## Title

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# A Panel of Biomarkers Associates With Increased Risk for Cardiovascular Events in Women With Systemic Lupus Erythematosus

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**Objective.** The increase in cardiovascular events (CVEs) in systemic lupus erythematosus (SLE) is not fully explained by traditional risk factors. We previously identified four biomarkers (proinflammatory high-density lipoprotein, leptin, soluble TNF-like weak inducer of apoptosis (sTWEAK), and homocysteine) that we combined with age and diabetes to create the predictors of risk for elevated flares, damage progression, and increased cardiovascular diseasein patients with SLE (PREDICTS) risk profile. PREDICTS more accurately identified patients with SLE at risk for progression of subclinical atherosclerosis than any individual variable. We examined whether PREDICTS can also identify patients with SLE at risk for future CVEs.

**Methods.** A total of 342 patients with SLE and 155 matched control subjects participated in this longitudinal prospective study. A high PREDICTS score was defined as three or more predictors or diabetes + one or more predictor. The biomarkers were measured at baseline using published methods. All major adverse CVEs (MACEs) were confirmed by medical record review.

**Results.** During 116 months of follow-up, 5% of patients with SLE died, 12% had a cerebrovascular event, and 5% had a cardiac event. Overall, 20% of patients with lupus experienced any new MACE compared with 5% of control subjects ($P < 0.0001$). More patients with SLE with a new MACE had high PREDICTS score at baseline (77%) versus patients with no new events (34%) ($P < 0.0001$). High baseline PREDICTS score also associated with cerebrovascular ($P < 0.0001$) and cardiac events ($P < 0.0001$) in SLE. Using Cox regression, a baseline high PREDICTS score associated with a 3.7-fold increased hazard ratio (HR) for a new MACE ($P < 0.0001$) in SLE. Hypertension (HR = 2.1; $P = 0.006$) was also a risk.

**Conclusion.** A high PREDICTS score and hypertension confer increased risk for new MACEs in patients with SLE.

## INTRODUCTION

Cardiovascular disease (CVD) has been recognized as a major cause of comorbidity and mortality in lupus (1). Studies consistently demonstrate that this increased risk persists even after accounting for traditional Framingham risk factors (2). This risk is most striking in young women with systemic lupus erythematosus (SLE), who are up to 50 times more likely than age- and risk factor–matched control subjects to have a myocardial infarction (MI) (3).

Despite the fact that traditional Framingham risk factors do not fully explain the increased risk of CVD in patients with SLE, there are currently no lupus-specific models that can be used to identify patients at increased risk for future major adverse cardiovascular events (MACEs). Expert panels in both the United States and Europe recommend that patients with SLE should be annually

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screened for traditional modifiable risk factors for CVD (4,5). However, models currently used to identify the highest-risk patients (and to identify optimum therapeutic targets for risk modification) all use traditional cardiac risk factors and consistently underestimate the risk in SLE (6). The incorporation of biomarkers that reflect inflammation could be useful in identifying patients with SLE at the highest risk for future MACEs.

Inflammation has been implicated in the pathogenesis of atherosclerotic CVD even in the general population (7,8); therefore, it is reasonable to consider that SLE-specific inflammation may contribute to the known cardiovascular risk. Several non-Framingham inflammatory biomarkers, including dysfunctional or proinflammatory high-density lipoprotein (HDL) (piHDL) (9–11), leptin (12), plasma soluble TNF-like weak inducer of apoptosis (sTWEAK) (13), and homocysteine (13,14), are individually associated with subclinical atherosclerosis in SLE. We previously demonstrated that piHDL, leptin, and sTWEAK—combined with clinical variables such as age and diabetes—create a risk profile that we named "predictors of risk for elevated flares, damage progression, and increased cardiovascular diseasein patients with SLE (PREDICTS)". The PREDICTS profile more accurately identified patients with SLE at risk for future subclinical atherosclerosis progression (measured as carotid plaque progression and intima–media thickness [IMT] progression) than any one variable alone. We set out to examine whether a high PREDICTS score could also identify patients susceptible to future MACEs in our longitudinal cohort.

## PATIENTS AND METHODS

**Study population.** Participants in the longitudinal Biomarkers of Atherosclerosis in SLE cohort study were recruited prospectively from the Rheumatology Practices of the University of California, Los Angeles (UCLA), and Cedars Sinai Medical Center in Los Angeles from February 2004 to January 2019. Eligible participants during the initial enrollment period were women who were 18 years of age or older and fulfilled the 1997 revised American College of Rheumatology (ACR) criteria for classification as having SLE (15). During the initial enrollment period between 2004 and 2013, subjects were excluded at baseline if they were taking statins or if they had creatinine levels of greater than 2.0 mg/dL because both are known to alter HDL inflammatory function (16,17); however, after 2014, enrollment was expanded to include men, patients on statins, and those in renal failure to ensure that the results applied to the general lupus population. In addition, all subjects were included in the longitudinal follow-up even if they initiated statins or developed renal failure after cohort entry. We planned to recruit subjects at a ratio of two patients with SLE to every one control subject. Control subjects reported no clinical manifestations of SLE on connective tissue screening questionnaires (18). Participants with SLE were asked to refer an age (±5 years)- and sex- matched friend as a control subject, and additional control subjects were recruited as needed by flyers placed in the UCLA outpatient medical clinics. The study was approved by the institutional review boards at UCLA and Cedars Sinai Medical Center; all participants gave written informed consent.

**Sample collection.** A total of 401 subjects with SLE and 197 control subjects were enrolled in the cohort at baseline. All eligible, consenting subjects provided a blood sample, underwent a carotid ultrasound, and completed a set of questionnaires at cohort entry. All subjects were invited to receive a second ultrasound and study visit at 36 months after cohort entry and a third ultrasound and visit at 120 months. Even if they did not attend the follow-up visits, subjects were included in this analysis if they had adequate clinical data available for at least 36 months after cohort entry. Plasma lipids, homocysteine, and levels of high-sensitivity CRP (hs-CRP) were measured in the UCLA clinical laboratory at baseline using standard methods. Organ damage was determined using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) (19). Body mass index was calculated from height and weight measurements. Information about cardiovascular events, cardiac risk factors, and current medications was obtained at baseline and follow-up from self-administered health history questionnaires and was confirmed by a study physician using chart review. Medical record review was also conducted to confirm event status for all subjects through July 2020 (or through the subject's last known follow-up visit). Subjects who were lost to follow-up before 2020 who had at least 36 months of follow-up data available were included in the analysis. Cardiovascular events were defined as MI, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or angina (confirmed with stress test). Cerebrovascular events were defined as a cerebrovascular accident (CVA) or a transient ischemic attack (confirmed by a physician). Peripheral arterial events were defined as arterial thrombosis requiring revascularization. MACEs were defined as all-cause mortality or any cardiovascular, cerebrovascular, or peripheral arterial event.

**Carotid ultrasound.** B (brightness)-mode gray-scale, color, and spectral Doppler techniques were used to investigate carotid arteries according to a standardized protocol, as previously described (9).

**Measurement of biomarkers.** Plasma leptin and sTWEAK were measured using enzyme-linked immunosorbent assay (R&D Systems). Plasma homocysteine, hs-CRP, and traditional lipid levels were measured in the UCLA clinical laboratory. HDL function was measured as described previously (9,20), using a cell-free assay based on the ability of HDL to prevent oxidation.

High PREDICTS score was defined as previously described (13). Briefly, we identified factors significantly associated with carotid plaque using Salford Predictive Modeling Software and multivariate analysis. These included increased age of 48 years or more, piHDL, leptin levels of 34ng/dL or greater, plasma sTWEAK levels of 373

pg/mL or greater, homocysteine levels of 12 mmol/L or greater, and diabetes. "High-risk" PREDICTS score was defined as three or more identified predictors or diabetes + one or more predictors.

**Statistical analysis.** Data were analyzed using SPSS 16.0 (SPSS, Inc.). Skewed continuous variables were logarithmically transformed to attain a normal distribution; nontransformed data are presented in figures and tables to facilitate the interpretation of results. For variables that did not attain a normal distribution by logarithmic transformation, nonparametric tests were used. Study groups were compared using the student's *t* test for continuous parametric variables, the Mann-Whitney test for nonparametric variables, and the $\chi^2$ test or Fisher's Exact test for categorical variables. The significance level was set at $P < 0.05$. Cox hazard regression was used to build models identifying risk factors associated with the time to future cardiovascular events in subjects with SLE.

## RESULTS

**MACEs were seen more frequently in subjects with SLE than in control subjects.** We first set out to determine how frequently new MACEs occurred in our longitudinal prospective cohort. A total of 401 patients with SLE and 197 control subjects have enrolled in our study since its inception. Of those, 342 subjects with SLE and 155 control subjects had at least 3 years of follow-up with available clinical data and were included in this analysis. Twenty-three subjects with SLE and 14 control subjects were lost to follow-up. Thirty-six subjects with SLE and 28 control subjects had less than 3 years of follow-up data available as of April 1, 2020. Mean follow-up was 120.4 ± 42.5 months for the entire cohort (119 ± 43.2 months in the SLE group and 123.3 ± 40.7 in the control group; *P* = not significant [ns]). Of the 342 subjects with SLE, 299 were enrolled in the original cohort and 43 were enrolled in the expanded cohort after 2014; 14 of the 155 control subjects were enrolled in the expanded cohort. Fifteen SLE subjects and no control subjects had a previous history of MACE at cohort entry (10 CVAs, four MIs, and one peripheral arterial clot).

There were 20 deaths in the cohort; 18 of these occurred in the SLE group (5.3%), whereas two occurred in the control group (1.3%) ($P = 0.05$). Causes of death were sudden death (eight SLE; one control), CVA (four SLE; zero controls), cancer (two SLE; one control), MI (two SLE; zero controls), pulmonary embolism (one SLE, zero controls), and sepsis (one SLE; zero controls).

Overall, 20% of patients with lupus experienced any new MACE (68) compared with 5.2% of control subjects (8) ($P < 0.0001$). MACEs occurred in 20.7% (n = 62) of patients with SLE from the original cohort versus 16.3% (n = 7) of those patients enrolled after 2014 (*P* = ns). All MACEs in the control subjects took place in subjects from the original cohort.

New cardiac events occurred in 5% (n = 18) of patients with SLE compared with 1.9% (n = 3) of control subjects ($P = 0.10$), whereas new cerebrovascular events occurred in 11.8% (n = 40) of patients with SLE versus 1.9% (n = 3) of control subjects ($P < 0.0001$). New peripheral vascular events occurred in 3.2% (n = 11) of patients with SLE versus 0.6% of control subjects (n = 1) ($P = 0.12$).

Cox regression analysis was performed to determine whether patients with SLE in our cohort still had an increased risk of a new MACE compared with control subjects after controlling for traditional cardiac risk factors. After analysis, subjects with SLE had a 4.2-fold increased hazard ratio (HR) for any MACE compared with control subjects (95% confidence interval [CI] 1.9-9.3; $P < 0.0001$) (Supplemental Table 1). Hypertension (HR = 2.5; $P = 0.001$) and increased age (HR = 1.01; $P = 0.04$) were also significantly associated with any MACE (Supplemental Table 1).

**Traditional cardiac risk factors and disease factors associated with MACEs.** Univariate analysis was next used to determine which baseline traditional cardiac risk factors, SLE disease factors, or demographic variables predicted MACEs in our cohort. Among subjects with SLE, hypertension, increased age, higher total cholesterol, higher low-density lipoprotein (LDL) cholesterol, and higher triglycerides were associated with MACEs during the follow-up period. Patients with events were significantly more likely to have been started on a statin during the follow-up period, more likely to have taken greater than 20 g of prednisone during their lifetime, and less likely to be taking hydroxychloroquine at baseline. Longer lupus disease duration and higher SDI at baseline were also significantly associated with MACEs. Among control subjects, only age and family history were significant predictors (Table 1).

Patients with SLE who went on to experience a new MACE were also significantly more likely to have increased carotid IMT ($P = 0.007$) and carotid plaque ($P < 0.0001$) at cohort entry, but there was no significant association with previous cardiovascular events. Among control subjects, there were also significant associations between baseline carotid plaque and IMT with new MACEs (Table 1).

**Traditional cardiac risk factors and disease factors associated with any new cardiac events.** We next set out to examine whether the associations between risk factors and cardiac or cerebrovascular events on their own differed from associations with overall MACEs. Among subjects with SLE, new cardiac events were associated with several traditional cardiac risk factors, including increased age, hypertension, diabetes, higher baseline total cholesterol, higher mean LDL cholesterol, and lower mean HDL cholesterol. A higher baseline SDI was significantly associated with future cardiac events. Statin use during the follow-up period was associated with cardiac events, whereas hydroxychloroquine use was inversely associated with these events. Baseline carotid plaque and higher IMT were also associated with future cardiac events in subjects with SLE (Supplemental Table 2). Age and statin use were the only significant factors associated with future cardiac events in control subjects; however, these results

**Table 1.** Baseline traditional and SLE-related cardiovascular risk factors in SLE and control subjects with or without a new MACE[a]

| Baseline Characteristics (Study Entry) | Control Subjects With No Event (n = 150) | Control Subjects with New Event (n = 8) | *P* Value | Subjects With SLE and No Event (n = 274) | Subjects With SLE and New Event (n = 68) | *P* Value* |
|---|---|---|---|---|---|---|
| Traditional cardiac risk factors at baseline | | | | | | |
| Male sex, % (n) | 3.3 (5) | 0.0 (0) | ns | 3.3 (9) | 1.5 (1) | ns |
| Age, mean ± SD, yr | 41.8 ± 13.4 | 58.9 ± 4.9 | **<0.0001** | 41.2 ± 12.8 | 47.9 ± 12.9 | **<0.0001** |
| Hypertension, % (n)[b] | 14.0 (21) | 37.5 (3) | 0.103 | 28.5 (78) | 60.3 (41) | **<0.0001** |
| Dyslipidemia, % (n)[c] | 21.3 (32) | 50.0 (4) | 0.08 | 18.2 (50) | 27.9 (19) | 0.08 |
| Total cholesterol, mean ± SD, mg/dL | 186.1 ± 40.8 | 208.9 ± 44 | ns | 178.5 ± 41.5 | 199.2 ± 50.4 | **<0.0001** |
| LDL cholesterol, mean ± SD, mg/dL | 105.9 ± 33.2 | 121.8 ± 37.6 | ns | 99.0 ± 33.8 | 113.3 ± 39.8 | **0.003** |
| HDL cholesterol, mean ± SD, mg/dl | 59.5 ± 16.8 | 58.5 ± 14.6 | ns | 57.6 ± 16.9 | 54.3 ± 17 | ns |
| Triglycerides, mean ± SD, mg/dL | 109.3 ± 57.8 | 143.8 ± 70.2 | ns | 110.9 ± 68.5 | 147.8 ± 114 | **0.01** |
| Ethnicity/Race, % (n)[d] | | | | | | |
| White | 54.0 (81) | 75.0 (6) | ns | 46.0 (126) | 55.9 (38) | ns |
| Black | 10.0 (15) | 12.5 (1) | ns | 13.9 (38) | 16.1 (11) | ns |
| Hispanic | 14.7 (22) | 0.0 (0) | ns | 21.9 (60) | 14.7 (10) | ns |
| Asian/Pacific Islander | 20.7 (31) | 12.5 (1) | ns | 14.2 (26) | 11.8 (8) | ns |
| Mixed/other | 0.6 (1) | 0.0 (0) | ns | 4.0 (12) | 1.5 (1) | ns |
| Nonwhite | 46.0 (69) | 25.0 (2) | ns | 54.0 (148) | 44.1 (30) | ns |
| Diabetes, % (n)[e] | 1.3 (2) | 0.0 (0) | ns | 4.7 (13) | 26.5 (18) | 0.08 |
| BMI, mean ± SD | 24.9 ± 5.1 | 24.9 ± 5.1 | ns | 26.0 ± 6.2 | 27.6 ± 7.4 | 0.11 |
| Smoking ever, % (n) | 24.7 (37) | 25 (2) | ns | 28.8% (79) | 26.5% (18) | ns |
| Smoke current, % (n)[f] | 8.7 (13) | 0 (0) | ns | 8.8 (24) | 4.4 (3) | ns |
| Family history of CAD, % (n)[g] | 15.8 (22) | 57.1 (4) | **0.02** | 21.6 (59) | 30.9 (21) | 0.11 |
| hs-CRP, mean ± SD | 2.3 ± 4 | 4.0 ± 4.8 | ns | 2.8 ± 6.7 | 4.2 ± 5.8 | 0.13 |
| Baseline plaque, % (n) | 14.7 (22) | 50.0 (4) | **0.03** | 13.5 (37) | 35.3 (24) | **<0.0001** |
| Baseline IMT, mean ± SD | 0.55 ± 0.13 | 0.68 ± 0.12 | **0.009** | 0.58 ± 0.15 | 0.53 ± 0.13 | **0.007** |
| Previous history of MACE, % (n) | 0 (0) | 0 (0) | ns | 4.7 (13) | 2.9 (2) | ns |
| On statin, % (n) | 6.7 (10) | 50.0 (4) | **0.002** | 10.9 (30) | 23.5 (16) | **0.006** |
| Lupus disease–related risk factors at baseline | | | | | | |
| Nephritis ever, % (n) | — | — | — | 29.2 (80) | 36.7 (25) | ns |
| Active nephritis, % (n) | — | — | — | 2.9 (8) | 5.9 (4) | ns |
| Disease duration, mean ± SD, yr | — | — | — | 11.3 ± 8.6 | 15.4 ± 10.1 | **0.001** |
| History of antiphospholipid antibody present (any), % (n) | — | — | — | 38.3 (105) | 48.5 (33) | 0.13 |
| Lifetime prednisone >20 g, % (n) | — | — | — | 29.2 (80) | 50.0 (34) | **<0.0001** |
| Mycophenolate, % (n) | — | — | — | 27.7 (76) | 23.5 (16) | ns |
| Azathioprine, % (n) | — | — | — | 13.1 (36) | 10.3 (7) | ns |

(Continued)

**Table 1.** (*Cont'd*)

| Baseline Characteristics (Study Entry) | Control Subjects With No Event (n = 150) | Control Subjects with New Event (n = 8) | *P* Value | Subjects With SLE and No Event (n = 274) | Subjects With SLE and New Event (n = 68) | *P* Value* |
|---|---|---|---|---|---|---|
| Methotrexate, % (n) | — | — | — | 5.9 (16) | 7.4 (5) | ns |
| Cyclophosphamide, % (n) | — | — | — | 1.1 (3) | 1.5 (1) | ns |
| Leflunomide, % (n) | — | — | — | 1.8 (5) | 4.4 (3) | ns |
| Hydroxychloroquine, % (n) | — | — | — | 72.5 (198) | 52.9 (36) | **0.002** |
| SDI baseline, mean ± SD | — | — | — | 1.2 ± 1.7 | 2.1 ± 0.3 | **<0.0001** |

Variables bolded if $P \leq 0.05$.
HDL, high-density lipoprotein; hs-CRP, high-sensitivity CRP; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; ns, not significant; SDI, Systemic Lupus Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus.
[a] MACEs were defined as all-cause mortality, cardiac events (defined as myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or angina [confirmed with stress test]), cerebrovascular event (cerebrovascular accident or a transient ischemic attack), or peripheral arterial disease (ankle brachial index < 0.9 or post-exercise decrease by 20%, claudication, or arterial thrombosis).
[b] Hypertension was defined as use of antihypertensive medication or a systolic blood pressure >140 mg Hg or a diastolic blood pressure > 90 mm Hg.
[c] Dyslipidemia was defined as any of the following, either alone or in combination: levels of LDL cholesterol ≥130 mg/dl, total cholesterol ≥200 mg/dl, HDL cholesterol ≥40 mg/dl, and/or triglycerides ≥150 mg/dl.
[d] Race/ethnicity categorization is based on patient self-description.
[e] Diabetes mellitus was defined as the presence of a fasting glucose ≥7.0 mmoles/l (126 mg/dl) or subjects receiving insulin or an oral hypoglycemic.
[f] Smoking was present if subjects had smoked any cigarettes within the last 3 months.
[g] Family history of cardiovascular disease is any parental history of myocardial infarction before age 60.
* *P* values were shown only if <0.15.

**Table 2.** Association of individual and composite PREDICTS biomarkers with events in subjects with SLE and control subjects

| Baseline Characteristics at Study Entry | Control Subjects With No Event [% (n)] | Control Subjects With New Event [% (n)] | *P* Value | Subjects With SLE With No Event [% (n)] | Subjects With SLE With New Event [% (n)] | *P* Value* |
|---|---|---|---|---|---|---|
| Any new MACE | n = 150 | n = 8 | | n = 274 | n = 68 | |
| piHDL present | 18.0 (27) | 25.0 (2) | ns | 46.0 (126) | 66.2 (45) | **0.003** |
| Leptin >34 ng/dL | 7.4 (11) | 28.6 (2) | 0.11 | 16.5 (45) | 39.7 (27) | **<0.0001** |
| TWEAK>373 pg/mL | 81.0 (119) | 71.4 (5) | ns | 82.2 (222) | 85.3 (58) | ns |
| Homocysteine > 12mmol/L | 14.7 (22) | 37.5 (3) | 0.11 | 30.7 (84) | 51.5 (35) | **0.001** |
| High PREDICTS baseline | 18.7 (28) | 50.0 (4) | **0.05** | 33.9 (93) | 76.5 (52) | **<0.0001** |
| Age> 48 years | 38.0 (57) | 100.0 (8) | **0.002** | 34.3 (94) | 55.9 (38) | **0.001** |
| Diabetes (any) | 1.3 (2) | 0.0 (0) | ns | 4.7 (13) | 10.3 (7) | 0.08 |
| Any new cardiac event | n = 155 | n = 3 | | n = 324 | n = 18 | |
| piHDL present | 18.1 (28) | 33.3 (1) | ns | 48.8 (158) | 72.2 (13) | **0.05** |
| Leptin >34 ng/dL | 9.1 (14) | 0.0 (0) | ns | 19.8 (64) | 44.4 (8) | **0.01** |
| TWEAK > 373pg/mL | 78.7 (122) | 66.7 (2) | ns | 82.4 (266) | 88.9 (16) | **ns** |
| Homocysteine> 12 mmol/L | 15.5 (24) | 33.3 (1) | ns | 34.3 (111) | 44.4 (8) | ns |
| High PREDICTS baseline | 20.1 (31) | 33.3 (1) | ns | 39.8 (129) | 88.9 (16) | **<0.0001** |
| Age > 48 years | 39.4 (61) | 100 (3) | ns | 36.4 (118) | 77.7 (14) | **<0.0001** |
| Diabetes (any) | 1.3 (2) | 0.0 (0) | ns | 4.9 (16) | 22.2 (4) | **0.02** |
| Any new cerebrovascular event | n = 155 | n = 3 | | n = 302 | n = 40 | |
| piHDL present | 17.40 (27) | 66.70 (2) | 0.09 | 48.3 (146) | 62.5 (25) | 0.09 |
| Leptin >34 ng/dL | 7.70 (12) | 66.70 (2) | **0.021** | 18.3 (55) | 42.5 (17) | **<0.0001** |
| TWEAK>373 pg/mL | 55.50 (122) | 64.0 (3) | ns | 82.9 (247) | 82.5 (33) | ns |
| Homocysteine> 12mmol/L | 15.50 (24) | 33.30 (1) | ns | 33.2 (100) | 47.5 (19) | 0.08 |
| High PREDICTS baseline | 19.4 (30) | 66.7 (2) | **0.11** | 38.1 (115) | 75.0 (30) | **<0.0001** |
| Age> 48 years | 40 (62) | 100 (3) | 0.07 | 37.4 (113) | 47.5 (19) | ns |
| Diabetes (any) | 1.3 (2) | 0.0 (0) | ns | 6.0 (18) | 5.0 (2) | ns |

Variables bolded if $P \leq 0.05$.
MACE, major adverse cardiovascular event; ns, not significant; piHDL, proinflammatory high-density lipoprotein; PREDICTS, predictors of risk for elevated flares, damage progression, and increased cardiovascular diseasein patients with SLE; SLE, systemic lupus erythematosus; TWEAK, TNF-like weak inducer of apoptosis.
* *P* values were shown only if <0.15.

should be interpreted with caution given the small number of events (n = 3) (Supplemental Table 2).

**Traditional cardiac risk factors and disease factors associated with any new cerebrovascular events.** New cerebrovascular events in subjects with SLE were significantly associated with hypertension, higher total cholesterol, higher LDL cholesterol, and triglycerides. Cerebrovascular events were also associated with active glomerulonephritis, a higher baseline SDI score, longer disease duration, and lifetime prednisone use of greater than 20 g. Hydroxychloroquine use at cohort entry was inversely associated with new cerebrovascular events (Supplemental Table 3). Among control subjects, increased age, statin use, hs-CRP, and baseline plaque were significantly associated with future cerebrovascular events; however, these results should be interpreted with caution because of the small number of events (n = 3) (Supplemental Table 3).

**Association of MACEs with nonstandard PREDICTS biomarkers.** We next examined whether the presence of the PREDICTS biomarkers at cohort entry associated with future MACEs. Using univariate analysis, we found that baseline piHDL function, leptin levels greater than 34 ng/dl, homocysteine levels greater than 12 mmol/L, and age greater than 48 years were significantly associated with future events (Table 2).

Overall, patients with SLE who experienced a new MACE were significantly more likely to have a high PREDICTS score at baseline (76.5%) compared with patients who had no new events (33.9%) ($P < 0.0001$). In addition, high baseline PREDICTS score was separately associated with cardiac events ($P < 0.0001$) and cerebrovascular events ($P < 0.0001$) in subjects with SLE (Table 2).

In comparison, only 13.2% of patients with SLE who went on to have an MACE had a baseline 10-year Framingham Risk Score (FRS) that was greater than 10% versus 6.2% of patients without an event ($P = 0.05$) (21) (Table 2). Only one patient with SLE in our cohort had an FRS that was greater than 20% at cohort entry.

Although no individual PREDICTS variables were associated with events among control subjects, a high overall PREDICTS score was significantly associated with future MACEs in control subjects ($P = 0.05$). Overall, the PREDICTS score had a favorable predictive profile for future cardiovascular events compared with a 10-year FRS greater than 10% (Table 2).

The sensitivity, specificity, positive predictive value, and negative predictive value of high PREDICTS score compared with the FRS in predicting future cardiovascular events are listed in Table 3. The area under the curve (AUC) for any new event for the PREDICTS score was 0.71 (95% CI 0.65-0.78), which was higher than the AUC for FRS greater than 10% at 0.54 (95% CI 0.46-0.61) (Table 3).

**High PREDICTS score at cohort entry is associated with an increased HR for developing future cardiovascular events or death in SLE.** Cox Regression analysis determined which variables most consistently associated with longer time to any new MACE in subjects with SLE. The model included significant or near-significant ($P \leq 0.1$) predictors on univariate analysis. Analysis showed that high baseline PREDICTS score was associated with an increased HR of 3.7 ($P < 0.0001$) for a future new MACE (Table 4). The event-free survival curve for patients with high versus low PREDICTS scores is shown in Figure 1.

Hypertension (HR = 2.1; $P = 0.006$) at cohort entry was also significantly associated with new MACEs in subjects with SLE (Table 4).

As noted above, we did not exclude subjects with prior MACEs from our cohort study. When we removed the 15 subjects with SLE with prior MACEs from the Cox regression analysis, our results were very similar, with baseline high PREDICTS score (HR = 3.4; $P < 0.0001$) and baseline hypertension (HR = 2.2; $P = 0.005$) as the significant predictors (data not shown).

**Table 3.** The prediction of future cardiovascular events in SLE: comparison of high PREDICTS at study entry with 10-year FRS >10% and >20%

| Characteristics† | Sensitivity (%) | Specificity (%) | Positive Predictive Value (%) | Negative Predictive Value (%) | AUC (95% CI) |
|---|---|---|---|---|---|
| Any new MACE | | | | | |
| FRS > 10% | 13.2 | 93.8 | 34.6 | 81.3 | 0.54 (0.46-0.61) |
| FRS > 20% | 1.5 | 100 | 100 | 80.4 | 0.51 (0.43-0.59) |
| High PREDICTSa | 76.5 | 66.1 | 35.9 | 91.8 | 0.71 (0.65-0.78) |
| Any new cardiac event | | | | | |
| FRS > 10% | 27.8 | 93.5 | 19.2 | 95.9 | 0.61 (0.46-0.76) |
| FRS > 20% | 0 | 100 | 0 | 94.8 | 0.50 (0.36-0.63) |
| High PREDICTSa | 88.9 | 60.2 | 11.0 | 99.0 | 0.75 (0.65-0.84) |
| Any new cerebrovascular event | | | | | |
| FRS > 10% | 5.0 | 92.1 | 8.0 | 88.0 | 0.50 (0.39-0.58) |
| FRS > 20% | 0 | 99.7 | 0 | 88.3 | 0.50 (0.40-0.59) |
| High PREDICTSa | 75.0 | 61.9 | 20.7 | 94.9 | 0.69 (0.40-0.59) |

AUC, area under the curve; CI, confidence interval; FRS, Framingham Risk Score; MACE, major adverse cardiovascular event; PREDICTS, predictors of risk for elevated flares, damage progression, and increased cardiovascular disease in patients with SLE; SLE, systemic lupus erythematosus.

[a] Includes three or more of the following predictors: age ≥ 48 years, proinflammatory high-density lipoprotein ≥ 0.94 FU, leptin ≥ 34 ng/mL, TNF-like weak inducer of apoptosis ≥ 373 pg/mL, and homocysteine ≥ 12 mmol/L or diabetes plus one or more predictor.

**Table 4.** Cox regression model of the relationship of traditional cardiac risk factors and nonstandard biomarkers to MACE in patients with SLE

| Variable | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Statin use (ever during study) | 1.32 | 0.70-2.49 | 0.39 |
| Disease duration, yr | 0.98 | 0.95-1.02 | 0.32 |
| Any antiphospholipid antibody | 1.49 | 0.91-2.46 | 0.12 |
| Lifetime prednisone >20 g | 1.42 | 0.76-2.63 | 0.27 |
| Family history of cardiovascular disease | 1.13 | 0.65-1.97 | 0.67 |
| Active nephritis (baseline) | 2.98 | 0.98-9.05 | 0.054 |
| Hypertension (baseline) | **2.12** | **1.24-3.62** | **0.006** |
| Dyslipidemia (baseline) | 0.82 | 0.44-1.53 | 0.53 |
| High baseline PREDICTS | **3.70** | **1.99-6.88** | **<0.0001** |
| Plaquenil use (baseline) | 0.87 | 0.52-1.46 | 0.60 |
| Any baseline carotid plaque | 1.54 | 0.85-2.78 | 0.15 |
| SDI Baseline | 1.10 | 0.95-1.27 | 0.22 |

CI, confidence interval; MACE, major adverse cardiovascular event; PREDICTS, predictors of risk for elevated flares, damage progression, and increased cardiovascular disease in patients with SLE; SDI, SLE, systemic lupus erythematosus.

We also examined which predictors were significantly associated with new cardiac events and new cerebrovascular events using Cox regression analysis. We found that only high baseline PREDICTS score significantly associated with new cardiac events on multivariate analysis (HR = 7.3; 95% CI 1.4-37.9; *P* = 0.02). Baseline high PREDICTS score (HR = 4.0; 95% CI 1.7-9.3; *P* = 0.001), active glomerulonephritis (HR = 5.5; 95% CI 1.7-18.1; *P* = 0.005), and hypertension (HR 2.4; 95% CI 1.2-4.8; *P* = 0.02) were all significantly associated with new cerebrovascular events (data not shown).

Finally, we examined whether SLE diagnosis and PREDICTS score would both still be independently predictive of future MACEs in the entire cohort of subjects with SLE and control subjects using Cox regression analysis. We found that high baseline PREDICTS score (HR = 3.8; *P* < 0.0001), SLE diagnosis (HR = 3.1; *P* = 0.005), and hypertension (HR = 2.3; *P* = 0.001) were all significantly associated with future MACEs (Table 5). When subjects with previous MACEs were excluded from the analysis, we found similar results, with high baseline PREDICTS score (HR = 3.7; *P* < 0.0001), SLE diagnosis (HR = 3.5; *P* = 0.002), and hypertension (HR = 2.4; *P* = 0.001) all still significantly associated with future MACEs, although statin initiation was also was significantly associated (HR = 2.1; *P* = 0.01).

## DISCUSSION

We previously found that the PREDICTS panel of four inflammatory biomarkers and two traditional cardiac risk factors (age and diabetes) had an overall better predictive capacity for subclinical atherosclerosis (both carotid plaque and higher IMT) in subjects with SLE compared with individual biomarkers or risk factors (13). We demonstrate here that patients with SLE with high PREDICTS scores at baseline were also significantly more likely to develop future MACEs within almost 10 years of follow-up compared with patients with low PREDICTS scores. Examined separately, patients with high baseline PREDICTS scores were also significantly more likely to develop new cardiac events and new cerebrovascular events.

Traditional cardiovascular risk factor prediction models consistently underestimate the future risk of events in patients with SLE. In one Canadian cohort study, the relative risk was 10.1 for MI and 7.9 for stroke even after controlling for traditional Framingham risk factors (2). More recently, a systematic review of risk algorithms in rheumatic diseases found that most models underestimated the cardiovascular risk in SLE and rheumatoid arthritis

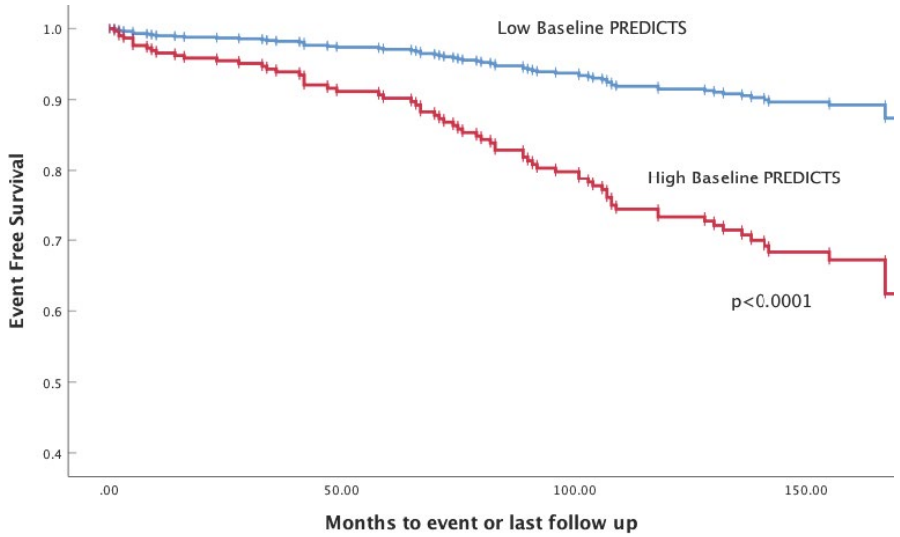


**Figure 1.** Major adverse cardiovascular event-free survival is higher in Systemic Lupus Erythematosus patients who had a low PREDICTS risk score at cohort entry, using Kaplan-Meier. PREDICTS, predictors of risk for elevated flares, damage progression, and increased cardiovascular diseasein patients with SLE.

**Table 5.** Cox Regression model of the relationship of traditional cardiac risk factors to the MACE-free survival in subjects with SLE and control patients, including PREDICTS

| Variable | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Initiation of statin | 1.60 | 0.88-2.90 | 0.12 |
| Family history of cardiovascular disease | 1.29 | 0.77-2.14 | 0.33 |
| Hypertension (baseline) | **2.30** | **1.38-3.82** | **0.001** |
| Dyslipidemia (baseline) | 0.88 | 0.49-1.59 | 0.68 |
| Male sex | 2.56 | 0.57-11.51 | 0.22 |
| Any baseline plaque | 1.37 | 0.81-2.33 | 0.24 |
| Nonwhite ethnicity | 0.84 | 0.52-1.34 | 0.46 |
| Body mass index | 0.99 | 0.96-1.03 | 0.70 |
| Smoking (ever) | 0.72 | 0.43-1.20 | 0.14 |
| SLE diagnosis | **3.12** | **1.40-6.93** | **0.005** |
| Baseline PREDICTS | **3.84** | **2.15-6.84** | **<0.0001** |

Variables bolded if $P \leq 0.05$.
CI, confidence interval; MACE, major adverse cardiac event; PREDICTS, predictors of risk for elevated flares, damage progression, and increased cardiovascular disease in patients with SLE; SLE, systemic lupus erythematosus.

(RA) (6). The few studies that examined the addition of biomarkers to a traditional risk factor panel in patients with rheumatic disease have largely demonstrated no improvement in predictive capacity. For example, the incorporation of hs-CRP did not significantly improve the prediction of the FRS or the second QResearch database risk algorithm panel in an RA cohort (22). Conversely, studies from the University of Toronto suggest that the use of serial measurements of hs-CRP or modification of the FRS by multiplying each item by two might be more useful for predicting cardiovascular events in SLE (23,24). In our SLE cohort, the PREDICTS panel performed better than either baseline hs-CRP or the traditional Framingham 10-year risk model at predicting future events. To our knowledge, this is the first study in SLE to demonstrate improvement in cardiovascular risk prediction using a combination of traditional risk factors and novel biomarkers.

Unfortunately, optimum cardiovascular prevention strategies for patients with lupus have also not been definitively established. One study concluded that the large number of patients with SLE required to conduct a definitive randomized clinical trial make it unlikely that a preventive cardiovascular trial could be successfully completed (25). Two prospective randomized trials of statins in patients with SLE were unable to demonstrate a benefit on progression of subclinical atherosclerosis in adults (26) or children (27). A subgroup analysis of the pediatric atherosclerosis prevention in paediatric lupus erythematosus study, however, suggested that pubertal patients with SLE with elevated hs-CRP levels did demonstrate decreased progression of carotid IMT (28), suggesting that inflammatory biomarkers might be useful for selecting patients most likely to benefit from interventions. A cross-sectional analysis of a large number of patients with SLE in Taiwan showed that statin therapies at standard doses significantly reduced all-cause mortality, but data were not robust enough to evaluate effects on cardiovascular events (29). Future studies will be needed to determine whether the selection of patients at high risk for progression of atherosclerosis using a lupus-specific model such as the PREDICTS score will improve the feasibility and success of conducting cardiovascular prevention trials.

There is accumulating evidence that inflammation plays a vital role in the pathogenesis of atherosclerosis in SLE (1,30). It may be that the novel biomarkers in the PREDICTS model better capture alternate pathways that contribute to disease pathogenesis in SLE than general markers of inflammation such as hs-CRP. For example, piHDL function may reflect both proteomic and lipidomic changes that uniquely occur in HDL particles from subjects with SLE (31–33). Dysfunctional HDL may also result from aberrant HDL oxidation resulting from SLE-specific low-density granulocytes and release of neutrophil extracellular traps (11,34). Leptin has been shown to influence many immune cell subsets (35) and may have specific proinflammatory effects on macrophages in SLE, including stimulation of phagocytosis and increased presentation of apoptosis-derived self-antigen to T cells (36). Leptin may also promote increased expression of inflammatory cytokines and oxidative stress in endothelial cells (37) and cardiomyocytes (38).

Homocysteine has also been linked to atherosclerosis in lupus in several previous studies (13,14,39). Homocysteine can contribute to oxidative damage (40), endothelial dysfunction (41), and lipid peroxidation (42). sTWEAK can upregulate IFN-α expression in peripheral blood mononuclear cells and is a promising biomarker for SLE nephritis (43,44) as well as cardiovascular disease in the general population (45). Thus, our finding that the PREDICTS panel combining inflammatory biomarkers and select traditional risk factors is more predictive of cardiovascular events than either traditional risk factors alone or individual PREDICTS components supports the hypothesis that complex inflammatory processes are critical to the pathogenesis of increased cardiovascular disease observed in patients with SLE.

Our study also found that patients with SLE had a four-fold increased HR for any new MACE compared with control subjects. This finding is consistent with multiple other reports, including a three-fold increased relative risk for MI or stroke that was seen in a recent meta-analysis of 24 longitudinal studies (46). This increased rate of events was seen in our cohort despite the fact that our subjects with SLE—in contrast to other SLE cohorts—did not have statistically different subclinical atherosclerosis presence or progression at baseline or 3-year follow-up than control subjects (13). In addition, baseline plaque prevalence of both SLE and control groups in our cohort was lower than that in other published studies (47,48). Regardless, we did find that the presence of carotid plaque and higher IMT at baseline were both significantly associated with future MACEs as well as future cardiac events on univariate analysis. These findings mirror those of Kao et al (49), which is the only other study, to our knowledge, to demonstrate an association between carotid artery subclinical atherosclerosis and future events in SLE.

Hydroxychloroquine use at baseline was significantly associated with a decreased risk for all future MACEs, cardiac events, and cerebrovascular events on univariate (but not multivariate) analysis. Other studies have suggested that hydroxychloroquine may have cardioprotective effects. In a recent retrospective cohort study using a large insurance database in Taiwan, hydroxychloroquine use was inversely associated with cardiac events, but not strokes, in SLE (50). Hydroxychloroquine was also associated with a decreased risk of cardiovascular events in one RA cohort (51). We did not find any other associations between baseline medication use and events. We recently published data demonstrating improvement in PREDICTS biomarkers over 12 weeks after the initiation of either mycophenolate mofetil or hydroxychloroquine (52). It is possible that we would have seen associations between medication use and risk of future cardiovascular events if we had detailed information regarding dose exposure to each medication over the length of the study, but unfortunately, these data are not available.

Interestingly, patients with SLE in our cohort who experienced an MACE were more likely to have been started on a statin than patients with SLE who did not have an event. All patients in the cohort underwent a baseline lipid panel and carotid ultrasound testing, and results were communicated with subjects, who in turn were instructed to share the results with their physicians. We cannot make definitive statements regarding when or why subjects in our study were started on new therapies; however, we presume that patients who had evidence of carotid atherosclerosis or hyperlipidemia (or those who experienced an MACE) were more likely to have been started on a statin. We also found that 50% of control subjects who experienced MACEs had been started on a statin compared with only 23.5% of subjects with SLE with MACEs. Again, we can only speculate, but this is consistent with other published data from large population databases that revealed that subjects with SLE are much less likely to be prescribed or to fill prescriptions for statins than patients with diabetes and patients in the general population (53,54).

There are some other limitations to our study; 5.7% of subjects with SLE and 7% of control subjects in our cohort were lost to follow-up. It is possible that these subjects would have impacted our event rate or the significance of the associations with PREDICTS score and/or other risk factors. It is reassuring, however, that the baseline characteristics of those lost to follow-up do not significantly differ from those of the patients included in the analysis (data not shown). In the early years of our cohort study, individuals with active renal disease, statin use, or male sex were initially excluded, which may have introduced bias away from patients with known inflammation and higher cardiovascular risk (16). In 2014, however, enrollment was expanded to allow our cohort to more broadly represent the broad spectrum of patients with lupus. It is possible that our event rate would have been even higher if those patients had been followed for the entire duration of the cohort. One advantage to our study design is that our biomarkers of interest were drawn at the baseline visit of a prospective longitudinal cohort study. However, the relatively small number of total events is a limitation to our study. Finally, it is important to note that the PREDICTS panel was derived to predict the progression of subclinical atherosclerosis, using many of the same patients included in this analysis. It is reassuring that our biomarker panel also is able to predict which patients go on to have MACEs even after accounting for the presence of baseline plaque in multivariate analysis; however, the PREDICTS panel will need to be further validated in independent cohorts.

In summary, the PREDICTS panel—a combination panel of independent variables, including four inflammatory biomarkers and two traditional cardiac risk factors—had overall better predictive capacity for longitudinal cardiovascular events or death in subjects with SLE than the Framingham risk factor panel. In subjects with SLE, a high PREDICTS score confers a 3.7-fold increased HR for the presence of any future major adverse cardiovascular event or death, a 7.3-fold increased HR for new cardiac events, and a 2.4-fold increased HR for new cerebrovascular events. The PREDICTS score could aid clinicians in identifying patients with SLE at risk for future cardiovascular events who could benefit from risk factor modification. Future studies will be needed to determine whether the PREDICTS score can be used in cardiovascular prevention studies to identify more protective treatment strategies.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. McMahon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Acquisition of data.** Skaggs, Grossman, Sahakian, Perry, FitzGerald, Charles-Schoeman, Gorn, Taylor, Moriarty, Ragavendra, Weisman, Wallace, Hahn, McMahon.

**Analysis and interpretation of data.** Skaggs, Hahn, McMahon.

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