Antiphospholipid syndrome

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Disclosures

- Consulting – Takeda, Alexion, Sanofi, Novartis, RallyBio, TargED
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- Membership on board of directors: Hemostasis and Thrombosis Research Society, USTMA Consortium
- Royalties – UpToDate.com

Learning objectives

At the end of this presentation, the learner will be able to

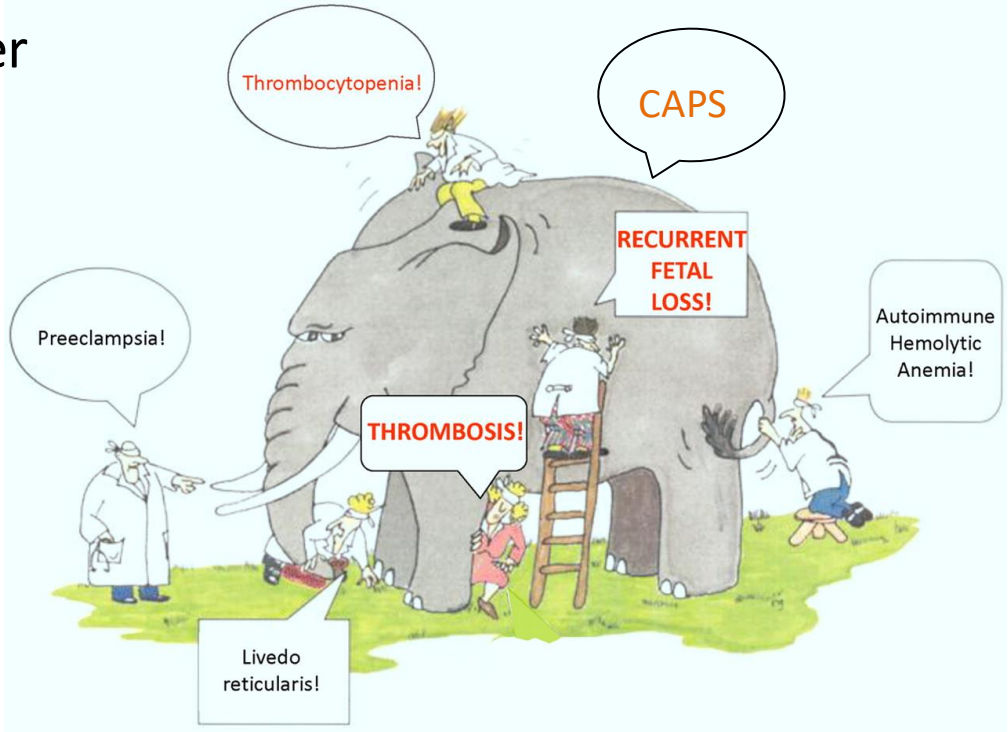
- Apply updated clinical and laboratory tools for the diagnosis of APS
- Identify evidence-based strategies for the treatment of thrombotic APS
- Identify pathogenic mechanisms and therapeutic targets for refractory and catastrophic APS

Outline

- APS diagnosis
- Thrombotic APS treatment
- Pathogenesis – APS is a thromboinflammatory disorder
- 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**



McCrae KR. Blood 2010

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

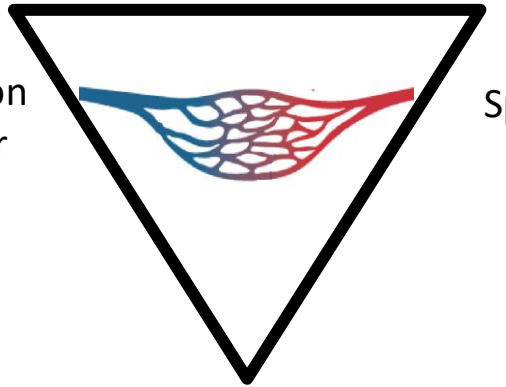
Responsible for
20%
of deep vein thrombosis

Responsible for
1 IN 5
recurrent miscarriages

Dabit et al. Curr Rheum Rep 2022; APS foundation of America, www.apsfa.org

Thrombosis in APS

ARTERIAL
Stroke/ TIA
Myocardial infarction
Peripheral vascular



VENOUS
DVT / PE
Splanchnic vein thrombosis
Cerebral venous sinus thrombosis

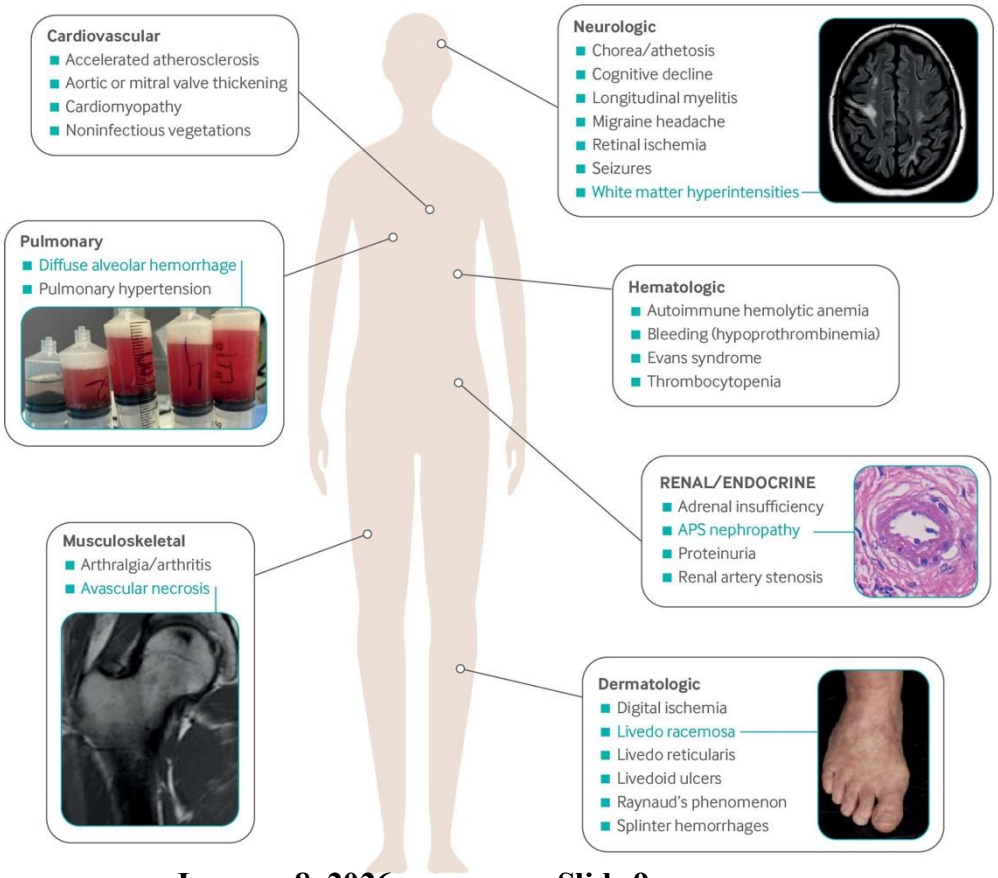
MICROVASCULAR
Catastrophic APS
Nephropathy
Pulmonary
Livedoid vasculopathy
Myocardial, adrenal

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_2GPI antibody of IgG or IgM isotype (>99th percentile)
Definite APS requires at least one clinical and one laboratory criteria

Miyakis et al. J Thromb Haemost 2006

Other *'non-criteria'* clinical manifestations



Jason S Knight et al. BMJ, 2023

ACR/EULAR classification criteria 2023

Barbhaiya et al. 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
D1. Macrovascular (Venous Thromboembolism [VTE])	
VTE with a high-risk VTE profile[c]	1
VTE without a high-risk VTE profile[c]	3
D2. Macrovascular (Arterial Thrombosis [AT])	
AT with a high-risk CVD profile[c]	2
AT without a high-risk CVD profile[c]	4
D3. Microvascular	
Suspected (one or more of the following)	2
Livedo racemosa (exam)	
Livedoid vasculopathy lesions (exam)	
Acute/chronic aPL-nephropathy (exam or lab)	
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)	
D4. Obstetric	
≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths	1
Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	3
PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	4
D5. Cardiac Valve	
Thickening	2
Vegetation	4
D6. Hematology	
Thrombocytopenia (lowest 20-130x10^9/L)	2

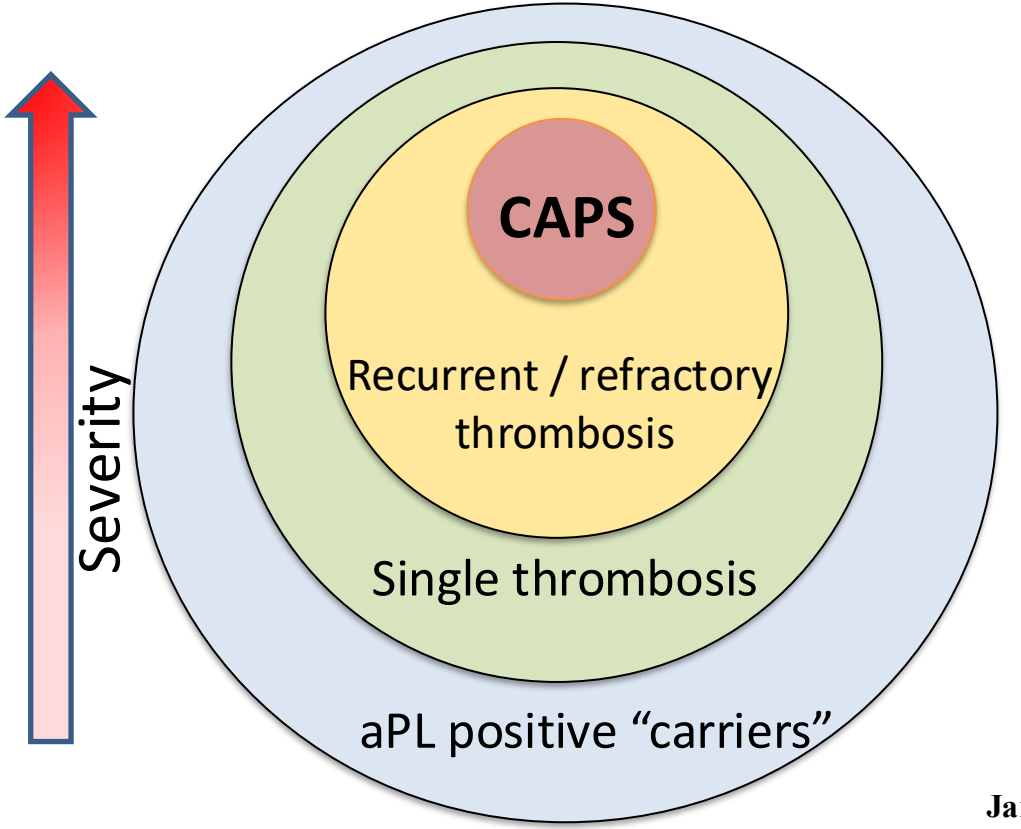
Laboratory (aPL) domains and criteria[e]	Weight
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])	
Positive LAC (single – one time)	1
Positive LAC (persistent)	5
D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])	
Moderate or high positive (IgM) (aCL and/or aβ_2GPI)	1
Moderate positive (IgG) (aCL and/or aβ_2GPI)	4
High positive (IgG) (aCL or aβ_2GPI)	5
High positive (IgG) (aCL and aβ_2GPI)	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

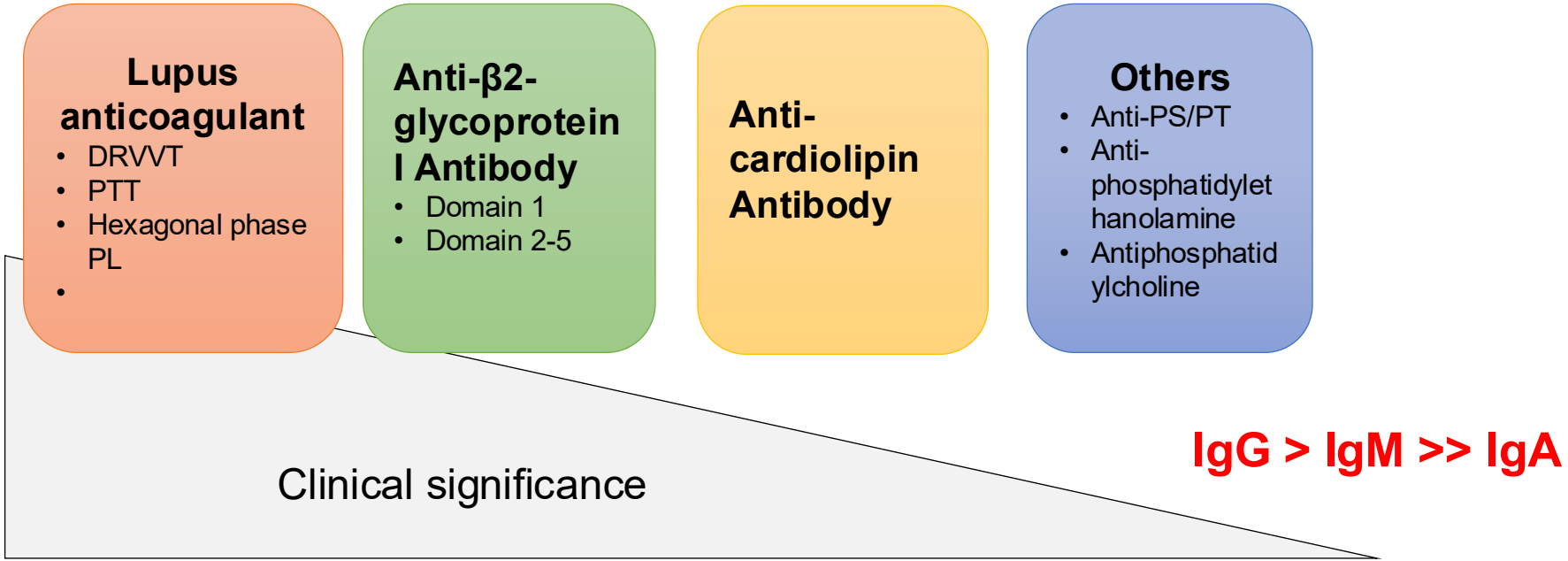
10

Spectrum of thrombotic APS severity



Not all aPL are created equal

All aPL are not created equal



DeGroot et al JTH 3: 2005, Galli et al Blood 102:2717, 2003

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-β2GPI antibodies
- **β2GPI** antibodies more significant than prothrombin or aCL antibodies
- **aCL** are of borderline significance

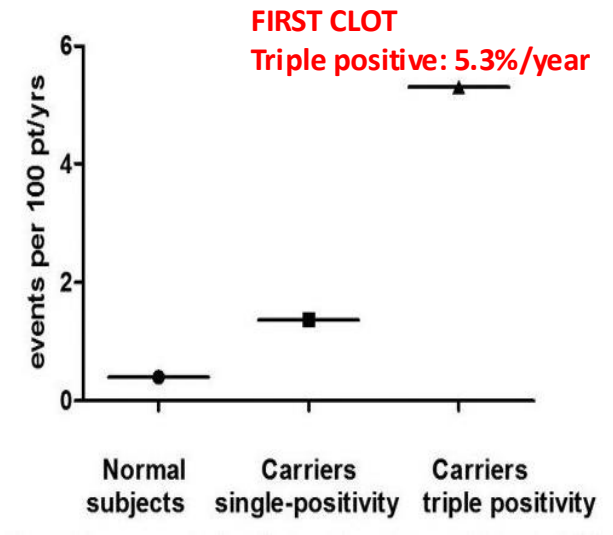
Risk highest for triple positive patients

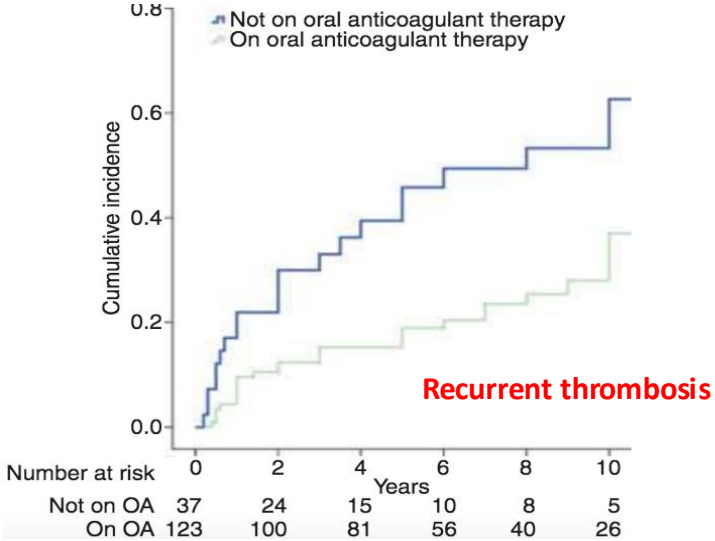
(Triple positive = lupus anticoagulant + anti-B2GPI + aCL)

DeGroot et al JTH 3: 2005, Galli et al Blood 102:2717, 2003

Triple positivity predicts first / recurrent thrombosis

Triple positive = lupus anticoagulant + anti-B2GPI + aCL





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

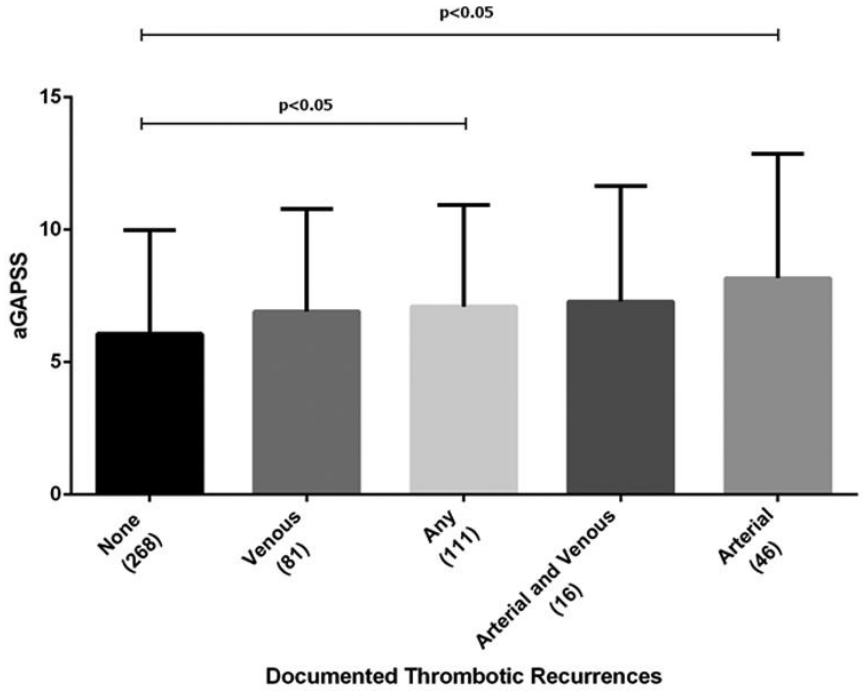
Does not identify patients at risk for CAPS or anticoagulation failure

Pengo et al. Blood 118:4714, 2011

Adjusted Global APS Severity (GAPSS) Score

Adjusted GAPSS	Points
Hyperlipidemia	3
Hypertension	1
Lupus anticoagulant	4
aCL IgG/IgM	5
Anti-B2GPI IgG/IgM	4

Radin et al. Semin Arthritis Rheum 2020

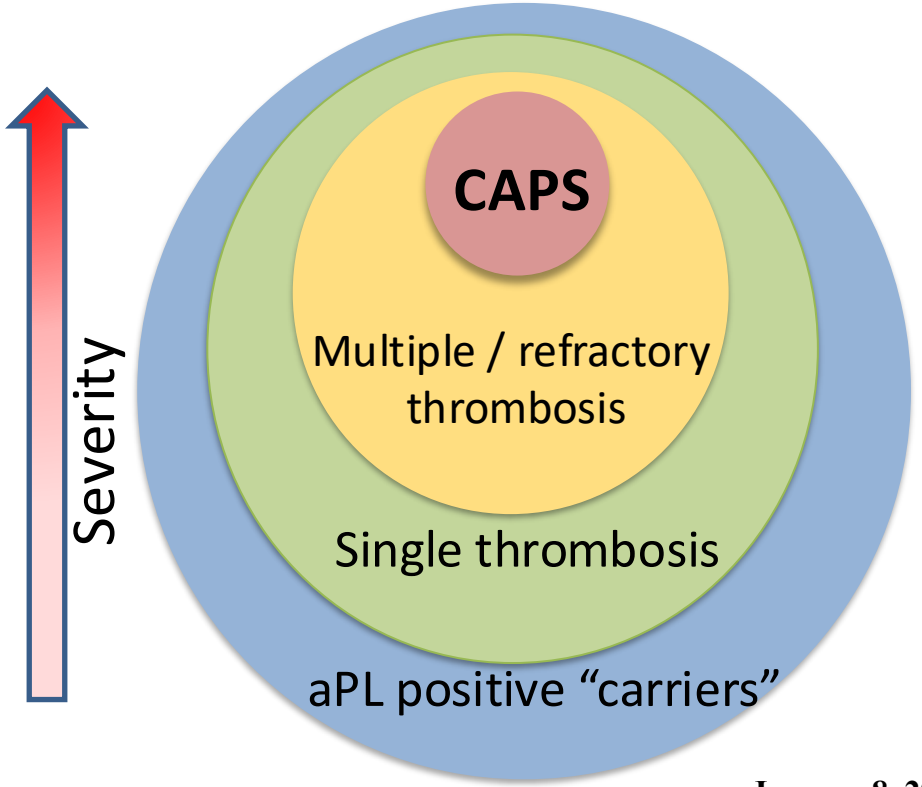


Patterns of thrombosis recurrence

- 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.

Niznik et al. Frontiers Immunol 2022

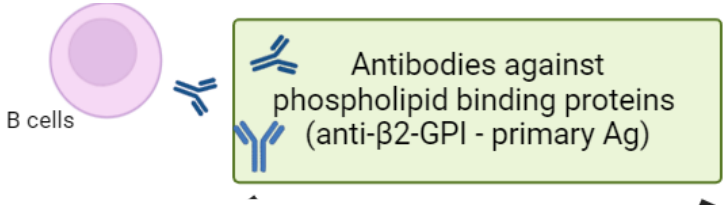
Key issues in the current APS landscape



1. Biomarkers to assess recurrence risk are suboptimal

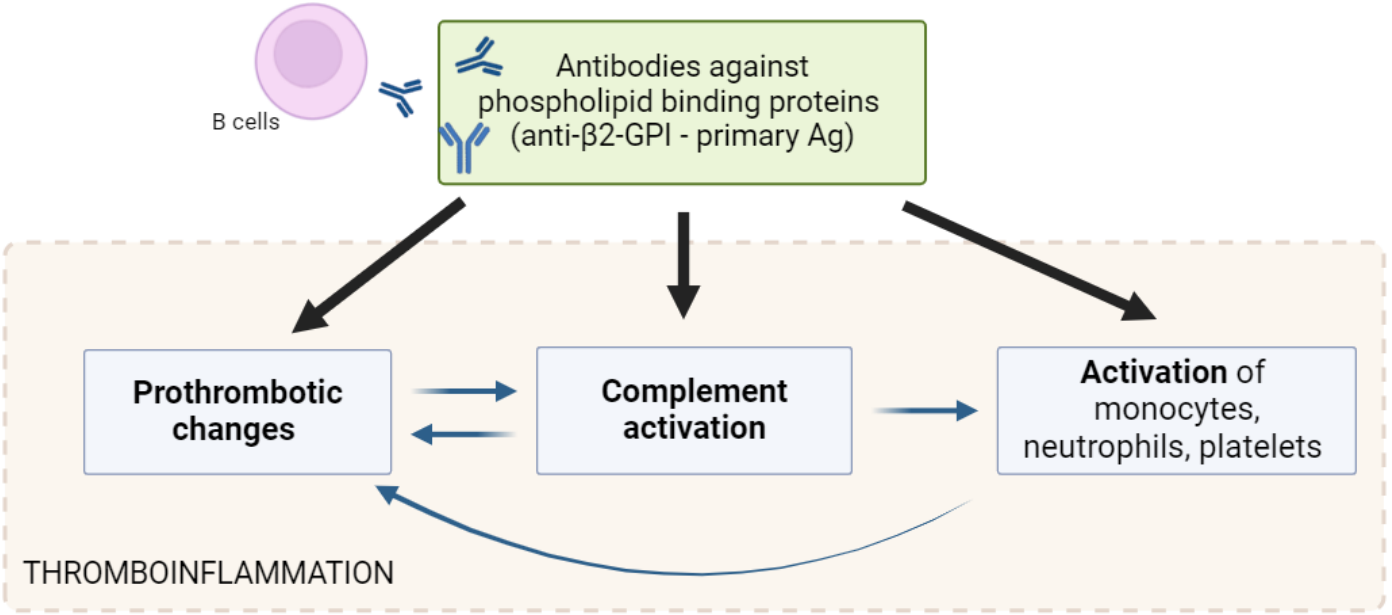
2. Suboptimal treatments for refractory APS and CAPS.

Pathogenesis of APS



Adapted from Garcia DA and Erkan D. NEJM 2019

Pathogenesis of APS



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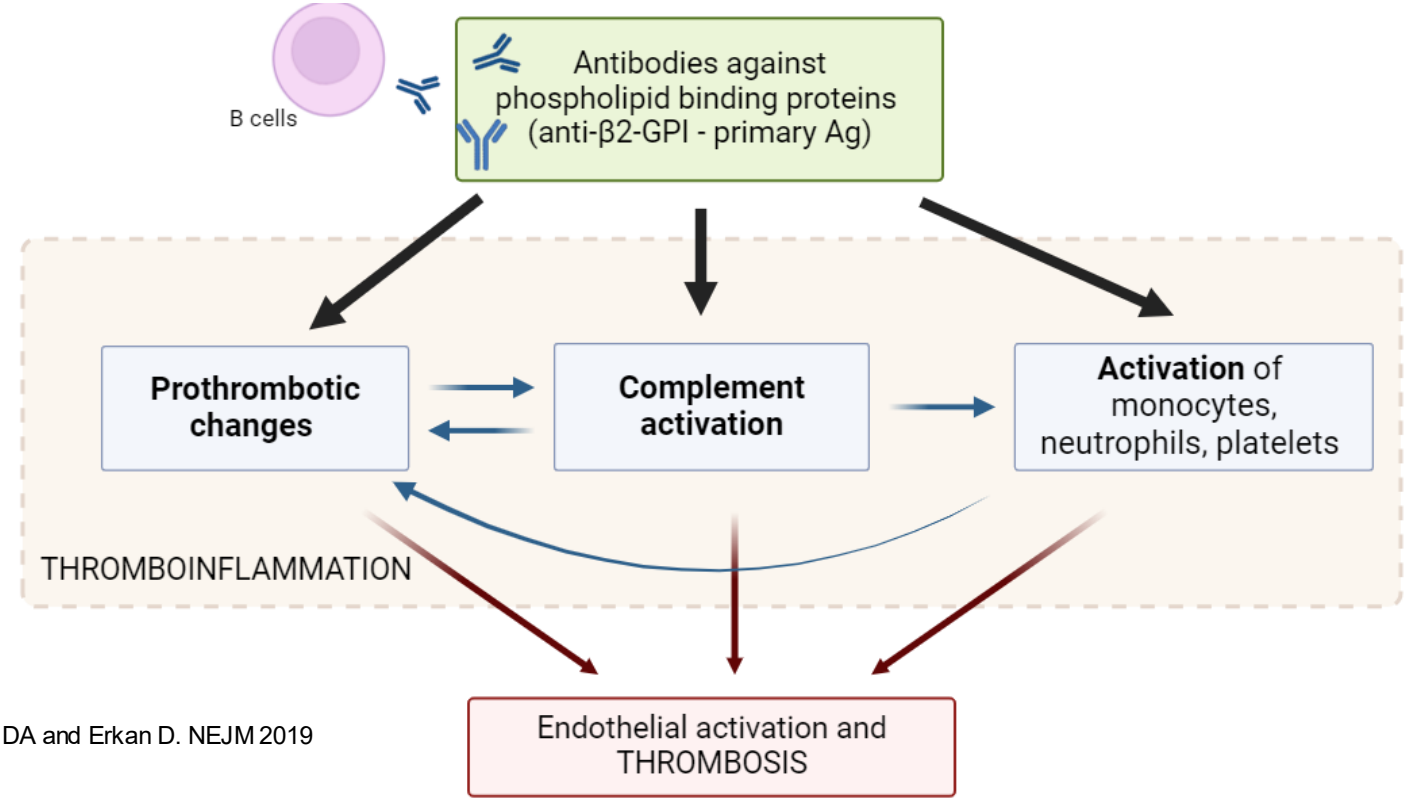
Pathogenesis of APS

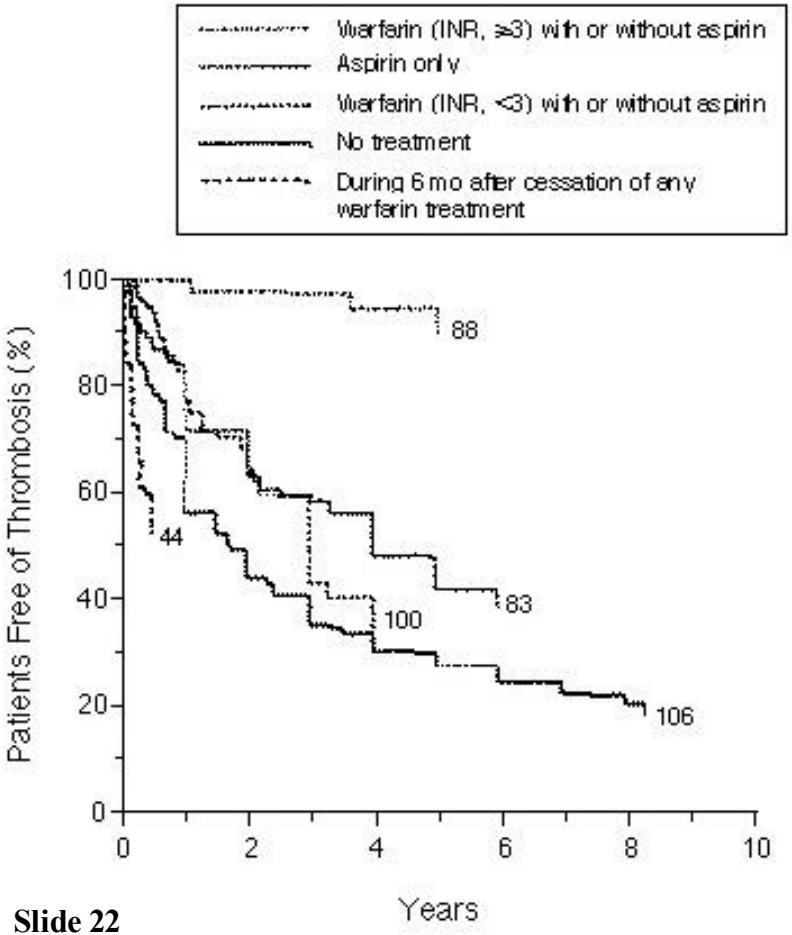


Adapted from Garcia DA and Erkan D. NEJM 2019

Outline

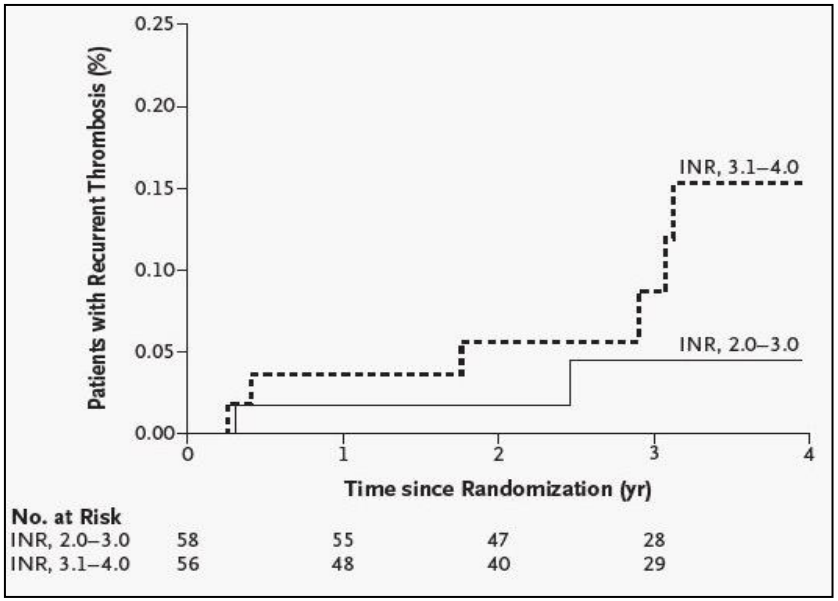
- APS diagnosis
- Thrombotic APS treatment
- Pathogenesis – APS is a thromboinflammatory disorder
- Refractory and catastrophic APS – is complement the key?

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



Khamastha et al. NEJM 1995

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

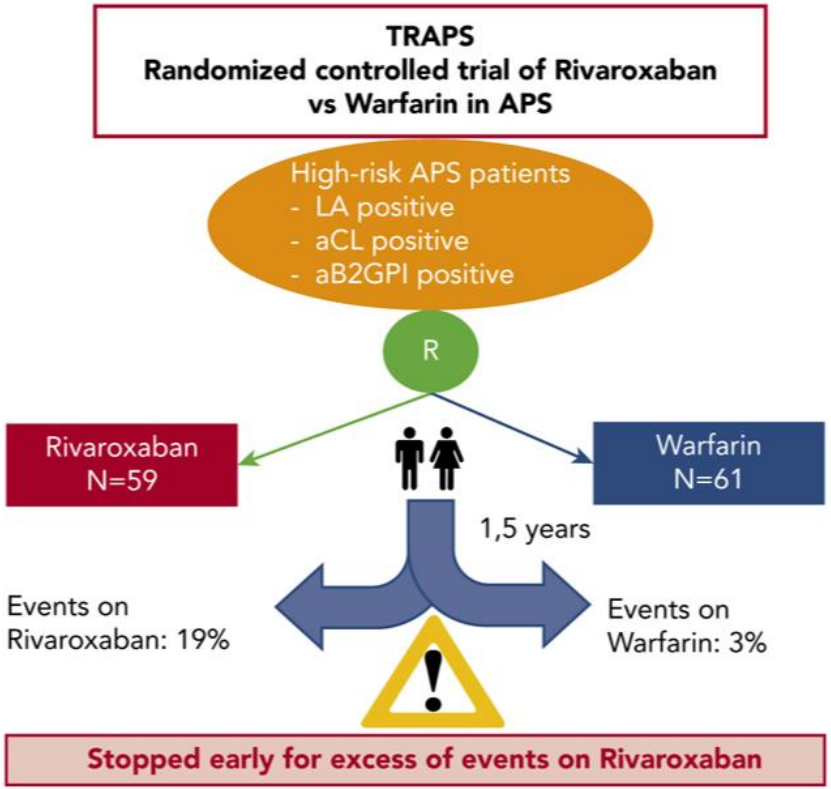
Warfarin with a higher target INR is sometimes used for recurrent clots.

Lim et al. JAMA 2006

Crowther et al. NEJM 349:1133, 2003

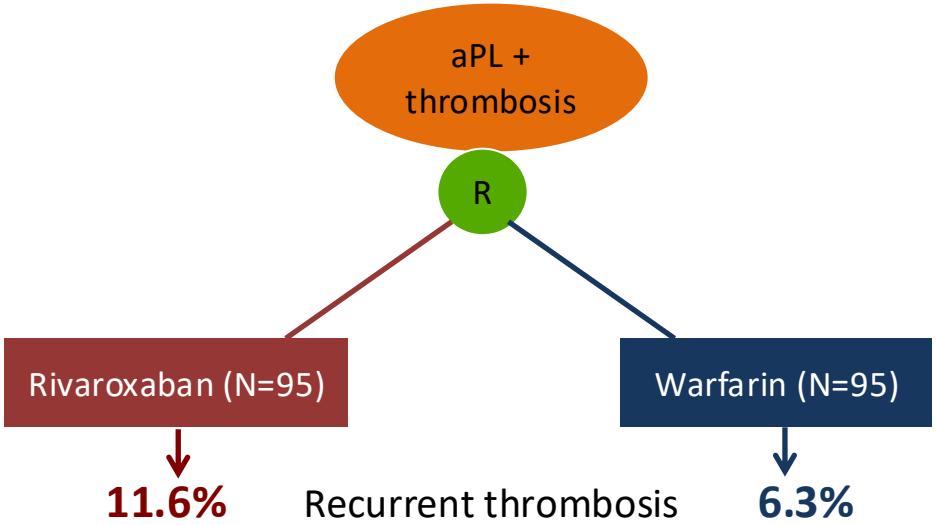
DOACs in triple positive APS?

Higher risk (triple positive) APS



Pengo et al. Blood 2018

What about DOACs for lower risk APS?



Non inferiority margin not met
(increased arterial events on rivaroxaban)

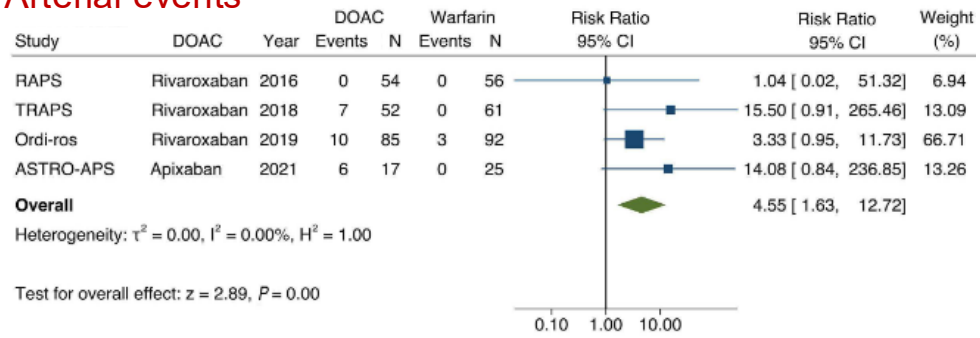
- ASTRO-APS trial (apixaban vs. warfarin)
- Thrombosis higher on apixaban (25% vs. 0%) – all stroke

Woller et al. Blood Advances 2021

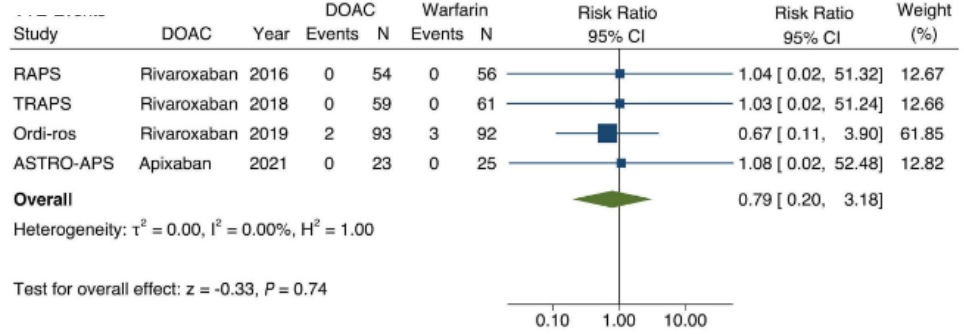
Ordi Ros et al. Ann Int Med 2019

Metanalysis of RCTs of warfarin vs. DOAC in APS

C Arterial events



D Venous events



Do not use
Triple positive
Arterial thrombosis

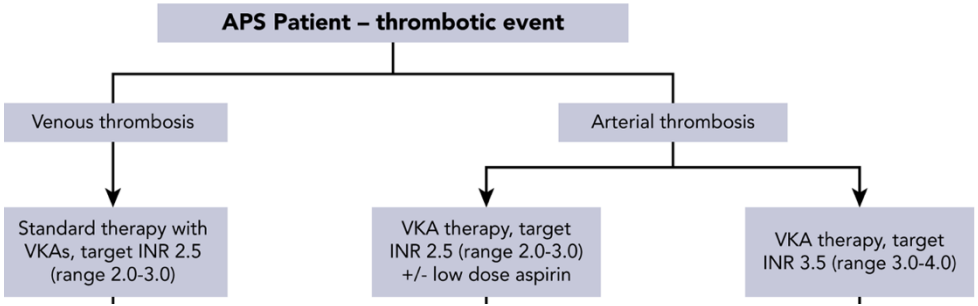
Less data for –
Low risk (single positive, low titer, IgM only), provoked thrombosis

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



Cohen and Isenberg. Blood 2021

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)

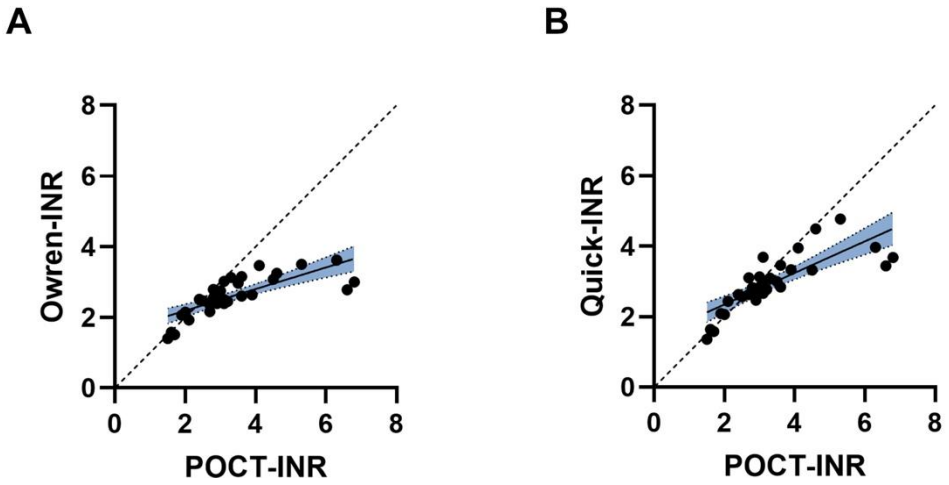
There is a small and clinically challenging proportion of anticoagulation refractory patients

Scenario 1 – is the point of care INR inaccurate?

Point of care (capillary whole blood) versus venipuncture (citrate whole blood)

Discordant INR (> 0.5 difference) in 8-12% of APS

More often in patients with lupus anticoagulant and aβ2GPI antibodies



Masucci et al. EJHaem 2022 Jul 9;3(3):899–902, Dush and Erdeljac. J Pharm Pract 2020;33(3):390-391, Perry et al. Thromb Haemost. 2005;94(6):1196-202.

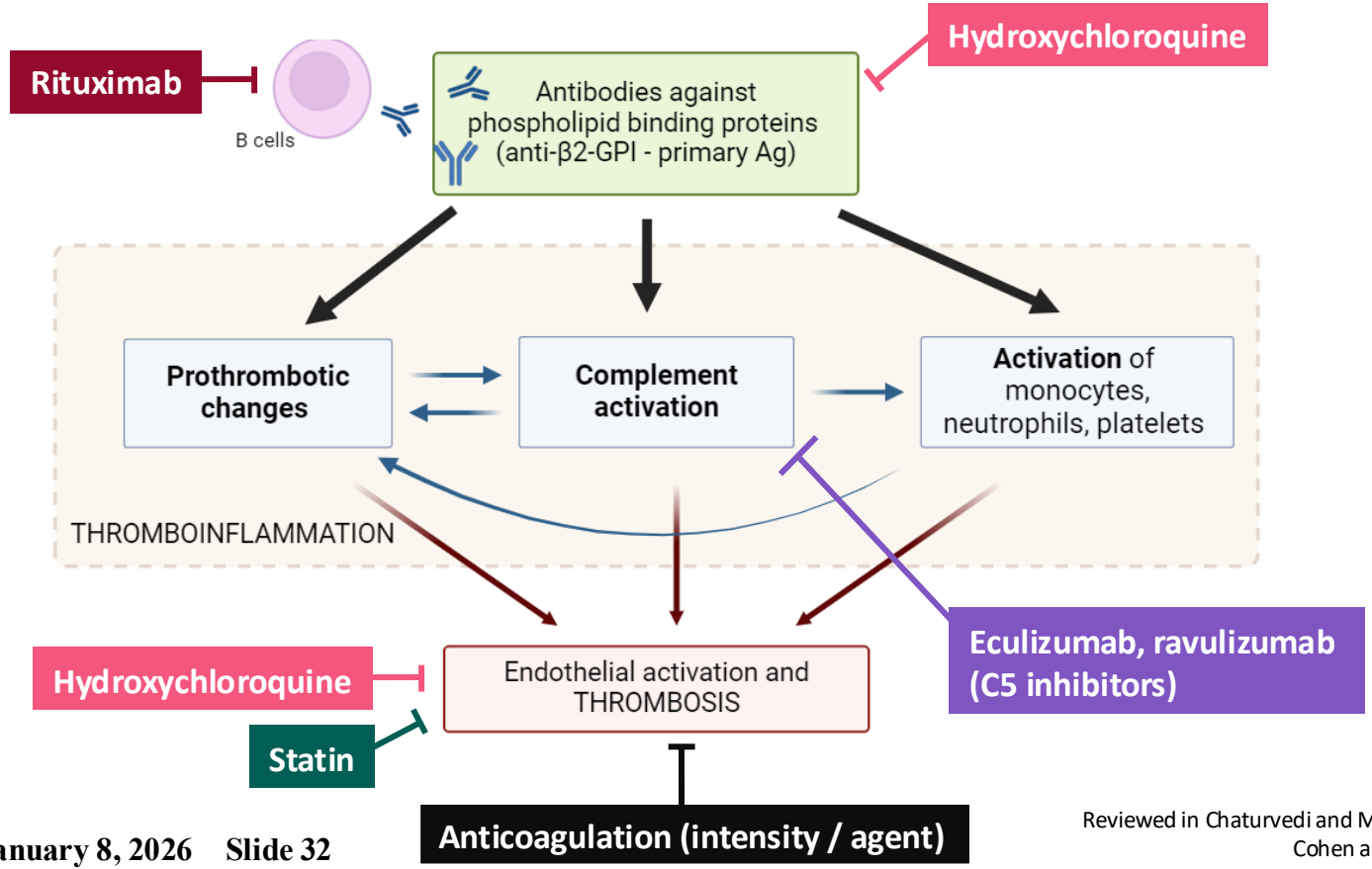
Scenario 1 – is the venipuncture INR inaccurate?

- 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 ≅ 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%

Sanfilippo et al. WMJ 2000, Moll S and Ortel TL. Ann Int Med 1997

APS – mechanisms and selected targets



Reviewed in Chaturvedi and McCrae. Blood Rev 2017, Cohen and Isenberg Blood 2021

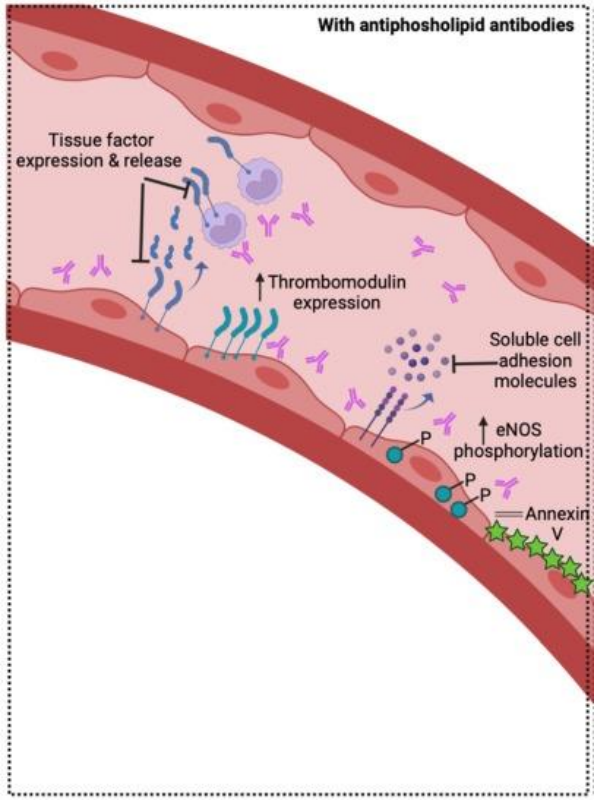
Scenario 2 - True warfarin refractory APS

Strategy	Mechanism / preclinical evidence
Increase anticoagulation intensity, change agent	Higher INR target, fondaparinux, enoxaparin
Hydroxychloroquine	Protects Annexin A5 shield on endothelium
Statins (fluvastatin)	↓ TF and adhesion molecules on endothelial cells
Rituximab	Targets CD20 (B cells) and may reduce aPL production
Terminal complement inhibition	Eculizumab (C5 inhibitor) inhibits terminal complement

Reviewed in Chaturvedi and McCrae. Blood Rev 2017, Cohen and Isenberg Blood 2021

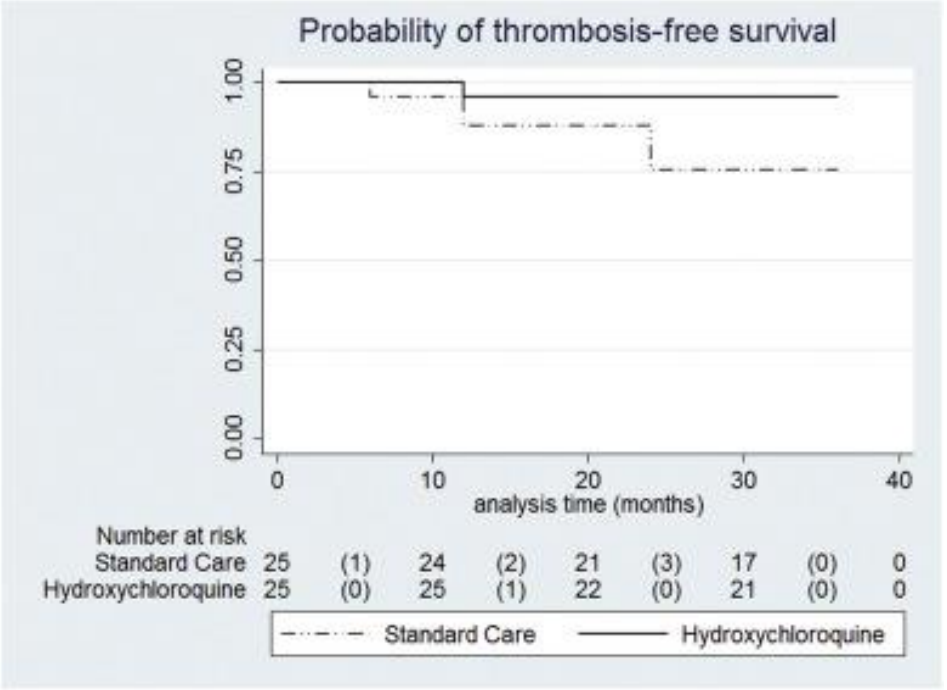
Hydroxychloroquine in APS – rationale for use

- Anti-inflammatory/anti-thrombotic effects
  - reduce adhesion molecule and TF in plasma
- Anti-thrombotic effects on endothelium
  - Protect Annexin V shield on endothelium
  - Reduce TF, increase TM expression
  - Reduce vasoconstrictor release (endothelin-1, NO)
- Reduces aPL titer
- Reduces thrombosis in mouse model of APS



Hydroxychloroquine in primary APS

- Pilot open label RCT of HCQ in primary APS (N=50)
- SOC therapy continued (warfarin +/- ASA)
- Recurrent thrombosis – 24% vs. 4%
- Adverse events in HCQ arm – 1 each retinopathy (reversed), diarrhea, CK elevation
- **Potential benefit > risk**



Kravvariti et al. Autoimmunity Rev 2020

Rituximab in APS

RITAPS - Pilot open label ph 2 study

- Primary APS with varied non-criteria manifestations (total N = 19)
- No change in titers

Manifestation	Complete or partial response
Thrombocytopenia	2/4
Cardiac valve disease	0/3
Skin ulcer	4/5
Nephropathy	1/1
Cognitive dysfunction	4/5

Erkan et al. Arthritis Rheum 2912

Rituximab in APS

Case review in literature

- N=24
- Thrombocytopenia (41.7%), skin involvement (33.3%), neuro/heart valve (12.5%), pulmonary or renal (4.2%)
- Responses
  - Complete 45.8%
  - Partial 29.2%

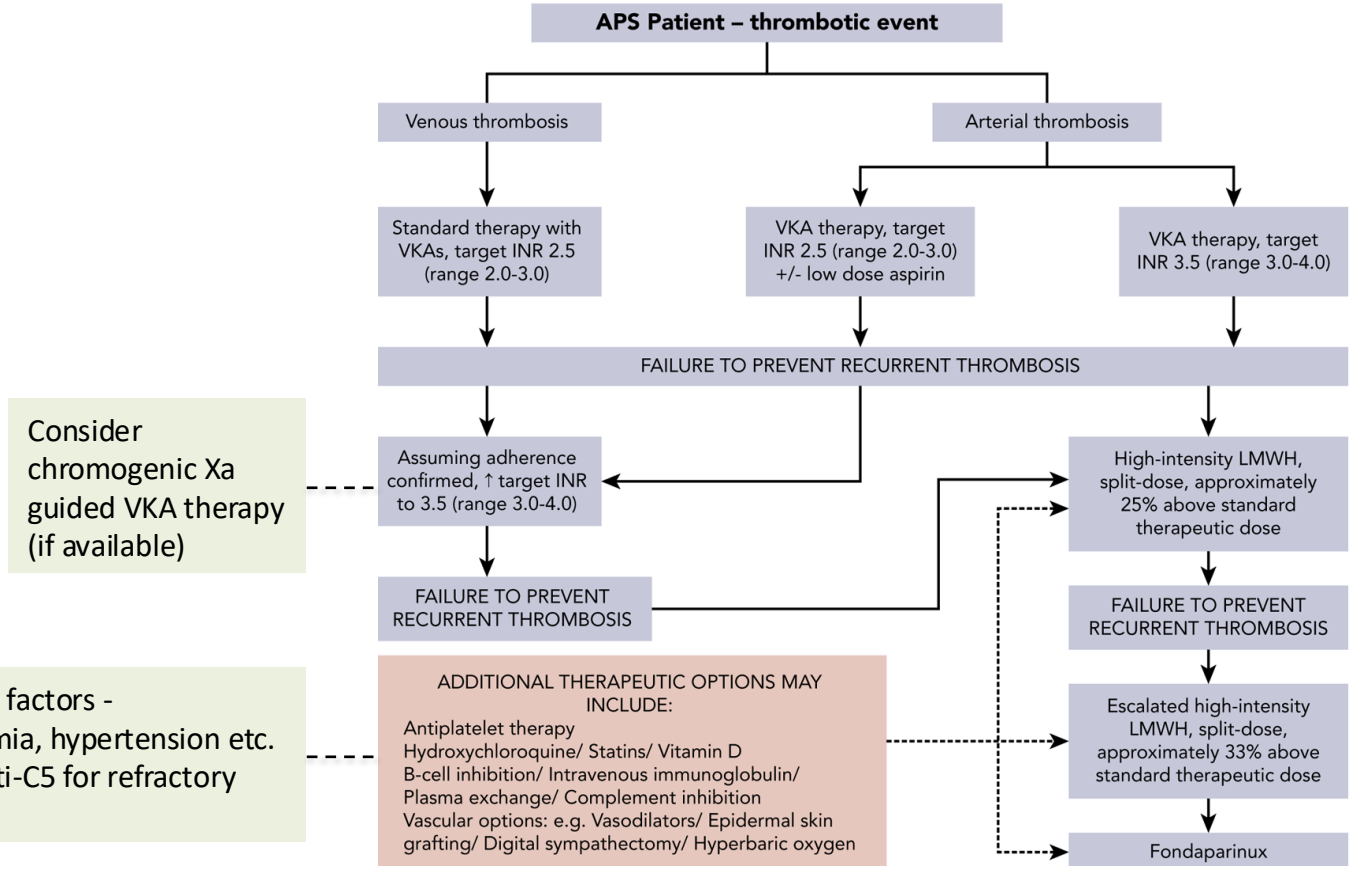
When to consider (off label)-

- Rituximab may improve some **non-criteria / microvascular** manifestations of APS
- No strong data for macrovascular thrombosis prevention
  - Can consider if recurrences continue despite adding HCQ/statin and anti-C5 is not available
- High response rate as salvage therapy in catastrophic APS

Anticoagulation FORUM National Conference

Pons et al. Med Clin (Barc) 2014

Treatment of recurrent thrombosis in APS



Cohen and Isenberg. Blood 2021

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
- Approximately 70% survival

Cervera, et al Arth Rheum 46:1019, 2002, Asherson RA et al. Medicine (Baltimore) 2001;80:355, Asherson et al. Lupus 2003;12:530

Ortel et al. Blood 2015;126:1285-93, Rodríguez-Pintó et al. Rheumatology 2018; 57:1264-70

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*

Asherson et al. Lupus 2003;12:530

CAPS Criteria are suboptimal in the real world

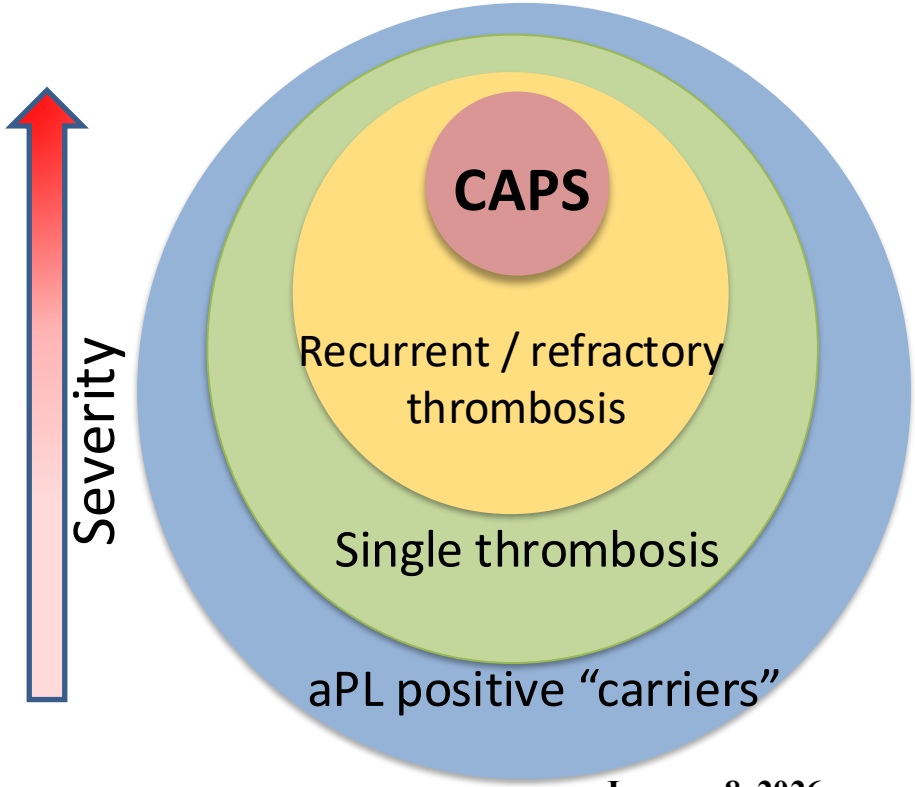
- CAPS criteria fail to identify most severely-ill APS patients
  - 152 ICU admissions in 134 APS patients

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)

Pineton de Chambrun et al. J Autoimmunity 2019

Key issues in the current APS landscape

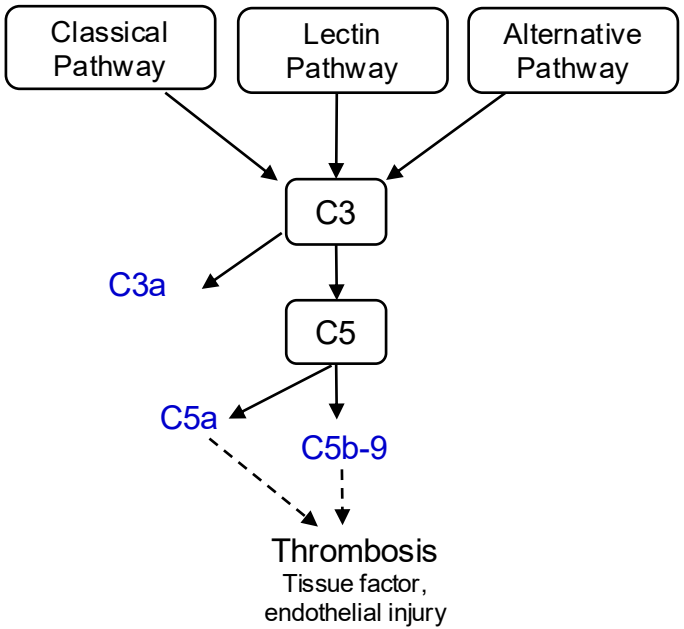


1. Suboptimal biomarkers for recurrence risk

2. Suboptimal treatments for refractory APS and CAPS.

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

Complement activation in APS and CAPS



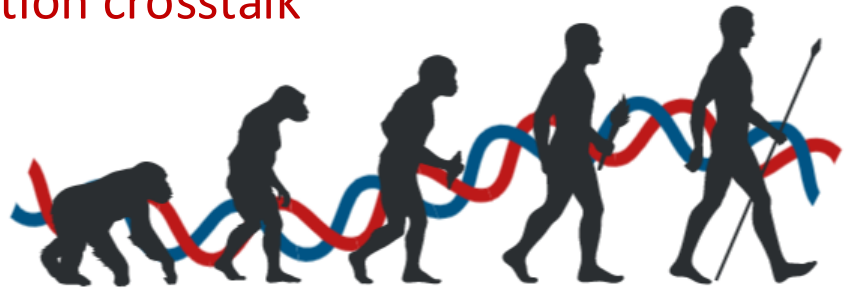
- Complement is critical for aPL-induced thrombosis in mice
- Evidence of complement activation in APS sera
- High rate of complement mutations in CAPS
- Anecdotal reports of eculizumab anti-C5) efficacy in refractory APS and CAPS)

Fischetti et al. Blood 2005, Devreese et al. Thromb Haemost 2010, Oku et al. Ann Rheum Dis 2009, Chaturvedi et al. Front Immunol 2019, Chaturvedi et al. Blood 2020

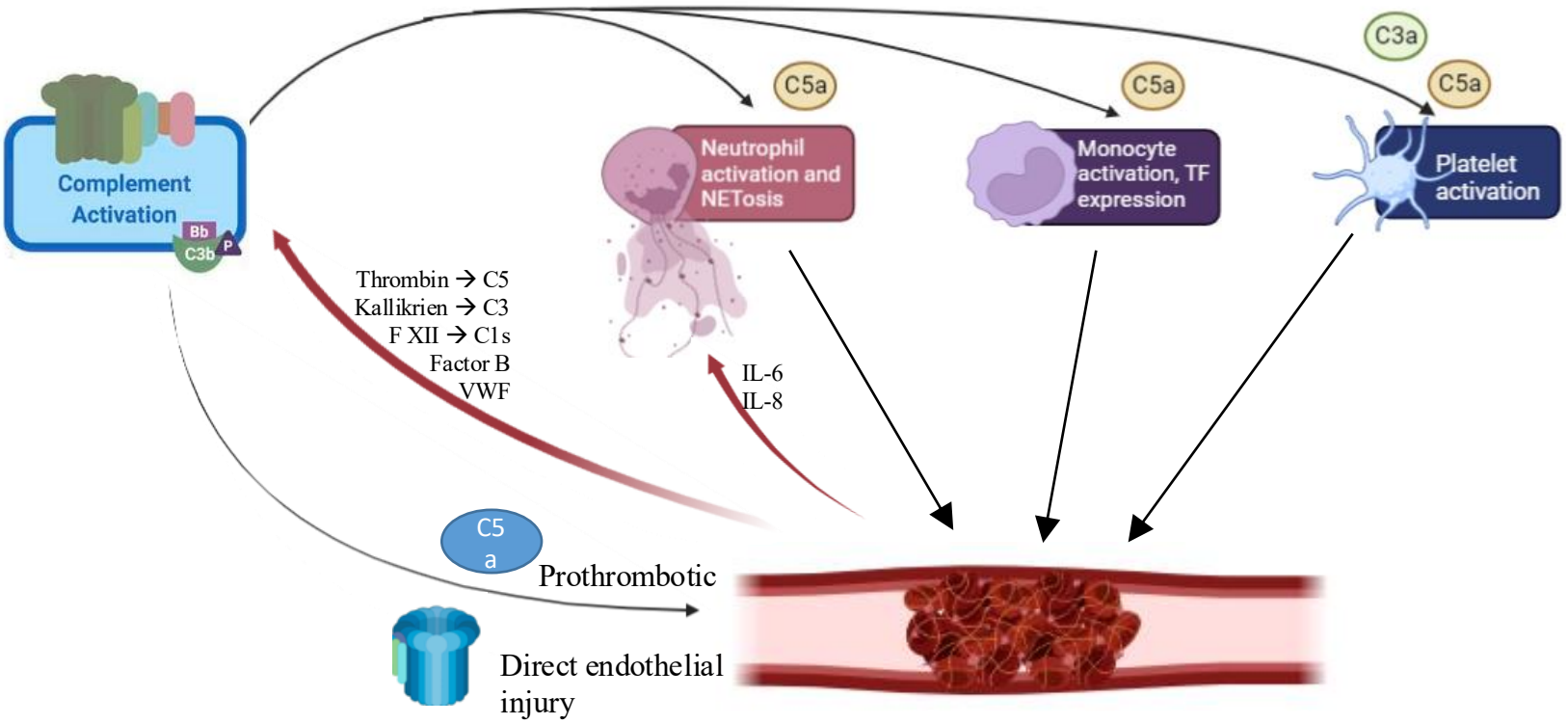
Complement and Coagulation – Similarities

- 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

Conway EM. J Thromb Haemost 2015



Complement and Thromboinflammation



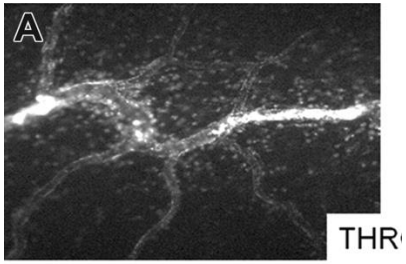
Adapted from Java A et al. JCI Insight 2020

Complement is critical for aPL mediated thrombosis

aPL+ IgG

LPS
("trigger")

Thrombosis

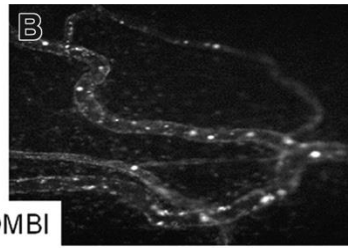


aPL+

aPL- IgG

LPS

Less/no Thrombosis



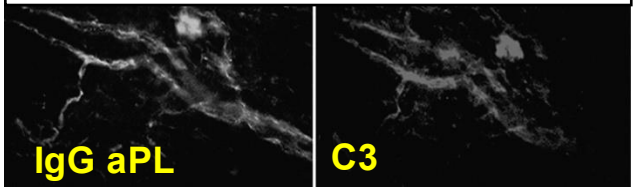
aPL-

aPL+ IgG

LPS

C6 -/- rat or
C5 inhibitor added

Co-localization of IgG and C3 in vessel

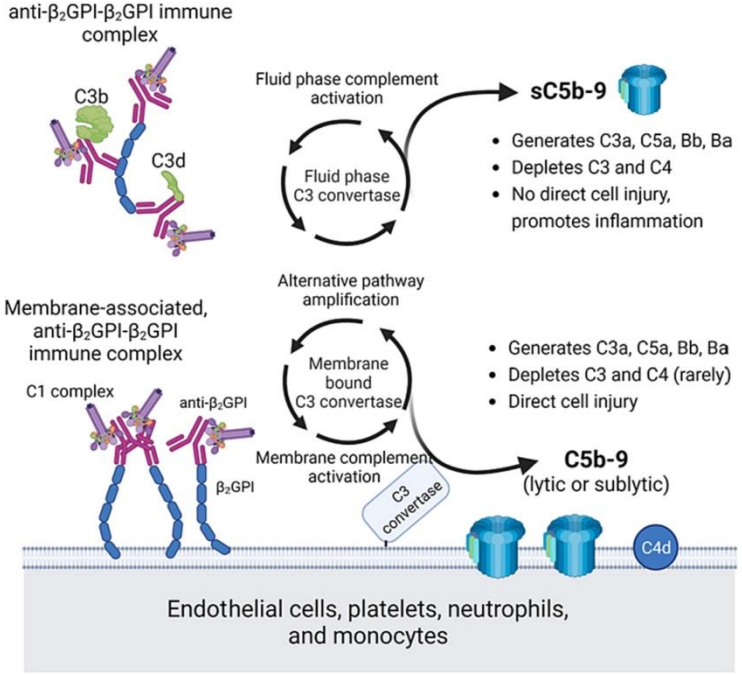


Fischetti et al Blood 2005;106:2340-46

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)

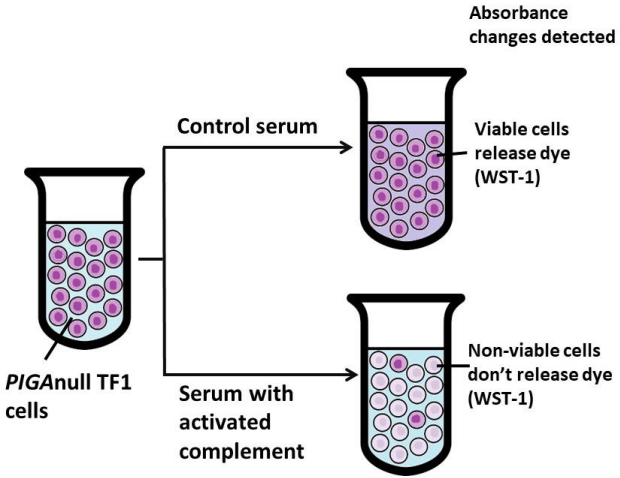
III. Other assays
- Antibodies against complement proteins
- Complement gene sequencing

- No consistent relationship with ‘active’ disease even in aHUS (prototypical complement disorder)
- Do nor reflect complement activity at the cell surface

Bu et al. AJKD 2015, Cole, Gerber, Chaturvedi. Clin Immunol 2023

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

- Principle: Cell line lacking surface CD55 and CD59 is susceptible to complement mediated killing.
- Detects pathologic complement activation on cell surface (not just circulating byproducts

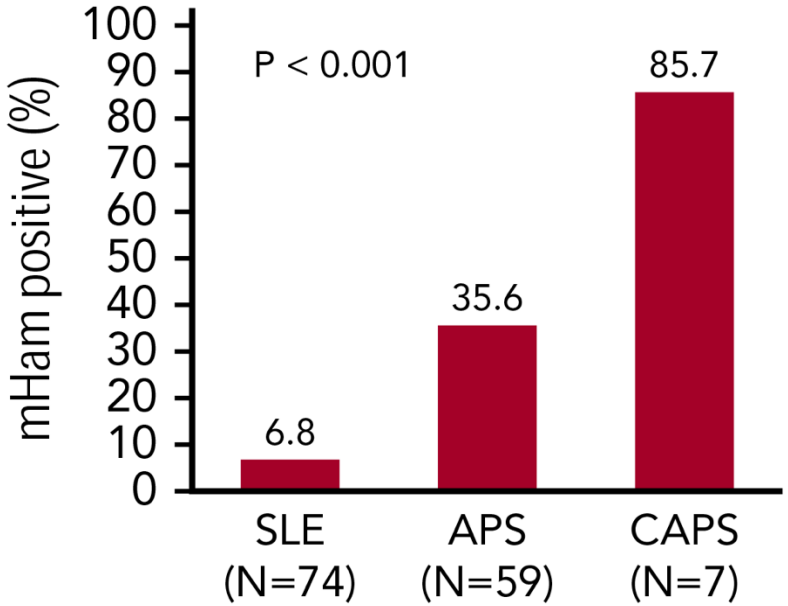


Available for clinical testing

Mham.machaondiagnostics.com

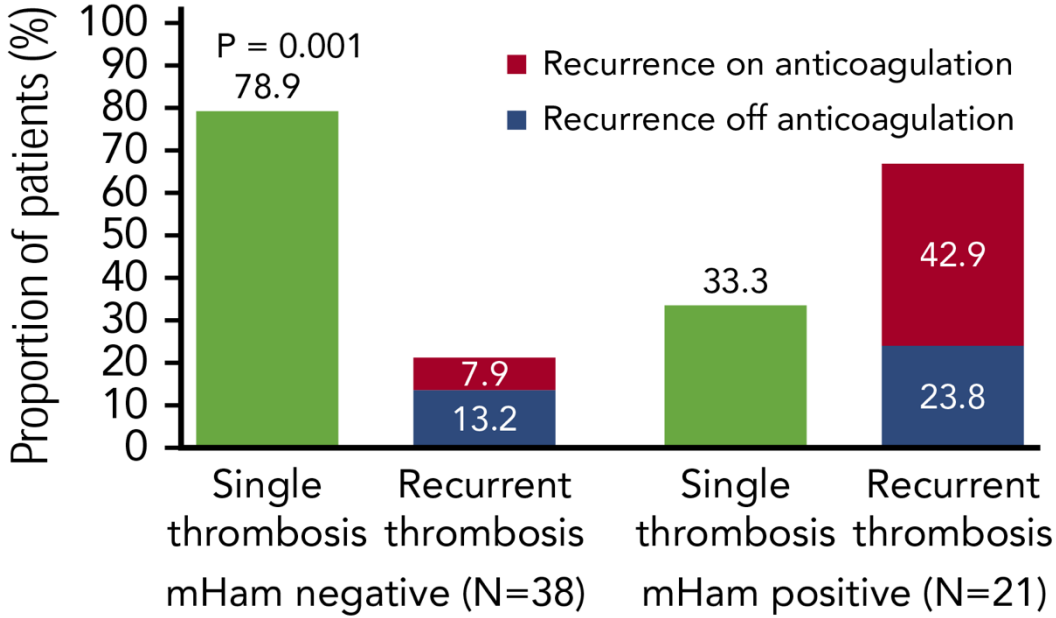
Gavriilaki et al. Blood 2015, Cole MA et al. Blood 2024

Complement activation is a feature of thrombotic APS



Chaturvedi et al. Blood 2020

Complement activation (mHam) predicts recurrent thrombosis and refractory thrombosis



Chaturvedi et al. Blood

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*

Unpublished data

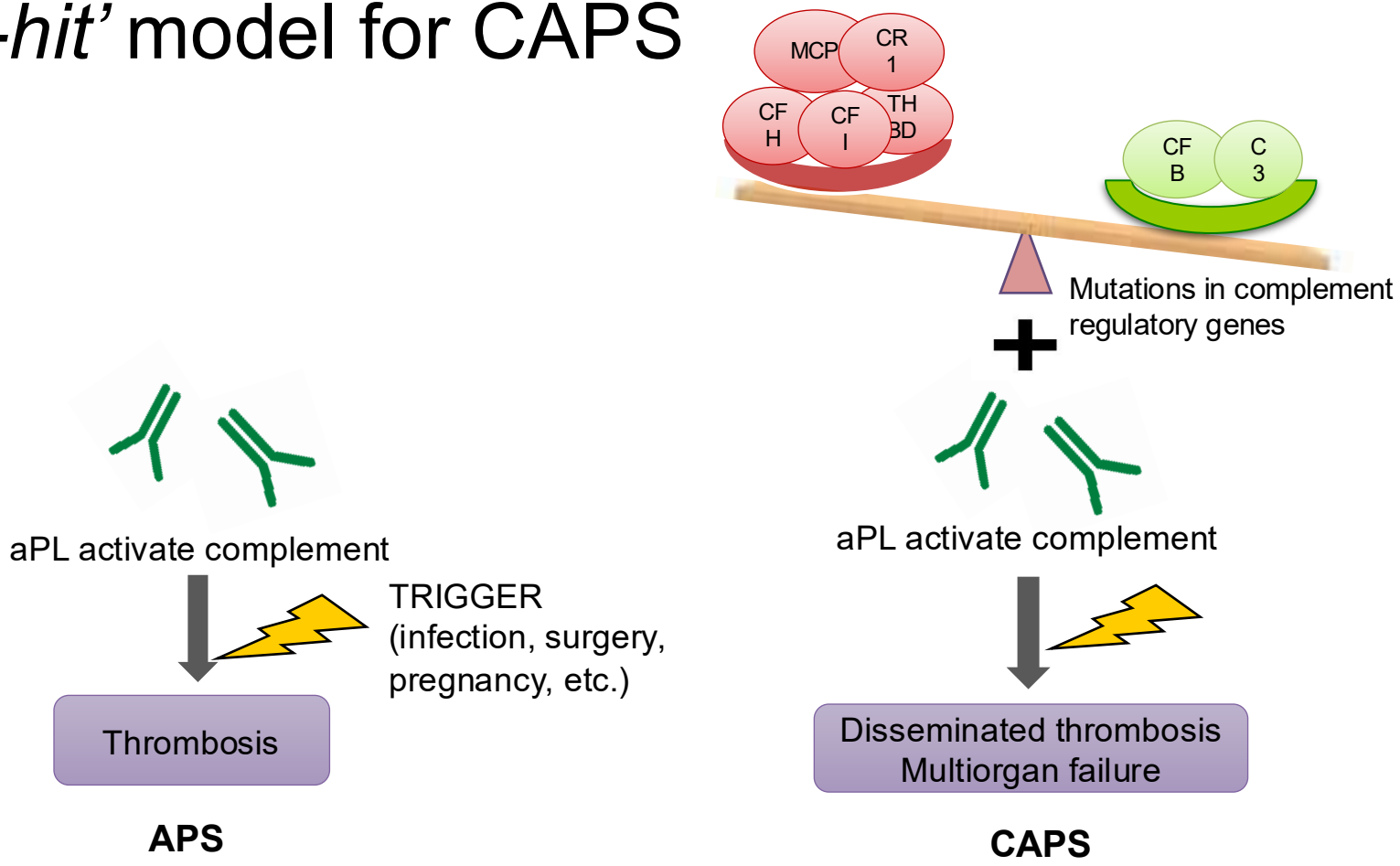
Environment – role of ‘triggers’ in CAPS

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)

Cervera et al. J Autoimm 2009

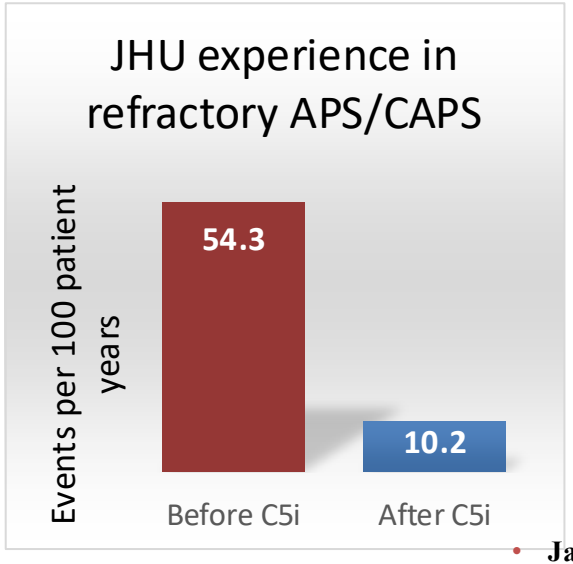
'Multi-hit' model for CAPS



Chaturvedi et al. Blood 2020

C5 inhibition in CAPS and refractory APS

- Multiple case reports of successful management of CAPS / APS
- Publication bias (we don't publish our failures), confounding



When to consider (if available, off label)

- **CAPS (or CAPS-like)**
- Recurrent thrombosis despite anticoagulation optimization, hydroxychloroquine, statin
- Recurrent thrombosis and cannot tolerate anticoagulation AT ALL (and functional complement assays are positive)

Ranjan et al. Arthritis Rheum 2025

Individualizing antithrombotic therapy for APS

aPL carrier	Single thrombosis	Recurrent / refractory thrombosis	CAPS
Consider aspirin if triple positive, other CV risk factors	• Warfarin INR 2-3 is standard of care • DOAC inferior especially for triple pos., arterial events • Add aspirin for arterial events	• Higher intensity warfarin • LMWH • Add antiplatelets • Adjuvant – HCQ, statin • B cell or Anti-C5	• Triple therapy – Plasma exchange/ IvIG + steroids + anticoagulation • Anti-C5 • Rituximab

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
- Better biomarkers are needed to identify
  - Patients at risk for refractory APS and CAPS
  - Patients who may be lower risk of recurrence even off anticoagulation
- Complement inhibition may be a viable strategy for refractory APS and CAPS

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