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MODERATE INTENSITY STATIN THERAPY DOES NOT INCREASE ADVERSE MUSCLE EVENTS: A NETWORK META-ANALYSIS OF 153,000 PATIENTS

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MODERATE INTENSITY STATIN THERAPY DOES NOT INCREASE ADVERSE MUSCLE EVENTS: A NETWORK META-ANALYSIS OF 153,000 PATIENTS

Ву

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ABSTRACT

Objective: To estimate relative risk of statin-associated musculoskeletal symptoms (SAMS) by statin therapy intensity.

Participants: Pubmed, Web of Science, Cochrane database, and clinicaltrials.gov were searched from January 1, 2010 - October 1, 2018 for doubled-blinded RCTs testing the effect of statin therapy on lipids with at least 1000 participants and two years of intended treatment. Two coders assessed articles for inclusion. Statin therapy was categorized

Setting: Network meta-analysis assessing multi-center RCTs across several countries.

by treatment intensity (placebo, moderate, high).

Outcomes: Pairwise and network meta-analysis (NMA) estimated relative risk (RR) and risk difference (RD) with random effects modeling. Heterogeneity was evaluated with the I² statistic. Outcomes included muscle symptoms (any, myalgia, and attrition due to muscle symptoms), rhabdomyolysis, and elevated creatine kinase (>10x upper limit of normal).

Results: Of 2801 RCTs, 24 (N=152,461) met inclusion criteria. NMA results indicated risk was significantly greater for high compared to moderate intensity statin therapy for any muscle problem (RR=1.04, 95% CI: 1.00,1.07; I²=0%), myalgia (RR=1.04, 95% CI: 1.00,1.08; I²=0%, NNH=173), attrition due to muscle problems (RR=1.37, 95% CI: 1.09,1.73, I²=0%, NNH=218), and elevated CK (RR=4.69, CI: 2.50, 8.80; I²=7%, NNH=527). Risk also was significantly higher for high intensity compared to placebo for any muscle problem (RR=1.05, 95% CI: 1.01,1.09, I²=0%), myalgia (RR=1.13, 95% CI: 1.05,1.23; I²=0%, NNH=182), attrition due to muscle problems (RR=1.55, 95% CI: 1.15,2.08, I²=0%, NNH=187), and elevated CK (RR=5.37, CI: 2.48, 11.61; I²=7%,

NNH=589). Due to inconsistency of results across sensitivity analyses, estimates were inconclusive for rhabdomyolysis and CK. There were no significant differences in risk between moderate intensity therapy and placebo for all outcomes.

Conclusions: For each 200 patients on high intensity statins, one additional patient may experience SAMS or discontinue due to SAMS. Moderate intensity statins did not cause significant increases in SAMS.

Trial Registration: Prospero #CRD42019112758

Article Summary:

Strengths

- High-quality, large RCTs analyzed with low risk of heterogeneity bias
- Novel use of network meta-analysis to compare treatment intensities allows for large analysis of dose-dependent effect
- Rigorous coding of outcome terms allows for more granular investigation of outcome

Weaknesses

- Study-level data precludes meta-analysis with regression for relevant covariables affecting risk of outcome
- Heterogeneity of terms across trials prevented analysis of full trial set for each outcome.

Key Words: Statins, myalgia, nocebo, rhabdomyolysis, network meta-analysis

Abbreviations:

Network Meta-Analysis (NMA) and pair-wise meta-analysis (MA), Risk Ratio (RR), Risk Difference (RD), Cholesterol Treatment Trialists' Collaboration (CTT), Statin Associated Muscle Symptoms (SAMS), Creatine Kinase (CK) & Upper Limit of Normal (ULN), End Stage Renal Disease (ESRD), Number Needed to Harm (NNH), Hazard Ratio (HR)



INTRODUCTION

The Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis on patient-level data from large RCTs demonstrated that statin therapy is efficacious in reducing major vascular events. 1,2 Statin therapy is now prominent in cholesterol management guidelines. 3-8 Statin-associated muscle symptoms (SAMS), however, may lead to nonadherence or discontinuation with therapy and ultimately to poorer cardiovascular outcomes. Most RCTs have shown small, insignificant increases in risk for SAMS, although patients taking statins may complain of muscle problems and may discontinue therapy due to muscle problems.³ For example, a 2016 meta-analysis found a nonsignificant increase in myopathy. However, it did not report on the more mundane myalgias that often cause statin attrition.³ These milder symptoms are the major public health concern, as statin non-adherence can lead to significant increases in risk of major adverse cardiovascular events.³ Observational studies suggest that these mild SAMS may occur as often as 7-29% of patients. One review suggested that clinical observations of increased muscle problems with statin therapy may be due to patient expectations.

SAMS also may be more likely with higher intensity therapy. Although this is assumed to be true, especially with the evidence against simvastatin 80 mg,^{10,11} few RCTs have examined high intensity therapy^{12,13}. This study used a network meta-analysis (NMA) to combine evidence across trials to estimate the risk of SAMS by treatment intensity. In contrast to pair-wise meta-analysis (MA) that directly estimates causal effects, a NMA can indirectly estimate risk between placebo and moderate, moderate and high, and

between placebo and high intensity treatment – even though placebo, moderate, and high intensity treatment levels were not compared within a single trial. Results contribute to the debate about whether muscle adverse events are due solely to patient expectations or whether statins might have an independent effect on symptoms. Finally, this study contributes to the ongoing debate as to whether statins cause myalgias and attrition due to muscle problems without marked creatine kinase (CK) elevations.

METHODS

The Trials. PubMed, Cochrane Database, Web of Science, and clinicaltrials.gov were searched (Prospero #CRD42019112758 for search terms and strategy) from January 1, 2010 to October 1, 2018 to identify eligible trials. Double-blinded RCTs to improve lipid levels that comparing statin therapy to placebo or higher-lower dose statin therapy were selected. In order to detect most adverse events, RCTs were selected that had at least 1,000 participants with two years of intended follow-up, where statin treatment was not given with other prescription drug therapies, and results contained reports on muscle-related adverse events. All included trials were coded for quality with Oxford Center for Evidence-based Medicine ratings¹⁴ and a five-point Jadad quality score.

Exposure Variable. Studies were classified by intensity of statin treatment ("high" or "moderate") according to American Heart Association definitions for potency in reduction of lipid levels. High intensity signifies an expected 50% or greater reduction in LDL-C levels when taking that statin (i.e., 80 mg atorvastatin) and moderate signifies 30-50% reduction in LDL-C. 15

Outcome Variables. Adverse muscle-related events were coded into five main outcomes. The first outcome was for any patient-reported muscle complaint coded from reports of "muscle aches", "pains", "cramps", "stiffness," "musculoskeletal disorders," etc. The second focused on only myalgia or muscle pain. The third focused on attrition due to musculoskeletal complaints. A fourth captured explicit reporting of rhabdomyolysis, with or without a trial definition. The fifth was elevated creatine kinase, greater than ten times the upper limit of normal (CK >10x ULN). This threshold was used to distinguish this outcome from less meaningful CK increases and also because CK>10xULN is commonly reported in RCTs. All outcomes were coded as reported by original investigators in published and online reports, and were independently coded by two people (JD, SW). Trial investigators were contacted for clarification, where needed.

Analysis. Published aggregate data from each trial were used. A crude estimate of incidence was calculated from the total number of cases observed divided by the total person-years (using the median or mean follow-up time for each study) and a chi square test was used to test for homogeneity in the proportion of incident cases across studies, within each arm, although these crude estimates ignored randomization. To facilitate interpretation and comparison of results to the original trials, risk of adverse effects was estimated with pooled relative risk (RR, random effects). A 0.50 continuity correction was added to aggregate frequencies for trials that observed zero cases of an outcome in either treatment arm. A pairwise meta analysis (MA) was used to estimate the RR (Mantel-Haenszel method) for causal effects of statins within treatment intensity

subgroups from direct (head-head comparison) trials. ^{16,17} Because aggregations across studies are only meaningfully interpreted when results are consistent across studies, heterogeneity among RCTs was assessed with an index of consistency across trials (I², Q)^{18,19} and funnel plots. When I² ≤25%, results are considered to be at low risk of bias due to heterogeneity; high values (>75%) indicate high risk of bias due to heterogeneity. ^{18,19} Residual I² represents the heterogeneity remaining after accounting for sub-groups of treatment intensity. Cochrane Q (a sub-component of I²) indicates the probability that the observed heterogeneity is due to chance. Sensitivity analyses included omitting outliers identified in funnel plots and using a 0.10 as a "continuity correction".

A network meta-analysis (NMA)²⁰ used *all* available pairs of comparisons for each outcome to estimate increased risk between placebo and moderate intensity, between moderate and high intensity therapy, and between placebo and high intensity. The RR was used to estimate effect size (frequentist, inverse variance method), so that results would be comparable across original studies and the pairwise meta-analysis above. In contrast to a MA which provides a direct estimate of causal effects, a NMA provides indirect estimates or measures of association. A ratio test was used to test for consistency between NMA and MA estimates.²¹ Heterogeneity was assessed with and I² and Q statistics.^{18,19} Number needed to harm (NNH) was estimated when the pooled RR was significantly greater than 1.0 and the pooled absolute risk reduction (risk difference, RD) was significantly greater than 0.0.

Patient and Public Involvement

Patients were not involved in design or implementation of this study.

RESULTS

Searches yielded 134 relevant reviews, including 2801 RCTs that reduced to 24 unique RCTs that met eligibility requirements (eFigure 1). Of the 24 RCTs: 17 were placebomoderate intensity comparisons. 22-42 3 were placebo-high intensity comparisons. 43-45 and 4 were moderate-high intensity comparisons^{10–13} (Table 1). The active blood pressure treatment arm of the HOPE trial³⁵ was excluded, but the statin only and placebo only arms were retained, allowing for a statin and placebo comparison. Two trials compared moderate and high intensity therapy using 80 mg/day of simvastatin. 10,11 All 24 RCTs scored the highest quality (1) on the Oxford rating and on the Jadad scale 18 scored 5/5 and 6 scored 4/5 (missing detail on random assignment). The RCTs included heterogenous patient populations, e.g., healthy middle-aged adults^{24,35,41,44} to ESRD patients. Sample sizes ranged from 1,255²² to 20,536³⁸ with follow-up periods from 1.9⁴⁴ to 6.7¹⁰ years. Of the 24 RCTs, six were included in the 2006 metaanalysis,⁴⁶ 17 in the 2014 systematic review,⁴⁷ 23 in the 2016 meta-analysis,³ and 18 in the 2013 NMA.⁴⁸ None of the previous analyses separated trials into sub-groups by treatment intensity. Crude estimates of incidence increased with intensity of treatment from placebo to moderate intensity to high intensity therapy, but with heterogeneity across trials (eTable 1).

Any Muscle Symptoms. Twenty-three trials reported some type of muscle symptom^{10,13,23–27,29,33,37,38,44,45} myositis,³² myalgia,^{12,22,28,30,31,40,43} myopathy,^{22,36} or discontinuation due to muscle-related symptoms.^{11,13,34} The pairwise meta-analysis pooled across subsets of trials indicated consistent trial results with non-significant

increases in risk for any muscle problem (Figure 1) between placebo and moderate intensity therapy and between placebo and high intensity therapy, but a significant increase between moderate and high intensity therapy (RR=1.05, CI: 1.01, 1.09; 4 RCTs, N=30,720; I²=0%). Sensitivity analyses indicated that results were essentially unchanged without an outlier²⁸ identified on the funnel plot, with a 0.10 correction, or without the simvastatin 80 mg trials. (eFigures 2-9).

The NMA pooled direct and indirect evidence from all 23 trials and suggested increased risk with higher intensity therapy. Results indicated a non-significant 1% increase in risk between placebo and moderate intensity therapy (Table 2), a significant 4% increase between moderate and high intensity therapy, and a significant 5% increase between placebo and high intensity therapy. Results were homogeneous across studies (I²=0%; Q, p=0.54) and closely paralled causal effect sizes estimated in the pairwise metanalysis (p=0.48). Pooled RDs between pairs of treatment groups were not significantly different from zero. Inclusion of the two simvastatin 80mg trials did not meaningfully change risk, but comparisons with high intensity were statistically significant, likely due to the increased sample size (eTable 2).

Myalgia or pain. Thirteen RCTs reported cases of myalgia, ^{23,27–30,40,42–45} attrition due to myalgia, ^{24,26} or pain and/or weakness. ³⁸ The pairwise meta-analysis indicated (Figure 2) non-significant increases in myalgia between placebo and moderate intensity and between placebo and high intensity, but a significant increase between moderate and high intensity (RR=1.04, 95% CI: 1.00;1.09, 2 RCT, n=22065; I²=0%). The three trials comparing placebo and high intensity therapies suggested moderate heterogeneity in

results (I²=45%). Funnel plots did not suggest bias by any of the studies and there were no zero cells (Figures 10-11). Inclusion of the simvastatin 80 mg trial did not meaningfully change the magnitude of risk, although results were significant for high intensity compared to moderate intensity therapy possibly due to increased sample size (eFigures 12-13).

The NMA results combining direct and indirect evidence for all 13 trials suggested a significant increase in myalgia with increased therapy intensity (Table 2). There was a non-significant 9% increase in risk between placebo and moderate intensity therapy, a significant 4% increase between moderate and high intensity therapy, and a 13% significant increase in risk for high intensity therapy compared to placebo without heterogeneity. Results were homogeneous across studies (I²=0%, Q, p=0.48) and were similar to those from the direct meta-analysis (p=0.63). The pooled RD was significant between high and moderate intensity (NNH=173) and between high intensity and placebo (NNH=154) with low heterogeneity (I²=20%; Q, p=0.25). Inclusion of the simvastatin 80 mg trial did not change the magnitude of risk although results were significant for high intensity compared to moderate intensity therapy (eTable 2).

Attrition. Attrition due to muscle problems was reported by eight RCTs that compared moderate intensity statin therapy with placebo, ^{23,24,26,30,34–36,38,42} three that compared moderate with high intensity therapy, ^{10,11,13} and none that directly compared high intensity to placebo. In the pairwise meta-analysis (Figure 3), patients on moderate intensity statin therapy had a non-significant increase in attrition due to muscle

problems compared to placebo. Patients on high intensity therapy had a 38% significantly higher attrition rate than those on moderate intensity (RR=1.38, 95% CI: 1.04, 1.82; 3 RCTs, N=20,719) with moderate heterogeneity across trials (I²=31%). Funnel plots did not suggest bias and there were no zero cells. Exclusion of the two simvastatin 80 mg trials left only one moderate-high intensity comparison RCT (eFigures 14-17).

The NMA results for the 11 trials suggested that risk for attrition increased with intensity of therapy. There was a non-significant 13% increase in risk between placebo and moderate intensity therapy (Table 2), a 37% significant increase in risk between moderate and high intensity, and a 55% significant increase in risk between placebo and high intensity therapy. Results were homogenous across studies (I²=0%; Q p=0.72) and closely paralled causal estimates provided by the meta-analysis, but the NMA provided an estimate for the placebo-high intensity comparison for which there were no head-to-head trials. The pooled RD between moderate and high intensity therapy was significant and the NNH was 218. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 186. Exclusion of the two simvastatin 80 mg trials resulted in lower, non-significant risk increases between moderate and high intensity therapy and between placebo and high intensity (eTable 2).

Rhabdomyolysis. Rhabdomyolysis was reported on by 14 moderate intensity-placebo comparison RCTs, ^{22–26,28–30,33,34,37–40} four moderate-high intensity comparison RCTs, ^{10–}

¹³ and three high intensity-placebo comparison RCTs.^{43–45} Incidence of rhabdomyolysis was very low and statistical comparisons were not conclusive.

Pairwise meta-analysis indicated non-significant increases in rhabdomyolysis incidence between placebo and moderate intensity therapy, between moderate and high intensity, and between placebo and high intensity therapy (Figure 4). Results were were inconclusive as they were not robust across sensitivity analyses. Approximately half (22/42) of the cells were zeros and RR increased for moderate-high intensity comparison with a smaller correction (eFigures 15-18) and removal of the simvastatin 80 mg trials meaningfully changed estimates (eFigues 19-20).

NMA results indicated increased risk for rhabdomyolysis with increased intensity of therapy, although the results were not statistically significant (Table 2). There was a non-significant 22% increase in risk between placebo and moderate intensity therapy, a non-significant 33% increase between moderate and high intensity, and a non-significant 62% increase between placebo and high intensity therapy with consistency across trials (I²=0%, Q p=0.99). Results remained non-significant after exclusion of simvastatin 80 mg trials (eTable 2), but suggested an increased RR for the placebo-moderate intensity therapy and decreased risk for moderate-high and placebo-high intensity comparisons. The NMA RR estimates based on all 21 trials were not significantly different from MA estimates based on estimates from the subsets of studies (p=0.31).

Elevated CK. Of 16 RCTs, 11 compared rates of elevated creatine kinase (CK>10xULN) between placebo and moderate intensity therapy, ^{22–25,30,33,34,37–41} three compared moderate to high intensity therapy^{10–12} and two compared high intensity therapy with placebo. ^{43,45} Incidence of elevated CK was low. Pairwise meta-analysis indicated (Figure 5) non-significant increases in CK elevation between placebo and moderate intensity therapy and between placebo and high intensity therapy. High intensity therapy caused a 388% significantly higher risk for elevated CK compared to moderate intensity therapy (RR=3.88, 95% CI: 1.05,14.31, 3 RCTs, n=26,558) with some heterogeneity among the three trials (I²=50%). Estimates were not stable across sensitivity analyses. Removal of two possible outliers^{10,24} (eFigures 21-24), adjustment for cells with zeros (9/32) (eFigures 25-26), and exclusion of simvastatin 80 mg trials meaningfully changed pooled RR estimates (eFigures 27,28).

Using evidence from all 16 trials, the NMA estimates indicated increased risk with increased intensity. NMA results indicated a non-significant 14% increase between placebo and moderate intensity therapy (Table 2), a significant 459% increase in CK elevation between moderate and high intensity, and 525% significant increase between placebo and high intensity with consistency across trials (I²=7%, Q p=0.37). The NMA RR estimates based on all 16 trials were not significantly different from MA estimates (p=0.57). The pooled RD between moderate and high intensity therapy was significant and the NNH was 527. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 589. Although results were homogeneous with the simvastatin 80 mg trials, exclusion of these trials meaningfully reduced risk associated

with statin therapy between moderate and high intensity and between placebo and high intensity therapy (eTable 2).

DISCUSSION

A novel contribution of this study was the application of NMA to estimate the doseresponse effect of statin therapy on muscle symptoms using clinically-meaningful categories of treatment intensity. The NMA estimates of RR closely paralleled the direct, causal estimates indicating reliability of estimates and increased risk with high intensity statin therapy. For patient-reported symptoms, there were nonsignificant increases in SAMS between placebo and moderate intensity therapy and significant increases between moderate and high intensity therapy. Because simvastatin 80mg therapy is now restricted because of muscle injury, ⁴⁹ analyses also were run with and without those trials. This did not meaningfully affect results for patient-reported outcomes. Rhabdomyolysis and elevated CK also showed increased risk with higher intensity, but because of low incidence (with 25-50% zero cells), possible outliers, and inconsistency with and without the simvastatin 80 mg trials, results were inconclusive.

Double-blinded RCTs and traditional meta-analyses^{3,46,47} suggest no significant increase in risk of muscle adverse events with statin therapy. Since most evidence comes from moderate intensity trials, possible adverse effects of high intensity therapy may be masked in aggregate estimates. Similarly, aggregation of heterogeneous outcomes and estimate for outcomes (e.g., myopathy) not explicitly reported by investigators could also mask an effect. In this study, high intensity therapy and focused

definitions of patient-reported muscle problems detected higher risk. However, the absolute excess of SAMS was less than 1% for all outcomes. In previous meta-analyses, absolute excess of muscle problems also was small, but non-significant.^{3,47} The 2016 meta-analysis estimated risk for extreme outcomes (myopathy and rhabdomyolysis), but did not analyze patient reports of milder SAMS that we present and that concern patients.

Dose-response analyses in individual RCTs, e.g., the TNT trial¹² comparing atorvastatin 10 mg to 80 mg and the SEARCH trial¹⁰ comparing simvastatin 20 mg to 80 mg, and an NMA that compared dosage increments within brands⁴⁸ suggested no systematic increase in risk for myalgia or CK with higher dosages. These negative findings may have been due to smaller sample sizes, smaller dosage increments in restricted comparisons, or exclusion of the simvastatin 80 mg trials.⁴⁸ In this study, results were homogeneous including the simvastatin 80mg trials, and indicated high intensity therapy significantly increased myalgia compared to placebo even after their exclusion. The previous NMA identified a dose-response relationship between statin dose and mildly elevated CK (2-3x ULN), but only for lovastatin and simvastatin.⁴⁸ CK>10xULN may be more interpretable than modest elevations, and in this study was significantly increased in high-intensity statin analyses. While removal of 80mg simvastatin trials had little effect on patient-reported symptoms, their exclusion resulted in smaller non-significant increases in risk for elevated CK. It is unclear if simvastatin 80mg was responsible for the significant increases in CK.

A practical question concerns how large an excess of cases might be observed with statin therapy for myalgia/pain, attrition due to muscle problems, and elevated CK or rhabdomyolysis. Although estimates based on observational studies suggest that incidence of mild SAMS might be as high as 30% among statin users,⁵⁰ RCTs suggest a much lower rate. In this study, pooled risk estimates suggested that for each 173 patients on high intensity therapy one additional patient will experience statin-caused myalgia compared to moderate intensity therapy. Results also indicated that for each 200 patient on high-intensity statins, one additional patient will discontinue therapy due to muscle problems. This represents numerous patients who are at greatest risk for major vascular events, as these are often higher risk patients. Discontinuation of statins in the elderly (>75 yrs) may result in 33% increased risk of a cardiovascular event within 3 months ⁵¹ and adherence to statins in those 65 and older may reduce mortality by a third.⁵²

Myalgias and attrition due to SAMS are important outcomes for the average patient, but have not received as much attention as rhabdomyolysis and myopathy. This study provides evidence that while blinded, moderate intensity statin-takers did not report significantly more general muscle problems or myalgias, but those on high intensity therapy did. Because many myalgia cases occurred without CK elevation increases, this also serves as evidence that SAMS occur in the absence of large elevations in CK. Clinicians with patients who are "statin intolerant" may consider decreasing intensity of statin therapy, rather than discontinuing it, in light of these findings.

This analysis also contributes to the "nocebo" debate. A large, unblinded follow-up of RCT patients suggested SAMS are expectation-related.²⁷ They observed an incidence of 2.02% and 2.00% muscle-related adverse events in statin and placebo groups, respectively, when double-blinded (HR=1.03) and 1.26% and 1.00% in the statin and usual care groups when unblinded (HR=1.41).²⁷ Both comparisons indicate absolute differences less than 1%. Thus, both nocebo and causal effects are small, although they have moderate relative increases with statin therapy. SAMS with moderate intensity therapy may be the result of patient expectations, but with high intensity therapy SAMS may be due to expectations and statin therapy. SAMS are also linked to CP450 drugdrug interactions.^{53,54}

A limitation of study-level meta-analyses is that definitions, assessment, and variable reporting of muscle-related outcomes differ across studies. Protocol differences likely resulted disparate incidence across studies. Estimates in this analysis may have underestimated SAMS by excluding patients with statin hypersensitivity, as four studies 12,35,38,43 (n=48,950) employed statin "washout" phases and eight trials 22,23,28,30,32–35,45 (n=34,042) excluded patients with known statin hypersensitivity. Collins et al. noted that "statin hypersensitivity" exclusion was a rare occurrence across these trials, as almost all patients enrolled were statin-naïve at screening. The risk of attrition due to SAMS and rhabdomyolysis was actually highest in SEARCH, where an eight week long, active run-in phase was conducted, 3,10 although no patients were excluded for elevated muscle enzymes. Further, adverse events may have been increased due to the

Conclusion

Statins likely cause SAMS, but at much lower rates than observational data suggest. We found significant increases in risk for patient-reported muscle problems on highintensity statins. Clinically-reported SAMS likely represent a combination of expectation effects, with or . bias and true adverse effects, with or without CK elevations.

Contributorship Statement:

The first author (JD) was responsible for the design and implementation of the study analyses. He was one coder in selecting studies for inclusion, compiled the data for the outcomes of interest, analyzed the data in R, and is responsible for the final manuscript in its entirety. SW (Faculty PI) was responsible for the oversight and implementation of the project. She was the second coder for all trials and offered guidance and support in all decisions regarding design and implementation of the analysis.

Competing Interests:

None to disclose

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Data Sharing Statement:

All original data is available upon request from the corresponding author, and will be made publicly available on Dryad repository.

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TABLE 1: DESCRIPTION OF THE TRIALS

| | Total sample | Special | Permit Prior | Ave | Run-in Period | Median Yrs F/U | |
|-------------------------------|--------------|-------------------|-----------------|-----|------------------|-------------------|--|
| Trial Name | size | Population | statin† | age | | | |
| | | • | | | | | |
| Placebo-Moderate | | | | | | | |
| 4D, A20 ²² | 1,255 | DM II, ESRD | Y, -HS | 66 | Placebo | 4.0 | |
| 4S, S20-S40 ²³ | 4,444 | MI or angina | Y, -HS | 59 | Placebo | 5.4 | |
| AFCAPS, L20-L40 ²⁴ | 6,605 | Healthy adults | N | 58 | Placebo+diet | 5.2 | |
| ALERT, F40-F80 ²⁵ | 2,094 | Renal Trans | N | 50 | None | 5.4 | |
| ASCOT, A10 ^{26,27} | 10,810 | HTN+CVD risk | N | 63 | Not statin | 3.3 | |
| ASPEN, A10 ²⁸ | 2,410 | DM II | Y, -HS | 61 | Placebo | 4.0 | |
| AURORA, R10 ²⁹ | 2,767 | ESRD | N | 64 | Placebo | 3.2 | |
| CARDS, A1030,31 | 2,838 | DM II | Y, -HS | 62 | Placebo | 4.0 | |
| CARE, P4032 | 4,159 | MI | Y, -HS | 59 | Placebo | 5.0 | |
| CORONA, R10 ³³ | 5,011 | ESRD | Y, -HS | 73 | Placebo | 2.7 | |
| GISSI-HF, R10 ³⁴ | 4,574 CHF | | Y, -HS | 68 | None | 3.9 | |
| , | 6,349 | Healthy, CVD | Y, -HS | 66 | Statin | 5.6 | |
| HOPE-3, R1035 | | Risk | , - | | | | |
| LIPID, P40 ³⁶ | 9,014 | MI or angina | Υ | 62* | Placebo+diet | 6.0 (mean) | |
| , | 1,640 | Coronary percut. | Υ | 60 | None | 3.9 | |
| LIPS, F80 ³⁷ | | intervention | | | | | |
| MRC/BHF (HPS), | 20,536 | | N | 64 | Placebo, | 5 (mean) | |
| S40 ^{38,39} | | CHD/CHD Risk | | | then statin | , , | |
| PROSPER, P40 ⁴⁰ | 5,804 | Elderly, CHD risk | Υ | 75 | Placebo | 3.2 (mean) | |
| WOSCOPS, P4041,42 | 6,604 | Healthy males | Υ | 55 | None | 4.9 (mean) | |
| · | | | | | | | |
| Placebo-High | | | | | | | |
| JUPITER, R2044 | 17,802 | Healthy adults | N | 66 | Placebo | 1.9 | |
| SPARCL, A80 ⁴³ | 4,731 | CVA/TIA | Υ | 63 | None | 4.9 | |
| TRACE, A40 ⁴⁵ | 3,002 | RA | N, -HS | 61 | None | 2.5 | |
| | | | | | | | |
| Moderate-High | | | | | | | |
| A to Z, S40-S80 vs 0- | | Acute Coronary | N | 61 | None | 1.98 | |
| S20 ¹¹ | 4,497 | Syndrome | | | | | |
| PROVE-IT, A80 vs | | Acute Coronary | Y, if | 58 | None | 2.0 (mean) | |
| P40 ¹³ | 4,162 | Syndrome | <80mg | | | | |
| SEARCH, S80 vs | | | Υ | 64 | Statin+ | 6.7 | |
| S20 ¹⁰ | 12,064 | MI | | | Placebo | | |
| TNT, A80 vs A10 ¹² | 10,001 | CHD | Υ | 61 | Statin | 4.9 | |

^{*}Median

[†]Y=Yes, N=No, -HS=statin hypersensitivity exclusion

TABLE 2: RELATIVE RISK AND RISK DIFFERENCE RESULTS FOR COMPARISONS OF TREATMENT INTENSITY PAIRS

| | Placebo – Moderate | | | Moderate – High Intensity | | | Placebo – High | | |
|--------------|-------------------------|----------------------------------|---------|---------------------------|---------------------------------|---------|--------------------------|---|---------|
| Outcom | Intensity RR (95% | RD (95% CI) | NN H | RR (95% | RD (95% CI) | NN H | RR (95% CI) | RD (95% | NN H |
| | ČI) | , | | ČI) | , , | | , | ČI) | |
| Any Probs | 1.01 (0.99,1. 03) | 0.000 (- 0.001,0.0 01) | | 1.04 (1.00,1. 07) | 0.004 (- 0.000,0.0 08) | | 1.05 (1.01, 1.09) | 0.00 4 (- 0.00 1, 0.00 8) | |
| Myalgia | 1.09 (0.99,1. 19) | 0.001 (- 0.000,0.0 01) | <u></u> | 1.04 (1.00- 1.08) | 0.006 (0.001, 0.010) | 173 | 1.13 (1.05- 1.23) | 0.00 7 (0.00 2, 0.01 1) | 182 |
| Attrition | 1.13 (0.93,1. 36) | 0.001 (- 000,0.00 1) | -() | 1.37 (1.09,1. 73) | 0.005 (0.002, 0.007) | 218 | 1.55 (1.15,2.0 8) | 0.00 5 (0.00 2, 0.00 8) | 187 |
| Rhabdo. | 1.22 (0.62,2. 40) | -0.000 (- 0.001,0.0 01) | | 1.33 (0.49,3. 61) | 0.002 (0.001,0.0 03) | | 1.62 (0.58,4.5 5) | 0.00 2 (0.00 0, 0.00 3) | |
| CK>10U LN | 1.14 (0.71,1. 85) | -0.000 (- 0.001,0.0 01) | | 4.69 (2.50, 8.80) | 0.002 (0.001, 0.003) | 527 | 5.37 (2.48,11. 61) | 0.00 2 (0.00 0, 0.00 3] | 589 |

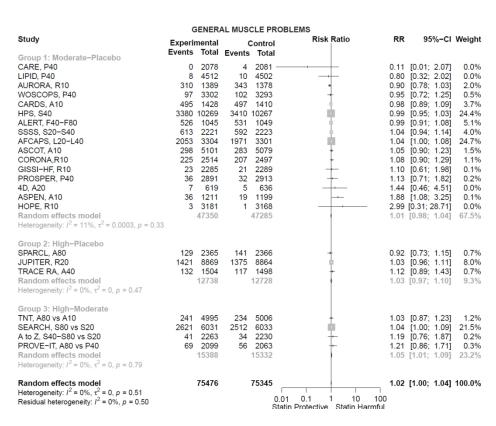


Figure 1

MYALGIA

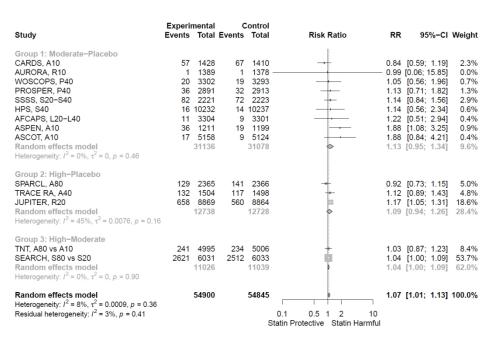


Figure 2

ATTRITION DUE TO MUSCLE SYMPTOMS

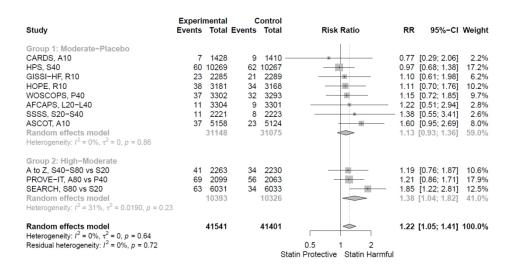


Figure 3

RHABDOMYOLYSIS

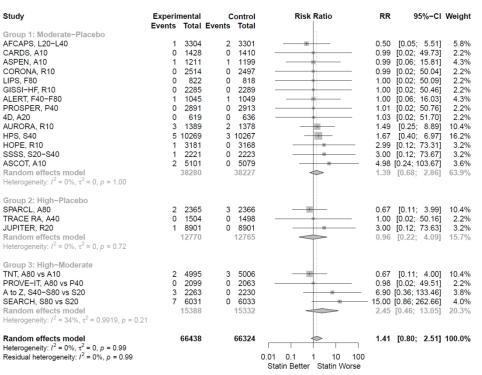


Figure 4

CK >10xULN

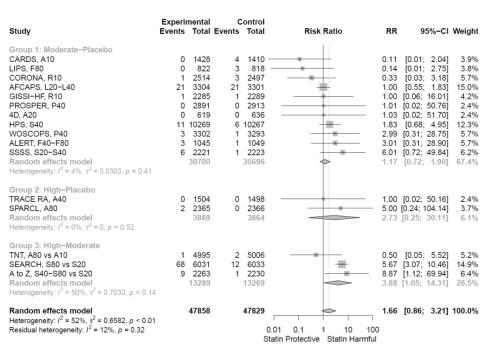


Figure 5

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eFigure 29 – CK > 10xULN. Continuity Correction = 0.1. Funnel plot.

eFigure 30 - CK > 10xULN. Exclusions of studies testing simvastatin 80 mg. Forest plot.

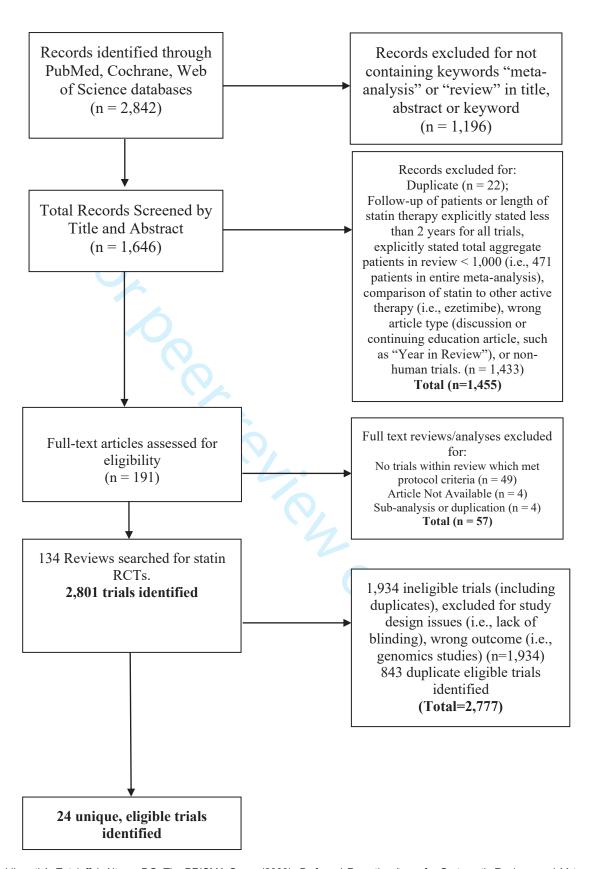
eFigure 31 - CK > 10xULN. Exclusions of studies testing simvastatin 80 mg. Funnel plot.

eTable 1 - Crude Incidence Rate Summary

eTable 2 - Network Meta-Analysis Results, Risk Ratio and Risk Difference summary with Number

Needed to Harm. Sensitivity analysis with exclusion of simvastatin 80 mg studies.

eFigure 1: PRISMA Flow Sheet



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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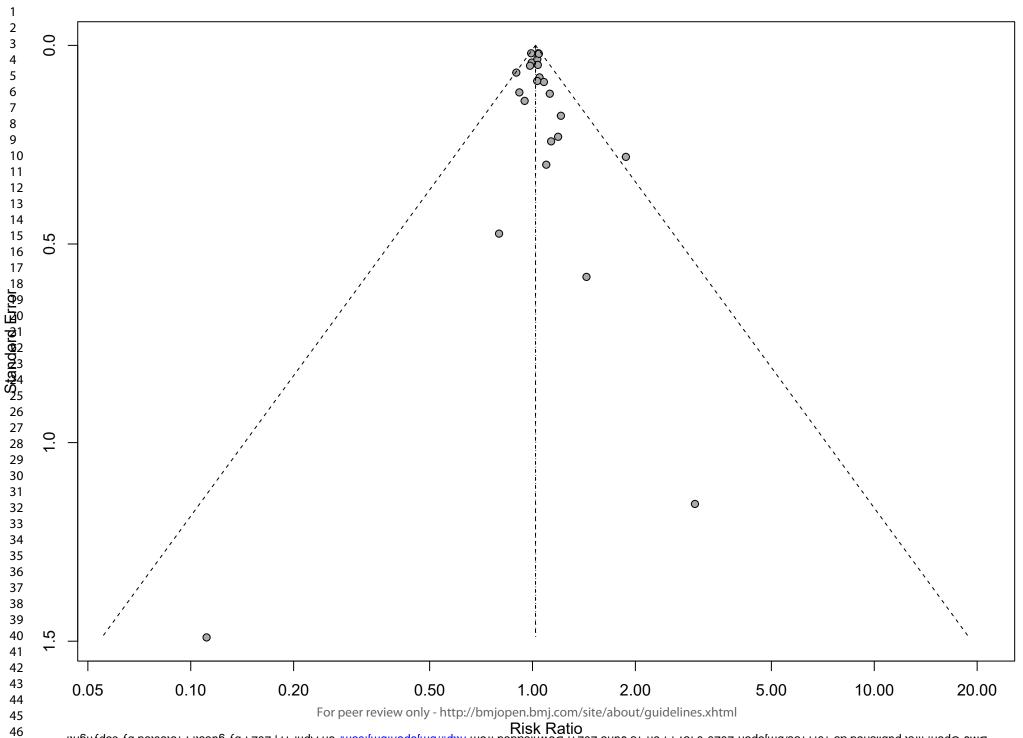
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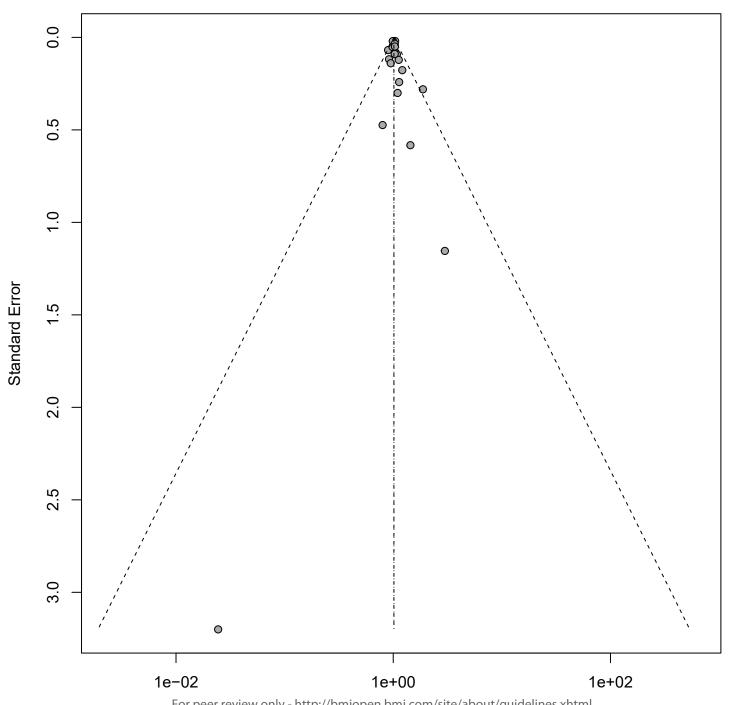
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| Study | Experi | mental | C | ontrol | Risk Ratio | RR | 95 | %-CI | Weight |
|---|---------------|--------|---------------|--------|------------------|------|----------|--------|--------|
| | Events | Total | Events | Total | | | | | |
| Group 1: Moderate-Placebo | | | | | | | | | |
| CARE, P40 | 0 | 2078 | 4 | 2081 | | 0.02 | [0.00; 1 | 12.94] | 0.0% |
| LIPID, P40 | 8 | 4512 | 10 | 4502 | - | 0.80 | [0.32; | 2.02] | 0.1% |
| AURORA, R10 | 310 | 1389 | 343 | 1378 | d | 0.90 | [0.78; | 1.03] | 2.6% |
| WOSCOPS, P40 | 97 | 3302 | 102 | 3293 | + | 0.95 | [0.72; | 1.25] | 0.6% |
| CARDS, A10 | 495 | 1428 | 497 | 1410 | ģ. | 0.98 | [0.89; | 1.09] | 4.7% |
| HPS, S40 | 3380 | 10269 | 3410 | 10267 | | 0.99 | [0.95; | 1.03] | 31.1% |
| ALERT, F40-F80 | 526 | 1045 | 531 | 1049 | ψ | 0.99 | [0.91; | 1.08] | 6.6% |
| SSSS, S20-S40 | 613 | 2221 | 592 | 2223 | ģ | 1.04 | [0.94; | 1.14] | 5.1% |
| AFCAPS, L20-L40 | 2053 | 3304 | 1971 | 3301 | | 1.04 | [1.00; | 1.08] | 31.6% |
| ASCOT, A10 | 298 | 5101 | 283 | 5079 | ķ | 1.05 | [0.90; | 1.23] | 1.9% |
| CORONA,R10 | 225 | 2514 | 207 | 2497 | } | 1.08 | [0.90; | 1.29] | 1.4% |
| GISSI-HF, R10 | 23 | 2285 | 21 | 2289 | + | 1.10 | [0.61; | 1.98] | 0.1% |
| PROSPER, P40 | 36 | 2891 | 32 | 2913 | + | 1.13 | [0.71; | 1.82] | 0.2% |
| 4D, A20 | 7 | 619 | 5 | 636 | +- | 1.44 | [0.46; | 4.51] | 0.0% |
| ASPEN, A10 | 36 | 1211 | 19 | 1199 | + | 1.88 | [1.08; | 3.25] | 0.2% |
| HOPE, R10 | 3 | 3181 | 1 | 3168 | • | 2.99 | [0.31; 2 | 28.71] | 0.0% |
| Random effects model | | 47350 | | 47285 | | 1.01 | [0.98; | 1.04] | 86.2% |
| Heterogeneity: $I^2 = 6\%$, $\tau^2 = 0.0002$, $p = 0.39$ | | | | | \mathbf{e}_{i} | | | | |
| | | | | | · U, | | | | |
| Group 2: High-Placebo | | | | | | | | | |
| SPARCL, A80 | 129 | 2365 | 141 | 2366 | O_{\bullet} | 0.92 | [0.73; | 1.15] | 0.9% |
| JUPITER, R20 | 1421 | 8869 | 1375 | 8864 | Ţ. | | [0.96; | - | 10.2% |
| TRACE RA, A40 | 132 | 1504 | 117 | 1498 | †// | 1.12 | [0.89; | 1.43] | 0.8% |
| Random effects model | | 12738 | | 12728 | | 1.03 | [0.97; | 1.10] | 11.9% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.47$ | | | | | | | | | |
| Group 3: High-Moderate | | | | | | | | | |
| TNT, A80 vs A10 | 241 | | | 5006 | † | | [0.87; | _ | 1.5% |
| PROVE-IT, A80 vs P40 | 69 | 2099 | 56 | 2063 | † | | [0.86; | - | 0.4% |
| Random effects model | | 7094 | | 7069 | þ | 1.07 | [0.91; | 1.25] | 1.9% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.42$ | | | | | | | | | |
| Random effects model | | 67182 | | 67082 | | 1.02 | [0.99; | 1.04] | 100.0% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.55$ | | | | | | | | | |

BMJ Open eFigure 3 (continued) - Traditional Meta-Analysis, General Muscle Problems. **Sensitivity Analysis, Continuity Correction = 0.1.**



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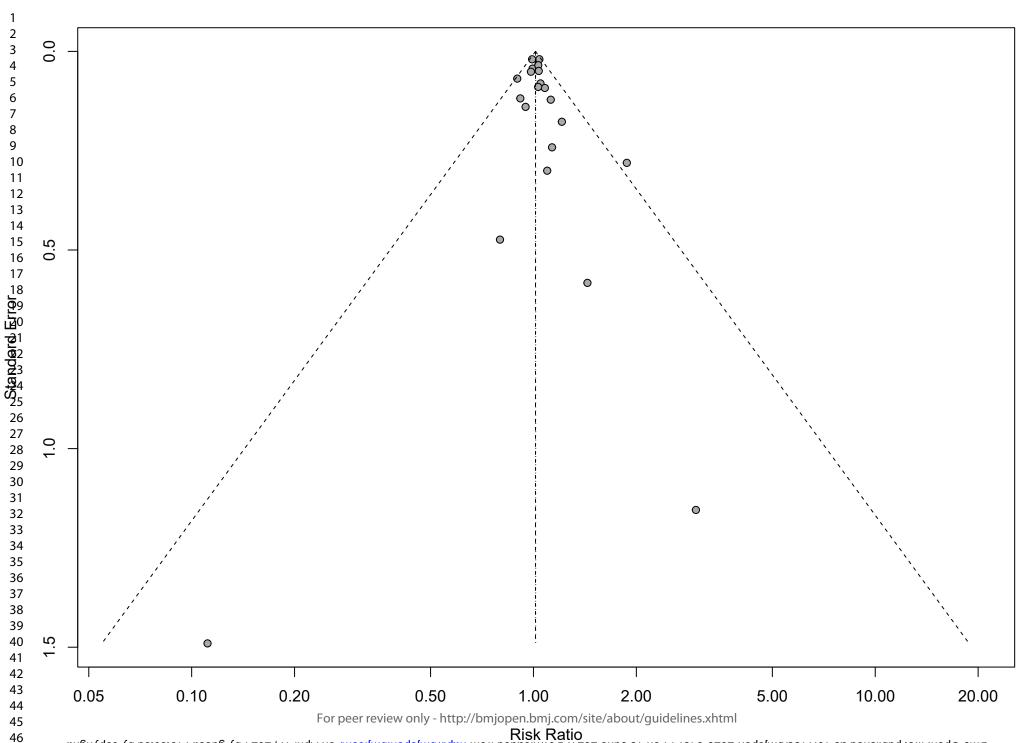
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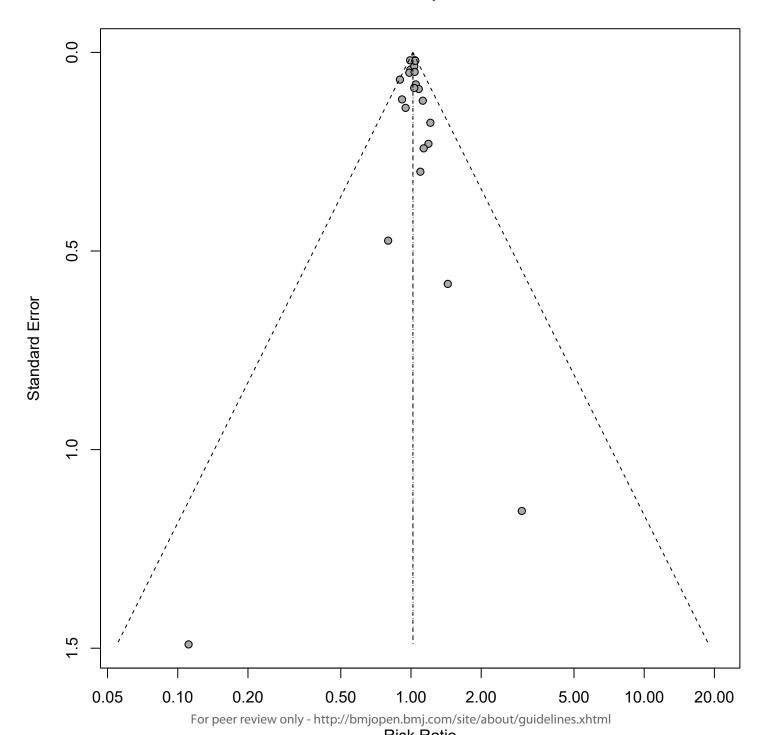
43

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45 46



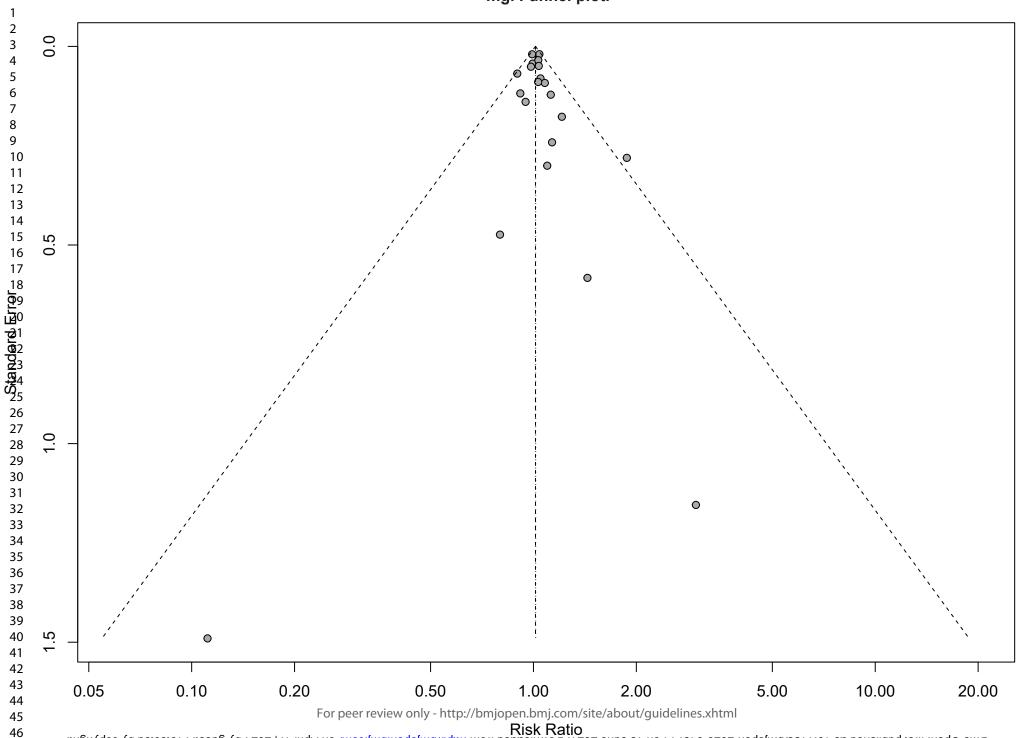
| Study | Experir | | | ontrol | Risk Ratio | RR | 95%-CI | Weight |
|---|----------------------------|------------|---------------|-----------------------|--|------------|----------------------|-----------|
| Group 1: Moderate-Placebo | Events | iotai | Events | Total | | | | |
| CARE, P40 | 0 | 2078 | 4 | 2081 | | 0.11 | [0.01; 2.07] | 0.0% |
| LIPID, P40 | 8 | 4512 | 10 | 4502 | - | 0.80 | [0.32; 2.02] | 0.0% |
| AURORA, R10 | 310 | 1389 | 343 | 1378 | + | 0.90 | [0.78; 1.03] | 2.1% |
| WOSCOPS, P40 | 97 | 3302 | 102 | 3293 | + | 0.95 | [0.72; 1.25] | 0.5% |
| CARDS, A10 | 495 | 1428 | 497 | 1410 | 4 | 0.98 | [0.89; 1.09] | 3.7% |
| HPS, S40 | 3380 | 10269 | 3410 | 10267 | | 0.99 | [0.95; 1.03] | 24.4% |
| ALERT, F40-F80 | 526 | 1045 | 531 | 1049 | ģ. | 0.99 | [0.91; 1.08] | 5.1% |
| SSSS, S20-S40 | 613 | 2221 | 592 | 2223 | ģ. | 1.04 | [0.94; 1.14] | 4.0% |
| AFCAPS, L20-L40 | 2053 | 3304 | 1971 | 3301 | | 1.04 | [1.00; 1.08] | 24.8% |
| ASCOT, A10 | 298 | 5101 | 283 | 5079 | + | 1.05 | [0.90; 1.23] | 1.5% |
| CORONA,R10 | 225 | 2514 | 207 | 2497 | <u> </u> | 1.08 | [0.90; 1.29] | 1.1% |
| GISSI-HF, R10 | 23 | 2285 | 21 | 2289 | | 1.10 | [0.61; 1.98] | 0.1% |
| PROSPER, P40 | 36 | 2891 | 32 | 2913 | | 1.13 | [0.71; 1.82] | 0.2% |
| 4D, A20 | 7 | 619 | 5 | 636 | - | 1.44 | [0.46; 4.51] | 0.0% |
| HOPE, R10 | 3 | 3181 | 1 | 3168 | | 2.99 | [0.31; 28.71] | 0.0% |
| Random effects model | | 46139 | | 46086 | | | [0.99; 1.04] | 67.5% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.6$ | | | | | • | | | |
| | | | | | 10. | | | |
| Group 2: High-Placebo | | | | | | | | |
| SPARCL, A80 | 129 | 2365 | 141 | 2366 | + | | [0.73; 1.15] | |
| JUPITER, R20 | 1421 | 8869 | 1375 | 8864 | | | [0.96; 1.11] | |
| TRACE RA, A40 | 132 | 1504 | 117 | 1498 | +0/ | | [0.89; 1.43] | |
| Random effects model | | 12738 | | 12728 | | 1.03 | [0.97; 1.10] | 9.3% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.47$ | 7 | | | | | | | |
| Croup 2: High Madagata | | | | | | | | |
| Group 3: High–Moderate | 044 | 4005 | 004 | E000 | | 4.00 | [0.07, 4.00] | 4.00/ |
| TNT, A80 vs A10 | 241 | 4995 | 234 | 5006 | <u> </u> | | [0.87; 1.23] | |
| SEARCH, S80 vs S20 | 2621 | 6031 | 2512 | 6033 | | | [1.00; 1.09] | |
| A to Z, S40–S80 vs S20 | 41 | 2263 | 34 | 2230 | <u>T</u> | | [0.76; 1.87] | 0.2% |
| PROVE-IT, A80 vs P40 | 69 | 2099 | 56 | 2063 | <u>†</u> | | [0.86; 1.71] | 0.3% |
| Random effects model | | 15388 | | 15332 | | 1.05 | [1.01; 1.09] | 23.2% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.79$ | 9 | | | | | | | |
| Random effects model | | 74265 | | 74146 | | 1.02 | [1.00; 1.04] | 100.0% |
| Heterogeneity: $I^2 = 0\%$, $\tau_2^2 = 0$, $p = 0.7$ | L | | | | o po (sito /ole o ut/ou sid - livr ulutral | | [,] | |
| Residual heterogeneity: $I^2 = 0\%$ $p = 0$ | or peer revie 75 | w only - h | ittp://bmjo | pen.bmj.c) | om/site/about/guidelines.xhtml 0.01 | 00 | | |
| Residual heterogeneity: $I^2 = 0\%$, $p = 0$. Profected by copyright. | no \moɔ.[md.ı | nəqo[md\\ | d from http: | wnloade | 19454547020445471654146647074754944 | 18/9811.01 | first published as ' | BMJ Open: |
| | | | | J | Camilia Totobaro Ctatali Halling | 41 | | |



eFigure 8 - GENERAL MUSCLE PROBLEMS. Exclusions of studies testing simvastatin 80 mg. Forest plot.

| Study | Experi | | C Events | ontrol | Risk Ratio | RR | 95 | %−CI | Weight |
|--|--------|-------|-------------|--------|---|------|----------------|-------|--------|
| Group 1: Moderate-Placebo | Events | IOlai | Events | iotai | 1 | | | | |
| CARE, P40 | 0 | 2078 | 4 | 2081 | | 0 11 | [0.01; | 2 071 | 0.0% |
| JPID, P40 | 8 | 4512 | 10 | 4502 | | | [0.32; | - | 0.1% |
| AURORA, R10 | 310 | 1389 | 343 | 1378 | 1 | | [0.78; | - | |
| WOSCOPS, P40 | 97 | 3302 | 102 | 3293 | 1 | | [0.70; | - | 0.6% |
| CARDS, A10 | 495 | 1428 | 497 | 1410 | | | [0.72, | - | 4.7% |
| HPS, S40 | 3380 | | | 10267 | T . | | [0.05; | - | 31.1% |
| ALERT, F40-F80 | 526 | 10209 | 531 | 1049 | - | | [0.93, | - | 6.5% |
| SSSS, S20-S40 | 613 | 2221 | 592 | 2223 | I | | - | - | 5.1% |
| · | | | | | Y Y | | [0.94; | - | |
| AFCAPS, L20-L40 | 2053 | 3304 | 1971 | 3301 | Ţ. | | [1.00; | - | 31.6% |
| ASCOT, A10 | 298 | 5101 | 283 | 5079 | Ţ | | [0.90; | - | 1.9% |
| CORONA,R10 | 225 | 2514 | 207 | 2497 | Ť | | [0.90; | - | 1.4% |
| GISSI-HF, R10 | 23 | 2285 | 21 | 2289 | | | [0.61; | - | 0.1% |
| PROSPER, P40 | 36 | 2891 | 32 | 2913 | + | | [0.71; | | |
| 4D, A20 | 7 | 619 | | 636 | - | | [0.46; | _ | 0.0% |
| ASPEN, A10 | 36 | 1211 | 19 | 1199 | | | [1.08; | - | |
| HOPE, R10 | 3 | 3181 | 1 | 3168 | - | | [0.31; 2 | - | 0.0% |
| Random effects model | | 47350 | | 47285 | | 1.01 | [0.98; | 1.04] | 86.2% |
| Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.0003$, $\rho = 0.3$ | 3 | | | | 71. | | | | |
| | | | | | | | | | |
| Group 2: High-Placebo | 400 | | | | | | | | |
| SPARCL, A80 | 129 | 2365 | 141 | 2366 | | | [0.73; | - | 0.9% |
| JUPITER, R20 | 1421 | 8869 | 1375 | 8864 | 7 | | [0.96; | - | 10.2% |
| TRACE RA, A40 | 132 | 1504 | 117 | 1498 | + | | [0.89; | - | |
| Random effects model | | 12738 | | 12728 | | 1.03 | [0.97; | 1.10] | 11.9% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.47$ | | | | | | | | | |
| Group 3: High-Moderate | | | | | | | | | |
| TNT, A80 vs A10 | 241 | 4995 | 234 | 5006 | + | 1.03 | [0.87; | 1.23] | 1.5% |
| PROVE-IT, A80 vs P40 | 69 | 2099 | 56 | 2063 | + | | [0.86; | _ | 0.4% |
| Random effects model | _ | 7094 | | 7069 | b | | [0.91; | - | 1.9% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.42$ | | | | | | | m -) | | |
| Random effects model | | 67182 | | 67082 | | 1.02 | Γ0.99 : | 1.041 | 100.0% |

eFigure 9 - GENERAL MUSCLE PROBLEMS. Exclusions of studies testing simvastatin 80 mg. Funnel plot.



1.03 [0.87; 1.23]

1.04 [1.00; 1.09]

1.04 [1.00; 1.09]

1.07 [1.01; 1.13] 100.0%

8.4%

53.7%

62.0%

Experimental Control **Events Total Events Total** Study Risk Ratio RR 95%-CI Weight **Group 1: Moderate-Placebo** CARDS, A10 1428 1410 0.84 [0.59; 1.19] 2.3% 57 67 AURORA, R10 1389 1378 0.99 [0.06; 15.85] 0.0% 3302 3293 WOSCOPS, P40 20 19 1.05 [0.56; 1.96] 0.7% 2891 2913 1.13 [0.71; 1.82] 1.3% PROSPER, P40 36 32 SSSS, S20-S40 82 2221 72 2223 1.14 [0.84; 1.56] 2.9% 16 10232 14 10237 HPS. S40 1.14 [0.56; 2.34] 0.6% 3304 3301 AFCAPS, L20-L40 11 1.22 [0.51; 2.94] 0.4% 36 1211 1199 0.9% ASPEN, A10 1.88 [1.08; 3.25] ASCOT, A10 17 5158 5124 1.88 [0.84; 4.21] 0.4% Random effects model 31136 31078 1.13 [0.95; 1.34] 9.6% Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.46Group 2: High-Placebo 2365 2366 SPARCL, A80 0.92 [0.73; 1.15] 5.0% 129 141 TRACE RA, A40 132 1504 117 1498 1.12 [0.89; 1.43] 4.8% JUPITER, R20 8869 8864 658 560 1.17 [1.05; 1.31] 18.6% Random effects model 12738 12728 1.09 [0.94; 1.26] 28.4% Heterogeneity: $I^2 = 45\%$, $\tau^2 = 0.0076$, p = 0.16Group 3: High-Moderate

Heterogeneity: $I^2 = 8\%$, $\tau^2 = 0.0009$, p = 0.36Residual heterogeneity: $I^2 = 3\%$, p = 0.41

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.90

TNT, A80 vs A10

SEARCH, S80 vs S20

Random effects model

Random effects model

5006

6033

11039

54845

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2512

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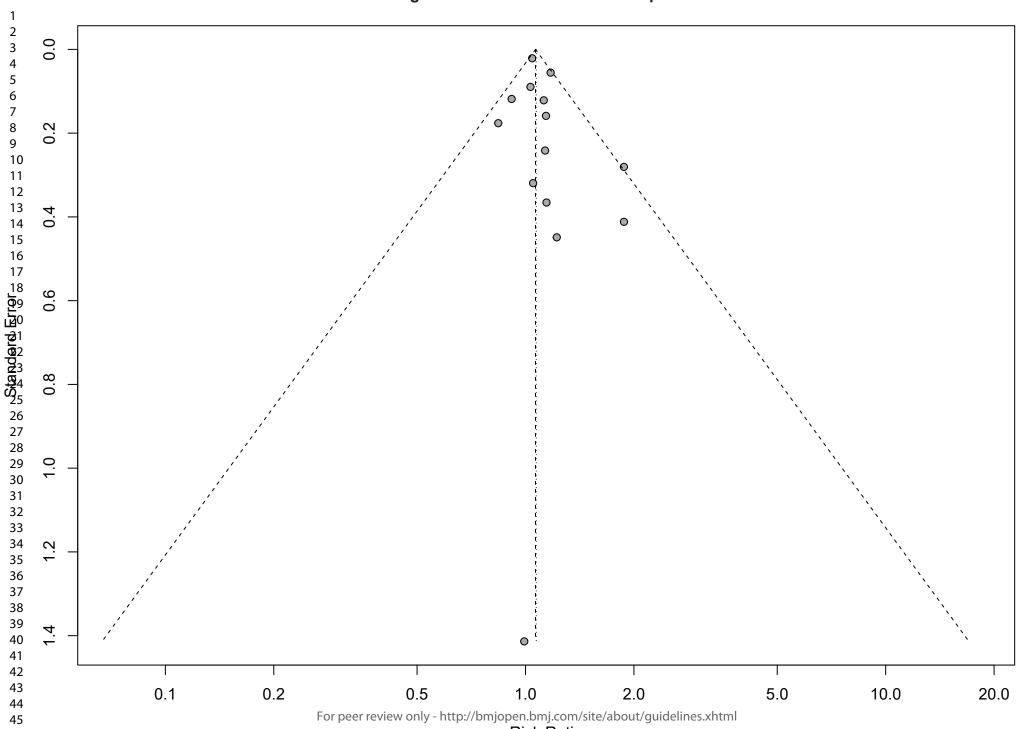
2621

4995

6031

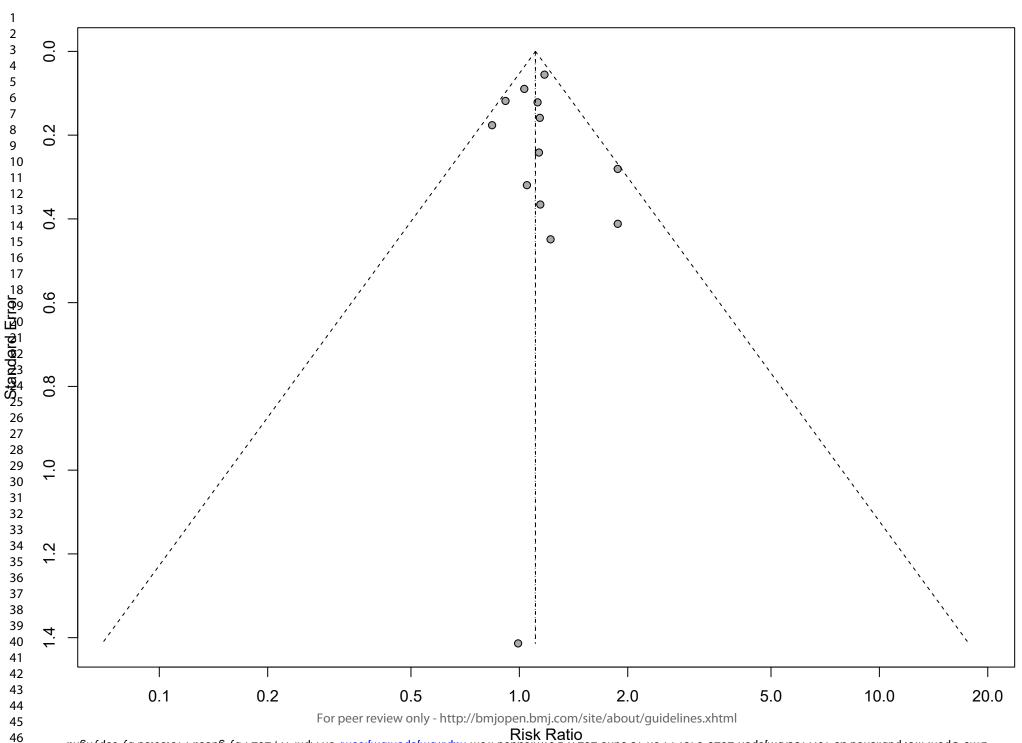
11026

eFigure 11 - MYAGLIA. Full funnel plot.



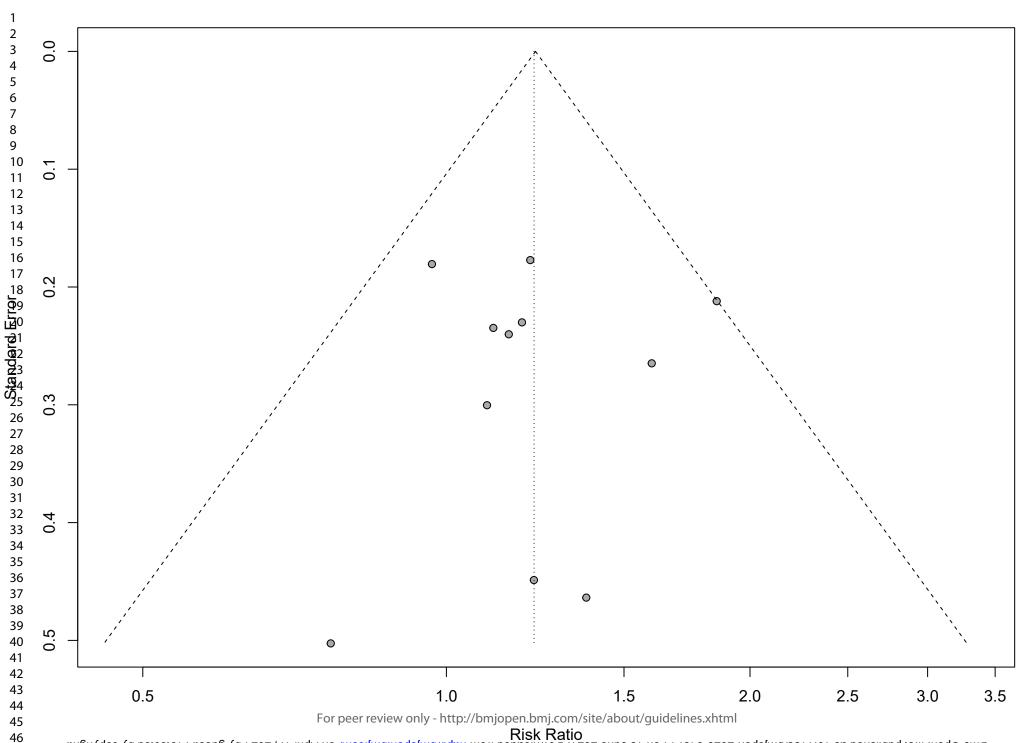
eFigure 12 - MYALGIA. Exclusions of studies testing simvastatin 80 mg. Forest plot.

| | Experir | nental | C | ontrol | | | | |
|--|---------|--------|--------|--------|------------------------------|---------------|---------------|--------|
| Study | • | | Events | Total | Risk Ratio | RR | 95%-CI | Weight |
| Group 1: Moderate-Placebo | | | | | | | | |
| CARDS, A10 | 57 | 1428 | 67 | 1410 | <u>-≖ ÷</u> | 0.84 | [0.59; 1.19] | 4.6% |
| AURORA, R10 | 1 | 1389 | 1 | 1378 | | — 0.99 | [0.06; 15.85] | 0.1% |
| WOSCOPS, P40 | 20 | 3302 | 19 | 3293 | | 1.05 | [0.56; 1.96] | 1.4% |
| PROSPER, P40 | 36 | 2891 | 32 | 2913 | - - | 1.13 | [0.71; 1.82] | 2.5% |
| SSSS, S20-S40 | 82 | 2221 | 72 | 2223 | - - | 1.14 | [0.84; 1.56] | 5.7% |
| HPS, S40 | 16 | 10232 | 14 | 10237 | | 1.14 | [0.56; 2.34] | 1.1% |
| AFCAPS, L20-L40 | 11 | 3304 | 9 | 3301 | | 1.22 | [0.51; 2.94] | 0.7% |
| ASPEN, A10 | 36 | 1211 | 19 | 1199 | <u></u> | 1.88 | [1.08; 3.25] | 1.8% |
| ASCOT, A10 | 17 | 5158 | 9 | 5124 | • • • • • | 1.88 | [0.84; 4.21] | 0.8% |
| Random effects model | | 31136 | | 31078 | > | 1.13 | [0.95; 1.34] | 18.7% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.46$ | | | | | | | | |
| Group 2: High-Placebo | | | | | | | | |
| SPARCL, A80 | 129 | 2365 | 141 | 2366 | 7 / 1 | | [0.73; 1.15] | |
| TRACE RA, A40 | 132 | 1504 | 117 | 1498 | | | [0.89; 1.43] | |
| JUPITER, R20 | 658 | 8869 | 560 | 8864 | + | | [1.05; 1.31] | |
| Random effects model | | 12738 | | 12728 | \Q | 1.09 | [0.94; 1.26] | 63.8% |
| Heterogeneity: $I^2 = 45\%$, $\tau^2 = 0.0076$, $p = 0.16$ | | | | | | | | |
| Group 3: High-Moderate | | | | | | | | |
| TNT, A80 vs A10 | 241 | 4995 | 234 | 5006 | | | [0.87; 1.23] | |
| Random effects model | | 4995 | | 5006 | ? | 1.03 | [0.87; 1.23] | 17.5% |
| Heterogeneity: not applicable | | | | | li i | | | |
| | | | | | | | | |
| Random effects model | | 48869 | | 48812 | | 1.11 | [1.03; 1.19] | 100.0% |
| Heterogeneity: $I^2 = 1\%$, $\tau^2 = 0.0002$, $p = 0.44$ | | | | | 0.1 0.5 4 0 4 | ` | | |
| Residual heterogeneity: $I^2 = 12\%$, $p = 0.33$ | | | | | 0.1 0.5 1 2 1 | - | | |
| | | | | S | tatin Protective Statin Harm | ul | | |



eFigure 14 - ATTRITION DUE TO MUSCLE SYMPTOMS. Full forest plot.

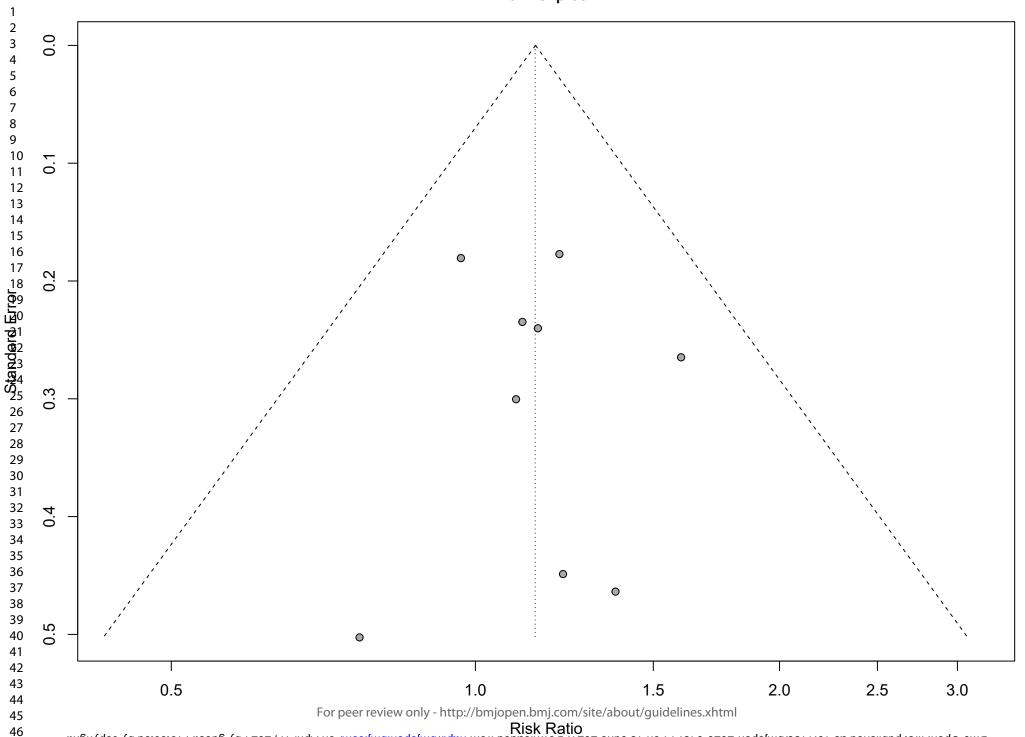
| | Experir | | | ontrol | Dist Date | D D | 050/ 01 | NA 7 - 1 - 1 - 1 |
|--|---------|-------|--------|--------|--------------------------------|------------|--------------|-------------------------|
| Study | Events | iotai | Events | iotai | Risk Ratio | RR | 95%−CI | weignt |
| Group 1: Moderate-Placebo | | | | | 1 : | | | |
| CARDS, A10 | 7 | 1428 | 9 | 1410 - | | 0.77 | [0.29; 2.06] | 2.2% |
| HPS, S40 | 60 | 10269 | 62 | 10267 | | 0.97 | [0.68; 1.38] | 17.2% |
| GISSI-HF, R10 | 23 | 2285 | 21 | 2289 | | 1.10 | [0.61; 1.98] | 6.2% |
| HOPE, R10 | 38 | 3181 | 34 | 3168 | | 1.11 | [0.70; 1.76] | 10.2% |
| WOSCOPS, P40 | 37 | 3302 | 32 | 3293 | - • | 1.15 | [0.72; 1.85] | 9.7% |
| AFCAPS, L20-L40 | 11 | 3304 | 9 | 3301 | | | [0.51; 2.94] | 2.8% |
| SSSS, S20-S40 | 11 | 2221 | 8 | 2223 | | | [0.55; 3.41] | |
| ASCOT, A10 | 37 | 5158 | 23 | | - | | [0.95; 2.69] | 8.0% |
| Random effects model | | 31148 | | 31075 | | 1.13 | [0.93; 1.36] | 59.0% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$ | | | | | 9/2 | | | |
| Group 2: High-Moderate | 4.4 | 0000 | 0.4 | 0000 | | 4.40 | [0.70, 4.07] | 40.00/ |
| A to Z, S40–S80 vs S20 | 41 | 2263 | 34 | 2230 | | | [0.76; 1.87] | 10.6% |
| PROVE-IT, A80 vs P40 | 69 | 2099 | 56 | 2063 | | | [0.86; 1.71] | 17.9% |
| SEARCH, S80 vs S20 Random effects model | 63 | 6031 | 34 | | | | [1.22; 2.81] | 12.5% |
| Heterogeneity: $I^2 = 31\%$, $\tau^2 = 0.0190$, $p = 0.23$ | | 10393 | | 10326 | | 1.30 | [1.04; 1.82] | 41.0% |
| Heterogeneity: $I = 31\%$, $\tau = 0.0190$, $p = 0.23$ | | | | | | | | |
| Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.64$ | | 41541 | | 41401 | | 1.22 | [1.05; 1.41] | 100.0% |
| Residual heterogeneity: $I^2 = 0\%$, $p = 0.72$ | | | | | 0.5 1 2 | | | |
| | | | | S | tatin Protective Statin Harmfu | I | | |



eFigure 16 - ATTRITION DUE TO MUSCLE SYMPTOMS. Exclusions of studies testing simvastatin 80 mg. Forest plot.

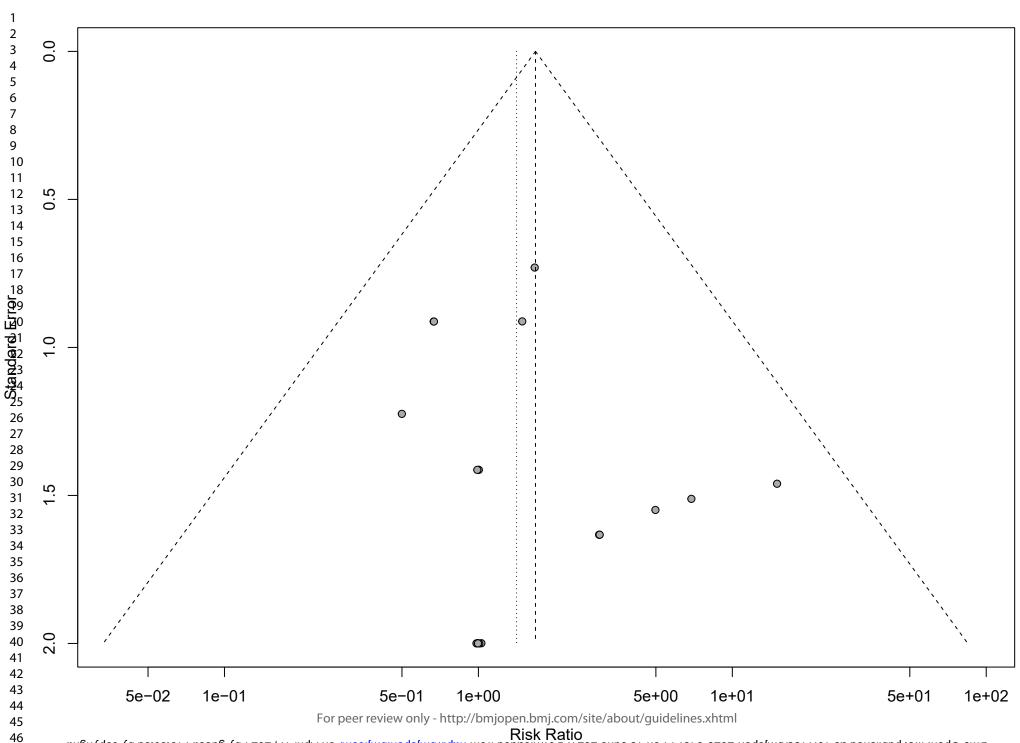
| | Experir | nental | С | ontrol | | | | |
|--|---------|--------|--------|--------|----------------------------|------|--------------|--------|
| Study | Events | Total | Events | Total | Risk Ratio | RR | 95%-CI | Weight |
| Group 1: Moderate-Placebo | | | | | | | | |
| CARDS, A10 | 7 | 1428 | 9 | 1410 | * | 0.77 | [0.29; 2.06] | 2.9% |
| HPS, S40 | 60 | 10269 | 62 | 10267 | | 0.97 | [0.68; 1.38] | 22.4% |
| GISSI-HF, R10 | 23 | 2285 | 21 | 2289 | | 1.10 | [0.61; 1.98] | 8.1% |
| HOPE, R10 | 38 | 3181 | 34 | 3168 | - • | | [0.70; 1.76] | 13.3% |
| WOSCOPS, P40 | 37 | 3302 | 32 | | - • | | [0.72; 1.85] | 12.7% |
| AFCAPS, L20-L40 | 11 | 3304 | 9 | | | | [0.51; 2.94] | 3.6% |
| SSSS, S20-S40 | 11 | 2221 | 8 | 2223 | | | [0.55; 3.41] | 3.4% |
| ASCOT, A10 | 37 | 5158 | 23 | | | | [0.95; 2.69] | 10.4% |
| Random effects model | | 31148 | | 31075 | | 1.13 | [0.93; 1.36] | 76.7% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$ | | | | | Ch. | | | |
| Group 2: High-Moderate | | | | | | | | |
| PROVE-IT, A80 vs P40 | 69 | 2099 | 56 | 2063 | | 1.21 | [0.86; 1.71] | 23.3% |
| Random effects model | | 2099 | | 2063 | | 1.21 | [0.86; 1.71] | 23.3% |
| Heterogeneity: not applicable | | | | | | | | |
| Random effects model | | 33247 | | 33138 | | 1.15 | [0.97; 1.35] | 100.0% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.91$ | | | | | | | | |
| Residual heterogeneity: $I^2 = 0\%$, $p = 0.8$ | 86 | | | | 0.5 1 2 | | | |
| | | | | | Statin Better Statin Worse | | | |

eFigure 17 - ATTRITION DUE TO MUSCLE SYMPTOMS. Exclusions of studies testing simvastatin 80 mg. Funnel plot.



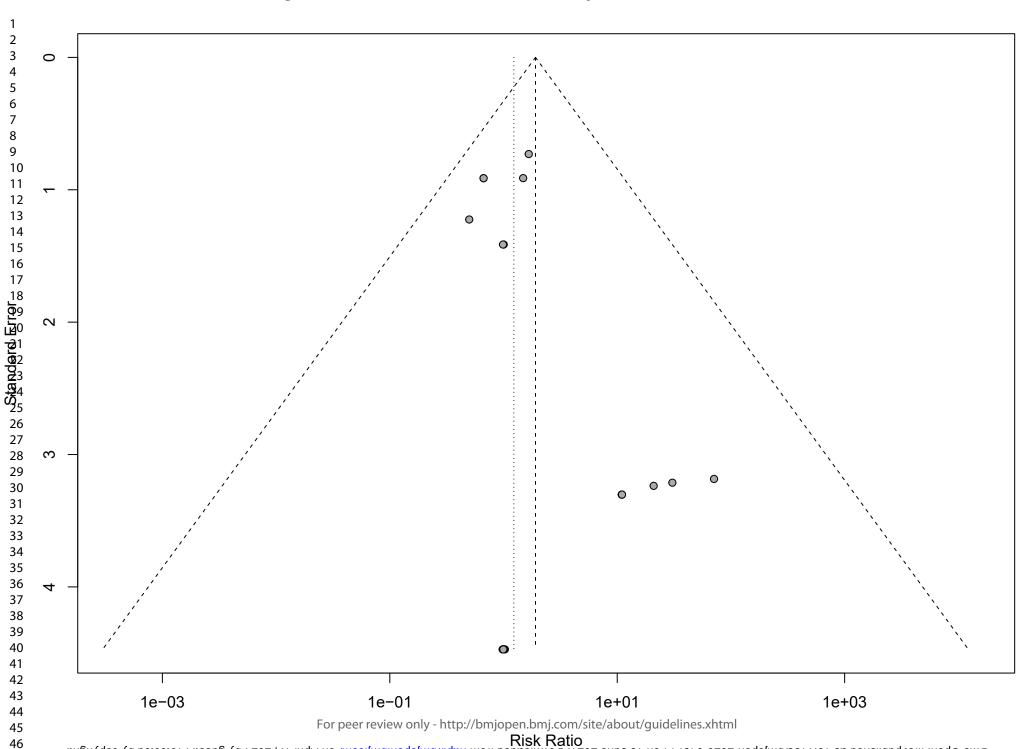
46

| 1 | Study | Experin | | | ontrol | Risk Ratio | RR | 95%-CI | Weight |
|----------|--|---------------|------------|---------------|-----------|---|------|----------------|--------|
| 2 | | Events | Total | Events | Total | | | | |
| 3 | Group 1: Moderate-Placebo | | | | | | | | |
| 4 | AFCAPS, L20-L40 | 1 | 3304 | 2 | 3301 | | 0.50 | [0.05; 5.51] | |
| 5 6 | CARDS, A10 | 0 | 1428 | 0 | 1410 | +: | 0.99 | [0.02; 49.73] | 2.2% |
| 7 | ASPEN, A10 | 1 | 1211 | 1 | 1199 | | 0.99 | [0.06; 15.81] | 4.3% |
| 8 | CORONA, R10 | 0 | 2514 | 0 | 2497 | * | 0.99 | [0.02; 50.04] | 2.2% |
| 9 | LIPS, F80 | 0 | 822 | 0 | 818 | * | 1.00 | [0.02; 50.09] | 2.2% |
| 10 | GISSI-HF, R10 | 0 | 2285 | 0 | 2289 | + | 1.00 | [0.02; 50.46] | 2.2% |
| 11 | ALERT, F40-F80 | 1 | 1045 | 1 | 1049 | | 1.00 | [0.06; 16.03] | 4.3% |
| 12 13 | PROSPER, P40 | 0 | 2891 | 0 | 2913 | | 1.01 | [0.02; 50.76] | 2.2% |
| 14 | 4D, A20 | | 619 | 0 | 636 | | 1.03 | [0.02; 51.70] | |
| 15 | AURORA, R10 | 3 | 1389 | 2 | 1378 | - i - | 1.49 | [0.25; 8.89] | 10.4% |
| 16 | HPS, S40 | 5 | 10269 | 3 | 10267 | | 1.67 | [0.40; 6.97] | 16.2% |
| 17 | HOPE, R10 | 1 | 3181 | 0 | 3168 | | 2.99 | [0.12; 73.31] | |
| 18 | SSSS, S20-S40 | 1 | 2221 | 0 | 2223 | | | [0.12; 73.67] | |
| 19 20 | ASCOT, A10 | 2 | 5101 | 0 | | | | [0.24; 103.67] | |
| 21 | Random effects model | | 38280 | | 38227 | | | [0.68; 2.86] | 63.9% |
| 22 | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$ | | 00200 | | | | 1.00 | [0.00, 2.00] | 00.070 |
| 23 | Therefore the first $T = 0.70$, $t = 0$, $p = 1.00$ | | | | | , | | | |
| 24 | Group 2: High-Placebo | | | | | | | | |
| 25 | SPARCL, A80 | 2 | 2365 | 3 | 2366 | | 0.67 | [0.11; 3.99] | 10.4% |
| 26 27 | TRACE RA, A40 | 0 | 1504 | 0 | 1498 | | 1.00 | [0.02; 50.16] | |
| 28 | • | 1 | 8901 | | 8901 | | | • | |
| 29 | JUPITER, R20 | ı | 12770 | 0 | | | 3.00 | [0.12; 73.63] | 3.2% |
| 30 | Random effects model | | 12//0 | | 12765 | | 0.96 | [0.22; 4.09] | 15.7% |
| 31 | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.72$ | | | | | | | | |
| 32 | O O III also Marila actio | | | | | | | | |
| 33 | Group 3: High-Moderate | 0 | 4005 | • | 5000 | _ | 0.07 | FO 4.4 4.00I | 40.40/ |
| 34 35 | TNT, A80 vs A10 | 2 | 4995 | 3 | 5006 | - | 0.67 | [0.11; 4.00] | |
| 36 | PROVE-IT, A80 vs P40 | 0 | 2099 | 0 | 2063 | | | [0.02; 49.51] | |
| 37 | A to Z, S40-S80 vs S20 | 3 | 2263 | 0 | 2230 | - | | [0.36; 133.46] | |
| 38 | SEARCH, S80 vs S20 | 7 | 6031 | 0 | 6033 | - | | [0.86; 262.66] | |
| 39 | Random effects model | | 15388 | | 15332 | | 2.45 | [0.46; 13.05] | 20.3% |
| 40 | Heterogeneity: $I^2 = 34\%$, $\tau^2 = 0.9919$, $p = 0.21$ | | | | | | | | |
| 41 42 | | | | | | | | | |
| 43 | Random effects model | | 66438 | | 66324 | > | 1.41 | [0.80; 2.51] | 100.0% |
| 44 | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\rho = 0.99$ | | | | | | | | |
| 45 | Residual heterogeneity: $I^2 = 0\%$, $p = 0.99$ For p | oeer review o | only - htt | p://bmjope | n.bmj.cor | က ် းစြာ(abopt/guidelines.xhtmp) 100 | | | |
| 46 | - · · | | | | | Statin Battar Statin Wares | | | |



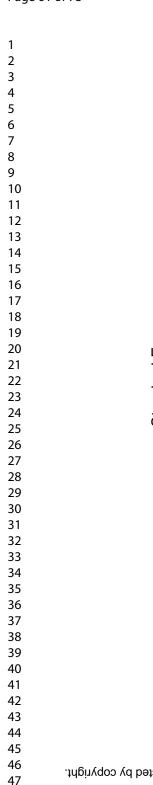
| Study | Experiment Events To | ntal otal Events | Control Total | Risk Ratio | RR | 95%-CI | Weight |
|---------------------------------------|----------------------------|---------------------|------------------|---------------------------------------|----------------|------------------|--------|
| Group 1: Moderate-Pla | cebo | | | | | | |
| AFCAPS, L20-L40 | | 304 2 | 3301 | - 1 | 0.50 | [0.05; 5.51] | 8.2% |
| CARDS, A10 | 0 1 | 428 0 | 1410 | | 0.99 | | 0.6% |
| ASPEN, A10 | 1 1: | 211 1 | 1199 | | 0.99 | [0.06; 15.81] | 6.2% |
| CORONA, R10 | 0 2 | 514 0 | 2497 | | 0.99 | • | 0.6% |
| LIPS, F80 | 0 | 822 0 | 818 | | 1.00 | | 0.6% |
| GISSI-HF, R10 | 0 2 | 285 0 | 2289 | | 1.00 | [0.00; 6417.49] | 0.6% |
| ALERT, F40-F80 | 1 1 | 045 1 | 1049 | | 1.00 | [0.06; 16.03] | 6.2% |
| PROSPER, P40 | 0 2 | 891 0 | 2913 | | 1.01 | [0.00; 6455.29] | 0.6% |
| 4D, A20 | 0 | 619 0 | 636 | | 1.03 | [0.00; 6578.85] | 0.6% |
| AURORA, R10 | 3 1 | 389 2 | 1378 | | 1.49 | [0.25; 8.89] | 14.8% |
| HPS, S40 | 5 10 | 269 3 | 10267 | | 1.67 | [0.40; 6.97] | 23.1% |
| HOPE, R10 | 1 3 | 181 0 | 3168 | * | 10.96 | [0.02; 7095.11] | 1.1% |
| SSSS, S20-S40 | 1 2: | 221 0 | 2223 | | 11.01 | [0.02; 7130.07] | 1.1% |
| ASCOT, A10 | 2 5 | 101 0 | 5079 | - | - 20.91 | [0.04; 11895.15] | 1.2% |
| Random effects model | 38: | 280 | 38227 | \(| 1.38 | [0.59; 3.22] | 65.6% |
| Heterogeneity: $I^2 = 0\%$, τ^2 | = 0, p = 1.00 | | | 6/1 | | | |
| Group 2: High-Placebo | | | | | | | |
| SPARCL, A80 | 2 2 | 365 3 | 2366 | | 0.67 | [0.11; 3.99] | 14.8% |
| TRACE RA, A40 | 0 1 | 504 0 | 1498 | | 1.00 | [0.00; 6380.08] | 0.6% |
| JUPITER, R20 | 1 8 | 901 0 | 8901 | • • • • • • | 11.00 | [0.02; 7125.08] | 1.1% |
| Random effects model | 12 | 770 | 12765 | | 0.82 | [0.15; 4.45] | 16.6% |
| Heterogeneity: $I^2 = 0\%$, τ^2 | = 0, p = 0.70 | | | | | | |
| Group 3: High-Modera | te | | | | | | |
| TNT, A80 vs A10 | 2 4 | 995 3 | 5006 | | 0.67 | [0.11; 4.00] | 14.8% |
| PROVE-IT, A80 vs P40 | 0 2 | 099 0 | 2063 | | 0.98 | [0.00; 6296.29] | 0.6% |
| A to Z, S40-S80 vs S20 | 3 2 | 263 0 | 2230 | * | - 30.55 | [0.06; 16583.28] | 1.2% |
| SEARCH, S80 vs S20 | 7 6 | 031 0 | 6033 | - | — 71.02 | [0.14; 36473.99] | 1.2% |
| Random effects model | 15 | 388 | 15332 | | 3.37 | [0.13; 85.29] | 17.8% |
| Heterogeneity: $I^2 = 39\%$, τ | 2 = 4.4154, p | = 0.18 | | | | | |
| Random effects model | | 438 | 66324 | <u> </u> | 1.23 | [0.62; 2.45] | 100.0% |
| Heterogeneity: $I^2 = 0\%$, τ^2 | = 0, p = 0.99 | | 1 | | 1. 1 | | |
| Residual heterogeneity: I^2 | = 0%, p ^F = 0.9 | greview only - | nttp://bmj | ppen longitcom/site/about/guidelingsx | khtml | | |

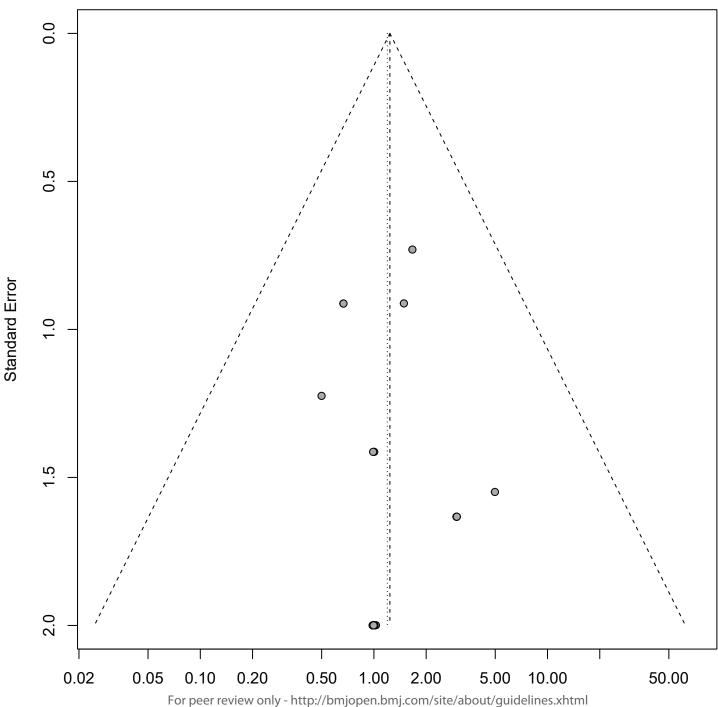
BMJ Open eFigure 21 - RHABDOMYOLYSIS. Continuity Correction = 0.1. Funnel Plot.



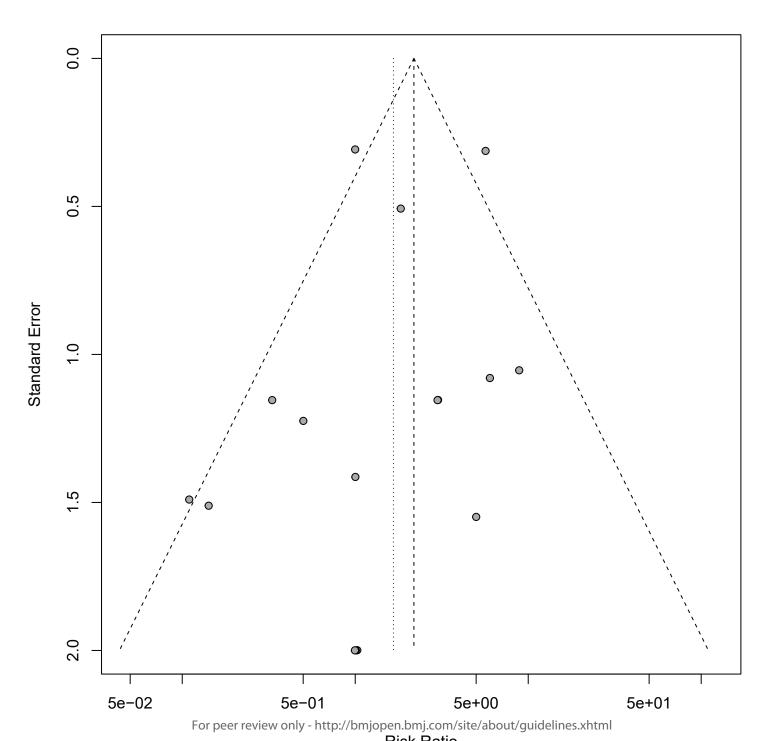
| 1 | Experin | nental | C | ontrol | · p···· | | |
|--|------------|--------------|---------------|-----------------|--|--------------|---------------------------------------|
| | • | | Events | Total | Risk Ratio | RR | 95%-CI Weight |
| Group 1: Moderate-Placebo | | | | | : | | |
| AFCAPS, L20-L40 | 1 | 3304 | 2 | 3301 | | 0.50 | [0.05; 5.51] 6.2% |
| CARDS, A10 | 0 | 1428 | 0 | 1410 | | 0.99 | [0.02; 49.73] 2.3% |
| ASPEN, A10 | 1 | 1211 | 1 | 1199 | | 0.99 | [0.06; 15.81] 4.7% |
| CORONA, R10 | 0 | 2514 | 0 | 2497 | <u>-</u> | 0.99 | |
| LIPS, F80 | 0 | 822 | 0 | 818 | | 1.00 | [0.02; 50.09] 2.3% |
| GISSI-HF, R10 | 0 | 2285 | 0 | 2289 | | 1.00 | [0.02; 50.46] 2.3% |
| ALERT, F40-F80 | 1 | 1045 | 1 | 1049 | | 1.00 | [0.06; 16.03] 4.7% |
| PROSPER, P40 | 0 | 2891 | 0 | 2913 | | 1.01 | [0.02; 50.76] 2.3% |
| 4D, A20 | 0 | 619 | 0 | 636 | | 1.03 | [0.02; 51.70] 2.3% |
| AURORA, R10 | 3 | 1389 | 2 | 1378 | | 1.49 | [0.25; 8.89] 11.2% |
| HPS, S40 | 5 | 10269 | 3 | 10267 | - • - | 1.67 | |
| HOPE, R10 | 1 | 3181 | 0 | 3168 | | - 2.99 | |
| SSSS, S20-S40 | 1 | 2221 | 0 | 2223 | | | [0.12; 73.67] 3.5% |
| ASCOT, A10 | 2 | 5101 | 0 | | | | [0.24; 103.67] 3.9% |
| Random effects model | | 38280 | | 38227 | | 1.39 | [0.68; 2.86] 69.3% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$ | | | | | | | |
| Crown 2: High Blooch | | | | | | | |
| Group 2: High-Placebo | 2 | 2265 | 2 | 0066 | | 0.67 | [0.44, 2.00] 44.00/ |
| SPARCL, A80 | 2 0 | 2365 1504 | 3 | 2366 1498 | | 0.67 1.00 | |
| TRACE RA, A40 JUPITER, R20 | 1 | 8901 | 0 | 8901 | 9/5/ | | [0.02; 50.16] 2.3% [0.12; 73.63] 3.5% |
| Random effects model | • | 12770 | U | 12765 | | 0.96 | [0.12, 73.03] 3.3% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.72$ | | 12//0 | | 12703 | | 0.90 | [0.22, 4.09] 17.170 |
| Heterogeneity. $T=0.70$, $t=0$, $\rho=0.72$ | | | | | | | |
| Group 3: High-Moderate | | | | | | | |
| TNT, A80 vs A10 | 2 | 4995 | 3 | 5006 | | 0.67 | [0.11; 4.00] 11.2% |
| PROVE-IT, A80 vs P40 | 0 | 2099 | 0 | 2063 | | 0.98 | [0.02; 49.51] 2.3% |
| Random effects model | | 7094 | | 7069 | | | [0.14; 3.63] 13.6% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$ | | | | | | | |
| | | | | | | | |
| Random effects model | ; | 58144 | | 58061 | <u></u> | 1.19 | [0.66; 2.18] 100.0% |
| Heterogeneity: $I^2 = 0\%$, $\tau_2^2 = 0$, $p = 1.00$ | | | | | 1 1 1 | I | |
| Residual heterogeneity: $I^2 = 0\%$, $p = 1.00$ | | 1 | L. 1. 7./L * | 0. | 01 0.1 1 10 | 100 | |
| For | beer revie | w only - | nttp://bmj | pen.bm g | ŧatinsiProtective ^{ide} Statin Plarmi | ul | |

eFigure 23 - RHABDOMYOLYSIS. Exclusions of studies testing simvastatin 80 mg. Funnel plot.





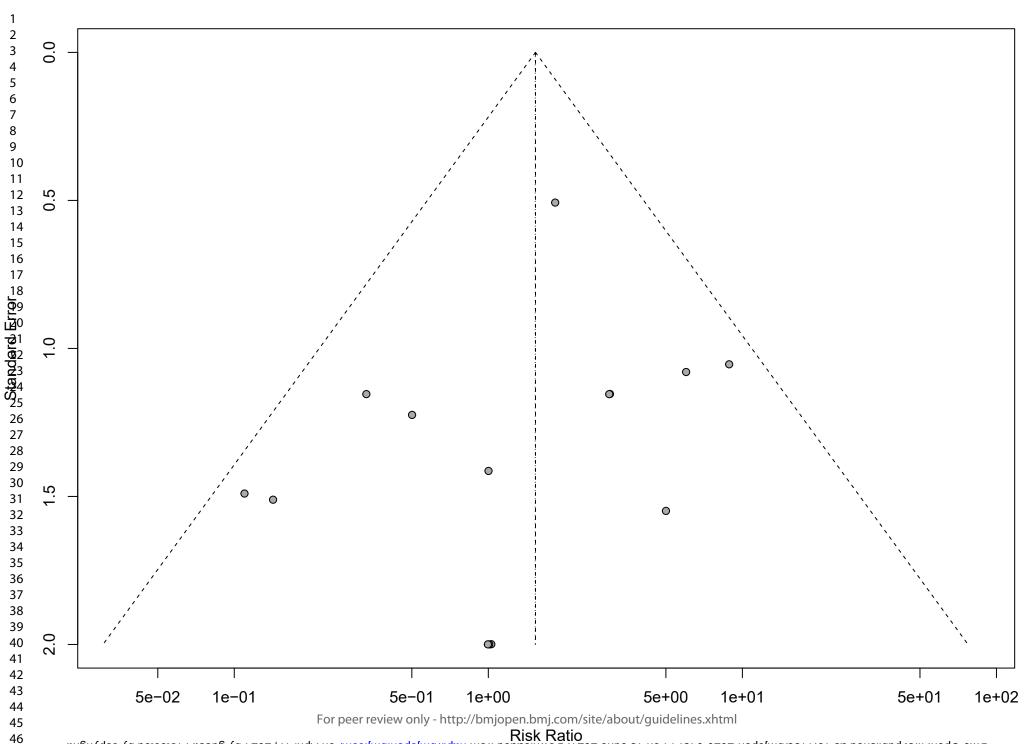
| | Experir | nental | C | ontrol | | | | |
|--|---------|--------|--------|--------|--|------|---------------|--------|
| Study | Events | Total | Events | Total | Risk Ratio | RR | 95%-CI | Weight |
| Group 1: Moderate-Placebo | | | | | | | | |
| CARDS, A10 | 0 | 1428 | 4 | 1410 | | 0.11 | [0.01; 2.04] | 3.9% |
| LIPS, F80 | 0 | 822 | 3 | 818 | | 0.14 | [0.01; 2.75] | 3.8% |
| CORONA, R10 | 1 | 2514 | 3 | 2497 | | 0.33 | [0.03; 3.18] | 5.7% |
| AFCAPS, L20-L40 | 21 | 3304 | 21 | 3301 | | 1.00 | [0.55; 1.83] | 15.0% |
| GISSI-HF, R10 | 1 | 2285 | 1 | 2289 | | 1.00 | [0.06; 16.01] | 4.2% |
| PROSPER, P40 | 0 | 2891 | 0 | 2913 | | 1.01 | [0.02; 50.76] | 2.4% |
| 4D, A20 | 0 | 619 | 0 | 636 | | 1.03 | [0.02; 51.70] | 2.4% |
| HPS, S40 | 11 | 10269 | 6 | 10267 | + | 1.83 | [0.68; 4.95] | 12.3% |
| WOSCOPS, P40 | 3 | 3302 | 1 | 3293 | - : • | 2.99 | [0.31; 28.75] | 5.7% |
| ALERT, F40-F80 | 3 | 1045 | 1 | 1049 | - : • | 3.01 | [0.31; 28.90] | 5.7% |
| SSSS, S20-S40 | 6 | 2221 | 1 | 2223 | + - | 6.01 | [0.72; 49.84] | 6.2% |
| Random effects model | | 30700 | | 30696 | \rightarrow | 1.17 | [0.72; 1.90] | 67.4% |
| Heterogeneity: $I^2 = 4\%$, $\tau^2 = 0.0303$, $p = 0.41$ | | | | | | | | |
| Group 2: High-Placebo | | | | | | | | |
| TRACE RA, A40 | 0 | 1504 | 0 | 1498 | N <u>, </u> | 1 00 | [0.02; 50.16] | 2.4% |
| SPARCL, A80 | 2 | 2365 | 0 | 2366 | | | 0.24; 104.14] | 3.7% |
| Random effects model | _ | 3869 | Ū | 3864 | | | [0.25; 30.11] | 6.1% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$ | | | | 0001 | | 2 | [0.20, 00] | 01170 |
| , , , , , , , , , , , , , , , , , , , | | | | | | | | |
| Group 3: High-Moderate | | | | | | | | |
| TNT, A80 vs A10 | 1 | 4995 | 2 | 5006 | | | [0.05; 5.52] | 5.2% |
| SEARCH, S80 vs S20 | 68 | 6031 | 12 | 6033 | | | [3.07; 10.46] | 14.9% |
| A to Z, S40–S80 vs S20 | 9 | 2263 | 1 | 2230 | | | [1.12; 69.94] | 6.4% |
| Random effects model | | 13289 | | 13269 | | 3.88 | [1.05; 14.31] | 26.5% |
| Heterogeneity: $I^2 = 50\%$, $\tau^2 = 0.7030$, $p = 0.14$ | | | | | | | | |
| Random effects model | | 47858 | | 47829 | | 1.66 | [0.86; 3.21] | 100.0% |
| Heterogeneity: $I^2 = 52\%$, $\tau^2 = 0.6582$, $p < 0.01$ | | | | | | | - · · • | |
| Residual heterogeneity: $I^2 = 12\%$, $p = 0.32$ | | | | (| 0.01 0.1 1 10 | 100 | | |
| | | | | S | tatin Protective Statin Harn | nful | | |



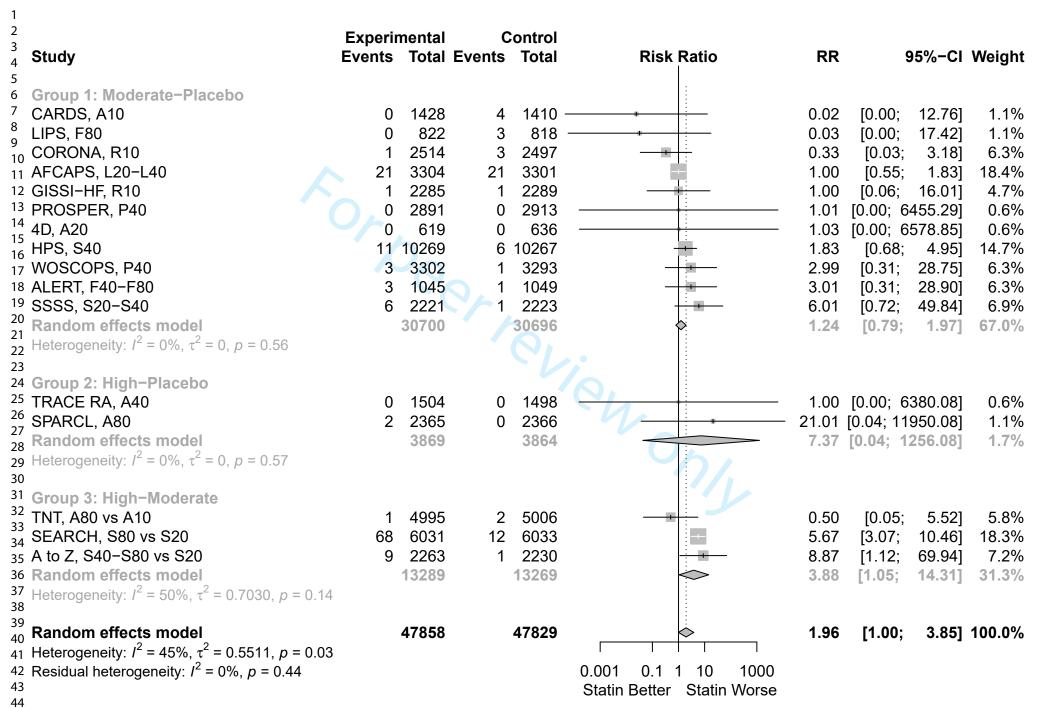
eFigure 26 - CK >10xULN. Outliers excluded. Forest plot.

| | Experiment | al Co | ontrol | | | | | |
|--|------------|-----------|--------------|----------------|----------------|------|---|--------|
| Study | Events Tot | al Events | Total | Risk F | Ratio | RR | 95%-CI | Weight |
| Group 1: Moderate-Placebo | | | | | <u>.</u> | | | |
| CARDS, A10 | 0 142 | 8 4 | 1410 — | | <u>:</u> | 0.11 | [0.01; 2.04] | 4.6% |
| LIPS, F80 | 0 82 | 2 3 | 818 — | | <u>:</u> :- | 0.14 | [0.01; 2.75] | 4.5% |
| CORONA, R10 | 1 25 | 4 3 | 2497 | - | <u>:</u> : | 0.33 | [0.03; 3.18] | 7.4% |
| GISSI-HF, R10 | 1 228 | 5 1 | 2289 | + | <u>:</u> | 1.00 | [0.06; 16.01] | 5.1% |
| PROSPER, P40 | 0 289 | 1 0 | 2913 | + | <u>:</u> | 1.01 | [0.02; 50.76] | 2.6% |
| 4D, A20 | 0 6 | - | 636 | | <u>:</u> | 1.03 | [0.02; 51.70] | 2.6% |
| HPS, S40 | 11 1026 | | 10267 | + | 1 | 1.83 | [0.68; 4.95] | 28.0% |
| WOSCOPS, P40 | 3 330 | | 3293 | - | - | | [0.31; 28.75] | 7.4% |
| ALERT, F40-F80 | 3 104 | | 1049 | | - | | [0.31; 28.90] | 7.4% |
| SSSS, S20-S40 | 6 222 | | 2223 | + | | | [0.72; 49.84] | 8.3% |
| Random effects model | 2739 | 6 2 | 27395 | * | > | 1.31 | [0.63; 2.73] | 77.8% |
| Heterogeneity: $I^2 = 10\%$, $\tau^2 = 0.1435$, $p = 0.38$ | 5 | | | | | | | |
| Group 2: High-Placebo | 0 45 | | 4.400 |), | | 4.00 | [0.00 | 0.00/ |
| TRACE RA, A40 | 0 150 | | 1498 | 11. | | | [0.02; 50.16] | 2.6% |
| SPARCL, A80 | 2 236 | | 2366 3864 | | • | | [0.24; 104.14] | 4.3% |
| Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$ | 386 | 9 | 3864 | | : | 2.73 | [0.25; 30.11] | 6.9% |
| Heterogeneity: $I = 0\%$, $\tau = 0$, $p = 0.52$ Group 3: High–Moderate | | | | | 1/_ | | | |
| TNT, A80 vs A10 | 1 499 | 5 2 | 5006 | - | | 0.50 | [0.05; 5.52] | 6.6% |
| A to Z, S40-S80 vs S20 | 9 226 | _ | 2230 | _ | • | | [1.12; 69.94] | 8.7% |
| Random effects model | 72! | | 7236 | | | | [0.13; 38.98] | 15.3% |
| Heterogeneity: $I^2 = 69\%$, $\tau^2 = 2.9371$, $\rho = 0.07$ | 7 | | | | | | | |
| Random effects model | 3852 | 3 3 | 38495 | <u> </u> | · > | 1.53 | [0.80; 2.91] | 100.0% |
| Heterogeneity: $I^2 = 8\%$, $\tau^2 = 0.1269$, $p = 0.36$ | | | Γ | | | | _ · · · · · · · · · · · · · · · · · · · | |
| Residual heterogeneity: $I^2 = 19\%$, $p = 0.25$ | | | 0.0 | 0.1 1 | 10 100 | | | |
| | | | | Statin Better | Statin Worse | | | |

BMJ Open eFigure 27 - CK >10xULN. Outliers excluded. Funnel plot.



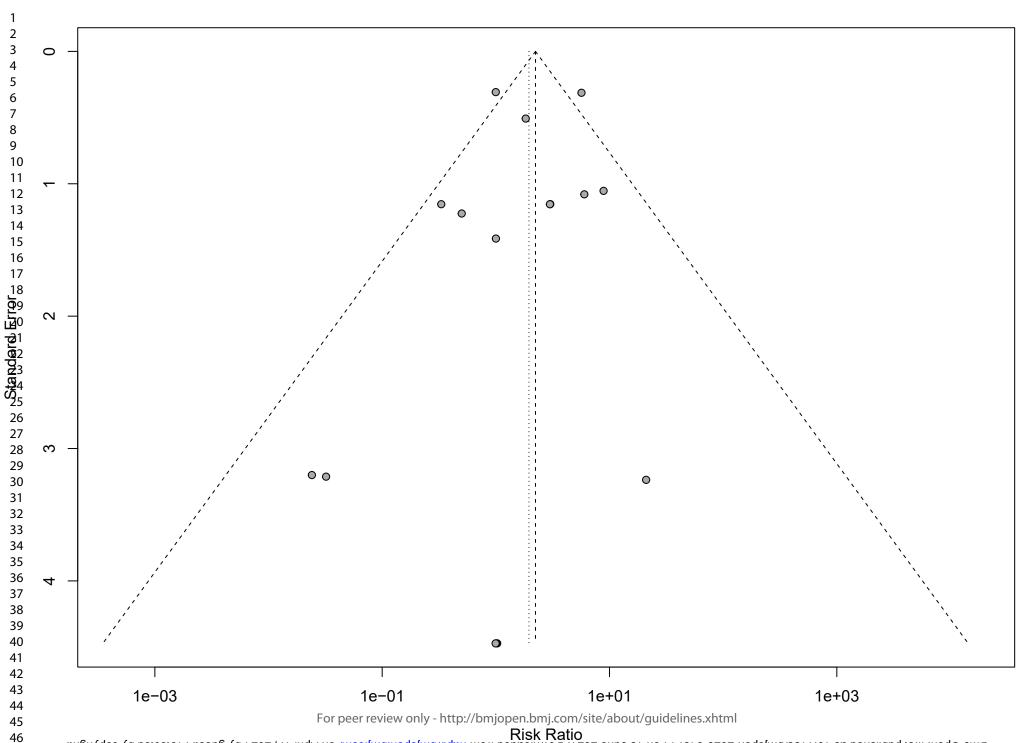
BMJ Open eFigure 28 - CK >10xULN. Continuity Correction = 0.1. Forest plot.



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45 46

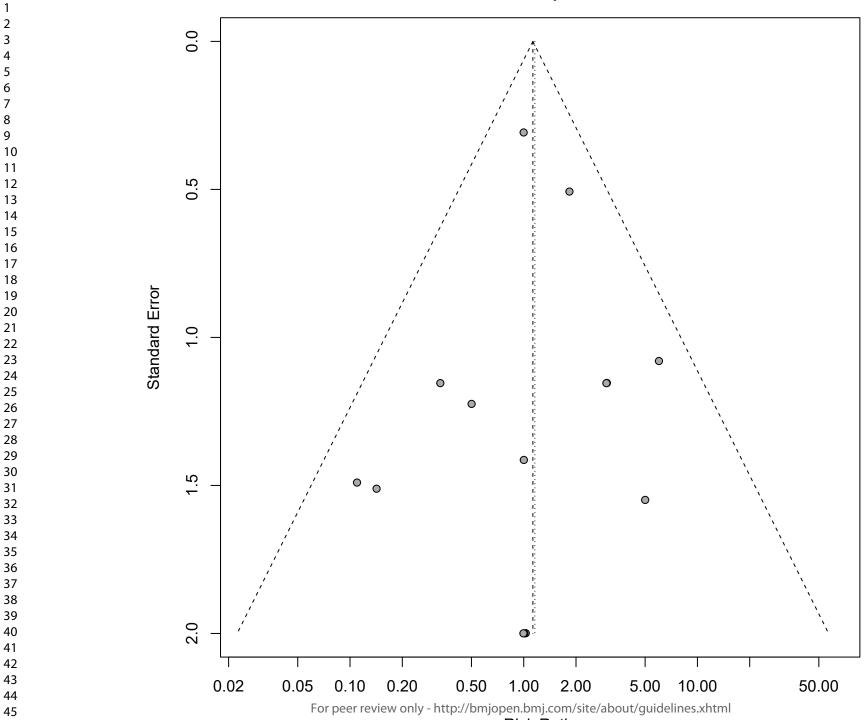
BMJ Open eFigure 29 – CK >10xULN. Continuity Correction = 0.1. Funnel plot.



eFigure 30 - CK >10xULN. Exclusions of studies testing simvastatin 80 mg. Forest plot.

| | Experime | ntal | Control | | | | |
|--|----------|------------------|--------------|---------------------------------|------------|-------------------------------|----------|
| Study | Events T | otal Events | Total | Risk Ratio | RR | 95%-CI | Weight |
| Group 1: Moderate-Placebo | | | | | | | |
| CARDS, A10 | 0 1 | 428 4 | 1410 | | 0.11 | [0.01; 2.04] | 2.2% |
| LIPS, F80 | _ | 822 3 | | • | 0.14 | [0.01; 2.75] | 2.1% |
| CORONA, R10 | | 514 3 | _ | | 0.33 | [0.03; 3.18] | |
| AFCAPS, L20-L40 | | 304 21 | | + | 1.00 | [0.55; 1.83] | |
| GISSI-HF, R10 | | 28 5 1 | 2289 | | 1.00 | [0.06; 16.01] | |
| PROSPER, P40 | | 891 (| | | 1.01 | [0.02; 50.76] | |
| 4D, A20 | | 619 | | | 1.03 | . , . | |
| HPS, S40 | 11 10 | | 10267 | • | 1.83 | [0.68; 4.95] | |
| WOSCOPS, P40 | | 302 | 3293 | - | 2.99 | [0.31; 28.75] | |
| ALERT, F40-F80 SSSS, S20-S40 | | 045 1 221 1 | 1049 2223 | | 3.01 | [0.31; 28.90] | |
| Random effects model | | 700 | 30696 | | 1.17 | [0.72; 49.84] [0.72; 1.90] | |
| Heterogeneity: $I^2 = 4\%$, $\tau^2 = 0.0303$, $p = 0.4^\circ$ | | 700 | 30030 | • | 1.17 | [0.72, 1.90] | 33.0 /0 |
| 110torogenetty. 7 = 470, t = 0.0000, p = 0.4 | I | | | | | | |
| Group 2: High-Placebo | | | | 2 / ₂ | | | |
| TRACE RA, A40 | 0 1 | 504 | 1498 | | 1.00 | [0.02; 50.16] | 1.2% |
| SPARCL, A80 | 2 2 | 365 0 | 2366 | | | [0.24; 104.14] | |
| Random effects model | 3 | 869 | 3864 | | 2.73 | [0.25; 30.11] | 3.2% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$ | | | | " | | | |
| | | | | | | | |
| Group 3: High-Moderate | | | | | | | |
| TNT, A80 vs A10 | | | 5006 | * | 0.50 | [0.05; 5.52] | |
| Random effects model | 4 | 995 | 5006 | | 0.50 | [0.05; 5.52] | 3.2% |
| Heterogeneity: not applicable | | | | | | | |
| Random effects model | 20 | 564 | 39566 | | 1 16 | [0.75; 1.78] | 100 0% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.55$ | 39 | JU -1 | 33300 | | 1.10 | [0.70, 1.70] | 100.0 /0 |
| Residual heterogeneity: $I^2 = 0\%$, $p = 0.35$ | | | (| 0.01 0.1 1 10 10 | 00 | | |
| r to state in the regarding. $r = 0.70$, $\rho = 0.40$ | | | | Statin Protective Statin Harmfi | | | |
| | | | _ | Clock of Claim Halling | ~ . | | |

eFigure 31 - CK >10xULN. Exclusions of studies testing simvastatin 80 mg. Funnel plot.



| | Placebo | Moderate Intensity | High intensity – with Simvastatin 80mg | High Intensity – without Simvastatin 80mg |
|---------------------|--|---|---|---|
| Any Muscle | 38.8 cases per 1000 | 41.1 cases per 1000 | 44.0 cases per 1000 | 32∮ cases per 1000 |
| Problems | person years (9661/248993.8; 19 arms)* | person years (10946/266265.8; 20 arms)* | person years (4654/105761.54; 7 arms)* | person years (1992/60873.1; 5 arms)* |
| Myalgia | 6.2 cases per 1000 person | 14.9 cases per 1000 | 38.9 cases per 1000 | 20.5 cases per 1000 |
| | years | person years | person years | pegson years |
| | (1060/169746.5; 12 arms)* | (3022/202684; 11 arms)* | (3781/97082.8; 5 arms)* | (1) \$60/56675.1; 4 arms)* |
| Attrition due to | 1.4 cases per 1000 person | 1.7 cases per 1000 person | 3.5 cases per 1000 person | 1634 cases per 1000 |
| Muscle | years | years | years | person years |
| | (198/145,857.2; 8 arms)* | (311/178940.2; 11 arms)* | (173/ 49086.44; 3 arms)* | (6 8 /4198; 1 arm)* |
| Rhabdomyolysis | 5.8 cases per 100,000 person years | 6.9 cases per 100,000 person years | 1.4 cases per 100,000 person years | 8.2 cases per 100,000 person years |
| | (13/225,713.6; 18 arms)** | (18/262803.8; 18 arms)** | (15/105822.3; 7 arms)** | (5/60933.9; 5 arms)** |
| Elevated CK | 2.7 cases per 10,000 person years | 2.9 cases per 10,000 person years | 9.4 cases per 10,000 person years | 0.8 cases per 10,000 person years |
| | (41/153,768.1; 13 arms)* | (61/207814.1; 14 arms)* | (80/84712.4; 5 arms)* | (3\\delta\)9824; 3 arms)* |
| * Incidence rates s | ignificantly different across t | rials, p<0.0001 | | <u>g</u> |
| | oportion of cases was not sig such small proportions (p>0 | nificantly different across tria.05) | als, although a chi square test | t may have been insensitive to rotected by copyright. |
| | For peer reviev | v only - http://bmjopen.bmj.com/ | site/about/guidelines.xhtml | |

eTABLE 2: NMA RESULTS WITHOUT A-Z⁴² and SEARCH⁴⁴ TRIALS

| | Placebo – Moderate Intensity | | | Moderate – High Intensity | | | Placebo – High Intensity | | |
|-----------|------------------------------|-----------------|-----|---------------------------|-----------------|-----|--------------------------|-----------------|-----|
| Outcome | RR | RD _ | NNH | RR | RD | NNH | RR | RD | NNH |
| | (95% CI) | (95% CI) | | (95% CI) | (95% CI) | | (95% CI) | (95% CI) | |
| Any Probs | 1.01 | 0.000 | | 1.02 | 0.003 | | 1.04 | 0.003 | |
| | (0.99, 1.04) | (-0.001, 0.001) | | (0.96, 1.09) | (-0.002, 0.007) | | (0.98, 1.10) | (-0.002, 0.007) | |
| Myalgia | 1.11 | 0.001 | | 1.01 | 0.005 | | 1.12 | 0.006 | 182 |
| | (0.97, 1.27) | (-0.000, 0.001) | UK | (0.88-1.16) | (-0.000, 0.009) | | (1.02-1.23) | (0.000, 0.010) | |
| Attrition | 1.13 | 0.001 | | 1.21 | 0.006 | | 1.36 | 0.006 | |
| | (0.93, 1.36) | (-0.000, 0.001) | | (0.86, 1.71) | (-0.005, 0.016) | | (0.92,2.03) | (-0.004, 0.016) | |
| Rhabdo. | 1.39 | 0.000 | | 0.70 | -0.000 | | 0.97 | 0.000 | |
| | (0.70,2.75) | (-000, 0.001) | | (0.22, 2.21) | (-0.000, 0.000) | | (0.32,3.00) | (-0.001, 0.001) | |
| CK>10ULN | 1.19 | -0.000 | | 1.07 | -0.000 | | 1.28 | 0.000 | |
| | (0.77, 1.85) | (-0.004, 0.000) | | (0.19, | (-0.000, 0.000) | | (0.23, 7.06) | (-0.000, 0.000) | |
| | | | | 5.94) | | | | | |
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PRISMA 2009 Checklist

| Section/topic | # | Checklist item 043714 | Reported on page # |
|------------------------------------|----|--|--------------------------|
| TITLE | | on 1 | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 (Title) |
| ABSTRACT | | ле 20 | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| INTRODUCTION | | o ad. | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5 (Intro) |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5-6 |
| METHODS | | bm | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number. | 3 (abstract) |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6-7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | With Prospero reg. |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 6-7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and ਉੱ y assumptions and simplifications made. | 6-7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specifications of whether this was done at the study or outcome level), and how this information is to be used in any data synthms. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |



PRISMA 2009 Checklist

| | | 1-2020 | |
|-------------------------------|----|---|--------------------|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis. | 8 |
| | | Page 1 of 2 Q | |
| Section/topic | # | Checklist item | Reported on page # |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| RESULTS | | ad ec | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8-9 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 8-11, Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summais data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figures |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Figures |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Results section |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Results section |
| DISCUSSION | | by <u>c</u> | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 15-16 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16-17 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 17-18 |
| FUNDING | | D S D D D D D D D D D D D D D D D D D D | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml | Title page |

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BMJ Open

INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS: A NETWORK META-ANALYSIS OF 153,000 PATIENTS

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Ву

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ABSTRACT

Objective: To estimate relative risk of statin-associated musculoskeletal symptoms (SAMS) by statin therapy intensity.

Setting: Network meta-analysis assessing multi-center RCTs across several countries.

Participants: Pubmed, Web of Science, Cochrane database, and clinicaltrials.gov were searched through January 2021 for doubled-blinded RCTs testing the effect of statin therapy on lipids with at least 1000 participants and two years of intended treatment.

Two coders assessed articles for final inclusion, quality, and outcomes. Treatment

intensity was categorized according to American Heart Association definitions.

Outcomes: Pairwise and network meta-analysis (NMA) estimated relative risk (RR) and risk difference (RD) with random effects modeling. Heterogeneity was evaluated with the I² statistic. Outcomes included muscle symptoms (any, myalgia, and attrition due to muscle symptoms), rhabdomyolysis, and elevated creatine kinase (>10x upper limit of normal).

Results: Of 2919 RCTs, 24 (N=152,461) met inclusion criteria. NMA results indicated risk was significantly greater for high compared to moderate intensity statin therapy for any muscle problem (RR=1.04, 95% CI: 1.00,1.07; I²=0%), myalgia (RR=1.04, 95% CI: 1.00,1.08; I²=0%, NNH=173), attrition due to muscle problems (RR=1.37, 95% CI: 1.09,1.73, I²=0%, NNH=218), and elevated CK (RR=4.69, CI: 2.50, 8.80; I²=7%, NNH=527). Risk also was significantly higher for high intensity compared to placebo for any muscle problem (RR=1.05, 95% CI: 1.01,1.09, I²=0%), myalgia (RR=1.13, 95% CI: 1.05,1.23; I²=0%, NNH=182), attrition due to muscle problems (RR=1.55, 95% CI: 1.15,2.08, I²=0%, NNH=187), and elevated CK (RR=5.37, CI: 2.48, 11.61; I²=7%,

NNH=589). Due to inconsistency of results across sensitivity analyses, estimates were inconclusive for rhabdomyolysis and CK. There were no significant differences in risk between moderate intensity therapy and placebo for all outcomes.

Conclusions: For approximately each 200 patients on high intensity statins, one additional patient may experience myalgia or discontinue therapy due to muscle problems compared to moderate intensity therapy.

Trial Registration: Prospero #CRD42019112758

Article Summary:

Strengths

- High-quality, large RCTs analyzed with low risk of heterogeneity bias
- Novel use of network meta-analysis to compare treatment intensities allows for large analysis of dose-dependent effect
- Coding of outcome terms directly as reported by investigators to minimize bias

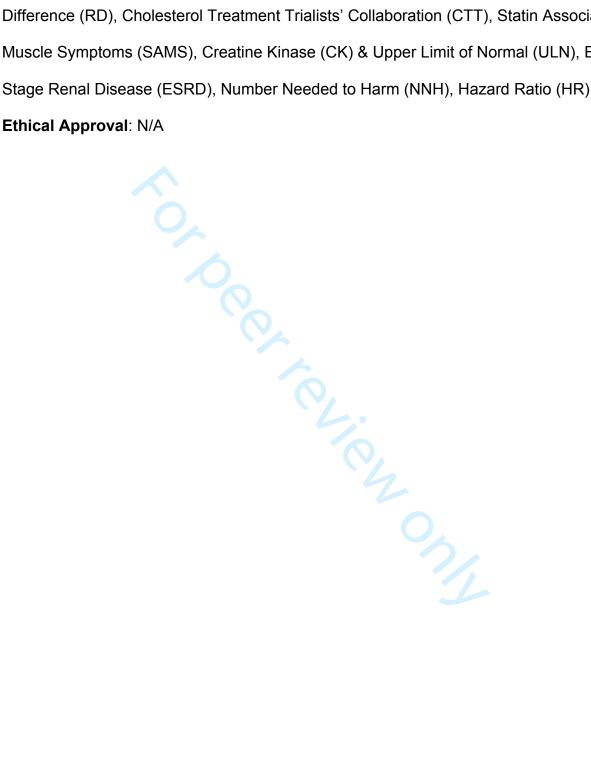
Weaknesses

- Study-level data precludes meta-analysis with regression for relevant covariables affecting risk of outcome
- Heterogeneity of terms across trials prevented analysis of full trial set for each outcome.

Key Words: Statins, myalgia, nocebo, rhabdomyolysis, network meta-analysis

Abbreviations:

Network Meta-Analysis (NMA) and pair-wise meta-analysis (MA), Risk Ratio (RR), Risk Difference (RD), Cholesterol Treatment Trialists' Collaboration (CTT), Statin Associated Muscle Symptoms (SAMS), Creatine Kinase (CK) & Upper Limit of Normal (ULN), End Stage Renal Disease (ESRD), Number Needed to Harm (NNH), Hazard Ratio (HR)



INTRODUCTION

The Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis on patient-level data from large RCTs demonstrated that statin therapy is efficacious in reducing major vascular events. 1,2 Statin therapy is now prominent in cholesterol management guidelines. 3-8 Statin-associated muscle symptoms (SAMS), however, may lead to nonadherence or discontinuation with therapy and ultimately to poorer cardiovascular outcomes. Most RCTs have shown small, insignificant increases in risk for SAMS, although patients taking statins may complain of muscle problems and may discontinue therapy due to muscle problems.³ For example, a 2016 meta-analysis found a nonsignificant increase in myopathy. However, it did not report on the more mundane myalgias that often cause statin attrition.³ These milder symptoms are the major public health concern, as statin non-adherence can lead to significant increases in risk of major adverse cardiovascular events.³ Observational studies suggest that these mild SAMS may occur as often as 7-29% of patients. One review suggested that clinical observations of increased muscle problems with statin therapy may be due to patient expectations.

SAMS also may be more likely with higher intensity therapy. Although this is assumed to be true, especially with the evidence against simvastatin 80 mg,^{10,11} few RCTs have examined high intensity therapy^{12,13}. This study used a network meta-analysis (NMA) to combine evidence across trials to estimate the risk of SAMS by treatment intensity. In contrast to pair-wise meta-analysis (MA) that directly estimates causal effects, a NMA can indirectly estimate risk between placebo and moderate, moderate and high, and

between placebo and high intensity treatment – even though placebo, moderate, and high intensity treatment levels were not compared within a single trial. Results contribute to the debate about whether muscle adverse events are due solely to patient expectations or whether statins might have an independent effect on symptoms. Finally, this study contributes to the ongoing debate as to whether statins cause myalgias and attrition due to muscle problems without marked creatine kinase (CK) elevations.

METHODS

The Trials. PubMed, Cochrane Database, Web of Science, and clinicaltrials.gov were searched for "systematic reviews" and "meta-analysis" in the title, abstract, or keywords prior to January 31, 2021to identify eligible trials (Prospero #CRD42019112758; see online supplement for search terms and strategy). Double-blinded RCTs to improve lipid levels comparing statin therapy to placebo or higher-lower dose statin therapy were selected. In order to detect most adverse events, RCTs were selected that had at least 1,000 participants with two years of intended follow-up, where statin treatment was not given with other prescription drug therapies, and results contained reports on muscle-related adverse events. Both authors independently reviewed trials for final inclusion and coded each for quality with Oxford Center for Evidence-based Medicine ratings¹⁴ and a five-point Jadad quality score. Any disagreements were reconciled by joint review and discussion.

Patient and Public Involvement. Patients were not involved in design or implementation of this study.

Exposure Variable. Studies were classified by intensity of statin treatment ("high" or "moderate") according to American Heart Association definitions for potency in reduction of lipid levels. ¹⁶ High intensity signifies an expected 50% or greater reduction in LDL-C levels when taking that statin (i.e., 80 mg atorvastatin) and moderate signifies 30-50% reduction in LDL-C. ¹⁶

Outcome Variables. Adverse muscle-related events were coded into five main outcomes. The first outcome was for any patient-reported muscle complaint coded from reports of "muscle aches", "pains", "cramps", "stiffness," "musculoskeletal disorders," etc. The second focused on only myalgia or muscle pain. The third focused on attrition due to musculoskeletal complaints. A fourth captured explicit reporting of rhabdomyolysis, with or without a trial definition. The fifth was elevated creatine kinase, greater than ten times the upper limit of normal (CK >10x ULN). This threshold was used to distinguish this outcome from less meaningful CK increases and also because CK>10xULN is commonly reported in RCTs. All outcomes were coded as reported by original investigators in published and online reports, and were independently coded by both authors. Ambiguities were resolved by contacting trial investigators.

Analysis. Published aggregate data from each trial were used. A crude estimate of incidence was calculated from the total number of cases observed divided by the total person-years (using the median or mean follow-up time for each study) and a chi square test was used to test for homogeneity in the proportion of incident cases across studies, within each arm, although these crude estimates ignored randomization. To

facilitate interpretation and comparison of results to the original trials, risk of adverse effects was estimated with pooled relative risk (RR). A 0.50 continuity correction was added to aggregate frequencies for trials that observed zero cases of an outcome in either treatment arm. A pairwise meta analysis (MA) was used to estimate the RR (Mantel-Haenszel method, random effects)¹⁷ for a statin effect by treatment intensity from direct (head-head comparison) trials in the meta package in R.¹⁸ Because aggregations across studies are only meaningfully interpreted when results are consistent across studies, heterogeneity among RCTs was assessed with an index of consistency across trials (I², Q)^{19,20} and funnel plots. When I² <25%, results are considered to be at low risk of bias due to heterogeneity; high values (>75%) indicate high risk of bias due to heterogeneity. 19,20 Residual I² represents the heterogeneity remaining after accounting for sub-groups of treatment intensity. Cochrane's Q (a subcomponent of I²) indicates the probability that the observed heterogeneity is due to chance. Sensitivity analyses included omitting outliers identified in funnel plots and using a 0.10 as a "continuity correction". In addition, analyses were conducted excluding the simvastatin 80 mg studies because of US FDA muscle-related safety warnings.²¹

A network meta-analysis (NMA), conducted in R,²² used *all* available pairs of comparisons for each outcome to estimate increased risk between the three levels of treatment exposure. Prespecified comparisons were between placebo and moderate intensity, between moderate and high intensity therapy, and between placebo and high intensity. The RR was used to estimate effect size (frequentist, inverse variance method, random effects), so that results would be comparable across original studies

and the pairwise meta-analysis above. In contrast to a MA which provides a direct estimate of the RR, a NMA provides estimates by combining direct and indirect evidence from all data. A ratio test was used to test for consistency between NMA direct and indirect estimates.²³ Heterogeneity was assessed with and I² and Q statistics.^{19,20} Number needed to harm (NNH, the inverse of the absolute difference in incidence) was estimated when the pooled RR was significantly greater than 1.0 and the pooled absolute risk reduction (risk difference, RD) was significantly greater than 0.0. Sensitivity analyses included replacement of zeros with 0.10 and with 0.0001.

RESULTS

Searches yielded 134 relevant reviews, including 2919 RCTs that reduced to 24 unique RCTs that met eligibility requirements (see online supplement). Of the 24 RCTs: 17 were placebo-moderate intensity comparisons, 24–44 3 were placebo-high intensity comparisons, 45–47 and 4 were moderate-high intensity comparisons 10–13 (Table 1). The active blood pressure treatment arm of the HOPE trial 37 was excluded, but the statin only and placebo only arms were retained, allowing for a statin and placebo comparison. Two trials compared moderate and high intensity therapy using 80 mg/day of simvastatin. 10,11 All 24 RCTs scored the highest quality (1) on the Oxford rating and on the Jadad scale 18 scored 5/5 and 6 scored 4/5 (missing detail on random assignment). The RCTs included heterogenous patient populations, e.g., healthy middle-aged adults 26,37,43,46 to ESRD patients. Sample sizes ranged from 1,255²⁴ to 20,536⁴⁰ with follow-up periods from 1.9⁴⁶ to 6.7¹⁰ years. Of the 24 RCTs, six were included in the 2006 meta-analysis, 48 17 in the 2014 systematic review, 49 23 in the 2016

meta-analysis,³ and 18 in the 2013 NMA.⁵⁰ None of the previous analyses separated trials into sub-groups by treatment intensity. Crude estimates of incidence increased with intensity of treatment from placebo to moderate intensity to high intensity therapy, but with heterogeneity across trials (online supplement).

Any Muscle Symptoms. Twenty-three trials reported some type of muscle symptom^{10,13,25–29,31,35,39,40,46,47} myositis,³⁴ myalgia,^{12,24,30,32,33,42,45} myopathy,^{24,38} or discontinuation due to muscle-related symptoms.^{11,13,36} The pairwise meta-analysis pooled across subsets of trials indicated consistent trial results with a 1% non-significant increase in risk between placebo and moderate intensity therapy, a 3% non-significant increase between placebo and high intensity therapy (Figure 1), and a 5% significant increase between moderate and high intensity therapy (RR=1.05, 95% CI: 1.01, 1.09; p=0.027, 4 RCTs, N=30,720; I²=0%). Sensitivity analyses indicated that RRs were essentially unchanged without an outlier³⁰ identified on the funnel plot, with a 0.10 correction, or without the simvastatin 80 mg trials. (online supplement).

The NMA pooled direct and indirect evidence from all 23 trials and suggested increased risk with higher intensity therapy. Results (Table 2) indicated a 1% non-significant increase in risk between placebo and moderate intensity therapy, a 4% significant increase between moderate and high intensity therapy (RR=1.04, 95% CI: 1.00, 1.08; p=0.031), and a 5% significant increase between placebo and high intensity therapy (RR=1.05, 95% CI: 1.01, 1.09; p=0.012). The RRs were consistent across studies (I²=0%; Q, p=0.54), were not significantly different between direct and indirect estimates (p=0.48), and were not sensitive to substitutions for zero values. Pooled RDs between

pairs of treatment groups were not significantly different from zero. There were no outliers in the NMA analysis. Exclusion of the two simvastatin 80mg trials did not meaningfully change risk, but comparisons with high intensity were not statistically significant, likely due to the decreased sample size (online supplement).

Myalgia or pain. Thirteen RCTs reported cases of myalgia, ^{25,29–32,42,44–47} attrition due to myalgia, ^{26,28} or pain and/or weakness. ⁴⁰ The pairwise meta-analysis indicated (Figure 2) a 13% non-significant increase in myalgia between placebo and moderate intensity, a 9% non-significant increase between placebo and high intensity, and a 4% significant increase between moderate and high intensity (RR=1.04, 95% CI: 1.00;1.09, p=0.040, 2 RCT, n=22065; I²=0%). The three trials comparing placebo and high intensity therapies suggested moderate heterogeneity in results (I²=45%). Funnel plots did not suggest bias by any of the studies and there were no zero cells (Figures 10-11). Exclusion of the simvastatin 80 mg trial did not meaningfully change the magnitude of risk, although results were non-significant for high intensity compared to moderate intensity therapy possibly due to decreased sample size (online supplement).

The NMA results combining evidence for all 13 trials suggested an increase in myalgia with increased therapy intensity (Table 2). There was a 9% non-significant increase in risk between placebo and moderate intensity therapy, a 4% significant increase between moderate and high intensity therapy (RR=1.04, 95% CI: 1.00, 1.08; p=0.046), and a 13% significant increase in risk for high intensity therapy compared to placebo without heterogeneity (RR=1.13, 95% CI: 1.05, 1.23; p=0.002). The RRs were

consistent across studies (I²=0%, Q, p=0.48) and direct and indirect estimates were not significantly different (p=0.63). The pooled RD was significant between high and moderate intensity (NNH=173) and between high intensity and placebo (NNH=154) with low heterogeneity (I²=20%; Q, p=0.25). Exclusion of the simvastatin 80 mg trial did not change the magnitude of risk although results were not significant for high intensity compared to moderate intensity therapy (online supplement).

Attrition. Attrition due to muscle problems was reported by eight RCTs that compared moderate intensity statin therapy with placebo, ^{25,26,28,32,36–38,40,44} three that compared moderate with high intensity therapy, ^{10,11,13} and none that directly compared high intensity to placebo. In the pairwise meta-analysis (Figure 3), patients on moderate intensity statin therapy had a 13% non-significant increase in attrition due to muscle problems compared to placebo. Patients on high intensity therapy had a 38% significantly higher attrition rate than those on moderate intensity (RR=1.38, 95% CI: 1.04, 1.82; p=0.024, 3 RCTs, N=20,719) with moderate heterogeneity across trials (I²=31%). Funnel plots did not suggest bias and there were no zero cells. Exclusion of the two simvastatin 80 mg trials left only one moderate-high intensity comparison RCT (online supplement).

The NMA results for the 11 trials suggested that risk for attrition increased with intensity of therapy. There was a 13% non-significant increase in risk between placebo and moderate intensity therapy (Table 2), a 37% significant increase in risk between moderate and high intensity (RR=1.37, 95% CI: 1.09, 1.73; p=0.007), and a 16%

significant increase in risk between placebo and high intensity therapy (RR=1.16, 95% CI: 1.15, 2.08; p=0.004). The RRs were consistent across studies (I²=0%; Q p=0.72) and closely paralled direct results provided by the meta-analysis, but the NMA provided an estimate for the placebo-high intensity comparison for which there were no head-to-head trials. The pooled RD between moderate and high intensity therapy was significant and the NNH was 218. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 186. Exclusion of the two simvastatin 80 mg trials resulted in a slightly lower risk estimate for the moderate to high comparison and a slightly higher estimate for the placebo to high comparison, and both were non-significant (online supplement).

Rhabdomyolysis. Rhabdomyolysis was reported on by 14 moderate intensity-placebo comparison RCTs, ^{24–28,30–32,35,36,39–42} four moderate-high intensity comparison RCTs, ^{10–13} and three high intensity-placebo comparison RCTs. ^{45–47} Incidence of rhabdomyolysis was very low and statistical comparisons were not conclusive. Pairwise meta-analysis indicated a 39% non-significant increase in rhabdomyolysis incidence between placebo and moderate intensity therapy, 145% non-significant increase between moderate and high intensity, and a 4% non-significant decrease between placebo and high intensity therapy (Figure 4). Results were inconclusive as estimates were not robust across sensitivity analyses. Approximately half (22/42) of the cells were zeros and RR increased for the moderate-high intensity comparison with a smaller correction and removal of the simvastatin 80 mg trials meaningfully changed effect sizes (online supplement).

NMA results based on all 21 trials indicated increased risk for rhabdomyolysis with increased intensity of therapy (Table 2). There was a 22% non-significant increase in risk between placebo and moderate intensity therapy, a 33% non-significant increase between moderate and high intensity, and a 66% non-significant increase between placebo and high intensity therapy with consistency across trials (I²=0%, Q p=0.99). Direct and indirect RR estimates were not significantly different (p=0.31). Results were not consistent after exclusion of simvastatin 80 mg trials or replacement of zeros, but remained nonsignificant (online supplement).

Elevated CK. Of 16 RCTs, 11 compared rates of elevated creatine kinase (CK>10xULN) between placebo and moderate intensity therapy, ^{24–27,32,35,36,39–43} three compared moderate to high intensity therapy^{10–12} and two compared high intensity therapy with placebo. ^{45,47} Incidence of elevated CK was low. Pairwise meta-analysis indicated (Figure 5) a 17% non-significant increase in CK elevation between placebo and moderate intensity therapy, a 173% non-significant increase between placebo and high intensity therapy, and a 288% significantly higher risk for high compared to moderate intensity (RR=3.88, 95% CI: 1.05,14.31; p=0.042, 3 RCTs, n=26,558) with some heterogeneity among the three trials (I²=50%). Estimates were not stable across sensitivity analyses. Removal of two possible outliers, ^{10,26} exclusion of simvastatin 80 mg trials, and adjustment for cells with zeros (9/32) meaningfully changed RR estimates (online supplement).

Using evidence from all 16 trials, the NMA estimates indicated increased risk with increased intensity. NMA results indicated a 14% non-significant increase between placebo and moderate intensity therapy (Table 2), a 359% significant increase in CK elevation between moderate and high intensity (RR=4.59, 95% CI: 2.32,9.10; p<0.0001), and a 425% significant increase between placebo and high intensity (RR=5.25, 95% CI: 2.29,12.03; p<0.0001). Results were consistent across trials (I²=7%, Q p=0.37) and direct and indirect RR estimates were not significantly different (p=0.57). The pooled RD between moderate and high intensity therapy was significantly different from zero and the NNH was 527. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 589. There were no outliers in the NMA analysis. Although results were homogeneous with the simvastatin 80 mg trials, exclusion of these trials meaningfully reduced risk associated with statin therapy between moderate and high intensity and between placebo and high intensity therapy; and smaller zero replacement values increased risk estimates (online supplement).

DISCUSSION

A novel contribution of this study was the application of NMA to estimate the doseresponse effect of statin therapy on muscle symptoms using clinically-meaningful
categories of treatment intensity. The NMA RR estimates closely paralleled the direct
estimates, indicating reliability of estimates and increased risk with high intensity statin
therapy. The network meta-analyses provide information about risk by utilizing all
available evidence, whereas traditional meta-analyses are limited only to direct, headto-head comparisons. For patient-reported symptoms, there were non-significant

increases in SAMS between placebo and moderate intensity therapy and significant increases between moderate and high intensity therapy. Because simvastatin 80mg therapy is now restricted because of muscle injury,⁵¹ analyses also were run with and without those trials. This did not meaningfully affect results for patient-reported outcomes. Rhabdomyolysis and elevated CK also showed increased risk with higher intensity, but because of low incidence (with 25-50% zero cells) and inconsistency across sensitivity analyses, results were inconclusive.

Double-blinded RCTs and traditional meta-analyses^{3,48,49} suggest no significant increase in risk of muscle adverse events with statin therapy. Since most evidence comes from moderate intensity trials, possible adverse effects of high intensity therapy may be masked in aggregate estimates. In this study, high intensity therapy and focused definitions of patient-reported muscle problems detected higher risk. However, the absolute excess of SAMS was less than 1% for all outcomes. In previous meta-analyses, absolute excess of muscle problems also was small, but non-significant.^{3,49} The 2016 meta-analysis estimated risk for extreme outcomes (myopathy and rhabdomyolysis), but did not analyze patient reports of milder SAMS that we present and that concern patients. We did not code for myopathy as an outcome, because we did not have access to patient-level data and could not determine if elevated CK co-occurred with myalgia.

Direct lower-higher dose comparisons in individual RCTs were not consistent, e.g., the SEARCH¹⁰ and A to Z trials found a significant increase in CK and the TNT trial¹² did

not. A NMA that compared dosage increments within brands⁵⁰ suggested no systematic increase in risk for myalgia or discontinuation with higher dosages. These negative findings may have been due to smaller sample sizes, smaller dosage increments in restricted comparisons, or exclusion of the simvastatin 80 mg trials.⁵⁰ In this study, results were homogeneous including the simvastatin 80mg trials and indicated high intensity therapy significantly increased myalgia compared to placebo even after their exclusion. The previous NMA did identify a dose-response relationship between statin dose and mildly elevated CK (2-3x ULN), but only for lovastatin and simvastatin.⁵⁰ CK>10xULN may be more interpretable than modest elevations, and in this study it was significantly increased with high-intensity statin therapy. While removal of 80mg simvastatin trials had little effect on patient-reported symptoms, their exclusion resulted in smaller non-significant increases in risk for elevated CK. It is unclear if simvastatin 80mg was responsible for the significant increases in CK.

A practical question concerns how large an excess of cases might be observed with statin therapy for myalgia/pain, attrition due to muscle problems, and elevated CK or rhabdomyolysis. Although estimates based on observational studies suggest that incidence of mild SAMS might be as high as 30% among statin users,⁵² RCTs suggest a much lower rate. In this study, pooled risk estimates suggested that for each 173 patients on high intensity therapy one additional patient will experience statin-caused myalgia and for each 218 patients one additional patient will discontinue therapy due to muscle problems compared to those on moderate intensity therapy. This represents numerous patients who are at greatest risk for major vascular events, as these are often

higher risk patients. Discontinuation of statins in the elderly (>75 yrs) may result in 33% increased risk of a cardiovascular event within 3 months ⁵³ and adherence to statins in those 65 and older may reduce mortality by a third.⁵⁴

Myalgias and attrition due to SAMS are important outcomes for the average patient, but have not received as much attention as rhabdomyolysis and myopathy. This study provides evidence that while blinded, moderate intensity statin-takers did not report significantly more general muscle problems or myalgias, but those on high intensity therapy did. Because many myalgia cases occurred without CK elevation increases, this also serves as evidence that SAMS occur in the absence of large elevations in CK. Clinicians with patients who are "statin intolerant" may consider encouraging the patient to first decrease intensity of statin therapy, rather than discontinuing it, in light of these findings.

This analysis also contributes to the "nocebo" debate. A large, unblinded follow-up of RCT patients suggested SAMS are expectation-related.²⁹ They observed an incidence of 2.03% and 2.00% muscle-related adverse events in statin and placebo groups, respectively, when double-blinded (HR=1.03) and 1.26% and 1.00% in the statin and usual care groups when unblinded (HR=1.41).²⁹ Both comparisons indicate absolute differences less than 1%. A recent N-of-1 trial⁵⁵also found minimal differences in muscle symptoms when patients took statin versus placebo (blinded), but significantly more muscle symptoms when taking a placebo versus taking nothing (unblinded). Both nocebo and causal effects are small, although they can result in increased SAMS. In a

clinical setting, SAMS with moderate intensity therapy may be the result of patient expectations, but with high intensity therapy SAMS may be due to expectations and statin therapy. Intensity of treatment and patient expectations may need to be considered before making changes in statin therapy in the absence of CK elevations.

A limitation of study-level meta-analyses is that definitions,⁵⁶ assessment, and variable reporting of muscle-related outcomes may differ across studies. Aggregation of heterogeneous outcomes and estimated outcomes (e.g., myopathy) not explicitly reported by investigators can mask an effect. Protocol differences may partially explain incidence disparities across studies. However, use of the RR to estimate effect size minimizes bias due to between-study variations in protocol (e.g., using a symptom checklist versus recording spontaneous mention of symptoms and then categorizing responses).

Estimates in this analysis may have under-estimated SAMS by excluding patients with statin hypersensitivity, as four studies ^{12,37,40,45} (n=48,950) employed statin "washout" phases and eight trials ^{24,25,30,32,34–37,47} (n=34,042) excluded patients with known statin hypersensitivity. Collins et al. noted that "statin hypersensitivity" exclusion was a rare occurrence across these trials, as almost all patients enrolled were statin-naïve at screening.³ The risk of attrition due to SAMS and rhabdomyolysis was actually highest in SEARCH, where an eight week long, active run-in phase was conducted, ^{3,10} although no patients were excluded for elevated muscle enzymes. ¹⁰ Also, an N-of-1 trial in patients who were considering stopping or who had stopped statin therapy because of

muscle symptoms found no difference in severity of patient-reported muscle symptoms between statin and placebo groups.⁵⁷ Because simvastatin 80 mg trials comprise a high proportion of high intensity treatment evidence, this may limit interpretation of CK and rhabdomyolysis risk. Also, adverse events may have been increased due to the presence of co-morbidities; only three trials studied healthy adults (n=30,756).^{26,37,46} A final limitation is that although risk estimates are based on the best available evidence and should provide relatively unbiased estimates, confidence intervals and alpha significance levels may be approximate due to multiple comparisons.

Conclusion

Statins likely cause SAMS, but at much lower rates than observational data suggest.

We found significant increases in risk for patient-reported muscle problems on highintensity statins. Clinically-reported SAMS likely represent a combination of expectation
bias and true adverse effects.

Contributorship Statement:

The first author (JD) was responsible for the design and implementation of the study analyses. He was one coder in selecting studies for inclusion, compiled the data for the outcomes of interest, analyzed the data in R, and is responsible for the final manuscript in its entirety. SW (Faculty PI) was responsible for the oversight and implementation of the project. She was the second coder for all trials and offered guidance and support in all decisions regarding design and implementation of the analysis.

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Competing Interests:

None to disclose

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Data Sharing Statement:

All data used in this analysis is available in the online supplement.

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Figure Legend:

Figure 1: Any Muscle Problems

Figure 2: Myalgia or Pain

Figure 3: Attrition Due to Muscle Symptoms

Figure 4: Rhabdomyolysis

Figure 5: CK >10x Upper Limit of Normal

TABLE 1: DESCRIPTION OF THE TRIALS

TABLE 2: RELATIVE RISK AND RISK DIFFERENCE RESULTS FOR F TREATME.

COMPARISONS OF TREATMENT INTENSITY PAIRS

| | Total sample | Special | Permit Prior | Ave | Run-in Period | Median Yrs F/U |
|--|--------------|-------------------------------|-----------------|-----|-------------------------|-------------------|
| Trial Name | size | Population | statin† | age | | |
| Placebo-Moderate | | | | | | |
| 4D, A20 ²⁴ | 1,255 | DM II, ESRD | Y, -HS | 66 | Placebo | 4.0 |
| 4S, S20-S40 ²⁵ | 4,444 | MI or angina | Y, -HS | 59 | Placebo | 5.4 |
| AFCAPS, L20-L40 ²⁶ | 6,605 | Healthy adults | N | 58 | Placebo+diet | 5.2 |
| ALERT, F40-F80 ²⁷ | 2,094 | Renal Trans | N | 50 | None | 5.4 |
| ASCOT, A10 ^{28,29} | 10,810 | HTN+CVD risk | N | 63 | Not statin | 3.3 |
| ASPEN, A10 ³⁰ | 2,410 | DM II | Y, -HS | 61 | Placebo | 4.0 |
| AURORA, R10 ³¹ | 2,767 | ESRD | N | 64 | Placebo | 3.2 |
| CARDS, A10 ^{32,33} | 2,838 | DM II | Y, -HS | 62 | Placebo | 4.0 |
| CARE, P4034 | 4,159 | MI | Y, -HS | 59 | Placebo | 5.0 |
| CORONA, R10 ³⁵ | 5,011 | ESRD | Y, -HS | 73 | Placebo | 2.7 |
| GISSI-HF, R10 ³⁶ | 4,574 | CHF | Y, -HS | 68 | None | 3.9 |
| HOPE-3, R10 ³⁷ | 6,349 | Healthy, CVD Risk | Y, -HS | 66 | Statin | 5.6 |
| LIPID, P40 ³⁸ | 9,014 | MI or angina | Υ | 62* | Placebo+diet | 6.0 (mean) |
| LIPS, F80 ³⁹ | 1,640 | Coronary percut. intervention | Y | 60 | None | 3.9 |
| MRC/BHF (HPS), S40 ^{40,41} | 20,536 | CHD/CHD Risk | N | 64 | Placebo, then statin | 5 (mean) |
| PROSPER, P40 ⁴² | 5,804 | Elderly, CHD risk | Υ | 75 | Placebo | 3.2 (mean) |
| WOSCOPS, P4043,44 | 6,604 | Healthy males | Υ | 55 | None | 4.9 (mean) |
| Placebo-High | | | 9, | | | |
| JUPITER, R20 ⁴⁶ | 17,802 | Healthy adults | N | 66 | Placebo | 1.9†† |
| SPARCL, A80 ⁴⁵ | 4,731 | CVA/TIA | Υ | 63 | None | 4.9 |
| TRACE, A40 ⁴⁷ | 3,002 | RA | N, -HS | 61 | None | 2.5 |
| Moderate-High | | | | 5 | | |
| A to Z, S40-S80 vs 0- S20 ¹¹ | 4,497 | Acute Coronary | N | 61 | None | 1.98 |
| PROVE-IT, A80 vs | 4,491 | Syndrome Acute Coronary | Y, if | 58 | None | 2.0 (mean) |
| P40 ¹³ | 4,162 | Syndrome | <80mg | 50 | 140116 | 2.0 (IIIEaII) |
| SEARCH, S80 vs | 7,102 | Syndrome | Y | 64 | Statin+ | 6.7 |
| S20 ¹⁰ | 12,064 | MI | ' | 0- | Placebo | 0.7 |
| TNT, A80 vs A10 ¹² | 10,001 | CHD | Υ | 61 | Statin | 4.9 |
| *Median | 10,001 | 0,10 | <u> </u> | 01 | Otatiii | 1.0 |

^{*}Median

[†]Y=Yes, N=No, -HS=statin hypersensitivity exclusion

^{††} Trial was designed for two years of follow-up, but met study end points and terminated the blinded portion of the study earlier.

| | RS Placebo – Moderate Intensity Moderate – High Intensity Placebo – High | | | | | | | | |
|---------------|---|--------------------------|-----|------------------------|-------------------------|-----|---|-------------------------|-----|
| Outcome | RR (95% CI) | RD (95% CI) | NNH | RR (95% CI) | RD (95% CI) | NNH | RR 5 (95% CI) | | NNF |
| Any Probs | 1.010 (0.988,1.033) | 0.000 (-0.001,0.001) | | 1.039 (1.004,1.075) | 0.004 (-0.000,0.008) | | 1.049 (1.010,1.089) | 0.004 | |
| Myalgia | 1.090 (.9997,1.188) | 0.001 (-0.000,0.001) | | 1.041 (1.001,1.083) | 0.006 (0.001, 0.010) | 173 | 1.134 (1.046,1.230) | 0.007 (0.002, 0.011) | 182 |
| Attrition | 1.127 (0.931,1.364) | 0.001 (-000,0.001) | 0 | 1.372 (1.091,1.726) | 0.005 (0.002, 0.007) | 218 | 1.155 (1.147,2.084) | | 187 |
| Rhabdo. | 1.225 (0.624,2.405) | -0.000 (-0.001,0.001) | | 1.326 (0.487,3.614) | 0.002 (0.001,0.003) | | 1.624 (0.579,4.553) | 0.002 (0.000, 0.003) | |
| CK> 10xULN | 1.143 (0.686,1.905) | -0.000 (-0.001,0.001) | | 4.594 (2.320,9.098) | 0.002 (0.001, 0.003) | 527 | 5.252 (2.293,12.028) | 0.002 (0.000, 0.003) | 589 |
| | | | | | | | om/ on April 17, 2024 by guest. Protected by copyright. | | |

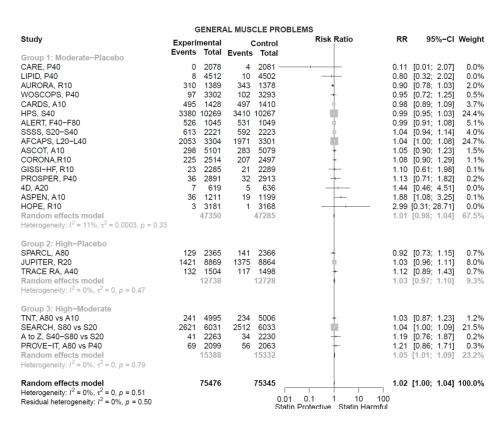


Figure 1

MYALGIA

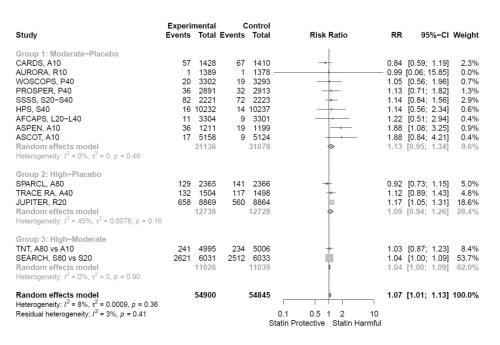


Figure 2

ATTRITION DUE TO MUSCLE SYMPTOMS

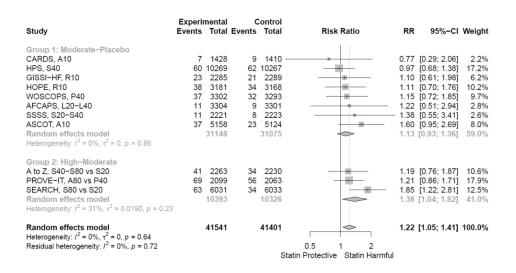


Figure 3

RHABDOMYOLYSIS

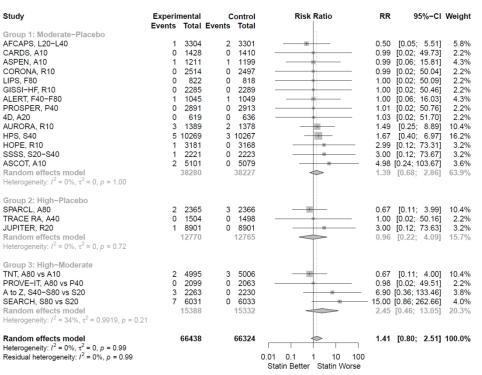


Figure 4

CK >10xULN

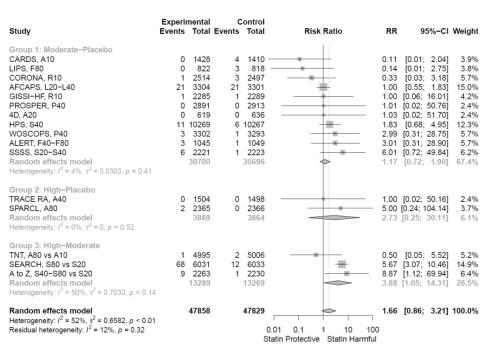


Figure 5

INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS:

A NETWORK META-ANALYSIS OF 153,000 PATIENTS

J.W. Davis & S.C. Weller

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- 3 PRISMA Flow Sheet
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- 7 ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot with data
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- 9 ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot with outliers excluded.
- 10 ANY MUSCLE PROBLEMS: Meta-Analysis Funnel plot with outliers excluded.
- 11 ANY MUSCLE PROBLEMS: Meta-Analysis Forest Plot with Continuity Correction = 0.1.
- 12 ANY MUSCLE PROBLEMS: Meta-Analysis Funnel Plot Continuity Correction = 0.1.
- 13 ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.
- 14 ANY MUSCLE PROBLEMS: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials

15 ANY MUSCLE PROBLEMS: SUMMARY TABLE

- 16 MYALGIA OR PAIN: Meta-Analysis Forest plot with data
- 17 MYALGIA OR PAIN: Meta-Analysis Funnel plot
- 18 MYALGIA OR PAIN: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.
- 19 MYALGIA OR PAIN: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials
- 20 MYALGIA OR PAIN: SUMMARY TABLE
- 21 ATTRITION: Meta-Analysis Forest plot with data

- 22 ATTRITION: Meta-Analysis Funnel plot
- 23 ATTRITION: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.
- 24 ATTRITION: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials

25 ATTRITION: SUMMARY TABLE

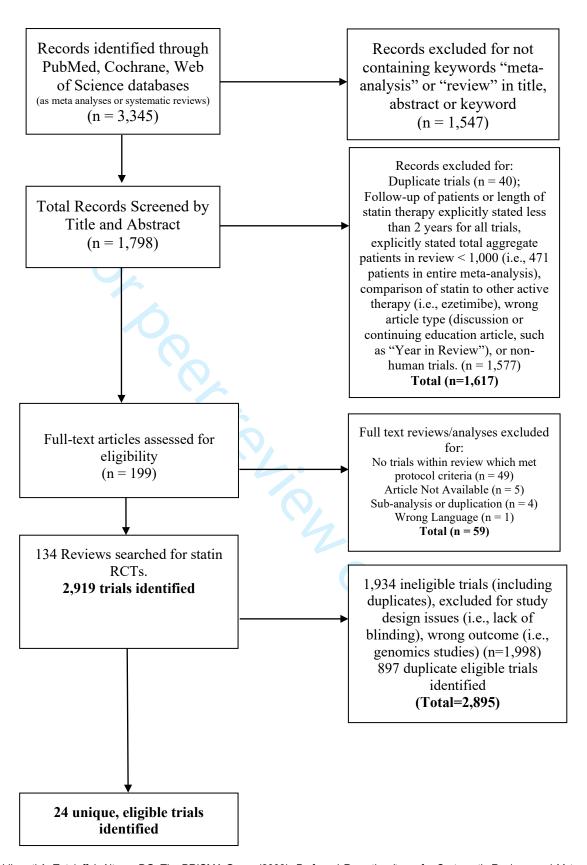
- 26 RHABDOMYOLYSIS: Meta-Analysis Forest Plot with Data
- 27 RHABDOMYOLYSIS: Meta-Analysis Funnel Plot
- 28 RHABDOMYOLYSIS: Meta-Analysis Forest Plot with Continuity Correction = 0.1.
- 29 RHABDOMYOLYSIS: Meta-Analysis Funnel Plot Continuity Correction = 0.1.
- 30 RHABDOMYOLYSIS: Meta-Analysis Forest Plot excluding simvastatin 80 mg trials.
- 31 RHABDOMYOLYSIS: Meta-Analysis Funnel Plot excluding simvastatin 80 mg trials

32 RHABDOMYOLYSIS: SUMMARY TABLE

- 33 CK > 10x ULN: Meta-Analysis Forest Plot with Data
- 34 CK >10x ULN: Meta-Analysis Funnel Plot
- 35 CK >10x ULN: Meta-Analysis Forest Plot with outliers excluded.
- 36 CK >10x ULN: Meta-Analysis Funnel Plot with outliers excluded.
- 37 CK > 10x ULN: Meta-Analysis Forest Plot with Continuity Correction = 0.1.
- 38 CK > 10x ULN: Meta-Analysis Funnel Plot with Continuity Correction = 0.1.
- 39 CK > 10x ULN: Meta-Analysis Forest Plot excluding simvastatin 80 mg trials.
- 40 CK >10x ULN: Meta-Analysis Funnel Plot excluding simvastatin 80 mg trials

41 CK >10x ULN: SUMMARY TABLE

- 42 R Code for Meta-Analysis
- 43 R Code for Network Meta-Analysis



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Search Procedure

PRISMA FLOWCHART explanation

- 1. PubMed, Cochrane Database, Web of Science, and clinicaltrials.gov were searched in November 2018 by a professional research librarian (Prospero #CRD42019112758). The search was updated for November 2018 through February 1, 2021. Web of Science was not searched in this second phase, as institutional access to the database had expired. The following page (eTable 3: Search Strategy) details the MEDLINE search and keywords for the combined search. The strategy was to search for all systematic reviews and meta-analyses, in English or Spanish, to identify RCTs for inclusion. Articles containing the term "systematic review" or "meta-analysis" in the title, abstract, or keywords were retained (1,646 from original search and 351 from the updated search = 1,997).
- 2. Based on information in the abstract, articles were retained that might contain a trial that met inclusion criteria (191 from original search and 8 more from the updated search = 199). Review of the full article eliminated an additional 59 articles, yielding 140 articles for full review. One author (JD) reviewed abstracts and full texts of articles.
- 3. Review of the 140 unique articles identified 2919 trials (2,801 from the original search and 118 trials in the updated search). Then, double-blinded RCTs were selected from these reviews that compared statin therapy to placebo or higher-lower dose statin therapy (24 unique trials).
- 4. The 24 eligible trials were independently judged by both authors (JD, SW) for inclusion, then coded for quality and outcomes. There was complete agreement on quality ratings with the Oxford Center for Evidence-based Medicine ratings and the Jadad quality score. Ambiguities in coding of outcomes were resolved by contacting the study PI.

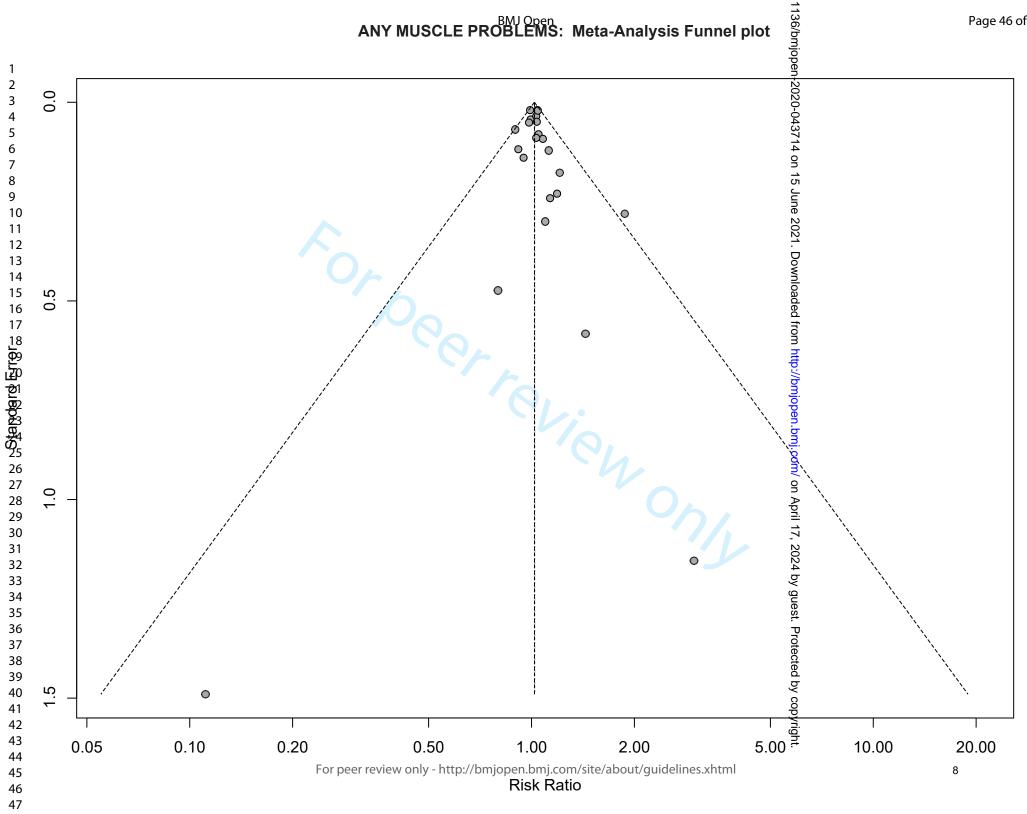
BMJ Open

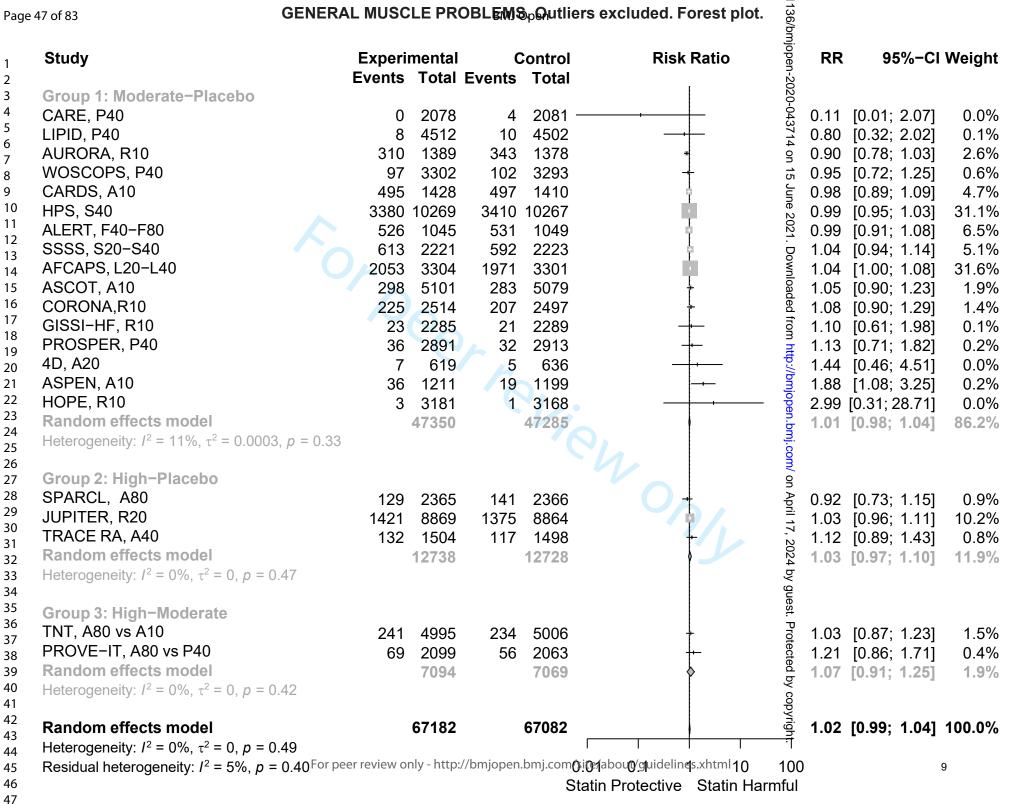
Sample Strategy: MEDLINE Search

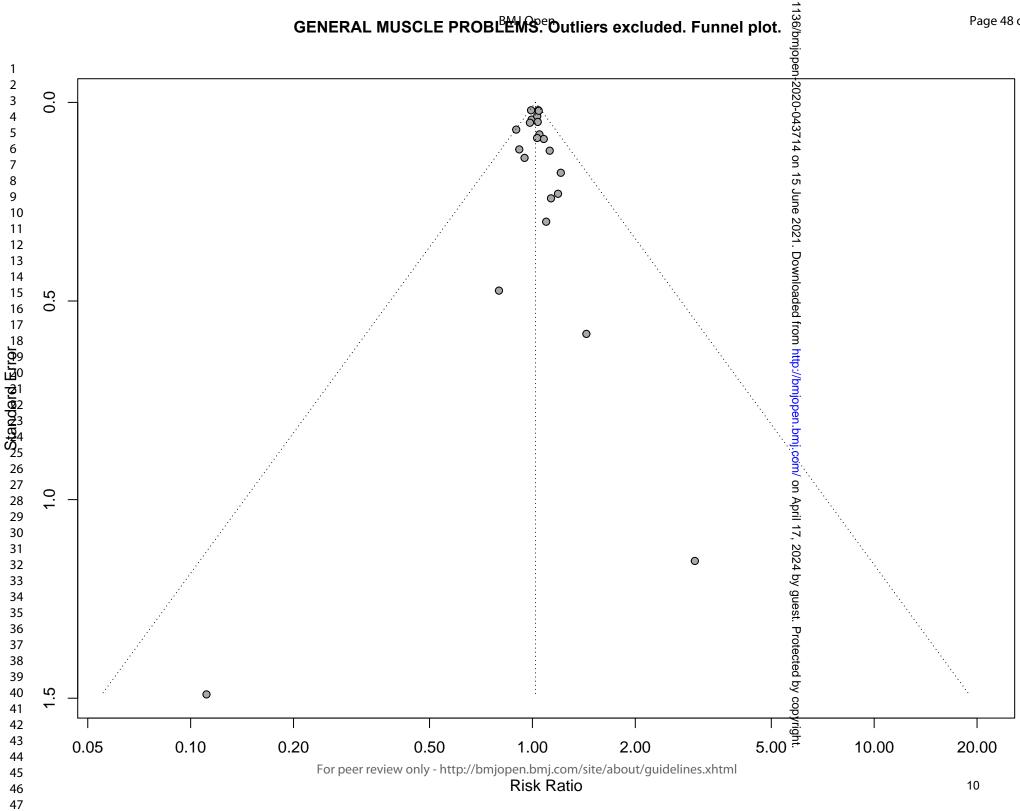
| 021 | Ovid: Current Search History | | | | |
|----------|--|-------------------|---------------------|---------|-------|
| _ | * 10 | | | Molters | Kluwe |
| C | Ny Account & Ask a Librarian Support & Training Help de Feedback I | ogged in as Julie | Trumble at Moody Me | | |
| Se | arch Journals Books Multimedia My Workspace ACC CardioSource Plus What's New | | | | |
| _ | AEDLINE(R) and Epub Ahead of Print, in-Process, in-Data-Review & Other Non-Indexed Citations and Daily <1946 to February | 26. 2021> | | | |
| # | Searches | Results | Туре | | |
| 1 | exp Hydroxymethylgiutaryi-CoA Reductase Inhibitors/ | 41740 | Advanced | | |
| 2 | (statin or statins).tw. | 40017 | Advanced | | |
| 3 | atorvastatin.tw. | 8871 | Advanced | | |
| 4 | cerivastatin.tw. | 664 | Advanced | | |
| 5 | fluvastatin.tw. | 1899 | Advanced | | |
| 6 | lovastatin.tw. | 3855 | Advanced | | |
| 7 | pravastatin.tw. | 4110 | Advanced | | |
| 8 | simvastatin.tw. | 9706 | Advanced | | |
| 9 | lipitor.tw. | 205 | Advanced | | |
| 10 | baycol.tw. | 14 | Advanced | | |
| 11 | lescol.tw. | 81 | Advanced | | |
| | mevacor.tw. | 48 | Advanced | | |
| 13 | altocor.tw. | 0 | Advanced | | |
| 14 | | 25 | Advanced | | |
| 15 | lipostat.tw. | 26 | Advanced | | |
| | zocor.tw. | 113 | Advanced | | |
| | mevinolin.tw. | 401 | Advanced | | |
| | compactin.tw. | 304 | Advanced | | |
| | fluindostatin.tw. | 4 | Advanced | | |
| 20 | | 3625 | Advanced | | |
| 21 | | 30952 | Advanced | | |
| 22 | A SECOND CONTRACTOR OF THE SECOND CONTRACTOR O | 4260 | Advanced | | |
| 23 | | 123 | Advanced | | |
| 24 | (6 methylcompactin or mk 803 or mk803 or mevinolin or monacolin k).mp. | 602 | Advanced | | |
| 25 26 | (megiutol or 3 hydroxy 3 methylgiutaric acid or 3 hydroxy 3 methylgientanediolc acid or beta hydroxy beta methylgiutarate).mp. (bristacol or cs 514 or cs514 or cs514 or clisor or epiastatin or lipemol or lipiat or ilostat or mevalotin or prareduct or pravacol or pravasin or rms 431 or rms431 or sq 31000 or sq31000 or selektine or vasten).mp. | 183 56 | Advanced | | |
| 27 | (crestor or zd 4522 or zd4522).mp. | 73 | Advanced | | |
| | (mk733 or mk 733 or synvinolin).mp. | 54 | Advanced | | |
| | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 | 63347 | Advanced | | |
| 30 | Animais/ not Humans/ | 4760183 | Advanced | | |
| 31 | 29 not 30 | 56479 | Advanced | | |
| 32 | limit 31 to (english or spanish) | 52717 | Advanced | | |
| 33 | Ilmit 32 to (meta analysis or "systematic review") | 1535 | Advanced | | |
| 34 | limit 32 to (systematic reviews pre 2019 or systematic reviews) | 3199 | Advanced | | |
| 35 | 33 or 34 | 3224 | Advanced | | |
| 36 | remove duplicates from 35 | 3202 | Advanced | | |
| 37 | Ilmit 36 to yr="1990 - 2017" | 2463 | Advanced | | |
| 38 | $(201801" \ or \ 201802" \ or \ 201803" \ or \ 201804" \ or \ 201805" \ or \ 201806" \ or \ 201807" \ or \ 201808" \ or \ 201809" \ or \ 201810" \ or \ 201811").ez.$ | 1083231 | Advanced | | |
| 39 | 37 or 38 | 1085687 | Advanced | | |
| 40 | 36 and 39 | 2668 | Advanced | | |
| 41 | Ilmit 36 to yr="2019 - 2020" | 443 | Advanced | | |
| 42 | 201812".ez. | 93882 | Advanced | | |
| | 202101*.ez. | 136550 | Advanced | | |
| | 42 or 43 | 230432 | Advanced | | |
| | 36 and 44 | 42 | Advanced | | |
| | 41 or 45 | 470 | Advanced | | |
| | Ilmit 36 to yr="2019 - 2021" | 501 | Advanced | | |
| | 36 and 42 | 20 | Advanced | | |
| | 47 or 48 | 512 | Advanced | | |
| | 49 not 46 | 42 | Advanced | | |
| 51 | from 50 keep 19, 26-27, 29, 33-37, 39, 42 | 11 | Advanced | | |

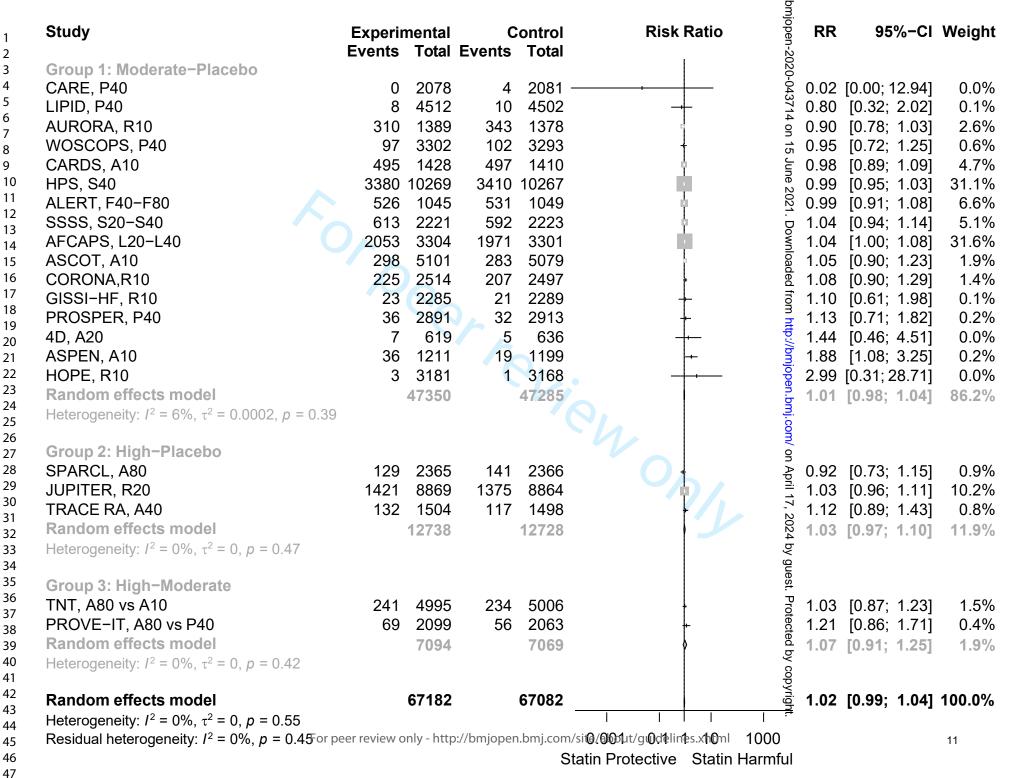
| | Placebo | Moderate Intensity | High intensity – with Simvastatin 80mg | High Intensity – without Simvastatin 80mg |
|----------------------------|---|--|---|--|
| Any Muscle Problems | 38.8 cases per 1000 person years (9661/248993.8; 19 | 41.1 cases per 1000 person years (10946/266265.8; 20 | 44.0 cases per 1000 person years (4654/105761.54; 7 | 32g7 cases per 1000 person years (1992/60873.1; 5 arms)* |
| | arms)* | arms)* | arms)* | (1 3 52/006/5.1, 5 arms) |
| Myalgia | 6.2 cases per 1000 person years | 14.9 cases per 1000 person years | 38.9 cases per 1000 person years | 20.5 cases per 1000 pegson years |
| | (1060/169746.5; 12 arms)* | (3022/202684; 11 arms)* | (3781/97082.8; 5 arms)* | (1 \$60/56675.1; 4 arms)* |
| Attrition due to Muscle | 1.4 cases per 1000 person years | 1.7 cases per 1000 person years | 3.5 cases per 1000 person years | 1634 cases per 1000 person years |
| | (198/145,857.2; 8 arms)* | (311/178940.2; 11 arms)* | (173/ 49086.44; 3 arms)* | $(6\frac{8}{6}/4198; 1 \text{ arm})*$ |
| Rhabdomyolysis | 5.8 cases per 100,000 person years | 6.9 cases per 100,000 person years | 1.4 cases per 100,000 person years | 8.2 cases per 100,000 person years |
| | (13/225,713.6; 18 arms)** | (18/262803.8; 18 arms)** | (15/105822.3; 7 arms)** | (5/60933.9; 5 arms)** |
| Elevated CK | 2.7 cases per 10,000 person years | 2.9 cases per 10,000 person years | 9.4 cases per 10,000 person years | 0. cases per 10,000 person years |
| | (41/153,768.1; 13 arms)* | (61/207814.1; 14 arms)* | (80/84712.4; 5 arms)* | $(3 \frac{8}{5} 9824; 3 \text{ arms})*$ |
| * Incidence rates si | ignificantly different across t | rials, p<0.0001 | | by gu |
| | oportion of cases was not sign such small proportions (p>0 | | als, although a chi square test | Pro |
| | | | | tected by |
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| | For peer reviev | v only - http://bmjopen.bmj.com/ | site/about/guidelines.xhtml | |

| Page · | 45 of 83 | ANY MUS | CLE PF | ROB Ľ EW | P S en Met | a-Analysis Forest plot with | ata. | | |
|----------|---|--------------|--------------|-----------------|-------------------|---|------|---------------|--------|
| | Study | Experi | mental | (| Control | Risk Ratio ਤੋਂ | RR | 95%-CI | Weight |
| 1 | | | | Events | | Risk Ratio mjopen-2020-043/14 on | | | |
| 2 | Group 1: Moderate-Placebo | | | | | 120 | | | |
| 3 | CARE, P40 | 0 | | 4 | 2081 | | 0.11 | [0.01; 2.07] | 0.0% |
| 4 5 | LIPID, P40 | 8 | 4512 | 10 | 4502 | | 0.80 | [0.32; 2.02] | 0.0% |
| 6 | AURORA, R10 | 310 | 1389 | 343 | 1378 | * 24 | 0.90 | [0.78; 1.03] | 2.0% |
| 7 | WOSCOPS, P40 | 97 | 3302 | 102 | 3293 | 9 | 0.95 | [0.72; 1.25] | 0.5% |
| 8 | CARDS, A10 | 495 | 1428 | 497 | 1410 | <u>†</u> | | [0.89; 1.09] | 3.7% |
| 9 | HPS, S40 | | 10269 | | 10267 | June 2021. | 0.99 | [0.95; 1.03] | |
| 10 | ALERT, F40-F80 | 526 | 1045 | 531 | 1049 | Ŷ 2 | 0.99 | [0.91; 1.08] | 5.1% |
| 11 12 | SSSS, S20-S40 | 613 | 2221 | 592 | 2223 | <u> </u> | 1.04 | [0.94; 1.14] | 4.0% |
| 13 | AFCAPS, L20–L40 | 2053 | | 1971 | 3301 | , | 1.04 | [1.00; 1.08] | 24.7% |
| 14 | ASCOT, A10 | 298 | 5101 | 283 | 5079 | † † | 1.05 | [0.90; 1.23] | 1.5% |
| 15 | CORONA,R10 | 225 | | 207 | 2497 | oad † | 1.08 | [0.90; 1.29] | 1.1% |
| 16 | GISSI-HF, R10 | 23 | | 21 | 2289 | | 1.10 | [0.61; 1.98] | 0.1% |
| 17 18 | PROSPER, P40 | 36 | | 32 | 2913 | | 1.13 | [0.71; 1.82] | 0.2% |
| 19 | 4D, A20 | 7 | 619 | 5 | 636 | | 1.44 | [0.46; 4.51] | 0.0% |
| 20 | ASPEN, A10 | 36 | 1211 | 19 | 1199 | | 1.88 | [1.08; 3.25] | |
| 21 | HOPE, R10 | 3 | 3181 | 1 | 3168 | - | 2.99 | [0.31; 28.71] | 0.0% |
| 22 | Random effects model | | 47350 | | 47285 |) Open | 1.01 | [0.98; 1.04] | 67.5% |
| 23 24 | Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.0003$, $p = 0.33$ | | | | | Downloaded from http://bm/jopen.bm/.com/ on April 17, 2024 by | | | |
| 25 | | | | | | ŋ.c | | | |
| 26 | Group 2: High-Placebo | | | | | om | | | |
| 27 | SPARCL, A80 | 129 | 2365 | 141 | 2366 | + 9 | 0.92 | [0.73; 1.15] | 0.7% |
| 28 | JUPITER, R20 | 1421 | 8869 | 1375 | 8864 | A A | 1.03 | [0.96; 1.11] | 8.0% |
| 29 30 | TRACE RA, A40 | 132 | 1504 | 117 | 1498 | | 1.12 | [0.89; 1.43] | 0.7% |
| 31 | Random effects model | | 12738 | | 12728 | , | 1.03 | [0.97; 1.10] | 9.3% |
| 32 | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.47$ | | | | | 024 | | | |
| 33 | | | | | | , p | | | |
| 34 | Group 3: High-Moderate | | | | | gue | | | |
| 35 | TNT, A80 vs A10 | 241 | 4995 | 234 | 5006 | \frac{1}{2} | 1.03 | [0.87; 1.23] | 1.2% |
| 36 37 | SEARCH, S80 vs S20 | 2621 | 6031 | 2512 | 6033 | į į | 1.04 | [1.00; 1.09] | 21.5% |
| 38 | A to Z, S40-S80 vs S20 | 41 | 2263 | 34 | 2230 | - | 1.19 | [0.76; 1.87] | 0.2% |
| 39 | PROVE-IT, A80 vs P40 | 69 | 2099 | 56 | 2063 | | | [0.86; 1.71] | 0.3% |
| 40 | Random effects model | | 15388 | | 15332 |) | | [1.01; 1.09] | 23.2% |
| 41 | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.79$ | | | | | guest. Protected by copyright. | | | |
| 42 43 | | | | | | righ | | | |
| 44 | Random effects model | | 75476 | | 75345 | <u> </u> | 1.02 | [1.00; 1.04] | 100.0% |
| 45 | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.51$ For pe | eer review o | nly - http:/ | //bmjopen. | bmj.com/ | site/about/guidelines.xhtml | ^ | | 7 |
| 46 | Residual heterogeneity: $I^2 = 0\%$, $p = 0.50$ | | | | | 0.01 0.1 1 10 10 | | | |
| 47 | | | | | 5 | tatin Protective Statin Harmfu | I | | |

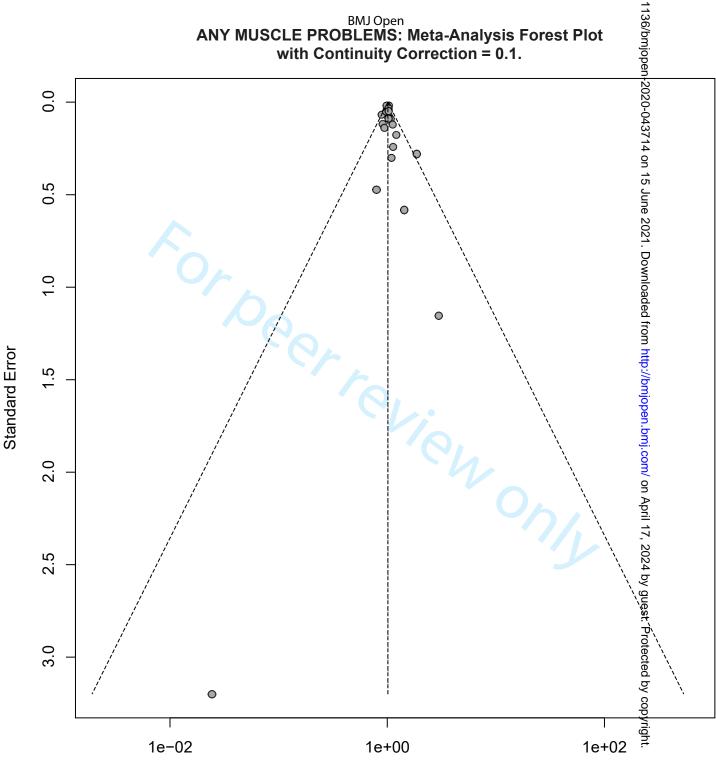












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46 47 Study

CARE, P40

LIPID, P40

AURORA, R10

CARDS, A10

ASCOT, A10

ASPEN, A10

SPARCL, A80

JUPITER, R20

TRACE RA, A40

TNT, A80 vs A10

HOPE, R10

4D, A20

CORONA.R10

GISSI-HF, R10

PROSPER, P40

Random effects model

Group 2: High-Placebo

Random effects model

Group 3: High-Moderate

PROVE-IT, A80 vs P40

Random effects model

HPS. S40

WOSCOPS, P40

ALERT. F40-F80

SSSS, S20-S40

AFCAPS, L20-L40

Group 1: Moderate-Placebo

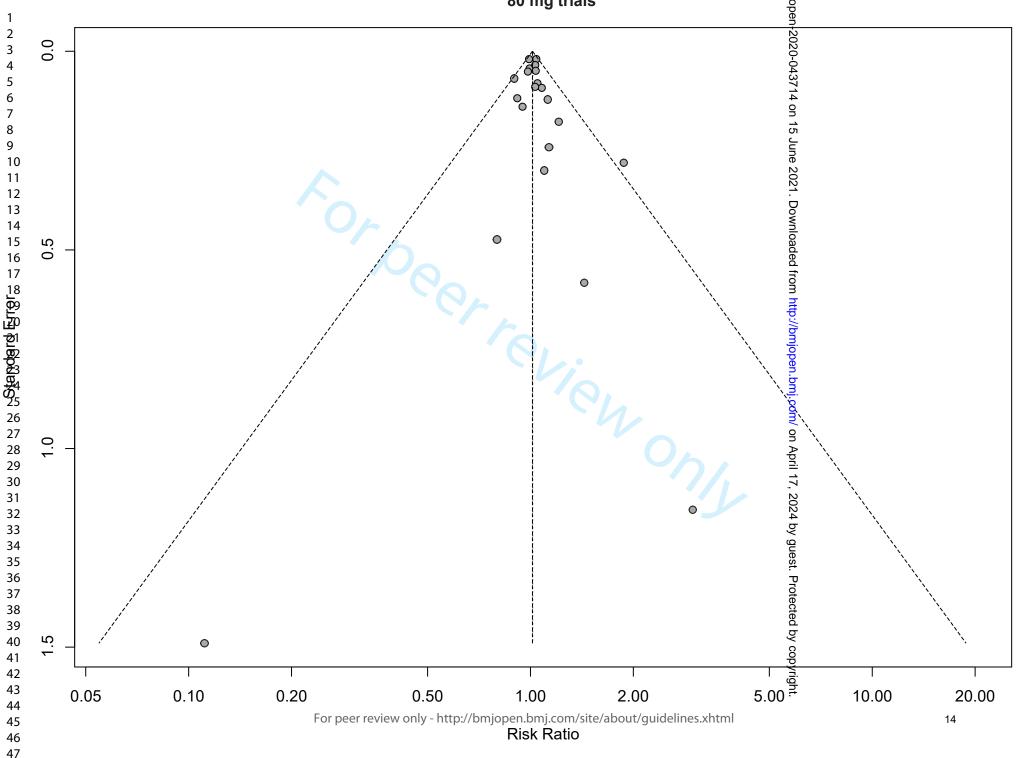
ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot excluding simvastatin 80 mg trials. /bmjopen-2020-043714 on 15 **Experimental** Control **Risk Ratio** RR 95%-CI Weight **Events Total Events Total** 2078 2081 0.11 [0.01; 2.07] 0.0% 0 8 4512 10 4502 0.80 [0.32; 2.02] 0.1% 1389 343 1378 0.90 [0.78; 1.03] 2.6% 310 97 3302 102 3293 0.95 [0.72; 1.25] 0.6% June 2021. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyrigh 495 1428 497 1410 0.98 [0.89; 1.09] 4.7% 3380 10269 3410 10267 0.99 [0.95; 1.03] 31.1% 526 1045 531 1049 0.99 [0.91; 1.08] 6.5% 613 2221 592 2223 5.1% 1.04 [0.94; 1.14] 2053 3304 1971 3301 31.6% 1.04 [1.00; 1.08] 298 5101 283 5079 1.05 [0.90; 1.23] 1.9% 225 2514 207 2497 1.08 [0.90; 1.29] 1.4% 23 2285 21 2289 1.10 [0.61; 1.98] 0.1% 2891 32 2913 0.2% 36 1.13 [0.71; 1.82] 7 619 5 636 0.0% 1.44 [0.46; 4.51] 1211 36 19 1199 1.88 [1.08; 3.25] 0.2% 3 3181 3168 0.0% 1 2.99 [0.31; 28.71] 47350 1.01 [0.98; 1.04] 47285 86.2% Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.0003$, p = 0.332365 129 141 2366 0.92 [0.73; 1.15] 0.9% 1421 8869 8864 1375 1.03 [0.96; 1.11] 10.2% 132 1504 1498 117 1.12 [0.89; 1.43] 0.8% 12738 12728 1.03 [0.97; 1.10] 11.9% Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.474995 234 5006 1.03 [0.87; 1.23] 1.5% 241 56 2063 2099 1.21 [0.86; 1.71] 0.4% 7094 1.07 [0.91; 1.25] 1.9% 7069 Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.4267182 67082 1.02 [0.99; 1.04] 100.0%

Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.49

Residual heterogeneity: $I^2 = 5\%$, p = 0.40 For peer review only - http://bmjopen.bmj.com@i@fabou@guidelines.xhtml10

Statin Protective Statin Harmful

ANY MUSCLE PROBLEMS: Meta-Analysis Funnel plot excluding simverstatin 80 mg trials



| | | | | ВМЈ С |)pen | | | 1136/hmionen-2 | |
|-------------------------|-------------------------|--------------------------|----------------------|-------------------------|----------------------------|--------|-------------------------|---|-----|
| | ANY MUSC | LE PROBLEMS | SUMN | MARY: PAIRWIS | SE AND NETWOR | RK MET | | 3 | |
| | Placebo – Mod | erate Intensity | | Moderate – Hig | jh Intensity | | Placebo – High | Intensity | |
| Outcome | RR (95% CI) | RD (95% CI) | NNH RR) (95% CI) | | RD (95% CI) | NNH | RR (95% CI) | RD (95% CI) | NNH |
| Direct, M-H | 1.011 (0.982, 1.042) | NA | | 1.046 (1.005, 1.089) | NA | | 1.030 | NA NA | |
| Direct, IV | 1.012 (0.989, 1.036) | 0.000 (-0.001, 0.001) | | 1.046 (1.005, 1.089) | 0.004 (-0.001, 0.009) | | 1.030 (0.967, 1.097) | 0.002 | |
| NMA, IV | 1.010 (0.988,1.033) | 0.0001 (-0.001,0.001) | Ó | 1.039 (1.004,1.075) | 0.0037 (-0.0005,0.0078) | | 1.049 (1.010,1.089) | 0.0037 | |
| NMA Excluding S80 | 1.011 (0.988,1.036) | 0.0001 (-0.001,0.001) | | 1.025 (0.963,1.091) | 0.0028 (-0.0022,0.0079) | | 1.036 (0.977,1.099) | 0.0029 (-0.0022,0.0079) | |
| NMA CC=0.10 | 1.010 (0.988,1.033) | 0.000* (-0.001,0.001) | | 1.039 (1.003, 1.075) | 0.0037 (-0.0005,0.0078) | | | 0.0037 (-0.0005,0.0079) | |
| NMA CC = 0.0001 | 1.010 (0.988,1.033) | 0.000* (-0.001,0.001) | | 1.039 (1.003,1.075) | 0.0037 (-0.0005,0.0078) | | | 0.0037 (-0.0005,0.0079) | |
| | | | | | | 0, | | n April 17 2024 by guest Protected by convright | |
| | | | | | | | | 1 | 41 |

95%-CI Weight

2.3%

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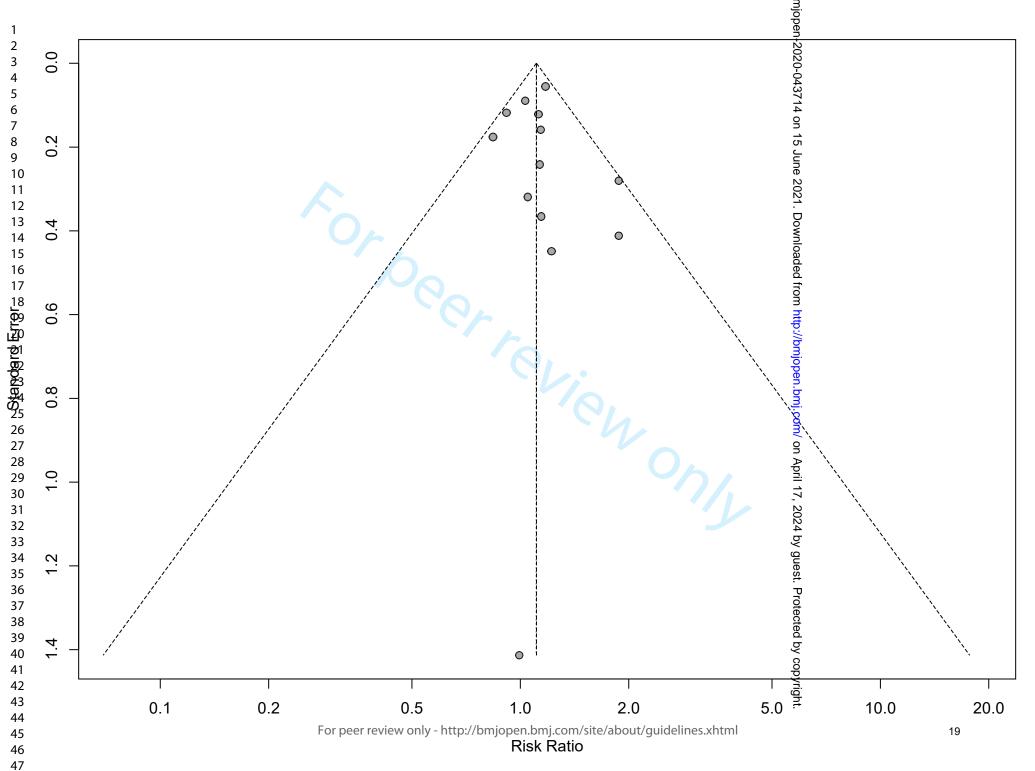
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45 46 47

| | Experii | nental | C | ontrol | | 020-0 | |
|--|---------|--------|---------------|--------|--|---|---------------|
| Study | • | | Events | Total | Risk Ratio | .020-043714 on | 95%-CI |
| Group 1: Moderate-Placebo | | | | | <u> </u> | | |
| CARDS, A10 | 57 | 1428 | 67 | 1410 | <u> </u> | 0.84 0.99 | [0.59; 1.19] |
| AURORA, R10 | 1 | 1389 | 1 | 1378 | : | 통 0.99 | [0.06; 15.85] |
| WOSCOPS, P40 | 20 | 3302 | 19 | 3293 | | [№] 1.05 | [0.56; 1.96] |
| PROSPER, P40 | 36 | 2891 | 32 | 2913 | | 1.13 | [0.71; 1.82] |
| SSSS, S20-S40 | 82 | 2221 | 72 | _ | | § 1.14 | [0.84; 1.56] |
| HPS, S40 | | 10232 | 14 | 10237 | | 룺 1.14 | [0.56; 2.34] |
| AFCAPS, L20-L40 | 11 | 3304 | 9 | 3301 | - | ਨੂੰ 1.22 | [0.51; 2.94] |
| ASPEN, A10 | 36 | 1211 | 19 | 1199 | | 1.88 | [1.08; 3.25] |
| ASCOT, A10 | 17 | 5158 | 9 | 5124 | <u>:</u> | <u>3</u> 1.88 | [0.84; 4.21] |
| Random effects model | | 31136 | | 31078 | | ∄ 1.13 | [0.95; 1.34] |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.46$ | | | | | | /bmjo | |
| Group 2: High-Placebo | | | | | | pen | |
| SPARCL, A80 | 129 | 2365 | 141 | 2366 | - - | 0.92 | [0.73; 1.15] |
| TRACE RA, A40 | 132 | 1504 | | 1498 | Y /_ | 8 1.12 | [0.89; 1.43] |
| JUPITER, R20 | 658 | 8869 | 560 | 8864 | = | 1.17 | [1.05; 1.31] |
| Random effects model | | 12738 | | 12728 | \Q | n 1.09 | [0.94; 1.26] |
| Heterogeneity: $I^2 = 45\%$, $\tau^2 = 0.0076$, $p = 0.16$ | | | | | | 1.05 1.14 1.14 1.188 1.13 1.14 1.188 1.13 0.92 1.109 1.04 1.04 1.04 1.04 | |
| Group 3: High-Moderate | | | | | | 202 | |
| TNT, A80 vs A10 | 241 | 4995 | 234 | 5006 | <u> </u> | £ 1.03 | [0.87; 1.23] |
| SEARCH, S80 vs S20 | 2621 | 6031 | 2512 | 6033 | + | ള് 1.04 | [1.00; 1.09] |
| Random effects model | | 11026 | | 11039 | 0: | est 1.04 | [1.00; 1.09] |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.90$ | | | | | | Protected 1.07 | |
| Random effects model | | 54900 | | 54845 | : 0 | ਰੂ 1.07 | [1.01; 1.13] |
| Heterogeneity: $I^2 = 8\%$, $\tau^2 = 0.0009$, $p = 0.36$ | | | | | | l <u>p</u> | - / |
| Residual heterogeneity: $I^2 = 3\%$, $p = 0.41$ | | | | | 0.1 0.5 1 2 1 | @ | |
| | | | | S | Statin Protective Statin Harm | | |
| | | | | | | jht. | |

MYALGIA OR PAIN: Meta-Analysis Forest plot excluding simvastatin 89 mg trials.

| | | | | | | en-2 | | | |
|--|-------------------|-------|-------------|-----------------|---------------------|--|--------|---------------|---------|
| Study | Experir Events | | C Events | ontrol Total | Risk R | en-2020-043714 on 15 atio | RR | 95%-CI | Weight |
| Group 1: Moderate-Placebo | | | | | : | on 1 | | | |
| CARDS, A10 | 57 | 1428 | 67 | 1410 | | 5 J. | n 84 | [0.59; 1.19] | 4.6% |
| AURORA, R10 | 1 | 1389 | 1 | 1378 | | line 2 | - 0.04 | [0.06; 15.85] | 0.1% |
| WOSCOPS, P40 | 20 | 3302 | 19 | 3293 | | | 1.05 | [0.56; 1.96] | 1.4% |
| PROSPER, P40 | 36 | 2891 | 32 | 2913 | <u> </u> | June 2021. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. | 1.13 | [0.71; 1.82] | 2.5% |
| SSSS, S20-S40 | 82 | 2221 | 72 | 2223 | - <u> </u> | – owr | 1.14 | [0.84; 1.56] | 5.7% |
| HPS, S40 | | 10232 | | 10237 | _ | | 1.14 | [0.56; 2.34] | 1.1% |
| AFCAPS, L20-L40 | 11 | | 9 | 3301 | | ded | 1.22 | [0.51; 2.94] | 0.7% |
| ASPEN, A10 | | 1211 | 19 | 1199 | <u> </u> | fror | 1.88 | [1.08; 3.25] | 1.8% |
| ASCOT, A10 | 17 | 5158 | 9 | 5124 | <u> </u> | _ = | 1.88 | [0.84; 4.21] | 0.8% |
| Random effects model | | 31136 | | 31078 | \(\sqrt{} | , ф:// | 1.13 | [0.95; 1.34] | 18.7% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.46$ | | | | | | bmj | | | |
| | | | | | | ope | | | |
| Group 2: High-Placebo | | | | | | n.b | | | |
| SPARCL, A80 | 129 | 2365 | 141 | 2366 | > | <u>j.</u> c | 0.92 | [0.73; 1.15] | 10.1% |
| TRACE RA, A40 | 132 | 1504 | 117 | 1498 | · // + | - M | 1.12 | [0.89; 1.43] | 9.6% |
| JUPITER, R20 | 658 | 8869 | 560 | 8864 | + | 9 | 1.17 | [1.05; 1.31] | 44.0% |
| Random effects model | | 12738 | | 12728 | \ | Apr | 1.09 | [0.94; 1.26] | 63.8% |
| Heterogeneity: $I^2 = 45\%$, $\tau^2 = 0.0076$, $p = 0.16$ | | | | | | ii 17 | | | |
| | | | | | | , 20 | | | |
| Group 3: High-Moderate | | | | | |)24 | | | |
| TNT, A80 vs A10 | 241 | | 234 | 5006 | 青 | by ç | 1.03 | [0.87; 1.23] | 17.5% |
| Random effects model | | 4995 | | 5006 | \Diamond | jues | 1.03 | [0.87; 1.23] | 17.5% |
| Heterogeneity: not applicable | | | | | | | | | |
| Dandom offacto model | | 40000 | | 40040 | | Protected | 4 4 4 | [4 02, 4 40] | 400.00/ |
| Random effects model | | 48869 | | 48812 | <u> </u> | | 7.77 | [1.03; 1.19] | 100.0% |
| Heterogeneity: $I^2 = 1\%$, $\tau^2 = 0.0002$, $p = 0.44$ | | | | | 0.1 0.5 1 | 2 10 | | | |
| Residual heterogeneity: $I^2 = 12\%$, $p = 0.33$ | | | | 9 | tatin Protective | × | | | |
| | | | | 3 | tatiii Fiotective v | _ | | | |
| | | | | | | ight. | | | |



BMJ Open 136/bmjopen-2020 MYALGIA OR PAIN SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESOULTS

| | Placebo – Mod | erate Intensity | | Moderate – Hig | jh Intensity | Placebo – Hig | Intensity | | |
|-------------|-------------------------|-------------------|-----------|-----------------------------|---------------------|---------------|---|------------------|-----|
| Outcome | RR | RD | NNH | RR | RD | NNH | RR 15 | RD | NNH |
| | (95% CI) | (95% CI) | | (95% CI) | (95% CI) | | (95% CI) | (95% CI) | |
| Direct, M-H | 1.130 (0.952, 1.341) | NA | | 1.043 (1.002, 1.086) | NA | | 1.092 (0.945, 1.261) | NA | |
| | , | | | , | | | Q | | |
| Direct, IV | 1.130 | 0.0007 | | 1.043 | 0.0046 | | 1.123 ⋛ | 0.0073 | 143 |
| | (0.952, 1.341) | (-0.0005, 0.0019) | ^ | (1.002, 1.086) | (-0.0030, 0.0123) | | (1.025, 1.230) | (0.0010, 0.0136) | |
| NMA, IV | 1.090 | 0.0007 | - | 1.041 | 0.0058 | 173 | 1.134 ਤੋਂ | 0.0065 | 154 |
| | (0.9997,1.188) | (-0.0005,0.0019) | | (1.001,1.083) | (0.0009,0.0107) | | (1.046,1.230) | (0.0016,0.0114) | |
| Excluding | 1.111 | 0.0007 | | 1.010 | 0.0048 | | 1.122 | 0.0055 | 182 |
| S80 | (0.971,1.270) | (-0.0004,0.0018) | | (0.881,1.158) | (-0.0003,0.0099) | | (1.021,1.233) | (0.0005,0.0106) | |
| | | | | | | | n.bmj.com/ on April 17, 2024 by guest. Protected by copyright | | |
| | | Farmanan | ا د د د د | lattine //lauraitana and la | mj.com/site/about/g | - خامادات | · | | 2 |

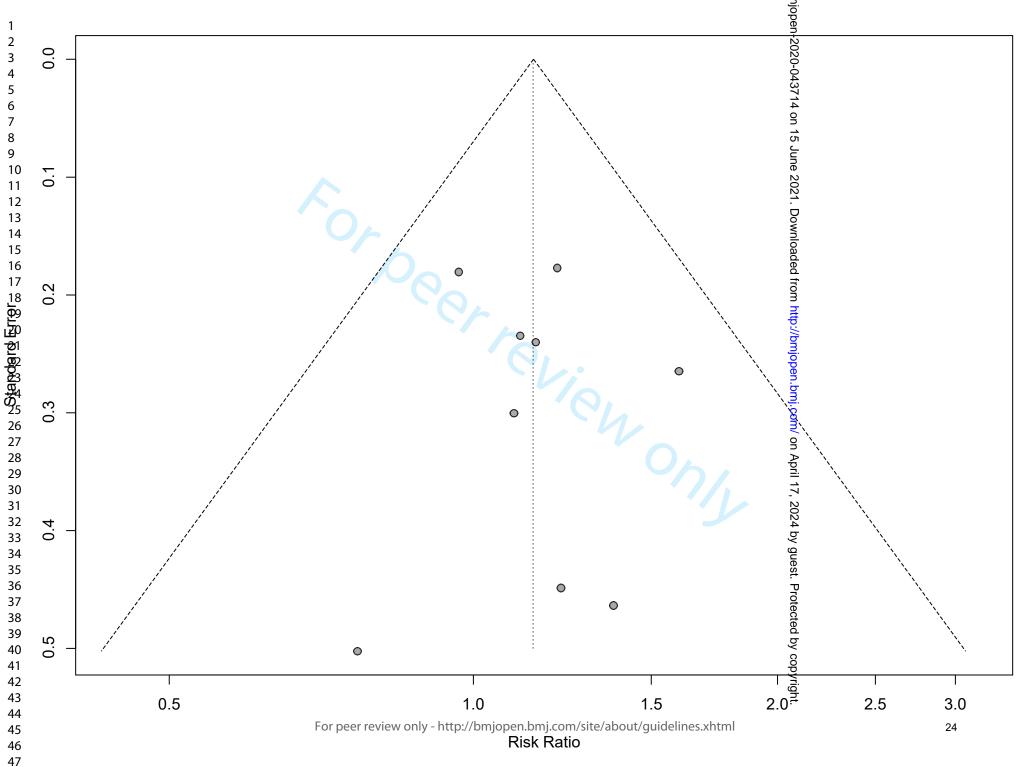
ATTRITION: Meta-Analysis Forest plot with data

| 59 of 83 | | | 1136/bmjc | | | | | |
|---|---|---|---|---|---|--|--|---------------------------------------|
| A | TTRITIO | N: Met | a-Analys | sis Fore | est plot with data 2020-043714 of the state | | | |
| | Experi | mental | С | ontrol | on 15 | | | |
| Study | | | Events | | Risk Ratio | RR | 95%−CI | Weight |
| Group 1: Moderate-Placebo CARDS, A10 HPS, S40 GISSI-HF, R10 HOPE, R10 WOSCOPS, P40 AFCAPS, L20-L40 SSSS, S20-S40 ASCOT, A10 Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$ Group 2: High-Moderate A to Z, S40-S80 vs S20 PROVE-IT, A80 vs P40 SEARCH, S80 vs S20 Random effects model Heterogeneity: $I^2 = 31\%$, $\tau^2 = 0.0190$, $p = 0.23$ | 7 60 23 38 37 11 11 37 | 1428 10269 2285 3181 3302 3304 2221 5158 31148 2263 2099 6031 10393 | 9 62 21 34 32 9 8 23 | 1410 10267 2289 3168 3293 3301 2223 5124 31075 2230 2063 6033 10326 | 1136/bmjopen-2020-043714 on 15 June 2021. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by Risk Ratio Risk Ratio | 0.77 0.97 1.10 1.11 1.15 1.22 1.38 1.60 1.13 1.19 1.21 1.85 1.38 | [0.29; 2.06] [0.68; 1.38] [0.61; 1.98] [0.70; 1.76] [0.72; 1.85] [0.51; 2.94] [0.55; 3.41] [0.95; 2.69] [0.93; 1.36] [0.76; 1.87] [0.86; 1.71] [1.22; 2.81] [1.04; 1.82] | 6.2% 10.2% 9.7% 2.8% 2.6% |
| Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.64$ Residual heterogeneity: $I^2 = 0\%$, $p = 0.72$ | | 41541 | | 41401 S | 0.5 1 2 statin Protective Statin Harmed by copyright. | 1.22 | [1.05; 1.41] | 100.0% |

| 83 | | | В | MJ Open | | 1136/bm) |
|--|---|--|---|--------------|------------------------------------|---|
| ATTRITION: | Meta- | Analysi | s Fores | t plot ex | ccluding simvastatin 80 mg tri | jopen- & 20-043714 on |
| | Experir | nental | C | ontrol | | 15 June |
| Study | Events | Total | Events | Total | Risk Ratio | RR |
| ASCOT, A10 Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$ | 7 60 23 38 37 11 11 37 | 1428 10269 2285 3181 3302 3304 2221 5158 31148 | 9 62 21 34 32 9 8 23 | 2223 | Risk Ratio | الق. مور الق |
| Group 2: High-Moderate PROVE-IT, A80 vs P40 Random effects model Heterogeneity: not applicable | 69 | 2099 2099 | 56 | 2063 2063 | | on April 17, 202 |
| Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.91$ Residual heterogeneity: $I^2 = 0\%$, $p = 0.86$ | | 33247 | | 33138 | 0.5 1 2 Statin Better Statin Worse | 56.13 21.21 5en:5mj.com/ on April 77, 2024 By guest. Protection |

| e 2021. | 95%-CI | Weight |
|------------------------------------|--|--------------------------------|
| Down.77 20.97 21.10 21.11 | [0.29; 2.06] [0.68; 1.38] [0.61; 1.98] [0.70; 1.76] | 2.9% 22.4% 8.1% 13.3% |
| 15 1.22 1.38 | [0.72; 1.85] [0.51; 2.94] [0.55; 3.41] | 12.7% 3.6% 3.4% |
| 91.60 1.13 | [0.95; 2.69] [0.93; 1.36] | |
| 21 21 0, 20 0, 20 0, 2024 | [0.86; 1.71] [0.86; 1.71] | |
| 4 by guest. Protecte | [0.97; 1.35] | 100.0% |

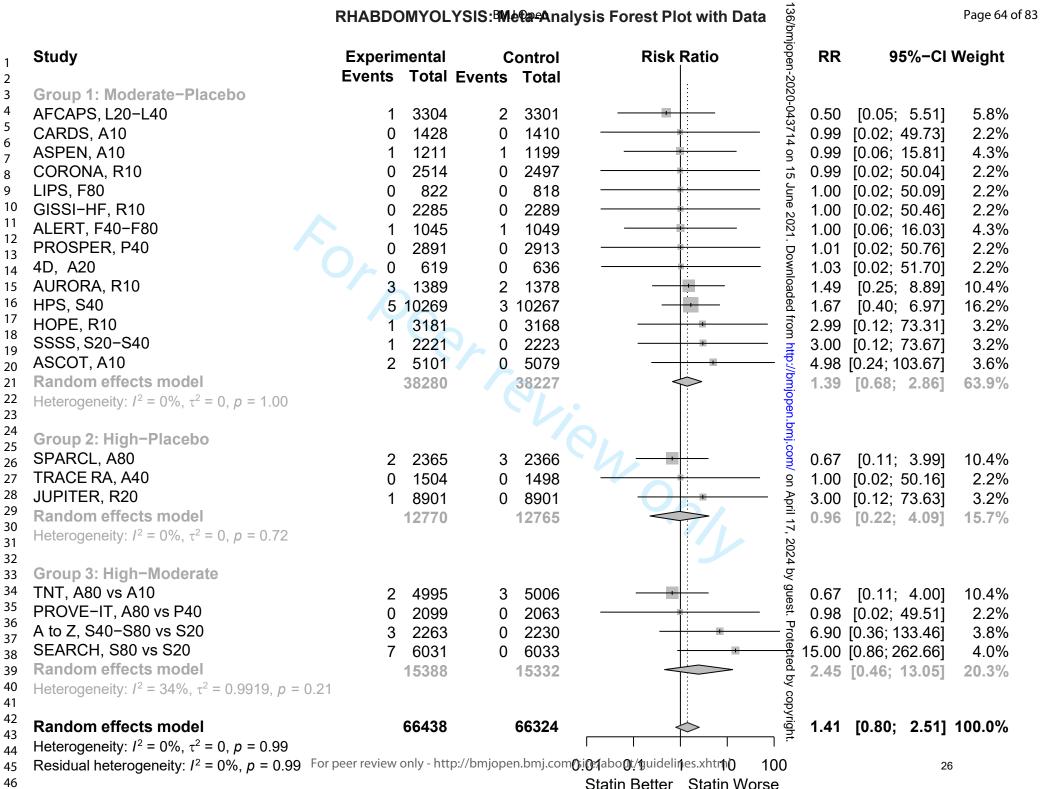


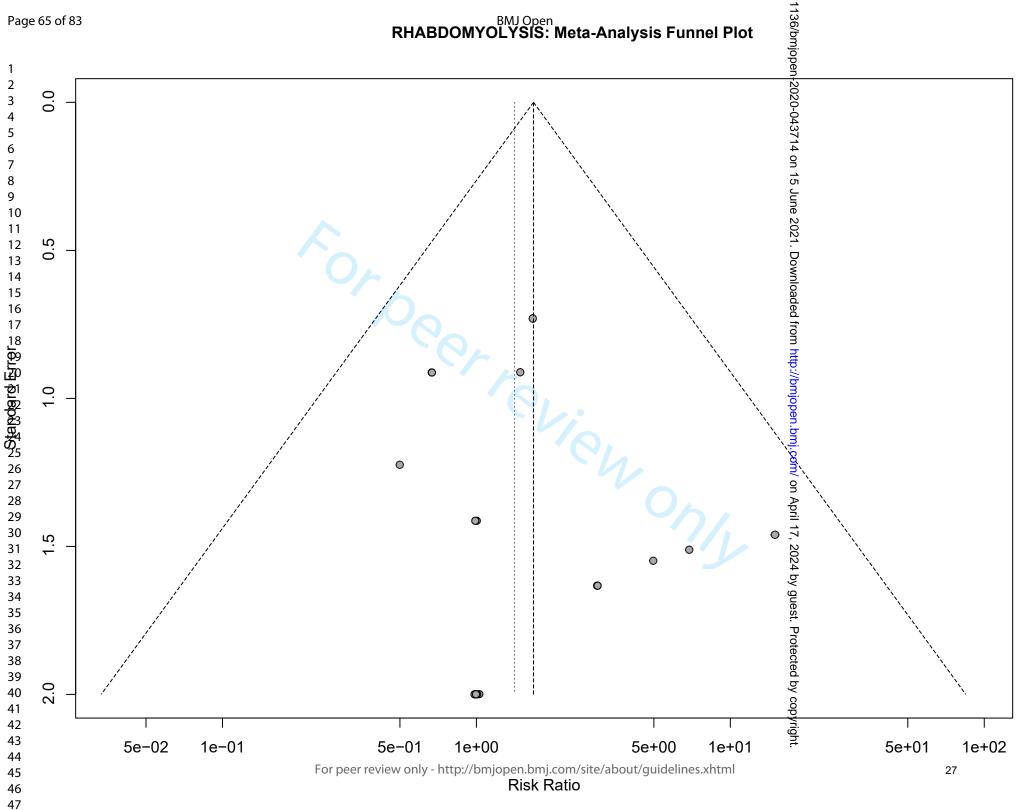


BMJ Open ATTRITION SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULT 043

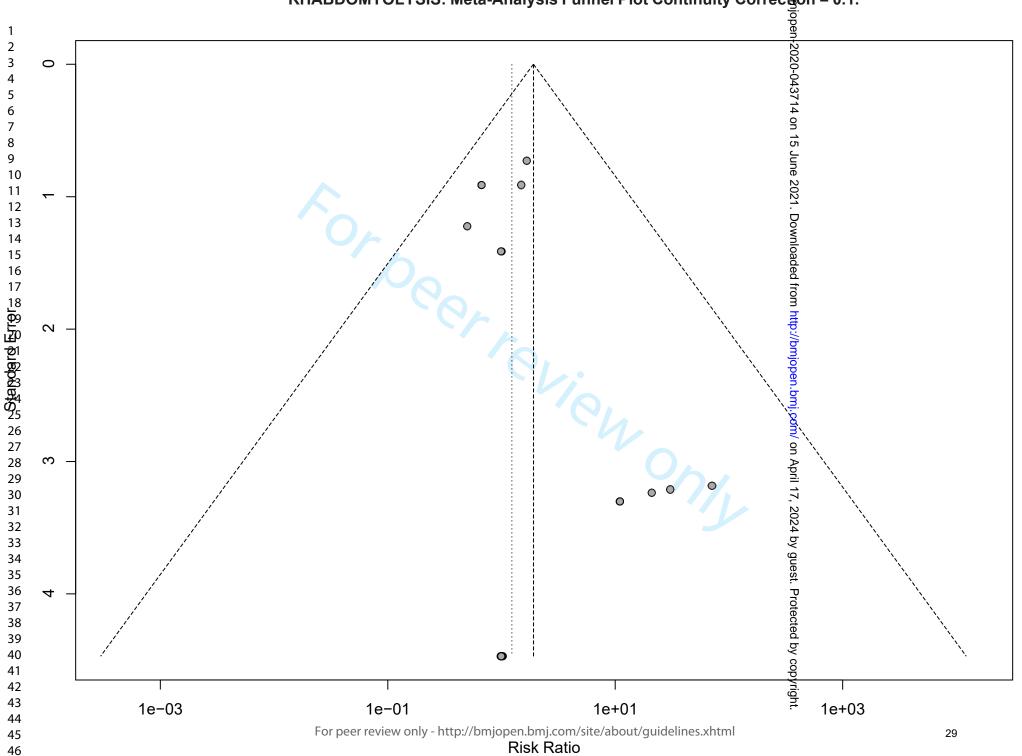
| | Placebo – Mod | erate Intensity | Moderate – Hig | gh Intensity | Placebo – High Intensity | | | | |
|------------------|-------------------------|-----------------------------|----------------|-------------------------|----------------------------|------|--|---------------------------|------|
| Outcome | RR (95% CI) | RD (95% CI) | NNH | RR (95% CI) | RD (95% CI) | NNH | RR (95% CI) | l DD | NNH |
| Direct, M-H | 1.127 (0.931, 1.364) | NA | | 1.378 (1.043, 1.822) | NA | | NA 2021. | NA | |
| Direct, IV | 1.127 (0.931, 1.364) | 0.0008 (-0.0004, 0.0020) | 1000 | 1.372 (1.091, 1.726) | 0.0046 (0.0018, 0.0074) | 200 | NA Ploaded | NA | |
| NMA, IV | 1.127 (0.931,1.364) | 0.0008 (-0.0004,0.0020) | -6 | 1.372 (1.091,1.726) | 0.0046 (0.0018,0.0074) | 218 | 1.155 5 (1.147,2.084) | 0.0054 (0.0023,0.0084) | 187 |
| Excluding S80 | 1.127 (0.931,1.364) | 0.0008 (-0.0004,0.0020) | | 1.211 (0.856,1.714) | 0.0057 (-0.0046,0.0161) | 176* | 1.365 (0.918,2.028) | | 154* |
| | | | | | | | n.bmj.com/ on April 17, 2024 by guest. Protected by copyright. | | |

RHABDOMYOLYSIS: BMe@a-Analysis Forest Plot with Data





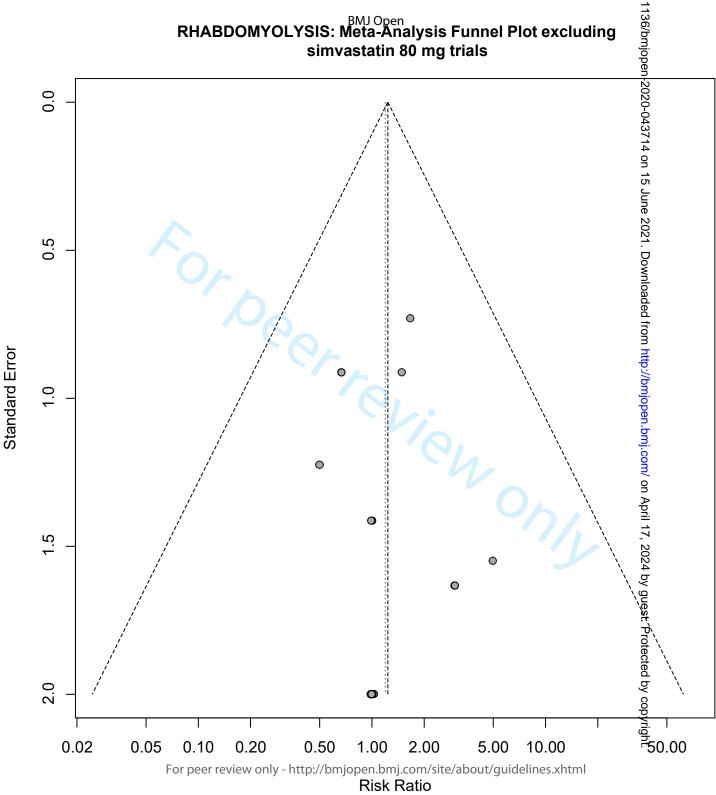
| Study | Experime Events | | | ontrol Total | Risk Ratio | RR | mjopen -2 | Weight | | | |
|---|---|----------------|-------------|-----------------|--|-------|--|--------|--|--|--|
| Group 1: Moderate-Placebo | | | | | | | | | | | |
| AFCAPS, L20-L40 | 1 | 3304 | 2 | 3301 | | 0.50 | ਸ਼੍ਰੇ0.05; 5.51] | 8.2% | | | |
| CARDS, A10 | 0 | 1428 | 0 | 1410 | <u> </u> | 0.99 | [ਊ.00; 6324.79] | 0.6% | | | |
| ASPEN, A10 | 1 | 1211 | 1 | 1199 | | 0.99 | ∮ 0.06; 15.81] | 6.2% | | | |
| CORONA, R10 | 0 | 2514 | 0 | 2497 | <u> </u> | 0.99 | [0,00; 6363.07] | 0.6% | | | |
| LIPS, F80 | 0 | 822 | 0 | 818 | <u> </u> | 1.00 | [§ .00; 6372.92] | 0.6% | | | |
| GISSI-HF, R10 | 0 | 2285 | 0 | 2289 | | 1.00 | [0.00; 6417.49] | 0.6% | | | |
| ALERT, F40-F80 | 1 | 1045 | 1 | 1049 | - ‡ | 1.00 | 1 0.06; 16.03] | 6.2% | | | |
| PROSPER, P40 | 0 | 2891 | 0 | 2913 | <u> </u> | 1.01 | [0 .00; 6455.29] | 0.6% | | | |
| 4D, A20 | 0 | 619 | 0 | 636 | <u> </u> | 1.03 | [<u>§</u> .00; 6578.85] | 0.6% | | | |
| AURORA, R10 | 3 | 1389 | 2 | 1378 | | 1.49 | ଧ୍ର୍ର[0.25; 8.89] | 14.8% | | | |
| HPS, S40 | 5 1 | 0269 | 3 | 10267 | | 1.67 | <u>\(\frac{1}{2} \) (0.40; 6.97) \) \(</u> | 23.1% | | | |
| HOPE, R10 | 1 | 3181 | 0 | 3168 | | 10.96 | [9 .02; 7095.11] | 1.1% | | | |
| SSSS, S20-S40 | | 2221 | 0 | 2223 | | 11.01 | [0 .02; 7130.07] | 1.1% | | | |
| ASCOT, A10 | | 5101 | 0 | 5079 | <u> </u> | | [004; 11895.15] | 1.2% | | | |
| Random effects model | 3 | 8280 | | 38227 | \(\langle | 1.38 | <u>3</u> 0.59; 3.22] | 65.6% | | | |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$ |) | | | | | | pen.bmj.co | | | | |
| SPARCL, A80 | | 2365 | 3 | 2366 | | 0.67 | $\frac{9}{2}[0.11; 3.99]$ | 14.8% | | | |
| TRACE RA, A40 | | 1504 | 0 | 1498 | | 1.00 | [9.00; 6380.08] | 0.6% | | | |
| JUPITER, R20 | | 8901 | 0 | 8901 | | 11.00 | [<u>₱</u> .02; 7125.08] | 1.1% | | | |
| Random effects model | | 2770 | | 12765 | | 0.82 | ₹0.15; 4.45] | 16.6% | | | |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$ Group 3: High-Moderate | | 0 | | | | | , 2024 by | | | | |
| TNT, A80 vs A10 | | 4995 | 3 | 5006 | _ | 0.67 | ଜ୍ଜ[0.11; 4.00] | 14.8% | | | |
| PROVE-IT, A80 vs P40 | 0 | 2099 | 0 | 2063 | | 0.98 | [0.00; 6296.29] | 0.6% | | | |
| A to Z, S40-S80 vs S20 | 3 | 2263 | 0 | 2230 | | 30.55 | [0506; 16583.28] | 1.2% | | | |
| SEARCH, S80 vs S20 | | 6031 | 0 | 6033 | <u>:</u> * | | [0214; 36473.99] | 1.2% | | | |
| Random effects model | 1 | 5388 | | 15332 | | | 9 .13; 85.29] | 17.8% | | | |
| Heterogeneity: $I^2 = 39\%$, τ^2 | $r^2 = 4.4154, \mu$ | 0.1 | 8 | | | | < | | | | |
| Random effects model | | 6438 | | 66324 | <u> </u> | 1.23 | © 2.45] | 100.0% | | | |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$. Residual heterogeneity: $I^2 = 0\%$ | = 0, <i>p</i> = 0.99 = 0%, <i>p</i> ^F er@ | 9 1988 revi | ew only - h | ttp://bmjc | pe o.looj ącomosite/alpoutoguideloogoxh | ntml | | 28 | | | |



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| | Experir | nental | C | ontrol | | p <u>e</u> | | |
|--|---------------|-----------|---------------|--------|--|-----------------------------|----------------|--------|
| Study | Events | Total | Events | Total | Risk Ratio | ₫ RR | 95%−CI | Weight |
| Group 1: Moderate-Placebo | | | | | I: | pen-2020-043754 | | |
| AFCAPS, L20-L40 | 4 | 3304 | 2 | 3301 | | 3 75 75 | [0 05: 5 51] | 6.2% |
| • | 1 0 | 1428 | 2 | 1410 | -]: | 06.40 | [0.05; 5.51] | |
| CARDS, A10 | 0 | | | | <u> </u> | - <u>@</u> .99 | [0.02; 49.73] | 2.3% |
| ASPEN, A10 | 1 | 1211 | 1 | 1199 | | € 99 | [0.06; 15.81] | 4.7% |
| CORONA, R10 | 0 | 2514 | 0 | 2497 | 1 | - (1 .99 | [0.02; 50.04] | 2.3% |
| LIPS, F80 | 0 | 822 | 0 | 818 | | - £00 | [0.02; 50.09] | 2.3% |
| GISSI-HF, R10 | 0 | 2285 | 0 | 2289 | <u></u> | - ½00 | [0.02; 50.46] | 2.3% |
| ALERT, F40-F80 | 1 | 1045 | 1 | 1049 | | [00 | [0.06; 16.03] | 4.7% |
| PROSPER, P40 | 0 | 2891 | 0 | 2913 | | - <u>≸</u> .01 | [0.02; 50.76] | 2.3% |
| 4D, A20 | 0 | 619 | 0 | 636 | | - <u>\$</u> .03 | [0.02; 51.70] | 2.3% |
| AURORA, R10 | 3 | 1389 | 2 | 1378 | - 12- | £ 49 | [0.25; 8.89] | 11.2% |
| HPS, S40 | 5 | 10269 | 3 | 10267 | - - - - - - - - - - | ∯.67 | [0.40; 6.97] | 17.5% |
| HOPE, R10 | 1 | 3181 | 0 | 3168 | | − <u>≨</u>. 99 | [0.12; 73.31] | 3.5% |
| SSSS, S20-S40 | 1 | 2221 | 0 | 2223 | | − 3 .00 | [0.12; 73.67] | 3.5% |
| ASCOT, A10 | 2 | 5101 | 0 | 5079 | - | — <u>≰</u> .98 | [0.24; 103.67] | 3.9% |
| Random effects model | | 38280 | | 38227 | | 8 .39 | [0.68; 2.86] | 69.3% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$ | | | | | | n.br | | |
| | | | | | 1 (2), | bmj.com | | |
| Group 2: High-Placebo | | | | | |) Mo | | |
| SPARCL, A80 | 2 | 2365 | 3 | 2366 | | g .67 | [0.11; 3.99] | 11.2% |
| TRACE RA, A40 | 0 | 1504 | 0 | 1498 | | - ≹.00 | [0.02; 50.16] | 2.3% |
| JUPITER, R20 | 1 | 8901 | 0 | 8901 | | − 3 00 | [0.12; 73.63] | 3.5% |
| Random effects model | | 12770 | | 12765 | | 7 -2 024 by gue&F | [0.22; 4.09] | 17.1% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.72$ | | | | | | 022 | | |
| | | | | | | yd 1 | | |
| Group 3: High-Moderate | | | | | | gue | | |
| TNT, A80 vs A10 | 2 | 4995 | 3 | 5006 | | e [∞] 67 | [0.11; 4.00] | 11.2% |
| PROVE-IT, A80 vs P40 | 0 | 2099 | 0 | 2063 | | - ∩≆GA | IN NO 10 511 | 2.3% |
| Random effects model | J | 7094 | · · | 7069 | | Ø 71 | [0.14; 3.63] | |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$ | | 7004 | | 1000 | | ted | [0.14, 0.00] | 101070 |
| rictor egenerative cost, to est, possible | | | | | | by a | | |
| Random effects model | | 58144 | | 58061 | | tected by copyright 100 | [0.66; 2.18] | 100.0% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$ | | 30 | | | | ⊤ ÿrigi | [3.55, 2.10] | |
| Residual heterogeneity: $I^2 = 0\%$, $p = 1.00$ | n | | | 0.0 | 01 0.1 1 10 | 100 | | |
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| | | , | , | | | 141 | | 00 |

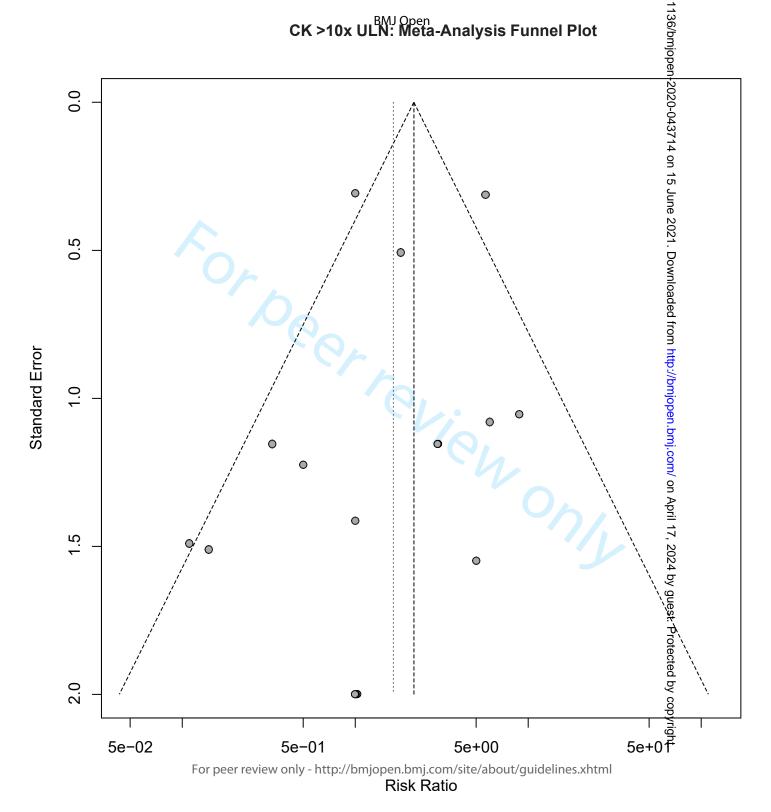




BMJ Open 136/bmjopen-2020 RHADOMYOLYSIS SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

| | Placebo – Mod | lerate Intensity | Moderate – Hig | h Intensity | Placebo – High Intensity | | | | |
|---------------|---|-------------------|----------------|----------------|--------------------------|--------|---|---------------------|-------|
| Outcome | RR | RD | NNH | RR | RD | NNH | RR 4 | RD | NNH |
| Outcome | (95% CI) | (95% CI) | 141411 | (95% CI) | (95% CI) | 141411 | (95% CI) | (95% CI) | ININI |
| Direct, M-H | 1.394 | NA | | 2.451 | NA | | 0.960 | , | |
| | (0.679, 2.864) | | | (0.460, | | | (0.225, | | |
| | (111, 11, 111, 111, 111, 111, 111, 111, | | | 13.053) | | | 4.092) | | |
| Direct, IV | 1.394 | 0.0001 | | 1.994 | 0.0004 | | 0.959 | 0.0001 | |
| | (0.679, 2.864) | (-0.0001, 0.0004) | | (0.556, 7.147) | (-0.0001, 0.0009) | | 1 (0.225. ⊇ | I (-0.0002, 0.0004) | |
| | | | | | | | 4.092) | | |
| NMA, IV | 1.225 | 0.0001 | | 1.326 | 0.0001 | | 1.624 | 0.0002 | - |
| | (0.624,2.405) | (-0.0002,0.0003) | N. | (0.487, 3.614) | (-0.0002,0.0004) | | 1.624 5 (0.579,4.553) | (-0.0001,0.0005) | |
| | , | | | V _L | | | (0.579,4.553) | | |
| NMA | 1.389 | 0.0001 | | 0.701 | 0.0001 | | 0.974 | 0.0002 | |
| Excluding S80 | (0.701,2.752) | (-0.0002,0.0003) | | (0.222, 2.209) | (-0.0002,0.0004) | | (0.316,2.997) | (-0.0001,0.0005) | |
| | | , | | | | | (0.010,2.0012 | | |
| NMA | 1.269 | 0.0000* | | 0.892 | 0.0001 | | 1.131 | 0.0001 | |
| CC=0.10 | (0.571,2.820) | (-0.0001,0.0002) | | (0.259,3.066) | (-0.0001,0.0003) | | (0.326,3.927 | (-0.0001,0.0003) | |
| | | , | | | | | (0.020,0.02.9 | | |
| NMA | 1.199 | 0.0000* | | 0.610 | 0.0000* | | 0.732 g | 0.0000* | |
| CC = 0.0001 | (0.514,2.799) | (-0.0000,0.0000) | | (0.161,2.317) | (-0.0000,0.0000) | | | (-0.0000,0.0000) | |
| | | | | | | ノム | (0.193,2.778) | | |
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| | | | | | | | Ratio | 5) 5 | | |
|--------|--|---------|--------------|---------|--------------|------------------|--|-------------------|----------------|---------------|
| | | Experir | | | ontrol | | 702 | | | |
| | Study | Events | Total | Events | Total | Risk | Ratio 5 | RR | 95%−CI | Weight |
| | Craye 4: Madarata Blacaba | | | | | ı | <u>۔</u> د ا | 2 | | |
| | Group 1: Moderate-Placebo | 0 | 1400 | 1 | 1110 | | | | [0.04, 0.04] | 2.00/ |
| | CARDS, A10 | 0 | 1428 | 4 | 1410 | | | 0.11 | [0.01; 2.04] | 3.9% |
| | LIPS, F80 | 0 | 822 | 3 | 818 | | June | 0.14 | [0.01; 2.75] | 3.8% |
|) | CORONA, R10 | 04 | 2514 | 3 | 2497 | | | | [0.03; 3.18] | 5.7% |
| | AFCAPS, L20–L40 | 21 | 3304 | 21 | 3301 | 7 | | 1.00 | [0.55; 1.83] | 15.0% |
| | GISSI-HF, R10 | 1 | 2285 | 1 | 2289 | | | 1.00 | [0.06; 16.01] | 4.2% |
| | PROSPER, P40 | 0 | 2891 | 0 | 2913 | | ¥ | 1.01 | [0.02; 50.76] | 2.4% |
| | 4D, A20 | 0 | 619 | 0 | 636 | | · | 1.03 | [0.02; 51.70] | 2.4% |
| • | HPS, S40 | | 10269 | 6 | 10267 | | : ed | 1.83 | [0.68; 4.95] | 12.3% |
| , | WOSCOPS, P40 | 3 | 3302 | 1 | 3293 | | | 2.99 | [0.31; 28.75] | 5.7% |
| ;) | ALERT, F40-F80 | 3 | 1045 | | 1049 | | | 3.01 | [0.31; 28.90] | 5.7% |
|) | SSSS, S20-S40 Random effects model | 6 | 2221 | | 2223 | J | - | 6.01 | [0.72; 49.84] | 6.2% |
| | | | 30700 | | 30696 | | <u> </u> | 1.17 | [0.72; 1.90] | 67.4% |
| | Heterogeneity: $I^2 = 4\%$, $\tau^2 = 0.0303$, $\rho = 0.41$ | | | | | | 2021. Downloaded from http://ornjopen |) } | | |
| | Croup 2: High-Bloocho | | | | | | ii | ; - | | |
| | Group 2: High-Placebo | 0 | 4504 | 0 | 1400 | \bigcirc | .bmj.com | 4.00 | [0 00, 50 40] | 0.40/ |
| | TRACE RA, A40 | 0 | 1504 | 0 | 1498 | 1/1 | | 1.00 | [0.02; 50.16] | 2.4% |
| , | SPARCL, A80 | 2 | 2365 | 0 | 2366 | | | | [0.24; 104.14] | 3.7% |
| } | Random effects model | | 3869 | | 3864 | |) | 2.73 | [0.25; 30.11] | 6.1% |
|) | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$ | | | | | | on April 17 | <u>!.</u> | | |
| ' | Group 3: High-Modorato | | | | | | | | | |
| | Group 3: High-Moderate TNT, A80 vs A10 | 4 | 400E | 2 | FOOG | _ | Zuz4 by guest. | 3 | [0.05, 5.50] | E 20/ |
| | SEARCH, S80 vs S20 | 68 | 4995 6031 | 2 | 5006 6033 | | by . | 0.50 | | 5.2% |
| | A to Z, S40–S80 vs S20 | 9 | 2263 | 12 1 | 2230 | | J. J | 0.07 | [3.07; 10.46] | 14.9% 6.4% |
| | Random effects model | _ | | 1 | | | | | [1.12; 69.94] | |
| , | Heterogeneity: $I^2 = 50\%$, $\tau^2 = 0.7030$, $p = 0.14$ | | 13289 | | 13269 | | | 3.00 | [1.05; 14.31] | 26.5% |
| ; | Therefore the first $p = 0.7030$, $p = 0.14$ | | | | | | | | | |
|) | Random effects model | | 47858 | | 47829 | | | 1,66 | [0.86; 3.21] | 100.0% |
|) | Heterogeneity: $I^2 = 52\%$, $\tau^2 = 0.6582$, $p < 0.01$ | | | | | | | | [5.55, 5.21] | / - |
| , | Residual heterogeneity: $I^2 = 12\%$, $p = 0.32$ | | | | (| 0.01 0.1 1 | 1 10 10 | Ď | | |
| | 1270, p = 0.02 | | | | | tatin Protective | ្សា Statin Harmfu | | | |
| | | | | | O | | | • | | |



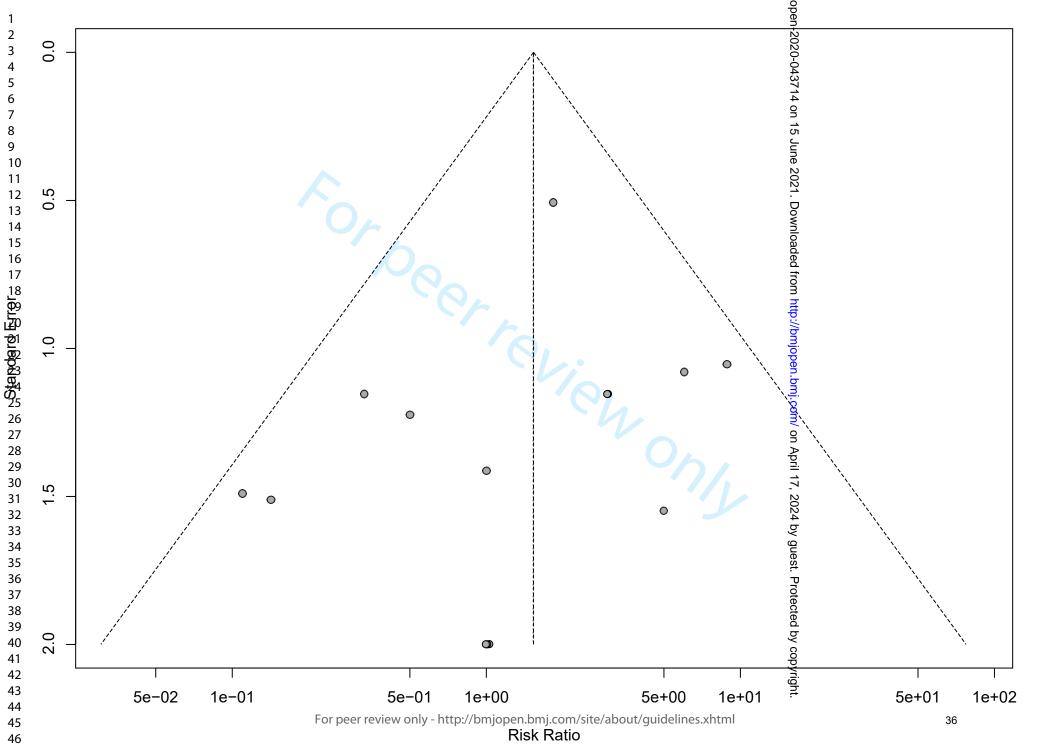
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CK >10x ULN: Meta-Analysis Forest Plot with outliers excluded.

| | Experir | nental | C | ontrol | | | 2020-043714 on | | |
|--|---------|--------------|--------|---------------|---------------|--|--|----------------|---------------|
| Study | Events | Total | Events | Total | Risk | Ratio | 4371 ² | 95%−CI | Weight |
| Group 1: Moderate-Placebo | | | | | | | | | |
| CARDS, A10 | 0 | 1428 | 4 | 1410 | | | 0.11 0.14 | | 4.6% |
| LIPS, F80 | 0 | 822 | 3 | 818 | | | | . , | 4.5% |
| CORONA, R10 | 1 | 2514 | 3 | 2497 | | | 0.33 | . , . | 7.4% |
| GISSI-HF, R10 | 1 | 2285 | 1 | 2289 | - | | 1.00 | · ' | 5.1% |
| PROSPER, P40 | 0 | 2891 | 0 | 2913 | - | 1 | 0.33 1.00 1.01 1.03 1.83 2.99 1.31 1.31 | [0.02; 50.76] | 2.6% |
| 4D, A20 HPS, S40 | 0 | 619 10269 | 0 | 636 | | | 1.03 | | 2.6% |
| WOSCOPS, P40 | 3 | 3302 | 6 1 | 10267 3293 | | | 1.83 ± 2.99 | | 28.0% 7.4% |
| ALERT, F40–F80 | 3 | 1045 | 1 | 1049 | | | 3.01 | [0.31, 28.73] | 7.4% 7.4% |
| SSSS, S20-S40 | 6 | 2221 | | 2223 | _ | | 6.01 | • | 8.3% |
| Random effects model | O | 27396 | 1 h | 27395 | < | | 1.31 | [0.63; 2.73] | 77.8% |
| Heterogeneity: $I^2 = 10\%$, $\tau^2 = 0.1435$, $p = 0.35$ | | | | | | | o O | [0.00, 2.70] | 111070 |
| , | | | | | | | pen | | |
| Group 2: High-Placebo | | | | | | | .bm | | |
| TRACE RA, A40 | 0 | 1504 | 0 | 1498 | | <u> </u> | 1.00 | [0.02; 50.16] | 2.6% |
| SPARCL, A80 | 2 | 2365 | 0 | 2366 | | | | [0.24; 104.14] | 4.3% |
| Random effects model | | 3869 | | 3864 | | | on April 17. | [0.25; 30.11] | 6.9% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$ | | | | | | | ori: | | |
| | | | | | | | | | |
| Group 3: High-Moderate | | | _ | | | | 2024 0.50 | | |
| TNT, A80 vs A10 | 1 | 4995 | 2 | 5006 | - | | 0.50 | | 6.6% |
| A to Z, S40–S80 vs S20 | 9 | 2263 | 1 | 2230 | | | ු 8.87 | [1.12; 69.94] | 8.7% |
| Random effects model | | 7258 | | 7236 | | ÷ | • ' | [0.13; 38.98] | 15.3% |
| Heterogeneity: $I^2 = 69\%$, $\tau^2 = 2.9371$, $p = 0.07$ | | | | | | | Prot | | |
| Random effects model | | 38523 | | 38495 | • |]: | Protected by | [0.80; 2.91] | 100 0% |
| Heterogeneity: $I^2 = 8\%$, $\tau^2 = 0.1269$, $p = 0.36$ | | 30323 | | JU-7JU | | | وا ا | [0.00, 2.01] | 100.0/0 |
| Residual heterogeneity: $I^2 = 19\%$, $p = 0.25$ | | | | (| 0.01 0.1 | | § 0 | | |
| · · · · · · · · · · · · · · · · · · · | | | | | Statin Better | | ovric | | |
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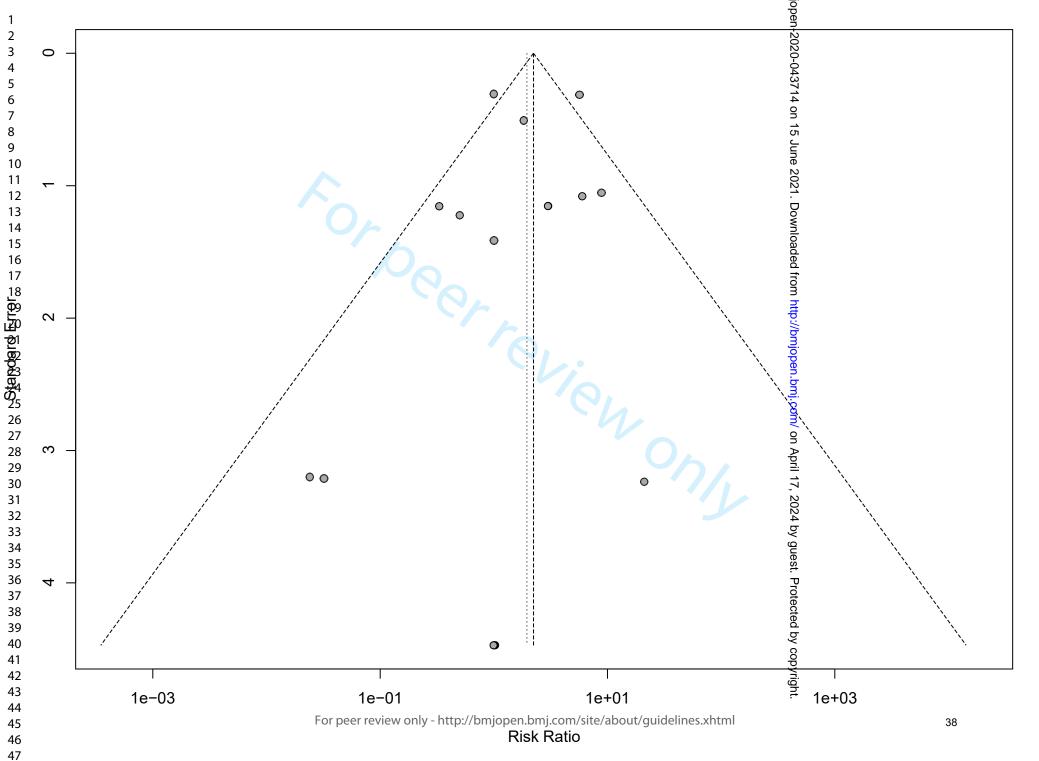
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CK >10x ULN: Meta-Analysis Forest Plot with Continuity Correction = 0.1.

| 1 | | | | | | | pen-2020-043714 | | |
|----------------------|--|--------|--------------|---------------|--------------|----------------------------|----------------------------------|---|----------------------|
| 2 | Experimental C | | | | ontrol | | 202 | | |
| 4 | Study | vents | Total | Events | Total | Risk Ratio | RR | 95%-0 | I Weight |
| 5 | | | | | | : | 1371 | | |
| 6 | Group 1: Moderate-Placebo | | | _ | | | 0 | | |
| 8 | CARDS, A10 | 0 | 1428 | 4 | 1410 | * | _ 0.02 | [0.00; 12.70 | - |
| 9 | LIPS, F80 | 0 | 822 | 3 | 818 | - | د 0.00 | [0.00; 17.42 | - |
| 10 | | 1 | 2514 | 3 | 2497 | -*_<u>+</u> | | [0.03; 3.18 | - |
| | AFCAPS, L20–L40 | 21 | 3304 | 21 | 3301 | | ²⁰ 1.00 | [0.55; 1.83 | - |
| | GISSI-HF, R10 | 1 | 2285 | 1 | 2289 | - 1 | 1.00 | [0.06; 16.0 | - |
| 14 | PROSPER, P40 | 0 | 2891 | 0 | 2913 | | Downloaded 1.83 | [0.00; 6455.29 | - |
| 15 | HD0 040 | 0 | 619 | 0 | 636 | : | nloa 1.03 | [0.00; 6578.8 | - |
| 16 | HPS, S40 | | 10269 | 0 | 10267 | T. | | [0.68; 4.9 | - |
| | WOSCOPS, P40 ALERT, F40-F80 | 3 | 3302 | 1 | 3293 1049 | | from 3.01 | [0.31; 28.75 | - |
| | SSSS, S20-S40 | 3 6 | 1045 2221 | | 2223 | | | [0.31; 28.90 [0.72; 49.84 | - |
| 20 | | O | 30700 | | 30696 | | 6.01 1.24 http://bmjopen | [0.72; 49.84 [0.79; 1.97 | - |
| 21 | 11-4 | | 30700 | | 30090 | <u> </u> | 3 1.24 | [0.79, 1.9 |] 07.070 |
| 22 | | | | | | | ope | | |
| 23 24 | Group 2: High-Placebo | | | | | | n.br | | |
| | TRACE RA, A40 | 0 | 1504 | 0 | 1498 | 2, | <u>3</u> . 2 1 00 | [0.00; 6380.08 | 31 0.6% |
| 26 | • | 2 | 2365 | 0 | | · // | - \$21.00 | [0.04; 11950.08 [0.04; 1256.08 [0.05; 5.52 [3.07; 10.46 [1.12; 69.94 [1.05: 14.37] | 3] 0.0 % 3] 1.1 % |
| 27 | Dandom offacts model | _ | 3869 | Ü | 3864 | | 7.37 | [0.04: 1256.08 | 1.7% |
| 28 29 | | | | | | | Apri | [0:0:, 1200:00 | 1 /0 |
| 30 | | | | | | | l 17 | | |
| 31 | Group 3: High-Moderate | | | | | | , 20 | | |
| 32 | TNT, A80 vs A10 | 1 | 4995 | 2 | 5006 | | ² / ₊ 0.50 | [0.05: 5.52 | 2] 5.8% |
| 33 34 | CEADOLL COOMS COO | 68 | 6031 | 12 | 6033 | | 9 5.67 | [3.07: 10.46 | 6] 18.3% |
| 3 4 35 | A to Z, S40-S80 vs S20 | 9 | 2263 | 1 | 2230 | - | ® 8.87 | [1.12: 69.94 | 7.2% |
| | Random effects model | | 13289 | - | 13269 | | ⊋ 3.88 | [1.05; 14.3 | 31.3% |
| 37 | | | | | | | 3.88 Protected by | - / | - |
| 38 | | | | | | | cted | | |
| 39 40 | Random effects model | | 47858 | | 47829 | | | [1.00; 3.8 | 5] 100.0% |
| 41 | Heterogeneity: $I^2 = 45\%$, $\tau^2 = 0.5511$, $p = 0.03$ | | | | | | | | |
| | Residual heterogeneity: $I^2 = 0\%$, $p = 0.44$ | | | | | 0.001 0.1 1 10 1000 | copyright | | |
| 43 | | | | | | Statin Better Statin Worse | <u> </u> | | |





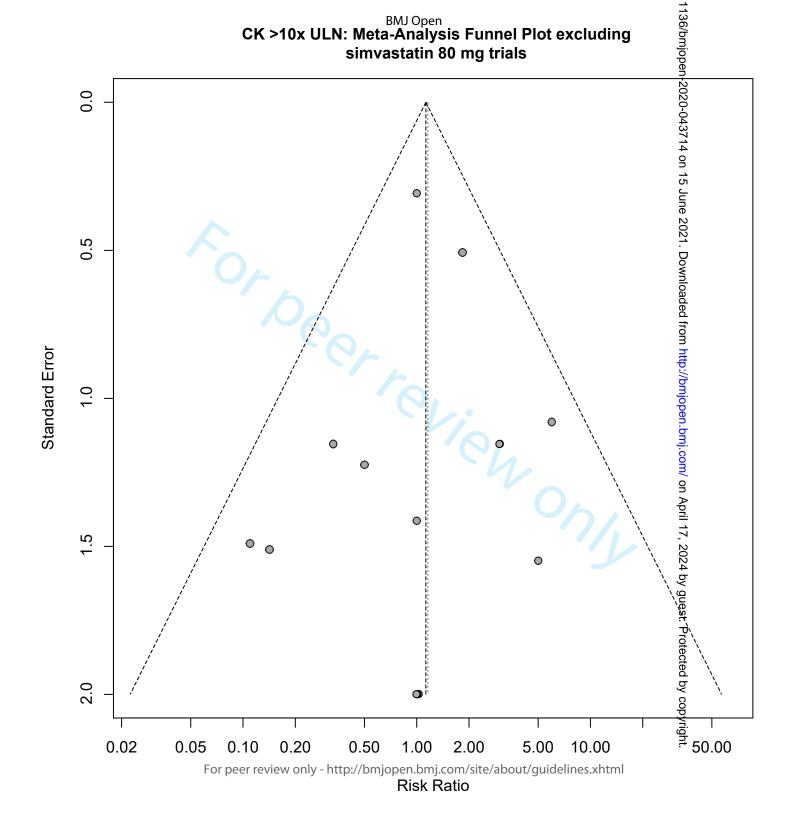


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CK >10x ULN: Meta-Analysis Forest Plot excluding simvastatin 80 mg trien-20.

| | Experim | nental | С | ontrol | | 2020-043714 | | |
|---|---------|-------------|--------|-------------------|------------------------------|--------------------------------------|-------------------------------|--------------|
| Study | Events | | Events | Total | Risk Ratio |)4371. | 95%−CI | Weight |
| Group 1: Moderate-Placebo | | | | | | 9 | | |
| CARDS, A10 | 0 | 1428 | 4 | 1410 ⁻ | <u>-</u> | 15 0.11 June 0.14 | [0.01; 2.04] | 2.2% |
| LIPS, F80 | 0 | 822 | 3 | 818 | * : | | [0.01; 2.75] | 2.1% |
| CORONA, R10 | 1 | 2514 | 3 | 2497 | | ²⁰ 0.33 | [0.03; 3.18] | 3.6% |
| AFCAPS, L20-L40 | 21 | 3304 | 21 | 3301 | | 1.00 | [0.55; 1.83] | 50.8% |
| GISSI-HF, R10 | 1 | 2285 | 1 | 2289 | | 9 1.00 | [0.06; 16.01] | 2.4% |
| PROSPER, P40 4D, A20 | 0 | 2891 619 | 0 | 2913 636 | | nloade 1.03 | [0.02; 50.76] | 1.2% 1.2% |
| 4D, A20 HPS, S40 | _ | 10269 | _ | 10267 | | 1.00 1.01 1.03 1.83 1.83 | [0.02; 51.70] [0.68; 4.95] | 18.7% |
| WOSCOPS, P40 | 3 | 3302 | 1 | 3293 | | ² 2.99 | [0.31; 28.75] | 3.6% |
| ALERT, F40-F80 | 3 | 1045 | | 1049 | | | [0.31; 28.90] | 3.6% |
| SSS, S20-S40 | 6 | 2221 | 1 | | - | 6.01 | [0.72; 49.84] | 4.1% |
| Random effects model | | 30700 | | 30696 | \(| 를 1.17 | [0.72; 1.90] | 93.6% |
| Heterogeneity: $I^2 = 4\%$, $\tau^2 = 0.0303$, $p = 0.41$ | | | | | | 3.01 6.01 1.17 1.00 | | |
| | | | | | 0. | bmj. | | |
| Group 2: High-Placebo | | | | | | .com | | |
| TRACE RA, A40 | 0 | 1504 | 0 | 1498 | | 0 | [0.02; 50.16] | 1.2% |
| SPARCL, A80 | 2 | 2365 | 0 | 2366 | | _≥ 5.00 | [0.24; 104.14] | 2.0% |
| Random effects model | | 3869 | | 3864 | | rii 2./3 | [0.25; 30.11] | 3.2% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$ | | | | | | 7, 2 | | |
| Group 3: High-Moderate | | | | | | 2024 | | |
| TNT, A80 vs A10 | 1 | 4995 | 2 | 5006 | | by guest. | [0.05; 5.52] | 3.2% |
| Random effects model | • | 4995 | _ | 5006 | | gues 0.50 | [0.05; 5.52] | 3.2% |
| Heterogeneity: not applicable | | | | | | | 2 | |
| | | | | | | Protected 1.16 | | |
| Random effects model | 3 | 39564 | | 39566 | \rightarrow | <u>_</u> ₫ 1.16 | [0.75; 1.78] | 100.0% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.55$ | | | | _ | | by 400 | | |
| Residual heterogeneity: $I^2 = 0\%$, $p = 0.46$ | | | | | | 10 8 | | |
| | | | | 5 | tatin Protective Statin Harm | | | |
| | | | | | | | | |



BMJ Open CK>10XULN SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

| | Placebo – Moderate Intensity | | | Moderate - Hig | nh Intensity | Placebo - High | ರ – High Intensity | | | |
|-------------|------------------------------|-------------------|----------|----------------|------------------|----------------|---|-------------------|-----|--|
| | i iacebo – moa | icrate interisity | | Moderate - m | girintensity | - | 9 | | | |
| Outcome | RR | RD | NNH | RR | RD | NNH | RR 15 | RD | NNF | |
| | (95% CI) | (95% CI) | | (95% CI) | (95% CI) | | (95% CI) د ا | (95% CI) | | |
| Direct, M-H | 1.171 | NA | | 3.880 | NA | | 2.731 | NA | | |
| • | (0.722, 1.900) | | | (1.052, | | | (0.428, 30.108) | | | |
| | , | | | 14.314) | | | 21. | | | |
| Direct, IV | 1.178 | 0.0000* | | 4.861 | 0.0030 | 333 | 2.720 | 0.0004 | | |
| | (0.700, 1.985) | (-0.0010, 0.0010) | | (2.388, 9.894) | (0.0011, 0.0049) | | (0.240, 30.828) | (-0.0016, 0.0025) | | |
| NMA, IV | 1.143 | -0.0003 | | 4.594 | 0.0019 | 527 | 5.252 | 0.0017 | 589 | |
| ŕ | (0.686, 1.905) | (-0.0012,0.0007) | | (2.320,9.098) | (0.0005,0.0034) | | (2.293,12.028) | (0.0002,0.0031) | | |
| NMA | 1.189 | 0.0002 | | 1.073 | -0.0000* | | 1.276 | 0.0002 | | |
| Excluding | (0.765,1.848) | (-0.0003,0.0006 | | (0.194,5.939) | (-0.0007,0.0007 | | (0.230,7.063) | (-0.0006,0.0009) | | |
| S80 | | | | |) | | (p :/ | (| | |
| NMA | 1.246 | -0.0002 | + | 5.123 | 0.0016 | 625 | 6 381 | 0.0013 | 770 | |
| CC=0.10 | (0.790,1.964) | (-0.0010,0.0005) | | (2.906,9.033) | (0.0004,0.0028) | 020 | 6.381 <u>3</u> . (3.094,13.161) | (0.0002,0.0025) | | |
| NMA | 1.297 | -0.0000* | | 5.115 | 0.0001 | | 6.636 | 0.0001 | | |
| CC = 0.0001 | (0.818,2.058) | (-0.0002,0.0001) | | (2.891,9.049) | (-0.0002,0.0003) | | (3.186,13.819 | (-0.0001,0.0003) | l | |
| | (0.010,2.000) | (0.0002,0.0001) | | (2.001,0.040) | (0.0002,0.0000) | | · · · · · · · · · · · · · · · · · · · | (0.0001,0.0000) | | |
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| | | | | | | | on April 17, 2024 by guest. Protected by copyright. | | | |
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| | | | | | | | | | | |

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Attrition MA:

```
AE_Drop_meta <- read.csv("C:/Users/14795/Desktop/Statin_Meta/Final
Sheets - Copy/Attrition.csv", header=T)
```

R Code for Meta-Analysis

BMJ Open

mb1_Attrition <- metabin(X1, Statin.Total, X2, Placebo.Total,

data = AE_Drop_meta, studlab = Study, label.right = "Statin Harmful", label.left = "Statin Protective",

allstudies=TRUE, incr=0.5, sm = "RR", digits=3,

r = FALSE, byvar = AE_Drop_meta\$Study.Intensity, bylab = "Study Design", comb.fixed = FALSE,

summary(mb1_Attrition)

```
## Attrition NMA:
##
p3 <- pairwise(list(treat1, treat2),
              list(X, X1),
              list(Total, Total.1),
              data=net_attrition, studlab = Study)
net3_attrition <- netmetabin(p3,</pre>
                                method = "Inverse", title =
"Attrition NMA",
                 reference.group = "Placebo", sm = "RR", comb.fixed
= FALSE,
                 studlab = p3\$Study)
                    net3_attrition
```



PRISMA 2009 Checklist

| | | 20 | |
|------------------------------------|----|--|--------------------------|
| Section/topic | # | Checklist item 43714 | Reported on page # |
| TITLE | | on 1 | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 (Title) |
| ABSTRACT | | ਰੇ 2 | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| INTRODUCTION | | ad. | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5 (Intro) |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5-6 |
| METHODS | | · | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number. | 3 (abstract) |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6-7 |
| / Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | With Prospero reg. |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 6-7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and சூர் assumptions and simplifications made. | 6-7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specifications of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| | | For neer review only - http://bmionen.hmi.com/site/about/quidelines.yhtml | 1 |



PRISMA 2009 Checklist

| | | 1-202 ₀ | |
|-------------------------------|----|---|--------------------|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis. | 8 |
| | | Page 1 of 2 Q | |
| Section/topic | # | Checklist item | Reported on page # |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| RESULTS | | ad ec | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8-9 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 8-11, Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summais data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figures |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Figures |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Results section |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Results section |
| DISCUSSION | | by <u>c</u> | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 15-16 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16-17 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 17-18 |
| FUNDING | | D S D D D D D D D D D D D D D D D D D D | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml | Title page |

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INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS: A NETWORK META-ANALYSIS OF 153,000 PATIENTS

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ABSTRACT

Objective: To estimate relative risk of statin-associated musculoskeletal symptoms (SAMS) by statin therapy intensity.

Setting: Network meta-analysis assessing multi-center RCTs across several countries.

Participants: Pubmed, Web of Science, Cochrane database, and clinicaltrials.gov were searched through January 2021 for doubled-blinded RCTs testing the effect of statin therapy on lipids with at least 1000 participants and two years of intended treatment.

Two coders assessed articles for final inclusion, quality, and outcomes. Treatment intensity was categorized according to American Heart Association definitions.

Outcomes: Pairwise and network meta-analysis (NMA) estimated relative risk (RR) and risk difference (RD) with random effects modeling. Heterogeneity was evaluated with the I² statistic. Outcomes included muscle symptoms (any, myalgia, and attrition due to muscle symptoms), rhabdomyolysis, and elevated creatine kinase (>10x upper limit of normal).

Results: Of 2919 RCTs, 24 (N=152,461) met inclusion criteria. NMA results indicated risk was significantly greater for high compared to moderate intensity statin therapy for any muscle problem (RR=1.04, 95% CI: 1.00,1.07; I²=0%), myalgia (RR=1.04, 95% CI: 1.00,1.08; I²=0%, NNH=173), attrition due to muscle problems (RR=1.37, 95% CI: 1.09,1.73, I²=0%, NNH=218), and elevated CK (RR=4.69, CI: 2.50, 8.80; I²=7%, NNH=527). Risk also was significantly higher for high intensity compared to placebo for any muscle problem (RR=1.05, 95% CI: 1.01,1.09, I²=0%), myalgia (RR=1.13, 95% CI: 1.05,1.23; I²=0%, NNH=182), attrition due to muscle problems (RR=1.55, 95% CI: 1.15,2.08, I²=0%, NNH=187), and elevated CK (RR=5.37, CI: 2.48, 11.61; I²=7%,

NNH=589). Due to inconsistency of results across sensitivity analyses, estimates were inconclusive for rhabdomyolysis and CK. There were no significant differences in risk between moderate intensity therapy and placebo for all outcomes.

Conclusions: For approximately each 200 patients on high intensity statins, one additional patient may experience myalgia or discontinue therapy due to muscle problems compared to moderate intensity therapy.

Trial Registration: Prospero #CRD42019112758

Article Summary:

Strengths

- High-quality, large RCTs analyzed with low risk of heterogeneity bias
- Novel use of network meta-analysis to compare treatment intensities allows for large analysis of dose-dependent effect
- Coding of outcome terms directly as reported by investigators to minimize bias

Weaknesses

- Study-level data precludes meta-analysis with regression for relevant covariables affecting risk of outcome
- Heterogeneity of terms across trials prevented analysis of full trial set for each outcome.

Key Words: Statins, myalgia, nocebo, rhabdomyolysis, network meta-analysis

Abbreviations:

Network Meta-Analysis (NMA) and pair-wise meta-analysis (MA), Risk Ratio (RR), Risk Difference (RD), Cholesterol Treatment Trialists' Collaboration (CTT), Statin Associated Muscle Symptoms (SAMS), Creatine Kinase (CK) & Upper Limit of Normal (ULN), End Stage Renal Disease (ESRD), Number Needed to Harm (NNH), Hazard Ratio (HR) Ethical Approval: N/A



INTRODUCTION

The Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis on patient-level data from large RCTs demonstrated that statin therapy is efficacious in reducing major vascular events. 1,2 Statin therapy is now prominent in cholesterol management guidelines. 3-8 Statin-associated muscle symptoms (SAMS), however, may lead to nonadherence or discontinuation with therapy and ultimately to poorer cardiovascular outcomes. Most RCTs have shown small, insignificant increases in risk for SAMS, although patients taking statins may complain of muscle problems and may discontinue therapy due to muscle problems.³ For example, a 2016 meta-analysis found a nonsignificant increase in myopathy. However, it did not report on the more mundane myalgias that often cause statin attrition.³ These milder symptoms are the major public health concern, as statin non-adherence can lead to significant increases in risk of major adverse cardiovascular events.³ Observational studies suggest that these mild SAMS may occur as often as 7-29% of patients. One review suggested that clinical observations of increased muscle problems with statin therapy may be due to patient expectations.

SAMS also may be more likely with higher intensity therapy. Although this is assumed to be true, especially with the evidence against simvastatin 80 mg, ^{10,11} few RCTs have examined high intensity therapy^{12,13}. This study used a network meta-analysis (NMA) to combine evidence across trials to estimate the risk of SAMS by treatment intensity. In contrast to pair-wise meta-analysis (MA) that directly estimates causal effects, a NMA can indirectly estimate risk between placebo and moderate, moderate and high, and

between placebo and high intensity treatment – even though placebo, moderate, and high intensity treatment levels were not compared within a single trial. Results contribute to the debate about whether muscle adverse events are due solely to patient expectations or whether statins might have an independent effect on symptoms. Finally, this study contributes to the ongoing debate as to whether statins cause myalgias and attrition due to muscle problems without marked creatine kinase (CK) elevations.

METHODS

The Trials. PubMed, Cochrane Database, Web of Science, and clinicaltrials.gov were searched for "systematic reviews" and "meta-analysis" in the title, abstract, or keywords prior to January 31, 2021to identify eligible trials (Prospero #CRD42019112758; see online supplement for search terms and strategy). Double-blinded RCTs to improve lipid levels comparing statin therapy to placebo or higher-lower dose statin therapy were selected. In order to detect most adverse events, RCTs were selected that had at least 1,000 participants with two years of intended follow-up, where statin treatment was not given with other prescription drug therapies, and results contained reports on muscle-related adverse events. Both authors independently reviewed trials for final inclusion and coded each for quality with Oxford Center for Evidence-based Medicine ratings¹⁴ and a five-point Jadad quality score. ¹⁵ Any disagreements were reconciled by joint review and discussion.

Patient and Public Involvement. Patients were not involved in design or implementation of this study.

Exposure Variable. Studies were classified by intensity of statin treatment ("high" or "moderate") according to American Heart Association definitions for potency in reduction of lipid levels. ¹⁶ High intensity signifies an expected 50% or greater reduction in LDL-C levels when taking that statin (i.e., 80 mg atorvastatin) and moderate signifies 30-50% reduction in LDL-C. ¹⁶

Outcome Variables. Adverse muscle-related events were coded into five main outcomes. The first outcome was for any patient-reported muscle complaint coded from reports of "muscle aches", "pains", "cramps", "stiffness," "musculoskeletal disorders," etc. The second focused on only myalgia or muscle pain. The third focused on attrition due to musculoskeletal complaints. A fourth captured explicit reporting of rhabdomyolysis, with or without a trial definition. The fifth was elevated creatine kinase, greater than ten times the upper limit of normal (CK >10x ULN). This threshold was used to distinguish this outcome from less meaningful CK increases and also because CK>10xULN is commonly reported in RCTs. All outcomes were coded as reported by original investigators in published and online reports, and were independently coded by both authors. Ambiguities were resolved by contacting trial investigators.

Analysis. Published aggregate data from each trial were used. A crude estimate of incidence was calculated from the total number of cases observed divided by the total person-years (using the median or mean follow-up time for each study) and a chi square test was used to test for homogeneity in the proportion of incident cases across studies, within each arm, although these crude estimates ignored randomization. To

facilitate interpretation and comparison of results to the original trials, risk of adverse effects was estimated with pooled relative risk (RR). A 0.50 continuity correction was added to aggregate frequencies for trials that observed zero cases of an outcome in either treatment arm. A pairwise meta-analysis (MA) was used to estimate the RR (Mantel-Haenszel method, random effects as implemented in the meta package in R)^{17,18} for a statin effect by treatment intensity from direct (head-head comparison) trials (online supplement contains detailed results for random effects with Mantel-Haenszel and inverse variance methods). Because aggregations across studies are only meaningfully interpreted when results are consistent across studies, heterogeneity among RCTs was assessed with an index of consistency across trials (I², Q)^{19,20} and funnel plots. When $1^2 < 25\%$, results are considered to be at low risk of bias due to heterogeneity; high values (>75%) indicate high risk of bias due to heterogeneity. 19,20 Residual I² represents the heterogeneity remaining after accounting for sub-groups of treatment intensity. Cochrane's Q (a sub-component of I²) indicates the probability that the observed heterogeneity is due to chance. Sensitivity analyses included omitting outliers identified in funnel plots and using a 0.10 as a "continuity correction". In addition, analyses were conducted excluding the simvastatin 80 mg studies because of US FDA muscle-related safety warnings.²¹

A network meta-analysis (NMA), conducted in R,²² used *all* available pairs of comparisons for each outcome to estimate increased risk between the three levels of treatment exposure. Prespecified comparisons were between placebo and moderate intensity, between moderate and high intensity therapy, and between placebo and high

intensity. The RR was used to estimate effect size (frequentist, inverse variance method, random effects), so that results would be comparable across original studies and the pairwise meta-analysis above. In contrast to a MA which provides a direct estimate of the RR, a NMA provides estimates by combining direct and indirect evidence from all data. A ratio test was used to test for consistency between NMA direct and indirect estimates.²³ Heterogeneity was assessed with and I² and Q statistics.^{19,20} Number needed to harm (NNH, the inverse of the absolute difference in incidence) was estimated when the pooled RR was significantly greater than 1.0 and the pooled absolute risk reduction (risk difference, RD) was significantly greater than 0.0.

Sensitivity analyses included replacement of zeros with 0.10 and with 0.0001.

RESULTS

Searches yielded 134 relevant reviews, including 2919 RCTs that reduced to 24 unique RCTs that met eligibility requirements (see online supplement). Of the 24 RCTs: 17 were placebo-moderate intensity comparisons, ^{24–44} 3 were placebo-high intensity comparisons, ^{45–47} and 4 were moderate-high intensity comparisons ^{10–13} (Table 1). The active blood pressure treatment arm of the HOPE trial³⁷ was excluded, but the statin only and placebo only arms were retained, allowing for a statin and placebo comparison. Two trials compared moderate and high intensity therapy using 80 mg/day of simvastatin. ^{10,11} All 24 RCTs scored the highest quality (1) on the Oxford rating and on the Jadad scale 18 scored 5/5 and 6 scored 4/5 (missing detail on random assignment). The RCTs included heterogenous patient populations, e.g., healthy middle-aged adults ^{26,37,43,46} to ESRD patients. Sample sizes ranged from 1,255²⁴ to

20,536⁴⁰ with follow-up periods from 1.9⁴⁶ to 6.7¹⁰ years. Of the 24 RCTs, six were included in the 2006 meta-analysis,⁴⁸ 17 in the 2014 systematic review,⁴⁹ 23 in the 2016 meta-analysis,³ and 18 in the 2013 NMA.⁵⁰ None of the previous analyses separated trials into sub-groups by treatment intensity. Crude estimates of incidence increased with intensity of treatment from placebo to moderate intensity to high intensity therapy, but with heterogeneity across trials (online supplement).

Any Muscle Symptoms. Twenty-three trials reported some type of muscle symptom^{10,13,25–29,31,35,39,40,46,47} myositis,³⁴ myalgia,^{12,24,30,32,33,42,45} myopathy,^{24,38} or discontinuation due to muscle-related symptoms.^{11,13,36} The pairwise meta-analysis pooled across subsets of trials indicated consistent trial results with a 1% non-significant increase in risk between placebo and moderate intensity therapy, a 3% non-significant increase between placebo and high intensity therapy (Figure 1), and a 5% significant increase between moderate and high intensity therapy (RR=1.05, 95% CI: 1.01, 1.09; p=0.027, 4 RCTs, N=30,720; I²=0%). Sensitivity analyses indicated that RRs were essentially unchanged without an outlier³⁰ identified on the funnel plot, with a 0.10 correction, or without the simvastatin 80 mg trials. (online supplement).

The NMA pooled direct and indirect evidence from all 23 trials and suggested increased risk with higher intensity therapy. Results (Table 2) indicated a 1% non-significant increase in risk between placebo and moderate intensity therapy, a 4% significant increase between moderate and high intensity therapy (RR=1.04, 95% CI: 1.00, 1.08; p=0.031), and a 5% significant increase between placebo and high intensity therapy (RR=1.05, 95% CI: 1.01, 1.09; p=0.012). The RRs were consistent across studies

(I²=0%; Q, p=0.54), were not significantly different between direct and indirect estimates (p=0.48), and were not sensitive to substitutions for zero values. Pooled RDs between pairs of treatment groups were not significantly different from zero. There were no outliers in the NMA analysis. Exclusion of the two simvastatin 80mg trials did not meaningfully change risk, but comparisons with high intensity were not statistically significant, likely due to the decreased sample size (online supplement).

Myalgia or pain. Thirteen RCTs reported cases of myalgia, ^{25,29–32,42,44–47} attrition due to myalgia, ^{26,28} or pain and/or weakness. ⁴⁰ The pairwise meta-analysis indicated (Figure 2) a 13% non-significant increase in myalgia between placebo and moderate intensity, a 9% non-significant increase between placebo and high intensity, and a 4% significant increase between moderate and high intensity (RR=1.04, 95% CI: 1.00;1.09, p=0.040, 2 RCT, n=22065; I²=0%). The three trials comparing placebo and high intensity therapies suggested moderate heterogeneity in results (I²=45%). Funnel plots did not suggest bias by any of the studies and there were no zero cells (online supplement). Exclusion of the simvastatin 80 mg trial did not meaningfully change the magnitude of risk, although results were non-significant for high intensity compared to moderate intensity therapy possibly due to decreased sample size (online supplement).

The NMA results combining evidence for all 13 trials suggested an increase in myalgia with increased therapy intensity (Table 2). There was a 9% non-significant increase in risk between placebo and moderate intensity therapy, a 4% significant increase between moderate and high intensity therapy (RR=1.04, 95% CI: 1.00, 1.08; p=0.046),

and a 13% significant increase in risk for high intensity therapy compared to placebo without heterogeneity (RR=1.13, 95% CI: 1.05, 1.23; p=0.002). The RRs were consistent across studies (I²=0%, Q, p=0.48) and direct and indirect estimates were not significantly different (p=0.63). The pooled RD was significant between high and moderate intensity (NNH=173) and between high intensity and placebo (NNH=154) with low heterogeneity (I²=20%; Q, p=0.25). Exclusion of the simvastatin 80 mg trial did not change the magnitude of risk although results were not significant for high intensity compared to moderate intensity therapy (online supplement).

Attrition. Attrition due to muscle problems was reported by eight RCTs that compared moderate intensity statin therapy with placebo, ^{25,26,28,32,36–38,40,44} three that compared moderate with high intensity therapy, ^{10,11,13} and none that directly compared high intensity to placebo. In the pairwise meta-analysis (Figure 3), patients on moderate intensity statin therapy had a 13% non-significant increase in attrition due to muscle problems compared to placebo. Patients on high intensity therapy had a 38% significantly higher attrition rate than those on moderate intensity (RR=1.38, 95% CI: 1.04, 1.82; p=0.024, 3 RCTs, N=20,719) with moderate heterogeneity across trials (I²=31%). Funnel plots did not suggest bias and there were no zero cells. Exclusion of the two simvastatin 80 mg trials left only one moderate-high intensity comparison RCT (online supplement).

The NMA results for the 11 trials suggested that risk for attrition increased with intensity of therapy. There was a 13% non-significant increase in risk between placebo and

moderate intensity therapy (Table 2), a 37% significant increase in risk between moderate and high intensity (RR=1.37, 95% CI: 1.09, 1.73; p=0.007), and a 16% significant increase in risk between placebo and high intensity therapy (RR=1.16, 95% CI: 1.15, 2.08; p=0.004). The RRs were consistent across studies (I²=0%; Q p=0.72) and closely paralled direct results provided by the meta-analysis, but the NMA provided an estimate for the placebo-high intensity comparison for which there were no head-to-head trials. The pooled RD between moderate and high intensity therapy was significant and the NNH was 218. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 186. Exclusion of the two simvastatin 80 mg trials resulted in a slightly lower risk estimate for the moderate to high comparison and a slightly higher estimate for the placebo to high comparison, and both were non-significant (online supplement).

Rhabdomyolysis. Rhabdomyolysis was reported on by 14 moderate intensity-placebo comparison RCTs, ^{24–28,30–32,35,36,39–42} four moderate-high intensity comparison RCTs, ^{10–13} and three high intensity-placebo comparison RCTs. ^{45–47} Incidence of rhabdomyolysis was very low and statistical comparisons were not conclusive. Pairwise meta-analysis indicated a 39% non-significant increase in rhabdomyolysis incidence between placebo and moderate intensity therapy, 145% non-significant increase between moderate and high intensity, and a 4% non-significant decrease between placebo and high intensity therapy (Figure 4). Results were inconclusive as estimates were not robust across sensitivity analyses. Approximately half (22/42) of the cells were zeros and RR increased for the moderate-high intensity comparison with a smaller correction and

removal of the simvastatin 80 mg trials meaningfully changed effect sizes (online supplement).

NMA results based on all 21 trials indicated increased risk for rhabdomyolysis with increased intensity of therapy (Table 2). There was a 22% non-significant increase in risk between placebo and moderate intensity therapy, a 33% non-significant increase between moderate and high intensity, and a 66% non-significant increase between placebo and high intensity therapy with consistency across trials (I²=0%, Q p=0.99). Direct and indirect RR estimates were not significantly different (p=0.31). Results were not consistent after exclusion of simvastatin 80 mg trials or replacement of zeros, but remained nonsignificant (online supplement).

Elevated CK. Of 16 RCTs, 11 compared rates of elevated creatine kinase (CK>10xULN) between placebo and moderate intensity therapy, 24–27,32,35,36,39–43 three compared moderate to high intensity therapy^{10–12} and two compared high intensity therapy with placebo. 45,47 Incidence of elevated CK was low. Pairwise meta-analysis indicated (Figure 5) a 17% non-significant increase in CK elevation between placebo and moderate intensity therapy, a 173% non-significant increase between placebo and high intensity therapy, and a 288% significantly higher risk for high compared to moderate intensity (RR=3.88, 95% CI: 1.05,14.31; p=0.042, 3 RCTs, n=26,558) with some heterogeneity among the three trials (I²=50%). Estimates were not stable across sensitivity analyses. Removal of two possible outliers, ^{10,26} exclusion of simvastatin 80

mg trials, and adjustment for cells with zeros (9/32) meaningfully changed RR estimates (online supplement).

Using evidence from all 16 trials, the NMA estimates indicated increased risk with increased intensity. NMA results indicated a 14% non-significant increase between placebo and moderate intensity therapy (Table 2), a 359% significant increase in CK elevation between moderate and high intensity (RR=4.59, 95% CI: 2.32,9.10; p<0.0001), and a 425% significant increase between placebo and high intensity (RR=5.25, 95% CI: 2.29,12.03; p<0.0001). Results were consistent across trials (I²=7%, Q p=0.37) and direct and indirect RR estimates were not significantly different (p=0.57). The pooled RD between moderate and high intensity therapy was significantly different from zero and the NNH was 527. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 589. There were no outliers in the NMA analysis. Although results were homogeneous with the simvastatin 80 mg trials, exclusion of these trials meaningfully reduced risk associated with statin therapy between moderate and high intensity and between placebo and high intensity therapy; and smaller zero replacement values increased risk estimates (online supplement).

DISCUSSION

A novel contribution of this study was the application of NMA to estimate the doseresponse effect of statin therapy on muscle symptoms using clinically-meaningful categories of treatment intensity. The NMA RR estimates closely paralleled the direct estimates, indicating reliability of estimates and increased risk with high intensity statin

therapy. The network meta-analyses provide information about risk by utilizing all available evidence, whereas traditional meta-analyses are limited only to direct, head-to-head comparisons. For patient-reported symptoms, there were non-significant increases in SAMS between placebo and moderate intensity therapy and significant increases between moderate and high intensity therapy. Because simvastatin 80mg therapy is now restricted because of muscle injury,⁵¹ analyses also were run with and without those trials. This did not meaningfully affect results for patient-reported outcomes. Rhabdomyolysis and elevated CK also showed increased risk with higher intensity, but because of low incidence (with 25-50% zero cells) and inconsistency across sensitivity analyses, results were inconclusive.

Double-blinded RCTs and traditional meta-analyses^{3,48,49} suggest no significant increase in risk of muscle adverse events with statin therapy. Since most evidence comes from moderate intensity trials, possible adverse effects of high intensity therapy may be masked in aggregate estimates. In this study, high intensity therapy and focused definitions of patient-reported muscle problems detected higher risk. However, the absolute excess of SAMS was less than 1% for all outcomes. In previous meta-analyses, absolute excess of muscle problems also was small, but non-significant.^{3,49} The 2016 meta-analysis estimated risk for extreme outcomes (myopathy and rhabdomyolysis), but did not analyze patient reports of milder SAMS that we present and that concern patients. We did not code for myopathy as an outcome, because we did not have access to patient-level data and could not determine if elevated CK co-occurred with myalgia.

Direct lower-higher dose comparisons in individual RCTs were not consistent, e.g., the SEARCH¹⁰ and A to Z trials found a significant increase in CK and the TNT trial¹² did not. A NMA that compared dosage increments within brands⁵⁰ suggested no systematic increase in risk for myalgia or discontinuation with higher dosages. These negative findings may have been due to smaller sample sizes, smaller dosage increments in restricted comparisons, or exclusion of the simvastatin 80 mg trials.⁵⁰ In this study, results were homogeneous including the simvastatin 80mg trials and indicated high intensity therapy significantly increased myalgia compared to placebo even after their exclusion. The previous NMA did identify a dose-response relationship between statin dose and mildly elevated CK (2-3x ULN), but only for lovastatin and simvastatin.⁵⁰ CK>10xULN may be more interpretable than modest elevations, and in this study it was significantly increased with high-intensity statin therapy. While removal of 80mg simvastatin trials had little effect on patient-reported symptoms, their exclusion resulted in smaller non-significant increases in risk for elevated CK. It is unclear if simvastatin 80mg was responsible for the significant increases in CK.

A practical question concerns how large an excess of cases might be observed with statin therapy for myalgia/pain, attrition due to muscle problems, and elevated CK or rhabdomyolysis. Although estimates based on observational studies suggest that incidence of mild SAMS might be as high as 30% among statin users,⁵² RCTs suggest a much lower rate. In this study, pooled risk estimates suggested that for each 173 patients on high intensity therapy one additional patient will experience statin-caused

myalgia and for each 218 patients one additional patient will discontinue therapy due to muscle problems compared to those on moderate intensity therapy. This represents numerous patients who are at greatest risk for major vascular events, as these are often higher risk patients. Discontinuation of statins in the elderly (>75 yrs) may result in 33% increased risk of a cardiovascular event within 3 months ⁵³ and adherence to statins in those 65 and older may reduce mortality by a third.⁵⁴

Myalgias and attrition due to SAMS are important outcomes for the average patient, but have not received as much attention as rhabdomyolysis and myopathy. This study provides evidence that while blinded, moderate intensity statin-takers did not report significantly more general muscle problems or myalgias, but those on high intensity therapy did. Because many myalgia cases occurred without CK elevation increases, this also serves as evidence that SAMS occur in the absence of large elevations in CK. Clinicians with patients who are "statin intolerant" may consider encouraging the patient to first decrease intensity of statin therapy, rather than discontinuing it, in light of these findings.

This analysis also contributes to the "nocebo" debate. A large, unblinded follow-up of RCT patients suggested SAMS are expectation-related.²⁹ They observed an incidence of 2.03% and 2.00% muscle-related adverse events in statin and placebo groups, respectively, when double-blinded (HR=1.03) and 1.26% and 1.00% in the statin and usual care groups when unblinded (HR=1.41).²⁹ Both comparisons indicate absolute differences less than 1%. A recent N-of-1 trial⁵⁵also found minimal differences in muscle

symptoms when patients took statin versus placebo (blinded), but significantly more muscle symptoms when taking a placebo versus taking nothing (unblinded). Both nocebo and causal effects are small, although they can result in increased SAMS. In a clinical setting, SAMS with moderate intensity therapy may be the result of patient expectations, but with high intensity therapy SAMS may be due to expectations and statin therapy. Intensity of treatment and patient expectations may need to be considered before making changes in statin therapy in the absence of CK elevations.

A limitation of study-level meta-analyses is that definitions,⁵⁶ assessment, and variable reporting of muscle-related outcomes may differ across studies. Aggregation of heterogeneous outcomes and estimated outcomes (e.g., myopathy) not explicitly reported by investigators can mask an effect. Protocol differences may partially explain incidence disparities across studies. However, use of the RR to estimate effect size minimizes bias due to between-study variations in protocol (e.g., using a symptom checklist versus recording spontaneous mention of symptoms and then categorizing responses).

Estimates in this analysis may have under-estimated SAMS by excluding patients with statin hypersensitivity, as four studies^{12,37,40,45} (n=48,950) employed statin "washout" phases and eight trials^{24,25,30,32,34–37,47} (n=34,042) excluded patients with known statin hypersensitivity. Collins et al. noted that "statin hypersensitivity" exclusion was a rare occurrence across these trials, as almost all patients enrolled were statin-naïve at screening.³ The risk of attrition due to SAMS and rhabdomyolysis was actually highest

in SEARCH, where an eight week long, active run-in phase was conducted,^{3,10} although no patients were excluded for elevated muscle enzymes.¹⁰ Also,an N-of-1 trial in patients who were considering stopping or who had stopped statin therapy because of muscle symptoms found no difference in severity of patient-reported muscle symptoms between statin and placebo groups.⁵⁷ Because simvastatin 80 mg trials comprise a high proportion of high intensity treatment evidence, this may limit interpretation of CK and rhabdomyolysis risk. Also, adverse events may have been increased due to the presence of co-morbidities; only three trials studied healthy adults (n=30,756).^{26,37,46} A final limitation is that although risk estimates are based on the best available evidence and should provide relatively unbiased estimates, confidence intervals and alpha significance levels may be approximate due to multiple comparisons.

Conclusion

Statins likely cause SAMS, but at much lower rates than observational data suggest. We found significant, but small increases in risk for patient-reported muscle problems on high-intensity statins. Complaints of SAMS in observational studies may be related to statin therapy or patient expectations, but more likely may be due to methodological biases or the generally high prevalence of muscle problems.

Contributorship Statement:

The first author (JD) was responsible for the design and implementation of the study analyses. He was one coder in selecting studies for inclusion, compiled the data for the outcomes of interest, analyzed the data in R, and is responsible for the final manuscript in its entirety. SW (Faculty PI) was responsible for the oversight and implementation of the project. She was the second coder for all trials and offered guidance and support in all decisions regarding design and implementation of the analysis.

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None to disclose

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Data Sharing Statement:

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi.org/10.5061/dryad.kprr4xh2q

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Figure Legend:

Figure 1: Any Muscle Problems

Figure 2: Myalgia or Pain

Figure 3: Attrition Due to Muscle Symptoms

Figure 4: Rhabdomyolysis

Figure 5: CK >10x Upper Limit of Normal

TABLE 1: DESCRIPTION OF THE TRIALS

TABLE 2: RELATIVE RISK AND RISK DIFFERENCE RESULTS FOR F TREATME.

COMPARISONS OF TREATMENT INTENSITY PAIRS

TABLE 1: DESCRIPTION OF THE TRIALS

| | Total sample | Special | Permit Prior | Ave | Run-in Period | Median Yrs F/U |
|-------------------------------|--------------|-------------------|-----------------|-----|------------------|-------------------|
| Trial Name | size | Population | statin† | age | | |
| | | • | | | | |
| Placebo-Moderate | | | | | | |
| 4D, A20 ²⁴ | 1,255 | DM II, ESRD | Y, -HS | 66 | Placebo | 4.0 |
| 4S, S20-S40 ²⁵ | 4,444 | MI or angina | Y, -HS | 59 | Placebo | 5.4 |
| AFCAPS, L20-L40 ²⁶ | 6,605 | Healthy adults | N | 58 | Placebo+diet | 5.2 |
| ALERT, F40-F80 ²⁷ | 2,094 | Renal Trans | N | 50 | None | 5.4 |
| ASCOT, A10 ^{28,29} | 10,810 | HTN+CVD risk | N | 63 | Not statin | 3.3 |
| ASPEN, A1030 | 2,410 | DM II | Y, -HS | 61 | Placebo | 4.0 |
| AURORA, R10 ³¹ | 2,767 | ESRD | N | 64 | Placebo | 3.2 |
| CARDS, A1032,33 | 2,838 | DM II | Y, -HS | 62 | Placebo | 4.0 |
| CARE, P4034 | 4,159 | MI | Y, -HS | 59 | Placebo | 5.0 |
| CORONA, R10 ³⁵ | 5,011 | ESRD | Y, -HS | 73 | Placebo | 2.7 |
| GISSI-HF, R10 ³⁶ | 4,574 | CHF | Y, -HS | 68 | None | 3.9 |
| | 6,349 | Healthy, CVD | Y, -HS | 66 | Statin | 5.6 |
| HOPE-3, R10 ³⁷ | | Risk | , | | | |
| LIPID, P40 ³⁸ | 9,014 | MI or angina | Υ | 62* | Placebo+diet | 6.0 (mean) |
| | 1,640 | Coronary percut. | Υ | 60 | None | 3.9 |
| LIPS, F80 ³⁹ | | intervention | | | | |
| MRC/BHF (HPS), | 20,536 | | N | 64 | Placebo, | 5 (mean) |
| S40 ^{40,41} | | CHD/CHD Risk | | | then statin | |
| PROSPER, P40 ⁴² | 5,804 | Elderly, CHD risk | Υ | 75 | Placebo | 3.2 (mean) |
| WOSCOPS, P4043,44 | 6,604 | Healthy males | Υ | 55 | None | 4.9 (mean) |
| | | | | | | |
| Placebo-High | | | | | | |
| JUPITER, R20 ⁴⁶ | 17,802 | Healthy adults | N | 66 | Placebo | 1.9†† |
| SPARCL, A80 ⁴⁵ | 4,731 | CVA/TIA | Υ | 63 | None | 4.9 |
| TRACE, A40 ⁴⁷ | 3,002 | RA | N, -HS | 61 | None | 2.5 |
| Moderate-High | | | | 6 | | |
| A to Z, S40-S80 vs 0- | | Acute Coronary | N | 61 | None | 1.98 |
| S20 ¹¹ | 4,497 | Syndrome | | | | |
| PROVE-IT, A80 vs | | Acute Coronary | Y, if | 58 | None | 2.0 (mean) |
| P40 ¹³ | 4,162 | Syndrome | <80mg | | | |
| SEARCH, S80 vs | | | Υ | 64 | Statin+ | 6.7 |
| S20 ¹⁰ | 12,064 | MI | | | Placebo | |
| TNT, A80 vs A10 ¹² | 10,001 | CHD | Υ | 61 | Statin | 4.9 |

^{*}Median

[†]Y=Yes, N=No, -HS=statin hypersensitivity exclusion

^{††} Trial was designed for two years of follow-up, but met study end points and terminated the blinded portion of the study earlier.

TABLE 2: RELATIVE RISK AND RISK DIFFERENCE RESULTS FOR COMPARISONS OF TREADMENT INTENSITY PAIRS

| | Placebo – Mo | derate Intensity | | Moderate – H | igh Intensity | | Placebo – High Intensity | | | |
|-----------|----------------|------------------|----------|---------------|---|-----|---|-------------------|-----|--|
| | | 1 | | | T | | 9 | | | |
| Outcom | RR | RD | NNH | RR | RD | NNH | RR a | RD | NNF | |
| е | (95% CI) | (95% CI) | | (95% CI) | (95% CI) | | (95% CI) | (95% CI) | | |
| Any | 1.010 | 0.000 | | 1.039 | 0.004 | | 1.010 | 0.004 | | |
| Probs | (0.988,1.033) | (- | | (1.004,1.075 | (- | | (1.010,1.089) | ₿ (-0.001, 0.008) | | |
| | | 0.001,0.001) | |) | 0.000,0.008) | | | <u>†</u> | | |
| Myalgia | 1.090 | 0.001 | | 1.041 | 0.006 | 173 | | 0.007 | 182 | |
| | (.9997,1.188) | (- | | (1.001,1.083 | (0.001, 0.010) | | (1.046,1.230) | (0.002, 0.011) | | |
| | | 0.000,0.001) | A |) | | | 9 | | | |
| Attrition | 1.127 | 0.001 | () | 1.372 | 0.005 | 218 | 1.155 | 0.005 | 187 | |
| | (0.931,1.364) | (-000,0.001) | | (1.091,1.726 | (0.002, 0.007) | | (1.147,2.084) | (0.002, 0.008) | | |
| | | | | | | | | · | | |
| Rhabdo. | 1.225 | -0.000 | | 1.326 | 0.002 | | 4 004 | 0.002 | | |
| | (0.624,2.405) | (- | | (0.487, 3.614 | (0.001,0.003) | | 1.624 | (0.000, 0.003) | | |
| | , , | 0.001,0.001) | | | | | (0.579,4.553) | . ` ′ ′ | | |
| CK> | 1.143 | -0.000 | | 4.594 | 0.002 | 527 | 5.252 | 0.002 | 589 | |
| 10xULN | (0.686, 1.905) | (- | | (2.320,9.098 | (0.001, 0.003) | | - | (0.000, 0.003) | | |
| | (0.000,, | 0.001,0.001) | |) | (33,3,3,3,3,3,3,3,3,3,3,3,3,3,3,3,3,3,3 | | (=:===,:====) | | | |
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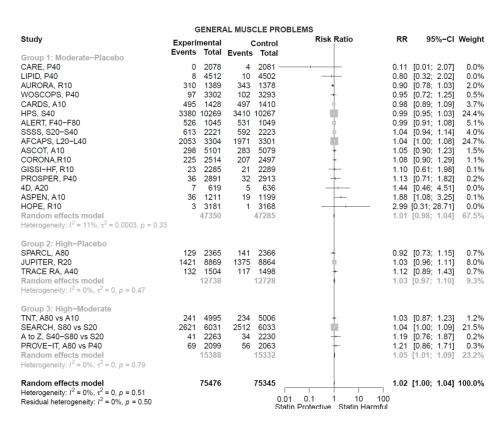


Figure 1

MYALGIA

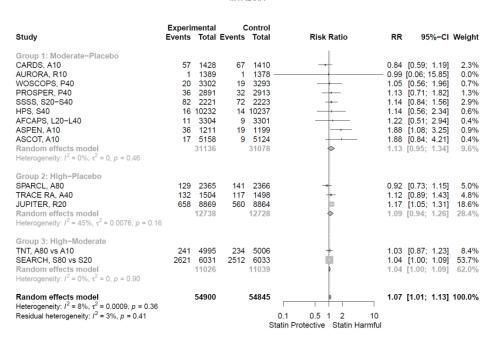


Figure 2

ATTRITION DUE TO MUSCLE SYMPTOMS

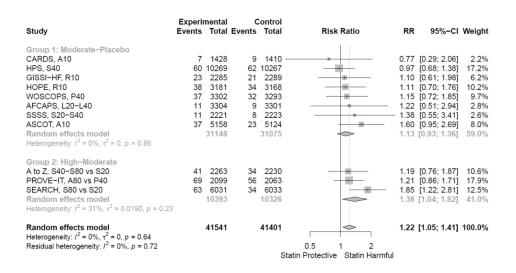


Figure 3

RHABDOMYOLYSIS

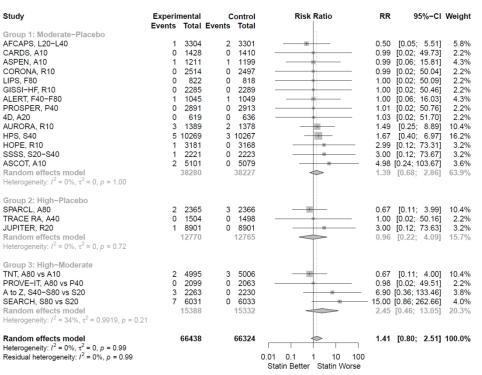


Figure 4

CK >10xULN

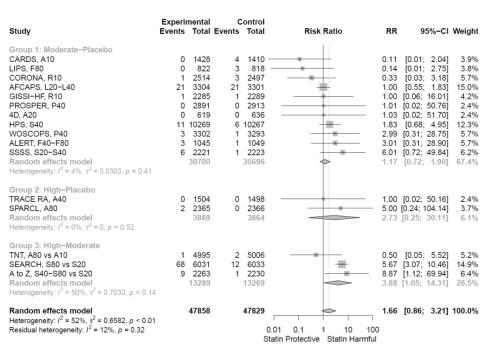


Figure 5

INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS:

A NETWORK META-ANALYSIS OF 153,000 PATIENTS

J.W. Davis & S.C. Weller

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- 7 ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot with data
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- 11 ANY MUSCLE PROBLEMS: Meta-Analysis Forest Plot with Continuity Correction = 0.1.
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15 ANY MUSCLE PROBLEMS: SUMMARY TABLE

- 16 MYALGIA OR PAIN: Meta-Analysis Forest plot with data
- 17 MYALGIA OR PAIN: Meta-Analysis Funnel plot
- 18 MYALGIA OR PAIN: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.
- 19 MYALGIA OR PAIN: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials
- 20 MYALGIA OR PAIN: SUMMARY TABLE
- 21 ATTRITION: Meta-Analysis Forest plot with data

- 22 ATTRITION: Meta-Analysis Funnel plot
- 23 ATTRITION: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.
- 24 ATTRITION: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials

25 ATTRITION: SUMMARY TABLE

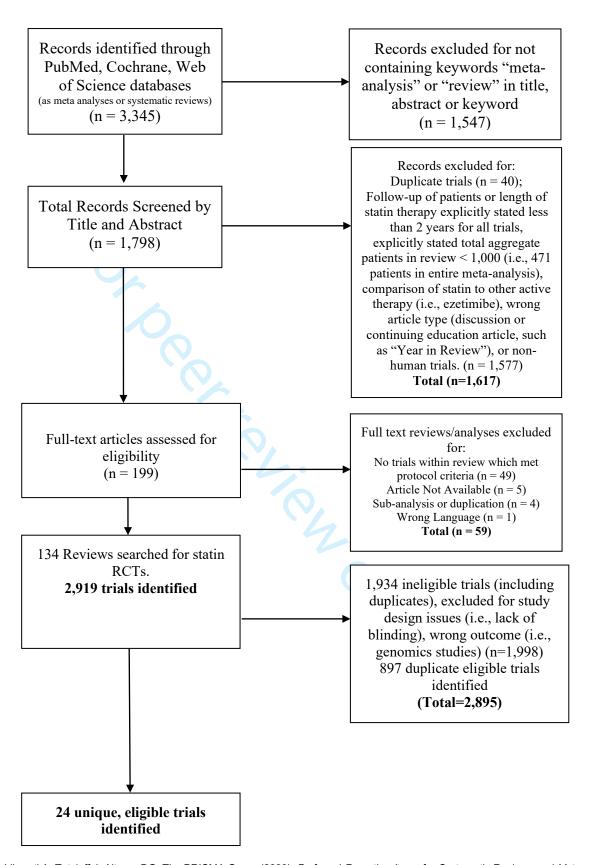
- 26 RHABDOMYOLYSIS: Meta-Analysis Forest Plot with Data
- 27 RHABDOMYOLYSIS: Meta-Analysis Funnel Plot
- 28 RHABDOMYOLYSIS: Meta-Analysis Forest Plot with Continuity Correction = 0.1.
- 29 RHABDOMYOLYSIS: Meta-Analysis Funnel Plot Continuity Correction = 0.1.
- 30 RHABDOMYOLYSIS: Meta-Analysis Forest Plot excluding simvastatin 80 mg trials.
- 31 RHABDOMYOLYSIS: Meta-Analysis Funnel Plot excluding simvastatin 80 mg trials

32 RHABDOMYOLYSIS: SUMMARY TABLE

- 33 CK > 10x ULN: Meta-Analysis Forest Plot with Data
- 34 CK >10x ULN: Meta-Analysis Funnel Plot
- 35 CK >10x ULN: Meta-Analysis Forest Plot with outliers excluded.
- 36 CK >10x ULN: Meta-Analysis Funnel Plot with outliers excluded.
- 37 CK > 10x ULN: Meta-Analysis Forest Plot with Continuity Correction = 0.1.
- 38 CK > 10x ULN: Meta-Analysis Funnel Plot with Continuity Correction = 0.1.
- 39 CK > 10x ULN: Meta-Analysis Forest Plot excluding simvastatin 80 mg trials.
- 40 CK >10x ULN: Meta-Analysis Funnel Plot excluding simvastatin 80 mg trials

41 CK >10x ULN: SUMMARY TABLE

- 42 R Code for Meta-Analysis
- 43 R Code for Network Meta-Analysis



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Search Procedure

PRISMA FLOWCHART explanation

- 1. PubMed, Cochrane Database, Web of Science, and clinicaltrials.gov were searched in November 2018 by a professional research librarian (Prospero #CRD42019112758). The search was updated for November 2018 through February 1, 2021. Web of Science was not searched in this second phase, as institutional access to the database had expired. The following page (eTable 3: Search Strategy) details the MEDLINE search and keywords for the combined search. The strategy was to search for all systematic reviews and meta-analyses, in English or Spanish, to identify RCTs for inclusion. Articles containing the term "systematic review" or "meta-analysis" in the title, abstract, or keywords were retained (1,646 from original search and 351 from the updated search = 1,997).
- 2. Based on information in the abstract, articles were retained that might contain a trial that met inclusion criteria (191 from original search and 8 more from the updated search = 199). Review of the full article eliminated an additional 59 articles, yielding 140 articles for full review. One author (JD) reviewed abstracts and full texts of articles.
- 3. Review of the 140 unique articles identified 2919 trials (2,801 from the original search and 118 trials in the updated search). Then, double-blinded RCTs were selected from these reviews that compared statin therapy to placebo or higher-lower dose statin therapy (24 unique trials).
- 4. The 24 eligible trials were independently judged by both authors (JD, SW) for inclusion, then coded for quality and outcomes. There was complete agreement on quality ratings with the Oxford Center for Evidence-based Medicine ratings and the Jadad quality score. Ambiguities in coding of outcomes were resolved by contacting the study PI.

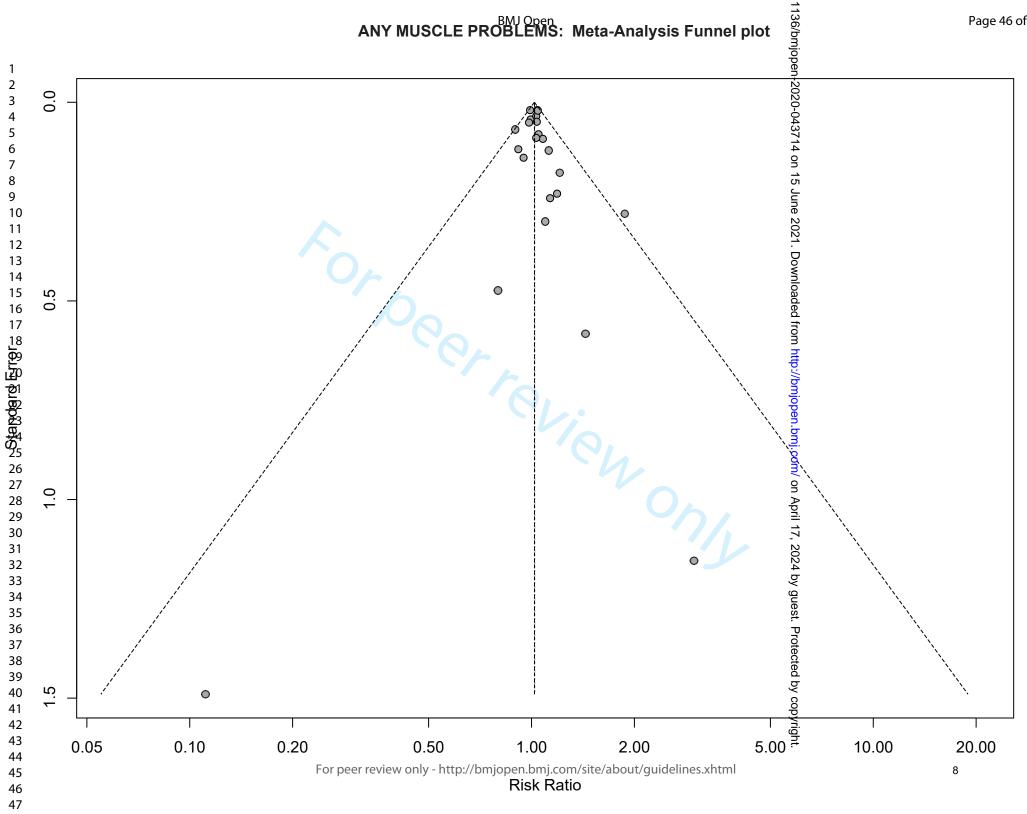
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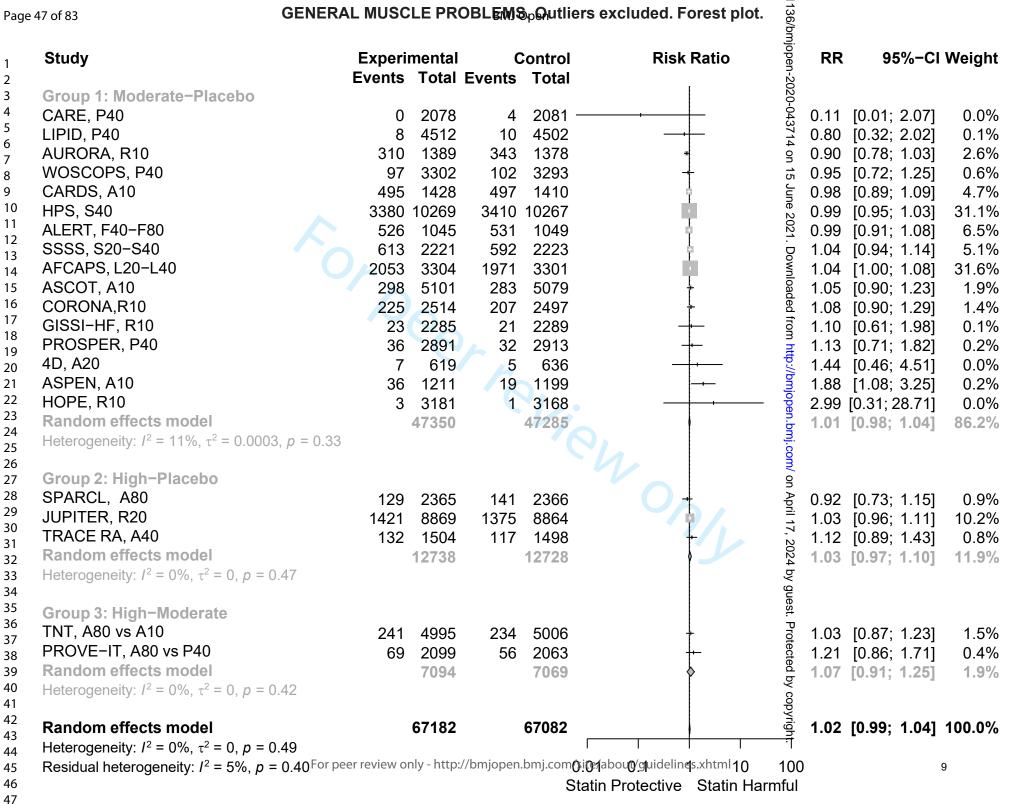
Sample Strategy: MEDLINE Search

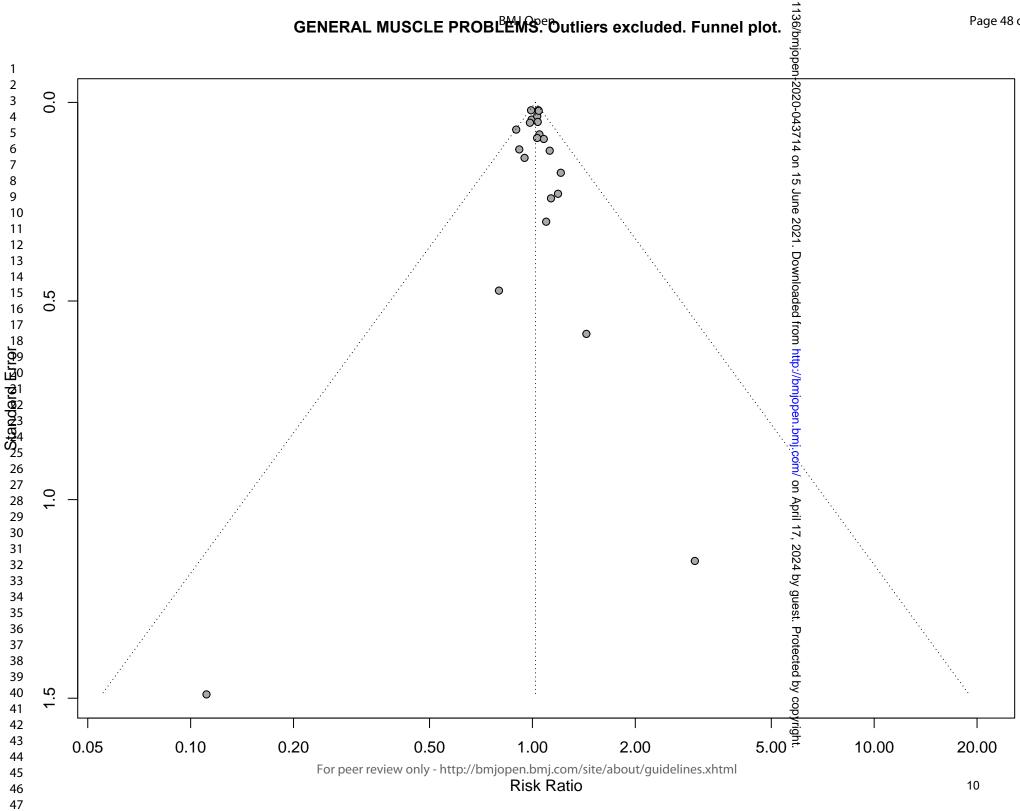
| 021 | Ovid: Current Search History | | | | |
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| Se | arch Journals Books Multimedia My Workspace ACC CardioSource Plus What's New | | | | |
| _ | IEDLINE(R) and Epub Ahead of Print, in-Process, in-Data-Review & Other Non-Indexed Citations and Daily <1946 to February | 26 2021> | | | |
| # | Searches | Results | Туре | | |
| 1 | exp Hydroxymethylglutaryi-CoA Reductase Inhibitors/ | 41740 | Advanced | | |
| 2 | (statin or statins).tw. | 40017 | Advanced | | |
| 3 | atorvastatin.tw. | 8871 | Advanced | | |
| 4 | certvastatin.tw. | 664 | Advanced | | |
| 5 | fluvastatin.tw. | 1899 | Advanced | | |
| 6 | lovastatin.tw. | 3855 | Advanced | | |
| 7 | pravastatin.tw. | 4110 | Advanced | | |
| 8 | simvastatin.tw. | 9706 | Advanced | | |
| 9 | lipitor.tw. | 205 | Advanced | | |
| 10 | baycol.tw. | 14 | Advanced | | |
| 11 | lescol.tw. | 81 | Advanced | | |
| | mevacor.tw. | 48 | Advanced | | |
| 13 | altocor.tw. | 0 | Advanced | | |
| 14 | | 25 | Advanced | | |
| 15 | lipostat.tw. | 26 | Advanced | | |
| | zocor.tw. | 113 | Advanced | | |
| | mevinolin.tw. | 401 | Advanced | | |
| | compactin.tw. | 304 | Advanced | | |
| | fluindostatin.tw. | 4 | Advanced | | |
| 20 | | 3625 | Advanced | | |
| 21 | | 30952 | Advanced | | |
| 22 | HMG-CoA Reductase Inhibitor*.mp. | 4260 | Advanced | | |
| 23 | (cl 981 or cl981 or liptonorm).mp. | 123 | Advanced | | |
| 24 | (6 methylcompactin or mk 803 or mk803 or mevinolin or monacolin k).mp. | 602 | Advanced | | |
| 25 26 | (megiutol or 3 hydroxy 3 methylgiutaric acid or 3 hydroxy 3 methylpentanediolic acid or beta hydroxy beta methylgiutarate).mp. (bristacol or cs 514 or cs514 or elisor or eptastatin or lipemol or lipiat or liostat or mevalotin or pravacul or pravacol or prav | 183 56 | Advanced Advanced | | |
| 27 | rms 431 or rms431 or sq 31000 or sq31000 or selektine or vasten).mp. (crestor or zd 4522 or zd4522).mp. | 73 | Advanced | | |
| | (mk733 or mk 733 or synvinoin).mp. | 54 | Advanced | | |
| | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 | 63347 | Advanced | | |
| 30 | Animals/ not Humans/ | 4760183 | Advanced | | |
| 31 | 29 not 30 | 56479 | Advanced | | |
| 32 | limit 31 to (english or spanish) | 52717 | Advanced | | |
| 33 | limit 32 to (meta analysis or "systematic review") | 1535 | Advanced | | |
| 34 | limit 32 to (systematic reviews pre 2019 or systematic reviews) | 3199 | Advanced | | |
| 35 | 33 or 34 | 3224 | Advanced | | |
| 36 | remove duplicates from 35 | 3202 | Advanced | | |
| 37 | limit 36 to yr="1990 - 2017" | 2463 | Advanced | | |
| 38 | (201801" or 201802" or 201803" or 201804" or 201805" or 201806" or 201807" or 201808" or 201809" or 201810" or 201811").ez. | 1083231 | Advanced | | |
| 39 | 37 or 38 | 1085687 | Advanced | | |
| 40 | 36 and 39 | 2668 | Advanced | | |
| 41 | limit 36 to yr="2019 - 2020" | 443 | Advanced | | |
| 42 | 201812*.ez. | 93882 | Advanced | | |
| 43 | 202101*.ez. | 136550 | Advanced | | |
| 44 | 42 or 43 | 230432 | Advanced | | |
| 45 | 36 and 44 | 42 | Advanced | | |
| 46 | 41 or 45 | 470 | Advanced | | |
| 47 | limit 36 to yr="2019 - 2021" | 501 | Advanced | | |
| 48 | 36 and 42 | 20 | Advanced | | |
| 49 | 47 or 48 | 512 | Advanced | | |
| 50 | 49 not 46 | 42 | Advanced | | |
| 51 | from 50 keep 19, 26-27, 29, 33-37, 39, 42 | 11 | Advanced | | |

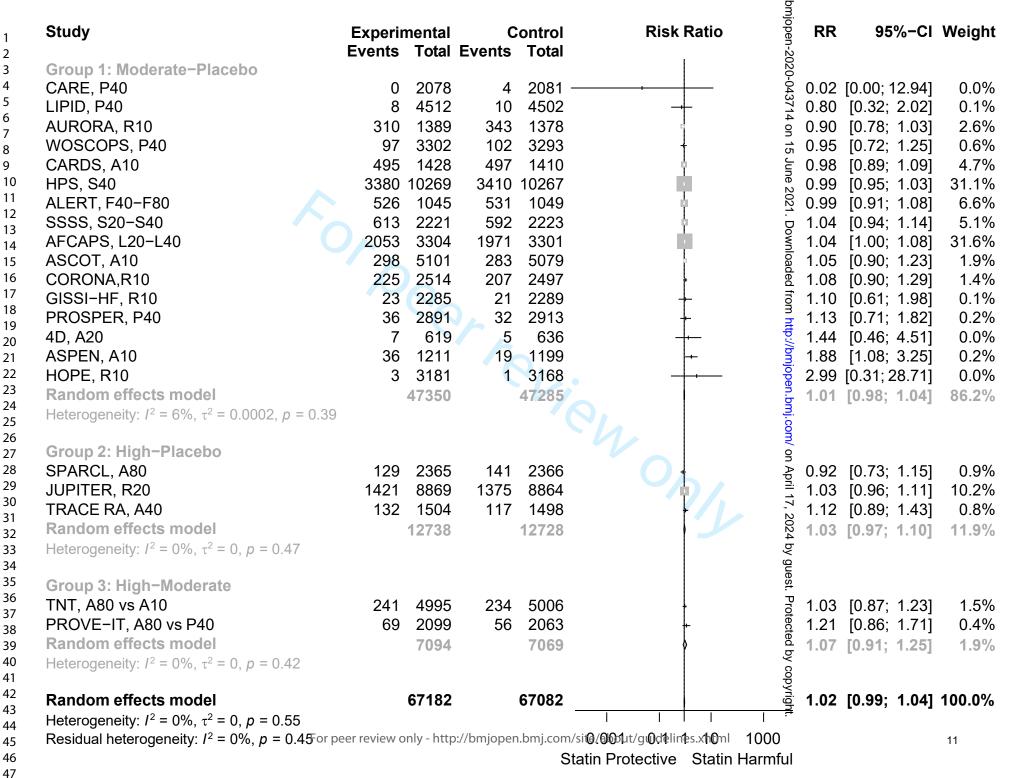
| | Placebo | Moderate Intensity | High intensity – with Simvastatin 80mg | High Intensity – without Simvastatin 80mg |
|----------------------------|---|--|---|--|
| Any Muscle Problems | 38.8 cases per 1000 person years (9661/248993.8; 19 | 41.1 cases per 1000 person years (10946/266265.8; 20 | 44.0 cases per 1000 person years (4654/105761.54; 7 | 32g7 cases per 1000 person years (1992/60873.1; 5 arms)* |
| | (9001/248995.8, 19 arms)* | arms)* | arms)* | (1552/008/3.1; 3 arms) |
| Myalgia | 6.2 cases per 1000 person years | 14.9 cases per 1000 person years | 38.9 cases per 1000 person years | 20.5 cases per 1000 pegson years |
| | (1060/169746.5; 12 arms)* | (3022/202684; 11 arms)* | (3781/97082.8; 5 arms)* | (1 \$60/56675.1; 4 arms)* |
| Attrition due to Muscle | 1.4 cases per 1000 person years | 1.7 cases per 1000 person years | 3.5 cases per 1000 person years | 1634 cases per 1000 person years |
| | (198/145,857.2; 8 arms)* | (311/178940.2; 11 arms)* | (173/ 49086.44; 3 arms)* | $(6\frac{8}{9}/4198; 1 \text{ arm})^*$ |
| Rhabdomyolysis | 5.8 cases per 100,000 person years | 6.9 cases per 100,000 person years | 1.4 cases per 100,000 person years | 8.2 cases per 100,000 person years |
| | (13/225,713.6; 18 arms)** | (18/262803.8; 18 arms)** | (15/105822.3; 7 arms)** | (5/60933.9; 5 arms)** |
| Elevated CK | 2.7 cases per 10,000 person years | 2.9 cases per 10,000 person years | 9.4 cases per 10,000 person years | 0. cases per 10,000 person years |
| | (41/153,768.1; 13 arms)* | (61/207814.1; 14 arms)* | (80/84712.4; 5 arms)* | $(3\frac{8}{5}9824; 3 \text{ arms})*$ |
| * Incidence rates si | ignificantly different across t | rials, p<0.0001 | | gu gu |
| | oportion of cases was not sign such small proportions (p>0 | | als, although a chi square test | Pro |
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| | For peer reviev | v only - http://bmjopen.bmj.com/ | site/about/guidelines.xhtml | |

| Page · | 45 of 83 | ANY MUS | CLE PF | ROB Ľ EW | P S en Met | a-Analysis Forest plot with § | ata. | | |
|----------|---|-------------|--------------|-----------------|-------------------|--|-------------------|-----------------|--------|
| | Study | Experi | mental | (| Control | Risk Ratio | . RF | 8 95%−CI | Weight |
| 1 | | | | Events | | Risk Ratio | | | |
| 2 | Group 1: Moderate-Placebo | | | | | 1.20 |) | | |
| 3 | CARE, P40 | 0 | | 4 | 2081 | · | 0.11 | [0.01; 2.07] | 0.0% |
| 4 5 | LIPID, P40 | 8 | 4512 | 10 | 4502 | - 3 | 0.80 | 0.32; 2.02] | 0.0% |
| 6 | AURORA, R10 | 310 | 1389 | 343 | 1378 | # 2 | 0.90 | 0 [0.78; 1.03] | 2.0% |
| 7 | WOSCOPS, P40 | 97 | 3302 | 102 | 3293 | † 9 | 0.95 | 5 [0.72; 1.25] | |
| 8 | CARDS, A10 | 495 | 1428 | 497 | 1410 | <u>†</u> | | 3 [0.89; 1.09] | 3.7% |
| 9 | HPS, S40 | | 10269 | | 10267 | June 2021. | 0.99 | 9 [0.95; 1.03] | |
| 10 | ALERT, F40-F80 | 526 | 1045 | 531 | 1049 | 9 2 | 0.99 | 9 [0.91; 1.08] | |
| 11 12 | SSSS, S20-S40 | 613 | 2221 | 592 | 2223 | <u> </u> | 1.04 | 1 [0.94; 1.14] | 4.0% |
| 13 | AFCAPS, L20–L40 | 2053 | | 1971 | 3301 | | 1.04 | 1 [1.00; 1.08] | 24.7% |
| 14 | ASCOT, A10 | 298 | 5101 | 283 | 5079 | † | 1.05 | 5 [0.90; 1.23] | 1.5% |
| 15 | CORONA,R10 | 225 | | 207 | 2497 | <u>+</u> 0ad | 1.08 | 3 [0.90; 1.29] | 1.1% |
| 16 | GISSI-HF, R10 | 23 | | 21 | 2289 | —————————————————————————————————————— | 1.10 | 0.61; 1.98] | |
| 17 18 | PROSPER, P40 | 36 | | 32 | 2913 | + 9 | 1.13 | 3 [0.71; 1.82] | 0.2% |
| 19 | 4D, A20 | 7 | 619 | 5 | 636 | - | 1.44 | 1 [0.46; 4.51] | |
| 20 | ASPEN, A10 | 36 | 1211 | 19 | 1199 | | 1.88 | 3 [1.08; 3.25] | |
| 21 | HOPE, R10 | 3 | 3181 | 1 | 3168 | - | 2.99 | 9 [0.31; 28.71] | 0.0% |
| 22 | Random effects model | | 47350 | | 47285 |) Per | 1.01 | [0.98; 1.04] | 67.5% |
| 23 24 | Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.0003$, $p = 0.33$ | | | | | Downloaded from http://pmjopen.pmj.com/ on April 17, 2024 by | | | |
| 25 | | | | | | nj.c | | | |
| 26 | Group 2: High-Placebo | | | | | | | | |
| 27 | SPARCL, A80 | 129 | 2365 | 141 | 2366 | + 9 | 0.92 | 2 [0.73; 1.15] | 0.7% |
| 28 | JUPITER, R20 | 1421 | 8869 | 1375 | 8864 | į į | 1.03 | 3 [0.96; 1.11] | 8.0% |
| 29 30 | TRACE RA, A40 | 132 | 1504 | 117 | 1498 | 1 | 1.12 | 2 [0.89; 1.43] | 0.7% |
| 31 | Random effects model | | 12738 | | 12728 | , | 1.03 | 3 [0.97; 1.10] | 9.3% |
| 32 | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.47$ | | | | | 024 |)) | | |
| 33 | | | | | | , p | - | | |
| 34 | Group 3: High-Moderate | | | | | gue | | | |
| 35 | TNT, A80 vs A10 | 241 | 4995 | 234 | 5006 | <u> </u> | 1.03 | 3 [0.87; 1.23] | 1.2% |
| 36 37 | SEARCH, S80 vs S20 | 2621 | 6031 | 2512 | 6033 | i a | [′] 1.0∠ | 1 [1.00; 1.09] | 21.5% |
| 38 | A to Z, S40-S80 vs S20 | 41 | 2263 | 34 | 2230 | +- 9 | 1.19 | 0.76; 1.87 | 0.2% |
| 39 | PROVE-IT, A80 vs P40 | 69 | 2099 | 56 | 2063 | | : 1.21 | I [0.86; 1.71] | 0.3% |
| 40 | Random effects model | | 15388 | | 15332 | guest. Protected by copyright. | 1.05 | 5 [1.01; 1.09] | 23.2% |
| 41 | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.79$ | | | | | ļ ⁹ | | | |
| 42 43 | | | | | | | | | |
| 44 | Random effects model | | 75476 | | 75345 | | 1.02 | 2 [1.00; 1.04] | 100.0% |
| 45 | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.51$ For pe | er review o | nly - http:/ | //bmjopen. | bmj.com/ | site/about/guidelines.xhtml | | | 7 |
| 46 | Residual heterogeneity: $I^2 = 0\%$, $p = 0.50$ | | | | |).01 0.1 1 10 10 | | | |
| 47 | | | | | S | tatin Protective Statin Harmfu | II | | |

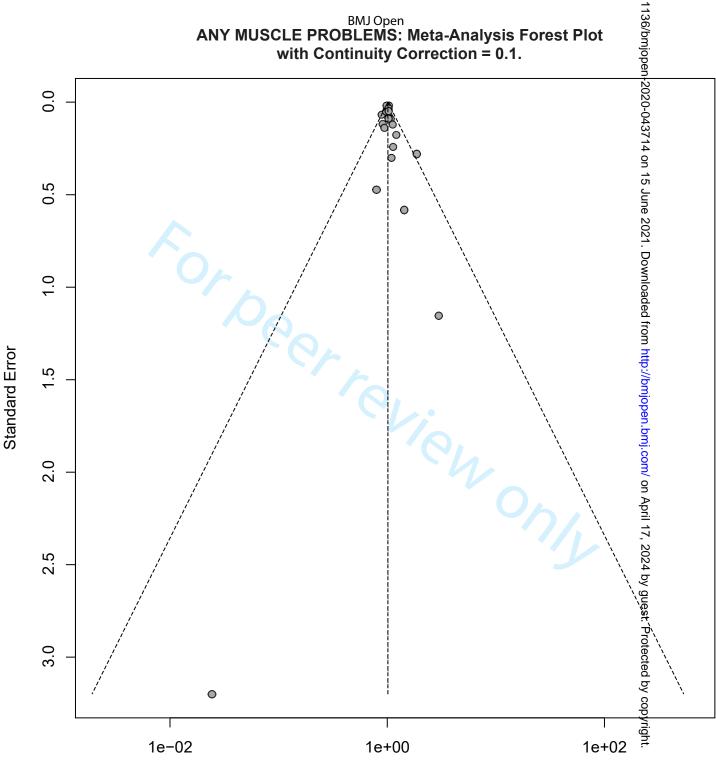












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46 47 Study

CARE, P40

LIPID, P40

AURORA, R10

CARDS, A10

ASCOT, A10

ASPEN, A10

SPARCL, A80

JUPITER, R20

TRACE RA, A40

TNT, A80 vs A10

HOPE, R10

4D, A20

CORONA.R10

GISSI-HF, R10

PROSPER, P40

Random effects model

Group 2: High-Placebo

Random effects model

Group 3: High-Moderate

PROVE-IT, A80 vs P40

Random effects model

HPS. S40

WOSCOPS, P40

ALERT. F40-F80

SSSS, S20-S40

AFCAPS, L20-L40

Group 1: Moderate-Placebo

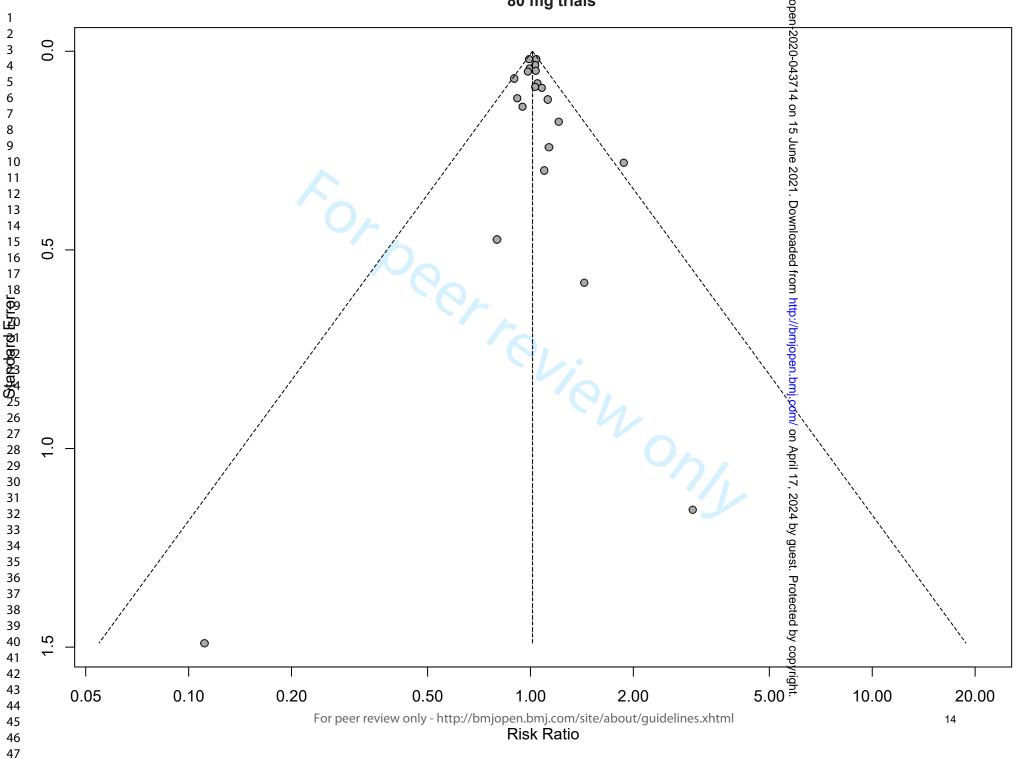
ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot excluding simvastatin 80 mg trials. /bmjopen-2020-043714 on 15 **Experimental** Control **Risk Ratio** RR 95%-CI Weight **Events Total Events Total** 2078 2081 0.11 [0.01; 2.07] 0.0% 0 8 4512 10 4502 0.80 [0.32; 2.02] 0.1% 1389 343 1378 0.90 [0.78; 1.03] 2.6% 310 97 3302 102 3293 0.95 [0.72; 1.25] 0.6% June 2021. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyrigh 495 1428 497 1410 0.98 [0.89; 1.09] 4.7% 3380 10269 3410 10267 0.99 [0.95; 1.03] 31.1% 526 1045 531 1049 0.99 [0.91; 1.08] 6.5% 613 2221 592 2223 5.1% 1.04 [0.94; 1.14] 2053 3304 1971 3301 31.6% 1.04 [1.00; 1.08] 298 5101 283 5079 1.05 [0.90; 1.23] 1.9% 225 2514 207 2497 1.08 [0.90; 1.29] 1.4% 23 2285 21 2289 1.10 [0.61; 1.98] 0.1% 2891 32 2913 0.2% 36 1.13 [0.71; 1.82] 7 619 5 636 0.0% 1.44 [0.46; 4.51] 1211 36 19 1199 1.88 [1.08; 3.25] 0.2% 3 3181 3168 0.0% 1 2.99 [0.31; 28.71] 47350 1.01 [0.98; 1.04] 47285 86.2% Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.0003$, p = 0.332365 129 141 2366 0.92 [0.73; 1.15] 0.9% 1421 8869 8864 1375 1.03 [0.96; 1.11] 10.2% 132 1504 1498 117 1.12 [0.89; 1.43] 0.8% 12738 12728 1.03 [0.97; 1.10] 11.9% Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.474995 234 5006 1.03 [0.87; 1.23] 1.5% 241 56 2063 2099 1.21 [0.86; 1.71] 0.4% 7094 1.07 [0.91; 1.25] 1.9% 7069 Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.4267182 67082 1.02 [0.99; 1.04] 100.0%

Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.49

Residual heterogeneity: $I^2 = 5\%$, p = 0.40 For peer review only - http://bmjopen.bmj.com@i@fabou@guidelines.xhtml10

Statin Protective Statin Harmful

ANY MUSCLE PROBLEMS: Meta-Analysis Funnel plot excluding simverstatin 80 mg trials



| | BMJ Open BMJ Open BMJ Open BMJ Open | | | | | | | | |
|-------------------------|--|--------------------------|------|-------------------------|----------------------------|--------|-------------------------|---|-----|
| | ANY MUSC | LE PROBLEMS | SUMN | IARY: PAIRWIS | SE AND NETWOR | RK MET | | 3 | |
| | Placebo – Mod | erate Intensity | | Moderate – Hig | cebo – High Intensity | | | | |
| Outcome | RR (95% CI) | RD (95% CI) | NNH | RR (95% CI) | RD (95% CI) | NNH | RR (95% CI) | RD (95% CI) | NNH |
| Direct, M-H | 1.011 (0.982, 1.042) | NA | | 1.046 (1.005, 1.089) | NA | | 1.030 | NA NA | |
| Direct, IV | 1.012 (0.989, 1.036) | 0.000 (-0.001, 0.001) | | 1.046 (1.005, 1.089) | 0.004 (-0.001, 0.009) | | 1.030 (0.967, 1.097) | 0.002 | |
| NMA, IV | 1.010 (0.988,1.033) | 0.0001 (-0.001,0.001) | Ó | 1.039 (1.004,1.075) | 0.0037 (-0.0005,0.0078) | | 1.049 (1.010,1.089) | 0.0037 | |
| NMA Excluding S80 | 1.011 (0.988,1.036) | 0.0001 (-0.001,0.001) | | 1.025 (0.963,1.091) | 0.0028 (-0.0022,0.0079) | | 1.036 (0.977,1.099) | 0.0029 (-0.0022,0.0079) | |
| NMA CC=0.10 | 1.010 (0.988,1.033) | 0.000* (-0.001,0.001) | | 1.039 (1.003, 1.075) | 0.0037 (-0.0005,0.0078) | | | 0.0037 (-0.0005,0.0079) | |
| NMA CC = 0.0001 | 1.010 (0.988,1.033) | 0.000* (-0.001,0.001) | | 1.039 (1.003,1.075) | 0.0037 (-0.0005,0.0078) | | | 0.0037 (-0.0005,0.0079) | |
| | | | | | | 0, | | n April 17 2024 by guest Protected by convright | |
| | | | | | | | | 1 | 41 |

95%-CI Weight

2.3%

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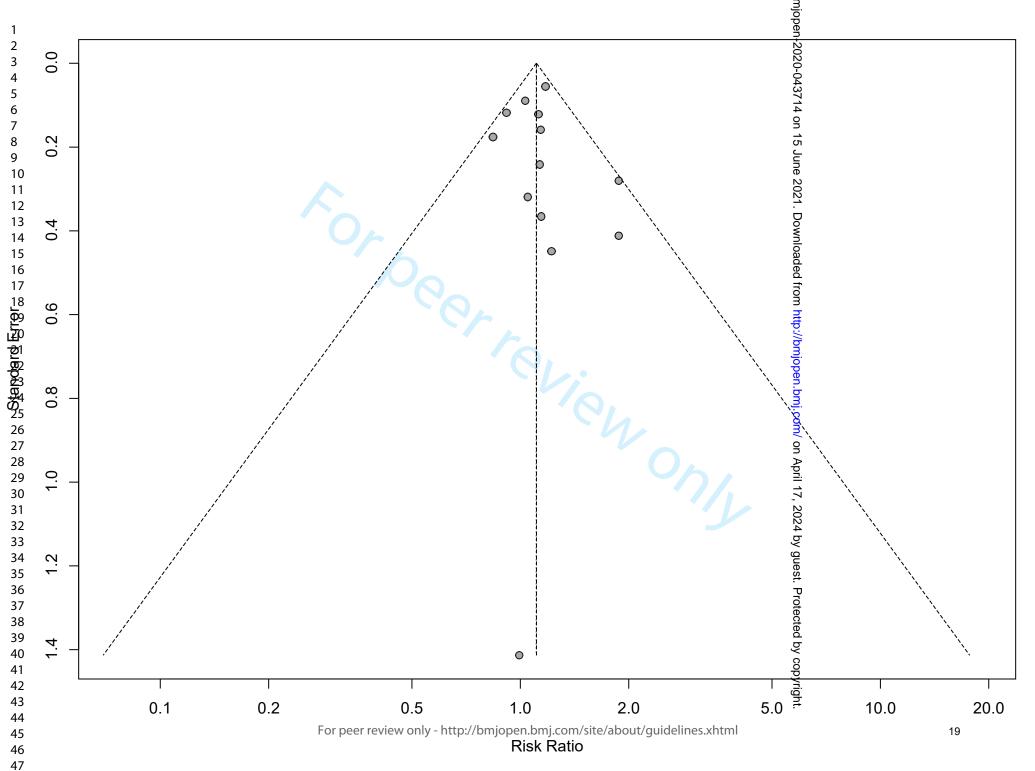
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45 46 47

| | Experii | mental | C | ontrol | | 020-0 | |
|--|---------|--------|---------------|--------|-------------------------------|---|---------------|
| Study | • | | Events | Total | Risk Ratio | .020-043714 on | 95%-CI |
| Group 1: Moderate-Placebo | | | | | <u> </u> | | |
| CARDS, A10 | 57 | 1428 | 67 | 1410 | <u> </u> | 0.84 0.99 | [0.59; 1.19] |
| AURORA, R10 | 1 | 1389 | 1 | 1378 | : | 통 0.99 | [0.06; 15.85] |
| WOSCOPS, P40 | 20 | 3302 | 19 | 3293 | | [№] 1.05 | [0.56; 1.96] |
| PROSPER, P40 | 36 | 2891 | 32 | 2913 | | 1.13 | [0.71; 1.82] |
| SSSS, S20-S40 | 82 | 2221 | 72 | _ | | § 1.14 | [0.84; 1.56] |
| HPS, S40 | | 10232 | 14 | 10237 | | 룺 1.14 | [0.56; 2.34] |
| AFCAPS, L20-L40 | 11 | 3304 | 9 | 3301 | | ਨੂੰ 1.22 | [0.51; 2.94] |
| ASPEN, A10 | 36 | 1211 | 19 | 1199 | | ₹ 1.88 | [1.08; 3.25] |
| ASCOT, A10 | 17 | | 9 | 5124 | <u>:</u> | <u>3</u> 1.88 | [0.84; 4.21] |
| Random effects model | | 31136 | | 31078 | | ∄ 1.13 | [0.95; 1.34] |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.46$ | | | | | | /bmjo | |
| Group 2: High-Placebo | | | | | | pen | |
| SPARCL, A80 | 129 | 2365 | 141 | 2366 | - - | 0.92 | [0.73; 1.15] |
| TRACE RA, A40 | 132 | 1504 | | 1498 | Y /_ | 8 1.12 | [0.89; 1.43] |
| JUPITER, R20 | 658 | 8869 | 560 | 8864 | = | 1.17 | [1.05; 1.31] |
| Random effects model | | 12738 | | 12728 | \Q | n 1.09 | [0.94; 1.26] |
| Heterogeneity: $I^2 = 45\%$, $\tau^2 = 0.0076$, $p = 0.16$ | | | | | | 1.05 1.14 1.14 1.188 1.13 1.14 1.188 1.13 0.92 1.109 1.04 1.04 1.04 1.04 | . / . |
| Group 3: High-Moderate | | | | | | 202 | |
| TNT, A80 vs A10 | 241 | 4995 | 234 | 5006 | <u> </u> | £ 1.03 | [0.87; 1.23] |
| SEARCH, S80 vs S20 | 2621 | 6031 | 2512 | 6033 | + | ള് 1.04 | [1.00; 1.09] |
| Random effects model | | 11026 | | 11039 | 0: | est 1.04 | [1.00; 1.09] |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.90$ | | | | | | Protected 1.07 | |
| Random effects model | | 54900 | | 54845 | : 0 | ਰੂ 1.07 | [1.01; 1.13] |
| Heterogeneity: $I^2 = 8\%$, $\tau^2 = 0.0009$, $p = 0.36$ | | | | | | l <u>p</u> | - / |
| Residual heterogeneity: $I^2 = 3\%$, $p = 0.41$ | | | | | 0.1 0.5 1 2 1 | @ | |
| | | | | S | Statin Protective Statin Harm | | |
| | | | | | | jht. | |

MYALGIA OR PAIN: Meta-Analysis Forest plot excluding simvastatin 89 mg trials.

| | | | | | | en-2 | | | |
|--|-------------------|-------|-------------|-----------------|---|--|--------|---------------|---------|
| Study | Experir Events | | C Events | ontrol Total | Risk R | en-2020-043714 on 15 atio | RR | 95%-CI | Weight |
| Group 1: Moderate-Placebo | | | | | : | on 1 | | | |
| CARDS, A10 | 57 | 1428 | 67 | 1410 | | 5 J. | n 84 | [0.59; 1.19] | 4.6% |
| AURORA, R10 | 1 | 1389 | 1 | 1378 | | line 2 | - 0.04 | [0.06; 15.85] | 0.1% |
| WOSCOPS, P40 | 20 | 3302 | 19 | 3293 | | | 1.05 | [0.56; 1.96] | 1.4% |
| PROSPER, P40 | 36 | 2891 | 32 | 2913 | <u> </u> | June 2021. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. | 1.13 | [0.71; 1.82] | 2.5% |
| SSSS, S20-S40 | 82 | 2221 | 72 | 2223 | - <u> </u> | – owr | 1.14 | [0.84; 1.56] | 5.7% |
| HPS, S40 | | 10232 | | 10237 | _ | | 1.14 | [0.56; 2.34] | 1.1% |
| AFCAPS, L20-L40 | 11 | | 9 | 3301 | | ded | 1.22 | [0.51; 2.94] | 0.7% |
| ASPEN, A10 | | 1211 | 19 | 1199 | <u> </u> | <u>+</u> fror | 1.88 | [1.08; 3.25] | 1.8% |
| ASCOT, A10 | 17 | 5158 | 9 | 5124 | <u> </u> | _ = | 1.88 | [0.84; 4.21] | 0.8% |
| Random effects model | | 31136 | | 31078 | \(\sqrt{} | , ф:// | 1.13 | [0.95; 1.34] | 18.7% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.46$ | | | | | | bmj | | | |
| | | | | | | ope | | | |
| Group 2: High-Placebo | | | | | | n.b | | | |
| SPARCL, A80 | 129 | 2365 | 141 | 2366 | > | <u>j.</u> c | 0.92 | [0.73; 1.15] | 10.1% |
| TRACE RA, A40 | 132 | 1504 | 117 | 1498 | · // + | - M | 1.12 | [0.89; 1.43] | 9.6% |
| JUPITER, R20 | 658 | 8869 | 560 | 8864 | + | 9 | 1.17 | [1.05; 1.31] | 44.0% |
| Random effects model | | 12738 | | 12728 | \ | Apr | 1.09 | [0.94; 1.26] | 63.8% |
| Heterogeneity: $I^2 = 45\%$, $\tau^2 = 0.0076$, $p = 0.16$ | | | | | | ii 17 | | | |
| | | | | | | , 20 | | | |
| Group 3: High-Moderate | | | | | |)24 | | | |
| TNT, A80 vs A10 | 241 | | 234 | 5006 | 青 | by ç | 1.03 | [0.87; 1.23] | 17.5% |
| Random effects model | | 4995 | | 5006 | \Diamond | jues | 1.03 | [0.87; 1.23] | 17.5% |
| Heterogeneity: not applicable | | | | | | | | | |
| Dandom offacto model | | 40000 | | 40040 | | Protected | 4 4 4 | [4 02, 4 40] | 400.00/ |
| Random effects model | | 48869 | | 48812 | <u> </u> | | 7.77 | [1.03; 1.19] | 100.0% |
| Heterogeneity: $I^2 = 1\%$, $\tau^2 = 0.0002$, $p = 0.44$ | | | | | 0.1 0.5 1 | 2 10 | | | |
| Residual heterogeneity: $I^2 = 12\%$, $p = 0.33$ | | | | 9 | tatin Protective | × | | | |
| | | | | 3 | tatiii Fiotective (| _ | | | |
| | | | | | | ight. | | | |



BMJ Open 136/bmjopen-2020 MYALGIA OR PAIN SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESOULTS

| | Placebo – Mod | erate Intensity | | Moderate – Hig | jh Intensity | Placebo – High Intensity | | | |
|-------------|-------------------------|-------------------|-----------|--------------------------------|---------------------|--------------------------|---|------------------|-----|
| Outcome | RR | RD | NNH | RR | RD | NNH | RR 15 | RD | NNH |
| | (95% CI) | (95% CI) | | (95% CI) | (95% CI) | | (95% CI) | (95% CI) | |
| Direct, M-H | 1.130 (0.952, 1.341) | NA | | 1.043 (1.002, 1.086) | NA | | 1.092 (0.945, 1.261) | NA | |
| | , | | | , | | | Q | | |
| Direct, IV | 1.130 | 0.0007 | | 1.043 | 0.0046 | | 1.123 ⋛ | 0.0073 | 143 |
| | (0.952, 1.341) | (-0.0005, 0.0019) | ^ | (1.002, 1.086) | (-0.0030, 0.0123) | | (1.025, 1.230) | (0.0010, 0.0136) | |
| NMA, IV | 1.090 | 0.0007 | - | 1.041 | 0.0058 | 173 | 1.134 ਤੋਂ | 0.0065 | 154 |
| | (0.9997,1.188) | (-0.0005,0.0019) | | (1.001,1.083) | (0.0009,0.0107) | | (1.046,1.230) | (0.0016,0.0114) | |
| Excluding | 1.111 | 0.0007 | | 1.010 | 0.0048 | | 1.122 | 0.0055 | 182 |
| S80 | (0.971,1.270) | (-0.0004,0.0018) | | (0.881,1.158) | (-0.0003,0.0099) | | (1.021,1.233) | (0.0005,0.0106) | |
| | | | | | | | n.bmj.com/ on April 17, 2024 by guest. Protected by copyright | | |
| | | Farmanan | ا د د د د | lattine //laurailaurailauraila | mj.com/site/about/g | - خامادات | · | | 2 |

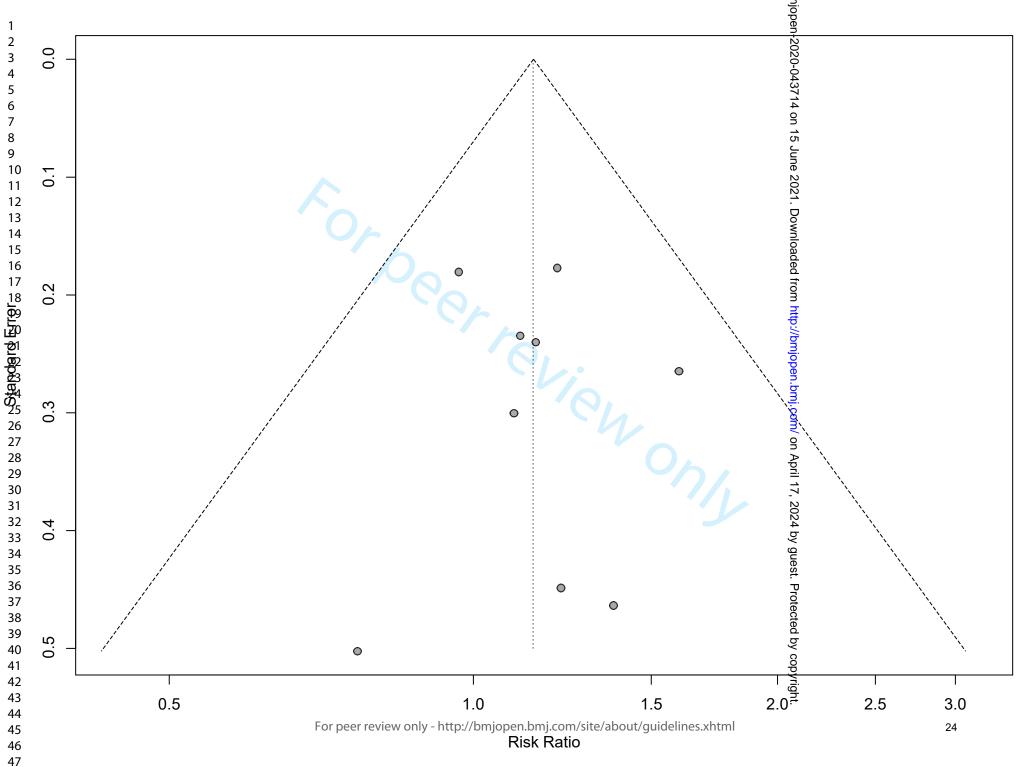
ATTRITION: Meta-Analysis Forest plot with data

| 59 of 83 | | | ВМЈ С |)pen | 1136/bmjc | | | |
|---|---|---|---|---|--|--|--|---------------------------------------|
| A | TTRITIO | est plot with data 2020-043714 | | | | | | |
| | Experi | mental | С | ontrol | on 15 | | | |
| Study | | | Events | | Risk Ratio | RR | 95%−CI | Weight |
| Group 1: Moderate-Placebo CARDS, A10 HPS, S40 GISSI-HF, R10 HOPE, R10 WOSCOPS, P40 AFCAPS, L20-L40 SSSS, S20-S40 ASCOT, A10 Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$ Group 2: High-Moderate A to Z, S40-S80 vs S20 PROVE-IT, A80 vs P40 SEARCH, S80 vs S20 Random effects model Heterogeneity: $I^2 = 31\%$, $\tau^2 = 0.0190$, $p = 0.23$ | 7 60 23 38 37 11 11 37 | 1428 10269 2285 3181 3302 3304 2221 5158 31148 2263 2099 6031 10393 | 9 62 21 34 32 9 8 23 | 1410 10267 2289 3168 3293 3301 2223 5124 31075 2230 2063 6033 10326 | 1136/bmjopen-2020-043714 on 15 June 2021. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by Risk Ratio Risk Ratio | 0.77 0.97 1.10 1.11 1.15 1.22 1.38 1.60 1.13 1.19 1.21 1.85 1.38 | [0.29; 2.06] [0.68; 1.38] [0.61; 1.98] [0.70; 1.76] [0.72; 1.85] [0.51; 2.94] [0.55; 3.41] [0.95; 2.69] [0.93; 1.36] [0.76; 1.87] [0.86; 1.71] [1.22; 2.81] [1.04; 1.82] | 6.2% 10.2% 9.7% 2.8% 2.6% |
| Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.64$ Residual heterogeneity: $I^2 = 0\%$, $p = 0.72$ | | 41541 | | 41401 S | 0.5 1 2 statin Protective Statin Harmed by copyright. | 1.22 | [1.05; 1.41] | 100.0% |

| 83 | | | В | MJ Open | | 1136/bm) |
|--|---|--|---|--------------|------------------------------------|---|
| ATTRITION: | Meta- | Analysi | s Fores | t plot ex | ccluding simvastatin 80 mg tri | jopen- & 20-043714 on |
| | Experir | nental | C | ontrol | | 15 June |
| Study | Events | Total | Events | Total | Risk Ratio | RR |
| ASCOT, A10 Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$ | 7 60 23 38 37 11 11 37 | 1428 10269 2285 3181 3302 3304 2221 5158 31148 | 9 62 21 34 32 9 8 23 | 2223 | Risk Ratio | الق. مور الق |
| Group 2: High-Moderate PROVE-IT, A80 vs P40 Random effects model Heterogeneity: not applicable | 69 | 2099 2099 | 56 | 2063 2063 | | on April 17, 202 |
| Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.91$ Residual heterogeneity: $I^2 = 0\%$, $p = 0.86$ | | 33247 | | 33138 | 0.5 1 2 Statin Better Statin Worse | 56.13 21.21 5en:5mj.com/ on April 77, 2024 By guest. Protection |

| e 2021. | 95%-CI | Weight |
|------------------------------------|--|--------------------------------|
| Down.77 20.97 21.10 21.11 | [0.29; 2.06] [0.68; 1.38] [0.61; 1.98] [0.70; 1.76] | 2.9% 22.4% 8.1% 13.3% |
| 15 1.22 1.38 | [0.72; 1.85] [0.51; 2.94] [0.55; 3.41] | 12.7% 3.6% 3.4% |
| 91.60 1.13 | [0.95; 2.69] [0.93; 1.36] | |
| 21 21 0, 20 0, 20 0, 2024 | [0.86; 1.71] [0.86; 1.71] | |
| 4 by guest. Protecte | [0.97; 1.35] | 100.0% |

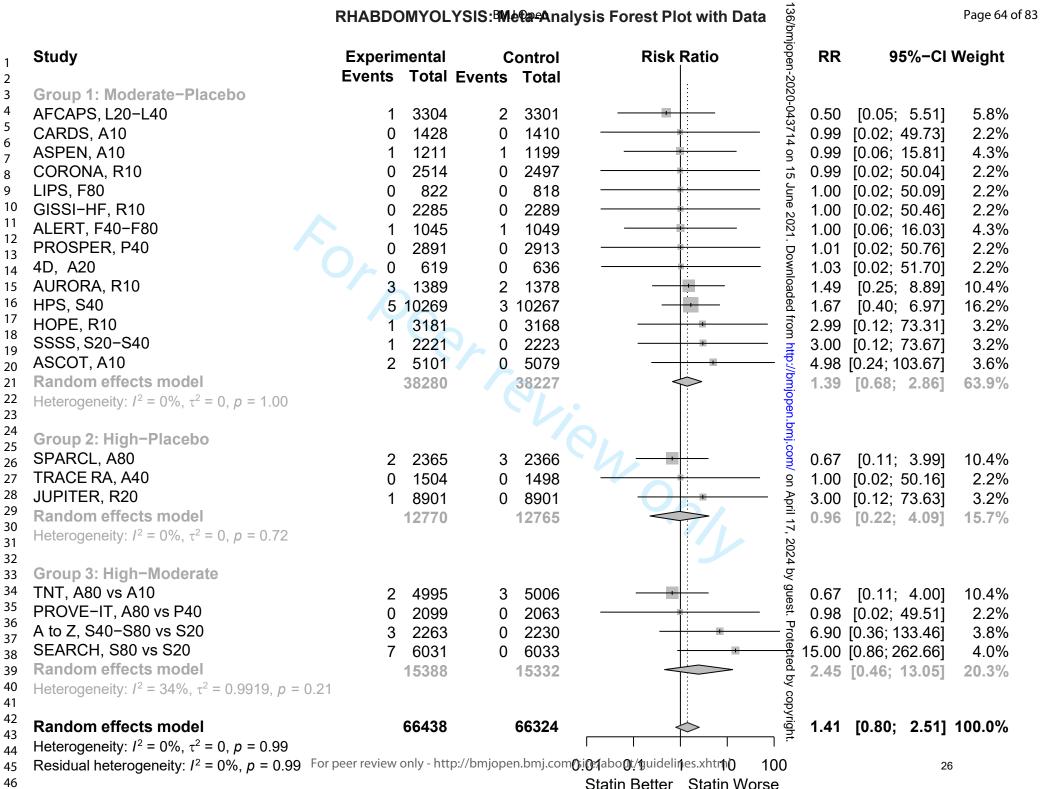


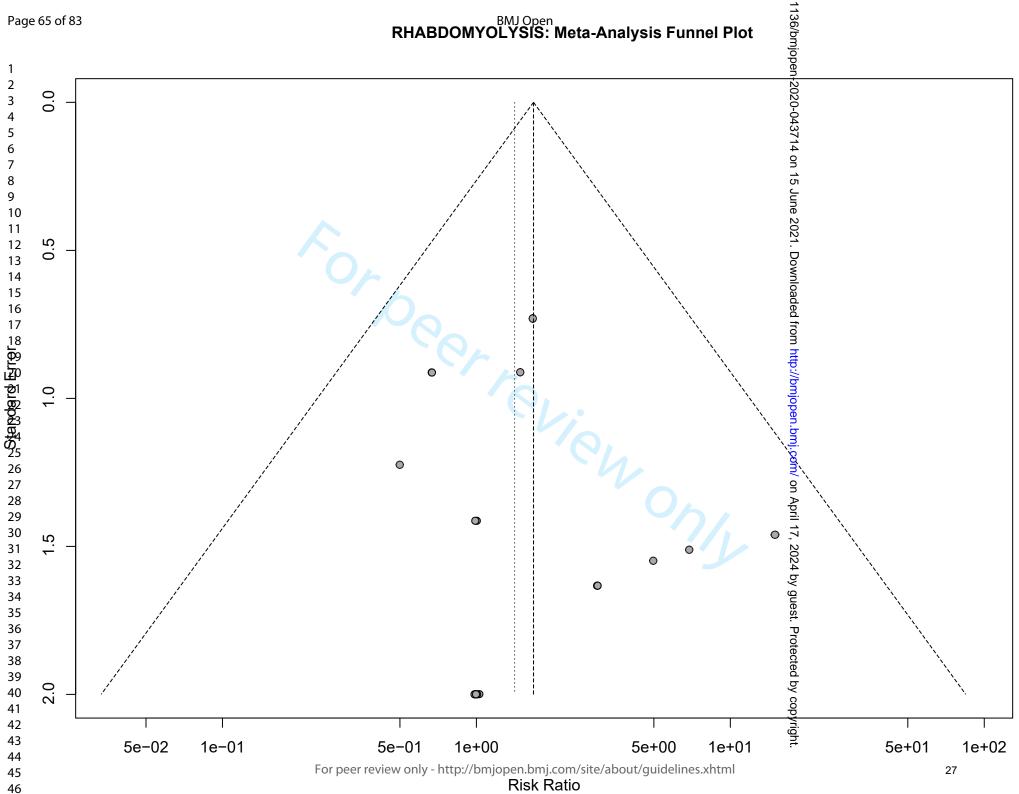


BMJ Open ATTRITION SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULT 043

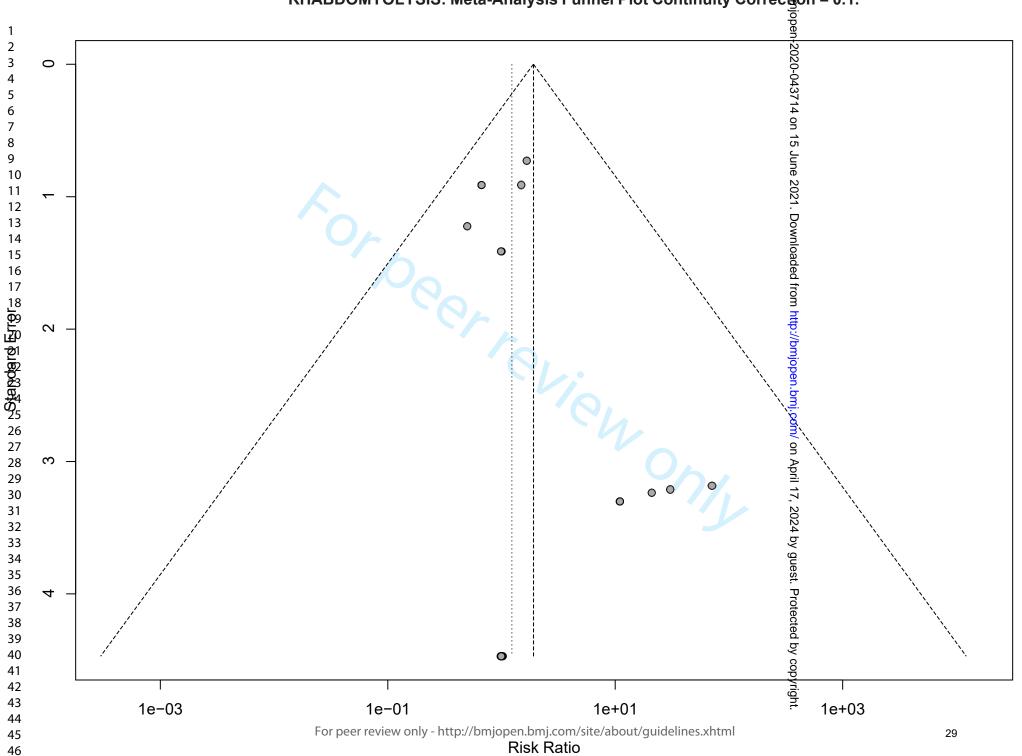
| | Placebo - Mod | erate Intensity | | Moderate – Hig | gh Intensity | | Placebo – Hi | | |
|------------------|-------------------------|-----------------------------|------|-------------------------|----------------------------|------|--|---------------------------|------|
| Outcome | RR (95% CI) | RD (95% CI) | NNH | RR (95% CI) | RD (95% CI) | NNH | RR (95% CI) | l DD | NNH |
| Direct, M-H | 1.127 (0.931, 1.364) | NA | | 1.378 (1.043, 1.822) | NA | | NA 2021. | NA | |
| Direct, IV | 1.127 (0.931, 1.364) | 0.0008 (-0.0004, 0.0020) | 1000 | 1.372 (1.091, 1.726) | 0.0046 (0.0018, 0.0074) | 200 | NA Ploaded | NA | |
| NMA, IV | 1.127 (0.931,1.364) | 0.0008 (-0.0004,0.0020) | -6 | 1.372 (1.091,1.726) | 0.0046 (0.0018,0.0074) | 218 | 1.155 5 (1.147,2.084) | 0.0054 (0.0023,0.0084) | 187 |
| Excluding S80 | 1.127 (0.931,1.364) | 0.0008 (-0.0004,0.0020) | | 1.211 (0.856,1.714) | 0.0057 (-0.0046,0.0161) | 176* | 1.365 (0.918,2.028) | | 154* |
| | | | | | | | n.bmj.com/ on April 17, 2024 by guest. Protected by copyright. | | |

RHABDOMYOLYSIS: BMe@a-Analysis Forest Plot with Data





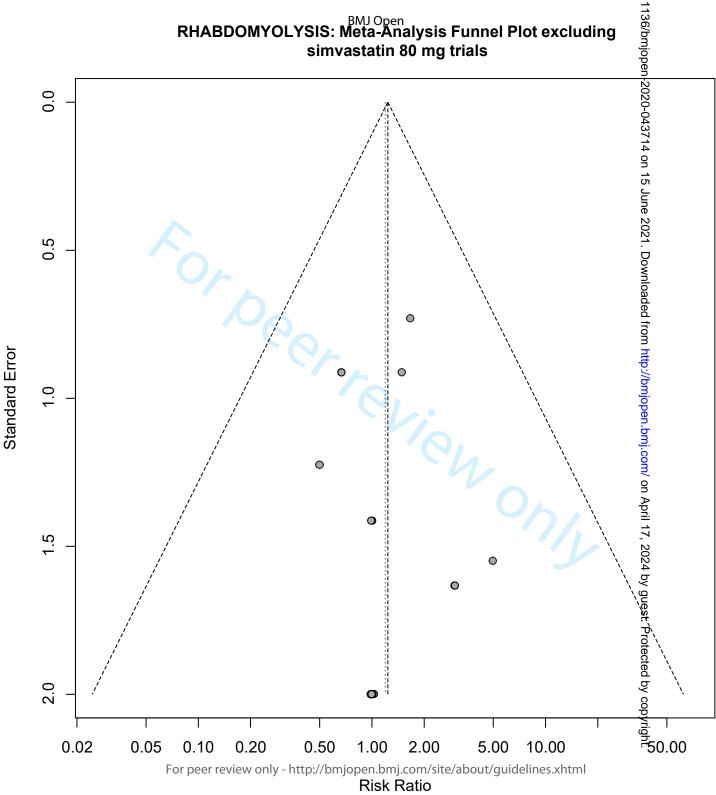
| Study | Experiment Events To | | Control Total | Risk Ratio | RR | njopen-2 95%−CI | Weight |
|---|--|---------------|------------------|---|---------|---------------------------------------|--------|
| Group 1: Moderate-Pla | cebo | | | <u> </u> | | 020 | |
| AFCAPS, L20-L40 | 1 33 |)4 2 | 3301 | | 0.50 | ၌0.05; 5.51] | 8.2% |
| CARDS, A10 | 0 14: | 28 0 | 1410 | | 0.99 | [ਊ.00; 6324.79] | 0.6% |
| ASPEN, A10 | 1 12 | l1 1 | 1199 | - • | 0.99 | ₫ 0.06; 15.81] | 6.2% |
| CORONA, R10 | 0 25 | 14 0 | 2497 | <u> </u> | 0.99 | [0.00; 6363.07] | 0.6% |
| LIPS, F80 | 0 8 | 22 0 | 818 | | 1.00 | [1 .00; 6372.92] | 0.6% |
| GISSI-HF, R10 | 0 22 | 35 0 | 2289 | | 1.00 | [0.00; 6417.49] | 0.6% |
| ALERT, F40-F80 | 1 10 | 15 1 | 1049 | | 1.00 | № 0.06; 16.03] | 6.2% |
| PROSPER, P40 | 0 28 | 91 0 | 2913 | | 1.01 | [0 .00; 6455.29] | 0.6% |
| 4D, A20 | 0 6 | 19 0 | 636 | <u>:</u> | 1.03 | [<u>§</u> .00; 6578.85] | 0.6% |
| AURORA, R10 | 3 13 | 39 2 | 1378 | | 1.49 | ഉ[0.25; 8.89] | 14.8% |
| HPS, S40 | 5 1026 | 3 | 10267 | | 1.67 | <u>\alpha(0.40;</u> 6.97] | 23.1% |
| HOPE, R10 | 1 31 | 31 0 | 3168 | | 10.96 | [9 .02; 7095.11] | 1.1% |
| SSSS, S20-S40 | 1 22: | | | | 11.01 | [0 .02; 7130.07] | 1.1% |
| ASCOT, A10 | 2 51 | | | <u> </u> | - 20.91 | [0.04; 11895.15] | 1.2% |
| Random effects model | 382 | 30 | 38227 | \langle | 1.38 | 3 0.59; 3.22] | 65.6% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$ | | | | | | pen.bmj.c | |
| SPARCL, A80 | 2 23 | 35 | 2366 | - | 0.67 | € [0.11; 3.99] | |
| TRACE RA, A40 | 0 15 | | | | 1.00 | [9.00; 6380.08] | |
| JUPITER, R20 | 1 89 | | | 1.02 | 11.00 | [2].02; 7125.08] | 1.1% |
| Random effects model | 127 | 70 | 12765 | | 0.82 | 1 0.15; 4.45] | 16.6% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$ Group 3: High-Modera | | | | - | | ', 2024 by | |
| TNT, A80 vs A10 | 2 49 | 95 3 | 5006 | | 0.67 | ଞ୍ଚି[0.11; 4.00] | 14.8% |
| PROVE-IT, A80 vs P40 | 0 20 | | | | 0.98 | [0.00; 6296.29] | 0.6% |
| A to Z, S40-S80 vs S20 | | | | | | [0506; 16583.28] | |
| SEARCH, S80 vs S20 | 7 60 | | | - | | [0214; 36473.99] | 1.2% |
| Random effects model | | | 15332 | | | ©.13; 85.29] | 17.8% |
| Heterogeneity: $I^2 = 39\%$, τ^2 | $e^2 = 4.4154, p =$ | 0.18 | | | | ₹ | |
| Random effects model | 664 | 38 | 66324 | \ | 1.23 | оруг 910.62 ; 2.45] | 100.0% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$ Residual heterogeneity: $I^2 = 0\%$ | = 0, <i>p</i> = 0.99 = 0%, <i>p</i> ^{Fer} 0.98 | review only - | http://bmjo | obe 0 j00 j tcom Q eigle/alpod l Q aniqd j0@0 x | html | | 28 |



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| | Experir | mental | C | ontrol | | þe | | |
|--|---------------|-----------|---------------|--------------------------|---|-------------------------------------|----------------|----------|
| Study | Events | Total | Events | Total | Risk Ratio | ⊼ृRR | 95%−CI | Weight |
| Group 1: Moderate-Placebo | | | | | I: | pen-2020-043 <i>1</i> 34 | | |
| AFCAPS, L20-L40 | 1 | 3304 | 2 | 3301 | | ¹³ 750 | [0 05: 5 51] | 6.2% |
| • | 1 | 1428 | 2 | 1410 | - | 06.40 | [0.05; 5.51] | |
| CARDS, A10 | 0 | | | | <u> </u> | · <u>@</u> .99 | [0.02; 49.73] | 2.3% |
| ASPEN, A10 | 1 | 1211 | 1 | 1199 | | € 99 | [0.06; 15.81] | 4.7% |
| CORONA, R10 | 0 | 2514 | 0 | 2497 | | · (<u>\$</u> .99 | [0.02; 50.04] | 2.3% |
| LIPS, F80 | 0 | 822 | 0 | 818 | | - £00 | [0.02; 50.09] | 2.3% |
| GISSI-HF, R10 | 0 | 2285 | 0 | 2289 | <u> </u> | - ½00 | [0.02; 50.46] | 2.3% |
| ALERT, F40-F80 | 1 | 1045 | 1 | 1049 | | [00 | [0.06; 16.03] | 4.7% |
| PROSPER, P40 | 0 | 2891 | 0 | 2913 | | - <u>≸</u> .01 | [0.02; 50.76] | 2.3% |
| 4D, A20 | 0 | 619 | 0 | 636 | - | - <u>\$</u> .03 | [0.02; 51.70] | 2.3% |
| AURORA, R10 | 3 | 1389 | 2 | 1378 | - - | £ 49 | [0.25; 8.89] | 11.2% |
| HPS, S40 | 5 | 10269 | 3 | 10267 | - • - | ₫.67 | [0.40; 6.97] | 17.5% |
| HOPE, R10 | 1 | 3181 | 0 | 3168 | | − 2.99 | [0.12; 73.31] | 3.5% |
| SSSS, S20-S40 | 1 | 2221 | 0 | 2223 | | − 3 00 | [0.12; 73.67] | 3.5% |
| ASCOT, A10 | 2 | 5101 | 0 | 5079 | - I | — <u>4</u> .98 | [0.24; 103.67] | 3.9% |
| Random effects model | | 38280 | | 38227 | | 8 .39 | [0.68; 2.86] | 69.3% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$ | | | | | | ⋾ | | |
| | | | | | (0) , | bmj.com. | | |
| Group 2: High-Placebo | | | | | No. | ŏm | | |
| SPARCL, A80 | 2 | 2365 | 3 | 2366 | | g .67 | [0.11; 3.99] | 11.2% |
| TRACE RA, A40 | 0 | 1504 | 0 | 1498 | | - €.00 | [0.02; 50.16] | 2.3% |
| JUPITER, R20 | 1 | 8901 | 0 | 8901 | | — 3 00 | [0.12; 73.63] | 3.5% |
| Random effects model | - | 12770 | | 12765 | | 0.96 | [0.22; 4.09] | 17.1% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.72$ | | | | | | 202, | [01==, 1100] | |
| 3 , , , , , , , , , , , , , , , , , , , | | | | | | 4 b) | | |
| Group 3: High-Moderate | | | | | <u> </u> | 7 -2 024 by gue- 6 -7 | | |
| TNT, A80 vs A10 | 2 | 4995 | 3 | 5006 | | ^{စ္တ} 67 | [0.11; 4.00] | 11.2% |
| PROVE-IT, A80 vs P40 | 0 | 2099 | 0 | 2063 | | · @ .98 | [0.02; 49.51] | 2.3% |
| Random effects model | U | 7094 | U | 7069 | | Ø.90 Ø 71 | [0.02, 49.51] | |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$ | | 1034 | | 7003 | | ted. | [0.14, 3.03] | 13.0 /0 |
| Heterogeneity. $T=0.70$, $t=0$, $p=0.00$ | | | | | li. | by | | |
| Random effects model | | 58144 | | 58061 | | steeted by copyright 100 | [0.66; 2.18] | 100 0% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$ | | JU 144 | | | | | [0.00, 2.10] | 100.0 /0 |
| | 0 | | | 0.4 | 01 0.1 1 10 | 100° | | |
| Residual heterogeneity: $I^2 = 0\%$, $p = 1.0$ | | ow only | http://hmic | 0.0 nan hm o r | 01 0.1 1 10 tatir⊱iPr∕eteeti⊽eideStatirh™arm | 100 6 1 | | 00 |
| FC | n heer revi | ew only - | nup.//billjc | phenini P o | เลแบบสดเลยเกลดาะอเษยแก่สมม | IUI | | 30 |

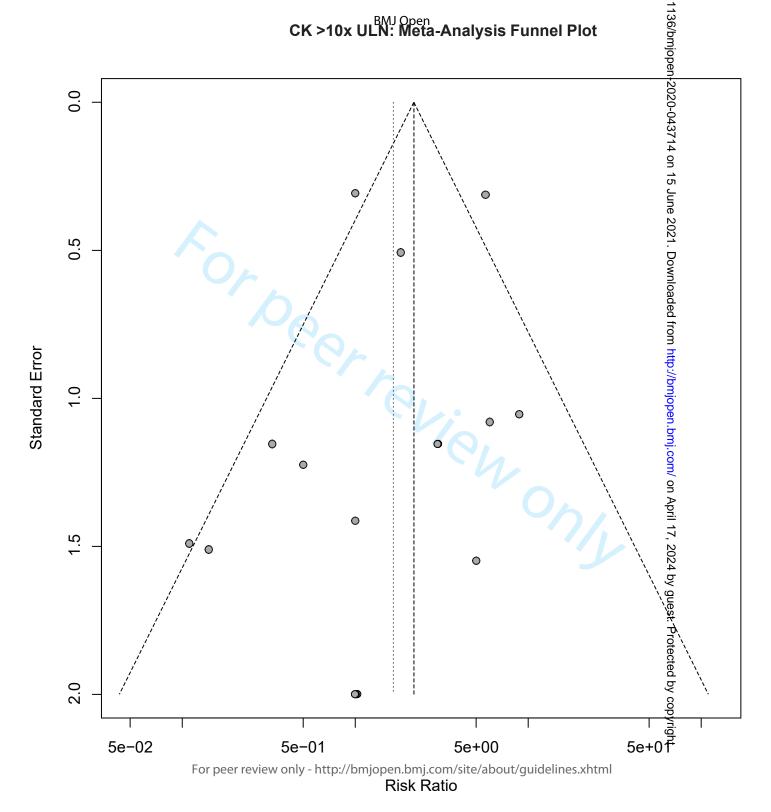




BMJ Open 136/bmjopen-2020 RHADOMYOLYSIS SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

| | Placebo – Mod | lerate Intensity | | Moderate – Hig | h Intensity | | Placebo – Hig | ıh Intensity | |
|---------------|---|-------------------|--------|----------------|-------------------|--------|---|---------------------|-------|
| Outcome | RR | RD | NNH | RR | RD | NNH | RR 4 | RD | NNH |
| Outcome | (95% CI) | (95% CI) | 141411 | (95% CI) | (95% CI) | 141411 | (95% CI) | (95% CI) | ININI |
| Direct, M-H | 1.394 | NA | | 2.451 | NA | | 0.960 | , | |
| | (0.679, 2.864) | | | (0.460, | | | (0.225, | | |
| | (111, 11, 111, 111, 111, 111, 111, 111, | | | 13.053) | | | 4.092) | | |
| Direct, IV | 1.394 | 0.0001 | | 1.994 | 0.0004 | | 0.959 | 0.0001 | |
| | (0.679, 2.864) | (-0.0001, 0.0004) | | (0.556, 7.147) | (-0.0001, 0.0009) | | 1 (0.225. ⊇ | I (-0.0002, 0.0004) | |
| | | | | | | | 4.092) | | |
| NMA, IV | 1.225 | 0.0001 | | 1.326 | 0.0001 | | 1.624 | 0.0002 | - |
| | (0.624,2.405) | (-0.0002,0.0003) | N. | (0.487, 3.614) | (-0.0002,0.0004) | | 1.624 5 (0.579,4.553) | (-0.0001,0.0005) | |
| | , | | | V _L | | | (0.579,4.553) | | |
| NMA | 1.389 | 0.0001 | | 0.701 | 0.0001 | | 0.974 | 0.0002 | |
| Excluding S80 | (0.701,2.752) | (-0.0002,0.0003) | | (0.222, 2.209) | (-0.0002,0.0004) | | (0.316,2.997) | (-0.0001,0.0005) | |
| | | , | | | | | (0.010,2.0012 | | |
| NMA | 1.269 | 0.0000* | | 0.892 | 0.0001 | | 1.131 | 0.0001 | |
| CC=0.10 | (0.571,2.820) | (-0.0001,0.0002) | | (0.259,3.066) | (-0.0001,0.0003) | | (0.326,3.927 | (-0.0001,0.0003) | |
| | | , | | | | | (0.020,0.02.9 | | |
| NMA | 1.199 | 0.0000* | | 0.610 | 0.0000* | | 0.732 g | 0.0000* | |
| CC = 0.0001 | (0.514,2.799) | (-0.0000,0.0000) | | (0.161,2.317) | (-0.0000,0.0000) | | | (-0.0000,0.0000) | |
| | | | | | | ノム | (0.193,2.778) | | |
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| | | | | | | | 17, 2024 by guest. Protected by copyright | | |
| | | | | | | | /rigt | | |
| | | | | | | | .∓ | | |

| | | | | | | | Ratio | 5) 5 | | |
|--------|--|---------|--------------|---------|--------------|------------------|--|-------------------|----------------|---------------|
| | | Experir | | | ontrol | | 702 | | | |
| | Study | Events | Total | Events | Total | Risk | Ratio 5 | RR | 95%−CI | Weight |
| | Craye 4: Madarata Blacaba | | | | | ı | <u>۔</u> د ا | 2 | | |
| | Group 1: Moderate-Placebo | 0 | 1400 | 1 | 1110 | | | | [0.04, 0.04] | 2.00/ |
| | CARDS, A10 | 0 | 1428 | 4 | 1410 | | | 0.11 | [0.01; 2.04] | 3.9% |
| | LIPS, F80 | 0 | 822 | 3 | 818 | | June | 0.14 | [0.01; 2.75] | 3.8% |
|) | CORONA, R10 | 04 | 2514 | 3 | 2497 | | | | [0.03; 3.18] | 5.7% |
| | AFCAPS, L20–L40 | 21 | 3304 | 21 | 3301 | 7 | | 1.00 | [0.55; 1.83] | 15.0% |
| | GISSI-HF, R10 | 1 | 2285 | 1 | 2289 | | | 1.00 | [0.06; 16.01] | 4.2% |
| | PROSPER, P40 | 0 | 2891 | 0 | 2913 | | ¥ | 1.01 | [0.02; 50.76] | 2.4% |
| | 4D, A20 | 0 | 619 | 0 | 636 | | · | 1.03 | [0.02; 51.70] | 2.4% |
| • | HPS, S40 | | 10269 | 6 | 10267 | | : ed | 1.83 | [0.68; 4.95] | 12.3% |
| , | WOSCOPS, P40 | 3 | 3302 | 1 | 3293 | | | 2.99 | [0.31; 28.75] | 5.7% |
| ;) | ALERT, F40-F80 | 3 | 1045 | | 1049 | | | 3.01 | [0.31; 28.90] | 5.7% |
|) | SSSS, S20-S40 Random effects model | 6 | 2221 | | 2223 | J | - | 6.01 | [0.72; 49.84] | 6.2% |
| | | | 30700 | | 30696 | | <u> </u> | 1.17 | [0.72; 1.90] | 67.4% |
| | Heterogeneity: $I^2 = 4\%$, $\tau^2 = 0.0303$, $p = 0.41$ | | | | | | 2021. Downloaded from http://ornjopen |) 5 | | |
| | Croup 2: High-Bloocho | | | | | | ii | ; - | | |
| | Group 2: High-Placebo | 0 | 4504 | 0 | 1400 | \bigcirc | .bmj.com | 4.00 | [0 00, 50 40] | 0.40/ |
| | TRACE RA, A40 | 0 | 1504 | 0 | 1498 | 1/1 | | 1.00 | [0.02; 50.16] | 2.4% |
| , | SPARCL, A80 | 2 | 2365 | 0 | 2366 | | | | [0.24; 104.14] | 3.7% |
| } | Random effects model | | 3869 | | 3864 | |) | 2.73 | [0.25; 30.11] | 6.1% |
|) | Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$ | | | | | | on April 17 | <u>!.</u> | | |
| ' | Group 3: High-Modorato | | | | | | | | | |
| | Group 3: High-Moderate TNT, A80 vs A10 | 4 | 400E | 2 | FOOG | _ | Zuz4 by guest. | 3 | [0.05, 5.50] | E 20/ |
| | SEARCH, S80 vs S20 | 68 | 4995 6031 | 2 | 5006 6033 | | by . | 0.50 | | 5.2% |
| | A to Z, S40–S80 vs S20 | 9 | 2263 | 12 1 | 2230 | | J. J | 0.07 | [3.07; 10.46] | 14.9% 6.4% |
| | Random effects model | _ | | 1 | | | | | [1.12; 69.94] | |
| , | Heterogeneity: $I^2 = 50\%$, $\tau^2 = 0.7030$, $p = 0.14$ | | 13289 | | 13269 | | | 3.00 | [1.05; 14.31] | 26.5% |
| ; | Therefore the first $p = 0.7030$, $p = 0.14$ | | | | | | | | | |
|) | Random effects model | | 47858 | | 47829 | | | 1,66 | [0.86; 3.21] | 100.0% |
|) | Heterogeneity: $I^2 = 52\%$, $\tau^2 = 0.6582$, $p < 0.01$ | | | | | | | | [5.55, 5.21] | / - |
| , | Residual heterogeneity: $I^2 = 12\%$, $p = 0.32$ | | | | (| 0.01 0.1 1 | 1 10 10 | Ď | | |
| | 1270, p = 0.02 | | | | | tatin Protective | Statin Harmfu | | | |
| | | | | | O | | | • | | |



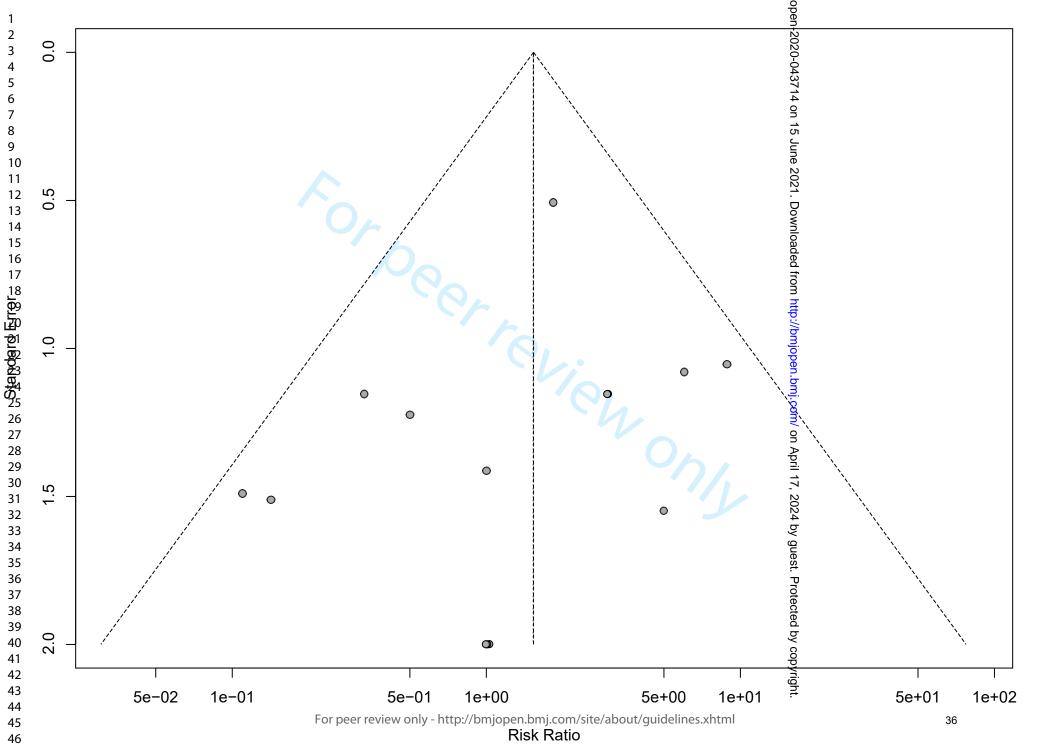
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CK >10x ULN: Meta-Analysis Forest Plot with outliers excluded.

| | Experir | nental | C | ontrol | | | 2020-043714 on | | |
|--|---------|--------------|--------|---------------|---------------|--|--|----------------|---------------|
| Study | Events | Total | Events | Total | Risk | Ratio | 4371 ² | 95%−CI | Weight |
| Group 1: Moderate-Placebo | | | | | | | | | |
| CARDS, A10 | 0 | 1428 | 4 | 1410 | | | 0.11 0.14 | | 4.6% |
| LIPS, F80 | 0 | 822 | 3 | 818 | | | | . , | 4.5% |
| CORONA, R10 | 1 | 2514 | 3 | 2497 | | | 0.33 | . , . | 7.4% |
| GISSI-HF, R10 | 1 | 2285 | 1 | 2289 | - | | 1.00 | | 5.1% |
| PROSPER, P40 | 0 | 2891 | 0 | 2913 | - | 1 | 0.33 1.00 1.01 1.03 1.83 2.99 1.31 1.31 | [0.02; 50.76] | 2.6% |
| 4D, A20 HPS, S40 | 0 | 619 10269 | 0 | 636 | | | 1.03 | | 2.6% |
| WOSCOPS, P40 | 3 | 3302 | 6 1 | 10267 3293 | | | 1.83 ± 2.99 | . , . | 28.0% 7.4% |
| ALERT, F40–F80 | 3 | 1045 | 1 | 1049 | | | 3.01 | [0.31, 28.73] | 7.4% 7.4% |
| SSSS, S20-S40 | 6 | 2221 | | 2223 | _ | | 6.01 | • | 8.3% |
| Random effects model | O | 27396 | 1 h | 27395 | < | | 1.31 | [0.63; 2.73] | 77.8% |
| Heterogeneity: $I^2 = 10\%$, $\tau^2 = 0.1435$, $p = 0.35$ | | | | | | | o O | [0.00, 2.70] | 111070 |
| , | | | | | | | pen | | |
| Group 2: High-Placebo | | | | | | | .bm | | |
| TRACE RA, A40 | 0 | 1504 | 0 | 1498 | | <u> </u> | 1.00 | [0.02; 50.16] | 2.6% |
| SPARCL, A80 | 2 | 2365 | 0 | 2366 | | | | [0.24; 104.14] | 4.3% |
| Random effects model | | 3869 | | 3864 | | | on April 17. | [0.25; 30.11] | 6.9% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$ | | | | | | | ori: | | |
| | | | | | | | | | |
| Group 3: High-Moderate | | | | | | | 202 | | |
| TNT, A80 vs A10 | 1 | 4995 | 2 | 5006 | - | | 2024 0.50 | | 6.6% |
| A to Z, S40–S80 vs S20 | 9 | 2263 | 1 | 2230 | | | ු 8.87 | [1.12; 69.94] | 8.7% |
| Random effects model | | 7258 | | 7236 | | ÷ | • ' | [0.13; 38.98] | 15.3% |
| Heterogeneity: $I^2 = 69\%$, $\tau^2 = 2.9371$, $p = 0.07$ | | | | | | | Prot | | |
| Random effects model | | 38523 | | 38495 | • |]: | Protected by | [0.80; 2.91] | 100 0% |
| Heterogeneity: $I^2 = 8\%$, $\tau^2 = 0.1269$, $p = 0.36$ | | 30323 | | JU-7JU | | | وا ا | [0.00, 2.01] | 100.0/0 |
| Residual heterogeneity: $I^2 = 19\%$, $p = 0.25$ | | | | (| 0.01 0.1 | | § 0 | | |
| · · · · · · · · · · · · · · · · · · · | | | | | Statin Better | | ovric | | |
| | | | | | | (| 파. | | |





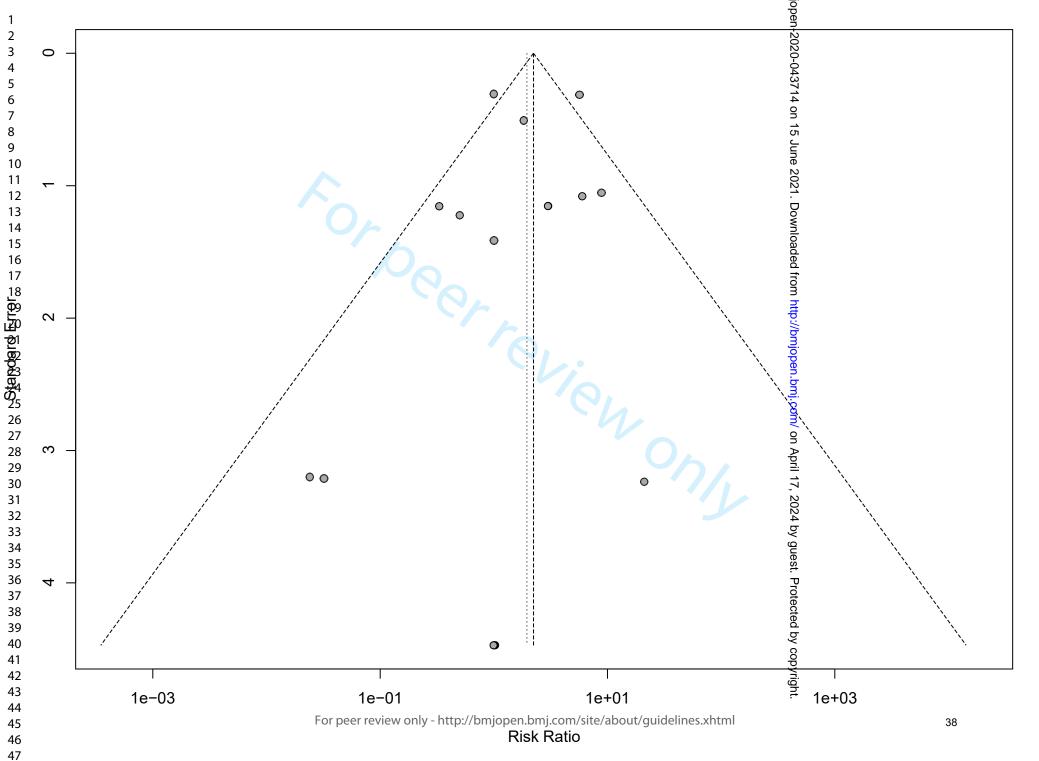
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CK >10x ULN: Meta-Analysis Forest Plot with Continuity Correction = 0.1.

| 1 | | | | | | | pen-2020-043714 | | |
|----------|--|---------|--------------|---------------|--------------|----------------------------|--------------------------------|---|----------|
| 2 | E | Experir | nental | C | ontrol | | 202 | | |
| 4 | Study | vents | Total | Events | Total | Risk Ratio | ₽ RR | 95%−C | l Weight |
| 5 | | | | | | : | 1371 | | |
| 6 | Group 1: Moderate-Placebo | _ | | _ | | | 0 | | |
| 8 | CARDS, A10 | 0 | 1428 | 4 | 1410 | * | _ 0.02 | [0.00; 12.76 | • |
| 9 | LIPS, F80 | 0 | 822 | 3 | 818 | * _ | د 0.00 | [0.00; 17.42 | • |
| 10 | | 1 | 2514 | 3 | 2497 | -* | | [0.03; 3.18 | • |
| | AFCAPS, L20–L40 | 21 | 3304 | 21 | 3301 | 1 | ²⁰ 1.00 | [0.55; 1.83 | • |
| | GISSI-HF, R10 | 1 | 2285 | 1 | 2289 | - 1 | 1.00 | [0.06; 16.01 | • |
| 14 | PROSPER, P40 | 0 | 2891 | 0 | 2913 | | Downloaded 1.83 | [0.00; 6455.29 | • |
| 15 | HD0 040 | 0 | 619 | 0 | 636 | | nloa 1.03 | [0.00; 6578.85 | • |
| 16 | HPS, S40 | | 10269 | 0 | 10267 | T. | | [0.68; 4.95 | - |
| | WOSCOPS, P40 ALERT, F40-F80 | 3 | 3302 | 1 | 3293 1049 | | from 3.01 | [0.31; 28.75 | • |
| | SSSS, S20-S40 | 3 6 | 1045 2221 | | 2223 | | | [0.31; 28.90 [0.72; 49.84 | • |
| 20 | | O | 30700 | | 30696 | | 6.01 1.24 http://bmjopen | [0.72; 49.84 [0.79; 1.97] | 4 |
| 21 | 11-4 | | 30700 | | 30090 | <u> </u> | 3 1.24 | [0.79, 1.97] |] 07.076 |
| 22 | | | | | | | ope | | |
| 23 24 | Group 2: High-Placebo | | | | | | า.br | | |
| | TRACE RA, A40 | 0 | 1504 | 0 | 1498 | | 2 1 00 | [0.00; 6380.08] | 0.6% |
| 26 | • | 2 | 2365 | 0 | | | - \$21.01 | [0.00, 0000.00] | 1.1% |
| 27 | Dandom offacts model | _ | 3869 | Ū | 3864 | | 7.37 | [0.04: 1256.08] | 1.7% |
| 28 29 | | | | | | | Apri | | 111 70 |
| 30 | | | | | | | I 17 | | |
| 31 | Group 3: High-Moderate | | | | | | , 20 | | |
| 32 | TNT, A80 vs A10 | 1 | 4995 | 2 | 5006 | | ²⁴ 0.50 | [0.04; 11950.08] [0.04; 1256.08] [0.05; 5.52 [3.07; 10.46] [1.12; 69.94] [1.05; 14.31] | 5.8% |
| 33 34 | | 68 | 6031 | 12 | 6033 | - | 5.67 في خ | [3.07; 10.46 | 18.3% |
| 35 | A to Z, S40-S80 vs S20 | 9 | 2263 | 1 | 2230 | | ® 8.87 | [1.12; 69.94] | 7.2% |
| | Random effects model | | 13289 | | 13269 | | <u>¬</u> 3.88 | [1.05; 14.31] | 31.3% |
| 37 | | | | | | | 3.88 Protected by | | |
| 38 | | | | | | | cted | | |
| 39 40 | Random effects model | | 47858 | | 47829 | <u></u> | | [1.00; 3.85 |] 100.0% |
| 41 | · · · · · · · · · · · · · · · · · · · | | | | | | сор | | |
| | Residual heterogeneity: $I^2 = 0\%$, $p = 0.44$ | | | | | 0.001 0.1 1 10 1000 | copyright | | |
| 43 | | | | | | Statin Better Statin Worse | <u> </u> | | |





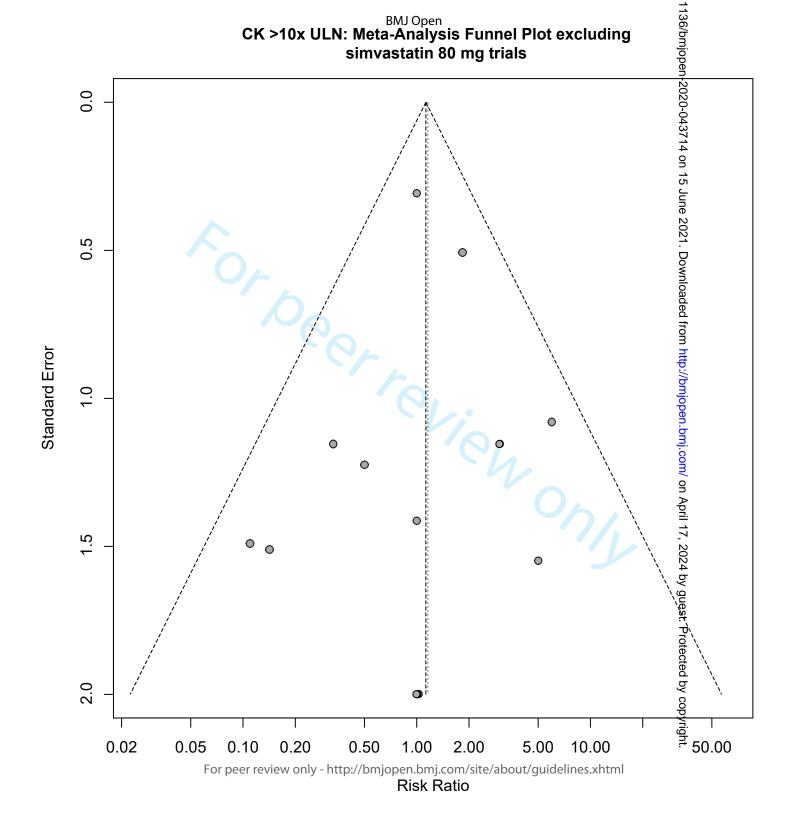


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CK >10x ULN: Meta-Analysis Forest Plot excluding simvastatin 80 mg trien-20.

| | Experim | ental | С | ontrol | | 2020-043714 | | |
|--|---------|-------------|--------|-------------------|------------------------------|--------------------------------------|-------------------------------|--------------|
| Study | Events | | Events | Total | Risk Ratio |)4371. | 95%−CI | Weight |
| Group 1: Moderate-Placebo | | | | | | 9 | | |
| CARDS, A10 | 0 | 1428 | 4 | 1410 ⁻ | <u>-</u> | 15 0.11 June 0.14 | [0.01; 2.04] | 2.2% |
| LIPS, F80 | 0 | 822 | 3 | 818 | * : | | [0.01; 2.75] | 2.1% |
| CORONA, R10 | | 2514 | 3 | 2497 | | ²⁰ 0.33 | [0.03; 3.18] | 3.6% |
| AFCAPS, L20–L40 | | 3304 | 21 | 3301 | | 1.00 | [0.55; 1.83] | 50.8% |
| GISSI-HF, R10 | | 2285 | 1 | 2289 | | 1.00 | [0.06; 16.01] | 2.4% |
| PROSPER, P40 4D, A20 | 0 | 2891 619 | 0 | 2913 636 | | nloade 1.03 | [0.02; 50.76] | 1.2% 1.2% |
| 4D, A20 HPS, S40 | | 0269 | _ | 10267 | | 1.00 1.01 1.03 1.83 1.83 | [0.02; 51.70] [0.68; 4.95] | 18.7% |
| WOSCOPS, P40 | | 3302 | 1 | 3293 | | ² 2.99 | [0.31; 28.75] | 3.6% |
| ALERT, F40-F80 | _ | 1045 | | 1049 | | | [0.31; 28.90] | 3.6% |
| SSS, S20-S40 | | 2221 | 1 | | - | 6.01 | [0.72; 49.84] | 4.1% |
| Random effects model | 3 | 30700 | | 30696 | \(| 를 1.17 | [0.72; 1.90] | 93.6% |
| Heterogeneity: $I^2 = 4\%$, $\tau^2 = 0.0303$, $p = 0.41$ | | | | | • | 3.01 6.01 1.17 1.00 | | |
| | | | | | 0. | bmj. | | |
| Group 2: High-Placebo | | | | | | .com | | |
| TRACE RA, A40 | | 1504 | 0 | 1498 | | 0 | [0.02; 50.16] | 1.2% |
| SPARCL, A80 | | 2365 | 0 | 2366 | | _≥ 5.00 | [0.24; 104.14] | 2.0% |
| Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.52$ | | 3869 | | 3864 | | rii 2./3 | [0.25; 30.11] | 3.2% |
| Heterogeneity: $T = 0\%$, $\tau^{2} = 0$, $\rho = 0.52$ | | | | | | 7, 2 | | |
| Group 3: High-Moderate | | | | | | 2024 | | |
| TNT, A80 vs A10 | 1 | 4995 | 2 | 5006 | | by guest. | [0.05; 5.52] | 3.2% |
| Random effects model | | 4995 | _ | 5006 | | ues 0.50 | [0.05; 5.52] | 3.2% |
| Heterogeneity: not applicable | | | | | | | | |
| | | | | | | Protected 1.16 | | |
| Random effects model | 3 | 9564 | | 39566 | \rightarrow | <u>_</u> ₫ 1.16 | [0.75; 1.78] | 100.0% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.55$ | | | | _ | | _by | | |
| Residual heterogeneity: $I^2 = 0\%$, $p = 0.46$ | | | | | | 10 8 | | |
| | | | | 5 | tatin Protective Statin Harm | | | |
| | | | | | | • | | |



BMJ Open CK>10XULN SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

| | Placeho - Mod | lerate Intensity | | Moderate - Hig | nh Intensity | | ರ Placebo – High | Intensity | |
|-------------|----------------|-------------------|----------|----------------|------------------|-----|---|-------------------|-----|
| | i iacebo – moa | icrate interisity | | Moderate - m | girintensity | | 그 Ideebo - I II몇II 으 | intensity | |
| Outcome | RR | RD | NNH | RR | RD | NNH | RR 15 | RD | NNF |
| | (95% CI) | (95% CI) | | (95% CI) | (95% CI) | | (95% CI) د ا | (95% CI) | |
| Direct, M-H | 1.171 | NA | | 3.880 | NA | | 2.731 | NA | |
| · | (0.722, 1.900) | | | (1.052, | | | (0.428, 30.10 | | |
| | , | | | 14.314) | | | 21. | | |
| Direct, IV | 1.178 | 0.0000* | | 4.861 | 0.0030 | 333 | 2.720 | 0.0004 | |
| | (0.700, 1.985) | (-0.0010, 0.0010) | | (2.388, 9.894) | (0.0011, 0.0049) | | (0.240, 30.828) | (-0.0016, 0.0025) | |
| NMA, IV | 1.143 | -0.0003 | | 4.594 | 0.0019 | 527 | 5.252 | 0.0017 | 589 |
| ŕ | (0.686, 1.905) | (-0.0012,0.0007) | | (2.320,9.098) | (0.0005,0.0034) | | (2.293,12.028) | (0.0002,0.0031) | |
| NMA | 1.189 | 0.0002 | | 1.073 | -0.0000* | | 1.276 ਹੈ | 0.0002 | |
| Excluding | (0.765,1.848) | (-0.0003,0.0006 | | (0.194,5.939) | (-0.0007,0.0007 | | (0.230,7.063) | (-0.0006,0.0009) | |
| S80 | | | | |) | | (p :/ | (| |
| NMA | 1.246 | -0.0002 | + | 5.123 | 0.0016 | 625 | 6 381 | 0.0013 | 770 |
| CC=0.10 | (0.790,1.964) | (-0.0010,0.0005) | | (2.906,9.033) | (0.0004,0.0028) | 020 | 6.381 <u>3</u> . (3.094,13.161) | (0.0002,0.0025) | |
| NMA | 1.297 | -0.0000* | | 5.115 | 0.0001 | | 6.636 | 0.0001 | |
| CC = 0.0001 | (0.818,2.058) | (-0.0002,0.0001) | | (2.891,9.049) | (-0.0002,0.0003) | | (3.186,13.819 | (-0.0001,0.0003) | l |
| | (0.010,2.000) | (0.0002,0.0001) | | (2.001,0.040) | (0.0002,0.0000) | | · · · · · · · · · · · · · · · · · · · | (0.0001,0.0000) | |
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Attrition MA:

```
AE_Drop_meta <- read.csv("C:/Users/14795/Desktop/Statin_Meta/Final
Sheets - Copy/Attrition.csv", header=T)
```

R Code for Meta-Analysis

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mb1_Attrition <- metabin(X1, Statin.Total, X2, Placebo.Total,

data = AE_Drop_meta, studlab = Study, label.right = "Statin Harmful", label.left = "Statin Protective",

allstudies=TRUE, incr=0.5, sm = "RR", digits=3,

r = FALSE, byvar = AE_Drop_meta\$Study.Intensity, bylab = "Study Design", comb.fixed = FALSE,

summary(mb1_Attrition)

```
## Attrition NMA:
##
p3 <- pairwise(list(treat1, treat2),
              list(X, X1),
              list(Total, Total.1),
              data=net_attrition, studlab = Study)
net3_attrition <- netmetabin(p3,</pre>
                                method = "Inverse", title =
"Attrition NMA",
                 reference.group = "Placebo", sm = "RR", comb.fixed
= FALSE,
                 studlab = p3\$Study)
                    net3_attrition
```



PRISMA 2009 Checklist

| | | 220 | |
|------------------------------------|----|--|--------------------|
| Section/topic | # | Checklist item 43714 | Reported on page # |
| TITLE | | on 1 | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 (Title) |
| ABSTRACT | | ਰੇ 2 | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| INTRODUCTION | | ad | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5 (Intro) |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5-6 |
| METHODS | | brr | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number. | 3 (abstract) |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6-7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | With Prospero reg. |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 6-7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and சூற் assumptions and simplifications made. | 6-7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specifications of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| | | For neer review only - http://bmionen.hmi.com/site/about/quidelines.yhtml | 1 |



PRISMA 2009 Checklist

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|-------------------------------|----|---|--------------------|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis. | 8 |
| | | Page 1 of 2 Q | |
| Section/topic | # | Checklist item | Reported on page # |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| RESULTS | | ad ec | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8-9 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 8-11, Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summais data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figures |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Figures |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Results section |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Results section |
| DISCUSSION | | by <u>c</u> | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 15-16 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16-17 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 17-18 |
| FUNDING | | D S D D D D D D D D D D D D D D D D D D | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml | Title page |

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 doi:10.1371/journal.pmed1000097

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