Antiphospholipid Syndrome

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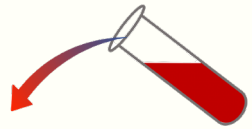
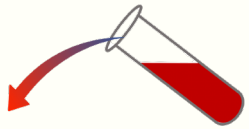
Jan 2024



Disclosures

- None

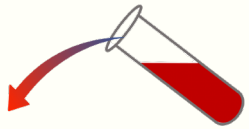


Topics To Cover

1. History and Pathophysiology

2. Definition and Lab Testing

3. Treatments
    - Thrombotic APS
    - APS with microthrombosis
    - Catastrophic APS
    - Non-thrombotic APS (Obstetric)
    - Immunosuppresion

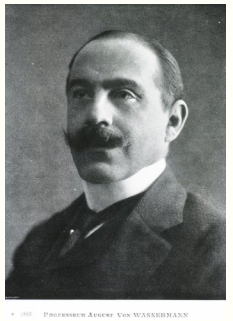


APS: A Brief History

1905

Wasserman developed test to detect treponemal antibody

- Based on complement fixation
- “Biologic false positives” soon reported



1940

Conley et al. recognized:

- association between false positive syphilis test and systemic lupus erythematosus
- many had phospholipid-dependent coagulation inhibitor, but did not bleed

1941

Pangborn purified antigen used for syphilis testing: “cardiolipin”

1960s and 1970s

- Link between the “lupus anticoagulant” and thrombosis recognized

1980s

- Term antiphospholipid syndrome used to refer to patients with a combination of either thrombosis *or* pregnancy complication *plus* laboratory evidence of antiphospholipid antibodies
  - “Primary” and “Secondary” APS defined

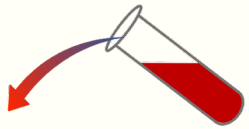
- Immunoassays for anti-cardiolipin Abs developed

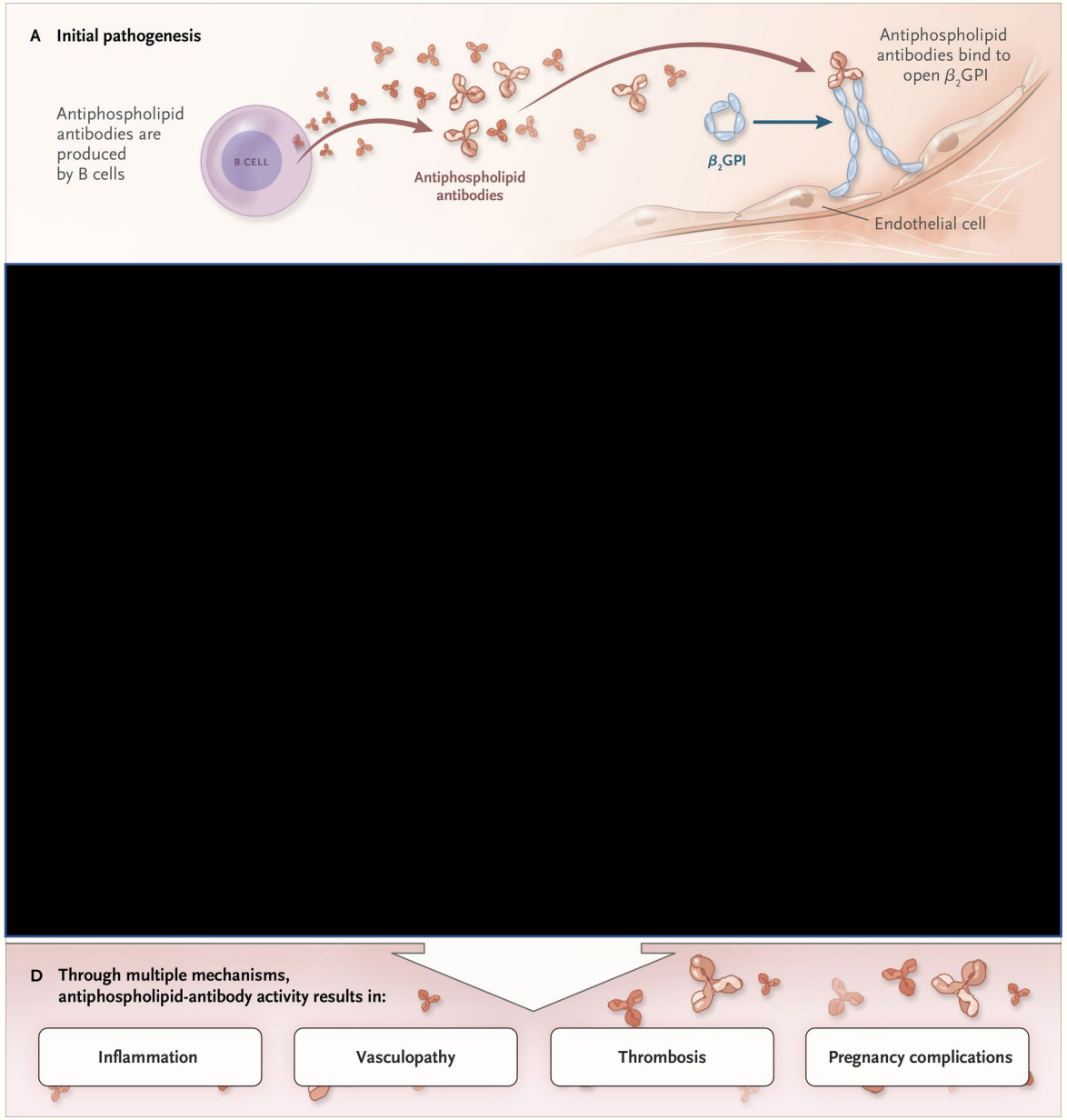
- Asherson and others published case reports of devastating, multi-organ thromboses
  - Now called “catastrophic APS” (CAPS)

1990s

- Multiple groups recognize **β2 glycoprotein I** as the primary target of antiphospholipid antibodies

- International consensus diagnostic criteria agreed upon (Sapporo 1998)





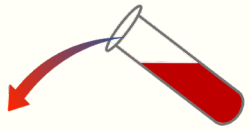
Garcia and Erkan. N Engl J Med 2018; 378:2010-2021

Diagnosis of APS

- Clinical Features

PLUS

- Lab evidence of aPL on at least 2 occasions, 12 weeks apart



Goals

- To develop new APS classification criteria with high specificity for use in observational studies and trials

- Will be used by clinicians to diagnose and treat patients, but this was not primary purpose

2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria

Medha Barbhaiya,[1*] Stephane Zuily,[2*] Ray Naden,[3†] Alison Hendry,[4] Florian Manneville,[5] Mary-Carmen Amigo,[6] Zahir Amoura,[7] Danieli Andrade,[8] Laura Andreoli,[9] Bahar Artim-Esen,[10] Tatsuya Atsumi,[11] Tadej Avcin,[12] Michael H. Belmont,[13] Maria Laura Bertolaccini,[14] D. Ware Branch,[15] Graziela Carvalheiras,[16] Alessandro Casini,[17] Ricard Cervera,[18] Hannah Cohen,[19] Nathalie Costedoat-Chalumeau,[20] Mark Crowther,[21] Guilherme de Jesus,[22] Aurelien Delluc,[23] Sheetal Desai,[24] Maria De Sancho,[25] Katrien M. Devreese,[26] Reyhan Diz-Kucukkaya,[27] Ali Duarte-Garcia,[28] Camille Frances,[29] David Garcia,[30] Jean-Christophe Gris,[31] Natasha Jordan,[32] Rebecca K. Leaf,[33] Nina Kello,[34] Jason S. Knight,[35] Carl Laskin,[36] Alfred I. Lee,[37] Kimberly Legault,[38] Steve R. Levine,[39] Roger A. Levy,[40] Maarten Limper,[41] Michael D. Lockshin,[1] Karoline Mayer-Pickel,[42] Jack Musial,[43] Pier Luigi Meroni,[44] Giovanni Orsolini,[45] Thomas L. Ortel,[46] Vittorio Pengo,[47] Michelle Petri,[48] Guillermo Pons-Estel,[49] Jose A. Gomez-Puerta,[50] Quentin Raimboug,[51] Robert Roubey,[52] Giovanni Sanna,[53] Surya V. Seshan,[54] Savino Sciascia,[55] Maria G. Tektonidou,[56] Angela Tincani,[10] Denis Wahl,[2] Rohan Willis,[57] Cecile Yelnik,[58] Catherine Zuily,[59] Francis Guillemin,[5] Karen Costenbader,[60] and Doruk Erkan,[1] on Behalf of the ACR/EULAR APS Classification Criteria Collaborators

Arthritis Rheumatol. 2023 Aug 28
doi: 10.1136/ard-2023-224609

2023 ACR/EULAR antiphospholipid syndrome classification criteria

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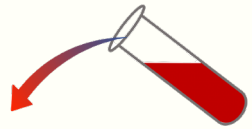
Ann Rheum Dis. 2023 Aug28
doi: 10.1002/art.42624

Methods

- Criteria generation via surveys and literature review
- Criteria reduction via modified Delphi and nominal group technique
- Criteria definition via guidance of real word scenarios
- Weighting via consensus-based multicentric decision analysis
- Threshold identification
- Validation using independent adjudicators' consensus



DRAFT ACR/EULAR ANTIPHOSPHOLIPID SYNDROME CRITERIA PRESENTED AT #ACR22

ENTRY CRITERION

≥ 1 documented clinical criterion + ≥ 1 positive aPL test

CLINICAL DOMAINS	Points	LABORATORY DOMAINS (aPL)	Points

Classify as APS if ≥ 3 points from clinical criteria AND ≥ 3 points from aPL domain

Barbhaiya, et al. Ann Rheum Dis. 2023 Oct;82(10):1258-1270

DRAFT ACR/EULAR ANTIPHOSPHOLIPID SYNDROME CRITERIA PRESENTED AT #ACR22

ENTRY CRITERION

≥ 1 documented clinical criterion + ≥ 1 positive aPL test

CLINICAL DOMAINS	Points
VENOUS THROMBOEMBOLISM	
• *With high VTE risk profile*	1
• *Without VTE high risk profile*	3
ARTERIAL THROMBOSIS	
• *With a high CVD profile*	2
• *Without a high CVD profile*	4
MICROVASCULAR INVOLVEMENT*	
• *Suspected*	2
• *Established*	5
OBSTETRIC	
• *≥ 3 consecutive losses (<10w) and/or fetal death (<16w)*	1
• *Fetal death (≥16w <34w) without PEC/PI with severe features*	1
• *Severe PEC or severe PI (<34w)*	3
• *Severe PEC and severe PI (<34w)*	4
CARDIAC VALVE	
• *Thickening*	2
• *Vegetation*	4
THROMBOCYTOPENIA (lowest 20-130G/L)	2

LABORATORY DOMAINS (aPL)	Points
LUPUS ANTICOAGULANT (LA) POSITIVITY	
• *One time*	1
• *Persistent*	5
Anti-cardiolipin (aCL) / anti-BP2GP1 positivity**	
• ***IgM only :*** *moderate-high for aCL and/or anti-B2GP1*	1
• ***Presence of IgG***	
◦ ***moderate positivity*** *for aCL and/or anti-B2GP1*	4
◦ ***high posivitity*** *for aCL* ***OR*** *anti-B2GP1*	5
◦ ***high positivity*** *for aCL* ***AND*** *anti-B2GP1*	7

Only count the highest weighted criterion within each domain
Do not count if there is an equally or more likely explanation than APS

Microvascular involvement:

-Suspected: *livedo racemosa, livedoid vasculopathy (without pathology), aPL nephropathy (no pathology available), pulmonary hemorrhage (symptoms or imaging)*

-Established: *livedoid vasculopathy (with pathology), aPL nephropathy (with pathology), pulmonary hemorrhage (BAL or pathology), Myocardial disease (imaging or pathology), Adrenal disease (imaging or pathology)*

aPL titers (by ELISA): moderate titer => 40-79U; high titer => ≥ 80U

Classify as APS if ≥ 3 points from clinical criteria AND ≥ 3 points from aPL domain

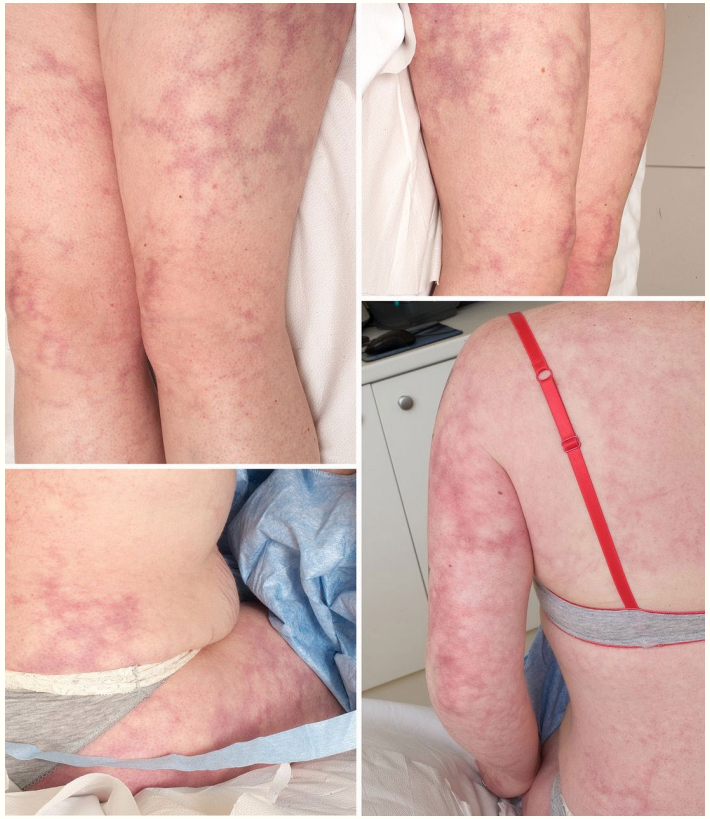
Barbhaiya, et al. Ann Rheum Dis. 2023 Oct;82(10):1258-1270

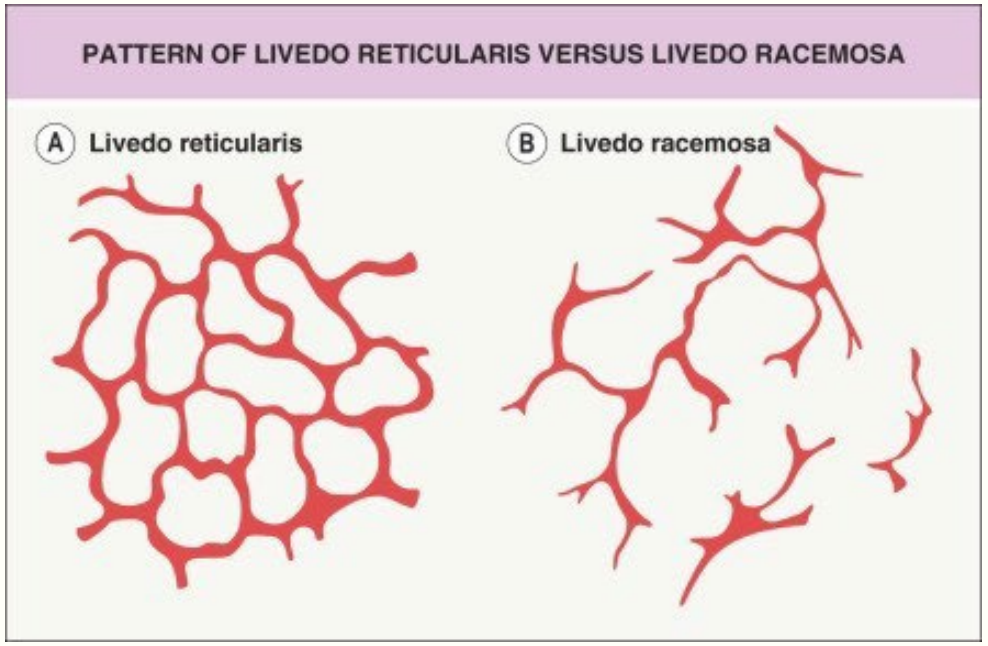
Novel Clinical Features

- Risk stratification of macrovascular events by traditional thrombosis risk factors
- Well-defined microvascular domain items
- Re-defined pregnancy morbidity definitions
- The addition of cardiac valve disease and thrombocytopenia

Barbhaiya, et al. Ann Rheum Dis. 2023 Oct;82(10):1258-1270

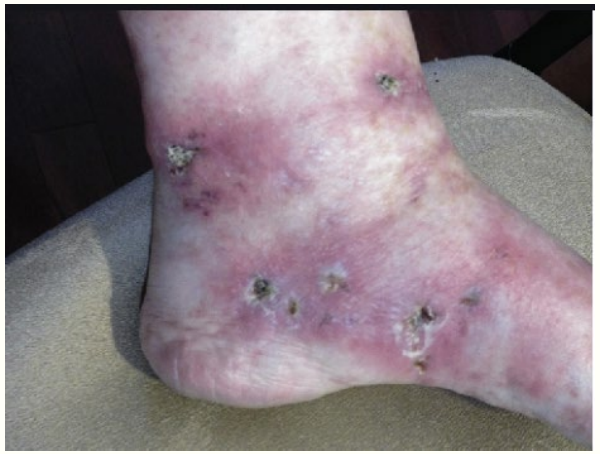
Skin Findings: a manifestation of vasculitis and/or microvascular thrombosis





Microthrombotic APS

- Diffuse Alveolar Hemorrhage
- Acute Renal Failure with unexplained thromb. microangiopathy on biopsy
- Chronic Kidney Disease with unexplained thromb. microangiopathy
- Livedoid vasculopathy (skin ulcers):



Novel Laboratory Features

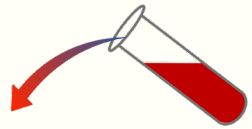
- Quantifying single-, double-, and triple-aPL positivity based on different domains and weights
- Separating aCL/aβ_2GPI IgG and IgM isotypes
  - To exclude aPL-positive patients with isolated aCL/aβ_2GPI IgM-only isotypes from the same research studies as those with IgG isotypes
- Defining two levels of aCL/aβ_2GPI positivity that will be interpreted as clinically relevant by most investigators

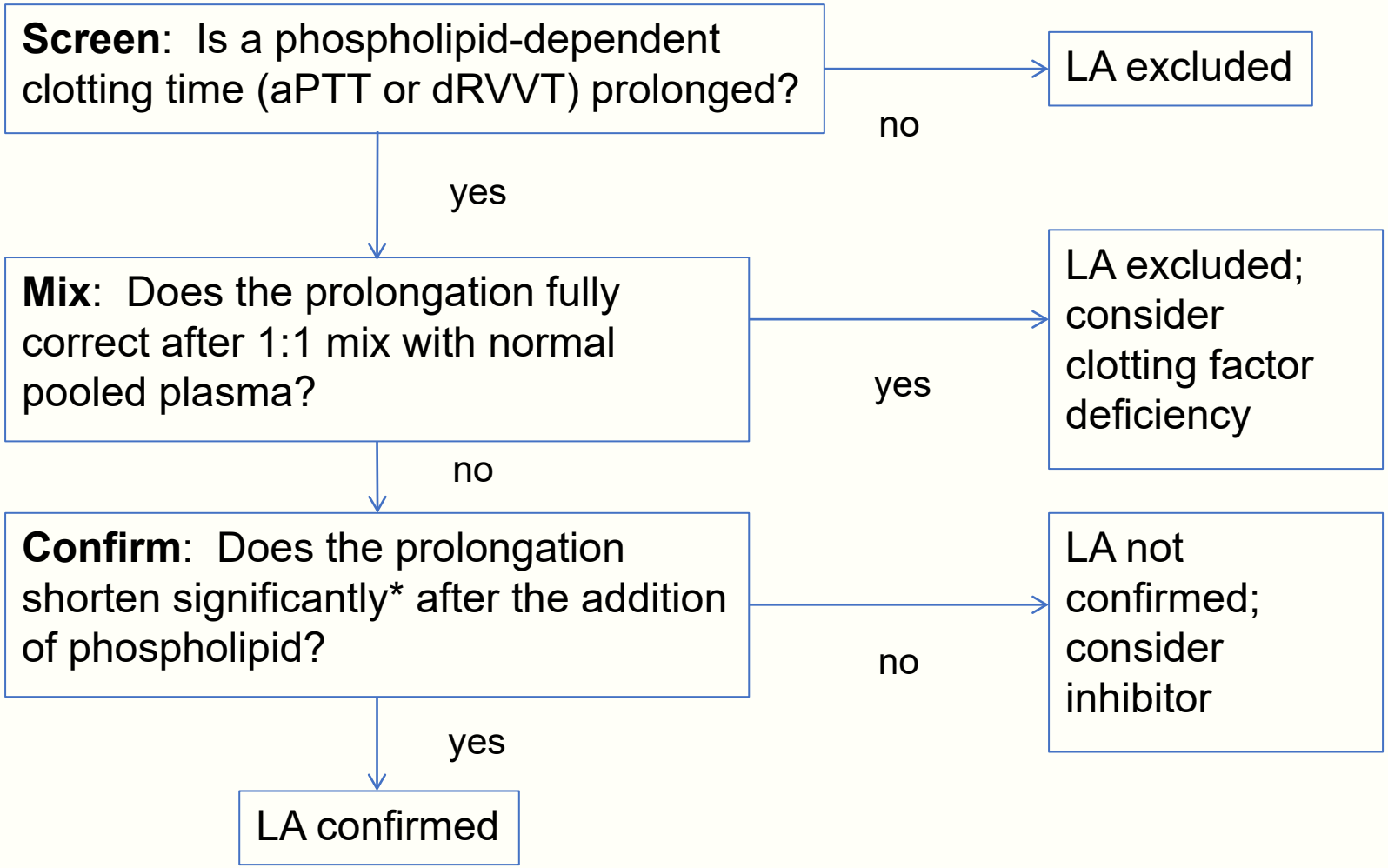
Barbhaiya, et al. Ann Rheum Dis. 2023 Oct;82(10):1258-1270

Lab Tests

- **DO ORDER**:
  - Anticardiolipin Antibodies (aCL) IgG, IgM(?)* Anti-β2Glycoprotein-I Antibodies (aβ2GPI) IgG, IgM(?)*
  - Lupus Anticoagulant
- **DO NOT ORDER:**
  - aCL IgA, aβ2GPI IgA; Anti-Domain-I Abs (aDI), Anti-Phosphatidylserine-Prothrombin Antibodies (aPS/PT), Anti-Prothrombin Abs
- **INTERPRET WITH CAUTION:**
  - aCL IgM*, aβ2GPI IgM*
  - Lupus anticoagulant, if "positive" & performed while patient on anticoagulant medication

*Chayoua et al. J Thromb Haemost. 2020 Jan;18(1):169-179

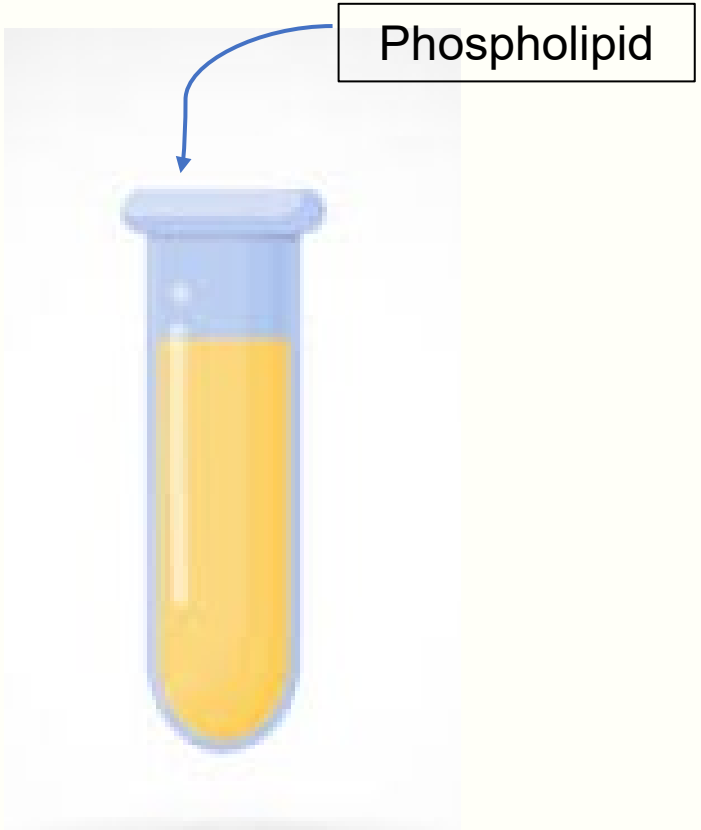




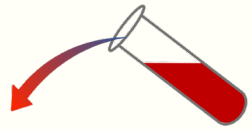
Laboratory testing for the lupus anticoagulant (LA). The interpretations above apply only to patients **not taking** anticoagulant medications. aPTT = activated partial thromboplastin time; dRVVT = dilute Russell viper venom time.
* Often defined as a ratio (pre:post addition of phospholipid) > 1.3

Patient : Normal pooled plasma
1:1;
PTT or DRVVT

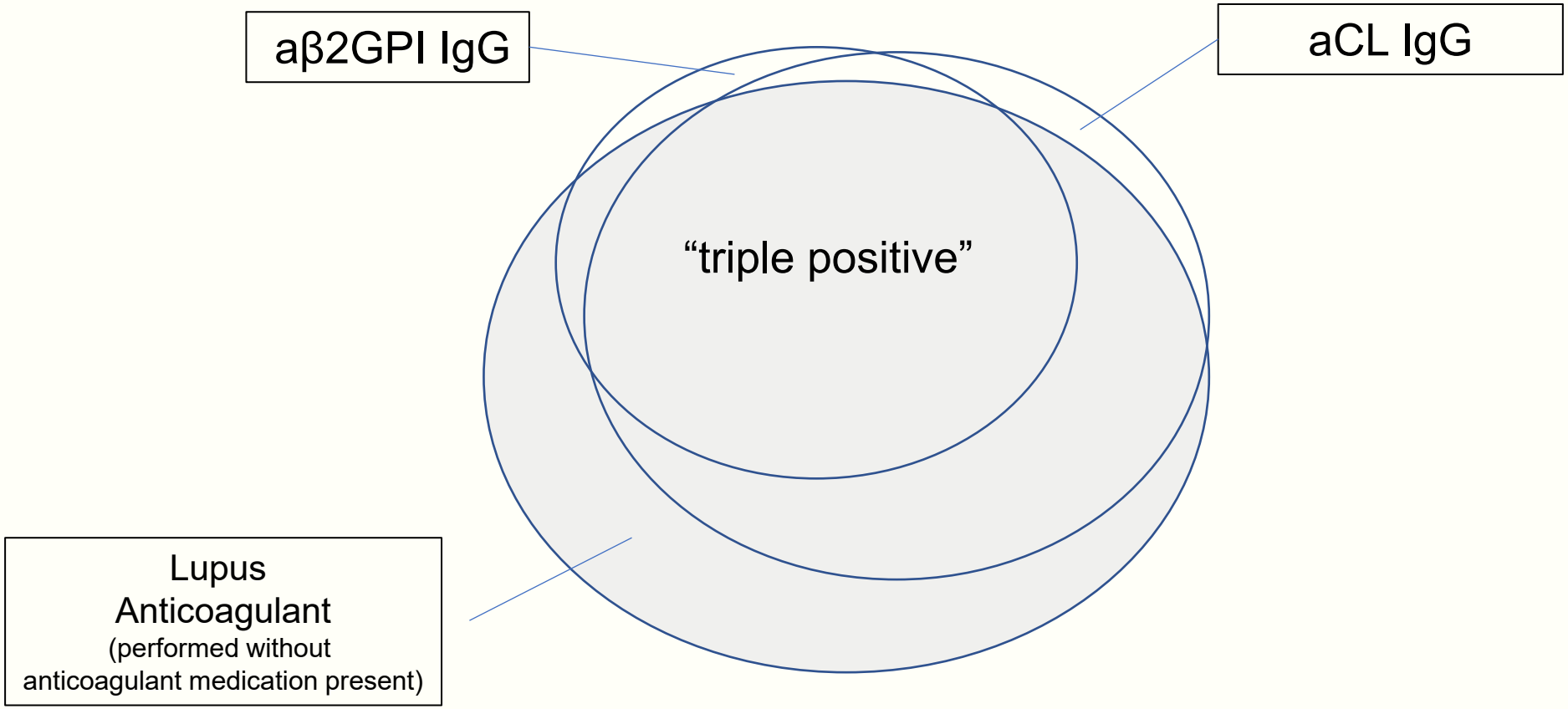
Patient : Normal pooled plasma
1:1;
PTT or DRVVT



Lupus Anticoagulant Testing

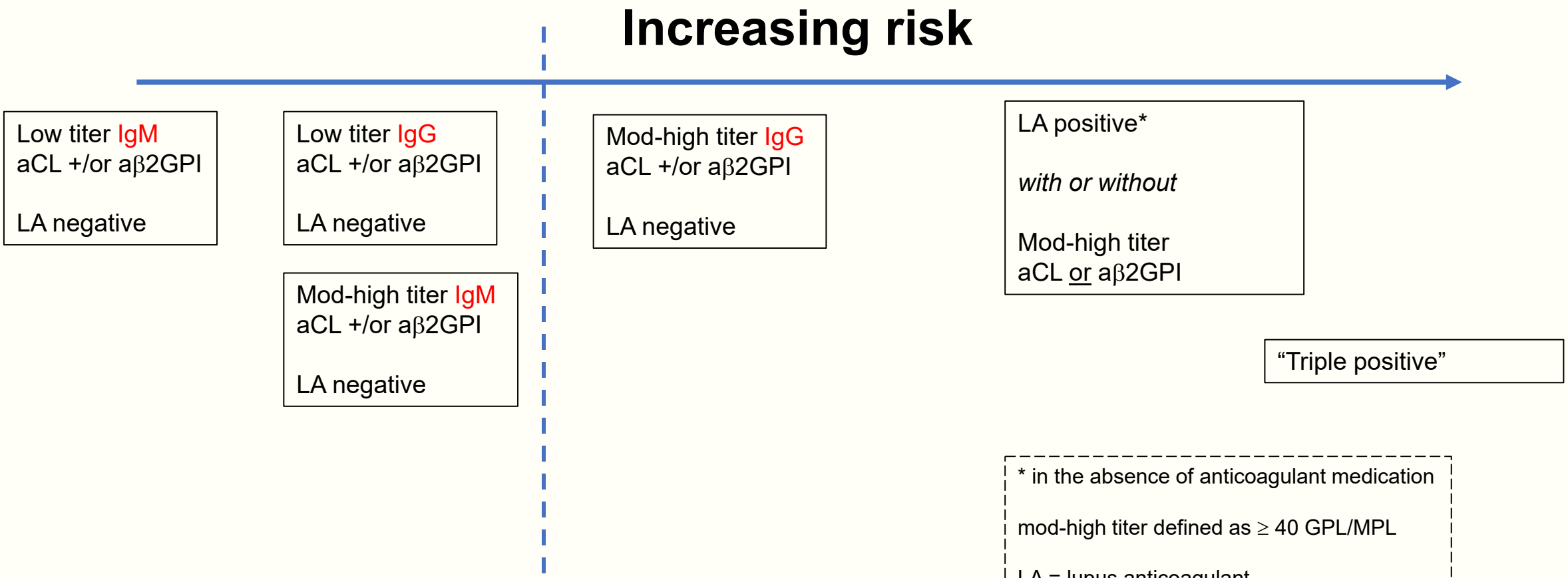


APS Lab Profile



Thrombosis Risk Spectrum

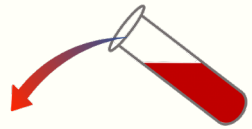
(findings present at least twice, at least 12 weeks apart)



Clinical Questions

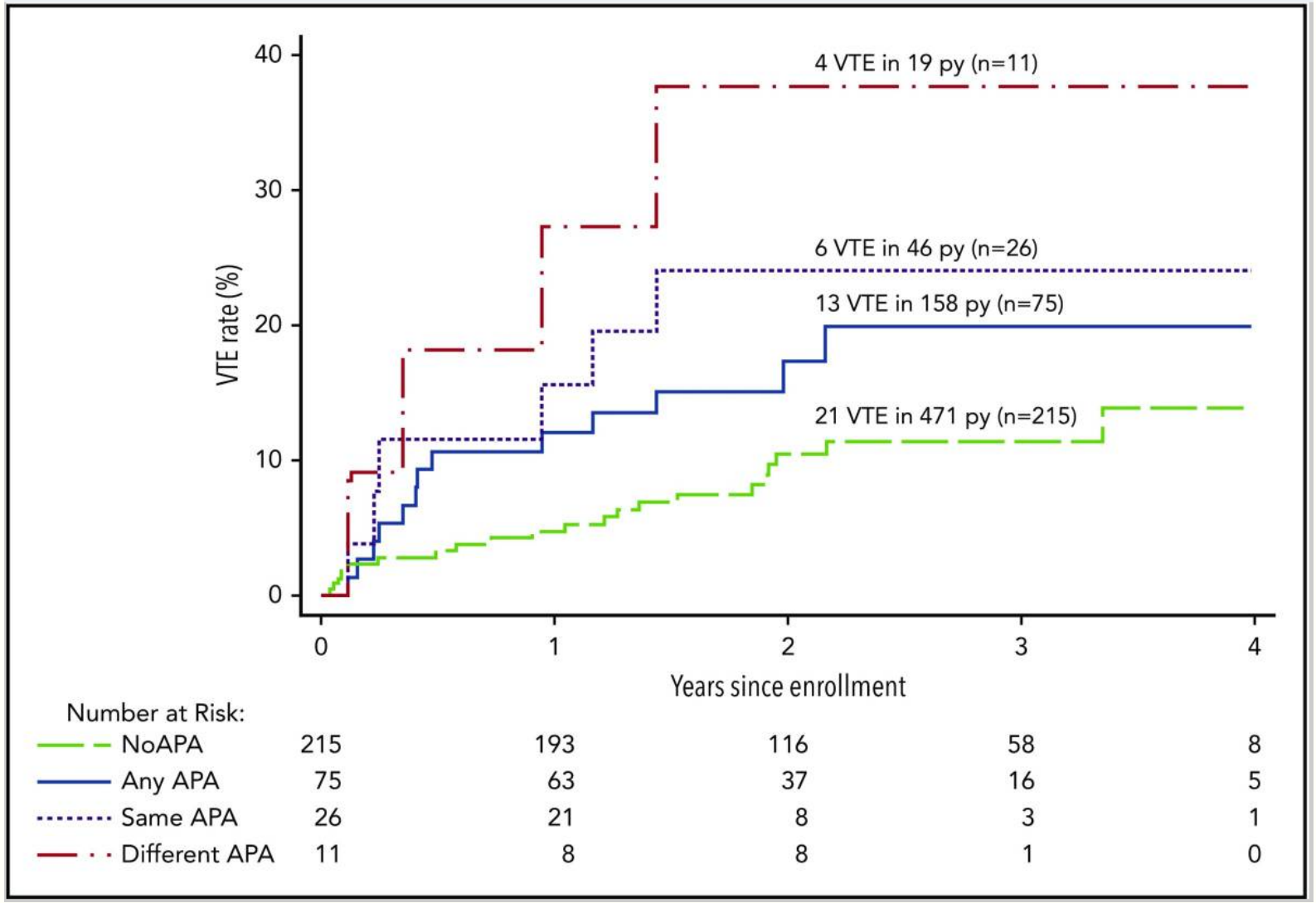
- Should aPL positivity affect decisions about the *duration* of anticoagulant therapy?
  - WITH transient major RF? (unknown, but probably not – don't check!)
  - WITHOUT a transient major RF (possibly – see subsequent slides)

- Should aPL positivity affect decisions about the *type* of anticoagulant therapy?
  - Probably, especially if triple positive (but it's complicated)



Presence of aPL is associated with recurrent VTE

> 300 patients with "unprovoked" VTE who stopped anticoagulant therapy after a normal d-dimer test



Kearon C, et al. Blood. 2018 May 10; 131(19): 2151–2160.

Presence of aPL is associated with recurrent VTE

Group	Patients	VTE events	Person-years	Event rate per 100 p-y (95% CI)
All patients	290	34	627	5.4 (3.8-7.6)
No aPL	215	21	471	4.5 (2.8-6.8)
Any aPL	75	13	158	8.2 (4.4-14.1)
aPL once	49	7	110	6.4 (2.6-13.1)
aPL twice	26	6	46	13.0 (4.8-28.4)
aPL only	11	1	28	3.6 (0.1-19.9)
IgG only	6	1	13	7.7 (0.2-42.9)
IgM only	5	0	14	0.0 (0.0-26.3)
Anti-β2GP1 only	1	0	2	0.0 (0.0-184.4)
LA only	52	8	108	7.4 (3.2-14.6)

Kearon C, et al. Blood. 2018 May 10; 131(19): 2151–2160.

Oral FXa inhibitor vs. warfarin for APS

blood®

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Vittorio Pengo,[1] Gentian Denas,[1] Giacomo Zoppellaro,[1] Seena Padayattil Jose,[1] Ariela Hoxha,[2] Amelia Ruffatti,[2] Laura Andreoli,[3] Angela Tincani,[3] Caterina Cenci,[4] Domenico Prisco,[4] Tiziana Fierro,[5] Pa
Alberto Tosetto,[9] Anna Falanga,[10] Ida Martinelli,[11] Sophie Testa,[12] Do

Annals of Internal Medicine

ORIGINAL RESEARCH

Rivaroxaban Versus Vitamin K Antagonist in Antiphospholipid Syndrome

A Randomized Noninferiority Trial

Josep Ordi-Ros, MD, PhD; Luis Sáez-Comet, MD, PhD; Mercedes Pérez-Conesa, MD; Xavier Vidal, MD, PhD;
Antoni Riera-Mestre, MD, PhD; Antoni Castro-Salomó,
Montserrat Mauri-Plana, MD, PhD; Cristina Solé, PhD; a

Check for updates

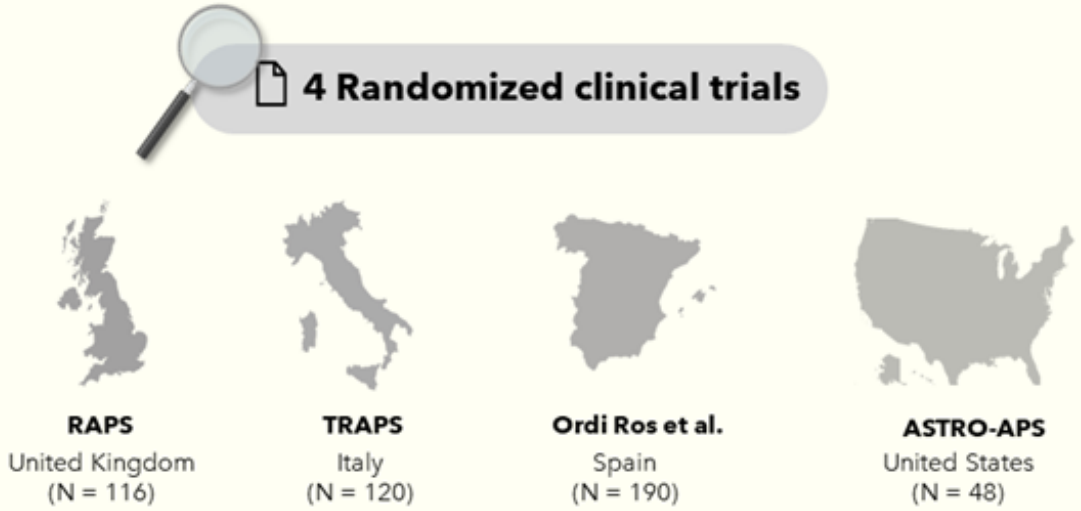
REGULAR ARTICLE

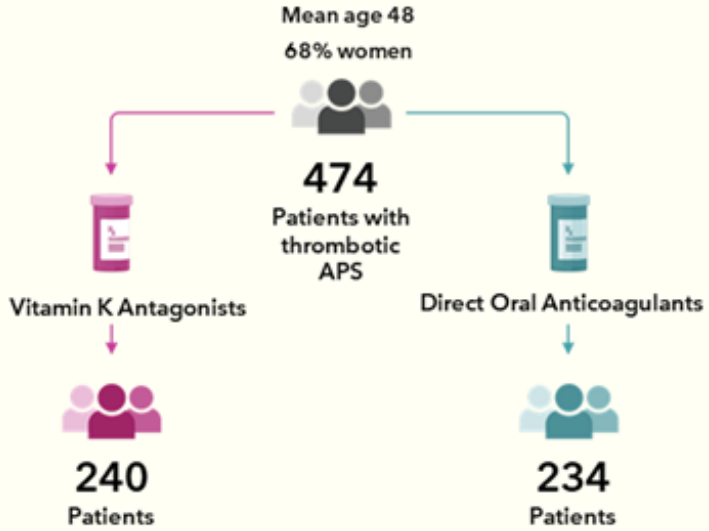
blood advances

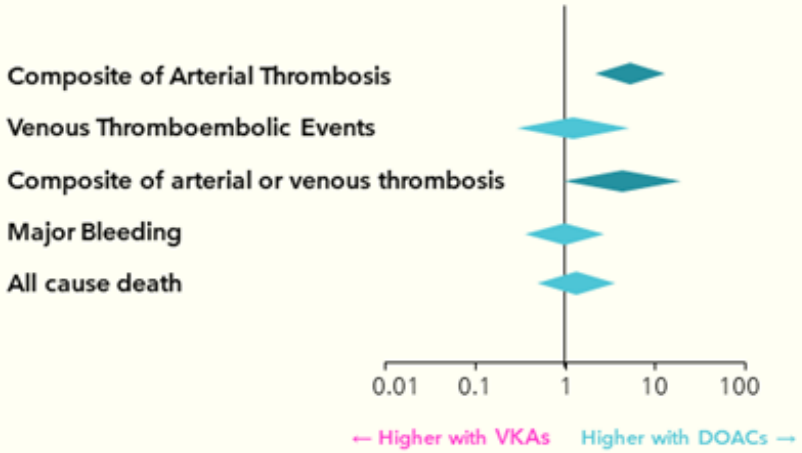
Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial

Scott C. Woller,[1,2] Scott M. Stevens,[1,2] David Kaplan,[2] Tzu-Fei Wang,[3] D. Ware Branch,[4] Danielle Groat,[5] Emily L. Wilson,[5] Brent Armbruster,[5] Valerie T. Aston,[5] James F. Lloyd,[6] Matthew T. Rondina,[2] and C. Greg Elliott[1,2]

DOACs vs. warfarin in APS







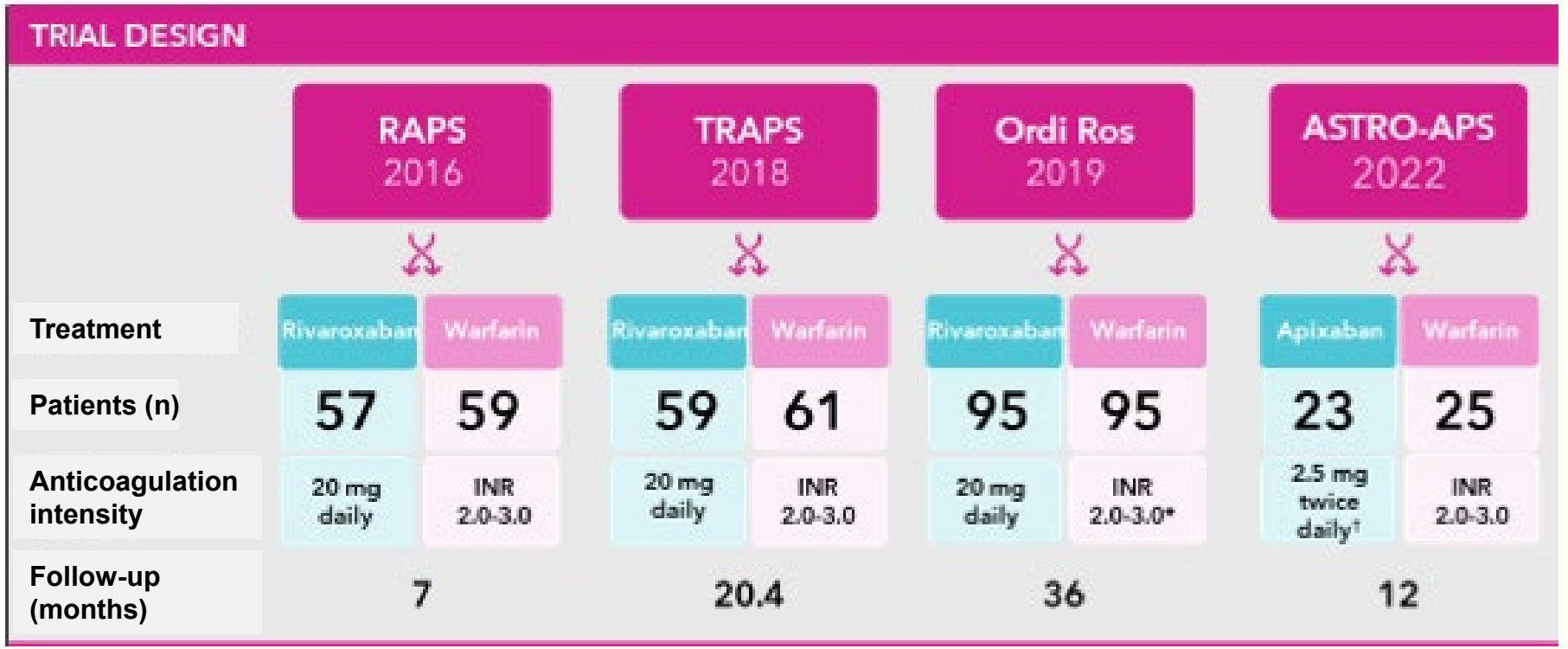
Use of DOACs compared with VKAs was associated with

- Increased odds of arterial thrombotic events
- No change in the odds of VTE or major bleeding

Results were consistent within subgroups

Khairani C, et al. J Am Coll Cardiol. 2023 Jan 3;81(1):16-30.

DOACs in Antiphospholipid Syndrome: 4 randomized trials



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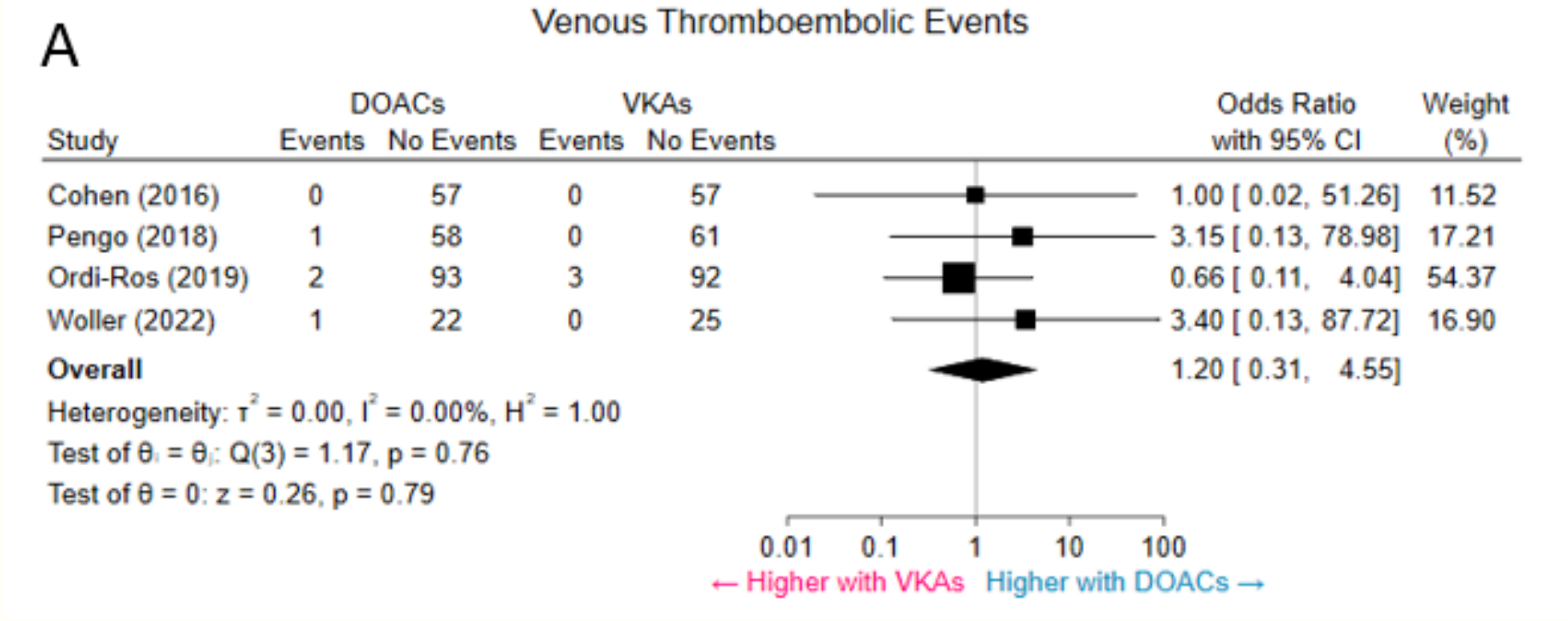

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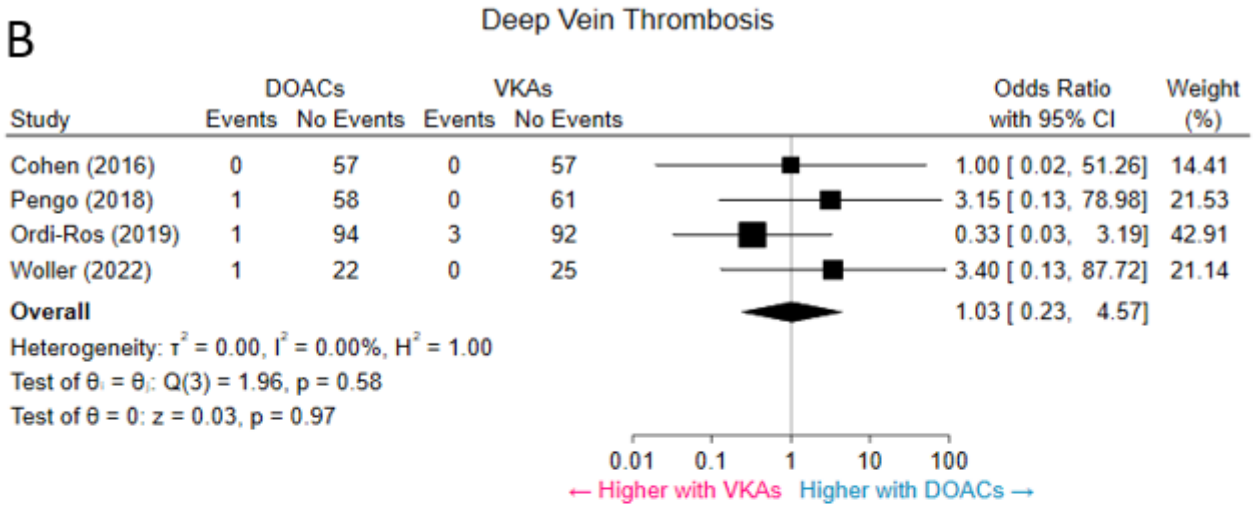

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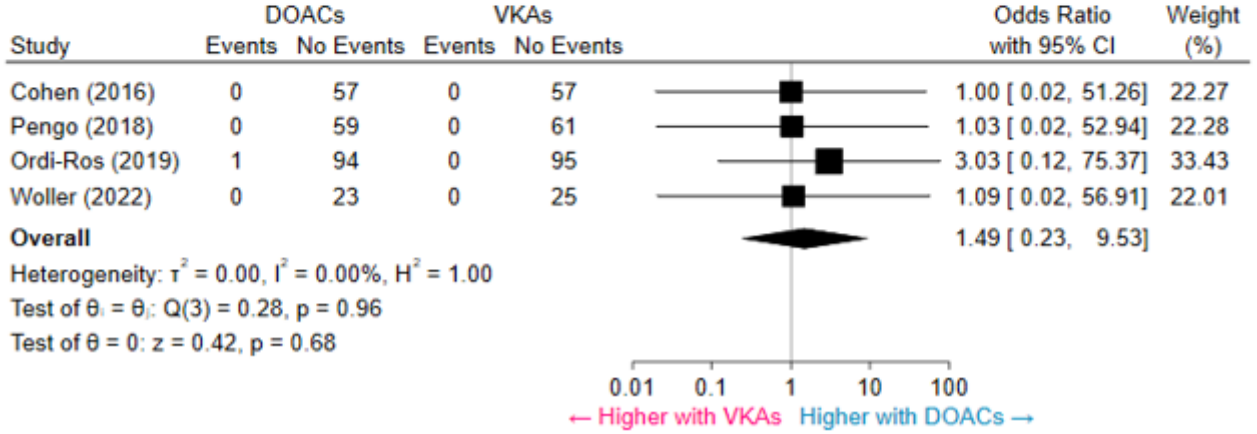

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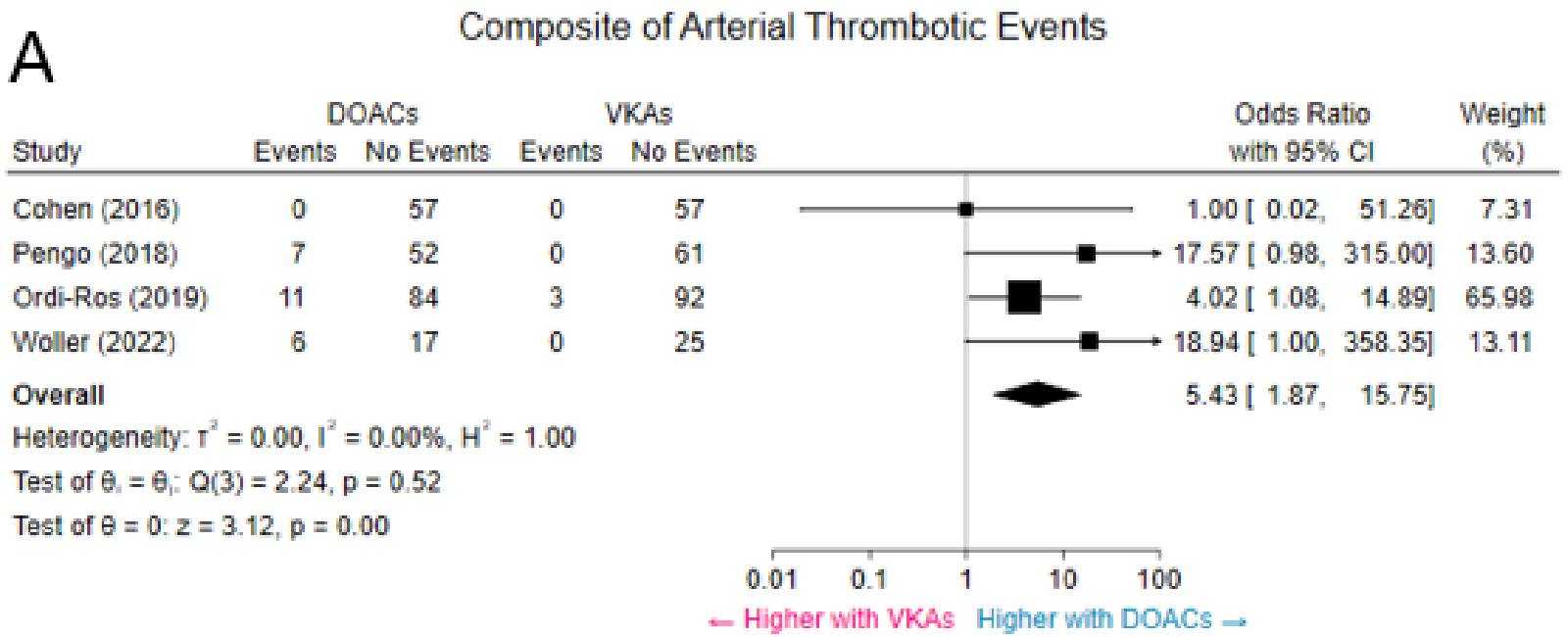

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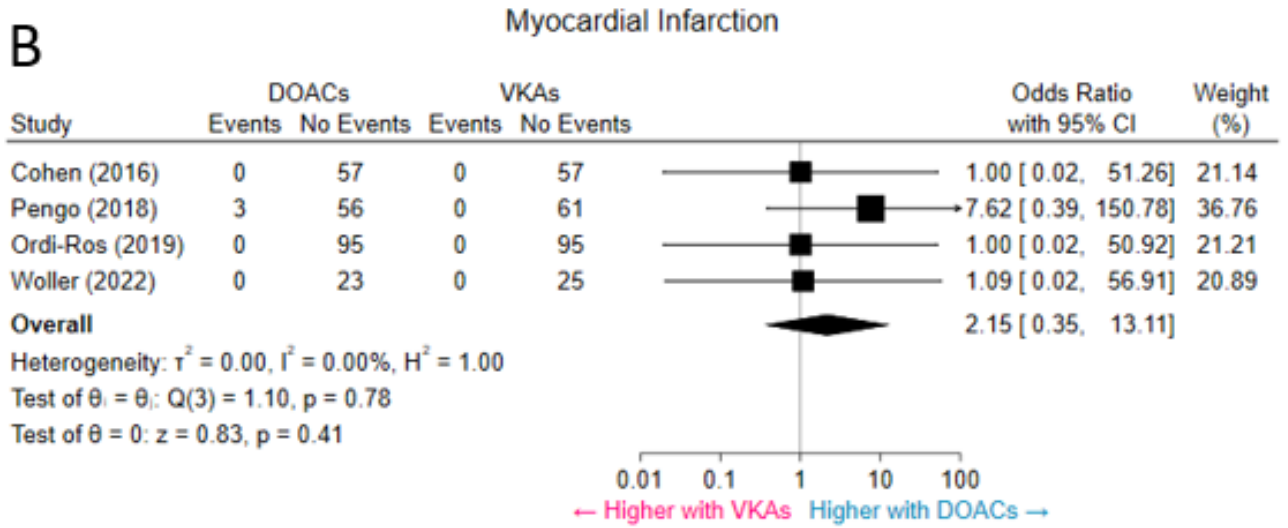

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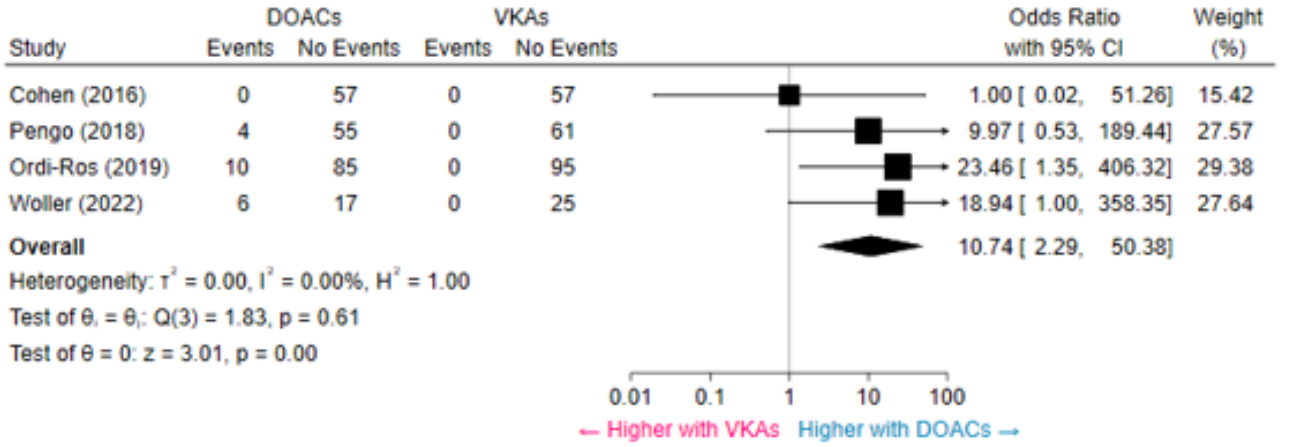
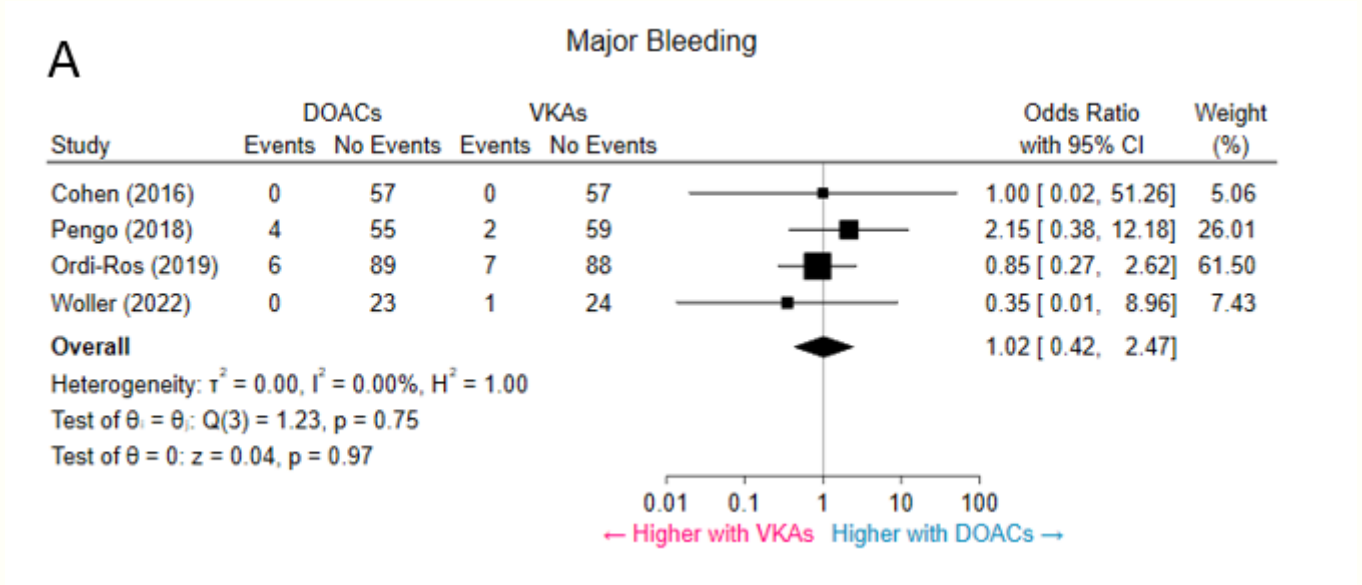


Khairani C, et al. J Am Coll Cardiol. 2023 Jan 3;81(1):16-30.



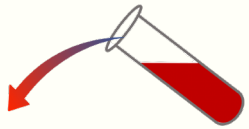
Khairani C, et al. J Am Coll Cardiol. 2023 Jan 3;81(1):16-30.

DOACs and APS: Summary

- Warfarin is preferred in "high-risk" APS patients (e.g. triple positive, strongly positive LA, patients with prior arterial events)

- The RCTs in the Khairani meta-analysis have limitations
  - Large majority of participants were APS patients doing well on warfarin – unclear if the findings would be similar in a study of APS patients *initiating* anticoagulant therapy

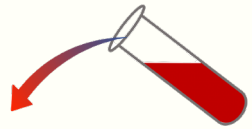
  - Patients with APS who are doing well on a FXa inhibitor may, after learning of the trial results, choose to continue FXa inhibitor treatment.



Don’t forget

- In patients at very high risk for arterial thrombosis, adding low-dose ASA to warfarin may have benefit that outweighs the risk (2-3-fold higher risk of major hemorrhage)
- Address other “traditional” atherosclerosis risk factors (HTN, smoking, DM) – have a low threshold to recommend statin
- Low-dose hydroxychloroquine *may* reduce thrombosis risk (monitor for chronic retinal toxicity), especially in patients with associated SLE*

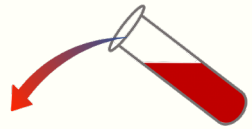
*Tektonidou et al. Arthritis Rheum. 2009 Jan 15;61(1):29-36



Current Therapy for Thrombotic APS

- Warfarin is cornerstone of treatment
  - Recurrent thrombosis more common than in patients without APS
  - Antiplatelet therapy, statins added in some cases

- Case reports and animal models
  - rituximab (anti-CD20 Ab)
  - eculizumab (anti-C5 Ab = complement inhibitor)
  - other immunomodulatory agents (mTOR inhibitors, MMF, azathioprine)



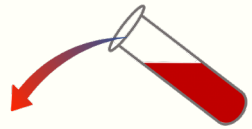
Catastrophic APS ("CAPS")

1) Involvement of three or more organs/tissues
2) Development of manifestations in less than a week
3) Histological evidence of intravascular thrombosis
4) Presence of antiphospholipid antibodies on two occasions six weeks apart

Definite if all present. **Probable** if 1-3 or 1,2, and 4 (even if only 1 aPL test)

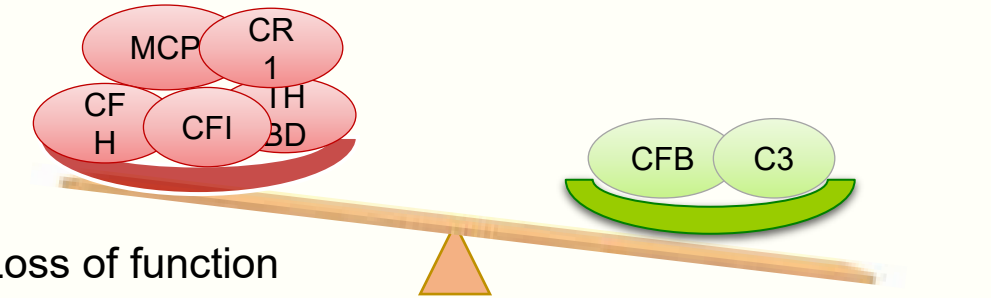
THERAPY (VERY low-quality evidence):

- Most experts suggest a combination of glucocorticoid, heparin and plasmapheresis or intravenous immune globulin
- Rituximab and/or complement blockade ?



Two-hit model for CAPS

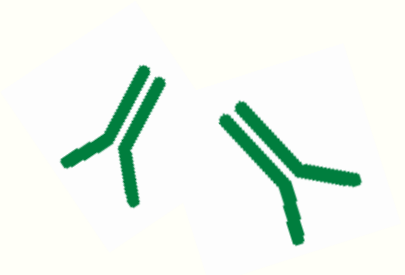
Chaturvedi S, et al. Blood. 2020 Jan 23;135(4):239-251



Loss of function mutations in inhibitory genes

+

Gain of function mutations in activating genes



aPL activate complement

TRIGGER (infection, surgery, pregnancy, etc.)

Thrombosis

APS "one hit"

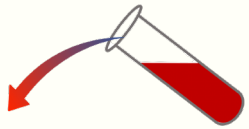
aPL activate complement

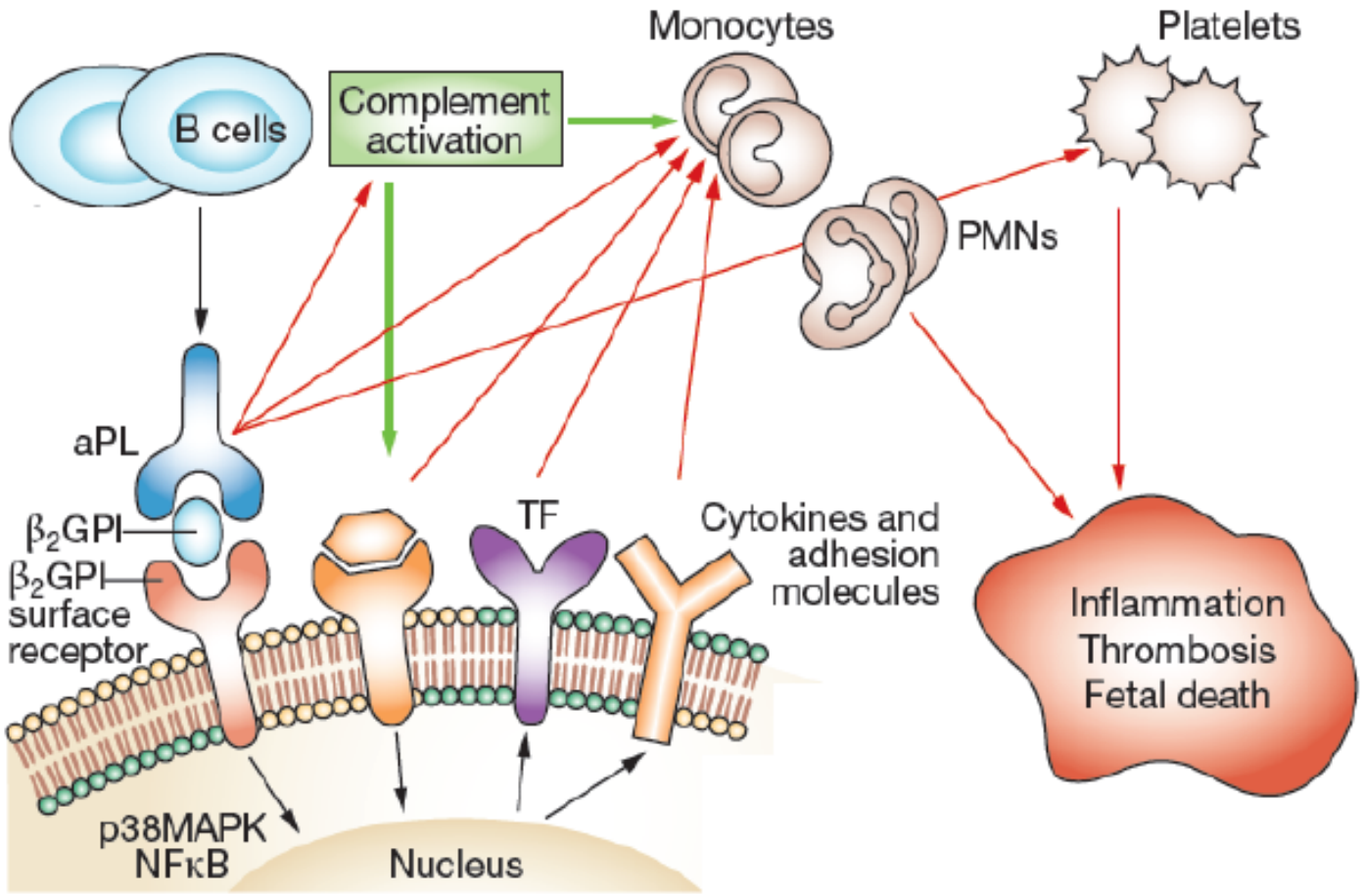
Disseminated thrombosis
Multiorgan failure

CAPS "two hits"

A Few words about 'Obstetric APS'

- LATE pregnancy complications are most characteristic
  - IUGR, pre-eclampsia, HELLP, intrauterine fetal demise
- Does not *necessarily* predict future thrombotic events
- May have different pathophysiology from Thrombotic APS
  - Complement seems especially important
- **IgM** aCL or anti-β2GPI Abs may correlate with pregnancy risk better they do than with thrombosis risk



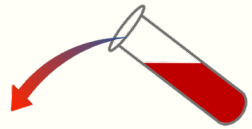


Erkan D, Lockshin MD. Nature Clinical Practice Rheumatology 2009;5:160

Immunosuppressive Therapy

- Hydroxycholoroquine (remember ophtho surveillance)
- Statins
- "DMARDs" (per rheumatology)
- B-cell inhibition
  - especially if indicated from rheum standpoint or because the patient also has ITP or AIHA
- Complement inhibition?
- mTOR inhibition?

- Andrade et al. 15th Interna:onal Congress on aPL Task Force Report on APS Treatment Trends Report. In: APS – Current Research Highlights and Clinical Insights. Eds: Erkan D, Lockshin MD. Springer, 2017.
- Dobrowolski C, Erkan D. Treatment of APS beyond an:coagula:on. Clin Immunol. 2018 Mar 3. pii: S1521--6616(18)30119--0
- Unlu O, Erkan D. CAPS: Candidate Therapies for Poten:ally Lethal Disease. Annu Rev Med. 2017 Jan 14;68:287--296



Immunosuppresive Therapy

Table 3. Our Treatment Strategies for Antiphospholipid-Antibody (aPL)–Positive Patients.*	
Hydroxychloroquine (200–400 mg per day)	Potential add-on treatment for recurrent thrombosis despite therapeutic-dose anticoagulant therapy
Statins	Potential add-on treatment for recurrent thrombosis despite therapeutic-dose anticoagulant therapy
Traditional immunomodulatory agents (e.g., azathioprine, 100–150 mg per day, or mycophenolate mofetil, 1000–3000 mg per day)†	An option for severe thrombocytopenia, hemolytic anemia, or both; an option for aPL nephropathy
Sirolimus†	More data needed
Rituximab (e.g., 1000 mg on days 0 and 15, repeated every 6 mo)†	An option for thrombocytopenia, hemolytic anemia, livedoid vasculopathy, and aPL nephropathy; an option for catastrophic APS that is refractory to standard treatment
Eculizumab†	An option for catastrophic APS that is refractory to standard treatment; an option for acute thrombotic microangiopathy in patients with aPL-related nephropathy

† The only clinical information about the use of this immunosuppressive agent or class of agents in patients with APS comes from case reports of hematologic or microthrombotic manifestations of APS or both.

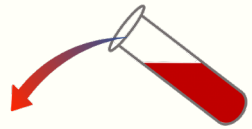
Adapted from Garcia and Erkan NEJM 2018; 378: 2010-2021.

Primary Thrombosis Prevention

- Insufficient evidence to demonstrate benefit or harm of using ASA versus placebo in persons with aPL*

- My Approach
  - Low threshold to give hydroxychloroquine (if connective tissue dz is present) and statin (if LDL:HDL ratio is borderline or high-risk)
  - Modify other RFs (HTN, smoking, obesity, DM)
  - Make decision about ASA based on other atherosclerosis risk factors

*Bala et al. Cochrane Database Syst Rev. 2017 Oct 2;10:CD012169



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- Garcia and Erkan. Diagnosis and Management of APS. NEJM 2018; 378: 2010-2021.
- Legault et al. McMaster RARE-Best practices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome. J . J Thromb Haemost 2018; 16: 1656–64
- Khairani et al. Direct Oral Anticoagulants vs Vitamin K Antagonists in Patients With Antiphospholipid Syndromes: Meta-Analysis of Randomized Trials. J Am Coll Cardiol. 2023 Jan 3;81(1):16-30
- Barbhaiya, et al. Ann Rheum Dis. 2023 Oct;82(10):1258-1270 (New Classification Criteria)