Management of cardiovascular complications in systemic lupus erythematosus

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Patients with SLE have an excess risk compared with the general population; this is particularly pronounced in younger women with SLE who have an excess risk of over 50-fold compared with population controls. There is a higher prevalence of subclinical atherosclerosis in patients with SLE compared with controls, as demonstrated by a variety of imaging modalities discussed in this review. The causality of the excess risk of CVD and subclinical atherosclerosis is multifactorial in patients with SLE. While traditional risk factors play a role, after controlling for the traditional Framingham risk factors, the excess risk is still 7.5-fold greater than the general population. This review will also cover novel cardiovascular risk factors and some SLE-specific variables that contribute to CVD risk. This review discusses the risk factor modification and the evidence available for treatment of these risk factors in SLE. There have not yet been any published randomized, controlled trials in patients with SLE with respect to CVD risk factor modifications. Thus, the treatment and management recommendations are based largely on published guidelines for other populations at high risk for CVD.

KEYWORDS: cardiac imaging ■ cardiovascular disease ■ cardiovascular risk factors ■ subclinical atherosclerosis ■ systemic lupus erythematosus

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In the last few decades, the prognosis of patients with systemic lupus erythematosus (SLE) has improved immensely. In the 1950s, the 5-year survival rate for SLE was approximately 50% according to a study performed in Toronto, Canada. Subsequent studies have found 5-year survival rates of 90% in patients with SLE [1]. A bimodal mortality pattern was first described in 1976 by Urowitz *et al.* in the Toronto Lupus cohort. Septicemia in the setting of high-dose prednisone was identified as an early cause of death in patients with more active SLE. Later in the disease course, death was associated with inactive SLE, long duration of prednisone therapy and myocardial infarction (MI) due to atherosclerotic heart disease [2]. More recent data from a large international cohort revealed a 60% decrease in the standardized all-cause mortality rates (SMR) from 1970–1979 (SMR: 4.9) to 1990–2001 (SMR: 2.0). However, the SMR trend for cardiovascular disease (including heart disease, arterial disease and stroke) did not decline from 1970 to 2001 [3]. A Swedish cohort followed from 1964 to 1994 demonstrated similar findings of improved overall survival for patients with SLE over the last two decades, but the risk of cardiovascular death remained (by 1985–1994 hazard ratio [HR] for risk of death by cardiovascular disease [CVD] event was 0.92; 95% CI: 0.72–1.18 compared with 1975–1984 HR: 0.88; 95% CI 0.72–1.06; while the 1985–1994 HR for risk of death attributed to SLE was 0.35; 95% CI: 0.26–0.48 compared with the 1975–1984 HR: 0.55; 95% CI: 0.43–0.70) [4].

This review will discuss the increased risk of CVD observed in patients with SLE, the role of traditional cardiovascular risk factors, the role of novel risk factors (some of which are lupus specific) and the imaging modalities used to identify patients at risk. We will conclude with a review of available treatments and management recommendations.

Scope of the problem

■ Premature onset of cardiovascular risk factors (& events)

Cardiovascular risk factors develop early in the course of SLE and in younger patients compared with the general population. An international inception cohort of 918 SLE patients in the Systemic Lupus International Collaborating Clinics (SLICC) Registry already presented with classic CVD risk factors (33% with hypertension and 36% with hypercholesterolemia) within 5.4 months of diagnosis of SLE, where the populations mean age at time of SLE diagnosis was 34.5 years [5]. Early onset and young age have also been observed in other longitudinal cohorts. In the Toronto Lupus Clinic, 75.4% of patients with SLE had developed hypercholesterolemia within

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3 years of diagnosis of SLE [6]. In the Hopkins Lupus Cohort, 53% of patients already had three or more known cardiovascular risk factors when the average patient age was only 38.3 years [7] (representative studies are listed in TABLE 1). Further discussion of the role of traditional cardiovascular risk factors will follow below.

A similar trend regarding increased occurrence of cardiovascular events (angina, MI or sudden death), especially among young patients with SLE, has been found. The frequency of cardiovascular events in two representative cohorts ranges from 6.6 to 8.3% [8,9]. In addition, patients with SLE have cardiovascular events at a much younger age compared with the general population. When the California Hospital Discharge Database was examined, women with SLE aged 18–44 years were 2.27-times more likely to be hospitalized for an acute MI compared with controls in the same age group. By multiplying the proportionate morbidity ratio for acute MI by the hospitalization frequency ratio between women with and without SLE, hospitalization due to acute MI was 8.5-times more common in patient with SLE aged 18–44 years [10]. Manzi *et al.* reported a 52.4-fold increased risk of MI in women with SLE aged 35–44 years and a 4.2-fold increase in women with SLE aged 55–64 years compared with women in the Framingham Offspring Study [9]. Having a cardiovascular event at a younger age has been demonstrated in many other SLE populations (representative studies listed in TABLE 2) [11,12]. It is important to note the small numbers of patients in each of these respective cohorts highlighted in TABLE 2. Compared with patients with HIV who have a large prospective, observational study that collects information on medication-related cardiovascular events in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) database [13,14], there is a lack of a large prospective cohort data for CVD events in patients with SLE (where the CVD risk is multifactorial). The SLICC international inception cohort, which is an ongoing study, may be able to address this knowledge gap in the future.

In addition to the increased risk for CVD at an early age, SLE patients have a higher risk of in-hospital mortality and prolonged hospitalization following MI compared with patients with a history of diabetes or patients without either disease [15].

Unaccounted for risk

When Bruce *et al.* compared 250 patients with SLE and 250 controls (mean age: 44.8 ± 12 years and 44.3 ± 15 years, respectively), the 10-year risk of CV-related events using the Framingham calculator was the same regardless of the higher prevalence of traditional risk factors in patients with SLE [16]. These findings confirmed an earlier retrospective outcome analysis performed by Esdaile *et al.* that demonstrated a 7.5-fold increase (95% CI: 5.1–10.4) in overall coronary heart disease (CHD; fatal and nonfatal MI) in SLE compared with the expected number predicted by traditional Framingham risk factors [17]. These studies suggest that SLE itself carries an independent risk for CVD in addition to the role of the traditional cardiovascular risk factors. The Framingham risk score uses age, sex, smoking, blood pressure (BP), cholesterol concentrations and diabetes to estimate the risk of coronary events and to stratify individuals into risk categories in order to determine prognosis and the need for clinical intervention [18,19]. The Framingham risk score calculator weighs advancing age heavily and probably overlooks the elevated risk in young patients with SLE who have developed CVD. There is no specific risk score calculator available for patients with SLE.

Imaging modalities

It is this early CVD risk factor development and the young age for cardiovascular events in patients with SLE, compounded by the stable rate of cardiovascular death over time [3,4], that has led to the search for methods to detect premature atherosclerotic disease and to monitor progression and regression of subclinical atherosclerosis. Many imaging modalities have been validated in the general population and young CVD at-risk populations, and have subsequently been studied in patients with SLE as described below. However, there is minimal CVD event information linked to the detection of subclinical atherosclerosis in patients with SLE.

B-mode carotid ultrasound

B-mode carotid ultrasound has been studied in the general population and has measured plaque index and intima-media thickness (IMT). Multiple studies have demonstrated an increasing incidence of cardiovascular events with the presence of plaque and the presence of increased IMT [20,21]. The reliability and reproducibility of these measurements has been verified in studies in the general population [22,23]. These measurements have been studied in young at-risk populations, such as children with familial hypercholesterolemia and insulin-dependent diabetes mellitus. These patients already developed increased IMT and carotid plaque compared

Table 1. Cardiovascular disease risk factors present in patients with systemic lupus erythematosus.

Author	Location	N	Study design	Risk factor and frequency (%)	Mean age at study inclusion	Mean age SLE diagnosis	Mean SLE disease duration at study inclusion	Ref.
Petri *et al.* (1992)	Baltimore, MD, USA	225	Prospective	Hypertension by questionnaire (48); hypertension treated (41); hypercholesterolemia (56); obesity by NHANES (38); obesity self report (56); smoker ever (56); smoker current (35); sedentary lifestyle (70); diabetes mellitus (7)	38.3 ± 12.1 years	NA	8.1 ± 6.9 years	[7]
Manzi *et al.* (1997)	Pittsburgh, PA, USA	33 with CVD, 465 without CVD	Prospective	With CVD: hypertension (72); hypercholesterolemia (18); diabetes (12); family history CVD (36); postmenopausal (48); renal disease (30); smokers ever (57); Without CVD: hypertension (63); hypercholesterolemia (4); diabetes (5); family history CVD (32); postmenopausal (29); renal disease (21); smokers ever (53)	NA NA	With CVD: 39 years; Without CVD: 34 years	With CVD: 13 years; Without CVD: 10 years	[9]
Svenungsson *et al.* (2001)	Sweden	26 with CVD, 26 without CVD	Cross-sectional	With CVD: smokers ever (77); diabetes mellitus (12) Without CVD: smokers ever (65); diabetes mellitus (4)	With CVD: 52.2 ± 8.2 years; Without CVD: 52.2 ± 8.2 years	NA NA	With CVD: 20.0 ± 9.9 years; Without CVD: 18.5 ± 9.5 years	[123]
Bruce *et al.* (2003)	Toronto, Canada	250	Prospective	Hypertension (33); hypercholesterolemia (34); low HDL-C < 35 mg/dl (13); smoker (17); diabetes mellitus (5); family history CVD (20); renal disease ever (71); nephrotic syndrome ever (10)	44.5 ± 12 years	30.9 ± 11.3 years	13.7 ± 9.7 years	[16]
Selzer *et al.* (2004)	Pittsburgh, PA, USA	214	Prospective	Hypertension (36); smoker (13.1); postmenopausal (43.5); renal disease (10.3)	45.2 ± 9.0 years	NA	9.1 years	[54]
Toloza *et al.* (2004)	AL, TX, PR, USA	546	Longitudinal	Sedentary lifestyle (59); smokers (13.6); family history of CVD (3.7); morbid obesity (15.3); diabetes mellitus (2.7); hypertension (34.6); hypercholesterolemia (23.9); low HDL-c < 35 mg/dl (81)	36.5 ± 12.3 years	NA	17.3 ± 16.0 months (from diagnosis to study inclusion)	[95]
Bessant *et al.* (2004)	UK	202	Cross-sectional	Hypertension (16.8); hypercholesterolemia (32.2); personal history of CVD (6.4); diabetes mellitus (1.0); smoker ever (21.2)	42.2 ± 12.2 years	NA	NA	[58]
Urowitz *et al.* (2007)	International	918	Prospective, longitudinal	Hypertension (33); hypercholesterolemia (36); diabetes mellits (3.6); postmenopausal (15); smoker current (16); family history CVD (18.2)	NA	34.1 ± 13.5 years	5.4 ± 4.1 months	[5]

Hypertension defined as >140/90 mmHg. Hypercholesterolemia defined as total cholesterol > 200 mg/dl.
CVD: Cardiovascular disease; HDL: High-density lipoprotein; NA: Not available; NHANES: National Health and Nutrition Examination Survey; SLE: Systemic lupus erythematosus.

with age-matched controls [24,25]. B-mode ultrasound has also been studied in patients with other autoimmune conditions, most notably rheumatoid arthritis (RA) and more recently in psoriatic arthritis (PsA). Patients with RA had a threefold increase in carotid atherosclerotic plaque compared with controls (44 vs 15%) even after controlling for age, cholesterol, tobacco use and hypertension [26]. After controlling for traditional cardiovascular risk factors, patients with PsA had a higher prevalence of subclinical atherosclerosis as measured by IMT [27].

Carotid IMT has been evaluated in intervention trials in the general population. The Arterial Biology for Investigation into the Treatment Effect of Reducing Cholesterol trial (ARBITER) demonstrated that patients after an acute coronary syndrome on high-dose atorvastatin demonstration reduced atherosclerosis progression and even regression of IMT over 12 months [28]. Furthermore, Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin (METEOR) was a primary prevention study that showed IMT progression could be slowed after treatment with rosuvastatin even if the 10-year Framingham risk score was less than 10% [29].

Roman *et al.* then applied B-mode ultrasound of the carotid arteries to patients with SLE and found a plaque prevalence of 37.1%, compared with 15.2% of controls [30]. A similar plaque prevalence of 40% was found by Manzi *et al.* [31]. SLE population differences in carotid plaque may exist. In contrast to the findings of Roman and Manzi, the Hopkins Lupus Cohort only found a carotid plaque prevalence of 8% [32]. The Manzi group was able to further demonstrate accelerated plaque progression over a mean 4.19-year follow-up compared with controls. This study identified carotid ultrasound as a potential surrogate marker for CVD progression to document change in CVD in future intervention trials in patients with SLE [33].

Electron beam computed tomography

Electron beam computed tomography (EBCT) has been used to assess coronary artery calcium (CAC) as a measure of subclinical CVD. The CAC value is a score associated with the number and severity of diseased vessels defined by quantitative coronary angiography. This imaging modality has also been verified in the general population without known CVD. Increasing CAC scores were associated with increasing age-adjusted rates (per 1000 person-years) of CVD events (i.e., death, nonfatal MI or coronary revascularization). Of particular interest, the presence of CAC was associated with CVD events in patients who were younger than 40 years of age in the general population, and higher CAC scores meant higher rates of events [34].

Electron beam computed tomography detects a similar prevalence (31%) of asymptomatic coronary artery calcification in patients with SLE, and also a higher calcification score compared with age-matched controls [35–37]. EBCT may be particularly useful in SLE patients who are younger since the Framingham risk calculator is less reliable in young patients with SLE as it relies heavily on age. This finding was highlighted in a study by Chung *et al.* that examined CAC scores by coronary EBCT in patients with SLE compared with controls [38]. The Framingham calculator found that 99% of SLE patients were low risk (meaning the 10-year risk estimate of cardiovascular events was < 1%), but the presence of CAC was found in 19% of patients. These patients would be inappropriately stratified if one were planning a clinical trial based on Framingham score and necessary pharmacological interventions (e.g., statin use for lipid lowering) would not be prescribed [38]. While EBCT may prove to be more useful in a young population compared with Framingham risk calculation, this imaging modality may have limited utility in patients with end-stage renal disease (ESRD) on hemodialysis. These patients have high calcification scores on EBCT, which may reflect an imbalance in the calcium-phosphorus product [39]. When studied in a Japanese population, EBCT was found to be inadequate for screening asymptomatic ESRD patients for coronary artery disease (CAD) because the sensitivity progressively decreased as the CAC increased, with the receiver operator characteristic curve accuracy reported to be approximately 0.77 [40]. Coronary EBCT may be a future modality used to classify patients with SLE based on cardiovascular risk, rather than Framingham calculations alone. However, future coronary EBCT studies will need to address the role of renal disease in SLE as part of this assessment.

Other imaging modalities

Other imaging modalities are being studied in patients with SLE, but their use is not yet widespread and their role remains to be elucidated. Myocardial perfusion defects using single photon emission CT were detected in 37.7% of SLE patients studied, and over 8.7 years of follow-up, 15 cardiovascular events occurred

(out of 122 SLE patients). By Cox modeling, the perfusion defects were strongly predictive of coronary events (HR: 13.0; 95% CI: 2.8–60.1; p = 0.001) [41]. Finally, cardiac MRI has been recently applied to SLE patients to identify areas of myocardial scarring, and it outperformed transthoracic echocardiography in detecting abnormalities [42].

Endothelial function: imaging

There is a growing body of evidence suggesting that inflammation leads to atherogenesis. An even earlier event in the pathogenesis of atherosclerosis is believed to be endothelial cell injury, resulting in endothelial dysfunction and an inflammatory response [43]. Endothelial function can be measured using brachial artery flow-mediated dilation (FMD). More specifically, this technique utilizes Doppler ultrasound of the brachial artery to measure the percentage increase in arterial diameter induced by changes in blood flow through the artery.

Measuring endothelial function has sparked recent interest because abnormalities in endothelial function have been associated with cardiovascular risk factors in the general population and in young high-risk populations [44,45]. Indeed, in a recent study in the Multi-Ethnic Study of Atherosclerosis (MESA) population, brachial FMD was used to predict incident cardiovascular events in population-based adults [46]. Furthermore, a number of intervention trials have shown improvement in endothelial function with the use of statins and angiotensin-converting enzyme (ACE) inhibitors [47,48]. Measurement of FMD may identify patients at risk for atherosclerosis at a time when it is potentially reversible [49].

Flow-mediated dilation is significantly different in SLE patients compared with controls (change of vessel diameter was 7.31 ± 5.2% vs 9.86 ± 3.87%, respectively; p = 0.013), and significantly reduced in SLE patients with cardiovascular complications compared with SLE patients without cardiovascular complications (change of vessel diameter was 5.54 ± 4.36% vs 8.81 ± 5.28%, respectively; p = 0.01) [50]. Furthermore, endothelial dysfunction remains significant in patients with SLE even after adjustment for other classic CVD risk factors. This study was also able to show that if endothelial dysfunction progressively worsened it was associated with greater IMT, providing further evidence of an association between FMD and subclinical atherosclerosis [51]. In addition, an early intervention trial in patients with SLE showed that after 8 weeks of atorvastatin, patients with or without a history of CVD had improved endothelium-dependent vasodilation [52].

Other measures of vascular responsiveness

Other newer imaging modalities may help to identify patients prior to the development of atherosclerosis, but these techniques will require further study to fully elucidate their role. These modalities include an ultrasound tracking system used to assess arterial stiffness, pulse-wave velocity (PWV) waveforms to assess arterial stiffness and laser Doppler fluxmetry to measure vascular responsiveness in the microcirculation. Abnormal mechanical properties of larger arteries have been observed in SLE patients without evidence of CVD by B-mode carotid ultrasound using an ultrasound echo-tracking system, which measures stiffness in the large arteries. Increased vascular stiffness was observed in both the common carotid artery and popliteal artery of patients with SLE (p = 0.01 and 0.005, respectively) compared with controls [53]. PWV waveforms from the right carotid and femoral arteries of patients with SLE without clinical CVD was measured with Doppler probes to assess for aortic stiffness in a cross-sectional study conducted by the Pittsburgh Lupus Registry. The risk factors associated with vascular stiffness (assessed by PWV) were the SLE-specific variables of lower white blood cell count, higher C3 levels and renal disease; whereas the traditional cardiovascular risk factors were more associated with carotid plaque and IMT [54]. Using laser Doppler fluxmetry, vascular responsiveness in the cutaneous microcirculation of patients with SLE was not significantly different than controls unless the patients also had Raynaud's phenomenon. Therefore, initial studies do not support the use of laser Doppler fluxmetry in distinguishing patients with SLE at an increased risk of CVD and patients with SLE not at increased risk of CVD [55].

Risk factors

Traditional risk factors

While many of the traditional CVD risk factors identified in the general population are present in patients with SLE, they are only part of the overall risk picture for patients with SLE. Nonetheless, their role cannot be discounted. According to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Guidelines for treatment of high blood cholesterol, the major risk factors for CVD in the general population are: hyperlipidemia

Table 2. Age at first cardiovascular disease event in patients with systemic lupus erythematosus.

Author	Location	N	Study design	Event type	Mean age at event	Mean age SLE diagnosis	Mean disease duration until event	Ref.
Gladman *et al.* (1987)	Toronto, Canada	45/507	Prospective	MI/angina/MI or angina	48 years (range: 25–73 years)	43 years (range: 9–68 years)	89 months (7.4 years) (range: 3–252 months)	[11]
Petri *et al.* (1992)	Baltimore, MD, USA	19/220	Prospective	Angina/MI/sudden cardiac death	NA	37.1 ± 11.5 years; p = 0.004 (47.1 ± 11.8 years is average age of entry into cohort; p = 0.0001)	12.3 ± 10.3 years (p = 0.01)	[8]
Sultan *et al.* (1994)	Brooklyn, NY, USA	30/200	Retrospective	MI/angina	47.5 years	29.8 years	13.9 years	[12]
Manzi *et al.* (1997)	Pittsburgh, PA, USA	33/498	Retrospective	MI/angina	48 years, range 22–72 years; rate ratio from 35–44-year-old age group 52.43 (95% CI: 21.6–98.5)	39 years; RR: 1.21 (95% CI: 1.09–1.35)	13 years; RR: 0.83 (95% CI: 0.74–0.92)	[9]
Fischer *et al.* (2004)	UK	15/41	Observational	MI	Age < 70 years; adjusted OR: 3.47 (95% CI: 1.47–8.06)	NA	NA	[59]
Bessant *et al.* (2004)	UK	9/202 9/64	Cross-sectional; prospective	CHD/CVA	48 years	NA	11.3 years	[58]

CHD: Coronary heart disease; CVA: Cerebrovascular accident; MI: Myocardial infarction; NA: Not available; OR: Odds ratio; RR: Relative risk; SLE: Systemic lupus erythematosus.

(and low levels of high-density lipoprotein [HDL]-cholesterol), hypertension, smoking, family history of premature CVD, age and diabetes mellitus [56].

Hypertension and hypercholesterolemia were found in patients with SLE in the inception cohort organized by the SLICC group, where at study enrollment these risk factors were present in 33 and 36% of patients, respectively. Only 15% of patients were postmenopausal, 16% were current smokers and 3.6% had diabetes [5]. Over 3 years of follow-up in the SLICC inception cohort, the percentage of patients with these traditional risk factors increased, as did the percentage of patients treated for hypertension (79.8% at enrollment to 88.9% over 3-year follow-up) and hypercholesterolemia (24.8% at enrollment to 37.7% over 3-year follow-up) [57]. Bessant *et al.* in the UK performed a cross-sectional study of 202 consecutive patients (92.1% female) attending an SLE clinic over 12 months and found that 16.8% of patients had hypertension (BP: >140/90), 32.2% had hypercholesterolemia (defined by total serum cholesterol > 5.2 mmol/l or > 200 mg/dl), 21% of patients were smokers, and only 1% were diabetics [58]. The increased frequency of traditional cardiovascular risk factors in patients with SLE has been documented in many other studies [8,9,17].

Imaging studies in patients with SLE have documented the association between carotid plaque by B-mode ultrasound findings and traditional CVD risk factors. Older age and hypercholesterolemia were independently related to the presence of carotid plaque in the study by Roman *et al.* [30]. Furthermore, Manzi *et al.* demonstrated that focal plaque was associated with increasing age, a previous coronary event, higher systolic BP and higher levels of low-density lipoprotein (LDL)-cholesterol. All of those risk factors, except the higher LDL-C, were also associated with increased severity of plaque [31]. Von Feldt was able to associate the presence of a CAC score higher than 0 on EBCT with advancing age and greater number of traditional CVD risk factors [37].

In SLE patients who had CVD events, Petri *et al.* demonstrated that age, antihypertensive treatment, maximum cholesterol level and obesity were associated risk factors [8]. This was further supported by Manzi *et al.* who demonstrated that postmenopausal status and hypercholesterolemia were associated with CVD events [9]. Finally, Fischer *et al.* demonstrated that having SLE and hyperlipidemia increased the adjusted odds ratio (OR) for acute MI

from 2.55 (95% CI: 1.23–5.30; p = 0.012) for SLE without hyperlipidemia to 18.26 (95% CI: 1.48–225; p = 0.024) for patients with SLE and hyperlipidemia [59].

Lupus-specific variables

The more traditional cardiovascular risk factors discussed previously do not account for all of the increase in risk observed in patients with SLE as revealed by Esdaile, Bruce and Bessant [16,17,58]. The role of corticosteroids, SLE disease activity, end-organ damage due to SLE, autoantibody production and 'lupus dyslipoproteinemia' in the development of CVD are reviewed in the next sections (see **Box 1**). Perhaps in the future, these variables will be part of a specific risk score calculator for patients with SLE.

Corticosteroids

The role of corticosteroids in CVD associated with SLE is unclear, since evidence suggests that steroids themselves may contribute to the problem. Alternatively, corticosteroids may be a surrogate marker for more active or inflammatory disease. In an early autopsy study performed by Bulkley *et al.*, greater than a 50% narrowing by atherosclerotic plaque was demonstrated in one of the three main coronary vessels in 42% of patients treated with steroids for over 1 year (average age: 30 years, range: 16–45; average duration: SLE 24 months, range: 9–96 months), but in none of the vessels of the patients who received steroids for less than 1 year (average age: 35 years, range: 8–62; average duration of SLE: 54 months, range: 24–120 months). In the 17 patients who received prednisone for less than 1 year, the dose ranged from 5 to 100 mg daily for an average of 6 months. In the 19 patients who received prednisone for more than 1 year, the dose ranged from 20 to 120 mg daily for an average of 38 months [60].

When assessing cardiovascular risk factors in SLE, MacGregor *et al.* found a corticosteroid dose-related effect. Above a daily dose of 10 mg of prednisolone, the triglyceride (TG) and Apo B levels were elevated compared with controls without SLE, but below a daily dose of 10 mg prednisolone there was no difference between controls and SLE patients [61]. Similarly, Petri *et al.* found that prednisone of over 10 mg daily was associated with hypercholesterolemia, defined as total cholesterol of more than 200 mg/dl. This was not divided into cholesterol subfractions [7]. Using longitudinal regression analysis, Petri also associated a 10 mg increase in prednisone with an increase in total cholesterol of 7.5 ± 1.46 mg%, a weight change of 5.5 ± 1.23 lb, and a change in mean arterial BP of 1.1 mmHg after adjustment for age, weight and antihypertensive drug use [32]. Using multiple logistic regression, Bruce *et al.* demonstrated that cumulative dose of steroids was one of the best predictors of sustained elevated total cholesterol of more than 5.2 mmol/l (>200 mg/dl) over 3 years of follow-up [6]. However, many studies have demonstrated that SLE itself is associated with a dyslipoproteinemia, which will be discussed below.

Manzi *et al.* compared SLE patients with and without a CVD event. A longer duration of corticosteroid use (11 vs 7 years; p = 0.002) was more common in the patients who had an event than in those without an event [9]. Bessant *et al.* retrospectively reviewed patients with SLE in the 3–6 months prior to a CVD event. Patients with SLE and CVD were more likely than SLE age-matched controls (without CVD) to have taken a mean dosage of prednisone of over 7.5 mg/day (p = 0.04) and more likely to have been treated with pulse methylprednisolone (p = 0.03) [62]. In both studies, SLE patients who had CVD events either had a longer duration of or a higher dosage of corticosteroids. However, it is unclear if corticosteroid use is merely a marker of cumulative SLE activity and inflammation or if the CVD events are a direct result of corticosteroid use.

Corticosteroids may also be associated with subclinical disease. Manzi *et al.* demonstrated that women with SLE who had a longer duration of prednisone use and higher cumulative dose of prednisone were more likely to have carotid plaque on ultrasound [31]. Thompson *et al.* demonstrated that IMT progression on ultrasound was associated with years of steroid use in a longitudinal study of women with SLE [33]. By contrast, Roman *et al.* demonstrated that patients with carotid plaque were less likely to be treated with prednisone as part of their clinical care [30]. Some of this discrepancy is probably related to differences in study design and the differing measures of steroid usage: duration of use versus cumulative dose versus mean daily dose. However, these three studies highlight the difficulty in studying the role of corticosteroids in the pathogenesis of atherosclerosis in patients with SLE.

Similarly, conflicting study results regarding corticosteroid use have been found in RA and PsA. Patients with RA have higher rates of hypertension and insulin resistance, which may be partially related to corticosteroid use.

However, studies utilizing prednisolone and disease-modifying antirheumatic drugs (e.g., methotrexate and sulfasalazine) or anti-TNF agents have shown improvements in insulin resistance and atherogenic index (ratio of total cholesterol/HDL-C) as summarized by John *et al.* [63]. A retrospective study of RA patients found that corticosteroid treatment early in disease significantly increased the risk of a cardiovascular event, but corticosteroid use at least 1 year before an event decreased the risk [64]. In a recent study in patients with PsA, multivariate regression analysis demonstrated that corticosteroid use did not have a significant effect on the development of hypertension or first CVD event after controlling for gender and age at onset of psoriasis, as well as their interactions with calendar time (from 1978 to 2004) [65]. Patients with RA and PsA also require further study to better define the role of corticosteroids in assessing their risk of CVD.

SLE disease activity & damage

In a study performed by Ibanez *et al.*, the association between Adjusted Mean Systemic Lupus Erythematosus Disease Activity Index-2000 (AMS) as a measure of disease activity and CAD was assessed. AMS was defined as the area under the curve of the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) over time divided by time interval; in other words, AMS summarizes disease activity over time. A total of 55 out of 575 patients had CAD, and CAD was significantly associated with higher AMS ($p = 0.046$), sex ($p = 0.009$), age ($p < 0.0001$) and disease duration ($p < 0.0001$) [66]. Manzi demonstrated that some lupus-specific variables (e.g., an older age at lupus diagnosis, longer lupus disease duration and longer duration of corticosteroid use) were more common in patients with SLE who had a CVD event compared with SLE patients without an event [9].

In the study performed by Roman and colleagues, the diagnosis of SLE itself, a longer duration of disease and greater disease damage (measured by SLICC-Damage Index [SLICC-DI]) were independent predictors of carotid plaque [30]. Similarly, Manzi *et al.* demonstrated that duration of lupus and disease damage (measured by SLICC-DI) were significantly associated with a higher carotid plaque index [31]. Ongoing SLE disease activity leads to disease damage; one hypothesis is that CVD is a chronic inflammatory process and that the disease itself could lead to damage in the vasculature.

Autoantibody production

Systemic lupus erythematosus is characterized by autoantibody production, which is pertinent to the discussion on CVD risk in SLE. Here we

Box 1. Risk factors for cardiovascular disease in systemic lupus erythematosus.

Traditional risk factors
- Age
- Smoking
- Hypertension
- Hypercholesterolemia
- Diabetes mellitus
- Family history

Novel cardiovascular disease risk factors
- Cytokines (TNF-α, IFN-α, IL-6 and low IL-10)
- Endothelial (sVCAM-1, VEGF, Ang-2, apoptosis of circulating angiogenic cells/endothelial progenitor cells and low annexin V binding)
- Elevated C-reactive protein
- Elevated homocysteine
- Metabolic syndrome/insulin resistance

Lupus-specific variables
- Corticosteroids
- SLE disease activity and SLE disease damage
- Antiphospholipid antibodies
- Anti-oxLDL antibodies, reduced antiphosphorylcholine antibodies
- Proinflammatory HDLs
- Lupus dyslipoproteinemia (high VLDL, high triglyceride, low HDL, high lipoprotein A); decreased lipoprotein lipase activity
- Renal disease

Ang-2: Angiopoietin-2; HDL: High-density lipoprotein; oxLDL: Oxidized low-density lipoprotein; SLE: Systemic lupus erythematosus; sVCAM: Soluble vascular cellular adhesion molecule; VLDL: Very low-density lipoprotein.

will discuss the potential role of anti-oxidized LDL (oxLDL) antibodies and antiphospholipid antibodies. Many studies indicate that immune reactions involving those antibodies modulate atherosclerosis. Antiphospholipid antibodies and anti-oxLDL have been associated with CAD mortality in the general population. However, the relationship is nonlinear, making antibody status difficult to use as a predictor of individual risk [67]. Patients with SLE and secondary antiphospholipid antibody syndrome (APS) had a higher prevalence of carotid plaque than patients with primary APS [68]. In patients with SLE, the prevalence of anticardiolipin antibodies is quoted between 24 and 39% and for lupus anticoagulant it is quoted as 15–30%. However, only 50% of patients with the antiphospholipid antibodies will have a clinical event (defined as arterial or venous thrombosis or pregnancy morbidity), and thus have APS [69]. The presence of antiphospholipid antibodies was associated with calcification scores above the 70th percentile by EBCT in patients with SLE [35]. A retrospective analysis carried out by Bessant *et al.* demonstrated that patients with SLE just prior to a CVD event (MI, angina, cerebrovascular accident [CVA] or peripheral vascular disease) were more likely to have the presence of lupus anticoagulant compared with patients with SLE without CVD, after controlling for disease duration [62]. The presence of antiphospholipid antibodies was an independent predictor of vascular events in multiple prior studies on SLE patients [70,71]. A specific antiphospholipid antibody, anti-β-2-glycoprotein I antibody, has also been associated with increased risk of acute coronary syndrome in the general population [72]. β-2-glycoprotein I was identified as a significant risk factor for arteriosclerosis obliterans in SLE patients, and was associated strongly with ischemic heart disease in patients with SLE [73].

Annexin V plays a role in atherosclerotic lesions since it is believed to form a protective shield over thrombogenic cell surface proteins. Decreased annexin V binding to the endothelium, caused by anticardiolipin IgG, was found in the sera of patients with SLE and CVD [73]. Thus, annexin V has been targeted for further study as a treatment to prevent plaque rupture and atherothrombosis, and as another possible mechanism for the treatment of CVD induced by antiphospholipid antibodies [74]. Further postulated pathologic mechanisms involving antiphospholipid antibodies and CVD include a polymorphism (-643T>C SNP) in the promoter for the *APOH* gene, which encodes β-2-glycoprotein I. This promoter gene was associated with the presence of carotid plaque in SLE patients [75].

In addition, antibodies against oxLDL have been found in patients with angiographic CAD [76]. The oxidation of LDL may lead to the formation of neoepitopes that bind to scavenger receptors of macrophages and lead to uptake of oxLDL, accelerating foam cell formation in the atherosclerotic plaque. In addition to the higher level of autoantibodies to oxLDL, patients with SLE also have a higher level of oxidized phospholipids on LDL compared with controls. The level of oxLDL was associated with arterial disease (defined as clinically evident MI, angina, peripheral claudication or thrombosis) [77]. Furthermore, β-2-glycoprotein I/oxLDL complexes have been identified that enhance uptake of the oxLDL by macrophages via scavenger receptors, as demonstrated through *in vitro* studies [78]. Antibodies to these β-2-glycoprotein I/oxLDL complexes were significantly higher in the serum of SLE patients with APS. The highest titers of the antibody were measured in patients with secondary APS and in the subset who had a prior history of arterial thrombosis [79]. This suggests a role for oxidative stress and autoimmunity in the development of CVD in patients with SLE.

In patients with an established history of hypertension, high levels of IgM antiphosphorylcholine (anti-PC) antibodies were shown to be atheroprotective; they resulted in less progression of IMT on carotid ultrasound (OR: 0.46; 95% CI: 0.25–0.85; p = 0.01) [80]. Decreased levels of anti-PC antibodies were observed in both SLE cases with CVD and SLE controls without CVD compared with population controls. In the same study, patients with SLE and CVD were found to have more antiphosphatidylserine (anti-PS) antibodies and antibovine serum albumin antibodies [81]. These studies suggest that antiphospholipid antibodies may play a role in CVD development in SLE, but further research is necessary to define this role with more precision.

Lipid abnormalities

While hypercholesterolemia is a classic CVD risk factor, the lipid profile in patients with SLE is unique compared with patients with diabetes or the general population with CVD. This phenomenon is often referred to as 'lupus dyslipoproteinemia'. Borba and Bonfa studied 36 consecutive SLE patients and demonstrated that SLE patients have elevated very low-density lipoprotein (VLDL)-cholesterol and TGs with lower levels of HDL-C compared with general

population controls. Interestingly, in active disease as measured by the disease activity index SLEDAI, this pattern was further enhanced. One exception was that LDL-C levels decreased with disease activity [82]. As discussed previously, the study by Svenuggson *et al.* showed the same dyslipoproteinemia with higher TG and low HDL levels. This correlated with higher disease activity (measured by SLE disease activity measure) and higher activity in the TNF system [83]. SLE disease activity (measured by SLEDAI) had an effect on the lipid profile as observed in a recent study where atherogenic ratios were evaluated. Total cholesterol/HDL and LDL/HDL ratios were measured in 52 patients with SLE at flare and at remission. The patients had higher median total cholesterol/HDL and LDL/HDL ratios during a flare than during remission. This study postulated that ongoing disease flares predispose patients with SLE to a more atherogenic lipid profile [84]. Hua *et al.* revealed further abnormalities in patients with SLE when they showed that higher VLDL concentrations differentiated SLE patients with CVD from SLE patients who did not have CVD and from general population controls. Interestingly, LDL did not differ significantly between study groups and neither did small, dense LDL [70]. As discussed above, the role of corticosteroids in this lipid profile is not clear.

Patients with SLE have higher lipoprotein A (LpA) levels compared with controls (42 ± 35 vs 26 ± 25 mg/dl; p = 0.01) [85]. Furthermore, when LpA levels were studied in 24 patients with active SLE, LpA levels were significantly higher than age- and sex-matched healthy population controls ($p < 0.001$) [86].

Lipoprotein lipase (LPL) is an enzyme responsible for the metabolism of VLDL to LDL and for the first step in chylomicron TG catabolism. Borba *et al.* found that SLE patients had abnormal chylomicron metabolism characterized by decreased lipolysis and chylomicron remnant removal from the plasma; this was associated with decreased LPL activity. Higher levels of VLDL and TG (as would be expected with decreased LPL activity) and lower levels of HDL were observed in the SLE patients in this study [87]. Furthermore, Reichlin *et al.* found that antibodies to LPL occurred in 47% of SLE patients, and this strongly correlated with higher total serum TGs [88].

The usual role of HDLs is to prevent LDL oxidation. SLE patients have more proinflammatory HDL (rather than normal HDL) compared with controls, and SLE patients with CVD have the highest level of proinflammatory HDL (piHDL). Levels of oxLDL correlate with the levels of piHDL, suggesting that these HDLs may be a novel marker for atherosclerotic risk in SLE patients [89]. A recent study by McMahon associated piHDL with carotid plaque in patients with SLE. Among the patients with SLE and plaque in their cohort, 86.7% had piHDL compared with 40.7% of the patients with SLE and no plaque. Patients with piHDL also had a higher mean number of plaques than patients with normal HDL (0.62 ± 1.2 vs 0.10 ± 0.49; $p < 0.001$) [90].

The differences in lipid profiles between patients with and without SLE are significant because LDL-C is a significant risk factor in the general population, but may be less important in SLE. Since LDL-C is a modifiable traditional risk factor in the general population and the basis on which treatment is selected for hypercholesterolemia, statin treatment may not have the same impact in SLE.

Renal disease

The role of chronic kidney disease in the development of CVD is well established but underrecognized in the general population [91,92]. Nephrotic syndrome (NS) is also associated with risk for CVD. Patients in the general population with NS (defined as proteinuria ≥ 3.5 g daily) were matched to general population controls (excluding diabetics) in a retrospective database analysis performed in northern California by Ordonez *et al.* There were 11 MIs among NS patients and none among controls ($p = 0.001$; lower bound of 95% CI for relative risk [RR] 2.8). When these investigators performed an unmatched analysis adjusted for hypertension and smoking at the diagnosis of NS, the RR of MI was 5.5 (95% CI: 1.6–18.3) and the RR of coronary death was 2.8 (95% CI: 0.7–11.3). This study was comprised of 142 patients (11 with SLE as the cause of NS, 131 with NS due to other diseases). When SLE patients were omitted from the overall NS group, the RRs for MI and coronary death remained unchanged [93]. Furthermore, NS has been associated with established CVD risk factors in the general population [91]. The study performed by Ordonez *et al.* confirmed that the diagnosis of hypertension at the time of NS diagnosis was more frequent than in the control subjects ($p \leq 0.001$) and the mean and maximum cholesterol levels recorded within 1 year before 6 months after the diagnosis were significantly ($p \leq 0.001$) higher for nephrotic subjects than for controls [93].

When studied in patients with SLE alone, the association of renal disease and established CVD risk factors has been demonstrated. In a

prospective study following 70 Spanish patients with lupus nephritis (LN) and 70 age- and sex-matched controls, patients with LN had a higher prevalence of hyperlipidemia (44 vs 2%; $p < 0.001$), hypertension (44 vs 9%; $p < 0.001$) and antiphospholipid antibodies (45 vs 22%; $p = 0.01$) at study onset. Outcomes were also evaluated in this study. There were nine deaths in the LN patients and one death in the control group (16 vs 2%; $p = 0.02$). Of these, cardiovascular or cerebrovascular events account for the deaths of five patients [94]. In addition, higher serum creatinine (not just NS) has been associated with CVD risk. Multiple cohorts have documented a higher serum creatinine in SLE patients compared with controls [16,95] and it has been associated with increased CVD risk [9,32,95].

Finally, the role of renal involvement in subclinical atherosclerosis is well documented. In SLE patients aged under 50 years, proteinuria (1331 vs 465 mg/day; $p = 0.02$) or impaired renal function ($p = 0.02$; OR: 2.6; 26 vs 6%) was more common in patients with CAC found by EBCT compared with SLE patients without CAC on EBCT [96]. Using PWV waveforms from the carotid arteries from B-mode ultrasound, higher aortic stiffness was found to be associated with renal disease [54]. Furthermore, juvenile onset SLE patients with nephrotic range proteinuria (>3.5 g per day) had significantly higher IMT, as measured by B-mode carotid ultrasound, than those without nephrotic range proteinuria ($p = 0.02$) [97].

The morbitidy and mortality of renal disease in patients with SLE has been well established. In a British population of patients with SLE followed for at least 10 years, an increase in damage score measured by SLICC-DI (mostly in the neuropsychiatric, renal and musculoskeletal categories) was associated with a higher overall risk of death (adjusted HR: 1.40; 95% CI: 1.14–1.72) [98]. Similarly, the Lupus in Minorities: Nature versus Nurture (LUMINA) cohort revealed that the renal domain of the SLICC-DI was independently associated with a shorter time to death (HR: 1.65; 95% CI: 1.02–2.66) [99]. However, the presence of ESRD due to LN was not associated with greater CVD morbidity or mortality than what is already observed in the general population patients with ESRD due to non-SLE causes when studied in a Veterans' Affairs population [100]. While it is clear that renal disease is associated with an increased risk of CVD in patients with SLE (and the general population), it is unclear how much additional risk can be attributed to renal disease compared with the traditional CVD risk factors. Further study is warranted to clarify how renal disease should factor into CVD risk estimates for patients with SLE.

Novel CVD risk factors

Endothelial function: biochemical markers of endothelial cell activation

Many soluble markers of endothelial dysfunction have been studied in atherosclerosis, including cytokines, chemokines, soluble adhesion molecules and acute phase reactants. Their clinical use is limited by their instability, inadequate laboratory performance and lack of standardization at this time; however, they may prove to be a valuable tool in the future [101]. There is emerging evidence that these observations may be helpful in patients with SLE. In addition to the mechanical abnormalities detected by measurement of FMD in endothelial dysfunction, biochemical markers of endothelial cell activation, such as soluble thrombomodulin, von Willebrand factor and tissue plasminogen activator, are increased in patients with SLE [102]. A study by Somers *et al.* revealed that increased plasminogen activator inhibitor type I (PAI-1; an inhibitor of tissue plasminogen activator) was related to a depressed FMD in patients with SLE [103]. Svenugsson *et al.* recently reported that soluble thrombomodulin was elevated in all SLE patients, but soluble vascular cellular adhesion molecule (sVCAM)-1 was elevated only in the patients with SLE and CVD. This is of further interest, since sVCAM-1 is associated with systemic TNF-α [104]. Prior work carried out by Svenuggsson *et al.* increased levels of TNF-α ($p = 0.009$), soluble TNF receptor 1 ($p = 0.001$) and soluble TNF receptor 2 ($p = 0.001$) in SLE patients with CVD compared with patients with SLE and no history of CVD or to general population controls. This group also identified a positive correlation between TNF-α and plasma TGs, VLDL TGs and VLDL-C [83]. VEGF is an important signaling protein and is a potent angiogenic and vasoactive molecule. SLE patients with a higher IMT value using B-mode ultrasound had significantly higher mean plasma VEGF levels compared with controls after adjusting for age, smoking and other Framingham risk factors [105]. Thus, these soluble biomarkers may have a future role in identifying SLE patients at risk for CVD.

The Tie-2 receptor (a vascular-specific tyrosine kinase receptor), through its interaction with angiopoietin (Ang)-1, maintains vessel integrity, inhibits vascular leakage, suppresses inflammatory gene expression, and prevents recruitment and transmigration of leukocytes. Ang-2 has

emerged as a key mediator of endothelial cell activation and facilitates endothelial cell inflammation by counterbalancing the effects of Ang-1 and disrupting these functions [106]. Ang-2 concentrations were measured from the plasma collected on patients in the European Trial on Olmesartan and Pravastatin in Inflammation (EUTOPIA). This population included 190 patients from Eastern Europe who were diagnosed with essential hypertension and atherosclerotic disease (either clinical history of CAD or peripheral vascular disease events, but cerebrovascular disease was excluded). Ang-2 concentrations were elevated in hypertensive patients compared with healthy controls (4.23 ± 3.1 vs 0.88 ± 0.43 ng/ml; $p < 0.0001$); and it was particularly elevated in those patients with atherosclerosis ($p = 0.02$). Furthermore, Ang-2 concentrations correlated with other vascular markers of endothelial cell activation, including VCAM-1 and ICAM-1 [107]. Ang-2 elevations have also been observed in patients with antineutrophil cytoplasmic antibody-associated vasculitis with renal involvement, and the concentration of Ang-2 correlated with the number of circulating endothelial cells ($r^2 = 0.48$; $p < 0.001$) [108]. More recently, Ang-2 has been studied in the serum of patients with SLE and compared with healthy controls. Mean serum Ang-2 concentrations were markedly elevated in patients with active SLE compared with inactive SLE (8.6 vs 1.4 ng/ml; $p = 0.010$) and healthy controls (8.6 vs 1.1 ng/ml; $p < 0.001$), and Ang-2 remained significantly elevated in patients with inactive SLE compared with healthy controls (1.4 vs 1.1 ng/ml; $p < 0.001$) [109]. Furthermore, Ang-2 was studied by immunohistochemistry in biopsies of human LN; protein expression of Ang-2 was upregulated in the glomeruli of these patients, while no Ang-2 was observed in renal tissue from healthy kidneys (nephrectomy due to trauma) [109]. Circulating Ang-2 needs to be evaluated in patients with SLE and CVD in future studies, but may be a future interesting biomarker of endothelial cell activation.

Endothelial dysfunction: endothelial progenitor cells

Maintaining vascular integrity after damage is a role played by endothelial progenitor cells (EPCs) and myelomonocytic circulating angiogenic cells. Decreased levels or abnormal function of those cells is an established atherosclerotic risk factor [110]. Hill *et al.* demonstrated an inverse relationship between the number of circulating EPCs and the Framingham risk score, and a direct correlation between the number of circulating EPCs and FMD in normal men without known CVD [111]. A recent study reported that SLE patients possess significantly fewer numbers of circulating EPCs. SLE patients also possess impaired differentiation of EPCs and circulating angiogenic cells into mature endothelial cells that are capable of producing VEGF. These abnormalities are triggered by IFN-α, which induces EPC and circulating angiogenic cell apoptosis. SLE EPCs/circulating angiogenic cells have increased IFN-α expression, which might promote accelerated atherosclerosis [112]. The observations on EPCs as important effector cells in this model are an intriguing new development in SLE and CVD, and will warrant further investigation.

Endothelial dysfunction: cytokines & their polymorphisms

In addition to the relationship between TNF-α and IFN-α, other cytokines and their associated polymorphisms (IL-10 and IL-6) have also been implicated in the relationship between CVD and SLE. IL-10 has an atheroprotective role compared with TNF-α, which is atherogenic. A community-based study in China showed a decreased risk of early carotid atherosclerosis for a specific *IL-10* genotype (*IL-10 -592C/C*) in a normal population [113]. While both IL-10 and TNF-α are increased in SLE patients with CVD compared with SLE patients without CVD or controls, the ratio of IL-10:TNF-α was reduced in patients with the *A-1087 IL-10 AA* genotype. The A allele frequency was also higher (38%) in patients with SLE and CVD compared with patients with SLE and no CVD (19%) [114].

IL-6 overproduction has been associated with SLE, CVD and C-reactive protein (CRP) elevations. Research studies have attempted to elucidate the role of IL-6; is it a passive bystander or does it play a direct role in the pathogenesis of SLE and CVD? Polymorphisms in the promoter region of the *IL-6* gene have been associated with an increased risk of MI in older individuals without SLE [115]. Roman *et al.* demonstrated that IL-6 and CRP correlated with arterial stiffness by radial artery applanation tonometry, a marker of vascular stiffness and a type of PWV analysis discussed previously using the radial artery (rather than the carotid or femoral arteries). Vascular stiffness was independent of atherosclerosis on carotid ultrasound [116].

Measurement of individual cytokines is laborious and may be difficult to interpret without an overall cytokine profile. The role of IL-10 and IL-6 and many other cytokines in SLE and CVD remains to be fully elucidated.

Elevated serum C-reactive protein

In addition to its relationship with arterial stiffness, an elevated level of serum CRP has been associated with MI and stroke in the general population. Its role in risk stratification remains unclear because it might improve risk prediction beyond the traditional Framingham calculation; however, further study will be required before it can be accepted as a standard CVD risk factor [117]. In patients with SLE, an elevated serum CRP has been associated with the presence of carotid plaque [31]. Elevated CRP has also been associated with the highest quartile of IMT on carotid ultrasound in SLE patients [54]. Patients in the LUMINA study who already had vascular events were more likely to have an elevated high sensitivity CRP (hsCRP) and this was also associated with the *GT20* allele in the CRP gene [118]. Further results from the LUMINA cohort showed that hsCRP is associated with SLE disease activity as measured by the Systemic Lupus Activity Measure, but not with overall damage accrual as measured by the SLICC-DI [119], and that the level of hsCRP is correlated with occurrence of cardiovascular outcomes in patients with SLE [120]. Finally, SLE patients without the traditional cardiovascular risk factors had increased odds of having any CAC along with more extensive CAC (higher CAC score) on EBCT compared with controls. However, after adjustment for hsCRP or soluble ICAM-1 levels, this increased risk disappeared, suggesting that inflammation and endothelial activation played a more significant role in SLE patients [121]. hsCRP may play a more significant role in risk stratification in patients with chronic inflammatory diseases, such as SLE, but further study is warranted before screening or diagnostic recommendations are finalized.

Homocysteine

Homocysteine is believed to be a toxin that results in endothelial injury and dysfunction in patients with CVD, but its exact role remains to be defined [122]. Homocysteine may have a role in differentiating between patients with SLE and CVD and those with CVD without SLE. Von Feldt *et al.* demonstrated that higher CAC scores on EBCT in patients with SLE were associated with higher plasma homocysteine concentrations, age, longer disease duration and renal disease compared with controls when multivariate logistic regression methods were applied [37]. Patients with SLE from the Toronto Lupus Cohort had higher mean homocysteine levels compared with age-matched controls, despite having higher folate levels [16]. Petri *et al.* found that a homocysteine level above 14.1 mmol/l was an independent risk factor for development of CAD in patients with SLE after controlling for established risk factors [32]. Svenugsson *et al.* demonstrated similar findings in a case–control study [123]. Roman *et al.* noted that atherosclerosis progression on carotid ultrasound in patients with SLE was increased across tertiles of homocysteine. Homocysteine concentration was significantly higher among patients with progressive plaque compared with patients without carotid plaque [124]. While the role of homocysteine is not completely defined, Von Feldt suggests that it may be a useful initial test in the evaluation of SLE patients in order to determine the presence and extent of subclinical atherosclerotic disease [125]. In addition to SLE, renal failure is a known cause of hyperhomocysteinemia [126]. A *post hoc* analysis of the Vitamins to Prevent Stroke (VITATOPS) trial was performed and revealed that adjusting for renal function eliminated the relationship between total plasma homocysteine and vascular risk assessed by carotid IMT and FMD of the brachial artery [127]. Since patients with SLE frequently have concomitant renal insufficiency, it will be important for future studies to address this relationship. The impact of lowering homocysteine to reduce the risk of CVD in patients must be defined because multiple randomized, controlled trials in the general population have shown no benefit to vitamin supplementation in lowering plasma homocysteine concentration [126].

Metabolic syndrome & insulin resistance

The metabolic syndrome, which is closely linked to insulin resistance, is another CVD risk factor in the general population and may play a particularly important role in women [128]. ATP III guidelines define the metabolic syndrome as the presence of three or more of the following risk determinants [56]:

- Abdominal obesity (measured by waist circumference of over 40 inches in men and over 35 inches in women);
- TGs of 150 mg/dl or more, HDL less than 40 mg/dl in men and less than 50 mg/dl in women;
- BP of 130/85 mmHg or higher;
- Fasting glucose of 110 mg/dl or more.

When studied in a SLE population of non-diabetics, the prevalence of metabolic syndrome (as defined by the ATP III criteria) was found

to be 18% in one group [129], and ranged up to 29.4% in another cohort [130]. Finally, a group in southern Spain found a prevalence of metabolic syndrome of 20% and that the frequency of CVD in the SLE group with the metabolic syndrome was 3.2-fold higher than in the SLE group without the metabolic syndrome (25 vs 7.8%; OR: 3.9; 95% CI: 1.4–11; p = 0.032) [131]. Decreased sensitivity to insulin has been observed in nondiabetic patients with SLE after calculating the Homeostatic Model Assessment equation for insulin sensitivity (HOMA-S) and was not correlated with disease activity or steroid therapy [129]. Furthermore, elevated fasting insulin levels were observed in 24 out of 87 female Chinese SLE patients and the insulin levels positively correlated with traditional cardiovascular risk factors, such as BP and TGs [132].

Increasing interest in the metabolic syndrome has been matched by similar attention to the role of adipose tissue in rheumatic diseases. White adipose tissue secretes a variety of peptides, termed adipokines (including leptin), that may play a role in modulating insulin sensitivity and atherogenesis [133]. Leptin levels were higher in SLE patients than in general population controls. In addition, a higher prevalence of metabolic syndrome was observed in patients with SLE than general population controls. Among SLE patients, leptin correlated with insulin levels, TGs, BMI, corticosteroid dosage and SLEDAI score [71].

Treatment & management recommendations

Despite the increased risk of CVD in patients with SLE, no formal guidelines exist for the prevention of CVD in the context of SLE. We present our recommendations for potentially modifiable risk factors based on data from other high-risk populations (e.g., diabetics) since multiple barriers, such as recruitment and retention, have been identified when studying risk factor reduction in SLE [134]. In addition, patient and physician awareness of the problem is insufficient and results in underappreciation of the significance of the problem [135,136]. Furthermore, patients list medication concerns at the forefront of factors that limit their study participation [137]. Primary or even secondary prevention of CVD requires the addition of multiple new medications, which will be difficult in patients who already have medication concerns. Therefore, until randomized, controlled studies comparing different treatment interventions and resultant CVD outcomes are undertaken, we recommend treating SLE as a CHD equivalent as outlined below using guidelines adapted from the NCEP ATP III criteria [56]. Furthermore, we also present the similarities and differences between the US guidelines and those published in Europe for the treatment management of CVD risk factors (Table 3) [138].

Hypercholesterolemia

In the general population, lipid modifications are outlined by the ATP III guidelines. The main target is lowering LDL-C and the target is based on risk stratification. Patients with a history of CHD and other CHD risk equivalents (e.g., diabetes, peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease) have at least a 20% risk of an event per 10 years. Patients in this category of risk have a goal LDL-C of less than 100 mg/dl. The European Guidelines set the same goal LDL-C of under 100 mg/dl for high-risk patients, with an optional goal of less than 80 mg/dl when feasible [138].

The Toronto group examined their treatment of hypercholesterolemia in patients with SLE and found that despite the fact that use of lipid-lowering agents had greatly increased over the past 6 years, only 28% of patients were receiving treatment [139]. In the study by Costenbader and colleagues, the use of pravastatin was examined in an open-label dose titration study where they found similar LDL and total cholesterol level reductions in patients with SLE given pravastatin compared with control patients with SLE. However, the decline in LDL and total cholesterol was less in patients with SLE who were also receiving glucocorticoids. There were no safety issues and no outcome assessments were performed owing to the small recruited sample size and high dropout rate (out of 662 potential subjects, only 41 patients enrolled, and 17 of those dropped out by month 2) [140].

There is only one cardiovascular event outcome study to date that evaluated cardiovascular outcomes after fluvastatin was used to treat renal transplant patients with SLE. Fluvastatin decreased LDL by 29.2% and reduced cardiac events by 73.4% [141]. Two other intervention trials in patients with SLE measured surrogate imaging markers of CVD. The first was an early intervention trial in patients with SLE demonstrating that after 8 weeks of atorvastatin, patients with and without a history of CVD had improved endothelium-dependent vasodilation as measured by FMD [52]. The second is the Lupus Atherosclerosis Prevention Study (LAPS)

performed by Petri *et al.* This was a randomized clinical trial of atorvastatin versus placebo in SLE patients. The outcome measures were CAC scores measured by helical CT and IMT by carotid ultrasound at baseline and after a 2-year follow-up. Despite atorvastatin treatment, there was an increase in CAC score and carotid IMT in both groups. A similar rate of adverse events (7% statin and 7% placebo group with transaminase elevations, creatine kinase elevations in 4% of statin and 8% placebo group) was reported in both groups; however, thymic hyperplasia was observed in 7% of the statin group and 0% of the placebo [142].

Interestingly, it has been suggested that statins themselves may play a role in modulating autoimmune disease, but these results have been limited to animal studies thus far [143]. A murine SLE model was treated with oral atorvastatin, which resulted in proliferation of T cells and increase of proinflammatory cytokines, but no survival benefit or LDL-C improvements were noted [144]. A preliminary study examining 14 patients with SLE found that rosuvastatin given for 3 months had a potent lipid-lowering effect, but did not have any effect on CRP, erythrocyte sedimentation rate, double-stranded DNA antibodies, complements or inflammatory cytokines [145].

When the ATP III guidelines are applied to SLE patients, the treatment approach is the same as patients with CHD. After checking a fasting lipid panel, an LDL level of less than 100 mg/dl means the patient is already at goal LDL. If the LDL level is between 100 and 129 mg/dl, lifestyle modifications should be initiated through dietary modification and moderate physical activity. If the LDL level is 130 mg/dl or more, then lipid-lowering therapy should be initiated with a statin. The lipid panel should be rechecked every 6 weeks with titration of the dose of the statin to the goal LDL level of lower than 100 mg/dl [56]. Similar to the US guidelines, the European guidelines base lipid-lowering therapy on a patient's individual risk. High-risk groups should receive statin treatment to LDL goals under 100 mg/dl and a goal LDL level of lower than 80 mg/dl where feasible [138]. While statins are used regularly, other aspects of the lipid profile may require additional treatment in patients with SLE, for example hypertriglyceridemia. In the future, modifications to oxLDL or pi-HDL may also play a role. However, no definitive recommendations can be made at this time regarding management of these newer cholesterol subfractions. Finally, the addition of hydroxychloroquine has been associated with

Table 3. Summary of cardiovascular risk factor treatment recommendations for patients with systemic lupus erythematosus.

Risk factor	Target value	Treatment	Ref.
Hypercholesterolemia	LDL < 100 mg/dl	If LDL is 100–129 mg/dl, then institute lifestyle modifications; If LDL is 130 mg/dl or higher, then initiate a statin and discuss lifestyle modification	[56,138–142,166]
Hypertension	< 130 mmHg systolic < 80 mmHg diastolic	If BP is between 130 and 140 systolic/80–90 diastolic, can discuss lifestyle modifications If BP is 140/90 mmHg or higher, should start on ACE inhibitor (or ARB), especially in setting of SLE with renal disease, diabetes or prior CVD event; Thiazide diuretics also remain an acceptable first choice; If still uncontrolled, start a second agent	[138,146–157]
Diabetes	Hemoglobin A1C ≤ 7.0%	Annual testing of fasting glucose for diagnosis, normal is 126 mg/dl or less; Glycemic control should be managed in conjunction with primary-care physician or specialist	[56,138,189]
Smoking	Stop smoking	Work in conjunction with primary-care physician; Smoking cessation clinic if available; Nicotine replacement therapy or bupropion if over ten cigarettes per day	[183]
Obesity	BMI < 25 kg/m^2	If BMI is higher than 25, consider referral to dietician; Discuss aerobic exercise plan; If possible, adjust steroid dose	[138,188]
Others: - Aspirin - Hydroxychloroquine - Corticosteroid - Hormones - Exercise	–	Unless an absolute contraindication, aspirin 81 mg daily in all patients with SLE; Unless an absolute contraindication, hydroxychloroquine daily in all SLE patients; Minimize corticosteroid use where possible; Oral contraceptives and hormone replacement only in properly selected patients and avoid in patients with antiphospholipid antibodies; Regular aerobic exercise for all SLE patients	[30,61,166,174,179–182,184–187]

ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BP: Blood pressure; CVD: Cardiovascular disease; LDL: Low-density lipoprotein; SLE: Systemic lupus erythematosus.

decreased LDL, increased HDL, and maybe improved glycemic control and antiplatelet effects (see below).

Hypertension

In the general population, treatment of hypertension has been associated with reductions in the incidence of stroke (35–40% reduction), MI (20–25% reduction) and congestive heart failure (50% reduction) [146]. For normal individuals aged 40–70 years, for each increase of 20 mmHg in systolic BP or 10 mmHg in diastolic BP, the risk of CVD doubles [147]. These observations have led to specific guidelines for management of hypertension in the Seventh Report of the Joint National Committee (JNC 7). The recommendations for patients with certain comorbidities, especially diabetes, are recommended to maintain a BP less than 130/80 mmHg [148]. The same BP recommendations of less than 130/80 for high-risk patients were stipulated in the European Guidelines [138].

For patients with SLE, screening BPs should be performed at every office visit. The treating rheumatologist should consider the results carefully. A quality improvement study was performed by Urowitz *et al.* and found that treatment for hypertension had increased over a 6-year interval (88% from 1990 to 1995 to 96% treated from 1996 to 2001), but a number of patients remained untreated (4%) [139]. If the BP is more than 140/90 mmHg, lifestyle modifications, including physical activity and dietary changes (reduce sodium intake, adopt the Dietary Approaches to Stop Hypertension [DASH] diet and moderation of alcohol consumption), can be recommended, along with recommendations for weight reduction. Concomitant attempts to reduce corticosteroid dose should be attempted, but should not sacrifice control of SLE. The goal for BP in patients with SLE should be the same as diabetics, less than 130/80 mmHg, and may require more than one drug to maintain. In the general population, the first antihypertensive treatment of choice according to JNC 7 guidelines is a thiazide diuretic, such as hydrochlorothiazide [148]. Thiazides would also be a safe choice in patients with SLE. If the patient still does not have control of BP, a second drug should be added. In SLE, β-blockers have been shown to precipitate Raynaud's phenomenon [149], and case reports have associated β-blockers with drug-induced lupus [150]; therefore, ACE inhibitors are a better second-choice agent in this population. The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that ramipril reduced risks of stroke, MI and death in high-risk patients in the general population [151]. Captopril was studied in patients with LN and severe hypertension, and was found to improve renal function in 64% of patients while also improving BP control [152]. The LUMINA study recently demonstrated that ACE inhibitor use was associated with longer time to renal disease and improved SLE disease activity [153]. Cardiovascular outcomes were not measured in this study, but ACE inhibitors would be a logical second choice and are likely to be incorporated into future guidelines for CVD risk reduction in patients with SLE. The angiotensin receptor blocker (ARB), losartan, was studied over 12 months of therapy in a small retrospective study of seven patients with SLE and demonstrated a significant reduction in systolic and diastolic BP, along with an 84.8% reduction in urinary protein excretion [154]. Furthermore, in the general population, ARBs have been demonstrated to favorably affect progression of diabetic nephropathy and nondiabetic renal disease [155]. ARBs are likely to be a good substitution for SLE patients with contraindictions to ACE inhibitors.

The European guidelines suggest that ACE inhibitors and ARBs can be employed as a first-choice medication. These guidelines promote the benefits of lowering BP independent of the drug employed; therefore, thiazides, β-blockers, calcium-channel blockers, ACE inhibitors and ARBs are all suitable choices for initiation and maintenance of hypertension [138]. However, the European guidelines also draw attention to the fact that thiazide diuretics often have dyslipidemic and diabetogenic effects (along with β-blockers) [138,156,157]. Physicians should consider these potential side effects when selecting antihypertensive medications in patients with pre-existing metabolic syndrome and substitute ACE inhibitors or ARBs for thiazide diuretics as the initial choice to control BP. Although SLE patients are not specifically addressed in the European guidelines, SLE patients frequently suffer from the metabolic syndrome and have multiple CVD risk factors, suggesting that an alternative first medication to be considered is an ACE inhibitor or an ARB in this population.

Aspirin, oral anticoagulants & NSAIDs

In the general population, primary prevention using aspirin reduces the risk of cardiovascular events as found in a meta-analysis of four randomized trials (RR: 0.85; 95% CI: 0.78–0.94) [158]. Guidelines have been established using the risk estimate for MI using the Framingham

calculation. For example, in patients whose cardiovascular risk exceeds 1.5% per year and whose risk of bleeding assuming no absolute contraindications is less than their risk of a CVD event, initiation of low-dose aspirin (81 mg/day) is recommended [159]. Examples of aspirin contraindications include allergy, bleeding diathesis, platelet disorders and active peptic ulcer disease. Concomitant use of other NSAIDs and a history of renal insufficiency are considered relative contraindications. Current recommendations for primary prevention in diabetics without established CVD remain unclear. Primary prevention studies to date have been underpowered to detect a reduction in primary cardiovascular outcomes (death from CVD, nonfatal MI or CVA) [160]. However, the Hypertension Optimal Treatment (HOT) trial demonstrated that aspirin given to diabetic patients with a single additional risk factor, hypertension, reduced MI events by 36% (p = 0.001) [161]. More definitive evidence may become available when the A Study of Cardiovascular Events in Diabetes (ASCEND) trial is completed. Addressing aspirin's role in primary prevention is further complicated because most of the primary prevention trials were performed solely in male patients. A prospective, nested, case-controlled study using 79,439 women enrolled in the Nurses' Health Study looked at aspirin as primary prevention. They found a risk reduction in death from CVD (RR: 0.62; 95% CI: 0.55–0.71); also the use of aspirin for 1–5 years was associated with significant reductions in cardiovascular mortality (RR: 0.75; 95% CI: 0.61–0.92) [162].

There is one study that examined mortality reduction in SLE. In this inception cohort of 333 patients with SLE in the UK, aspirin was associated with a 70% reduction of all-cause mortality, and antiphospholipid antibodies were not associated with increased mortality [163]. A Markov decision analysis performed by Wahl *et al.* suggested that the benefit of primary prophylaxis in both venous and arterial thrombotic events with aspirin outweighed its risk of bleeding complications in patients with SLE. The observed benefit was even greater in patients with SLE and antiphospholipid antibodies, and translated into a survival benefit of 11 versus 3 months in patients with SLE alone [164]. One study demonstrated that a longer duration of aspirin use was beneficial to patients with SLE. Aspirin treatment at 81 mg/day played a protective role against thrombosis in patients with SLE and antiphospholipid antibodies (HR per month: 0.98; p = 0.05) [165].

There are no randomized, controlled trials measuring CVD outcomes following primary prevention with low-dose aspirin in patients with SLE. Minimal standard treatment would include treating SLE patients with a history of CVD, positive antiphospholipid antibodies or lupus anticoagulant, history of hypertension, diabetes mellitus, hypercholesterolemia and a history of smoking in the absence of a contraindication [166]. Bleeding risk may be higher in SLE patients who are concomitantly taking corticosteroids and should be monitored closely. Despite these concerns, there is evidence that treating all SLE patients with low-dose aspirin (81 mg/day), barring an absolute contraindication, should be considered in patients with SLE.

There is no clear role for warfarin anticoagulation for primary prevention of CVD in patients with SLE, nor is there a role for primary prevention using warfarin in the general population [167]. For subjects in the general population at high risk of CVD, the role of clopidogrel plus aspirin in primary prevention was studied. In this trial, there was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors [168]. There are no studies defining the role of clopidogrel in patients with SLE and so the strategy for primary prevention remains uncertain.

The use of NSAIDs in patients with SLE is not absolutely contraindicated [169]. However, LN is a risk factor for NSAID-induced renal failure. Furthermore, patients with SLE and normal renal function will frequently experience a decrease in glomerular filtration rate while taking NSAIDs [170]. One report evaluating dermatologic conditions in patients with SLE who take NSAIDs found a fourfold increase in allergic reactions compared with other chronic arthritides [171]. There is no evidence that patients with SLE have a greater risk of gastrointestinal side effects, such as peptic ulcer disease, but this should be monitored closely in patients who are concomitantly taking corticosteroids. We would recommend prophylactic use of a proton pump inhibitor for patients who are given NSAIDs, with special attention given to patients who also take corticosteroids. A COX-2 inhibitor in patients who take corticosteroids may be a better choice than a traditional nonselective NSAID since this class of medication has been demonstrated to have less gastrointestinal side effects in patients with RA and osteoarthritis [172]. We suggest avoiding NSAID use in SLE patients with even a slightly abnormal glomerular filtration rate.

Antimalarial medications

Antimalarial treatments, such as hydroxychloroquine, have been associated with significant benefits in patients with SLE. Patients with carotid plaque by B-mode ultrasound were less likely to be treated with hydroxychloroquine in Roman's study [30]. In another study, patients were less likely to be receiving treatment with hydroxychloroquine just prior to a cardiovascular event [62]. In a recently published study of 1930 patients with SLE, risk factors for thrombosis were examined. After adjusting for disease severity and incorporating propensity scores, hydroxychloroquine use was protective for thrombosis with an odds ratio of 0.67 (95% CI: 0.50–0.90; p = 0.008) [173]. A recent systematic review examining the benefits of antimalarial use in SLE patients found moderate evidence for protection against thrombosis. However, evidence supporting an effect on subclinical atherosclerosis was weak. Owing to the strong evidence that antimalarial use prolonged survival and reduced the number of SLE flares, the authors declared that antimalarials should be given to most patients with SLE throughout the course of their disease [174]. Hydroxychloroquine has also been studied in RA and shown to reduce the risk of diabetes; in patients who took the drug for more than 4 years (n = 384), the adjusted RR of developing diabetes was 0.23 (95% CI: 0.11–0.50; p < 0.001) [175]. Further traditional risk reduction was observed in patients with RA who took antimalarials as shown by lower TGs and LDL levels compared with patients on other therapies [176]. We would recommend the use of antimalarials in all patients with SLE unless there is a direct contraindication to treatment, such as G6PD deficiency, or a complication due to therapy, such as retinal toxicity.

Immunosuppressant medications

Roman's study demonstrated that patients with carotid plaque by B-mode ultrasound were less likely to have been treated with prednisone and cyclophosphamide when analyzed by multivariate analysis [30]. As discussed previously, corticosteroids play a complicated role. Most likely, doses below 7.5 mg daily of prednisone are not harmful [7,32,61].

Mycophenolate mofetil (MMF) has been studied in patients with renal and cardiac transplants and found to reduce allograft vasculopathy and intimal thickening compared with those treated with azathioprine, as reviewed by Gibson and Hayden [177]. Furthermore, a retrospective study found a 20% decrease in cardiovascular mortality among MMF-treated diabetic patients receiving renal transplants compared with patients on regimens without MMF [178]. While there are no specific studies regarding cardiovascular outcomes in patients with SLE who take MMF, extrapolating the transplant data suggests this may be a useful choice for treating LN. Immunosuppressant medications should be used judiciously and corticosteroid dosage should be minimized, but control of SLE should not be sacrificed to avoid CVD risk.

Estrogens & hormone replacement therapy

Patients with antiphospholipid antibodies are at increased risk of thrombosis. Thus, general recommendations include discontinuing estrogen usage, despite a lack of randomized, controlled trials [179]. A prospective study evaluating patients with SLE who took hormone replacement therapy (HRT) revealed that HRT was not a risk factor for CAD, despite the presence of antiphospholipid antibodies in 74.6% of HRT users [180]. However, the role of hormones in patients with SLE who lack antiphospholipid antibodies has been more clearly defined. Both the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) study and the LUMINA study found that exogenous hormones were safe to use in their patient populations as long as SLE was stable, and did not increase the risk of arterial thrombosis in lower risk patients [181,182]. Based on risk and needs, we would recommend oral contraceptive and HRT use in properly selected patients who do not have antiphospholipid antibodies.

Lifestyle modification: smoking cessation, exercise & obesity

Lifestyle modifications that are recommended to SLE patients with CVD risk factors include smoking cessation, regular physical activity and weight loss. In the study by Bessant *et al.*, patients that experienced CVD events were more likely to be smokers [62]. Furthermore, a large study demonstrated that smoking was associated with increased risk of all types of thrombosis (including MI and CVA) in patients with SLE (OR: 1.26; p = 0.001) [173]. The benefits of smoking cessation are also apparent in control of SLE disease activity. A study by Ghaussy *et al.* demonstrated that current smokers had significantly higher (p < 0.001) SLEDAI scores (15.6 ± 7.8) compared with ex-smokers (9.63 ± 6.00) and never smokers (9.03 ± 5.75). This association remained significant (p = 0.001) after adjusting for all covariates [183].

Exercise capacity is an independent predictor of cardiac events and mortality in the general population, and may be even more significant in women [184]. Patients with SLE have been shown to have worsened exercise capacity compared with controls [185]. Improved cardiovascular fitness was demonstrated in SLE patients who were enrolled in supervised cardiovascular training [186]. Exercise was safe and did not worsen disease control in patients with SLE [187].

Obesity is a risk factor for CVD in the general population, as reviewed by Cannon [188]. Obesity is also frequently observed in SLE patients and is associated with development of carotid plaque and CVD [8,31]. In the general population, weight loss has been associated with improved BP control, improved glycemic control and improved lipid profiles (e.g., metabolic syndrome) [188]. We recommend weight loss through diet and regular aerobic exercise to all patients with SLE.

Diabetes mellitus

Patients with SLE may also develop diabetes, which has been observed in approximately 5–7% of patients with SLE [7]. Since diabetes is also considered a CHD equivalent by ATP III guidelines, establishing glycemic control to minimize complications is imperative [56]. The European guidelines also stress the importance of adequate glycemic control and also set strict goals for hypertension and hypercholesterolemia management in diabetics, as previously discussed [138]. Guidelines for the optimal screening interval in the general population have yet to be determined by a randomized, controlled trial. However, diagnosis is made with a fasting plasma glucose of 126 mg/dl or more [189]. Testing for diabetes should be performed annually in all patients with SLE and may include fasting blood glucose or hemoglobin A1C testing. Particular consideration should be given to patients on corticosteroids.

Vitamin D

There is a vast emerging literature on the risk of CVD in patients who are low or deficient in 25-hydroxyvitamin D (25-OH-D) [190]. The Third National Health and Nutrition Examination Survey (NHANES-III) found that the 25-OH-D levels were lower in women, minorities, and participants with obesity, hypertension, diabetes mellitus and high serum TG levels [191]. Patients with SLE often have low levels of 25-OH-D, sometimes critically low at under 10 ng/ml [192]. In patients with SLE, lower levels of 25-OH-D levels were significantly associated with a variety of risk factors, including higher diastolic BP, LDL-C, LpA and BMI, as well as self-reported hypertension and diabetes, higher SLE disease activity (SLEDAI) and damage scores (SLICC-DI) [193]. Whether vitamin D supplementation will reduce CVD and CVD events remains to be studied prospectively in patients with SLE and in the general population. We recommend supplementing all SLE patients with vitamin D deficiency (<30 ng/ml) as part of a comprehensive fracture prevention plan and await further research on its role in CVD outcomes [95].

Treatment summary

The current literature review highlights the lack of available data demonstrating that treatment of cardiovascular risk factors (or SLE-specific treatment strategies) results in decreased cardiovascular events in patients with SLE. The current treatment information is mostly extrapolated from other high-risk populations. Randomized, controlled trials in patients with SLE are a necessity in order to determine the best treatment approach.

Future perspective

While the excess risk of CVD in patients with SLE is well documented, the exact etiology of the excess risk remains to be elucidated. Perhaps in the future, a more specific risk score calculator will become available for patients with SLE. Multiple imaging modalities can identify subclinical atherosclerosis; however, endothelial dysfunction may prove to be an even more effective modality by capturing earlier disease. Multidetector CT is an evolving technology for studying CVD in the general population and may eventually replace EBCT. Further study is needed to support its validity as a new surrogate marker for CVD in patients with SLE. Many possible CVD biomarkers have been identified, but their possible clinical utility requires investigation. Randomized, controlled trials are a necessity in order to determine the best treatment approach. Treatment recommendations for patients with SLE are based on other high-risk populations since there are no randomized, controlled trials that demonstrate the efficacy of interventions on cardiovascular events in SLE. Trials in patients with SLE are urgently required. In the coming years, the role of statins, antihypertensive agents, aspirin and immunomodulatory treatments will be better defined and are likely to be complemented by discoveries of novel and SLE specific risk factors.

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Executive summary

Scope of the problem

- Overall survival of patients with systemic lupus erythematosus (SLE) has improved, but the risk of cardiovascular disease (CVD) remains high despite improved treatments. This risk is particularly pronounced in premenopausal women with SLE aged 35–44 years who have a more than 50-fold excess risk compared with the general population.
- Cardiovascular risk factors, cardiovascular events and subclinical atherosclerosis all occur at a younger age in patients with SLE compared with the general population.
- After controlling for traditional Framingham risk factors, patients with SLE still have a 7.5-fold (95% CI: 5.1–10.4) excess risk of overall coronary heart disease. This suggests that SLE itself carries an independent risk for CVD and exposes the failure of the Framingham risk calculator to capture a younger at-risk population.

Imaging modalities

- Subclinical atherosclerosis can identify patients at risk of CVD events and is detected by B-mode carotid ultrasound and coronary electron beam computed tomography. In the future, these modalities may be supplanted by measuring endothelial function through flow-mediated dilation in the brachial artery.

Risk factors: traditional, novel & lupus-specific

- Hypertension and hypercholesterolemia are more prevalent in patients with SLE compared with population controls, are associated with subclinical atherosclerosis, and have been identified in patients with SLE who have had CVD events. However, these traditional risk factors are not the only risk factors present in patients with SLE and CVD.
- SLE disease activity, SLE disease damage, excessive corticosteroid use, renal disease, antiphospholipid antibodies and anti-oxidized low-density lipoprotein (oxLDL) antibodies may all be lupus-specific factors associated with increased CVD risk. Furthermore, SLE patients have a specific lipid profile associated with an elevated CVD risk.
- A variety of novel risk factors have been identified in the general population and SLE patients as possible risk factors for CVD: biochemical markers of endothelial activation, differences in endothelial progenitor cells, cytokines and their associated polymorphisms, elevated serum C-reactive protein, elevated serum homocysteine and the metabolic syndrome/insulin resistance.

Treatment

- Treatment recommendations for patients with SLE are based on other high-risk populations since there are no randomized, controlled trials that demonstrate the efficacy of interventions on cardiovascular events in SLE.
- Lifestyle modifications and/or statins should be used to lower LDL-cholesterol below 100 mg/dl as suggested in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines. European guidelines suggest possibly lowering LDL levels below 80 mg/dl when feasible.
- Hypertension should be treated to maintain a blood pressure less than 130/80 mmHg. First-choice medication for patients with SLE should probably be angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), especially in patients with concomitant lupus nephritis or diabetes mellitus. The Joint National Committee 7 guidelines still suggest use of thiazide diuretics, which is also an acceptable initial treatment approach.
- Low-dose daily aspirin therapy is recommended in patients with SLE barring an absolute contraindication.
- Use of antimalarial medications in all patients with SLE is recommended.
- Use of corticosteroids should be minimized and immunosuppressant medications should be used judiciously, but control of SLE should not be sacrificed to minimize CVD risk.
- Smoking cessation, regular aerobic exercise and maintaining a normal BMI are recommended in all patients with SLE.

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