IT 2004 21 78 23 65 0.76 [0.47, 1.24]
ASPEN 2006 75 309 63 281 1.08 [0.81, 1.45]
BONE 2007 31 100 7 29 1.28 [0.63, 2.61]
METEOR 2007 12 58 6 23 0.79 [0.34, 1.86]
Total 172 1200 134 1068 0.99 [0.81, 1.22]
Q = 2.25, df = 5, p = 0.81; I² = 0.0%
Permanent discontinuation for AEs
Chan 1996 1 48 1 48 1.00 [0.06, 15.53]
Bruckert 2003 19 607 15 622 1.30 [0.67, 2.53]
PREVEND IT 2004 3 78 4 65 0.62 [0.15, 2.69]
CARDS 2004 17 572 22 557 0.75 [0.40, 1.40]
ASPEN 2006 10 309 11 281 0.83 [0.36, 1.92]
BONE 2007 17 100 2 29 2.47 [0.60, 10.05]
METEOR 2007 5 58 4 23 0.50 [0.15, 1.68]
ASCOT−LLA 2011 77 2189 68 2256 1.17 [0.85, 1.61]
Total 149 3961 127 3881 1.05 [0.83, 1.33]
Q = 5.57, df = 7, p = 0.59; I² = 0.0%
Permanent discontinuation for MS
Chan 1996 1 48 0 48 3.00 [0.13, 71.85]
Bruckert 2003 0 607 3 622 0.15 [0.01, 2.83]
ASPEN 2006 1 309 0 281 2.73 [0.11, 66.72]
BONE 2007 2 100 0 29 1.49 [0.07, 30.10]
METEOR 2007 2 58 0 23 2.03 [0.10, 40.81]
ASCOT−LLA 2011 18 2189 16 2256 1.16 [0.59, 2.27]
Total 24 3311 19 3259 1.17 [0.64, 2.14]
Q = 2.66, df = 5, p = 0.75; I² = 0.0%
Favours statins
Favours placebo
0.05
0.25
1
20
Risk Ratio

◂**Fig. 4** Relative risks (95% confidence intervals) of adverse events, serious adverse events, total permanent discontinuations, discontinuations due to adverse events and adverse muscle symptoms. *AE* adverse event, *CI* confidence interval, *MS* muscle-related symptoms

experiencing an AE could tolerate a statin in the long term [47]. In fact, muscle complaints are frequently reported by older adults, and the reasons can be diverse (i.e. sarcopenia, increased physical activity, diseases that lead to or increase susceptibility to muscle problems, medications with known muscular toxicity) [10]. Such misattribution may prevent a substantial number of older adults from taking statins and mean they forego potential cardiovascular benefits and experience more incident events as a consequence [10].

The 'nocebo effect' may also provide some explanation for the higher prevalence of SAMS in real-world practice [48]. The 'nocebo effect' refers to the idea that subjective AEs such as aches and pain are due to patients' expectations of harm from statin therapy because of their awareness and concerns about possible statin-related side effects [49]. In fact, the misattribution bias and 'nocebo effect' (if participants believe they are taking statins whether or not they are) may also occur in RCTs. Despite this, they affect statin and placebo groups equally, so their presence will not distort the estimates of treatment effects. In this meta-analysis, the incidence of adverse muscle symptoms was similar between statin and placebo groups (7.7 vs. 7.5%), further indicating that the AEs observed in the statin group were not necessarily related to the study treatment.

It is worth noting that the generalisability of our study findings may be limited to routine clinical settings because of the inadequate representation of real-world populations. Participants within a clinical trial are more homogeneous than real-world populations regarding demographic, functional and clinical aspects. In this meta-analysis, most included trials involved predominantly White and older adults aged < 80 years. Therefore, our study results may not apply to very old populations and other races or ethnicities. Trial participants also tend to be more motivated and to have better physical and psychological functioning, so the risk of statin-related AEs for these individuals is likely to be lower [50]. In view of this, evidence from clinical registries that reflect day-to-day clinical practice can be complementary to randomised evidence and provide some value for informing clinical decision making while also acknowledging the design limitations.

4.3 Limitations

Several limitations in this review need to be raised. First, the evidence quality of the outcomes in this review was rated from low to moderate, so the results should be interpreted with caution. Second, individual patient data from three identified trials [26, 28, 29] could not be obtained, which lowers the study power. Third, a median follow-up of 3 years in included trials may limit study ability to assess the safety and tolerability of statins over the long term. However, common and immediate side effects of statins such as SAMS are more likely to be clinically concerning issues that were reported to contribute to a high rate of statin discontinuations within the early period (1–2 years) of treatment initiation [10]. Fourth, all the included trials were industry sponsored and therefore may be biased in favour of the sponsor's drugs. However, this limitation is likely to be minimal as all the reported AEs were recorded by blinded personnel. Additionally, as seven included trials did not perform further subgroup analysis by age and participants' mean age in three trials was unknown, we were unable to conduct a subgroup analysis or meta-regression to assess whether age increases the risk of statin-related AEs and the incidence of treatment discontinuations of statins. Moreover, some trials had a small sample and unbalanced treatment arms, which may influence the accuracy of the results. While no heterogeneity was observed in the meta-analyses of all outcomes, the small study effect appeared to be negligible. Finally, the study results may have generalisability considerations for patients in routine clinical settings.

5 Conclusions

In this meta-analysis of RCTs, we found no evidence of an excess incidence of adverse muscle symptoms, total AEs, SAEs and treatment discontinuations attributable to statins compared with placebo among older adults without CVD. As statin intolerance and discontinuation remain important and unresolved clinical issues, further evidence from high-quality RCTs designed to assess the safety and tolerability of statins in older adults without CVD exclusively is warranted to provide more reliable evidence.

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Compliance with Ethical Standards

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Conflict of interest MN has participated on an advisory board for Amgen, who make a lipid-lowering agent. ZZ, LA, AC and MB have no conflicts of interest that are directly relevant to the content of this article.

Ethical approval Not applicable for this meta-analysis.

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