Current View of the Treatment of Antiphospholipid Syndrome

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Antiphospholipid antibodies

- 40% of SLE patients
  → 40% thrombosis

- Recurrent miscarriages = 1% of the population
  → 10% = APS

Anticardiolipin antibodies can be found in 2% to 5% of a normal population

These antibodies increase in prevalence with increasing age, with IgG and IgM aCL being observed in 12% to 52% of an elderly population
Panel 1: Clinical manifestations of antiphospholipid syndrome

Frequent (>20% of cases)
- Venous thromboembolism
- Thrombocytopenia
- Miscarriage or fetal loss
- Stroke or transient ischaemic attack
- Migraine
- Livedo reticularis

Less common (10-20% of cases)
- Heart valve disease
- Pre-eclampsia or eclampsia
- Premature birth
- Haemolytic anaemia
- Coronary artery disease

Unusual (<10% of cases)
- Epilepsy
- Vascular dementia
- Chorea
- Retinal artery or vein thrombosis
- Amaurosis fugax
- Pulmonary hypertension
- Leg ulcers
- Digital gangrene
- Osteonecrosis
- Antiphospholipid syndrome nephropathy
- Mesenteric ischaemia

Rare (<1% of cases)
- Adrenal haemorrhage
- Transverse myelitis
- Budd-Chiari syndrome
Classification for this syndrome needed at least one clinical manifestation
together with positive tests for circulating antiphospholipid antibodies, including lupus anticoagulant or anticardiolipin, or both, at medium-high values, detected at least twice in 6 weeks.

SYDNEY REVISION OF SAPPORO CRITERIA (2006)

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.

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.
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-glycoprotein 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.
Main modifications

- Time elapsed between two positive determinations = **12 weeks** to assure the detection of persistent antibodies only; and anti-β2-glycoprotein 1,

- Both anti-β2-glycoprotein 1 IgG and IgM,

- Medium titres of anticardiolipin, or anti-β2-glycoprotein 1 > than the 99th percentile.
Non-APS criteria antiphospholipid antibodies

- Anticardiolipin IgA
- Anti-β2GPI IgA
- Antiphosphatidylserine
- Antiphosphatidylethanolamine
- Prothrombin alone (aPT-A)
- Phosphatidylserine-prothrombin (aPS/PT) complex
Preliminary criteria for the classification of catastrophic APS

1. Evidence of involvement of three or more organs, systems, or tissues.

2. Development of manifestations simultaneously or in less than a week.

3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue.

4. Laboratory confirmation of the presence of antiphospholipid antibodies
Management of thrombosis
Management of thrombosis

• **secondary thromboprophylaxis:** patients with APS who have already had a thrombotic event and antiphospholipid Abs

• **primary thromboprophylaxis:** antibody carriers without previous thrombosis, which can be either
  - purely asymptomatic individuals,
  - patients with systemic lupus erythematosus,
  - or women with obstetric APS
Secondary thromboprophylaxis in APS

2 key issues:
• arterial and venous events should be treated differently?

• APS same treatment as the general population?
Secondary thromboprophylaxis in APS

Management of Antiphospholipid Antibody Syndrome
A Systematic Review

Wendy Lim, MD
Mark A. Crowther, MD
John W. Eikelboom, MBBS

JAMA. 2006;295:1050-1057
Secondary thromboprophylaxis in APS

Patients With Antiphospholipid Antibodies*

*Importance of transient antiphospholipid antibodies is uncertain.
Secondary thromboprophylaxis in APS

Table 1. Summary of selected studies

<table>
<thead>
<tr>
<th>Author, year (ref.)</th>
<th>No.</th>
<th>Type of study</th>
<th>Sapporo criteria for aPL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosove, 1992 (12)</td>
<td>70</td>
<td>Retrospective cohort</td>
<td>No</td>
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<tr>
<td>Derksen, 1993 (24)</td>
<td>19</td>
<td>Retrospective cohort</td>
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<td>Khamashta, 1995 (13)</td>
<td>147</td>
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<td>Krcic-Barrie, 1997 (25)</td>
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<tr>
<td>Munoz-Rodriguez, 1999 (14)</td>
<td>47</td>
<td>Retrospective cohort</td>
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<tr>
<td>Ruiz-Irastorza, 2002 (15)</td>
<td>66</td>
<td>Retrospective cohort</td>
<td>Yes</td>
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<tr>
<td>Wittkowsky, 2006 (27)</td>
<td>36</td>
<td>Retrospective cohort</td>
<td>Yes</td>
</tr>
<tr>
<td>Giron-Gonzalez, 2004 (23)</td>
<td>158</td>
<td>Prospective cohort</td>
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<tr>
<td>Ames, 2005 (17)</td>
<td>67</td>
<td>Prospective cohort</td>
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<td>Ginsberg, 1995 (19)</td>
<td>16</td>
<td>Prospective cohort subgroup analysis</td>
<td>No</td>
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<td>Prandoni, 1996 (20)</td>
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<td>Retrospective cohort subgroup analysis</td>
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<td>Rance, 1997 (26)</td>
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<td>Retrospective cohort subgroup analysis</td>
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<tr>
<td>Schulman, 1998 (21)</td>
<td>68</td>
<td>RCT subgroup analysis</td>
<td>No</td>
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<tr>
<td>Levine, 2004 (22)</td>
<td>720</td>
<td>RCT subgroup analysis</td>
<td>No</td>
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<td>Crowther, 2003 (16)</td>
<td>114</td>
<td>RCT</td>
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</tr>
<tr>
<td>Finazzi, 2005 (18)</td>
<td>109</td>
<td>RCT</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* aPL = antiphospholipid antibodies; RCT = randomized controlled trial.
† Six unspecified events.
‡ Eighteen patients died at the time of the presenting event and were not subject to followup.
Secondary thromboprophylaxis in APS

<table>
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<tr>
<th>Author, year (ref.)</th>
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<th>Type of study</th>
<th>Sapporo criteria for aPL</th>
<th>Thrombotic events at diagnosis, arterial/venous</th>
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<tr>
<td>Rosove, 1992 (12)</td>
<td>70</td>
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<td>No</td>
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<td>Derksen, 1993 (24)</td>
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<td>Wittkowsky, 2006 (27)</td>
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<td>Retrospective cohort</td>
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<tr>
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<td>RCT</td>
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<td>RCT</td>
<td>Yes</td>
<td>44/75</td>
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</table>

* aPL = antiphospholipid antibodies; RCT = randomized controlled trial.
† Six unspecified events.
‡ Eighteen patients died at the time of the presenting event and were not subject to followup.
A Systematic Review of Secondary Thromboprophylaxis in Patients With Antiphospholipid Antibodies

GUILLERMO RUIZ-IRASTORZA,¹ BEVERLEY J. HUNT,² AND MUNther A. KHAMASHTA²
# Secondary thromboprophylaxis in APS recommendations

<table>
<thead>
<tr>
<th>Patients with definite antiphospholipid syndrome and first venous event*</th>
<th>Indefinite anticoagulation to a target INR 2.0–3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with definite antiphospholipid syndrome and arterial event*</td>
<td>Indefinite anticoagulation to a target INR 3.0–4.0 or combined antithrombotic treatment</td>
</tr>
<tr>
<td>Patients with definite antiphospholipid syndrome and recurrent events despite warfarin with a target intensity of 2.0–3.0</td>
<td>Indefinite anticoagulation to a target INR 3.0–4.0 or alternative therapies such as extended therapeutic dose low-molecular-weight heparin</td>
</tr>
<tr>
<td>Patients with venous thromboembolism with single positive or low-titre antiphospholipid antibodies</td>
<td>As per usual recommendations for deep vein thrombosis treatment</td>
</tr>
<tr>
<td>Patients with arterial thrombosis with single positive or low-titre antiphospholipid antibodies</td>
<td>As per usual recommendations for arterial thrombosis</td>
</tr>
</tbody>
</table>

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 in AP(S)

- The risk of thrombosis among healthy patients with antiphospholipid antibody (1% per year).
  


- Among 552 randomly selected blood donors, no thrombotic events were observed after 12 months of follow-up among patients found to have aCL.
  
Primary thromboprophylaxis in AP(S)


- no difference between asymptomatic antiphospholipid antibody carriers given low-dose aspirin and those given placebo
- rate of thrombosis in patients given placebo was zero,
- study was underpowered to detect a beneficial effect of aspirin.
Primary thromboprophylaxis in APS

- Observational studies have consistently shown a protective effect of aspirin in asymptomatic antiphospholipid antibody carriers with systemic lupus erythematosus

- Risk of severe hemorrhages under aspirin ~1%
Primary thromboprophylaxis in APS

Patients With Antiphospholipid Antibodies

Prior Thrombosis?

No

Pregnant?

No

No Treatment or Low-Dose Aspirin
In patients with SLE, the incidence of thrombosis was 2 per 100 person-years in a prospective cohort of 551 patients of whom 49% had either LA or aCL.

Primary thromboprophylaxis in APS

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

Table 2: Primary thromboprophylaxis in patients with antiphospholipid antibodies
Stratification according to the immunological profile?

AP patients with triple positivity for lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein 1 are at the highest risk for venous and arterial thrombosis and for obstetric complications.
Pregnancy management

- preconception counselling
- complete profile of antiphospholipid antibodies
- frequent prenatal visits
- uterine and umbilical artery Doppler assessments
Pregnancy management

Classify pregnant women in one of the following groups:

1. **recurrent early miscarriage** and no other features of APS,

2. **one or more previous fetal deaths** (at more than 10 weeks’ gestation) or previous early delivery (at less than 34 weeks’ gestation) because of severe pre-eclampsia or placental insufficiency.

Pregnancy management

1. Patients With Antiphospholipid Antibodies
   - Prior Thrombosis?
     - No
       - Yes
         - Consider Prophylactic Unfractionated Heparin or Low-Molecular-Weight Heparin Plus Aspirin, Particularly if Prior Pregnancy Loss
     - No
       - Pregnant?
         - Yes
           - Consider Prophylactic Unfractionated Heparin or Low-Molecular-Weight Heparin Plus Aspirin, Particularly if Prior Pregnancy Loss
         - No

2. Strength of Evidence
   - A Strong
   - B Moderate
   - C Weak
### Pregnancy management

<table>
<thead>
<tr>
<th>Antiphospholipid syndrome without previous thrombosis and recurrent early (pre-embryonic or embryonic) miscarriage</th>
<th>Low-dose aspirin alone or together with either unfractionated heparin (5000-7500 IU subcutaneously every 12 h) or LMWH (usual prophylactic doses)</th>
</tr>
</thead>
</table>
| 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 (7500–10 000 IU subcutaneously every 12 h in the first trimester; 10 000 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 subcutaneously, 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. Some experts argue that in the absence of better evidence, it is prudent to monitor antifactor 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
Traitement du CAPS

- Pronostic vital engagé ?
  - NON
  - Héparine IV + corticothérapie
  - Amélioration ?
    - OUI
      - INTENSIFICATION THÉRAPEUTIQUE
        - Cyclophosphamide si poussée lupique
        - ou Prostacycline
        - ou Fibrinolytiques
  - NON
    - OUI
      - ↓ Corticothérapie + AVK
    - NON

- Traitement des facteurs déclenchant (ex. : antibiothérapie)
  - Héparine IV + corticothérapie IV +/- IgIV +/- Échanges plasmatiques
  - Amélioration ?
    - OUI
    - NON
Future therapies
Future therapies

VOIE INTRINSEE

VOIE EXTRINSEE

AVK

Protéine C

Protéine C activée

IIa, PS, thrombomoduline

PL

aPL

Dabigatran
Ximelagatran
Hirudines

FIBRINOLYSE

TPA

Fibrine soluble

Fibrinogène

Fibrine insoluble

Plasmine

Plasminogène

PDF

L.A.
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)
Future therapies
Future therapies

Inhibition of Complement

• Circulating levels of C' components are lower in APS.

• Reduced expression of DAF + greater deposition of C3 and C4 components in endometrial tissue from aPL-positive women with recurrent miscarriage.


Inhibition of Complement

• **C3 and C9 colocalisation with aPL in the mesenteric vessels of a rat model of thrombosis.** Fischetti F. Thrombus formation induced by antibodies to beta2-glycoprotein I is complement dependent and requires a priming factor. Blood 2005;106:2340-6

• **Blocking C3, C4 or C5 by molecular inhibitors or gene knockout prevents fetal loss driven by aPL in vivo.** Girardi G Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. J Clin Invest 2003;112:1644-54

• **Anti-C5 monoclonal antibodies inhibit aPL-mediated thrombosis in mouse.** Pierangeli SS, Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia. Arthritis Rheum 2005;52:2120-4

• **C5a receptor antagonist peptide inhibits aPL-driven in vivo thrombosis and ex vivo TF expression and activity in mice.** Pierangeli SS, Antiphospholipid syndrome treatment beyond anticoagulation: are we there yet? Lupus 2010;19:475-85
Future therapies

Rituximab

• **Decrease of ApL**


Future therapies

- **Inhibition of ApL binding through beta(2)-glycoprotein I**


Future therapies
Inhibition of GPIIb/IIIa receptor

aPL promote upregulation of the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor on activated platelets exposing negative phospholipids

GPIIb/IIIa receptor antagonist prevents aPL-induced thrombosis in a well-characterised mouse microcirculation model of thrombotic APS,

GPIIb/IIIa-knockout mice were protected from aPL-related pathogenesis

Pierangeli SS. Intracellular signaling triggered by antiphospholipid antibodies in platelets and endothelial cells: a pathway to targeted therapies. Thromb Res 2004;114:467-76
Future therapies

• in vitro evidence that aPL drive activation of both NF-kB and p38MAPK

Dunoyer-Geindre S, NFkappaB is an essential intermediate in the activation of endothelial cells by anti-beta2-glycoprotein I antibodies. Thromb Haemost 2002;88:851-7


Vega-Ostertag M. Involvement of p38 MAPK in the up-regulation of tissue factor on endothelial cells by antiphospholipid antibodies. Arthritis Rheum 2005;52:1545-54
**Future therapies**

**Statins**

• **In vitro, fluvastatin and to a lesser extent simvastatin inhibit aPL-induced endothelial cell activation**

Meroni PL. Statins prevent endothelial cell activation induced by antiphospholipid (anti-beta2-glycoprotein I) antibodies: effect on the proadhesive and proinflammatory phenotype. Arthritis Rheum 2001;44:2870-8


• **In vivo fluvastatin and pravastatin prevent aPL-mediated thrombosis and inflammation and pregnancy loss.**


Fluvastatin reduces inflammatory proteins in monocytes from patients with the APS and aPL-positive asymptomatic patients. Pierangeli SS, Lupus 2010;19:475-85
Conclusions

- Better definition of the disease
- Better indications of the treatment
- Stratification of the risk
- Lack of RCT
- Future therapies?