Antiphospholipid syndrome: an update on managing thrombosis 2019

Prof Beverley Hunt
Thrombosis & Haemostasis, King’s College & Guy’s & St Thomas’ Trust, London
Medical Director of Thrombosis UK
Twitter @bhwords
The difficulties in managing APS

- A “new” disease
- Diagnosis - protean symptoms and signs
- Assays are not clear cut
- Consensus on antithrombotic management?
- ?DOACs
- Pregnancy – gathering evidence
- Pathogenesis?!
Clinical manifestation of antiphospholipid syndrome

- Stroke
- Epilepsy
- Vascular dementia
- Pulmonary emboli
- Pulmonary hypertension
- Portal vein thrombosis
- Budd-Chiari syndrome
- Pregnancy morbidity
- Livedo reticularis
- Osteonecrosis
- Digital gangrene
- Retinal vein thrombosis
- Amaurosis fugax
- Heart valve disease
- Coronary artery disease
- Adrenal thrombosis
- Thrombocytopenia
- Deep vein thrombosis
- Chorea
- Leg ulcers

Images courtesy of Y. Shoenfeld


The antiphospholipid (Hughes) syndrome

- Definition: A persisting antiphospholipid antibody associated with thrombosis &/or pregnancy morbidity
- Used to consider:
  - PRIMARY isolated
  - SECONDARY associated with another autoimmune disease, usually SLE, also myaesthenia gravis, rheumatoid arthritis
  - But nw considered “just another autoimmune disease”
- It is a MULTISYSTEM disorder -skin, valves, thrombocytopenia etc
Characteristics of aPL–related thromboses

1) Thrombosis without inflammation
2) Affects ANY vascular bed
   - Venous
   - Microvascular
   - Arterial
   - Placental
3) Recurrent thromboses tend to occur in the SAME vascular bed
4) aPL promote atherosclerosis in some patients (hyperlipidaemia)
5) Each patient has their own syndrome, not always full house.
Figure 1 Pathophysiology of antiphospholipid antibody-associated thrombosis

APS is a multisystem disorder

10-20% have livedo reticularis

30% have cardiac valve abnormalities but rarely haemodynamic problems

Mild thrombocytopenia (plt >80 x 10^9/l) is a common feature

......and evidence of other autoimmune disease
- lupus
- 12% have positive Coombs test
- thyroid disease
- coeliac disease, ITP etc
Livedo legs in a case of Sneddon’s syndrome
Neurological aspects of APS

Large vessel
• Stroke and TIA (+ livedo = Sneddon’s syndrome)
• Sinus thromboses

Medium sized vessels
• Ophthalmic - central retinal artery & venous occlusion
• Lacunar infacts

Microvascular
• Sudden sensineural deafness
• Cerebral leakoaraiosis
• Multiple sclerosis-like illness
• Ischaemic retinopathy

Any damage - Epilepsy
Ischaemic leukoaraiosis in APS

MB, 44yo Male

- Lupus anticoagulant positive (2017 & 2018)
- ACL and anti-B2GP antibody ELISA negative
Detecting antiphospholipid antibodies

• Definition- 2 positive tests on two occasions more than 12 weeks apart
• Either a lupus anticoagulant &/or anticardiolipin antibodies &/or anti-β2 glycoprotein I antibodies
• Anti β2-glycoprotein-I antibodies (added in 2006)- how useful is this in reality?
• aPL often interfere with other functional thrombophilia assays -Protein C, antithrombin.
• Frequently low free Protein S
Anti-beta2 glycoprotein I adds little to routine testing in patients with previous thrombosis but important in

1) defining those who are “triple positive”

2) pregnancy where a significant subset that are only positive for anti-beta2 glycoprotein I

Galli Thromb Haemost 2002; 88: 729-32
CRITERIA FOR LUPUS ANTICOAGULANTS

Detect antibodies that inhibit in vitro phospholipid coagulation reactions

1. Prolongation of a phospholipid dependant clotting test (usually APTT).
2. There should be a relative correlation of the defect by the addition of phospholipids.
3. Clotting time of a mixture of test and normal plasma should be longer than the clotting time of normal plasma (how true? Only 25% in our patients).
Interpreting lupus anticoagulant testing using the dilute Russell viper venom (RVV) test

All stages are dependent on phospholipid thus if aPL present, they will remove phospholipid and prolong the clotting time.
Interpreting lupus anticoagulant testing using the dilute Russell viper venom (RVV) test

If aPl is removed by adding fragmented platelets then this will remove aPL and clotting time will correct to normal.
Laboratory lupus anticoagulant testing

- APTT tests vary in their sensitivity to LA concentration of phosphatidyl serine
- Guidelines  
- NEQAS have shown 18% of labs failed to detect LA
  Jennings Brit J Haem 2002; 119: 364-69
- Need for international reference & standardisation material
NON PATHOGENIC ANTIPHOSPHOLIPID ANTIBODIES
(ANTI-B$_2$GPI NEGATIVE)

Drugs
- Procainamide, hydralazine, beta blockers
- Quinine
- Phenothiazines, phenytoin
- Alpha interferon

Infectious disease
- Syphilis, Lyme disease
- Tuberculosis
- Bacterial endocarditis
- Mycoplasma pneumonia
- HIV
- Hepatitis A/B/C virus
- B19 parvovirus
Predicting risk of thrombosis in APS

• Lupus anticoagulant higher risk of thrombosis than ACA (Galli 2002)

• High titre ACA > risk than low titre ACA

• Triple positivity > double > single (LA/ACA/antibeta2GPI) (Pengo 2010)
When to treat thrombotic APS?

Two positive aPL 12 weeks apart &

a thrombotic event proven by imaging

MR direct thrombus imaging in comparison to venography in imaging DVT
Management of thrombosis in APS

- Our old data (1995) - 70% risk of recurrent thrombosis - but tertiary centre seeing v worse cases
- Long-term oral anticoagulation for unprovoked thrombosis target INR of 3-4 especially arterial or microvascular disease

- Regular follow-up
- Vigorously treat atherogenic risk factors
Figure 1. Kaplan–Meier Analysis of the Interval from Each Episode of Thrombosis or Change in Treatment to the Next Episode of Thrombosis or Censoring Event in the Same Patient, Throughout the Follow-up Period, According to Antithrombotic Treatment.

The total number of such intervals for the patients while they were receiving each treatment is shown after each curve. INR denotes international normalized ratio.
Comparison of two intensities of warfarin
Crowther et al. New Engl J 2003; 349: 1133-8

• Randomised, double-blind study
• 114 patients randomised to INR 2-3 & 3-4 for 2.7 years
• Thrombosis rate 10.7% & 3.4% 9 no significant difference
• Bleeding rate: no difference

• Recommended INR target of 2-3

• BUT
Comparison of two intensities of warfarin
Crowther et al. New Engl J 2003; 349: 1133-8

- Patients were excluded if previous warfarin failure: recurrent thromboses at INR 2-3

- Only 20% of patients had previous arterial thrombotic events

- At high intensity INR, treatment failures occurred usually when INR <3.0, yet analysed according to intention to treat.

- 10% were also taking aspirin
Our management of thrombotic APS in 2018

Previous unprovoked venous thrombosis:
Target INR 2-3

Previous provoked VTE: short term anticoagulation

Previous arterial thrombosis & recurrent VTE:
Target INR 3-4
Risk benefit analysis of warfarin in APS

66 pts with previous thrombosis & INR 3-4.
Recurrent thrombosis 9.1/100 pt years
(INRs 2--2.5 at time of event).
Risk of major bleed 6/100 pt years
(Intracranial 1.5/100 pt years).

Risks similar to other groups of patients treated at lower target INRS.
The INR in APS patients - “a nightmare”

Day-day monitoring
• Anticoagulant clinics concern re “high” INRs & some patient knows when INR is too low!

Secondary APS have changing polypharmacy (NSAIDs, antimalarials,
• INR affected by thromboplastin? (recomb relipidated TF)
• Self monitoring, different method, many not reliable in APS patients

Clinical decisions
• When to stop?
• Pregnancy
• Thrombocytopenia - continue unless platelet count <70
• What to do when oral anticoagulation fails?
Healthy patients with antiphospholipid antibodies

- No evidence-base
- Offer regular review
- Maximise lifestyle choices and reduce obesity
- Thromboprophylaxis at time of haemostatic stress
- Contraception - POP, Depo-Provera, Mirena coil, no HRT
- ALIPAS – ARC study – open comparison of low dose warfarin v aspirin closed due to poor recruitment
- PLEASE DON’T GIVE ASPIRIN!
<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>Aspirin (\text{no. of deaths/total no. of participants})</th>
<th>Placebo (\text{no. of deaths/total no. of participants})</th>
<th>Hazard Ratio for All-Cause Mortality (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>BMDT (1988)</td>
<td>270/3429</td>
<td>151/1710</td>
<td>0.89 (0.74–1.08)</td>
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<tr>
<td>PHS (1989)</td>
<td>217/11,037</td>
<td>227/11,034</td>
<td>0.96 (0.80–1.14)</td>
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<tr>
<td>ETDRS (1992)</td>
<td>340/1856</td>
<td>366/1855</td>
<td>0.93 (0.81–1.06)</td>
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<tr>
<td>HOT (1998)</td>
<td>284/9399</td>
<td>305/9391</td>
<td>0.93 (0.79–1.09)</td>
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<tr>
<td>TPT (1998)</td>
<td>113/1268</td>
<td>110/1272</td>
<td>1.03 (0.80–1.32)</td>
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<tr>
<td>PPP (2001)</td>
<td>62/2226</td>
<td>78/2269</td>
<td>0.81 (0.58–1.13)</td>
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<td>WHS (2005)</td>
<td>609/19,934</td>
<td>642/19,942</td>
<td>0.95 (0.85–1.06)</td>
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<td>JPAD (2008)</td>
<td>34/1262</td>
<td>38/1277</td>
<td>0.91 (0.57–1.43)</td>
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<td>POPADAD (2008)</td>
<td>94/638</td>
<td>101/638</td>
<td>0.93 (0.72–1.21)</td>
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<tr>
<td>AAA (2010)</td>
<td>176/1675</td>
<td>186/1675</td>
<td>0.95 (0.78–1.15)</td>
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<tr>
<td>JPPP (2014)</td>
<td>297/7220</td>
<td>303/7244</td>
<td>0.98 (0.84–1.15)</td>
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<tr>
<td>ASCEND (2018)</td>
<td>748/7740</td>
<td>792/7740</td>
<td>0.94 (0.85–1.04)</td>
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<tr>
<td>ARRIVE (2018)</td>
<td>160/6270</td>
<td>161/6276</td>
<td>0.99 (0.80–1.24)</td>
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<tr>
<td>ASPREE (2018)</td>
<td>558/9525</td>
<td>494/9589</td>
<td>1.14 (1.01–1.29)</td>
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Overall \( (I^2=0\%, P=0.67) \)

<table>
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<tr>
<th></th>
<th>0.75</th>
<th>1.0</th>
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<tr>
<td>Aspirin</td>
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<tr>
<td>Placebo</td>
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Aspirin Better Placebo Better
Catastrophic APS


Definition: acute, multiple vascular occlusions associated with high titre aPL
Rare. Precipitated by infection, surgery.
High mortality despite Rx (50%)

Management: plasma exchange, anticoagulation (argatroban), intravenous gammaglobulin, cyclophosphamide
Future management of thrombotic disease in APS

• Improving imaging – MR direct thrombus imaging, CT/VQ Spect

• Intervention radiology- stenting to relieve post thrombotic syndrome

• Ritoximab - no

• Stem cell transplantation- no

• DOACs – probably not…
TRAPS
Randomized controlled trial of Rivaroxaban vs Warfarin in APS

High-risk APS patients
- LA positive
- aCL positive
- aB2GPI positive

Rivaroxaban N=59

Warfarin N=61

1,5 years

Events on Rivaroxaban: 19%

Events on Warfarin: 3%

Stopped early for excess of events on Rivaroxaban

Vittorio Pengo et al. Blood 2018;132:1365-1371
Cumulative incidence of events (death, thromboembolic events, and major bleeding) in the rivaroxaban group (dotted and dashed line) and in the warfarin group (solid line).

Vittorio Pengo et al. Blood 2018;132:1365-1371

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Cumulative incidence of events (death, thromboembolic events, and major bleeding) in the rivaroxaban group (dotted and dashed line) and in the warfarin group (solid line).

Rivaroxaban
11 events (+2)
- Stroke 4
- MI 3
- Bleeds 4

Warfarin
2 events
Both bleeds

Vittorio Pengo et al. Blood 2018;132:1365-1371
Increased risk of thrombosis in APS patients treated with DOACs. Results from an international patient-level data meta-analysis.


- 47 trials & 447 patients
- Rivaroxaban (n=290), dabigatran (144), apixaban (13)
- 73 (16%) had recurrent thrombosis
- Triple positive highest risk (56%)
- Previous arterial thrombosis (32%)
- DOACs NOT FOR ROUTINE USE IN APS
DOACS & APS

• DOACs should not be used in APS

• ……Unless had an unprovoked VTE, treated with DOAC from start, doing well & later found to be aPL single or double positive?

• New trial RisAPS (sponsored by ARC) will look at high dose rivaroxaban (15mg bd) vs, warfarin in cerebral APS
APS

- Complex to diagnose
- Complex to treat

But rewarding outcomes!