

# Modified Framingham Risk Factor Score for Systemic Lupus Erythematosus

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**ABSTRACT. Objective.** The traditional Framingham Risk Factor Score (FRS) underestimates the risk for coronary artery disease (CAD) in patients with systemic lupus erythematosus (SLE). We aimed to determine whether an adjustment to the FRS would more accurately reflect the higher prevalence of CAD among patients with SLE.

**Methods.** Patients with SLE without a previous history of CAD or diabetes followed regularly at the University of Toronto Lupus Clinic were included. A modified FRS (mFRS) was calculated by multiplying the items by 1.5, 2, 3, or 4. In the first part of the study, using one-third of all eligible patients, we evaluated the sensitivity and specificity of the FRS and the different multipliers for the mFRS. In the second part of the study, using the remaining 2/3 of the eligible patients, we compared the predictive ability of the FRS to the mFRS. In the third part of the study, we assessed the prediction for CAD in a time-dependent analysis of the FRS and mFRS.

**Results.** There were 905 women (89.3%) with a total of 95 CAD events included. In part 1, we determined that a multiplier of 2 provided the best combination of sensitivity and specificity. In part 2, 2.4% of the patients were classified as moderate/high risk based on the classic FRS and 17.3% using the 2FRS (the FRS with a multiplier of 2). In part 3, a time-dependent covariate analysis for the prediction of the first CAD event revealed an HR of 3.22 ( $p = 0.07$ ) for the classic FRS and 4.37 ( $p < 0.0001$ ) for the 2FRS.

**Conclusion.** An mFRS in which each item is multiplied by 2 more accurately predicts CAD in patients with SLE. (J Rheumatol First Release February 15 2016; doi:10.3899/jrheum.150983)

## Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS

CARDIOVASCULAR DISEASE

FRAMINGHAM RISK SCORE

Patients with systemic lupus erythematosus (SLE) are at a much higher risk for coronary artery disease (CAD) than age- and sex-matched controls, from 3.4 times higher in SLE compared with age- and sex-matched controls, and 52.4 times higher in women aged 35–44 years<sup>1,2</sup>. Since it was first identified<sup>3</sup>, many have attempted to explain the relationship between SLE and CAD<sup>4</sup>. This premature development is likely associated with a combination of disease- and

therapy-related factors, classic CAD risk factors, genetic factors, or a combination of all of these<sup>5,6,7,8,9,10,11,12</sup>. In the general population, risk for CAD is often evaluated through the use of instruments such as the Framingham Risk Score (FRS)<sup>13</sup> or the Reynolds Risk Score<sup>14</sup>. The FRS was developed to assess the risk for CAD, defined as myocardial infarction (MI), angina pectoris, or coronary heart disease death in the general population. When applied to patients with SLE, it significantly underestimates the true risk of CAD<sup>2,5</sup>. It would be advantageous to have a modification of the FRS so that it more accurately reflects the risk factor score components while retaining the relative value of each, which had been derived from large populations. We assumed for our study that the relative risk for each of the factors was similar for the SLE population as for the general population, because a recalibration of the relative risk in SLE would involve large numbers of patients not available for such a study.

The aims of our study were to (1) identify which multiplying factor was optimal to predict CAD in patients with SLE, (2) determine whether the multiplier outperformed the original FRS in predicting CAD in the 10-year period following the evaluation of the FRS, and (3) determine whether the multiplier outperformed the original FRS in predicting CAD when FRS was evaluated repeatedly at each clinic visit.

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## MATERIALS AND METHODS

**Patients.** Patients with SLE (based on 4 American College of Rheumatology criteria or 3 criteria with biopsy-proven SLE) were followed at 2- to 6-month intervals at the University of Toronto Lupus Clinic since 1970. At each visit, patients underwent a complete assessment including a clinical history, physical examination, and laboratory evaluation according to a standard protocol. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index 2000<sup>15</sup>. All data were entered onto a computerized database. Information on cardiovascular risk factors and outcomes were collected prospectively.

All patients seen at the University of Toronto Lupus Clinic were eligible for entry into our study. We excluded patients with a history CAD or diabetes prior to the development of CAD. CAD was defined as MI, angina, or sudden death. MI was diagnosed on the basis of typical chest pain and enzyme and/or echocardiogram change. Angina was defined as a typical change in pain relieved by rest or nitroglycerine. All this information has been collected in our protocol since 1970. Because of the rare occurrence of CAD in an adult cohort prior to age 30 years, only visits when the patient was between 30 and 75 years were included.

**FRS and modified FRS (mFRS) evaluation.** FRS was calculated for each patient and patients' risks were categorized as very low to low (< 10%), moderate (10–20%), or high (> 20%) based on their 10-year absolute risk. We combined patients with very low and low risks and compared them with patients with moderate or high risk.

The mFRS was calculated using the multipliers 1.5, 2, 3, or 4 for each component of the FRS.

In the first part of our study, we used one-third of all eligible patients to calculate sensitivity and specificity to identify the best constant to be used in the mFRS. The resulting sensitivity and specificity were plotted to identify the most appropriate constant to use.

In the second part of our study, we compared the original FRS to the mFRS as defined above. Using the remaining two-thirds of all eligible patients, we evaluated the ability of the FRS and the mFRS to predict CAD in the 10 years following the measurement.

By design, FRS evaluated the risk of CAD in the following 10 years. In clinical practice, patients with SLE came regularly for followup visits. The FRS can be evaluated more than once every 10 years. In the third part of our study, we evaluated the original FRS as well as the mFRS at every clinic visit where all of the data for the calculation of the score were available. Then we evaluated how well the FRS and mFRS identified patients who developed CAD using multiple values of the FRS and mFRS through the course of their followup.

**Data imputation.** In the SLE database, most variables were available for all visits with the exception of high-density lipoprotein (HDL), which was available in only 40% of all visits. Multiple imputations were carried out on all missing HDL using total cholesterol, sex, and age as the plausible variables that represented the uncertainty about the characteristics each patient had. Minimum and maximum possible values were set and each patient was given 10 imputed HDL. We assumed the missing were at least at random and the Markov Chain Monte Carlo method was used. This was the better strategy for handling missing data compared to other methods such as dropping cases with missing variables and simple imputation using means of complete cases, which would be biased<sup>16</sup>. In the second phase of the analysis, the multiple imputed datasets were analyzed using standard procedures (for example, Cox regression) for complete data; in the last stage, the results were combined from multiple analysis using procedures under the multiple imputation methodology framework. We then imputed values for HDL using multiple imputations<sup>17,18,19,20</sup>.

**Statistical analysis.** Descriptive statistics were used to describe the different study groups used in each part of our study.

In the absence of a validation cohort such as ours with the same length of followup and number of patients, the best approach to derive robust results was to split the cohort into a testing or derivation group and a testing and validation group. In the first part of our study, using one-third of all eligible

patients randomly selected, we evaluated the sensitivity and specificity of the FRS and different multipliers for the mFRS. We used 1.5, 2, 3, and 4 as multipliers. We used the equation from Agresti and Coull to evaluate the variance of each sensitivity and specificity estimate<sup>21</sup>. Using the results of the multiple imputation, we selected the best multiplier for the mFRS.

In the second part of our study, using the remaining two-thirds of the eligible patients, we compared the predictive ability of the FRS to the mFRS. We measured the FRS and mFRS at a date closest to 10 years prior to the first CAD event reported for each patient (or last visit for patients without events). We then ran a Cox proportional hazard model for the time-to-event prediction of CAD using the FRS and mFRS separately. We compared the HR and 95% CI for the FRS and mFRS.

In the first and second parts of our study, we used a single value of the FRS and the mFRS on each subject. However, with multiple clinic visits over time, we had access to the FRS and mFRS at varying timepoints in the course of their followup. In this setting, it may be the case that the likelihood of CAD depended more on the current value of the FRS or mFRS than on their value at an arbitrary timepoint. Therefore, in the third part of our study, we used all of the available clinic visits prior to the first CAD event or last clinic visit of the patients retained in the second part of our study. We ran time-dependent covariate time-to-event (Cox) analysis for the prediction of CAD. Using this analysis allowed for the inclusion of independent variables whose value for a given subject does differ over time<sup>22</sup>. We ran separate models for the FRS and for the mFRS, respectively. Model calibration was tested using methods of Grønnesby and Borgan<sup>23</sup>.

## RESULTS

A total of 1013 patients with 22,287 clinic visits were included from the University of Toronto Lupus Clinic database. This group was composed of 905 women (89.3%) and 718 whites (70.9%), 110 blacks (10.9%), 87 Asians (8.6%), and 98 others (9.7%). Mean time to first CAD event or last clinic visit from entry to our study was  $9.0 \pm 8.1$  years. The mean number of visits available for analysis for each patient was  $22.0 \pm 20.7$ . There were a total of 95 CAD events (Table 1).

Table 1. Descriptive statistics.

Characteristics	1/3 Sample, Part 1	2/3 Sample, Part 2
Sample size, n	335	678
Female sex, n (%)	301 (89.9)	604 (89.1)
Age, yrs, mean $\pm$ SD	43.7 $\pm$ 11.0	42.4 $\pm$ 10.8
Disease duration, yrs, mean $\pm$ SD	10.0 $\pm$ 9.2	9.4 $\pm$ 8.8
CAD, n (%)	33 (9.9)	62 (9.1)
hsCRP, (n) mean $\pm$ SD	(n = 90) 4.5 $\pm$ 8.6	(208) 7.3 $\pm$ 13.9
Elevated, (n) n (%)	(n = 90) 30 (33.3)	(208) 85 (40.9)
Current smoker, n (%)	70 (20.9)	124 (18.3)
Blood pressure, mean $\pm$ SD		
Diastolic	78.5 $\pm$ 10.7	78.0 $\pm$ 11.3
Systolic	126.3 $\pm$ 19.4	124.4 $\pm$ 18.4
Cholesterol, mean $\pm$ SD	5.2 $\pm$ 1.6	5.1 $\pm$ 1.3
Elevated, n (%)	131 (39.3)	268 (40.2)
HDL, mean $\pm$ SD		
Original, (n) mean $\pm$ SD	(n = 109) 1.6 $\pm$ 0.5	(184) 1.5 $\pm$ 0.5
Imputed, (n) mean $\pm$ SD	(n = 335) 1.6 $\pm$ 0.4	(687) 1.6 $\pm$ 0.3
Time to CAD/last clinic visit, yrs, mean $\pm$ SD	6.3 $\pm$ 3.5	5.7 $\pm$ 3.5

CAD: coronary artery disease; hsCRP: high-sensitivity C-reactive protein; HDL: high-density lipoprotein.

**Part 1: Sensitivity and specificity analysis.** One-third (n = 335) of the study patients were used for our analysis. We used 1 clinic visit per patient. We selected the visit closest to 10 years prior to the first CAD event or last clinic visit. Thirty-three patients (9.9%) developed CAD. The descriptive statistics are found in Table 1. The original FRS points obtained for each item were multiplied by 1.5, 2, 3, or 4. Using both the mFRS and the original FRS, we evaluated the number of patients who would be classified as very low and low risk and those who would be classified as moderate and high risk. We then compared the categorization to the presence of CAD and evaluated sensitivity and specificity for the FRS and each of the mFRS (Table 2). While the 1.5 multiplier provided an appropriate moderate/high risk categorization, the sensitivity was very low (19.7%). A multiplier of 2.0 still gave a reasonable categorization for moderate/high risk with increased sensitivity while retaining a good specificity (Table 2). When targeting the at-risk population, a higher specificity is desirable.

**Part 2: Testing FRS and 2FRS (the FRS with a multiplier of 2) in the prediction of future CAD.** For this part of the analysis, we used the remaining two-thirds of patients (n = 678). Sixty-two of these patients had a CAD event. In this group of patients, 16 (2.4%) of the patients were classified as moderate/high risk based on the classic FRS and 117 (17.3%) using the 2FRS. The sensitivity and specificity (95% CI) for FRS was 6.8 (0–14.9) and 98.1 (96.5–99.6), respectively. For the 2FRS, it was 34.5 (21.3–47.8) and 84.4 (81.3–87.6), respectively.

The mean  $\pm$  SD 10-year risk provided by the FRS was 2.3  $\pm$  4.0 for patients who did not develop CAD and 4.9  $\pm$  5.8 for the patients who did (p < 0.0001). For the 2FRS, the mean  $\pm$  SD 10-year risk was 5.9  $\pm$  10.4 for patients who did not develop CAD and 12.6  $\pm$  15.2 for the patients who did (p < 0.0001).

The difference in 10-year risk between patients who had CAD and those who did not was 2.6  $\pm$  4.2 for the FRS and 6.5  $\pm$  11.1 for the 2FRS (p < 0.0001).

The results from the time-to-event analysis for the prediction of CAD within 10 years from the measurement of the FRS and 2FRS revealed that the HR was 3.11 (95% CI 0.61–15.78, p = 0.16) for the FRS and 2.14 (95% CI 1.15–3.96, p = 0.02) for the 2FRS.

Table 2. Sensitivity and specificity for the FRS and the mFRS using a multiplier of 1.5, 2, 3, or 4.

Variable	Moderate/ high Risk, %	Sensitivity		Specificity	
		Sensitivity	95% CI	Specificity	95% CI
FRS	2.9	13.0	0–26.6	98.2	96.3–100.0
1.5 FRS	11.5	19.7	3.7–35.7	89.4	85.2–93.5
2 FRS	20.3	31.5	13.3–49.7	80.9	76.1–85.7
3 FRS	29.7	45.5	26.8–64.1	72.0	66.6–77.5
4 FRS	32.7	46.1	27.4–64.7	68.8	63.1–74.5

FRS: Framingham Risk Factor Score; mFRS: modified FRS.

**Part 3: Time-dependent covariate analysis.** In the third part of our study, we evaluated the original FRS as well as the mFRS at every clinic visit using the 678 patients from part 2 where all of the data needed were available. There were 12,381 visits. The average time between visits was 5.4  $\pm$  6.8 months and each patient had an average of 18.3  $\pm$  17.7 visits included in our analysis.

Proportional hazard time-to-event analysis was performed using time-dependent covariate analysis for the prediction of the first CAD using the classic FRS and the modified 2FRS separately. The HR were 3.22 (95% CI 0.92–11.18, p = 0.07) and 4.37 (95% CI 2.39–7.98, p < 0.0001) for the FRS and 2FRS, respectively (Table 3). The model calibration tests, according to the Grønnesby and Borgan method<sup>23</sup>, showed chi-square values from 0.02 to 0.73, all with nonsignificant p values, indicating that all model fittings were adequate.

## DISCUSSION

In patients with SLE, the FRS underestimates the true risk of CAD<sup>2,5</sup>. The FRS is evaluated by the addition of points based on the values of each of the following variables: age, total cholesterol, HDL, blood pressure, smoking, and diabetes. Of all these variables, age has the most important contribution to the total number of points. The observed incidence of CAD is much higher in younger women with SLE than in the general population — up to 50 times higher in women with SLE aged 35–44 years old<sup>1</sup>. By design, the FRS is unlikely to identify young women as having a significant risk of CAD.

Different changes have been proposed to address this issue. Kawai, *et al*<sup>24</sup> suggested using coronary age-modified risk score in the FRS evaluation: coronary age derived from the coronary artery calcium score. Seventeen percent of the patients with SLE had a change in their age in the FRS evaluation. One percent was classified as intermediate risk using the classic FRS while none was classified as high risk. Using the age modification, the new score assigned 5% to the intermediate and another 3% to the high risk category. The Kawai study did not have sufficient followup to determine the sensitivity and specificity of the proposed modification to FRS. Moreover, specialized imaging techniques are required to acquire the coronary artery calcium score.

It has been shown that the other classic risk factors used in the FRS also contribute to the increase in CAD in patients with SLE<sup>6,11</sup>. Changing only the age component of the FRS is probably not sufficient — the contribution of the other factors in the FRS should not be ignored. We propose increasing the point value of each of the variables in the FRS by a constant and using this mFRS to classify patients with SLE into risk categories. One of the main advantages of this proposed approach of multiplying each point value by a constant is that the mFRS retains the relative contribution of each of the various components found in the original FRS tool gleaned from large population studies. This means that the contribution of elevated cholesterol compared with the



Table 3. Results of multivariate time-dependent analysis for coronary artery disease using the FRS and 2FRS.

Model	Variable	HR	95% CI	p
FRS only	FRS	3.215	0.941–10.990	0.066
FRS and AMS	AMS	1.058	1.013–1.106	0.0109
	FRS	3.440	0.999–11.850	0.0536
FRS and SLEDAI-2K	FRS	3.495	1.019–11.990	0.0499
	SLEDAI-2K	1.060	1.021–1.100	0.002
FRS and treatment	Antimalarial	0.682	0.412–1.130	0.1371
	FRS	3.253	0.935–11.320	0.0674
	Immunosuppressive	1.008	0.582–1.745	0.9775
	Steroids	3.254	1.706–6.205	0.0003
2FRS only	2FRS	4.368	2.404–7.936	< 0.0001
2FRS and AMS	AMS	1.061	1.012–1.113	0.016
	2FRS	4.529	2.443–8.396	< 0.0001
2FRS and SLEDAI-2K	2FRS	4.563	2.451–8.493	< 0.0001
	SLEDAI-2K	1.063	1.021–1.107	0.0035
2FRS and treatment	Antimalarial	0.709	0.429–1.173	0.1806
	2FRS	4.655	2.535–8.545	< 0.0001
	Immunosuppressive	1.097	0.633–1.901	0.7412
	Steroids	3.413	1.787–6.519	0.0002

FRS: Framingham Risk Factor Score; 2FRS: FRS with a multiplier of 2; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; AMS: adjusted mean SLEDAI.

contribution of elevated blood pressure remains unchanged. The modification's effect is simply to increase the total number of points, and as a consequence, the risk category assigned to an individual.

We first determined the most appropriate multiplier factor. We tested 4 different multiplication factors: 1.5, 2, 3, and 4, and our analysis confirmed that a factor of 2 gave the most appropriate categorization of moderate/high risk with sufficient sensitivity and specificity. We then confirmed that the 2FRS provided a more accurate prediction of CAD risk in patients with SLE than the original FRS (20% vs 2.9%, respectively), better highlighting the SLE population to be targeted for more intensive risk factor modification.

Whereas the FRS is a 1 point in time score, which assesses a 10-year risk, we have previously shown that risk factors over time are more highly predictive of CAD than a single point in time<sup>11</sup>. In our current study, we show that 2FRS over time is predictive of CAD whereas the original FRS is not.

Our study has a few limitations. We did not recalibrate the contribution of individual components of the FRS in SLE, but accepted the relative weights derived from the general population. Likewise, we did not evaluate the effect of each of the factors on the various outcomes. However, we demonstrated that the predictive value of the 2FRS more closely approximated the prevalence of CAD in this large observational cohort. Our paper was based on the original FRS, which included angina. We did a sensitivity analysis omitting angina alone, leaving a smaller number of outcomes. Nevertheless, the conclusion is unchanged: the 2FRS is the best indicator for the outcome of the sensitivity and specificity analyses and the survival analysis. However, because of the smaller number of outcomes, we will stay with our original analysis.

The mFRS where each item is multiplied by 2 more accurately identifies patients at moderate/high risk of CAD (13.6%) and more accurately predicts subsequent CAD (score of 14.6 vs 4.7). Therefore, the mFRS should be used to identify patients with SLE for more intensive risk factor modification.

## REFERENCES

- Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol* 1997;145:408-15.
- Goldberg RJ, Urowitz MB, Ibañez D, Nikpour M, Gladman DD. Risk factors for development of coronary artery disease in women with systemic lupus erythematosus. *J Rheumatol* 2009;11:2454-61.
- Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. *Am J Med* 1976;60:221-5.
- Nikpour M, Urowitz MB, Gladman DD. Premature atherosclerosis in systemic lupus erythematosus [review]. *Rheum Dis Clin North Am* 2005;31:329-54, vii-viii.
- Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, du Berger R, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;44:2331-7.
- Bruce IN, Urowitz MB, Gladman DD, Hallett DC. Natural history of hypercholesterolemia in systemic lupus erythematosus. *J Rheumatol* 1999;26:2137-43.
- Asanuma Y, Oeser A, Shintani AK, Turner E, Olsen N, Fazio S, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349:2407-15.
- Urowitz MB, Ibañez D, Gladman DD. Atherosclerotic vascular events in a single large lupus cohort: prevalence and risk factors. *J Rheumatol* 2007;34:70-5.
- Urowitz MB, Gladman D, Ibañez D, Fortin P, Sanchez-Guerrero J, Bae S, et al; Systemic Lupus International Collaborating Clinics.

- Accumulation of coronary artery disease risk factors over three years: data from an international inception cohort. *Arthritis Rheum* 2008;59:176-80.
10. Karp I, Abrahamowicz M, Fortin PR, Pilote L, Neville C, Pineau CA, et al. Recent corticosteroid use and recent disease activity: independent determinants of coronary heart disease risk factors in systemic lupus erythematosus? *Arthritis Rheum* 2008;59:169-75.
  11. Nikpour M, Urowitz MB, Ibañez D, Harvey PJ, Gladman DD. Importance of cumulative exposure to elevated cholesterol and blood pressure in development of atherosclerotic coronary artery disease in systemic lupus erythematosus: a prospective proof-of-concept cohort study. *Arthritis Res Ther* 2011;13:R156.
  12. Magder LS, Petri M. Incidence of and risk factors for adverse cardiovascular events among patients with systemic lupus erythematosus. *Am J Epidemiol* 2012;176:708-19.
  13. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743-53.
  14. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;297:611-9.
  15. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:288-91.
  16. Rubin DB. *Multiple imputation for nonresponse in surveys*. New York: John Wiley & Sons; 1987.
  17. SAS Documentation. SAS version 9.3. 2011.
  18. Rubin DB. Inference and missing data. *Biometrika* 1976;63:581-92.
  19. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc* 1996;91:473-89.
  20. Barzi F, Woodward M. Imputations of missing values in practice: results from imputations of serum cholesterol in 28 cohort studies. *Am J Epidemiology* 2004;160:34-45.
  21. Agresti A, Coull BA. Approximation is better than "exact" for interval estimation of binomial proportions. *Am Stat* 1998; 52:119-26.
  22. Kleinbaum DG, Klein M. *Survival analysis: a self-learning text*, third edition. New York: Springer; 2012:241-88.
  23. Grønnesby JK, Borgan O. A method for checking regression models in survival analysis based on the risk score. *Lifetime Data Anal* 1996;2:315-28.
  24. Kawai VK, Solus JF, Oeser A, Rho YH, Raggi P, Bian A, et al. Novel cardiovascular risk prediction models in patients with systemic lupus erythematosus. *Lupus* 2011;20:1526-34.