A multicenter prospective registry of patients with Antiphospholipid Syndrome in Greece (The Greek APS registry)

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ABSTRACT

Antiphospholipid syndrome (APS) is a hypercoagulable state characterized by vascular thromboses, pregnancy morbidity and the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant, anticardiolipin antibodies and anti-beta 2 glycoprotein I (anti-β2GPI) antibodies. APS can clinically present with arterial and venous thrombotic manifestations and/or pregnancy morbidity as well as various non-classical manifestations such as heart valve abnormalities, thrombotic renal microangiopathy, skin involvement and thrombocytopenia. A small percentage (<1%) of patients with APS develop systemic, multiorgan life-threatening complications defined as catastrophic APS. Treatment mainly consists of anticoagulant and/or antiplatelet agents. The aim of the current project is to create a Greek Registry of consecutive patients with APS followed regularly in university centers with detailed recording of demographic, disease-related serological and clinical parameters, prevalence of comorbidities including traditional risk factors for thrombosis, infections and neoplasms, and the current and previous use of different antithrombotic or anti-inflammatory regimens.

Keywords: autoimmune diseases, antiphospholipid syndrome, registry.
INTRODUCTION
Antiphospholipid syndrome (APS) is a hypercoagulable state characterized by vascular thromboses, pregnancy morbidity and the presence of antiphospholipid antibodies (aPL): namely lupus anticoagulant, anticardiolipin antibodies and anti-beta 2 glycoprotein I (anti-b2GPI) antibodies. Antiphospholipid syndrome can be primary (primary APS) or associated with underlying autoimmune disease, mainly Systemic Lupus Erythematosus (SLE-associated APS). A small percentage (<1%) of patients with APS develop the catastrophic form of APS (catastrophic APS) which is characterized by multiple organ involvement developing over a short period of time (1 week), usually associated with microthrombosis. However, most aPL-positive patients in the general population (~5%) remain asymptomatic, and should be evaluated for APS based on the Updated Sapporo APS Classification Criteria in order to prevent overdiagnosis of the syndrome. Data from large cohorts/registries are invaluable in determining factors predisposing to recurrent thrombosis in aPL-positive and APS patients. The largest such cohort worldwide is the European cohort of APS including 1,000 patients from 13 European countries. Data from the cohort were first published in 2002, and on the 10-year follow-up revealed thrombotic events in approximately 30% of the patients: most commonly strokes, transient ischemic attacks, deep vein thromboses and pulmonary embolism. The most common obstetric complication was early pregnancy loss (16.5% of pregnancies), intrauterine growth restriction (26.3%) and prematurity (48.2%). Ninety-three (9.3%) patients died, and the most frequent causes of death were severe thrombosis (36.5%) and infections (26.9%). Predictors of high thrombotic risk were (i) a positive LA test, (ii) Persistent positivity of anticardiolipin antibodies or anti-b2GPI antibodies in medium-high titres, and (iii) Triple aPL positivity.

PATIENTS AND METHODS
We will create a Greek Registry of consecutive patients with APS followed regularly in university centers. A detailed set of clinical and laboratory characteristics, as well as morbidity and mortality data will be extracted from the patients’ medical records in a de-identified fashion after informed consent. They will then be recorded in a computerized database, using a secure website especially designed for the purposes of the present study. Every database entry will have a unique key code, generated through a combination of the subject’s and associated healthcare organization’s initials and year of birth, and year of initial visit to the healthcare center. The data from all the centers will be recorded over a period of 12 months and will be completed by the treating physician on a pre-specified form, either in print (mailed or faxed) or online. The database will be updated yearly by telephone communication of the researchers with the treating physicians, and in 3 years using a complete medical and laboratory review of the medical record in each participating healthcare center. The following data will be recorded:

1. Demographic characteristics of patients with APS (age, gender, employment status);
2. The prevalence of primary APS and of secondary APS: APS associated with SLE (≥4/11 ACR criteria), lupus-like (3/11 ACR criteria), rheumatoid arthritis, Sjögren’s syndrome, systemic sclerosis, vasculitis;
3. The prevalence of catastrophic APS;
4. The prevalence and the spectrum arterial and venous thrombosis and pregnancy morbidity manifestations of APS;
5. The prevalence and the spectrum of non-classical (non-criteria) manifestations of patients with APS (thrombocytopenia, livedo reticularis, APS nephropathy);
6. The immunological profile of antiphospholipid antibodies (aPL): the frequency of different antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies and anti-beta 2 glycoprotein I) and their titre and isotype (IgG, IgM);
7. The frequency of hospitalizations over the past year and the causes of hospitalizations;
8. Current and previous use of different medications (anticoagulants, antplatelets, corticosteroids, immunosuppressives);
9. The prevalence of traditional risk factors for thrombosis and other comorbidities (body mass index, smoking, alcohol, hypertension, diabetes mellitus, hyperlipidemia, osteoporosis); and

AIMS OF THE STUDY
To describe the epidemiologic, clinical and laboratory characteristics of APS in Greece, as well as investigate research hypotheses regarding factors affecting disease prognosis and severity. Specific objectives of the analysis include:

1. Information on the prevalence of the various syndrome categories in Greece (according to international guidelines): (i) Primary APS, (ii) Associated with underlying autoimmune disease (such as SLE) with detailed recording of disease associations, (iii) Thrombotic APS (manifesting solely with vascular thromboses), (iv) Obstetrical APS (purely manifesting with complications of pregnancy), (v) Combination of thrombotic and obstetrical APS, and (vi) Catastrophic APS;
2. Description of the range and frequency of thrombotic and obstetrical complications of APS in Greece and potential associations of syndrome type with patient age and gender;

3. Description of the range and frequency of non-criteria syndrome manifestations, such as thrombocytopenia, livedo reticularis and kidney injury, as well as their correlation with “classic” APS manifestations and aPL profile (isotype, titers, double or triple positivity);

4. Systematic review and presentation of the current therapeutic approach to APS by Greek physicians: We will analyze the various types of antithrombotic therapy used (classic, combination of antithrombotic and antiplatelet treatment, low-molecular weight heparin, novel oral anticoagulants), as well as co-administration of hydroxychloroquine (based on recent data) and immunomodulating therapies (corticosteroids/immunosuppressives) and biologic therapies;

5. The frequency of comorbidities and their potential associations with certain clinical manifestations (i.e., arterial hypertension and arterial versus venous thrombosis), as well as syndrome type (i.e., incidence of fractures in primary APS versus SLE-associated APS);

6. The frequency of hospitalizations of patients with APS due to the syndrome itself or due to other reasons, in association with their clinical and laboratory characteristics; and

7. The prevalence and incidence of infectious disease and cancer in patients with APS, and possible correlations with certain disease characteristics.

**APPENDIX – MEMBERS OF GREEK ASSOCIATION FOR RHEUMATOLOGY APS STUDY GROUP**

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**REFERENCES**


