

Antiphospholipid Antibody Syndrome (APS)

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ISTH Workshop

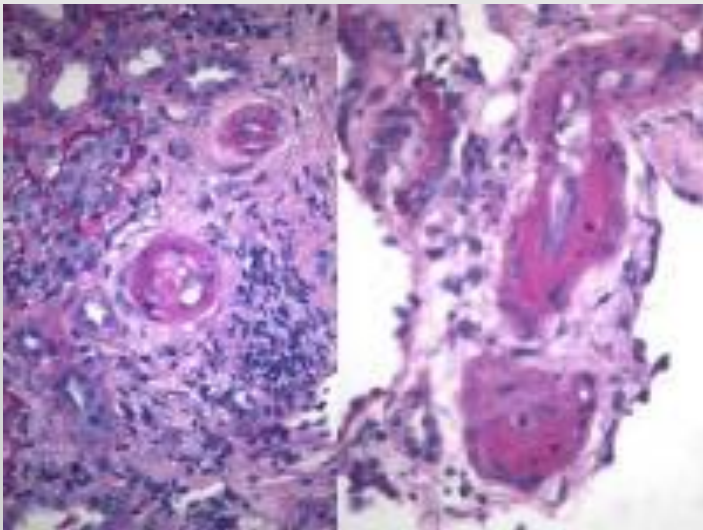
Bangkok 2017



APS is...

a syndrome of (unprovoked)
venous, arterial and
microvascular thrombosis

rarely associated with other
(non-ischaemic) conditions



Antiphospholipid antibodies - what are they?

Lupus Anticoagulant (LA)



Anti-β2 GPI

Anticardiolipin antibodies (ACL)

Heterogeneous antibodies against phospholipid-binding proteins (β2 GPI, prothrombin, others...)

Common in healthy populations - prevalence of LA 1-3.6%

prevalence of ACL 1-5.6%

Even higher in the elderly, often transient - not useful in population screening

Minority of APL positive cases develop symptoms

Stronger association of LA with thrombosis than ACL - role of specific antibodies (β2 GPI) still under debate

What we know about APS...



**autoantibodies
to phospholipid-
binding proteins...**

VTE

ATE

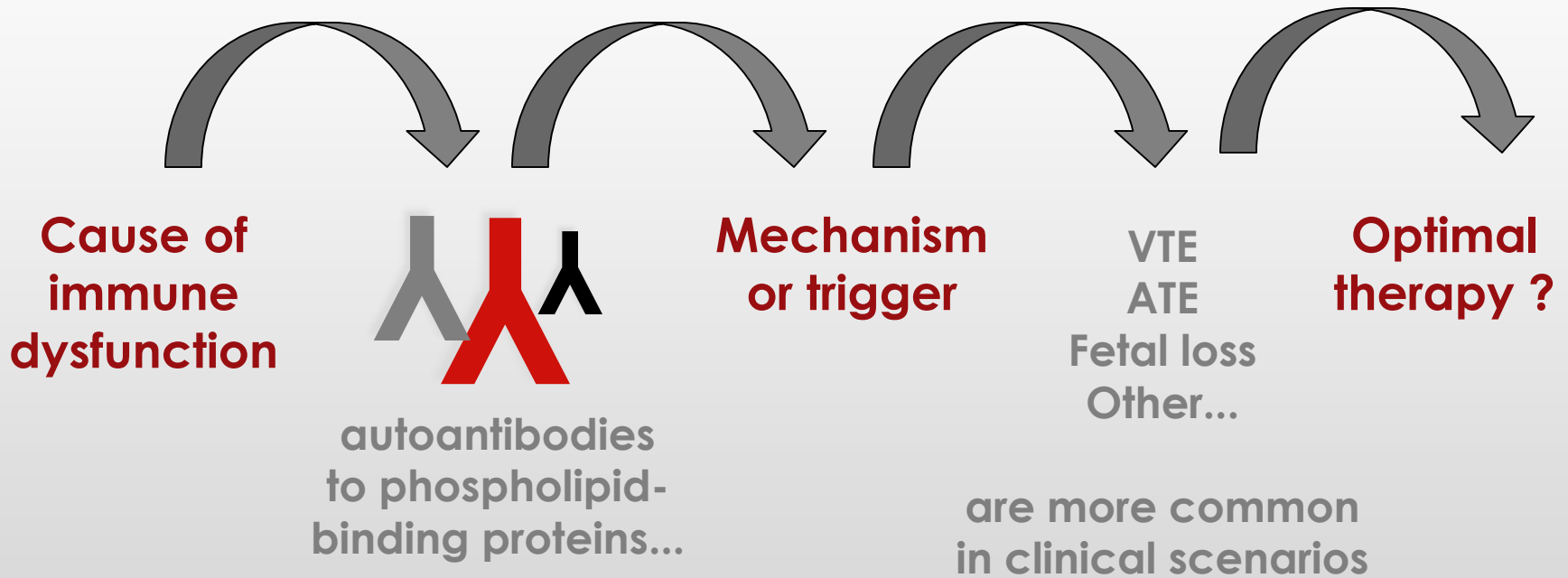
Atypical thrombosis

Fetal loss

Other...

**are more common
in clinical scenarios**

What we **don't** know about APS...



Antiphospholipid (antibody) syndrome (APS)

Venous thrombosis

Arterial thrombosis (esp stroke/TIA)

Microvascular thrombosis

Pregnancy loss, other obstetric complications

Livedo reticularis

Cardiac valvular disease (mitral > aortic)

Renal thrombotic microangiopathy

Thrombocytopenia

Haemolytic anaemia

Cognitive impairment, other non-ischaemic changes

Ruiz-Irastorza et al The Lancet 2010

Which APL are pathogenic?

Lupus anticoagulant – strongest predictor of thrombosis

40x increase stroke risk, 5x MI risk in women <50

Strong assocn with recurrent miscarriage <24 weeks

Anticardiolipin – persistent ACL+LA- showed more thrombosis than ACL-LA- lupus patients

Both IgG and IgM ACL associated with miscarriage risk

β 2-GPI antibodies

Not associated with thrombosis, miscarriage in 3 reviews

Highest risk in “triple positive” (LA+ACL+GPI+)

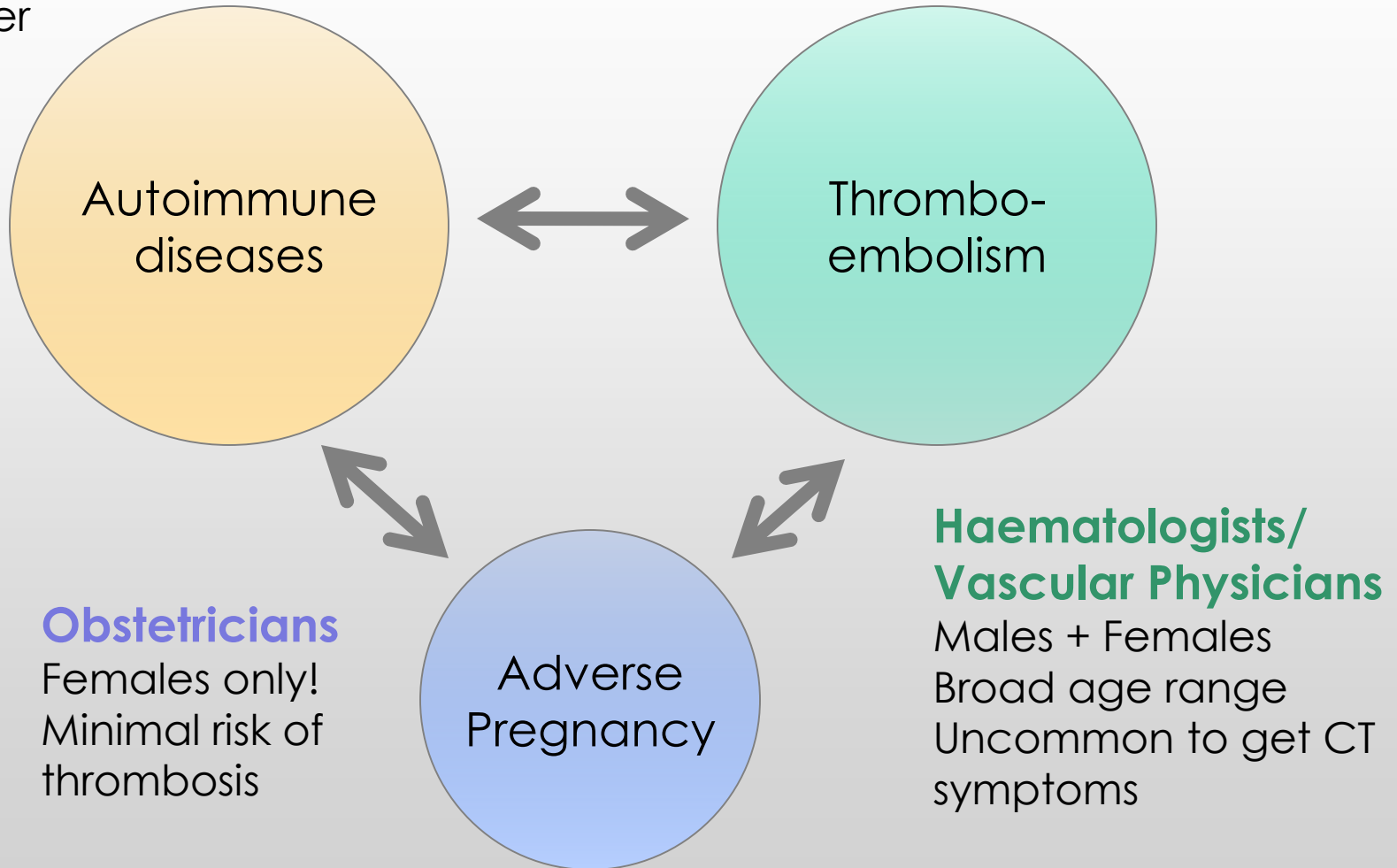
?Improved specificity if anti-domain 1 of β 2-GPI

Ruiz-Irastorza et al The Lancet 2010

Rheumatologists

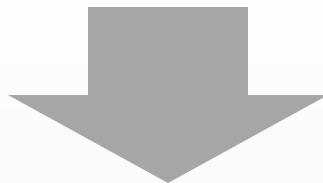
Female predominant
SLE and CT disorders
Younger

...are these patient groups
comparable?

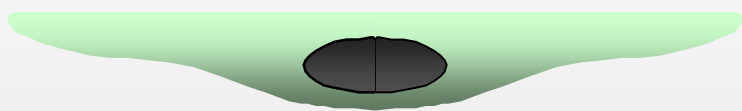




Antiphospholipid antibodies activate



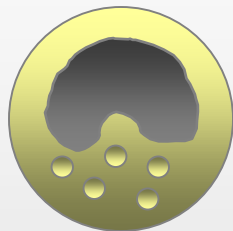
Endothelium



Adhesion molecules expressed
Tissue factor upregulated

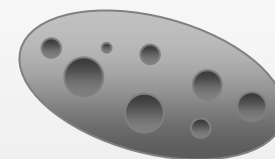
Interaction with
Protein C,
prothrombin, plasmin

Monocytes



Tissue factor upregulated

Platelets

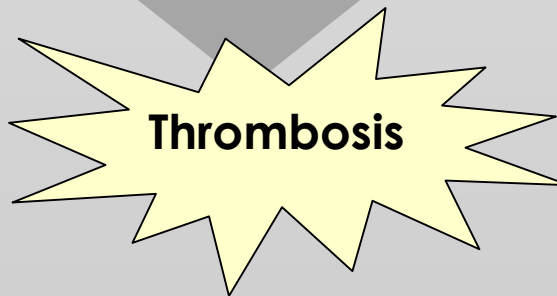


TxA₂ upregulated
GPIIb-IIIa
expression

**Complement
activation**

Prothrombotic state

Secondary triggers: inflammation, oestrogen, smoking



Thrombosis

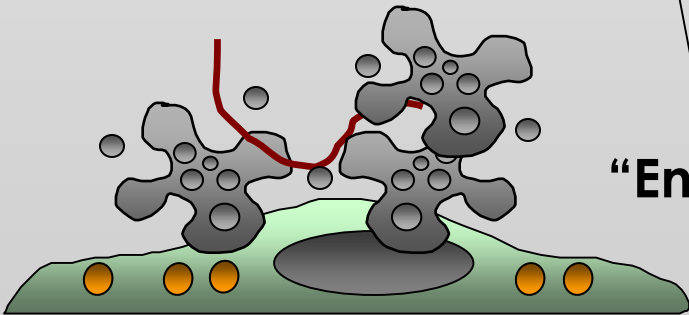
(Microvascular)
thrombosis

Thrombocytopenia

Endothelial
inflammation

Ischaemic organ
failure

Systemic
inflammation



“Endotheliopathy” or
TMAs

Endothelial
damage

Coagulation
activation

Complement
activation

APS syndrome

Heparin-induced
Thrombocytopenia

HELLP

Atypical HUS

Drug-induced TTP

Transplant-
associated TTP

International Consensus Criteria for Antiphospholipid Syndrome

APL requires at least one clinical and laboratory criteria:

Clinical

Vascular thrombosis - arterial, venous or small vessel in any tissue, without inflammation

Pregnancy morbidity - unexplained fetal loss >10 weeks, premature birth w eclampsia or placental insufficiency, recurrent early fetal losses <10 weeks

Laboratory

Lupus anticoagulant positive

Anticardiolipin antibody (mod-high titre)

Anti- β 2GPI antibody

APL must be detected on 2 or more occasions, *at least 12 weeks apart*

(The Sydney Criteria for APS) *Miyakis J Thromb Haem 2006*

Practice point

When should we test for APL?

Samples can be negative when presenting with an acute VTE and serial samples may show a positive APL

NOACs (rivaroxaban and apixaban) will give false positive LAC results – if essential, retest after NOAC ceased or transition to LMWH for several weeks

Must repeat after 12 weeks to meet criteria

Consider APL testing in: atypical sites of VTE (e.g.cerebral sinus)

recurrent VTE without a family history

younger patients with arterial events

combined arterial and venous thrombi

unexplained multiorgan failure and likely

microvascular ischaemia

Aspirin for primary thrombosis prevention in APL patients

APLASA study: 98 asymptomatic, persistently APL+ subjects randomised to 81 mg aspirin or placebo - prospective follow-up

Incidence of acute thrombosis **2.75/100 pt-years in ASA-treated**
0/100 pt-years in placebo-treated

Similar outcomes in observational cohort of 74 nonrandomised individuals - 61 on ASA (2.7/100 pt-years) and 13 not (0/100 pt-years)

9/10 patients with events had systemic autoimmune disease or thrombotic risk factors - thrombosis risk also higher (11%) in those with high titre APL and/or LA positive

Asymptomatic APL+ individuals have a low risk of acute thrombosis
do not benefit from aspirin

Erkan Arthritis Rheum 2007

Practice point

What is the significance of a positive APL test?

Not much in the absence of a vascular event or recurrent miscarriage...

Take care not to diagnose APL without confirming persistence (testing at least 12 weeks apart) of antibodies, transient APL antibodies are common and of uncertain significance

Anticardiolipin antibody titre and lupus anticoagulant ratios do not correlate with clinical events – is a second “hit” needed?

APL may persist despite immunosuppression/plasmapheresis

Beta-2 GPI antibody assays are highly variable in performance – this assay is not suitable to replace standard testing – but “triple positive” cases may be at higher risk of thrombosis

Overall, clinical history guides therapy rather than assay results...

How much warfarin do APL patients need after VTE?

114 APS patients - low risk, ~75% with VTE, randomised to either high-intensity (INR 3.5) or moderate-intensity (INR 2.5)
recurrence rates (3.4% mod, 10.7% high intensity)
major bleeding (2.2% mod, 3.6% high intensity)

Excluded pts with high bleeding risk, those with events on warfarin
Inadequate numbers with arterial TE ***Crowther NEJM 2003***

Similar study of **109 patients**, with equivalent recurrence and bleeding rates at standard and high-intensity warfarin

Finazzi JTH 2005

What is the risk of a first TE event in APLA-positive individuals?

no prospective data

What is the risk of recurrent VTE in APLA-positive individuals?

after 6 months Rx

APLA positive **29% recurrence** over 4 years

APLA negative **14% recurrence** over 4 years

RR 2.1

Schulman Am J Med 1998

after 3 months Rx for first idiopathic VTE:

APLA positive **4/16 recurrence**

APLA negative **2/61 (HR 4.0, CI 1.2-13)**

Kearon N Engl J Med 1999

No data regarding risk of recurrent arterial events in APLA

APL and recurrent thromboembolism:

Evidence for increased risk is weak *Ruiz-Astoria 2007*

Most studies retrospective, combine ATE and VTE, inconsistent definitions of APL, single test

Recurrence rates high (19-29%) in untreated patients (cohort studies), much less on warfarin

DURAC subgroup analysis: recurrence in 29% with first VTE and anticardiolipin antibodies cf 14% without ($p < 0.01$)

Lower risk recurrence in APL patients after VTE than ATE

Eichinger and Kyrle, ISTH 2009

Systematic analysis of 8 **prospective but poor-quality studies** of patients with a first APL-related thrombotic event: **40% higher risk of recurrence** off AC in APL+ (n=588) compared to APL- (n=1914)
(RR 1.4, 95%CI 0.99-2.36)

Garcia, Blood 2013

Hydroxychloroquine plus AC in primary APS

Primary APS patients with 1 or 2 prior episodes of VTE on VKA
(2 w stroke, no obstetric events)

Prospective, but non-randomised study

VKA only (n=20) **6 venous events (30%) despite therapeutic INRs**
(TTR claimed 98% incl 30d before recurrence)

VKA + HCQ (n=20) **0 events over 6 and 36 months**

VTE events – 3 femoral, 3 tibial DVTs at 12-18 months, 50% recurred at site of prior thrombus

Minor bleeding rates equal (10% in both groups)

Small numbers, short follow-up, but suggests addition of HCQ warrants further investigation – is recommended in SLE patients as “prophylaxis”

Schmidt-Tanguy et al J Thromb Haemost 2014

Practice point

Use of warfarin in APS

Warfarin remains the “standard of care” for APS patients with venous thromboembolism

In typical VTE, an **INR range of 2.0-3.0** is sufficient

Use warfarin rather than NOACs for atypical VTE (cerebral sinus or mesenteric/portal vein thrombi) – no evidence yet

Consider higher INR range for arterial events (and add aspirin if possible)

If patients progress on warfarin, or need temporary interruption of VKA, switch to **twice daily LMWH**

When using LMWH, aim for an anti-Xa peak of 1.0U/mL

LMWH may be preferable to warfarin in “unstable” patients

Practice point

Can we use NOACs in APL patients?

Remember that patients with “strong” antibodies can be resistant to warfarin and other anticoagulants...

Patients with a **typical presentation of VTE** (leg vein DVT or small-volume PE) may respond normally to NOACs

NOACs can be used for **secondary prevention** after an initial period of “stabilisation” with warfarin or LMWH

LMWH (twice daily) is a preferred option in unstable or unwell patients, can monitor anti-Xa to ensure levels high (>1 U/mL)

Insufficient evidence to use NOACs in atypical VTE sites, patients with arterial events (warfarin plus aspirin preferred) and in catastrophic APL

Would a b.d. dosed NOAC be preferable to once daily?

Would APL patients benefit from a higher dose-intensity?

Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial

Hannah Cohen, Beverley J Hunt, Maria Eftymiou, Deepa R J Arachchilage, Ian J Mackie, Simon Clawson, Yvonne Sylvestre, Samuel J Machin, Maria L Bertolaccini, Maria Ruiz-Castellano, Nicola Muirhead, Caroline J Doré, Munther Khamashta, David A Isenberg*, for the RAPS trial investigators*

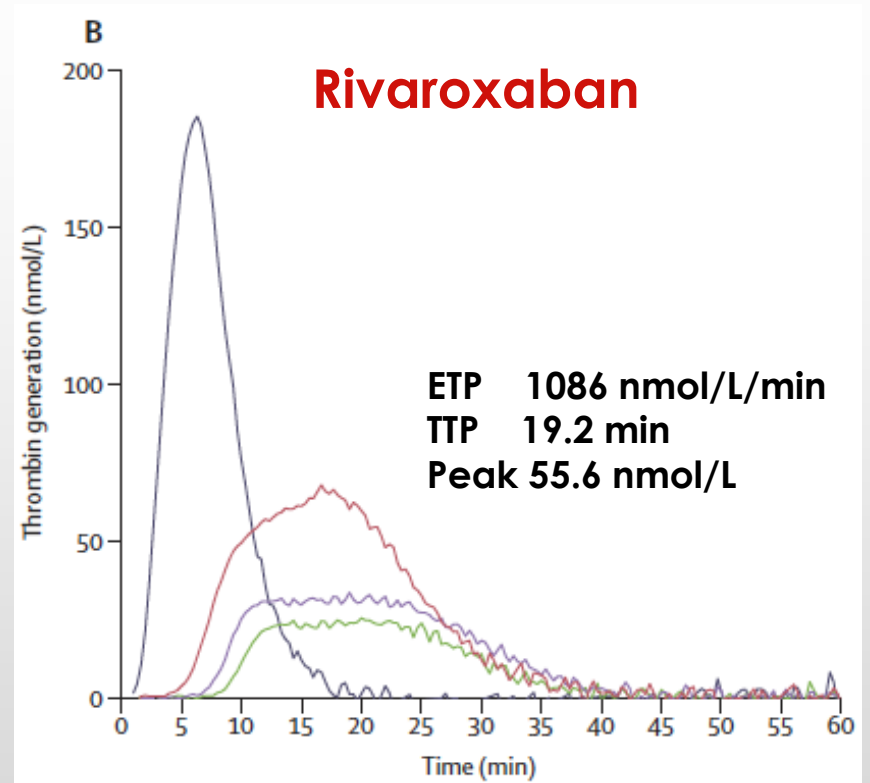
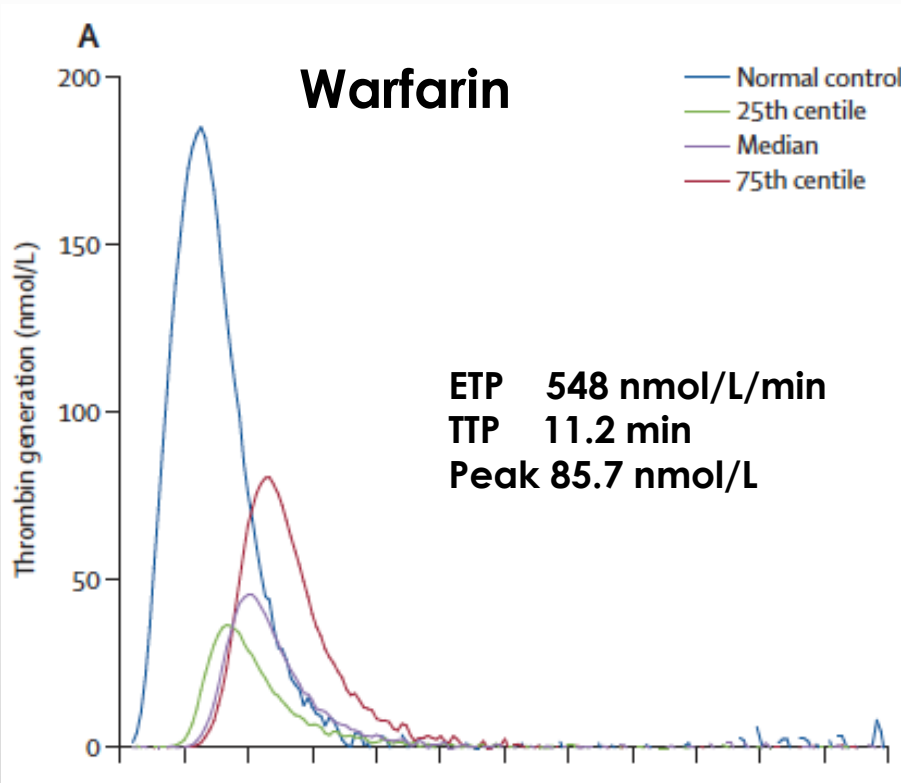
116 patients w previous VTE, confirmed APL on standard-intensity warfarin, randomised to continue or rivaroxaban (n=56)

Primary outcome – laboratory assay of thrombin generation differed between anticoagulants, no difference in activation markers (D-dimer, TAT, P1+2)

Serious AEs in 4 of each group, no thrombosis or major bleeding seen in either group. Study suggests rivaroxaban is a suitable alternative in this type of APL patient

Cohen et al Lancet Haematol 2016

RAPS trial: thrombin generation (ETP) profiles on therapy



Higher endogenous thrombin potential (AUC) but lower and delayed peak thrombin on rivaroxaban – does this matter?

Arterial thromboembolism and APL ...

A probable risk factor in early stroke/MI, etc

Minimal evidence for altered management - not listed in ACCP guidelines

Patients will often receive combined antiplatelet and anticoagulant therapy, at least initially

Tend to have indefinite prophylaxis cf. VTE cases

Consider **combined** antiplatelet/anticoagulant therapy
- role of higher intensity warfarin uncertain, likely to increase bleeding risk...

Intensity of anticoagulation in APL?

Venous thrombosis

Warfarin INR 2.0-3.0

Arterial (non-cerebral) thrombosis

Warfarin INR 2.0-3.0

Stroke

ASA **or** Warfarin (INR 1.4-2.8)

Lim et al JAMA 2006

(only 3 studies eligible, few stroke pts, most low-titre ACL)

Venous thrombosis (first)

Warfarin INR 2.0-3.0

Arterial or recurrent events
(high risk of recurrence at std INR)

Warfarin INR 3.0-4.0

Ruiz-Irastorza et al Arth Rheum 2007

(incl observational studies, 16 studies, 1740 patients)

Ruiz-Irastorza et al The Lancet 2010

Prevention of recurrent miscarriage for APL+ women

Metanalysis of 13 studies (women with prior miscarriage and APL: n=849) - poor quality studies (50% with allocation concealment):

UFH plus aspirin (n=140, 2 trials) reduced pregnancy loss compared to **aspirin** alone (RR 0.46, 95% CI 0.29-0.71)

LMWH plus aspirin (n=98, 1 trial) equivalent to **aspirin** (RR 0.78, 95% CI 0.39-1.57)

Aspirin alone (n=286, 3 trials) did not significantly reduce pregnancy loss (RR 1.05 95% CI 0.66-1.68)

Combined UFH and aspirin may reduce pregnancy loss by 54% - further randomised controlled studies needed to establish effects of LMWH

ACCP 2012 Guidelines – recommend UFH or prophylactic LMWH plus low-dose aspirin in those with confirmed APL and 3 or more early pregnancy losses over no treatment (Grade 1B)

Catastrophic Antiphospholipid Syndrome (CAPS)

Proposed Diagnostic Criteria

1. Involvement of 3 or more organs, systems, tissues
2. Simultaneous onset symptoms or within 1 week
3. Small vessel occlusion (histologically confirmed)
4. APL positive (LA or ACL)

Definite CAPS

All four criteria

Probably CAPS

Other combinations, no biopsy, etc

Cervera et al (CAPS Registry Project Group) *Ann Rheum Dis* 2005

Practice point

Managing refractory thrombosis/catastrophic APL

Anticoagulation alone can be insufficient to control progressive thromboembolism, with any agent

Monitored heparin or LMWH is a good baseline

Targeting the pathogenic antibody is critical in severe cases:

Plasmapheresis (daily)

Immunosuppression with steroids, cyclophosphamide

Rituximab (can be given after daily plasmapheresis)

Case series and anecdotal cases only to guide treatment

Platelet count can be a useful marker, rises as microvascular events come under control...

Observational data supports use of plasmapheresis, rituximab, eculizumab and defibrotide...

Potential new therapies in APL

N-acetyl cysteine – scavenge oxygen radicals

Statins – upregulate endothelial NO synthase

Hydroxychloroquine- antiplatelet and prevents disruption of Annexin A5 matrix on endothelium by APL

Inhibitors of PDI – higher ratio of oxidised β 2GPI in APS, TF

Eculizimab – inhibits complement C5

Inhibitors of B-cell activating factor (BAFF) – belimumab approved in SLE, prevented thrombosis in mousemodel

Inhibitors of FXIa – dysregulated in APS

Giannakopoulos and Krilis NEJM 2013

Antiphospholipid antibody syndrome

How I treat....

Asymptomatic APL+ individuals - nothing...

APL+ VTE - standard VKA, LMWH if refractory,
extended duration, not always indefinite

APL+ ATE - VKA and/or ASA, indefinite

APL+ obstet - prophyl LMWH ?plus ASA

Catastrophic APL – anticoagulation must be
combined with strategies to remove Ab (Pex,
steroids, rituximab)