POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

COORDINATORI
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TROMBOFILIA

Elena Rossi
Fondazione Policlinico A. Gemelli IRCCS
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DICHIARAZIONE

Elena Rossi

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Consulenza ad aziende con interessi commerciali in campo sanitario **(Novartis, Amgen, Bristol, Takeda, Sobi, Grifols, Janssen)**
- Partecipazione ad Advisory Board **(Novartis, Amgen, Bristol, Takeda, Sobi, Grifols, Janssen)**

Di cosa si e'parlato o scritto a New Orleans 2023….

- Utilità dei test per trombofilia si/no:
  per capire? per la prevenzione? per la terapia?
- Popolazioni speciali (i pazienti ambulatoriali con cancro)
- Trombofilia acquisita (APS)
- Gravidanza e trombofilia
- Quali test? Andare oltre i dosaggi funzionali
- Selezione del paziente

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).

Click image for video of experts discussing the new guidelines.

Learn more about the development process behind the VTE guidelines.

VTE Guideline Development

Download the PDF

Understanding Blood Clots

Download the PDF

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

Point/Counterpoint: The case for/against thrombophilia testing in many/most adults with unprovoked thrombosis.

Sponsor: EDUCATION

Program: Spotlight Sessions
Hematology Disease Topics & Pathways:
Clinical Practice (Health Services and Quality)

Monday, December 12, 2022: 2:45 PM-4:00 PM
288-290 (Ernest N. Morial Convention Center)

Chair:
Wendy Lim, MD, MSc, McMaster University

Disclosures:
Lim: *Pfizer:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS-Pfizer Alliance:* Honoraria; *Aspen:* Membership on an entity's Board of Directors or advisory committees; *Sobi:* Membership on an entity's Board of Directors or advisory committees.

The role of thrombophilia testing in clinical practice remains controversial. In the absence of clinical trials evaluating thrombophilia testing and its effect on decision-making and clinical outcomes, the utility of thrombophilia testing is largely guided by expert opinion. Thrombophilia testing is frequently requested and performed in patients with a family history of thrombosis, in patients with established thrombosis and in women with pregnancy complications. The merits and pitfalls of thrombophilia testing in these scenarios will be discussed and debated.

Point/Counterpoint: There case FOR thrombophilia testing in many/most adults with unprovoked thrombosis.

Stephan Moll, MD

University of North Carolina School of Medicine, Chapel Hill, NC

Point/Counterpoint: There case AGAINST thrombophilia testing in many/most adults with unprovoked thrombosis

Deborah M. Siegal, MD

Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada; Department of Medicine, University of Ottawa, Ottawa, ON, Canada

Thrombophilia

"Hereditary and/or acquired conditions associated with an increased predisposition to thrombosis"

Inherited

Antithrombin deficiency
Protein S deficiency
Protein C deficiency
Factor V Leiden (G1691A)
Prothrombin gene mutation (G20210A)

Acquired

Antiphospholipid syndrome
Myeloproliferative neoplasms
Paroxymal nocturnal hemoglobinuria
Cancer
Surgery
Immobility
Estrogens (pregnancy, oral contraceptives, hormone replacement)

VTE risk factors

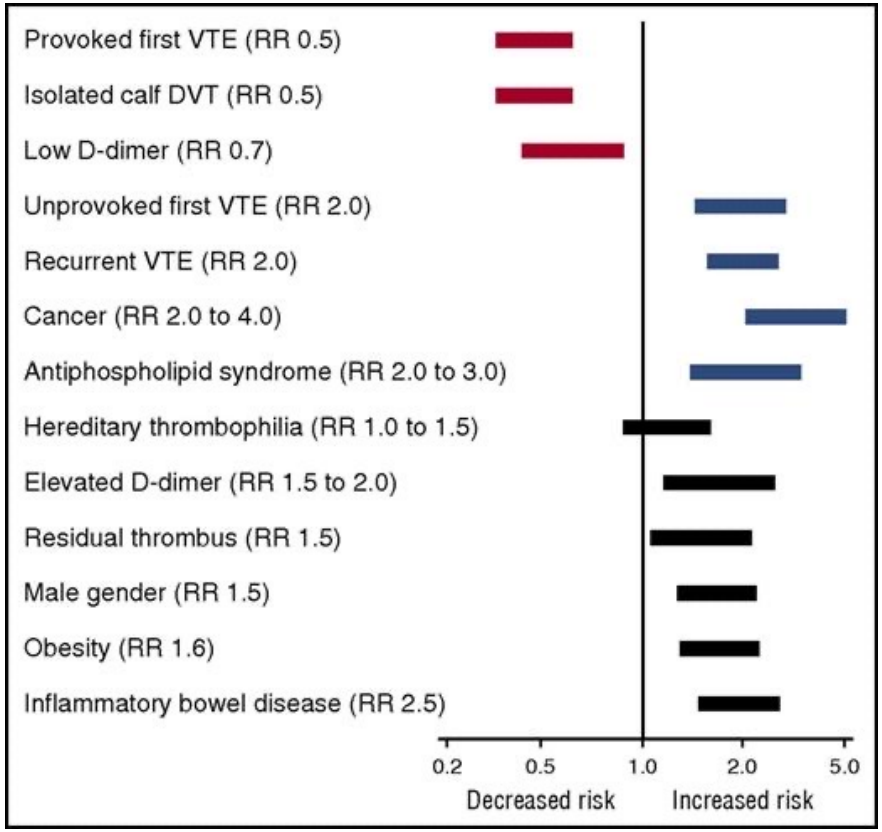
Weak risk factors (OR <2)	Moderate risk factors (OR 2-9)	Strong risk factors (OR>10)
• Bed rest >3 days • Diabetes mellitus • Arterial hypertension • Immobility due to sitting (e.g. prolonged travel) • Increasing age • Laparoscopic surgery • Obesity • Pregnancy • Varicose vains	• Arthroscopic knee surgery • Autoimmune diseases • Blood transfusion • Cantral venous lines • Intravenous catheters • Chemotherapy • Congestive heart failure or respiratory failure • Erythropoiesis-stimulating agents • Hormone replacement therapy • In vitro fertilization • Oral contraceptive therapy • Post-partum period • Infection (pneumonia,, HIV) • Inflammatory bowel disease • Cancer • Paralytic stroke • Superficial vein thrombosis • Thrombophilia	• Fracture of lower limb • Hospitalization for heart failure or atrial fibrillation • Hip or knee replacement • Major trauma • Myocardial infarction • Previuos VTE • Spinal cord injury

Kostantinides SV, et al. Eur Heart J 2019

Thrombophilia	Risk of first VTE (RR)	Risk of recurrence (?)
PTG20210A hetero	3.8	1.45
FV Leiden hetero	4.9	1.56
FV Leiden homo	18	1.2-2.65
FVL+PTG20210A	20	1.0-4.81
Protein C	24.1	2.8
Protein S	30.6	
Antithrombin	28.2	
APLA	-	1.41
ACA	1-6	1.53
LAC	2-6	2.83

Solo studi caso-controllo o metanalisi!

Segal J, et al. JAMA 2009, Ljferring WM, et al. Circulation 2010



Risk factor for recurrence

Lentz SR, Hematology Am Soc Hematol Educ Program 2016

DASH Predictive Score

Characteristic	Score
D-dimer abnormal 30 d after stopping anticoagulant therapy	+2
Age ≤ 50	+1
Sex: male	+1
Hormone-use provoked VTE	−2
Final score	**Annual risk (95% CI)**
≤1	3.1% (2.3–3.9)
2	6.4% (4.8–7.9)
≥3	12.3% (9.9–14.7)

HERDOO2 Rule

	Predictor	Scoring
H	Hyperpigmentation	1 point total, if any one of these criteria is present
E	Edema	
R	Redness of either leg	
D	D-dimer ≥ 250 µg/L while anticoagulated	1
O	Obesity with BMI ≥ 30 kg/m^2	1
O	Older age, ie, ≥ 65 years	1

Decision Making:		
Women:	0-1	Discontinue anticoagulation
	≥2	Continue anticoagulation
All men		Continue long-term anticoagulation

Tosetto A, et al. J Thromb Haemost 2012, Rodger MA, et al. BMJ 2017

Prevalence of VTE based on D-dimers positivity was comparable between patients on anticoagulation and patients without anticoagulation

Vicky Mai, *Emily S.L. Martens, Marc Righini, Sam Schulman, Venkatesh Thiruganasambandamoorthy, Susan Kahn, Veronica Bates, Amanda Pecarskie, Michael J. Kovacs, Shaun Visser, Sudeep P Shivakumar, Melanie Tan, Marc A. Rodger, Dimitrios Scarvelis, Aurelien Delluc, Philippe Girard, Menno V Huisman, Philip S. Wells, Frederikus A Klok, Gregoire Le Gal*

The PREDICTORS study is an international prospective multicenter observational cohort study of outpatients with suspected VTE recurrence. The aim of the study is to evaluate the performance of D-dimers in patients with a history of VTE based on anticoagulation status.

D-dimer measurements were used in the diagnostic management of 482 patients, of which, 168 patients were on anticoagulation and 314 were not on anticoagulation.

Amongst patients on anticoagulation, 4/90 (4.4%; 95%CI 1.2%-11.0%) and 21/78 (26.9%) had recurrent VTE at enrollment in patients with negative and positive D-dimers, respectively. During follow-up, no recurrent VTE occurred in patients with negative D-dimers.

Amongst patients without anticoagulation, 2/79 (2.5%; 95%CI 0.3%-8.9%) and 117/235 (49.8%) had recurrent VTE at enrollment in patients with negative and positive D-dimers, respectively. One recurrent VTE occurred during follow-up amongst patients with initial negative D-dimers (1.3%; 95%CI 0.0-7.0%).

Prevalence of VTE based on D-dimers positivity was comparable between patients on anticoagulation and patients without anticoagulation

“ Before ordering a test decide what you will do if it is 1) positive or 2) negative. If both answers are the same, don’t take the test”
A. Cochrane

Caveats

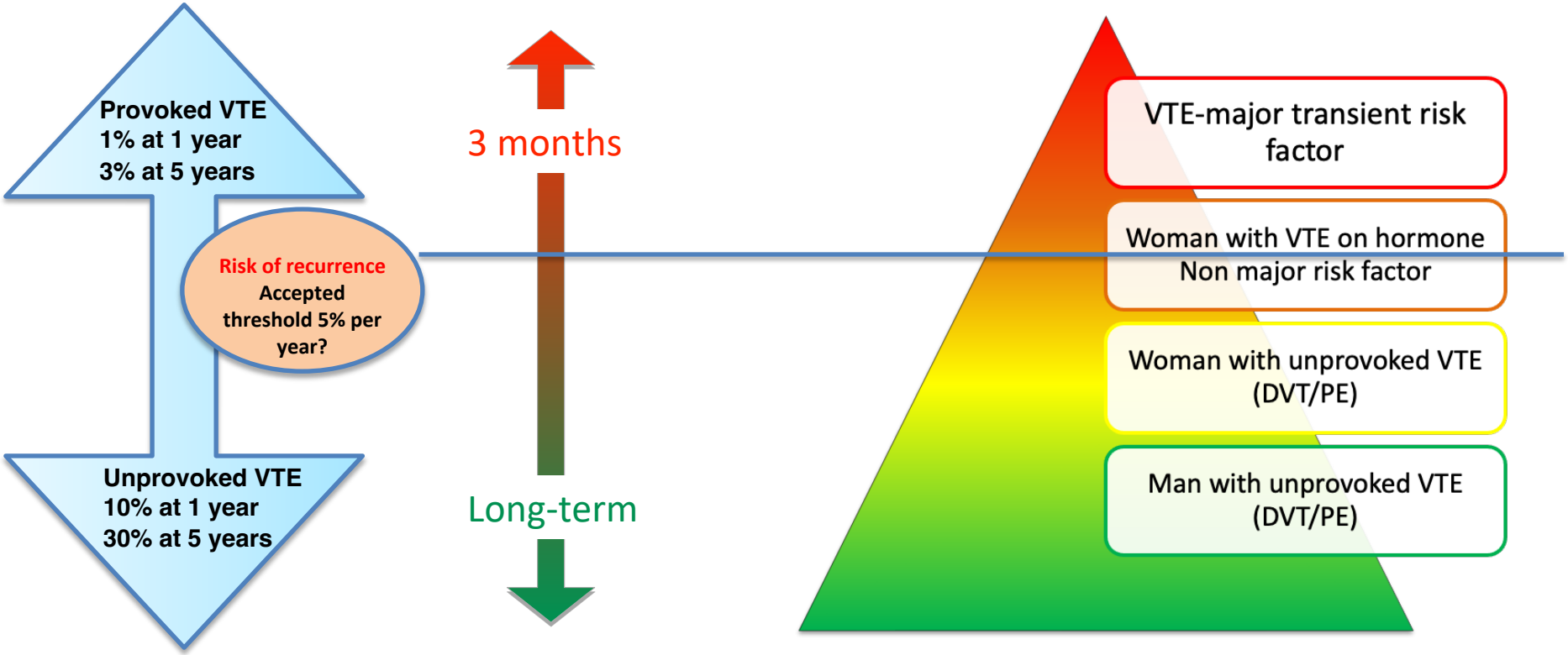
1. Over-focus on the thrombophilia
2. Wrong test is ordered
3. Misinterpretation of tests
4. Wrong decision making based on test result
5. Cost of testing

Two comments….

"One cannot be dogmatic about thrombophilia testing due to non-existence of quality clinical outcome studies whether decision on length of anticoagulation after a VTE based on thrombophilia testing results has an impact on clinical outcomes or quality of life"

"I should perform thrombophilia testing to detect strong thrombophilia that would be ONE of the reasons to continue anticoagulation when the patient and I do not quite know whether to stop or continue anticoagulation after a VTE"

Intermediate risk of recurrence or higher risk patients who hate to be on blood thinners


Provoked VTE
1% at 1 year
3% at 5 years
Risk of recurrence
Accepted threshold 5% per year?
Unprovoked VTE
10% at 1 year
30% at 5 years
3 months
Long-term
VTE-major transient risk factor
Woman with VTE on hormone
Non major risk factor
Woman with unprovoked VTE (DVT/PE)
Man with unprovoked VTE (DVT/PE)

Thrombophilia testing YES

1. DVT/PE, intermediate risk recurrence
2. Unprovoked VTE at unusual locations
3. Arterial thrombosis in the young, unexplained
4. VTE, patients requests testing
5. Family members (if "strong thrombophilia" in index pt)
6. Pregnancy loss, unexpleined

Thrombophilia testing NO

1. Most common mutations (up to 5% of population) confer SMALL absolute increase in risk for first VTE -most carriers never experience VTE
2. Not strong predictors of recurrent VTE
3. Do not affect acute management and clinical risk factors generally guide long-term management
4. Family history associated with increased risk irrespective of mutations
5. Important harms: false reassurance by negative test, unnecessary anxiety,insurability issues, cost
6. Testing may be helpful in limited situations but requires counseling and interpretation

Thrombophilia Gene Mutations for the Prediction of Venous Thromboembolism in Ambulatory Cancer Patients

Danielle Carole Roy, *Tzu-Fei Wang, Ranjeeta Mallick, Philip S. Wells, Marc Carrier and Steven Hawken*

Table 1. Distribution of Thrombophilia Gene Mutations in Ambulatory Cancer Patients According to Occurrence of Venous Thromboembolism (VTE)

Predictors		VTE (n=438) Yes (n=39)	VTE (n=438) No (n=399)	No. of Missing values	*P-value*
Prothrombin gene G20210A	Mutated	1 (2.56)	8 (2.01)	0	*0.5715*
	Wild	38 (97.44)	391 (97.99)		
Factor XI gene	Mutated	31 (79.49)	300 (75.19)	0	*0.6967*
	Wild	8 (20.51)	99 (24.81)		
FGG gene	Mutated	12 (31.58)	166 (42.03)	5	*0.2313*
	Wild	26 (68.42)	229 (57.97)		
SERPINE10 gene	Mutated	0	3 (0.75)	1	*1.0000*
	Wild	39 (100.00)	395 (99.25)		
Factor V gene K858R	Mutated	14 (35.90)	182 (45.61)	0	*0.3116*
	Wild	25 (64.10)	217 (54.39)		
Factor XIII gene	Mutated	17 (44.74)	174 (43.72)	2	*1.000*
	Wild	21 (55.26)	224 (56.28)		
Factor V Leiden	Mutated	6 (15.38)	14 (3.52)	0	***0.0052****
	Wild	33 (84.62)	385 (96.49)		
ABO gene	A, B or AB	31 (79.49)	234 (58.94)	2	***0.0152****
	O	8 (20.51)	163 (41.06)		

Abbreviations: FGG= Fibrinogen gamma chain, VTE= Venous Thromboembolism
*Significant difference (alpha<0.05)

The role of inherited thrombophilia on the risk of VTE in cancer patients is unclear and determination of thrombophilic status is not part of clinical practice.

Blood samples at baseline visit from patients enrolled in AVERT trial (apixaban as thromboprophylaxis in ambulatory cancer patients with intermediate to high risk for VTE) were used to perform a panel of thrombophilia gene mutations.

The panel includes Prothrombin G20210A mutation, Factor XI, Fibrinogen gamma chain (FGG), SERPINA10, Factor V K858R, Factor XIII, Factor V Leiden and, ABO blood gene mutations.

During the 7-months of follow-up, there were 39 VTE events including 25 deep vein thrombosis (DVT), 13 pulmonary embolisms (PE), and 1 DVT with PE.

DRAFT ACR/EULAR ANTIPHOSPHOLIPID SYNDROME CRITERIA PRESENTED AT #ACR22

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

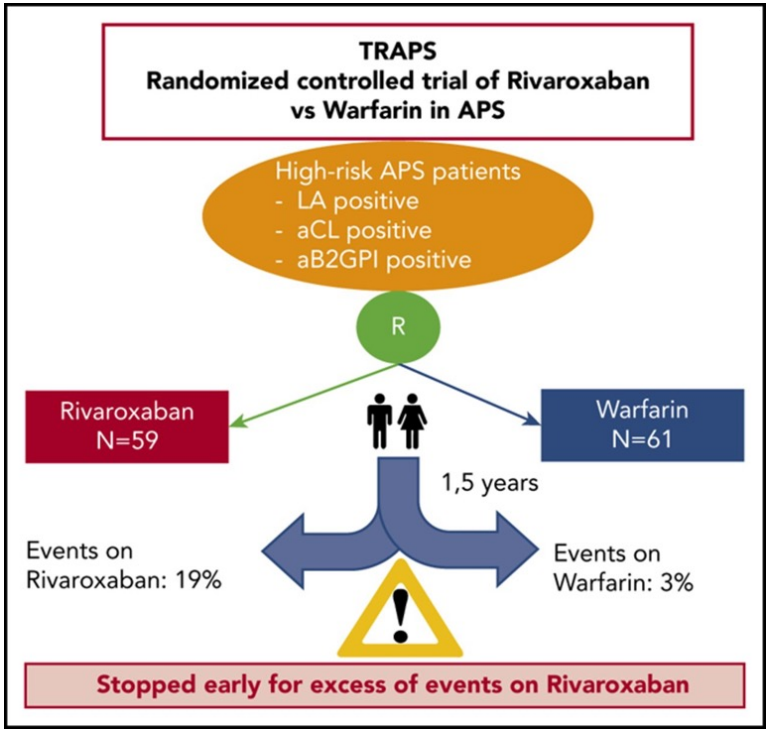
Adapted by @Lupusreference from #ACR22 session 13S150 (Erkan et al.)

RAPS TRIAL

Rivaroxaban vs Warfarin in antiphospholipid syndrome

Warfarin recommended for:

- triple positive
- arterial thrombosis
- organ involvement with small vessel disease
- heart valve disease according to Sydney criteria



Cohen H, et al. Lancet Haematol 2016, Pengo V, et al. J Thromb Haemost 2021

Anticoagulation Practice, Recurrent Thrombosis, and Major Bleeding in Antiphospholipid Syndrome - a Multicentre Observational Study in the United Kingdom

Christina Crossette-Thambiah, *Indika Rajakaruna, Zain Odho, Andrew Doyle, Karen Breen, Michael Laffan and Deepa Jayakody Arachchillage*

Table 1: Baseline Characteristics, thrombotic and bleeding complications and the treatments of the patients included in the study

Baseline Characteristics (n=500)	Number (%)	Baseline Characteristics (n=500)	Number (%)
Male	333 (66.6%)	**Vascular Risk Factors**	
Female	166 (33.4%)	HTN	69 (13.8%)
Age 18-30	56 (11.2%)	T2DM	46 (9.2%)
Age 31-50	160 (32%)	Hypercholesterolaemia	128 (25.6%)
Age 51-70	212 (42.4%)	Smoking	63 (12.6)
Age >71	72 (14.4%)	High BMI	43 (8.6%)
Triple aPL positive (LA+B2MG+aCL)	155 (31%)	**Current Anticoagulant**	460/500 (92%)
Double aPL positive (LA+B2MG/LA+aCL/acl+ B2MG)	163 (32.6%)	Warfarin	342 (74.3%)
Single aPL positive (LA/B2MG/aCL)	182 (36.4%)	Other VKA	10 (2.1%)
Thrombotic APS	461 (92.2%)	DOAC	86 (18.7%)
Obstetric APS	69 (13.8%)	LMWH	16 (3.5%)
Underlying AI disease	187 (37.3%)	Fondaparinux	16 (3.5%)
Thrombosis		Antiplatelet treatment	102 (20.4)
Venous	304 (65.9%)	Hydroxychloroquine	109(21.8%)
Arterial	192(41.6%)	Recurrent Thrombosis	192 (41.6%)
Microvascular	22(4.8%).	Major Bleeding	13 (2.6%)
Nature of Thrombosis		Minor Bleeding	16 (3.2%)
DVT	146 (31.7%)		
PE	92 (20%)		
CVA	114 (24.7%)		
TIA	20 (4.3%)		
CVST	100 (21.7		
PVT	15 (3.3%)		

LA: lupus anticoagulant ,B2MG beta2Microglobulin, aCL anticardiolipin, DVT Deep Vein Thrombosis, PE Pulmonary embolus, CVA Cerebrovascular Accident, TIA Transient Ischemic Attach, CVST Cerebral Venous Sinus Thrombosis, PVT Portal Vein Thrombosis, HTN. Hypertension, T2DM Type 2 Diabetes, BMI Body Mass Index, VKA Vitamin K Antagonist, DOAC Direct Oral Anticoagulant, LWMH Low Molecular Weight Heparin

Dual or triple aPL status, smoking, hypertension, and ischemic heart disease were significantly associated with recurrent thrombosis on univariate but not multivariate analysis, confirming a multifactorial contribution for thrombosis.

In both univariate and multivariate analysis, increasing age was significantly associated with major bleeding (HR 1·05, 95%CI 1.01-1·10; P = 0·022). Notably, a higher target INR was associated with major bleeding.

VKA remains the main anticoagulant of use in patients with thrombotic APS, even if there are wide variations in the practice within the UK which are mostly, but not wholly, adherent to national guidelines especially in the context of triple positive thrombotic disease and arterial thrombosis.

A Role of Immunothrombosis in Acquired Antibody-Mediated Thrombophilia's: Classical Complement and Neutrophil Activation in APS and HIT

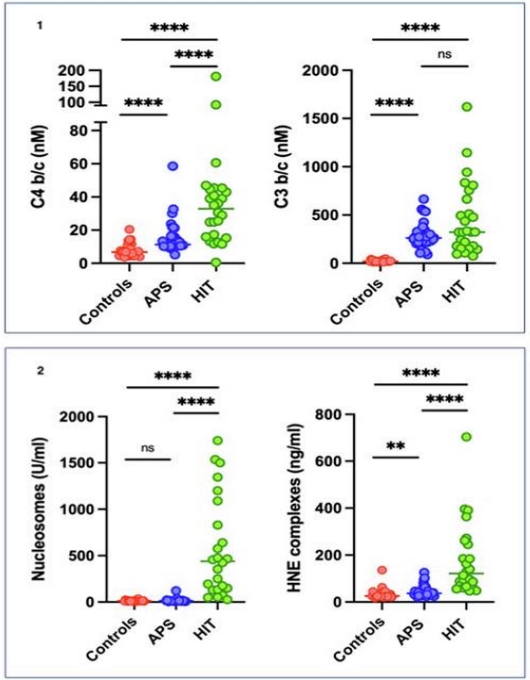
Annina Capraru, *Tiphaine Ruggeri, Noelia Schärz, Laura Delvasto-Nunez, Justine Brodard, Gerard van Mierlo, Johanna A. Kremer Hovinga Strebel, Anne Angelillo-Scherrer, Ilse Jongerius, Sacha S. Zeerleder*

There is growing evidence that complement- and neutrophil activation in the form of neutrophil extracellular traps (NETs) play an important role in the pathogenesis of thrombosis, the so-called **"immunothrombosis"**.
It has been demonstrated, that complement activation products efficiently induce neutrophil activation in the form of NETs resulting in thrombosis (ex. sepsis, PNH), and viceversa therapeutic complement inhibition prevents neutrophil activation.

Patients with APS and HIT showed significantly higher levels of complement activation products both classical (C4b/c) and alternate (C3b/c) pathway as compared to healthy controls.

Similarly elastase-a1antitrypsin complexes (HNE) and nucleosomes, which are markers for neutrophil activation, were higher in HIT and APS patients compared to healthy subjects.

Furthermore C4b/c levels were significantly higher in APS high-risk compared to low-to-intermediate risk patients.



Anticoagulation and/or Antiplatelet in Thrombotic Antiphospholipid Syndrome with Previous Arterial Thromboembolism: A Retrospective Cohort

Norah Alnegheimish, *Eric Kaplovitch, Rita Selby and Jameel Abdulrehman,*

From an initial 891 patients with at least one positive antiphospholipid antibody test, 120 patients met criteria for thrombotic APS and had a previous ATE. 62 patients were excluded for different reasons. After exclusions, 58 patients with a total of 89 thrombotic events were included in the analysis with a cumulative follow up of 248.4 years.

Antithrombotic regimen	Years of follow up	Thrombotic events	ATE	MB	CRNMB
		events per 100 patients-years (95% CI)			
VKA (target INR 2-3)	121.2	3.3 (0.9-8.4)	3.3 (0.9-8.4)	4.1 (1.3-9.6)	11.6 (6.3-19.4)
VKA (target INR 2-3) with AP	78.0	2.6 (0.3-9.3)	2.6 (0.3-9.3)	5.1 (1.4-13.1)	20.5 (11.7-33.3)
VKA (target INR >3) with AP	19.6	0 (0-18.8)	0 (0-18.8)	0 (0-18.8)	15.3 (3.2-44.7)
AP alone	29.6	6.8 (0.8-24.4)	3.4 (0.1-18.8)	3.4 (0.1-18.8)	3.4 (0.1-18.8)
Overall	248.4	3.2 (1.4-6.3)	2.8 (1.1-5.8)	4.0 (1.9-7.4)	13.7 (9.5-19.1)

Table 2. Outcomes in thrombotic antiphospholipid patients with previous arterial thrombosis. CI – confidence interval; VKA – vitamin K antagonist; INR – international normalized ratio; ATE – arterial thromboembolism; MB – major bleeding; CRNMB – clinically relevant non-major bleeding; AP – antiplatelet therapy.

There were a total of 10 MB events including 4 intracranial bleeding (ICB), 1 gastrointestinal bleeding, and 5 other types of MB. ICB occurred in 3 patients on VKA (t INR 2-3) and 1 on VKA (t INR 2-3) with AP.

This retrospective cohort of 58 patients with TAPS and a previous ATE demonstrated a numerically higher risk of recurrent thrombosis with AP alone and a numerically higher risk of MB with the combination VKA and AP.

Comparative Analysis of Direct Oral Anticoagulants and Vitamin K Antagonists in Antiphospholipid Syndrome Patients

Maha AT Elsebaie, *Zoe Alexandra Wickham, Stephanie Debragga, Juan Li and Manila Gaddh*

A total of 153 patients with confirmed APS diagnosis were included in the study. Study subjects must have experienced acute thrombosis between 01/01/2012 and 12/31/2018 and started anticoagulation therapy with DOACs or VKAs.

The authors found no statistically significant differences in risk of recurrent thrombosis or CRB events among patients who were started on DOAC vs. VKAs. The number of arterial thrombosis events was minimal and similar in both treatment groups: N=3 in DOAC group vs. N=5 in the VKA group.

Patients treated with rivaroxaban had a similar risk of recurrent thrombosis (log rank, *p*-value=0.629) and CRB events (log rank, *p*-value=0.631) compared to those treated with apixaban.

The risk of recurrent thrombosis was not affected by degree of aPL positivity or previous history of arterial thrombosis in multivariate models (HR 0.791, 95% CI 0.357 - 1.751)

Comparative Analysis of Direct Oral Anticoagulants and Vitamin K Antagonists in Antiphospholipid Syndrome Patients

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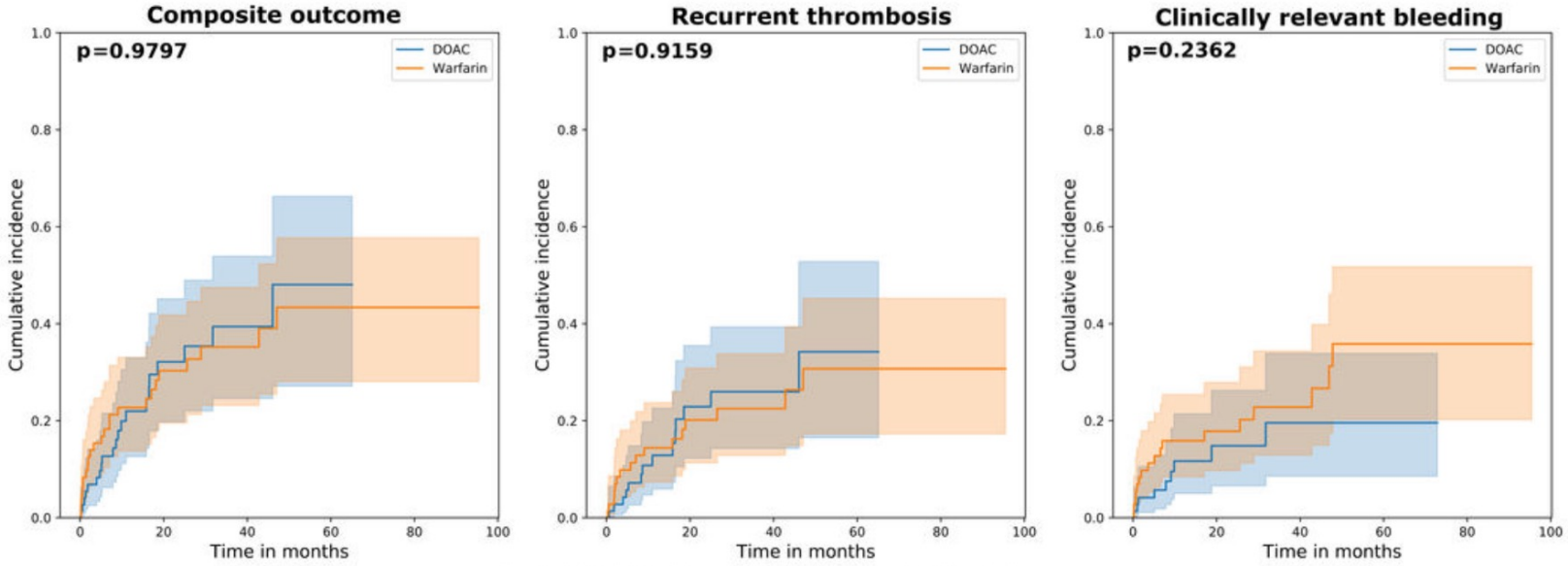

Late-Breaking Abstracts Session

Program: General Sessions

Tuesday, December 13, 2022: 9:00 AM-10:30 AM
Hall E (Ernest N. Morial Convention Center)

Co-chairs:
David A. Garcia, MD, University of Washington and Olatoyosi Odenike, MD, University of Chicago

Disclosures:
No relevant conflicts of interest to declare.

This highly anticipated session highlights the Joint Program Committees' selections of the highest-impact abstracts, featuring substantive, novel, and groundbreaking data that were not available by the general abstract submission deadline and would otherwise not be presented at the ASH annual meeting.

LBA-5 Low-Molecular-Weight Heparin Versus Standard Pregnancy Care for Women with Recurrent Miscarriage and Inherited Thrombophilia (ALIFE2): An Open-Label, Phase III Randomized Controlled Trial

Siobhan Quenby, MD PhD[1], Katie Booth[2*], Louise Hiller, PhD[2*], Arri Coomarasamy[3*], Eva Hamulyák, MD[4*], Luuk Scheres[5*], Paulien G. de Jong[4*], Thijs van Haaps[4*], Lauren J. Ewington[2*], Shreeya Tewary[2*], Mariëtte Goddijn, MD PhD[4*] and* ***Saskia Middeldorp, MD, PhD***[6]

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[4]*Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands*
[5]*Radboud University Medical Center, Nijmegen, Netherlands*
[6]*Internal Medicine, Radboud University Medical Center, Nijmegen, Nijmegen, Netherlands*

LBA-5 (MIDDELDORP)

Blood Thinners During Pregnancy Made No Difference to Live Birth Rate in Women with Recurrent Miscarriage and Inherited Thrombophilia

The ALIFE2 study showed that with standard pregnancy care – and without expensive testing and burdensome medication use – slightly more than

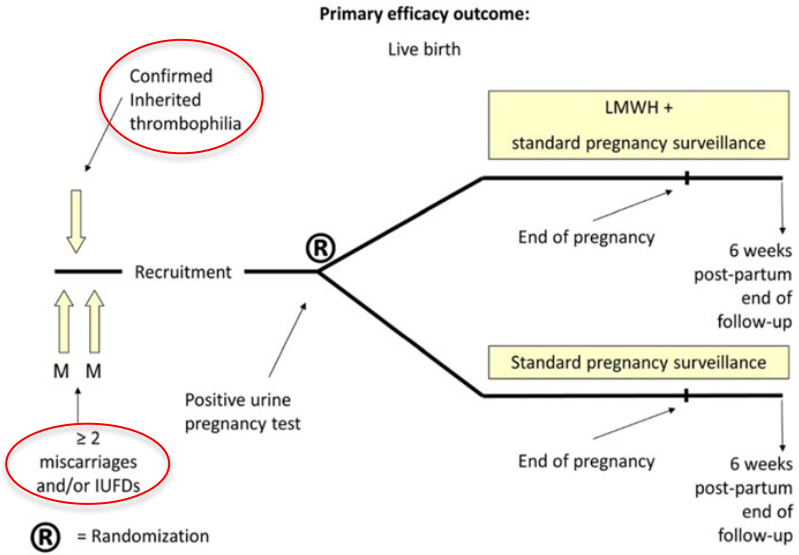
70% of women had a live birth.

The research, which may positively impact reproductive health care for people with blood disorders, **recommends against routine testing for thrombophilia** in this population of pregnant women, as the tests are costly and should only be done if it will have clinical impact.

2022 PRESS BRIEFING HIGHLIGHTS | 64th ASH Annual Meeting & Exposition

Low-Molecular-Weight Heparin Versus Standard Pregnancy Care for Women with Recurrent Miscarriage and Inherited Thrombophilia (ALIFE2): An Open-Label, Phase III Randomized Controlled Trial

Siobhan Quenby, *Katie Booth, Louise Hiller, Arri Coomarasamy, Eva Hamulyák, Luuk Scheres, Paulien G. de Jong, Thijs van Haaps, Lauren J. Ewington, Shreeya Tewary, Mariëtte Goddijn and Saskia Middeldorp.*



The ALIFE 2 trial was an investigator-initiated, international open-label randomized controlled trial.

Patients eligible were women (18-42 years) who had two or more pregnancy losses and confirmed inherited thrombophilia (factor V Leiden, prothrombin 20210A mutation, antithrombin, protein C or protein S deficiency) and were actively trying to conceive or less than 7 weeks pregnant.

Between August 2012 and January 2021, a total of 10,626 women with recurrent miscarriage were assessed for eligibility: among 428 women with inherited thrombophilia, 326 women conceived and were randomized: 164 were assigned to the LMWH group and 162 were assigned to the standard surveillance group.

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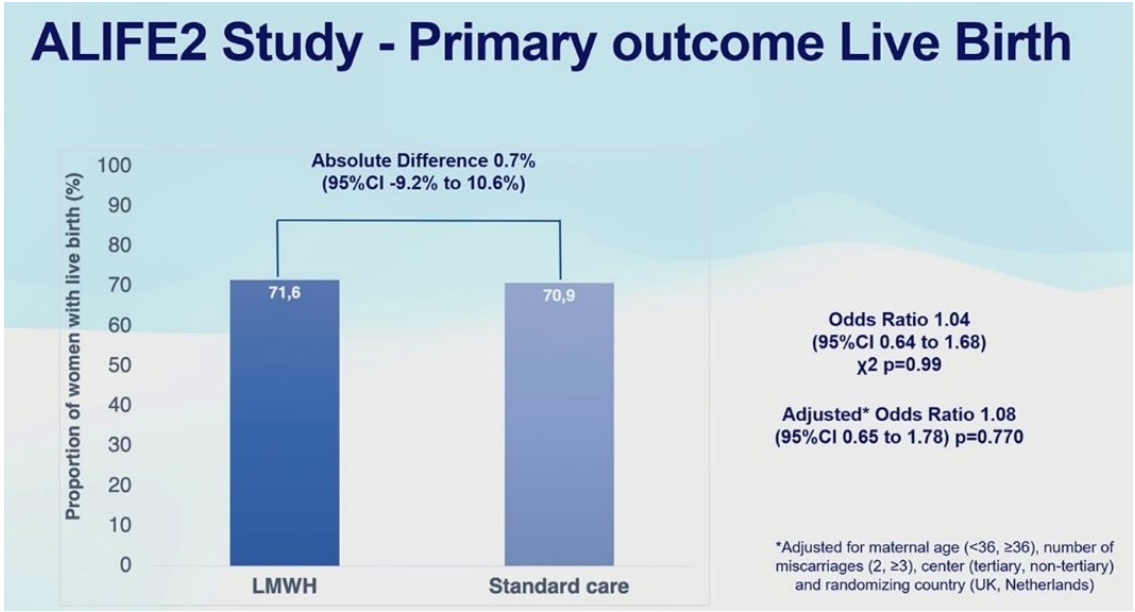

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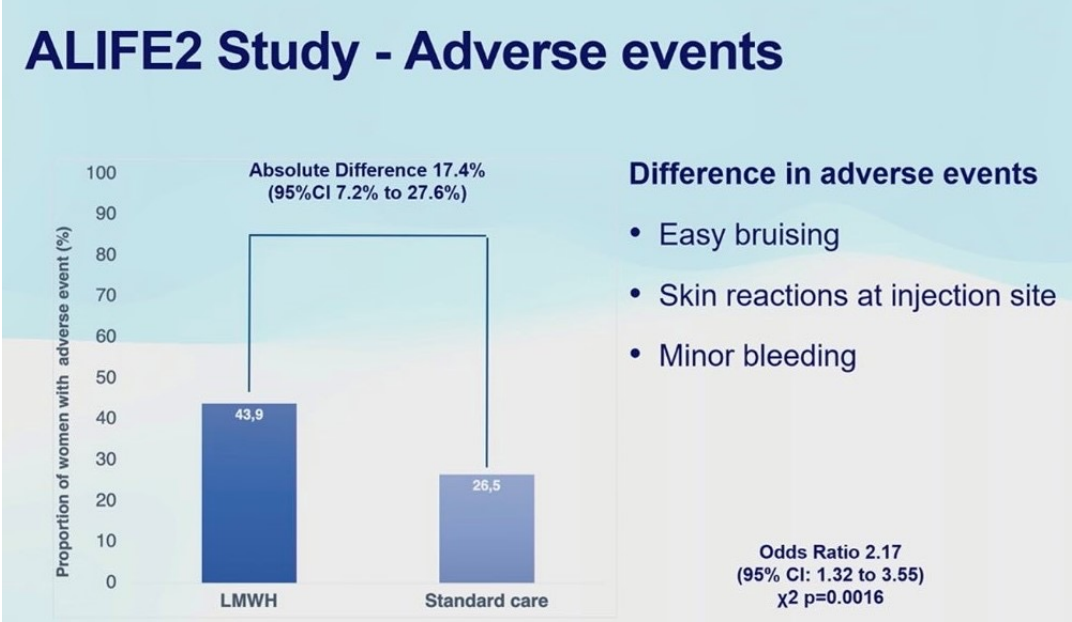

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	LMWH (N=164)	Standard care (N=162)
Mean age – years (SD)	33.5 (5.2)	33.3 (5.3)
Number of miscarriages – 3 or more	118 (72%)	110 (68%)
Factor V Leiden hetero/homozygous	95 (58%)/ 5 (3%)	89 (55%)/ 0 (0%)
Prothrombin mutation hetero/homozygous	39 (24%)/0 (0%)	44 (27%)/ 2 (1%)
Antithrombin deficiency	2 (1%)	5 (3%)
Protein C deficiency	5 (3%)	8 (5%)
Protein S deficiency	23 (14%)	21 (13%)
Combined thrombophilia	5 (3%)	7 (4%)

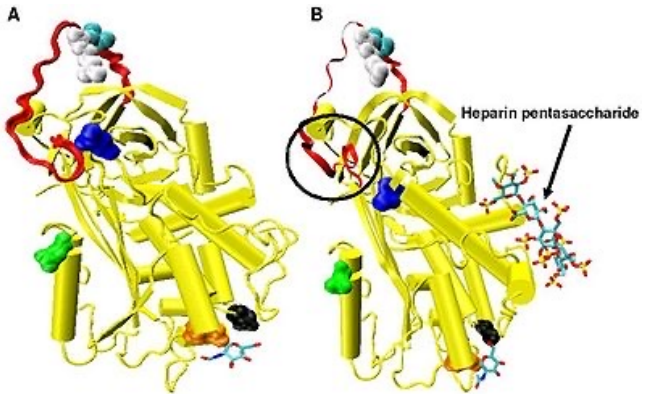
Molecular and Biological Characterization of Transient Antithrombin Deficiency: A New Concept in Congenital Thrombophilia

Maria Eugenia Eugenia de la Morena-Barrio, *Carlos Bravo-Perez, Belen De La Morena-Barrio, Antonia Miñano, Jose Padilla, Rosa Cifuentes-Riquelme, Pedro Garrido, Vicente Vicente, Javier Corral*

This work included a total of 444 consecutive unrelated subjects, referred from more than 20 European hospitals during 23 years (1998-2021), with potential antithrombin deficiency, based on at least one positive functional assay.

Using high-throughput nucleotide sequencing for genetic analysis of *SERPINC1, a* genetic defect was observed in 84.6% of 305 cases with constitutive deficiency: 248 in *SERPINC1* and 10 had N-glycosylation defects.

In 61 cases of 139 cases (43.9%) who had normal antithrombin activity in at least one sample, all with thrombosis, had missense *SERPINC1* mutations (N=48), with two recurrent mutations (p.Ala416Ser, antithrombin Cambridge II, N=15 and p.Val30Glu, antithrombin Dublin, N=12) or N-glycosylation defects (N=13).



Two mechanisms explained transient deficiency: the limitation of current functional methods to detect some variants, and the influence of external factors (conformational stress, generation of thrombin, alcohol intake) on the pathogenic consequences of these mutations.

Antithrombin deficiency is underestimated and cases with moderate risk of thrombosis may be missed if only functional methods and classical diagnostic algorithms are used.

A Multidisciplinary Quality Improvement Project to Improve Appropriate Inherited Thrombophilia Testing at VA Connecticut

Jenny J Xiang, *Talib Dosani, Ronald G. Hauser, Danielle Cosentino, Naseema Merchant, Michal G. Rose*

Many guidelines and expert opinions do not recommend inherited thrombophilia testing in unselected patients and in patients with VTE occurring in the setting of major transient risk factors.

From 2019 to 2021, 75% of inherited thrombophilia testing (protein C, S and antithrombin deficiencies and Factor V Leiden and prothrombin mutations) at VA Connecticut were ordered by non-hematologists. Of these orders, 55% of tests were ordered by primary care clinicians, 29% by inpatient teams, and the remainder by non-hematology specialists.

Approximately 10% of testing by non-hematologists had abnormal results, generating further hematology consults and workup. Given that testing has limited clinical utility and can result in unnecessary downstream healthcare use, there is a need to improve guideline concordant and appropriate thrombophilia testing by non-hematologists.

A best practice alert (BPA) was established for inpatient and outpatient inherited thrombophilia testing at the time of order entry. BPA notified the ordering clinician that inherited thrombophilia testing rarely impacts the choice or duration of anticoagulation and is not recommended for most patients. The BPA recommended that as an alternative, clinicians can consider a hematology electronic consult (e-consult) for guidance and education regarding appropriate patient selection for testing.

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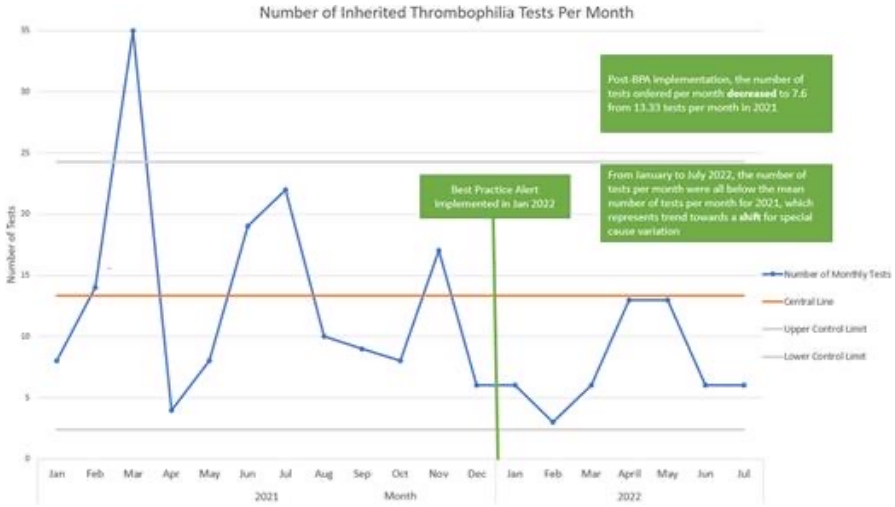

After BPA implementation in Jan 2022, the mean number of monthly inherited thrombophilia tests from January to Jul 2022 decreased to 7.6 tests from 13.3 tests in 2021. The average cost of testing per month decreased from $653 to $366 with an estimated $2004 saved after intervention implementation. The mean number of hematology e-consults increased to 3.4 consults per month during the first five months of the intervention period from 2.5 consults per month in 2021.

Cosa abbiamo portato a casa da New Orleans 2023

- Indaghiamo la trombofilia per individuare familiari portatori e fare prevenzione(soprattutto per la trombofilia severa)
- Indaghiamo la trombofilia per i casi in cui la durata dell'anticoagulazione non è definita e sempre in condivisione con il paziente
- Indaghiamo per Anticorpi antifosfolipidi→ AVK in trombosi arteriose e nei triplo positivi
- Non indaghiamo nella poliabortività perché l'eventuale profilassi con LMWH non cambia la natalità
- I dosaggi funzionali non bastano: si va verso il gene sequencing
- Allerta dai sistemi informatici ospedalieri al momento della richiesta di test