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Review Article

Chronic rheumatologic disorders and cardiovascular disease risk in women

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ABSTRACT

Cardiovascular disease (CVD) is a major health threat to women worldwide. In addition to traditional CVD risk factors, autoimmune conditions are increasingly being recognized as contributors to adverse CVD consequences in women. Chronic systemic autoimmune and inflammatory disorders can trigger premature and accelerated atherosclerosis, microvascular dysfunction, and thrombosis. The presence of comorbid conditions, duration of the autoimmune condition, disease severity, and treatment of underlying inflammation are all factors that impact CVD risk and progression. Early identification and screening of CVD risk factors in those with underlying autoimmune conditions may attenuate CVD in this population. Treatment with non-steroidal anti-inflammatory drugs, corticosteroids, disease modifying agents and biologics may influence CVD risk factors and overall risk. Multi-disciplinary and team-based care, clinical trials, and collaborative team-science studies focusing on systemic autoimmune conditions will be beneficial to advance care for women.

1. Introduction

The immune system evolved to protect the body from invading organisms by identifying foreign antigens and damage-associated molecular patterns. Through its robust vascular circulation along with its lymphatic network, the heart often comes into contact with immune cells that can be misdirected during chronic inflammatory states such as autoimmune diseases [1]. Chronic rheumatologic disorders increase the risk of cardiovascular disease (CVD), with the risk inversely proportional to disease severity [2]. Several factors may contribute to this link between autoimmune disease and CVD. First, antibodies to self-antigens on vessel endothelial and smooth muscle cells direct the adaptive immune cells to damage the cardiac microvasculature [1,3]. Autoantibodies can also lead to activation of the coagulation system, culminating in thrombosis within coronary vessels with subsequent ischemia [4]. Inflammatory cytokines prime the cells of the innate and adaptive immune systems to direct their cytotoxic activities towards cardiac cells, inducing vascular, myocardial, and valvular dysfunction [1]. Lastly, some autoimmune diseases are characterized by the overactivity of specific cells leading to chronic pericardial, endocardial, and myocardial inflammation.

Compared to men, women are more susceptible to most autoimmune conditions (Fig. 1) and disproportionately affected. Sex hormone changes due to estrous cycling, pregnancy, and menopause impact

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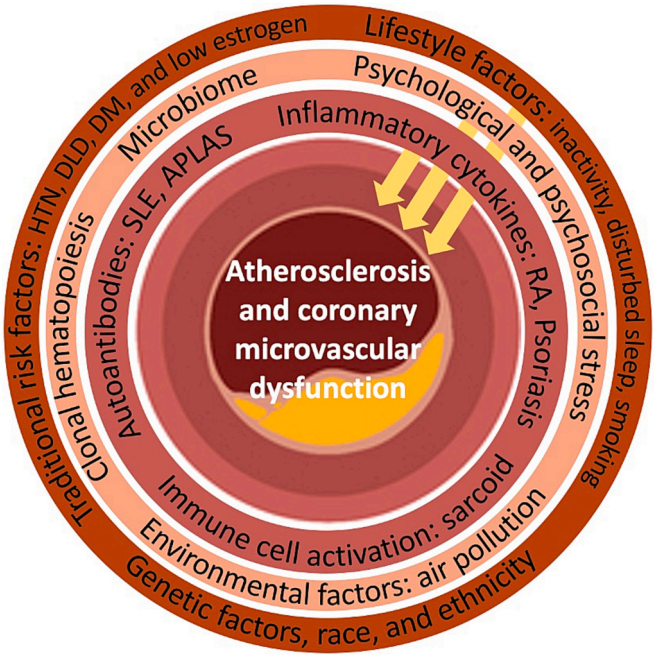

Fig. 1. Multiple mechanisms contribute to autoimmune dysfunction and chronic inflammation that trigger endothelial dysfunction, microvascular dysfunction, and atherosclerotic plaque formation in women with rheumatologic conditions.

immune function. While sex hormones likely play a role, women are also more susceptible to psychological and social stressors, which adversely impact immune function and inflammation [5]. Therefore, in a particular female, there is a complex interplay between the individual's stress susceptibility, hormonal milieu, environment, and genetic and predisposing factors that determine autoimmune disease severity and impact on their cardiovascular system. With multiple mechanisms at play that may interact with traditional risk factors for CVD (Fig. 2), the surveillance and treatment of patients with rheumatologic autoimmune conditions deserve special attention.

2. Cardiac manifestations in autoimmune disorders

Chronic autoimmune rheumatologic disorders may affect most cardiac structures, including the conduction system, valves, myocardium, coronary vasculature, pericardium, endocardium and periadventitial tissues. Patients with rheumatologic conditions have accelerated atherosclerosis that is not fully explained by traditional risk factors [6]. The exact mechanism for this premature and aggressive coronary and other major vessel atherosclerosis is unclear, but is believed to be related to chronic systemic inflammation that accompanies these disorders. Furthermore, in addition to accelerated obstructive coronary artery disease (CAD), many women lack obstructive CAD, but those women with autoimmune conditions may experience angina due to cardiac ischemia from mechanisms such as abnormal microvascular vasoreactivity, impaired vasodilation, capillary rarefaction and/or heightened prothrombic activity [7].

Traditional risk assessments such as the Framingham risk score do not fully account for these inflammatory disorders. Indeed, the Framingham risk score underestimates cardiovascular risk by 103 % in women and 65 % in men in patients with rheumatoid arthritis (RA) [8]. The AHA/ACC guidelines on CVD prevention consider rheumatologic disorders as a “risk enhancer.” [9] However, this risk assessment tool still characterized only 41 % of RA patients with known coronary calcifications as being high risk for coronary atherosclerosis [10].

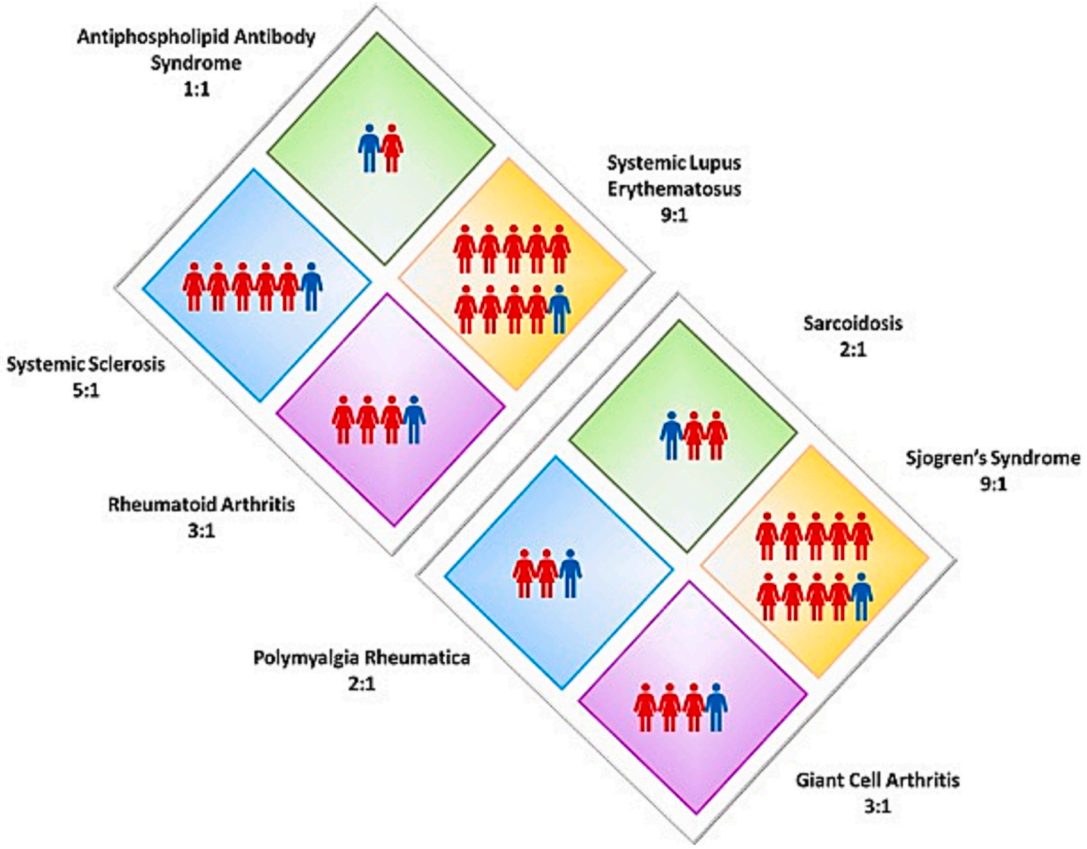

Fig. 2. Chronic systemic autoimmune disorders are highly prevalent in women.

Arrhythmias and conduction system abnormalities are often present in patients with rheumatologic disorders and can be the first manifestation of cardiac disease, and at times may be responsible for sudden cardiac death [11]. Myocardial and pericardial involvement may be present in up to 50 % of patients with rheumatologic disorders [12]. Having a heightened awareness of such cardiac pathologies is pivotal for adequate screening and timely detection of cardiac complications in patients with rheumatologic disorders. This manuscript highlights common specific rheumatologic conditions, discusses associated CVD risks and recommendations for screening and primary prevention when available, and addresses key knowledge gaps (Table 1).

3. Systemic lupus erythematosus (SLE)

In SLE circulating immune complexes and autoantibodies can affect the myocardium, endocardium, microvascular and epicardial coronary arteries, cardiac valves, and the pericardium. SLE has a predilection for women, with a 9:1 female to male ratio. Additionally, there is a racial and ethnic predisposition, with Black, Asian, Native American, and Hispanic women being 2–3 times more likely than White women to develop SLE [13]. SLE has been associated with higher rates of myocardial infarction (MI), which has been identified as the leading cause of death in SLE [14]. Premenopausal women (aged 35–44 years) with SLE were noted to have a 50-fold increased risk of MI than age-matched controls [15]. Women with SLE frequently report chest pain not only due to obstructive atherosclerosis CAD but also microvascular dysfunction/disease, with studies demonstrating impaired vasodilator reserve on stress imaging [16,17].

Valvular heart disease has been frequently described in patients with SLE. These endocardial lesions include diffuse valvular thickening, valvular nodules, marantic vegetations, and associated valvular stenosis or regurgitation and have been described in up to 25 % of patients with SLE, especially those with anticardiolipin antibodies [18]. Valve thickening was more frequent than valve dysfunction; however, both were more likely with advanced age and with greater SLE activity [18]. Arrhythmias (such as sinus tachycardia, atrial fibrillation, and atrial ectopy) may be present in up to 10 % of patients with SLE. Underlying mechanisms responsible for arrhythmias and conduction disorders include myocardial fibrosis, inflammation, autoantibody infiltration into the myocardium and conduction tissue, and myocardial ischemia [19].

Patients with SLE are also at increased risk of developing hypertension, particularly with renal involvement [20]. They are also at increased risk of developing heart failure, with approximately equal chance of developing heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). The risk of developing heart failure is directly associated with the inflammatory burden, as demonstrated by C-reactive protein (CRP) levels [21]. SLE patients were found to have increased heart failure mortality and the additional risk of other adverse cardiac events, including atrial fibrillation, stroke, and venous thromboembolism, compared with control subjects [22]. In 437 African American women in the Georgians Organized Against Lupus cohort, there was a significant association between organ damage and depression [23]. Women with the most severe organ damage had the greatest need for social support, highlighting the importance of addressing psychosocial stress and societal factors in women with SLE.

Table 1
Knowledge gaps.

- Investigation of pathways connecting functional auto-antibodies, sex hormones, and triggers of immune mechanisms that lead to intravascular inflammation
- Mechanisms of sex hormone contribution to autoimmune dysfunction with aging
- Does autoimmune dysfunction directly impact the myocardium (i.e., myofibroblasts, cardiomyocytes, myocardial energetics, and stiffness/diastolic dysfunction), or does it mainly trigger endothelial dysfunction and microvascular damage?
- Trials utilizing early intervention strategies of anti-atherosclerotic medications such as aspirin, statin, and ACE-I in patients with conditions such as SLE and RA
- Specific trials in at-risk rheumatic patients testing the impact of disease-modifying therapies on CVD outcomes
- Utility of coronary artery calcium screening in young women with autoimmune conditions to initiate primary prevention strategies
- Studies testing whether manipulation or psycho-neuro-immune axis by stress reduction techniques impacts CVD outcomes in women with autoimmune dysfunction
- Interventions focusing on improving social support in women living with chronic autoimmune conditions

4. Rheumatoid arthritis (RA)

RA is a persistent inflammatory state characterized by autoantibodies that primarily target joint synovium but can, to a lesser degree, affect other non-articular organs through a similar set of immune mediators [24–27]. RA increases the risk of CVD, including both the cumulative burden of RA and flares [28]. Women with RA experienced a 45 % increased risk of CVD-related death compared with women without RA independent of other risk factors [11]. In RA, inflammation has been shown to increase arterial stiffness, cause endothelial dysfunction, affect lipid metabolism, and destabilize atherosclerotic plaque predisposing patients to plaque rupture/erosion and MI. There are several studies that have observed increased risk of heart failure in patients with RA compared to non-RA patients, even after adjusting for CVD risk factors [29,30]. Attenuation of RA activity has been associated with fewer CVD events. Control of RA activity and inflammation and has been shown to improve outcomes [31]. Glucocorticoids and cyclooxygenase-inhibitors, which are part of the treatment for RA, have been associated with increased CVD risk in a dose-dependent manner. The association between glucocorticoid use and increased CVD risk, however, is unclear since increases in inflammation leads to increased steroid use. Therefore, tapering and stopping glucocorticoids to the lowest dose when clinically feasible is recommended [32]. Methotrexate and other disease-modifying antirheumatic drugs (DMARDS) reduce atherosclerosis and decrease the risk of CVD events in patients with RA [33]. Patients with inadequate response to DMARDS have a higher risk of developing acute coronary syndrome than those with RA controlled by DMARDS [34]. Despite its limited efficacy for RA activity and progression, hydroxychloroquine has been shown to improve metabolic profile and to a lesser extent cardiovascular events, and may be considered in combination with other DMARDS [35].

5. Psoriasis

Psoriasis is a chronic inflammatory condition mediated by a complex interplay of cytokines, chemokines, T cells, dendritic cells, and possibly skin microbiota that often leads to distinct skin lesions through increased epidermal turnover [36,37]. This chronic immune-mediated inflammation that drives psoriasis can also affect other organ systems [36–39]. Studies have shown an increased risk of CVD mortality from MI and stroke in those with severe psoriasis and psoriatic arthritis [40]. Methotrexate and tumor necrosis factor (TNF)-α inhibitors have been found to reduce the incidence of CVD events. Some data suggest that TNF-α inhibitors may be superior to methotrexate in reducing CVD events in psoriatic patients, especially with a longer duration of treatment [40]. The potential mechanisms of CVD in women with psoriasis could be due to altered adipokine profile, increased inflammation, and increased insulin resistance [41].

6. Scleroderma/systemic sclerosis (SSc)

Scleroderma/SSc is a chronic, progressive disease triggered by immune dysfunction that leads to fibrosis of multiple organs and has a poor prognosis in its severe form [42]. Pathogenesis of cardiac dysfunction in scleroderma stems from secondary complications due to pulmonary

hypertension and coronary microvascular changes that lead to increased cardiac myocyte cell death with replacement fibrosis [43,44]. This adverse remodeling leads to heart failure, conduction abnormalities, pericardial disease, and valvular disease. Cardiac involvement in scleroderma, like other systemic features, is not primarily inflammatory and patients can have very significant, non-inflammatory pericardial effusions [45].

While 70 % of patients with scleroderma are asymptomatic, typical scleroderma-induced heart disease symptoms include angina, environment-triggered chest pain, heart failure symptoms, and palpitations [43,46]. High rates of asymptomatic presentations and increased morbidity and mortality of those with SSc-induced cardiac disease emphasize the importance of detection through screening. Some professional organizations have suggested that all SSc patients receive baseline and yearly screening, including an echocardiogram, electrocardiogram, and serum B-natriuretic peptide (BNP) [47]. High sensitivity troponin T and N-terminal-proBNP levels were elevated in SSc compared to controls, even in those SSc patients without traditional cardiovascular risk factors [48].

7. Sjogren's syndrome

Primary Sjogren's syndrome is characterized by lymphocytic infiltration of the exocrine glands resulting in eye and mouth dryness, in addition to B-cell hyperactivity, but can also have systemic features. The disease disproportionately affects women, and a higher prevalence of CVD risk factors has been described in women with Sjogren's, including hypertension and hypertriglyceridemia, as compared to age and sex-matched controls [49]. Some studies have demonstrated an increased risk of MI and cerebrovascular events in individuals with Sjogren's, while others have suggested a more neutral relationship [50–52]. One study reported that the risk of cerebral infarction in Sjogren's is restricted to those with concomitant anti-Ro/SSA and anti-LA/SSB antibodies [50]. Supporting the concept that a causal link may exist between Sjogren's and CVD risk, studies have suggested that the condition to be independently associated with arterial wall thickening, subclinical atherosclerosis, and venous thromboembolic disease [50,52].

8. Dermatomyositis and polymyositis (DM/PM)

DM/PM are inflammatory muscle diseases with a complex pathophysiology that may affect the cardiovascular system and lungs and are more prevalent among women. In affected skeletal muscles, microvascular injury is the initial pathological change, preceding perimysial muscle fiber atrophy. Histological analysis of biopsy samples from affected muscles in DM/PM patients show evidence of endothelial cell sloughing and consequent deposition of membrane attack complexes [53,54]. Management focuses on reducing microvascular injury, rescuing endothelial cell function, and promotion of angiogenesis by producing growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor, or monocyte chemoattractant protein-1, which may counteract the microvascular rarefaction in DM/PM. An abnormally up-regulated type-I interferon (IFN) signature is a hallmark of DM/PM [53]. Plasmacytoid dendritic cells (pDCs) are an important source of type-I IFN [55]. Infiltrating pDCs are abundant in biopsies from diseased muscle in DM/PM [56].

9. Antiphospholipid syndrome (APLS)

APLS is a rare acquired autoimmune disorder associated with thrombotic and obstetric complications due to antiphospholipid antibodies (APAB). The syndrome can be primary or associated with other autoimmune disorders, often SLE. Women have a higher risk of major CVD events than men [57]. Both venous and arterial (commonly the cerebral circulation) thromboembolism can occur with APLS. Management includes evaluating the APAB profile and assessing for concomitant autoimmune diseases and other CVD risk factors. Antiplatelet agents may reduce the risk of a first thrombotic event in individuals with a high-risk profile. Evidence-based guidelines recommend lifelong vitamin K antagonists, preferably warfarin, in patients with thrombotic APLS. Direct oral anticoagulants are not recommended for use in high-risk APLS but can be used in patients with low-risk venous thromboembolism. In obstetric APLS, combination therapy with low dose aspirin plus heparin remains the conventional strategy [58].

Catastrophic antiphospholipid syndrome (CAPS) is a life-threatening subset of APLS, characterized by rapidly progressive multiorgan failure with high mortality due to widespread small vessel thrombosis. Although rare, CAPS is associated with a mortality rate that may reach 30 % [58]. A study in White, Black, and Asian ethnic groups with APLS, with and without anti-beta-2-glycoprotein I antibodies showed that only Asians were at higher risk for the elevated antibodies [59]. Statins may prevent obstetrical complications in APLS patients. A report suggested significantly lower adverse maternal and fetal/neonatal outcomes associated with pravastatin given after the onset of preeclampsia or intrauterine growth retardation compared to those without pravastatin [60].

10. Takayasu's Arteritis

Takayasu Arteritis (TAK), a large vessel vasculitis involving the media and adventitia of the aorta and its major branches, is defined by granulomatous inflammation, endothelial dysfunction, accelerated atherosclerosis, and aneurysm formation [6,61,62]. Women account for 80 % of cases with a peak incidence between 20 and 30 years old [63,64]. Association with HLA-B52 is well established and may account for the high prevalence seen in Asia, where allele frequency is high (11 % in Asia compared to <2 % in Northern Europe) [63,64]. Symptoms and signs of TAK include pulselessness, claudication, lightheadedness, and cyanosis, with early constitutional symptoms. The American College of Rheumatology established criteria for classification of TAK which includes onset $\leq$ 40 years, extremity claudication, subclavian or aortic bruit, >10 mm Hg difference in systolic blood pressure between arms, decreased brachial pulse, and arteriogram abnormality [63]. The incidence of CVD events in TAK is as high as 15.4 % at 10-years and the prevalence of stroke and MI at 8.9 % and 3.4 % respectively [65]. Systemic glucocorticoids are the mainstay therapy, although use of steroid-sparing agents, such as methotrexate, azathioprine, TNF alpha inhibitors, and IL-6 inhibitors have grown in popularity, in part, to avoid the risks associated with long-term steroid use. The importance of disease monitoring with imaging, biomarkers, and symptoms cannot be stressed enough, as both under and overtreatment are associated with increased risk of CVD events [6].

11. Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR)

GCA is a large and medium vessel vasculitis that affects the carotids, the aorta, and upper extremities [66,67]. PMR is more common than GCA, and approximately half of patients with GCA will have PMR in their lifetime [68]. Both increase in prevalence with age, affect women 2–3-times more than men, and are more common in Scandinavian and Northern European descents [66]. Pathogenesis of GCA involves T-cell mediated fragmentation of the internal lamina resulting in hyperplasia and luminal stenosis [69]. Common symptoms of GCA include headache, scalp tenderness, jaw claudication, constitutional symptoms, and ophthalmic complications [66,70]. PMR is characterized by pain and morning stiffness of the shoulders, hip girdle, and neck.

Temporal artery biopsy is the standard for diagnosing GCA and, when combined with elevated acute phase reactants, provides the highest sensitivity. Although not routinely recommended, increased fluorodeoxyglucose uptake in the subclavian arteries has been observed

in approximately one-third of patients with PMR, although the clinical implications remain incompletely understood [71]. GCA is associated with increased risk of coronary and other vascular events, including aortic aneurysm and dissection - with the highest risk (potentially 5-fold increased risk) <1 month from diagnosis [72,73]. High-dose corticosteroid therapy for 2–4 weeks followed by an erythrocyte sedimentation rate and C-reactive protein-guided taper is the mainstay treatment for GCA [74]. As seen with TAK, steroid-sparing agents are sometimes helpful in reducing the risks of chronic steroid use.

12. Sarcoidosis

Sarcoidosis, a multisystem inflammatory disease of unknown etiology, is characterized by non-caseating granulomatous deposition in various organs, most commonly the lungs [75]. It affects women at twice the rate compared with men and shows significant heterogeneity among races [76,77]. In 4500 patients with pulmonary sarcoidosis the rates of ischemic heart disease and MI were lower than the reference population >60 years of age, but higher in those <50 and between 50 and 59 years [78]. Sarcoidosis can be chronic and marked by persistently elevated inflammatory markers, which increases CVD risk [79]. There may be a direct relationship between the degree of inflammation and worsening hypertension among sarcoidosis patients [80]. This relationship needs further study, especially in younger patients, who may not be routinely screened for CVD risk factors.

13. Impact of inflammatory condition treatment on CVD risk

Cardiometabolic diseases such as obesity and prediabetes are prevalent in many autoimmune conditions. Given increased CVD risk, it is important to identify and treat CVD risk factors such as hypertension, hyperlipidemia, encourage healthy weight and dietary choices, and counsel on tobacco cessation. While pain may prevent patients from being physically active, it is important to encourage regular physical activity as tolerated such as walking, low impact exercises, swimming, and resistance training [81–84]. Coronary calcium score is a powerful risk marker and predictor of future CVD risk and may be helpful in discussing primary prevention strategies such as statins [85]. In a large registry of patients with RA (n = 395) compared to non-RA (n = 45,815) who were evaluated for suspected CAD with coronary CT angiography, patients with RA had a higher prevalence of coronary artery calcification [86]. Similarly, patients with SLE compared to non-SLE patients also have a greater burden of coronary artery calcification, even at younger ages [87]. While stable coronary calcification within the media is a marker of risk, it is the unstable, inflammatory plaques with lipid-rich core and micro-calcifications that are prone to rupture and lead to events. Investigation of plaque characterization and type of calcification using advanced imaging techniques such as optical coherence tomography and non-invasive imaging of plaque activity may improve risk stratification of women with autoimmune conditions [88,89]. For example, identification of higher risk intra-plaque calcifications may lead to more aggressive deployment of treatment strategies. It is important for clinicians to identify and treat CVD risk factors in women with autoimmune conditions early and testing such as echocardiography and coronary artery calcium score can be considered as appropriate. Updated recommendations for primary prevention of CVD in women have been recently published to guide clinical care [90]. Targeting inflammation has been investigated in multiple CVD trials, with mixed results [91–94]. The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) showed that Canakinumab (150 mg every 3 months), an antibody targeting IL-1β, reduced the rates of recurrent CVD events among patients with history myocardial infarction and elevated inflammatory markers [91]. Another anti-inflammatory agent, colchicine, a relatively inexpensive and widely used medication for treatment of pericarditis and gout, has been studied [95,96]. In the Colchicine Cardiovascular Outcomes Trial (COLCOT), this agent was effective in preventing major adverse cardiac events in patients with recent myocardial infarction [92]. In patients with stable CAD, colchicine was effective in reducing cardiovascular events [97]. While observational studies have shown that methotrexate is associated with reduced risk of CVD, the Cardiovascular Inflammation Reduction Trial (CIRT) showed no benefit of low dose methotrexate in reducing events in patients with prior myocardial infarction [93,94,98].

While treating inflammatory conditions may improve cardiovascular risk, two medication classes may increase risk, including non-steroidal anti-inflammatory medications (NSAIDs) and corticosteroids. NSAIDs inhibit cyclooxygenase and reduce prostaglandin I2 (prostacyclin) production by the vascular endothelium, resulting in increased risk of myocardial ischemia and stroke, and should be used cautiously [99]. While corticosteroids are particularly beneficial in patients with a chronic inflammatory disease, they can significantly cause or enhance atherosclerotic risk factors, including hypertension, glucose intolerance, weight gain, and dyslipidemia (DLD), and consequently increase the risk of premature CAD. The risk of these adverse effects increases with prednisolone doses above 7.5 mg [100]. Conventional synthetic disease-modifying antirheumatic drugs include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. Biologic DMARDS include anti-TNF (adalimumab, certolizumab, golimumab, infliximab), anti-IL-6 (tocilizumab, sarilumab), anti-T-cell co-stimulation (abatacept), anti-B cell (rituximab), and anti-IL-1 (anakinra) agents. It is unknown whether or not the targeted synthetic disease-modifying antirheumatic drugs (tsDMARDS: baricitinib, upadacitinib) affect CVD risk [101]. A large clinical trial on tofacitinib showed increased CVD risk in RA patients who had at least one other risk factor [102]. Cardiovascular side effects of hydroxychloroquine include the rare likelihood of cardiomyopathy and QT prolongation [103]. Anti-TNF agents have been associated with exacerbation of heart failure and should be cautiously used in individuals with pre-existing heart failure.

14. Autoimmune disorders in pregnancy

Autoimmune disorders primarily limited to the joints, such as RA, are typically well tolerated during pregnancy without significant consequences for mother or baby [104]. However, conditions characterized by widespread inflammation and autoantibodies such as SLE and APLS can result in adverse maternal and fetal outcomes [104]. Pregnancy complications in SLE include miscarriage, gestational diabetes (particularly if systemic steroids are required), preterm birth, fetal growth restriction and risk of hypertensive disorders of pregnancy as high as 13–35 % [104,105]. Risk of complications is reflective of disease activity in the year prior to conception, and women are at high risk of pregnancy complications if they have disease complicated by lupus nephritis, anti-Ro/SSA or anti-La/SSB antibodies, or APLS positivity [104]. Pregnancy risk is further complicated by underlying cardiovascular risk factors such as diabetes, hypertension or obesity [104]. Hypertension during pregnancy not only increases the risk of hypertensive disorders and CVD post-partum in the mother, but is also associated with cardiac structural changes, adverse cardiometabolic risk, and increased CVD risk in the offspring [106–108]. For example, The Nord-Trøndelag Health (HUNT) Study demonstrated that children of hypertensive pregnancies had higher blood pressures in young adulthood compared to normotensive pregnancies [109]. Pregnancy is considered contraindicated in women with autoimmune disorders complicated by pulmonary arterial hypertension, advanced heart failure, severe restrictive lung disease, or chronic kidney disease (Cr >2.8 mg/dL) [105]. Patients with APLS are typically treated with low dose aspirin and low molecular weight heparin during pregnancy to improve pregnancy outcomes [104,105].

15. Conclusions

In addition to traditional CVD risk factors, chronic systemic autoimmune disorders are important risk enhancers that significantly affect

women. Underlying autoimmune dysfunction and inflammation predispose to premature and accelerated atherosclerosis, heart failure, systemic endothelial and microvascular dysfunction, and thrombosis. The presence of comorbid conditions, the duration of autoimmune condition, disease severity, and suppressive treatment of underlying inflammation are all factors that impact CVD risk. Early identification and screening of CVD risk factors in those with underlying autoimmune conditions may attenuate CVD in this population. Multi-disciplinary, team-based care, clinical trials, and collaborative team-science studies focusing on systemic autoimmune conditions will be beneficial to advance care for women.

Ethical statement

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

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Declaration of competing interest

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