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Pathogenesis and Treatment of Atherosclerosis in Lupus

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Premature atherosclerosis (ATH) is a major cause of increased morbidity and mortality in systemic lupus erythematosus (SLE). Urowitz et al. first described a bimodal pattern of mortality in SLE in 1976, with early deaths (<1 year) due to SLE disease activity, and later deaths primarily due to cardiovascular disease (CVD) [1]. This bimodal pattern has been confirmed in multiple subsequent studies [2]. Overall, there appears to be a 2 to 10-fold increased risk of myocardial infarction in SLE patients compared to the general population [3]. The risk is even more striking in young SLE patients; for example Manzi et al. also found that women with SLE in the 35–44- year age group were over 50 times more likely to have a myocardial infarction than were women of similar age in the Framingham Offspring Study [4].

Cardiovascular events may also result in greater morbidity and mortality in SLE patients; SLE patients have higher risk of in-hospital mortality and prolonged length of hospitalizations compared to both diabetic patients and non-SLE, non-diabetic patients [5]. Despite improvements in overall lupus mortality, the increased risk of mortality from cardiovascular disease appears to have remained constant. Data from a large international cohort suggests that although standardized all-cause mortality rates (SMR) for SLE decreased from 4.9 in 1970–1979 to 2.0 in 1990–2001, the SMR for cardiovascular disease in lupus did not decrease over the same time period [6].

Pathogenesis of Atherosclerosis

The mechanisms of the increased and accelerated atherosclerotic risk for SLE patients remain to be determined. It is likely that multiple mechanisms are operative, resulting from a complex interplay between traditional cardiac risk factors and SLE-driven inflammation.

Even in the general population, it has become clear that atherosclerosis is not just a consequence of passive accumulation of lipids in the vessel wall, but also a result of

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inflammation [7]. As in the pathogenesis of SLE itself, the interplay of multiple inflammatory mediators, including leukocytes, cytokines, chemokines, adhesion molecules, complement, and antibodies, results in the formation of atherosclerotic plaques [7]. Changes in the vascular endothelium can accelerate the formation of the atherosclerotic plaque. In response to hemodynamic stresses such as hypertension [8], or inflammatory mediators such as oxidized LDL (OxLDL) or cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF), the vascular endothelium undergoes a series of inflammatory changes that result in endothelial cell activation (ECA)[7]. Activated endothelial cells up-regulate leukocyte adhesion molecules such as VCAM-1, ICAM-1, and E-selectin [8]. Chemoattractant cytokines such as monocyte chemoattractant protein-1 (MCP-1), IL-6, and IL-8 are also expressed [8], thus inducing a cascade of pro-inflammatory, pro-atherogenic changes in the endothelium that results in migration of monocytes into the subendothelial space. T cells are also recruited to the subendothelium by similar mechanisms, although at lower numbers.

Next, low density lipoproteins (LDL) are transported into artery walls, where they become trapped and seeded with reactive oxygen species to become oxLDL [9]. OxLDL in turn stimulate ECA and are also phagocytized by infiltrating monocytes / macrophages, which then become the foam cells around which atherosclerotic lesions are built [7, 9]. Monocytes and T cells infiltrate the margin of the plaque formed by foam cells. Muscle cells from the media of the artery are stimulated to grow, and ultimately encroach on the vessel lumen [7]. Myocardial infarction occurs when one of these plaques ruptures, or when platelets aggregate in the narrowed area of the artery [7].

HDL Prevents oxidation and Inflammation

There are many mechanisms designed to clear OxLDL from the subendothelial space, such as macrophage engulfment using scavenger receptors, and enhanced reverse cholesterol transport mediated by HDL [10]. Both HDL and its major apolipoprotein constituent, apolipoprotein A-1 (apoA-I) have also been shown to prevent and reverse LDL oxidation and endothelial cell activation [10]. Thus, HDL function could be of equal or even greater importance to HDL quantity in preventing atherosclerosis. However, during the acute phase response, such as in the postsurgical period or during influenza infection, HDL can be converted from their usual anti-inflammatory state to pro-inflammatory (piHDL) [11]. Thus, HDL can be described as a “chameleon like lipoprotein;” anti-inflammatory in the basal state and proinflammatory during the acute phase response [10]. This acute phase response, however, can also become chronic, and may be a mechanism for HDL dysfunction in SLE [12].

Identification of SLE patients at risk for Cardiovascular Events

Traditional and SLE-specific Risk Factors for Atherosclerosis in SLE

Before therapeutic strategies to prevent cardiovascular complications in SLE patients can be implemented, it is critical to first identify at-risk patients. Traditional Framingham cardiac risk factors are likely to increase risk in lupus patients in a similar manner to the general population. Indeed, traditional risk factors such as hypertension [13–15],

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hypercholesterolemia [1, 4, 15], diabetes mellitus [1, 15], older age [4, 14, 15], tobacco use [16, 17], and postmenopausal status [4, 14] have all been associated with atherosclerotic disease in SLE. Petri et al. found that 53% of SLE patients from the Hopkins Lupus Cohort had at least 3 traditional cardiac risk factors [15]. Some traditional risk factors may also interact with management of SLE disease activity; for example smoking decreases responsiveness to antimalarial therapy [18, 19]. Some risks like diabetes and hyperlipidemia may also be increased as secondary effects of glucocorticoid therapy [20], while others may be directly influenced by SLE disease activity itself. For instance, high levels of very low density lipoprotein (VLDL) and triglycerides (TG) and low levels of high density lipoprotein (HDL) have been described as the “lupus pattern,” and are more strikingly noted in patients with active disease [21].

Although traditional cardiac risk factors clearly play a role in the pathogenesis of atherosclerosis in SLE, they do not fully explain the increased risk. For example, after controlling for gender, blood pressure, diabetes, cholesterol, smoking, and left ventricular hypertrophy in a Canadian cohort, Esdaile et al found the relative risk attributed to SLE for MI was 10.1 and 7.9 for stroke [22]. In a separate cohort, Chung et al found that 99% of SLE patients were identified as low risk using the Framingham risk calculator, with a 10-year risk estimate of <1%; however, 19% of SLE patients in the cohort had coronary calcium on EBCT [23]. Similarly, in a SLE cohort from Toronto, the mean Framingham 10-year risk of a cardiac event did not differ between 250 patients with SLE and 250 controls [24]. This study did reveal, however, a higher prevalence of non-traditional cardiac risk factors in patients with SLE, including premature menopause, sedentary lifestyle, and increased waistto-hip ratio [24]. Thus, while SLE patients are subject to the same traditional risk factors as the general population [22, 25, 26], these factors do not adequately account for the significantly increased level of cardiovascular disease.

SLE Specific Risk Factors

Disease activity, Duration, and Damage

The association between SLE disease activity and atherosclerosis has been variable. One inception cohort study found no association between disease activity (measured using SLEDAI-2K) and cardiovascular events [27], while several other studies found that higher SLEDAI scores did predict MI and /or stroke [28–30]. Similarly, although one study found that higher mean disease activity scores were significantly associated with subclinical atherosclerosis (increased coronary calcium scores) [31]; Manzi et al. found an inverse relationship between SLE activity and carotid plaque [32], while several other studies found no association between disease activity and progression of atherosclerosis [33–35]. Renal disease activity also appears to be a risk factor for atherosclerosis in patients with SLE; in one large study, both pediatric and adult patients with ESRD and SLE had significantly higher mortality due to cardiovascular disease than age-matched non-SLE patients with ESRD [36]. A history of previous nephritis has also been associated with subclinical atherosclerosis in some [37–39] [40], but not all studies [41, 42]. Interestingly, although low complement levels are considered markers of disease activity in SLE, several groups have

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found higher C3 levels to be associated with longitudinal progression of carotid plaque [43] and IMT [44], and cross-sectional presence of coronary calcium [45].

The association between atherosclerosis and disease duration and damage in SLE has been more consistent; several cross-sectional cohort studies have seen significant associations between longer disease duration and carotid plaque [32, 42] and coronary calcium scores [31, 37]. Higher SLICC damage index (SDI) scores have also been associated with coronary artery disease [46], progression of coronary calcium [47], and carotid plaque both in a cross-sectional [42] and in a longitudinal study [33].

Potential Biomarkers for Atherosclerosis in SLE

It would be ideal for clinicians to have a biomarker or biomarker panel that could easily identify patients at future risk for cardiovascular disease. Multiple potential biomarkers have been identified, although most of these are still in preliminary phases of investigation. Here we will highlight novel biomarkers with the strongest evidence, including those that have been associated either with cardiovascular events or with prospective longitudinal measures of subclinical atherosclerosis. Many other potential biomarkers have been identified in cross-sectional studies; Table 1 includes those biomarkers that have evidence of an association even after accounting for potential confounding factors by using multivariate analysis.

Antiphospholipid antibodies

Although antiphospholipid antibodies (aPL) cause venous and arterial clotting, and have been associated with myocardial infarctions in the general population [48], the association with atherosclerosis in SLE patients has been inconsistent. In the LUMINA cohort study, aPL were an independent risk factor for cardiovascular or cerebrovascular events [49]. In the Hopkins Lupus cohort, lupus anticoagulant was the only antiphospholipid associated with myocardial infarction [50]. More recently, however, there was no association of aPL with events in an inception cohort of 1,249 SLE patients [27]. Several studies using measures of subclinical atherosclerosis have not found any significant associations with aPL after adjustment for confounding factors [32, 42, 51, 52].

CRP

CRP is a well established predictor of cardiovascular events in the general population, especially in combination with hypercholesterolemia [53]. It is thought that CRP is not solely a marker of systemic inflammation, but rather may play a direct role in the pathogenesis of atherosclerosis. For example, CRP has been shown in vitro to activate complement [54], and to stimulate endothelial cells to express adhesion molecules [55] and MCP-1 [56]. In SLE subjects, however, the role of CRP as a predictor of atherosclerosis is less clear. Elevated CRP levels have been associated with cardiovascular events in the LUMINA cohort [16, 57] and high-sensitivity CRP (hs-CRP) levels were associated with cardiovascular mortality in a prospective Swedish Lupus Cohort [58]. Hs-CRP has also been associated with both cross-sectional [59] and longitudinal progression of carotid IMT [34]. Several other studies, however, did not find an association between atherosclerosis and CRP in SLE [35, 42, 52, 60].

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pro-Inflammatory HDL

As noted above, anti-inflammatory HDL function is as important as quantity in prevention of atherosclerosis [10]. During states of chronic inflammation, such as in patients with SLE, HDL can be converted from their usual anti-inflammatory state to pro-inflammatory, and can actually increase oxidation of LDL and inflammation [11]. Our group has found that HDL function is abnormal in many women with SLE; 45% of women with SLE, compared to 20% of rheumatoid arthritis patients and 4% of controls, had pro-inflammatory HDL (piHDL) that was unable to prevent oxidation of LDL [12]. HDL dysfunction has also been described in primary antiphospholipid syndrome, as HDL isolated from aPL patients had blunted beneficial effects on vascular cell adhesion molecule 1 expression, superoxide production, and monocyte adhesion following activation of human aortic endothelial cells [61]. Subsequent studies in our longitudinal cohort of 300 SLE patients and 168 controls have demonstrated that piHDL is strongly associated both with cross-sectional [41] and longitudinal progression of carotid plaque and IMT [35].

Paraoxonase

Serum paraoxonase (PON1) is a serum esterase that is secreted primarily by the liver, and is associated with HDL in plasma. PON1 has been identified as one of the important components of HDL that prevents lipid peroxidation and blocks the pro-inflammatory effects of mildly oxidized LDL [10]. Decreased levels of PON activity have also been associated with atherosclerosis in the general population [62]. Altered levels of PON activity have also been seen in patients with SLE. In one study, PON activity was reduced in SLE and antiphospholipid syndrome patients compared to controls, although there was no reduction in the total antioxidant capacity of the plasma [63]. In another study of 55 SLE patients, titers of anti-apoA1 antibodies were inversely correlated to PON1 activity, and in-vitro studies confirmed that apo-AI antibodies have a direct inhibitory effect on PON activity [64]. Decreased PON activity has been associated with increased carotid artery IMT and abnormal flow-mediated dilation in patients with primary Antiphospholipid Antibody Syndrome (APS) [61] and was also associated with atherosclerotic events in a small cross-sectional study of 37 patients with SLE [65].

Adipocytokines

The adipokine leptin is an anorectic peptide that acts on the hypothalamus to modulate food intake, body weight, and fat stores [66]. Obese people have high circulating leptin levels, but they develop leptin resistance similar to insulin resistance in type II diabetes [66]. Hyperleptinemia in the general population associates with hypertension, metabolic syndrome, oxidative stress, and atherosclerosis [66]. Conversely, adiponectin levels are inversely correlated with adipose tissue mass [67], and are reduced in type II diabetes and cardiovascular disease [67].

Several small cohort studies have shown elevated leptin levels in adult [68–70] and pediatric [71] SLE patients. In our cohort, leptin levels were significantly higher in the SLE patients with carotid plaque than in those without plaque, and also weakly correlated with carotid IMT in both a crosssectional [72] and prospective longitudinal study [35] even after accounting for confounding factors such as age, hypertension, and diabetes. In another

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cohort, adiponectin levels were significantly and independently associated with carotid plaque in SLE [73]. However, Chung et al. found no significant relationship between leptin or adiponectin levels and coronary calcification in SLE [74].

Homocysteine

Homocysteine is another predictor of atherosclerosis in the general population [75]. Homocysteine may play a direct role in the pathogenesis of SLE through its toxic effects on the endothelium [76]. Homocysteine also increases free oxygen radicals [77], stimulates monocytes to secrete MCP-1 and IL-8 [78], enhances foam cell formation in vessel walls [79], and is prothrombotic [80]. Hyperhomocysteinemia can result from increased age, renal insufficiency, medications such as methotrexate, genetic, and/or dietary factors [81, 82].

In one cohort study of 337 SLE patients, hyperhomocysteinemia was an independent predictor of stroke and cardiovascular events [83]. In several other studies, elevated levels of homocysteine in SLE correlated with cross sectional [24, 37, 84–86] and longitudinal progression [33, 44, 47] of subclinical atherosclerosis in SLE. In other recent studies of SLE, however, homocysteine did not correlate with atherosclerosis [42, 45, 51].

Biomarker Panels

Through our longitudinal cohort study of cardiovascular disease in SLE at UCLA, we have identified several potential biomarkers for the progression of subclinical atherosclerosis. These include piHDL, leptin ≥ 34 ng/mL, soluble TNF-like weak inducer of apoptosis (sTWEAK) ≥ 373 pg/mL, homocysteine ≥ 12mmol/L, age ≥ 48, and history of diabetes [35]. Although each identified variable was predictive for the longitudinal development of carotid plaque in multivariate analysis, no individual variable reflected a balanced risk profile with strong positive and negative predictive values (PPV and NPV), specificity (Sp), and sensitivity (Sn). For example presence of diabetes had 98% Sp for the presence of plaque in our cohort; however, Sn was only 13%[35].

We next hypothesized that a panel of predictors may give a more complete assessment of atherosclerotic risk that any one individual predictor. Using this theory, we created a risk variable, *PREDICTS*, with low risk defined as the baseline presence of 0–2 predictors and high risk as ≥3 predictors or diabetes plus ≥1 predictor. In multivariate analysis controlling for other CV risk factors and disease factors, patients with high baseline *PREDICTS* risk had a **27.7** fold increased odds ratio (OR) for any carotid plaque at baseline or follow-up ($p<0.001$), a **15.5** fold increased OR for new plaque progression, and **8.0** fold increased OR for IMT progression ($p<0.001$). The high *PREDICTS* variable had a NPV for plaque presence of 94%, a PPV of 64%, Sp of 79%, and Sn of 89%, giving this combination variable better overall predictive value compared to any individual marker [35]. This panel will need to be refined and validated in other SLE cohorts, but it does highlight the concept that a combination of risk factors may more accurately capture the processes that lead to the development of ATH in our patients than any individual marker.

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Subclinical Measures of Atherosclerosis

Cardiovascular events are the “gold standard” outcome measurement in atherosclerosis clinical trials and cohort studies. However, the length of time required for cardiac events to accumulate combined with a desire to detect and initiate preventive treatments in our patients prior to the onset of cardiovascular damage has led to the development of surrogate markers. A variety of surrogate measurements have been used to detect the incidence of subclinical atherosclerosis in SLE patients. In a cross-sectional study using carotid ultrasound as a surrogate measure, Roman et al. found that carotid plaque was present in 37% of SLE patients compared with 15% of controls [42]. In a shortterm longitudinal follow-up study in this cohort, atherosclerosis developed or progressed in SLE patients at an average rate of 10% per year. Further studies using carotid plaque as a surrogate measure have reflected similar prevalences [32, 33, 51] and rates of progression [43] of subclinical atherosclerosis in SLE. Furthermore, a recent prospective observational study by Kao et al found that both baseline carotid IMT and presence of plaque were predictive of future cardiovascular events independent of traditional CV risk factors and medication use [87].

Other modalities have also been used to screen for subclinical atherosclerosis in SLE patients. In one study using electron beam computerized tomography, coronary calcification was present in 31% of SLE patients compared to 9% of controls (11). In another study using dual-isotope single photon emission computed tomographic (SPECT) myocardial perfusion imaging, 38% of SLE patients had perfusion defects [88]. When another marker of subclinical atherosclerosis, endothelial dysfunction, was evaluated by ultrasound, 55% of SLE patients had impaired flow-mediated dilation compared to 26.3% of control subjects [89].

In addition to abnormalities of the macrovasculature in SLE, there is evidence to suggest abnormal coronary microvascular function. When positron emission tomography (PET) scanning was used, abnormal Coronary Flow Reserve (CFR) was seen even in SLE patients with normal coronary arteries [90]. Abnormal stress myocardial perfusion imaging (shown by adenosine stress cardiac magnetic resonance imaging (MRI)) was found in 44% of SLE patients with angina and chest pain in the absence of obstructive CAD; quantitative myocardial perfusion reserve index (MPRI) was also observed to be lower in patients with SLE than controls, and the presence of SLE was a significant predictor of myocardial perfusion reserve index [91]. It should be reiterated, however, that although these measures of subclinical atherosclerosis are significantly linked to coronary events in the general population [92], only abnormal carotid IMT, plaque, and myocardial perfusion have been shown to predict future cardiovascular events in SLE [88].

Management Strategies for Prevention of Cardiovascular Complications in SLE:

Minimizing Framingham risk factors

In the future, it is likely that novel “SLE-specific” risk prediction panels will be developed and validated for identification of high-risk patients who should be targeted with therapeutic interventions to prevent cardiovascular complications. Currently, expert panels in both the

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US and in Europe recommend that SLE patients should be annually screened for traditional modifiable risk factors for cardiovascular disease, including smoking status, blood pressure, BMI, diabetes, and serum lipids [93, 94]; however, no randomized clinical trials for the prevention of atherosclerosis in SLE exist to guide clinicians once high risk patients are identified [95]. Our current screening and treatment strategies are extrapolated from the best available evidence for the general population, with some modifications for consideration of lupus-specific issues.

Hypertension: anti-hypertensives—Because of the high relative risk for cardiovascular morbidity and mortality in SLE, it has been suggested that SLE should be considered a cardiac risk equivalent similar to diabetes [96]. Therefore SLE patients should be treated to the target blood pressure levels of 130/80, as recommended by the Joint National Committee (JNC 7) for those with other high-risk co-morbid conditions [36, 97]. No optimum SLE-specific antihypertensive medication regimen has been established [98]; however, ACE inhibitors, are generally the drug of choice in patients with renal disease [99], and are recommended as first line therapy in rheumatic disease patients by the European League Against Rheumatism guidelines because of their potential favorable effects on inflammatory markers and endothelial function [100]. In addition, in one cross-sectional study, carotid atherosclerosis was associated with ACE-inhibitor non-use [101]. Angiotensin receptor blockers (ARB) can also be considered in patients who cannot tolerate ACE inhibitor therapy [102]. Thiazide diuretics are recommended as first line therapy for hypertension in the general population by JNC 7, and would generally also be a safe choice in SLE subjects [36]. Calcium channel blockers may be useful in patients with co-existing Raynaud's phenomenon or pulmonary hypertension, but have been associated in several cases with development of subacute cutaneous lupus [103]. Beta-blockers have been shown to precipitate Raynaud's phenomenon [104], and thus should be used with caution in SLE subjects..

Dyslipidemia: Statin use—Statins are widely used in the general population to reduce cardiovascular morbidity [105–107]. In addition to their lipid lowering properties, statins have a variety of direct anti-inflammatory and immunomodulatory effects, including a diminished secretion of pro-inflammatory cytokines and chemokines [108–110]. Statins also inhibit adhesion molecules, reactive oxygen species formation, T-cell activation, and the upregulation of nitric oxide synthesis [111]. In an in-vivo study of statins in a mouse model of SLE and atherosclerosis, the *gld*.apoE$^{-/-}$ mouse, simvastatin therapy decreased atherosclerotic lesion area and reduced lymphadenopathy, renal disease, and pro-inflammatory cytokine production, even though it did not alter cholesterol levels [112].

Although there is an abundance of data to support the use of statins in primary and secondary prevention of atherosclerosis in the general population [105, 113, 114], the data in lupus patients has been much less consistent. In a recent small study of 21 patients with SLE, statin use improved disease activity measured by SLAM-R scores at 6 months, but did not result in any changes in levels of potential cardiac biomarkers such as TNF-alpha VEGF, IL-6, or sCD40L [115]. In another small study of 60 SLE patients, atorvastatin 40mg daily resulted in decreased lipid and C-reactive protein levels, and slowed progression of coronary

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calcium, but demonstrated no change in myocardial perfusion defects compared to placebo [116]. In a trial of 33 post-renal transplant lupus patients, those randomized to fluvastatin therapy had a 73% reduction in cardiac events, although this difference did not quite reach statistical significance (p=0.06). Atorvastatin 20 mg daily for 8 weeks improved endothelium-dependent vasodilation in 64 women with SLE, even after accounting for the presence of traditional cardiac risk factors [117]. In the largest trials conducted, however, the results were less promising. For example, in a 2-year randomized controlled trial of atorvastatin 40 mg daily in 200 women with SLE, statins did not significantly prevent progression of coronary calcium, IMT, or disease activity [118]. Similarly, a randomized controlled trial of atorvastatin conducted in 221 pediatric SLE patients, the APPLE trial, also demonstrated improvements in lipid levels and hs-CRP levels, but showed no significant impact on IMT progression [119]. Many trials that have demonstrated a preventive effect of statins in the general population have larger sample sizes and a longer follow-up duration [120], so it is possible that increased sample sizes and study lengths might have resulted in positive studies. A secondary analysis of the APPLE trial did indicate that in pubertal SLE patients with high baseline hs-CRP levels, atorvastatin did decrease IMT progression. This suggests that identification of high-risk patients for inclusion in clinical trials may increase the likelihood that beneficial therapeutics will have positive trial results. Further investigations are needed to clarify the role that statins could play in the prevention of atherosclerosis in rheumatic disease populations. Until further studies are conducted to determine the safety and efficacy of statin therapy in a broader population of patients with SLE, statin therapy should be limited to published guidelines such as the National Cholesterol Education Panel [121].

The Impact of Modulators of Lupus Disease Activity on Cardiovascular Disease

Anti-malarial therapy

Multiple retrospective cohort studies have demonstrated improved overall survival [122, 123] in SLE patients treated with antimalarial agents. There is some evidence to suggest that hydroxychloroquine may confer some protection by modulating cardiovascular risk. For instance, anti-malarials may have indirect cardioprotective benefits by improving lipid profiles [124] [125] and improving glycemic control [126]. There is also a reduced incidence of thrombotic events in SLE patients treated with antimalarials [19, 122, 127, 128]. In two prospective lupus cohort studies, anti-malarial use was associated with a 50–60% decreased risk for cardiovascular events. Non-use of hydroxychloroquine was associated with higher aortic stiffness [129] and plaque on carotid ultrasound [42], two subclinical measures of atherosclerosis. Although the exact mechanisms by which anti-malarials exert protection are not well understood, the recent understanding that hydroxychloroquine is an antagonist of TLR 7 and 9 signaling is intriguing, given the postulated roles of IFN-alpha in endothelial dysfunction and abnormal vascular repair [130]. Prospective randomized studies demonstrating a cardioprotective effect of hydroxychloroquine in patients with SLE are needed.

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Azathioprine

One retrospective case-control study of SLE patients with documented coronary artery disease found that patients with CAD were more likely to have been treated with azathioprine [131]. Azathioprine use was also associated with cardiac events in the multi-ethnic LUMINA cohort [16] and with increased carotid IMT in the pediatric SLE APPLE cohort [38]. Further studies will be needed to determine whether these associations are due to a direct effect of azathioprine, confounding by indication (that is, patients treated with azathioprine have more severe disease than the general lupus population), or the inability of azathioprine to overcome the inflammation that leads to atherosclerosis.

Glucocorticoids

Glucocorticoid use may impact traditional cardiac risk factors such as hypertension, obesity and diabetes [132]. Additionally, prednisone doses >10 mg/day have been shown to independently predict hypercholesterolemia in SLE [133]. Conflicting data exists, however, regarding the overall risk of glucocorticoid therapy: Both longer duration of corticosteroid treatment [32, 84] and a higher accumulated corticosteroid dose [32, 39, 41, 46, 85] have been associated with a higher incidence of atherosclerosis in various cohorts of patients with SLE. In the APPLE study of pediatric lupus patients, however, the highest and lowest cumulative doses of corticosteroids were associated with increased IMT, while moderate doses were associated with decreased IMT. Roman et al. also found that former or current use of prednisone and average dose of prednisone was significantly less in patients with carotid plaque [42], implying that there may be a threshold dose where the anti-inflammatory effects of glucocorticoids may be atheroprotective, while higher doses may be atherogenic. Until such a threshold is determined, we recommend following the EULAR recommendations that the lowest possible dose of corticosteroids be used in individual patients [100].

Mycophenolate mofetil (MMF)

Mycophenolate mofetil has several potential anti-atherogenic effects. In animal models, MMF inhibits NADPH-oxidase, thereby inhibiting oxidative stress [134]. In patients with carotid artery stenosis, 2 weeks of MMF therapy resulted in increased numbers of regulatory T cells and decreased plaque expression of inflammatory genes [102]. In two separate animal models of SLE and atherosclerosis, MMF treatment significantly reduced atherosclerotic burden in addition to autoantibody circulation [135] and recruitment of $CD4^+$ T cells to atherosclerotic plaques [136]. Studies in both renal and cardiac transplant patients have found decreases in atherosclerosis [137] and in cardiovascular mortality associated with mycophenolate use [138]. A small prospective observational study from our own group of SLE patients suggests that 12-week treatment with MMF and hydroxychloroquine, but not azathioprine, results in significant improvement of pro-inflammatory HDL function (unpublished data). In a recently published longitudinal SLE cohort study, however, exposure of subjects to MMF was not associated with a reduction of IMT or coronary calcium progression [139]. Larger, prospective studies will need to be undertaken to clarify the potential role of MMF in prevention of progression of atherosclerosis in SLE.

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Consideration for future clinical trials

As previously noted, no randomized clinical trials to date have positively identified a successful therapeutic strategy for preventing cardiovascular morbidity in patients with SLE. Unfortunately, there have been barriers to conducting such prevention trials. In one recent randomized controlled pilot trial of cardiovascular preventive medications in a Boston cohort, only 16.8% of eligible patients were willing to participate. Of the 41 patients who did enroll in the trial, over half dropped out within 6 months [98]. Some reasons for clinical trial non-participation and drop-out included patient and treating physician fears regarding placebo use, reluctance to add additional medications to an already complicated medical regimen, and fear of changing treatment when patients felt either “too well” or “too ill.” [95]. Future successful trials will need to be designed with these barriers in mind, and will likely require extensive patient and physician education.

In order to maximize clinical impact, future trials of lupus therapeutics should also examine the effect of new medications on cardiovascular disease. Although lengthy prospective longitudinal studies that demonstrate a reduction in cardiovascular events may not be practical, demonstration of improvements in surrogate measures of atherosclerosis such as imaging modalities or biomarkers could signal additional cardioprotective benefits for new lupus treatments. In addition, examination of lupus specific biomarkers could provide a more thorough understanding of the cardiovascular impact of new drugs. For example, one drug recently approved for rheumatoid arthritis, tocilizumab, was associated with increased mean total and LDL cholesterol; however, and it also altered the content of high-density lipoprotein cholesterol towards an anti-atherogenic phenotype (decreased HDL associated serum amyloid A and increased PON) and decreased some (CRP, Lp(a), D-dimer), but not all other markers associated with cardiac risk [140]. Although additional studies will be needed to confirm that alterations in biomarkers and measures of subclinical atherosclerosis can lead to improved patient outcomes, the goal of future lupus therapeutics should be to develop treatments that both improve short-term disease activity and decrease long-term comorbidities such as cardiovascular disease.

In summary, the prevalence of atherosclerosis is higher in patients with SLE and occurs at an earlier age. The lupus related factors that account for this increased risk are likely numerous and related to the factors described in this review. Identification of at-risk subjects and increasing our understanding of pathogenesis of atherosclerosis in SLE is critical if we are to improve the quality of care and improve mortality in this vulnerable population

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Key Points:

- Cardiovascular disease is a significant contributor to morbidity and mortality in SLE
- SLE-specific risk factors for accelerated atherosclerosis exist but are not well understood
- Identification of SLE-specific biomarkers and screening tests should provide the means to recognize at-risk patients
- Current treatment strategies aim to target modifiable cardiac risk factors

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Table 1.

Traditional and non-traditional cardiac risk factors in patients with SLE

Biomarkers	Studies Demonstrating Significant Association with Overt Clinical or Subclinical Atherosclerosis	Reference
Adiponectin	Higher levels associated with carotid plaque in crosssectional study of 119 SLE and 71 controls	[141]
Annexin A5	Increased Carotid IMT and abnormal Flow-mediated Dilation, cross-sectional study of 133 SLE patients	[142]
Antiphospholipid Antibodies	Associated with cardiovascular events in two cohort studies, but not with events in another large inception cohort of 1249 SLE patients	[49, 50]; not associated [27, 32, 42, 51,52]
Asymmetric dimethylarginine (ADMA)	Associated with arterial stiffness but not carotid atherosclerosis in cross-sectional study of 125 SLE patients	[143]
C3, C5a	Increased C3 levels associated with carotid plaque progression in 217 SLE and 104 controls; C3 and C5a associated with carotid IMT progression in 101 SLE patients; also associated with coronary calcium in cross-sectional study of 75 SLE patients; also with increased aortic stiffness	[43, 44]; [45, 59]
CRP/hsCRP	Associated with cardiovascular events and mortality in two large SLE cohorts; associated with cross-sectional and longitudinal IMT progression in some but not all studies	Positive association [16, 34, 57–59] No association: [35, 42, 52, 60]
Erythrocyte NO production	Negatively associated with carotid IMT in cross sectional study of 191 SLE and RA subjects (data combined)	[144]
E-selectin	Higher levels associated with carotid plaque in crosssectional study of 119 SLE and 71 controls and with cross-sectional coronary calcium in 109 SLE and 78 controls	[141, 145]
Fatty acid-binding protein4 (FAB4)	Associated with increased carotid IMT, cross-sectional study of 60 SLE, 34 controls	[146]
Homocysteine	Associated with stroke and arterial thrombosis in a prospective cohort study of 337 patients and with subclinical ATH in several (but not all) longitudinal and cross-sectional cohorts	[83] [24, 33, 37, 44, 47, 84–86]; not associated: [42, 45, 51]
ICAM	Associated with cross-sectional coronary calcium in 109 SLE and 78 controls	[145]
Type I IFN activity	Decreased endothelial function, increased IMT, Increased coronary calcification in cross sectional study of 95 SLE, 38 controls	[147, 148]
Leptin	Associated with carotid plaque in cross sectional study of 250 SLE, 122 controls; also associated with plaque in longitudinal study of 210 SLE, 100 controls	[35, 149]
oxidized LDL; oxidized phospholipids on LDL (Ox-PAPC)	Ox-LDL Positive association with a history of cardiovascular disease in two small retrospective case-control study of SLE subjects with CVD vs. without and in one cross-sectional study of carotid IMT; Ox-PAPC associated with carotid IMT in crosssectional study of 178 SLE patients	[85, 150]; [39]
autoantibodies to oxidized LDL	Positive association with a history of cardiovascular disease in a retrospective case-control study of 26 SLE subjects with CVD and 26 without	[85]; no association [151, 152].
anti-oxidized phosphatidylserine	Low levels associated with higher carotid plaque in cross-sectional study of 144 pts, 122 controls	[153]
Anti- phosphorylcholine (Anti-PC antibodies)	Inversely correlated with the presence of vulnerable carotid plaques in 114 SLE patients and 122 controls	[154]
piHDL	Associated with cross-sectional carotid plaque and IMT in 276 SLE patients and with longitudinal carotid plaque and IMT progression in prospective cohort of 210 SLE and 100 controls	[35, 52]

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Biomarkers	**Studies Demonstrating Significant Association with Overt Clinical or Subclinical Atherosclerosis**	**Reference**
TNF-α	Associated with cross-sectional coronary calcium in 109 SLE and 78 controls	[145]
sTWEAK	Associated with longitudinal carotid plaque progression in prospective cohort of 210 SLE and 100 controls	[35]
VCAM	Associated with cross-sectional coronary calcium in 109 SLE and 78 controls	[145]
Low Vitamin 25(OH)D	Associated with carotid plaque in cross-sectional study of 51 SLE subjects	[101]
von Willebrand factor (vWf)	Associated with cardiovascular events in longitudinal prospective cohort of 182 SLE patients	[155, 156]
Whole blood viscosity	Positively associated with carotid IMT in cross sectional study of 191 SLE and RA subjects (data combined)	[144]