L'art est facile mais la critique est difficile

SAPL

Pr. Thierry MARTIN
Clinical Immunology
National Reference Center for Rare Systemic Autoimmune Diseases
INSERM U 1109
Strasbourg University Hospital

WINTER SCHOOL RESO 2021

Disclosures

- Consultant/advisor: GlaxoSmithKline, Amgen, Abbvie, Boehringer Ingelheim, Roche-Chugaï

- Grant/research support: CSL Behring, GlaxoSmithKline, Janssen, LFB, Astra Zeneca

Est il légitime/justifié de critiquer les recommandations internationales ?

BLOING!
BLOING!

Recommendation

EULAR recommendations for the management of antiphospholipid syndrome in adults

Maria G Tektonidou,[1] Laura Andreoli,[2] Marteen Limper,[3] Zahir Amoura,[4] Ricard Cervera,[5] Nathalie Costedoat-Chalumeau,[6] Maria Jose Cuadrado,[7] Thomas Dörner,[8] Raquel Ferrer-Oliveras,[9] Karen Hambly,[10] Munther A Khamashta,[11] Judith King,[12] Francesca Marchiori,[13] Pier Luigi Meroni,[14] Marta Mosca,[15] Vittorio Pengo,[16] Luigi Raio,[17] Guillermo Ruiz-Irastorza,[18] Yehuda Shoenfeld,[19] Ljudmila Stojanovich,[20] Elisabet Svenungsson,[21] Denis Wahl,[22] Angela Tincani,[2] Michael M Ward[23]

ARD
RMDOpen

Paper

16th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends

Lupus
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SAGE

Hannah Cohen[1,2], Maria J Cuadrado[3], Doruk Erkan[4], Ali Duarte-Garcia[5,6], David A Isenberg[2,7], Jason S Knight[8], Thomas L Ortel[9], Anisur Rahman[7], Jane E Salmon[10], Maria G Tektonidou[11], David J Williams[2,12], Rohan Willis[13], Scott C Woller[14] and Danieli Andrade[15]

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Diagnosis and Management of the Antiphospholipid Syndrome

David Garcia, M.D., and Doruk Erkan, M.D.

Les Hôpitaux Universitaires de STRASBOURG
RESO

Clinical practice in APS is highly variable, in part because it is a rare disorder, and because knowledge about its diagnosis/classification, clinical spectrum and management is continuously advancing.

There is a great heterogeneity among studies on the laboratory and clinical criteria used to define APS and the treatment approaches used over the past four decades. These factors make it often difficult to know the best approach to apply in daily practice.

Tektonidou *et al ARD 2019*

Les Hôpitaux Universitaires de STRASBOURG

RESO

Diagnostic

Critères Sapporo 1998/révisés 2004

Thrombose veineuse ou artérielle

Accident obstétrical

Présence d'aPL à > 12 semaines d'intervalle

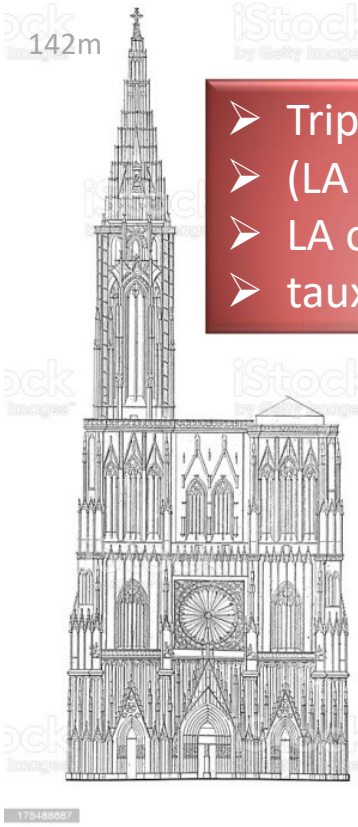
- **Anticorps anti-cardiolipine IgG ou IgM**: > 40 GPL (pour les IgG) ou MPL (pour les IgM) ou > 99e percentile (par ELISA standardisé).
- **Anticorps anti-β2GP1 IgG ou IgM** (> 99e percentile) (par ELISA standardisé).

Wilson *Arthritis Rheum*, 1999 / Miyakis, *J Thrombo Haemost* 2006

Critères de classification vs diagnostiques

	Sensibilité	Spécificité
Essais cliniques	+	+++
Diagnostic en pratique	+++	+

“A major risk factor is the high-risk aPL profile”



Stratification du risque: aPL profile

- Triple +
- (LA +aCl ou aβ2GP1)
- LA ou double +
- taux élevés persistants aPL

Tx moyen/élevé: **aCL f IgG and/or IgM isotype >40 IgG phospholipid (GPL) units or >40 IgM phospholipid (MPL) units, or >the 99th percentile, measured by a standardised ELISA. Antibeta2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma in titre >the 99th percentile, measured by a standardised ELISA**

- aCL ou a βGP1 tx faibles/modérés

Ruiz-Irastorza *et al*,Lupus 2011

Myakis *et al, J Thrombo Haemost 2006*

HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

Pathogenic antiphospholipid antibody: an antigen-selected needle in a haystack

Patricia Lieby, Vincent Poindron, Stamatiki Roussi, Cyril Klein, Anne-Marie Knapp, Jean-Claude Garaud, Martine Cerutti, Thierry Martin, and Jean-Louis Pasquali

Antiphospholipid antibodies represent a heterogeneous group of autoantibodies directed against anionic phospholipids (PLs) usually linked to protein cofactors. Their presence during the antiphospholipid syndrome is associated with risks of thrombosis and fetal losses. Among 5 randomly selected monoclonal antiphospholipid antibodies, all originating from a single patient suffering from this autoimmune disease, only 1 induced fetal losses when passively injected into pregnant mice. Its antiphospholipid activity was dependent on annexin A5, and its variable regions contained mainly 3 replacement mutations. To clarify the role of these mutations in the pathogenicity of the antibody, they were in vitro reverted to the germ line configuration. The resulting "germ line" antibody reacted with multiple self-antigens and only partially lost its reactivity against PLs, but it was no more dependent on annexin A5 and, more importantly, was no more pathogenic. This study illustrates that the in vivo antigen-driven maturation process of natural autoreactive B cells can be responsible for pathogenicity. (Blood. 2004;104:1711-1715)

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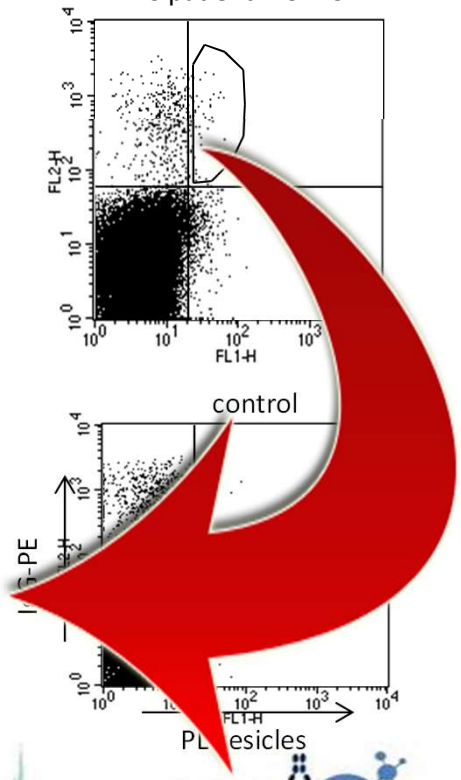
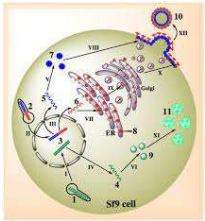
blood®

APS patient B CD19+

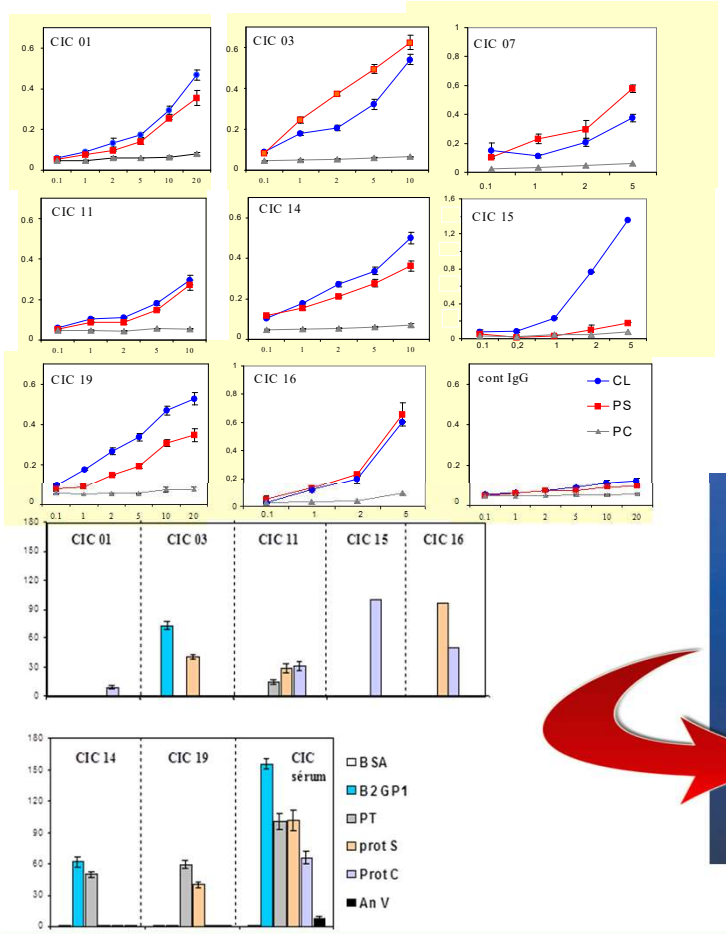


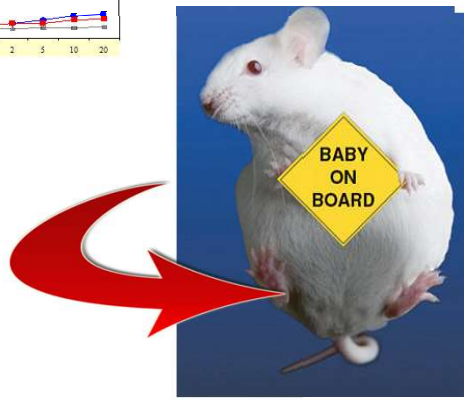


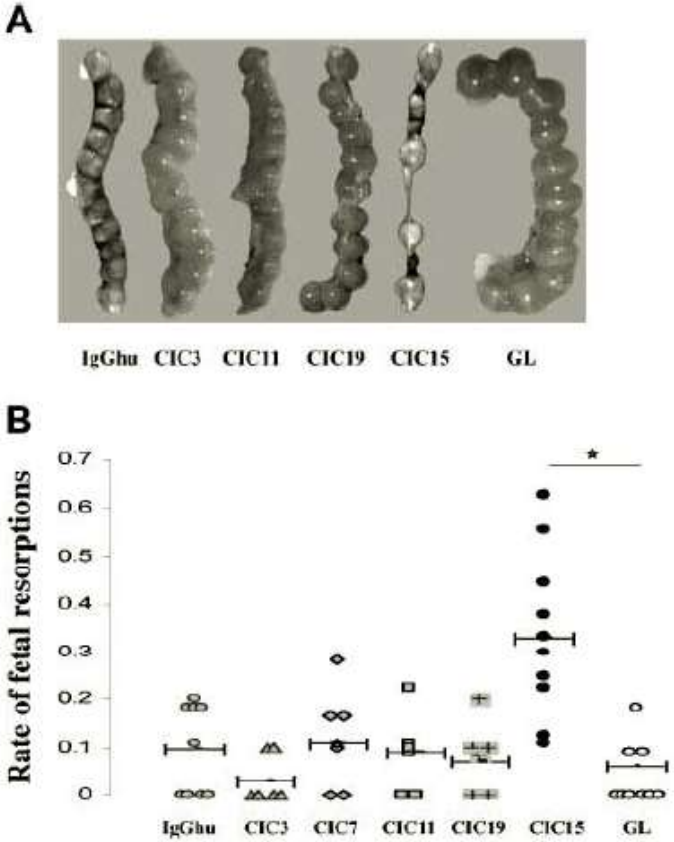
mAb

RT-PCR
VH-VL cloning

Single cell culture







Lieby *et al Blood 2004*

	controle	CIC 01	CIC 03	CIC 11	CIC 14	CIC 19	CIC 07	CIC 15	CIC 16
Test de coagulation DRVVT									
Temps (s)	43,5	60,1	45,85	45,25	45	45,1	47.7	49,1	47,2
Confirmation (s)	na	46,4	na	na	na	na	na	na	na
Rapport	-	1,29	-	-	-	-	-	-	-
Inhibition de la génération de thrombine									
mAc conc.									
1 µg/ml	0	0	12	0	14	5	nd	-	-
5 µg/ml	0	15	20	0	16	12		-	-
10 µg/ml	0	32	45	0	20	16		10	40
20 µg/ml	0	58	nd	nd	nd	18		85	70

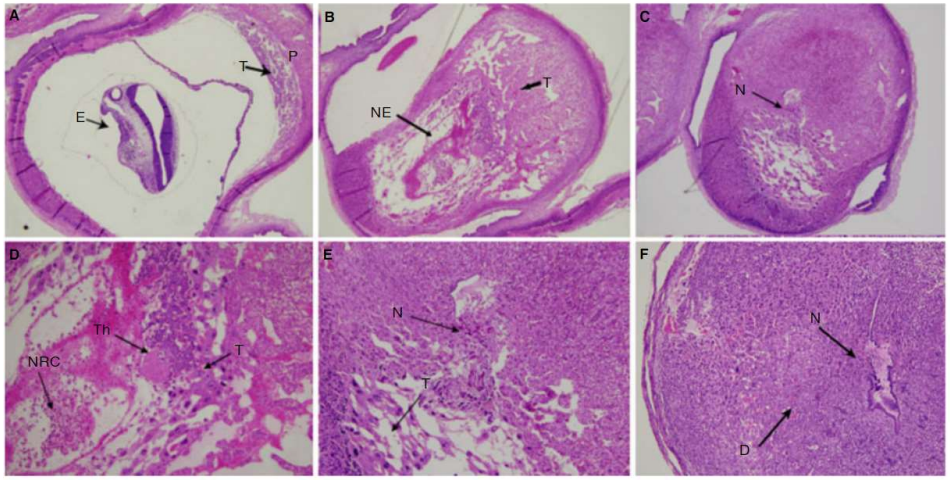
Journal of Thrombosis and Haemostasis, **9**: 1937–1947 DOI: 10.1111/j.1538-7836.2011.04475.x

ORIGINAL ARTICLE

Evidence for heterogeneity of the obstetric antiphospholipid syndrome: thrombosis can be critical for antiphospholipid-induced pregnancy loss

V. POINDRON,*[1] R. BERAT,†[1] A. M. KNAPP,* F. TOTI,‡§ F. ZOBAIRI,‡ A. S. KORGANOW,* M. P. CHENARD,¶ C. GOUNOU,† J. L. PASQUALI,* A. BRISSON† and T. MARTIN*

**National Referral Center for Systemic Autoimmune Diseases, Clinical Immunology Department, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg and CNRS UPR 9021, Strasbourg; †Molecular Imaging and NanoBioTechnology, IECB, CBMN UMR-5248 CNRS Université de Bordeaux-1 ENITAB, Avenue des Facultés, Talence; ‡U. 770 INSERM, Hôpital de Bicêtre; Université Paris-Sud-11, Faculté de Médecine, Le Kremlin-Bicêtre; §Université de Strasbourg, Faculté de Médecine, Institut d'Hématologie & Immunologie, Strasbourg; and ¶Pathology Department, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg, Strasbourg, France*



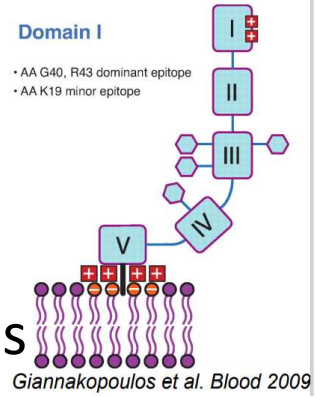
Poindron *et al JTH 2011*

En pratique quotidienne:

Tant que stratification moléculaire pas meilleure:

- Je me méfie du « low risk »
- J'évalue (sérieusement) les autres risques CV (A&V)

Sound of silence



Giannakopoulos et al. Blood 2009

- **Rien sur épitope**:
  - aβ2GP1 associés à thromboses et SAPLO sont dirigés contre D1 ≠ D4 et 5
- **LA**: faux positifs par NOAC, héparine, états inflammatoires avec CRP ↑↑
- **aPs/pt** → LA, LA isolé souvent IgM aPs/Pt peu associé à thrombose

SAPLO: SAPL obstétrical

Martinuzzo GE, *J Lab Hematol* 2014
Ruinemans-Koerts, *Lupus* 2015; **Durigutto, *Haematologica* 2019**

Prophylaxie primaire

- **In asymptomatic aPL carriers with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with LDA (75–100 mg daily) is recommended (LoA: 9,1 [1,5])**

ELSEVIER

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies: An international and collaborative meta-analysis

Laurent Arnaud [a,b,c,*,1], Alexis Mathian [a,b,c,1], Amelia Ruffatti [d], Doruk Erkan [e], Maria Tektonidou [f], Ricard Cervera [g], Ricardo Forastiero [h], Vittorio Pengo [i], Marc Lambert [j], Maria Angeles Martinez-Zamora [k], Juan Balasch [k], Stephane Zuily [l], Denis Wahl [l,2], Zahir Amoura [a,b,c,2]

11 studies
1208 patients – 138 Thrombot.Ev.
Global OR aspirin (n= 607) no aspirin (n=601) = 0,50 (95%CI:027-0,93)
- **arterial but not venous**
- **asymptomatic (460 pts): 0.50**
- **SLE: 0.55**
- **APS obstetrical: 0.25**

Prophylaxie secondaire SAPL

In patients with definite APS and first venous thrombosis:
Treatment with VKA with a target INR 2–3 is recommended (LoA 9,9 [0,3]). *

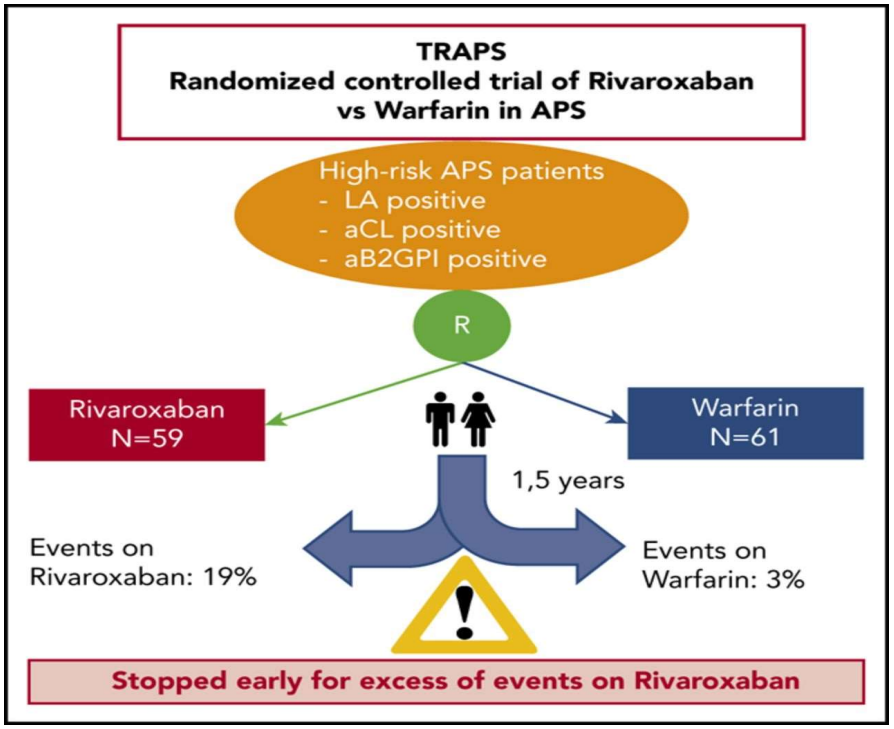
Introduction AVK sous couvert héparine/hbpm

Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent Events. DOACs could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg, allergy or intolerance to VKA) (LoA: 9,1[1,3]).

* Crowther MA *NEJM* 2003

CONTENT CONTROL
CENSORED
CONTENT CONTROL

TRAPS study


TRAPS
Randomized controlled trial of Rivaroxaban vs Warfarin in APS
High-risk APS patients
- LA positive
- aCL positive
- aB2GPI positive
R
Rivaroxaban N=59
Warfarin N=61
1,5 years
Events on Rivaroxaban: 19%
Events on Warfarin: 3%
Stopped early for excess of events on Rivaroxaban

TRAPS study

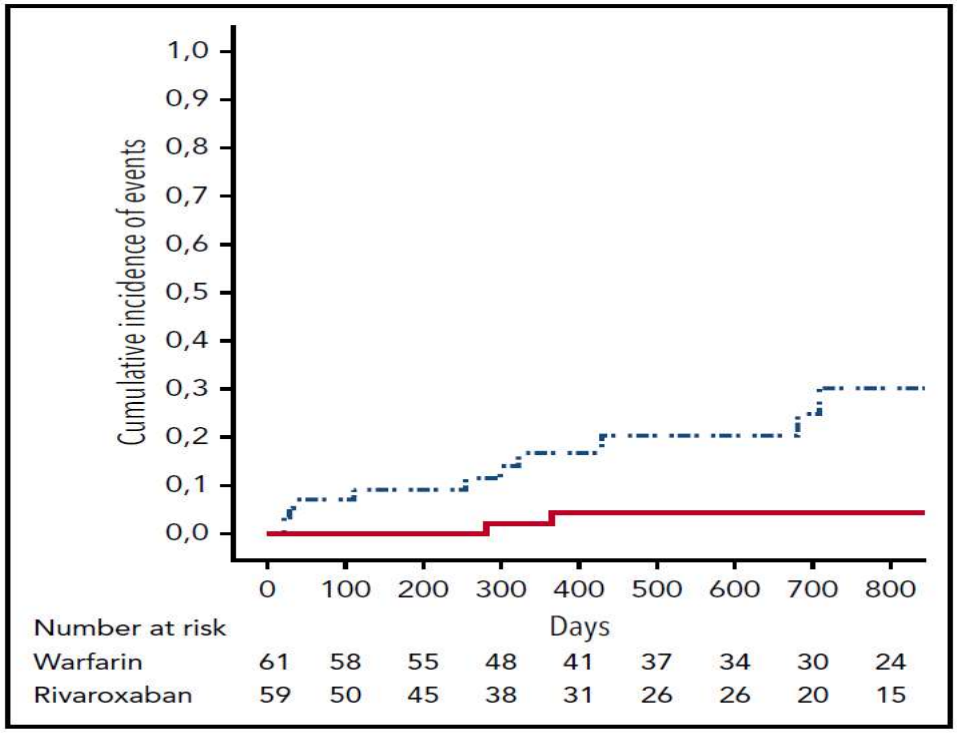


Figure 1. Cumulative incidence of events (death, thromboembolic events, and major bleeding) in the rivaroxaban group (dotted and dashed line) and in the warfarin group (solid line).

TEE in 7 pts in Rivaroxaban groupe vs 0 in VKA

- 4 ischemic stroke
- 3 MI

V Pengo *Blood* 2018

ORIGINAL RESEARCH | 19 NOVEMBER 2019

Annals of Internal Medicine®

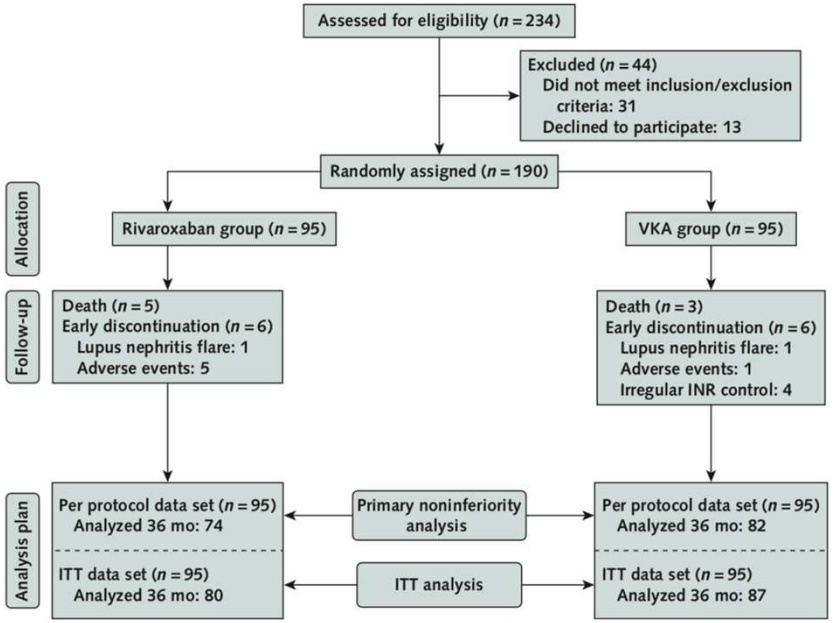
Rivaroxaban Versus Vitamin K Antagonist in Antiphospholipid Syndrome: A Randomized Noninferiority Trial

Population : SAPL non obstétricaux

Intervention : Rivaroxaban 20 mg/j ou Coumadine INR 2-3 (3-4 si récurrent)

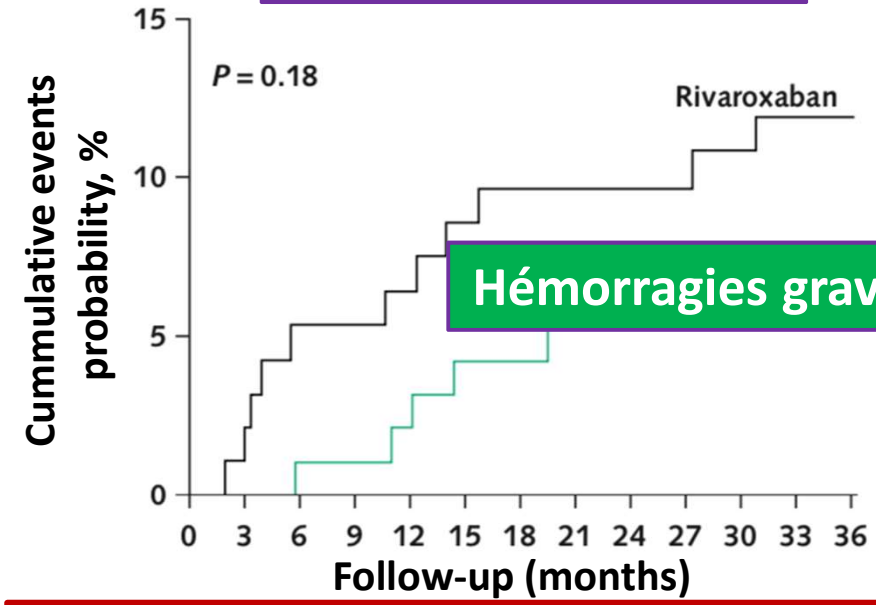
Outcome : thrombose Suivi 36 mois

Analyse : non infériorité marge RR = 1.40

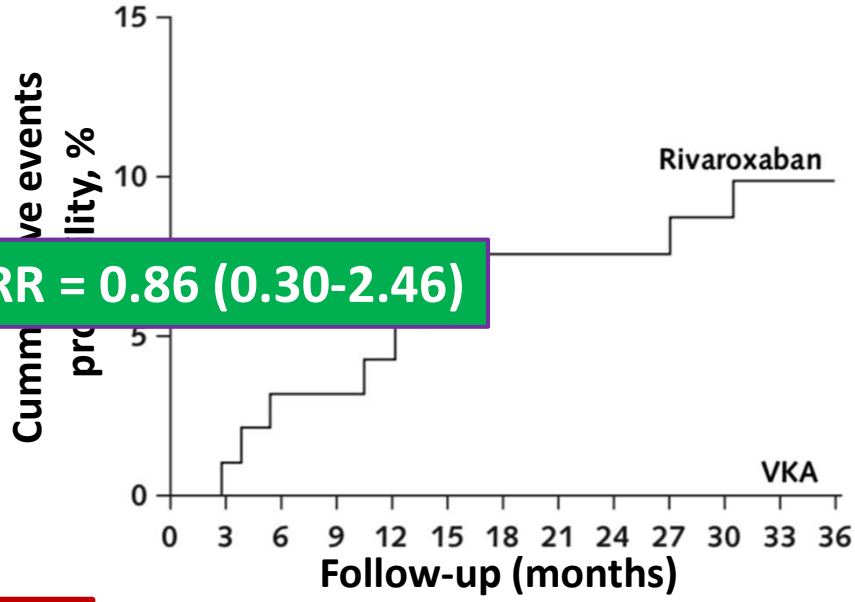


Ordi-Ros J *Ann Intern Med* 2019

All thrombotic events



Strokes



Hémorragies graves : RR = 0.86 (0.30-2.46)

All events : RR = 1.83 (0.71-4.76) ➔ Rejet NI
Arterial events : RR = 4.44 (0.95-11.73), p = 0.06

RR = 19 (1.12-322), p < 0.001

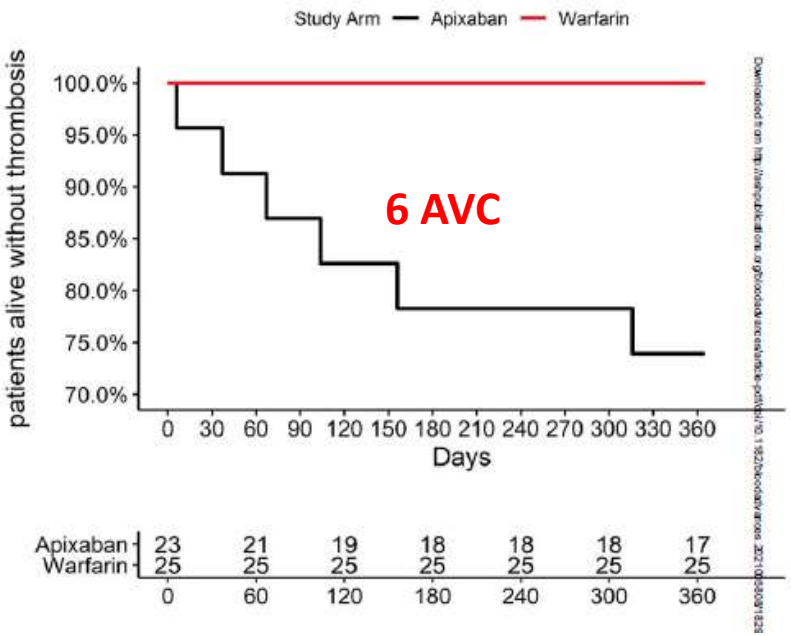
blood advances

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

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

Tracking no: ADV-2021-005808R2

Scott Woller (University of Utah School of Medicine, Department of Internal Medicine, United States) Scott Stevens (University of Utah School of Medicine, Department of Internal Medicine, United States) David Kaplan (University Utah, United States) Tzu-Fei Wang (University of Ottawa, The Ottawa Hospital and Ottawa Hospital Research Institute, Canada) D. Branch (University of Utah Health, United States) Danielle Groat (Intermountain Medical Center, United States) Emily Wilson (INTERMOUNTAIN HEALTHCARE, United States) Brent Armbruster (Intermountain Medical Center, United States) Valerie Aston (Intermountain Medical Center, United States) James Lloyd (INTERMOUNTAIN HEALTHCARE, United States) Matthew Rondina (University of Utah Health Sciences Center, United States) C. Elliott (University of Utah School of Medicine, Department of Internal Medicine, United States)



- **> 25eme patient dose ↑ 2,5 à 5 mg/j**
- **> 30eme patient accidents artériels exclus**

RESEARCH Open Access

A single-arm feasibility cohort study of rivaroxaban in antiphospholipid syndrome

Kimberly Legault[1*], Mark Blostein[2], Marc Carrier[3], Susan Khan[2], Sam Schulman[1], Sudeep Shivakumar[4], Cynthia Wu[5] and Mark A. Crowther[1]

Abstract

Background: There is uncertainty regarding the safety and effectiveness of direct oral anticoagulant agents in patients with antiphospholipid syndrome (APS). We performed a multicenter feasibility study to examine our ability to identify and obtain consent from eligible APS patients and to obtain 95% adherence with daily rivaroxaban administration, in order to inform and power a larger study. Clinical outcomes of bleeding and thrombosis were also collected.

Methods: APS patients with prior venous thromboembolism (VTE) were recruited over 2 years (Oct 2014–Sept 2016) and followed for ≥ 1 year. Patients were assessed clinically every 3 months and had pill counts performed every 6 months. Numbers of patients fulfilling study criteria, as well as those consenting to participate, were tracked, and percentage adherence based on pill counts was recorded. These data were compared against the feasibility endpoints. Rates of thrombosis and bleeding were calculated. Criterion for feasibility was obtaining consent from 135 of 150 identified APS patients over 2 years.

Results: Ninety-six eligible patients were identified, and 14 declined participation. Eighty-two patients were followed for a mean of 19 months, representing 129.8 patient-years. Average rivaroxaban adherence was 95.0%. During follow-up, there were 4 thromboembolic events (2 cerebrovascular and 2 VTE). There were no episodes of major bleeding.

Conclusions: Adequately powered comparative trials using patient-important outcomes in APS are unlikely to be successful due to inability to recruit sufficient numbers of study subjects. This study does not reveal a higher than expected risk of recurrent thromboembolic disease compared to historical cohorts; however, this is an uncontrolled study in relatively low-risk APS patients.

Trial registration: The study was registered with clinicaltrials.gov, identifier NCT02116036, April 16, 2014.

Keywords: Antiphospholipid syndrome, Feasibility studies, Hemorrhage, Rivaroxaban, Thromboembolism

- Accidents veineux unique
- Discussion avec Patients ?
- IRM cérébrale

In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines.
Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence (LoA: 8.9 [1.4]),

In patients with definite APS and recurrent venous thrombosis despite treatment with VKA with a target INR of 2–3:

A. Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing, should be considered.

B. If the target INR of 2–3 had been achieved, addition of LDA, increase of INR target to 3–4 or change to LMWH may be considered.

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 57, No. 8, December 15, 2007, pp 1487–1495
DOI 10.1002/art.23109
© 2007, American College of Rheumatology

ORIGINAL ARTICLE

INR>3 si artériel ou veineux récurrent

A Systematic Review of Secondary Thromboprophylaxis in Patients With Antiphospholipid Antibodies

GUILLERMO RUIZ-IRASTORZA,[1] BEVERLEY J. HUNT,[2] AND MUNTHER A. KHAMASHTA[2]

Les Hôpitaux Universitaires de STRASBOURG

RESO

Accidents artériels

6. In patients with definite APS and first arterial thrombosis: A. Treatment with VKA is recommended over treatment with LDA only (2b/C).	9.4 (0.8)
B. Treatment with VKA with INR 2–3 or INR 3–4 is recommended, considering the individual's risk of bleeding and recurrent thrombosis (1b/B). Treatment with VKA with INR 2–3 plus LDA may also be considered (4/C).	9.0 (1.3)

13th International Congress on antiphospholipid antibodies:
AVK INR>3 ou AVK INR 2-3 + LDA

- la base= AVK INR 2-3
- Évaluer risques CV/ hémorragique → ajout LDA ou INR 3-4
- Récidive: INR 3-4

SAPL obstétrical

9. In women with a history of obstetric APS only (no prior thrombotic events), with or without SLE: A. With a history of ≥3 recurrent spontaneous miscarriages <10th week of gestation and in those with a history of fetal loss (≥10th week of gestation), combination treatment with LDA and heparin at prophylactic dosage during pregnancy is recommended (2b/B).	9.6 (0.9)
B. With a history of delivery <34 weeks of gestation due to eclampsia or severe pre-eclampsia or due to recognised features of placental insufficiency, treatment with LDA or LDA and heparin at prophylactic dosage is recommended considering the individual's risk profile (2b/B).	9.5 (0.8)

Low-molecular-weight heparin and aspirin in the prevention of recurrent early-onset pre-eclampsia in women with antiphospholipid antibodies: the FRUIT-RCT

Marion E van Hoorn [1], William M Hague [2], Mariëlle G van Pampus [3], Dick Bezemer [4], Johanna I P de Vries [5], FRUIT Investigators

Affiliations + expand

PMID: 26771908 DOI: 10.1016/j.ejogrb.2015.12.011

RCT multi-centrique interrompu pour pb de recrutements
Analyse sur 32 femmes:
- 0/16 LMVH + LDA
- 1/16 LDA

Eur J Obstet Gynecol Reprod Biol. 2016

ORIGINAL ARTICLE

Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT

J. I. P. DE VRIES,* M. G. VAN PAMPUS,† W. M. HAGUE,‡ P. D. BEZEMER,§ J. H. JOOSTEN*
and ON BEHALF OF FRUIT INVESTIGATORS
*Department of Obstetrics and Gynaecology, VU University Medical Center, Amsterdam; †Department of Obstetrics and Gynaecology, University Medical Center, Groningen, the Netherlands; ‡Department of Obstetrics and Gynaecology, University of Adelaide, Women's and Children's Hospital, Adelaide, Australia; and §Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands

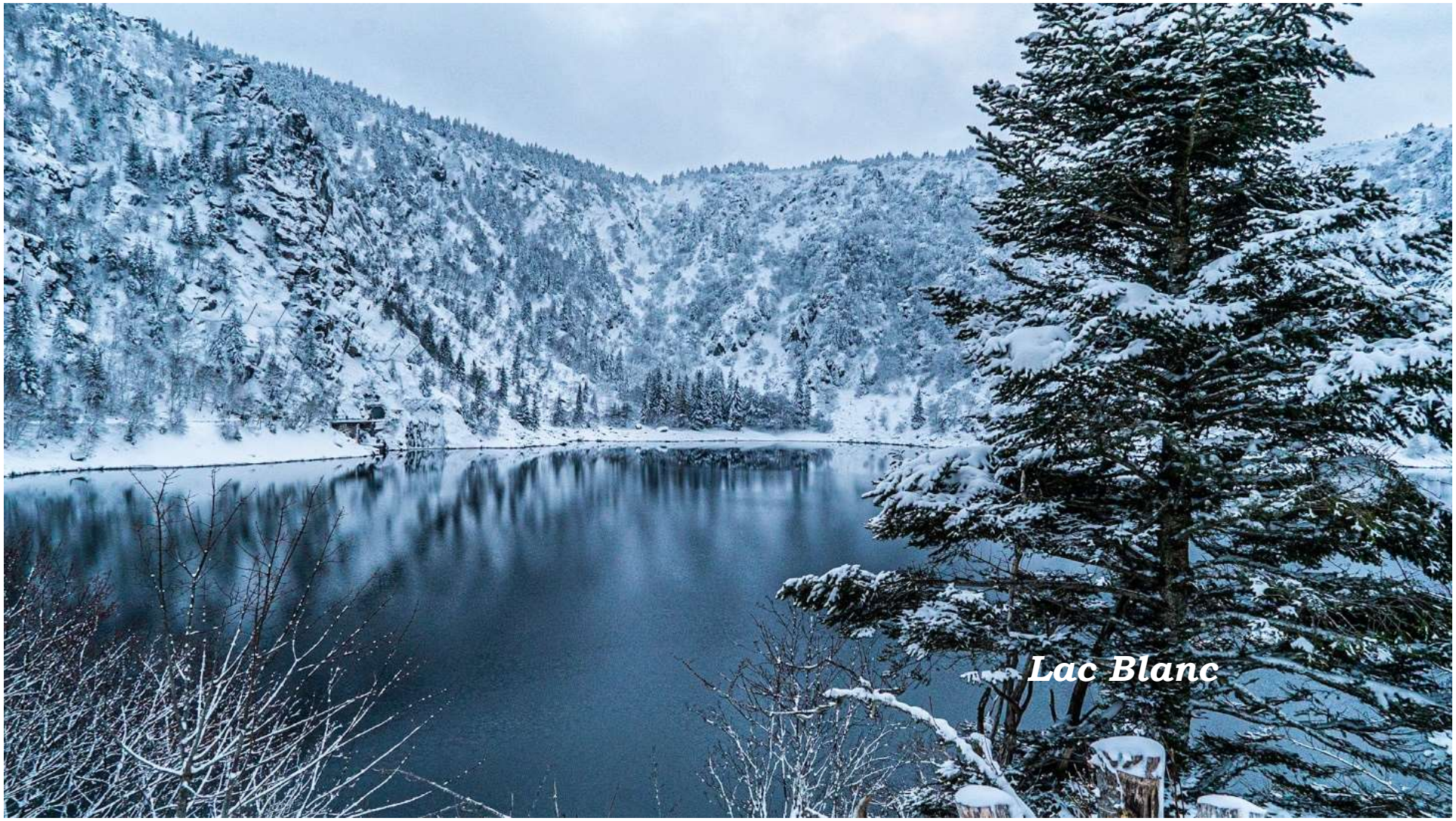
Systematic Review and Meta-Analysis
Medicine
OPEN

2021

Meta-analysis on aspirin combined with low-molecular-weight heparin for improving the live birth rate in patients with antiphospholipid syndrome and its correlation with D-dimer levels

Ting Shi, MD[a], Zhong-Deng Gu, MD[b], Qi-zhi Diao, MD[c,*]

J Thromb Haemost 2012


Lac Blanc