Introduction

The main cause of atherosclerosis is lipid metabolism disorder, which then leads to accumulation of lipids and complex carbohydrates in the intima, causing hemorrhage and thrombosis, followed by fibrous tissue proliferation and calcium deposition, accompanied by gradual degeneration and calcification of the arterial middle layer, and finally resulting in thickening and hardening of the arterial wall and narrowing of the vascular lumen (1). The disease often involves the great and middle muscular arteries, and when it develops to block the arterial lumen, the tissue or organ supplied by the artery will be ischemic or necrotic. Because the lipids that accumulate in the arterial intima are yellowish, it is called atherosclerosis (2). It is the main cause of cerebral infarction and peripheral vascular diseases.

Background: It was a meta-analysis on the efficacy of statins in the treatment of atherosclerosis.

Methods: The PubMed, Medline, Embase, Web of Sciences, and other Chinese and English databases were used to retrieve literature on randomized controlled trials (RCTs) of statins in the treatment of atherosclerosis, published from January 2000 to January 2021. The Cochrane Handbook for Systematic Reviews of Intervention 5.0.2 was used to conduct bias risk assessment, and Review Manager 5.3 software (RevMan) was used for meta-analysis.

Results: A total of 12 articles with 1,180 participants were included in the meta-analysis. In the observation group, the plaque area [mean difference (MD) =−1.21; 95% confidence interval (CI): −2.03 to −0.38; Z =2.87; P=0.004], total cholesterol (TC) level (MD =−0.72; 95% CI: −1.01 to −0.43; Z =4.83; P<0.00001), triglyceride (TG) level (MD =−0.43; 95% CI: −0.76 to −0.09; Z =2.51; P=0.01), and the low-density lipoprotein (LDL-C) level (MD =−0.79; 95% CI: −1.41 to −0.18; Z =2.54; P=0.01) were lower, while the clinical effective rate (MD =3.64; 95% CI: 1.39 to 5.1; Z =2.54; P=0.01) was higher, and the difference was notable. No notable difference was noted in intra-media thickness (IMT) (MD =−0.41; 95% CI: −0.88 to −0.06; Z =1.7; P=0.09), hypersensitive C-reactive protein (hs-CRP) level (MD =−1.61; 95% CI: −3.59 to 0.37; Z =1.7; P=0.09), and high-density lipoprotein (HDL-C) level (MD =0.14; 95% CI: −0.02 to 0.30; Z =2.54; P=0.09) between the 2 groups.

Discussion: The use of statins in the treatment of atherosclerosis can reduce the levels of TC, TG, and LDL-C, mitigate clinical symptoms, and reduce blood lipids with good efficacy.

Keywords: Statins; atherosclerosis; blood lipids; meta-analysis

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Clinical manifestations of atherosclerosis depend on the degree of ischemia of the involved organs, and organ failure may occur in severe cases (3-5).

The main treatment protocols are to lower lipids and widen blood vessels, together with anticoagulant therapy (6). Research in the field of biomedicine has found that statins demonstrate good effects on lowering blood lipids and improving vascular endothelium. Lowering blood lipids mainly involves reducing cholesterol in serum, liver, and aorta, and lowering very low-density lipoprotein cholesterol (VLDL-C) and LDL-C, which can effectively prevent coronary heart disease and delay atherosclerosis (7-9). However, as few meta-analyses have been conducted on the effects of statins in the treatment of atherosclerosis, and there have been limitations in the existing studies such as small sample size and different research focuses, it is impossible to effectively judge the actual treatment effects of statins on atherosclerosis (10). In the study, RCTs involving statins and atherosclerosis were recruited to investigate the efficacy of statins, and meta-analysis was conducted for a systematic analysis.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1243).

**Methods**

**Literature retrieval**

With “atherosclerosis” AND “clinical treatment” OR “atherosclerosis” AND “statins” as the subject terms, relevant literature was retrieved using Chinese and English databases such as PubMed, Medline, Embase, Web of Sciences, Chinese Biomedical Literature, Wanfang Chinese Biomedical Association Digital Journals, Wanfang Digital Journals Full-text Database, and Weipu Chinese Sci-tech Journals Full-text Database.

**Inclusion and exclusion criteria**

Inclusion criteria: (I) the research participants were atherosclerotic patients who met the diagnostic criteria of the World Health Organization (WHO) or the American Diabetes Association (ADA) or the Clinical Research Guidelines for New Chinese Medicines; (II) the age of participants was 45–88 years old; (III) original research report of randomized design of different groups; (IV) literature of statins intervention; (V) literature containing indexes of blood lipid levels, plaque area, and adverse reactions; (VI) literature in either Chinese or English language.

The exclusion criteria were as follows: (I) patients with diabetes, liver and kidney dysfunction, heart failure, and other co-morbidities; (II) literature with special populations such as pregnant women and children as participants; (III) literature using other intervention methods; (IV) non-original research reports, including reviews, individual case reports, meta-analyses, and summary of treatment experience; (V) literature of pharmacokinetic testing; (VI) animal experiment literature; (VII) literature with no control group set, poor balance between groups, and no comparability between groups; (VIII) literature with incomplete information.

**Literature screening**

Literature screening was performed by 2 assessors independently. After literature retrieval, the titles were input into NodeExpress 3.2 first to establish a literature database, with duplicates removed subsequently. After the preliminary screening, the 2 assessors read the titles and abstracts to eliminate any literature that obviously did not meet the inclusion criteria, and then carefully read the full text. In the case of disagreement, a consensus was reached through discussion or under the discretion of a third person.

Certain information of the included literature was extracted such as the first author, year of onset, number of samples, age of participants, intervention measures, and outcome indexes.

**Data extraction**

The 2 assessors independently used the self-developed data extraction table to extract data, which was then cross-checked after the extraction. The information extracted included: (I) publication information; (II) baseline data; (III) intervention measures and control measures; (IV) outcome indexes: clinical treatment effective rate, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), intra-media thickness (IMT), hypersensitive C-reactive protein (hs-CRP), and so on.

**Literature bias risk assessment**

Two assessors independently performed bias risk
assessment. The assessment criteria included selection bias, implementation bias, measurement bias, follow-up bias, and other biases. Specifically, the criteria included whether it was a random sequence, whether it adopted the allocation concealment, whether participants were blinded, whether the outcome assessor was blinded, whether the data was complete, whether there was selective reporting, and whether there were other biases. Any inconsistencies were resolved by discussion or inviting another one for arbitration.

**Statistical methods**

The bias analysis tool in Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 was used to assess the bias risk. The software Stata12.0 was used to process the data of included literature, and the RevMan 5.3 was used for meta-analysis. The combined effect size test adopted t test and 95% confidence interval (CI). The t test result was expressed as a P value, with P<0.05 as the threshold for significance. If heterogeneity sources were found, a fixed effects model (FEM) was used for meta-analysis; if sources of heterogeneity were not found, a random effects model (REM) was used for meta-analysis.

**Results**

**Literature retrieval and information extraction**

A total of 72 articles were retrieved, and 30 articles remained after the assessors had carefully read the abstract sections. After further reading the full-text according to the inclusion and exclusion criteria, 18 articles were excluded, with 12 RCTs finally retained (11-22) (Figure 1, Table 1).

**Bias risk assessment**

(I) Random sequence generation: all 12 reports included used a random grouping method. (II) Allocation...
concealment: all of the 12 articles did not mention whether the blind method was used, suggesting unclear risk. (III) Blindness of participants: none of the 12 documents mentioned whether participants signing an informed consent form, or whether test personnel were blinded, suggesting unclear risk. (IV) Blindness of the outcome assessor: none of the 12 articles reported whether the outcome assessors were blinded, suggesting unclear risk. (V) Data completeness: the outcome data of 12 articles were complete, suggesting low risk. (VI) Selective report: none of the 12 articles were selective reports, suggesting unclear risk. (VII) Other biases: all references suggest unclear risk (Figures 2, 3).

**Clinical effective rate**

A total of 3 of the 12 articles reported on the effective rate, involving 208 participants, including 104 in the observation group and 104 in the control group. The heterogeneity between two groups was small ($I^2=0\%$, $P=0.49$), with FEM used for analysis. It was evident from Figure 4 that the combined effect size was ($MD=3.64; 95\% \text{ CI}: 1.39 \text{ to } 9.53; Z=2.64; P=0.008$), which indicated that when statins were used to treat atherosclerosis, the effective rate was higher versus the conventional treatment (Figure 4).

**Patch area**

A total of 3 of the 12 articles reported on the plaque area, involving 264 participants, including 133 in the observation group and 131 in the control group. There was a certain degree of heterogeneity between the two groups ($I^2=97\%$, $P<0.00001$), and REM was used for analysis (Figure 5). The combined effect size was ($MD=-1.21; 95\% \text{ CI}: -2.03 \text{ to } -0.38; Z=2.87; P=0.004$), which indicated that statins demonstrated better effects on alleviating the symptoms of atherosclerosis.

**IMT**

A total of 3 of the 12 articles reported on the IMT, involving 454 participants, including 228 in the observation group, and 226 cases in the control group. There was a certain degree of heterogeneity between the two groups ($I^2=96\%$, $P<0.00001$), and the REM was used for analysis (Figure 6). The combined effect size was ($MD=-0.41; 95\% \text{ CI}: -0.60 \text{ to } -0.22; Z=2.87; P=0.004$).
Figure 2: The bias analysis bar chart of included studies.

Figure 3: The bias risk assessment results.

Figure 4: Forest plot of clinical effective rate.
CI: −0.88 to −0.06; Z = 1.7; P=0.09), which indicated that there was no notable difference in IMT between the 2 groups after treatment.

**hs-CRP**

A total of 3 of the 12 articles reported on hs-CRP, involving a total of 236 participants, including 121 in the observation group, and 115 cases in the control group. There was a certain degree of heterogeneity between the two groups (I² =98%, P<0.00001); therefore, REM was used for analysis (Figure 7). The combined effect size was (MD =−1.61; 95% CI: −3.59 to 0.37; Z =1.7; P=0.09), which showed that there was no notable difference in hs-CRP level between the 2 groups of participants after treatment.

**TC**

A total of 10 of the 12 articles reported on the TC, involving 858 participants included, including 431 cases in the observation group and 427 cases in the control group. There was a certain degree of heterogeneity between the two groups (I² =82%, P<0.00001); therefore, REM was used for analysis (Figure 8). The combined effect size was (MD =−0.72; 95% CI: −1.01 to −0.43; Z =4.83; P<0.00001), which indicated that statins were more effective at reducing TC level.

**TG**

A total of 9 of the 12 articles reported on the TG, involving 773 participants, including 391 cases in the observation...
group and 382 cases in the control group. There was a certain degree of heterogeneity between the two groups ($I^2=95\%$, $P<0.00001$); therefore, the REM was used for analysis (Figure 9). The combined effect size was ($MD = -0.43; 95\% CI: -0.76$ to $-0.09; Z = 2.54; P=0.01$), which indicated that statins were more effective in lowering TG levels.

**HDL-C**

A total of 9 of the 12 articles reported on HDL-C, involving total of 788 participants, including 396 cases in the observation group and 392 cases in the control group. There was a certain degree of heterogeneity between the two groups ($I^2=92\%, P<0.00001$); therefore, the REM was used for analysis (Figure 11). The combined effect size was ($MD = -0.14; 95\% CI: -0.02$ to $0.30; Z = 2.54; P=0.09$), which indicated that there was no notable difference in HDL-C levels of the 2 participant groups after treatment.

**Publication bias**

The RevMan 5.3 was used to analyze the publication bias (Figure 12). It was evident that the patient’s clinical effective
Discussion

Atherosclerosis is one of the main causes of vascular disease and is associated with a high incidence of cerebral infarction and myocardial infarction (23). According to related studies, the mortality rate of acute cerebral infarction caused by atherosclerosis has been increasing annually over recent years. The stability of atherosclerotic plaque is affected by various cellular components, and hyperlipidemia has also been found to be closely related to atherosclerosis (24,25). Therefore, reducing the patient’s blood lipid level can effectively control the occurrence and development of atherosclerosis (26). Statins are also known as 3-hydroxy-3 methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, which can not only potently reduce TC and LDL levels, but also reduce TG level to a certain extent, and improve HDL level. Consequently, statins are comprehensive lipid-lowering drugs (27). The action mechanism is to competitively inhibit HMG-CoA reductase and block the intracellular mevalonic acid metabolism pathway, reducing intracellular cholesterol synthesis. The number and activity of LDL receptors on the cell membrane surface increases via feedback stimulation, which further clears serum cholesterol. Thus, stains are clinically used in the treatment of atherosclerosis on account of their cholesterol lowering action (28).

This study aimed to systematically evaluate the clinical efficacy of statins in the treatment of atherosclerosis. A total of 12 reports were included, and meta-analysis was applied.
Figure 12 The funnel chart of each index (A) clinical effective rate; (B) plaque area; (C) IMT; (D) hs-CRP; (E) TC; (F) TG; (G) LDL-C; (H) HDL-C. IMT, in intra-media thickness; hs-CRP, hypersensitive C-reactive protein; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein.
It was found that there was no notable difference in IMT, hs-CRP, and HDL-C in participants after treatment, which failed to support that statins can reduce IMT, hs-CRP, and increase HDL-C levels. By comparing the plaque area of the 2 participant groups after treatment, it was found that the plaque area of the observation group was lower than that of the control group, suggesting that the treatment effects of statins were better. Moreover, the levels of TC, TG, and LDL-C in the observation group were lower than those in the control group. This may have been due to the reduction of cholesterol synthesis via the increased number of LDL receptors on the cell membrane surface. After treatment, the clinical effective rate of the observation group was higher than that of the control group, confirming that statins were superior in the treatment of atherosclerosis.

Conclusions

In conclusion, the use of stains in the treatment of atherosclerosis can effectively mitigate the clinical symptoms of patients and alleviate their discomfort, demonstrating broad application prospects. This research can provide a reference for the clinical treatment of atherosclerosis. However, some limitations should be noted. There was large publication bias in some reports. In addition, some reports contained a small sample size, and the meta-analysis results were not accurate enough. Therefore, in the future, it is necessary to incorporate a larger sample size to verify the efficacy of stains in the treatment of atherosclerosis.

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Footnote

Reporting Checklist: We present the study in accordance with the PRISMA reporting checklist. available at https://dx.doi.org/10.21037/apm-21-1243

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1243). The authors have no conflicts of interest to declare.

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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