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META-ANALYSIS OF STATINS IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH PULMONARY HYPERTENSION

Jie Li*, RuiChen Hu, Mo Liang
Department of Respiratory Medicine, Hunan Provincial People's Hospital/The first affiliated hospital of Hunan Normal University, Changsha 410016, China.
Corresponding Author: Jie Li, Email: lijie230630@163.com

Abstract: Objective To systematically evaluate the meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH). Methods: Systematically searching PubMed,CBM, VIP and Wanfang databases, and comprehensively collecting randomized controlled trials (RCT) of statins in the treatment of chronic obstructive pulmonary disease with pulmonary hypertension. According to the inclusion and exclusion criteria, literatures were screened, Meta were extracted and methodological quality was evaluated, and meta-analysis was performed by RevMan 5. 0 software. Results: Seven RCTs were included, with a total of 356 patients. Including 2 placebo-controlled trials and 5 non-placebo-controlled trials. Meta-analysis showed that: ① statin could improve the mean pulmonary arterial pressure (mPAP) [MD=-3. 83 mmHg, 95% ,CI(-5. 2, -2. 43)}, and the pulmonary arterial systolic pressure (PASP) [MD =-5. 66 mmhg, 95%, cl (-7 ... ②statin can significantly reduce the endothelin -1(ET-1) value [MD =-3. 51 pg/m1, 95% Cl, (-4. 77,-2. 55)] and increase the nitric oxide (NO) value [SMD = 1. 06,95%, CI (0 .. ③statin can improve the percentage of forced expiratory volume in the first second (FEV,%) [MD = 2. 92,95%, CI (-2.83,8.68)]. Conclusion: Statins can significantly improve pulmonary artery pressure, pulmonary function and clinical efficacy in COPD patients with PH.
Keywords: Chronic obstructive pulmonary disease; Statins; Meta analysis

Pulmonary hypertensionStatins, that is, 3- hydroxy -3- methylglutaryl-coenzyme A [3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)] reductase inhibitors, mainly inhibit the conversion of HMG-CoA to mevalonic acid, MVA) competitively, thus blocking cholesterol synthesis and lowering blood cholesterol levels. Large-scale clinical trials 4s, LIPID, CARE, WOSCOPS, AF CAPS/TEX CAPS and HPS have proved that statins can significantly reduce the incidence and mortality of coronary heart disease and play an important role in primary and secondary prevention of cardiovascular diseases. At present, statins are widely used in clinic: simvastatin, atorvastatin, lovastatin, pravastatin, fluvastatin, rosuvastatin and pitavastatin. After cerivastatin was approved for listing in 1998, it was delisted in 2001 because of the high incidence of fatal rhabdomyolysis. With the incidence of hyperlipidemia increasing year by year [1-2], the utilization rate of statins is also rising rapidly. In 2011, simvastatin became the second largest prescription drug in the United States. Many studies have shown that besides lowering blood lipid, statins have many clinical effects, which are called pleiotropic effects of statins, mainly including: reducing or eliminating inflammatory reaction, anti-oxidative stress, improving endothelial cell function, inhibiting smooth muscle cell proliferation, inhibiting tumor cell proliferation, regulating immunity, anticoagulation, stabilizing plaque, promoting bone anabolism, promoting angiogenesis, etc. The multiple effects of statins provide a new way to prevent and treat many clinical diseases, such as cardiovascular diseases, respiratory diseases, diabetes, kidney diseases, multiple sclerosis, malignant tumors and osteoporosis, and its role in chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension. PH) has become the focus of clinical attention in recent years.

Statins are very important drugs for the prevention and treatment of hypercholesterolemia and atherosclerotic diseases at present, and their adverse reactions include myopathy, elevated liver enzymes and increased risk of diabetes. With the increasing incidence of coronary heart disease and the discovery of the pleiotropic effects of statins, the usage and clinical application range of statins are also expanding, and the safety of statins has increasingly attracted the attention of clinicians and academic circles. In recent years, people began to explore the role of meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) [3-6]. Statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) is one of the most popular studies. At present, many studies have reported the Meta-analysis relationship of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH), but the results are quite different. In this study, the related studies were comprehensively collected and quantitatively analyzed by systematic evaluation and meta-analysis, so as to provide statins for the treatment of COPD complicated with pulmonary hypertension.

Chronic obstructive pulmonary disease (COPD) is a common disease that seriously endangers human health. It is characterized by incomplete reversible airflow restriction and has a high mortality. An epidemiological survey involving seven regions in China shows that the total prevalence of COPD among people over 40 years old is 8.2%, and the prevalence rate in rural areas is even higher, reaching 8.8%. It is estimated that it is currently the fourth leading cause of death in the world, and it is expected to become the third leading cause of death in the world by 2025. When COPD

patients are complicated with pulmonary hypertension, the survival rate and quality of life deteriorate rapidly, and the prognosis becomes worse [4]. Studies have shown that the risk of death will increase by more than 4 times for every 1OmmHg increase in average pulmonary artery pressure. Therefore, effective control of pulmonary hypertension plays an important role in delaying the progression of COPD and improving the survival rate of patients. The conventional treatment of COPD complicated with PH is mainly aimed at the primary disease, improving symptoms, including continuous low-flow oxygen inhalation through nasal catheter, controlling respiratory tract infection, relieving spasm and asthma, relieving cough and phlegm, diuresis, anticoagulation, etc. These methods can't prevent the progress of PH from getting worse, so new treatment methods need to be studied. Many studies at home and abroad have shown that statins can inhibit the inflammatory reaction of COPD patients, reduce the risk of all-cause mortality and acute exacerbation, and improve the quality of life. A large number of animal experiments have found that statins can improve cardiopulmonary vascular remodeling and reduce pulmonary artery pressure. At present, domestic and foreign studies have explored the therapeutic effect and possible mechanism of these drugs on COPD complicated with PH, but the sample size is small, the methodological quality is low, and the research results are not consistent. At present, for the treatment of COPD-related PH, the role and choice of drugs are limited. Statins, that is, 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors, have the functions of anti-inflammation, anti-oxidation, improving endothelial function, stabilizing plaque, reducing the activation of neuroendocrine, improving myocardial remodeling, anticoagulation, anti-platelet, stimulating endothelial progenitor cell differentiation, etc. [5-7], and their role in PH has been paid more and more attention. Up to now, many clinical trials have observed the efficacy and safety of statins in the treatment of COPD complicated with PH, but most of them have small sample size, low methodological quality and inconsistent research results. In recent years, more and more evidences show that statin can dilate blood vessels, inhibit the proliferation of smooth muscle cells, improve endothelial function, promote angiogenesis, and inhibit inflammatory reaction, which are independent of their lipid-lowering effects, thus improving the remodeling of cardiopulmonary blood vessels and reducing pulmonary artery pressure. They may be promising drugs for treating PH, inhibiting the development of cor pulmonale and improving the prognosis of cor pulmonale. Most of the existing related studies are non-randomized controlled clinical studies, and the sample size is small, and the clinical efficacy is not completely consistent. There is insufficient evidence that statins can reduce the pulmonary artery pressure and improve the therapeutic effect in patients with stable COPD and PH. Therefore, it is necessary to make a systematic and quantitative comprehensive analysis of the existing research results by using meta-analysis method, so as to guide clinical rational drug use and provide reliable evidence for its efficacy and safety.

With the continuous expansion of drug use, the safety of statins has been paid more and more attention. Generally speaking, these drugs are well tolerated, with fewer adverse reactions, and liver transaminase elevation and myotoxicity are recognized adverse reactions at present. Large-scale randomized controlled clinical trials show that the incidence of the increase of alanine aminotransferase, ALT) and aspartate aminotransferase,AST) in the lowest dose treatment is about 0.1 %~0.2%, even in the approved high dose range, it is only 2%~3%[8~11]. The results of such experiments and observational studies also show that the increase of liver enzymes in patients taking statins will not exceed 3 times of the upper limit of normal value. Myotoxicity is the most typical and serious adverse reaction of statins, mainly manifested as myalgia, myositis and rhabdomyolysis with or without elevated serum creatine kinase, CK). The criteria and incidence of muscle adverse reactions reported in different studies are also different. A systematic review of 21 clinical trials indicates that the incidence of mild myalgia, myopathy and rhabdomyolysis caused by statin therapy is 190,5,1.6/100,000 person-years, respectively. In observational studies, the incidence of mild adverse reactions related to statin is much higher than that of experimental studies (about 5%~10%). Studies have pointed out that about 25%~50% of patients with coronary heart disease stop taking statins for one year. Although there are many factors influencing drug withdrawal, most of them think that adverse reactions are the main reason for their non-compliance. The mechanism of statin-induced muscle adverse reactions has not been fully clarified. Studies have found that factors such as advanced age, women with low body mass index, strenuous physical exercise, high-dose use of statins and combined use with drugs that interfere with the distribution and metabolism of statins may increase the risk of statin adverse reactions. In addition, the adverse reactions of statins also showed obvious individual differences.

Systematic evaluation is a comprehensive literature research method, which systematically and comprehensively collects the existing research results according to the research purpose, screens out the documents that meet the standards according to strict quality evaluation principles and methods, and scientifically synthesizes them qualitatively or quantitatively, and finally draws comprehensive and reliable conclusions. Meta-analysis is a quantitative synthesis method in systematic evaluation, which can avoid the limitation of single small sample study, enlarge the sample size, increase the efficacy of statistical test, quantitatively estimate the average level of research effect and evaluate the inconsistency of research results. Sub-group analysis includes a small number of studies, which may lead to unstable merger results.

In this study, evidence-based medicine systematic review and meta-analysis were used to study the correlation of meta-analysis polymorphism of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH), so as to provide scientific basis for clinical application of statins in respiratory system, prediction of statins toxicity, guidance of individualized medication, reduction of adverse reactions and improvement of drug compliance.Through systematic evaluation and Meta-analysis, the best current research evidence can be produced to solve the problems in disease prevention, diagnosis, treatment and prognosis,This study focuses on the changes of indexes before and after treatment, refers to "Impacting standard deviations for changes from baseline" recommended by Cochrane's manual, and estimates the Meta value and standard deviation of the changes of indexes in

the two groups thus promoting rational drug use and scientific health decision [12], and the shortcomings of the original research can also be found, providing new ideas and directions for future research.

COPD is a chronic respiratory disease that seriously harms human health, and can cause systemic adverse effects. Long-term hypoxia, high inflammatory level, oxidative stress, etc. lead to the injury and abnormal proliferation of pulmonary vascular endothelium, resulting in a decrease in the production and release of nitric oxide, NO), and an increase in the synthesis and secretion of endothelin-1 (ET-1), which leads to pulmonary vascular contraction and remodeling: inflammation [such as interleukin-6 (IL-6) Combined with pulmonary arteriole microthrombosis, pulmonary circulation resistance continues to increase, eventually leading to pH. When the patient is complicated with PH, the survival rate and quality of life deteriorate rapidly, and the prognosis becomes worse. At present, the treatment of COPD-related PH, drug action and choice are quite limited. Statins have been paid more and more attention because of their pleiotropic effects in pH. Up to now, many clinical trials have explored the role and possible mechanism of statins in CO PD complicated with PH, but the sample size is small and the clinical effects are not consistent [13-16]. This study explored the effects and safety of statins on the quality of life, dyspnea symptoms, pulmonary function, pulmonary artery pressure, vasoactive substances and inflammatory factors of COPD patients with PH by systematic evaluation and Meta-analysis, in order to provide scientific basis for developing new treatment methods.

1 DATA AND METHODS

Literature search computer search PubMed, embase, the Cochrane library, web of science, CBM, CNKI, VIP and WanFang Data, and trace the references included in the research. The key words include statins, COPD and PH-related words. Statin-related drugs: "hydroxymethylglutaryl CoA reductase inhibitor, statin, HMG-CoA reducer inhibitor, statin, simvastatin, lovastatin, fluvastatin, atorvastatin, pravastatin, rosuvastatin, cerivastatin, mevastatin". Related to COAD: "Chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, chronic airway obstruction, chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, chronic ie, Obstructive Airway Disease、ChronicAirflow Obstruction、Pulmonary Disease，Chronic Obstructive"[17-20]. PH correlation: "Pulmonary hypertension; Pulmonary hypertension; Pulmonary hypertension; Pulmonary hypertension; Lung; Hypertension; pulmonary hypertension; pulmonary arterial hypertension; pulmonary vascular disease; PH; PA H; Hypertension,Pulmonary "。 Search by combining free words with subject words. Some search terms are connected by the logical symbol OR, AND the three search terms are connected by the logical symbol AND. The retrieval time is from the database establishment to March 23, 2017.

The research subjects have published prospective randomized controlled studies or well-designed non-randomized controlled studies on the efficacy of statin alone or in combination with conventional therapy in the treatment of stable COPD patients with PH.

1.1 Types of Patients

The types of patients are in line with the relevant diagnostic criteria of COPD Diagnosis and Treatment Guide formulated by COPD Group of Respiratory Branch of Chinese Medical Association in 2007 and the definition of American Thoracic Association. Patients diagnosed as COPD are all in the stable stage of the disease, and no acute exacerbation occurred in the first half year of the trial. The diagnostic criteria of pulmonary hypertension are mPAP≥25mmHg measured by right heart catheter at sea level rest or MPAP ≥ 30mmhg during exercise [21-23]. If there is no data of right cardiac catheter, Doppler ultrasound showed PASP≥40 mmHg.

1.1.1 Inclusion criteria

(1) The original data are published original documents, and the content is about the study of the curative effect of statin alone or in combination with conventional treatment on stable COPD patients with PH. (2) The original literature is a prospective randomized controlled study or a well-designed non-randomized controlled study. (3) There are clear counting data at the end of follow-up in the original literature. (4) The follow-up rate of the study is over 95%.

1.1.2 Outcome indicators

① Pulmonary function: forced expiratory volume in the first second (FEV),FEV, the percentage of the expected value (FED %}, forced vital capacity (FVC) and FEV,/FVC; ② Pulmonary artery pressure: sPAP and mPAP; ③ Borg dyspnea score; ④ Exercise endurance: 6 min walking distance (6 MWD); ⑤ Adverse reactions.

Exclusion criteria (1) Studies with inaccurate or unclear diagnostic criteria for unreported cases were excluded, and studies with pulmonary hypertension caused by primary PH and other types and heart diseases (including rheumatic heart disease, valvular heart disease, congenital heart disease, history of cardiothoracic surgery [24-25], autoimmune diseases, severe liver and kidney dysfunction, malignant tumor, asthma and active tuberculosis) were reported. (2) No available raw data is provided and the request is fruitless; (3) Repeatedly published literatures, and only the studies with the most complete data are collected; (4) The original data is not a study that directly compares the curative effect of patients with stable COPD and PH with statin and conventional treatment. (5) At the same time, it is accompanied by heart diseases such as valvular heart disease and congenital heart disease, autoimmune diseases, malignant tumors, abnormal liver function, kidney diseases and systemic inflammatory diseases, and the selected persons have not taken statins for nearly 3 months. (6) The original literature data cannot be used.

1.2 Methods

1.2.1 Interventions

This study is to analyze the published papers with the method of systematic evaluation to obtain the final results and quantify them. The quality of the original data directly affects the credibility of this study. The final concern of this study is whether conventional therapy combined with statin can improve pulmonary artery pressure in stable COPD patients with PH compared with conventional therapy alone [26] and improve clinical efficacy. Treatment group: atorvastatin (20 mg /dqd) or simvastatin (4mg/d qd) or fluvastatin (40mg/d qd) or pravastatin (40mg/d qd)+ conventional treatment. Control group: Conventional treatment or conventional treatment plus placebo. Conventional treatment includes low-flow oxygen inhalation through nasal catheter, control of respiratory tract infection, relieving cough, relieving asthma and eliminating phlegm.

1.2.2 Data sources

Data sources used in data retrieval (1)Pubmedo(2) China Biomedical Literature Database (CBM) o③ VIP information resource system. (4) Wanfang Data Knowledge Service Platform. Search strategy: keyword search and keyword search, combined with literature tracing and manual search. COPD, chronic obstructive pulmonary disease, pulmonary hypertension and statins were used as key words. The related literatures were searched with obstructive pulmonary disease, chronic pulmonary hypertension [27-28] and statins as key words. The English key words are: pulmonary disease, chronic, pulmonary hvperten-sion, statin. The language is limited to Chinese or English. The original literature sample size and follow-up years are not limited. According to the inclusion and exclusion criteria, the literature is screened and cross-checked. The screening process is as follows: first, read the title; if it meets the inclusion criteria, further read the abstract; if it meets the inclusion criteria, continue to read the full text; if it meets the inclusion criteria, it will be included.

1.2.3 Literature screening

Before the formal screening, two researchers randomly selected 10 literatures from the search results independently, and pre-screened them according to the pre-established screening criteria, so as to discuss whether the screening criteria are appropriate, and at the same time train the researchers to use the selection criteria uniformly and normatively. During the formal screening, two evaluators independently screen and cross-check according to the final inclusion and exclusion criteria. In case of disagreement, an agreement can be reached through discussion or reference to the opinions of a third party. First of all, read the titles and abstracts of the literature for preliminary screening, search for the full text of the literature retained in the preliminary screening and those that can't be determined whether or not to be excluded, then screen the full text for the second time, and list the excluded literature and its reasons during the full text screening.

1.2.4 Data extraction

Before starting data extraction, select several representative literatures, and use the pre-established data extraction table for pre-test to check whether it has some defects such as missing some important items, too many items, etc., and further revise and improve them. Two researchers independently extracted the information included in the study and cross-checked, and any disagreement was resolved through discussion or third-party arbitration. The extracted contents mainly include: ① Basic information included in the study: the title of the literature, the first author, the publication time, the country of publication and the source of the literature, etc. ② Research methods and possible bias: grouping method, whether grouping method is hidden, whether blind method is adopted, and whether withdrawal and withdrawal are described; ③ Characteristics of research subjects: number of cases, age, sex ratio, research location, diagnosis criteria of cases, inclusion and exclusion criteria of research subjects, COPD stage and whether there are any complications, etc. ④ Intervention measures: drug name, administration route, dosage, treatment time, control mode, etc. ⑤ Measurement data information of various outcome indicators before and after treatment; Mean and its standard deviation, the number of adverse reactions (any adverse reactions occurring during the trial, including gastrointestinal reactions, elevated transaminase and CK, etc., are included in this paper, excluding those who can be relieved by themselves without special treatment, drug reduction or withdrawal); Including research methods of key elements of quality evaluation, basic data of patients in experimental group and control group [29], intervention measures and methods, and observation time; Before and after treatment, pulmonary arterial pressure, endothelin -1, nitric oxide, improvement of pulmonary function (FEV, 0o) and adverse reactions during treatment were observed.

1.3 Data Extraction

Before starting data extraction, select several representative literatures, and use the pre-established data extraction table for pre-test to check whether it has some defects such as missing some important items and too many items, and further revise and improve them. Two researchers independently extracted the information included in the study and cross-checked, and any disagreement was resolved through discussion or third-party arbitration. The extracted contents mainly include: ① Basic information included in the study: the title of the literature, the first author, the publication time, the country of publication and the source of the literature, etc. ② Research methods and possible bias: grouping methods, whether grouping methods are hidden, whether blind methods are adopted, and whether withdrawal and withdrawal are described; ③ Characteristics of research subjects: number of cases, age, sex ratio, research place, diagnosis criteria of cases, inclusion and exclusion criteria of research subjects, COPD stages and complications, etc. ④

Intervention measures: drug name, administration route, dosage, treatment time, control mode, etc. ⑤ Measurement data information of various outcome indicators before and after treatment: mean and its standard deviation, the number of adverse reactions (any adverse reactions during the trial, including gastrointestinal reactions, elevated transaminase and CK, etc., are included in this paper, excluding those who can be relieved by themselves without special treatment, drug reduction or withdrawal).

1.4 Evaluation Index of Curative Effect

the most important outcome variables in the original literature involved in this study are the improvement of pulmonary artery pressure (including PASP and mPAP) and pulmonary function [the first second forced expiratory volume (FEV) or the percentage of the first second forced expiratory volume to the expected value (FEV%)]; Secondary outcome: the improvement of blood endothelin -1(ET-1) and nitric oxide (NO).

1.5 Statistical Analysis

(1) First, clinical and statistical homogeneity analysis is conducted to find out whether there are factors that affect clinical heterogeneity. At the same time, P-value and I-value are used to judge whether there is heterogeneity among the studies. P < O.10 is taken as the standard of heterogeneity; I ≤ 50% indicates that the heterogeneity is acceptable, and I ≥ 75% indicates that the heterogeneity is obvious, so it cannot be combined for analysis. If there is no obvious statistical and clinical heterogeneity in the included study, the fixed effect model is used for analysis; Otherwise, the source of heterogeneity should be analyzed. If there is no obvious clinical heterogeneity, the random effect model can be carefully combined and analyzed. The continuous variables PASP, mPAP, FEV% are expressed by mean standard deviation, and the effect quantity is expressed by 95%. RevMan 5.0 software is used for statistics. Sub-group analysis is carried out when necessary. (2) You can also use Revman5.3 software provided by Cochrane Collaborative Network for Meta-analysis. The data were analyzed by the changes of indexes before and after treatment. Since all the original studies included only reported the average and standard deviation of indexes before and after treatment, the following formula was used to calculate the average and standard deviation of the changes before and after treatment.

$$M_{change} = M_{final} - M_{baseline}$$

$$SD_{change} = \sqrt{SD^2_{baseline} + SD^2_{final} - (2 \times Corr \times SD_{baseline} \times SD_{final})}$$

The formula is from "impacting standard deviations for changes from baseline" in Cochrane handbook for systematic reviews of interventions (version 5.1.0), 16.1.3.2, and the value of Corr is set to 0.5, which is substituted into the formula for calculation. Mean difference (MD) or standardized mean difference, SMD) and its 95% confidence interval < confidence interval, CI) are used as the combined statistics of measurement data, and odds ratio, OR) and its 95% CI are used as the combined statistics of counting data. Yin test was used to test the heterogeneity among the included research results. When the heterogeneity test results are P > 0.10, I < 50%, it can be considered that there is homogeneity among multiple studies. Meta-analysis is carried out by using the fixed effect model, whereas statistics are combined by using the random effect model. To explore the source of heterogeneity, subgroup analysis was carried out according to the type, dosage and treatment time of statins, and sensitivity analysis was carried out by switching effect model, eliminating low-quality studies and only including stable patients. Begg rank correlation method and Egger linear regression method were used to test publication bias (Stata I 2.0). All p values are bilateral tests, and P ≤0.05 is considered statistically significant [30-35].

2 RESULTS

2.1 A Total of 115 Related Literatures were Retrieved

By reading the titles and abstracts, obviously irrelevant literatures were excluded, followed by reviews, conference reports and repeatedly published literatures. A total of 15 literatures were collected. Read the full text carefully one by one to further screen, and exclude the literature with blank research, non-clinical trials, different intervention methods and incomplete data. Finally, 7 articles were included, totaling 356 patients (see Figure 1). Seven papers are randomly grouped, only two of them specifically describe the random allocation method [5,9], and the rest are not clearly described; A double-blind, well-hidden, placebo-controlled study was used in one study, and the rest of the control groups were treated with routine treatment. See Table 1 for the general situation of literature inclusion and Table 2 for methodological evaluation of literature quality.

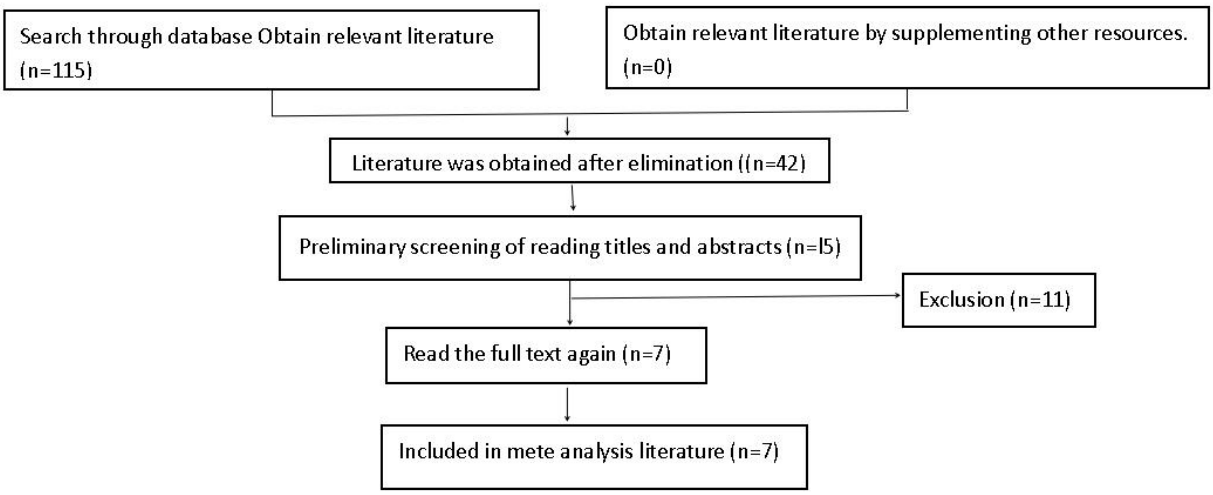

Figure 1 The Progres and Results of Researches Included and Excluded

Table 1 The General Data of Inclusive Researches

document	case load(T/C)	Gender (male/female)	Age (years)	complication	Smoking situation	Intervention measure treatment group	control group	Observation time (months)	adverse effect
Yu Fengxia (2012)	78/78	128/38	64.8 ± 6.7	without	mention	Statin ten others	other	12	Unmentioned
Zhang Yuqing(2010)	27/28	47/8	67 ± 4.0	without	mention	Statin ten others	other	6	have
Wang Lingling(2011)	35/56	46/24	63 ± 45.2	without	mention	Statin ten others	other	6	Unmentioned
LeeTMC(2009)	27/26	39/14	71±6	without	mention	Statin ten others	Ten other placebos	3	without
Cao Yanhong(2012)	18/18	24/12	66 ± 7.0	without	Unmentioned	Statin ten others	other	3	Unmentioned
Tang yanfen(2010)	18/17	23/12	65 ± 6.0	without	Unmentioned	Statin ten others	Ten other placebos	3	Unmentioned
Liu yunli(2010)	31/31	52/10	67 ± 4.0	without	Unmentioned	Statin ten others	other	6	Unmentioned

Table 2 The Quality Evaluation on the Research Methods

document	Random method	Allocation hidden	Blind line	Baseline comparison
Yu Fengxia(2012)	Undescribed	Undescribed	Undescribed	be comparable
Zhang Yuqing(2010)	Undescribed	Undescribed	Undescribed	be comparable
Wang Lingling(2011)	Undescribed	Undescribed	Undescribed	be comparable
LeeTM(2012)	Computer random number	be	Double blind	be comparable
Cao Yanhong(2012)	table of random number	Undescribed	Undescribed	be comparable
Tang yanfen(2010)	Undescribed	Undescribed	Undescribed	be comparable
Liu yunli(2010)	Undescribed	Undescribed	Undescribed	be comparable

2.2 Results of Meta-analysis

2.2.1 Improvement of mPAP

4 literatures[6~9] studied the improvement of mpap by statin, a total of 156 patients, and the longest follow-up period was 6 months. The statistical heterogeneity among studies (P = 0. 93, I = 0%), using the fixed effect model, the mean difference of combined effects (MD) was-3. 83 mmHg, the 95% confidence interval (CI) was (-5. 22,-2. 43), and the overall test efficiency was Z = 5. 37 (Therefore, it can be considered that the difference between the statin group and

the control group is statistically significant, and the stain treatment significantly improves mPAP compared with the control group.

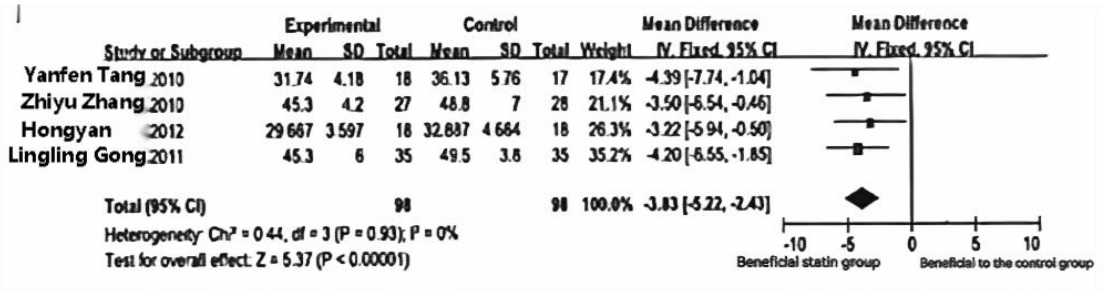

Figure 2 Mets Analysis of the Effect of STALIN on mPAP in Stable COPD Patients Compared with Conventional Treatment

2.2.2 Improvement of PASP

3 literatures[5,8,10] studied the improvement of pasp by statin, with a total of 200 patients, and the longest follow-up period was 12 months. There was no statistical heterogeneity among the studies (P = 0.22, I = 34%), and the fixed effect model was adopted. The mean difference of combined effects (MD) was-5.66mm Hg, the 95% confidence interval (CI) was (-7.15,-4.56), and the overall test efficiency was Z = 7.43 (P < Therefore, it can be considered that there is a significant difference between the statin group and the control group, and statin treatment significantly improves PASP compared with the control group.

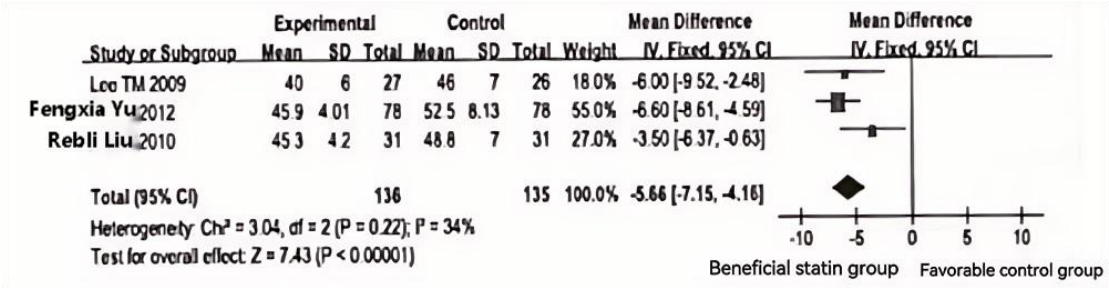

Figure 3 Mets analysis of the effect of STALIN on PASP in stable COPD patients compared with conventional treatment

2.2.3 Improvement of ET-1

5 articles[3-6,9] studied the improvement of ET-1 by statin, with a total of 184 patients, and the longest follow-up period was 6 months. There is no statistical heterogeneity among the studies (P = 0. 91, I = 0%), and the fixed effect model is adopted. The mean difference of combined effects (MD) is-3. 51 mmHg, the 95% confidence interval (CI) is (-4. 66,-2. 55), and the overall test efficiency Z = 7. 8 (Therefore, it can be considered that there is a significant difference between the statin group and the control group, and statin treatment significantly improves ET-1 compared with the control group.

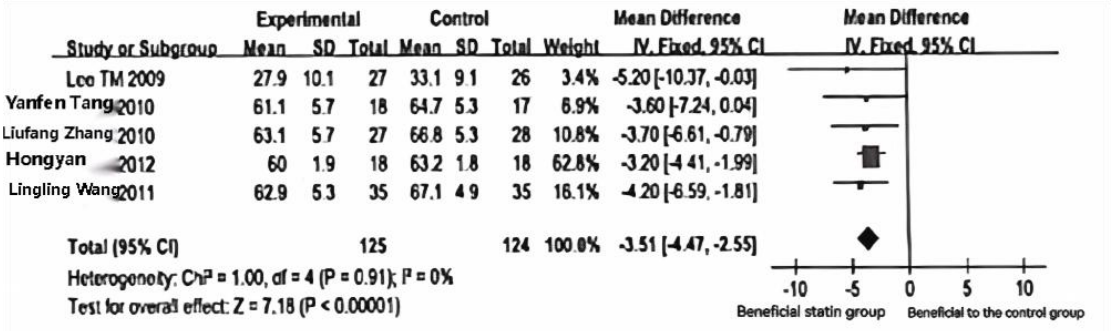

Figure 4 Mets Analysis of the Effect of STALIN on ET-1 in Stable COPD Patients Compared with Conventional Treatment

2.2.4 Improvement of NO

3 literatures[8-10] studied the improvement of no by statin, with a total of 235 patients, and the longest follow-up period was 12 months. There was no statistical heterogeneity among the studies (P = 0. 28, I = 34%), and the fixed effect model was adopted. The standard mean difference (SMD) of combined effects was 1. 39, the 95% confidence interval (CI) was (0. 86,1. 91), and the overall test efficiency was Z = 8. 25 (P < Therefore, it can be considered that the

difference between the statin group and the control group is statistically significant, and the statin treatment significantly improves the NO level compared with the control group.

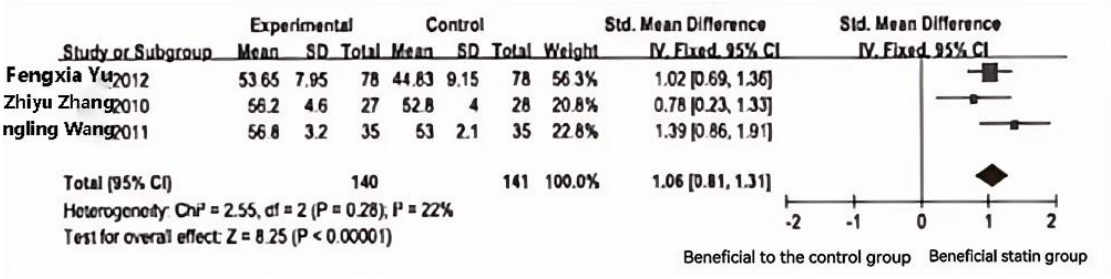

Figure 5 Mets Analysis of the Effect of STALIN on NO in Stable COPD Patients Compared with Conventional Treatment

2.2.5 Improvement of FEV%

6 literatures[5, 9, 13-15, 18,] studied the improvement of fev% by statin, with a total of 174 patients, and the longest follow-up period was 12 months. Test the heterogeneity p = 0. 0002, I = 79%, and use the random effect model to analyze. The mean difference (MD) of combined effects is 2.92, the 95% confidence interval (CI) is (-2.83,8.68), and the overall test efficiency Z = 0.99 (P < 0.0001, see Figure 6). It can be considered that there is a significant difference between the statin group and the control group. Compared with the control group, statin treatment improves FEV,% by%.

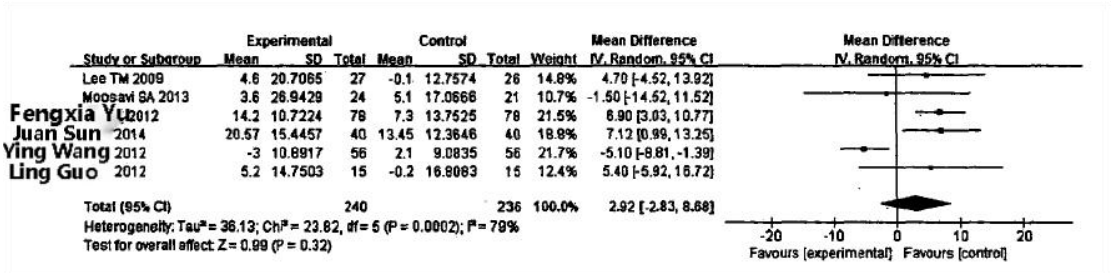

Figure 6 Weta Analysis of the Improvement of FEV,% between Statins and Control Group

2.2.6 Adverse reactions included in the study

Only one document [5] reported a slight increase of alanine aminotransferase after oral atorvastatin (no specific value was provided), and other documents mentioned related adverse reactions.

3 DISCUSSION

In recent years, there have been a lot of reports on the treatment of COPD complicated with PH with statins. Li Min et al. [44] and Ge Xiaoyan [30] respectively made a M eta analysis of them and concluded that statins can significantly reduce pulmonary arterial pressure and improve pulmonary function. Compared with this study, this study has the following characteristics: ① This study collected the related literature published by PubMed, Embase, Web of Science, The Cochrane Library and four Chinese databases as of February 2015. The research of Li Min et al. and Ge Xiaoyan did not search EMBASE before September 2013, and then a large number of original studies were published with different results, so the literature included in this paper is more comprehensive; ② The outcome indicators are more comprehensive. This paper evaluates the curative effect from five aspects: quality of life, dyspnea symptoms, exercise endurance, pulmonary arterial pressure and pulmonary function, and discusses the possible mechanism from four aspects: NO, ET-1, IL-6 and hs-CRP. Besides, the occurrence of adverse reactions is compared, and the curative effect, safety and possible mechanism of statins on COPD complicated with PH are comprehensively evaluated. However, previous studies only reported several indicators, but did not evaluate the safety. ③ The published meta-analysis compares the indexes of the experimental group and the control group after treatment, regardless of whether the baseline is comparable. This study focuses on the changes of indexes before and after treatment, refers to "Impacting standard deviations for changes from baseline" recommended by Cochrane's manual, and estimates the Meta value and standard deviation of the changes of indexes in the two groups before and after treatment by consulting relevant literature to determine the parameter values in the formula, so as to compare whether there are differences in the changes of the two groups' outcomes, which is more comparable.

Statins are widely used in primary and secondary prevention of hyperlipidemia and coronary heart disease in clinic because of their effect of lowering plasma LDL cholesterol concentration. Generally speaking, statins are well tolerated, but adverse reactions such as muscle toxicity and hepatotoxicity may occur in some patients, which leads to the decrease of treatment compliance, thus increasing the risk of cardiovascular events in patients to some extent. In recent

years, the safety of statins has attracted wide attention from all walks of life [36-42], and a large number of studies have explored the relationship between genes and adverse reactions. Meta-analysis is a quantitative synthesis method in systematic evaluation, which can avoid the limitation of single small sample study, enlarge the sample size, increase the efficacy of statistical test, quantitatively estimate the average level of research effect and evaluate the inconsistency of research results.Among them, the meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) has become a research hotspot, but the results are controversial. In order to avoid the limitation of a single study, this study comprehensively collected the published meta-analysis literature about statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) at home and abroad, and through strict methodological quality evaluation and meta-analysis method, more comprehensive and objective evaluation provided the basis for clinical individualized medication.

In the treatment of COPD patients with PH, reducing pulmonary artery pressure is the most important part of treatment. According to the recommendations of the existing guidelines, it is difficult to fundamentally prevent the progression of PH from getting worse in the treatment of COPD complicated with pH. Statins, independent of lipid-lowering effects, have many effects such as anti-inflammation, anti-oxidation, anti-apoptosis and improvement of vascular endothelial function, which can reduce pulmonary artery pressure [43]. They may be promising drugs for treating PH, suppressing the development of cor pulmonale and improving the prognosis of cor pulmonale.

COPD is the key pathological link in the development of pulmonary heart disease, which is very common in clinic. Finding, preventing or lowering PH in time is of great significance for delaying the occurrence and development of right heart failure and reducing mortality. In the past, antihypertensive drugs, such as A receptor blocker, potassium channel opener, calcium antagonist, angiotensin-converting enzyme inhibitor, leukotriene receptor antagonist, prostacyclin and its analogues, endothelin receptor antagonist, etc., often caused a significant decrease in systemic circulation pressure when reducing pulmonary arterial pressure, and the therapeutic effect was not ideal, so they were rarely used clinically.

The results of this study also suggest that compared with the control group, statins can improve the dyspnea of COPD patients with PH (MD=-3. 37, 95%, CI:-4. 61~-2. 14,P <0.000 O1), but the results are unstable due to the small number of included studies (2), so the conclusion needs to be further confirmed. 6MWD is an important index to evaluate exercise endurance, which is mainly used to evaluate the therapeutic effect of patients with moderate and severe heart and lung diseases. It is one of the endpoint observation indexes of clinical trials and one of the prediction indexes of patient survival rate. Meta-analysis showed that simvastatin and atorvastatin could significantly increase 6 MWD of patients [44-45], suggesting that they could improve exercise endurance, cardiopulmonary function and quality of life of patients. In addition, there is only one study to discuss the therapeutic effect of pravastatin and rosuvastatin on COPD complicated with PH, so the curative effect of pravastatin and rosuvastatin can't be confirmed. There are few reports of adverse reactions in the included literature, so they can't be combined with Meta-analysis. The existing research results show that there is no significant difference in the incidence of adverse reactions of statins in COPD complicated with PH compared with the control group, and the safety is acceptable. This may be related to the short observation time and the absence of adverse reactions, which suggests that the future research should extend the treatment time, pay attention to the observation of adverse reactions, and make detailed records, so as to provide real and reliable information for the evaluation of drug safety. This study shows that compared with the control group, short-term application of statin in stable COPD patients with PH can improve the pulmonary artery pressure. However, the heterogeneity of FEV% was not completely accepted (P = 0.12, I = 58%), which may be related to the basic condition of patients, infection and control, nutritional support, airway spasm control, data acquisition methods, instruments and subjective factors. Considering that there is no obvious clinical heterogeneity, random effect model analysis was adopted. The results showed that the statin group was effective in improving FEV%. The above results are consistent with those of Lee et al.

FEV,% is a good index to evaluate moderate and severe airflow restriction in pulmonary function examination, which is easy to operate and has little variability. FEV can detect mild airflow restriction, and these two indexes are of great significance to evaluate the diagnosis, treatment and prognosis of COPD patients. Meta-analysis of this study showed that there was no significant difference in FEV% between the statin treatment group and the control group, but when the following sensitivity analysis was carried out, the results changed substantially: ① When the low-quality studies were excluded, the combined results showed that compared with the control group, the FEV% of patients in the statin group decreased more obviously; ② Only those studies that reported stable patients were included in sensitivity analysis, and the hMetaerogeneity among studies was significantly reduced (I = 0%). The results showed that statins could significantly improve the lung function of patients, which was consistent with the meta-analysis results of Li Min et al. (FEV%: MD=9.79,95%CI: 6.05, 13.53). The above sensitivity analysis results all indicate that the original meta-analysis results are unstable. There has been controversy about whether statins can delay or improve the changes of pulmonary function in COPD patients, which may be related to the severity of the patients' illness and the length of follow-up. For example, a meta-analysis [22] which integrated 12 RCTs showed that statins could significantly improve FEV% of COPD patients, while another meta-analysis which only included stable COPD patients found that the treatment group had no significant improvement on FEV% [31]. According to the drug types and doses, subgroup analysis and sensitivity analysis by switching effect model within subgroups showed that the effects of different types and doses of statins on pulmonary function indexes of COPD patients complicated with PH were unstable, and the existing research failed to draw reliable conclusions. Statins are very important drugs for the prevention and treatment of hypercholesterolemia and atherosclerotic diseases at present, and their adverse reactions include myopathy, elevated liver enzymes and increased risk of diabetes. With the increasing incidence of coronary heart disease and the discovery

of the pleiotropic effects of statins, the usage and clinical application range of statins are also expanding, and the safety of statins has increasingly attracted the attention of clinicians and academic circles. In recent years, people began to explore the role of meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension.According to the sub-group analysis and sensitivity analysis within the group, we found that statins can significantly improve FEV% of moderate and severe airflow restriction index when the treatment time is less than or equal to 3 months, but this improvement effect has no statistical significance after a long time of treatment. In addition, no matter whether the treatment time exceeds 3 months, FEV index has no statistical significance. In the literature screening, four studies were excluded because they failed to report the diagnostic criteria and could not contact the authors, which may lead to data omission. We speculate that long-term statin therapy may not reverse the lung function damage in patients. Because the number of studies divided into some subgroups is small, the reliability of the combined results is affected. It is suggested that large-scale randomized controlled clinical trials with multiple doses and drugs should be carried out in the future to compare the curative effects of different doses and different kinds of statins, so as to obtain more specific and reliable results.

The follow-up time of all the included studies was at least 3 months and at most 12 months. The follow-up time was relatively short, and the long-term curative effect of statin, such as disability rate and mortality rate, could not be given, so the long-term curative effect could not be concluded. All the included trials reported the improvement of pulmonary artery pressure, and 7 trials (2 placebo and 5 open trials) with 356 cases showed that statin therapy could improve pulmonary artery pressure and benefit COPD patients with PH. Among them, a placebo-controlled trial adopted strict randomization, hidden allocation and double-blind, with high methodological quality and reliable results. Among all the included studies, only one study reported adverse reactions, with slight increase of ALT, drug reduction or withdrawal, which decreased to normal. The rest of the studies did not mention adverse reactions, which should be paid attention to and improved in future research and treatment reports. According to the report of the American Lipid Society (NI,A) Statin Safety Evaluation Working Group, liver transaminase elevation occurred in 0. 5%~2. 0% of cases [46], and it was dose-dependent. The ratio of liver enzymes < ALT or AST > 3 times the upper limit of normal (ULN) was < 1% after the initial dose and moderate dose of statin treatment.

All the documents included in this paper are published documents, most of which are in China, and the lack of grey documents and research data in other countries limits the universality of the application of this research conclusion. In the literature screening, four studies were excluded because they failed to report the diagnostic criteria and could not contact the authors, which may lead to data omission. The sample size of the original studies included is all small, only two studies have used the correct random allocation method and blind method, and the result data are complete. The methodological quality of other studies is generally low, and the correct random allocation method is rarely used, and the blind method is not clear, which leads to the possibility of selection bias, measurement bias and implementation bias, which weakens the credibility of the systematic evaluation results. Only two of the included studies reported the readmission rate, fatality rate or the incidence of cardiopulmonary events, while the rest of the studies mainly observed laboratory indicators. Therefore, there is not enough evidence to prove that statins can improve the readmission rate, fatality rate, the incidence of cardiopulmonary events and other clinical endpoints of COPD complicated with PH. At present, the clinical trial time is mostly 3 or 6 months, and the long-term curative effect of drugs cannot be observed. Therefore, the treatment time should be extended to evaluate its long-term curative effect. The indexes included in this paper are basically quantitative data. Although the difference between the two groups is statistically significant, its clinical value remains to be verified [47-48], and its clinical significance needs to be further explored. In addition, in data analysis, the standard deviation of the mean difference of each index before and after treatment in a single study was estimated by using Cochrane's recommended method and the coefficients in other related studies, which may be slightly different from the real value, but will not have a substantial impact on the results. Sub-group analysis includes a small number of studies, which may lead to unstable merger results.

In this study, evidence-based medicine systematic review and meta-analysis were used to study the correlation of meta-analysis polymorphism of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH), so as to provide scientific basis for clinical application of statins in respiratory system, prediction of statins toxicity, guidance of individualized medication, reduction of adverse reactions and improvement of drug compliance.

To sum up, simvastatin can improve FEV,FEV,% ,FVC levels, reduce mPAP and increase 6MWD in COPD patients with PH, but the current evidence is not enough to prove that it can reduce sPAP in patients, and there is no effective evidence to judge its influence on FEV, /FVC. Atorvastatin can effectively reduce the levels of sPAP and mPAP and increase 6M WD, but the current evidence is not enough to prove that it can improve the indexes of lung function. Fluvastatin can significantly reduce patients' sPAP, but there is no effective evidence to judge its effect on lung function. The safety of statins in the treatment of COPD complicated with PH remains to be studied. Therefore, a series of high-quality, large-sample, multi-center randomized controlled trials are still needed to further confirm the efficacy and safety of statins in the treatment of COPD complicated with PH [49], in order to draw more reliable conclusions to guide clinical practice.

4 CONCLUSION

Statins can obviously improve exercise endurance and reduce pulmonary artery pressure in COPD patients complicated with PH, and its mechanism may be related to statins increasing NO, decreasing ET 1 and inflammatory factors IL-6,.

hs-CRP levels in circulating blood. However, the results of improving dyspnea, lung function and its safety, and whether there are differences in statin treatment effects of different drug types, doses and treatment time are unstable, and it is still necessary to carry out a randomized controlled trial with strict design and standardized implementation of large samples to make it clear. Meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH). The current research is not enough to prove that statins can increase the incidence of adverse reactions of other statins, but the reliability of the results may be affected due to the small number of original studies involving other statins. It is suggested that more large-scale multi-ethnic population and well-designed epidemiological studies should be carried out to study the correlation of meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) [50-51] and the role of genes and environmental factors.

Generally speaking, statins can significantly increase 6MWD and reduce pulmonary arterial pressure in COPD patients complicated with PH, and its mechanism may be caused by increasing circulating NO, decreasing ET-1 and decreasing the levels of inflammatory factors IL-6 and HS-CRP, but there is still no clear conclusion on the quality of life, dyspnea symptoms, lung function and its safety. There may be differences in curative effects among different statins: simvastatin and atorvastatin can significantly increase the patient's 6MWD and reduce the pulmonary artery pressure, while fluvastatin can significantly reduce the pulmonary artery pressure. Other therapeutic indexes of these three drugs and those of other statins need to be confirmed by further research. Different doses of statins may have different therapeutic effects: 10mg/d and 20mg/d statins can significantly increase patients' 6MWD and reduce pulmonary arterial pressure, but the effect on pulmonary function can't be confirmed. 40mg/d statins can significantly reduce patients' pulmonary arterial pressure [52-53], but the effect on 6MWD and pulmonary function still needs further study. There may be differences in the therapeutic effects of statins in different treatment time: when the treatment time is less than or equal to 3 months, statins can significantly increase 6MWD, improve FEV% of moderate and severe airflow restriction index and reduce pulmonary artery pressure, but the effect on FEV 1/FVC still needs further research to confirm. When the treatment time is more than 3 months, 6MWD increases significantly, but it is not enough to prove that it can improve lung function. Different types, doses and treatment time of statins may have no significant difference in the improvement mechanism and safety of PH in COPD patients. The reliability of this system evaluation is affected to some extent due to the limitation of the quality of research methodology.

Based on the current evidence, statins can effectively improve pulmonary arterial pressure and respiratory function in COPD patients with PH, but its effect on long-term death and disability needs further study.

5 SUGGESTIONS

According to the conclusion of this study and the limitations in the process of systematic evaluation and Meta-analysis, the following suggestions are put forward: ① The pleiotropic effects of statins can be used clinically to improve the PH of COPD patients, but the monitoring of adverse reactions should be strengthened. In the future, more strictly designed, large-sample, multi-center randomized controlled trials should be carried out, and the dose-effect relationship of statins other than simvastatin and atorvastatin should be increased, and the treatment time should be appropriately prolonged, so as to evaluate the long-term therapeutic effect of statins in COPD complicated with PH. ② When conditions permit, the meta-analysis polymorphism of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) should be detected before using statins, so as to evaluate and avoid possible serious adverse reactions, and at the same time reduce the probability of non-compliance with statins for fear of toxic and side effects. It is hoped that in the future, more epidemiological studies with strict design, large sample size, multi-drug types involving people other than Europeans will be carried out, and information such as treatment time and drug dosage will be reported in detail, so as to further study the interaction between gene-gene and gene-environment.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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