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QRISK3 improves detection of cardiovascular disease risk in patients with systemic lupus erythematosus

Nicola Edwards,¹ Alexander W W Langford-Smith,¹ Benjamin J Parker,^{2,3} Ian N Bruce,^{2,3} John A Reynolds,^{2,3} M Yvonne Alexander,¹ Eoghan M McCarthy,² Fiona L Wilkinson¹

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NE and AWWL-S contributed equally.

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¹Translational Cardiovascular Science, The Centre for Bioscience, Manchester Metropolitan University, Manchester, UK

²NIHR Manchester Musculoskeletal Biomedical Research Centre, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

³Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

Correspondence to
Dr Fiona L Wilkinson; F. Wilkinson@mmu.ac.uk

ABSTRACT

Objective 10-year cardiovascular disease (CVD) risk scores are calculated using algorithms, including Framingham (worldwide) and QRISK2 (UK). Recently, an updated QRISK3 model was introduced, which considers new variables including SLE and steroid prescription, not included in QRISK2 and Framingham algorithms. We sought to determine the extent to which QRISK3 improves identification of high-risk patients with SLE and whether the score relates to standard and novel markers of SLE-specific endothelial dysfunction.

Methods Framingham and QRISK2/3 scores were calculated in patients with SLE (n=109) and healthy controls (n=29) using clinical measures. In a smaller cohort (n=58), markers of inflammation and endothelial dysfunction, including CD144⁺ endothelial microvesicles (EMVs), triglycerides, vascular cell adhesion molecule (VCAM) and high-sensitivity C reactive protein (hsCRP) were quantified by flow cytometry and ELISA, respectively.

Results Patients with SLE demonstrated significantly higher QRISK3 scores than controls (5.0%vs0.3%, p<0.001). 21/109 patients with SLE (19%) and 24/109(22%) were newly identified as being at high risk of a CV event when using QRISK3 versus QRISK2 (29vs8patients) and QRISK3 versus Framingham (29vs5patients; p<0.001), respectively. These 'new QRISK3' patients with SLE were more likely to have lupus nephritis, be anticardiolipin antibody positive, currently prescribed corticosteroids, had a higher Body Mass Index and systolic blood pressure (BP) than low-risk patients with SLE. Rates of antiplatelet (8/21) and statin use (5/21) were low in the new QRISK3 group. EMVs, hsCRP and triglyceride levels were significantly higher in new QRISK3 patients compared with low-risk patients with SLE (p<0.05). Furthermore, pulse wave velocity and VCAM were significantly elevated in all high versus low QRISK3 patients.

Conclusions QRISK3 captures significantly more patients with SLE with an elevated 10-year risk of developing CVD, which is associated with measures of endothelial dysfunction; EMVs and systolic BP. The adoption of QRISK3 will enhance management of CVD risk in patients with SLE for improved outcome.

INTRODUCTION

Cardiovascular disease (CVD) risk is evaluated using algorithms, comprising variables

(eg, age, blood pressure (BP) and cholesterol) that can have an independent or a synergistic impact on CVD risk¹ to identify asymptomatic individuals and initiate CVD risk management. Patients with SLE have a fivefold increased risk of myocardial infarction compared with healthy controls,² rising to fifty-fold in younger women (35–44years).³ Traditional risk algorithms (eg, Framingham) show only marginal differences between SLE and controls, and thus underestimate CVD risk of a patient with SLE.² SLE-related factors (disease activity, immunological factors and medications) are believed to play a substantial role in CVD risk and poorer cardiovascular outcomes following a CV event.^{4,5}

Strategies to more accurately predict CVD risk in SLE have involved modification of traditional calculators by doubling the score and proposing SLE-specific risk tools⁶; however, they are not in regular clinical use since risk assessment and treatment is provided by primary care physicians.

Enhanced understanding of the pathophysiology of subclinical atherosclerosis and more sensitive CVD biomarkers (eg, high-sensitivity C reactive protein; hsCRP) may help identify those at high risk. Endothelial dysfunction, as assessed by endothelial microvesicle (EMV) release or aortic pulse wave velocity (PWV), have also shown promise as potential biomarkers. We have previously demonstrated elevated levels of EMVs in patients with SLE, which were reduced with immunosuppression,⁴ reflecting their potential to monitor endothelial activation.

Since 2008, the QRISK2 algorithm has been used in the UK to calculate the likelihood of a major cardiovascular event over the following 10-year period. A score of ≥10% is deemed to be 'high risk', indicating the need for clinical intervention (National Institute for Health and Care Excellence guidelines).⁷ An updated

Table 1 Baseline cardiovascular measures of controls, low risk and newly identified high QRISK3 patients with SLE

| Variable | Controls (n=29) | Newly identified high QRISK3 patients* (n=21) | P values | Low-risk patients with SLE (n=80) | Newly identified high QRISK3 patients*(n=21) | P values |
|-----------------------------------|--------------------|---|------------------|-----------------------------------|--|------------------|
| Age (years),mean±SD | 36.66±12.95 | 42.16±12.36 | 0.130 | 38.02±10.68 | 42.16±12.36 | 0.155 |
| Female | 29(100%) | 19(90%) | 0.420 | 78(97%) | 19(90%) | 0.507 |
| Ethnicity: Caucasian | 23(79%) | 13(62%) | 0.213 | 58(73%) | 13(62%) | 0.292 |
| BMI (kg/m ²) | 22.6(21.3,25.3) | 31.8(24.3,37.0) | 0.003 | 25.3(22.2,28.4) | 31.8(24.3,37.0) | 0.026 |
| BP systolic (mm Hg) | 118.0(111.0,130.0) | 141.0(127.0,159.0) | 0.001 | 122.0(110.8,128.3) | 141.0(127.0,159.0) | <0.001 |
| HDL cholesterol (mmol/L) | 1.7(1.5,2.0) | 1.5(1.3,1.8) | 0.037 | 1.7(1.2,2.0) | 1.5(1.3,1.8) | 0.222 |
| Non-HDL cholesterol (mmol/L) | 2.6(2.3,3.2) | 3.2(2.5,3.6) | 0.115 | 2.7(2.2,3.2) | 3.2(2.5,3.6) | 0.053 |
| Type 2 diabetes | 0(0%) | 3(14%) | 1.000 | 0(0%) | 3(14%) | 0.008 |
| Rheumatoid arthritis | 0(0%) | 0(0%) | 1.000 | 5(6%) | 0(0%) | 0.312 |
| Chronic kidney disease(stages3–5) | 0(0%) | 5(24%) | 0.010 | 3(4%) | 5(24%) | 0.021 |
| Migraines | 3(10%) | 1(5%) | 0.630 | 8(10%) | 1(5%) | 0.681 |
| Severe mental illness | 2(7%) | 2(9%) | 1.000 | 3(4%) | 2(9%) | 0.277 |
| Current smoker | 4(14%) | 6(29%) | 0.286 | 15(19%) | 6(29%) | 0.368 |
| Antihypertensive | 3(10.34%) | 15(71%) | <0.001 | 13(16%) | 14(67%) | <0.001 |
| Current oral corticosteroids | 0(0%) | 21(100%) | <0.001 | 46(58%) | 21(100%) | <0.001 |

Variables included in QRISK3 algorithm are shown; severe mental illness inclusive of depression, schizophrenia and bipolar disorder. Unless otherwise stated, values are shown as number (percentage) or median (lower, upper quartile). Data were analysed by Mann-Whitney U and Fisher's exact tests as appropriate. Bold type denotes $p < 0.05$.

*Newly identified high QRISK3 patients refers to patients with SLE newly identified as possessing high cardiovascular risk ($\geq 10\%$) when using QRISK3 vs QRISK2. Patients with SLE identified as high risk by both algorithms were not included in the analysis (n=8). BMI, Body Mass Index; BP, blood pressure; HDL, high-density lipoprotein.

QRISK3 algorithm, incorporating additional risk factors including SLE, was released in May 2017, becoming the first widely used calculator to address SLE-associated CVD risk.⁸ Our aim was to identify (1) differences in CVD risk estimates when using QRISK3 compared with QRISK2 and Framingham algorithms; (2) differences in traditional CVD risk factors, between newly identified high-risk patients with SLE, low-risk patients with SLE and controls; (3) SLE-specific factors driving the increased risk; and (4) novel biomarkers that could be integrated into future algorithms to enhance detection of subclinical CVD.

METHODS

Patients

Patients with SLE (n=109; 1997 American College of Rheumatology criteria)⁹ and healthy controls (n=29) were recruited from the rheumatology department in the Manchester Royal Infirmary. See online supplementary information for clinical/laboratory assessments, CVD risk identification and statistical analysis.

RESULTS

Demographics

Patients with SLE were, on average, 4 years older than controls, with no differences detected in gender, ethnicity or traditional cardiovascular risk factors (systolic pressure

levels, high-density lipoprotein (HDL)/non-HDL cholesterol, rates of smoking and diabetes; online supplementary file 1).

CVD risk identification

Patients with SLE had higher absolute Framingham (2.2% vs 1.2%, $p=0.013$), QRISK2 (1.7% vs 0.3%, $p=0.001$) and QRISK3 (5.0% vs 0.3%, $p<0.001$) scores than controls. The QRISK3 score was higher in patients with SLE compared with QRISK2 and Framingham models. In total, 5 (4.6%) and 8 (7%) patients with SLE were designated as high risk by Framingham and QRISK2 algorithms, respectively, rising to 29 (27%) patients with QRISK3 ($p<0.001$). QRISK3 identified 21 additional patients (19%) as high risk who would have otherwise been designated as low risk of CVD using QRISK2 (new QRISK3 group), rising to 24 extra patients when using the Framingham algorithm.

Since SLE is not included in QRISK2 or Framingham models, SLE was removed from the calculation to determine whether additional patients would still be identified. Three patients with SLE were newly identified by QRISK3 versus QRISK2. In the control group, no differences were observed between any risk algorithm.

Differences in CVD risk factors

The new QRISK3 group had a significantly higher Body Mass Index (BMI), systolic BP, lower HDL cholesterol

Table 2 Clinical and immunological measures of low risk and new QRISK3 patients

| Variable* | Low-risk patients with SLE | New QRISK3 group | P values |
|---------------------------------------|--|--|------------------|
| Disease duration (years) | 13.0(8.0,19.0) | 12.0(6.7,15.0) | 0.326 |
| ACR criteria: malar rash | 35(70%) | 14(67%) | 0.785 |
| ACR criteria: discoid rash | 25(50%) | 6(29%) | 0.120 |
| ACR criteria: photosensitivity | 34(68%) | 14(67%) | 1.000 |
| ACR criteria: oral ulcers | 36(72%) | 14(67%) | 0.777 |
| ACR criteria: serositis | 15(30%) | 6(29%) | 1.000 |
| ACR criteria: arthritis | 44(88%) | 14(67%) | 0.047 |
| ACR criteria: renal disorder | 19(38%) | 14(67%) | 0.038 |
| ACR criteria: neurological disorder | 4(8%) | 2(9%) | 1.000 |
| ACR criteria: haematological disorder | 30(60%) | 11(52%) | 0.605 |
| ACR criteria: immunological disorder | 39(78%) | 14(67%) | 0.375 |
| ACR criteria: ANA-positive† | 46(94%) | 18(86%) | 0.352 |
| Anti-dsDNA antibodies† | 15(30%) | 9(43%) | 0.429 |
| Anticardiolipin antibodies† | 4(8%) | 7(33%) | 0.027 |
| Low C3+lowC4 levels† | 5(10%) | 2(9%) | 1.000 |
| Current oral corticosteroids | 19(38%) | 21(100%) | <0.001 |
| Prednisolone dose (mg/day) | 7.5(5.0,11.3) | 10(5.5,15.0) | 0.304 |
| Current immunosuppressive use | 29(58%) | 13(62%) | 0.582 |
| Current antimalarial use | 36(72%) | 17(81%) | 0.556 |
| SLEDAI-2K (n=58) | 2.5(0.25,4.0) | 3.0(2.0,4.5) | 0.444 |
| BILAG-2004 (n=58) | 1.5(0.25,6.75) | 5.5(0.0,9.3) | 0.542 |
| CD144+EMVs/mL (n=58) | 1.51×10 ⁶ (1.05×10 ⁶ ,2.23×10 ⁶) | 2.45×10 ⁶ (2.05×10 ⁶ ,5.56×10 ⁶) | 0.019 |
| Pulse wave velocity(n=58) | 7.00(6.00,7.70) | 7.60(7.05,9.50) | 0.110 |
| Triglycerides (mg/dL) (n=58) | 0.80(0.60,1.30) | 1.45(1.05,2.53) | 0.022 |
| hsCRP (mg/L) (n=58) | 0.89(0.54,3.01) | 6.70(4.47,8.18) | <0.001 |
| VCAM-1 (mg/L) (n=58) | 420.76(349.23,492.32) | 502.65(439.72,567.21) | 0.099 |
| BLyS (mg/L) (n=58) | 0.48(0.35,0.61) | 0.61(0.39,0.72) | 0.534 |

*n=71 unless otherwise stated.

†Indicated by laboratory reference range. Data were analysed by Mann-Whitney U and Fisher's exact tests.

ACR, American College of Rheumatology;BILAG-2004, British Isles Lupus Assessment Group Disease Activity Index;BLyS, B-lymphocyte stimulator;C3, complement component C3;C4, complement component C4;dsDNA, double-stranded DNA;EMV, endothelial microvesicle;hsCRP, high-sensitivity C reactive protein;SLEDAI-2K, SLE Disease Activity Index 2000;VCAM, vascular cell adhesion molecule-1.

levels, were more likely to have chronic kidney disease (CKD) and to be taking oral corticosteroids than controls (table 1).

Despite significantly higher rates of antihypertensive use in the new QRISK3 group, newly identified patients had significantly higher systolic BP levels, glucocorticoid use, CKD, BMI and type 2 diabetes than low-risk patients (table 1). Similar results were obtained when comparing the new QRISK3 versus Framingham low-risk groups.

Differences in SLE-related factors

To determine the key SLE-specific factors that may be driving the increased CVD risk, we investigated a cohort for whom more detailed clinical data were available (n=71). Lupus nephritis (p=0.038), elevated levels of anticardiolipin antibodies (p=0.027) and current steroid use were higher (p<0.001) in the new QRISK3 group (table 2).

No differences in disease activity, rates of antimalarial use or additional immunosuppressive therapy were identified between new QRISK3 and low-risk patients (table 1).

Of the newly identified patients, 15(71.4%) were on anti-hypertensives. The mean BP for those patients was higher than the recommended treatment thresholds at 147/97; five(23.8%) patients were on a statin, eight(38.1%) were on an antiplatelet and six(28.6%) were smokers.

Associations between endothelial dysfunction, inflammation and QRISK

EMVs correlated positively with QRISK3 score across all participants (r=0.332, p=0.001) but not with QRISK2 or Framingham scores. New QRISK3 patients demonstrated higher levels of circulating EMVs than low-risk patients (p=0.019, table 2; figure 1). PWV did not distinguish between the new QRISK3 and low-risk groups;

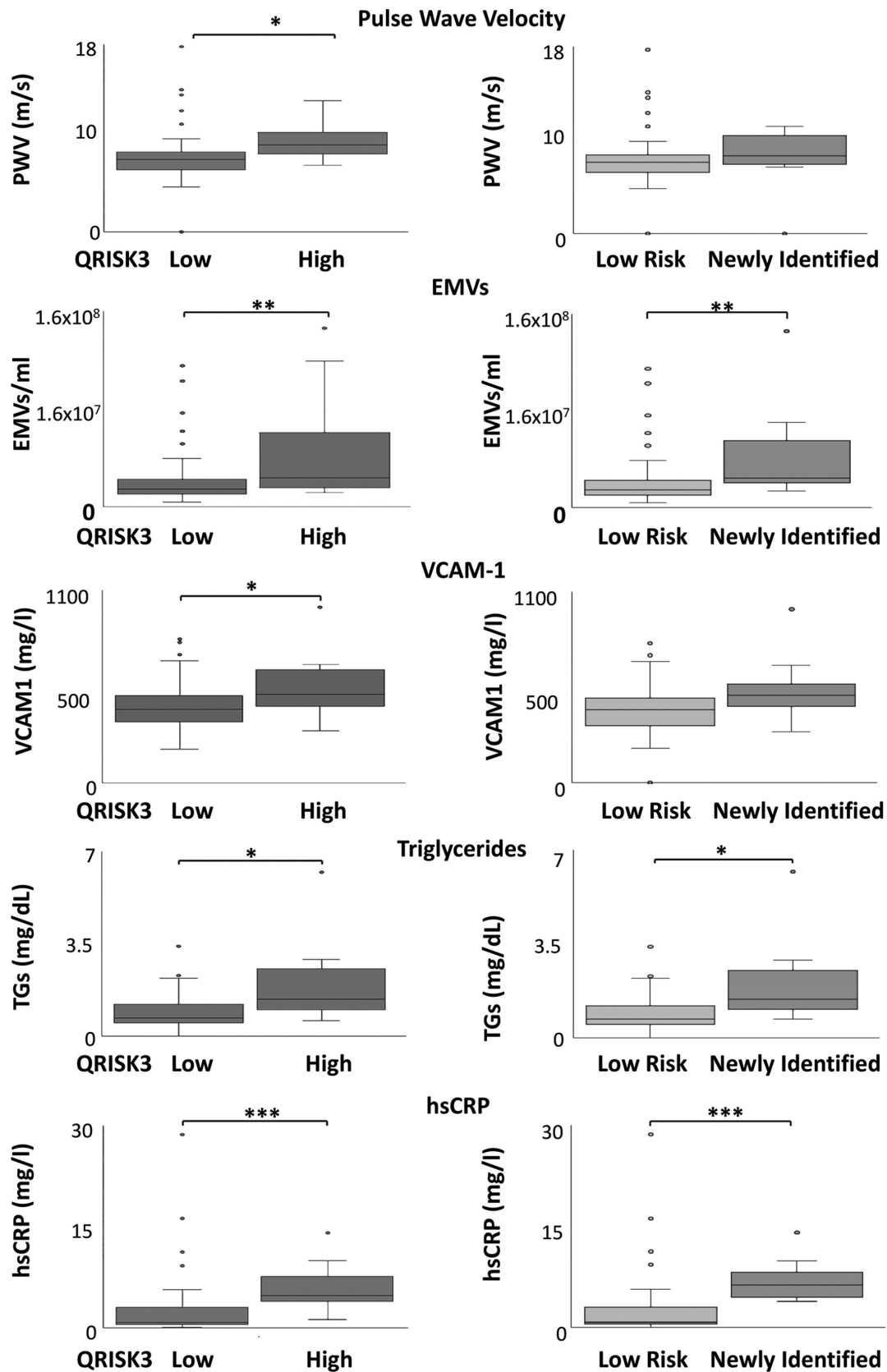


Figure 1 Measures of endothelial activation/dysfunction are associated with QRISK3. Increased pulse wave velocity (PWV; $p=0.017$), EMVs ($p=0.024$), VCAM-1 ($p=0.042$), triglycerides ($p=0.015$) and hsCRP ($p=0.001$) levels are associated with high QRISK3 score. Newly identified patients also demonstrate significantly higher EMVs ($p=0.020$), triglycerides ($p=0.016$) and hsCRP levels ($p<0.001$). Data represent patients with SLE: low QRISK3 ($n=49$), high QRISK3 ($n=11$), low risk ($n=49$), newly identified ($n=8$). Data were analysed by Mann-Whitney U test. EMV, endothelial microvesicle; hsCRP, high-sensitivity C reactive protein; TG, triglyceride; VCAM-1, vascular cell adhesion molecule-1.

however, both PWV and EMVs were higher in all high vs low QRISK3 groups ($p < 0.05$; figure 1). Triglycerides and hsCRP were also higher in new QRISK3 patients compared with low risk, with no difference in VCAM and B-lymphocyte stimulator (BLyS) levels, although VCAM was significantly higher in all high-risk versus low-risk QRISK3 groups (figure 1). No differences were detected between high and low QRISK2 groups with regard to PWV, EMVs, VCAM or BLyS levels (data not shown).

DISCUSSION

QRISK3 identified three times as many patients with high CVD risk than QRISK2, rising to five times with Framingham, many of whom were not on appropriate risk factor modification treatment. Detection of CVD risk in SLE is complex, with traditional tools failing to identify at-risk patients, while SLE-specific tools are not widely incorporated in clinical practice. Our findings suggest that the QRISK3 tool will successfully identify more patients with SLE with high risk of CVD since it can be used easily in primary care, where the majority of CVD risk management is conducted in the UK, while providing an SLE-inclusive risk similar to specialised SLE calculators.¹⁰

When SLE was removed from the QRISK3 calculation, three patients were newly identified as high risk, indicating that SLE is the main driver of increased risk. Both renal disease and corticosteroid use are known to impact on atherosclerosis along with the traditional risk factors including diabetes, BMI and hypertension⁵; however, 40% of the variation in time to diagnosis of CVD remains unexplained by the QRISK3 algorithm. Therefore, additional measures of CV health/risk may further enhance detection of subclinical atherosclerosis.

The newly identified QRISK3 group exhibited elevated levels of anticardiolipin antibodies, EMVs and hsCRP; all are further predictors of endothelial dysfunction and cardiovascular events in autoimmune disease.^{4 11} EMVs, containing bioactive molecules, are released into the bloodstream following endothelial activation, such as that occurring under conditions of inflammation.¹² The role of EMVs in cell signalling, damaging or protective, in SLE remains to be elucidated and is under investigation in our laboratory. EMVs are potential biomarkers of vascular disease since they are elevated in a number of CVD-related conditions, including SLE,^{4 12 13} and are modulated by lipid-lowering and immunosuppressive therapies.^{4 14} Incorporation of EMVs, hsCRP and anticardiolipin antibodies into future derivations of risk tools may enhance detection of subclinical CVD.

BP control was suboptimal in high-risk patients and triglyceride levels distinguished newly identified QRISK3 patients from low-risk patients, while antiplatelet and statin use was low in the new QRISK3 group. Thus, the QRISK3 tool will highlight to primary care physicians a previously unrecognised cohort of patients with SLE who would benefit from more aggressive management

strategies—tighter BP control, use of statins and antiplatelets—to reduce overall CVD risk. These drugs have also been shown to improve endothelial function,¹⁵ a key initiating factor of CVD, and can reduce EMV levels, reflecting a reduction in endothelium activation.¹⁴

Our study has some limitations. As in any SLE study, a high proportion of patients are women, limiting generalisability of our observations to male patients. The relatively low patient numbers may have limited identification of SLE-related factors as an influence in the newly identified high-risk group, while we were unable to assess the effect of change in therapy on altering the QRISK score. Future work will follow a larger cohort prospectively and validate the benefit of incorporating novel biomarkers into future CVD risk algorithms.

We have demonstrated that QRISK3 enhances CVD risk detection in patients with SLE, with more than 20% of patients being newly identified as at high risk of CVD, in comparison with the QRISK2 and Framingham algorithms, with potential for risk factor modification. Anticardiolipin antibody positivity and measures of endothelial dysfunction are key determinants of this enhanced risk. The new QRISK3 algorithm will enhance physicians' ability to detect CVD risk and alert them to treat modifiable risk factors to improve patient outcomes.^{1 23451}

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