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

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1 **Article Title:** The safety and tolerability of statin therapy in primary prevention in older adults: A systematic
2 review and meta-analysis

3 **Running Title:** The risk of statins in healthy elderly

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15

16

17 **Abstract**

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

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

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

28 **Results** Eleven trials including 18,192 participants were identified (mean age 73.7 years; 43% females).
29 Compared with placebo, statins neither increase the risks of muscle-related symptoms (RR 1.01; 95% CI 0.90 to
30 1.12), total adverse events (AEs) and serious AEs nor lead to more total permanent treatment discontinuations and
31 discontinuations due to AEs or specifically due to muscle-related symptoms. No evidence of heterogeneity was
32 observed in any of these outcomes.

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

36 **Keywords** Hydroxymethylglutaryl-CoA Reductase Inhibitors; Safety; Primary prevention; Aged; Meta-Analysis

37 **Key Points**

- 38
- The present meta-analysis of randomised controlled trials systematically evaluated the safety and
39 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
40 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 AE-related
41 treatment discontinuations of statins relative to placebo in older adults without CVD.
- 42
- 43

44

45 **1 Introduction**

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

55 Compared with younger adults, older adults seem to be more susceptible and less resilient to statin-related
56 adverse events (AEs) and drug-drug interactions owing to decreased physiologic reserve, multiple morbidities and
57 polypharmacy [8, 9]. Statin-associated muscle symptoms (SAMS) are the most commonly reported AEs in clinical
58 practice, occurring in approximately 7% to 29% of statin-users and contributing to up to 75% of treatment
59 discontinuations of statins within two years of treatment initiation [10]. The clinical presentation of SAMS is
60 highly heterogeneous, mainly characterised by muscle pain or aches (myalgia), muscle weakness, stiffness and
61 cramp, with normal or slightly elevated creatine kinase (CK) concentrations [10]. For older adults, SAMS may
62 substantially impact their independence and quality of life by exacerbating physical deconditioning and frailty
63 [11]. Two rare and severe forms of SAMS - myopathy (defined as muscle symptoms with CK $>10 \times$ the upper
64 limit of normal [ULN]) and rhabdomyolysis (defined as muscle symptoms with CK $>40 \times$ ULN when
65 accompanied with renal impairment and/or myoglobinuria) are devastating and potentially life-threatening [10].
66 In real-world populations, it was estimated that the myopathy and rhabdomyolysis occur in 5 and 1.6 patients per
67 100,000 person-years, respectively [12].

68 The high incidence and prevalence of SAMS and other statin-related AEs were mainly observed in non-
69 randomised scenarios, including observational studies, patient registries and routine clinical settings [13].
70 However, owing to the lack of a comparator in these contexts, any relation between reported AEs and statin use
71 can only be seen as associative. In contrast, results yielded using data from randomised controlled trials (RCTs)
72 that enable the establishment of causal relations, should provide more reliable evidence of actual statin attributable

73 AEs. Therefore, we conducted a systematic review and meta-analysis of RCTs to comprehensively evaluate the
74 safety and tolerability of statins versus placebo in primary prevention in older adults, with a focus on the risk of
75 SAMS. We also assessed the incidence of total AEs, serious AEs (SAEs), and permanent treatment
76 discontinuations between statin and placebo groups, as these outcomes present the general safety and tolerability
77 profiles of a treatment.

78

79 **2 Methods**

80 **2.1 Systematic Review Registration**

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

84

85 **2.2 Data Sources and Study Selection**

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

94

95 **2.3 Selection Criteria**

96 We included studies that met the following criteria: 1) double-blind RCTs of statins versus placebo with at least
97 one-year follow-up and; 2) reporting at least one outcome of interest (defined below in section 2.4 Outcomes) in
98 (subgroup of) participants aged 65 years or more without overt CVD.

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

104

105 **2.4 Outcomes**

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

108 Other outcomes included myopathy, rhabdomyolysis, any AE (refers to the AEs recorded in the original trial;
109 we did not exclude adverse muscle symptoms, myopathy and rhabdomyolysis if these outcomes were counted as
110 AEs in the original trial), any SAE (defined as adverse experiences that were considered serious including life-
111 threatening, causing death or a permanent disability or incapacity, resulting in or prolonging hospitalisation) [18],
112 permanent treatment discontinuation of statins or placebo due to any reason, AEs or adverse muscle symptoms.

113

114 **2.5 Data Extraction and Quality Assessment**

115 Two reviewers (Z.Z., L.A.) independently extracted data using a predefined, standardised data extraction sheet.
116 When trial outcome data was published in a form that corresponded to our age eligibility criteria (age \geq 65 years)
117 it was extracted directly from the publication in aggregate form. If there was no subgroup data provided for the
118 over 65 age group, we requested individual patient data from the corresponding authors and/or pharmaceutical
119 sponsors of the original trial and performed the appropriate analysis for that age group. The risk of bias of included
120 trials was assessed using the Cochrane's Risk of Bias Tool (RevMan Version 5.3.5, The Cochrane Collaboration)
121 [19]. We assessed the overall risk of bias for each trial based on the judgement of each domain as high, low or
122 unclear risk and rated it by the highest risk assigned across individual domains. We used the Grading of
123 Recommendations Assessment, Development, and Evaluation (GRADE) approach to rate the quality of evidence
124 for each outcome across all the trials as very low, low, moderate or high, with a 'Summary of findings' table
125 created [20]. More details can be found in our published protocol [14].

126

127 2.6 Data Synthesis and Analysis

128 To account for a between-study variation in the effect sizes of an outcome, we employed the DerSimonian and
129 Laird random-effects models to perform meta-analyses of outcomes (except for myopathy and rhabdomyolysis)
130 [21]. Results of the analyses were presented as risk ratios (RRs) with 95% confidence intervals (95% CIs). We
131 provided a narrative statement for myopathy and rhabdomyolysis as most included trials reported zero events of
132 these two outcomes in both arms.

133 Between-study heterogeneity was assessed using the I^2 statistic [22]. I^2 values of 0%-40%, 30%-60%, 50%-
134 90%, and 75%-100% correspond to negligible, moderate, substantial and considerable heterogeneity, respectively
135 [21]. Subgroup analyses were conducted for the primary outcome based on pre-specified factors including follow-
136 up duration (<3-year, \geq 3-year), the dose intensity of statins (standard, intensive, multiple) [23], and the solubility
137 of statins (hydrophilic, lipophilic). As only nine trials reported the primary outcome, we were unable to assess
138 publication bias using funnel plots and Egger's regression test as planned [24]. A leave-one-out sensitivity analysis
139 was conducted by iteratively removing one study at a time to assess the impact of every single study. Meta-
140 regression was not conducted to minimise the risk of false positives [25].

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

143

144 3 Results

145 3.1 Trials Retrieved and Study Characteristics

146 The trial selection flowchart is presented in Fig. 1. Of 9,751 citations identified initially by our new established
147 search, 71 articles were retrieved for full review and two publications from one trial (Heart Outcomes Prevention
148 Evaluation [HOPE]-3 trial [26]) met our eligibility criteria in the database search. However, this trial had a wider
149 age-range criterion and was excluded later as separate data for older adults could not be obtained [27]. Ten RCTs
150 selected from the Cochrane review and one from the manual search were included in the final analyses, with a
151 total of 18,192 subjects included (mean age 73.7 years; 43% females; median follow-up 3.0 years).

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

155 The characteristics of the included RCTs are summarised in Table 1. Trials conducted by Bruckert et al. and
156 Chan et al. exclusively enrolled older adults without overt CVD [30, 31]. Data from 3 trials were derived from
157 the post-hoc analyses of the primary trials [32-34]. Data from 4 trials were extracted from individual patient data
158 [35-38]. Data from the PROSPER trial [39] were obtained from the meta-analysis by Teng et al. [40] and data
159 from the ASCAPS-*TexCAPS* trial [41] were from the meta-analysis by Iwere et al [42].

160

161 3.2 Risk of Bias and Quality of Evidence

162 Results of the risk of bias assessment are presented in Fig. 2. In terms of the rating of methodological quality
163 items across all included trials, half of the trials were rated as having an unclear risk of bias for the random
164 sequence generation and for the allocation concealment. Most of the trials were rated as having an unclear or high
165 risk for the item of ‘other bias’ because they were funded by pharmaceutical companies. For the remaining items,
166 the majority of included trials were rated as having a low risk of bias. In terms of the methodological quality for
167 each individual trial, eight trials (*ASCAPS-*TexCAPS* 1998* [41], *PROSPER 2002* [39], *CARDS 2004* [34],
168 *PREVEND IT 2004* [37], *ASPEN 2006* [38], *Bone 2007* [36], *METEOR 2007* [35] and *ASCOT-LLA 2011* [32, 43])
169 were rated as having an unclear risk of bias, and three trials (*Chan 1996*, [31] *Bruckert 2003*, [30] *JUPITER 2010*
170 [33, 44]) were rated as having a high risk of bias.

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

173

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

178 **Supplementary Table 1.** ‘Summary of findings’ generated by the GRADE [20]

179

180 3.3 Adverse Muscle Symptoms

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

184 **Fig. 3** Relative risks along with 95% confidence intervals of adverse muscle symptoms between the statin and
185 placebo groups. *CI* confidence interval.

186

187 3.4 Myopathy and rhabdomyolysis

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

191

192 3.5 AE and SAE

193 Six trials with 34.3% (581/1694) of participants treated with statins versus 30.0% (468/1560) treated with placebo
194 reported AEs. Seven trials with 28.0% (2238/7989) of participants treated with statins versus 28.5% (2270/7958)
195 treated with placebo reported SAEs. The risks of both AEs (6 trials; RR 0.99, 95% CI 0.95 to 1.04, $p = 0.95$, $I^2 =$
196 0.0%) and SAEs (RR 1.01, 95% CI 0.97 to 1.05, $p = 0.89$, $I^2 = 0.0\%$) did not differ significantly between statin
197 and placebo (Fig. 4).

198

199 3.6 Permanent Treatment Discontinuation

200 There were no significant differences observed in the incidence of total permanent treatment discontinuations (6
201 trials; RR 0.99, 95% CI 0.81 to 1.22, $p = 0.81$, $I^2 = 0.0\%$), permanent treatment discontinuations due to AEs (8
202 trials; RR 1.05, 95% CI 0.83 to 1.33, $p = 0.59$, $I^2 = 0.0\%$) and due to adverse muscle symptoms (6 trials; RR 1.17,
203 95% CI 0.64 to 2.14, $p = 0.75$, $I^2 = 0.0\%$) of statins versus placebo (Fig. 4).

204 **Fig. 4** Relative risks along with 95% confidence intervals of adverse events, serious adverse events, total
205 permanent discontinuations, discontinuations due to adverse events and adverse muscle symptoms. *AE* adverse
206 event, *CI* confidence interval, *MS* muscle-related symptoms.

207

208 **3.7 Subgroup analyses**

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

211 **Supplementary Fig. 1** Subgroup analysis of adverse muscle symptoms in terms of the solubility of statins. *CI*
212 confidence interval

213 **Supplementary Fig. 2** Subgroup analysis of adverse muscle symptoms in terms of the dose intensity of statins.
214 *CI* confidence interval

215 **Supplementary Fig. 3** Subgroup analysis of adverse muscle symptoms in terms of the length of follow-up of
216 trials. *CI* confidence interval

217

218 **3.8 Sensitivity analysis**

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

221 **Supplementary Fig. 4** Leave-one-out sensitivity analysis for the primary outcome. *RR* relative risk, *CI* confidence
222 interval

223

224 **4. Discussion**

225 **4.1 Principal Findings**

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

232 We did not evaluate the risk of other purported statin-related AEs such as diabetes and haemorrhagic stroke,
233 as they may only emerge after long-term statin exposure in large numbers of patients [45]. In a cohort study of
234 22,340 older adults, 45% discontinued statins within one year of treatment initiation [46]. It therefore seems likely
235 that participants may be more concerned about the more immediate side effects of statins such as SAMS.

236

237 **4.2 Comparison with Other Studies and Possible Explanations**

238 Prior to our study, a meta-analysis by Teng et al [40] using published data from statin trials showed no increased
239 risk of myalgias, SAEs and AE-related treatment discontinuations associated with statin use versus placebo/usual
240 care in older adults without CVD. Our study updated their study findings by adding new data from four clinical
241 trials, applying stringent selection criteria, and looking into additional safety-related outcomes which are
242 clinically-relevant. Another meta-analysis of RCTs of older adults with and without CVD history by Iwere et al
243 [42] also showed no significant difference in the risks of muscle-related symptoms and AE-related treatment
244 discontinuations between statin and placebo/usual care groups.

245 Whilst our study findings were consistent with previous meta-analyses of RCTs, they do not concur with the
246 high prevalence of SAMS and other statin-related AEs observed in routine clinical settings. In the absence of a
247 comparator group in real-world scenarios, it is possible that patients and their health providers may misattribute
248 symptoms to statins if that patient was currently taking statin drugs. Evidence for this is seen in a large cohort
249 study in a routine care setting, in which more than 90% of statin-users who were re-challenged after suffering an
250 AE could tolerate a statin long-term [47]. In fact, muscle complaints are frequently reported by older adults and
251 the reasons can be diverse (i.e. sarcopenia, increased physical activity, diseases that lead to or increase the
252 susceptibility to muscle problems, medications with known muscular toxicity) [10]. Such misattribution may
253 prevent a substantial number of older adults from taking statins, and mean they forego potential cardiovascular
254 benefits with more incident events as a consequence [10].

255 The “nocebo effect” may also provide some explanation for the higher prevalence of SAMS in real-world
256 practice [48]. The ‘nocebo effect’ refers to the idea that subjective AEs such as aches and pain are due to patients’
257 expectations of harm from statin therapy, because of their awareness and concerns about possible statin-related
258 side effects [49]. In fact, the misattribution bias and ‘nocebo effect’ (if participants believe they are taking statins
259 whether or not they are) may also occur in RCTs. Despite this, they impact statin and placebo groups equally.
260 Hence their presence will not distort the estimates of treatment effects. In this meta-analysis, the incidence of

261 adverse muscle symptoms was found to be similar between statin and placebo groups (7.7% vs. 7.5%), further
262 indicating that the AEs observed in the statin group were not necessarily related to the study treatment.

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

272 **4.3 Limitations**

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

288

289 **5. Conclusions**

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

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308 providing the data from METEOR trial, and Pfizer for providing the data from BONE and ASPEN trials.

309

310 **Compliance with Ethical Standards**

311 **Ethical approval** Not applicable for this meta-analysis.

312 **Sources of funding** No.

- 313 **Conflict of interests** MN was on an Advisory Board for Amgen who make a lipid-lowering agent. ZZ, LA, AC and MB
314 declare that they have no conflict of interests.

Table 1 Baseline characteristics and outcomes reported of the included trials

Study name	Year	Country	Patients (n) (Statin /placebo)	Mean age (Age range), year	Median follow-up, year	Female (%)	Statins (mg/d)	Dosage Intensity	Baseline LDL-C (mmol/L)	run-in (week)	Stop early	Outcome reported
Chan et al[31]	1996	China	96 (48/48)	77 (≥65)	1.0	51	Pravastatin ^a (15mg/d)	Standard	5.27	Dietary (12)	No	MS, AE, TPD, PD-AE, PD-MS
ASCAPS- TexCAPS[41]	1998	U.S.	1416 (715/701)	NR (65-75)	5.2	25	Lovastatin ^b (20-40 mg/d)	Standard	4.06	Dietary (12) Placebo (2)	Yes	MY
PROSPER[39]	2002	Scotland, Ireland, The Netherlands	3239 (1585/1654)	75(70-82)	3.3	59	Pravastatin ^a (40mg/d)	Standard	3.80	Placebo (4)	No	MS, MY, RB, SAE
Bruckert et al[30]	2003	France, Italy, Spain, Belgium, Israel	1229 (607/622)	76(69-92)	1.0	75	Fluvastatin XL ^b (80mg/d)	Standard	5.18	None	Yes	MS, MY, AE, SAE, TPD, PD- AE, PD-MS
PREVEND IT[37]	2004	The Netherlands	143 (78/65)	70(65-76)	3.83 (mean)	27	Pravastatin ^a (40mg/d)	Standard	4.30	None	No	TPD, PD-AE
CARDS[34]	2004	UK and Ireland	1129 (572/557)	69(65-77)	3.9	31	Atorvastatin ^b (10mg/d)	Standard	3.06	Placebo (6)	Yes	MS,MY,RB, AE, SAE, PD-AE

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Study name	Year	Country	Patients (n) (Statin/plac ebo)	Mean age (Age range), year	Median follow-up, year	Female (%)	Statins (mg/d)	Dosage Intensity	Baseline LDL-C (mmol/L)	run-in (weeks)	Stop early	Outcome reported
ASPEN[38]	2006	14 countries	590 ^c (309/281)	69(65-78)	4	34	Atorvastatin ^b (10mg/d)	Standard	2.98	Placebo (6)	No	MS,MY,RB,AE,P D,PD-AE,PD-MS
Bone et al[36]	2007	U.S.	129 (100/29)	69(65-78)	1	100	Atorvastatin ^b (10-80mg/d)	Multiple	3.4-4.9	None	No	MS, RB,AE,SAE,PD,P D-AE,PD-MS
METEOR[35]	2007	U.S. and Europe	81 (58/23)	NR (65-74)	1.8	77	Rosuvastatin ^a 40mg/d	Intensive	3.99	None	No	MS,MY,RB,AE, SAE, PD, PD-AE, PD-MS
JUPITER[33, 44]	2010	26 countries	5695 (2878/2817)	74 ^d (70-97)	1.9	52	Rosuvastatin ^a 20mg/d	Intensive	2.80	Placebo (4)	Yes	MS,MY,RB,SAE
ASCOT- LLA[32, 43]	2011	UK,Sweden, Norway, Denmark, Finland,Ireland	4445 (2189/2256)	NR (≥65)	3.3	20	Atorvastatin ^b 10mg/d	Standard	3.44	None	Yes	MS,RB, SAE, PD-AE,PD-MS

ASCAPS-TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study; **PROSPER:** Pravastatin in Elderly Individuals at Risk of Vascular Disease; **PREVEND IT:** Prevention of Renal and Vascular Endstage Disease Intervention Trial; **CARDS:** Collaborative Atorvastatin Diabetes Study; **ASPEN:** The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; **METEOR:** Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; **JUPITER:** Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; **ASCOT-LLA:** Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm; **MS:** Muscle-related symptoms **MY:** Myopathy; **RB:** Rhabdomyolysis; **TPD:** Total permanent discontinuation; **PD-AE:** Permanent discontinuation due to AEs; **PD-MS:** Permanent discontinuation due to muscle-related symptoms; **HTN:** Hypertension; **NR:** Not reported; **a:** Hydrophilic; **b:** Lipophilic; **c:** Patients with the history of angina were excluded; **d:** Median.

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