



Review

Assessment and management of the heightened risk for atherosclerotic cardiovascular events in patients with lupus erythematosus or dermatomyositis



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ABSTRACT

For patients with lupus erythematosus (LE) or dermatomyositis (DM), there is an urgent need to address a heightened risk of clinical events, chiefly heart attacks and strokes, caused by atherosclerotic cardiovascular disease (ASCVD). Patients with LE or DM frequently exhibit high levels of conventional risk factors for ASCVD events, particularly dyslipoproteinemia and hypertension; an amplified burden of atherosclerotic plaques; and increased age- and sex-adjusted rates of ASCVD events compared with the general population. The rate of ASCVD events exceeds what would be expected from conventional risk factors, suggesting that disease-specific autoimmune processes exacerbate specific, known pathogenic steps in atherosclerosis. Importantly, despite their heightened risk, patients with LE or DM are often undertreated for known causative agents and exacerbators of ASCVD. Herein, we propose an approach to assess and manage the heightened risk of ASCVD events in patients with LE or DM. Our approach is modeled in large part on established approaches to patients with diabetes mellitus or stage 3 or 4 chronic kidney disease, which are well-studied conditions that also show heightened risk for ASCVD events and have been explicitly incorporated into standard clinical guidelines for ASCVD. Based on the available evidence, we conclude that patients with LE or DM require earlier and more aggressive screening and management of ASCVD. We suggest that physicians consider implementing multipliers of conventional risk calculators to trigger earlier initiation of lifestyle modifications and medical therapies in primary prevention of ASCVD events, employ vascular imaging to quantify the burden of subclinical plaques, and treat to lower lipid targets using statins and newer therapies, such as PCSK9 inhibitors, that decrease ASCVD events in nonautoimmune cohorts. More clinical vigilance is needed regarding surveillance, prevention, risk modification, and treatment of dyslipidemias, hypertension, and smoking in patients with LE or DM. All of these goals are achievable.

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What is known about this subject in regard to women and their families?

- Lupus erythematosus and dermatomyositis, two multisystem autoimmune diseases, have a high female predominance.
- Patients with lupus erythematosus or dermatomyositis have increased conventional risk factors for atherosclerotic cardiovascular disease (ASCVD), an amplified burden of atherosclerotic plaques compared with the general population, and increased age- and sex-adjusted rates of ASCVD and thrombotic events.
- The number of ASCVD events exceeds what would be expected from conventional ASCVD risk factors alone, suggesting that disease-specific autoimmune processes exacerbate atherosclerosis.

What is new from this article as messages for women and their families?

- We propose an approach to manage the heightened risk of atherosclerotic cardiovascular disease events in patients with lupus erythematosus (LE) or dermatomyositis (DM), modeled on established approaches for patients with diabetes mellitus or chronic kidney disease.
- We suggest that physicians consider implementing multipliers of conventional risk calculations to trigger earlier initiation of lifestyle modifications and medical therapies to lower ASCVD event risk, treat to lower lipid targets using statins and newer therapies (e.g., PCSK9 inhibitors), and employ vascular imaging to quantify subclinical plaque burden.
- More clinical vigilance is needed regarding surveillance, prevention, risk modification, and treatment of dyslipidemias, hypertension, and smoking in patients with LE or DM; these management strategies will help improve outcomes for patients with LE or DM, the large majority of whom are women.

Introduction

Lupus erythematosus (LE) and dermatomyositis (DM) are multi-system autoimmune connective tissue diseases with systemic and cutaneous manifestations. The two diseases have many overlapping features, such as similar skin manifestations, range of significant systemic comorbidities, involvement of internal organs (including the lungs and myocardium), substantially impaired quality of life, and risk of premature mortality. LE in particular also affects the brain and kidneys. Polymyositis is distinct from DM (Findlay et al., 2015) and is outside the scope of this article.

Ongoing improvements in the management of LE and DM have substantially decreased early mortality, which was previously a

feature of both diseases (Hochberg et al., 1983; Urowitz et al., 1976). Early deaths arose from remarkably high rates of infection in the context of active autoimmune disease and high doses of glucocorticoids. As early mortality has diminished, life expectancy has increased (Doria and Briani, 2008; Li et al., 2020; Nossent et al., 2007). Accordingly, atherosclerotic cardiovascular disease (ASCVD), always an important source of morbidity and mortality in LE and DM, has become even more prominent (Bohan et al., 1977; Urowitz et al., 1976). The increasing problem of ASCVD later in life indicates how far the field has progressed in helping these patients (Rao et al., 2019), as well as the increasing need to incorporate assessment and management of the risk for ASCVD events into routine clinical care for patients with LE or DM.

LE and DM patients often have elevated levels of conventional ASCVD risk factors, such as dyslipoproteinemia and hypertension, which are exacerbated by some anti-inflammatory medications. These patients have an increased burden of atherosclerotic plaques, as well as increased age- and sex-adjusted rates of ASCVD and thrombotic events, principally heart attacks and strokes. Their event burden exceeds what would be expected from their conventional ASCVD risk factors.

Despite the high risk for ASCVD events, statin use in patients with LE remains low (Masson et al., 2020; Munguia-Realpozo et al., 2019). Physicians may be concerned about statin-associated muscle symptoms (SAMS) and reluctant to treat patients with DM with these medications. Hypertension is common in patients with LE (Munguia-Realpozo et al., 2019), and >30% of patients with LE in a recent series from an LE specialty clinic were persistently hypertensive with a much higher rate of atherosclerotic vascular events than patients with LE from the same clinic who were normotensive on treatment (Tselios et al., 2020). Smoking was also significantly associated with higher ASCVD event rates in patients with LE (Tselios et al., 2020). Unfortunately, conventional calculators of ASCVD event risk do not account for the presence of LE or DM, nor do they calculate the risk of an ASCVD event in the next 10 years (10-year risk) for anyone age <40 years (they will calculate the lifetime risk of an ASCVD event for individuals down to 20 years of age). An added difficulty is the near impossibility of large-scale, long-term, prospective, randomized, controlled trials limited to patients with LE or DM to evaluate the effects of lipid-lowering and blood pressure-lowering therapies on ASCVD events.

Herein, we present an overview of the pathogenesis of ASCVD (Figure 1 and associated text), specific processes in LE and DM that may make ASCVD worse (Tables 1 and 2), and clinical evidence of increased atherosclerosis and ASCVD events in these conditions (Table 3). Based on this information, we present a step-by-step approach (Figure 2, Table 4, and Table 5) for the assessment and management of the heightened risk of ASCVD events in patients with LE and DM. Our proposed approach is modeled in large part on established approaches to patients with diabetes mellitus or stage 3 or 4 chronic kidney disease (CKD), which are well-studied conditions that also show a heightened risk of ASCVD events and have been explicitly incorporated into standard clinical guidelines

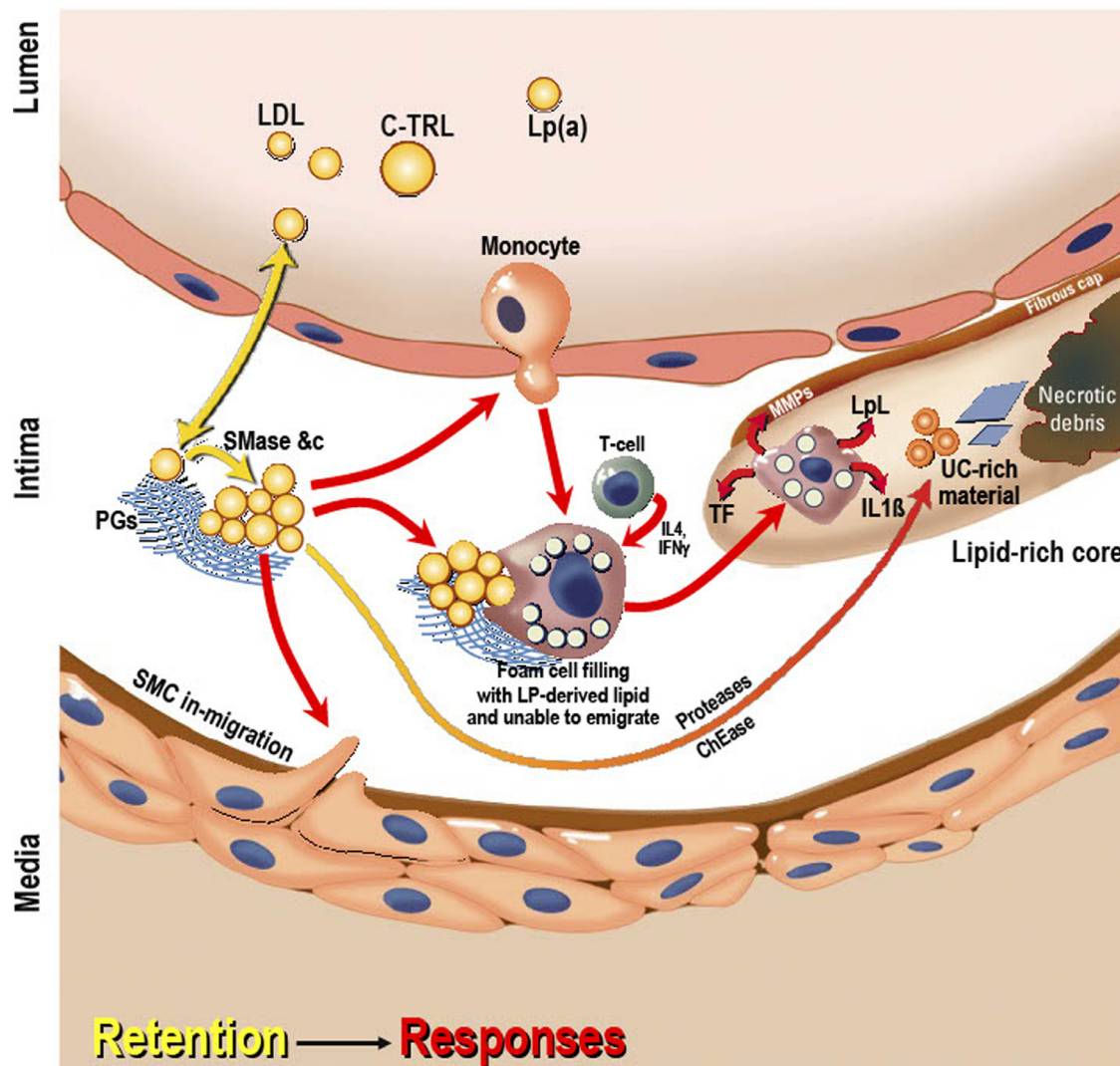


Fig. 1. Response-to-retention model of initiation and progression of atherosclerosis (adapted with permission from Williams and Tabas, 2005). Arrows are color-coded to indicate crucial mechanisms in the retention of cholesterol-rich atherogenic apolipoprotein-B-lipoproteins within the arterial wall, which is the key initiating step in atherogenesis (yellow), and then local responses to the retained and modified lipoproteins that lead to plaque growth and evolution (red). The main text describes molecular mechanisms for early retention and aggregation of apoB-lipoproteins within the arterial wall and then the acceleration of lipoprotein retention after plaque initiation and other subsequent maladaptive responses. ChEase, cholesteryl esterase; C-TRL, cholesterol- and triglyceride-rich apoB-containing lipoprotein; foam cell, a macrophage or smooth muscle cell that has accumulated intracellular droplets of lipid; IFN, interferon; IL, interleukin; LDL, low-density lipoprotein; LP, lipoprotein; Lp(a), lipoprotein(a); LpL, lipoprotein lipase; MMPs, matrix metalloproteinases; PGs, proteoglycans; SMase, sphingomyelinase; SMC, smooth muscle cell; TF, tissue factor; UC, unesterified cholesterol.

for ASCVD (Arnett et al., 2019; Jellinger et al., 2017; Mach et al., 2020).

Why do LE and DM exacerbate atherosclerosis, thrombosis, and ASCVD events? A primer on the pathogenesis of atherosclerosis, the role of risk factors, targets for therapy, and likely effects of LE and DM

By now, a large body of literature has established that the key initiating event in atherosclerosis is the retention, or trapping, of plasma-derived low-density lipoprotein (LDL) and related cholesterol-rich lipoproteins within the subendothelial region of the arterial wall (Fig. 1; Borén and Williams, 2016; Borén et al., 2020; Williams and Tabas, 1995). The principal protein of all atherogenic lipoproteins, including LDL, is a large hydrophobic molecule called apolipoprotein-B (apoB), and each atherogenic lipoprotein particle contains exactly one molecule of apoB. In the earliest stages of atherogenesis, specific domains of apoB adhere directly to specific elements of the subendothelial arterial ma-

trix, particularly at branch points, to drive lipoprotein retention (Borén and Williams, 2016; Skálén et al., 2002; Steffensen et al., 2015; Williams and Fisher, 2015; Williams and Tabas, 1995). These retained lipoproteins become aggregated under the action of local enzymes, such as lipoprotein lipase and the secretory sphingomyelinase (Borén and Williams, 2016; Ruuth et al., 2018; Tabas et al., 1993; Williams and Tabas, 1995). The resulting material provokes a series of strikingly maladaptive responses that accelerate further lipoprotein retention and progression of the atherosclerotic plaque (Fig. 1).

One of these maladaptive responses is the recruitment of macrophages and T cells into the arterial wall. The macrophages then phagocytose retained, aggregated apoB-containing lipoproteins, thereby accumulating intracellular droplets of lipid. Importantly, local antiemigration signals within progressing plaques prevent the macrophages from leaving (Llodrá et al., 2004; Williams and Tabas, 2005; van Gils et al., 2012). Persistent macrophages in atherosclerotic plaques release several harmful products, such as proteins that bridge between LDL and the arterial matrix to pro-

Table 1
Specific processes in LE and DM that could accelerate atherosclerosis and then increase the risk of atherosclerotic cardiovascular disease events

Pathogenic step	Explanation
Plaque initiation	Worsening of causative agents (dyslipoproteinemia: elevated plasma triglycerides, with low levels of high-density lipoprotein cholesterol) and exacerbators (hypertension, renal disease), associated with LE or DM per se and with therapies, particularly glucocorticoids (Amaya-Amaya et al., 2014; Borba and Bonfá, 1997; Sherer and Shoenfeld, 2006; Szabó et al., 2017; Tselios et al., 2020). Possible effects beyond conventional factors: increased LDL retention through effects on arterial matrix and susceptibility of LDL to aggregate owing to changes in its lipidome specific to LE and DM (Ferreira et al., 2019; Raouf et al., 2018; Ruuth et al., 2018). Endothelial dysfunction (a known feature of LE and DM; Sciatti et al., 2019; Vincze et al., 2014) might include increased permeability to the entry of LDL and other apolipoprotein-B lipoproteins.
Plaque growth	Worsening of causative agents (dyslipoproteinemia) and exacerbators (hypertension, renal disease). Increased immune-cell responses to retained lipoproteins, a finding in mouse models of LE after they are made hypercholesterolemic (George et al., 1997; Gu et al., 1999; Ma et al., 2008; Qiao et al., 1993; Stanic et al., 2006). Endothelial dysfunction in this context might include increased expression of chemoattractants and cell adhesion molecules. Increased induction and intra-arterial secretion of local proaggregation enzymes (lipoprotein lipase and secretory sphingomyelinase) released from activated endothelium and local persistent immune cells (macrophages; Marathe et al., 1998).
Plaque destabilization Formation of occlusive thrombus	Decreased collagen synthesis; increased protease production (Santiago-Raber et al., 2020; Zhang et al., 2015). Systemic procoagulant state and hyperresponsive platelets that increase the likelihood of the formation of an occlusive thrombus after plaque rupture or erosion. Procoagulant microvesicles have been implicated, particularly tissue factor-positive microvesicles (Liu et al., 2016). Endothelial dysfunction in this context might include impairment of the anticoagulant luminal surface and impaired vasodilation, thereby facilitating occlusion.

DM, dermatomyositis; LDL, low-density lipoprotein; LE, lupus erythematosus

mote more avid LDL retention, additional sphingomyelinase that promotes further LDL aggregation, proteases that weaken the fibrous cap overlying the plaque and predisposing to its rupture or erosion, and tissue factor that ensures robust clot formation upon plaque rupture or erosion (Fig. 1). Abnormal enrichment of cell membranes or membrane fragments with lipoprotein-derived cholesterol, or the development of frank crystals of cholesterol, has been reported to provoke additional maladaptive responses, such as activation of prothrombotic pathways, Toll-like receptors, and the NLRP3 inflammasome; release of mature interleukin-1 β (IL1 β); and apoptosis (Duell et al., 2010; Liu et al., 2007; Rajamäki et al., 2010; Sun et al., 2009). Atherosclerosis begins early in life, often during childhood (Borén et al., 2020; Enos, 1953; McMahan, 2005; Strong and McGill, 1962). After many decades, an advanced end-stage plaque ruptures or erodes, and it is typically the clot itself that blocks the arterial lumen to cause an ischemic event downstream (Davies, 1992). Most atherosclerotic heart attacks are caused by ruptured plaques that were <50% occlusive, in large part because such plaques are typically so numerous (Falk et al., 1995; Mann and Davies, 1996).

This pathogenic understanding, called the response-to-retention model, unifies a large body of experimental work in animals and, more importantly, extensive human clinical trials and human Mendelian randomization studies that have separated contributors from noncontributors to ASCVD. Thus, we have been able to reclassify conventional risk factors, which are epidemiologic concepts with no inferences about causality, into *causative agents* (LDL and other apoB-lipoproteins <70 nm in diameter to allow their entry into the arterial wall), *exacerbating factors* that worsen the disease but only if abundant apoB-lipoproteins are present (smoking, diabetes mellitus, hypertension, male sex), and mere *bystanders* that are associated with future ASCVD events but do not directly affect disease progression (elevated plasma homocysteine levels, periodontal disease, elevated C-reactive protein [CRP] levels; Borén and Williams, 2016; Williams and Fisher, 2015). Nearly all causative agents and exacerbators that can be modified have proven to be successful targets for therapy to reduce ASCVD events. Bystanders have been tested but failed. Since at least 1980, the clinical management of causative agents and exacerbating factors has resulted in a large population-wide drop in age- and sex-adjusted rates of ASCVD events in the United States and elsewhere (Ford et al., 2007; Greenland and Lloyd-Jones, 2007; Nemetz et al., 2016). Nev-

ertheless, further work needs to be done: ASCVD remains the leading killer in the world (World Health Organization, 2021).

In systemic LE (SLE) and cutaneous LE (CLE), patients often exhibit a dyslipoproteinemia that can include elevated plasma triglycerides (TGs) with low levels of high-density lipoprotein cholesterol (HDLc; Table 1, Table 2). Of note, the dyslipoproteinemia in SLE patients correlates with LE disease activity measured by the SLE Disease Activity Index (Borba and Bonfá, 1997; Szabó et al., 2017) and is typically worsened by glucocorticoids (Petri et al., 1994; Tselios et al., 2020). An additional feature of SLE dyslipidemia that is often mentioned is an increase in oxidized LDL. Unfortunately, LDL oxidation has repeatedly failed as a therapeutic target and now appears to be merely a bystander in ASCVD (Borén and Williams, 2016; Williams and Fisher, 2015). Numerous large-scale prospective randomized clinical trials of antioxidant administration, including under conditions that protect LDL from oxidative modifications *ex vivo*, failed to show cardiovascular benefit (Greenberg, 2005; Stocker and Keaney, 2004). Moreover, several components of the heart-healthy lifestyle, such as aerobic exercise and the consumption of polyunsaturated fat and moderate amounts of alcohol, are pro-oxidant (Borén and Williams, 2016; Williams and Fisher, 2005; 2015).

More recently, plasma levels of HDLc have also come into serious doubt as important participants in ASCVD, owing to negative results so far from clinical trials of HDL-raising agents and from human Mendelian randomization studies (Borén and Williams, 2016; Holmes et al., 2015; Voight et al., 2012). Low plasma levels of HDLc appear to be mainly a marker for high levels of cholesterol- and triglyceride-rich apoB-containing lipoproteins (C-TRLs), an important class of atherogenic lipoproteins in overnutrition, obesity, the metabolic syndrome, and type 2 diabetes mellitus (Williams and Wu, 2016). These latter conditions are overrepresented in patients with LE or DM, especially during treatment with glucocorticoids (Table 1, Table 2 and the section, below, on “Increased prevalence of conventional risk factors for ASCVD events in patients with LE or DM”).

In the context of LE and DM, three points deserve special emphasis. First, specific processes in LE and in DM plausibly affect several specific steps in the pathogenesis of atherosclerosis and then ASCVD events. The most straightforward connection is an increase in LE and DM in known causative agents and exacerbators for atherosclerosis and ASCVD events (Table 1 and the section,

Table 2

Prevalence of conventional risk factors for ASCVD events in SLE, CLE, DM, and juvenile DM compared with nonautoimmune cohorts

Autoimmune disease and Risk factor for ASCVD events	Odds ratio (95% confidence interval) or percentage (p-value)	Reference
SLE		
Presence of metabolic syndrome	45.2% vs. 32.7% in controls ($p = .04$)	das Chagas Medeiros et al., 2016
Diabetes mellitus	OR: 6.00 (1.36–26.53) 9.7% vs. 2.9% in controls ($p = .004$) 15.11% vs. 3.6% in controls ($p = .001$)	Bruce et al., 2003 das Chagas Medeiros et al., 2016 Yang et al., 2012
Current smoker	0.86 (0.59–1.24), NS	Bruce et al., 2003
Hypercholesterolemia	0.92 (0.73–1.17), NS	Bruce et al., 2003
Hypertriglyceridemia	41.4% vs. 23.8% in controls ($p = .004$)	das Chagas Medeiros et al., 2016
Low HDLc	62.5% vs. 51.5% in controls ($p = .08$), NS OR: 1.27 (0.78–2.06), NS	das Chagas Medeiros et al., 2016 Bruce et al., 2003
Hypertension	OR: 2.59 (1.79–3.75) 49.3% vs. 21.8% in controls ($p = .0001$) 50% vs. 8.63% in controls ($p \leq .001$)	Bruce et al., 2003 das Chagas Medeiros et al., 2016 Yang et al., 2012
Family history of premature CAD	1.16 (0.80–1.69), NS	Bruce et al., 2003
CLE		
Presence of metabolic syndrome	48.3% vs. 24.4% in controls ($p = .003$)	Akarsu et al., 2017
Diabetes mellitus	15.7% vs. 12.2% in controls ($p = .38$), NS 10% vs. 11% in controls ($p = .852$), NS	Singh et al., 2016 Akarsu et al., 2017
Current smoking	39.6% vs. 20.6% in controls ($p = .001$) 56.7% vs. 31.7% in controls ($p = .003$)	Singh et al., 2016 Akarsu et al., 2017
Dyslipidemia	66.7% vs. 46.3% in controls ($p = .016$)	Akarsu et al., 2017
Hypertriglyceridemia	43.3% vs. 22.0% in controls ($p = .006$)	Akarsu et al., 2017
Low HDLc	61.7% vs. 23.2% in controls ($p \leq .001$)	Akarsu et al., 2017
Hypertension	54.8% vs. 46.8% in controls ($p = .16$), NS 30% vs. 17.1% in controls ($p = .069$), NS	Singh et al., 2016 Akarsu et al., 2017
Family history of premature CAD	4.1% vs. 3.9% in controls ($p = .95$), NS	Singh et al., 2016
DM		
Presence of metabolic syndrome	41.7% vs. 7.0% in controls ($p < .001$)	de Moraes et al., 2013
Diabetes mellitus	17.9% vs. 1.0% in controls ($p < .001$) 13.0% vs. 9.7% in controls ($p = .0027$)	de Moraes et al., 2013 Lai et al., 2013
Smoking (unspecified current or former)	10.7% vs. 11.4% in controls ($p = .877$), NS	de Moraes et al., 2013
Dyslipidemia and/or hyperlipidemia	67.9% vs. 49.5% in controls ($p = .013$) 11.8% vs. 8.5% in controls ($p = .0015$)	de Moraes et al., 2013 Lai et al., 2013
Hypertension	47.6% vs. 18.1% in controls ($p < .001$) 28.7% vs. 22.6% in controls ($p \leq .0001$)	de Moraes et al., 2013 Lai et al., 2013
Family history of premature CVD	23.8% vs. 8.6% in controls ($p = .004$)	de Moraes et al., 2013
Juvenile DM		
Diabetes mellitus	2.72 (1.25–5.89)	Silverberg et al., 2018
Dyslipidemia	1.74 (0.58–5.20), NS	Silverberg et al., 2018
Hypertension	11.64 (7.63–17.76)	Silverberg et al., 2018
Obesity	2.27 (1.30–3.98)	Silverberg et al., 2018

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CLE, cutaneous lupus erythematosus; CVD, cardiovascular disease; DM, dermatomyositis; HDLc, plasma concentration of high-density lipoprotein cholesterol; NS, not significant; OR, odds ratio; SLE, systemic lupus erythematosus

PubMed was searched from 1990 to 2021 for each type of risk factor for ASCVD events in combination with each of the autoimmune diseases listed. All studies were reviewed by at least two co-authors (EK, MG). This table includes studies in which ASCVD event risk factor rates in patients with these autoimmune diseases were statistically compared with rates in a nonautoimmune control group from the same study.

below, on “Increased prevalence of conventional risk factors for ASCVD events in patients with LE or DM”). Table 1 also lists processes in LE and DM that could accelerate atherosclerosis and increase ASCVD event risk beyond the increased prevalence of conventional risk factors. In Table 1, we summarize the possible effects of LE and DM on four steps in atherogenesis and then ASCVD events—namely, plaque initiation, plaque growth, destabilization-rupture, and the formation of an occlusive arterial thrombus.

To the extent that LE and DM accelerate atherogenesis and then ASCVD events (Table 1), one could infer that treatment of

LE or DM might blunt these harmful effects. Some data in mouse models of LE support this assertion (Richez et al., 2013), and in the section, below, on “Management of the heightened risk of ASCVD events in LE and DM: pharmacologic interventions and treatment goals”, we review data from human patients, especially during treatment with hydroxychloroquine (Plaquenil), a disease-modifying anti-rheumatic drug. In contrast, despite their anti-inflammatory properties, glucocorticoids (a common treatment in LE and DM) have been associated with increased atherosclerosis in LE and DM, at least in part from worsening hyperlipidemia, hy-

Table 3
Increased rates of ASCVD events in SLE, CLE, DM, and juvenile DM compared with nonautoimmune cohorts

Type of ASCVD event	Odds ratio (95% confidence interval) or percentage (p-value)	Reference
SLE		
Composite ASCVD events (MI, stroke, cardiovascular death)	2.05 (1.15–3.44) ^{a,b}	Hesselvig et al., 2017
Composite CHD (MI, angina, CAD, chronic CAD, CHF due to CAD)	7.5 (5.1–10.4) ^c 2.27 (2.14–2.42) ^c	Esdaile et al., 2001 Zöller et al., 2012
MI	2.2 (1.4–3.4) (SLE without LN) ^c 18.3 (5.1–65) (SLE with LN) ^c 3.04 (1.81–5.11) ^d 10.1 (5.8–15.6) ^c (nonfatal)	Hermansen et al., 2017 Hermansen et al., 2017 Gu et al., 2019 Esdaile et al., 2001
Stroke	2.1 (1.5–2.9) (SLE without LN) ^c 4.1 (1.9–8.7) (SLE with LN) ^c 1.96 (1.52–2.5) ^d 7.9 (4.0–13.6) ^c	Hermansen et al., 2017 Hermansen et al., 2017 Gu et al., 2019 Esdaile et al., 2001
Death due to CAD	1.6 (1.1–2.5) (SLE without LN) ^c 7.8 (3.0–20) (SLE with LN) ^c 17.0 (8.1–29.7) ^c	Hermansen et al., 2017 Hermansen et al., 2017 Esdaile et al., 2001
CLE		
Composite ASCVD events (MI, stroke, cardiovascular death)	1.31 (1.16–1.49) ^{a,b}	Hesselvig et al., 2017
Composite CHD (MI, angina, CAD, chronic CAD, CHF due to CAD)	1.87 (1.55–2.21) ^c	Zöller et al., 2012
Ischemic heart disease (CAD, MI, angina)	0.94 (0.57–1.54), NS ^{a,b}	Singh et al., 2016
Stroke or TIA	2.97 (1.13–7.78) ^{a,b}	Singh et al., 2016
Cardiovascular death	1.68 (0.76–3.75), NS ^{a,b}	Singh et al., 2016
DM		
Composite ASCVD events (MI, stroke)	2.45 (1.42–4.22) ^a 1.91 (1.07–3.41) ^{a,b}	Rai et al., 2015
CHD	13.8% vs. 9.1% in controls ($p \leq .0001$) ^e	Lai et al., 2013
MI	3.37 (1.67–6.80) ^c 3.51 (1.88–6.54) ^a 2.92 (1.48–5.78) ^{a,b} 1.3 (0.9–1.9), NS ^f	Lai et al., 2013 Rai et al., 2015 Jung et al., 2020 Jung et al., 2020
Ischemic stroke	1.67 (1.19–2.34) ^c 1.4 (1.0–1.9) ^f 1.81 (0.76–4.32) ^a 1.33 (0.54–3.31), NS ^{a,b} 4.8% vs. 0% in controls ($p = .024$) ^f ; median ages of DM and control cohorts were 41.5 and 42 years, respectively	Lai et al., 2013 Jung et al., 2020 Rai et al., 2015 de Moraes et al., 2013 de Moraes et al., 2013
Hemorrhagic stroke only	1.3 (0.8–2.0), NS ^f	Jung et al., 2020
Death from MI	1.73 (0.88–3.37), NS ^a	Jung et al., 2020
Death from ischemic stroke	2.00 (1.19–3.36) ^a	Jung et al., 2020
Death from hemorrhagic stroke	2.31 (1.13–4.70) ^a	Jung et al., 2020
Juvenile DM		
Ischemic stroke or TIA	10.82 (2.46–47.65) ^c 6.00 (1.43–25.19) ^{a,b}	Silverberg et al., 2018 Silverberg et al., 2018

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CLE, cutaneous lupus erythematosus; DM, dermatomyositis; LN, lupus nephritis; MI, myocardial infarction; NS, not significant; SLE, systemic lupus erythematosus; TIA, transient cerebrovascular ischemic attack PubMed was searched from 1990 to 2021 for each type of ASCVD event in combination with each of the autoimmune diseases listed. All studies were reviewed by at least two co-authors (EK, MG). This table includes studies in which ASCVD event rates in patients with these autoimmune diseases were statistically compared with the rates in a nonautoimmune control group from the same study. A meta-analysis of studies that met these same criteria was also included. Unless otherwise indicated, stroke includes both ischemic and hemorrhagic strokes.

^a Adjusted for age and sex

^b Adjusted for other factors

^c Adjusted for age, sex, and conventional ASCVD risk factors

^d Meta-analysis

^e Age- and sex-matched cohorts

^f Unadjusted odds ratios

pertension, and dysglycemia (Table 1; Amaya-Amaya et al., 2014; Monção et al., 2018; Sherer and Shoenfeld, 2006; Sholter and Armstrong, 2000; Tselios et al., 2020; Tselios et al., 2016).

The second, and related, point to emphasize is the common misperception that vasculitis, or arteritis, drives accelerated atherosclerosis and ASCVD event risk in LE and DM. In fact, vasculi-

tis is an uncommon component of either LE or DM (Callen, 2010; Ramos-Casals et al., 2006). Thus, in general, other processes must be involved (Table 1).

The third point to emphasize is that accelerated atherosclerosis is not necessarily a general feature of all systemic inflammatory conditions. Preindustrial forager-horticulturists have elevated

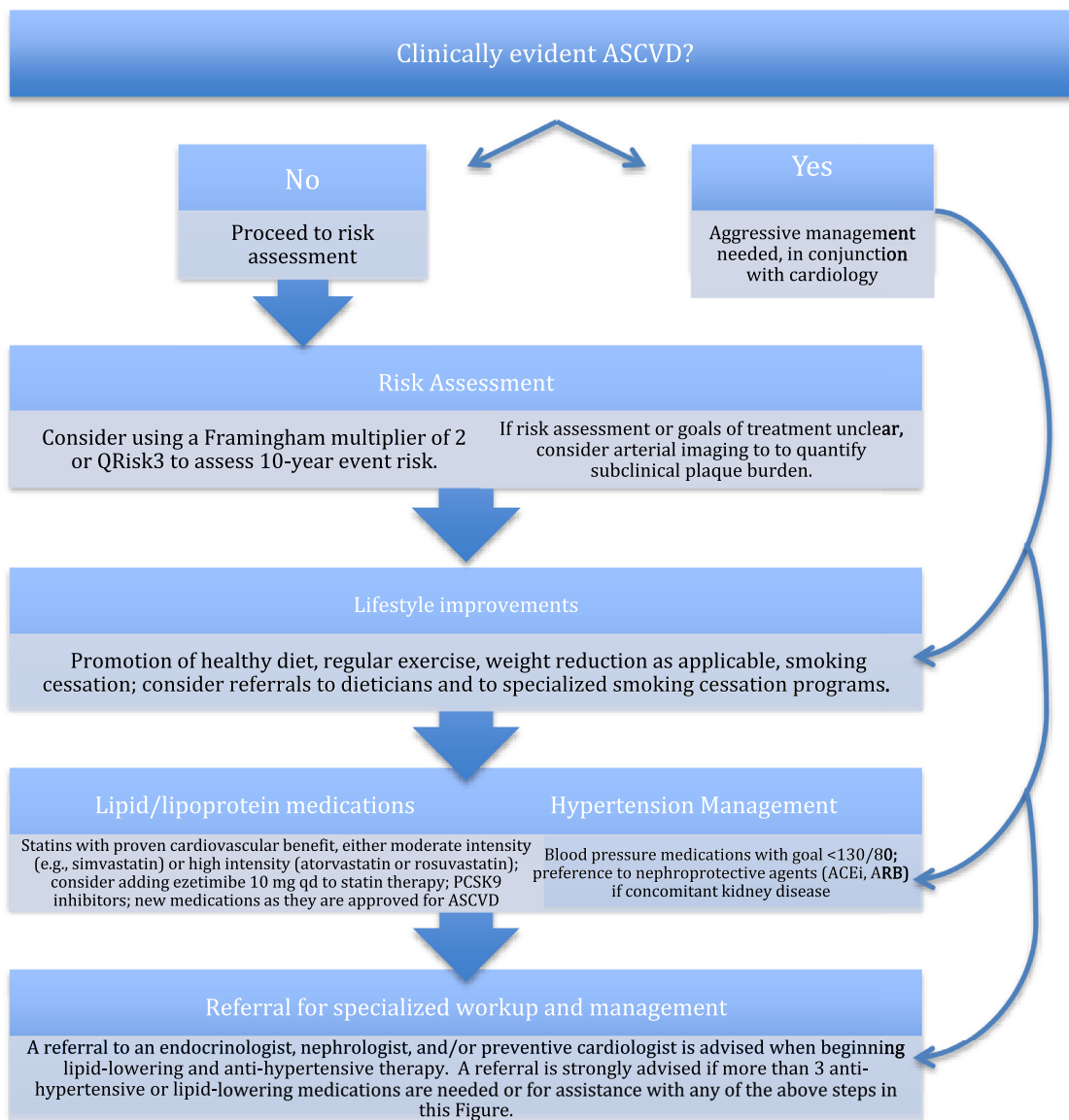


Fig. 2. Proposed flow chart for clinicians managing atherosclerotic cardiovascular disease event risk in patients with lupus erythematosus or dermatomyositis.

plasma CRP levels from a chronic burden of infectious diseases, yet remarkably little ASCVD (Kaplan et al., 2017). Periodontal disease induces systemic immune activation, but there is no evidence that periodontal interventions improve ASCVD event risk in industrialized societies (Lockhart et al., 2012; Priyamvara et al., 2020). Cross-sectional studies of patients with inflammatory bowel disease (ulcerative colitis or Crohn's disease) have given a mixed picture—specifically, no association with cardiovascular mortality (Cainzos-Achirica et al., 2020) and heterogenous results regarding ASCVD event risk (Cainzos-Achirica et al., 2020; Lee et al., 2021), including some large-scale work showing no increased ASCVD event risk (Osterman et al., 2011). The simplest explanations are that systemic immune activation without abundant plasma apoB-lipoproteins cannot produce atherosclerosis (forager-horticulturists). Or, in the context of modern lifestyles in which apoB-lipoproteins are abundant, as in periodontal and related diseases and perhaps inflammatory bowel disease, these conditions activate components of the immune system that are apparently not relevant, or not strongly relevant, to the specific processes involved in atherosclerosis or ASCVD events (Fig. 1; Table 1). Hypercholes-

terolemic mouse models of atherosclerosis have also shown dissociation between certain specific systemic inflammatory modifications and arterial plaque development (Levin et al., 2011; Koojiman et al., 2015). This body of work stands in contrast to numerous studies in LE, DM, and rheumatoid arthritis that have consistently shown increased atherosclerosis and ASCVD events in those patients, as emphasized in Table 3 and elsewhere, suggesting again that treatment of these specific autoimmune diseases might confer cardiovascular benefit (see the section, below, on “Management of the heightened risk of ASCVD events in LE and DM: pharmacologic interventions and treatment goals”).

Increased prevalence of conventional risk factors for ASCVD events in patients with LE or DM

Patients with SLE have an increased prevalence of conventional risk factors for ASCVD events (Table 2). Several cohort studies have shown that patients with SLE have an increased prevalence of dyslipidemia, obesity, diabetes, hypertension, and metabolic syndrome compared with rates of these conditions in the general population

(Bessant et al., 2006; Bruce et al., 2003; das Chagas Medeiros et al., 2016; Yang et al., 2012). Even when controlling for these risk factors, however, patients with SLE still have a significantly increased risk of ASCVD events compared with the general population (see the section, below, on “Increased burden of atherosclerosis and increased age- and sex-adjusted risk of ASCVD events in patients with LE or DM”) (Esdaile et al., 2001).

Although perhaps to a lesser extent, patients with CLE without concomitant SLE also have increased ASCVD risk factors, such as high rates of metabolic syndrome, hypertriglyceridemia, and reduced HDLc, compared with healthy controls (Table 2; Akarsu et al., 2017; Lagogianni et al., 2005). Increased rates of smoking in CLE, indoor lifestyle reflected by low serum vitamin D levels, and high rates of psychiatric comorbidity in patients with CLE may also exacerbate ASCVD event risk (Guo and Nambudiri, 2021).

The published literature on the prevalence of risk factors for ASCVD events in DM is less extensive than in LE. Nevertheless, patients with DM have an increased prevalence of several conventional risk factors for ASCVD (Table 2). Metabolic syndrome is highly prevalent in patients with DM, and a history of hypertension appears to be a risk factor for the development of additional components of metabolic syndrome in these patients (de Moraes et al., 2013). Along related lines, dyslipoproteinemia is a common feature in patients with DM, characterized by high plasma TGs and low HDLc, both of which are associated with an increased risk of ASCVD events (Wang et al., 2013). In the study by Wang et al. (2013) of 41 untreated patients with DM and 41 age- and sex-matched healthy controls, the patients with DM had significantly higher levels of TGs (193 ± 68 vs. 94.8 ± 47 mg/dl mean \pm standard deviation; $p < .001$) and significantly lower levels of HDLc (44.1 ± 19 vs. 51.8 ± 13 mg/dl mean \pm standard deviation; $p < .01$). Also, non-HDLc (a parameter that captures cholesterol carried by LDL and other atherogenic apoB-lipoproteins; described in more detail under “Assessment of the heightened risk of ASCVD events in patients with LE or DM”) and VLDL cholesterol were significantly higher in their patients with DM than in the controls ($p < .05$ and $< .001$, respectively), suggesting that the specific form of chronic inflammation in untreated DM is associated with abnormal serum lipid profiles (Wang et al., 2013). Furthermore, vascular abnormalities have been reported in patients with DM, including decreased flow-mediated dilation of the brachial artery, increased arterial stiffness, and increased carotid artery intimal-medial thickness (Vincze et al., 2014). As an additional contributor to adverse cardiovascular outcomes, myocarditis can occur as a primary manifestation of DM, leading to conduction abnormalities, restrictive cardiomyopathy, and congestive heart failure (Lundberg, 2006; Schwartz et al., 2016).

As noted above, atherosclerosis often begins in childhood (Borén et al., 2020; Enos, 1953; Head et al., 2019; McMahan, 2005; Strong and McGill, 1962), raising concern for patients with juvenile DM. Silverberg et al. (2018) studied a cohort of 1407 patients with juvenile DM compared with age-, sex-, and race-matched controls and reported that the disease, like adult DM, is also associated with hypertension (odds ratio [OR]: 11.64; 95% confidence interval [CI], 7.63–17.76), obesity (OR: 2.27; 95% CI, 1.30–3.98), uncomplicated diabetes (OR: 2.72; 95% CI, 1.25–5.89), and lipodystrophy (OR: 43.32; 95% CI, 5.93–316.46), as well as transient ischemic attacks and/or cerebral infarctions (OR: 6.00; 95% CI, 1.43–25.19; Tables 2 and 3). Of note, their study did not adjust for cumulative glucocorticoid use (Silverberg et al., 2018). Patients with juvenile DM or a history of juvenile DM may need to be followed closely with early screening for subclinical ASCVD, possibly including non-invasive arterial imaging, as discussed below in the section on “Use of arterial imaging to assess the heightened risk of ASCVD events in patients with LE or DM”.

Increased burden of atherosclerosis and increased age- and sex-adjusted risk of ASCVD events in patients with LE or DM

Evidence exists that patients with SLE have an increased atherosclerotic plaque burden compared with the general population. A study using arterial ultrasonography found that patients with SLE have a two-fold higher number of plaques in femoral and carotid arteries even after adjusting for conventional risk factors. This rate is comparable to the increase in plaque burden in diabetes mellitus and rheumatoid arthritis, two conditions that are well known to have increased rates of ASCVD events (Tektonidou et al., 2017). Other studies have also found that patients with SLE have an increased prevalence of atherosclerotic plaques and premature accumulation of plaque compared with controls, even after adjusting for conventional ASCVD risk factors, and a younger age at onset of subclinical atherosclerosis compared with controls, as assessed by carotid artery ultrasonography (Asanuma et al., 2003; Roman et al., 2003). Although we could not find comparative data on the atherosclerotic plaque burden in patients with DM, increased carotid artery intimal-medial thickness has been reported (Vincze et al., 2014).

Patients with SLE experience an increased risk of ASCVD events compared with the general population (Table 3). A recent pooled meta-analysis revealed an overall risk of myocardial infarction (MI) 3.04 times higher than in the general population (95% CI, 1.81–5.11) and a risk of stroke 1.96 times higher (95% CI, 1.52–2.5; Gu et al., 2019). Other studies estimate this risk to be even higher, with estimates of patients with LE having up to 10.1 times (95% CI, 5.8–15.6) the risk of MI and 17.0 times (95% CI, 8.1–29.7) the risk of death due to coronary heart disease after adjusting for baseline ASCVD risk factors (Esdaile et al., 2001). Women with LE age 35 to 44 years may have 50 times higher risk of MI than women of that age in the general population in whom MIs are uncommon (95% CI, 21.6–98.5; Manzi et al., 1997). This makes their risk of an MI higher than for women in that age range with many genetic dyslipidemias, hypertension, smoking, or diabetes mellitus.

Regarding CLE without systemic manifestations, numerous cohort studies have found increased rates of ASCVD events compared with the general population, although to a lesser degree than in patients with SLE (Table 3; Hesselvig et al., 2017; Singh et al., 2016; Zöller et al., 2012). Patients with DM also have an increased risk of ASCVD events compared with the general population (Table 3). One retrospective cohort study found elevated age- and sex-adjusted OR of a composite of MI or stroke of 2.45 (95% CI, 1.42–4.22) in patients with DM (Rai et al., 2015). Similar results were found in another study: an OR adjusted for age, sex, and other conventional risk factors of 3.37 (95% CI, 1.67–6.80) was calculated for the risk of MI in DM, and 1.67 (95% CI, 1.19–2.34) for ischemic stroke (Lai et al., 2013).

In addition to elevated ASCVD event risk, the rates of mortality from ASCVD are increased in patients with DM compared with the general population (Jung et al., 2020). The age- and sex-adjusted OR was found to be 2.00 (95% CI, 1.19–3.36) for death from ischemic stroke, and 2.31 (95% CI, 1.13–4.70) for death from hemorrhagic stroke in patients with DM.

Assessment and management of heightened risk of ASCVD events in patients with LE or DM

As noted in the Introduction, prospective randomized controlled clinical trials of therapies in patients with LE or DM to detect an effect on subsequent ASCVD events are not realistic. A typical ASCVD event trial recruits thousands of participants and must follow them for years. Small trials have been conducted of statins in patients with LE, but using only surrogate endpoints (Petri et al.,

2011), some of which, such as the coronary artery calcium (CAC) score, were subsequently shown to be unsuitable for assessing therapeutic responses to statins (Borén et al., 2020; van Rosendaal et al., 2021), despite their value in assessing baseline risk as discussed below in the section on “Use of arterial imaging to assess the heightened risk of ASCVD events in patients with LE or DM”.

Thus, much of the information we present in this section is correlative or inferred from strategies that have been developed for more widely studied conditions, particularly diabetes mellitus and stage 3 or 4 CKD, that also are associated with an elevated ASCVD event risk, but have been shown to benefit from therapies to lower plasma LDL levels, lower blood pressure, and even address diabetes or CKD itself (Doumouras et al., 2021; Sarnak et al., 2003; Sjöström et al., 2012). Thus, the precise extent to which modifying ASCVD risk factors will lower ASCVD event risk in patients with LE or DM remains unproven, but we infer that the benefits will be similar to those in other populations. Our proposed approach to the management of ASCVD risk for these patients is outlined in Figure 2.

Assessment of heightened risk of ASCVD events in patients with LE or DM

A key component of assessment of the risk of future atherosclerotic cardiovascular events is the absence or presence of clinically evident ASCVD (Fig. 2; Table 4). Risk assessment and management in patients without clinically evident ASCVD is called primary prevention. In patients who already have clinically evident ASCVD, such as a prior MI, angina, atherosclerotic stroke, transient cerebrovascular ischemic attacks, or symptomatic peripheral vascular disease, it is called secondary prevention. Secondary prevention is more aggressive than primary prevention because the risk of another ASCVD event is much higher. If the patient already has clinically evident ASCVD, referral to cardiology and/or endocrinology for appropriately aggressive treatment is considered a standard approach (Fig. 2).

Patients with LE or DM should undergo conventional lipid/lipoprotein testing and monitoring, meaning plasma levels of total cholesterol (TC), TGs, LDLc, and HDLc. Some work indicates that nonfasting plasma TG levels may be more informative than fasting TGs for assessment of ASCVD event risk (Bansal et al., 2007), especially for women (Nordestgaard et al., 2007). Nevertheless, nonfasting TGs are not typically measured under standardized conditions and therefore vary with the timing and content of the last meal (McBride, 2007). In the United States, lipid/lipoprotein samples are typically taken from fasting patients, usually simultaneously with a sample for fasting plasma glucose levels, whereas nonfasting samples are typically used for lipid/lipoprotein analyses in Europe. A simple approach for interpreting TG levels is that samples should be labeled as fasting or not. Importantly, plasma levels of TC, directly measured LDLc, HDLc, and apoB are minimally or not affected by the fed/fasting state.

From these conventional parameters, non-HDLc can be calculated by taking the TC and subtracting what is not important in ASCVD, meaning HDLc (thus, TC minus HDLc). Non-HDLc comprises cholesterol carried by LDL and all other atherogenic apoB-lipoproteins, including TG-rich C-TRLs, and predicts event risk better than just LDLc. Some calculators of ASCVD risk no longer ask for LDL levels, relying instead on TC and HDLc (QRISK@3-2018 risk calculator 2021). Patients can also be tested for plasma levels of apoB, the major protein of all atherogenic lipoproteins, which is a better predictor of events than non-HDLc when the values are discordant (i.e., one value is high when the other is not; Sniderman et al., 2019). In nonautoimmune cohorts, discordance of plasma apoB levels from non-HDLc or LDLc has been calculated to occur in ap-

proximately 20% to 60% of individuals, indicating a clinically relevant issue (Sniderman et al., 2019). Currently, European guidelines rely on routine measurement of plasma apoB levels more than U.S. guidelines do (Arnett et al., 2019; Jellinger et al., 2017; Mach et al., 2020). In the context of LE or DM, we recommend a plasma apoB measurement with the first lipid/lipoprotein profile or when first feasible, to determine if there is discordance with non-HDLc levels. An elevated plasma apoB level (>110 mg/dl) in the absence of other conventional risk factors for ASCVD events would reclassify a patient with LE or DM from high to very high risk (Table 4). Plasma levels of lipoprotein(a) (Lp[a]), an atherogenic particle similar to LDL known to be pathogenic in ASCVD or thrombotic events, should also be tested, and the measurement is currently performed only once in a lifetime because the levels are almost entirely genetically determined (Page and Watts, 2021; Sniderman, 2002; Wu et al., 2019). Again, in the absence of other conventional risk factors for ASCVD events, a high plasma Lp(a) level will justify reclassification of a patient with LE or DM from high to very high risk and hence even more aggressive LDL lowering (Table 4). Interventions specific for lowering Lp(a) levels are currently being evaluated in clinical trials (Table 5).

In addition to lipoprotein-related parameters, the major exacerbators of ASCVD should also be monitored, particularly hypertension and smoking. Glycemic control, assessed routinely by fasting plasma glucose levels and blood levels of glycated hemoglobin (hemoglobin A_{1c}) should be monitored in patients with obesity, metabolic syndrome, high plasma TG levels, or diabetes mellitus, as well as during glucocorticoid therapy. Several cohort studies have indicated that hemoglobin A_{1c} levels below the diabetic range or even below the prediabetic range positively correlate with subclinical atherosclerotic plaque burden, particularly in otherwise low-risk individuals (Rossello et al., 2021; Santos et al., 2021; Scicali et al., 2016).

In LE, certain disease-specific factors have been reported to be independent predictors of ASCVD events beyond conventional risk factors (Tselios et al., 2016). Lupus disease activity and duration, cumulative damage, a history of corticosteroid use, the presence of serum antiphospholipid antibodies, and lupus nephritis were shown to independently predict premature coronary events (Tselios et al., 2016; Hermansen et al., 2017) and could also be used to reclassify a patient with LE from high to very high risk (Table 4).

So-called advanced lipid testing, such as nuclear magnetic resonance and ion mobility fractionation to determine numbers of lipoprotein particles of each class and size range, have been available for decades but have not been incorporated into guidelines owing to limited evidence that they add predictive power beyond plasma apoB measurements. Likewise, serum levels of CRP have been studied for years, but with limited evidence of added predictive power beyond the set of conventional risk factors. Elevations in CRP have been associated with higher ASCVD event risk in patients with LE (Tselios et al., 2016), but because CRP is a general acute phase reactant, its specificity and hence its clinical significance in autoimmune conditions is not well defined, because there could be many diverse reasons for the elevation that may be unrelated to ASCVD event risk. Accordingly, CRP has not been widely adopted by preventive cardiologists. It appears as a primary factor in only one major calculator for ASCVD event risk, the Reynolds Risk Score, and is considered an optional risk enhancer in some cardiovascular guidelines.

Of note, three major clinical trials that tested the effects of canakinumab (Ridker et al., 2017), methotrexate (Ridker et al., 2019), and colchicine (Tardif et al., 2019) as anti-inflammatory agents in nonautoimmune ASCVD failed so far to achieve a cardiovascular indication for these agents in the United States or Europe (Chilazi et al., 2021; McKee, 2018). Levels of CRP are sometimes used to assess disease activity in rheumatoid arthritis, but

Table 4
Proposed approach for management of ASCVD event risk in LE and DM, based on established approaches for other high-risk conditions, namely, diabetes mellitus or stage 3 or 4 chronic kidney disease (adapted from [Jellinger et al., 2017](#); [Arnett et al., 2019](#); [Mach et al., 2020](#)).

Risk category	Risk factors/10-year risk	LDLc, mg/dL	Non-HDLc, mg/dL	ApoB, mg/dL
Recent recurrent ASCVD events	Any patient with clinically evident ASCVD who experiences a second atherosclerotic vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, regardless of other medical conditions	<40	No explicit recommendations	No explicit recommendations
Extreme risk	Patients with LE or DM and clinically evident ASCVD (angina, prior myocardial infarction, atherosclerotic stroke or transient cerebrovascular ischemic attack, and/or symptomatic peripheral vascular disease)	<55	<80	<70
Very high risk	Patients with LE or DM with ≥ 1 conventional risk factors for ASCVD events ^a , or evidence of subclinical atherosclerosis on imaging ^b , or the presence of certain LE-specific factors ^c	<70	<100	<80
High risk	Patients with LE or DM without conventional risk factors for ASCVD events ^a , evidence of subclinical atherosclerosis on imaging ^b , or other comorbidities	<100	<130	<90

ApoB, apolipoprotein-B; ASCVD, atherosclerotic cardiovascular disease; DM, dermatomyositis; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; LE, lupus erythematosus

^a Conventional risk factors for ASCVD events: Major risk factors are age (men age >45 years, women age >55 years), high LDLc (>160 mg/dl), high non-HDLc (≥ 190 mg/dl), high plasma apoB (>110 mg/dl), cigarette smoking, hypertension (blood pressure $\geq 130/80$), low HDLc (≤ 40 mg/dl in men, ≤ 50 mg/dl in women), family history of premature ASCVD events (age <55 years in first-degree male relative, <65 years in first-degree female relative), stage 3 or 4 chronic kidney disease, diabetes mellitus. Additional risk factors are abdominal obesity, polycystic ovarian syndrome, and/or high plasma Lp(a). A calculated 10-year ASCVD event risk of $\geq 7.5\%$ by the Framingham risk score $\times 2$ or QRisk3 calculator could also be used to reclassify a patient with LE or DM from high to very high risk.

^b Evidence of subclinical atherosclerosis on imaging can include a nonzero coronary artery calcium score, carotid or femoral plaque on ultrasound, or image-evident plaque on coronary computed tomography angiography.

^c In LE, certain disease-specific factors, particularly high disease activity, long duration, high cumulative damage, a history of corticosteroid use, the presence of serum antiphospholipid antibodies, and lupus nephritis, can also be used to reclassify a patient from high to very high risk.

Table 5
Therapies to lower plasma lipids and reduce ASCVD events

Therapies approved by the FDA to lower plasma LDLc levels and/or ASCVD event risk

Statins:

Moderate intensity (e.g., simvastatin)

High intensity (notably, randomized, double-blinded, controlled, clinical trials of atorvastatin and rosuvastatin show that they each reduce plasma LDLc levels and reduce ASCVD events; both are off-patent)

Two humanized inhibitory monoclonal antibodies against PCSK9 protein (evolocumab, alirocumab) from two different companies; each lowers plasma levels of LDLc to approximately 30 mg/dl and reduces ASCVD event risk ([Sabatine et al., 2017](#); [Schwartz et al., 2018](#)) and are FDA-approved for both effects.

Ezetimibe, a cholesterol absorption inhibitor, approved for lowering LDLc; also shown to decrease ASCVD events in two key clinical trials, IMPROVE-IT ([Cannon et al., 2015](#)) and EWTOPIA 75 ([Ouchi et al., 2019](#)), but not FDA-approved for this indication.

Icosapent ethyl, lowers plasma levels of triglycerides and apolipoprotein-B, and has several other apparently beneficial effects ([Kastelein and Stroes, 2019](#)); FDA-approved for ASCVD event reduction in patients at a high ASCVD event risk who have plasma triglyceride levels of ≥ 150 mg/dl.

Bile acid sequestrants, which lower plasma LDL cholesterol concentrations and ASCVD event risk but can have significant gastrointestinal side effects in some patients and can raise plasma concentrations of triglycerides ([Hegele et al., 2015](#)).

Bempedoic acid, a new agent that inhibits ATP citrate lyase, an enzyme that leads to both fatty acid and cholesterol biosynthesis in a step that is upstream of HMG-CoA reductase, the target of statins ([Ruscica et al., 2021](#)). Bempedoic acid appears to have no effects in muscle ([Ruscica et al., 2021](#)). Bempedoic acid was recently FDA-approved for LDL lowering in heterozygous familial hypercholesterolemia or established ASCVD. Bempedoic acid is available alone and in a fixed combination with ezetimibe. Effects on ASCVD events are currently unknown, but under evaluation in the CLEAR Outcomes trial of statin-intolerant patients.

Candidate therapies under investigation in dyslipoproteinemias and ASCVD events

Pemafibrate is a new fibrate that lowers plasma triglyceride concentrations and is under evaluation in the PROMINENT trial for effects on ASCVD events in the context of baseline statin therapy. Previous ASCVD event trials of fibrates added to statins failed to achieve their primary prespecified outcomes on ASCVD event reduction ([Hegele et al., 2015](#)), but the PROMINENT trial has a different design that specifically focuses on patients with high plasma triglycerides and low HDLc ([Ruscica et al., 2021](#)).

Liver-directed, modified siRNA against PCSK9 mRNA, recently approved in Europe for lowering LDLc; after two loading doses it is administered only twice per year, which may improve convenience and compliance ([Khvorova, 2017](#); [Ray et al., 2020](#)).

Antisense oligonucleotide against APOC3 mRNA, approved in Europe for familial chylomicronemia syndrome, which is a rare condition of extremely high plasma triglycerides. The medication is currently under evaluation in patients with plasma triglycerides of 200 to 500 mg/dl and high ASCVD event risk ([Tardif and Gaudet, 2021](#)).

Humanized monoclonal antibody against ANGPTL3, now FDA-approved for homozygous familial hypercholesterolemia, a rare syndrome of extremely high LDL levels and under evaluation in more common circumstances ([Raal et al., 2020](#)).

Antisense oligonucleotide against LPA mRNA, which encodes the unique Apo(a) protein moiety of Lp(a), now under evaluation for patients with high plasma levels of Lp(a).

ASCVD, atherosclerotic cardiovascular disease; FDA, U.S. Food and Drug Administration; LDL, low-density lipoprotein; LDLc, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a)

tools other than CRP are used to assess disease activity in LE and DM. In LE, DM, and other conditions, physicians should explore secondary causes of dyslipoproteinemia, especially dysgammaglobulinemia, renal failure, type 2 diabetes mellitus, obesity, and glucocorticoid use (Jellinger et al., 2017).

For patients with LE or DM and no clinically evident atherosclerotic cardiovascular disease (primary prevention), physicians should consider using calculators to assess future ASCVD event risk, but with modifications (Fig. 2). As outlined above (“Increased burden of atherosclerosis and increased age- and sex-adjusted risk of ASCVD events in patients with LE or DM”), conventional risk assessment fails to fully account for observed levels of ASCVD events in patients with LE or DM (Alenghat, 2016; Esdaile et al., 2001). In rheumatoid arthritis, a common high-risk autoimmune condition, there is evidence to support simply multiplying the conventional 10-year Framingham risk score (FRS) by 1.5 (Agca et al., 2017; Peters et al., 2010). Multiplying the FRS by 2 has been reported to more accurately predict the risk of future ASCVD events in patients with SLE than the original score, based on one longitudinal cohort study (Urowitz et al., 2016). The American College of Cardiology ASCVD Risk Estimator Plus is a convenient online calculator related to the FRS that gives both the 10-year risk of an ASCVD event and the total residual lifetime risk (American College of Cardiology. ASCVD risk estimator plus [Internet] 2021).

Additionally, physicians could consider using the online Qrisk3 calculator, which includes SLE status and glucocorticoid use among other parameters in addition to conventional risk factors (Hippisley-Cox et al., 2017; QRISK@3-2018 risk calculator 2021). The Qrisk3 score was also reported to perform better than conventional scores to predict the risk of future ASCVD events in an SLE cohort (Edwards et al., 2018). Although studied directly in LE cohorts, this approach likely applies to the DM population as well, given the similarities in accelerated ASCVD event risk in the two diseases. Work is underway to devise calculators that account for severity and disease activity of LE in estimating future ASCVD event risk, but these calculators are currently available only as research tools (Petri et al., 2019).

Use of arterial imaging to assess heightened risk of ASCVD events in patients with LE or DM

In recent years, arterial imaging to detect subclinical atherosclerotic plaques in primary prevention has added substantial predictive power for ASCVD events beyond the conventional set of risk factors (Fig. 2; Table 4). These methods include carotid ultrasonography to measure intimal-medial thickness and especially total carotid plaque area; baseline CAC scores, which quantify calcified coronary plaques and correlate with the presence of noncalcified, rupture- or erosion-prone plaques, especially in older patients (see below); femoral ultrasonography to detect plaque (Fernández-Friera et al., 2015; Laclaustra et al., 2016); abdominal aortic ultrasonography to detect plaque (Fernández-Friera et al., 2015); and coronary computed tomography (CT) angiography, which visualizes calcified and noncalcified plaques, as well as other parameters of plaque quality (Budoff et al., 2020; Stojan et al., 2020; SCOT-HEART Investigators, 2018). Several of these imaging methods have already been used to study atherosclerotic plaque burden in cohorts of patients with LE (Eder et al., 2014; Kao et al., 2013; Stojan et al., 2020). In nonautoimmune populations, these methods have proven particularly useful in cases at intermediate calculated risk or if the clinician suspects higher, or even lower, risk than indicated by conventional risk calculators (Soni et al., 2021).

For example, in younger adults or early middle-age patients in whom the calculated 10-year risk of an ASCVD event is low, even if multiplied by two, management can be guided by assessing the presence of subclinical atherosclerosis by these imaging methods

(Fig. 2; Table 4). To date, carotid ultrasonography is the only imaging modality with direct evidence of adding predictive power for future ASCVD events in patients with LE (Eder et al., 2014; Kao et al., 2013; Tselios et al., 2016). In the future, assessments of subclinical atherosclerosis by carotid or femoral artery ultrasonography or coronary CT angiography may be considered for younger adults within these high-risk populations. Of note, CAC scores, which are convenient, low in radiation dose, and add significant predictive power in nonautoimmune populations, may be unsuitable for patients under the age of 35 to 40 years because of the time it takes to develop calcified regions within atherosclerotic plaques (Multiethnic Study of Atherosclerosis, 2021). These patients often have subclinical coronary plaques, but until those plaques develop calcifications, they remain invisible on CAC.

Currently, the most commonly used imaging techniques to detect subclinical atherosclerosis are CAC scans in middle-aged or older patients, and carotid ultrasonography and CT angiography in patients of any age. Simultaneous carotid, iliofemoral, and abdominal aortic ultrasonography, as well as CAC, of apparently healthy 40- to 54-year-old patients in one study showed that the technique that most commonly detected atherosclerotic plaques was iliofemoral ultrasonography. Iliofofemoral plaque was evident in 44% of all participants, versus 31% by carotid ultrasonography and only 18% by nonzero CAC score (Fernández-Friera et al., 2015). This finding may eventually provoke a change in imaging guidelines to prioritize the iliofemoral bed. In the clinical setting, atherosclerotic plaques often show up as incidental findings from other imaging methods, such as chest or abdominal CT, positron emission tomography, abdominal or femoral ultrasonography performed for other reasons, and so forth. In the context of LE or DM, we recommend that any finding of subclinical atherosclerotic plaque justifies reclassification to at least the very high-risk category (Table 4).

Management of heightened risk of ASCVD events in LE and DM: Lifestyle, including smoking cessation

Conventional modifiable risk factors, such as hypertension, obesity, diabetes mellitus, and dyslipidemia, are prevalent in patients with LE, and each independently associates with increased risk of ASCVD events (Tselios et al., 2016). These modifiable risk factors should be mitigated through lifestyle interventions as a first-line approach, as in the general population (Fig. 2). The approach should include promotion of a healthy diet, weight reduction as needed, encouragement of regular physical activity, and providing resources for smoking cessation. These lifestyle characteristics all correlate with lower risks of future ASCVD events (Al Rifai et al., 2018; Booth et al., 2016).

Management of heightened risk of ASCVD events in LE and DM: Pharmacologic interventions and treatment goals

Published data indicate that SLE, DM, and perhaps even CLE should be considered high-risk conditions for ASCVD events (see above, “Increased burden of atherosclerosis and increased age- and sex-adjusted risk of ASCVD events in patients with LE or DM”). The lack of prospective randomized trial data on the management of ASCVD event risk in patients with LE or DM necessitates extrapolation from other diseases known to increase ASCVD risk for which there are randomized trial data, particularly diabetes mellitus and stage 3 and 4 CKD. The presence of diabetes mellitus or stage 3–4 CKD automatically places a patient in the high-risk category (Jellinger et al., 2017). Therefore, we suggest that it is reasonable to do the same for patients with LE or DM (Table 4). Moreover, for diabetes or CKD, the presence of conventional risk factors and/or clinically evident ASCVD increases risk categorization, and we suggest the same for LE and DM (Table 4). Goals for plasma concentra-

tions of LDLc, non-HDLc, and apoB would follow these categories, with increasingly stringent goals depending on the risk (Table 4; Jellinger et al., 2017; Mach et al., 2020). There are several different pharmacologic therapies targeting cholesterol and other lipids that can be considered for use in patients with lupus and DM (Table 5 and the section, below, on “Management of the heightened risk of ASCVD events in LE and DM: special considerations”). Also, as noted in Figure 2, Table 4, and the section, above, on “Use of arterial imaging to assess the heightened risk of ASCVD events in patients with LE or DM”, management in primary prevention can be escalated by a finding of subclinical atherosclerotic plaques on imaging.

A study using the modified risk calculators FRSx2 and QRisk3 (see “Assessment of the heightened risk of ASCVD events in patients with LE or DM”, above) found that nearly half of their cohort of 100 patients with SLE had indications for statins, but very few were treated (Masson et al., 2020). This information emphasizes that more aggressive assessment and management of ASCVD event risk are needed in this population. In patients with LE, statins remain first-line medications for hyperlipidemia given their favorable safety profile and known efficacy in lowering plasma LDL levels, including in LE cohorts (Costenbader et al., 2007; Mok et al., 2011; Plazak et al., 2011; Yu et al., 2015). Most importantly, numerous randomized controlled trials have demonstrated that statins, such as simvastatin, atorvastatin, and rosuvastatin, lower ASCVD events in nonautoimmune populations (Table 5; Borén et al., 2020).

Additionally, the use of hydroxychloroquine, a first-line medication for both LE and DM, has been associated with beneficial effects on lipid profiles and thrombosis risk (Jung et al., 2010; Petri, 1996; Ruiz-Irastorza et al., 2006; Tektonidou et al., 2017). A recent cohort study showed an inverse relationship between the use of hydroxychloroquine and major adverse cardiovascular events when controlling for confounders for both SLE (adjusted hazard ratio: 0.65; 95% CI, 0.46–0.90) and patients with CLE (adjusted hazard ratio: 0.71; 95% CI, 0.42–1.19; not significant; Haugaard et al., 2021). These data provide additional justification for the use of this medication in LE and DM. Patients with active LE or DM show increased dyslipidemia and other processes implicated in atherosclerosis and ASCVD events (Table 1), suggesting that steroid-sparing management of disease activity might provide cardiovascular benefits (Borba and Bonfá, 1997).

Control of hypertension should be emphasized in this patient population as well. Although clinical trial data are lacking in LE and DM, early detection and aggressive management of elevated blood pressures are likely to be beneficial (Munguia-Realpozo et al., 2019). Blood pressure goals in this population should be set at <130/80, given that this target, which is now conventional for the general population, has been shown to be associated with lower rates of atherosclerotic vascular events in patients with SLE (Tselios et al., 2020) and may be reasonable to extrapolate to DM patients as well. In this context, preference may be given to nephroprotective agents, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers, in this population, given the comorbid condition of lupus nephritis. Given the importance of blood pressure control in patients with LE, and presumably DM, we advocate continuing the current practice of blood pressure checks at every clinic visit, regardless of specialty.

Management of heightened risk of ASCVD events in LE and DM: Special considerations

In patients with DM, special considerations should be taken into account regarding appropriate lipid-lowering therapies. In clinical practice, many primary care physicians are hesitant to prescribe statins, the first-line anti-atherosclerotic therapy, to patients with a history of DM owing to concerns about SAMS or perhaps an

exacerbation of DM-associated muscle symptoms. Although there is understandable reluctance regarding the use of statins in patients with DM, SAMS are often subjective and may resolve with time, and worsening of DM muscle symptoms with statins has not been systematically demonstrated.

Importantly, in double-blinded studies, placebos have provoked levels of SAMS similar to statins (Finegold et al., 2014; Gupta et al., 2017; Wood et al., 2020). One recent double-blinded study included a quantitative evaluation and attributed approximately 90% of SAMS in a general population cohort to the placebo effect (i.e., not from statins, but from an expectation of harm; Wood et al., 2020). Statin-induced necrotizing autoimmune myopathy (SINAM) is an exceptionally rare but devastating complication of statin therapy, with approximately 2 to 3 cases in every 100,000 patients treated with a statin, with fatal complications at ≤ 0.2 events per million prescriptions for statins (Chemello et al., 2017; Gawey et al., 2020). SINAM is a distinct entity from dermatomyositis. In SINAM, autoantibodies targeting HMGCoA reductase play a key role, which can aid diagnosis (Gawey et al., 2020). Treatment of this rare side effect is immediate cessation of statin therapy, plus aggressive immunosuppression with high-dose glucocorticoids and/or intravenous immunoglobulins (Gawey et al., 2020).

Based on decades of extensive safety data, the U.S. Food and Drug Administration recently removed its contraindication against statin use in all pregnant patients, thereby allowing women at very high ASCVD event risk to continue these medications during pregnancy (U.S. Food and Drug Administration. Statins 2021). This change in guidance further underscores the safety of statins and is of particular relevance to patients with LE or DM, many of whom are women of childbearing age and may be candidates for these medications.

Of note, statins have been proven to be fairly well tolerated by patients, even with inflammatory myopathies. Cohort studies have reported only a few patients with statin-associated adverse events, including uncommon muscle symptoms, elevated liver enzymes, nausea, diarrhea, and elevated creatinine (Bae et al., 2020). In a study by Bae et al. (2020) of 33 patients with inflammatory muscle disease, no significant changes in idiopathic inflammatory muscle disease activity measures or assessments of inflammation were found compared with a control group with idiopathic inflammatory muscle disease not on statin therapy (Bae et al., 2020).

Patients who develop SAMS can switch to a different or lower-intensity statin often with a resolution of symptoms. Lower doses, including statin administration every other day or twice per week, are commonly used strategies in lipid clinics. The cholesterol absorption inhibitor, ezetimibe, remains mostly within the enterohepatic circulation and has only rarely been associated with muscle symptoms (Darkes et al., 2003). Ezetimibe is safe to use as an initial or adjunct therapy. Ezetimibe lowers LDL levels by 15% to 20% and is a good option in combination with a statin, particularly as an alternative to doubling or quadrupling the statin dose. Bempedoic acid, alone or in combination with ezetimibe, has emerged as another alternative, although without trial data available yet on ASCVD events (Table 5).

An argument can be made to proceed directly to PCSK9 inhibitory monoclonal antibodies in statin-intolerant patients, including those with LE or DM, owing to the strong LDL-lowering effects of these agents and proven ASCVD event reduction with few side effects (Table 5). In addition, if patients are symptomatic with inflammatory myositis, it would be reasonable to consider bypassing statins as a first-line agent and instead starting with a PCSK9 inhibitor, on a case-by-case basis for the appropriate patient. Although initially difficult to gain insurance approval, PCSK9 inhibitory monoclonal antibodies have become more widely available and appear to be safe for long-term use in inflammatory myopathies, including for patients who test positive for the anti-

HMGCoA reductase antibody associated with SINAM (Tiniakou et al., 2019). PCSK9 inhibitory monoclonal antibodies (alirocumab and evolocumab) bring plasma LDLc levels to approximately 30 mg/dl and, as noted, decrease the risk of future ASCVD events (Sabatine et al., 2017; Schwartz et al., 2018).

Patients with LE have increased rates of CKD owing to lupus nephritis. CKD increases the risk of ASCVD events and is treated as a high-risk condition by all current guidelines. The SHARP trial demonstrated that 20 mg simvastatin plus 10 mg ezetimibe per day significantly decreased the risk of future ASCVD events in patients with CKD, and the combination was well tolerated. Physicians should consider using this combination in patients with LE who have concomitant CKD secondary to lupus nephritis (Baigent et al., 2011; Shrestha et al., 2019).

Although there is a lack of prospective, randomized controlled data, there may be benefits from antiplatelet therapies, such as low-dose aspirin, in this population. In the absence of robust trial data, physicians may consider initiating an antiplatelet agent, such as aspirin, for select patients in this population for primary prevention, especially patients age <75 years who have evidence of subclinical atherosclerosis on imaging, positive antiphospholipid antibodies, high plasma levels of Lp(a), and/or a high CAC score. Importantly, guidelines for aspirin use for secondary prevention should be closely adhered to, as in the general population.

Conclusion

Patients with LE or DM are at increased risk of ASCVD events. Patients with these diseases require earlier and more aggressive screening and management. Physicians should consider implementing multipliers of conventional risk calculations to trigger initiation of therapies that have proven benefit in primary prevention of ASCVD events in other populations, more readily using vascular imaging to quantify subclinical plaque burden, especially in patients for whom the calculated 10-year ASCVD event risk is low, and treating to lower lipid/lipoprotein targets. Earlier screening should also include evaluation of plasma apoB levels and a one-time Lp(a) assessment. Therapies must take into account unique considerations for patients with inflammatory myopathies in whom non-statin agents may be preferred. Known exacerbators of ASCVD, such as hypertension, smoking, obesity, diabetes mellitus, and CKD, should be tightly and aggressively controlled. Glucocorticoids, which are often used in the treatment of LE and DM, provoke hyperlipidemia, hypertension, and hyperglycemia and have been associated with increased risk of ASCVD events. These medications should be avoided whenever possible, particularly given the availability of more modern therapies. Primary LE and DM disease activity should be controlled.

As noted, large-scale randomized controlled trials of lipid- and blood pressure-lowering agents in patients with LE or DM seem unfeasible. Nevertheless, high-quality cohort studies will continue help guide screening and therapeutic approaches to prevent ASCVD events in patients with LE or DM. Currently, more clinical vigilance is needed regarding surveillance, prevention, risk modification, and treatment of dyslipoproteinemias, hypertension, and smoking in patients with LE or DM.

Conflicts of interest

Dr Douglas Jacoby serves on lipid advisory boards and steering committees at AstraZeneca and Novartis. Dr Kevin Jon Williams reports an ownership interest in Hygieia, Inc. and Gemphire Therapeutics, Inc. All other authors have no conflicts of interest to declare.

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Study approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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