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Original article

# Comparable or higher prevalence of comorbidities in antiphospholipid syndrome *vs* rheumatoid arthritis: a multicenter, case-control study

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## Abstract

**Objectives.** Evidence on comorbidity prevalence in antiphospholipid syndrome (APS) and its difference from high comorbidity burden rheumatic diseases is limited. Herein, we compare multiple comorbidities between APS and RA.

**Methods.** A total of 326 patients from the Greek APS registry [237 women, mean age 48.7 (13.4) years, 161 primary APS (PAPS), 165 SLE-APS] were age/sex matched (1:2 ratio) with 652 patients from a Greek multicentre RA cohort of 3115 patients. Prevalence of cardiovascular (CV) risk factors, stroke, coronary artery disease (CAD), osteoporosis, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), depression and neoplasms were compared between APS and RA patients using multivariate regression analysis.

**Results.** Hyperlipidemia and obesity (BMI $\geq 30\,kg/m^2$) were comparable while hypertension, smoking, stroke and CAD were more prevalent in APS compared with RA patients. Osteoporosis and depression were more frequent in APS, while DM, COPD and neoplasms did not differ between the two groups. Comparison of APS subgroups to 1:2 matched RA patients revealed that smoking and stroke were more prevalent in both PAPS and SLE-APS *vs* RA. Hypertension, CAD and osteoporosis were more frequent only in SLE-APS *vs* RA, whereas DM was less prevalent in PAPS *vs* RA. Hyperlipidaemia was independently associated with CV events (combined stroke and CAD) in PAPS and SLE-APS, while CS duration was associated with osteoporosis in SLE-APS.

**Conclusion.** Comorbidity burden in APS (PAPS and SLE-APS) is comparable or higher than that in RA, entailing a high level of diligence for CV risk prevention, awareness for depression and CS exposure minimization.

**Key words:** antiphospholipid syndrome, rheumatoid arthritis, comorbidities, cardiovascular disease burden, osteoporosis, depression

CLINICAL SCIENCE

## Introduction

The coexistence of various comorbid conditions in patients with rheumatic musculoskeletal diseases (RMDs) has been associated with increased morbidity and mortality risk [1]. Assessment and early management of comorbidities is crucial in order to prevent or minimize their impact on disease outcomes.

Antiphospholipid syndrome (APS) is a rare autoimmune disorder characterized by a plethora of thrombotic and obstetric manifestations in the presence of antiphospholipid antibodies [2] and can be either primary (PAPS) or related to other autoimmune disorders, most often SLE-APS. Besides cardiovascular (CV)

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**Rheumatology key messages**

- Comorbidity burden in APS is higher or comparable to RA, entailing high level of diligence.
- Major cardiovascular events are more frequent in APS *vs* RA, necessitating adequate cardiovascular risk management.
- Early acknowledgment of other comorbidities, like depression, in APS is important for better disease outcomes.

manifestations, one of the leading causes of morbidity and mortality in APS associated with an interaction between thrombo-inflammatory and atherosclerotic mechanisms [3, 4], little is known about the prevalence of comorbidities in APS and especially in comparison to other RMDs of high comorbidity burden. An increased prevalence of common comorbidities has been recognized in a variety of RMDs [5–7]. RA is associated with a wide range of comorbid conditions, including CV events and related risk factors, depression, solid malignancies, chronic obstructive pulmonary disease and osteoporosis [8].

Our aim was to compare the prevalence of major comorbidities in a large multicentre, age- and sex-matched case-control study of patients with APS, either PAPS or SLE-APS, and patients with RA.

## Methods

### Study population

We included all patients with APS (PAPS and SLE-APS) from the Greek APS Registry and matched 1:2 for age and sex patients with RA from a multicentre, longitudinal cohort of Greek RA patients, comprising 3115 patients. APS patients fulfilled the 2006 updated Sapporo criteria [2] and those with SLE-related APS additionally met $\geq$4 SLICC classification criteria for SLE [9]. Patients with RA fulfilled the 1987 American college of Rheumatology criteria [10] for RA while those who concurrently met the classification criteria for APS were excluded from the study. Because differences between the PAPS and SLE-APS patients may lead to bias, each subgroup of APS patients (PAPS and SLE-APS) was matched 1:2 for age and sex with their RA counterparts in order to evaluate any differentiation in the prevalence of comorbidities between each APS subgroup and RA. Ethics committee approval was obtained by the local institutional boards of participating centres and informed consent was provided by all patients before their inclusion in the study.

In APS and RA groups, demographic and patient characteristics as well as information about the presence of each comorbid condition was collected from the medical records of the patients. The comorbidities examined in the study included CV risk factors such as arterial hypertension (use of antihypertensive treatment or blood pressure higher than 139/89), smoking (current or ever), hyperlipidaemia (use of lipid-lowering medication or total cholesterol of 240 mg/dl and/or low-density lipoprotein 130 mg/dl and/or triglycerides of 160 mg/dl and above) and obesity (BMI $\geq$ 30 kg/m$^2$), CV events [stroke, coronary artery disease (CAD)], osteoporosis, diabetes mellitus (DM) (diagnosis requiring treatment with antidiabetic drugs), chronic obstructive pulmonary disease (COPD), depression and neoplasms. Stroke was defined as the presence of ischaemic or haemorrhagic stroke based on clinical manifestations and relevant imaging findings. CAD was defined as the presence of at least one of the following: myocardial infarction or angina pectoris based on clinical diagnosis and ischaemic changes in the electrocardiogram and/or specific changes in cardiac enzymes and/or typical findings in a coronary angiography. COPD included emphysema and/or chronic bronchitis diagnosis. Osteoporosis was defined as bone density below 2.5 standard deviations that of a young adult or radiologically evident osteoporotic fracture, and depression when antidepressant treatment was administered by a psychiatrist, and neoplasm when it was biopsy proven.

### Statistical analysis

Values related to categorical variables are expressed as percentages. Continuous variables are presented as means (S.D.). Comparisons were performed using a $\chi^2$ test for categorical data and Student's *t test* for continuous data. The prevalence of specific comorbidities between APS and RA groups was compared by logistic regression analysis. Apart from the matched variables of age and sex, we controlled the difference in the prevalence of comorbidities for a set of pre-specified confounders with biological plausibility, and the results of the univariate analysis. In detail, multivariable logistic regression models additionally included CS treatment duration, hypertension, smoking, hyperlipidaemia and obesity for stroke, CAD and major CV events (combined stroke and CAD), CS treatment duration for osteoporosis and for diabetes mellitus, smoking and CS treatment duration for COPD, disease duration and CS treatment duration for depression, and disease duration and smoking for neoplasms. We sought to retain a ratio of 5–10 events (i.e. patients with CV risk factor or CV event or comorbidity assessed) per covariate used in the logistic multivariate analysis.

Multivariate analysis adjusted for the same set of confounders was also performed to assess differences in prevalent comorbidities within the APS group. All statistical tests were two-tailed and a *P*-value $<$0.05 was

considered statistically significant. All analyses were carried out using the SPSS version 24.0.

## Results

### Demographics and patient characteristics

A total of 326 consecutively registered patients with APS [237 women, mean age at inclusion 48.7 (13.4) years, mean disease duration 8.5 (6.9) years] were included in the study and matched 1:2 for age and sex with 652 RA patients (Table 1). The two groups were comparable regarding disease duration, BMI and mean daily CS dosage but mean duration of CS treatment was higher in APS *vs* matched RA patients **(**Table 1**)**.

From the entire APS group, 240 APS patients (116 PAPS) had thrombotic APS, 37 (17 PAPS) had purely obstetric APS, and 49 (28 PAPS) had a history of both thrombotic and obstetric complications. Regarding treatment, 241 APS patients were on oral anticoagulants or heparin, 56 patients additionally received antiplatelet treatment, and 53 patients (22 with purely obstetric APS, 21 with thrombotic APS and 10 with thrombotic and obstetric APS) were only on antiplatelets. Additionally, 140 (85%) of SLE-APS patients compared with 56 (16.4%) of matched RA patients were on HCQ treatment at the time of enrolment in the registries.

Among APS subgroups, 161 patients with PAPS (108 women, mean age 48.6 (13.5) years) and 165 patients with SLE-APS [129 women, mean age 48.9 (13.4) years] were matched 1:2 for age and sex with 322 and 330 RA patients, respectively. SLE-APS patients had longer disease duration [10.1 (7.3) *vs* 8.6 (7.5) years, $P$ =0.037], higher mean CS dosage [6.6 (4.6) *vs* 5.6 (2.5) mg, $P$ =0.003] and higher mean duration of CS treatment [52.7 (43.9) *vs* 31.9 (35.6) months, $P$ <0.001] compared with matched RA patients (Table 1).

### Comorbidities

Regarding CV risk factors, the prevalence of arterial hypertension [29.8% *vs* 20.9%, $P$ <0.001; odds ratio (OR) = 1.87 (95% CI: 1.33, 2.64)] and ever smoking [53.7% *vs* 40.5%, $P$ <0.001; OR = 1.75 (95% CI: 1.33, 2.30)] was significantly higher in patients with APS than in those with RA, while hyperlipidaemia (24.2% *vs* 20.7%, $P$ =0.146) and obesity (21% *vs* 19.6%, $P$ =0.668) were comparable between APS and matched RA patients (adjustment for age and sex for all the above CV risk factors) (Table 2).

Regarding CV events, stroke [20.3% *vs* 1.4%, $P$ <0.001; OR = 13.8 (95% CI: 6.5, 29.1)] and CAD [4.9% *vs* 2.0%, $P$ =0.014; OR = 2.54 (1.21–5.34)] were more prevalent in APS compared with RA patients, as well as the major CV events (combined stroke and CAD) after adjustments for potential confounders.

Among the other comorbidities evaluated, osteoporosis [20.3% *vs* 14.1%, $P$ =0.018; OR = 1.61 (95% CI: 1.09, 2.40)] and depression [16.3% *vs* 10.1%, $P$=0.007; OR = 1.73 (95% CI: 1.16, 2.59)] were more frequent in APS compared with RA, while the prevalence of diabetes mellitus (5.5% *vs* 8.9%, $P$ =0.058) and chronic obstructive pulmonary disease (3.4% *vs* 2.2%, $P$ =0.640) was comparable between the two groups. Adjustment for CS treatment duration was performed for all the above comorbidities (Table 2). The overall prevalence of malignancies did not differ between APS and RA (4.3% *vs* 4.1%, $P$ =0.979). In patients with APS, the most frequent malignancies were the Hodgkin's and non-Hodgkin's lymphomas (5/14, 36%) and breast cancer (3/14, 21%), while the latter was the most frequent diagnosed neoplasm among the RA patients (7/27, 26%) followed by thyroid cancer and haematologic malignancies (4/27, 15%).

The comparison between each of two subgroups of APS patients and 1:2 matched RA patients, respectively, revealed that smoking and stroke were significantly more prevalent in both PAPS and SLE-APS subgroups *vs* RA (Tables 3 and 4). Moreover, arterial hypertension [34.6% *vs* 18.5%, $P$ <0.001; OR = 2.88 (95% CI: 1.78, 4.65)] and CAD [8.5% *vs* 1.8%, $P$ =0.001; OR = 5.0 (1.89–13.28)] were significantly more frequent in SLE-APS *vs* RA patients (Table 4) but comparable between PAPS and matched RA patients (Table 3). Regarding

**Table 1** Demographic and patient characteristics of antiphospholipid syndrome and 1:2 age/sex-matched RA patients

| | APS | RA | PAPS | RA matched to PAPS | SLE-APS | RA matched to SLE-APS |
|---|---|---|---|---|---|---|
| Number of patients | 326 | 652 | 161 | 322 | 165 | 330 |
| Female, *n* (%) | 237(72.7) | 474(72.7) | 108 (67) | 216 (67) | 129 (78) | 258 (78) |
| Age at inclusion (years) | 48.7 (13.4) | 48.9 (13.5) | 48.6 (13.5) | 49.0 (13.6) | 48.9 (13.4) | 48.9 (13.4) |
| Disease duration (years) | 8.5 (6.9) | 8.3 (7.5) | 6.9 (6.1) | 8.0 (7.4) | 10.1 (7.3) | 8.6 (7.5)** |
| BMI (kg/m$^{2)}$ | 26.8 (5.0) | 26.2 (4.8) | 26.7 (4.4) | 26.5 (4.7) | 26.9 (5.7) | 26.1 (4.8) |
| CS treatment Mean daily dose (mg) | 5.9 (3.9) | 5.6 (2.4) | 5.2 (2.8) | 5.5 (2.3) | 6.6 (4.6) | 5.6 (2.5)** |
| Mean duration (months) | 40.9 (35.7) | 32.7 (35.8)* | 28.9 (18.1) | 33.6 (36.0) | 52.7 (43.9) | 31.9 (35.6)** |

Data are shown as mean (S.D.) and *n* (%). $P$ <0.05 for the comparison between the entire APS group and matched RA patients $P$ <0.05 for the comparison between the SLE-APS subgroup and matched RA patients. APS: antiphospholipid syndrome; PAPS: primary APS.

**Table 2** Comparison of comorbidities between the entire antiphospholipid syndrome cohort *vs* 1:2 age/sex-matched RA patients

| | APS ($n = 326$) | RA ($n = 652$) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| Arterial hypertension | 97 (29.8%) | 136 (20.9%) | 1.61 (1.19, 2.18) | 1.87 (1.33, 2.64) |
| Smoking (ever) | 175 (53.7%) | 264 (40.5%) | 1.70 (1.30, 2.22) | 1.75 (1.33, 2.30) |
| Hyperlipidaemia | 79 (24.2%) | 135 (20.7%) | 1.23 (0.89, 1.68) | 1.29 (0.92, 1.81) |
| Obesity | 48 (21.0%) | 105 (19.6%) | 1.09 (0.74, 1.59) | 1.07 (0.73, 1.58) |
| Stroke | 66 (20.3%) | 9 (1.4%) | 18.1 (8.91, 36.9) | 13.7 (6.5, 29.1)[a] |
| Coronary artery disease (CAD) | 16 (4.9%) | 13 (2.0%) | 2.54 (1.21, 5.34) | – |
| Major cardiovascular events (combined stroke and CAD) | 79 (24.2%) | 22 (3.4%) | 9.16 (5.58, 15.02) | 9.97 (5.44, 18.28)[a] |
| Osteoporosis | 66 (20.3%) | 92 (14.1%) | 1.55 (1.09, 2.19) | 1.61 (1.09, 2.40)[b] |
| Diabetes mellitus | 18 (5.5%) | 58 (8.9%) | 0.60 (0.35, 1.03) | 0.58 (0.33, 1.02)[b] |
| Chronic obstructive pulmonary disease | 11 (3.4%) | 14 (2.2%) | 1.59 (0.71, 3.55) | 1.22 (0.53, 2.83)[c] |
| Depression | 53 (16.3%) | 66 (10.1%) | 1.72 (1.17, 2.54) | 1.73 (1.16, 2.59)[d] |
| Neoplasms | 14 (4.3%) | 27 (4.1%) | 1.04 (0.54, 2.01) | 1.01 (0.51, 1.99)[e] |

Data are shown as *n* (%). All multivariate logistic regression model-derived odds ratios (ORs) were adjusted for the matched variables (age and sex) and the following potential confounders: [a]Cs treatment duration, hypertension, smoking, hyperlipidaemia, obesity; [b]Cs treatment duration; [c]Cs treatment duration, smoking; [d]disease duration Cs treatment duration; [e]disease duration, smoking. Multivariate analysis for coronary artery disease was not performed due to small number of events in APS and RA groups. APS: antiphospholipid syndrome; OR: odds ratio.

**Table 3** Comparison of comorbidities between primary antiphospholipid syndrome *vs* 1:2 age/sex matched RA patients

| | PAPS ($n = 161$) | RA ($n = 322$) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| Arterial hypertension | 40 (24.8%) | 75 (23.3%) | 1.09 (0.70, 1.69) | 1.17 (0.91, 1.95) |
| Smoking (ever) | 87 (54.0%) | 142 (44.1%) | 1.49 (1.02, 2.18) | 1.51 (1.02, 2.23) |
| Hyperlipidaemia | 40 (24.8%) | 62 (19.3%) | 1.39 (0.88, 2.18) | 1.52 (0.93, 2.49) |
| Obesity | 20 (17.1%) | 51 (19.3%) | 0.86 (0.49, 1.52) | 0.86 (0.49, 1.53) |
| Stroke | 36 (22.4%) | 4 (1.2%) | 22.9 (8.0, 65.6) | 19.9 (6.6, 59.9) [a] |
| Coronary artery disease (CAD) | 2 (1.2%) | 7 (2.2%) | 0.57 (0.12, 2.76) | – |
| Major cardiovascular events (combined stroke and CAD) | 38 (23.6%) | 11 (3.4%) | 8.73 (4.32, 17.64) | 10.58 (4.38, 25.54) [a] |
| Osteoporosis | 19 (11.8%) | 42 (13.0%) | 0.89 (0.50, 1.59) | 0.95 (0.51, 1.79)[b] |
| Diabetes Mellitus | 5 (3.1%) | 29 (9.0%) | 0.33 (0.12, 0.85) | 0.32 (0.12, 0.89)[b] |
| Chronic obstructive pulmonary disease | 3 (1.9%) | 6 (1.9) | 1.0 (0.25, 4.05) | 0.91 (0.21, 3.86) [c] |
| Depression | 23 (14.3%) | 30 (9.3%) | 1.62 (0.91, 2.90) | 1.72 (0.94, 3.15)[d] |
| Neoplasms | 5 (3.1%) | 12 (3.7%) | 0.83 (0.29, 2.39) | 0.77 (0.25, 2.34)[e] |

Data are shown as *n* (%). PAPS: primary antiphospholipid syndrome. All multivariate logistic regression model-derived odds ratios (ORs) were adjusted for the matched variables (age and sex) and the following potential confounders: [a]Cs treatment duration, hypertension, smoking, hyperlipidaemia, obesity; [b]Cs treatment duration; [c]Cs treatment duration, smoking; [d]disease duration, Cs treatment duration; [e]disease duration, smoking. Multivariate analysis for coronary artery disease was not performed due to the small number of events in PAPS and RA groups.

other comorbidities, SLE-APS patients had higher frequency of osteoporosis [28.5% *vs* 15.2%, $P = 0.002$; OR = 2.36 (95% CI: 1.37, 4.09)] and comparable prevalence of diabetes *vs* RA. Conversely, PAPS patients had comparable prevalence of osteoporosis *vs* matched RA patients and lower prevalence of diabetes [3.1% *vs* 9.0%, $P = 0.025$; OR = 0.32 (95% CI: 0.12, 0.89)]. A trend for higher prevalence of depression in both PAPS [14.3% *vs* 9.3%, $P = 0.079$; OR = 1.72 (95% CI: 0.94, 3.15)] and SLE-APS [8.2% *vs* 10.9%, $P = 0.068$; OR = 1.67 (95% CI: 0.96, 2.88)] *vs* RA patients was observed although this difference was statistically not significant. No differences were noted between groups for the prevalence of COPD and neoplasms.

Within the APS group, major CV events (combined stroke and CAD) were associated with female gender (OR = 2.35, $P = 0.038$) in the entire APS group, and with hyperlipidaemia in the whole APS group and the PAPS and SLE-APS subgroups (OR = 3.43, $P = 0.002$; OR = 4.08, $P = 0.020$; and OR = 3.08, $P = 0.047$,

TABLE 4 Comparison of comorbidities between SLE-Antiphospholipid syndrome *vs* 1:2 age/sex-matched RA patients

| | SLE-APS ($n = 165$) | RA ($n = 330$) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| Arterial hypertension | 57 (34.6%) | 61 (18.5%) | 2.33 (1.52, 3.56) | 2.88 (1.78, 4.65) |
| Smoking (ever) | 88 (53.3%) | 122 (37%) | 1.95 (1.33, 2.85) | 2.01 (1.37, 2.96) |
| Hyperlipidaemia | 39 (23.6%) | 73 (22.1%) | 1.09 (0.70, 1.70) | 1.11 (0.69, 1.77) |
| Obesity | 28 (23.9%) | 54 (19.7%) | 1.28 (0.76, 2.15) | 1.27 (0.74, 2.15) |
| Stroke | 30 (18.2%) | 5 (1.5%) | 14.4 (5.5, 38.0) | 7.8 (2.7, 22.6)[a] |
| Coronary artery disease (CAD) | 14 (8.5%) | 6 (1.8%) | 5.0 (1.89, 13.28) | – |
| Major cardiovascular events (combined stoke and CAD) | 41 (24.8%) | 11 (3.3) | 9.59 (4.78, 19.25) | 9.92 (4.03, 24.37)[a] |
| Osteoporosis | 47 (28.5%) | 50 (15.2%) | 2.23 (1.42, 3.51) | 2.36 (1.37, 4.09)[b] |
| Diabetes Mellitus | 13 (7.9%) | 29 (8.8%) | 0.89 (0.45, 1.76) | 0.88 (0.44, 1.79)[b] |
| Chronic obstructive pulmonary disease | 8 (4.9%) | 8 (2.4%) | 2.05 (0.76, 5.57) | 1.11 (0.36, 3.43)[c] |
| Depression | 30 (18.2%) | 36 (10.9%) | 1.82 (1.07, 3.07) | 1.67 (0.96, 2.88)[d] |
| Neoplasms | 9 (5.5%) | 15 (4.6%) | 1.21 (0.52, 2.8) | 1.36 (0.56, 3.31)[e] |

Data are shown as *n* (%). SLE-APS: SLE-antiphospholipid syndrome. All multivariate logistic regression model-derived odds ratios (ORs) were adjusted for the matched variables (age and sex) and the following potential confounders: [a]Cs treatment duration, hypertension, smoking, hyperlipidaemia, obesity; [b]Cs treatment duration; [c]Cs treatment duration, smoking; [d]disease duration, Cs treatment duration; [e]disease duration, smoking. Multivariate analysis for coronary artery disease was not performed due to the small number of events in SLE-APS and RA groups.

respectively). Osteoporosis was associated with older age, female gender, and CS duration both in the entire APS group (OR = 1.09, $P < 0.001$; OR = 4.57, $P = 0.002$; and OR=1.105, $P < 0.001$, respectively) and in the SLE-APS subgroup (OR = 1.11, $P < 0.001$; OR = 6.89, $P = 0.003$; and OR = 1.012 $P = 0.008$, respectively). In PAPS patients, osteoporosis was associated only with age (OR = 1.10, $P < 0.001$). For depression, there was a trend with age only in the entire APS group (OR = 1.02, $P = 0.053$).

## Discussion

To our knowledge, this is the first study that compared the prevalence of a variety of comorbidities between APS (PAPS and SLE-APS) and another chronic systemic autoimmune disorder of high comorbidity burden such as RA, demonstrating a comparable or higher comorbidity burden in APS *vs* RA.

One of the main findings was the higher (hypertension, smoking) or comparable (hyperlipidaemia, obesity) prevalence of CV risk factors and the higher prevalence of CV disease events including stroke and CAD, in APS *vs* RA patients. Thrombosis at any vascular bed is the hallmark of APS and the prevalence of stroke and coronary artery events in the APS group might be biased by the thrombogenic nature of the disease itself. Growing evidence demonstrates a thrombo-inflammatory process in APS pathogenesis involving a complex antiphospholipid antibody-mediated vascular inflammatory cascade, endothelial cell dysfunction and systemic atherogenesis in interrelationship with thrombotic mechanisms. The increased prevalence of CV events among APS patients in the current study possibly reflects the interplay between the two major pathogenetic processes of CV disease in APS, the hypercoagulable state and the accelerated atherosclerosis.

A link between atherosclerosis and APS has been investigated over the past two decades. A higher prevalence of subclinical atherosclerosis in APS in the form of intima-media thickness, carotid plaques or coronary arterial calcifications compared with healthy controls has been previously reported [11, 12] while recent data has shown a similar risk of carotid and femoral plaques in APS and diabetes mellitus—a CV disease risk equivalent—after adjustment for traditional CV risk factors [13]. In addition, microvasculopathy in the context of thromboinflammation has been considered as a potential pathologic mechanism in silent myocardial perfusion disease in APS as it was shown by sporadic cardiac magnetic resonance (CMR) or PET-CT studies and a recent stress CMR study [14]. Circulating antiphospholipid antibodies, mainly anti$\beta_2$GPI antibodies can cross-react with oxidized low-density lipoprotein (oxLDL) and the oxLDL–$\beta_2$GPI complexes induce the differentiation of macrophages to foam cells and the development of atherosclerotic lesions [3, 15–17] while emerging research has provided important insight into mechanisms like endothelial progenitor dysfunction associated with $\beta_2$GPI-specific T-cell reactivity [18] or type I interferon signature [19, 20] which may further explain the atherosclerotic component of CV disease in APS.

To interpret the increased prevalence of CV events in APS in our study, it is prudent to also take into consideration the contribution of the traditional CV risk factors. Both PAPS and SLE-APS patients in this study had a higher prevalence of ever smoking and a comparable prevalence of hyperlipidaemia and obesity to RA patients. Smoking has been correlated to the formation of antiphospholipid antibodies [21] and is considered one of the main

predictors of CV events in APS [22]. In addition, hypertension was more prevalent among APS patients and especially in SLE-APS *vs* RA patients. Arterial hypertension has been recognized as an independent risk factor for thrombosis in asymptomatic antiphospholipid antibody carriers [23, 24] and for thrombotic recurrences in patients with definite APS [25, 26].

The additional impact of SLE on CV burden in the SLE-APS subgroup, as it was expressed by the higher prevalence of CAD in the SLE-APS *vs* the PAPS subgroup in our cohort and others [25], can be explained by the cardinal role of SLE-specific mechanisms in the development of CV disease, including the endothelium dysfunction induced by various factors such as the enhanced neutrophil extracellular trap (NET) activity [27] or the type I IFNs-mediated inhibition of vascular repair [28, 29], the impact of disease activity and renal involvement [30] and the proatherogenic role of CS use. Recently, it was shown that the hospitalization rates for myocardial infarction and stroke among SLE patients have gradually increased over a 15-year observation period (1996–2011) and were 12 times higher than those in the general population [31]. Consistently to our results, in a multicentre European cohort of 1000 APS patients, significantly more coronary events were developed in the SLE-APS (3.8%) compared with PAPS group (1.2%) over a 10-year follow-up period [25]. Moreover, an earlier vascular ultrasound study comprising 70 SLE-APS and 25 PAPS patients reported a significantly higher prevalence of carotid plaques in SLE-APS compared with PAPS patients [32]. However, in a recent study, the relative risk estimates for atherosclerotic plaques in carotid and/or femoral arteries were comparable between PAPS and SLE-APS (2.72 and 2.63 *vs* healthy controls, respectively) adjusting for age, gender and traditional CV risk factors [13] and in older studies no differences were found between PAPS and SLE-APS regarding intima media thickness and arterial stiffness [11, 12]. Overall, this data mirrors the complexity and the multifactorial process of CV disease development in APS, supporting the need for further research in order to elucidate any differences between PAPS and SLE-APS and their impact on APS management [33].

An interesting finding of our study was the higher prevalence of depression in APS compared with RA patients. Epidemiology of depression has been thoroughly studied in RMDs with significant variability in the reported results associated with the heterogeneity in the criteria used to define depression. In two recent meta-analyses, the estimated depression rate in SLE was 24% and 35%, respectively [34, 35], while according to a meta-analysis of 72 studies in RA patients [36], the prevalence of depression ranged between 17% and 39%. No study so far has examined the prevalence of depression in PAPS. In our study, the use of antidepressants was 18% in SLE-APS, 14% in PAPS and 10% in RA patients. Our results are in accordance with other studies, reporting a higher prevalence of depression and anxiety in SLE patients compared with RA [37, 38], that might be attributed to the higher disease burden of SLE-APS due to multiorgan involvement. Depression has a significant impact on patients' quality of life and adherence to treatment, whilst lately has also been recognized as an independent predictor for atherosclerosis [39] Although frequently neglected by physicians, its early recognition and appropriate management is crucial in this group of patients.

In terms of the other comorbidities, patients with SLE-APS presented higher rates of osteoporosis compared with RA patients, while PAPS patients had lower frequency of diabetes mellitus than those with RA. Both observations are mainly associated with the differences in CS use between SLE-APS and PAPS patients. Osteoporosis was found to be independently associated with CS treatment duration in the SLE-APS group. CSs are not routinely administered in PAPS, except for severe cases such as haemolytic anaemia, severe thrombocytopenia, alveolar haemorrhage, livedoid vasculitis or rarely catastrophic APS. For that reason, PAPS patients are usually spared of the adverse effects of a prolonged administration of CSs such as osteoporosis or diabetes mellitus. In our study, the duration of CS was significantly higher in SLE-APS than PAPS patients. However, the 29-month mean duration of use, and the mean daily dose of 5 mg prednisone in patients with PAPS are also high and may have contributed to an extent to the development of some of the investigated comorbidities. Except their use by indication in the above-mentioned severe manifestations of PAPS, the incongruity in CS use in PAPS patients in our study may be the result of an initial misclassification of some patients with PAPS as SLE-APS. APS and SLE share several clinical and laboratory criteria such as seizures, thrombocytopenia or haemolytic anaemia, and immunological criteria including antiphospholipid antibodies but also low/moderate antinuclear antibodies ($\leq$1/320) or slightly decreased complement levels, making the differentiation between PAPS and SLE-APS difficult and often leading to unnecessary treatment with steroids or immunosuppressives [40, 41]. A recently published study showed that 28% of 214 patients with indisputable PAPS could be theoretically classified as SLE [41]. These classification obstacles have been addressed by the newly developed ACR/EULAR classification criteria for SLE stating that each criterion should be scored only if no other more likely cause than SLE exists [42]. Overall, there is no doubt that the use of CS in both PAPS and SLE-APS should be minimized and finally be discontinued as soon as possible after their introduction.

A comparable prevalence of COPD between APS and RA was also detected in our study. Given a potential prognostic role of COPD for worse outcomes in RMDs including hospitalizations, emergency visits and mortality [43], awareness about its coexistence with APS is also needed. Neoplasms were also similarly prevalent between APS and RA but any relationship between APS and specific malignancies is not yet clearly defined [44].

The strengths of this study include the assessment of a large number of comorbidities among patients with APS (PAPS and SLE-APS), the comparison with a chronic inflammatory RMD of high comorbidity burden such as RA and the similar disease duration between APS and RA patient groups. Our study has also some limitations. Firstly, the RA group is not a random population sample as age and sex matching to APS patients resulted in a rather 'younger than most RA registries' population and an overrepresentation of female patients. However, both age and sex are related with several of the examined comorbidities, especially CV risk factors and events [45, 46], which supports our decision for matching. In addition, besides CS, no comparison could be made between APS and RA for other medications because anticoagulants and antiplatelets represent the main treatments in APS (not used in RA) and different disease modifying agents are used in SLE-APS *vs* RA (e.g. much higher use of biologics and much lower use of HCQ in RA *vs* SLE-APS). Another limitation of the study is the available information only on 'current use' and not on 'duration of use' of immunosuppressive therapies and HCQ, as well as of aspirin (among APS patients) that could more accurately assess potential associations with some of the examined comorbidities [33]. Additionally, the paucity of data relevant to disease activity in SLE such as the SLEDAI index or the prevalence of lupus nephritis did not allow a further analysis of these potential contributors. Finally, we did not use any standardized questionnaire for the assessment of depression and the diagnosis was based only on administered antidepressant treatment by a psychiatrist. This may explain the lower prevalence of depression in our study compared with others.

In conclusion, APS patients, including both PAPS and SLE-APS, have a high comorbidity burden, higher or comparable to that in RA that merits a similar level of diligence. Regular assessment and management of both traditional and disease-related CV risk factors, awareness for mood disorders, screening and management of osteoporosis and consistent efforts for minimization of CS exposure, should be part of routine patient care in APS.

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