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Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study

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Abstract. Bartoloni E, Baldini C, Schillaci G, Quartuccio L, Priori R, Carubbi F, Bini V, Alunno A, Bombardieri S, De Vita S, Valesini G, Giacomelli R, Gerli R (University of Perugia, Perugia; University of Pisa, Pisa; Terni University Hospital, Terni; University of Udine, Udine; Sapienza University of Rome, Rome; University of L'Aquila, L'Aquila; and University of Perugia, Perugia; Italy). Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study. *J Intern Med* 2015; **278**: 185–192.

Objective. Systemic autoimmune diseases, in particular systemic lupus erythematosus and rheumatoid arthritis, are characterized by a high risk of premature cardiovascular (CV) events. Disease-related characteristics and traditional CV disease risk factors may contribute to atherosclerotic damage. However, there are limited data on the risk of overt CV events in primary Sjögren's syndrome (pSS).

Methods. We retrospectively analysed a cohort of patients with 1343 pSS. Disease-related clinical and laboratory data, traditional CV disease risk factors and overt CV events were recorded. Prevalence of traditional CV disease risk factors and of major CV events was compared between a subgroup of 788 female patients with pSS aged from 35 to 74 years and 4774 age-matched healthy women.

Results. Hypertension and hypercholesterolaemia were more prevalent, whereas smoking, obesity and diabetes mellitus were less prevalent, in women with pSS than in control subjects. Cerebrovascular events (2.5% vs. 1.4%, $P = 0.005$) and myocardial infarction (MI) (1.0% vs. 0.4%, $P = 0.002$) were more common in patients with pSS. In the whole population, central nervous system involvement (odds ratio (OR) 5.6, 95% confidence interval (CI) 1.35–23.7, $P = 0.02$) and use of immunosuppressive therapy (OR 1.9, 95% CI 1.04–3.70, $P = 0.04$) were associated with a higher risk of CV events. Patients with leucopenia had a higher risk of angina ($P = 0.01$).

Conclusions. pSS is associated with an increased risk of cerebrovascular events and MI. Disease-related clinical and immunological markers may have a role in promoting CV events.

Keywords: atherosclerosis, autoimmune disease, cardiovascular disease risk factors, Sjögren's syndrome.

Introduction

Traditional modifiable and nonmodifiable cardiovascular (CV) disease risk factors have well-recognized major roles in the induction and progression of atherosclerosis (ATS) and are considered significant predictors of CV events and mortality in the general population [1]. In addition, these risk factors significantly contribute to intima–media thickness and plaque progression, which are reproducible markers of subclinical ATS and useful tools for prediction of CV events, as recently demonstrated in patients with systemic autoimmune diseases [2–4]. In this setting, it is now clear that chronic inflammatory/autoimmune rheumatic diseases are characterized by an acceleration

of ATS. However, the prevalence and the contribution of traditional CV disease risk factors to ATS burden in these patients remain uncertain [5, 6].

Furthermore, the intriguing observation that the relationship between traditional CV risk factors and both ATS progression and CV mortality in some chronic inflammatory autoimmune disorders, such as rheumatoid arthritis (RA), is not as linear as commonly found in the general population [7] has led to hypothesize that other factors may also play a role. The magnitude of the problem in RA is further strengthened by the evidence that some traditional CV disease risk factors, such as body mass index and dyslipidaemia, appear to exert a paradoxical protective effect on vascular outcome [8]. Taken together, these observations suggest that multiple and complex mechanisms may contribute to the premature ATS damage and CV disease mortality in these patients. Indeed, it is recognized that altered immune system function and inflammatory factors contribute to both initiation and progression of ATS in patients with systemic rheumatic diseases, in particular RA and systemic lupus erythematosus (SLE) [6–10].

Primary Sjögren's syndrome (pSS) shares many clinical, inflammatory and immunological features with RA and SLE. However, unlike RA and SLE, pSS frequently presents a benign and indolent course, often without the need for immunosuppressive therapy [11]. Therefore, pSS may represent an interesting model to investigate the complex mechanisms underlying ATS progression in patients with chronic inflammatory/autoimmune diseases.

Small case–control studies have demonstrated signs of endothelial dysfunction and precocious arterial wall damage in pSS patients without previous CV disorders [12–16]. Disease duration and several clinical and immunological features, including joint involvement, parotid swelling, Raynaud's phenomenon, leucopenia and anti-SSA/Ro and anti-SSB/La antibodies, seem to contribute to subclinical ATS damage in these patients [12–16]. By contrast, the prevalence and the role of traditional CV disease risk factors in the induction of precocious ATS have not been extensively investigated [17, 18]. In addition, the risk of clinically manifested major CV events and long-term CV outcome in patients with pSS remain unclear. Therefore, we performed a large-scale, multicentre, retrospective, cross-sectional study in a cohort of patients with pSS to investigate possible associations between CV events and traditional CV risk factors as well as disease-related clinical and serological characteristics. Data from a subset of female patients (the majority of our study group) have also been compared with a large age-matched control population of women to compare the prevalence of traditional CV disease risk factors and major CV events.

Materials and methods

Study population

We retrospectively analysed a cohort of 1343 patients who fulfilled the 1993 European Community Study Group diagnostic [19] and/or the revised classification criteria for pSS proposed in 2002 by the American-European Consensus Group (AECG) [20] and who were regularly followed in five Italian rheumatology centres.

Clinical variables and outcomes

Clinical and laboratory data were systematically collected from patient medical records according to specific criteria defined in our previous study [21]. Briefly, clinical data included age at diagnosis and inclusion, history of xerophthalmia, xerostomia, recurrent parotid enlargement, extra-glandular manifestations (i.e. joint, skin, lung, heart, kidney, central and peripheral nervous system involvement), myositis, Raynaud's phenomenon and lymphoproliferative disorder. Disease-specific laboratory markers included cytopenia, low complement C3 and C4 levels, hypergammaglobulinaemia, rheumatoid factor (measured by nephelometry), antinuclear antibodies (detected by indirect immunofluorescence on HEp-2 cells), anti-SSA/Ro and anti-SSB/La antibodies (measured by enzyme-linked immunosorbent assay) and cryoglobulins. Finally, ongoing and previous therapies, including symptomatic therapy, glucocorticoids (GCs) (i.e. prednisone or equivalent $\leq$7.5 mg/day), hydroxychloroquine (HCQ) and immunosuppressants (ISs) (methotrexate, azathioprine, leflunomide, cyclophosphamide, mycophenolate mofetil and rituximab), were recorded.

The following CV disease risk factors were considered in this study: smoking (defined as previous/current use of at least one cigarette/day), hypertension (physician diagnosis and/or prior/ongoing antihypertensive therapy), hypercholesterolaemia (total serum cholesterol level >240 mg dL^{-1} in at

least three assays), hypertriglyceridaemia (serum triglyceride level >150 mg dL^{-1} in at least three assays), high-density lipoprotein cholesterol (HDL-c) level (reduced <40 mg dL^{-1}, normal 40–60 mg dL^{-1}, increased >60 mg dL^{-1} in at least three assays), low-density lipoprotein cholesterol level (reduced <130 mg dL^{-1}, normal 130–160 mg dL^{-1}, increased >160 mg dL^{-1} in at least three assays), diabetes mellitus (DM) (ongoing treatment with insulin or oral hypoglycaemic agents and/or glucose level >126 mg dL^{-1} in at least two fasting glycaemia tests) and obesity (according to body mass index). Finally, we evaluated the prevalence of CV events, defined as myocardial infarction (MI), cerebrovascular events and heart failure. CV events were recorded only if the diagnosis was confirmed by hospital discharge records and/or available specific laboratory and diagnostic examinations. Angina was evaluated, but was not included in the list of CV events because it is not generally considered a 'hard' coronary end-point in epidemiological studies [22].

The Italian 'Progetto Cuore' registry was initiated to evaluate the prevalence of CV disease risk factors and CV events in the Italian general population (http://www.cuore.iss.it/eng/default.asp). We used data from this registry to compare the prevalence of traditional CV disease risk factors and major overt vascular events (MI, cerebrovascular events and heart failure) in patients with pSS in this study with the prevalence in a control population. Due to the very small number of men enrolled in our study, we considered only the group of apparently healthy women included in the registry (4774 subjects aged between 35 and 74 years; mean±SD, 55 ± 11 years); consequently for the present analysis, we selected women within the same age range (mean ± SD, 56 ± 10 years) from amongst our cohort of patients with pSS (n = 788).

Statistical analysis

The Shapiro–Wilk test was used to assess the normal distribution of variables. The chi-squared test and the Mann–Whitney *U*-test were used for comparisons of categorical variables and non-normally distributed continuous variables, respectively. Goodness-of-fit chi-squared test was used to compare the observed frequencies in our sample with the frequencies in subjects from the Italian general population enrolled in the Progetto Cuore registry (matched for age range).

Separate multivariate logistic regression models were fitted to test the relationships, adjusted for age at diagnosis and follow-up duration, between CV events and both organ involvement and administered therapies, incorporating as predictors the variables that showed a P-value of ≤0.25 in bivariate analysis (Hosmer DW, Lemeshow S. Applied Logistic Regression. John Wiley &Sons, New York. 2000). Goodness of fit of logistic models was assessed using the Hosmer–Lemeshow test. Odds ratios with 95% confidence intervals were also calculated. Statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). A two-sided P-value of <0.05 was considered significant.

Results

The overall study cohort included 1284 female and 59 male pSS patients with a mean (±SD) age of 57 ± 14 years (range 17–89 years) at enrolment and a mean (±SD) disease duration from diagnosis of 5 ± 6 years (range 0.5–42). All patients fulfilled at least four of the six European Community Study Group diagnostic criteria and 1110 (83%) also satisfied the AECG classification criteria.

A total of 794 patients had a documented minor salivary gland biopsy. A normal (Chisholm and Mason score of 0) or a nonspecific sialadenitis pattern (Chisholm and Mason score <3) was detected in 72 of these patients (9%), whereas the remaining 722 patients displayed a grade 3 or 4. Moreover, 383 of the 794 patients (48%) with minor salivary gland biopsy data were also classified by focus score (FS). A normal or nonspecific sialadenitis pattern (FS 0) was observed in 72 patients (19%), whilst 74 (19%) and 237 (62%) patients had an FS of 1 and >1, respectively.

The prevalence of clinical and serological features characterizing the whole population of pSS patients is shown in Table 1. Xerophthalmia represented the most frequently reported symptom of pSS, followed by xerostomia. Articular involvement was the most prevalent extra-glandular manifestation. Visceral systemic involvement was reported in 543 patients, and approximately one-third of patients were characterized by peripheral leucopenia. The main immunological features were antinuclear antibodies and anti-SSA/Ro positivity. Finally, the majority of patients had been treated or were receiving treatment with symptomatic therapy alone, GCs or HCQ, and only 18% of patients required treatment with IS agents.

Table 1 *Clinical, laboratory and treatment data from 1343 patients with primary Sjögren's syndrome*

	Frequency (%)
Clinical characteristics	
Xerophthalmia	94
Xerostomia	89
Articular involvement	62
Parotid enlargement	30
Raynaud's phenomenon	21
Purpura	8
Systemic visceral involvement[a]	40
Laboratory measurements	
Antinuclear antibodies	68
Anti-SSA/Ro antibodies	68
Anti-SSB/La antibodies	36
Rheumatoid factor	51
Hypergammaglobulinaemia	47
Leucopenia	28
Low C3 and/or C4	23
Treatment	
Symptomatic therapy	58
Low-dose glucocorticoids	45
Hydroxychloroquine	45
Immunosuppressants	18

[a]Lung, heart, skin, gastrointestinal tract, kidney and peripheral and central nervous systems.

Table 2 *Prevalence of traditional cardiovascular (CV) disease risk factors and overt CV events in 974 patients with primary Sjögren's syndrome*

	Frequency (%)
Traditional CV disease risk factors	
Hypertension	34
Hypercholesterolaemia	32
Increased LDL-c	21
Reduced HDL-c	10
Hypertriglyceridaemia	11
Obesity	12
Smoking	12
Diabetes mellitus	5
Major CV events	
Cerebrovascular events	2.7
Heart failure	1.8
Myocardial infarction	1.0

LDL-c, low-density lipoprotein cholesterol; HDL-c, low-density lipoprotein cholesterol.

Next, we evaluated the prevalence of traditional CV disease risk factors and overt CV disease in 974 patients with complete evaluable data. As shown in Table 2, hypertension was the most prevalent CV disease risk factor, followed by hypercholesterolaemia. Cerebrovascular events represented the most common overt CV manifestation, followed by heart failure, angina and MI. Overall, 5% of patients reported at least one clinically overt CV disease. Amongst all clinical and serological variables analysed, higher age at enrolment and diagnosis ($P \leq 0.0001$ for both) and longer disease duration ($P \leq 0.04$) were significantly associated with an increased prevalence of CV events. Moreover, patients who developed at least one CV event had a higher frequency of visceral involvement (8% vs. 4%; $P \leq 0.02$), in particular in the lung (12% vs. 5%; $P \leq 0.05$) and central nervous system (23% vs. 5%; $P \leq 0.04$), and were more frequently treated with GC (8% vs. 4%; $P = 0.006$) and IS (10% vs. 5%; $P \leq 0.009$) therapies. Central nervous system involvement and use of GC and IS therapies were identified as predictors of CV events, independently of age at diagnosis and disease duration, in adjusted multivariate analysis (Table 3).

Within this cohort of patients with complete assessment of CV disease risk factor, we then compared subjects without evidence of any of these risk factors with those with at least one risk factor. A total of 407 and 567 patients had no and at least one traditional CV disease risk factors, respectively. Compared to patients with CV disease risk factors, circulating anti-SSA/Ro and anti-SSB/La antibodies ($P \leq 0.001$ and $P \leq 0.04$, respectively), leucopenia ($P \leq 0.02$), hypergammaglobulinaemia ($P \leq 0.001$) and hypocomplementaemia ($P \leq 0.001$) were more common in patients without any CV disease risk factors. Based on these findings and the previous demonstration that anti-SSA/SSB antibodies and leucopenia are associated with subclinical ATS in patients with pSS [14, 15], we investigated the possible relationship between these laboratory characteristics of pSS and CV disease risk factors in the entire cohort. Patients with evidence of circulating anti-SSA/SSB antibodies were characterized by a higher frequency of parotid enlargement ($P \leq 0.0001$), purpura ($P \leq 0.005$), extra-glandular involvement ($P \leq 0.0001$), lymphoma ($P \leq 0.02$), hypergammaglobulinaemia, rheumatoid factor positivity, leucopenia ($P \leq 0.0001$ for all) and use of

Table 3 *(a) Organ involvement, (b) Treatment-related variables as predictors of cardiovascular events in multivariate logistic regression analysis*

		95% CI		
	OR	Lower	Upper	*P*-value
(a)				
Age at diagnosis, years	1.067	1.039	1.095	<0.0001
Disease duration, years	1.059	1.015	1.104	0.008
Visceral involvement, yes/no	1.789	0.972	3.294	0.062
Lung involvement, yes/no	1.567	0.620	3.958	0.342
Central nervous system involvement, yes/no	5.666	1.352	23.749	0.018
(b)				
Age at diagnosis, years	1.068	1.040	1.096	<0.0001
Disease duration, years	1.055	1.009	1.103	0.019
GC therapy, yes/no	1.970	1.083	3.582	0.026
IS therapy, yes/no	1.966	1.044	3.700	0.036

OR, odds ratio; CI, confidence interval; GC, glucocorticoid; IS, immunosuppressant.

HCQ ($P \leq 0.005$) and IS therapies ($P \leq 0.03$). With regard to CV disease risk factors, anti-SSA/SSB-positive patients were less likely to be smokers ($P \leq 0.01$) and had lower rates of hypertension ($P \leq 0.04$), hypercholesterolaemia ($P \leq 0.0001$) and hypertriglyceridaemia ($P \leq 0.02$) compared to anti-SSA/SSB-negative patients. Similarly, patients with leucopenia had a higher prevalence of xerostomia ($P \leq 0.02$), parotid enlargement ($P \leq 0.002$), Raynaud's phenomenon ($P \leq 0.01$) and purpura, extra-glandular involvement, lymphoma, hypocomplementaemia, hypergammaglobulinaemia, rheumatoid factor and cryoglobulin positivity ($P \leq 0.0001$ for all) as well as use of GC ($P \leq 0.01$) and IS therapies ($P \leq 0.002$). Of interest, the rates of hypertension ($P \leq 0.01$), DM ($P \leq 0.02$) and hypercholesterolaemia ($P \leq 0.001$) were lower, whereas the risk of angina was higher ($P \leq 0.01$) in patients with leucopenia, compared to those with a normal white cell count.

Finally, the prevalence of traditional CV disease risk factors and CV events observed in the selected cohort of 788 female patients with pSS in comparison with the control group is shown in Table 4. Hypertension and hypercholesterolaemia were more prevalent, whereas smoking, obesity and DM were less prevalent in patients compared to control subjects. Of note, cerebrovascular events and MI were both more common amongst patients with pSS than control subjects.

Discussion

An increasing number of studies have clearly demonstrated increased morbidity and premature mortality due to CV disease in patients with RA and SLE [6, 23]. Although patients with pSS show signs of precocious subclinical ATS [12, 16], conclusive evidence of increased CV events or deaths in these patients is currently lacking. In addition, the prevalence and role of traditional CV disease risk factors and their interaction with disease-related features of this systemic autoimmune disorder have not been fully investigated [12–18].

In the present study, we demonstrated in a large cohort of patients with pSS that older age and longer disease duration were associated with an increased risk of total CV events. This finding suggests that either the disease itself or disease-related features may represent a risk for the development of CV disease in patients with pSS. By comparing the prevalence of traditional CV disease risk factors in a cohort of nearly 800 adult women with pSS and in more than 4500 control female subjects, we found that smoking, obesity and DM were less common, whereas the rates of hypertension and hypercholesterolaemia were higher in patients with pSS than in the general population.

The lower proportion of smokers in our pSS cohort compared to the general population is in line with the findings of other studies [12, 13, 17, 24, 25] and may be related to the exacerbation of oral and ocular discomfort by smoking. It is interesting to note that cigarette smoking exerts a well-recognized adverse effect in patients with some autoimmune diseases; in particular, in RA, smoking represents the main environmental exposure implicated in disease development, anticyclic citrullinated peptide antibody production and disease progression [26]. On the other hand, patients with pSS who smoke do not have an increased risk of extraglandular manifestations and are character-

Table 4 *Prevalence of traditional cardiovascular (CV) disease risk factors and overt CV events in women with primary Sjögren's syndrome (pSS) and in age-matched control female subjects*

	pSS, $n = 788$	Control group, $n = 4774$	*P*-value
Hypertension	32%	28%	0.021
Hypercholesterolaemia	30%	23%	<0.001
Smoking	13%	23%	<0.001
Obesity	11%	21%	<0.001
Diabetes mellitus	4%	7%	0.001
Cerebrovascular events	2.5%	1.4%	0.005
Heart failure	1.5%	1.0%	0.139
Myocardial infarction	1.0%	0.4%	0.002

ized by a lower salivary gland biopsy FS and a lower frequency of anti-SSA/SSB antibody positivity compared to nonsmokers [24], as confirmed by the present findings. This suggests a different effect of smoking on immunopathogenic pathways of pSS and RA [27].

Similar to RA, which is often characterized by a low body mass index [28], the prevalence of obesity was low in the present pSS cohort. In both diseases, this may be the result of chronic inflammation. Furthermore, the low frequency of DM observed in the present series, which confirms data from different Italian and English cohorts [12, 13, 25], is inconsistent with the results reported from Spanish pSS cohorts, in which a higher prevalence of DM was shown in comparison with the general population [17, 29]. Of note, however, the clinical and immunological disease expression was characterized by a higher prevalence of extraglandular involvement and lower frequency of antinuclear antibody positivity in these Spanish diabetic patients with pSS [29]. In addition, differences in genetic and metabolic background, dietary intake, lifestyle habits and local guidelines for DM screening and treatment may partially explain such conflicting data.

In agreement with our results, hypertension was demonstrated in a similar proportion of patients with pSS in studies from the UK [25] and Spain [29], thus suggesting its particular role as a potential risk factor for CV disease in these patients. Moreover, it is noteworthy that our cases derived from a cohort of patients who had been or were mainly being treated with low-dose GC therapy alone and were not taking IS drugs (such as cyclosporine), which are known to increase blood pressure levels. These results highlight the importance of routine monitoring of blood pressure in patients with pSS.

In agreement with our findings, about one-third of patients with pSS had high cholesterol levels in two Spanish cohorts [17, 29]. The finding of high cholesterol levels in the entire cohort of patients with pSS in this study is in apparent contrast with the usual pSS lipid profile of low levels of cholesterol and HDL-c and normal or high levels of triglycerides [18, 25, 30]. The potential interesting relationship between this metabolic alteration and pSS-related inflammatory/immunological features is also supported by a number of observations. Higher antinuclear antibody positivity, a marker of immune system hyperactivity, and higher levels of erythrocyte sedimentation rate, which reflects a chronic inflammatory state, have been demonstrated in pSS subjects with dyslipidaemia and hypertriglyceridaemia, respectively, compared to normolipidaemic patients [25, 31]. Moreover, total cholesterol and HDL-c levels are predictive of increased immunoglobulin G serum concentration, which is an indirect marker of B lymphocyte hyperactivity, and low levels of total cholesterol and HDL-c have been mainly observed in anti-SSA/SSB-positive patients [13, 30]. In this context, it is important to note that our patients with circulating anti-SSA/SSB antibodies showed not only a greater disease severity but also a lower prevalence of hypertension and hypercholesterolaemia compared to patients lacking these autoantibodies. Of interest, greater disease severity and lower prevalence of hypertension and hypercholesterolaemia were similarly observed in patients with leucopenia compared to those with a normal white cell count.

Although these findings seem to support a close interaction between some traditional CV disease risk factors and disease-specific features of pSS, we found that patients without overt evidence of traditional risk factors indeed presented circulating anti-SSA/SSB antibodies, leucopenia, hypergammaglobulinaemia and hypocomplementaemia more frequently than subjects with one or more CV disease risk factors. These findings, in line with the results of previous studies [17, 29], appear to further support the independent role of disease-related features in favouring ATS in pSS. This is consistent with the evidence that macrovascular

impairment of endothelium-independent function and intima–media layer thickening in pSS are associated with leucopenia and circulating anti-SSA/SSB antibodies [12, 13].

Few data on the prevalence of major CV events in patients with pSS have been reported, and these are conflicting. Case–control studies with a mean follow-up of 5 years demonstrated a similar prevalence of major CV events (between 5% and 11%) in patients with pSS and control subjects, although in one study stroke occurred in pSS patients with lupus anticoagulant positivity (i.e. a well-known risk factor that can explain the CV event) [17, 32]. However, two nationwide prospective studies demonstrated a significant twofold increased risk of ischaemic stroke and coronary artery disease in Swedish patients with pSS compared to the general population [33, 34]. Recently, in a large nationwide cohort study with a mean follow-up of 4 years, a higher prevalence of stroke was demonstrated in Asian patients with pSS in comparison with control subjects, with a similar prevalence of MI in the two groups [35].

In the present series, it is interesting that a significantly higher prevalence of both MI and cerebrovascular events was observed in patients with pSS relative to the general population. We found that CV events were more common in patients with more severe and extensive disease, including lung and central nervous system involvement, and with greater need to use GC and IS therapies to control disease manifestations.

The notion that the disease has a role in promoting CV events is also strengthened by the demonstration that the patient subset with leucopenia (a haematological marker associated with more severe disease) had a sixfold higher risk of developing angina compared to those with a normal white cell count. This finding is important as it is generally considered that, compared with men, women are protected from ATS by oestrogens and are characterized by a lower prevalence of spontaneous angina and organic coronary artery disease [36].

We are aware that the relevance of our findings is not comparable to that of data from very large cohort studies to assess the epidemiology of CV disease in the general population, such as for example the Framingham Heart Study. However, to our knowledge, this was the first cross-sectional study to investigate the prevalence of traditional CV disease risk factors and events in a large cohort of Italian patients with pSS in comparison with control subjects in an extensive population-based registry. Two major limitations may affect data interpretation. First, a potential intrinsic bias may be related to the retrospective data collection, although it is considered that the same standardized protocols were used for registration of traditional CV disease risk factor and CV events. Secondly, the data have been collected from a university-based cohort including patients with probably more active or drug-resistant disease, as shown by the relatively high percentage of patients treated with IS drugs. Nevertheless, the present study provides the first evidence that, similar to individuals with other autoimmune diseases, patients with pSS may be characterized by increased risk of major cardiac and cerebrovascular events in comparison with healthy subjects.

Although prospective longitudinal cohort studies with a longer follow-up are required, we believe that the present findings provide substantial progress in our understanding of the role of traditional CV disease risk factors and disease-related features in promoting ATS in patients with pSS.

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Conflict of interest statement

None of the authors has any potential conflict of interests to declare.

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