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Effect of statins on chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials

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Competing interests

None of all authors have any financial or non-financial competing interests in this manuscript.

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Abbreviation list

COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; RCT, randomized controlled trials; CVD, cardiovascular disease; GOLD, the Global Initiative for Chronic Obstructive Lung Disease; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, a ratio of FEV1 to forced vital capacity; LDL-C, low-density lipoprotein cholesterol; RR, relative risk; CI: confidence interval; MD, mean difference.

Abstract

Background: Much controversy persists regarding the place of statins in the treatment of patients with chronic obstructive pulmonary disease (COPD). This systematic review and meta-analysis sought to determine the clinical efficacy of statin therapy in COPD.

Methods: We searched Medline, Embase, Cochrane databases, and Pubmed for relevant clinical studies. Randomized controlled trials comparing the effects of statins to placebo in COPD populations were included. Pooled estimates were calculated using a random-effects model. Heterogeneity was determined using the I^2 statistic.

Results: Ten trials with a total of 1471 patients were included. Statin treatment was associated with a larger improvement in exercise capacity, lung function, and St. George's Respiratory Questionnaire score compared with placebo, but there were no statistically significant differences in inflammatory markers, all-cause mortality, and safety outcomes; however, subgroup analysis indicated that statins improved clinical outcomes in the subjects from trials enrolling patients with overt cardiovascular disease, elevated baseline C-reactive protein, or high level of cholesterol.

Conclusions: The findings from this systematic review suggest a role for statins in COPD patients with coexisting cardiovascular disease, evidence of increased systemic inflammation, or hyperlipidemia, in terms of improving exercise tolerance and pulmonary function. These findings need to be confirmed by randomized controlled trials specifically designed to test this hypothesis and identify appropriate patients for statin use.

Keywords: COPD; statins; pulmonary; pooled analysis

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive illness characterized by poorly reversible airflow limitation, lung function decline, and chronic inflammation. It is currently the fourth leading contributor of morbidity and mortality in the world, which results in increasing socioeconomic and individual disease burden[1]. There is no curative treatment for COPD, and existing medications have not been conclusively shown to reduce the progressive deterioration of lung function seen in many patients. Smoking cessation is a key intervention, but this doesn't abolish disease progression[1, 2]. Effective therapy aiming for better management of COPD is urgently needed.

Statins are widely used for treating hypercholesterolemia. They function by inhibiting 3-hydroxy-3-methylglutaryl coenzymeA reductase. In addition to their lipid lowering capacity, they also possess anti-inflammatory and immunomodulatory effects[3]. Recent research has shown that they may decrease airway inflammation, and reduce the level of systemic inflammatory marker such as C-reactive protein (CRP)[4-5]. With the accumulating evidence that COPD is both a pulmonary/airway and systemic inflammatory disease, the pleiotropic effects of statins may confer potential benefits in COPD patients[6]. Statins have been reported to reverse the progression of pulmonary emphysema and inhibit airway hyper-reactivity in rodent models[7-8]. Based on the findings, observational studies have been conducted which suggest that statins had positive effects on reducing exacerbation rates and COPD related mortality[9-10]. By contrast, results from randomized clinical trials to test the efficacy of statins in a highly selected COPD population are much more controversial, suggesting little benefit[3, 11].

This systematic review and meta-analysis was performed to evaluate the clinical impact of adding statin therapy compared to placebo in randomized controlled trials (RCTs) in COPD. In addition, we planned subgroup analysis based on inclusion vs. exclusion of patients with comorbid cardiovascular disease (CVD), high vs. low baseline CRP value, elevated vs. normal cholesterol level, and severity of COPD. We believe that this is the first such review.

Methods

Search strategies

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (registered in the PROSPERO international prospective register of systematic reviews, CRD42017060594)[12]. Relevant articles were identified and selected by searching the databases: Medline (1966 to April 2017), Embase (1980 to April 2017), Cochrane controlled trials register (The Cochrane Library Issue 4, 2017), and PUBMED (updated to April 2016). Detailed information of our search strategy is provided in the appendix 1. We examined bibliographies in relevant articles and conference proceedings. Internet-based sources of information on the results of clinical trials in statin and COPD were scanned for additional articles. There were no restrictions for language or publication date placed on the searches. Both full manuscripts and abstracts were considered.

Inclusion and exclusion criteria

Original studies were eligible for inclusion if they met the following criteria: (1) randomized, placebo-controlled; (2) evaluated the clinical efficiency of statin treatment in patients with COPD of any severity, defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline; (3) had drop-out rate less than 20%; (4) provided data on at least one outcome of interest; (5) used a given patient population only once, if the same group appeared in other publications, only the most recent or complete report of a clinical trial was incorporated.

Data extraction

Two independent reviewers (WZ and YZ) separately screened the titles and abstracts, performed duplicate checking, and reviewed full articles that met the inclusion criteria. Data were independently abstracted from each identified reference with a predesigned review form, and disagreement was resolved by consensus. We retrieved study design and characteristics, patient clinical characteristics and demographics, intervention information, clinical outcomes, and duration of follow-up. The primary outcomes were exercise tolerance (6-minute walk distance) and lung function (forced expiratory volume in 1 second (FEV_1) % of predicted value, FEV_1 predicted;

a ratio of FEV_1 to forced vital capacity, FEV_1/FVC). Additional outcomes included CRP and pulmonary-related inflammatory markers (median neutrophil percentage in induced sputum), all-cause mortality, quality of life, acute exacerbations, drug discontinuation, low-density lipoprotein cholesterol (LDL-C), total cholesterol, and adverse events.

Quality assessment

We assessed the risk of bias of each fully published trial according to the Cochrane risk of bias tool. The main domains were checked, including random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, attrition bias, selective reporting, and other bias. The judgments were expressed as “low risk”, “high risk”, or “unclear risk” of bias. Any disagreements were resolved by discussion and consensus.

Statistical analysis

Data analysis was performed using a random-effects model using Stata/SE 11.0 (StataCorp, College Station, TX). For all dichotomous data, the relative risk (RR) and 95% confidence intervals (CIs) were calculated for each independent study and for the summary statistic, with values of <1 favoring statins. For studies reporting zero events in a treatment or control arm, we applied a half-integer continuity correction to calculate the relative risk (RR) and variance[13]. The mean difference (MD) and 95% CIs were calculated for continuous data. The RR or MD for each clinical event was considered to be significantly different if the *P* value was less than 0.05 (two sided). The magnitude of heterogeneity between trials was evaluated using the I^2 statistic, with a value of 50% or more indicating a substantial level of heterogeneity. Publication bias was assessed using the Begg’s and Egger’s tests.

We performed subgroup analyses to address the clinical efficacy of statins in trials enrolling patients with concomitant CVD, evidence of systemic inflammation (raised CRP), elevated cholesterol level, or severe airflow limitation. Sensitivity analyses and meta-regression were conducted to examine the robustness of the findings and explore other important clinical differences among the studies.

Results

Study description

The study selection process is outlined in **Figure 1**. We identified 2921 citations. From them, twenty potentially eligible RCTs were identified[4-5, 11, 14-30]. Studies were excluded from the systematic review if they did not include COPD patients as the study population, did not have a completely randomized design, were commentaries and review articles, or were experimental reports in non-human species. Ultimately, 10 of the 20 studies were selected[4-5, 11, 14-20]; of those not included, three were excluded because they did not use a placebo control[21-23], three because they used the same dataset as another study included in this meta-analysis[24-26], one because it was a post-hoc analysis of a large statin-heart failure RCT[27], one because one-quarter of the recruited patients did not complete the study[28], one because most of the patients did not fulfil GOLD criteria for COPD[29], and one because no outcomes of interest were reported[30]. All the included trials were published as peer-reviewed articles, and all of them were in English. **Table 1** shows the baseline characteristics in each of the individual studies.

Patients

A total of 1471 COPD patients were recruited to these 10 trials; 728 were randomized to the statin group and 743 to the control group. Mean age ranged from 49 years to 72 years. Across the trials, the proportion of male subjects and current smokers ranged from 52% to 100% and 0% to 81%, respectively. Mean baseline FEV % predicted ranged from 42% to 76%. Study duration ranged from 1 to 12 months, with a mean follow-up of 4.4 months. Patients were permitted to take standard COPD medications including long-acting muscarinic antagonists, long-acting β2-agonists, inhaled corticosteroids, and use supplemental oxygen. Two studies were multicenter trials[11, 20]. All the trials recruited COPD patients without recent statin usage, except for one[4]. Four of the ten studies excluded participants with CVD[4, 11, 15-16], and eight only enrolled stable COPD patients without a recent exacerbation[4-5, 14-18, 20]. Four types of statins were investigated in these trials: simvastatin, atorvastatin, rosuvastatin, and pravastatin.

Trial quality

Methods of randomization and allocation concealment were adequately addressed in the majority of trials. Among the 10 included studies, nine were either double- or triple-blind, and the remaining one used a single-blind design[5]. All trials clearly stated withdrawal rates, which varied across trials and tended to be slightly lower in statin treatment group (4.4%) than in placebo group (5.2%). A summary of the "Risk of bias" assessment is presented in **Figure 1S.**

Clinical outcomes

Exercise capacity

Figure 2 displays the change in 6-mintue walk distance, which was studied in five trials[5, 14-16, 19]. Overall there was a significant benefit in 6-mintue walk distance with statins; 6-minute walk distance was greater by 15.5 m (95% CI: 1.43 to 29.65 m; *P*=0.03). There was no observed heterogeneity between studies (I^2=0%).

Lung function

Data for FEV_1 were available in seven RCTs[5, 11, 15, 17-20] (**Figure 3**). The Improvement in FEV_1 % predicted was numerically but not significantly greater with statin therapy than with placebo (MD, 3.2%; 95% CI: -0.30% to 6.78%; *P*=0.07).

Five studies evaluated the effect of statins on FEV_1/FVC[11, 17-20] (**Figure 4**). Statin usage was associated with a significant improvement in FEV_1/FVC (MD, 2.7%; 95% CI: 0.05 to –5.25%; *P*=0.05). Tests of heterogeneity on all measures of spirometry were not significant (I^2<5%). Taken together, our data suggested that statin therapy might improve the lung function by a small amount.

Inflammatory status

The effect of statins on CRP was determined in six studies[4-5, 15-17, 20]. There was a non-significant trend in CRP reduction in patients receiving statins compared with placebo (**Figure 2S**). There was a moderate degree of statistical heterogeneity among these six trials (I^2=56.6%).

Three RCTs reported data on neutrophils percentage in sputum[4-5, 16]. There was no difference between statin and placebo groups (MD, -0.79%; 95% CI: -9.99% to 8.40%; *P*=0.87) (**Figure 3S**). Statistical heterogeneity was significant (I^2=82.6%).

Quality of life

The impact of statins on health-related life quality of COPD patient was evaluated using St George's Respiratory Questionnaire in three trials[5, 11, 15] (**Figure 5**). There was a larger improvement with statin, as compared to placebo (MD, -8.9; 95% CI: -150 to -2.32; *P*=0.008). Between-trial heterogeneity was not obvious (I^2=0%).

All-cause mortality

Four eligible trials that enrolled a total of 1054 patients reported all-cause mortality[11, 14, 16, 19]. There were 29 deaths among 518 individuals in the treatment groups and 31 deaths among 536 individuals in the control groups. There was not statistically significant difference (RR, 0.97; 95% CI: 0.60–1.58; *P*=0.91) (**Figure 4S**). There was no significant heterogeneity of findings across the studies (I^2=0%).

Drug safety

As expected, statin therapy was associated with greatly reduced serum LDL-C and total cholesterol levels (data not shown), which confirmed a good compliance with statin usage study participants. Furthermore, withdrawal rate and the incidence of serious adverse events were both comparable between the statin and placebo groups (data not shown).

Publication bias

There was no obvious evidence for publication bias, as detected by the Begg's and the Egger's tests.

Subgroup analysis

Cardiovascular comorbidity

Statins improved exercise tolerance in participants from the trials enrolling COPD patients with cardiovascular comorbidities, as evidenced by a significantly increased 6-minute walk distance (MD, 19.1 m; 95% CI: 3.8 m to 34.4 m; *P*=0.01; I^2=0%). In addition, there were trends towards better FEV_1% predicted (MD, 3.75%; 95% CI: -0.08% to 7.58%; *P*=0.06; I^2=0%) and FEV_1/FVC (MD, 2.74%; 95% CI: -0.31% to 5.78%; *P*=0.08; I^2=20.4%), and lower CRP. By contrast, no benefits were

observed in patients from those studies that completely excluded patients with existing or potential CVD.

Systemic inflammation

We conducted a subgroup analysis according to baseline CRP levels, since the efficiency of statin on reducing inflammation has been shown to be related to baseline CRP[17]. In COPD patients with higher mean baseline CRP levels (baseline CRP value > 3 mg/L), the statin treated patients had a numerically better improvement in FEV_1 % predicted (MD, 4.41%; 95% CI: -0.52% to 9.33%; *P*=0.08; I^2=0%) and significantly better FEV_1/FVC (MD, 5.00%; 95% CI: 1.02% to 8.98%; *P*=0.01); however this was not seen in patients with had lower baseline CRP levels. These observations were further strengthened by another subgroup analysis, based on the efficiency of statins in reducing systemic inflammation, which showed that they ameliorated the lung function parameters only in subjects from trials reporting decreased CRP levels after treatment.

Cholesterol level

A subgroup analysis was performed to test whether the benefits from statins were mediated through their lipid-lowering capacity. In studies conducted in the subjects with higher baseline LDL-C levels (baseline LDL-C value > 120 mg/dl), a significant benefit was seen for FEV_1 predicted: MD, 3.82%; 95% CI: -0.43% to 8.08%; P=0.08; I2=0%; FEV_1/FVC: MD, 3.61%; 95% CI: 0.86% to 6.36%; P=0.01; I2=0%). This effect was not seen in studies conducted in patients with lower baseline LDL-C levels.

Disease severity

Baseline FEV_1% predicted had no effect on the outcomes of statin treatment.

Sensitivity analysis

A sensitivity analysis was performed by using both random- and fixed-effect models, and practically the same outcomes were found, except the result of CRP, which significantly favored the statin group when using the fixed-effect model. Restricting our analysis to RCTs that only recruited stable COPD patients, or statin-naïve patients, or with longer observational period (more than 3 months) did not significantly alter the pooled results or any heterogeneity.

Meta-regression

Meta-regression analysis found that patient number, statin class, methods of blinding (single/double/triple), or observational period had no significant effects on the major clinical outcomes.

Discussion

In this systematic review and meta-analysis, pooled analysis of 10 RCTs to determine the efficacy of statins in treating patients with COPD generated some important observations. First, statins improved exercise tolerance, pulmonary function, and health-related life quality of COPD patients. Second, COPD patients with comorbid CVD, increased systemic inflammation, or hyperlipidaemia appeared to benefit more from statin therapy than the others of this population. Third, there was no association between statins and survival rate, although only a few trials in this analysis focused on this outcome and the mean study duration was short.

Other than being the first-line cholesterol-lowering medications for prevention of atherosclerotic CVD, statins have attracted growing interests for treating patients with COPD, with the underlying rationale related to their pleiotropic properties and the disease pathogenesis. The usefulness of various statins at different doses has been determined in both rat and mice models, which reported direct and protective effects on the broncho-pulmonary system[31]. Observational studies and a related systematic review support the conclusions from the animal researches, showing reduced morbidity and mortality in COPD patients receiving statins[9, 32-34]. By contrast, the largest prospective statin-COPD study (the STATCOPE trial) suggested that simvastatin did not reduce the exacerbation rate, and had no effect on lung function or health-related quality of life in patients with COPD[11]. These discordant results led to increasing controversy regarding the important but still unsolved puzzle: should patients with COPD be prescribed statins, unless they had identified lipid levels?

The current collective evidence suggests a role for statin therapy in several different aspects of COPD-specific outcomes. It also appears that patients with comorbid CVD and higher baseline lipids may have greater benefits including lung function benefits, whereas they had no effects in those with normal LDL-C level. These observations suggest COPD patients at elevated cardiovascular risk might be the appropriate subgroup for statin use. This finding accords with that suggested by Young et al in their STATCOPE critique, suggesting that statins maybe indicated in as many as 60-80% of COPD patients who have high cardiovascular risk and who have been historically under-treated with statin therapy, leading to poor outcomes in this ‘unhealthy non-user’ group[3]. This may explain the discrepancy between the result of our analysis and that of STATCOPE

trial, since in that study patients who met the indications for statin use based on their cardiovascular risk profiles were excluded.

COPD is increasingly recognized as a systemic disease that affects not only airway and lung, but also the cardiovascular system[35-36]. There appears to be a close relationship between COPD and an increased incidence of CVD[37]. A pooled analysis of two large epidemiologic researches recruiting more than 20,000 adults, reported that the prevalence of CVD in COPD patients was more than two times higher than in people without[38]. Furthermore, a substantially high cardiovascular mortality in patients with COPD has been observed, particularly in those with mild and moderate airflow limitataion[39]. In one of the largest COPD trials, cardiovascular events were responsible for 27% of the deaths, compared with 35% due to respiratory causes[40]. Since statins have been proven to reduce morbidity and mortality from CVD through inhibiting cholesterol biosynthesis, it is reasonable to assume that COPD patients with concomitant CVD or hyperlipemia would benefit from therapy with statins.

Unexpectedly, we found that statins appear to possess an ability to improve lung function in patients with COPD, which implies a direct benefit on statins on the pulmonary system. In support of this conclusion, previous studies identified a comparable decrease in mortality of COPD patients with both high and low cardiovascular risks, which also suggests a positive effect of statins outside of their cardiovascular-protective effects[32]. More interestingly, the sub-group analyses showed that statins appeared to exert their protective effect on pulmonary function only in patients with higher baseline CRP value. A plausible explanation for this phenomenon might be that statin-derived benefits may be primarily confined to COPD population with coexisting systemic inflammation. Previous research has reported a correlation between change in CRP, one of the most sensitive markers of inflammation, and improved clinical outcomes of COPD patients with statin use[17]. Our data suggest that since statins may downregulate inflammation only in patients with concomitant CVD or hyperlipemia, the inclusion of patients without these characteristics in studies may mask possible treatment effects. Exclusion of cardiovascular comorbidity that is normally associated with coexisting systemic inflammation, could have masked the potential pulmonary benefits of statins in the STATCOPE trial. Taken together, these observations lead to the hypothesis that the underlying mechanism of beneficial effects in COPD patients could be a result of inhibition of systemic inflammation by statins.

Unlike the results of observational studies, we showed no effects of statin therapy on mortality in COPD patients[1, 10], but the small patient cohorts in the RCTs were smal and the study periods were short, so the long-term effects of statins on life expectancy of COPD population remained unclear.

Whilst our findings suggested more prominent benefits from statin therapy in COPD patients with CVD, evidence of systemic inflammation, or hyperlipidaemia. It should be recognised that these three factors are commonly presented in COPD individuals, and are indications for statin use irrespective of the presence of COPD[41]. While this study demonstrated potential benefits of statins on lung function, a diagnosis of COPD is not, of itself, an indication for routine use of statins. Equally COPD is not a contraindication to statin treatment, so patients with COPD should be evaluated comprehensively for CVD and cardiovascular risks, in order to identify those warranting statin therapy. The data from this analysis suggests that, by identifying patients who meet current indications for statins, those with COPD might also benefit through their an effects on lung function and exercise capacity.

Limitations

This systematic review and meta-analysis has limitations. First, the overall study size of the contributing studies was small. Second,sSeveral important specific outcomes of COPD including acute exacerbations could not be analyzed, due to a lack of trials reporting such outcomes. Third, although this study highlighted a statin-induced benefit in trials recruiting participants with comorbid CVD, only some of them enrolled 100% of whom had both COPD and CVD. Future studies with rigorously predefined patient characteristics are warranted to better understand the potential benefits associated with statin use. Fourth, despite generally similar demographic characteristics and minimal evidence of heterogeneity among these RCTs, some confounding factors such as type of statin with different doses might have caused potential bias, and made it difficult to analyze the primary intervention of our interest. However, the inclusion of only randomized studies with a placebo controlled design and the use of random-effect model might be helpful to mitigate some of the possible study heterogeneities. Our attempts to investigate sources of heterogeneity through sensitivity analysis and meta-regression did not identify any factors significantly associated with treatment effect size. All these approaches support the robustness of this analysis, however, the

influences of unmeasured covariates cannot be completely ruled out.

Conclusions

The systematic review and meta-analysis showed that statins might improve exercise tolerance, lung function, and health-related quality of life in patients with COPD, particularly those with comorbid CVD, elevated systemic inflammation, or hyperlipidaemia. The findings support routine cardiovascular risk assessment in COPD population to identify patients who have a cardiovascular indication for statin treatment, since it might also bring direct benefits to pulmonary system. Finally, we feel that our observations justify a large RCT to test the hypotheses generated by this systematic review.

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Contributors

YF, CW, and PWJ contributed to the study conception and the review protocol. WZ and YZ performed database search, article evaluation, and data extraction. YF, WZ, and CWL planned and performed the statistical analysis. All authors contributed to the interpretation of data. YF and PWJ drafted and revised the manuscript. All authors have read and approved the final version.

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Figure legends

Figure 1 Flow of study selection.

Figure 2 Summary effects of statins versus placebo on changes in 6-minute walk distance.

Figure 3 Summary effects of statins versus placebo on changes in FEV_1% predicted.

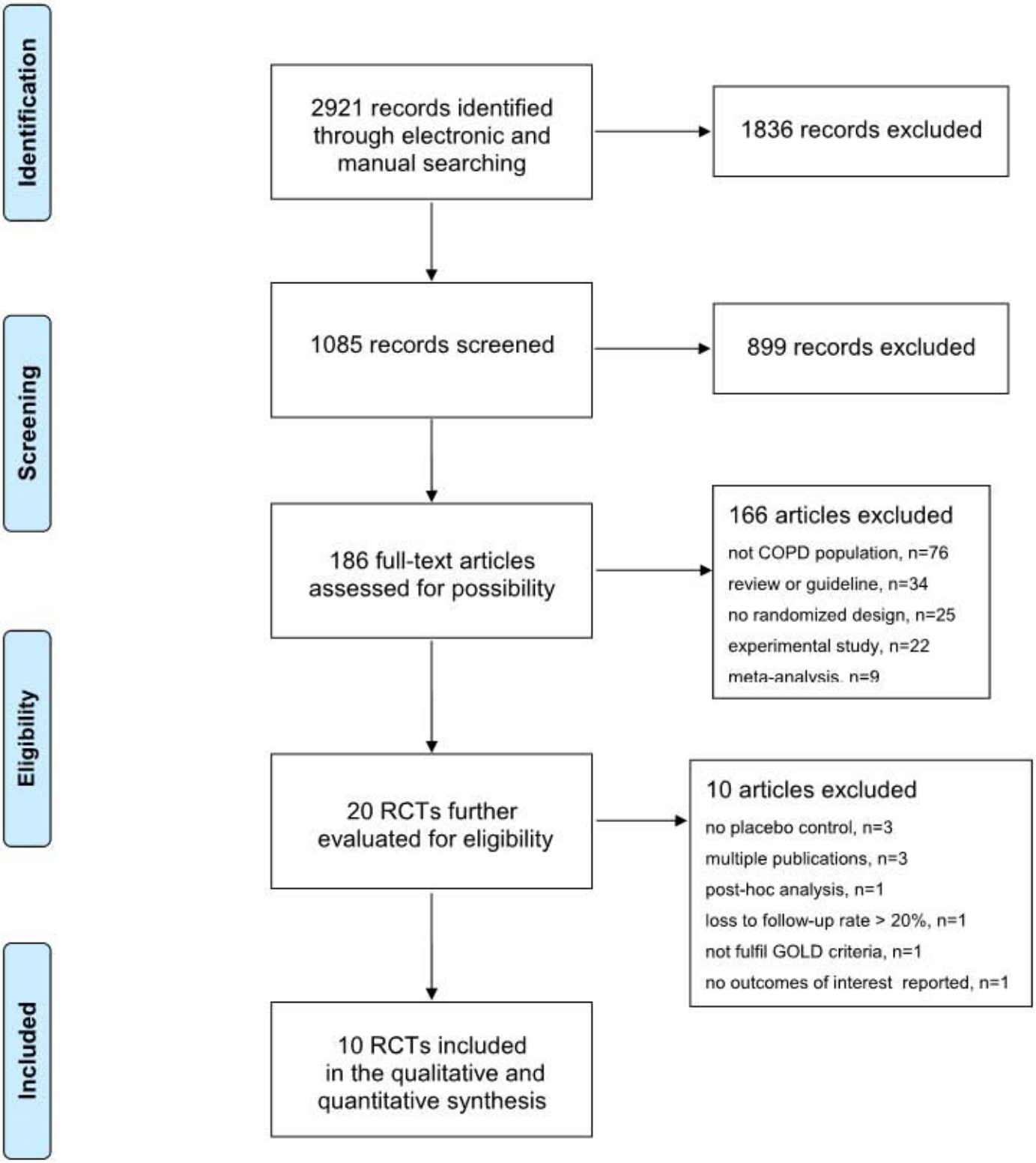
Figure 4 Summary effects of statins versus placebo on changes in FEV_1/FVC.

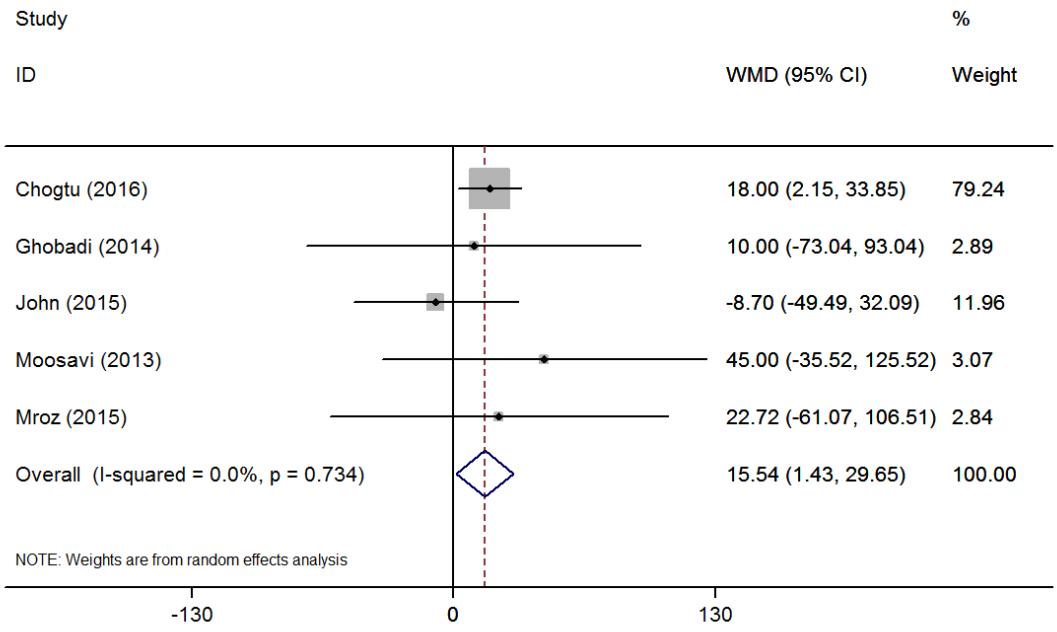
Figure 5 Summary effects of statins versus placebo on changes in SGRQ score.

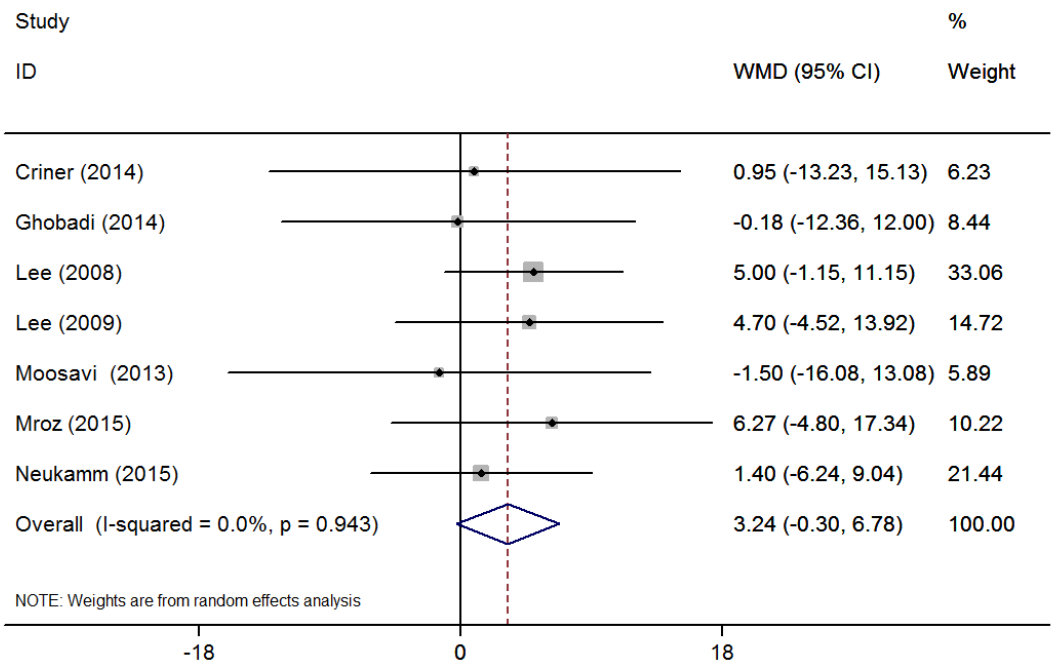
Table 1 Characteristics of studies included in the analysis

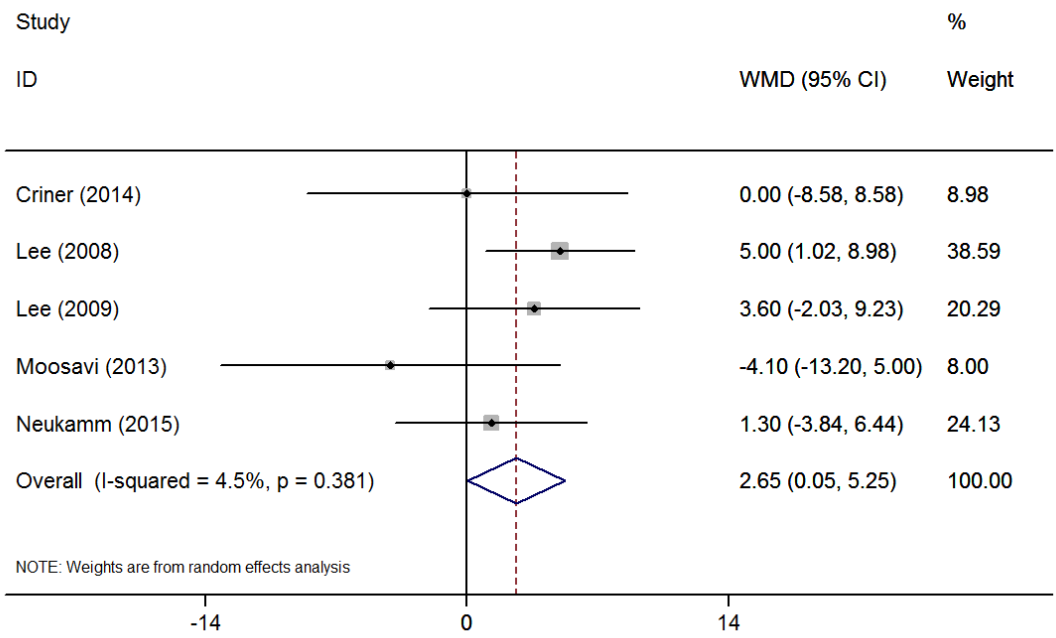
Study/Intervention	Medication	Dose	Multicenter	Blind	Duration, month	Patient number	Age, y	FEV1	Current smoker, n (%)	Statin naive	CVD excluded
Chogtu 2016[14] Treatment	rosuvastatin	10mg/day	single	double	3	32	61.4±8.4	-	-	Yes	No
Control	placebo					30	65.9±9.7		-		
Criner 2014[11] Treatment	simvastatin	40mg/day	Multi	double	12	433	62.2±8.5	41.6%	133 (30.7%)	Yes	Yes
Control	placebo					452	62.3±8.4		143 (31.6%)		
Ghobadi 2014[15] Treatment	atorvastatin	40mg/day	single	double	2.1	25	47.3±7.5	76.3%	0 (0%)	Yes	Yes
Control	placebo					25	50.2±8.2		0 (0%)		
John 2015[16] Treatment	simvastatin	20mg/day	single	double	1.5	33	64±7.3	53.9%	7 (21%)	Yes	Yes
Control	placebo					37	65±7.3		15 (41%)		
Lee 2008[17] Treatment	pravastatin	40mg/day	single	double	6	62	70±8	53.5%	50 (81%)	Yes	No
Control	placebo					63	71±6		48 (76%)		
Lee 2009[18] Treatment	pravastatin	40mg/day	single	double	6	32	71±8	56.6%	22 (81%)	Yes	No
Control	placebo					33	72±6		21 (81%)		
Maneechotesuwan[4] 2015 Treatment	simvastatin	20mg/day	single	double	1	26	68.4±7.8	55.7%	5 (24%)	No	Yes
Control	placebo					26	68.4±7.8		5 (24%)		

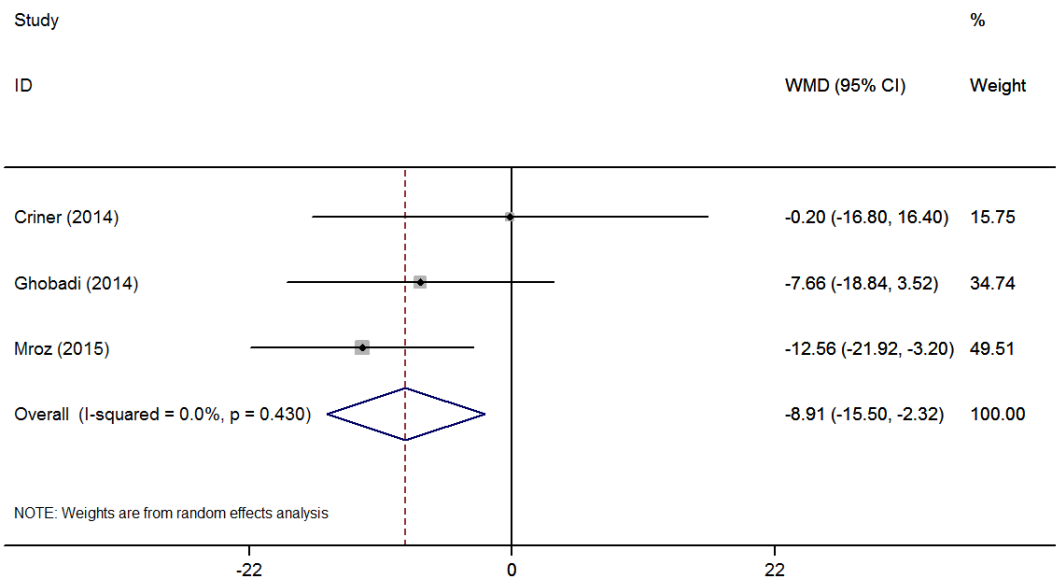
Moosavi 2013[19] Treatment	atorvastatin	40mg/day	single	triple	6	24	65±11	43.8%	-	Yes	No
Control	placebo					21	68±14		-		
Mroz 2015[5] Treatment	atorvastatin	40mg/day	single	single	3	12	64.6±7.0	56.9%	5 (42%)	Yes	No
Control	placebo					6	68.4±6.5		2 (40%)		
Neukamm 2015[20] Treatment	rosuvastatin	10mg/day	Multi	double	3	49	66±0.8	50.2%	12 (26%)	Yes	No
Control	placebo					50	63±1.0		23 (49%)		


Identification
Screening
Eligibility
Included
2921 records identified through electronic and manual searching
1836 records excluded
1085 records screened
899 records excluded
186 full-text articles assessed for possibility
166 articles excluded
not COPD population, n=76
review or guideline, n=34
no randomized design, n=25
experimental study, n=22
meta-analysis, n=9
20 RCTs further evaluated for eligibility
10 articles excluded
no placebo control, n=3
multiple publications, n=3
post-hoc analysis, n=1
loss to follow-up rate > 20%, n=1
not fulfil GOLD criteria, n=1
no outcomes of interest reported, n=1
10 RCTs included in the qualitative and quantitative synthesis









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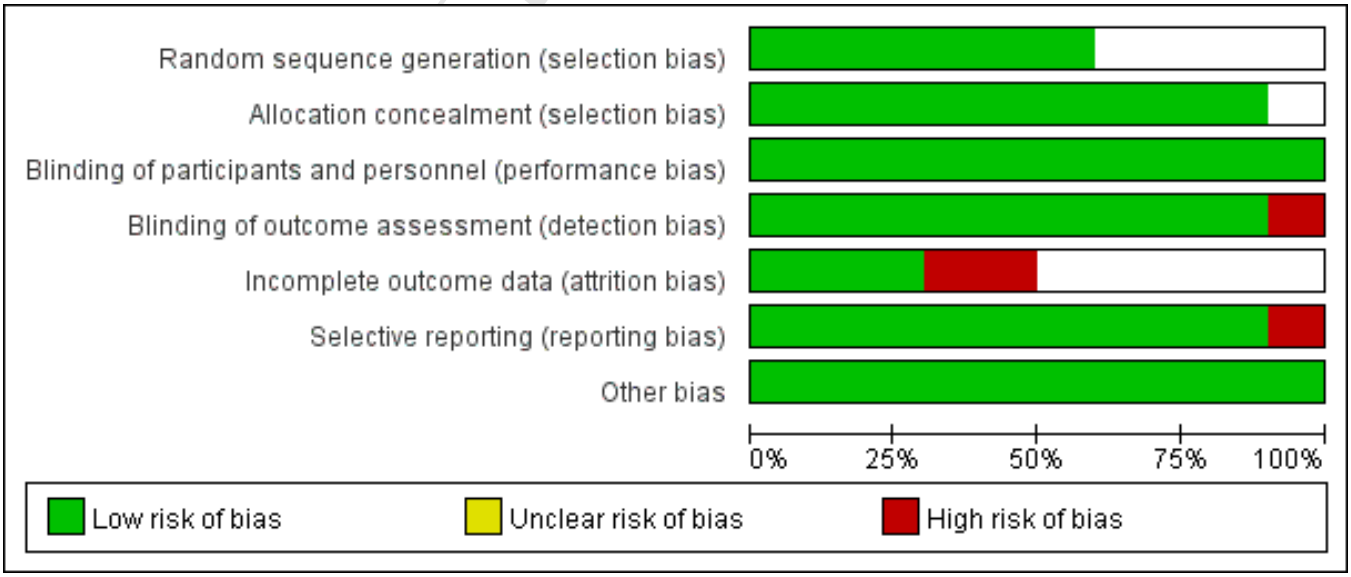
e-Appendix 1. Search strategies

We searched Medline (1966 to April 2017), Embase (1980 to April 2017), Cochrane controlled trials register (The Cochrane Library Issue 4, 2017), and PUBMED (updated to April 2016) for eligible articles, using the terms: "chronic obstructive pulmonary disease", "COPD", "obstructive", "bronchitis", "airway obstruction", "emphysema", "mediastinal emphysema", "subcutaneous emphysema", "chronic obstructive lung disease", "COLD", "pulmonary heart disease", "chronic pulmonary heart disease", and "cor pulmonale", combined with the following individual search terms: "hydroxy methylglutaryl coenzyme a reductase inhibitor", "hydroxy methylglutaryl coenzyme a reductase", "HMG-COA", "HMG COA", "statin", "statins", "simvastatin", "lovastatin", "mevastatin", "pravastatin", "atorvastatin", "fluvastatin", "rosuvastatin", "cerivastatin", and "pitavastatin". Articles from these searches and relevant references cited therein were reviewed. Studies were included without any restrictions for language or publication date.

e-Figure 1. Summary assessment of risk of bias.



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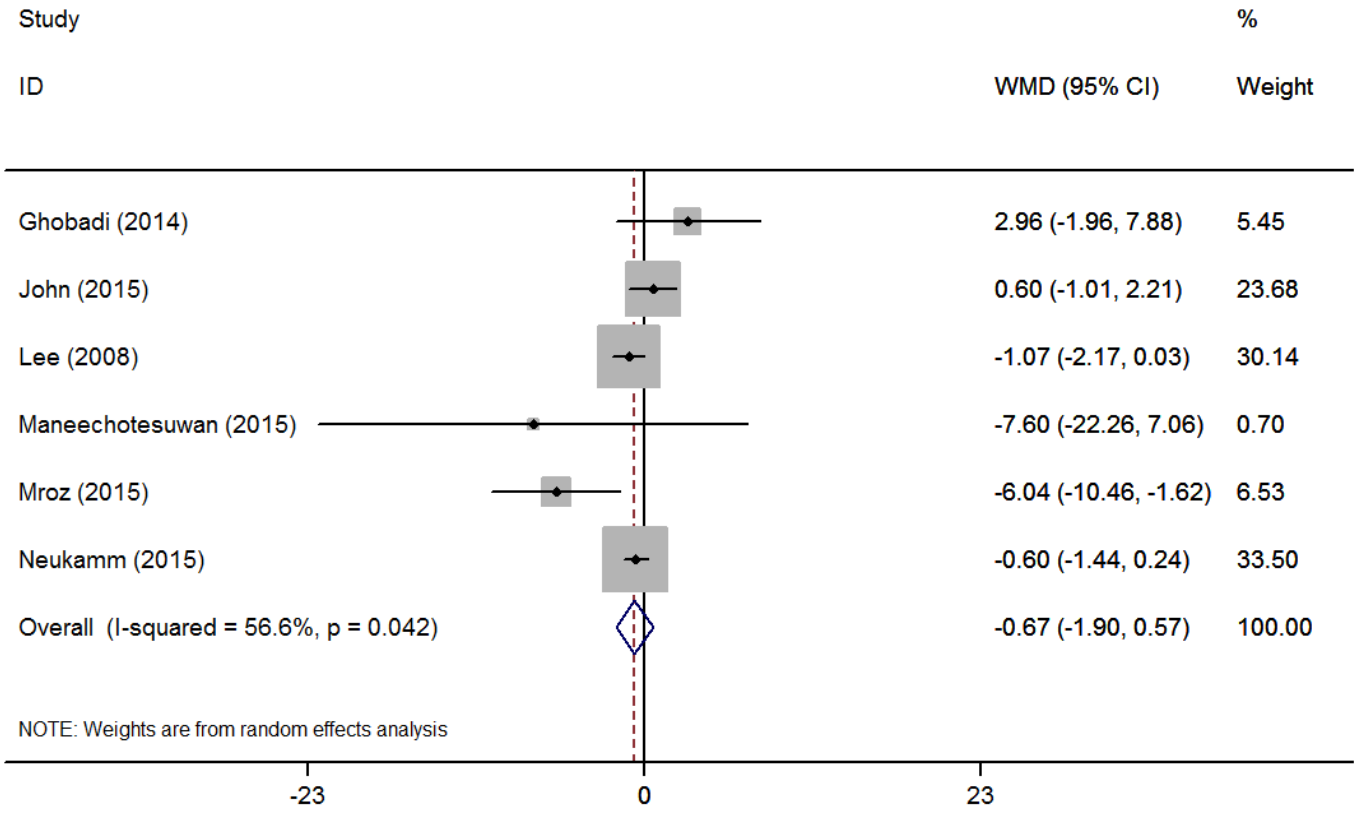
e-Figure 2. Summary effects of statins versus placebo on changes in CRP.



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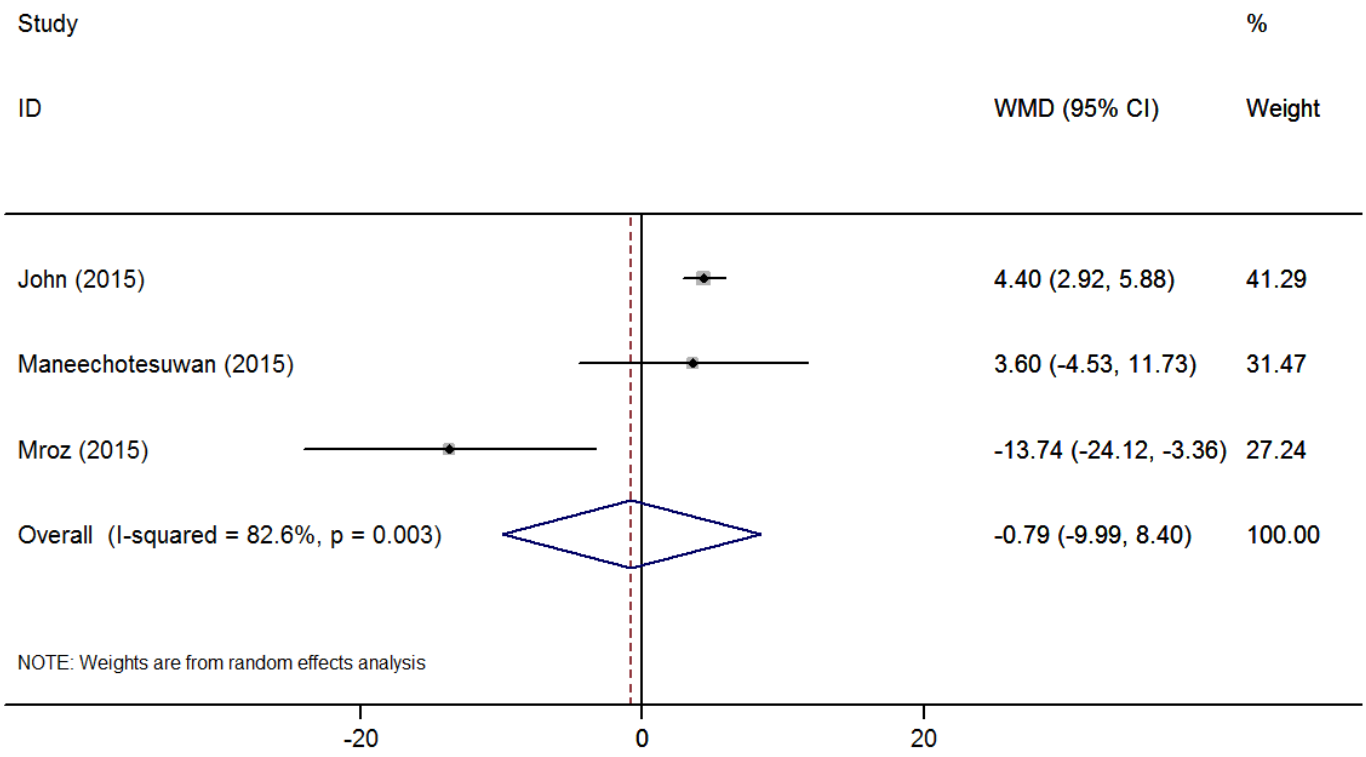
e-Figure 3. Summary effects of statins versus placebo on changes in neutrophils percentage in sputum.



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e-Figure 4. Summary effects of statins versus placebo on changes in all-cause mortality.