



Antiphospholipid Syndrome Update 2025



Tarinee Rungjirajittranon MD.
Division of Hematology, Department of Medicine
Faculty of Medicine Siriraj Hospital

SCOPE OF TALK

01 **Diagnosis
of APS**

02 **Reproduction
and
positive aPL/APS**

03 **Treatment
of APS**





SCOPE OF TALK

- 1 2023 ACR/EULAR APS classification criteria and clinical implications**
- 2 Antiphospholipid antibodies/APS and reproductive issues**
- 3 Role of DOACs in thrombotic APS**



SCOPE OF TALK

- 1 2023 ACR/EULAR APS classification criteria and clinical implications**
- 2 Antiphospholipid antibodies/APS and reproductive issues**
- 3 Role of DOACs in thrombotic APS**

2023 ACR/EULAR APS CLASSIFICATION CRITERIA

At least one clinical criterion + A positive aPL test

Macrovascular (VTE) With a high-risk VTE profile Without a high-risk VTE profile	Macrovascular (arterial thrombosis) 1 With a high-risk CVD profile 2 3 Without high-risk CVD profile 4
Microvascular Suspected livedo racemosa, livedoid vasculopathy, acute/chronic aPL-nephropathy, pulmonary hemorrhage Established livedoid vasculopathy, acute/chronic aPL-nephropathy, pulmonary hemorrhage, myocardial disease, adrenal hemorrhage	Obstetric 2 ≥ 3 consecutive pre-fatal (<10w) and/or early fetal (10w 0d-15w 6 d) deaths 1 Fetal death (16W 0d-33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features 1 PEC with severe features (<34W od) or PI with severe features (<34W od) with/without fetal death 3 PEC with severe features (<34W od) and PI with severe features (<34W od) with/without fetal death 4
Cardiac valve Thickening Vegetation	Hematology 2 Thrombocytopenia 2 4 (lowest $20-130 \times 10^9/L$)
Lupus anticoagulant Positive lupus anticoagulant (single-one time) Positive lupus anticoagulant (persistent)	aPL test by solid phase assay (ELISA) persistent 1 Moderate or high positive IgM (aCL and/or $a\beta_2GPI$) 1 5 Moderate positive IgG (aCL and/or $a\beta_2GPI$) 4 High positive IgG (aCL or $a\beta_2GPI$) 5 High positive IgG (aCL and $a\beta_2GPI$) 7

At least 3 points from clinical domains AND At least 3 points from laboratory domains

2023 ACR/EULAR APS CLASSIFICATION CRITERIA

At least one clinical criterion + A positive aPL test

Macrovascular (VTE) With a high-risk VTE profile Without a high-risk VTE profile	Macrovascular (arterial thrombosis) 1 With a high-risk CVD profile 2 3 Without high-risk CVD profile 4
Microvascular Suspected livedo racemosa, livedoid vasculopathy, acute/chronic aPL-nephropathy, pulmonary hemorrhage Established livedoid vasculopathy, acute/chronic aPL-nephropathy, pulmonary hemorrhage, myocardial disease, adrenal hemorrhage	Obstetric 2 ≥ 3 consecutive pre-fatal (<10w) and/or early fetal (10w 0d-15w 6 d) deaths 1 Fetal death (16W 0d-33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features 1 PEC with severe features (<34W od) or PI with severe features (<34W od) with/without fetal death 3 PEC with severe features (<34W od) and PI with severe features (<34W od) with/without fetal death 4
Cardiac valve Thickening Vegetation	Hematology 2 Thrombocytopenia 2 4 (lowest $20-130 \times 10^9/L$)
Lupus anticoagulant Positive lupus anticoagulant (single-one time) Positive lupus anticoagulant (persistent)	aPL test by solid phase assay (ELISA) persistent 1 Moderate or high positive IgM (aCL and/or $a\beta_2GPI$) 1 5 Moderate positive IgG (aCL and/or $a\beta_2GPI$) 4 High positive IgG (aCL or $a\beta_2GPI$) 5 High positive IgG (aCL and $a\beta_2GPI$) 7

At least 3 points from clinical domains AND At least 3 points from laboratory domains

SUMMARY OF MAIN DIFFERENCES

2006 Revised Sapporo criteria

- Broader set of clinical manifestations can be applied to diagnosis of APS
- Additional methodologies to ELISA are available.
- Potential use of 99th percentiles to define cutoff values.

2023 ACR/EULAR classification

- Clinical criteria restricted to certain clinical manifestations (with weightings).
- Include non-criteria manifestations (microvascular thrombosis, thrombocytopenia, cardiac valve involvement)
- Solid phase aPL as measured by ELISA, with grading as moderate (40-79 units) or high levels (≥ 80 units)
- LA positivity as per ISTH SSC guidance, and persistence not mandated

2023 ACR/EULAR classification criteria in existing research cohorts: an international study

Silvia G. Foddai ^{1,2,‡}, Massimo Radin ^{1,2,‡}, Irene Cecchi ^{1,2,‡}, Elena Rubini^{1,2},
Alice Barinotti^{1,2}, Paula Alba³, Carla Gimén Alonso³, Daniela Rossi^{1,2},
Dario Roccatello^{1,2,§}, Savino Sciascia ^{1,2,*,§}



N= 249

185 APS (64 carriers)

(55 VTE, 63 arterial thrombosis,
67 pregnancy morbidities)

Revised Sapporo criteria



N= 95 have APS

New classification criteria

90 patients (48.6%) did not meet
criteria due to high CVD risk,
pregnancy criteria



32/90 (25.5%)

**fulfilled new criteria after at
least 6 months follow-up**

-21 patients: OB manifestations
despite standard care
-11 patients: new thrombotic
events while treating with
warfarin

RESULTS FROM SIRIRAJ HOSPITAL

Confirmed APS
(Revised Sapporo criteria)

ACR/EULAR
criteria-met
(N = 74, 43.3%)

ACR/EULAR
criteria-unmet
(N = 97, 56.7%)

Causes of unmet requirements for new criteria

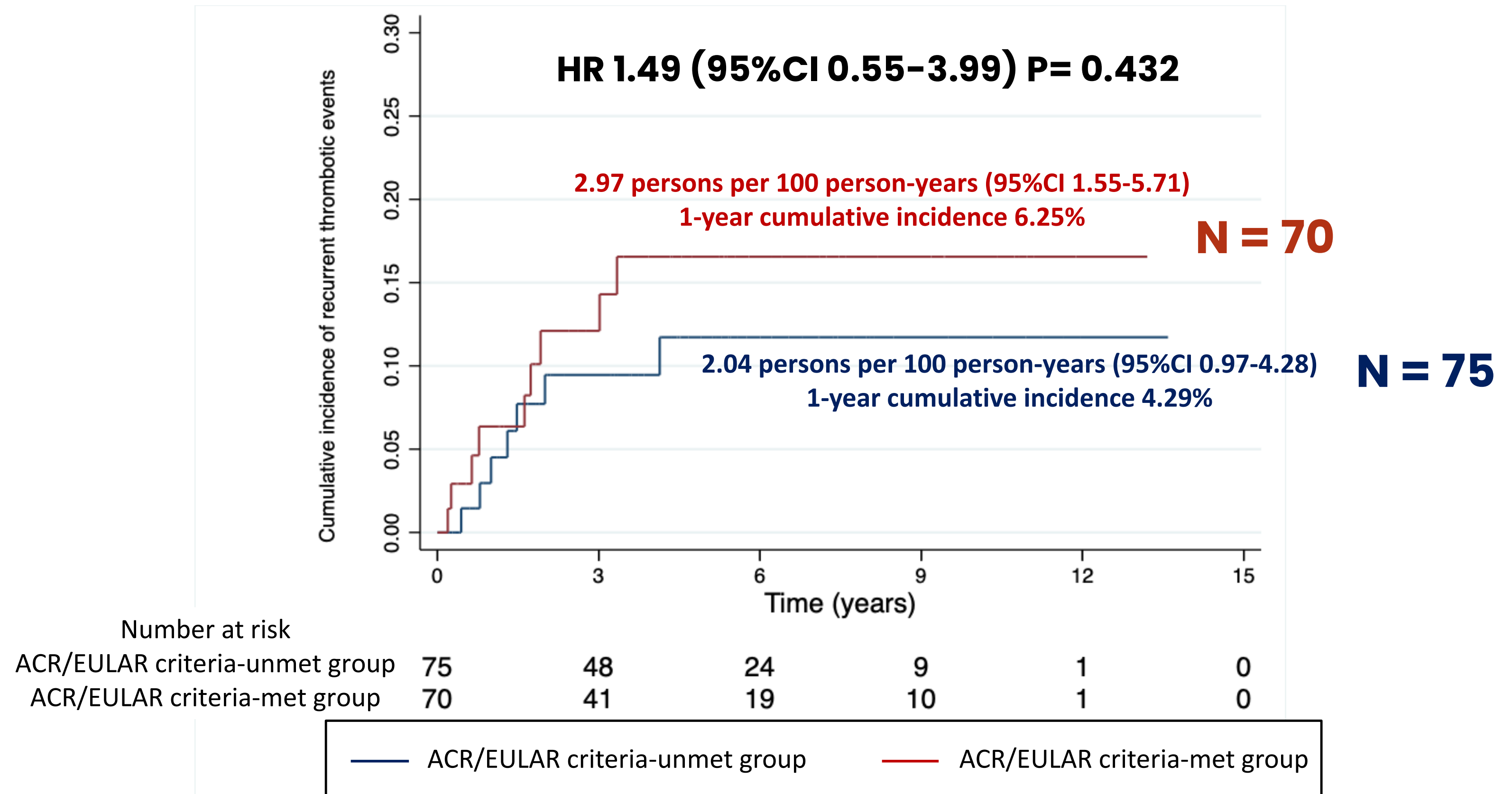
- Positive for IgM subtype (65.6%)
- Not fulfilled by obstetric APS criteria (18.8%)
- With high-risk VTE profile (11.5%)
- With high-risk CVD profile (4.1%)

N = 171 patients
(thrombotic APS 145, obstetric APS 26)

Only 4 obstetric APS patients met new criteria

RESULTS FROM SIRIRAJ HOSPITAL

Recurrent thrombotic events in thrombotic APS (N=145)





POINT OF CONSIDERATION

1

Patients not meeting classification criteria may still have APS

2

Diverse clinical manifestations should be recognized but properly attributed to APS

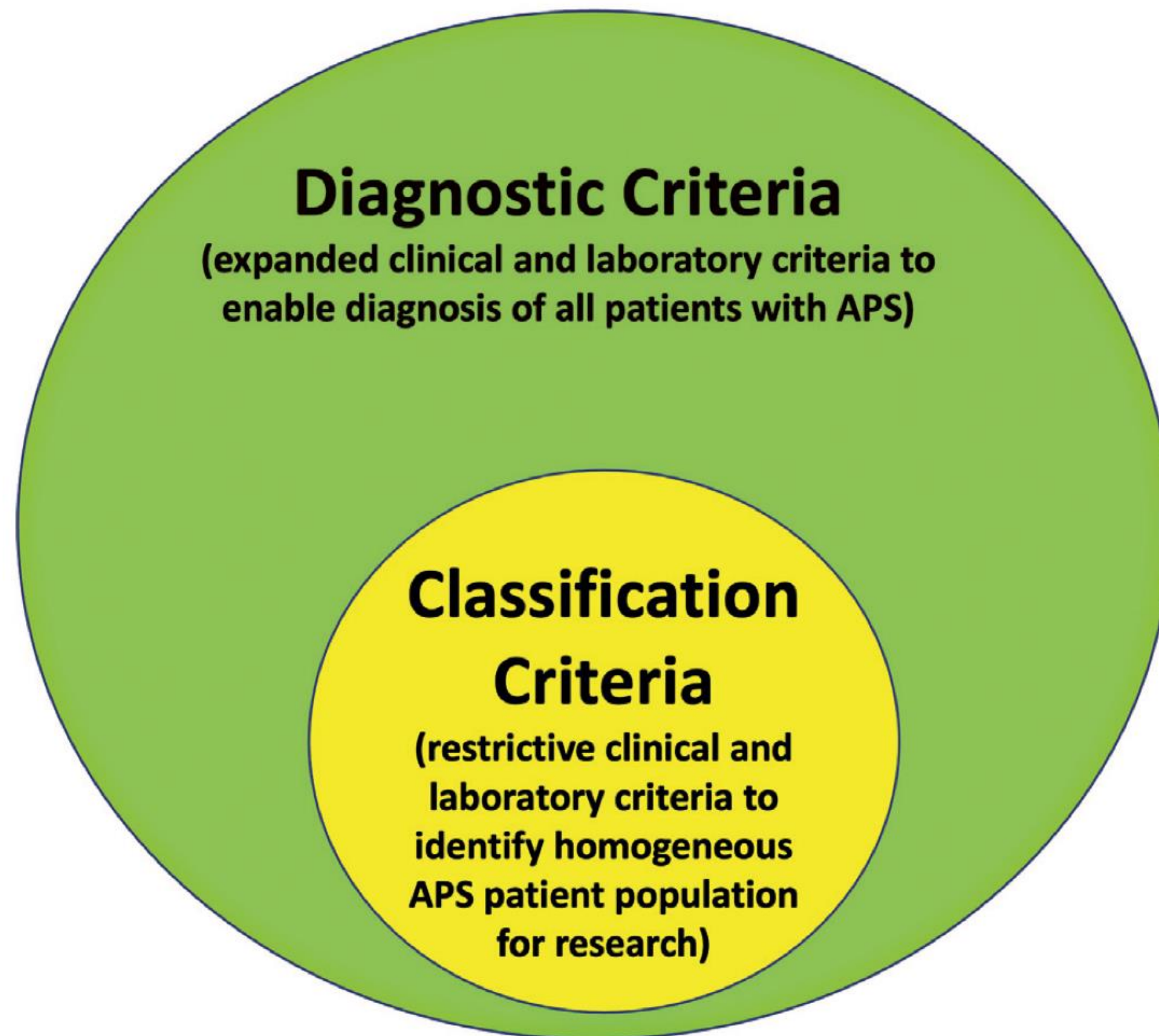


KEY MESSAGE #1

**Diagnostic
criteria**



**Classification
criteria**





SCOPE OF TALK

- 1 2023 ACR/EULAR APS classification criteria and clinical implications**
- 2 Antiphospholipid antibodies/APS and reproductive issues**
 - Role of Thromboprophylaxis in APS Patients Undergoing Assisted Reproductive Technology
 - Role of aPL testing and LMWH use in recurrent implantation failure
- 3 Role of DOACs in thrombotic APS**

CASE STUDY



A 35-year-old woman

- ➔ She was diagnosed SLE 2 years ago.
- ➔ She was diagnosed asymptomatic aPL carrier (LA persistent positivity)
- ➔ She took low-dose aspirin (81 mg/day) as a primary thromboprophylaxis
- ➔ SLE was inactive disease activity for almost a year. She plans to have a baby.
- ➔ **Are there any roles of treatment when she is undergoing assisted reproductive technology?**



APS AND ART

Recommendations for patients with
APS/aPL positivity undergoing ART

**Disease in remission or stable
(at least for 6 months)**



APS AND ART

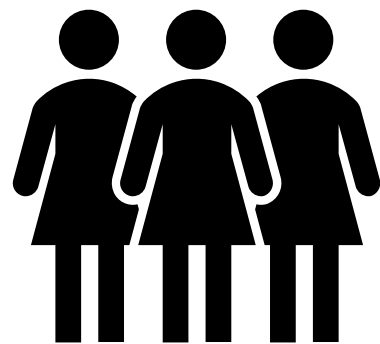
EULAR 2017	ACR 2020*		
Patients with positive aPL/APS should receive anticoagulation (at the dosage as would be recommended during pregnancy) and/or low-dose aspirin. (level of evidence 3, grade of recommendation D)	Negative aPL	–	Strongly recommend
	Positive aPL (no clinical APS)	Prophylactic heparin during ART procedures	Conditionally recommend
	Obstetric APS	Prophylactic heparin during ART procedures	Strongly recommend
	Thrombotic APS	Therapeutic heparin during ART procedures	Strongly recommend

*Very low strength of evidence

ACR, American College of Rheumatology; aPL, antiphospholipid antibodies; EULAR, European League Against Rheumatism



IVF AND APS/SLE

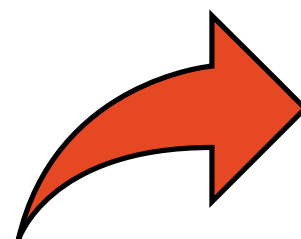


37 women (SLE +/-APS)

in remission

97 IVF procedures

Treated with steroids, HCQ, ASA, LMWH



Outcomes

Pregnancy rate 28%

Live birth rate 85%

Pregnancy rate in with and without
APS/+ve aPL

25% vs 32% (P=0.63)



Complications

8% of procedures

4 SLE flares

4 thromboembolic events



IVF AND APL POSITIVITY

Prophylactic LMWH

- Start at the beginning of ovarian stimulation
- Withhold 12–36 hours prior to oocyte retrieval
- Resume following oocyte retrieval
- No optimal duration of prophylactic LMWH in asymptomatic aPL carriers (discuss with patients and infertility specialist)

Low-dose aspirin

- Start after oocyte retrieval in indicated patients

APS AND ART



Prevention of thrombotic complication

Recommendations for patients with APS/aPL positivity undergoing ART

**Disease in remission or stable
(at least for 6 months)**

Negative
aPL

Proceed with
ART

Positive aPL
No clinical APS

Proceed with ART
Prophylactic
heparin

Obstetric
APS

Proceed with ART
Prophylactic
heparin

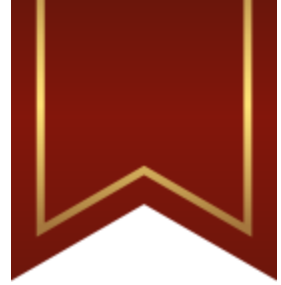
Thrombotic
APS

Proceed with ART
Therapeutic
heparin



SCOPE OF TALK

- 1 2023 ACR/EULAR APS classification criteria and clinical implications**
- 2 Antiphospholipid antibodies/APS and reproductive issues**
 - Role of Thromboprophylaxis in APS Patients Undergoing Assisted Reproductive Technology
 - Role of aPL testing and LMWH use in recurrent implantation failure
- 3 Role of DOACs in thrombotic APS**



IVF AND APL POSITIVITY



Recurrent implantation failure

More than **two or more embryo transfers** fail to result in a pregnancy



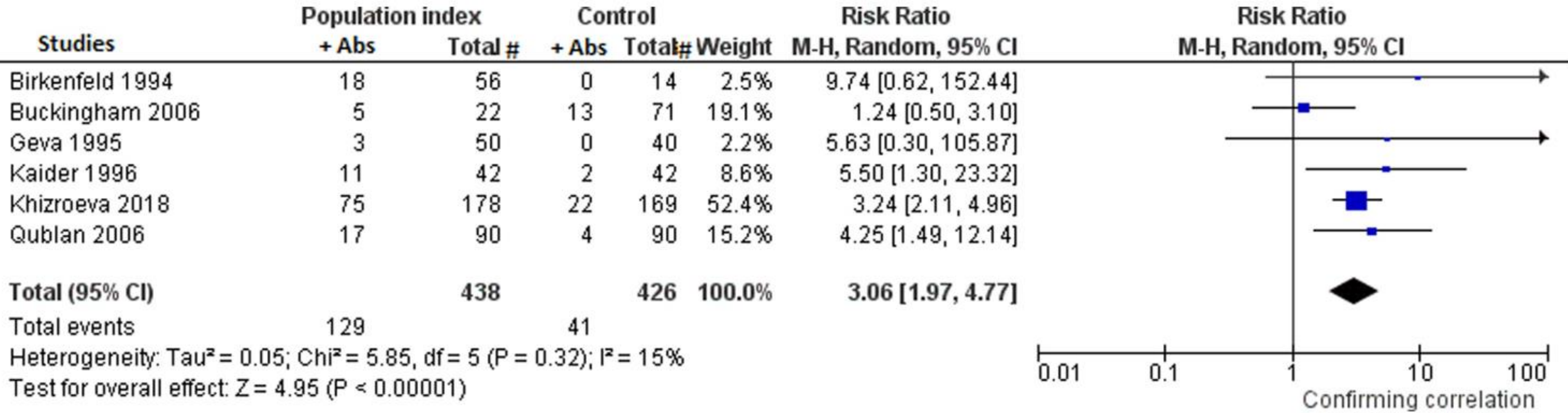
Role of aPL testing ??



Role of LMWH ??
(increase success rate)

Presence of antiphospholipid antibodies is associated with increased implantation failure following *in vitro* fertilization technique and embryo transfer: A systematic review and meta-analysis

RR 3.06 (1.97–4.77)

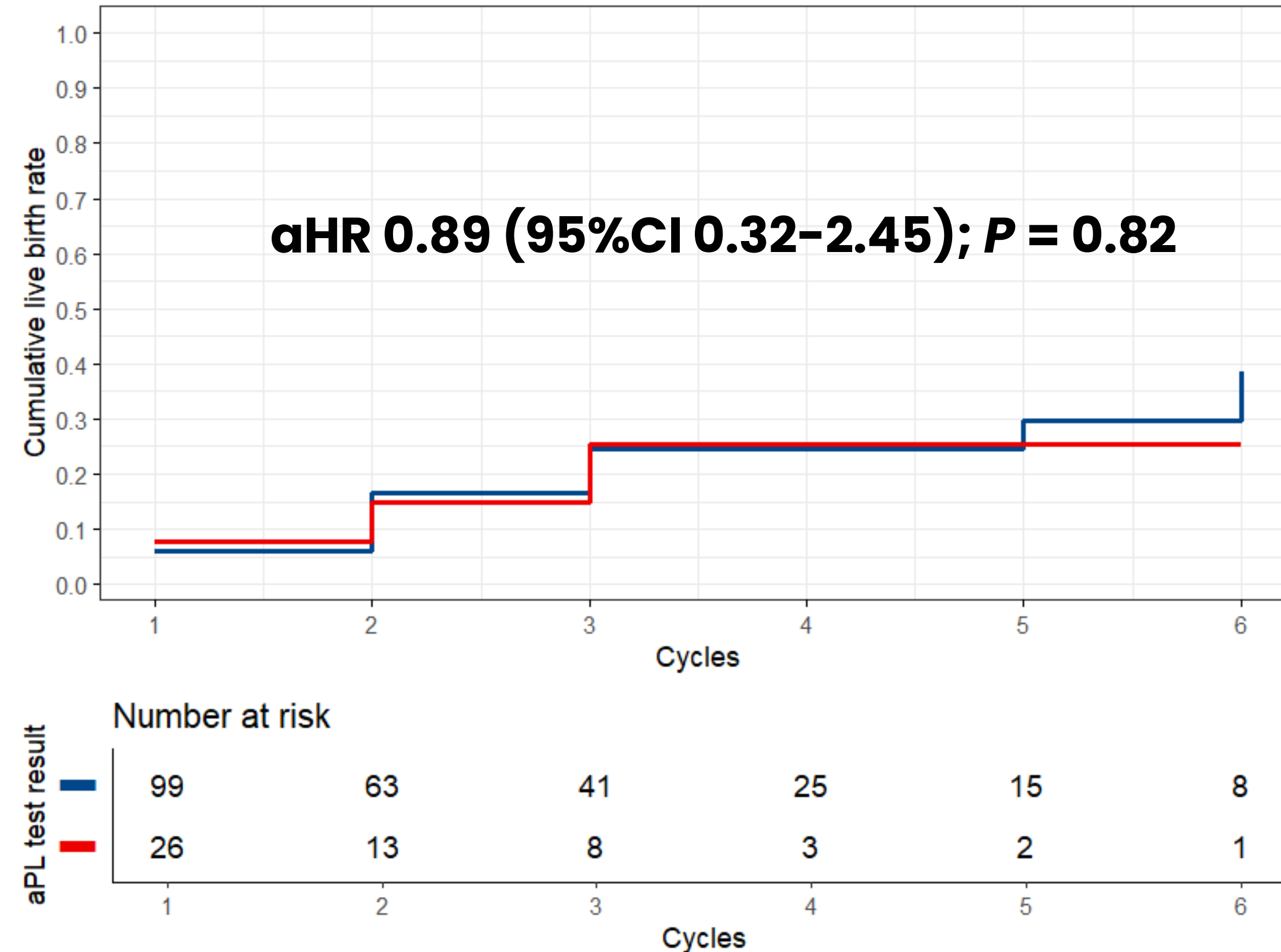


The prevalence of antiphospholipid antibodies in women experiencing at least two implantation failures in IVF-ET without diagnosis of antiphospholipid syndrome **is significantly greater than** women who had a successful implantation

RESULTS FROM SIRIRAJ HOSPITAL

aPL test result — Negative — Positive

aHR 0.89 (95%CI 0.32–2.45); $P = 0.82$



125 women with RIF
(26 aPL+ve 99 aPL –ve)
total 327 embryo transfer events
(53 events:274 events)

Cumulative live birth rates

aPL-negative women 38% (95%CI 15–56)
aPL-positive women 25%(95%CI 0–46)

Prophylactic LMWH and live birth rates

crude RR 2.20; 95% CI, 0.73–6.62; $P = 0.16$

ESHRE good practice recommendations on recurrent implantation failure[†]

ESHRE Working Group on Recurrent Implantation Failure, D. Cimadomo ¹, M.J. de los Santos ², G. Griesinger ^{3,4}, G. Lainas ⁵, N. Le Clef ⁶, D.J. McLernon ⁷, D. Montjean ⁸, B. Toth⁹, N. Vermeulen ⁶, and N. Macklon ^{10,*}

 Assessment of APA and APS is recommended in RIF women with additional risk factors for thrombophilia and can be considered in women without such risk factors.

 Low molecular weight heparin (LMWH) is not recommended to increase the chance of pregnancy or live birth in women with RIF.

✓ **should be selected with suspected patients with clinical symptoms (recurrent pregnancy loss, history of thrombosis)**

✓ **Should be excluded before ART due to specific clinical management**

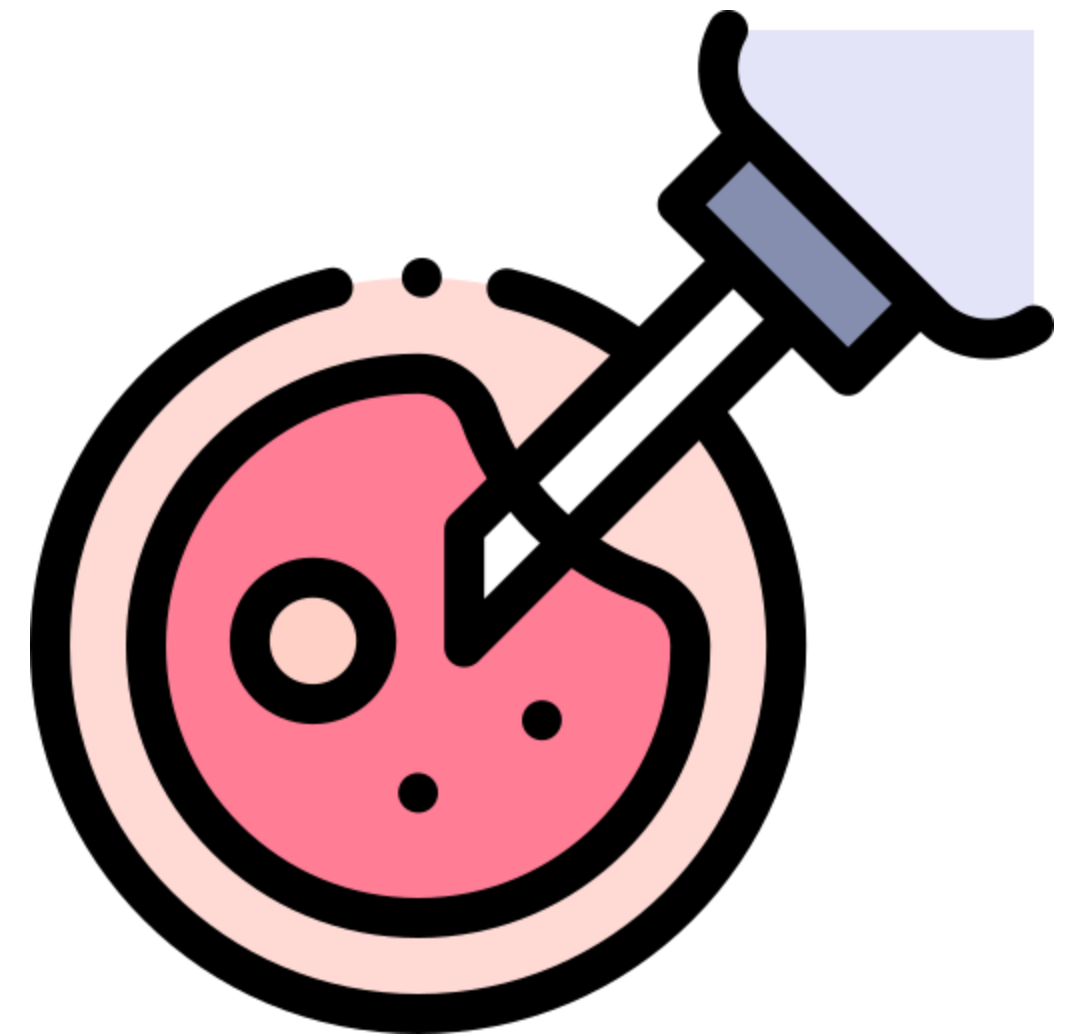
✓ **Limited well-designed studies**

KEY MESSAGES #2

Limited studies exist on RIF, aPL testing, and the benefits of LMWH

Consider aPL testing in RIF women with suspected clinical symptoms including thrombosis, recurrent pregnancy loss

LMWH can be considered for thromboprophylaxis in aPL carriers/APS patients, but there is no strong evidence supporting an improvement in live birth rates





SCOPE OF TALK

- 1 2023 ACR/EULAR APS classification criteria and clinical implications**
- 2 Antiphospholipid antibodies/APS and reproductive issues**
- 3 Role of DOACs in thrombotic APS**

DOACs AND THROMBOTIC APS

4 Randomized Clinical Trials



RAPS
United Kingdom
(N = 116)



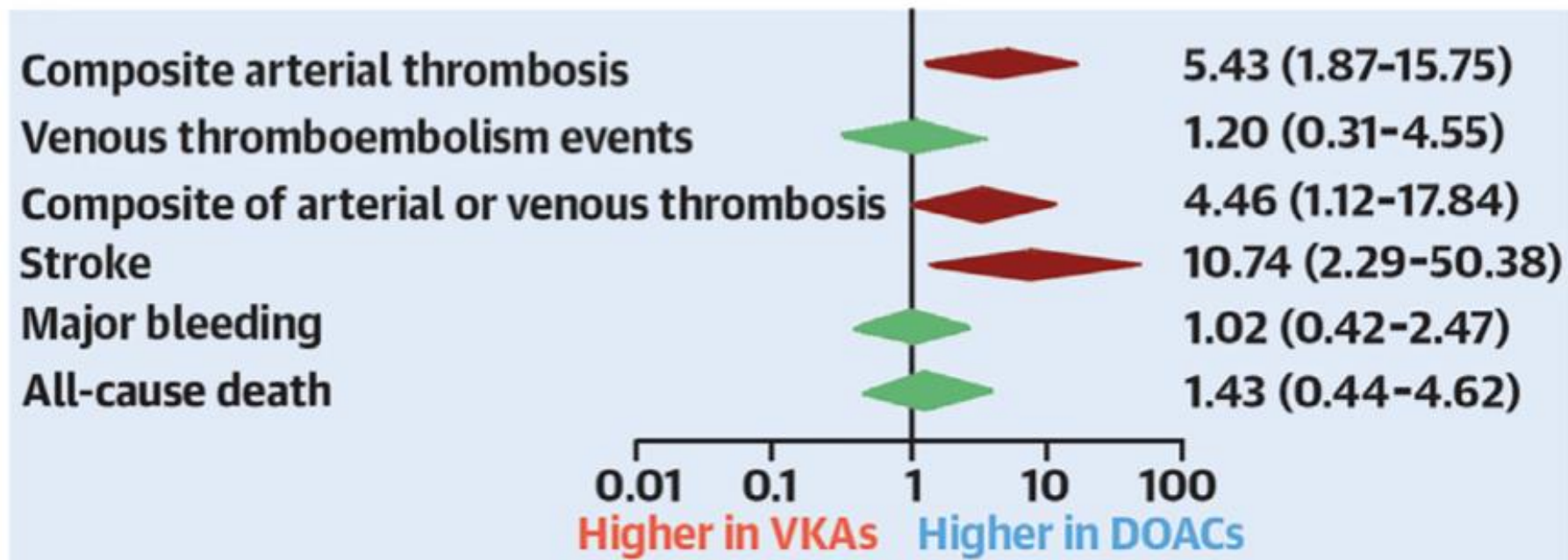
TRAPS
Italy
(N = 120)



Ordi-Ros et al
Spain
(N = 190)



ASTRO-APS
United States
(N = 48)



Mean age 48 y 68% Women



474 patients
with thrombotic APS



Vitamin K
Antagonists



Direct Oral
Anticoagulants



**Use of DOACs Compared With VKAs Was
Associated With:**

- Increased odds of arterial thrombotic events, especially stroke
- No change in the odds of VTE or major bleeding

Results were consistent within subgroups

DOACs AND THROMBOTIC APS

Baseline Characteristics	RAPS (2016) (N=116)	TRAPS (2018) (N=120)	EUDRA (Ordi-Ros et al) (2019) (N=190)	ASTRO-APS (2022) (N=48)
Type of DOACs	Rivaroxaban 20 mg	Rivaroxaban 20 mg	Rivaroxaban 20 mg	Apixaban 2.5/5 mg bid
Antibody profile	Triple positive 28%	Triple positive 100%	Triple positive 60.5%	Triple positive 30.4%
History of arterial thrombosis*	None	18.6%/23.0%	27.4%/26.3%	13.0%/28.0%
History of venous thrombosis*	100%/100%	64.4%/63.9%	61.1%/64.2%	73.9%/56.0%
History of arterial & venous thrombosis*	None	16.9%/13.1%	11.6%/9.5%	13%/16%
Primary endpoint	Difference in mean ETP change	Thrombosis, major bleeding, and vascular deaths	Thrombosis	Thrombosis (arterial, venous)

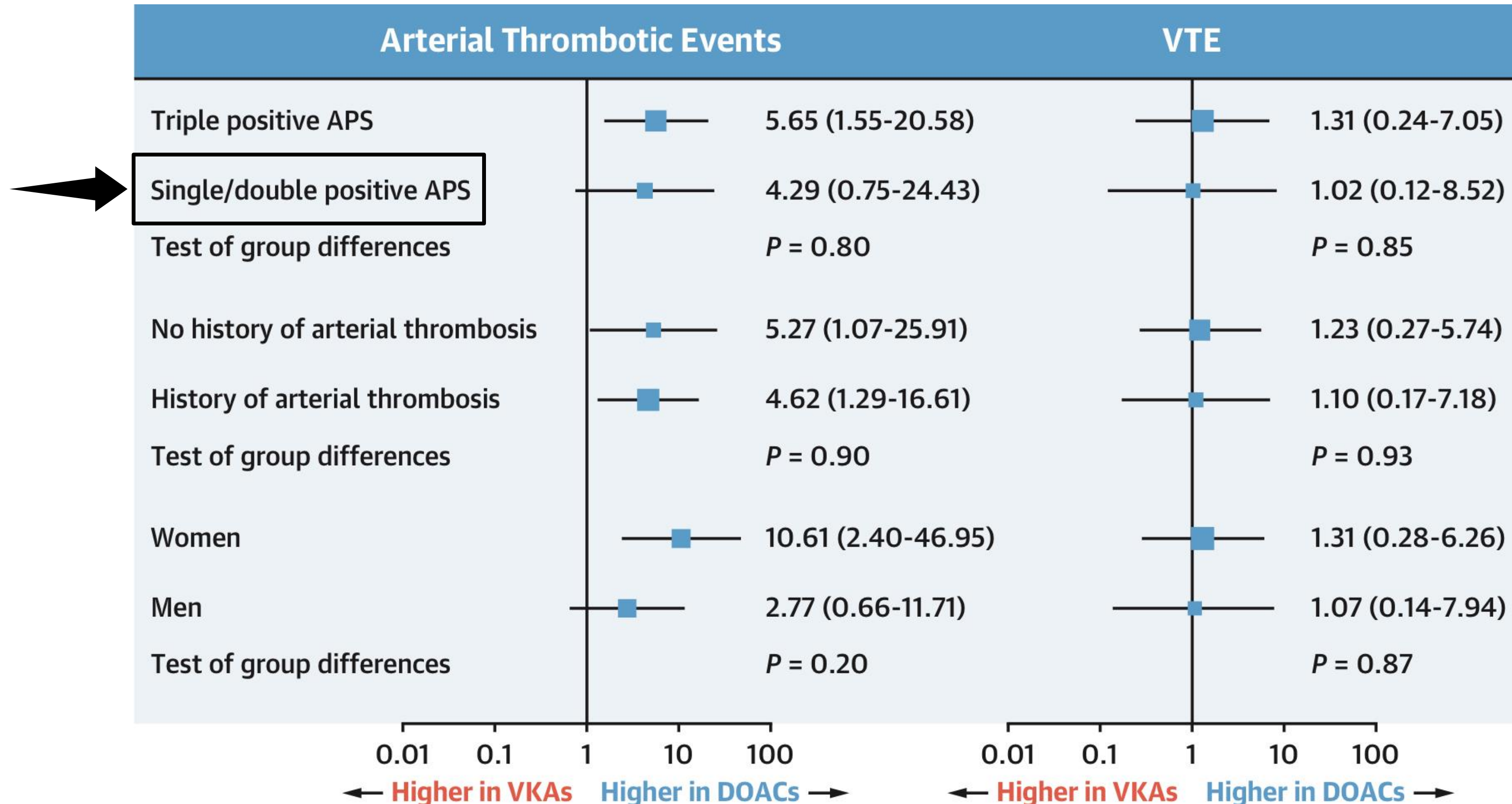
***(DOACs/VKA)**

DOACs AND THROMBOTIC APS

Baseline Characteristics	RAPS (2016) (N=116)	TRAPS (2018) (N=120)	EUDRA (Ordi-Ros et al) (2019) (N=190)	ASTRO-APS (2022) (N=48)
Thrombotic event (%)*	0%/0%	12%(stroke,MI)/0%	11.6%/6.3% (both sites)	26.1%(stroke)/0%
Comments	-No clinical thrombosis both arms -Not powered to compare clinical outcomes -Short duration follow-up time (42 days)	-All patients in the study were triple positive APS	-The presence of livedo, small vessel, or cardiac valvular disease associated with recurrent thrombosis	-The protocol was modified twice. 1) Increase dosage of apixaban 2) Exclude prior arterial thrombosis 3) MRI brain before enrollment

*(DOACs/VKA)

SUBGROUP ANALYSIS



RECOMMENDATIONS & GUIDELINES

EULAR 2019	- Avoid in triple positive APS, arterial thrombosis - DOACs can be considered in VKA allergy, patients with good adherence but unable to achieve a target INR
ISTH 2020 & APS task force 2020	- Avoid in high risk APS (arterial thrombosis, triple positive, small vessel thrombosis, heart valve disease (Sydney criteria)) - Non-high risk APS with good adherence (with VTE x 1 time): share decision-making with the patient - Non-high risk APS with VKA allergy, unable to achieve a target INR: suggest alternative VKAs - Switch to VKA in triple positive patients treated with DOACs, if the patients decline >> surveillance with MRI brain

EULAR, European League Against Rheumatism; ISTH, International Society of Thrombosis and Hemostasis

RECOMMENDATIONS & GUIDELINES

British Society of Hematology 2024

Naïve to DOACs	↗	triple positive	Recommend against DOACs (grade 1B)
	↘	single, double positive	Suggest against DOACs (grade 2C)
Already on DOACs	↗	triple positive	Recommend switching to VKA (grade 1B)
	↘	single, double positive	May continue or switch to VKA after discussion with patient (grade 2C)
APS with stroke	→	any	Recommend against the initiation of DOACs (grade 1B)

KEY MESSAGES #3



AVOID DOACs

- Triple-positive APS
- Arterial thrombosis
- Small vessel thrombosis
- aPL-related heart valve disease



May be considered DOACs

- Single-positive or double-positive APS
 - First episode VTE
 - No history of arterial thrombosis
 - Unable to achieve a target INR, VKA allergy, intolerance

After discuss with patients

ThankYOU