

Soluble CD163 and incident cardiovascular events in patients with systemic lupus erythematosus: An observational cohort study

Dear Editor,

The increased prevalence of cardiovascular events (CVE) in systemic lupus erythematosus (SLE) is not fully explained by traditional risk factors. Accordingly, prediction models such as Framingham score are not accurate at identifying CVE risks in this population [1]. sCD163, the soluble form of the scavenger receptor CD163 on macrophage, have been implicated in several inflammatory or autoimmune diseases including SLE [2]. Our group previously showed that sCD163 is a biomarker of accelerated atherosclerosis in SLE patients [3]. The aim of this study was to determine whether sCD163 was associated with incident CVE in SLE.

All SLE patients included in the randomized, double-blind, placebo-controlled, multicenter PLUS trial were screened [4]. Patients without history of CVE at inclusion and with a follow-up period of >20 months were analyzed [5]. sCD163 level was measured using enzyme-linked immunosorbent assay on serum collected at PLUS inclusion. The primary outcome was the incident CVE (see Supporting Information).

Among the 573 SLE patients of the PLUS study, 442 (37 [IQR: 29–48]; 90.5% female) were analyzed for the primary outcome with a median follow up of 110 (IQR: 99–120) months (Fig. S1). Ninety-nine (22.4%) were smokers, 60 (13.6%) had hypertension, 51 (11.6%) a BMI >30 kg/m², 34 (7.7%) dyslipidaemia and 11 (2.5%) diabetes. No patients had an eGFR <60 mL/min/1.73 m². Antiphospholipid antibodies were found in 217 (49.1%) patients. The median duration of SLE disease at baseline was of 7 (IQR: 3–12) years (Table S1).

Overall, 29 (6.6%) patients experienced at least one CVE that occurred at a median of 67 (IQR: 31–91) months after inclusion. CVE included coronary heart disease ($n = 14$), ischemic stroke ($n = 11$),

peripheral arterial disease requiring revascularization ($n = 2$), aortic aneurysm requiring surgery ($n = 1$) and sudden cardiac death ($n = 1$). Six patients had more than one CVE.

At PLUS inclusion, the median level of sCD163 in serum was 324.1 ng/ml (IQR: 218.4–470.1) (Fig. S2). By using maximally selected Log-Rank statistic, the cut point in sCD163 value that provided the best separation between the SLE patients who developed CVE and those who did not was 263 ng/ml (Fig. S3). In a multivariate Cox regression model with CVE as the dependent variable, dyslipidemia (HR 3.0 [95% CI: 1.2–7.5]), age (HR 1.7 [95% CI: 1.3–2.3]), and sCD163 > 263 ng/ml (HR 2.7 [95% CI: 1.1–7.0]) were associated with the occurrence of CVE (Table S2). Accordingly, Kaplan–Meier analysis showed that a concentration of sCD163 >263 ng/ml in serum at inclusion was associated with the occurrence of CVE during follow up (Fig. 1). Interestingly, multivariate Cox regression model with sCD163 >263 ng/ml as the dependent variable showed that BMI (OR 1.1 [95% CI: 1.0–1.1]), SLEDAI (OR 1.1 [95% CI: 1.0–1.3]) and the use of immunosuppressive drugs (OR 1.6 [95% CI: 1.1–2.4]) were associated with increased sCD163 (Table S3). In addition, sCD163 appeared to correlate with the SLEDAI activity score at inclusion (Fig. S4).

The present study demonstrates that a high level of sCD163—with a cut-off value of 263 ng/ml—is associated with incident CVE in SLE patients.

sCD163 may reflect SLE activity as suggested by its association with SLEDAI score and the use of immunosuppressive drugs. In the general population, CD163⁺ macrophages contribute to atherosclerotic lesions and plaque progression [6]. In SLE, CD163⁺ macrophages have been implicated in the pathogenesis of lupus nephritis [2]. High sCD163 level in serum may thus reflect the involvement of CD163⁺ macrophages

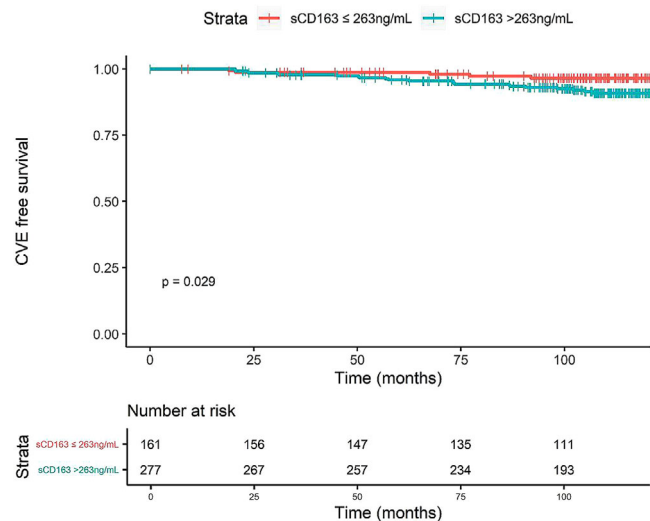


Fig. 1 Kaplan–Meier curves reflecting cumulative proportion of systemic lupus erythematosus (SLE) patients free of CVE according to sCD163 level. Analysis was performed on 438 patients. Abbreviation: CVE, cardiovascular event.

in both atherosclerosis and SLE and indicate the implication of SLE immune dysregulation in atherosclerotic inflammatory process [7, 8]. In our cohort, sCD163—known to be coupled with impaired insulin sensitivity and obesity [9]—was associated with BMI. Accordingly, sCD163 may reflect the chronic low-grade inflammation arising from adipose tissue macrophage that contribute—overweight being a strong contributor to lupus-associated atherosclerosis [10]—to the burden of CVE in SLE.

Our study has some limits: the primary outcome was not available for all PLUS patients, the small number of CVE limits statistical power and sCD163 was only assessed once at inclusion.

Moreover, the cut-off value of 263 ng/ml showed a good sensitivity (86.2%) but a poor specificity (37.5%) for CVE in SLE. Accordingly, such cut-off value seems more efficient to identify SLE patients at very low risk of CVE. Our study has also several strengths. It is an ancillary longitudinal study of a clinical trial including more than 400 SLE with an extended follow-up. Its primary endpoint focuses on incident CVE in contrast to most studies assessing the risk for CVE in SLE.

Macrophage-specific sCD163 serum level reflects lupus disease activity and is associated with CVE in SLE patients at apparent low cardiovascular risk. Stratifying patients according to sCD163 levels may help tailoring preventive treatment of SLE-related atheroma with statin or aspirin.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Ethics statement

The study was approved by the Comité de Protection des Personnes, St Louis Hospital, Paris (PLUS) and by the Comité de Protection des Personnes SUD-EST II, Lyon. All participants gave written informed consent to participate at the time of study enrollment.

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[Correction included on 13 July 2022 after original online publication: The copyright and legal statement has been updated.]

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1: Flow chart.

Figure S2: sCD163 concentration in SLE patients.

Figure S3: Maximally selected Log-Rank statistic for the cutpoint in sCD163 value.

Figure S4: sCD163 in SLE patients correlates with SLEDAI.

Table S1: Characteristics of SLE patients at inclusion.

Table S2: Risk factors for cardiovascular events in SLE patients.

Table S3: Risk factors for high sCD163 in SLE patients. ■