ICT 2023

28th International Congress on Thrombosis

Antiphospholipid Syndrome

Vittorio Pengo

20'

Declaration of Conflict Of Interest

□ **I have no potential conflict of interest to report**

□ **I have the following potential conflict(s) of interest to report**

Lecture fees, Werfen group, Milan, Italy

Antiphospholipid Syndrome: classification criteria

One clinical criteria (arterial or venous thrombosis or pregnancy loss)

+

One laboratory criteria: Lupus Anticoagulant, IgG/IgM anticardiolipin antibodies, AND IgG/IgM anti β2-GPI antibodies.
[Positive 12 week apart]

APS, antiphospholipid syndrome; β2-GPI, β2-glycoprotein I

The need to express results as aPL profiles

	Lupus Anticoagulant	Anti-cardiolipin ab	Anti β2-Glycoprotein I ab
Triple positive*	Positive	Positive	Positive
Double positive*	Negative	Positive	Positive
Single positive	Positive	Negative	Negative
Single positive	Negative	Positive	Negative
Single positive	Negative	Negative	Positive

*same isotype (IgG or IgM)

Antiphospholipid antibody profiles as risk factors of 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

MASSIVE POLMONARY EMBOLISM

MC/ Male

18 yrs of age

Unprovoked

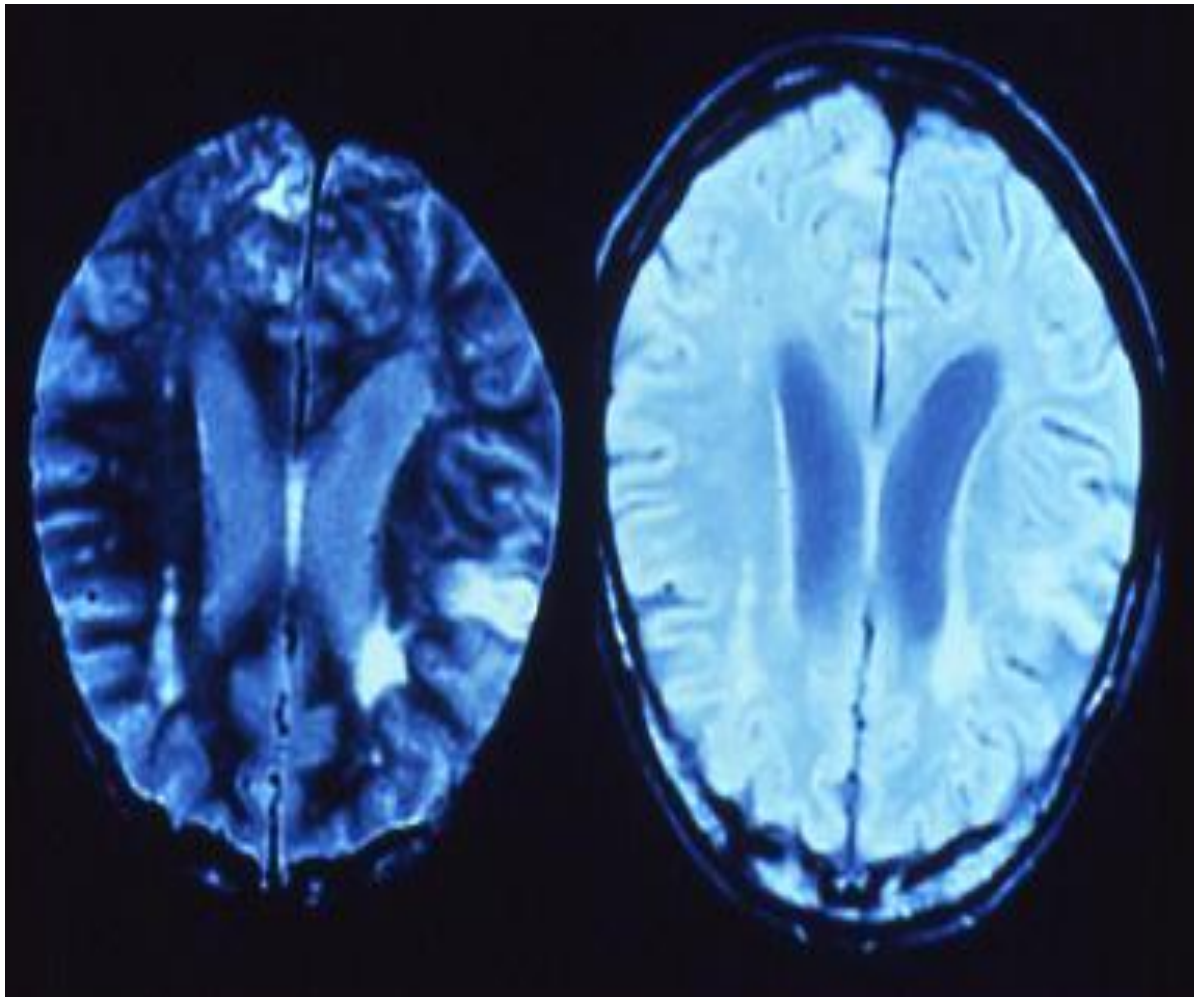
Proximal DVT/PE

TRIPLE POSITIVE

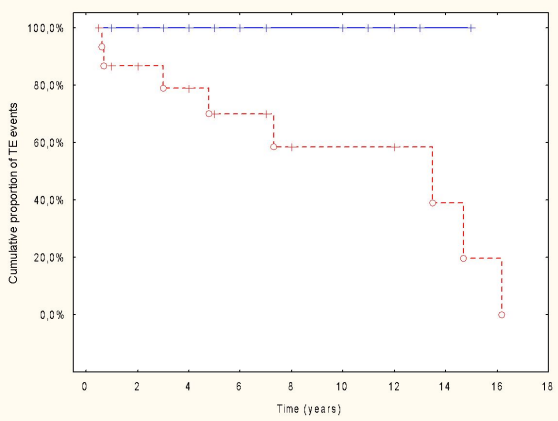
Multiple cerebral infarctions in 48 years old female

(N. C.) with hemiparesis and epilepsy

TRIPLE POSITIVE

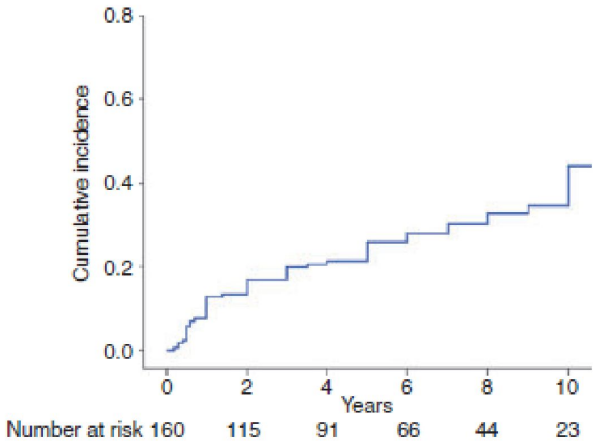


Courtesy of Clinical Reumatology, Padua



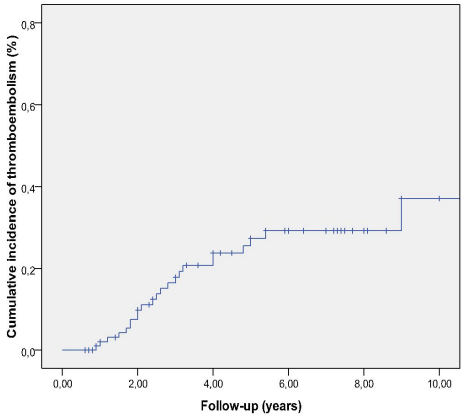
Ruffatti A, Pengo V et al. 2006

16 triple positive obstetric APS



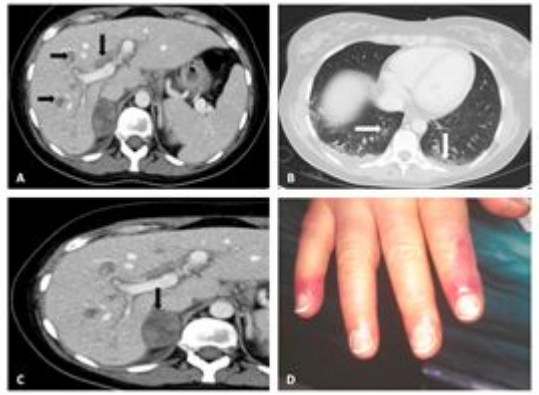
Pengo V, JTH 2010

160 triple positive thrombotic APS patients



Pengo V, Blood 2011

104 carriers of triple positivity



14 patients with **Cathastrophic APS**
All of them **TRIPLE POSITIVE**
Ruffatti A, Pengo V J Autoimm 2018

CTEPH
17 of 23 (74%) aPL positive patients had a triple IgG positive profile (LA+, aCL+, aB2GPI+).
Thromb Haemost 2019

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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] Paolo Gresele,[5] Arturo Cafolla,[6] Valeria De Micheli,[7] Angelo Ghirarduzzi,[8] Alberto Tosetto,[9] Anna Falanga,[10] Ida Martinelli,[11] Sophie Testa,[12] Doris Barcellona,[13] Maria Gerosa,[14] and Alessandra Banzato[1]

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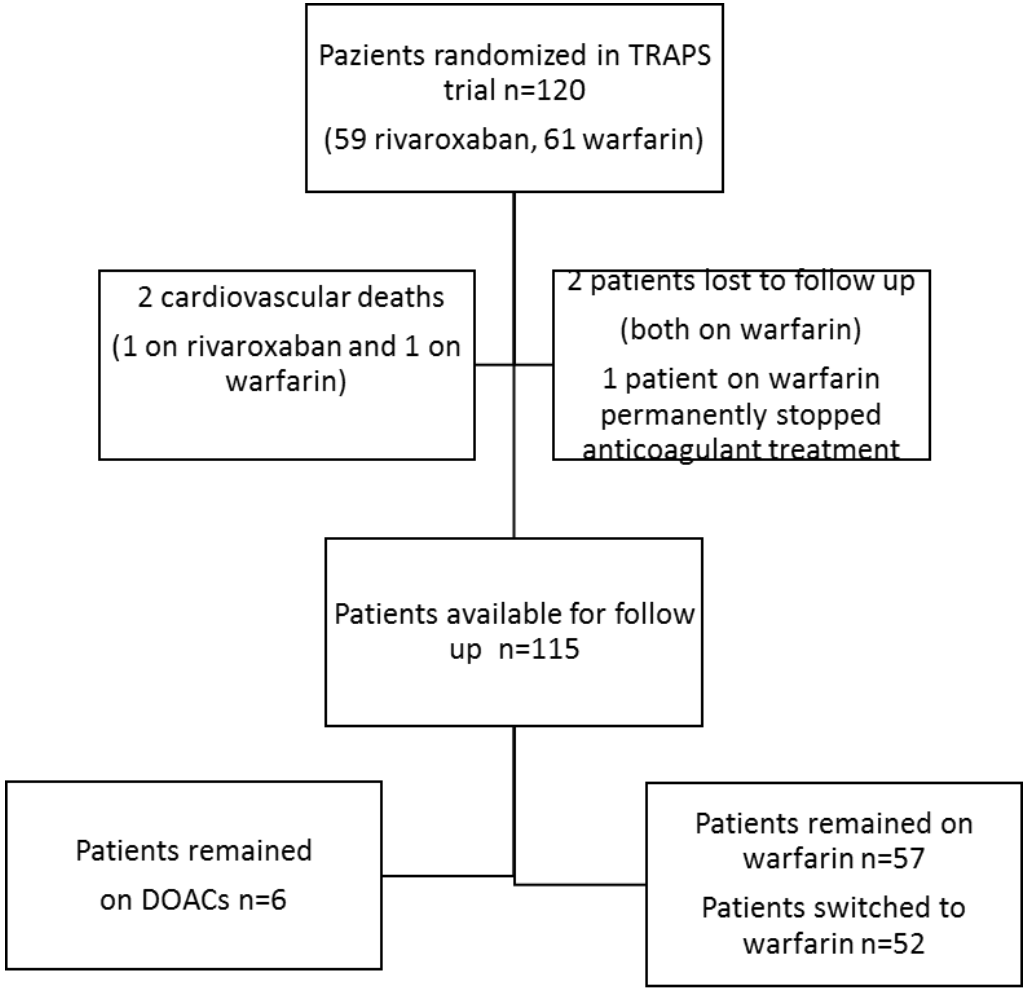
Pengo et al. Blood. 2018;132(13):1365-1371

TRAPS-Results

Stopped early after 120 patients randomized due to excess arterial thromboembolic events in rivaroxaban arm

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	7 (12)	0	—	—	7 (12)	0	—	—
Ischemic stroke	4 (7)	0			4 (7)	0		
Myocardial infarction	3 (5)	0			3 (5)	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	—	—

Trial of Rivaroxaban in AntiPhospholipid Syndrome (TRAPS): Two-year outcomes after the study closure



Pengo V et al., JTH 2020

Trial of Rivaroxaban in AntiPhospholipid Syndrome (TRAPS): Two-year outcomes after the study closure

Eight events (thrombosis, major bleeding, vascular death) were reported during the two-year follow-up period

Two thrombotic events (1DVT on dabigatran 150mg bid and 1 ischemic stroke on rivaroxaban 20mg qd) occurred in the 6 patients who remained on DOACs (33.3%) and 6 (3 thrombotic, 2 hemorrhagic an 1 vascular death) occurred in the 109 patients on warfarin (5.5%).

On Cox regression, the risk of cumulative events was significantly higher in the DOACs group (HR 6.9; 95%CI 1.4-34.5, p=0.018).

Pengo V et al. JTH. 2020

Annals of Internal Medicine

ORIGINAL RESEARCH

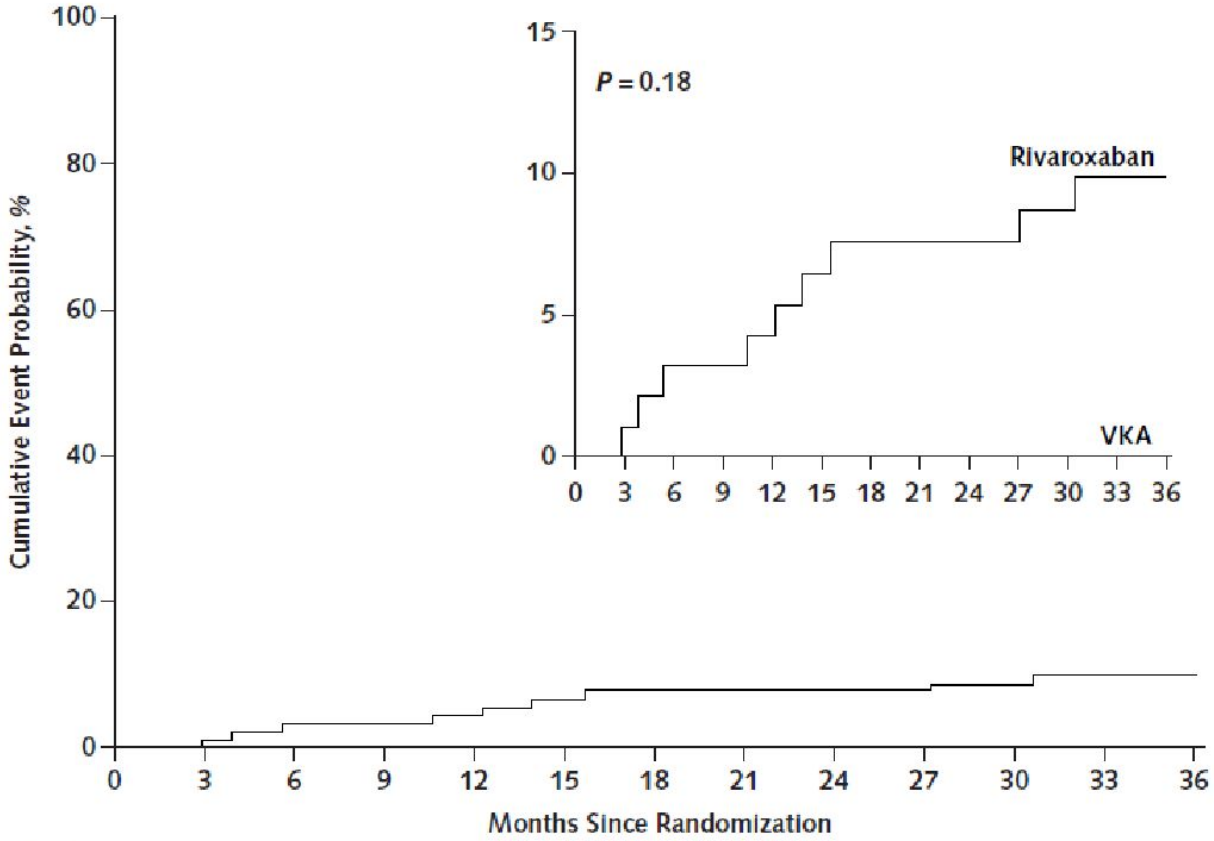
Rivaroxaban Versus Vitamin K Antagonist in Antiphospholipid Syndrome

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, MD, PhD; Jordi Cuquet-Pedragosa, MD; Vera Ortiz-Santamaria, MD; Montserrat Mauri-Plana, MD, PhD; Cristina Solé, PhD; and Josefina Cortés-Hernández, MD, PhD

This article was published at Annals.org on 15 October 2019.

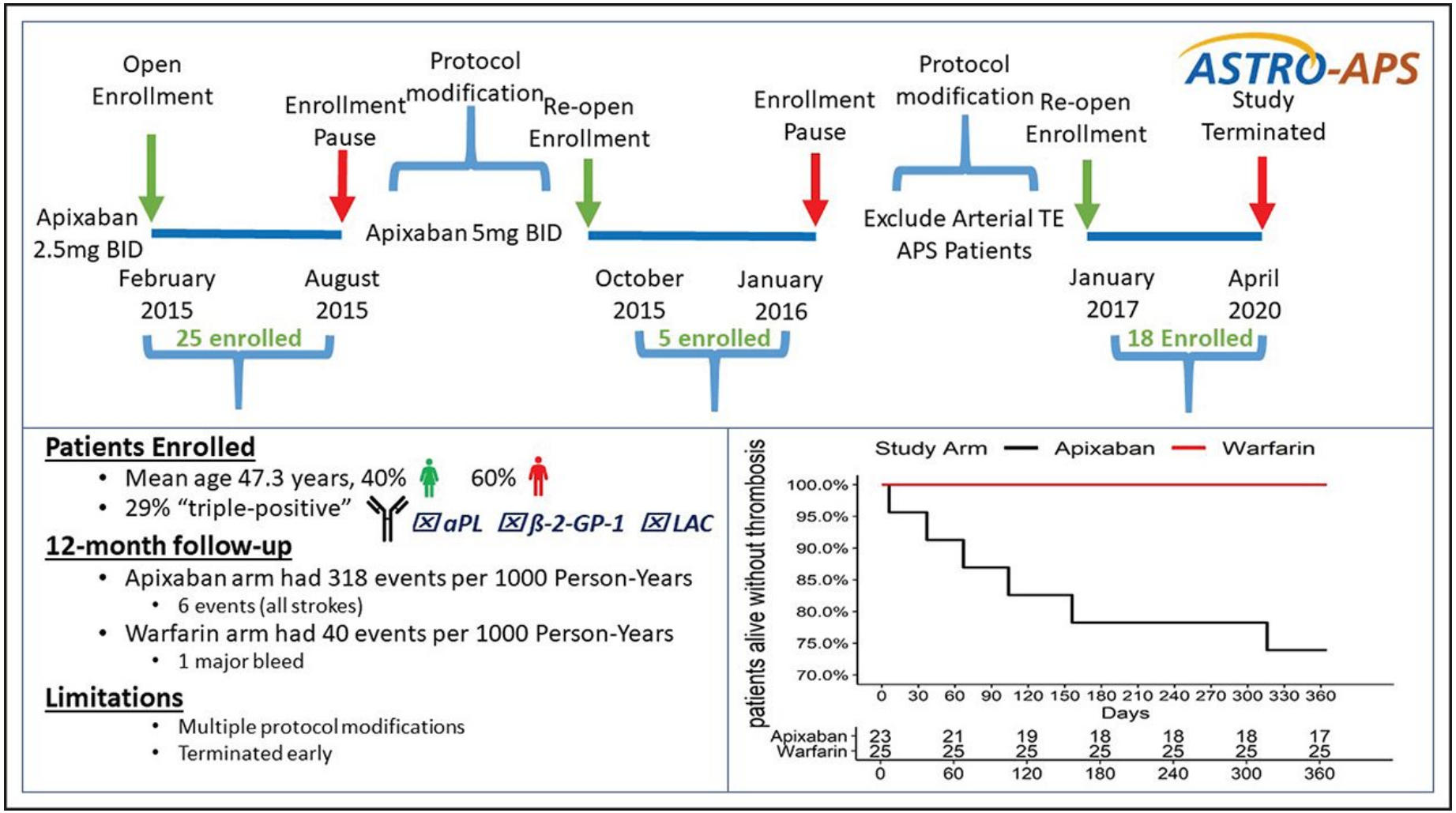
Time to Stroke Event in the Per Protocol Population



Patients at risk, *n*													
Rivaroxaban	95	92	88	88	87	84	81	80	80	80	79	78	78
VKA	95	95	94	94	93	90	89	88	86	83	82	81	81

9/0

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



syndrome: a randomized trial, Blood Adv, 2022,

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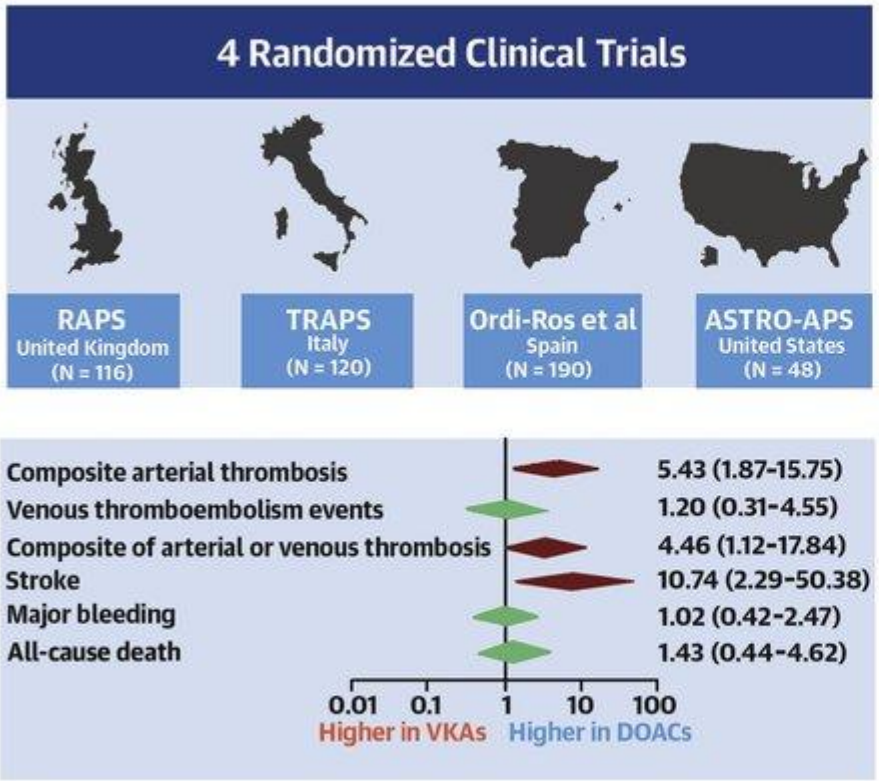
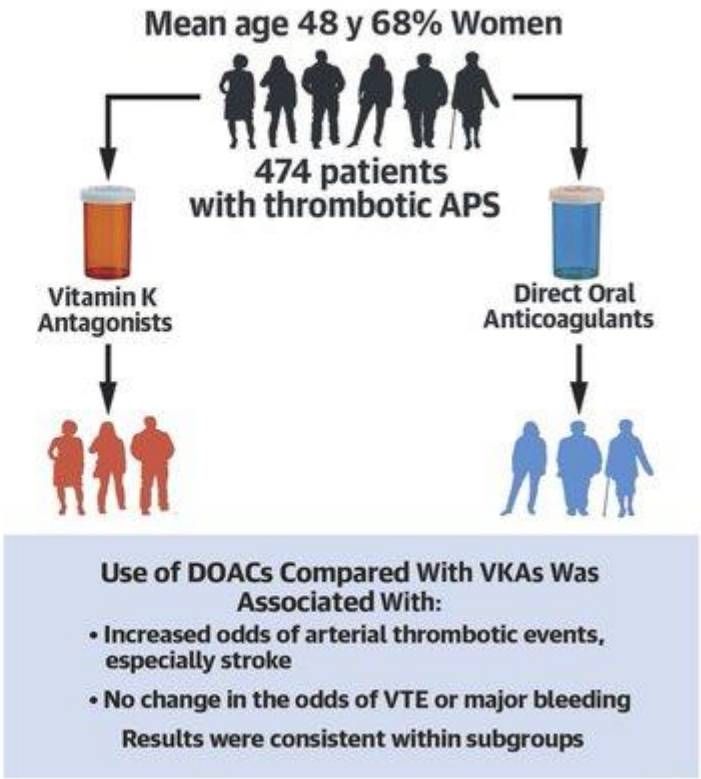
CENTRAL ILLUSTRATION: Use of Direct Oral Anticoagulants vs Vitamin K Antagonists in Thrombotic Antiphospholipid Syndrome

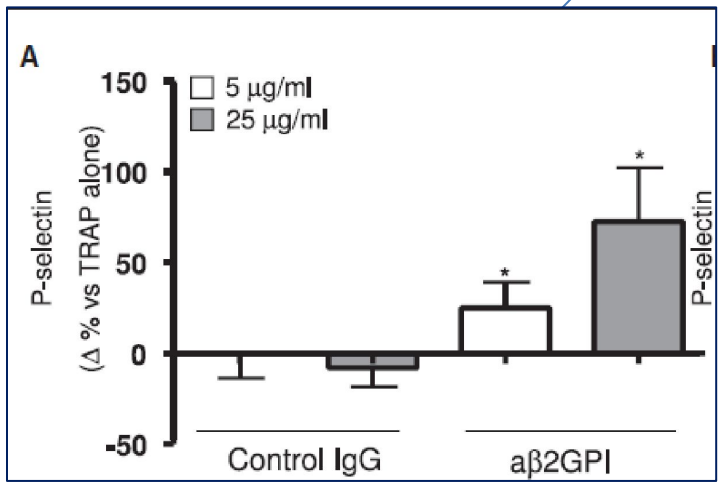




Khairani CD, et al. J Am Coll Cardiol. 2023;81(1):16-30.

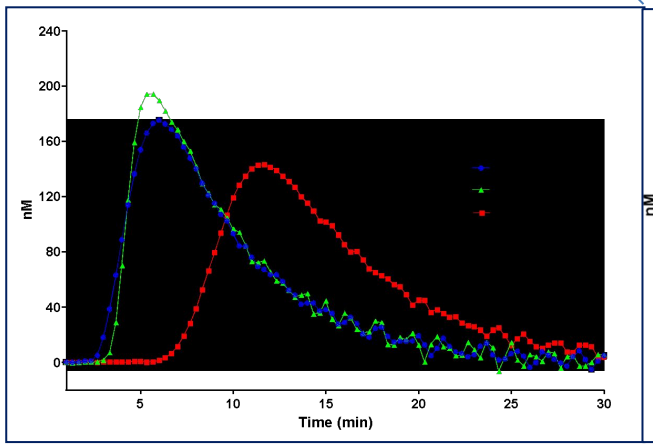
High-risk tetra-positive APS patients
LA+ aCL +aβ2GPI + aPS/PT+

Platelet activation
↑ P-selectin

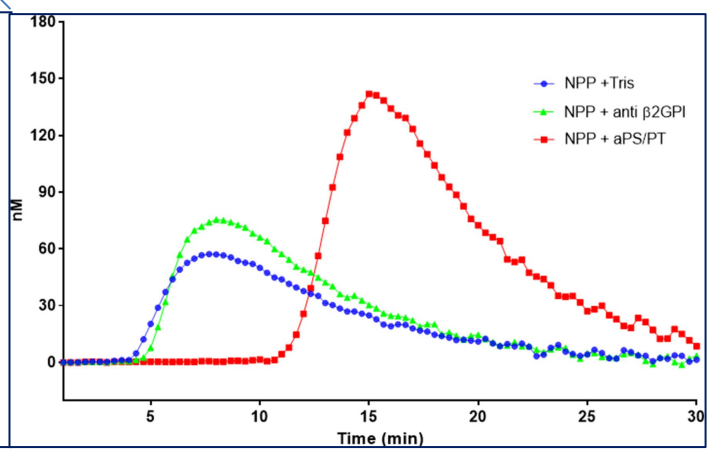


aβ2GPI

LAC



aPC-Resistance



aPS/PT

Pontara E, Cattini MG, Cheng C, Bison E, Denas G, Pengo V. J Thromb Haemost. 2021;19(3):805-813.
Cheng C, Bison E, Pontara E, Cattini MG, Tonello M, Denas G, Pengo V. Lupus. 2022 Oct;31(11):1328-1334.

Warfarin resurgence (DOACs contraindicated)

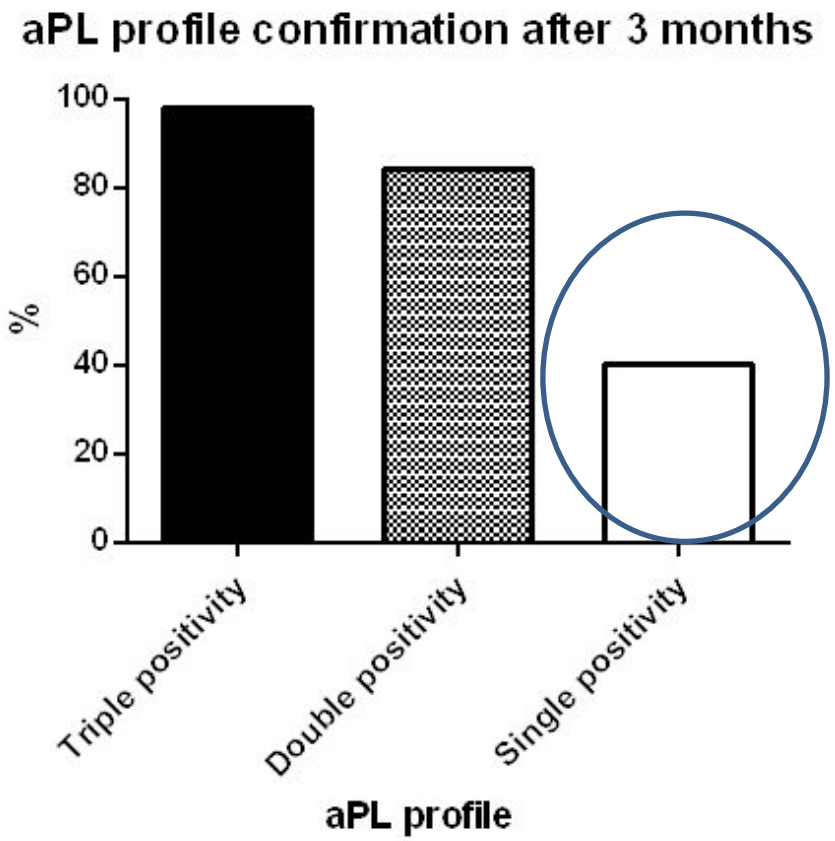
- Prosthetic Mechanical Heart Valves (RE-ALIGN study)[1]
- Antiphospholipid syndrome (TRAPS study triple positivity)[2]
- Rheumatic Heart Disease-Associated Atrial Fibrillation (INVICTUS Investigators)[3]

1. Eikelboom JW et al. NEJM 2013; 369:1206-1214.
2. Pengo V et al. Blood 2018 Sep 27;132(13):1365-1371.
3. Connolly J et al. NEJM 2022 Aug 28. Online ahead of print.

The need to express results as aPL profiles

	Lupus Anticoagulant	Anti-cardiolipin ab	Anti β2-Glycoprotein I ab
Triple positive*	Positive	Positive	Positive
Double positive*	Negative	Positive	Positive
Single positive	Positive	Negative	Negative
Single positive	Negative	Positive	Negative
Single positive	Negative	Negative	Positive

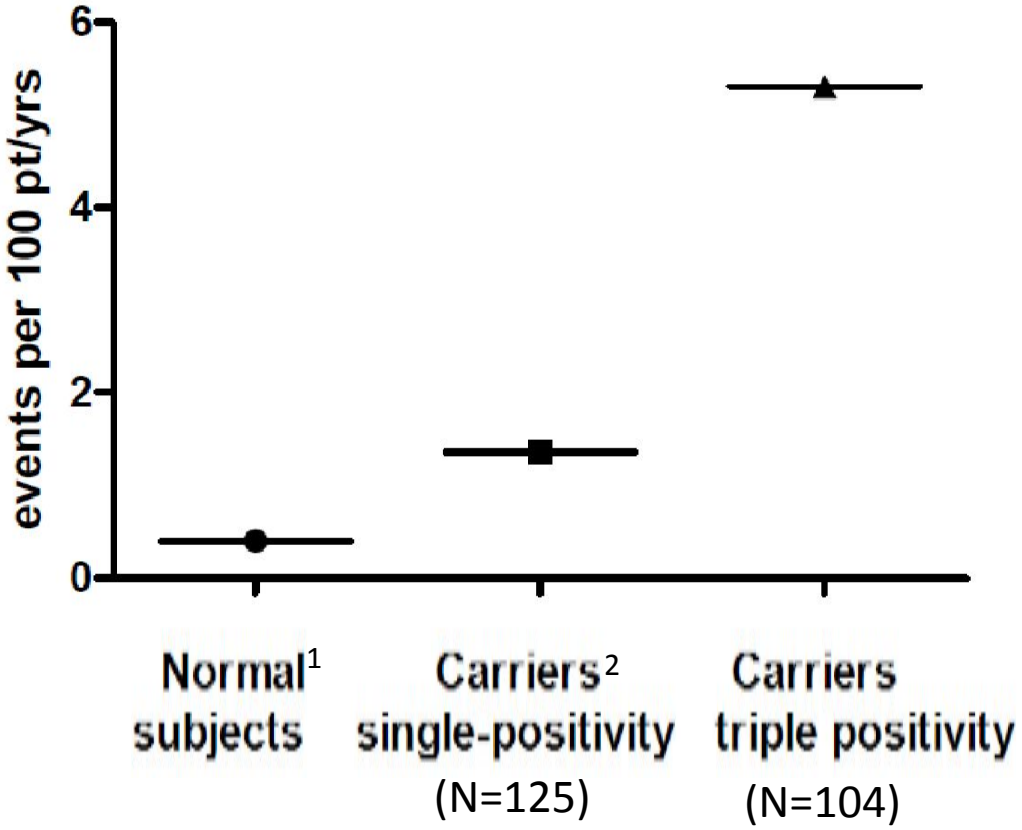
*same isotype (IgG or IgM)



Pengo V et al. JTH 2013

Average annual rates of first cardiovascular events (including VTE)

Data from a multi-centre prospective study of 104 patients with high-risk antiphospholipid profile (triple positive), followed up for a mean of 4.5 years.



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[1]Roger et al. Circulation. 2011 Feb 1;123(4):e18-e209.
[2]Ruffatti A et al. Ann Rheum Dis 2011;70(6):1083-6.
[3]Pengo et al. Blood 2011;118(17):4714-4718

Uncertainties

Type of antithrombotic treatment and duration

Single positive aCL and thrombosis
Single positive aβ2GPI and thrombosis
Double positive (aCL and aβ2GPI) and thrombosis
Isolated LAC and thrombosis
Carriers of triple (tetra positivity) positivity
Triple positive patients testing negative thereafter (idrossicloroquine)
Triple positive patients with provoked VTE

SHARED DECISION MAKING WITH PATIENTS

Conclusions

We should not use DOACs in triple positive APS patients

As Triple positive are often (always) tetra-positive (anti phosphatidyl-serine/prothrombin antibodies), reduction of prothrombin by VKA may be crucial for the reduction of thrombus formation.

Whether this statement might be extrapolated to patients with single or double aPL positivity is not known. An exception could be single positive LAC where aPS/PT are often present.

Special thanks to my collaborators

University of Padua
Established in 1222

Gentian Denas
Elisa Bison
Elena Pontara
Maria Grazia Cattini
Chunyan Chen
Seena Padayattil Jose
Giacomo Zoppellaro
Alessandra Banzato

Anatomical Theatre of Padua

Aula Magna (Great Hall)

How to solve uncertainties

Clinical trials are difficult to carry out due to the fact that rare diseases are involved.

Registers might be helpful

START 2 Register PHOSPHOLIPID: To participate in the registry please contact:
e.antonucci@fondazionearianna.org or
vittorio.pengo@unipd.it

Conflict of interest declaration

Advisory board: Daiichi-Sankyo, Bayer HealthCare

Lecture fees: Werfen Group, Daiichi-Sankyo, Bayer HeathCare, Pfizer/BMS.