Cardiovascular disease burden in cutaneous lupus erythematosus: A systematic review and meta-analysis

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Introduction

The association between cardiovascular disease (CVD) and systemic lupus erythematosus (SLE) is well-established, but CVD burden in cutaneous lupus erythematosus (CLE) yet to be elucidated.[1] Given these parallels, and the association between chronic inflammation and endothelial dysfunction, we performed a systematic review and meta-analysis to appreciate the effect of CLE on CVD burden.

Methods

Search Strategy

We performed a systematic search of PubMed, EMBASE and Cochrane for all studies published before December 25, 2021. The search strategy used a combination of keywords: "cutaneous lupus erythematous OR cutaneous lupus OR discoid lupus OR acute cutaneous lupus OR subacute cutaneous lupus OR chronic cutaneous lupus" AND "cardiovascular OR heart disease OR cardiovascular disease OR hypertension OR myocardial infarction OR coronary artery disease".

Eligibility Criteria

Observational studies reporting CV related endpoints in patients with CLE were eligible for inclusion. Studies were excluded for the following:

1. Patients concomitant SLE
2. Interventional studies
3. Sample size less than 10
4. Conference abstracts, reviews, protocols, case-reports and non-english manuscripts

Statistical Analysis

Only studies reporting hazard ratios (HR) adjusted for comorbidities and 95% confidence intervals (CI) estimating risk of CV events in CLE were eligible for quantitative analysis. Meta-analysis of pooled HR for included studies was performed with **Cochrane Review Manager (RevMan) version 5.4 (Cochrane Collaboration, Oxford, UK) using the fixed-effects model** and a 2-sided P value of less than 0.05 was considered statistically significant.

Results

Trial characteristics

Our initial search returned 1252 unique articles, of which 13 underwent full review. **Seven studies reporting on 5,597,839 patients (7,244 cases; 5,590,595 controls)** were eligible for inclusion (**Table 1**).

Review of CVD Burden in CLE

- No evidence of increased incidence of elevated blood pressure (BP) in patients with CLE compared to healthy controls (HC).[3,4]
- Higher frequencies of dyslipidemia,hypertriglyceridemia, reduced HDL and metabolic syndrome in CLE.[3]
- Mean cholesterol, triglyceride and LDL levels were significantly higher patients with in CLE.[6]
- Mean HDL was significantly lower in patients with CLE.[6]
- No evidence to suggest that CLE is associated with an increased risk of ischemic heart disease (**HR 0.94, 95% CI 0.57-1.54**), congestive heart failure (CHF) (**HR 1.27, 95% CI 0.65-2.49**), peripheral artery disease (PAD) (**HR 2.06, 95% CI 0.99-4.32**) or CV related death (**HR 1.68, 95% CI 0.76-3.65**, $p>0.05$).[7]

Table 1. Main characteristics and findings of studies included in review

Study, *design*	CLE Disease subset	Sample size (case/control)	CV-related exclusion criteria	Summary of findings
Ahlehoff et al. 2017,[2] *population-based cohort*	Unspecified	3224/5,590,070	Prior MI or stroke	39% increased risk for VTE relative to HC (HR 1.39, 95% CI 1.1-1.78), 3.1 times the rate of having a VTE compared to HC (IR 3.06, 95% CI 2.43-3.86)
Akarsu et al. 2017,[3] *cross-sectional*	DLE	60/82	On anti-HLD, hypoglycemic, and anti-HTN treatment	Increased incidence of dyslipidemia, hypertriglyceridemia, reduced HDL and metabolic syndrome ($p<0.05$), no increased incidence of elevated BP ($p>0.05$)
Cocchi, Parodi, and Rebora 1991,[4] *cross-sectional*	DLE and SCLE	127/254	N/A	No increased incidence of elevated BP across all CLE subsets and overall cases relative to HC ($p>0.05$)
Hesselvig et al. 2017,[5] *population-based cohort*	Unspecified	3282/5,513,739	Prior CVD in last 12 months	31% increased risk of composite CV events (HR 1.31, 95% CI 1.16-1.49)
Lagogianni et al. 2005,[6] *cross-sectional*	DLE	30/34	Comorbid metabolic or endocrine disease, on medications with metabolic effects (e.g., steroids), smoking, obesity	Increased mean cholesterol, triglycerides, LDL and decreased HDL relative to HC ($p<0.001$)
Singh et al. 2016,[7] *population-based cohort*	Unspecified	155/155	CVD prior to CLE diagnosis	3 fold increased risk for CVA (HR 2.97, 95% CI 1.13-7.78), no increased risk for any CV event, ischemic heart disease, CHF, PAD or CV related death ($p>0.05$)
Zöller et al. 2012,[8] *population-based cohort*	DLE	126/No HC	CAD (main or secondary diagnosis) before or at the same time as first hospitalization for DLE	Overall, 86% more cases of CAD than expected after hospitalization in all DLE patients (SIR 1.86, 95% CI 1.55-2.21), 76% more cases in males (SIR 1.76, 95% CI 1.32-2.29), 94% more cases in females (SIR 1.94, 95% CI 1.52-2.44)

Abbreviations: DLE, discoid lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus; MI, myocardial infarction; HLD, hyperlipidemia; HTN, hypertension; CAD, coronary artery disease; VTE, venous thromboembolism; CVA, cerebrovascular accident; TIA, transient ischemic attack; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SIR, standardized incidence ratio; IR, incidence rate.

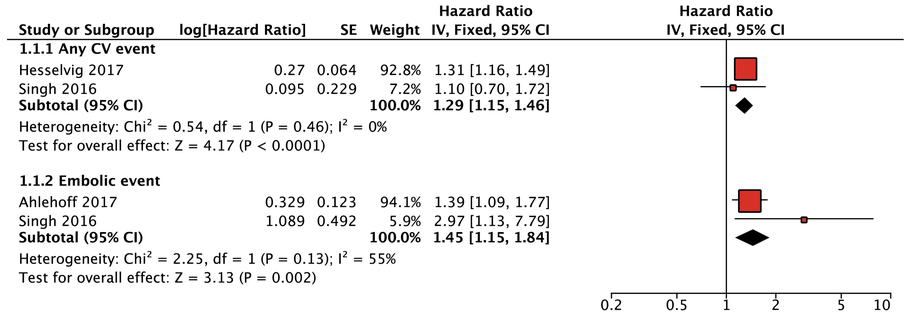

Figure 1. Association between CLE and risk of any CV event or embolic event (fixed-effects model). *CLE, cutaneous lupus erythematosus; CV, cardiovascular; HR, hazard ratio; CI, confidence interval*

Results cont.

Meta-analysis of CVD Burden

- Patients with CLE were at a **29% increased risk for any CV event when compared to controls** (HR= 1.29, 95% CI 1.15-1.46, $p<0.001$, as shown in **Figure 1**).
- CLE was associated with a **45% increased risk for embolic events (e.g., CVA and VTE)** (HR 1.45, 95% CI 1.15-1.84, $p<0.0$, as shown in **Figure 1**).

Limitations

- Population-based studies depend on ICD codes, may lead to misclassification of CLE and include patients that have progressed to SLE.
- CV outcomes and adjusted comorbidities varied across studies, serving as a potential source of heterogeneity
- Pre-existing CVD risk factors may confound CVD burden attributed to CLE

Conclusions

- Patients with CLE may be at an increased risk for CV events and subsets of CVD.
- The limited literature available on CV outcomes in patients with CLE suggests that CVD burden is under-appreciated in this patient population.

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