Antiphospholipid Syndrome (APS)and Heparin-Induced Thrombocytopenia (HIT)

“I don’t want to clot or bleed!”

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Potential COI: Keith McCrae, M.D.

Source	Role
Dova	Advisory board (ITP)
Pfizer	Advisory board (Cancer-associated thrombosis)
Oscotec	Consultant/PI

Similarities and Differences Between APS and HIT

APS

- Venous thrombosis
- Arterial thrombosis
- Antibody mediated
- Antigen identified
- Spontaneous
- Often chronic
- ? Response to DOAC
- Other manifestations common

HIT

- Venous thrombosis
- Arterial thrombosis
- Antibody mediated
- Antigen identified
- Drug-induced
- Self-limited
- Responds to DTI/DOAC
- Other manifestations uncommon

Overview

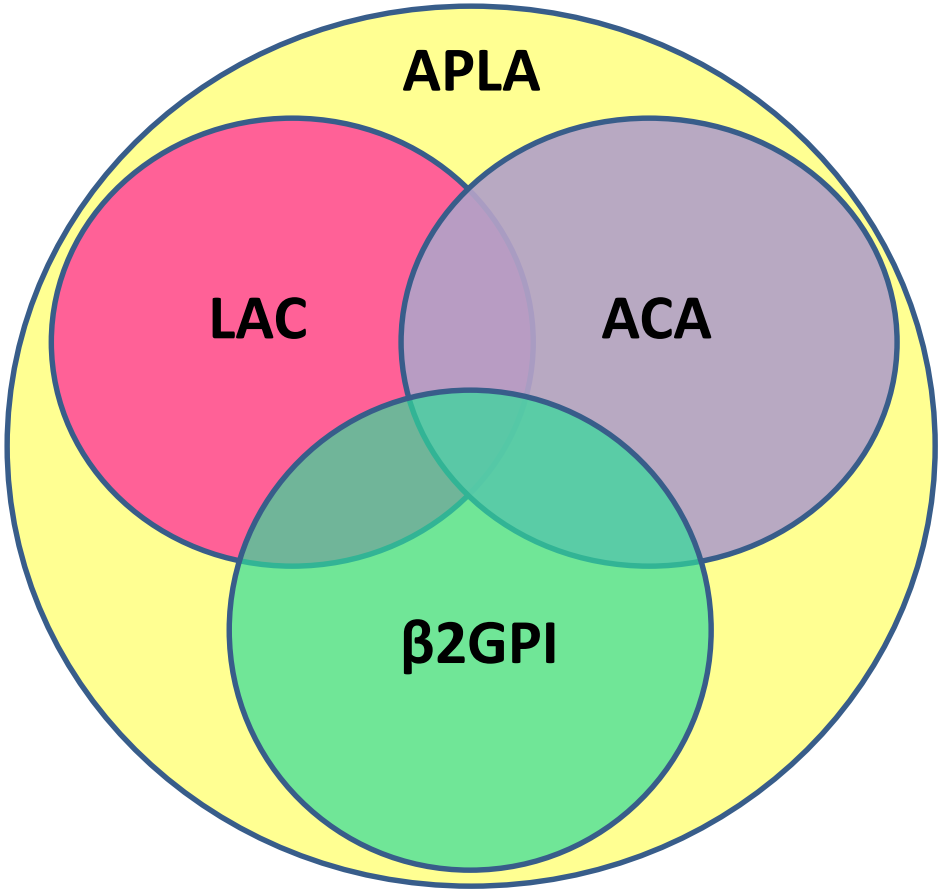
APS

- What are antiphospholipid antibodies?
- Laboratory diagnosis
- Risk of primary and recurrent thrombosis
- ~~Pregnancy loss~~
- Management
  - Anticoagulation
  - other

HIT

- Review of 2018 ASH HIT Guidelines in case-based format
- Highlight several specific recommendations relevant to practice

Antiphospholipid Antibodies



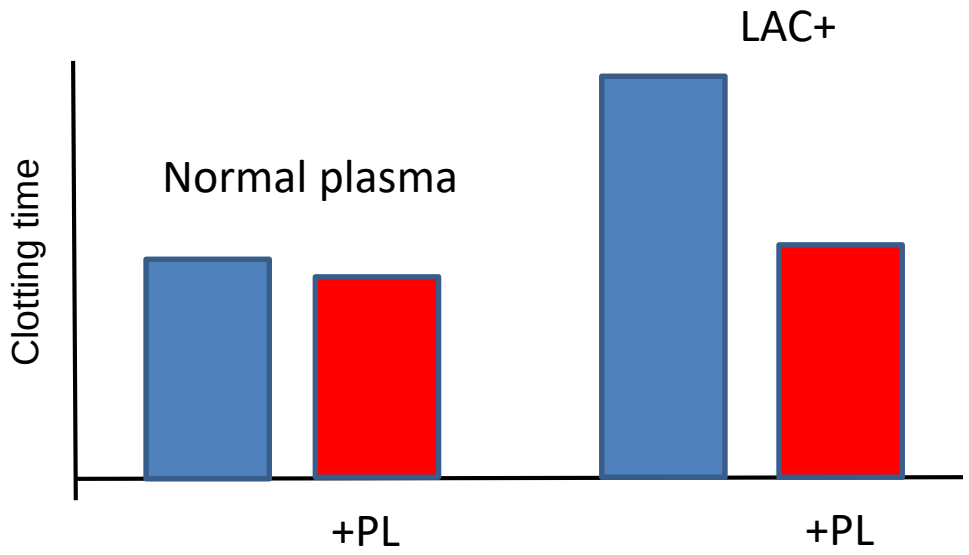
I. Immunologic tests
- Anticardiolipin
- Anti-β2-glycoprotein I
- Anti-prothrombin
- Anti-phosphatidylserine
- Anti-phosphatidylethanolamine
- Anti-phosphatidylcholine

II. Functional tests
- Lupus anticoagulant
  - aPTT
  - DRVVT
  - Hexagonal phase PL
  - PNP
  - TTI
  - Others

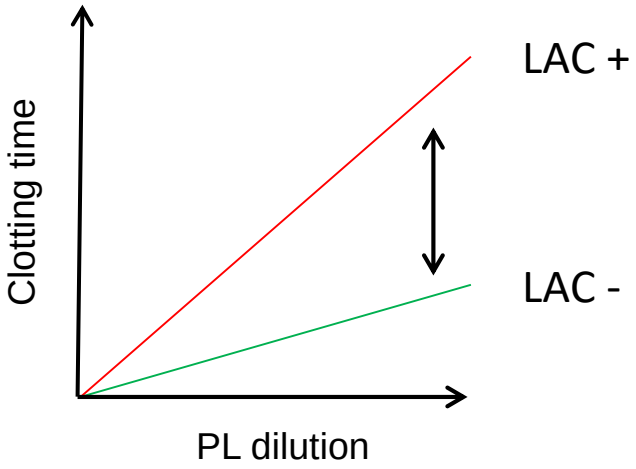
III. Others
- Annexin V resistance

Principles of Lupus Anticoagulant Testing

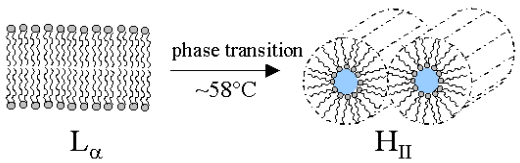
Plasma + Activator + Phospholipid = Clot



- Clotting time of LAC+ plasma shortens (corrects) with exogenous PL
  - DRVVT
  - Hexagonal phase PL
  - PTT
  - Others



- Clotting time of LAC+ plasma demonstrates greater prolongation at higher PL dilutions
  - TTI
  - Dilute PT
  - KCT



ISTH Criteria for Diagnosis of a Lupus Anticoagulant (LAC)

1. **Positive screening test:** usually aPTT
2. **Positive mixing study** (i.e. test remains prolonged after mixing patient plasma with normal plasma): can use either aPTT or DRVVT mixing study
3. **Demonstration of phospholipid dependence:** Examples: Hexagonal Phase Phospholipid Neutralization test, Platelet phospholipid neutralization, DRVVT ratio – all clot-based assays
4. **Exclusion of other potential inhibitors** that could account for observed results: heparin, DTI, factor VIII inhibitor

Brandt et al Thromb Haemost 1995 Oct;74(4):1185-90
Pengo et al J Thromb Haemost 2009 Oct;7(10):1737-40

LAC Diagnosis

Component Results

Component	Value	Range	Status
Beta 2 Glycoprotein, IgG	**147 (H)**	<20 SGU	Fin
Comment:			
< 20 SGU	Negative		
20-80 SGU	Low Positive		
> 80 SGU	High Positive		
Beta 2 Glycoprotein, IgM	**35 (H)**	<20 SMU	Fin
Comment:			
< 20 SMU	Negative		
20-80 SMU	Low Positive		
> 80 SMU	High Positive		
Cardiolipin Ab, IgG	**>150 (H)**	0 - 9 GPL	Fin
Comment:			
<10 GPL	Negative		
10-40 GPL	Equivocal		
>40 GPL	Positive		
Cardiolipin Ab, IgM	**33 (H)**	0 - 11 MPL	Fin
Comment:			
<12 MPL	Negative		
12-40 MPL	Equivocal		
>40 MPL	Positive		
Cardiolipin Ab, IgA	**31 (H)**	0 - 11 APL	Fin
Comment:			
<12 APL	Negative		
12-40 APL	Equivocal		
>40 APL	Positive		
Platelet Neut	**Positive (A)**	NEGAT	Fin
DRVVT Screen	**151.0 (H)**	35.7 - 48.6 sec	Fin
DRVVT Confirm Ratio	**2.83 (H)**	0.88 - 1.16	Fin
DRVVT 1:1 Mix	**100.5 (H)**	35.7 - 48.6 sec	Fin
Hex Phase Screen	**143.2 (H)**	45.7 - 62.9 sec	Fin
Hex Phase Confirm	**85.7 (H)**	46.8 - 60.8 sec	Fin
Hex Phase Delta	**57.5 (H)**	<5.6 delta sec	Fin
APTT Screen	**101.6 (H)**	25.6 - 33.1 sec	Fin
Immediate PTT 1:1 Mix	**62.9 (H)**	<33.2 sec	Fin
Incubated PTT 1:1 Mix	**69.2 (H)**	<36.0 sec	Fin
Thrombin Time	16.4	<18.6 sec	Fin
Interpretation(Lupus Anticoagulant)			Fin

(NOTE)
Performing Pathologist:

Interpretation:
Abnormal - see comment below.

SIGNIFICANT FINDINGS: 1) Lupus Anticoagulant: POSITIVE. 2) Anticardiolipin Antibody: IgG POSITIVE. 3) Beta 2 Glycoprotein I Antibody: IgG and IgM POSITIVE. 4) Warfarin effect.

Positive serologies

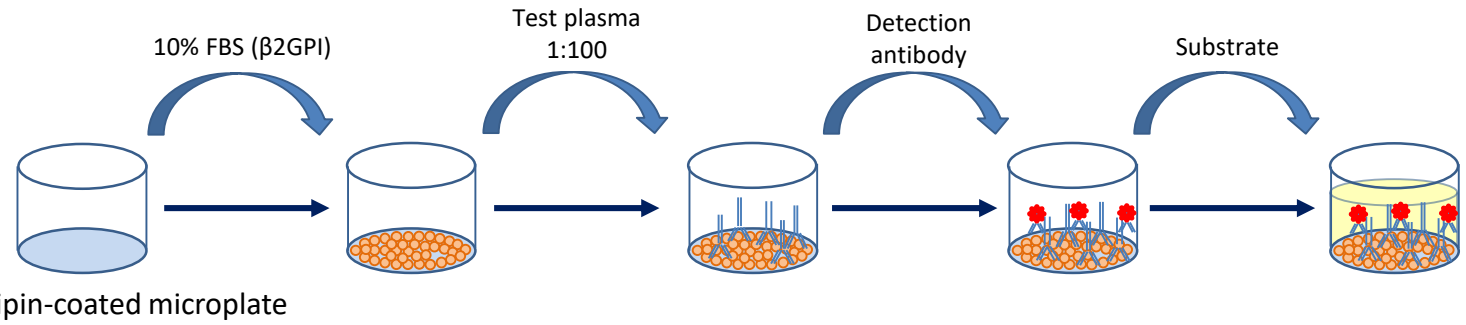
Phospholipid dependent

Positive screening test

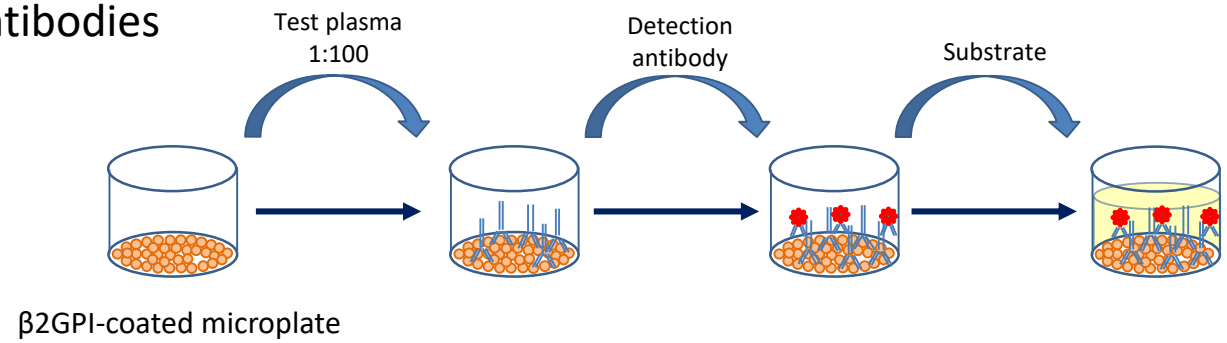
Immediate acting inhibitor on mixing study

Solid Phase APL Assays

Anticardiolipin antibodies



Anti-β2GPI antibodies



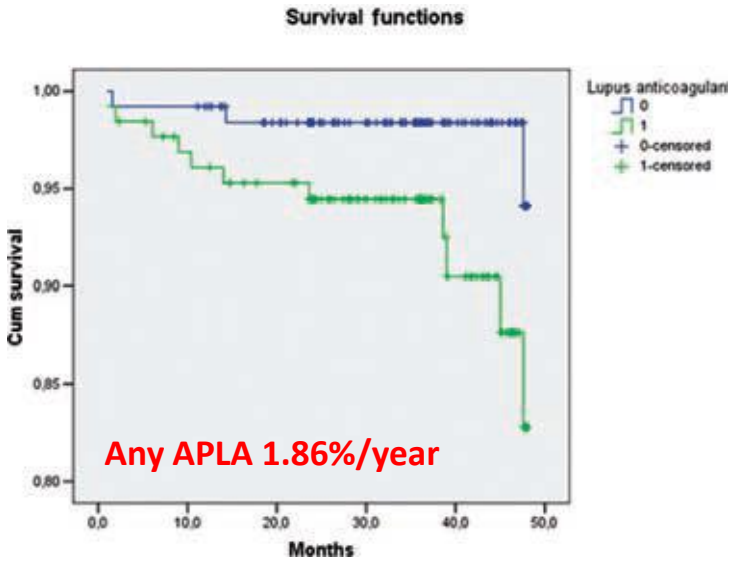
- These tests may or may not detect the same antibodies
- Most pathologic antiphospholipid antibodies are β2GPI-dependent

ISTH Criteria for Definite APS

- *Clinical*
  - Vascular thrombosis—one or more clinical episodes
  - Pregnancy morbidity
    - Three or more consecutive spontaneous abortions before 10th week
    - One or more unexplained deaths beyond 10 weeks
    - One or more premature births at or before the 34th week of gestation because of eclampsia or severe preeclampsia or severe placental insufficiency
- *Laboratory*
  - LAC on 2 or more occasions at least 12 weeks apart, detected by ISTH guidelines
  - aCL antibody of IgG or IgM isotype in serum or plasma, in medium or high titer (>40 GPL or MPL, or the 99th percentile) on 2 or more occasions at least 12 weeks apart, measured by standardized ELISA
  - Anti-β_2GPI antibody of IgG or IgM isotype in serum or plasma (in titer > 99th percentile), present at two or more occasions, at least 12 weeks apart, measured by standardized ELISA

Definite APS requires at least one clinical and one laboratory criteria

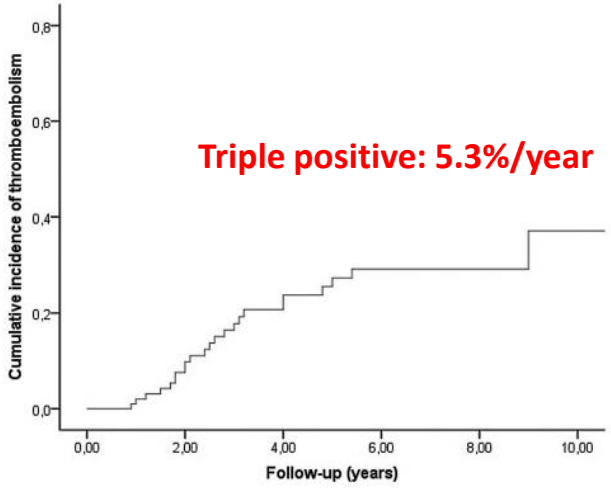
Absolute Risk of Primary Thrombosis with Antiphospholipid Antibodies

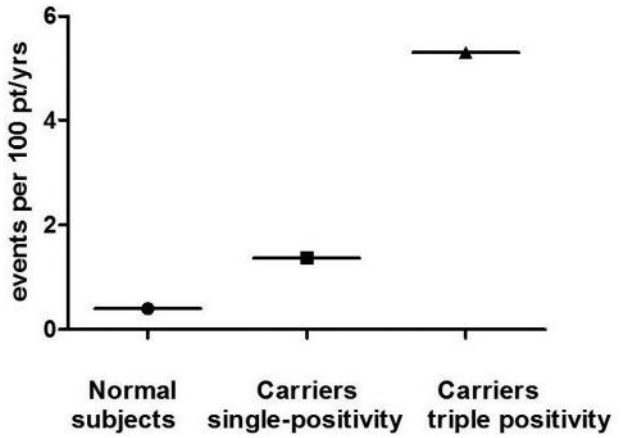


Ruffatti et al Ann Rheum Dis 70:1083, 2011

Conclusions:

- APL are significant risk factors for first thrombosis
- Aspirin did not significantly affect the risk of TE

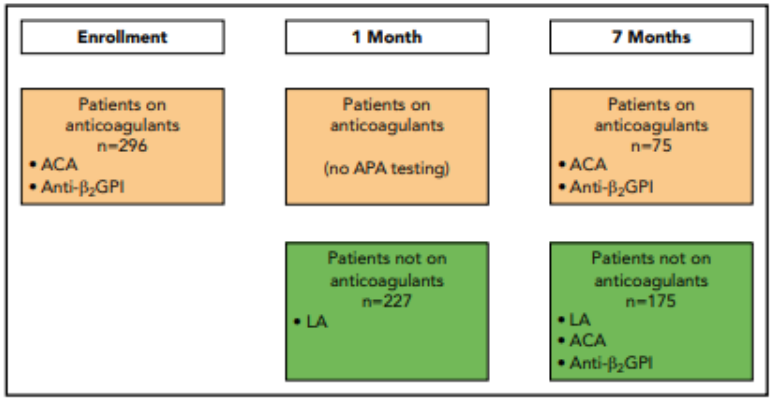




Pengo et al. Blood 118:4714, 2011

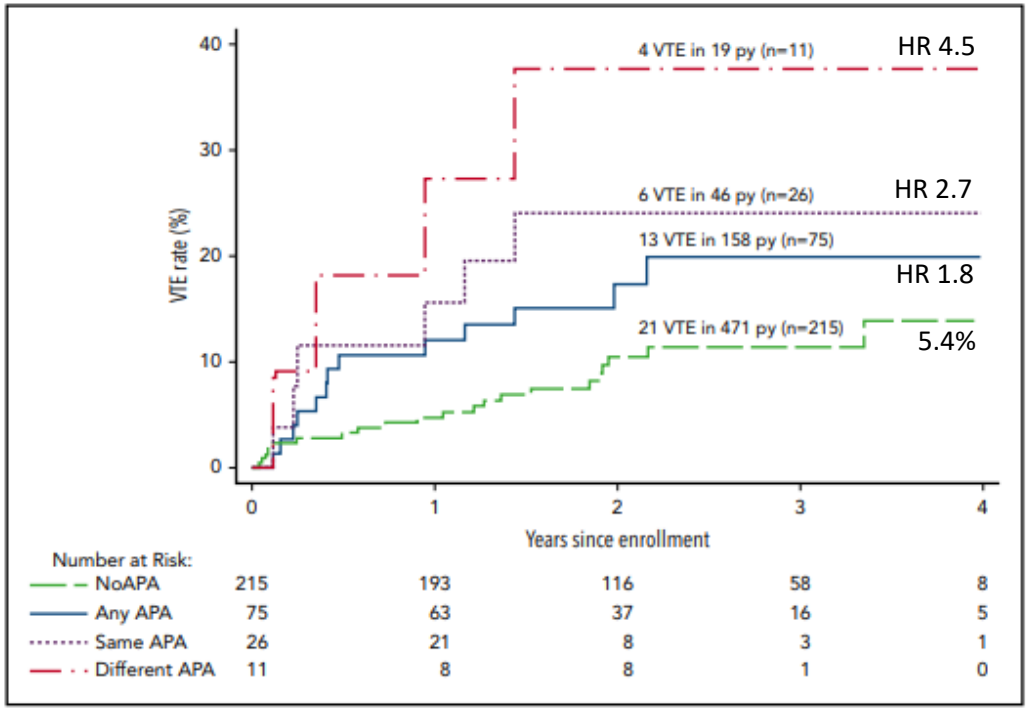
Risk of Recurrent VTE in Patients with APLA

Study outline



- Prospective study design
- All patients enrolled at point when discontinuation of anticoagulant therapy was considered
- Only patients with negative D-dimer (measured at enrollment and at 1 month) in whom anticoagulation was not considered were enrolled
- APA testing performed at enrollment (ACA and anti-β2GPI), at 1 month (LA only) and at 7 months (LAC, ACA, anti-β2GPI)

Results



- No APA = no APA at any follow up study visit
- Any APA = any type of APA detected at least once at any follow up study visit
- Same APA = same type of APA detected more than once on any follow up study visit
- Different APA = different types of APA detected at any follow up study visit, at same or different occasions

Kearon et al, Blood 2018

Criteria and Non-Criteria Manifestations of APS

***Panel* 1: Clinical manifestations of antiphospholipid syndrome**

Frequent (>20% of cases)
- Venous thromboembolism
- Thrombocytopenia
- Miscarriage or fetal loss
- Stroke or transient ischaemic attack
- Migraine
- Livedo reticularis

Less common (10–20% of cases)
- Heart valve disease
- Pre-eclampsia or eclampsia
- Premature birth
- Haemolytic anaemia
- Coronary artery disease

Unusual (<10% of cases)
- Epilepsy
- Vascular dementia
- Chorea
- Retinal artery or vein thrombosis
- Amaurosis fugax
- Pulmonary hypertension
- Leg ulcers
- Digital gangrene
- Osteonecrosis
- Antiphospholipid syndrome nephropathy
- Mesenteric ischaemia

Rare (<1% of cases)
- Adrenal haemorrhage
- Transverse myelitis
- Budd-Chiari syndrome

Ruiz-Irastorza et al Lancet 376:1498, 2010

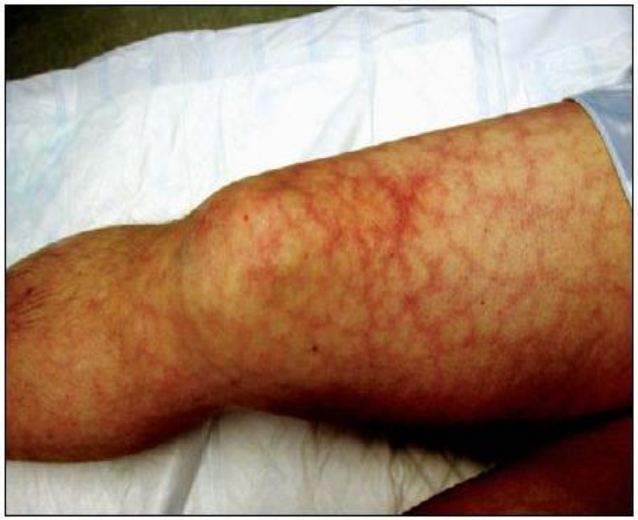


Table 2. Clinical features at disease onset in 1,000 patients with antiphospholipid syndrome*

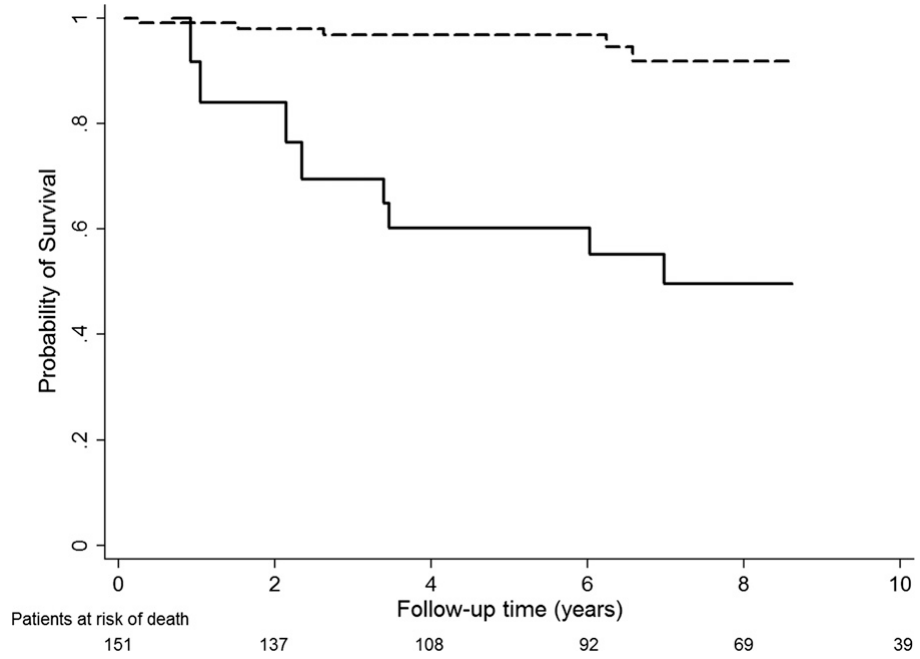
Manifestation	No. (%) of patients
Deep vein thrombosis	317 (31.7)
Thrombocytopenia (<100,000 platelets/μl)	219 (21.9)
Livedo reticularis	204 (20.4)
Stroke	131 (13.1)
Superficial thrombophlebitis	91 (9.1)
Pulmonary embolism	90 (9.0)
Fetal loss	83 (8.3)
Transient ischemic attack	70 (7.0)
Hemolytic anemia	66 (6.6)
Skin ulcers	39 (3.9)
Epilepsy	34 (3.4)
Pseudovasculitic skin lesions	26 (2.6)
Myocardial infarction	28 (2.8)
Amaurosis fugax	28 (2.8)
Digital gangrene	19 (1.9)

* Some patients had several associated presenting manifestations.

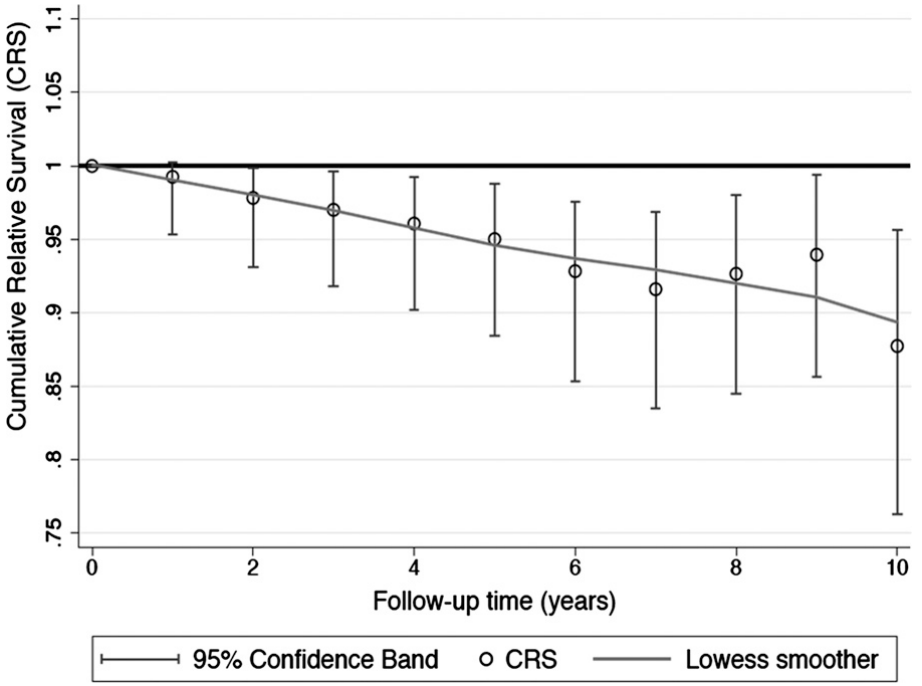
Cervera, et al Arth Rheum 46:1019, 2002

Mortality Associated With Lupus Anticoagulant

Patient with thrombosis at 3y



Compared to general population



Gebhart et al Blood 125:3477, 2015

APS Task Force Guidelines for Thrombosis Management

- 4.1. We recommend that patients with either arterial or venous thrombosis and aPL who do not fulfill criteria for APS be managed in the same manner as aPL-negative patients with similar thrombotic events. *1C recommendation.*

- 4.2. We recommend that patients with definite APS and a first venous event receive oral anticoagulant therapy to a target INR 2.0–3.0. *1B recommendation*.

- 4.3. Patients with definite APS and arterial thrombosis should be treated with warfarin at an INR >3.0 or combined antiaggregant-anticoagulant (INR 2.0–3.0) therapy. *Non-graded recommendation due to lack of consensus.*

- 5.1. We recommend indefinite antithrombotic therapy in patients with definite APS and thrombosis. *1C recommendation*.

Ruiz-Irastorza et al, Lupus 2011

Intensity of Anticoagulation in Patients with APLA

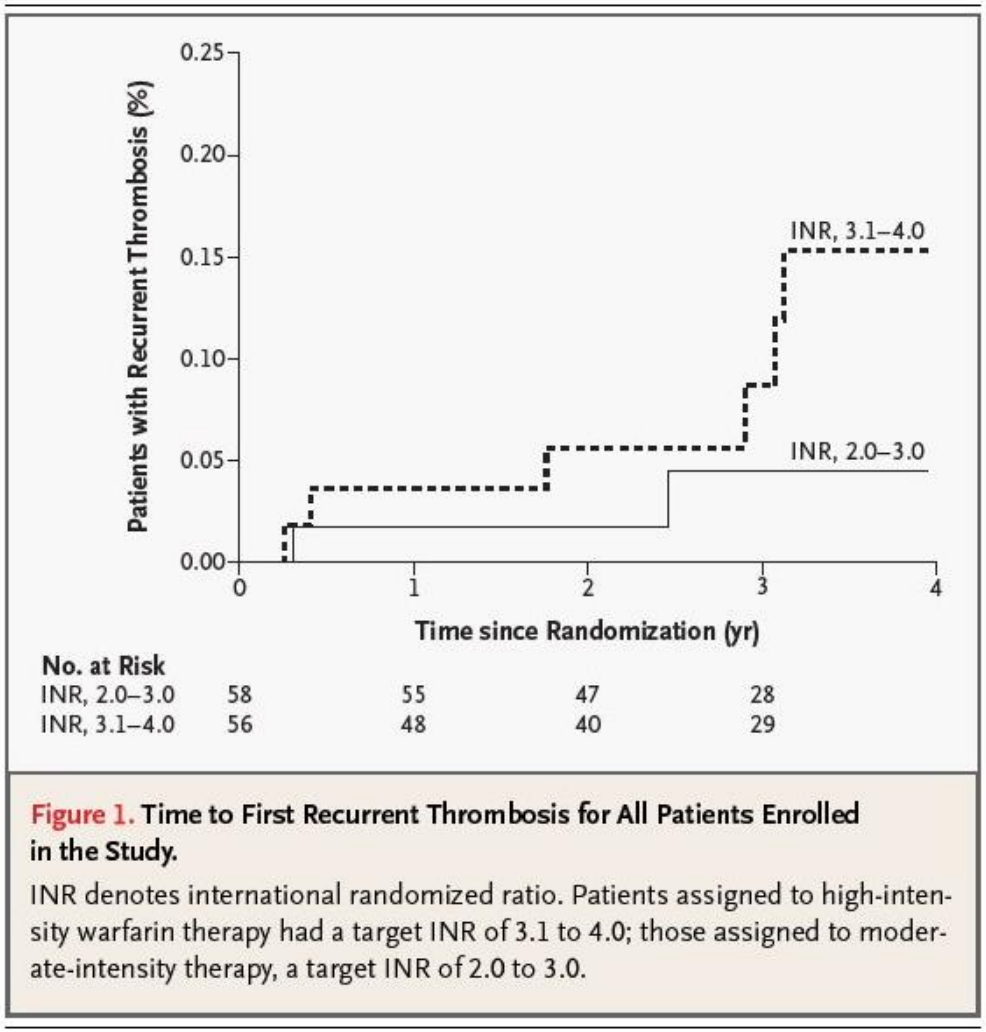


Figure 1. Time to First Recurrent Thrombosis for All Patients Enrolled in the Study.

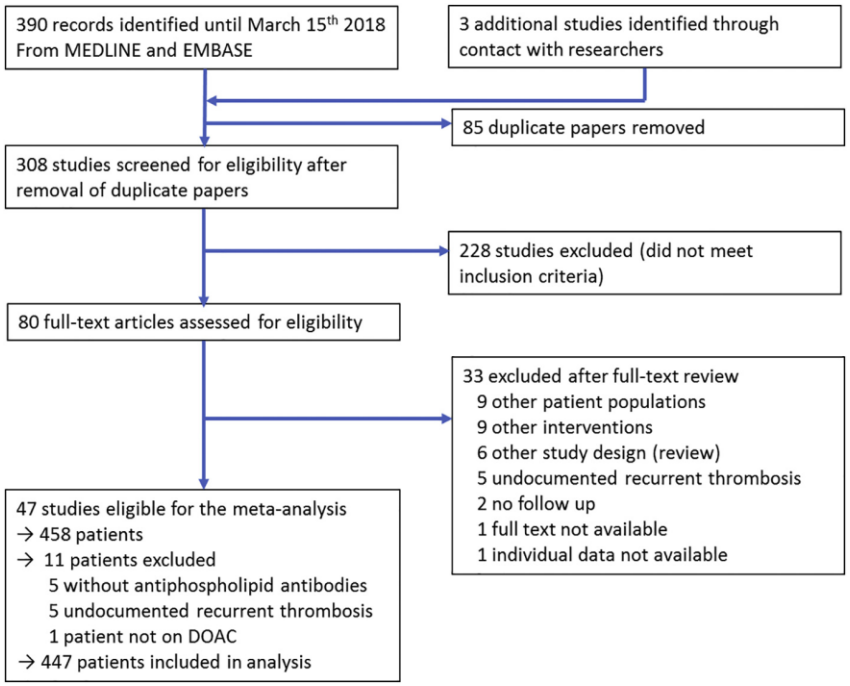
INR denotes international randomized ratio. Patients assigned to high-intensity warfarin therapy had a target INR of 3.1 to 4.0; those assigned to moderate-intensity therapy, a target INR of 2.0 to 3.0.

Crowther et al. NEJM 349:1133, 2003

- We recommend testing for APL in patients with unprovoked proximal DVT or PE after stopping anticoagulation (for at least 7d) as the presence of APL will influence the balance of risks and benefits and support long term anticoagulant therapy (2B)
- **The target INR for VKA therapy in APS should normally be 2.5 (target range 2.0-3.0) (1A)**

Keeling BJH 157:47, 2012 (British Guidelines)

DOACs in APS



- Overall, 73/447 of (16%) developed recurrent thrombosis
  - 28 VTE
  - 31 ATE
  - 13 small vessel
  - 8 unknown
  - Mean time to thrombosis 12.5 months
- Triple positive
  - 56% recurrent thrombosis
  - Mean time to thrombosis 16.1 months

Dufrost et al, Autoimm Rev 2018

Study	Design/ Primary endpoint
RAPS (NCT02116036) (Hamilton, ON)	Pilot, single arm feasibility/ability to enroll and consent patients with APS
RAPS (UC London)	RCT: rivaroxaban vs warfarin/inhibition of thrombin generation times ETP with rivaroxaban higher than warfarin, no thrombosis in either arm
TRAPS (NCT02157272) (U Padova)	RCT: rivaroxaban vs warfarin in triple positive APS/recurrent ATE or VTE (terminated early)
RAPS (NCT02926170) (Val d'Hebron, Barcelona)	RCT: Rivaroxaban vs acenocoumarol (completed)
ASTRO-APS (NCT02295475)	RCT: open label, warfarin vs apixaban/ recurrent VTE (recruiting)

Trial of Rivaroxaban vs Warfarin in High-Risk APS (TRAPS study)

- Randomized, open label study: Rivaroxaban 20 mg/d vs warfarin (INR 2.0-3.0)
- Triple positive APL patients

Table 4. Adjudicated efficacy and safety outcomes

Outcome, n	"As treated" analysis				ITT analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	*P*	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	*P*
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01	13 (22)	2 (3)	7.4 (1.7-32.9)	.008
Arterial thrombosis Ischemic stroke Myocardial infarction	7 (12) 4 (7) 3 (5)	0 0 0	—	—	7 (12) 4 (7) 3 (5)	0 0 0	—	—
Venous thromboembolism	0	0			1 (2)	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3	4 (7)	2 (3)	2.3 (0.4-12.5)	.3
Death	0	0	—	—	1 (2)	0	—	—

Numbers in parentheses denote percentage with respect to total.

—, statistical analysis not applicable.

Pengo et al, Blood 2018

Non-Anticoagulant Treatment

- **Hydroxychloroquine**
  - Primary APS
    - Schmidt-Tanguy, JTH 11:1927, 2013. RCT, 20 pts/arm, treated with OA vs OA+HCQ. Recurrent DVT in 6 in OA, 0 in OA/HCQ.
  - SLE
    - Petri, Arth Rheum, 1994. Prospective cohort study, OR 0.36 for thrombosis in HCQ treated patients
    - Ruiz-Irastorza, Lupus, 2006. Prospective cohort study, HR 0.28 (arterial/venous)
- **Rituximab**
  - Erkan, Arth-Rheum, 2013. Phase II pilot, Rituximab 1000 mg d1 and d15, 1 year follow up. All patients with positive results on d1 had positive results at 24 weeks and 52 weeks. 10-20% response in some non-criteria manifestations
- **Statins**
  - Erkan, Arth Ann Rheum Dis, 2014. Single arm, 3 months biomarker study of fluvastatin on inflammatory biomarkers. Significant reductions seen in several, including TNFα, IL-6, IL-1β, VEGF
- **Eculizumab**
  - Several reports of potential benefit in catastrophic APS
  - Under study to enable renal transplant in CAPS

Preliminary Criteria for Diagnosis of Catastrophic Antiphospholipid Syndrome

1) Evidence of involvement of three or more organs, systems and/or tissues[a]

2) Development of manifestations simultaneously or in less than a week

3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue[b]

4) Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)[c]

Definite catastrophic APS

- All four criteria

Probable catastrophic APS

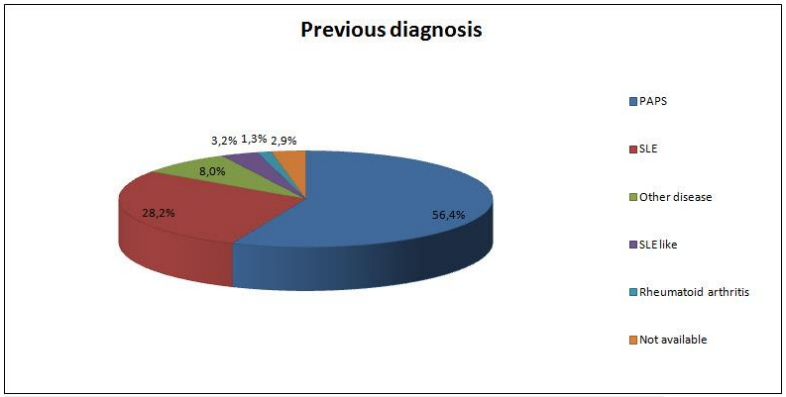
- All four criteria, except for only two organs, systems and/or tissues involvement
- All four criteria, except for the absence of laboratory confirmation at least six weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS
- 1, 2 and 4
- 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

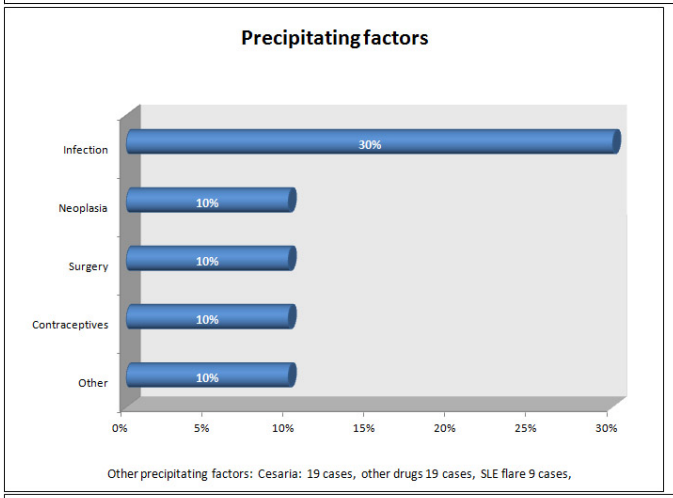
Asherson et al, Lupus 2003

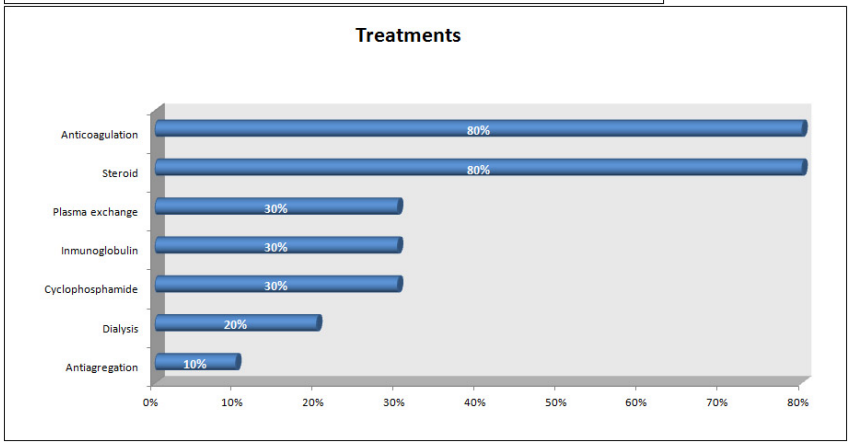
Characteristics of CAPS

- 69% female
- Most cases associated with systemic autoimmune disease
- 65% of cases triggered by precipitating factor
- Multi-organ involvement
- Microangiopathic hemolytic anemia (MAHA) common
- Mortality 37-50%
- Clinical spectrum
  - Usually associated with malignancy in older patients
  - Often associated with infection in younger patients
  - Cases associated with autoimmune disease had greater brain and heart involvement and higher mortality (48%)

Rodriguez-Pinto et al, Autoimm Rev, 2015







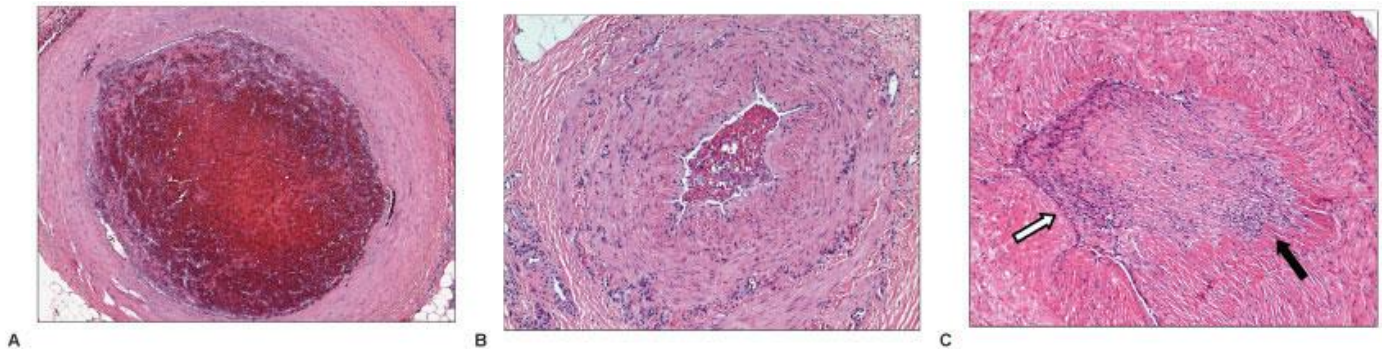
https://ontocrf.grupocostaisa.com/es/web/caps/statistics

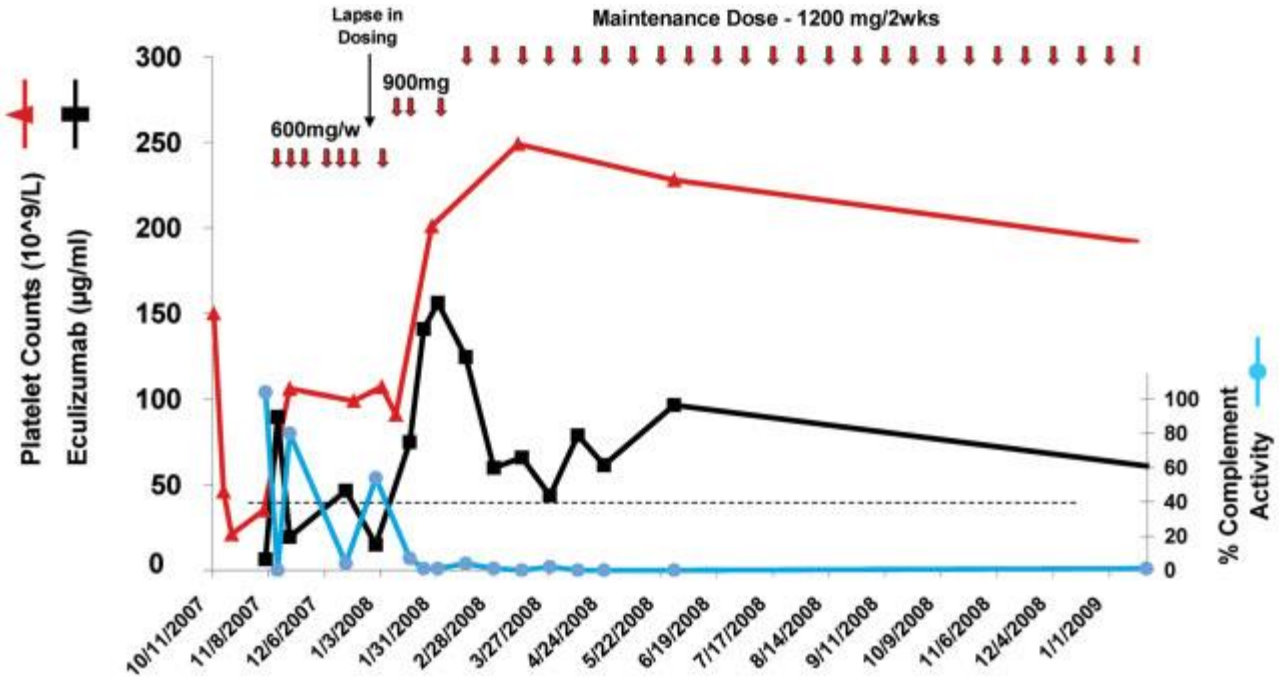
McMaster RARE-Bestpractices Clinical Practice Guideline on Diagnosis and Management of CAPS

1. For patients suspected of having CAPS, the panel suggests using the preliminary criteria for classification of the catastrophic antiphospholipid syndrome for diagnosis of CAPS	• Conditional recommendation, very low certainty of evidence
2. For patients suspected of having CAPS, the panel suggests either using or not using biopsy to diagnose CAPS	• Conditional recommendation, very low certainty of evidence
4. For first-line treatment of patients with CAPS, the panel suggests combination therapy with glucocorticoid, heparin and plasmapheresis or IVIG over single agents or other combinations of therapies	• Conditional recommendation, very low certainty of evidence
5. For first-line treatment of patients with CAPS, the panel recommends using therapeutic-dose anticoagulation	• Strong recommendation, very low certainty of evidence
8. For first-line treatment of patients with CAPS, the panel suggests using antiplatelet agents as add-on therapy. In patients for whom anticoagulation is contraindicated for reasons other than bleeding, the CAPS guideline panel recommends using antiplatelet agents as an alternative	• For add-on therapy: conditional recommendation, very low certainty of evidence • For alternative therapy to anticoagulation: strong recommendation, very low certainty of evidence
9. For first-line treatment of patients with CAPS, the panel suggests not using rituximab.	• Conditional recommendation, very low certainty of evidence
10. For first-line treatment of patients with CAPS, the panel suggests not using glucocorticoids.	• Conditional recommendation, very low certainty of evidence

Legault et al, JTH 2018

Eculizumab in Catastrophic APS





Shapira et al Arth Rheum 64:2719, 2012

Eculizumab in CAPS

Reference	Patient	Prior Treatment	Eculizimab	Outcome
Shapira, Arth Rheum 2012	28 yo male, SLE, PE since age 12, BKA from arterial thrombosis, abd ischemia	Heparin, argatroban, fondaparinux, Cytoxan, steroids, IVIG, lepirudin, bivalirudin, DAPT, PLEX	Eculizumab, 900 mg then 1200 q 2wks for > 1 yr	Resolution of anemia, thrombocytopenia, thrombotic events
Kronbichler, Medicine 2014	30 yo female, ITP, primary APS, CAPS after pregnancy, MI, renal failure	Plaquenil, heparin, steroids, rituximab, PLEX, dialysis	Eculizumab x 3 months, mycophenylate, steroids (C3 mut)	Resolution of MAHA, thrombocytopenia, partial relapse, dialysis dependent
Lonze Am J Transp, 2014	3 patients, 2 with prior CAPS, for renal transplant	Prednisone, rituximab, anticoagulation	Eculizumab, 900 mg weekly begun d1 after transplant, then 1200 q 2 wks	Successful engraftment up to 4 years, continued treatment
Strakhan, Case Rep Hem 2014	36 yo female, with hypertension, AKI, strokes, NSTEMI, MAHA, + LAC	PLEX, steroids	Eculizumab 900 mg/wk x 4 then 1200 q 2 wks	Gradual improvement of MAHA, continued dialysis
Zikos J Clin Rheum, 2015	47 yo male with h/o APS, multifocal thromb, thrombocytopenia. Later, renal/liver infarct	Heparin, PLEX, IVIg, steroids, argatroban, heparin	Eculizumab 900 mg x 2, then 1200 mg every 7-10 days	Gradual improvement in all parameters, but remains dialysis dependent
Rovere-Querini, Med 2018	33 yo female, FVL+. APS triple +, developed TMA at 30 wks preg	Rituximab, LDA, heparin	Eculizumab 600 mg, C-section at 32 wk, repeat Ec afterwards	Stabilization of thrombocytopenia, renal function, Hgb

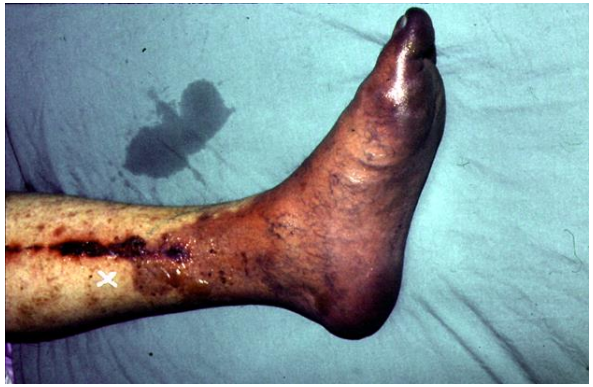
Summary

- APS is a markedly prothrombotic disease associated with both arterial and venous thrombosis
- Lupus anticoagulants have the strongest association with the development of thrombosis
- Patients with triple positive APLA have the highest risk of thrombosis: >5% annually
- Recurrence rates are high
- CAPS is a mult-system thrombotic disorder associated with mortality approaching 50%
- Multi-modality therapy is indicated for patients with a diagnosis of CAPS
- A role for eculizumab in CAPS has been suggested

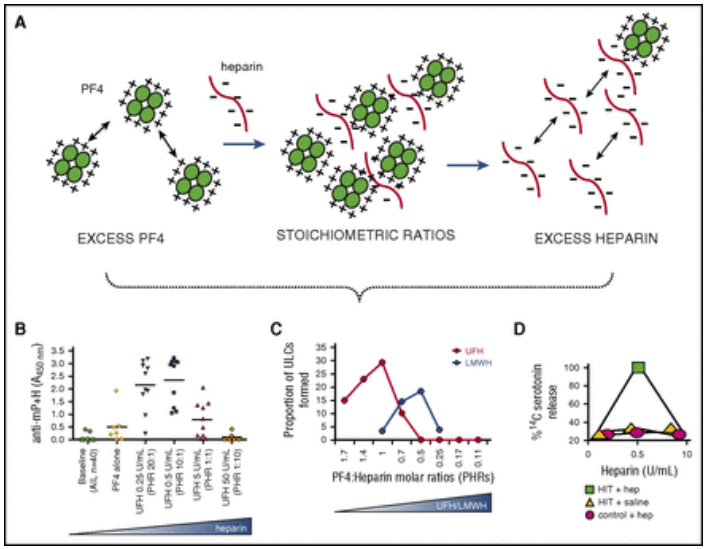
Heparin-Induced Thrombocytopenia

2018 *ASH HIT Guidelines*

- Terminology
  - HIT (asymptomatic thrombocytopenia)
  - HITT (with thrombosis)
- Occurs in 1-3% of patient treated with UFH, 0.2% with LMWH
  - Overall, thrombosis develops in 30-50% of patients with thrombocytopenia
- More common in patients undergoing cardiac/orthopedic surgery, trauma, or with cancer
- 4T scoring system used to assess pretest probability of HIT
- Laboratory studies
  - Heparin-PF4 antibodies, if negative, have high negative predictive value
  - Functional studies (^{14}C-serotonin release) more specific
- Treatment of acute HIT requires discontinuation of heparin and institution of alternative anticoagulation (argatroban, bivalirudin, fondaparinux)
- Avoid warfarin in acute HIT due to risk of Coumadin skin necrosis

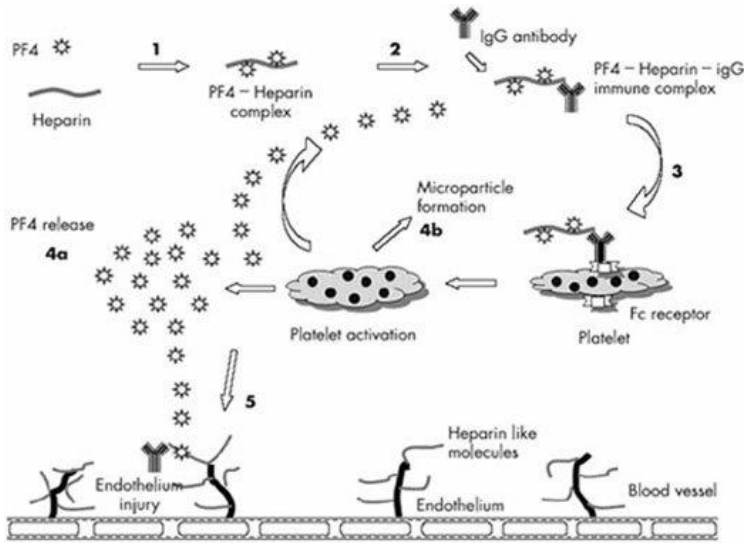


Formation of HIT Immune Complexes



Arepally, Blood 2017

- Formation of ultra-large, antigenic immune complexes of PF4 and heparin
- Recognition of immune complexes by HIT antibodies
- Binding of immune complexes to platelets, monocytes and endothelial cells, causing cellular activation and procoagulant activity
- Direct interactions of PF4 with cellular GAG (heparin-like)



https://www.medscape.org/viewarticle/569661

HIT is a profoundly hypercoagulable state

HIT is an iatrogenic disorder mediated by IgG antibodies that bind **PF4-heparin** complexes

These antibodies cause a **hypercoagulable state** by activating platelets and other vascular cells

One-third to one-half of patients with HIT develop venous, arterial, or microvascular thrombosis

Case 1: Medical Inpatient Admission

82 year old male

Past Medical History: Diabetes, Hypertension, Heart Failure

Medications: Metformin, Ramipril, Aspirin, Furosemide

Admitted to: Internal Medicine ward with heart failure exacerbation secondary to poor compliance with diet and diuretics

Treated with:

- Intravenous Furosemide, Nitroglycerin patch
- ***Subcutaneous unfractionated heparin (UFH)*** 5,000 IU Q12H started on admission for DVT prophylaxis

Case 1: Medical Inpatient Admission

- No fever or signs of infection. No other new medications. No signs or symptoms of thromboembolism.
- No exposure to heparin in the 3 months prior to this admission
- **Bloodwork:** **Day 0 is admission date**

Date	**Day 0**	**+1**	**+2**	**+3**	**+4**	**+5**	**+6**	**+7**
Platelets (x 10^9)	200	220	206	210	220	230	150	67
Hemoglobin (g/dL)	13.5	13.1	13.3	13.0	13.0	13.3	13.1	13.3

Considering your patient's progressive thrombocytopenia and heparin exposure, you are concerned about the possibility of HIT.

Which of the following most accurately describes his clinical probability of HIT?

A. Probably low probability, given overall clinical context
B. Probably high probability, given overall clinical context
C. Low probability, based on 4Ts score
D. Intermediate probability, based on 4Ts score
E. High probability, based on 4Ts score

Recommendation.

- In patients with **suspected HIT**, the panel recommends using the **4Ts score** to estimate the probability of HIT **rather than a gestalt approach** *(strong recommendation, moderate certainty)*

REMARKS:

- Missing or inaccurate information may lead to a faulty 4Ts score and inappropriate management decisions
- Every effort should be made to obtain ***accurate and complete information*** necessary to calculate the 4Ts score. If key information is missing it may be prudent to err on the side of a higher 4Ts score.
- Reassess frequently. If there is a change in clinical picture, the 4Ts score should be recalculated.

Our patient:
Platelets 67, > 50% drop.
Onset of drop on day +6.
No thrombosis.
No other cause for thrombocytopenia.

HIGH probability:
6-8 points

INTERMEDIATE probability:
4-5 points

LOW probability:
≤ 3 points

Lo *J Thromb Haemost* 2006
ASH 2009 Clinical Guide

4T's	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥ 20 x 10^9/L	Platelet count fall 30-50% or platelet nadir 10-19 x 10^9/L	Platelet count fall < 30% or platelet nadir < 10 x 10^9/L
Timing of platelet count fall	Clear onset between days 5-14 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 fall, but not clear (e.g. missing platelet counts) or onset after day 14 or fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall ≤ 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus	Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed)	None
oTher causes of thrombocytopenia	None apparent	Possible	Definite

How should the 4Ts score be interpreted?

Meta-analysis:
1. Patients with suspected HIT
2. Evaluated by 4Ts
3. Evaluated by a reference standard

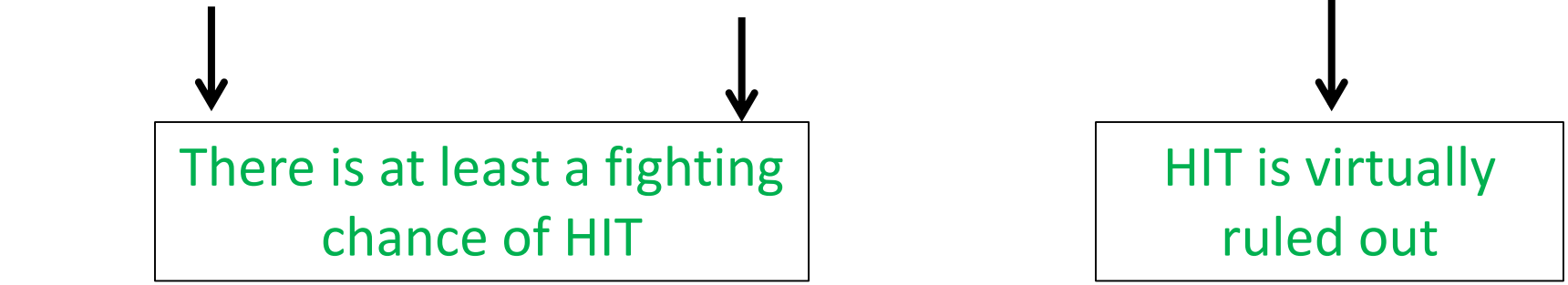
→

13 eligible studies (3068 patients)
- 1712 (55.8%) low probability
- 1103 (36.0%) intermediate probability
- 253 (8.2%) high probability

PPV of High 4Ts score: **64% (40-82%)**

PPV of Interm. 4Ts score: **14% (9-22%)**

NPV of Low 4Ts score: **99.8% (97-100%)**



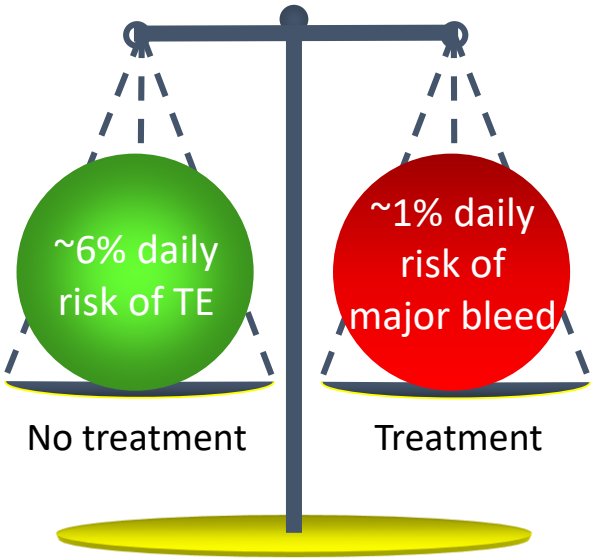
Cuker et al., Blood 2012;120:4160

Your patient's 4Ts score indicates high probability for HIT, and you have sent off the HIT ELISA (result is pending). Currently, your patient is receiving subcutaneous UFH 5,000 units twice daily.

How should you manage his anticoagulants while you are waiting for diagnostic test confirmation?

A. Continue heparin as the diagnosis of HIT is not confirmed
B. Stop heparin, wait for ELISA result
C. Stop heparin, start non-heparin anticoagulant at prophylactic intensity
D. Stop heparin, start non-heparin anticoagulant at therapeutic intensity
E. Stop heparin, provide a platelet transfusion as platelet count is only 67

To treat or not treat for HIT: A high-stakes decision



Greinacher et al., Blood 2000:96;846; Lubenow et al., JTH 2005:3;2428; Lewis et al., Chest 2006:129;1407

Recommendation.

In patients with suspected HIT and <u>HIGH PROBABILITY</u> 4Ts score:

- The panel recommends discontinuation of heparin and initiation of a non-heparin anticoagulant at **<u>therapeutic intensity</u>** *(strong recommendation, moderate certainty)*

Which of the following non-heparin anticoagulants would be appropriate at this point?

A. Argatroban
B. Rivaroxaban
C. Fondaparinux
D. Danaparoid
E. Any of the above

Recommendation.

- In patients with acute HIT, the panel *suggests* treatment with **argatroban, bivalirudin, danaparoid, fondaparinux or a direct oral anticoagulant (DOAC)**

Evolution of clinical practice guidelines

Guideline	Recommendations for treatment of acute HIT
ACCP 2012	Argatroban (1C) Danaparoid (1C)
BCSH 2012	Danaparoid (1B) Argatroban (1C) Fondaparinux (2C)
ASH 2018	Argatroban Bivalirudin Danaparoid Fondaparinux DOACs

Linkins et al., Chest 2012;141:e495S; Watson et al., Br J Haematol 2012;159:528; Cuker et al., Blood Adv 2018 in press

Evidence for DOACs

Drug	N	HITT	DOAC first	Thrombotic events	Major bleeds
Rivaroxaban	49	31 (63%)	25 (51%)	1/49	0/49
Apixaban	21	8 (38%)	7 (33%)	0/21	0/21
Dabigatran	11	6 (55%)	3 (27%)	1/11	0/11

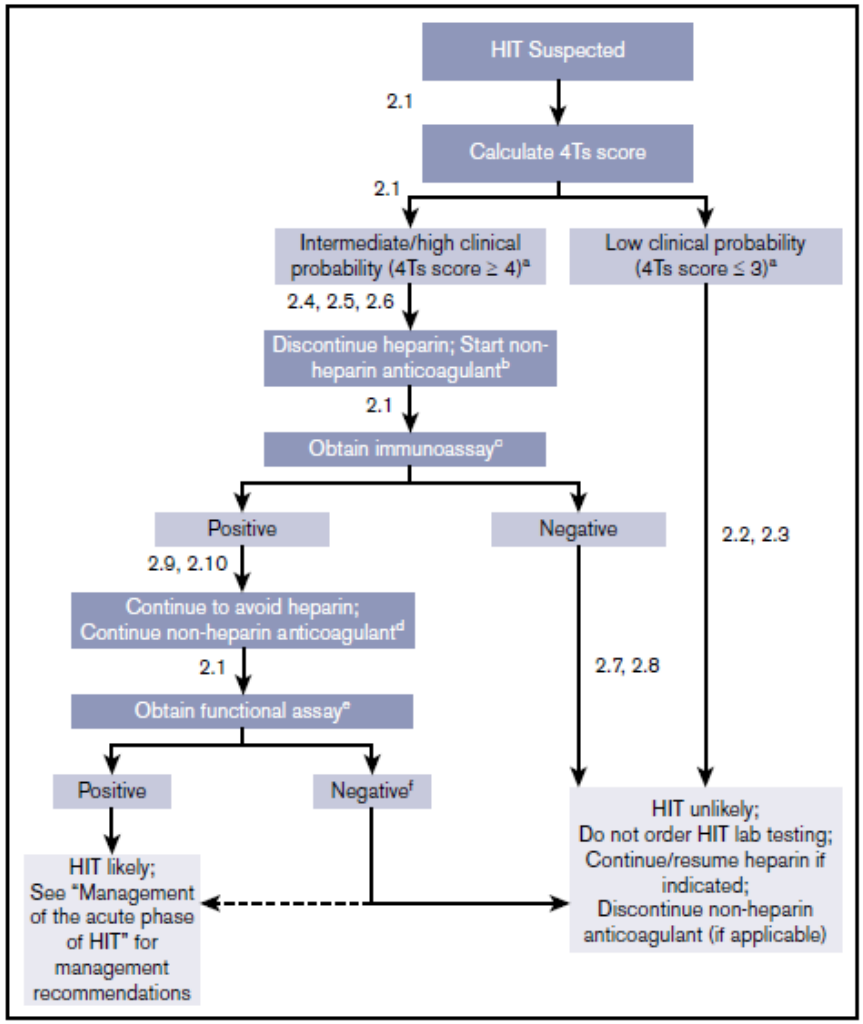
Limitations of evidence:
Small numbers
Selection bias
Reporting bias

Need more evidence:
~~RCTs~~
Single center case series
Multicenter registries

Warkentin et al., Blood 2017;130:1104; Davis et al., Eur J Haematol 2017;99:332

Clinical Context	Implications for Anticoagulant Selection
Critical illness Increased bleeding risk Potential need for urgent procedures	**Argatroban or Bivalirudin** (shorter duration of effect)
Life- or limb-threatening thrombosis	Parenteral non-heparin anticoagulant preferred (**Argatroban, Bivalirudin, Danaparoid, Fondaparinux**) • *Few such patients treated with DOACs*
Clinically stable patients at average bleeding risk	**Fondaparinux or DOACs** reasonable/preferred • Fixed dosing, no routine lab monitoring, can be given out of hospital, less expensive

Algorithm for Diagnosis and Management of Patients with HIT



Cuker et al Blood, 2018

Recommendation 2.2
In patients with suspected HIT and a low-probability 4Ts score, the ASH guideline *panel recommends against HIT laboratory testing* (strong recommendation, moderate certainty in the evidence about effects).

Recommendation 2.7
In patients with an intermediate-probability 4Ts score and a negative immunoassay, the ASH guideline panel recommends *discontinuation of the non-heparin anticoagulant and resumption of heparin*, if indicated (strong recommendation, moderate certainty in the evidence about effects).

Recommendation 3.4
In patients with acute HITT or acute isolated HIT, the ASH guideline panel *recommends against routine insertion of an IVC filter* (strong recommendation, moderate certainty in the evidence about effects).

Recommendation 3.5
In patients with acute HITT or acute isolated HIT, the ASH guideline panel *recommends against initiation of a VKA before platelet count recovery (usually a platelet count of ≥ 150 x 10^9/L)* (strong recommendation, moderate certainty in the evidence about effects)

Acknowledgements

ASH HIT panel members

Adam Cuker, University of Pennsylvania

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Stephen Rodner, Patient representative

Nancy Santesso, McMaster University

Sixten Selleng, University of Greifswald

Theodore Warkentin, McMaster University

Ashleigh Wex, Patient representative

Effect of LAC and Anticoagulants on Clinical Laboratory Assays

Test	Lupus Anticoagulant	UFH	LMWH	Fondaparinux	Warfarin	DTI	Anti-Xa
PT	Normal to prolonged	Normal to mild prolongation	Normal	Normal	Prolonged	Variable	Variable
aPTT	Usually prolonged	Prolonged	Mild prolongation	Minimal	Normal to mild prolongation	Prolonged	Variable
TCT	Normal	Prolonged	Variable prolongation	Normal	Normal	Prolonged	Normal
dRVVT	Usually prolonged	Prolonged	Variable effect	Normal	Prolonged	Prolonged	Prolonged
Anti-Xa	Not present	Elevated	Elevated	Elevated	Not present	Not present	Elevated

Differs from LAC

Possibly similar to LAC

Same effect as LAC (can't diagnose)

Modified from Ortel TL. Curr Rheum Rep, 2012

Relative Risk of Thrombosis with Antiphospholipid Antibodies

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)

DeGroot et al JTH 3:1993, 2005

Table 1. Strength of the association between lupus anticoagulants, anticardiolipin antibodies, and thrombosis

Type of thrombosis	Lupus anticoagulants*	Odds ratio range	Anticardiolipin antibodies*†	Odds ratio range
Arterial	2/2	8.65-10.84	13/19	NS-18
Venous	5/5	4.09-16.2	2/12	NS-2.51
Any‡	2/2	5.71-7.3	1/2	NS-3.66

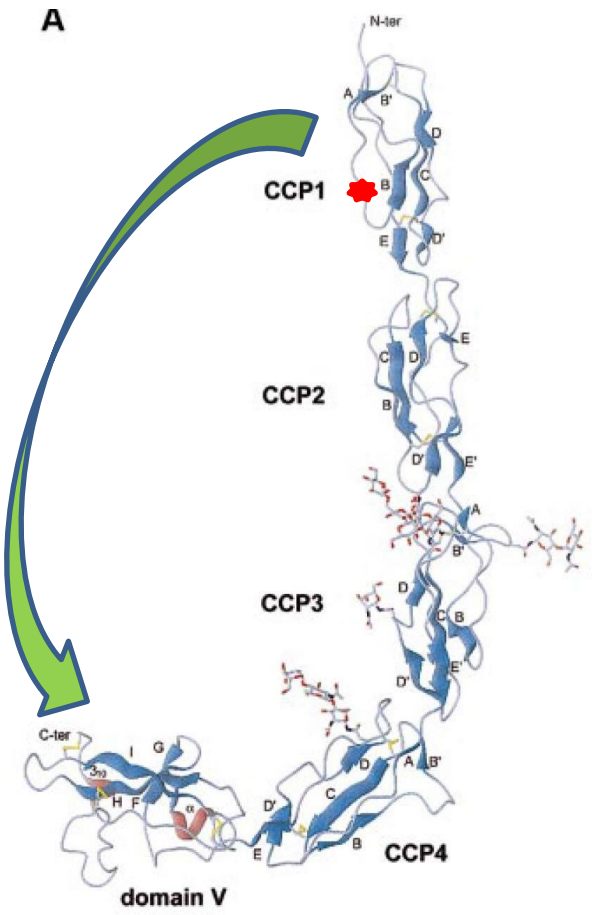
NS indicates not significant.
*No. of statistically significant associations/total no. of available associations.
†No distinction was made between anticardiolipin isotypes.
‡No distinction was possible between arterial and venous thrombosis.

Gali et al Blood 102:2717, 2003

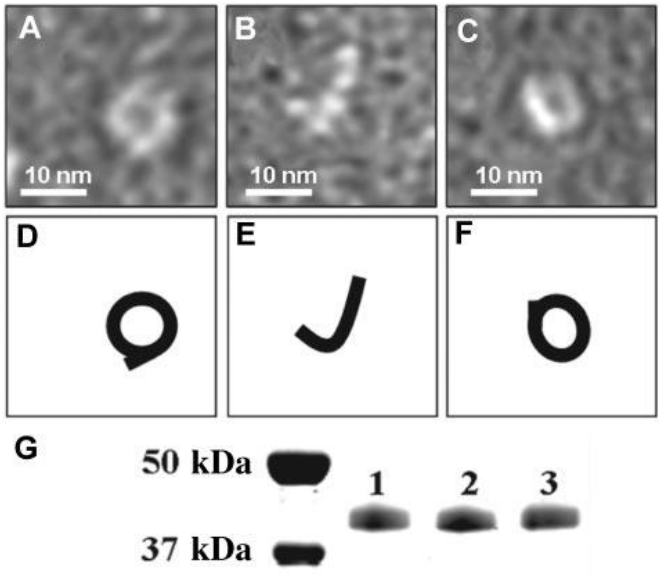
Conclusions:

- LAC is a stronger and more definitive risk factor for thrombosis than ACA or anti-β2GPI antibodies
- β2GPI antibodies are a more significant risk factor than prothrombin antibodies
- ACA alone are of uncertain significance as a thrombotic risk factor
- Risk with LAC and anti-β2GPI antibodies is additive

β_2-Glycoprotein I (β_2GPI)



Schwarzenbacher et al. EMBO J 18:6228, 1989



Ağar et al Blood 116:1336, 2010

- 5 domain CCP family protein, with 4 typical and one atypical CCP (sushi) domain
- Binds LPS, apoptotic cells, vWF.
- Domain 5: phospholipid binding
- Domain 1: (R39-R43)—binding site for most pathologic antibodies
- Proposed to circulate in coiled form in plasma, shielding antibody binding site, but unfold following binding to PL

Aspirin/Heparin in Obstetrical APS

	Rai, 1997		Kutteh, 1996		Farquharson, 2002		Laskin, 2009	
	ASA	ASA/ Hep	ASA	ASA/ Hep	ASA	ASA/ Hep	ASA	ASA/ Hep
N	45	45	25	25	47	51	20	22
Live birth	19 (42%)	32 (71%)	11 (44%)	20 (80%)	34 (72%)	40 (78%)	15 (75%)	17 (77.2%)
Stats	3.37 (1.4, 8.1)		P <0.05		1.39 (0.55, 3.47)		P = 0.75	
Design	• Randomized • ASA + preg • UFH 5000 bid with FHR		• Alternate allocation • ASA before conception • Adjusted dose UFH		• Randomized • ASA/LMWH (5000 U daily) begun week 12 • ITT analysis		• Randomized as part of larger trial for RPL with APL, thrombophilia or ANA • ASA/LMWH (5000 U daily) beginning at randomization	
Notes	• No benefit after 13 wks • No benefit for IUGR, premature delivery		• Mean heparin dose 13,500 U bid • No benefit for IUGR, preterm delivery		• No benefit for IUGR, preterm delivery		• No benefit for IUGR, preterm delivery • Trial stopped early due to poor recruitment and no difference at 4 year analysis	

Of the interventions examined, only unfractionated heparin combined with aspirin was shown to reduce the incidence of pregnancy loss (RR 0.46, 95% CI 0.29-0.71) when compared with aspirin alone. LMWH combined with aspirin had no statistically significant effect when compared with aspirin alone (RR 0.78, 95% CI 0.39-1.57)……Empson et al, Cochrane Collaboration, 2012