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# The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria

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on Behalf of the ACR/EULAR APS Classification Criteria Collaborators

*This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the EULAR Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.*

*Classification criteria are essential in clinical and basic science research because they allow investigators to study relatively homogeneous populations of patients recruited from a single or multiple research sites. In clinical settings, diagnoses are made by health care professionals evaluating an individual patient's symptoms, signs, and results of laboratory and imaging studies in order to guide therapeutic recommendations. Patients diagnosed with a particular disease may or may not fulfill classification criteria for that disease. Classification criteria, in the hands of an experienced clinician with expertise in rheumatology, may inform a diagnostic evaluation, but improperly applied classification criteria may lead to misdiagnosis.*

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**Objective.** To develop new antiphospholipid syndrome (APS) classification criteria with high specificity for use in observational studies and trials, jointly supported by the American College of Rheumatology (ACR) and EULAR.

**Methods.** This international multidisciplinary initiative included 4 phases: 1) Phase I, criteria generation by surveys and literature review; 2) Phase II, criteria reduction by modified Delphi and nominal group technique exercises; 3) Phase III, criteria definition, further reduction with the guidance of real-world patient scenarios, and weighting via consensus-based multicriteria decision analysis, and threshold identification; and 4) Phase IV, validation using independent adjudicators' consensus as the gold standard.

**Results.** The 2023 ACR/EULAR APS classification criteria include an entry criterion of at least one positive antiphospholipid antibody (aPL) test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1–7 points each) clustered into 6 clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and 2 laboratory domains (lupus anticoagulant functional coagulation assays, and solid-phase enzyme-linked immunosorbent assays for IgG/IgM

anticardiolipin and/or IgG/IgM anti–$\beta_2$-glycoprotein I antibodies). Patients accumulating at least 3 points each from the clinical and laboratory domains are classified as having APS. In the validation cohort, the new APS criteria versus the 2006 revised Sapporo classification criteria had a specificity of 99% versus 86%, and a sensitivity of 84% versus 99%.

**Conclusion.** These new ACR/EULAR APS classification criteria were developed using rigorous methodology with multidisciplinary international input. Hierarchically clustered, weighted, and risk-stratified criteria reflect the current thinking about APS, providing high specificity and a strong foundation for future APS research.

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## INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial, venous, or microvascular thrombosis, pregnancy morbidity, or nonthrombotic manifestations in patients with persistent antiphospholipid antibodies (aPL). Classification of APS, for the identification of homogeneous research cohorts, is currently based on the Sapporo criteria published in 1999 (1) and revised in 2006 (2). The revised Sapporo criteria for APS require clinical features (thrombosis or pregnancy morbidity) and laboratory tests (for lupus anticoagulant [LAC], IgG/IgM anticardiolipin antibodies [aCL], and/or IgG/IgM anti–$\beta_2$-glycoprotein I antibodies [anti-$\beta_2$GPI]) with at least 2 aPL tests performed at least 12 weeks apart (2).

Since the introduction of the Sapporo criteria, advancements in our understanding of APS include better characterization of aPL-associated nonthrombotic clinical manifestations, identification of the role of traditional thrombosis risk factors in aPL-positive individuals, and risk stratification by aPL profile (3,4). Furthermore, the revised Sapporo criteria have been criticized for not incorporating evidence-based definitions, e.g., aPL positivity, microvascular disease, or pregnancy morbidity, resulting in the inclusion of a heterogeneous group of "aPL-positive" patients with different risk profiles for research (4,5). More stringent methodology, using data-driven and expert-based approaches to develop robust classification criteria in rheumatic diseases, is now available (6). Thus, new classification criteria can better ensure future high-quality, risk-stratified epidemiologic studies and clinical trials in APS, leading to improved patient care and management recommendations.

Given the limitations of the current criteria (7–9), an international effort, jointly supported by the American College of Rheumatology (ACR) and EULAR, was initiated with the goal of using rigorous methodology to develop a new APS classification system based on a more modern disease understanding, allowing for the weighting of individual criterion, and demonstrating excellent operating characteristics with the highest possible specificity. Maximizing the specificity of the 2023 ACR/EULAR APS classification criteria was a major goal at the outset, as overly inclusive criteria may decrease the ability of investigators to understand disease pathophysiology and treatment effects in clinical trials and research.

## METHODS

### Methodologic overview

Our 4-phase methodology (see Supplementary Section 1, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42624) was similar to the methodologies used in the development of recent rheumatic disease classification criteria (10–16). The phases were as follows: Phase I, criteria generation; Phase II, criteria reduction; Phase III, criteria definition, further reduction, and weighting through a consensus-based multicriteria decision analysis (MCDA) methodology (17–19), as well as classification threshold identification; and Phase IV, validation.

The initiative was overseen by a 24-member international multidisciplinary Steering Committee, led by principal investigators from North America (DE) and Europe (SZ); 13 members were from the Americas, 9 from Europe, and 2 from New Zealand. Steering Committee members were selected based on their expertise in APS and/or methodologies; 3 patients (US and Europe) represented the patient experience. The Steering Committee assembled 1) a core planning group; 2) a master group of 54 international physician-scientists designated as "Collaborators" (40% from Europe, 40% from North America, and 20% from South America, based on their clinical and/or research APS interest); and 3) domain-specific subcommittees. Members of these relevant Steering Committee groups are listed in Appendix A.

### Phase I (criteria generation) and Phase II (criteria reduction) overview

In Phase I, we generated a comprehensive list of candidate criteria, using both consensus-based and evidence-based methods. We e-mailed a survey with open-ended questions to the master group (n = 54) to identify potential criteria and different APS subpopulations. We systematically clustered responses by organ systems to avoid duplication and improve interpretability, and reviewed the literature for additional items.

In Phase II, we reduced the generated list using systematic reviews, meta-analyses (20–24), and expert consensus. We administered 2 consecutive surveys (61 expanded master group members, 19 Steering Committee members) assessing the specificity of each Phase I item in differentiating APS from similar conditions. We ranked items by mean survey score, hierarchically organized them into domains by specificity, and eliminated low-specificity items by nominal group technique during an in-person meeting (25,26). Within each domain, the Steering Committee agreed that only the highest specificity item should be scored, consistent with classification criteria methodology (6). In addition, the Steering Committee discussed the need for "entry criteria," i.e., minimum criteria required to identify the relevant patient population to whom the classification criteria would be applied (for further details on Phases I and II, see ref. 8).

### Phase III (criteria definition, further reduction, and weighting, and classification threshold identification) overview

In Phase III, we defined criteria generated during Phase I/II as part of clinical (Phase III-A) and laboratory (Phase III-B) domains, further reduced the number of criteria using expert consensus

and real-world patient scenarios (Phase III-C), and determined criteria weights and the threshold above which cases would be consistently classified as APS (Phase III-D). We also finalized the entry criteria. For details, see Supplementary Section 3, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42624.

### Phase IV (validation) overview

In Phase IV, using 2 separate validation cohorts, we compared performance characteristics of the revised Sapporo criteria to those of the new APS classification criteria against consensus by independent adjudicators, i.e., representing the "gold standard." We made an a priori decision to have 2 validation cohorts, in order to demonstrate consistency and validity. We assembled cohorts by asking Phase IV Collaborators (selected among the original 54 members and 20 additional members, none of whom were involved in Phase III) to contribute 30 cases evaluated for "APS suspicion," i.e., a clinical APS manifestation with any positive or negative aPL test result or no aPL test, or a positive aPL test result with no clinical APS manifestation. Of the 30 cases, half were considered "likely" and half "not likely" to be APS for research purposes. We collected clinical and laboratory data relevant to the revised Sapporo criteria and new classification criteria using a standardized form; cases were randomly assigned to 2 different cohorts.

APS classification for each case was verified by 3 independent adjudicators (a rheumatologist from North America [RR], an internist/clinical immunologist from Europe [ZA], and a hematologist from Europe [HC]), who were blinded with regard to the Phase III discussions and unaware of the proposed classification criteria. Adjudicators participated in a moderated discussion of discordant cases at the end of each validation cohort assessment until agreement was reached. Moderated discussions were aimed at focusing adjudicators on factors relevant for APS case classification, avoiding additional information to reduce bias.

### Phase IV (validation) statistical analysis

Assuming a total discordance of 20%, i.e., disagreement between expert consensus and new criteria, a power of 80%, and an alpha risk of 5%, an estimated sample size of 243 would be necessary to detect a difference in performance characteristics between the revised Sapporo and new APS classification criteria. We incorporated 2 validation cohorts (n = 284 per cohort) in Phase IV. Sensitivity, specificity, and Wald 95% confidence intervals (95% CIs) for each validation cohort were comparatively evaluated for the revised Sapporo and new APS classification criteria, each against independent adjudicators' consensus. Nonoverlapping CIs and a *P* value threshold of <0.05 denoted significance. For details, see Supplementary Section 6, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42624.

Statistical analyses were performed using SAS version 9.4 (SAS Institute). This study was approved by the Hospital for Special Surgery Institutional Review Board, and by individual centers as needed.

## RESULTS

### Phase I (criteria generation) and Phase II (criteria reduction)

Phase I generated 152 candidate criteria, expanded to 261 items with subgroups and candidate criteria with potential negative weights. Subsequent reduction methods resulted in 27 candidate criteria, hierarchically organized into 6 additive domains (macrovascular, microvascular, obstetric, cardiac valve, hematologic, and laboratory) (for details, see the Table in Supplementary Section 2 at https://onlinelibrary.wiley.com/doi/10.1002/art.42624).

During an in-person meeting, the Steering Committee agreed that to maximize specificity, candidate clinical criteria must be interpreted in the context of a "clinically acceptable" aPL profile, emphasizing the importance of "entry criteria." Following this meeting, modified Delphi exercises were carried out, as follows: 1) all members voted in favor of entry criteria requiring at least 1 clinical and 1 laboratory criterion; and 2) the majority voted in favor of a time restriction between the clinical and laboratory criterion as part of the entry criteria (8).

### Phase III (criteria definition, further reduction, and weighting, and classification threshold identification)

**Phase III-A, clinical definitions.** The Steering Committee developed clinical candidate definitions (Phase III-A) for the following features: 1) macrovascular thrombosis and traditional venous thromboembolism (VTE) and cardiovascular disease (CVD) risk factors (see Supplementary Section 8, at https://onlinelibrary.wiley.com/doi/10.1002/art.42624); 2) microvascular disease; 3) pregnancy morbidity; 4) cardiac valve involvement; and 5) thrombocytopenia (Tables 1 and 2) (details will be published elsewhere).

**Phase III-B, laboratory definitions.** The Steering Committee agreed on the following criteria for laboratory items (Phase III-B): 1) International Society on Thrombosis and Haemostasis (ISTH) guidelines should be followed for LAC testing and interpretation (Table 1) (27); and 2) single (one-time) LAC positivity may be relevant when repeat testing is unavailable. Pending assessment and refinement during the subsequent Phase III-C, the Steering Committee recommended that 1) there should be 2 levels of aCL/anti-$\beta_2$GPI positivity ("moderate" and "high" positivity) based

**Table 1.** Definitions of the 2023 ACR/EULAR antiphospholipid syndrome (APS) classification criteria

**Clinical Criteria**

**Domain 1 — Macrovascular (venous thromboembolism)**

**Venous thromboembolism** (otherwise unexplained* and confirmed by appropriate testing): Includes (but is not limited to) pulmonary embolism, deep vein thrombosis of the legs/arms, splanchnic thrombosis, renal vein thrombosis, cerebral venous thrombosis, and retinal vein thrombosis/occlusion.

**Domain 2 — Macrovascular (arterial thrombosis)**

**Arterial thrombosis** (otherwise unexplained* and confirmed by appropriate testing): Includes (but is not limited to) myocardial infarction (coronary artery thrombosis), peripheral/splanchnic/retinal artery thromboses, stroke based on international definitions (35,36), and other organ infarcts (e.g., kidney, liver, or spleen) in the absence of visualized thrombus.

**Domain 3 — Microvascular**

**Suspected:**

**Livedo racemosa (by physical examination):** Otherwise unexplained* violaceous, "net-like," blotchy mottling of the skin. Note: livedo racemosa with nonuniform, irreversible, broken, and asymmetric persistent discoloration should be scored; *livedo reticularis with uniform, reversible, unbroken, and symmetric discoloration should not be scored*.

**Livedoid vasculopathy lesions** (**by physical examination):** Otherwise unexplained* painful papules and erythematous-violaceous purpuric plaques, which may rapidly evolve into hemorrhagic vesicles or bullae. Note: if ruptured, can result in painful small ulcers or reticulate, confluent, geometric, and painful ulcers.

**Antiphospholipid antibody (aPL) nephropathy (by physical examination or laboratory tests):** Otherwise unexplained* persistent: a) new-onset hypertension or deterioration of previously well-controlled hypertension; b) proteinuria ≥0.5 gm in 24-hour urine specimen or protein:creatinine ratio ≥0.5 mg/mg (50 mg/mmoles); c) acute renal failure (increased serum creatinine levels above normal); or d) glomerular microscopic hematuria.

**Pulmonary hemorrhage (by clinical symptoms and imaging):** Respiratory symptoms (e.g., dyspnea, cough, hemoptysis) AND otherwise unexplained* pulmonary infiltrates on imaging suggestive of pulmonary hemorrhage.

**Established**:

**Livedoid vasculopathy** (**by pathology** once livedoid vasculopathy lesions described above are present): Otherwise unexplained* thrombosis of the small dermal vessels and/or endothelial proliferation.

**aPL nephropathy** (**by pathology** once suspected aPL-nephropathy definition above is fulfilled) (37): a) **Acute renal vascular** or **glomerular thrombotic microangiopathy lesions**, including fibrin thrombi in arterioles or glomeruli without inflammatory cells or immune complexes; and b) **chronic renal vascular** or **glomerular lesions**, described as arterial or arteriolar organized microthrombi with or without recanalization, fibrous and fibrocellular (arterial or arteriolar) occlusions, focal cortical atrophy with or without thyroidization, fibrous intimal hyperplasia, or chronic/organized glomerular thrombi. Note: in patients with systemic lupus erythematosus, aPL nephropathy occurs independent of lesions attributable to lupus nephritis.

**Pulmonary hemorrhage** (**by bronchoalveolar lavage [BAL] or pathology** once suspected pulmonary hemorrhage definition above is fulfilled): Otherwise unexplained* progressive hemorrhagic return on BAL with aliquots or hemosiderin-laden macrophages (>20%), OR lung biopsy demonstrating capillaritis or microthrombosis.

**Myocardial disease (by imaging or pathology)**: Otherwise unexplained* non-ST segment elevation myocardial infarction with a normal coronary angiogram (myocardial infarction with nonobstructive coronary arteries, or MINOCA) AND cardiac magnetic resonance imaging (CMRI) abnormalities as per the 2018 Society for CMRI expert consensus (38) including: a) late gadolinium enhancement either transmurally or subendocardially; b) T2 abnormalities (weighted imaging or mapping); or c) perfusion MRI abnormalities, OR histologically by thrombosis of the small vessels of the heart.

**Adrenal hemorrhage or microthrombosis (by imaging or pathology):** Otherwise unexplained* computed tomography (CT) or magnetic resonance imaging (MRI) demonstrating hemorrhage, OR histologically by thrombosis of the adrenal (micro)vasculature, e.g., adrenal plexus, adrenal vein.

**Domain 4 — Obstetric**

**Prefetal death (preembryonic or embryonic loss):** Otherwise unexplained* pregnancy loss before 10 weeks 0 days of gestation.

**Fetal death**: Otherwise unexplained* pregnancy loss between 10 weeks 0 days and 15 weeks 6 days gestation (early fetal death), or between 16 weeks 0 days and 34 weeks 0 days gestation.

Note: if a detailed analysis of the fetal morphology or genetic constitution is not performed or unavailable, reasonable clinical judgment should be used based on careful history and review of available medical records.

**Preeclampsia with severe features** (39): **Preeclampsia** defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive or hypertensive (chronic†) patient AND new onset of one or more of the following: a) proteinuria ≥0.3 mg/mg (30 mg/mmoles) in a random urine specimen or b) dipstick protein ≥2+ if a quantitative measurement is unavailable AND one or more of the following "severe features":

**Severe blood pressure elevation:** Systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg on 2 occasions at least 4 hours apart while the patient is on bed rest (antihypertensive therapy may be initiated upon confirmation of severe hypertension, in which case severe blood pressure elevation criteria can be satisfied without waiting until 4 hours have elapsed).

**Central nervous system dysfunction:** New-onset headache unresponsive to medication and not accounted for by alternative diagnosis.

**Visual disturbances**.

**Pulmonary edema**.

**Impaired liver function**: Abnormally elevated blood concentrations of liver enzymes (more than twice the upper limit of normal concentrations), or severe persistent right upper quadrant or epigastric pain unresponsive to medications, not accounted by alternative diagnosis.

**Renal dysfunction**: Serum creatinine concentration >1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease.

**Thrombocytopenia**: platelet count of $<100 \times 10^9$/liter.

(Continued)

**Table 1.** (*Cont'd*)

**Placental insufficiency with severe features: Intrauterine fetal growth restriction** defined as biometry indicating estimated fetal weight of less than the 10th percentile for gestational age or postnatal birth weight less than the 10th percentile for gestational age in the absence of fetal-neonatal syndromes or genetic conditions associated with growth restriction AND one or more of the following "severe features":
- **Abnormal or non-reassuring fetal surveillance test(s)** suggestive of fetal hypoxemia, e.g., a nonreactive non-stress test.
- **Abnormal Doppler flow velocimetry waveform analysis** suggestive of fetal hypoxemia, e.g., absent end-diastolic flow in the umbilical artery.
- **Severe intrauterine fetal growth restriction** suggested by fetal biometry indicating an estimated fetal or postnatal birth weight of <3rd percentile for gestational age.
- **Oligohydramnios**, e.g., an amniotic fluid index ≤5 cm, or deepest vertical pocket <2 cm.
- **Maternal vascular malperfusion on placental histology** suggested by placental thrombosis/infarction, inadequate remodeling of the uterine spiral arteries (decidual vasculopathy), decreased vasculosyncytial membranes, increased syncytial knots, or decidual inflammation (40). Note: Maternal vascular malperfusion on placental histology can be detected in the placentas of aPL-negative patients with intrauterine growth restriction and/or preeclampsia, and even in normal pregnancies; thus, these findings are not specific for APS.

**Domain 5 – Cardiac valve**

**Valve thickening** (otherwise unexplained*): Based on World Heart Federation echocardiographic criteria (41), mitral valve thickening is defined as >4 mm between ages 20–39 years and >5 mm for those older than age 40 years, and >3 mm for *other valves* for any age (valve thickening can be associated with valvular dysfunction [regurgitation or stenosis]).

**Valve vegetation** (otherwise unexplained*): Based on the American Society of Echocardiography guidelines (42), valve vegetation is defined as shaggy, lobulated, or rounded masses typically located on the atrial side of atrioventricular valves (mitral valve and tricuspid valve) or ventricular side of the aortic valve, but can be located on any side of any valve (size is highly variable but usually <1 cm); on echocardiogram, despite the "echo texture" and location of aPL-associated vegetations resembling infective endocarditis, they may appear less amorphous, more rounded, and not associated with valvular destruction, in contrast to a true infective endocarditis; they can be associated with valvular dysfunction (regurgitation or stenosis).

**Domain 6 – Hematology**

**Thrombocytopenia**: Otherwise unexplained* lowest platelet count ever between 20 and 130 × $10^9$/liter, confirmed on peripheral blood smear and by repeat testing.

* Refer to Supplementary Section 4 (https://onlinelibrary.wiley.com/doi/10.1002/art.42624) for the definition of "otherwise unexplained," which requires the exclusion of "equally likely" or "more likely" causes based on investigator's judgment. Clinical domain items with an "equally or more likely" cause should not be scored (note: venous thromboembolism and cardiovascular risk factors [see Table 2] required for Domains 1 and 2 scoring are not reasons for exclusion).

† Patients with chronic hypertension can be classified as having superimposed preeclampsia if there is a sudden increase in baseline hypertension and/or proteinuria after 20 weeks' gestation.

## Laboratory Criteria

**Domain 7 — aPL test by coagulation-based functional assay**

**Lupus anticoagulant (LAC) assay** performed and interpreted based on the International Society of Thrombosis and Hemostasis (ISTH) guidelines (27), which can be summarized as follows:
- A 3-step procedure (screening – mixing study – confirmation) with 2 screening test systems (diluted Russell's viper venom time and a sensitive activated partial thromboplastin time [low phospholipids and silica as activator]) is necessary to confirm the presence of LAC. The LAC test should be considered positive if at least 1 of the 2 test systems yields a positive result following all 3 steps (phospholipid-dependent correction of the prolonged screening tests).
- Results of LAC testing should be interpreted with caution, as false positive and negative results can occur during anticoagulation (thus, LAC testing is ideally performed in patients not receiving anticoagulants), as an acute-phase response (e.g., acute thrombosis) due to acute-phase reactants (e.g., Factor VIII and C-reactive protein), and in pregnancy due to increase in blood coagulation factors.
- Samples from patients receiving anticoagulants (vitamin K antagonists, heparin, direct oral anticoagulants, indirect Factor Xa inhibitor) should be marked positive or negative on the LAC assay only if reviewed/confirmed by an individual with expertise in performing/interpreting the LAC assay, e.g., expert laboratory personnel.

**Domain 8 — aPL test by solid phase–based assay**

**Anticardiolipin antibody (aCL) and anti–$\beta_2$-glycoprotein I antibody (anti-$\beta_2$GPI)** thresholds of *moderate* (40–79 units) and *high* (≥80 units) should be determined based on standardized enzyme-linked immunosorbent assay (ELISA) results, not based on other testing modalities such as new automated platforms with variations of the solid phase (e.g., magnetic microparticles and microspheres) and various detection systems (e.g., chemiluminescent immunoassay [CLIA], multiplex flow immunoassay [MFI], or flow cytometry).
- Correlation of the numerical values between the moderate/high thresholds of ELISA and automated platforms varies substantially. For instance, based on the ISTH Scientific and Standardization Committee (SSC) LA/aPL Subcommittee estimates from one study, an IgG aCL ELISA value of 40–79 units corresponds to a CLIA value of 200–400 units and MFI of 700–2,000 (33). While these data may provide future guidance, there is currently no direct application and therefore, more validation studies are needed.
- Recommendations to maintain homogeneity, consistency, and comparability of clinical research studies include the following: a) results of analytical platforms should not be mixed; b) pending additional studies and official guidance from the ISTH SSC LAC/aPL Subcommittee for semiquantitative comparisons on aCL/anti-$\beta_2$GPI moderate/high thresholds of ELISA and automated platforms, we recommend delaying use of the automated platforms for APS classification; and c) if no options exist beside the use of automated platform results for APS research, researchers should direct efforts to identifying and validating moderate/high thresholds of their platform, correlating it with aCL/anti-$\beta_2$GPI ELISA moderate/high thresholds (these measures should be discussed in their methods, and supported by official guidance).

**Table 2.** Definitions of high-risk venous thromboembolism (VTE) and cardiovascular disease (CVD) profiles based on current general population guidelines (refer to Supplementary Section 8 at https://onlinelibrary.wiley.com/doi/10.1002/art.42624)

1. **To determine if a thrombotic event occurred in a patient with a high-risk VTE or high-risk CVD profile**, investigators should make every effort to collect and review risk factor data based on patient report or medical record review. If clinically relevant VTE or CVD risk factors at the time of an historical thrombotic event are unknown in the data source, then the lowest possible non-zero weight should be assigned to the macrovascular event to avoid overestimation of antiphospholipid antibody (aPL) contribution to thrombosis.

2. **High-risk VTE profile is defined based on 1 or more major OR 2 or more minor VTE risk factors,** if timeline/severity is associated with the event based on investigator's judgment (timelines based on general population guidelines are provided when available).
   a. ***Major VTE risk factors*** (any of the following at the time of the event):
      **Active malignancy** with no or noncurative treatment received, ongoing curative treatment including hormonal therapy, or recurrence/progression despite curative treatment at the time of the event.
      **Hospital admission** confined to bed (only bathroom privileges) with an acute illness for at least 3 days within 3 months prior to the event.
      **Major trauma** with fractures or spinal cord injury within 1 month prior to the event.
      **Surgery** with general/spinal/epidural anesthesia for >30 minutes within 3 months prior to the event.
   b. ***Minor VTE risk factors*** (2 or more of the following at the time of the event):
      **Active systemic autoimmune disease or active inflammatory bowel disease** using disease activity measures guided by current recommendations.
      **Acute/active severe infection** according to guidelines, e.g., sepsis, pneumonia, SARS-CoV-2.
      **Central venous catheter** in the same vascular bed.
      **Hormone replacement therapy, estrogen containing oral contraceptives, or ongoing in vitro fertilization treatment.**
      **Long distance travel** (≥8 hours).
      **Obesity** (body mass index [BMI] ≥30 kg/m²).
      **Pregnancy or postpartum period** within 6 weeks after delivery.
      **Prolonged immobilization** not counted above, e.g., leg injury associated with reduced mobility, or confined to bed out of hospital for at least 3 days.
      **Surgery** with general/spinal/epidural anesthesia for <30 minutes within 3 months prior to the event.

3. **High-risk CVD profile is defined based on 1 or more high CVD risk factors OR 3 or more moderate CVD risk factors**, if timeline/severity is associated with the event based on investigator's judgment (timelines based on general population guidelines are provided when available).
   a. ***High CVD risk factors*** (any of the following at the time of the event):
      **Arterial hypertension** with systolic blood pressure (BP) ≥180 mm Hg or diastolic BP ≥110 mm Hg.
      **Chronic kidney disease** with estimated glomerular filtration rate ≤60 ml/minute for more than 3 months.
      **Diabetes mellitus** with organ damage* or long disease duration (type 1 for ≥20 years; type 2 for ≥10 years).
      **Hyperlipidemia** (severe) with total cholesterol ≥310 mg/dl (8 mmoles/liter) or low-density lipoprotein (LDL)–cholesterol >190 mg/dl (4.9 mmoles/liter).
   b. ***Moderate CVD risk factors*** (3 or more of the following at the time of the event):
      **Arterial hypertension** on treatment, or with persistent systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg.
      **Current tobacco smoking**.
      **Diabetes mellitus** with no organ damage* and short disease duration (type 1 <20 years; type 2 <10 years).
      **Hyperlipidemia** (moderate) on treatment, or with total cholesterol above normal range and <310 mg/dl (8 mmoles/liter), or LDL-cholesterol above normal range and <190 mg/dl (4.9 mmoles/liter).
      **Obesity** (BMI ≥30 kg/m²).

* Diabetes mellitus diagnosis based on a hemoglobin A1c ≥6.5%, or a fasting plasma glucose ≥126 mg/dl (7.0 mmoles/liters), or symptoms of diabetes (e.g., polyuria, polydipsia, or unexplained weight loss) with a random plasma glucose concentration ≥200 mg/dl (11.1 mmoles/liter). According to the 2019 ESC/EASD guidelines on diabetes, organ damage is defined by proteinuria, chronic kidney disease, left ventricular hypertrophy, or retinopathy (see ref. 43).

on enzyme-linked immunoassay (ELISA) techniques; 2) IgG aCL and IgG anti-$\beta_2$GPI positivity should be evaluated in combination; and 3) IgG and IgM isotypes should not be additively considered (details will be published elsewhere).

Finally, given the limited data for or against the definition of aPL "persistence" (i.e., 2 positive tests for aPL at least 12 weeks apart) (1,2,28), the Steering Committee decided not to change the definition.

**Phase III-C, finalization of the entry criteria.** The Steering Committee agreed that an entry criteria time restriction of 3 years (versus 5 years in the revised Sapporo criteria) between a clinical criterion and a positive aPL test result improves certainty for APS classification; however, this decision was based on limited data (29) and on primarily Steering Committee consensus (modified Delphi exercise). The final entry criteria, requiring the presence of at least 1 clinical criterion and 1 laboratory criterion (positivity for LAC, moderate- or high-level IgG/IgM aCL positivity, or moderate- or high-level IgG/IgM anti-$\beta_2$GPI positivity) within 3 years of each other, are presented in Figure 1.

**Phase III-C, real-world case collection and analysis.** Of 314 potential APS cases in the derivation cohort (mean ± SD age 44.7 ± 14.6 years; 79% female) collected from 17 sites, including 8 from Europe (47%), 7 from North America (41%), and 2 from South America (12%), case collectors rated 137 cases

(44%) as "highly likely" and 177 cases (56%) as "equivocal or unlikely" to be APS. Duration between aPL positivity and any candidate clinical criteria was ≤3 years in 89% of cases (30).

**Phase III-C, consensus discussions for further criteria reduction and final definitions.** Discussions and decisions based on derivation cohort results, literature review, and expert consensus are summarized in Supplementary Section 5 (https://onlinelibrary.wiley.com/doi/10.1002/art.42624). Eventually, the definitions and hierarchical order of items within each of 8 additive and independent domains (6 clinical, 2 laboratory) were finalized (Table 3). The Steering Committee also concluded that 1) patients with concomitant systemic autoimmune disease could be classified as having APS, but individual candidate criterion should not be scored if other "equally likely" or "more likely" causes for that criterion cannot be excluded, similar to other criteria sets (12); 2) "persistent" aPL should be scored based on 2 consecutive results; and 3) "moderate" level aCL/anti-$\beta_2$GPI positivity should be defined as 40–79 ELISA units and "high" level as ≥80 ELISA units.

**Phase III-D, criteria weighting based on MCDA and classification threshold identification.** During the in-person meeting, the MCDA exercise calculated weights based on 81 pairwise consensus-based decisions. Table 3 shows the resulting point-based classification system, with hierarchical levels in each domain identified based on their relative weights.

Following the in-person meeting, the minimum classification threshold was determined based on individual assessment of the 192 unique derivation cohort cases remaining after eliminating duplicates and cases not meeting the entry criteria. Of 192 cases, full agreement with APS classification was achieved for 116 cases (60%) (90 classified as APS, 26 as not APS). Agreement was relatively high for 37 cases (19%), with 80–93% agreeing with the classification (17 as APS, 20 as not APS). However, there were variable responses (50–80%) for the remaining 39 cases (20%).

Within each domain, descriptive analysis of the 192 cases showed that most respondents considered that 1) the presence of 1 "B" level clinical criterion, even with "C" or higher-level laboratory criteria, was insufficient for APS classification, but 2 or more "B" level (and/or 1 or more "C" or higher-level) clinical criteria were acceptable; and 2) the presence of 1 or 2 "B" level laboratory criteria, even with "C" or higher-level clinical criteria, was insufficient for APS classification (Table 3).

During several teleconferences, all cases without 100% agreement were discussed with the guidance of the descriptive analysis until full consensus was achieved. Key conceptual issues addressed included the following: 1) the need to emphasize specificity over sensitivity to improve homogeneity of APS patients in research and to avoid enrolling misclassified patients in clinical trials with potentially toxic investigational medications; and 2) structuring the classification system to include an acceptable clinical criterion and an acceptable aPL laboratory criterion. Relative weights derived from 1000Minds analysis supported these ranking exercises, with one exception: combined weights of the "B" level macrovascular (VTE) and obstetric domains were low; the Steering Committee agreed that the combination would not meet the threshold for an acceptable clinical profile. As a result, consensus for the preliminary threshold for APS classification was achieved.

Despite Steering Committee agreement on the "APS" threshold, detailed analysis of the 39 cases with variable responses demonstrated the most frequently encountered controversial scenarios. These scenarios were 1) moderate- or high-titer IgM aCL/anti-$\beta_2$GPI alone ("B" level) (Table 3) with an acceptable clinical criterion (12 [31%] of 39 cases); 2) VTE or arterial thrombosis alone in patients with high-risk profiles for VTE or CVD ("B" level), with an acceptable laboratory criterion (9 [23%] of 39 cases); and 3) occurrence of 3 or more consecutive prefetal deaths (at <10 weeks) and/or early fetal deaths (at 10–16 weeks), or 1 or more fetal deaths (at ≥16 weeks to <34 weeks) alone ("B" level) in the context of an acceptable laboratory criterion (8 [21%] of 39 cases).

The 2023 ACR/EULAR APS classification criteria are presented in Figure 1. According to these criteria, patients should be classified as having APS if they fulfill the entry criteria (at least 1 clinical and 1 laboratory criterion within 3 years of each other) and accumulate at least 3 points from clinical domains and 3 points from laboratory domains.

## Phase IV (validation)

We collected 568 potential APS cases from 29 international sites, including Europe (16 centers [55%]), North America (11 centers [38%]), South America (1 center [3%]), and Asia (1 center [3%]), to assess the performance characteristics of the preliminary classification criteria.

In the first validation cohort (n = 284), independent adjudicators classified 98 cases (35%) as "APS" and 180 (63%) as "No APS." Six cases (2%) were excluded—1 case was excluded due to unresolved disagreement on classification, and 5 cases were excluded due to being unclassifiable because of incomplete data.

Following assessment of the first cohort, assessment of the second validation cohort was carried out based on adjudicators' recommendations, as follows: 1) the definition of placental insufficiency was further characterized (Table 1); and 2) each case was assessed using complete individual VTE/arterial thrombosis risk factor data, rather than the overall risk factor profile. In the second validation cohort (n = 284), the adjudicators classified 113 cases (40%) as "APS" and 162 cases (57%) as "No APS"; 9 subjects (3%) were excluded as they were unclassifiable due to incomplete data.

**Table 3.** Relative weights of additive classification criteria items based on 1000Minds analysis for antiphospholipid syndrome (APS) classification

| Domain | Level | Original weight | Simplified weight* | Final weight |
|---|---|---|---|---|
| ***Clinical*** | | | | |
| 1. Macrovascular (venous thromboembolism [VTE]) | A. No | 0 | 0 | 0 |
| | B. VTE with high-risk profile | 1.3 | 0.4 (a) | 1 |
| | C. VTE without high-risk profile | 7.2 | 2.4 (b) | 3 |
| 2. Macrovascular (arterial thrombosis [AT]) | A. No | 0 | 0 | 0 |
| | B. AT with high-risk profile | 6.1 | 2 | 2 |
| | C. AT without high-risk profile | 12.3 | 4.1 | 4 |
| 3. Microvascular | A. No | 0 | 0 | 0 |
| | B. Suspected | 6.2 | 2.1 | 2 |
| | C. Established | 13.5 | 4.5 | 5 |
| 4. Obstetric | A. No | 0 | 0 | 0 |
| | B. ≥3 consecutive prefetal (<10 weeks) and/or early (10–16 weeks) fetal deaths, or ≥1 fetal death (16–34 weeks) alone† | 1.3 | 0.4 (a) | 1 |
| | C. Preeclampsia with severe features OR placental insufficiency with severe features (<34 weeks) with or without fetal death‡ | 5.6 | 1.9 (b) | 3 |
| | D. Preeclampsia with severe features AND placental insufficiency with severe features (<34 weeks) with or without fetal death | 12.3 | 4.1 | 4 |
| 5. Cardiac valve | A. No or not tested | 0 | 0 | 0 |
| | B. Valve thickening | 6.1 | 2 | 2 |
| | C. Valve vegetation | 12.4 | 4.1 | 4 |
| 6. Hematology | A. No or not tested | 0 | 0 | 0 |
| | B. Thrombocytopenia (20–130 × $10^9$/liter) | 6.8 | 2.3 | 2 |
| ***Laboratory*** | | | | |
| 7. Antiphospholipid antibody (aPL) testing by coagulation-based functional assays: lupus anticoagulant test | A. Negative or not tested | 0 | 0 | 0 |
| | B. Positive (single—one time) | 9.4 | 3.1 (c) | 1 |
| | C. Positive (persistent) | 15.1 | 5.0 | 5 |
| 8. aPL testing by solid-phase assays: IgG/IgM anticardiolipin (aCL) and IgG/IgM anti–$\beta_2$-glycoprotein I (anti-$\beta_2$GPI) antibody enzyme-linked immunosorbent assay (persistent¶) | A. Negative or not tested | 0 | 0 | 0 |
| | B. Moderate or high positive (IgM alone) (aCL and/or anti-$\beta_2$GPI)§ | 1.3 | 0.4 (d) | 1 |
| | C. Moderate positive (IgG) (aCL and/or anti-ß$_2$GPI) | 10.8 | 3.6 | 4 |
| | D. High positive (IgG) (aCL or anti-$\beta_2$GPI) | 15.0 | 5.0 | 5 |
| | E. High positive (IgG) (aCL and anti-$\beta_2$GPI) | 20.4 | 6.8 | 7 |

(a) The simplified weight was rounded up to "1" to prevent a "0" score, as this clinical criterion would contribute to the APS classification score in the context of other low-scoring clinical criteria.
(b) The simplified weight was rounded up to "3" as this criterion alone was determined to be sufficient for APS classification.
(c) The simplified weight was reduced to "1" due to an unexpected high proportion relative to the persistent lupus anticoagulant (LAC) positivity, and to decrease the likelihood of a case with a single test showing postive for LAC to be classified as APS.
(d) The simplified weight was rounded up to "1" to prevent a "0" score.
* Simplified weights were calculated by dividing original weights by 3, followed by rounding up (for ≥0.5) or down (for <0.5), unless otherwise indicated.
† One or more fetal death alone (no preeclampsia with severe features or placental insufficiency with severe features) between 16 weeks 0 days and 34 weeks 0 days of gestation was not scored during the 1000Minds exercise as the decision was to eventually apply the same score as obstetric level B.
‡ Placental insufficiency with severe features was not scored during the 1000Minds exercise as the decision was to eventually apply the same score as for preeclampsia with severe features.
§ Moderate-level (40–79 units) and high-level (≥80 units) aCL/anti-$\beta_2$GPI are based on enzyme-linked immunosorbent assays (refer to Table 1 for details).
¶ "Persistent" defined as a positive result on at least 2 occasions, at least 12 weeks apart.

Characteristics of the first validation cohort (n = 278) and second validation cohort (n = 275) are shown in Table 4. Of the 553 patients, the age of the majority of them was 40 years or higher, and the cohort was predominantly White and female, consistent with APS demographics from other international cohorts (31). For both validation cohorts, the operating characteristics of the 2023 ACR/EULAR APS classification criteria, using the independent adjudicators' consensus as the gold standard, demonstrated very high specificity of 99% in each cohort (95% CI 0.98–1.00 in cohort 1, and 95% CI 0.97–1.00 in cohort 2), whereas the revised Sapporo criteria for APS had a specificity of 91% (95% CI 0.86–0.95) in cohort 1 and 86% (95% CI 0.81–0.92) in cohort 2. The sensitivity of the new ACR/EULAR APS criteria was 83% (95% CI 0.75–0.90) in cohort 1 and 84% (95% CI 0.77–0.91) in cohort 2, compared to a sensitivity of 100% (95% CI 1.00–1.00) in cohort 1 and 99% (95% CI 0.98–1.00) in cohort 2 using the revised Sapporo criteria (Table 5) (see Supplementary Section 7 for further analysis).

**Entry Criteria**[a]
At least one documented[b] clinical criterion listed below (domains 1-6)
*plus*
A positive antiphospholipid antibody (aPL) test
(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti-$\beta_2$-glycoprotein-I antibodies [IgG or IgM])
within three years[b] of the clinical criterion

**If absent, do not attempt to classify as APS - If present, apply additive criteria**

**Additive clinical and laboratory criteria**[a]
Do not count a clinical criterion if there is an equally or more likely explanation than APS.
Within each domain, only count the highest weighted criterion towards the total score.

| Clinical domains and criteria | Weight | | Weight |
|---|---|---|---|
| **D1. Macrovascular (Venous Thromboembolism [VTE])** | | **D2. Macrovascular (Arterial Thrombosis [AT])** | |
| VTE with a high-risk VTE profile[c] | 1 | AT with a high-risk CVD profile[c] | 2 |
| VTE without a high-risk VTE profile[c] | 3 | AT without a high-risk CVD profile[c] | 4 |
| **D3. Microvascular** | | **D4. Obstetric** | |
| Suspected (one or more of the following) | 2 | ≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths | 1 |
| Livedo racemosa (exam) | | | |
| Livedoid vasculopathy lesions (exam) | | | |
| Acute/chronic aPL-nephropathy (exam or lab) | | | |
| Pulmonary hemorrhage (symptoms and imaging) | | | |
| | | Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features | 1 |
| Established (one of more of the following) | 5 | | |
| Livedoid vasculopathy (pathology[d]) | | | |
| Acute/chronic aPL-nephropathy (pathology[d]) | | PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death | 3 |
| Pulmonary hemorrhage (BAL or pathology[d]) | | | |
| Myocardial disease (imaging or pathology) | | PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death | 4 |
| Adrenal hemorrhage (imaging or pathology) | | | |
| **D5. Cardiac Valve** | | **D6. Hematology** | |
| Thickening | 2 | Thrombocytopenia (lowest 20-130x$10^9$/L) | 2 |
| Vegetation | 4 | | |

| Laboratory (aPL) domains and criteria[e] | Weight | | |
|---|---|---|---|
| **D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])** | | **D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-$\beta_2$-glycoprotein-I antibody [a$\beta_2$GPI] ELISA [persistent])** | |
| Positive LAC (single – one time) | 1 | Moderate or high positive (IgM) (aCL and/or a$\beta_2$GPI) | 1 |
| Positive LAC (persistent) | 5 | Moderate positive (IgG) (aCL and/or a$\beta_2$GPI) | 4 |
| | | High positive (IgG) (aCL or a$\beta_2$GPI) | 5 |
| | | High positive (IgG) (aCL and a$\beta_2$GPI) | 7 |

**TOTAL SCORE**
Classify as Antiphospholipid Syndrome for research purposes if there are
at least 3 points from clinical domains AND at least 3 points from laboratory domains

**Figure 1.** 2023 ACR/EULAR APS classification criteria. [a] Refer to Table 1 for the definitions of clinical and laboratory criteria including the moderate- and high-titer anticardiolipin antibody (aCL) IgG/IgM or anti–$\beta_2$-glycoprotein I antibody (a$\beta_2$GPI) IgG/IgM positivity. [b] Antiphospholipid antibody (aPL) positivity must be confirmed within +/– three years of the documented (by medical records) clinical criterion. [c] Refer to Table 2 for the definitions of high-risk profiles. [d] Suspected microvascular definition for each corresponding item should be first fulfilled. [e] For the purpose of laboratory domain scoring: 1) "persistent" aPL test results (at least 12 weeks apart) should be scored based on two consecutive positive lupus anticoagulant (LAC), two consecutive highest aCL, and/or two consecutive highest a$\beta_2$GPI results (two consecutive results with one moderate positive and one high positive aCL/a$\beta_2$GPI should be marked as "moderate positive" if there are no additional consecutive high results available); 2) for prospective data collection, two consecutive positive aPL results are required within three years of the clinical criterion; 3) for retrospective data collection, two consecutive positive aPL results and at least one positive aPL result within three years of the clinical criterion are required; 4) if there are multiple LAC assays performed on patients receiving anticoagulants (vitamin K antagonists, heparin, direct oral anticoagulants, indirect Factor Xa inhibitor), the results of the tests performed without anticoagulants should be included in the assessment unless the results of the tests performed with anticoagulants are reviewed/confirmed by an individual who has expertise in performing/interpreting the LAC assay (refer to Table 1 for details); 5) moderate (40–79 units) and high (≥80 units) level aCL/a$\beta_2$GPI are based on enzyme-linked immunosorbent assays (ELISAs) (refer to Table 1 for details); and 6) for prospective studies, the most recent aPL test (LAC and/or moderate-high level aCL/a$\beta_2$GPI) should be positive to maintain homogeneity of research cohorts. D1–D8 = domains 1–8; CVD = cardiovascular disease; BAL = bronchoalveolar lavage; Exam = physical examination; Lab = laboratory tests.

**Table 4.** Demographic and clinical characteristics of 553 cases used in both validation cohorts, by independent adjudicators' consensus for antiphospholipid syndrome (APS) classification

| Characteristic | Validation cohort 1 (n = 278) | | Validation cohort 2 (n = 275) | |
|---|---|---|---|---|
| | APS (n = 98) | No APS (n = 180) | APS (n = 113) | No APS (n = 162) |
| Demographics | | | | |
| Age, mean ± SD years | 45.2 ± 14.7 | 43.3 ± 14.5 | 43.2 ± 12.9 | 42.8 ± 14.7 |
| Age range, years | 20–84 | 20–84 | 18–85 | 18–85 |
| Female, no. (%) | 73 (75) | 143 (79) | 88 (78) | 136 (84) |
| Race, no. (%) | | | | |
| Asian | 6 (6) | 15 (8) | 7 (6) | 16 (10) |
| Black | 2 (2) | 6 (3) | 5 (4) | 13 (8) |
| Other | 4 (4) | 4 (2) | 6 (4) | 6 (4) |
| White | 86 (88) | 155 (86) | 95 (84) | 127 (8) |
| Ethnicity, no. (%) | | | | |
| Hispanic/Latin American | 12 (12) | 13 (7) | 10 (9) | 23 (14) |
| Not allowed to record | 10 (10) | 6 (3) | 11 (10) | 10 (6) |
| Not Hispanic/Latin American | 61 (62) | 141 (78) | 78 (69) | 103 (64) |
| Other | 15 (15) | 20 (11) | 14 (12) | 26 (16) |
| Region of residence, no. (%) | | | | |
| Asia | 4 (4) | 5 (3) | 3 (3) | 9 (6) |
| Europe | 52 (53) | 121 (67) | 66 (58) | 92 (57) |
| North America | 38 (39) | 47(26) | 40 (35) | 54 (33) |
| South America | 4 (4) | 7 (4) | 4 (4) | (7 (5) |
| Other systemic rheumatic disease, no. (%) | | | | |
| Systemic lupus erythematosus | 30 (31) | 59 (33) | 42 (37) | 50 (31) |
| Other* | 2 (2) | 9 (5) | 3 (3) | 12 (7) |
| Entry criteria, no. (%) | | | | |
| Met | 98 (100) | 58 (32) | 113 (100) | 55 (34) |
| Not met | 0 | 122 (68) | 0 | 107 (66) |
| Clinical characteristics | | | | |
| Macrovascular (any), no. (%) | 76 (78) | 60 (33) | 87 (77) | 46 (28) |
| Venous thromboembolism | 52 (53) | 38 (21) | 62 (55) | 32 (20) |
| Arterial thrombosis | 38 (39) | 25 (14) | 44 (39) | 19 (12) |
| Microvascular, no. (%) | 18 (18) | 7 (4) | 30 (27) | 14 (9) |
| Pregnancy morbidity (any), no./total (%) | 34/73 (47) | 41/143 (29) | 46/88 (52) | 53/136 (33) |
| ≥1 prefetal death <10 weeks | 15/34 (44) | 35/41 (85) | 19/46 (41) | 39/53 (74) |
| ≥1 early fetal death 10–16 weeks | 1/34 (3) | 3/41 (7) | 8/46 (17) | 3/53 (6) |
| ≥1 fetal death 16–34 weeks only, without preeclampsia or placental insufficiency | 10/34 (29) | 7/41 (17) | 14/46 (30) | 4/53 (8) |
| Preeclampsia and/or placental insufficiency (with or without fetal death) | 15/34 (44) | 8/41 (20) | 20/46 (44) | 14/53 (26) |
| Cardiac valve, no. (%) | | | | |
| Thickening only | 4 (4) | 5 (3) | 4 (4) | 2 (1) |
| Vegetation (with or without thickening) | 3 (3) | 3 (2) | 9 (8) | 0 |
| Hematologic, no. (%) | | | | |
| Thrombocytopenia | 24 (25) | 23 (13) | 27 (24) | 28 (17) |
| Laboratory characteristics† | | | | |
| Lupus anticoagulant positive, no. (%) | | | | |
| Positive (single—once) | 10 (10) | 13 (7) | 4 (4) | 14 (9) |
| Positive (persistent) | 72 (74) | 41 (23) | 97 (86) | 41 (25) |
| IgG/IgM aCL/anti-$\beta_2$GPI positive, no. (%)‡ | | | | |
| Moderate or high positive (IgM alone) (aCL and/or anti-$\beta_2$GPI) | 13 (13) | 8 (4) | 11 (10) | 8 (5) |
| Moderate positive (IgG) (aCL and/or anti-ß$_2$GPI) with or without IgM | 16 (16) | 9 (5) | 10 (9) | 11(7) |
| High positive (IgG) (aCL or anti-$\beta_2$GPI) with or without IgM | 19 (19) | 2 (1) | 22 (20) | 8 (5) |
| High positive (IgG) (aCL and anti-$\beta_2$GPI) with or without IgM | 21 (21) | 5 (3) | 26 (23) | 3 (2) |

* Based on the case collector physician's diagnosis, "other" systemic rheumatic diseases reported included Behçet's disease (n =1), IgG4-related disease (n =1), mixed connective tissue disorder (n = 6), polymyalgia rheumatica (n = 1), rheumatoid arthritis (n = 4), Sjögren's syndrome (n =7), spondyloarthropathy (n = 4), and systemic sclerosis (n = 2).
† Based on the case collector physician's assessment of antiphospholipid antibody positivity.
‡ Moderate (40–79 units) and high (≥80 units) positive anticardiolipin (aCL)/anti–$\beta_2$-glycoprotein I (anti-$\beta_2$GPI) antibodies are based on enzyme-linked immunosorbent assays (refer to Table 1 for details).

**Table 5.** Operating characteristics of the 2023 ACR/EULAR antiphospholipid syndrome (APS) classification criteria versus the revised Sapporo APS classification criteria compared against independent adjudicators' consensus in two distinct validation cohorts

| | Validation cohort 1 (n = 278) | | Validation cohort 2 (n = 275) | |
|---|---|---|---|---|
| | 2023 ACR/EULAR APS criteria | Revised Sapporo APS criteria | 2023 ACR/EULAR APS criteria | Revised Sapporo APS criteria |
| Criteria met, no. of subjects | 83 | 120 | 97 | 143 |
| Specificity (95% CI) | 0.99 (0.98–1.00) | 0.91 (0.86–0.95) | 0.99 (0.97–1.00) | 0.86 (0.81–0.92) |
| Sensitivity (95% CI) | 0.83 (0.75–0.90) | 1.00 (1.00–1.00) | 0.84 (0.77–0.91) | 0.99 (0.98–1.00) |

95% CI = 95% confidence interval.

## DISCUSSION

The 2023 ACR/EULAR APS classification criteria comprise an additive, weighted system, assessing an individual's relative probability of APS and defining a threshold for APS classification for research purposes. The new criteria were developed in 4 rigorous phases under the guidance of international physician-scientists experienced in the evaluation and management of APS patients, while utilizing international cohorts totaling ~900 patients spanning the spectrum of APS. The new criteria are a paradigm shift in APS classification, given that: 1) these carefully defined clinical and laboratory criteria, based on literature review and expert consensus, improve the reliability and precision of classification; 2) the criteria are differentially weighted and organized into 8 hierarchical domains; and 3) the criteria were validated based on 2 international cohorts of patients referred for suspicion of APS, demonstrating very high specificity (99%) relative to the revised Sapporo criteria (86%).

In contrast to making a diagnosis, which requires consideration of a broad range of features (including rare ones), available clinical tests, and differential diagnoses pertaining to the epidemiology in a specific region, the goal of classification criteria is to enroll individuals with a condition of interest manifesting key features of the disease to form relatively homogeneous cohorts for comparability across clinical studies and trials (32). Thus, classification criteria intentionally include standardized and stringent definitions (32); very high specificity is required, even at the cost of sensitivity. Our goal was to achieve high specificity relative to the revised Sapporo criteria to improve homogeneity in APS research. While 99% specificity is a highly desirable performance characteristic of the new criteria for clinical trials and studies, the sensitivity of 84% captures a broad spectrum of patients referred for APS suspicion in whom the investigators are confident of APS classification.

The novel clinical features of the new APS classification criteria include the following: 1) risk stratification of macrovascular events by traditional thrombosis risk factors (although the revised Sapporo criteria acknowledged the need to recognize subgroups with and without thrombosis risk factors [2], our criteria are the first to offer a weighted assessment); 2) well-defined microvascular domain items thought to be mechanistically distinct from moderate-to-large vessel disease; 3) re-structured definitions of pregnancy morbidity to improve patient selection in obstetric studies; and 4) the addition of cardiac valve disease and thrombocytopenia, to capture and quantify the magnitude of heterogeneous APS manifestations.

The novel laboratory features of the new APS classification criteria include the following: 1) quantifying single-, double-, and triple-aPL positivity based on different domains and weights; 2) separating aCL/anti-$\beta_2$GPI IgG and IgM isotypes, to avoid including aPL-positive patients with isolated aCL/anti-$\beta_2$GPI IgM isotypes (i.e., no other aPL positivity) in the same research studies as those with aCL/anti-$\beta_2$GPI I IgG isotypes; and 3) defining 2 levels of aCL/anti-$\beta_2$GPI positivity that will be interpreted as clinically relevant by most investigators. These decisions were based on literature reviews (33), Phase III-C relative risk analyses (30), and Steering Committee consensus (for details as well as the rationale for not including IgA isotypes or other solid-phase assay–based aPL tests, see Supplementary Section 5 [https://onlinelibrary.wiley.com/doi/10.1002/art.42624]). Although the Steering Committee agreed that only LAC assays and aCL/anti-$\beta_2$GPI ELISAs should be included to ensure homogeneity, because automated laboratory systems are increasingly used in various countries, the Steering Committee suggested further studying the moderate/high thresholds in new automated platforms in association with clinical criteria from the new classification criteria (Table 1).

During the development and validation phases, we identified 3 "controversial" clinical scenarios not meeting the APS classification threshold by Steering Committee consensus but rated as APS by outside adjudicators, i.e., "false negatives" by the new criteria. These scenarios, and others below the threshold, are equivocal or uncertain for classification purposes, given the lack of strong literature support and physician agreement. Because the Steering Committee achieved a clear APS classification threshold above the controversial cases, as supported by the literature, and agreed that highly specific classification criteria are imperative for achieving homogeneity in APS research, along with ethical concerns of enrolling patients with controversial scenarios in the same clinical trials (e.g., trials of long-term anticoagulation therapy) as patients with highly likely APS, the Steering Committee deemed it acceptable to exclude these subgroups from current APS classification but to further study them independently (Table 6).

While using the new classification criteria, researchers should pay attention to certain points. First, clinical expertise and attentiveness are required to attribute clinical criteria to APS; as this can be challenging when "equally or more likely" causes exist, the item in question should not be scored. For example, in the clinical scenario of an acceptable aPL profile and concomitant heparin-induced thrombocytopenia, the hematologic domain should not be scored. Similarly, in a patient with systemic lupus erythematosus (SLE) with an acceptable aPL profile and preeclampsia, the obstetric item should not be scored if the preeclampsia can be equally or more likely explained as attributable to SLE. Second, as the primary goal is to ensure high-quality prospective studies and clinical trials, complete information on patients' VTE and CVD risk profiles is essential to evaluate the macrovascular domain. However, immediate real-world implementation of this concept may be challenging for retrospective studies, due to inadequate documentation including risk factor data. In this case, the Steering Committee agreed with taking a conservative bias approach such that the lowest possible nonzero weight should be assigned to macrovascular domain items with unknown risk factor data to avoid APS misclassification. Finally, the accurate assessment of "positive" aPL test results for APS classification is critical due to the following reasons: 1) despite LAC test limitations, i.e., false negative/positive results, the Steering Committee agreed that the test is extremely important if performed according to ISTH guidelines (27); and 2) defined levels for "moderate" and "high" positivity apply to ELISA tests but not to other methodologies, e.g., automated platforms (33).

The 2023 ACR/EULAR APS classification criteria have several strengths. First, international cases capturing the spectrum of APS contributed to its development, reducing the risk of selection bias and increasing generalizability. Second, to avoid the bias of circular reasoning (34), multidisciplinary participants in Phases III and IV were distinct. Third, use of 2 independent validation cohorts ultimately strengthened our results, demonstrating similar performance characteristics with overlapping confidence intervals. In fact, as the criteria were not changed between the 2 validation cohorts, our Phase IV results can be viewed as a single validation cohort with an interim analysis. Fourth, the new classification system allows for individual domain modification, allowing for future incorporation of additional clinical or new commercially available laboratory items if shown to be highly specific for APS, or new VTE and CVD risk factors based on future guidelines. Fifth, our criteria incorporate "entry criteria" to reflect current thinking that only cases with at least a minimal degree of clinical and laboratory suspicion for APS should be considered for classification. By intentionally collecting suspected APS cases for validation, we were able to test our entry criteria in a sensitivity analysis. Last, our model with absolute point requirements from both clinical and laboratory domains refines previous single-threshold models and more accurately reflects actual APS clinical decision-making.

As a limitation, our cohorts do not represent all possible subpopulations; however, we anticipate that investigators will test external validity in other cohorts, e.g., aPL-positive SLE patients, non-White race/ethnicities, pediatrics, or nonacademic cohorts. The Steering Committee emphasized that large population-based studies in APS, accounting for social determinants of health and access to care, are needed to better establish disease prevalence overall and across sociodemographic groups. Absent a definitive gold standard, validating a classification system for an evolving disease definition such as APS can be challenging. As acknowledged by other classification criteria development efforts (10), although independent adjudicators may have inherent biases toward established criteria, our careful selection of individuals, based on the adjudicators' expertise and with the adjudicators being blinded to relevant discussions about literature review and expert consensus–based decisions, reduced the bias of circular reasoning. Furthermore, the opportunity for adjudicators to discuss controversial cases in-depth, and to achieve consensus on all cases except one, ultimately strengthened their combined opinion.

**Table 6.** High-priority antiphospholipid syndrome (APS) research agenda to guide the future update of the 2023 ACR/EULAR APS classification criteria

| |
|---|
| **Patients with clinical AND laboratory criteria but NOT fulfilling the APS classification criteria** |
| • Venous thromboembolism (VTE) or arterial thrombosis (AT) alone, i.e., no other clinical criteria, in patients with high-risk VTE or CVD profiles, AND laboratory criteria score ≥3 |
| • Otherwise unexplained 3 or more consecutive prefetal deaths (<10 weeks) and/or early fetal death (10 weeks 0 days to 15 weeks 6 days) alone, i.e., no other clinical criteria, AND laboratory criteria score ≥3 |
| • Otherwise unexplained 1 or more fetal death (16 weeks 0 days to 34 weeks 0 days) alone, i.e., no other clinical criteria, AND laboratory criteria score ≥3 |
| • Moderate-titer (40–79 units) or high-titer (≥80) IgM anticardiolipin (aCL) or IgM anti–$\beta_2$-glycoprotein I (anti-$\beta_2$GPI) antibodies based on enzyme-linked immunosorbent assays (ELISAs) alone, i.e., no other antiphospholipid antibody (aPL) test positivity, and clinical criteria score ≥3 |
| **Patients fulfilling the clinical criteria but NOT the laboratory criteria** |
| • Other aCL/anti-$\beta_2$GPI testing platforms, e.g., automated laboratory systems, to determine the "moderate" and "high" thresholds corresponding to ELISA |
| • "Other" solid-phase assay–based aPL tests to determine their relevance |
| **Patients fulfilling the laboratory criteria but NOT the clinical criteria** |
| • "Other" potential aPL-related clinical manifestations to determine their specificity and frequency (see ref. 8) |

In conclusion, using rigorous data-driven and expert-based methodology, including international multidisciplinary collaborators with APS expertise, methodologists, and patients, we have incorporated heterogenous aPL-related clinical and laboratory manifestations into a set of hierarchically clustered, weighted, and risk-stratified classification criteria reflecting current thinking about APS, providing high specificity and an improved foundation for APS research.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Erkan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Barbhaiya, Zuily, Naden, Amigo, Avcin, Bertolaccini, Branch, de Jesus, Devreese, Frances, Garcia, Levine, Levy, Lockshin, Ortel, Seshan, Tektonidou, Wahl, Willis, Guillemin, Costenbader, Erkan.

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## ADDITIONAL DISCLOSURES

Dr. Levy is an employee of GlaxoSmithKline.

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## APPENDIX A: ACR/EULAR APS CLASSIFICATION CRITERIA STEERING COMMITTEE MEMBERS, ADJUDICATORS, AND COLLABORATORS

The Core Planning Group of the Steering Committee included authors Medha Barbhaiya, Karen Costenbader, Doruk Erkan, Francis Guillemin, Alison Hendry (joined during Phase III), Florian Manneville (joined during Phase IV), Ray Naden, and Stephane Zuily. Additional members of the Steering Committee included authors Mary-Carmen Amigo, Tadej Avcin, Maria Laura Bertolaccini, D. Ware Branch, Guilherme de Jesus, Katrien M. Devreese, Camille Frances, David Garcia, Steve R. Levine, Roger A. Levy, Michael D. Lockshin, Thomas L. Ortel, Surya V. Seshan, Maria G. Tektonidou, Denis Wahl, and Rohan Willis. The Phase III Consensus Meeting Collaborator was author Mark Crowther. The Phase III/IV Case Collector Collaborators were authors Casini Alessandro, Danieli Andrade, Laura Andreoli, Bahar Artim-Esen, Tatsuya Atsumi, H. Michael Belmont, Graziela Carvalheiras, Ricard Cervera, Nathalie Costedoat-Chalumeau, Ali Duarte-Garcia, Sheetal Desai, Maria De Sancho, Reyhan Diz-Kucukkaya, Aurelien Delluc, Jean-Christophe Gris, Natasha Jordan, Rebecca K. Leaf, Jason S. Knight, Carl Laskin, Alfred I. Lee, Kimberly Legault, Nina Kello, Maarten Limper, Karoline Mayer-Pickel, Pier Luigi Meroni, Jack Musial, Giovanni Orsolini, Vittorio Pengo, Michelle Petri, Guillermo Pons-Estel, Quentin Raimboug, Jose A. Gomez-Puerta, Giovanni Sanna, Savino Scaiscia, Angela Tincani, Cecile Yelnik, and Catherine Zuily. The Phase IV Independent Adjudicators were authors Zahir Amoura, Hannah Cohen, and Robert Roubey.

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