Efficacy and safety of statin therapy in pulmonary hypertension: a systematic review and meta-analysis

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Background: Pulmonary hypertension (PH) is a multi-causal disease and no satisfactory therapeutic strategies for it. Statins have been suggested as potential drugs in PH, whose effects in different clinic types of PH have not been conclusive. In this study, we included randomized controlled clinical trials (RCTs) evaluating the efficacy and safety of statins therapy in PH.

Methods: We searched databases including Medline, Embase, Cochrane, PubMed and Web of science, with time up to January 1, 2019. With 95% confidence interval (CI), weighted mean difference (WMD) or standardized mean difference (SMD) was pooled and calculated in a random or fixed effect model according to I2 statistic.

Results: A total of nine RCTs with 657 patients were included. Four types of statins (atorvastatin, pravastatin, rosuvastatin and simvastatin) were used at different doses (10–80 mg daily) for up to 6 months. In the pooled-data analysis, compared with placebo, there were significant improvements in pulmonary arterial pressure (PAP), in addition to low-density lipoprotein (LDL) in patients treated with statins, but not in 6-minute walking distance (6MWD), cardiac index (CDI). No more adverse events and all-cause mortality were revealed. Subgroup analysis indicated that statins could decrease PAP in the subtype of PH due to chronic obstructive pulmonary disease (COPD), but not pulmonary arterial hypertension (PAH).

Conclusions: This study indicates that statins can efficiently and safely reduce PAP in PH, especially in the subtype due to COPD. Further RCTs are needed to focus on the efficacy and safety of statin therapy in different subtypes of PH.

Keywords: Pulmonary hypertension (PH); chronic obstructive pulmonary disease (COPD); pulmonary arterial hypertension (PAH); statins; meta-analysis

Introduction

Pulmonary hypertension (PH) is a fatal disorder characterized by persistently increased pulmonary arterial pressure (PAP) of various causes, which is defined as an increase of the mean PAP above 25 mmHg at rest (1). According to primary causes, PH is categorized into five clinic subtypes (2): (I) pulmonary arterial hypertension (PAH), including idiopathic, heritable forms and PAH

associated with connective tissue disease and congenital heart disease, etc.; (II) PH due to left heat disease; (III) PH due to lung diseases and/or hypoxia [chronic obstructive pulmonary disease (COPD), etc.]; (IV) chronic thromboembolic PH (CTPH) and other pulmonary artery obstructions; (V) PH with unclear and/or multifactorial mechanisms. These subtypes give rise to mechanisms regarding vasoconstriction, vascular wall thickening, stenosis, along with remodeling, thrombosis and blood viscosity and volume increasing caused by chronic hypoxia. The long-term progression would produce aggravated cardiac load, ultimately, cor pulmonale which severely affects the respiratory and cardiovascular systems. Current routine medications for PH include vasodilators, such as endothelin receptor antagonists, prostacyclin analogues (prostanoids) and their likes (3,4), anticoagulants, diuretics, cardiotonic agents and oxygen, etc. However, the prognosis has been always unsatisfactory since the lack of mechanism-targeted therapy. Besides, given the treatments of PH differing with respect to their types, more effective and targeted therapy is urgently needed.

Statins, as HMG-CoA reductase inhibitors, have pleiotropic effects, such as lipid-lowering, anti-proliferative, antioxidant, anti-inflammatory and endothelial cell functions maintaining properties (5-7), which may be helpful in attenuating the progression of PH. It was reported that statins can prevent and reverse pulmonary vascular remodeling in several animal models of PH (8). An observational study showed there were significant improvements in 6-minute walking distance (6MWD), cardiac output and right ventricular systolic pressures in PH treated with simvastatin (9). However, Anand et al. found that there was no significant improvement in 6MWD and mortality with statin therapy, compared to placebo (10). Some meta-analyses showed that statins treatment had no effect of PAP in PH patients (11-13). An increasing number of studies have been focused on statin therapy in PH these years, even though the results were controversial (14-16). And statins have been suggested as novel and effective drugs for PH in some vivo and vitro studies (5-7).

Given the undetermined situation, we performed this systematic review and meta-analysis to evaluate the efficacy and safety of statin therapy in randomized controlled trials (RCTs) of PH and a subgroup analysis concerning PAH and PH due to COPD, with the expectation to provide evidence regarding the role of statin therapy in PH, especially those due to PAH and COPD.

Methods

Search strategies

We searched Medline (1946 to December week 4, 2018), Embase (1974 to January 2019), Cochrane controlled trials register (The Cochrane Library Issue 1, 2019), and PubMed (updated to January, 2019), Web of science (1990–2019) for eligible articles, using the terms: "pulmonary hypertension", "pulmonary arterial hypertension", and "PAH", combined with the following individual search terms: "HMG-CoA reductase inhibitor", "statin", "statins"; "atorvastatin", "cerivastatin", "fluvastatin", "lovastatin", "pravastatin", "pitavastatin", "rosuvastatin", "simvastatin". Studies were included without any restrictions on language, sex, age or publication date. These studies and relevant references cited therein were reviewed. Both abstracts and full manuscripts were considered. Moreover, no patient and public involvement should be ethically stated in this meta-analysis.

Inclusion and exclusion criteria

Studies were eligible for inclusion as the following criteria: (I) they were RCTs; (II) they evaluated the clinical efficiency of statin therapy in patients with PH; (III) the trials provided data on at least one outcome of interest: PAP, exercise tolerance (6MWD), cardiac index (CDI), low-density lipoprotein (LDL), all-cause mortality and adverse events; (IV) if the same patient group appeared in other publications, only the latest or complete report was incorporated.

Data extraction and management

Two independent reviewers (F Chen and M Yang) 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. Disagreement was resolved by consensus with the third author (C Wan). The details from each study included general characteristics of the study (publication year, area, study design), participants (age, gender, number of patients in treatment and control group, diagnosis, PAP and LDL before treatment) and intervention (statin types, dose, background treatment and duration). We extracted data on the following outcomes: PAP, exercise tolerance (6MWD),

CDI, LDL, adverse events and all-cause mortality.

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 (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. The judgments were expressed as "low risk", "high risk", or "unclear risk" of bias. Any disagreements were resolved by discussion and consensus.

Statistical analysis

The data analysis was performed with Stata 12.0 (StataCorp, College Station, TX, USA). We used the random-effect model to conduct the meta-analysis and assessed heterogeneity with the I^2 statistic and the fixed-effect model was used when the value of P>0.1. The weighted mean difference (WMD) and 95% confidence intervals (CIs) were calculated with continuous data. When the different measurements became variable, standardized mean difference (SMD) was used. We performed subgroup analysis to estimate the clinical efficacy of statins in trials enrolling patients with concomitant COPD and patients diagnosed with PAH. When assessment of the influences of individual studies on the pooled effects was necessary, sensitivity analysis was conducted by withdrawing trials one by one. P value less than 0.05 was considered statistical significance.

Results

Search results

Our literature search found 783 potential relevant publications and 391 were removed because of duplication. Of the remains, 16 clinic trials comparing the treatment effects of statins with placebo in PH patients were identified. Ultimately, nine RCTs completely fulfilled the criteria for consideration and the data in which were extracted to further analysis (17-25). The search process is shown in *Figure 1*. All the selected studies were shown in English and published during 2008–2017. And publishing areas were

as follows: Brazil, Taiwan, Germany, United States, China, Iran and India. The clinical features of included studies are shown in *Table 1*.

Patients

A total of 657 PH patients were recruited to these 9 trials; 330 were randomized to the statin group and 327 to the control group. Mean age ranged from 33 to 72 years. Study duration ranged from 12 weeks to 6 months. The subjects were permitted to receive basic treatment such as diuretics, long-acting muscarinic antagonists, long-acting β2-agonists, oxygen supplement and anticoagulant therapy. Four types of statins were investigated: atorvastatin, pravastatin, rosuvastatin and simvastatin.

Trial quality

The quality of the included studies was generally high. Methods of randomization and allocation concealment were adequately addressed in the majority of trials. Among the 9 included studies, 7 were double-blind, 1 was triple-blind and the remaining 1 was unclear. The blinding of participants and outcome assessors was reported in all studies, reflecting an overall low risk of detection bias. A summary of the "Risk of bias" assessment is presented in *Figure 2*.

Clinic outcomes

PAP
Data on PAP were available in five studies (18,21-23,25). Overall there was a significant decrease of PAP in PH patients treated with statins compared with placebo group (WMD =–3.51, 95% CI: –5.35 to –1.68; P<0.001) (*Figure 3*). There was a small heterogeneity among studies (I^2=5.5%). In the subgroup analysis, there was a significant improvement of PAP in COPD patients (WMD =–4.13, 95% CI: –6.27 to –1.99; P<0.001) (*Figure 4A*), but not in PAH (WMD =3.49, 95% CI: –2.03 to 9.02; P=0.215) (*Figure 4B*).

Exercise capacity
Most of included studies reported 6MWD, an indicator of exercise capacity. In this study, 6MWD were extracted from five trials (19-21,23,24). There was no significant benefit in 6MWD with statins in PH subjects (WMD =–2.66, 95% CI: –20.11 to 14.79; P=0.765) (*Figure 3*). Statistical heterogeneity was small (I^2=9.0%). In subgroup analysis,
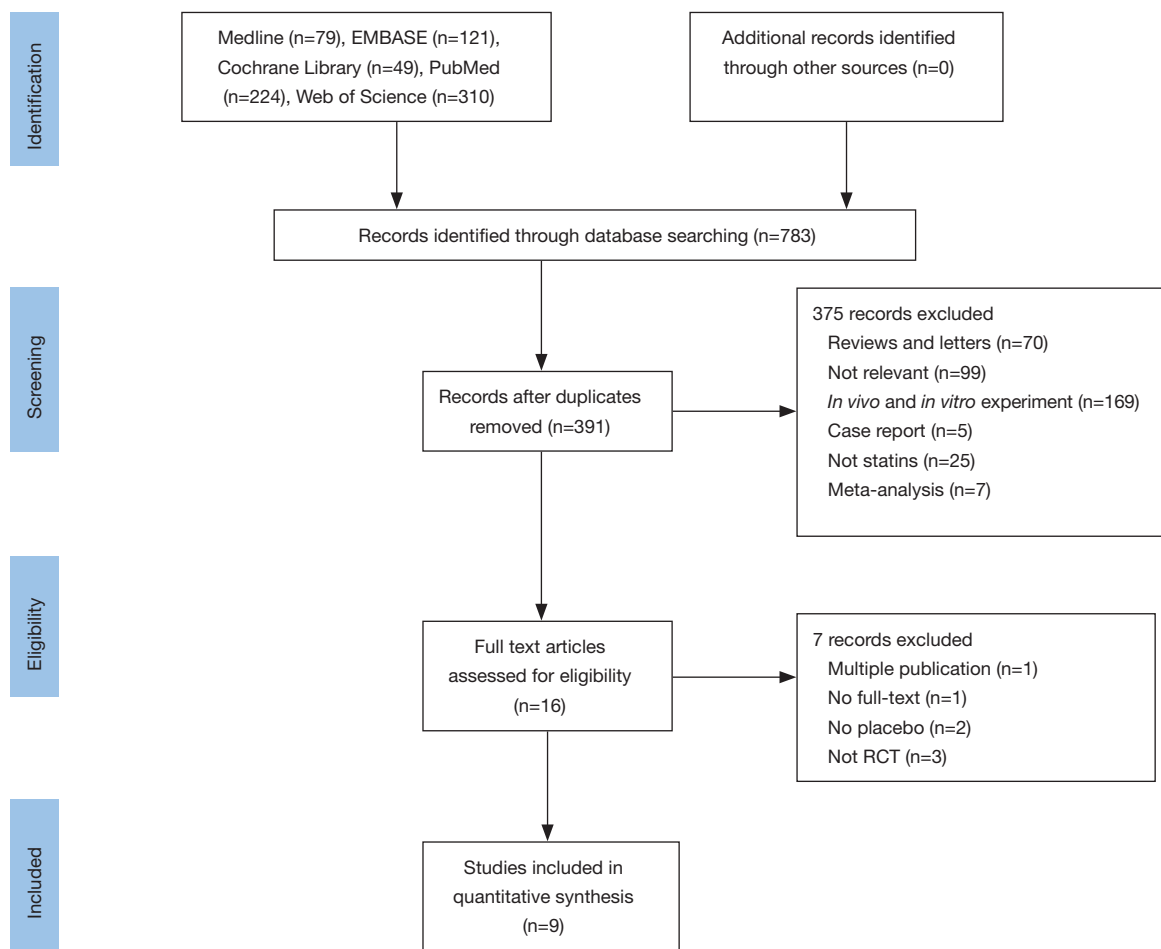
Figure 1 PRISMA flowchart outlining the literature search process.

statins neither improved 6MWD in the COPD (WMD =22.75, 95% CI: –15.78 to 61.29; P=0.247) (*Figure 4C*), nor in PAH (WMD =–14.52, 95% CI –39.05 to 10.01; P=0.246) (*Figure 4D*).

Cardiac index

Only three trails evaluated the effect of statin therapy on CDI (18,19,21). There was no improvement with statins, compared to placebo (WMD =0.14; 95% CI: –0.02 to 0.29; P=0.086) (*Figure 3*), the statistical heterogeneity was not significant (I^2=0%).

Serum LDL

The effect of statins on serum LDL was determined in four studies. As expected, there was a significant decrease in the level of LDL (SMD =–0.63, 95% CI: –0.86 to –0.40; P<0.001) (*Figure 3*). No observed heterogeneity among

studies (I^2=0%).

Adverse events

A total of 7 eligible trials including 550 individuals reported adverse events (17-21,23,24). In this meta-analysis, the adverse events contained clinical deterioration, hemoptysis, syncope, skeletal muscle pain, liver function abnormalities, bleeding, insomnia, etc. There was no obvious discrepancy in adverse events between the placebo and statin groups [risk ratio (RR) =1.08, 95% CI: 0.89 to 1.31; P=0.444] (*Figure 3*) and no significant heterogeneity among the studies (I^2=0.0%).

All-cause mortality

Five eligible trials reported all-cause mortality (19-21,23,24). There were 11 deaths among 219 patients in the statin groups and 14 deaths among 215 patients in the control

Table 1 Clinical features of included studies

Study	Year	Area	Study design	Age (statins/control) (years)	Patients (statins/control)	Control treatment	Disease	PH group	PAP (mmHg)	LDL	Gender (M/F)	Statins	Dose (mg/day)	Treatment time (months)	Follow-up time (months)
Barreto	2008	Brazil	Randomized, double-blind, placebo-controlled trial	34.6±12.3/33.7±11.1	30/30	Placebo	IPAH or PAH-CHD	1	53±16	NA	24/36	Rosuvastatin	10	6	6
Lee	2009	Taiwan (China)	Randomized, double-blind, placebo-controlled trial	71±8/72±6	27/26	Placebo	COPD + PH	3	>25	145±46/148±50 mg/dL	39/14	Pravastatin	40	6	6
Wilkins	2010	Germany	Randomized, double-blind, placebo-controlled trial	43.2 [19–67]/49.1 [24–73]	19/23	Placebo	PAH	1	55.8±10.3/55.7±12.5	NA	10/32	Simvastatin	80	6	12
Kawut	2011	United States	Randomized, double-blind, placebo-controlled trial	50.5±14.3/51.0±13.6	32/33	Placebo	PAH	1	NA	110±22/104±21 mg/dL	9/56	Simvastatin	40	6	6
Zeng	2012	China	Randomized, double-blind, placebo-controlled trial	35±13/37±13	112/108	Placebo	PAH or CTPH	1 or 4	69±19/66±20	2.3±0.7/2.3±0.8 mmol/L	76/144	Atorvastatin	20	6	6
Liu	2013	China	Randomized, controlled trial	66.2±7.4/64.9±8.2	33/35	No statin	PHD	3	52.7±8.1/51.7±7.9	NA	43/25	Atorvastatin	20	6	6
Moosavi	2013	Iran	Randomized, triple-blind, parallel-group trial	65±11/68±14	24/21	Placebo	COPD + PH	3	>40	109±33/104±31 mg/dL	28/17	Atorvastatin	40	6	6
Chogtu	2016	India	Randomized, double-blind, placebo-controlled trial	61.4±8.4/65.9±9.7	32/30	Placebo	COPD + PH	3	30< sPAP <75	NA	NA	Rosuvastatin	20	3	3
Arian	2017	Iran	Randomized, double-blind, controlled trial	65.8±11.5/63.7±7.6	21/21	No statin	COPD + PH	3	47.9±15.4/49.2±16.3	133.4±27.8/111.1±27.3 mg/dL	11/23	Atorvastatin	40	6	6

PH, pulmonary hypertension; PAP, pulmonary arterial pressure; LDL, low-density lipoprotein; M, male; F, female; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; CHD, congenital heart disease; NA, not available; COPD, chronic obstructive pulmonary disease; CTPH, chronic thromboembolic pulmonary hypertension; PHD, pulmonary heart disease; sPAP, systolic pulmonary arterial pressure.
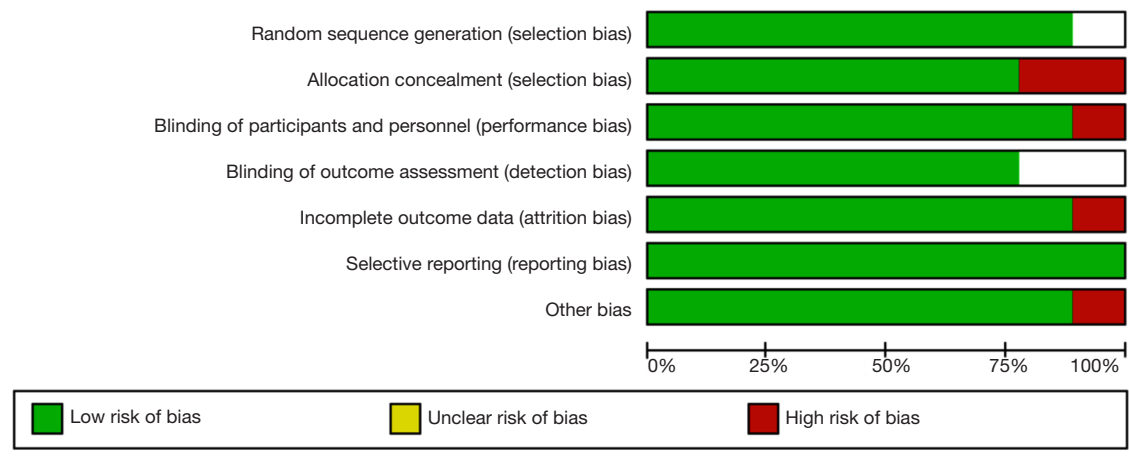
Figure 2 Risk of bias graph.

groups. There was no statistically significant difference in all-cause mortality (RR =0.77, 95% CI: 0.36 to 1.65; P=0.514) (*Figure 3*). The heterogeneity among trials was not significant (I^2=0.0%).

Sensitivity analysis

The leave-one-out sensitivity analysis for the effect of statins on PAP in PH patients that was performed by using both random and fixed effect models, and practically the same outcomes were found. No pooled results or heterogeneity of this meta-analysis was significantly altered (*Figure 5*).

Discussion

This systematic review and meta-analysis assessed the efficacy and safety of statins in PH with nine RCTs, which yielded the following outcomes. First, statin therapy could significantly reduce PAP, as well as LDL level in patients with PH, whereas 6MWD and CDI showed no statistical amelioration. Second, there were nonsignificant trends toward rise of the incidence rate of adverse events and all-cause mortality in a short term. Third, according to the subgroup analysis, there was an obvious reduction of PAP in PH due to COPD, but not PAH, treated with statins.

PH, means an abnormal augment of PAP due to elevated pulmonary vascular resistance, whose main vascular changes are vasoconstriction, thrombosis and vascular remodeling associated with smooth-muscle cell and endothelial-cell proliferation (4). Since the pleiotropic properties with

regard to cardiovascular system of statin drugs, a couple of researches have paid attentions to statin therapy in PH. The outcomes concerning PAP in this study were in agreement with that of several studies applying animal models (26-28). Carlin *et al.* revealed that some sorts of statins such as Fluvastatin could reduce PAP in PH rats (26). The finding of Li *et al.* showed that rosuvastatin administration could ameliorate mean PAP in Monocrotaline-induced PAH in rats, which might result from the regulation of Rho-associated coiled-coil-containing kinase 1 (ROCK-1), proliferating cell nuclear antigen (PCNA), and endothelial nitric oxide synthase (eNOS) expression (27). That is to say, the present outcomes confirm and extend the previous outcomes regarding the favorable impacts of statins on PAP. Also, the potential mechanisms deserve attention, in the included RCTs of this meta-analysis, Lee *et al.* inferred that statins inhibiting the generation of endothelin 1 (ET-1) was one of the possible reasons, as urinary ET-1 levels were significantly reduced in pravastatin-treated patients (18). Combined with analyses of antecedent researches, it is reasonable to infer that statins decrease PAP by prompting apoptosis, an important physiological process to reverse pulmonary artery remodeling, inhibiting smooth-muscle cell proliferation, promoting secretion of vasodilators such as prostacyclin and nitric oxide, inhibiting endothelin generation and anti-inflammatory, etc. (29-32).

However, not all the related researches favor statins' improving PAP, making us consider possible reasons. In the RCT conducted by Moosavi *et al.*, Atorvastatin therapy did not notably ameliorate the systolic PAH (SPAH) in PH and they got an idea that, small sample size could be
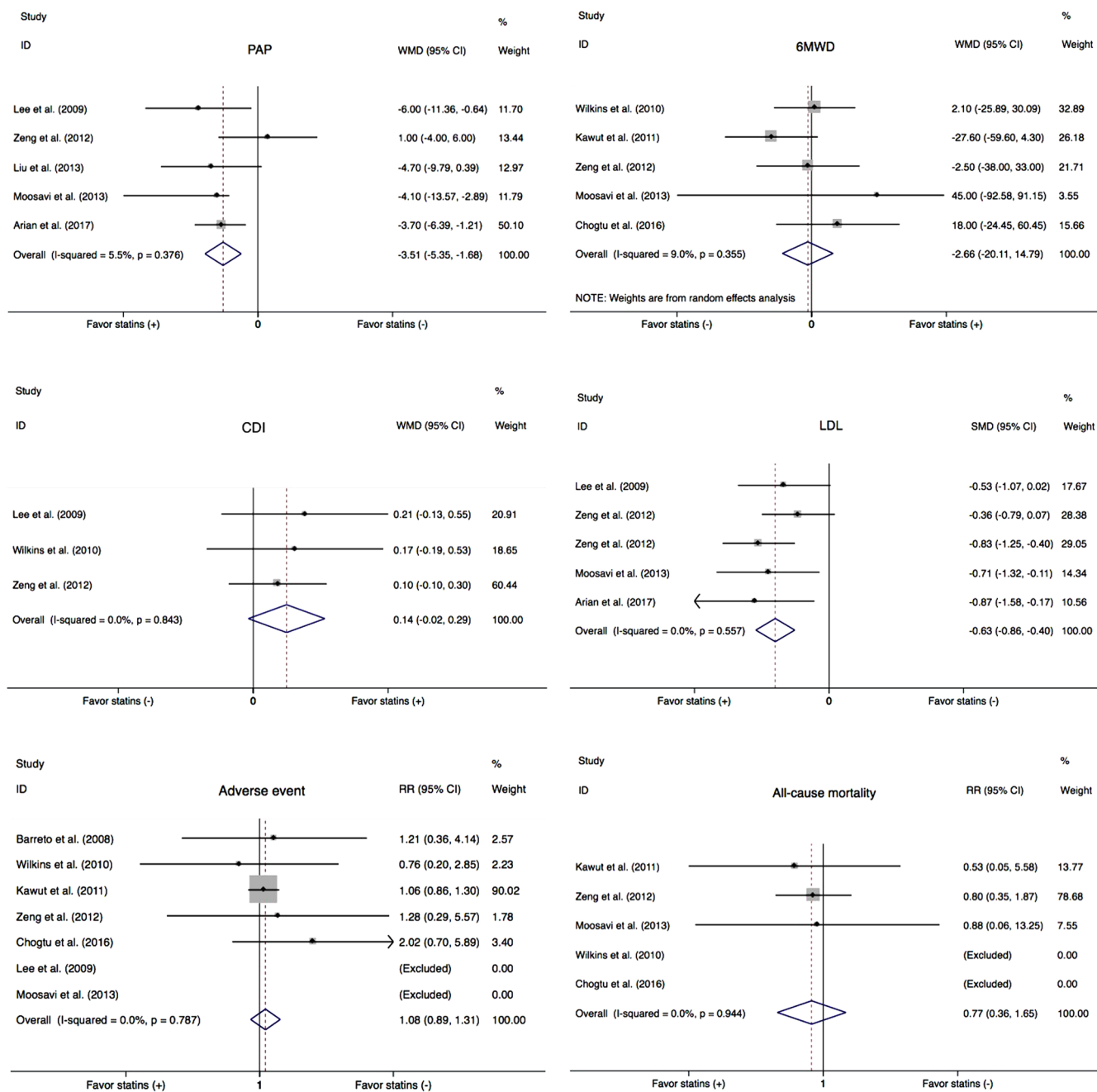
Figure 3 Summary effects of statins in PH. PAP, pulmonary arterial pressure; WMD, weighted mean difference; CI, confidence interval; 6MWD, 6-minute walking distance; CDI, cardiac index; LDL, low-density lipoprotein; SMD, standardized mean difference; RR, risk ratio; PH, pulmonary hypertension.
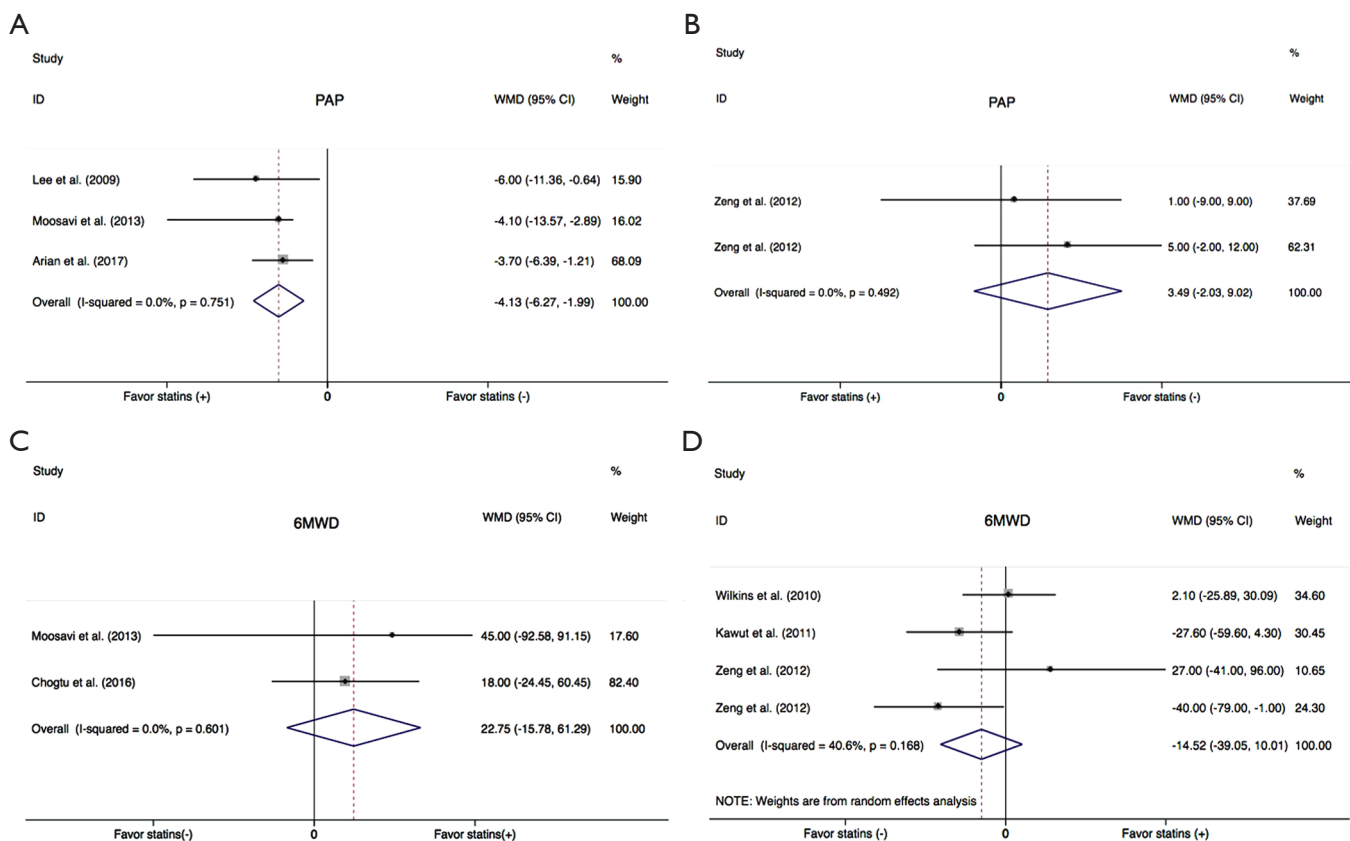
Figure 4 Summary effects of statins on PAP (A,B) and 6-minute walk distance (C,D) in COPD (A,C) and PAH (B,D). PAP, pulmonary arterial pressure; WMD, weighted mean difference; CI, confidence interval; 6MWD, 6-minute walking distance; PAH, pulmonary arterial hypertension; COPD, chronic obstructive pulmonary disease.

a main account for it (23). Given the discordant results, we can make a speculation that results might be affected by the sorts and dosages of statins, clinic types of PH, background diseases, other drugs, duration and sample size, etc. For instance, previous study showed that pravastatin, instead of simvastatin, slowed down the progression of PH (33). Moreover, Carlin *et al.* reported that some sorts of statins like fluvastatin may be more effective in PAP (26). Statins differ in metabolism, pharmacological lipophilicity, structure and solubility, which may give rise to different efficacy in PH. In the five included RCTs concerning PAP, four applying atorvastatin showed improvements in PAP except Zeng *et al.*, who used atorvastatin at 10 mg/day whereas others used at 20 or 40 mg per day. This might indicate that atorvastatin plays a protective part in PH, and the dosage of significant effects should not be lower than 20 mg (18,21-23). In addition, there would be biases because of PH patients' older ages and background diseases. This study excluded background diseases, since

severe gastrointestinal disorders and liver dysfunction could undermine the absorption and metabolism of drugs. Although it was suggested that patients with COPD at elevated cardiovascular risk might be the appropriate subgroup for statins (34,35), potential impacts of cardiovascular diseases remain controversial. Of course, drug interaction cannot be neglected, such as the interplay between statins and clopidogrel, being used in cardiovascular diseases frequently, consequently promoting platelet aggregation, which does harm to cardiovascular system, as well as weakens beneficial effects of statins. Potential influencing factors above could also explain the unexpected outcomes of 6MWD, which correlates with markers of disease severity in PH, such as pulmonary haemodynamics (36). According to the pathogenesis, the improvement of 6MWD may be later than that of PAP, indicating a longer duration is needed for the change. And another plausible explanation for it was that 6MWD depends largely on motivation and encouragement, making
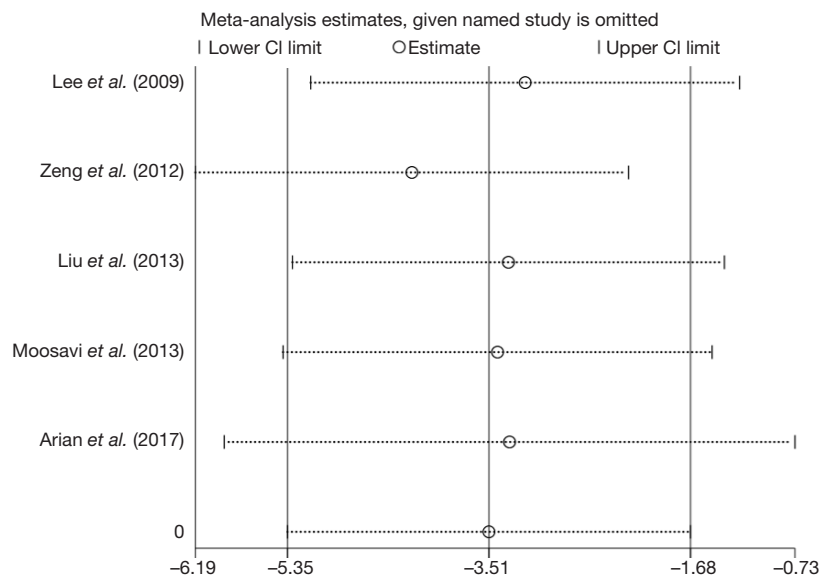
Figure 5 The leave-one-out sensitivity analysis for the effect of statins on PAP in PH patients. CI, confidence interval; PAP, pulmonary arterial pressure; PH, pulmonary hypertension.

it difficult to standardize (37). On basis of information above, a well-conducted study is necessary.

PAH and PH due to COPD, as two clinic subtypes of PH, differ in primary causes and pathogenesis. Previous studies have indicated the effects of statin therapy in PAH and COPD were inconsistent (10,17,24,38). In our meta-analysis, PH due to COPD patients appeared to benefit more than the PAH from statins. There were possible reasons. First, ever-increasing researches have proved that COPD is a chronic systemic inflammation (35,39). Inflammation and hypoxia impair pulmonary blood vessels, ultimately leading to PH. It is noticeable, COPD patients conspicuous changes in pulmonary vascular remodeling (40). Moreover, anti-inflammation and maintaining endothelial cell function properties make statins favourable to PH due to COPD (5,7). Actually, statin therapy has played a major role in the prevention and reversal of PH secondary to hypoxia in studies. Second, PAH as the group 1 of PH, which comprises various causes of diseases, such as idiopathic (IPAH), heritable forms, congenital systemic-to-pulmonary shunts and other conditions (20). It is worth nothing that, the nine included RCTs, only one (Zeng *et al.*) reported the change value of PAP in whole PH patients and the subgroups of PAP in PAH patients (connective tissue disorder and congenital heart disease), combined with the research of Rysz-Górzynska *et al.* showing that statins treatment had nonsignificant change

of PAP among PAH patients (11). It is possible that these mixed diseases included in PAH group limit the overall efficacy of statins. However, the direct pulmonary vascular effect of statin in PAH is unclear. Therefore, it is advisable to explore the causes of PAH simultaneously. On basis of the ever-growing incidence rate of COPD, it would be promising to get more efficient and valuable results if future studies recruit more PH combined with COPD patients to determine the role of statin therapy.

In terms of safety, common statin-induced adverse effects containing liver impairing, bleeding, irregular menstrual cycles, abdominal distention and their likes (10). Several rare but serious, such as rhabdomyolysis, new-onset diabetes, and possibly acute kidney injury make it necessary to determine the safety of statin therapy in PH concerning does, type and time (41). Nakano *et al.* suggested statin therapy was relatively safe among PH patients, which was similar to this study's (42). Further, there was a research revealed statins' significant chemopreventive effect to reduce cancer risk in COPD (42,43). However, in view of the short-term duration our finding, while PH requiring long-term drug therapy, we should consider the results dialectically. Liang *et al.* made a subgroup analysis showing that fluvastatin had a significant impact on liver, and the incidence rate of adverse events increased when the dose of statins more than 40 mg. They also indicated side effects associated with statin therapy were more obvious in the first

2 years (44). It is worth nothing that this study only assessed the liver function, with the recruited patients were not all suffering PH. Nonetheless, future researches can still base on it, further optimize the inclusion and exclusion criteria, increase indicators to better assess the safety of statins, especially long-term safety.

Limitation

This systematic review and meta-analysis has limitations. First, the overall scale of the contributing studies was small and the confidence intervals were wide, which are limited by the source data. Second, several important specific outcomes of COPD and PAH including adverse events and all-cause mortality could not be analyzed in subgroups, due to lack of reported outcomes in trials. Third, despite generally similar demographic characteristics and minimal evidence of heterogeneity among these RCTs, some confounding factors such as different types and doses of statins, which might have caused potential biases. Fourth, our study only includes three subtypes of PH patients (types 1, 3 and 4), therefore the outcomes may not suitable for all groups of the PH patients. Future clinic trials with rigorously predefined patient inclusion criteria are warranted to better research the potential role of statin therapy in PH.

Conclusions

This systematic review and meta-analysis showed that with routine treatment, adding statins could be beneficial for PAP, but not 6MWD and CDI in PH. And during short-term therapy, adverse events and mortality were not apparent, suggesting a relative safety. It is advisable that more future researches should focus on the efficacy and safety of statin therapy in different subtypes of PH.

Acknowledgments

Footnote

Conflicts of Interest: The authors declare they have no conflict of interests.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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