**Extra-criteria manifestations of antiphospholipid syndrome: Risk assessment and management**

Semin Arthritis Rheum. 2018 Aug;48(1):117-120.
doi: 10.1016/j.semarthrit.2017.12.006.
Extracriteria manifestations of antiphospholipid syndrome: Risk assessment and ma
nagement. Radin M, Ugolini-Lopes MR, Sciascia S, Andrade D. PMID:29395258

# Extra-criteria manifestations of Antiphospholipid Syndrome: risk assessment and management

Massimo Radin[1], Michelle Remião Ugolini-Lopes[2], Savino Sciascia[1] and Danieli Andrade[2,3]

[1]Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, Department of Clinical and Biological Sciences, and SCDU Nephrology and Dialysis, University of Turin and S. Giovanni Bosco Hospital, Turin, Italy.

[2]Hospital dasClinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR

[3] Co-Chair of APS ACTION

**Running Title:** Extra-manifestation of APS: Risk and management

**Key words:**

Antiphosphospholipid syndrome - APS –livedo- thrombocytopenia– GAPSS– aGAPSS – risk score - thrombosis

**Corresponding Author:**

Massimo Radin, MD;

Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, S. Giovanni Bosco Hospital

Piazza del Donatore di Sangue 3, 10154, Turin, Italy.

Email massimo.radin@unito.it Tel +390112402056 Fax +390112402052

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

**Total word count:**

**Abstract**

**Objectives:**

Extra-criteria manifestations of antiphospholipid syndrome (APS) might impact on prognosis and morbidity of the disease. In this study, we aimed to evaluate a population of patients with primary APS(PAPS) whether the extra-criteria manifestations were more frequently found in subjects with higher adjusted Global APS Score (aGAPSS) values when compared to patients with thrombotic and/or obstetric APS("criteria" manifestations) only.

**Methods:**

Clinical records were analyzed to retrieve extra-criteria manifestation of APS, cardiovascular risk factors and antiphospholipid antibodies profile. The aGAPSS was calculated by adding the points, as follows: 3 for hyperlipidaemia, 1 for arterial hypertension, 5 for anticardiolipin antibodies IgG/IgM, 4 for anti-b2 glycoprotein I IgG/IgM and 4 for lupus anticoagulant.

**Results:**

This retrospective multicenter study included 89 consecutive PAPS [mean age 43.1(S.D.±12.9), female 67%, 52% arterial and 65% venous]. Twenty-seven patients (30.3%) had a history of livedo,

19(21.3%) had a history of confirmed thrombocytopenia,3(3.4%) had biopsy-proven antiphospholipid antibodies (aPL)-related nephropathy and 3(3.4%) had a history of valvulopathy. Patients with extra-criteria manifestations presented a mean aGAPSS significantly higher [mean 10.30(S.D.±3.57,range 4-17) vs mean 8.16(S.D.±3.52;range 4-16,p=0.005). When comparing patients with and without extra-criteria manifestations, the first group had significantly higher incidence of anti-ß2GPI antibodies positivity (59% and 33%, respectively, p=0.015), double aPL positivities (53% and 31%, respectively, p=0.034), cerebrovascular events history(52% and24%, respectively, p=0.007) and arterial hypertension (52% and 24%, respectively, p=0.007).

**Conclusions:**

Our results suggest that patients with higher aGAPSS, might be at higher risk for developing extra-criteria manifestations of APS and should therefore undergo a thorough laboratory and instrumental evaluation.

## 1.1 Introduction

The antiphospholipid syndrome (APS) is characterized by antiphospholipid antibodies (aPL) associated with thrombosis (arterial and/or venous) and/or pregnancy morbidity. The current Sydney classification criteria [1] do not consider a range of non-thrombotic clinical manifestations that are frequently observed in association with the presence of aPL, the *so-called* extra-criteria manifestations [2]. Although extra-criteria manifestations, such as thrombocytopenia, *livedo reticularis*, aPL related-nephropathy, cardiac valve disease, cognitive dysfunction and skin ulcers are relatively common, their accurate prevalence and associated thrombotic risk are unknown [3]. Furthermore, despite the diagnostic value of these extra-criteria manifestations has yet to be determined, they might be highly relevant and reveal correlations with prognosis or morbidity [4].

In fact, patients with APS still suffer for a significant burden of morbidity and mortality regardless a proper management with the current therapeutic tools; thus, it is imperative to increase the efforts in determining optimal prognostic markers, risk assessments measures and therapies to prevent complications.

Recently, the Global APS Score (GAPSS) and the adjusted GAPSS (aGAPSS), a simplified version of the same score, were designed to

evaluate the risk of patients to develop any clinical manifestation of APS [5–8]. These scores are important to predict which patients are at higher risk and that consequently will need closer follow-up and eventually specific treatment. It is debated whether patients with non-criteria manifestations are at a higher recurrence risk [4].

The purpose of this study was to evaluate in a population of patients with primary APS (PAPS). whether the extra-criteria manifestations were more frequently found in subjects with higher aGAPSS values when compared to patients with thrombotic and/or obstetric APS ("criteria" manifestations) only.

**2.1 Patients and methods:**

**2.2 Patients**

This retrospective multicenter study included 89 consecutive primary APS patients who attended the Hospital das Clinicas, Sao Paulo, Brazil and S. Giovanni Bosco Hospital, Turin, Italy. Inclusion criteria included the persistent aPL positivity and the fulfillment of the Sydney criteria for APS [1].

Both centers are tertiary referral hospitals and are responsible for the management of severe APS patients.

## 2.3 Extra-criteria manifestations of APS

Medical records were retrospectively checked for extra-manifestations of APS. *Livedo reticularis* and *racemosa* were assessed by physical examination as per standard of care of centers. Thrombocytopenia was defined as platelets level <100,000 $mm^3$ and confirmed with at least two examinations with a complete blood count and evaluation of the peripheral blood smear. aPL-related nephropathy was assessed with kidney biopsy [9] and valvulopathy was confirmed with echocardiography [10].

## 2.4 Autoantibody detection

The aPL profile included anticardiolpin antibodies (aCL), lupus anticoagulant (LA) and anti-ß2 glycoprotein I (anti-ß2GPI) antibodies. Plasma samples were tested for the presence of LA according to the recommended criteria from the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies [11,12]. The aCL and anti-ß2GPI were detected by ELISA as described previously [13].

## 2.5 Cardiovascular risk factors assessment

Cardiovascular risk factors (including hypertension, dyslipidemia, diabetes, hormone replacement therapy and smoking) were assessed following the National Institute for Health and Care Excellence (NICE) guidelines [16]. In detail, enrolled patients underwent a physical examination, blood pressure determination and phlebotomy for vascular risk factors. Arterial hypertension was defined as an appropriately sized cut-off (140/90 mmHg or higher)[15], high blood pressure on at least two occasions or use of oral antihypertensive medications. Serum total and high-density lipoprotein (HDL) cholesterol levels were determined with standardized enzymic methods and interpreted according to current cut-off values [15].

**2.6 Adjusted GAPSS calculation**

The cumulative aGAPSS was calculated for each patient as previously reported by adding together all points corresponding to the risk factors [5]. After its first description, GAPSS was prospectively validated [7] and applied in a cohort of patients with PAPS [8]. To increase the generalizability of the findings, in this study we applied an adjusted version of GAPSS (aGAPSS). This comprises only aPL testing included in the current classification criteria for APS (excluding aPS-PT, not routinely available in all the laboratories). Data are presented as aGAPSS.The aGAPSS was calculated by adding the points

corresponding to the risk factors, based on a linear transformation derived from the ß regression coefficient as follows: 3 for hyperlipidaemia, 1 for arterial hypertension, 5 for aCLIgG/IgM, 4 for anti-b2 glycoprotein I IgG/IgM and 4 for LA.

### 2.8 Statistical analysis

Categorical variables are presented as number (%) and continuous variables are presented as mean (S.D.). The significance of baseline differences was determined by the chi-squared test, Fisher's exact test or the unpaired t-test, as appropriate. A two-sided P-value <0.05 was statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

### 3.1 Results:

A total of 89 consecutive PAPS patients [mean age 43.1 (S.D.±12.9), female 67%] were included in the analysis. Fourty-six patients had at least one episode of arterial thrombosis (51.7%) and 58 (65.2%) had at least one episode of venous thrombosis. Demographic, clinical and laboratory characteristics are summarized in Table 1.

| Patients Characteristics | All (89) | % |
|---|---|---|
| Female sex | 67 | 75,2 |
| Age, mean (S.D.), years | 43,1 (12,9) | |
| Venous thrombosis, n | 58 | 65,2 |
| Arterial thrombosis, n | 46 | 51,7 |

| | | |
|---|---|---|
| Stroke, n | 34 | 38,2 |
| Pregnance Morbidity | 34 | 38,2 |
| Arterial Hypertension, n | 24 | 29,9 |
| Hyperlipidemia, n | 20 | 22,5 |
| Smoking, n | 14 | 15,7 |
| Diabetes, n | 7 | 7,8 |
| LA, n | 73 | 82 |
| aCL IgG/M, n | 56 | 62,9 |
| Anti-Beta2GPI IgG/IgM, n | 41 | 46,1 |
| Double aPL positive | 37 | 41,6 |
| Triple aPL positive | 22 | 24,7 |
| aGAPSS, mean (S.D) | 9,15 (3,7) | |
| Extra Criteria Manifestations | | |
| Livedo, n | 27 | 30,3 |
| Thrombocytopenia, n | 19 | 21,3 |
| Valvulopathy, n | 3 | 3,4 |
| Biopsy proven APS Nephropaty, n | 3 | 3,4 |

Table 1. Demographic, clinical and laboratory characteristics of the cohort
*aPL= Antiphospholipid antibodies; S.D. = standard deviation; aGAPSS = adjusted global antiphospholipid score*

When considering the extra-manifestation of APS, 27 patients (30.3%) had a history of livedo, of those 21 patients had *livedoreticularis*and six *livedoracemosa*. Nineteen patients (21.3%) had a history of confirmed thrombocytopenia(range 30,000/µl-100,000/µl), three patients (3.4%) had biopsy-proven aPL-related nephropathy and three patients (3.4%) had a history of valvulopathy. Table 2 summarizes the characteristics of patients between groups.

| | **Livedo (27)** | **Thrombocytopenia (19)** | **No extra-criteria manifestation (45)** |
|---|---|---|---|
| **Age (mean, SD)** | 48 ±11.4 | 41.9 ±14.2 | 33 ±12.9 |

| | | | |
|---|---|---|---|
| **Sex (females)** | 23 (85.2%) | 12 (63.2%) | 33 (73.3%) |
| **Hyperlipidemia** | 10 (37%) | 3 (15.8%) | 9 (20%) |
| **Arterial Hypertension** | 13 (48.1%)* | 5 (26.3%) | 8 (7.8%) |
| **Smoking** | 5 (18.5%) | 2 (10.5%) | 8 (7.8%) |
| **Diabetes** | 1 (3.7%) | 0 | 6 (13.3%) |
| **LA** | 22 (81.5%) | 16 (84.2%) | 38 (84.4%) |
| **aCL IgG/M** | 18 (66.7%) | 16 (84.2%)* | 24 (53.3%) |
| **Anti-Beta2GPI IgG/IgM** | 15 (55.6%) | 11 (57.9%) | 15 (33.3%) |
| **Triple aPL positivity** | 7 (25.9%) | 8 (42.1%) | 9 (20%) |
| **aGAPSS (mean, SD)** | 10.4 ± 3.9* | 10.6 ± 3.8* | 8.16 ±3.15 |

Table 2. Patients cardiovascular risk factors and aPL positivity between groups
*aPL= Antiphospholipid antibodies; S.D. = standard deviation; aGAPSS = adjusted global antiphospholipid score*
**statistically significantly different when compared with the group of "No extra-criteria manifestation"*

Patients with extra-criteria manifestations presented a mean aGAPSS of 10.30 (S.D. ±3.57, range 4-17), significantly higher when compared with patients without extra-criteria manifestations of APS (8.16; S.D. ±3.52; range 4-16; p = 0.005). When comparing patients with and without extra-criteria manifestations, the first group had significantly higher incidence of anti-ß2GPI antibodies positivity (59% and 33%, respectively, p=0.015), double aPLpositivities (53% and 31%, respectively, p=0.034), cerebrovascular events history (52% and 24%, respectively, p=0.007) and arterial hypertension (52% and 24%, respectively, p=0.007).

Similarly, when considering patients with *livedo* (both *reticularis* and *racemosa*), significantly higher aGAPSS values were seen when compared to patients with no extra-criteria manifestations [mean

aGAPSS 10.4 (S.D. ±3.9, range 4-17) Vs. mean aGAPSS 8,16 (S.D. ±3.52; range 4-16;); p=0.014].Further statistically significant differences were seen in the livedo group when compared to the extra-criteria group when analyzing the rate of arterial events (74% and 47%, respectively, p=0.02), cerebrovascular events (70% and 24%, respectively, p<0.001) and arterial hypertension (44% and 71%, respectively, p=0.004). Interestingly, the livedo group had significantly lower rate of venous events (44% and 71%, respectively, p=0.025). When considering only patients with livedoreticularis, the same statistically significant differences were seen. However, due to the small number of patients with livedoracemosa, a similar analysis could not be performed considering only the subgroup of patients with livedoracemosa.

Likewise, when considering patients with thrombocytopenia, significantly higher aGAPSS values were seen when compared to patients with no extra-criteria manifestations [mean aGAPSS 10.6 (S.D. ±3.8, range 4-17) p=0.018]. In patients with thrombocytopenia was also observed higher rate of aCL positivity (84% and 53%, respectively, p=0.02).

Due to the small number of patients with biopsy proven APS nephropathy (aGAPSS range 8-14) and valvulopathy (aGAPSS range 9-14), statistical differences could not be calculated separately for these

manifestations. No statistical significant differences were observed when comparing separately each cardiovascular risk factor (smoking, diabetes, dyslipidemia) nor other thrombotic risk factor (hormonal therapy, immobilization, surgery, malignancy).

**4.1 Discussion:**

The GAPSS score was conceived and validated in a comprehensive series of studies evaluating different patients populations [5,16–18]. The GAPSS model evaluates the risk profile of patients to develop thrombosis or pregnancy morbidity in the context of aPL positivity, based on traditional cardiovascular risk factors and aPL profile, considered as independent risk factors for developing any clinical APS manifestation. Very recently, in a systematic review that included 2273 patients, GAPSS was found to be a valid tool to stratify patients with aPL according to their thrombotic risk, being the highest levels of GAPSS found in patients who experienced thrombosis, especially arterial. Furthermore, the GAPSS was also proven to identify patients at higher risk of developing recurrences of any clinical manifestations of APS[19].

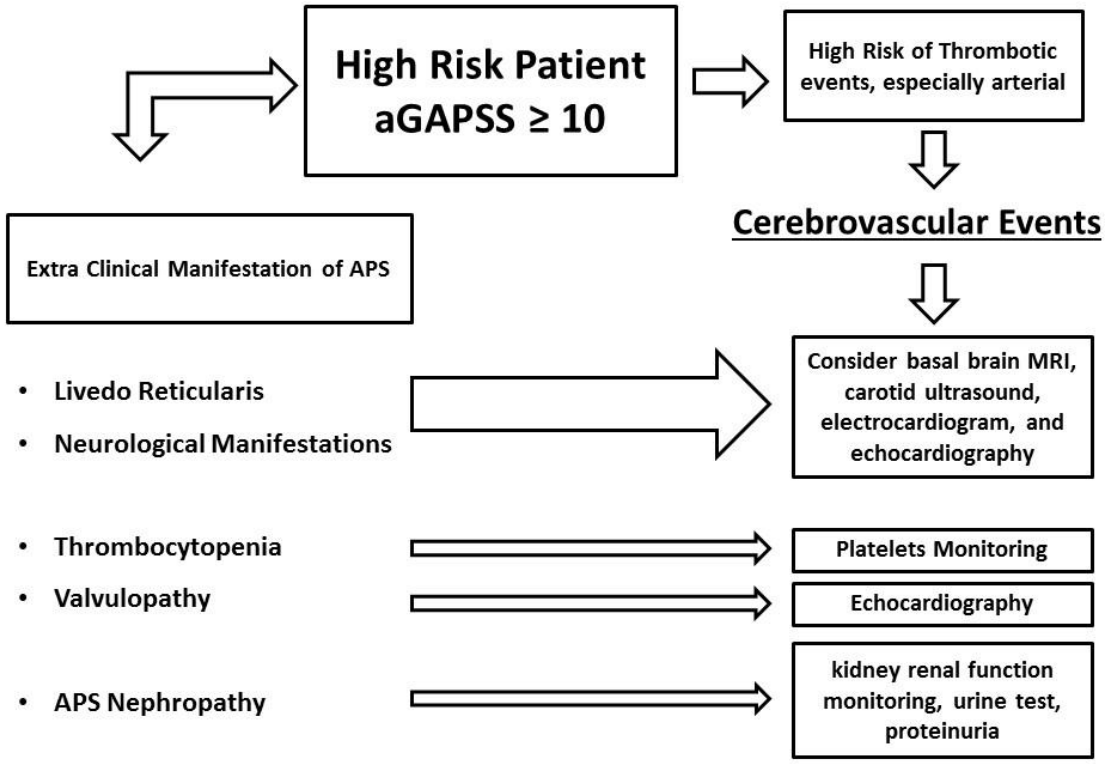
In the original GAPSS, anti-phosphatidylserine/prothrombin antibodies (aPS-PT) were included in the score. However, these are not currently part of the international consensus classification criteria [1]

and aPS-PT antibodies are not routinely tested in most clinical laboratories. For the above reasons, in our current study we applied the aGAPSS (excluding aPS-PT), already tested and validated in previous studies [20–22].

In this study, we highlight the clinical relevance of extra-criteria manifestations in risk assessment of APS using the aGAPSS.

Our cohort included 89 thrombotic PAPS patients and 49% of those patients experienced at least one extra-criteria clinical manifestation of APS. Higher levels of aGAPSS were seen in patients with extra-criteria clinical manifestations of APS, both when analyzing the extra-criteria manifestations as a group or as single manifestations.

Our results support the idea that patients with higher risk profile should undergo careful routine evaluation and risk assessment (Figure 1).




This is particularly important for the risk of developing arterial events, that include the potentially most life-threatening manifestations of the syndrome, being the central nervous system the most common affected site [23] and that was found in this analysis highly associated with extra-criteria manifestations of APS.

A throughout analysis of laboratory and instrumental investigation should be warranted in higher risk APS patients. aGAPSS might represents a substantial tool in identifying this particular subgroup and in quantifying the risk of developing any other clinical manifestation of APS, highly impacting on the clinical follow-up of patients and potentially in therapeutic long-term choices. Such patients

may require intensified diagnostic workout during the follow-up (e.g routine echocardiography and routine microscopic examination of the urine sediment).

**Limitations of the study**

We acknowledge few limitations for our study.

The use of a cross-sectional approach might influence the reproducibility of the results, as individual aGAPSS scores could variate at different time points. Further prospective analysis to confirm our findings is highly needed. However, one should consider the fact that APS is a rare condition and extra-criteria manifestations are present just in a subset of APS patients [4]. While a longitudinal study would be highly informative, a prospective data collection may require international joint efforts. From that perspective, it is worth mentioning the AntiPhospholipid syndrome alliance for clinical trials and International networking (APS ACTION) is the first-ever international research network that has been created specifically to design and conduct well-designed, large-scale, multicenter clinical studies in persistently aPL-positive patients [24–27].

Secondly, due to the retrospective nature of the data collection, the diagnosis of aPL-related nephropathy could only be assessed if the patient underwent a renal biopsy. Furthermore, extra-criteria

neurological manifestations of APS are an heterogeneous group of clinical entities, sometimes very common in the general population (e.g. migraine, mood disorders), making their attribution to aPL might challenging.

Finally, the effect of therapy and therapy compliance could not be properly assessed, as treatment was heterogeneously controlled in this cohort and varied according to the clinical manifestations and the clinician's judgment.

## Conclusion

To date, identifying APS patients who are at high risk for developing any thrombotic event is still an unmet clinical need and remains a major challenge for the treating physicians. Following the findings of our study, we suggest that PAPS patients with a higher risk profile according to aGAPSS might be at higher risk for developing extra-criteria manifestations (such as thrombocytopenia, livedo and/or nephropathy) and should therefore undergo a throughout laboratory and instrumental evaluation.

With the help of joint efforts and multicenter prospective studies confirming our findings, aGAPSS might aid the treating clinician for risk stratification of APS patients.

## 5.1 References


[1] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306. doi:10.1111/j.1538-7836.2006.01753.x.

[2] Sciascia S, Amigo M-C, Roccatello D, Khamashta M. Diagnosing antiphospholipid syndrome: “extra-criteria” manifestations and technical advances. Nat Rev Rheumatol 2017. doi:10.1038/nrrheum.2017.124.

[3] Rosa RF, Ugolini-Lopes MR, Zeinad-Valim AK, D’Amico E, Andrade D. Difficult Clinical Situations in the Antiphospholipid Syndrome. Curr Rheumatol Rep 2015;17:29. doi:10.1007/s11926-015-0502-7.

[4] Abreu MM, Danowski A, Wahl DG, Amigo M-C, Tektonidou M, Pacheco MS, et al. The relevance of "non-criteria" clinical manifestations of antiphospholipid syndrome: 14th International Congress on Antiphospholipid Antibodies Technical Task Force Report on Antiphospholipid Syndrome Clinical Features. Autoimmun Rev 2015;14:401–14.

doi:10.1016/j.autrev.2015.01.002.

[5] Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. GAPSS: the Global Anti-Phospholipid Syndrome Score. Rheumatology (Oxford) 2013;52:1397–403. doi:10.1093/rheumatology/kes388.

[6] Sciascia S, Bertolaccini M. Thrombotic risk assessment in APS: the Global APS Score (GAPSS). Lupus 2014;23:1286–7. doi:10.1177/0961203314541317.

[7] Sciascia S, Cuadrado MJ, Sanna G, Murru V, Roccatello D, Khamashta MA, et al. Thrombotic risk assessment in systemic lupus erythematosus: validation of the global antiphospholipid syndrome score in a prospective cohort. Arthritis Care Res (Hoboken) 2014;66:1915–20. doi:10.1002/acr.22388.

[8] Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. The global anti-phospholipid syndrome score in primary APS. Rheumatol (United Kingdom) 2014;54. doi:10.1093/rheumatology/keu307.

[9] Nochy D, Daugas E, Hill G, Piette J-C. [Anti-phospholipid syndrome nephropathy]. Ann Med Interne (Paris) 2003;154:51–8.

[10] Amigo M-C. What do we know about the cardiac valve lesion in the antiphospholipid syndrome (APS)? Lupus 2014;23:1259–61. doi:10.1177/0961203314534307.

[11] Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost 1995;74:1185–90.

[12] PENGO V, TRIPODI A, REBER G, RAND JH, ORTEL TL, GALLI M, et al. Update of the guidelines for lupus anticoagulant detection. J Thromb Haemost 2009;7:1737–40. doi:10.1111/j.1538-7836.2009.03555.x.

[13] Harris EN, Gharavi AE, Patel SP HG. Evaluation of the anti-cardiolipin antibody test: report of an international workshop held 4 April 1987. Clin Exp Immunol 1986;68:22.

[14] Amengual O, Atsumi T, Khamashta MA, Koike T, Hughes GR. Specificity of ELISA for antibody to beta 2-glycoprotein I in patients with antiphospholipid syndrome. Br J Rheumatol 1996;35:1239–43.

[15] D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro

JM, et al. General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. Circulation 2008;117:743–53. doi:10.1161/CIRCULATIONAHA.107.699579.

[16] Sciascia S, Baldovino S, Schreiber K, Solfietti L, Radin M, Cuadrado MJ, et al. Thrombotic risk assessment in antiphospholipid syndrome: the role of new antibody specificities and thrombin generation assay. Clin Mol Allergy 2016;14:6. doi:10.1186/s12948-016-0043-2.

[17] Oku K, Amengual O, Bohgaki T, Horita T, Yasuda S, Atsumi T. An independent validation of the Global Anti-Phospholipid Syndrome Score in a Japanese cohort of patients with autoimmune diseases. Lupus 2015;24:774–5. doi:10.1177/0961203314561284.

[18] Zuily S, de Laat B, Mohamed S, Kelchtermans H, Shums Z, Albesa R, et al. Validity of the global anti-phospholipid syndrome score to predict thrombosis: a prospective multicentre cohort study. Rheumatology (Oxford) 2015;54:2071–5. doi:10.1093/rheumatology/kev238.

[19] Sciascia Savino, Radin Massimo, Sanna Giovanni, Cecchi Irene, Roccatello Dario BML. Clinical utility of the Global

AntiphosPholipid Syndrome Score (GAPSS) for risk stratification: a pooled analysis. Rheumatology (Oxford) 2017;Accepted f.

[20] Radin M, Schreiber K, Costanzo P, Cecchi I, Roccatello D, Baldovino S, et al. The adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) for risk stratification in young APS patients with acute myocardial infarction. Int J Cardiol 2017. doi:10.1016/j.ijcard.2017.02.155.

[21] Fernandez Mosteirin N, Saez Comet L, Salvador Osuna C, Calvo Villas JM, Velilla Marco J. Independent validation of the adjusted GAPSS. Role of thrombotic risk assessment in the real-life setting. Lupus 2017:96120331770349. doi:10.1177/0961203317703493.

[22] Radin Massimo, Schreiber Karen, Cecchi Irene, Roccatello Dario CMJ and SS. The risk of ischaemic stroke in primary APS patients: a prospective study. Eur J Neurol 2017;Accepted F.

[23] Cervera R, Piette J-C, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019–27.

[24] Sciascia S, Sanna G, Khamashta MA, Cuadrado MJ, Erkan D,

Andreoli L, et al. The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: a systematic review. Ann Rheum Dis 2015;74:2028–33. doi:10.1136/annrheumdis-2014-205663.

[25] Erkan D, Lockshin M, APS ACTION members. APS ACTION - AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking. Lupus 2012;21:695–8. doi:10.1177/0961203312437810.

[26] Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. Arthritis Care Res (Hoboken) 2013;65:1869–73. doi:10.1002/acr.22066.

[27] Chighizola CB, Andreoli L, de Jesus GR, Banzato A, Pons-Estel GJ, Erkan D, et al. The association between antiphospholipid antibodies and pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. Lupus 2015;24:980–4. doi:10.1177/0961203315572714.

**Acknowledgments:** None

**Disclosure of Conflicts of Interest:** None declared

**Funding:** None declared

**Legend of Tables and Figures:**

***Table 1.*** *Demographic, clinical and laboratory characteristics of the cohort*

***Table 2.*** *Patients cardiovascular risk factors and aPL positivity between groups*

***Figure 1****. Proposed recommendations for extra-criteria manifestations management*