Journal of Thrombosis and Haemostasis, **4**: 295–306

SPECIAL ARTICLE

International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS)

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To cite this article: Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RHWM, de Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; **4**: 295–306.

Summary. New clinical, laboratory and experimental insights, since the 1999 publication of the Sapporo preliminary classification criteria for antiphospholipid syndrome (APS), had been addressed at a workshop in Sydney, Australia, before the Eleventh International Congress on antiphospholipid antibodies. In this document, we appraise the existing evidence on clinical and laboratory features of APS addressed during the forum. Based on this, we propose amendments to the Sapporo criteria. We also provide definitions on features of APS that were not included in the updated criteria.

Keywords: anticardiolipin, antiphospolipid syndrome, β_2 glycoprotein-I, classification criteria, lupus anticoagulant, thrombosis.

Introduction

Since the formulation of the international preliminary classification (Sapporo) criteria for antiphospholipid syndrome (APS) [1], a significant body of work in basic research and studies on laboratory and clinical manifestations of APS has appeared. A preconference workshop, preceding the Eleventh International Congress on antiphospholipid antibodies (aPL), considered revisions to the international classification criteria for APS. Members of the workshop panel included all of the authors and the individuals listed in the Appendix.

Some of the authors presented the current evidence in their area of expertise (see Addendum) providing relevant literature on predictors of outcome, risk factors, associations between clinical and laboratory features and accuracy of tests. The evidence was also reviewed and graded (according to criteria listed in Table 1) by three members of the committee (SM, MDL, SAK) not involved in the presentation of specific topics. An open discussion followed, to reach consensus. Where data were limited or incongruent, expert opinion supplements the recommendations, as indicated.

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Received 30 August 2005, accepted 2 November 2005

Update of the classification criteria

Table 2 contains the revised classification criteria for APS. The Sapporo classification divided the APS criteria into clinical and laboratory; this categorization was maintained in the current revision.

Studies validating the Sapporo criteria [2,3] are few. Tested against patients with systemic lupus erythematosus (SLE) and lupus-like disease (LLD), the criteria have high sensitivity and specificity [2], but the high frequency of aPL in older populations and of thromboembolic disease in hospitalized patients suggests that the Sapporo criteria would perform poorly in these populations. The association of aging and of common risk factors for cardiovascular disease with thrombosis may cause classification bias (Evidence Level I) [4]. No published data provides a valid estimation of an age boundary for diagnosing APS. Standard definitions of premature cardiovascular disease [5] and conditions conferring risk for thrombosis (listed in Table 2) [6,7] should be taken into account (Evidence Level I). Thrombosis may be more frequent when multiple risk factors coexist. Strict exclusion criteria

Table 1 Classification of evidence used in this article for evaluating studies regarding the association of risk factors with clinical conditions and/or disease outcome*

Evidence Level	Description
Class I	Prospective study in a broad spectrum of the representative population or Meta-analysis of randomized-controlled trials
Class II	Prospective study in a narrow spectrum of the representative population or Well-designed cohort or case–control analytic study or Retrospective study in a broad spectrum of the representative population
Class III	Retrospective study in a narrow spectrum of the representative population
Class IV	Study design where predictor is not applied in a blinded fashion or Descriptive case series or Expert opinion

*Throughout this article wherever studies of different Evidence Levels are quoted for the same issue, only the higher Evidence Level is provided.

therefore seem impractical. The committee concurs that additional factors contributing to thrombosis should be assessed and that APS patients should be stratified according to: (a) the presence or (b) absence of other – inherited or acquired – contributing causes of thrombosis (Table 2).

Evidence arising from clinical experience and the few relevant publications suggests that the 'fetal death' (Type 2a) Sapporo pregnancy morbidity criterion is the most specific, while the 'recurrent early abortion' (Type 2c) criterion may be the most sensitive (Level of evidence IV). The specificity of recurrent early abortion is uncertain because of the difficulty in excluding other known or suspected causes. The pre-eclampsia/placental insufficiency (Type 2b) Sapporo criterion may be relatively insensitive or non-specific. To enhance specificity, this criterion included only cases requiring delivery before 34 weeks' gestation. It appears that some investigators have incorrectly interpreted this criterion to include any preterm birth because of pre-eclampsia or placental insufficiency. In (small) populations unselected [8] or at risk for recurrent pre-eclampsia [9], aPL are not associated with pre-eclampsia or placental insufficiency (Evidence Level II). We recognize that there is no widely accepted definition for placental insufficiency, that timing of delivery is subject to physician judgment, and that there are no specific histopathologic placental abnormalities characteristic of either APS or 'severe' placental insufficiency (Evidence Level III) [10]. Well-designed, prospective studies to determine the contribution of APS to the overall problem of preterm birth from severe pre-eclampsia or placental insufficiency are not available. The committee finds no advantage to removing the pre-eclampsia/placental insufficiency criterion; there is a need for optimizing its performance instead. We recommend adherence to strict definitions of eclampsia and severe pre-eclampsia [11,12], we provide the commonly used clinical definitions for placental insufficiency (Table 2), and we suggest that the criterion for APS classification be any of these conditions associated with the decision of a qualified clinician to deliver a morphologically normal fetus prior to 34 weeks' gestation.

Both lupus anticoagulant (LA) and anticardiolipin (aCL) immunoglobulin isotype G (IgG) and M (IgM) are maintained as laboratory APS criteria, and IgG and IgM anti-β_2 glycoprotein-I (anti-β_2GPI) assays are added in the revised criteria (Table 2).

Medium and high titers of IgG and IgM aCL antibodies associate with clinical manifestations of APS, and were selected as criteria in Sapporo. However, the threshold used to distinguish moderate–high levels from low levels has no standard [13], and definition of the level that best corresponds to the risk of clinical manifestations is difficult [14]. Based on the best available evidence (Evidence Level II) [15–19], and until an international consensus is reached, the committee introduces a clear statement on threshold for positive: >40 GPL or MPL units, or >99th percentile (Table 2).

The revized criteria introduce a concept of subclassification of APS patients into four different categories of aPL assay positivity, specified in Table 2. Certain issues of specificity and predictive value of laboratory assays remain unresolved, whereas evidence suggests that multiple aPL positivity is associated with a more severe course of the disease, increasing significantly the rate of thrombosis (Evidence Level II) [20–23]. Investigators encouraged to subclassify patients with positive laboratory assays that fulfil the criteria for APS in clinical studies, according to the guidelines in Table 2.

Antiphospholipid syndrome requires the combination of at least one clinical and one laboratory criterion. A remote test avoids false results from interference with the event; however, in extreme cases, a positive test separated many years from a clinical manifestation also risks misclassification, as a causative relationship between event and test would then be in doubt. The Sapporo statement encouraged investigators to provide applicable information, but relevant existing data are rather poor. The stability of the laboratory testing over time is reassuring [24], yet spontaneous variation of aPL in individual patients occurs in up to a quarter of cases (Evidence Level II). Whether disease activity and treatment contribute to assay variability is unknown [25–27]. The committee suggests that researchers should not classify APS if more than 5 years separate the clinical event and the positive laboratory test, and that an allowance of at least 12 weeks between symptom and test will assist assessment of the relationship between clinical manifestations and aPL (Table 2). These time limits are valid independently of which feature of APS (clinical or laboratory) occurs first.

Persistent positivity of laboratory tests is important; the Sapporo criteria suggested an interval of at least 6 weeks between the two positive tests. In fact, there are no data to validate this interval. There are concerns that transient presence of epiphenomenal aPL – not infrequent in clinical practice – could risk misclassification (Evidence Level II) [28]. This committee proposes that increasing the interval to 12 weeks is

Table 2 Revized classification criteria for the antiphospholipid syndrome

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met*

Clinical criteria

1. Vascular thrombosis†

One or more clinical episodes‡ of arterial, venous, or small vessel thrombosis§, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions [11], or (ii) recognized features of placental insufficiency¶, or

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria**

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies) [82,83].

2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or $>$ the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA [100,129,130].

3. Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer $>$ the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures [112].

*Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation. †Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to: (a) the presence, and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) such cases include: age (>55 in men, and >65 in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥ 30 kg m^{-2}, microalbuminuria, estimated GFR <60 mL min^{-1}), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfil criteria should be stratified according to contributing causes of thrombosis. ‡A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found. §Superficial venous thrombosis is not included in the clinical criteria. ¶Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), e.g. a non-reactive non-stress test, suggestive of fetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g. absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, e.g. an amniotic fluid index of 5 cm or less, or (iv) a postnatal birth weight less than the 10th percentile for the gestational age. **Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-β_2 glycoprotein-I antibody present alone.

unlikely to affect sensitivity (Table 2); coupled with the prior proposal of an analogous interval between clinical manifestation and assay performance, it provides greater reassurance that the aPL detected are relevant to a predisposition to APS. We emphasize that proposed time intervals are based on expert opinion. Studies validating these time frames are imperative.

The committee advises against using the term 'secondary' APS. We could not find differences in the clinical consequences of aPL among patients in these two categories (Evidence Level I) [13,29]. Most patients with so-called secondary APS have SLE. It is unknown if APS and SLE are two diseases coinciding in an individual, if underlying SLE offers a setting for the development of APS, or if APS and SLE represent two elements of the same process [30,31]. Some cases with 'secondary' APS are classified as LLD. The interface between SLE, LLD and APS merits further consideration. Rather than distinguishing between patients with 'primary' and 'secondary' APS, documenting the coexistence of SLE (or other disease) is more advantageous for classification.

Finally, the entity of the Catastrophic Antiphospholipid Syndrome was outside the agenda of this workshop; a relevant consensus statement has been released [32].

Features associated with APS, but not included in the revised criteria

This panel also discussed clinical and laboratory features not included in the revised classification criteria for APS. These include: (i) heart valve disease, (ii) livedo reticularis (LR), (iii) thrombocytopenia, (iv) nephropathy, (v) neurological manifestations, (vi) IgA aCL, (vii) IgA anti-β_2GPI, (viii) antiphosphatidylserine antibodies (aPS), (ix) antiphosphatidylethanolamine (aPE) antibodies, (x) antibodies against prothrombin alone (aPT-A), and (xi) antibodies to the phosphatidylserine–prothrombin (aPS/PT) complex. Some of the features above are undoubtedly frequent but not specific in patients with APS. The committee considered that adoption of these features as independent criteria for definite APS may decrease diagnostic specificity, even though their association with APS is recognized.

Another issue is how to classify (i) cases with aPL and non-criteria clinical manifestations of APS, and (ii) the infrequent cases that fulfil the clinical criteria, but test positive only for non-criteria aPL. Some members of the committee proposed the term 'probable APS'. This concept was not

Table 3 Definition of aPL-associated cardiac valve disease

aPL-associated cardiac valve disease is:
Coexistence of aPL (Laboratory Criteria for APS) *along with*
Echocardiographic detection of lesions *and/or*
Regurgitation* *and/or* stenosis of mitral *and/or* aortic valve or any combination of the above.
Valve examination can be performed with TTE and/or with TEE
Defining valve lesions include:
Valve thickness >3 mm,
Localized thickening involving the leaflet's proximal or middle portion,
Irregular nodules on the atrial face of the edge of the mitral valve, *and/or* the vascular face of the aortic valve.
The presence and severity of regurgitation and/or stenosis should be documented with Doppler echocardiography.
Interpretation should be carried out by two expert echocardiographers.
Both functional capacity and objective assessment of heart status should be reported according to the revized NYHA Criteria for Diagnosis of Heart Disease [131].
Confirmation of valve disease may also be provided by histopathological findings of Libman-Sacks endocarditis in patients with concomitant SLE [132].
In all the above cases, the presence or history of rheumatic fever and infective endocarditis must be excluded.
Patients who fulfill Clinical Criteria for APS are excluded from the definition above.
Researchers should also state if the patient meets the American College of Rheumatology (ACR) revized criteria for SLE [133,134].

*Investigators are advised to consider moderate-severe mitral valve regurgitation as criterion for aPL-associated cardiac valve disease, as mild regurgitation is very common in the general population.

adopted, because the features listed above cannot be used as alternative criteria for APS. With these limitations in mind, we believe it would be reasonable to use these features, which were not selected for diagnosis of individual patients as 'probable APS', 'features associated with APS' or 'non-criteria features of APS'. For clinical studies, patients falling into any of these categories should be classified separately from those that fulfill the revised classification criteria for APS. This policy may help clarify unsettled issues (specificity, associations of aPL with clinical manifestations, and differences in outcome and impact of treatment) between those features and definite APS. Thus, this committee encourages the separate recognition of non-criteria features of APS, and proposes a terminology (Tables 3–6). The evidence that precludes adoption as criteria is summarized in the section on Specific issues.

Specific issues

Cardiac manifestations

Heart valve lesions (vegetations, valve thickening and dysfunction) are frequent in APS, independent of SLE [33], but data are contradictory because of differences in echocardiography technique and descriptions for findings, inconsistent associations with aPL, and population heterogeneity[1] (Evidence Level II) [36,37]; confounding factors associated with cardiac valve disease include age, hypertension and obesity (Evidence Level I) [38]. The committee proposes a minimal consensus regarding the valve dysfunction and provides relevant definitions of heart valve lesions in APS (Table 3), but recommends against adoption as criteria. Determination of aPL in patients coming to medical attention because of valve disease should be individualized rather than routine.

Coronary artery disease (CAD) fulfills the thrombosis criterion for APS; we recommend that patients be stratified according to thrombosis risk stratification guidelines (Table 2). The workshop advises against routine performance of aPL tests in patients with CAD unless the patient's young age and lack of identifiable risk factors suggest a rare etiology.

Few data exist concerning the incidence of ventricular dysfunction in APS (Evidence Level IV). The committee advises that the rare cases with biopsy-proven myocardial microthrombosis, or with intracardiac thrombi be recognized as meeting the thrombosis criterion for APS (Evidence Level IV). Detection of cardiac microthrombosis or intracardiac thrombi without apparent explanation warrants aPL testing.

Neurological manifestations

Transient cerebral ischemia and stroke fall within the spectrum of thrombosis; thus, pertinent stratification recommendations apply. A consensus report on these manifestations has been published [39].

Antiphospholipid antibodies correlate with physical disability in the elderly [40] (Evidence Level II). In one small study of APS patients without SLE [41], long-term presence of LA is a risk factor for dementia (Evidence Level II). In SLE patients, persistent elevation of aPL is associated with cognitive dysfunction (Evidence Level I) [42,43]. Prospective studies deny an association between migraine and aPL (Evidence Level I) [44,45]. In patients with multiple sclerosis (MS), an association between aPL and clinical course cannot be supported (Evidence Level I) [46]. Patients with concomitant MS and SLE may be an exception, but studies are contradictory (Evidence Level II) [47,48]. Transverse myelopathy (TM) is a rare entity within APS [33]. Limited data suggest that in the 1% of SLE patients who manifest TM, the latter is associated with aPL (Evidence Level IV) [49]. Contradictory data exist on the relationship between aPL and seizures in SLE (Evidence Level I) [50,51] and in epilepsy patients (Evidence Level II) [52,53]. In unselected APS patients, epilepsy has been retrospectively associated with SLE, CNS ischemic events, thrombocytopenia, and LR (Evidence Level II) [54]. It is uncertain whether aPL can influence the clinical course of epilepsy, as relevant prospective data are missing. This committee considers that

[1]For instance, although mitral valve thickness >3 mm, measured with TEE, correlated significantly with aCL >40 GPL in one study [34], the average mitral valve thickness in the control population of another study was 3.2 mm with Doppler echocardiography [35].

Table 4 Definition of aPL-associated livedo reticularis (LR)

aPL-associated LR is the coexistence of aPL (Laboratory Criteria for APS) and LR.

Livedo reticularis is the persistent, not reversible with rewarming, violaceous, red or blue, reticular or mottled, pattern of the skin of trunk, arms or legs. It may consist of regular unbroken circles (regular LR) or irregular-broken circles (livedo racemosa). The width of the branching pattern can be ≥10 mm (large LR) or < 10 mm (fine LR). Four variants may be recognized: fine livedo racemosa, large livedo racemosa, fine regular LR, and large regular LR.

Pathologic changes confirmative, but not required, for LR classification and diagnosis include partial or complete occlusion of the lumen of small- to medium-sized arteries and/or arterioles at the dermis-subcutis border with no evidence of perivascular inflammatory infiltrate and negative direct immunofluorescence examination [62].

Patients who fulfill Clinical Criteria for APS are excluded from the definition above.

Table 5 Definition of aPL-associated nephropathy (APLN)

aPL-associated nephropathy [66,68] is the coexistence of aPL (Laboratory Criteria for APS) along with the histopathologic detection of:

Thrombotic microangiopathy involving both arterioles and glomerular capillaries *and/or*

One or more of:

- Fibrous intimal hyperplasia involving organized thrombi with or without recanalization
- Fibrous and/or fibrocellular occlusions of arteries and arterioles
- Focal cortical atrophy
- Tubular thyroidization (large zones of atrophic tubules containing eosinophilic casts)

Vasculitis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, malignant hypertension, and other reasons for chronic renal ischemia are exclusions.

Patients who fulfill Clinical Criteria for APS are excluded from the definition above

If SLE is also present, the above lesions should be distinguished from those associated with lupus nephropathy.

Table 6 Definition of aPL-associated thrombocytopenia

aPL-associated thrombocytopenia is the coexistence of aPL (Laboratory Criteria for APS) *along with* the following:

Thrombocytopenia ($< 100 \times 10^9$ L^{-1}), confirmed at least twice 12 weeks apart.

Exclusion of patients with thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, pseudo-thrombocytopenia, and heparin-induced thrombocytopenia [135,136].

Thrombocytopenia is further characterized as moderate (platelet count $50–100 \times 10^9$ L^{-1}) or severe ($< 50 \times 10^9$ L^{-1}).

Subclassification of patients according to the presence or absence of SLE is advantageous.

Patients who fulfill Clinical Criteria for APS are excluded from the definition above.

there is insufficient evidence to include cognitive dysfunction, headache or migraine, MS, TM, and epilepsy in the revized APS classification criteria; however, the data concerning cognitive dysfunction are suggestive and warrant further study.

Skin manifestations

Livedo reticularis is more prevalent among APS patients with SLE, and in females (Evidence Level II) [33,55]. Studies of associations with specific aCL isotypes or LA are contradictory (Evidence Level II) [56–60]. In unselected APS patients, LR has been retrospectively correlated with aCL and arterial thrombosis, but not with anti-β_2GPI or LA, venous thrombosis, or pregnancy morbidity (Evidence Level II) [61]. There are no prospective studies on the ability of LR to predict thrombosis, with the exception of the rare Sneddon's syndrome (Evidence Level II) [62]. The LR lesions can lead to ischemia and tissue infarction, called livedo vasculitis (purpuric macules, cutaneous nodules, and/or painful ulcerations) [63]; stating its presence is advisable. Inclusion of LR as an independent clinical criterion for APS would not serve to classify homogeneous patient groups, and definition is required (Table 4). The committee advises subclassification of LR variants for clinical studies. Although histologic findings sometimes may be helpful in most LR cases, there are no pathognomonic findings [62]; performing a biopsy is not routinely indicated or encouraged by this committee.

Other skin manifestations of APS include skin ulcerations, pseudo-vasculitic lesions, digital gangrene, superficial phlebitis, malignant atrophic papulosis-like lesions, subungual splinter hemorrhages [63], and anetoderma (a circumscribed area of loss of dermal elastic tissue) (Evidence Level IV) [64]. They are rare, and none merits inclusion as a criterion.

Renal manifestations

Antiphospholipid antibodies correlate with lesions of renal small-artery vasculopathy and chronic renal ischemia (Evidence Level III) [65–68]. The committee recommends the term 'aPL-associated nephropathy' (APLN) to describe this entity (Table 5). Renal lesions are identical in SLE–APS and non-SLE–APS patients, and have been associated with extra-renal vascular thrombosis and pregnancy complications in SLE patients (Evidence Level II) [65,66,69,70]. They are independent of lupus nephritis and do not correlate with the rate of loss of renal function or end-stage renal disease [65,66]. Apart from thrombotic microangiopathy, which represents an acute event, other lesions of APLN reflect chronic vascular damage, are more frequent [66,68], and may be non-specific. In almost all reported cases, the diagnosis of APLN derived from multiple findings. Histologic criteria for APLN have not been validated. Patients with histologically proven APLN satisfy the thrombosis criterion for APS, provided that other conditions resulting in similar renal lesions are excluded. This committee does not suggest routine performance of renal biopsy in APS; this decision should be guided by conventional clinical indications.

Thrombocytopenia

Antiphospholipid antibodies are frequently found in patients initially diagnosed with idiopathic thrombocytopenic purpura (ITP), prospectively associated with thrombosis (Evidence Level I) [71,72]. This may suggest that aPL confers a high risk of thrombosis in patients with ITP, or that ITP is a first

symptom of APS, as it may be of SLE. Thrombocytopenia is more common in patients with APS and SLE than in patients with APS alone (Evidence Level II) [33]. Antibodies directed against platelet glycoproteins are associated with thrombocytopenia (but not with thrombosis) in patients with aPL [73], and also in patients with APS, comparable with ITP patients [74] (Evidence Level III). The committee consented that thrombocytopenia occurring in patients with persistent aPL, in the absence of clinical manifestations of APS, should be considered to be different from ITP: such patients have an increased thrombotic risk and require closer follow-up. On the other hand, inclusion of thrombocytopenia as an independent clinical criterion for APS would likely add little to sensitivity with a potential cost in specificity; a clear distinction from thrombocytopenia because of SLE and ITP are required, and relevant data from prospective studies are inadequate. We propose the term 'aPL-associated thrombocytopenia' (Table 6) to stratify patients for clinical studies. We propose a platelet count $< 100 \times 10^9$ L^{-1} as the upper cut-off limit for thrombocytopenia in APS (Evidence Level II) [33]. This relatively stringent limit (vs. 150×10^9 L^{-1}) could serve the criteria target of maximum specificity, while including the severe and moderate cases.

Lupus anticoagulant

Lupus anticoagulant better correlates with thrombosis (Evidence Level I) [75], pregnancy morbidity (Evidence Level II) [76], and thrombosis in SLE patients (Evidence Level I) [77] than does aCL. Inter-laboratory agreement is relatively poor for the large number of LA assays on the market [78,79]. The present committee recommends that laboratories performing LA comply with existing rules to improve inter-laboratory concordance (Evidence Level II) [78,80–83].

No definite recommendation can be given on the assays of choice for LA testing. Both activated partial thromboplastin time (APTT)-based assays and dilute Russell's viper venom time (dRVVT) are suitable for LA (Evidence Level II) [79,80], provided that the APTT used for LA testing is LA sensitive. One positive test suffices for LA positivity; as no single test is 100% sensitive for LA, it is advised to use two or more tests with different assay principles before the presence of LA is excluded.

Unless one uses an LA test system that includes a heparin neutralizer (most of the commercial dRVVT-assays), the thrombin time should always be measured to exclude unforeseen presence of unfractioned heparin. If the patient is on oral anticoagulants, measurement of LA is better postponed (Evidence Level III) [84], or patient samples be diluted 1 : 2 with normal plasma before the test is performed, provided that international normalized ratio (INR) is < 3.5. When INR is > 3.5, the LA testing is unworkable (Evidence Level IV). Several phospholipids (rabbit brain extract, hexagonal phase phospholipids, defined phospholipid vesicles, washed-activated platelets, frozen-thawed platelets and lyophilized platelet extracts) have been used successfully in LA confirmation assays; no evidence exists for superiority of any particular one.

Little objective information and no relevant guidelines exist to define a positive-screening test [82]. The use of fixed-time cut-off limits in different laboratories with different instruments was discouraged by this panel. For dRVTT and other LA assays, better precision can be achieved when individual laboratories determine their own cut-off levels for positive results (Evidence Level II) [78,80,85]. Use of normalization ratios (test sample : control sample) is the best way to compensate for inter- and intra-assay variation. Clotting time ratios (test/control) of > 1.1 for the dRVTT and > 1.2 for KCT are applied in many laboratories, and indicate LA according to earlier guidelines [86,87]. Ratios have high specificity but may have low sensitivity (Evidence Level II) [80]. An appropriate way to establish cut-off levels is to measure LA in 40 healthy controls and determine the geometric mean + 2SD.

The interpretation of the confirmation procedure – the so-called lupus ratio (mathematically identical with the screen/confirm ratio), or the confirm/normal ratio – that offers the highest risk for thromboembolic complications remains uncertain. Integration of screening and confirmation into a single assay makes LA testing less time consuming, and may increase diagnostic accuracy and inter-laboratory agreement (Evidence Level III) [88]. Nevertheless, the result of the LA test that best correlates with clinical events of APS cannot be concluded. Until further evidence is provided, the committee advises considering positive every sample outside the normal range (Evidence Level IV).

The use of widely available pooled patient plasmas for positive controls (instead of the traditional plasma samples of local LA-positive patients) is currently advised [83]. Plasma spiked with monoclonal antibodies will soon be available; its use and standardization through participation in multicenter studies (e.g. ECAT and Scientific and Standardization Committee [SSC]) are encouraged.

Two new methods enable discrimination between β_2GPI and prothrombin antibodies causing LA. The first uses cardiolipin vesicles and can only be used in an APTT-based assay [89]. The second is based on changes in the final calcium concentration in the assay, but does not work when a mixture of both anti-β_2GPI and antiprothrombin antibodies is present [90]. In patients with autoimmune diseases, β_2GPI-dependent LA strongly correlates with a history of thrombosis, in contrast to the β_2GPI-independent assay (Level of Evidence II) [91]. An international multicenter trial to confirm this assertion will begin shortly.

Anticardiolipin assay

Interlaboratory agreement on aCL measurement remains marginal with both home-based and commercial assays (Evidence Level I) [14,92,93]. Discrepancies are mainly because of cut-off, calibration, and other methodological issues. Expression of aCL assays in ranges of positivity achieves better interlaboratory and inter-run agreement than do quantitative readouts [94]. We note that IgM aCL tends to give false-positive results, particularly in the low-positive

range, especially in the presence of rheumatoid factor or cryoglobulins [95,96].

The ISTH-SSC recommended in 2002 that the aCL test should be replaced by anti-β_2GPI and the LA tests [97]. However, the best available evidence indicates that anti-β_2GPI cannot yet be considered a substitute for aCL (Evidence Level II) [21,22,98]; this committee recommends that aCL continue to be a laboratory criterion for APS.

To optimize standardization, new reference samples (monoclonal antibodies, named HCAL and EY2C9) [99] will be distributed from the Center for Disease Control and Prevention to investigators free of charge. They will have to be validated against existing calibrators, and their specificity, avidity and stability over time should be monitored. Because these preparations cannot mirror the heterogeneity present in patient samples [100], firm recommendations cannot be given at this time.

IgA aCL

The IgA aCL are usually detected together with either IgG and/or IgM isotypes in patients with APS (Evidence Level II) [101–103], and agreement among patients grouped according to aCL titers for IgA seems lower than those for the other isotypes [104]. Specificity and standardization considerations for the other aCL isotypes apply also to the IgA aCL assay. In patients with collagen disease, IgA aCL associates with thrombocytopenia, skin ulcers and vasculitis, indicating a patient subgroup at risk for specific clinical manifestations (Evidence Level III) [105], and it is highly prevalent in African–American SLE patients [106]. Hence, this isotype appears to identify patient subgroups rather than adding diagnostic power. The committee consents that IgA aCL cannot be considered as a laboratory criterion for APS.

Anti-β_2GPI

By majority[2], the committee agreed that IgG and IgM anti-β_2GPI should be included as part of the modified Sapporo criteria. Anti-β_2GPI antibodies are an independent risk factor for thrombosis (Evidence Level II) [107,108] and pregnancy complications (Evidence Level I) [109,110], though some studies deny these associations mainly because of methodological differences and lack of standardization [107,108]. Inter-laboratory variation of anti-β_2GPI is better than that found with the aCL assay for both home-made [111] and commercial kits [112] (Evidence Level II). The anti-β_2GPI assay shows higher specificity than aCL for APS diagnosis (Evidence Level II) [21,22,113–115]. In 3–10% of APS patients, anti-β_2GPI may be the only test positive (Evidence Level I) [23,98,116]. The association of anti-β_2GPI with pre-eclampsia and/or eclampsia in unselected pregnant women who tested negative for aCL (Evidence Level I) [109] implies that the inclusion of anti-β_2GPI may also help clarify this pregnancy morbidity.

Methodology and standardization limitations expressed for aCL also apply for anti-β_2GPI [111,112]. Laboratories measuring anti-β_2GPI are encouraged to standardize the types of plates; purity, concentration and source of β_2GPI; and calibrators and units of measurement [18,112]. Validation of monoclonal anti-β_2GPI [99] antibodies and comparison with the existing standards is encouraged. High titers of anti-β_2GPI antibodies are associated with high risk of thrombosis, but it is difficult to define boundaries for medium and high titers at this stage. Until an international consensus is reached, this committee proposes a threshold for positive anti-β_2GPI antibodies $>$ 99th percentile of controls. The possible interference of cryoglobulins and rheumatoid factors should be considered in the interpretation of IgM anti-β_2GPI. Outside the context of clinical studies, testing for anti-β_2GPI can be helpful for APS diagnosis, particularly when aCL and LA are negative and APS is strongly suspected.

IgA anti-β_2GPI and other ELISAs for aPL detection

Data are inadequate for establishing IgA anti-β_2GPI as an independent risk factor for APS in the absence of other anti-β_2GPI isotypes (Evidence Level III) [117]. IgA anti-β_2GPI are the most frequently detected antibodies in patients in specific ethnic groups (Evidence Level II) [118,119]. A significant proportion of IgA anti-β_2GPI-positive tests has no apparent association with any clinical manifestation of APS (Evidence Level IV). Although a few Evidence Level II studies report association of aPE antibodies with thrombosis and fetal loss [120,121], experience with these antibodies is inadequate. Uniform guidelines how to perform the test, units of measurement and control materials do not exist. The committee concludes that it is premature to recommend that tests for an aPL other than IgG and IgM anti-β_2GPI be included in the revized-Sapporo criteria.

Antiprothrombin antibodies

Antiprothrombin antibodies detected by ELISA are a heterogeneous population including antibodies against prothrombin alone (aPT-A) and antibodies to the phosphatidylserine–prothrombin complex (aPS/PT). Data on the clinical associations of aPT-A are contradictory, and they imply low specificity of these antibodies for APS diagnosis (Evidence Level II) [122–127]. A systematic review on antiprothrombin antibodies and risk of thrombosis in APS failed to reveal an association, irrespective of isotype, site and type of event, or presence of SLE [107]. Both the sensitivity and specificity of aPS/PT are higher than those for aPT-A, whereas 95% of patients with aPS/PT are also LA positive, suggesting that aPS/PT can also serve as a confirmatory assay for LA (Evidence Level II); these results, however, only come from one study [128], and concerns regarding aPS/PT arise from multivalent antibody binding; the possibility of measuring antibodies against non-complexed

[2]Consensus was not reached regarding this issue. Two members of the committee considered that existing evidence does not justify inclusion of anti-β_2GPI as a criterion.

phospholipids present in the sample needs to be excluded. Prospective studies examining the association of aPT-A or aPS/PT with APS clinical features are still missing. This committee considers that the inclusion of antiprothrombin antibodies in the classification criteria for APS is premature.

Acknowledgements

This work was supported by an unrestricted grant from the American Autoimmune Related Diseases Association Inc. (AARDA).

Conflict of interest statement

No conflicts of interest are declared for this document.

Addendum

Contribution of each author to this manuscript was as follows:
SM: grading of the evidence, synthesis, and writing of the manuscript
MDL: grading of the evidence, manuscript editing
SAK: grading of the evidence, manuscript editing, and authors coordination
The following authors contributed to parts of the manuscript as listed:
TA: thrombocytopenia, antiprothrombin antibodies
DWB: obstetric manifestations
RLB: neurological manifestations
RC: cardiac manifestations
RHWMD: lupus anticoagulant
PGdG: lupus anticoagulant
TK: thrombocytopenia, antiprothrombin antibodies
PLM: renal manifestations
GR: anticardiolipin, anti-β_2GPI
YS: skin manifestations
AT: anticardiolipin, anti-β_2GPI
PGV: renal manifestations.

Appendix: Members Of The Workshop Panel

In addition to the authors, the workshop panel comprised the following individuals:

Marie-Claire Boffa, MD (Hôpital de la Pitié, Paris, France), Benjamin Brenner, MD (Rambam Medical Center, Haifa, Israel), Joab Chapman, MD (Sheba Medical Center, Tel-Hashomer, Israel), Philippe de Moerloose, MD (University Hospital, Geneva, Switzerland), Doruk Erkan, MD (Hospital for Special Surgery, Cornell Medical Center, New York, NY), Thomas Exner, PhD (St. Vincents Hospital, Sydney, Australia), Ricardo R. Forastiero, MD (Favaloro University, Buenos Aires, Argentina), Monica Galli, MD (Ospedali Riuniti, Bergamo, Italy), E. Nigel Harris, MD (Morehouse School of Medicine, Atlanta, GA), Thomas Lecompte, PhD (Université de Nancy, France), Steven R. Levine, MD (The Mount Sinai School of Medicine, New York, NY), Roger A. Levy, MD (Universitario Pedro Ernesto, Rio de Janeiro, Brazil), Gabriella Moroni, MD (Ospedale Maggiore, Milan, Italy), Michelle Petri, MD (John Hopkins University, Baltimore, MD), Silvia Pierangeli, PhD (Morehouse School of Medicine, Atlanta, GA), Jacob H. Rand, PhD (Montefiore Medical Center, New York, NY), Joyce Rauch, MD (McGill University, Montreal, Canada), Veronique Regnault, PhD (INSERM, Nancy, France), Robert A. S. Roubey, MD (The University of North Carolina at Chapel Hill, NC), Marielle Sanmarco, MD (Hopital de la Conception, Marseille, France), Yaniv Sherer, MD (Sheba Medical Center, Tel-Hashomer, Israel), Maria Tektonidou, MD (Department of Pathophysiology, University of Athens, Greece), Pierre Youinou, PhD (Brest University Hospital, Brest, France), and Denis Wahl, MD (INSERM, Nancy, France).

This workshop was chaired by Drs. Ronald Derksen, Steven Krilis, Michael Lockshin, and Spiros Miyakis.

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