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REVIEW

Imaging for screening cardiovascular involvement in patients with systemic rheumatologic diseases: more questions than answers

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Cardiovascular involvement due to systemic rheumatologic diseases (SRDs) remains largely underdiagnosed despite causing excess mortality and limiting the favourable effect of therapeutic developments on survival. Traditional risk scoring systems are poorly calibrated for SRD patients. There is an unmet need to develop a cardiovascular (CV) risk stratification tool and screening algorithm for CV involvement dedicated to asymptomatic patients with SRDs. Even though accelerated atherosclerosis is the most prominent cause of major CV events, a more comprehensive approach is crucial to detect different pathological processes associated with SRDs that are leading to CV complications. In that regard, incorporation of imaging parameters obtained from echocardiography and carotid ultrasound (CUS) might help to improve risk models, to detect and monitor subclinical CV involvement. These two imaging modalities should be an integral part of screening SRD patients with suspicion of CV involvement on top of electrocardiogram (ECG). Cardiac magnetic resonance and multi-slice computerized tomography angiography and nuclear imaging modalities seem very important to complement echocardiography and CUS for further evaluation. However, to answer the question 'Should asymptomatic patients with SRDs undergo screening with echocardiography and CUS on top of ECG?' necessitates large studies performing cardiac screening with a standard approach by using these imaging methods to obtain longitudinal data with hard CV outcomes.

Keywords rheumatologic diseases • risk assessment • cardiovascular complications • multimodality imaging

Introduction

Cardiovascular (CV) system can be involved by many aspects during the course of systemic rheumatologic diseases (SRDs) (*Table 1*). CV complications are associated with excess mortality and limit the favourable effect of therapeutic developments on survival in SRDs. Yet, CV involvement remains underestimated or silent most of the time.[1] Monitorization of subclinical CV diseases and early diagnosis might protect from the dismal course related to CV complications by modifying the therapeutic approach.[2] This review focuses on the rational and potential yields of imaging as part of screening CV involvement in SRDs and highlights gaps in evidence.

Rationale for screening atherosclerotic CV disease

Accelerated atherosclerosis has long been known as the leading cause of excess mortality in SRDs, particularly in those with inflammatory arthritis.[3] Inflammation acts synergistically with traditional risk factors to promote atherosclerosis and the control of inflammatory activity has been shown to reduce the residual risk of recurrent CV events on top of optimal control of traditional risk factors.[2,4] There is higher rate of incident CV events,[5] case fatality,[6,7] and recurrences after an index event, even when patients are managed similarly

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Table 1 Targets for screening cardiovascular involvement in systemic rheumatologic diseases

	Major	Other
Rheumatoid arthritis	Accelerated atherosclerosis	Amyloidosis
	Heart failure	Myocarditis
		Pericarditis
		Valvular lesions
Spondyloarthropaties	Accelerated atherosclerosis	Rhythm abnormalities
	Valvular lesions (aortic regurgitation)	Heart failure
Systemic lupus erythematosus	Accelerated atherosclerosis	Myocarditis
	Valvulitis/Valvular lesions	Coronary vasculitis/thrombosis
	Pulmonary arterial hypertension	Rhythm abnormalities
	Microvascular dysfunction	
	Pericarditis	
Systemic sclerosis	Pulmonary arterial hypertension	Rhythm abnormalities
	Microvascular dysfunction	Pericarditis
	Cardiomyopathy/heart failure	Valvular lesions?
		Accelerated atherosclerosis?
Antiphospholipid syndrome	Valvular lesions	Coronary thrombosis
Systemic vasculitis		
Large vessel vasculitis	Aortic aneurysms	Coronary arteritis
	Valvular lesions (aortic regurgitation)	Group IV pulmonary hypertension
	Cardiomyopathy	
Medium size vessel vasculitis	Cardiomyopathy	Pericarditis
	Coronary vasculitis	
	Coronary aneurysms (Kawasaki disease)	
Small vessel vasculitis	Heart failure	Pericarditis
	Microvascular dysfunction	Endocarditis (Churg–Strauss syndrome)

and despite having similar classical risk factors in rheumatoid arthritis (RA) patients as compared to their non-RA counterparts.[8] Likewise, patients with systemic lupus erythematosus (SLE) are at increased risk for myocardial infarction and stroke.[9] Importantly, female gender is preponderant and patients with SRDs are younger than the general population having comparable severity of atherosclerosis[10] (*Figure 1*, Supplementary data online, *Video S1*). Of note, the excess risk of mortality from CV events in patients with RA and SLE was shown to be comparable to the risk associated with type 2 diabetes mellitus.[6,11]

This malignant course is partly explained by vulnerable plaques prone to rupture with excess inflammatory activity as shown in pathologic specimens, despite less severe stenotic lesions.[12] Consequently, the presentation is atypical with more frequent silent myocardial infarction, sudden cardiac death despite less frequent angina,[1] explaining the poor outcome after CV events and limited success of secondary prevention.[4] Vigilant and aggressive assessment of risk and subclinical CV involvement in patients with SRDs seems therefore indispensable. However classical risk scoring systems are poorly calibrated for SRD patients, reaching almost 50% underestimation by Framingham score in patients with RA and SLE.[13,14] Patients who are mostly women with persistently elevated inflammatory markers are placed at low risk categories by age and gender giving a false sense of security. Although not validated, the proposed solution by EULAR (European League Against Rheumatism) to improve risk stratification is to introduce a multiplication factor of 1.5 when using the Framingham or European SCORE systems for patients with RA.[15] This approach is extended to all SRDs as Class IIb indication in European Society of Cardiology (ESC) guidelines for CV prevention[16] despite the lack of use of any multiplier for SRDs in American College of Cardiology/American Heart Association (ACC/AHA) prevention guidelines.[17]

Imaging for screening atherosclerotic CV disease

There is low level of agreement for the use of carotid ultrasound (CUS) for risk stratification and screening asymptomatic carotid plaques in patients with RA in EULAR recommendations and no imaging is recommended for screening CV disease for SRD in general.[15] Yet, in two large studies, CUS findings re-classified RA patients into more appropriate CV risk groups.[18,19] In addition, evidence shows that; (i) carotid intima media thickness is a robust marker of atherosclerosis in large populations,[18] (ii) carotid plaques are prevalent in patients with SRDs, have rapid progression, particularly in association with high levels of systemic inflammation,[20] and (iii) carotid atherosclerosis predicts incident acute coronary syndromes in RA.[21] On the other hand, higher coronary calcium scores have been found in patients with established RA and SLE than those with early or no disease.[22,23] However, coronary calcium score is not sensitive for vulnerable

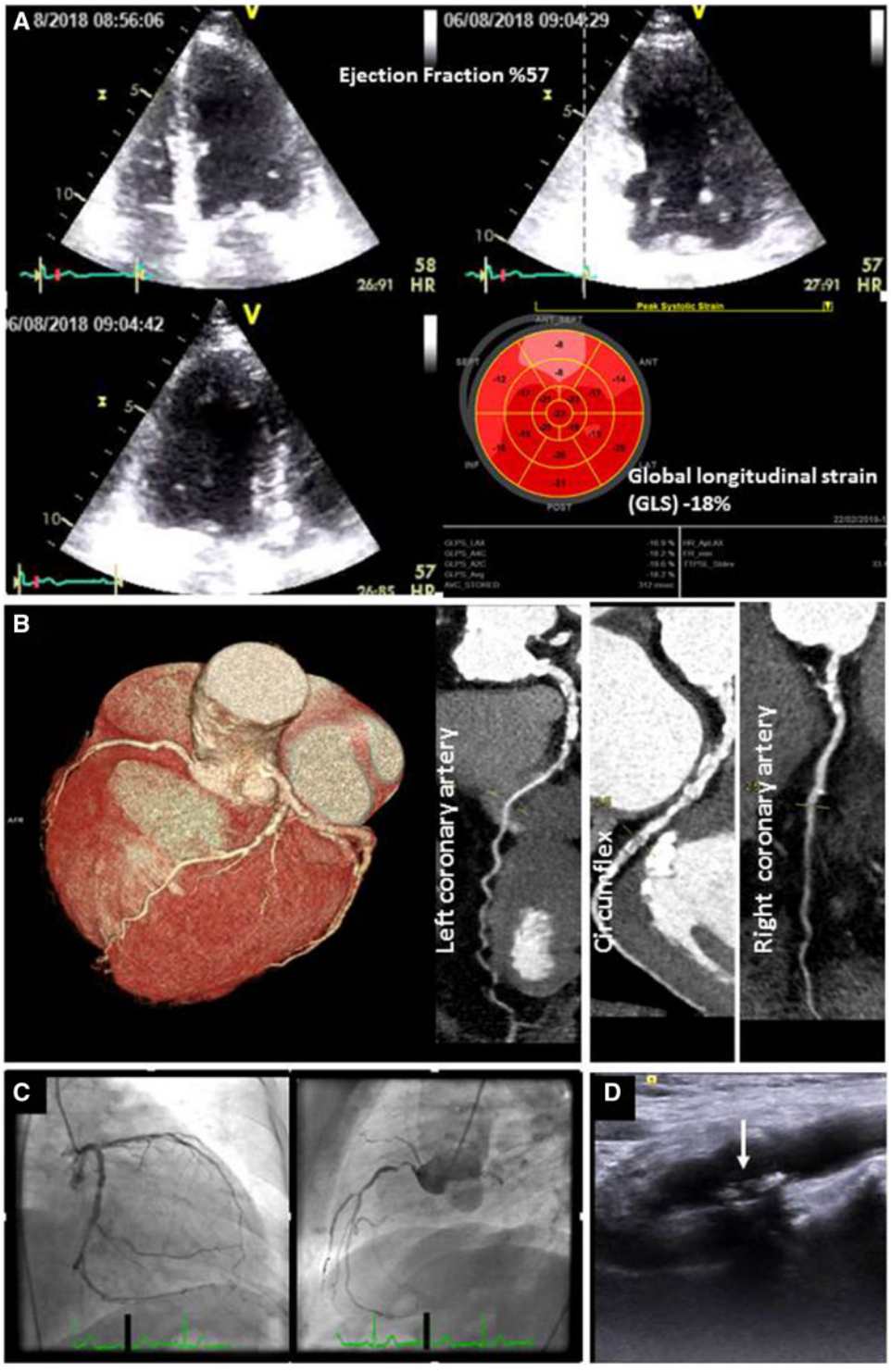

Figure 1 A 48-year-old women, suffering from rheumatoid arthritis for 10 years, apparently asymptomatic with severe functional disability due to joint pain and no traditional risk factors for atherosclerosis (*A*). Mildly reduced global longitudinal strain with subtle segmental heterogeneity, no visual wall motion abnormality. (*B*) Multi-slice computerized tomography angiography and (*C*) conventional angiography confirms severe three-vessel disease. (*D*) Carotid plaques of the patient (arrow).

mixed or non-calcified plaques that are frequent in patients with SRDs;[23] hence, clinical judgment about risk should prevail. Primary prevention guidelines of ESC and ACC/AHA recommend to consider carotid plaques and coronary calcium score, respectively, as additional risk prediction tools to reclassify risk estimate among individuals at borderline and intermediate risk.[17] Whether CUS or calcium score for screening and monitoring subclinical atherosclerosis in SRD patients modifies the outcome awaits further investigation.

Arterial stiffness by pulsed-wave velocity and endothelial function by flow-mediated dilatation have also been used to assess atherosclerosis in RA, SLE, and systemic sclerosis (SSc) in several small series that consistently showed functional abnormalities. However, the predictive value of these vascular tests to detect CV events in SRDs is not established.[24]

Multi-slice computerized tomography angiography (MCTA) is the best non-invasive modality to assess coronary lesions anatomically and plaque composition and reliably shows increased incidence of silent coronary atherosclerosis in patients with RA, SLE, and psoriatic arthritis.[23] Radiation exposure limits its use for serial follow-up in relatively young, asymptomatic patients. Furthermore, relative implications of anatomical vs. functional assessment are unknown. Several fold increased risk of myocardial ischaemia in exercise echocardiography and increased mortality in patients with ischaemia were shown in RA.[25] However, wall motion score at rest is insensitive while stress echocardiography and stress-rest single-photon emission tomography are moderately sensitive to detect ischaemia. Importantly, not only flow limiting coronary artery disease but also inflammation, microvascular dysfunction, or fibrosis can cause perfusion abnormalities.[26]

Rational for screening non-atherosclerotic vascular impairment

Non-atherosclerotic mechanisms including microvascular dysfunction, obliterative vasculopathy, thrombosis, and small vessel vasculitis are added to CV risk in all SRDs, particularly in SSc. Vasculopathic process in small coronary vessels triggers endothelial dysfunction, intimal proliferation, immune system activation, and thrombogenicity, all leading to obliterative vasculopathy. Intermittent spasms of intramyocardial coronary arteries with ischaemia–reperfusion episodes (intramyocardial Raynaud) are responsible from patchy fibrosis in early stages.[27] Later, obliterative vasculopathy of intramyocardial arteries is irreversible and leads to extensive fibrosis, irrespective of coronary territories. These changes are associated with rapid deterioration of ventricular function, life threatening arrhythmias (*Figure 2*, Supplementary data online, *Videos S2.1-4*), and increased risk of death in patients with SSc.[28]

Primary systemic vasculitis (i.e. Churg–Strauss Syndrome, granulomatosis with polyangiitis, and polyarteritis nodosa) can also cause severe myocardial damage due to intramyocardial coronary vasculitis besides epicardial coronary arteritis.[29]

Importantly, early perfusion defects caused by non-atherosclerotic vascular impairments may be reversible with treatment.[26]

Imaging for screening non-atherosclerotic vascular impairment

The assessment of coronary flow reserve (CFR) by transthoracic Doppler echocardiography is readily available and reflects microvascular dysfunction in the absence of epicardial coronary lesions. CFR is the ratio of hyperaemic to baseline peak diastolic velocity of the coronary flow during adenosine or dipyridamole infusion. Reduced CFR has been shown in patients with SRDs independently of traditional atherosclerotic risk factors.[30] Significant impairment of CFR can occur due to inflammation, intramyocardial fibrosis, and vascular damage.[26] Although, CFR by Doppler echocardiography seems safe and feasible for screening microcirculatory disturbances, more data are needed to understand its prognostic and therapeutic implications in asymptomatic, low–moderate risk SRD patients. Perfusion defects can be assessed more accurately by contrast-enhanced CMR and impaired myocardial blood flow reserve by positron emission tomography (PET) with rest-stress quantification of myocardial blood flow in the absence of flow limiting atherosclerotic lesions in patients with SRDs.[27,31,32] However, rigorous assessment of ischaemia by advanced imaging tools should be driven by a judicious use of resting echocardiography with strain imaging and CUS or calcium score in asymptomatic patients with low to intermediate CV risk.[26]

Rational for screening myocardial involvement

Heart failure (HF) due to ischaemic and non-ischaemic causes, is a common complication and an important cause of CV mortality in SRDs.[33] Inflammation can damage the myocardium directly by triggering fibroblast activity, leading to myocardial remodelling by reactive fibrosis. Chronic inflammation, drug toxicity, antiphospholipid antibodies, immune complex deposition, vasculitis, microvascular dysfunction, and renal dysfunction can all underlie primary myocardial damage. Myocarditis is a serious but an uncommon manifestation of SRDs. Although recovery is possible with early diagnosis and treatment, irreversible HF, ventricular arrhythmias, and sudden cardiac death may occur.[34] Despite being subclinical most of the time, the presentation and progression are variable and unpredictable (*Figure 3*, Supplementary data online, *Video S3A, B*). Myocarditis is associated with poor prognosis and can be the initial manifestation; particularly in SLE.[34,35] In postmortem series, histologic evidence of myocarditis has been reported up to 57% of SLE patients which is far more frequent than recognized clinically.[35]

Symptoms and electrocardiogram (ECG) are of limited value to detect myocardial involvement, therefore adequate size studies with imaging modalities are needed.

Imaging for screening myocardial involvement

Echocardiography is the first line imaging tool to detect myocardial morphological and functional changes. Speckle-tracking imaging (STI)

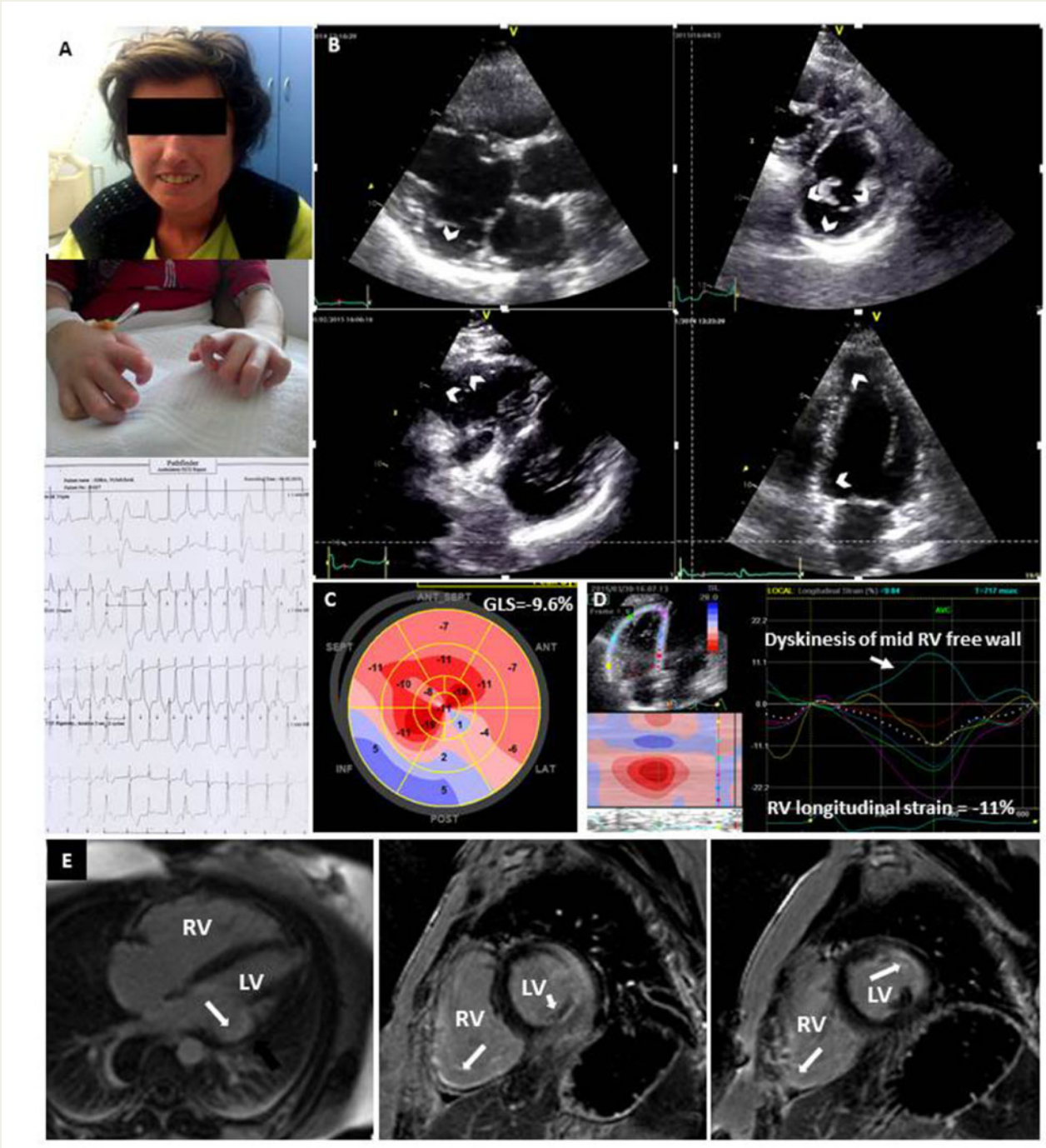

Figure 2 (*A*) A 36-year-old women with palpitation, suffering from systemic sclerosis for 15 years, had multiple episodes of non-sustained ventricular tachycardia on Holter. (*B*) Severe regional wall motion abnormalities in left (LV) and right ventricle (RV) (arrows). (*C, D*) Global longitudinal strain (GLS) shows severe regional LV and RV systolic dysfunction. (*E*) Cardiac magnetic resonance shows enlarged RV and transmural late gadolinium hyperenhancement on both LV and RV walls (arrows) despite no significant epicardial coronary lesion or pulmonary hypertension.

is a method that increases the sensitivity of echocardiography for detecting subclinical myocardial dysfunction when ejection fraction is still preserved, irrespective of underlying mechanism. Preliminary data suggest that echocardiography with STI could be a promising tool for screening early myocardial involvement and for monitoring the effects of anti-inflammatory treatment in SRDs.[36,37]

CMR, PET, and PET/CMR enable tissue characterization and help to differentiate inflammation, fibrosis, and oedema from ischaemic lesions (*Figure 4*, Supplementary data online, *Video S4*).[34,38–40] However, there is not enough evidence to counterbalance the cost and limited availability of CMR or PET as screening and serial follow-up tools to assess myocardial involvement in asymptomatic SRD

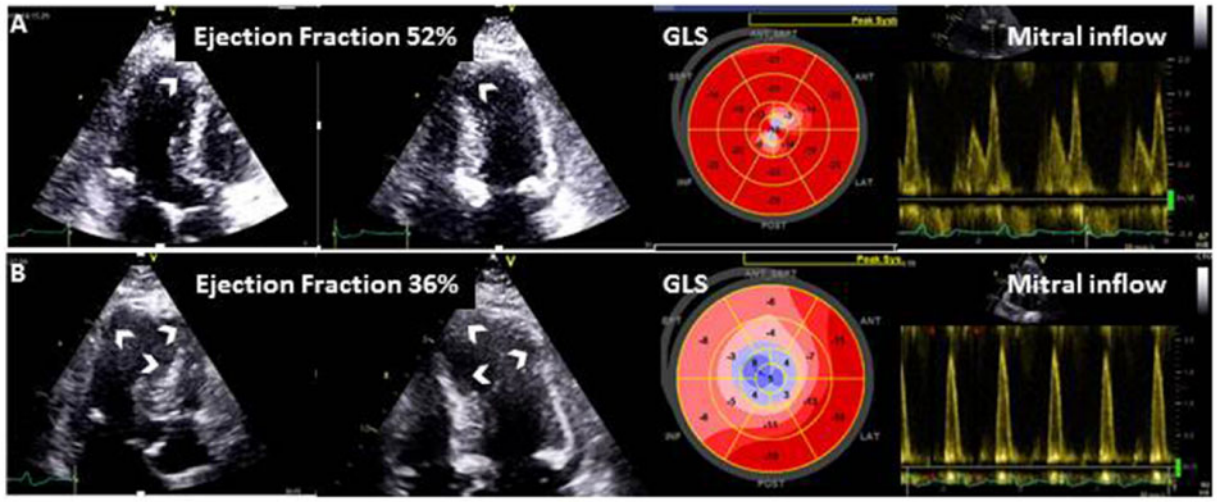

Figure 3 A 50-year-old women with systemic sclerosis, clinically stable over the last 10 years. (*A*) Asymptomatic during next to last visit, mild wall motion abnormality at the apex. (*B*) Chest pain 4 months later, severe regional wall motion abnormalities and restrictive diastolic function despite normal coronary angiography. GLS, global longitudinal strain.

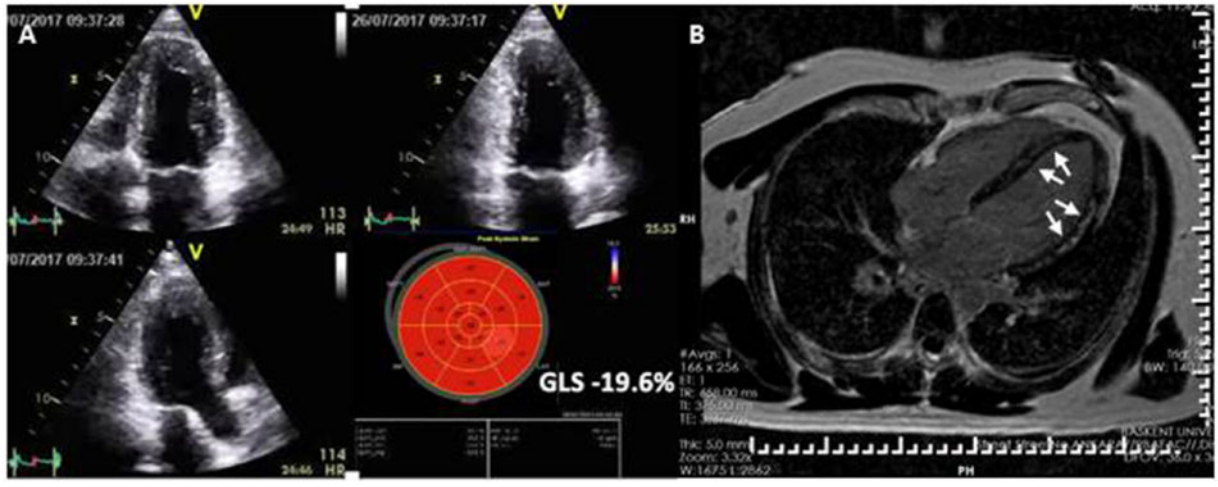

Figure 4 Lupus myocarditis in a 32-year-old woman with chest pain, arrhythmias, elevated C-reactive protein, troponins, and normal coronaries. (*A*) 2D echocardiography shows normal systolic function, but global longitudinal strain (GLS) is at the lower limit of normal. (*B*) Cardiac magnetic resonance shows extensive mid-wall late gadolinium hyperenhancement (arrows).

patients. Of note, these tools can be more accurate than echocardiography in SRD patients with predominant right ventricular (RV) inflammation, fibrosis, or dysfunction due to pulmonary hypertension (PH).[36]

Rational for screening valvular involvement

Valvular involvement is common in SRD patients reaching a frequency of 80% in SLE by transoesophageal echocardiography.[41] Valvular regurgitation is the most frequent consequence. Progression to surgery is around 4–10%.[42] Antiphospholipid antibody positivity significantly increases the risk of valvulitis and endocarditis.[43] Libman–Sacks endocarditis (non-bacterial vegetations) that can be encountered in up to 11% of SLE patients,[44] is an independent cause of stroke and associated with mortality in SLE and antiphospholipid syndrome (APLS) (*Figure 5*, Supplementary data online, *Video S5*).[41,45] Aortic regurgitation is an important complication of ankylosing spondylitis and large vessel vasculitis (LVV) mainly in association with root dilatation and/or extension of fibrosis into the valve.[46]

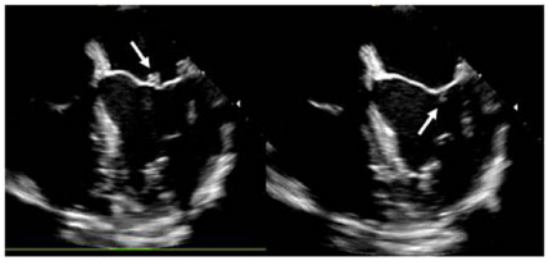

Figure 5 Libman–Sacks vegetations on both sides of mitral leaflet tips (arrows) in a 48-year-old woman with antiphospholipid syndrome and acute ischaemic stroke.

Most of the valvular abnormalities are clinically silent and overlooked without echocardiography although acute aortic or mitral valvulitis can be the initial presentation particularly in SLE and AS.[46,47] Infective endocarditis should always be considered in these immune compromised patients particularly in those with underlying valvulopathy in case of clinical deterioration.

Imaging for screening valvular involvement

Echocardiography is key to detect and characterize valvular damage and has been recommended as a screening tool for valvular pathologies in asymptomatic patients with APLS and SLE.[43,44] Typical valvular lesions include fibrotic thickening, retraction of the leaflets, nodules, or sterile vegetations most frequently effecting mitral and aortic valves.[27,47] Tricuspid valve can also be involved (*Figure 6*, Supplementary data online, *Video S6A, B*). However, no evidence supports routine assessment of valvular involvement in other asymptomatic SRD patients without relevant findings.

Rationale for screening PH

PH is a poor prognosticator irrespective of its cause. All groups of PH can be encountered as a complication of SRD. Pulmonary arterial hypertension (PAH) is an important cause of mortality particularly in SSc affecting 6–12% of the patients.[48] Other than PAH, LV dysfunction and pulmonary involvement can cause PH in SSc. The presence of antiphospholipid antibodies increases the risk for chronic thrombo-embolic PH. Moreover, vasculitis of large pulmonary arteries can cause PH in Takayasu's arteritis (TA).[49] Early diagnosis by screening PH in SSc has been shown to impact survival and patient management.[50]

Imaging for screening PH

Yearly echocardiographic screening is only recommended for detecting PH related to SSc spectrum disorders by the European guidelines.[51,52] In other SRDs, echocardiographic screening for PH is indicated only if patients are symptomatic. Echocardiography also provides information about the LV dysfunction which is the most common cause of PH. RV adaptation to elevated pulmonary artery pressure is not uniform among patients and is the main determinant of survival in PAH including SRD patients. Other imaging modalities, particularly CMR, are complementary to echocardiography to define RV function and to help the differential diagnosis of PH.[53]

Pericardial involvement

Pericardial effusion and pericarditis are frequent in SRDs, whereas haemodynamically significant effusions or chronic constrictive pericarditis are unlikely.[47] Imaging for pericardial involvement is useful for the differential diagnosis of chest pain. Documentation of pericardial involvement could help to make the diagnosis of SRDs, particularly SLE. Pericardial effusion is a poor prognostic factor in patients with PAH.[51] However, no evidence supports screening asymptomatic SRD patients for pericardial involvement. Computerized tomography and CMR are complementary to echocardiography to assess the size and location of effusion, pericardial thickness, or calcification whenever needed in symptomatic patients.

Rational for screening large vessels

Giant cell arteritis (GCA) and TA are the most common LVVs, characterized by involvement of aorta and its main branches. Aortic aneurysms are common in GCA than TA, both can cause vascular stenosis and occlusions.[53] Stroke or acute coronary syndrome can be the initial manifestation. Pulmonary arterial lesions can lead to group IV PH in TA.[49] Cardiac complications including cardiomyopathy and severe hypertension are among major causes of mortality in TA.[54] Behçet's syndrome is another vasculitis that can cause pulmonary artery and aortic aneurysms and stenoses.[55] Isolated aortitis or LVV secondary to SRDs as a rare manifestation, can also be seen. As patients can be asymptomatic, early documentation of pathologies are critical for intensifying treatment such as vigorous control of hypertension or optimizing immune suppression.

Imaging for screening large vessels

Ultrasound of temporal and axillary arteries is useful for the diagnosis of cranial GCA. Magnetic resonance is recommended for documentation of vasculitic involvement in aorta and its branches. PET, MCTA, and/or ultrasound may be used as alternative modalities. All of the above imaging modalities have the capability to document inflammation and complications of LVV.[56] Addition of echocardiographic screening in the initial workup might help to detect cardiac complications of LVV (*Figure 7*, Supplementary data online, *Video S7A, B*) whereas no evidence supports the use of transoesophageal

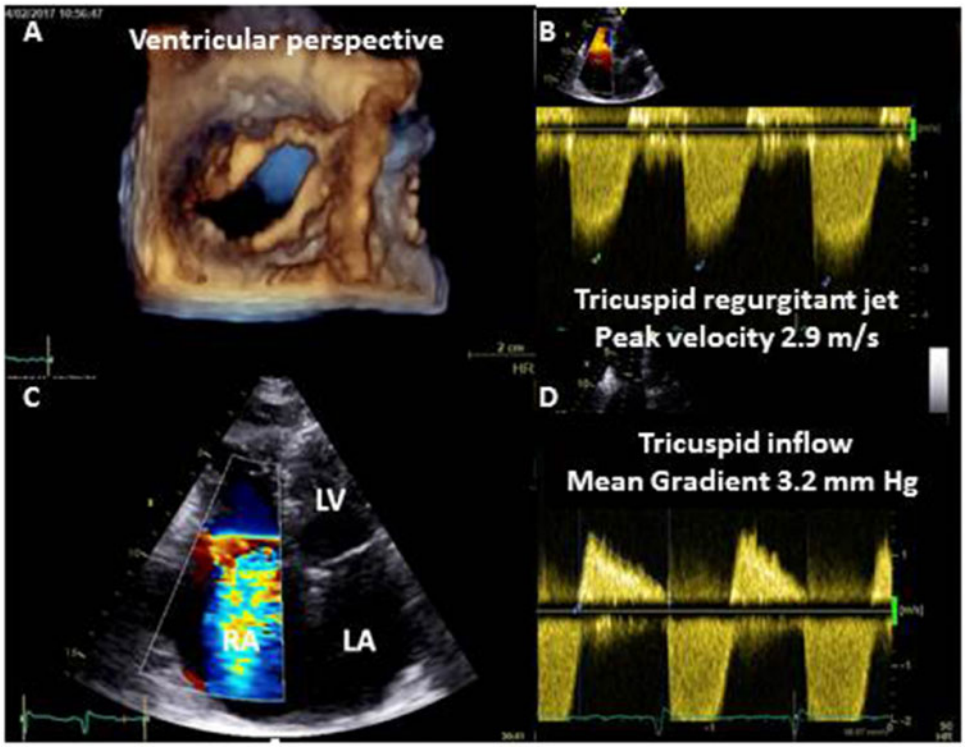

Figure 6 Lupus valvulitis. (*A*) Thickened, fibrotic, retracted tricuspid leaflets with (*B*, *C*) severe regurgitation and (*D*) mild stenosis. Mitral leaflets were less severely affected in this patient. LA, left atrium; LV, left ventricle.

echocardiography for screening structural abnormalities of the aorta in asymptomatic patients.

General comments

CV involvement due to SRDs remains largely underdiagnosed despite high rates of CV complications leading to poor survival. Traditional risk scoring systems underestimate CV risk in SRD patients. Primary prevention guidelines recommend clinical judgement to be applied on a case-by-case basis regarding the impact of imaging for screening patients with SRDs, except for PH in SSc.[16,17,51] Rigorous CV risk assessment and early referral to a cardiologist are key to optimize the outcome. Although accelerated atherosclerosis is the most prominent cause of major CV events, the contribution of other causes of cardiac pathologies should also be considered (*Figure 8*).

Echocardiography and CUS or calcium score, in addition to ECG, should be an integral part of screening in SRD; especially in RA, SLE, and SSc patients with suspicion of CV involvement. Echocardiography has great potential to detect subclinical myocardial dysfunction, valvular, macro- and microvascular damage by means of its versatile use at a low cost, free of radiation, and nephrotoxicity. The addition of CUS to traditional risk scoring systems, improves risk estimation for atherosclerotic complications in these patients. CMR, MCTA and nuclear imaging complement echocardiography and CUS to obtain more data about CV complications. They should also be considered whenever the level of suspicion remains high despite inconclusive echocardiographic and/or CUS findings (*Figure 9*).

Future research and gaps in evidence

Development of a CV risk stratification tool and screening algorithm dedicated to asymptomatic patients with SRDs is an unmet need. In that regard, imaging parameters obtained from echocardiography and CUS or calcium scoring might help to improve risk models, to detect, and monitor subclinical CV involvement. Certainly, some CV abnormalities are more progressive and life threatening than others and necessitate closer follow-up. But those have been incompletely defined so far. Existing imaging studies in SRDs have heterogeneous outcome measurements, inclusion criteria, follow-up durations, and different patient populations and do not allow to pool the data to define the prevalence, incidence, and progression of CV diseases related to SRDs and to conduct insightful meta-analyses. So far, the answer to 'Should asymptomatic patients with SRDs undergo screening with echocardiography and CUS on top of ECG?' remains an extrapolation of the pieces of evidence from heterogeneous studies. Obviously, large studies performing cardiac screening with a standard approach by using echocardiography and CUS to obtain longitudinal data with hard endpoints are awaited in order to implement imaging

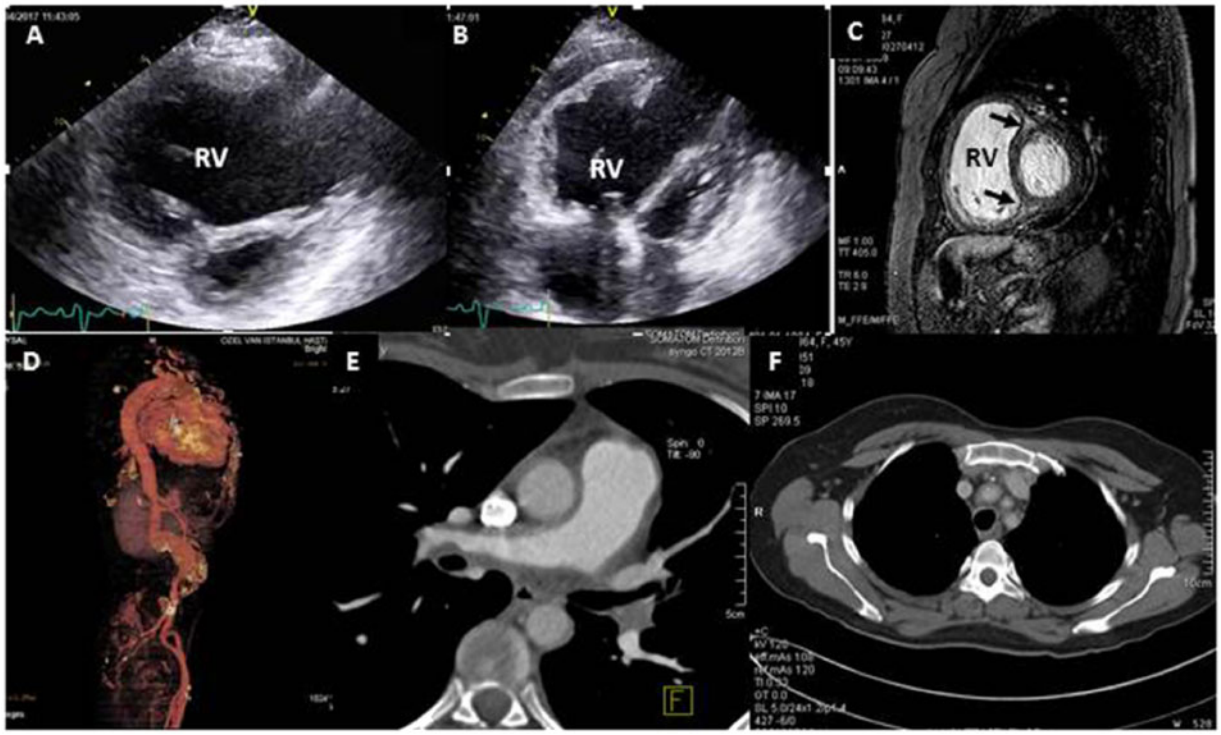

Figure 7 A 44-year-old woman with Takayasu's arteritis. Cardiac involvement is secondary to pulmonary hypertension which is caused by pulmonary vasculitis. (*A*, *B*) Right ventricle (RV) is severely dilated with poor function and pericardial effusion. (*C*) Cardiac magnetic resonance confirms RV dilatation and shows late gadolinium hyperenhancement at interventricular junctions (arrows), (*D*) Multi-slice computerized tomography angiography shows aneurysms and narrowings along the aorta, (*E*) enlarged main pulmonary artery and narrowing of left and right pulmonary arteries by severe wall thickening, and (*F*) narrowing of aortic arch branches by severe wall thickening.

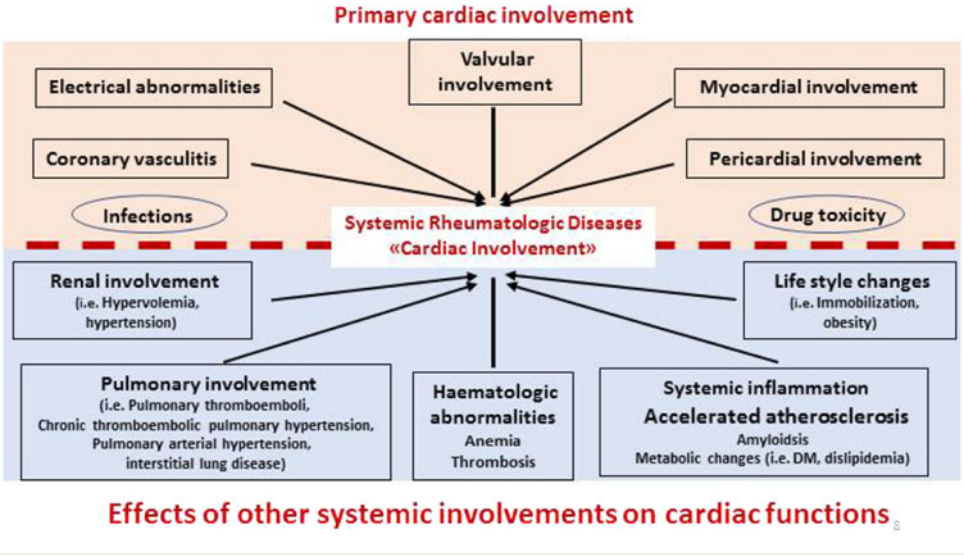

Figure 8 Causes of cardiac pathologies in systemic rheumatologic diseases.

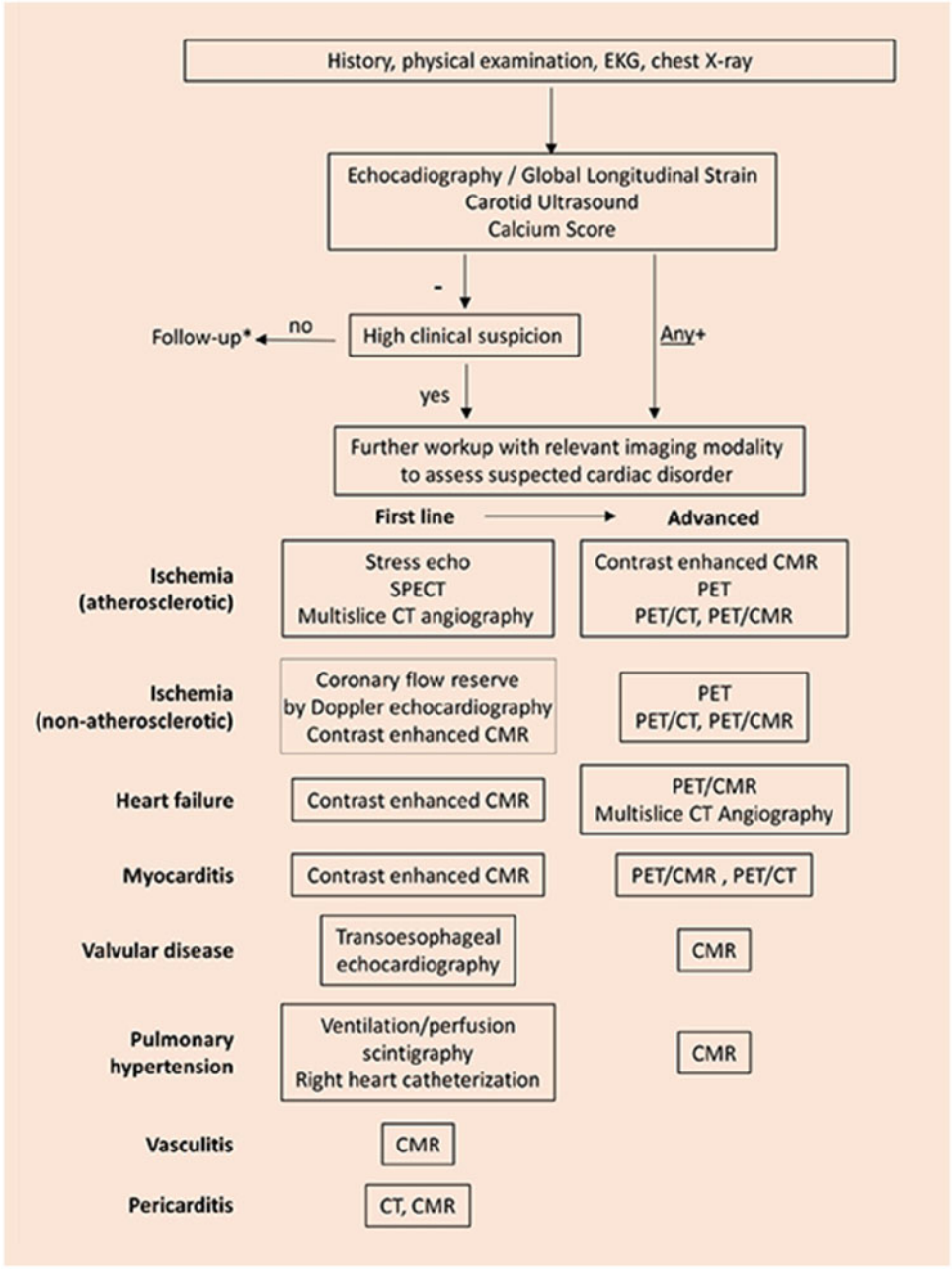

Figure 9 Proposal of screening algorithm for cardiovascular involvement with imaging in systemic rheumatologic diseases. CFR, coronary flow reserve; CMR, cardiac magnetic resonance; CT, computerized tomography; PET, positron emission tomography; SPECT, single-photon emission computed tomography. (*Follow-up should be individualized except for PH related to SSc spectrum disorders.)

as part of screening, patient monitorization, and formulate a follow-up timetable. Consequently, future research should aim to:

- test whether incorporating echocardiography and CUS into screening protocols favourably impacts the outcome,
- define high risk subgroups who need routine screening and monitorization with imaging,
- answer when imaging should be repeated if no CV involvement is detected initially, and when it should be repeated if any CV abnormality is detected,
- explore whether asymptomatic cardiac involvement impacts treatment strategy and is useful to monitor response to treatment,
- evaluate and validate cost-effective imaging protocols for screening and monitoring subclinical CV involvement.

In conclusion, more questions than answers remain to be explored to formulate CV prevention guidelines dedicated to SRD patients and to optimize the outcome where CV imaging seems to be pivotal.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Conflict of interest: none declared.

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