

# Performance of Cardiovascular Risk Equations versus Vascular Ultrasound in Systemic Lupus Erythematosus in a Black African Population

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## Abstract

**Introduction:** Cardiovascular risk is increased in systemic lupus erythematosus. Cardiovascular events are the first cause of death in lupus after five years duration. Prevention of cardiovascular events needs a good evaluation of the risk. In this work, we tried to evaluate the performance of conventional and adjusted forms of cardiovascular risk equations to predict high risk in lupus patients, in comparison with carotid ultrasound. **Method:** We realized a cross-sectional study during the period from 24 August 2017 to 22 November 2018. Consenting patient meeting the 1997 American college of Rheumatology criteria of systemic lupus erythematosus were recruited. The clinical characteristics and the treatment data were informed. Traditional cardiovascular risk factors were also investigated, and the assessment of cardiovascular risk was performed by Framingham and SCORE equations and their modified forms (multiplication by a factor of 1.5). Carotid ultrasound was used to detect atherosclerosis by measuring intima media thickness and searching for carotid plaques. In last, we compared cardiovascular risk levels by equations to results of carotid ultrasound. Statistical analysis and data collection were performed using SPSS 23.0 software. **Results:** Forty-nine patients with a sex ratio of 0.13 and a mean age of 33.5 ( $\pm 11.3$ ) years were enrolled. More than half of patients had dyslipidemia. More than 80% of the population were at low cardiovascular risk according to the equations. However, 16% of cases had carotid atherosclerosis. Between 50% and 100% of patients having atherosclerosis were considered at low or moderate risk by equations. The best

sensitivity to predict cardiovascular risk was given by modified Framingham (50%). **Conclusion:** In our study, conventional and modified risk equations had a bad performance to predict cardiovascular risk in systemic lupus erythematosus.

## Keywords

Cardiovascular Risk Equations, Carotid Ultrasound, Systemic Lupus Erythematosus

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## 1. Introduction

Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune diseases. Its course is characterized by two mortality peaks, one early related to disease activity and infectious complications and the other late (beyond 5 years) secondary to cardiovascular events. Cardiovascular mortality is estimated to account for 10% - 20% of overall mortality in SLE [1]. The risk of cardiovascular events is increased (50-fold) during SLE. Almost one-third of patients have carotid plaques [2]. It is therefore important to be able to assess the risk accurately to better prevent cardiovascular events [3]. In general population, it is possible to estimate the absolute coronary and cerebrovascular risk in each patient, by using equations established. The most used are Framingham and Systematic Coronary Risk Evaluation (SCORE). All the same, these equations have limits. Indeed, their predictive value is imprecise in young subjects, they do not take into account certain risk factors and their geographic validity is not clear [4] [5]. In SLE, inflammation which is the promoting factor for atherosclerosis is not taken into account by the risk equations. There is a very strong correlation between coronary atherosclerosis and ultrasound measurement of carotid intima-media thickness. In the general population, intima-media thickness and carotid plaque are independent prognostic markers of the risk of cardiovascular events [6]. Non-invasive ultrasound methods can detect atherosclerosis in 28% - 40% of lupus patients and therefore constitute in this sense an objective and efficient tool for prejudging the vascular risk of patients [7].

A study in American population has shown that cardiovascular diseases related to atherosclerosis in SLE are more frequent in black subjects [8]. However, the cardiovascular risk of SLE remains poorly studied in sub-Saharan Africa.

Therefore, we conducted this study with the objective of evaluating the performance of cardiovascular risk equations in predicting this risk in SLE compared to vascular ultrasound in defining high cardiovascular risk.

## 2. Method

Our study took place at the Aristide Le Dantec teaching hospital in Dakar in the internal medicine, cardiology and biochemistry departments. It was a descriptive and analytical cross-sectional study done during the period from 24 August 2017

to 22 November 2018. All consenting patients meeting the 1997 American college of Rheumatology (ACR) criteria of SLE were included consecutively [9]. Patients with chronic kidney disease, HIV infection or history of cardiovascular events were not included.

The clinical characteristics of SLE, as time to diagnosis, all clinical abnormalities related to the disease, and the disease activity assessed by the clinical Systemic Lupus Erythematosus Disease Activity Index (cSLEDAI) were recorded from their medical file [10]. Treatment data (duration, dosage and cumulative dose of corticosteroids, background therapy and other treatments) were specified. The classical cardiovascular risk factors as age, gender, diabetes, hypertension, smoking, physical inactivity, overall and abdominal obesity and dyslipidemia were investigated. The assessment of cardiovascular risk was performed by the Framingham and SCORE equations and their modified forms (SCORE/m and Framingham/m) adjusted (multiplication by a factor 1.5).

The definition of different levels of risk is presented in **Table 1**.

Vascular ultrasound was performed by a cardiologist using a device with a linear probe with a frequency of 3 to 13 Mhz. Measurement of carotid intima-media thickness (cIMT) was performed on the common carotid artery at 1.5 cm from the bulb using an automated method. Vascular ultrasound also detected the existence of carotid plaques. Carotid atherosclerosis was defined by a cIMT  $\geq$  0.9 mm and/or the presence of carotid plaques [11]. In last, we determined the proportion in which patients with carotid atherosclerosis were classified as high or very high risk. In the same way, we searched the proportion of patients having carotid atherosclerosis but classified at low or moderate risk.

Statistical analysis and data collection were performed using SPSS 23.0 software. Quantitative variables were expressed as mean plus or minus standard deviation and qualitative variables as number and percentage. The results were presented in tables.

### 3. Results

#### Characteristics of our study population

We recruited 49 patients with a sex ratio of 0.13 and a mean age of 33.5 ( $\pm$ 11.3) years. Cutaneous and hematological manifestations were predominant, followed by rheumatological and renal involvement. Serous and neurological manifestations were rarer. The disease was active. Most of patients were on

**Table 1.** Interpretation of the values of Framingham, SCORE and their modified forms.

Cardiovascular level risk	Framingham/Framingham/m	SCORE/SCORE/m
Very high risk	> 20%	>15%
High risk	15% - 20%	5% - 15%
Moderate risk	10% - 15%	1% - 5%
Low risk	5% - 10%	<1%

Very low risk

≤5%

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corticosteroids and hydroxychloroquine. Cyclophosphamide was the most immunosuppressive used followed by azathioprine. In **Table 2**, socio-demographic and clinical data of the patients are summarized.

#### **Traditional cardiovascular risk factors**

Diabetes, hypertension, smoking, and sedentary lifestyle were noted in 2, 6 and 3 patients respectively. Obesity was present in 4 cases and 3 patients met the definition of metabolic syndrome. Dyslipidemia was found in more than half of the cases (63.26%). More than a quarter (26.53%) had low-HDL cholesterolemia. High triglyceridemia was found in 34.6% of cases. Hyperuricemia was noted in 48% of patients. Renal insufficiency was noted in 4 patients.

#### **Cardiovascular risk equations**

Most of our study population (more than 80%) was classified at low cardiovascular risk according to the risk equations.

The results of the cardiovascular risk assessment according to the Framingham and SCORE equations and their modified version are shown in **Table 3**.

#### **Carotid atherosclerosis**

The mean cIMT was 0.587 ( $\pm 0.15$ ) mm and carotid atherosclerosis with carotid

**Table 2.** characteristics of our study population.

<b>Socio-demographic and clinical data</b>	<b>Number</b>
Sex ratio M/F	6/43 (0.13)
Age mean (years)	33.5 ( $\pm 11.3$ )
Disease duration (month)	60 ( $\pm 59.3$ )
Diagnostic delay (month)	30.16 ( $\pm 39.2$ )
Clinical manifestations	
Cutaneous	32 (65%)
Rheumatology	21 (42%)
Hematology	31 (63%)
Renal	20 (40%)
Neurology	5 (10%)
Serous	4 (8%)
Disease activity	6.59 ( $\pm 5.6$ )
Treatment data	
Corticosteroids	46 (93%)
Duration (month)	36.46 ( $\pm 53.4$ )
Daily dose (mg/day)	22.61 ( $\pm 18.9$ )
Cumulative dose (mg)	894.94 ( $\pm 2618.4$ )
Hydroxychloroquine	48 (97%)

Immunosuppressive 18 (36%)

**Table 3.** Cardiovascular risk level according to the Framingham and SCORE equations and their modified versions.

Cardiovascular risk level	Framingham n (%)	Adjusted Framingham n (%)	SCORE n (%)	Adjusted SCORE n (%)
Very low risk	40 (82%)	37 (75%)	NA*	NA*
Low risk	6 (12%)	4 (8%)	46 (94%)	44 (90%)
Moderate risk	2 (4%)	5 (10%)	3 (6%)	4 (8%)
High risk	1 (2%)	3 (6%)	0	1 (2%)
Very high risk	0	0	0	0

NA = no applicable.

**Table 4.** Carotid ultrasound findings in lupus patients.

Carotid Atherosclerosis	Systemic lupus erythematosus
IMT mean (mm)	0.587
IMT mean right (mm)	0.587
IMT mean left (mm)	0.592
IMT $\geq$ 0.9 mm n (%)	2 (4%)
Plaques n (%)	8 (16%)

IMcT = carotid intima média thickness.

plaques was present in 8 patients (16%).

**Table 4** summarizes the vascular ultrasound data of our study population.

#### Performance of risk equations in predicting high cardiovascular risk in lupus

Classical equations underestimated the cardiovascular risk. In fact, between 75% and 100% of patients having carotid atherosclerosis were classified in moderate or low cardiovascular risk by this equation. Only between 0 to 25% of patients with carotid atherosclerosis were considered at very high or high cardiovascular risk. In the same way, the adjusted equation underestimated also the risk. From 50% to 87.5% patient classified at moderate or low cardiovascular risk had carotid atherosclerosis. The modified SCORE had a bad sensibility (12.5%) and the modified Framingham offered the best sensibility (50%) in atherosclerosis prediction. In contrast, their specificity was very good because from 90% to 100% of patients having carotid atherosclerosis were at low or moderate risk. In **Table 5**, we presented the correlation between the cardiovascular risk level with the presence or not of carotid atherosclerosis.

## 4. Discussion

It is currently well documented that cardiovascular risk is increased in autoim-

mune diseases. Ischemic complications are thought to be the first cause of mortality after 5 years of SLE progression [1]. But evidence from the literature suggests **Table 5**. Prediction of cardiovascular risk by the classical equations and their modified forms compared to the vascular ultrasound.

Cardiovascular risk level	Carotid ultrasound		
	Without ATH * n (%)	With ATH* n (%)	Total (%)
<b>Framingham (%)</b>			
Moderate/low	40 (97.4)	6 (75)	46 (93.6)
Very high/high	1 (2.6)	2 (25)	3 (6.4)
<b>Framingham/m (%)</b>			
Moderate/low	37 (90)	4 (50)	41 (83.3)
Very high/high	4 (10)	4 (50)	8 (16.7)
<b>SCORE (%)</b>			
Moderate/low	41 (100)	8 (100)	49 (100)
Very high/high	0 (0)	0 (0)	0 (0)
<b>SCORE/m (%)</b>			
Moderate/low	41 (100)	7 (87.5)	48 (97.9)
Very high/high	0 (0)	1 (12.5)	1 (2.1)
<b>Total (%)</b>	41 (100)	8 (100)	49 (100)

ATH = atherosclerosis

Framingham	Framingham/m	SCORE	SCORE/m
Sensitivity = 25%	Sensitivity = 50%	Sensitivity = 0%	Sensitivity = 12.5%
Specificity = 97%	Specificity = 90%	Specificity = 100%	Specificity = 100%

that in SLE, the equations classically use for predicting cardiovascular risk are not suitable because they underestimate this risk [2]. In the general population, Framingham and SCORE equations have been validated at the individual level for predicting cardiovascular risk [4] [5]. Cardiovascular risk may be more widespread in Africa where access to care is more limited and screening for atherosclerosis is less easy and less systematic [12]. However, it remains little studied in sub-Saharan Africa, some publications concern rheumatoid arthritis [13] [14] [15]. It is in this context that we conducted a cross-sectional study to assess the performance of equations in predicting this cardiovascular risk during SLE compared to carotid ultrasound in defining high risk. Carotid ultrasound was used for its greater accessibility and safety. Also, this methodology has been used in several previous studies [16] [17].

The increased cardiovascular risk in SLE is partly due to the higher frequency of traditional factors in this population [18]. In our study, dyslipidemia was present in more than half of the cases. It concerned a low-HDL-cholesterolemia and a high triglyceridemia. Similarly, almost half of the patients had hyperuricemia. Similar results have been reported in the literature [17] [19].

Carotid atherosclerosis was noted in 16% of patients. In the meta-analysis of SLE and atherosclerosis, 44 out of 71 studies found a higher prevalence of plaques in SLE cases than in controls (23.6% versus 13%) [17].

Cardiovascular complications are an important mortality factor in SLE. So, their early detection is a necessary element in the management of this disease. Similarly, the assessment of cardiovascular risk appears to be important in the prevention of these complications.

In SLE, earlier atherosclerosis is due to high prevalence of traditional factors but also disease related factors. That is why conventional equations underestimate the cardiovascular risk in SLE because they don't consider these specific factors [2] [20] [21]. The Framingham score is heavily weighted for age and male sex, so the risk of coronary heart disease in young women with SLE is grossly underestimated. The inability to accurately assess the true risk of cardiovascular disease for each individual patient has resulted in an inability to modify mortality associated with cardiovascular events and morbidity in LSE, in contrast to the trend observed for other causes of mortality, such as lupus nephritis [22]. In our study, the cardiovascular risk is underestimated by the conventional equations (Framingham and SCORE) compared to the carotid ultrasound. The Hopkins Lupus Cohort Study compared the prediction of major cardiovascular events between the Framingham equation, the American College of Cardiology (AHA/ACC) equation and a formula that considered SLE factors and traditional risk factors. This study concluded that the Hopkins lupus cohort formula was superior to the Framingham and AHA/ACC equations [23]. In the retrospective series by Esdaile *et al.*, the observed coronary event rate was 7.5 times (95% CI: 5.1 - 10.4) higher than expected based on the Framingham score, while the ischemic stroke rate was 7 times (95% CI: 4.0 - 13.6) higher, with an absolute risk of coronary events of 12.9% (1.5% per year) and ischemic strokes of 6.1% (0.70% per year), after a mean follow-up of 8.6 years [20]. Kawai *et al.* found no significant difference in the level of cardiovascular assessed by the Framingham score between SLE cases and controls. Furthermore, in this study, the Framingham cardiovascular level of lupus patients did not predict the existence of subclinical atherosclerosis detected by coronary calcifications [24]. Urowitz proposed an adjustment of the Framingham score by a factor of 1.5, 2 and 3. Thus, he found that a factor of 2 improved the sensitivity with good specificity of the Framingham score [25].

After adjustment (multiplying by a factor of 1.5), we find that the modified Framingham and SCORE equation still have a low sensitivity, respectively 50% and 12.5%, compared to carotid vascular ultrasound.

A recent study assessed the performance of eight clinical risk prediction scores (including Framingham, SCORE and their modified forms) to identify individuals with SLE at high cardiovascular disease risk, as defined by the presence of atherosclerotic plaques. In this study, most of the five generic and three "SLE-adapted" clinical risk scores underestimated high cardiovascular risk defined by atheroscle-

rotic plaque presence in patients with SLE [26].

Our work is limited by the small sample size and cross-sectional nature of the study. A prospective study to determine the occurrence of cardiovascular events would better assess the performance of these equations.

## 5. Conclusion

Most of our study population was classified in low cardiovascular according to the Framingham, SCORE and their modified forms of risk equations. These equations had a poor predictive value of high cardiovascular compared to the carotid ultrasound (sensitivity  $\leq 50\%$ ). The modified Framingham offered the best sensitivity of 50% for LS.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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