State of current management of the heightened risk for atherosclerotic cardiovascular events in an established cohort of patients with lupus erythematosus

Megan Zhao, Rui Feng, Victoria P Werth, Kevin Jon Williams

ABSTRACT

Objective Patients with lupus erythematosus (LE) are at heightened risk for clinical events, chiefly heart attacks and strokes, from atherosclerotic cardiovascular disease (ASCVD). We recently proposed new guidelines to assess and manage ASCVD event risk specifically in LE. Here, we examined current cardiovascular management in light of these new recommendations.

Methods We studied our entire UPenn Longitudinal Lupus Cohort of patients with cutaneous LE, without (CLE-only) or with (CLE+SLE) concurrent systemic LE, for whom we had full access to medical records (n=370, LE-ASCVD Study Cohort).

Results Of our LE-ASCVD Study Cohort, 336 out of 370 (90.8%) had a designated primary-care physician. By the new guidelines, the most recent low-density lipoprotein (LDL) levels were above-goal for 249 out of 370 (67.3%). Two-hundred sixty-six (71.9%) had hypertension, which was undertreated or untreated in 198 out of 266 (74.4%). Of current smokers, 51 out of 63 (81.0%) had no documented smoking cessation counselling or referrals. Diabetes and triglyceridaemia were generally well managed. Of the cohort, 278 qualified for two widely used online estimators of ASCVD event risk in primary prevention: the ACC-ASCVD Risk Estimator Plus and QRisk3. We also stratified these 278 patients into our recently defined categories of ASCVD event risk in LE. These three methods for estimating ASCVD event risk showed clinically meaningful discordance for 169 out of 278 (60.8%). The documented rate of ASCVD events in the first 10 years after enrolment was 13.5% (95% CI 8.9%, 17.9%), similar between CLE-only and CLE+SLE, indicating an at-risk population despite the preponderance of women and an average age at enrolment of only 47 years.

Conclusion Patients with LE exhibit an increased prevalence of conventional risk factors for ASCVD events. Moreover, it is unclear how to accurately assess their future ASCVD event risk, except that it is substantial. Efforts are underway to improve ASCVD event risk estimation and guideline implementation in patients with lupus.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Patients with lupus erythematosus (LE) are at a heightened risk for clinical events, chiefly heart attacks and strokes, caused by atherosclerotic cardiovascular disease (ASCVD).

WHAT THIS STUDY ADDS

- This study adds to the current literature by providing recent real-world data on management of ASCVD event risk in light of both longstanding and more recent cardiovascular recommendations, including guidelines specifically for patients with LE.

INTRODUCTION

Patients with lupus erythematosus (LE) suffer from a heightened risk of clinical events, chiefly heart attacks and strokes, caused by atherosclerotic cardiovascular disease (ASCVD). Several clinical features of LE contribute to the problem. First, patients with LE exhibit an increased prevalence of conventional risk factors for ASCVD events, particularly dyslipoproteinaemia and hypertension, and glucocorticoid use often exacerbates additional conditions related to cardiovascular risk, such as obesity, the metabolic syndrome, so-called ‘pre-diabetes’ (defined as dysglycemia to an extent that indicates a high risk of developing diabetes).
and type 2 diabetes mellitus. Moreover, patients with cutaneous LE (CLE) smoke at higher rates than in the general population. Second, numerous studies using arterial ultrasonography, coronary CT angiography and other methods have shown that patients with LE carry an increased burden of atherosclerotic plaques compared with the general population. Third, the increased rate of ASCVD events among patients with LE persists even after adjustment for age and sex and, more strikingly, even after adjustment for other conventional risk factors for ASCVD events. We have suggested that autoimmune processes specific to LE may exacerbate specific, known pathogenic steps in atherosclerosis.

Despite their high plaque burden and heightened risk for ASCVD events, however, patients with LE remain undertreated for the causative agents of ASCVD, meaning low-density lipoprotein (LDL) and other cholesterol-rich apolipoprotein-B (apoB)-containing lipoproteins, and key exacerbators of ASCVD, such as hypertension, smoking and hyperglycaemia. As part of our efforts to address this problem, we recently proposed a system for assessing patients with CLE and SLE using four defined categories of ASCVD event risk, with corresponding guidance for clinical management of patients with LE in each ASCVD event risk category using lifestyle modifications and modern medications. These guidelines were explicitly modelled after risk categories and therapeutic goals that have been established for two well-studied conditions, diabetes mellitus and stage 3–4 chronic kidney disease (CKD), which also show heightened risk for ASCVD events and have been incorporated into standard clinical guidelines for management of ASCVD event risk. Importantly, these risk categories separate patients without clinically evident ASCVD (primary prevention) from patients who already have clinically evident ASCVD, for example, a prior myocardial infarction (MI) or ischaemic stroke (secondary prevention).

In the current work, we performed a single-centre study of all 370 patients with CLE, without (CLE-only) or with (CLE+SLE) concurrent SLE, within our established longitudinal cohort at the University of Pennsylvania Health System (UPHS) for whom we have full access to their medical records. Our goal was to assess the state of current management of ASCVD event risk through conventional therapeutic targets, chiefly hyperlipidaemia, hypertension, smoking, pre-diabetes and diabetes mellitus, in the light of the new recommendations. We also studied two earlier and still widely used online tools for estimating the risk of an ASCVD event in the next 10 years (‘10-year ASCVD event risk’) for individuals without clinically evident ASCVD from the general population, that is, not specifically designed for patients with CLE: the American College of Cardiology (ACC) ASCVD Risk Estimator Plus and the QRisk3 calculator. We also explored a number of possible differences between the key subgroups of patients with CLE-only versus patients with CLE+SLE that could affect clinical assessments or management in this context.

**METHODS**

**The LE-ASCVD Study Cohort**

We previously reported the UPenn Longitudinal Lupus Cohort, which is our established cohort of patients receiving care at UPHS whom we have been recruiting from our specialty Dermatology clinic since 2007 based on a diagnosis of CLE, without or with concurrent SLE.

For the current study, we required full access to longitudinal and recent medical records. Thus, we included only active UPHS patients and patients whose records from outside hospitals were either linked or faxed into the UPHS electronic medical record (‘LE-ASCVD Study Cohort’). An important feature of our approach is that, for these patients, we had access to all charted information that was available to the clinical care team. Our database consisted of clinical information for these patients, including ASCVD events, conventional parameters relevant to the management of future ASCVD event risk and missing/unmeasured or out-of-date data relevant to clinical care. Data were collected from each patient’s enrolment through 1 August 2021. We entered this information into the University’s secure RedCap system (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee, USA) to ensure compliance with confidentiality requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

**Collection and interpretation of clinical data**

Our approaches for collecting and interpreting these data are described in detail in the online supplemental methods, in the Demographic and clinical data collected for the RedCap database and Three systems to estimate the risk of a future ASCVD event for individual patients within the LE-ASCVD Study Cohort sections. Of note, the QRisk3 takes SLE, but not CLE, into account. Non-high-density lipoprotein cholesterol (non-HDLc), a convenient parameter that captures the cholesterol carried in plasma by LDL and all other atherogenic apoB-containing lipoproteins, was calculated as the plasma concentration of total cholesterol (TC) minus plasma HDLc.

All previously documented or newly incident major adverse atherosclerotic cardiovascular events (MAACE) were noted along with the event date and were defined as atherosclerotic MI, atherosclerotic ischaemic heart disease other than MI such as angina and coronary revascularisation, atherosclerotic (non-embolic) ischaemic stroke or transient cerebrovascular ischaemic attack, or newly diagnosed symptomatic peripheral arterial disease. Major adverse cardiovascular events (MACE) that were clearly not atherosclerotic were excluded, such as coronary vasospasm without documentation of nearby plaque, venous thrombosis or pulmonary embolism, embolic stroke unrelated to atherosclerosis and heart failure from non-ischaemic causes (chronic hypertension, diabetes mellitus, non-ischaemic valvular disorders, post-myocarditis, and congenital or genetic defects). Hospitalisation for chest pain, shortness of breath or palpitations
with merely a suspicion of ischaemic origin also did not meet conventional definitions for MAACE.

Statistical analyses

Categorical parameters are given as n (%). Continuous variables are given as mean±SD, if normally distributed, or as median (IQR), if non-normally distributed.

To assess the correlation between the numerical estimates of 10-year ASCVD event risk from the QRisk3 versus the ACC Risk Estimator Plus for all patients in the LE-ASCVD Study Cohort for whom we could use both, we calculated a Pearson’s correlation coefficient (r) and fit a linear regression. Documented MAACE were tabulated for the period before enrolment into the cohort and then for the entire period of study after enrolment. Event-free survival rates since enrolment in the LE-ASCVD Study Cohort were computed according to Kaplan-Meier, along with 95% CIs.29 30

Because of differences in the underlying autoimmune disease in patients with CLE-only versus patients with CLE+SLE, we separately complied or calculated a number of clinically relevant parameters for these two well-defined subgroups of patients within the LE-ASCVD Study Cohort. These parameters include separate tabulations of estimates of 10-year ASCVD event risk with corresponding assessments of lipid/lipoprotein management, separate assessments of blood pressure management and smoking cessation, separate correlations between the two different online estimators of 10-year ASCVD event risk when applied to patients within these subgroups, separate tabulations of chart-diagnosed antiphospholipid syndrome (APS) and separate Kaplan-Meier MAACE-free survival curves. We also report several SLE-specific features of the CLE+SLE subgroup that can be relevant to assessment and management of ASCVD event risk, such as the presence of lupus nephritis, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)31 and use of systemic medications, particularly ones with reported cardiovascular effects, such as hydroxychloroquine and prednisone.1

RESULTS

The UPenn Longitudinal Lupus Cohort currently consists of 529 patients with CLE.21-23 On review, we found that 370 of them have electronic medical records that are fully accessible within UPHS and therefore could be included in our LE-ASCVD Study Cohort.

Table 1 shows demographics and other characteristics of the LE-ASCVD Study Cohort. Consistent with our previous reports,1 21 23 the LE-ASCVD Study Cohort was predominantly female, with nearly 9 out of 10 identifying as white or black, consistent with the UPHS catchment area. Average age was 47.1±14.9 years at enrolment and 54.8±15.9 years at the end of the data collection period (table 1). Average length of time since enrolment into the UPenn Longitudinal Lupus Cohort was 7.7±4.5 years.

As of their most recent medical encounter, 14.6% of the patients in our LE-ASCVD Study Cohort had clinically evident ASCVD, meaning a diagnosis of MAACE as defined in the Methods section, which classifies these individuals as candidates for secondary prevention (extreme risk in table 1 and in figure 1A; no patient qualified for the highest risk category from Keyes et al of recent recurrent ASCVD events). Just over half of the LE-ASCVD Study Cohort had concurrent SLE (CLE+SLE), with 22.1% of those patients having a history of lupus nephritis (table 1) and 11.6% with APS (online supplemental table S1). Of the entire study cohort, 10.0% had a history of stage 3 or 4 chronic kidney disease (CKD; table 1). Median times since diagnosis of CLE or concurrent SLE were over a decade (online supplemental table S1).

Almost three-quarters of the patients in the LE-ASCVD Study Cohort had hypertension (table 1), defined as a systolic blood pressure ≥130, a diastolic pressure ≥80 mmHg and/or on antihypertensive medication, following the recently updated joint guidelines from the ACC and the American Heart Association (AHA).17 32 Of the study cohort, 29.5% were former smokers, and 17.0% are current smokers (table 1). Of the subgroup with at least one set of simultaneous height and weight measurements, approximately one-third were overweight or normal weight (36.2%), one-third overweight (30.3%) and one-third obese (33.5%; table 1 and online supplemental table S1).33 Pre-diabetes was present in 18.1%, and diabetes in 10.5%, of the LE-ASCVD Study Cohort (table 1). A diagnosis of depression was common (37.6%; online supplemental table S1), as previously reported for CLE.34

Regarding management, over 90% of the patients in the LE-ASCVD Study Cohort had a primary-care physician (PCP) listed in the electronic medical record (table 1). Median time elapsed since the last visit with a PCP was 10 months (online supplemental table S1). Number of physician providers, excluding trainees, was 3.8±2.8 per patient (mean±SD; online supplemental table S1). Most patients in the study cohort had seen a rheumatologist, and under half had seen a cardiologist, nephrologist or endocrinologist (online supplemental table S1).

Assessments and management of lipid/lipoprotein levels as targets to lower ASCVD event risk

Almost 90% of patients in the LE-ASCVD Study Cohort had plasma lipid/lipoprotein levels checked at least once, with a median elapsed time of 35 months since the most recent panel, that is, almost 3 years (online supplemental table S1). Among the conventional parameters relevant to future ASCVD event risk, the lipid/lipoprotein panels in the patients’ electronic charts uniformly included plasma concentrations of TC, LDLc, triglycerides (TG) and HDLc, but not apolipoprotein-B (apoB) nor a one-time assay for lipoprotein (a) (Lp(a)).35-37 We found that PCPs checked just over 60% of the most recent lipid/lipoprotein values, and non-PCPs checked the rest. Of the non-PCPs, rheumatologists checked lipid/lipoprotein
values in more patients than did other subspecialists (online supplemental table S1).

Based on data from the electronic charts, including absence (primary prevention) or presence (secondary prevention) of clinically evident ASCVD, as well as major conventional risk factors for ASCVD events, we classified patients from the LE-ASCVD cohort into the four defined categories of ASCVD event risk from our recently proposed guidelines for patients with LE—namely, high risk, very high risk, extreme risk and recent recurrent ASCVD events.\(^1\) By analogy with established guidelines for diabetes mellitus, the newly proposed ASCVD event risk categories for patients with LE do not distinguish between types of lupus, such as CLE-only or CLE+SLE, although certain disease-specific factors in LE are taken into account, particularly high disease activity, long duration, high cumulative damage, a history of corticosteroid use, the presence of serum antiphospholipid antibodies, and lupus nephritis, as well as stage 3 or 4 CKD from any cause.\(^1\)

Next, we compared current clinical care with

<table>
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<tr>
<th>Category</th>
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<th>Value</th>
<th>n in LE-ASCVD Study Cohort or subgroup</th>
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<tr>
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</tr>
<tr>
<td>Female</td>
<td></td>
<td>305 (82.4%)</td>
<td>370 (entire LE-ASCVD Study Cohort)</td>
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<tr>
<td>White</td>
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<td>190 (51.4%)</td>
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<td>141 (38.1%)</td>
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<tr>
<td>Hispanic</td>
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<td>17 (4.6%)</td>
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<td>Clinical course and care in the cohort</td>
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<tr>
<td>Age at enrolment into the cohort</td>
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<td>Age as of 1 August 2021</td>
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<tr>
<td>Length of time since enrolment into the cohort</td>
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<td>7.7±4.5 years</td>
<td>370</td>
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<td>Extreme risk for future ASCVD events*</td>
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<td>History of lupus nephritis</td>
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<td>109 (29.5%)</td>
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<tr>
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<td>63 (17.0%)</td>
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<tr>
<td>Pre-diabetes§</td>
<td></td>
<td>67 (18.1%)</td>
<td>370</td>
</tr>
<tr>
<td>Diabetes mellitus§</td>
<td></td>
<td>39 (10.5%)</td>
<td>370</td>
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<tr>
<td>Patients with a listed PCP in the chart</td>
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<td>336 (90.8%)</td>
<td>370</td>
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<tr>
<td>Patients with documented PCP visit in the chart</td>
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<td>279 (75.4%)</td>
<td>370</td>
</tr>
</tbody>
</table>

Here and elsewhere, categorical parameters are given as n (%). Continuous variables are given as mean±SD, if normally distributed, or as median (IQR), if non-normally distributed.

*Extreme ASCVD event risk was defined by Keyes et al as ‘Patients with LE … and clinically evident ASCVD’, that is, secondary prevention in the context of LE.\(^1\)

†An additional five (1.4%) patients in the LE-ASCVD Study Cohort were in CKD stage 5, meaning an eGFR below 15 mL/min/1.73 m².

‡Hypertension was defined following the recently updated joint guidelines from the ACC and the American Heart Association,\(^32\) here based on averaged blood pressure readings from the most recent year of follow-up, plus the list of active prescriptions in the electronic charts. Three hundred forty-one patients (92.3% of the LE-ASCVD cohort) had two or more readings in their electronic charts in this period; 28 patients (7.6%) had only one reading; and 1 patient had no available blood pressure value in the most recent year.

§Following criteria from the American Diabetes Association, HbA₁c values of 5.7%–6.4% indicate pre-diabetes, and HbA₁c ≥6.5% is diagnostic for diabetes mellitus.\(^38\) Accordingly, pre-diabetes was defined here as chart-diagnosed or the most recent HbA₁c was 5.7%–6.4%, without a diagnosis of overt diabetes on the chart. Diabetes was defined as chart-diagnosed or the most recent HbA₁c was ≥6.5%. The most recent HbA₁c value for some patients with a diagnosis of diabetes mellitus was below 6.5%; we still classified them under diabetes unless a clinician had marked the diagnosis on the chart as resolved or in remission.\(^38\)

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; LE, lupus erythematosus; PCP, primary care provider.
Cutaneous lupus

Figure 1  Assessment and management of plasma low-density lipoprotein cholesterol (LDLc) concentrations in the LE-ASCVD Study Cohort. (A) Classification of study cohort patients into the four categories of atherosclerotic cardiovascular disease (ASCVD) event risk defined by the newly proposed guidelines of Keyes et al for patients with lupus.1 Also indicated are numbers of patients with LDLc levels above (red) or within (green) the newly proposed goals for each risk category. Patients without an available LDLc value are indicated in blue. (B) Absence (red) or presence (green) of an active prescription for an LDL-lowering medication in the electronic charts of patients classified into each of the four newly proposed categories of ASCVD event risk for patients with lupus and whose most recent plasma LDLc levels were above the newly proposed goals; these are the patients indicated in red in (A). (C) Estimated risks for patients with CLE-only of an ASCVD event in the next 10 years (“10-year ASCVD event risk”) by the online ACC Risk Estimator Plus and absence (red) or presence (green) of an active prescription for an LDL-lowering medication in the electronic chart. Patients are grouped according to the cut-offs for estimated 10-year ASCVD event risk from the ACC/AHA guidelines for primary prevention of cardiovascular disease in the general population (0.0%–4.9%, 5.0%–7.4%, etc.).25 As noted in the online supplemental methods, patients below age 40 years without clinically evident ASCVD for whom we had sufficient data for the ACC ASCVD Risk Estimator Plus (n=21/180) were scaled up to 40, and patients above age 79 years without clinically evident ASCVD (n=10/180) were scaled down to 79. Data are presented with these additional patients included (here) or presented separately in their own columns (online supplemental figure S1C). Also shown here are data for patients with clinically evident ASCVD (meaning secondary prevention, for which the ACC ASCVD Risk Estimator Plus does not apply), as well as data for patients with no clinically evident ASCVD but insufficient information in the electronic chart for the ACC Risk Estimator (rightmost column). (D) Estimated 10-year ASCVD risks for patients with CLE+SLE by the online ACC Risk Estimator Plus. Labels and groupings follow (C). Data are presented with (here) or without (online supplemental figure S1D) age scaling (n=27/190 scaled up; n=5/190 scaled down). At the top of each column in panels A–D is indicated the total number of patients represented by that column. Numbers of patients represented by each tinted portion of each column are also given. CLE, cutaneous lupus erythematosus.

the new therapeutic goals for each of these categories of ASCVD event risk for patients with LE.1

We found that almost one-quarter of patients with LE classified at high risk for an ASCVD event had plasma LDLc concentrations that were above the newly recommended ranges (n=12/54, 22.2%; red in the leftmost column of figure 1A). More strikingly, approximately three-quarters of patients with LE classified at either very high risk (199/262, 76.0%) or extreme risk (38/54, 70.4%) for an ASCVD event also had plasma LDLc concentrations above the newly recommended ranges (red in the middle two columns of figure 1A). For the 249 patients with LE whose most recent LDLc value was above-goal, the time elapsed since that above-goal LDLc was 36 months (IQR 13–95), that is, 3 years (online supplemental table S1). Data for non-HDLc levels were similar: 14.8% (8/54), 66.4% (174/262) and 64.8% (35/54) of our patients with LE in these three categories of ASCVD event risk had values above the newly recommended ranges (online supplemental figure S1A).

Regarding lipid/lipoprotein management in primary prevention, nearly all high-risk patients with out-of-range LDLc levels were not on any LDL-lowering medications recorded in their charts (n=11/12), and 69.3% (n=138/199) of very high-risk patients with out-of-range LDLc levels were not on any LDL-lowering medications (figure 1B). Again, data for non-HDLc levels were similar: 87.5% (7/8) and 70.7% (123/174) of patients with LE in these two categories of ASCVD event risk with out-of-range non-HDLc levels were not on any LDL-lowering medications (online supplemental figure S1B). Thus, over two-thirds of patients with LE classified at high or very high ASCVD event risk with out-of-range LDLc or non-HDLc values according to the newly published guidelines were on no LDL-lowering medications.
Of the 54 patients with LE classified at extreme ASCVD event risk (secondary prevention), fewer than one in five achieved plasma concentrations of LDLc (7/54, 13.0%) or non-HDLc (10/54, 18.5%) within the new goals. Approximately half were untreated by the new guidelines, meaning on LDL-lowering medications but still with out-of-range values for LDLc (28/54, 51.9%) or non-HDLc (25/54, 46.3%). About 20% were untreated, meaning out-of-range values for LDLc (10/54, 18.5%) or non-HDLc (also 10/54, 18.5%) yet on no LDL-lowering medications. The remainder of patients with LE classified at extreme ASCVD event risk had no LDLc (9/54, 16.7%) or HDLc (also 9/54, 16.7%) values available from the charts despite documentation of clinically evident ASCVD, the key requirement for this risk category.

We used the ACC ASCVD risk estimator plus\textsuperscript{24, 25} to estimate the risk of an ASCVD event in the next 10 years (‘10-year ASCVD event risk’) for all patients in the LE-ASCVD Study Cohort meeting the criteria of no clinically evident ASCVD (primary prevention, n=316/370, 85.4% of the study cohort; figure 1A, table 1), with sufficient available clinical data to allow use of this online risk estimator (n=278), and ages 40–79 years, a stated requirement for this online calculator to estimate 10-year ASCVD event risks (n=215). By performing age scaling as described in the online supplemental methods, we included an additional 48 patients below the age of 40 years (13.0% of the LE-ASCVD Study Cohort) and 15 patients above 79 years (4.1% of the study cohort) without clinically evident ASCVD and with sufficient data for this online ASCVD event risk estimator, to analyse the entire subset of 278 patients just mentioned, that is, nearly 90% of the LE-ASCVD Study Cohort who had no clinically evident ASCVD (278/316, 88.0%).

Data relevant to our estimates of 10-year ASCVD event risk in the study cohort are shown in figure 1C (patients with CLE-only, n=180/370) and figure 1D (patients with CLE+SLE, n=190/370). The first four columns of figure 1C and the first four columns of figure 1D display data for the entire subset of 278 patients, stratified by estimates of their 10-year ASCVD event risk from the ACC ASCVD Risk Estimator Plus following the cut-offs of Arnett et al\textsuperscript{2} in the ACC/AHA guidelines for primary prevention of cardiovascular disease in the general population—namely, 0.0%–4.9% estimated 10-year ASCVD event risk (low), 5.0%–7.4% (borderline), 7.5%–19.9% (intermediate) and ≥20% (high).

Of the patients with an estimated 10-year ASCVD event risk of 7.5% to 19.9% from the ACC ASCVD risk estimator plus, over half were not on any LDL-lowering medication (n=23 out of 41 in figure 1C, and n=25 out of 37 in figure 1D). Of patients with an estimated 10-year ASCVD event risk ≥20%, 31.8% of patients with CLE-only and 63.6% of patients with CLE+SLE were not on an LDL-lowering medication recorded in the chart, although the total number of patients with CLE+SLE in this estimated risk stratum was low (n=11, figure 1D). Online supplemental figure S1C (CLE-only) and S1D (CLE+SLE) shows nearly identical results from the original subset of 215 patients with LE with no clinically evident ASCVD, sufficient data for this online risk estimator, and aged 40–79 years with no age scaling.

Our visual comparison of the first four columns of figure 1C versus figure 1D suggested that patients from the CLE-only subgroup who were eligible for the online ACC Risk Estimator of 10-year ASCVD event risk (ie, primary prevention) were skewed away from 0.0%–4.9% estimated 10-year ASCVD event risk and towards the stratum of ≥20.0%, compared with eligible patients with CLE+SLE. To test this impression, we computed means±SDs of the estimates of 10-year ASCVD event risk across eligible patients with CLE-only versus eligible patients with CLE+SLE (ie, across the first four columns in figure 1C vs figure 1D). This analysis showed significantly higher conventionally estimated 10-year ASCVD event risk in primary-prevention patients from the CLE-only subgroup (10.28%±11.45%, which is above Arnett et al’s key cut-off of 7.5%\textsuperscript{25}) than from the CLE+SLE subgroup (7.25%±9.57%, which is below 7.5%; n=133 and 145, respectively; p between the subgroups by Student’s unpaired two-tailed t-test=0.017). Data on rates of untreated hypertension and tobacco smoking between the CLE-only and CLE+SLE subgroups, presented below, support this finding. In contrast, the prevalence of clinically evident ASCVD in the CLE-only subgroup and in the CLE+SLE subgroup were similar, at 13.9% (25/180, figure 1C) and 15.3% (29/190, figure 1D), respectively.

Of the patients with LE who already have clinically evident ASCVD and are therefore candidates for secondary prevention of ASCVD events, 28.0% of patients with CLE-only (7/25 in figure 1C) and 31.0% of patients with CLE+SLE (9/29 in figure 1D) were not on any LDL-lowering medication; these figures comprise extreme risk patients on no LDL-lowering medication who have either (1) no LDLc value available (5 out of 9 from figure 1A), (2) the most recent LDLc value within goal (1 out of 7 from figure 1A) or (3) the most recent LDLc value above goal (10 from figure 1B).

Online supplemental figure S1E shows data for patients in the LE-ASCVD Study Cohort stratified by their most recent plasma LDLc concentrations, and then within each LDLc concentration range, we indicate treatment, or not, with an LDL-lowering medication. In each LDLc concentration range, except for the lowest (≤70mg/dL) and the highest (≥190mg/dL), over 60% of our patients with LE were on no LDL-lowering medications. There was no LDLc value available in the chart for 45 patients (12.2% of the entire LE-ASCVD Study Cohort), nearly all of whom were on no LDL-lowering medications (n=39/45, 86.7%). Online supplemental figure S1F shows data from stratifying patients with LE by their most recent plasma non-HDLc concentrations. Similar to our findings with LDLc, in each concentration range of non-HDLc, except for the lowest (<80mg/dL) and the highest (≥220mg/dL), over 60% of patients with LE were on no
Cutaneous lupus

Assessments and management of hypertension

As noted above, almost three-quarters of the LE-ASCVD Study Cohort had hypertension (266/370; table 1). Rates were similar in patients with CLE-only (n=125/180, 69.4%, figure 2A) and in patients with CLE+SLE (n=141/190, 74.2%, figure 2B). Of the 266 hypertensive patients in our LE-ASCVD Study Cohort, approximately one-fourth were well managed, meaning normotensive on antihypertensive medications (68/266, with similar rates for CLE-only and CLE+SLE; green in each leftmost column of figure 2A,B). Almost one-half were undertreated, meaning on antihypertensive medications but still hypertensive (122/266 overall, with 47/125 CLE-only, 37.6%, and 75/141 CLE+SLE, 53.2%; green in each middle column of figure 2A,B). Almost one-third were untreated, meaning hypertensive yet on no antihypertensive medication, a problem that seems more prevalent in patients with CLE-only (76/266 overall, with 48/125 CLE-only, 38.4%, and 28/141 CLE+SLE, 19.9%; red in each middle column of figure 2A,B). These data indicate that hypertension is a common but undermanaged problem in patients with cutaneous LE, without or with concurrent systemic LE, consistent with recently published literature using these blood pressure cut-offs in cardiovascular risk assessment and management of patients with SLE.17

Smoking status and management

Figure 2C,D indicates the prevalence and management of tobacco smoking in the LE-ASCVD Study Cohort for patients with CLE-only and CLE+SLE, respectively. Of the former smokers in our cohort, the overwhelming majority quit smoking without any documentation in the chart of smoking cessation counselling or referral to a specialised smoking cessation clinic. Similarly, the overwhelming majority of current smokers have no documentation in their charts of smoking cessation counselling or clinic referral. Consistent with prior literature,3–5 never-smokers were a somewhat lower percentage (47.2%) of the CLE-only subgroup than the CLE+SLE subgroup (58.9%; blue columns in figure 2C,D).

Assessments and management of glycated haemoglobin (HbA1c) and plasma triglyceride levels

Just over half of the patients in the LE-ASCVD Study Cohort had their HbA1c levels checked at least once, with a median time elapsed time of 36 months since the last assay, that is, 3 years (online supplemental table S1). As with lipid/lipoprotein values, PCPs checked just over 60% of the most recent HbA1c levels, and non-PCPs checked

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**Figure 2**  Assessment and management of blood pressure (BP) and smoking, key exacerbators of atherosclerotic cardiovascular disease (ASCVD) event risk, in the LE-ASCVD Study Cohort. (A) Prevalence and management of hypertension for patients with CLE-only (n=180). Under treated or untreated hypertension was defined by a systolic BP ≥130 and/or a diastolic BP ≥80 mm Hg, indicated here as ‘BP≥130/80 mm Hg’. Red indicates patients with no record of an active prescription for an antihypertensive medication in the electronic chart; green indicates patients on at least one antihypertensive medication. (B) Prevalence and management of hypertension for patients with CLE+SLE (n=190). Labels and groupings follow (A). (C) Prevalence and management of tobacco smoking for patients with CLE-only. Red indicates patients with no chart documentation of either smoking cessation counselling or a referral to a smoking cessation clinic; green indicates patients with a record of one or both of these interventions. Data from never-smokers are also shown (blue). (D) Prevalence and management of tobacco smoking for patients with CLE+SLE. Labels and groupings follow (C). CLE, cutaneous lupus erythematosus.
the rest. Of the non-PCPs, rheumatologists checked HbA1c levels in more patients than did other subspecialists (online supplemental table S1).

Online supplemental figure S2A shows assessment, or not, of HbA1c values in the LE-ASCVD Study Cohort after stratification by obesity and/or current or previous glucocorticoid (GC) use, two common factors in patients with lupus that impair glycaemic control. Of note, 51.0% of non-obese patients with LE on glucocorticoids, 30.6% of obese patients with LE not on glucocorticoids and 38.6% of obese patients with LE on glucocorticoids had no HbA1c value in their electronic charts (red in online supplemental figure S2A). In those three groups, 17.0%, 47.2% and 31.8% of the patients had documented pre-diabetes or diabetes (blue and yellow in online supplemental figure S2A), suggesting that obesity is a bigger driver of dysglycemia in the LE-ASCVD Study Cohort than are GCs. For comparison, the figure for non-obese patients with LE not on glucocorticoids is 23.4% (n=36/154; left-most column in online supplemental figure S2A). For patients whose most recent HbA1c value was indicative of pre-diabetes or diabetes, meaning ≥5.7%,38 the median time elapsed since that abnormal value was 48 months, that is, 4 years (online supplemental table S1).

For patients with LE with a diagnosis of pre-diabetes, almost half (33/67, 49.3%) did not meet either of the two key criteria for well-managed pre-diabetes—namely, documentation of lifestyle modification counselling or an active prescription for metformin prescription in their charts38–42 (online supplemental figure S2B). For patients with LE with diabetes, however, over three-quarters were well managed, generally defined as the most recent HbA1c ≤7%,38–42 and only 10.3% (4/39) had a most recent HbA1c >7% (online supplemental figure S2B).

Regarding triglyceride management, only 10.0% (10/100) of non-obese patients with LE on glucocorticoids, 5.6% (4/72) of obese patients with LE not on glucocorticoids and 9.1% (4/44) of obese patients with LE on glucocorticoids had no plasma triglyceride value in their electronic charts (online supplemental figure S2C). Of all patients in the LE-ASCVD Study Cohort with available triglyceride values (n=331 out of 370, 89.5%), only 0.6% had very high levels (≥2500 mg/dL) and only 6.0% had high levels (200–499 mg/dL; online supplemental figure S2C). These data indicate that hypertriglyceridaemia was not a common problem in our LE-ASCVD Study Cohort even among patients with obesity and/or glucocorticoid therapy.

Comparisons of three different systems for estimating the risk of future ASCVD events in patients with LE

We examined three systems for estimating the risk of future ASCVD events in patients with LE—namely, the newly proposed risk categories of Keyes et al, which include both primary and secondary prevention,1 and the two widely used online risk calculators, cited above, that estimate 10-year ASCVD event risk and are limited to primary prevention. To compare these systems in our LE-ASCVD Study Cohort, we focused on the subset of patients for whom both the QRisk3 and the ACC ASCVD Risk Estimator Plus could be used, meaning sufficient data in the electronic chart and no clinically evident ASCVD (n=278 out of 370 when including age scaling, ie, the same number classified by the ACC ASCVD Risk Estimator Plus in figure 1C.D, ie, 135+145). We separated these 278 patients into ‘high risk’ (n=43 out of 278; blue dots in figure 3A and online supplemental figure S3A) and ‘very high risk’ (n=235/278; yellow dots in figure 3A and online supplemental figure S3B) following the categories of Keyes et al1 None of these 278 patients with LE met the criteria for the categories of ‘Extreme Risk’ or ‘Recent Recurrent ASCVD Events’ from Keyes et al, because both of those categories require clinically evident ASCVD, hence, secondary prevention and ineligible for the QRisk3 or the ACC ASCVD Risk Estimator Plus.

Figure 3A shows estimates of each of these patient’s 10-year ASCVD event risk from the QRisk3 and from the ACC calculator. Online supplemental figure S3A shows both estimates of 10-year ASCVD event risk for only patients with LE who were stratified into the ‘High Risk’ category of Keyes et al, with the axes expanded for ease of viewing the data. Online supplemental figure S3B shows both 10-year ASCVD event risk estimates for only the LE patients stratified into the ‘Very High Risk’ category of Keyes et al. Online supplemental figure S3B allows an unobstructed view of the data for these very high risk patients, indicating that many of them had remarkably low estimates of 10-year ASCVD event risk from one or both of the online calculators, a point we return to in figure 3B.

To directly compare the numerical estimates of 10-year ASCVD event risk from the QRisk3 and the ACC ASCVD Risk Estimator Plus in our LE-ASCVD Study Cohort, we performed Pearson’s correlation with age scaling (figure 3A, n=278 patients) and without age scaling (online supplemental figure S3C, n=215 patients, ie, the same number classified by the ACC ASCVD Risk Estimator Plus in online supplemental figure S1C, D, ie, 102+113). Correlations were highly statistically significant, with p values of 1.48×10−52 and 5.83×10−33, respectively. Nevertheless, the r² values were surprisingly low, at 0.57 and 0.49, respectively. In other words, in our study cohort, only about half of the variation in one widely used online 10-year ASCVD risk estimate can be statistically attributed to variation in the other. Moreover, the y-intercepts were 6.3% and 7.3%, which are substantial compared with the cut-offs in the ACC/AHA guidelines for primary prevention of cardiovascular disease in the general population,25 and indicate generally higher 10-year ASCVD risk estimates from the QRisk3 than from the ACC ASCVD Risk Estimator Plus, particularly at the latter’s lower end. Visual inspection of figure 3A and online supplemental figure S3A–C demonstrates this point as well.

We also conducted these analyses for patients with CLE-only and for patients with CLE+SLE separately (online supplemental figure S4A, B). Of note, the correlation
between values from the QRisk3 and the ACC Risk Estimator Plus was much better for the CLE-only subgroup than for CLE+SLE ($r^2$ values were 0.774 and 0.502, respectively, both with age scaling; $r^2$ and $p$ values for the correlations were only slightly affected by excluding age scaling). The y-intercepts also differed, at 2.93% and 9.32%, respectively.

**Figure 3B** indicates clinically meaningful agreement (green) and discordance (red, white) among the three systems for estimating the risk of a future ASCVD event for individual patients in the LE-ASCVD Study Cohort. We compared the two online calculators with the newly proposed categories of ASCVD event risk for patients with LE from Keyes et al by using the key cut-off of 7.5% estimated 10-year ASCVD event risk from the ACC/AHA guidelines for primary prevention of cardiovascular disease in the general population.**25** Pearson’s linear correlation was used to test the statistical relationship between the two numerical estimates of 10-year ASCVD event risk, and the calculated regression line is indicated in dashed red with key parameters given on the right. (B) Clinically meaningful agreement (green) and discordance (red, white) among the three systems for estimating the risk of a future ASCVD event for individual patients in the LE-ASCVD Study Cohort. The two pie charts tabulate patients with LE at ‘High Risk’ as defined by Keyes et al (n=43/278) and at ‘Very High Risk’ (n=235/278). Green indicates clinically meaningful agreement, defined here as classification of a patient with LE into the ‘High Risk’ or ‘Very High Risk’ categories of Keyes et al, with estimates of 10-year ASCVD event risk ≥7.5% from both of the online calculators. Red indicates clinically significant discordance between the two online calculators, meaning one estimate of 10-year ASCVD event risk <7.5% but the other ≥7.5% for the same patient with LE. White indicates discordance between Keyes et al versus both of the online risk estimators, that is, these patients are at high or very high risk according to Keyes et al, yet both online calculators gave estimates of 10-year ASCVD event risk <7.5%. Numbers of patients represented by each portion of each pie chart are given in the small filled black rectangles.
the online calculators. Red indicates clinically significant discordance between the two online calculators, meaning one estimate of 10-year ASCVD event risk <7.5% but the other ≥7.5% for the same patient with LE. White indicates discordance between Keyes et al versus both of the online risk estimators, that is, these patients are at high or very high risk according to Keyes et al, yet both online calculators gave estimates of 10-year ASCVD event risk <7.5%. By these definitions of clinically meaningful agreement and discordance, the three systems for estimating the risk of a future ASCVD event were in agreement for only 109 of the 278 patients with LE (39.2%), that is, discordance for almost two-thirds of patients with LE that could affect their clinical management. Online supplemental figure S3D shows similar findings for the 215 patients with LE without age scaling.

Clinically documented ASCVD events and actual 10-year ASCVD event rate in the LE-ASCVD Study Cohort

Because of discordances among the three systems for estimating ASCVD event risk in our primary-prevention patients (figure 3, online supplemental figure S3), we sought to determine the actual 10-year ASCVD event rate in patients who were enrolled into the LE-ASCVD Study Cohort without clinically evident ASCVD, that is, in primary prevention. Figure 4 shows the Kaplan-Meier curve of event-free survival, with 95% CIs, since enrolment. For completeness, online supplemental figure S5 shows the cumulative incidence of all documented MAACE in our LE-ASCVD Study Cohort, including the period before enrolment (indicated at time 0) and then all first MAACE after enrolment (time >0). Table 2 gives a breakdown of the types of MAACE. To test a possible association of skin disease activity with ASCVD events in our study cohort, we compared scores from the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) that were available for patients with an ASCVD event (median 15, IQR 6–22, n=49) versus without an event (median 13, IQR 6–26, n=277) and found no statistically significant difference (p by the unpaired Wilcoxon rank-sum test=0.91).

The rate of ASCVD events for patients in the first 10 years after enrolment into our LE-ASCVD Study Cohort was calculated as one minus the event-free survival at the 10-year time point of the Kaplan-Meier survival curve (figure 4). Thus, the 10-year ASCVD event rate was 13.5% (95% CI 8.9%, 17.9%). The 10-year ASCVD events rates calculated separately for patients with CLE-only and patients with CLE+SLE were similar, at 13.2%
rates are well above Arnett’s key cut-off of 7.5%, indicating an at-risk population.

These 10-year ASCVD event rates in our LE-ASCVD Study Cohort are even more striking, given the preponderance of women and the patients’ relative youth at enrolment (table 1). For comparison, the ACC ASCVD Risk Estimator Plus gives an estimate of 10-year ASCVD event risk of 13.5% for a 47-year-old woman if she has a combination of diabetes, current smoking, treated hypertension, an HDLc of 40 mg/dL and a non-HDLc of 196 mg/dL if Caucasian and 131 mg/dL if African-American. These results support the use of guidelines that treat lupus as a diabetes-equivalent in the context of ASCVD event risk.

### DISCUSSION

Our results indicate that patients with CLE are undertreated compared with the new guidelines for conventional therapeutic targets to prevent ASCVD events and, accordingly, these patients experience a significant burden of major adverse ASCVD events despite our youngish, predominantly female LE-ASCVD Study Cohort. Moreover, current methods give discordant estimates of the risk for future ASCVD events, possibly because the online risk calculators were not designed specifically for patients with CLE. Thus, for patients with cutaneous LE, it is unclear how to accurately assess their future ASCVD event risk—except that it is substantial—and this uncertainty may complicate clinical management.

Management of ASCVD event risk has become a major issue in LE because of therapeutic success: patients with lupus are now much less likely to die prematurely from lupus directly or from infections, and so they are living long enough to develop clinically significant atherosclerotic cardiovascular disease.

Specific areas of current concern include under-management of plasma LDLc, non-HDLc and presumably apoB levels to the new guidelines; under-administration or non-administration of LDL-lowering therapies in primary and even secondary prevention; under-management of hypertension to recently revised blood pressure goals; under-use of resources for smoking cessation; infrequent or absent monitoring of LDLc and HbA1c levels; infrequent monitoring even of above-goal values; under-management of pre-diabetes; and, as noted above, clinically meaningful discordances in estimates of the risk for future ASCVD events and substantial 10-year ASCVD event rates. Areas of current success include high levels of linkage with a PCP; evidence of widespread awareness among PCPs and subspecialists of conventional therapeutic targets for management of ASCVD event risk; generally well-managed diabetes mellitus; and a low prevalence of hypertriglyceridaemia in the LE-ASCVD Study Cohort even in patients with obesity and/or GC use.

Our findings add to a growing literature emphasising the gaps between typical or usual real-world care versus ideal guideline-based care in the management of ASCVD event risk in patients with lupus and in non-autoimmune populations, even ones at high risk. Several studies have looked at rates of cardiovascular events in CLE cohorts. To our knowledge, however, ours is the first study to focus on the management of ASCVD event risk in CLE, although there is a prior literature in SLE. In one published study, a large proportion of a cohort of 110 patients with SLE had indications for statins for primary or secondary prevention, but only about half of them were treated to guidelines. In a recently reported cohort of 1532 patients with SLE, 639 had hypertension defined by the new cut-offs of ≥130/≥80 mm Hg or on antihypertensive medications, but approximately three-quarters of these hypertensive patients with SLE (471/639, 73.7%) were undertreated or untreated, nearly identical to our figure of 74.4%

<table>
<thead>
<tr>
<th>Type of MAACE</th>
<th>Number affected (% of the 370 patients in the LE-ASCVD Study Cohort)</th>
<th>Time from enrolment to event in years, given as median (IQR); and number of events (n)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal atherosclerotic MI</td>
<td>14 (3.8%)</td>
<td>6.5 (4–11); n=12</td>
</tr>
<tr>
<td>Newly diagnosed ischaemic heart disease other than MI</td>
<td>31 (8.4%)</td>
<td>8.0 (5–13); n=25</td>
</tr>
<tr>
<td>Atherosclerotic (non-embolic) ischaemic stroke or transient cerebrovascular ischaemic attack</td>
<td>15 (4.1%)</td>
<td>11.0 (7–14); n=10</td>
</tr>
<tr>
<td>Newly diagnosed symptomatic peripheral vascular disease (PVD)</td>
<td>3 (0.8%)</td>
<td>5.0; n=3</td>
</tr>
<tr>
<td>Any MAACE</td>
<td>54 (14.6%)</td>
<td>9.0 (5–13); n=36</td>
</tr>
</tbody>
</table>

*Any patient who experienced two or more MAACE before and since enrolment was counted only once in any given row but was counted in two or more rows if the types of MAACE differed. Thus, the sum of the numbers of patients affected by each specific type of MAACE (63 total, 50 since enrolment) is slightly larger than the number of patients affected by any MAACE (54 total, 36 since enrolment).

†Time and n in this column exclude the 14 events that were documented in patients with lupus before their enrolment in the LE-ASCVD Study Cohort. IQRs are given for each type of MAACE only if n≥6.

MAACE, major adverse atherosclerotic cardiovascular event; MI, myocardial infarction.

(198/266, figure 2A,B). Moreover, patients with lupus with blood pressures in the newly defined range for stage 1 hypertension, meaning 130–139/80–89 mmHg, had more than twice the rate of atherosclerotic cardiovascular events than did normotensive patients with lupus during a decade or so of follow-up. In other SLE cohorts as well, persistent hypertension has been associated with a much higher incidence of ASCVD events, compared with ASCVD event rates in normotensive patients with SLE.

A noteworthy finding from our study was the similarity in 10-year ASCVD event rates in patients with CLE-only and in patients with CLE+SLE (online supplemental figure S6A, B). Moreover, the prevalence of clinically evident ASCVD was also similar between the two subgroups (figure 1C,D). These findings emphasise that skin-only lupus should prompt earlier and more aggressive assessment and management of ASCVD event risk. Several factors may have contributed to this similarity in incidence and prevalence of ASCVD events between these two key subgroups. First, we found that primary-prevention patients in the CLE-only subgroup had substantially higher average conventional estimates of 10-year ASCVD event risk than did the primary-prevention patients in the CLE+SLE subgroup. Thus, it may be that patients with CLE-only have a greater burden of conventional ASCVD risk factors, meaning causative agents and non-autoimmune exacerbators, whereas patients with CLE+SLE have a greater burden of LE. Previous reports of high rates of tobacco smoking in patients with CLE, along with our own data on smoking, show the same pattern. Second, once a patient in our study Cohort had a diagnosis of CLE, it did not take much systemic involvement to qualify for SLE. Accordingly, the average SLEDAI scores in the CLE+SLE subgroup were 2.36±3.68 (online supplemental table S1). This average is lower than some benchmarks in the SLE literature, for example, a SLEDAI score ≥6.0 is often considered clinically important to affect the decision to treat systemic disease, and increases or decreases ≥1 are considered meaningful. On the other hand, in our CLE+SLE subgroup, the rate of lupus nephritis was 22.1% (table 1) and of APS was 11.6% (online supplemental table S1), indicating a substantial minority with severe forms of systemic disease that are known to be directly relevant to cardiovascular health. Third, close monitoring of patients with CLE-only for the development of new SLE may have meant that their SLE would have been caught earlier and treated earlier than usual.

In non-autoimmune populations, treatment of therapeutic targets to manage ASCVD event risk, particularly hypercholesterolaemia and hypertension, remains suboptimal in the USA and worldwide. Particularly striking are under-utilisation of evidence-based LDL-lowering and blood pressure-lowering medications in patients with diabetes mellitus, even when those patients are at extreme ASCVD event risk owing to the additional presence of clinically evident atherosclerosis (secondary prevention) on top of their type 2 diabetes.

Reasons for this widespread pattern of undertreatment might stem from prioritisation of immediate clinical problems over long-term care, difficulties for patients and providers in sustaining long-term treatment for subclinical conditions, time needed to disseminate and implement recent guidelines, access to care, the difficulties of polypharmacy, evidence-based and non-evidence-based concerns from patients and providers over potential side effects, and lifestyle and medication adherence. Further research is needed so that rational strategies can be developed to address under-management of ASCVD event risk.

Among conventional therapeutic targets in the management of ASCVD event risk, levels of LDLc, non-HDLc and apoB can be managed without great concern of a lower limit using current agents, in contrast to blood pressure or plasma glucose levels. Conventional interventions to assist smoking cessation and to manage pre-diabetes also come with few risks.

Notably, our results emphasise the need to clarify how to appropriately assess the risk of future ASCVD events in patients with CLE. We demonstrated discordance among the three systems that we used: the new risk classifications from Keyes et al specifically for patients with lupus, the ACC ASCVD Risk Estimator Plus, and the QRisk3 calculator. A similar discordance between the Framingham Risk Score and QRisk3 was recently reported for patients with SLE in one study but less so in another study with a far smaller cohort. As a statistical matter, multiplying the 10-year estimate from the ACC Risk Estimator Plus by 1.5, as has been proposed, would not improve the r² value of the correlation with QRisk3. Recent reports suggest that QRisk3 may be a better predictor for patients with lupus than other estimators of future ASCVD event risk. This point might be particularly important for patients with CLE+SLE, for whom the QRisk3 and ACC Risk Estimator Plus showed a weaker correlation and a higher y-intercept than for patients with CLE-only (online supplemental figure S4A, B). Taken together, prior literature and our current work emphasise the need to compare different ASCVD risk assessments against the gold standard, meaning actual ASCVD events that occur over the ensuing decade. Such a study might be feasible retrospectively on longstanding well-documented longitudinal cohorts of patients with lupus.

Additional clinical parameters that may enhance assessment of ASCVD event risk in patients with lupus may include plasma apoB measurements, one-time assessments of plasma lipoprotein (a) levels, which are still largely genetically determined, and arterial imaging to detect subclinical plaque by iliofemoral or carotid ultrasoundography or MRI; coronary, iliofemoral, or carotid CT angiography; and in older patients coronary artery calcium scores.

Study limitations and strengths

Study limitations include the retrospective design, from a single medical centre. In our database, like many others, there are possible inaccuracies in smoking status because assays of cotinine, a recognised marker of nicotine use, are not part of routine care. Lifestyle modifications or medications discussed at a clinic visit but not

entered into the charts could indicate a different level of management. In addition, the standard of care for diabetes testing includes assays besides HbA1c, such as fasting glucose levels, oral glucose tolerance tests, and random plasma glucose levels, which may also be used to diagnose and assess pre-diabetes and diabetes. As noted in online supplemental figure S2A, many patients in our LE-ASCVD Study Cohort had no available HbA1c values, which affects our statistics on prevalence of pre-diabetes and diabetes and their management.

Study strengths include a well-characterised longitudinal cohort followed for over 14 years, with key parameters available in the electronic charts. Our LE-ASCVD Study Cohort included all patients in the parent longitudinal cohort for whom we had full access to medical records; thus, we obtained what should be an accurate snapshot of real-world clinical care. The study assessed all available conventional therapeutic targets in managing ASCVD event risk, which has not been previously done in a comprehensive manner in patients with CLE. Moreover, our results identified specific, key issues in clinical management and decision-making.

CONCLUSIONS

Patients with cutaneous LE, without or with systemic LE, are undertreated compared with the new guidelines and, accordingly, they experience a significant burden of ASCVD events. Moreover, it is unclear how to accurately assess future ASCVD event risk in these patients—except that it is substantial—and this uncertainty may complicate clinical management. Based on our findings, efforts are now underway to improve ASCVD event risk estimation and guideline implementation in patients with CLE-only and in patients with CLE+SLE.

Author affiliations

1Corporal Michael J. Crescenz Veterans’ Administration Medical Center, Philadelphia, Pennsylvania, USA
2Department of Dermatology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
3Department of Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania, USA
4Department of Cardiovascular Sciences, Department of Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA

Twitter Megan Zhao @meganzhao0505 and Kevin Jon Williams @werthlab

Contributors: Contributions: MZ, VPW and KJW were involved in conceptualising the project, writing the manuscript and editing the manuscript. MZ was responsible for data collection, and MZ and KJW were responsible for data verification. MZ, RF and KJW were responsible for data analysis; MZ, VPW, KJW are guarantors.

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ORCID iDs

Megan Zhao http://orcid.org/0000-0002-8005-9111
Rui Feng http://orcid.org/0000-0003-4151-7228
Victoria P Werth http://orcid.org/0000-0003-3030-5369
Kevin Jon Williams http://orcid.org/0000-0002-0000-2159

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