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Investigational echocardiography for the detection of heart involvement in rheumatic musculoskeletal diseases

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Coordinator: Prof. Giovanni Targher

Signature

Tutor: Prof. Davide Gatti

Signature

PhD candidate: Dott. Alessandro Giollo

Signature

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Alessandro Giollo
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Intellectual and publication statements

The candidate confirms that the work submitted is his own, except where work that has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter I. Section 1.1, 1.4, and 1.5 are based on work from a jointly authored publication by myself, LA Bissell and MH Buch [Giollo A, Bissell LA, Buch MH. *Cardiovascular outcomes of patients with rheumatoid arthritis prescribed disease modifying anti-rheumatic drugs: a review*. Expert Opin Drug Saf. 2018 Jul;17(7):697-708]. Section 1.1 and 1.6 are partially based on several publications I co-authored before starting my PhD course.

Chapter II. This chapter is based on my own publication [Giollo A, Cioffi G, Ognibeni F, et al. *Tumour necrosis factor inhibitors reduce aortic stiffness progression in patients with long-standing rheumatoid arthritis*. Arthritis Res Ther. 2021 Jun 3;23(1):158]. I wrote the *CASIMIRO* protocol with the supervision of Dr Ombretta Viapiana and submitted it to the ethical committee. Echocardiography studies were performed by Dr Federica Ognibeni and Dr Giovanni Cioffi. I was responsible for recruitment, data collection, analysis, and writing.

Chapter III. This chapter is based on my own publication [Giollo A, Cioffi G, Ognibeni F, et al. *Sex-Specific Association of Left Ventricular Hypertrophy With Rheumatoid Arthritis*. Front Cardiovasc Med. 2021 Jun 10;8:676076]. I was responsible for patient recruitment, data collection, analysis, and writing. Echocardiography studies were performed by Dr Federica Ognibeni and Dr Giovanni Cioffi.

Chapter IV. This chapter reports data published as abstract only. The *SCARLET* study was co-designed with Dr Giulia Vinco at the Division of Cardiology, University of Verona (Italy). Data analysis was performed both by myself and Dr Giulia Vinco. Dr Giulia Vinco performed all echocardiography studies, including speckle-tracking and pulse-cancellation imaging analyses. I was responsible for recruitment, data collection, analysis, and writing.

Chapter V. This chapter reports unpublished data. Echocardiography assessments of the *ULYSSYS* study were performed by Dr Federica Ognibeni and Dr Giovanni Cioffi. I was responsible for recruitment, data collection, analysis, and writing.

Chapter VI. This chapter is partially based on work from a jointly authored publication by A Giollo, LA Bissell, and MH Buch [Giollo A, Bissell LA, Buch MH. *Cardiovascular outcomes of patients with rheumatoid arthritis prescribed disease modifying anti-rheumatic drugs: a review*. Expert Opin Drug Saf. 2018 Jul;17(7):697-708].

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List of publications and presentations arising from this thesis

Original articles

Giollo A, Cioffi G, Ognibeni F, Bixio R, Fassio A, Adami G, Orsolini G, Dalbeni A, Idolazzi L, Gatti D, Rossini M, Viapiana O. Sex-Specific Association of Left Ventricular Hypertrophy With Rheumatoid Arthritis. Front Cardiovasc Med. 2021 Jun 10;8:676076.

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Oral presentations (first author)

2021 Italian Society of Rheumatology (Società Italiana di Reumatologia, SIR) congress (upcoming). Giollo A, Cioffi G, Ognibeni F et al. Detection Of Myocardial Fibrosis Using Advanced Echocardiography In Patients With Systemic Sclerosis.

2021 LUPUS/CORA congress 2021. Parallel 06 SLE: Cardiovascular (and vascular) risk management. Giollo A, Vinco G, Orsolini G, et al. Assessment Of

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Poster presentations (first author)

2021 EULAR congress. Giollo A, Cioffi G, Orsolini G, et al. POS0218 Tumor-Necrosis Factor Inhibitors Improve Aortic Stiffness In Patients With Longstanding Rheumatoid Arthritis. Ann Rheum Dis 2021;80:326-327.

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Abstract

Introduction. Patients with rheumatic musculoskeletal diseases (RMDs) face a risk of cardiovascular disease (CVD) that is significantly higher than the general population. It has long been recognised that RMDs can affect the musculoskeletal system as the heart. However, RMDs-primary heart involvement (RMDs-pHI) has been poorly characterised, and it is difficult to ascertain its contribution to the increased CVD risk of RMDs patients. Other than the effect of traditional cardiovascular risk factors, several factors that are disease-specific may contribute to RMDs-pHI, such as a chronic inflammatory insult to the vessels, pro-inflammatory lipids, the effects of anti-rheumatic therapies, and autoimmune or post-repairing biological processes. Detection of RMDs-pHI has prognostic implications.

Aim. This doctoral thesis aimed to investigate by ultrasound the plethora of cardiac abnormalities in patients with RMDs and to correlate those findings with the clinical characteristics of the diseases.

Methods. This was a prospective observational study based at the Division of Rheumatology, University of Verona (Italy). We recruited outpatients with established diagnoses of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). All patients underwent a baseline assessment of cardiovascular and disease-related data. We also used standard transthoracic echocardiography (TTE) and additional investigational TTE techniques to determine cardiac abnormalities. Study outcomes were: 1) left ventricular (LV) volumes and mass, including an assessment of LV hypertrophy (LVH); 2) myocardial strain, using speckle-tracking echocardiography (STE); 3) arterial stiffness, as measured by the aortic stiffness index (AoSI); 4) myocardial fibrosis, identified by pulse-cancellation imaging (eSCAR).

Results. We found that among RA patients, women were more likely to progress to LVH than men, irrespective of their CVD risk profile. Patients with RA also had an increased AoSI, but the use of tumor necrosis factor-alpha inhibitors compared to csDMARDs was protective against the progression of aortic stiffness, especially with accumulating CVD risk factors. SLE patients had myocardial fibrosis detected by eSCAR in the inferior and inferoseptal basal segments in 17%, which was associated with the long-term exposure to glucocorticoids. Patients with SSc had myocardial scars with a similar pattern to SLE patients in 25%, but also with ischemic patterns. However, digital ulcers were independently associated with non-ischemic fibrosis. In both SLE and SSc patients, myocardial fibrosis localized in areas of impaired myocardial

deformation as shown by STE, suggesting that myocardial fibrosis was associated with subclinical myocardial dysfunction.

Conclusion. We showed that myocardial abnormalities are frequent in RMDs patients and can be effectively detected with manageable TTE techniques. Moreover, specific cardiac lesions were associated with features of disease severity in SLE and SSc patients. The implementation of echocardiography studies in the Rheumatology core assessment could allow cardiovascular risk stratification of patients with RMDs. This could help reduce costs and optimise resources.

Lay summary

Rheumatic musculoskeletal diseases predominantly involve the joints, but it is well known that they can also affect the cardiovascular system, leading to an excess of cardiovascular disease-related accidents and mortality. The raised incidence of cardiovascular events among those patients cannot be explained only by accelerated atherosclerosis or over-represented traditional cardiovascular risk factors. Interestingly, more recently, there has been growing interest in heart involvement by rheumatic musculoskeletal diseases. Patients with several rheumatic musculoskeletal diseases are prone to heart failure with preserved systolic function. However, this entity is not clinically evident, and it can be revealed only with particular imaging. In this work, we sought to investigate advanced echocardiography to detect and characterise those cardiac abnormalities that could reveal this subclinical 'primary' heart involvement in patients with rheumatic musculoskeletal diseases. We studied three different rheumatic musculoskeletal diseases that encompass the clinical spectrum of rheumatology: rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis. Herein, we provide evidence that measures of aortic stiffness, left ventricular mass and function, myocardial strain and fibrosis, can efficiently and often reveal subtle myocardial abnormalities in our patients. We also show that some manifestations of each disease are associated with those abnormalities and can be used as a clue to detect primary heart involvement in their management.

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Chapter I. Introduction

On the involvement of the heart and cardiovascular system in rheumatic musculoskeletal diseases

Rheumatic musculoskeletal diseases (RMDs) are common multifactorial diseases that share features of chronic inflammation and autoimmunity. Overall, patients with RMDs face a higher occurrence of comorbidities, mortality, and disability than the general population. Hence, the burden of RMDs on health and social costs are high worldwide [Tang, 2011; Clarke, 1993; Clarke, 1997; Salmon, 2019; Fautrel, 2020].

Rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis encompass the spectrum of autoimmune diseases across RMDs, as they comprise a significant proportion of patients routinely under the care of most divisions of rheumatology.

Rheumatoid Arthritis (RA) is the prototypical autoimmune rheumatic disease that affects 0.5-1% of the population [Symmons, 2002]. It is characterised by a symmetrical, often erosive, inflammatory polyarthritis, typically associated with circulating rheumatoid factor (RF) and the more specific, anti-citrullinated peptide antibodies (ACPA). RA is associated with significant morbidity and mortality and thus considerable individual and societal economic costs.

Systemic lupus erythematosus (SLE) is a multi-system inflammatory disease with autoimmune pathogenesis. It has a chronic course with frequent relapses. In SLE, autoantibodies and immune-complexes activate to cause tissue damage. SLE severity is variable but has a relevant impact on the health of affected patients, further worsened by progressive end-organ damage and accumulation of comorbidities, especially CVD. Globally, the estimated prevalence in the past fifteen years was 9-241 cases per 100’000 inhabitants/year, and the estimated

incidence was 0.3-23.2 cases per 100’000 inhabitants/year [Gergianaki, 2018]. The incidence of SLE has been growing during the past forty years, likely thanks to better recognition of mild disease [Fanouriakis, 2021]. SLE has a predilection for young females [Margery-Muir, 2017] and persons of Afro-American or Hispanic ethnicities [Lewis, 2017].

Systemic sclerosis (SSc) is a rare, incurable, systemic RMD characterised by a progressive accumulation of fibrosis within tissues and organs. The estimates of the prevalence of SSc vary worldwide, ranging from less than 150 cases in Northern Europe and Japan to 275-443 every million people in Southern Europe, North America and Australia. Incidence is 10-21/1'000'000 every year [Barnes et al, 2012]. SSc affects women more often than men, and it is often life-threatening disease, primarily due to an increased risk of lung fibrosis and cancer.

There is a robust body of evidence that chronic inflammation, autoimmunity and other factors contribute to an overall increased risk of CVD events in patients with RMDs. Aside from this knowledge, little is known about the effect of RMDs-related factors on specific components of the cardiovascular system, especially the heart. Subclinical abnormalities of the myocardial function have been shown in the majority of RMDs patients and are associated with CVD events [Rivera, 2021]. However, there is convincing literature that the heart is primarily involved in patients with RMDs. Hence, a substantial challenge in rheumatology is the one trying to define this 'primary heart involvement (pHI)' and the characteristics of RMDs that could be associated with it.

Indeed, the type of heart involvement in RMDs is diverse. Several pHI-related manifestations have been described, including myocarditis, endocarditis, and pericardial disease; acute coronary syndromes; cardiomyopathy; and arrhythmia. Associated lesions include myocardial dysfunction, ischemia, or fibrosis; degenerative valvulopathy; conduction abnormalities. For this reason, it is impossible to study all patterns of pHI involvement at a glance, but there is a need to identify and assess the few main lesions that can imply a broader spectrum of heart damage in patients with RMDs.

No consensus has been reached on what lesions to be considered nor the proper technique to detect pHI in trials and routine practice so far. Since the incidence rate of clinically evident CVD events occurring in RMDs patients is too low to design studies with such outcomes, there is a need for CVD surrogates. Many efforts have been put into this task [Bruni, 2021], with several studies investigating imaging and biomarkers as tools to detect primary heart involvement in RMDs (RMDs-pHI).

The primary aim of this thesis was to demonstrate the feasibility of echocardiography in patients with RMDs-pHI. We wanted to show that there are abnormalities of the cardiovascular system in patients with rheumatic and musculoskeletal diseases, as detected by echocardiography using some advanced techniques.

The secondary aim was to describe one or more associations between those abnormalities and the characteristics of rheumatic and musculoskeletal diseases or their treatment.

The final goal was to inform physicians on prognostic stratification of those patients who most likely will have RMDs-pHI.

1.1 Cardiovascular disease in rheumatoid arthritis

1.1.1 Epidemiology of cardiovascular disease in RA

Patients with RA have an increased risk of CVD compared with the general population [Castaneda, 2015; Chung, 2013; Turesson, 2004; Han, 2006], causing >50% of premature deaths [Avina-Zubieta, 2008], mainly attributed to accelerated atherosclerosis. A large meta-analysis comprising over 111,000 patients with RA reported a standardised mortality ratio (SMR) for CVD mortality of 1.50 (95% CI 1.39, 1.61), with specific SMR for ischaemic heart disease (IHD) of 1.59 (95% CI 1.46, 1.73) and cerebrovascular accidents (CVA) of 1.52 (95% CI 1.40, 1.67) [Avina-Zubieta, 2012]. Another meta-analysis of over 120,000 patients provided a pooled estimate SMR of 1.77 (95% CI 1.65 to 1.89) for fatal myocardial infarction (MI) and 1.46 (95% CI 1.31,1.63) for fatal stroke [Meune, 2010].

Levy et al. reported an odds ratio for MI for patients with RA of 1.63 (95% confidence interval (CI) 1.34, 2) compared to the general population [Levy, 2008], whilst another meta-analysis reported a pooled relative risk of MI (adjusted for age and sex) of 1.69 (95% CI 1.50, 1.90) in those with RA [Schieir, 2017]. Evidence suggests the risk is similar to that seen in that of diabetes mellitus (DM) [van Halm, 2009].

Interestingly, the relative risk of CVD appears to be greater in younger patients; Fransen et al. reported increased CVD events in those less than 50 years (relative risk (RR) 2.59 (1.77–3.79), compared to those older than 65 years (RR 1.27 (1.16–1.38) when compared to the general population [Fransen, 2016].

Some studies suggest that the accelerated risk is present in those with a recent diagnosis of RA [Kerola, 2012; Lindhardsen, 2011], including the Rochester Epidemiology Project, which confirmed patients with early RA had a 10-year CVD risk profile similar to that of subjects five to ten years older without RA [Kremers, 2008]. Abnormalities of arterial stiffness have been shown to progress, particularly during the first six years from the time of RA diagnosis [Gonzalez-Juanatey, 2011; Giles, 2011]. However, observational studies provided evidence that a significant increase in the risk of CVD deaths occurs 7-10 years after

disease onset [Avina-Zubieta, 2008; Radovits, 2010]. Data from a population-based incidence cohort of RA patients indicate that the overall mortality gap between RA patients and the general population is not closing [Gabriel, 2008]. Conversely, one meta-analysis concluded no increase in CVD events and CVD mortality in RA inception cohorts [Avina-Zubieta, 2008]. A possible explanation of this discrepancy is that more aggressive control of disease activity in RA may lead to significant improvements in CVD outcomes. A more recent prospective cohort study reported a decline in CVD events in patients with RA with low disease activity [Meek, 2014], indicating perhaps earlier recognition of RA and the advent of early inflammatory arthritis clinics with more aggressive treatment may be reducing the CVD risk. Indeed, a large study in Finland of over 14,500 patients from 2000-2008 with recent-onset RA (80% receiving RA medication) found patients had no increased risk for CVD mortality compared to the general population in the early years of follow-up [Kerola, 2015]. In contrast, after adjustment for improved mortality in the general population, the Norfolk Arthritis Register Disease recently reported no reduction in CVD mortality in those with inflammatory polyarthritis between two cohorts ten years apart [del Rincon, 2001].

1.1.2 Potential mechanisms of increased CVD risk in RA

Risk factors for CVD in RMDs comprise traditional and non-traditional (systemic inflammation and RMDs-disease factors) as detailed below. The combination of these risk factors has yielded the strongest prediction for future CVD events [Solomon, 2010].

1.1.1.1 Traditional CVD risk factors, accelerated atherosclerosis and coronary artery disease

The traditional CVD risk factors comprise hypertension, smoking, dyslipidemia, DM and premature family history of CVD. Although they alone do not explain the heightened risk of CVD in RA [del Rincon, 2001], they remain important, modifiable factors to address [Han, 2006], with a meta-analysis confirming in particular, hypertension, type 2 DM, smoking and hypercholesterolemia as key

traditional factors increasing the risk of CVD in RA [Baghdadi, 2015]. In addition, there is evidence for potentiation of this increased risk when in the presence of active RA disease, highlighting an interplay between the two [Innala, 2011].

As seen in the general population, older age and the male sex are associated with greater CVD risk in RA [Naranjo, 2008]. Essential hypertension is reported in up to 57% of patients with RA [Solomon, 2010] and can predict CVD events, with a hazard ratio of 3.67 (95% CI 2.0, 6.4, p = 0.001) derived from the Swedish Rheumatoid Arthritis Registry [Innala, 2011]. The prevalence of DM is greater in patients with RA [Jiang, 2015; Solomon, 2010], with recent data suggesting a further heightened risk of CVD for patients with both RA and DM [Curtis, 2018].

Smoking exposure in RA exemplifies a complex gene-environment interaction. In individuals with the HLA-DR4-positive ('shared epitope') genotype, smoking increases the citrullination of proteins and the production of ACPA [Scott, 2011]. Therefore not only does smoking increase CVD risk through its 'traditional' effects on the endothelium and blood pro-coagulation, it is also an independent risk factor for developing RA and predicting severe disease and poor treatment response [Soderlin, 2012]. This relationship of smoking with ACPA is especially interesting given that citrullinated proteins have been found within atherosclerotic plaques [Sokolove, 2013].

Dyslipidaemia is reported in up to 30% of RA cohorts [Naranjo, 2008], with increased total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and decreased high-density lipoprotein cholesterol (HDL-C) [Yoo, 2004]. Dyslipidaemia can be seen within one year of RA diagnosis [Kerola, 2012] and has been reported prior to the onset of RA [van Halm, 2007]. Dyslipidaemia is independently associated with CVD events in RA [Naranjo, 2008]; however, the observations are more complex. Some studies report reduced TC, LDL-C and HDL-C in RA [Boyer, 2012], with these patients carrying a higher risk of CVD [Myasoedova, 2011]. This inverse relationship between lipid levels and CVD risk, or 'lipid paradox' may be explained by the changes in lipids in the presence of inflammation; CRP and disease activity tend to negatively correlate with TC,

LDL-L and HDL-C but not with TC/HDL-C [Boyer, 2012], suggesting the latter may perform better as a predictor of CVD risk in RA. In addition, an interaction between lipids and inflammation has been identified in RA; both lower LDL-C and TC/HDL-C associate with an even greater risk of CVD in the presence of inflammation [Myasoedova, 2011]. The exact basis for this remains unclear, but evidence to support alteration of lipid function with inflammation [Charles-Schoeman, 2012] is focussing current lines of investigation.

The cardio-metabolic state described in RA has suggested an apparent paradox of the conventionally described association of body mass index (BMI) and mortality [Libby, 2002]. In RA, low BMI has been associated with higher CVD risk [Danesh, 2008], whereas higher BMI is associated with CVD risk factors but does not seem to translate into increased CVD events [41]. Rheumatoid cachexia, often present in RA and characterised by low muscle mass (sarcopenia) with high-fat mass, may also contribute to CVD risk [Abou-Raya, 200]. Other more generalised risks in RA include a sedentary lifestyle [Danesh, 2004] and chronic kidney disease; however, the link of CVD with Vitamin D deficiency, hyperuricaemia and hyperhomocysteinaemia remains to be confirmed in RA [Cannon, 2004].

1.1.1.2 Systemic inflammation, disease activity and immune-disruption

It has long been recognised that inflammation plays a role in atherosclerosis [Collaboration CRPCHDG, 2011]. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial highlighted the relevance of inflammation as a modifiable risk factor, and it provided evidence that reducing high-sensitivity CRP levels with rosuvastatin could lead to a significant decrease in the incidence of major CVD events, even in non-dyslipidaemic patients [Swerdlow, 2012]. CRP has been found in atherosclerotic lesions, can induce endothelial cell adhesion molecule expression, augment monocyte migration into the atherosclerotic lesion, and mediate monocyte uptake of LDL-C [Ridker, 2017]. In the general population, CRP has been shown to predict future CVD events [Skeoch, 2015], and as indicated earlier, the cardioprotective effect of statins is attributable to both reduction of lipids and

CRP [Choy, 2014]. However, whether there is a causal relationship between CRP and CAD is not clear, with genetic Mendelian randomisation studies suggesting this is unlikely [Aubry, 2007]. A Mendelian randomisation study of IL-6 receptor signalling does seem to indicate a causal effect on coronary artery disease [van den Oever, 2013]. Secondary prevention of CAD has been proved an achievable target after IL-1 inhibition [Mackey, 2012; Ridker, 2017], while the Cardiovascular Inflammation Reduction (CIRT) Trial [Ridker, 2019] showed that low-dose MTX did not reduce the occurrence of MACE in patients with DM or metabolic syndrome with stable CAD.

RA and atherosclerosis thus share immuno-inflammatory pathways [Goodson, 2005], with an overlap of innate and cell-mediated immune processes [Solomon, 2003]. Whilst coronary artery angiographic involvement and atherosclerotic burden seem comparable, patients with RA appear to have more inflammatory vessel wall lesions and vulnerable plaque compared to the general population [Crilly, 2009; Agca, 2017]. In addition, CRP has been associated with increased CVD events in RA and can predict future CVD events and CVD related death [Arnab, 2013; Solomon, 2015].

The Feiring Heart Biopsy Study compared the findings of paraffin-embedded, formalin-fixed specimens from the right atrium collected during coronary artery bypass grafting in patients with or without RMDs. Epicardial inflammatory cell infiltrates were found in 56 % of patients with RMDs and 60% non-RMDs patients and were related to younger age at presentation. However, there was more collagen deposition within the myocardium in RMDs patients compared to controls. These findings suggest differences in extracellular matrix composition and/or mass, which might play a role in cardiac remodelling in RMDs patients [Andersen, 2016; Hollan, 2013; Hollan, 2007].

RA-specific features have been associated with a higher CVD risk. RA disease duration is recognised as an independent risk factor for CVD, associating with greater risk of MI [Kaushik, 2015] and surrogate measures of CVD [Sahari, 2014]. Longitudinal studies have reported time-averaged disease activity scores associated with CVD events [Baker, 2015; Kremers, 2004]. As mentioned earlier,

seropositivity for RF or ACPA may also increase CVD risk [Solomon, 2010; Ajeganova, 2013], with ACPA associated with many surrogate measures of CVD [Cavagna, 2012]. However, the association between seropositivity and several outcomes, including CHD, stroke, CVD, fatal CVD, and overall mortality, was not confirmed in more than 160,000 postmenopausal women in the Women's Health Initiative study [Kremers, 2004]. Other RA-disease specific risk factors include poor prognostic markers, subcutaneous nodules [Summers, 2010], radiographic erosions [Metsios, 2009], and higher health assessment questionnaire–disability indexed (HAQ-DI) responses [Hollan, 2015], with evidence for at-risk genetic polymorphisms [Dougados, 2014] have also been associated with increased risk of CVD. Rheumatoid nodules and DAS28 has been recently independently associated with ascending aortic FDG uptake in anti-CCP antibody-positive RA patients without clinical CVD [Suissa, 2006]. Nevertheless, in the Women's Health Initiative study [Baker, 2015], subcutaneous nodules and erosions appeared no longer significant once adjusted for disease activity. Collectively, this study, in particular, highlights disease activity as the pivotal driver of CVD risk.

A recent report from a large, international cohort evaluated the traditional and RA-specific elements discussed above. A longitudinal study of 5638 patients with RA and no prior CVD showed that both traditional CVD and RA-specific factors had significantly different prevalence among women and men, that there was a sex difference in CVD event rates in patients with RA for all ages above 40 years, and this was independent of traditional CVD risk factors and markers of RA disease activity. Of particular interest, RA characteristics accounted for approximately 30% of CVD risks [Arts, 2015]. This report highlights the importance of addressing both traditional and RA-specific factors to reduce CVD.

1.1.1.3 Arterial stiffness and endothelial dysfunction

Increasing arterial stiffness is one of the first steps in the atherosclerotic process [Berger, 2021]. Pulse wave velocity (PWV) and augmentation index (AIx) are two methods to assess arterial stiffness and are currently considered independent predictors of major CVD events and all-cause mortality [Mattace-Raso, 2006;

Laurent, 2001; Horinaka, 2011; Mitchell, 1997]. These surrogate markers of subclinical atherosclerosis provide some essential prognostic information in addition to traditional CVD risk factors.

Arterial stiffness is one of the earliest detectable manifestations within the atherosclerotic vessel wall [Cavalcante, 2011; Cohn, 2004], and it acts as a strong independent predictor of CVD events and all-cause mortality in various populations [Vlachopoulos, 2010]. As shown in Figure 1, when structural and functional changes of the elastic fibres within the arterial wall occur, arteries progressively lose their low-stretch bearing component, longitudinal elasticity and geometry, leading to collagen deposition with decreased elasticity and stiffness, elongation and increased tortuosity [Segers, 2020]. While this phenomenon is strictly related to ageing, it can also be accelerated with increased CVD risk factors and inflammation (i.e. early vascular ageing). Arterial stiffness eventually results in higher driving pressures and increased energy demands for the heart while leading to higher diastolic-systolic pressure differences (i.e., widening of pulse pressure). Increased arterial pressures and pulsatility impose higher mechanical stress on the vessels and organs, leading to strong associations between arterial stiffness and organ damage in the heart, kidney, or brain [Chirinos, 2019].

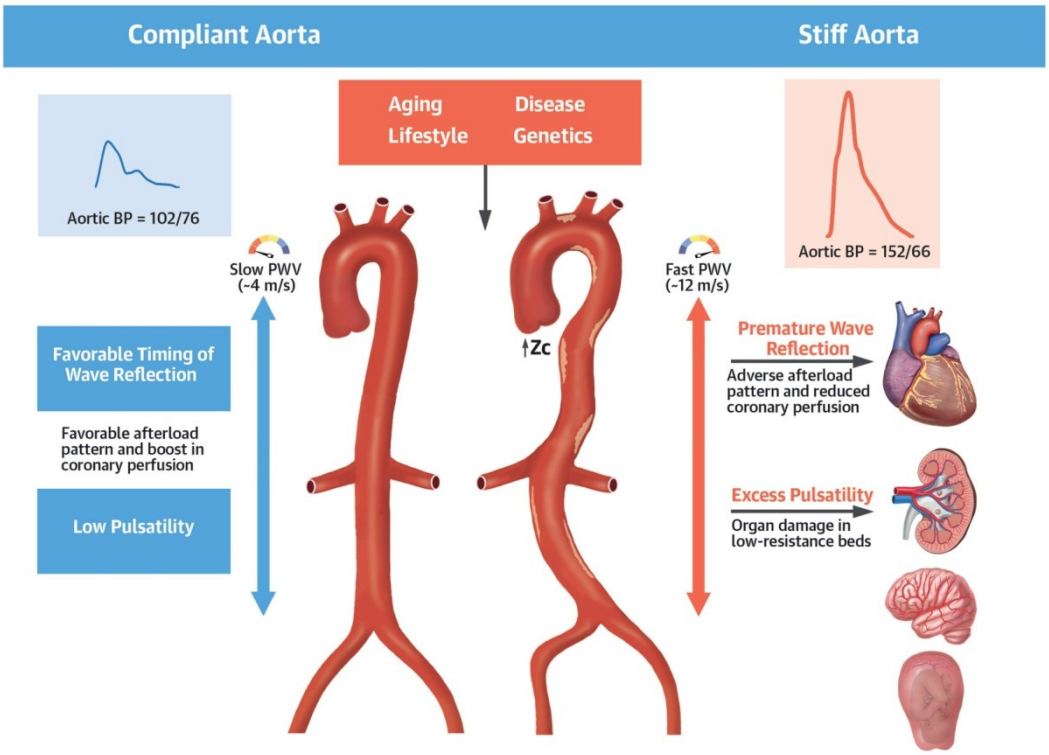

Figure 1. Role of large artery stiffness in health and disease.

In healthy young adults, a compliant aorta (left): (a) effectively buffers excess pulsatility due to the intermittent left ventricular ejection; (b) exhibits a slow pulse wave velocity (PWV), which allows pulse wave reflections to arrive at the heart during diastole, increasing diastolic coronary perfusion pressure but not systolic ventricular load. A number of factors (ageing, lifestyle, etc.) increase aortic wall stiffness, which leads to several adverse hemodynamic consequences. Aortic stiffening leads to increased aortic root characteristic impedance (Zc) and forward wave amplitude on one hand and premature arrival of wave reflections to the heart on the other. These hemodynamic changes result in adverse patterns of pulsatile load to the left ventricle in systole and reduced coronary perfusion pressure in diastole, ultimately promoting myocardial remodelling, dysfunction, failure and a reduced perfusion reserve (even in the absence of epicardial coronary disease). This adverse hemodynamic pattern also results in excessive pulsatility in the aorta, which is transmitted preferentially to low-resistance vascular beds (such as the kidney, placenta and brain), because in these organs, microvascular pressure is more directly coupled with aortic artery pressure fluctuations. PWV=pulse wave velocity; Zc=characteristic impedance; BP=blood pressure. From Chirinos, J.A. et al. J Am Coll Cardiol. 2019;7(9):1237-63) [Chirinos, 2019].

There is growing evidence that increased arterial stiffness may account for the excess risk of CVD in RA [Klocke, 2003; Prati, 2014; Moroni, 2017; Kotani, 2017; Gonzalez-Gay , 2008; Bordy, 2018]. The majority of studies investigating the relationship between arterial stiffness and RA compared with controls found an increase in arterial stiffness. Arterial stiffness may be influenced by disease duration [Gunter, 2017], disease activity [Tam, 2018], inflammatory biomarkers [Crilly, 2009], and serological status [Gunter, 2017]. In addition, our group reported that the echocardiography-based Aortic Stiffness Index (AoSI) was significantly higher (almost twice as high) in RA patients than in controls matched for CVD risk [Cioffi, 2016].

The endothelial activation in the microvasculature has received great attention as the potential driver of the arterial stiffening of large vessels such as the aorta in RA [Bordy, 2018]. Endothelial dysfunction is a systemic condition that affects both the macro and the microcirculation of RA patients. Microvascular endothelial is a functional and reversible alteration of endothelial cells and leads to a shift in the properties of the endothelium towards reduced vasodilation, a pro-inflammatory state, and proliferative and prothrombotic properties. Evidence suggests that microvascular endothelial dysfunction contributes to CVD development, as it precedes and predicts the development of atherosclerosis and associated risk factors [Bordy, 2018].

Data from cross-sectional and longitudinal studies of large or small cohorts of patients with RA demonstrate no correlation between microvascular and macrovascular endothelial dysfunction [Sandoo, 2011], suggesting that endothelial dysfunction in the macro and microvasculature reflects different aspects of the vascular pathology in RA. In RA, microvascular endothelial dysfunction did not correlate with traditional markers of endothelial activation (e.g. dimethylarginines) nor characteristics of RA severity such as disease activity markers, disease duration, or inflammatory markers. Interestingly though, circulating IL-1β [Ikonomidis, 2014] or TNF [Yki-Jarvinen, 2003] levels seem to correlate with microvascular endothelial function, and targeted therapies against those cytokines have provided CVD benefit in patients at very high CVD risk.

1.2 Cardiovascular disease in systemic lupus erythematosus

1.2.1 Epidemiology of CVD in SLE

The link between the increased CVD risk and SLE has been recognized early [Fanouriakis, 2021]. Urowitz et al. observed a bimodal pattern of mortality, with a first peak within five years of diagnosis due to disease activity, infections and lupus nephritis, and a second attributable to atherosclerosis and CVD events [Urowitz, 1976]. Women between 35 and 44 years of age with SLE have a 50 times greater risk of acute myocardial infarction [Manzi, 1997]. Over time, the management of the disease has progressively improved, and this has led to an overall reduction in mortality, making CVD events the leading cause of death for these patients.

According to a recent systematic review and meta-analysis [Restivo, 2021], patients with SLE had a RR of 1.98 (95% CI: 1.18-3.31) of symptomatic CVD events compared to the unexposed cohort. The meta-regression analysis showed that younger patient (age per year increase β = -0.12 95% CI: -0.20, -0.4), belonging to studies conducted in continent different from America (β = -0.89; -95% CI: 1.67, -0.10), after 2000 (β = 0.87; 95% CI: 0.09, 1.65) and with a higher quality score 0.80 (95% CI: 0.31, 1.29) had a higher risk of CVD events.

While cardiovascular mortality is decreasing in the general population, no similar pattern is observed in SLE patients [Bjornadal, 2004]. The American College of Rheumatology (ACR) suggests considering SLE and inflammatory rheumatic diseases as important cardiovascular risk factors independent of traditional ones [Whelton, 2017].

According to a study based on data from Danish administrative registries, the absolute 10-year risks of MI between 1996 to 2018 was 2.17% (95% CI: 1.66% to 2.80%) for SLE patients vs 1.49% (95% CI: 1.26% to 1.75%) for control subjects [Yafasova, 2021]. SLE patients also had a higher associated risk of HF and other CVD outcomes compared with matched control subjects. Among patients

developing HF, a history of SLE was associated with higher mortality [Yafasova, 2021].

The risk of cerebrovascular events is also increased, and the most severe manifestation is stroke. It has an incidence of between 3 and 20%, especially in the first five years after diagnosis [Saadatnia, 2012]. One systematic review and metanalysis of 26 cohort and cross-sectional studies found a twofold to a threefold higher risk of stroke and MI in SLE patients compared to controls [Yazdany, 2020]. Another meta-analysis found a 2- and 3-fold increased risk of ischemic and haemorrhagic stroke in SLE, respectively, compared to the general population [Holmqvist, 2015]. In these patients, the stroke caused by systemic inflammation and the prothrombotic state tends to occur in the first year after diagnosis [Pons-Estel, 2017; Arkema, 2017]. Stroke not related to disease activity generally occurs later and is mainly due to traditional cardiovascular risk factors, which are frequent comorbidities in SLE [Schoenfeld, 2013]. Stroke should be considered in any patient who presents sudden symptoms and signs of neurological deficit or altered state of consciousness [Nikolopoulos, 2019]. In a patient with SLE, the sudden onset of headache should also lead to suspicion of sinus venous thrombosis, subarachnoid haemorrhage or cerebral vasculitis [de Amorim, 2017].

1.2.2 Potential mechanisms of increased CVD risk in SLE

The prognosis for SLE has improved considerably in recent decades, leading to new comorbidities, such as CVD, which is now the main cause of death in this population [Wu, 2016]. Some studies have suggested that SLE is an independent CVD risk factor [Chazal, 2020]. It has also been shown that traditional CVD risk factors, such as hypertension, dyslipidemia and diabetes, do not fully explain the excess CVD morbidity and mortality [Kirchler, 2021].

1.2.2.1 Traditional CVD risk factors, accelerated atherosclerosis and coronary artery disease

Numerous recent studies have highlighted the association between SLE and accelerated atherosclerosis [Asanuma, 2003]. In the context of autoimmune diseases, both traditional and other cardiovascular risk factors play a role in the

progression of atherosclerosis. In SLE, the sedentary lifestyle, obesity and hypercholesterolemia are frequent [Bruce, 2003]. Despite having a better lipidemic pattern than patients with RA, SLE patients had a reduced cholesterol efflux capacity, with a consequent increase in the medial-intimal thickness at the carotid level. This data suggests that the risk is not influenced only by the classic markers of dyslipidemia but by different and specific mechanisms of the single diseases not yet known [Quevedo-Abeledo, 2020].

Subclinical atherosclerosis is more prevalent in SLE patients than in healthy controls [Bruce, 2005]. The ccIMT correlates with atherosclerotic plaques in the coronary artery and the incidence of cardiovascular events [Stein, 2008]. The ultrasound measurable ccIMT is significantly increased in 40% of SLE patients, while age-matched healthy controls reach 16% [Roman, 2003]. Very similar to patients with RA and DM, patients with SLE have two times more atherosclerotic plaques in the carotid and femoral artery [Tektonidou, 2017].

1.2.2.2 Arterial stiffness and endothelial dysfunction

One meta-analysis [Mendoza-Pinto, 2020] reported an increase in arterial stiffness in SLE compared with controls. The increase in arterial stiffness is neither age-correlated [Ding, 2016] or fully explained by CVD risk factors [Stortz, 2020; Parra, 2019; Karp, 2016]. However, hypertension accounted for 14.3% of the variance of PWV, and the effects of inflammation on arterial stiffness may be less significant with ageing [Montalban-Mendez, 2018]. Arterial stiffness has been correlated with damage [Valero-Gonzalez, 2014] but not with the punctual disease activity as assessed by SLEDAI [Valero-Gonzalez, 2014; Sacre, 2014; Santos, 2012]. In addition, intima-media thickness and PWV values were significantly higher in patients having both SLE and anti-phospholipid syndrome (APS) than in patients with SLE or APS alone [Jurcut, 2012].

Patients with SLE duration less than five years without CVD risk factors had a high rate of endothelial dysfunction [Taraborelli, 2018]. Another study has shown that SLE patients have an increased PWV, an indicator of increased aortic stiffness [Bjarnegråd, 2006]. It was also found that in SLE patients, an increase in

PWV precedes the increase in ccIMT and that its worsening could help identify an active disease state [Shang, 2008]. The increased arterial stiffness is given both by the presence of atherosclerotic plaques and by vascular and perivascular inflammation: this would explain why anti-inflammatory drugs, such as statins and anti-TNF α, reduce arterial stiffness [Maki-Petaja, 2009].

1.2.2.3 Autoantibodies, anti phospholipids and disease severity

SLE is an independent risk factor for CVD [Fanouriakis, 2021]. This increased CVD risk of SLE patients is justified by duration and activity of the disease, older age at diagnosis, exposure to glucocorticoids (GCs), and chronic kidney disease [Iaccarino, 2013]. Additional risk factors could be early menopause, to which women with SLE are predisposed, and hyperhomocysteinemia [Bruce, 2003].

It is essential to emphasize the role of local and systemic inflammation in atherogenesis and CVD risk in SLE. In particular, 1) the role of type I interferons (IFN), which is associated with endothelial dysfunction, coronary calcifications and inhibition of pro-angiogenic pathways [Somers, 2012; Thacker, 2010]; 2) neutrophil extracellular traps (NETs), which cause endothelial damage directly or indirectly by stimulating the production of type I IFN [Lewandowski, 2016; Mozzini, 2017]. A recent study found elevated levels of NETs in patients at risk of disease reactivation or severe [Moore, 2020]; 3) complement activation, which stimulates the activation of the endothelium and the recruitment of leukocytes, in particular monocytes, at the level of the atherosclerotic plaque [Hansson, 2002; Viedt, 2000]; 4) the deposition of immune complexes in the vessel wall, which stimulates the expression of VCAM-1 [Janssen, 1994]; 5) the lower availability of endothelial progenitor cells and anti-apo-B-100 autoantibodies, which cause a reduction in endothelial renewal and LDL clearance respectively [Giannelou, 2017; Svenungsson, 2015].

Finally, aPL antibodies seem to have an increasing independent effect on CVD risk [Giannelou, 2017]. Anti phospholipids are found in several SLE patients. Antiphospholipid syndrome (APS) is a systemic autoimmune disease associated with arterial and venous thrombotic events and recurrent fetal loss. The

association of aPL with SLE dramatically increases the occurrence of CVD disease, mainly driven by CVA and MI. aPL antibodies are also associated with accelerated atherosclerosis and peripheral artery disease (PAD). According to a systematic review and metaanalysis [Merashli, 2020], all aPL are related to PAD, whereas lupus anticoagulant is associated with critical limb ischaemia and failed revascularisation.

Patients with APS have endothelial dysfunction, accelerated endothelial proliferation and intimal hyperplasia, atherogenesis, platelet activation, inflammatory products secretion and coagulation-fibrinolytic dysregulation [Polytarchou, 2020]. Due to the vascular nature of APS, various organs and tissues may be affected, including the cardiac system. The cardiac involvement in APS is multifactorial: thrombosis plays an important role as well as immune-mediated injury. The most common cardiac manifestations are valvulopathies, ranging from valve thickening through non-bacterial thrombotic endocarditis (NBTE; Libman-Sacks endocarditis) to regurgitation and severe valvular damage and CAD. Valvulopathies and CAD are the main cardiac manifestations in APS, while other less common cardiac manifestations include myocardial dysfunction, pulmonary hypertension and intracardiac thrombus [Kolitz, 2019].

According to a prospective multicenter cohort study including 125 patients (91 primary APS (PAPS), 18 APS-SLE, and 16 carriers), APS was associated with HFpEF as it was detectable in 14.4% of APS patients [Pastori, 2021]. By multivariate analysis, hypertension (OR 19.49, 95% CI 2.21-171.94, $p = 0.008$), age (OR 1.07, 95% CI 1.00-1.14, $p = 0.044$), and aβ2GPI IgG > 40 GPL (OR 8.62, 95% CI 1.23-60.44, $p = 0.030$) were associated with HFpEF.
The left ventricular and right ventricular diastolic function were significantly more impaired in patients with APS [Paran, 2007].

1.3 Cardiovascular disease in systemic sclerosis

1.3.1 Epidemiology of CVD in SSc

The management of patients with SSc should include a preventive measure of the increased CVD burden those patients carry. A meta-analysis of cohort studies including 14'813 SSc patients revealed that SSc was associated with an increased risk of CVD. The pooled HR for CVD was 2.36 (95% CI 1.97-2.81); for PAD was 5.27 (95%CI 4.27-6.51); for MI was 2.36 (95% CI 1.71-3.25); and for stroke was 1.52 (95% CI 1.18-1.96) [Cen, 2021].

In the last four decades, there has been a change in the mortality rates in SSc: those due to complications related to the disease have decreased, while the mortality rates due to atherosclerotic cardiovascular and cerebrovascular diseases have gradually increased [Belch et al., 2008]. Regarding coronary artery involvement, Man et al. [Man et al., 2013] reported that the incidence of myocardial infarction in patients with systemic sclerosis was 4.4 per 1,000 people per year (compared to 2.5 /1,000 / years in age- and sex-matched healthy controls). Similar results were also demonstrated in the cross-sectional cohort study (1980-2016) by Kurmann et al. [Kurmann et al., 2020], where the prevalence of cardiovascular events adjusted for traditional CVD risk factors is three times higher in the SSc population than in controls (HR, 2.66; 95% CI, 1.39-5.11): this increased cardiovascular risk is mainly due to coronary heart disease (HR, 2.60; 95% CI, 1.25-5.41).

Man et al. [Man et al., 2013] reported an incidence of stroke in SSc patients of 4.8 per 1,000 people/year (compared to 2.5 / 1,000 / year in age- and sex-matched healthy controls). In the cohort study by Chiang et al. [Chiang et al., 2013], it was shown that the presence of SSc is independently associated with a higher risk of developing ischemic stroke, with a 43% increase in risk compared to healthy controls (95% CI 12%, 83%; P = 0.004) and how the drugs for the treatment of SSc did not modify the risk.

A nationwide observation retrospective cohort study based in Taiwan showed that the SSc cohort exhibited a significantly higher risk (HR = 2.15, 95% CI = 1.47 to 3.14) of PAD than did the non-SSc cohort. Patients with heart failure exhibited the highest risk of PAD (adjusted HR = 2.10, 95% CI = 1.20 to 3.70). Moreover, even without any comorbidities, the SSc cohort exhibited a significantly higher risk (adjusted HR = 4.17 fold, 95% CI = 1.98 to 8.77) of PAD than did the non-SSc cohort [Hsieh, 2021].

1.3.2 Potential mechanisms implicated in CVD risk in SSc

The pathology of CVD in SSc is poorly understood. However, in SSc, it does not seem that traditional CVD risk factors have such a relevant role as they have in RA or SLE. Nevertheless, the incidence of CVD events is increased among SSc patients compared to matched controls.

1.3.2.1 Traditional CVD risk factors, accelerated atherosclerosis and coronary artery disease

Although atherosclerotic disease has not typically been considered a significant systemic feature in SSc, MI and stroke are more common in patients with SSc than in controls [Man et al., 2013; Ngian et al., 2012].

The reason why patients with systemic sclerosis develop atherosclerosis has not yet been determined. Traditional risk factors such as hypertension, dyslipidemia, DM and obesity are typically no more prevalent in patients with SSc than in controls [Man et al., 2013; Ngian et al., 2012] and therefore do not explain the increased risk of atherosclerotic CVD. There is some evidence that new atherosclerotic risk markers such as homocysteine, Lp(a) and oxLDL are more prevalent in systemic sclerosis, but these findings have not been confirmed in larger studies [Mani et al., 2019].

According to some authors, the prevalence of atherosclerosis of the great epicardial coronary arteries is similar to that of the general population [Akram et al., 2006]. This similarity was repeated in an autopsy study that compared 58 cases of SSc with 58 controls, where the frequency of coronary atherosclerosis of the epicardial vessel was similar (48% vs 43%), while atherosclerotic lesions of

the small coronary arteries or arterioles occurred in 17% of SSc patients, compared to only 2% of controls [D'Angelo et al., 1969]. A study by Khurma et al. [Khurma et al., 2008] showed that signs of coronary atherosclerosis assessed by observation of coronary calcification on coronary CT were present in 56.2% of SSc patients and only 18.8% of controls matched by age, gender and race. In a meta-analysis of 14 studies, a mean difference in carotid intima-media thickness (IMT) as assessed by carotid ultrasound of 0.11 mm (95% CI 0.05 mm, 0.17 mm) was shown between SSc patients and controls [Au et al., 2011].

Cerebrovascular atherosclerosis also appears to have increased in SSc: all the studies that evaluated intracerebral calcification or hyperintensity of the white matter showed a higher prevalence in patients with SSc compared to controls [Au, 2011].

Numerous studies conducted in the 1990s have demonstrated the existence of PAD in SSc, both in the upper and lower limbs, with a prevalence, estimated clinically and angiographically, ranging from 4 to 58% [Magda, 2015]. It has also been shown that atherosclerotic involvement of the renal arteries in SSc occurs with a prevalence of up to 26%, with a higher percentage of intimal thickening and luminal occlusion in SSc patients than controls found at autopsy [Trostle, 1988; Shanmugam, 2010].

1.3.2.2 Vasculopathy and fibrosis

Microangiopathy is the hallmark of SSc. Data suggest that CVD risk scores and macrovascular parameters are strongly correlated with microvasculopathy in patients with SSc, but the relationship between subclinical atherosclerosis and small vessel disease remains unknown. Arterial stiffening and CVD risk scores are positively associated with the degree of progression of peripheral microvasculopathy assessed with nailfold videocapillaroscopy (NVC) [Pagkopoulou, 2021]. Other groups showed that only secondary, not primary, Raynaud phenomenon (RP) is associated with reduced myocardial flow reserve (MFR) using positron emission tomography/computed tomography (PET/CT), and that patients with SSc-RP have reduced MFR compared to those with primary

RP and patients with other RMDs [Feher, 2021]. Vascular endothelial dysfunction could be involved in the high CVD risk of patients with SSc and pulmonary artery hypertension (PAH), according to a recent systematic review and meta-analysis [Theodorakopoulou, 2021]. Microangiopathy is a unique feature of SSc, as it does not seem to be influenced by gender or SSc-specific autoantibodies [van Leeuwen, 2021].

Diffuse fibrosis is another hallmark of SSc. Myocardial fibrosis is highly prevalent in SSc-related compared to other types of myocarditis [De Luca, 2020]. Increased T1 values at CMR imaging, potentially suggesting microscopic fibrosis, were observed more frequently in patients with dcSSc and were associated with interstitial lung disease and more frequent CVD events during follow-up [Terrier, 2020]

1.3.2.3 Pulmonary vascular disease

Pulmonary vascular disease, namely pulmonary hypertension (PH), occurs in 10 to 40 per cent of patients with SSc. Three main PH entities occur in SSc.

SSc-associated pulmonary arterial hypertension (SSc-PAH) is due to a primary vasculopathy of the small muscular pulmonary arterioles (group 1 PH). SSc-PAH is common in patients with a longstanding limited cutaneous disease with mild or absent ILD. SSc-PAH is an independent risk factor for mortality among patients with SSc [Quinn, 2020]. PH due to hypoxemia or chronic lung disease (group 3 PH) is slightly less common than SSc-PAH, and it has a worse prognosis, occurring in patients with diffuse cutaneous scleroderma and advanced fibrotic lung disease. Finally, pulmonary venous hypertension caused by left heart disease (group 2 PH) is commonly found in SSc patients with valve disease o heart failure. Chronic thromboembolism (group 4 PH), pulmonary capillary hemangiomatosis and veno-occlusive disease can also occur in a small number of patients.

PH is typically progressive and, if severe, can naturally lead to cor pulmonale and right-sided heart failure. Dyspnea with exertion and diminished exercise tolerance are the most common initial symptoms but are commonly absent until the disease

is relatively advanced. Thrombosis of the pulmonary vessels is a common late-stage complication and is a frequent cause of death.

1.4 Cardiovascular safety of immune-modulating therapies for RMDs

Overall, DMARDs have been shown to reduce CVD mortality and events such as MI [Naranjo, 2008; van Tuyl, 2010]. Subclinical atherosclerosis and endothelial dysfunction are demonstrable features even in early RA and improve after therapy with DMARDs [van Halm, 2006]. However, consistent with the strength of evidence, highlighting disease activity as a predominant RA-specific/inflammatory risk factor of CVD, treatment of RA with immunomodulatory DMARDs likely lower CVD risk by conferring control of disease activity and dampening systemic inflammation. Current evidence demonstrates that early aggressive treatment of RA is able to reduce mortality [Fent, 2017] and CVD risk [Solomon, 2006].

1.4.1 Glucocorticoids

Despite the advent of conventional synthetic DMARDs (csDMARDs) and more advanced targeted therapies, glucocorticoids (GC) are still widely used in RA and SLE. There is uncertainty regarding the risk of incident CVD in patients with RA exposed to GCs in observational studies, as this has often been confounded by indication due to high disease activity [del Rincón, 2014]. The use of oral GC in RA has been associated with an increased risk of CVD events compared to those receiving methotrexate (MTX) monotherapy [Ravindran, 2009]. Several observational studies appeared to show a significant increase in CVD risk, occurring even at low doses between 5-10 mg daily of prednisone equivalent [Roubille, 2017; Boers, 2003]. However, Avina-Zubieta et al. suggested that in RA, the long-term effect of cumulative exposure to GCs is associated with an increased incidence of MI independently of the current dosage [Best, 2018]. Subsequently, a different study has proposed that the minimum daily prednisone dose threshold associated with an increase in all-cause mortality is 8–15 mg [Ozen, 2017]. Accordingly, a meta-analysis of six RCTs (average dose of prednisone equivalent: 5–10 mg daily) demonstrated no increased risk of CVD

events [Panoulas, 2008]. Finally, the 7-year analysis of the ESPOIR cohort supported the good safety profile of very low-dose GC for early active RA using a composite outcome of death, CVD (including myocardial ischaemia, CVA and heart failure), severe infection and fracture [Mazzantini, 2010].

Patients treated with GCs have classically been associated with an increased prevalence of certain CVD risk factors. In RA, corticosteroids induce hypercholesterolemia, but in patients with high disease activity, aggressive treatment of RA with combination therapy with prednisolone has been shown to rapidly improve TC/HDL-C [Panoulas, 2008], reflective of the lipid paradox which is typically observed in active RA. Chronic exposure to low to medium doses of oral GC has also been associated with a significantly increased risk of diabetes mellitus (DM) [Micha, 2011]; in the National Data Bank for Rheumatic Diseases, the adjusted hazard ratio for DM was 1.31 (95% CI 1.15, 1.49) for GC in patients with RA without baseline DM [Roubille, 2015]. It is also widely held that GC therapy may raise blood pressure (BP) in both normotensive and hypertensive people [Jin, 2017]; however, little is known of their impact on BP with RA [Deyab, 2017]. Long-term GC exposure above 7.5 mg daily of prednisolone has been associated with a high prevalence of hypertension, independent of other risk factors for hypertension or disease activity [Mangoni, 2017]. Therefore, evidence suggests that GCs, when given in low doses (<7.5mg daily prednisolone), probably do not cause clinically significant increased BP; however, patients with RA on higher doses of prednisolone should be regularly screened for hypertension and effectively treated, should the latter occur.

1.4.2 Conventional synthetic DMARDs

Methotrexate has a favourable effect on the CVD burden in RA. A systematic review concluded in patients with RA, psoriasis or polyarthritis, MTX lowered the risk of CVD and MI by 21% and 18%, respectively [Woodman, 2017]. A large meta-analysis reported a RR of all CVD events with the use of MTX of 0.72 (95% CI 0.57, 0.91) [Charles-Schoeman, 2017]. A Chinese Registry of over 13,000 patients with RA reported the use of MTX was negatively associated with the presence of CVD (OR 0.77, 95% CI 0.60–1.00) [Navarro-Millan, 2013].

Treatment with MTX alone or in combination with SSZ or HCQ showed significant CVD risk reduction compared to RA patients who never used csDMARDs [Solomon, 2006], independent of the presence of hypertension, DM or hypercholesterolemia. Moreover, in one study, MTX has demonstrated a similar CVD risk-reducing effect to more advanced disease suppression therapies such as tumour necrosis factor inhibitors (TNFi) [Ravindran, 2009]. Interestingly, treatment with MTX as monotherapy or in combination with TNFi (effect suggested to be more pronounced in the former) has been associated with improvement of endothelial function in patients with inflammatory arthritis independent of change in disease activity [Rempenault, 2018]. Therefore, modes of action other than the anti-inflammatory effect may contribute to endothelial function improvement. With respect to CVD risk factors, a prospective cohort study indicated the risk of DM was not affected by the use of MTX [Roubille, 2015]. Woodman et al. demonstrated that although greater arterial stiffness measures precede those with increases in BP in patients with RA treated with DMARDs, these effects did not occur amongst those treated with MTX, suggesting MTX may confer a protective effect against stiffness-mediated increases in BP in RA [Serelis, 2011]. The effect of MTX on dyslipidaemia is complex and probably partly explained by the paradoxical effect of inflammation on lipids. In a randomised control trial in early RA, MTX as monotherapy or in combination with other csDMARDs or TNFi was associated with improvements in the HDL function profile at two years [Wang, 2018]; however, treatment initially led to increased TC, LDL-C and HDL-C with triple therapy [Barnabe, 2011].

Although hydroxychloroquine (HCQ) confers limited efficacy on disease activity and progression, it may benefit the metabolic profile and, to a lesser extent, CVD events in patients with RA. A recent meta-analysis showed that mean differences in levels of TC, LDL-C,HDL-C and triglycerides between HCQ users and non-users were -9.8 mg/dL (95% CI -14.0 to -5.6), -10.6 mg/dL (95% CI -14.2 to -7.0), +4.1 mg/dL (95% CI 2.2 to 6.0) and -19.2 mg/dL (95% CI -27.2 to -11.1) respectively [Dixon, 2007]. The incidence of diabetes was also lower for HCQ ever users than never users (HR 0.59 (95% CI 0.49 to 0.70) among RA patients

[Dixon, 2007]. A second meta-analysis by Mathieu et al. involving a total of 24,923 HCQ users (any indication) and 36,327 non-users demonstrated patients with RA on HCQ had a significant decrease in the occurrence of DM (RR 0.33, 95% CI 0.18, 0.59) [Mathieu, 2017]. This study also reported a nearly significant decrease in the occurrence of CVD events in the HCQ group (RR−0.25, 95% CI −0.52, 0.02) alongside a significant improvement in lipid parameters [Mathieu, 2017].

Prolonged use of sulfasalazine (SSZ) appears to be associated with a reduced risk of CVD disease in RA [Naranjo, 2008]. A case-control study showed that treatment with SSZ was associated with significant CVD risk reduction independent of hypertension, DM and hypercholesterolemia [Solomon, 2006]. However, the safety and efficacy of SSZ have been demonstrated mostly in combination with GCs or other csDMARDs, resulting in reduced mortality alongside the lower progression of joint damage and a similar prevalence of comorbidity compared with SSZ monotherapy [Fent, 2017]. Triple therapy, including SSZ in the early RA TEAR trial, was associated with improvements in the HDL function profile comparable to MTX monotherapy or MTX + etanercept combination therapy [Wang, 2018]. Although levels of TC, LDL-C, and HDL-C increased initially [Barnabe, 2011], at two years, triple therapy was associated with higher HDL-C, lower LDL-C, and lower TC/HDL-C compared to those who received MTX monotherapy or MTX plus etanercept combination therapy [Wang, 2018].

Data on CVD safety of leflunomide (LEF) are scarce and inconclusive. In a nested case-control study in the US, compared with RA patients receiving MTX monotherapy, the use of cytotoxic immunosuppressive agents other than MTX was associated with an increased risk of CVD events (OR 1.8, 95% CI 1.1–3.0) [Ravindran, 2009]. However, in this study, MTX was compared with any other DMARDs such as azathioprine, cyclosporine, or leflunomide, including both monotherapy and combination treatment. Hypertension is an important risk factor for CVD development in patients with RA [Frostegård, 2005], and it has been suggested that LEF treatment may have a contributing effect [Solomon, 2011].

LEF may be associated with poor artery compliance [Klarenbeek, 2010], which may contribute to the CVD burden and increased BP. It is well known that a small percentage of patients with RA (2-4.7%) develop hypertension when taking LEF, usually occurring within the first 2-4 weeks of treatment [Desai, 2016]. Although LEF is not contraindicated in hypertension, other DMARDs should be considered first. If hypertension occurs after commencing LEF, anti-hypertensives may be used, but a dose reduction or cessation of therapy may be required if BP control is not attained.

Cyclophosphamide (CYC)-associated cardiotoxicity is dose-dependent, but it is a significant problem mainly in cancer polychemotherapy [Gottdiener, 1981; Braverman, 1991]. It is generally not seen with the low-doses adopted for the treatment of inflammatory-autoimmune major organ involvement (e.g. lung) of SLE or SSc patients. CYC-associated cardiotoxicity is not related to the cumulative dose administered. The cardiotoxic effect of CYC could be mediated primarily by acrolein, a metabolite that damages the myocardium and endothelial cells. Echocardiography is recommended prior to administration of CYC, especially if adverse prognostic factors are present (older age, decreased EF, prior radiation to the mediastinum or left chest wall).

Adverse cardiac effects associated with using other csDMARDs such as mycophenolate mofetil (MMF), azathioprine (AZA) or calcineurin inhibitors are scarce and inconclusive.

1.4.3 TNF-inhibitors

TNFi are often the first line bDMARDS used in RA following the failure of csDMARDs. Several studies have provided evidence that TNFi reduces CVD events in RA [Charles-Schoeman, 2017; Souto, 2015]. One meta-analysis suggested a pooled adjusted RR of 0.46 (95% CI 0.28, 0.77) for all CVD events [Souto, 2015]; another meta-analysis quoted a RR of 0.70 (95% CI 0.54, 0.90) [Roubille, 2015]. In an inception cohort of 1829 patients with RA, those using TNFi had a lower HR for incident coronary heart disease compared to those using MTX (0.33 versus 0.24) [Low, 2017], suggesting a specific action of TNFi on the

atherosclerotic process or better disease control than csDMARDs. Also, a meta-analysis determined that while both TNFi and MTX use were associated with comparable reductions in risk of CVD events, only TNFi use was associated with a reduced risk of stroke [Roubille, 2015]. TNFi appears to reduce the likelihood of overall CVD events in individuals with RA, though this reduction is not as pronounced in the individual outcome measures [Sattin, 2016] Although the mechanisms are unclear, the improvement is assumed as a consequence of a reduction in systemic inflammation rather than the specific action of therapeutic agents, supported by Dixon et al. who found no difference in risk of MI in those using TNFi compared to DMARDs, but did see a reduction in TNFi responders compared to non-responders [Dixon, 2007].

TNFi are contraindicated in patients with RA who have congestive heart failure; subsequent studies investigating a potential beneficial role for TNFi in heart failure resulted in paradoxical negative results. However, no signal of specific CVD adverse effects has emerged with over twenty years of use of these agents. Some data suggest RA disease activity increases the risk of heart failure, and therefore the reduction in disease activity from TNFi use negates any increased risk from the drug itself [Listing, 2008].

The use of TNFi has been associated with a reduced incidence of type 2 DM. Among patients with RA or psoriasis, the adjusted risk of DM was lower for individuals starting a TNFi or HCQ compared with initiation of other non-biologic DMARDs [Solomon, 2011]. There are no reports of hypertension occurring in association with TNFi; indeed, several small studies support the potential BP-lowering effect of TNFi in RA patients [Klarenbeek, 2010]. Nonetheless, in a US epidemiological study of RA patients, treatment with TNFi did not reduce the risk of incident hypertension compared with non-bDMARDs [Desai, 2016].

The effect of TNFi on lipids has been evaluated with a meta-analysis of 25 RCTs of patients with chronic inflammatory arthritis treated with bDMARDs and tofacitinib [Souto, 2015]. Moderate changes in TC, HDL-C and LDL-C were observed only in patients treated with tocilizumab (TCZ) or tofacitinib but not with TNFi. However, slight differences could exist among different TNFi or according to treatment response.

1.4.4 Non-TNFi biologics

It is well recognised that TCZ (a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R)) causes an increase in TC and LDL-C [Bacchiega, 2017]. The impact of TCZ on lipids in active RA was evaluated in the MEASURE trial, a randomised, multicentre, placebo-controlled study [McInnes, 2015]. TCZ induced elevations in LDL-C but altered HDL particles towards an anti-inflammatory composition and favourably modified most measured vascular risk surrogates. Comparing TCZ with adalimumab, LDL-C and HDL-C increased more while HDL-SAA, sPLA2 IIA and Lp(a) decreased more with TCZ [Gabay, 2016]. TCZ adversely impacted both LDL-C as well as triglycerides in patients with RA. The changes in hepatic LDL receptor expression following TCZ imply that adverse lipid changes may be a direct hepatic effect of TCZ [Strang, 2013].

Despite these concerns with dyslipidemia, a multi-database population-based cohort study showed no evidence of an increased CVD risk among RA patients treated with TCZ versus TNFi [Kim, 2017]. One study demonstrated an association between baseline TC/HDL-C and an increased risk of major cardiovascular adverse events (MACE) in RA patients treated with TCZ; however, the risk of CVD events while receiving treatment was associated with control of disease activity and not lipid changes [Rao, 2015]. More recently, a randomised multicenter study compared the CVD safety of TCZ vs ETA in 3080 seropositive RA patients with active disease and inadequate response to csDMARDs [Giles, 2016]. Overall, there was no significant difference in the hazard of MACE with TCZ compared to ETA (HR 1.05; 95% CI 0.77, 1.43), though an estimated 5% increase in TCZ compared with ETA among RA patients with severe active disease and elevated baseline CVD risk was noticed. Average increases in LDL-C were higher for TCZ vs ETA.

Reasons for this may include the effect of the inhibition of IL-6 signalling on decreasing Lp(a) serum levels [Schultz, 2010]; RA patients treated with TCZ demonstrate lower plasma concentrations of Lp(a) compared with patients, not on bDMARD therapy [Garcia-Gomez, 2017]. Inhibition of IL-6 signalling also improves insulin sensitivity in humans with immunological diseases, suggesting

that elevated IL-6 levels in type 2 DM might be causally involved in the pathogenesis of insulin resistance [Schultz, 2010]. In addition, TCZ can lead to the reduction of proinflammatory components and proatherogenic proteins associated with HDL-C [Lee, 2016] and CVD biomarkers such as NT-proBNP and troponin [Welsh, 2016]. TCZ has also been shown to improve endothelial function and aortic stiffness [Bacchiega, 2017; Protogerou, 2011].

Abatacept (ABA) (a fusion protein inhibiting T-cell co-stimulation) appears to be associated with a reduced risk of CVD in patients with RA. An observational study suggested that ABA may be associated with a lower risk of MI compared with TNFi [Zhang, 2016]. A recent large population-based cohort of patients with RA reported ABA use was associated with a modestly reduced CVD risk when compared with TNFi, particularly in patients with DM [Kang, 2018]. In support of this, treatment with ABA has been shown to improve whole-body insulin sensitivity in RA patients without affecting β-cell function [Ursini, 2015], although a second study on a small, negative-control cohort of ABA-treated individuals failed to find any significant effect [Stagakis, 2012]. Interestingly, mice studies have demonstrated that CD28-CD80/86 co-stimulation of T-cells (prevented by abatacept) appears to have a role in the pathogenesis of atherosclerosis [Ewing, 2013].

Data on CVD outcomes in RA patients treated with rituximab (RTX, a chimeric anti-CD20 monoclonal antibody) are scarce. There is preliminary evidence for an improvement of CVD parameters and metabolic profile of patients treated with RTX [Hsue, 2014]. Amelioration of arterial stiffness assessed by means of flow-mediated dilation (FMD) along with an improvement of plasma TC and HDL-C levels was observed in two small studies of RA patients refractory to TNFi treated with RTX [Gonzalez-Juanatey, 2008; Kerekes, 2009]. An open, observational and prospective study of 24 patients treated with RTX reported a significant reduction in aortic stiffness measured by pulse wave velocity (PWV) although also with a significant increase of TC and HDL-C after 12 months [Provan, 2015]. Another study indicated beneficial effects on the proatherogenic profile of HDL-C following RTX treatment along with improvement of disease activity [Raterman,

2013]. Anti-CD20 therapy could also reduce the concentration of pro-thrombotic markers such as fibrinogen, D-dimer, and tPA [Jin, 2009].

A meta-analysis reporting a positive association between serum IL-1RA levels with risk of CVD in the general population after adjustment for multiple confounders [Herder, 2017] has generated much interest in IL-1 as a viable therapeutic target. The positive results of the CANTOS study mentioned earlier (that evaluated canakinumab in secondary prevention) support this assertion. Research is ongoing to assess the benefit of IL-1β inhibition in DM [Peiró, 2017]. In RA, IL-1 inhibition has been shown to improve vascular and left ventricular function and is associated with the reduction of nitrooxidative stress and endothelin [Ikonomidis, 2008]. Although promising for atherosclerosis, the minimal clinical efficacy of IL-1 targeted therapy for RA joint pathology remains a limitation.

Belimumab is a monoclonal antibody that specifically inhibits the biological activity of soluble B-lymphocyte stimulator protein. There were no safety concerns on belimumab-associated cardiotoxicity from RCTs or observational studies. A recent case report suggested that belimumab could help improve cardiac function in an SLE patient with HFpEF [Baniaam, 2021]

1.4.5 Targeted synthetic DMARDs

Small-molecule compounds targeting Janus kinases (JAKs) have been recently introduced to the therapeutic armamentarium, offering an essential alternative to bDMARDs for the treatment of inflammatory diseases. Specific safety concerns around JAKs inhibitors use for early RA patients include a higher risk of herpes zoster reactivation compared to bDMARDs [Pawar, 2020] and venous thromboembolism (VTE) [Yates, 2021]. The phase trial programmes prior to authorisation indicate baricitinib is associated with increased LDL-C, HDL-C and triglyceride levels, but not LDL-C/HDL-C [Taylor, 2018]. Tofacitinib has been associated with increased TC, LDL-C and triglycerides, abnormalities reduced by atorvastatin [McInnes, 2014]. However, in patients with active RA exposed to baricitinib for a maximum of almost seven years, both baricitinib 2 mg and 4 mg

maintained a similar safety profile to earlier analyses and no new safety signals were identified [Genovese, 2020].

Post-marketing evaluation of CVD event rates with long-term treatment is warranted further to characterise these findings and their possible clinical implications. Reassuringly, tofacitinib was associated with a low incidence of CVD events in a large phase 3 programme [Charles-Schoeman, 2016]. However, additional concerns about an increased incidence of myocardial infarction and lung cancer with tofacitinib have risen from the unpublished, food and drug administration (FDA)-mandated, ORAL Surveillance clinical trial [https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing]. This study compared tofacitinib to TNF-alpha inhibitors in 4362 patients with RA older than 50 years of age with at least one additional CVD risk factor. Results showed that tofacitinib did not reach the non-inferiority criteria compared to TNFi of co-primary endpoints of major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer). Hence, more real-life data are needed to elucidate the CVD risks of JAKi compared to other biologics.

1.5 Current management of CVD risk in RMDs

As a result of this growing body of evidence, European League Against Rheumatism (EULAR) produced guidance on the reduction of CVD in RA in 2010, updated in 2016 [Agca, 2017]. The key recommendations are to control RA disease activity, assess for CVD risk at least once every five years using appropriate 10-year CVD risk score calculators (multiplying the risk by 1.5 if RA is not included in the model) and to address modifiable traditional risk factors. The guidelines also recommended advocating healthy lifestyles, smoking cessation and exercise, along with cautious use of NSAIDs and minimal use of corticosteroids. Despite this advice, the management of CVD risk factors in RA remains currently suboptimal.

The 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus [Fanouriakis, 2019] have a section on CVD. Low-

dose aspirin may reduce the risk for incident CVD in SLE (HR 0.24 in one retrospective study) [Fasano, 2017; Iudici, 2016]. Routine use of statins is not recommended for all SLE patients but should be considered on the basis of lipid levels and the presence of other traditional risk factors. Indeed, RCTs of statins in SLE failed to show a clear benefit over placebo, although cIMT and not hard endpoints were used as a surrogate marker for CVD in those studies [Petri, 2011; Schanberg, 2012]

EULAR recommends the calculation of the 10-year CVD risk using the Systematic Coronary Risk Evaluation (SCORE) [Piepoli, 2016], although the actual risk is underestimated in patients with SLE. In an Italian, multicentre, cross-sectional study of Italian SLE patients (including the ones in this thesis) aimed to estimate CVD-risk using SCORE, QRISK3 and PCS, the mean estimated CVD-risk in SLE patients was globally low using the SCORE, QRISK3 and Progetto Cuore score (PCS). The PCS seemed to better intercept those patients at moderate/high risk, at least in Italian SLE patients, while QRISK3 predicted the highest CVD risk [Cacciapaglia, 2020]. The lack of disease-specific CVD-risk factors (such as autoantibodies profiles or organ involvement) probably accounts for the underestimation of CVD risk using the SCORE and PCS. A smaller study based in the UK found that QRISK3 could capture significantly more patients with SLE with an elevated 10-year risk of developing CVD than the Framingham score. Moreover, QRISK3 was associated with endothelial dysfunction [Edwards, 2018]

Currently, there is no consensus from scientific societies on the management of CVD in SSc patients. The Framingham score (FRS) and the ACC / AHA cardiovascular risk score were developed to guide the clinician in evaluating cardiovascular risk and in the appropriate modification of the risk factor to reduce the likelihood of an atherosclerotic event in the individual. In the population study by Reto et al. [Reto, 2020], it was shown that these scores have low performance in patients with SSc, dramatically underestimating the risk of cardiovascular events by 4-5 times. Currently, guidelines on the management of myocarditis,

pericarditis, endocarditis or arrhythmias and pulmonary hypertension are borrowed from those of cardiovascular or thoracic societies.

1.6 Primary heart involvement in rheumatic musculoskeletal diseases

While the clinical spectrum of cardiac symptoms across RMDs is variegate (

Table 1), the types of cardiovascular imaging developed for the assessment of RMDs-pHI, and the current evidence of an imaging-based detection of RMDs-pHI in RA, SLE and SSc patients, are described in the following sections.

Table 1. Cardiac manifestations of rheumatic and musculoskeletal diseases.

Symptoms and signs	Cardiopalm
	Chest pain
	Dyspnea
Minor EKG abnormalities	Conduction abnormalities
	ST abnormalities
	T wave abnormalities
Major arrhythmias	Supraventricular tachycardia
	AV block
	Ventricular tachycardia
	Ventricular fibrillation
Syncope and sudden death	
Cardiogenic shock	
Decompensated heart failure	
Acute coronary syndrome with normal coronarogram	

AV, atrioventricular. EKG, electrocardiogram.

1.6.1 Investigational cardiovascular techniques for the detection of RMDs-pHI

1.6.1.1 Transthoracic echocardiography

Conventional transthoracic echocardiography (TTE) is a well-established and widely available imaging technique for the non-invasive detection of cardiovascular complications. It allows an accurate non-invasive assessment of cardiac chamber morphology and volumetry, as well as ventricular systolic and diastolic function and the presence and severity of valvular heart diseases. In addition, advanced echocardiographic features are now available, such as speckle tracking echocardiography (STE), which evaluates and quantifies active myocardial deformation (strain), identifying abnormalities in early and subclinical phases of disease (before reduction of LVEF).

Doppler echocardiography also allows the assessment of aortic stiffness. With the aorta being the major elastic vessel in the body, aortic stiffness likely represents the most informative measurement of arterial stiffness. Amongst the several principles, techniques and devices that have been proposed to measure arterial stiffness in humans, Doppler-echocardiography is one of the cheapest, fast, widely available and reliable methods to assess aortic stiffness. Moreover, it can be easily integrated into a routine echocardiography assessment.

More recently, a novel assessment integrating scar imaging echocardiography with an ultrasound multi-pulse scheme (eSCAR) has proved to be effective in detecting ischemic myocardial scars in patients with CAD [Gaibazzi, 2016] and hypertrophic cardiomyopathy [Gaibazzi, 2021].

The main limitation of TTE is being operator-dependent and the difficulty in obtaining good quality assessments in particular conditions (e.g. chest conformation, obesity). However, due to its wide availability, ease of use and low cost, TTE could represent the cornerstone of screening for pHI abnormalities in RMDs patients.

1.6.1.2 Cardiovascular magnetic resonance imaging

Cardiac magnetic resonance (CMR) imaging is the method of choice for assessing morphology, function, micro and macrovascular perfusion and the possible presence of edematous or fibrotic areas of the heart [Lee, 2008]. CMR imaging is able to distinguish ischemic areas in the myocardial tissue, as well as to differentiate oedema, fat and fibrotic elements [Mavrogeni, 2016]. Traditional sequences showed important limitations and provided only qualitative information. Currently, T1 and T2 maps provide quantitative information that can be used in clinical practice. In the study of acute myocardial pathology, both ischemic and inflammatory, myocardial oedema can be visualized using T2 maps [Kellman, 2007]. T1 maps allow visualizing the involvement of the myocardium in the SLE when it is still in the preclinical stage [Puntmann, 2013]. They are acquired 1 and 15 minutes after administration of the contrast medium (gadolinium), respectively defining the sequence EGE ("early gadolinium enhancement") and LGE ("late gadolinium enhancement"). The latter allows the detection of myocardial scar, which appears as a bright area in contrast to the healthy myocardium, which appears black - "bright is dead" [Mavrogeni, 2018]. Scar detection is preferably performed 15-20 minutes after gadolinium administration to maximize tissue characterization [Mavrogeni, 2016]. Both recent and older scars retain the contrast medium and appear bright [Kim, 1996]. The CMR-LGE allows evaluation of the aetiology of myocardial scar, which may or may not be ischemic [Raney, 2006].

In cases where diffuse myocardial fibrosis is present, associated with diastolic dysfunction, heart failure and sudden cardiac death, LGE may not identify it, as it requires a normal myocardial area to highlight areas of fibrosis [Taylor, 2016]: in this case the T1 maps and the quantification of the extracellular volume estimate the extent of fibrosis more precisely and earlier, even if this has not yet been universally accepted [Mavrogeni, 2018; Taylor, 2016].

CMR can be useful in assessing ventricular motility by quantifying myocardial deformity, i.e. the "strain". In particular, two “CMR-tagging” techniques, “SENC” (Strain Encoding magnetic resonance imaging) and “DENSE” (Displacement

Encoding with Stimulated Echos), allow to calculate the strain and have been validated in vivo. However, they have important temporal resolution limitations and better measure strain in not too thin areas of the heart wall. The strain is underestimated if the tag does not correspond to the start of cardiac contraction. Specific software is required for strain calculation. Techniques remain mainly used in research rather than clinical practice [Amzulescu, 2019; Seetharam, 2019]. CMR can also be useful in evaluating heart valves: it estimates hemodynamic abnormalities and can highlight thickness, prolapse, the fusion of valve flaps and any vegetation [Cawley, 2009].

The limitations of the CMR are related to the high costs of the procedure and its low availability. Although there is no evidence of direct nephrotoxicity, gadolinium has been associated with systemic nephrogenic fibrosis. Patients with permanent pacemakers, implantable defibrillators or surgical iron clips are traditionally contraindicated [Barison, 2021]. It is recommended that CMR not be used during the first trimester of pregnancy, as there is no data on the possible teratogenic effects of gadolinium. Precautions must also be taken in case of breastfeeding [Mavrogeni, 2016].

1.6.1.3 Other imaging techniques for the investigation of RMDs-pHI

In addition to echocardiography and CMR imaging, various imaging methods were evaluated in order to identify abnormalities of myocardial function, including subclinical. However, these techniques are burdened by high costs, poor availability except in some specialized centres and little specificity for myocardial lesions due to SLE.

PET/CT angiography is an imaging method that uses [11C]-PK11195, a molecule that acts as a selective ligand on the peripheral benzodiazepine receptor expressed by activated macrophages, to assess the degree of vascular inflammation in SLE [Mavrogeni, 2016] in particular in those symptomatic subjects but with inflammation index values in the normal range [Pugliese, 2010]. It also allows the detection of aortocoronary calcifications, which appear to be related to the activity and duration of the disease, BMI and PWV [Romero-Diaz, 2012; Norby, 2011].

Radiological exposure and the use of iodized contrast media are the main limitations to the use of PET/CT in the diagnosis and follow-up of cardiovascular involvement in SLE [Mavrogeni, Dimitroulas, Sfikakis, Kitas, 2013].

Myocardial perfusion scintigraphy is a method of investigation that allows direct evaluation of myocardial perfusion. It is based on the injection of a small amount of radioactive tracer followed by the acquisition of images through a gamma camera. Myocardial tomoscintigraphy includes two evaluations: at rest, where the radiotracer is injected in conditions of rest, and under stress (physical or pharmacological) where the radiopharmaceutical is injected at the end of the stress test or after the administration of vasodilator or beta-agonist drugs [Prvulovich, 2006]. The tracer is distributed in the myocardial tissue in a manner proportional to the blood flow. Three tracers are commercially available: Thallium-201, Technetium 99m - Sestamibi and Technetium 99m - Tetrafosmin, and currently available data do not indicate the superiority of one over the others [Kapur, 2002]. Perfusion anomalies have been detected in both SLE patients with symptoms and without symptoms [Sun, 2001]. Myocardial scintigraphy has a low spatial resolution, not allowing to detect of small subendocardial or intramyocardial lesions and microvascular disease [Mavrogeni, Dimitroulas, Sfikakis, Kitas, 2013]. In clinical practice, nuclear studies are applied only in patients with known coronary artery disease to establish the extent of myocardial ischaemia before and after interventional procedures.

Thallium-201 radiotracer single-photon emission computed tomography (SPECT) has been identified as a scintigraphic imaging modality to demonstrate stress perfusion defects that would depend on SSc-related microvascular or fibrotic cardiac abnormalities [Kahan, 1986]. The reported prevalence of cardiac anomalies identified with this method is very varied, reaching up to 82% of SSc patients [Kahan, 2006]. Although SPECT appears to have greater sensitivity to identify potential cardiac anomalies, the clinical significance of these anomalies remains uncertain [Parks, 2014].

An overview of cardiovascular imaging methods to investigate RMDs-pHI is described in

Table 2.

Table 2. Comparison of different cardiovascular imaging methods to investigate primary heart involvement in rheumatic and musculoskeletal diseases.

Imaging modality	Work-up	Follow-up	Pros and cons
Echocardiography	Primary imaging method for diagnosing LV dilation and systolic dysfunction Etiological evaluation Prognostic evaluation (ventricular function; mitral regurgitation severity; the presence of diastolic dysfunction)	Prognostic assessment (improvement of right / left ventricular function; improvement of mitral regurgitation; improvement of the restrictive left ventricular filling pattern)	The best method for follow up - should be repeated regularly
CMR	Accurate assessment of volumes and systolic function Differential diagnosis Etiological diagnosis Prognostic stratification (involvement of the right ventricle, LGE)	Increasingly used in prognostic evaluation	The role of the CMR in the follow up needs to be evaluated further
CT	Etiologic evaluation (exclusion of CAD in patients with a low pre-test probability)		
PET/SPECT	Tissue characterization - may be helpful in the etiological diagnosis of left ventricular dysfunction, which has implications in terms of prognosis and treatment		

CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; CT, computer tomography; LGE, late gadolinium enhancement; LV, left ventricle; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

1.6.3 Primary heart involvement in rheumatoid arthritis

1.6.3.1 Myocardial involvement

Abnormalities of heart structure and mass

Rheumatoid arthritis is a systemic, immune-mediated disease involving both musculoskeletal and extra-articular domains. CVD is one of the most common extra-articular manifestations of RA, which can manifest early with abnormalities in left ventricular (LV) geometry and LV hypertrophy (LVH) [Rudominer, 2009; Giles, 2010]. In particular, concentric LV remodelling is common among RA patients. This association remained significant after adjustment for CVD risk factors and comorbidities [Myasoedova, 2013], suggesting that RA-intrinsic factors could be significantly related to the susceptibility of LVH.

LVH is a risk factor for CAD and poor CVD outcomes in the general population [Levy, 1990] as well as in several settings of patients at increased risk for CVD events [Levy, 1990; Kannel, 1992; Cioffi, 2013; Gerdts, 2015; Sulemane, 2017], including RA patients. Several mechanisms, including long-term pressure, such as systemic hypertension or aortic stenosis, can cause LVH. The findings that LVH may precede hypertension and that patients with similar degrees of hypertension may have marked differences in LV mass strongly suggest that genetic and gender-related factors can promote and retard the development of LVH [Pontremoli, 2000]. Gender also leads to a predisposition to RA. The incidence of this condition is twice higher in females than males, and disease severity or treatment response differs according to gender [Favalli, 2019]. However, it is unknown whether susceptibility to LVH in RA patients is gender-driven.

RA has been associated with increased or decreased left ventricular mass (LVM), depending on the different imaging techniques used to assess it. Echocardiography-defined LVH is associated with CVD morbidity and mortality [Levy, 1990]. LVH is the leading adaptive process that the human heart puts into responding to physiologic (physical exercise, state of pregnancy) or pathologic stimuli triggering left ventricular (LV) mass growth. These stimuli are primarily represented by systemic arterial hypertension and type 2 diabetes mellitus, two of

the most common causes of LVH, together with overweight and obesity in the clinical setting. As a rule, LVH develops and progresses for a long time in an asymptomatic way and predicts adverse CVD outcomes in the general population and several sets of patients at increased risk for CVD events [Cioffi, 2021].

Our [Cioffi, 2015; Giollo, 2020] and other [Myasoedova, 2013] groups showed that echocardiography-detected LV concentric remodelling (normal LVM index (LVMi) and relative wall thickness (RWT) > 0.42 cm), concentric hypertrophy (increased LVMi and RWT >0.42 cm) are peculiar of patients with chronic inflammatory arthritis (Figure 1). These findings are in keeping with the presumed non-ischemic nature of RA associated cardiomyopathy. Two meta-analyses comprising 25 and 16 individual studies [Aslam, 2013, Corrao, 2015], respectively, showed higher mean differences LVMI of +6.2 g/m^2 and +0.47 g/m^2, respectively, in the RA compared to non-RA groups. In patients with RA, even when evaluated fairly early in the context of primary prevention, some maladaptive cardiac changes, including concentric remodelling, LVH or dysfunction, have been documented [Rudominer, 2009], particularly when systemic arterial hypertension or DM coexist. However, in clinical practice, echocardiography-detected LVH is often found in patients with RA who have none of these pathologies [Cioffi, 2021].

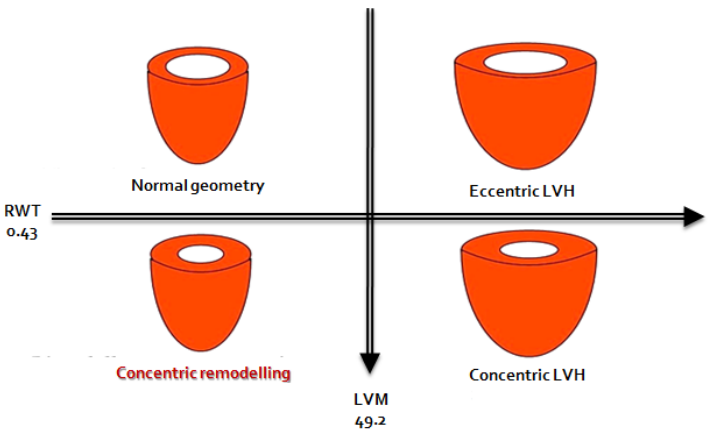

Figure 2. Normal and pathologic left ventricular geometry.

Concentric remodelling or hypertrophy is frequently found in patients with rheumatoid arthritis. LVH, left ventricular hypertrophy; LVM, left ventricular mass; RWT, relative wall thickness.

However, cross-sectional studies reporting lower or higher LV mass associations with RA therapies are difficult to interpret. Indeed, studies that have utilized cardiovascular magnetic resonance (CMR) imaging to measure LVM reported lower LVMI in RA patients (differences of -14.7 g/m^2, -4.558 g/m^2 and -14.7 g, respectively). For example, the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis was a cohort study of subclinical CVD in 7 patients with RA compared to 225 non-RA control subjects from a cohort enrolled in the Baltimore Multi-Ethnic Study of Atherosclerosis [Giles, 2010]. After adjustment for confounders, the mean LVM was 26 grams lower in patients with RA than controls ($P < 0.001$; -18%), thus suggesting that the progression to heart failure in RA may occur through reduced myocardial mass rather than hypertrophy.

Both modifiable and nonmodifiable factors may contribute to lower levels of CMR-detected LVM and volumes. In a UK-based study of patients with established RA and no history of CVD who underwent CMR imaging, there was evidence of reduced LV systolic function and LV mass index (LVMI) (- 4.56 g/m^2 (- 8.92, - 0.20), $p = 0.041$) after adjustment for traditional CVD risk factors. Such findings suggest cardiac pathology other than atherosclerosis in RA [Bissell, 2020]. However, CMR measures are predominantly associated with conventional cardiovascular risk factors; male sex and systolic blood pressure independently increase LVMI. Positive associations of CRP and RA disease duration with LVMI, and current corticosteroid use with lower LVMI, have been reported [Plein, 2020].

Early untreated RA patients had a lower mean LVM at baseline than non-RA controls as assessed by CMR imaging, but after a year of treatment, mean LVM increased in the RA group from 78.2g to 81.4g ($p=0.01$). This study suggests RA itself may be associated with a decline in LVM, perhaps similar to the sarcopenia seen in peripheral muscle in RA. In addition, treatment of RA may facilitate the re-gain of some muscle mass [Park, 2021]. However, in a prospective observational TTE study [Davis, 2017] in RA patients without clinical HF, while

LVMI in RA and non-RA groups declined significantly over 4-5 years, rates were not statistically different.

Myocarditis

Acute myocarditis is rare in RA, and it has been poorly characterised. It is usually associated with active articular disease and with other extra-articular manifestations [Sigal, 1989]. Both granulomatous and lymphocytic interstitial myocarditis have been reported in RA.

Myocardial dysfunction

Immune regulation and inflammation play a role in the pathogenesis and progression of acute and chronic HF [Park, 2021]. RA patients remain at two-fold higher risk of HF mortality than non-RA patients [Park, 2021]. Among patients with HF with RMDs, distinct left ventricular ejection fraction trajectory patterns are associated with different specific individual RMDs. Compared with non-RMDs controls with HF, patients with RA, inflammatory bowel disease, and SLE were significantly more likely than controls to have HF with preserved or midrange EF [Rivera, 2021]. Huang and colleagues [Huang, 2021] studied an electronic health record (EHR)-based RA cohort with data pre-/post-RA incidence. Among 9087 RA patients, 8.2% developed HF during ten years of follow-up. Elevated inflammation was associated with increased risk for HF at both five- and ten-year follow-up (HR=1.66 [1.12-2.46] and 1.46 [1.13-1.90], respectively), which was also seen for HFpEF at five years (HR=1.72 [1.09-2.70]) and ten years (HR=1.45 [1.07-1.94]). However, HFrEF was not associated with inflammation for either follow-up time.

Myocardial dysfunction in RA patients is challenging to assess in practice because it is mainly detected only at a subclinical level before an HF event occurs. Indeed, in RA vs non-RA individuals without clinical CVD, the conventional measure of systolic function, ejection fraction (EF), does not differ significantly by either trans-thoracic echocardiography (TTE) [Aslam, 2013; Midtbo, 2017; Fine, 2014; Cioffi, 2017] or cardiovascular magnetic resonance (CMR) imaging [Ntusi, 2019]. However, systolic strain, assessed by speckle tracking echocardiography (STE) or

tissue tagging in CMR, is a more sensitive predictor of systolic dysfunction and CVD clinical endpoints, including mortality [Sengeløv, 2015] in general population studies. While EF reflects the change in LV volume only, systolic strain assesses myocardial deformation during systole coupled to LV volume. GLS is reported as a negative value, reflecting shortening of the LV axis during contraction; a more negative value reflects more significant contraction with normal values in the -15.9% to -22.1% range [Yingchoncharoen, 2013]. Our group provided evidence that GLS is lower (i.e. worse function) in RA patients than controls matched for CVD risk factors [Cioffi, 2017]. Furthermore, we found that low GLS predicted future CVD hospitalizations [Cioffi, 2017]. Lower values of GLS have been reported by other groups in RA vs non-RA individuals without clinical HF [Fine, 2014; Ntusi, 2019].

Interestingly, LV diastolic dysfunction (LVDD) could occur before systolic HF and is a characteristic finding in HF with preserved EF (HFpEF) [Sharma, 2014]. Although clinically silent, LVDD represents the earliest sign of cardiac involvement. In the general population, LVDD is associated with age, female sex, and hypertension. However, in premenopausal women with RA, LVDD was much more common, and the age of onset was reduced [Kim, 2021]. DD is assessed by Doppler echocardiography by measurement of transmitral blood flow velocities in early (E) and late (A) diastole, septal and/or lateral mitral valve annular velocities (e'), and tricuspid regurgitant jet velocity [Nagueh, 2016].

One meta-analysis of case-control studies [Aslam, 2013] found a higher prevalence of LVDD in RA patients vs non-RA controls without clinical HF (26-3% vs 1-21.7%, respectively). A prospective echocardiography study [Davis, 2017] comparing RA (n=160) vs non-RA (n=1391) patients without HF showed a progressive decline in multiple measures of diastolic function in the RA group only.

Myocardial fibrosis

Myocardial dysfunction HF are increased in RA, yet there are few studies of the myocardium in RA. Cardiovascular MRI findings indicating myocardial

inflammation/fibrosis are correlated with RA disease activity and alterations in the myocardial structure known to precede clinical HF. Focal fibrosis identified by cardiovascular MRI was detected as LGE in 19/60 (32%) and T2-weighted imaging in 7/60 (12%) RA patients, 5 of whom also had LGE [Kobayashi, 2017]. After adjustment for relevant confounders, higher odds of LGE with each swollen joint (odds ratio [OR] 1.87, P = 0.008), each log unit higher C-reactive protein level (OR 3.36, P = 0.047), and each log unit higher NT-proBNP (OR 20.61, P = 0.009) were found. NT-proBNP was also significantly higher (135%) among those with T2-weighted imaging than those without T2-weighted imaging or LGE. Higher LV mass index and LV mass:end-diastolic volume ratio were observed in those with T2-weighted imaging than those with no myocardial abnormalities and those with LGE without T2-weighted imaging. In active RA, myocardial T1 relaxation times are prolonged, suggesting diffuse inflammation or fibrosis. Local myocardial scars and inflammation, visible as LGE, are also common, as are impairments of LV systo-diastolic function [Holmström, 2016]. Subclinical CVD is frequent in RA, including focal and diffuse myocardial fibrosis and inflammation, which are associated with impaired strain and RA disease activity. CMR T1 mapping provides potential added value as a biomarker for disease monitoring and study of therapies to reduce diffuse myocardial fibrosis in RA [Ntusi, 2015]. Focal fibrosis on LGE was found in 46% of RA patients compared with no control subjects. Patients with RA had larger areas of focal myocardial edema (10% vs. 0%), higher native T1 values (973 ± 27 ms vs. 961 ± 18 ms; p = 0.03), larger areas of involvement as detected by native T1 >990 ms (35% vs. 2%; p < 0.001), and expansion of ECV (30.3 ± 3.4% vs. 27.9 ± 2.0%; p < 0.001) compared with control subjects.

1.6.3.2 Pericardial effusion and pericarditis

Clinically evident pericarditis can be detected occasionally in RA [Guedes, 2001], but it rarely presents with constrictive pericarditis or rapidly progressive effusive pericarditis that is known to be associated with high morbidity and mortality. Pericarditis occurs predominantly in male patients with severely destructive and nodular RA and often in association with vasculitis or other extra-articular

features of RA [Voskuyl, 1996]. Most RA patients develop pericarditis after the onset of arthritis; however, pericarditis may also precede the diagnosis of RA. The prognosis of RA patients with clinical pericarditis appears to be impaired, in particular in the first year after diagnosis, and the age and cardiac status best predict survival [Hara, 1990]. Treatment with non-steroidal anti-inflammatory drugs, corticosteroids or DMARDs seems appropriate in the majority of patients with a definite diagnosis of RA-associated pericarditis, though in severe cases, pericardiectomy is needed [Romanowska-Próchnicka, 2013].

1.6.3.3 Valvular heart disease

The RA population has a higher incidence of VHD than the general population in that 30% of patients with RA have valvulopathy [Kitas, 2001]. A study of transesophageal echocardiography demonstrated that 80% of RA patients had some mitral regurgitation and 33% aortic regurgitation [Guedes, 2001]. However, the rate of aortic stenosis (AS) progression in the RA population was less than that of the reported rate of AS progression in the general population [Bois, 2017]. These results suggest that patients with RA who have mild or moderate AS should undergo echocardiographic surveillance for disease progression similar to that of the general population.

1.6.3. Conduction abnormalities

There is evidence that TNF-α, interleukin-1 and interleukin-6, can modulate the expression and function of ion channels both by directly acting on cardiomyocytes [Lazzerini, 2006], thus predisposing to arrhythmias RA patients. Patients with RA also have abnormalities of the structure or function of the left atrium, indicative of an atrial myopathy [Packer, 2020; Tłustochowicz, 1995; Wisłowska, 1999; Engelmann, 2005]. Systemic inflammation causing increased circulating concentrations of inflammatory proteins, ischaemic heart disease, and heart failure are essential factors for the initiation and recurrence of atrial fibrillation (AF) in this patient group. The development of an atrial myopathy leads to AF but also contributes to pulmonary venous hypertension and VTE. Indeed, the risk ratio of AF in patients with RA is 29% higher than in the general population and can occur any time during the disease course. However, it can be the first disease

manifestation [Ungprasert, 2017]. It has been shown that the rate of successful cardioversion is lower in patients with RA who have AF and a high inflammatory burden with persistently increased serum inflammatory indices [Engelmann, 2005; Issac, 2007; Liu, 2007]. Increased P wave dispersion in electrocardiography, which is considered to be a predictor of AF, also occurs more frequently in patients with RA and seems to be highly associated with the level of systemic inflammation [Guler, 2007]. Autonomic nervous system (ANS) dysfunction due to the neurotoxic effect of chronic systemic inflammatory process associated with RA and the side-effects of therapeutic agents is evident in about 60% of patients with RA. The main pattern of ANS deregulation is impairment of cardiovascular reflexes and altered heart rate variability, indicative of reduced cardiac parasympathetic activity and elevated cardiac sympathetic activity manifesting as atrial ectopic beats, impaired heart rate control and inappropriate atrial tachycardia [Sheldon, 2015]. Increased sympathetic and decreased parasympathetic activity can play a crucial role in developing both AF and VT in patients with RA [Schwemmer, 2006]. Conduction disturbances such as complete AV block in RA patients are rarely encountered and related to rheumatoid nodules, CAD, and non-specific inflammatory lesions [Ahern, 1983; Wallberg-Jonsson, 1997; Solomon, 2003].

1.6.4 Primary heart involvement in systemic lupus erythematosus

1.6.4.1 Myocardial involvement

Abnormal heart structure and mass

Unlike RA, left ventricle structure and mass have not been systematically studied in SLE patients. However, excess LVH may contribute to the increased CVD morbidity and mortality observed in SLE patients. Echocardiography assessed LVM (38.3 versus 32.8 $g/m^{2.7}$), EF (71% versus 67%), and prevalence of LVH (17.9% versus 6.4%) were higher in SLE patients than in control subjects (all $P<0.001$) [Pieretti, 2007]. Electrocardiography (EKG)-defined LVH was also found frequently in SLE patients [Bourré-Tessier, 2015; Puntmann, 2013]. Electrocardiography abnormalities suggestive of LVH were found in 5.4% of

adult SLE patients from 19 centres participating in the Systemic Lupus International Collaborating Clinics (SLICC) Inception Registry [Bourré-Tessier, 2015]. LV EDV was significantly reduced compared to healthy control subjects in a Dutch study of 102 patients with SLE (88% women; mean age, 43 ± 14 years) with several CVD risk factors [Gegenava, 2020].

Myocarditis

Myocarditis is the most characteristic type of myocardial involvement in SLE. It may be due to the disease itself, but also to CAD or drug toxicity [Kao, 2002; D'Cruz, 2001]. Myocardial involvement at autopsy was found more frequently in the past, while nowadays it is limited to 8% of cases, probably thanks to the introduction of corticosteroid therapy [Godeau, 1981; Bulkley, 1975]. On histology, small areas of fibrinous necrosis with lymphocytes and plasma cells are observed; areas of myocardial fibrosis are found in patients treated with corticosteroids. Immunofluorescence highlights the deposition of granular pattern immune complexes and complement fragments in the vessel walls and perivascular tissues, supporting the hypothesis that immune complexes mediate lupus myocarditis [Bidani, 1980; Bulkley 1975; Doherty, 1985]. Some studies show an association between anti-RoSSA and the development of myocarditis [Logar, 1990]. Lupus myocarditis occurs similarly to myocarditis from other causes: patients report dyspnoea, tachycardia and arrhythmias, although myocardial involvement is more frequently subclinical. Electrocardiographic abnormalities of the ST segment and T wave may be found, but none are specific to myocarditis. Cardiac enzymes can be within normal limits [Tincani, 2006]. Ultrasound can show areas of regional or global hypokinesia, which is a non-specific finding indicative of myocardial dysfunction, possibly due to myocarditis [Doria, 2005]. During the past twenty years, CMR imaging has also emerged in the early diagnosis of myocarditis in SLE patients [Singh, 2005]. However, the gold standard of myocarditis diagnosis remains endomyocardial biopsy, despite being an invasive procedure subject to sampling errors [Tincani, 2006]. It is crucial to recognize myocarditis early to avoid progression to ventricular dysfunction, dilated cardiomyopathy and heart failure [Doria, 2005].

Myocardial dysfunction

Convincing evidence supports the presence of cardiovascular abnormalities in SLE patients even in the absence of overt cardiac symptoms. A significant reduction of myocardial GLS has been demonstrated in patients with SLE compared to healthy volunteers, denoting early systolic dysfunction before any decrease in LVEF [Farag, 2020; Elnady, 2016; Nikdoust, 2018]. Also, the presence of early-stage, clinically silent LVDD has been demonstrated in patients with severe SLE in terms of increases in LM, LV EDV, left atrial volume and right heart parameters [Leone, 2020]. These subclinical cardiac abnormalities may indicate pathways of myocardial remodelling in the context of systemic inflammation. GLS appears to be able to derive indirect information about the presence of myocardial fibrosis through the analysis of myocardial dynamics. Indeed, the presence of myocardial fibrosis causes abnormal endocardial thickening by an increase in myocardial stiffness and a consequent reduction of myocardial strain [Pastore, 2020].

In patients with SLE, impairment of LV GLS is also associated with CVD events [Gegenava, 2020]. Survival curves showed that patients with SLE with more impaired LV GLS (based on the median value of -15%) experienced significantly higher cumulative rates of cardiovascular events compared with those with less impaired LV GLS. On multivariate Cox regression analysis, LV GLS demonstrated an independent association with CVD events (hazard ratio, 2.171; 95% CI, 1.015-4.642; P = .046), whereas LVEF was not significantly associated with the outcome.

A systematic review and metanalysis demonostrated that patients with SLE exhibited an increase in the left atrial diameter (LAD) (WMD-weighted mean difference (95 %CI) 0.18 (0.06-0.29); p = 0.002), left ventricular internal diameter in diastole (LVDd) (WMD (95 %CI) 0.07 (0.02-0.12); p = 0.01), and the left ventricular mass index (LVMI) (WMD (95 %CI) 5.69 (2.69-8.69); p = 0.0002). In contrast, the left ventricular systolic function (WMD (95 %CI) -1.62 (-1.69 to -0.75); p < 0.00001) and diastolic function including E/A ratio and E/E' ratio

(WMD (95 % CI) -0.13 (-0.24 to -0.01); p = 0.04; WMD (95 % CI) 1.71 (0.43 to 2.99); p = 0.009) were decreased in SLE patients [Chen, 2016].

Cardiovascular MRI is also helpful to detect subclinical myocardial impairment [Puntmann, 2013]. In SLE patients evaluated with CMR imaging with T1 mapping and compared with a control group, the absolute values of left ventricular end-diastolic volume (LV EDV), LVEF, GLS, GCS, left ventricular twist angle (LVtw), torsion (Tor) and myocardial comprehensive index (MCI) decreased, left ventricular end-diastolic mass, left ventricular end-systolic mass and peak strain dispersion (PSD) increased in the mild-to-moderate and the severe groups ($P_2 < 0.05$, $P_3 < 0.05$) [Feng, 2021].

Myocardial fibrosis

Drug-naive patients with new-onset SLE, even those with inactive disease, are likely to have a silent cardiac impairment. Clinical assessment and cardiac MRI studies were performed in 50 drug-naive patients with new-onset SLE, 60 with longstanding SLE, and 50 healthy subjects in a prospective 3-centre survey [Guo, 2018]. Native myocardial T1 and extracellular volume (ECV) were the primary outcomes of myocardial fibrosis, and they were elevated in the patients with new-onset SLE independently of SLE disease activity. Moreover, 12% in the new-onset SLE group were LGE positive, with a mean size of the scar detected by LGE of 0.5% of the LV. In the longstanding SLE group, 40% had LGE (mean LGE size 2.1% of the LV). In a prior study, mid-wall myocardial fibrosis as detected by LGE occurred in 15/41 SLE patients and was strongly associated with ageing, but not with SLE duration or severity. Extensive LGE was also related to diastolic dysfunction and impaired exercise capacity [Seneviratne, 2016]

1.6.4.5 Pericardial effusion and pericarditis

Pericarditis is one of the most characteristics and studied manifestations of SLE [Tincani, 2006]. The pericardium can be the subject of acute and chronic inflammatory processes, thus manifesting itself in acute pericarditis, with serofibrinous characteristics, or in chronic pericarditis, with fibrotic elements. Immunofluorescence immunoglobulins and fragments of complement factor C3

are detected: this demonstrates the role of immune complexes in the development of pericarditis [Bidani, 1980]. Pericardial involvement in autopsy studies reaches 62% in SLE patients [Kao, 2002].

Pericardial anomalies are found on ultrasound in 11% - 54% of patients with SLE [Doria, 2004], while clinical pericarditis is estimated to be 25% in patients with SLE in the course of the disease. Asymptomatic pericardial effusion found randomly on ultrasound is present in 40% of patients with SLE and is, therefore, more frequent than clinical pericarditis [Tincani, 2006]. Pericarditis is more frequent at the onset of SLE or during exacerbations, but in fact, it can appear at any time [Doria, 2005]. It can appear as an isolated attack or recurrent episodes [Bridgen, 1960]. Acute pericarditis presents with a characteristic chest pain in the precordial or retrosternal region, which worsens in supine decubitus, often pleuritic and sometimes associated with dyspnoea. Patients may report fever, tachycardia, and muffled heart tones; pericardial rubs are rarely heard, probably because they last for a few hours and then fade [Miner, 2014]. The ECG shows elevation of the ST segment and sharp T waves, generally transient findings [Godeau, 1981].

Echocardiography is the standard method for investigating pericardial abnormalities, as it is able to demonstrate the presence of effusion or thickening of the pericardial sheets [Tincani, 2006]. In patients with pericardial effusion, rather than with thickening of the leaflets, pericardial pain and a state of active disease are also more likely in other sites; when present, the pericardial effusion is generally contained and does not cause haemodynamic problems [Leung, 1990]. Invasive procedures such as pericardiocentesis are rarely used [Tincani 2006]: it can have both therapeutic purposes, in case the effusion is due to cardiac tamponade, and diagnostic, to exclude neoplastic or infectious pericarditis [Sinnaeve, 2019]. There is often concomitant pleural effusion [Tselios, 2017]. Complications such as cardiac tamponade, constrictive pericarditis and purulent pericarditis are rare events [Doria, 2005].

1.6.4.6 Valvular heart disease and Libman-Sacks endocarditis

Valvular anomalies are detected in up to 50% of SLE patients [Tselios, 2017]. Valvular insufficiency is defined as a defective closing mechanism and is due to structural alterations such as thickening of the flaps or the presence of sterile vegetations: it is the most frequent valvular functional anomaly, often of a mild degree and at the level of the mitral and aortic valves. Valve stenosis and rupture of the tendon cords are rare. Involvement of the right heart at the tricuspid and pulmonary valves level is less frequent and generally secondary to pulmonary hypertension [Tincani, 2006].

The most characteristic valvulopathy of SLE is *Libman-Sacks* endocarditis, also called "atypical warty endocarditis", endocarditis of non-infectious origin that presents with 1-4 mm warty lesions in valve leaflets, papillary muscles and mural endocardium, especially at the level of the mitral [Libman-Sacks, 1924]. Generally, it has no symptoms or heart sounds [Doherty, 1985]. A correlation emerged between the positivity to antiphospholipid antibodies and the onset of cardiac valvulopathy, which appears to be secondary to the presence of these antibodies [Tincani, 2006]. From a histological point of view, warts can be of two types: 1) active lesions with deposition of fibrin and mononuclear cells, more frequent in young patients and which rarely become hemodynamically significant; 2) consolidated lesions with fibrotic elements and calcifications, more frequent in patients with a long history of disease and more often associated with valvular dysfunction, in particular insufficiency [Doherty, 1985]. In rare cases, more than one valve may be involved at the same time [Hachiya, 2014].

The diagnosis is based on transthoracic and especially trans-oesophagal echocardiography for the visualization of the vegetations [Roldan, 2008]. In SLE, valve anomalies evolve over time in 40% of cases, and this could be due to the intermittent course of inflammation, while in 24% of cases, the irregularities are resolved [Roldan, 1998]. Libman-Sacks endocarditis can be asymptomatic or present with infarcts of embolic origin, especially cerebral [Miner, 2014]. Libman-Sacks endocarditis predisposes to the onset of bacterial endocarditis;

therefore, antibiotic prophylaxis is recommended in situations where it is indicated [Tincani, 2006].

1.6.4.7 Conduction abnormalities

Cardiac arrhythmias have been reported to be highly prevalent among SLE patients. However, the direct relationship to the underlying disease is unclear, and often the arrhythmia is a manifestation of CAD or lupus-related cardiomyopathy. As in RA, heart rate variability in SLE may be related to coexisting cardiac autonomic dysfunction [Laganà, 1996].

Conduction abnormalities in SLE are most commonly recognized as a manifestation of neonatal lupus. Congenital heart blocks can occur in children born to mothers with anti-RoSSA antibodies, with or without lupus, and result from transplacental passage of maternal anti-RoSSA antibodies [Kao, 2002]. QTc interval prolongation is often observed in SLE patients, also related to the chronic use of hydroxychloroquine, a QTc-prolonging medication. A QTc ≥440 msec was found in 15.3% of SLE patients, and it was associated with the total SLICC damage index (SDI). Neither the specificity nor the level of anti-Ro/SSA was associated with QTc duration [Bourré-Tessier, 2015]. Extensive studies have not confirmed the association of anti-RoSSA and QTc elongation [Massie, 2014].

EKG abnormalities, including nonspecific ST-T changes (30.9%), possible LVH (5.4%), and supraventricular arrhythmias (1.3%), could be frequent [Bourré-Tessier, 2015]. Another study aimed to determine the prevalence of EKG-CVD in SLE patients and examine the risk factors associated with EKG-CVD [Al Rayes, 2017]. EKG-CVD was defined as the presence of one or more of the following four elements (EKG-4): ST-segment or T-wave abnormalities, left ventricular hypertrophy (LVH), left axis deviation (LAD), left bundle branch block (LBBB) and right bundle branch block (RBBB). EKG-5 included the same elements as EKG-4 and the Q-wave. Of 487 SLE patients, 104 (21.4%) and 118 (24.2%) patients had one or more EKG-4 and EKG-5 elements, respectively. A higher prevalence of EKG-CVD was found in patients with a longer SLE disease duration, and the burden of EKG-CVD features increased with age. Advanced

age, active SLE disease, and damage were associated with EKG4 and EKG-5, while treatment of hyperlipidemia was protective.

1.6.5 Primary heart disease in systemic sclerosis

1.6.5.1 Myocardial involvement

Abnormalities of heart structure and mass

The size and dimensions of cardiac chambers may be abnormal in SSc patients, but this has never been reported consistently across several imaging methods [Dumitru, 2021]. More often, signs of LVH or RVH or LV or RV dilation have been reported [Bulkley, 1976; Chaosuwannakit, 2018; Muresan, 2016; Nordin, 2014; Morelli, 1996]. However, it is unclear the contribution of PH in these abnormalities.

Myocarditis

Myocarditis has also been recognized as a possible complication of scleroderma and is generally associated with musculoskeletal myositis [Parks, 2014]. SSc myocarditis has unique clinical, histological and prognostic features.

As for the clinic, it tends to present more frequently with heart failure and upper-class dyspnea, although subclinical onset is the predominant mode of onset of the disease [De Luca, 2020].

As for the histological characteristics, SSc myocarditis tends to have higher degrees of myocardial fibrosis than other myocarditis acquired by endomyocardial biopsy [De Luca, 2020]. It is interesting to note that the degree of myocardial fibrosis is directly correlated with the extent of skin fibrosis assessed by mRSS, thus creating a high-risk association between skin and heart involvement [De Luca, 2020]. Histopathology on cardiac samples from SSc patients revealed upregulation of adhesion molecules of the endothelium [Pieroni, 2014], concentric intimal hypertrophy in arterioles [Mueller, 2015], infiltration of activated T lymphocytes and macrophages and various degrees of myocardial fibrosis [Mueller, 2015; Bosello, 2019; De Luca, 2017], arguing the importance of all

three pathogenetic mechanisms of the disease: vascular abnormalities, immune activation with inflammatory load and fibrosis.

Regarding the prognostic characteristics, SSc myocarditis is associated with a worse prognosis than other myocarditis proven by endomyocardial biopsies [De Luca, 2020]. Cardiac MRI allows the identification of myocarditis [Allanore, 2006]; otherwise, this can also be diagnosed and monitored through the determination of the MB isoenzyme creatine kinase associated with echocardiography [Kerr, 1993]. To date, no standard treatment has been established for SSc myocarditis. According to the study by Pussadhamma [Pussadhamma, 2020], treatment with moderate-dose steroids appears to be adequate in SSc patients with myocarditis without apparent cardiac dysfunction, for whom low systolic output and high heart rate could be indicators of a promising response. The outcome of such therapy will not be good if applied to patients with SSc who have significant cardiac dysfunction, i.e. significantly elevated levels of NT-proNBP or hs-cTnT or reduced left ventricular systolic function [Pussadhamma, 2020]. Patients with SSc are at risk of developing restrictive cardiomyopathy from myocardial fibrosis and chronic inflammatory constrictive cardiomyopathy of the pericardium [Byers, 1997].

Myocardial fibrosis

The presence of myocardial fibrosis in the middle left ventricular segments at baseline MRI is an independent predictor of heart failure during follow-up, suggesting early screening of patients with SSc [Rodriguez-Reyna, 2019]. No SSc-associated serum antibody was associated with myocardial fibrosis or perfusion defects [Rodriguez-Reyna, 2015].

Myocardial fibrosis is unequivocally considered the hallmark of SSc heart disease. Traditionally, the fibrotic process has been regarded as the result of ischemic necrosis and reperfusion injury following intermittent vasospasm and early microvascular damage, according to necropsy studies [Bulkley, 1976]. However, autoimmune and inflammatory responses to cell damage play a fundamental role in the activation of fibroblasts and in the differentiation of myofibroblasts [Mueller, 2015].

There are two main types of myocardial fibrosis: reactive interstitial fibrosis and replacement myocardial fibrosis [Karamitsos, 2019]. Reactive interstitial fibrosis, which is characterized by a diffuse microscopic distribution in the myocardium and sometimes by a localized perivascular distribution, is observed in arterial hypertension, valvular heart disease, diabetic cardiomyopathy, hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy and cardiac senescence. Unlike replacement fibrosis, interstitial fibrosis is not induced by cell death and is a gradual process that can be reversed if the cause is treated promptly [Lopez, 2004]. It is considered a marker of the severity of the underlying disease. If the condition worsens, it is followed by myocyte apoptosis and irreversible replacement fibrosis [Weber, 1991]. Replacement fibrosis typically occurs after injury or death of myocytes, mainly in acute ischemic conditions, in which cellular apoptosis triggers fibroblasts and promotes the deposition of fibrous collagen tissue in the myocardium [Sutton, 2000]. Usually, a localized macroscopic distribution follows. Replacement myocardial fibrosis can also occur in myocarditis, hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, sarcoidosis and may demonstrate widespread distribution in toxic cardiomyopathies, chronic renal failure and as part of systemic inflammatory diseases [Karamitsos, 2009] . It is often present in the terminal stages of heart failure. Another type of fibrosis is infiltrative interstitial fibrosis induced by the progressive deposition of insoluble amyloid (amyloidosis) or glycosphingolipids (Anderson-Fabry disease) in the heart [Mewton, 2011].

Ischemic necrosis may explain focal areas of replacement fibrosis, but it does not explain diffuse interstitial fibrosis, also detectable in patients with subclinical heart disease by endomyocardial biopsy [Fernandes, 2003]. Indeed, SSc patients commonly manifest the progression of cardiac dysfunction despite composite treatment with vasoactive and antiplatelet drugs. Recent studies using MRI with delayed enhancement seem to reject the hypothesis of the vascular mechanism as the primary cause of myocardial fibrosis in SSc. In SSc patients presenting with subclinical heart disease, fibrosis was found to have a non-coronary distribution with a predominantly linear pattern [Tzelepis, 2007; Hachulla, 2009], similar to the fibrotic remodelling pattern that follows myocardial lymphocyte infiltration in

sarcoidosis and other forms of inflammatory cardiomyopathy or idiopathic dilated cardiomyopathy [Pieroni, 2014]. Furthermore, the inflammatory and autoimmune nature of SSc, as well as its possible association with myositis, suggests that myocardial inflammation may play a crucial role in SSc heart disease [Pieroni, 2014]. The dual nature of cardiac damage in SSc (ischemic and inflammatory), therefore, may explain the two patterns of fibrotic changes on endomyocardial biopsy: replacement fibrosis and interstitial/perivascular fibrosis.

In general, several pathological conditions affecting the atrial or ventricular myocardium can cause myocardial fibrosis. The leading causes are shown in Figure 22 [Shenasa, 2019].
Myocardial fibrosis in SSc differs from that observed in coronary atherosclerotic disease in that it does not correspond to a regional distribution related to a single coronary artery. The main differences in myocardial involvement in systemic sclerosis versus changes in coronary atherosclerotic disease are summarized in Table X.

Myocardial dysfunction

Myocardial involvement is more common and more severe in the diffuse cutaneous SSc variant, although patients with the limited cutaneous SSc variant also have significant heart disease [Kucharz, 2017]. The aetiology underlying myocardial involvement is probably multifactorial, with early microvascular damage and late fibrotic changes. It is believed, in fact, that it is the microvascular alterations (functional vasospastic episodes of the small coronaries and arterioles - the so-called "myocardial Raynaud's phenomenon") and not the traditional atherosclerotic disease that plays an essential role in the development of myocardial blood flow disorders in SSc [Lambova, 2014].

Early myocardial manifestations of SSc are often nonspecific, making the evaluation of susceptible patients problematic. Patients with cardiac manifestations can remain undiagnosed, potentially allowing the disease to progress silently [Rodriguez-Reyna, 2019].

Left ventricular systolic dysfunction is much less common in SSc than diastolic dysfunction, with an estimated incidence of 11-15% depending on the diagnostic technique [Parks, 2014]. Overt clinical systolic heart failure (heart failure with reduced ejection fraction) in patients with SSc typically presents insidiously. It is thought to be due to focal ischaemia from microvascular disease, leading to myocardial inflammation and fibrosis [Allanore, 2010].

Right ventricular dysfunction in SSc may result from preserved or reduced ejection fraction ventricular systolic insufficiency involving the left ventricle, or of primary right ventricular abnormalities or secondary to PAH [Maron, 2016]. A summary of the diagnostic and therapeutic approach of left and right ventricular dysfunction is proposed in Table XI.
Clinically, diastolic dysfunction of both ventricles is significantly more common than systolic dysfunction [Meune, 2016]: in fact, diastolic dysfunction is not limited to the left ventricle alone, but a surprisingly high prevalence of right ventricular diastolic abnormalities has been reported. In patients with SSc [Parks, 2014]. Diastolic dysfunction is the basis of the preserved ejection fraction clinical heart failure syndrome, which is highly prevalent in SSc [Allanore, 2010]. Diastolic dysfunction reflecting impaired ventricular filling depends on a rigid or fibrotic ventricle, which may eventually lead to upstream effects, such as atrial dilation and associated arrhythmias, pulmonary venous congestion and oedema, or ventricular systolic dysfunction [Allanore, 2010; Hinchcliff, 2013]. Ventricular diastolic dysfunction is rapidly identified through tissue Doppler echocardiography (TDE) which allows determining the rate of myocardial contraction and relaxation, the pattern of tissue movement and the "myocardial strain rate" (SR) [Uematsu, 1997; Derumeaux, 2002; Smiseth, 2003].

Cardiac MRI has emerged as a sensitive technique for identifying myocardial dysfunction in SSc. Imaging techniques include a late gadolinium enhancement technique to assess myocardial fibrosis, a T2-weighted imaging technique to identify inflammatory lesions, and accurate measurement of chamber sizes and volumes to assess ejection fraction or size of the chambers [Bouiez, 2010; Tzelepis, 2007]. The diastolic ventricular function and the kinetic pattern can be

examined during cardiac MRI, and right ventricular dysfunction can be more easily identified with MRI than with echocardiography [Bouiez, 2010].

1.6.5.2 Pericardial effusion and pericarditis

Pericardial abnormalities in SSc can manifest as fibrinous pericarditis, chronic fibrous pericarditis, pericardial adhesions, pericardial effusion and rarely as pericardial tamponade or constrictive pericarditis [Lambova, 2014]. Pericardial pathology is clinically evident in over 5% - 16% of cases [Champion, 2008] and with a higher prevalence in patients with lcSSc (30%) than in dcSSc (16%) [Gowda, 2001]. Patients with pericarditis were most strongly associated with the presence of anti-topoisomerase I antibodies [Simeon-Aznar, 2012; Fernandez Morales, 2017].

Pericardial effusions usually occur after the manifestations of other clinical features of SSc. Nevertheless, it should be noted that large pericardial effusion events (including those with consequent development of cardiac tamponade) have been described prior to the presence of skin thickening and the diagnosis of systemic sclerosis: this suggests that SSc should also be considered in the diagnostic algorithm for the pericardial effusion of unknown origin [Subramaniam, 2013; Champion, 2008; Meier, 2012]. Still, with regard to the clinical condition of severe pericardial effusion, Fernandez Morales [Fernandez Morales, 2017] noted the association between this and scleroderma renal crisis in 12.5% of cases: a possible explanation for this association could be decreased renal cortical perfusion due to heart failure or the use of diuretics in the case of cardiac tamponade which would precipitate renal ischemia [Dunne, 2011]. Severe pericardial effusions should therefore be recognized as a risk factor for the development of scleroderma renal crisis [Fernandez Morales, 2017].

Pericardial effusion can also develop as secondary effusions to PAH in the context of right heart failure or in the context of renal failure [Champion, 2008]. Clinically, SSc-associated pericardial disease does not differ from severe pericardial manifestations of other causes, with dyspnoea and chest pain being the most frequent symptoms. In most cases, pericardial involvement in SSc is

clinically silent and benign, small in magnitude and has no prognostic significance [Gowda, 2001].

On echocardiography, effusion can be detected in up to 41% of patients [Gowda, 2001]. In autopsies, pericardial involvement is found in about 70-80% of patients [Champion, 2008].

Pericardial effusions are typically treated only if symptomatic. If right heart failure with concomitant pericardial effusion is suspected, diuresis should be performed with caution. Pericardiocentesis can be performed if severely symptomatic or if tamponade is present; however, it is contraindicated in patients with significant pulmonary arterial hypertension or right ventricular dysfunction due to concern about acute right heart decompensation [Hung, 2019].

Symptomatic acute pericarditis is an uncommon manifestation of SSc, with an incidence of about 10% [Braunwald, 2015]. Acute pericarditis classically presents with symptoms of retrosternal chest pain that are almost always pleuritic in nature [Braunwald, 2015]. Irradiation to the left arm is not uncommon, but the most characteristic irradiation of pericarditis is at the edge of the trapezius, a particular sign of pericarditis [Shabetai, 2003]. Pericardial pain almost always finds relief in the sitting position, slightly leaning forward, while it worsens in the supine position. Associated symptoms include wheezing, coughing, and occasional hiccups.

Pericarditis is easily diagnosed by echocardiography, which may be requested after the results of the electrocardiogram (ST-T changes, low voltage) and chest radiology (enlarged, globular heart).

The treatment of pericarditis in the SSc patient mirrors that of standard therapy, including therapy with NSAIDs or colchicine for a duration of 1-3 months. Corticosteroids are avoided due to the increased risk of transformation into symptomatic chronic pericarditis and due to the risk of precipitation of the scleroderma renal crisis; they are reserved for refractory cases only [Hung, 2019].

1.6.5.3 Valvular heart disease

There is a low incidence of valvular disease in SSc; the most common valve anomaly is a nodular thickening of the mitral and aortic valves, which can be associated with valve regurgitation, which is usually not hemodynamically significant. However, with an increasingly ageing population, SSc patients may also develop aortic stenosis, the diagnosis of which may be confused by multifactorial dyspnea [Hung, 2019].

1.6.5.4 Conduction abnormalities

Arrhythmias are common in SSc patients: approximately 25-75% of patients with SSc present with an abnormal electrocardiogram [Muresan, 2016]. Arrhythmias are associated with poor prognosis and represent 6% of the overall causes of death in the EUSTAR database [Tyndall, 2010]. The most common electrophysiological abnormalities include premature ventricular beats, PR prolongation, left anterior fascicular block and intraventricular conduction defects [Vacca, 2014].

Arrhythmias and conduction abnormalities are believed to be the result in part of conduction system fibrosis [Lubitz, 2008] and, above all, of myocardial damage and fibrosis [Follansbee, 1985]: an autopsy study, in fact, showed that the conduction system is relatively spared from the myocardial changes observed in patients with systemic sclerosis, and therefore it has been hypothesized that conduction disturbances are a consequence of damaged myocardium rather than damage to conduction tissue [Ridolfi , 1976]. Atrial and ventricular tachyarrhythmias result from myocardial fibrosis, while conduction defects and bradyarrhythmias are a consequence of conduction system fibrosis [Varga, 2012].

In a study by Ferri [Ferri, 1985], rhythm disturbances were demonstrated in 30% of patients, but when 24-hour ECG Holter monitoring was performed, supraventricular arrhythmias were documented in 66% of SSc patients and ventricular arrhythmias were found in 90%, with multiform premature ventricular beats in 40%, paired ventricular tachycardia sequences in 28%, and one or more ventricular tachycardia sequences in 13%. Despite the widespread occurrence of ventricular arrhythmias, sudden cardiac death is not very common in SSc: a large

observational study reported sudden cardiac death in 18 (5%) of 391 deaths occurring in 1258 patients with SSc [Follansbee, 1993].

Supraventricular arrhythmias are considered more common in SSc patients, occur in about two-thirds of cases and are much more frequent than ventricular tachyarrhythmias [Clements, 1981.

Conduction anomalies occur in one fifth to one third of patients with systemic sclerosis [Roberts, 1981]: the most common are branch blocks, followed by first-degree atrioventricular blocks. High-grade atrioventricular blocks are rare [Roberts, 1981]. Also, in the study by Ferri [Ferri, 1985], the resting ECG showed conduction defects in 19% of cases and ST-T alterations in 5%. Additionally, this prevalence increased to 34% for ST-T changes and 33% for AV block when 24-hour Holter monitoring was performed. A prolongation of the QTc interval has also been reported, which can lead to life-threatening tachyarrhythmias [Morelli, 1996].

Cardiac diagnostic workup in SSc patients to investigate possible electrical involvement is described. The standard 12-lead ECG and Doppler echocardiography should be performed routinely in all SSc patients, even if the patient is asymptomatic. If the patient complains of palpitations, syncope or dizziness, the following steps should include exercise testing, tilt-table testing and 24-hour Holter ECG monitoring [Vacca, 2014].

The patient should also be questioned about the presence of systemic diseases that can be associated with arrhythmias, such as chronic obstructive pulmonary disease, hyperthyroidism, pericarditis and congestive heart failure. Furthermore, in SSc, various complications could favour arrhythmias, such as life-threatening infections linked to severe intestinal motility disorders or electrolyte imbalances due to involvement of the intestine or kidneys [Gyger, 2013].

Invasive electrophysiological studies are indicated in patients with atrioventricular block, intraventricular conduction disturbances, sinus node dysfunction, tachycardia and unexplained syncope or palpitations [Seferovic, 2006].

Treatment protocols should follow general cardiology guidelines for the management of different forms of arrhythmias [Varga, 2012].

Chapter II. The interaction of cardiovascular disease risk factors with DMARDs on aortic stiffness progression in rheumatoid arthritis patients

2.1 Introduction

Rheumatoid arthritis is a chronic immune-mediated and inflammatory disease characterized by a 48% increased risk of cardiovascular (CVD) events and a 50% higher incidence of CVD-related mortality compared with the general population [Aviña-Zubieta, 2008; Aviña-Zubieta, 2012]

There is growing evidence that increased arterial stiffness may account for the excess risk of CVD in RA [Klocke, 2003; Prati, 2014; Moroni, 2017; Kotani, 2017; Gonzalez-Gay 2008; Bordy, 2018]. Arterial stiffness is one of the earliest detectable manifestations within the atherosclerotic vessel wall [Cavalcante, 2011; Cohn, 2004], and it acts as a strong independent predictor of CVD events and all-cause mortality in various populations [Vlachopoulos, 2010]. When structural and functional changes of the elastic fibres within the arterial wall occur, arteries progressively lose their low-stretch bearing component, longitudinal elasticity and geometry, leading to collagen deposition with decreased elasticity and stiffness, elongation and increased tortuosity [Segers, 2020]. While this phenomenon is strictly related to ageing, it can also be accelerated with increased CVD risk factors and inflammation (early vascular ageing). Arterial stiffness eventually results in higher driving pressures and increased energy demands for the heart while leading to higher diastolic-systolic pressure differences (i.e., widening of pulse pressure). Increased arterial pressures and pulsatility impose higher mechanical stress on the vessels and organs, leading to strong associations between arterial stiffness and organ damage in the heart, kidney, or brain [Chirinos, 2019].

With the aorta being the major elastic vessel in the body, aortic stiffness likely represents the most informative measurement of arterial stiffness [Chirinos, 2019]. Amongst the several principles, techniques and devices that have been proposed

to measure arterial stiffness in humans, Doppler-echocardiography is one of the cheapest, fast, widely available and reliable methods to assess aortic stiffness. Moreover, it can be easily integrated into a routine echocardiography assessment.

Aortic stiffness was significantly increased in RA patients [Tam, 2018; Kocabay, 2012; Provan, 2011], and it was associated with worse CVD outcomes [Cioffi, 2016]. Interestingly, treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) or tumor-necrosis factor inhibitors (TNFi) appeared to be the effective strategy to improve aortic stiffness in early RA patients [Tam, 2018; Tam, 2012; Plein, 2020].

Most clinical trials have been successful at demonstrating a beneficial effect of csDMARDs and TNFi on CVD outcomes in RA of short duration [Burggraaf, 2019; Bissell, 2016; Charles-Schoeman, 2017] when CVD risk profile is still favourable, and inflammation is at its highest. However, patients with RA are subject to a great accumulation of CVD risk factors in a disproportionate manner than the general population, and this can happen even when RA patients receive long-term therapy with good outcomes in terms of disease activity control [Mortimer, 2019; Jafri, 2017; Sugiyama, 2010; England, 2020]. In such patients with longstanding and established disease, whether csDMARDs and TNFi can still have an effect on aortic stiffness is largely unknown. This knowledge could encourage retention of csDMARDs or TNFi for their CVD benefit beyond the control of inflammation.

2.2 Aim of this study

The aim of this study was to comparatively describe aortic stiffness progression in longstanding and established RA patients treated with csDMARDs or TNFi. The hypothesis was that TNFi could halter the progression of aortic stiffness whereas csDMARDs not.

2.2.1 Primary objective

The primary objective was to show the different progression of the aortic stiffness index in a group of patients treated with TNFi compared to those treated with csDMARDs.

2.2.2 Secondary objectives

The secondary objectives were to determine the interplay between CVD risk factors and the TNFi and csDMARDs on aortic stiffness progression.

2.3 Methods

2.3.1 Core design

The *Cardiovascular ASsessment of IMmune Inflammatory Rheumatic disOrders* (CASIMIRO) was a prospective observational study started in 2014 at the Division of Rheumatology, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona (Italy) as a primary CVD prevention program and a broad cardiovascular investigation of RMDs patients diagnosed with chronic inflammatory arthritis (RA, psoriatic arthritis and spondyloarthritis), SLE and SSc.

The CASIMIRO study comprised an assessment of CVD risk factors and a TTE of RMDs patients without signs of overt CVD. All participants underwent an evaluation of CVD risk factors and were offered a TTE study during the recruitment period.

All participants underwent a standard TTE study performed by a single experienced cardiologist, who was blind to clinical and laboratory data of subjects. On the same day of the TTE examination, a detailed CVD and rheumatological history and assessment were obtained. All recruited patients underwent a clinical evaluation by senior rheumatologists, including assessments of disease activity, disease duration, body weight and height, medical history and CVD and RA medications.

Laboratory tests including inflammatory markers, serology, lipids and glucose levels were performed within two weeks before or after aortic stiffness assessment. Follow-up and instrumental assessments were performed yearly thereafter.

2.3.2 Ethics

The study was approved by the institutional review board of the University of Verona (1707CESC) and conformed to the ethical guidelines of the Declaration of Helsinki as revised in 2000. All patients gave written informed consent signing a specific institutional consent form.

2.3.3 Study population

We recruited non-institutionalized individuals >18 years of age affected with RMDs and referred them to our outpatient clinics in the Division of Rheumatology, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona (Italy). The inclusion and exclusion criteria are reported in

Table 3.

Table 3. Inclusion and exclusion criteria of the CASIMIRO study.

Inclusion criteria:

1. Age > 18 and < 75 years
2. Diagnosis of RMDs:
    a. Diagnosis of rheumatoid arthritis according to the 2010 ACR/EULAR definition [Aletaha, 2010], or
    b. Diagnosis of systemic lupus erythematosus according to the 1997 ACR criteria [Hochberg, 1997], or
    c. Diagnosis of systemic sclerosis according to the 2013 ACR/EULAR [van de Hoogen, 2013]
3. Informed consent

Exclusion criteria:

1. Previous cardiovascular disease diagnoses, events, or procedures (any known cardiovascular disease including myocardial infarction, stroke, coronary revascularization, transient ischemic attack, hospitalization for unstable angina, peripheral artery disease, symptomatic carotid artery disease)
2. Uncontrolled systemic arterial hypertension
3. Diabetes mellitus
4. Pulmonary hypertension
5. Cardiac arrhythmia, PM or ICD
6. More than three cardiovascular disease factors among systemic hypertension, family history of coronary artery disease, smoking, hypercholesterolemia
7. Life expectancy < 2 years for any cause
8. Congenital heart disease
9. Primitive cardiomyopathy
10. Valvulopathies
11. End-stage renal disease
12. Left ventricular ejection fraction < 35%
13. Patients who had started CVD or RA medications within six weeks from the first visit

ACR, American College of Rheumatology; CVD, cardiovascular disease; EULAR, European League Against Rheumatism; ICD, implantable cardiac defibrillator; RMDs, rheumatic musculoskeletal diseases.

2.3.4 Study protocol and outcomes

In this first analysis, we included only patients with a diagnosis of RA according to the 2010 ACR/EULAR definition (inclusion criteria 2a). Furthermore, we consulted medical notes to assess whether significant changes in medications had been recorded so that all patients who did not change DMARD treatment during follow-up were selected for the study. Participants were consecutively screened and recruited from March 2014 to March 2016. All recruited patients underwent a clinical evaluation by senior rheumatologists, including assessments of disease activity, disease duration, body weight and height, medical history and CVD and RA medications. Recruited patients were then referred for aortic stiffness assessment that was performed within two weeks. Laboratory tests including inflammatory markers, serology, lipids and glucose levels were performed within two weeks before or after aortic stiffness assessment. Follow-up assessments at 12 months were performed between March 2015 and March 2017.

2.3.4.1 Primary outcome

The primary outcome was the comparison of the aortic stiffness index in the TNFi and csDMARDs groups at follow up.

2.3.4.2 Secondary outcomes

The secondary outcome was the interaction between treatment groups and CVD risk factors on the aortic stiffness progression.

2.3.5 Study procedures

2.3.5.1 Aortic stiffness assessment

Aortic stiffness was evaluated by Doppler-echocardiography. All Doppler-echocardiographic studies were performed by an expert sonographer using an Alpha Esaote Biomedica machine (Florence, Italy) equipped with a 2.5–3.5 MHz annular-array transducer and following a standardized protocol. Images were stored on compact disks or magneto-optical disks and forwarded for final interpretation to a senior cardiologist blinded to the identity of the subject. Aortic stiffness was assessed at the level of the aortic root, using a two-dimensional

guided M-mode evaluation of systolic (AoS) and diastolic (AoD) aortic diameters, 3 cm above the aortic valve together with blood pressure measured by cuff sphygmomanometer. AoD was obtained at the peak of the R wave at the simultaneously recorded electrocardiogram, while AoS was measured at the maximal anterior motion of the aortic wall [Nistri, 2008; Stefanadis, 1990]. For each diameter, five measurements were averaged. Values of SBP, DBP, AoS and AoD were used to calculate the aortic stiffness index (AoSI) using the following validated formula:

$$AoSI = \frac{ln\left(\frac{SBP}{DBP}\right)}{(AoS - AoD)} / AoD$$

Intraclass correlation coefficient (ICC) with a two-way random model was used to assess the absolute reliability of aortic diameters and BP measurement in 50 patients. ICC values (95% CI) were 0.91 (0.86-0.94) for AoS, 0.93 for AoD, 0.92 for SBP and 0.94 for DBP respectively. ICC for calculated AoSI was 0.92.

2.3.5.2 CVD risk assessment

The following CVD risk factors were collected: age; gender; systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were measured at the end of echocardiographic evaluation in supine position; weight and height with the calculation of body mass index (BMI); lipids including total cholesterol, low-density cholesterol and high-density cholesterol, and triglycerides; waist circumference; renal function; and smoking status. We defined obesity when body mass index (BMI) ≥ 30 kg/m2. Dyslipidemia was defined as levels of total serum cholesterol >190 mg/dL and or triglycerides >150 mg/dL or pharmacologically treated high lipid serum levels. Systemic arterial hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or medically treated hypertension. To assess renal function, we considered the glomerular filtration rate (GFR) estimated with the CKD-EPI equation [Levey, 2009] and defined renal dysfunction as estimated GFR < 60 ml/min 1.73 m^2.

2.3.5.3 RA-disease activity assessment

Data on disease duration, anti-citrullinated peptides antibodies (ACPA) and rheumatoid factor (RF) were collected. Serum biomarkers of RA-related inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) were measured. RA disease activity was evaluated by the clinical disease activity index (CDAI) score [Aletaha, 2005] and disease-activity score in 28-joints (DAS28) [van der Heijde, 1990]. Patients were defined as having remission, low, moderate or high disease activity according to CDAI values. Current immunomodulating agents, including conventional synthetic DMARDs and biologic DMARDs, glucocorticoid use and dose (in prednisone-equivalent milligrams daily), and NSAIDs use were recorded.

2.3.5.4. Serum lipids and fasting glucose

In addition to inflammatory markers and serostatus, the following blood tests were performed in local laboratories: total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol, tryglicerides (TG), and serum fasting glucose (SFG).

2.3.6 Statistical analysis

Continuous data are reported as mean values ± standard deviation (SD) or absolute numbers (percentage) for categorical variables. Treatment group comparisons of categorical variables were performed by chi-squared or Fisher test as appropriate; for continuous variables, independent samples T-test was used. Paired samples T-test was used to determine significant changes from baseline of continuous variables including AoSI, arterial blood pressure, lipids, glucose, inflammatory markers and RA disease activity scores. Treatment group comparisons of follow-up AoSI were performed in the whole study population using two-way analysis of covariance (ANCOVA) with Sidak's correction for multiple comparisons, with treatment group and the number of CVD risk factors categorized into three groups (0-1, 2-3, or >3) as factors, and baseline AoSI, age and SBP as covariates. The choice of covariates was made upon prior data from our study [Cioffi, 2016]. All analyses were performed using the statistical package

SPSS 22.0 (SPSS Inc. Chicago. Illinois), and statistical significance was identified by two-tailed $p < 0.05$. Figures were obtained using the GraphPad Prism software version 7.00.

2.4 Results

2.4.1 Baseline characteristics of csDMARDs and TNFi patients

The study population consisted of 107 white RA individuals, 43 patients in the csDMARDs group and 67 in the TNFi group. The TNFi group included RA patients with an inadequate response to csDMARDs (80%) or unable to tolerate csDMARDs (20%).

All patients had established RA and disease duration longer than two years. Most patients (74%) were in remission or low-disease activity, while disease activity was moderate only in 26% and high in none. High values of ESR (>40 mm/h) or CRP (>10 mg/L) were found in 11.8% and 8% only, respectively. Excluding age and sex, 92% of RA patients had at least one CVD risk factor, 58% two or more and 26% three or more. There were more than two CVD risk factors in 28.6% of csDMARDs and 29.0% of TNFi groups, respectively (p=0.469). Patients in the csDMARDs and TNFi groups were equally balanced for the proportion of CVD risk factors and medications, and there were no significant differences in baseline SBP, DBP, or serum lipids. The proportions of patients taking angiotensin-converting enzyme and angiotensin II receptor blockers, calcium channel antagonists, diuretics or beta-blockers were not significantly different between the two groups. With regard to RA characteristics, the two groups differed only for greater use of hydroxychloroquine in the csDMARD group (

Table 4).

Table 4. Baseline characteristics of the study population.

Variables	csDMARDs (n=43)	TNFi (n=64)	P-value
Cardiovascular disease risk factors			
Age, median years (IQR)	58.6 (53.0, 66.0)	58.1 (49.3, 67.0)	0.839
Female sex	33 (76.7)	54 (84.4)	0.321
Obesity	5 (11.6)	7 (10.9)	0.999
Hypertension	19 (44.2)	30 (46.9)	0.784
Anti-hypertensive drug	17 (39.5)	28 (43.8)	0.784
Smoking status, ever	18 (42.9)	30 (46.9)	0.684
Dyslipidemia	30 (40.2)	34 (59.8)	0.085
Current statin use	13 (34.2)	10 (15.9)	0.033
Diabetes mellitus	3 (7.0)	3 (4.7)	0.676
Anti-diabetic medication	1 (2.3)	1 (1.5)	0.999
CVD risk factors, median (IQR)	2 (1, 3)	2 (1, 3)	0.199
Rheumatoid arthritis characteristics and treatment			
RF and/or ACPA positive	28 (65.1)	33 (51.6)	0.165
Disease duration, median years (IQR)	14.1 (11.5)	15.4 (10.5)	0.538
Methotrexate	38 (88.4)	52 (81.3)	0.192
Leflunomide	5 (17.9)	12 (19.0)	0.999
Hydroxychloroquine	9 (31.0)	5 (7.8)	0.009
Prednisone > 5 mg daily	7 (7.7)	5 (5.5)	0.823
NSAIDs	6 (20.7)	22 (34.4)	0.227

ACPA, anti-citrullinated peptides antibodies; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; TNFi, tumour necrosis factor inhibitors. All data reported as absolute numbers (percentage) otherwise specified. P-value refers to Chi-squared or Fisher test for categorical variables or independent samples T-test for continuous variables.

2.4.2 Decreased aortic stiffness with TNFi compared to csDMARDs

The two groups did not differ significantly for baseline AoSI (5.95±3.73% vs 6.08±4.20%, p=0.867). However, follow-up AoSI was significantly increased in the csDMARDs group (mean difference 1.00%, 95% CI 0.59, 1.42; p<0.0001) but not in the TNFi group (mean difference 0.15%, 95% CI -0.28, 0.60, p=0.477). Patients on TNFi had significantly lower follow-up AoSI than the csDMARD group (6.11±0.18% vs 7.13±0.22%; adjusted mean difference, aMD -1.02, 95% CI -1.581, -0.457, p<0.001; ANCOVA).

2.4.3 Interaction of treatment and CVD risk factors on aortic stiffness

There was a statistically significant two-way interaction between the treatment group and the number of CVD risk factors on AoSI at follow-up, whilst controlling for baseline AoSI, age, and SBP ($p<0.0001$, $\eta^2=0.038$). Follow-up AoSI was lower in the TNFi compared to the csDMARDs group (Figure 3) both when CVD risk factors were 1-2 (aMD -1.143, 95% CI -2.102, -0.185, p=0.019) and when CVD risk factors were more than two (aMD -4.806, 95% CI -6.128, -3.484, $p<0.001$). We also compared the effect on aortic stiffness of TNFi and csDMARDs therapy across RA patients according to the presence of the most prevalent CVD risk factors in our study population: hypertension, dyslipidemia, and smoking. Adjusted AoSI means at follow-up were significantly higher than baseline in the csDMARDs group but not in the TNFI group (Figure 4).

2.4.4 Changes in lipids, glucose and blood pressure induced by DMARD therapy

Overall, favourable changes in lipids and glucose after DMARD therapy were found (Table 5). There was a significant reduction in TC, VLDL, LDL and HDL in the csDMARDs group. SFG was reduced both in the csDMARDs and TNFi groups. However, blood pressure (both SBP and DBP) was significantly increased in the csDMARDs group, whereas DBP was significantly decreased in the TNFi group. We found no significant correlations between changes in AoSI and serum lipids, glucose, or arterial blood pressure.

Table 5. Longitudinal changes in CVD risk factors and RA disease activity according to the treatment group.

	csDMARDs			TNFi		
	Baseline	**12-months**	**P-value**	**Baseline**	**12-months**	**P-value**
Cardiovascular disease risk factors						
TGL	123 (68)	114 (50)	<0.001	113 (48)	106 (46)	0.023
LDL	122 (32)	112 (19)	<0.001	125 (26)	126 (30)	0.535
HDL	69 (12)	66 (10)	<0.001	74 (22)	74 (19)	0.609
TC	212 (3)	200 (19)	<0.001	221 (30)	218 (38)	0.161
SFG	88 (8)	85 (15)	<0.001	94 (13)	91 (11)	0.001
SBP	130 (19)	135 (19)	<0.001	136 (19)	135 (21)	0.152
DBP	80 (10)	83 (11)	<0.001	86 (10)	82 (10)	<0.001
BMI	25.5 (4.5)	25.5 (4.5)	0.442	25.6 (4.1)	25.6 (4.1)	0.226
Rheumatoid arthritis disease activity						
ESR	20 (20)	16 (17)	<0.001	20 (17)	19 (14)	0.001
CRP	5.7 (8.2)	4.6 (8.7)	<0.001	2.40 (2.51)	2.49 (2.15)	0.410
CDAI	10 (10)	10 (10)	0.173	9 (7)	11 (10)	<0.001
DAS28	2.05 (1.35)	2.54 (1.36)	0.002	2.64 (0.77)	2.81 (1.23)	0.108

AoSI, aortic stiffness index; BMI, body mass index, CDAI, clinical disease activity score index; CRP, c-reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, disease activity score-28; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; HDL; high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SFG, serum fasting glucose; TC, total cholesterol; TGL, triglycerides; TNFi, tumour necrosis factor inhibitors. All data reported as mean (standard deviation). P-value refers to paired samples t-test comparisons between values at baseline and 12-months.

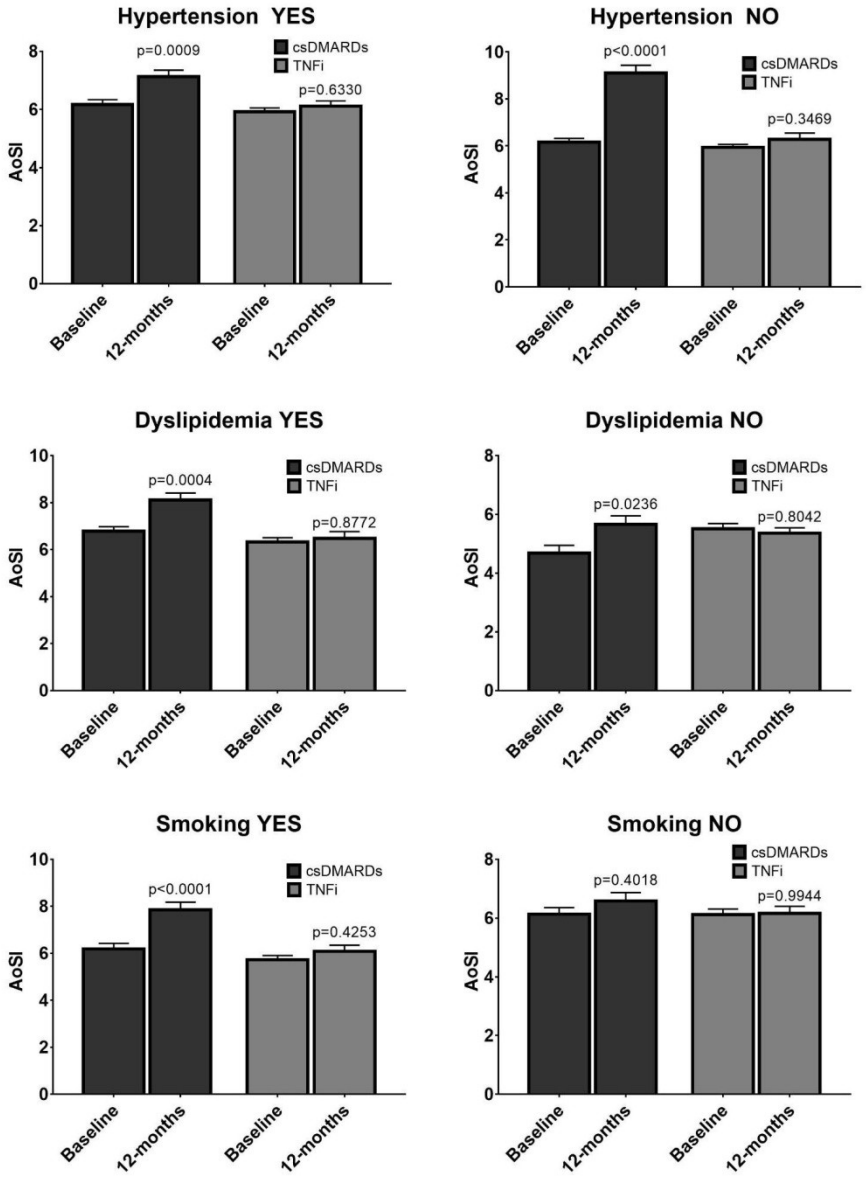

Figure 3. Follow-up aortic stiffness index (AoSI) values according to the treatment group and cardiovascular disease risk factors.

Grouped bar charts representing means (bars) and standard errors of the mean (vertical error bars) of follow-up aortic stiffness index (AoSI) values according to treatment group and cardiovascular disease risk factors.

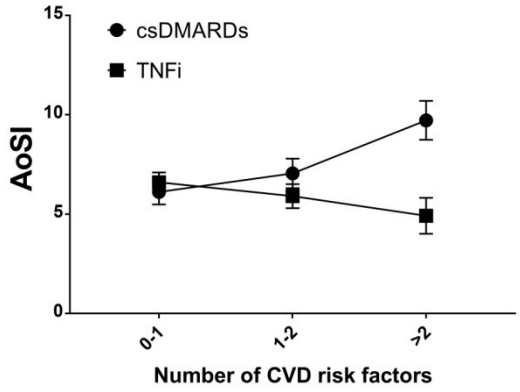

Figure 4. Interaction between treatment and cardiovascular disease risk factors on the aortic stiffness index.

2.5 Discussion

The original finding of this study shows that arterial stiffness progression can be hampered by TNFi not only in early but even in long-standing RA. Those individuals show a greater number of CVD risk factors than early RA patients [England, 2013] and higher CVD mortality than the general population [Aviña-Zubieta, 2012]. Hence, control of CVD risk in such patients is the most important outcome to achieve, along with control of disease activity.

Prior studies on the effect of TNFi on arterial stiffness focused on early RA patients with short disease duration and relatively low CVD risk. We noticed favourable effects in terms of reduction of aortic stiffness with TNFi compared to csDMARDs in a cohort of patients with several CVD risk factors. TNFi can reduce endothelial dysfunction and reduce carotid intima-media thickness [Del Porto, 2007]. Skin microvascular responses assessed by laser Doppler imaging improved in patients with active RA and no previous history of CVD who responded to TNFi or MTX [Galarraga, 2010]. Short-term treatment with TNFi also increased circulating endothelial progenitor cells concurrently with a proportional decrease of disease activity [Spinelli, 2013]. Our results, along with the previous evidence, are consistent with the hypothesis that the vascular-

protective effect could be effectively achieved by inhibition of TNF [Giollo, 2018].

The effect of TNFi on arterial stiffness in RA was deemed to be independent of the reduction of systemic inflammation in patients with very high disease activity [Plein, 2020]. Herein, the proportion of patients with high disease activity was very low; hence we provided further evidence that the beneficial effect of TNF-alpha inhibition on arterial stiffness goes beyond the DMARDs-associated reduction of systemic inflammation. Indeed, we also found no association between inflammatory markers or disease activity scores and aortic stiffness. However, the relationship between disease activity and AoSI was difficult to ascertain as all changes in disease activity scores were subtle and non-clinically meaningful, as they did not lead to treatment changes.

The third result of our study is that TNFi may be more beneficial than csDMARDs in the presence of some CVD risk factors such as hypertension, dyslipidemia and smoking. Although traditional CVD risk factors alone do not explain the heightened risk of CVD in RA [Del Rincon, 2001], a meta-analysis confirmed hypertension, type 2 DM, smoking, and hypercholesterolemia as key traditional factors increasing the risk of CVD in RA [Baghdadi, 2015]. Hence, we analysed changes in aortic stiffness according to the presence of each of these CVD risk factors, except for DM due to the scarcity of patients with DM in our study population.

There was a sharp cardiovascular benefit of TNFi over csDMARDs in hypertensive RA patients. Moreover, TNFi therapy significantly decreased DBP values at follow up, while SBP and DBP were both increased in the csDMARDs group. Essential hypertension was reported in up to 57% of patients with RA and can predict CVD events [HR 3.67, 95% CI 2.0, 6.4, p = 0.001] [Innala, 2011]. Several small studies support the potential BP-lowering effect of TNFi in RA patients [Klarenbeek, 2010]. Nonetheless, in a US epidemiological study of RA patients, treatment with TNFi did not reduce the risk of incident hypertension compared with non-bDMARDs [Desai, 2016]. Interestingly, we showed that TNFi decreased AoSI and DBP also in normotensive RA patients, suggesting that the

main driver of decreased BP is the TNFi-mediated favourable effect on arterial stiffness.

Patients with RA and dyslipidemia on TNFi also showed reduced arterial stiffness. Moreover, one year of therapy with TNFi did not increase blood lipids, a finding that is in line with a meta-analysis of 25 RCTs of patients with chronic inflammatory arthritis that failed to demonstrate an effect of TNFi on TC, HDL-C, and LDL-C [Souto, 2015]. Similar results were obtained by a recent RCT investigating the cardiovascular safety of tocilizumab against etanercept [Giles, 2020]. Conversely, there was a significant reduction of lipids with csDMARDs despite worse results on the progression of aortic stiffness, suggesting that arterial stiffness in RA may be scarcely associated with serum lipid levels. This finding can be partially explained by the higher number of patients taking HCQ in the csDMARD group. Although HCQ confers limited efficacy on disease activity and progression of RA, HCQ increases HDL and reduces levels of TC, LDL-C, and triglycerides [Rempenault, 2018]. Additionally, we noticed decreased glucose across treatment groups, consistent with the lower incidence of diabetes with the use of HCQ [Rempenault, 2018; Solomon, 2011] or TNFi [Solomon, 2011] among RA patients.

Finally, we showed an effect on arterial stiffness of TNFi therapy in smokers. Cigarette smoking is the strongest known lifestyle or environmental risk factor for RA [Sugiyama, 2010; Klareskog, 2006; Karlson, 2010; Makrygiannakis, 2008] and RA treatment failure [Saevarsdottir, 2011]. Moreover, smoking can damage the vascular wall, possibly leading to impaired prostacyclin production and enhanced platelet-vessel wall interactions [Nowak, 1987]. This can reduce the elastic properties of the aorta, resulting in stiffening and trauma to the wall [Christodoulos, 1997]. Smoking, as well as passive exposure to smoke, impairs endothelium-dependent vasodilation of normal coronary arteries and reduces coronary flow reserve [Celermajer, 1996; Barua, 2001; Sumida, 1998; Kaufmann, 2000; Celermajer, 1993]. Smoking can also potentiate the endothelial dysfunction induced by hypercholesterolemia [Johnson, 2010].

2.6 Study limitations and strengths

The main strength of this study consists of including a real-life cohort of RA patients with longstanding disease, several CVD risk factors and stable treatment. This kind of patient represents most patients we manage daily in our outpatient clinics. We used a prospective design, stringent entry criteria, and a reliable method for the assessment of aortic stiffness, which could be easily implemented in clinical practice.

With regard to study limitations, we have to underline the relatively small sample size and the cross-sectional design of the study (patients were not randomized for treatment arms). Disease activity and lifestyle modifications are difficult to evaluate outside a clinical trial, but the vast majority of patients had stable disease activity, and behavioural changes were very rare and of minimal clinical impact. Furthermore, we certainly cannot draw conclusions on RA patients on non-TNFi biologics as they were not included. Moreover, we could not substantiate a reduction of CVD events in RA patients with decreased arterial stiffness as the study was not powered for this outcome. Finally, smoking status was recorded as a binomial variable (ever vs never), and the number of pack-years was not calculated.

Chapter III. Left ventricular hypertrophy is overly represented in women with rheumatoid arthritis

3.1 Introduction

Rheumatoid arthritis is a systemic, immune-mediated disease involving both musculoskeletal and extra-articular domains. CVD is one of the most common extra-articular manifestations of RA, which can manifest early with abnormalities in left ventricular (LV) geometry and LV hypertrophy (LVH) [Rudominer, 2009; Giles, 2010]. In particular, concentric LV remodelling is common among RA patients. This association remained significant after adjustment for CVD risk factors and comorbidities [Myasoedova, 2013], suggesting that RA-intrinsic factors could be significantly related to the susceptibility of LVH.

LVH is a risk factor for coronary heart disease (CHD) and poor CVD outcomes in the general population [Levy, 1990] as well as in several settings of patients at increased risk for CVD events [Levy, 1990; Kannel, 1992; Cioffi, 2013; Gerdts, 2015; Sulemane, 2017], including RA patients. Several mechanisms, including long-term pressure, such as systemic hypertension or aortic stenosis, can cause LVH. The findings that LVH may precede hypertension and that patients with similar degrees of hypertension may have marked differences in LV mass strongly suggest that genetic and gender-related factors can promote and retard the development of LVH [Pontremoli, 2000]. Gender also leads to a predisposition to RA. The incidence of this condition is twice higher in females than males, and disease severity or treatment response differs according to gender [Favalli, 2019]. However, it is unknown whether susceptibility to LVH in RA patients is gender-driven.

3.2 Aim of this study

In this study, we sought to test the hypothesis that gender is the RA-associated factor most strictly associated with LVH.

3.2.1 Primary objective

The primary objective was to investigate whether female RA patients have a higher risk than males of progression to LVH.

3.2.2 Secondary objective

The secondary objective was to determine if the specificity of gender is an independent risk factor for LVH.

3.3 Methods

3.3.2 Core design and ethics

The study core design and ethics are illustrated in Chapter 2.

3.3.3 Study population

The study population included non-institutionalized subjects > 18 years of age with RA diagnosed according to the 2010 ACR/EULAR classification criteria. The design of the study was observational prospective. Participants were consecutively recruited from March 2014 to March 2016 at the Division of Rheumatology, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona (Italy).

3.3.4 Study protocol and outcomes

For this sub-study, we analysed patients who had data on clinical, laboratory and echocardiographic evaluations performed at baseline and at the longest available follow-ups (median 36 [24-50] months). To overstate the differences between RA patients with the LVH phenotype and those without, considering the changes in LV mass over time, we divided patients into two groups according to the LVH status at follow-up compared to baseline. Accordingly, we defined “LVH” for all participants who had LVH at follow up, irrespective of LVH status at baseline. Thus this group comprised patients with persistent and de novo LVH. Conversely, the “non-LVH” group included individuals who had no LVH at follow-up, hence,

including both patients who had no LVH at baseline and follow-up and those in whom LV mass normalised over time.

3.3.4.1 Primary outcome

The primary outcome was the comparison between the proportion of RA men and women with LVH at follow-up.

3.3.4.2 Secondary outcomes

The secondary outcome was the independent association of gender with LVH at follow-up.

3.3.5 Study procedures

3.3.5.1 Echocardiography

All participants underwent a TTE examination performed by an experienced cardiologist who had no information regarding the patients' clinical and laboratory data. On the same day of the echocardiographic examination, a thorough cardiovascular and dietary anamnesis was collected. A standard ECG was also performed for all patients in the study. Doppler-echocardiographic studies were performed using Alpha Esaote Biomedica (Florence, Italy), following a standardised protocol by experienced cardiologists, with the patient in the left lateral decubitus position. Each echocardiographic examination comprised at least two digital recordings of 2D apical 4-chamber, 2-chamber, and 3-chamber views (each recording containing two cardiac cycles). All echocardiographic images were obtained with a frame rate > 60 frames per second. Echocardiographic exams were saved to a hard disk (as DICOM files) for off-line blinded reading.

LV chamber dimensions and wall thicknesses were measured according to the American Society of Echocardiography guidelines, and LV mass was calculated using a validated formula [Devereux, 1986]. LV mass was normalised for height to the 2.7 power, and LV hypertrophy was defined as LV mass > 49.2 g/m2.7 for men and > 46.7 g/m2.7 for women [de Simone, 1995]. Relative wall thickness was calculated as the ratio 2*end-diastolic posterior wall thickness/LV diameter

and indicated concentric LV geometry if > 0.43 (the 97.5 percentile in a normal population) [de Simone, 2005].

LV end-diastolic and end-systolic volumes were measured by the biplane method of disks from 2D apical 4 and 2 chamber view and used to calculate LV ejection fraction (LVEF). Volumetric measures were indexed to body surface area.

Assessment of LV diastolic function was based on widely-accepted diastolic function parameters (E/A ratio and medial mitral annulus early diastolic velocity e'), and LV diastolic dysfunction was diagnosed using validated cut-offs of prognostic relevance, as previously reported [Nagueh, 2016]. Right ventricular function was assessed by means of the tricuspid annular systolic velocity and estimation of pulmonary pressures. Finally, the presence or absence of valvular heart diseases was evaluated.

3.3.5.2 CVD risk assessment

The following CVD risk factors were collected: age; gender; systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were measured at the end of echocardiographic evaluation in supine position; weight and height with the calculation of body mass index (BMI); lipids including total cholesterol, low-density cholesterol and high-density cholesterol, and triglycerides; waist circumference; renal function; and smoking status. We defined obesity when body mass index (BMI) ≥ 30 kg/m2. Dyslipidemia was defined as levels of total serum cholesterol >190 mg/dL and or triglycerides >150 mg/dL or pharmacologically treated high lipid serum levels. Systemic arterial hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or medically treated hypertension. To assess renal function, we considered the glomerular filtration rate (GFR) estimated with the CKD-EPI equation [Levey, 2009] and defined renal dysfunction as estimated GFR < 60 ml/min 1.73 m^2.

3.3.5.3 RA-disease activity assessment

Data on disease duration, anti-citrullinated peptides antibodies (ACPA) and rheumatoid factor (RF) were collected. Serum biomarkers of RA-related inflammation (CRP and ESR) were measured. RA disease activity was evaluated

by the clinical disease activity index (CDAI) score and disease-activity score in 28-joints (DAS28). Patients were defined as having remission, low, moderate or high disease activity according to CDAI values. Current immunomodulating agents, including conventional synthetic DMARDs and biologic DMARDs, glucocorticoid use and dose (in prednisone-equivalent milligrams daily), and NSAIDs use were recorded.

3.3.6 Statistical analysis

Data are reported as mean values ± standard deviation (medians and interquartile ranges for non-normally distributed variables) or percentages. Between-group comparisons of categorical and continuous variables were performed by $\chi 2$ test and independent samples Student's T-test, as appropriate. The study population was stratified by LVH at follow up. Longitudinal changes of echocardiography measures were analysed with the paired-sample T-test. Cox regression was run to identify the factors independently related to LVH. Variables that were significantly related to LVH at follow-up in univariable tests ($p < 0.05$) were included in the multivariable logistic regression analysis. In order to avoid overfitting, only the following variables were included in the multivariable model: sex, age, BMI and SBP. Log cumulative hazard functions were computed by univariate and multivariate Cox proportional hazards analyses to identify the prognosticators of LVH. All analyses were performed using the statistical package SPSS 20.0 (SPSS Inc. Chicago. Illinois), and statistical significance was determined by two-tailed $p < 0.05$.

3.4 Results

3.4.1 Patient disposition

The study population consisted of 145 white RA patients consecutively enrolled in the study with >1 follow up visit. Treatment included methotrexate in 48%, bDMARDs in 59%, and glucocorticoid therapy in 58% (90% of patients were taking prednisone-equivalent ≤ 5 mg daily); nearly one-third were exposed to NSAIDs occasionally during the three months before baseline, but none were

chronic NSAIDs users. Disease activity was moderate or high in 38%. Patients had a median of 2 CVD risk factors, and at least one was present in 92%. A history of current or prior smoking was found in 44%; hypertension was diagnosed in 40%, of whom 92% were on active treatment; dyslipidemia was present in 66% of whom 41% was on treatment with statins; obese patients were 12%, and metabolic syndrome was diagnosed in 11%; no patient had diabetes mellitus.

3.4.2 Baseline characteristics of RA patients according to gender

Women were also more frequently dyslipidemic and on lipid-lowering than men and had significantly shorter waist circumference (

Table 6). Blood pressure levels and medications did not differ between the sexes. With regard to RA-specific characteristics, disease activity (CDAI) was higher in women who also used MTX less frequently than men. Inflammatory markers (ESR and CRP) did not differ significantly.

Table 6. Baseline characteristics of RA patients according to gender.

Variables	Male RA patients (n=24)	Female RA patients (n=121)	P-value
CVD risk factors			
Age, years	58.0 (46.0)	59.3 (61.0)	0.628
Body mass index, kg/m^2	25.7 (12.3)	24.6 (28.1)	0.493
Waist circumference, cm	98.0 (39.0)	90.0 (80.0)	0.002
Hypertension, %	60.9	46.3	0.199
Systolic blood pressure, mmHg	131.0 (70.0)	130.0 (100.0)	0.873
Diastolic blood pressure, mmHg	80.0 (40.0)	80.0 (50.0)	0.531
Use of antihypertensives, %	63.6	44.2	0.096
ACEi/ARBs	54.5	24.8	0.005
Beta-blockers	21.1	13.6	0.565
Calcium-channel blockers	9.1	7.1	0.999
Smoking status, ever, %	82.6	36.7	<0.001
Dyslipidemia, %	54.2	67.8	0.241
Use of statins, %	18.2	28.4	0.319
Metabolic syndrome, %	16.7	9.9	0.473
eGFR, ml/min/1.73m2	103.5 (12.3)	91.5 (98.0)	0.112
RA-specific characteristics			
C-reactive protein, mg/L	1.6 (20.9)	1.6 (67.7)	0.539
ESR, mm/h	7.8 (72.0)	17.8 (75.0)	0.160
Rheumatoid factor, %	52.4	52.7	0.977
ACPA, %	61.9	54.6	0.539
Disease duration, years	14.0 (33.0)	14.0 (49.0)	0.466
CDAI	5.0 (25.0)	9.0 (41.0)	0.078
Current biologic DMARD use, %	65.2	79.6	0.135
Current MTX use, %	73.9	42.2	0.006
Current glucocorticoid therapy, %	63.6	55.6	0.485
Current NSAIDs use, %	26.1	28.7	0.800

ACEi, ace-inhibitors; ACPA, anti-citrullinated peptide antibodies; ARBs, angiotensin II receptor blockers; CDAI, clinical disease activity index; CRP, c-reactive protein; DMARDs, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; LV, left ventricular; LVH, left ventricular hypertrophy; NSAIDs, non-steroidal anti-inflammatory drugs; TNF, tumor necrosis factor. Data are reported as median (IQR).

LVH was detected in similar proportions (36.4% vs 33.3%, p=0.777) between women and men at baseline. Concentric LV remodelling was found in a non-significantly higher proportion of women compared to men (28.1% *vs* 20.8%; p=0.463). Women had significantly lower LV-EDV and LV-ESV (both p<0.001) and non-significantly lower CI (p=0.096) than men, though all patients had normal LV function and LV volumes. Diastolic dysfunction was found in 26.4% of women and 33.3% of men, respectively (p=0.490).

3.4.3 Female sex is associated with LVH in RA

At follow-up, there were 42/145 RA patients with LVH, of whom 13/45 had new-onset LVH. We found a significantly higher proportion of women who had LVH compared to men (40/121 vs 2/24, 33% vs 8%, p=0.015), and a non-significant higher proportion of new-onset LVH in women than men (12/121 vs 1/24, 9.9% vs 4.2%, p=0.695). More women progressed to or remained with LVH while LVH normalised in a higher proportion of men (Figure 5). Women with RA had significantly decreased LV volumes and slightly reduced LV EF, and significantly increased LVMI (Table 7).

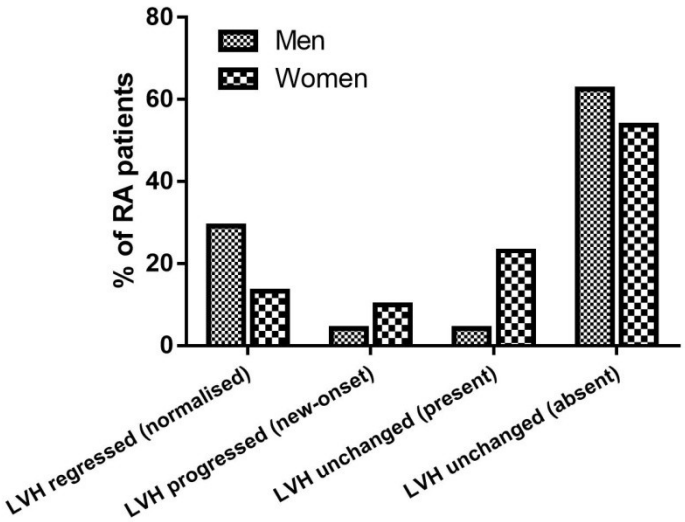

Figure 5. Proportions of RA patients showing LVH regression, LVH progression, and stable LVH at follow-up.

Table 7. Changes in echocardiography measures at follow-up.

	Male RA patients (n=24)					Female RA patients (n=121)				
	Baseline	**Follow-up**	**MD**	**95% CI**	**P-value**	**Baseline**	**Follow-up**	**MD**	**95% CI**	**P-value**
LV EF, %	64.5 (4.7)	62.7 (5.5)	-1.9	-7.8, 4.1	0.476	67.7 (6.4)	62.3 (4.2)	-5.4	-4.5, -0.2	0.030
LVM/BSA, g/m^2	108.9 (19.3)	100.0 (17.9)	-8.9	-0.5, -17.4	0.039	93.4 (20.4)	95.2 (21.6)	1.8	-5.7, 1.9	0.335
LVMi, $g/h^{2.7}$	43.3 (10.5)	43.0 (11.5)	-0.3	-1.4, 2.0	0.737	43.0 (6.7)	46.9 (9.2)	3.9	0.5, 7.3	0.028
LV septum, cm	1.14 (0.13)	1.05 (0.10)	-0.09	-0.03, 0.05	0.661	1.03 (0.15)	0.99 (0.16)	-0.04	-0.06, 0.03	0.571
LV EDD/BSA, cm	2.5 (0.3)	2.5 (0.2)	0.02	-0.06, 0.11	0.604	2.7 (0.3)	2.7 (0.3)	-0.07	-0.1, -0.02	0.009
LV ESD/BSA, cm	1.6 (0.3)	1.5 (0.3)	-0.10	-0.03, 0.23	0.111	1.6 (0.2)	1.7 (0.3)	-0.04	-0.1, 0.02	0.152
LV EDV, mL	103.9 (21.0)	104.2 (25.3)	0.3	-10.1, 9.5	0.951	81.9 (20.9)	76.3 (18.2)	-5.6	-9.4, -1.8	0.004
LV ESV, mL	36.3 (10.1)	39.5 (10.7)	3.3	-8.4, 1.8	0.192	28.8 (14.3)	24.8 (7.7)	-4.0	-6.4, -1.5	0.002
E/A	0.95 (0.28)	0.91 (0.28)	-0.04	-0.05, -0.01	0.331	0.94 (0.32)	0.89 (0.27)	-0.05	-0.0, 0.11	0.071

BSA, body surface area; E/A, ratio between early and late maximal velocity of the left ventricular filling (transmitral flow pattern, pulse wave technique): EDD, end-diastolic diameter; EF, ejection fraction; ESD, end-systolic diameter; LV, left ventricular; LVM, left ventricular mass; LVMi, left ventricular mass index;

We then tested in cox regression analysis whether female sex was independently associated with LVH. In univariable analysis, the female sex had the strongest association with LVH, followed by age, BMI, waist circumference, blood pressure levels, and renal function. In multivariable analysis, female sex was still independently associated with LVH along with BMI and SBP (

Table 8). A second model was run, including only RA-specific factors. CRP was associated with LVH at univariable analysis, but statistical significance was lost after adjusting for gender (

Table 6).

Table 8. CVD-risk factors associated with the presence of LVH at follow-up.

	Univariable			Multivariable		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Female sex	4.162	1.005-17.231	0.049	6.557	1.389-30.963	0.018
Age, years	1.062	1.027-10.097	<0.001	1.038	0.996-1.083	0.079
BMI, kg/m^2	1.086	1.033-1.141	0.001	1.172	1.063-1.292	0.001
Waist circumference, cm	1.016	0.992-1.040	0.187			
Systolic blood pressure, mmHg	1.027	1.013-1.041	<0.001	1.029	1.005-1.054	0.016
Diastolic blood pressure, mmHg	1.037	1.006-1.068	0.017			
Use of antihypertensives	1.720	0.892-3.316	0.106			
ACEi/ARBs	1.078	0.559-2.078	0.822			
eGFR, ml/min/1.73m^2	0.981	0.964-0.999	0.035			
Dyslipidemia	1.024	0.537-1.954	0.942			
Use of statins	0.991	0.481-2.042	0.981			
Metabolic syndrome	1.541	0.680-3.495	0.300			
Smoking history	0.988	0.530-1.840	0.969			

ACEi, ACE-inhibitors; BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate. Univariable and multivariable Cox regression analyses.

Table 9. RA-specific variables associated with LVH.

	Univariable			Multivariable		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Female sex	4.385	1.059-18.160	0.042	5.140	1.238-21.337	0.024
CRP, mg/L	1.025	1.004-1.047	0.022	1.019	0.997-1.041	0.089
ESR, mm/h	1.007	0.993-1.021	0.339			
Rheumatoid factor	1.237	0.647-2.366	0.519			
ACPA	1.383	0.700-2.731	0.351			
Disease duration, years	0.997	0.967-1.028	0.832			
CDAI	1.017	0.981-1.053	0.365			
Current MTX use	0.534	0.272-1.049	0.069			
Current glucocorticoid therapy	1.429	0.712-2.866	0.315			
Current biologic DMARD therapy	0.871	0.352-2.152	0.765			

BMI: body mass index; CRP: C-reactive protein; DBP: diastolic blood pressure; ESR, erythrocyte sedimentation rate; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure. Univariable and multivariable Cox regression analyses.

3.5 Discussion

To our knowledge, the present study is the first one to show that LVH is associated with gender in RA patients. RA has a female predominance, and several gender-specific factors have been associated with the presence of RA and disease activity. Clinical expression of RA varies by sex, with women less likely than men to develop extraarticular features such as subcutaneous nodules and interstitial lung disease [Sokka, 2009; Kelly, 2014]. However, it has never been reported that LVH is more represented in women with RA than men.

While it was already established that RA could impair myocardial structure [Cioffi, 2015], different patterns of heart remodelling across sexes could explain why women with RA progress to LVH more likely than men. We found that women had significantly smaller LV volumes than men at baseline and over time and that LVMI increased during follow-up. We previously showed that patients typically show abnormal concentric LV remodelling compared to matched controls [Lundorff, 2020]. Herein, we observed that this pattern is more characteristic of women. Our findings have clinical relevance since women free of heart disease but with higher LVMI and more LVH at echocardiography are at higher risk of acute myocardial infarction, heart failure and CVD death [Cioffi, 2020].

This association between LVH, changes in LV geometry and gender could be related primarily to non-traditional CVD risk factors that are RA disease-related [Cuspidi, 2014]. Disease duration is independently related to LV mass, suggesting a pathophysiological link between chronic inflammation and LVH [Manrique-Arija, 2021]. An overall greater systemic inflammation due to the disease could justify the larger burden of LVH in women with RA. We observed that women with RA used MTX less frequently than men, and concordantly, higher CRP levels were slightly associated with LVH. Our results agree with other studies reporting that markers of RA chronicity such as disease duration, damage, and CRP are related to LV remodelling [Cioffi, 2015] and LV mass [Crowson, 2018].

Gender is a non-modifiable CVD risk factor. However, BMI was also associated with LVH and independently from gender. Our findings show that bodyweight control is an important outcome in RA patients. In keeping with our observations,

excessive body weight was associated with poor disease control and unfavourable CVD outcomes in RA patients. [Gabriel, 2010]. In patients with well-controlled, established RA, obesity and total fat mass are also associated with more inadequate control of inflammation from diagnosis [Ahlers, 2020].

LVH is usually the response to a chronic pressure or volume load. The two most common conditions associated with LV pressure or volume overload states are systemic hypertension and aortic or mitral valvulopathy. While valvulopathy was an exclusion criterion for this study, half of the study population was hypertensive. Consistent with this, blood pressure levels were significantly associated with LVH at univariable analysis, informing that hypertension is a modifiable CVD risk factor for LVH in RA. However, we believe that the influence of gender on LVH in RA patients was independent of hypertension for several reasons. First, the proportion of hypertensive women with RA was lower than men RA as expected. Second, the use of antihypertensives was not significantly associated with LVH progression, especially ACEi and ARBs, which should be protective. Third, blood pressure levels were not different between groups, suggesting that hemodynamic state at baseline did not differ between women and men. Finally, we observed that 14/54 (26%) women with RA had no hypertension but still progressed to LVH. Hence, we argue that the relationship between the female sex and LVH does not depend on a different hemodynamic response to pressure load in women compared to men.

Therefore, we could not explain the high burden of LVH in RA women with an excess of CVD risk factors. While LVH is also often associated with MetS, dyslipidemia and smoking in the general population, we failed to show similar associations in our RA patients. Nevertheless, there were significant differences between women and men RA patients in terms of those features. Women with RA met the criteria for MetS less frequently and were also far less frequent smokers than men. Females were more frequently dyslipidaemic than males, but we did not find a significant association between LVH and lipids or statin use.

Our findings suggest that RA-intrinsic factors may interact with bodyweight in excess to developing LVH in women with RA.

3.6 Study strengths and limitations

We acknowledge as a limitation that the effect size of gender on LVH should be assessed in an independent cohort since this study was originally conceived as an exploratory study. However, we tried to overcome the limitations of unmeasured confounders by performing multivariate analyses to control for several factors. One strength of this study is the inclusion of a sample of RA patients with established disease, ensuring that our findings can apply to the vast majority of chronic RA patients we routinely assess in clinics in real life.

Chapter IV. Myocardial fibrosis in systemic lupus erythematosus as assessed by eSCAR and its associations with glucocorticoid therapy

4.1 Introduction

SLE is a multi-systemic autoimmune and inflammatory disease burdened by increased cardiovascular mortality [Bengtsson, 2012; Palmieri, 2009; Manzi, 1997]. However, the notion of primary myocardial involvement in chronic inflammatory and autoimmune diseases, such as RA [Ntusi, 2015], SSc [Krumm, 2016] or small vessel vasculitis [Pugnet, 2017; Greulich, 2017] is a relatively recent acquisition.

To date, there are no shared guidelines regarding characterization of the myocardial involvement related to the inflammatory process, nor therapeutic indications on how to treat this type of organ involvement. The studies that provided the best correlation with clinical data of the disease were conducted with CMR imaging methods and highlighted the presence of myocardial fibrosis (scar) with a non-ischemic pattern. Those studies have confirmed the presence of an inflammatory process of the myocardium, at least partially independent of the conventional CVD risk factors.

Recently, it has been described that 30-40% of patients with SLE have late enhancement with gadolinium (LGE) at CMR imaging, suggesting myocardial fibrosis of inflammatory origin [Winau, 2018]. The importance of myocardial scars detected with CMR imaging is evidenced by numerous studies that have established its prognostic role in ischemic heart disease, as well as in primary cardiomyopathies and valvular heart disease [Kwong, 2006; Gulati, 2013]. Myocardial fibrosis has been associated with sudden cardiac death, arrhythmias or heart failure. At present, CMR imaging, exploiting the technique of LGE, has established itself as the non-invasive diagnostic gold standard in tissue characterization and in the detection of myocardial scars [Wu, 2001; Wagner, 2003]. However, high costs, limited availability, technical execution times, patient compliance, have excluded CMR from routine application on a large scale. Visualization of fibrosis with the LGE technique also requires preserved renal function as it requires the administration of gadolinium contrast agent.

Echocardiography, on the other hand, thanks to its widespread use, extreme portability of machinery and low costs, has now widely entered clinical practice as an essential diagnostic tool for the routine study of patients with SLE. Also, using a contrast agent is not ideal for patients with lupus nephritis who often have some degree of renal failure.

eSCAR is a novel echocardiographic technique, based on the cancellation of the tissue signal through a sequence of pulses emitted by the probe (multipulse-scheme) in opposition of phase or amplitude to each other, which has been shown to have a high degree of concordance with the CMR-LGE in differentiating the fibrous-scar tissue (scar) which appears echogenic, compared to the normal myocardial tissue, which is cancelled (anechoic) by this method [Gaibazzi 2016]. Scar detection by eSCAR in the clinical scenario of the patient with SLE could make a contribution to the risk stratification in those patients with normal or not severely reduced global kinetics who today do not find effective prognostic stratification methods. Echocardiography is a simple, quick, reliable, inexpensive and biologically harmless method, since it does not use ionizing radiation, strong magnetic fields or contrast agents. To date, there are no studies that have investigated fibrosis detected by eSCAR in SLE patients.

4.2 Aim of this study

The aim of this study is to demonstrate the feasibility of eSCAR for the detection of myocardial scars in SLE patients.

4.2.1 Primary objective

The main objective is to highlight an association between eSCAR and clinically relevant events in patients with SLE, i.e. to study the role of the eSCAR technique as a predictor of clinical outcomes and primarily disease flare.

4.2.2 Secondary objective

The secondary objective is to compare the clinical and echocardiographic characteristics between patients with SLE and controls without SLE.

4.3 Methods

4.3.1 Core design and ethics

The core design and ethics are described in Chapter 2. We will refer to this substudy as the *eSCAR in systemic Lupus ErythemaTosus* (SCARLET) study.

4.3.2 Study population

Consecutive patients with an established diagnosis of SLE, according to 1997 criteria were referred for screening from the local Rheumatology department between August 2019 and March 2020. Patients meeting inclusion and exclusion criteria as described in

Table 3 were enrolled on the study. A case-control sub-analysis included 32 subjects recruited for the study named *Strain imaging in the evaluation of trastuzumab-related cardiotoxicity in patients with HER-2 positive breast cancer*, which served as a control group. These subjects with newly diagnosed breast cancer but who did not have any prior history of cardiac disease underwent a baseline echocardiographic examination before any cancer treatment was performed.

4.3.3 Study protocol and outcomes

In the SCARLET study, we assessed SLE patients at baseline for disease and CVD variables. Enrolled participants underwent a TTE study with evaluation of eSCAR and STE, and were followed up until 01/06/2021.

4.3.3.1 Primary outcome

The primary outcome was the comparison in the proportion of patients with eSCAR among SLE patients and controls.

4.3.3.2 Secondary outcomes

The secondary outcome was the occurrence of a clinically relevant event among:

1. Death;
2. Hospitalisations for CVD and non-CVD events;
3. Major cardiovascular events [Hicks, 2018]:
    a. Stroke and transient ischemic attack;
    b. Acute coronary syndrome (acute myocardial infarction, unstable angina);
    c. Revascularisation (aortocoronary bypass, percutaneous transcatheter angioplasty);
4. Cardiac arrhythmic events (atrial fibrillation, atrial flutter, supraventricular tachycardia; ventricular tachycardia or fibrillation, sudden cardiac death, appropriate shock; atrioventricular block);
5. Heart failure (new-onset of dyspnea or myocardial dysfunction);
6. Peripheral artery disease (claudication intermittent or arterial vascular ulcers);
7. Venous or arterial thromboembolism;

8. Cancer (excluding non-melanoma skin cancers);
9. Infection requiring systemic antibiotic therapy.
10. SLE flare according to the SELENA trial definitions [Petri et al., 1999] as reported in
11. ***Table*** 10.

Table 10. The flare of SLE definition.

Mild or moderate flare	Severe flare
A change in SLEDAI ≥3 points, or	Increase in SLEDAI> 12 points, or
New / worse skin lesions, stomatitis, serositis, arthritis, fever, or	New/worse CNS-SLE, vasculitis, nephritis, myositis, platelets < 60,000, haemolytic anemia with Hb < 7 g / dL, requiring doubling or prednisone dose > 0.5 mg / kg / day, or hospitalisation for SLE
Increased prednisone <0.5 mg / kg / day, or	Prednisone dosage > 0.5 mg / kg / day, or
Introduction of NSAIDs / hydroxychloroquine, or	New immunosuppressant, or
Increase of ≥1 points in Physician's Global Assessment (PGA)	Increase of > 2.5 points in Physician's Global Assessment (PGA)

4.3.4 Study procedures

4.3.4.1 Pulse-cancellation imaging

Ultrasound multi-pulse scheme (eSCAR) has proved to be effective in detecting ischemic myocardial scars in patients with CAD [Gaibazzi, 2016] and hypertrophic cardiomyopathy [Gaibazzi, 2021]. In this study we tested this TTE modality to detect myocardial scars (eSCAR signals) in SLE patients.

In order to perform eSCAR, the left ventricle contrast opacification (LVO) setting (power-modulation/pulse inversion harmonic imaging [transmit 1.6 MHz/receive 3.2 MHz]) was used for scar detection (eSCAR technique), without any contrast administration [Gaibazzi, 2021]. With this setting, the ‘‘linear’’ signals from normal myocardium are cancelled, while signals from abnormal myocardial tissue (fibrotic/disarrayed myocardium or calcified tis-sues) are enhanced as they have a ‘‘nonlinear’’ response (similar to the nonlinear acoustic behaviour of microbubbles). Starting from the 2D standard-setting, the “iscan” button, which automatically optimizes gain and time-gain compensation, was used once (set at 0 dB), after which

the LVO setting was activated. The LVO setting was finely tuned to an intermediate mechanical index, between 0.40 and 0.47, and general gain set between 70% and 77%, depending on the individual subject echogenicity. This eSCAR setting exponentially enhances the contrast between scar and normal myocardium, allowing detection of myocardial fibrosis. Visual analysis of eSCAR images was used for the assessment of the presence/absence and segmental distribution of myocardial scar by a blinded echocardiographer. A 17-segment model was used for assessing the segmental distribution of the eSCAR signal.

4.3.4.2 Speckle-tracking echocardiography

Speckle tracking echocardiography (STE) evaluates and quantifies active myocardial deformation (strain), identifying abnormalities in early and subclinical phases of disease (before reduction of LVEF). STE was performed using a dedicated commercially available Qlab 9 (cardiac motion quantification (CMQ); Phillips Medical Systems) software package. Longitudinal strain for individual myocardial segments was measured from the apical 4-chamber, 2-chamber and 3-chamber views (17 segment AHA/ASE model) (84). In the end-diastole, automated border tracking was enabled before manual adjustment using a point and click approach to ensure that endocardial and epicardial borders were included in the region of interest. In the case of poor tracking, fine-tuning was performed manually after cine-loop playback and tracing were repeated and adjusted until tracking was considered optimal by visual analysis. Individual myocardial segments that returned positive strain values and those with persistently poor tracking despite manual optimisation were excluded

from the analysis. Peak strain for the segment was defined as the peak negative value on the time strain curve for the entire cardiac cycle. Peak regional longitudinal strain was measured in 17 myocardial regions, and a weighted mean was used to derive global longitudinal strain (GLS).

4.3.4.3 CVD risk assessment

The following CVD risk factors were collected: age; gender; systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were measured at the end of echocardiographic evaluation in supine position; weight and height with the calculation of body mass index (BMI); lipids including total cholesterol, low-density

cholesterol and high-density cholesterol, and triglycerides; waist circumference; renal function; and smoking status. We defined obesity when body mass index (BMI) ≥ 30 kg/m2. Dyslipidemia was defined as levels of total serum cholesterol >190 mg/dL and or triglycerides >150 mg/dL or pharmacologically treated high lipid serum levels. Systemic arterial hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or medically treated hypertension. To assess renal function, we considered the glomerular filtration rate (GFR) estimated with the CKD-EPI equation [Levey, 2009] and defined renal dysfunction as estimated GFR < 60 ml/min 1.73 m^2.

4.3.4.4 SLE assessment

We collected the variables investigating the organ involvement, medication assumed, and the dose of glucocorticoid therapy. A senior rheumatologist systematically assessed disease activity and damage for each participant and calculated the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI).

4.3.4.5 Laboratory

The following blood tests were performed in local laboratories: full blood counts (FBC), complement C3 and C4, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and creatinine. The autoantibody status was also tested with commercial assays and recorded, including anti-dsDNA antibodies (indirect immunofluorescence (IIF) and chemiluminescent immunoassay (CLIA)), anti-phospholipid (aPL) antibodies (lupus anticoagulant, anti-beta2 GPI IgG and IgM, anti-cardiolipin IgG and IgM) and Extractable Nuclear Antigen Antibodies (ENA) panel.

4.3.5 Statistical analysis

Given the exploratory nature of the study, it was not considered necessary to perform a power analysis. Frequency variables (categorical) are reported as absolute numbers and relative percentages. Continuous variables, except where otherwise defined, are reported as mean and standard deviation. The associations of interest between Categorical variables were analyzed with the Chi-square or the Fisher test where

appropriate. The differences between the means for the eSCAR+ ed eSCAR- were analyzed by Student's T test. We used the survival analysis according to Kaplan-Meyer and the log-rank test to compare the likelihood of remaining SLE flare-free during follow-up in the eSCAR+ and eSCAR- groups. No corrections have been made for covariates given the smallness of the sample in the studio. Statistical significance was considered for a value of $p < 0.05$. All analyzes were performed using IBM SPSS Statistics version 20 software (USA) and graphs using GraphPad Prism 7 software (USA).

4.4 Results

4.4.1 Baseline characteristics of SLE patients

Most of our SLE patients were affected by long-standing disease, with the age of onset being about 29 years and an average time since diagnosis of 14 years. The clinical manifestations of SLE were quite heterogeneous. Disease-associated damage and disease activity were low overall, with 7 out of 27 (26%) patients having a SLEDAI of 0.

The most common symptoms were arthritis (74%) and mucocutaneous manifestations (59%). In 41% of our SLE patients, leukopenia or thrombocytopenia were observed at disease onset. Neurolupus, pericarditis and pleurisy (serositis) have been found less frequently. Fourty-four percent of patients also had lupus nephritis. Nineteen percent of patients fulfilled criteria for antiphospholipid syndrome (APS), mostly obstetric type.

The complement C3 level was reduced in 56% of our SLE patients, as well as the C4 level, while they were both decreased in 33%. Anti-dsDNA antibodies were detected in 74% of our patients. Anti-RoSSA antibodies were present in 41% of patients, anti-LaSSB, anti-U1RNP and anti-Sm antibodies each in 22% of the study population.

As for medical treatment (Table 11), hydroxychloroquine, as expected, was the most widely used drug: 85% of patients had it as current therapy, and all patients had had it as previous treatment. The mean prednisone dose was 3.8 mg daily. Mycophenolate mofetil (MMF) was used previously by 48% of patients and was a current medication in 37%, while methotrexate (MTX) was taken previously by 44%

of patients and was a current therapy in 15% of cases. Prior (not current) yclophosphamide use was reported in 11%. Biologic drugs (rituximab and belimumab) were used in by 44% of patients and were current therapies in 30%.

Table 11. Characteristics of disease and therapy of patients with SLE.

Disease characteristics	
Time since SLE diagnosis, years	13.6 [8.5-21.1]
Age at disease onset, years	28.6 [17.8-34.1]
SLEDAI	2 [0-6]
SDI	1 [0-2]
Arthritis, n (%)	20 (74)
Neurological, n (%)	3 (11)
Lupus nephritis, n (%)	12 (44)
Mucocutaneous manifestations, n (%)	16 (59)
Cytopenia, n (%)	11 (41)
Antiphospholipid syndrome, n (%)	5 (19)
Serositis, n (%)	3 (11)
Laboratory	
Haemoglobin, g/dL	12.9 [12.3-13.4]
Leukocytes, $10^6/mm^3$	4600 [3500-7000]
Platelets, $10^6/mm^3$	219 [183-288]
eGFR MDRD, $mL/min/m^2$	101 [84-122]
ESR, mm/h	15 [6-23]
CRP, mg/L	2 [1-3.2]
Anti-dsDNA, n (%)	20 (74)
Anti-Sm, n (%)	6 (22)
Anti RoSSA, n (%)	11 (41)
Anti-LaSSB, n (%)	6 (22)
Anti-U1RNP, n (%)	6 (22)
Complement C3, g/L	87 [63-99]
Complement C4, g/L	13 [9-18]
Antiphosfolipid, n (%)	9 (33)
Current treatment	
Glucocorticoids, n (%)	16 (59)
Prednisone current dosage, mg/die	3.8±6.2
Hydroxychloroquin, n (%)	23 (85)
Mycophenolate mofetil, n (%)	10 (37)
Methotrexate, n (%)	4 (15)
Azathioprine, n (%)	3 (11)
Cyclosporine, n (%)	0 (0)
Cyclophosphamide, n (%)	0 (0)
Biologic drugs, n (%)	8 (30)
Past treatment	
Glucocorticoids, n (%)	27 (100)
Prednisone cumulative dosage, g	20.4 [6.0-28.5]
Hydroxychloroquine, n (%)	27 (100)
Mycophenolate mofetil, n (%)	13 (48)
Methotrexate, n (%)	12 (44)
Azathioprine, n (%)	17 (63)
Cyclosporine, n (%)	5 (19)
Cyclophosphamide, n (%)	3 (11)
Biologic drugs, n (%)	12 (44)

Data reported as absolute numbers (%) or median (25th-5th percentile). CRP, C-reactive protein; ESR; erhytrocyte sedimentation rate; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index 2000.

4.4.2 Cardiovascular risk in patients with SLE and controls

Cardiovascular risk factors were assessed in both SLE patients and controls (Table 12). The two groups did not significantly differ from any considered CVD risk factor (including age, gender, BMI, the proportion of smokers and hypercholesterolemia). However, there was a higher proportion of patients who had hypertension in the group of patients with SLE. As established by the study protocol, none of our patients had diabetes mellitus.

All hypertensive SLE patients (n=8) had long-lasting hypertension. Most of them (6/8, 75%) had also a history of lupus nephropathy, one also had a history of gestational hypertension. These patients were being treated with ACE inhibitors or sartans (7/8, 88%), often associated with diuretics (6/8, 75%) or other classes of antihypertensive drugs. Finally, the cumulative dose of glucocorticoid was higher in the hypertensive group than in the non-hypertensive group.

Table 12. Cardiovascular disease risk factors in patients with SLE and controls

Cardiovascular risk factors	SLE patients (n = 27)	Controls (n = 32)	P-value
Age, years	45±11	46±7	0.797
Male gender, n (%)	3 (11)	0 (0)	0.090
BMI, kg/m^2	23±3	23±4	0.999
Smokers, n (%)	10 (37)	8 (25)	0.399
Hypertension, n (%)	8 (30)	3 (9)	0.091
Hypercholesterolemia, n (%)	4 (15)	6 (19)	0.728

BMI, body mass index.

4.4.3 Echocardiography of patients with SLE and controls

Table 13 summarizes the main echocardiographic characteristics of SLE patients and controls. All patients had a preserved systolic function. Compared with the controls, LV-EDV and LV-ESV were significantly higher in SLE patients, while LV-EF was lower, although the means of these parameters remained within the normal range. Conversely, there were no significant differences between the two groups in terms of LV mass, left atrial volume and the diastolic function indexes. There was a significant difference regarding s' tricuspid wave velocity resulting significantly lower in the SLE patient group ($p=0.01$).

Myocardial scar, detected by using the eSCAR technique, was found in 5/27 patients with SLE (19%) and was not found in the control group. Figure 6 shows the myocardial scar distribution in these patients. The myocardial infero-septal segments in all these patients were affected, and in one case, the inferior myocardial wall was also affected. An example of the eSCAR sign is illustrated in **Errore. L'origine riferimento non è stata trovata.**.

Table 13. Echocardiography of SLE patients and controls.

	SLE patients (n = 27)	Controls (n = 32)	P-value
Standard echocardiogram			
LV EDV index, mL/m^2	53.8±11	49.1±6.9	0.04
LV ESV index, mL/m^2	20.9±5.2	17.9±3.7	0.01
LV EF, %	61.2±4.2	63.7±2.9	0.009
LV mass index, g/m^2	64±14.7	65±17.6	0.87
LAVI, mL/m^2	22.8±6.9	24±6.3	0.49
E velocity (cm/s)	74.3±21.7	77.9±17.8	0.47
A velocity (cm/s)	60±18.6	66.6±17.6	0.16
Deceleration time, ms	183.8±74.5	182.5±60.7	0.94
E/A ratio	1.3±0.6	1.2±0.4	0.72
E/E' ratio	6.9±2.5	6.7±2.1	0.85
TRPG, mmHg	17.5±4.1	19.4±4.3	0.29
TAPSE, mmHg	24±7.2	24.3±2.7	0.82
S' tricuspidal velocity, cm/s	10.3±5.1	13.2±1.7	0.01
Longitudinal strain			
GLS global (%)	-21±2	-23.9±1.8	<0.0001
GLS 4chamber (%)	-21.5±2.7	-22.8±1.9	0.03
GLS 2chamber (%)	-21.6±2.4	-22.8±2.1	0.04
GLS 3chamber (%)	-20.9±2.6	-22.5±2.4	0.01
GLS base (%)	-19±2.6	-22.8±2.9	<0.0001
GLS mid (%)	-19.5±2	-23.5±3.4	<0.0001
GLS apex (%)	-25.1±3	-25.5±3.3	0.6
GLS anterior (%)	-21.9±2.4	-23.8±4.3	0.03
GLS antero-septal (%)	-22.6±3.2	-25.8±3.6	0.001
GLS infero-septal (%)	-20.9±2.5	-23.5±2.8	<0.0001
GLS inferior (%)	-21.2±2.4	-25±3.5	<0.0001
GLS infero-lateral (%)	-20.3±2.6	-22.6±2.7	0.001
GLS antero-lateral (%)	-21.4±2.7	-23.5±2.7	0.004
Myocardial fibrosis			
eSCAR, n (%)	5 (19)	0 (0)	0.01
eSCAR anterior, n (%)	0 (0)	0 (0)	ND
eSCAR antero-septal, n (%)	0 (0)	0 (0)	ND
eSCAR infero-septal, n (%)	5 (19)	0 (0)	0.01
eSCAR inferior, n (%)	1 (4)	0 (0)	0.29
eSCAR infero-lateral, n (%)	0 (0)	0 (0)	ND
eSCAR antero-lateral, n (%)	0 (0)	0 (0)	ND

EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longidutinal strain; LAVI, left atrial volume index; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation peak gradient.

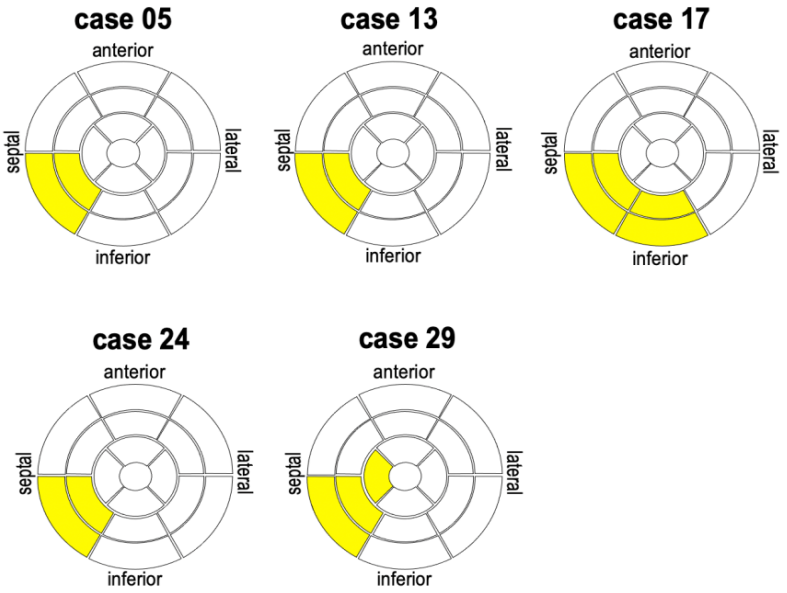

Figure 6. Myocardial fibrosis in five SLE patients as described by a 17-segment "bull's eye" scheme.

Yellow segments depict the localization of the eSCAR sign.

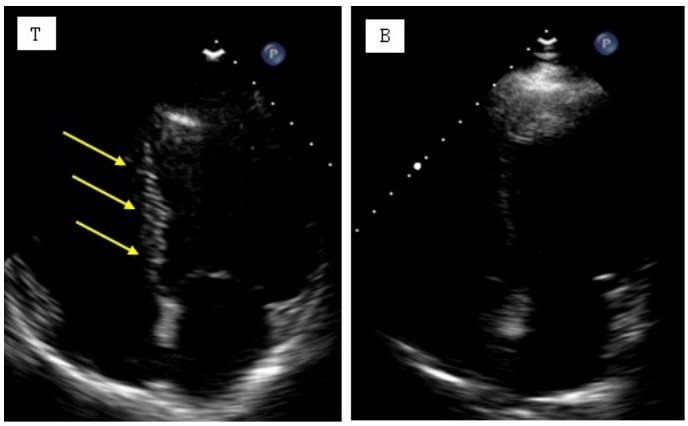

Figure 7. The echocardiographic scar (eSCAR) sign as detected by pulse cancellation imaging.

Myocardial fibrosis in the interventricular septum (eSCAR+ patient) is shown in panel A). The absence of myocardial fibrosis (eSCAR- patient) is shown in panel B.

Longitudinal strain (GLS) was significantly decreased in all myocardial segments in SLE patients compared with controls, except for the myocardial apical region (-25.1 ± 3 in the SLE group vs -25.5 ± 3.3 in controls). Specific myocardial strain single segments showed a correlation between the SLEDAI and the cumulative prednisone dose (Figure 8).

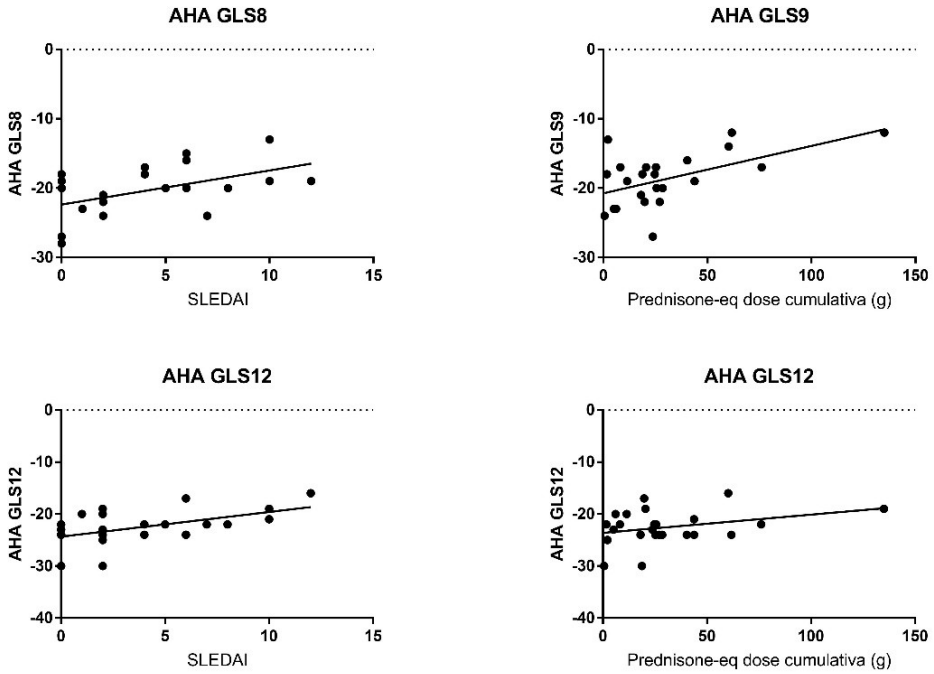

Figure 8. Correlations between SLEDAI, cumulative prednisone dose and myocardial strain single segments.

SLEDAI and AHA GLS8 (r = 0.497, p = 0.014), AHA GLS12 (r = 0.540, p = 0.006); cumulative prednisone dose and AHA GLS9 (r = 0.524, p = 0.009), AHA GLS 12 (r = 0.319, p = 0.129). AHA, American Heart Association; GLS, global longidutinal strain.

4.4.4 Clinical characteristics of SLE patients, stratified by the presence or the absence of myocardial scar by the eSCAR technique

We compared clinical and echocardiography of patients with myocardial scars (eSCAR+) to those without myocardial scar (eSCAR-) (

Table 14). The distribution of CVD risk factors was similar in the two groups. The eSCAR+ group were non-significantly younger (39 vs 47 years), had more frequently hypertension and were exposed more frequently to tobacco smoke. There were no differences in BMI, while there was a higher percentage of hypercholesterolemic patients among the eSCAR-.

There was no significant difference with respect to SLE disease duration, age at onset or SLEDAI. However, in the eSCAR+ group, there was a trend towards an earlier disease onset (26 vs 31 years) and a higher disease activity (SLEDAI 4.4 vs 3.4), but a slightly shorter disease duration (13.1 vs 15.3 years). Patients who were eSCAR+ had a higher cumulative steroid dose (40.0 vs 24.0 g), as well as the current steroid dose (11.0 vs 2.5 mg daily), although this was not statistically significant.

The eSCAR+ group showed a slightly lower eGFR than the eSCAR- (96 vs 105 ml/min/1.73m^2), although all values exceeded 60 ml/min/1.73m^2. Levels of C3 and C4 showed greater reduction of C3 in eSCAR+ patients (72 vs 85 g/L).

Table 14. Comparison of eSCAR+ and eSCAR- SLE patients according to clinical characteristics, standard echocardiography and myocardial strain.

	LES eSCAR+ (n = 5)	LES eSCAR – (n = 22)	P-value
Cardiovascular risk factors			
Age, years	39.0±8.9	46.6±11.4	0.181
Male sex, n (%)	1 (20)	2 (9)	0.999
BMI, kg/m^2	24.1±2.5	23.4±3.2	0.68
Smokin status (ever), n (%)	3 (60)	7 (32)	0.326
Hypertension, n (%)	2 (40)	6 (27)	0.616
Dyslipidemia, n (%)	0 (0)	4 (18)	0.561
SLE characteristics			
Disease duration, years	13.1±9.4	15.3±11.0	0.837
Age at diagnosis, years	25.9±14.6	31.3±13.7	0.441
SLEDAI	4.4±4.5	3.4±3.1	0.570
SDI	0.8±0.8	0.9±1.1	0.833
Antiphospholipid syndrome, n (%)	1 (20)	5 (23)	0.999
Current prednisone dose, mg daily	11.0±12.2	2.5±2.7	0.192
Cumulative prednisone dose, g	40.0±25.0	24.3±30.3	0.338
Laboratory			
Hemoglobin, g/dL	12.7±7.3	12.9±12.2	0.699
eGFR, mL/min per m^2	95.6±54.1	105.4±27.2	0.556
ESR, mm/h	19±11	19±18	0.976
CRP, mg/L	1.5±1.4	5.4±12.6	0.551
Complement C3, g/L	72±15	85±24	0.234
Complement C4, g/L	15±12	15±9	0.947

BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erhytrocyte sedimentation rate; SDI, SLICC damage index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index 2000.

4.4.5 Differences in standard echocardiography and strain analysis in eSCAR+ and eSCAR- SLE patients

Regarding the echocardiographic parameters, there were no significant differences in the standard echocardiographic variables. However, we found a significant inverse correlation between left ventricular mass and the cumulative dose of glucocorticoid received and (Figure 9).

In contrast, most GLS values were significantly lower in the eSCAR+ group, especially in basal and inferoseptal segments (**Errore. L'autoriferimento non è valido per un segnalibro.**).

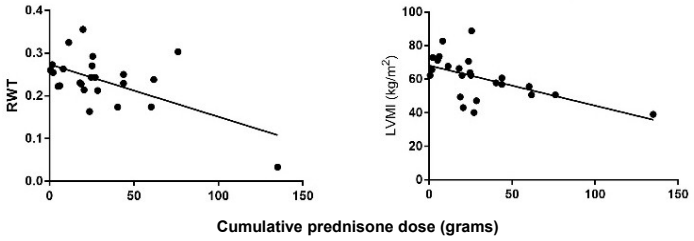

Figure 9. The inverse relationship between myocardial mass and glucocorticoids.

LVMI, left ventricular mass index; RWT, relative wall thickness. Pearson's r and p-value respectively: r = -0.587, p = 0.003 for RWT; r = -0.565, p = 0.004 for LVMI.

Table 15. Comparison of eSCAR+ and eSCAR- SLE patients according to standard echocardiography and myocardial strain.

	LES eSCAR+ (n = 5)	LES eSCAR – (n = 22)	P-value
Standard echocardiography			
LV-EDV index, mL/m^2	56.7±18.5	53.3±9.3	0.53
LV-ESV index, mL/m^2	22.4±8	20.7±4.7	0.53
LV-EF, %	60.7±3.2	61.3±4.4	0.76
LV mass index, g/m^2	67.7±20.7	63.3±13.6	0.55
LA volume index, mL/m^2	19.8±7.7	23.5±6.7	0.28
E velocity, cm/s	76.2±15.1	73.8±23.1	0.82
A velocity, cm/s	56.5±20.6	60.8±18.6	0.64
Deceleration time, ms	225.2±30.8	175.1±78.4	0.17
E/A ratio	1.5±0.6	1.2 ±0.5	0.37
E/E' ratio	7.8±3.7	6.7±2.2	0.4
TAPSE, mm	22±2.4	25.2±7.6	0.46
S' velocity, cm/s	12±1.8	9.9±5.5	0.47
Speckle tracking echocardiography			
GLS global (%)	-18.4±1.5	-21.6±1.7	0.001
GLS 4 chambers (%)	-18.2±2.2	-22.2±2.3	0.002
GLS 2 chambers (%)	-18.9±1.9	-22.2±2.1	0.003
GLS 3 chambers (%)	-19.8±3.6	-21.1±2.4	0.31
GLS basal (%)	-15.7±2.4	-19.7±2.2	0.001
GLS mid (%)	-17.3±1.4	-20±1.9	0.005
GLS apex (%)	-23.1±1.1	-25.5±3.1	0.1
GLS anterior (%)	-18.8±1.9	-22.5±2	0.001
GLS anteroseptal (%)	-20.7±2.1	-23.1±3.3	0.13
GLS inferoseptal (%)	-17.3±2.1	-21.7±1.9	<0.0001
GLS inferior (%)	-18.5±2.1	-21.7±2.2	0.006
GLS inferolateral (%)	-18.3±3.3	-20.7±2.4	0.05
GLS anterolateral (%)	-18.8±2.7	-21.9±2.4	0.01

EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longidutinal strain; LAVI, left atrial volume index; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation peak gradient.

4.4.6 Myocardial fibrosis and eSCAR as predictors of SLE flares

Thirty-one clinical events were reported in 15/27 (56%) patients during a median follow-up time of 11.2 months (range 5.3-13.3) and are summarized in Table 16. In more detail, these events were ten infections requiring antibiotic therapy, two CVD events, and one malignancy; the remaining were SLE flares. There were no deaths.

In the eSCAR+ group, all patients experienced clinical events: in particular, there were two infections in the same patient (paucisymptomatic Severe Acute Respiratory Syndrome (SARS)-CoronaVirus2 (CoV2) infection and bacterial pneumonia), and nine flares of SLE in 5/5 (100%) subjects. In the eSCAR- group, 9/22 (41%) patients had at least one adverse event, including five infections (one episode of recurrent nail infection with hospitalization for onychectomy; one episode of upper respiratory tract infection; one lower respiratory tract infection; one relapsed erysipelas, one SARS-CoV2 infection), one cancer (renal cell carcinoma), one cardiovascular event (arterial ulcer), and nine flares of SLE in 6/22 (27%).

Table 16. Clinical outcomes and disease flare in eSCAR+ and eSCAR- SLE patients.

	SLE eSCAR+ (n = 5)	**SLE eSCAR – (n = 22)**	**P-value**
Cardiovascular events	0 (0)	1 (5)	0.999
Malignancy	0 (0)	1 (5)	0.999
Infections	1 (20)	5 (23)	0.999
SLE flare	5 (100)	6 (27)	0.006
Death	0 (0)	[5] 0 (0)	0.999

Eighteen SLE flares were recorded in 11/27 (41%) patients. Four out of 27 patients (15%) had more than one flare. In 6/11 patients, flares were classified as mild/moderate, while they were severe in 5/18 patients (3/5 eSCAR+ and 2/22 eSCAR- respectively); no flare required hospitalization.

eSCAR+ patients were significantly less likely than eSCAR- to maintaining their flare-free status during follow-up (Figure 10). All eSCAR+ patients had at least one flare and 3/5 more than one flare. Finally, half of the eSCAR+ patients had an SLE flare within nine months following echocardiography.

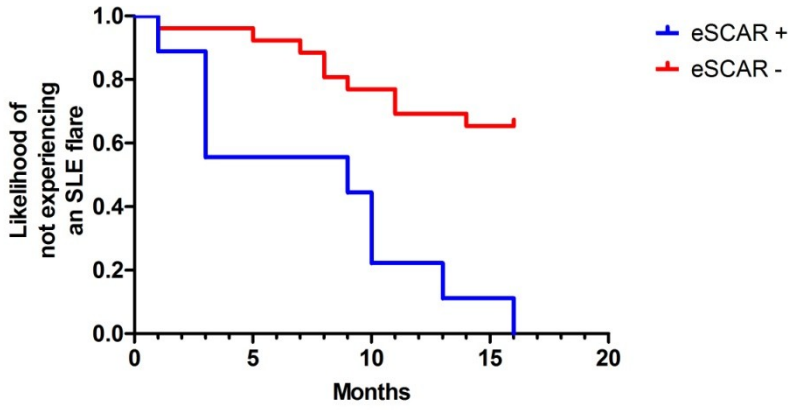

Figure 10. Survival curves for the status of maintining flare-free status during follow-up.

Hazard ratio (logrank) eSCAR+ | eSCAR-: 4.910; 95% CI 1.432, 16.83; p=0.0001.

4.5 Discussion

The main result of this pilot study is that echocardiography with eSCAR effectively detected myocardial fibrosis in SLE patients in clinical quiescence. Moreover, eSCAR was significantly associated with a greater probability of disease flare.

Myocardial fibrosis by eSCAR was not detected in any patient of the control group, suggesting it characterises SLE patients. Furthermore, in all eSCAR+ patients the infero-septal myocardial segment was affected, thus showing a common pattern in terms of localization of fibrosis. Notably, the eSCAR+ patients presented standard TTE values within normal ranges, suggesting that myocardial fibrosis appears before standard TTE was able to identify it. This is consistent with what was expected, given that our patients with SLE had a low risk of CVD and did not report any symptoms attributable to heart disease. However, there were also subclinical and very mild abnormalities of myocardial structure, as differences in indexed volumes (LV EDV, LV ESV) and standard LV function parameters (LV EF) were noticed in SLE patients compared to controls. Interestingly though, decreased GLS was found in patients with SLE, except in the apical regions. Myocardial strain analysis with evaluation of the GLS is a more sophisticated method than standard TTE to assess the contraction of myocardial tissue and a more sensitive technique for the early diagnosis of subclinical lupus myocardiopathy [du Toit, 2017; Farag, 2020]. We found abnormal GLS in most myocardial segments, but more significantly ($p < 0.0001$) in the inferoseptal segments where the eSCAR sign was detected. This suggests that the detection of eSCAR was actually associated with areas of myocardial fibrosis with focal reduced contractile function, and therefore it may have a clinical prognostic value. All these findings are also in agreement with the hypothesis that myocardial fibrosis precedes left ventricle dysfunction in SLE.

Myocardial fibrosis assessed by eSCAR also had prognostic implications in our study. Indeed, eSCAR+ patients were significantly less likely than eSCAR- to maintaining a status of SLE flare-free during follow-up (within one year). Specifically, all eSCAR+ patients had at least one flare, and most of them had more than one flare. This result suggests that patients with myocardial involvement in eSCAR have a more aggressive and active disease. In support of this hypothesis, the eSCAR+ group had a significantly higher cumulative glucocorticoid exposure as

well as the current daily dosage. Therefore, eSCAR+ patients had a more active disease than the eSCAR-, which required a higher dose of steroid in order to keep it in remission. Furthermore, eSCAR+ patients had a tendency to have earlier disease onset and higher disease activity as assessed by the SLEDAI, a score that currently does not consider the presence of cardiac involvement [Gladman, 2002]. Finally, eSCAR+ SLE patients had lower complement C3 fraction. Low levels of complement C3 correlate with increased disease activity [Justiz-Vaillant, 2020]. Furthermore, lupus myocardiopathy itself appears to be associated with deposits of immune complexes and complement activation in the myocardial vessels [Bidani, 1980].

eSCAR+ SLE patients were more frequently smokers than eSCAR-, though this difference was not statistically significant. Smoking is a well-known risk factor for the development of SLE [Costenbader, 2004]. More conflicting are the data regarding the role of cigarette smoking in determining a more aggressive disease phenotype. One study has highlighted the possible role of smoking in the pathogenesis of SLE with anti-dsDNA autoantibodies positivity, which was associated with lupus vasculitis and nephritis in women who smoked more than 10 pack/years [Barbhaiya, 2018]. Yet, another study found a negative association between cigarette smoking (> 10 pack/years) and the development of lupus nephritis [Leffers, 2021].

As pulse-cancellation imaging was developed to detect ischemic myocardial scars originally [Gaibazzi, 2016], we cannot exclude an underlying coronary artery disease in our eSCAR+ SLE patients. Indeed, in order to do this, a coronary angiography study should have been performed. However, the eSCAR sign was localised in non-coronary territories and this study population had very few cardiovascular risk factors. We included almost exclusively pre-menopausal women, and the main difference in conventional CVD risk factors between eSCAR+ and eSCAR- SLE patients was the proportion of those with hypertension. All hypertensive patients had long-standing disease, mostly associated with lupus nephropathy and in all cases well controlled with therapies, and no patient had a history of organ damage. Only two eSCAR+ patients had hypertension, but STE showed significant alterations of the strain in eSCAR+ patients. It cannot be excluded that these abnormalities may be

related to hypertension rather than fibrosis, as STE has proved to be more sensitive than standard echocardiography in evaluating post-hypertensive cardiac damage [Cameli, 2016]. Nevertheless, GLS in several myocardial segments and LVM were associated with disease activity and glucocorticoids use, and not with hypertension.

4.6 Study strengths and limitations

The first limitation of the study is the limited series of 27 patients with SLE; it is, in fact, a first of its kind pilot study. Secondly, patients with severe organ involvement (in particular renal and vascular) were excluded. Therefore we may have underestimated the prevalence of lupus myocarditis, which is generally associated with more severe disease activity patterns. On the other hand, it is remarkable to have found areas of myocardial fibrosis in about 1 out of 5 patients with clinically quiescent disease. Third, the clinical follow-up of these patients was limited to a period of less than one year, which is too short to assess whether there was a higher incidence of clinical events in eSCAR+ patients than in eSCAR-. Fourth, the validation of the eSCAR technique through CMR is currently underway. The eSCAR and CMR-LGE images should then be compared and confirmed for the presence or absence of myocardial fibrosis in the eSCAR+ and eSCAR- patients, respectively. However, the eSCAR method has already been validated with CMR-LGE in a population of patients with a recent STEMI infarction [Gaibazzi, 2016]. Finally, no biomarker assays that can be associated with the presence of eSCAR have been performed so far.

4.7 Conclusions

The eSCAR method could detect early myocardial damage and allow treatment in order to prevent the evolution towards heart failure. This is especially relevant as lupus myocardiopathy has a high mortality [Apte, 2008; Jacobsen, 1998]. Early identification of lupus myocardiopathy and subsequent adjustment of therapy could reduce the incidence of CVD events [Hicks, 2018] in SLE patients.

Lupus cardiac involvement manifests with major arrhythmias, cardiogenic shock or acute coronary syndrome [Tanwani, 2018]. It is difficult to diagnose in a pre-clinical setting but can evolve into heart failure [Comarmond, 2017]. Hence, more sensible

imaging than clinical examination or ECG is needed to stratify SLE patients at higher risk of CVD events. Although CMR imaging is currently the gold standard in the characterization of myocardial fibrosis, the eSCAR technique could be integrated in the routine echocardiographic assessment of SLE patients, as it proved to be easy, cheap and rapid (15 minutes) to perform and well tolerated. Conversely, CMR has several disadvantages to its application for cardiovascular screening [Barison, 2021]. For instance, te proportion of SLE patients with chronic kidney disease varies between 20 and 65% [Gergianaki, 2018]; in these patients, who could have a high pre-test probability of cardiac involvement, CMR is not feasibile.

Chapter V. Myocardial fibrosis in systemic sclerosis as assessed by echocardiography and its associations with vasculopathy

5.1 Introduction

Systemic sclerosis (SSc) is an autoimmune disease of the connective tissue characterized by vascular dysfunction and multi-organ fibrosis. The heart is one of the major organs commonly involved by fibrosis, with an estimated clinical prevalence of 15-35% [Steen, 2000].

Early myocardial manifestations of primary heart involvement (pHI)-SSc are often nonspecific, making patients' stratification problematic. Patients with cardiac manifestations can remain undiagnosed, potentially allowing the disease to progress silently [Rodriguez-Reyna, 2019]. Once clinically evident, however, cardiac involvement has a very poor prognosis [Steen, 2000; Allanore, 2010]. Indeed, Sc-related primary cardiac involvement accounts for about one-third of the total deaths of SSc patients [Tyndall, 2010; Ferri, 2012].

Myocardial fibrosis is considered a hallmark of pHI-SSc. It is believed that this fibrosis is, at least initially, a consequence of functional vasospastic ischemic episodes of the small coronaries and arterioles [Lambova, 2014].

To date, there are no shared guidelines regarding the characterization of myocardiopathy related to the inflammatory process, nor therapeutic indications on how to treat this organ involvement [Bissell, 2017]. It is reasonable to think that the early identification of this involvement, ideally with a non-invasive imaging modality, is the key to facilitating appropriate and timely therapeutic interventions.

The gold standard diagnostic test for associated SScpHI remains the endomyocardial biopsy. However, this remains an invasive diagnostic investigation that cannot be proposed outside third-level cardiac centres. EMB has also significant risks of associated morbidity as well as sampling errors given the mosaic pattern of myocardial fibrosis.

In the last decade, CMR imaging has emerged as a powerful non-invasive imaging modality capable of characterizing myocardial tissue. Late gadolinium enhancement (LGE) imaging is an established technique for the non-invasive detection of substitutive myocardial fibrosis [Bing, 2019]. What limits its use as a universal diagnostic modality are its high costs, the need for a contrast agent (gadolinium), the technical times of the procedure, the scarcity of available resources and the need a compliant patient.

Transthoracic echocardiography (TTE), on the other hand, thanks to its widespread use, extreme portability of machinery and low costs, has now widely entered clinical practice as an essential diagnostic tool for the routine study of patients with SSc. Unfortunately, TTE was deemed to have insufficient sensitivity and specificity for tissue characterization and visualisation of myocardial fibrosis. However, *scar imaging echocardiography with ultrasound multipulse scheme* or *eSCAR* is a novel TTE modality that can effectively differentiate normal myocardium from scars. This technique has been recently developed and validated to detect post-ischemic myocardial scarsa in a population of patients with recent ST elevation myocardial infarction (STEMI) [Gaibazzi, 2016]. This work also showed that myocardial scars as seen with eSCAR have an accurate regional correspondence with LGE visualised by CMR imaging. This makes the eSCAR method extremely attractive for widespread clinical use, particularly for large-scale screening programs. To date, there are no studies that have investigated the role of myocardial fibrosis detected by eSCAR in SSc.

5.2 Aim of this study

The aim of this study was to demonstrate the feasibility of eSCAR for the detection of myocardial scars in SSc patients.

5.2.1 Primary objective

The main objective of the study was to highlight the presence of fibrotic scar through the eSCAR technique in patients with SSc, to estimate its frequency in the SSc population and describe its patterns.

5.2.2 Secondary objectives

The secondary objectives were to compare the clinical and echocardiographic characteristics between eSCAR+ patients and eSCAR- SSc patients, and to identify those clinical-laboratory characteristics helpful to identify the SSc population with greater risk of myocardial fibrosis.

5.3 Methods

5.3.3 Core design and ethics

This substudy belongs to the core CASIMIRO study, which design and ethics are described in Chapter II. We will refer to this substudy as the "*ULtrasound for the detection of mYocardial Scars in SYstemic Sclerosis* (ULYSSYS)" study.

5.3.4 Study population

The study population included all patients with SSc referred to the Scleroderma Clinic of the Division of the Rheumatology, AOUI Verona. Consecutive patients with an established diagnosis of SSc according to the 2013 criteria were referred for screening from the local Rheumatology department between November 2020 and February 2021. Patients meeting inclusion and exclusion criteria as described in

Table 3 were enrolled on the study.

5.3.5 Study protocol and outcomes

In the ULYSSYS study, participants were approached during routine visits and referred to echocardiography as per the annual routine screening for PH [Bissell, 2017]. Patients enrolled underwent TTE, including eSCAR assessment and STE, clinical and laboratory assessments.

The exploratory outcome was the comparison in the proportion of patients with eSCAR among SSc patients and controls.

5.3.6 Study procedures

5.3.6.1 Pulse-cancellation imaging

Ultrasound multi-pulse scheme (eSCAR) has proved to be effective in detecting ischemic myocardial scars in patients with CAD [Gaibazzi, 2016] and hypertrophic cardiomyopathy [Gaibazzi, 2021]. In this study we tested this TTE modality to detect myocardial scars (eSCAR signals) in our SSc patients.

In order to perform eSCAR, the left ventricle contrast opacification (LVO) setting (power-modulation/pulse inversion harmonic imaging [transmit 1.6 MHz/receive 3.2 MHz]) was used for scar detection (eSCAR technique), without any contrast administration [Gaibazzi, 2021]. With this setting, the ‘‘linear’’ signals from normal myocardium are cancelled, while signals from abnormal myocardial tissue (fibrotic/disarrayed myocardium or calcified tis-sues) are enhanced as they have a ‘‘nonlinear’’ response (similar to the nonlinear acoustic behaviour of microbubbles). Starting from the 2D standard-setting, the “iscan” button, which automatically optimizes gain and time-gain compensation, was used once (set at 0 dB), after which the LVO setting was activated. The LVO setting was finely tuned to an intermediate mechanical index, between 0.40 and 0.47, and general gain set between 70% and 77%, depending on the individual subject echogenicity. This eSCAR setting exponentially enhances the contrast between scar and normal myocardium, allowing detection of myocardial fibrosis. Visual analysis of eSCAR images was used for the assessment of the presence/absence and segmental distribution of myocardial scar by

a blinded echocardiographer. A 17-segment model was used for assessing the segmental distribution of the eSCAR signal.

5.3.6.2 Speckle-tracking echocardiography

Speckle tracking echocardiography (STE) evaluates and quantifies active myocardial deformation (strain), identifying abnormalities in early and subclinical phases of disease (before reduction of LVEF). Speckle tracking echocardiography (STE) was performed using a dedicated commercially available Qlab 9 (cardiac motion quantification (CMQ); Phillips Medical Systems) software package. Longitudinal strain for individual myocardial segments was measured from the apical 4-chamber, 2-chamber and 3-chamber views (17 segment AHA/ASE model). In the end-diastole, automated border tracking was enabled before manual adjustment using a point and click approach to ensure that endocardial and epicardial borders were included in the region of interest. In the case of poor tracking, fine-tuning was performed manually after cine-loop playback and tracing were repeated and adjusted until tracking was considered optimal by visual analysis. Individual myocardial segments that returned positive strain values and those with persistently poor tracking despite manual optimisation were excluded from the analysis. Peak strain for the segment was defined as the peak negative value on the time strain curve for the entire cardiac cycle. Peak regional longitudinal strain was measured in 17 myocardial regions, and a weighted mean was used to derive global longitudinal strain (GLS).

5.3.6.3 Aortic stiffness assessment

Aortic stiffness was evaluated by Doppler-echocardiography. All Doppler-echocardiographic studies were performed by an expert sonographer using an Alpha Esaote Biomedica machine (Florence, Italy) equipped with a 2.5–3.5 MHz annular-array transducer and following a standardized protocol. Images were stored on compact disks or magneto-optical disks and forwarded for final interpretation to a senior cardiologist blinded to the identity of the subject. Aortic stiffness was assessed at the level of the aortic root, using a two-dimensional guided M-mode evaluation of systolic (AoS) and diastolic (AoD) aortic diameters, 3 cm above the aortic valve together with blood pressure measured by cuff sphygmomanometer. AoD was obtained at the peak of the R wave at the simultaneously recorded electrocardiogram, while AoS was measured at the maximal anterior motion of the

aortic wall [Nistri, 2008; Stefanadis, 1990]. For each diameter, five measurements were averaged. Values of SBP, DBP, AoS and AoD were used to calculate the aortic stiffness index (AoSI) using the following validated formula:

$$AoSI = \frac{ln\left(\frac{SBP}{DBP}\right)}{(AoS - AoD)} / AoD$$

Intraclass correlation coefficient (ICC) with a two-way random model was used to assess the absolute reliability of aortic diameters and BP measurement in 50 patients. ICC values (95% CI) were 0.91 (0.86-0.94) for AoS, 0.93 for AoD, 0.92 for SBP and 0.94 for DBP respectively. ICC for calculated AoSI was 0.92.

5.3.6.4 CVD risk assessment

The following CVD risk factors were collected: age; gender; systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were measured at the end of echocardiographic evaluation in supine position; weight and height with the calculation of body mass index (BMI); lipids including total cholesterol, low-density cholesterol and high-density cholesterol, and triglycerides; waist circumference; renal function; and smoking status. We defined obesity when body mass index (BMI) ≥ 30 kg/m2. Dyslipidemia was defined as levels of total serum cholesterol >190 mg/dL and or triglycerides >150 mg/dL or pharmacologically treated high lipid serum levels. Systemic arterial hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or medically treated hypertension. To assess renal function, we considered the glomerular filtration rate (GFR) estimated with the CKD-EPI equation [Levey, 2009] and defined renal dysfunction as estimated GFR < 60 ml/min 1.73 m^2.

5.3.6.5 SSc assessment

All variables were collected as per the EUSTAR protocol [Meier, 2012]. We collected from clinical charts the variables investigating the organ involvement, medication assumed, and the cumulative dose of iloprost received. The modified Rodnan skin score (mRSS) was systematically assessed in each patient to define the entity of skin involvement. Scleroderma subsets are classified as “diffuse SSc” if skin thickening extends proximal to the elbows and knees or includes the trunk. The

SSc subset is classified as “limited SSc” if skin thickening is confined to the elbows and knees, or the face. Other skin subsets were classified as sine scleroderma or undefined. Interstitial lung disease (ILD) patterns were assessed.

5.3.6.6 Assessment of pulmonary function

All data of pulmonary function were provided by tests performed within six months of echocardiography. For all analyses, we considered the following variables: forced vital capacity (FVC) and total lung capacity (TLC). Forced vital capacity (FVC) has become the preferred surrogate marker for SSc-ILD despite the paucity of validation studies. Diffusing capacity for carbon monoxide (DLCO) and DLCO adjusted for alveolar volume (DLCO/VA) were also measured and collected.

5.3.6.7 Laboratory

The following blood tests were performed in local laboratories: full blood counts (FBC), complement C3 and C4, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, creatine kinase (CK), and N-terminal pro b-type natriuretic peptide (NTproBNP). The autoantibody status was also recorded.

5.3.7 Statistical analysis

Given the exploratory nature of the study, it was not considered necessary to perform a power analysis. In order to identify the main patterns of eSCAR involvement, a principal component analysis was conducted using the 16 variables of the segments involved. The feasibility of the analysis was demonstrated by the presence of at least one correlation > 0.300 for each variable considered. The first five component model was reduced to three components based on the visual inspection of the plot, respecting the criteria of interpretability. The correlations between the three components and the continuous variables of interest were evaluated by Pearson's test. Subsequently, we arbitrarily decided to compare the patients presenting the most frequent eSCAR pattern (termed eSCAR+) with all the others (termed eSCAR-).

Frequency variables (categorical) are reported as absolute numbers and relative percentages. Continuous variables, except where defined otherwise, are reported as mean and standard deviation. The associations of interest between categorical variables were analyzed with the Chi-square test or Fisher's test, where appropriate.

The differences between the means for the eSCAR+ and eSCAR- group were analyzed by Student's T-test. For multiple comparisons, multivariable logistic regression analysis was used with the conditional stepwise method.

Statistical significance was considered for a value of $p < 0.05$. All analyzes were performed using IBM SPSS Statistics version 20 software (USA) and graphs using GraphPad Prism 7 software (USA).

5.4 Results

5.4.1 Characteristics of SSc patients

The flow chart describing patient selection for the ULYSSIS study is shown in Figure 11. The Verona cohort includes 405 SSc patients followed at the Division of Rheumatology, University of Verona (n = 405). We approached 221 SSc patients fulfilling the 2013 ACR/EULAR SSc criteria, of which 140 were screened. The patient screening took place between November 2020 and February 2021, and those meeting the inclusion and exclusion criteria (n = 92) were recruited. Informed consent was obtained from all patients prior to inclusion.

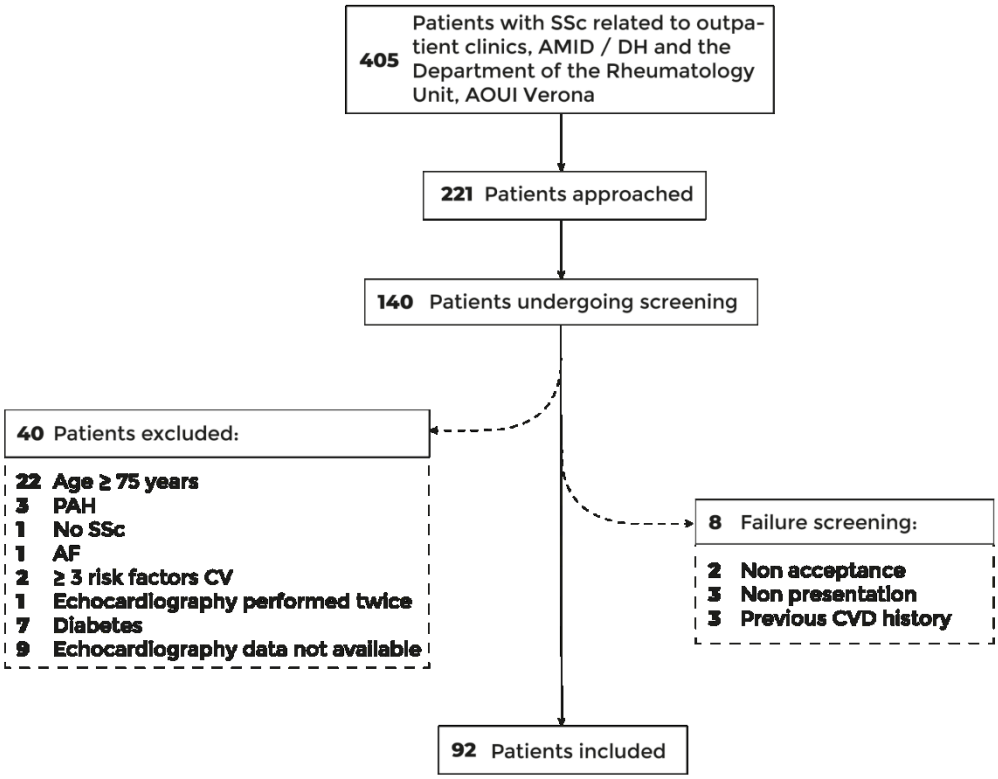

Figure 11. The ULYSSYS study flow-chart

All patients had an established diagnosis of SSc. 97.3% of the population had at least 10 years duration. This was a predominantly female population (87%), and 60.9% were under 60.

Most of the SSc patients were being treated with vasodilators (iloprost 85.9%). 40.2% of patients were on DMARD therapy, more frequently hydroxychloroquine (39.1%) and mycophenolate (17.4%).

Concerning the clinical manifestations of SSc, the most frequent involvement was digital vasculopathy present in over half of the study population and gastrointestinal (oesophagal 50.0%). Over 40% of patients had a history of digital ulcers. About one in three patients (32.6%) had SSc-ILD, mostly NSIP type (96.7% within SSc-ILD). With regard to skin involvement, the most frequent pattern was limited scleroderma. No patient had PH per protocol.

Only 10.9% of patients had two cardiovascular risk factors and 43.5% a single factor; 45.7% did not have any risk factors. The most represented was tobacco

smoking in one-third of patients, followed by arterial hypertension with 15/92 (16.3%) patients receiving ACEi, and dyslipidemia with 26/92 (28.3%) patients taking a statin. No patient was diabetic per-protocol (

Table 17).

Table 17. Baseline characteristics of the ULYSSYS study SSc participants.

Baseline	SSc patients, n=92
Disease subtype, n (%)	
lcSSc	52 (56.5)
dcSSc	38 (41.3)
Sine scleroderma/non specified	2 (2.2)
Disease duration, median (IQR), years	13.0 (6.0, 18.5)
Medications, n (%)	
Current use of DMARDs	37 (40.2)
Previous use of cyclophosphamide	7 (7.6)
Current glucocorticoid use	19 (20.7)
Current therapy with vasodilators	92 (100)
Iloprost	79 (85.9)
Sildenafil	6 (6.5)
Bosentan	13 (14.3)
Calcium channel blockers	35 (38.0)
Clinical profile, n (%)	
Skin involvement	90 (97.8)
mRSS, median (IQR)	18.0 (11.0, 24.0)
Calcinosis	21 (22.8)
Musculoskeletal involvement	6 (6.5)
Joint contractures	6 (6.5)
Vasculopathy	50 (54.3)
Digital pitting scars	23 (25.0)
Raynaud's phenomenon duration, median (IQR), years	18.0 (11.0, 24.0)
Digital ulcerations	41 (44.6)
Lung involvement	30 (32.6)
Gastroenteric involvement	53 (57.6)
Heart involvement	7 (7.6)
Renal involvement	1 (1.1)
Autoantibodies, n (%)	
Anti-centromere	43 (46.7)
Anti-Scl70	27 (29.3)
Anti-Ro/SSA	17 (18.5)
Anti-RNA polymerase III	9 (9.8)
Anti-U3RNP	4 (4.3)
Anti-phospholipids	19 (20.7)
Cardiovascular risk profile, n (%)	
Dyslipidaemia	14 (15.2)
Hypertension	15 (16.3)
Smoking	31 (33.7)
Family history of CVD	1 (1.1)
Patients with any CVD risk factors	50 (54.3)
Age, median (IQR), years	56.0 (51.3, 66.0)
Female sex	80 (87)

CVD, cardiovascular disease; dcSSc, diffuse cutaneous Systemic Sclerosis; DMARDs, disease-modifying anti-rheumatic drugs; IQR, interquartile range (2th-75th percentile); lcSSc, limited cutaneous Systemic Sclerosis; mRSS, modified Rodnan skin score.

5.4.2 Specific pattern of myocardial fibrosis in SSc patients

The eSCAR sign was found in 42/92 (45.6%) of the SSc patients enrolled in the study. The diagrams shown in Figure 12, and Figure 13 illustrate the location of the detected fibrotic scar. The main pattern of fibrotic involvement involved the basal, mid inferoseptal and anterior segments. The second most common pattern of fibrotic involvement was found in the apical segments. More rarely, the presence of eSCAR was detected on the free wall of the left ventricle. The analysis of the main components made it possible to identify three main patterns of eSCAR: (1) lateral and anterior basal and mid segments; (2) septal and lower basal and mid segments; (3) apical segments. This subdivision was able to explain 59% of the total variance, and each component explains respectively 21.3%, 20.3% and 17.3% of the total variance. However, the distinction between the three patterns was not complete, as a proportion of patients with pattern (2) also had the pattern (1).

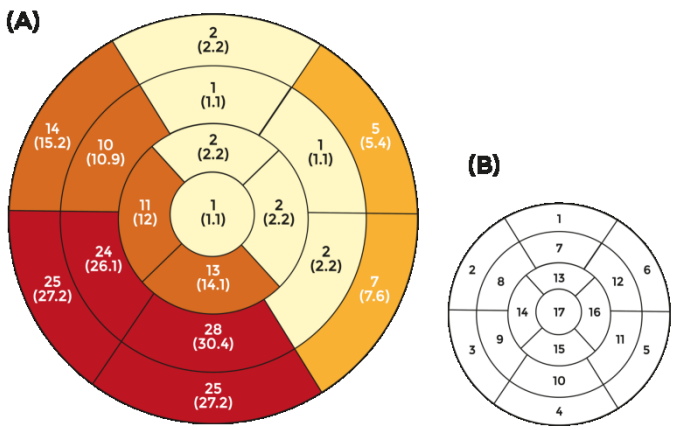

Figure 12. eSCAR localisation in a 17-segments bulls-eye diagram of the left ventricle.

(A) Number of patients (percentage) with eSCAR. (B) 17-segments model for reference: 1, basal anterior; 2 basal anteroseptal; 3, basal inferoseptal; 4 basal inferior; 5, basal inferolateral; 6, basal anterolateral; 7, medium anterior; 8, medium anteroseptal; 9, medium inferoseptal; 10, medium inferior; 11, medium inferolateral; 12, medium anterolateral; 13, apical anterior; 14, apical septal; 15, apical inferior; 16, apical lateral; 17, apex.

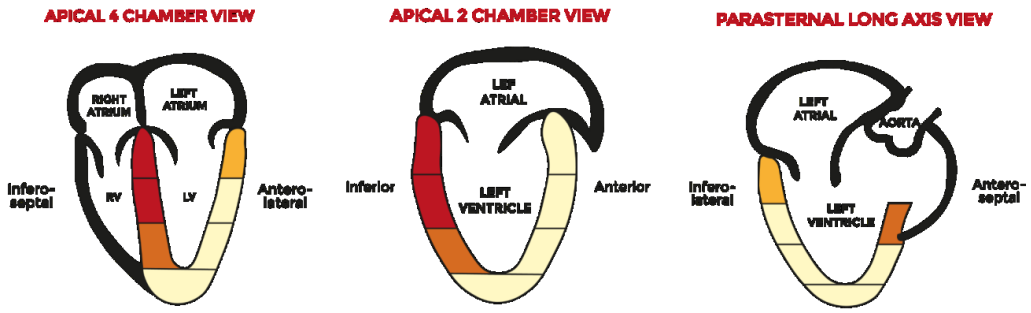

Figure 13. eSCAR findings in apical 4 chamber, apical 2 chamber and parasternal long axis views.

Table 18 highlights the significant correlations of the three different eSCAR patterns with measures of myocardial structure. Pattern (1) correlated with inferior basal strain, right ventricular function; pattern (2) was related to anteroseptal basal strain, and diastolic function; pattern (3) was associated with a reduced strain in the anterior medial longitudinal segment and left ventricular mass.

Table 18. Significant correlations between the three main eSCAR patterns and measures of myocardial mass, function and deformation.

	eSCAR apical		eSCAR lateral		eSCAR septal	
	r	P-value	r	P-value	r	P-value
GLS basal anteroseptal	-0.124	0.452	-0.110	0.507	-0.377	0.018
GLS basal inferolateral	-0.173	0.293	-0.374	0.019	-0.005	0.975
E/E' ratio	-0.002	0.981	0.234	0.025	0.263	0.011
RVEF	0.068	0.522	0.237	0.023	-0.095	0.366
Observed:predicted LVM	0.242	0.023	0.011	0.919	-0.063	0.559

FVC, forced vital capacity; GLS, global longitudinal strain; LVM, left ventricular mass; RVEF, right ventricle ejection function.

We previously showed that eSCAR involved preferentially the inferior and inferoseptal basal and mid segments of SLE patients. Likewise, the most represented eSCAR pattern in SSc patients was the involvement of the inferior or inferoseptal segments. Hence, we decided to compare SSc patients in group 1 (now termed the 'eSCAR+' group) with all other patients (merged group 2 and 3, now termed the 'eSCAR-' group). We justify this choice as a consequence of a more careful selection of patients who had a high probability of presenting a fibrotic scar that showed associations with the characteristics of SSc rather than other confounding factors (for example, atherosclerotic disease). Finally, the eSCAR+ groups comprised 25 SSc patients (27%), who were compared with 67 eSCAR- SSc patients.

5.4.3 Impaired myocardial strain in eSCAR+ SSc patients

Comparing patients with or without the myocardial fibrotic scar, we noted evidence of a significant reduction in systolic function as assessed by global longitudinal strain (GLS) analysis in the eSCAR+ patient group versus the eSCAR- group (longitudinal GLS 3-chamber: -17.11 vs -19.31, p = 0.015). In particular, this

reduction was evident in the cardiac segments where the eSCAR fibrotic scar was detected (the basal anteroseptal segment) (Table 19).

Table 19. Comparison of speckle tracking echocardiography(strain) in eSCAR+ and eSCAR- patients.

Speckle tracking echocardiography	eSCAR+ (n= 25)	eSCAR- (n=67)	P-value
GLS global (%)	- 20.24 ± 2.39	- 20.42 ± 3.65	0.895
GLS 4-chambers (%)	- 20.66 ± 1.91	- 20.09 ± 4.12	0.720
GLS 2-chambers (%)	- 23.02 ± 5.23	- 21.97 ± 3.89	0.924
GLS 3-chambers (%)	- 17.11 ± 2.60	- 19.31 ± 5.26	0.015
GLS apical:			
- anterior	- 19.60 ± 6.12	- 17.72 ± 4.42	0.857
- inferior	- 26.89 ± 7.79	- 23.65 ± 5.46	0.581
- lateral	- 18.91 ± 2.04	- 18.13 ± 5.12	0.508
- septal	- 22.68 ± 7.14	- 21.76 ± 7.04	0.844
GLS basal:			
- anterior	- 23.35 ± 3.82	- 22.75 ± 8.36	0.752
- anteroseptal	- 14.09 ± 4.74	- 18.66 ± 7.46	0,109
- inferior	- 22.69 ± 8.49	- 22.78 ± 6.94	0.818
- lateral	- 19.99 ± 7.68	- 22.55 ± 7.01	0.218
- septal	- 14.26 ± 4.63	- 18.07 ± 8.79	0.081
GLS mid:			
- inferior	- 23.09 ± 6.12	- 22.58 ± 5.07	0.917
- septal	- 14.80 ± 5.69	- 17.50 ± 7.53	0.056
- anterior	- 20.54 ± 3.28	- 19.73 ± 6.52	0.026
- anteroseptal	- 14.70 ± 4.96	- 18.13 ± 5.20	0.010
- lateral	- 18.64 ± 5.79	- 20.09 ± 5.73	0.270

GLS, global longitudinal strain.

Table 20 shows the echocardiographic characteristics of patients with SSc, stratified by the presence or absence of myocardial scar displayed in the eSCAR. Although not statistically significant, subjects with myocardial fibrosis showed a slight increase in the E/E' ratio (6.58 vs 5.83, p = 0.085) due to a higher E velocity (76.60 vs 69.79 cm, p = 0.135) and a slight reduction in the LV-EDV index (43.76 vs 44.75 ml / m2, p = 0.086) and LV-ESV index (13.41 vs 14.68 ml / m^2, p = 0.091), however with values within the normal range.

We also evaluated the relationship between the presence of myocardial fibrosis and atherosclerotic disease by measuring aortic stiffness. There were no differences in AoD or AoS. Conversely, we noticed lower AoSI values in the eSCAR+ group than in the eSCAR- group.

Table 20. Comparison of standard echocardiography and aortic stiffness in eSCAR+ and eSCAR- patients.

Standard echocardiography	**eSCAR+ (n= 25)**	**eSCAR- (n=67)**	**P-value**
LV-EDV index, mL/m^2	43.76 ± 6.77	44.75 ± 8.06	0.086
LV-ESV index, mL/m^2	13.41 ± 2.48	14.68 ± 2.48	0.091
LV-EF, %	68.75 ± 6.47	66.91 ± 7.01	0.299
LV mass index, g/m^2	39.23 ± 14.07	39.97 ± 11.13	0.608
LA volume index, mL/m^2	17.12 ± 2.76	17.95 ± 3.39	0.215
E velocity (cm/s)	76.60 ± 16.60	69.79 ± 15.60	0.135
A velocity (cm/s)	71.28 ± 18.20	71 ± 15.88	0.378
Deceleration time, ms	206.68 ± 51.60	213.37 ± 53.62	0.592
E/A ratio	1.12 ± 0.29	1.01 ± 0.24	0.134
E/E' ratio	6.58 ± 1.97	5.83 ± 1.41	0.085
TAPSE, mm	25.48 ± 3.22	24.66 ± 3.91	0.178
S' velocity, cm/s	14.44 ± 2.29	13.76 ± 2.44	0.202
Aortic stiffness			
AoD, mm	29.62 ± 4.03	29.04 ± 3.00	0.456
AoS, mm	31.47 ± 3.86	30.77 ± 3.19	0.379
AoSI	4.72 ± 4.12	6.74 ± 7.65	0.059

EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LAVI, left atrial volume index; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion; AoD, aortic diameter in diastoler; AoS,, aortic diameter in systole; AoSI, aortic stiffness index..

5.4.4 Digital ulceration and body weight are associated with myocardial fibrosis in SSc patients

Comparing the demographics in the study populations shows that myocardial fibrosis patients had a significantly lower body weight and BMI than eSCAR-

Table 21).

Another clinical data of interest regards the history of digital ulcers: eSCAR+ patients present with a greater frequency of history of digital ulcers compared to the eSCAR- counterpart (64.0 vs 37.4%, p = 0.022), despite a similar duration of the Raynaud phenomenon. Other manifestations of SSc were not markedly different between the two groups.

Pulmonary function tests were similar, although the proportion of patients with severe ILD was small.

Table 21. Clinical characteristics of patients with SSc, stratified by the presence or absence eSCAR.

SSc characteristics	eSCAR+ (n= 25)	eSCAR- (n=67)	P-value
BMI, kg/m^2	21.82 ± 3.51	24.37 ± 4.01	0.006
Disease duration, years	12.6 ± 7.38	13.13 ± 8.16	0.775
Raynaud's phenomen duration, years	16.17 ± 7.93	18.90 ± 12.14	0.325
Disease subtype,			
lcSSc, n (%)	19 (76)	33 (49.3)	0.053
dcSSc, n (%)	6 (24)	32 (47.8)	
SSc sine scleroderma/non specified, n (%)	0 (0)	2 (3)	
Modified Rodnan skin score (mRSS)	6.64 ± 3.38	7.22 ± 4.95	0.592
Digital vasculopathy, n (%):	13 (52)	33 (49.3)	0.815
Pitting scar, n (%)	7 (28)	16 (23.9)	0.685
Digital ulcerations, n (%)	16 (64)	25 (37.3)	0.022
Videocapillaroscopy:	6 (46.2)	13 (46.4)	
early, n (%)	6 (46.2)	9 (32.1)	
active, n (%)	0 (0)	2 (7.1)	0.705
late, n (%)	1 (7.7)	4 (14.3)	
aspecific, n (%)			
Interstitial lung disease, n (%):	5 (20)	25 (37.3)	0.115
NSIP, n (%)	5 (100)	22 (88)	0.999
UIP, n (%)	0 (0)	3 (12)	0.999
Spirometry:			
FVC (%)	115.36 ± 19.36	111.75 ± 26.94	0.541
TLC (%)	101.1 ± 15.78	97.89 ± 19.16	0.456
DLCO (%)	75.25 ± 14.17	71.38 ± 15.48	0.278
DLCO/VA (%)	50.50 ± 20.66	55.82 ± 21.88	0.296
Musculoskeletal involvement:			
Joint contractures, n (%)	2 (8)	4 (6)	0.661
Calcinosis, n (%)	7 (28)	14 (20.9)	0.470
Gastrointestinal involvement:			
Esophageal, n (%)	12 (48)	34 (50.7)	0.815
Gastric, n (%)	6 (24)	12 (17.9)	0.560
SIBO, n (%)	1 (4)	1 (1.5)	0.472
Stipsis, n (%)	4 (16)	11 (16.4)	0.999

5.4.5 Autoimmunity and biochemical characteristics of eSCAR+ SSc patients

The percentage of SSc patients who had ACA was significantly higher in the eSCAR+ group than in the eSCAR- group (68 vs 38.8%, p = 0.013), while eSCAR+ patients with anti-Scl70 antibodies were numerically less (8 vs 37.3%, p = 0.06). Patients with anti-U3RNP antibodies were also more frequent in the eSCAR group (12 vs 1.5%, p = 0.060).

Regarding the laboratory data, there were no significant differences in renal function, haemoglobin, indexes of inflammation, uric acid, complement, levels of NT-proBNP and CK (Table 22).

Table 22. Immunology and biochemistry of the eSCAR+ and eSCAR- patients.

Biochemical analysis	eSCAR+ (n= 25)	eSCAR- (n=67)	P - value
Hemoglobin, g/dL	13.48 ± 0.77	13.38 ± 1.09	0.665
eGFR, mL/min/1.73m^2	91.32 ± 14.70	90.44 ± 15.43	0.806
Uric acid, mg/dL	4.56 ± 1.27	4.16 ± 0.93	0.100
BNP, pg/mL	100.58 ± 54.27	136.58± 183.39	0.152
CK, U/L	84.83 ± 35.95	96.53 ± 42.15	0.222
C3 complement, g/L	1.07 ± 0.19	1.08 ± 0.17	0.893
C4 complement, g/L	0.22 ± 0.07	0.21 ± 0.06	0.401
VES, mm/h	13.12 ± 11.42	17.72 ± 14.89	0.121
PCR, mg/L	2.50 ± 5.39	2.82 ± 4	0.754
Autoantibodies			
ACA, n (%)	17 (68)	26 (38.8)	0.013
Anti-Scl70, n (%)	2 (8)	25 (37.3)	0.006
Anti-RNA polimerase III, n (%)	1 (4)	8 (11.9)	0.435
Anti-phospholipids, n (%)	8 (32)	11 (16.4)	0.100
Anti-RoSSA, n (%)	7 (28)	10 (14.9)	0.225
Anti-U3RNP, n (%)	3 (12)	1 (1.5)	0.060

5.4.6 Lower exposure to prostanoids in eSCAR+ SSc patients

eSCAR+ patients have a shorter duration of treatment and a lower cumulative received dose of iloprost than the eSCAR-. No association was demonstrated for the use of other vasodilators (sildenafil, bosentan or calcium channel blockers). In eSCAR+ patients, there was also a significant increase in the use of statins (32 vs 11.9%, p = 0.033). For the remaining drugs, we were unable to demonstrate a significant difference in their use between the two patient populations, including prior use of cyclophosphamide (Table 23).

Table 23. Comparison of medications in the eSCAR+ and eSCAR- groups.

SSc therapy	eSCAR+ (n= 25)	eSCAR- (n=67)	P - value
Vasodilators			
Iloprost, n (%)	19 (76)	60 (89.6)	0.174
- treatment duration, years	7.02 ± 5.38	10.28 ± 7.45	0.029
- cumulative dose received, mg	991.37 ± 888.08	1419.67 ± 1105.48	0.058
Sildenafil, n (%)	2 (8)	4 (6)	0.661
Bosentan, n (%)	4 (16)	9 (13.6)	0.747
Calcium channel blocker, n (%)	10 (40)	22 (32.8)	0.285
Cardiovascular pharmacology			
ACE inhibitors, n (%)	4 (16)	11 (16,4)	0.999
Beta blockers, n (%)	3 (12)	6 (9)	0.700
Statin, n (%)	8 (32)	8 (11.9)	0.033
Anticoagulant, n (%)	2 (8)	9 (13.4)	0.721
Diuretics	3 (12)	9 (13.4)	0.999
Antiplatelet agents	13 (52)	26 (40)	0.303
Immunomodulators			
Current use of disease-modifying drugs, n (%)	7 (28)	30 (44.8)	0,144
Mycofenolate, n (%)	4 (16)	12 (17.9)	0.999
Methotrexate, n (%)	2 (8)	6 (9)	0.999
Hydroxychloroquine, n (%)	8 (32)	28 (41.8)	0.392
Azathioprine, n (%)	1 (1.1)	5 (7.5)	0.999
Rituximab, n (%)	0 (0)	3 (4.5)	0.560
Tocilizumab, n (%)	0 (0)	2 (3)	0.999
Leflunomide, n (%)	0 (0)	1 (1.5)	0.999
Previous use of cyclosphosphamide, n (%)	0 (0)	7 (10.4)	0.183
Current use of prednisone, n (%)	4 (16)	30 (44.8)	0.144
Daily dose, mg	2.5 ± 3.53	3.48 ± 1.95	0.539

ACE, angiotensin converting enzyme.

5.4.7 CVD risk factors are equally distributed in eSCAR- and eSCAR- SSc patients

The two patient groups did not differ significantly for any cardiovascular risk factors considered (including age, gender, BMI, the proportion of smokers, hypertension, hypercholesterolemia, and family history of CVD) (Table 24).

Table 24. Cardiovascular characteristics of the eSCAR+ and eSCAR- patients.

Cardiovascular risk profile	eSCAR+ (n= 25)	eSCAR- (n=67)	P-value
Age, years	55.32± 8.36	58.04±10.44	0.245
Male, n (%)	4 (16)	8 (11.9)	0.729
BMI, kg/m^2	21.82±3.51	24.37±4.01	0.006
Smoking, n (%)	10 (40)	21 (31.3)	0.435
Hypertension, n (%)	3 (12)	12 (17.9)	0.752
Dyslipidaemia, n (%)	3 (12)	11 (16.4)	0.751
Family history of CVD	0 (0)	1 (1.5)	0.999

BMI, body mass index; CVD, cardiovascular disease.

5.4.8 Digital ulcers are an independently associated with myocardial fibrosis

We evaluated through multivariable logistic regression analysis whether the association between digital ulcers and eSCAR+ was independent of BMI. The analysis confirmed that history of digital ulcers was the strongest independent predictor of myocardial scars, increasing by five-times the likelihood of having eSCAR+. BMI was also independently associated to eSCAR+ by a factor 3 (Table 25).

Table 25. Independent association of digital ulcers and body mass index with myocardial fibrosis (eSCAR+).

Logistic regression	OR	95% CI inf	95% CI sup	P-value
Digital ulcers	3.264	1.195	8.915	0.021
BMI (kg/m^2)	0.816	0.700	0.950	0.009

Forward stepwise logistic regression (Nagelkerke R^2 0.205, p=0.01). BMI, body mass index.

5.5 Discussion

This clinical study represents the first study aiming at investigating the presence of myocardial fibrosis in SSc patients through a non-invasive, inexpensive and easily available TTE technique.

pHI-SSc is one of the main causes of mortality in SSc patients and is associated with a poor prognosis (up to 70% of mortality reported at five years) [Ferri, 2002]. However, there are no clinical clues characterizing pHI-SSc. Cardiac involvement is mostly subclinical, with a clinically manifest rate of involvement estimated at around 30% [Kahan, 2006; Parks, 2014; Tyndall, 2010]. Therefore, if, on the one hand, the subclinical myocardial involvement can have a prognostic value in itself, it has also and above all a value as a global prognostic stratification factor in the SSc patient.

Even in a phase of early subclinical involvement, nuclear imaging and CMR imaging studies have demonostrated functional or perfusion abnormalities due to remodelling of the small coronary arteries [Kahan, 1986; Kahan, 2006; Allanore, 2008; Hachulla, 2009; Mavrogeni, 2015]. These microvascular anomalies lead to a reduced reserve of coronary flow resulting in myocardial fibrosis [Mavrogeni, 2015]. It has been shown that myocardial fibrosis in SSc has a non-coronary distribution [Steen, 2004; Mavrogeni, 2016] and progresses to biventricular systolic and diastolic dysfunction.

Fibrosis, therefore, represents an important and recognized feature of the disease and represents a serious negative prognostic factor. The advantage of using CMR imaging to identify localised areas of fibrotic myocardium through the LGE technique is undoubtedly invaluable in the diagnostic study of a patient at risk. However, the impossibility of applying large-scale CMR imaging study remains: this poses a serious limitation in the classification and study of scleroderma patients. On the other hand, routine TTE does not have enough sensitivity and specificity to detect areas of edematous and fibrotic myocardium [Mavrogeni, 2013]. Furthermore, although an abnormal TTE is indicative of a dysfunctional myocardium, the presence of normal TTE does not preclude myocardial lesions in symptomatic patients.

The first important finding was that the eSCAR echocardiographic technique efficiently detected myocardial scars in 46% of SSc patients. More importantly, 27% of them (one every three SSc patients) had a recurrent pattern of fibrosis involving

the basal and mid anteroseptal segments. Our findings are substantially in keeping with prior CMR imaging studies [Krumm, 2017; Hachulla, 2009; Dumitru, 2021; Rodriguez-Reyna, 2015] and further confirms the ability of the eSCAR technique as a non-invasive cardiac tissue study.

In our study, we found that routine TTE was ineffective in distinguishing between the SSc population with and without myocardial fibrosis. The ejection fraction value, often used as an indicator of systolic function, did not show significant differences in the two groups. The same was noticed for other measures indicative of diastolic dysfunction (TAPSE, E/E' ratio, LV-EDV index) or myocardial toxicity biomarkers (NTproBNP, CK). This findings were expected, as pHI-SSc has been associated with an increase in NTproBNP, high-sensitivity cardiac troponin T and CK levels only once overt systolic or diastolic dysfunction developed [Chighizola, 2012; Jurisic, 2013; Bosello, 2019].

We noted that even eSCAR+ patients had standard TTE values within the limits of normality, suggesting that myocardial fibrosis appears earlier than the abnormalities seen with traditional echocardiography. However, consistent with prior studies [Zairi, 2018], myocardial strain was impaired in the eSCAR+ group, indicating the presence of subclinical cardiac involvement not detected by standard echocardiography. Myocardial strain as detected by the measurement of GLS with STE has many advantages over the evaluation of systolic function based on the ejection fraction: the latter appears to be an insufficient evaluation method due to the complex movement of the myocardium, characterized by three-dimensional movements (longitudinal shortening, radial thickening and circumferential shortening, as well as a twisting movement due to the helical nature of the heart muscle). Left ventricular ejection fraction mainly depends on radial and circumferential myocardial deformation caused by mid myocardial and epicardial fibres. Conversely, the longitudinal function is predominantly influenced by subendocardial fibres, which are more susceptible to evident myocardial damage with conserved EF [Spethmann, 2014]. In our study, a greater reduction in GLS (i.e. values more tending to zero) was shown in eSCAR+ compared to eSCAR- SSc patients. This difference was particularly evident for the GLS 3-chambers and the GLS basal anteroseptal, GLS basal septal, GLS mid anteroseptal and GLS mid-septal

segments. Moreover, GLS reductions matched with segments of myocardial fibrosis as detected by eSCAR. This agreement was not perfect, as the GLS antero-basal was not significantly reduced in eSCAR+, albeit eSCAR identified myocardial fibrosis in that area. Nonetheless, all these findings reinforce the validity eSCAR technique as a more sensitive study method to capture fibrosis-associated abnormalities of myocardial function.

Our secondary objective was seeking possible clinical or biochemical indicators that would allow differentiating the eSCAR+ from the eSCAR- patients. Among eSCAR+ patients, a history of digital ulcers was much more frequent than in eSCAR- patients, whereas there was no significant difference both as regards the presence of overall digital vasculopathy and the duration of Raynaud's phenomenon. Moreover, eSCAR+ patients had the same duration and frequency of digital vasculopathy as the eSCAR- patients. The increase in frequency of history of digital ulcers in eSCAR+ could underlie advanced endothelial dysfunction, which would in turn explain the greater prevalence of myocardial fibrosis. Interestingly, though, the exposure to iloprost showed significant protection against myocardial fibrosis. Indeed, the duration of prostanoid treatment and the cumulative dose received were both significantly shorter in eSCAR+ than in eSCAR-SSc patients. This result partially correlates with the protective role of vasodilator therapy in the manifestations of pHI-SSc [Valentini, 2019]. However, we failed to demonstrate protective effects from other vasodilators (sildenafil, bosentan and calcium antagonists) or aspirin. It is also noteworthy that the current clinical practice recommends against iloprost therapy in patients with CAD, though some reports [Tumer, 2019; Aydin, 2017; Aydin, 2019] have shown that iloprost could have a protective role against coronary ischemia.

eSCAR+ patients had considerably and significantly lower BMI than eSCAR- patients, suggesting nutritional impairment in the former. Weight loss is the main outcome in the longitudinal evaluation of malnutrition, which is in turn associated with significant mortality and gastrointestinal involvement [Bagnato, 2021]. Although we did not find correlations between the frequency and type of gastrointestinal involvement and eSCAR+, several patients had oesopagheal involvement and potential inadequate calories intake. Hence, evidence of a low BMI

in our eSCAR+ SSc patients could be indicative of greater disease severity [Caimmi, 2017].

Myocardial fibrosis identified by eSCAR was associated with ACA, while patients who had anti-Scl70 antibodies were significantly less represented in this group. This finding is original, as no associations have been reported between myocardial fibrosis and SSc-related autoantibodies. Historically, increased risk of myocardial involvement has been associated with anti-Scl70 antibodies or diffuse skin involvement [Nihtyanova, 2010]. However, there are no autoantibodies specific for cardiac involvement in SSc. Different patient selection, exclusion of those with PAH and longer disease duration could account for this discrepancy from prior studies. The high frequency of ACA in eSCAR+ SSc patients might hinder that microvascular angiopathy is the culprit of myocardial fibrosis [Markusse, 2017]. The presence of ACA in SSc has been associated with overt expressions of vasculopathy, such as digital ulcers and SSc-PAH. In keeping with the observation that eSCAR was associated with microvasculopathy rathern than an inflammatory insult, eSCAR did not significantly associate with any immune-modulatory therapy. Patients with anti-U3RNP antibodies were also more frequent in the eSCAR group. Interestingly, a multicentre study of 132 SSc patients based in the UK showed that those with anti-U3RNP were at highest risk of developing cardiac involvement [Nihtyanova, 2020].

Finally, we did not find an imbalance in the frequency of traditional CVD risk factors in SSc patients with myocardial fibrosis. Traditional risk factors are no more prevalent in patients with SSc than in healthy controls [Man, 2013; Ngian, 2012]. However, the aortic stiffness index (AoSI) was associated with the eSCAR- group. This result led us to consider the presence of subclinical atherosclerotic disease in eSCAR- patients, as recently highlighted by some research groups [Caimmi, 2020; Makol, 2021].

5.6 Study strengths and limitations

The first objective limitation concerns the eSCAR technique. This has been validated with studies identifying ischemic scars in post-AMI patients [Gaibazzi, 2016]. Hence, we cannot completely rule out microvascular angina. Our study lacks an

assessment of the coronary circulation with functional tests (e.g. stress test) or biochemical analysis of cardiac biomarkers (e.g. troponin).

Second, some study limitations depend on the population selected for the study. The duration of the disease in our patients was indicative of advanced disease (about seven years in the eSCAR+ patients). The lack of a cohort of recently diagnosed SSc patients may have overestimated some associations. Focusing on the primary forms of myocardial involvement of the SSc, we did not analyze the SSc patients with the presence of a coronary ischemic scar, which, however, is important to identify for the clinical and prognostic management of the patient. The exclusion criteria of our study could be stringent, with the risk of selecting a cohort of SSc patients not exactly representative of the general picture. Finally, further limitations of the study concern the methods applied. Indeed, there was no validation of the eSCAR technique through cardiac MRI or endomyocardial biopsy.

Chapter VI. Conclusion

The assessment, characterisation and treatment of RMDs-pHI are critical unmet needs in the management of RMDs with the involvement of the cardiovascular system.

We sought to investigate whether echocardiography equipped with advanced techniques could help stratify RMDs patients according to the presence of RMDs-pHI.

Our results seem to indicate that TNFi treatment could be associated with reduced arterial stiffness in patients with established, long-standing RA with several CVD risk factors. Although long-term TNFi therapy can be challenging due to the high CVD burden, our data encourage the assessment of AoSI in RA patients and maintain TNFi therapy, whereas AoSI is abnormally high. This can be particularly relevant in such RA patients at high CVD risk.

Since LVH is a risk factor for acute haemodynamic decompensation, our data support the knowledge that RA patients have a higher likelihood than the general population to suffer from HF. It is likely that gender could have a vital role to determine LVH, not due to conventional risk factors. More attention should be paid to LVH in women with RA as abnormal LV remodelling could be more likely to develop and progress than in men and offset the female sex protection in cardiovascular risk. According to our data, RA has a different impact on LVH in men and women.

We have also highlighted subclinical myocardial involvement through the use of advanced echocardiography methods in patients with SLE without a history of heart disease or symptoms possibly linked to it. Myocardial fibrosis was found in 19% of patients with SLE: these patients were significantly less likely not to have an SLE flare during the clinical follow-up. This suggests that the eSCAR patients suffer from a more aggressive disease than observed in the traditional clinical examination: in fact, the eSCAR patients had higher cumulative and current dosages of steroid, SLEDAI, complement consumption and a more reduced renal function. In addition, the strain was found to be altered in almost all cardiac segments in the eSCAR

patient group compared to the eSCAR- group, especially in the infero-septal segment where eSCAR fibrosis was found. Studies on larger samples of SLE patients will be needed to better evaluate the diagnostic and prognostic role of these echocardiographic techniques in SLE patients.

We conducted a similar study in a larger cohort of patients with SSc. Myocardial involvement may be even more clinically relevant in such patients compared to other RMDs. The most interesting finding is that areas of myocardial fibrosis can be effectively found in a relevant proportion of SSc patients, and those are correlated with vasculopathy. Hence, our results will help identify clinically those patients who are at the highest risk of having myocardial fibrosis.

Rheumatology has focused on weak outcomes such as disease activity or global damage. However, RMDs-pHI could be associated with hard outcomes such as mortality and hospitalisations. The prioritisation of CVD co-morbidity in the modern era has ensured CVD outcomes are included as an extended goal in the management of RMDs. The extreme clinical variability of RMDs explains why it is difficult to make prognostic predictions on an individual patient level in practice.

Overall, our results help patients' stratification and provide simple, reliable and cost-effective methods that could be easily implemented in the routine practice of rheumatologists in the next years. In this regard, an important objective in the management of CVD morbidity in RMDs in our clinical practice is establishing dedicated pathways in the assessment and stratification of CVD risk to tailor effective management strategies (traditional and anti-inflammatory). Integrated, multidisciplinary care and lifestyle intervention tailored to RMDs populations are needed to achieve successful outcomes. Cardiology and rheumatology combined clinics and working groups remain an exception among tertiary centres, and further research is needed to address whether this approach as a standard would be feasible and effective in ameliorating the CVD outcomes of RA patients in the long term.

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