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Statins versus placebo for people with chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Statins versus placebo for people with chronic obstructive pulmonary disease

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ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable respiratory disease. COPD exacerbations are associated with worse quality of life, increased hospitalisations, and increased mortality. Currently available pharmacological interventions have variable impact on exacerbation frequency. The anti-inflammatory effects of statins may lead to decreased pulmonary and systemic inflammation, resulting in fewer exacerbations of COPD. Several observational studies have shown potential benefits of statins for patients with COPD.

Objectives

This review aims to evaluate available evidence on benefits and harms associated with statin therapy compared with placebo as adjunct therapy for patients with COPD. Primary objectives include the following.

• To determine whether statins reduce mortality rates in COPD.

• To determine whether statins reduce exacerbation frequency, improve quality of life, or improve lung function in COPD.

• To determine whether statins are associated with adverse effects.

Search methods

We identified trials from the Cochrane Airways Trials Register, which contains studies identified through multiple electronic searches and handsearches of other sources. We also searched trial registries and reference lists of primary studies. We conducted the most recent search on 20 May 2019.

Selection criteria

Parallel, randomised controlled trials recruiting adults with COPD.

Data collection and analysis

We used standard methods as expected by Cochrane. Prespecified primary outcomes were number of exacerbations, all-cause mortality, and COPD-specific mortality.

Main results

Eight studies including 1323 participants with COPD were included in the review. Participants had a mean age of 61.4 to 72 years, and most were male (median 73.4%). Mean baseline forced expiratory volume in one second (FEV_1) ranged from 41% to 90% predicted. All studies compared moderate- or high-intensity statin therapy versus placebo. The duration of treatment ranged from 12 weeks to 36 months.

We found no statistically significant difference between statins and placebo in our primary outcome of number of exacerbations per person-year (mean difference (MD) -0.03, 95% confidence interval (CI) -0.25 to 0.19, 1 trial, 877 participants), including number of exacerbations requiring hospitalisation per person-year (MD 0.00, 95% CI -0.10 to 0.10, 1 trial, 877 exacerbations). This evidence was of moderate quality after downgrading for unclear risk of bias. Our primary outcomes of all-cause mortality (odds ratio (OR) 1.03, 95% CI 0.61 to 1.74, 2 trials, 952 participants) and COPD-specific mortality (OR 1.25, 95% CI 0.38 to 4.13, 1 trial, 877 participants) showed no significant difference between statins and placebo, with wide confidence intervals suggesting uncertainty about the precision of the results. This evidence was of low quality after downgrading for unclear risk of bias and imprecision.

Results of the secondary outcomes analysis showed no clear differences between statins and placebo for FEV_1 (% predicted) (MD 1.18, 95% CI -2.6 to 4.97, 6 trials, 325 participants) but did show a statistically significant improvement in FEV_1/forced vital capacity (FVC) (MD 2.66, 95% CI 0.12 to 5.2; P = 0.04; 6 trials, 325 participants). A sensitivity analysis excluding two trials at high risk of bias showed no statistically significant difference in FEV_1/FVC (MD 2.05, 95% CI -0.87 to -4.97; P = 0.17; 4 trials, 255 participants). We also found no significant differences between the two groups in functional capacity measured by six-minute walk distance in metres (MD 1.79, 95% CI -52.51 to 56.09, 3 trials, 71 participants), with wide confidence intervals suggesting uncertainty about the precision of the results. Results show no clear difference in quality of life, which was reported in three trials, and a slight reduction in C-reactive protein (CRP) in the intervention group, which was statistically significant (MD -1.03, 95% CI -1.95 to -0.11; I^2 = 0%, P = 0.03; 3 trials, 142 participants). We noted a significant reduction in interleukin (IL)-6 in the intervention group (MD -2.11, 95% CI -2.65 to -1.56; I^2 = 0%, P ≤ 0.00001; 2 trials, 125 participants). All trials mentioned adverse events and indicated that statins were generally well tolerated. One study reported adverse events in detail and indicated that rates of all non-fatal adverse events (the number of serious adverse events per person-year) were similar in both groups (0.63 ± 1.56 events (intervention group) and 0.62 ± 1.48 events (control group); P > 0.20) for all comparisons, except for non-fatal serious adverse events involving the gastrointestinal tract, which were more frequent in the intervention group (in 30 patients (0.05 events per person-year) vs 17 patients (0.02 events per person-year); P = 0.02). Another trial lists the total numbers and percentages of adverse events in the intervention group (12 (26%)) and in the control group (21 (43%)) and of serious adverse events in the intervention group (4 (9%)) and in the control group (3 (6%)).The other trials stated that researchers found no significant adverse effects of statins but did not report adverse events in detail.

Authors' conclusions

A small number of trials providing low- or moderate-quality evidence were suitable for inclusion in this review. They showed that use of statins resulted in a reduction in CRP and IL-6, but that this did not translate into clear clinical benefit for people with COPD. Further randomised controlled trials are needed to explore this topic.

PLAIN LANGUAGE SUMMARY

Statins for chronic obstructive pulmonary disease (COPD)

Review question

We reviewed the evidence on the effects of statins on adults with COPD. We found eight relevant studies.

Background

Chronic obstructive pulmonary disease (COPD) is the name for a group of progressive lung conditions that cause breathing difficulties. This group includes emphysema and chronic bronchitis. Statins are medicines that can help lower the level of cholesterol in the blood. It has been suggested that through their anti-inflammatory properties statins might help reduce the number of exacerbations in people with COPD.

Study characteristics

We included eight studies involving 1323 participants comparing the benefits and harms of statins and placebo (an identical looking treatment with no therapeutic benefit) in people with COPD.

Key results

We found that statins reduced the level of inflammation in people with COPD but that this did not result in any clear improvement in exacerbations, mortality, functional capacity, quality of life, or lung function. Statins were generally well tolerated and were associated with few adverse effects.

Quality of the evidence

This evidence was of low or moderate quality, and most came from trials of short duration.

This review is current to May 2019.

Summary of findings for the main comparison. Statins compared to placebo as adjunct therapy for chronic obstructive pulmonary disease (COPD)

Statins compared to placebo as adjunct therapy for chronic obstructive pulmonary disease (COPD)

Patient or population: adults with chronic obstructive pulmonary disease (COPD)
Setting: outpatients
Intervention: statins
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with statins				
Number of exacerbations per person-year Follow-up: range 12 months to 36 months	Mean number of exacerbations was 1.39 per person-year	MD 0.03 lower (0.25 lower to 0.19 higher)	-	877 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	
Exacerbations requiring hospitalisation per person-year Follow-up: range 12 months to 36 months	Mean number of exacerbations requiring hospitalisation was 0.31 per person-year	MD 0.00 (0.1 lower to 0.1 higher)	-	877 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	
All-cause mortality Follow-up: range 6 months to 36 months	62 per 1000	64 per 1000 (39 to 104)	OR 1.03 (0.61 to 1.74)	952 (2 RCTs)	⊕⊕⊖⊖ LOW[b,c]	
COPD-specific mortality Follow-up: range 12	11 per 1000	14 per 1000 (4 to 45)	OR 1.25 (0.38 to 4.13)	877 (1 RCT)	⊕⊕⊖⊖ LOW[a,c]	

months to 36 months			
Quality of life	Two studies used the St. George's Respiratory Questionnaire (SGRQ). One study reported median change from baseline score and found no significant improvement in any of the domains of the SGRQ (total SGRQ median change from baseline -0.18 (10th, 90th percentiles -11.01, 9.7) in the intervention group and 0.02 (10th, 90th percentiles -12.47, 10.73) in the control group; P = 0.3783) or the Short Form Health Survey (SF-36) with statin treatment. One study found that the median SGRQ score decreased significantly from 54.5 to 42 in the intervention group compared with no change in the control group (68 to 70 points; non-significant). A third trial found that mean change in Clinical COPD Questionnaire (CCQ) total score (P = 0.96) and symptom score (P = 0.12) was not significant at 12 weeks but did not provide further data	(3 RCTs)	Not applicable
Adverse events	One study found that rates of all non-fatal adverse events were similar in both groups for all comparisons, except for non-fatal serious adverse events involving the gastrointestinal tract, which were more frequent in the intervention groups. One study reported the total numbers and percentages of adverse events (12 (26%) in the intervention group and 21 (43%) in the control group) and serious adverse events (4 (9%) in the intervention group and 3 (6%) in the control group). One study reported no adverse events, although 1 person was not included in the final analysis owing to serious adverse events and there was 1 case of CAP. One study reported that rosuvastatin was well tolerated, but common adverse drug reactions were gastric intolerance, myalgia, and elevated AST. Pedal oedema was seen in 2 patients in the placebo group who were on calcium channel blockers. Four studies reported no side effects	(8 RCTs)	Not applicable

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

AST: aspartate transaminase; CAP: community-acquired pneumonia; CI: confidence interval; MD: mean difference; OR: odds ratio; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one point as unclear risk of selection and detection bias.
[b]Downgraded by one point as unclear risk of selection and detection bias, unclear risk of reporting bias.
[c]Downgraded by one point for imprecision as small number of studies and events with wide confidence intervals.

BACKGROUND

Description of the condition

"Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, which is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. Exacerbations negatively impact health status, rates of hospitalisation and disease progression" (GOLD 2019). It is estimated that 65 million people worldwide have moderate to severe COPD (WHO 2015). Although mortality from cancer, heart disease, and stroke has decreased, mortality from COPD has increased by 102% (Jemal 2005). COPD is currently the third leading cause of death worldwide (WHO 2018). A systematic review of population studies of COPD estimated prevalence of 9% to 10% in adults over 40 years of age (Halbert 2006). A Burden of Obstructive Lung Disease Initiative (BOLD) (Buist 2005) study estimated the population prevalence of GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 2 or higher COPD at 8.5% to 22.2% across 12 international cities and observed significant variation in prevalence across sites (Buist 2007). The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study reported a crude prevalence rate of GOLD stage 1 or higher COPD of 9.7% to 19.7% across five South American cities (Menezes 2005). In a prevalence study in Austria, 26.1% of the population over 40 years of age had GOLD stage 1 or higher COPD (Schirnhofer 2007). In the United States, the estimated economic cost of COPD and asthma combined is $68 billion (NHLBI 2012).

Exacerbations of COPD are responsible for the largest portion of the COPD burden on the healthcare system (Strassels 2001). GOLD defines a COPD exacerbation as "an acute worsening of respiratory symptoms that result in additional therapy" (GOLD 2019). Acute exacerbations are associated with worse quality of life (Barnes 2013), increased hospitalisations (Mullerova 2014), increased mortality (Seemungal 2008), inflammation (Lopez-Campos 2015; Seemungal 2001), and lung hyperinflation (Parker 2005; Van Geffen 2018). Several interventions are available to prevent exacerbations, including smoking cessation, pulmonary rehabilitation, and disease management programmes; patient education; non-invasive ventilation; pneumococcal and influenza vaccinations; and use of long-acting bronchodilators, inhaled corticosteroids, phosphodiesterase 4 inhibitors, antioxidants, mucolytic agents, and antibiotics (Qureshi 2014). The effects of these interventions on exacerbation frequency are limited, with pharmacological interventions leading to a 14% to 35% reduction (Han 2011). Smoking cessation has been shown to modify the accelerated rate of decline in lung function that is the hallmark of COPD (Godtfredsen 2008). A recent trial showed that triple therapy (combination of an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting beta-agonist (LABA)) resulted in improved lung function compared to dual therapy with either inhaled glucorticoid-LABA or LAMA-LABA (Lipson 2018), but it remains to be conclusively proven whether any of the existing pharmacological interventions for COPD modify the long-term decline in lung function (GOLD 2019). The importance of finding treatments that can have this kind of impact cannot be overstated.

COPD is increasingly considered a multi-system disease involving pulmonary and systemic inflammation (Young 2013). The lung inflammatory response comprises increased concentrations of pro-inflammatory cytokines, as well as innate and adaptive immune cells (Sinden 2010). A systematic review found that people with COPD had raised levels of several inflammatory markers, including interleukin-6 (IL-6) and C-reactive protein (CRP), indicating the presence of persistent systemic inflammation (Gan 2004). Pulmonary and systemic inflammation is thought to be central to symptoms, exacerbations, and mortality (Young 2009). In addition, many patients with COPD have multiple comorbidities, particularly those who are elderly (Clini 2013).

Description of the intervention

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and are among the most powerful available cholesterol-lowering drugs. Currently available statins include simvastatin, pravastatin, rosuvastatin, atorvastatin, fluvastatin, pitavastatin, and lovastatin (FDA 2015). They are oral drugs that are taken daily, usually on a long-term basis.

How the intervention might work

Statins are competitive inhibitors of HMG-CoA reductase - the enzyme that catalyses the rate-limiting step in cholesterol biosynthesis (Istvan 2001). Statins have multiple biochemical effects in addition to their lipid-lowering properties, including anti-inflammatory effects (Antonopoulos 2012). They are inhibitors of IL-6 and CRP and have extrahepatic effects, including effects in the lung (Yeganeh 2014). The anti-inflammatory effects of statins may lead to decreased pulmonary and systemic inflammation, resulting in fewer exacerbations, reduced decline in lung function, and improved life expectancy in COPD (Young 2013). Evidence also suggests that dyslipidaemia and surfactant disturbance may contribute to inflammation and increased airway resistance in COPD (Chai 2017; Hohlfeld 1997; Morissette 2015).

Several observational studies have shown potential benefits of statins as adjunct therapy for patients with COPD. Researchers report reduced all-cause mortality (Frost 2007; Ishida 2007; Lahousse 2013; Lawes 2012; Mancini 2006; Raymakers 2017; Sheng 2012), fewer COPD exacerbations (Balmoun 2008; Bartziokas 2011; Huang 2011; Ingebrigtsen 2015; Wang 2013), and reduced decline in lung function (Alexeeff 2007). However, observational studies have limitations because of the uncontrolled nature of the populations studied. Systematic reviews and meta-analyses including observational studies on the effects of statins on mortality in COPD showed moderate to considerable heterogeneity (Cao 2015; Li 2017; Lu 2019), along with evidence of publication bias (Horita 2014).

Numerous controlled trials including thousands of participants have studied statins from a safety perspective and have reported that they are generally well tolerated (Baigent 2005; Bays 2005; Finegold 2014; Kashani 2006; Silva 2006). Clinicians can monitor well-recognised adverse effects on muscle and on liver function (Bays 2014; Rosenson 2014). Statins are also associated with increased risk of type 2 diabetes (Sattar 2014).

Why it is important to do this review

Statins are widely available; beneficial effects, when they occur, lead to reduction in exacerbations, hospital admissions, and mortality among patients with COPD, and have wide-reaching implications for international healthcare systems and millions of people worldwide. Like all drugs, statins have side effects

and should not be prescribed unless they are known to benefit the patient. A meta-analysis of randomised controlled trials is necessary to fully evaluate evidence from randomised controlled trials on statins as adjunct therapy in COPD.

OBJECTIVES

This review aims to evaluate available evidence on benefits and harms associated with statin therapy compared with placebo as adjunct therapy for patients with COPD. Primary objectives include the following.

- To determine whether statins reduce mortality rates in COPD.
- To determine whether statins reduce exacerbation frequency, improve quality of life, or improve lung function in COPD.
- To determine whether statins are associated with adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs) reported as full text, published as abstract only, or providing only unpublished data.

Types of participants

We included adults (≥ 18 years of age) with a diagnosis of COPD as defined by GOLD criteria (GOLD 2015; Rabe 2007), or by American Thoracic Society (ATS) or European Respiratory Society (ERS) criteria (Celli 2004). We included participants with stable and unstable COPD.

Types of interventions

We included trials comparing any statin at any dose given for 12 weeks or longer versus placebo.

Types of outcome measures

Primary outcomes

- Number of exacerbations (exacerbations will be further defined as exacerbations requiring short-acting bronchodilators only, exacerbations requiring short-acting bronchodilators and a course of antibiotics or steroids, exacerbations requiring emergency department attendance, and exacerbations requiring hospital admission)
- All-cause mortality
- COPD-specific mortality

Secondary outcomes

- Validated quality of life measures (e.g. St. George's Respiratory Questionnaire (Jones 1992), self-reported Chronic Respiratory Questionnaire (Guyatt 1987))
- Functional capacity (e.g. six-minute walk distance test (Balke 1963), incremental shuttle walking test (Singh 1992), endurance shuttle walking test (Revill 1999))
- Lung function including spirometric measurements (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC)
- Measures of airway inflammation such as CRP, IL-6, and tumour necrosis factor (TNF)-alpha
- Adverse events/Side effects

Reporting by researchers of one of more of the outcomes listed here is not an inclusion criterion for this review.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Trials Register on 20 May 2019. The Cochrane Airways Trials Register is maintained by the Information Specialist for the Group and contains studies identified from several sources.

- Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, via the Cochrane Register of Studies (CRS).
- Weekly searches of MEDLINE Ovid.
- Weekly searches of Embase Ovid.
- Monthly searches of PsycINFO Ovid.
- Monthly searches of the Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO.
- Monthly searches of Allied and Complementary Medicine (AMED) EBSCO.
- Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings, are provided in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We searched the following trials registries on 20 May 2019.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We did not apply restrictions to searches based on date, type, or language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' and clinical trials websites for trial information.

We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) on 07 June 2019.

Data collection and analysis

Selection of studies

Two review authors (AW and LP) independently screened titles and abstracts to identify potential studies for inclusion in the review; we coded studies identified by the search as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved full-text study reports/publications; two review authors (AW and LP) independently screened the full text, identified studies for

inclusion, and identified and recorded reasons for exclusion of ineligible studies. We encountered no disagreements, so the need to consult a third review author (MNC) did not arise. We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (see Figure 1) and a Characteristics of excluded studies table.

Figure 1. Study flow diagram.

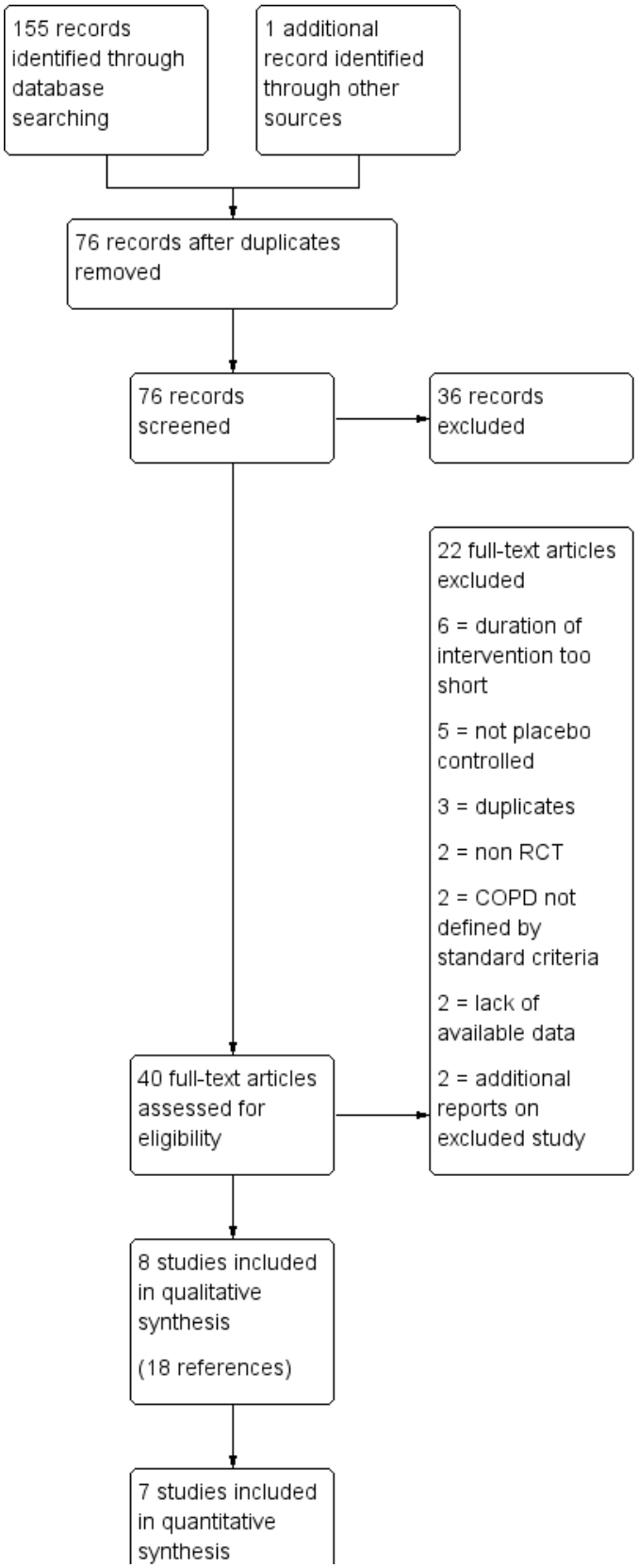
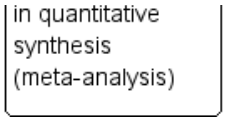


Figure 1. (Continued)



Data extraction and management

Two review authors (AW and LP) used a data collection form that was piloted on one study in the review to record the following study characteristics and outcome data from included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study setting, withdrawals, and dates of study.
- Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
- Interventions: interventions, comparison, concomitant medications, and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected and time points reported.
- Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (AW and LP) independently extracted outcome data from included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We resolved disagreements by reaching consensus. One review author (AW) transferred data into the Review Manager file (RevMan 2014). We double-checked that data were entered correctly by comparing data presented in the systematic review versus data provided in the study reports. A second review author (AK) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (AW and MNC) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion and assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised risk of bias judgements across different studies for each of the domains listed. We blinded separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). When information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for studies that contribute to those outcomes.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and reported deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data by calculating odds ratios (ORs) and 95% confidence intervals (CIs), and continuous data by calculating mean differences (MDs) or standardised mean differences (SMDs) and 95% CIs. We entered data presented as a scale with a consistent direction of effect.

Meta-analysis was undertaken only when this was meaningful (i.e. when treatments, participants, and the underlying clinical question are similar enough for pooling to make sense).

We narratively described skewed data reported as medians and interquartile ranges.

Our review did not include trials with multiple intervention arms, but if future updates of the review should identify this type of trial, we will include only the relevant arms. When two comparisons (e.g. drug A vs placebo and drug B vs placebo) were combined in the same meta-analysis, we halved the control group to avoid double-counting.

Unit of analysis issues

Our analysis took into account the level at which randomisation occurred. The study participant was the unit of analysis in all included studies. We used rate ratios to analyse data to avoid a unit of analysis error.

Dealing with missing data

We contacted investigators to verify key study characteristics and obtain missing numerical outcome data when possible. When this was not possible, and we thought that the missing data might introduce serious bias, we performed a sensitivity analysis to explore the impact of including such studies in the overall assessment of results.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. We interpreted I^2 as per the *Cochrane Handbook for Systematic Reviews of Interventions*: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: may show considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

As we included fewer than 10 studies in the review, we were unable to create a funnel plot to explore possible small study and publication biases.

Data synthesis

We used a random-effects model and performed a sensitivity analysis using a fixed-effect model.

'Summary of findings' table

We created a 'Summary of findings' table by using the following outcomes: number of exacerbations, all-cause mortality, COPD-specific mortality, quality of life, and adverse effects. We used the eight GRADE (Grades of Recommendation, Assessment, Development and Evaluation) considerations (study limitations, consistency of effect, imprecision, indirectness, publication bias, magnitude of effect, possible confounders, and dose-response gradient) to assess the quality of a body of evidence as it relates to studies contributing data to the meta-analyses for prespecified outcomes. We applied methods and recommendations as described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software. We justified all decisions to downgrade the quality of studies by using footnotes, and we made comments to aid readers' understanding of the review, when necessary.

Subgroup analysis and investigation of heterogeneity

Given the small number of trials included in this review, it was not possible to carry out subgroup analysis. We had planned to carry out the following subgroup analyses.

- Baseline severity of COPD (we will categorise baseline severity in three ways: (1) through GOLD spirometric assessment: GOLD 1: mild (FEV_1 ≥ 80% predicted), GOLD 2: moderate (50% ≤ FEV_1 < 80% predicted), GOLD 3: severe (30% ≤ FEV_1 < 50% predicted), GOLD 4: very severe (FEV_1 < 30% predicted); (2) by number of exacerbations (those with fewer than two previous exacerbations and those with two or more previous exacerbations); and (3) through a combination of spirometric assessment and number of exacerbations (comparison of those with FEV_1 < 50% predicted and those who have had two or more previous exacerbations vs the rest of the study population).
- Smoking status (current smokers/former smokers/never smokers).
- Statin dose (low-, moderate-, or high-intensity dose, as per American Heart Association (AHA) guidelines) (Stone 2014).

We had planned to use the following outcomes in subgroup analyses.

- Number of exacerbations.
- Mortality (all-cause and COPD-specific).

We planned to use the formal test for subgroup interactions provided in Review Manager (RevMan 2014).

Sensitivity analysis

We planned to perform sensitivity analyses to assess whether results of our primary outcomes were sensitive to blinding, completeness of follow-up, publication status, and funding. We also planned to perform a sensitivity analysis that would exclude studies including participants with underlying hypercholesterolaemia or cardiovascular disease. Again, given the small number of studies included in this review, it was not possible to perform these sensitivity analyses.

RESULTS

Description of studies

Results of the search

One hundred fifty-five references were identified through searches of online databases, and one additional reference was found by searching other resources (drug company websites, reference lists of systematic reviews, clinicaltrials.gov, and who.int). After 79 duplicates were removed, 36 of the remaining 76 references were excluded by screening references and abstracts. Full texts were consulted for the remaining 40 references, and 18 met inclusion criteria, representing eight studies. We excluded 24 studies with reasons (see Figure 1). Of note, two studies were identified that were suitable for inclusion in the review, but they had to be excluded due to lack of available data. Full details of the search history can be found in Appendix 1 and Appendix 2.

Included studies

Eight studies met the inclusion criteria, randomly assigning 1323 participants with a diagnosis of COPD to statin or placebo.

Design and duration

All eight studies were randomised, parallel-group, placebo-controlled trials. One of the studies blinded participants but not personnel (Mroz 2015). The remaining seven studies blinded both participants and personnel. One trial lasted for three years (Criner 2014), three for six months (Lee 2008; Lee 2009; Moosavi 2013), and four for 12 weeks (Balaguer 2016; Chogtu 2016; Mroz 2015; Neukamm 2014).

Participant inclusion and exclusion criteria

Full details of the inclusion and exclusion criteria for each trial can be found in Characteristics of included studies. Criteria varied between trials. Various definitions of COPD were used - three trials used GOLD criteria (Balaguer 2016; Criner 2014; Neukamm 2014), four used American Thoracic Society (ATS) criteria (Lee 2008; Lee 2009; Moosavi 2013; Mroz 2015), and one used both GOLD and ATS criteria (Chogtu 2016). Three studies included only those with at least moderate COPD (Balaguer 2016; Criner 2014; Mroz 2015). Criner 2014 and Mroz 2015 also required participants to have a smoking history of at least ten pack-years. Three studies included only patients with pulmonary hypertension secondary to COPD (Chogtu 2016; Lee 2009; Moosavi 2013). Three trials excluded participants with a history of hypercholesterolaemia or cardiovascular disease (Balaguer 2016; Criner 2014; Neukamm 2014).

Baseline characteristics of participants

Full baseline characteristics of the participants in each trial can be found in Characteristics of included studies. Mean age ranged from 61.4 to 72 years. Most participants were male (range 49% to 100%, median 73.4%). One trial did not give any information on gender, percentage of current smokers, or percentage predicted FEV_1 (Chogtu 2016). Another trial gave no information on smoking

history (Moosavi 2013). The remaining six trials all reported the percentage of current smokers, which ranged from 0% to 81%, with a median of 41.7%. Three trials reported pack-year history, with means ranging from 35 to 51.2 pack-years (Criner 2014; Neukamm 2014), and with medians of 30 to 40 years (Chogtu 2016). Seven trials reported percentage predicted FEV_1, with baseline means ranging from 41.5% to 59.6%.

Characteristics of the intervention

All studies compared moderate- or high-intensity statin therapy versus placebo (Stone 2014). Two studies used high-intensity statin therapy: one used atorvastatin 20 mg orally twice daily for six months (Moosavi 2013), and the other used atorvastatin 40 mg orally once daily for 12 weeks (Mroz 2015). The remaining six studies used moderate-intensity statin therapy: two used pravastatin 40 mg orally once daily for six months (Lee 2008; Lee 2009), one simvastatin 40 mg orally once daily for 12 to 36 months (Criner 2014), one simvastatin 40 mg orally once daily for 12 weeks (Balaguer 2016), and two rosuvastatin 10 mg orally once daily for 12 weeks (Chogtu 2016; Neukamm 2014). In all studies, the duration of the intervention was the same as the duration of the trial.

Outcomes and analysis structure

Two trials reported COPD exacerbations (Criner 2014; Neukamm 2014). Criner 2014 reported exacerbations in detail, including total number of exacerbations, number of exacerbations per person-year, time to first exacerbation, and severity of exacerbations. Neukamm 2014 reported frequency of total exacerbations and frequency of exacerbations requiring hospitalisation. Chogtu 2016 stated "median COPD exacerbations in rosuvastatin group were less compared to placebo group with a significant difference" but did not provide any other data. The remaining trials did not provide any information on exacerbations.

Two trials reported all-cause mortality (Criner 2014; Moosavi 2013). Criner 2014 was the only trial to report the specific causes of death and was the only trial to study COPD-specific mortality.

Lung function was reported in all eight trials.

Three studies reported quality of life measures. Both Criner 2014 and Mroz 2015 used the St. George's Respiratory Questionnaire (SGRQ). Chogtu 2016 used the Clinical COPD Questionnaire (CCQ).

Six trials looked at functional capacity. Lee 2008 and Lee 2009 reported this using the Naughton exercise stress test. The remaining four trials looked at six-minute walking distance (6MWD) (Balaguer 2016; Moosavi 2013; Mroz 2015; Neukamm 2014).

Five trials reported measures of airway inflammation. Lee 2008 and Neukamm 2014 reported post-treatment CRP and IL-6. Mroz 2015 reported post-treatment CRP. Balaguer 2016 reported post-treatment IL-6 and IL-8. Moosavi 2013 stated that "no significant difference in the CRP was found between the two groups at baseline or 6 months" but did not provide any data.

All of the trials mentioned adverse events. Criner 2014 listed the cause of serious non-fatal adverse events as number of events per person-year. Neukamm 2014 listed the total numbers and percentages of adverse events, serious adverse events, and suspected unexpected serious adverse reactions. Balaguer 2016 stated that "no participants reported adverse effects from simvastatin treatment". Chogtu 2016 stated that "rosuvastatin was well tolerated by patients. Common adverse drug reactions were gastric intolerance, myalgia, and elevated AST". Lee 2008 and Lee 2009 stated that "pravastatin was very well-tolerated by all patients, and none had any significant subjective side effects". Moosavi 2013 stated that "atorvastatin was very well-tolerated by all patients, and none of them had any significant subjective side effects". Mroz 2015 stated that "no side effects of the treatment were reported during the study period".

Studies at high risk of bias/those with high or uneven withdrawal rates

No studies were rated as having high risk of bias for either of the selection bias parameters. Mroz 2015 was rated as having high risk of bias for detection and performance bias. Balaguer 2016 and Lee 2009 were rated as having high risk for attrition bias. Reporting bias is reflected in the GRADE ratings of affected outcomes.

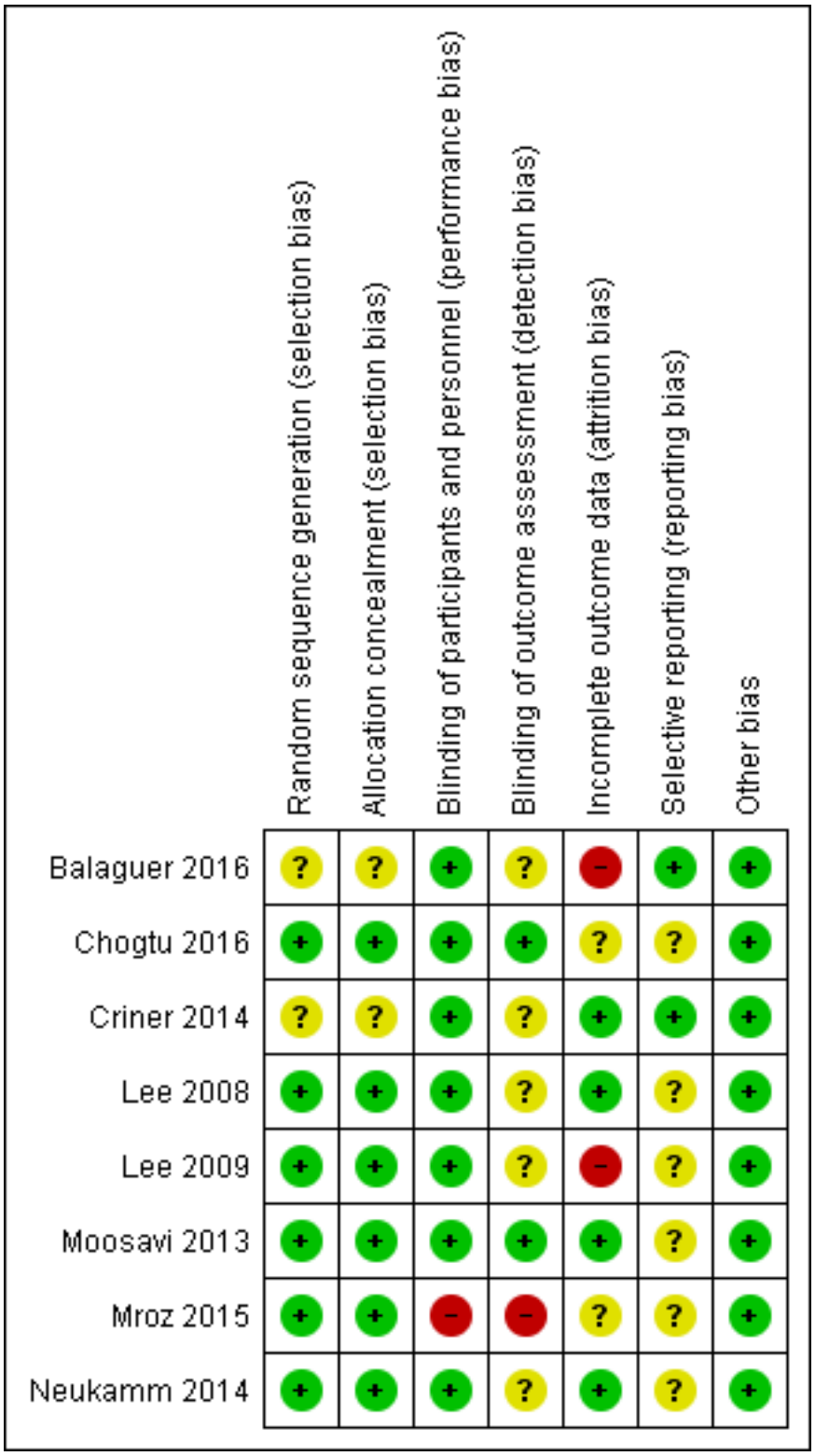
Excluded studies

We report reasons for exclusion of 17 studies in Characteristics of excluded studies. We excluded two studies as we were unable to identify published results despite apparent completion of the studies six and seven years ago. We contacted the study authors but received no response. Six trials were less than 12 weeks in duration. Two publications did not report randomised controlled trials. Five trials were not placebo controlled, and two trials did not use a standard or validated definition of COPD for its participants. Three reports were identified as duplicates at the full-text review stage, and two were additional reports on studies that were already excluded.

Risk of bias in included studies

Details of our risk of bias judgements can be found in Characteristics of included studies. An overview of our risk of bias judgements is outlined in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

None of the included studies were rated as having high risk of bias for either of the two allocation parameters (random sequence generation and allocation concealment). Six studies fully described methods of random sequence generation and allocation concealment and were rated as having low risk of bias (Chogtu 2016; Lee 2008; Lee 2009; Moosavi 2013; Mroz 2015; Neukamm 2014). Two studies did not provide details of random sequence

generation or allocation concealment and were therefore rated as having unclear risk of bias (Balaguer 2016; Criner 2014).

Blinding

One trial was rated as having high risk of performance and detection bias, as it explicitly stated that it was a single-blind study and that personnel were not blinded at any stage (Mroz 2015). The remaining seven trials were rated as having low risk of performance bias, as all were double-blind studies in which participants and investigators were blinded. Two trials were rated as having low risk of detection bias, as study authors stated that outcome assessors were blinded (Chogtu 2016; Moosavi 2013). The five remaining trials were rated as having unclear risk of detection bias, as none provided details of blinding of outcome assessors (Balaguer 2016; Criner 2014; Lee 2008; Lee 2009; Neukamm 2014).

Incomplete outcome data

Four studies were rated as having low risk of attrition bias, as the rate of dropouts was low and similar between groups (Criner 2014; Lee 2008; Moosavi 2013; Neukamm 2014). Three of these studies also used intention-to-treat analysis. Two studies were rated as having unclear risk of attrition bias (Chogtu 2016; Mroz 2015). Chogtu 2016 reported few postrandomisation dropouts but all occurred in the intervention group (6.25%). In Mroz 2015, only one person dropped out following randomisation; however given the small sample size, this represented 16.7% of the control group. It is unclear whether an intention-to-treat analysis was used in either of these trials. Two studies were rated as having high risk of attrition bias, as postrandomisation dropout rates were high (25% in each arm in Balaguer 2016, and 15.6% in the intervention arm and 21.2% in the placebo arm in Lee 2009). Study authors did not state whether an intention-to-treat analysis was performed.

Selective reporting

Six studies could be linked with their protocols. Two of these studies fully reported their outcomes and were rated as having low risk of reporting bias (Balaguer 2016; Criner 2014). One study reported its primary and secondary endpoints as specified in the protocol but did not provide any outcome data for its stated tertiary outcomes and therefore was rated as having unclear risk of bias (Neukamm 2014). Three studies did not clearly report all outcomes specified in the protocol and were also rated as having unclear risk of bias (Chogtu 2016; Moosavi 2013; Mroz 2015). Two studies could not be linked to their protocols (Lee 2008; Lee 2009). Neither showed clear evidence of selective outcome reporting, and they were rated as having unclear risk of bias.

We did not construct a funnel plot to assess reporting bias, as we included fewer than 10 studies in the review.

Other potential sources of bias

All trials were rated as having low risk of other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Statins compared to placebo as adjunct therapy for chronic obstructive pulmonary disease (COPD)

Primary outcomes

Number of COPD exacerbations

Criner 2014 was the only study to report the number of exacerbations in detail. The definition of exacerbations used was "an increase in severity or new onset of two or more respiratory symptoms (cough, sputum, wheezing, dyspnoea, or chest tightness) lasting for at least three days and requiring treatment with antibiotics or systemic glucocorticoids". Criner 2014 reported a total of 1982 acute COPD exacerbations in 877 participants (965 exacerbations among 430 in the intervention group, and 1017 exacerbations among 447 in the control group). There was no statistically significant difference between groups, with 1.36 ± 1.61 exacerbations per person-year in the intervention group and 1.39 ± 1.73 exacerbations per person-year in the control group (P = 0.54; mean difference (MD) -0.03, 95% confidence interval (CI) -0.25 to 0.19; Analysis 1.1). A total of 296 of 877 participants (33.8%) had three or more exacerbations during the study (141 (32.8%) among 430 in the intervention group and 155 (34.7%) among 447 in the control group; the difference was not significant). There was no clear difference in the median number of days to the first exacerbation (223 days (95% CI 195 to 275) in the intervention group and 231 days (95% CI 193 to 303) in the control group; P = 0.34).

Criner 2014 also reported the number of exacerbations categorised by severity: the number of exacerbations requiring hospitalisations was 205 in the intervention group and 240 in the control group. The mean number of exacerbations requiring hospitalisation per person-year was 0.31 (95% CI 0.24 to 0.38) in the intervention group and 0.31 (95% CI 0.23 to 0.38) in the control group (MD 0.00, 95% CI -0.10 to 0.10; Analysis 1.2). Age, gender, smoking status, GOLD stage, oxygen therapy, and location did not influence the mean exacerbation rates.

Neukamm 2014 was the other study that reported numbers of exacerbations. "Exacerbation" was defined according to current GOLD guidelines as "having an acute event characterised by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variation and leads to a change in medication". Researchers reported the frequency of exacerbations during the treatment period as 15% in the intervention group and 27% in the placebo group, but this difference was not statistically significant (P = 0.16). They reported exacerbations requiring hospitalisation during the treatment period as 4 (9%) in the intervention group and 3 (6%) in the control group. It is unclear whether these numbers represent events or people.

All-cause mortality

Statin treatment had no effect on all-cause mortality, which was reported in two trials (Criner 2014; Neukamm 2014). No statistically significant difference was seen between groups (odds ratio (OR) 1.03, 95% CI 0.61 to 1.74; I^2 = 0%, P = 0.91; 2 trials, 952 participants; Analysis 1.3), with no heterogeneity. A wide confidence interval suggests uncertainty about the precision of the result. This evidence was downgraded to low quality given the unclear risk of selection, detection, and reporting bias and the imprecision of trial results.

COPD-specific mortality

COPD-specific mortality was described in one trial (Criner 2014), which reported six deaths due to acute exacerbation in the intervention group (1.4%) and five in the placebo group (1.1%) (OR 1.25, 95% CI 0.38 to 4.13, 1 trial, 877 participants; Analysis 1.4). This result had a very wide confidence interval, which again suggests uncertainty about the precision of the result.

Quality of life

Quality of life measures were reported in three studies, but we were unable to pool the data, given the way they were reported. Both Criner 2014 and Mroz 2015 used the SGRQ, and Chogtu 2016 used the CCQ. Criner 2014 reported median change from baseline score and found no significant improvement in any of the domains of the SGRQ (total SGRQ median change from baseline -0.18 (10th, 90th percentiles -11.01, 9.7) in the intervention group and 0.02 (10th, 90th percentiles -12.47, 10.73) in the control group; P = 0.3783) nor on the Short Form Health Survey (SF-36), with statin treatment. Mroz 2015 found that the median SGRQ score decreased significantly (P = 0.012) from 54.5 to 42 in the intervention group and noted no change in the control group (68 to 70 points; non-significant) but did not provide a between-group analysis. Chogtu 2016 found that mean change in CCQ total score (P = 0.96) and symptom score (P = 0.12) was not significant at 12 weeks but did not provide further data.

Functional capacity

Six studies reported functional capacity. Lee 2008 and Lee 2009 reported the Naughton exercise stress test, and four trials reported 6MWD (Balaguer 2016; Moosavi 2013; Mroz 2015; Neukamm 2014). Neukamm 2014 simply stated that there was no difference in the 6MWD between the two groups but provided no data. The remaining three trials were included in the meta-analysis, which showed no statistically significant difference between the two groups (MD 1.79, 95% CI -52.51 to 56.09; I^2 = 0%, P = 0.95; 3 trials, 71 participants). This result has wide confidence intervals, which exceed the minimum clinically important distance for the 6MWD, suggesting uncertainty about the precision of the result. This analysis includes unpublished data from Mroz 2015. A baseline imbalance between the two groups was evident in Mroz 2015, with baseline 6MWD of 404 m (standard deviation (SD) 138.31 m) in the control group and 367 m (SD 81.69) in the intervention group. A sensitivity analysis excluding Mroz 2015 showed similar results (MD 5.33, 95% CI -54.34 to 64.99; I^2 = 0%, P = 0.86; 2 trials, 54 participants).

Lung function including spirometric measurement

Five studies reported FEV_1 (% predicted) in a way that could be included in the meta-analysis. After corresponding with study authors, we included unpublished data from Mroz 2015. No statistically significant difference was evident between intervention and control groups (MD 1.18, 95% CI -2.6- to 4.97; I^2 = 0%, P = 0.54; 6 trials, 325 participants; Analysis 1.6). A sensitivity analysis excluding Mroz 2015 showed similar results (MD 0.52, 95% CI -3.36 to 4.40; I^2 = 0%, P=0.54; 5 trials, 308 participants). The same six studies also reported FEV_1/FVC (%) in a way that could be included in the meta-analysis. Results showed slightly higher FEV_1/FVC in the intervention group than in the placebo group (MD 2.66, 95% CI 0.12 to 5.2; I^2 = 0%, P = 0.04; 6 trials, 325 participants; Analysis 1.7). A sensitivity analysis excluding Lee 2009, which was at high risk of attrition bias, and Mroz 2015, which was at high risk of performance and detection bias, showed no statistically significant difference between groups for either FEV_1 (% predicted) (MD -0.06, 95% CI -4.35 to 4.22; I^2 = 0%, P = 0.98; 4 trials, 255 participants) or FEV_1/FVC (%) (MD 2.05, 95% CI -0.87 to -4.97; I^2 = 0%, P = 0.17; 4 trials, 255 participants). Again, Mroz 2015 showed a baseline imbalance between the two groups, with baseline FEV_1 (% predicted) of 50.4 (SD 11.55) in the control group and 59.58 (SD 20.43) in the intervention group.

Airway inflammation

Five trials reported measures of airway inflammation. Balaguer 2016 reported post-treatment IL-6 and IL-8 as mean and standard deviations. Lee 2008 reported post-treatment CRP and IL-6 as mean values with standard deviations. Mroz 2015 reported post-treatment CRP in graph form as median values with 25th and 75th percentiles. Neukamm 2014 reported post-treatment CRP and IL-6 as median values with 25th and 75th percentiles. They found a significant reduction in high-sensitivity CRP level (20% vs 11%; P = 0.017) and a significant attenuation of the rise in the level of IL-6 (8% vs 30%; P = 0.028) in the intervention group compared with the control group. Moosavi 2013 stated that "no significant difference in the CRP was found between the two groups at baseline or 6 months" but did not provide any figures. In correspondence with study authors, Mroz 2015 provided mean + SD for CRP and Moosavi 2013 provided figures for positive and negative CRP. Three studies were included in the meta-analysis of CRP, which showed a significant slight reduction in CRP in the intervention group (MD -1.03, 95% CI -1.95 to -0.11; I^2 = 0%, P = 0.03; 3 trials, 142 participants; Analysis 1.8) (Balaguer 2016; Lee 2008; Mroz 2015). Again there was a baseline imbalance between the two groups in Mroz 2015, with baseline CRP (mg/L) of 4.76 (SD 7.99) in the control group and 9.33 (SD 6.32) in the intervention group. A sensitivity analysis excluding Mroz 2015 showed similar results (MD -1.05, 95% CI -1.98 to -0.12; I^2 = 31%, P = 0.03; 2 trials, 125 participants). Two studies were included in the meta-analysis of IL-6, which showed a significant reduction in IL-6 in the intervention group (MD -2.11, 95% CI -2.65 to -1.56; I^2 = 0%, P ≤ 0.00001; 2 trials, 125 participants; Analysis 1.9) (Balaguer 2016; Lee 2008).

Adverse events

Criner 2014 reported rates of serious non-fatal adverse events and indicated that rates of all non-fatal adverse events (the number of serious adverse events per person-year) were similar in both groups (0.63 ± 1.56 events (intervention group) and 0.62 ± 1.48 events (control group)). This finding was not statistically significant, with P > 0.20 for all comparisons, except for non-fatal serious adverse events involving the gastrointestinal tract, which were significantly more frequent in the intervention groups (in 30 patients (0.05 events per person-year) vs 17 patients (0.02 events per person-year); P = 0.02). Neukamm 2014 lists the total numbers and percentages of adverse events (12 (26%) in the intervention group and 21 (43%) in the control group) and serious adverse events (4 (9%) in the intervention group and 3 (6%) in the control group). Study authors state that there were no suspected unexpected serious adverse reactions in either group. Balaguer 2016 states that "no participants reported adverse effects from simvastatin treatment"; however study authors also state that "one patient in intervention group not included in final analysis had a severe exacerbation of COPD requiring ICU admission, one patient in the intervention group had a severe adverse event and wasn't included

in the final analysis, one patient in control group not included in final analysis died from CAP". Chogtu 2016 stated that "rosuvastatin was well tolerated by patients. Common adverse drug reactions were gastric intolerance, myalgia, and elevated AST. The increase in blood sugar was seen in three patients in rosuvastatin group and two in placebo group. Pedal edema was seen in two patients in the placebo group who were on calcium channel blockers. Seventeen per cent of patients in rosuvastatin group had elevated AST at three months, which reversed after one month of stopping drug. Two patients had elevated CPK at three months, with associated muscle pain, which was < three times upper limit of normal (ULN) and reversed on stoppage of medicine". Lee 2008 and Lee 2009 stated that "pravastatin was very well-tolerated by all patients, and none had any significant subjective side effects". Moosavi 2013 stated that "atorvastatin was very well-tolerated by all patients, and none of them had any significant subjective side effects, such as abnormal levels of liver and muscle enzymes". Mroz 2015 stated that "no side effects of the treatment were reported during the study period".

DISCUSSION

Summary of main results

Eight studies including 1323 participants with chronic obstructive pulmonary disease (COPD) were included in the review. Participants had a mean age of 61.4 to 72 years, and most were male (median 73.4%). Mean baseline forced expiratory volume in one second (FEV_1) ranged from 41.5% to 59.6% predicted. All studies compared moderate- or high-intensity statin therapy versus placebo (Stone 2014). The duration of the intervention ranged from 12 weeks to 36 months. Statin treatment did not improve the number or severity of exacerbations, mortality, lung function, functional capacity, or quality of life. It was associated with a small reduction in C-reactive protein (CRP) and interleukin-6 (IL-6). Many findings, including our primary outcomes of all-cause and COPD-specific mortality, had wide confidence intervals, suggesting uncertainty about the precision of the results. Statins were generally well tolerated with no increased incidence of adverse events in the intervention groups other than an increase in non-fatal serious adverse events involving the GI tract in one trial.

Overall completeness and applicability of evidence

Most participants included in this review (877/1323) came from one large randomised controlled trial (RCT) (Criner 2014). This RCT (mean follow-up 641 ± 354 days in the intervention group, 639 ± 351 days in the control group) was also much longer in duration than the other trials, in which follow-up ranged from 12 weeks to six months. This trial looked at a highly selected group of participants with COPD. Three trials - Balaguer 2016; Criner 2014; Neukamm 2014 - including the two trials that looked at the primary outcomes of number of exacerbations and COPD-specific mortality excluded participants with a history of hypercholesterolaemia or cardiovascular disease (Criner 2014; Neukamm 2014). This is not representative of the majority of the population with COPD, who have multiple comorbidities, particularly cardiovascular disease. In fact, it is difficult for investigators to find potential participants for these trials, given the high incidence of cardiovascular disease and cardiovascular disease risk factors in people with COPD (Chen 2015). Also, most participants had moderate to severe COPD, making the results less applicable to those with mild COPD. Trials were conducted across many different continents, which does make the results more applicable to the international population.

Certainty of the evidence

We GRADED the primary outcomes as having moderate- or low-certainty evidence (Summary of findings for the main comparison). Reasons for downgrading of evidence were risk of bias and imprecision. We noted unclear risk of detection and selection bias in the trial that reported the number of exacerbations and COPD-specific mortality. We detected unclear risk of selection, detection, and reporting bias in trials reporting all-cause mortality. Researchers reported a small number of events with wide confidence intervals in both COPD-specific and all-cause mortality. Follow-up in these trials ranged from 12 weeks to 36 months, and we noted a vast difference in sample size among trials, with the number of participants ranging from 18 to 885. Four of our outcomes - number of exacerbations, COPD-specific mortality, quality of life, and adverse events - were not included in the meta-analysis, as they were reported in a usable way by only one trial.

One study included in the meta-analysis was single-blind and was at high risk of performance and detection bias. Two trials were at high risk of attrition bias. When sensitivity analyses were performed while removing trials at high risk of bias, this did not change the conclusions of the review.

Two studies that were identified as suitable for inclusion in the review had to be excluded due to lack of available data, as no results were available, although trials were completed six and seven years ago. This raises concerns of possible publication bias.

Potential biases in the review process

We performed a thorough search for all relevant published and unpublished data by searching clinical trial registries and checking reference lists, in addition to searching several electronic databases. Given the small number of studies included in the review, we were unable to create a funnel plot to assess publication bias. We contacted the authors of Lee 2008 and Lee 2009 before including these in the review, as they had a number of similarities, and we were concerned that they might be multiple reports of the same study. Study authors confirmed that these were different studies with different participants. We contacted the investigators of all included studies to obtain further information on study characteristics and outcomes. We received data from only two of the investigators (Moosavi 2013; Mroz 2015). We also contacted the authors of the two studies that we excluded due to lack of available data but received no reply. Given the high rate of reporting bias, unavailable data from these eight studies could potentially change the outcome of the review if this information should be included in future reviews. We could not perform all planned subgroup and sensitivity analyses, given the small number of included studies.

Agreements and disagreements with other studies or reviews

We found one systematic review and meta-analysis of RCTs looking at the effects of statins for COPD (Zhang 2017). The Zhang review included three more trials than this Cochrane Review because it included trials with a duration of intervention less than 12 weeks. Both reviews show no difference in all-cause mortality. The Zhang review showed improvement in quality of life, six-minute walk distance, and FEV_1/forced vital capacity (FVC). Those review

authors did not see a difference in CRP, whereas our review showed a statistically significant reduction in both CRP and IL-6. Differences in findings between the two reviews may be explained by their inclusion of three trials with a very short duration of intervention (four to eight weeks). Researchers also found no benefit among participants from studies that excluded people with existing or potential cardiovascular disease.

A meta-analysis that included both cohort studies and RCTs showed that statins were associated with a significant reduction in the risk ratio (RR) of all-cause mortality (RR 0.72, 95% confidence interval (CI) 0.63 to 0.84; P < 0.01), with considerable heterogeneity (I^2 = 86.8%) (Lu 2019). This meta-analysis did not include either of the RCTs included in our review and reported all-cause mortality. Review authors showed a reduction in the risk ratio of COPD-specific mortality and acute exacerbations of COPD but did not provide any data on the significance of these results. They also showed improvement in lung function and in six-minute walk distance and a reduction in CRP and IL-6. Review authors did not comment on the quality of the studies included in the meta-analysis. Another systematic review, which included one RCT (Lee 2008), along with observational studies, found that statins may reduce morbidity in COPD (Dobler 2009).

Several systematic reviews and meta-analyses of observational studies showed an association between statin use and decreased mortality and exacerbations in people with COPD. Li 2017 showed a significant reduction in the hazard ratio (HR) of all-cause mortality (HR 0.65, 95% CI 0.57 to 0.74; P < 0.01), with substantial heterogeneity (I^2 = 64%). There was no significant reduction in COPD-specific mortality. Review authors also showed a significantly reduced risk of exacerbations (HR 0.58, 95% CI 0.48 to 0.72; P < 0.01), with considerable heterogeneity (I^2 = 83%), including exacerbations requiring hospitalisation (HR 0.75, 95% CI 0.67 to 0.83; P = 0.03), with substantial heterogeneity (I^2 = 64%). Subgroup analyses for all-cause mortality show that effect size was reduced in the prospective studies and in the higher-quality studies. Review authors did not adjust for confounders in their analysis, and some of the included studies did not control for confounders. Cao 2015 showed that statins significantly reduced all-cause mortality (HR 0.62, 95% CI 0.52 to 0.73; P = 0.001), with substantial heterogeneity (I^2 = 70.1%). There was no significant reduction in COPD-specific mortality. Review authors also showed a significantly reduced risk of exacerbations (HR 0.64, 95% CI 0.55 to 0.75; P = 0.011), with substantial heterogeneity (I^2 = 66.1%). Horita 2014 found that statins may significantly reduce all-cause mortality (HR 0.81, 95% CI 0.75 to 0.86; P < 0.001), with moderate heterogeneity (I^2 = 52%).

Our review goes against these results, as we have not demonstrated that statins result in a difference in morbidity or mortality among people with COPD. A large cohort study indicates that statin use may be associated with reduced risk of exacerbations of COPD only in patients with coexisting cardiovascular disease (Ingebrigtsen 2015). This cohort of patients was not included in the majority of trials that analysed our outcomes; this may be why disagreement is apparent between the findings of this review and of observational studies done in a more general population with COPD. The high level of heterogeneity in these reviews reflects the variation in included studies. Most of the trials in our review were short (six months or less in duration) and therefore were not designed to demonstrate the long-term benefits of statins, unlike observational studies, which tend to follow participants for longer periods.

AUTHORS' CONCLUSIONS

Implications for practice

This review did not show any clear clinical benefit or harm in prescribing statins for patients with COPD for whom statins were not otherwise indicated, but many results were uncertain. We did see a significant reduction in CRP and IL-6 among patients who received statins, but this did not translate into improved clinical outcomes.

Implications for research

Further long-term RCTs on this topic are needed - ideally studies that include participants who are more representative of the real-world cohort of COPD patients, many of whom have multiple comorbidities including cardiovascular disease. Given the established role of statins in the management of people with cardiovascular disease, it is unlikely there will ever be the clinical equipoise to undertake such an RCT in this cohort of people. Future studies would need to be powered to detect whether patients in whom statins reduce inflammatory markers are less likely to suffer exacerbations and hospitalisations. We included trials of 12 weeks or longer, as we believe this is the minimum time necessary to ascertain whether statins had any effect on outcomes among people with COPD. Future trials should be at least six months in duration to assess whether a reduction in inflammatory markers is associated with a clinical effect (EMA 2012).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Balaguer 2016

Methods	**Aim:** to further explore the pleiotropic effects of statins in COPD, we designed a randomised pilot clinical trial to investigate comprehensively their potential effects on (1) lung function, (2) systemic and pulmonary inflammation, (3) endothelial function and growth factors involved in vascular homeostasis (erythropoietin (Epo) and vascular endothelial growth factor (VEGF)), and (4) serum uric acid (UA) **Design:** pilot, double-blind, randomised, placebo-controlled clinical trial **Duration:** 12 weeks **Location:** Spain
Participants	**Population:** 24 participants were randomly assigned to receive simvastatin 40 mg daily (12) and placebo (12). 18 were included in the primary analysis (9 simvastatin and 9 placebo) **Baseline characteristics:** Mean age (years): simvastatin 69.3, placebo 66.4 % male: simvastatin 88.9, placebo 77.8 % FEV_1 predicted: simvastatin 53.4, placebo 48.2 (post bronchodilator) % baseline severity of COPD: simvastatin: GOLD A 44.4, GOLD B 11.1, GOLD C 33.3, GOLD D 11.1; placebo: GOLD A 33.3, GOLD B 11.1, GOLD C 33.3, GOLD D 22.2 % current smokers: none **Inclusion criteria:** former smokers with stable COPD and moderate to severe airflow limitation **Exclusion criteria:** hospitalisation or treatment changes within the previous 12 weeks, other concomitant chronic inflammatory disease, history of active coronary artery disease, cerebrovascular or peripheral vascular disease, a fasting level of total cholesterol > 220 mg/dL, had received statin therapy before
Interventions	Simvastatin 40 mg orally once daily **Comparison:** placebo **Concomitant medications:** LA-b2: simvastatin 8 (88.9%), placebo 7 (77.8%) LA anticholinergic: simvastatin 7 (77.8%), placebo 6 (66.7%) Inhaled corticosteroids: simvastatin 6 (66.7%), placebo 7 (77.8%) SA-b2: simvastatin 4 (44.4%), placebo 2 (22.2%) SA anticholinergic: simvastatin 1 (11.1%), placebo 2 (22.2%)

Balaguer 2016 *(Continued)*

	ASA: simvastatin 2 (22.2%), placebo 2 (22.2%) ACEI: simvastatin 2 (22.2%), placebo 3 (33.3%) ARBs: simvastatin 2 (22.2%), placebo 2 (22.2%) Diuretics: simvastatin 2 (22.2%), placebo 2 (22.2%)
Outcomes	**Lung function:** FEV_1, FVC, DLCO, 6MWD **Systemic and pulmonary inflammation:** sputum and blood IL-6 and IL-8, blood leukocytes, neutrophils, CRP, uric acid **Adverse events** **Others:** endothelial function (vascular stiffness), circulating vascular growth factors
Notes	**Funding:** this study was funded by SEPAR 2006. All funds were used to carry out all laboratory analyses and ELISAs **Possible conflicts of interest:** study authors declare that they have no competing interests **Study number:** NCT02070133 **Definitions:** COPD was defined using GOLD criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information given on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Not stated how attrition bias was accounted for; high dropout rate (25%) in both groups
Selective reporting (reporting bias)	Low risk	All stated outcomes reported
Other bias	Low risk	None identified

Chogtu 2016

Methods	**Aim:** to evaluate the effects of rosuvastatin on pulmonary function and echocardiogram in patients with COPD and related secondary PH as compared to placebo; to evaluate the effects of rosuvastatin on exercise capacity and quality of life in COPD patients

Chogtu 2016 *(Continued)*

	Design: interventional, randomised, prospective, double-blind, placebo-controlled, parallel study **Duration:** 12 weeks **Location:** India
Participants	**Population:** 62 patients were randomised into rosuvastatin (32) and placebo (30) groups. 60 were included in the primary analysis (30 rosuvastatin and 30 placebo) **Baseline characteristics:** Mean age (years): rosuvastatin 61.4, placebo 65.9 % male: not stated % FEV_1 predicted: not stated % baseline severity of COPD: not stated % current smokers: not stated **Inclusion criteria:** patients of either gender between 40 and 80 years of age; patients with diagnosis of COPD as per ATS standards and GOLD guidelines, with routine echocardiography showing mild to severe PAH (30 mmHg < systolic pulmonary artery pressure (sPAP) > 75 mmHg); patients who were stable for at least 2 weeks **Exclusion criteria:** patients with asthma, periodic wheezing, bronchiectasis, pneumothorax, pleural effusion, or pulmonary embolism liner disorder; patients with cardiac disorders such as arrhythmias or unstable angina pectoris; patients on lipid-lowering agents; patients unable to perform 6MWT; pregnant/lactating women
Interventions	Rosuvastatin 10 mg orally once daily **Comparison:** placebo **Concomitant medications:** not stated
Outcomes	**Lung function:** FEV_1, FVC, PEFR **Fuctional capacity:** 6-minute walk test **Quality of life:** CCQ **Adverse events** **Others:** echocardiography measurements
Notes	**Funding:** nil **Possible conflicts of interest:** no conflicts of interest **Study number:** CTRI/2012/12/003223 **Definitions:** COPD was defined using ATS and GOLD criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out using a pre-established computer-based sequence

Chogtu 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomisation was carried out using a pre-established computer-based sequence; sequentially numbered, sealed, opaque envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The randomised code number was noted in the clinical file of each patient and in a separate register to identify the patient. Rug kits were labelled with a patient-specific randomisation code to blind the investigator. Patients were maintained on treatment in a double-blind fashion for 3 months, and the treatment code was opened when the last patient completed his follow-up period
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators who carried out the endpoint assessments - QOL questionnaire scoring, echocardiogram, PFT, and 6MWT - were also blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Low number of postrandomisation dropouts, but all occurred in the intervention group (6.25%). Unclear whether intention-to-treat analysis was used
Selective reporting (reporting bias)	Unclear risk	Reported outcomes stated in protocol; outcomes incompletely reported; subgroup analysis reported for one outcome only
Other bias	Low risk	None identified

Criner 2014

Methods	**Aim:** to examine the effects of daily treatment with simvastatin for at least 12 months (range 12 to 36) on the rate of exacerbation among patients with moderate to severe COPD and no other indications for statin treatment **Design:** randomised, double-blind, parallel-group, placebo-controlled multi-centre trial **Duration:** 12 to 36 months **Location:** 45 centres in Canada and the USA
Participants	**Population:** 885 participants were randomly assigned to receive simvastatin 40 mg daily (N = 433) and placebo (N = 453). 877 were included in the primary analysis (430 simvastatin and 447 placebo) **Baseline characteristics:** Mean age (years): simvastatin 62.2, placebo 62.3 % male: simvastatin 57.5, placebo 55.1 % FEV_1 predicted: simvastatin 41.5, placebo 41.6 (post bronchodilator) % baseline severity of COPD: simvastatin: GOLD 2 - 33, GOLD 3 - 32.3, GOLD 4 - 33; placebo: GOLD 2 - 36.3, GOLD 3 - 34, GOLD 4 - 31.4 % current smokers: simvastatin 30.7, placebo 31.6 **Inclusion criteria:** 40 to 80 years of age, at least moderate COPD, smoking history of 10 or more pack-years, using supplemental O_2 or having a history of receiving a course of systemic corticosteroids for respiratory, visiting an emergency department or being hospitalised for a COPD exacerbation within the past year, free of coronary artery or peripheral vascular disease **Exclusion criteria:** patients who are on statins or should be on statins based on established risk stratification; asthma; acute exacerbation in the previous 4 weeks; bronchiectasis; participants using niacin, azole antifungals, fibric acid derivatives, erythromycin, clarithromycin, telithromycin, diltiazem, am-

Criner 2014 *(Continued)*

	lodipine, ranolazine, HIV protease inhibitors, amiodarone, gemfibrozil, cyclosporine, verapamil, danazol, nefazodone, and red yeast rice extracts; active liver disease; alcoholism; hypersensitivity to statins. Subsequently, patients with diabetes and those on amlodipine or high-dose verapamil were withdrawn from the study
Interventions	Simvastatin 40 mg orally once daily **Comparison:** placebo **Concomitant medications:** patients were on ICS, LAMA, and LABA in various combinations
Outcomes	**COPD exacerbations:** exacerbation rate, time to first exacerbation, exacerbation severity **All-cause mortality** **COPD-specific mortality** **Lung function:** FEV_1, FVC **Quality of life:** SGRQ, SF-36 **Adverse events:** non-fatal serious adverse events, fatalities **Others:** lipid levels, number of acute cardiovascular events
Notes	**Funding:** NHLBI and Canadian Institutes of Health Research **Possible conflicts of interest:** Dr. Bailey reports being a consultant to DLA Piper Law Firm re: Chantix risks and benefits. Multiple study authors receive grant support and personal fees from pharmaceutical companies outside the submitted work **Study number:** NCT01061671 **Definitions:** COPD was defined using GOLD 2007 criteria; an exacerbation was defined as an increase in severity or new onset of 2 or more respiratory symptoms (cough, sputum, wheezing, dyspnoea, or chest tightness) lasting at least 3 days and requiring treatment with antibiotics or systemic glucocorticoids

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomly assigned in a 1:1 ratio; method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study - placebo medication identical to simvastatin in taste, smell, consistency, and appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinding of outcome assessment provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Postrandomisation dropouts similar and below 20% in each group (simvastatin 19 (4.4%); placebo 25 (5.5%)). Intention-to-treat analysis performed

Criner 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol are reported in the trial
Other bias	Low risk	None identified

Lee 2008

Methods	**Aim:** to determine whether pravastatin administration is effective in improving exercise capacity in patients with COPD, and whether baseline or serial changes in hs-CRP over time are associated with corresponding changes in exercise capacity **Design:** randomised, placebo-controlled, double-blind, parallel-group clinical trial **Duration:** 6 months (plus run-in period of 2 weeks) **Location:** Taiwan
Participants	**Population:** 125 participants were randomly assigned to pravastatin (62) or placebo (63). 107 participants completed the study (53 pravastatin and 54 placebo) **Basline characteristics:** Mean age (years): pravastatin 70 (± 8), placebo 71 (± 6) % male: pravastatin 79, placebo 73 % current smokers: pravastatin 81, placebo 76 % FEV_1 predicted: pravastatin 51, placebo 56 **Inclusion criteria:** stable COPD (ATS criteria) for > 3 months, 40 to 80 years of age **Exclusion criteria:** acute exacerbations of COPD, any active infection, renal disease (serum creatinine concentration 1.5 mg/dL or 133 mol/L) for 3 months before entry into the study. To exclude patients with asthma, people with 1 of the following features were excluded from the study: history of perennial allergic rhinitis, periodic wheezing, pulmonary embolism, improvement in FEV_1 of 15% from predicted values after inhalation of a bronchodilator; before they were enrolled in this study, no patients had ever received cholesterol-lowering agents
Interventions	Pravastatin 40 mg orally once daily for 6 months **Comparison:** placebo **Concomitant medications:** All medications for COPD were kept constant throughout the study. Other concomitant medications considered necessary for each patient's well-being could be given at the investigator's discretion Steroid dependent: pravastatin 30 (48%), placebo 33 (52%) Theophylline: pravastatin 53 (86%), placebo 54 (86%)
Outcomes	**Lung function:** FEV_1, FVC **Functional capacity:** Naughton exercise stress test, Borg dyspnoea scale **Airway inflammation:** CRP, IL-6 **Adverse events:** no significant subjective side effects **Others:** serum lipids

Lee 2008 *(Continued)*

Notes	**Funding:** grants CMFHT9501, CMFHR9502, CMFHR9503, and CM-TMU9601 from the Chi-Mei Medical Center, Tainan, Taiwan; grant NSC 95-2314-B-384-009 from the National Science Council, Taiwan, Republic of China. Pravastatin was in part a generous gift from Sankyo Company, Ltd., Tokyo, Japan **Possible conflicts of interest:** not stated **Study number:** PMID: 18312772 **Definitions:** COPD was defined using ATS criteria (FEV_1 < 80% predicted values and FEV_1/FVC ratio < 70%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each patient received a randomised code number, according to which the study assistant supplied the study drug
Allocation concealment (selection bias)	Low risk	Special drug packaging was used to maintain blindness of treatment; a sealed envelope, with information on treatment allocation, was kept in the clinical file of each patient
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinding of outcome assessment provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Postrandomisation dropouts were similar and below 20% in both groups (pravastatin 9 (14.5%), placebo 9 (14.3%))
Selective reporting (reporting bias)	Unclear risk	Trial protocol against which to check all prespecified outcomes could not be located; all outcomes stated in the report were reported
Other bias	Low risk	None identified

Lee 2009

Methods	**Design:** randomised, double-blind, parallel-group, placebo-controlled, single-centre trial **Duration:** 6 months (plus 2-week run-in period) **Location:** Taiwan
Participants	**Population:** 65 participants were randomly assigned to pravastatin (32) or placebo (33). 53 participants completed the study (27 pravastatin and 26 placebo) **Baseline characteristics:** Mean age (years): pravastatin 71, placebo 72 % male: pravastatin 74.1, placebo 73.1 % FEV_1: pravastatin 55.9, placebo 57.4

Lee 2009 *(Continued)*

	% current smokers: pravastatin 81, placebo 81 **Inclusion criteria:** COPD (ATS criteria); stable for at least 3 months; 40 to 80 years of age; routine echo showed pulmonary hypertension **Exclusion criteria:** acute exacerbations of COPD, any active infection, or renal disease (serum creatinine concentration 1.5 mg/dL or 133 µmol/L) for at least 3 months before entry into the study; asthma; periodic wheezing; pulmonary embolism; history of perennial allergic rhinitis; improvement in FEV_1 > 15% from predicted values after inhalation of a bronchodilator. No patients had received cholesterol-lowering agents before they were enrolled in the study
Interventions	Pravastatin 40 mg orally once daily for 6 months **Comparison:** placebo **Concomitant medications:** all medication for COPD was kept constant throughout the study. Other concomitant medication considered necessary for the well-being of each patient could be given at the investigator's discretion Steroid dependent: pravastatin 16 (59%), placebo 14 (54%) Theophylline: pravastatin 25 (93%), placebo 26 (96%) Beta2-adrenoreceptor agonist: pravastatin 20 (74%), placebo 21 (81%) Anticholinergics: pravastatin 10 (37%), placebo 8 (31%) Nocturnal oxygen supplementation: pravastatin 1 (4%), placebo 1 (4%)
Outcomes	**Lung function:** FEV_1, FVC, TLC, IC **Functional capacity:** Naughton exercise stress test, Borg dyspnoea scale **Airway inflammation:** plasma and urinary ET-1 **Adverse events:** no significant subjective side effects **Others:** changes in cardiac index and systolic pulmonary artery pressure measured on echocardiogram
Notes	**Funding:** Chi-Mei Medical Center (grant numbers CMFHT9501, CMFHR9702, 97CM-TMU01); Department of Health, Taiwan, Republic of China (DOH97-TD-I-111-TM001). Pravastatin was, in part, a generous gift from Sankyo Co. Ltd. (Tokyo, Japan) **Possible conflicts of interest:** none stated **Study number:** PMID: 18831711 **Definitions:** COPD was defined by ATS criteria (FEV_1 < 80% of predicted values and FEV_1/FVC ratio < 70%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each patient received a randomised code number, according to which the study assistant supplied the study drug
Allocation concealment (selection bias)	Low risk	Special drug packaging was used to maintain blindness to treatment; a sealed envelope, with information on the treatment allocated, was kept in the clinical file of each patient

Lee 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinding of outcome assessment were provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Postrandomisation dropouts were slightly higher and above 20% in the placebo group (pravastatin 5 (15.6%), placebo 7 (21.2%)). It is not stated whether an intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Trial protocol against which to check all prespecified outcomes could not be located. Most outcomes measured were surrogate outcomes
Other bias	Low risk	None identified

Moosavi 2013

Methods	**Aim:** to investigate the effects of atorvastatin on reducing pulmonary hypertension of patients with COPD **Design:** randomised, triple-blind, parallel-group, controlled trial **Duration:** 6 months **Location:** Iran
Participants	**Population:** 45 patients were randomly assigned to atorvastatin (24) or placebo (21). 36 patients completed the study (19 atorvastatin and 17 placebo) **Baseline characteristics:** Mean age (years): atorvastatin 65, placebo 68 % male: atorvastatin 62.5, placebo 61.9 % FEV_1: atorvastatin 44, placebo 43.5 **Inclusion criteria:** systolic pulmonary hypertension > 40 mmHg; no history of prostanoids, statins, endothelin antagonists, and phosphodiesterases; able to do 6MWT; obstructive pattern in PFTs and functional class II, III (NYHA); over 18 years of age **Exclusion criteria:** PAH with underlying cause other than COPD; LDL < 70 mg/dL; ALT or AST > 3x upper limit of normal
Interventions	Atorvastatin 20 mg orally twice daily for 6 months **Comparison:** placebo **Concomitant medications:** not specified
Outcomes	**All-cause mortality** **Lung function:** FEV_1, FVC **Functional capacity:** 6MWD **Airway inflammation:** CRP

Moosavi 2013 *(Continued)*

	Adverse events: no significant subjective side effects
	Others: systemic pulmonary arterial hypertension, cardiac output, right ventricular size, oxidised LDL levels, patients' signs and symptoms
Notes	**Funding:** Tehran University of Medical Sciences
	Possible conflicts of interest: not stated
	Study number: IRCT201108257411N1
	Definitions: COPD was defined using ATS criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation software and block randomisation method were used to determine randomised sequence
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes were used for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, research analyser, and outcome assessors (other than the data co-ordinating person) were blind until the study was completed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, research analyser, and outcome assessors (other than the data co-ordinating person) were blind until the study was completed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Postrandomisation dropouts were similar and below 20% in both groups (atorvastatin 4 (16.7%), placebo 3 (14.3%)). An intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Not all outcomes specified in the protocol were reported
Other bias	Low risk	None identified

Mroz 2015

Methods	**Aim:** to determine whether statins have an anti-inflammatory effect on the lungs of COPD patients
	Design: randomised, single-blind, placebo-controlled, parallel-group pilot study
	Duration: 12 weeks (plus 4-week washout period)
	Location: Poland
Participants	**Population:** 18 patients randomly assigned to atorvastatin (12) or placebo (6). 17 patients completed the study (12 atorvastatin and 5 placebo)
	Baseline characteristics:
	Mean age (years): atorvastatin 64.6, placebo 68.4
	% male: atorvastatin 91.7, placebo 100

Mroz 2015 *(Continued)*

	% FEV_1: atorvastatin 59.6, placebo 50.4 % current smokers: atorvastatin 41.7, placebo 40 **Inclusion criteria:** male and female adults aged ≥ 40 years who have signed an informed consent form before initiation of any study-related procedure; patients with moderate to very severe stable COPD (stage II to IV) according to GOLD guidelines; patients with postbronchodilator FEV_1 < 80% of predicted normal and a postbronchodilator FEV_1/FVC < 0.70 at visit 1; current smokers or ex-smokers with a smoking history of at least 10 pack-years **Exclusion criteria:** pregnant or nursing (lactating) women; women of childbearing potential, unless they are using effective methods of contraception during dosing of study treatment; patients with a clinically significant abnormality at visit 1; patients with a clinically relevant laboratory abnormality at visit 1; patients with a history of malignancy of any organ system (including lung cancer); patients contraindicated for treatment with statins; patients unable to perform acceptable spirometry and lung volumes procedures; patients who have had a COPD exacerbation that required treatment with antibiotics and/or OCS and/or hospitalisation in the 6 weeks before visit 1; patients who have had a respiratory tract infection within 4 weeks before visit 1; patients requiring oxygen therapy (> 15 hours/d) on a daily basis for chronic hypoxaemia; patients with any history of asthma or onset of symptoms before age 40 years; patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, tuberculosis); patients with primary bronchiectasis; patients with a diagnosis of α-1-antitrypsin deficiency; patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation; patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation programme during the study; patients receiving certain medications; patients using other investigational drugs within 30 days before visit 1
Interventions	Atorvastatin 40 mg orally once daily for 12 weeks **Comparison:** placebo **Concomitant medications:** all patients received formoterol at a dose of 12 µg twice daily by easyhaler and/or tiotropium bromide 18 µg once daily by handihaler as maintenance and salbutamol MDI 200 mg as reliever treatment. Relief mediation with salbutamol MDI 200 µg as required was provided for additional symptom control as needed (but not within 6 hours before each visit). During 4 weeks of washout period, ICSs were withdrawn
Outcomes	**Lung function:** FEV_1, IC, RV, TLC, DLCO **Functional capacity:** 6MWD **Airway inflammation:** CRP **Quality of life:** SGRQ **Adverse events** **Others:** change in CD45+ cell expression measured by immunohistochemistry; changes in expression of genes measured using microarrays in lung biopsy (TBB) samples; intimal medial thickness in common carotid artery; serum lipids
Notes	**Funding:** study was supported by National Science Centre (NCN) Project No: N N402 593440 **Possible conflicts of interest:** none declared **Study number:** NCT01748279 **Definitions:** definition of COPD was based on presence of clinical symptoms (chronic cough and/or exertional dyspnoea), exposure to cigarette smoke (> 10 pack-years smoking), and postbronchodilator FEV_1/FVC ratio < 0.7 (ATS criteria)
Risk of bias	

Mroz 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised (2:1) using sequentially numbered containers
Allocation concealment (selection bias)	Low risk	Patients were randomised (2:1) using sequentially numbered containers
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was a single-blind study; personnel were not blinded at any stage
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was a single-blind study; personnel were not blinded at any stage
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were no postrandomisation dropouts in the atorvastatin group and 1 (16.7%) in the placebo group
Selective reporting (reporting bias)	Unclear risk	Not all outcomes specified in the protocol were clearly reported
Other bias	Low risk	None identified

Neukamm 2014

Methods	**Design:** randomised, double-blind, parallel-group, placebo-controlled, multi-centre trial **Duration:** 12 weeks **Location:** Norway
Participants	**Population:** 99 participants randomly assigned to rosuvastatin (49) or placebo (50). 94 patients were included in the final analysis (47 rosuvastatin and 47 placebo) **Baseline characteristics:** Mean age (years): rosuvastatin 66, placebo 63 % male: rosuvastatin 55, placebo 49 % FEV_1: rosuvastatin 48.3, placebo 52.1 % current smokers: rosuvastatin 26, placebo 49 **Inclusion criteria:** stable COPD without exacerbation the last 3 weeks before inclusion; COPD stage I to IV according to GOLD criteria; between 40 and 80 years of age **Exclusion criteria:** other diagnosed lung disease except chronic asthmatic bronchitis and mild bronchiectasis without or with few physical signs (diagnosed by high-resolution computed tomography); history of or active coronary artery disease, cerebrovascular or peripheral vascular disease; history of or clinically significant congestive heart failure, valvular heart disease, clinically significant arrhythmias, or conduction delays; uncontrolled arterial hypertension (defined as blood pressure above 180/110 mmHg with or without the use of antihypertensive medication); body mass index > 40 kg/m^2; history of diabetes mellitus or measured fasting glucose > 11 mmol/L; history of hypercholesterolaemia or measured total cholesterol > 8 mmol/L; known poliomyelitis, motor neuron disease, cranial or temporal arteritis, stroke, or myopathy; neutropenia or anaemia (Hb < 8 g/dL); history of chronic renal fail-

Neukamm 2014 *(Continued)*

	ure, serum creatinine > 176 mol/L (2.0 mg/dL), or creatine kinase > 3 times the upper limit of normal (ULN); acute or chronic liver disease (serum transaminases > 3 times the ULN); pregnancy (self-reported) and blood test before inclusion; active abuse of drugs or alcohol or poor compliance anticipated; statin use within the last 4 weeks before study start or previously; clear indication for statin use; prior diagnosis of statin-induced myopathy or hypersensitivity reaction to another statin including rosuvastatin; history of malignant disease of any kind within 5 years before inclusion; history of uncontrolled hypothyroidism; participation in another pharmaceutical or medical device clinical trial study within 4 weeks before inclusion; use of concomitant medications that are known to interact with rosuvastatin, including warfarin and other coumarin (vitamin K antagonist) anticoagulants, cyclosporine, gemfibrozil, and antacid, before inclusion
Interventions	Rosuvastatin 10 mg orally once daily for 12 weeks **Comparison:** placebo identical in appearance **Concomitant medications:** Antihypertensive treatment: rosuvastatin 12 (26%), placebo 10 (21%) ICS (including LABA): rosuvastatin 36 (77%), placebo 34 (72%) LABA only: rosuvastatin 2 (4%), placebo 3 (6%) LAMA: rosuvastatin 30 (64%), placebo 27(58%) Anti-inflammatory treatment: rosuvastatin 2 (4%), placebo 0 Oestrogen: rosuvastatin 4 (9%), placebo 3 (6%)
Outcomes	**Exacerbations:** frequency, exacerbations requiring hospital admission **Lung function:** FEV_1, FVC **Functional capacity:** 6MWD, MMRC dyspnoea scale **Airway inflammation:** CRP, IL-6 **Adverse events:** adverse events and serious adverse events **Others:** change in endothelium-dependent vascular function measured using peripheral arterial tonometry and expressed as the reactive hyperaemia index
Notes	**Funding:** grants from the Norwegian Extra Foundation for Health and Rehabilitation and the Norwegian Association of Heart and Lung Patients. Support from the Investigator-Sponsored Study Programme of AstraZeneca. Medication was provided by AstraZeneca. The sponsors, including AstraZeneca, played no role in study design; collection, analysis, and interpretation of the data; or writing of or decision to submit the manuscript for publication **Possible conflicts of interest:** TO received grants, personal fees, and non-financial support from Abbott Laboratories; personal fees from Siemens Healthcare; grants, personal fees, and non-financial support from AstraZeneca; and personal fees from Roche Diagnostics. AN has received a speaker fee from AstraZeneca. All other study authors have no conflicts of interest to declare **Study number:** NCT00929734 **Definitions:** COPD was defined by GOLD criteria. Exacerbation was defined according to current GOLD guidelines as having an acute event characterised by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variation and leads to a change in medication

Risk of bias

Bias	Authors' judgement	Support for judgement

Neukamm 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	A computer-generated list of random numbers was used for allocation of patients to treatment/placebo, with 1:1 allocation using fixed random block sizes of 4
Allocation concealment (selection bias)	Low risk	Patients and all staff involved in the trial were blinded to the allocation. A data and safety monitoring board was responsible for applying a randomisation number to each participant from the randomisation code list generated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Postrandomisation dropouts were similar and below 20% in both groups (rosuvastatin 2 (4.1%); placebo 3 (6%)). An intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Primary and secondary endpoints as stated in the trial protocol were clearly reported. Tertiary outcome results were not fully reported
Other bias	Low risk	None identified

6MWD: six-minute walking distance; 6MWT: six-minute walk distance test; ACEI: angiotensin-converting enzyme inhibitor; ALT: alanine aminotransferase; ARB: angiotensin-receptor blocker; ASA: aminosalicylic acid; AST: aspartate aminotransferase; ATS: American Thoracic Society; CCQ: Clinical COPD Questionnaire; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DLCO: diffusing capacity of the lungs for carbon monoxide; ELISA: enzyme-linked immunosorbent assay; Epo: erythropoietin; ET-1: endothelin-1; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global initiative for Chronic Obstructive Lung Disease; hs-CRP: high-sensitivity C-reactive protein; IC: inspiratory capacity; ICS: inhaled corticosteroid; IL: interleukin; LA: long-acting; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; LDL: low-density lipoprotein; MDI: metered-dose inhaler; MMRC: Modified Medical Research Council; NHLBI: National Heart, Lung and Blood Institute; NYHA: New York Heart Association; OCS: oral corticosteroid; PAH: pulmonary arterial hypertension; PEFR: peak expiratory flow rate; PFT: pulmonary function test; QOL: quality of life; RV: residual volume; SA: short-acting; SF-36: Short Form Health Survey; SGRQ: St. George's Respiratory Questionnaire; sPAP: systolic pulmonary pressure; TBB: transbronchial biopsy; TLC: total lung capacity; UA: uric acid; ULN: upper limit of normal; VEGF: vascular endothelial growth factor.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12611000165987	Not randomised, not placebo controlled
Arian 2018	Not placebo controlled
Arutyunov 2007	Not placebo controlled
Du 2018	Not placebo controlled
Eudract no 2009-017689-22	6 weeks' duration
Eudract number 2007-003916-74	Unable to identify published results despite apparent completion of study. Study authors contacted but no response received
John 2015	6 weeks' duration

Study	Reason for exclusion
Kaczmarek 2010	Not placebo controlled
Maneechotesuwan 2015	4 weeks' duration, cross-over trial
Mohammed 2012	4 weeks' duration
Morris 2017	COPD not defined by standard criteria
NCT00655993	9 weeks' duration, cross-over trial
NCT00680641	2 months' duration
NCT00700921	Unable to identify published results despite apparent completion of study. Study authors contacted but no response received
Rizvi 2013	Quasi-experimental design, not placebo controlled
Rossi 2017	COPD not defined by standard criteria
Undas 2009	Not placebo controlled

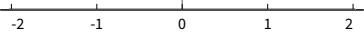
DATA AND ANALYSES

Comparison 1. Statins versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of exacerbations	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Exacerbations requiring hospitalisation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 All-cause mortality	2	952	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.61, 1.74]
4 COPD-specific mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Six-minute walk distance	3	71	Mean Difference (IV, Fixed, 95% CI)	1.79 [-52.51, 56.09]
6 FEV_1 (% predicted)	6	325	Mean Difference (IV, Fixed, 95% CI)	1.18 [-2.60, 4.97]
7 FEV_1/FVC (%)	6	325	Mean Difference (IV, Fixed, 95% CI)	2.66 [0.12, 5.20]
8 CRP (mg/L)	3	142	Mean Difference (IV, Fixed, 95% CI)	-1.03 [-1.95, -0.11]
9 Il-6 (pg/mL)	2	125	Mean Difference (IV, Fixed, 95% CI)	-2.11 [-2.65, -1.56]

Analysis 1.1. Comparison 1 Statins versus placebo, Outcome 1 Number of exacerbations.

Study or subgroup	Favours statin N	Favours statin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Criner 2014	430	1.4 (1.6)	447	1.4 (1.7)		-0.03[-0.25,0.19]

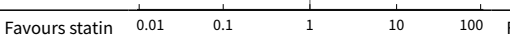


Analysis 1.2. Comparison 1 Statins versus placebo, Outcome 2 Exacerbations requiring hospitalisation.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Criner 2014	430	0.3 (0.7)	447	0.3 (0.8)		0[-0.1,0.1]

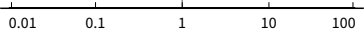
Analysis 1.3. Comparison 1 Statins versus placebo, Outcome 3 All-cause mortality.

Study or subgroup	Statin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Moosavi 2013	1/24	1/21		3.7%	0.87[0.05,14.82]
Criner 2014	28/430	30/477		96.3%	1.04[0.61,1.77]
Total (95% CI)	**454**	**498**		**100%**	**1.03[0.61,1.74]**
Total events: 29 (Statin), 31 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.9); I²=0%					
Test for overall effect: Z=0.12(P=0.91)					



Analysis 1.4. Comparison 1 Statins versus placebo, Outcome 4 COPD-specific mortality.

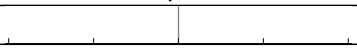
Study or subgroup	Statin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Criner 2014	6/430	5/447		1.25[0.38,4.13]



Analysis 1.5. Comparison 1 Statins versus placebo, Outcome 5 Six-minute walk distance.

Study or subgroup	Statin N	Statin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balaguer 2016	9	455.6 (69.6)	9	444.4 (106)		42.95%	11.2[-71.65,94.05]
Moosavi 2013	19	339 (155)	17	340 (106)		39.86%	-1[-87,85]
Mroz 2015	12	384.8 (83.8)	5	400 (139.3)		17.19%	-15.25[-146.23,115.73]
Total ***	**40**		**31**			**100%**	**1.79[-52.51,56.09]**
Heterogeneity: Tau²=0; Chi²=0.12, df=2(P=0.94); I²=0%							

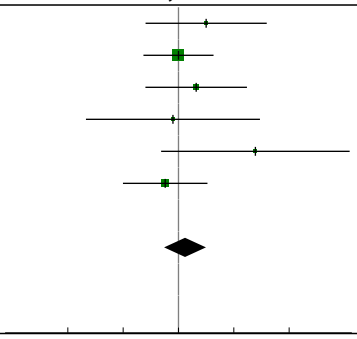
Study or subgroup	Statin N	Statin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=0.06(P=0.95)							



Favours placebo Favours statin

Analysis 1.6. Comparison 1 Statins versus placebo, Outcome 6 FEV_1 (% predicted).

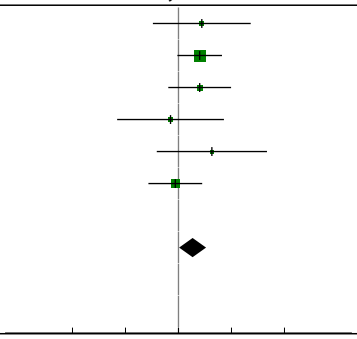
Study or subgroup	Statin N	Statin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balaguer 2016	9	53.1 (12.9)	9	48.1 (10.7)		11.95%	5[-5.95,15.95]
Lee 2008	53	55 (19)	54	55 (14)		35.72%	0[-6.33,6.33]
Lee 2009	27	60.5 (20.4)	26	57.3 (13)		17.02%	3.2[-5.97,12.37]
Moosavi 2013	19	47.6 (28.4)	17	48.6 (19.3)		5.79%	-1[-16.72,14.72]
Mroz 2015	12	61.5 (21.3)	5	47.6 (13.7)		4.94%	13.9[-3.14,30.94]
Neukamm 2014	47	49.3 (18.9)	47	51.7 (18.9)		24.58%	-2.4[-10.04,5.24]
Total ***	**167**		**158**			**100%**	**1.18[-2.6,4.97]**
Heterogeneity: Tau^2=0; Chi^2=3.85, df=5(P=0.57); I^2=0%							
Test for overall effect: Z=0.61(P=0.54)							



Favours placebo Favours statin

Analysis 1.7. Comparison 1 Statins versus placebo, Outcome 7 FEV_1/FVC (%).

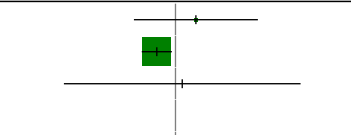
Study or subgroup	Statin N	Statin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balaguer 2016	9	46.3 (11.5)	9	41.9 (8.2)		7.59%	4.4[-4.83,13.63]
Lee 2008	53	58 (14)	54	54 (7)		36.53%	4[-0.21,8.21]
Lee 2009	27	58.5 (13.1)	26	54.5 (8.5)		18.42%	4[-1.92,9.92]
Moosavi 2013	19	55.9 (15.5)	17	57.4 (15.3)		6.37%	-1.5[-11.57,8.57]
Mroz 2015	12	54.1 (14.9)	5	47.8 (7)		5.98%	6.3[-4.1,16.7]
Neukamm 2014	47	47.3 (12.8)	47	47.9 (12.3)		25.11%	-0.6[-5.67,4.47]
Total ***	**167**		**158**			**100%**	**2.66[0.12,5.2]**
Heterogeneity: Tau^2=0; Chi^2=3.44, df=5(P=0.63); I^2=0%							
Test for overall effect: Z=2.05(P=0.04)							



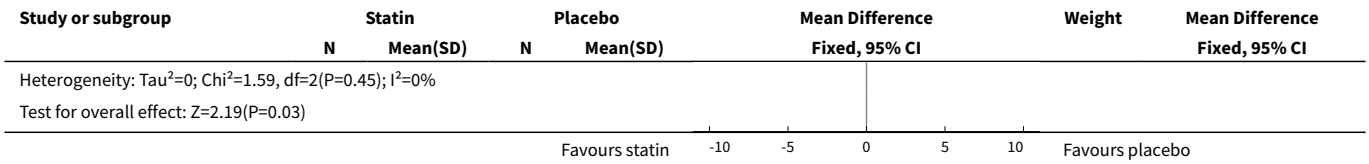
Favours placebo Favours statin

Analysis 1.8. Comparison 1 Statins versus placebo, Outcome 8 CRP (mg/L).

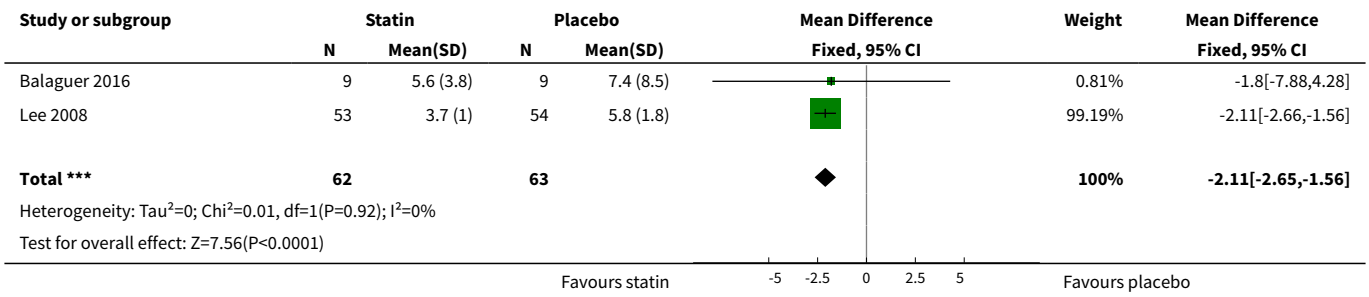
Study or subgroup	Statin N	Statin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balaguer 2016	9	5.1 (5.3)	9	3.8 (2.9)		5.47%	1.3[-2.65,5.25]
Lee 2008	53	2.7 (2.5)	54	3.9 (2.6)		93.03%	-1.19[-2.15,-0.23]
Mroz 2015	12	5.7 (3.3)	5	5.2 (8.3)		1.5%	0.43[-7.11,7.97]
Total ***	**74**		**68**			**100%**	**-1.03[-1.95,-0.11]**



Favours statin Favours placebo



Analysis 1.9. Comparison 1 Statins versus placebo, Outcome 9 Il-6 (pg/mL).



APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via the Cochrane Register of Studies (CRS))	From inception	Monthly
MEDLINE (Ovid)	1946 onwards	Weekly
Embase (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly
AMED (EBSCO)	From inception	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards

(Continued)

Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 2. Search strategy to identify relevant trials from the CAGR

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All

#2 MeSH DESCRIPTOR Bronchitis, Chronic

#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)

#4 COPD:MISC1

#5 (COPD OR COAD OR COBD):TI,AB,KW

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 MeSH DESCRIPTOR Hydroxymethylglutaryl-CoA Reductase Inhibitors

#8 statin*

#9 atorvastatin

#10 fluvastatin

#11 lovastatin

#12 pitavastatin

#13 pravastatin

#14 rosuvastatin

#15 simvastatin

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15

#17 #6 AND #16

[In search line #4, MISC1 denotes the field in which the reference record has been coded for condition, in this case, COPD]

CONTRIBUTIONS OF AUTHORS

- Conceiving the review - all authors.
- Designing the review - all authors.
- Co-ordinating the review - AW.
- Collecting data for the review - all authors.
- Designing search strategies - AW, MNC, LS.
- Undertaking searches - AW, LS.
- Screening search results - AW, LP.
- Organizing retrieval of papers - AW, LP.
- Screening retrieved papers against inclusion criteria - AW, LP.
- Appraising quality of papers - AW, LP.
- Extracting data from papers - AW, LP, MNC.
- Writing to authors of papers for additional information - AW.
- Providing additional data about papers - AW.
- Obtaining and screening data from unpublished studies - AW, MNC.
- Managing data for the review - AW.
- Entering data into RevMan - AW, MNC.
- Analysing data - AW, AK.
- Interpreting data - AW, AK.
- Providing a methodological perspective - AK.
- Providing a clinical perspective - MH.
- Writing the review - all authors.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor): edited the review; advised on methodology, interpretation, and content; and approved the final review before publication.
Chris Cates (Co-ordinating Editor): checked data entry before the full write-up of the review.
Wouter H. van Geffen (Editor): edited the review; advised on methodology, interpretation, and content; and approved the final review before publication.
Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on interpretation and content; and edited the review.
Emma Jackson (Assistant Managing Editor): conducted peer review; and edited the plain language summary and reference sections of the protocol and the review.
Elizabeth Stovold (Information Specialist): designed the search strategy; ran the searches; and edited the search methods section.

DECLARATIONS OF INTEREST

MTH: my institution has received grant money from Novartis, and I have received payments for delivering lectures from GSK, Novartis, Astra, Menarini, and Boehringer Ingelheim. I have never received any funds or support in the area of statins in COPD.

AK: none known.

MNC: has received honoraria from AstraZeneca for providing CME lectures to GPs. She has also attended respiratory meetings for CME, for which accommodations, transport, and registration fees were paid by Novartis, Gilead, and Abbott.

LMP: none known.

AW: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

One of the study authors (ME) was no longer able to participate in the review process.