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Original article

Benefits of statins in chronic obstructive pulmonary disease patients with pulmonary hypertension: A meta-analysis

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ABSTRACT

Purpose: This meta-analysis was performed to evaluate the efficacy of statins in chronic obstructive pulmonary disease (COPD) patients with pulmonary hypertension (PH).
Methods: A systematic search was made of MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases. Randomized clinical trials on treatment of COPD-PH with the statins, compared with placebo, were reviewed. Studies were pooled to weighted mean differences (WMD), with 95% confidence interval (CI).
Results: Five trials (enrolling 270 participants) met the inclusion criteria.
Compared with placebo, the statins presented significant effects on systolic pulmonary artery pressure (WMD -4.52 mmHg; 95% CI -6.32 to -2.72 mmHg) and 6-min walk distance (6MWD) (WMD 32.46 m; 95% CI 13.63–51.29 m).
Conclusions: Statins therapy significantly improves PH and 6MWD in COPD patients with PH.

1. Introduction

Chronic obstructive pulmonary disease (COPD) with its comorbidities is one of the five major causes of death worldwide [1]. Pulmonary hypertension (PH) is a serious condition classified into five groups based on its pathogenesis, with Group 3 due to lung diseases and/or hypoxia [2].

The prevalence of PH in COPD (COPD-PH) is generally dependent on the severity of the disease, but also on the definition of PH and the method of diagnostic assessment [3]. Several studies in patients with Global Initiative for Chronic Obstructive Lung Disease stage IV showed that up to 90% have mean pulmonary artery pressure (mPAP) > 20 mmHg, with most ranging between 20 and 35 mmHg. About 1–5% of COPD patients have mPAP > 35–40 mmHg at rest [4]. Oswald-Mammosser et al. [5] found that the 5-year survival rate was only 36% in COPD patients with an mPAP > 25 mmHg compared with 62% in those with an mPAP < 25 mmHg. Taking into account that COPD is the fourth major cause of death worldwide [1], this often unrecognized comorbidity is most likely an underestimated worldwide healthcare burden. However, there is no approved specific vasoactive therapy for the treatment of COPD-associated PH currently. Therefore searching effective medicine or setting up a novel strategy is critical in the long-term management of COPD-associated PH.

Statins, inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, are formerly used to reduce cholesterol levels in clinic. Recent studies have suggested that statins have comprehensive protective effects on vascular system independent of reducing of cholesterol levels, such as improving endothelial function, suppressing vascular smooth muscle cell proliferation, inducing vascular cell apoptosis, ameliorating inflammation and oxidative stress, stabilizing atherosclerotic plaques, as well as inhibiting thrombogenic response [6–8]. These pleiotropic beneficial effects suggest that statins might have potential values in the treatment of a variety of vascular diseases including PH. Studies indicate that statins attenuate the development of several types of animal models of PH [9–11]. On the basis of a few clinical studies that have shown a trend towards reduced PH with statins in COPD-associated PH [12,13], some authors have suggested that statins may have a role as a novel therapy in COPD-PH.

Thus, this meta-analysis was conducted to verify the efficacy of statins in COPD patients with PH.

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2. Methods

2.1. Data sources and searching

The study was designed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [14]. MEDLINE, Cochrane, ISI Web of Science and SCOPUS database were searched for articles published until July 2019.

2.2. Study selection

Study inclusion criteria were: comparison of statins with placebo in COPD-associated PH (systolic pulmonary artery pressure > 25 mmHg); randomized protocol design. Search strings of databases was ("statins" OR "atorvastatin" OR "rosuvastatin" OR "pravastatin" OR "simvastatin" OR "fluvastatin" OR "pitavastatin") AND ("COPD" OR "chronic obstructive pulmonary disease" OR "PH" OR "pulmonary hypertension" OR "pulmonary artery pressure"). The reference lists of relative articles were also screened to further identify potential studies.

2.3. Data extraction and quality assessment

Two reviewers independently screened articles for fulfillment of inclusion criteria. Reviewers compared selected trials and discrepancies were resolved by consensus. Data tables were made to extract all relevant data from texts, tables and figures of each included studies, including author, year of publication, treatment category, patient number and age, Detsky quality score, and outcomes such as systolic pulmonary artery pressure (SPAP), 6-min walk distance (6 MWD), and forced expiratory volume in 1 s (FEV_1). Quality of trials was evaluated by the Detsky method [15].

Of 3321 articles identified by the initial search, 241 were retrieved for more detailed evaluation, and 5 articles [12,13,16–18] were included in the study (Fig. 1).

2.4. Data synthesis and statistical analysis

Meta-analysis was supplemented when applicable; otherwise, outcomes were presented in a narrative way. Software RevMan 5.1 (the Cochrane Collaboration, Copenhagen) was employed for data analysis. Weighted mean difference (WMD) for SPAP, 6 MWD and FEV_1, with corresponding 95% confidence intervals (CI), were calculated for individual trials. I^2 statistic and Chi^2 test were used to examine the heterogeneity. If significant heterogeneity ($p \leq 0.10$ for Chi^2 test results or $I^2 \geq 50\%$) was obtained, we used a random-effects model, otherwise a fixed-effects model was used. P value < 0.05 was considered as statistical significance.

Publication bias was evaluated using plots of study results against precision of the study (funnel plots) for each outcome.

3. Results

3.1. Characteristics of subjects in included trials

Baseline characteristics of trials included in the study are reported in Table 1. A total of 270 patients were included, 137 assigned to statins treatment and 133 to placebo group.

3.2. Systolic pulmonary artery pressure

Data on systolic pulmonary artery pressure were available from five randomized trials (262 patients). Compared with placebo, statins significantly decreased SPAP from baseline to the end of follow-up (WMD −4.52 mmHg; 95% CI −6.32 to −2.72 mmHg). There was no significant heterogeneity ($I^2 = = 0\%$; $P = = 0.82$) (Fig. 2).

3.3. 6-Min walk distance

Data from 2 trials (107 patients) showed that, compared with

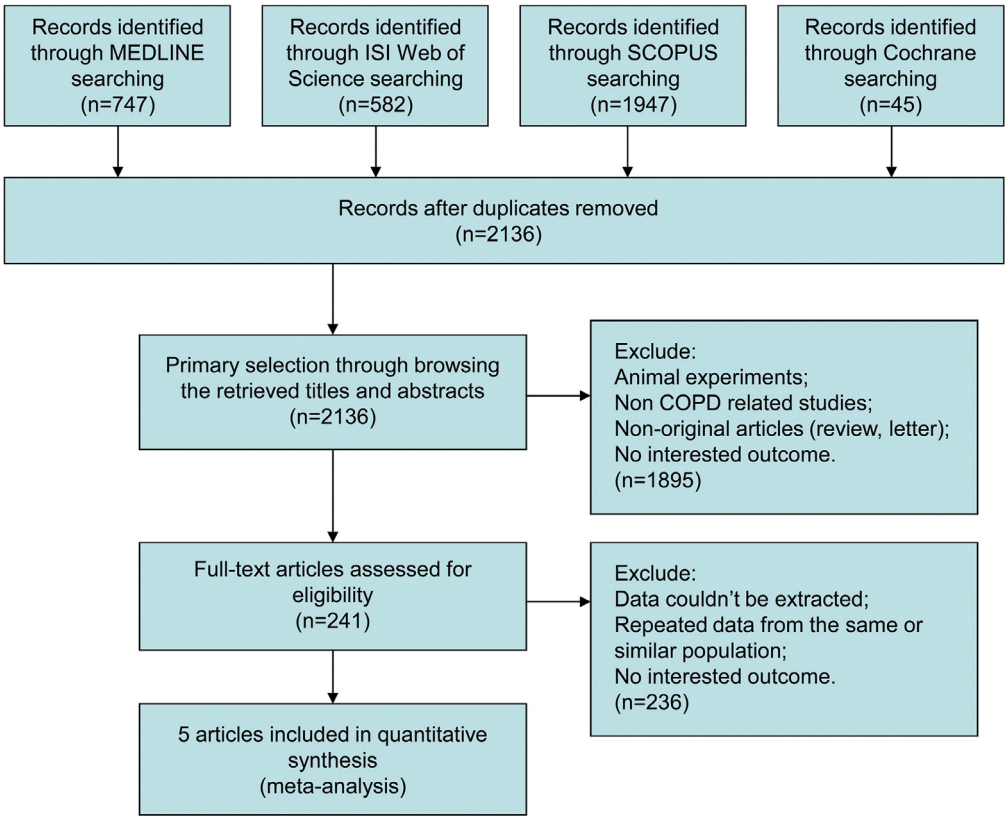

Fig. 1. Flow chart for selection of studies.

Table 1
Baseline characteristics of trials included in meta-analysis.

Study	Year	Quality Score	Follow -Up months	Diagnostic criteria for COPD	Define of PH
Arian (12)	2017	18	6	ATS standards	SPAP > 25 mmHg
Chogtu (16)	2016	18	3	ATS standards and GOLD guidelines	SPAP > 30 mmHg
Lee (13)	2009	20	6	ATS standards	SPAP ≥ 35 mmHg
liu (17)	2013	19	6	GOLD guidelines	SPAP > 30 mmHg
Moosavi (18)	2013	19	6	ATS standards	SPAP > 40 mmHg

Dose/day	n	Age, years (SD)	Male,%	SPAP, mmHg (SD)	6MWD, meters (SD)
Atorvastatin 40 mg	21	65.8 (11.5)	36	47.9 (15.4)	NR
Placebo	21	63.7 (7.6)	28	49.2 (16.3)	NR
Rosuvastatin 10 mg	32	61.4 (8.4)	NR	NR	NR
Placebo	30	65.9 (9.7)	NR	NR	NR
Pravastatin 40 mg	27	71 (8)	74.1	47 (8)	NR
Placebo	26	72 (6)	73.1	47 (7)	NR
Atorvastatin 20 mg	33	66.2 (7.4)	60.6	52.7 (8.1)	NR
Placebo	35	64.9 (8.2)	65.8	51.7 (7.9)	NR
Atorvastatin 40 mg	24	65 (11)	62.5	48.5 (6.9)	238 (124)
Placebo	21	68 (14)	61.9	49.7 (11.4)	284 (100)

Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; 6MWD, 6-min walk distance; NR, not reported; PH, pulmonary hypertension; SD, standard deviation; SPAP, systolic pulmonary artery pressure.

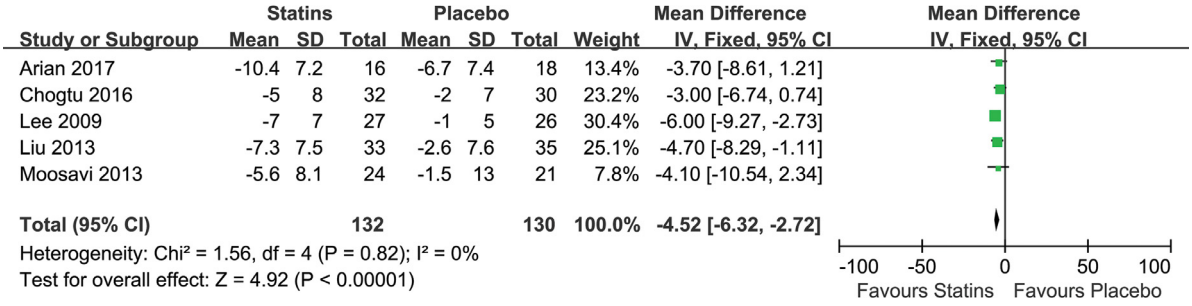

Fig. 2. Effects of statins versus placebo on systolic pulmonary artery pressure.

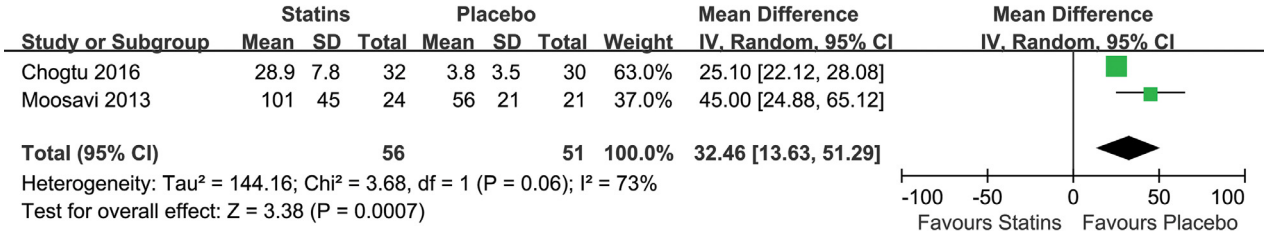

Fig. 3. Effects of statins versus placebo on 6-min walk distance.

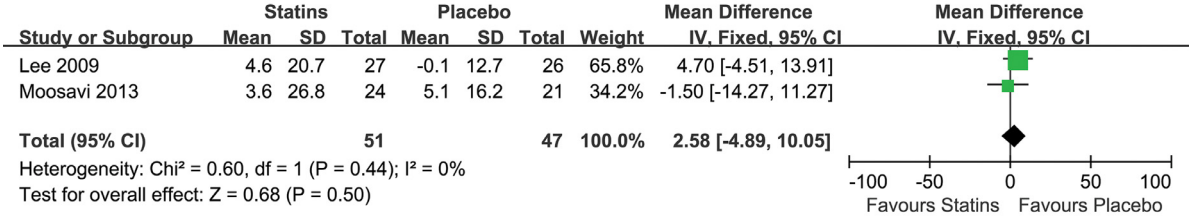

Fig. 4. Effects of statins versus placebo on Forced expiratory volume in 1 s.

placebo, the use of statins was associated with significant increase in mean change in 6 MWD from baseline to the end of follow-up (WMD 32.46 m; 95% CI 13.63–51.29 m; I^2 = = 73%; P = = 0.06) (Fig. 3).

3.4. Forced expiratory volume in 1 s

The change of FEV_1 was evaluated in two studies (98 patients). There was no statistical significant difference in mean change in FEV_1 from baseline to the end of follow-up between the two groups (WMD 2.58%; 95% CI −4.89–10.05%; p = = 0.50) (Fig. 4).

3.5. Publication bias

No publication bias was detected in outcome analysis.

4. Discussion

In this meta-analysis, we found that statins could significantly improve SPAP and 6 MWD in COPD patients with PH, even in small doses. Prevalence estimates for PH in COPD patients are not well-established, as right heart catherization is not routinely executed in this patient population [19]. Echocardiography is believed the best non-invasive method to screen for COPD-PH. However, the ability to define peak tricuspid regurgitation velocity to estimate the right ventricular systolic pressure is limited in these patients [20]. A study included 998 COPD patients with a mean FEV_1 of 33% showed that, while the mean mPAP was 20.3 mmHg, only 2.7% had severe PH, defined as an mPAP $\geq$ 40 mmHg, with 1.1% of these patients having only COPD as an attributable cause of PH [4].

There has been a special attention in pleiotropic effects of statins in recent years [21]. One of the applications considered for statins related to patients with primary or secondary PH. The beneficial effects of statins on pulmonary arterial pressure (PAP) in animals have been shown recently [22]. PH is a common complication of COPD characterized by reduced life expectancy, poor prognosis, and high healthcare costs [23]. A new theory holds that the main contributor to PH is endothelial dysfunction and inflammatory mechanisms [24]. Statins can be useful given their anti-inflammatory, antioxidant, and antithrombogenic properties and improve endothelial cell function in COPD patients with PH [25].

Endothelial progenitor cells (EPCs) have been shown to be involved in COPD pathogenesis, and the number of circulating EPCs has been correlated with disease severity [26]. The number of circulating EPCs are decreased in COPD patients as a result of excessive lung use in response to hypoxemia and cell apoptosis [26,27]. EPCs may be a novel therapeutic target for the treatment of COPD-associated PH because mounting evidence suggests that early EPCs transplantation significantly improves exercise tolerance and pulmonary hemodynamics in PH patients [28]. Some studies found that statins could promote EPCs proliferation, suppress the aging of circulating EPCs, improve EPCs migration and adhesion activities, reduce PAP in patients with COPD [17,29].

This study met most of the methodological criteria suggested for systematic reviews [30]. Inclusion criteria were clearly defined. Several relevant databases were searched for published articles in any language. Attempts were made to minimize error and bias in the process of study selection, data extraction and quality assessment. Trial quality was formally assessed, included appropriate criteria, and the results were clearly reported. However, the current meta-analysis was not patient level and therefore results should be considered provisional. Further large, long-term randomized controlled trials comparing the statins with placebo are required to confirm the extent of these benefits. Specific future research should examine the long-term efficacy and safety of the different doses of statins, as well as their effects on the natural history of COPD-PH when used early in the disease progression. Data from the literature are still scarce and most studies are too small to generate strong messages that can help the clinician in selecting a correct therapeutic approach.

5. Conclusions

In conclusion, statins provided greater improvement in systolic pulmonary artery pressure and 6-minute walk distance in COPD patients with PH. This meta-analysis demonstrates that statins was beneficial in the management of COPD-associated PH.

Declaration of Competing Interest

None of the authors has a conflict of interest to declare.

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