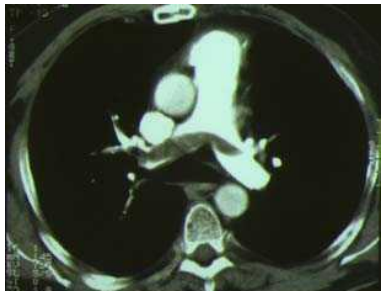
# SAPL en 2023 : Etat de l'art et perspectives

Pr Y BENHAMOU

service de Médecine Interne Vasculaire et Thrombose

CHU de ROUEN

# Nouveaux critères de classification : amendement de Sydney en 2006



- **Thromboses vasculaires :**
  - un ou plusieurs épisodes de thromboses artérielles ou veineuses quel que soit l'organe et le tissu, confirmé (s) par l'imagerie, le Doppler( sauf TVS) ou l'histopathologie (qui ne doit pas révéler de vascularite).

- **Manifestations obstétricales** :
  - Une ou plusieurs morts fœtales (> 10 SA) inexpliquées (morphologie normale)
  - Un enfant ou plus prématuré(s) (< 34 SA), du à une éclampsie ou à une insuffisance placentaire attestée
  - 3 ou plus avortements spontanés (< 10 SA) sans cause anatomique, hormonale ni génétique.

Miyakis et al. J thromb Hemost 2006, 4: 295-306 (Sydney)

# Nouveaux critères de classification : amendement de Sydney en 2006

- LA (lupus anticoagulant) selon les recommandations de l'ISTH persistant au delà de **12 semaines.**

- Titres d'aCL moyens ou élevés par méthodes ELISA standardisées : IgG et/ ou IgM > 40 GPL /MPL (ou > 99$^{ème}$ percentile) persistants plus de **12 semaines.**

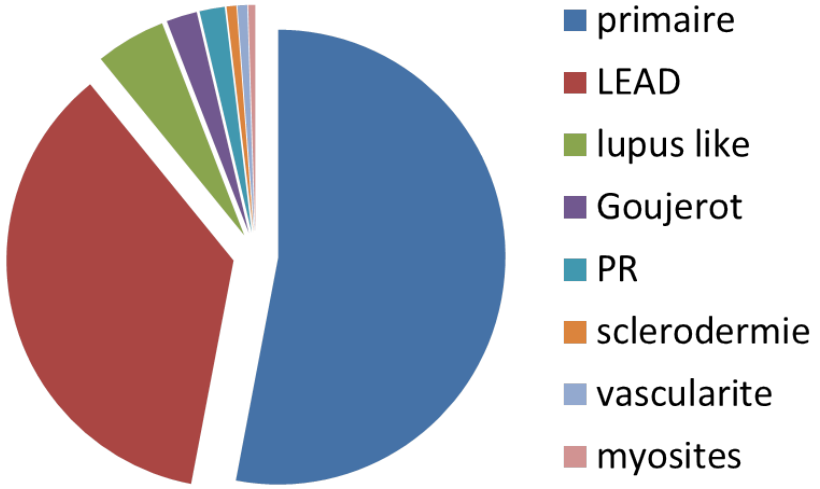
- Anti-β2-glycoprotéine I (par ELISA standardisé) : IgG et /ou IgM > 99ème percentile, persistants **12 semaines.**

- Enfin, le délai entre la détection des APL et les premières manifestations thrombotiques ne doit pas excéder **5 ans.**

Miyakis et al. J thromb Hemost 2006, 4: 295-306 (Sydney)

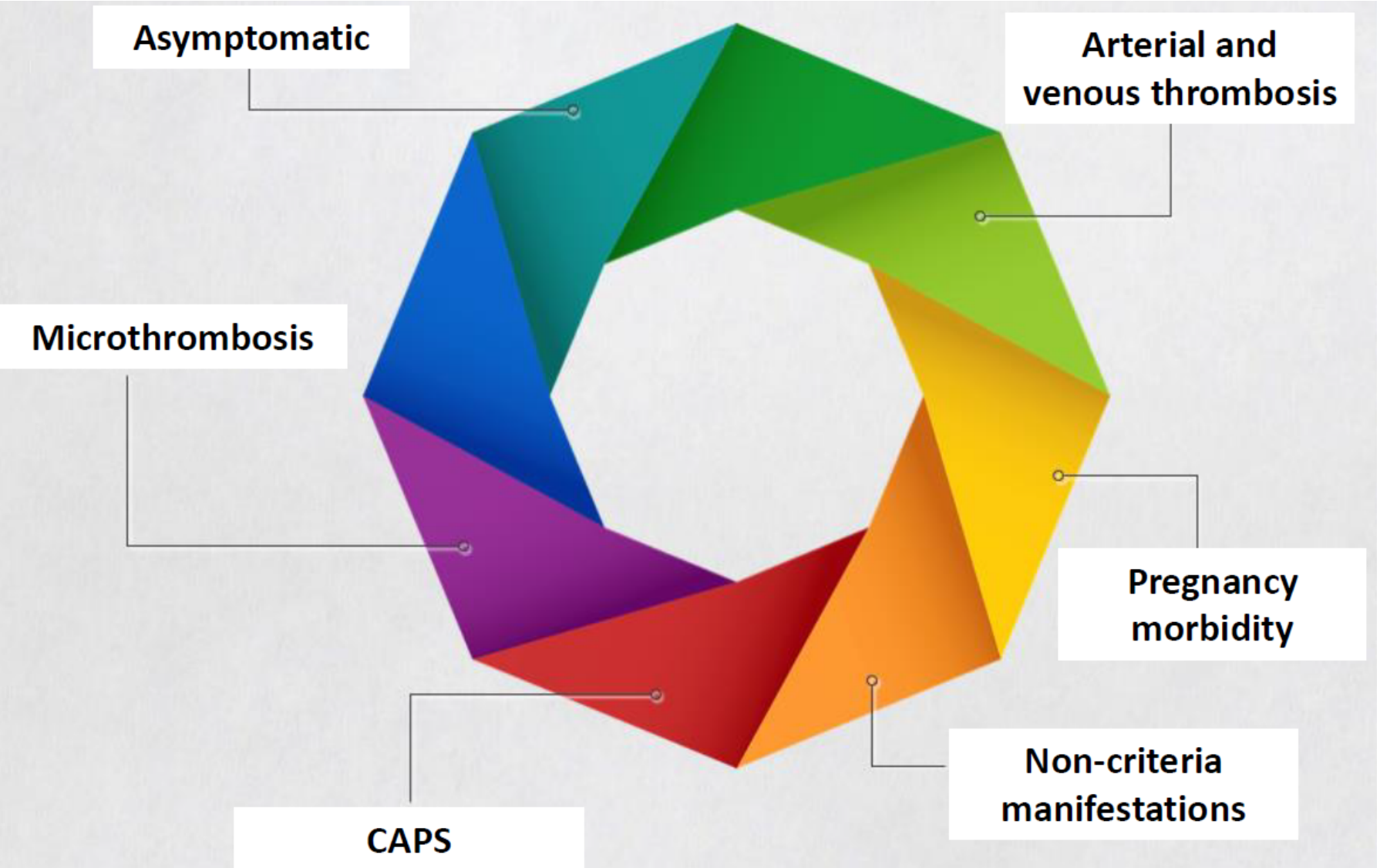
# SAPL: épidémiologie descriptive

| Manifestations cliniques | Pourcentage |
|---|---|
| SAPL primaire | 50-55% |
| SEX ratio | 8 femmes/2 hommes |
| Age du début | 34 +/-13 ans |
| Veine | 37.2% |
| Artère | 27% |
| Veine + artère | 15.2% |
| Obstétrique | 12.3% |
| Microcirculation | 8.3% |
| Profil immunologique | ACL > 80% et ACC >50% |
| Taux de récidives thrombotiques à 10 ans | 15%-30% |



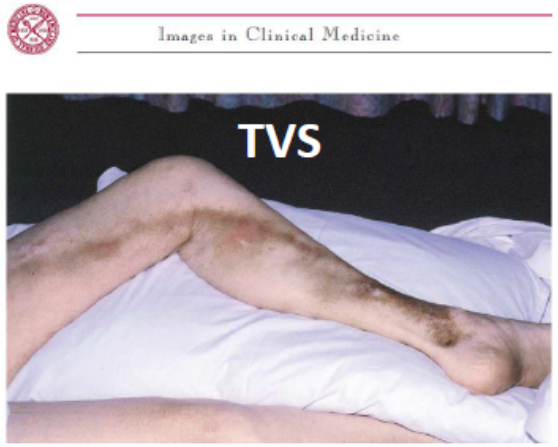

Cervera R, *et al. Ann Rheum Dis* 2014

# SAPL: Large spectre de manifestations cliniques

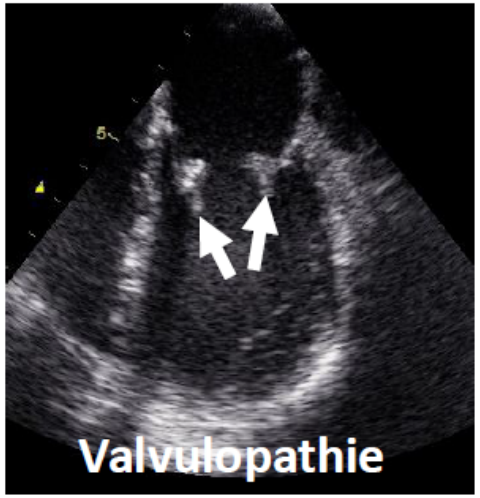


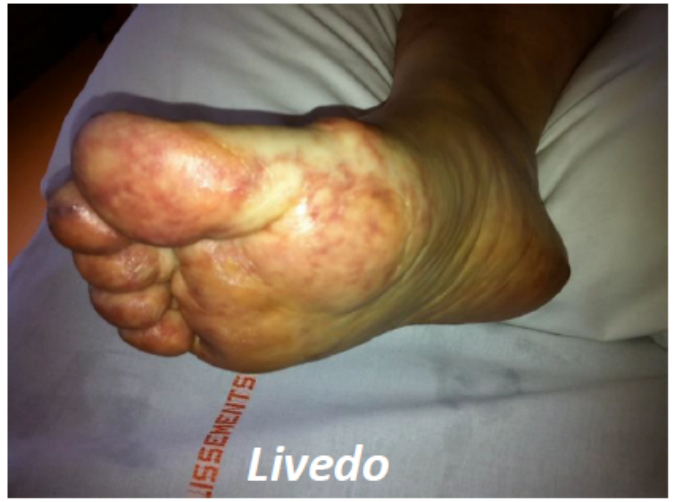

Zuilly et al. APS ACTION

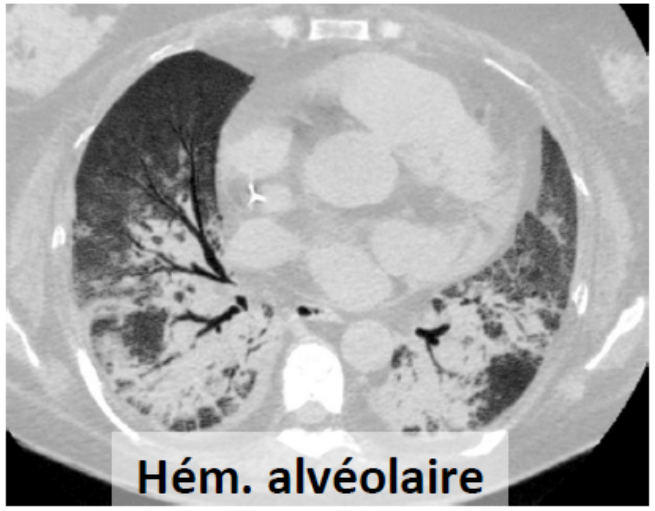
# « Non-criteria » classifications

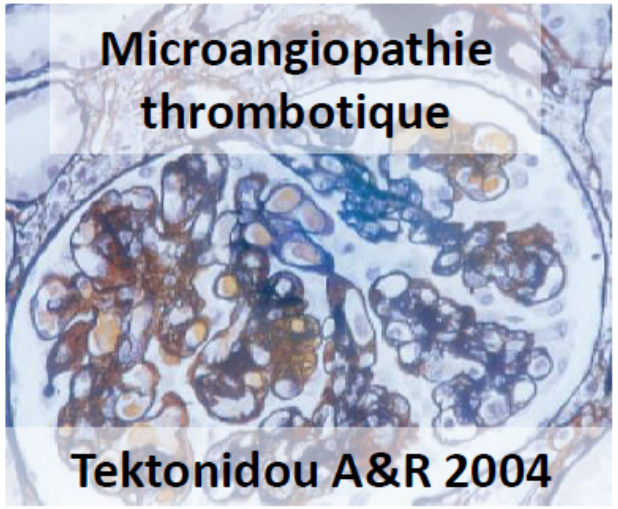


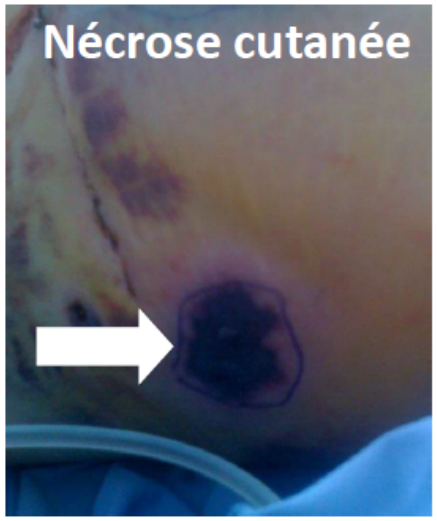

Lucia N Engl J Med 2001



# « Non-criteria » classifications

**Table 1** Main clinical manifestations related to the APS that appeared during the 10-year follow-up (1999–2009) of the total cohort of 1000 patients

| Clinical manifestation* | 0 year† (n=1000) No. (%) | 0–5 year (n=1000) No. (%) | 5–10 year (n=796)‡ No (%) | 0–10 year (n=1000) No (%) |
|---|---|---|---|---|
| Thrombocytopenia (<100 000/μL) | 296 (29.6) | 37 (3.7) | 50 (6.3) | 87 (8.7) |
| *Livedo reticularis* | 241 (24.1) | 26 (2.6) | 55 (6.9) | 81 (8.1) |
| Stroke | 198 (19.8) | 24 (2.4) | 29 (3.6) | 53 (5.3) |
| Transient ischaemic attacks | 111 (11.1) | 23 (2.3) | 24 (3.0) | 47 (4.7) |
| Deep vein thrombosis | 389 (38.9) | 21 (2.1) | 22 (2.7) | 43 (4.3) |
| Pulmonary embolism | 141 (14.1) | 21 (2.1) | 14 (1.7) | 35 (3.5) |
| Epilepsy | 70 (7.0) | 17 (1.7) | 15 (1.9) | 32 (3.2) |
| Skin ulcers | 55 (5.5) | 17 (1.7) | 14 (1.7) | 31 (3.1) |
| Valve thickening/dysfunction | 116 (11.6) | 17 (1.7) | 29 (3.6) | 46 (4.6) |
| Vegetations | 27 (2.7) | 14 (1.4) | 7 (0.9) | 21 (2.1) |
| Myocardial infarction | 55 (5.5) | 9 (0.9) | 10 (1.2) | 19 (1.9) |
| Superficial thrombophlebitis | 117 (11.7) | 9 (0.9) | 8 (1.0) | 17 (1.7) |
| Autoimmune haemolytic anaemia | 97 (9.7) | 9 (0.9) | 31 (3.9) | 40 (4.0) |
| **Obstetric manifestation§** | **(n=1580)** | **(n=105)** | **(n=83)** | **(n=188)** |
| Pre-eclampsia/eclampsia | 82 (5.2) | 8 (7.6) | 4 (4.8) | 12 (6.4) |
| Early pregnancy loss (<10 weeks) | 560 (35.4) | 18 (17.1) | 13 (15.7) | 31 (16.5) |
| Late pregnancy loss (≥10 weeks) | 267 (16.9) | 7 (6.7) | 2 (2.4) | 9 (4.8) |
| Live birth | 753 (47.6) | 80 (76.2) | 57 (68.7) | 137 (72.9) |
| Live birth with prematurity¶ | 80 (10.6) | 28 (35.0) | 38 (66.7) | 66 (48.2) |
| Live birth with intrauterine growth restriction¶ | 11 (1.5) | 11 (13.7) | 25 (43.8) | 36 (26.3) |

Cervera R, *et al. Ann Rheum Dis* 2014

# Critères SAPL ACR/EULAR (préliminaires)

**CRITERES D'ENTREE :**

≥ 1 critère clinique

En l'absence d'autre explication que le SAPL

| CLINIQUE | Points |
|---|---|
| Maladie veineuse thromboembolique (MVTE)<br>• Avec profil de risque élevé de MVTE<br>• Sans profil de risque de MVTE | **1**<br>**3** |
| Atteinte valvulaire cardiaque<br>• Epaississement<br>• Végétation | **2**<br>**4** |
| Thrombopénie (20-130G/l) | **2** |

Idem anciens critères SAUF que :

- Les thromboses avec F de R ne suffisent plus
- Le microvasculaire sans histo compte quand même pour 2 points
- Les FCS disparaissent quasiment
- La MFIU sans insuffisance placentaire aussi
- Le caractère systémique est mieux pris en compte (valves et plaq)

# Critères SAPL ACR/EULAR (préliminaires)

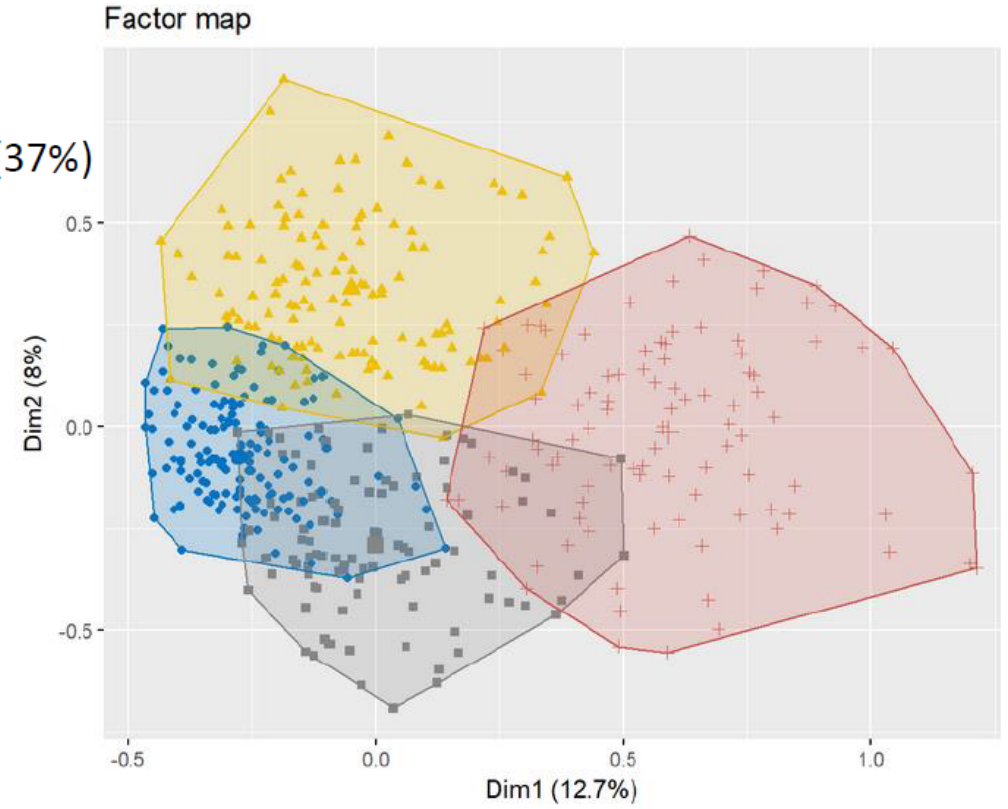
| | Points |
|---|---|
| **Anticoagulant circulant lupique positif**<br>• 1 fois<br>• Persistant (> 12 semaines) | <br>**1**<br>**5** |
| **Anticorps anticardiolipine (aCL) et antiβ2GP1**<br>• Seulement en IgM<br>• IgG<br>  • Positivité modérée (ELISA 40-79U) en ACL **ET/OU** en anti-β2GP1<br>  • Positivité forte (ELISA ≥ 80 U) en ACL **OU** en anti-β2GP1<br>  • Positivité forte (ELISA ≥ 80 U) en ACL **ET** en anti-β2GP1 | <br>**1**<br><br>**4**<br>**5**<br>**7** |

Idem anciens critères SAUF que IgM seules ne suffisent plus

*ACR 2022 session 13S150 (Erkan D et al.)*

# Determination of four homogeneous subgroups of patients with antiphospholipid syndrome: a cluster analysis based on 509 cases

**Cluster 2**
- Un peu plus d'hommes (37%)
- 45.77 ans
- **SAPL artériel (88.5%)**
- Livedo (35%)
- Valvulopathie (21%)
- FDR CV (diabète, HTA, dyslipidémie)




**Cluster 4**
- Femmes 71%
- 33.1 ans
- **SAPL microvasculaire (31%)**
- **Néphropathie** APL
- **CAPS** 77%
- Valvulopathie 41%
- TVP (74%)
- ACC 88%
- Thrombopénie 46%

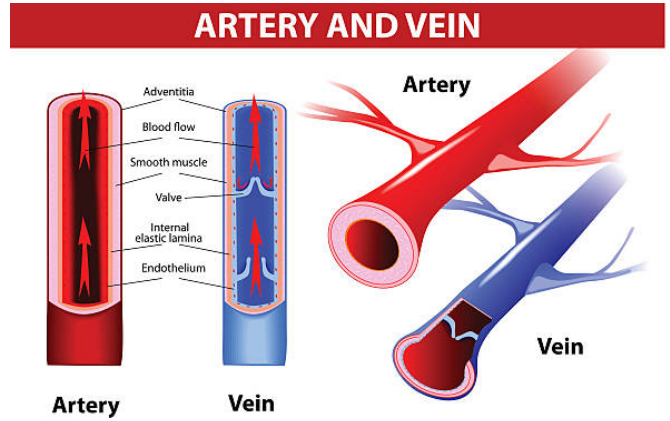
**Cluster 1**
- Femmes (82.3%)
- 34.4 ans
- SAPL veineux (77%)
- Pas de maladie autoimmune (0.6%)

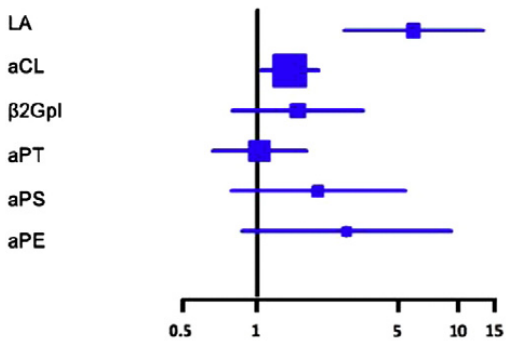
**Cluster 3**
- Femmes (92%)
- 30.6 ans
- SAPL veineux (77%)
- Lupus (77%)
- Thrombopénie (48%)

Nguyen et al, Rheumatology 2022,

# APL isolé :
# traiter ou ne pas traiter ?

# APL et profil biologique

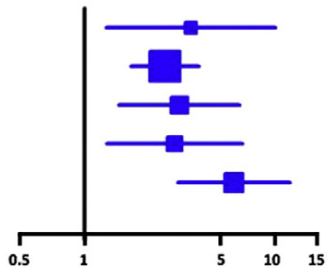



| | OR [95%CI] | No. studies | No. patients | p ass. | p het. |
|---|---|---|---|---|---|
| LA | 6.14 [2.74; 13.8] | 5 | 1650 | <0.001 | 0.66 |
| aCL | 1.46 [1.06; 2.03] | 12 | 5375 | 0.02 | Random |
| β2GpI | 1.61 [0.76; 3.43] | 4 | 1915 | 0.22 | Random |
| aPT | 1.03 [0.60; 1.77] | 3 | 1639 | 0.92 | Random |
| aPS | 2.03 [0.74; 5.58] | 1 | 276 | 0.17 | Random |
| aPE | 2.82 [0.84; 9.44] | 2 | 474 | 0.09 | Random |

aCL: anti-cardiolipin, aPE: anti-phosphatidyl ethanolamine, aPS: anti-phosphatidyl serine, aPT: anti-prothrombin,
LA: lupus anticoagulant, No: number of, OR (95%CI): odds ratio and 95% confidence interval,
p ass: p-value for association, p het: p-value for heterogeneity, β2GpI: anti-β2 Glycoprotein I

**Fig. 2.** Risk of venous thrombosis according to type of antiphospholipid antibody (global forest plot).




| | OR [95%CI] | No. studies | No. patients | p ass. | p het. |
|---|---|---|---|---|---|
| LA | 3.58 [1.29; 9.92] | 8 | 3760 | 0.01 | Random |
| aCL | 2.65 [1.75; 4.00] | 17 | 8289 | <0.001 | Random |
| β2GpI | 3.12 [1.51; 6.44] | 3 | 1671 | 0.002 | 0.44 |
| aPT | 2.95 [1.31; 6.66] | 2 | 1327 | 0.009 | 0.27 |
| aPS | 6.00 [3.07; 11.7] | 2 | 1331 | <0.001 | 0.47 |

aCL: anti-cardiolipin, aPE: anti-phosphatidyl ethanolamine, aPS: anti-phosphatidyl serine, aPT: anti-prothrombin,
LA: lupus anticoagulant, No.: number of, OR (95%CI): odds ratio and 95% confidence interval,
p ass: p-value for association, p het: p-value for heterogeneity, β2GpI: anti-β2 Glycoprotein I

**Fig. 3.** Risk of arterial thrombosis according to type of antiphospholipid antibody (global forest plot).

*Reynaud et al, Autoimmunity review 2014*

# APL et profil biologique

## The antiphospholipid triangle

M. GALLI
*Department of Hematology – Oncology, Ospedali Riuniti, Bergamo, Italy* *JTH 2010*

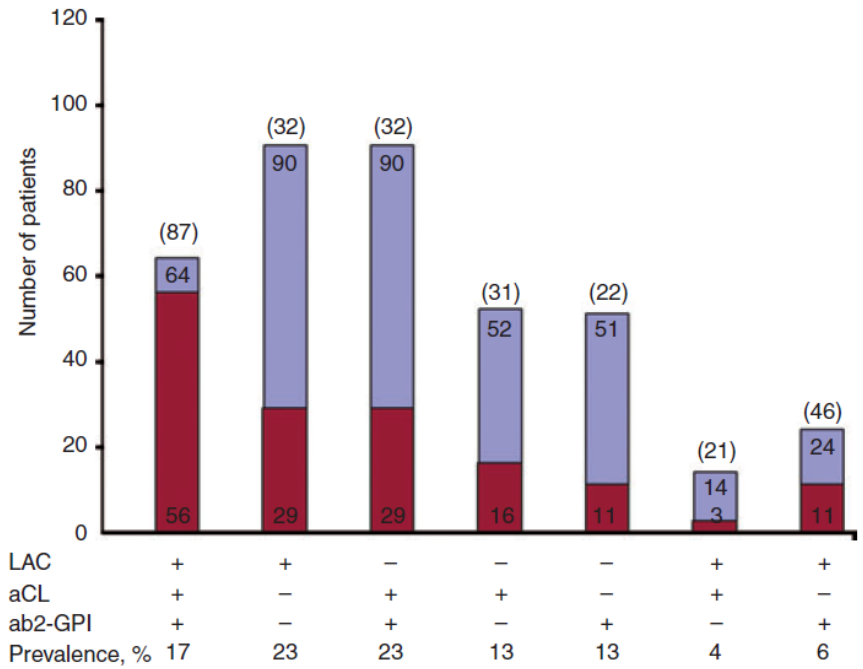



**Fig. 1.** Cumulative analysis of the incidence and association with thombosis of aPL profiles in 385 patients*.

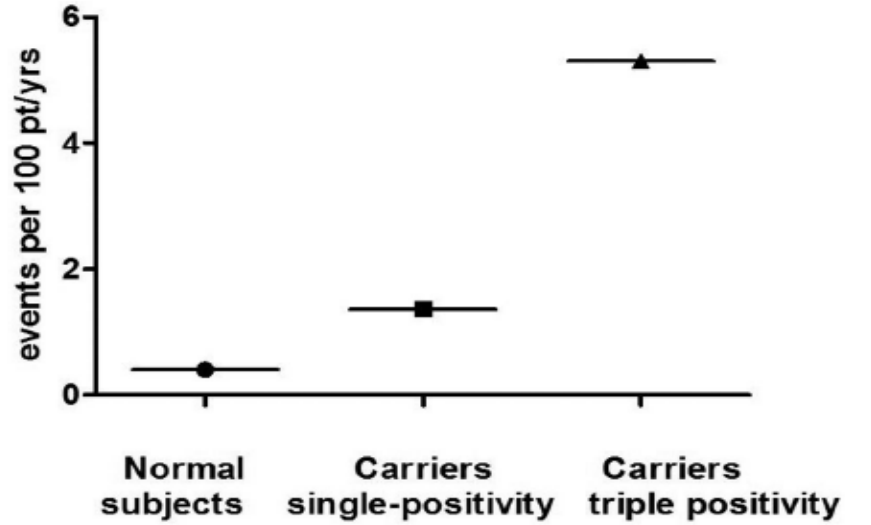



**Figure 2. Average annual rates of first cardiovascular events (including VTE) in a white normal population (●), in single aPL-positive carriers (■), and that shown in triple-positive carriers in this study (▲).**

**5.3% /an de thromboses; 37.1% sur 4.5 ans de suivi.**

*Pengo et al. Blood 2011*

# APL et profil biologique

**Box 1 Definitions of medium-high antiphospholipid antibody (aPL) titres, and of high-risk and low-risk aPL profile**

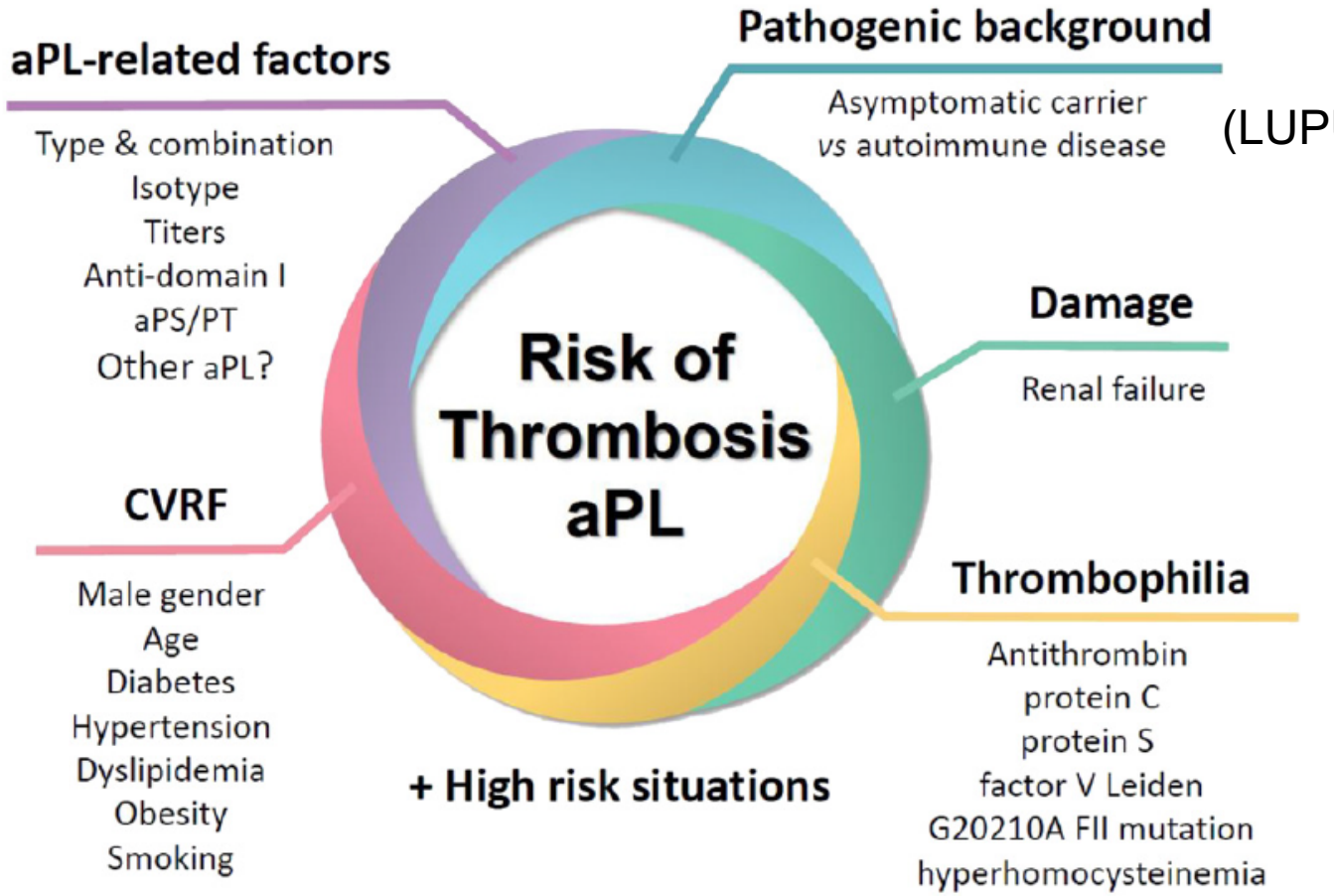
| Profil à haut risque de thrombose | Profil à faible risque de thrombose |
|---|---|
| Présence à au moins deux reprises séparées d'au moins 12 semaines de :<br>• ACCL<br>• ou de 2 APL (parmi ACCL, ACL et aβ2GPI) (double positivité)<br>• ou des 3 APL (triple positivité)<br>• ou d'un taux persistant de l'un des APL à titre élevé (cf paragraphe 2.4) | Présence isolée d'ACL ou aβ2GPI à titre faible ou modéré |

**Low-risk aPL profile.**
► Isolated aCL or antibeta2 glycoprotein I antibodies at low-medium titres, particularly if transiently positive.[3]

**A chaque profil , une attitude thérapeutique différente ?????**

Recos EULAR APS 2019/ PNDS 2022

# APL isolés : Que faire ?




(LUPUS++++ OR*4)

(HTA OR*4)

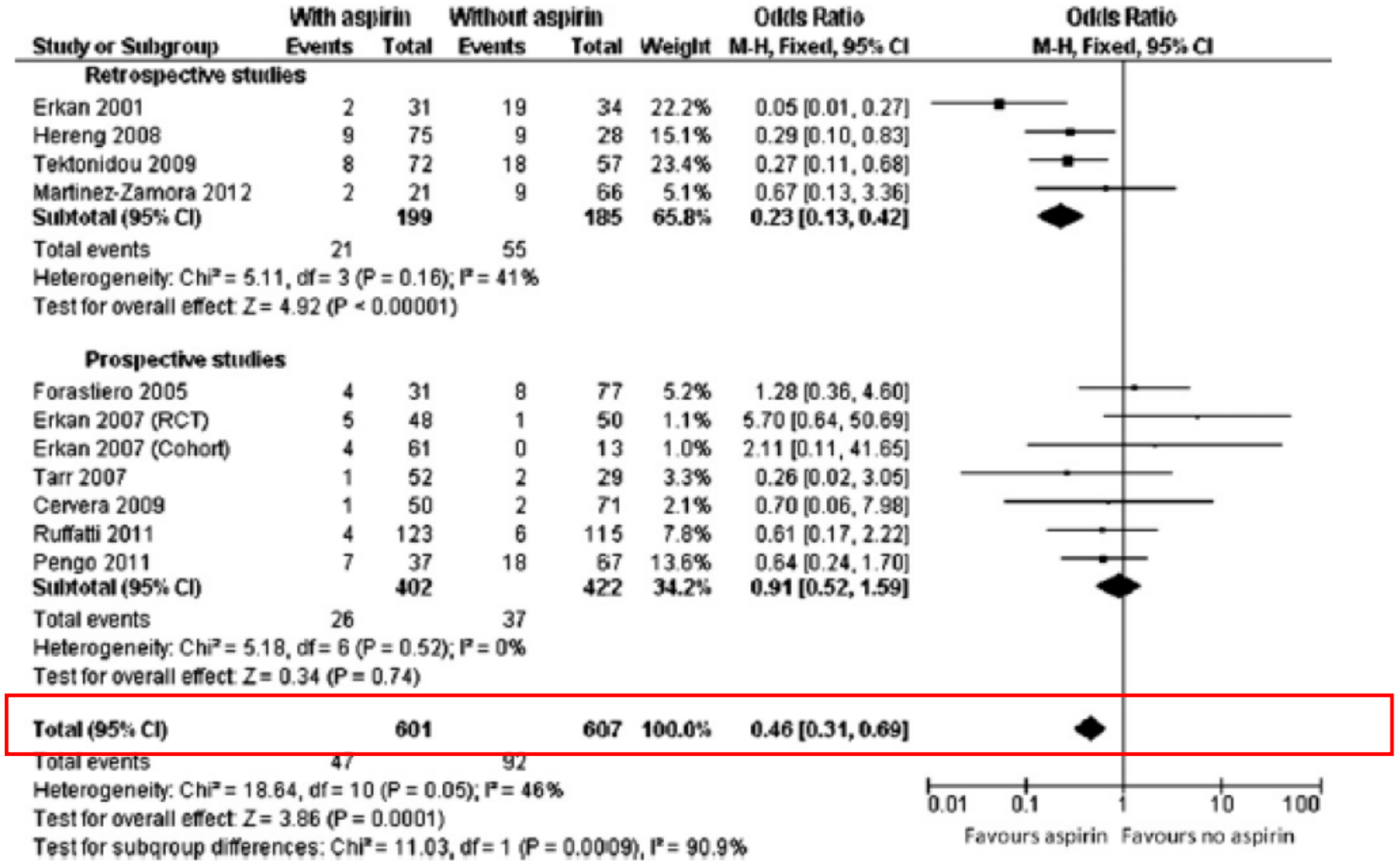
Introduction d'un traitement ?

Lequel ?

*Arnaud et al; autoimmunity review 2017*

# Traitement ou pas ?

## Méta-analyse (1)




*Arnaud et al. Autoimmunity rev 2014*

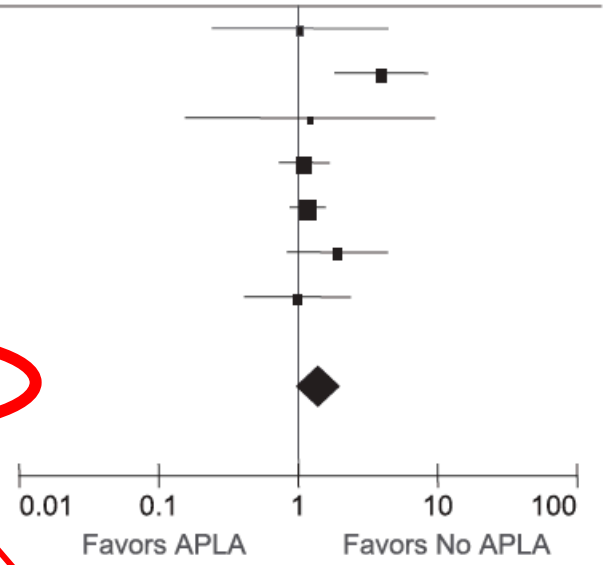
# SAPL thrombotique

# SAPL et profil biologique et risque de récidive

| Study or Subgroup | APLA Events | APLA Total | No APLA Events | No APLA Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Ginsberg 1995 | 2 | 11 | 6 | 34 | 5.1% | 1.03 [0.24, 4.39] |
| Kearon 1999 | 4 | 6 | 12 | 71 | 13.5% | 3.94 [1.83, 8.48] |
| Kearon 2004 | 1 | 17 | 6 | 124 | 2.7% | 1.22 [0.16, 9.49] |
| Rodger 2008 | 56 | 384 | 31 | 235 | 25.0% | 1.11 [0.74, 1.66] |
| Schulman 2006 | 38 | 116 | 194 | 694 | 30.1% | 1.17 [0.88, 1.56] |
| Taliani 2009 | 3 | 6 | 76 | 291 | 12.3% | 1.91 [0.84, 4.36] |
| Wahlander 2005 | 5 | 48 | 49 | 465 | 11.3% | 0.99 [0.41, 2.36] |
| **Total (95% CI)** | | **588** | | **1914** | **100.0%** | **1.41 [0.99, 2.00]** |
| Total events | 109 | | 374 | | | |

Heterogeneity: Tau² = 0.08; Chi² = 10.96, df = 6 (P = 0.09); I² = 45%

Test for overall effect: Z = 1.92 (P = 0.06)




**Lupus anticoagulant** *vs* **no APLA**
**OR = 2.83 (0.83-9.64)**

**Anticardiolipin** *vs* **no APLA**
**OR = 1.53 (0.76-3.11)**

**A chaque anticorps son risque ?**

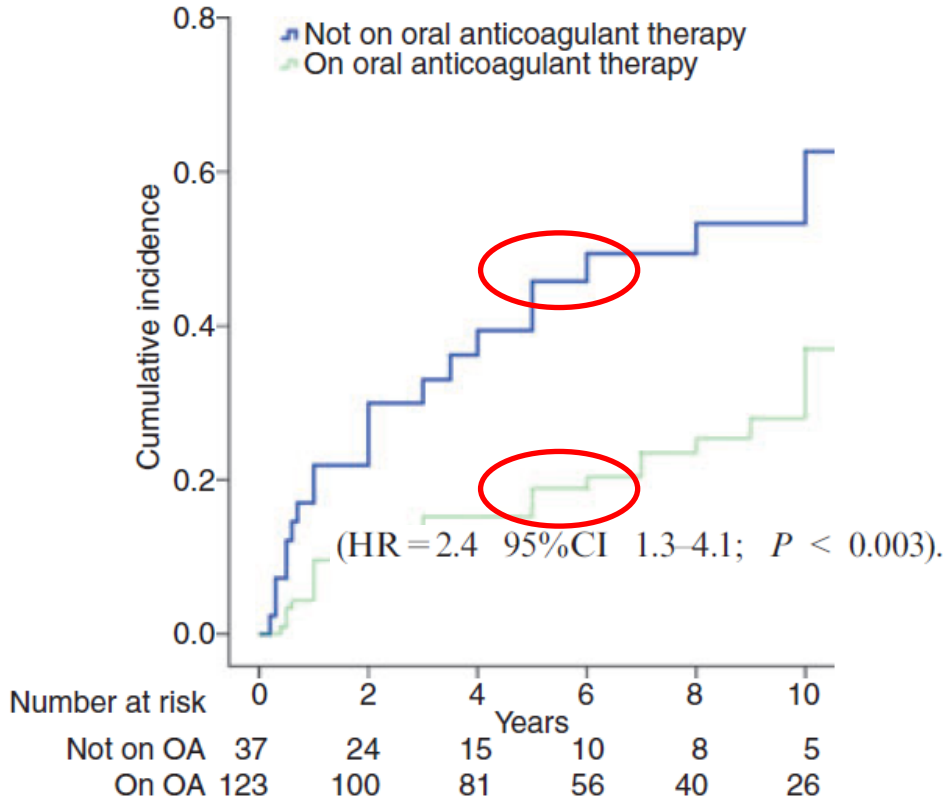
*Garcia et al. BLOOD 2015*

# Clinical course of high-risk patients diagnosed with antiphospholipid syndrome

V. PENGO,* A. RUFFATTI,† C. LEGNANI,‡ P. GRESELE,§ D. BARCELLONA,¶ N. ERBA,** S. TESTA,††
F. MARONGIU,* E. BISON,* G. DENAS,* A. BANZATO,* S. PADAYATTIL JOSE* and S. ILICETO*

**Table 2** Sites of thromboembolic events at presentation

| Site | N |
|---|---|
| Venous sites | |
| Venous thrombosis of the lower limbs | 54 |
| Pulmonary embolism | 14 |
| Venous thrombosis of the upper limbs | 2 |
| Retinal thrombosis | 2 |
| Inferior vena cava thrombosis | 1 |
| Mesenteric vein thrombosis | 1 |
| Jugular vein thrombosis | 1 |
| Tricuspid valve thrombosis | 1 |
| Arterial sites | |
| Stroke | 27 |
| TIA | 15 |
| Arterial thrombosis of the lower limbs | 15 |
| Myocardial infarction | 8 |
| Renal artery thrombosis | 2 |
| Retinal artery thrombosis | 1 |
| Mesenteric ischemia | 1 |
| Cutaneous necrosis | 3 |

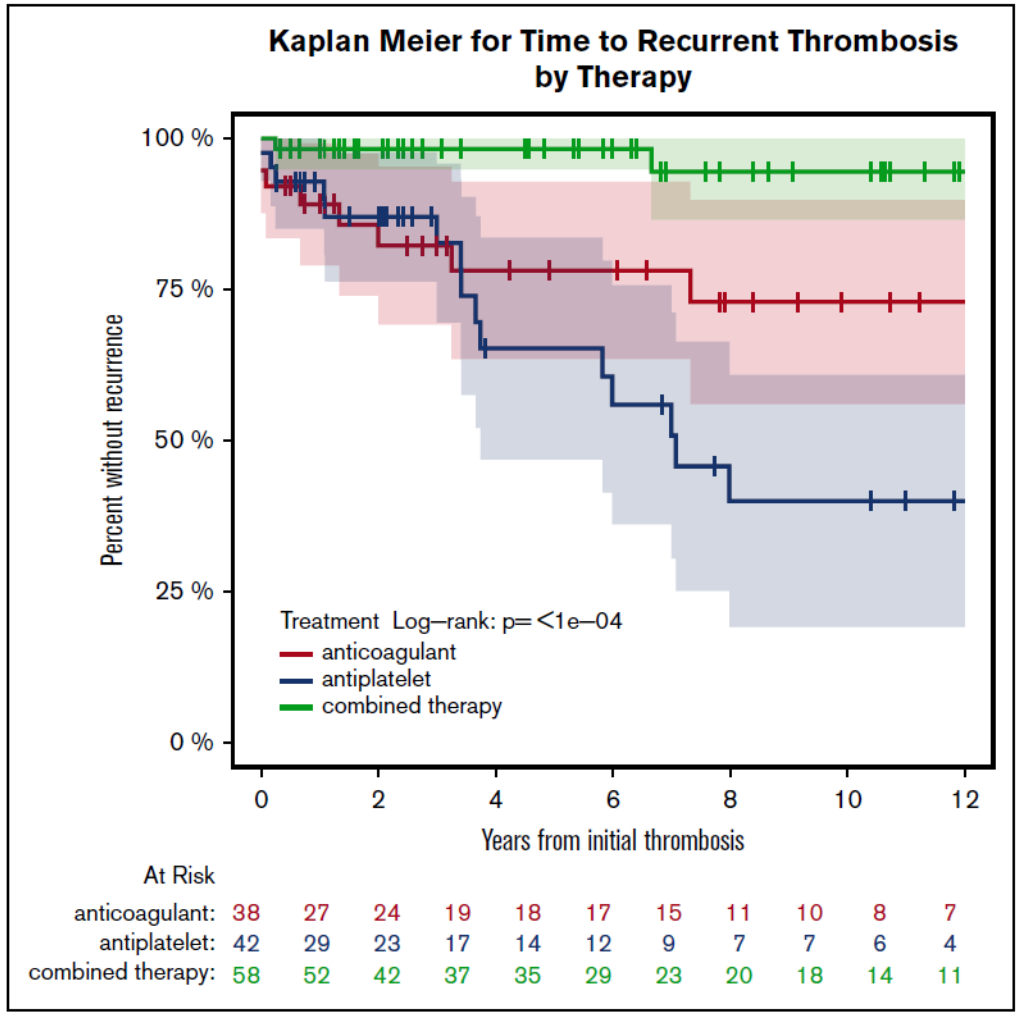



*Pengo et al, JTH 2010*

# Recurrent thrombosis in patients with antiphospholipid antibodies and arterial thrombosis on antithrombotic therapy

blood advances

William G. Jackson,[1] Clara Oromendia,[2] Ozan Unlu,[3] Doruk Erkan,[4] and Maria T. DeSancho,[5] on behalf of the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking




(hazard ratio, 0.30; 95% CI, 0.08-0.83; $P < .025$

HR : ?

**Mono ou bithérapie ?**

# Recommandations EULAR 2019/PNDS

## 6.5 Traitement d'une première thrombose

### 6.5.1 SAPL « veineux »

La prophylaxie secondaire d'un évènement thrombotique repose sur un traitement par AVK avec une cible d'INR entre 2 et 3.

### 6.5.2 SAPL « artériel »

Les patients avec un SAPL thrombotique artériel ont un risque de récidive plus élevé que ceux avec une forme veineuse et une tendance à récidiver dans le même type de vaisseaux. La prophylaxie secondaire repose principalement sur un traitement par AVK avec une cible d'INR entre 2 et 3. Certaines équipes préfèrent une prophylaxie avec un INR cible entre 3 et 4 ou bien un traitement par AVK avec une cible d'INR entre 2 et 3 associé à l'acide acétylsalicylique à faibles doses.

Recos EULAR APS 2019/ PNDS 2022

# SAPL et AOD

**Table 2** Characteristics and status of completed and recruiting randomized controlled trials (RCTs) of direct oral anticoagulants in thrombotic antiphospholipid syndrome (APS)

| | RAPS [79] | TRAPS [7,82] | ASTRO-APS [7,83] |
|---|---|---|---|
| Chief Investigator | H. Cohen | V. Pengo | S. Woller |
| Study design | Phase 2/3 RCT | Phase 3 RCT | Phase 2/3 RCT |
| No. of patients | 116 | 536 | 200 |
| APS subgroups | Previous VTE, target INR of 2.5; no thrombosis > 3 months; patients with arterial thrombosis excluded | Triple-positive thrombotic APS; arterial, venous and/or biopsy-proven microthrombosis | Thrombotic APS, VTE or arterial, target INR of 2.3, 3.0 or 3.5; no thrombosis > 6 months; definite, likely or historical APS |
| Intervention | Rivaroxaban 20 mg once daily versus warfarin target INR of 2.5 | Rivaroxaban 20 mg once daily versus warfarin target INR of 2.5 | Apixaban 2.5 mg or 5 mg twice daily versus warfarin target INR of 2.5 |
| Primary outcome(s) | Thrombin generation – endogenous thrombin potential | Thrombosis – arterial or venous, major bleeding or death (composite) | Thrombosis - arterial and/or venous, bleeding |
| Duration of recruitment | Jun 2013 to November 2014 | December 2014 to January 2018 | February 15 to December 2019 |
| Status | Completed and results published | Terminated January 2018 (see text) | Ongoing: protocol modified after potential safety signal (see text) |

*Cohen et al, JTH 2018*

# SAPL et AOD

## Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial

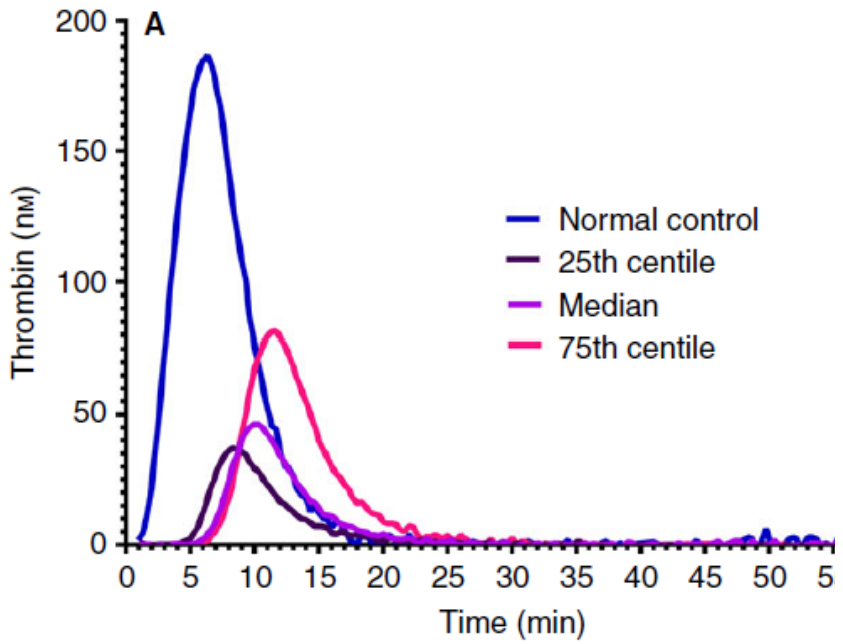
Hannah Cohen, Beverley J Hunt, Maria Efthymiou, Deepa R J Arachchillage, Ian J Mackie, Simon Clawson, Yvonne Sylvestre, Samuel J Machin, Maria L Bertolaccini, Maria Ruiz-Castellano, Nicola Muirhead, Caroline J Doré, Munther Khamashta*, David A Isenberg*, for the RAPS trial investigators

| | Rivaroxaban (n=57) | Warfarin (n=59) |
|---|---|---|
| Demographics | | |
| Mean (SD) age (years) | 47 (17) | 50 (14) |
| Women | 42 (74%) | 42 (71%) |
| Men | 15 (26%) | 17 (29%) |
| Mean (SD) BMI (kg/m²) | 28 (6) | 30 (6) |
| Stratification variables | | |
| SLE | 11 (19%) | 11 (19%) |
| Sites | | |
| University College London Hospital | 23 (40%) | 25 (42%) |
| Guy's and St Thomas' Hospitals | 34 (60%) | 34 (58%) |
| Rivaroxaban dose | | |
| 20 mg once daily | 55 (96%) | N/A |
| 15 mg once daily* | 2 (4%) | N/A |
| Thrombotic event with no or subtherapeutic anticoagulation‡ | | |
| Deep vein thrombosis§ | 32 (56%) | 37 (63%) |
| Pulmonary embolism | 25 (44%) | 22 (37%) |
| Thrombin generation | | |
| ETP (nmol/L per min)† | 555 (497–619) | 542 (469–626) |
| Lag time (min) | 7·3 (6·4–8·2) | 7·6 (6·6–8·7) |
| Time to peak thrombin generation (min) | 10·8 (9·7–12·0) | 11·7 (10·3–13·2) |
| Peak thrombin generation (nmol/L) | 93·8 (78·8–111·7) | 79·9 (64·9–98·2) |

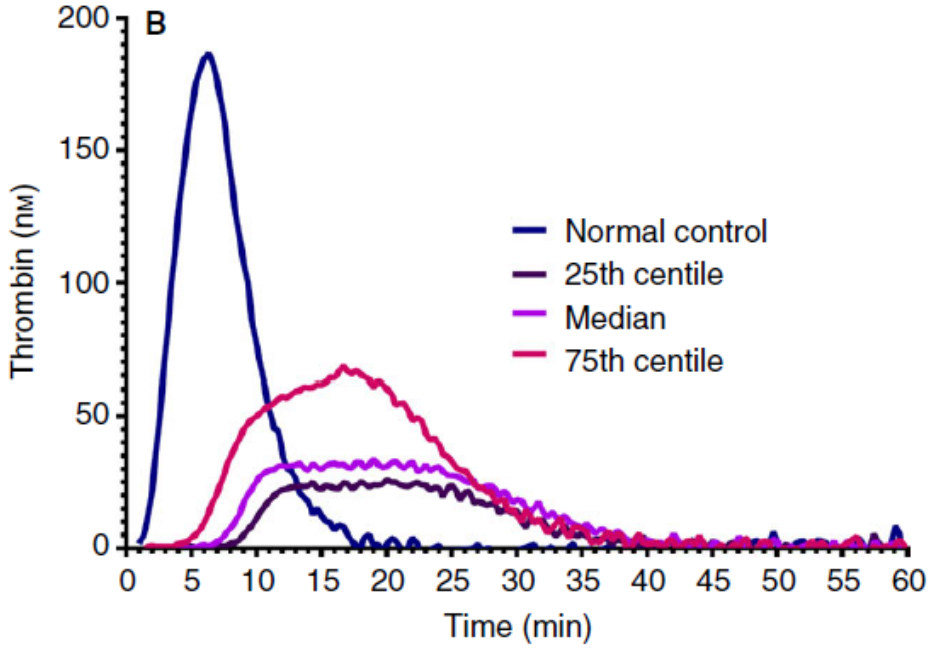
*Cohen et al, Lancet Hematol 2016*

# SAPL et AOD

Warfarine




Rivaroxaban




Findings Of 116 patients randomised between June 5, 2013, and Nov 11, 2014, 54 who received rivaroxaban and 56 who received warfarin were assessed. At day 42, ETP was higher in the rivaroxaban than in the warfarin group (geometric mean 1086 nmol/L per min, 95% CI 957–1233 *vs* 548, 484–621, treatment effect 2·0, 95% CI 1·7–2·4, p<0·0001). Peak thrombin generation was lower in the rivaroxaban group (56 nmol/L, 95% CI 47–66 *vs* 86 nmol/L, 72–102, treatment effect 0·6, 95% CI 0·5–0·8, p=0·0006). No thrombosis or major bleeding were seen. Serious adverse events occurred in four patients in each group.

Interpretation ETP for rivaroxaban did not reach the non-inferiority threshold, but as there was no increase in thrombotic risk compared with standard-intensity warfarin, this drug could be an effective and safe alternative in patients with antiphospholipid syndrome and previous venous thromboembolism.

# SAPL et AOD

## 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]

| 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* |
| **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) |
| **Medications at time of randomization, n (%)** | | |
| Hydroxychloroquine | 15 (25) | 23 (38) |
| Corticosteroids | 11 (19) | 13 (21) |
| Other immunosuppressive drugs | 17 (29) | 21 (34) |
| Aspirin | 11 (19) | 10 (16) |
| Statins | 7 (12) | 10 (16) |

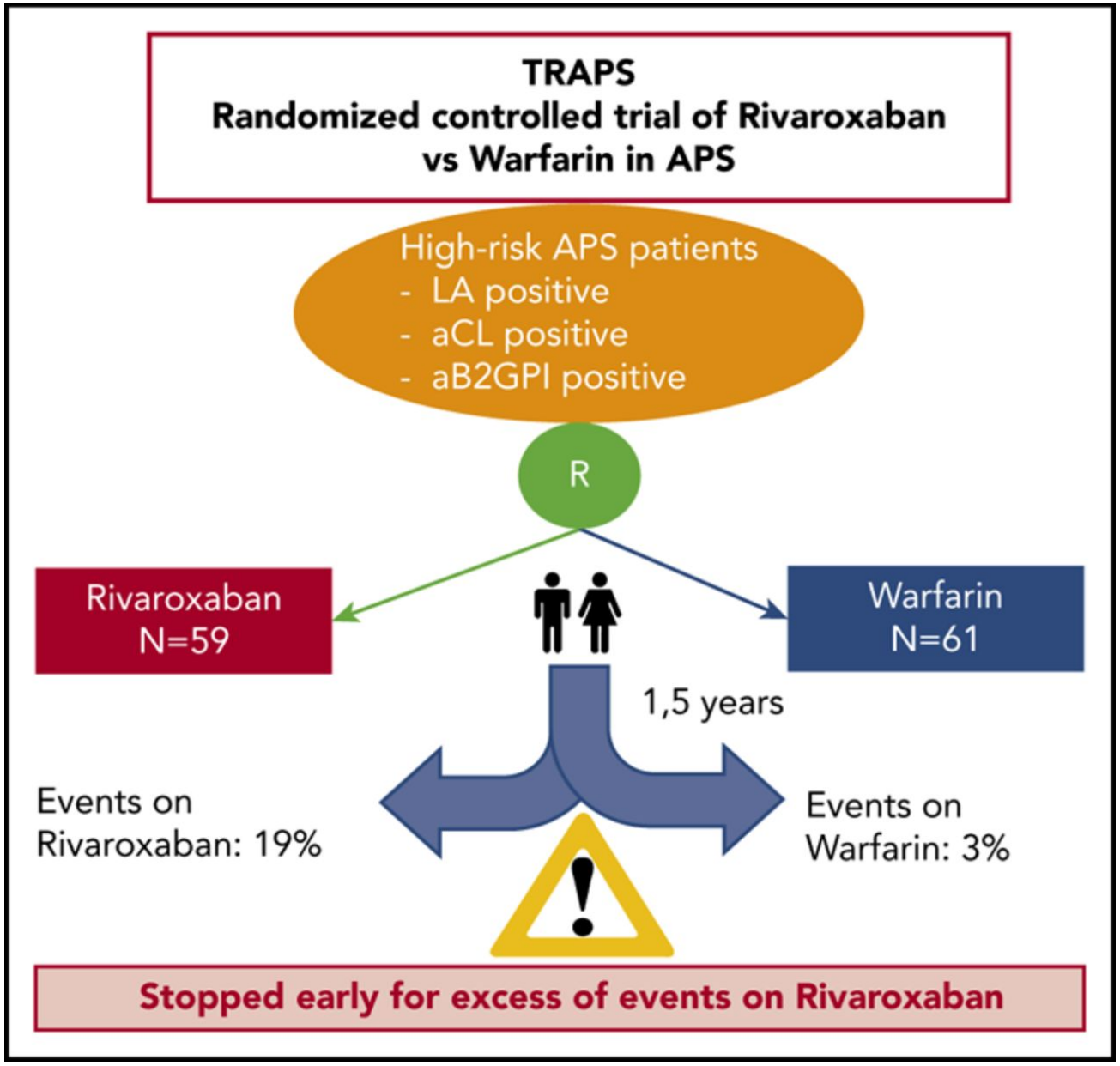
*Pengo et al , Blood 2018*

# SAPL et AOD

| 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**<br>Ischemic stroke<br>Myocardial infarction | 7 (12)<br>4 (7)<br>3 (5) | 0<br>0<br>0 | — | — | 7 (12)<br>4 (7)<br>3 (5) | 0<br>0<br>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 | — | — |

*Pengo et al , Blood 2018*

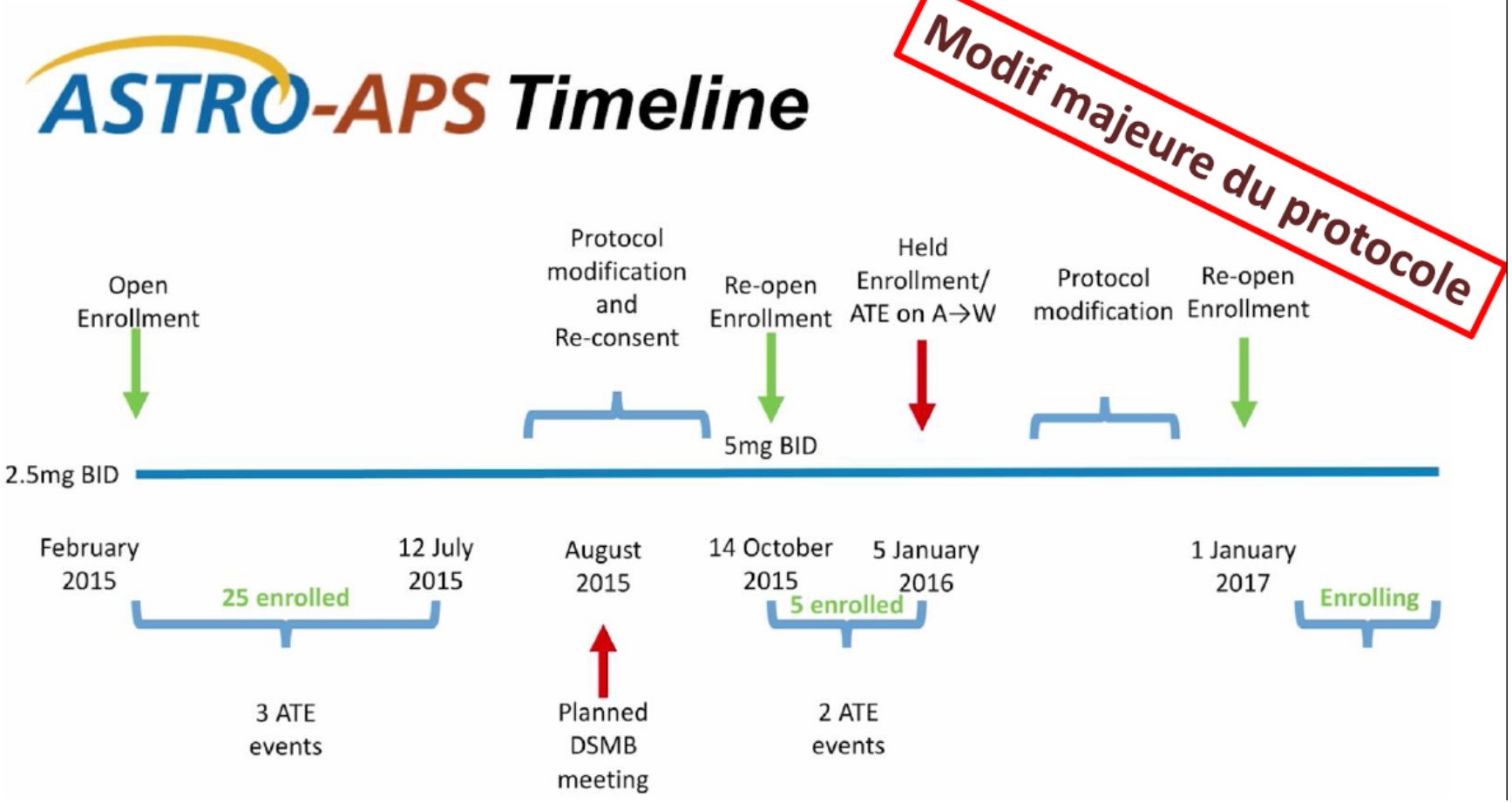
# SAPL et AOD




*Pengo et al, Blood 2018*

# Etude ASTRO APS

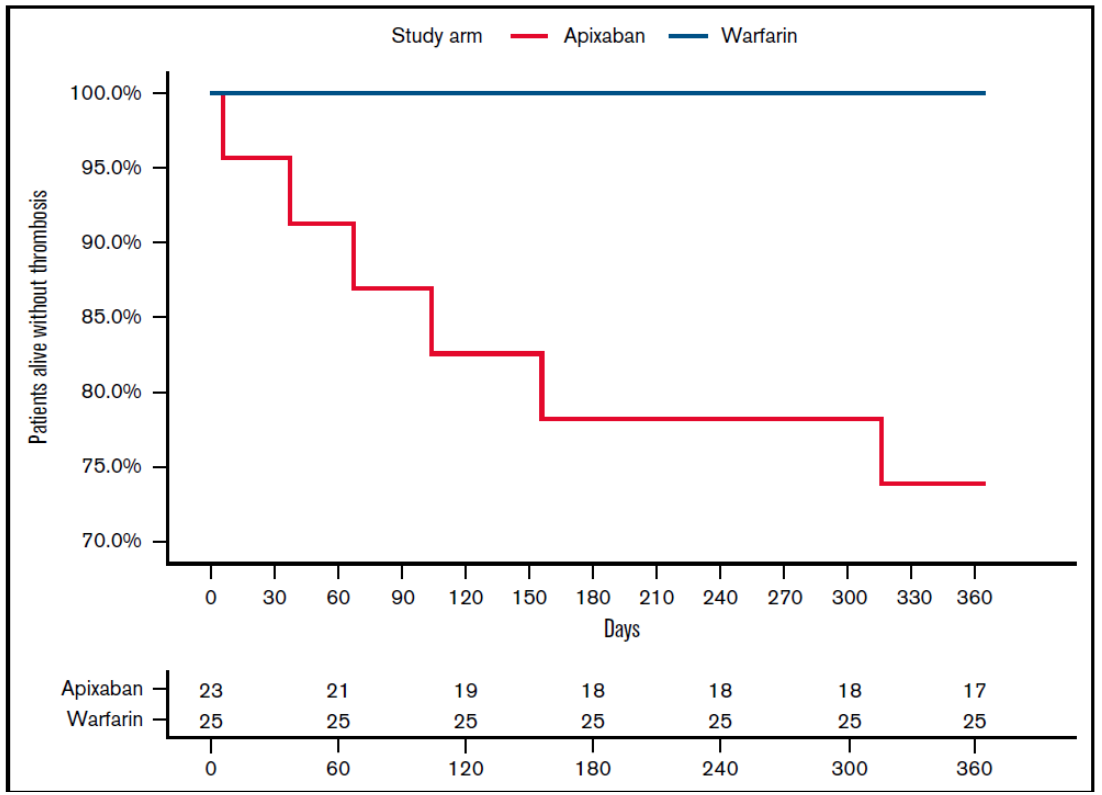
**Etude randomisée en ouvert comparant AVK vs. Apixaban 5 x2/j en prévention secondaire des thromboses chez des patients atteints de SAPL (n=200)**




48 PATIENTS 23 apixaban et 25 Warfarin

**Table 2. Details for each participant that experienced a thrombotic or major bleed event during the study**

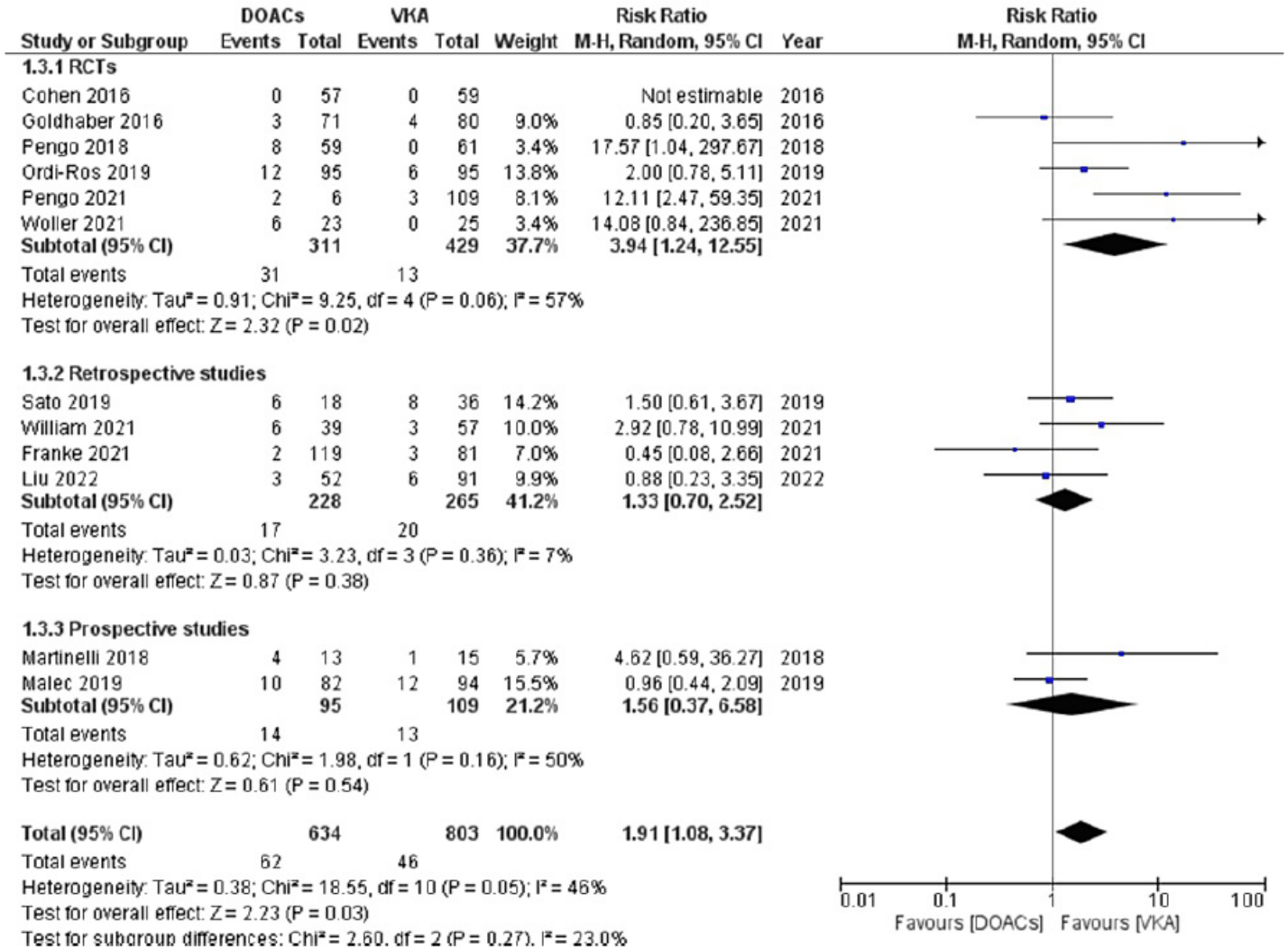
| ID | Age | Sex | BMI | Treatment | History | Positivity level* | Type | Event type | Days to event |
|---|---|---|---|---|---|---|---|---|---|
| 24 | 40 | Female | 39.3 | Apixaban | Stroke, DVT, PE, pregnancy loss | Single | Likely | Stroke | 156 |
| 16 | 43 | Female | 36.9 | Apixaban | DVT | Triple | Definite | Stroke | 67 |
| 12 | 47 | Female | 19.4 | Apixaban | Stroke, TIA, DVT, pregnancy loss | Double | Likely | Stroke | 37 |
| 2 | 51 | Female | 25.5 | Apixaban | Stroke, other arterial thrombosis, DVT, PE | Triple | Definite | Stroke | 316 |
| 32 | 66 | Male | 39.3 | Apixaban | DVT | N/A | Historical | Stroke | 104 |
| 3 | 69 | Female | 23.2 | Apixaban | Stroke, pregnancy loss | N/A | Historical | Stroke | 6 |
| 27 | 62 | Female | 30.5 | Warfarin | Stroke, DVT, PE | N/A | Historical | Major bleed† | 319 |




Woller *et al.*, Blood Advances 2022

# Efficacy and Safety of Direct Oral Anticoagulants in Patients With Antiphospholipid Syndrome: A Systematic Review and Meta-Analysis

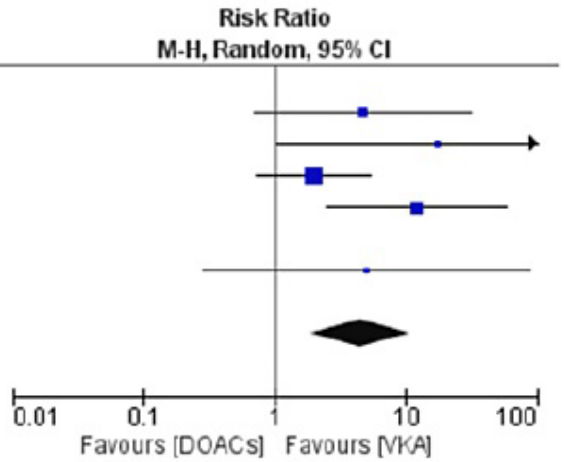
Keerthi Gullapalli [1], Rohan M. Prasad [1], Abdullah Al-abcha [1], Zahin Hussain [2], Aseel Alsouqi [3], Osama Mosalem [1], Borys Hrinczenko [4]



**A**

| Study or Subgroup | DOACs Events | DOACs Total | VKA Events | VKA Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Cohen 2016 | 0 | 7 | 0 | 12 | | Not estimable | 2016 |
| Martinelli 2018 | 4 | 6 | 1 | 7 | 17.2% | 4.67 [0.70, 31.22] | 2018 |
| Pengo 2018 | 8 | 59 | 0 | 61 | 8.5% | 17.57 [1.04, 297.67] | 2018 |
| Ordi-Ros 2019 | 10 | 58 | 5 | 57 | 43.2% | 1.97 [0.72, 5.39] | 2019 |
| Pengo 2021 | 2 | 6 | 3 | 109 | 22.9% | 12.11 [2.47, 59.35] | 2021 |
| Franke 2021 | 0 | 3 | 0 | 4 | | Not estimable | 2021 |
| Woller 2021 | 2 | 7 | 0 | 7 | 8.3% | 5.00 [0.28, 88.53] | 2021 |
| **Total (95% CI)** | | **146** | | **257** | **100.0%** | **4.50 [1.91, 10.63]** | |
| Total events | 26 | | 9 | | | | |

Heterogeneity: Tau² = 0.18; Chi² = 4.87, df = 4 (P = 0.30); I² = 18%
Test for overall effect: Z = 3.43 (P = 0.0006)

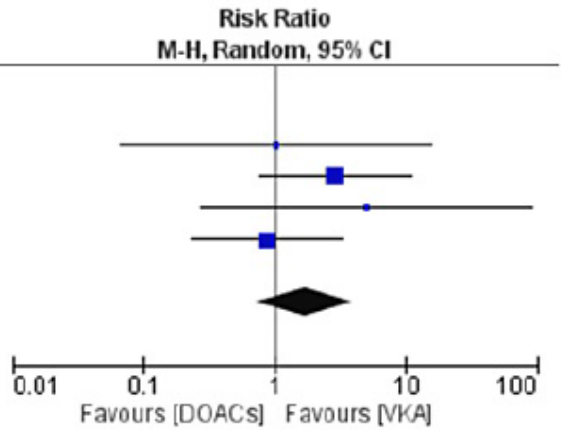



Triple positif

**B**

| Study or Subgroup | DOACs Events | DOACs Total | VKA Events | VKA Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Cohen 2016 | 0 | 50 | 0 | 47 | | Not estimable | 2016 |
| Martinelli 2018 | 0 | 7 | 0 | 8 | | Not estimable | 2018 |
| Ordi-Ros 2019 | 1 | 37 | 1 | 38 | 9.7% | 1.03 [0.07, 15.82] | 2019 |
| William 2021 | 6 | 39 | 3 | 57 | 41.4% | 2.92 [0.78, 10.99] | 2021 |
| Woller 2021 | 2 | 9 | 0 | 9 | 8.6% | 5.00 [0.27, 91.52] | 2021 |
| Liu 2022 | 3 | 52 | 6 | 91 | 40.3% | 0.88 [0.23, 3.35] | 2022 |
| **Total (95% CI)** | | **194** | | **250** | **100.0%** | **1.70 [0.73, 3.99]** | |
| Total events | 12 | | 10 | | | | |

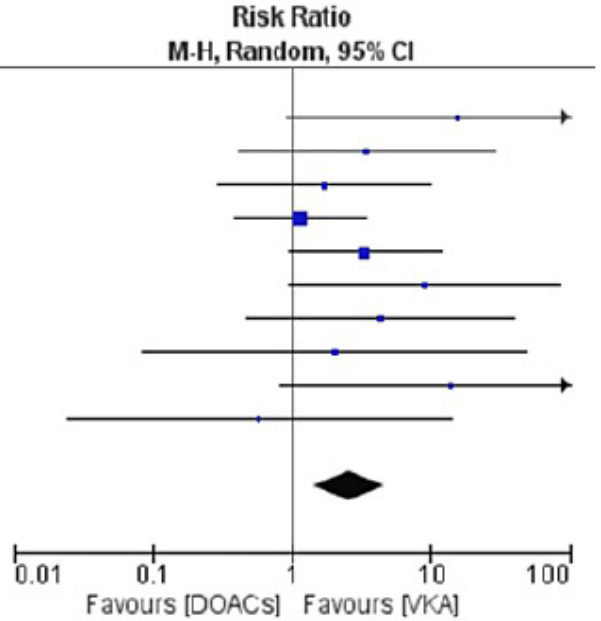
Heterogeneity: Tau² = 0.00; Chi² = 2.24, df = 3 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)




Double ou simple positif

| Study or Subgroup | DOACs Events | DOACs Total | VKA Events | VKA Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Cohen 2016 | 0 | 57 | 0 | 59 | | Not estimable | 2016 |
| Pengo 2018 | 7 | 59 | 0 | 61 | 4.3% | 15.50 [0.91, 265.46] | 2018 |
| Martinelli 2018 | 3 | 13 | 1 | 15 | 7.7% | 3.46 [0.41, 29.36] | 2018 |
| Malec 2019 | 3 | 82 | 2 | 94 | 11.2% | 1.72 [0.29, 10.04] | 2019 |
| Sato 2019 | 4 | 18 | 7 | 36 | 29.4% | 1.14 [0.38, 3.40] | 2019 |
| Ordi-Ros 2019 | 10 | 95 | 3 | 95 | 22.1% | 3.33 [0.95, 11.73] | 2019 |
| Pengo 2021 | 1 | 6 | 2 | 109 | 6.9% | 9.08 [0.95, 86.64] | 2021 |
| William 2021 | 3 | 39 | 1 | 57 | 7.1% | 4.38 [0.47, 40.62] | 2021 |
| Franke 2021 | 1 | 119 | 0 | 81 | 3.4% | 2.05 [0.08, 49.70] | 2021 |
| Woller 2021 | 6 | 23 | 0 | 25 | 4.4% | 14.08 [0.84, 236.85] | 2021 |
| Liu 2022 | 0 | 52 | 1 | 91 | 3.5% | 0.58 [0.02, 13.95] | 2022 |
| **Total (95% CI)** | | **563** | | **723** | **100.0%** | **2.61 [1.44, 4.71]** | |
| Total events | 38 | | 17 | | | | |

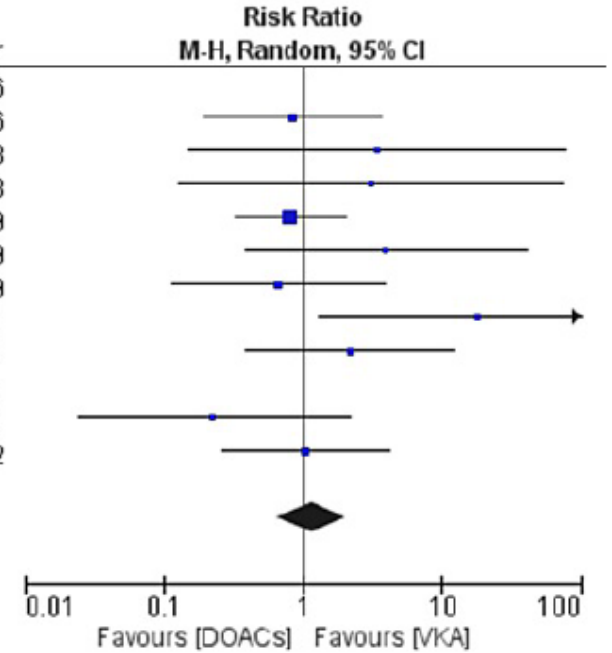
Heterogeneity: Tau² = 0.00; Chi² = 8.07, df = 9 (P = 0.53); I² = 0%
Test for overall effect: Z = 3.18 (P = 0.001)




Récidive artérielle

| Study or Subgroup | DOACs Events | DOACs Total | VKA Events | VKA Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Cohen 2016 | 0 | 57 | 0 | 59 | | Not estimable | 2016 |
| Goldhaber 2016 | 3 | 71 | 4 | 80 | 13.6% | 0.85 [0.20, 3.65] | 2016 |
| Martinelli 2018 | 1 | 13 | 0 | 15 | 3.3% | 3.43 [0.15, 77.58] | 2018 |
| Pengo 2018 | 1 | 59 | 0 | 61 | 3.2% | 3.10 [0.13, 74.61] | 2018 |
| Malec 2019 | 7 | 82 | 10 | 94 | 29.2% | 0.80 [0.32, 2.01] | 2019 |
| Sato 2019 | 2 | 18 | 1 | 36 | 5.7% | 4.00 [0.39, 41.23] | 2019 |
| Ordi-Ros 2019 | 2 | 95 | 3 | 95 | 9.7% | 0.67 [0.11, 3.90] | 2019 |
| Pengo 2021 | 1 | 6 | 1 | 109 | 4.5% | 18.17 [1.29, 256.40] | 2021 |
| William 2021 | 3 | 39 | 2 | 57 | 9.9% | 2.19 [0.38, 12.52] | 2021 |
| Woller 2021 | 0 | 23 | 0 | 25 | | Not estimable | 2021 |
| Franke 2021 | 1 | 119 | 3 | 81 | 6.2% | 0.23 [0.02, 2.14] | 2021 |
| Liu 2022 | 3 | 52 | 5 | 91 | 14.8% | 1.05 [0.26, 4.22] | 2022 |
| **Total (95% CI)** | | **634** | | **803** | **100.0%** | **1.17 [0.66, 2.07]** | |
| Total events | 24 | | 29 | | | | |

Heterogeneity: Tau² = 0.07; Chi² = 9.82, df = 9 (P = 0.36); I² = 8%
Test for overall effect: Z = 0.53 (P = 0.60)




Récidive veineuse

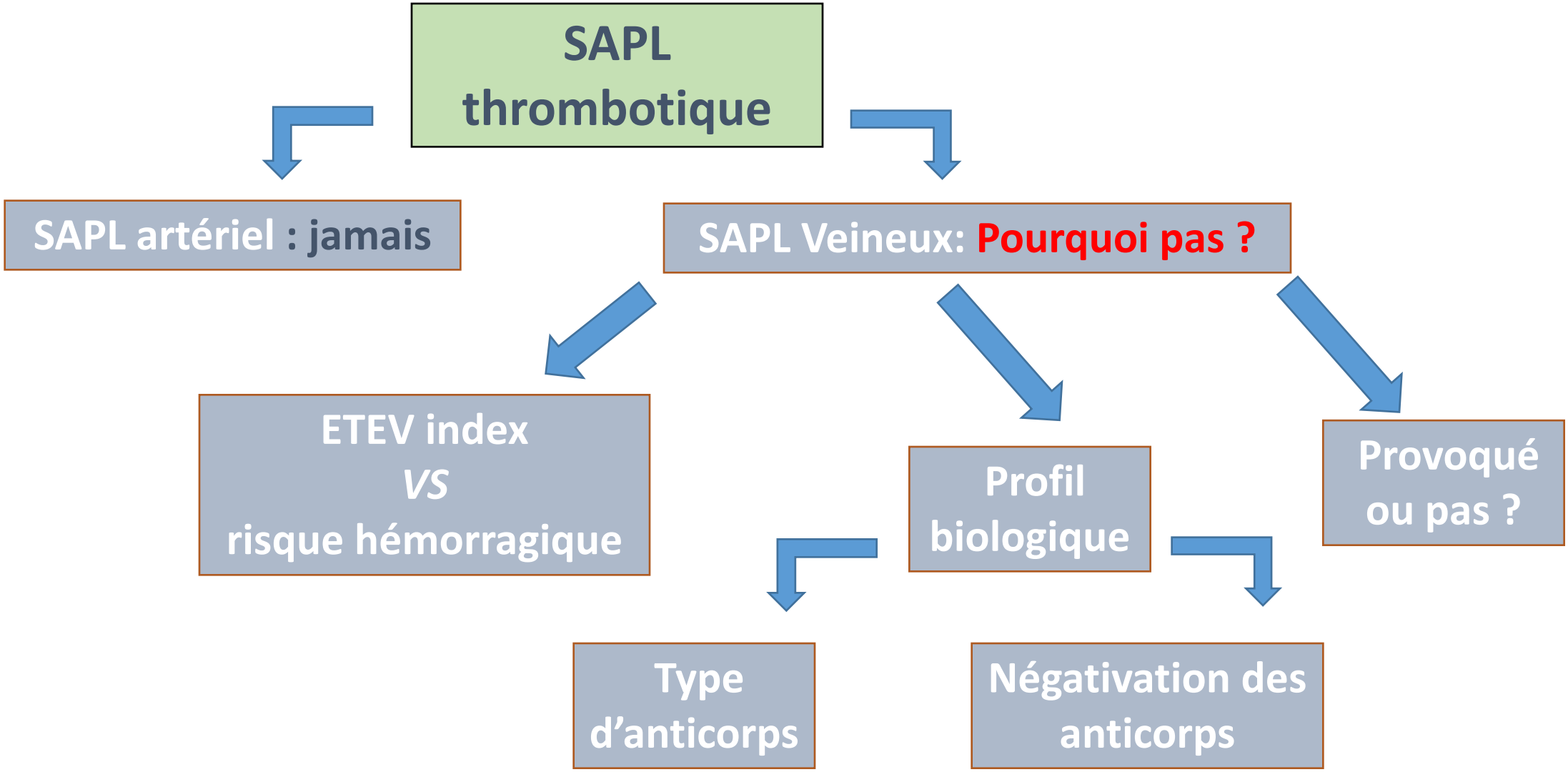
# Recommandations EULAR 2019

| Secondary thromboprophylaxis in APS | |
|---|---|
| 4. In patients with definite APS and first venous thrombosis:<br>A. Treatment with VKA with a target INR 2–3 is recommended (1b/B). | 9.9 (0.3) |
| B. Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events (1b/B). 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) (5/D). | 9.1 (1.3) |
| C. In patients with unprovoked first venous thrombosis, anticoagulation should be continued long term (2b/B). | 9.9 (0.3) |
| D. In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines (5/D). Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence (5/D). | 8.9 (1.4) |
| 5. In patients with definite APS and recurrent venous thrombosis despite treatment with VKA with target INR of 2–3:<br>A. Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing, should be considered (5/D). | 9.6 (0.8) |
| 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 (4–5/D). | 9.4 (0.7) |

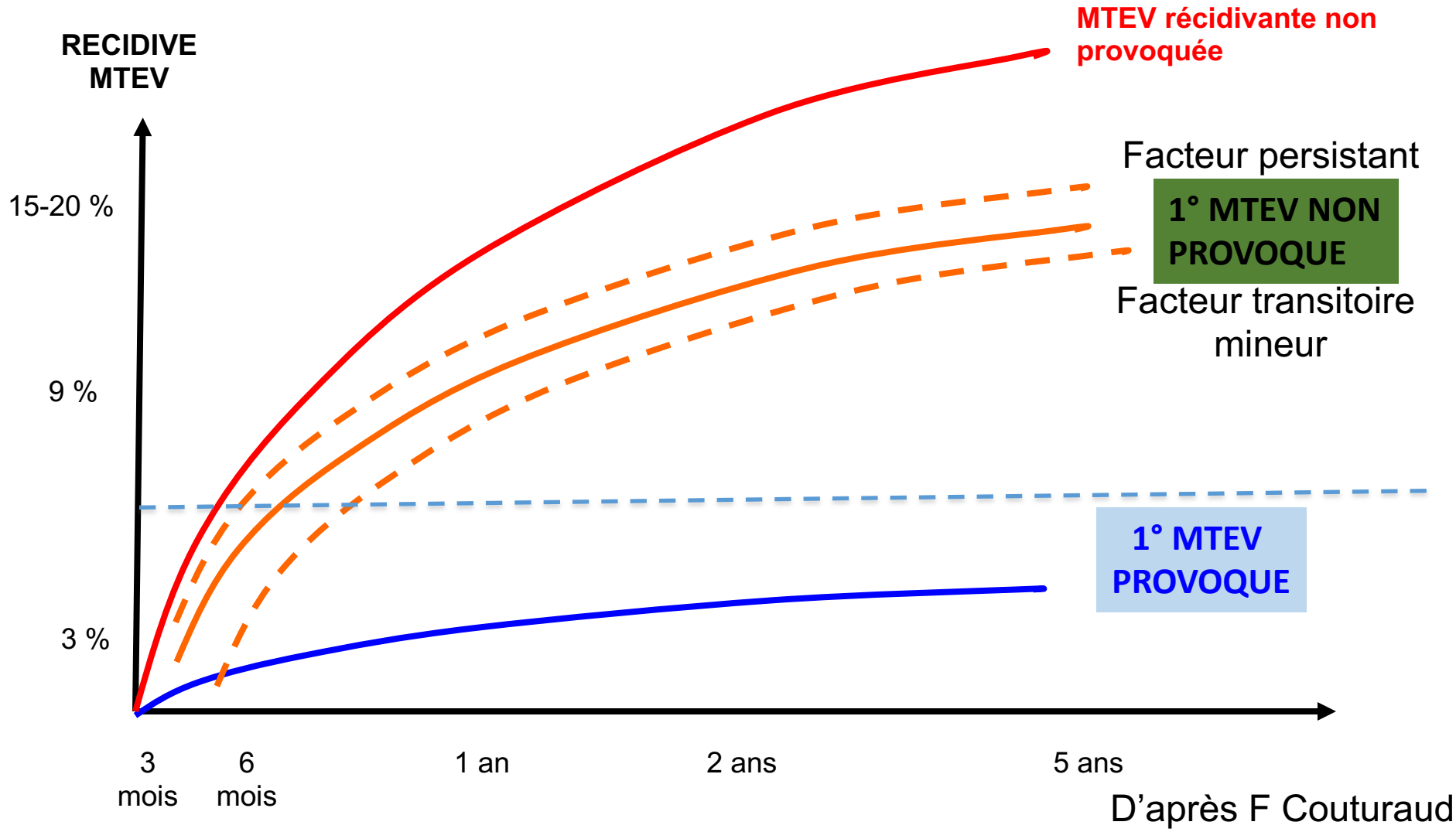
Recos EULAR APS 2019

# Quelle durée de traitement :
# à vie ?
# Ou y a-t-il une place pour une médecine personnalisée?

# Prévention secondaire au cours du SAPL : traitement à vie ???



# SAPL et risque de récidive



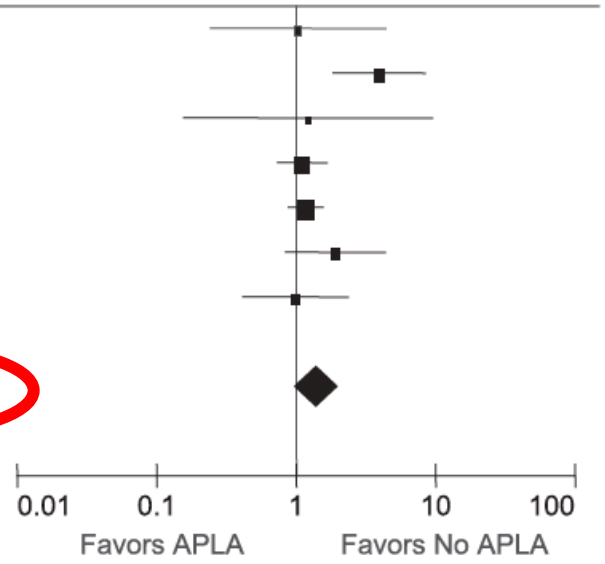

*Levine, TH 1995, BTS, BMJ 1992, Schulman, NEJM 1995, Kearon, NEJM 1999, Agnelli,NEJM 2004*

# SAPL et risque de récidive

| Study or Subgroup | APLA Events | APLA Total | No APLA Events | No APLA Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Ginsberg 1995 | 2 | 11 | 6 | 34 | 5.1% | 1.03 [0.24, 4.39] |
| Kearon 1999 | 4 | 6 | 12 | 71 | 13.5% | 3.94 [1.83, 8.48] |
| Kearon 2004 | 1 | 17 | 6 | 124 | 2.7% | 1.22 [0.16, 9.49] |
| Rodger 2008 | 56 | 384 | 31 | 235 | 25.0% | 1.11 [0.74, 1.66] |
| Schulman 2006 | 38 | 116 | 194 | 694 | 30.1% | 1.17 [0.88, 1.56] |
| Taliani 2009 | 3 | 6 | 76 | 291 | 12.3% | 1.91 [0.84, 4.36] |
| Wahlander 2005 | 5 | 48 | 49 | 465 | 11.3% | 0.99 [0.41, 2.36] |
| **Total (95% CI)** | | **588** | | **1914** | **100.0%** | **1.41 [0.99, 2.00]** |
| Total events | 109 | | 374 | | | |

Heterogeneity: Tau² = 0.08; Chi² = 10.96, df = 6 (P = 0.09); I² = 45%

Test for overall effect: Z = 1.92 (P = 0.06)




Risque de récidive en présence d'un SAPL est de l'ordre de 13% par an

*Garcia, BLOOD 2015*

# Evènement thrombotique index

## EP *versus* TVP proximale

**Fréquence d'une récidive similaire**
**Létalité de la récidive différente**

| | | Présentation clinique de la récidive | | |
|---|---|---|---|---|
| Phénotype initial | Phénotype récidive | LAFIT | WODIT PE-DVT | PADIS EP-TVP |
| **EP** | ***EP*** | **75%** | **60%** | **78%** |
| | ***Non provoquée*** | **100%** | **85%** | **87%** |
| | ***Létalité*** | **15%** | **10%** | **8%** |
| **TVP** | ***TVP*** | **90%** | **81%** | 90% |
| | ***Non provoquée*** | **100%** | **100%** | 90% |
| | ***Létalité*** | **0%** | **0%** | 0% |

*Kearon 1999; Agnelli 2001; Agnelli 2003; Couturaud 2015*

# Dans la vraie vie ça donne quoi ???

**Femme 35 ans, traitée par AVK pour 1 EP non grave ayant conduit au diagnostic de SAPL**

**EP initiale => récidive comme EP dans 80% => mortalité 10%**

***EP et SAPL :*** *Incidence annuelle d'une récidive* ***= 13%***

*Incidence annuelle d'une récidive mortelle* = (13%*80%*10%) + (13%*20%*2%)= ***1,6%***

**TVP initiale => récidive comme TVP dans 70-80% => mortalité 2%**

***TVP et SAPL :*** *Incidence annuelle d'une récidive* ***= 13%***

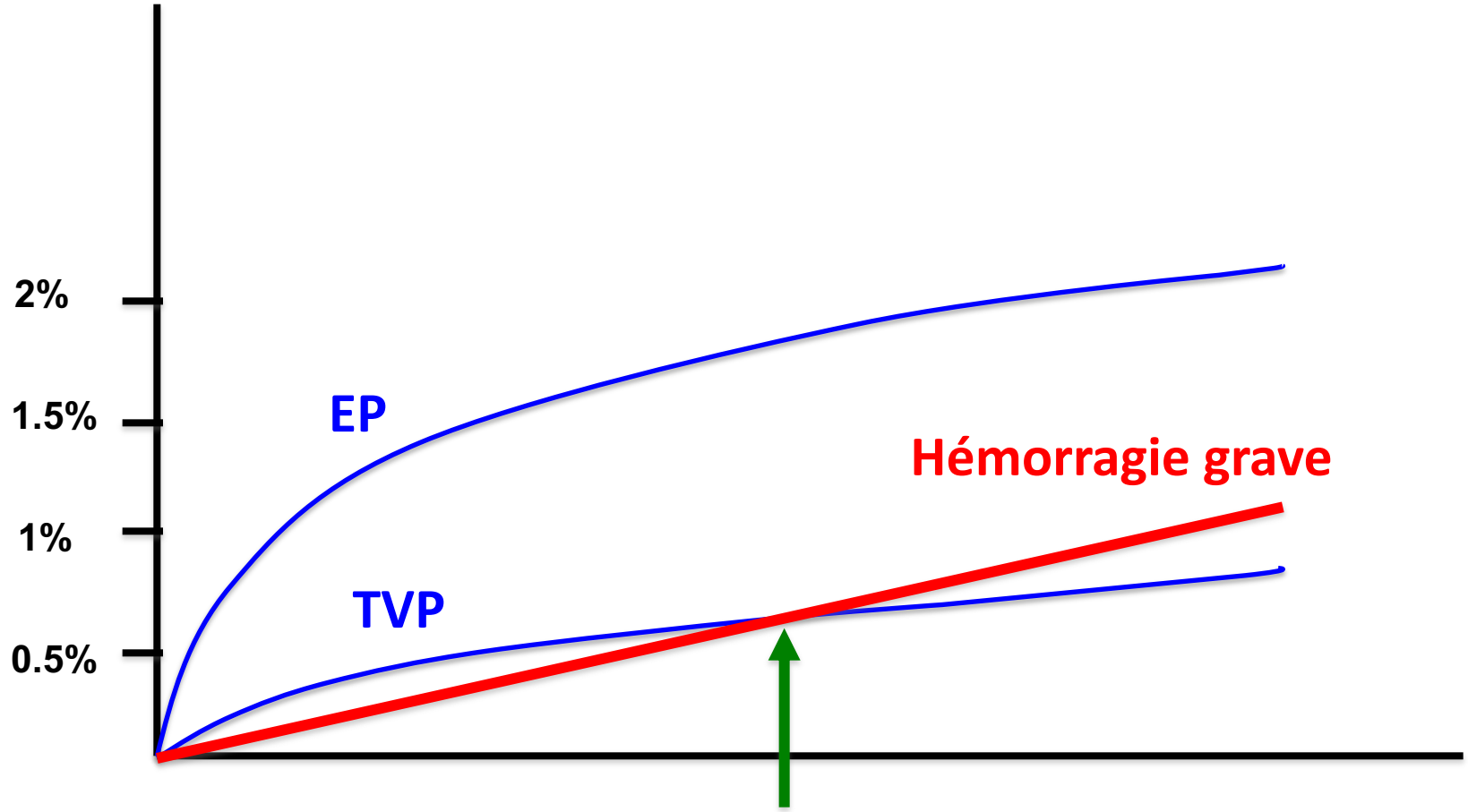
*Incidence annuelle d'une récidive mortelle* = (13%*70%*2%) + (13%*30%*10%)= ***0,4 %***

Incidence annuelle d'un saignement mortel( AVK)

**≥ 0.5 %/an**

*Beyth, 1998, Palareti, 1996, Landefeld, 1993, Kuijer 1999, White 1999, Margaglione 2000, HASBLED score 2011*

# Dans la vraie vie ça donne quoi ???




**Croisement à 1 an, 2 ans, plus ?**

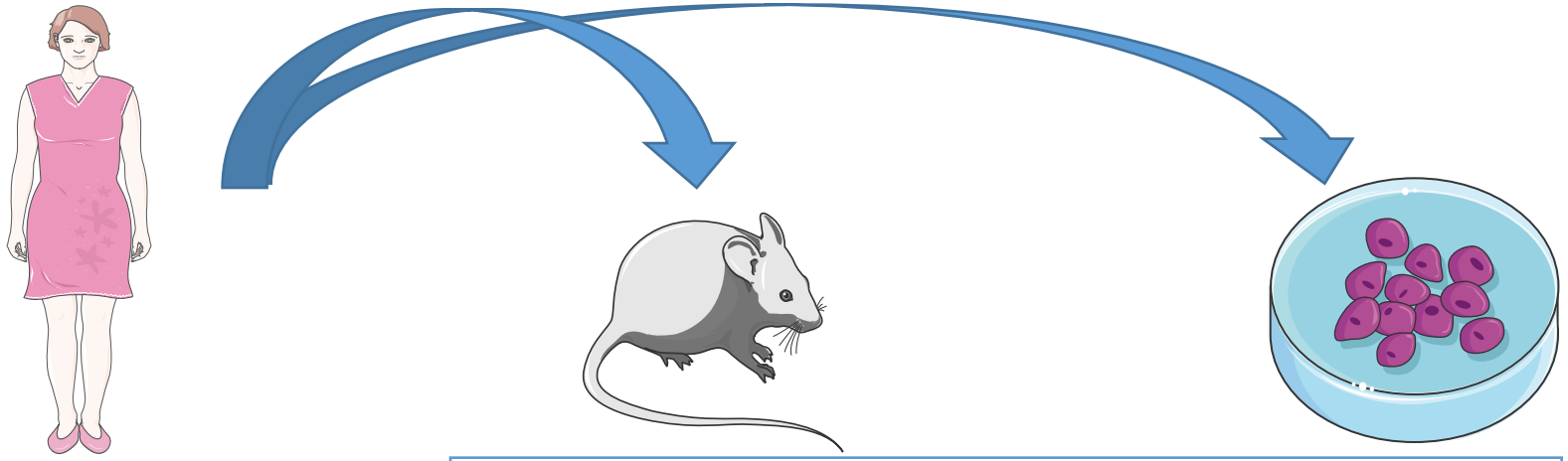
*Le Mao R, Tromeur C, Couturaud F. Press Med 2017*

# Recommandations EULAR 2019

| | |
|---|---|
| Secondary thromboprophylaxis in APS | |
| 4. In patients with definite APS and first venous thrombosis:<br>A. Treatment with VKA with a target INR 2–3 is recommended (1b/B). | 9.9 (0.3) |
| B. Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events (1b/B). 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) (5/D). | 9.1 (1.3) |
| C. In patients with unprovoked first venous thrombosis, anticoagulation should be continued long term (2b/B). | 9.9 (0.3) |
| D. In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines (5/D). Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence (5/D). | 8.9 (1.4) |
| 5. In patients with definite APS and recurrent venous thrombosis despite treatment with VKA with target INR of 2–3:<br>A. Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing, should be considered (5/D). | 9.6 (0.8) |
| 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 (4–5/D). | 9.4 (0.7) |

Recos EULAR APS 2019

# La physiopathologie simplifiée
# Du SAPL




**Auto-anticoprs pathogènes et si disparition de ces anticorps , ça donne quoi ???**

Benhamou et al. *Vascular Pharmacology* 2015

# SAPL et négativation des AC

## Anticoagulation withdrawal in antiphospholipid syndrome: a retrospective matched-control study

CM Yelnik[1,2], G Urbanski[2], E Drumez[3], C Caron[4], H Maillard[2], S Morell-Dubois[2], S Dubucquoi[1,5,6], D Launay[1,2,5], E Hachulla[1,2,5], PY Hatron[1,2], A Duhamel[3] and M Lambert[1,2,5]

**Table 1** Baseline characteristics of the study population

| *Characteristics* | *Cases* n = *28* | *Controls* n = *28* |
|---|---|---|
| Women | 22 (78.6) | 22 (78.6) |
| Missing data | 0 | 0 |
| Age, years median (IQR) | 32 (23–50) | 33 (23–50) |
| Missing data | 0 | 0 |
| Clinic APS phenotype | | |
| Arterial thrombosis | 3 (10.7) | 3 (10.7) |
| Venous thrombosis | 24 (85.7) | 24 (85.7) |
| CAPS | 1 (3.6) | 1 (3.6) |
| Triple aPL positivity | 9 (33.4) | 8 (29.6) |
| aPL disappearance | 8 (29.6) | 9 (33.4) |
| Missing data for completed aPL profile | 1 | 1 |

# SAPL et négativation des AC

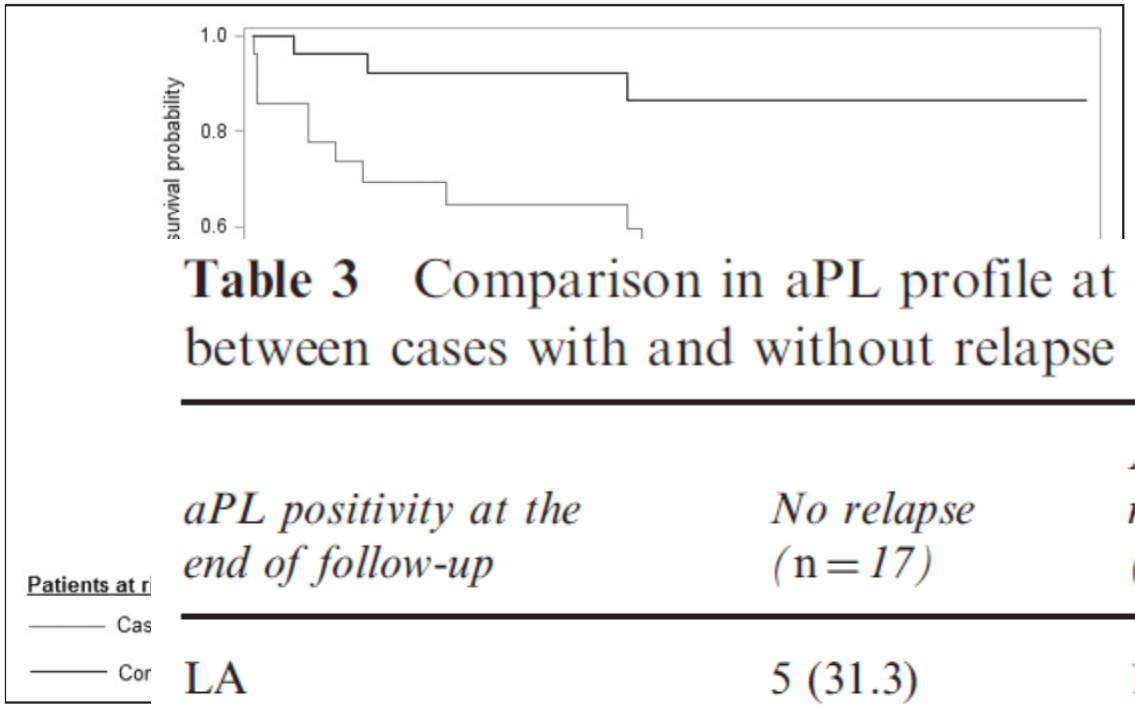



**Table 3** Comparison in aPL profile at end of follow-up between cases with and without relapse

| *aPL positivity at the end of follow-up* | *No relapse (n = 17)* | *At least one relapse (n = 13)* | p *value* |
|---|---|---|---|
| LA | 5 (31.3) | 11 (84.6) | *0.004* |
| aCL | 4 (25.0) | 9 (69.2) | *0.017* |
| Anti-β2GP1 positivity | 3 (18.8) | 9 (69.2) | *0.006* |
| Single aPL positivity | 5 (31.3) | 3 (23.1) | *0.70* |
| Triple aPL positivity | 2 (12.5) | 8 (61.5) | *0.016* |
| aPL disappearance | 7 (43.8) | 1 (7.7) | *0.044* |

**Pas d'anticorps pas de récidives ???**

# Et l'avenir dans le SAPL ……

**Box 2 Research agenda**

**Risk stratification.**

- Better definition of high-risk and low-risk aPL profile. Better delineation of the risk associated with different aPL profiles to allow improved classification of patients in research studies.

**Secondary thrombosis prevention.**

- Controlled studies of the efficacy and safety of treatment with VKA with target INR of 3–4 versus combination treatment of VKA with target INR of 2–3 and LDA for patients with a history of first arterial thrombosis.
- Duration of VKA in provoked first venous thrombosis.
- Controlled studies of the efficacy of therapy of VKA alone versus VKA plus HCQ for patients with a history of first arterial thrombosis.
- Controlled studies of the efficacy and safety of targeted therapies (eg, B cell depletion therapy, complement inhibitors, or mammalian target of rapamycin (mTOR) inhibitors) in recurrent arterial thrombotic events despite treatment with VKA with a target INR of 3–4.
- Adjunctive treatment for recurrent arterial thrombosis: HCQ, statins or vitamin D. Evaluation of the role of platelet inhibitors (other than LDA), for example, ADP receptor inhibitors, adenosine reuptake inhibitors and others.
- Discontinuation of VKA treatment in patients who became negative for aPL in repeated measurements.

**Et non provoquée ???**

Recos EULAR APS 2019

# Conclusion

**SAPL en 2023:**

Le traitement de référence reste les AVK mais une place pour les AOD est à définir

Les enjeux futurs :

Amélioration des critères de Classifications cliniques et Biologiques

Modèle de prédiction du risque de récidive : modulation de la durée de traitement

La thérapeutique doit devenir multimodale et personnalisée : apport de l'immunomodulation (cf Behcet), de la vasculoprotection

# Pour en savoir plus …