Trombofilia acquisita

Prof. E. Campello
UOC Clinica Medica 1
Dipartimento di Medicina
Azienda Ospedale-Università Padova

Master in Medicina vascolare e Malattie trombotico-emorragiche
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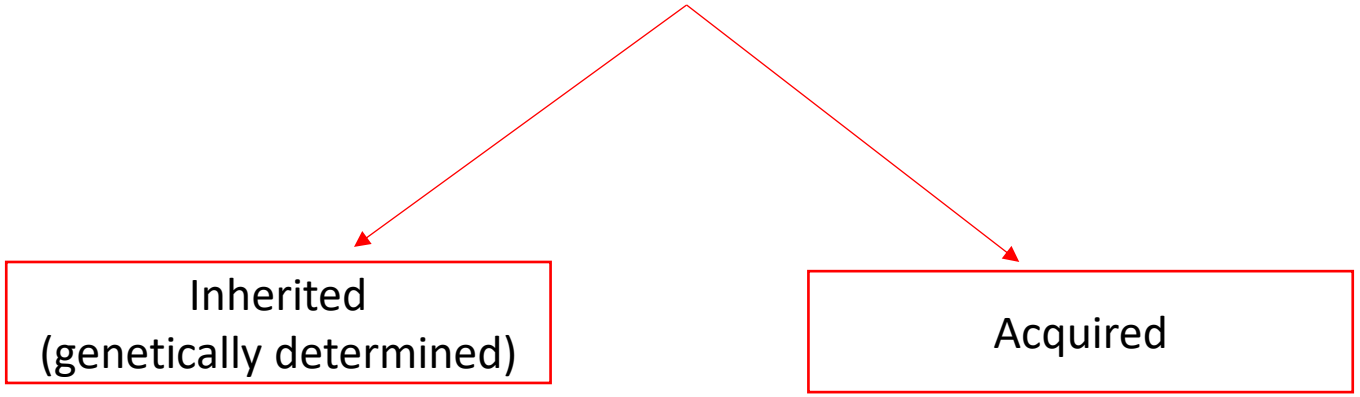
Thrombophilia

A propensity to develop venous thromboembolism on the basis of an underlying hypercoagulable state attributable to inherited or acquired disorders of blood coagulation or fibrinolysis.



Main causes of thrombophilia

Hereditary	Acquired
Factor V Leiden	Antiphospholipid syndrome
Prothrombin mutation G20210A	Cancer
AT deficiency	Myeloproliproliferative syndrome
PC deficiency	Paroxysmal nocturnal hemoglobinuria (PNH)
PS deficiency	
Dysfibrinogenemia	
Controversial (low TFPI, PAI1 polymorphisms)	
Novel thrombophilia	
Unknown	
Hyperhomocysteinemia	

Thrombophilia and risk of thrombosis

Table 1. Increased thrombotic risk in hereditary and acquired thrombophilia

Thrombophilia	Relative risk for a first VTE (compared to community controls)
Hereditary thrombophilia	
Factor V Leiden	
Heterozygous	3-7x
Homozygous	80x
Prothrombin G20210A	
Heterozygous	2-3x
Homozygous	5x
Double heterozygosity (FVL and prothrombin G20210A)	6x
AT deficiency	5x
Protein C deficiency	4-6.5x
Protein S deficiency	1-3x
Pseudohomozygous FVL	80x
Factor IX Padua	10x
AT resistance	2-3x
Non-0 blood type	2x
Factor VIII ≥150 IU/dL	3-5x
Factor IX ≥129 IU/dL	2.3x
Factor XI ≥121 IU/dL	2x
Acquired thrombophilia	
Antiphospholipid antibody syndrome	3-10x
Hyperhomocysteinaemia	1.5-3x

Campello E. et al. Expert Rev Hematol 2019

Acquired thrombophilia

Acquired high levels of coagulation factors and anticoagulants deficiency

- majority of the acquired VTE risk factors characterized by elevated procoagulant factors and/or reduced anticoagulants

- Surgery
- Trauma
- Acute medical conditions
- Inflammation
- Cancer and myeloproliferative disorders
- Obesity

- Pregnancy
- Hormonal therapy
- Cancer
- Nephrotic syndrome

Thrombophilia and risk of thrombosis

Table 2. Thrombotic risk in acquired thrombophilia and main hypercoagulable changes in coagulation pathways

Acquired thrombophilia	Relative risk for a first VTE	Haemostatic changes
Surgery	1.7-2.8x	• release or exposure of TF
Trauma	3-5x	• ↓ AT • hypofibrinolysis (↑ PAI-1)
Pregnancy	5-50x	• ↑ procoagulant factors (fibrinogen, VII, VIII, X, vW) • ↓ protein S • acquired APC resistance
Oestrogen–progestogen therapies	2-9x	• ↓ protein S • ↓ TFPI
Cancer	4-7x	• release of TF • ↑ procoagulant factors • ↓ anticoagulant factors • platelet activation
Myeloproliferative neoplasms	3x	• ↑ procoagulant factors • ↓ protein S • acquired APC resistance • ↑ platelet-induced thrombin generation
Economy class syndrome	2-4x	• Hypofibrinolysis (↑ prothrombin fragment F1+F2, ↓ tPA) • Haemoconcentration
Obesity (BMI ≥30 Kg/m^2)	2-3x	• ↑ procoagulant factors (fibrinogen, VII, VIII, X, vW) • hypofibrinolysis (↑ PAI-1) • ↑ platelet aggregation

Campello E. et al. Expert Rev Hematol 2019

Trombofilia acquisita

1. Sindrome da anticorpi antifosfolipide
2. Iperomocisteinemia
3. Neoplasia
4. Sindromi mieloproliferative
5. Emoglobinuria parossistica notturna
6. Obesità

Antiphospholipid syndrome is an autoimmune acquired disorder characterized by thrombosis and/or pregnancy morbidity and the presence of antibodies directed to phospholipid and pohospholipid binding proteins

SINDROME DA ANTICORPI ANTIFOSFOLIPIDE

La sindrome da anticorpi anti-fosfolipidi (APS) è una sindrome caratterizzata dalla presenza di 1) **anticorpi anti-fosfolipidi (aPL) e**
2) un quadro clinico caratterizzato da trombosi (venose e arteriose) o aborti ricorrenti.

Può esistere da sola (APS primaria) o in associazione ad altre malattie autoimmuni, tra cui il Lupus Eritematoso Sistemico (APS secondaria).

L'APS di solito esordisce nei giovani adulti o negli adulti di mezza età, ma può presentarsi a tutte le età.

Antiphospholipid antibodies

- ✓ in acute and chronic infections
- ✓ in malignant neoplasms
- ✓ in drug-induced disorders
- ✓ in autoimmune diseases
- ✓ in rheumatic diseases
- ✓ ……
- ✓ in the healthy subject

Autoimmunity Reviews 9 (2010) A299–A304

Contents lists available at ScienceDirect

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

The geoepidemiology of the antiphospholipid antibody syndrome

Martina Biggioggero, Pier Luigi Meroni *

Division of Rheumatology, Department of Internal Medicine – University of Milan, Istituto G. Pini, Italy
IRCCS Istituto Auxologico Italiano, Milan, Italy

aPL antibodies are present in:

- 1-5% of healthy individuals
- 20% of rheumatoid arthritis patients
- 30-40% of systemic lupus erythematosus patients

Epidemiology of APS

- Overall APS prevalence- 50 per 10000 people
- Female-to-male ratio 5:1
- Young-adults (15 - 50 years)
- Prevalence of aPL in thrombosis 5 - 20%
- Prevalence of aPL in poliabortivity 10 - 20%

Duarte-Garcia et al, Arthritis Rheumatol 2019
Cervera et al. Arthrtitis Rheum 2002

Arthritis Care & Research
Vol. 65, No. 11, November 2013, pp 1869–1873
DOI 10.1002/acr.22066

BRIEF REPORT

Estimated Frequency of Antiphospholipid Antibodies in Patients With Pregnancy Morbidity, Stroke, Myocardial Infarction, and Deep Vein Thrombosis: A Critical Review of the Literature

LAURA ANDREOLI,[1] CECILIA B. CHIGHIZOLA,[2] ALESS
GUILLERMO J. PONS-ESTEL,[4] GUILHERME RAMIRE DE
ON BEHALF OF APS ACTION

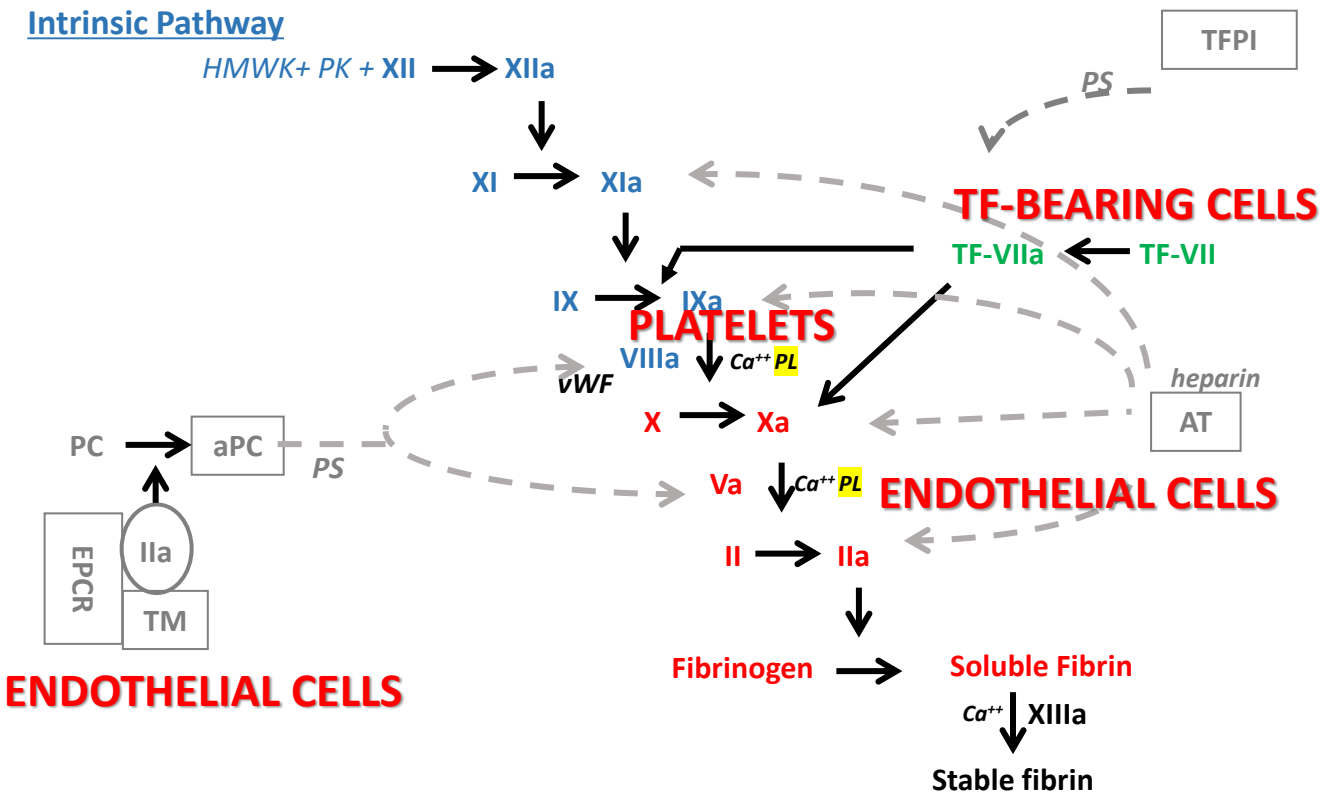
Significance & Innovations

- Antiphospholipid Syndrome Alliance For Clinical Trials and International Networking (APS ACTION) is an international research network devoted to APS.
- One of the first needs of APS ACTION was to understand the frequency of antiphospholipid antibodies (aPL) in the general population with aPL-associated clinical manifestations.
- According to our best literature estimates, the overall aPL frequency is 6% for pregnancy morbidity, 13.5% for stroke, 11% for myocardial infarction, and 9.5% for deep vein thrombosis.
- Literature is impinged by several limitations that prevented precise estimates of aPL frequency in general-population patients with thrombosis or pregnancy morbidity.

PATOLOGIE ASSOCIATE

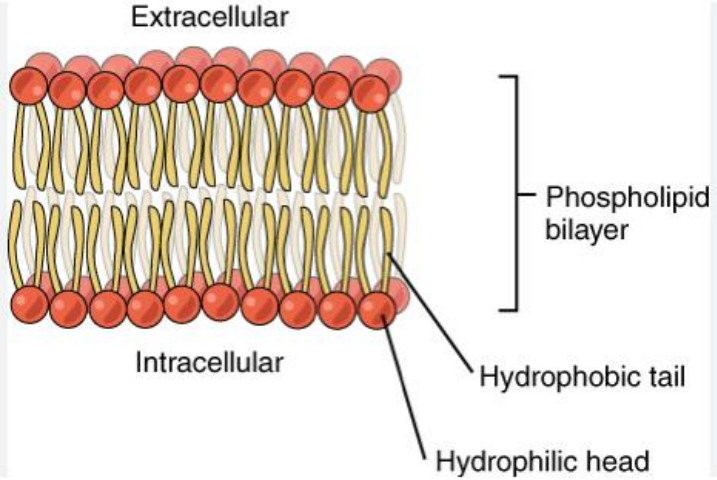
- SLE - 25-50%
- Sjögren syndrome - 42%
- Rheumatoid arthritis - 33%
- Autoimmune thrombocytopenic purpura - 30%
- Psoriatic arthritis - 28%
- Systemic sclerosis - 25%
- Mixed connective-tissue disease - 22%
- Polymyalgia rheumatica or giant cell arteritis - 20%
- Behçet syndrome - 20%
- Autoimmune hemolytic anemia - Unknown
- Infections

Coagulation cascade

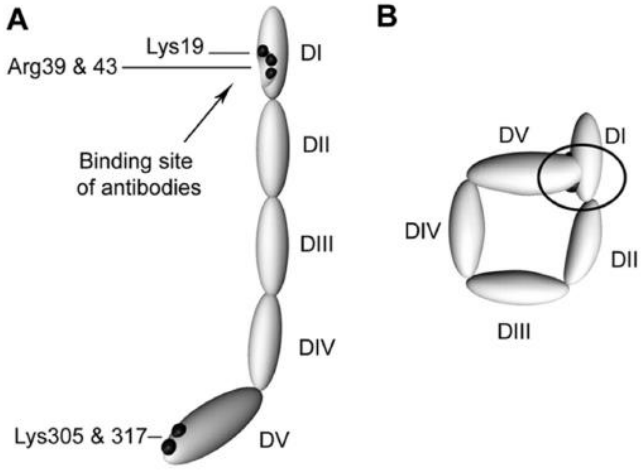


Antiphospholipid Syndrome Pathophysiology

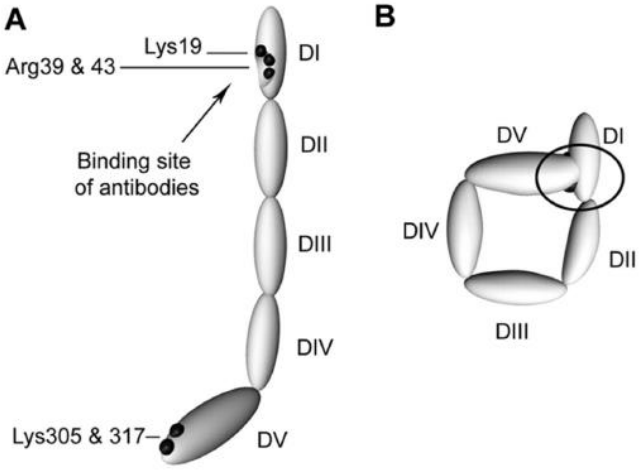
APLA were originally thought to react with anionic phospholipids (such as cardiolipin), however, it is now known that most APLA are directed against phospholipid binding proteins expressed on, or bound to, an appropriate surface such as a cellular membrane.



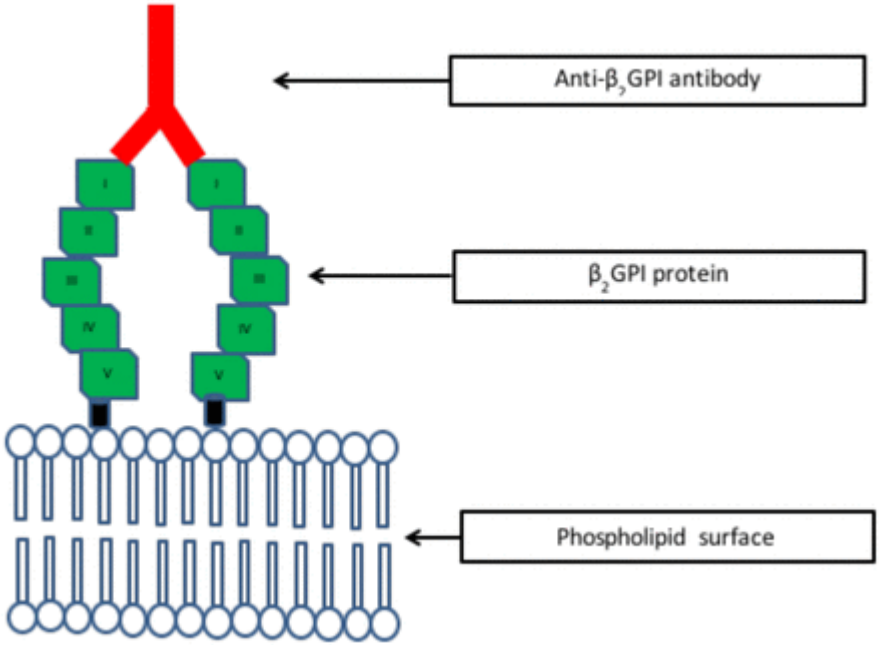
One hypothesis postulates a defect in cellular apoptosis, which exposes membrane phospholipids to the binding of various plasma proteins, such as beta-2 GPI.



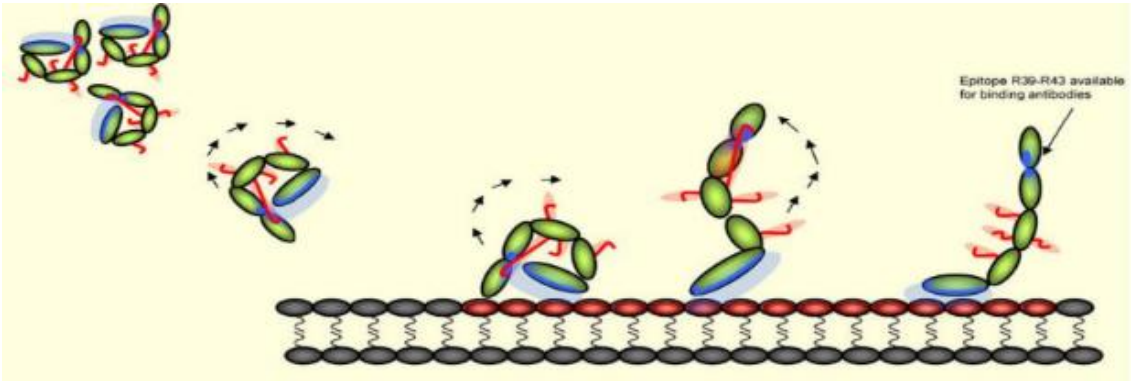
Antiphospholipid Syndrome Pathophysiology

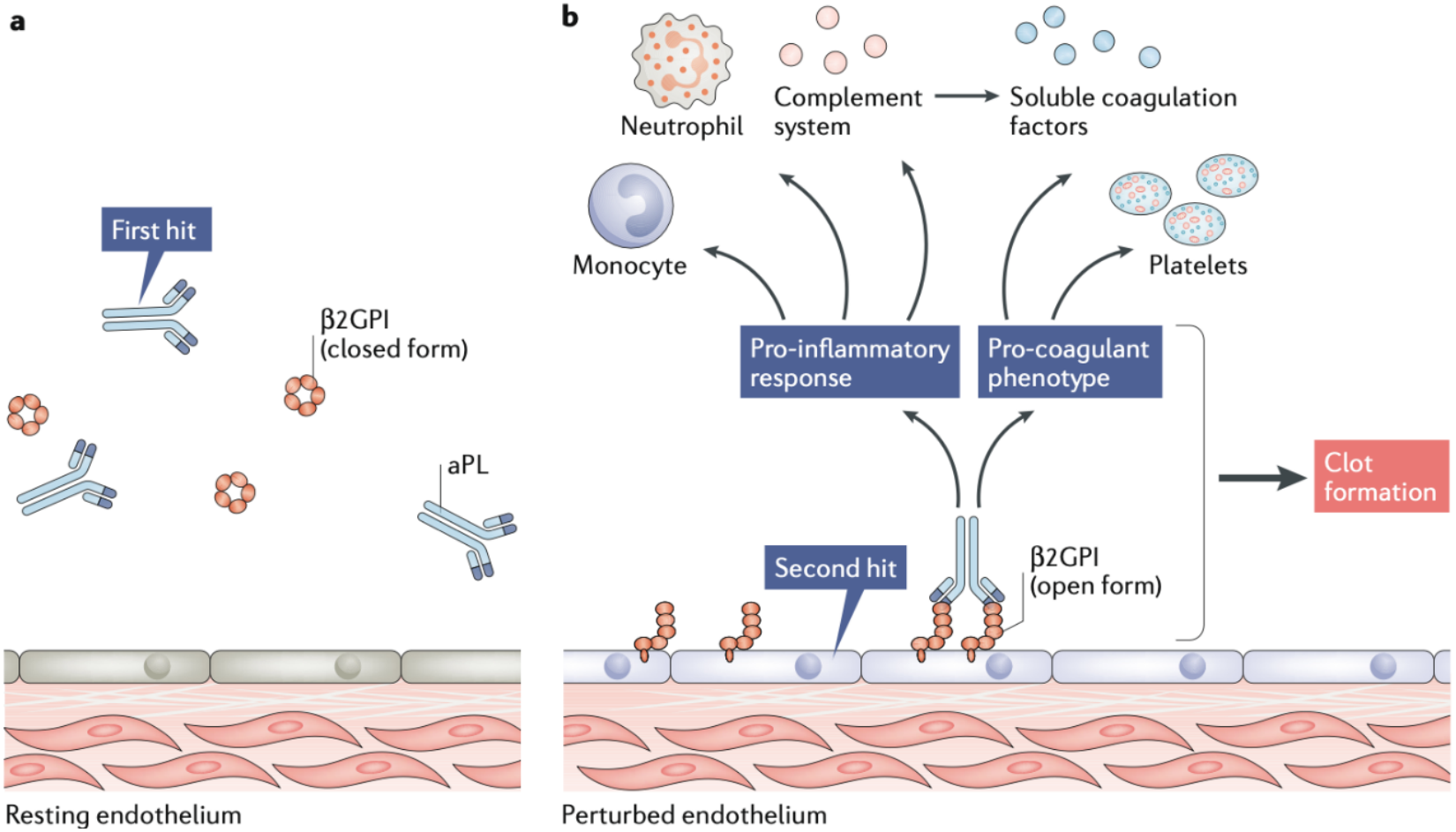


Anticorpi anti-beta2 glicoproteina I



- b2GPI is the main target Ag of APLA and b2GPI-dependent aPL are pathogenic.
- b2GPI can be present on the surface of several cells (EC, Mo, PP, trophoblast……).
- Its conformational changes may affect Ab binding (ox/red) and cell membrane receptor engagement.



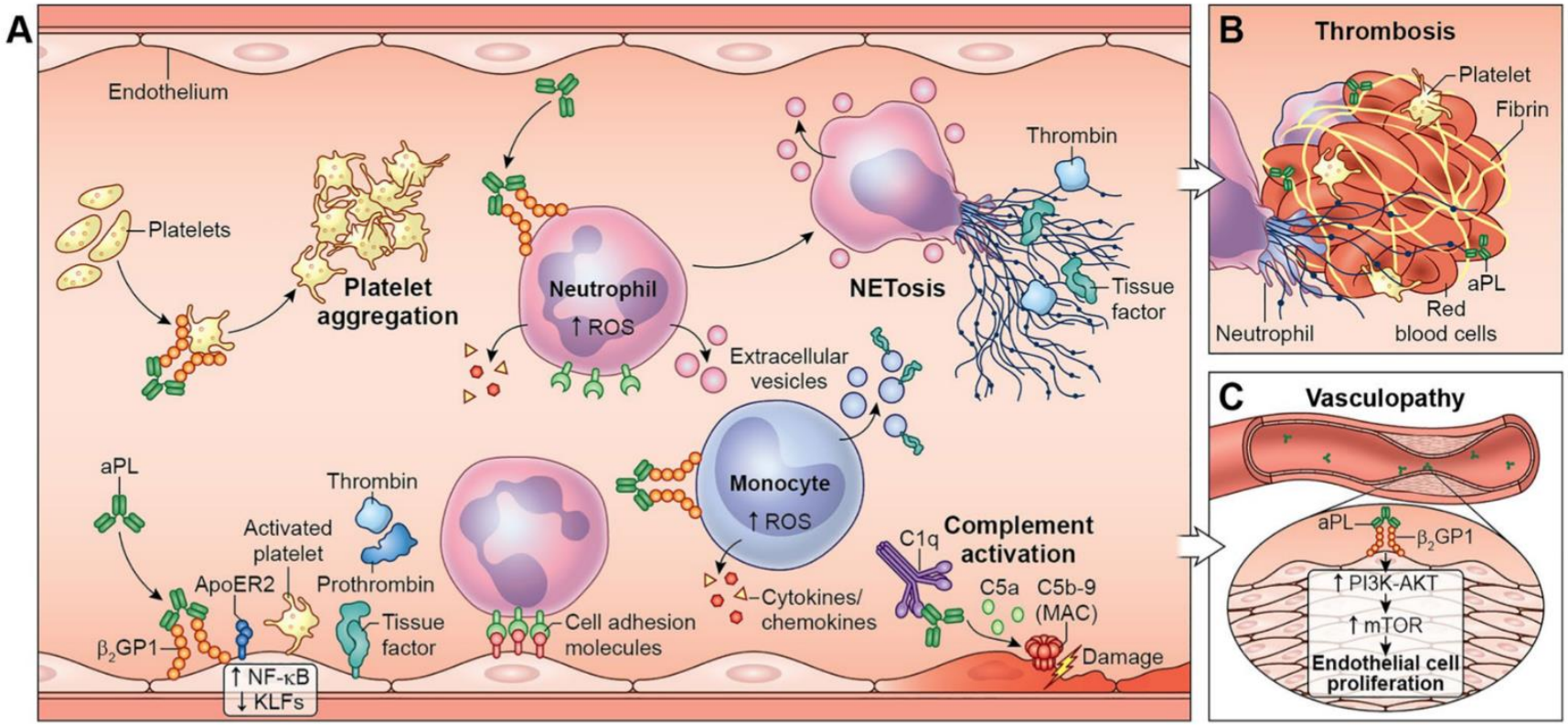


Meroni et al. Nat Rev Rheum 2018

Table 2 Some mechanistic highlights of APS pathophysiology

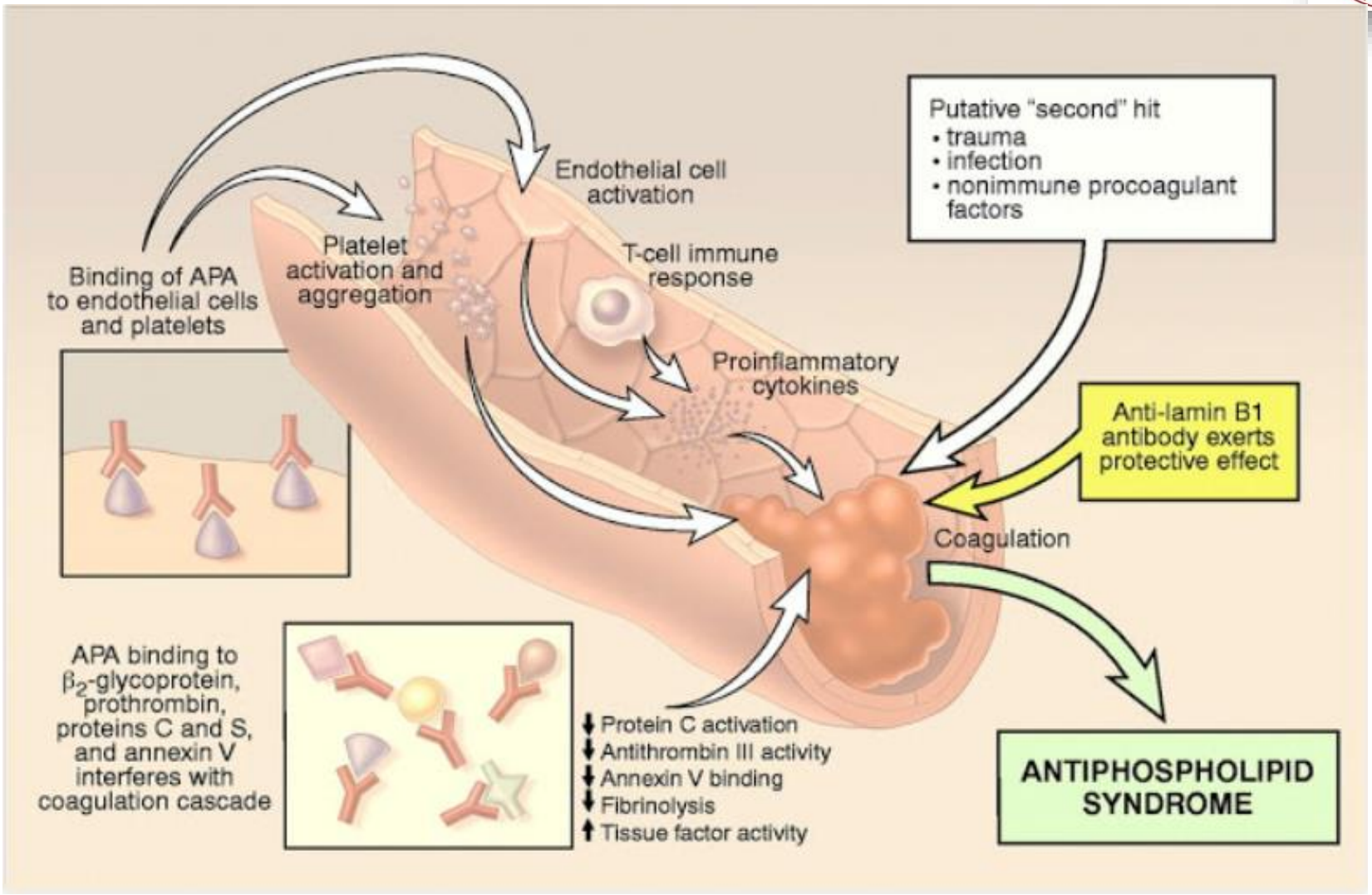
Cell or pathway	In vitro, aPL…	In patients, we can find…
Endothelial cells	Increase expression of tissue factor and adhesion molecules [33, 34]	More endothelium-derived microparticles [35, 36]
Platelets	Induce activation under shear stress [37]	Increased platelet-leukocyte aggregates [38]
Monocytes	Trigger expression of tissue factor [39–42] and pro-inflammatory cytokines [43–45]	Increased tissue factor-expressing monocytes [46–48]
Neutrophils	Promote release of prothrombotic neutrophil extracellular traps (NETs) [49]	High levels of circulating NETs [49] and anti-NET antibodies [50]
Complement	Trigger cell lysis as measured by modified Ham test [51]	High levels of complement split products [52–54]
Coagulation	Interfere with coagulation inhibitors, especially protein C and antithrombin [55, 56]	High levels of the active free thiol form of factor XI [57]
Fibrinolysis	Interfere with activity of tissue plasminogen activator [58]	High levels of plasminogen activator inhibitor-1 (PAI-1) [59–61]

Knight and Kanti. Sem Immun 2022



Knight and Kanti. Sem Immun 2022

Antiphospholipid Syndrome Pathophysiology



http://manualidimedicina.blogspot.it/2016/05/sindrome-catastrofica-da-anticorpi.html

Antiphospholipid Syndrome Pathophysiology

Inhibition of natural anticoagulant activity

- impaired activation of PC
- impaired APC capacity to inactivate FV and FVIII
- inhibition of heparin binding and activation of AT
- inhibition of TFPI

Reduced stimulation of tPA (reduced fibrinolysis)

Cellular activation (activation of platelets to enhance endothelial adherence; activation of vascular endothelium, which, in turn, facilitates the binding of platelets and monocytes; reaction of antibodies to oxidized low-density lipoprotein)

Complement activation (C3a – C5a)

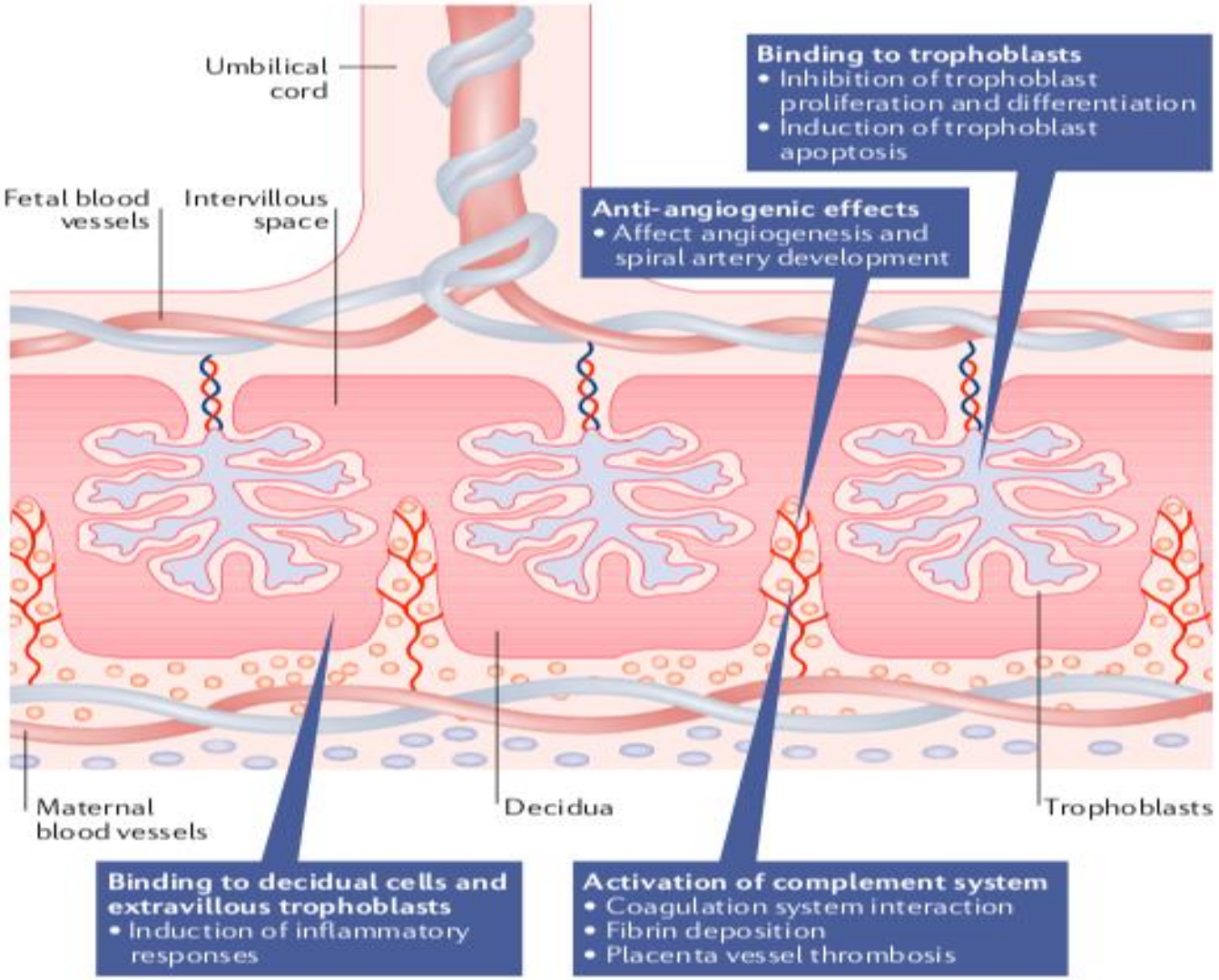
Key points in vascular APS

- Clotting is usually localized in common APS
- This finding supports an upstream key pathogenic role for the endothelium rather than for other cell types (i.e. Mo, neutrophils, PP) or fluid phase components involved in the coagulation cascade.
- We still do not know the reasons for the selective arterial (and particular anatomical localizations) or venous vessels involvement.

Obstetric vs vascular APS

- Obstetric APS is a specific subset within the APS box. Maternal thrombosis & progression to SLE are scarce (Alijotas-Reiget al *Autoimmun Rev* '15)
- IgG fractions from pure obstetric APS display different *in vitro* effects on monocyte & trophoblast cell (Lambrianides et al *J Immunol* '10; Poulton et al *Am J Reproduct Immunol* '15)
- Passive transfer of aPL IgG in naive pregnant animals does not need the *2° hit* to induce fetal loss (Meroni et al *Nat Rev Rheumatol* '11)

Il ruolo degli anti-β2GPI

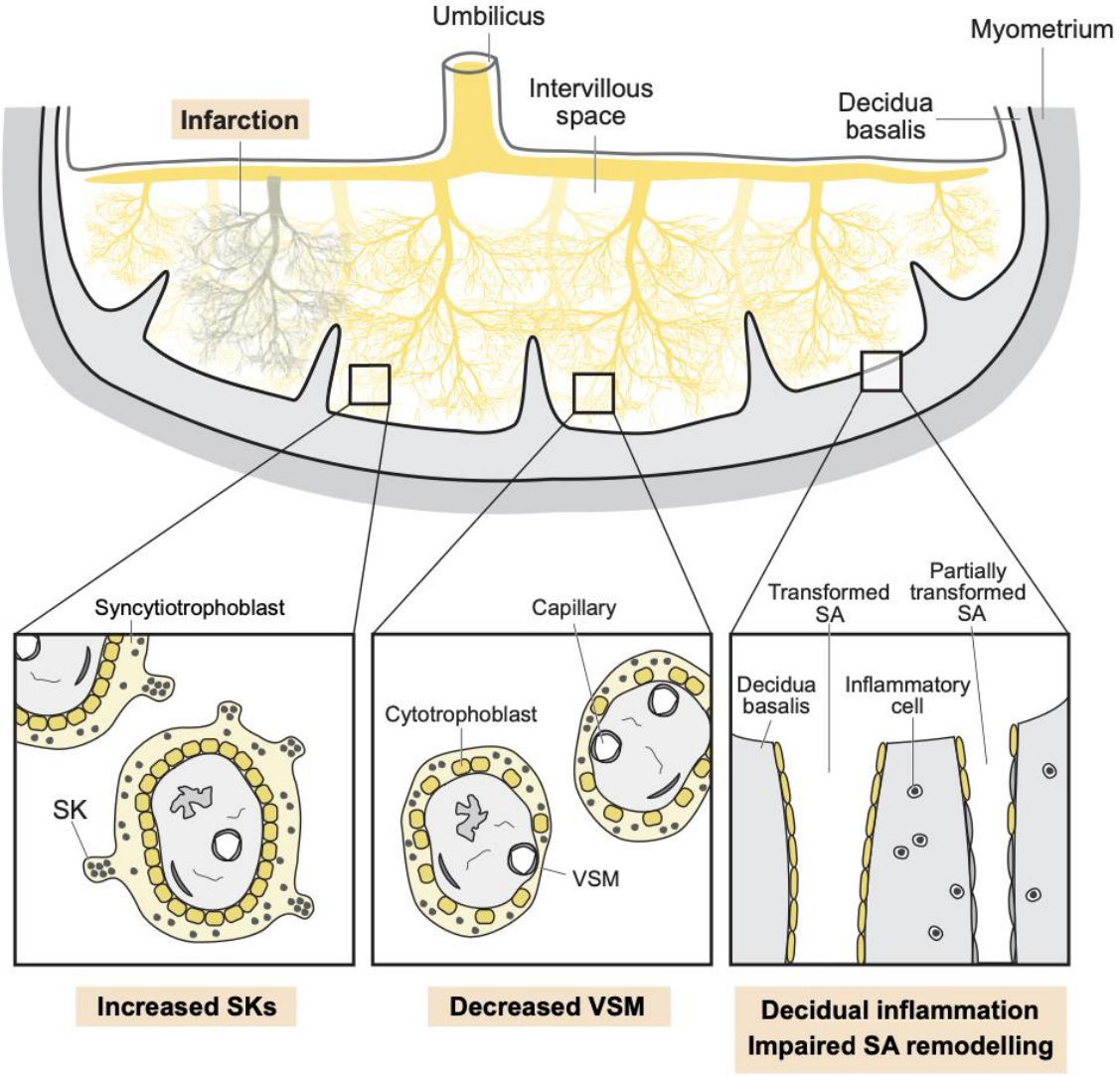


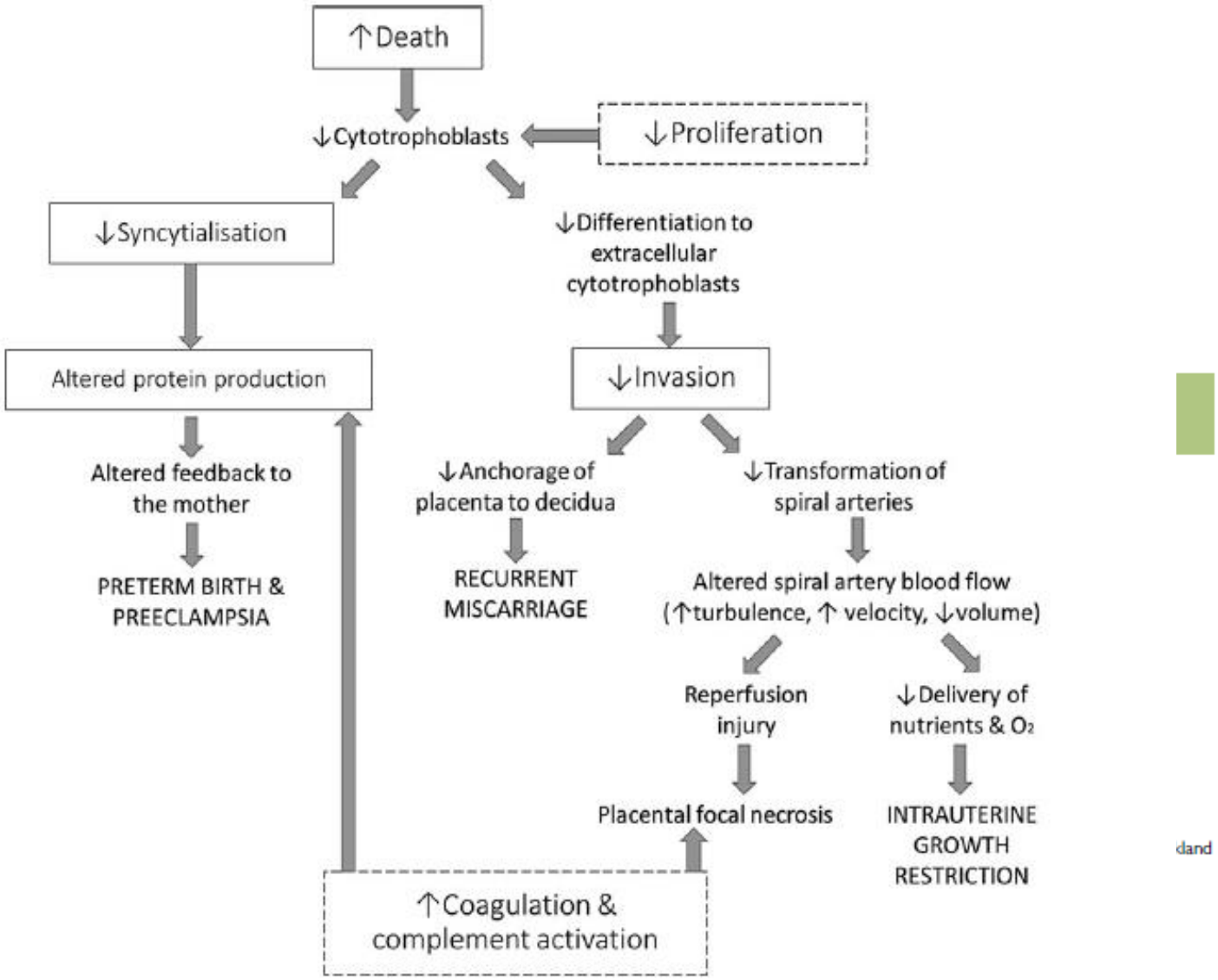
Meroni et al, Nat Rev Rheum 2018

More common	Not common	Unknown
Placental infarction Impaired spiral artery remodelling Decidual inflammation Villous trophoblast changes: ↑ Syncytial knots ↓ VSM Deposition of C4d	Spiral artery atherosis Spiral artery thrombosis Fibrin deposition Intervillous thrombi Villitis Chorioamnionitis Fibrinoid necrosis of villi Villous stromal oedema Avascular villi Placental vessel thrombosis Fibromuscular sclerosis Deposition of C3/C3 split products	Intervillous hemorrhage Villous stromal fibrosis Changes in expression of: β_2GPI Annexin A5

Vial and Chamley. Autoimmun Rev 2015

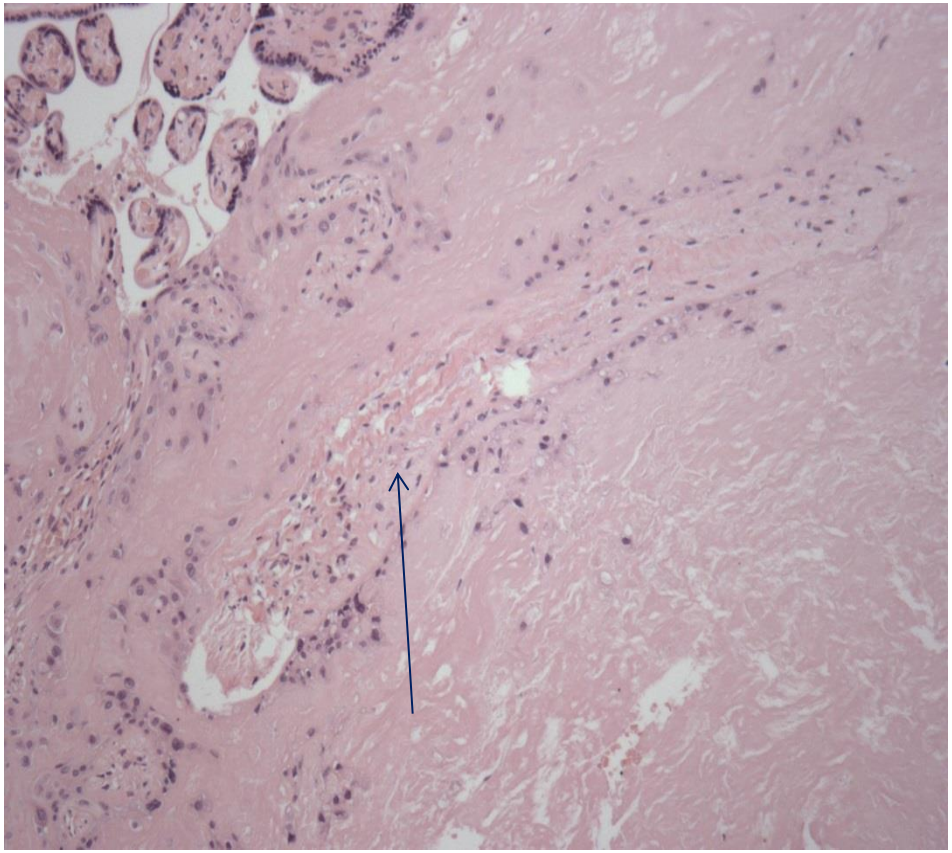
Placental thrombosis is NOT the main pathogenic pathway





It has been repeatedly shown that drugs such as heparin and hydroxychloroquine can prevent the binding of aPL to trophoblasts in vitro, thus counteracting the pregnancy-induced harm to APL

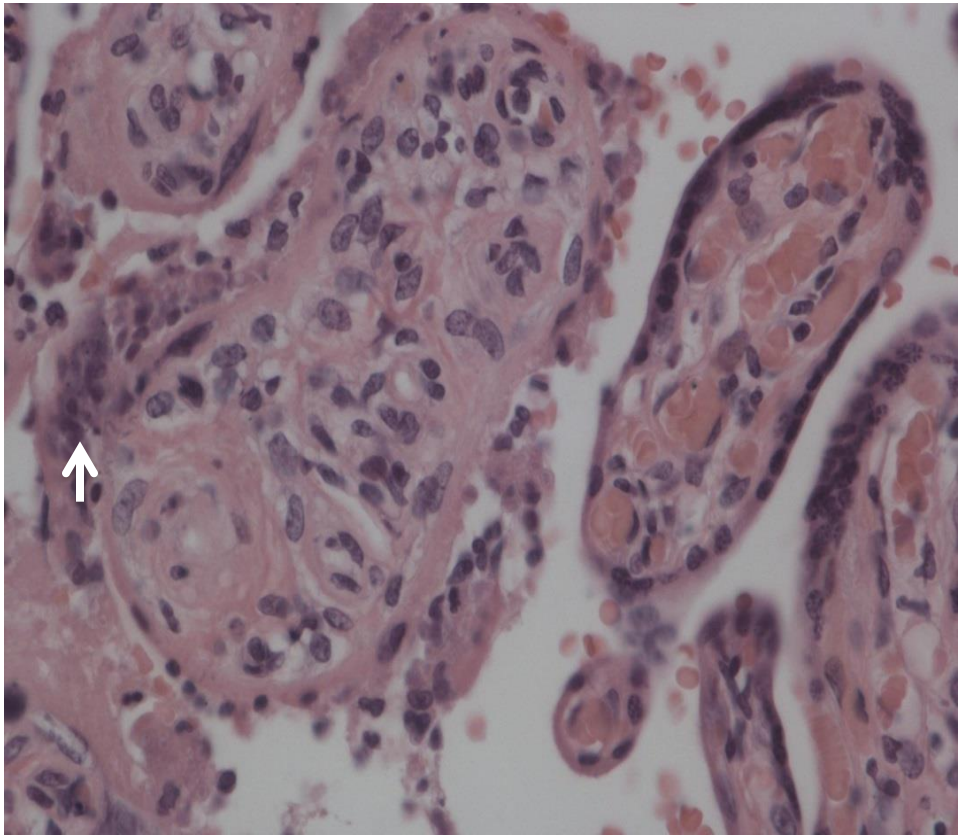
La placenta nell'APS. Decidua (versante materno)



- **Infarto placentare, vale a dire la necrosi ischemica dei villi sostenuta dalla trombosi delle arterie spirali uterine**
- **Alterato rimodellamento delle arterie spirali;**
- **Infiammazione della decidua.**

Viall CA et al, 2015

La placenta nell'APS. Villi (versante fetale)



- **Aumento dei noduli sinciziali, che corrispondono ad aree di aggregazione dei nuclei all'interno del sinciziotrofoblasto**
- **Diminuzione delle sottili, anucleate membrane vasculo-sinciziali che ricoprono i capillari fetali e sono specializzate negli scambi materno-fetali;**
- **Depositi di C4d un prodotto inerte di degradazione del complemento.**

Viall CA et al, 2015

Antiphospholipid Syndrome Diagnosis

At least one clinical criterion and one laboratory criterion must be present:

The clinical criteria consist of vascular thrombosis and pregnancy morbidity.

Vascular thrombosis: ≥1 clinical episodes of arterial, venous, or small-vessel thrombosis in any tissue or organ confirmed by findings from imaging studies, Doppler studies, or histopathology. Investigation is warranted if a history of VTE, acute ischemia, myocardial infarction, or stroke (especially when recurrent) is present in a younger individual (males < 55 y; females < 65 y) or in the absence of other risk factors.
Miyakis S et al. JTH 2006

Pregnancy morbidity:
- ≥1 late-term (>10 weeks' gestation) spontaneous abortions
- ≥1 premature births of a morphologically healthy neonate at or before 34 weeks' gestation because of severe preeclampsia or eclampsia or severe placental insufficiency
- ≥3 unexplained, consecutive, spontaneous abortions before 10 weeks' gestation

Diagnosi di laboratorio

1. Dosaggio anticorpi tramite test ELISA (test di cattura)
2. Dosaggio dell'attività antifosfolipidica → LAC

Laboratory criteria

1. LUPUS ANTICOAGULANT

2. ANTICARDIOLIPIN ANTIBODIES IgG AND/OR IgM AT MEDIUM-HIGH LEVELS

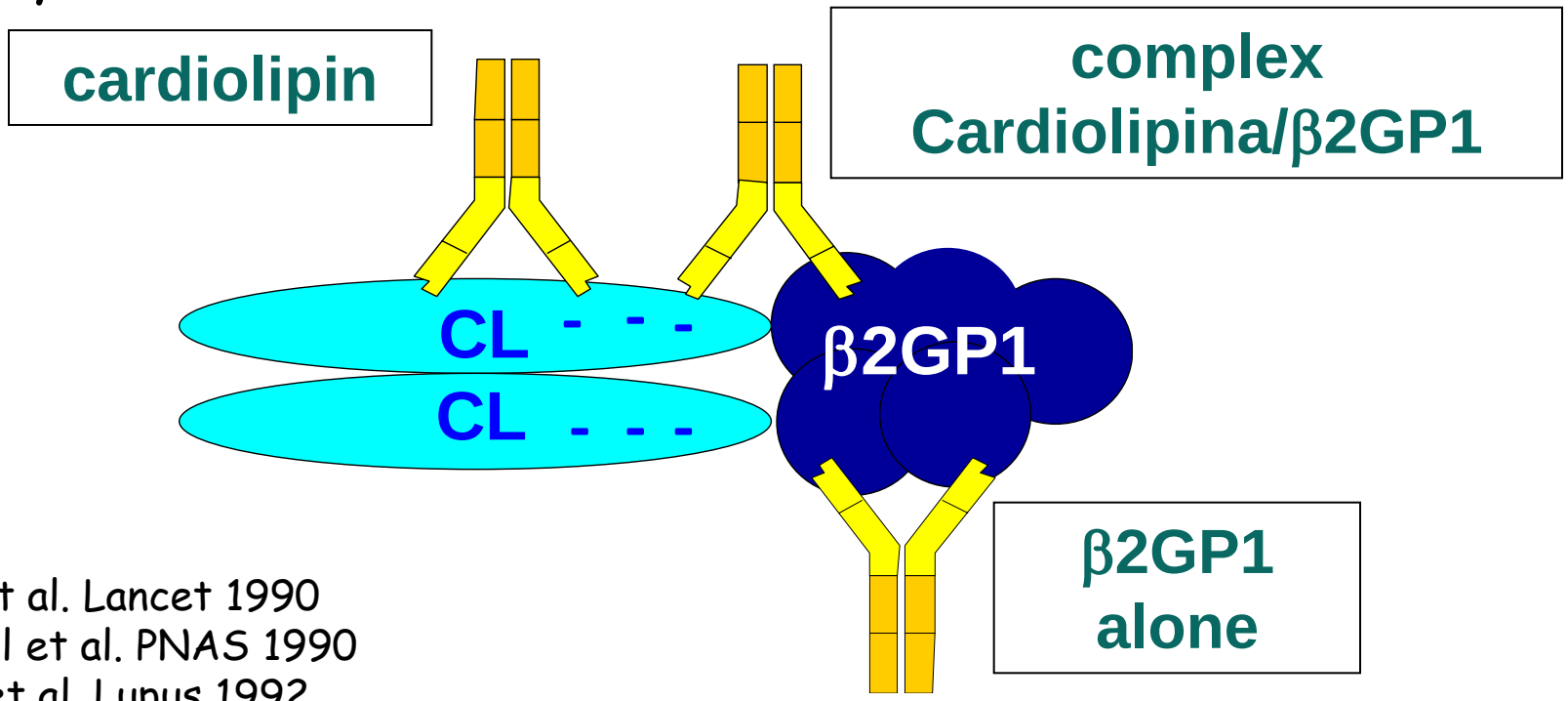
3. ANTI-B2-GLICOPROTEIN I ANTIBODIES IgG AND/OR IgM AT MEDIUM-HIGH LEVELS

Present on two or more occasions, at least 12 weeks apart

Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.

Anti-cardiolipin Antibodies

aCL are heterogeneous antibodies that in immunoassay's bind to a complex of phospholipids and plasma proteins, mainly B2GPI.



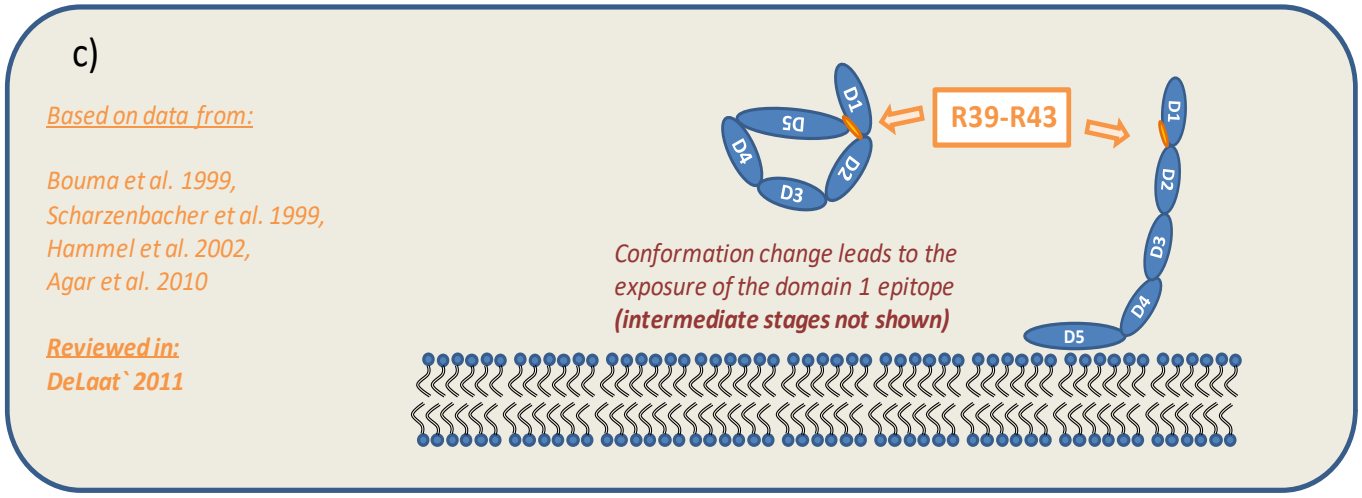
Galli et al. Lancet 1990
McNeil et al. PNAS 1990
Hunt et al. Lupus 1992

Anti-β2glycoprotein I antibodies

- Anti- β2GPI antibodies are specific to the β2GPI, a cofactor with affinity for anionic phospholipids which inhibits in vitro the activation of prothrombin and the ADP-dependent platelet aggregation.

De Laat et al. Blood 2006

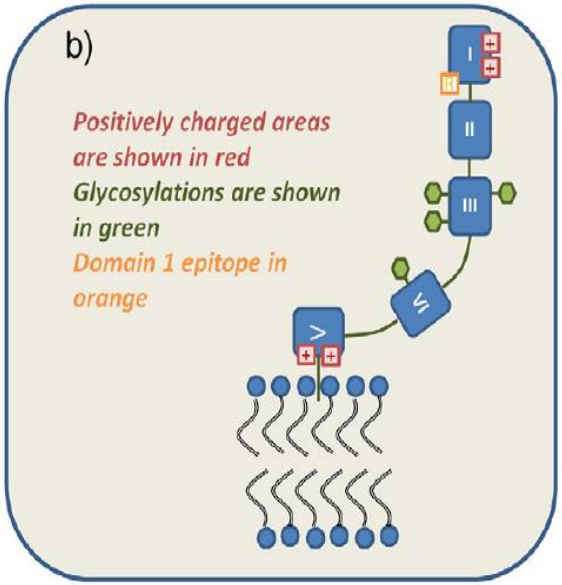
B2GPI - Structure

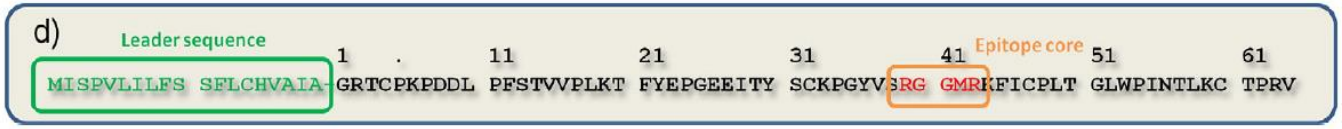


de Laat B, et al. Blood. 2006.

Mahler M, et al. *Autoimmun Rev* , 2012

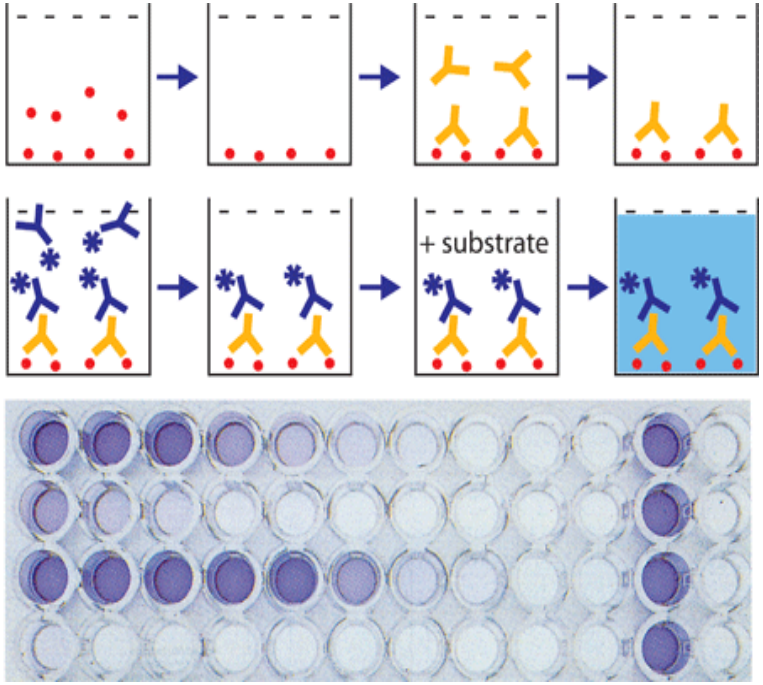
B2GPI - Structure





de Laat B, et al. Blood. 2004.
Mahler M, et al. *Autoimmun Rev* , 2012

Laboratory tests



Test ELISA

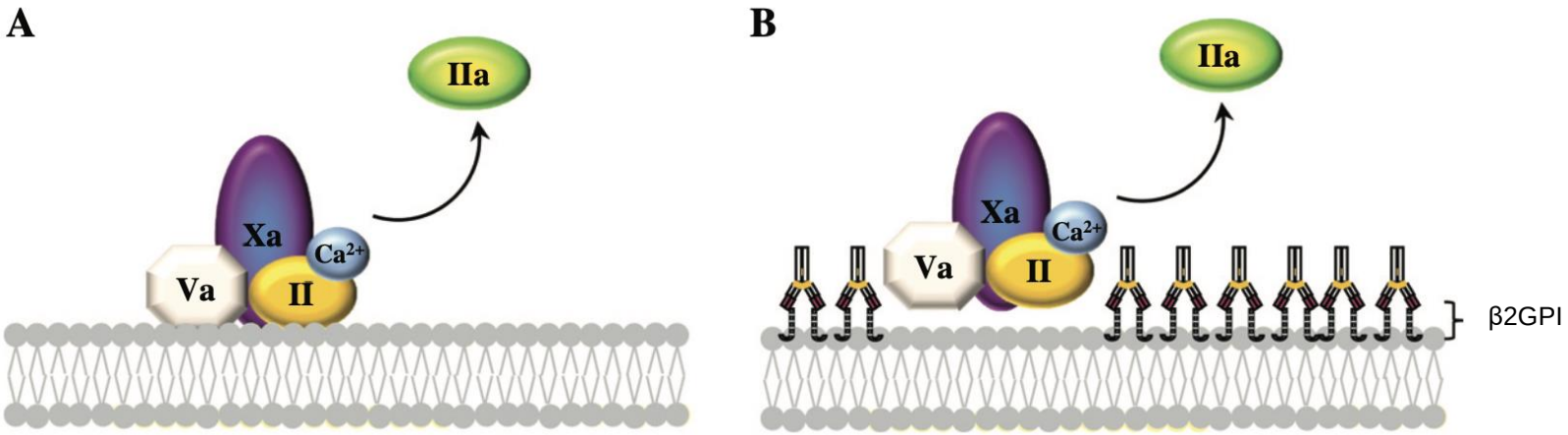
Diagnosi di laboratorio - LAC

Il nome lupus anticoagulant può sembrare strano e confondente per due ragioni:

- Il nome di questi autoanticorpi deriva dal fatto che questi sono stati identificati per la prima volta in pazienti affetti da LES (lupus eritematoso sistemico) ma in realtà questo test non viene utilizzato nella diagnosi di LES e spesso gli anticorpi LA non sono presenti in questi pazienti. Gli autoanticorpi LA possono svilupparsi in pazienti non affetti da patologie autoimmuni ma da altri tipi di patologie o che vengono sottoposti ad alcune terapie. Questi anticorpi sono presenti normalmente nel 2-4% della popolazione e possono svilupparsi anche in persone prive di fattori di rischio.
- Il termine "anticoagulant" deriva dal fatto che questi anticorpi interferiscono con i test di laboratorio utilizzati nella valutazione dei processi coagulativi. Ad esempio inibiscono le reazioni chimiche che portano alla coagulazione nel test del tempo di tromboplastina parziale (PTT), un test utilizzato routinariamente nella valutazione della coagulazione. In vivo, la presenza di LA è associata ad un aumentato rischio di sviluppare coagulazione inappropriata. È importante però sottolineare che di per se, il LA non causa eventi emorragici nell'organismo.

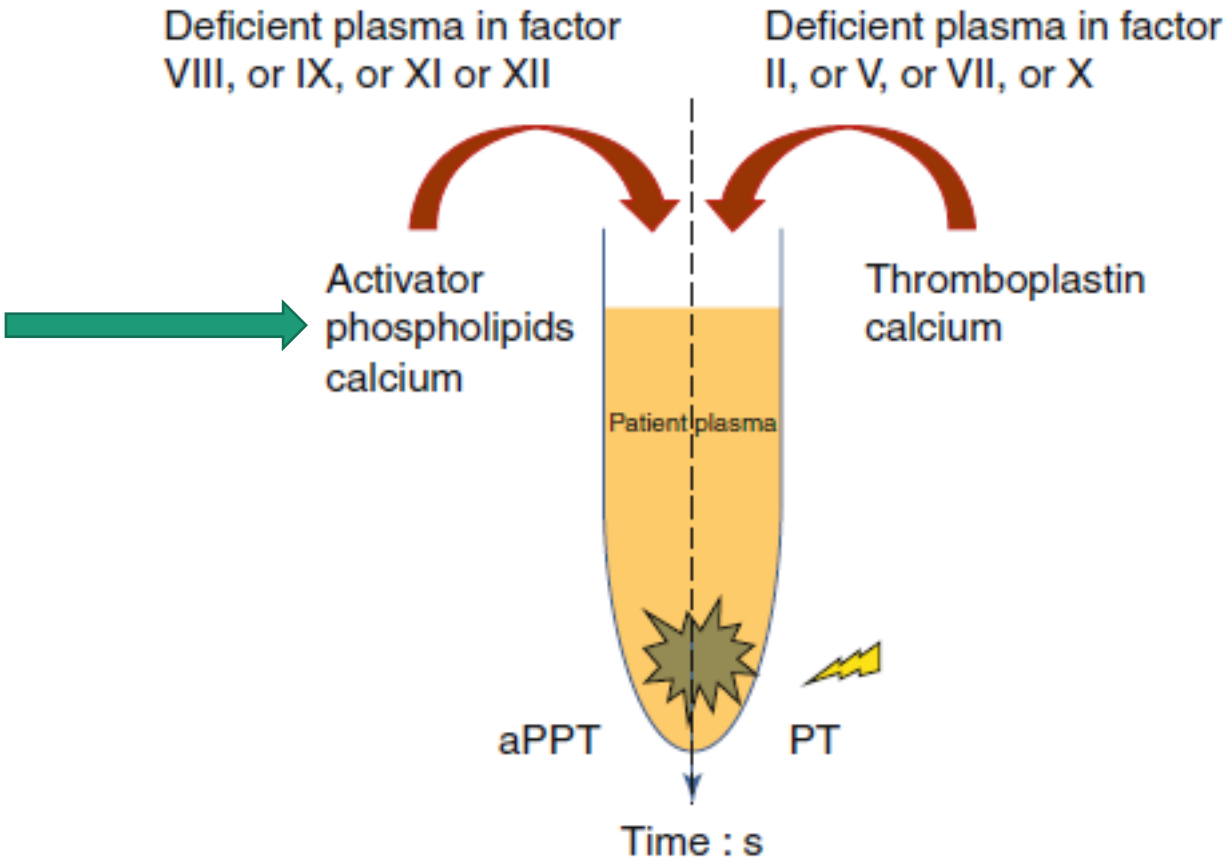
Lupus perche scoperto nei pazienti con LES
Anticoagulant perchè allunga il PTT

LUPUS ANTICOAGULANT



LAC is an in vitro phenomenon determining a phospholipid (PL)-dependent elongation of clotting times

Diagnosi di laboratorio - LAC

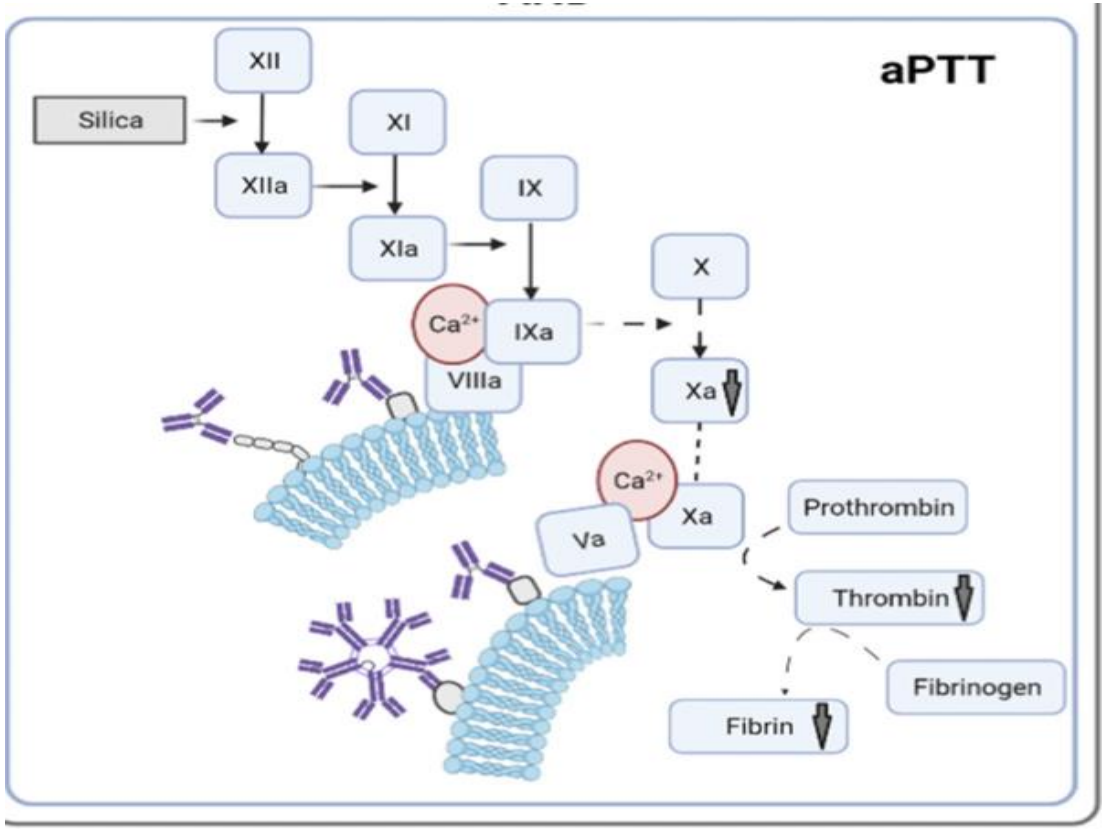


Diagnosi di laboratorio - LAC

Gli anticorpi LA non possono essere misurati in maniera diretta ma esistono molteplici test utilizzabili per la loro rilevazione. Di solito la presenza di LA viene accertata tramite l'utilizzo di un pannello di test:

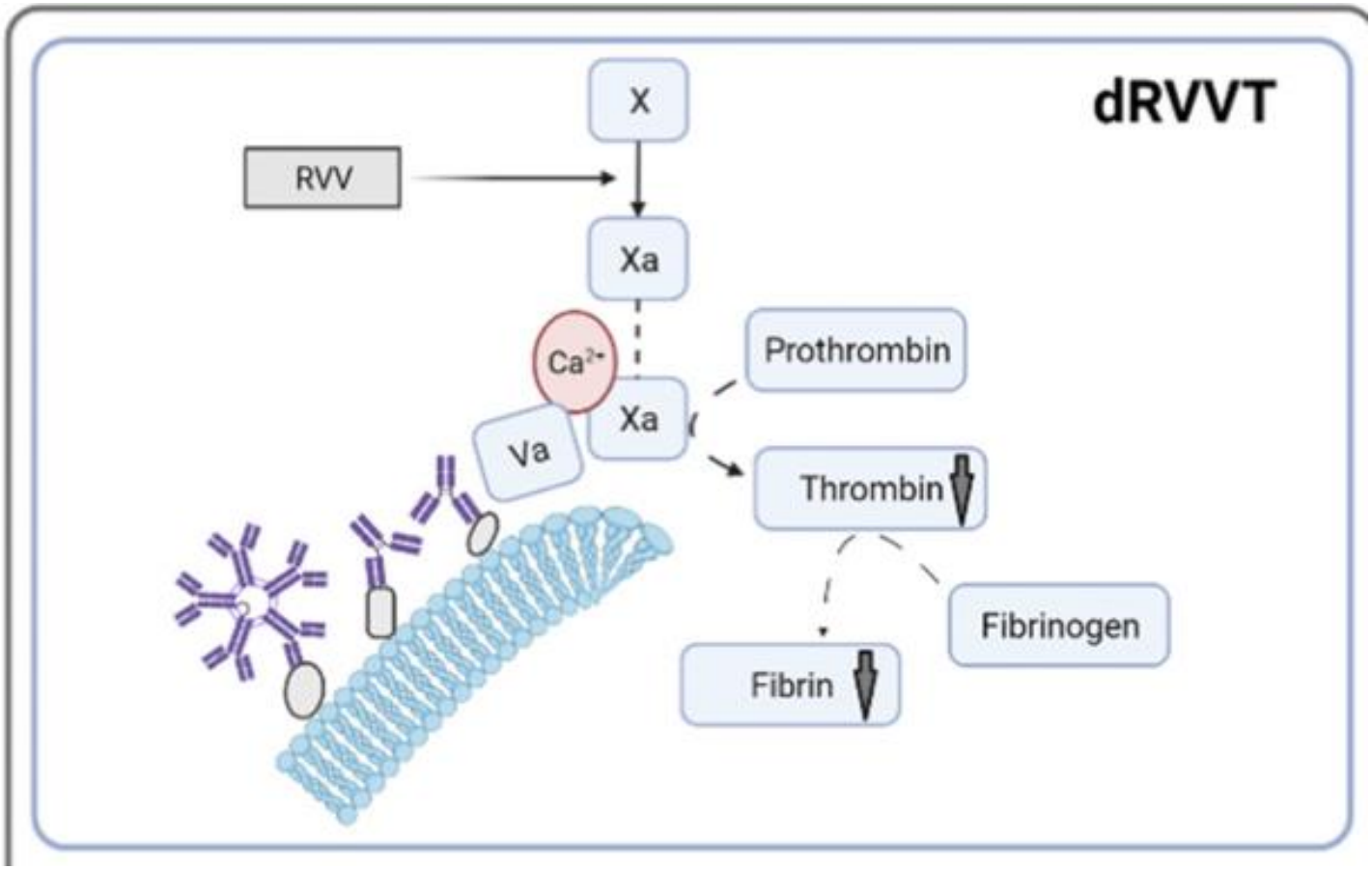
- In presenza di LA il tempo necessario alla coagulazione in test dipendenti da reagenti contenenti fosfolipidi, risulta allungato. Per questo motivo i primi test per il LA sono di norma il PTT, il PTT LA-sensibile o il test con veleno di vipera di Russel diluito (dRVVT).
- La presenza o l'assenza di LA viene quindi confermata tramite esami successivi ai risultati dei test di primo livello

LUPUS ANTICOAGULANT



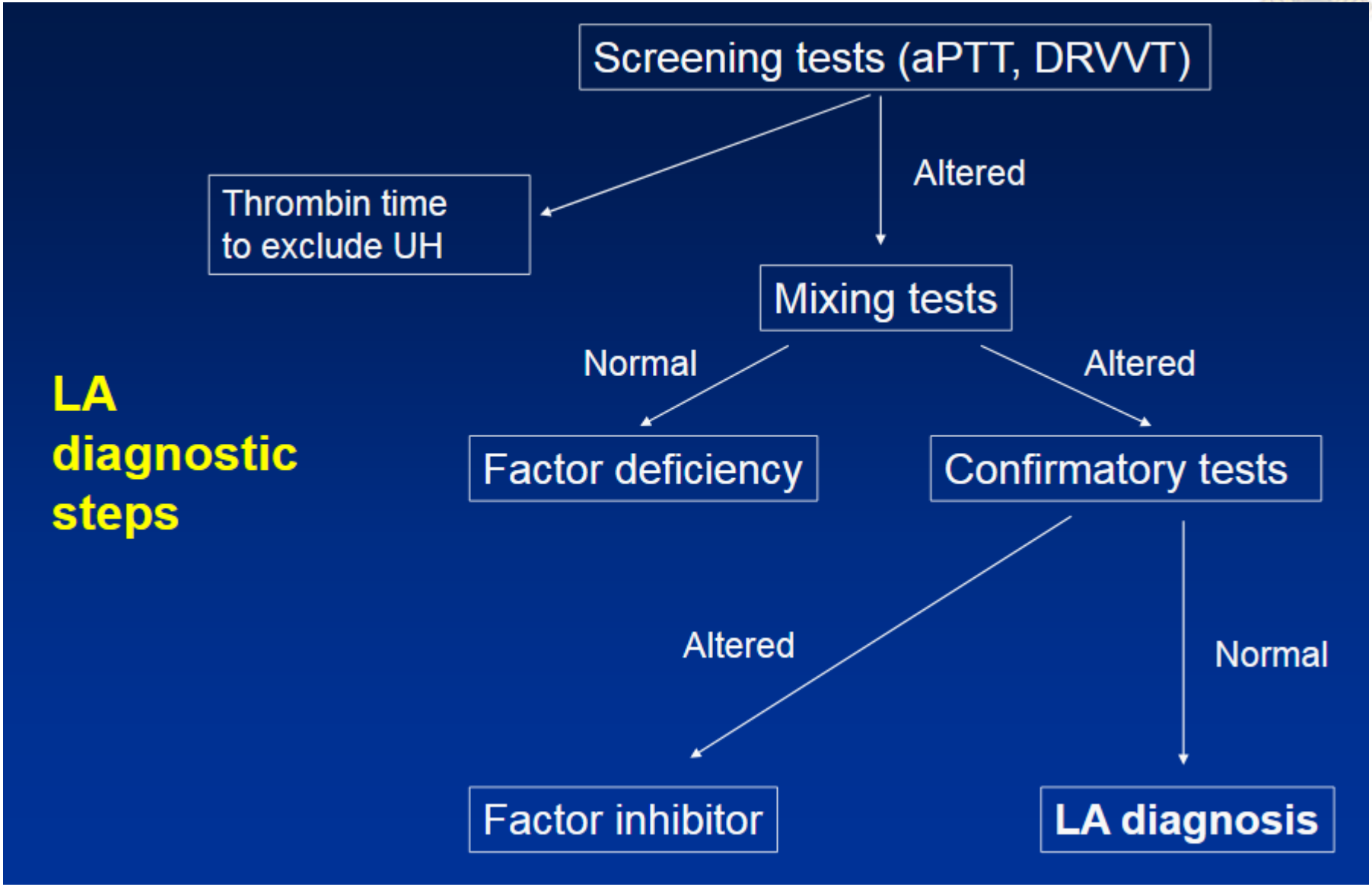
Devreese et al, JCM. 2022

LUPUS ANTICOAGULANT



Devreese et al, JCM. 2022

Diagnosi di laboratorio - LAC



- dRVVT Screen
- dRVVT Confirm

- Silica Clotting Time Screen
- Silica Clotting Time Confirm

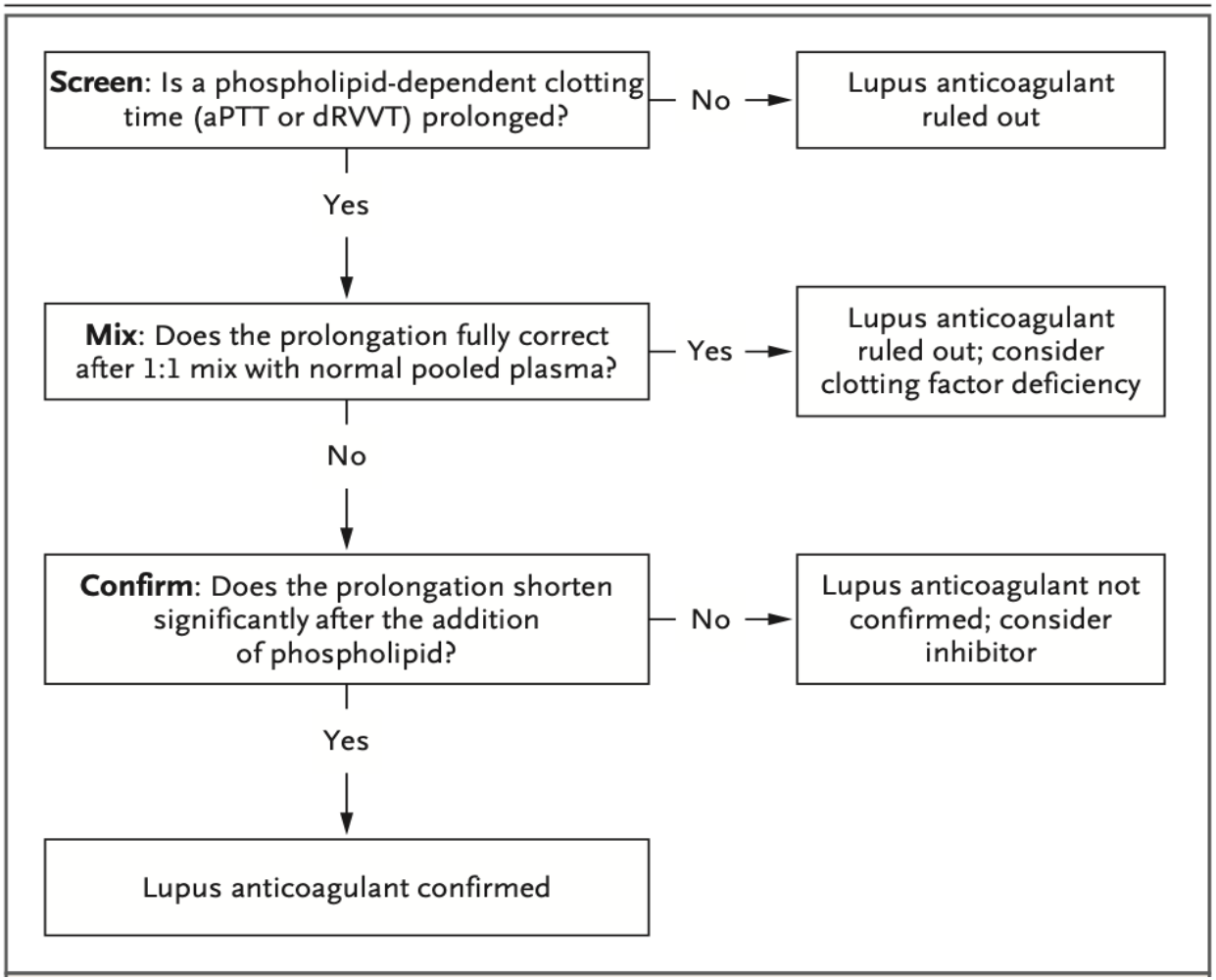
- **dRVVT Screen**: reagente liofilo costituito da **veleno di vipera di Russell diluito**, ioni calcio e una **quantità ridotta di fosfolipidi** che lo rendono un reattivo particolarmente sensibile alla presenza di LAC.

- **dRVVT Confirm**: reagente liofilo che, oltre a quanto già presente nel reagente dRVVT Screen, contiene un **alto quantitativo di fosfolipidi a doppio strato** che neutralizzano l'effetto del LAC e riportano i tempi di coagulazione a valori inferiori.

- **SCT Screen**: reagente costituito da **silice colloidale per l'attivazione della via intrinseca** della coagulazione e da un **ridotto contenuto di fosfolipidi** che lo rendono un reattivo particolarmente sensibile alla presenza di LAC.

- **SCT Confirm:** reagente che, oltre a quanto già presente nel reagente SCT Screen, contiene un **alto quantitativo di fosfolipidi a doppio strato** che neutralizzano l'effetto del LAC e riportano i tempi di coagulazione a valori inferiori.

LAC testing and interpretation



Garcia and Erkan, NEJM 2018

Antiphospholipid Syndrome Laboratory diagnosis

International Society on Thrombosis and Hemostasis criteria for the laboratory identification of lupus anticoagulant [9].

Positive screening test (phospholipid-dependent coagulation assay)

- Two or more screening tests recommended: Dilute Russell's viper venom time (DRVVT) and a sensitive aPTT (low phospholipids with silica as activator)

Evidence of inhibition in mixing studies (exclude factor deficiency)

- 1:1 mixing of patient plasma with normal plasma does not correct the prolonged clotting time
- LA cannot be conclusively identified if thrombin time is prolonged

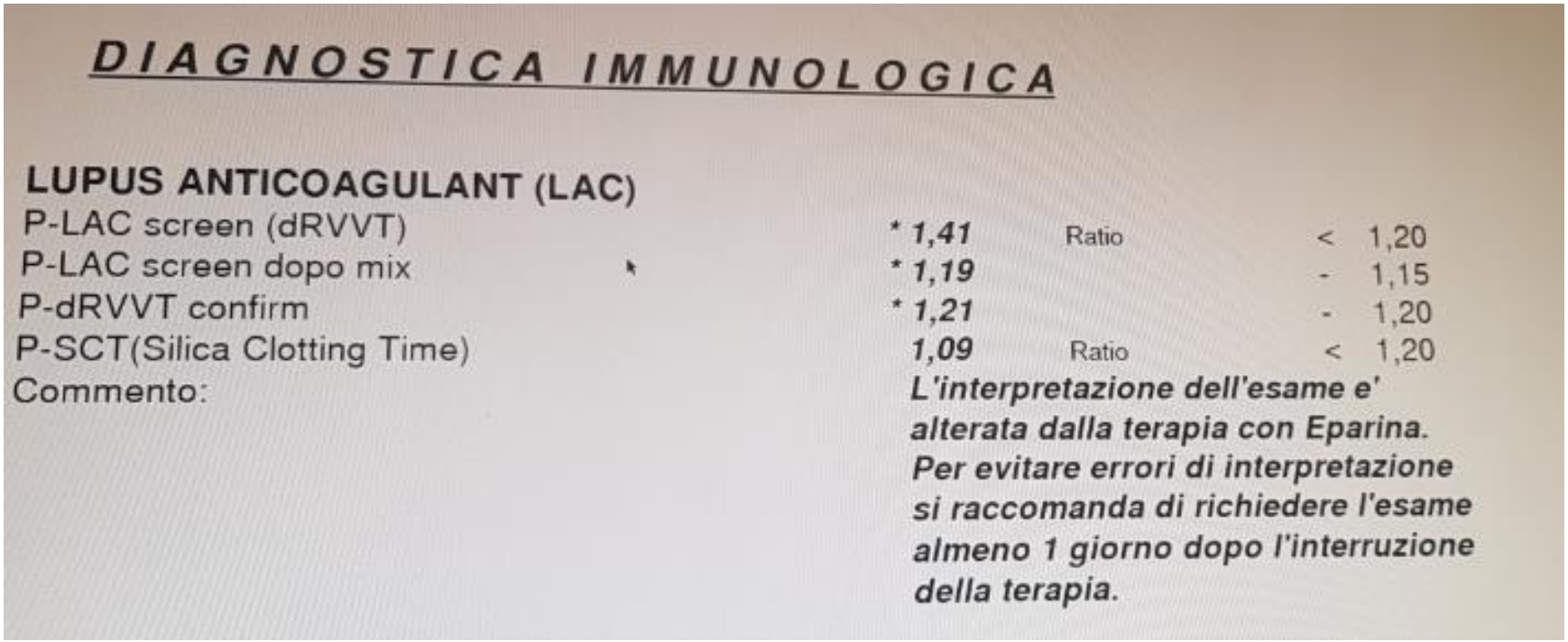
Evidence that inhibition is *phospholipid dependent*

- Confirmatory test(s) performed by performing tests in which increased phospholipid corrects or reduces the prolonged clotting time
- Examples: DRVVT confirm, hexagonal phase phospholipid, platelet neutralization test, others

Exclusion of coagulation inhibitors

- Heparin
- Direct thrombin or factor Xa inhibitors (DOAC)
- Coagulation factor inhibitors (e.g. factor VIII inhibitor)

Antiphospholipid Syndrome
Laboratory diagnosis



DIAGNOSTICA IMMUNOLOGICA

LUPUS ANTICOAGULANT (LAC)

P-LAC screen (dRVVT)	* 1,41	Ratio	<	1,20
P-LAC screen dopo mix	* 1,19		-	1,15
P-dRVVT confirm	* 1,21		-	1,20
P-SCT(Silica Clotting Time)	1,09	Ratio	<	1,20

Commento:

L'interpretazione dell'esame e' alterata dalla terapia con Eparina. Per evitare errori di interpretazione si raccomanda di richiedere l'esame almeno 1 giorno dopo l'interruzione della terapia.

	ESAME	RISULTATO	POSSIBILE INTERPRETAZIONE
Step 1	PTT LA-sensibile (PTT_LA) e/o test del veleno di vipera Russel diluito (DRVVT)	Normale	In genere non sono necessari ulteriori test. Nel caso di forte sospetto della presenza di inibitori, può essere ripetuto il test.
		Prolungato	Possibile presenza di inibitori → Step 2
Step 2	Test di miscela: il plasma in esame e quello ottenuto da un pool di plasmi normali vengono mescolati in parti uguali e utilizzati per ripetere il test PTT-LA e/o DRVVT	Normale	I test iniziali erano prolungati per la presenza di fattori diversi dalla presenza di inibitori, come ad esempio, la carenza di fattori della coagulazione.
		Prolungato	Se il plasma "normale" mescolato con quello in esame non corregge il risultato, allora è molto probabile la presenza di LA → Step 3

Step 3	Test di conferma (correzione o neutralizzazione): viene eseguito nuovamente il test PTT-LA o DRVVT ma aggiungendo un eccesso di fosfolipidi. Il rapporto normalizzato viene calcolato dividendo il risultato dei test eseguiti senza l'eccesso di fosfolipidi per questo risultato.	Positivo (rapporto alto)	Se superiore al valore limite di riferimento, la presenza di LA è assai probabile
		Negativo (rapporto basso)	Potrebbe essere presente un inibitore specifico diverso da LA. Devono essere eseguiti ulteriori test per la ricerca di anticorpi diretti verso specifici fattori della coagulazione, come il fattore VIII. Diversamente dalla presenza di LA, responsabile di trombosi, la presenza di inibitori specifici per fattori della coagulazione può portare a gravi emorragie.

Ratio > 1.3

Antiphospholipid Syndrome Laboratory diagnosis

Patients with APS may have one or more abnormal results from these laboratory tests; the following laboratory tests should be considered in a patient suspected of having APS:

- aCL antibodies (IgG, IgM)
- Anti–beta-2 glycoprotein I antibodies (IgG, IgM)
- Activated partial thromboplastin time (aPTT)
- LA tests such as DRVVT (A threshold of approximately 1.6 for the DRVVT ratio has been recommended for helping discriminate APS from non-APS. [13])

- CBC count (thrombocytopenia, hemolytic anemia)

Thrombocytopenia is fairly common (22% at presentation, 30% cumulatively) and is therefore associated with paradoxical thrombosis. However, patients with platelet counts of less than 50,000/µL may have an increased risk of bleeding.
Hemolytic anemia has been well described in patients with APS and is associated with the presence of IgM aCL antibodies.
A low ANA level may be present and does not necessarily imply coexisting SLE.

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RECOMMENDATIONS AND GUIDELINES

jth

Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis

Update of the guidelines for lupus anticoagulant detection and interpretation

Katrien M. J. Devreese[1,2] | Philip G. de Groot[3] | Bas de Laat[3] | Doruk Erkan[4] | Emmanuel J. Favaloro[5] | Ian Mackie[6] | Marta Martinuzzo[7] | Thomas L. Ortel[8,9] | Vittorio Pengo[10] | Jacob H. Rand[11] | Armando Tripodi[12,13] | Denis Wahl[14,15] | Hannah Cohen[16,17]

Patient Selection for LA Testing[1,2,12,13,82-88]

1. LA testing should be performed, together with testing for aCL, and aβ2GPI, to assess the risk profile, in patients who are likely to have APS:
   - younger patients (<50 years) with unprovoked venous thromboembolism (VTE)
   - VTE at unusual sites
   - younger patients (<50 years) with ischemic stroke, transient ischemic attack or other evidence of brain ischemia
   - arterial thrombosis in other sites in younger patients (<50 years)
   - microvascular thrombosis
   - recurrent VTE unexplained by subtherapeutic anticoagulation, patient nonadherence, or malignancy
   - pregnancy morbidity: fetal loss after 10 weeks, recurrent early (first trimester) miscarriages, prematurity (<34 weeks' gestation) associated with severe (pre)eclampsia, HELLP syndrome, placental insufficiency (fetal growth restriction), stillbirth
   - systemic lupus erythematosus: testing for LA is part of the diagnostic criteria and contributes to risk assessment
2. LA testing could be considered in the following situations:
   - immune thrombocytopenia, particularly with presence of arthralgias or arthritis, hair loss, sun sensitivity, mouth ulcers, rash, thromboembolism
   - livedo reticularis, particularly with presence of symptoms of other systemic autoimmune diseases or mild thrombocytopenia
   - younger patients (<50 years) with noncriteria clinical manifestations, ie those not included in the Sydney criteria, eg cognitive dysfunction, valvular heart disease with presence of evidence of other systemic autoimmune diseases
   - patients of younger age (<50 years) following provoked VTE when the provoking environmental factor is disproportionally mild
   - patients with unexplained prolonged aPTT as an incidental finding

Consider the following before ordering LA testing

- Results of LA testing during an acute phase response (eg, in the setting of an acute thrombotic event) should be interpreted with caution, as false positive and negative results can occur
- Ideally, LA testing should be performed in patients not receiving any anticoagulant treatment as false positives and false negatives can occur
- LA testing may be clinically desirable in anticoagulated patients; the following points should be noted:
  - In VKA-treated patients, the interpretation of LA results is challenging because of the prolonged basal clotting time. If feasible, perform LA testing 1 to 2 weeks after discontinuation of the VKA, with consideration of LMWH bridging
  - If patients are tested during treatment with LMWH, samples should be taken, when feasible, at least 12 hours after the last dose of LMWH was administered and as near as possible to the next dose, with anti-Xa activity levels checked alongside the LA test
  - If feasible to temporarily interrupt DOAC anticoagulation (on a pragmatic, empirical basis at least 48 hours after the last dose, and longer in patients with renal impairment), LA testing can be performed, with the DOAC level checked alongside the LA test
- Incorporation of information on the patient's anticoagulation status in the request is mandatory
- Results of LA testing during pregnancy should be interpreted with caution as false positive and negative results can occur. Repeat testing should be considered at an appropriate time post-delivery to obtain reliable LA results

Interpretation of results

- Results to be interpreted according to the local cutoff values stated in the report. The cutoff value may impact upon diagnosis (eg, weak positive LA) as it will determine whether a patient is classified to be LA positive or not.
- LA is reported with a final conclusion as positive or negative
- Results should always be related to the results of aCL and aβ2GPI to assess the risk profile
- Comments on the final conclusion should be provided if relevant (eg on possible interferences)
- Results should be interpreted in a clinical context, with knowledge of anticoagulation
- Information provided in the request on the patient's anticoagulation status should also be incorporated into the report
- A close interaction between the laboratory and the clinician is essential

Repeat testing

- Repeat testing is required after an initial positive result on a second occasion after at least 12 weeks to confirm persistent positivity

Laboratory Criteria-aPL risk stratification

Box 1 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 standardised ELISA. Antibeta2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma in titre >the 99th percentile, measured by a standardised ELISA.[1]

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 antibeta2 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 antibeta2 glycoprotein I antibodies at low-medium titres, particularly if transiently positive.[3]

Tektonidou MG, et al. Ann Rheum Dis 2019

Antiphospholipid Syndrome Diagnosis

APS clinical "non-criteria" recognized by the 2006 consensus statement:
cardiac valve disease,
livedo reticularis,
thrombocytopenia,
nephropathy,
skin ulcers,
transient ischemic attacks

Additional antibodies directed against phospholipid/phospholipid-protein complexes for which testing may be useful in selected cases (seronegative APS, because they are not part of the 2006 consensus criteria) :

- IgA aCL
- IgA beta-2 glycoprotein I
- Anti-phosphatidylserine antibodies
- Anti-phosphatidylethanolamine antibodies
- Anti-prothrombin antibodies
- Antibodies against the phosphatidylserine-prothrombin complex

Miyakis S et al. JTH 2006

aPS / PT test utility

- Improves the diagnostic sensitivity of true APS patients (bridges the seronegative gap)
- Antibodies to PS + PT complex are clinically more important than those to isolated PS or PT
- They contribute to the 'risk stratification'
- High correlation with LAC
- Useful as a confirmatory test when it is difficult to repeat the LAC
- Simple and reproducible test with respect to the sample
- There is no need to stop anticoagulant therapy
- Easy sample handling (quality, handling, storage)

Peculiarities of the Domain 1 IgG assay

- High correlation with Triple-Positivity
- Confirmation: anti-Domain 1 antibodies are a more specific marker for more severe APS situations than the presence of antibodies directed to other parts of the B2-Glycoptrotein 1 protein (domain 4/5) associated with other cardiovascular diseases
- Therapy Monitoring: Anti-Domain 1 antibodies have been proposed as a test for therapeutic monitoring in the treatment of APS1 conditions2
- Prognostic use: anti-Domain 1 antibodies are the most clinically relevant marker, due to the high correlation with thrombosis.

1. Andreoli L. et al, *Reumatismo, 2010; 62(3):189-194*
2. Ioannou Y. et al, Lupus, (2010) 19, 400–405
3. De Laat B. et al Nat Clin Practice 2008; 4 (4): 192-199

An update on laboratory detection and interpretation of antiphospholipid antibodies for diagnosis of antiphospholipid syndrome: guidance from the ISTH-SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies

Katrien M. J. Devreese[1] | Maria Laura Bertolaccini[2] | D. Ware Branch[3] |

Antiphospholipid antibody tests -which ones to test for?

We recommend:

- Concurrent testing for LA, aCL IgG and IgM, and aβ2GPI IgG and IgM
  - Measurement of LA in citrated plasma according to the ISTH-SSC recommendations by a 3-step methodology (screening, mixing, and confirmation) with parallel testing in APTT and dRVVT as first-choice clotting tests [12]
  - Pretest DOAC removal (with LA testing pre-/post-DOAC removal procedure) can be used in patients during DOAC therapy
  - LA testing during VKA is reliable in some situations but should always be interpreted with care
  - TSVT/ET can be used in patients during anti-Xa DOAC or VKA therapy, keeping in mind that TSVT/ET does not have 100% sensitivity
  - Measurement of aCL of IgG/IgM isotype and aβ2GPI of IgG/IgM isotype in plasma or serum by solid phase assays (ELISA or non-ELISA systems), according to the ISTH-SSC recommendations [37]

We do not recommend:

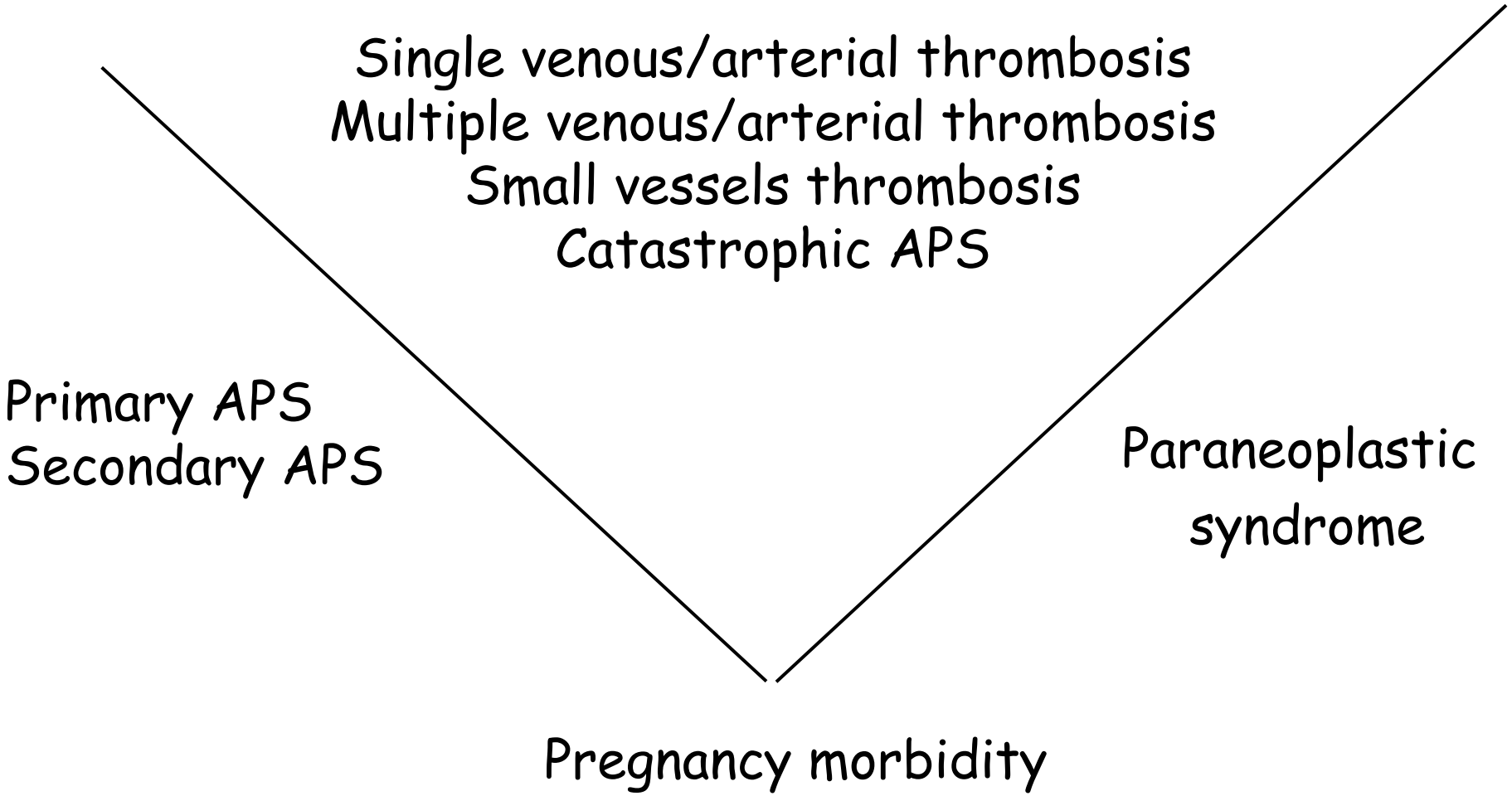
- aPS/PT IgG/IgM or aDI in the first-line diagnostic tests
- To replace LA with aPS/PT

We recommend using aPS/PT and aDI in specific situations:

- aPS/PT can be useful if LA testing is unreliable or uncertain
- aDI can be used to confirm the specificity and pathogenicity of aβ2GPI

ANTIPHOSPHOLIPID SYNDROME

CLINICAL SPECTRUM



- Primary APS
- Secondary APS- associated with SLE, and other connective tissue diseases

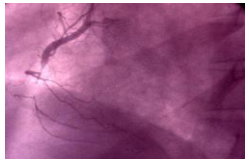
Clinical criteria
Vascular thrombosis

One or more clinical episodes of

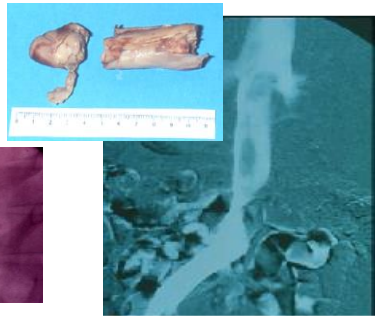
- ✓ arterial,
- ✓ venous,
- ✓ or small vessel thrombosis,

in any tissue or organ.

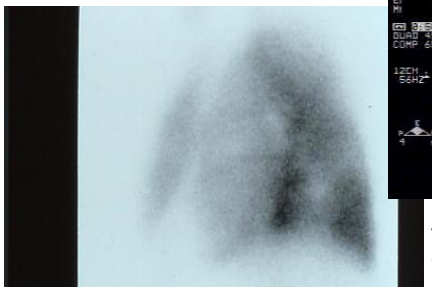
Clinical pictures



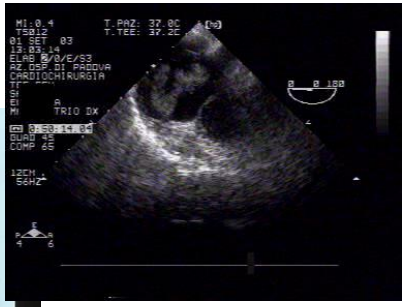
Trombosi arteria coronaria con area infartuale



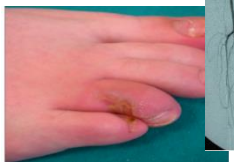
Trombosi della vena cava inferiore e della vena iliaca comune di sinistra



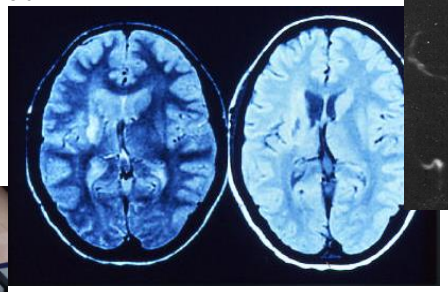
Tromboembolia polmonare



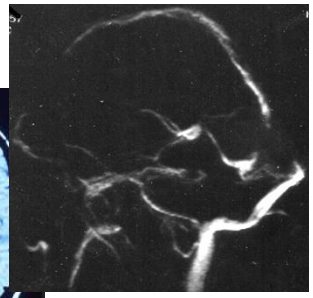
Trombo adeso alla parete libera dell'atrio destro



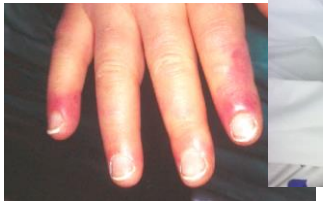
Trombosi arterie tibiale posteriore, interossea e tibiale anteriore di sinistra

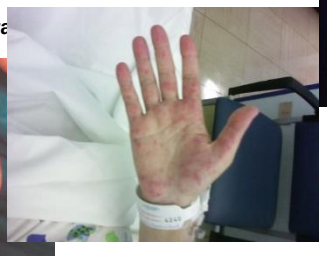


Trombosi dell'arteria cerebrale media di sinistra



Trombosi del seno venoso sagittale superiore

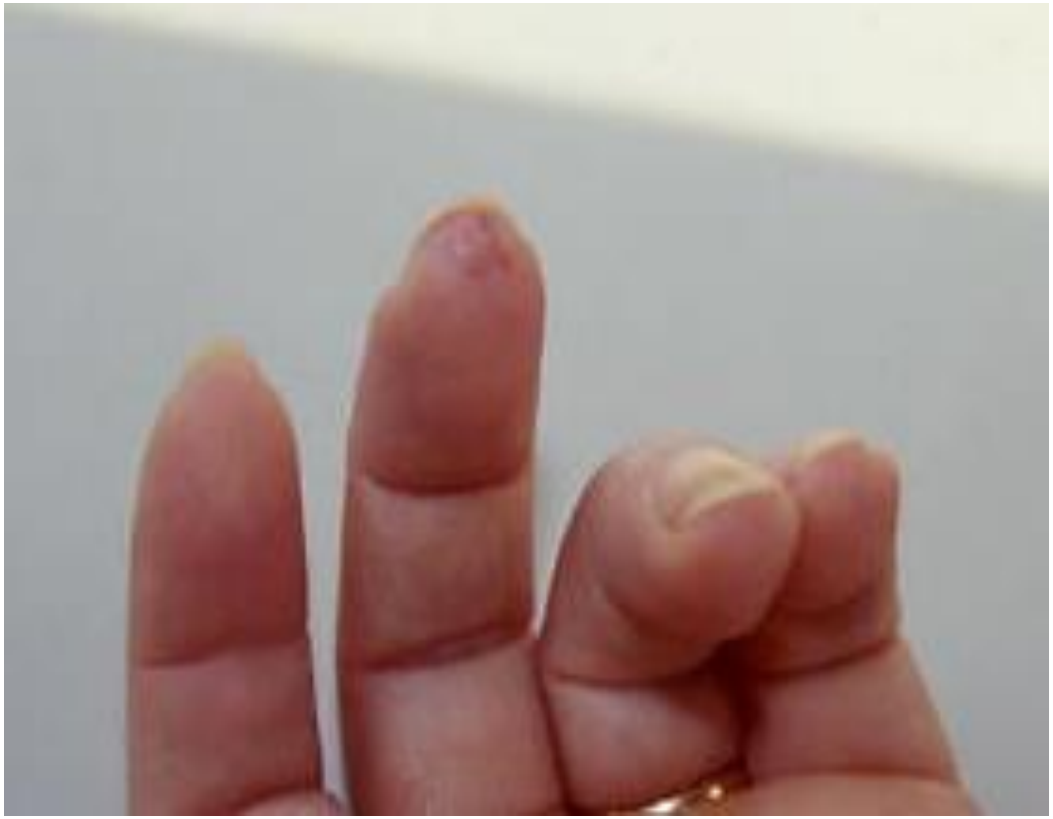




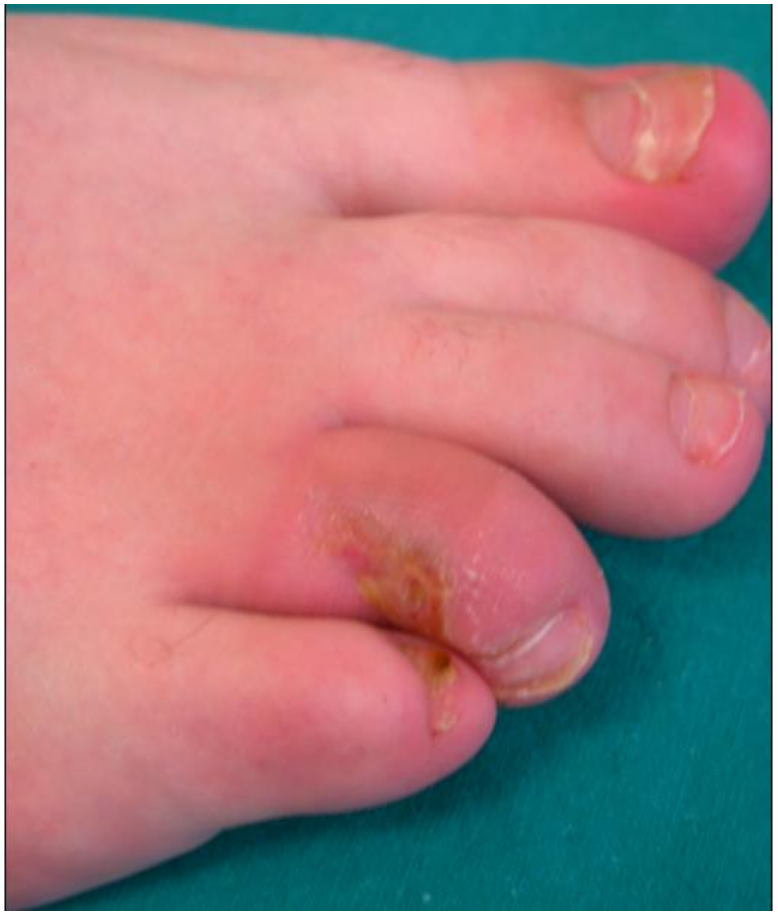
Trombosi del microcircolo

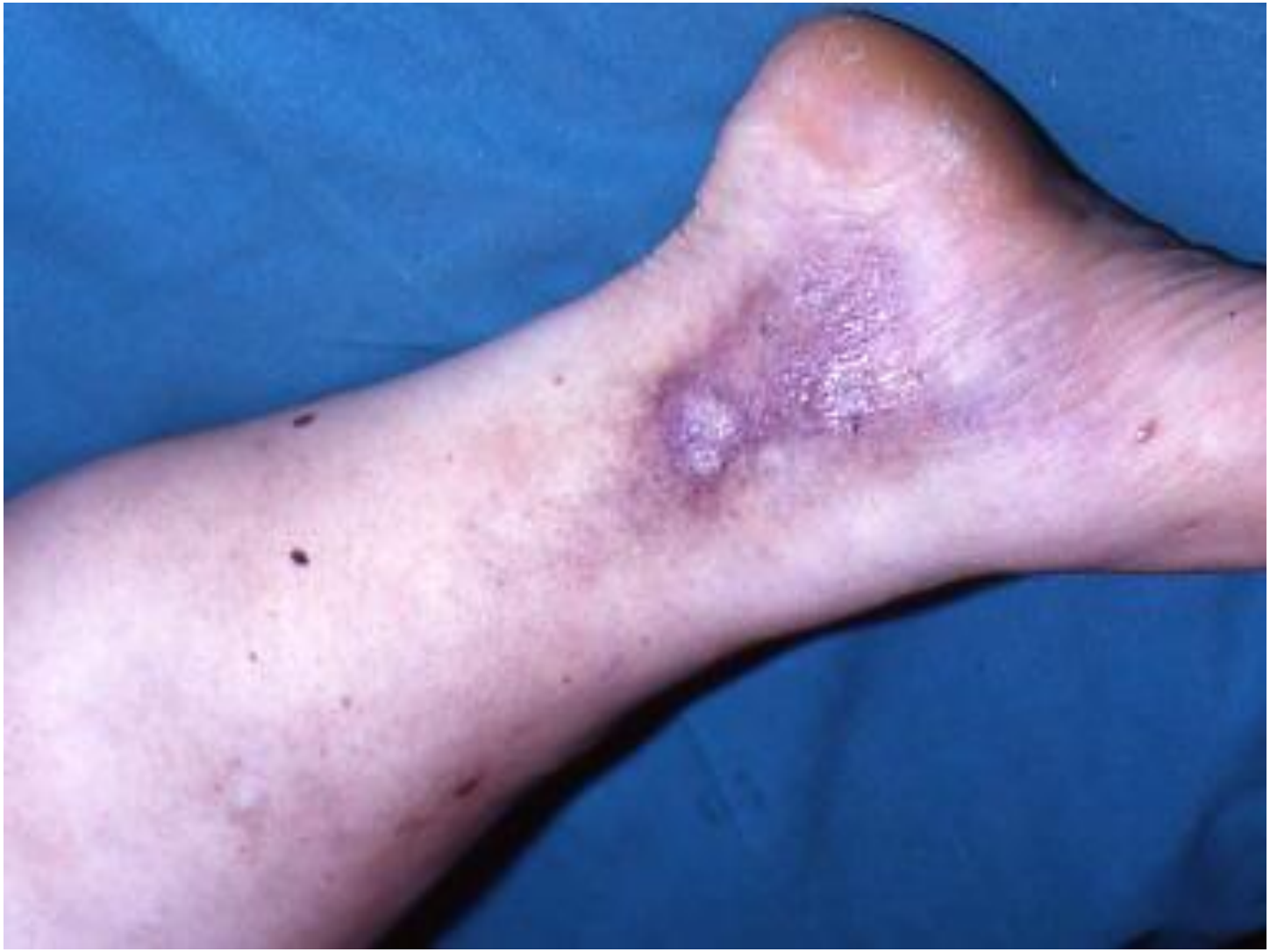
Microlivedo acrale fissa

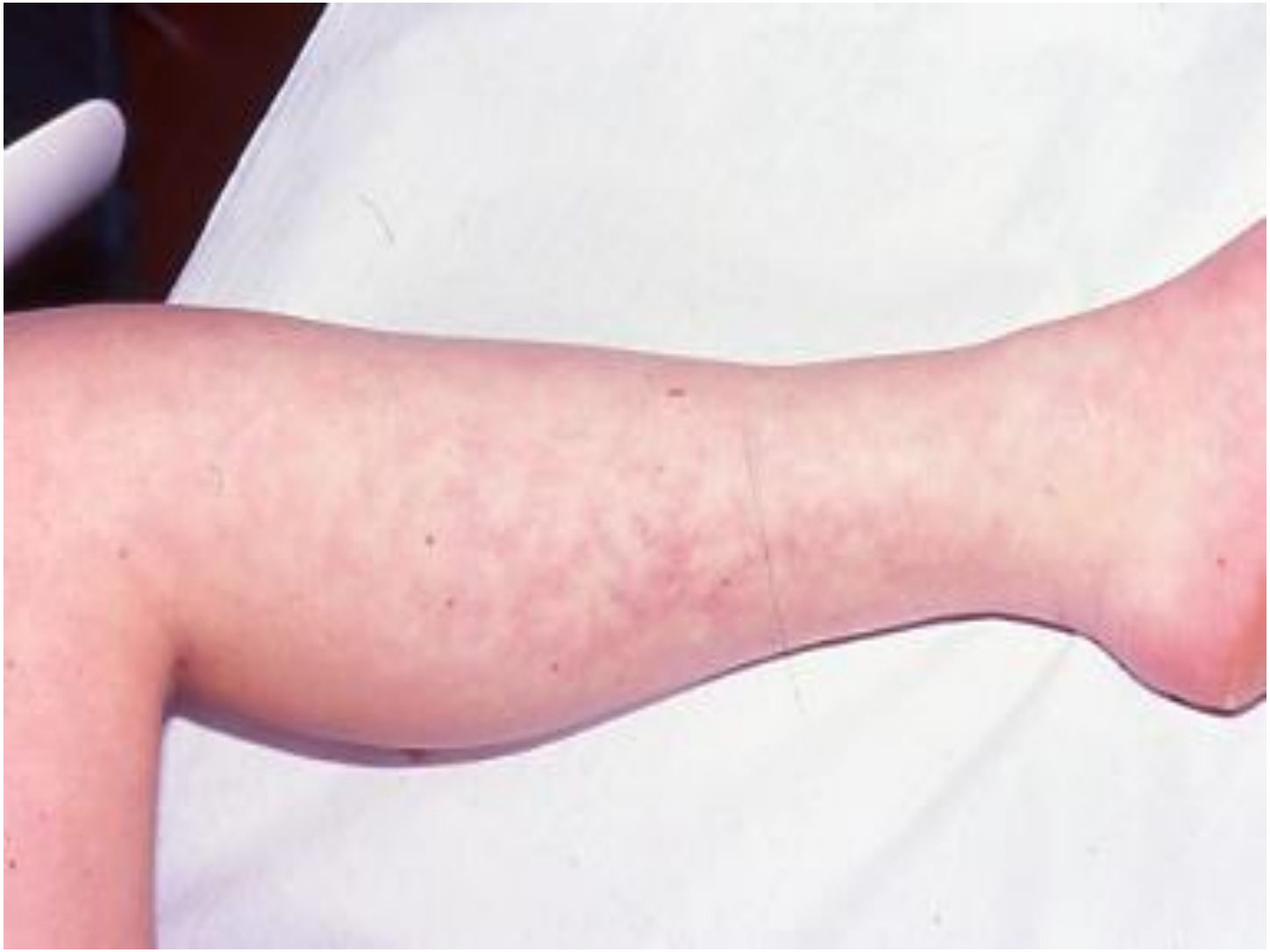
(F. B. ♀ anni 44)



Trombosi arterie tibiale posteriore, interossea e tibiale anteriore di sinistra.
(K. F. ♀ anni 17)





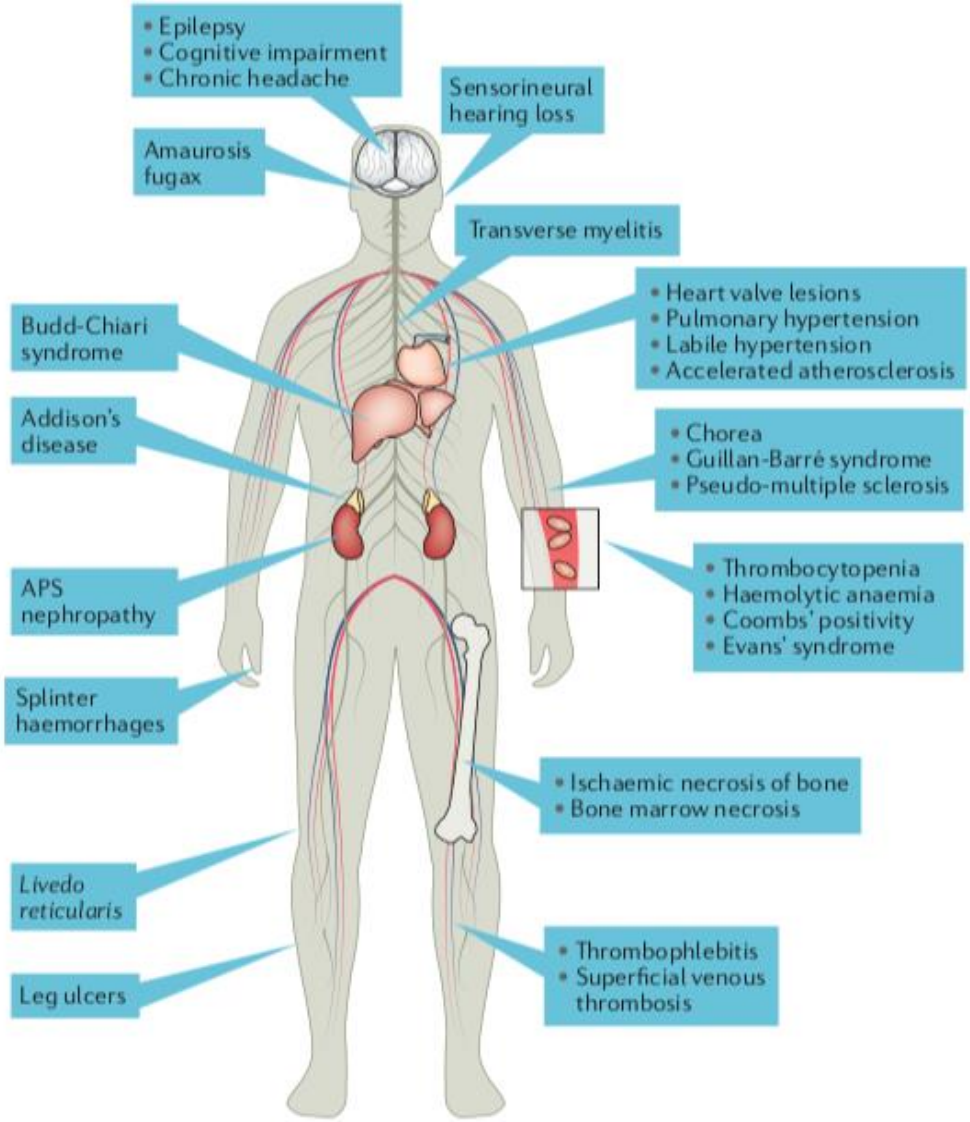


Antiphospholipid Syndrome
Clinical features

- Peripheral venous system
- Central nervous system (stroke, sinus thrombosis, seizures, chorea, reversible cerebral vasoconstriction syndrome)
- Peripheral nervous system (peripheral neuropathy including Guillain–Barré syndrome)
- Hematologic (thrombocytopenia, hemolytic anemia)
- Obstetric (pregnancy loss, eclampsia)
- Pulmonary (PE, pulmonary hypertension)
- Dermatologic (livedo reticularis, purpura, infarcts/ulceration)
- Cardiac (Libman-Sacks valvulopathy, MI, diastolic dysfunction)
- Ocular (amaurosis, retinal thrombosis)
- Adrenal (infarction/hemorrhage)
- Musculoskeletal (avascular necrosis of bone)
- Renal (thrombotic microangiopathy)

The kidney is a major target organ in APS. Nephropathy in APS is characterized by small-vessel vaso-occlusive lesions associated with fibrous intimal hyperplasia of interlobular arteries, recanalizing thrombi in arteries and arterioles, and focal atrophy.

Extra-criteria clinical manifestations of APS



Sciascia et al. Nat Rev Rheum 2017

2023 ACR/EULAR classification criteria

2023 Clinical criteria Thrombosis

Table 1 Definitions of the 2023 ACR/EULAR antiphospholipid syndrome (APS) classification criteria

Clinical criteria
Domain 1 — Macrovascular (venous thromboembolism)
Venous thromboembolism (otherwise unexplained* and confirmed by appropriate testing): Includes (but is not limited to) pulmonary embolism, deep vein thrombosis of the legs/arms, splanchnic thrombosis, renal vein thrombosis, cerebral venous thrombosis, and retinal vein thrombosis/occlusion.
Domain 2 — Macrovascular (arterial thrombosis)
Arterial thrombosis (otherwise unexplained* and confirmed by appropriate testing): Includes (but is not limited to) myocardial infarction (coronary artery thrombosis), peripheral/splanchnic/retinal artery thromboses, stroke based on international definitions,[35 36] and other organ infarcts (eg, kidney, liver, or spleen) in the absence of visualised thrombus.
Domain 3 — Microvascular
Suspected:
Livedo racemosa (by physical examination): Otherwise unexplained* violaceous, "net-like," blotchy mottling of the skin. Note: livedo racemosa with nonuniform, irreversible, broken, and asymmetric persistent discoloration should be scored; *livedo reticularis with uniform, reversible, unbroken, and symmetric discoloration should not be scored.*
Livedoid vasculopathy lesions (by physical examination): Otherwise unexplained* painful papules and erythematous-violaceous purpuric plaques, which may rapidly evolve into haemorrhagic vesicles or bullae. Note: if ruptured, can result in painful small ulcers or reticulate, confluent, geometric, and painful ulcers.
Antiphospholipid antibody (aPL) nephropathy (by physical examination or laboratory tests): Otherwise unexplained persistent: (a) new-onset hypertension or deterioration of previously well-controlled hypertension; (b) proteinuria≥0.5 gm in 24-hour urine specimen or protein:creatinine ratio ≥0.5 mg/mg (50 mg/mmoles); (c) acute renal failure (increased serum creatinine levels above normal); or (d) glomerular microscopic hematuria.
Pulmonary hemorrhage (by clinical symptoms and imaging): Respiratory symptoms (eg, dyspnoea, cough, hemoptysis) AND otherwise unexplained* pulmonary infiltrates on imaging suggestive of pulmonary hemorrhage.
Established:
Livedoid vasculopathy (by pathology once livedoid vasculopathy lesions described above are present): Otherwise unexplained thrombosis of the small dermal vessels and/or endothelial proliferation.
aPL nephropathy (by pathology once suspected aPL-nephropathy definition above is fulfilled)[37]: (a) **Acute renal vascular or glomerular thrombotic microangiopathy lesions**, including fibrin thrombi in arterioles or glomeruli without inflammatory cells or immune complexes; and (b) **chronic renal vascular or glomerular lesions**, described as arterial or arteriolar organised microthrombi with or without recanalisation, fibrous and fibrocellular (arterial or arteriolar) occlusions, focal cortical atrophy with or without thyroidization, fibrous intimal hyperplasia, or chronic/organised glomerular thrombi. Note: in patients with systemic lupus erythematosus, aPL nephropathy occurs independent of lesions attributable to lupus nephritis.
Pulmonary hemorrhage (by bronchoalveolar lavage [BAL] or pathology once suspected pulmonary hemorrhage definition above is fulfilled): Otherwise unexplained* progressive haemorrhagic return on BAL with aliquots or hemosiderin-laden macrophages (>20%), OR lung biopsy demonstrating capillaritis or microthrombosis.
Myocardial disease (by imaging or pathology): Otherwise unexplained* non-ST segment elevation myocardial infarction with a normal coronary angiogram (myocardial infarction with nonobstructive coronary arteries, or MINOCA) AND cardiac magnetic resonance imaging (CMRI) abnormalities as per the 2018 Society for CMRI expert consensus[38] including: (a) late gadolinium enhancement either transmurally or subendocardially; (b) T2 abnormalities (weighted imaging or mapping); or (c) perfusion MRI abnormalities, OR histologically by thrombosis of the small vessels of the heart.
Adrenal hemorrhage or microthrombosis (by imaging or pathology): Otherwise unexplained* CT or MRI demonstrating hemorrhage, OR histologically by thrombosis of the adrenal (micro)vasculature, for example, adrenal plexus, adrenal vein.

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2023 ACR/EULAR classification criteria

Domain 4 — Obstetric

Prefetal death (preembryonic or embryonic loss): Otherwise unexplained* pregnancy loss before 10 weeks 0 days of gestation.

Fetal death: Otherwise unexplained* pregnancy loss between 10 weeks 0 days and 15 weeks 6 days gestation (early fetal death), or between 16 weeks 0 days and 34 weeks 0 days gestation. Note: if a detailed analysis of the fetal morphology or genetic constitution is not performed or unavailable, reasonable clinical judgeoccasions at least 4 hours hours apartment should be used based on careful history and review of available medical records.

Preeclampsia with severe features:[39] **Preeclampsia** defined as a systolic blood pressure≥140 mm Hg or diastolic blood pressure≥90 mm Hg on 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive or hypertensive (chronic†) patient AND new onset of one or more of the following: (a) proteinuria ≥0.3 mg/mg (30 mg/mmoles) in a random urine specimen or (b) dipstick protein ≥2+ if a quantitative measurement is unavailable AND one or more of the following "severe features":

- **Severe blood pressure elevation**: Systolic blood pressure≥160 mm Hg or diastolic blood pressure≥110 mm Hg on 2 occasions at least 4 hours apart while the patient is on bed rest (antihypertensive therapy may be initiated on confirmation of severe hypertension, in which case severe blood pressure elevation criteria can be satisfied without waiting until 4 hours have elapsed).
- **Central nervous system dysfunction**: New-onset headache unresponsive to medication and not accounted for by alternative diagnosis.
- **Visual disturbances.**
- **Pulmonary oedema.**
- **Impaired liver function**: Abnormally elevated blood concentrations of liver enzymes (more than twice the upper limit of normal concentrations), or severe persistent right upper quadrant or epigastric pain unresponsive to medications, not accounted by alternative diagnosis.
- **Renal dysfunction**: Serum creatinine concentration >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease.
- **Thrombocytopenia**: platelet count of $<100 \times 10^9$/liter.

Placental insufficiency with severe features: **Intrauterine fetal growth restriction** defined as biometry indicating estimated fetal weight of less than the 10th percentile for gestational age or postnatal birth weight less than the 10th percentile for gestational age in the absence of fetal-neonatal syndromes or genetic conditions associated with growth restriction AND one or more of the following "severe features":

- **Abnormal or non-reassuring fetal surveillance test(s)** suggestive of fetal hypoxemia, e.g., a nonreactive non-stress test
- **Abnormal Doppler flow velocimetry waveform analysis** suggestive of fetal hypoxemia, e.g., absent end-diastolic flow in the umbilical artery.
- **Severe intrauterine fetal growth restriction** suggested by fetal biometry indicating an estimated fetal or postnatal birth weight of<3 rd percentile for gestational age.
- **Oligohydramnios**, e.g., an amniotic fluid index≤5 cm, or deepest vertical pocket<2 cm.

Maternal vascular malperfusion on placental histology suggested by placental thrombosis/infarction, inadequate remodelling of the uterine spiral arteries (decidual vasculopathy), decreased vasculosyncytial membranes, increased syncytial knots, or decidual inflammation.[40] Note: Maternal vascular malperfusion on placental histology can be detected in the placentas of aPL-negative patients with intrauterine growthrestriction and/or preeclampsia, and even in normal pregnancies; thus, these findings are not specific for APS.

2023 Clinical criteria
Obstetric

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2023 ACR/EULAR classification criteria

2023 Clinical criteria
Additional criteria

Domain 5 – Cardiac valve
Valve thickening (otherwise unexplained*): Based on World Heart Federation echocardiographic criteria,[41] mitral valve thickening is defined as>4 mm between ages 20–39 years and>5 mm for those older than age 40 years, and>3 mm for other valves for any age (valve thickening can be associated with valvular dysfunction (regurgitation o stenosis)).
Valve vegetation (otherwise unexplained*): Based on the American Society of Echocardiography guidelines,[42] valve vegetation is defined as shaggy, lobulated, or rounded masses typically located on the atrial side of atrioventricular valves (mitral valve and tricuspid valve) or ventricular side of the aortic valve, but can be located on any side of an valve (size is highly variable but usually <1 cm); on echocardiogram, despite the "echo texture" and location of aPL-associated vegetations resembling infective endocarditis, they may appear less amorphous, more rounded, and not associated with valvular destruction, in contrast to a true infective endocarditis; they can be associated with valvular dysfunction (regurgitation or stenosis).
Domain 6 – Haematology
Thrombocytopenia: Otherwise unexplained* lowest platelet count ever between 20 and 130×10^9/liter, confirmed on peripheral blood smear and by repeat testing.

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2023 ACR/EULAR classification criteria

2023 Laboratory criteria

Domain 7 — aPL test by coagulation-based functional assay
Lupus anticoagulant (LAC) assay performed and interpreted based on the International Society of Thrombosis and Hemostasis (ISTH) guidelines[27], which can be summarised as follows:
A 3-step procedure (screening – mixing study – confirmation) with 2 screening test systems (diluted Russell's viper venom time and a sensitive activated partial thromboplastin time [low phospholipids and silica as activator]) is necessary to confirm the presence of LAC. The LAC test should be considered positive if at least 1 of the 2 test systems yields a positive result following all 3 steps (phospholipid-dependent correction of the prolonged screening tests).
Results of LAC testing should be interpreted with caution, as false positive and negative results can occur during anticoagulation (thus, LAC testing is ideally performed in patients not receiving anticoagulants), as an acute-phase response (eg, acute thrombosis) due to acute-phase reactants (eg, Factor VIII and C-reactive protein), and in pregnancy due to increase in blood coagulation factors.
Samples from patients receiving anticoagulants (vitamin K antagonists, heparin, direct oral anticoagulants, indirect Factor Xa inhibitor) should be marked positive or negative on the LAC assay only if reviewed/confirmed by an individual with expertise in performing/interpreting the LAC assay, for example, expert laboratory personnel.
Domain 8 — aPL test by solid phase–based assay
Anticardiolipin antibody (aCL) and anti–β_2-glycoprotein I antibody (anti-β_2GPI) thresholds of moderate (40–79 units) and high (≥80 units) should be determined based on standardised ELISA results, not based on other testing modalities such as new automated platforms with variations of the solid phase (eg, magnetic microparticles and microspheres) and various detection systems (eg, chemiluminescent immunoassay (CLIA), multiplex flow immunoassay (MFI), or flow cytometry).

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2023 ACR/EULAR classification criteria

Entry Criteria[a]
At least one documented[b] clinical criterion listed below (domains 1-6)
plus
A positive antiphospholipid antibody (aPL) test
(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti-β_2-glycoprotein-I antibodies [IgG or IgM])
within three years[b] of the clinical criterion

↓

If absent, do not attempt to classify as APS - If present, apply additive criteria

↓

Additive clinical and laboratory criteria[a]
Do not count a clinical criterion if there is an equally or more likely explanation than APS.
Within each domain, only count the highest weighted criterion towards the total score.

Clinical domains and criteria	Weight	Clinical domains and criteria	Weight
D1. Macrovascular (Venous Thromboembolism [VTE])		**D2. Macrovascular (Arterial Thrombosis [AT])**	
VTE with a high-risk VTE profile[c]	1	AT with a high-risk CVD profile[c]	2
VTE without a high-risk VTE profile[c]	3	AT without a high-risk CVD profile[c]	4
D3. Microvascular		**D4. Obstetric**	
Suspected (one or more of the following)	2	≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths	1
Livedo racemosa (exam)			
Livedoid vasculopathy lesions (exam)			
Acute/chronic aPL-nephropathy (exam or lab)			
Pulmonary hemorrhage (symptoms and imaging)			
		Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
Established (one of more of the following)	5		
Livedoid vasculopathy (pathology[d])			
Acute/chronic aPL-nephropathy (pathology[d])			
Pulmonary hemorrhage (BAL or pathology[d])			
Myocardial disease (imaging or pathology)			
Adrenal hemorrhage (imaging or pathology)			
		PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	3
		PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	4
D5. Cardiac Valve		**D6. Hematology**	
Thickening	2	Thrombocytopenia (lowest 20-130x10^9/L)	2
Vegetation	4		

Laboratory (aPL) domains and criteria[e]	Weight	Laboratory (aPL) domains and criteria[e]	Weight
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])		**D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])**	
Positive LAC (single – one time)	1	Moderate or high positive (IgM) (aCL and/or aβ_2GPI)	1
Positive LAC (persistent)	5	Moderate positive (IgG) (aCL and/or aβ_2GPI)	4
		High positive (IgG) (aCL or aβ_2GPI)	5
		High positive (IgG) (aCL and aβ_2GPI)	7

↓

TOTAL SCORE
Classify as Antiphospholipid Syndrome for research purposes if there are
at least 3 points from clinical domains AND at least 3 points from laboratory domains

The 2023 ACR/EULAR APS classification criteria are presented in figure.

According to these criteria, patients should be classified as having APS if they fulfil the entry criteria (at least 1 clinical and one laboratory criterion within 3 years of each other) **and accumulate at least three points from clinical domains and three points from laboratory domains.**

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ULAR classification criteria

Entry Criteria[a]

At least one documented[b] clinical criterion listed below (domains 1-6)

plus

A positive antiphospholipid antibody (aPL) test
(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti-β_2-glycoprotein-I antibodies [IgG or IgM])
within three years[b] of the clinical criterion

↓

If absent, do not attempt to classify as APS - If present, apply additive criteria

↓

Additive clinical and laboratory criteria[a]

Do not count a clinical criterion if there is an equally or more likely explanation than APS.
Within each domain, only count the highest weighted criterion towards the total score.

Clinical domains and criteria	Weight		Weight
D1. Macrovascular (Venous Thromboembolism [VTE])		**D2. Macrovascular (Arterial Thrombosis [AT])**	
VTE with a high-risk VTE profile[c]	1	AT with a high-risk CVD profile[c]	2
VTE without a high-risk VTE profile[c]	3	AT without a high-risk CVD profile[c]	4
D3. Microvascular		**D4. Obstetric**	
Suspected (one or more of the following)	2	≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths	1
Livedo racemosa (exam)			
Livedoid vasculopathy lesions (exam)			
Acute/chronic aPL-nephropathy (exam or lab)			
Pulmonary hemorrhage (symptoms and imaging)		Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
Established (one of more of the following)	5		
Livedoid vasculopathy (pathology[d])			
Acute/chronic aPL-nephropathy (pathology[d])		PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	3
Pulmonary hemorrhage (BAL or pathology[d])			
Myocardial disease (imaging or pathology)		PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	4
Adrenal hemorrhage (imaging or pathology)			
D5. Cardiac Valve		**D6. Hematology**	
Thickening	2	Thrombocytopenia (lowest 20-130x10^9/L)	2
Vegetation	4		

Laboratory (aPL) domains and criteria[e]	Weight		
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])		**D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])**	
Positive LAC (single – one time)	1	Moderate or high positive (IgM) (aCL and/or aβ_2GPI)	1
Positive LAC (persistent)	5	Moderate positive (IgG) (aCL and/or aβ_2GPI)	4
		High positive (IgG) (aCL or aβ_2GPI)	5
		High positive (IgG) (aCL and aβ_2GPI)	7

↓

TOTAL SCORE

Classify as Antiphospholipid Syndrome for research purposes if there are
at least 3 points from clinical domains AND at least 3 points from laboratory domains

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Antiphospholipid Syndrome
Thrombotic risk

DIAGNOSI CERTA:
tripli positivi (LAC +, IgG o IgM acL >40 U, IgG o IgM B2GPI > 40 U, stesso isotipo) + comprovata trombosi venosa/arteriosa e/o Perdita gravidica

spt
Età < 50 aa
VTE non provocato, sito atipico, microcircolo
Perdita gravidica dopo la 10 SG
IgG aCl e aB2GPI ad alto titolo
LAC fortemente positivo (2 test positivi)

Può non servire ripetere dopo 12 settimane!

IgM sono meno protrombotici → di solito soggetti più anziani e con eventi atero-trombotici.

Antiphospholipid Syndrome Thrombotic risk

DIAGNOSI probabile/possibile:
doppia positività (perlopiù LAC negativo, IgG o IgM acL >40 U, IgG o IgM B2GPI > 40 U, stesso isotipo) + comprovata trombosi venosa/arteriosa e/o Perdita gravidica

Pazienti con rischio di eventi trombotici inferiore

Il titolo antiB2GPI non è sufficiente a dare attività LAC

Più importante nella morbidità gravidica

Trattare la clinica (trombosi) non considerare gli anticorpi

Antiphospholipid Syndrome
Thrombotic risk

DIAGNOSI incerta/improbabile:

singola positività + comprovata trombosi venosa/arteriosa e/o Perdita gravidica

Trattare l'evento clinico (trombosi) non la sindrome

Antiphospholipid Syndrome Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

4.2 Therapeutic Range for High-Risk Groups

4.2. For patients with antiphospholipid syndrome with previous arterial or venous thromboembolism, we suggest VKA therapy titrated to a moderate-intensity INR range (INR 2.0-3.0) rather than higher intensity (INR 3.0-4.5) (Grade 2B).

Chest 2012;141;48S-52S
DOI 10.1378/chest.11-2286

Antiphospholipid Syndrome Therapy

Summary of treatment recommendations for APS and APLA.

Clinical setting	Recommendation	Additional comments
First venous thrombosis in APS	Anticoagulation with VKA (INR 2–3)	No clear benefit of high intensity anticoagulation Insufficient data to support routine DOAC use
Arterial thrombosis in APS	ASA + standard intensity anticoagulation with VKA (INR 2–3), or High intensity VKA anticoagulation (INR 3–4) in high risk patients	One study showed no benefit of ASA + VKA over ASA in APS with stroke; results are not generalizable since APLA tested only at baseline and lower target INR
Recurrent thrombosis in APS	Confirm that therapeutic INR is maintained May consider LMWH or high intensity anticoagulation with VKA (INR 3–4). Consider adjunctive hydroxychloroquine, statin	No clinical trial data. Based on clinical observation and expert opinion.

The optimal duration of anticoagulation is unclear, the current recommendation is that anticoagulation for secondary prophylaxis should be continued indefinitely.

Rates of recurrent thrombosis > 30% have been reported even in anticoagulated patients with APLA

Blood Reviews 31 (2017) 406–417

Trombofilia: profilassi secondaria

Table 11 Categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long-term

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

Konstantinides SV et al ESC 2020

Antiphospholipid Syndrome Therapy

Pazienti con
TEV idiopatico o associati a stati FdR permanenti (trombofilia, autoimmunità)
Embolia polmonare
Tripla positività

→ Considerare Long-term therapy

Pazienti con
TEV provocato
Singolo test positivo

→ Considerare breve durata di trattamento

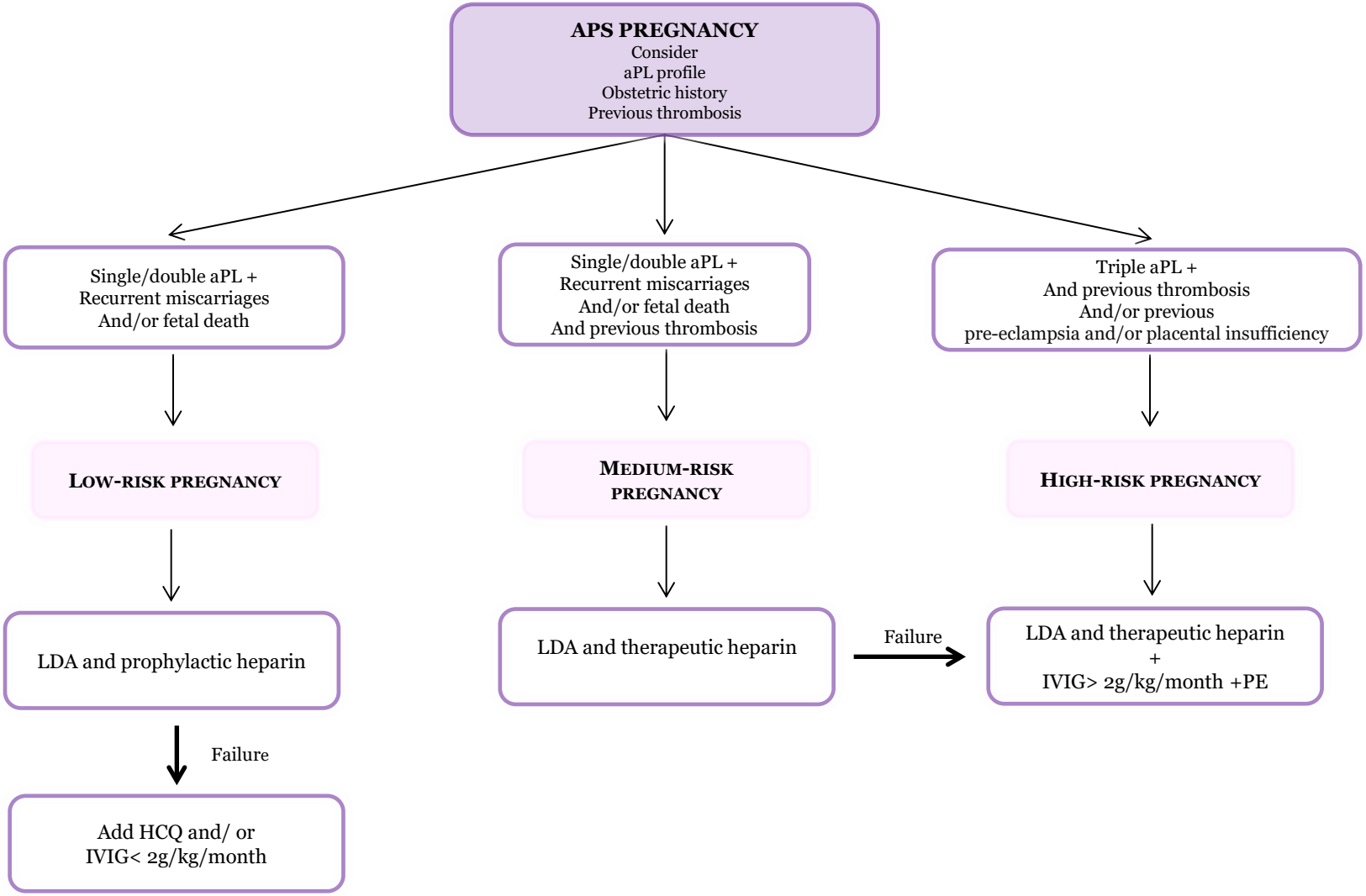
Antiphospholipid Syndrome Therapy

Obstetric APS (without prior thrombosis)	ASA + LMWH Prophylactic dose LMWH continued until 6 weeks post-partum	
Obstetric APS with prior thrombosis	Low dose aspirin with therapeutic dosing of LMWH. After pregnancy, may be transitioned back to VKA to continue anticoagulation indefinitely.	Start LMWH (and stop VKA) at or prior to diagnosis of pregnancy.

The most common approach, endorsed by the ACCP guidelines is the combination of heparin (unfractionated or low molecular weight; prophylactic or intermediate dose) and low dose aspirin (75–100 mg) daily for women who fulfill the clinical and serologic criteria for obstetric APS.

In women with APS and prior thrombosis, aspirin and therapeutic dose LMWH should be employed.

Blood Reviews 31 (2017) 406–417



Hoxha, A. , Simioni, P. . Obstetric Antiphospholipid Syndrome. In: Žigon, P. , editor. Antiphospholipid Syndrome - Recent Advances in Clinical and Basic Aspects

DOAC e APS

Table 4. Adjudicated efficacy and safety outcomes

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 Ischemic stroke Myocardial infarction	7 (12) 4 (7) 3 (5)	0 0 0	—	—	7 (12) 4 (7) 3 (5)	0 0 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	—	—

Numbers in parentheses denote percentage with respect to total.

—, statistical analysis not applicable.

Nello studio sono stati inclusi solo pazienti ad alto rischio con tripla positività per lupus anticoagulant, anticardiolipina e anticorpi anti-b2-glicoproteina I dello stesso isotipo.

Pengo V. et al. Blood 2018

DOAC e APS

47 studi → 447 pazienti con APS
29% con tripla positività
290 (65%) RIVA – 13 (3%) API – 144 (32%) DABI

73 pazienti (16%) ha manifestato una recidiva trombotica durante trattamento con DOAC dopo una durata media di 12,5 mesi.
Tasso di recidiva simile (16,9% anti-Xa e 15% dabigatran).

Tripla positività associata a un rischio quadruplicato di recidiva (56% vs 23%; OR = 4,3 [2,3–7,7]).

Nei pazienti trattati con anti-Xa, storia di trombosi arteriosa associata a recidiva (32% vs 14%; OR = 2,8 [1,4–5,7]).

Dufrost V et al. Autoimmunity Rev 2018

DOAC e APS

47 studi → 447 pazienti con APS
29% con tripla positività
290 (65%) RIVA – 13 (3%) API – 144 (32%) DABI

73 pazienti (16%) ha manifestato una recidiva trombotica durante trattamento con DOAC dopo una durata media di 12,5 mesi.

Tripla positività OR = 4,3 [2,3–7,7]
Storia di trombosi arteriosa OR = 2,8 [1,4–5,7]

Sub-group analisi dopo l'esclusione dei pazienti con tripla positività e con anamnesi di trombosi arteriosa.

290 pazienti con APS con precedente evento venoso isolato trattati con DOAC;
25 (8,6%) pazienti hanno avuto recidiva.
→ tasso di recidiva è inferiore nei pazienti con APS con manifestazioni venose isolate non ad alto rischio.

Dufrost V et al. Curr Rheumatology Reports 2020

Treatment

Primary thromboprophylaxis in aPL-positive subjects

1. 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 LDA (75–100 mg daily) is recommended (**2a/B**).

2. In patients with SLE and no history of thrombosis or pregnancy complications:
A. With high-risk aPL profile, prophylactic treatment with LDA is recommended (**2a/B**).
B. With low-risk aPL profile, prophylactic treatment with LDA may be considered (**2b/C**).

3. In non-pregnant women with a history of obstetric APS only (with or without SLE), prophylactic treatment with LDA after adequate risk/benefit evaluation is recommended (**2b/B**).

Tektonidou MG, et al. Ann Rheum Dis 2019

Treatment

Secondary thromboprophylaxis in APS - VTE

In patients with definite APS and first venous thrombosis:
A. Treatment with VKA with a target INR 2–3 is recommended (1b/B).
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)

C. In patients with unprovoked first venous thrombosis, anticoagulation should be continued long term (2b/B).

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

Tektonidou MG, et al. Ann Rheum Dis 2019

Treatment

Secondary thromboprophylaxis in APS – arterial thrombosis

In patients with definite APS and first arterial thrombosis:
A. Treatment with VKA is recommended over treatment with LDA only (2b/C).

B. Treatment with VKA with INR 2–3 or INR 3–4 is recommended, considering the individual's risk of bleeding and recurrent thrombosis (1b/B). Treatment with VKA with INR 2–3 plus LDA may also be considered (4/C).

Tektonidou MG, et al. Ann Rheum Dis 2019

Treatment

Secondary thromboprophylaxis in APS – recurrent thrombosis

In patients with definite APS and recurrent thrombosis despite adequate treatment with VKA:

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

Tektonidou MG, et al. Ann Rheum Dis 2019

When antithrombotic treatment is not enough?

- Hydroxychloroquine
- Rituximab
- Belimumab
- Statins
- Eculizumab
- Anti-TNF-alpha
- IV Immunoglobulin 400 mg/kg/daily for 5 days

Catastrophic antiphospholipid syndrome (CAPS) is a rare, life-threatening disease characterized by thrombosis in multiple organs with histopathologic evidence of multiple microthromboses, and laboratory confirmation of high aPL titers

< 1% develop catastrophic anti-phospholipid syndrome→ small vessel thrombosis in ≥ 3 organs in < 1 week in the presence of APLA, with histopathologic confirmation of small vessel thrombosis in the absence of inflammation. It is associated with high (50%) mortality.

Table 1 The preliminary criteria for classification of the catastrophic antiphospholipid syndrome

Criteria
Evidence of involvement of three or more organs, systems and/or tissues*
Development of manifestations simultaneously or in less than a week
Confirmation by histopathology of small vessel occlusion in at least one organ or tissue†
Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)‡
Definite catastrophic APS
All four criteria
Probable catastrophic APS
All four criteria, except for only two organs, systems and/or tissues involved
All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart because of the early death of a patient never tested for aPL before the catastrophic APS
1, 2 and 4
1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

Trattamento della sindrome catastrofica

50% fatale

- Eparina non frazionata in infusione continua
- Metilprednisolone bolo 1 g ev
- IgG EV
- Plasmaferesi
- Nel follow-up ciclofosfamide (se SLE), rituximab (anti CD20), eculizumab (anti-C5a)

Caso clinico 1: DRM donna 59 aa

Giunge alla mia attenzione ottobre 2024 per valutazione terapia anticoagulante

In anamnesi: un parto gemellare alla 38 SG cesareo, non aborti, ciclo mestruale regolare, menopausa dal 2014,in passato mai terapia estroprogestinica, nel 2018 intervento per prolasso vescicale, correzione alluce valgobilaterale, recente intervento chirurugco vascolare per stent sifone carotideo sin (Aprile 2024). Ex fumatrice (1pacchetto/die in gioventu poi 4-5/die, ha smesso nel 2012), ipercolesterolemia.

Caso clinico 1: DRM donna 59 aa

Giunge alla mia attenzione ottobre 2024 per valutazione terapia anticoagulante

APP:

1) 12/2023 riscontro occasionale di occlusione arteria succlavia sin (occlusione breve della succlaviaall'origine con furto asintomatico della vertebrale) in occasiona di impossibilità alla misurazione della pressione,evento occorso subito dopo infezione COVID 19 paucisintomatica.
2) Nel corso della TAC vasi extracranici edintracranici eseguita per la valutazione dell'occlusione della succlavia, riscontro di aneurisma di 8 mm al sifonedell'art carotide interna sin trattata con stent in aprile 2024. Iniziata terapia con statina e antiaggregante.

Caso clinico 1: DRM donna 59 aa

Giunge alla mia attenzione ottobre 2024 per valutazione terapia anticoagulante

APP:
3) Subito la dimissione (aprile 2024) TVP dx femorale superficiale, poplitea, asse gemellare trattata con Arixtra 5mg per 3 meai successivamente Apixaban 5 mg x 2 attualmente in corso. Un EcoDoppler venoso AAII del 22/07/24 ha mostrato completa ricanalizzazione della trombosi

In acuto riscontro di **anticorpi anticardiolipina IgG 96 U**, anti beta2GPI1 neg con LAC dubbio (in corso di arixtra), dopo 40 giorni conferma di anticorpi anticardiolipina IgG 130 con LAC non eseguito per terapia con arixtra, dopo 3 mesi riscontro di anticardiolipina IgG 74, LAC con interferenza analitica.

Caso clinico 1: DRM donna 59 aa

Giunge alla mia attenzione ottobre 2024 per valutazione terapia anticoagulante

Si tratta di trombosi arteriosa succlavia idiopatica (subito dopo COVID asintomatico) in nuotatrice non agonista con fattori di rischio cardiovascolare e trombosi venosa profonda secondaria con positività singola per anticorpi antifosfolipide anticardiolipina IgG a titolo moderato/alto.

Terapia in atto: cardioaspirin, Eliquis 5 mg x 2, ramipril 2,5 mg, rosuvastatina/ezetimibe.

Caso clinico 1: DRM donna 59 aa

1) Puntualizziamo la diagnosi (ultimo controllo era a luglio, antibeta2GP1 misurati solo 1 volta, LAC dubbio)

Nuovo controllo anticardiolipina, anti-beta2GP1e LAC, trombofilia, JAk2 auotimmunità

Consiglio si non assumere la cp di Eliquis della mattina, eseguire il prelievo in wash-out da terapia anticoagulante

→ LAC negativo, anticorpi anti-beta2GPI1 negativi, **anti-cardiolipina IgG 65 U**

Caso clinico 1: DRM donna 59 aa

Familiarità per TEV (madre con trombosi post partum a 38aa). Ipercolesterolemia (CT 240 con LDL 120) in trattamento con statine recentemente introdotte. Ipertensione arteriosa. Ex-fumatrice (ha smesso nel 2012 dopo aver fumato per circa 30 anni).
In Gennaio 2024, dopo recente infezione da COVID19, riscontro di occlusione all'origine dell'arteria succlavia sinistra per 1.5 cm circa (non riusciva più a misurare la pressione a sinistra), concomitante riscontro di aneurisma del sifone carotideo sinistro di 8 mm trattato per via neuroradiologica con stent in Aprile 2024. Successivo riscontro di anticardiolipina ad alto titolo. Lo screening trombofilico completo escludeva presenza di JAK2, LAC o antibeta2 o altre trombofilie ereditarie.

TP in atto: Cardioaspirin 100 mg, Eliquis 5 mg 1 cp x2/die, Rampril 2.5 mg, Rosuvastatina/Ezetimibe 10/10 mg.

ECOCOLORDOPPLER TRONCHI SOVRAAORTICI A RIPOSO:
A DESTRA:
Carotide comune nei limiti per calibro, decorso e regimi di flusso; ispessimento intimale diffuso.
Alla biforcazione carotidea presente piccola placca eccentrica a localizzazione posteriore, isoecogena, omogenea, a superficie regolare che si prolunga all¿origine dell¿arteria carotide interna ove realizza stenosi del 10% circa.
Arterie carotide esterna e succlavia nei limiti per calibro, decorso e regimi di flusso.
Arteria vertebrale nei limiti per calibro, presenta spettro doppler nei limiti con flusso normodiretto.
A SINISTRA:
Carotide comune nei limiti per calibro, decorso e regimi di flusso; ispessimento intimale diffuso.
Alla biforcazione carotidea presente placca eccentrica a localizzazione posteriore, isoecogena, omogenea, a superficie regolare che si prolunga all¿origine dell¿arteria carotide interna ove realizza stenosi del 15% circa.
Arterie carotide esterna nei limiti per calibro, decorso e regimi di flusso.
Arteria succlavia nei limiti per calibro e decorso, presenta segnale doppler monofasico come da nota occlusione prossimale dell'arteria succlavia a monte.
Arteria vertebrale nei limiti per calibro, presenta spettro doppler nei limiti con flusso invertito (furto di succlavia completo).

CONCLUSIONI: Vasculopatia carotidea bilaterale di grado lieve. Noto furto di succlavia sinistra da occlusione del vaso all'origine con buon compenso da parte dell'arteria vertebrale che risulta simmetrica rispetto alla controlaterale.
FOLLOW UP: Ecocolordoppler TSA di controllo tra circa 12 mesi.

Caso clinico 1: DRM donna 59 aa

2) Quale terapia?

- Occlusione carotidea in fattori di rischio cardiovascolare

Antiaggregante, statina, STOP fumo

- TEV secondario ricanalizzato in singola positività anticorpi antifosfolipide

Si mantiene DOAC a dosaggio terapeutico

→ follow-up tra un anno se non cambiamenti del profilo anticorpi STOP anticoagulante e si prosegue solo antiaggregante

Caso clinico 2: GE 53 aa maschio

Giunge alla mia attenzione novembre 2024per valutazione terapia anticoagulante

In anamnesi:
Donatore di sangue che nel 2022 per riscontro di Coombs positivo esegue anticorpi antifosfolipide con riscontro di
LAC positivo
anticorpi anti-cardiolopina IgG (152 U)
Anti-beta2GPI IgG (345 U)

Confermati dopo 3 mesi
NO eventi trombotici, no patologie correlate, stop donazione

Caso clinico 2: GE 53 aa maschio

Giunge alla mia attenzione novembre 2024per valutazione terapia anticoagulante

In anamnesi:
In agosto 2023 emorragia cerebellare in fistola AV durale sottoposto a intervento NCH, una settimana dopo embolia polmonare massiva in corso di ricovero, compariva anche ematoma otturatorio un mese dopo inizio di eparina.

Il paziente ha intrapreso coumadin fino a maggio 2024 quando è stato sospeso per ematoma gluteo post-traumatico.

Da allora in enoxaparina 4000 U/die tutt'ora in corso.

Terapia in atto: levotiroxina, triesinfendile, lamotrigina, tavor, inhixa 4000/die

Caso clinico 2: GE 53 aa maschio

Giunge alla mia attenzione novembre 2024per valutazione terapia anticoagulante

Si tratta di sdr da anticorpi antifosfolipide con triplice positività e un evento di EP massiva secondario ad intervento NCH.
Alto rischio emorragico (3 episodi: cerebellare spontanea, otturatoria in eparina, glutea in coumadin).

→ Discusso il rapporto rischio beneficio si concorda di iniziare anticoagulante orale diretto a basso dosaggio comeprevenzione di eventiali eventi trombotici maggiori e con il minimo rischio emorragico.Consiglio pertanto Eliquis 2,5 mg 1 cp x 2 e rilascio PT per 12 mesi.Rivedrò il sig. Gentili tra un anno con esito di anticorpi antifosfolipide recente.

Hyperhomocysteinemia

Hyperhomocysteinemia refers to the condition where there is greater than 15 micromol/L of homocysteine in the blood.

The estimated prevalence of mild hyperhomocysteinemia is 5 to 7% in the general population.

Elevated levels of homocysteine have been associated with increased cardiovascular, cerebrovascular, and thromboembolic diseases.

While there are clear associations between homocysteine and cerebrovascular disease, the evaluation and treatment remain controversial as studies have shown conflicting results in its effect in lowering risks for cardiovascular and cerebrovascular disease.

Hyperhomocysteinemia

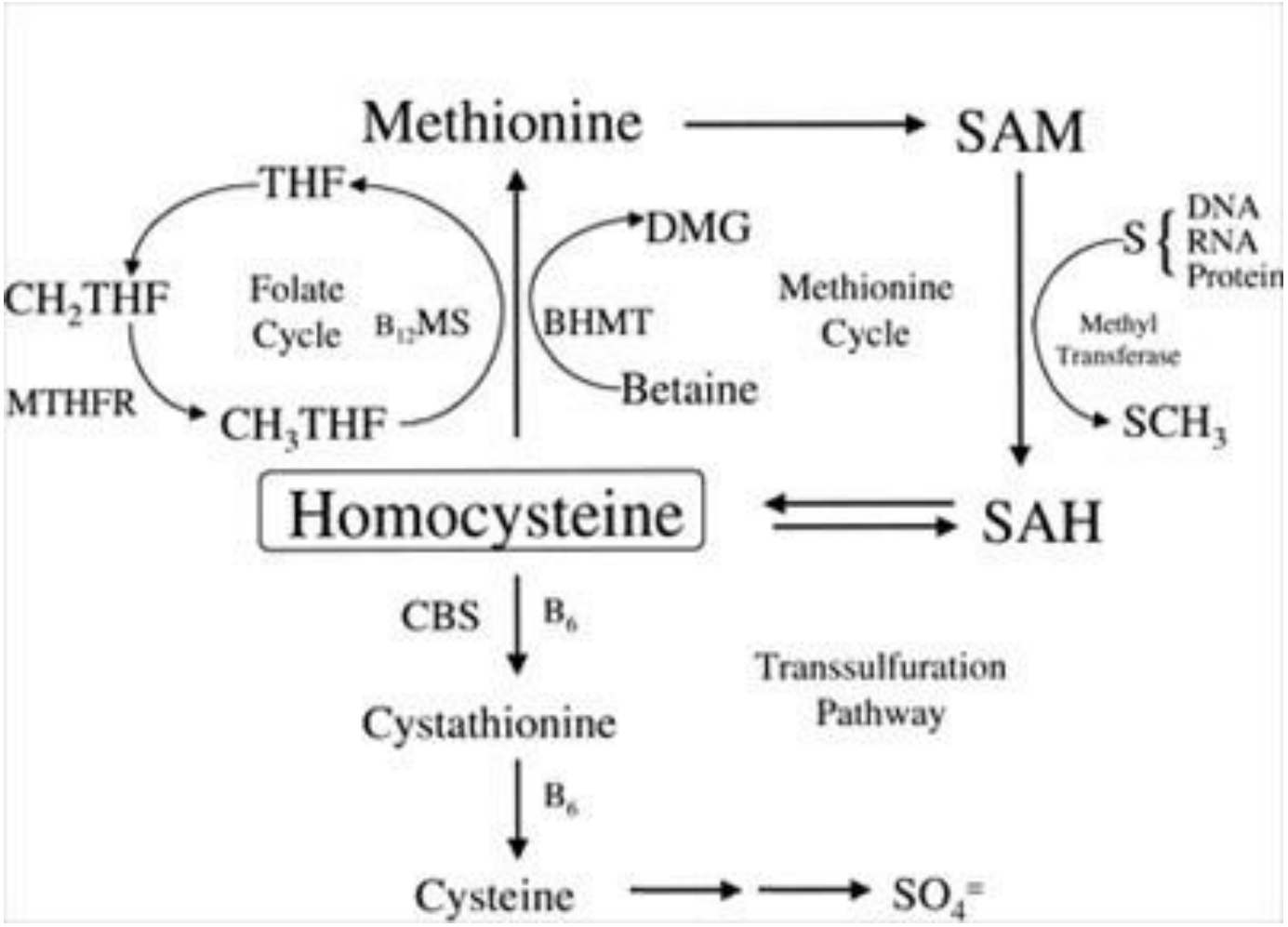
There has been clear evidence that lowering homocysteine levels decreases cardiovascular risks **in patients with homocystinuria, a rare autosomal recessive disorder, which can lead to atherosclerotic disease at a young age.**

Also, some studies have shown that lowering homocysteine levels can be beneficial in slowing the acceleration of brain atrophy.

On the other hand, a meta-analysis by the American Heart Association showed that homocysteine-lowering therapies did not significantly affect averting stroke and have a non-significant impact on coronary heart disease

Hyperhomocysteinemia

Hyperhomocysteinemia refers to the condition where there is greater than 15 micromol/L of homocysteine in the blood.



Iperomocisteinemia

Hyperhomocysteinemia is classified into three levels:

Moderate homocysteine levels of 15–30 umol/L
Intermediate 30-100 umol/L
severe > 100 umol/L

Hyperhomocysteinemia

Hyperhomocysteinemia

- Both genetic and acquired factors contribute to plasma homocysteine levels

mutations of
- N^5-methyltetrahydrofolate reductase

(thermolabile variant of MTHFR)
- cystathionine β-synthase genes

- deficiencies of folate/B12/B6
- hypothyroidism
- psoriasis
- chronic renal failure
- IBD
- rheumatoid arthritis
- organ transplantation
- antifolate drugs/B12 antagonists
- lifestyle factors

- Bigger role for environmental causes
- Mild thrombophilia

Iperomocisteinemia e ipercoagulabilità

- Ridotta vasodilatazione endoteliale
- Aumentato stress ossidativo
- Disfunzione endoteliale
- Iperaggregazione piastrinica

- Aumentata infiammazione → aumento livelli di FVIII e VWF
- Ipofibrinolisi

Elevated levels of homocysteine can increase the risk of atherosclerosis by causing endothelial layer injury, promoting inflammation, and increasing oxidative stress

Iperomocisteinemia e omocisteinuria

Sindromica (ectopia cristallina, glaucoma, distacco retinico, ritardo)

Rara

Difetto omozigote o doppio eterozigote di CBS o MTHFR

Può anche presentarsi in età adulta solo con TEV

Livelli omocisteina 100-400 micromol/L

Iperomocisteinemia e omocisteinuria

The initial evaluation of hyperhomocysteinemia includes a thorough history and physical exam to look for any signs and symptoms of homocystinuria, a rare but deadly disease.

It would present as an ectopic lens and developmental delay in children, whereas in adults, it would manifest as vascular disease. Other signs and symptoms include a family history of homocystinuria, osteoporosis, glaucoma, and retinal detachment, especially in children and young adults.

In these patients, homocysteine levels should be obtained.

Iperomocisteinemia moderata-lieve

Polimorfismo molto frequente del gene MTHFR (C677T) causa termolabilità dell'enzima in omozigosi.

Scoperto nel 1995

Polimorfismo presente dal 15 al 50% in molte popolazioni

Si associa ad un aumento di circa 20-30% dei livelli di omocisteina a digiuno quando presente in omozigosi ed in presenza di bassi livelli di folato plasmatico + interazione dei livelli di vitamin B12.

→ Aumento del rischio di trombosi arteriosa: IMA 16-30%, stroke 59%

Livelli di omocisteina ≥25 micromol/L

Thrombophilia and risk of thrombosis

Table 1. Increased thrombotic risk in hereditary and acquired thrombophilia

Thrombophilia	Relative risk for a first VTE (compared to community controls)
Hereditary thrombophilia	
Factor V Leiden	
Heterozygous	3-7x
Homozygous	80x
Prothrombin G20210A	
Heterozygous	2-3x
Homozygous	5x
Double heterozygosity (FVL and prothrombin G20210A)	6x
AT deficiency	5x
Protein C deficiency	4-6.5x
Protein S deficiency	1-3x
Pseudohomozygous FVL	80x
Factor IX Padua	10x
AT resistance	2-3x
Non-0 blood type	2x
Factor VIII ≥150 IU/dL	3-5x
Factor IX ≥129 IU/dL	2.3x
Factor XI ≥121 IU/dL	2x
Acquired thrombophilia	
Antiphospholipid antibody syndrome	3-10x
Hyperhomocysteinaemia	1.5-3x

Campello E. et al. Expert Rev Hematol 2019

Iperomocisteinemia moderata-lieve

In patients who do not have signs and symptoms of homocystinuria, the decision to measure homocysteine levels and pursue treatment remains controversial.

According to the American Heart Association (AHA), homocysteine levels do not predict cardiovascular disease development. Lowering homocysteine levels does not improve clinical outcomes, nor does it prevent future cardiovascular and thromboembolic diseases with treatment

On the other hand, some studies showed that lowering the homocysteine level was beneficial. One study was able to show that lowering hyperhomocysteinemia through folic acid supplementation would reduce carotid atherosclerosis progression. In addition, a randomized control study noted that patients who have mild cognitive impairment and received 0.8 mg of folic acid, 0.5 mg of vitamin B12, and 20 mg of B6 for 24 months were noted to have decreased brain atrophy and a slowing of cognitive decline.

Hyperhomocysteinemia and Risk of First Venous Thrombosis: The Influence of (Unmeasured) Confounding Factors

Monica Ospina-Romero, Suzanne C. Cannegieter, Martin den Heijer, Carine J. M. Doggen, Frits. R. Rosendaal, and Willem M. Lijfering*

* Correspondence to Dr. Willem M. Lijfering, Department of Clinical Epidemiology C7-P, Albinusdreef 2, 2333 ZA Leiden, P.O. Box 9600, 2300 RC Leiden, The Netherlands (e-mail: w.m.lijfering@lumc.nl).

Initially submitted May 16, 2017; accepted for publication January 4, 2018.

Table 5. Risk of Venous Thrombosis in Men and Women According to Categories of Homocysteine Concentration, Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis, the Netherlands, 1999–2004

Homocysteine Concentration, mg/L	All Patients		RDD Controls		Adjusted for Age and Sex		Adjusted for Age, Sex, and Other Factors[a]	
	No.	%	No.	%	OR	95% CI	OR	95% CI
				Men				
<1.60	370	44	241	49	1.00	Referent	1.00	Referent
1.60–1.79	143	17	89	18	1.01	0.74, 1.39	1.01	0.71, 1.44
1.80–2.09	123	14	57	12	1.36	0.96, 1.95	1.34	0.89, 2.03
2.10–2.29	58	7	28	6	1.25	0.77, 2.03	1.13	0.66, 1.93
≥2.30	156	18	76	15	1.26	0.92, 1.74	1.08	0.75, 1.57
				Women				
<1.60	518	62	227	62	1.00	Referent	1.00	Referent
1.60–1.79	107	13	65	14	0.89	0.63, 1.25	0.75	0.48, 1.15
1.80–2.09	64	8	37	9	0.88	0.58, 1.35	0.76	0.45, 1.29
2.10–2.29	45	5	26	6	0.95	0.57, 1.58	0.77	0.42, 1.43
≥2.30	105	12	41	9	1.41	0.95, 2.08	0.96	0.59, 1.54

Abbreviations: CI, confidence interval; OR, odds ratio; RDD, random-digit dialing.

[a] Additionally adjusted for body mass index, smoking, statin use, cardiovascular disease, sports activity, and (in women) hormone use.

Hyperhomocysteinemia

Hyperhomocysteinemia

- Both genetic and acquired factors contribute to plasma homocysteine levels

mutations of
- N^5-methyltetrahydrofolate reductase (thermolabile variant of MTHFR)
- cystathionine β-synthase genes

- deficiencies of folate/B12/B6
- hypothyroidism
- psoriasis
- chronic renal failure
- IBD
- rheumatoid arthritis
- organ transplantation
- antifolate drugs/B12 antagonists
- lifestyle factors

- Bigger role for environmental causes
- Mild thrombophilia

genetic determination of MTHFR or other enzyme systems in the absence of hyperhomocysteinemia is not associated with VTE → only test homocysteine levels!

Iperomocisteinemia e TEV

- *MTHFR* polymorphisms do not increase the risk of VTE or pregnancy complications independent of plasma homocysteine levels.

→ no clinical rationale for DNA testing for MTHFR polymorphisms.

- Screening homocysteinemia is also discouraged because lowering levels with vitamin supplementation does not reduce thrombotic risk.

Varga EA, Kujovich JL. Clin Genet 2012

Iperomocisteinemia e TEV

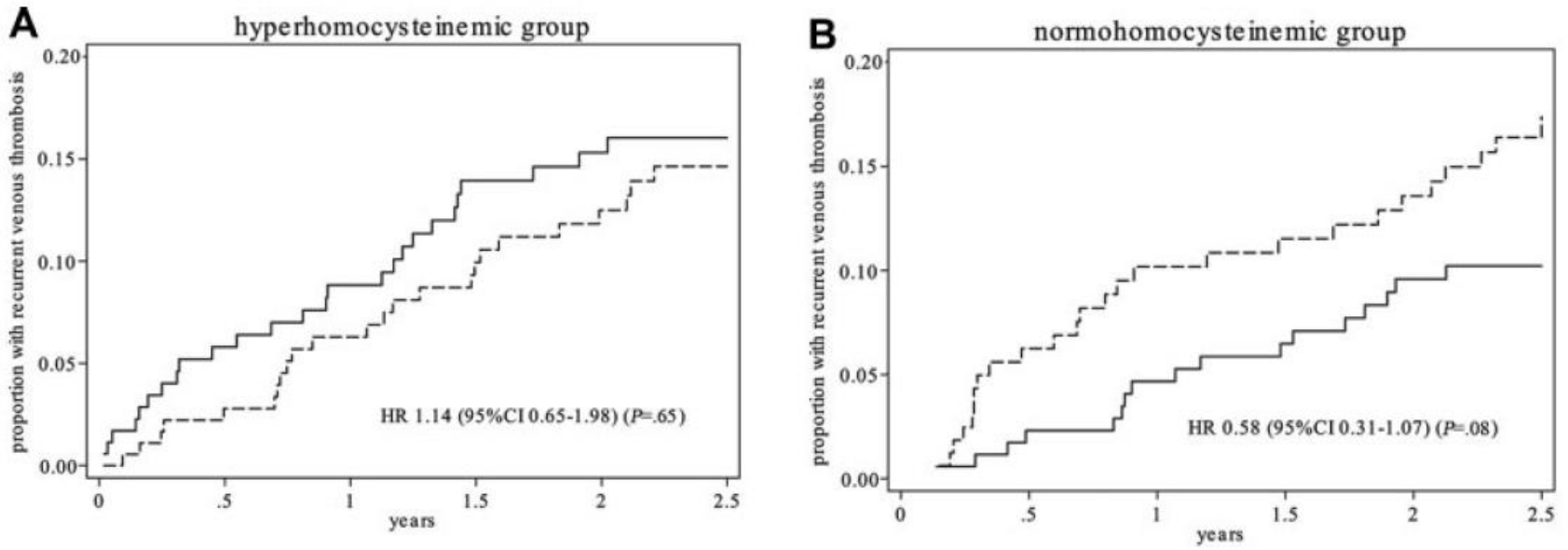


Figure 2. Recurrent thrombosis cumulative incidence. Recurrent thrombosis cumulative incidence in patients treated with multivitamin (solid line) or placebo (dashed line) in a hyperhomocysteinemic and a normohomocysteinemic group.

den Heijer M et al. Blood 2007

Iperomocisteinemia e ipercoagulabilità

- Risultati discordanti dalle metanalisi circa il ruolo di supplementazione vitaminica e prevenzione secondaria per ictus e TEV

- Nessuna associazione per SCA

→ Livelli >130 micromol/L sono suggestivi di omocisteinuria (prevalenza 0,2%) e si accompagnano a trombosi venosa e arteriosa in giovane età (25 aa), anche recidivante.

→ Livelli >50 micomol/L si associano a MTHFR termolabile nel 49% dei casi

Iperomocisteinemia e trattamento

Treatment / Management

Go to:

Several studies have tried to demonstrate the efficacy of vitamin supplementation to reduce cardiovascular and thromboembolic risk. The American Heart Association explained that folic acid supplementation (0.2 to 15 mg/d) could lower homocysteine levels. However, randomized control trials have been controversial in showing cardiovascular risk reduction with folic acid supplementation unless a patient has homocystinuria.[5][7]

In patients with homocystinuria with severe hyperhomocysteinemia, homocysteine-lowering treatments with pyridoxine, folic acid, and hydroxocobalamin did reduce cardiovascular risk.[8]

Iperomocisteinemia e trattamento

In patients who have hyperhomocysteinemia without homocystinuria, treatment remains controversial. Randomized control trials have not been able to show a reduction in cardiovascular risk for those who lower homocysteine levels using homocysteine-lowering therapies.[7][6][23] However, studies have also shown that it can potentially reduce carotid atherosclerosis progression, have mild primary stroke prevention benefits, and delay brain atrophy in patients with mild cognitive impairment in patients who have been treated with homocysteine-lowering medications.[4][9] Therefore, the clinician must have a detailed discussion of the risks and benefits of obtaining and treating an elevated homocysteine level. Compared to the risks, placing a patient on a vitamin B supplement readily over-the-counter seems to have more benefits.

Iperomocisteinemia e ipercoagulabilità – what to do

- Misurare livelli di omocisteina in tutti i pazienti con evento trombotico venoso o arterioso giovanile idiopatico (20-40 aa)
- Valutare habitus sindromico
- Misurare livelli di acido folico e vitamin B12 per delineare il profilo vitaminico → correggere ipovitaminosi con polivitaminici
- Genetica per omocisteinuria se livelli > 100
- Ruolo supplementazione vitaminica non chiaro quando il profilo vitaminico è normale

Iperomocisteinemia e ipercoagulabilità – what to do

The first step would be to discuss the patient's intake of foods with folic acid, vitamin B6, and B12 to see if the patient is meeting the recommended dietary amount for these vitamins.

If they are not meeting these requirements, recommendations can be made to increase foods rich in these vitamins, such as fruits and vegetables, as a portion of the general population does not meet the Recommended Dietary Allowance (RDA) for these nutrients.

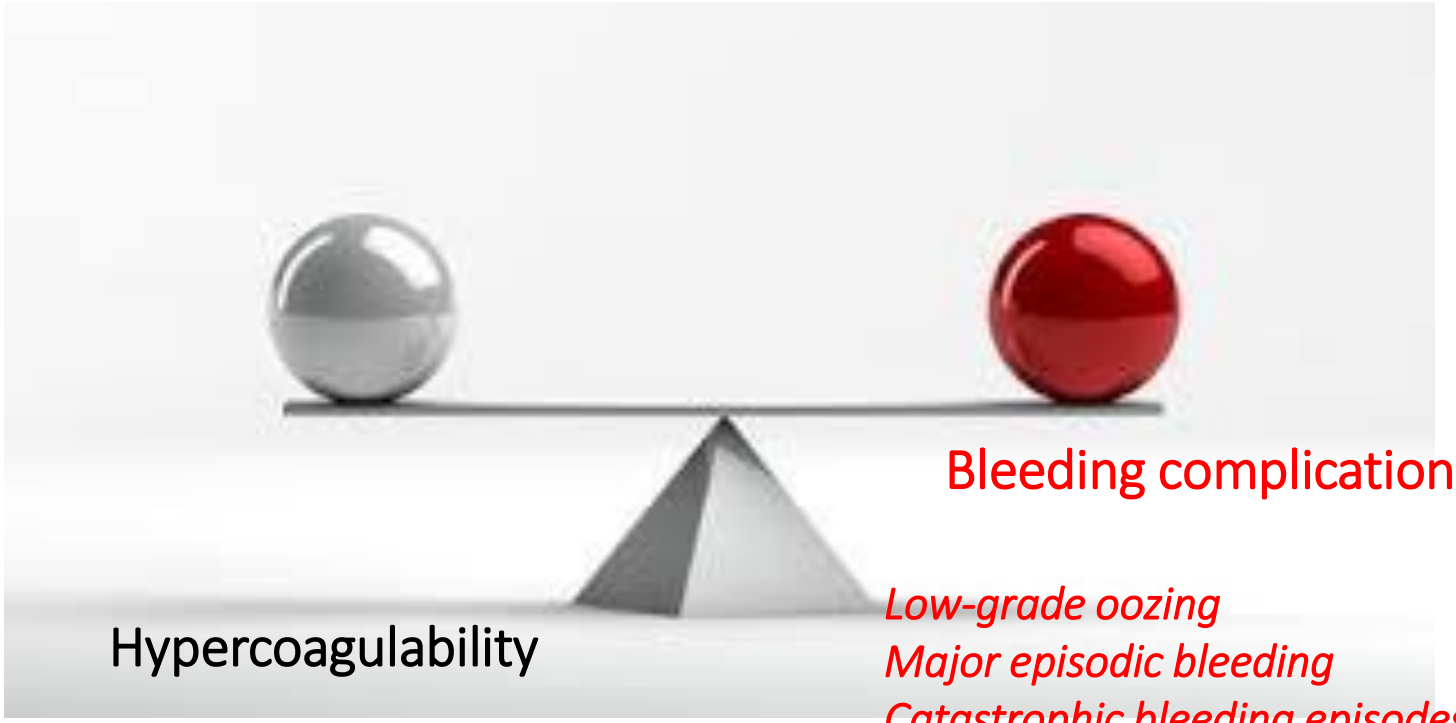
For patients with signs and symptoms of homocystinuria or mild cognitive impairment, the benefits of vitamin B supplementation outweigh the risks; therefore, supplementation is recommended.

There is not enough evidence to support the use of homocysteine-lowering treatments across the board for all other patients

Hyperhomocysteinemia

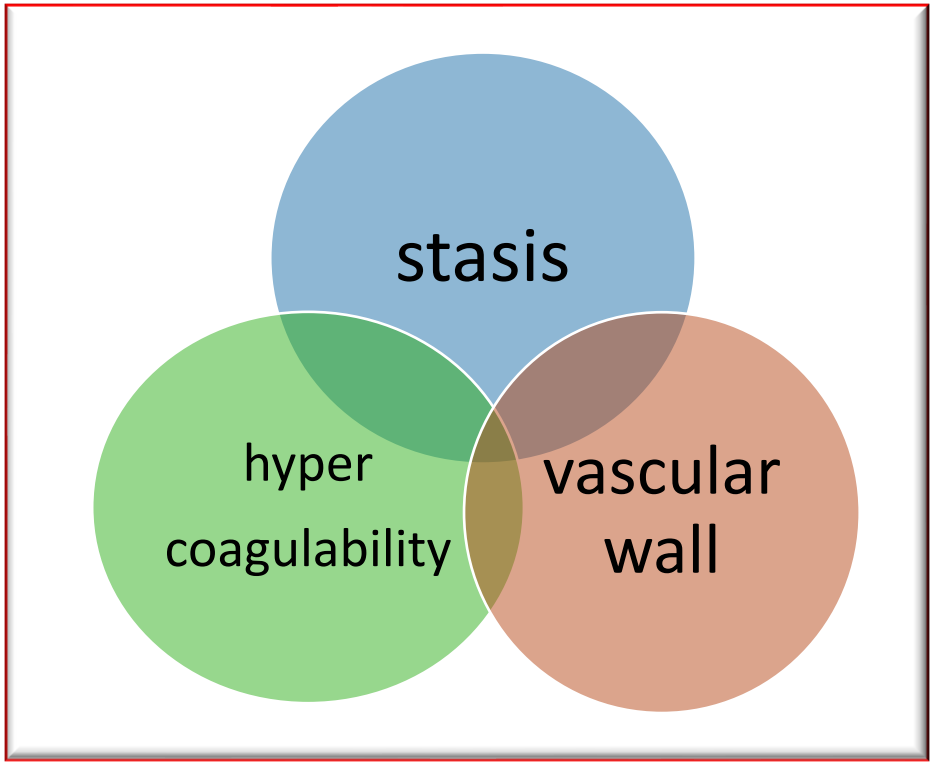
Phillip Son; Lindsay Lewis.

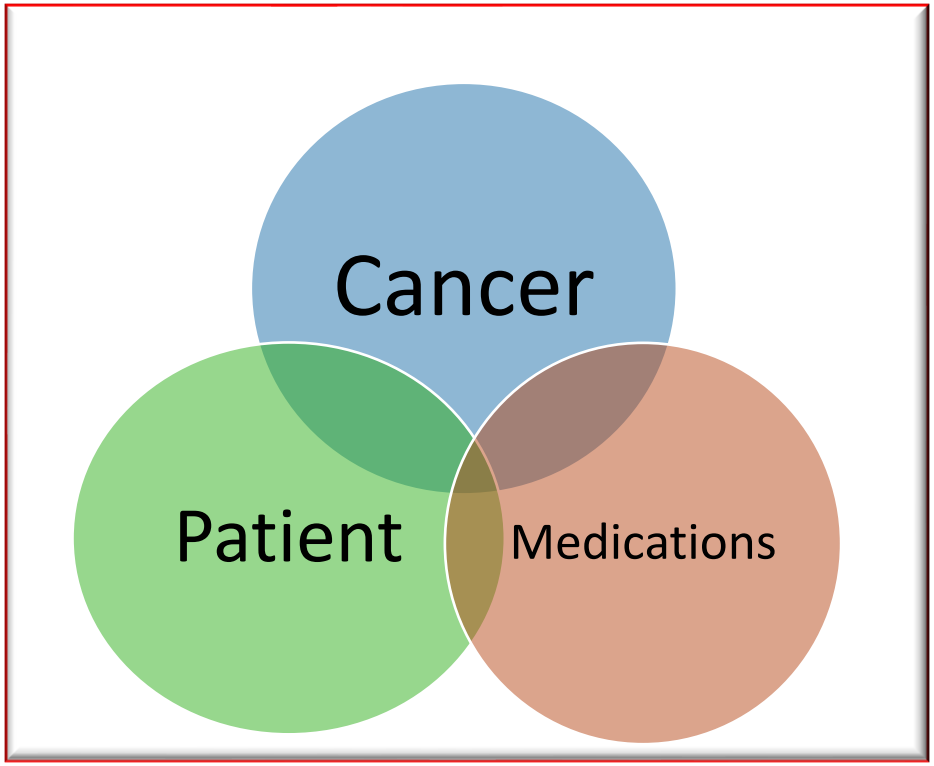
Hemostatic balance in cancer



Venous thromboembolism
Arterial thrombosis
Thrombotic microangiopatic disease
Disseminated intravascular coagulation

Hemostatic balance in cancer





Epidemiology of cancer-associated thrombosis

Among all cancer patients, 10–15% develop symptomatic VTE during their disease → incidence at autopsy ~ 50%.

Cancer accounts for ~20% of VTE and confers a 4- to 6.5-fold higher VTE risk.

Patients with idiopathic VTE have 3- to 4-fold increased likelihood of being
diagnosed with a malignancy within a year.

Patients with cancer and VTE have worse survival co
controls without VTE matched for age, gender, cance
of diagnosis (1-year survival rate 12% vs 36%).

Armand Trousseau, 1801–1867

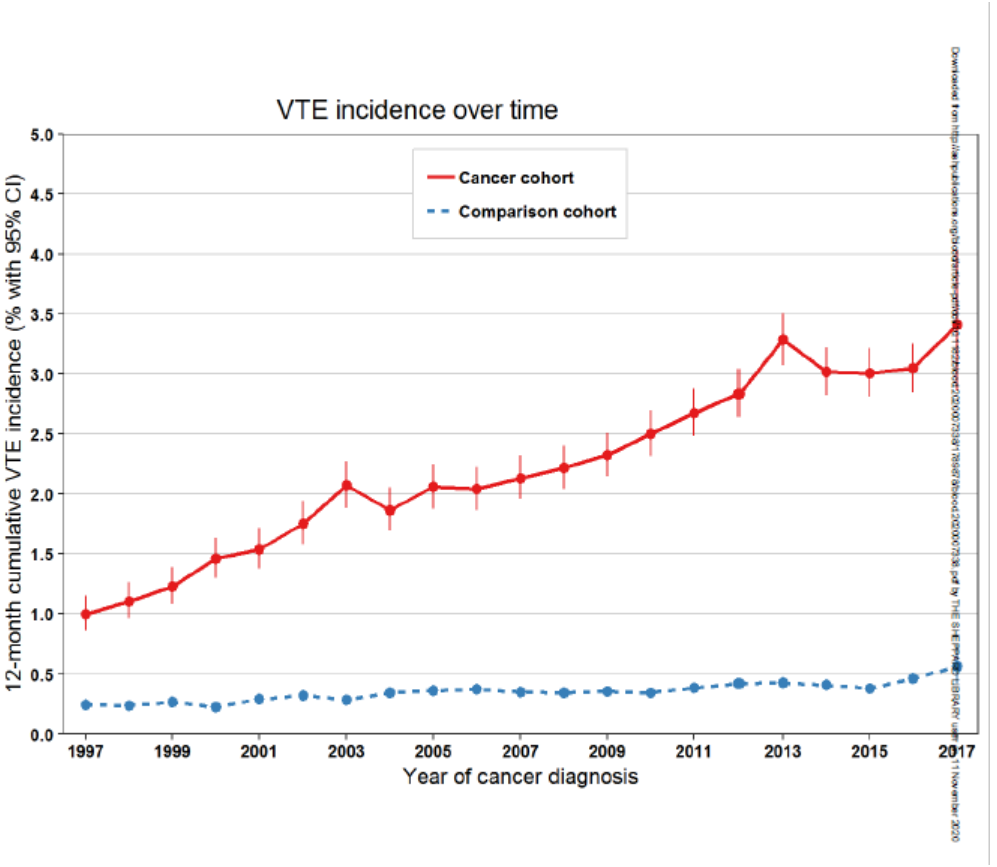
Ashrani AA et al Coagulation in cancer 2009
Levi M. Thromb Res 2014

Epidemiologia della trombosi associata a cancro

Incidenza cumulativa di TEV nei 6 mesi successivi la diagnosi di cancro 1.69% (95% CI, 1.66%-1.73%) → HR 11.1 (95% CI, 10.5-11.6)

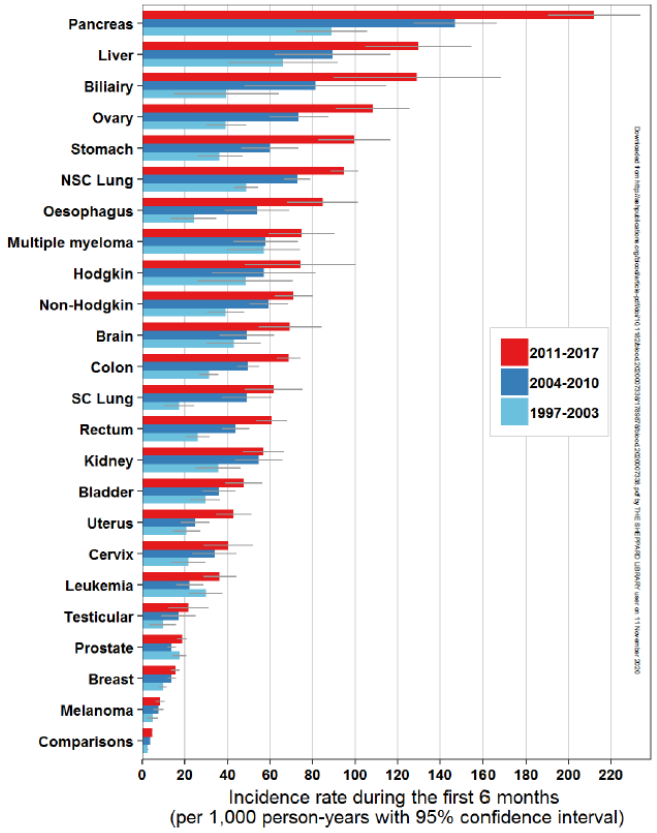
Incidenza cumulativa di TEV nei 12 mesi successivi la diagnosi di cancro 2.3% (95% CI, 2.2%-2.3%) → HR 8.5 (95% CI, 8.2-8.8)

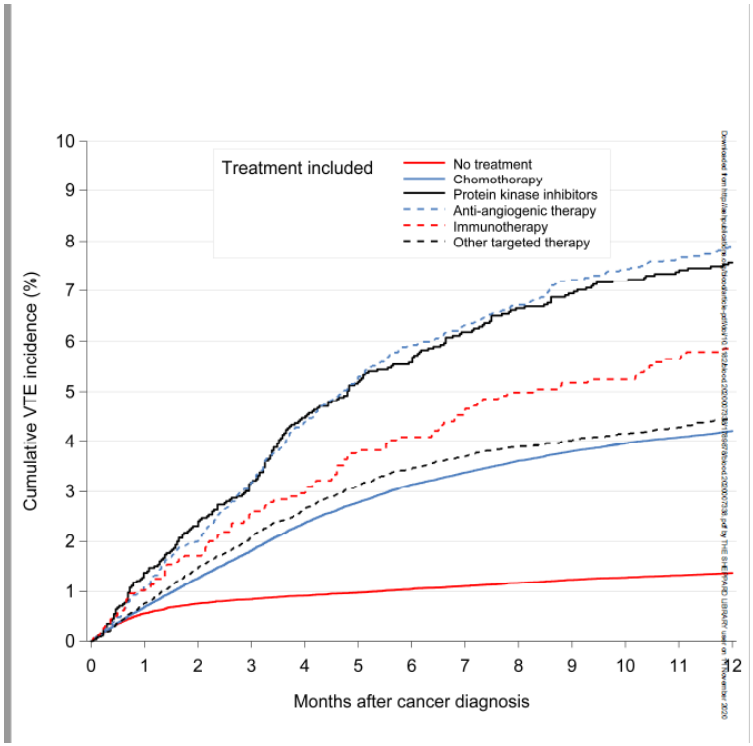
L'incidenza a 12 mesi è aumentata da 1.0% (95% CI, 0.9%-1.2%) nel 1997 a 3.4% (95% CI, 2.9%-4.0%) nel 2017



Mulder F. et al. Blood 2021

Epidemiologia della trombosi associata a cancro





Fattori di rischio per TEV:

- ✓ Pregresso TEV
- ✓ Metastasi
- ✓ Chirurgia
- ✓ CT
- ✓ Inibitori delle protein-chinasi
- ✓ Fattori anti-angiogenetici
- ✓ Immunoterapia

Mulder F. et al. Blood 2021

What's new?

Data from the RIETE registry spanning 2001 to 2020 to investigate temporal trends in clinical characteristics and treatments for cancer-associated thrombosis

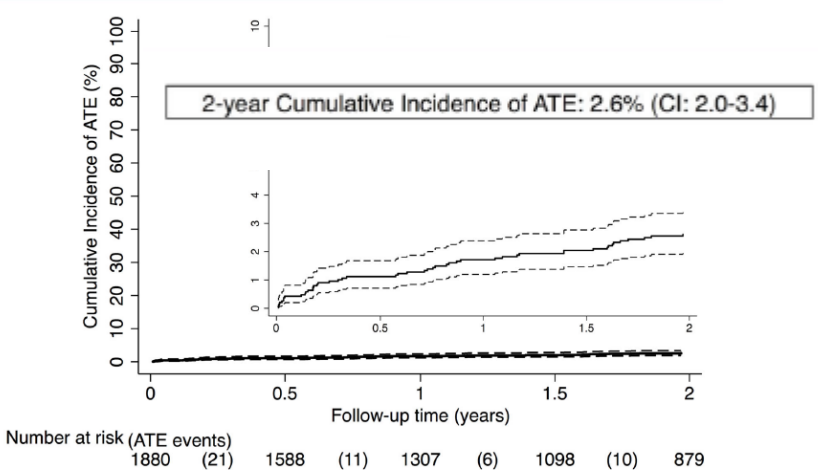
17,271 patients with cancer-associated thrombosis

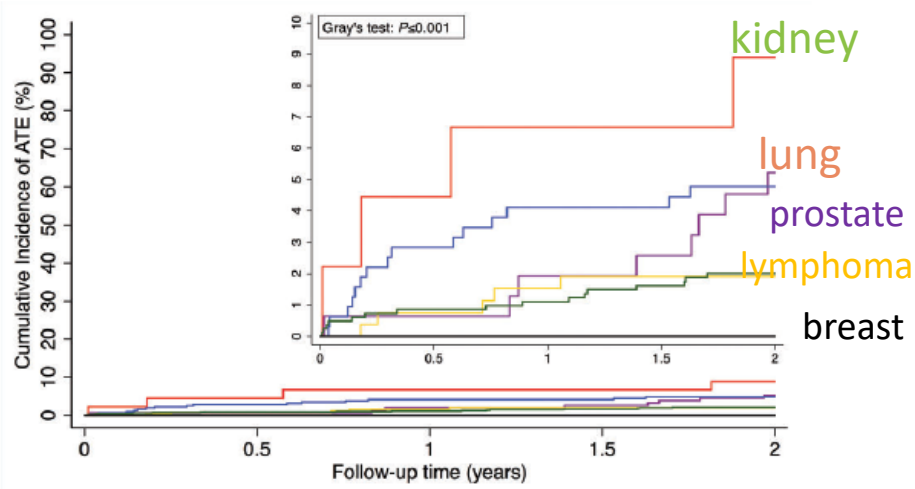
TABLE 2 Cancer Characteristics

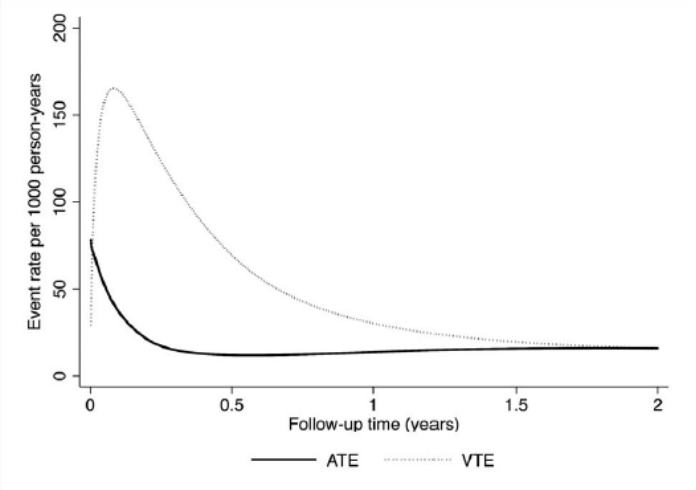
	2001-2005 (n = 3,068)	2006-2010 (n = 4,266)	2011-2015 (n = 4,864)	2016-2020 (n = 5,073)	*P* Value for Trend
Time from cancer diagnosis, mo	4 (0-18)	4 (0-19)	4 (0-19)	4 (0-24)	<0.01
Metastases					
Yes	1,529 (49.8)	2,302 (54.0)	2,664 (54.8)	2,855 (56.3)	<0.01
Sites of cancer					
Lung	390 (12.7)	679 (15.9)	835 (17.2)	916 (18.1)	<0.01
Colorectal	417 (13.6)	635 (14.9)	693 (14.2)	633 (12.5)	0.01
Breast	366 (11.9)	499 (11.7)	623 (12.8)	755 (14.9)	<0.01
Prostate	358 (11.7)	402 (9.4)	372 (7.6)	336 (6.6)	<0.01
Hematologic	206 (6.7)	327 (7.7)	410 (8.4)	353 (7.0)	0.53
Bladder	207 (6.7)	235 (5.5)	221 (4.5)	238 (4.7)	<0.01
Brain	172 (5.6)	194 (4.5)	164 (3.4)	170 (3.4)	0.59
Stomach	136 (4.4)	185 (4.3)	184 (3.8)	179 (3.5)	0.02
Uterine	128 (4.2)	174 (4.1)	178 (3.7)	218 (4.3)	0.99
Pancreas	118 (3.8)	193 (4.5)	273 (5.6)	285 (5.6)	<0.01
Ovary	101 (3.3)	142 (3.3)	167 (3.4)	224 (4.4)	<0.01
Kidney	71 (2.3)	94 (2.2)	100 (2.1)	133 (2.6)	0.32
Unknown origin	107 (3.5)	110 (2.6)	81 (1.7)	37 (0.7)	<0.01
Oropharynx	43 (1.4)	81 (1.9)	76 (1.6)	89 (1.8)	0.59
Biliary tract	42 (1.4)	44 (1.0)	86 (1.8)	48 (0.9)	0.53
Melanoma	13 (0.4)	42 (1.0)	44 (0.9)	58 (1.1)	0.95
Liver	19 (0.6)	29 (0.7)	46 (0.9)	42 (0.8)	0.20
Esophagus	28 (0.9)	46 (1.1)	58 (1.2)	47 (0.9)	0.66
Other sites	146 (4.8)	155 (3.6)	253 (5.2)	312 (6.2)	<0.01
Therapy for cancer					
Chemotherapy	1,552 (51.3)	2,164 (52.2)	2,324 (52.2)	2,370 (52.1)	0.79
Radiotherapy	309 (10.2)	496 (12.0)	709 (16.7)	693 (16.1)	<0.01
Chemo- and radiotherapy	189 (6.3)	311 (7.5)	471 (11.2)	421 (9.9)	<0.01
Hormonal therapy	315 (34.2)	334 (23.4)	569 (14.0)	588 (13.9)	<0.01
Immunotherapy	0	2 (2.8)	13 (2.7)	243 (7.4)	<0.01
None of the above	1,212 (39.5)	1,713 (40.2)	1,916 (39.4)	1,935 (38.1)	0.22

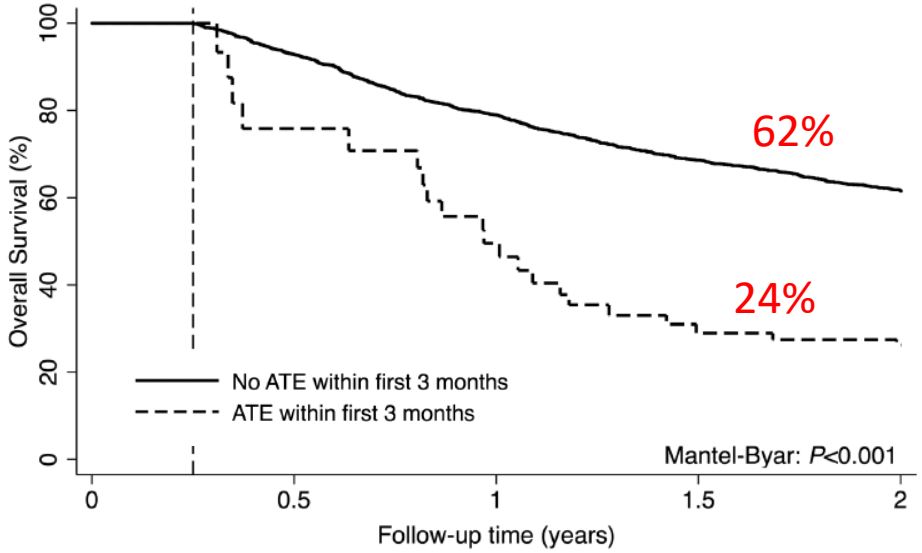
Bertoletti L. et al, JACC Cardioncology 2023

Epidemiology of cancer-associated thrombosis









Grilz E et al Haematologica 2018

Risk factors of cancer-associated thrombosis

Patient-related

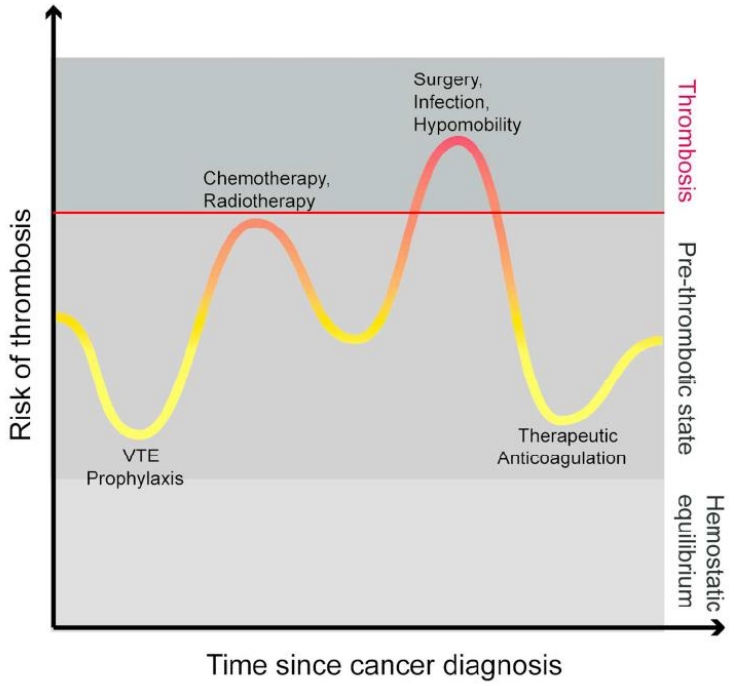
- Medical comorbidities
- Previous VTE
- Varicose veins
- Hereditary risk factors (i.e. FV Leiden)

Tumor-related

- Site of cancer
- Stage of cancer
- Histological grade
- Time since cancer diagnosis

Treatment-related

- Surgery
- Platinum-based and other chemotherapy
- Hormonal therapy
- Anti-angiogenesis agents
- Erythropoiesis stimulating agents
- Central venous catheters
- Blood transfusions
- Hospitalization - Immobility



Adapted from Ay C et al Thromb Haemost 2017

Cancer-associated **DIC**

Overall incidence in consecutive patients with cancer 7-20%

Bleeding presenting symptom in 64% and thrombosis in 7% of patients

Mucin-producing adenocarcinoma → chronic DIC → thrombotic manifestations
Acute leukemia → acute DIC → hemorrhagic presentations
Solid tumor → chronic DIC → nonbacterial thrombotic endocarditis

Surgery and chemotherapy are important risk factors

Cancers commonly associated with DIC

Clinical parameter	Cancer type
Acute DIC (localized or systemic bleeding, echymosis)	Acute promyelocytic leukemia (APL)
	Acute non-M3 myeloid leukemia (AML)
	Acute lymphocytic leukemia (ALL)
	Prostate cancer[a]
	Mucin-producing adenocarcinomas (e.g., pancreatic[a], gastrointestinal, ovary, thyroid, gallbladder)
	Lymphoma (e.g., Stage IV, natural killer)
	Chronic myelocytic leukemia (CML)
Chronic DIC (Thrombosis)	Solid tumors (e.g., lung, breast, prostate[a], pancreatic cancer[a])

[a] Can be associated with either chronic or acute DIC

Saba HI et al Coagulation in cancer 2009

Epidemiology of bleeding in cancer

~ 10% of all cancer patients have at least one bleeding episode and ~30% of patients with hematologic malignancies

Localized bleeding or generalized hemorrhagic diathesis

Catastrophic bleeding episodes may occur

- epistaxis
- gum bleeding
- prolonged oozing from wounds
- large ecchymoses and hematoma with minimal trauma
- mucosal bleeding (hematuria, vaginal or gastrointestinal bleeding, hemoptysis)

Johnstone C et al Ann Palliat Med 2018
Green D et al Sem Thromb Hemost 2007

Pathophysiology of bleeding in cancer

Tumor-related

Local

- Tumor invasion
- Abnormal tumor vasculature
- Tumor regression

Systemic

- Thrombocytopenia
- Platelet dysfunction
- Coagulation factor abnormalities
- Dysproteinemias

Treatment-related

- Thrombocytopenia
- Platelet dysfunction
- Radiation therapy
- Immunotherapy
- Coagulation factor abnormalities
- Oral anticoagulants
- Aspirin, nonsteroidal anti-inflammatory agents

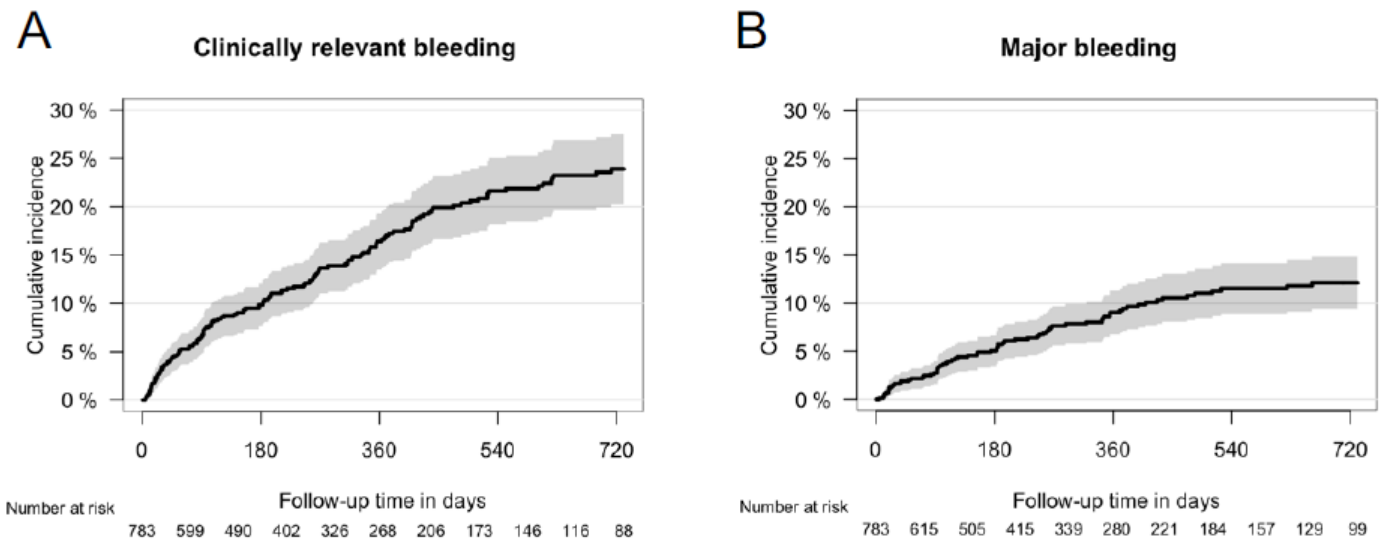
Coagulation abnormalities:

- Platelet dysfunction
- Disseminated intravascular coagulation
- Liver disease
- Vitamin K deficiency
- Acquired anticoagulants
- Enhanced fibrinolytic activity

Johnstone C et al Ann Palliat Med 2018
Green D et al Sem Thromb Hemost 2007

What's new? – Bleeding risk

Prospective cohort study, Vienna Cancer, Thrombosis and Bleeding Study (CAT-BLED)
791 patients (48% female, median age 63 [54-70] years) with various cancer types, 65.5% stage IV

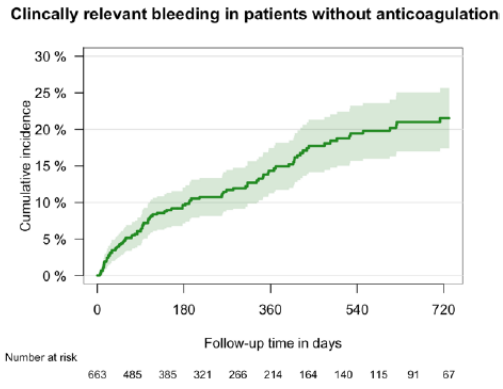


12-month cumulative incidence of first CRB and MB was **16.6%** (95%CI: 13.7-19.6) and **9.1%** (95% CI: 6.8-11.3)

Englisch C et al. Blood 2024

What's new? – Bleeding risk

C



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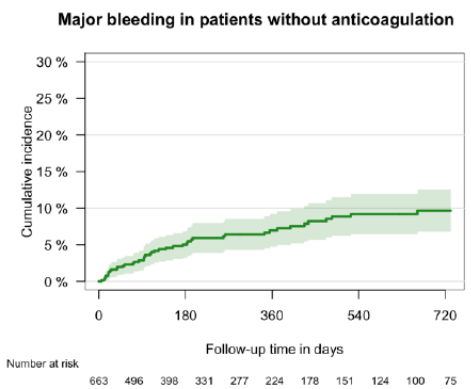
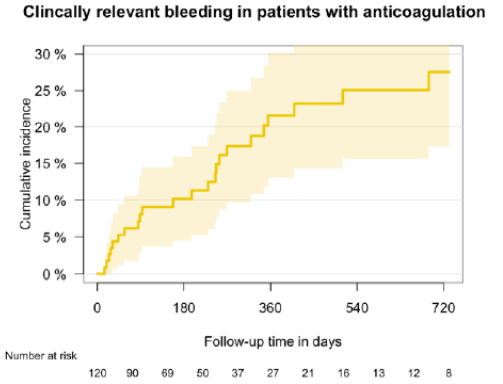


14.4% (95%CI: 11.2-17.5) and **7.0**% (95% CI: 4.7-9.2)

E



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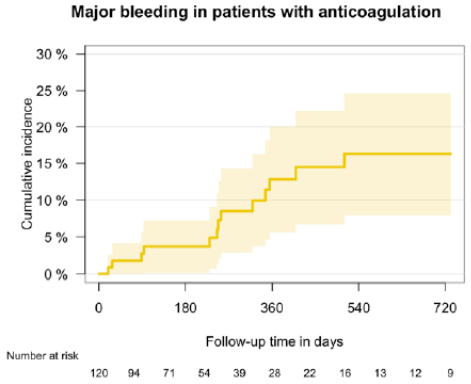


Table 3. Risk factors for clinically relevant bleeding (CRB) and major bleeding (MB) at study inclusion in patients without anticoagulation. SHR – subdistribution hazard ratio, BMI – body mass index

	CRB		MB	
	SHR	95% CI	SHR	95% CI
Age (continuous per increase of 1, years)	0.99	0.98-1.01	1.01	0.99-1.03
BMI (continuous per increase of 1, kg/m2)	0.97	0.95-1.01	0.98	0.94-1.02
Hemoglobin (continuous per increase of 1, mg/dL)	0.88	0.79-0.98	0.79	0.67-0.92
Platelets (continuous per increase of 10, G/L)	1.02	1.00-1.03	1.01	0.98-1.04
Leucocytes (continuous per increase of 1, G/L)	1.03	0.98-1.07	0.99	0.91-1.07
Creatinine (continuous per increase of 1, mg/dL)	1.09	0.92-1.30	1.09	0.82-1.46
Albumin (continuous per increase of 1, g/L)	0.95	0.92-0.99	0.91	0.87-0.95
Aspartate transaminase (U/L, per 10 increase)	1.02	1.00-1.04	1.03	1.00-1.05
Alanine transaminase (U/L, per 10 increase)	1.02	0.99-1.05	1.03	1.00-1.06
Alkaline phosphatase (U/L, per 10 increase)	1.01	0.99-1.02	1.02	1.00-1.03
Stage IV (versus I, II, III)	0.53	0.35-0.79	0.72	0.38-1.37
Head & Neck versus other cancer type	2.38	1.46-3.88	3.16	1.65-6.03
Gastrointestinal versus other cancer types	1.06	0.68-1.66	1.02	0.50-2.07
Luminal gastrointestinal versus other cancer type	1.13	0.66-1.94	0.76	0.30-1.93
Pancreas versus other cancer types	0.76	0.33-1.72	1.48	0.58-3.78
Lung versus other cancer types	0.98	0.62-1.55	0.55	0.24-1.21
Presence of recurrent/progressive cancer	1.05	0.71-1.57	1.63	0.89-2.97
1st line versus other treatment line	0.96	0.65-1.43	0.60	0.33-1.11
Palliative therapy versus curative therapy	1.19	0.55-2.56	1.32	0.41-4.26
History of any bleeding	1.49	0.89-2.49	1.09	0.49-2.46

Englisch C et al. Blood 2024

What's new – Bleeding risk

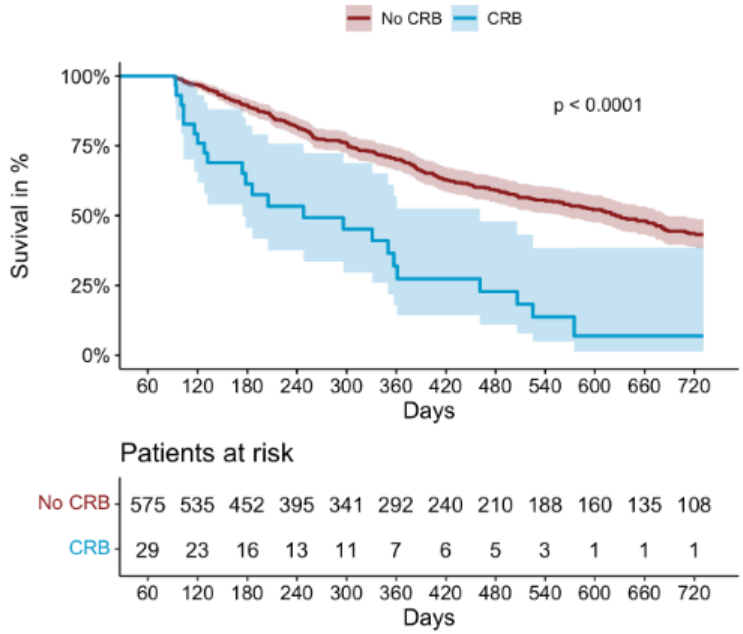
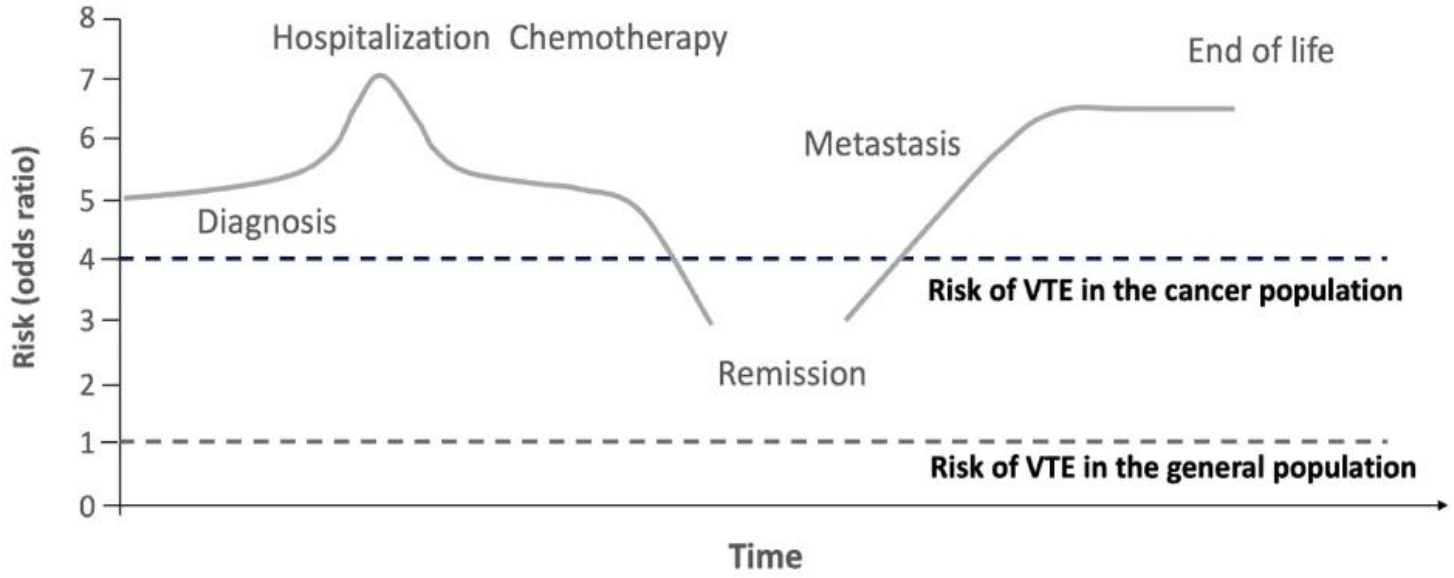


Figure 4. Landmark analysis of overall survival according to the occurrence of clinically relevant bleeding (CRB). Overall survival curves are displayed stratified by the occurrence of CRB within 3 months after study inclusion.

Patients with CRB were at an increased risk of all-cause mortality (multivariable transition **HR [95%CI]: 5.80 [4.53-7.43]**)

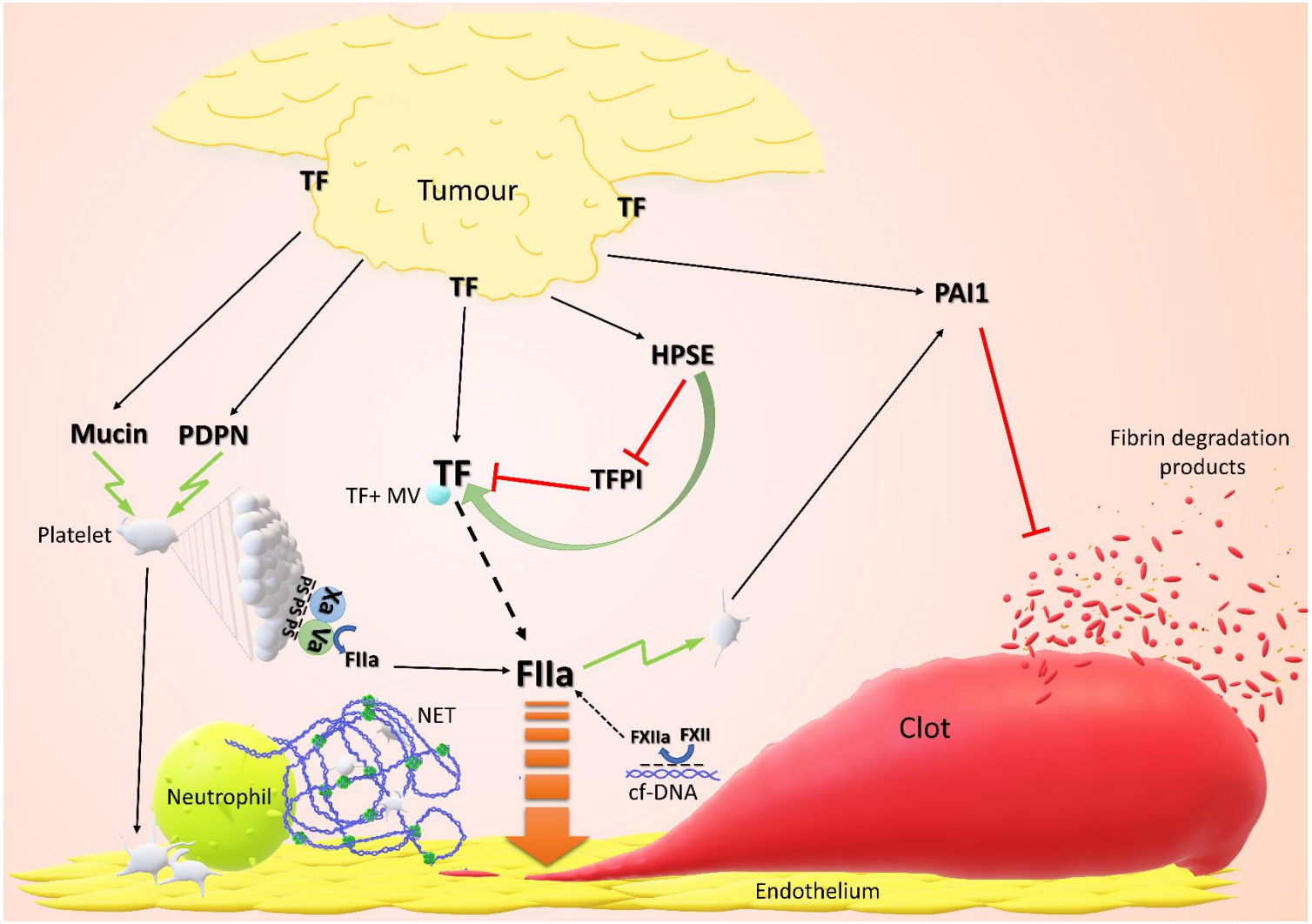
Englisch C et al. Blood 2024

VTE risk varies over the natural history of cancer



Adapted from Lyman GH, *Cancer* 2010;7:1334–1349

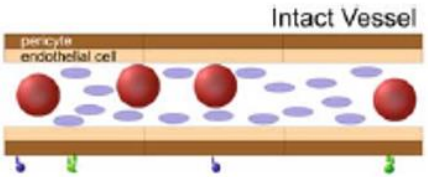
Hypercoagulability in Cancer

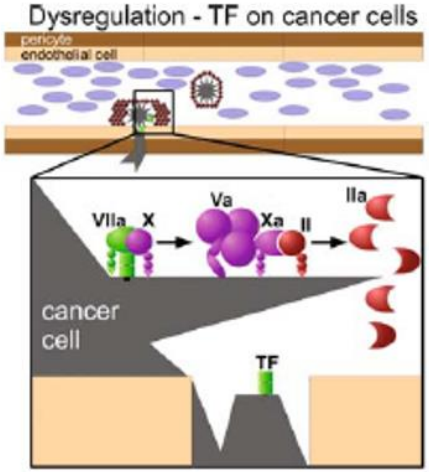


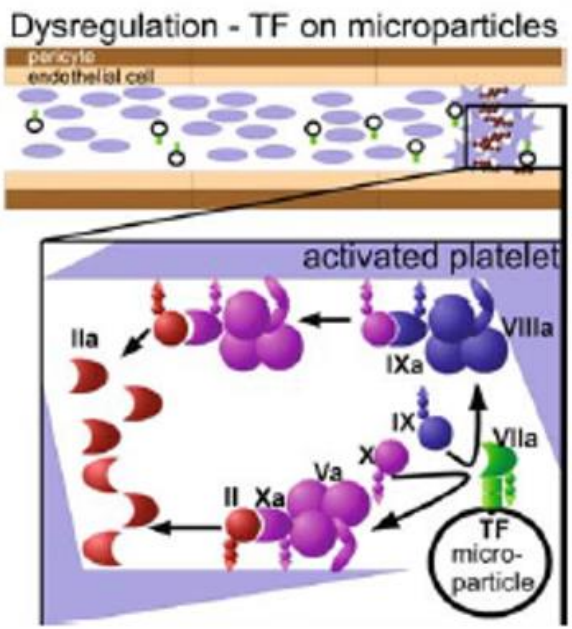
Campello E. et al. BJC 2019

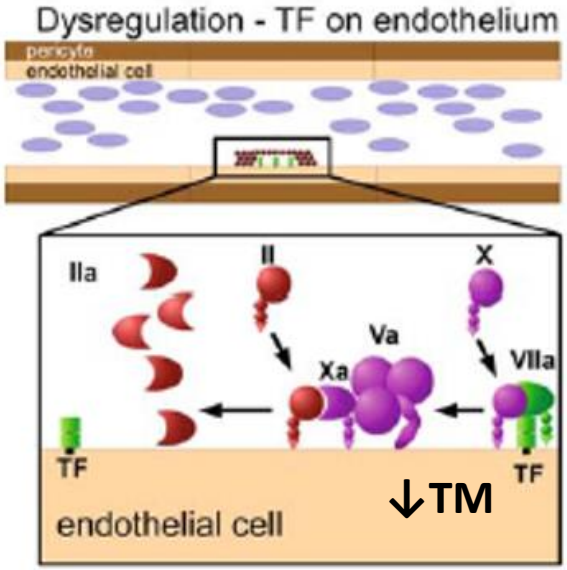
Hypercoagulability in Cancer-1

- Tissue factor expression on tumor cells
- Tissue factor on endothelium
- Tissue factor – positive microvesicles





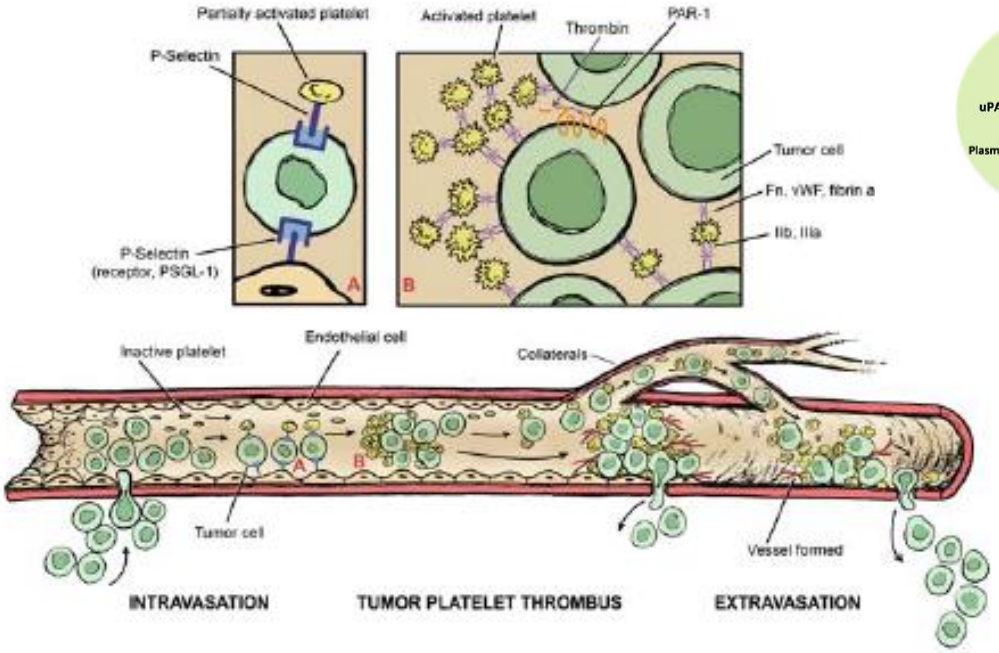


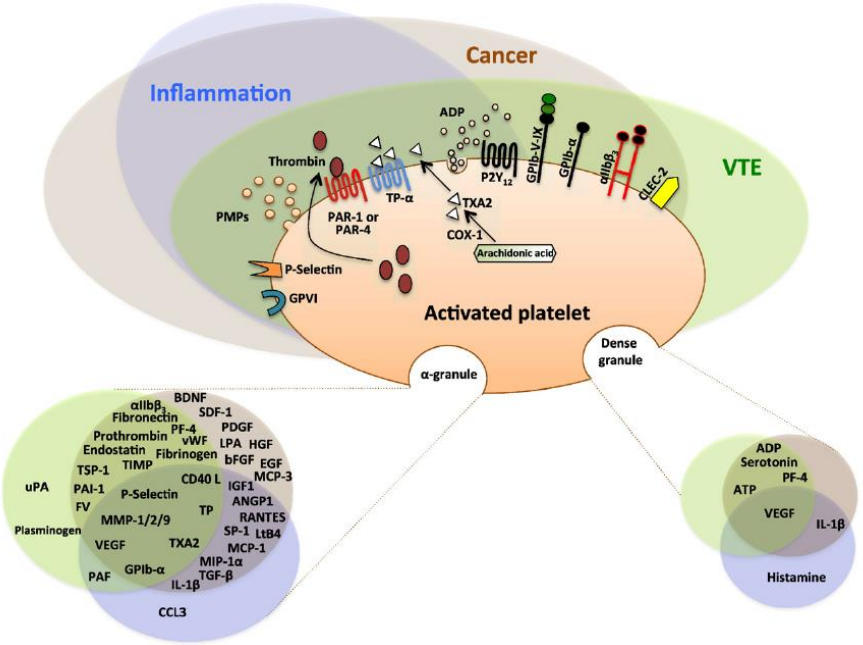


Monroe DM, Hoffman M Coagulation in cancer 2009

Hypercoagulability in Cancer-2

- Thrombocytosis
- Platelet activation and aggregation
- Platelet adhesion

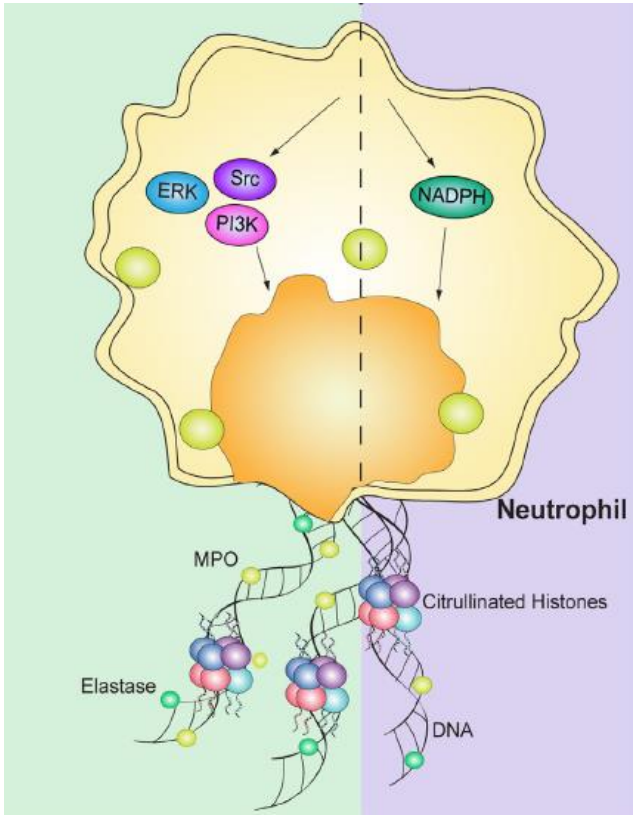


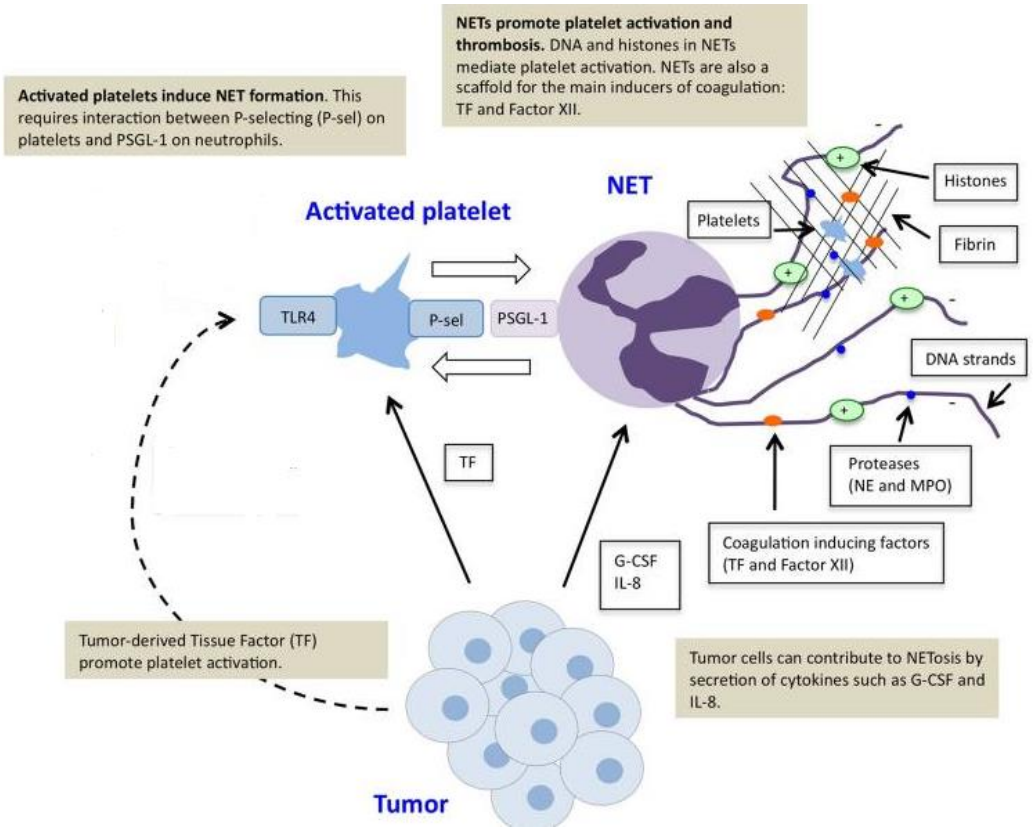


Monroe DM, Hoffman M Coagulation in cancer 2009
Mezouar S et al. Thromb Res 2016

Hypercoagulability in Cancer-3

- Cytokines release
- Activation of inflammatory cells
- NETosis

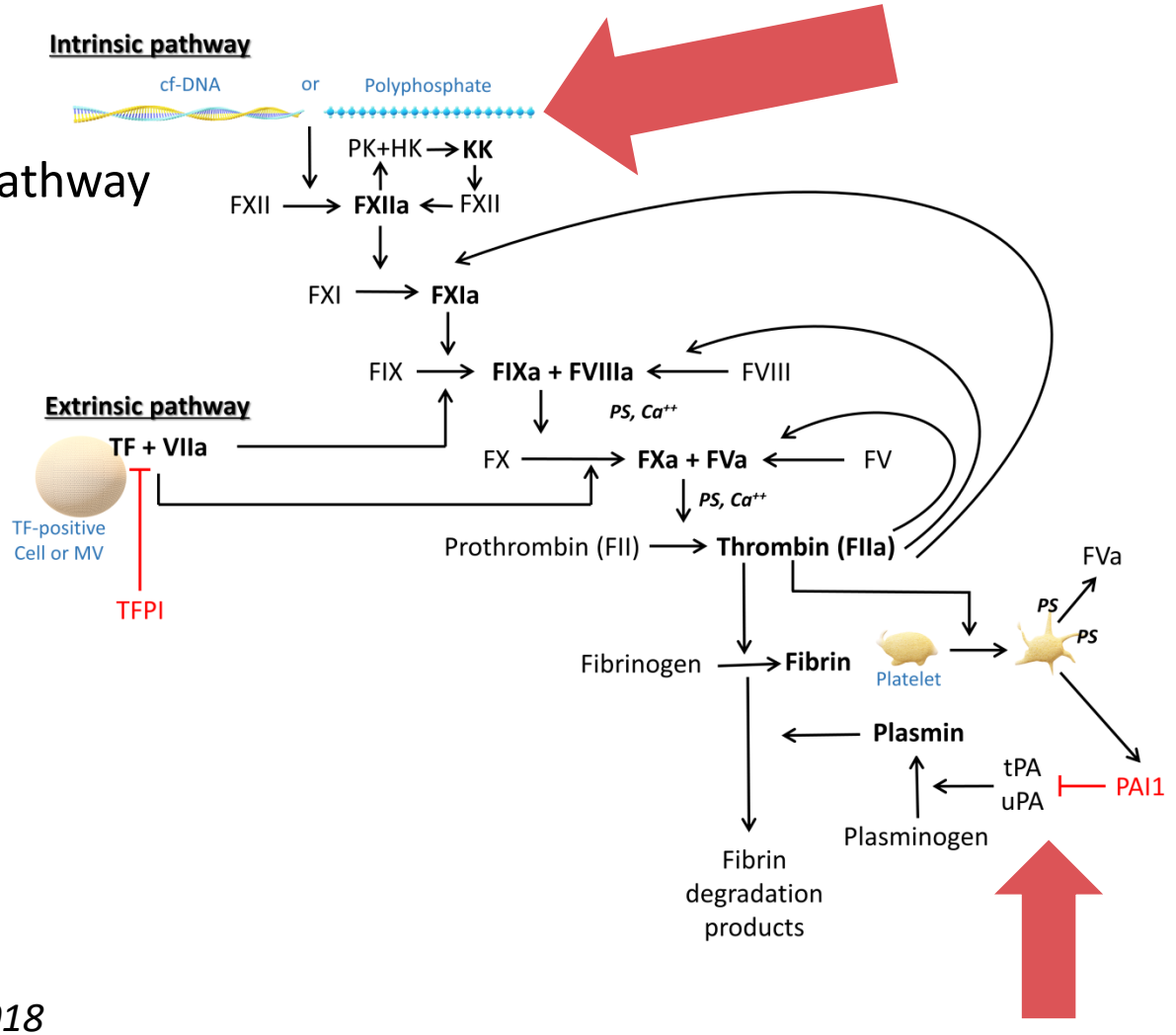




Carestia A et el Front Immunol 2016
Olsson AK et al Front Immunol 2016

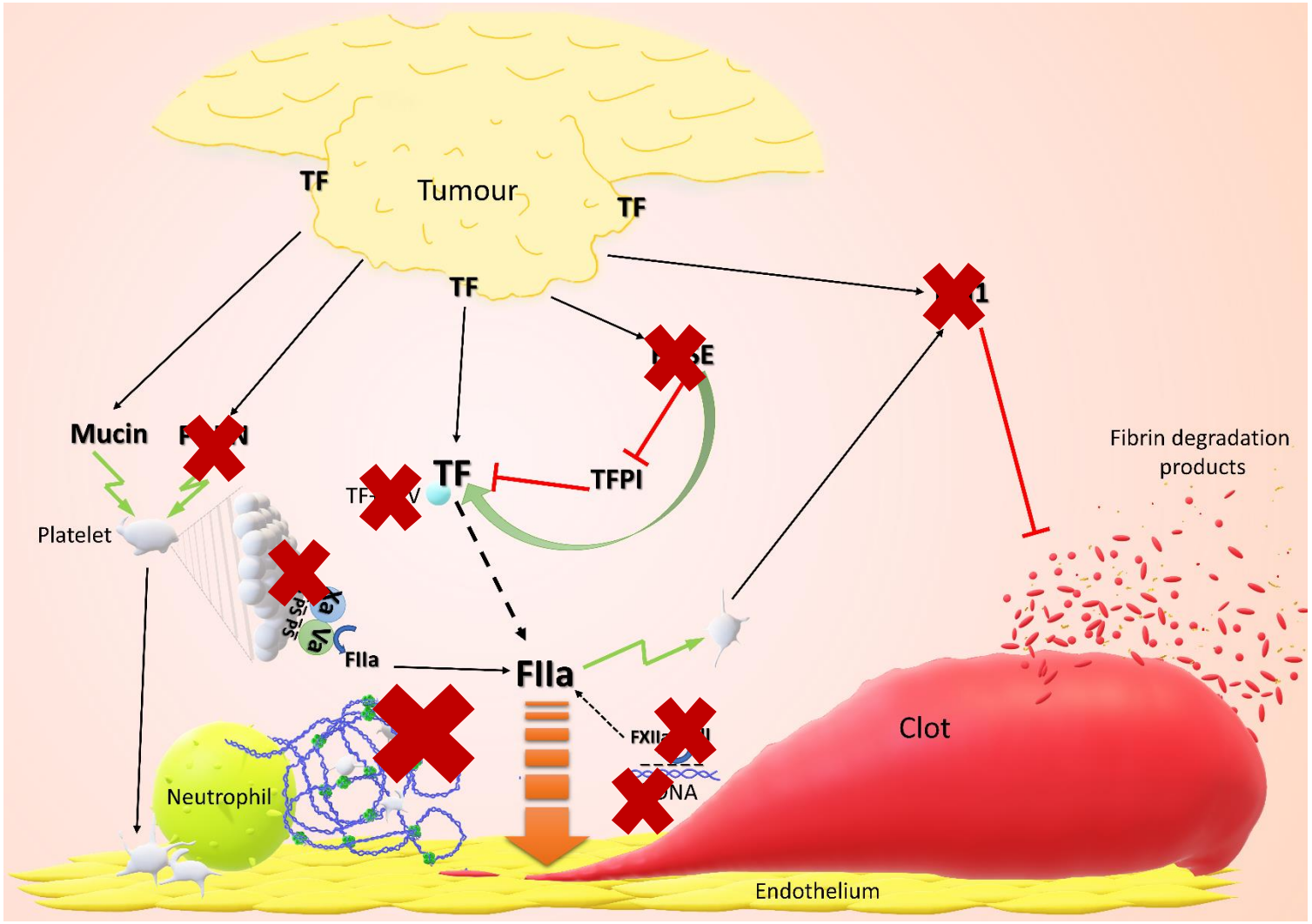
Hypercoagulability in Cancer-4

- Activation of the intrinsic pathway
- Hypofibrinolysis



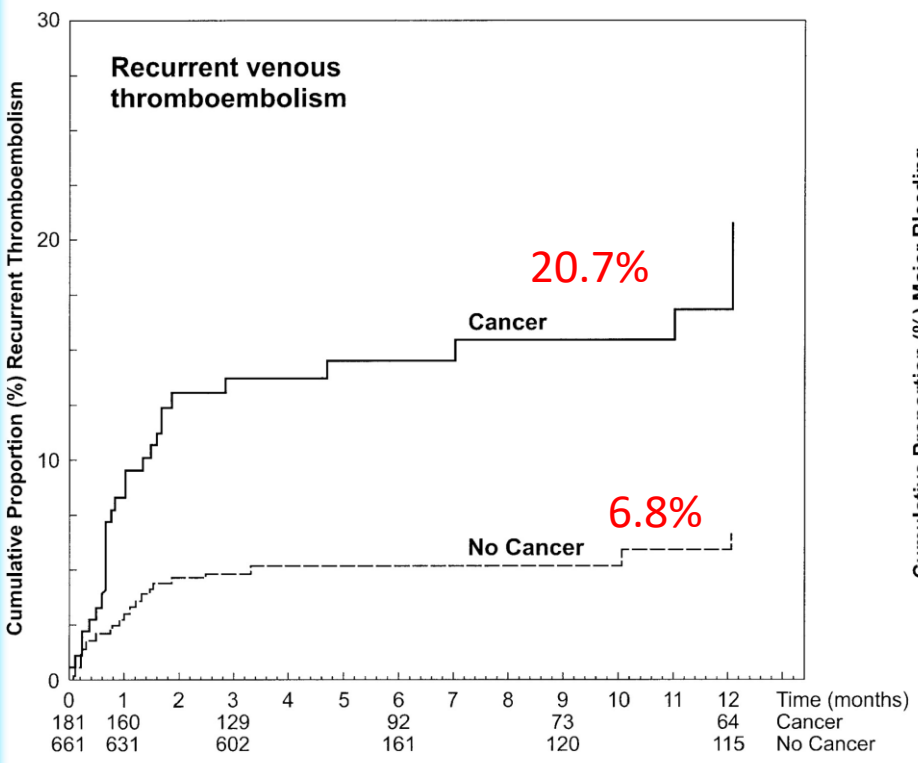
Campello E. et al Thromb Haemost 2018

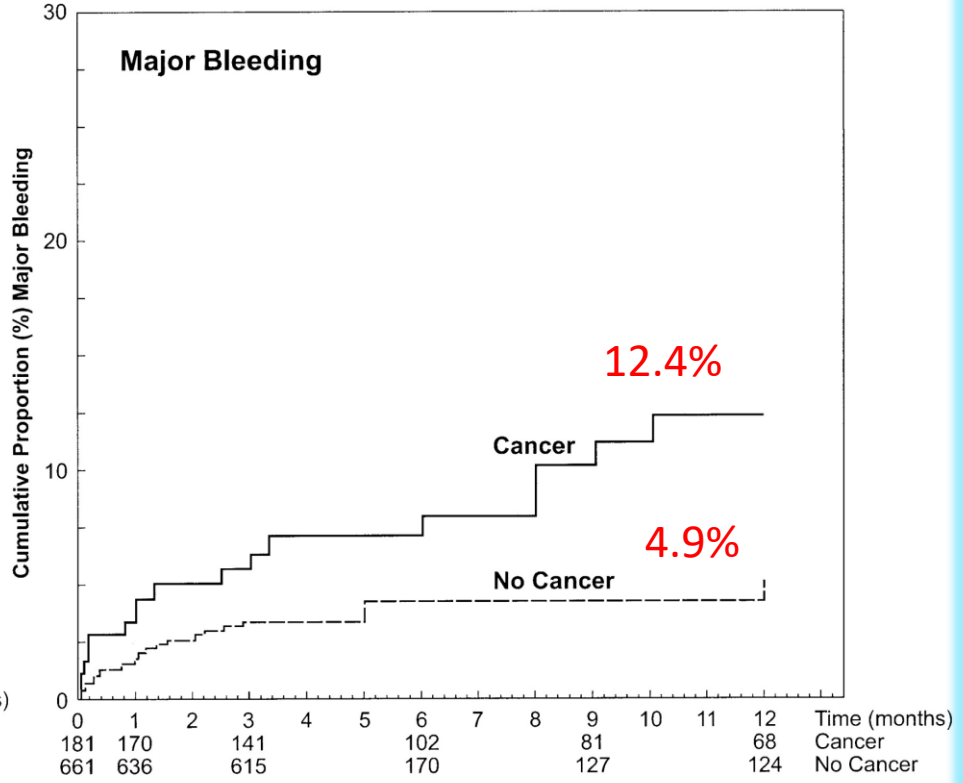
Hypercoagulability in Cancer



Campello E. et al. BJC 2019

Thrombosis in cancer is peculiar





HR 3.2 [1.9-5.4]

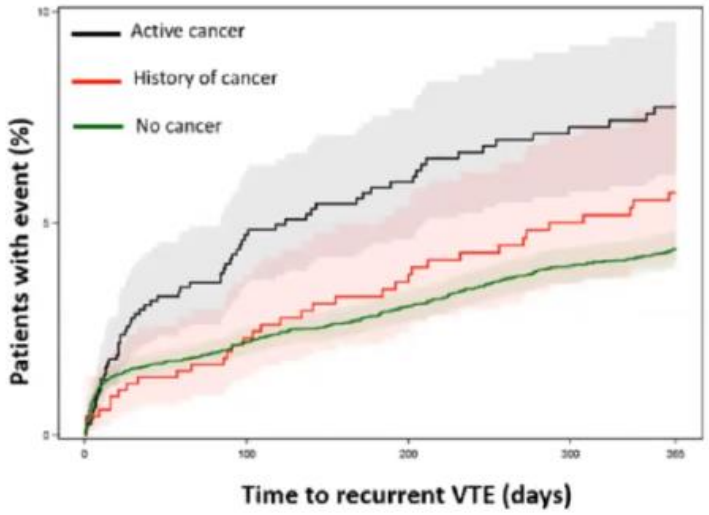
HR 2.2 [1.2-4.1]

Prandoni P. et al. Blood 2002

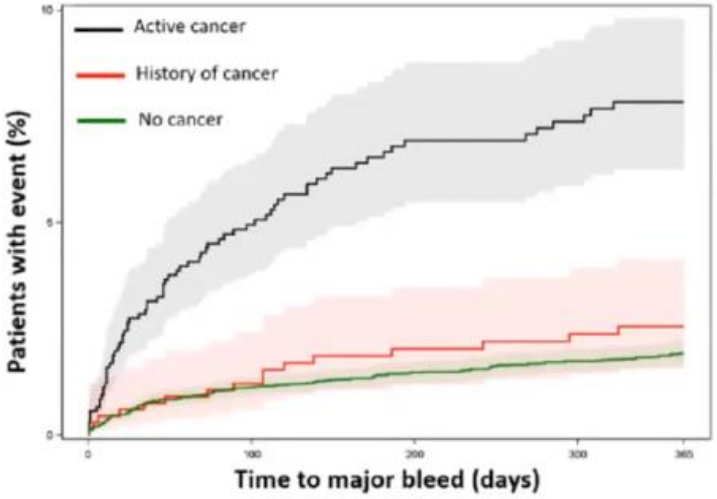
Cancer-associated VTE: clinical course in Garfield

1075 patients with active cancer and 674 with history of cancer

Active vs no cancer
HR 1.57, 95% CI 1.2–2.0



Active vs no cancer
HR 2.0, 95% CI 1.7–2.3



Weitz J et al. J Thromb Thrombol 2020

Cancer patient is peculiar

1. drug-drug interactions with antitumor therapy and medications used for supportive care

2. side effects of anticancer treatment, e. g. thrombocytopenia or gastrointestinal disorders such as mucositis, nausea and vomiting or diarrhoea, have to be considered

3. critical impairment of renal function

4. liver function may be severely reduced

5. VTE management should have no or only minimal impact on the patient's quality of life, which is frequently already compromised

Treatment for cancer-associated thrombosis: the guidelines 2011-2016

Society	Recommendations
ESMO 2011[1]	◆ **LMWH** recommended for long-term (6 months) anticoagulant therapy ◆ Recommendations for duration of therapy depend on the type of cancer, stage of disease and cancer treatment
ACCP 2016[2]	◆ **LMWH** preferred over VKA or NOAC therapy ◆ There is no preference between VKA, dabigatran, rivaroxaban, apixaban or edoxaban ◆ Extended therapy (>3 months) recommended over 3 months of therapy
ESC 2014[3]	◆ **LMWH** should be considered for the first 3–6 months ◆ **LMWH** or **VKAs** should be considered for extended anticoagulation beyond the first 3–6 months
ASCO 2015[4,5]*	◆ **LMWH** recommended over UFH for the first 5–10 days ◆ **LMWH** preferred over VKAs for the first 6 months of treatment. VKAs are an acceptable alternative if LMWH is not available ◆ For extended anticoagulation (beyond 6 months) LMWH or VKAs may be considered for selected patients# with active cancer ◆ Use of NOACs is not currently recommended for patients with cancer and VTE owing to limited data

1. Mandala M *et al*, *Ann Oncol* 2011;22:vi85–vi92; 2. Kearon C *et al*, *Chest* 2016;doi: 10.1016/j.chest.2015.11.026;
3. Konstantinides S *et al*, *Eur Heart J* 2014;35:3033–3069; 4. Lyman GH *et al*, *J Clin Oncol* 2013;17:2189–2204;
5. Lyman GH *et al*, *J Clin Oncol* 2015;33:654–656

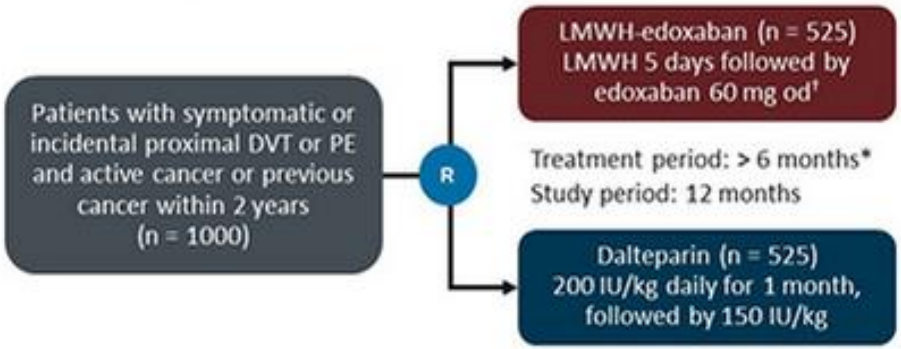
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Hokusai VTE Cancer – Study Design

- Prospective, randomized, open-label, multicenter non-inferiority study comparing dalteparin with LMWH-edoxaban for 12 months[a]



- Primary outcome: Composite of recurrent VTE (symptomatic VTE, incidental VTE or death due to PE) or major bleeding[b]

- Broad spectrum of cancers
- 53% metastatic
- 72% receiving chemotherapy

Raskob GE et al. NEJM 2018

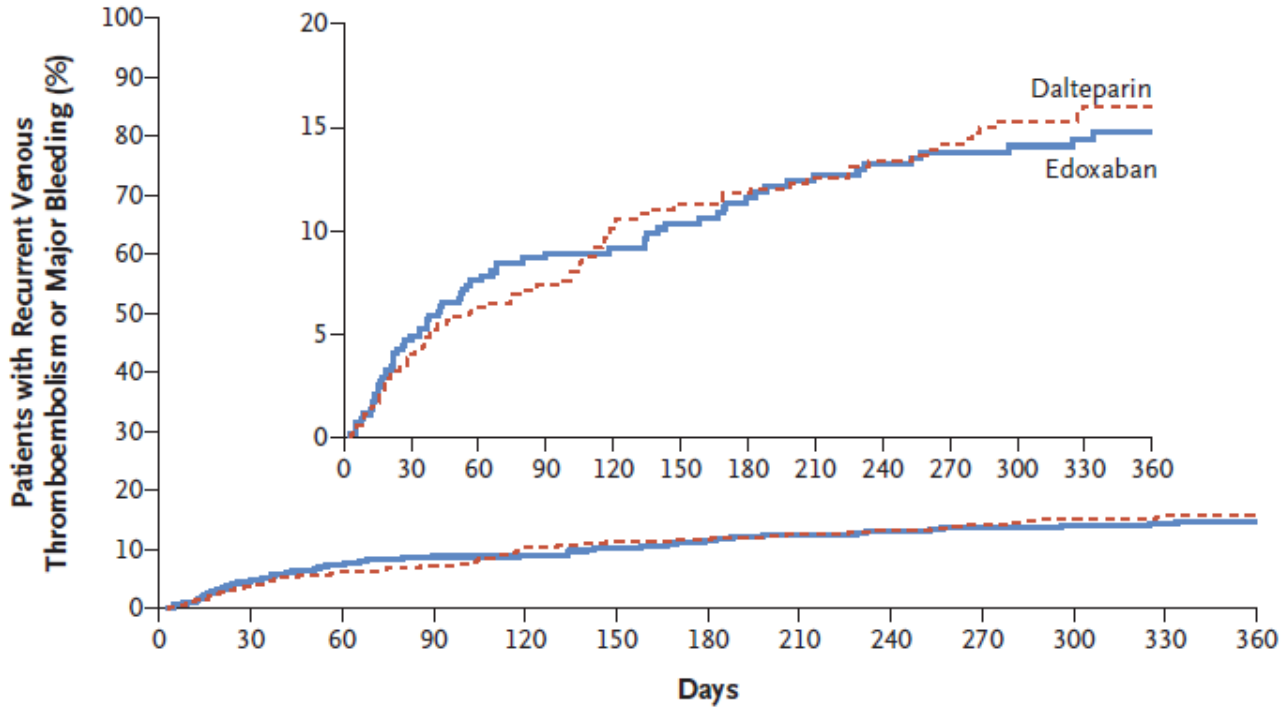
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Edoxaban (N=522)	Dalteparin (N=524)
Age — yr	64.3±11.0	63.7±11.7
Male sex — no. (%)	277 (53.1)	263 (50.2)
Weight		
Mean — kg	78.8±17.9	79.1±18.1
≤60 kg — no. (%)	83 (15.9)	78 (14.9)
Creatinine clearance of 30–50 ml/min — no. (%)	38 (7.3)	34 (6.5)
Platelet count of 50,000–100,000 per μl — no. (%)	32 (6.1)	23 (4.4)
Active cancer — no. (%)	513 (98.3)	511 (97.5)
Metastatic disease — no. (%)	274 (52.5)	280 (53.4)
Recurrent cancer — no. (%)	163 (31.2)	152 (29.0)
ECOG performance status — no. (%)¶		
0	155 (29.7)	148 (28.2)
1	243 (46.6)	246 (46.9)
2	123 (23.6)	124 (23.7)

This article was published on December 12, 2017, at NEJM.org.

Table 2. Clinical Outcomes during the Overall Trial Period.*

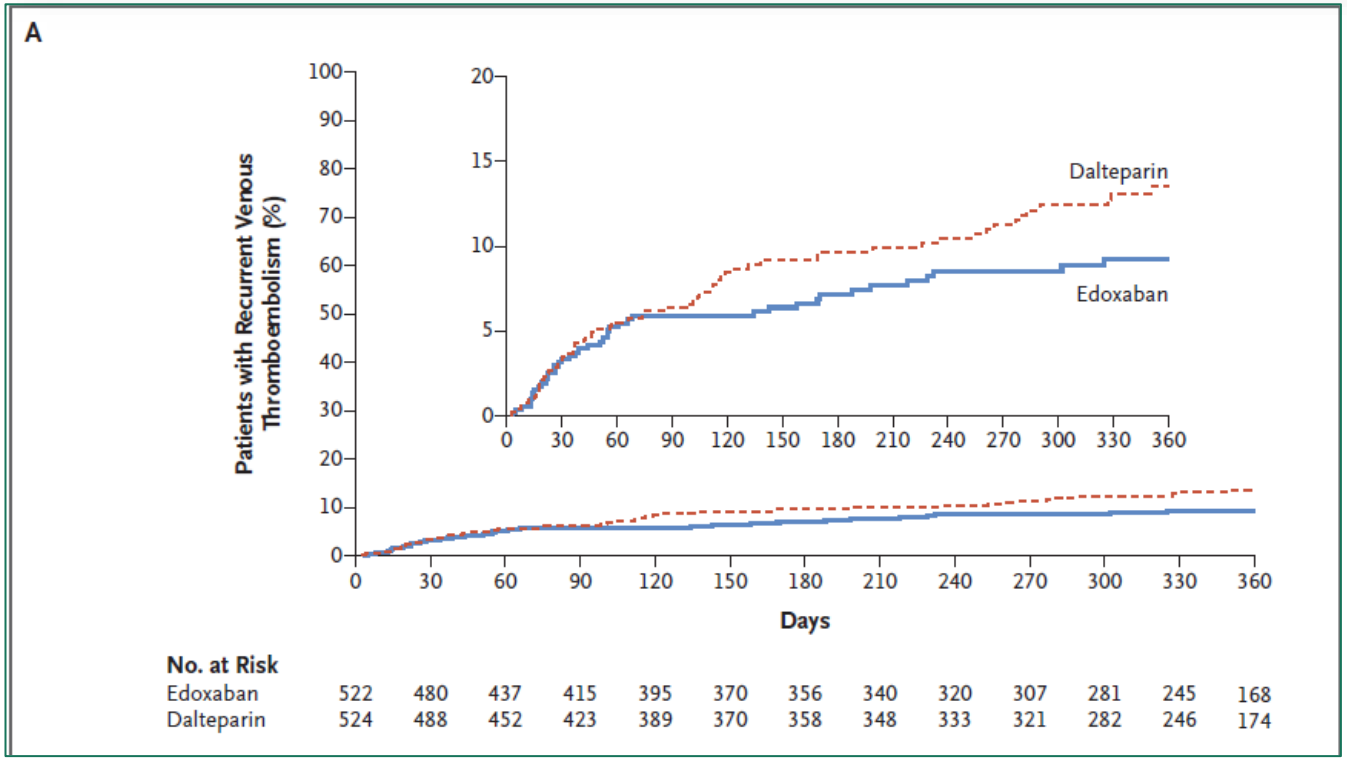
Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Recurrent venous thromboembolism or major bleeding — no. (%)	67 (12.8)	71 (13.5)	0.97 (0.70–1.36)	0.006 for noninferiority; 0.87 for superiority



Raskob GE et al. NEJM 2018

Table 2. Clinical Outcomes during the Overall Trial Period.*

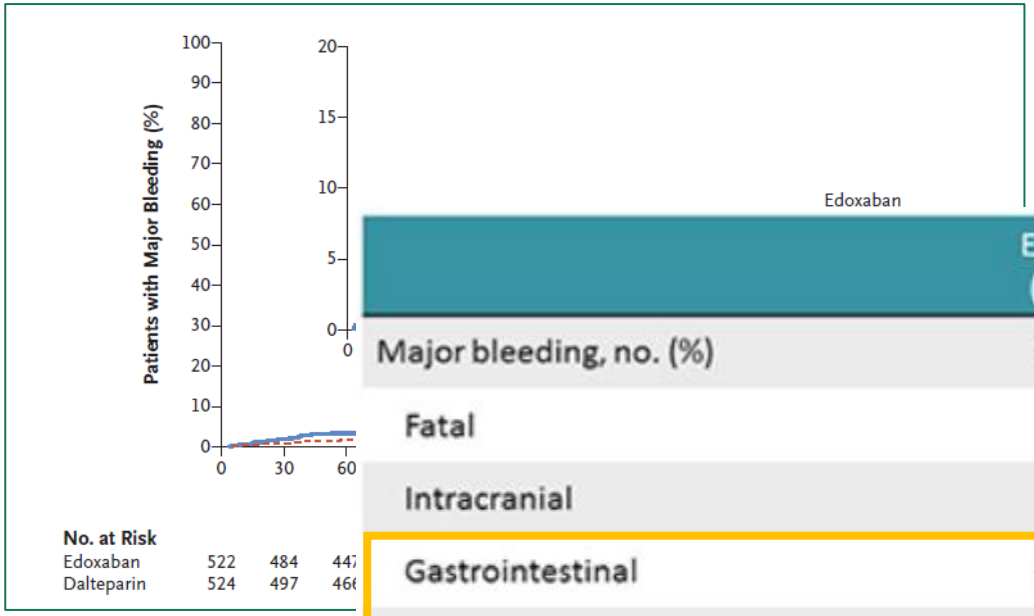
Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Secondary outcomes				
Recurrent venous thromboembolism — no. (%)	41 (7.9)	59 (11.3)	0.71 (0.48–1.06)	0.09
Recurrent deep-vein thrombosis — no. (%)	19 (3.6)	35 (6.7)	0.56 (0.32–0.97)	
Recurrent pulmonary embolism — no. (%)†	27 (5.2)	28 (5.3)	1.00 (0.59–1.69)	



Raskob GE et al. NEJM 2018

Table 2. Clinical Outcomes during the Overall Trial Period.*

Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Major bleeding — no. (%)	36 (6.9)	21 (4.0)	1.77 (1.03–3.04)	0.04



Edoxaban

	Edoxaban (n = 522)	Dalteparin (n = 524)
Major bleeding, no. (%)	33 (6.3)	17 (3.2)
Fatal	0	2 (0.4)
Intracranial	2 (0.4)	4 (0.8)
Gastrointestinal	20 (3.8)	6 (1.1)
Upper	17 (3.3)	3 (0.6)
Lower	3 (0.6)	3 (0.6)
Urogenital	5 (1.0)	0
Other	6 (1.1)	7 (1.3)

Raskob GE et al. NEJM 2018

Table 2. Clinical Outcomes during the Overall Trial Period.*

Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Major bleeding — no. (%)	36 (6.9)	21 (4.0)	1.77 (1.03–3.04)	0.04
Severity of major bleeding among those with major bleeding — no./total no. (%)‡				
Category 1	0	0		
Category 2	24/36 (66.7)	8/21 (38.1)		
Category 3	12/36 (33.3)	12/21 (57.1)		
Category 4	0	1/21 (4.8)		
Clinically relevant nonmajor bleeding — no. (%)§	76 (14.6)	58 (11.1)	1.38 (0.98–1.94)	
Major or clinically relevant nonmajor bleeding — no. (%)§¶	97 (18.6)	73 (13.9)	1.40 (1.03–1.89)	
Death from any cause — no. (%)	206 (39.5)	192 (36.6)	1.12 (0.92–1.37)	

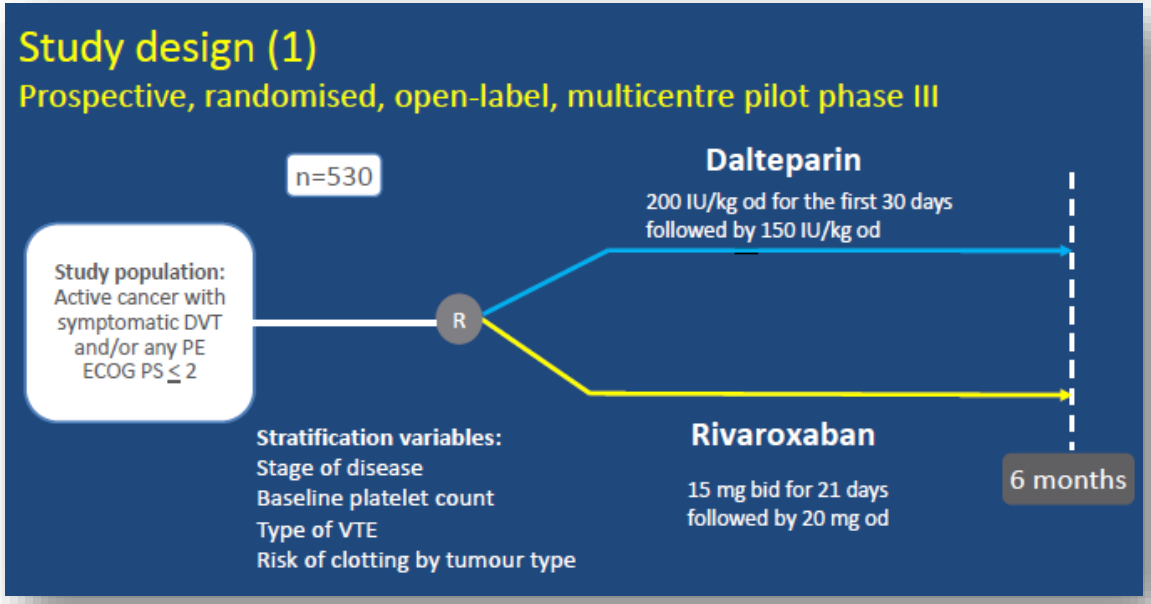
Raskob GE et al. NEJM 2018

VOLUME 36 · NUMBER 20 · JULY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

RAPID COMMUNICATION

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)



- Broad spectrum of cancers
- 406 patients randomized
- 58% metastatic

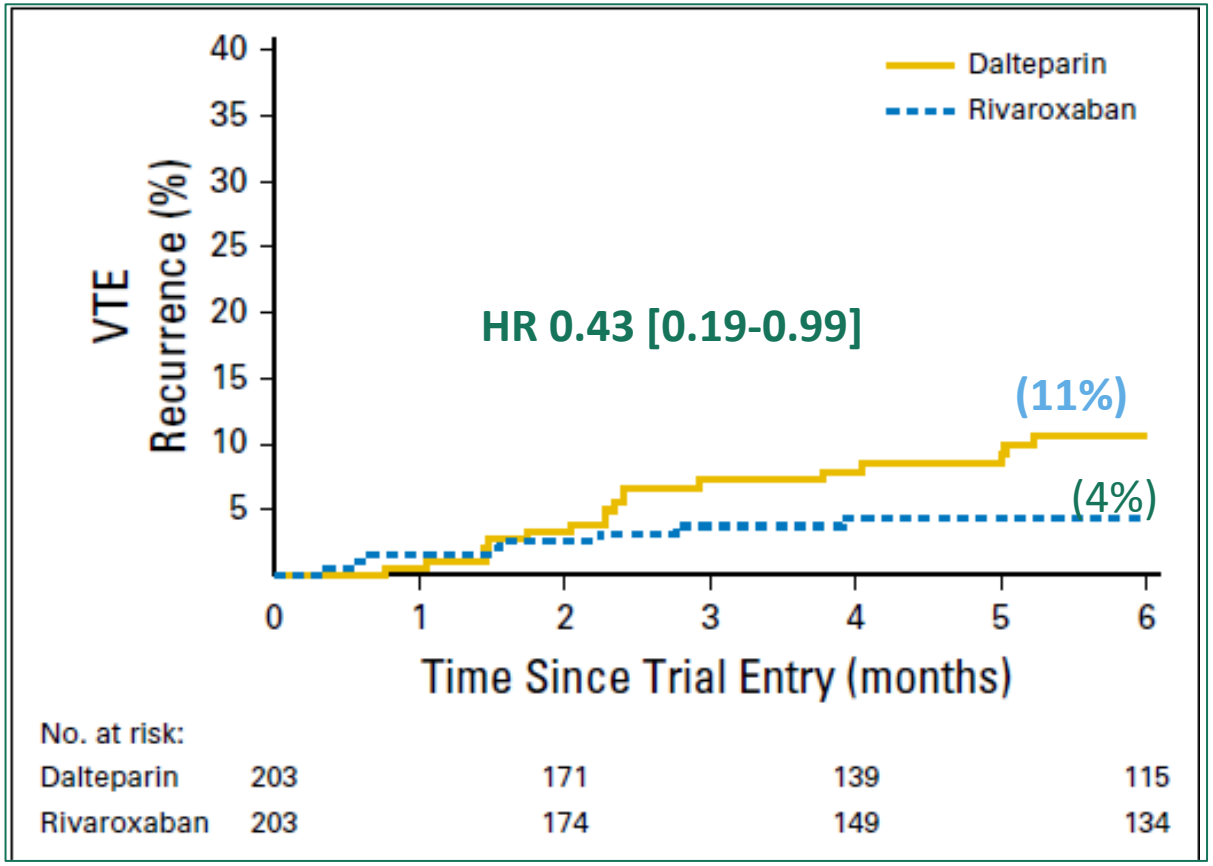
Primary otucome: VTE recurrence over 6 months

Young AM et al. JCO 2018

VOLUME 36 · NUMBER 20 · JULY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

RAPID COMMUNICATION



Young AM et al. JCO 2018

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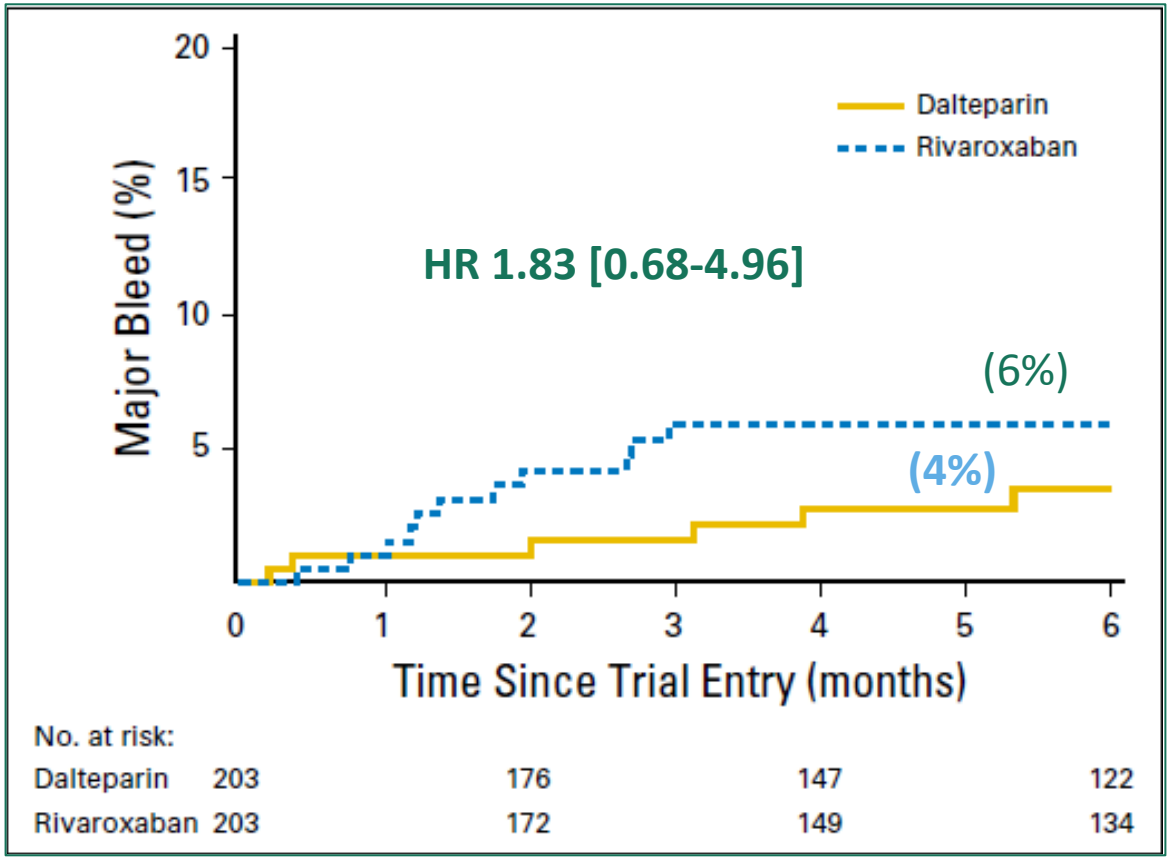
RAPID COMMUNICATION



Young AM et al. JCO 2018

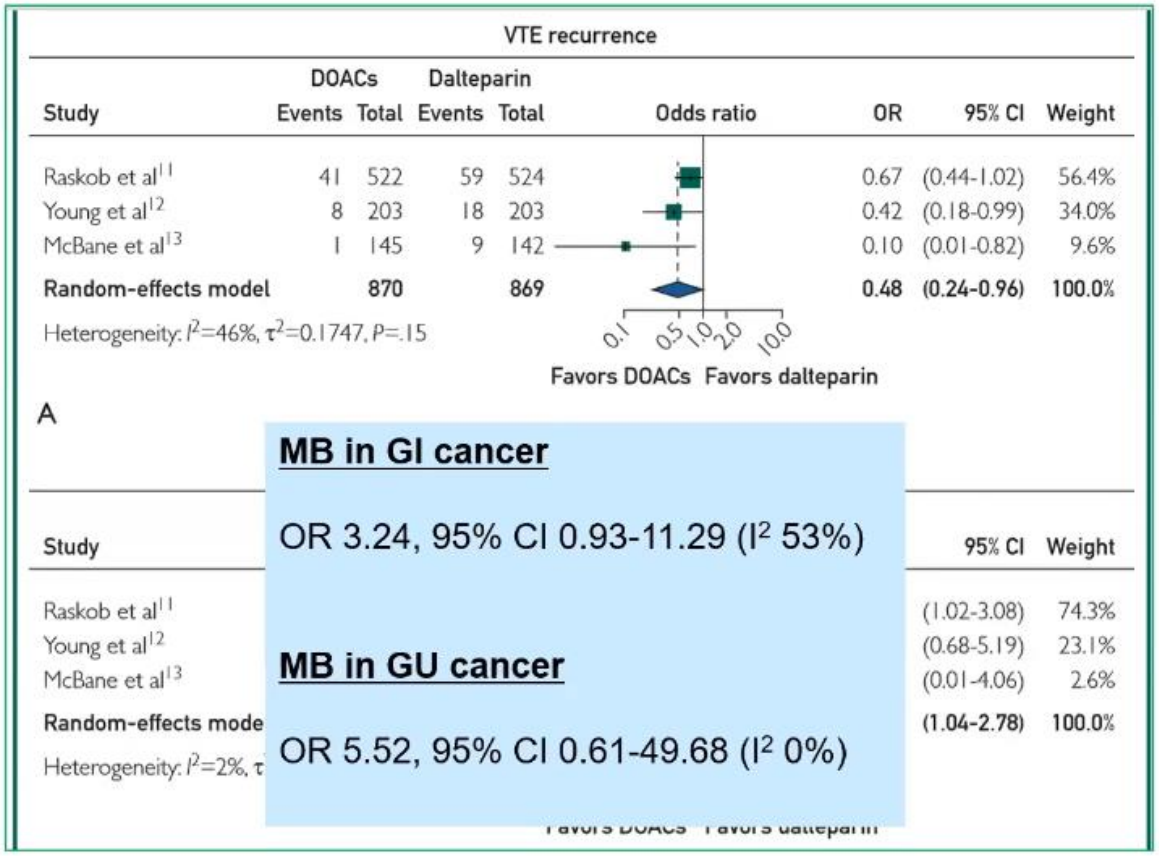
Table 3. Bleeding Events

Type of Bleed	Dalteparin (n = 203)	Rivaroxaban (n = 203)
Major bleeding	6	11
Sites of maior bleed*		
GI		
Esophageal	1	3
Stomach	3	2
Lower GI	0	1
Site unknown	0	2
Genitourinary		
Hematuria	0	1
Other		
Epistaxis	0	1
Intraoperative hemorrhage	0	1
Hematoma	1	0
Abdominal hematoma related to surgical clip	1	0
Site of CRNMB*		
GI		
Oral	0	1
Upper GI	0	2
Lower GI	1	0
Colon and rectum	2	1
Anus	0	3
Hemorrhoidal	0	2
Genitourinary		
Hematuria	1	9
Vagina	0	1
Menorrhagia	0	1
Penis	1	0
Other		

Gastric/esophageal cancers were especially at risk for major bleeding (36% in RIVA vs 11% in DALTE).

Young AM et al. JCO 2018

DOACs for cancer-associated VTE



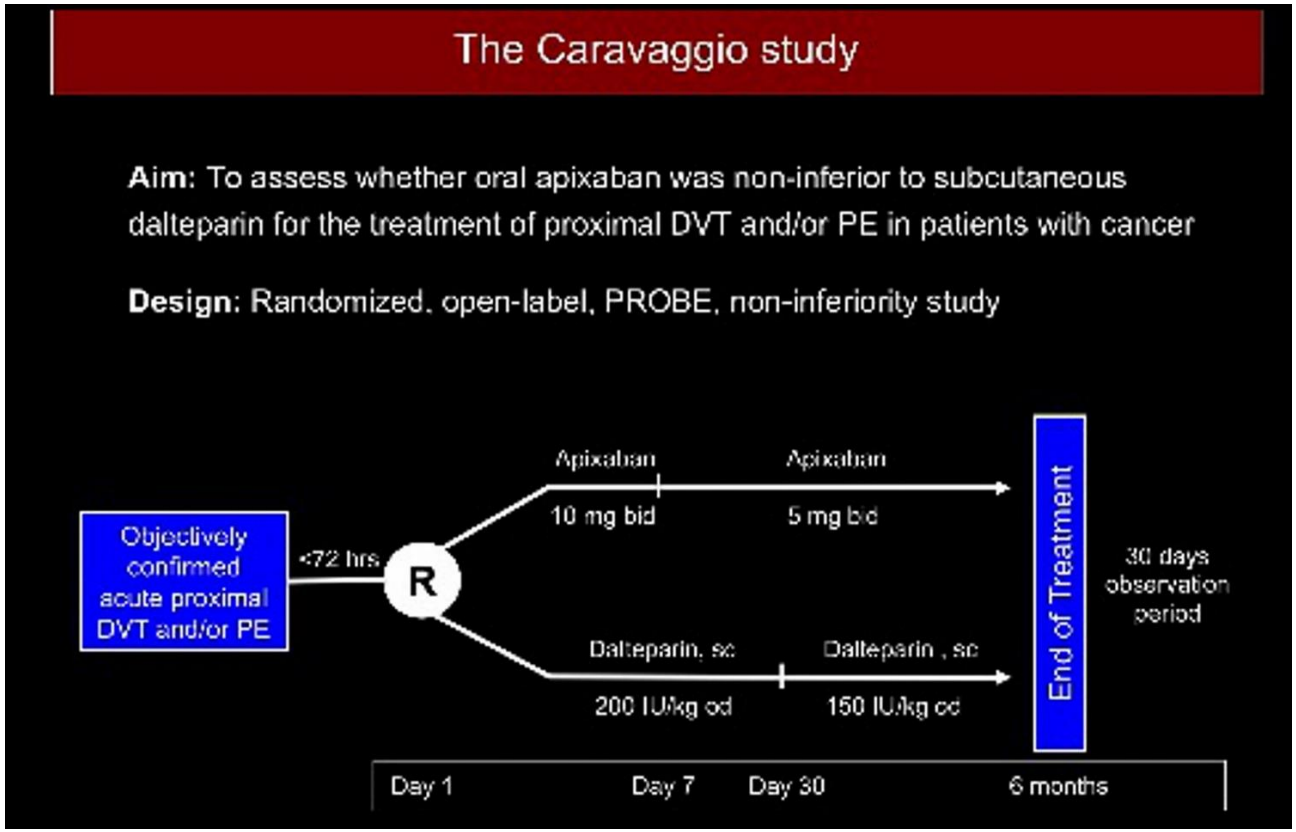
Fuentes HE, Mayo Clinic Procedures 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Guy Meyer, M.D., Andres Muñoz, M.D., Menno V. Huisman, M.D., Jean M. Connors, M.D., Alexander Cohen, M.D., Rupert Bauersachs, M.D., Benjamin Brenner, M.D., Adam Torbicki, M.D., Maria R. Sueiro, M.D., Catherine Lambert, M.D., Gualberto Gussoni, M.D., Mauro Campanini, M.D., Andrea Fontanella, M.D., Giorgio Vescovo, M.D., and Melina Verso, M.D., for the Caravaggio Investigators*

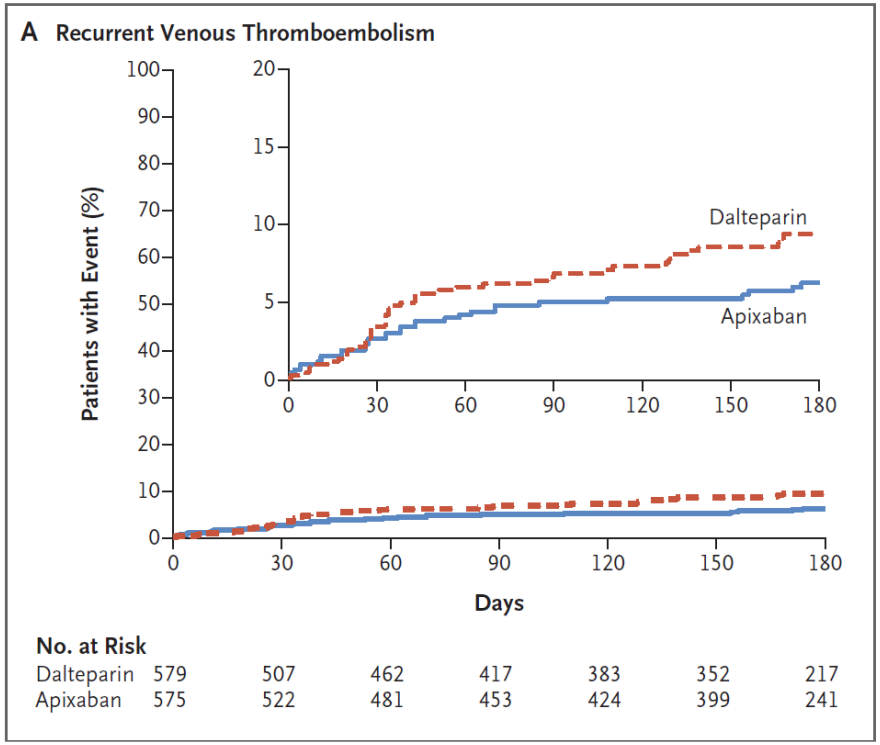


- Broad spectrum of cancers
- 1170 patients randomized
- 67% locally advanced or metastatic

NEJM 2020

ORIGINAL ARTICLE

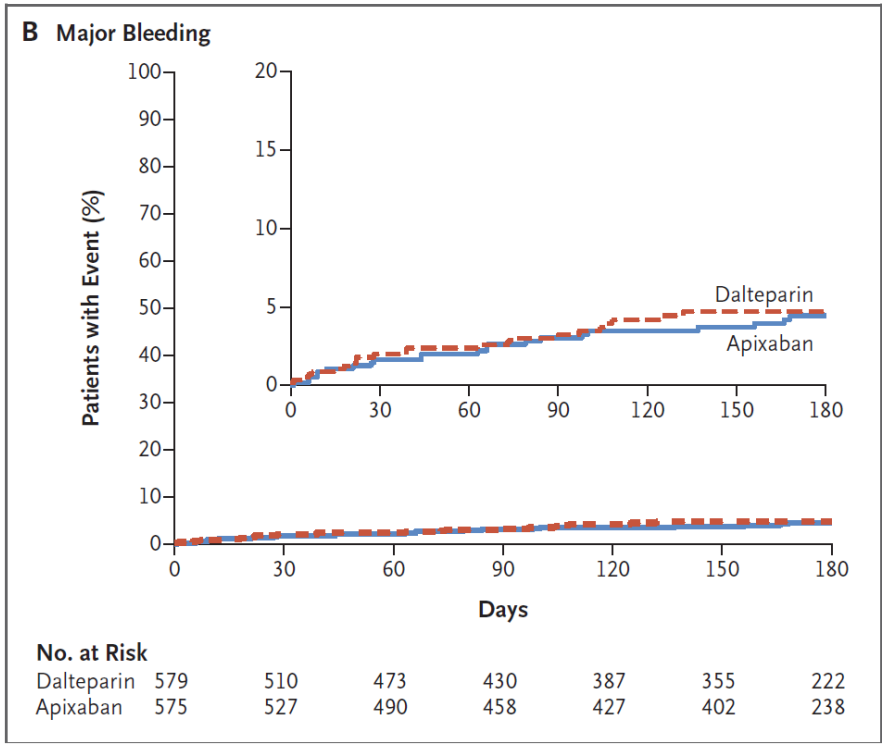
Outcome	Apixaban (N=576)	Dalteparin (N=579)	Hazard Ratio (95% CI)	P Value
Primary efficacy outcome — no. (%)†				
Recurrent venous thromboembolism‡	32 (5.6)	46 (7.9)	0.63 (0.37–1.07)	<0.001 for noninferiority; 0.09 for superiority
Recurrent deep-vein thrombosis	13 (2.3)	15 (2.6)	0.87 (0.34–2.21)	
Recurrent pulmonary embolism	19 (3.3)	32 (5.5)	0.54 (0.29–1.03)	
Fatal pulmonary embolism§	4 (0.7)	3 (0.5)	1.93 (0.40–9.41)	



Agnelli G. et al NEJM 2020

ORIGINAL ARTICLE

Primary safety outcome — no. (%)				
Major bleeding¶	22 (3.8)	23 (4.0)	0.82 (0.40–1.69)	0.60
Major gastrointestinal bleeding	11 (1.9)	10 (1.7)	1.05 (0.44–2.50)	
Major nongastrointestinal bleeding	11 (1.9)	13 (2.2)	0.68 (0.21–2.20)	



Eventi

Apixaban 22 su 576 (3.8%)

Dalteparina 23 su 579 (4%)

HR 0.82 (0.40-1.69)

Agnelli G. et al NEJM 2020

DOACs e trombosi associata a cancro

Major Bleeding	Apixaban	Dalteparin
Major bleeding, n (%)	22 (3.8%)	23 (4.0%)
Fatal†	0	2
Abdominal	1	0
Intracranial	0	2
Intraspinal	0	1
Pericardial	1	0
Intra-articular	0	1
Retroperitoneal	0	1
Cutaneous	1	1
Genito-urinary	4	1
Lung	1	1
Muscle	0	2
Upper airways	1	2
Gastrointestinal	11	10
Upper	5	6
Lower	6	4
Undetermined site	2	2

Clinically Relevant Non-Major Bleeding	Api	Dalte
CRNM bleeding, n (%)	52 (9.0%)	34 (5.9%)
Abdominal	1	1
Intramuscular	1	1
Cutaneous	6	4
Genito-urinary	19	10
Hematuria	15	7
Vaginal bleeding	4	3
Lung	3	2
Upper airways	12	3
Gastrointestinal	11	15
Upper	2	8
Lower	9	7
Undetermined site	1	0

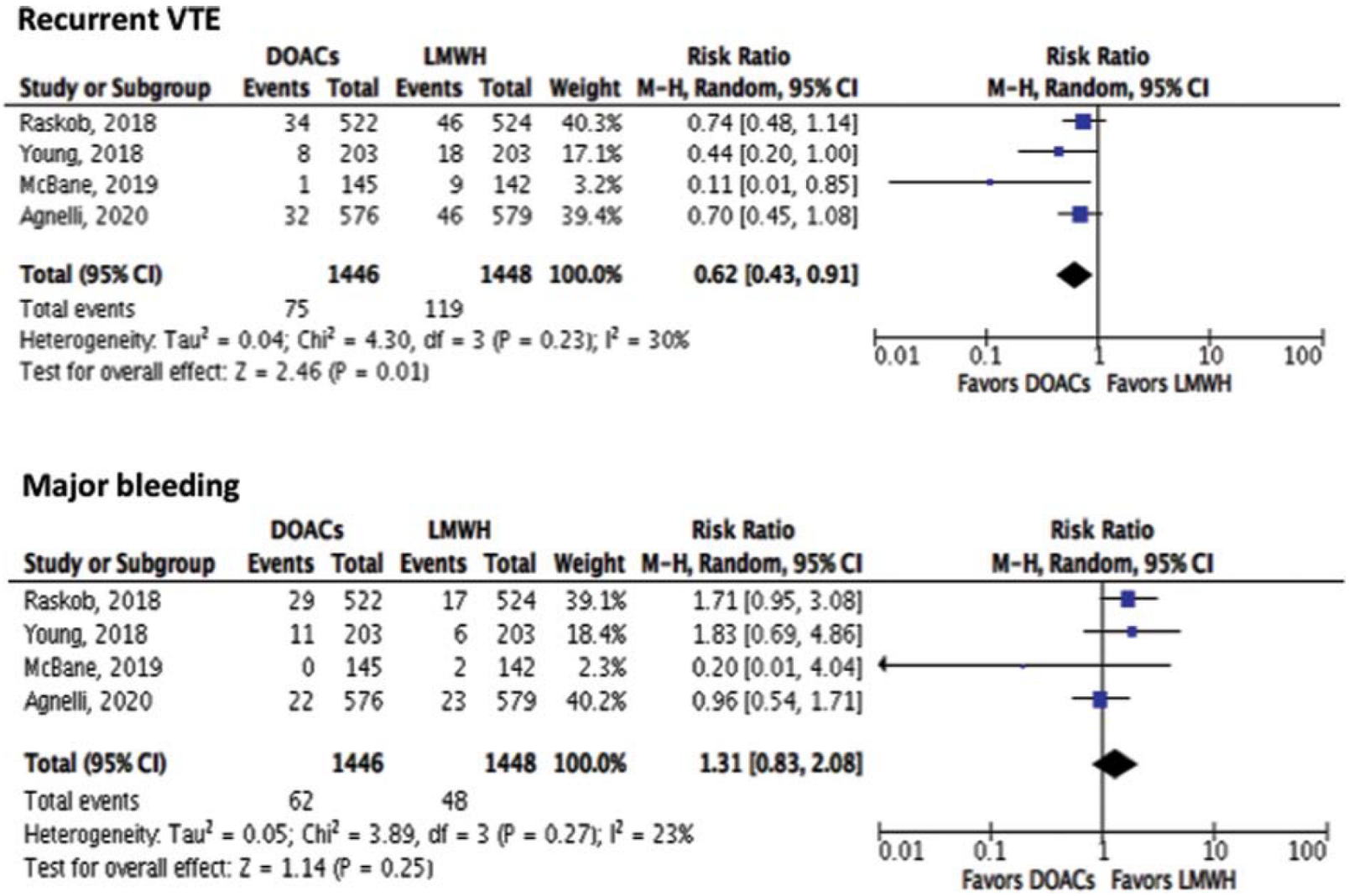
Agnelli G. et al. NEJM 2020

DOACs e trombosi associata a cancro

Cancer type	Apixaban (N=576)				Dalteparin (N=579)			
			Site of bleeding				Site of bleeding	
	Number at risk	Major bleeding n (%)	Lower GI	Upper GI	Number at risk	Major bleeding n (%)	Lower GI	Upper GI
Total GI cancer	188	9 (4.8)	3	4	187	9 (4.8)	3	3
Colorectal	121	5 (4.1)	1	2	113	6 (5.3)	3	2
Resected	33	0	0	0	29	0	0	0
Non resected	88	5	1	2	84	6	3	2
Pancreatic or Hepatobiliary	44	2 (4.5)	1	1	43	0	0	0
Resected	5	0	0	0	6	0	0	0
Non resected	39	2	1	1	37	0	0	0
Upper gastrointestinal	**23**	**2 (8.7)**	**1**	**1**	**31**	**3 (9.7)**	**0**	**1**
Resected	**5**	**0**	**0**	**0**	**2**	**0**	**0**	**0**
Non resected	**18**	**2**	**1**	**1**	**29**	**3**	**0**	**1**

Ageno W. et al. TH 2021

Treatment of CAT – the PRESENT



ig. 2 Forest plot of the main study outcomes comparing direct oral anticoagulants (DOACs) and low-molecular-weight heparin (LMWH).

Giustozzi M. et al. TH 2020

DOACs in CAT

- Oral administration
- ↓ recurrent VTE rate
- No monitoring

- ↑ bleeding
- Drug-drug interactions

8.6 Recommendations for the regimen and the duration of anticoagulation after pulmonary embolism in patients with active cancer

Recommendations	Class[a]	Level[b]
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs.[360–363]	IIa	A
Edoxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[366]	IIa	B
Rivaroxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[367]	IIa	C
For patients with PE and cancer, extended anticoagulation (beyond the first 6 months)[c] should be considered for an indefinite period or until the cancer is cured.[378]	IIa	B
In patients with cancer, management of incidental PE in the same manner as symptomatic PE should be considered, if it involves segmental or more proximal branches, multiple subsegmental vessels, or a single subsegmental vessel in association with proven DVT.[376,377]	IIa	B

ESC 2020

National Comprehensive Cancer Network®

THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM (CONTINUED)

DOACs (preferred for patients without gastric or gastroesophageal lesions)[a]
- Apixaban (category 1)[b]
  - 10 mg PO every 12 hours for 7 days followed by 5 mg PO every 12 hours[12-15,30,31]
- Edoxaban (category 1)
  - Initial therapy with LMWH[c,3,4] or UFH[d,e,5] for at least 5 days followed by edoxaban 60 mg PO daily (or 30 mg PO daily in patients with Cockcroft-Gault estimated CrCl 30–50 mL/min or weight <60 kg or concomitant potent p-glycoprotein inhibitors)[e,6,7]
- Rivaroxaban
  - 15 mg PO every 12 hours for the first 21 days followed by 20 mg daily[8-11]

LMWH (preferred for patients with gastric or gastroesophageal lesions)
- Dalteparin (category 1)
  - 200 units/kg SC daily for 30 days, then switch to 150 units/kg once daily[e,f,4,16,17]
- Enoxaparin
  - 1 mg/kg SC every 12 hours (can consider decreasing intensity to 1.5 mg/kg daily after first month)[g,3,18-20]

DOACs (if above regimens not appropriate or unavailable)[a]
- Dabigatran
  - Initial therapy with LMWH[c,3,4] or UFH[d,5] for at least 5 days followed by dabigatran 150 mg PO every 12 hours[e,21,22]

Fondaparinux[23,24]
- 5 mg SC daily (<50 kg)
- 7.5 mg SC daily (50–100 kg)
- 10 mg SC daily (>100 kg)

UFH (category 2B)[5]
- IV 80 units/kg bolus, followed by 18 units/kg/h adjusted to target aPTT of 2–2.5 X control or per hospital SOPs, followed by SC 250 units/kg every 12 hours (category 2B)
- SC 333 units/kg load, followed by 250 units/kg every 12 hours[25]

Warfarin[h,26-28]
- Start warfarin concurrently with LMWH, fondaparinux, or UFH (see dosing below)
- Warfarin 5 mg daily adjusted to INR 2–3 (2.5 mg daily initial dose for liver disease or use with interacting medications)
  - LMWH[3,4] + warfarin[h] options:
    - Dalteparin 200 units/kg SC daily[4] or 100 units/kg SC every 12 hours
    - Enoxaparin 1 mg/kg SC every 12 hours[3]
  - Fondaparinux + warfarin[h,23,24]
    - 5 mg SC daily (<50 kg)
    - 7.5 mg SC daily (50–100 kg)
    - 10 mg SC daily (>100 kg)
  - UFH[5] + warfarin[h] options:
    - IV 80 units/kg bolus, followed by 18 units/kg/h adjusted to target aPTT of 2–2.5 X control or per hospital SOPs
    - SC 333 units/kg load, followed by 250 units/kg every 12 hours

ANTICOAGULANT OPTIONS: CONTRAINDICATIONS AND WARNINGS

Agent(s)	Contraindications and Warnings
LMWH	• Use with caution in patients with renal dysfunction. Consider dose adjustments or alternative therapy for patients with severe renal disfunction (CrCl <30 mL/min). • Follow package insert for renal dysfunction and body weight dosing. • Anti-Xa monitoring (peak and trough) of LMWH has been recommended for patients with severe renal dysfunction, although limited data are available to support the clinical relevance of anti-Xa levels. • Absolute contraindication: recent/acute HIT • Relative contraindication: past history of HIT
Fondaparinux	• Contraindicated in patients with CrCl <30 mL/min • Use with caution in patients with moderate renal insufficiency (CrCl 30–50 mL/min), weight <50 kg, or age >75 y
UFH	• Absolute contraindication: recent/acute HIT • Relative contraindication: past history of HIT
Warfarin	Relative contraindications: • Concomitant inhibitors and inducers of CYP2C9, 1A2, or 3A4
DOACs: Apixaban, dabigatran, edoxaban, and rivaroxaban	Contraindications: • Stage IV/V chronic kidney disease: ‣ Apixaban[h]: CrCl <25 mL/min ‣ Dabigatran, edoxaban, and rivaroxaban: CrCl <30 mL/min • Active/clinically significant liver disease: ‣ Apixaban or edoxaban: alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 x ULN; total bilirubin >1.5 x ULN ‣ Dabigatran or rivaroxaban: ALT/AST >3x ULN • Strong dual inhibitors/inducers of CYP3A4 and P-glycoprotein (P-gp): see prescribing information for rivaroxaban[8] and apixaban[12] • Inducers/inhibitors of P-gp: see prescribing information for dabigatran[21] and edoxaban[6] Relative contraindications, use with caution: • DOACs have been associated with an increased risk of gastrointestinal and possibly genitourinary tract bleeding, and should be used with caution in patients with genitourinary or gastrointestinal tract lesions, pathology, or instrumentation. • Use with caution in patients with compromised renal or liver function. • For patients receiving nephrotoxic or hepatotoxic chemotherapy consider monitoring patients more closely with laboratory testing. • Consider drug-drug interactions.

Factors to consider in tailoring anticoagulation

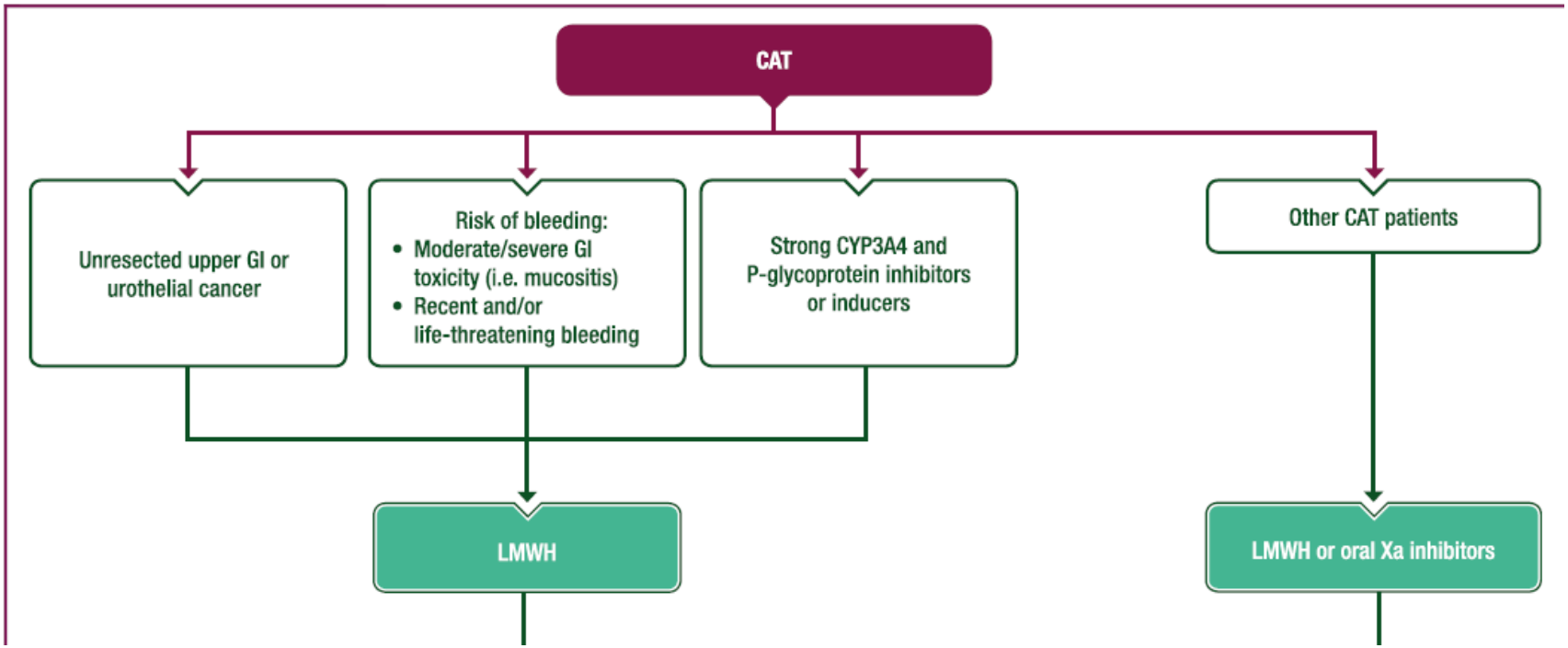
Tumor types	Luminal GI tumors Urothelial tumors
Risk of bleeding	GI toxicities from chemotherapy Thrombocytopenia Renal impairment
Drug-drug interactions	Inducers and inhibitors CYP3A4 and P-gp

Society	Recommendations
AT9 (CHEST) 2021[1]	◆ we recommend **an oral Xa inhibitor** (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and treatment phases of therapy (strong recommendation, moderate-certainty in the evidence of effects).
ASH 2021[2]	◆ Initial anticoagulation (first 7 days): either **DOAC (rivaroxaban, apixaban) or LMWH** (conditional recommendation, very low certainty in the evidence of effects) ◆ LMWH preferred over UFH (strong recommendation, moderate certainty in the evidence of effects) or fondaparinux (conditional recommendation, very low certainty in the evidence of effects) ◆ Short term (initial 3-6 months): **DOAC** (rivaroxaban, apixaban, edoxaban or dabigatran) preferred over VKAs or LMWH. (conditional recommendation, low certainty in the evidence of effects) ◆ LMWH preferred over VKA (conditional recommendation, moderate certainty in the evidence of effects)

1. Stevens SM, CHEST 2021; 2. Lyman Ghet al., Blood advances 2021; 2. NCCN Guidelines - https://www.nccn.org/professionals/physician_gls/default.aspx#vte

Society	Recommendations
AT9 (CHEST) 2021[1]	◆ Edoxaban and rivaroxaban appear to be associated with a higher risk of GI major bleeding than LMWH in patients with CAT and a luminal GI malignancy, while apixaban does not. ◆ Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies
ASH 2021[2]	◆ NOACs should be used carefully in patients with gastrointestinal cancers ◆ UFH might be preferred over LMWH for patients with creatinine clearance < 30 mL/min ◆ Different NOACs have different drug-drug interactions

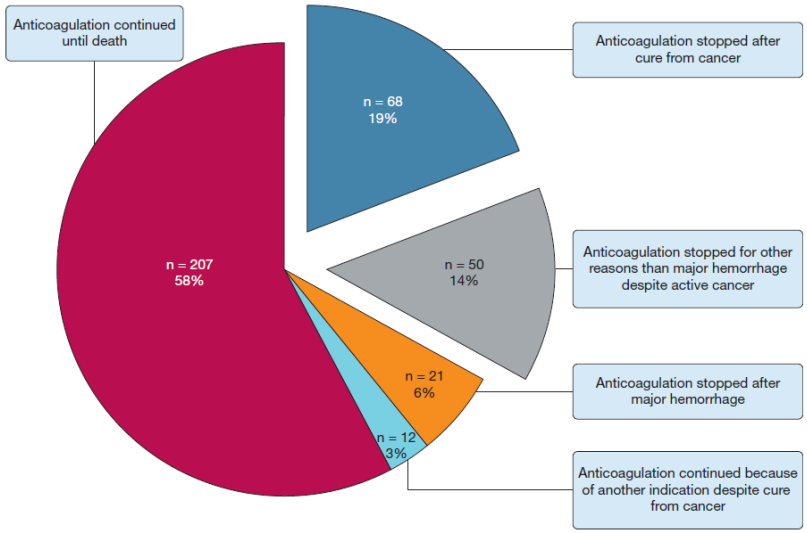
1. Stevens SM, CHEST 2021; 2. Lyman Ghet al., Blood advances 2021; 2. NCCN Guidelines - https://www.nccn.org/professionals/physician_gls/default.aspx#vte



Re-assessment every 3 months

Falanga A et al. Ann Oncology 2023

How long should the patient be anticoagulated?



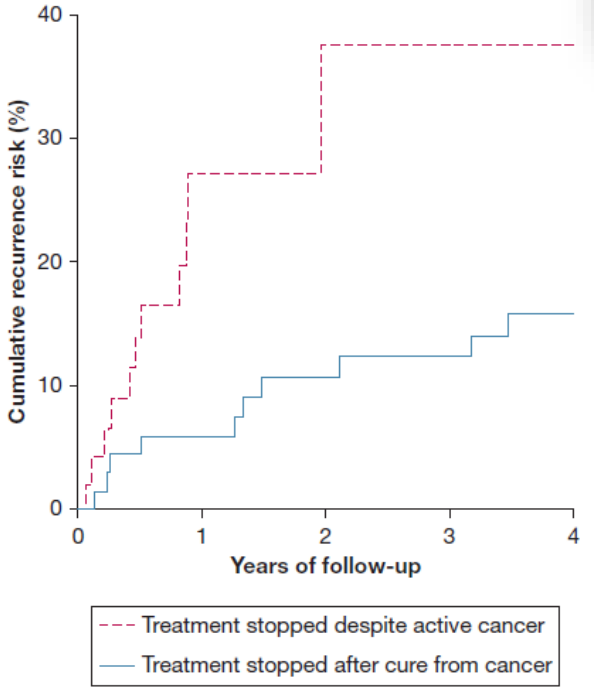


TABLE 2] Risk of Recurrent Venous Thromboembolism and Major Hemorrhage

Category	Events/Cumulative Follow-Up; Incidence Rate (95% CI)	
	Recurrent VTE	Major Hemorrhage
While on anticoagulant treatment for total cohort	33/282 y; 12/100 PY (8.1-16)	53/240 y; 22/100 PY (17-29)
Anticoagulant treatment stopped after cancer cured	10/311 y; 3.2/100 PY (1.5-5.9)	4/303 y; 1.3/100 PY (0.4-3.4)
Anticoagulant treatment stopped for reasons other than major hemorrhage despite active cancer	11/59 y; 19/100 PY (9.3-33)	3/59 y; 5.1/100 PY (1.1-15)

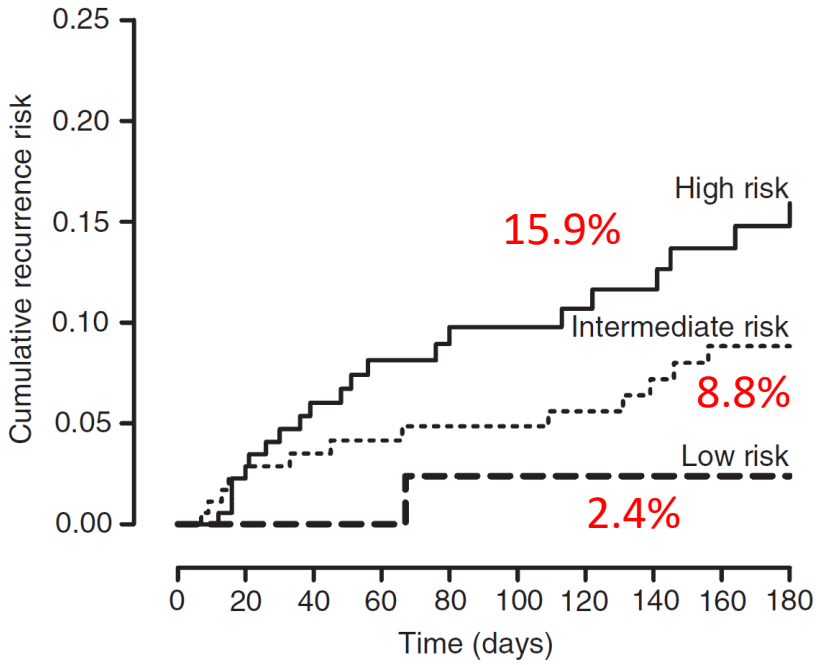
Van der Hulle T et al. Chest 2016

How long should the patient be anticoagulated?

Table 2. Ottawa Score for Recurrent VTE Risk in Cancer-Associated Thrombosis

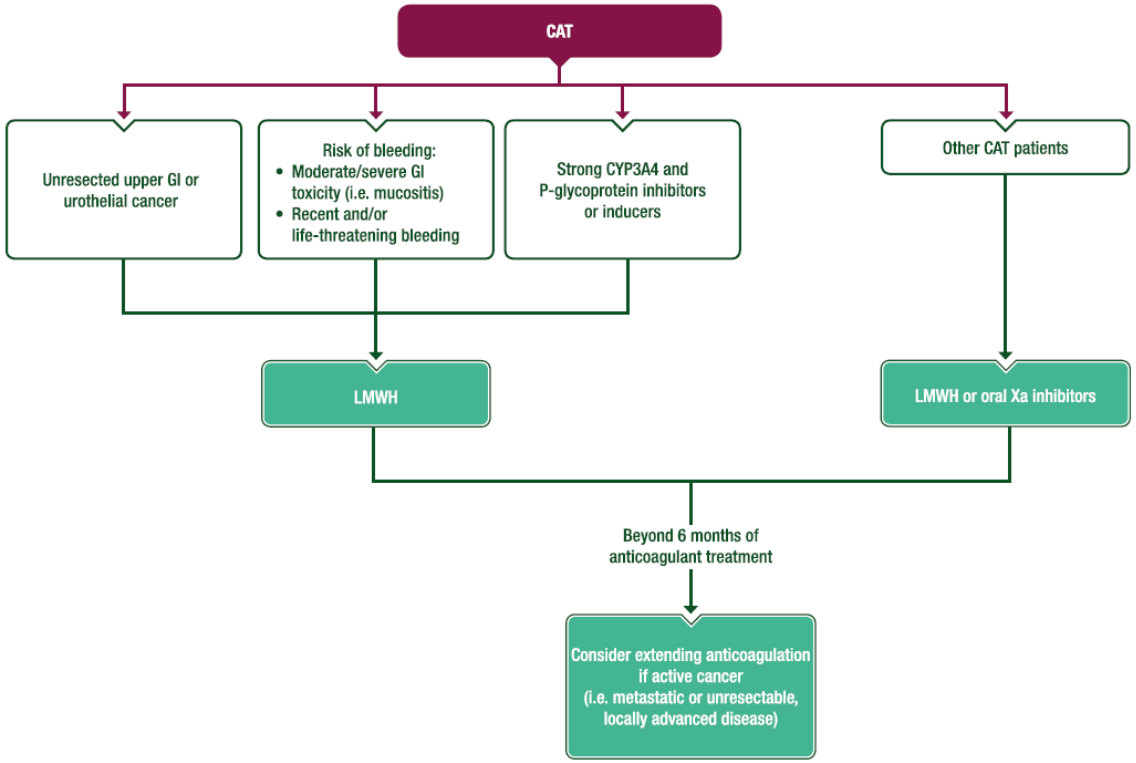
Variable	Regression Coefficient	Points
Female	0.59	1
Lung cancer	0.94	1
Breast cancer	−0.76	−1
TNM* stage I	−1.74	−2
Previous VTE	0.40	1

≥ 1 High risk
0 Intermediate risk
≤-1 Low risk



Louzada ML et al. Circulation 2012

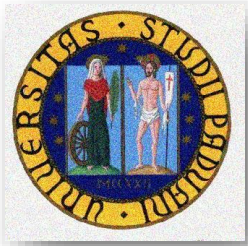
Den Exter P et al. JTH 2013



Periodic assessment of the risk-benefit profile and patient preferences remain crucial to evaluate the need for anticoagulation or dose adjustments

Extended anticoagulation beyond the initial 6 months **with LMWH, apixaban, edoxaban, rivaroxaban or VKAs** should be considered for patients with **active cancer in whom the risk of recurrent thrombosis is higher and may outweigh that of bleeding** [III, B].

Falanga A et al. Ann Oncology 2023



Patients with active cancer and acute VTE

- Luminal GI cancers
- Genito-urinary cancers
- GI abnormalities

DOAC [LMWH]
for 6 – 12 months

Every 3 months reassess the need and the patient's tolerance of anticoagulation treatment.

Complete cancer remission

YES

End DOAC [LMWH]

NO

Ongoing anti-cancer therapy
Metastatic – progressive disease

YES

Continue DOAC/LMWH

NO

Stable disease
Previous VTE
Female
Lung

DOAC (low dosage)

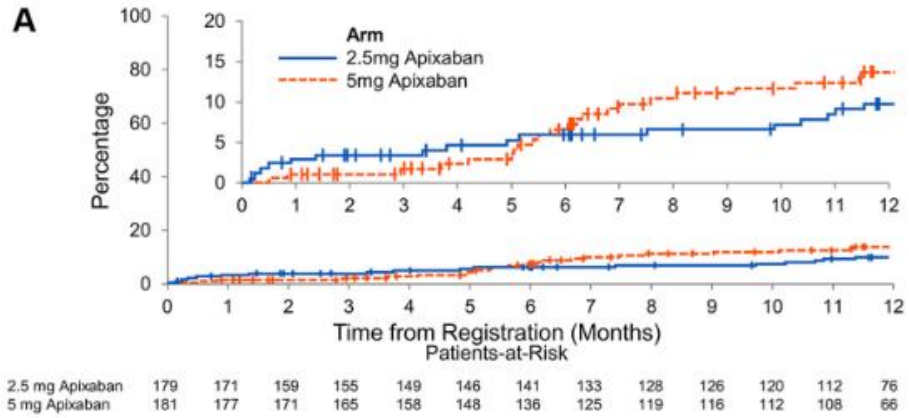
Continue LMWH (prophylaxis)

Patients preference

From Ay C et al. ESMO open 2017 and Lee AYY Thromb Res 2017

What's new? – Secondary prevention

Randomized, double-blind trial compared apixaban 2.5 mg to 5 mg twice daily for 12 months among cancer patients with VTE who had completed 6 – 12 months of anticoagulation.
Primary outcome was combined MB+ CRNMB



HR 0.72; 95% CI, 0.38-1.37; P = .39

360 patients included
Bleeding occurred in 8.9% in 2.5 mg group vs. 12.2% in 5 mg group

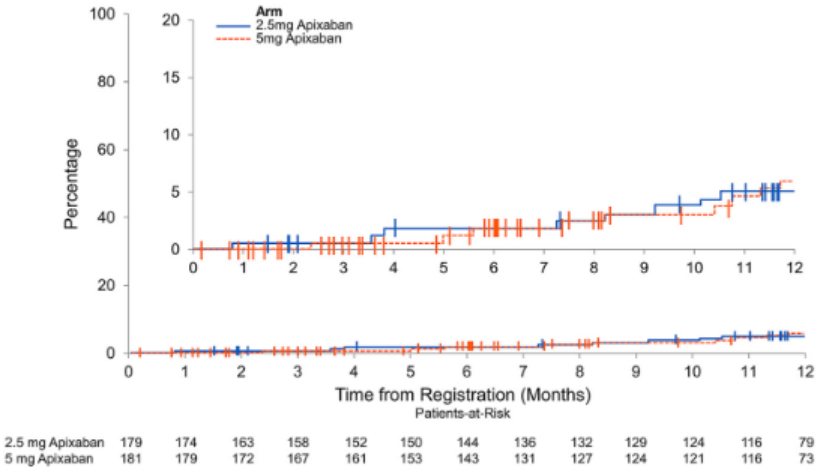
MB occurred in 2.8% of 2.5 mg group vs. 2.2% of 5 mg group (HR, 1.26; 95% CI, 0.34-4.66; P = .73).

→ For secondary prevention of cancer-associated VTE, apixaban 2.5 mg compared with 5 mg twice daily did not lower combined bleeding events

Robert D. McBane II, et al. JTH 2024

What's new? – Secondary prevention

Randomized, double-blind trial compared apixaban 2.5 mg to 5 mg twice daily for 12 months among cancer patients with VTE who had completed 6 – 12 months of anticoagulation. Primary outcome was combined MB+ CRNMB



Recurrent VTE or arterial thrombosis occurred in 5.0% in 2.5 mg vs. 5.0% in 5 mg group

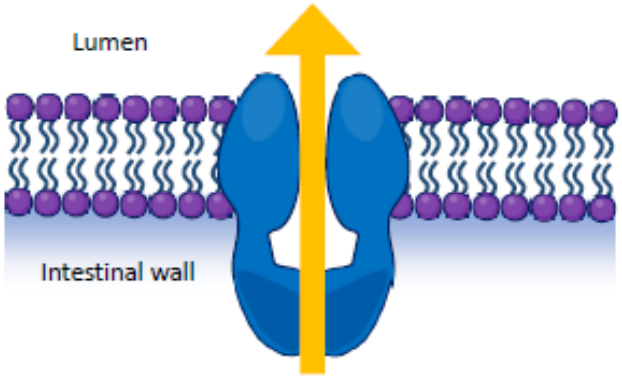
HR 1.0; 95% CI, 0.40-2.53; P = 1.00

Robert D. McBane II, et al. JTH 2024

DOACs

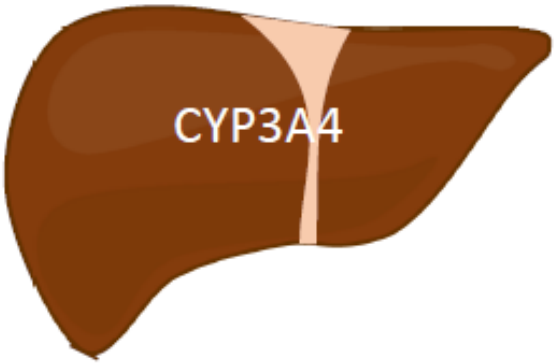
Drug-Drug Interactions

P-glycoprotein drug efflux pump



Inhibitors: ↓ efflux, ↑ DOAC
Inducers: ↑ efflux, ↓ DOAC

Hepatic CYP3A4 Metabolism



Inhibitors: ↓ metabolism, ↑ DOAC
Inducers: ↑ metabolism, ↓ DOAC

May also have combined effects

effects may also be enhanced by the presence of impaired renal function.

DOACs

Drug-Drug Interaction Potential

Indication	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Bioavailability	50%	3-7% *(also subject to hydrolysis)*	62%	66% (100% when taken with food)
P-glycoprotein substrate	Yes	Yes	Yes	Yes
Hepatic metabolism	73% (CYP3A4)	20% (not CYP3A4)	50% (only 4% CYP3A4)	65% (CYP3A4 and CYP2J3)
Renal clearance	27%	80%	50%	35%

Europace. 2015 Oct;17(10):1467-507.

Drug-drug interactions

DOACs and warfarin are substrates of key metabolic and transport pathways

Anticoagulant	CYP3A4 (metabolic)	P-gp (transport)	Other CYP metabolizing enzymes
LMWH	No	No	No
VKA	Major	No/minor	All (major CYP2C9)
Apixaban	Major	Major	Minor (1A2, 2C8, 2C9, 2C19)
Rivaroxaban	Major	Major	No
Edoxaban	Minor	Major	No
Dabigatran	No	Moderate	No

Adapted from Carrier M. Dublin ISTH SSC 2018

Drug-drug interactions

Inhibitors of CYP3A4 and/or P-gp may increae risk of bleeding on DOACs

Chemotherapies	CYP3A4	P-gp
Doxorubicin	↓	
Topotecan	↓	
Vinblastine	↓	
Mitotane	↑	
Venetoclax		↓

Supportive care	CYP3A4	P-gp
Ondansetron	↓	
Methhylpredn.	↓	
Dexamethasone	↑	↑
Tamoxifen	↓	↓

Kinase inhibitors	CYP3A4	P-gp
Afatinib		↓
Alectinib		↓
Ceritinib	↓	
Dasatinib	↓	
Ibrutinib		↓
Idelasilib	↓	↓
Imatinib	↓	
Lapatinib	↓	↓
Nilotinb	↓	↓
Osimertinib	↓	
Vemurafenib	↑	↓
Lenvatinib	↑	↑

Adapted from Carrier M. Dublin ISTH SSC 2018

Interazioni farmacologiche

TABLE III Anticancer therapies associated with gastrointestinal (GI) toxicity[a]

Drug class	Agent or agents	Types of toxicity
Alkylating agent (in high doses)[21]	Cyclophosphamide, bendamustine, busulfan, ifosfamide, melphalan	Stomatitis
Antimetabolite[21]	5-Fluorouracil, cytarabine, floxuridine, methotrexate	Diarrhea, stomatitis
Antimitotic agent[21]	Vinblastine, vincristine	Stomatitis, constipation
Checkpoint inhibitor[22]	Ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab	Colitis, diarrhea
EGFR inhibitor[22]	Cetuximab	Diarrhea
	Erlotinib, afatinib, gefitinib	Diarrhea, GI bleeding or perforation
Immunomodulating agent[21]	Interleukin 2	Stomatitis, colitis
MEK inhibitor[22]	Trametinib	Diarrhea
Nitrosourea[21]	Carmustine, lomustine	Diarrhea
PI3K inhibitor[22]	Idelalisib	Colitis
Topoisomerase inhibitor[21]	Etoposide	Stomatitis
	Irinotecan	Diarrhea, stomatitis
VEGF or VEGFR inhibitor[22]	Axitinib, bevacizumab	GI bleeding or perforation

[a] The list of therapies in the table is incomplete; agents are provided as examples.
EGFR = epidermal growth factor receptor; MEK = mitogen-activated protein kinase kinase; PI3K = phosphatidylinositol-4,5-bisphosphate 3-kinase; VEGF(R) = vascular endothelial growth factor (receptor).

Inoltre, dato che i NAO sono associati a un rischio più elevato di episodi di sanguinamento maggiore del tratto GI superiore, devono essere usati con cautela nei pazienti sottoposti a regimi CT associati a tossicità del tratto GI superiore → considerare apixaban o EBPM

Carrier M. et al. Current Oncology 2018

VTE primary prophylaxis in cancer

Clinically overt VTE in cancer after surgery: 1-3% depending on the type of surgery.

40% of VTE events occurred after >21 days postsurgery, and 46% of the deaths postsurgery due to VTE.

ENOXACAN study (abdominal and pelvic surgery): incidence of VTE significantly lower in patients with continued enoxaparin 30 days versus 1 week post-surgery (4.8% vs 12.0%, respectively; p=0.02)

FAME study (abdominal surgery): incidence of VTE in prolonged vs the short term prophylaxis 7.3% vs 16.3% - RR reduction 55% [15%-76%], p=0.012.
Major bleeding events similar (0.5% vs 1.8%)

After major cancer surgery (abdominal and pelvic cancer surgery), extended thromboprophylaxis for approximately 1 month is recommended following hospital discharge.

VTE primary prophylaxis in cancer

Recommendation 3.1. All patients with malignant disease undergoing major surgical intervention should be offered pharmacologic thromboprophylaxis with either unfractionated heparin (UFH) or LMWH unless contraindicated because of active bleeding, or high bleeding risk, or other contraindications (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.2. Prophylaxis should be commenced preoperatively (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.5. Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7 to 10 days. Extended prophylaxis with LMWH for up to 4 weeks post-operatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, or history of VTE, or with additional risk factors. In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis (Type: evidence based; Evidence quality: high; Strength of recommendation: moderate to strong).

VTE primary prophylaxis in cancer – hospitalized patients

Recommendation 1.1. Hospitalized patients who have active malignancy and acute medical illness or reduced mobility should be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.2. Hospitalized patients who have active malignancy without additional risk factors may be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.3. Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion, nor to patients undergoing stem-cell/bone marrow transplantation (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

VTE primary prophylaxis in cancer

<u>Primary thromboprophylaxis in outpatients</u>

The rate of symptomatic VTE was low in studies (< 4% - NNT 40-50), even in high-risk patients

Pre-emptive anticoagulation can prevent VTE → associated bleeding risk

→ routine LMWH prophylaxis in this setting is not recommended by clinical practice guidelines

VTE primary prophylaxis in cancer – ambulatory patients

Table II. Risk prediction scores for venous thromboembolism in patients with cancer.

	Khorana score [86]	CATS score [88]	PROTECHT score [89]	CONKO score [87]
Site of cancer				
Stomach, pancreas*	2	2	2	2[a]
Lung, lymphoma, gynecologic, genitourinary excluding prostate[†]	1	1	1	1[a]
Pre chemotherapy platelet count ≥ 350 x 10^9/L	1	1	1	1
Pre chemotherapy leukocyte count > 11 x 10^9/L	1	1	1	1
Haemoglobin level < 10 g/dL or use of red cell growth factors	1	1	1	1
Body mass index ≥ 35 kg/m²	1	1	1	
Soluble P-selectin ≥ 53.1 ng/mL		1		
D-Dimer ≥ 1.44 µg/mL		1		
Cisplatin or carboplatin-based chemotherapy			1	
Gemcitabine-based chemotherapy			1	
Karnofsky performance status < 80 %				1

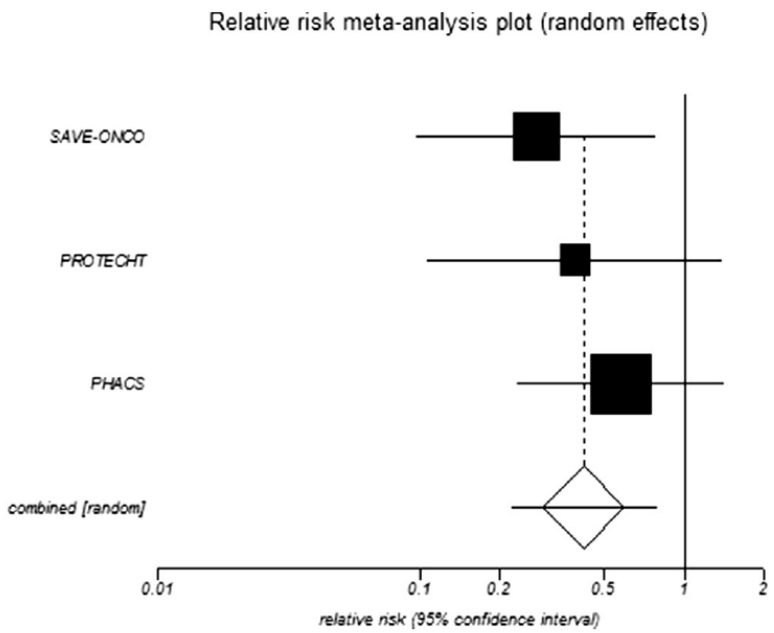
* In the CATS score, primary brain tumour is added as a very high-risk cancer site.
† In the CATS score, myeloma and cancer of the kidney are added as high-risk cancer sites.
[a] The CONKO score was originally developed in 312 patients with pancreatic cancer only.

Patients with a summary score of 0–2 are considered to be at low-to-intermediate risk for venous thromboembolism, while patients with a summary score of ≥ 3 are considered to be at high risk for venous thromboembolism.

Khorana: risk of VTE from < 0.8 % per 2.5 months within the low-risk group (0 points) to 6.7–7.1 % within the high risk-group (≥ 3 points).

Voigtlaeder M et al. Vasa 2018

Primary thromboprophylaxis



	Prophylaxis	Placebo Observation	Relative risk (95% CI)	
SAVE-ONCO	4/271	15/279	0.27 (0.10-0.78)	5.4% vs 1.4% (NNT = 25)
PROTECHT	3/70	5/45	0.39 (0.11-1.40)	11.1% vs 4.5% (NNT = 15)
PHACS	6/50	10/48	0.58 (0.23-1.41)	21% vs 12% (NNT = 12)
combined [random]			0.41 (0.22-0.78)	

primary thromboprophylaxis may be considered in carefully selected patients with a perceived high risk of developing VTE during the course of their anti-cancer treatment.

Khorana AA et al. Thromb Res 2017

Primary thromboprophylaxis

VTE RISK ASSESSMENT IN CANCER OUTPATIENTS

Khorana Predictive Model for Chemotherapy-Associated VTE[1]

Patient Characteristic	Risk Score
• Site of primary cancer	
▸ Very high risk (stomach, pancreas)	2
▸ High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
• Prechemotherapy platelet count 350 x 10^9/L or higher	1
• Hemoglobin level less than 10 g/dL or use of red cell growth factors	1
• Prechemotherapy leukocyte count higher than 11 x 10^9/L	1
• BMI 35 kg/m^2 or higher	1

Total Score	Risk Category	Risk of Symptomatic VTE[2]
0	Low	0.3–1.5%
1, 2	Intermediate	1.8–4.8%
3 or higher	High	6.7–12.9%

Khorana AA et al. Thromb Res 2017

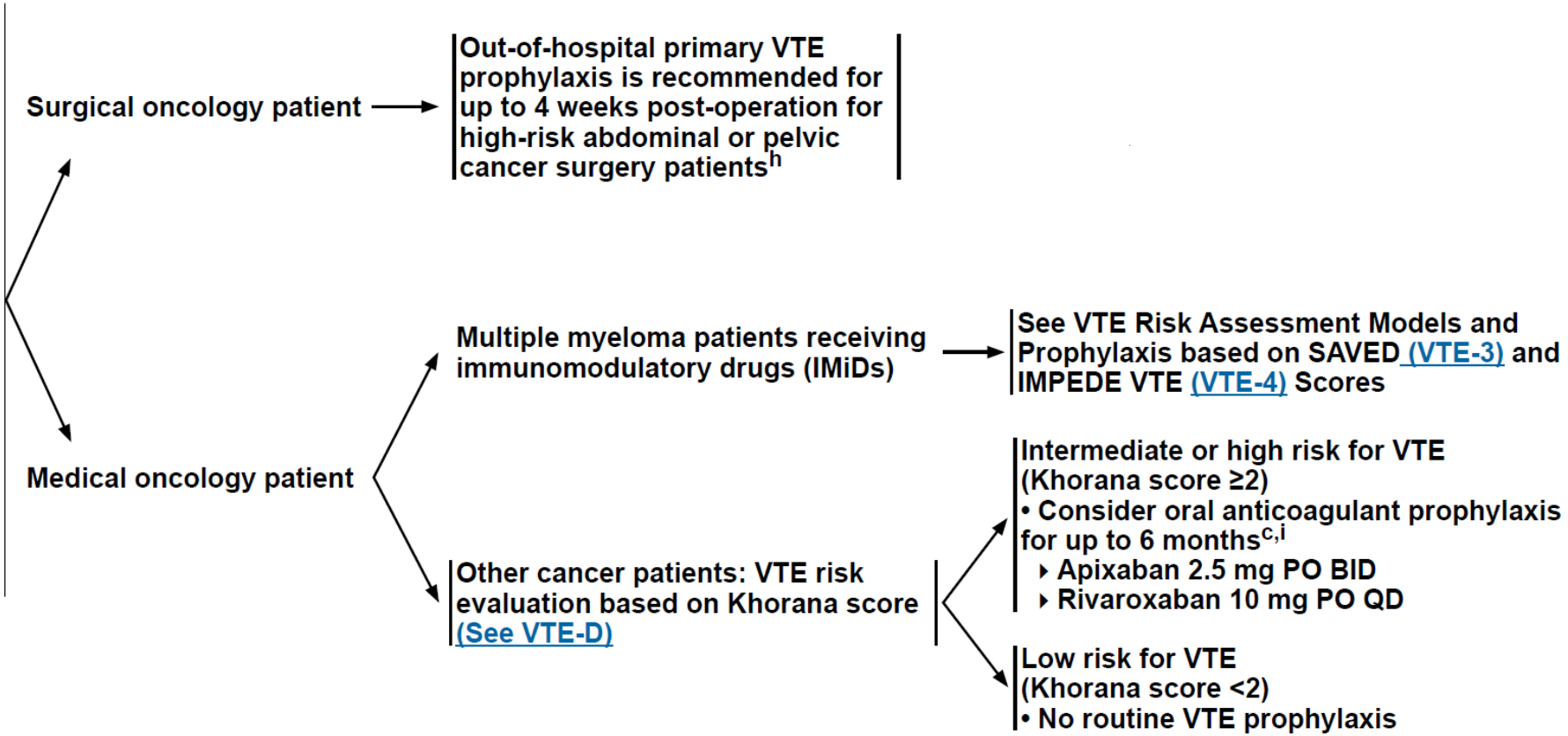
Primary thromboprophylaxis

Table 5 Summary of published trials for primary thromboprophylaxis in high-risk patients

Trial	VTE occurrence (%)	Major bleeding (%)	Clinically relevant non-major bleeding (%)	Mortality (%)
AVERT[76]	4.2 vs 10.2	3.5 vs 1.8	7.3 vs 5.5	12.2 vs 9.8
Apixaban vs placebo	Apixaban significantly reduced the rate of VTE compared to placebo. Major bleeding was higher in the intention-to-treat analysis. There was no difference in non-major bleeding			
CASSINI[77]	2.60 vs 6.41	1.98 vs 0.99	2.72 vs 1.98	20.0 vs 23.8
Rivaroxaban vs placebo	Rivaroxaban significantly reduced the rate of VTE compared to placebo during the on-treatment period. There was no difference in the rate of major or non-major bleeding			

Abbreviation: VTE, venous thromboembolism.

VTE prophylaxis following discharge and for ambulatory cancer patients



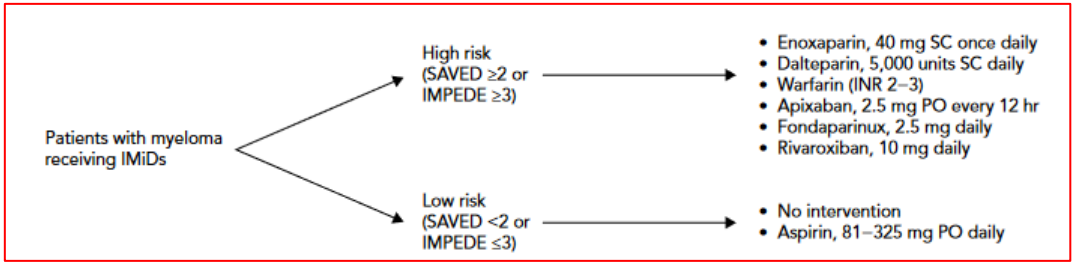
Prevenzione nel paziente con mieloma

Table 2. CAT Risk Assessment Models for Patients With MM Receiving IMiDs

IMPEDE VTE Score		SAVED Score	
IMiD therapy	+4	Surgery within 90 d	+2
BMI ≥25 kg/m^2	+1	Asian race	–3
Pelvic, hip, or femur fracture	+4	VTE history	+3
Erythropoiesis-stimulating agents	+1	Age ≥80 y	+1
Dexamethasone		Dexamethasone	
Low dose (≤160 mg/mo)	+2	Standard dose (120–160 mg/cycle)	+1
High dose (>160 mg/mo)	+4	High dose (>160 mg/cycle)	+2
Doxorubicin	+3		
Ethnicity/Race = Asian/Pacific Islander	–3		
History of VTE before MM diagnosis	+5		
Tunneled central line or central venous catheter	+2		
Existing thromboprophylaxis			
Therapeutic LMWH or warfarin	–4		
Existing thromboprophylaxis			
Prophylactic LMWH or aspirin	–3		

Abbreviations: BMI, body mass index; CAT, cancer-associated thrombosis; IMiD, immunomodulatory drug; LMWH, low-molecular-weight heparin; MM, multiple myeloma; VTE, venous thromboembolism.

Il rischio di trombosi tra i pazienti con MM trattati con farmaci immunomodulatori (IMiD) in monoterapia è di circa il 3-4% → fino al 26% con l'aggiunta di glucocorticoidi ad alte dosi, antracicline o eritropoietina.



Streiff MB, et al. NCCN Clinical Practice Guidelines in Oncology, Version 1.2022

Therapies for prophylaxis

Pharmacologic (anticoagulant) prophylaxis		
Hospitalized medical patients[b]	UFH	5,000 U every 8 hours[c]
	Dalteparin	5,000 U once daily
	Enoxaparin	40 mg once daily
	Fondaparinux[d]	2.5 mg once daily
Surgical patients[b]	UFH	5,000 U 2-4 hours preoperatively and every 8 hours[c] thereafter[e]
	Dalteparin	2,500 U 2-4 hours preoperatively[e] and 5,000 U once daily thereafter[f]
		Or 5,000 U 2-4 hours preoperatively[e] or 10-12 hours preoperatively and 5,000 U once daily thereafter[f]
	Enoxaparin	40 mg 2-4 hours preoperatively[e] or 10-12 hours preoperatively and 40 mg once daily thereafter[f]
	Fondaparinux[d]	2.5 mg once daily beginning 6-8 hours postoperatively
Outpatients[b]	Dalteparin[d,g]	5,000 U once daily
	Enoxaparin[d,g]	40 mg once daily
	Fondaparinux[d,h]	2.5 mg once daily
	Apixaban[d]	2.5 mg orally twice daily
	Rivaroxaban[d]	10 mg orally once daily

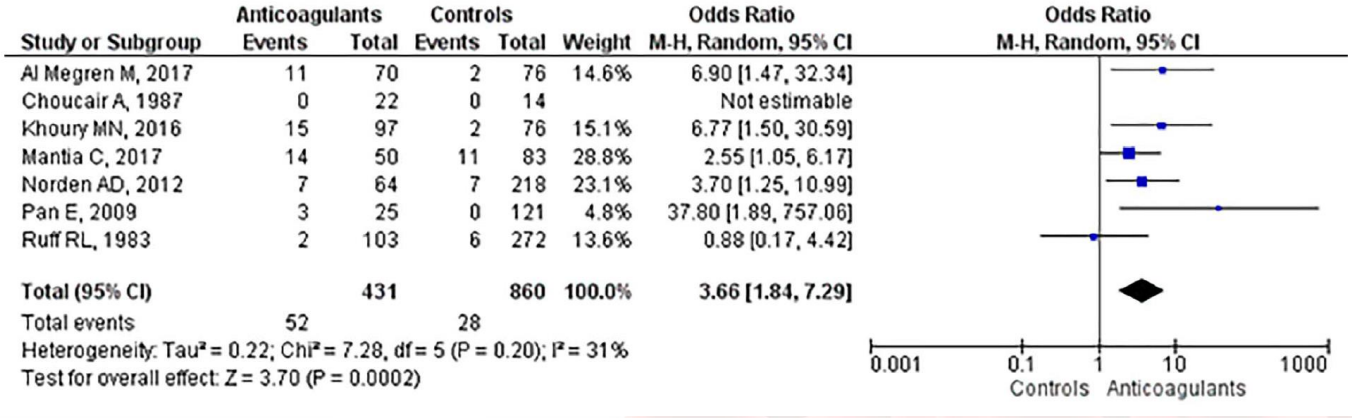
Controindications for anticoagulation

Patients for whom anticoagulation is of uncertain benefit
Patient receiving end-of-life/hospice care
Very limited life expectancy with no palliative or symptom reduction benefit
Asymptomatic thrombosis with concomitant high risk of serious bleeding
Patient characteristics and values
Preference or refusal
Nonadherence to dosing schedule, follow-up, or monitoring

- Particular issues on cancer associated thrombosis-

Neoplasia cerebrale

- Il rischio di TEV è elevato anche nei pazienti con malattia del SNC, con **un'incidenza del 20-30%**
- I tumori primitivi o metastatici del SNC sono associati ad un **alto rischio di emorragia intracranica spontanea**
- Alcuni studi hanno dimostrato che i livelli terapeutici di anticoagulazione con EBPM
    - Metastasi cerebrali: nessun aumento del rischio di emorragia intracranica
    - Tumore primitivo: aumento di 3 volte del rischio di emorragia intracranica



Study or Subgroup	Anticoagulants Events	Total	Controls Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Al Megren M, 2017	11	70	2	76	14.6%	6.90 [1.47, 32.34]
Choucair A, 1987	0	22	0	14		Not estimable
Khoury MN, 2016	15	97	2	76	15.1%	6.77 [1.50, 30.59]
Mantia C, 2017	14	50	11	83	28.8%	2.55 [1.05, 6.17]
Norden AD, 2012	7	64	7	218	23.1%	3.70 [1.25, 10.99]
Pan E, 2009	3	25	0	121	4.8%	37.80 [1.89, 757.06]
Ruff RL, 1983	2	103	6	272	13.6%	0.88 [0.17, 4.42]
Total (95% CI)		**431**		**860**	**100.0%**	**3.66 [1.84, 7.29]**
Total events	52		28			

Heterogeneity: Tau² = 0.22; Chi² = 7.28, df = 5 (P = 0.20); I² = 31%
Test for overall effect: Z = 3.70 (P = 0.0002)

Duong A. et al. J Oncol Pharm Practice 2020
Porfidia A. et al. Brain and Behavior 2020

Neoplasia cerebrale

1) Hokusai-VTE cancer → sottorappresentati (74 pazienti)
2) Select-D → sottorappresentati (3 pazienti)
3) Caravaggio → esclusi

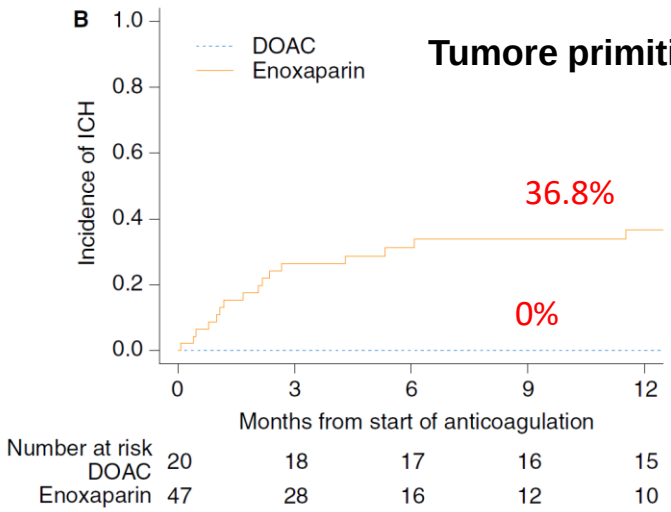
3 tumori primitivi – No emorragie

31 pazienti in Edoxaban → 2 (6.5%) emorragie maggiori
43 pazienti in Dalteparin → 4 (9.3%) emorragie maggiori

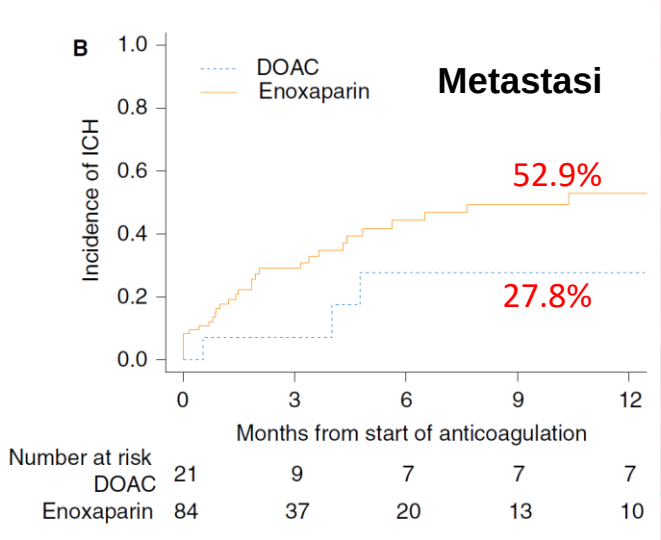
Duong A. et al. J Oncol Pharm Practice 2020

Neoplasia cerebrale

- Studio retrospettivo di coorte
- 67 pazienti con tumore primitivo (20 con DOACs 5 Rivaroxaban, 15 Apixaban)
- 105 pazienti con metastasi cerebrale (21 con DOACs 11 Rivaroxaban, 5 Apixaban, 5 Dabigatran)



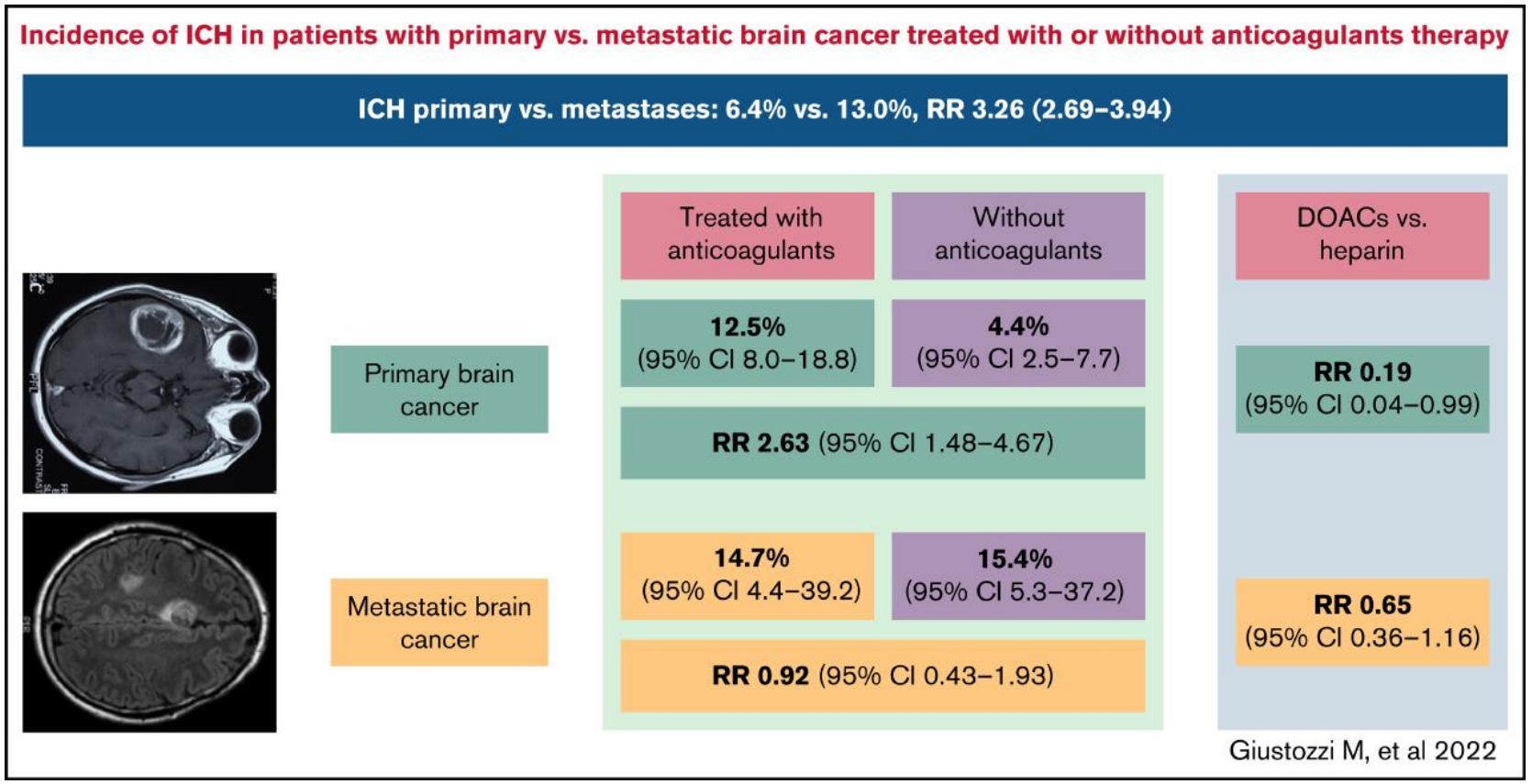
major ICH 0% DOACs vs. 0% vs. 18.2% EBPM p=0.049



major ICH 11.1% DOACs vs. 17.8% EBPM p=0.38

Carney BJ et al. JTH 2019

Neoplasia cerebrale

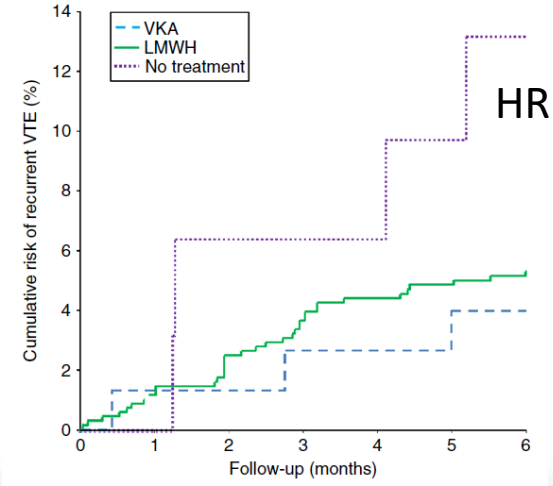


Giustozzi M. et al. Blood Advances 2022

Embolia polmonare incidentale

Table 2 Primary and secondary outcomes for total cohort and stratified by management

	Weight pooled risk in % (95% CI)				
Outcome	Total cohort	LMWH	VKA	Other	None
(A) Pooled outcomes after 6 months of follow-up and stratified by initial management					
Recurrent VTE	5.8 (3.7–8.3)	6.2 (3.5–9.6)	6.4 (2.2–12)	4.3 (3.3–12)	12 (4.7–23)
Major hemorrhage	4.7 (3.0–6.8)	3.9 (2.3–5.9)	13 (6.4–20)	6.4 (0.2–20)	6.4 (1.3–15)
Mortality	37 (28–47)	37 (29–44)	28 (18–40)	58 (38–77)	47 (28–66)



HR 2.6 [0.91–7.3]

van der Hulle et al. JTH 2016

Recurrent incidence rate in subsegmental incidental PE vs centrally located 7.8% (2.8–14.9%) and 5.5% (95% CI 2.9–8.8%), HR 1.3 (0.57–3.0)

Supplementary Table 9 **Management of pulmonary embolism in specific clinical situations**

Clinical setting	Suggested management[a]	Comments
Subsegmental PE	Single subsegmental PE in an outpatient without cancer and without proximal DVT: • Clinical surveillance. Single subsegmental PE in a hospitalized patient, a patient with cancer, or if associated with confirmed proximal DVT: • Anticoagulant treatment. Multiple subsegmental PE: • Anticoagulant treatment.	• Poor interobserver agreement for the diagnosis of subsegmental PE; diagnosis to be confirmed by an experienced thoracic radiologist. • Suggestion based on indirect evidence, only limited data available.
Incidental PE	If single subsegmental PE: • Proceed as above. In all other cases: • Anticoagulant treatment.	• Suggestion based on retrospective cohort data.

CAT → incidentali e subsegmentarie si anticoagulano

ESC 2020

Trombosi venose distali isolate

ORIGINAL ARTICLE

Clinical course of isolated distal deep vein thrombosis in patients with active cancer: a multicenter cohort study

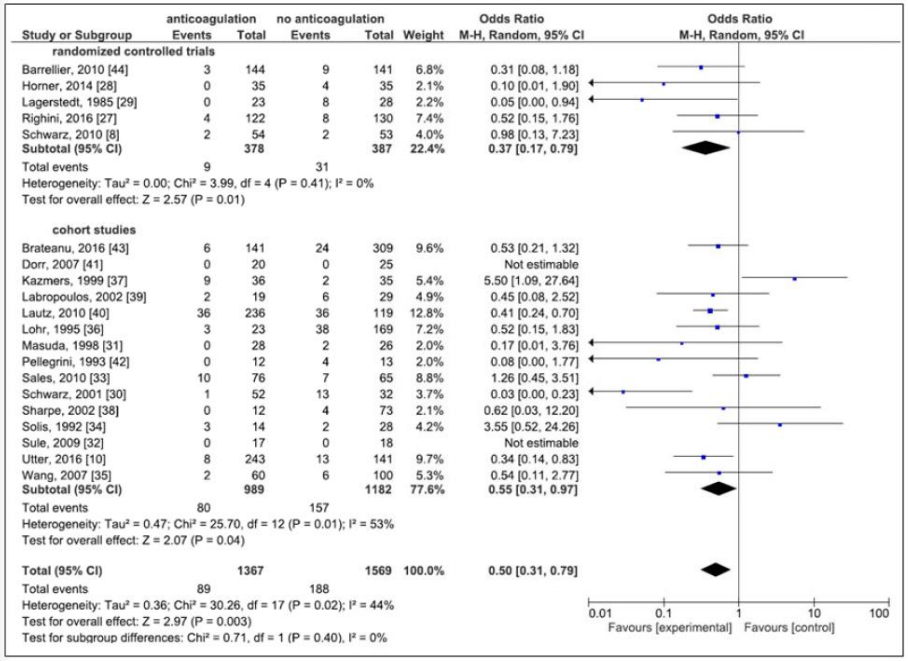
High incidence rate of recurrent VTE after isolated distal DVT (13.2 events per 100 patient-years).

Cancer patients with IDDVT have a high risk of VTE recurrence.

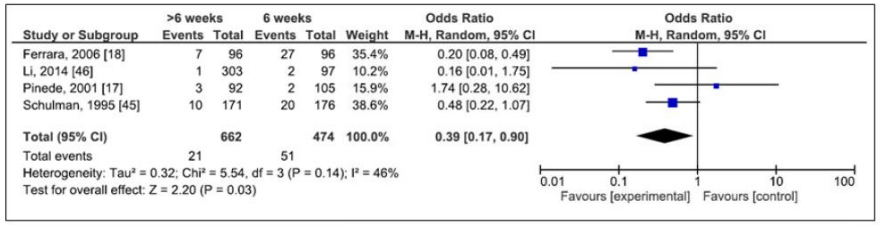
Recurrent VTE after treatment withdrawal was significantly higher in patients treated for ≤ 6 weeks (HR 4.42 [1.75-11.15]) than patients treated for > 3 months.

Dentali F. et al. JTH 2017

Trombosi venosa distale isolata



Recurrent VTE in patients receiving anticoagulation (both therapeutic and prophylactic doses) or no anticoagulation



Recurrent venous thromboembolism in patients receiving anticoagulant treatment > 6 weeks vs. 6 weeks.

Franco L. et al. JTH 2017

Trombosi venosa distale isolata

AMERICAN COLLEGE OF CHEST PHYSICIANS
The Global Leader in Clinical Chest Medicine

Recommendation: In patients with acute isolated distal DVT of the leg and i) without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (Grade 2C), and ii) with severe symptoms or risk factor for extension, we suggest anticoagulation over serial imaging of the deep veins (Grade 2C).

Additional Comments

The following factors may favor choosing anticoagulation:

1. D-dimer is positive (particularly when markedly so without an alternative reason)
2. Thrombosis is extensive (eg, > 5 cm in length, involves multiple veins, > 7 mm in maximum diameter)
3. Thrombosis is close to the proximal veins
4. There is no reversible provoking factor for DVT
5. The patient has active cancer
6. The patient has a history of VTE
7. The patient has inpatient status
8. The patient has COVID-19
9. The patient is highly symptomatic
10. The patient prefers to avoid repeat imaging

The following factors may favor choosing serial imaging:

1. Thrombosis is confined to the muscular veins of the calf (ie, soleus, gastrocnemius)
2. There is a high or moderate risk for bleeding
3. The patient prefers to avoid anticoagulation

active cancer is risk factor for extension of distal DVT and for VTE recurrence

VTE recurrence

Recurrent VTE despite anticoagulation

Roule out non-compliance – mechanical vein compression -HIT

- Full-dose LMWH therapy
  - Increase dosage by 20-25% (consider anti-Xa activity) – switch to DOACs
    - **Consider vena cava filter**
- Reduced LMWH regimen
  - LMWH full dose therapy
- VKA therapeutic INR
  - Permanently switch to LMWH or DOACs
- VKA sub-therapeutic INR
  - LMWH and target INR
- DOAC
  - Switch LMWH/Fondaparinux

Trombocitopenia

- Sostituzione/infiltrazione del midollo osseo
- Effetto collaterale della chemioterapia
- Sepsi/infezioni

- Rischio di sanguinamento maggiore inversamente correlato alla conta piastrinica e aumenta in modo sproporzionato a valori piastrinici <25 × 10 9 /L (tasso stimato ~15%/Y vs. ~0,07%/y in una popolazione generale e relativamente sana).

- Neoplasie ematologiche aumento del sanguinamento di grado WHO ≥2 con conta piastrinica <80 × 109/L → No relazione tra l'aumento del sanguinamento e la diminuzione della conta piastrinica al di sotto di questa soglia

- Altri studi non hanno mostrato una chiara relazione inversa tra conta piastrinica comprese tra 10 e 50 × 109/L e sanguinamento

Falanga A et al Hemasphere 2022

Trombocitopenia

Grades of Thrombocytopenia

	Grade 1	Grade 2	Grade 3	Grade 4
Platelet range ($\times 10^9$/L)	<100 to 75	<75 to 50	<50 to 25	<25

Platelets ($\times 10^9$/L)	Venous thromboembolism	Atrial fibrillation	Mechanical heart valve
100			
Grade 1	Continue therapeutic-dose anticoagulation • If TP stable *: continue same anticoagulation class • If TP not stable *: use LMWH		
75			
Grade 2			
50			

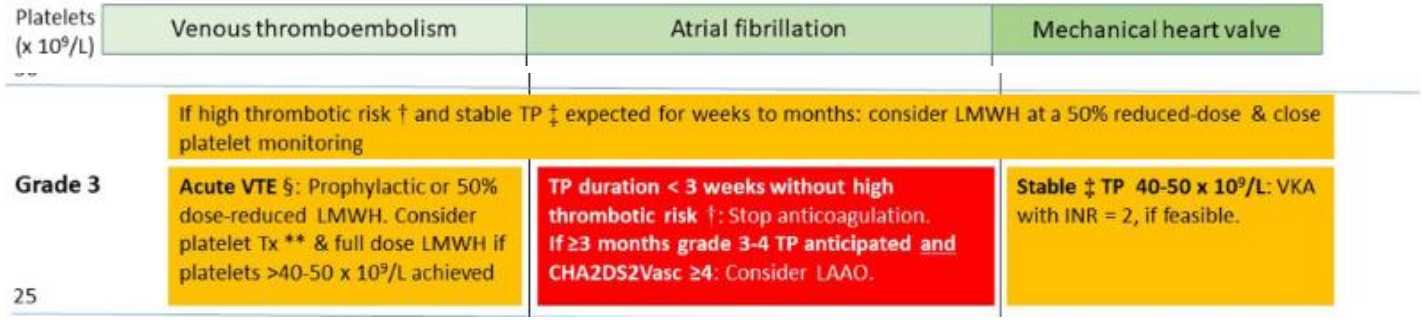
Stable grade 1–2 TP is defined as platelet counts, which are <u>not expected to decrease to grade 3–4 TP in the coming days to weeks.</u>

Falanga A et al Hemasphere 2022

Trombocitopenia

Grades of Thrombocytopenia

	Grade 1	Grade 2	Grade 3	Grade 4
Platelet range ($\times 10^9$/L)	<100 to 75	<75 to 50	<50 to 25	<25



†AF with arterial thromboembolism in the past 3 mo; AF with CHA2DS2-VASc ≥ 6; VTE in past 3 mo; mechanical heart valves where full-dose anticoagulation was not possible.
‡Stable grade 3 TP defined as platelet counts, which are not expected to decrease to grade 4 TP in the coming days to weeks.

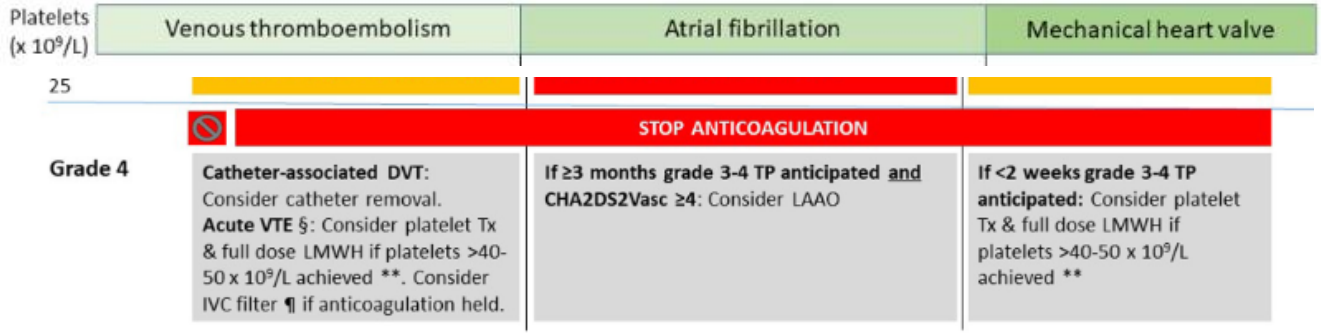
** Transfusion strategy can be used for a maximum of 14 d

Falanga A et al Hemasphere 2022

Trombocitopenia

Grades of Thrombocytopenia

	Grade 1	Grade 2	Grade 3	Grade 4
Platelet range ($\times 10^9$/L)	<100 to 75	<75 to 50	<50 to 25	<25



†AF with arterial thromboembolism in the past 3 mo; AF with CHA2DS2-VASc ≥ 6; VTE in past 3 mo; mechanical heart valves where full-dose anticoagulation was not possible.

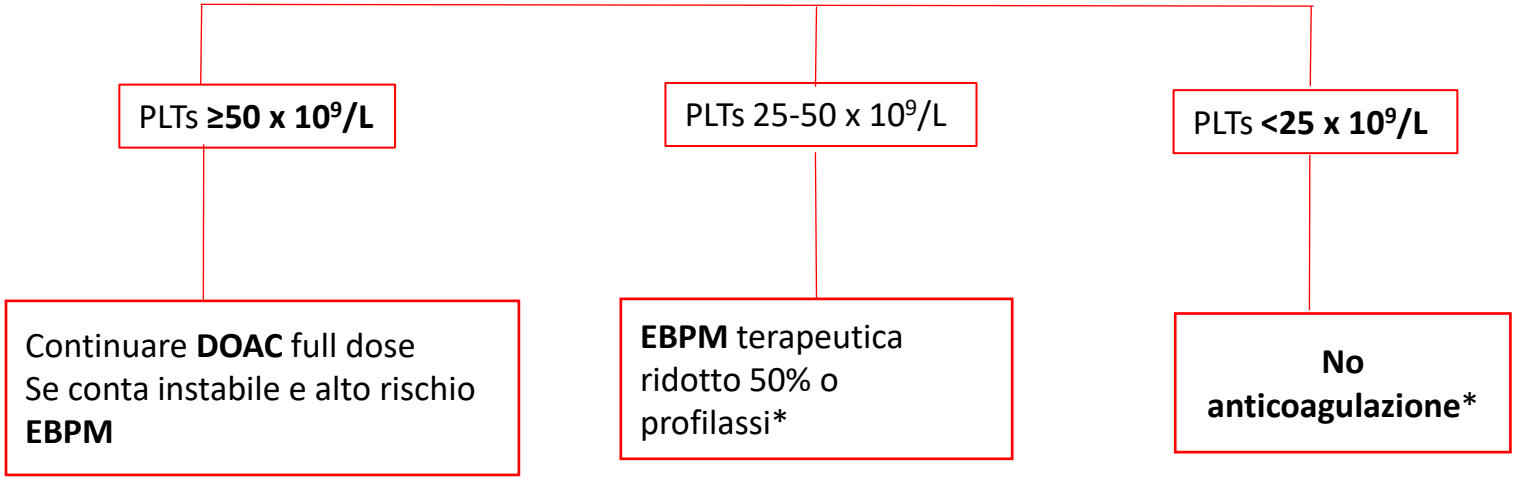
‡Stable grade 3 TP defined as platelet counts, which are not expected to decrease to grade 4 TP in the coming days to weeks.

** Transfusion strategy can be used for a maximum of 14 d

Falanga A et al Hemasphere 2022

Trombocitopenia e DOAC

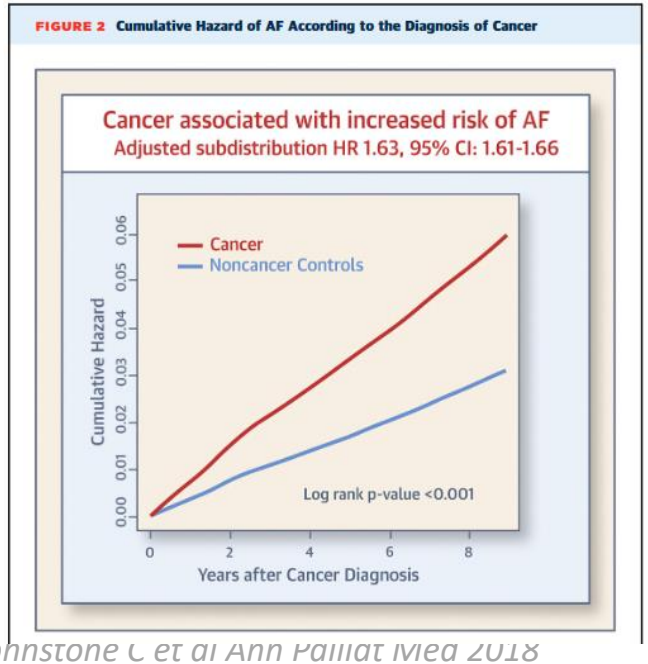
1) Hokusai-VTE cancer → esclusi se conta piastrinica < 50,000/mL
2) Select-D → esclusi se conta piastrinica < 100,000/mL
3) Caravaggio → esclusi se conta piastrinica ≤ 75,000/mL

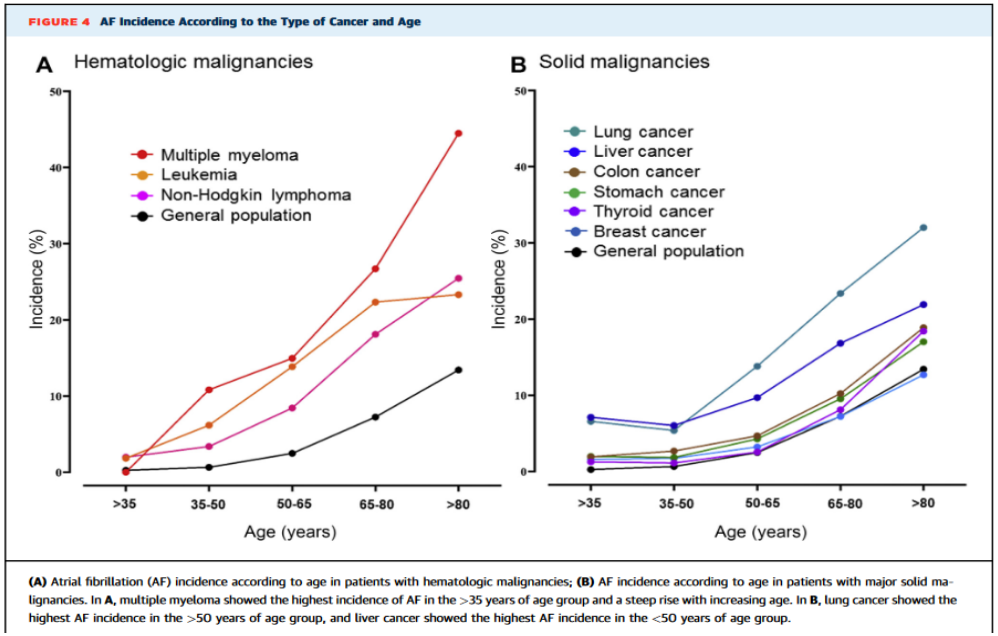


*Se rischio trombotico molto alto → EBPM full dose e aumentare conta piastrinica con trasfusione o TPO-mimetici

Epidemiologia della FA associata a cancro

816,811 pazienti con nuova diagnosi di cancro da registro koreano 2009- 2016 vs. age- and sex-matched controlli senza cancro.
Median follow-up 4.5 anni

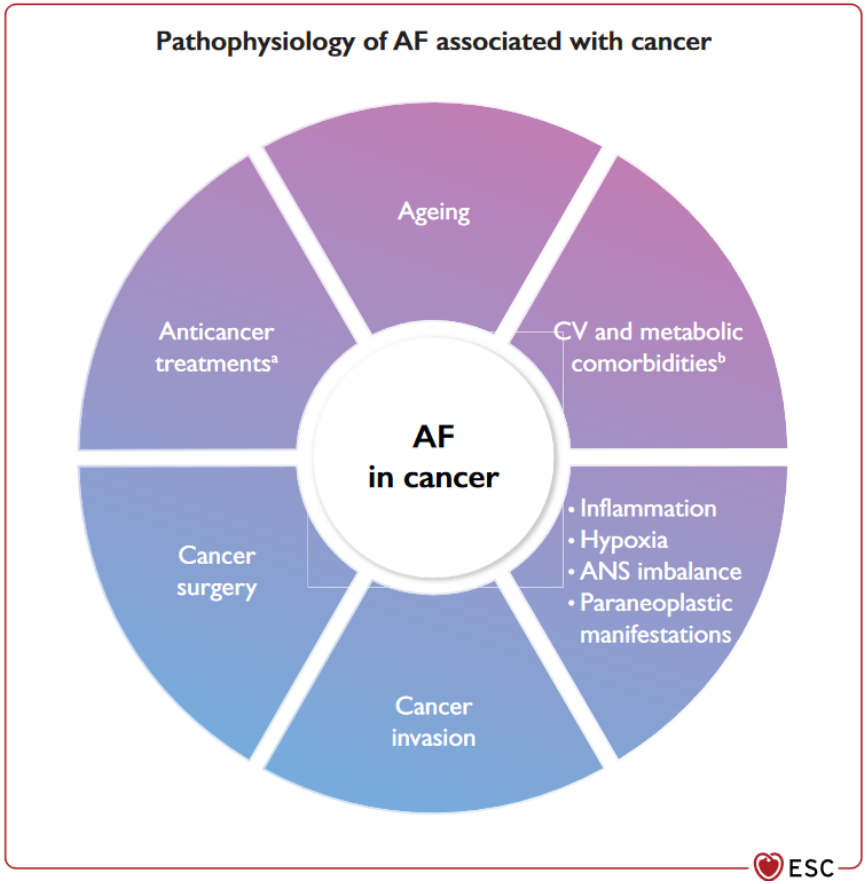




Mieloma multiplo (aHR: 3.34; 95% CI: 2.98 to 3.75)
K polmone (aHR: 2.69; 95% CI: 2.45 to 2.95)

Johnstone C et al Ann Palliat Med 2018
Green D et al Sem Thromb Haemost 2007

Fibrillazione atriale e cancro



Fattori di rischio per FA nel cancro:

- ✓ Stato infiammatorio di per se
- ✓ Chirurgia
- ✓ Radioterapia
- ✓ Terapia oncologica (agenti alchilanti, antracicline, Immune Checkpoint Inhibitors, Bruton Tyrosine Kinase Inhibitors)

Madnick DL, Current Cardiology Reports 2022
Lyon AR. et al. ESC 2022

Fibrillazione atriale e cancro

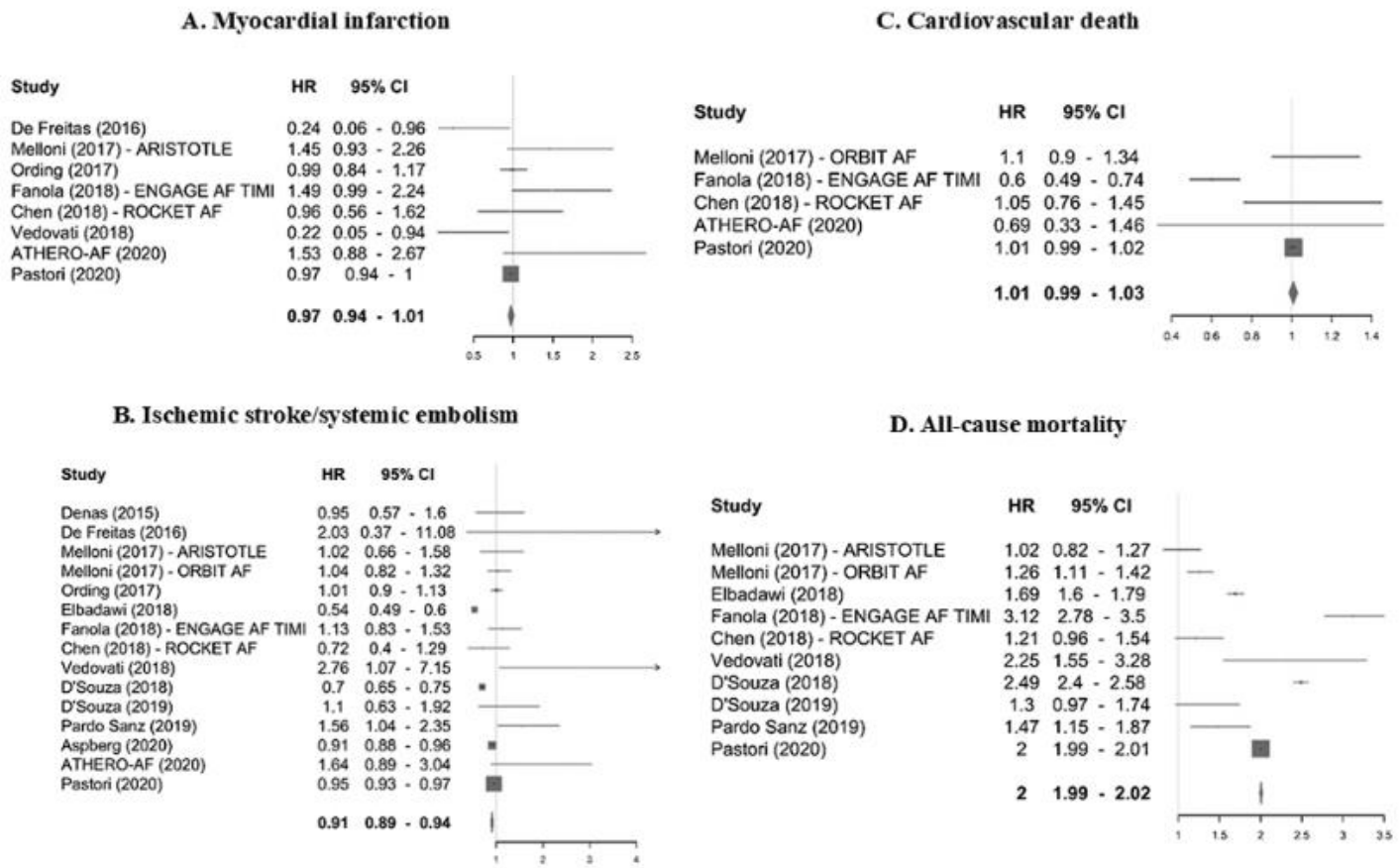


Fig. 3 Forest plots for each cardiovascular endpoint

Pastori D. et al Internal and Emergency Med 2023

Fibrillazione atriale e cancro

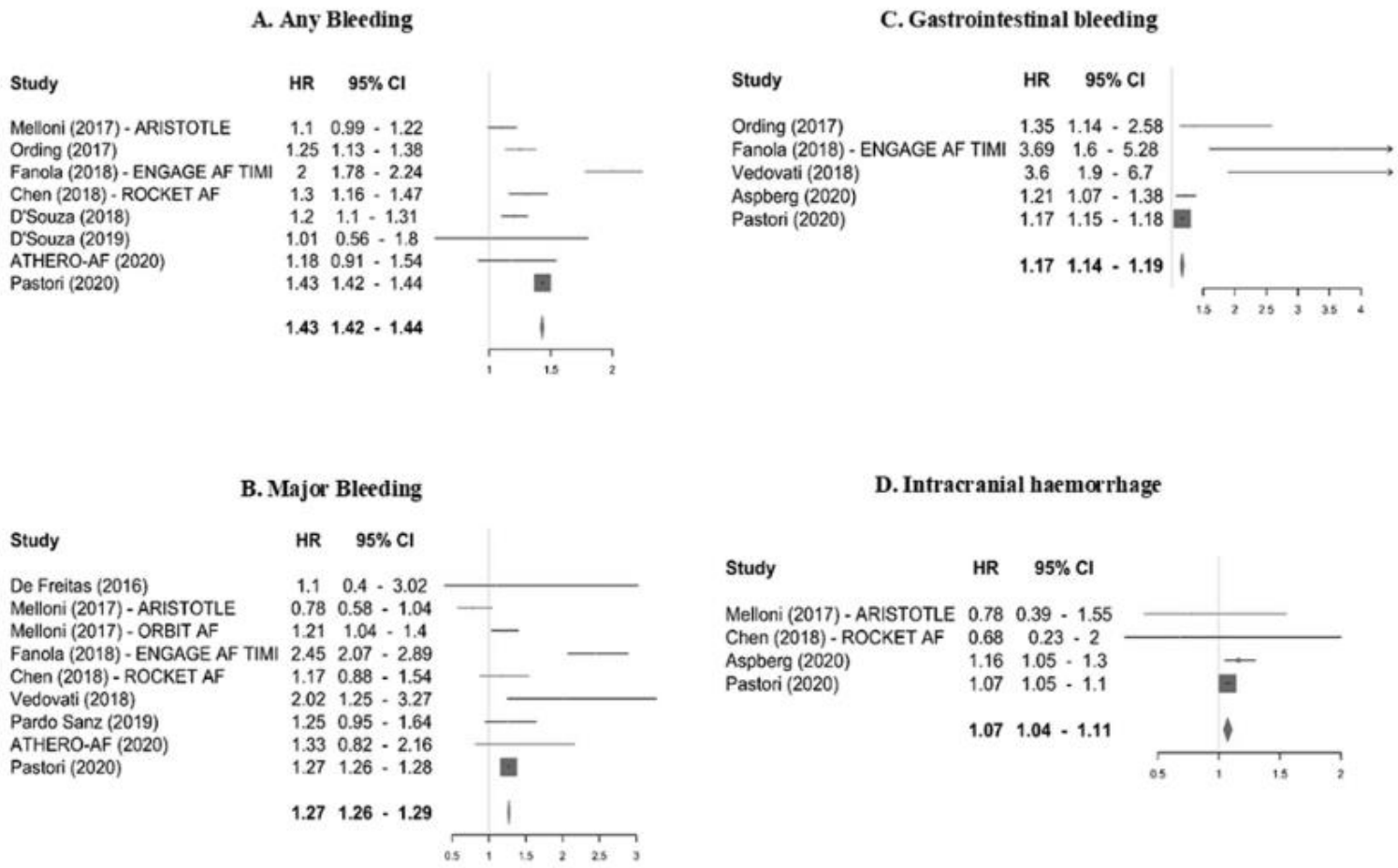
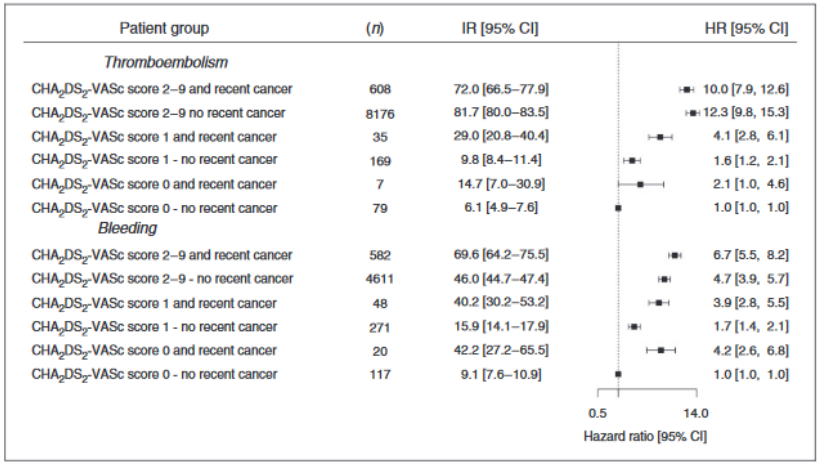


Fig. 2 Forest plots for each bleeding endpoint

Pastori D. et al Internal and Emergency Med 2023

Profilassi per FA nel cancro è challenging



Patient group	(*n*)	IR [95% CI]	HR [95% CI]
Thromboembolism			
CHA_2DS_2-VASc score 2–9 and recent cancer	608	72.0 [66.5–77.9]	10.0 [7.9, 12.6]
CHA_2DS_2-VASc score 2–9 no recent cancer	8176	81.7 [80.0–83.5]	12.3 [9.8, 15.3]
CHA_2DS_2-VASc score 1 and recent cancer	35	29.0 [20.8–40.4]	4.1 [2.8, 6.1]
CHA_2DS_2-VASc score 1 - no recent cancer	169	9.8 [8.4–11.4]	1.6 [1.2, 2.1]
CHA_2DS_2-VASc score 0 and recent cancer	7	14.7 [7.0–30.9]	2.1 [1.0, 4.6]
CHA_2DS_2-VASc score 0 - no recent cancer	79	6.1 [4.9–7.6]	1.0 [1.0, 1.0]
Bleeding			
CHA_2DS_2-VASc score 2–9 and recent cancer	582	69.6 [64.2–75.5]	6.7 [5.5, 8.2]
CHA_2DS_2-VASc score 2–9 - no recent cancer	4611	46.0 [44.7–47.4]	4.7 [3.9, 5.7]
CHA_2DS_2-VASc score 1 and recent cancer	48	40.2 [30.2–53.2]	3.9 [2.8, 5.5]
CHA_2DS_2-VASc score 1 - no recent cancer	271	15.9 [14.1–17.9]	1.7 [1.4, 2.1]
CHA_2DS_2-VASc score 0 and recent cancer	20	42.2 [27.2–65.5]	4.2 [2.6, 6.8]
CHA_2DS_2-VASc score 0 - no recent cancer	117	9.1 [7.6–10.9]	1.0 [1.0, 1.0]

Figure 2. Incidence rates per 1000 person years and hazard ratios of thromboembolism and bleeding according to CHA_2DS_2-VASc score and recent cancer. IR: incidence rate per 1000 person years; HR: hazard ratio.

- ✓ Aumento del rischio trombotico
- ✓ Aumento del rischio emorragico
- ✓ Interazioni farmacologiche con farmaci antineoplastici
- ✓ Trombocitopenia

Rischi differenti nei pazienti oncologici rispetto ai pazienti non oncologici, nonostante lo stesso punteggio CHA2DS2-VASc → **dovrebbe essere usato con cautela nei pazienti con cancro**

HAS-BLED non tiene in considerazioni i fattori specifici di rischio emorragico nel cancro

D'Souza M et al Eur J Prev Cardiol 2018

DOACs e FA

Sottoanalisi ARISTOTELE (18,183 pazienti con FA randomizzati a apixaban vs warfarin)
1236 (6%) partecipanti con storia di cancro attivo o remoto

Table 4b Effects of Apixaban Versus Warfarin in Patients with Atrial Fibrillation and Cancer (Active and Remote) and No Cancer

	Active Cancer			Remote Cancer			No Cancer			
	Event (Rate*)			Event (Rate*)			Event (Rate*)			
	Apixaban (n = 76)	Warfarin (n = 81)	HR (95% CI)	Apixaban (n = 539)	Warfarin (n = 540)	HR (95% CI)	Apixaban (n = 8493)	Warfarin (n = 8454)	HR (95% CI)	*P* Value†
Ischemic outcomes										
Stroke or SE	0 (0)	5 (3.8)	NA	15 (1.5)	9 (0.9)	1.71 (0.75-3.90)	196 (1.3)	251 (1.6)	0.77 (0.64-0.93)	.1852
Death from any cause	5 (3.7)	11 (8.1)	0.45 (0.16-1.29)	49 (4.9)	31 (3.0)	1.63 (1.04-2.56)	548 (3.4)	626 (4.0)	0.87 (0.77-0.97)	.0127
Ischemic stroke	0 (0)	3 (2.3)	NA	14 (1.4)	6 (0.6)	2.39 (0.92-6.22)	147 (0.9)	166 (1.1)	0.88 (0.70-1.10)	.1348
MI	0 (0)	1 (0.8)	NA	12 (1.2)	11 (1.1)	1.12 (0.49-2.54)	78 (0.5)	90 (0.6)	0.86 (0.63-1.16)	.8371
PE/DVT	0 (0)	1 (0.8)	NA	3 (0.3)	3 (0.3)	1.02 (0.21-5.07)	27 (0.2)	33 (0.2)	0.81 (0.49-1.35)	.9635
Bleeding outcomes										
ISTH major bleeding	1 (0.8)	5 (4.5)	0.19 (0.02-1.59)	23 (2.7)	27 (3.1)	0.87 (0.50-1.52)	303 (2.1)	430 (3.1)	0.69 (0.59-0.80)	.3485
Major or CRNM bleeding	6 (5.2)	10 (9.5)	0.56 (0.20-1.54)	47 (5.6)	57 (6.6)	0.84 (0.57-1.24)	560 (4.0)	810 (5.9)	0.67 (0.60-0.75)	.507
Any bleeding	27 (31.4)	30 (34.9)	0.93 (0.55-1.56)	177 (25.9)	215 (31.8)	0.82 (0.67-0.99)	2149 (17.6)	2815 (25.4)	0.71 (0.67-0.75)	.2412
Intracranial bleeding	0 (0)	2 (1.8)	NA	0 (0)	7 (0.8)	0 (0-infinity)	52 (0.4)	113 (0.8)	0.45 (0.32-0.63)	.9991
Net composite end point										
Composite efficacy end point‡	5 (3.7)	16 (12.1)	0.30 (0.11-0.83)	69 (7.1)	49 (4.8)	1.46 (1.01-2.10)	734 (4.7)	841 (5.4)	0.86 (0.78-0.95)	.0028
Composite end point§	6 (4.4)	18 (13.9)	0.32 (0.13-0.81)	87 (9.1)	71 (7.2)	1.26 (0.92-1.73)	948 (6.0)	1124 (7.3)	0.83 (0.76-0.90)	.0048

- Sicurezza ed efficacia di apixaban nel trial originale confermata nei pazienti con cancro attivo e remoto
- Aumento del beneficio netto (ictus/embolia sistemica, infarto del miocardio e morte) nel cancro attivo vs. non cancro con apixaban

Melloni C. et al Am J Med 2017

DOACs e FA

Sottoanalisi ENGAGE AF-TIMI 48 (21 105 pazienti con FA randomizzati a edoxaban vs. warfarin)
1153 pazienti (5.5%) hanno sviluppato neoplasia (recidiva o nuova diagnosi nel follow-up)

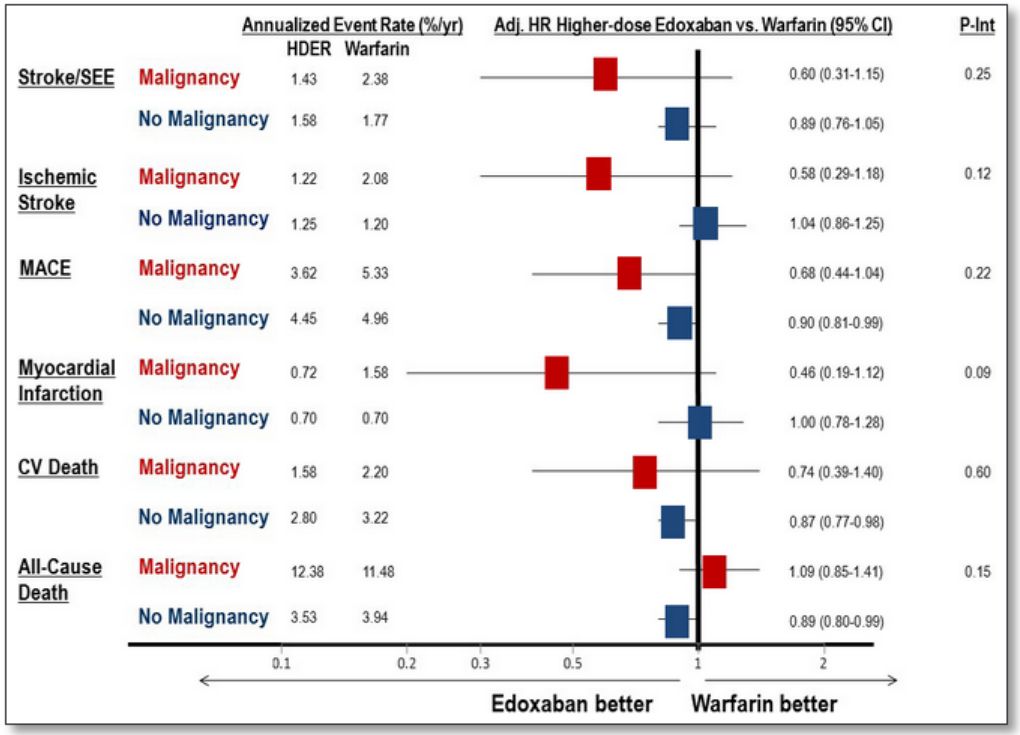


Figure 3 Efficacy end points by malignancy status in the higher-dose edoxaban regimen vs warfarin

Non differenza statisticamente significativa per edoxaban vs. warfarin nell'outcome di efficacia se presenza di neoplasia

Edoxaban HR 0.60 [95% CI, 0.31–1.15] per neoplasia vs. HR 0.89 [95% CI, 0.76–1.05]senza neoplasia

significativa interazione tra trattamento ed end point ischemico composito (ictus ischemico/embolia sistemica/infarto del miocardio) con maggiore efficacia di edoxaban full dose vs. warfarin nei pazienti con neoplasia (**HR 0.54, 95%CI 0.31 -0.93**)

Fanola Cl et al J Am Heart Ass 2018

DOACs e FA

Sottoanalisi ENGAGE AF-TIMI 48 (21 105 pazienti con FA randomizzati a edoxaban vs. warfarin)
1153 pazienti (5.5%) hanno sviluppato neoplasi (recidiva o nuova diagnosi nel follow-up)

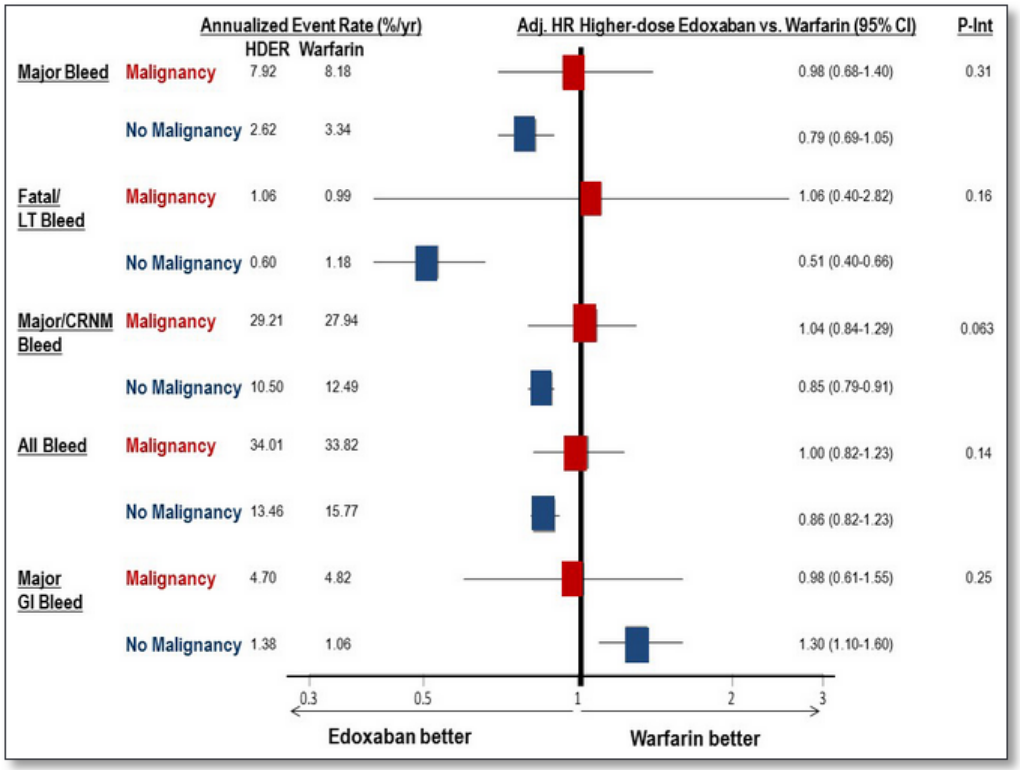


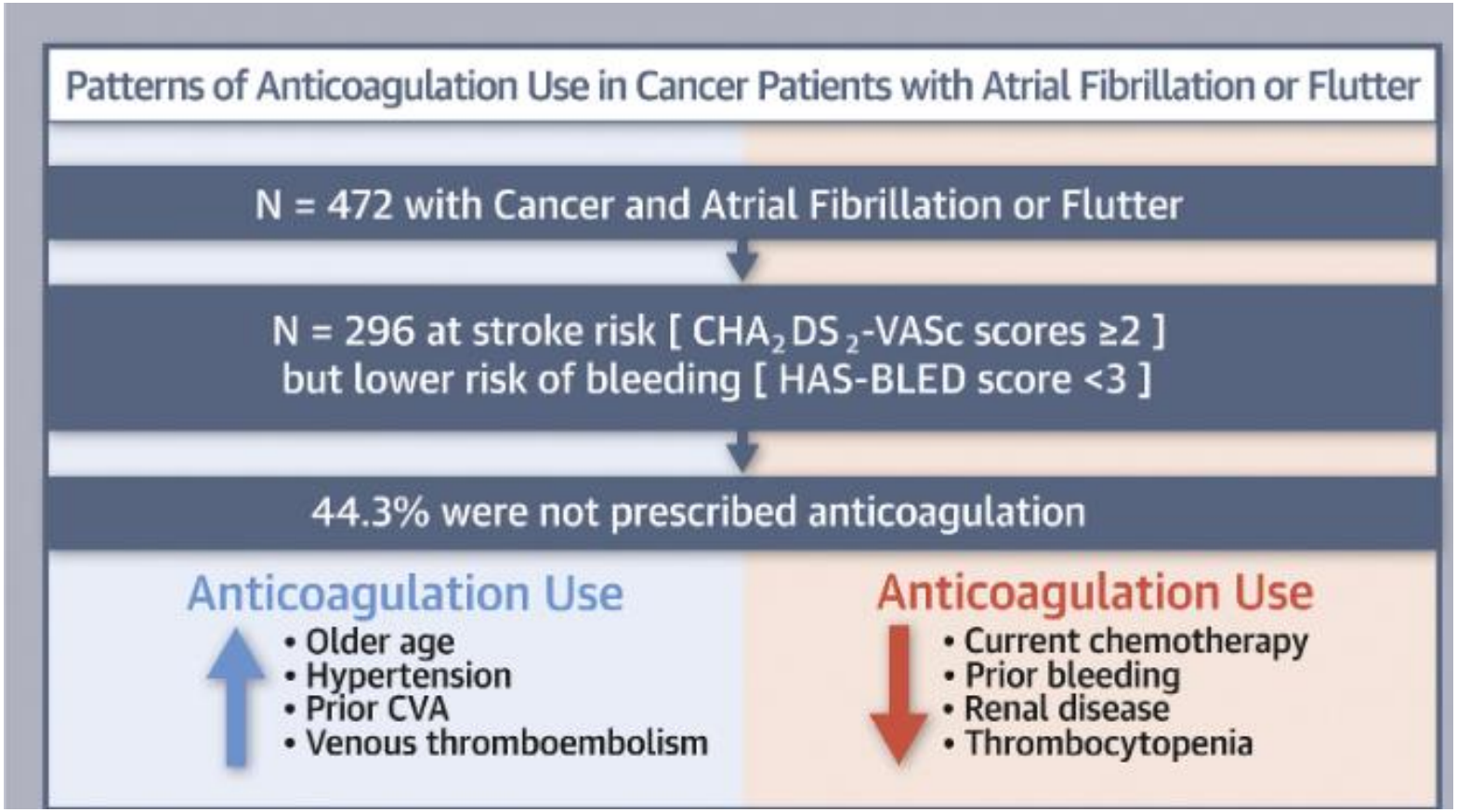
Figure 5 Safety end points by malignancy status in the higher-dose edoxaban regimen (HDER) vs

Non differenza statisticamente significativa per edoxaban vs. warfarin nell'outcome di sicurezza se presenza di neoplasia

Edoxaban HR 0.98 [95% CI, 0.69–1.40] per neoplasia vs. HR 0.79 [95% CI, 0.69–1.05] senza neoplasia

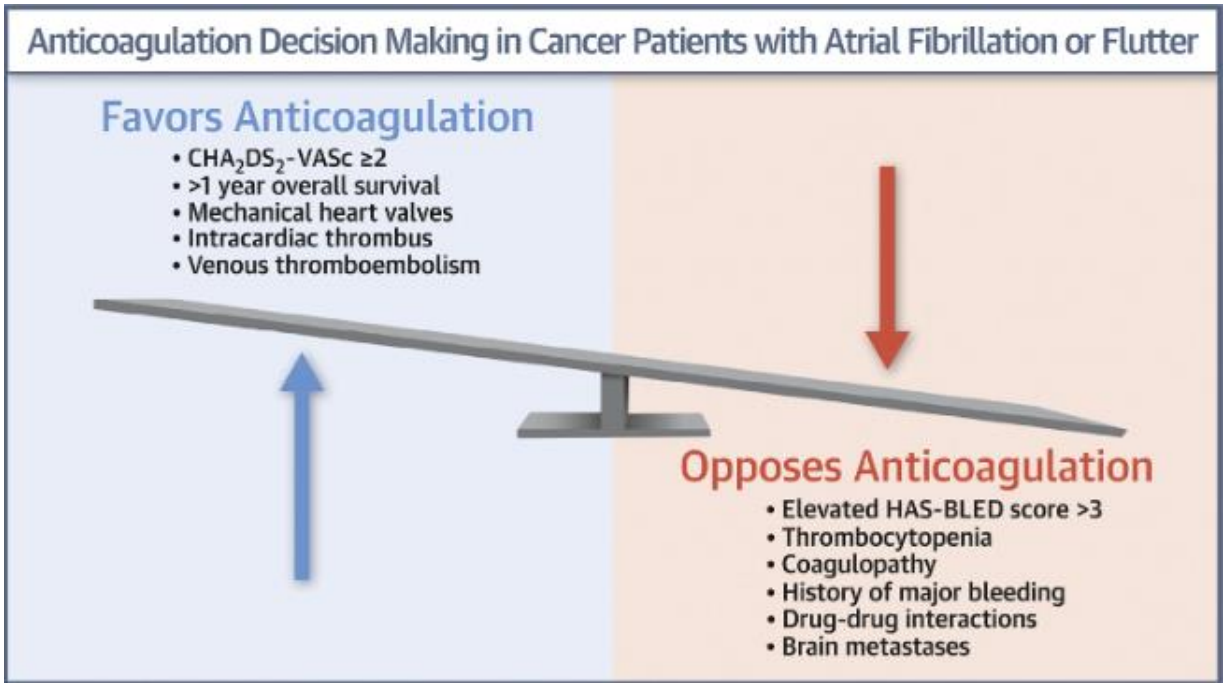
Fanola Cl et al J Am Heart Ass 2018

Real word



Fradley MG, et al JACC CardioOncol 2020

Possibile strategia



LA collaborazione multidisciplinare tra oncologi, cardiologi ed esperti di trombosi è essenziale nell'attuazione di strategie terapeutiche sicure ed efficaci per questi pazienti.

Fradley MG, et al JACC CardioOncol 2020

ESC Guidelines

1) CHA2 DS2 -VASc score should be considered for risk stratification for stroke/systemic thromboembolism taking into account that it may underestimate the actual thromboembolic risk.

2) Long-term anticoagulation is recommended for stroke/systemic thromboembolism prevention in patients with cancer with AF and a CHA2 DS2-VASc score ≥2 (men) or ≥3 (women) as per the 2020 ESC Guidelines

3) Long-term anticoagulation should be considered for stroke/systemic thromboembolism prevention in patients with cancer with AF and a CHA2 DS2-VASc score = 1 (men) or = 2 (women) as per the 2020 ESC Guidelines

4) **Patients with cancer, AF, and CHA2 DS2-VASc score 0 (men) or 1 (women) may have a higher thrombotic risk than patients without cancer and may be considered for therapeutic anticoagulation after consideration of the bleeding risk.**

Lyon AR. et al. ESC 2022

ESC Guidelines

5) NOAC should be considered for stroke prevention in preference to LMWH and VKA (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis) in patients without a high bleeding risk, significant drug–drug interactions, or severe renal dysfunction

6) LMWH should be considered in patients with active cancer and AF who are not suitable for NOAC

7) Heart rate control strategy, preferably with beta-blockers, should be considered in patients who develop well-tolerated AF while they are receiving active cancer treatment

Lyon AR. et al. ESC 2022

Strategie non farmacologiche per FA

Nei pazienti oncologici con rischio emorragico proibitivo o interazioni farmacologiche significative, la chiusura dell'auricola atriale può essere un'opzione alternativa. Tuttavia, tuttavia è ancora necessaria l'anticoagulazione e la terapia antipiastrinica periodo post-procedurale per prevenire la trombosi durante l'endotelizzazione.

NB Rischio di trombosi correlato al dispositivo potrebbe essere potenzialmente aumentato in questa popolazione con ipercoagulabilità.

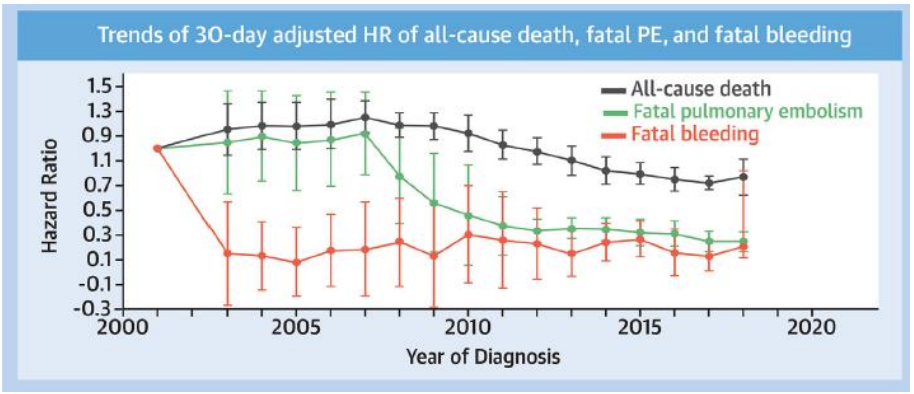
LAA occlusion may be considered for stroke prevention in patients with cancer with AF and contraindications for long-term anticoagulation with a life expectancy >12 months.[273,539]	IIb	C

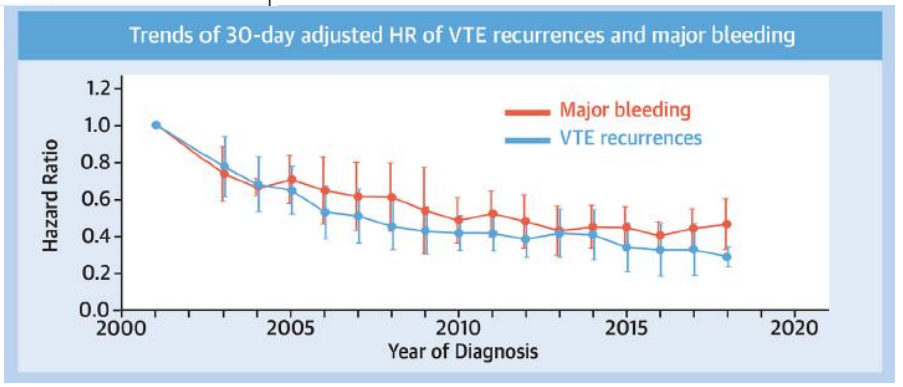
Fanola Cl et al J Am Heart Ass 2018
Lyon AR. et al. ESC 2022

What's new? – Acute anticoagulant treatment

TABLE 4 Thirty-Day Outcomes

	2001-2005	2006-2010	2011-2015	2016-2020	*P* Trend
All patients	3,068	4,266	4,864	5,073	
PE recurrences	50 (1.6)	48 (1.1)	44 (0.9)	35 (0.7)	<0.01
DVT recurrences	45 (1.5)	34 (0.8)	43 (0.9)	23 (0.5)	<0.01
VTE recurrences	95 (3.1)	81 (1.9)	86 (1.8)	57 (1.1)	<0.01
Major bleeding	95 (3.1)	114 (2.7)	92 (1.9)	113 (2.2)	<0.01
Gastrointestinal	43 (1.4)	47 (1.1)	48 (1.0)	44 (0.9)	0.01
Intracranial	11 (0.4)	9 (0.2)	6 (0.1)	20 (0.4)	0.59
Genitourinary	15 (0.5)	16 (0.4)	6 (0.1)	8 (0.2)	0.01
Hematoma	14 (0.5)	15 (0.4)	9 (0.2)	13 (0.3)	0.06
Retroperitoneal	1 (0.0)	9 (0.2)	9 (0.2)	11 (0.2)	0.20
Overall death	364 (11.9)	514 (12.0)	454 (9.3)	428 (8.4)	<0.01
Fatal PE	77 (2.5)	87 (2.0)	41 (0.8)	30 (0.6)	<0.01
Fatal initial PE	67 (2.2)	76 (1.8)	34 (0.7)	29 (0.6)	<0.01
Fatal recurrent PE	10 (0.3)	11 (0.3)	7 (0.1)	1 (0.0)	<0.01
Fatal bleeding	33 (1.1)	30 (0.7)	17 (0.3)	15 (0.3)	<0.01





Bertoletti L. et al, JACC Cardioncology 2023

Nuovi scenari terapeutici

FIGURE 1 Schematic Representation of Processes Required for Hemostasis

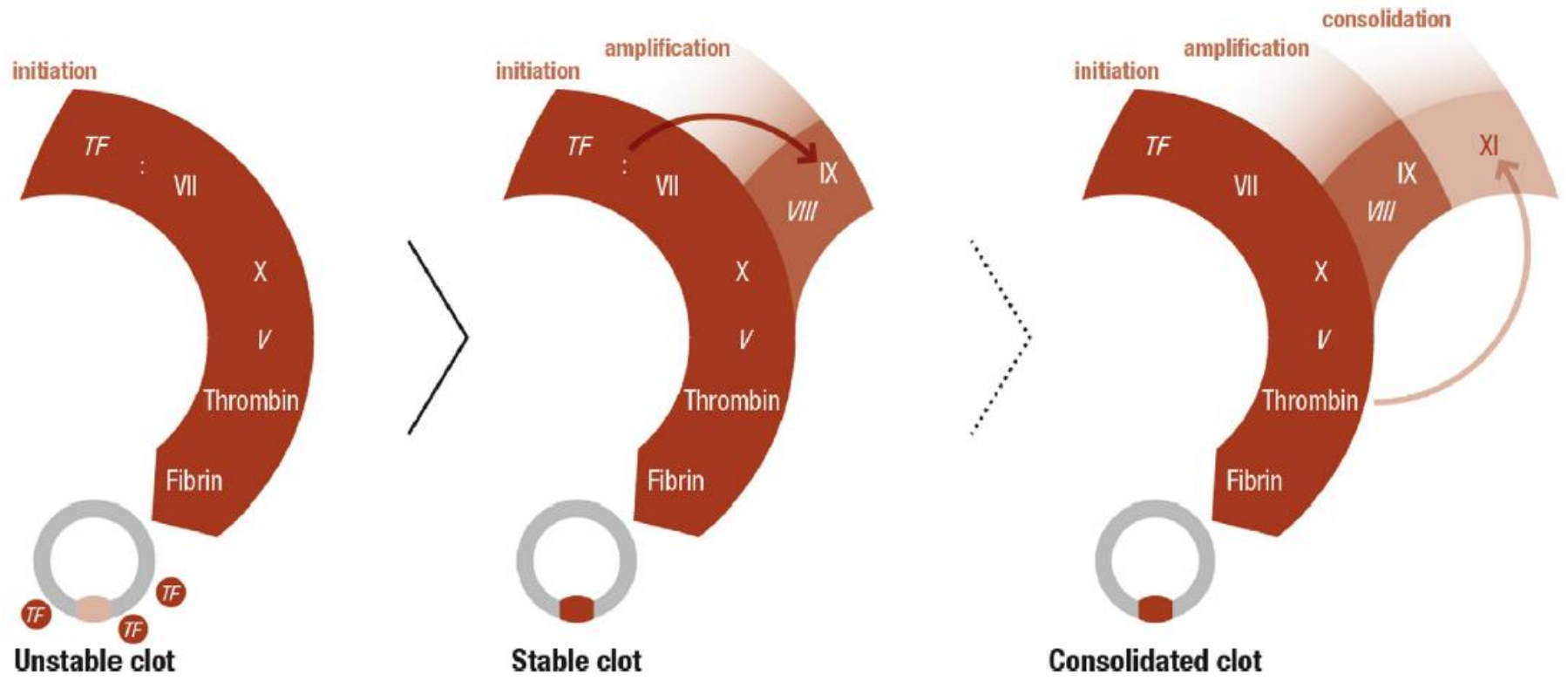
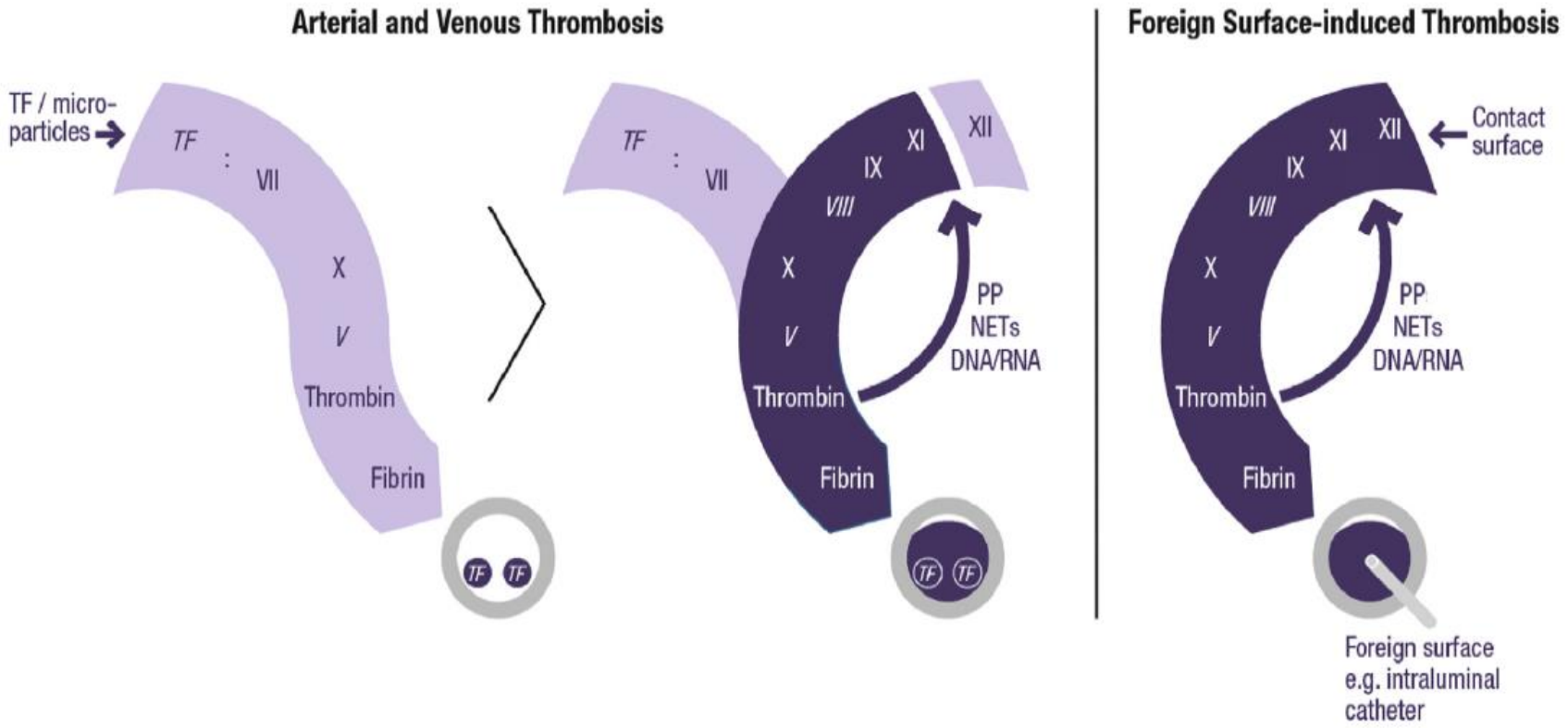
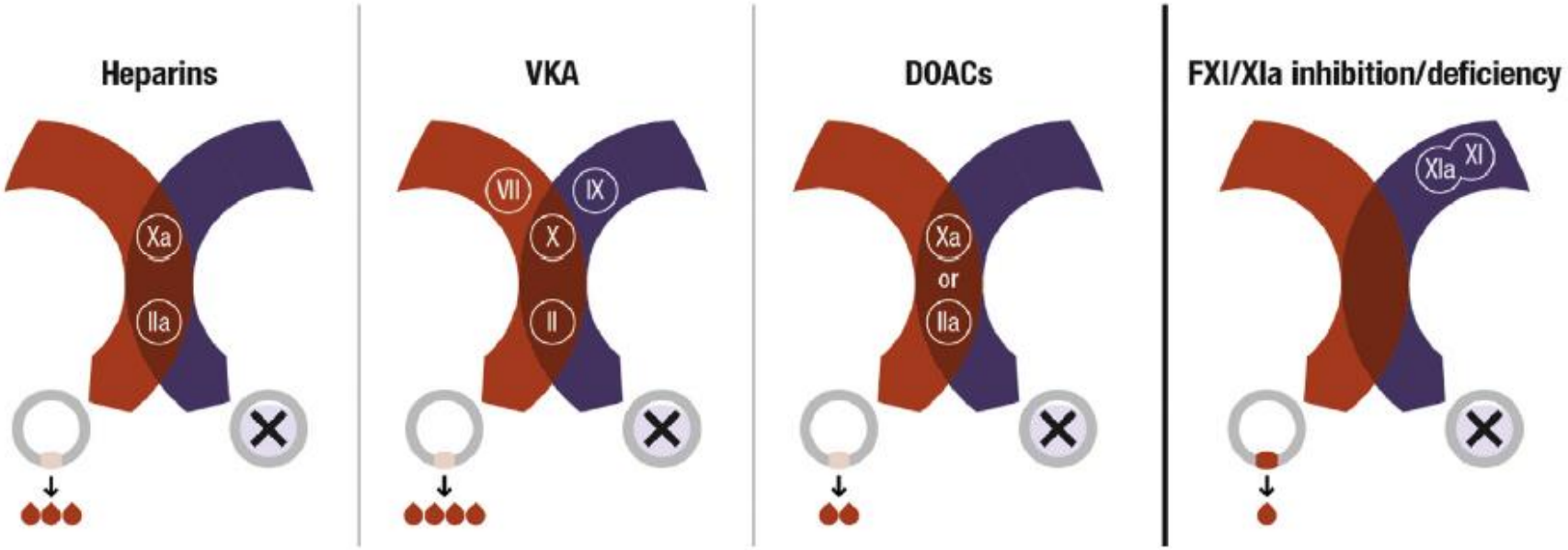


FIGURE 2 Schematic Representation of Processes That Contribute to Thrombosis



Nuovi scenari terapeutici

FIGURE 3 Impact of Various Anticoagulants on Hemostasis Versus Thrombosis



Pharmacological features of factor XI directed strategies

Feature	ASO	Antibodies	Aptamers	Small molecules
Delivery	Parenteral (sc)	Parenteral (IV or sc)	Parenteral (IV or sc)	Parenteral (IV) or oral
Specific	YES	YES	YES	YES
Onset of action	Delayed	Immediate	Immediate	Immediate
Offset of action	Delayed	Delayed	Rapid	Rapid
Renal clearence	No	No	No	Yes
Hepatic metabolism	No	No	No	Yes
Potential clinical indications	Chronic	Acute or chronic	Acute or chronic	Acute or chronic
Examples	ONIS-FXI$_{Rx}$ FXI-LICA (BAY2976217)	Osocimab (BAY1213790) Abelacimab (MAA868) AB023 (Xisomab 3G3)	FELIPA	Milvexian (BMS-986177/JNJ-70033093) Asundexian (BAY2433334)

Fredenburgh JC, Gross PL, Weitz, JI. Blood 2017
Li et al Front Cardiovasc Med 2022

Preventing activation of factor XI Abelacimab

Compounds	Route	Stage	Indication	N	Status
Antibodies					
Abelacimab	S.C. [2]	Phase II	Total knee arthroplasty	412	Published [61]
		Phase II	AF [5]	1200	Not recruiting (NCT04755283)
		Phase III	Cancer-associated VTE [10]	1655	Recruiting (NCT05171049)
		Phase III	GI/GU-associated VTE [10]	1020	Recruiting (NCT05171075)
Osocimab	I.V. [3]	Phase II	Total knee arthroplasty	813	Published [62]
Xisomab 3G3	I.V. [3]	Phase II	ESRD [4]	27	Published [63]
		Phase II	Thrombosis in chemotherapy	50	Recruiting (NCT04465760)
MK-2060	I.V. [3]	Phase II	ESRD [4]	489	Recruiting (NCT05027074)
REGN9933	I.V. [3]	Phase I	PK [8] & PD [9] in healthy	72	Recruiting (NCT05102136)

Abelacimab (MAA868) → monoclonal antibody that binds the procoagulant enzymatic site of both FXI (zymogen) and the active form FXIa. By binding to the catalytic domain, abelacimab locks both the FXI and activated FXIa taking them out of the coagulation system

- Phase II study of 400 patients undergoing total knee replacement vs. heparin
- Patients randomized to single IV of abelacimab 30, 75, or 150 mg, or to subcutaneous enoxaparin 40 mg
- Incidence of VTE 13%, 5%, and 4% with abelacimab doses vs. 22% with enoxaparin, assessed by venography or objective confirmation of symptomatic events 8–12 days after the operation.
- Bleeding was low 2% with the lower two doses abelacimab and none in the highest dose abelacimab or enoxaparin

Verhamme P. et al. N. Engl. J. Med. 2021

Preventing activation of factor XI Abelacimab

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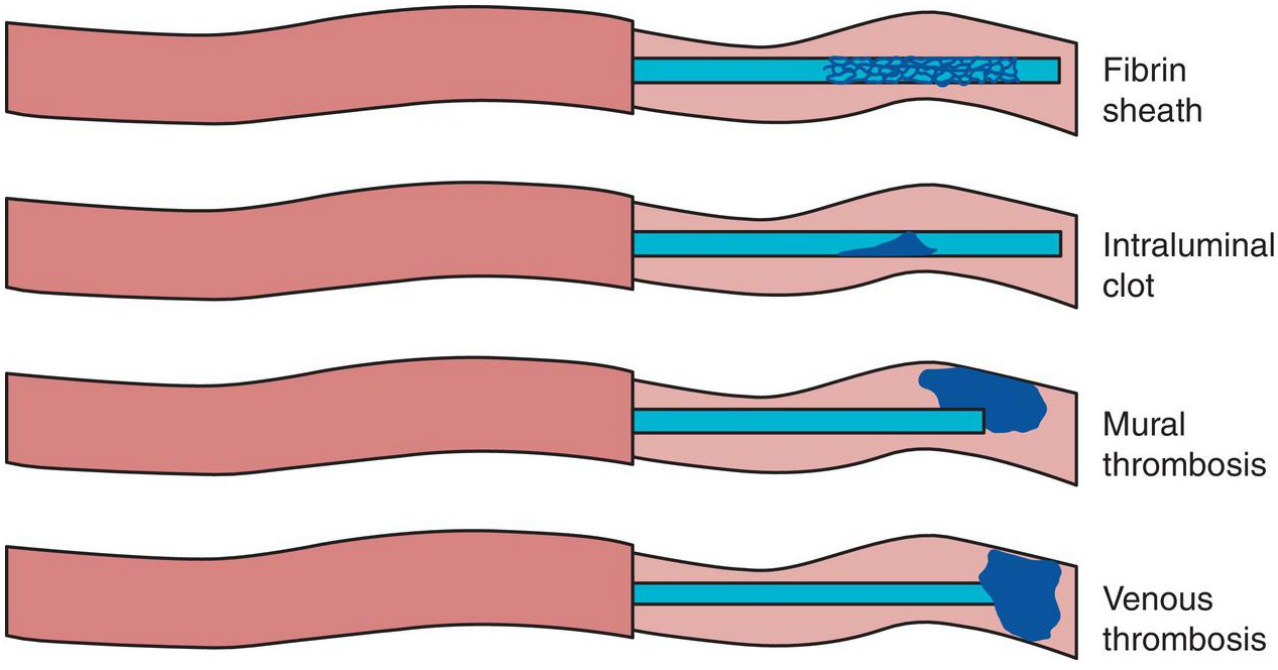
Abelacimab (MAA868)

More advanced phase III studies are ongoing in the prevention of cancer-associated VTE comparing the efficacy of abelacimab vs. dalteparin (MAGNOLIA; NCT05171075) and vs. apixaban (ASTER; NCT05171049)

ASTER MAGNOLIA

Xisomab 3G3 (AB023) → phase II trial to assess the efficacy in preventing catheter-associated thrombosis in cancer patients receiving chemotherapy is currently underway (NCT04465760)

Catheter-related thrombosis (CRT)



2-15% (symptomatic)

https://doi.org/10.1017/CBO9781139942430.030

Risk of CRT

+	-	
PICC	Port, CVC	**Catheter-related**
2 lumen or more (and size)	1 lumen	
Materials / Type of use		
Left side	Right side	
V. subclavia	V. jugularis	
BMI≥25	BMI<25	**Patient-related**
No anticoagulation	Anticoagulation	
Infection	No infection	
Type of cancer		
Prior CVC/CRT		
Insertion attempts		**Operator-related**

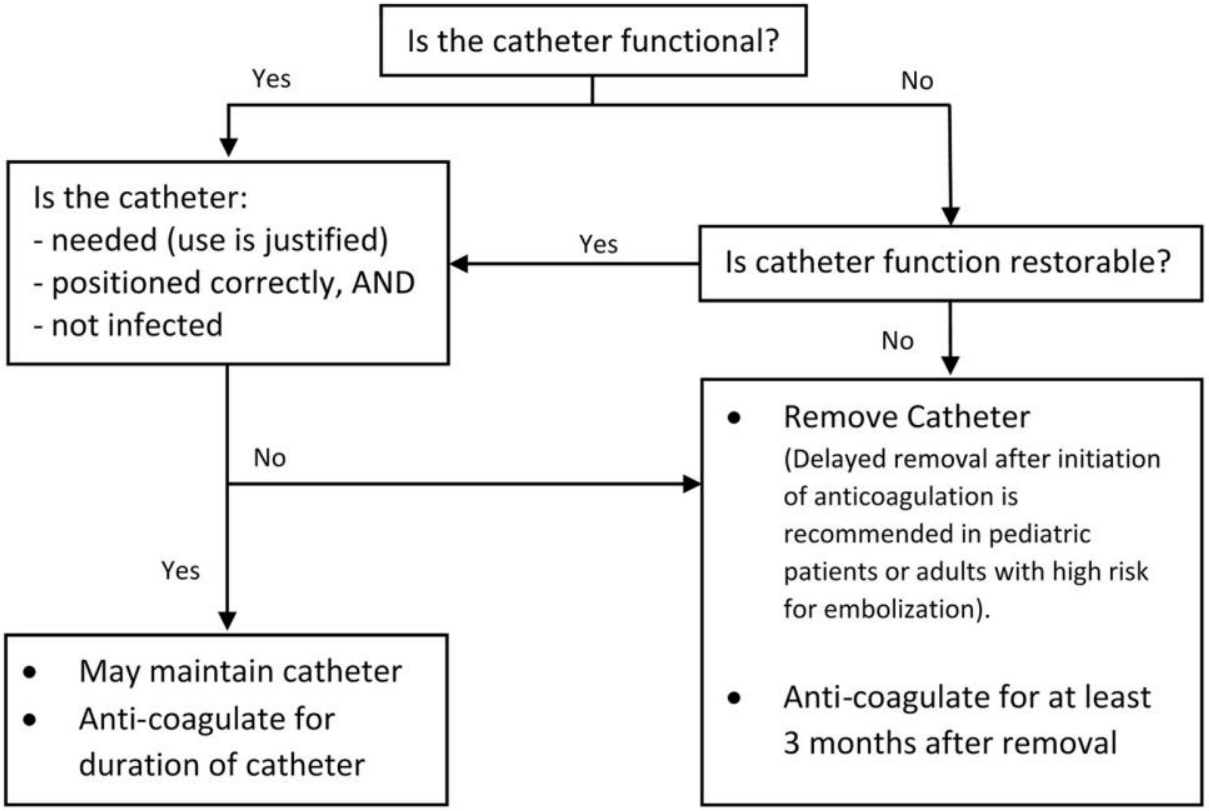
10.1177/1179554920953097

Update on Guidelines for the Prevention of Cancer-Associated CRT

- **CVC** on the right side, in the jugular vein, and the distal catheter tip should be located at the junction of the superior vena cava and the right atrium
- **Implanted ports** over peripherally inserted CVC
- The panel does **not** recommend prophylactic anticoagulation for CVC

https://doi.org/10.1002/onco.13596

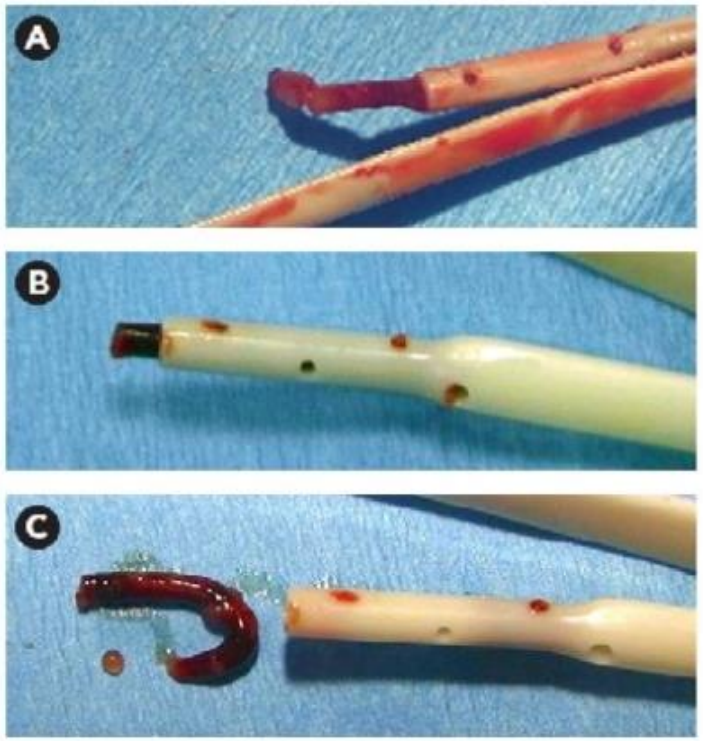
Treatment of CRT



https://doi.org/10.1016/j.thromres.2020.01.017
doi/10.1002/onco.13596

Treatment of intraluminal clots

- Alteplase 2 mg or Urokinase
- Restoration frequency: 84-92%



Source: Atlas of Dialysis Vascular Access | Tushar J. Vachharajani, MD, FASN, FACP

http://dx.doi.org/10.1136/bmjspcare-2019-002106
https://doi.org/10.1016/S0140-6736(09)60220-8

Risk of PE after catheter removal for CRT

626 patients with active hematologic malignancy and CVC-associated DVT

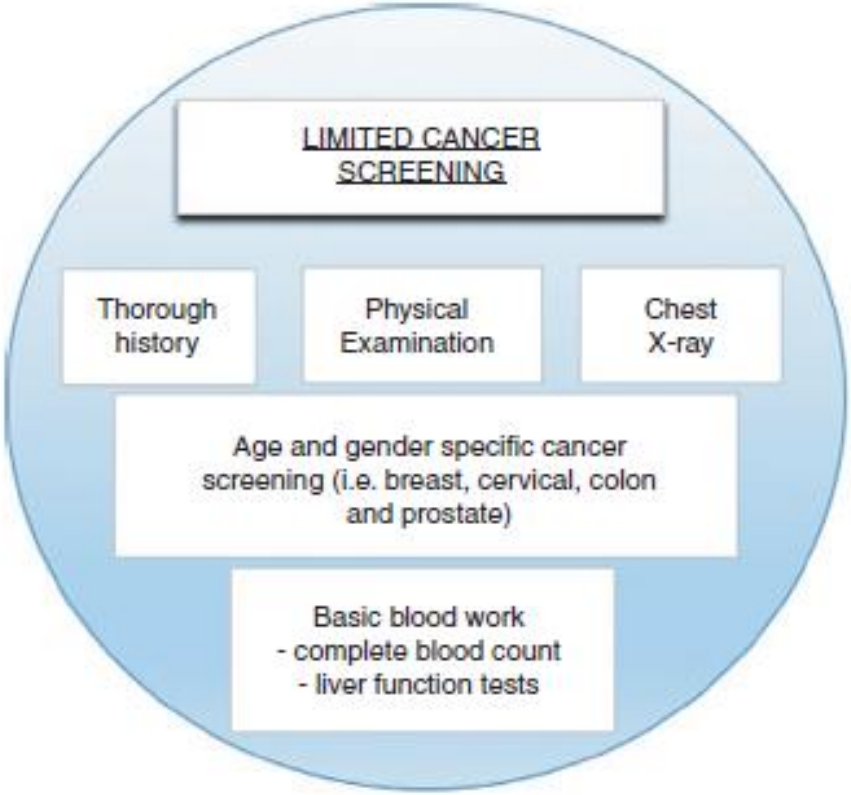
		n	PE within 7 d, n (%)	*P*	PE or death within 7 d, n (%)	*P*
AC +	Early removal (≤48 hours)	255	2 (0.78)		3 (1.18)	>.9*
AC +	Delayed or no removal	225	1 (0.44)	>.9*	3 (1.33)	
	Removal only	116	0		3 (2.59)	

https://doi.org/10.1182/bloodadvances.2021004698

Sequelae of CRT

- Pulmonary embolism (10-15%)
- Infection/sepsis
- Loss of venous access
- PTS/vena cava syndrome
- Reduced quality of life

Unprovoked VTE and occult cancer



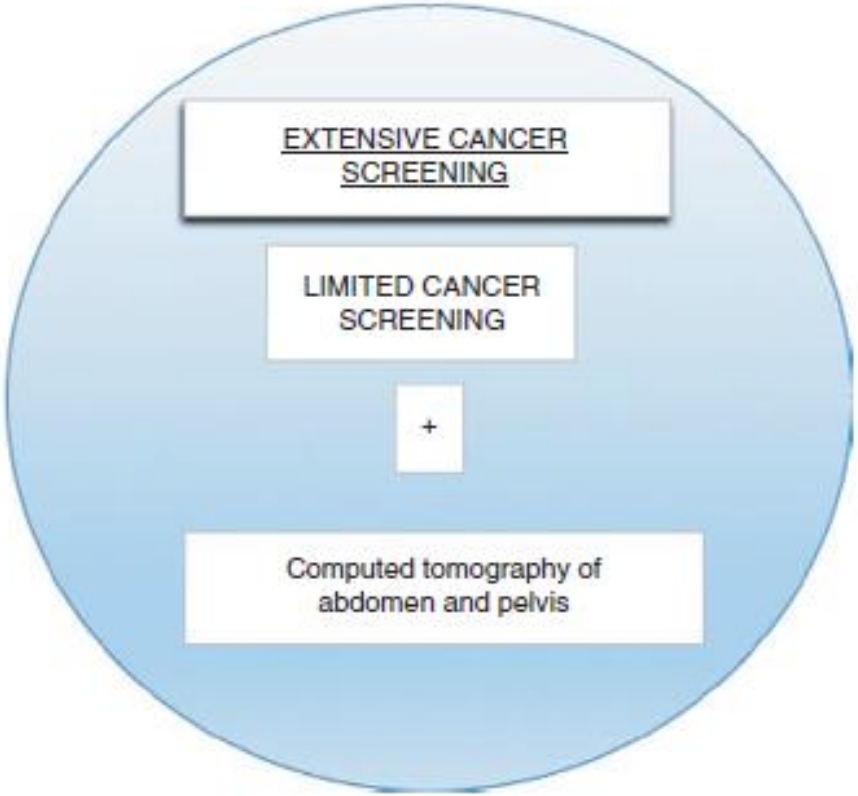


FIGURE 1 Strategies for limited vs extensive occult cancer screening.

Res Pract Thromb Haemost. 2017;1:9–13.

Unprovoked VTE and occult cancer

TABLE 1 Summary of prospective studies of occult cancer screening in unprovoked VTE

Author (Year) [Reference]	Study design	Sample size	Outcomes			Quality of evidence
			Cancers diagnosed with initial screening	Cancers missed during initial screening	Cancer-related deaths	
Van Doormaal et al. (2011)[10]	OBS	630	2.4% (limited) vs 3.5% (extensive) OR: 1.56 (95% CI; 0.53-4.55)	5.0% (limited) vs 3.7% (extensive) HR: 0.86 (95% CI; 0.38-1.96)	2.8% (limited) vs 5.0% (extensive) HR: 1.79 (95% CI; 0.74-4.35)	Moderate (non-randomized study)
Carrier et al. (2015)[8]	RCT	854	14 (limited) vs 19 (extensive) (P=.28)	Absolute difference 0.25% (95% CI, −1.12 to 1.63)	1.4% (limited) vs 0.9% (extensive) (P=.75)	High
Robin et al. (2016)[9]	RCT	394	absolute risk difference 3.6% (95% CI, −0.4 to 7.9, P=.07)	absolute risk difference 4.1% (95% CI, 0.8 to 8.4, P=.020)	2.5% (limited) vs 1.0% (extensive)	High
Prandoni et al. (2016)[11]	RCT	195	absolute difference 2.0% (95% CI, −7.2 to 11.2, P=.81)	2 (limited) vs 2 (extensive)	4.0% (limited) vs 2.0% (extensive)	Moderate (prematurely terminated; small sample size)

OBS, prospective observational study; RCT, randomized controlled trial; OR, odds ratio; HR, hazard ratio.

In summary, while awaiting validated tools to identify subsets of patients with unprovoked VTE who would benefit from extensive screening, patients should only undergo a thorough medical history, physical examination, basic laboratory investigations (ie, complete blood count and liver function tests), chest X-ray as well as age- and gender-specific cancer screening (breast, cervical, colon, and prostate).

Res Pract Thromb Haemost. 2017;1:9–13.

Unprovoked VTE and occult cancer

TABLE 2 RIETE prediction score for occult cancer detection cancer after venous thromboembolism

Variable	Points
Male sex	1
Age >70 years	2
Chronic lung disease	1
Anemia	2
Platelet count $\geq 350 \times 10^6/mm^2$	1
Post-operative status	−2
Prior venous thromboembolism	−1
High risk	≥3

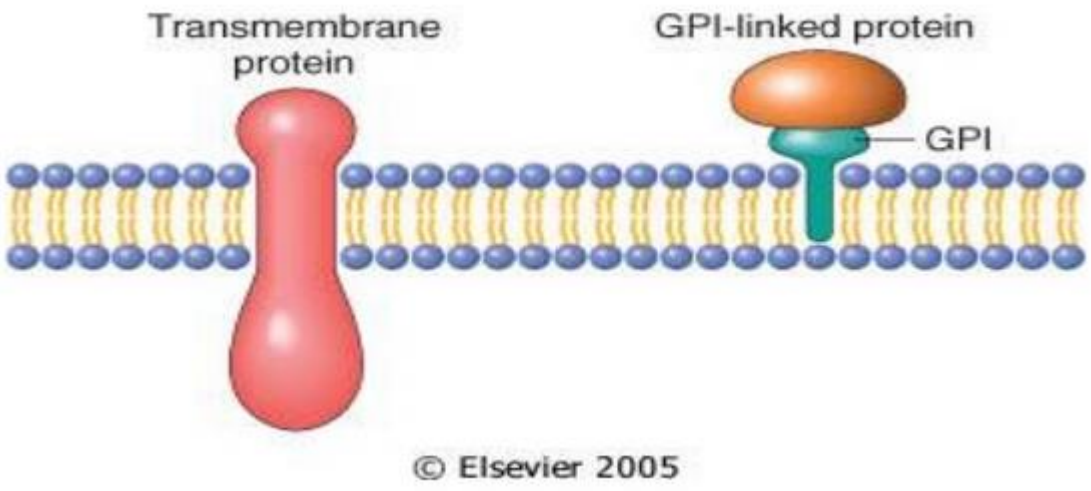
Res Pract Thromb Haemost. 2017;1:9–13.

Emoglobinuria parossistica notturna (PNH)

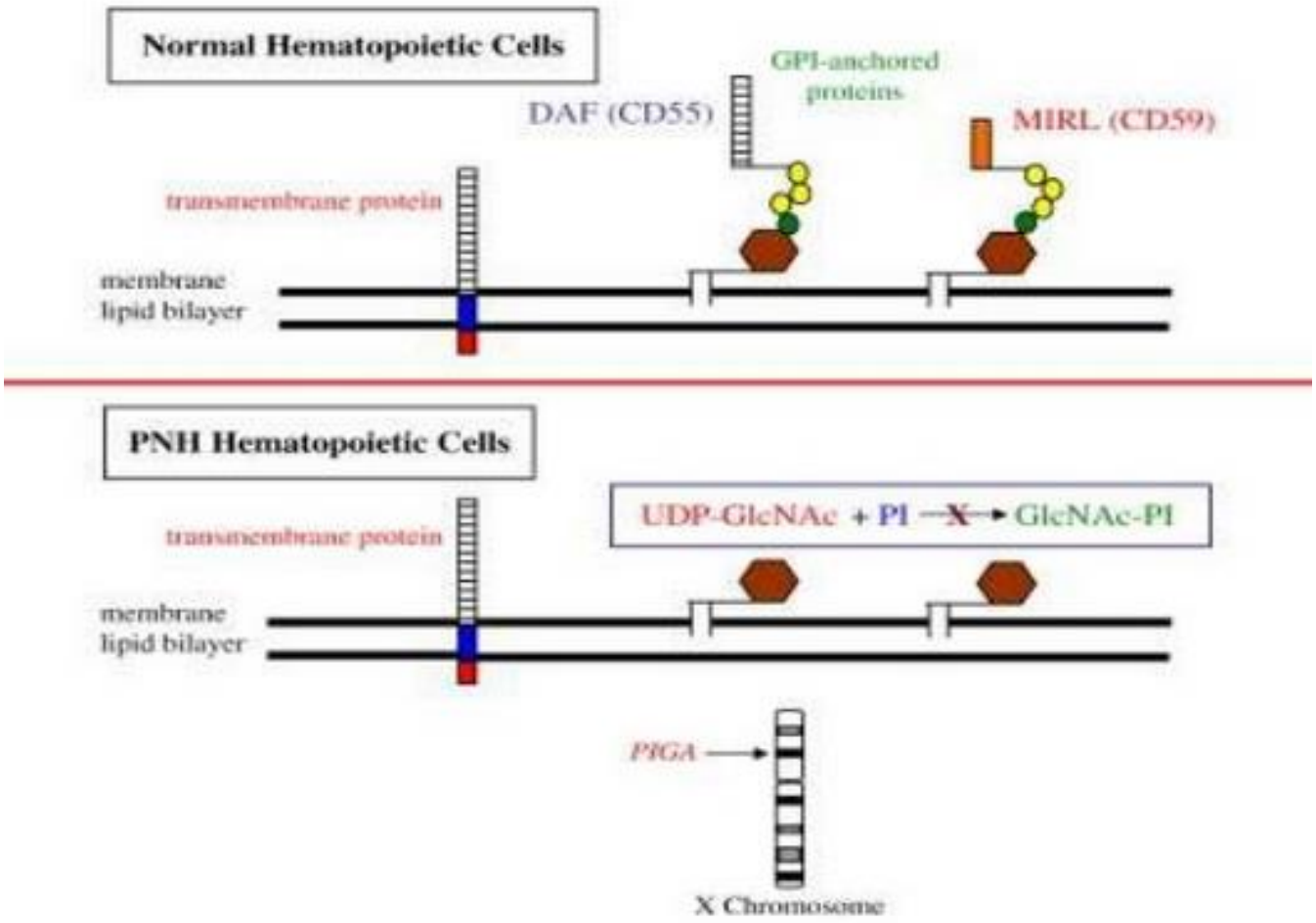
Paroxysmal nocturnal haemoglobinuria (PNH) is a rare condition with an estimated prevalence of approximately 16 per million.

Patients suffering from PNH present with cardiovascular, gastrointestinal, neurological or haematological symptoms.

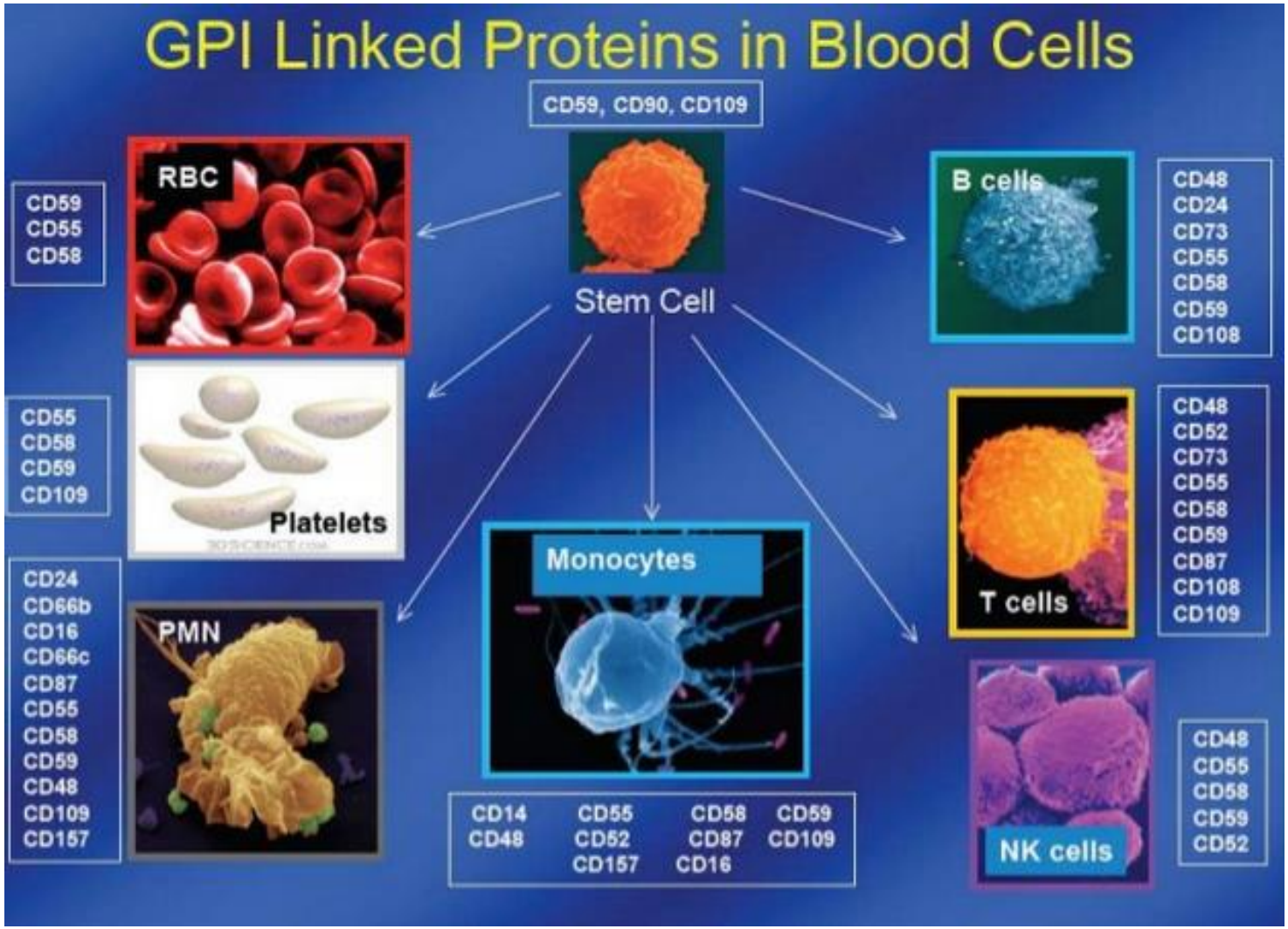
thrombophilic disorders due to an acquired mutation within the phosphatidyl-inositol glycan A (*PIG-A*) gene, which encodes for an enzyme involved in the biosynthesis of glycosylphosphatidylinositol (GPI)-anchor molecule



Emoglobinuria parossistica notturna (PNH)



Emoglobinuria parossistica notturna (PNH)



Emoglobinuria parossistica notturna (PNH)

The typical clinical features of this condition also encompass complement-mediated intravascular hemolytic anemia and bone marrow failure.

The deficient factors proteins entail also the complement regulatory proteins CD55 and CD59, which then lead to increased complement sensitivity of PNH cells, intravascular hemolysis, inflammation and systemic release of hemoglobin.

Thromboembolism is the most frequent cause of mortality in PNH patients, accounting for approximately 40–67% of deaths.

Emoglobinuria parossistica notturna (PNH)

thrombosis may occur at any site in patients with PNH

venous thrombosis >>> arterial complications (85%)

The most involved sites are intra-abdominal and cerebral veins, whilst multiple sites can be involved in over 15% of cases.

Hepatic vein thrombosis (also known as Budd-Chiari syndrome) is one of the most common sites of thrombosis, affecting 7.5–25% of PNH patients

Emoglobinuria parossistica notturna (PNH)

Mechanisms of hypercoagulability:

- Platelet activation,
- Complement-mediated hemolysis,
- Impaired bioavailability of nitric oxide (NO) and of the fibrinolytic system,
- Inflammation

Diagnosis:

Hemolysis
flow cytometric (FCM) analysis of glycosyl phosphatidylinositol-anchored proteins (GPI-AP). Flow cytometry should be used to diagnose PNH (recommendation level A)

FCM assays mainly were based on the detection of **CD59** (membrane inhibitor of reactive lysis) and **CD55** (decay accelerating factor) on RBCs and granulocytes → To exclude rare inherited deficiencies of a single GPI-AP, the diagnosis of PNH requires decreased expression of both CD55 and CD59

binuria parossistica notturna (PNH)

TABLE 1 High-risk groups that should be screened for PNH

1. Patients with evidence of haemolysis without obvious cause
• Coombs negative haemolytic anaemia
• Haemoglobinuria/haemosiderinuria
• Cytopenia due to bone marrow dysfunction
• Haemolysis with signs of renal dysfunction
2. Patients with evidence of bone marrow dysfuncti
a. Patients with AA
b. Patients with MDS
• Any type of MDS with evidence of haemolysi
• MDS with any of the following
○ Hypoplastic BM
○ Refractory cytopenia
c. Patients with unexplained cytopenia
3. Patients with unexplained thrombosis
• And evidence of haemolysis without obvious cause
• Venous and arterial thrombosis with any of the following
○ Unusual sites (eg intra-abdominal veins, cerebral veins, dermal veins)
○ Any cytopenia
○ Nonresponsive to anticoagulant
○ In patients of young age

AA, aplastic anaemia; BM, bone marrow; eGFR, estimated glomerular filtration rate; MDS, myelodysplastic syndrome.

5.3.3 | Eculizumab

Management of classic PNH has been revolutionised by the development of eculizumab. This humanised monoclonal antibody blocks the activation of terminal complement C5 and prevents the formation of C5a and C5b-9. An induction dose of 600 mg is given IV every 7 days for four doses, followed by 900 mg 7 days later and maintenance therapy of 900 mg every 14 days (recommendation level A). Up to 50% of patients experienced headaches after the first dose of eculizumab, caused by the acute increase of NO levels.[47] The main risk of termi-

Emoglobinuria parossistica notturna (PNH)

I pazienti con piccoli cloni (ossia, < 10% rilevati mediante citometria a flusso) che sono in gran parte asintomatici generalmente non hanno bisogno di trattamento. Le indicazioni per il trattamento comprendono

- Emolisi sintomatica che richiede trasfusioni
- Trombosi
- Altre citopenie

Misure di supporto comprendono supplementazione orale di ferro e folati e talvolta trasfusioni. I corticosteroidi (p. es., prednisone 20-40 mg per via orale 1 volta/die) possono controllare i sintomi e stabilizzare i valori dei globuli rossi in > 50% dei pazienti e possono essere utilizzati quando l'eculizumab non è disponibile. Tuttavia, a causa degli effetti avversi dell'uso a lungo termine, i corticosteroidi devono essere evitati per il trattamento cronico.

Emoglobinuria parossistica notturna (PNH)

Cross sectional study evaluating the presence of PNH clones in patients with prevalent venous thromboembolism using a high sensitivity flow cytometry assay for erythrocytes and neutrophils.

Among the 388 patients enrolled in the study one patient had a detectable PNH clone of 0.02% in the neutrophil population (0.26%; 95% CI 0.05 to 1.45) and no detectable erythrocyte clone.

The presence of PNH clones in patients with idiopathic venous thrombosis is rare. Screening for PNH clones among VTE patients might be better reserved for patients with signs of hemolysis.

Thromb Res. 2015;135(6):1107-9

Sindromi mieloproliferative

Philadelphia-negative myeloproliferative neoplasms (MPNs) include:

- Polycythemia vera (PV),
- Essential thrombocythemia (ET),
- prefibrotic/early primary myelofibrosis (prePMF), and primary myelofibrosis (PMF)

Thromboses in about 1/3 of cases.
incidence of thrombosis per 100 patients years was **2.6 in PV**, 1.9 in ET, 1.9–2.1 in prePMF, and 1.75 in PM.

In a recent population-based study, the rate of early VTE after diagnosis was nearly **10-fold increased** in the MPN patients in comparison with the control participants, declining with the follow-up to a 3.2-fold increased rate.

High risk of splanchnic vein thrombosis and cerebral vein thrombosis.

De Stefano et al. Blood Cancer Journal (2018) 8:65

Sindromi mieloproliferative

In MPN patients, age older than 60 years and previous thrombosis are the major predictors of vascular complication. In a multicenter series of 1545 PV patients, previous VTE (HR, 2.6) and age > 65 years (HR 1.7) predicted VTE.

Hereditary thrombophilia (FV leiden e prothrombin G20210A)

JAK2 V617F mutation (in ET e PMF)

→ The risk factors for recurrence were age > 60 years and history of remote thrombosis.

De Stefano et al. Blood Cancer Journal (2018) 8:65

Sindromi mieloproliferative

la mutazione JAK2V617F o la mutazione JAK2 exon12 sono presenti nel 95% dei pazienti affetti da policitemia vera.

La sovrapposizione dei risultati clinici e di laboratorio si verifica a causa di un'eziologia comune. Le mutazioni del gene Janus chinasi 2 (*JAK2*) sono responsabili per la policitemia vera e anche nella maggior parte dei casi di trombocitemia essenziale e di mielofibrosi primaria. Il Janus kinase 2 è un membro della famiglia degli enzimi della tirosina chinasi di tipo I ed è coinvolto nella trasduzione del segnale per il eritropoietina, trombopoietina e recettori del fattore stimolante le colonie di granulociti. Anche il gene del recettore della trombopoietina (*MPL*) e il gene della calreticulina (*CALR*) sono mutati in una proporzione significativa di pazienti con trombocitemia essenziale e mielofibrosi primaria e, raramente, nella policitemia vera.

Sindromi mieloproliferative

Table 2. Thrombotic risk in acquired thrombophilia and main hypercoagulable changes in coagulation pathways

Acquired thrombophilia	Relative risk for a first VTE	Haemostatic changes
Surgery	1.7-2.8x	• release or exposure of TF
Trauma	3-5x	• ↓ AT • hypofibrinolysis (↑ PAI-1)
Pregnancy	5-50x	• ↑ procoagulant factors (fibrinogen, VII, VIII, X, vW) • ↓ protein S • acquired APC resistance
Oestrogen–progestogen therapies	2-9x	• ↓ protein S • ↓ TFPI
Cancer	4-7x	• release of TF • ↑ procoagulant factors • ↓ anticoagulant factors • platelet activation
Myeloproliferative neoplasms	3x	• ↑ procoagulant factors • ↓ protein S • acquired APC resistance • ↑ platelet-induced thrombin generation
Economy class syndrome	2-4x	• Hypofibrinolysis (↑ prothrombin fragment F1+F2, ↓ tPA) • Haemoconcentration
Obesity (BMI ≥30 Kg/m^2)	2-3x	• ↑ procoagulant factors (fibrinogen, VII, VIII, X, vW) • hypofibrinolysis (↑ PAI-1) • ↑ platelet aggregation

Sindromi mieloproliferative

Treatment of VTE and duration of secondary prophylaxis

Acute treatment with heparin

DVT of legs or PE in MPN patients should be treated the same as DVT or PE occurring in the non-MPN patients[19]. Therefore, low-molecular-weight heparin (LMWH) or fondaparinux is suggested over i.v. or s.c unfractionated heparin; early initiation of vitamin K-antagonists (VKA) aiming for targetting an international normalized ratio 2.5 (range 2.0–3.0) is recommended[19]. At present, there are no data to support in MPN patients with VTE the current ACCP recommendation of early use of direct oral anticoagulants (DOACs) in non-cancer patients with VTE[20].

Relatively frequent cases of heparin-induced thrombocytopenia have been reported in MPN patients so that special care is due during the heparin course in monitoring a drop of the platelet count[31–33].

De Stefano et al. Blood Cancer Journal (2018) 8:65

Sindromi mieloproliferative

There is not a clear decision guide for the optimal duration of anticoagulant treatment after an MPN-related VTE, and the lack of firm evidence.

In MPN patients, the overall rate of recurrent thrombosis after VTE is 6.0 to 6.5 per 100 patient-years;

Long-term treatment with VKA (INR 2.0–3.0) is associated with a clear benefit, reducing the incidence rate of recurrence from 48 to 69% with respect to off-treatment.

Accordingly, discontinuation of VKA treatment produces in patients off therapy a 2.2-fold increased risk of novel thrombotic events in comparison with patients who continued treatment.

Incidence of recurrence on treatment remains high.

De Stefano et al. Blood Cancer Journal (2018) 8:65

Sindromi mieloproliferative

Aspirin

In the GIMEMA cohort, multivariable analysis showed that besides VKA, also antiplatelet agents effectively prevented recurrence in patients with VTE (HR 0.42, 95% CI 0.22–0.77). However, in the 114 patients with VTE at usual sites, long-term treatment with aspirin did not retain statistical significance in preventing recurrence (HR 0.53, 95%CI 0.27–1.03)[28].

Cytoreductive treatment

Cytoreductive treatment (hydroxyurea in 82% of the cases) halved the risk in the overall GIMEMA cohort (HR 0.53; 95% CI 0.38–0.73); however, a secondary analysis confirmed the efficacy of cytoreductive treatment only in patients with first arterial thrombosis (53% reduction in the risk), whereas in patients with first VTE the influence was more limited (34% reduction in the risk) and not statistically significant[28].

De Stefano et al. Blood Cancer Journal (2018) 8:65

Sindromi mieloproliferative

The rate of major bleeding during antithrombotic treatment

In the GEMFIN cohort, there was no significant difference in hemorrhagic events based on whether the patients were on VKA or not on VKA (1.8 vs. 1.5 per 100 pt-years, respectively)[29].

In the ELN cohort, the incidence of major bleeding per 100 patient-years was 2.4 on VKA and 0.7 off VKA[30]. The cumulative probability of major bleeding at 1 year of VKA treatment was 2.8%[30], which appears higher than the counterpart value of 1.2–2.2% recorded in the VKA arms of trials comparing VKA vs. DOACs[37–40].

In the GIMEMA cohort, the association of antiplatelet agents plus VKA increased major bleedings per 100 pt-years compared with antiplatelet agents or VKA alone (2.8 vs. 0.8 and 0.9, respectively)[28].

De Stefano et al. Blood Cancer Journal (2018) 8:65

Sindromi mieloproliferative

Table 1. Evidence-based practice of primary and secondary antithrombotic prophylaxis by cytoreductive and antiplatelet/anticoagulant treatment in polycythemia vera and essential thrombocythemia

	Primary prophylaxis	Secondary prophylaxis after VTE
Polycythemia vera	Phlebotomy (HCT < 0.45) (all patients) Hydroxyurea (age > 60 years) Low-dose aspirin (all patients)	Phlebotomy (HCT < 0.45) (all patients) Hydroxyurea (all patients) Indefinite VKA treatment (especially patients with CVT and BCS) Low-dose aspirin (selected patients after 6 months of treatment with VKA)
Essential thrombocythemia	Hydroxyurea (age > 60 years) Consider anagrelide (especially age < 40 years) Low-dose aspirin (age > 60 years, CVRF, JAK2*V617F*)	Hydroxyurea (all patients) Consider anagrelide (especially age < 40 years) Indefinite VKA treatment (especially patients with CVT and BCS) Low-dose aspirin (selected patients after 6 months of treatment with VKA)

BCS, Budd-Chiari syndrome; CVRF, cardiovascular risk factors; CVT, cerebral vein thrombosis; HCT, haematocrit; VKA, vitamin K Antagonists; VTE, venous thromboembolism.

Barbui T. et al. Curr Opinion Hematol 2017

Sindromi mieloproliferative

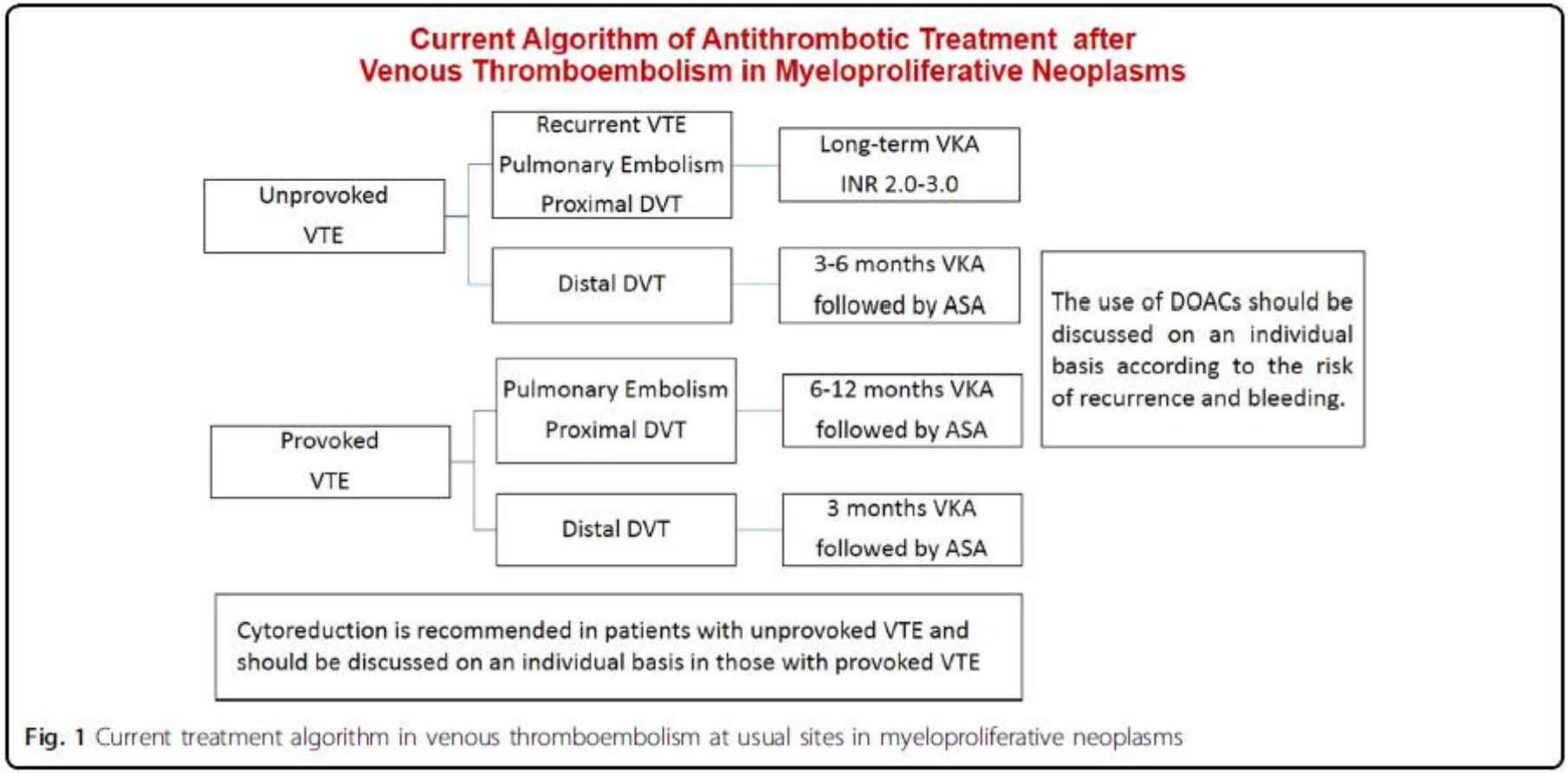


Fig. 1 Current treatment algorithm in venous thromboembolism at usual sites in myeloproliferative neoplasms

Anticoagulazione long-term per trombosi splancniche e cerebrali.

De Stefano et al. Blood Cancer Journal (2018) 8:65

Sindromi mieloproliferative

A multicenter real-life study on anticoagulant treatment with direct oral anticoagulants in patients with Ph-negative myeloproliferative neoplasms

Alessandra Serrao, Massimo Breccia, Mariasanta Napolitano, Luciano Fiori, Marco Santoro, Emilia Scalzulli, Michelina Santopietro, Cristina Santoro, Simona Raso, Antonio Chistolini

The DOACs were started as front line anticoagulant treatment or after a previous treatment with VKA and the dosage was administered according to VTE and AF guidelines

Rivaroxaban in 26 (37%) cases, apixaban in 21 (29%), edoxaban in 14 (20%) and dabigatran in 10 (14%)

Thirty-six patients presented VTE: 26/36 were of typical sites and 10/36 were of atypical sites (including splanchnic venous thrombosis and cerebral sinus vein thrombosis).

No thrombotic complications during DOACs therapy in VTE population.

No major or CRNM bleedings were reported.

AJH 2020

Obesità

Ipercoagulabilità e obesità

→ aumento dei livelli di fattore VIII e di fattore di von Willebrand
→ Aumento dei livelli di PAI-1 (= riduzione della fibrinolisi)

Le persone obese hanno quasi due volte il rischio sia di PE che DVT ed i pazienti obesi con meno di 40 anni hanno quasi un rischio quintuplo vs. i non obesi

Obesità - prevenzione

ACCP 2008

Low-molecular-weight heparin given either at increased fixed doses (e.g., enoxaparin 40 mg every 12 h) or preferably weight-based doses using actual body weight (e.g., anti-FXa 40–75 IU/kg once daily) with or without accompanying peak anti-FXa-level monitoring.

As stated, the current recommendations by the ACCP guidelines are to consider weight-based dosing

→ Paziente di 150 Kg (40 U/Kg daily = 6000 U/die)

Obesità – terapia fase acuta

Eparina a basso peso molecolare, MAX 100 U/Kg x 2/die
MAX 10, 000 U x 2

Fondaparinux 10 mg/die per pazienti > 100 Kg (copre bene fino a 120 Kg)

Eparina non frazionata ev con monitoraggio PTT per BMI > 40 Kg/m2

Obesità – terapia fase cronica

Warfarin

DOACs

Received: 11 March 2021 | Accepted: 21 April 2021

DOI: 10.1111/jth.15358

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RECOMMENDATIONS AND GUIDELINES

Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation

Karlyn A. Martin[1] | Jan Beyer-Westendorf[2] | Bruce L. Davidson[3] | Menno V. Huisman[4] | Per Morten Sandset[5] | Stephan Moll[6]

	Phase 3 Studies Comparing DOACs with VKA in VTE		Phase 4 Studies Comparing DOAC with VKA in VTE (Including Retrospective and Prospective Studies and Meta-analyses)	
	BMI >35 or BW >120 kg	BMI >40	BMI >35 or BW >120 kg	BMI >40
Apixaban	X	X	Similar outcomes[6]	Similar outcomes[5,6]
Dabigatran	X	X	X	X
Edoxaban	X	X	X	X
Rivaroxaban	Similar outcomes[7]	X	Similar outcomes[5,8-10]	Similar outcomes[5,9]
Pooled DOAC	Similar outcomes[11]	X	Similar outcomes[12-16]	Similar outcomes[12]

Note: Similar outcome = DOAC compared with LMWH/VKA; X = no available data.

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TABLE 3 Summary guidance statements

Summary Guidance Statements for use of DOACs in Patients with Obesity
1). Consistent with the 2016 ISTH SSC recommendations, we conclude that the use of any DOAC is appropriate for patients with BMI up to 40 kg/m^2 or weight 120 kg. For patients with BMI >40 kg/m^2 or weight >120 kg, we recommend that the individual DOACs should be used as follows:
2). For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA, weight-based LMWH (per manufacturers' recommendations), and fondaparinux are also options.

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4). We suggest not to use dabigatran, edoxaban, or betrixaban for VTE treatment and prevention in patients with BMI >40 kg/m^2 or weight >120 kg, given unconvincing data for dabigatran, and lack of clinical or PK/PD data for edoxaban and betrixaban.

5). We suggest not to regularly follow peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.

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TABLE 2 Expected impact of bariatric surgery procedures on absorption of DOACs

DOAC	Site of Absorption in Gastrointestinal Tract	Surgical Intervention and Anticipated Effect on Absorption		
		Gastric Banding	Partial/Sleeve Gastrectomy	RYGB
Apixaban	Primarily upper GI tract, with possible limited absorption in the colon; absorption decreased by when delivered to the distal small bowel compared with oral administration[39]	Unlikely affected	Unlikely affected	Possibly reduced
Dabigatran	Lower stomach and proximal small intestine[41,42,49]	Possibly reduced	Possibly reduced	Possibly reduced
Edoxaban	Proximal small intestine, dependent on acidic environment [43,44]	Possibly reduced	Possibly reduced	Possibly reduced
Rivaroxaban	Largely stomach, some small intestine, but absorption reduced when released distal to stomach[43-45]	Possibly reduced	Possibly reduced	Possibly reduced

Abbreviations: DOAC, direct oral anticoagulant; RYGB, Roux-en-Y gastric bypass.

6). We suggest not to use DOAC for treatment or prevention of VTE in the acute setting after bariatric surgery (because of concerns of decreased absorption), and instead, to initiate such patients on parenteral anticoagulation in the early postsurgical phase. We suggest that switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability.