Quale terapia anticoagulante nella sindrome da anticorpi antifosfolipidi?

Vittorio Pengo

APS treatment according to possible pathophysiology?

- Venous thromboembolism (stasis/coagulation are the main drivers)
- Arterial thromboembolism (platelet the main driver? Endothelial dysfunction? Embolic source? In situ thrombosis?)
- Obstetric APS (β2GPI is present in placenta and trophoblast tissues; damage mediated by complement activation?)
- Cathastrophic APS (platelets might be the main driver)

APS treatment in pts with VTE

- VKA is a standard treatment in VTE
- Intensity (INR 2.0-3.0): two randomised trial

Crowther et al., NEJM 2003; 349: 1133

Finazzi et al., JTH 2005

- Duration of treatment ?

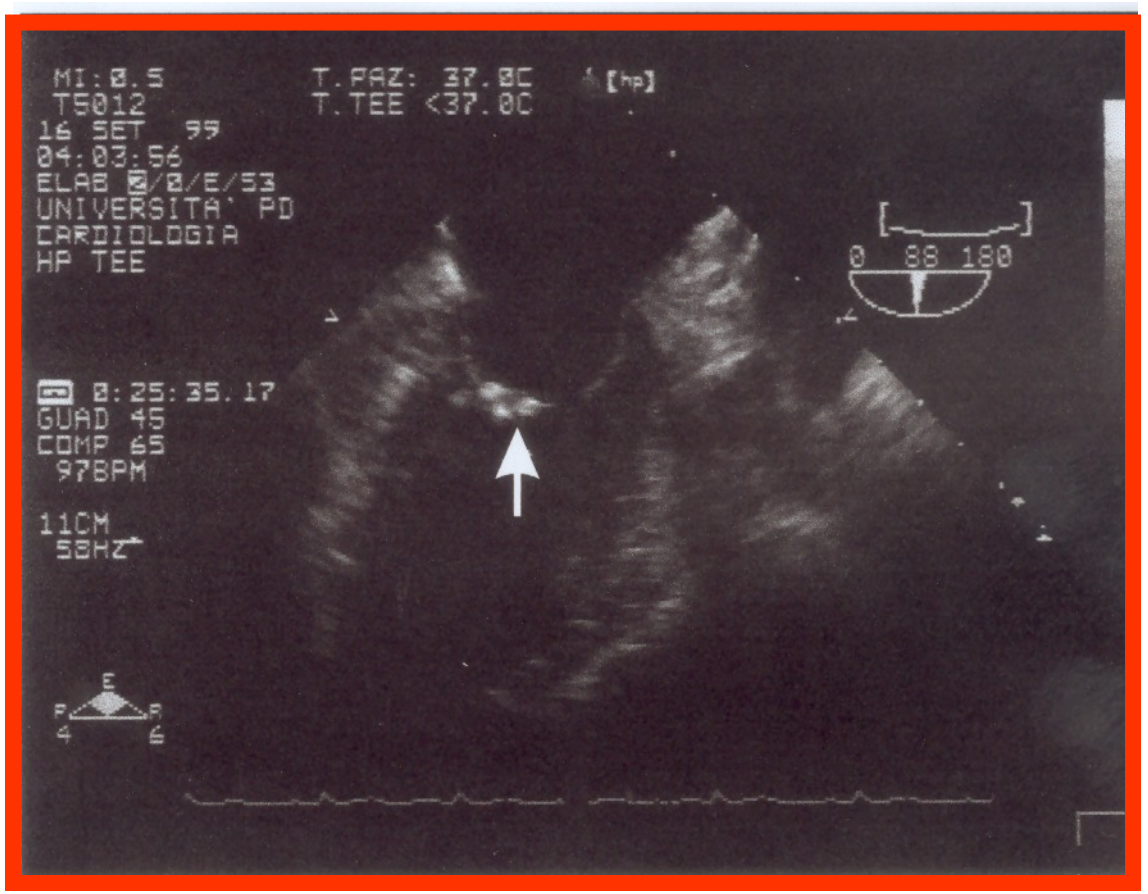
APS treatment in pts with ATE

- VKA treatment in VTE (reasonable if embolic source)
- Intensity (INR 2.0-3.0): two randomized trial
- Intensity INR>3 in one retrospective study Khamashta MA, NEJM 1995
- Antiplatelet agents on top of anticoagulation (reasonable in case of atherothrombosis, thrombosis in situ, ATE recurrence): ASA 100mg/die

Minor stroke and multiple mitral valve thickening in 20 year of age young women

NONBACTERIAL THROMBOTIC ENDOCARDITIS (LIBMAN-SACKS ENDOCARDITIS)

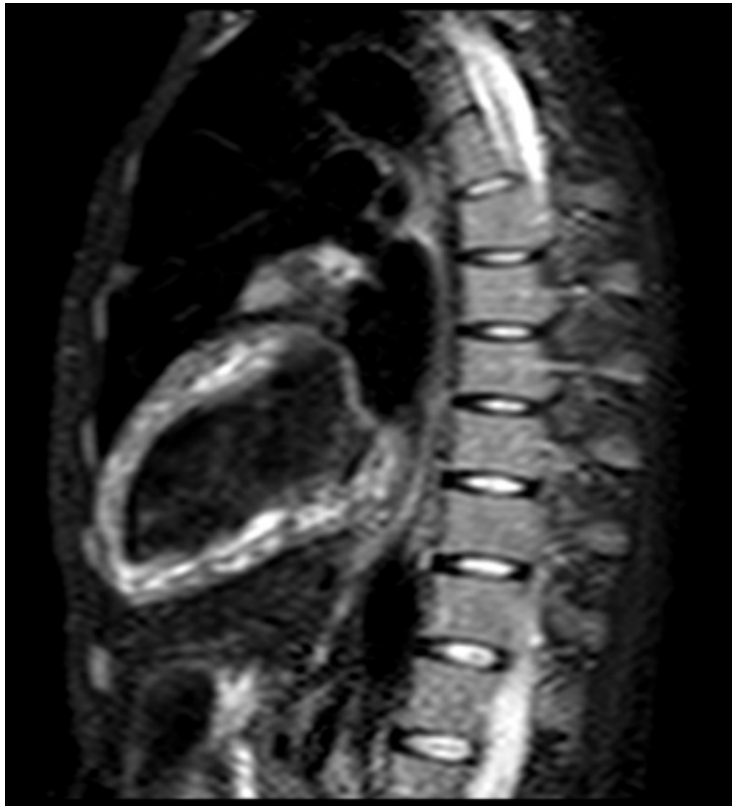
VKA reasonable



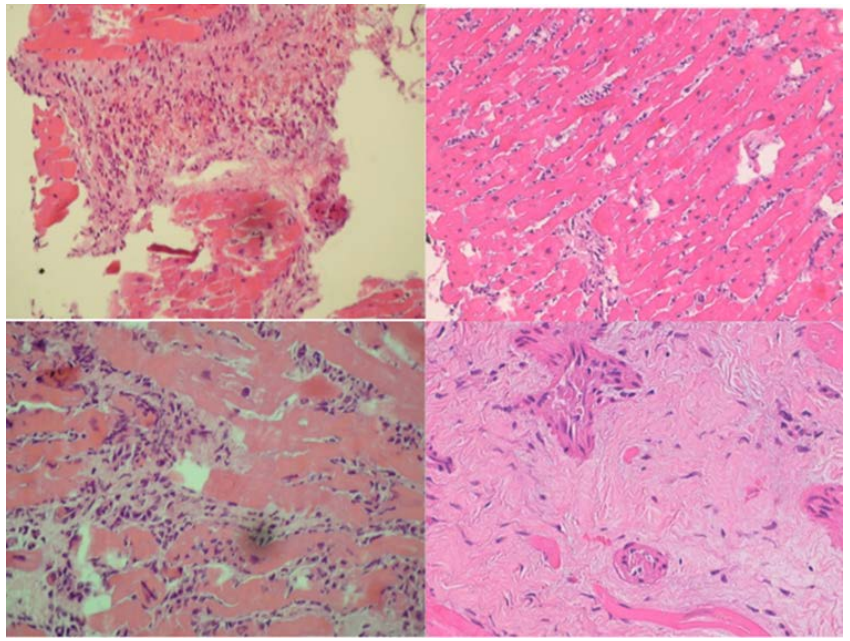
Clinical Cardiology, Padua

Cardiac RNM and endocardial biopsy

VKA + ASA reasonable



Diffuse endocardial late gadolinum enhancement (LGE) compatible with myocardial damage from microvascular injury and no-reflow.



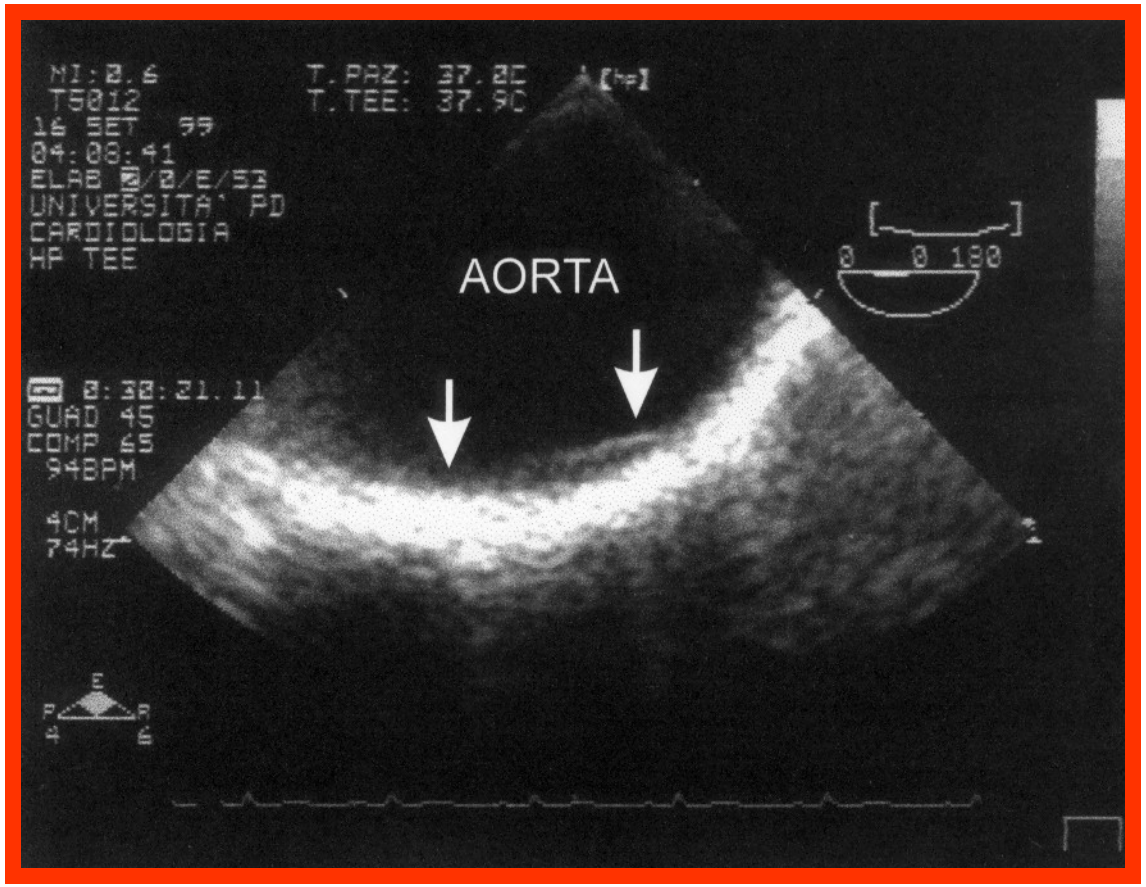
Panels in the left show reparative fibrosis likely due to ischaemic damage. Right side panels, show extensive thrombosis and microvascular thrombosis.

Denas G, Pengo V et al. Autoimm Rev 2014

Minor stroke and multiple mitral valve thickening in 20 year of age young women

VKA + ASA
reasonable

AORTIC ARCH SOFT PLAQUE



Clinical Cardiology, Padua

Obstetric APS

- ASA for prevention of CAPS, HELLP syndrome, Eclampsia
- LMWH inhibits complement activation (Girardi), favors implantation, binds beta2GPI
- Hydrossichloroquine: effects on hemostasis, complement, inflamation, reduced soluble TF levels

- *Upgrade of treatment in special cases:*
- Plasmapheresis
- Immunoglobulin

TREATMENT OF PREGNANT PATIENTS WITH APS

Favourable outcome

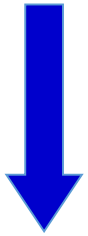
Kutteh et al, 1996
UH + LDA *vs* LDA 80% *vs* 40%
(significant difference)

Rai et al, 1997
UH + LDA *vs* LDA 71% *vs* 42%
(significant difference)

Farquharson et al, 2002
LMWH + LDA *vs* LDA 78% *vs* 72%
(no significant difference)

PATIENTS WITH PREVIOUS PREGNANCY MORBIDITY ALONE

PROPHYLAXIS OF PREGNANCY LOSS



ONE DAILY DOSE OF HEPARIN

+

LOW DOSE ASPIRIN

TREATMENT OF PREGNANT PATIENTS WITH APS

PATIENTS WITH PREVIOUS VASCULAR THROMBOSIS ALONE OR ASSOCIATED TO PREVIOUS PREGNANCY MORBIDITY

THROMBOSIS PROPHYLAXIS

+

PROPHYLAXIS OF PREGNANCY LOSS

FULL DOSE HEPARIN

±

LOW DOSE ASPIRIN

- **No clinical trials**
- **There is agreement on full anticoagulation with UH or LMWH**
- **LDA is generally combined**

- **Tincani et al. Lupus. 2003;12: 524-9.**
- **Ruitz-Irastorza et al. Ann NY Acad Sci. 2005; 1051: 606-12.**

CAPS conditional recommendation, very low certainty of evidence

For treatment of patients with CAPS, the CAPS guideline panel suggests:

Combination therapy with glucocorticoid, unfractionated heparin, and plasma exchange or IVIG over single agents or other combinations of therapies.

Legault K, Pengo V et al.McMasterRARE-Bestpractices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome. J Thromb Haemost. 2018

Why DOACs might be an option in thrombotic APS?

- DOACS are at least as effective and safe as warfarin in preventing venous and arterial thromboembolism and significantly reduces cerebral bleeding.

- DOACS do not need laboratory monitoring thus being very much appreciated by the young population of patients with thrombotic APS.

What are the evidence for DOACS use in thrombotic APS?

- No clear evidence of efficacy and safety
- Results of a single randomized trial testing a surrogate end-point with secondary encouraging secondary clinical end points (RAPS)
- Results from Case Reports and Case Series are conflicting

A prospective, randomized clinical trial comparing rivaroxaban vs warfarin in high risk patients with antiphospholipid syndrome (TRAPS)

Objective:

In persistently triple aPL-positive APS patients with or without other systemic autoimmune diseases, to determine the efficacy and safety of rivaroxaban 20 mg qd as compared to warfarin (INR 2.0-3.0) in thrombosis prevention of **persistently triple aPL-positive APS patients**.

Type of study:

Non inferiority trial

End point:

Cumulative: Thromboembolism, bleeding, total mortality.

Sample size:

536 subjects (268 in the reference group and 268 in the treatment group)

Starts: 2015 **Ends:** 2020

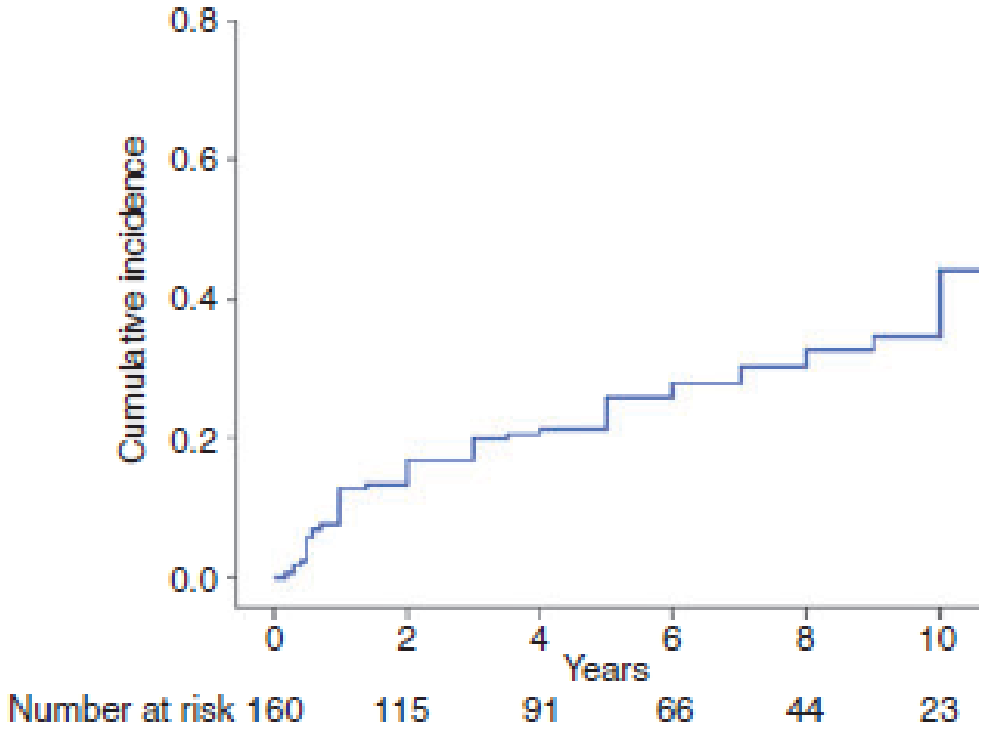
Antiphospholipid profiles as risk factors for thrombosis

Lupus anticoagulant/ Anti-cardiolipin antibodies/ Anti-β2-glycoprotein I antibodies	Thrombosis (N=340) no.(%)	No thrombosis (N=278) no.(%)	Odds Ratio			
			univariate	95% CI	Multivariate°	95% CI
LA+/aCL+/ab2+	**34 (10)**	**2 (1)**	**14.9**	**3.5-62.7**	**33.3**	**7.0-157.6**
LA+/aCL-/ab2-	0 (0)	5 (2)	NA	-	NA	-
LA-/aCL+/ab2+	18 (5)	13 (5)	1.2	0.6-2.5	2.2	1.0-5.2
LA-/aCL+*/ab2-	7 (2)	13 (5)	0.5	0.2-1.2	0.8	0.3-2.1
LA-/aCL-/ab2+	4 (1)	4 (1)	0.9	0.2-3.5	1.3	0.3-5.7

* > 40 GPL/MPL

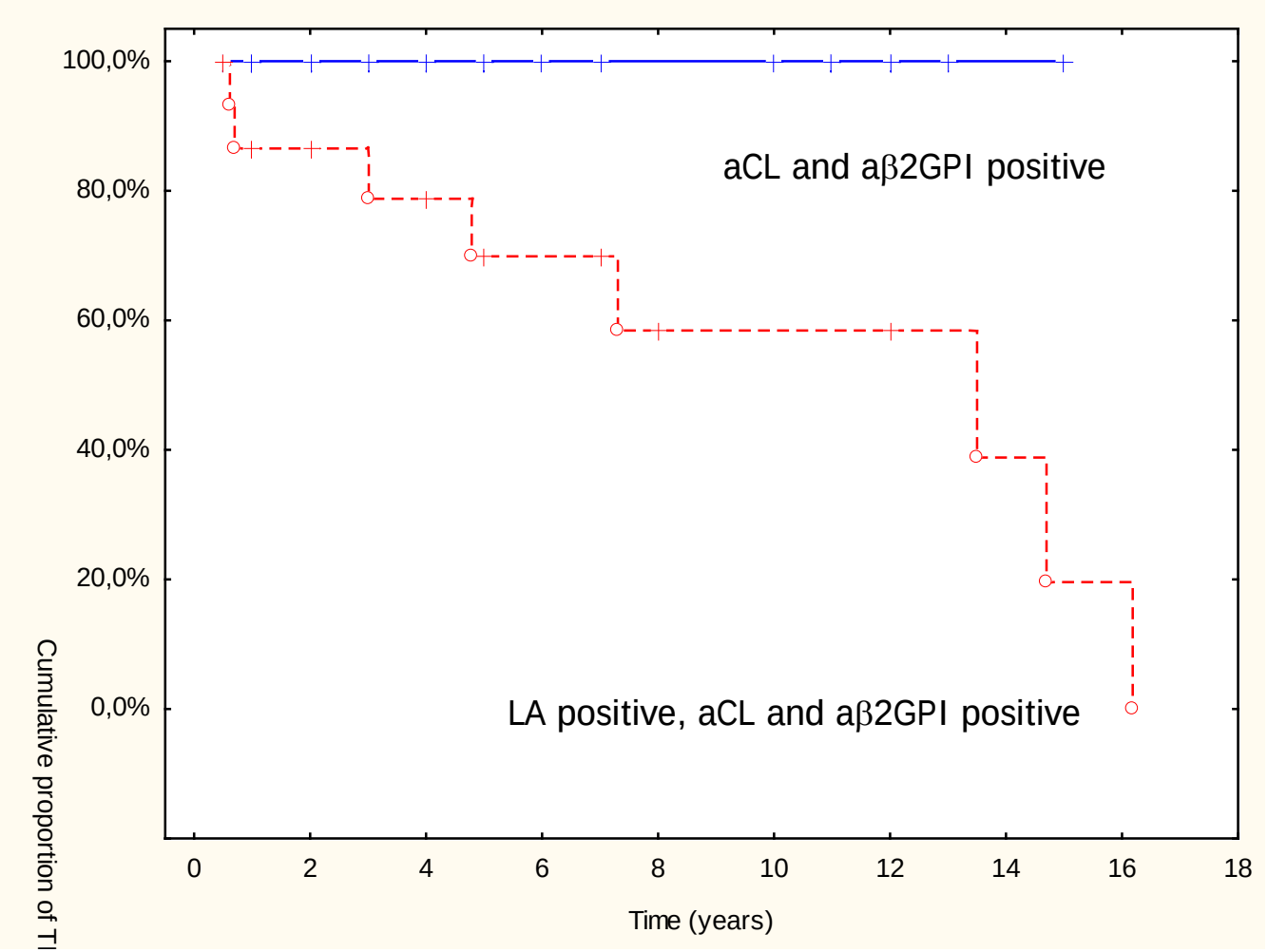
V Pengo et al, 2005

Cumulative incidence of thromboembolic events in high risk triple positive APS patients (n=160)



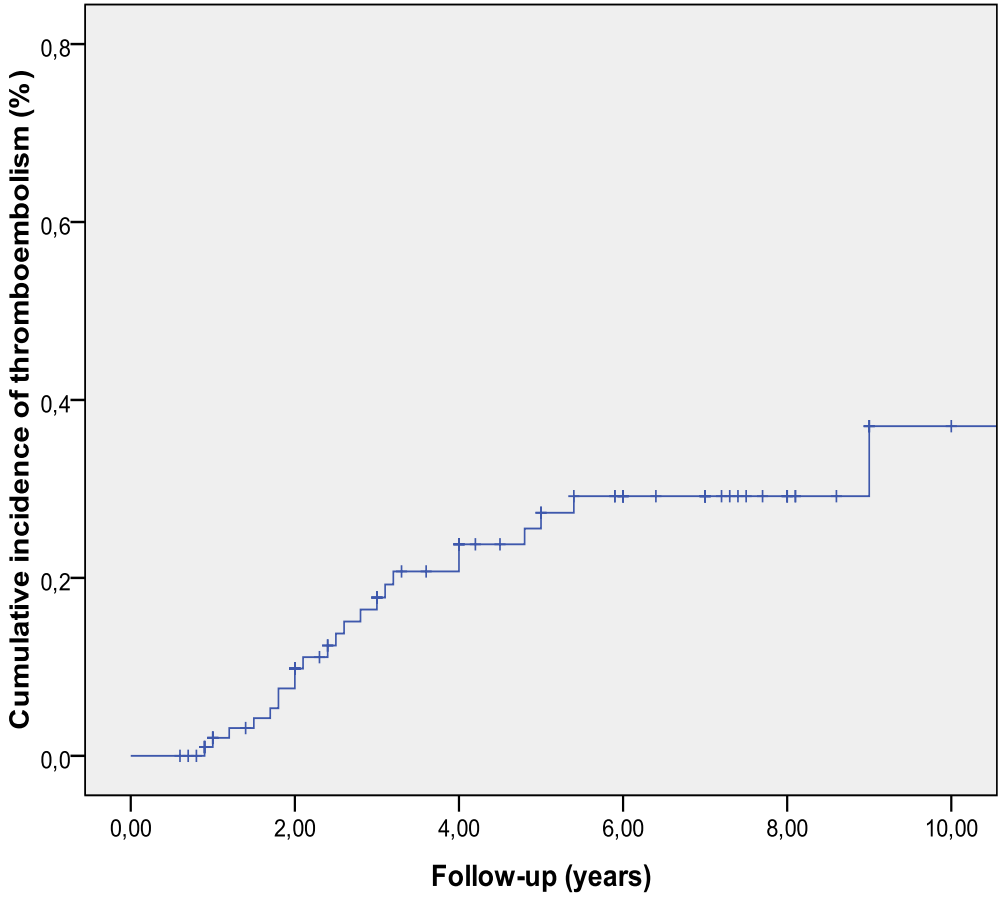
Pengo V, JTH 2010

Antiphospholipid profile and subsequent TE in obstetric APS



Ruffatti A, Pengo V et al. 2006

Cumulative incidence of thromboembolic events in the follow up period of 104 carriers of triple positivity for antiphospholipid antibody tests.



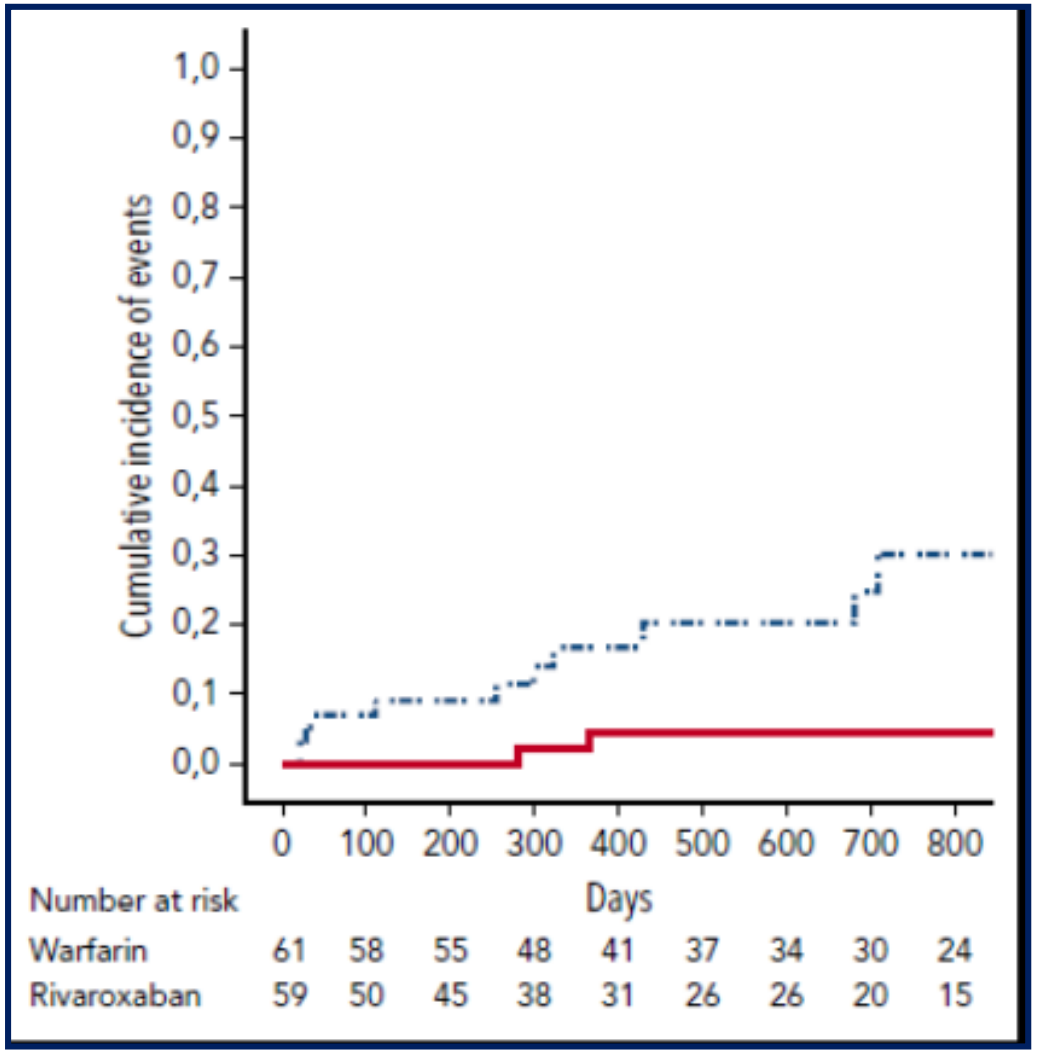
Pengo V, Blood 2011

TRAPS Trial

RESULTS

Characteristic	Rivaroxaban (n = 59)	Warfarin (n = 61)
Females, n (%)	39 (66)	38 (62)
Age, y	46.5 ± 10.2*	46.1 ± 13.2*
Body mass index, kg/m²	26.1 ± 6.1*	25.5 ± 5.9*
CrCl, mL/min	117.0 ± 38.6*	109.3 ± 36.7*
Hemoglobin, g/L	131.7 ± 17.6*	135.9 ± 17.1*
Platelet count, ×10⁹/L	214.9 ± 73.8*	209.3 ± 63.5*
APS laboratory test positivity, n		
LA: dRVVT/aPTT/both	16/5/38	14/7/40
aCL: IgG or IgG + IgM/IgM only	57/2	52/9
aβ2GPI: IgG or IgG + IgM/IgM only	57/2	52/9
Autoimmune disease, n (%)	24 (41)	25 (41)
Systemic lupus erythematosus	10	15
Other autoimmune disease	14	10
Previous thrombotic events, n (%)		
Arterial events	11 (19)	14 (23)
Stroke	8	8
Acute myocardial infarction	0	2
Other sites	3	4
Venous events	38 (64)	39 (64)
Deep vein thrombosis and/or pulmonary embolism	36	32
Other sites	2	7
Venous and arterial events	10 (17)	8 (13)
Pregnancy morbidity, n (%)†	16 (41)	12 (32)

Cumulative incidence of events



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	—	—

Why rivaroxaban does not work?

Possible explanations

- Poor adherence (but based on pill count in TRAPS adherence was excellent)

- Insufficient drug concentration
  - ✓ High rate of elimination by kidney (young patients with high creatinine clearance)
  - ✓ Prevention of arterial events in animals requires much higher dose compared to venous thrombosis
  - ✓ High interindividual variability

- Different mechanism of action with respect to warfarin.
  - ✓ Difference in thrombin generation
  - ✓ Warfarin reduces functional coagulation factors in the extrinsic and intrinsic pathways of coagulation
  - ✓ The importance of the intrinsic pathway in thrombin generation is highlighted by the ability of warfarin to better attenuate thrombin generation with prosthetic material