Impact of cardiovascular risk factors in antiphospholipid syndrome: an observational study from the Spanish national registry

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Abstract

Objective

To determine the burden and impact of cardiovascular risk factors (CRF) in antiphospholipid syndrome (APS) patients.

Methods

Analysis of the patients diagnosed with APS identified in the Spanish Hospital Discharge Database between 2016 and 2017. We analysed the admissions due to arterial (ATE) and venous thromboembolic events (VTE) and evaluated the incidence and the attributed risk of each CRF.

Results

5424 admissions in patients diagnosed with APS were identified. 64.6% were women and the mean age was 54.6. The mortality rate was 3.1%. Overall, 35.8% of patients had hypertension, 14% were diabetic, 21.7% hypercholesterolaemic, 9.9% obese and 26.7% smokers. Thromboembolic events (67.9% arterial and 32.1% venous) accounted for 11.9% of admissions and 7.1% of deaths. Male sex (OR 1.83, 95% CI 1.41–2.21), cholesterol (OR 1.25, 95% CI 1.01–1.54) and smoking (OR 1.49, 95% CI 1.22-1.81) were independently associated with thromboembolic events. Meanwhile, patients with ATE were older (57 vs. 54.1 years p=0.033), and presented more secondary APS (17.1% vs. 10.6%, p=0.034), hypertension (47.7% vs. 33.5%, p=0.001), diabetes (16.9% vs. 9.6%, p=0.017), cholesterol (34.3% vs. 17.8%, p<0.001) and smoking habit (41.2% vs. 24%, p<0.001) when compared with VTE. Risk factors independently associated with ATE events were male sex (OR=1.61, 95% CI=1.30–2.03), hypertension (OR=1.30, 95% CI=1.03–1.64), cholesterol (OR=1.51, 95% CI=1.18–1.94) and smoking habit (OR=1.84, 95% CI=1.47–2.32), while VTE events were determined by male sex (OR=2.06, 95% CI=1.53–2.77) and obesity (OR=1.61, CI=1.02–2.52).

Conclusion

Thromboembolic events in APS were in part determined by a high prevalence of CRF. The identification of distinct profiles may allow us to undertake a more personalised approach to reduce thromboembolic events and to individualise anticoagulant and antiplatelet therapy.

Key words

antiphospholipid syndrome, thromboembolic events, arterial thrombosis, venous thrombosis, cardiovascular risk factors

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Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by thrombosis in arterial and/or venous territories and/or obstetric manifestations in the presence of antiphospholipid antibodies (1, 2). However, while the presence of antiphospholipid antibodies itself seems necessary for the development of thrombosis, other conditions such as infection, concomitant autoimmune diseases and other prothrombotic factors are often needed as a trigger for thrombosis in APS patients ("second-hit hypothesis") (3, 4). As a matter of fact, previous reports have found that more than half patients with APS with thrombosis had concurrent risk factors (5-8). Among these, cardiovascular risk factors (CRF) have a proven key role in thrombosis (9-11). Nevertheless, previous studies have shown that arterial and venous thromboembolic risk factors are not the same (12, 13). Consequently, a better identification and control of CRF in patients with antiphospholipid antibodies seems crucial to prevent new and recurrent thrombosis, reduce cardiovascular disease and guide a more personalised management according to different risk profiles.

Therefore, our objective was to determine the burden and impact of CRF on APS thromboembolic events by studying patients' admissions through the Spanish Hospital Discharge Database.

Materials and methods

Patients

We performed an analysis of data extracted from the Spanish Hospital Discharge Database (SNHDD), a registry belonging to the Spanish Ministry of Health. The SNHDD includes demographic and epidemiological data and up to 20 discharge diagnoses carried out during admission and defined by the International Classification of Diseases (ICD-10) from January 1st, 2016. We selected hospital admissions from 2016 to 2017 for patients with a diagnosis within the ICD-10 code D68.61 (antiphospholipid syndrome) at any position in the list. The study complies with the Declaration of Helsinki and was approved by the local research ethics committee (PI 149/21). The database was provided after all potential patient identifiers were deleted and data was anonymously given.

Assessment of thromboembolic events

Since the main diagnosis was the defining reason for admission or the cause of death, all the main diagnoses were decodified and clustered into groups such as infections, digestive-surgical conditions, neoplasms, neurological diseases, respiratory diseases, cardiovascular disease, and so on. Among these, thromboembolic events were identified and further divided between arterial and venous. Venous thromboembolic events (VTE) were composed by acute pulmonary embolism, lower extremity acute deep vein thrombosis and vein thrombosis affecting other territories such as the iliac, portal, spleen, cava, subclavian, jugular, renal and upper extremities veins. Arterial thromboembolic events (ATE) included acute cerebrovascular disease, such as stroke and transient ischaemic attack (TIA), coronary events and peripheral arterial disease such as lower extremity arterial thromboembolism, aortic thromboembolism or aortic syndrome, intestinal ischaemia and infarction, renal or suprarenal infarction.

Identification of cardiovascular risk factors and secondary APS

ICD-10 coding was also used to analyse CRF. Patients were tagged as hypertense if they had a diagnosis of primary hypertension (code I10), hypertensive cardiac disease (I11), hypertensive chronic kidney disease (I12), hypertensive cardiac and chronic kidney disease (I13) or secondary hypertension (I15). Diabetes included type 1 diabetes mellitus (E10), type 2 diabetes mellitus (E11) and other types of diabetes mellitus (E12). High cholesterol was defined by pure hypercholesterolaemia (E78) or hyperlipidaemia (E78.2 and E78.5) and obesity by the homonymous code E66. Smoking was classified according to tobacco consumption (Z72.0) or nicotine dependence (F17).

Autoimmune diseases that could define secondary APS were also recorded: systemic lupus erythematosus (M32), rheumatoid arthritis (M05 and M06), systemic sclerosis (M34), mixed con-

nective tissue disease (M35.1), undifferentiated and others (M35.9). Primary Sjögren's syndrome (M35) was considered if the patient did not present systemic lupus erythematosus (SLE).

Statistical analysis

Categorical variables were reported as frequencies and percentages while continuous variables were presented as mean and standard deviation. The significance of baseline differences between thromboembolic events was determined by the Chi-square, Fisher's or Student's t-test, as appropriate. Secondly, different multivariable logistic regression analyses were performed to determine the factors related to thromboembolism, ATE, VTE, cerebrovascular, coronary and peripheral arterial events. For all the analyses, a significance level of 0.05 was set. Statistical analysis was performed using SPSS v. 26.0 (IBM, Spain) and Stata v. 16 (StataCorp. 2019. Stata Statistical Software: Release 16) software.

Results

Population characteristics

Between 2016 and 2017, 5,424 hospital admissions in patients diagnosed with APS were identified in the SNHDD. The population characteristics are shown in Table I. 64.6% were women and the mean age was 54.6 years. 1,287 patients (24%) were classified as secondary APS due to the presence of additional autoimmune diseases: SLE in 19%, rheumatoid arthritis in 1.9%, primary Sjögren's syndrome (in 1.2%, systemic sclerosis in 1,1% and mixed, undifferentiated and others in 0.8%. Classical CRFs were present in a substantial number of patients: 35.8% were identified as hypertensive, 14% diabetic, 21.7% hypercholesterolaemic and 9.9% obese. Smoking habit was detected in 26.7% of patients. The mean average in-hospital stay was 8.8 days and the global mortality was 3.13% (170 deaths).

Thromboembolic events

647 admissions (11.9%) were caused by thromboembolic disease: venous 208 patients (32.1%) and arterial 439 patients (67.9%). VTE events included pulmonary embolism (49.5%), lower extremity acute deep vein thrombosis (32.7%), iliac vein thrombosis (5.3%), portal vein thrombosis (3.8%), spleen vein thrombosis (2.4%) and vein thrombosis affecting other territories such as cava, subclavian, jugular, renal vein and upper extremities (6.3%). ATE events included acute cerebrovascular disease (59.1%), coronary artery events (28.5%), and peripheral arterial thromboembolism (12.4%), affecting lower extremities (4.1%), aorta (3.4%), bowel (2.5%), renal/suprarenal (1.8%) and other territories (0.7%). The mean age of patients with thromboembolic events was 56 years and 49.9% of patients were women. The associated mortality was 1.9% and thromboembolic events caused 7.1% of all deaths. After adjustment, male sex (OR 1.83, 95% CI 1.41–2.21), high cholesterol (OR 1.25, 95% CI 1.01–1.54) and smoking (OR 1.49, 95% CI 1.22–1.81) were independently associated with thromboembolic events (Table II).

Differences among arterial and venous thromboembolic risk factors

Some differences were found when comparing ATE and VTE groups (Table III). As compared to VTE patients, those with ATE were older (57 *vs*. 54.1 years p=0.033) and presented a higher proportion of cardiovascular risk factors such as hypertension (47.7% vs. 33.5%, p=0.001), diabetes (16.9% *vs*. 9.6%, p=0.017), high cholesterol (34.3% *vs*. 17.8%, p<0.001) and smoking (41.2% *vs*. 24%, p<0.001). In addition, secondary APS was more frequent in patients with ATE (17.1% *vs*. 10.6%, p=0.034). Although no differences were found in mortality, patients with ATE had a longer average in-hospital stay (11.7 *vs*. 8.9 days, p=0.039).

In the multivariable analyses, the independent risk factors related to ATE were male sex (OR 1.61, 95% CI 1.30–2.03), hypertension (OR 1.30, 95% CI 1.03–1.64), high cholesterol (OR 1.51, 95% CI 1.18–1.94) and smoking (OR 1.84, 95% CI 1.47–2.32), while male sex (OR 2.06, 95% CI 1.53–2.77) and obesity (OR 1.61, CI 1.02–2.52) were the only risk factors independently associated with VTE events (Table IV).

Risk factors associated with specific arterial territories (cerebrovascular, coronary and peripheral) were also evaluated (Table V). Male sex (OR 1.50, 95% CI 1.14–1.99) hypertension (OR 1.50, 95% CI 1.14–1.96) and smoking (OR 1.66, 95% CI 1.25–2.20) were the independent risk factors for cerebrovascular events; male sex (OR 1.85, 95% CI 1.23–2.78), high cholesterol (OR 2.13, 95% CI 1.42–3.18) and smoking (OR 2.09, 95% CI 1.39–3.12) were independently associated with coronary events; and age (OR 1.02, 95% CI 1.01–1.04) and smoking (OR 2.27, 95% CI 1.21–4.26) were the only predictors of peripheral artery events.

Table I. Patient's characteristics.

Admissions in patients with antiphospholipid syndrome (n=5424)		
Age (years) (mean, SD)	54.6	(17.8)
Female, n (%)	3504	(64.6)
Secondary APS, n (%)	1287	(24)
SLE, n (%)	1031	(19)
Hypertension, n (%)	2005	(37)
Diabetes, n (%)	787	(14.5)
Cholesterol, n (%)	1176	(21.7)
Obesity, n (%)	521	(9.6)
Smoking habit, n (%)	1418	(26.1)

SD: standard deviation; APS: antiphospholipid syndrome; SLE: systemic lupus erythematosus.

Table II. Factors related to thromboembolic events.

	OR	95% Confidence interval
Age	1.01	0.99-1.01
Male sex	**1.83**	**1.51-2.21**
Hypertension	1.15	0.93-1.42
Diabetes	0.86	0.66-1.12
Cholesterol	**1.25**	**1.01-1.54**
Obesity	1.14	0.85-1.52
Smoking habit	**1.49**	**1.22-1.81**

Discussion

This is one of the largest studies exploring risk factors for thrombosis in APS. Our results revealed a high prevalence of CRF and a clear association with thromboembolic events. This analysis of the Spanish National Registry confirms that venous and arterial events are related to different risk factors; among the latter, cerebrovascular, coronary and peripheral arterial events have also specific risk profiles.

Almost 12% of admissions were due to thromboembolic events, similar to pre-

Table III. Differences among arterial and venous thromboembolic events.

	Arterial thromboembolic events (n= 439)	Venous thromboembolic events (n= 208)	*p*-value
Age (years) (mean, SD)	57 (14.8)	54.1 (18.2)	**0.033**
Sex female, n (%)	219 (50%)	104 (50.1%)	0.999
Secondary APS, n (%)	75 (17.1%)	22 (10.6%)	**0.034**
Hypertension, n (%)	185 (47.7%)	64 (33.5%)	**0.001**
Diabetes, n (%)	74 (16.9%)	20 (9.6%)	**0.017**
Cholesterol, n (%)	133 (34.3%)	34 (17.8%)	**<0.001**
Obesity, n (%)	41 (10.6%)	27 (14.1%)	0.218
Smoking habit n (%)	181 (41.2%)	50 (24%)	**<0.001**
Average stay (days) (mean, SD)	11.7 (19.5)	8.9 (6.5)	**0.039**
Deaths, n (%)	9 (2.1%)	3 (1.4%)	0.760

SD: standard deviation.

Table IV. Factors related to arterial and venous thromboembolic events.

	Arterial thromboembolic event		Venous thromboembolic event	
	OR	95% Confidence interval	OR	95% Confidence interval
Age	1.01	0.99-1.01	1.00	0.99-1.01
Male sex	**1.62**	**1.30-2.03**	**2.06**	**1.53-2.77**
Hypertension	**1.30**	**1.03-1.64**	0.88	0.62-1.24
Diabetes	0.92	0.68-1.25	0.642	0.39-1.05
Cholesterol	**1.51**	**1.18-1.94**	0.692	0.47-1.02
Obesity	0.95	0.66-1.37	**1.61**	**1.02-2.52**
Smoking habit	**1.84**	**1.47-2.32**	0.79	0.55-1.13

Table V. Factors related to cerebrovascular, coronary and peripheral events.

	Cerebrovascular events (n=260)		Coronary events (n=125)		Peripheral events (n= 54)	
	OR	95% CI	OR	95% CI	OR	95% CI
Age	1	0.99-1.01	1.01	0.99-1.02	**1.02**	**1.01-1.04**
Male sex	**1.50**	**1.14-1.99**	**1.85**	**1.23-2.78**	1.01	0.51-2
Hypertension	**1.50**	**1.14-1.96**	1.07	0.69-1.67	0.81	0.40-1.61
Diabetes	0.88	0.60-1.29	0.87	0.52-1.49	1.08	0.45-2.58
Cholesterol	1.25	0.91-1.72	**2.13**	**1.42-3.18**	0.88	0.41-1.91
Obesity	0.70	0.43-1.13	1.14	0.77-2.25	0.95	0.33-2.75
Smoking habit	**1.66**	**1.25-2.20**	**2.09**	**1.39-3.12**	**2.27**	**1.21-4.36**

vious studies (14, 15). Unlike previous reports showing that venous thromboembolic events were more frequent at disease onset, a higher incidence of arterial thrombosis was found during a 10-year follow-up period (14, 16). Our data support that, once patients have full-blown APS and are thus likely under anticoagulant treatment, recurrent events are more frequent in the arterial bed (17, 18).

In this study, patients admitted with ATE were older, had more CRF such as hypertension, diabetes, hypercholesterolemia and smoking habit and presented a higher incidence of secondary APS than those who suffered VTE. This is consistent with the association of atherosclerosis with arterial thrombosis and of obesity and immobilisation with venous thromboembolic disease (21, 22). In addition, autoimmune diseases, mostly SLE, have a proven role in endothelial damage (23-25). Thus, our study confirms the results of other groups showing two clear clinical phenotypes in APS (5, 6, 7, 12, 26-31). In addition, we found that hypertension was particularly related with stroke, hypercholesterolaemia with coronary disease and advanced age with peripheral arterial thrombosis, with smoking being the strongest risk factor for all ATE. While these differences have been clearly proven in the general population, they had not been properly assessed in patients with APS (32-34).

Our results lead to three major considerations. First, being the main modifiable risk factors for thrombosis, early CRF detection and management should be a priority in patients with APS. Second, our data may support combination therapy with anticoagulant and antiplatelet agents in patients with arterial events, an option that is gaining acceptance (17, 19). In addition, additional antiplatelet therapy might also be considered in patients with APS and venous thrombosis with high atherosclerotic burden and/or the presence of classical CRF. Third, additional measurements should be enhanced and promoted to attenuate the thrombotic risk, mainly in arterial territories (35). Among these, statins and hydroxychloroquine have proven antithrombotic effects in addition to their role as lipid-lowering and immunomodulatory agents, respectively (36-38). Indeed, the antithrombotic benefits of hydroxychloroquine have been recently shown in a study within the Lupus-Cruces cohort, in which this drug was identified as the main protector against cardiovascular damage accrual in patients with SLE and antiphospholipid antibodies (39). A small open-label randomised prospective study have also suggested the role of adding hydroxychloroquine to standard of care in preventing thrombosis in patients with primary APS (40). Thus, hydroxychloroquine is clearly a drug to be explored in the future care of patients with antiphospholipid antibodies.

Our study has several limitations. Mainly, a number of potentially relevant variables were not contained in the registry. Having data regarding the specific antiphospholipid antibody profiles, disease course (*e.g.* whether APS diagnosis was made before or during admission, arterial/venous/obstetric events at presentation, etc.) and treatments (including anticoagulants, antiaggregants and antimalarials) prior to the index event would have yielded more solid conclusions regarding thromboembolic

risk factors and potential therapeutic approaches. Besides, more precise information regarding CRF, such as the low-density lipoprotein-cholesterol values, the body mass index, the pack-year smoking history, as well as lipid-lowering, antidiabetic and/or antihypertensive treatment, would have defined the impact of the CRF with more accuracy. In parallel, immunosuppressant and corticosteroid treatment in patients with secondary APS, which may have had an impact on these CRF, was not available due to database structure. Finally, all the data were obtained from hospital admissions, with the resultant limitation in power and the potential selection bias. Although thrombotic events not being among the causes of hospital admissions were not retrieved, thromboembolic events in APS are usually severe enough as to be among the diagnosis at discharge. On the other hand, it has to be highlighted that the differences between primary and secondary APS were not considered since patients with SLE are admitted because of other causes, such as flare, nephritis or infection. Therefore, the two populations are not equivalent and the comparison would have been inaccurate. Altogether, we believe that these limitations could have been counterbalanced by the size and the nation-wide spectrum of our study population.

In conclusion, our study reveals that thromboembolic events in APS were largely determined by a high prevalence of CRF. As a consequence, their prompt identification and aggressive management should be one of the priorities among patients with antiphospholipid antibodies. In addition, the identification of distinct risk profiles among patients with APS should lead to a more personalised therapeutic approach, which could include different combinations of anticoagulant, antiplatelet and antimalarial agents.

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