

Personalizing therapy for the Antiphospholipid Syndrome

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Disclosures

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- Research support (to institution): Takeda, Sanofi, Argenx, Sobi
- Board of directors: United States TMA Consortium, HTRS

Learning objectives

At the end of this session, the learner will be able to :

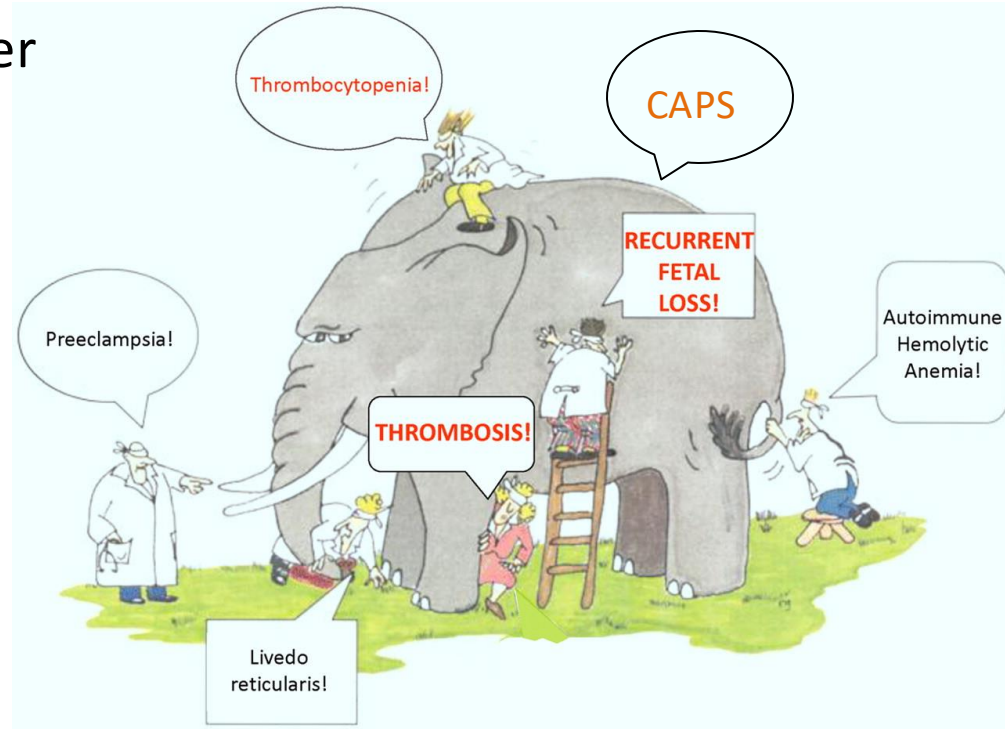
- Apply clinical and laboratory tools to diagnose APS
- Identify appropriate treatment strategies for venous and arterial thrombosis in APS
- Identify strategies for anticoagulation failure in thrombotic APS
- Recognize and treat catastrophic APS

Outline

- Current landscape of APS
- Pathogenesis – APS is a thromboinflammatory disorder
- Diagnosis and treatment of thrombotic APS
- Refractory and catastrophic APS – is complement the key?

Antiphospholipid syndrome (APS)

- Systemic **autoimmune** disorder characterized by arterial or venous **thrombosis and/or pregnancy morbidity** accompanied by persistently **positive antiphospholipid antibody tests**



Epidemiology of APS

- Incidence: 1-2/100,000 per year
- Prevalence: 40-50/ 100,000
- Prevalence in patients with thrombosis: 9-10%

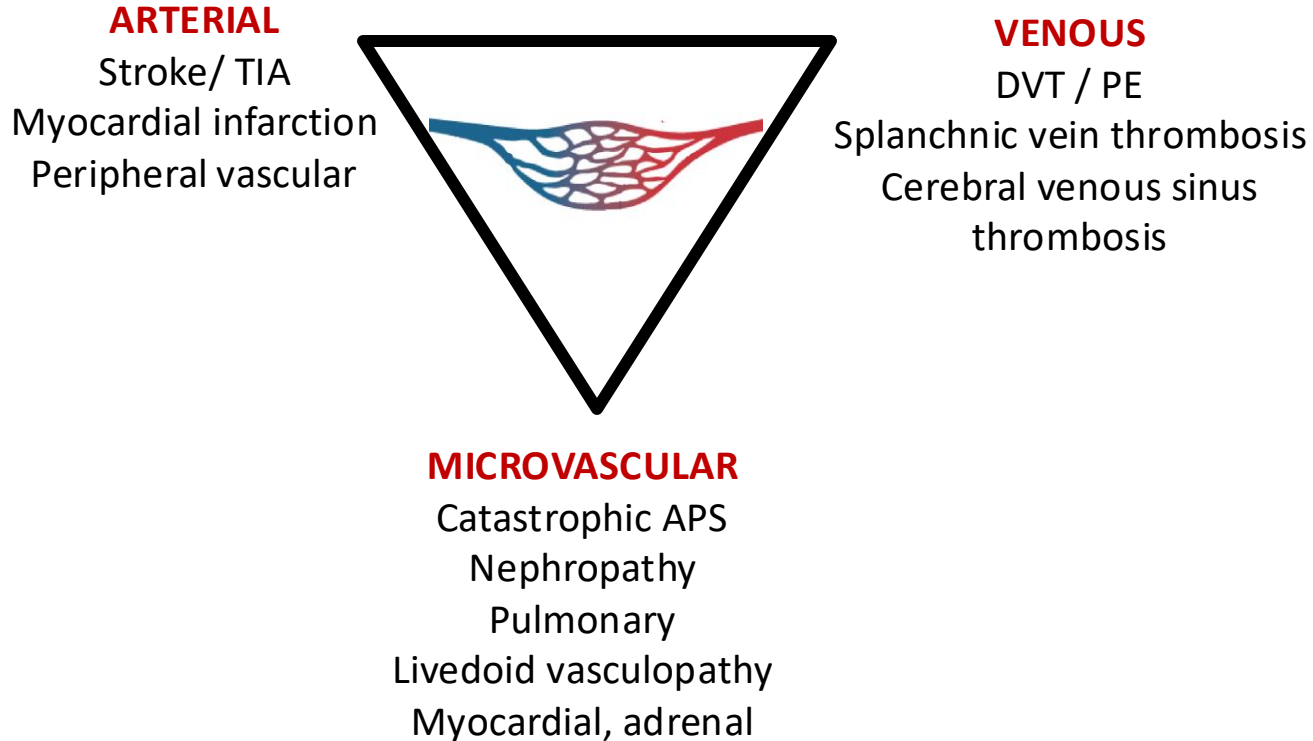
#1
cause of
stroke in young
people (<50
years)

Responsible for
1 IN 3
strokes in people
under 50

Responsible for
20%
of deep vein
thrombosis

Responsible for
1 IN 5
recurrent
miscarriages

Thrombosis in APS



Revised Sapporo Criteria for APS

CLINICAL CRITERIA

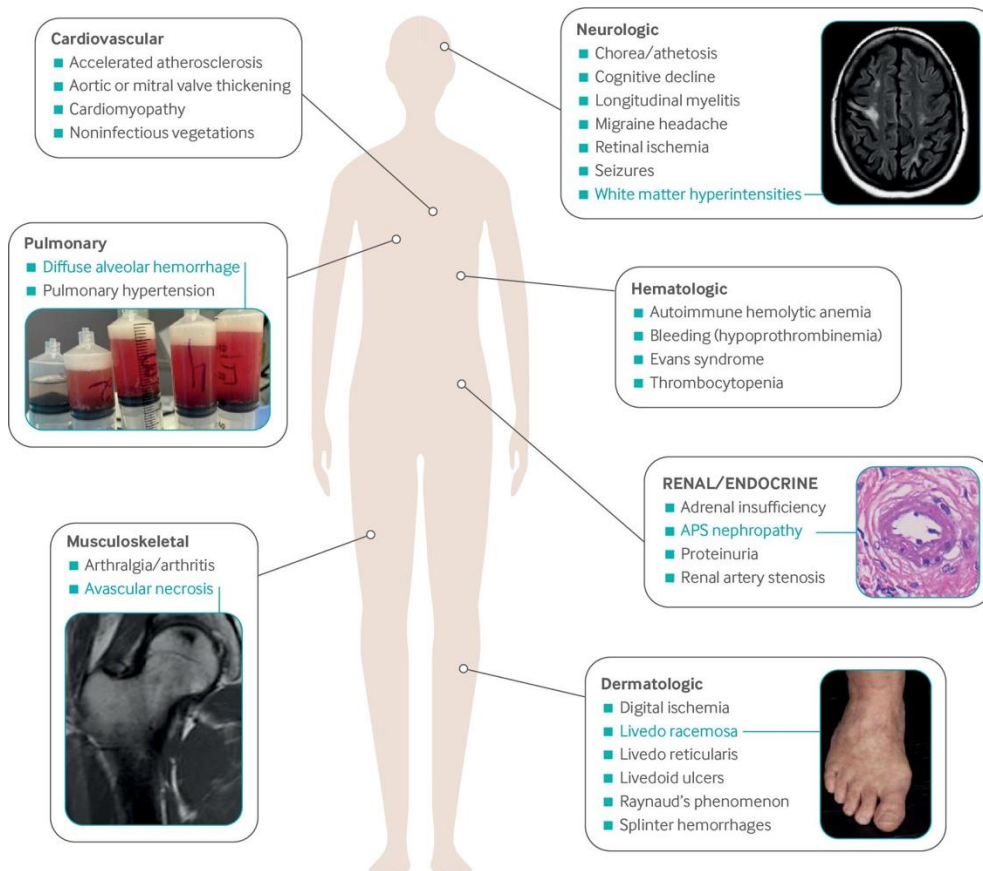
- **Thrombosis – venous arterial or microvascular**
- **Pregnancy morbidity**
(3 or more spontaneous abortions before 10th week, any unexpected death beyond 10 weeks, Any premature births at or before the 34th week of gestation because of eclampsia or severe preeclampsia or severe placental insufficiency)

LABORATORY CRITERIA (all on 2 or more occasions at least 12 weeks apart)

- - Lupus anticoagulant
- - aCL antibody of IgG or IgM isotype (>99th percentile, > 40 IU/L)
- - Anti- β_2 GPI antibody of IgG or IgM isotype (>99th percentile)

Definite APS requires at least one clinical and one laboratory criteria

Other *'non-criteria'* clinical manifestations



ACR/EULAR classification criteria 2023

Additive clinical and laboratory criteria^(a)
Do not count a clinical criterion if there is an equally or more likely explanation than APS.
Within each domain, only count the highest weighted criterion towards the total score.

Clinical domains and criteria	Weight	Weight	
D1. Macrovascular (Venous Thromboembolism [VTE])		D2. Macrovascular (Arterial Thrombosis [AT])	
VTE with a high-risk VTE profile ^(c)	1	AT with a high-risk CVD profile ^(c)	2
VTE without a high-risk VTE profile ^(c)	3	AT without a high-risk CVD profile ^(c)	4
D3. Microvascular		D4. Obstetric	
Suspected (one or more of the following)	2	≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths	1
Livedo racemosa (exam)		Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
Livedoid vasculopathy lesions (exam)		PEC with severe features (<34w 0d) <u>or</u> PI with severe features (<34w 0d) with/without fetal death	3
Acute/chronic aPL-nephropathy (exam or lab)		PEC with severe features (<34w 0d) <u>and</u> PI with severe features (<34w 0d) with/without fetal death	4
Pulmonary hemorrhage (symptoms and imaging)			
Established (one of more of the following)	5		
Livedoid vasculopathy (pathology ^(d))			
Acute/chronic aPL-nephropathy (pathology ^(d))			
Pulmonary hemorrhage (BAL or pathology ^(d))			
Myocardial disease (imaging or pathology)			
Adrenal hemorrhage (imaging or pathology)			
D5. Cardiac Valve		D6. Hematology	
Thickening	2	Thrombocytopenia (lowest 20-130x10 ⁹ /L)	2
Vegetation	4		
Laboratory (aPL) domains and criteria^(e)		Weight	
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])		D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β₂-glycoprotein-I antibody [aβ₂GPI] ELISA [persistent])	
Positive LAC (single – one time)	1	Moderate or high positive (IgM) (aCL and/or aβ ₂ GPI)	1
Positive LAC (persistent)	5	Moderate positive (IgG) (aCL and/or aβ ₂ GPI)	4
		High positive (IgG) (aCL <u>or</u> aβ ₂ GPI)	5
		High positive (IgG) (aCL <u>and</u> aβ ₂ GPI)	7

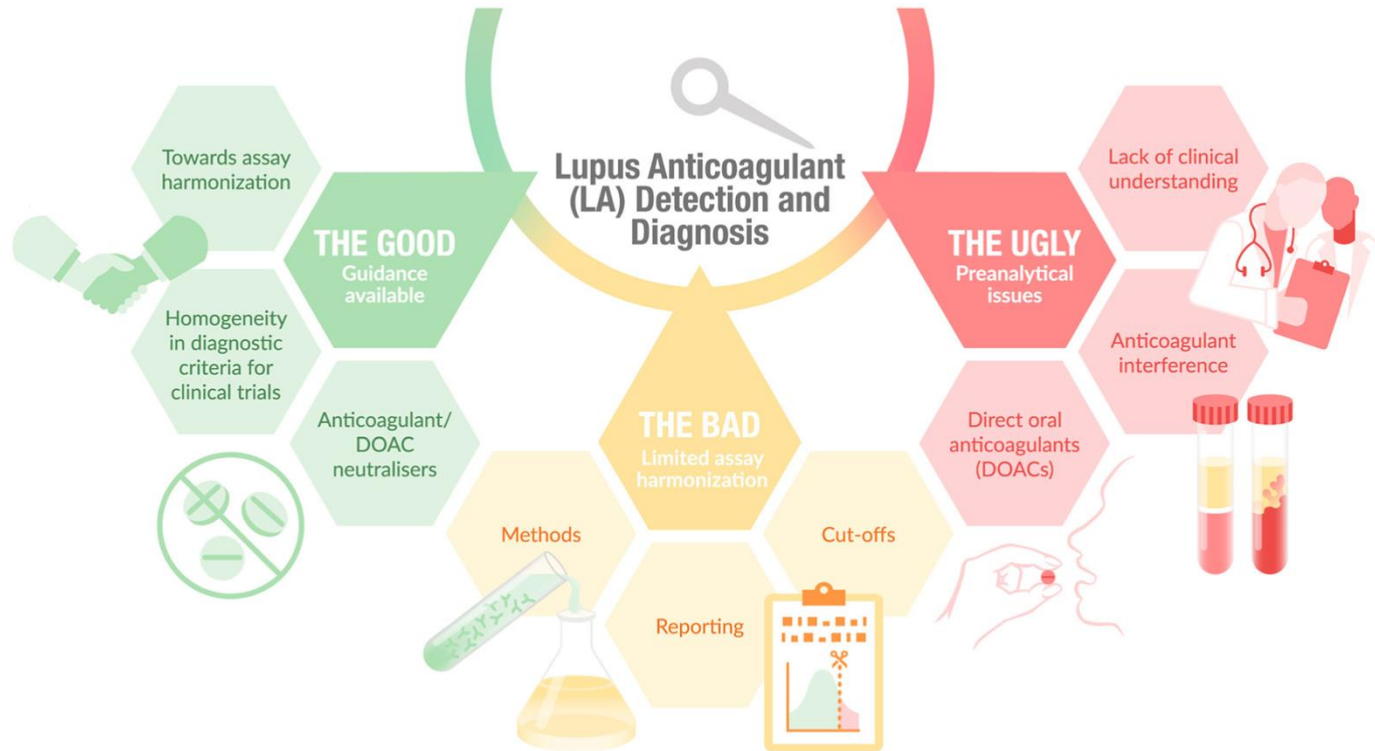


TOTAL SCORE

Classify as Antiphospholipid Syndrome for research purposes if there are at least 3 points from clinical domains AND at least 3 points from laboratory domains

10

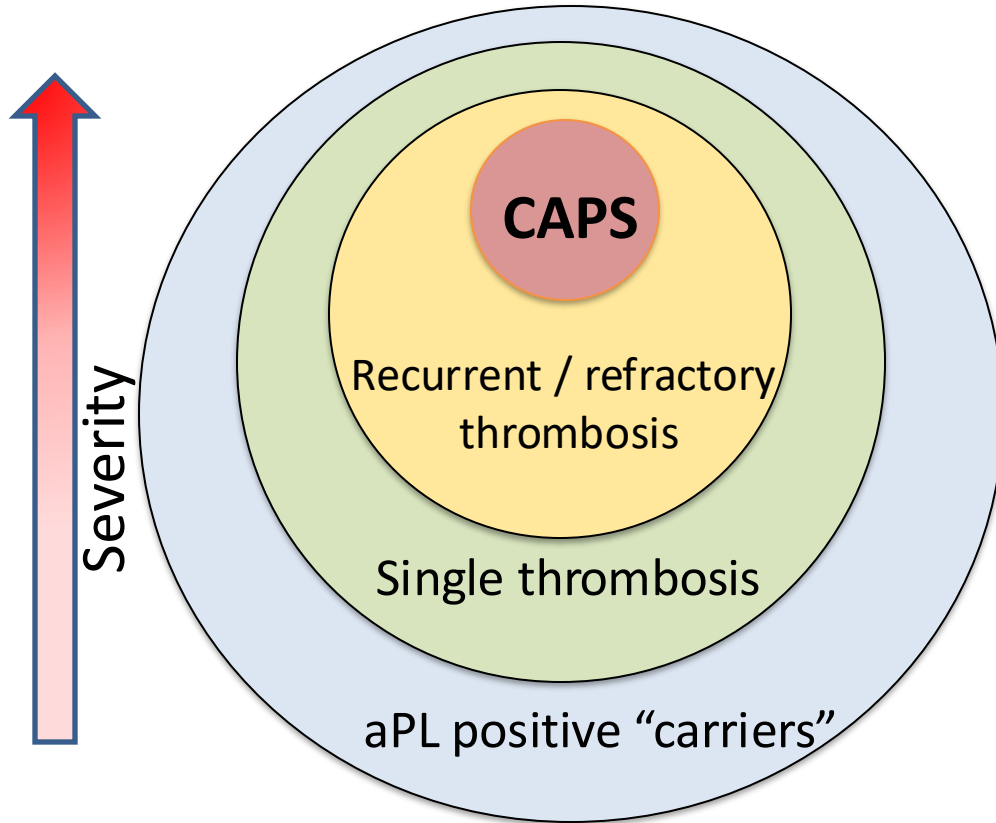
Lupus anticoagulant testing – pitfalls



Anticoagulants interfere with LA testing

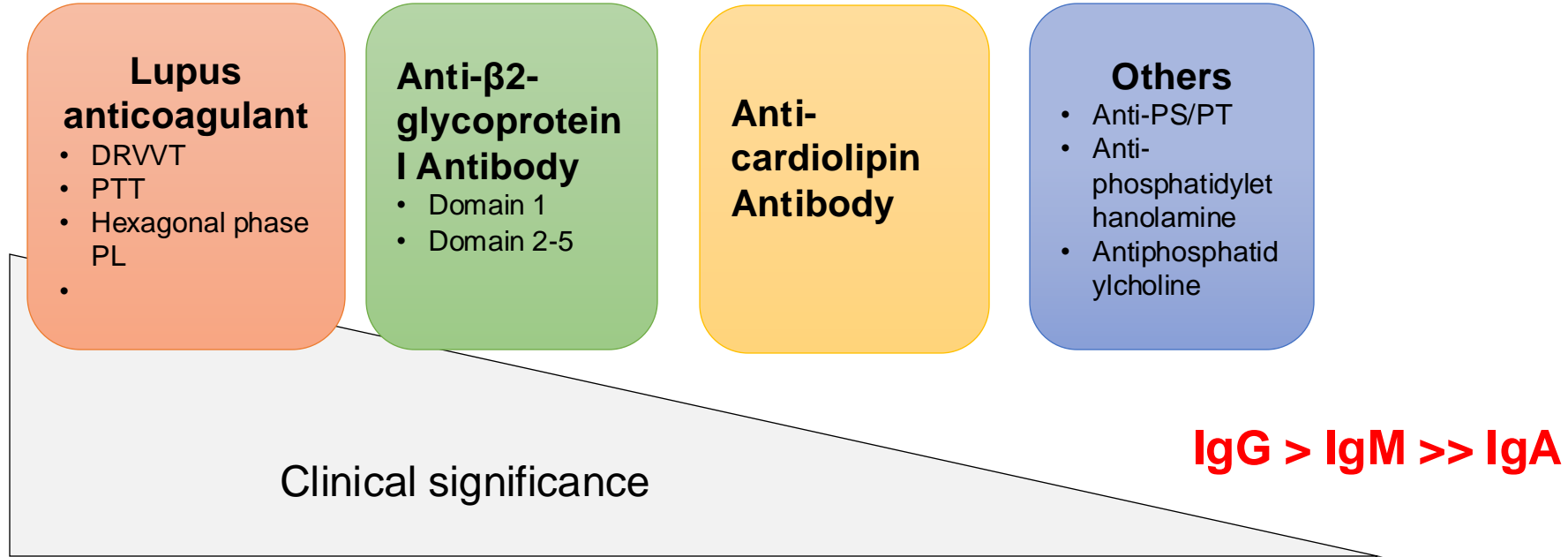
Anticoagulant class	Effect	Common strategies
Direct oral anticoagulants	False positives even with low concentrations	Hold anticoagulant Use DOAC neutralizer (DOAC-STOP)
Warfarin	Can prolong DRVVT, aPTT, (PT)	Mixing 1:1 with normal plasma corrects
Unfractionated and low molecular weight heparins	Can prolong DRVVT, aPTT,	Heparinase, heparin neutralizing reagents

Spectrum of thrombotic APS severity



Not all aPL are created equal

All aPL are not created equal



Risk of thrombosis with different aPL

Table 2 Odds ratios (OR) and 95% CI for thrombosis for antiphospholipid antibodies

Assay	OR (95% CI)
Lupus anticoagulants	3.6 (1.2–10.9)
Anti- β_2 -Glycoprotein antibodies	2.4 (1.3–4.2)
Antiprothrombin antibodies	1.4 (1.0–2.1)

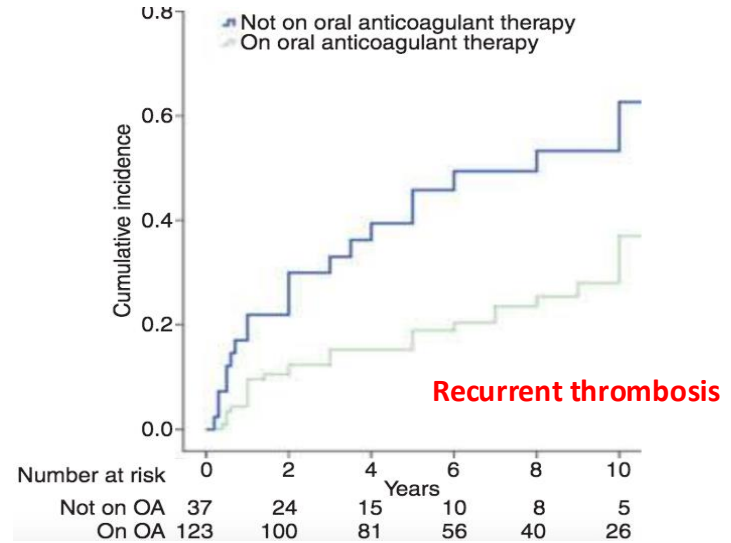
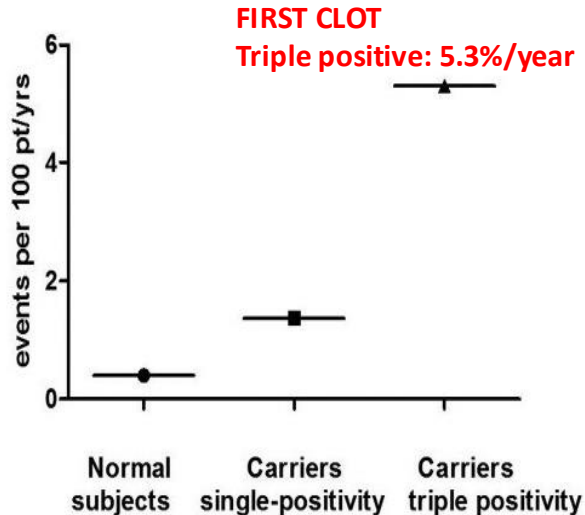
- **Lupus anticoagulant** is stronger risk factor for thrombosis than aCL or anti- β_2 GPI antibodies
- **β_2 GPI** antibodies more significant than prothrombin or aCL antibodies
- **aCL** are of borderline significance

Risk highest for triple positive patients

(Triple positive = lupus anticoagulant + anti-B2GPI + aCL)

Triple positivity predicts first / recurrent thrombosis

Triple positive = lupus anticoagulant + anti-B2GPI + aCL



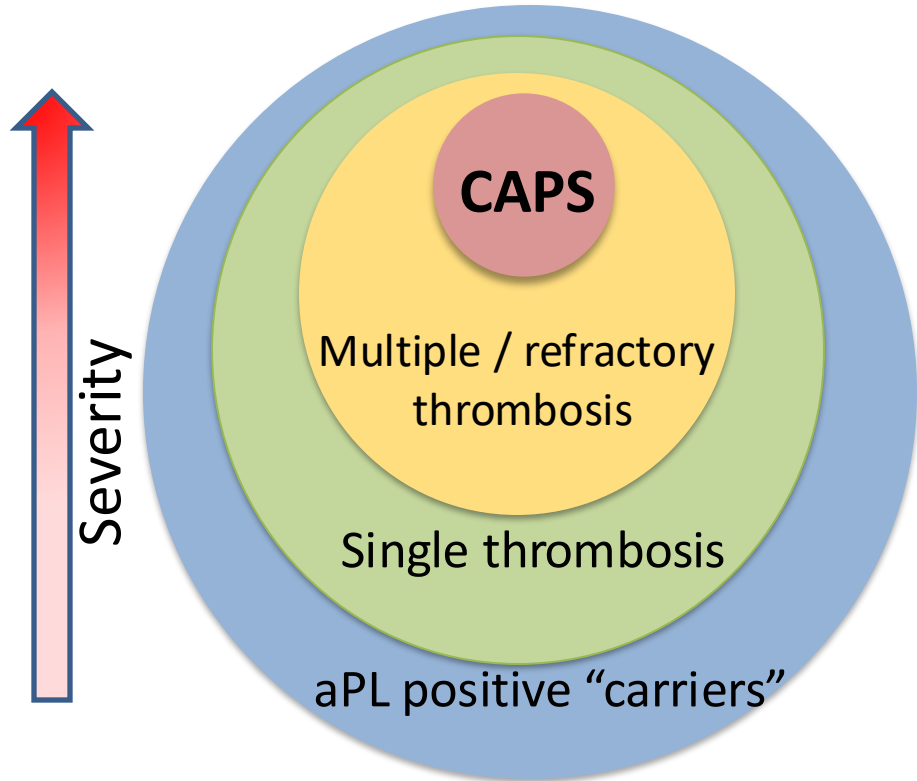
N=160, triple positive, with thrombosis
123 on long term anticoagulation

Does not identify patients at risk for CAPS or anticoagulation failure

Patterns of thrombosis recurrence

- Preceding thrombosis site predicts site of recurrence
- Recurrence risk persists over time
- Arterial thrombosis recurrence is more common
- Higher aGAPSS score is associated with recurrence risk
 - Role of double / triple positivity
 - Role of modifiable risk factors (hypertension, hyperlipidemia)
- No reliable predictors of anticoagulant failure or catastrophic APS.

Key issues in the current APS landscape

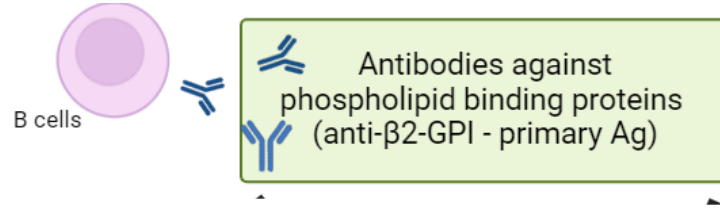


1. Biomarkers to assess recurrence risk are suboptimal
2. Suboptimal treatments for refractory APS and CAPS.

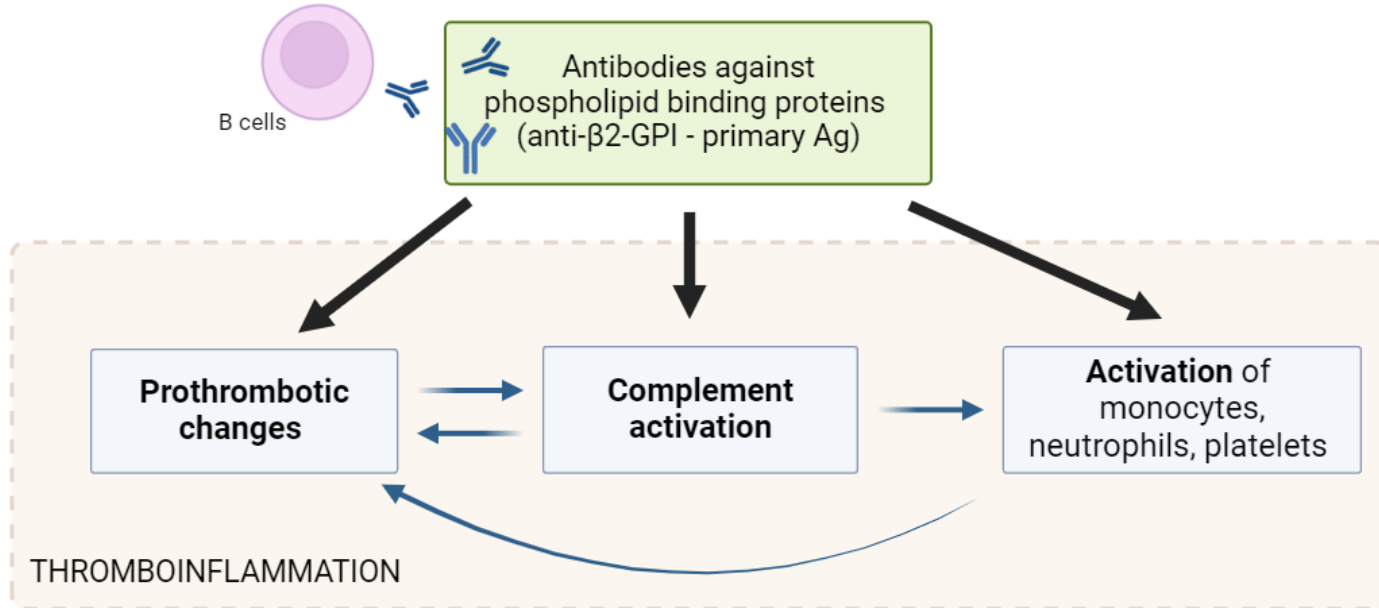
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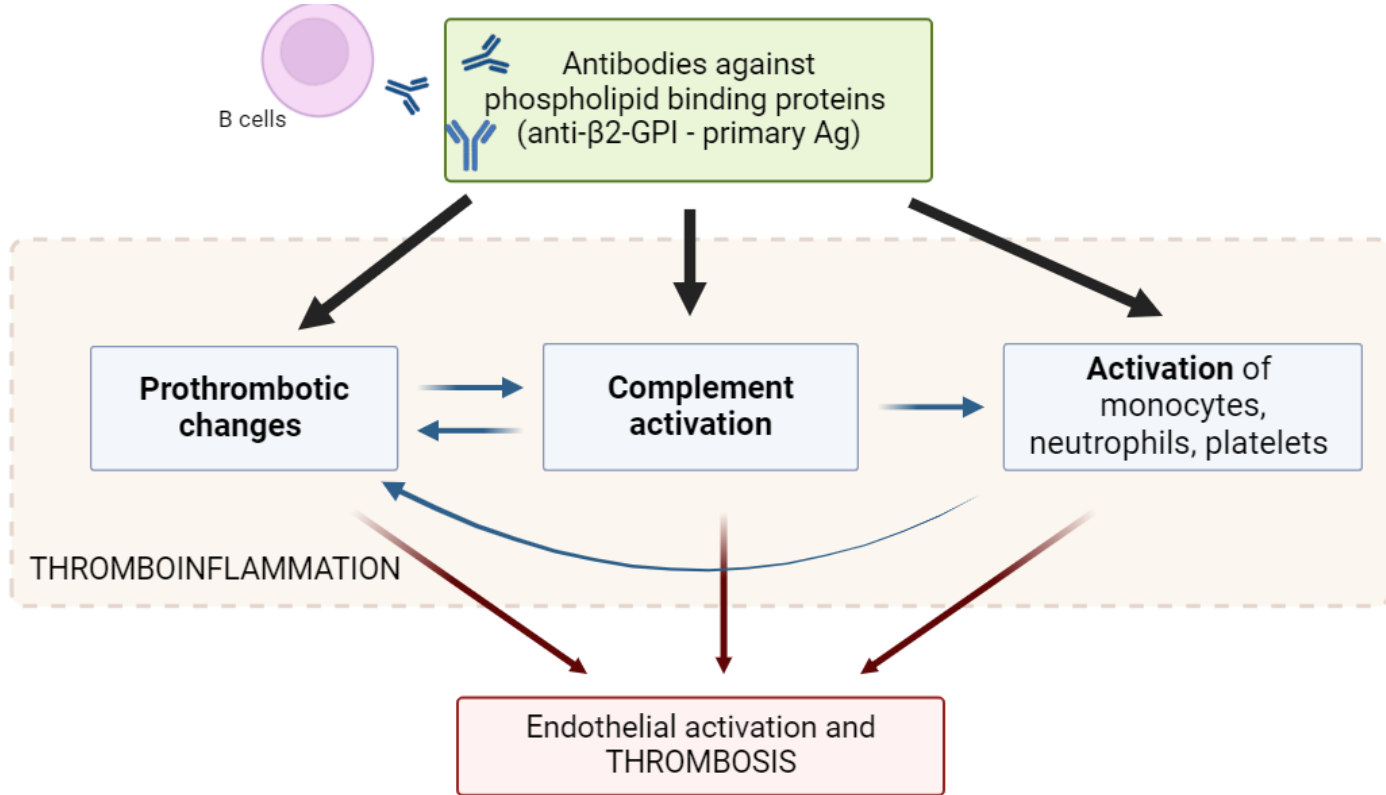
Pathogenesis of APS



Pathogenesis of APS



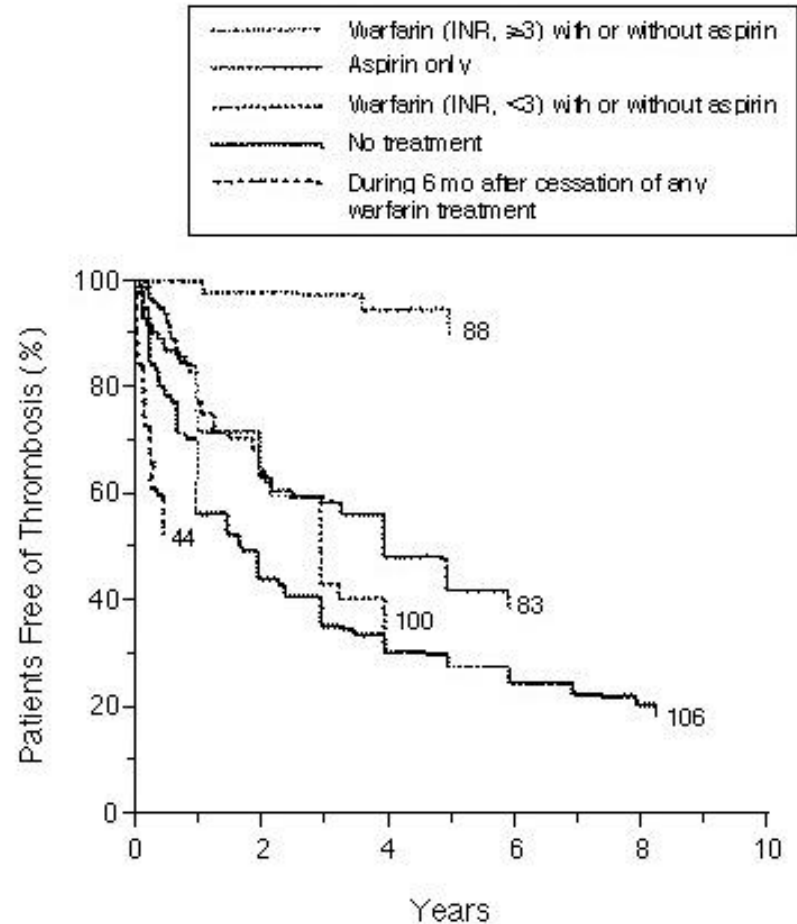
Pathogenesis of APS



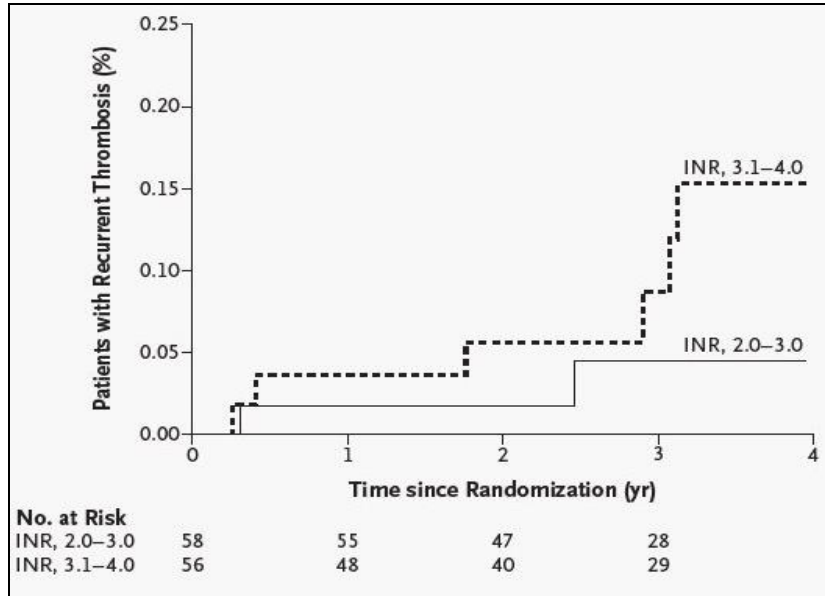
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- **Treatment of thrombotic APS**
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Long-term anticoagulation with standard intensity vitamin K antagonist (warfarin) is the standard of care for thrombotic APS



Intensity of anticoagulation in APS



Recurrence rates were not lower with high (INR 3-4) versus moderate (INR 2-3) intensity warfarin.

- Target INR 2.5 (2-3)

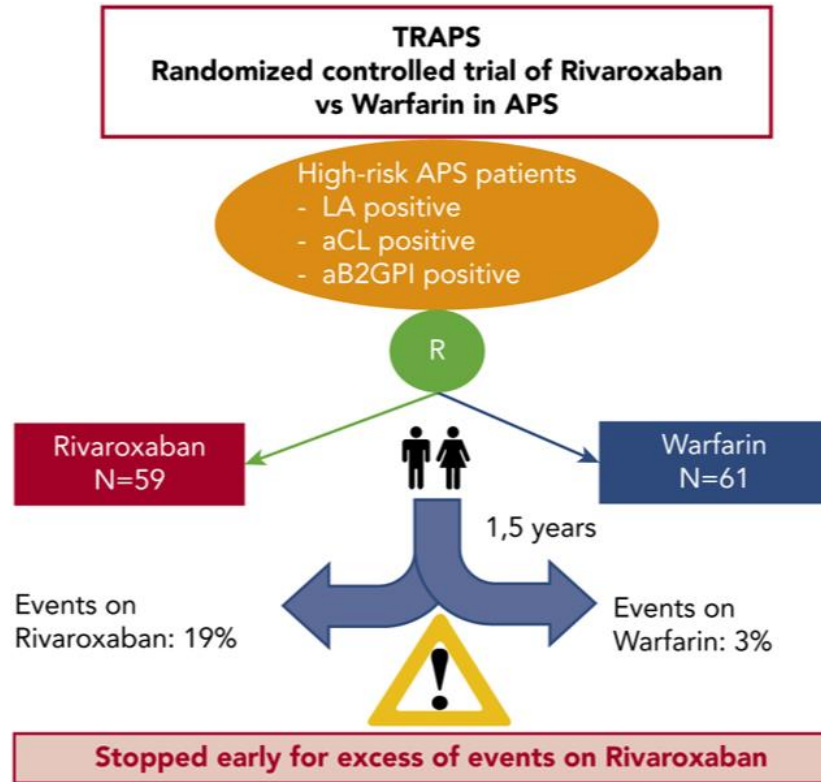
BUT

Warfarin with a higher target INR is sometimes used for recurrent clots.

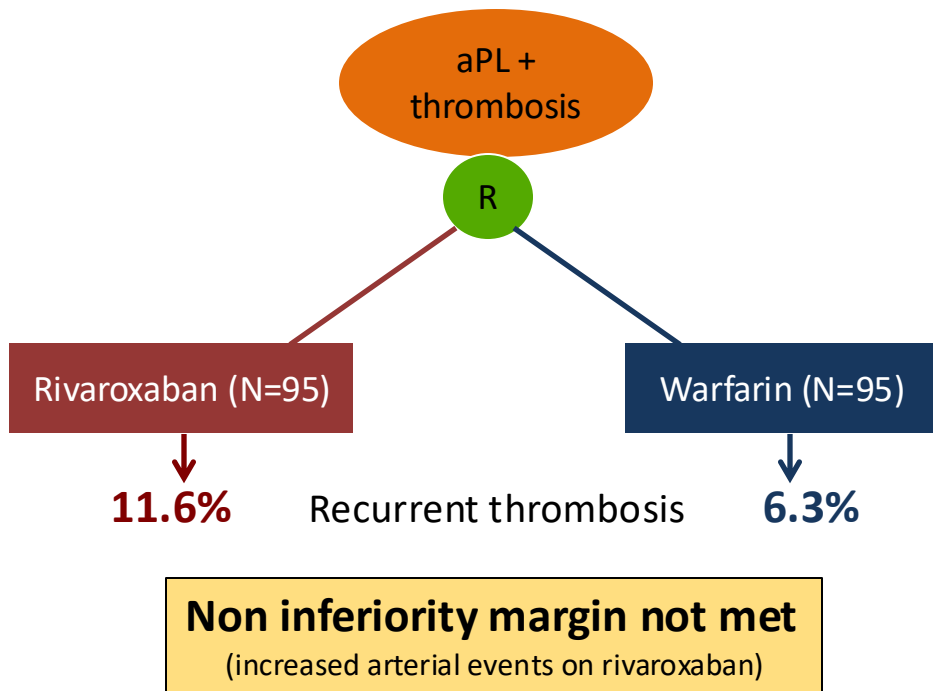
Lim et al. JAMA 2006

DOACs in triple positive APS?

Higher risk
(triple positive)
APS



What about DOACs for lower risk APS?

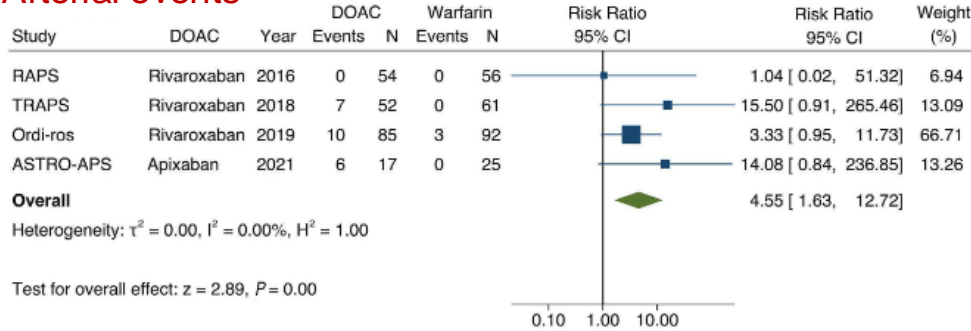


- ASTRO-APS trial (apixaban vs. warfarin)
- Thrombosis higher on apixaban (25% vs. 0%) – all stroke

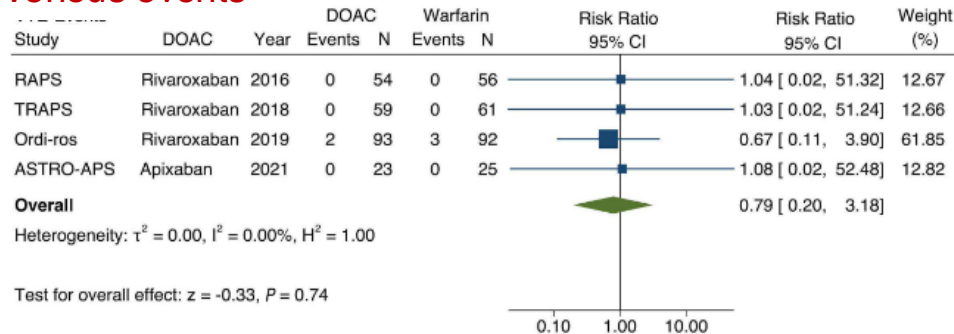
Woller et al. Blood Advances 2021

Metanalysis of RCTs of warfarin vs. DOAC in APS

c Arterial events



d Venous events



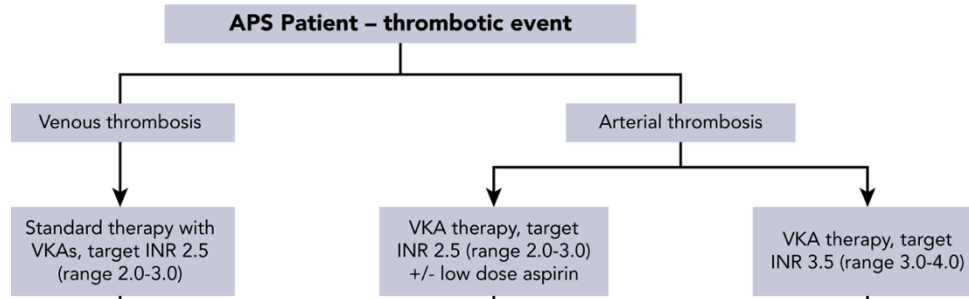
Do not use
Triple positive
Arterial thrombosis

Less data for –
Low risk (single positive,
low titer, IgM only),
provoked thrombosis

Can we use DOACS for lowest risk APS?

- Single positive APS, IgM only APS
 - Patients who have done well on DOAC for years
-
- We don't really know!
 - Single positive APS has low recurrence rate (3.06 per 100 patient years) (Bakow et al. Thromb Res 2024)
 - Reasonable to continue DOAC in patients with low-risk APS who have done well for > 1-2 years (shared decision making)
 - Warfarin remains still standard of care

Treatment of a first thrombosis in APS



VKA refractory thrombosis

- Some retrospective studies suggest high thrombosis even on therapeutic anticoagulation (with VKS, warfarin)
 - From specialized centers, selection bias (10-60%)
 - Lower rates in randomized trials in APS (? Selection bias)

There is a small and clinically challenging proportion of anticoagulation refractory patients

Scenario 1 – is the INR inaccurate?

- LA prolongs phospholipid dependent coagulation tests
- INR is falsely elevated in 6-7%
- Workarounds:
 - Empiric higher INR targets (3-4) at recurrence
 - Use a non-clot-based assay – chromogenic Xa
 - INR 2-3 \cong Xa 20 – 40%
 - can establish individualized INR range using Xa

Date	2/9	2/15	2/22	3/8	3/15	3/22	3/27	4/5
INR	1.7	2.6	2.7	3.8	5.6	5	4.6	5.1
Chr Xa	107%	86%	81%	51%	21%	35%	48%	33%

LA can also interfere with unfractionated heparin monitoring

- aPL with LA activity can prolong phospholipid dependent coagulation tests including aPTT
- Workarounds:
 - Using heparin anti-Xa for monitoring
 - Individualized aPTT range based on patient's baseline (2 x baseline)
 - LA resistant aPTT reagents (higher phospholipid content)

Scenario 2 - True warfarin refractory APS

Strategy	Mechanism / preclinical evidence
Increase anticoagulation intensity, change agent	Higher INR target, fondaparinux, enoxaparin

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Hydroxychloroquine	Protects Annexin A5 shield on endothelium, reduce aPL titer
Statins (fluvastatin)	↓ TF and adhesion molecules on endothelial cells

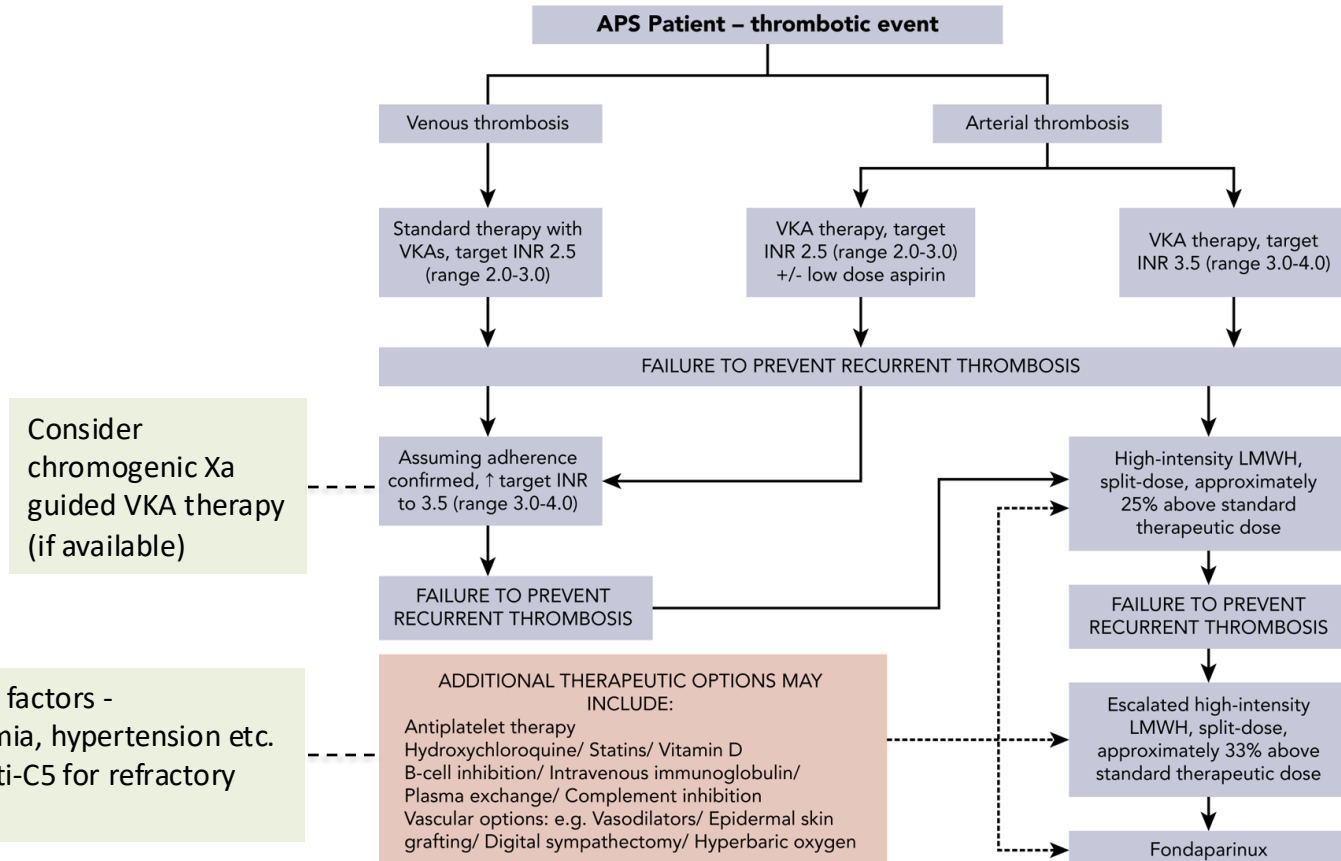
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Terminal complement inhibition	Eculizumab (C5 inhibitor) inhibits terminal complement

Treatment of thrombosis in APS



Catastrophic APS

- Rapidly developing widespread thrombosis with multiorgan failure
- Often 'triggered' by surgery, infection, pregnancy/delivery, etc.
- Rare (<1 % of APS) but carries up to 40-50% mortality despite best available therapy

Current standard of care:

- Anticoagulation + steroids + plasma exchange/ IVIG
- Rituximab for salvage

Diagnosis of CAPS

INTERNATIONAL CONSENSUS CRITERIA

1. Evidence of involvement of ≥ 3 organs, systems, and/or tissues

2. Development of manifestations simultaneously or in ≤ 1 week

3. Laboratory confirmation of the presence of aPL

4. Histopathologic confirmation of small vessel occlusion in at least one organ or tissue

Unless patient dies before repeat testing can be done (probable CAPS)

Or a 3rd event at >1 week and <1 months while on anticoagulation (probable CAPS)

Often not done in critically sick patients who are often thrombocytopenic and on aggressive anticoagulation

- Definite CAPS- 4 criteria met
- Probable APS- 3 criteria met*

CAPS Criteria are suboptimal in the real world

- CAPS criteria fail to identify most severely-ill APS patients
 - 152 ICU admissions in 134 APS patients

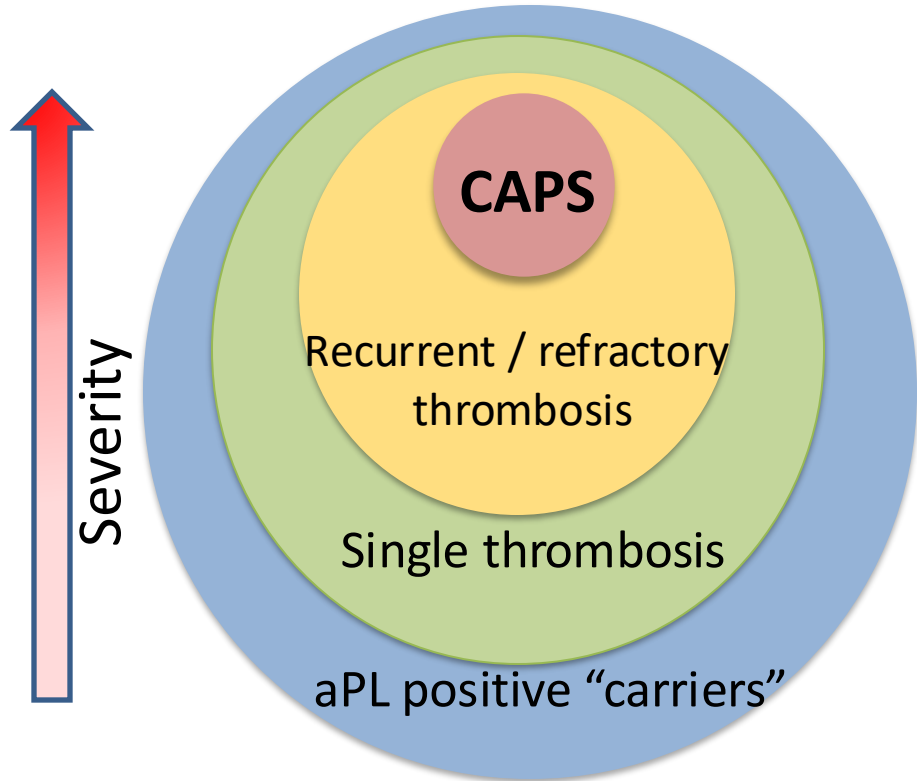
Classification by CAPS criteria	N	Mortality
Definite CAPS	11	27.3%
Probable CAPS	60	18.3%
Not CAPS	81	25.9%

- If it looks like CAPS, acts like CAPS → treat as CAPS (even if not quite meeting criteria)

Outline

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- Pathogenesis – APS is a thromboinflammatory disorder
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- Refractory and catastrophic APS – is complement the key?

Key issues in the current APS landscape

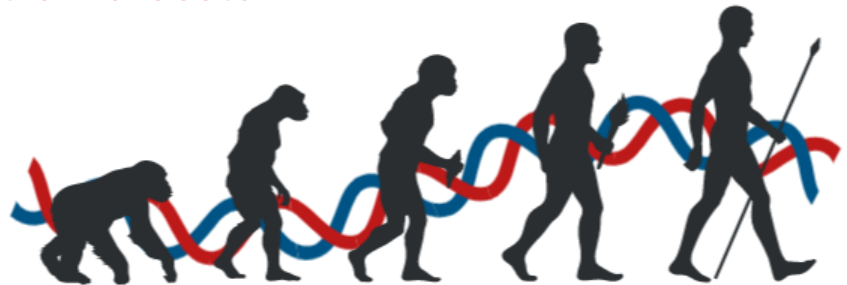


1. Suboptimal biomarkers for recurrence risk
2. Suboptimal treatments for refractory APS and CAPS.

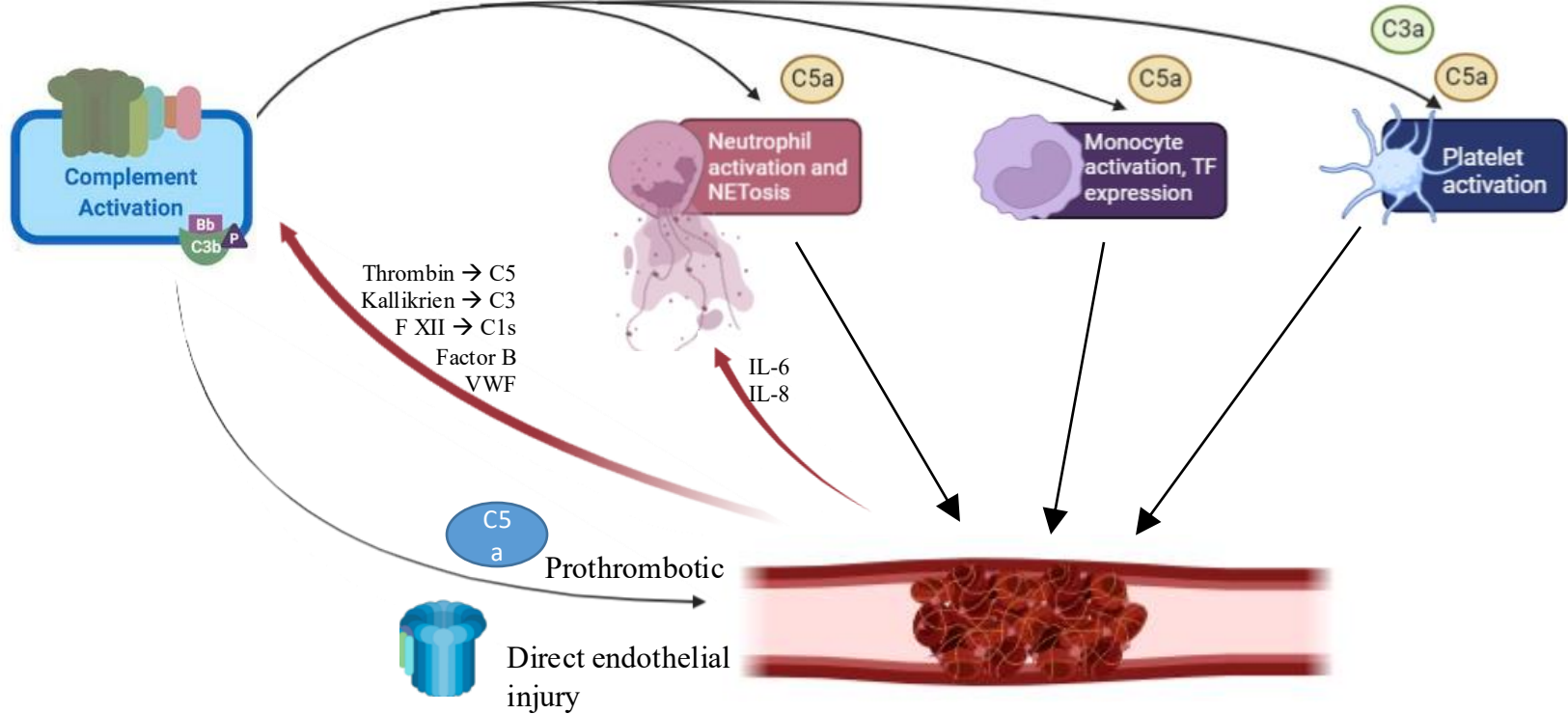
Can complement activation be a biomarker and a therapeutic target for refractory APS and CAPS?

Complement and Coagulation – Similarities

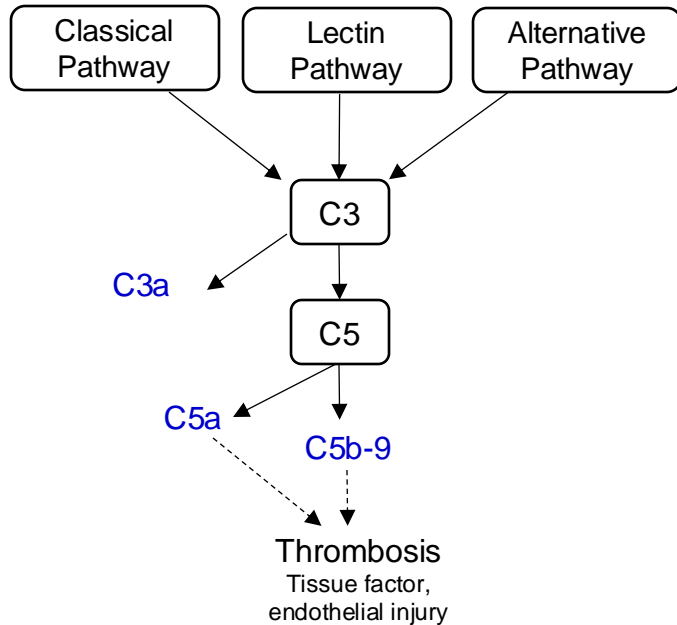
- Evolutionarily conserved pathways that mediate host defense (infection and bleeding)
- Serine proteases that activate in a cascading manner and are highly regulated
- Extensive complement x coagulation crosstalk



Complement and Thromboinflammation



Complement activation in APS and CAPS

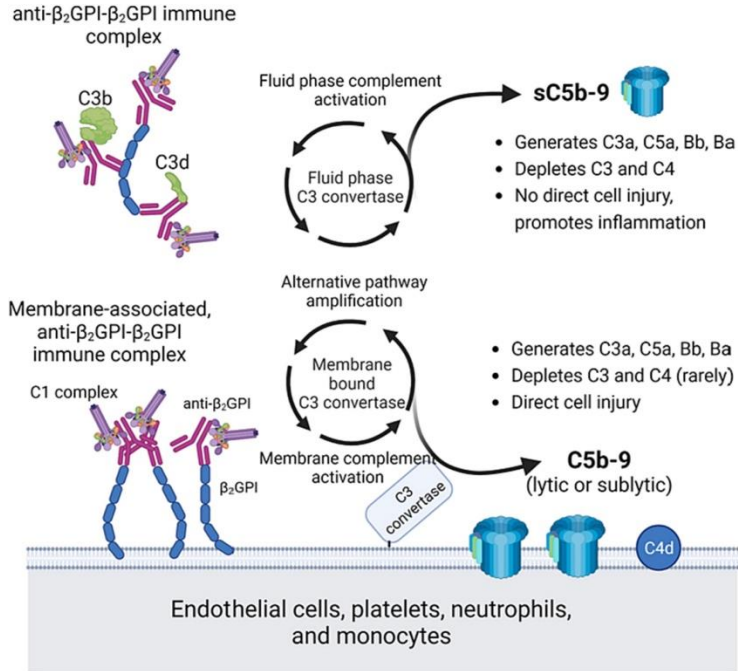


- Complement is critical for aPL-induced thrombosis in mice
- Evidence of complement activation in APS sera
- Anecdotal reports of eculizumab anti-C5) efficacy in refractory APS and CAPS)

Complement in patients with APS

- C5b-9 increased in patients with aPL and stroke compared with non-APS related stroke.
 - *Davis and Bray. Clin Exp Rheumatol. 1992*
- Higher levels of Bb and C3a in APS sera.
 - *Breen et al. Thromb Haemost 2012, Devreese et al. Thromb Haemost. 2010*
- Hypocomplementemia in primary APS sera.
 - *Oku et al. Ann Rheum Dis 2009*
- Association between these serum markers and aPL related thrombotic events is uncertain.

Challenge with serum complement proteins as biomarkers of disease activity



I. Fluid phase complement activation assays

- Quantification of complement proteins (C4 and C5)
- Quantification of complement activation products (C5b9, C5a, C3a, Bb, C1q, etc)

II. Cell based complement activation assays

- Cell bound complement activation fragments
- Ex vivo endothelial C5b9 deposition assays
- Modified Ham assay
- Hemolytic assays (CH50, AH50)

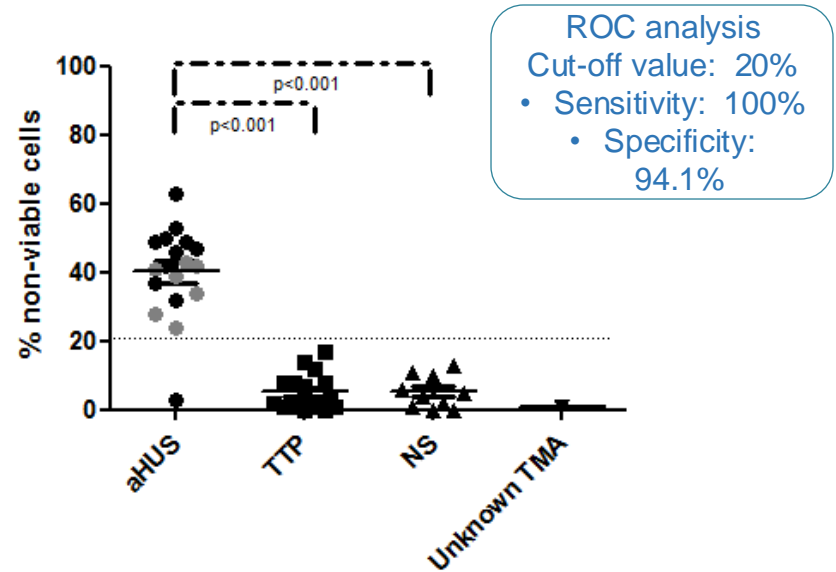
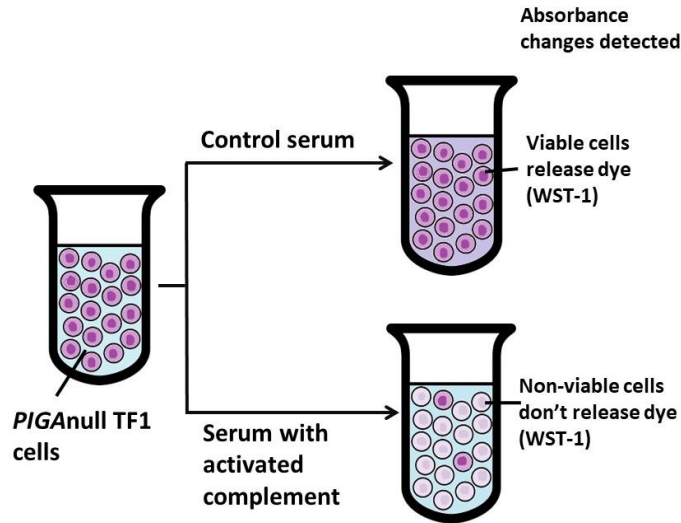
III. Other assays

- Antibodies against complement proteins
- Complement gene sequencing

- No consistent relationship with 'active' disease even in aHUS (prototypical complement disorder)
- Do not reflect complement activity at the cell surface

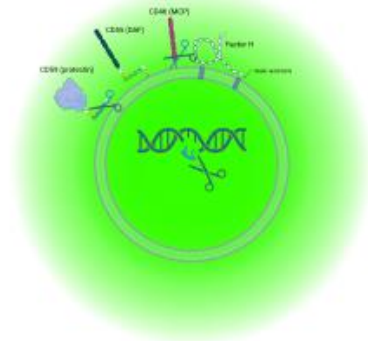
Modified Ham (mHam) - Cell based functional assay for complement activation

Principle: Cell line lacking surface CD55 and CD59 is susceptible to complement mediated killing.

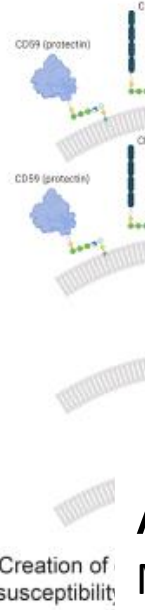


MHam 2.0 Bioluminescent modified Ham

A



1. Genetic engineering of autonomously bioluminescent cell line.



2. Creation of susceptibility

MACHAON
DIAGNOSTICS

Order Now

Introducing mHam 2.0

A New Era of Confidence in Diagnosing
Complement-Mediated Diseases

Available now through our exclusive
partnership with Johns Hopkins Medicine.

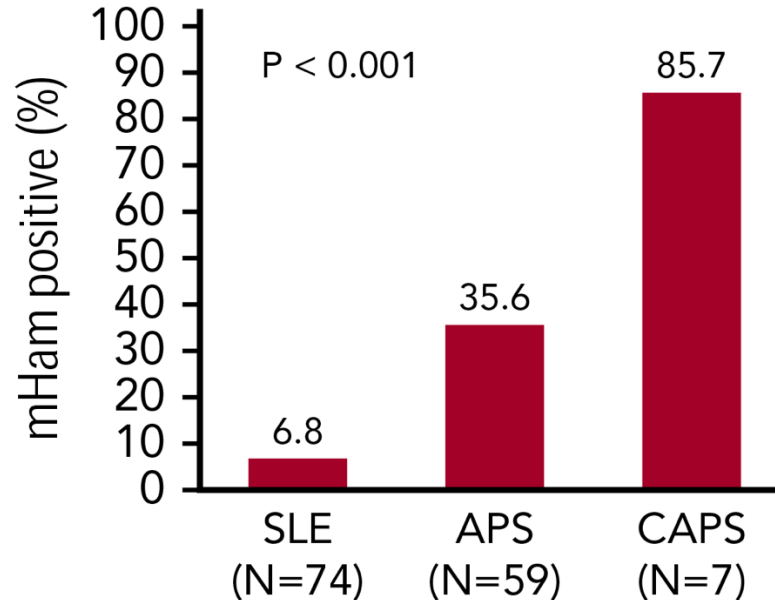
Order Now

The advertisement features a dark green background with a circular graphic on the right composed of white, red, and yellow segments. A glowing green light emanates from the center of the circle.

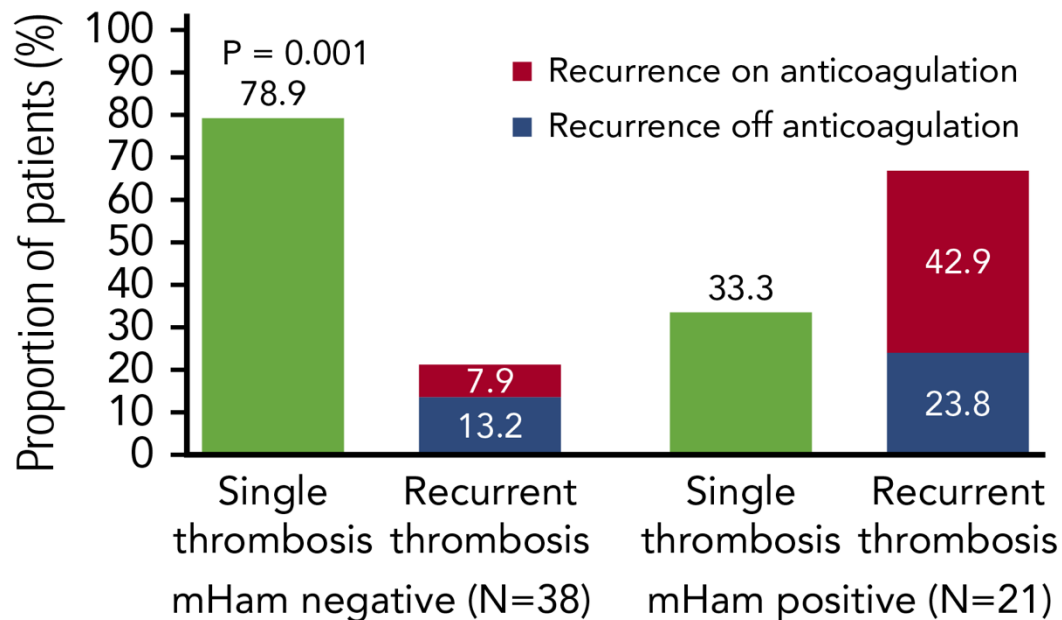
Available for clinical testing

Mham.machaondiagnosics.com

Complement activation is a feature of thrombotic APS



Complement activation (mHam) predicts recurrent thrombosis and refractory thrombosis



CAPS is associated with rare variants in complement regulatory genes

Diagnosis	N	Rare germline C' mutations (%)*
aHUS	17/33	51.5%
Normal	10/43	23.3%
CAPS	9/19	47.3%
SLE	6/21	28.6%
APS	12/55	21.8%

*MAF < 0.005

Rare variants in the following genes

THBD (2)

Homozyg CFHR1- CFHR3 del (1)

CR1 (3)

CFHR4 (1)

CFI (2)

Genes on panel: *CFH, CFB, CFI, CFD, CFP, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, C3, CD46 (MCP), THBD, CR1, DGKE*

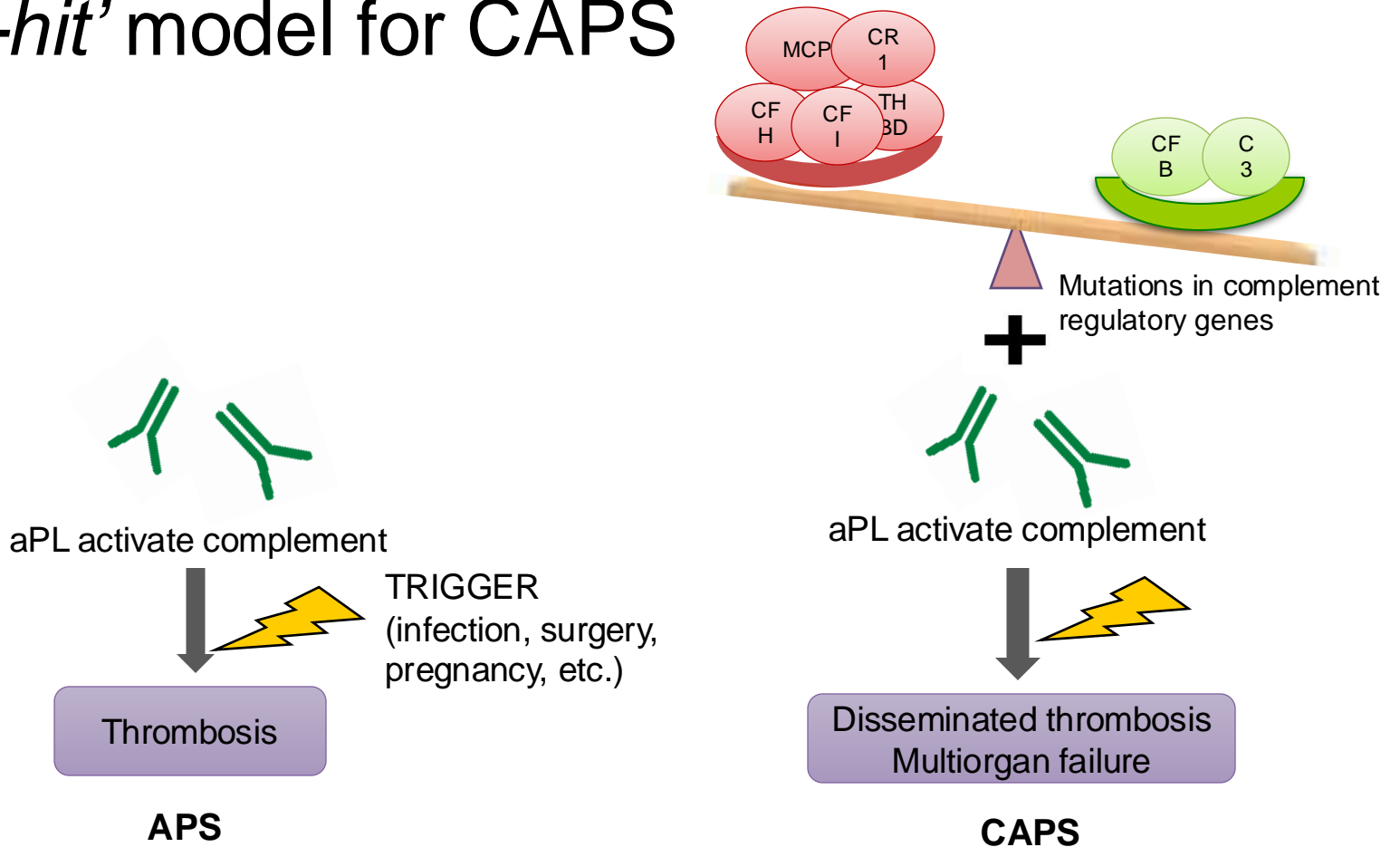
Environment – role of ‘triggers’ in CAPS

Precipitating factors in 280 patients from the CAPS registry

Precipitating factors	N	(%)
Infection	62	22%
Surgery	28	10%
Oral anticoagulation withdrawal/low INR	22	8%
Medications	20	7%
Obstetric complications	19	7%
Neoplasia	14	5%
SLE flare	8	3%

- Often complement amplifying conditions
- Many complement disorders have exacerbations in the presence of these conditions (e.g. PNH, aHUS)

'Multi-hit' model for CAPS

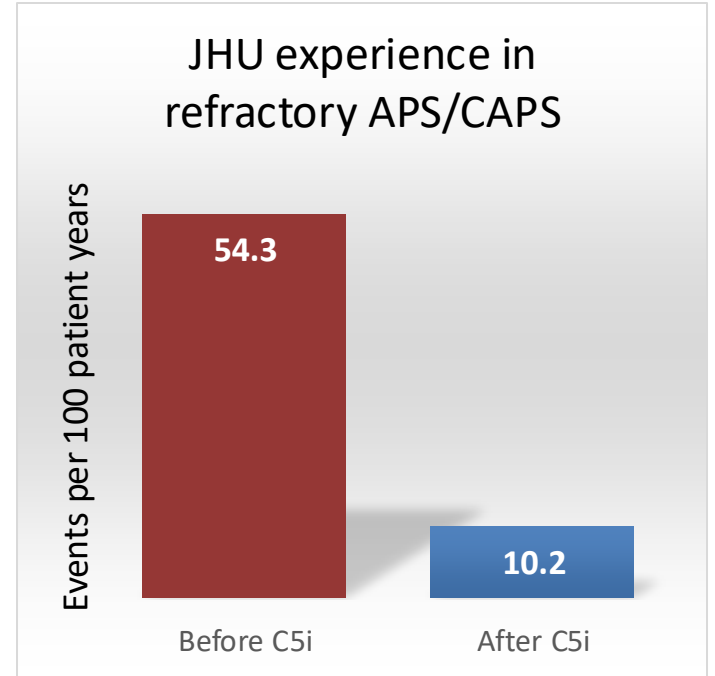


Eculizumab is effective in a subset of CAPS

- Retrospective cohort of 11 triple positive patients with CAPS refractory to anticoagulation, steroids, and plasma exchange
- Eculizumab → Clinical response in 5 / 11
- Non responders more likely to be on dialysis before eculizumab
- Responders had lower platelet count and a TMA like picture
- Consider eculizumab in CAPS refractory to previous therapies or with features of a thrombotic microangiopathy

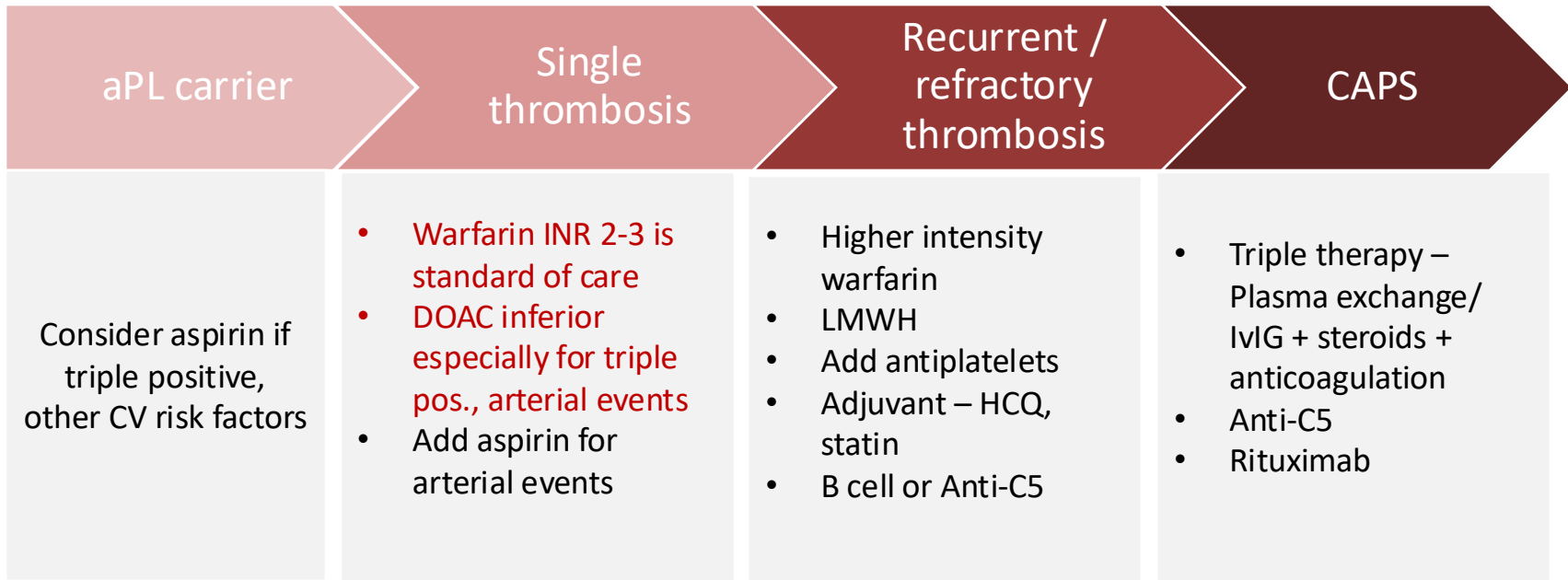
Eculizumab for CAPS and refractory APS

- Multiple case reports that eculizumab is effective in refractory CAPS
 - Poor outcomes are unlikely to be reported – publication bias



Ranjan N, Unpublished data

Individualizing antithrombotic therapy for APS



Screen for and address risk factors – hypertension, hyperlipidemia, hormones, obesity

Evaluate and manage bleeding risk

Summary

- APS is a thromboinflammatory disorder
- Vitamin K antagonist (warfarin) is the treatment of choice for thrombotic APS
- Triple positivity (LA + aCL + anti-b2GPI) predicts first/recurrent thrombosis
- CAPS patients do best with triple therapy : anticoagulation + steroids + plasma exchange (Salvage: rituximab, eculizumab)

(May need to relax CAPS criteria in real world practice)

Acknowledgements

Hopkins Research team

- Robert Brodsky, MD
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