Review Article
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Systemic lupus erythematosus and cardiovascular risk: clinical score, pharmacological and non-pharmacological therapy aspects: a systematic review

Abstract

Introduction: Patients with Systemic Lupus Erythematosus (SLE) have high rates of cardiovascular risk (CVR).

Objectives: Perform a systematic review and meta-analyses, assessing the impact of clinical scores and the use of drug treatments.

Method: A systematic review and meta-analyses were carried out, based on the entire structure of the Cochrane handbook, using a PICO strategy (**Patient or Problem**: SLE; **Intervention**: clinical scores, drug and non-drug treatment; **Control or Comparison**: control individuals; **Outcomes**: atherosclerosis and/or cardiovascular risk), in order to identify studies that addressed these outcomes.

Results: A total of 4030 articles were identified, 4 articles were selected in order to identify the CVR through the Framingham score. The meta-analyses identified a non-impact of the Framingham score in relation to the CVR (mean difference: 0.18 [-0.49, 0.86] 95% CI) (p=0.53), 3 studies evaluated the CVR by the use of corticosteroid therapy, it was 1.32 [0.91, 1.93] 95% CI) (p=0.14), but without statistical significance; in relation to the use of hydroxychloroquine, revealed a protective factor of CVR of 0.18 [0.06, 0.56] 95%CI) (p=0.003).

Conclusion: There is a need for a more specific clinical score to signal CVR in SLE, the use of drug and non-drug treatment must weigh risks and benefits.

Keypoints

This is a complete review with meta-analysis showing clinical, treatment approaches in cardiovascular risk.

This review was prepared using Cochrane tools.

Studies were judged for risk of bias using the ROBINS-I tool.

The GRADE strategy was to assess the level of evidence.

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José Alexandre Mendonça,[1,2,3] Rebecca Marcelino Ribeiro,[2] Pedro de Siqueira Petean,[2] William Barros Hyppolito Ferreira,[3] Nayara Mota Carvalho,[3] Carolina Pelisson Carvalho[3]

[1]Postgraduate Program in Health Sciences Pontifical Catholic University of Campinas, Sao Paulo, Brazil
[2]Scientific Initiation Program, Pontifical Catholic University of Campinas, Sao Paulo, Brazil
[3]Rheumatology Service, Pontifical Catholic University of Campinas, Sao Paulo, Brazil

Correspondence: José Alexandre Mendonça, Rheumatology Service, Pontifical Catholic University of Campinas (PUCC), Sao Paulo, Brazil. PUCC Adress Avenue John Boyd Dunlop, no number, Jardim Ipaussurama, Campinas, ZIP Code 13060-604, Tel +55 019 3343-8600; Email scpa@hmcp.puc-campinas.br

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Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune, multisystem inflammatory disease that predominantly affects females, with a prevalence of 8.7/100,000 inhabitants,[1–4] with genetic, hormonal and environmental factors as main variables, which can cause injuries to different organs and systems, such as the cardiovascular system.[5]

Patients with SLE have accelerated atherosclerosis that can develop as cerebrovascular disease, peripheral vascular disease, and coronary artery disease, which is an important cause of morbidity in these patients. According to the Framingham Off Spring Study[5] the incidence rate of coronary events in SLE women aged 35 to 44 years were 50 times more likely to be stricken by a myocardial infarction than women of similar age without SLE.

The Framingham score is a clinical score validated for the general population which is also used in some studies with SLE patients. This score only predicts future events of coronary heart disease, but does not predict the risk of stroke, transient ischemic attack and heart failure, which are also important outcomes in the lupus population. This score includes age, total cholesterol, HDL, systolic blood pressure, smoking; these factors represent a 10-year CVR in these lupus patients; however they still require accuracy improvement.[6]

In this connection, SLE has been considered an independent risk factor for cardiovascular events (CVE), due to an early and accelerated atherogenesis and the chronic inflammatory process of the disease itself, in addition to obesity, often caused by chronic use of corticosteroids.[4,7–15] These patients have an increase in traditional risk factors for atherosclerosis, such as high blood pressure, diabetes mellitus, metabolic syndrome and dyslipidemia, and non-traditional risk factors such as kidney disease and higher levels of oxidized low-density lipoprotein.[5]

Treatment, in turn, includes changes in lifestyle, such as physical activity, adaptation to the Mediterranean diet and smoking cessation, in addition to drug therapy with the use of non-steroidal anti-inflammatory drugs, corticosteroids, immunosuppressants and antimalarials.[3,5,7–16]

Drug treatment with glucocorticoids interferes with CVR, being considered an independent risk factor for CVE. Likewise, its use predisposes the onset of metabolic syndrome, since, despite reducing systemic inflammatory rates, it contributes to an increase in typical CVR factors. On the other hand, antimalarials, as well as statins, control dyslipidemia and, the latter, even improves the endothelial function and reduces vessel thickness. In this way, they reduce

the CVR rate.[8,11,15,17,18] The objective of this study is to carry out a qualitative and quantitative systematic review with the evaluation of CVR characterizing the evaluation of clinical and therapeutic pharmacological and non-pharmacological score outcome.

Methods

This survey followed the recommendations for the preparation of systematic reviews proposed by Cochrane, PRISMA recommendations (Preferred Reporting Items of Systematic reviews and Meta-Analyses).[19–21] A systematic search was carried out in MEDLINE, LILACS and PubMed using the PICO strategy (Patient or Problem: SLE; Intervention: clinical scores; Control or Comparison: control individuals; Outcomes: atherosclerosis and/or CVR), after a question was asked, in order to identify studies that addressed the use of clinical scores in the diagnosis of CVR or atherosclerosis in patients with SLE, in addition to pharmacological and non-pharmacological treatment of this disease.

Three search strategies were adopted using a combination of controlled vocabulary and words from the text by Mesh terms (Medical Subject Headings): PubMed (((Lupus AND (cardiovascular risk)) OR (atherosclerosis); LILACS (((Lupus) AND (score)) AND (atherosclerosis); MEDLINE (((Lupus) AND (score)) AND (atherosclerosis).

Therefore, the selection process was carried out, applying the inclusion and exclusion criteria, carried out by 2 readers in two stages: first by reading only titles and abstracts, and second by reading the articles in full, judging, also, the methodological and statistical quality of the articles in this last stage, as shown below. Inclusion criteria: Scientific, cross-sectional, observational studies - randomized, non-randomized and clinical trials that specifically address the subject of the study; publication date during the period of the last 10 years until 01/15/2021; languages portuguese, spanish and english; SLE patients; studies evaluating the use of clinical score for CVR, pharmacological and non-pharmacological treatment. Exclusion criteria: Clinical cases, literature reviews, systematic reviews and meta-analyses; studies that did not present the outcome addressed.

From the selected papers, the Cochrane[22] tool was applied to assess the risk of bias, through selection bias, attrition, direction, inconsistency and imprecision, always considering the pre-intervention, intervention and post-intervention domains. Judging as low, moderate, serious and critical bias. The articles had their main data collected, divided into a group for evaluating the clinical score for CVR and a selection of articles for pharmacological treatments, including corticosteroids, hydroxychloroquine, statins and non-pharmacological treatments.

Regarding the level of evidence, the GRADEpro[23] tool was used, and for meta-analysis the Review Manager[21] software, which considers the evaluation of randomized and non-randomized studies, judging low, moderate and high levels of evidence. To assess the risk of bias for non-randomized studies, the ROBINS tool was used-I.[21,22]

Results

The literature survey yielded 4726 articles (4189 in MEDLINE via PubMed and 537 in LILACS). A total of 4276 articles were excluded, yielding at the end, 450 articles. After this process, the selection was initiated based on the inclusion and exclusion criteria. The following flowchart describes this process (Figure 1). The Cochrane[22] risk-of-bias assessment tool was then applied to the 11 papers finally included.

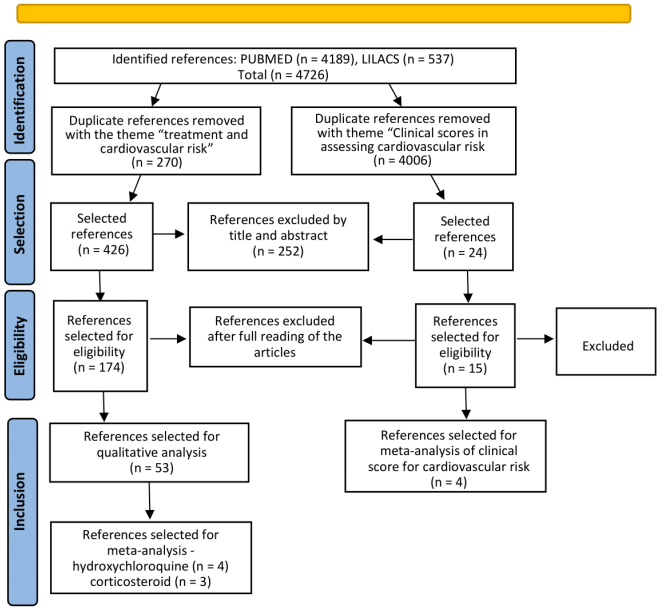

Figure 1 PRISMA Flowchart of the selection of systematic review papers in relation to the clinical score for CVR, pharmacological and non-pharmacological therapy, according to the Cochrane Collaboration model.

The articles were subdivided into drug treatment versus non-drug treatment and clinical scores associated with CVR. The meta-analysis was performed according to the Review Manager software.

The meta-analysis identified a non-impact of the Framingham score in relation to the CVR (*mean difference:* 0.18 [-0.49, 0.86] 95%CI), in view of the outcomes outlined in the studies, which characterize CVR, such as the thickening of the intima-media layer and ultrasound carotid calcification and increased arterial stiffness, parallel to the subclinical atherosclerosis detected (Figure 2).

The meta-analysis on corticosteroid therapy lost statistical significance due to the low effect estimate of 1.46 (p=0.14), making it impossible to determine whether there is indeed a risk relationship for cardiovascular events, despite the high number of patients evaluated in the studies, with a risk of 1.32, for the use of corticosteroid therapy (Figure 3).

The meta-analysis of hydroxychloroquine demonstrated that this drug is a protective factor for cardiovascular outcomes, with an estimated effect of Z equal to 2.96 (p=0.003) (figure 4). Using the Cochrane tool, ROBINS-I,[21,22] risk of bias analysis was performed in non-randomized studies regarding the clinical Framingham score, pharmacological and non-pharmacological treatment of the studies included, evaluating the following domains: confounders, data loss, outcome measures, selection bias, attrition, direction, inconsistency and imprecision (Figure 5).

The GRADEpro[23] tool evaluates meta-analysis studies that demonstrate a variable level of evidence in relation to interventions, through the imprecision concept, which mainly reflects a high number of patients, the concept of inconsistency, which mainly evaluates the presence of interval of adequate confidence and heterogeneity between studies.

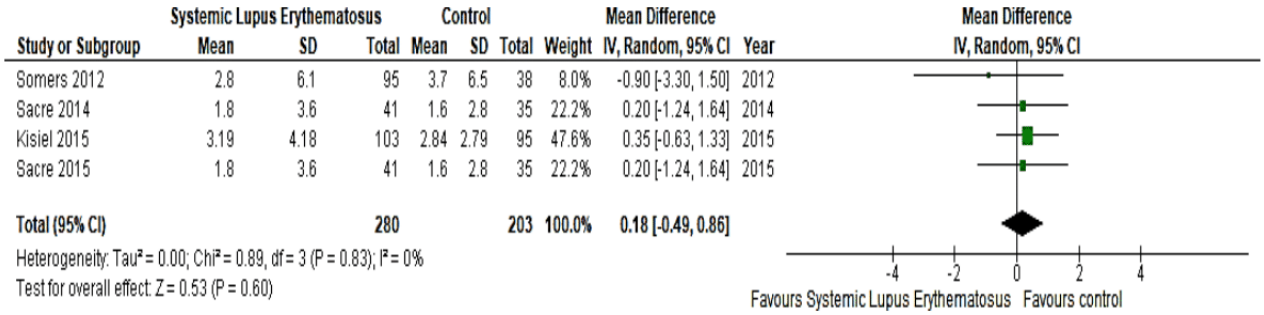

Figure 2 Forest plot represents the meta-analysis of studies, characterizing the influence of the Framingham clinical score on CVR in SLE patients compared to control groups.

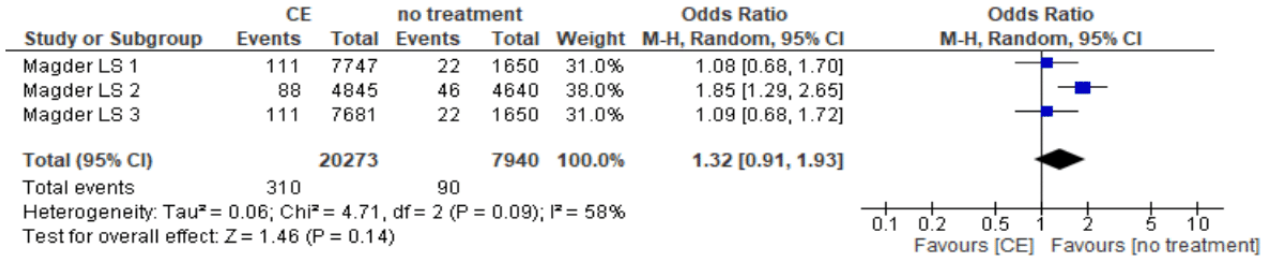

Figure 3 Forest plot represents the meta-analysis of the study with 3 subgroups evaluated in the period from 1987 to 2010, characterizing the influence of glucocorticoid use on the CVR in patients with SLE, compared to control groups.

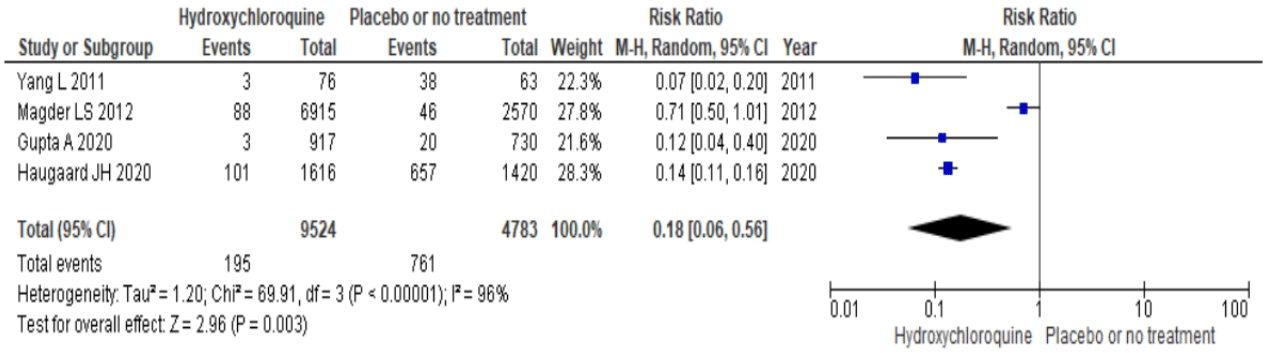

Figure 4 Forest plot represents the meta-analysis of the studies, characterizing the influence of the use of hydroxychloroquine on CVR in patients with SLE, compared to control groups.

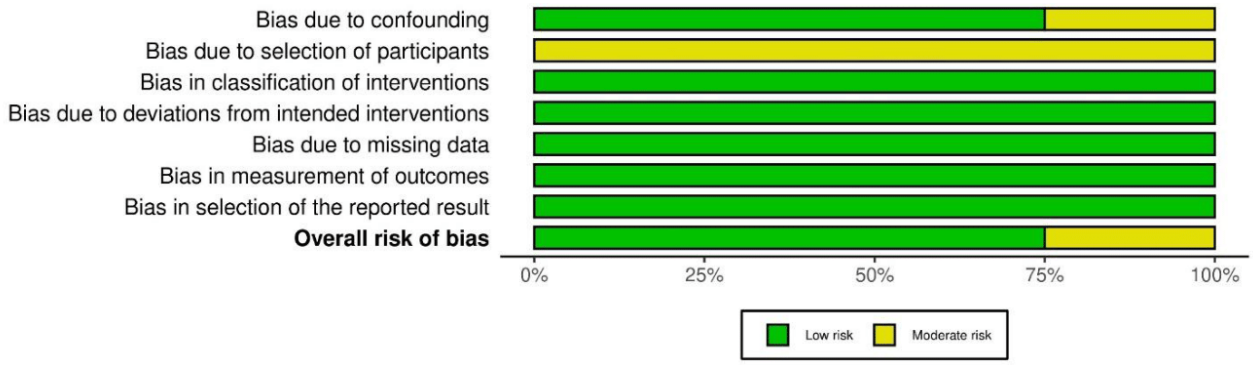

Figure 5 ROBINS-I: Risk of bias in non-randomized studies of the Framingham clinical score, use of corticosteroids and hydroxychloroquine.

Table 1 characterizes a low level of evidence, featuring inconsistency, substantial variation in effect estimates between studies, with distant confidence intervals (CI) with no overlap between them, imprecision marked by ''n'' sample <200 patients among the studies, with only one favorable study for the Framingham score, in relation to the CVR and with a very low mean (0.35) but with a moderate weight (47.6%).

Table 2 demonstrates an important level of evidence, characterized by adequate imprecision, with a large numerical sample of patients, but with a low relative risk of 0.24. Table 3 demonstrates an important level of evidence, characterized by adequate imprecision, with a large numerical sample of patients, but an important inconsistency in the face of extended confidence intervals, but with a relative risk of 1.32.

Table 1 Assessment of the level of evidence of Framingham score studies for CVR

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with Score Framinghan - Systemic Lupus Erythematosus			
	Low				
Cardiovascular Risk assessed with: score Framinghan mean timing of exposure: mean 4	0 per 1.000	0 per 1.000 (0 to 0)	RR 0.18 (-0.49 to 0.86)	280 cases 203 controls (4 observational studies)	⊕⊕◯◯ Low[a,b]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; RR, risk ratio

Table 2 Assessment of the level of evidence of studies on the use of hydroxychloroquine and CVR

Outcome № of participants (studies)	Anticipated absolute effects* (95% CI)		Relative effect(95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with Hydroxychloroquine				
Cardiovascular Risk	159 per 1.000	38 per 1.000 (14 to 102)	RR 0.24 (0.09 to 0.64)	14307 (4 observational studies)	⊕⊕⊕⊕ HIGH	IMPORTANT

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; RR, risk ratio

Table 3 Assessment of the level of evidence of studies on the use of corticotherapy and CVR

Outcome № of participants (studies)	Relative effect(95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Difference			
		Study population			
Cardiovascular Risk in LES and corticothera.py (CVR) assessed with: Events № of participants: 28213 (3 observational studies)	RR 1.32 (0.91 to 1.91)	1.10% High	1.50%	(1 to 2.2) 0.4% more (0,1 fewer to 1 more)	⊕⊕⊕⊕ High
		0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; RR, risk ratio The Framingham score in the selected studies showed a tendency to classify individuals with SLE and the control group in the same CVR category (low risk) and, when correlated with coronary age, its score increased, but not significantly. Another factor capable of increasing the Framingham score found in Moya et al[24] and Sacre et al.[25] was the cumulative dose of glucocorticoids. Among the traditional risk factors, those that demonstrated greater relevance in the progression of carotid plaque were chronological age and serum cholesterol.

In the qualitative evaluation of studies for non-pharmacological treatments, in view of dietary changes, all interventions proved to be beneficial for reducing CVR in lupus patients. Hypocaloric and hypoglycemic diets promoted weight loss in patients (-2.4kg +/- 2.2; (p<0.01); -3.9kg+/- 0.9, (p<0.01), respectively) and in the evaluation of the correlation between fiber intake and weight loss, r=-0.3, (p=0.04).[26] The Mediterranean diet also helped patients to obtain a reduction of 87% in anthropometric indices, 96% in disease activity, 95% in serum C-reactive protein (CRP) and 62% and 26% in disease activity scores (Systemic Lupus Erythematosus Disease Activity Index - SLEDAI, with p variation from 0.039 to p <0.001).[26]

The habit of smoking was directly associated with the presence of atherosclerosis and calcified carotid plaque (p=0.003),[28] in addition to CVS, with a risk ranging from 1.48 to 2.49 times greater than that of non-smokers (OR2.04 - 95%CI 1.15, 3.68, p=0.02),[29,30] metabolic syndrome (OR 5.06; 95% CI 1.87, 13.68)[31] and mortality rate due to CVR (HR3.4(95% CI 1.3, 9.2), p=0.02).[32] Smoking has also

been shown to be associated with increased levels of atherogenesis biomarkers, such as cystatin C and VCAM-1, and EPC (endothelial progenitor cell), which regenerate the endothelium of blood vessels.[33–35]

In the qualitative evaluation of studies for pharmacological treatments such as salicylates, compared to the use of other therapies, an improvement of the lipid profile and reduction of CVR (HR0.10, 95% CI:0.014,0.69; p=0.020)[36] in lupus patients, was observed as well as the use of statins at higher doses (HR 0.14.95% CI 0.08,0.25), with an absolute risk reduction of 56 people (95% CI 45.1, 69.4) for every 10,000 people-years in lupus patients with dyslipidemia.[37]

The use of biological therapies, in general, presented a reduction of 26% (HR: 0.74, 95% CI: 0.64, 0.86, p<0.001) in the risk of peripheral arterial disease[38], and when compared to their form of use, the Intermittent use was associated with greater arterial thickening compared to continuous use (0.508mm+/-0.128vs0.571 mm+/-0.139, p=0.043).[39]

Methotrexate alone was also associated with a greater ability to improve the lipid profile of these patients (p=0.005).[40] However, the use of azathioprine and cyclophosphamide promoted a higher risk of cardiovascular events (OR1.47(95%CI1.04–2.07), p<0.05, OR 1.88(95%CI1.01,3.49), p=0.045, respectively).[30]

Therefore, it was observed that vitamin D and calcium supplementation in SLE patients resulted in 25(OH) vitamin D (54.54±21.8nmol/l increased serum levels as compared to baseline (37.72±16.31nmol/l, p=0.004), which, in turn, was associated with CRP lower serum levels (r=−0.29, p=0.05) and lower D-dimer (r=-0.34, p=0.02)[41]. However, it was also demonstrated that patients with high levels of 25(OH) vitamin D had more arterial intima-media thickening (r=0.36, p=0.01) and higher carotid pulse wave velocity (r=0.35, p=0.02). Calcium levels were higher in vitamin D and calcium supplementation users with altered arterial thickness (9.55 ± 0.39 vs 9.13 ± 0.53, p=0.041),[41] and calcemia was directly related to arterial thickening (r=0.36, p=0.01).[41]

Discussion

The present work aims to elucidate the use of clinical scores as a tool in the diagnosis of CVR in patients with SLE, in addition to relating drug and non-drug therapies to that risk. As for the scores, during the literature survey, the Framingham score for clinical assessment of atherosclerosis/CVR, was the most used score and has within its measures the traditional risk factors for such events. Regarding this score, it was observed that alone it does not provide benefits in the diagnosis of CVR in patients with SLE, as it does not include important specific factors that influence CVR, mainly the use of corticotherapy. As demonstrated in this meta-analysis, there was no significant difference in the Framingham score in relation to the SLE versus control groups, as it did not present a statistically significant effect estimate (0.53; p=0.60), in Figure 2. The risk of bias was low between the studies when analyzing the different domains, verified in Figure 5. The levels of evidence of these studies were low, since they had a small sample "n", and inconsistency, due to the substantial variation of the effect estimates between the studies, characterized by distant confidence intervals.

Regarding the meta-analysis calculation studies for corticosteroid therapy in SLE, there was no estimate of the effect (1.46; p=0.14), despite the studies reflecting the trend towards non-treatment in the figure 3. The risk of bias was low across studies and across domains (Figure 3). The level of evidence of the studies was high due to the high number of patients, with RR equal to 1.32.

Regarding the meta-analysis calculation studies for hydroxychloroquine, there is an important and significant effect estimate, equal to 2.96 and p=0.003, respectively. The studies had a low risk of bias (Figure 4) and a high level of evidence, due to a high number of patients and non-distant CI in relation to 3 studies (Table 3). Hydroxychloroquine in several studies is a cardiovascular protective factor that reduced the incidence of atrial fibrillation and major cardiovascular events.

Statins and salicylates, in turn, also yielded a beneficial CVR outcome. However, glucocorticoids, azathioprine, cyclophosphamide deserve caution in their use. Corticosteroid therapy, in particular, was associated with a worsening in the lipid and metabolic profile and a higher incidence of comorbidities, such as obesity, insulin resistance and metabolic syndrome, although such therapy is capable of reducing the levels of disease activity, the immune and inflammatory markers which validates the rheumatologist's practice.

As for non-drug therapy, smoking cessation and adoption of hypoglycemic, hypocaloric and Mediterranean diets can be an interesting strategy, since smoking was considered a potentiating factor for CVR and dietary changes were able to improve the lipid profile of patients, reducing dyslipidemia and obesity; in addition, they both reduce disease activity rates and being associated with lower levels of serum inflammatory markers.

SLE is a multifactorial disease which main variables are: genetic, hormonal, environmental and infectious factors, which can cause damage to different organs and systems. Patients with SLE have accelerated atherosclerosis that can be manifested as coronary artery disease, being an important cause of morbidity in these patients. In this systematic review and meta-analysis, clinical scores were evaluated as a diagnostic tool in the detection of CVR. The use of the Framingham score did not demonstrate benefits in the diagnosis of the atherosclerotic profile of these patients with the disease studied, when compared to the control group, since, in most studies, both populations were clinically classified as low risk, even in lupus patients exhibiting the disease plaques.

The most relevant factor found for the progression of atherosclerosis was the state of SLE activity, as this was able to increase the likelihood of plaques appearance even in patients with low CVR verified by the most validated clinical score, the Framingham score.

Conclusion

Through this systematic review and meta-analysis, it was possible to conclude that non-pharmacological interventions, such as lifestyle changes especially dietary measures and smoking cessation are extremely relevant to reduce CVR and comorbidities that enhance this risk. Regarding drug treatment, it was concluded that hydroxychloroquine is a great ally in the rheumatologist's practice both for reducing CVR and for controlling the disease itself, as well as the use of salicylates and statins to control comorbidities that potentiate CVR in some patients. However, caution should be exercised regarding corticosteroid therapy, the use of cyclophosphamide, as well as other therapies, such as azathioprine in particular, considering that they accelerate the atherosclerotic process which was observed in some studies.

However, the present study has limitations to be considered. The variability of outcomes studied with different analytical measures restricts some inferences and potential confirmations, requiring further studies, especially with meta-analyses, to better help in the clinical practice decision-making in connection with the CVR outcome, which significantly increases the mortality rate in some patients with this disease.

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Declaration

Author information: These authors contributed equally: J.A.M., C.P.C., R.M.R., P.S.P., W.B.H.F. and N.M.C.

Additional information: Correspondence and requests for materials should be addressed to Carolina Pelisson Carvalho.

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Data availability: All data generated or analyzed during this study are included in this published article.

The datasets generated and analyzed during the present study are not publicly available due to the fact that the PROSPERO platform:

(https://www.crd.york.ac.uk/prospero/#register) was not available at the time of writing this review, despite using all the Cochrane-oriented tools for constructing the meta-analysis (Review Manager (RevMan- https://revman.cochrane.org/#/myReviews)); risk of bias tool (ROBINS-I) - https://www.riskofbias.info/welcome/home/current-version-of-robins-i) and level of evidence (https://www.gradepro.org/), following good systematic review and meta-analysis practices.

Acknowledgments

None.

Conflicts of interest

The authors declare no competing interests.

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