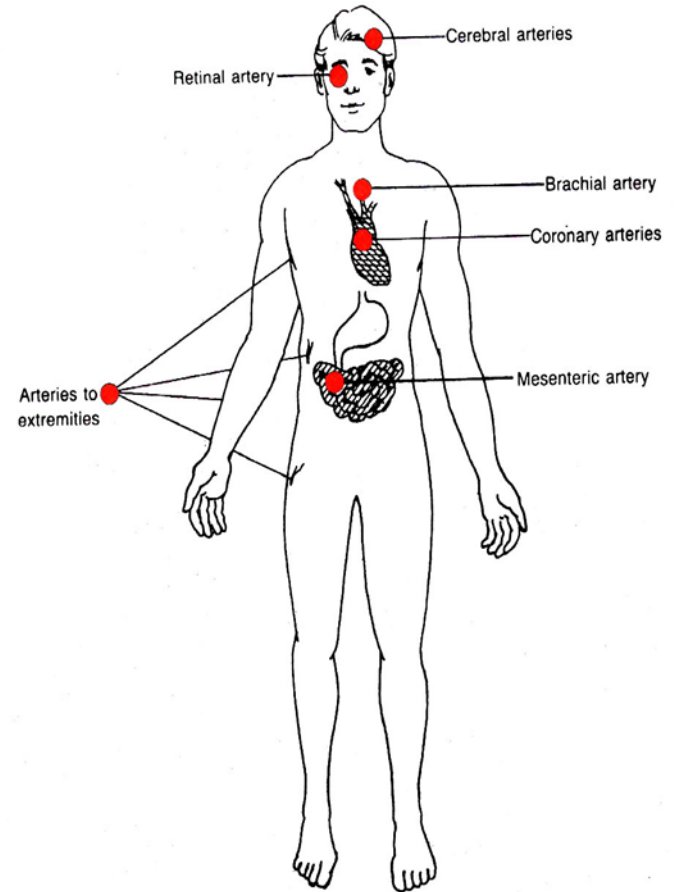
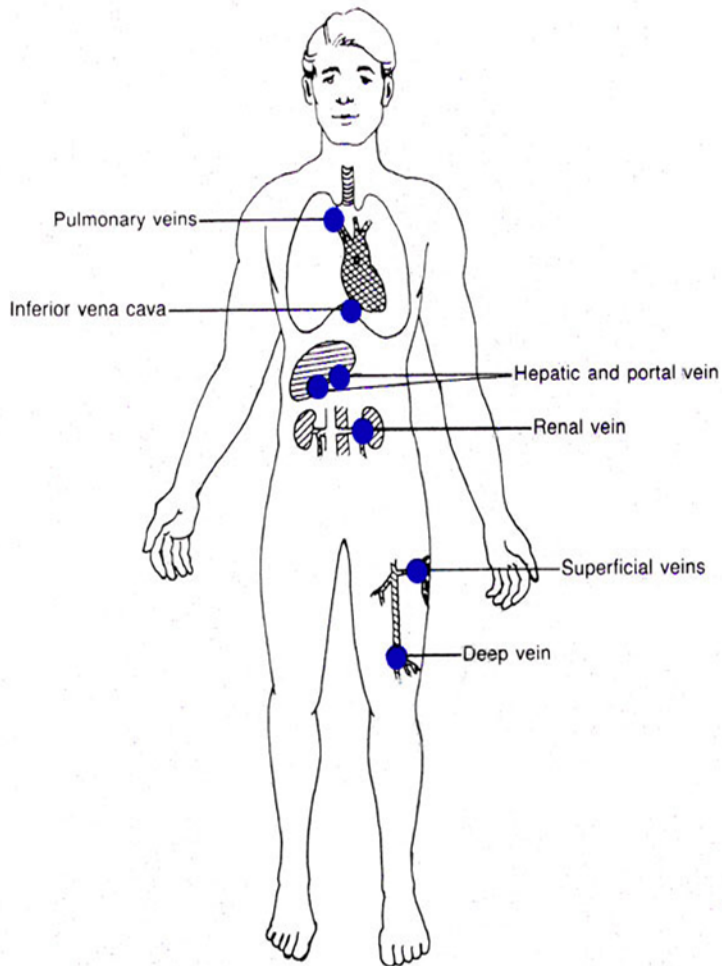




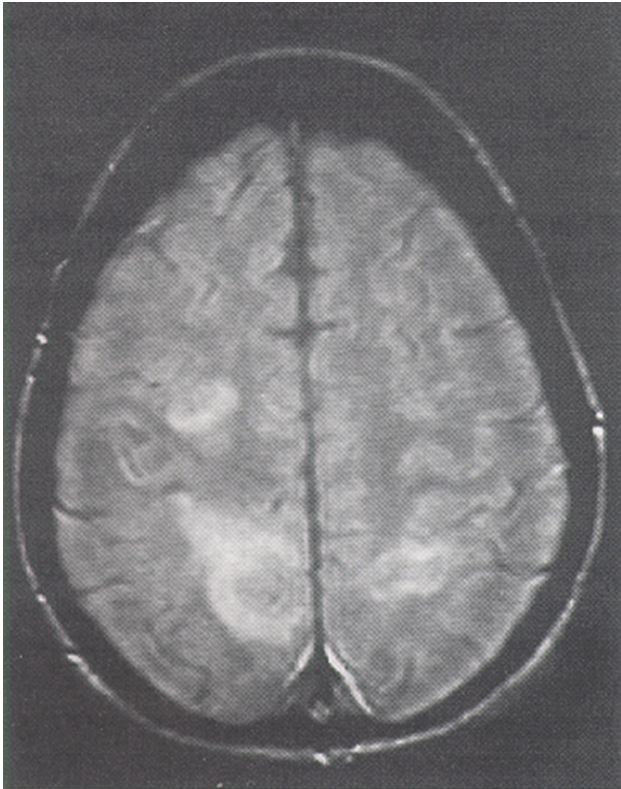
Dr Deepa Jayakody Arachchillage

Consultant haematologist & honorary senior lecturer

APS



Persistently positive aPL (LA, aCL, anti- β 2GPI on ≥ 2 occasions 12 weeks apart associated with thrombosis &/or pregnancy morbidity



Multiple Strokes in a Young Woman (Brain MRI)



APS morbidity

APS is the most common cause of acquired identifiable thrombophilia

Andreoli et al, 2013 analysed 120 full-text papers:
overall aPL frequency was estimated as

- 6% for pregnancy morbidity
- 13.5% for stroke
- 11% for MI
- 10 % for VTE

APS morbidity

- 1/3 of new strokes < 50 years age
- 10-15% women with recurrent pregnancy losses
- aPL present in 30-40% SLE. One third of those patients have clinical manifestations of APS (thromboembolic disease and pregnancy loss)

aPL and thrombotic risk

- Risk of thrombosis is highest with Triple positivity [Triple positivity > double > single (Pengo et al. 2010)]
- High titre ACA > risk than low titre ACA
- IgG > IgM

Who should be tested for aPL

Features indicating an increased likelihood of APS and therefore should be tested for aPL at the diagnosis of thrombosis

- Idiopathic VTE in young patients
- History of Systemic lupus erythematosus (SLE) or other autoimmune disease
- Presence of livedo reticularis (~25%)
- Prolonged APTT prior to starting anticoagulation
- Recurrent thrombosis
- VTE at unusual sites
- History of arterial thrombosis without clear risk factors
- Thrombocytopenia (~30%)
- Recurrent miscarriages/still birth/severe pre-eclampsia
- Cardiac valve abnormalities in the absence other explanation (~11.6%)

LA testing

- Testing for LA at acute VTE can be confounded by acute changes & the effects of anticoagulants
- Whilst on VKAs, ISTH guidelines are to be followed (Pengo et al, 2009)

Patients on DOACs

- APTT or DRVVT based tests should not be used to detect LA when there is a detectable drug level
- TVT/ECT combination can be used to detect LA in patients on direct FXa inhibitors, further studies assessing and sensitivity for LA of this test combination are required before recommending for routine use (Arachchillage et al, 2015)
- Methods to absorb DOACs from plasma are used to allow testing for LA in some centres, they need further validation studies before recommending for routine clinical use (Cox-Morton et al, 2019)
- Testing of LA using APTT and DRVVT based test can be performed at 3/12 , after switching to LMWH (sample taken just before the next dose of LMWH) after an adequate washout period for oral anticoagulant depending on renal function

Asymptomatic carriers

- Thromboprophylaxis is not recommended for asymptomatic, aPL positive individuals (no convincing evidence of benefit)
- Triple positive aPL ?
- Lifestyle modifications
- Thromboprophylaxis in high risk situations
- Contraception -POP, Depo-Provera, Mirena coil
- Avoid systemic HRT- Transdermal or gel

Treatment of APS with thrombosis

- Secondary prevention of thromboembolic events is the primary therapeutic goal
- Anticoagulation rather than immunosuppression
- Choice of anticoagulant ?
- Target INR?

Treatment of thrombosis

- VKA is the main long term anticoagulant of choice
- Despite warfarin anticoagulation, 30% of triple positive patients have recurrent thrombotic events within 10 years and is significantly higher in patients without anticoagulation (P =0.002) (Pengo et al, 2010)

What INR range?

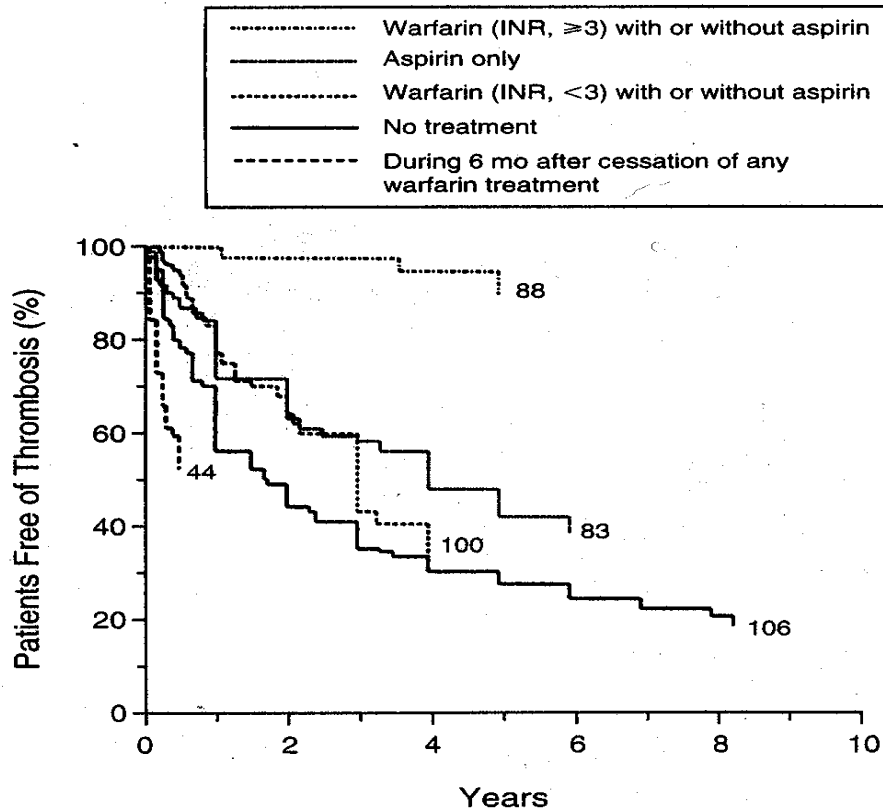


Figure 1. Kaplan–Meier Analysis of the Interval from Each Episode of Thrombosis or Change in Treatment to the Next Episode of Thrombosis or Censoring Event in the Same Patient, Throughout the Follow-up Period, According to Antithrombotic Treatment.

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.

- 147 APS patients with thrombosis (80/147 with venous and 67/147 with arterial)-recurrent thrombosis was high as 69% (101/147) over 10-year period
- APS patients with thrombosis should receive long-term anticoagulation therapy maintaining INR of ≥ 3.0 with or without low-dose aspirin

Treatment of VTE

- RCT (Crowther *et al*, 2003) -114 patients randomised to INR 2-3 & 3-4 for 2.7 years
- Only 24% (27/114) patients with arterial thrombosis
- 10.7% in high intensity vs 3.4 % in the standard-intensity arm
- MB- no difference
- At high intensity arm, treatment failures occurred usually when INR <3.0, yet analysed according to intention to treat
- 10% were also taking aspirin
- high-intensity warfarin was not superior to standard-intensity for the prevention of thrombosis

Treatment of VTE

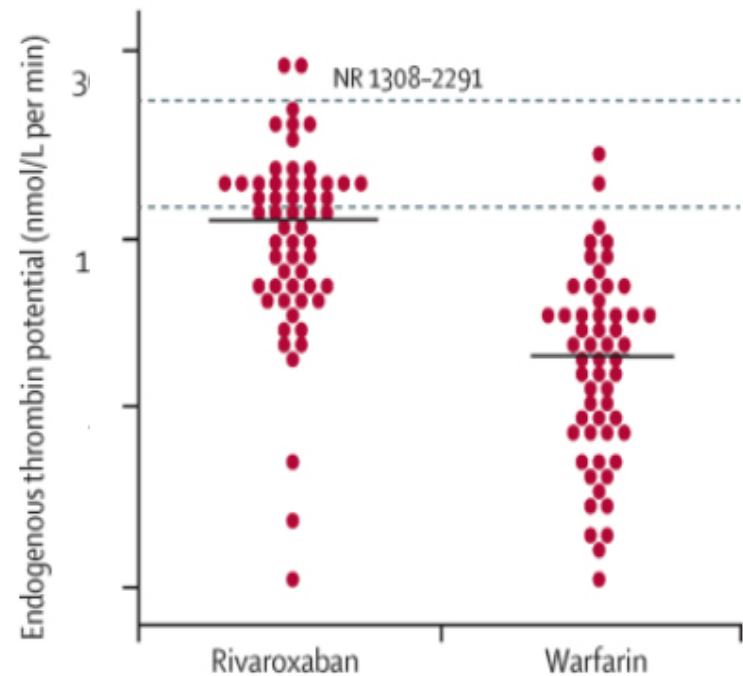
- RCT (Finazzi et al, 2005) -109 patients
- Only 40% (44/109) patients with arterial thrombosis
- RT- 6/54 (11.1%) in high intensity vs 3/55 (5.5 %) in the standard-intensity arm
- MB - 2/54 high intensity vs 3/55 standard-intensity
- High-intensity warfarin was not superior to moderate-intensity for the prevention of thrombosis

Warfarin

- Narrow therapeutic range
- Multiple interactions with drugs and food
- Variable responsiveness of thromboplastins to LA, leading to misleading INR results
- However, in the majority of patients with APS monitoring of INR is not a major issue and the problem is limited to specific thromboplastins (Tripodi *et al*,2001).
- Role of DOCAs??

DOACs in APS

- 3 RCTs – rivaroxaban vs warfarin in APS
- RAPS- 116 Patients (57 riva vs 59 warfarin)
- Only 16% triple positive
- Primary outcome :
% change in ETP from
randomisation to day 42
- 210 days follow-up
- no recurrent thrombosis
in either arm



DOACs in APS- 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%)

TAPS trial

TRAPS Randomized controlled trial of Rivaroxaban vs Warfarin in APS

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

R

Rivaroxaban
N=59

Warfarin
N=61



1,5 years

Events on
Rivaroxaban: 19%

Events on
Warfarin: 3%



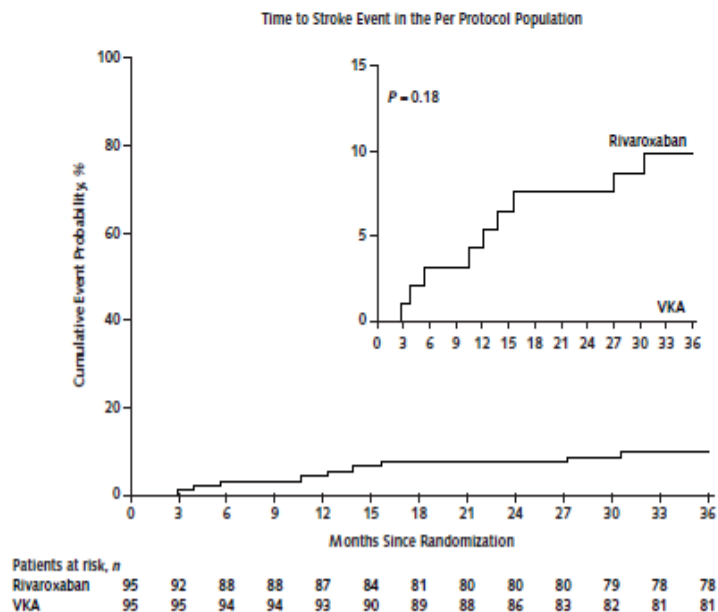
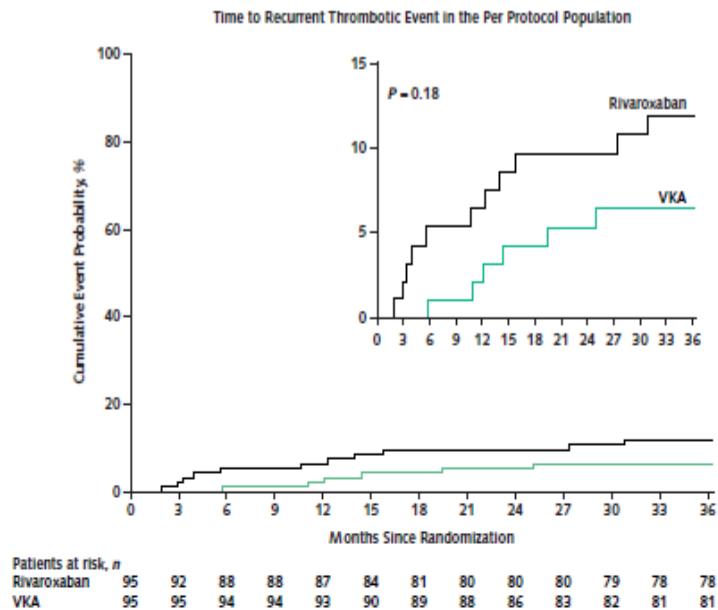
Stopped early for excess of events on Rivaroxaban

- Primary outcome: Cumulative incidence of TE, MB, and vascular death
- 569 days follow-up- arterial thrombosis 12% (7/59 which include 4 ischemic strokes and 3 MI) in rivaroxaban arm, no recurrence in warfarin arm
- 4/7 patients had RT on rivaroxaban arm had previous arterial thrombosis

Rivaroxaban Versus Vitamin K Antagonist in Antiphospholipid Syndrome

A Randomized Noninferiority Trial

- 3-year, open-label, randomized noninferiority trial: 190 with thrombotic APS from 6 university hospitals in Spain
- Rivaroxaban (20 mg/d or 15 mg/d) vs dose-adjusted VKAs (INR 2.0 to 3.0, or 3.1 to 4.0 in patients with a history of RT)
- Primary efficacy outcome: proportion of patients with new TE
- Primary safety outcome: MB



- Recurrent TE in 11 (11.6%) in the rivaroxaban vs 6 (6.3%) in the VKA group (RR in the rivaroxaban group, 1.83 [95% CI, 0.71 to 4.76])
- 9 stroke in rivaroxaban vs 0 in VKAs (RR, 19.00 [CI, 1.12 to 321.9])
- MB - 6 /95 (6.3%) in rivaroxaban vs 7/95 (7.4%) in the VKA group (RR, 0.86 [CI, 0.30 to 2.46]).
- Post hoc analysis suggested an increased risk for recurrent TE in Rivaroxaban - with previous arterial thrombosis, livedo reticularis, or APS-related cardiac valvular disease
- No difference in the recurrence in single or dual positive APS in the two arms

Intention-to-treat data do not differ perceptibly from those of the per protocol analyses. *P* values are from a log-rank test. VKA = vitamin K antagonist.

EMA and MRHA recommendations on DOACs in APS

- DOACs are not recommended for patients with a history of thrombosis and APS, *'in particular for patients who are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies)'* EMA-May 2019 and MHRA -June 2019

BSH Task force recommendations on use of DOACs in APS

Patients with arterial thrombosis

- For anticoagulation for treatment and secondary prophylaxis of arterial thrombosis, we recommend vitamin K antagonists (VKAs) and do not recommend DOACs (Grade 1B)

Patients with triple positive APS and VTE

- We recommend against the initiation of DOACs for treatment or secondary prophylaxis in patients with VTE and known triple positive APS (Grade 1B)
- For patients with triple positive APS who are currently on a DOAC, we recommend switching from the DOAC to a VKA after discussion with patients regarding the available evidence. For those patients who do not wish to switch, we recommend continuation of the DOAC over no anticoagulation (Grade 1B)

BSH Task force recommendations on use of DOACs in APS

Patients with non-triple positive APS and VTE

- There is insufficient evidence to make strong recommendations in this group of patients
- We suggest against the initiation of DOACs for treatment or secondary prophylaxis in patients with VTE and known non-triple positive APS (Grade 2C)
- Patients who are already on a DOAC may continue or switch to a VKA after discussion with the patient taking into account of the clinical history, treatment adherence and previous experience. For those patients who do not wish to switch, we recommend continuation of the DOAC over no anticoagulation (Grade 2C)

APS and arterial thrombosis

- Relatively limited data available from RCT
- No satisfactory RCTs comparing standard intensity VKAs with antiplatelet treatment

The Antiphospholipid Antibodies and Stroke Study (APASS)

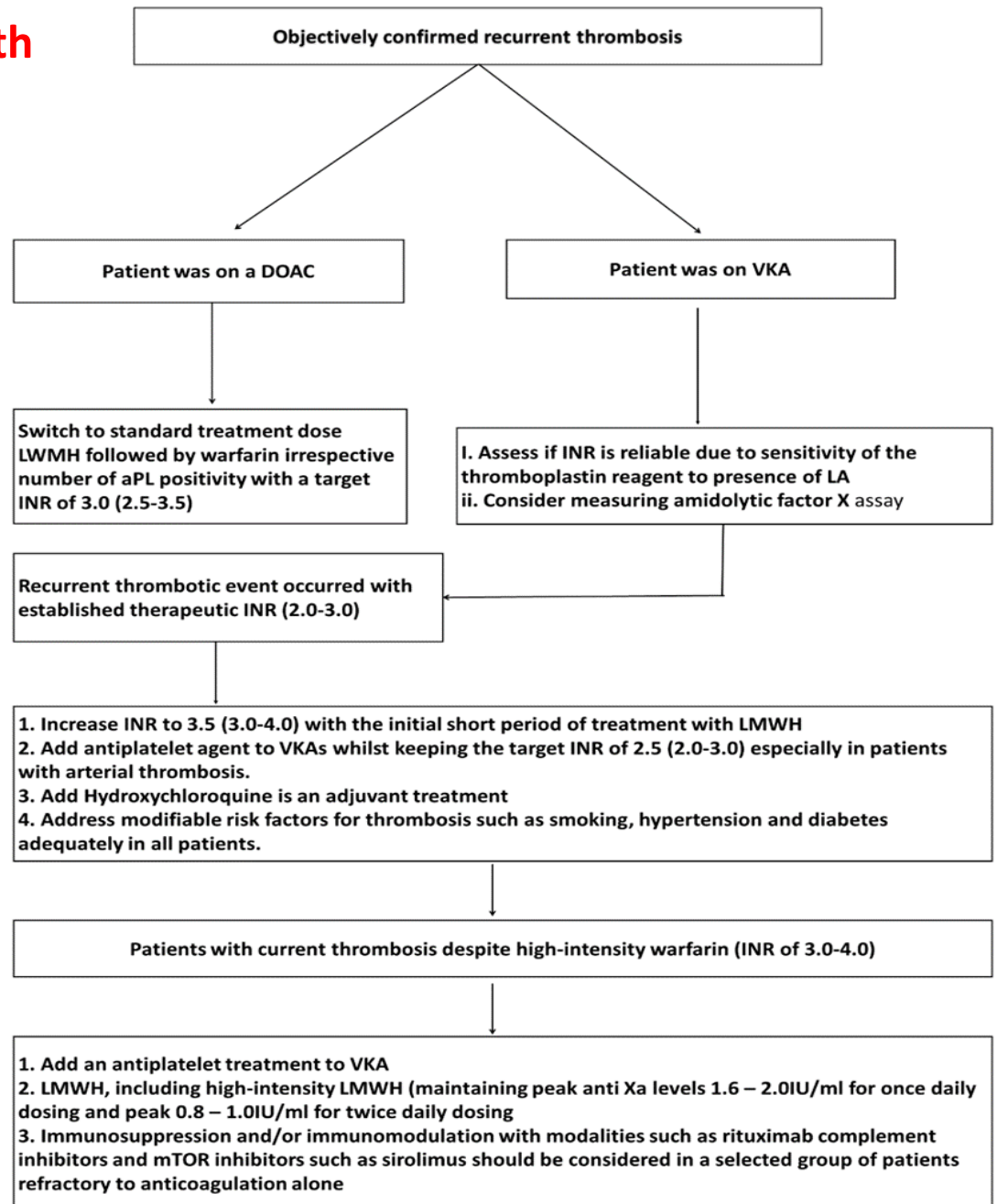
- Anticoagulation (with target INR 1.4–2.8) over aspirin (325 mg/day) in prevention of stroke found no benefit of warfarin
- aPL status was tested within 90 days of the index stroke by a central independent laboratory

Major limitations:

- Mean age 60 years (likely to have multiple risk factors for stroke, independent of aPL)
- aPL were tested only once at the time of an initial ischemic stroke and
- Of 726 aPL-positive patients, 52.6% had low positive aCL including IgA aCL which are not a recognised APS laboratory criterion

Current therapeutic recommendations range from single or dual antiplatelet treatment to VKA with a target INR of 2.5 (2.0-3.0) or 3.5 (3.0-4.0)

Management of patients with recurrent thrombosis in antiphospholipid syndrome despite therapeutic anticoagulation



Summary

- APS is complex multisystem disease
- Warfarin remained standard of treatment for long term anticoagulation in thrombotic APS
- DOACs may have a role in selected group of patients with single or dual positive aPL , based on clinical assessment
- Patients with recurrent thrombosis, may need support from specialist centres

Thank you

