EFFECTS OF STATINS ON SERUM LIPIDS, DISEASE ACTIVITY, C-REACTIVE PROTEIN AND CAROTID INTIMA-MEDIA THICKNESS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS: A SYSTEMIC REVIEW AND MATA-ANALYSIS

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ABSTRACT

Introduction*: Cardiovascular disease presents an early and high rate trend in patients with systemic lupus erythematosus(SLE). Statins not only have excellent lipid-lowering effects, but also have anti-inflammatory and immune-regulating effects. Whether statins can affect serum lipids, disease activity, C-reactive protein (CRP) and carotid intima-media thickness (CIMT) in SLE patients is unclear, so we conducted a systematic review and meta-analysis to address this issue.*

Case presentation*: Literatures were obtained by searching Pubmed, Embase, Medline and Cochrane Databases as of 29 February 2020. Stata software (ver.15.0) was used for data analysis. We calculated the difference between baseline and follow-up data for each group, then analyzed and compared them. We used the random-effects model and standard mean difference (SMD) and its 95% confidence interval (CI) for meta-analysis. The I2 index was used to evaluate the heterogeneity. In the presence of high heterogeneity, sensitivity analysis and subgroup analysis were performed. In total, 6 studies met our inclusion criteria, including 5 randomized, double-blind, placebo-controlled studies and 1 controlled trail. A total of 535 subjects were included in the study. Of which 284 were in the statin group and 251 were in the control group. Compared with the control group, TC [-1.329(-1.928,-0.731), P<0.001; I2=85.8%, P<0.001] and LDL[-1.853(-3.139,-0.567), P=0.005; I2=94.0%, P<0.001] in the statin group significantly decreased. But statins had no statistical significance in reducing TG [-1.303(-2.771,0.166), P=0.082; I2=94.0%, P<0.001] and increasing HDL [1.095(-0.852,3.043), P=0.27; I2=96.6%, P<0.001]. Meanwhile, the effect of statins on disease activity in patients with SLE was not statistically significant [-0.695(-1.889,0.500), P=0.254; I2=96.5%, P<0.001]. In addition, the statin group had no significant effect on reducing CRP[-0.609(-1.290,0.073), P=0.08; I2=90.6%, P<0.001] and CIMT[-0.149(-0.724,0.429), P=0.617; I2=42%, P=0.189].*

Conclusion*: Statins can reduce TC and LDL in SLE patients, but have no statistically significant effect on TG, HDL, SLEDAI, CRP and CIMT. Due to the high heterogeneity, the limitations of randomized controlled trials and the impact of other drugs included in the study, these results need to be carefully interpreted. Currently, a larger sample of high-quality studies are needed to verify this conclusion.*

Keywords: *systemic lupus erythematosus, statin, serum lipids, C-reactive protein, meta-analysis.*

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple systems with the appearance of autoantibodies. The occurrence of SLE is the result of the interaction of genes, epigenetics, and environmental factors, and is highly heterogeneous. The disease is mainly caused by the disappearance of immune tolerance, abnormalities of T cells and B cells[(1)]. With the continuous improvement of diagnosis and treatment technology, the survival rate of SLE patients has greatly improved, but the long-term survival rate has not changed significantly. A large number of studies have shown that regardless of the length of time to diagnose SLE, cardiovascular disease (CVD) is always the leading cause of death in SLE patients. Especially in the first year after diagnosis, the risk of cardiovascular

events in SLE patients is significantly increased[2, 3]. In addition, studies have found that the risk of myocardial infarction in SLE patients is 3.04 times higher than in the general population[3].

The increased risk of cardiovascular disease in SLE patients can not be fully explained by the increased prevalence of traditional atherosclerosis. It may be due to pathophysiological agents such as type I interferon and other inflammatory cytokines, oxidative stress, the production of granulocytes and extracellular chromatin traps, anti-phospholipid antibodies and other autoantibodies causing lipoprotein dysfunction, which collectively leads to endothelial damage and atherosclerotic dyslipidemia[4]. Atherosclerosis is one of the important factors in the development of cardiovascular disease. In previous clinical studies, it was found that the incidence of atherosclerosis in SLE patients was as high as 12% (42/349), and the median age of onset was 41.09±18.53 years. This confirmed that patients with SLE not only had a high incidence of atherosclerosis, but also had an early onset tendency[5]. However, the current mechanism is not clear, and further research is needed to improve long-term survival with early intervention.

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. They are currently the most effective lipid-lowering drugs, which not only can strongly reduce total cholesterol (TC) and low density lipoprotein (LDL), and can reduce triacylglycerol (TG) to a certain extent, can also increase high density lipoprotein (HDL). The mechanism of action of statins is to competitively inhibit the endogenous cholesterol synthesis rate-limiting enzyme HMG-CoA reductase, block the intracellular valproate metabolism pathway, and reduce intracellular cholesterol synthesis. Thereby, the number and activity of LDL receptors on the cell membrane surface are stimulated, which increase serum cholesterol clearance and decrease levels. In addition to lipid-lowering effects, recent studies have found that statins have a variety of non-lipid-lowering effects, including inhibition of atherosclerosis and thrombosis[6, 7], alleviation of rejection after organ transplantation[8, 9], treatment of osteoporosis[10] and prevention on cancer mortality in some cancer types[11], reducing risk of cognitive impairment(6) and other effects.

In recent years, the anti-inflammatory and immunomodulatory effects of statins have also been explored. Studies have shown that the use of statins can reduce the overall mortality of patients with systemic autoimmune rheumatism[12]. Statins can play an anti-inflammatory role by inhibiting the upregulation of adhesion molecules and the release of cytokines and chemokines in leukocytes and endothelial cells. In addition, statins can also play an immunomodulatory role by inhibiting the expression of MHC class II molecules on antigen-presenting cells, thereby inhibiting the activation of T cells[13]. At present, statins are increasingly used in patients with SLE, but the role of statins in preventing cardiovascular disease in SLE patients and the effect on SLE disease activity are still controversial. Therefore, the purpose of this meta-analysis was to clarify the effects of statins on serum lipid profile, disease activity, C-reactive protein (CRP), and carotid intima-media thickness (CIMT) in patients with SLE.

Methods

Search strategy

In order to find all available literatures, we designed the study based on the 2009 PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines[14]. Literatures were searched in Pubmed, Embase, Medline and Cochrane Databases. Literature search was performed using the following search terms and their combinations: systemic lupus erythematosus, lupus, systemic lupus, SLE, statin, statins, atorvastatin, rosuvastatin, pravastatin, fluvastatin, simvastatin , pitavastatin, lovastatin, cerivastatin. All literatures we searched were updated to February 29, 2020. There were no limitations on geographical location or ethnicity.

Study selection

Selected studies needed to meet the following criteria:

• study design: controlled trials with parallel or cross-over design,

• study population: all SLE patients enrolled fulfilled the American College of Rheumatology (ACR) criteria(15),

• comparison intervention: with and without statins,

• outcome measure: serum lipid (TG, TC, HDL, LDL), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)(16), CRP or CIMT of each group at baseline and follow-up.

Exclusion criteria were:

• literature type belonged to review, case report, mice experiment, case-control study, cohort study,

• lack of control group at study design,

• non-interventional studies, 4. lack of sufficient information, only provided lipid profile, SLEDAI, CRP, CIMT before or after intervention.

Data extraction and quality assessment

The following information will be extracted in the selected studies:

• name of the first author,
• study region,
• study design,
• statin type,
• statin dose,
• duration of treatment,
• whether use of SLE medication,
• number of patients enrolled,
• age of patients,
• gender of patients,
• body mass index (BMI),
• SLE duration,
• baseline and follow-up serum lipid profile , SLEDAI, CRP, CMIT.

All enrolled studies performed a systematic assessment of bias using the Cochrane criteria[17]. The systematic evaluation items including: the random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), assessment of outcome (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Low risk of bias suggested that reasonable bias was unlikely to seriously alter the outcome, unclear risk of bias suggested that reasonable bias had some suspicion of results, and high risk of bias suggested that bias seriously reduced the credibility of results. Two independent researchers searched and selected the available studies, then evaluated the quality of the studies. When there were any discrepancies, they reached a consensus through consultations.

Statistic analysis and quantitative data synthesis

All statistical analyses were performed using Stata software (ver. 15.0). We obtained the changes in the relevant data of statin groups and control groups by calculating the baseline and follow-up data: measure post-treatment - measure at baseline. The effect of statins on patients with SLE was evaluated by comparing the changes in the relevant data between the two groups. The average effect size and heterogeneity were obtained by using a random-effects model. Heterogeneity was assessed by I2 values, with 25, 50, and 75% representing low, medium, and high heterogeneity, respectively. When high heterogeneity occurs, the source of heterogeneity was sought through subgroup analysis, sensitivity analysis, and publication bias. When the measurement results were median and inter-quartile range, the mean and standard deviation (SD) were estimated by the formula(18). When only the mean standard error (SEM) was reported, SD was calculated by the following formula: SD = SEM×sqrt (n), where n was the number of subjects. SDs of the mean difference were calculated using the following formula: SD =square root [(SDpre-treatment) 2 + (SDpost-treatment) 2 - (2R×SDpre-treatment×SDpost-treatment)], assuming a correlation coefficient (R) = 0.5. Among all the statistical results, $p<0.05$ was considered statistically significant.

Results

Literature search and quality assessment

There were 591 articles in the initial literature search process. Next, duplicate articles were excluded, leaving 490 articles. Based on the title and abstract, we searched for valid literature in the database, excluding 453 articles. Among these remaining articles, according to the inclusion and exclusion criteria, 14 were reviews, 5 were case reports, 3 were mouse trials and 9 were lack of sufficient information. The flow chart of article selection process is shown in Figure 1.

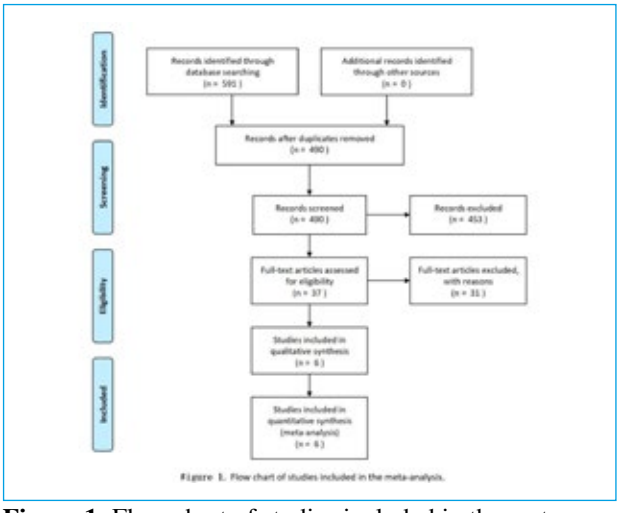

Figure 1: Flow chart of studies included in the meta-analysis.

Finally, 6 articles were included in the study[19-24]. Table 1 summarizes the risks of bias in all included studies. Of all the selected studies, one was controlled trial[19] and the rest were randomized,

double-blind, placebo-controlled study[20-24]. In addition, one of them had insufficient data on random sequence generation and allocation concealment[19].

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (dection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ferreira et al.(2007)	U	U	U	U	L	L	L
Petri et al.(2010)	L	U	L	L	H	L	L
Mok et al.(2011)	L	L	L	L	L	L	H
Plazak et al.(2011)	L	L	L	L	L	L	L
Fatemi et al.(2014)	L	L	L	L	L	L	L
Sokoll et al.(2014)	L	L	L	L	L	L	L

Table 1: Quality assessment of the included studies.
H: high risk of bias; L: low risk of bias; U: unclear risk of bias.

Characteristics of included studies

The main characteristics of all the included studies are presented in Table 2. A total of 535 subjects were included in 6 studies, of which 284 were in the statin group and 251 were in the control group. These studies were published between 2007 and 2014, and were performed in Brazil[19], USA(20), China[21], Poland[22], Iran[23], and UK[24]. The types of statins studied include atorvastatin[19-20,22-24] and rosuvastatin[21], with doses ranging from 10 to 40 mg everyday. The duration of statin treatment was between 8 weeks and 2 years. In the six studies, the serum lipid profiles, SLEDAI, CRP, and CIMT data of the statin group and the control group at baseline and follow-up are shown in Table 3.

Study	Region	Study design	Statin type	Dose of statin	Treatment duration	Use of SLE medication	Sample size (n)		Age (years)		Gender (Female/Male)		Body mass index (kg/m²)		Duration of SLE	
							statin	control	statin	control	statin	control	statin	control	statin	control
Ferreira et al.(2007)	Brazil	Controlled trial	Atorvastatin	20 mg/d	8 weeks	YES	64	24	32±8	34±7.5	64/0	24/0	24.7±4.2	26.9±5.2	8.5±4.9 (months)	8.5±4.7 (months)
Petri et al.(2010)	USA	Randomized, double-blind, placebo-controlled trial	Atorvastatin	40 mg/d	2 years	NA	99	101	18-78	18-78	89/10	95/6	NA	NA	NA	NA
Mok et al.(2011)	China	Randomized, double-blind placebo-controlled trial	Rosuvastatin	10 mg/d	12 months	YES	36	36	51.3±10.4	50.3±9.2	34/2	36/0	NA	NA	12.4±8.1 (years)	11.2±5.9 (years)
Plazak et al.(2011)	Poland	Randomized, double-blind, placebo-controlled trial	Atorvastatin	40 mg/d	1 year	YES	28	32	41.8±13.4	41.4±12.4	26/4	30/2	NA	NA	NA	NA
Fatemi et al.(2014)	Iran	Randomized, double-blind clinical trial	Atorvastatin	20 mg/d	3 months	YES	45	45	38.8±11	37±11.5	43/2	41/4	NA	NA	8±0.65 (years)	7±0.7 (years)
Sokoll et al.(2014)	UK	Randomized, double-blind, placebo-controlled study	Atorvastatin	40 mg/d	12 months	YES	12	13	≥40	≥40	12/0	13/0	26.36±8.58	26.43±2.71	15.06±19.38(years)	6.75±10.27 (years)

Table 2: Characteristics of studies included in the meta-analysis.
NA means data was not available.

Study			Ferreira et al.(2007)	Petri et al.(2010)	Mok et al.(2011)	Plazak et al.(2011)	Fatemi et al.(2014)	Sokoll et al.(2014)
Baseline	Cholesterol(mg/dl)	Statin	162±36	181.6±38.1	185.6±42.5	197.2±46.4	160±8.5	168.6±46.8
		Control	162±23	190.1±36.9	180.2±37.5	174.0±31.0	157±8.0	209.9±37.1
	Triglyceride(mg/dl)	Statin	115±55	NA	137.3±64.7	141.8±53.2	144±5	111.6±69.1
		Control	136±119	NA	113.4±60.2	106.3±44.3	137.5±4	109.0±54.0
	LDL-C(mg/dl)	Statin	92±30	NA	101.3±40.2	112.1±38.7	125±7.75	98.6±40.6
		Control	95±18	NA	93.6±34.8	100.6±31.0	128±5.75	114.0±25.9
	HLD-C(mg/dl)	Statin	47.28±12	NA	57.2±13.5	54.1±11.6	39±1.5	46.4±10.4
		Control	41±8	NA	63.0±16.2	54.1±11.6	39±1.75	71.9±22.4
	SLEDAI	Statin	4.47±5.0	2.0±3.0	1.4±1.5	4±4.5	3±0.5	3.5±3.08
		Control	3.33±3.95	1.9±2.33	1.8±2.0	4±3.0	3±0.5	2.63±3.65
	CRP(mg/l)	Statin	NA	5.6±8.5	1.26±0.58	4.4±4.1	2.8±0.2	6.6±8.4
		Control	NA	6.3±9.2	1.38±0.75	4.0±8.9	3.1±0.2	3.0±2.7
	CIMT(mm)	Statin	NA	0.59*	0.68±0.11	NA	NA	0.57±0.1
		Control	NA	0.57*	0.66±0.15	NA	NA	0.58±0.13
Follow-up	Cholesterol(mg/dl)	Statin	128±34	150.7±40.7	144.2±35.2	170.1±27.1	143±9.0	124.9±24.0
		Control	NA	195.6±42.2	190.2±45.6	174.0±27.0	161±7.5	212.6±39.4
	Triglyceride(mg/dl)	Statin	97±45	NA	NA	106.3±44.3	134±5.0	94.8±54.9
		Control	NA	NA	NA	115.2±53.2	140±4.0	103.7±41.6
	LDL-C(mg/dl)	Statin	61±29	NA	65.3±27.8	89.0±23.2	104±7.0	57.6±22.0
		Control	NA	NA	106.3±41.0	100.6±31.0	132±5.75	122.2±20.5
	HLD-C(mg/dl)	Statin	47.39±12	NA	NA	54.1±11.6	44±2.0	49.5±8.1
		Control	NA	NA	NA	54.1±11.6	38±2.5	70.0±17.8
	SLEDAI	Statin	3.08±3.6	2.2±4	NA	4±5	1.7±0.4	NA
		Control	4.33±4.17	2.0±3	NA	2±3	3±0.4	NA
	CRP(mg/l)	Statin	NA	4.6±5.9	0.88±0.28	2.7±1.7	2.5±0.3	1.9±1.2
		Control	NA	4.5±7.9	1.28±1.08	3.9±5.1	3.2±0.2	3.4±2.3
	CIMT(mm)	Statin	NA	0.66*	0.67±0.13	NA	NA	0.59±0.1
		Control	NA	0.66*	0.70±0.14	NA	NA	0.57±0.14

Table 3: Data of the statin group and the control group at baseline and follow-up.
Values are expressed as mean ± (SD). NA means data was not available. only provided mean.*

Effects of statins therapy on serum lipids and disease activity in SLE patients

In the study of the effects of statins on patients with SLE, 5 studies were used to assess cholesterol, 3 studies evaluated triglycerides, 4 studies evaluated LDL, 3 studies evaluated HDL, 4 studies evaluated SLEDAI, 5 studies evaluated CRP, and 2 studies evaluated CIMT. Figure 2 shows the forest plot for all studies. A systematic review and meta-analysis showed that statins in SLE patients can reduce TC [-1.329(-1.928,-0.731), P<0.001; I2=85.8%, P<0.001] and LDL [-1.853(-3.139,-0.567), P=0.005; I2=94.0%, P<0.001].

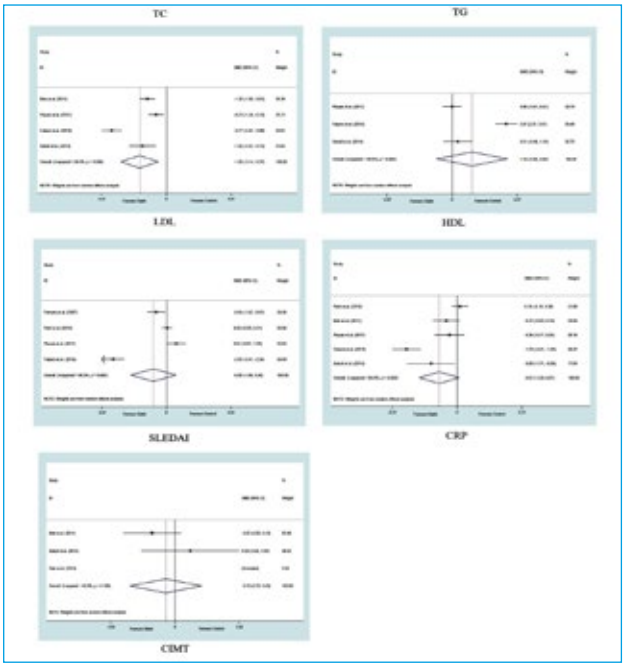

Figure 2: Meta-analysis of the results.

But statins had no significant statistical significance in reducing TG [-1.303(-2.771,0.166), P=0.082; I2=94.0%, P<0.001] and increasing HDL [1.095(-0.852,3.043), P=0.27; I2=96.6%, P<0.001]. Meanwhile, the effect of statins on disease activity in patients with SLE was not statistically significant [-0.695(-1.889,0.500), P=0.254; I2=96.5%, P<0.001]. In addition, compared with the control group, the statin group had no significant effect on reducing CRP [-0.609(-1.290,0.073), P=0.08; I2=90.6%, P<0.001] and CIMT [-0.149(-0.724,0.429), P=0.617; I2=42%, P=0.189].

Subgroup and sensitivity analysis

Studies about the effects of statins on serum lipids, SLEDAI, and CRP were highly heterogeneous, so we performed sensitivity analysis and sub-

group analysis. Sensitivity analysis was performed by eliminating the studies one by one. The results showed that the pooled effects of statins on TC, LDL, HDL, and SLEDAI in patients with SLE did not differ due to any single study. However, the sensitivity analysis result of the effect of statins on TG in SLE patients suggested that when Sokoll's study was excluded, statins can significantly reduce TG [-1.826 (-3.650, -0.002), P = 0.05]. In addition, after excluding the Petri's study, the results showed that statins appeared to reduce CRP in SLE patients [-0.807 (-1.541, -0.072), P = 0.031].

Studies	Number of studies	Total sample size	SMD	95% CI	P	Heterogeneity I2
1.Subgroup outcomes of TC						
< 1 year	1	90	-0.977	-1.197,-0.757	<0.001	0
≥ 1 year	4	357	-2.538	-3.096,-1.980	<0.001	-
2.Subgroup outcomes of TG						
< 1 year	1	90	-2.761	-3.341,-2.180	<0.001	-
≥ 1 year	2	85	-0.615	-1.285,0.055	0.072	51.30%
3.Subgroup outcomes of LDL						
< 1 year	1	90	-3.773	-4.467,-3.079	<0.001	-
≥ 1 year	3	157	-1.154	-1.670,-0.637	<0.001	51.90%
4.Subgroup outcomes of HDL						
< 1 year	1	90	2.969	2.366,3.572	<0.001	-
≥ 1 year	2	85	0.090	-0.337,0.517	0.679	0
5.Subgroup outcomes of SLEDAI						
< 1 year	2	178	-1.680	-3.913,0.553	0.140	97.10%
≥ 1 year	2	260	0.219	-0.239,0.677	0.348	61.00%
6.Subgroup outcomes of CRP						
< 1 year	1	90	-1.725	-2.210,-1.239	<0.001	-
≥ 1 year	4	357	-0.244	-0.610,0.121	0.190	57.60%

Table 4: The results of subgroup analysis.
A. Subgroup analysis based on treatment time.

We divided enrolled studies into two subgroups according to the length of time they were treated with statins. One subgroup was treated for less than one year, and one subgroup was treated for one year or more. Table 4A shows the results of subgroup analysis of serum lipid, SLEDAI, and CRP. Regardless of the length of statin use, the results in each subgroup suggested that TC was significantly reduced in the statin group. At the same time, compared with the control group, the statin group can also reduce LDL levels, regardless of whether the treatment time is greater or less than one year. In addition, the results of the subgroup analysis also showed that in each subgroup, the effects of statins on TG, HDL, SLEDAI, and CRP in SLE patients were not statistically significant.

Next, we grouped the data based on the types and doses of statins used, and analyzed the data. Table 4B shows the results of the subgroup analysis. The results showed that both rosuvastatin subgroup and atorvastatin subgroup can reduce TC and LDL. In addition, whether atorvastatin is used at a dose of 20 mg/d or 40 mg/d can also reduce TG levels, which is statistically significant. This subgroup with atorvastatin 20 mg/d can significantly reduce SLEDAI levels, but the use of a dose of 40 mg/d seems to have no effect on SLEDAI.

Meanwhile, the results of the rosuvastatin subgroup and atorvastatin subgroup showed no statistically significant effect on HDL and CRP.

Studies	Number of studies	Total sample size	SMD	95% CI	P	Heterogeneity I2
1.Subgroup outcomes of TC						
Atorvastatin 40mg/d	3	285	-0.911	-1.155,-0.666	<0.001	0
Atorvastatin 20mg/d	1	90	-2.538	-3.096,-1.980	<0.001	-
Rosuvastatin 10mg/d	1	72	-1.261	-1.768,-0.754	<0.001	-
2.Subgroup outcomes of TG						
Atorvastatin 40mg/d	2	85	-0.681	-1.122,-0.240	0.002	51.30%
Atorvastatin 20mg/d	1	90	-2.761	-3.341,-2.180	<0.001	-
3.Subgroup outcomes of LDL						
Atorvastatin 40mg/d	2	85	-0.945	-1.400,-0.490	<0.001	67.00%
Atorvastatin 20mg/d	1	90	-3.773	-4.467,-3.079	<0.001	-
Rosuvastatin 10mg/d	1	72	-1.316	-1.827,-0.806	<0.001	-
4.Subgroup outcomes of HDL						
Atorvastatin 40mg/d	2	85	0.090	-0.337,0.517	0.679	0
Atorvastatin 20mg/d	1	90	2.969	2.366,3.572	<0.001	-
5.Subgroup outcomes of SLEDAI						
Atorvastatin 40mg/d	2	260	0.139	-0.106,0.383	0.266	61.00%
Atorvastatin 20mg/d	2	178	-1.451	-1.821,-1.081	<0.001	97.10%
6.Subgroup outcomes of CRP						
Atorvastatin 40mg/d	3	285	-0.056	-0.289,0.178	0.640	65.00%
Atorvastatin 20mg/d	1	90	-1.725	-2.210,-1.239	<0.001	-
Rosuvastatin 10mg/d	1	72	-0.366	-0.832,0.100	0.124	-

Table 4: The results of subgroup analysis.
B. Subgroup analysis based on the types and doses of statins used.

Publication bias

The Begg's test and the Egger's test were used to detect publication bias in the meta-analysis. The funnel plots for the effect of statins on lipid profile, SLEDAI, CRP and CIMT were symmetrical, and the P values obtained by the Begg's test and Egger's test were > 0.05 (Table 5), indicating that there were no potential publication bias in the studies.

	TC	TG	LDL	HDL	SLEDAI	CRP	CIMT
Pr>|z|	0.462	1.000	0.734	1.000	0.308	0.462	1.000
P>|t|	0.475	0.736	0.498	0.909	0.432	0.275	-

Table 5: . Assessment of publication bias in the meta-analysis.

Discussion

Cardiovascular disease remains the leading cause of shortened life expectancy and death in SLE patients[25], and atherosclerosis has been known to increase cardiovascular morbidity. Current studies have found that atherosclerotic lesions are not only associated with intima disintegration, arterial wall deformation, and abnormal accumulation of lipoproteins[26], specific immune function also plays a key role in the formation and development of atherosclerosis. Therefore, SLE, characterized by systemic inflammation, can accelerate atherosclerosis and lead to cardiovascular disease. Statins not only can regulate serum lipid, but also can reduce proinflammatory cytokines and chemokines such as interleukin(IL)-6, IL-8, tumor necrosis factor(TNF)-α and monocyte chemotactic protein(MCP)-1[25], and play a beneficial role in improving the endothelial cells, antioxidant and anti-inflammatory[27].

In the past, statins have a certain effect on the treatment of autoimmune diseases, including multiple sclerosis[28] and rheumatoid arthritis[29]). At present, more and more clinical treatment researches on SLE patients are being carried out. Therefore, we conducted a meta-analysis to study the effect of statins on the lipid profile, disease activity, inflammatory indicators of SLE patients, and the changes in CIMT, a predictor of atherosclerosis. Our results showed that statins significantly reduced TC and LDL in SLE patients, but had little effect on the remaining lipid profile. In addition, statin therapy did not significantly improve disease activity or inflammatory markers in SLE patients.

Genetic analysis and randomized clinical trials strongly suggested that LDL-C is associated with atherosclerotic disease and that HDL also plays a complex role in atherogenesis[30]. Statin therapy significantly reduced LDL, TG and increased HDL levels in patients at high risk of cardiovascular events[31]. In the included studies, after statin intervention, the levels of TC, TG and LDL in the statin group decreased significantly, while the HDL levels also increased[19-24]. However, the results of meta-analysis showed that statins had a significant effect on the TC and LDL of SLE patients and the rest of the lipid levels had no statistically significant regulatory effect compared with the control group. Previously, Paula Sánchez's research also suggested that statins can reduce TC and LDL-C, slightly increase HDL-C levels, and have a statistically significant effect(32). This conclusion is similar to our results. In the sensitivity analysis, after excluding one study(24), the results showed that statin therapy also seemed to reduce TG levels in patients with SLE. The above results indicated that statins have an effect on serum lipid levels in SLE patients, but larger studies are still needed to support this conclusion.

SLEDAI is an indicator of SLE activity, and although statins have been found in some studies to significantly reduce the SLEDAI score[19,23], our meta-analysis showed no statistically significant effect on the SLEDAI score of SLE patients in the statin group compared to the control group. This is consistent with Sahebkar's findings[33]. CRP is an inflammatory biomarker. In previous studies, CRP was found to be the only independent risk factor for infection in patients with SLE[34]. The level of CRP in infected patients was significantly higher than that in non-infected patients[34]. In addition, CRP is a good biomarker for cardiovascular disease and an independent and powerful predictor of cardiovascular adverse events[35]. In the four studies included[21-24], the CRP of SLE patients was significantly lower than that of the control group, but another study[20] found that statins did not reduce CRP and had no anti-inflammatory effect on SLE. Meta-analysis results showed that statin treatment of SLE did not have a statistically significant reduction in CRP levels, but the results after excluding a study[20] suggested that statins had a significant effect on reducing CRP levels in patients with SLE. Therefore, reducing CRP levels in SLE patients is beneficial to prevent cardiovascular disease. We need more high-quality and large-scale studies to evaluate the impact of statins on CRP levels in SLE patients.

CIMT is a reliable, simple and non-invasive ultrasound evaluation index that can effectively evaluate subclinical atherosclerosis in SLE patients, which has been proved in many studies[36]. CIMT levels were significantly higher in SLE patients than in healthy controls, suggesting a higher risk of atherosclerosis[36]. In one of the included studies, CIMT in patients treated with statins was significantly lower than in the control group[21]), while in the other, CIMT was unchanged[24]. Our meta-analysis also showed that statin therapy was not statistically significant in preventing the development of carotid atherosclerosis.

Therefore, there is still uncertainty in the prevention of cardiovascular diseases in SLE patients with statins. In addition, the limited follow-up period also has a potential impact on current conclusions. The longest treatment time in these studies was 2 years, and the shortest treatment time was 8 weeks. At present, the effect of statins on patients' serum lipid levels is relatively clear, but the effects on inflammation indicators, disease activity, and CIMT are still uncertain with the prolongation of the disease course and the effects of other drugs. Meanwhile, some studies have found that the use of statins can cause hypertransaminasemia[37], autoimmune necrotizing myopathy[38] and autoimmune hepatitis[39]. The safety is uncertain, so it is still uncertain whether the statin can be used for a long time and listed as a routine drug for patients with SLE.

In the 6 studies, except that Petri's study did not mention whether there are other drug treatments, the patients in the remaining studies all have combination treatments of other drugs, including glucocorticoids, antimalarial drugs, immunosuppressants, etc. Glucocorticoids have multiple therapeutic uses and have effective anti-inflammatory effects in patients with SLE, but long-term use of glucocorticoids can

also cause dyslipidemia and even cause atherosclerosis[40]. Many immunosuppressants also have the risk of causing hyperlipidemia[41]. Antimalarial drugs have shown in previous studies that they have a hypolipidemic effect on patients with SLE[42]. Therefore, the combined treatment of these drugs also has a certain effect on the blood lipids and inflammation indicators of SLE patients, which may have an impact on our conclusions.

The advantage of our meta-analysis is that there are no ethnic and geographic restrictions, and the effect of statins was evaluated by comparing the difference between the groups before and after treatment. But there are also some limitations worth considering. First, the meta-analysis lacks sufficient randomized controlled trials and sample sizes, so there are still some problems with the accuracy of the conclusions. Secondly, we did not contact the authors to obtain the missing information, resulting in fewer studies being included.

Conclusion

In summary, the results of our meta-analysis suggested that statins had the effect of reducing TC and LDL in SLE patients, but the effects on TG, HDL, disease activity SLEDAI score, inflammatory indicators CRP and CIMT were not statistically significant. Due to the high heterogeneity, the limitations of randomized controlled trials and the impact of other drugs included in the study, these results need to be carefully interpreted. The evidence is limited and more high-quality randomized controlled trials with large samples are needed.

References

1) Shaikh MF, Jordan N, D'Cruz DP. Systemic lupus erythematosus. Clin Med (Lond) 2017;17(1): 78-83.
2) Aviña-Zubieta JA, To F, Vostretsova K, De Vera M, Sayre EC, Esdaile JM. Risk of Myocardial Infarction and Stroke in Newly Diagnosed Systemic Lupus Erythematosus: A General Population-Based Study. Arthritis Care Res (Hoboken) 2017; 69(6): 849-856.
3) Gu MM, Wang XP, Cheng QY, Zhao YL, Zhang TP, Li BZ, et al. A Meta-Analysis of Cardiovascular Events in Systemic Lupus Erythematosus. Immunol Invest 2019; 48(5): 505-520.
4) Kostopoulou M, Nikolopoulos D, Parodis I, Bertsias G. Cardiovascular Disease in Systemic Lupus Erythematosus: recent data on epidemiology, risk factors and prevention. Curr Vasc Pharmacol 2019.
5) Zhu M, Mo H, Li D, Luo X, Zhang L. Th17/Treg imbalance induced by increased incidence of atherosclerosis in patients with systemic lupus erythematosus (SLE). Clin Rheumatol 2013; 32(7): 1045-52.
6) Yang Z, Wang H, Edwards D, Ding C, Yan L, Brayne C, Mant J. Association of blood lipids, atherosclerosis and statin use with dementia and cognitive impairment after stroke: A systematic review and meta-analysis. Ageing Res Rev 2020; 57: 100962.
7) Kronenberg RM, Beglinger S, Stalder O, Méan M, Limacher A, Beer JH, Aujesky D, et al. Statin therapy and recurrent venous thromboembolism in the elderly: a prospective cohort study. Sci Rep 2019; 9(1): 14804.
8) Vallakati A, Reddy S, Dunlap ME, Taylor DO. Impact of Statin Use After Heart Transplantation: A Meta-Analysis. Circ Heart Fail 2016; 9(10).
9) Raphael J, Collins SR, Wang XQ, Scalzo DC, Singla P, Lau CL, et al. Perioperative statin use is associated with decreased incidence of primary graft dysfunction after lung transplantation. J Heart Lung Transplant 2017; 36(9): 948-956.
10) Lin SM, Wang JH, Liang CC, Huang HK. Statin Use Is Associated With Decreased Osteoporosis and Fracture Risks in Stroke Patients. J Clin Endocrinol Metab 2018; 103(9): 3439-3448.
11) Jeong GH, Lee KH, Kim JY, Eisenhut M, Kronbichler A, van der Vliet HJ, et al. Statin and Cancer Mortality and Survival: An Umbrella Systematic Review and Meta-Analysis. J Clin Med 2020; 9(2).
12) Jorge AM, Lu N, Keller SF, Rai SK, Zhang Y, Choi HK. The Effect of Statin Use on Mortality in Systemic Autoimmune Rheumatic Diseases. J Rheumatol 2018; 45(12): 1689-1695.
13) Meroni PL, Luzzana C, Ventura D. Anti-inflammatory and immunomodulating properties of statins. An additional tool for the therapeutic approach of systemic autoimmune diseases. Clin Rev Allergy Immunol 2002; 23(3): 263-77.
14) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6(7): e1000097.
15) Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25(11): 1271-7.
16) Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992.35(6): 630-40.
17) Green JHaS. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.2. , The Cochrane Collboration, London 2009.
18) Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13.
19) Ferreira GA, Navarro TP, Telles RW, Andrade LE, Sato EI. Atorvastatin therapy improves endothelial-dependent vasodilation in patients with systemic lupus erythematosus: an 8 weeks controlled trial. Rheumatology (Oxford) 2007; 46(10): 1560-5.
20) Petri MA, Kiani AN, Post W, Christopher-Stine L, Magder LS. Lupus Atherosclerosis Prevention Study (LAPS). Ann Rheum Dis 2011; 70(5): 760-5.
21) Mok CC, Wong CK, To CH, Lai JP, Lam CS. Effects of rosuvastatin on vascular biomarkers and carotid ather-

osclerosis in lupus: a randomized, double-blind, placebo-controlled trial. Arthritis Care Res (Hoboken) 2011; 63(6): 875-83.
22) Plazak W, Gryga K, Dziedzic H, Tomkiewicz-Pajak L, Konieczynska M, Podolec P, et al. Influence of atorvastatin on coronary calcifications and myocardial perfusion defects in systemic lupus erythematosus patients: a prospective, randomized, double-masked, placebo-controlled study. Arthritis Res Ther 2011; 13(4): R117.
23) Fatemi A, Moosavi M, Sayedbonakdar Z, Farajzadegan Z, Kazemi M, Smiley A. Atorvastatin effect on systemic lupus erythematosus disease activity: a double-blind randomized clinical trial. Clin Rheumatol 2014; 33(9): 1273-8.
24) Sokoll KB, Batuca J, Lopez LB, Hensor E, Emery P, Alves JD, et al. Effects of atorvastatin on atherosclerosis and atherogenesis in systemic lupus erythematosus: a pilot study. ISRN Immunol 2014; Article ID: 295239.
25) Teixeira V, Tam LS. Novel Insights in Systemic Lupus Erythematosus and Atherosclerosis. Front Med (Lausanne) 2017; 4: 262.
26) Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W Jr, Rosenfeld ME, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1994.89(5): 2462-78.
27) Zhou Q, Liao JK. Pleiotropic effects of statins. Basic research and clinical perspectives. Circ J 2010; 74(5): 818-26.
28) Pihl-Jensen G, Tsakiri A, Frederiksen JL. Statin treatment in multiple sclerosis: a systematic review and meta-analysis. CNS Drugs 2015; 29(4): 277-91.
29) Huang CY, Lin TT, Yang YH, Lin LY, Tsai CT, Hwang JJ, et al. Effect of statin therapy on the prevention of new-onset acute coronary syndrome in patients with rheumatoid arthritis. Int J Cardiol 2018; 253: 1-6.
30) Sanin V, Pfetsch V, Koenig W. Dyslipidemias and Cardiovascular Prevention: Tailoring Treatment According to Lipid Phenotype. Curr Cardiol Rep 2017; 19(7): 61.
31) Wang C, Wang F, Cao Q, Li Z, Huang L, Chen S. Effect and safety of combination lipid-lowering therapies based on statin treatment versus statin monotherapies on patients with high risk of cardiovascular events. Aging Med (Milton) 2018; 1(2): 176-184.
32) Sánchez P, Toro-Trujillo E, Muñoz-Velandia OM, García AA, Fernández-Ávila DG. Therapeutic Impact of Statins on the Lipid Profile and Cardiovascular Risk in Patients With Systemic Lupus Erythematosus: Systematic Review of the Literature and a Meta-analysis. Reumatol Clin 2019; 15(6): e86-e91.
33) Sahebkar A, Rathouska J, Derosa G, Maffioli P, Nachtigal P. Statin impact on disease activity and C-reactive protein concentrations in systemic lupus erythematosus patients: A systematic review and meta-analysis of controlled trials. Autoimmun Rev 2016;15(4): 344-53.
34) Wang J, Niu R, Jiang L, Wang Y, Shao X, Wu M, et al. The diagnostic values of C-reactive protein and procalcitonin in identifying systemic lupus erythematosus infection and disease activity. Medicine (Baltimore) 2019; 98(33): e16798.
35) Avan A, Tavakoly Sany SB, Ghayour-Mobarhan M, Rahimi HR, Tajfard M, Ferns G. Serum C-reactive protein in the prediction of cardiovascular diseases: Overview of the latest clinical studies and public health practice. J Cell Physiol 2018; 233(11): 8508-8525.
36) Henrot P, Foret J, Barnetche T, Lazaro E, Duffau P, Seneschal J, et al. Assessment of subclinical atherosclerosis in systemic lupus erythematosus: A systematic review and meta-analysis. Joint Bone Spine 2018; 85(2): 155-163.
37) Villani R, Navarese EP, Cavallone F, Kubica J, Bellanti F, Facciorusso A, et al. Risk of Statin-Induced Hypertransaminasemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Mayo Clin Proc Innov Qual Outcomes 2019; 3(2): 131-140.
38) Mirlesse N, Egervari K, Bornand A, Lecluse J, Lobrinus JA, Scheffler M, et al. Statin-induced autoimmune necrotizing myopathy with pharyngeal muscles involvement. Age Ageing. 2020.
39) Qasim Agha O, Kaur S, Vijayavel N. Statin-induced necrotising autoimmune myopathy and autoimmune hepatitis presenting with dysphagia. BMJ Case Rep 2020.13(2).
40) Ross IL, Marais AD. The influence of glucocorticoids on lipid and lipoprotein metabolism and atherosclerosis. S Afr Med J 2014; 104(10): 671-4.
41) Subramanian S, Trence DL. Immunosuppressive agents: effects on glucose and lipid metabolism. Endocrinol Metab Clin North Am 2007; 36(4): 891-905; vii.
42) Tao CY, Shang J, Chen T, Yu D, Jiang YM, Liu D, et al. Impact of antimalarial (AM) on serum lipids in systemic lupus erythematosus (SLE) patients: A systematic review and meta-analysis. Medicine (Baltimore) 2019; 98(14): e15030.

Author contributions
MHY: study design. LL and LL: data collection. CXH, WYH and SJC: statistical analysis. CXH: paper writing. MHY: paper revision. All authors approved the submitted version of the manuscript.

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