Traditional and disease-related non-computed variables affect algorithms for cardiovascular risk estimation in Sjögren's syndrome and rheumatoid arthritis

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ABSTRACT

Objective. *Several cardiovascular (CV) risk algorithms are available to predict CV events in the general population. Their performance and validity in rheumatic disease patients is suboptimal as some disease-specific variables which strongly contribute to the pathogenesis of CV disease are not included in these CV algorithms. We aimed to evaluate the performance of two CV algorithms and investigate which variables not included in the score contribute to CV risk score in a cohort of rheumatoid arthritis (RA) and Sjögren's syndrome (SS) patients.*

Methods. *A consecutive cohort of 77 RA and 68 SS patients without prior CV events was included. Clinical and serological features and traditional CV risk factors were collected. The 10-year CV risk was assessed by Reynold Risk Score (RSS) and "Progetto Cuore" algorithms.*

Results. *Prevalence of traditional CV risk factors and 10-year risk of fatal and non-fatal CV events assessed by RSS and "Progetto Cuore" were similar between the two cohorts. Multiple linear regression model showed that, among variables not included in both algorithms, body mass index (BMI) and disease activity were predictors of "Progetto Cuore" while BMI and bone erosions of RSS in RA. In SS, C-reactive protein was predictor of "Progetto Cuore" while hypertension, ESSDAI and LDL-cholesterol of RSS.*

Conclusion. *The 10-year risk of fatal and non-fatal CV events is similar in RA and SS. Traditional CV risk factors, as hypertension, strongly contribute to CV risk in these patients. Inflammatory parameters and disease activity are two disease-specific variables which should be included in CV algorithm assessment in rheumatic disease patients.*

Introduction

Rheumatoid arthritis (RA) and Sjögren's syndrome (SS) represent two interesting models to evaluate mechanisms underlying the increased cardiovascular (CV) risk associated with systemic autoimmune diseases, as the former represents the prototype of chronic inflammatory diseases and the second of conditions related to immune system dysregulation (1, 2). Moreover, SS, a disease mainly characterised by glandular involvement alone or mild systemic manifestations, does not require immunosuppressive or chronic corticosteroid therapy, thus allowing a reliable analysis of atherosclerotic damage and CV risk (3).

In the last years, population-based studies and meta-analysis provided definite evidence that both diseases are associated with increased CV mortality and morbidity due to a significant increased prevalence of CV events, in particular myocardial infarction and stroke, as compared to age and sex-matched population (4-7). Indeed, mortality from CV events accounts for about 50% of causes of death in RA patients, representing the leading cause of mortality (6). Conversely, meta-analysis on more than 60,000 patients demonstrated higher prevalence of CV events without evidence of an increased risk of mortality in SS cohorts (8). More importantly, the increased CV mortality often characterises young patients free from traditional CV risk factors. As a consequence, research of etiopathogenetic mechanisms underlying early atherosclerosis and analysis of factors contributing to this increased risk is imperative to allow an effective prevention of long-term CV morbidity and mortality (9). Indeed, traditional CV risk factors, although highly prevalent

in such patients in both pathologies, only partially account for the increased CV comorbidity and the contribution of chronic inflammatory mechanisms and immune system dysregulation is currently under investigation (10-12).

In this context, a plausible estimate of the risk of CV mortality or long-term risk of CV events would be desirable in order to introduce effective prevention measures (13). In particular, the identification of patient subgroups at higher risk and the elucidation of disease contribution to such risk represent two important unmet needs. Several validated algorithms are currently available for estimation of long-term CV risk in the general population including the Reynolds Risk Score (RRS), the Systematic COronary Risk Evaluation (SCORE), the "Progetto Cuore", an Italian algorithm with a similar performance to SCORE and the Framingham (14-17). However, all these algorithms have lower predictive performance in RA patients as compared to general population, as variables related to chronic inflammation and autoimmune mechanisms are not adequately computed in such scores (18). In this setting, the performance of QRISK3, an algorithm which includes RA among variables, and of Expanded Risk Score in RA (ERS-RA), which includes RA-specific items, is also sub-optimal (18-20). The application of a 1.5 multiplication factor if RA is not already included in the algorithm, as recommended by European League Against Rheumatism (EULAR), results in underestimation or, sometimes, overestimation of CV risk in RA population (21).

To our knowledge, the performance of these algorithms in SS patients has never been investigated. In this setting, it is plausible that the different pathogenesis characterising RA and SS could account for different CV mechanisms and, consequently, for a different CV risk. Of consequence, the aim of this study was to compare the prevalence of traditional CV risk factors and the performance of two risk algorithms, such as the "Progetto Cuore" and the RRS, in the two diseases and to evaluate the contribution of disease specific variables in the risk of CV events estimated by the two algorithms.

Methods

Consecutive RA patients fulfilling the 2010 American College of Rheumatology (ACR)/EULAR classification criteria (22) and primary SS patients diagnosed according to 2016 ACR/EULAR criteria (23) were enrolled. The following clinical and serologic data were collected on enrolment: age, sex, smoking status (current, former, never), body mass index (BMI), systolic and diastolic blood pressure, lipid profile, including total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides, diabetes mellitus (DM) and hypertension. Dyslipidaemia was defined as the use of lipid-lowering medications and/or LDL-cholesterol target according to their CV risk as defined by ESC/EAS Guidelines for the management of dyslipidaemias (24). Hypertension was defined either as a history of hypertension or current use of blood pressure lowering drugs. DM was defined based on previous medical history and/or use of oral hypoglycaemic medications or insulin. Moreover, prior history of CV events was recorded, including acute coronary syndrome (ST- and non-ST elevation myocardial infarction, coronary revascularisation and unstable angina), stable angina pectoris, ischemic stroke and peripheral artery disease (with or without revascularisation procedures). All CV events were retrieved by review of medical charts and subjects with previous CV events were excluded. As presence of DM configures a high CV risk, independently of any other CV risk factor, patients with DM were excluded from the analysis (25). Disease-specific variables were collected at baseline for each condition. For RA, specific variables included disease duration since diagnosis, presence of radiographic erosions, Health Assessment Questionnaire (HAQ) disability index as function index and Disease activity index 28 (DAS28) by erythrocyte sedimentation rate (ESR) and Clinical Disease Activity Index (CDAI) as measures of disease activity. For SS, specific variables included disease duration since diagnosis, history of parotid swelling, extra-glandular involvement, purpura and diagnosis of lymphoma. EULAR SS Disease Activity Index (ESSDAI) and EULAR SS Patient Reported Index (ESSPRI) were recorded as measure of disease activity and functional status, respectively. Serologic status included rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) in RA and RF, anti-Ro/SSA and anti-La/SSB as determined according to local assays for SS. Finally, ongoing anti-hypertensive and lipid-lowering therapies and anti-rheumatic drugs, including conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), biologic (b) DMARDs and ongoing corticosteroid therapy were recorded.

Two different algorithms were used to estimate the individual 10-year risk of CV disease. The RSS was developed in 2007 with data from a 10-year study of 24,558 women in the United States without DM and estimates the 10-year risk for heart attack, ischaemic stroke, coronary revascularisation or CV mortality based on age, gender, smoking status, total cholesterol, HDL-cholesterol, high sensitivity (hs) CRP, systolic blood pressure and family history of heart attack in patient's parents before the age of 60. RSS demonstrated high accuracy for global CV risk prediction allowing to reclassify 40% to 50% of women at intermediate risk into higher- or lower-risk categories (14). The risk is stratified as low (score <5%), medium (≥5% and <10%) and high (≥10%) (14). The "Progetto Cuore" algorithm has been funded by the Italian Ministry of Health to estimate the impact of CV diseases in the general population by specific parameters like prevalence, incidence and mortality rates. The "Progetto Cuore" algorithm items are defined according to Italian population characteristics and is structured in a set of continuous variables evaluating the 10-year risk of major fatal and non-fatal CV events based on age, sex, DM, smoking, total cholesterol, HDL-cholesterol and systolic blood pressure. The risk is stratified as low (score <3%), intermediate (≥3%-19%) and high (≥20%) (16, 26). Variables included in both scores are illustrated in Table I.

Table I. Variables included in RSS and "Progetto Cuore" algorithms.

Variables	Reynolds risk score	Progetto Cuore
Age	✓	✓
Gender	✓	✓
Smoking status	✓	✓
Systolic blood pressure (mmHg)	✓	✓
Total cholesterol	✓	✓
HDL-cholesterol	✓	✓
hsCRP	✓	
Family history of heart attack before the age of 60 years	✓	
DM status		✓
Hypertension/on anti-hypertensive treatment		✓
Outcome	10-year risk for heart attack, ischaemic stroke, coronary revascularisation or CV mortality	Future heart attack, stroke, or other major heart disease in the next 10 years

This study, conforming to the ethical guidelines of the Declaration of Helsinki, was approved by the local Ethical Committee.

Statistical analysis

Variables were compared by Mann-Whitney U-test, chi-squared test and Fisher's exact test, as appropriate. Bonferroni correction for multiple comparisons was applied and data considered significant for $p \leq 0.002$ for non-demographic variables. Demographic variables are considered different for $p \leq 0.05$.

In order to establish whether variables not included in the calculation algorithm could anyway influence the CV risk score, four distinct multiple forward linear regression models were built for RA and SS and both CV risk score estimation algorithms. The variables included in each model are shown in Table II.

Table II. Variables included in the forward multiple regression models.

Rheumatoid arthritis	
Progetto Cuore	*Reynolds Risk Score*
Anti-CCP	Anti-CCP
b/tsDMARDs	cDMARDs
BMI	b/tsDMARDs
Bone erosions	BMI
cDMARDs	Bone erosions
CRP	DAS28-ESR
DAS28-ESR	Hypertension
Diastolic blood pressure	LDL-cholesterol
LDL-cholesterol	Ongoing GCs
Ongoing GCs	RF
RF	

Sjögren's syndrome	
Progetto Cuore	*Reynolds Risk Score*
BMI	BMI
CRP	ESSDAI
ESSDAI	ESSPRI
ESSPRI	Hypertension
LDL-cholesterol	LDL-cholesterol
Ongoing GCs	Ongoing GCs

Anti-CCP: anti-citrullinated peptide antibodies; b/tsDMARDs: biologic/targeted disease-modifying anti-rheumatic drugs; BMI: body mass index; cDMARDs: conventional DMARDs; CRP: C reactive protein; DAS28-ERS: Disease Activity Index 28 (DAS28)-erythrocyte sedimentation rate; GCs: glucocorticoids; RF: rheumatoid factor; ESSDAI: EULAR SS Disease Activity Index; ESSPRI: EULAR SS Patient Reported Index.

Results

The study population included 77 RA patients (87% female) with mean age 48 (9 SD) years and 68 SS patients (96% female) with mean age 50 (14 SD) years at inclusion. Age at disease diagnosis and sex did not differ between groups. Demographic, clinical and laboratory features are reported in Table III. As shown, RA patients displayed significant longer mean disease duration. Both diseases were characterised by low activity, as shown by the mean values of disease-specific activity scores. Erosive damage was detected in 23% of RA patients while 48% of SS patients were characterised by extra-glandular involvement along disease course. As for serologic features, prevalence of RF positivity was not different between the two groups. Anti-CCP antibodies were detected in 74% of RA patients and about one third of SS patients were anti-Ro and/or anti-La positive. Notably, ongoing corticosteroid therapy was similar between the two diseases.

Prevalence of traditional CV risk factors was not different between the two cohorts. Smoking status revealed a higher prevalence of former smokers among SS patients compared to RA, despite it did not reach statistical significance due to Bonferroni correction. Finally, according to the RSS, the mean 10-year estimated risk of CV event was 4.3 (4.9 SD) % in SS and 3.8 (3.1 SD) % in RA patients (p not significant). According to the "Progetto Cuore" algorithm, the 10-year risk of fatal and non-fatal CV events was 4.1 (4.8 SD) % in SS and 4.4 (4 SD) % in RA patients (p not significant).

As shown in Table IV, the multiple linear regression models showed that, in RA patients, both BMI and DAS-28-ESR were predictors of "Progetto Cuore" score while BMI and bone erosions were predictors of RSS. In SS patients, only CRP was predictor of "Progetto Cuore" score while hypertension, LDL-cholesterol and ESSDAI were predictors of RSS.

Discussion

The results of the present study allowed to evaluate features of CV risk associated to two rheumatic diseases characterised by a predominant inflammatory pathogenesis, such as RA, and by a dysregulation of the immune system, such as SS. There is solid evidence that both diseases are characterised by an increased morbidity and, in many cases, early mortality from CV events but, at present, whether this risk has distinctive features according to the different pathology is not known. In this study

Table III. Clinical and serologic features of RA and SS patients.

Variable	SS n=68	RA n=77	*p*
Age at enrolment	58 (12)	59 (8.4)	0.303
Female sex, n (%)	65 (96)	67 (87.0)	0.130
Age at diagnosis	50 (14)	48 (9)	0.582
Disease duration (months)	101 (95)	137 (72.3)	**<0.0001**
Smoking status, n (%)			0.007
Never smoker	44 (65)	55 (71)	
Current smoker	9 (13)	18 (23)	
Former smoker	15 (22)	4 (5)	
Hypertension, n (%)	20 (29)	31 (40)	0.234
Diabetes, n (%)	3 (4)	8 (10)	0.297
BMI	25.2 (4.7)	26.0 (5.9)	0.522
HAQ	n.a.	0.55 (0.58)	
CRP (mg/dL)	0.4 (0.4)	0.5 (0.6)	0.994
Rheumatoid factor, n (%)	36 (53)	60 (78)	0.003
Anti-CCP, n (%)		57 (74)	
Bone erosions, n (%)		14 (23)	
DAS28-ESR		2.8 (1.4)	
CDAI		2.4 (5.1)	
Anti-Ro and/or La, n (%)	24 (35)		
Anti-Ro, n (%)	27 (40)		
Anti-La, n (%)	1 (1)		
Parotid swelling	21 (31)		
Extra-glandular	33 (48)		
Purpura	6 (9)		
Lymphoma	7 (10)		
ESSPRI	4.0 (2.1)		
ESSDAI	2.3 (4.1)		
cDMARDs, n (%)		62 (80)	
b/tsDMARDs, n (%)		48 (62)	
Ongoing GCs, n (%)	8 (12)	18 (23)	0.086
Antiplatelet agents, n (%)	6 (9)	4 (5)	0.516
Anticoagulants, n (%)	1 (1)	0 (0)	0.469
Lipid-lowering treatment, n (%)	11 (16)	11 (14)	0.932
Antihypertensive treatment, n (%)	21 (31)	31 (40)	0.317
Systolic blood pressure	126 (15)	125 (14)	0.505
Diastolic blood pressure	76 (10)	75 (9)	0.355
Total cholesterol (mg/dL)	192 (35)	203 (42)	0.113
Hypercholesterolaemia, n (%)	15 (22)	23 (30)	0.380
Hypertriglyceridaemia, n (%)	7 (10)	15 (19)	0.191
HDL-cholesterol (mg/dL)	57 (11)	61 (17)	0.117
Total/HDL-cholesterol ratio	3.48 (0.79)	3.50 (1.01)	0.751
Triglycerides (mg/dL)	94 (36)	106 (52)	0.447
LDL-cholesterol (mg/dL)	117 (32)	120 (36)	0.594
Progetto Cuore score	4.1 (4.8)	4.4 (4.0)	0.185
Reynolds Risk score	4.3 (4.9)	3.8 (3.1)	0.437

Data are shown as mean (SD) or number (%). Data are considered significant for $p \leq 0.002$ for non-demographic and $p \leq 0.05$ for demographic variables.

CV: cardiovascular; BMI: body mass index; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; ACPA: anti-citrullinated peptide antibodies; DAS28-ERS: Disease Activity Index 28 (DAS28)-erythrocyte sedimentation rate; CDAI: Clinical Disease Activity Index; ESSDAI: EULAR SS Disease Activity Index; ESSPRI: EULAR SS Patient Reported Index; cDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs: biologic DMARDs; GCs: glucocorticoids; HDL: high density lipoprotein; LDL: low density lipoprotein; SS: Sjögren's syndrome; RA: rheumatoid arthritis.

we compared two cohorts characterised by female predominance, similar mean age at disease onset and sharing a common low disease activity and inflammatory background at enrolment, as shown by the comparable mean CRP concentration. Moreover, concomitant treatment with drugs known to modify CV risk, as anti-platelet agents, lipid-lowering and anti-hypertensive drugs, was not different between cohorts. This allowed the comparison of CV risk factors and long-term CV disease risk in two substantially homogeneous populations. Moreover, this is the first study assessing 10-year CV risk in SS by two validated score algorithms, namely the "Progetto Cuore", an algorithm considering also non-fatal CV events and poorly explored in rheumatic diseases, and the RSS, a score including hsCRP as inflammatory biomarker. This represents an adjunctive strength as chronic, low-grade, systemic inflammation is one of the main underlying mechanisms of atherosclerosis and endothelial activation in patients with systemic inflammatory and autoimmune diseases (10). Prevalence of traditional CV risk factors as well as the 10-years risk of fatal and non-fatal CV events was similar in RA and SS according to the two algorithms. Moreover, stratifying the mean CV risk score, both groups of patients were categorised in low risk according to RSS and in intermediate risk according to "Progetto Cuore". Lacking a general population control group, the interpretation of these results deserves caution. Moreover, the opposite effect of concomitant therapy with csDMARDs, targeted (t) and bDMARDs, assumed by the great majority of RA patients, should be accounted in result interpretation. In this setting, convincing evidence, albeit derived mainly form observational studies, supports a positive effect of csDMARDs, as methotrexate and hydroxychloroquine, in lowering CV risk or reducing incidence of some traditional CV risk factors in RA patients (10, 27-29). On the other hand, the CV and metabolic effects of bDMARDs and, in particular, tsDMARDs, may largely vary depending on the biologic used (10, 28). In SS cohort, 30% of patients were taking hydroxychloroquine and one patient was treated with rituximab for articular involvement, thus limiting a direct comparison with RA patients. On the other hand, ongoing corticosteroid therapy, known to be associated with a dose-dependent increased risk of hypertension, DM and CV events, was similar between groups (30). However, the categorisation of our SS patients, a cohort characterised by low disease activity and free from concomitant therapies known to increase CV risk, in the intermediate 10-year CV risk category requires further studies to assess influence of disease features on predictive ability of

Table IV. Results of multiple regression analysis.

Rheumatoid arthritis											
Progetto Cuore						*Reynolds Risk Score*					
Variable	**B**	**SE**	**β**	**t**	***p***	**Variable**	**B**	**SE**	**β**	**t**	***p***
Constant	-3.441	2.469		-1.394	0.169	Constant	-0.007	2.055		-0.003	0.997
BMI	0.234	0.096	0.296	2.435	0.018	BMI	0.179	0.077	0.300	2.337	0.023
DAS28-ESR	0.823	0.401	0.250	2.055	0.044	Bone erosions	-2.104	1.034	-0.261	-2.035	0.047
$R^2_{adj} = 0.162$, p=0.002						$R^2_{adj} = 0.151$, p=0.006					
Sjögren's syndrome											
Progetto Cuore						*Reynolds Risk Score*					
Variable	**B**	**SE**	**β**	**t**	***p***	**Variable**	**B**	**SE**	**β**	**t**	***p***
Constant	2.383	0.755		3.158	0.002	Constant	-2.973	2.258		-1.317	0.193
CRP	4.102	1.252	0.374	3.277	0.002	HTN	3.877	1.257	0.352	3.084	0.003
						LDL-cholesterol	0.048	0.018	0.312	2.724	0.008
						ESSDAI	0.271	0.132	0.233	2.051	0.045
$R^2_{adj} = 0.127$, p=0.002						$R^2_{adj} = 0.196$, p=0.001					

these algorithms and their application in clinical practice for CV risk reduction and prevention. We acknowledge that EULAR recommendations suggest the application of a 1.5 multiplication factor if RA is not already included in algorithm (21). The application of 1.5 multiplier was not performed in our two cohorts. Indeed, no similar recommendations are available for patients with systemic autoimmune diseases, in particular SS, so the application of EULAR recommendations in RA cohort alone may have hampered data comparison. Moreover, as demonstrated in a recent meta-analysis, the available algorithms either underestimate or, sometimes, overestimate the CV risk in RA patients even after correcting for the 1.5 multiplier (18). Thus, the application of the correction factor would not have influenced the results in our RA cohort.

In this paper we also aimed to evaluate which variables not included in "Progetto Cuore" and RSS algorithms may independently predict the CV risk score. Interestingly, two parameters of inflammatory state, as disease activity and CRP, were both significant contributors of CV risk score assessed by "Progetto Cuore" in RA and SS and by RSS in SS. The result reinforces the pivotal role of inflammation in contributing to CV risk in these patients and may suggest that algorithms which include this variable, as RSS, may perform better in assessing CV risk in patients with systemic autoimmune diseases. Interestingly, in a recent prospective study aimed to evaluate changes of CV algorithms after 5 years of bDMARD therapy in an Italian RA cohort, a significant reduction of RSS was observed when kept at 5 years the same age at baseline, thus suggesting that inflammatory background may affect score result (31). Moreover, disease activity is confirmed as pivotal variable contributing to CV in our RA cohort. Interestingly, the negative predictive role of bone erosions, an indirect marker of active disease, may suggest a potential beneficial effect of biologic anti-rheumatic therapies, more frequently used in patients with active and resistant disease. Convincing evidence supports that suppression of disease activity by anti-rheumatic therapies has fundamental role in lowering CV risk in RA patients (32). In this setting, the performance of CV algorithms as ERS-RA, which incorporate RA-specific factors as disease duration, disease activity and function, should be further evaluated in prospective studies with major clinical CV endpoints (33).

Notably, hypertension and LDL-cholesterol resulted significant predictors of CV score according to RSS algorithm in SS patients. Hypertension exerts a pivotal role in the risk of CV disease in patients with systemic autoimmune diseases (34, 35). The importance of hypertension as CV risk factor in these patients is further corroborated by the evidence of its contribution, as an independent variable, to CV risk assessed by RRS in SS cohort. As illustrated, the RRS includes as variable the registration of systolic blood pressure at single time point, thus not reflecting the presence of hypertension according to international recommendations. In the "Progetto Cuore" algorithm, prescription of anti-hypertensive therapy is included as separate item in addition to single-point systolic blood pressure registration. In this setting, an established diagnosis of hypertension is likely to better predict CV risk than a single systolic blood pressure assessment, thus reflecting the importance of including hypertension, and not only a single blood pressure value, in algorithms evaluating the risk of CV events and mortality in these patients. Similarly, an atherogenic lipid profile, mainly correlated to high grade inflammation, strongly contributes to CV risk in these patients (36). Notably, adequate control of disease activity, oxidative stress and systemic inflammatory state by anti-rheumatic therapies may exert a positive effect on lipid profile and CV outcome (37, 38).

Finally, BMI emerged as independent predictor of CV risk according to both algorithms in RA cohort. Patients with RA are characterised by normal or low BMI related to decrease in lean mass, preservation of fat mass and low muscle density, a phenotype known as

"sarcopenic obesity" or "rheumatoid cachexia", which promotes insulin resistance and metabolic syndrome (39-41). Moreover, low or normal BMI with visceral fat accumulation due to chronic inflammation, the so-called "obesity paradox", has been associated with higher disease activity and risk of atherosclerosis in these patients (42). Altogether, these data support the importance to calculate BMI, visceral adiposity and fat mass composition in RA as they may represent variables predictive of higher CV risk.

A strength of the present study is the evaluation of "Progetto Cuore" algorithm performance in Italian patients with systemic inflammatory and autoimmune diseases. Very few studies explored its performance and predictive ability in these patients. In a retrospective analysis of an Italian cohort of psoriatic arthritis patients, Navarini *et al*. evaluated the performance of five algorithms, including the "Progetto Cuore", in CV risk estimation showing that, despite a good discriminative ability between patients with and without CV events, this algorithm performed poorly in terms of calibration, with a significantly different distribution of observed events compared to predicted ones (43). Moreover, although preliminary, this is the first study exploring the performance of CV risk algorithms in predicting 10-year CV risk in SS patients.

The main limitation of this study is its cross-sectional design. As inflammatory parameters and disease activity were collected at a single timepoint, they do not adequately reflect the natural fluctuation of inflammatory burden observed in these patients. Moreover, the interference of concomitant biologic therapy in RA patients should be accounted in data interpretation.

In conclusion, the results of the present study, although preliminary, suggest that the underlying CV risk in RA and SS may have different mechanisms. Notably, middle-age SS patients, free from immunosuppressive therapy, which may exert adverse CV effect, are characterised by intermediate 10-years risk of non-fatal and fatal CV events. Further prospective studies are needed to identify which CV algorithm has the best predictive performance in these patients and which variables should be included in score calculation. Surely, the aforementioned results support the importance to include disease activity parameters and inflammatory biomarkers in the estimation of long-term CV risk both in RA than SS patients and reinforce the hypothesis that controlling disease activity in RA may have a positive effect in lowering CV disease risk. Moreover, adequate control and regular monitoring of traditional CV risk factors, in particular hypertension, represent an essential strategy for prevention of long-term risk of CV events in such patients. Undoubtedly, future efforts should focus on developing new models and identifying disease-specific variables which have the best predictive value in estimate and predict CV disease risk. Larger cohorts followed longitudinally for clinical CV disease would provide a better assessment of CV risk calculator in order to introduce a preventive and management model through targeting the molecular pathogenetic mechanisms of each disease and traditional CV risk factors.

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