

# Cardiovascular risk profiles in a lupus cohort: what do different calculators tell us?

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## ABSTRACT

**Background** Cardiovascular disease (CVD) is the leading cause of death worldwide and this risk is increased in patients with SLE who may not conform to traditional cardiovascular risk profiles.

**Aims** To determine the prevalence of high CVD risk among patients with SLE calculated using different risk calculators, and to characterise those identified as high risk.

**Methods** A cross-sectional analysis to estimate CVD risk using the Framingham Risk Equation (Framingham score) and an SLE-specific CVD risk equation (SLE score) was undertaken using data from a single centre cohort. The characteristics of patients identified as 'high risk' by the SLE score only (the 'missed group') were compared with those identified by the Framingham score (the 'conventional group').

**Results** 146 patients were included; 22 (15%) and 44 (30%) were determined to be at 'high risk' based on the Framingham and SLE scores, respectively. Patients in the 'missed group' were less likely to have traditional risk factors and were more likely to be female (81% vs 50%;  $p=0.03$ ), younger (mean age 54 vs 69 years  $p<0.01$ ) and have lower systolic blood pressure (132 vs 143 mm Hg;  $p=0.05$ ). Of those deemed high risk, only a minority were treated to target blood pressure and lipid levels.

**Conclusions** A large proportion of patients with SLE could be re-classified as high risk using a formula that incorporates SLE disease-related parameters. These patients have different profiles to those identified using a conventional risk model. Optimal CVD risk assessment and management warrants further attention in SLE.

## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, and the ability to reliably predict CVD risk has been the basis of numerous risk calculators.<sup>1</sup> These calculators take into account different predictive factors that may have independent or synergistic effects on risk, using data derived from general population cohorts.<sup>2</sup> The risk scores derived from these calculators allow clinicians to stratify asymptomatic individuals and institute appropriate management strategies.

Patients with SLE have increased rates of CVD for reasons that are not fully understood. Contributing factors include persistent

inflammation related to systemic disease activity, use of medications such as glucocorticoids and possibly effects of cytokines.<sup>3</sup> The overall increased risk of CVD in the SLE population exceeds that predicted by increased rates of traditional risk factors seen in this population, and the effect of disease itself on premature CVD appears to be substantial.<sup>4,5</sup>

There are numerous generic cardiovascular risk calculators available which are often applied to patients with SLE. In Australia, the National Vascular Disease Prevention Alliance (NVDPA) has adopted the Framingham equation ('Framingham score'—see online supplementary appendix 1)<sup>6</sup> as the basis for an absolute risk calculator widely used by primary care physicians and specialists.<sup>7</sup> Designed for the general population, the Framingham score is based on conventional risk factors such as age and gender. As a result, patients with SLE who tend to be young adults may have a risk score that underestimates their true risk.<sup>5</sup> An attempt to address this gap was made by Petri *et al.*, who devised a novel CVD risk formula (referred to as the 'SLE score'—see online supplementary appendix 2) that seeks to provide a more accurate estimate based on data derived from the Hopkins Lupus Cohort.<sup>8</sup> In this study, we calculated the prevalence of high CVD risk using both the Framingham and SLE scores and assessed the characteristics of patients who may be missed when using conventional CVD risk assessment models.

## METHODS

### Monash Lupus Cohort

The Monash Lupus Clinic database is a longitudinal, observational cohort in which demographic and disease-related information are captured prospectively. A cross-sectional analysis was conducted using the most recent data for all patients seen between December 2007 and September 2012. Consenting patients who met American College of



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Rheumatology classification criteria and had sufficient data to calculate both risk scores were included. This study was approved by the Monash Health Human Research Ethics Committee.

### Exposure variables

Blood pressure measurements were recorded at each clinic review using a manual sphygmomanometer with the most recent blood pressure and fasting cholesterol readings being used in conjunction with current smoking status and history of type 2 diabetes mellitus to derive the Framingham score as per the Framingham Heart Study Calculator.<sup>6</sup>

To calculate the SLE score as derived by Petri *et al* 2012,<sup>8</sup> integer scores based on Cox proportional hazards were applied to both traditional risk factors and disease-specific variables. SLE disease activity data index (SLEDAI) was measured at each visit, with the adjusted mean SLEDAI (AMS)<sup>9</sup> used to reflect disease activity over time. Mean C3 was used to identify those with hypocomplementaemia, and those with repeated measurements of lupus anticoagulant positivity in a greater than 3-month period were identified as being lupus anticoagulant positive.<sup>10</sup>

### Outcome variables

Ten-year CVD risk was calculated using both calculators, and categorised as low, intermediate or high (<10%, 10%–15%, >15%, respectively). The two risk scores defined CVD as fatal or non-fatal myocardial infarction, angina, stroke, peripheral artery disease or the need for revascularisation. Results were examined based on treatment thresholds of CVD event risk >15% as per the NVDPA guidelines.<sup>7</sup> CVD events were taken to include past events and those which occurred during the study period. Only unique events and patients were included in final prevalence counts. These were documented at each visit based on patient self-reporting and review of medical history. As the risk scores were calculated at most recent visit and any known CVD events occurred prior to this assessment, the relative predictive power of the two risk scores could not be assessed in this study. Use of CVD prevention therapy, including antihypertensive and lipid-lowering medication, was documented, and the proportion of patients achieving NVDPA target blood pressure and lipid levels was calculated.

### Statistical methods

We calculated the prevalence of high CVD risk using each score, and then identified the subset of patients deemed to be high risk via the SLE score but not the Framingham score (referred to as the 'missed group'). We then compared the demographics and disease-related characteristics of this group with those deemed high risk by the Framingham score (the 'conventional group'). Fisher's exact test (categorical variables) and Mann-Whitney rank test (continuous variables) were used to estimate the statistical evidence of a difference in the prevalence of characteristics between the conventional and missed

group. The kappa-coefficient was used to measure the agreement between the two CVD risk prediction scores. All analyses were conducted using Graphpad Prism.

## RESULTS

### Traditional risk factors

One hundred and eighty-four patients with SLE were identified in the Monash Lupus Clinic database. Of these, 146 (79%) patients were included in this analysis, having sufficient cardiovascular parameters for risk calculation. These patients were followed for on average  $3.4 \pm 1.7$  years over an average of  $16.3 \pm 10.0$  visits. The demographics and disease-related characteristics of participants are outlined in table 1. Overall, the patients were predominantly female (82%) with a mean age of 49 years. The prevalence of traditional cardiovascular risk factors was found to be similar to published prevalence estimates for a demographically similar section of the Australian population.<sup>11</sup> The prevalence of diabetes (3.0%), smoking (18%) and hypertension (blood pressure >140/90 mm Hg, 16%) were similar to the general population of females aged 45–54 years. In contrast, hypercholesterolaemia (>5.5 mmol/L) was significantly less prevalent in the SLE sample (18% vs 33%;  $p$  value <0.01).

### SLE activity

Disease-specific variables in the SLE score included AMS, complement level (low mean C3) and the presence of lupus anticoagulant.<sup>8</sup> In our cohort, 111 participants (76%) were identified as having AMS>2, 54 (37%) had hypocomplementaemia and 9 (6%) were lupus anticoagulant positive. One hundred and thirty-six (93%) of participants were on hydroxychloroquine, while 62 (42%) of participants were on a synthetic disease-modifying anti-rheumatic drug other than hydroxychloroquine. Of the 79 (54%) participants on prednisolone, the median dose was 7.5 mg/day (IQR 5–10).

### Risk categorisation

The mean $\pm$ SD 10-year risk provided by the Framingham score was  $7.8 \pm 9.0$  compared with  $15.9 \pm 16.1$  by the SLE score ( $p$ <0.01). Overall, 22 (15%; 95% CI 9% to 21%) participants were deemed high risk according to the Framingham score compared with 44 participants (30%; 95% CI 23% to 38%) when using the SLE score ( $p$ <0.01) (see table 2). Female gender was more frequent among patients deemed high risk using the SLE score (70% vs 50%,  $p$ <0.01). Twenty-seven patients (18% overall) were assigned as high risk when using the SLE score but not the Framingham score ('missed group'). Only five (3%) patients were identified as high risk by the Framingham score but not the SLE score. Five (23%) of those deemed high risk by the Framingham score experienced a CVD event, compared with nine (20%) of those deemed high risk when using the SLE score. The two scores had a moderate overall agreement of 78% (negative per cent agreement: 95%; positive per cent agreement: 39%; kappa statistic point estimate 0.40, 95% CI 0.23 to 0.55).

**Table 1** Demographics of the SLE population

| Parameter                                | Descriptive statistics* (n=146) |
|--|---------------------------------|
| <b>Demographics</b>                      |                                 |
| Age (years)                              | 49±15                           |
| <b>Sex</b>                               |                                 |
| Female                                   | 120 (82)                        |
| Male                                     | 26 (18)                         |
| <b>Ethnicity</b>                         |                                 |
| Caucasian                                | 88 (60)                         |
| Asian                                    | 56 (38)                         |
| Hispanic                                 | 2 (1)                           |
| <b>Conventional CVD risk factors</b>     |                                 |
| Current smoker                           | 27 (18)                         |
| Diabetes mellitus                        | 5 (3)                           |
| Systolic blood pressure (mm Hg)          | 148±16                          |
| Hypertension <sup>†</sup>                | 24 (16)                         |
| Body mass index (kg/m <sup>2</sup> )     | 25.1±5.8                        |
| Total cholesterol (mM)                   | 4.8±1.3                         |
| Hypercholesterolaemia <sup>‡</sup>       | 27 (18)                         |
| <b>SLE disease parameters</b>            |                                 |
| Number of ACR criteria met               | 5±1.3                           |
| Adjusted mean SLEDAI                     | 4.5±3.1                         |
| Low C3 <sup>§</sup>                      | 54 (37)                         |
| Lupus anticoagulant positive             | 9 (6)                           |
| On hydroxychloroquine                    | 136 (93)                        |
| On sDMARD <sup>¶</sup>                   | 62 (42)                         |
| On glucocorticoids                       | 79 (54)                         |
| Prednisolone dose (mg)**                 | 7.5                             |
| Lupus nephritis (class I/II)             | 1 (1)                           |
| Lupus nephritis (class III–V)            | 3 (2)                           |
| <b>Cardiovascular disease parameters</b> |                                 |
| CVD events                               | 25 (17)                         |
| On antihypertensives                     | 45 (31)                         |
| On lipid-lowering medications            | 14 (10)                         |

\*Data as mean ± SD for continuous variables and number (%) for categorical variables.

†Blood pressure ≥140/90 mm Hg.

‡Total cholesterol >5.5 mM.

§Low C3 <0.8 mg/L.

¶sDMARD other than hydroxychloroquine.

\*\*Median prednisolone dose for those on prednisolone.

ACR, American College of Rheumatology; CVD, cardiovascular disease; sDMARD, synthetic disease modifying antirheumatic drug.

Table 3 provides an overview of the differences in the characteristics of patients with SLE identified to be high risk by the Framingham score (the ‘conventional group’) compared with those identified as high risk by the SLE score alone (the ‘missed group’). The missed

**Table 2** Risk categorisation by risk scores (n=146)

| Risk calculator  | 10-year CVD risk |                        |            |
|------------------|------------------|------------------------|------------|
|                  | High (>15%)      | Intermediate (10%–15%) | Low (<10%) |
| Framingham score | 22 (15)          | 14 (10)                | 110 (75)   |
| SLE score        | 44 (30)          | 30 (21)                | 72 (49)    |

CVD, cardiovascular disease.

group was younger (mean age 54 vs 69 years;  $p<0.01$ ), more likely to be female (81 vs 50%;  $p=0.03$ ), have a lower body mass index (24.1 vs 28.0;  $p=0.02$ ) and lower blood pressure (132 vs 143 mm Hg;  $p=0.05$ ) when compared with the conventional group.

### CVD events

Prior to study commencement, and during the period of follow-up, 25 (17%) patients experienced a CVD event, 80% of whom were female. Of these patients, five (20%) were identified as high risk using the Framingham score, whereas nine (36%) were deemed to be high risk using the SLE score. Specific CVD events identified included nine cerebrovascular accidents (36%), eight (32%) clinically proven individuals with angina, four (16%) non-fatal myocardial infarctions and four (16%) patients requiring coronary revascularisation.

### Risk factor amelioration

Of the 49 participants deemed high risk by either score, only 20 (41%) were on antihypertensive and/or lipid-lowering therapy. Of those on therapy, 11 (55%) and 2 (10%) met NVDPA guideline targets for blood pressure and cholesterol, respectively. Only one patient (5%) had achieved target levels for both blood pressure and cholesterol.

### DISCUSSION

The increased risk of CVD in patients with SLE is well recognised. Previous studies have focused on traditional CVD risk factors and secondary risk stratifiers via surrogate markers such as coronary calcium scoring,<sup>12</sup> and have identified that SLE poses risk of CVD not fully attributable to traditional risk factors measured in the Framingham score. The current study, which compared the Framingham score with the recently described SLE score, demonstrates differences in the estimated prevalence of high cardiovascular risk in patients with SLE when using different risk estimation algorithms.

The findings indicate that females are under-represented when the Framingham risk model is used.<sup>13</sup> Despite 80% of CVD events observed in this study occurring in female patients, females represented only 50% of those deemed high risk when utilising the Framingham score. This is in contrast to a female representation of 81% in the missed group, which reflects the gender ratio of patients with observed CVD events. The SLE score

**Table 3** Differences in the characteristics of patients with SLE by high CVD risk group

|  | Descriptive statistics by high CVD risk group* |                           | Evidence of difference <sup>†</sup> p value |
|--|--|---------------------------|---|
| Parameter  | Missed group (n=27)                            | Conventional group (n=22) |   |
| Demographics   |  |                           |   |
| Age (years)  | 54±14  | 69±9                      | p<0.01                                      |
| Sex: female  | 22 (81)  | 11 (50)                   | p=0.03                                      |
| Ethnicity  |  |                           |   |
| Caucasian  | 20 (74)  | 17 (77)                   | p=1.00 p=1.00                               |
| Asian  | 7 (26)   | 5 (23)                    |   |
| Conventional CVD risk factors  |  |                           |   |
| Current smoker   | 9 (33)   | 8 (36)                    | p=1.00                                      |
| Diabetes mellitus  | 1 (4)  | 3 (14)                    | p=0.31                                      |
| Systolic blood pressure (mm Hg)                                      | 132±21   | 143±17                    | p=0.05                                      |
| Hypertension <sup>‡</sup>  | 9 (33)   | 12 (55)                   | p=0.16                                      |
| Body mass index (kg/m <sup>2</sup> )                                 | 24.1±3.1                                       | 28.0±7.1                  | p=0.02                                      |
| Total cholesterol (mM)   | 5.0±1.0  | 5.0±0.8                   | p=0.78                                      |
| Hypercholesterolaemia <sup>§</sup>                                   | 8 (30)   | 3 (14)                    | p=0.30                                      |
| SLE disease parameters   |  |                           |   |
| Number of ACR criteria met   | 4.8±1.1  | 5.1±1.2                   | p=0.30                                      |
| Adjusted mean SLEDAI   | 5.72±3.3                                       | 2.95±2.5                  | p<0.01                                      |
| Low mean C3 <sup>¶</sup>   | 17 (63)  | 5 (23)                    | p<0.01                                      |
| Lupus anticoagulant positive   | 5 (19)   | 1 (5)                     | p=0.19                                      |
| On glucocorticoids   | 19 (70)  | 8 (36)                    | p=0.02                                      |
| Cardiovascular disease parameters                                    |  |                           |   |
| CVD events   | 4 (15)   | 5 (23)                    | p=0.71                                      |
| On CVD prevention therapy  | 13 (48)  | 7 (32)                    | p=0.38                                      |
| Treated to NVDPA guideline targets (those on CVD prevention therapy) |  |                           |   |
| Antihypertensive   | 9 (33)   | 1 (5)                     | p=0.02                                      |
| Lipid-lowering agent   | 1 (4)  | 0 (0)                     | p=1.00                                      |

\*Data as mean ± SD for continuous variables and (%) for categorical variables.

†Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.

‡Blood pressure ≥140/90 mm Hg.

§Total cholesterol (>5.5 mM).

¶Low C3 <0.8 mg/L.

ACR, American College of Rheumatology; CVD, cardiovascular disease; NVDPA, National Vascular Disease Prevention Alliance

may capture patients whose CVD risk is underestimated because of their gender and low body mass index.

A cross-sectional study performed in Canada found an increased rate of traditional CVD risk factors in a lupus cohort compared with matched controls.<sup>14</sup> In contrast, our population had similar rates of traditional risk factors compared with population controls. This may be explained by the increased proportion of patients of Asian ethnicity in our study, which may influence the prevalence of traditional risk factors observed in the Australian cohort.

Our data suggest that when markers of disease activity are taken into consideration as proposed by the SLE score, 18% of patients could be re-classified as at high risk for

future CVD events. Strikingly, only one patient achieved both blood pressure and cholesterol targets consistent with the NVDPA guidelines. This highlights that greater attention should be paid towards CVD risk assessment and optimal management in routine lupus follow-up. The use of a disease-specific risk calculator, such as the SLE score, can form the basis of such assessment.

There are some limitations in our comparison of the two CVD risk scores that unfortunately cannot be addressed by the design of this cross-sectional study with relatively few CVD events. Given the cross-sectional nature of this study, only the most recent clinical and biochemical readings were used to calculate both CVD risk scores which may not accurately represent disease risk over time. For



example, it is well appreciated that there are numerous factors that may impact on the accuracy and variability of blood pressure readings over time.<sup>15</sup> While the utilisation of the most recent results reflects current practice in a primary care setting for risk calculation, it is worthwhile noting that a single elevated reading does not necessarily signify hypertension or increased cardiovascular risk, and multiple readings should be recorded before a change in therapy is instituted.

The predictive value of the lupus-specific risk calculator needs to be validated in a large prospective study. Our findings demonstrate that the new SLE score results in a twofold increase in 10-year cardiovascular risk, which is consistent with a study by Urowitz *et al.*<sup>16</sup> In this study of the Toronto Lupus Cohort, they have suggested a modified Framingham score, doubling the traditional Framingham score to more accurately represent the CVD risk in the lupus cohort. Both scoring systems demonstrate that there is indeed a problem with underestimation of cardiovascular risk by using traditional scoring systems. In contrast to the Hopkins SLE score, lupus activity parameters were not specifically taken into account in the modified Framingham score. Future studies should explore the different calculators in its predictive power to see whether measures of disease activity may further stratify risk more appropriately.

A significant proportion of patients with SLE were re-classified as high risk in this cross-sectional study using a formula that incorporates SLE disease-related parameters, and females were under-represented when using a score based on traditional risk factors alone. Despite high awareness of these issues, there was a low attainment of target cholesterol and blood pressure levels in high-risk patients. Further attention should be paid to optimal CVD risk categorisation and management in SLE.

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**Competing interests** None declared.

**Patient consent** This was a retrospective study carried out on consenting patients of the Monash Lupus Clinic Database.

**Ethics approval** This study was approved by the Monash Health Human Research Ethics Committee.

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**Data sharing statement** Access to de-identified data from the Monash Lupus Clinic and Australian Lupus Registry is available in accordance with the Australian Lupus Registry and Biobank Data and Biospecimen Use Policy and Procedures. Researchers interested in using the study data used for this study or data from the Monash Lupus Clinic and Australian Lupus Registry and Biobank more broadly should make an enquiry via the 'Contact Us' page on the Australian Lupus Registry website (<https://www.lupusregistry.com/contact-us>).

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## REFERENCES

1. World Health Organization. Cardiovascular diseases (CVDs), Fact Sheet No 317. 2015 <http://www.who.int/mediacentre/factsheets/fs317/en/>.
2. Lowe LP, Greenland P, Ruth KJ, *et al.* Impact of Major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. *Arch Intern Med* 1998;158:2007–14.
3. Sinicato NA, da Silva Cardoso PA, Appenzeller S. Risk factors in cardiovascular disease in systemic lupus erythematosus. *Curr Cardiol Rev* 2013;9:15–19.
4. Lee AB, Godfrey T, Rowley KG, *et al.* Traditional risk factor assessment does not capture the extent of cardiovascular risk in systemic lupus erythematosus. *Intern Med J* 2006;36:237–43.
5. Skamra C, Ramsey-Goldman R. Management of cardiovascular complications in systemic lupus erythematosus. *Int J Clin Rheumatol* 2010;5:75–100.
6. Boston University. Framingham Heart Study. Cardiovascular Disease (10-year risk) Boston. 2015 <https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php>.
7. National Vascular Disease Prevention Alliance. *Guidelines for the management of absolute cardiovascular disease risk 2012: national Stroke Foundation*, 2012.
8. Petri MLS. Systemic lupus erythematosus Cardiovascular Risk Equation. [abstract]. *Arthritis Rheum* 2012;64.
9. Ibañez D, Urowitz MB, Gladman DD. Summarizing disease features over time: I. adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. *J Rheumatol* 2003;30:1977–82.
10. Pengo V, Tripodi A, Reber G, *et al.* Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. *J Thromb Haemost* 2009;7:1737–40.
11. Australian Bureau of Statistics. *Australian Health survey: first results, 2011-2012-Australia*. Canberra: ABS, 2012.
12. Romero-Díaz J, Vargas-Vóracková F, Kimura-Hayama E, *et al.* Systemic lupus erythematosus risk factors for coronary artery calcifications. *Rheumatology* 2012;51:110–9.
13. Ridker PM, Buring JE, Rifai N, *et al.* Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds risk score. *JAMA* 2007;297:611–9.
14. Bruce IN, Urowitz MB, Gladman DD, *et al.* Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto risk factor study. *Arthritis Rheum* 2003;48:3159–67.
15. Kallioinen N, Hill A, Horswill MS, *et al.* Sources of inaccuracy in the measurement of adult patients' resting blood pressure in clinical settings: a systematic review. *J Hypertens* 2017;35:421–41.
16. Urowitz MB, Ibañez D, Su J, *et al.* Modified Framingham Risk factor score for systemic lupus erythematosus. *J Rheumatol* 2016;43:875–9.