Antiphospholipid syndrome (APS)

The antiphospholipid syndrome (APS) is defined by the development of **venous and/or arterial thromboses**, often multiple, and **pregnancy morbidity** (mainly, recurrent fetal losses), in the presence of antiphospholipid antibodies (aPL), **namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-β2 glycoprotein-I (β2GPI) antibodies**.

CONSIDERATIONS

APS was initially described in patients with SLE, but it was soon recognized as a primary form in those people who did not have features of other systemic autoimmune disease.

A European study on 1000 patients showed that APS was associated with SLE in 36% of the cases.

- Although APS is recognised as a disease of young women, owing the association with SLE and pregnancy loss, men can also be affected.

- It is estimated that aPL can be found in 9.5% of the patients with unexplained venous thrombosis and in 13% of those with stroke.

- However the presence of aPL is not limited to those people who have the typical picture of APS.

- These autoantibodies are detectable in several different conditions, mainly in patients with systemic autoimmune diseases, but also in infectious conditions, cancer, with use of particular drugs, and even in healty individuals.

Antiphospholipid syndrome (APS)

The aPL can appear in different scenarios:

- asymptomatic “carrier” patients for aPL,
- “classical” APS with recurrent venous and/or arterial thrombosis,
- APS affecting otherwise healthy women with recurrent pregnancy loss,
- patients with aPL positivity with non-thrombotic aPL manifestations (i.e, thrombocytopenia, hemolytic anemia or livedo reticularis)
- a life-threatening form characterized by a rapid development of microthrombosis that led to rapid multiorgan failure, which is termed catastrophic APS.

- The relevance of testing for aPL concerns their pathogenic role.

- In vitro and in vivo studies in animal models have shown that aPL are mediators of both thrombosis and pregnancy morbidity by the engagement of multiple pathogenetic mechanisms involving inflammation and distruption of the coagulation pathway.

- Moreover aPL are considered as a risk factor for the development of APS, so they should be assessed in patients with systemic AD in order to establish and adeguate prophylaxis.

Antiphospholipid antibodies

- aPL are a family of the immunoglobulins IgG, IgM, IgA or combination of these isotypes, which are initially thought to recognise anionic phospholipids, particular cardiolipin. Over the years, these concept has changed and different specificities have been described for aPL.

- aPL mostly recognise phospholipid-binding proteins rather than phospholipids.

Lupus anticoagulant

- Lupus anticoagulant (LA) is a functional measurement of the ability of hetergeneous aPL that interfere with phospholipid-dependent stages of blood coagulation **in vitro** and **inhibit** both the intrinsic and common pathways of **coagulation**.
- LA-positive results are associated with a **thrombotic tendency rather than bleeding** generally associated with coagulation inhibitors.

Conditions in which aPL have been detected

Systemic disorders	Infections	Drugs	Other
SLE	Leprosy	Hydralazine	Diabetes
Rheumatoid arthritis	Syphilis	Procainamide	Malignancy
Sjogren Syndrome	HIV	Phenytoin	Sarcoidosis
Scleroderma	Hepatitis C	Interferon	Accelerated atheroma
Myositis	Cytomegalovirus	Quinine/quinidine	Healthy adults and childrens
Systemic Vasculitis	Mycoplasma		
Crohn’s disease	Parvovirus		

Anticardiolipid

- The aCL test was originally described in 1983 as a radioimmunoassay.
- The first aCL ELISA was carried out in 1985.
- The **addition of serum** was essential for performance of the assay, owing to the presence of **b2GPI**, a glycoprotein that binds negatively charged phospholipids such as cardiolipin itself.
- Therefore an aCL assay can detect several subpolulation of autoantibodies:

  Directed against phospholipid-binding proteins (b2GPI-dependent aCL)

  Phospholipid

  Phospholipid-binding protein/phospholipid complex.

- A positive test for aCL may be less specific for APS since it is commonly found in other conditions expecially infections.
- These aCL are generally IgM and low titres do not associate with clinical manifestation of APS.
- The role of IgA is still debated.
- The IgG are associated with clinical complications.

Anti beta2-glicoprotein I

- Identified in 1990 as a cofactor of aCL binding to cardiolipin.
- The role of the b2GPI, a normal plasma glycoprotein is not well understood probably acts as a natural anticoagulant.
- Anti-b2GPI are more specific than aCL in predicting thrombosis and differentiating pathogenic from non-pathogenic antibodies
- 3-10% of patients with APS have anti-b2-GPI as the only positive test.

Antibodies to phospholipids	Antibodies to phospholipid-binding protein
Cardiolipin	B2-GPI
Phosphatidylserine	Prothrombin
Phosphatidic acid	Annexin V
Phosphatidylinositol	Protein C
Phosphatidylcholine	Protein S
Phopsphatidylethanolamine	Factor XIIG
	C4 binding protein
	Complement C4 and C5
	Thrombin
	Other

Epidemiology

✓Prevalence of the aPL in the general population ranges between 1–5%.

✓However, only a minority of these individuals develop the APS.

✓Some estimates indicate that the incidence of the APS is around 5 new cases per 100,000 persons per year and the prevalence around 40–50 cases per 100,000 persons.

✓Conversely, aPL are positive in approximately 13% of patients with stroke, 11% with myocardial infarction (MI), 9.5% of patients with deep vein thrombosis (DVT) and 6% of patients with pregnancy morbidity.

✓The prevalence of the catastrophic APS is scarce (less than 1% of all cases of APS).

New mechanisms in APS pathogenesis

The pathogenesis of APS is not yet fully understood; however, pathways involving several cells (including platelets, monocytes and endothelial cells), activation of the coagulation and complement systems and inhibition of fibrinolytic processes are all known to be involved in the development of thrombosis in APS.

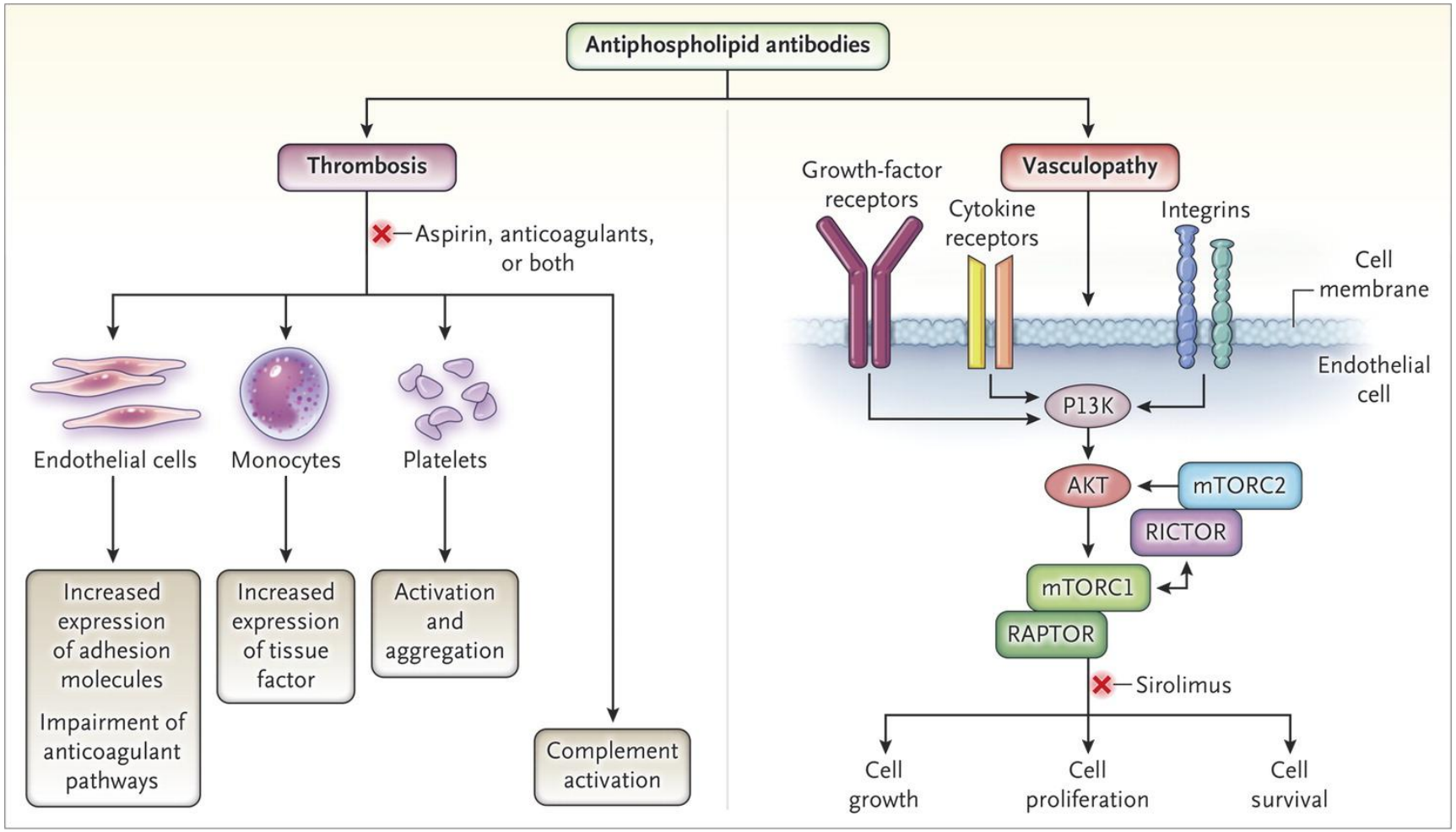
Severe intimal hyperplasia inducing vasculopathy in patients with aPL is also thought to potentially lead to arterial occlusions (mainly caused by stenotic lesions) and pregnancy morbidity.

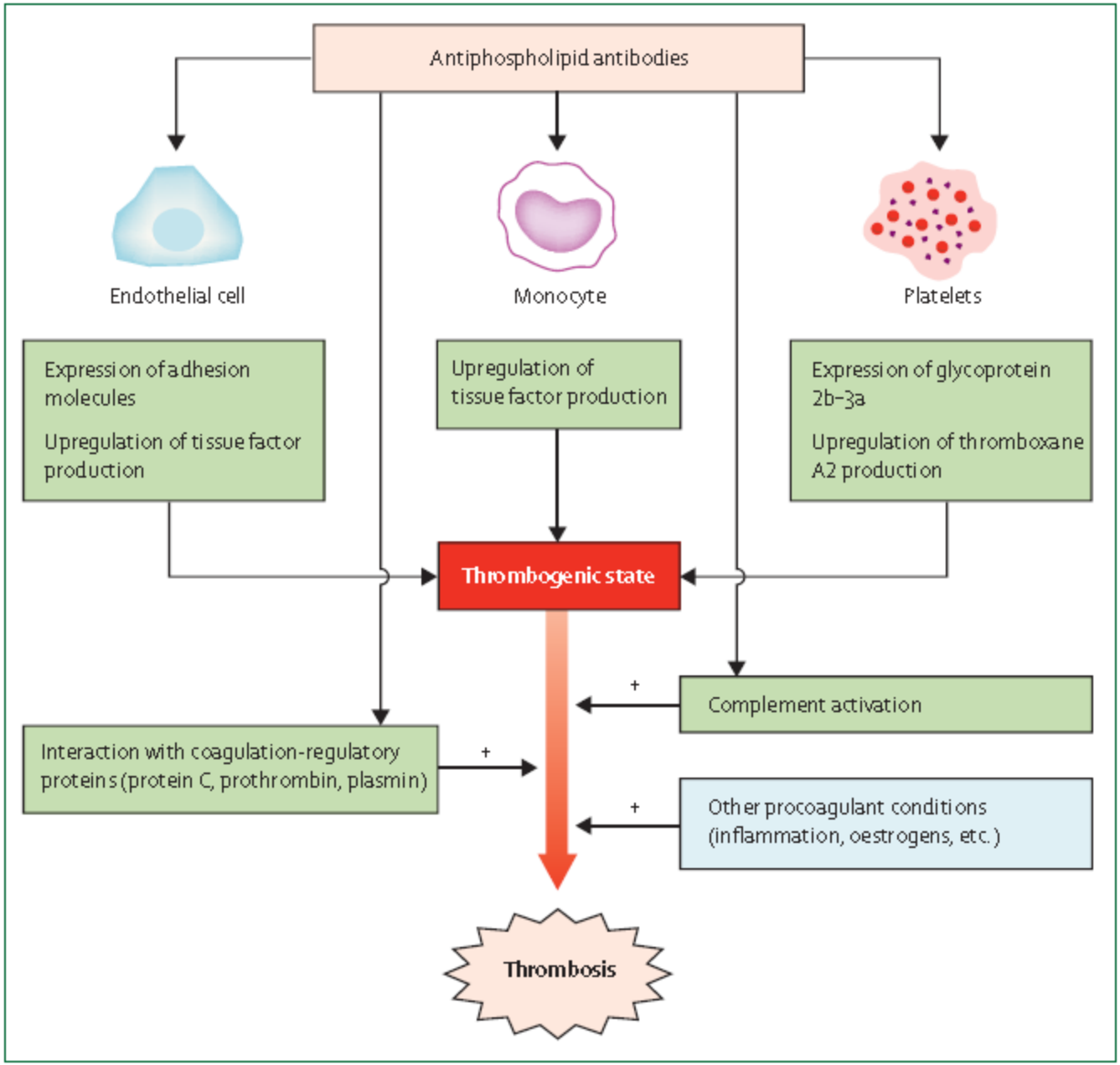
Pathogenesis

Many of the autoantibodies associated with APS are directed against a number of **plasma proteins and proteins expressed on, or bound to, the surface of vascular endothelial cells or platelets.**

The involvement of aPL in clinically important normal procoagulant and anticoagulant reactions and on certain cells altering the expression and secretion of various molecules are the basis for possible mechanisms by which aPL may develop thrombotic events in patients with APS.

Pathogenesis of Thrombosis and Vasculopathy in the Antiphospholipid Syndrome. Although multiple mechanisms have been implicated in the pathogenesis of thrombosis, the cause of vasculopathy remains elusive. Antiphospholipid antibodies, in binding to vascular endothelial cells in the kidneys, brain, or other organs, activate the signaling pathway of the mammalian target of rapamycin (mTOR).




Antiphospholipid antibodies
Endothelial cell
Monocyte
Platelets
Expression of adhesion molecules
Upregulation of tissue factor production
Upregulation of tissue factor production
Expression of glycoprotein 2b–3a
Upregulation of thromboxane A2 production
Thrombogenic state
Complement activation
Interaction with coagulation-regulatory proteins (protein C, prothrombin, plasmin)
Other procoagulant conditions (inflammation, oestrogens, etc.)
Thrombosis

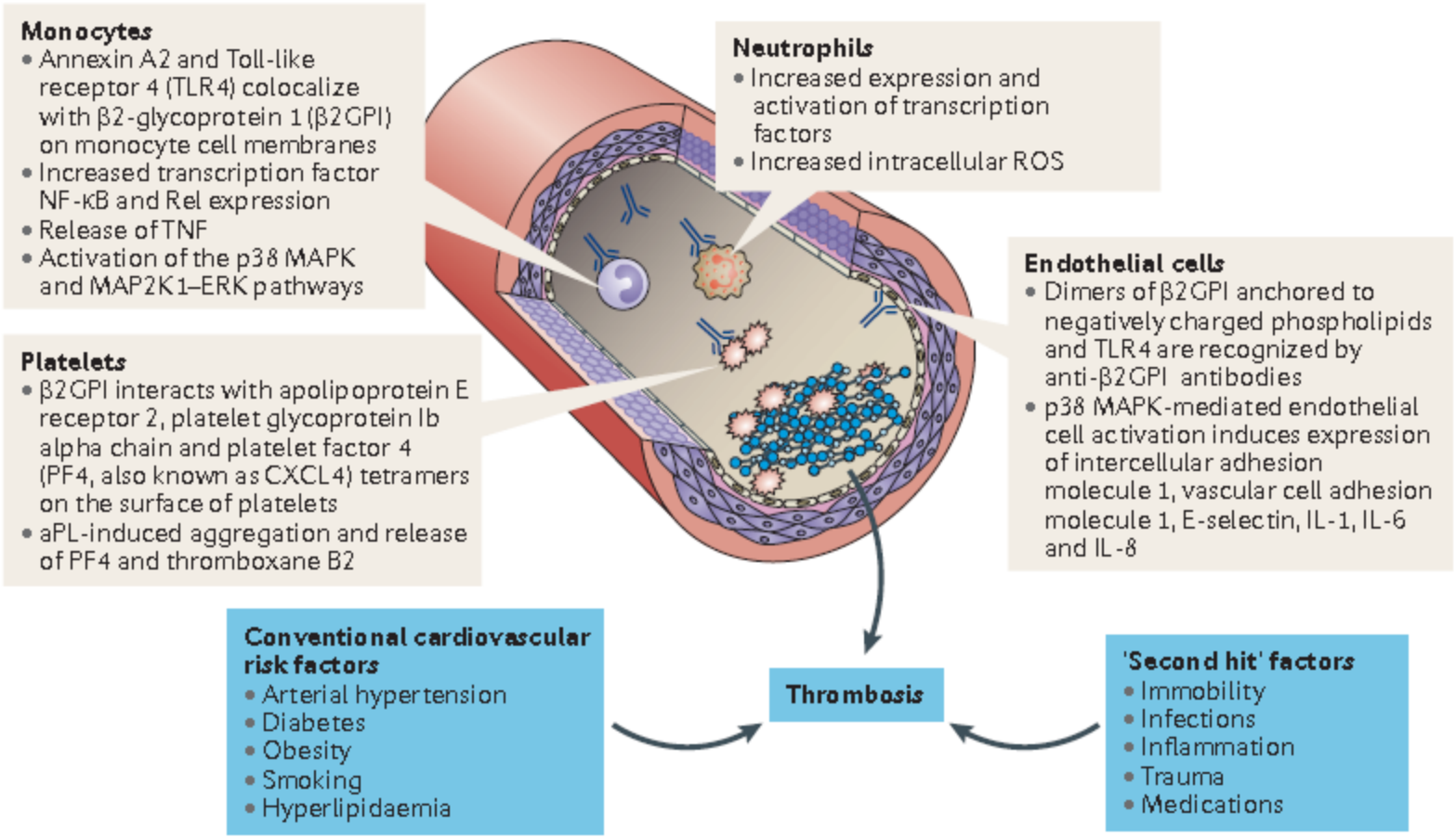


Figure 2 | **Mechanisms of thrombogenesis induced by antiphospholipid antibodies.** The actions of antiphospholipid antibodies (aPL) encourage clot formation through interactions with endothelial cells, neutrophils, platelets and monocytes. These mechanisms contribute to a procoagulant state that is necessary but not sufficient for clotting. Clot formation seems to require two steps: the presence of aPL provides the 'first hit', which results in clotting when accompanied by another procoagulant condition, a 'second hit'. Conventional cardiovascular risk factors further contribute to thrombosis. MAP2K1–ERK, dual specificity mitogen-activated protein kinase kinase 1–extracellular signal-regulated kinase; p38 MAPK, p38 mitogen-activated protein kinase; Rel, proto-oncogene c-Rel; ROS, reactive oxygen species.

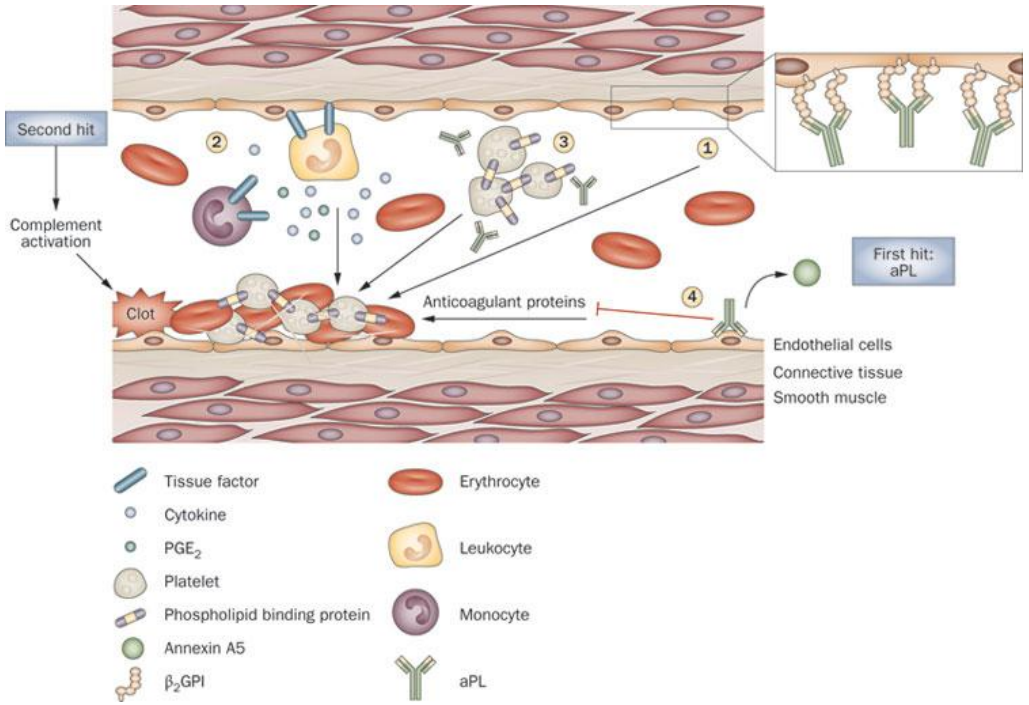
Pathogenic clotting mechanisms mediated by aPL

(1) aPL interact with endothelial cells, primarily through binding of β2GPI on the cell surface, and induce a procoagulant and proinflammatory endothelial phenotype.

(2) aPL upregulate tissue factor expression on endothelial cells and blood monocytes, and promote endothelial leukocyte adhesion, cytokine secretion and PGE2 synthesis.

(3) aPL recognize phospholipid-binding proteins expressed on platelets—aPL binding potentiates platelet aggregation induced by another agonist.

(4) aPL interfere with plasma components of the coagulation cascade, by inhibiting anticoagulant activity, by affecting fibrinolysis, and by displacing the binding of the natural anticoagulant annexin A5 to anionic structures. These mechanisms all contribute to a procoagulant state that is necessary but not sufficient for clotting. Clot formation seems to require two steps: the presence of aPL provides the 'first hit', which produces clotting when accompanied by another procoagulant condition, a 'second hit'. Complement activation seems to be necessary for clot formation in vivo. Abbreviations: aPL, anti-phospholipid autoantibodies; β2GPI, β2 glycoprotein I; PGE2, prostaglandin E2.



Diagnostic criteria

In 1999, a preliminary set of APS classification criteria was established following an expert workshop held in Sapporo, Japan.

During a subsequent workshop in 2004 in Sydney, Australia, experts proposed some changes to the Sapporo criteria, the main modification being the inclusion of the presence of antibodies against β2-glycoprotein 1 (β2GPI) among the lab-based findings.

TABLE 1. Sapporo Criteria for Diagnosing APLA Syndrome

Presence of 1 Clinical Event AND a Repeatedly* Positive Lab Test

Clinical Events	Lab Tests
Blood clot (=thrombosis) *Venous* • Deep vein thrombosis (DVT)=clot in leg or arm • Pulmonary embolism (PE)=clot in lung • Other (in eye=retinal vein thrombosis; around brain=sinus vein thrombosis; in abdomen=mesenteric, portal, or hepatic vein thrombosis; etc) *Arterial* • Stroke • Heart attack • Leg or arm arterial clot (=ischemia or gangrene) • Other (in eye=retinal artery thrombosis; in abdomen=mesenteric artery thrombosis, etc)	• Lupus anticoagulant confirmed with clotting tests that depend on phospholipids OR • Medium or high levels of anticardiolipin IgG or IgM antibodies
Pregnancy loss, defined as one of the following†: • Three or more losses before the 10th week of pregnancy • One or more losses at or after the 10th week of pregnancy • One or more premature deliveries at or before the 34th week of pregnancy because of eclampsia, preeclampsia, or placental insufficiency	

Antiphospholipid Syndrome Criteria

Sydney revision of Sapporo criteria 2006

CLINICAL CRITERIA

1. **Vascular Thrombosis**

2. **Pregnancy Morbidity**:
   a) death of normal fetus at ≥ 10 wks
   b) premature birth at ≤ 34 wks due to preeclampsia
   c) ≥3 consecutive abortions at <10wks
   d) placental insufficiency at < 34 wks

LAB CRITERA

1. anti-Cardiolipin IgG / IgM
2. anti–beta-2 glycoprotein I (GP1)
3. Lupus anticoagulant (LAC)

- medium to - high titer
- at least X 2 times
- 12 wks apart

Clinical criteria

Vascular thrombosis

- One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ.
- Thrombosis should be supported by objective validated criteria—ie, unequivocal findings of appropriate imaging studies or histopathology. For histopathological support, thrombosis should be present without substantial evidence of inflammation in the vessel wall.

Laboratory criteria

- Lupus anticoagulant 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 Hemostasis (Scientific Subcommittee on lupus anticoagulant/phospholipid-dependent antibodies).
- Anticardiolipin antibody of IgG or IgM isotype, or both, in serum or plasma, present in medium or high titres (ie, >40 GPL or MPL, or greater than the 99th percentile) on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA.
- Anti-β2-gycoprotein 1 antibody of IgG or IgM isotype, or both, in serum or plasma (in titres greater than the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA, according to recommended procedures.

Pregnancy morbidity, defined by one of the following criteria:

- One or more unexplained deaths of a morphologically healthy fetus at or beyond the 10th week of gestation, with healthy fetal morphology documented by ultrasound or by direct examination of the fetus.
- One or more premature births of a morphologically healthy newborn baby before the 34th week of gestation because of: eclampsia or severe pre-eclampsia defined according to standard definitions or recognised features of placental failure.
- Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical 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 patients according to one of the three criteria.

No new clinical features were included as criteria; however, several extra-criteria manifestations **were highlighted**.

In a validation study of the Sydney APS classification criteria, only 59% of patients who met the Sapporo classification criteria also met the revised Sydney criteria.

By emphasizing risk stratification, the Sydney APS classification criteria provided a more homogeneous basis for selecting patients for APS research than did the Sapporo criteria; investigations into inherited and acquired risk factors for thrombosis in patients with APS were strongly recommended in the Sydney criteria, especially for patients included in clinical research studies.

Although the Sydney APS classification criteria were not designed for clinical purposes, they represent the best available tool to limit over-diagnosis of APS in clinical practice.

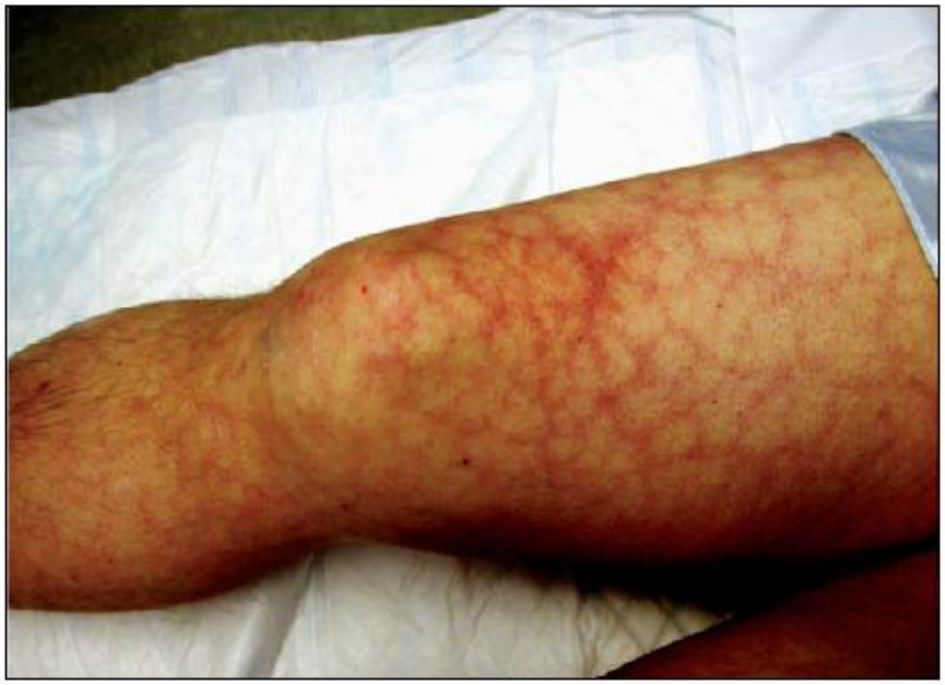
Extra-criteria clinical manifestations

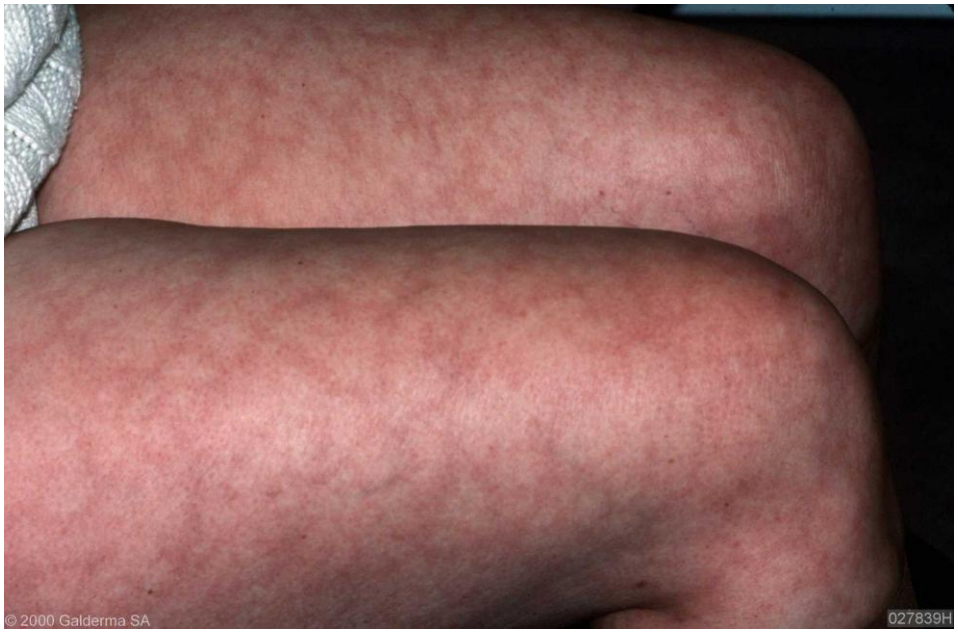
The recognition of livedo reticularis as an extra-clinical manifestation of APS was particularly important, as this feature can sometimes be associated with thrombosis.

Similarly, migraine can be associated with thrombotic events in patients with aPL, although migraine is considered to be important but not critical to clinical decision-making in patients with APS..

Livedo reticularis

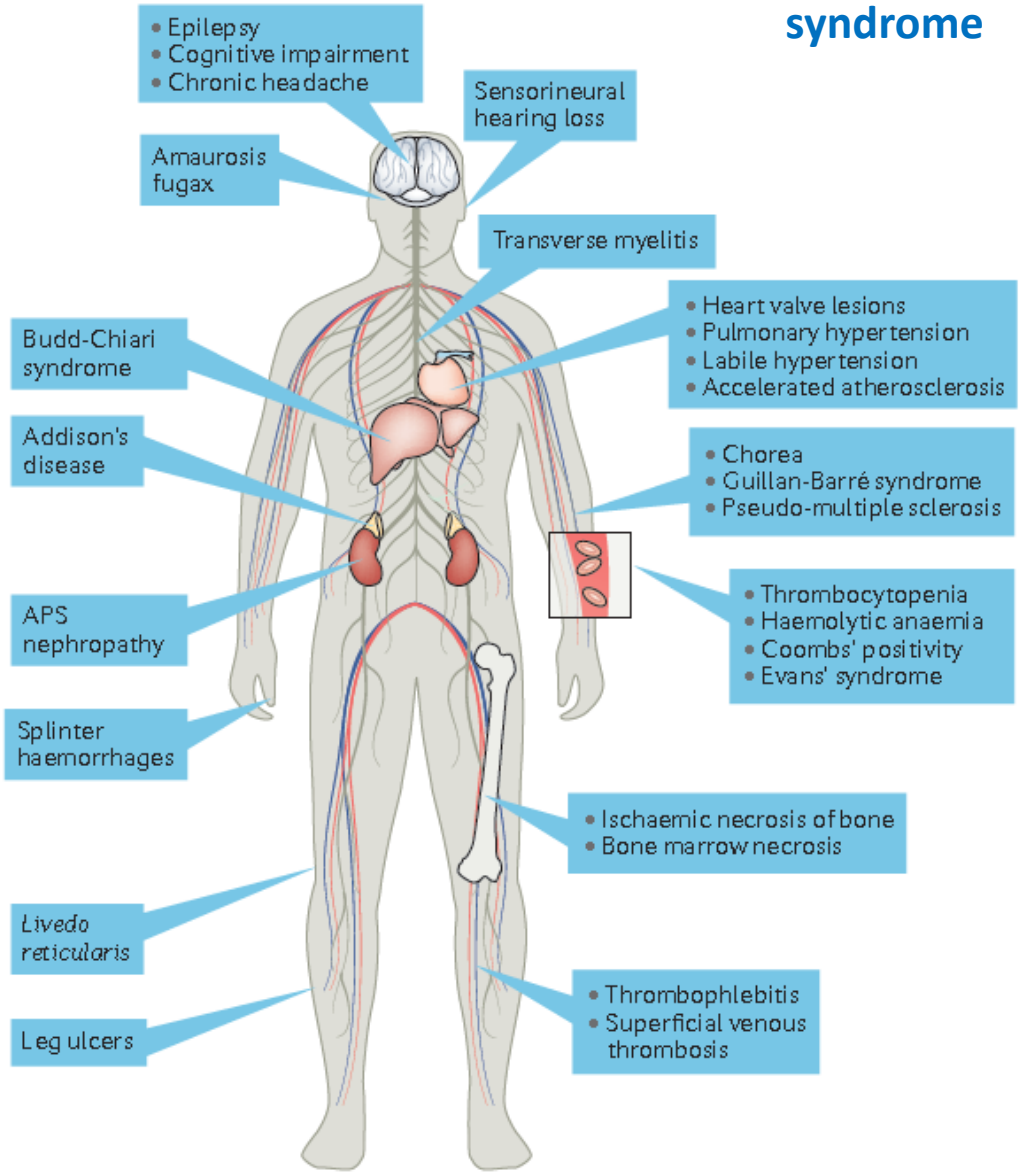
Reddish-violet reticular discoloration of the skin that mainly affects the limbs. It is caused by an interruption of blood flow in the dermal arteries, either due to spasm, inflammation, or vascular obstruction, and is associated with diseases of varying etiology and severity.





Thrombocytopenia, valvular heart disease (valve thickening, vegetations and regurgitation), antiphospholipid antibody-related nephropathy, livedo reticularis and skin ulcers are relatively common features of APS.

Extra-criteria clinical manifestations of antiphospholipid syndrome



APS

- APS is considered to be the most common acquired form of thrombophilia globally.
- Arteries, veins and the microvasculature can all potentially be affected by thrombosis, creating a vast set of clinical phenotypes observable in patients with APS.
- However, not all clinical features of APS can be explained by an underlying thrombosis; several other mechanisms such as inflammation, the complement pathway and platelet activation also have a role in the pathophysiology of the syndrome.
- Venous thromboembolic events were the most frequently observed clinical manifestation in a European cohort of 1,000 patients with APS.
- By contrast, cerebrovascular events were the most frequently observed arterial manifestation of APS.
- Pregnancy complications included recurrent (≥3) first trimester miscarriages, unexplained fetal death and premature birth before 34 weeks of gestation related to severe pre-eclampsia, eclampsia or placental insufficiency.

Box 2 | Main findings of the aPL Task Force on Clinical Manifestations

Below is a summary of the main findings of a review of the quality of evidence and available data for antiphospholipid antibodies (aPL), as presented at the 14th International Antiphospholipid Congress in Rio de Janeiro in 2014 (REFS 15,16).

Superficial vein thrombosis (SVT)
Low overall quality of evidence to support the suggestion that SVT is a result of antiphospholipid antibodies (aPL) or antiphospholipid syndrome (APS), unless other features of APS are present[15].

Thrombocytopenia
Low quality of evidence to support the inclusion of thrombocytopenia as a main clinical feature of APS in the classification criteria for APS. Thrombocytopenia does not reduce the risk of future thrombosis[15].

aPL-related nephropathy
Moderate quality of evidence to support the inclusion of biopsy-confirmed aPL-related nephropathy in the classification criteria for APS[146,147].

Valvular heart disease (VHD)
Moderate quality of evidence to support the inclusion of VHD in the APS classification criteria[15].

Livedo reticularis
Moderate quality of evidence to support the inclusion of *livedo reticularis* in the APS classification criteria[15].

Neurological manifestations
Neurological manifestations such as migraine, myelitis, seizures and chorea were analysed separately by the task force. There was moderate overall quality of evidence to support the suggestion that chorea and longitudinal myelitis, but not migraine or seizures, should be included in the APS classification criteria[15].

Clinical manifestations - thrombosis

- APS is a non inflammatory disease in which the most critical pathological process is thrombosis.
- Arterial or venous thrombosis, with or without a history of adverse pregnancy, can be present.
- As any organ and any size of vessel may be affected, the range of clinical features is extremely wide.

Thrombocytopenia

- The presence of thrombocytopenia is considered to be of critical importance when managing patients with APS.
- When the most frequent causes for thrombocytopenia have been ruled out, testing for aPL should be considered even in the absence of other aPL-related manifestations.
- Despite thrombocytopenia being commonly seen in patients with APS in clinical practice, overall, the evidence does not support its inclusion as a core clinical feature of the syndrome.
- aPL-related thrombocytopenia is rarely severe, more often being mild to moderate, and is usually associated with a minimal risk of bleeding.

Neurological manifestations
Central nervous system

- Very broad spectrum.
- Cerabral ischemia is the most common arhtrerial thrombotic manifestation.
- The age of onset of the cerebral ischemia in APS is several decades earlier than in the typical stroìke population and the ischaemic events may occur in any territory.
- A less common form of cerebral thrombotic disease associated with aPL is sagittal venous sinus thrombosis.

- Migraine is one of the most common complaints in patients with APS, but its associatioon with aPL is still controversial.

- Althouth the prevalence of headache is similar to that reported for the general population, aPL are significantly more prevalent in the group of patients with headache than in patients without.

- Cognitive deficits associated with APS may vary from mild neurocognitive disorders to severe vascular dementia.
- Patients often complain of poor concentration or forgetfulness.
- Verbal memory deficits, decreased psycomotor speed and decreased overall productivity have been correlated with aPL.
- Some patients with APS may exhibit features often seen in multiple sclerosis: myelitis, balance and sensory problems.

Heart

- Several cardiac condition have been associated with aPL.
- Heart valve lesions are the most common cardiac manifestarion.
- The prevalence have been reported in 35/75% of patients.
- The predominant functional abnormality is regurgitation, wherease stenosis is rare.
- Mitral valve is the most common affected site followed by aortic and tricuspid.

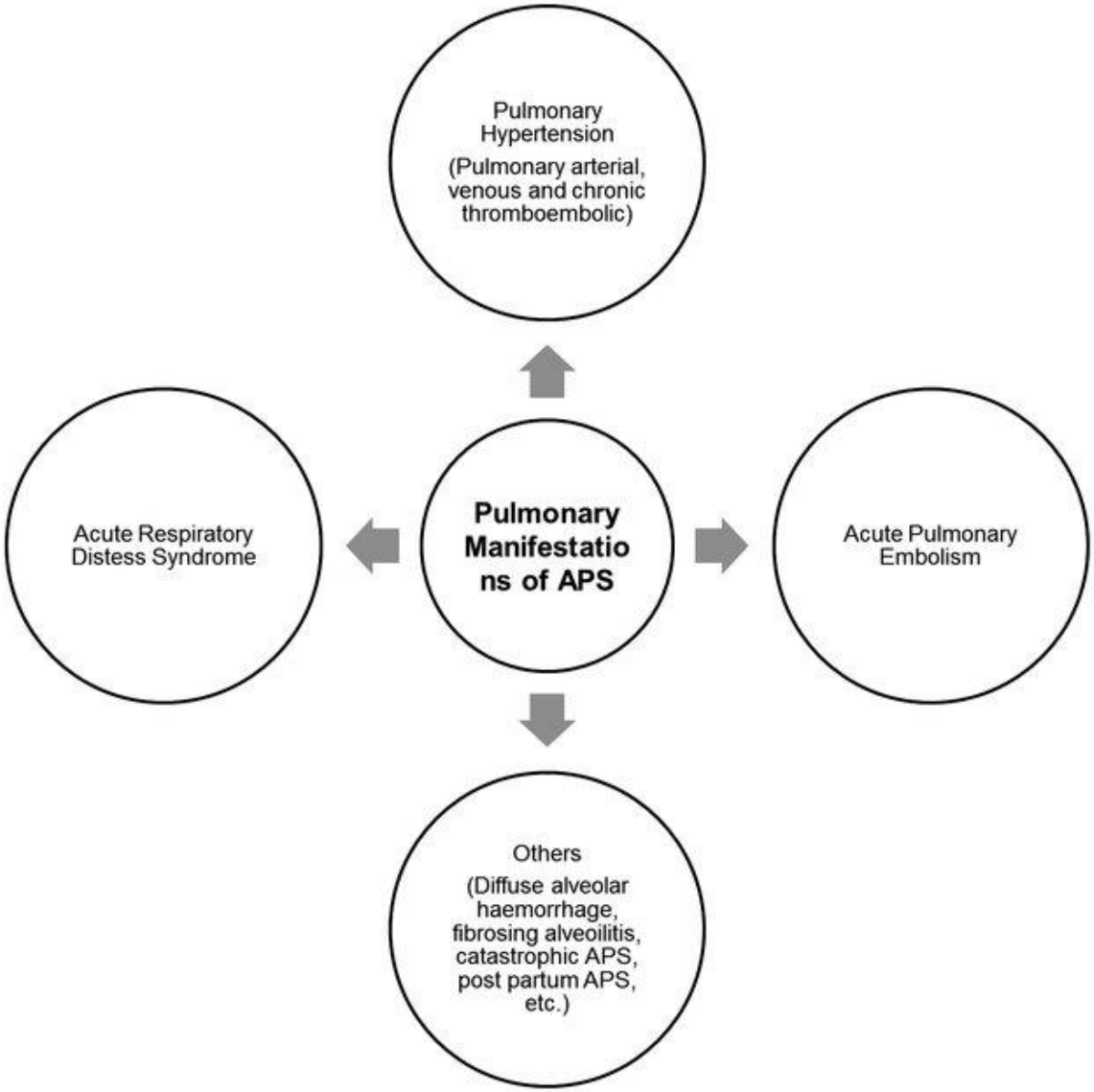
- Acute coronary syndromes are well documented.

- The association with sudden cardiac death and myocardial infarction is still debated.

Lungs

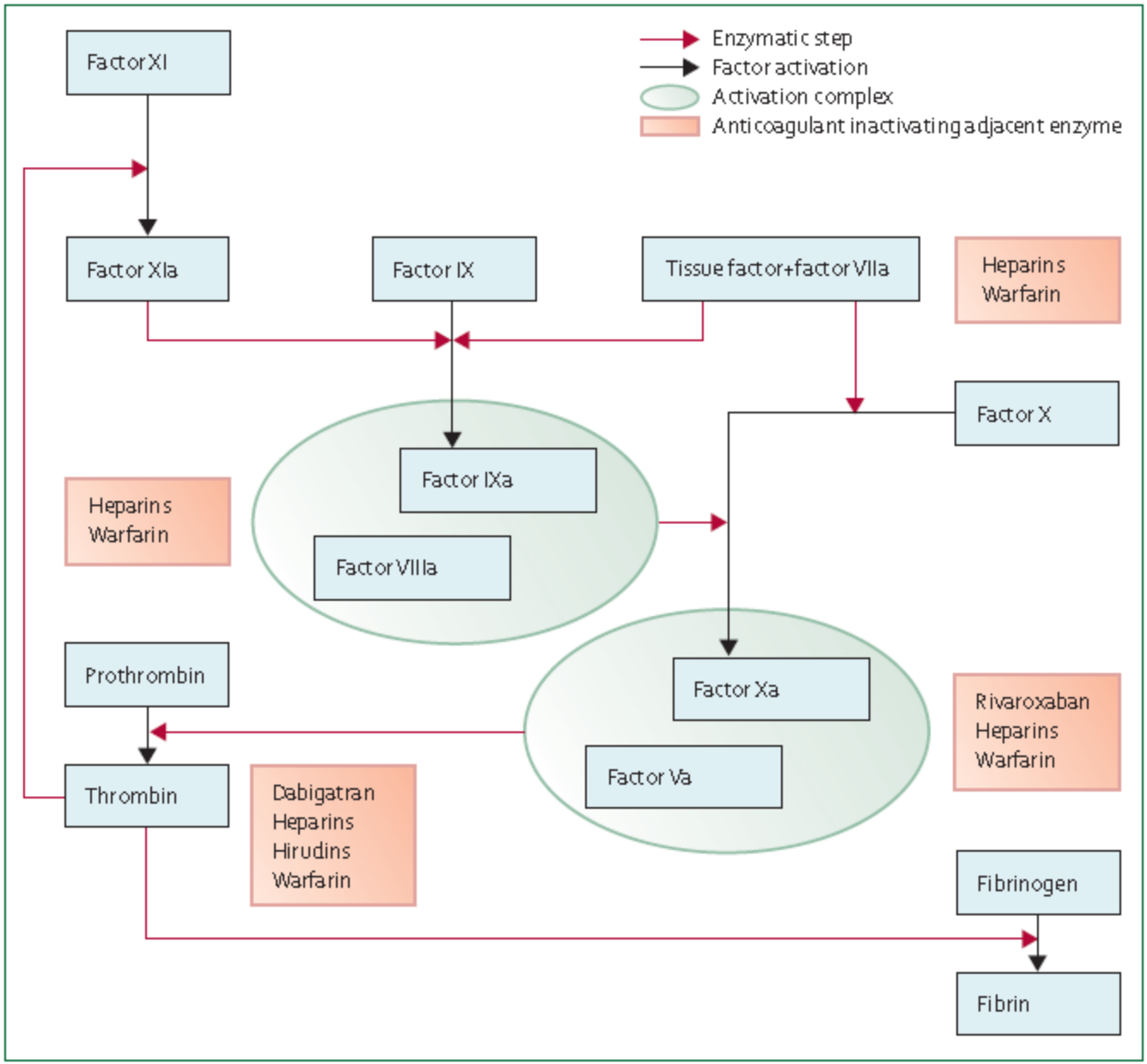
- Broad spectrum of pulmonary involvement.
- Pulmonary embolism and infarction.
- Pulmonary hypertension is found in around 1.8-3.5% of patients.

Pulmonary manifestations of antiphospholipid syndrome (APS)



Renal manifestations

- The kidneys are major targets for damage in APS and thrombotic events can occur in any vessel within the renal vasculature; clinical manifestations depend on the site and size of the vessels involved.
- A prompt recognition of renal involvement in APS could affect the outcome for the patient, so investigating renal involvement is critical for decision-making by physicians.
- Pathology is dominated by fibrin thrombi or by organizing thrombi with focal recanalization.
- Acute lesions often present as **thrombotic microangiopathy**, whereas chronic lesions can present as arteriosclerosis, fibrous intimal hyperplasia, focal cortical atrophy or fibrous obliteration of arteries and arterioles.
- Such lesions have been observed in patients with primary APS, as well as in patients with SLE who are aPL-positive (patients with SLE and secondary APS, and patients with SLE who are aPL-positive but do not have APS). Inflammation is rare in APS, creating a clear-cut distinction between renal manifestations that are APS-related and those caused by immune complex deposition (such as those seen in lupus nephritis), which is particularly important for patients with secondary APS.


Enzymatic step
Factor activation
Activation complex
Anticoagulant inactivating adjacent enzyme
Factor XI
Factor XIa
Factor IX
Tissue factor+factor VIIa
Heparins
Warfarin
Factor X
Factor IXa
Factor VIIIa
Heparins
Warfarin
Prothrombin
Factor Xa
Factor Va
Rivaroxaban
Heparins
Warfarin
Thrombin
Dabigatran
Heparins
Hirudins
Warfarin
Fibrinogen
Fibrin

CATASTROPHIC APS

International consensus for classification criteria

1. Clinical evidence of vessel occlusions affecting 3 or more organs or systems.
2. Development of the manifestations simultaneously or in less than a week.
3. Confirmation by histopathology of small vessel occlusion in at least one organ.
4. Serological confirmation of the presence of aPL (LA and/or aCL).

-**Definite catastrophic APS**: All 4 criteria.

-**Probable catastrophic APS**:

-1, 2 & 4

-1, 3 & 4 and the development of the third event in more than a week but less than a month, despite anticoagulation

Clinical risk scores - Other thrombotic risk factors

The presence of other cardiovascular risk factors are of great importance in predicting the risk of thrombosis in patients with APS, since these may

1) increase thrombotic risk
2) be modifiable.

While persistence and high levels of APLA are the major risk factor for thrombosis in APS, these patients may also have other risk factors that contribute to thrombotic risk.

Multiple other risk factors such as the presence of SLE, inherited thrombophilia, immobilization, pregnancy and atherosclerotic cardiovascular disease may also increase thrombotic risk.

Outcomes

The highest morbidity was attributed **to neurologic damage**, which was more common among patients with arterial thrombosis as an initial manifestation.

The “Euro-Phospholipid Project”, a 10-year survival rate of 91% was reported.

The main causes of death were thrombosis (36.5%) and infections (26.9%).

Patients with APS still develop significant morbidity and mortality despite current treatment (mainly oral anticoagulants and/or antiaggregant agents); therefore, it is imperative to increase the effort in determining optimal prognostic markers and therapeutic measures to prevent these important complications of the APS.

	Secondary prophylaxis
Patients with definite antiphospholipid syndrome and first venous event*	Indefinite anticoagulation to a target INR 2·0–3·0
Patients with definite antiphospholipid syndrome and arterial event*	Indefinite anticoagulation to a target INR 3·0–4·0 or combined antithrombotic treatment
Patients with definite antiphospholipid syndrome and recurrent events despite warfarin with a target intensity of 2·0–3·0	Indefinite anticoagulation to a target INR 3·0–4·0 or alternative therapies such as extended therapeutic dose low-molecular-weight heparin
Patients with venous thromboembolism with single positive or low-titre antiphospholipid antibodies	As per usual recommendations for deep vein thrombosis treatment
Patients with arterial thrombosis with single positive or low-titre antiphospholipid antibodies	As per usual recommendations for arterial thrombosis

INR=international normalised ratio. *Less aggressive or long-lasting antithrombotic treatments might be appropriate in low-risk patients.

Table 1: **Recommendations for secondary prophylaxis in patients with antiphospholipid antibodies and thrombosis**

	Primary thromboprophylaxis
Patients with systemic lupus erythematosus and lupus anticoagulant and/or persistently positive anticardiolipin	Hydroxychloroquine and consider low-dose aspirin
Patients with obstetric antiphospholipid syndrome	Low-dose aspirin or no therapy
Asymptomatic carriers of antiphospholipid antibodies	No therapy or low-dose aspirin
All patients with antiphospholipid antibodies	Strict control of vascular risk factors
High-risk situations (surgery, post partum, long-lasting immobilisation)	Adequate thrombophylaxis

Table 2: **Primary thromboprophylaxis in patients with antiphospholipid antibodies**

	Regimen
Antiphospholipid syndrome without previous thrombosis and recurrent early (pre-embryonic or embryonic) miscarriage	Low-dose aspirin alone or together with either unfractionated heparin (5000–7500 IU subcutaneously every 12 h) or LMWH (usual prophylactic doses)
Antiphospholipid syndrome without previous thrombosis and fetal death (more than 10 weeks' gestation) or previous early delivery (<34 weeks gestation) due to severe pre-eclampsia or placental insufficiency	Low-dose aspirin plus: • Unfractionated heparin (7500–10000 IU subcutaneoulsy every 12 h in the first trimester; 10000 U subcutaneously every 12 h in the second and third trimesters, or every 8–12 h adjusted to maintain the mid-interval aPTT* 1·5 times the control mean) • LMWH (usual prophylactic doses)
Antiphospholipid syndrome with thrombosis	Low-dose aspirin plus: • Unfractionated heparin (subcutaneously every 8–12 h adjusted to maintain the mid-interval aPTT* or heparin concentration (anti-Xa activity)* in the therapeutic range) • LMWH (usual therapeutic dose—eg, enoxaparin 1 mg/kg subcutaneously, or dalteparin 100 U/kg subcutaneously every 12 h, or enoxaparin 1·5 mg/kg/day subcutanously, or dalteparin 200 U/kg/day subcutaneously)†

aPTT= activated partial thromboplastin time. LMWH=low-molecular-weight heparin. *Women without a lupus anticoagulant in whom the aPTT is normal can be monitored with the aPTT. Women with lupus anticoagulant should be monitored with antifactor Xa activity. †Need for dose adjustments over the course of pregnancy remains controversial.[91] Some experts argue that in the absence of better evidence, it is prudent to monitor anti-factor Xa LMWH concentrations 4–6 h after injection with dose adjustment to maintain a therapeutic antifactor Xa concentration (0·6 to 1·0 U/mL if a twice-daily regimen is used; slightly higher if a once-daily regimen is chosen).

Table 3: **Suggested regimens for the treatment of antiphospholipid syndrome in pregnancy**

Panel 3: Potential future therapies for antiphospholipid syndrome

- Combination antiaggregant therapy (low-dose aspirin plus clopidogrel or dipyridamole)
- Oral antifactor Xa drugs (rivaroxaban, apixaban)
- Direct thrombin inhibitors (dabigatran)
- Statins (fluvastatin, rosuvastatin)
- Hydroxychloroquine
- B-cell depletion (rituximab)