POST-SAN DIEGO 2023

Novità dal Meeting della Società Americana di Ematologia

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Verona

Palazzo della Gran Guardia

15-16-17 Febbraio 2024

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Disclosures of Elena Rossi

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Grifols			x			x	
Jannsen			x			x	
GSK			x			x	

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Verona, 15-16-17 Febbraio 2024

2022

ASH Clinical Practice Guidelines on Venous Thromboembolism

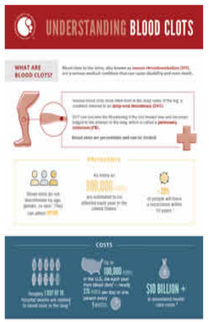
In 2014, in response to long-standing member interest, ASH initiated an effort to develop evidence-based clinical practice guidelines for hematology that meet the highest standards of development, rigor and trustworthiness. Development of these guidelines, including systematic evidence review, was supported by the McMaster University GRADE Centre, a world leader in guideline development. With their partnership, ASH brought together ten panels of more than 100 thrombosis experts to review evidence and formulate more than 200 recommendations on venous thromboembolism (VTE).

Learn more about the development process behind the VTE guidelines.

VTE Guideline Development

Download the PDF

Understanding Blood Clots



Download the PDF

Click image for video of experts discussing the new guidelines.

AVAILABLE GUIDELINES

- Adaptation of ASH Prophylaxis and Management of VTE Guidelines for Latin America
- Anticoagulation Therapy
- Cancer
- Diagnosis
- Heparin-Induced Thrombocytopenia
- Pediatrics
- Pregnancy
- Prevention in Hospitalized Surgical Patients
- Prophylaxis for Medical Patients
- Treatment
- Use of Anticoagulation in COVID-19 Patients

COMING SOON

- Thrombophilia
- Adaptation of ASH VTE Guidelines for Latin America

2023

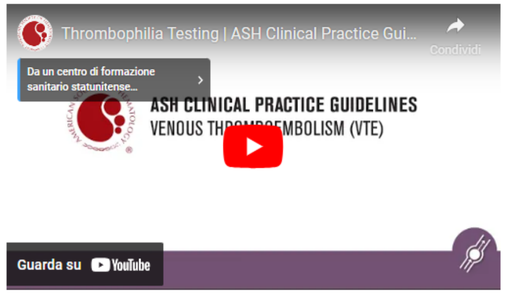
ASH VTE Guidelines: Thrombophilia Testing

Thrombophilias include a variety of genetic mutations that are associated with increased risk of VTE. Thrombophilia, either acquired or hereditary, can be identified in many patients presenting with venous thromboembolism (VTE). The currently most commonly tested hereditary thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations Factor V Leiden (FVL) and prothrombin G20210A (PGM). Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2- glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome (APS), are also generally included in a thrombophilia testing panel.

Thrombophilia testing can be performed in patients with VTE, particularly if they are young, have recurrent episodes, have thrombosis at unusual sites, or have a positive family history of the disease. The purpose of these guidelines is to provide evidence-based recommendations about whether thrombophilia testing and tailoring management based on the test result would improve patient-important outcomes.

Access the full guidelines on the Blood Advances website:

American Society of Hematology 2023 Guidelines for Management of Venous Thromboembolism: Thrombophilia Testing



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THROMBOPHILIA TESTING

Antithrombin deficiency

Protein C deficiency

Protein S deficiency

FV Leiden

PT G20210A

Lupus anticoagulant

Anti beta2glycoprotein 1 antibodies

Anticardiolipin antibodies

MTHFRs

Factor VIII

Factor IX

Factor XI activity

PAI-1

4G/5G PAI-1 promoter polymorphism

THROMBOPHILIA TESTING: some caveats

Table 4. **The effects of oral factor Xa inhibitors and oral thrombin inhibitors on tests for hereditary thrombophilia**

Thrombophilia	Tests	Effect on test
Factor V Leiden mutation	PCR	Not affected
Prothrombin G20210A mutation	PCR	Not affected
Protein C deficiency	Protein C activity: clot-based assays	Interference by oral factor Xa inhibitors and dabigatran
	Protein C activity: amidolytic assays	Not affected
	Protein C antigen assays	Not affected
Protein S deficiency	Protein S activity: clot-based assays	Interference by oral factor Xa inhibitors and dabigatran
	Protein S antigen assays	Not affected
Antithrombin deficiency	Antithrombin activity: anti-Xa–based assays	Interference by oral factor Xa inhibitors
	Antithrombin activity: anti-IIa–based assays	Interference by dabigatran
	Antithrombin antigen assays	Not affected

PCR, polymerase chain reaction.

Chiasakul T, Bauer KA. The dos, don'ts, and nuances of thrombophilia testing. Hematology Am Soc Hematol Educ Program. 2023 Dec 8;2023(1):593-599.

THROMBOPHILIA TESTING

Antithrombin deficiency

Protein C deficiency

Protein S deficiency

FV Leiden

PT G20210A

Lupus anticoagulant

Anti beta2glycoprotein 1 antibodies

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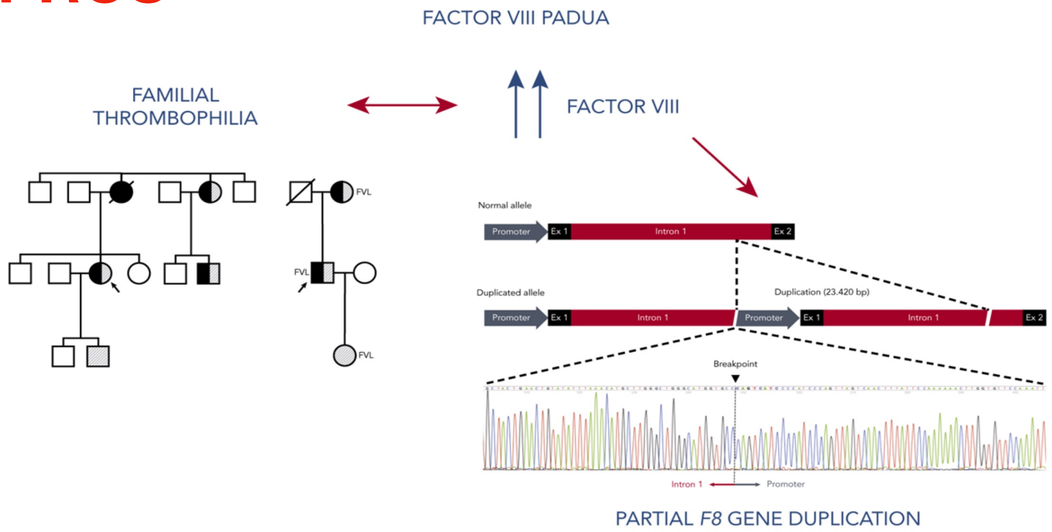
FVIII testing: PROS

In the Leiden Thrombophilia Study, patients with FVIII:C >150 IU/dL had an increased risk of venous thrombosis compared with those with FVIII:C <100 IU/dL.

Risk factor	Adjusted odds ratio (95% CI)
Blood group (non-O *vs* O)*	1·5 (1·0–2·2)
vWF antigen (IU/L)†	
<1000	1
1000–1249	1·1 (0·7–1·9)
1250–1499	1·3 (0·7–2·2)
⩾1500	1·2 (0·6–2·1)
FVIII coagulant activity (IU/L)‡	
<1000	1
1000–1249	2·3 (1·3–3·8)
1250–1499	3·0 (1·6–5·7)
⩾1500	4·8 (2·3–10·0)

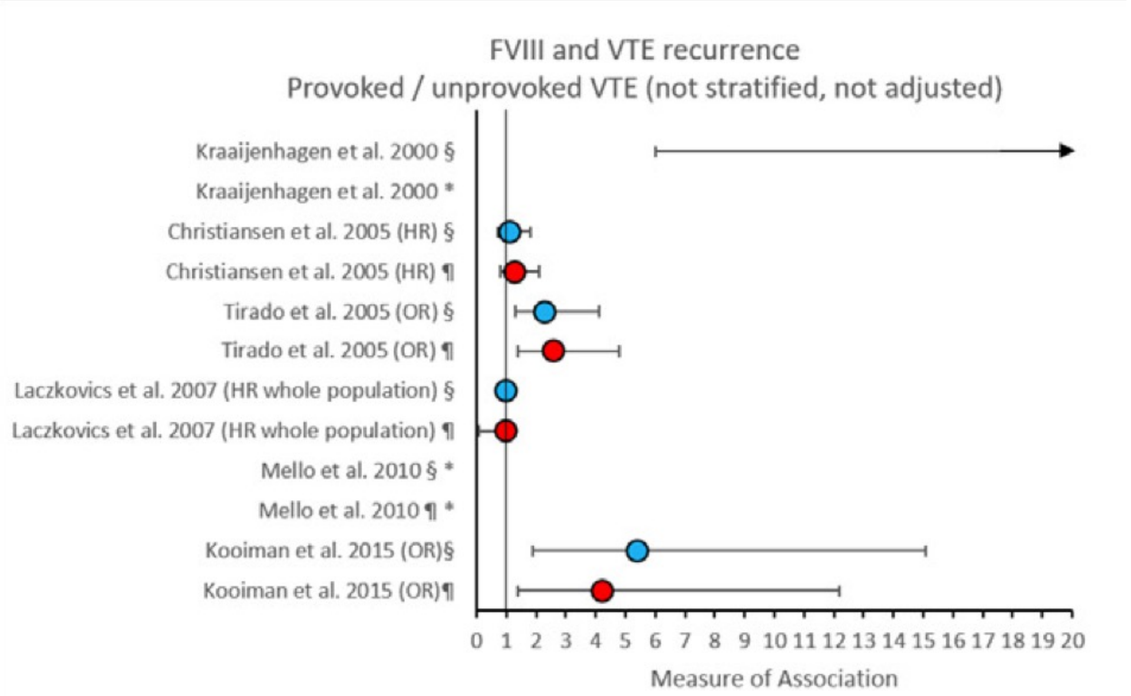


Simioni et al. described in two Italian families with a history of juvenile VTE and extremely and persistent elevated FVIII levels (>400%) a 23.4-kb tandem duplication of the proximal portion of the F8 gene. This mutation is associated with a >45-fold increased activity of F8 gene in endothelial cells.

Koster T, et al. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. Lancet. 1995 Jan 21;345(8943):152-5.
Simioni P et al. Partial F8 gene duplication (factor VIII Padua) associated with high factor VIII levels and familial thrombophilia. Blood. 2021 Apr 29;137(17):2383-2393.

FVIII testing: CONS

In a recent systematic review, 9 of 16 studies failed to identify FVIII:C as an independent risk factor for recurrence.



1. FVIII:C is generally measured using a one-stage clot-based assay: potential for **interference** in one-stage FVIII:C assays by heparins and lupus anticoagulants.

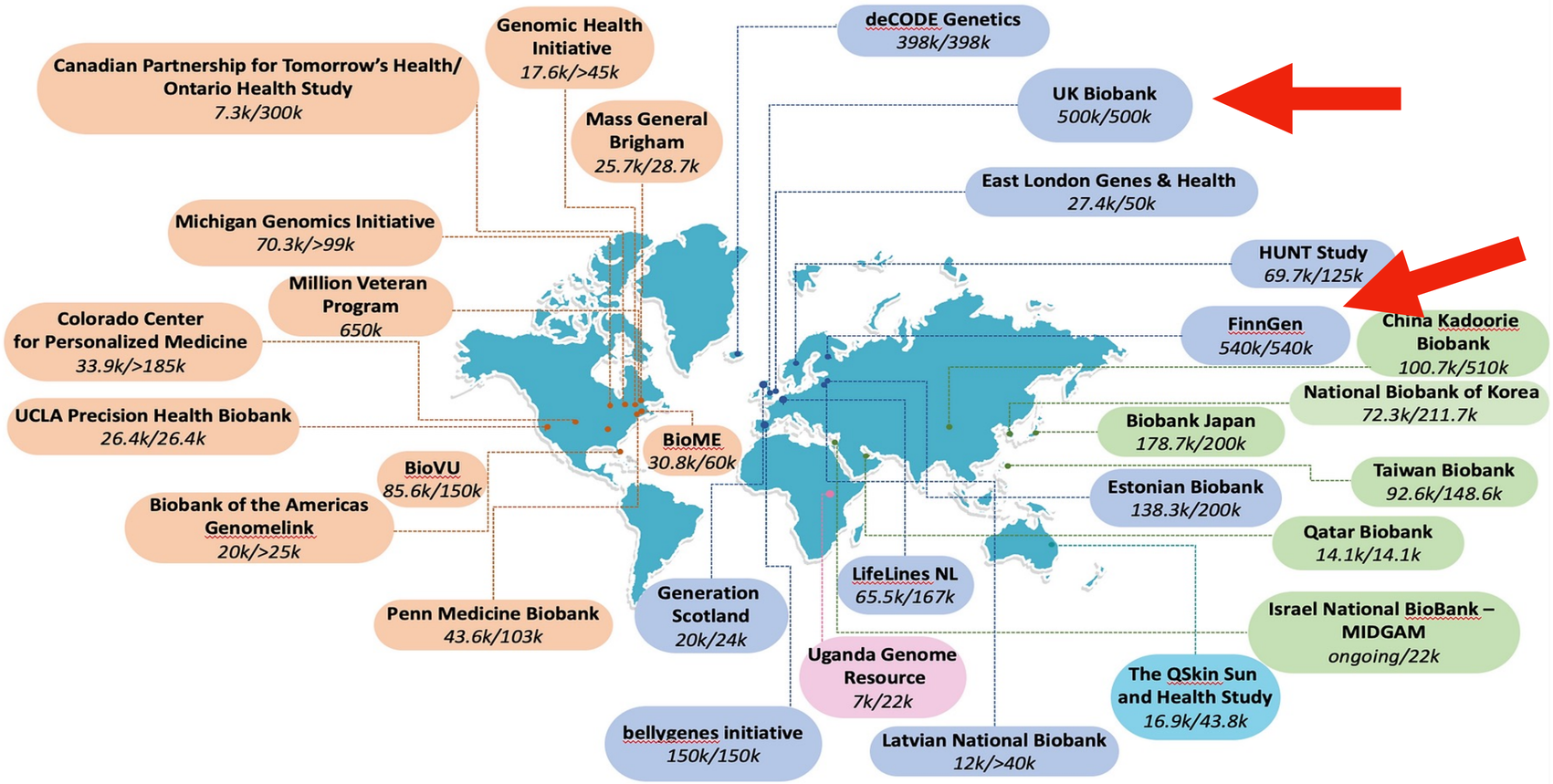
2. Elevated FVIII:C is often defined as above the 90th percentile of the population. However, there is uncertainty regarding what **cutoff** values should be considered "elevated," since cutoffs were >150% in the Leiden Study and >234% in the Vienna study.

3. The concomitant presence of an underlying **inflammatory disorder** is present in association with elevated C-reactive protein and fibrinogen levels along with FVIII:C.

4. **Other factors** such as body mass index, age, glucose, and triglyceride levels have been associated with FVIII levels elevation.

Bosch A, Uleryk E, Avila L. Role of factor VIII, IX, and XI in venous thrombosis recurrence risk in adults and children: A systematic review. Res Pract Thromb Haemost. 2023 Feb 2;7(2):100064.
Sachs UJ, Kirsch-Altena A, Müller J. Markers of Hereditary Thrombophilia with Unclear Significance. Hamostaseologie. 2022 Dec;42(6):370-380.

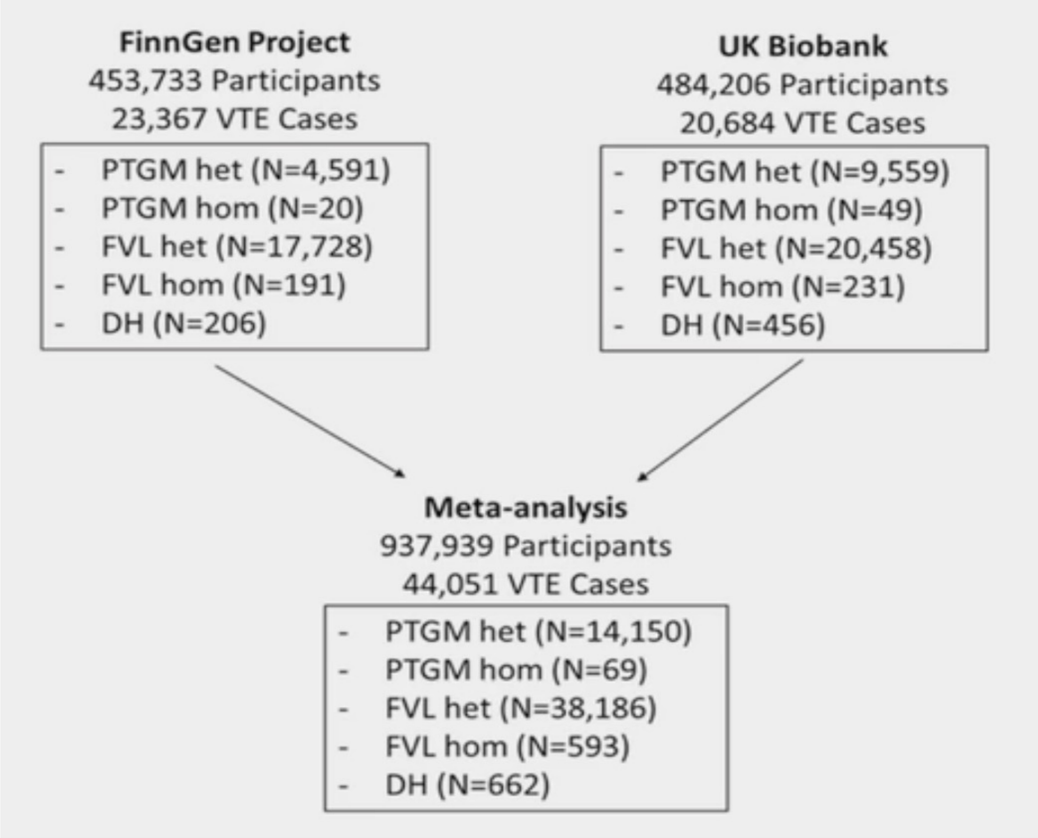
Global BioBank Meta website



Biobanks have become a frontline resource for investigations of genetic traits and how they relate to clinical phenotypes. A biobank is a large-scale biomedical database and research resource containing de-identified genetic, lifestyle and health information and biological samples.

Ryu J. Oral presentation ASH 2023

Ryu J. Thrombosis risk in double Heterozygous carriers of factor V Leiden and Prothrombin G20210A across 937,939 Individuals



FVL and PTG are present in 2-5% of European populations.

Heterozygosity for either allele increases risk for venous thromboembolism by approximately 3 to 8- fold.

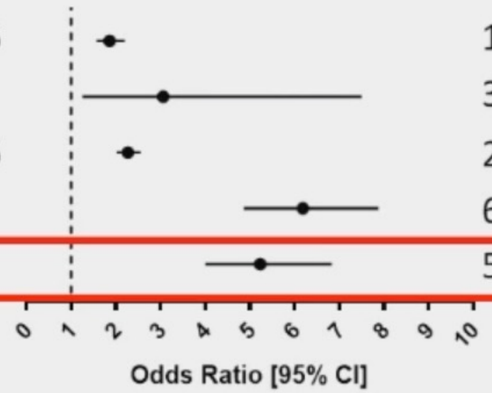
Clinical impact of double heterozygosity (DH) remains unclear.

Literature reports discordant data with a VTE risk around 5 to 20-fold in DH.

Ryu J. Thrombosis risk in double Heterozygous carriers of factor V Leiden and Prothrombin G20210A across 937,939 Individuals

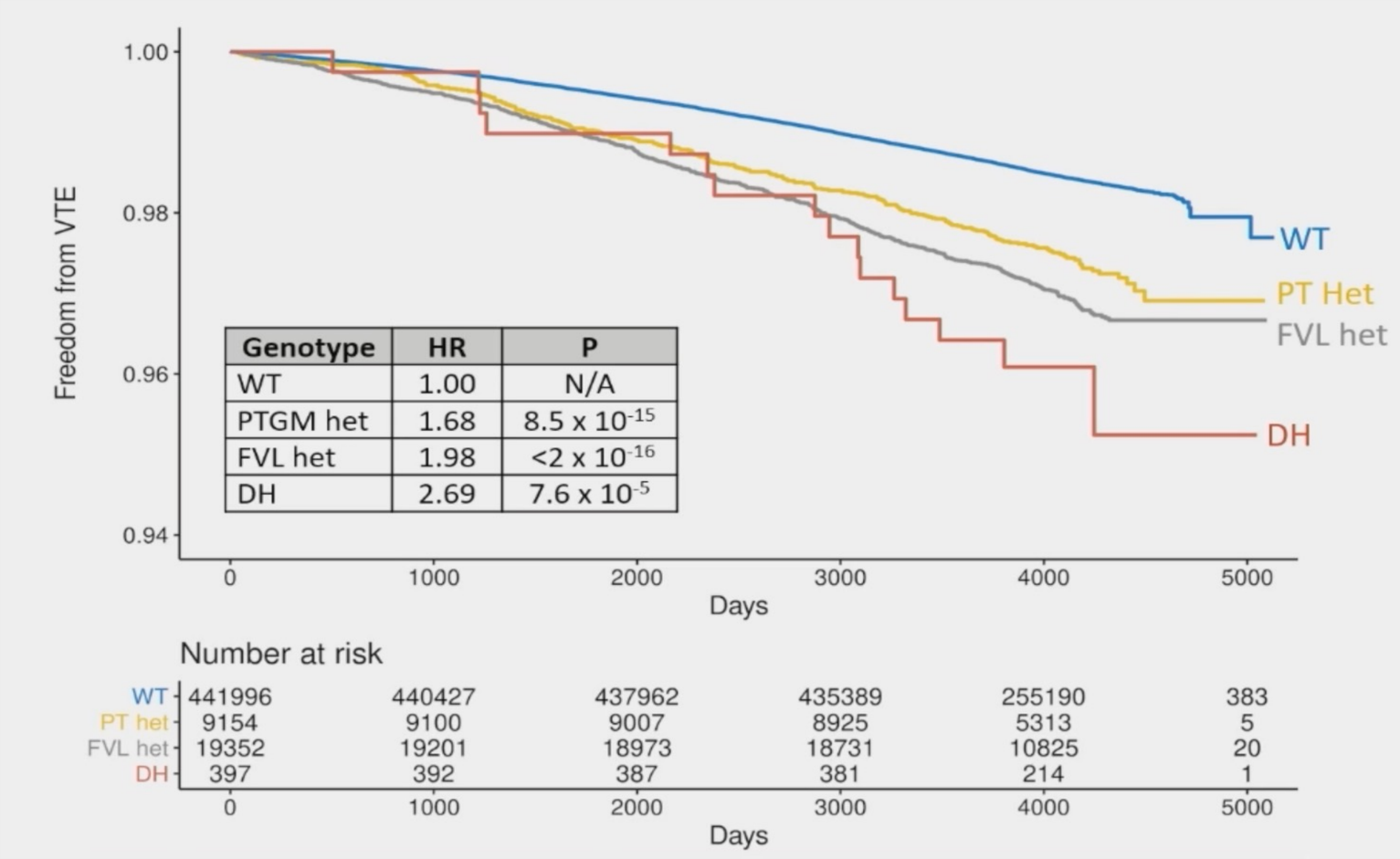
Firth's Model Adjusted for Age, Sex, and Ancestry

Genotype	Carriers/total (%)	Cases	Controls	OR [95% CI]	*P* value
		Carriers/Non-carriers			
PTGM het	14,150/899,016 (1.5)	1,077/39,271	13,073/845,595	1.86 [1.57 - 2.21]	8.6×10^{-13}
PTGM hom	69/923,052 (<0.01)	7/39,271	62/845,595	3.07 [1.26 - 7.43]	0.014
FVL het	38,186/884,935 (4.3)	3,582/39,271	34,604/845,595	2.28 [2.03 - 2.56]	1.9×10^{-43}
FVL hom	593/885,288 (0.06)	87/39,271	335/845,595	6.19 [4.63 - 7.88]	1.1×10^{-49}
DH	662/885,528 (0.07)	122/39,271	540/845,595	5.24 [4.01 - 6.84]	4.8×10^{-34}



Prevalence of Double Heterozygosity Carriers = 0.075%
Prevalence of FVL Homozygosity Carriers = 0.067%

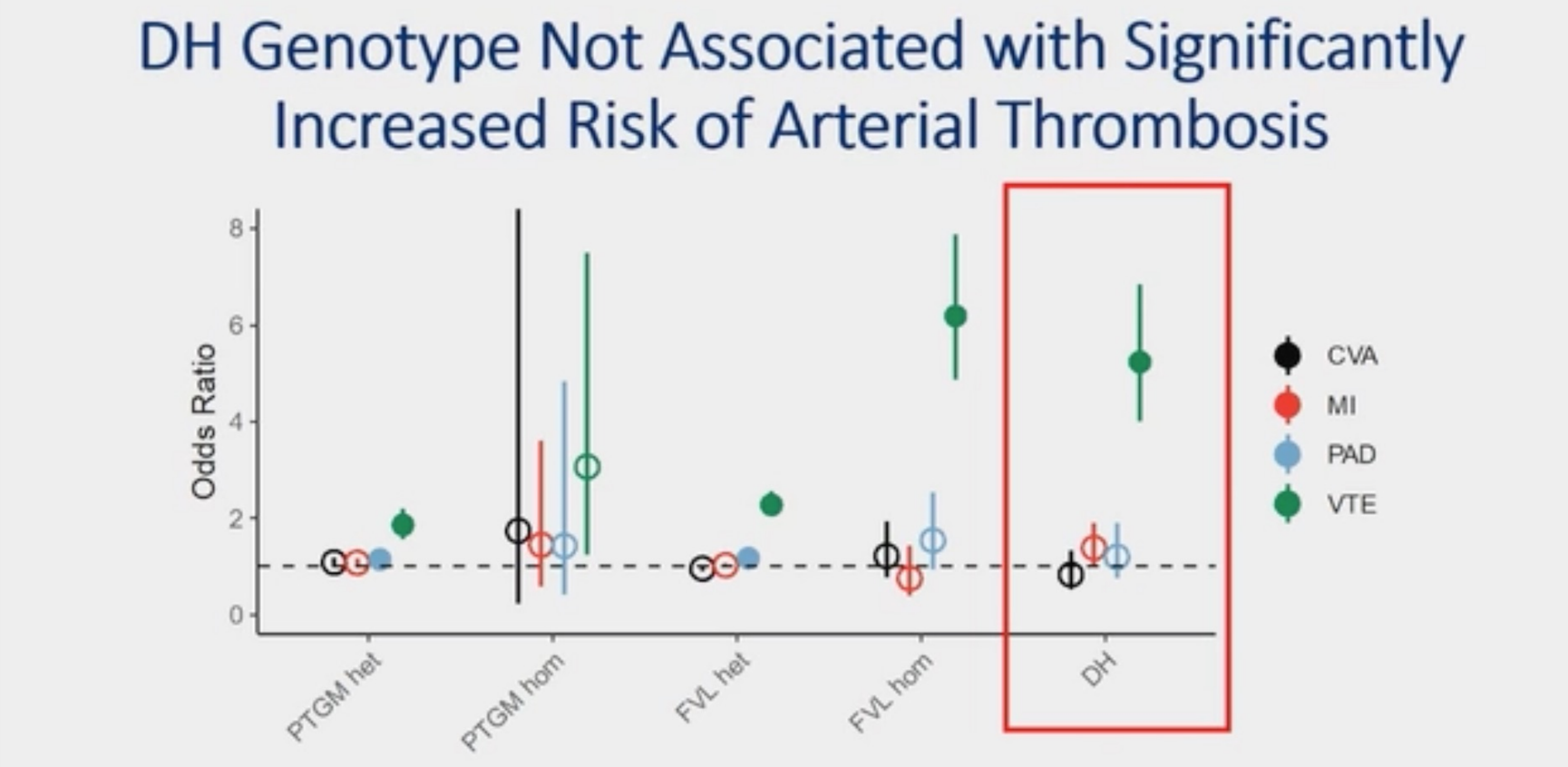
Ryu J. Thrombosis risk in double Heterozygous carriers of factor V Leiden and Prothrombin G20210A across 937,939 Individuals



Genotype	HR	P
WT	1.00	N/A
PTGM het	1.68	8.5×10^{-15}
FVL het	1.98	$<2 \times 10^{-16}$
DH	2.69	7.6×10^{-5}

Risk of venous thrombosis for DH individuals is approximately twice that of individuals who carry only a single variant.

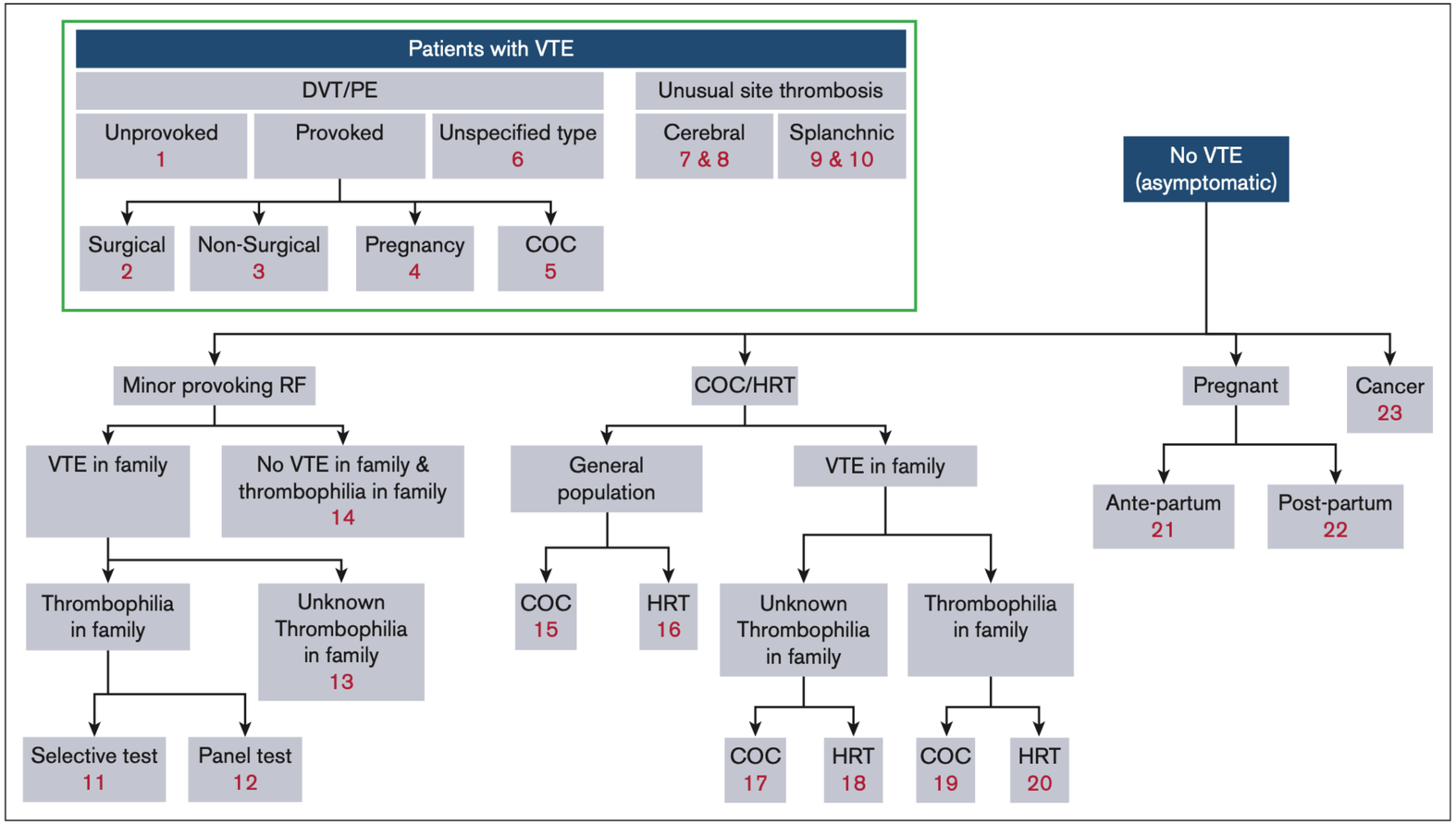
Ryu J. Thrombosis risk in double Heterozygous carriers of factor V Leiden and Prothrombin G20210A across 937,939 Individuals



There is no detectable increase in risk of arterial thrombosis in DH carriers.

ASH CLINICAL PRACTICE GUIDELINES
VENOUS THROMBOEMBOLISM (VTE)

ASH guidelines: Thrombophilia

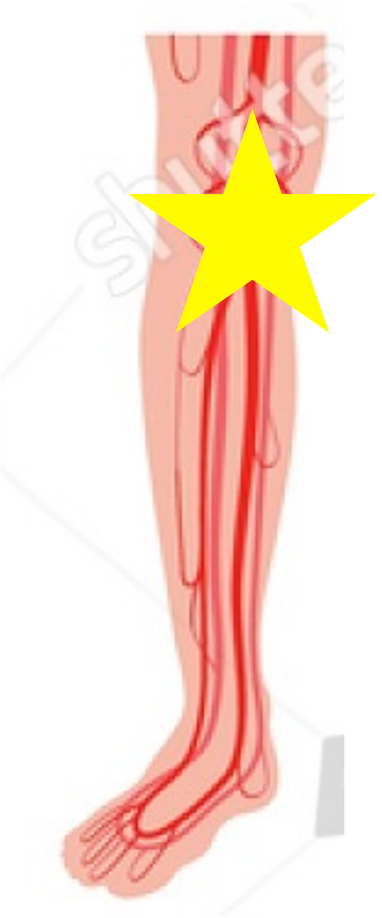


Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.

PATIENTS WITH UNPROVOKED VTE

For patients with unprovoked VTE who have completed primary short-term treatment, the ASH guideline panel suggests not to perform thrombophilia testing to guide the duration of anticoagulant treatment.

In the ASH VTE treatment guideline, indefinite antithrombotic therapy is suggested for most patients with unprovoked VTE.



Outcomes	Impact of thrombophilia testing strategy per 1000 patients (620 fewer patients treated with indefinite anticoagulation)
Recurrent VTE	42 more VTE recurrences (ranging from 17 to 67)
Major Bleeding - Low Risk (0.5% per year)	4 fewer major bleeds (ranging from 1 to 9)
Major Bleeding – High Risk (1.5% per year)	11 fewer major bleeds (ranging from 2 to 28)

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.

Provoking Risk Factors for VTE

Transient Risk Factors
(resolve after provoked VTE)

MAJOR Risk Factor (occurs within 3 mth)
- Surgery, gen anesthesia > 30 min
- Confined to hospital bed ≥ 3 days with acute illness
- Cesarean section

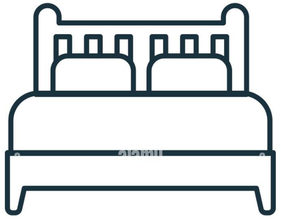
MINOR Risk Factor (occurs within 2 mth)
- Estrogen therapy (OCP, HRT)
- Pregnancy, puerperium
- Confined to bed out of hospital ≥ 3 days with acute illness
- Leg injury, reduced mobilty ≥ 3 days

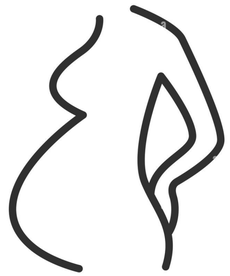
Chronic (Persistent) Risk Factors
(persistent after VTE occurs)

- Active cancer (ongoing chemo; recurrent or progressive disease)
- Inflammatory bowel disease
- Autoimmune disorder (e.g., antiphospholipid syndrome, rheumatoid arthritis)
- Chronic infection
- Chronic immobility (e.g., spinal cord injury)

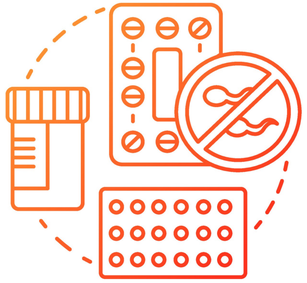
PATIENTS WITH PROVOKED VTE

NOT TEST





TEST



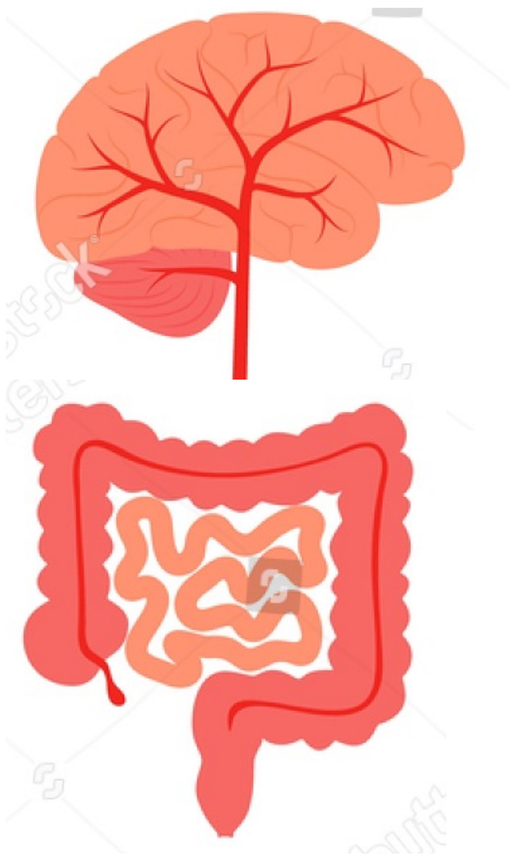
According to the ASH VTE treatment guideline, most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment.

According to the ASH VTE treatment guideline, most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment.

The panel suggests indefinite anticoagulant treatment for patients with thrombophilia and stopping anticoagulant treatment for patients without thrombophilia.

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.

PATIENTS WITH VTE AT UNUSUAL SITE



The unifying concept of benefits underlying recommendations for unusual VTE is that **the impact of recurrent events for patients with CVT or splanchnic thrombosis and thrombophilia is higher than we would normally accept.**

For patients with CVT or splanchnic thrombosis who have completed primary treatment in a setting where anticoagulation would be discontinued, the ASH guideline panel suggests thrombophilia testing to guide anticoagulant treatment duration.

The panel suggests indefinite anticoagulation for patients with thrombophilia.

In a setting where anticoagulation would be continued indefinitely, the ASH guideline panel suggests not to perform thrombophilia.

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.

INDIVIDUALS WITH FAMILY HISTORY OF VTE

LOW-RISK THROMBOPHILIA AND MINOR PROVOKING RISK FACTORS

NOT TEST

HIGH-RISK THROMBOPHILIA AND MINOR PROVOKING RISK FACTORS

TEST for all hereditary thrombophilia

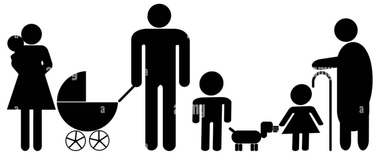
UNKNOWN THROMBOPHILIA AND MINOR PROVOKING RISK FACTORS

NOT TEST

Thrombophilia defect in the family	RR for first VTE, positive vs negative (95% CI)
FVL (FVL)	2.71 (2.06-3.56)
Prothrombin (PT) mutation	2.35 (1.46-3.78)
Antithrombin (AT) deficiency	12.17 (5.45-27.17)
Protein C (PC) deficiency	7.47 (2.81-19.81)
Protein S (PS) deficiency	5.98 (2.45-14.57)

And Double Heterozygosity??
OR 5.24

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.



INDIVIDUALS WITH FAMILY HISTORY OF VTE

Family History	Impact of selective thrombophilia strategy in first degree relatives of patients with VTE per 1000 episodes (500 more patients treated with thromboprophylaxis)	
	VTE	Major Bleeding
Low Risk		2.18 more bleeds (0.66 to 4.54)
FVL Heterozygous	5.04 fewer VTE (0.91 to 7.96)	
Prothrombin mutation	4.84 fewer VTE (0.80 to 8.07)	
High Risk		
Antithrombin Deficiency	21.25 fewer VTE (3.80 to 32.79)	
Protein C Deficiency	20.28 fewer VTE (3.32 to 32.37)	
Protein S Deficiency	19.79 fewer VTE (3.20 to 31.82)	

The number of VTE episodes prevented in a second-degree family history is half of that estimated in individuals with a first-degree family history.

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.

INDIVIDUALS WITH FAMILY HISTORY OF THROMBOPHILIA BUT NO FAMILY HISTORY OF VTE

LOW-RISK THROMBOPHILIA AND MINOR PROVOKING RISK FACTORS

NOT TEST

HIGH-RISK THROMBOPHILIA AND MINOR PROVOKING RISK FACTORS

TEST for all hereditary thrombophilia

The panel suggests thromboprophylaxis in individuals with thrombophilia and no thromboprophylaxis in individuals without thrombophilia

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.

HORMONE USE

For women from the general population, even if with a family history of VTE, who are considering using COCs or HRT, the ASH guideline panel recommends not performing thrombophilia testing to guide the use of COCs or HRT.

	Impact of thrombophilia testing strategy on VTE per 1000 women / year (69-142 fewer using COC or HRT)*	
	COC	HRT
General Population	0.26 fewer VTE (0.09 to 0.65)	0.29 fewer VTE (0.01 to 1.98)
Family History of VTE (1st degree) and Unknown Thrombophilia	1.17 fewer VTE (0.06 to 1.55)	0.94 fewer VTE (0.01 to 5.16)

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.

HORMONE USE

For women with a family history of VTE and known low-risk thrombophilia in the family, the ASH guideline panel suggests not testing for the known familial thrombophilia to guide the use of COC or HRT.

For women with a family history of VTE and known anti-thrombin, protein C, or protein S deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia.

The panel suggests avoidance of COCs and HRT for women with high-risk thrombophilia

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.

PREGNANCY

For women with a family history of VTE and known homozygous FVL, a combination of FVL and PGM, or an antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia.

The panel suggests antepartum thromboprophylaxis for women with the same familial thrombophilia.

For women with a first-degree family history of VTE and known homozygous FVL, a combination of FVL and PGM, antithrombin deficiency, *protein C* deficiency, or *protein S* deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia.

The panel suggests postpartum thromboprophylaxis for women with the same familial thrombophilia.

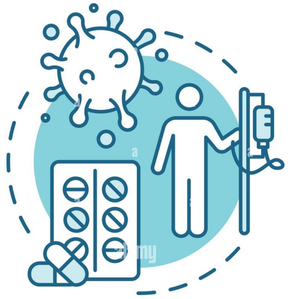
These recommendations do not address heterozygous FVL or PT mutations alone, as the ASH guidelines on the management of VTE in the context of pregnancy suggest not prescribing thromboprophylaxis for these women.

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.

PREGNANCY

Family History	Impact of thrombophilia strategy per 1000 pregnancies (Postpartum thromboprophylaxis used in 250-500* more pregnancies)	
Homozygous FVL	19.35 fewer VTE (12.16 to 24.14)	1.06 fewer bleeds (3.51 fewer to 10.07 more)
Combination of FVL and PGM	9.05 fewer VTE (4.63 to 12.33)	
Antithrombin deficiency	9.70 fewer VTE (5.90 to 11.97)	0.53 fewer bleeds (1.76 fewer to 5.03 more)
Protein C deficiency	2.02 fewer VTE (0.82 to 2.66)	
Protein S deficiency	3.94 fewer VTE (1.34 to 5.32)	

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.



CANCER

For ambulatory patients with cancer receiving systemic therapy who have a family history of VTE and are otherwise determined to be at **low or intermediate risk** for VTE, the ASH guideline panel suggests testing for hereditary thrombophilia.

The panel suggests ambulatory thromboprophylaxis using DOAC for patients with thrombophilia and no thromboprophylaxis for patients without thrombophilia.

	Impact of thrombophilia testing strategy per 1000 patients who are first degree relatives of patients with VTE/ 6 months (142 more patients receive thromboprophylaxis)	
	VTE	**Major Bleeding**
Low Risk for VTE	6.85 fewer VTE (23.37 fewer to 0.16 more)	0.33 more bleeds (0.10 fewer to 2.02 more)
Intermediate Risk for VTE	9.04 fewer VTE (30.85 fewer to 0.21 more)	0.74 more bleeds (0.22 fewer to 4.49 more)

Middeldorp S, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138.

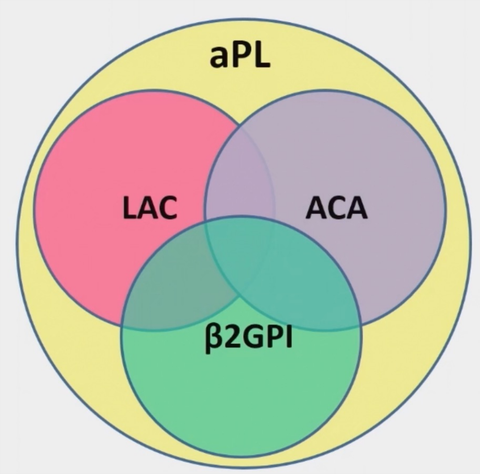
ASH GUIDELINES: are there some weak points?

(1) the importance of paroxysmal nocturnal hemoglobinuria (PNH) screening in patients with atypical sites of thromboses (eg, splanchnic or cerebral venous sinus thrombosis) in which there may be evidence of hemolysis or cytopenias;

JAK 2 mutations in unusual site thrombosis?

(2) the importance of warfarin as thromboprophylaxis in antiphospholipid syndrome as opposed to direct acting oral anticoagulants (DOACs).

Juneja M, Szer J. Commentary on the 2023 ASH guidelines for thrombophilia testing in venous thromboembolism. Blood Adv. 2023 Nov 14;7(21):6428-6429.



McCrae KR. How to diagnose and manage antiphospholipid syndrome

APL are found in association with several autoimmune disorders, but most common in normal individuals (2-4%).

APS prevalence ~ 50 cases/100,000.

ENTRY CRITERION
≥ 1 documented clinical criterion + ≥ 1 positive aPL test

CLINICAL DOMAINS	Points
VENOUS THROMBOEMBOLISM	
• *With high VTE risk profile*	1
• *Without VTE high risk profile*	3
ARTERIAL THROMBOSIS	
• *With a high CVD profile*	2
• *Without a high CVD profile*	4
MICROVASCULAR INVOLVEMENT*	
• *Suspected*	2
• *Established*	5
OBSTETRIC	
• *≥ 3 consecutive losses (<10w) and/or fetal death (<16w)*	1
• *Fetal death (≥16w <34w) without PEC/PI with severe features*	1
• *Severe PEC or severe PI (<34w)*	3
• *Severe PEC and severe PI (<34w)*	4
CARDIAC VALVE	
• *Thickening*	2
• *Vegetation*	4
THROMBOCYTOPENIA (lowest 20-130G/L)	2

LABORATORY DOMAINS (aPL)	Points
LUPUS ANTICOAGULANT (LA) POSITIVITY	
• *One time*	1
• *Persistent*	5
Anti-cardiolipin (aCL) / anti-BP2GP1 positivity**	
• ***IgM only :*** *moderate-high for aCL and/or anti-B2GP1*	1
• ***Presence of IgG***	
• ***moderate positivity*** *for aCL and/or anti-B2GP1*	4
• ***high posivitity*** *for aCL* ***OR*** *anti-B2GP1*	5
• ***high positivity*** *for aCL* ***AND*** *anti-B2GP1*	7

Only count the highest weighted criterion within each domain
Do not count if there is an equally or more likely explanation than APS

Microvascular involvement:
*-**Suspected:** livedo racemosa, livedoid vasculopathy (without pathology), aPL nephropathy (no pathology available), pulmonary hemorrhage (symptoms or imaging)*
*-**Established:** livedoid vasculopathy (with pathology), aPL nephropathy (with pathology), pulmonary hemorrhage (BAL or pathology), Myocardial disease (imaging or pathology), Adrenal disease (imaging or pathology)*

***aPL titers (by ELISA): moderate titer => 40-79U; high titer => ≥ 80U**

Classify as APS if ≥ 3 points from clinical criteria AND ≥ 3 points from aPL domain

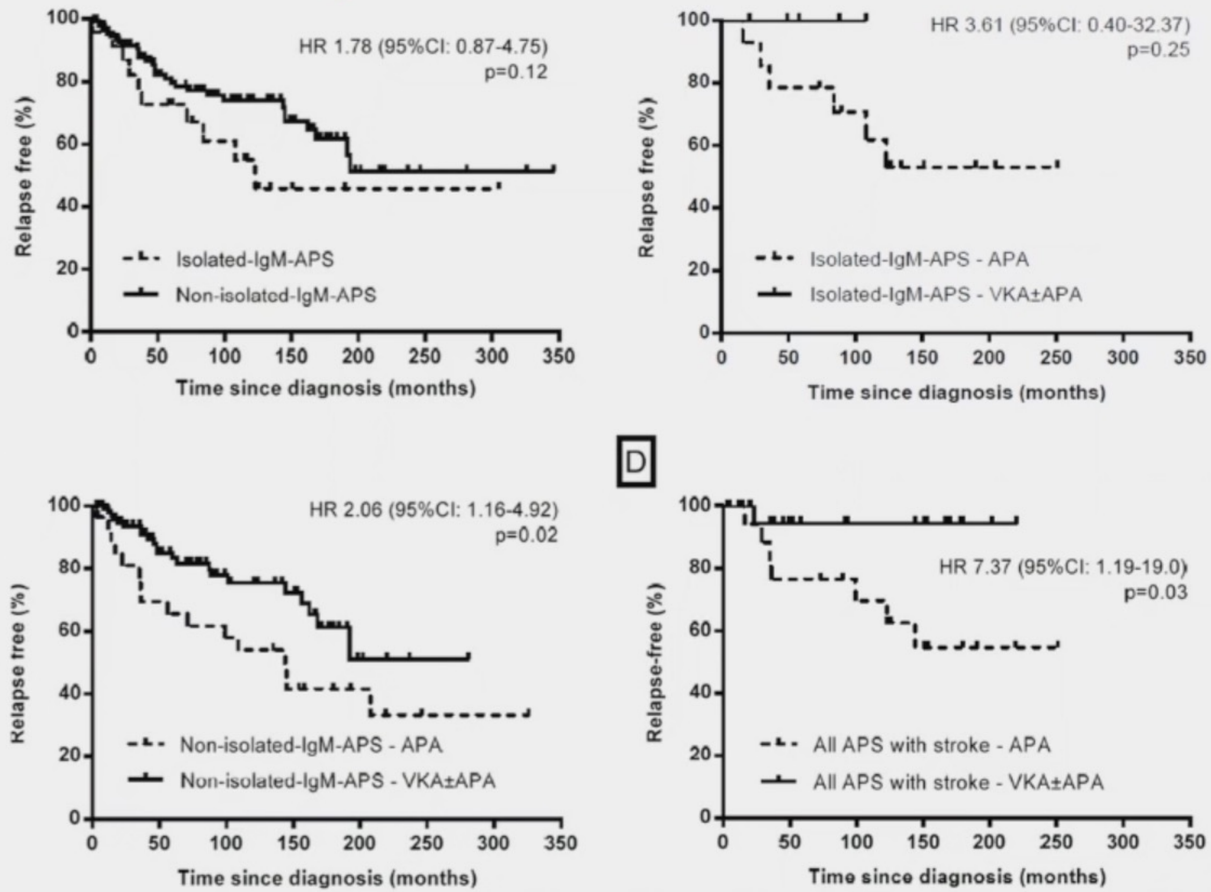
Education Program ASH 2023

Clinical Importance of IgM Isotype in APS?

- **Del Ross et al, Thromb Res 136:883, 2015**; retrospective analysis of 106 patients
  - Overall thrombosis rate: VTE 41.5%, ATE 45.3%, PE 10.4%, microvascular 2.8%
  - Overall frequency of IgG and IgM antibodies did not differ (P = 0.88)
  - 13 patients (12.3%) positive for isolated IgM aPL (all positive for aCL and aβ2GPI)
    - All medium to high levels, and 100% persistent over mean follow up of 10.2 years
    - Higher incidence of cerebrovascular disease (46.1% vs 30.0%; NS)
    - Higher mean age at time of thrombosis (P = 0.002)
    - Higher incidence of retinal thrombosis (P = 0.005, OR 27.6)

- **Urbanski et al, Stroke 49:2770, 2018**; Retrospective analysis of 168 APS patients, mean follow up 92.5 months
  - 24 (14.3%) had isolated IgM (9 IgM aCL, 2 isolated IgM aβ2GPI)
  - IgM antibodies were persistent, and remained isolated in 70.8%
  - Stroke more frequently led to APS diagnosis in isolated IgM aPL patients (OR 3.1, 95% CI 1.3-11.5, P = 0.018)
  - Use of antiplatelet agents alone (APA) was more common in isolated IgM APS (14/20 vs 28/134; P < 0.0001)
    - In patients presenting with stroke, APA alone used in 9/10 isolated IgM vs 10/33 non-isolated IgM (P = 0.002)

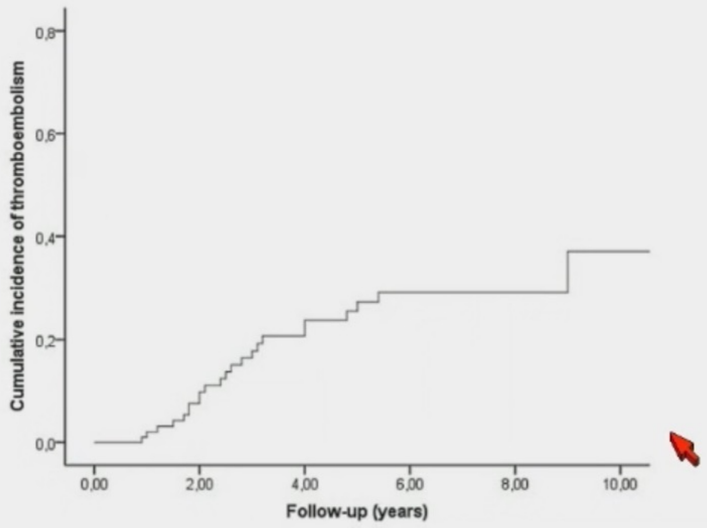
Clinical Importance of IgM Isotype in APS? (Urbanski et al)



- No difference in relapse-free survival between IgM-APS and non-isolated IgM APS
- Decreased relapse (thrombosis) free survival in both isolated IgM-APS, non-isolated IgM APS and the pooled cohort in patients on APA alone vs APA + VKA

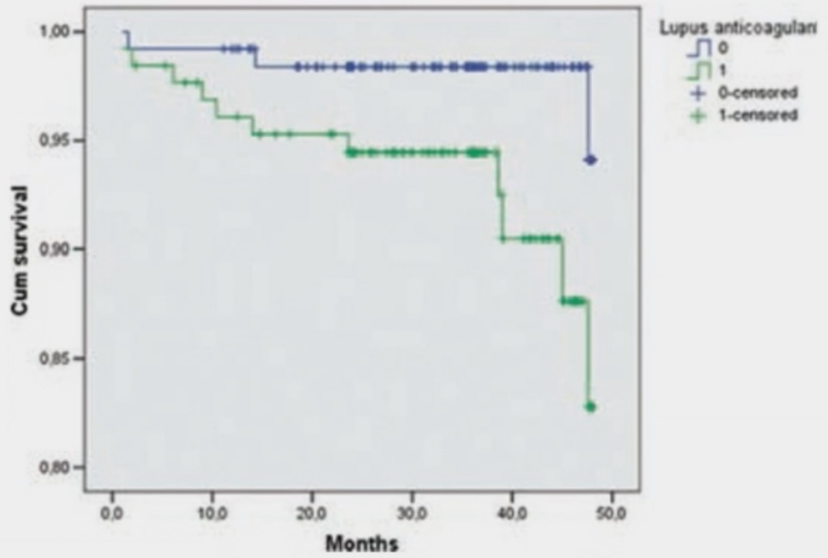
Absolute Risk of Thrombosis with aPL

Triple positive: 5.3%/year

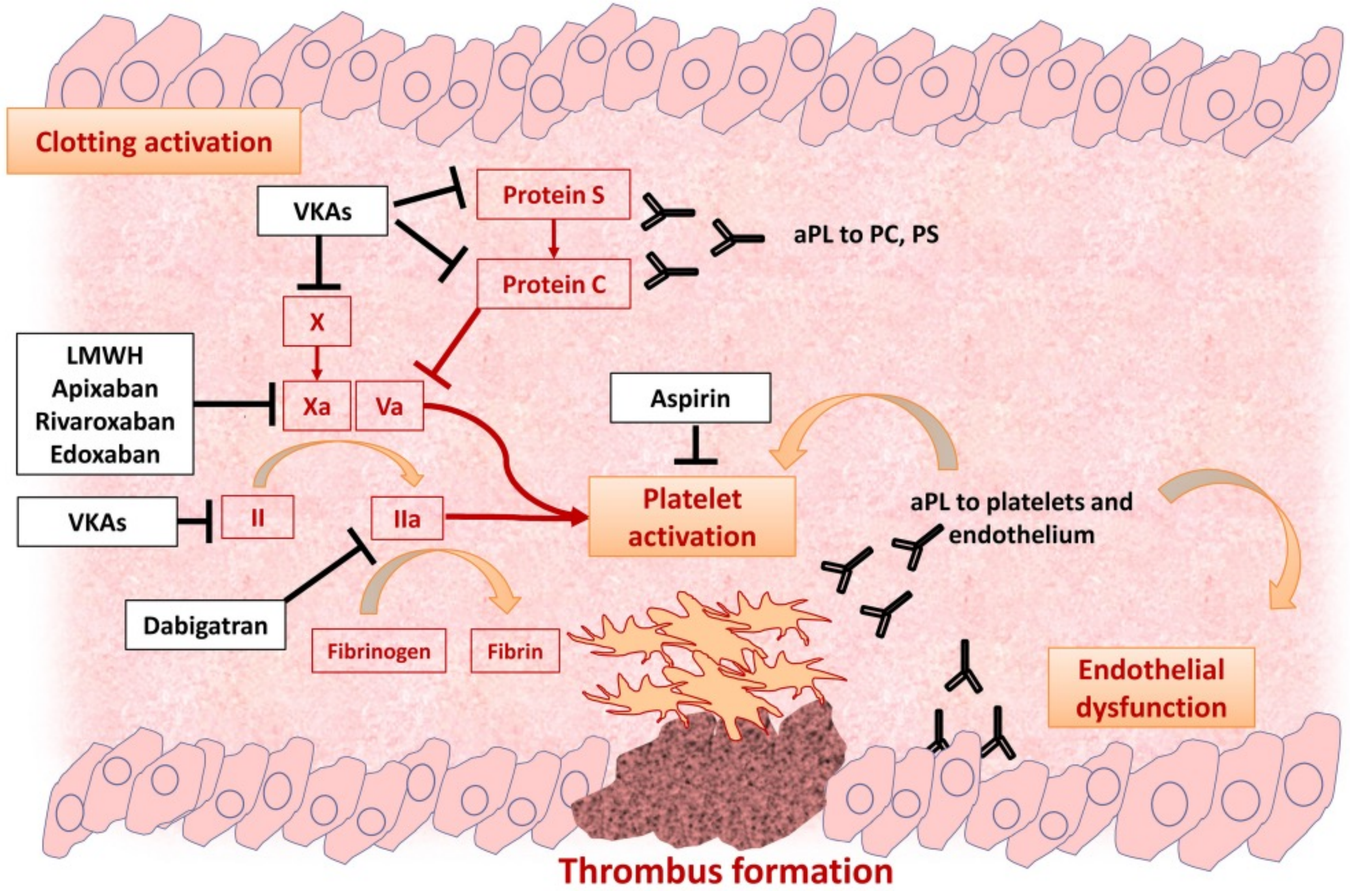


Pengo et al. Blood 118:4714, 2011

Any aPL 1.86%/year



Ruffatti et al Ann Rheum Dis 70:1083, 2011



Interaction between aPL and coagulation factors in clot formation and actions of anticoagulant drugs

Pastori D, et al. Use of Direct Oral Anticoagulants in Patients With Antiphospholipid Syndrome: A Systematic Review and Comparison of the International Guidelines. Front Cardiovasc Med. 2021 Aug 3;8:715878.

EULAR Recommendations

In asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with low - dose aspirin (LDA) (75 – 100 mg daily) is recommended

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

- ***Medium-high aPL titres***
  - Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma present in titres >40 IgG phospholipid (GPL) units or >40 IgM phospholipid (MPL) units, or >the 99th percentile, measured by a standardized ELISA.
  - Anti β2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma in titre >the 99th percentile, measured by a standardized ELISA.
- ***High-risk aPL profile***
  - The presence (in 2 or more occasions at least 12 weeks apart) of lupus anticoagulant (measured according to ISTH guidelines), or of double (any combination of lupus anticoagulant, aCL antibodies or anti β2 glycoprotein I antibodies) or triple (all three subtypes) aPL positivity, or the presence of persistently high aPL titres
- ***Low-risk aPL profile.***
  - Isolated aCL or anti β2 glycoprotein I antibodies at low-medium titres, particularly if transiently positive.

Tektonidou et al. Ann Rheum Dis 78:1296, 2019

A recent systematic revision collected 5 RCTs enrolling patients with thrombotic APS who received DOACs or VKA.

Table 1 Characteristics of included randomised trials

Study	Country	DOAC	Duration of follow-up	Sample size	Age, years	BMI, kg/m^2, mean (SD)	Female sex, %	Triple positive, %	Previous thrombotic event, %	
									Arterial	Venous
Woller *et al*[22] ASTRO-APS	USA	Apixaban 2.5 mg (5 mg) two times per day	365 days	Apixaban n=23 VKA n=25	Apixaban mean 46 (SD 12) VKA mean 49 (SD 14)	Apixaban 31 (8) VKA 32 (6)	Apixaban 83 VKA 84	Apixaban 30 VKA 28	Apixaban 26 VKA 44	Apixaban 87 VKA 72
Ordi-Ros *et al* [27] EUDRA-2010-019764-36	Spain	Rivaroxaban 20 mg once daily	35.4 months	Rivaroxaban n=95 VKA n=95	Rivaroxaban median 47 (IQR 40–55) VKA median 51 (IQR 38–63)	Rivaroxaban 28 (5.1) VKA 29 (6.0)	Rivaroxaban 64 VKA 63	Rivaroxaban 17.2 VKA 8.8	Rivaroxaban 39 VKA 36	Rivaroxaban 73 VKA 74
Pengo *et al*[25] TRAPS	Italy	Rivaroxaban 20 mg once daily	611 days	Rivaroxaban n=59 VKA n=61	Rivaroxaban mean 46.5 (SD 10) VKA mean 46.1 (SD 13)	Rivaroxaban 26.1 (6) VKA 25.5 (6)	Rivaroxaban 66 VKA 62	Rivaroxaban 100 VKA 100	Rivaroxaban 19 VKA 23	Rivaroxaban 64 VKA 64
Cohen *et al*[24] RAPS	UK	Rivaroxaban 20 mg once daily	210 days	Rivaroxaban n=57 VKA n=59	Rivaroxaban mean 47 (SD 17) VKA mean 50 (SD 14)	Rivaroxaban 28 (6) VKA 30 (6)	Rivaroxaban 74 VKA 71	Rivaroxaban 12 VKA 20	Rivaroxaban 0 VKA 0	Rivaroxaban 100 VKA 100
Goldhaber *et al*[26] RE-COVER, RE-COVER II and RE-MEDY	USA	Dabigatran etexilate 150 mg two times per day	210 days	Dabigatran etexilate n=71 VKA n=80	Dabigatran etexilate mean 48 (SD 15) VKA mean 47 (SD 19)	Dabigatran etexilate 29 (7) VKA 29 (6)	Dabigatran etexilate 34 VKA 39	N/A	Dabigatran etexilate 0 VKA 0	Dabigatran etexilate 100 VKA 100

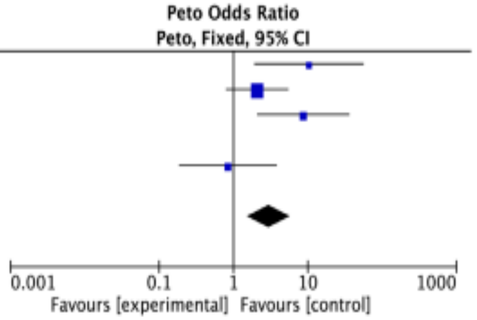
BMI, body mass index; DOAC, direct oral anticoagulant; N/A, not available; VKA, vitamin K antagonist.

Adelhelm JBH, et al. Therapy with direct oral anticoagulants for secondary prevention of thromboembolic events in the antiphospholipid syndrome: a systematic review and meta-analysis of randomised trials. Lupus Sci Med. 2023 Oct;10(2):e001018.

A New thrombotic event

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	6	23	0	25	14.9%	10.33 [1.90, 56.25]	2022
Ordi-Ros et al. 2019	12	95	6	95	45.6%	2.08 [0.79, 5.48]	2019
Pengo et al. (TRAPS) 2018	8	59	0	61	20.9%	8.68 [2.08, 36.23]	2018
Cohen et al. (RAPS) 2016	0	57	0	58		Not estimable	2016
Goldhaber et al. 2016	3	71	4	80	18.6%	0.84 [0.18, 3.82]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**3.01 [1.56, 5.78]**	
Total events	29		10				

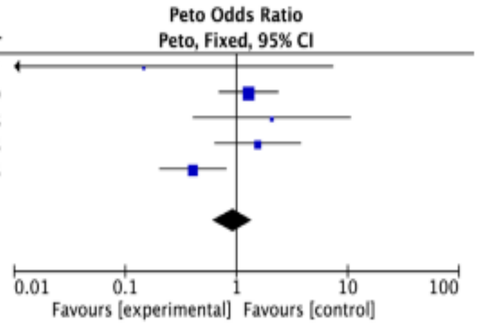
Heterogeneity: $Chi^2 = 7.43$, df = 3 (P = 0.06); $I^2 = 60\%$
Test for overall effect: Z = 3.30 (P = 0.0010)



B Overall bleeding event

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	0	23	1	25	1.0%	0.15 [0.00, 7.41]	2022
Ordi-Ros et al. 2019	31	95	26	95	41.1%	1.28 [0.69, 2.38]	2019
Pengo et al. (TRAPS) 2018	4	59	2	61	5.9%	2.08 [0.40, 10.66]	2018
Cohen et al. (RAPS) 2016	14	57	10	58	19.6%	1.55 [0.63, 3.80]	2016
Goldhaber et al. 2016	14	71	31	80	32.4%	0.41 [0.20, 0.81]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**0.92 [0.62, 1.37]**	
Total events	63		70				

Heterogeneity: $Chi^2 = 9.54$, df = 4 (P = 0.05); $I^2 = 58\%$
Test for overall effect: Z = 0.40 (P = 0.69)



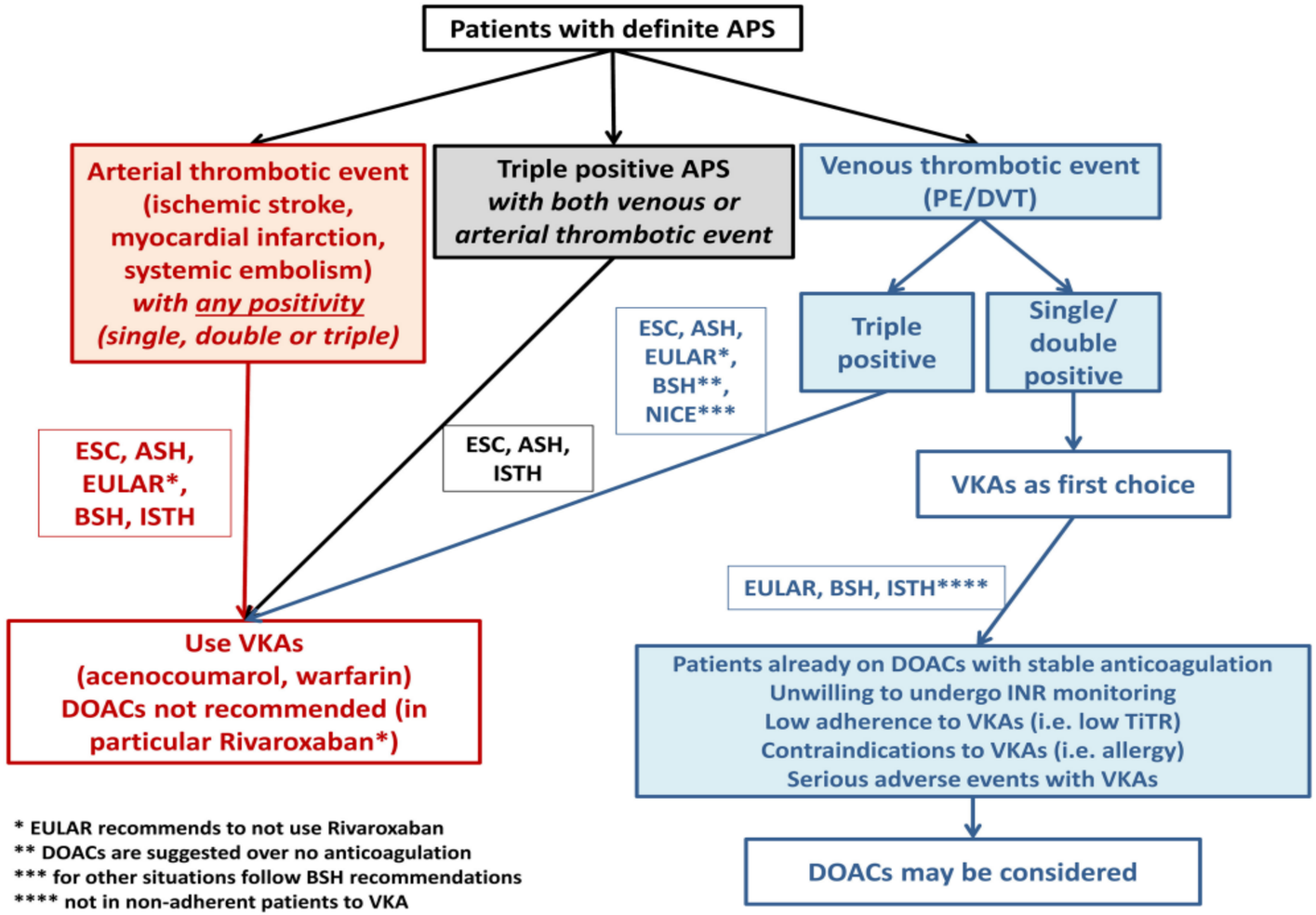
A recent systematic revision collected 5 RCTs enrolling patients with thrombotic APS who received DOACs or VKA.

DOACs were significantly worse than VKA for secondary prophylaxis, especially among patients with a history of AT (OR 5.5 (95% CI 2.1 to 14.7) p=0.0006).

Although less harmful, DOACs were also inferior to VKA in patients with a history of VT (OR 2.7 (95% CI 1.2 to 6.1) p=0.01).

The risk of thrombosis for the subgroup of aPL triple-positive patients was higher with DOACs than VKA (OR 3.8 (95% CI 1.66 to 8.65) p=0.002).

Adelhelm JBH, et al. Therapy with direct oral anticoagulants for secondary prevention of thromboembolic events in the antiphospholipid syndrome: a systematic review and meta-analysis of randomised trials. Lupus Sci Med. 2023 Oct;10(2):e001018.



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