Dr. Luca Brullo
Dr.ssa Paola Gnerre

Medicina 1 P.O Levante
Medicina 2 P.O Levante
Ospedale San Paolo
Savona

Le aree grigie del TEV

Caso clinico 1

Anamnesi Patologica Prossima:

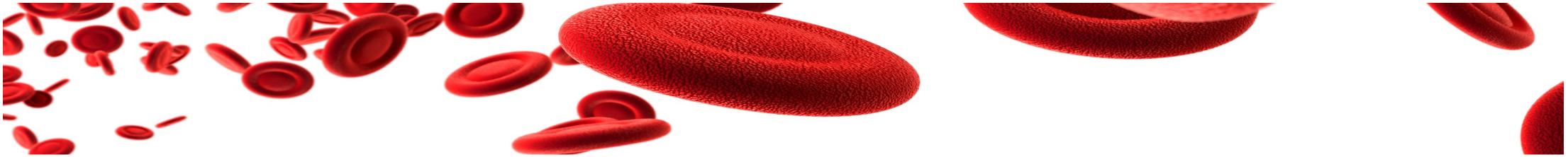
- A Giugno 2023 diagnosi di carcinoma della mammella sinistra QIE con linfoadenopatie ascellari patologiche; posta indicazione a neoadiuvante
- In data 18/08/2023 posizionato PICC arto superiore destro
- In data 20/08 iniziata terapia neoadiuvante con paclitaxel
- In data 21/08 comparsa di parestesie all'intero arto superiore destro con edema e dolore intenso soprattutto in regione ascellare a livello di braccio.
- Riscontro ecografico di trombosi su PICC di vena brachiale, ascellare e succlavia estesa fino alla giugulare interna

ESAMI EMATICI

Hb 12.1 g/dl
PLT 234000/mmc
Creatinina 0.86 mg/dL
AST/ALT 18/22 U/L

MANTIENE IL PICC O RIMUOVE PICC E POSIZIONA UN DIFFERENTE CVC?

CHE TERAPIA IMPOSTERESTE?



- ✓La paziente è dimessa in terapia con Enoxaparina 8000 1 fl sc x 2 e il PICC è mantenuto in sede
- ✓In data 25/09 nuovo accesso in PS per febbre senza franco richiamo d'organo
- ✓Paziente portatrice di PICC
- ✓Eseguite emocolture da PICC e da periferico + urinocoltura
- ✓In data 26/09 comunicata positività di emocolture da CVC e da periferico per stafilococco MRSA

RIMUOVERESTE IL PICC?

Rimosso il PICC

SE SI, QUANDO?

Dopo 48 ore di terapia antibiotica

Dimessa in data 11/10

Ritenuta conclusa CHT ed avviato anastrozolo

ALLA DIMISSIONE PROSEGUIRESTE TERAPIA ANTICOAGULANTE E SE SI PER QUANTO TEMPO?

E’ stata avviata terapia con DOAC (Edoxaban 60 1 cpr) e proseguita per un totale di sei mesi

Catheter-related venous thrombosis

- ✓Catheter-related venous thrombosis is estimated to contribute to 10 percent of all vein thromboses (DVT) in adults
- ✓The majority (70 to 80 percent) of thrombotic events occurring in the superficial and deep veins of the upper extremity are due to intravenous catheters.
- ✓The remainder are due to mechanical compression from anatomic abnormalities

- ✓Among the possible complications, PE and post-thrombotic syndrome (PTS) were less frequently reported in patients with UEDVT compared to those with lower extremity DVT (LEDVT).
- ✓Mortality was higher in patients with UEDVT versus LEDVT (9.7 vs 6.7 per 100 person-years), which might reflect the higher prevalence and the greater severity of underlying cancer.

MANTIENE IL PICC O RIMUOVE PICC E POSIZIONA UN DIFFERENTE CVC?

CHE TERAPIA IMPOSTERESTE?

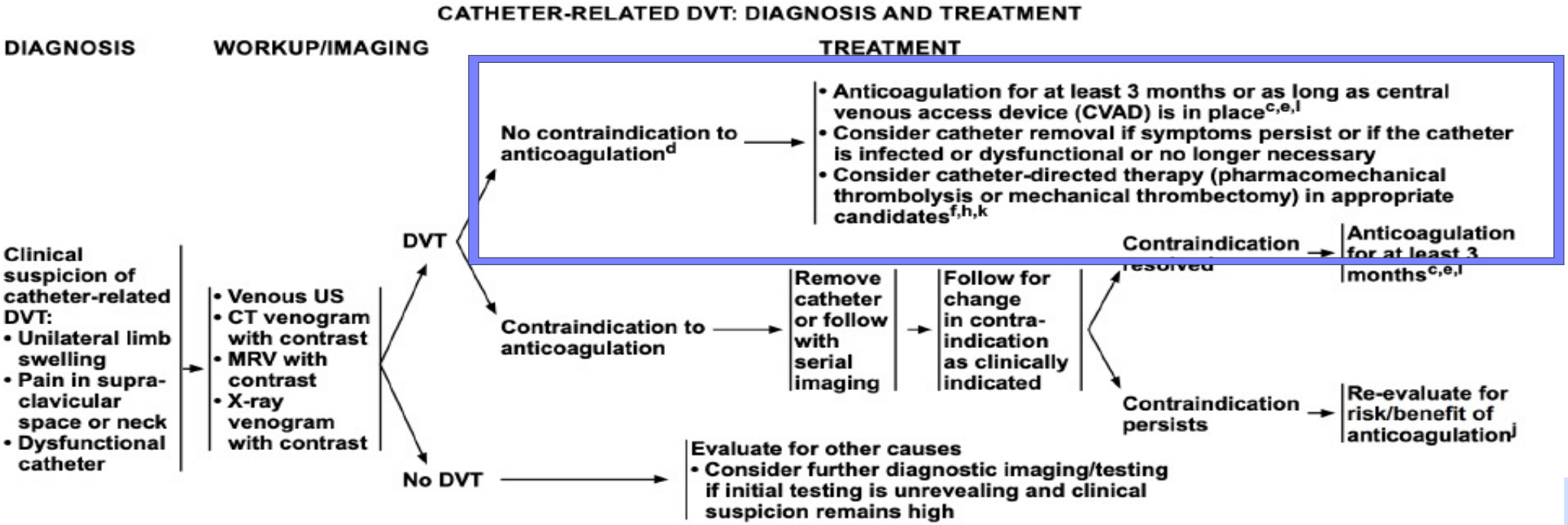
Treatment of deep vein thrombosis

- ✓The recommendations for the treatment of upper extremity DVT are based largely upon indirect evidence from the experience with DVT of the lower extremities
- ✓Despite a lack of direct evidence proving safety and efficacy of anticoagulation for upper extremity DVT, **anticoagulant therapy** remains the cornerstone of therapy with a goal of relieving acute symptoms and preventing embolization
- ✓Anticoagulation with LMWH or LMWH followed by Warfarin

Linee Guida - quale terapia?

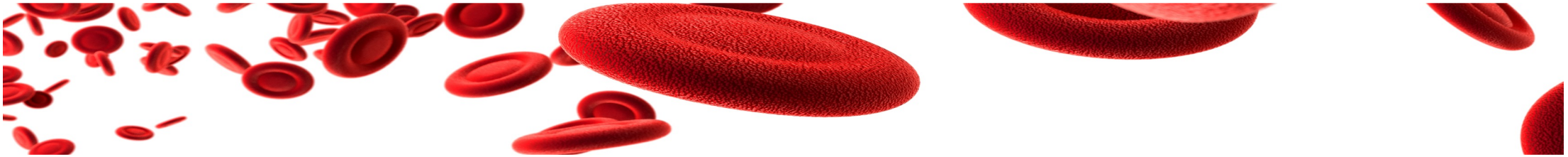
National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Acute Deep Vein Thrombosis (DVT)



Società	Anno	Profilassi	Terapia
ISTH	2014	against	- Suggest anticoagulation with LMWH without CVAD removal if functional and required for ongoing therapy - Recommend removal of a nonfunctional, infected, or incorrectly positioned catheter and suggest anticoagulation with LMWH - Suggest a short duration of anticoagulation of 3 to 5 days, if clinically practical, prior to removal of a CVAD - Suggest 3 to 6 months of anticoagulation for a symptomatic, CVDAC upper-extremity DVT - Suggest anticoagulation for the duration the catheter remains in place for individuals with ongoing risk factors, such as persistent CVDA
ESMO	2015	No specific recommendation	- HBPM is preferable to VKA - Anticoagulation should be maintained throughout the time the CVDA is used - If the CVDA is not functional, it should be removed after 3-5 days of anticoagulation
ITAC			atheter is
ASC			
NCC			- If anticoagulation is contraindicated, CVDA should be removed or followed with serial imaging and reconsider if the contradiction remains - Anticoagulation for CRT at least 3 months or while CVC remains inserted - Consider catheter-directed therapy (pharmacomechanical thrombolysis or mechanical thrombectomy) in appropriates candidates.
ACCP	2021	No specific recommendation	No specific recommendation
ASH	2021	Suggests not using oral or parenteral primary thromboprophylaxis	-In patients receiving anticoagulation for CRT suggest keeping over removing the CVDA -Patients with infected, mispositioned, or malfunctioning CVDAs or those no longer requiring their CVDA should have it removed -Similarly, patients who cannot receive anticoagulant treatment may need CVDA removal if not required for optimal care

- ✓ Suggest 3 to 6 months of anticoagulation or maintain throughout the time the CVDA is used with LMWH or LMWH followed by Warfarin for a symptomatic
- ✓ If the CVDA is not functional, it should be removed after 3-5 days of anticoagulation



Quando rimuovere il CVC?

Tendenzialmente l'atteggiamento concorde della letteratura è che l'obiettivo del trattamento dovrebbe essere quello di proteggere l'accesso venoso e di risolvere i sintomi. La rimozione comunque è sempre indicata quando il catetere:

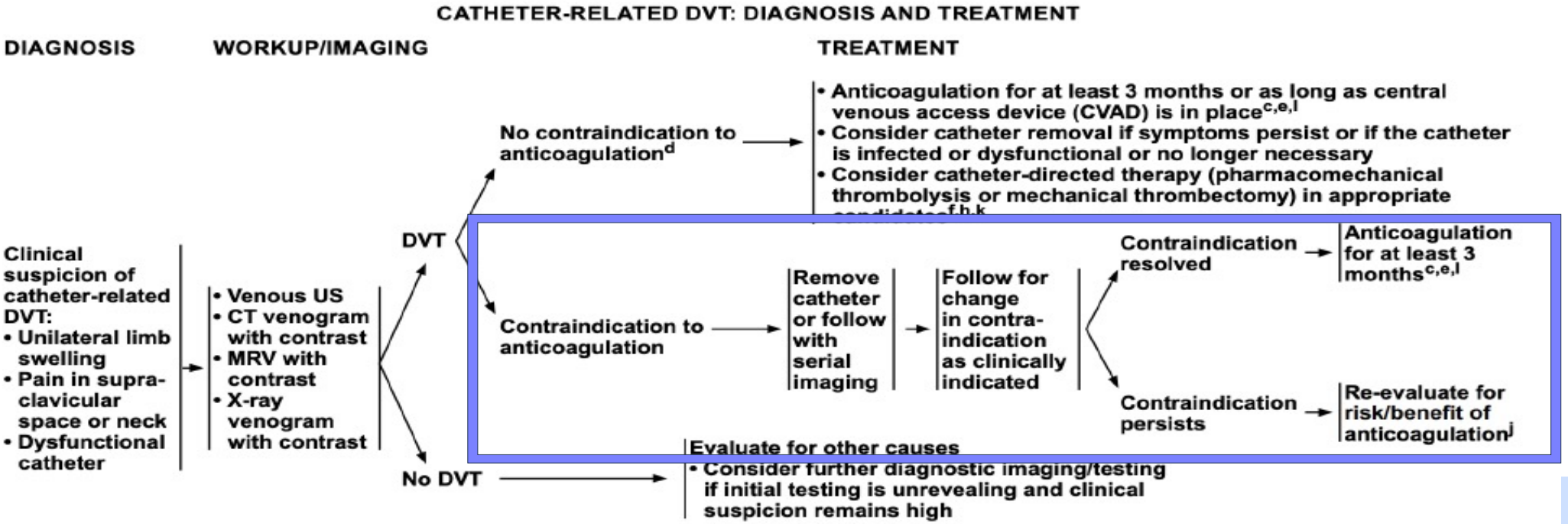
- ✓non funziona
- ✓È infetto
- ✓È sposizionato
- ✓Non serve più
- ✓Persistono i sintomi di trombosi nonostante l'avvio di tp anticoagulante

The optimal duration of anticoagulation when the catheter stays in place has not been defined.

Linee Guida - quale terapia?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Acute Deep Vein Thrombosis (DVT)



E i DOAC?

There are no RCTs evaluating the DOACs for the treatment of UEDVT; however, several prospective or retrospective cohort studies were published in the past few years.

Res Pract Thromb Haemost. 2021

904.OUTCOMES RESEARCH-NON-MALIGNANT CONDITIONS | NOVEMBER 13, 2019

Treatment of Upper Extremity Deep Vein Thrombosis with Apixaban and Rivaroxaban

Damon E. Houghton, MDMS, Jordan Cochuyt, David O. Hodge, MS, Danielle Vlazny, PA-C, Ana I Casanegra, MD, Lisa Peterson, RN, David A Froehling, MD, Robert D. McBane, MD, Waldemar E. Wysokinski, MD PhD

Consecutive patients with VTE were enrolled into the Mayo Clinic VTE Registry, between March 1, 2013 and July 22, 2019, were followed prospectively.

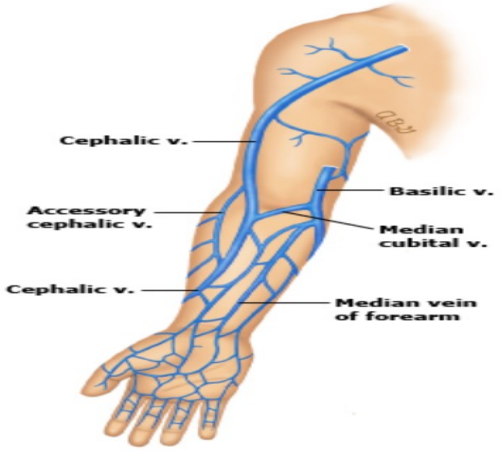
Table 1: Baseline Characteristics and Three Month Outcomes of VTE recurrence and Bleeding for UE-DVT

	LMWH / Warfarin (n=61)	Apixaban / Rivaroxaban (n=73)	Total (n=134)	p value
Age, Mean (SD)	61.3 (14.2)	55.8 (16.0)	58.3 (15.4)	0.04[1]
BMI, Mean (SD)	27.1 (5.5)	29.0 (6.0)	28.2 (5.8)	0.0496[1]
Male, N (%)	39 (63.9)	40 (54.8)	79 (59.0)	0.28[2]
Concurrent PE, N (%)	9 (14.8)	7 (9.6)	16 (11.9)	0.36[2]
CrCl <50ml/min, Mean (SD)	12 (19.7)	5 (6.8)	17 (12.7)	0.03[2]
Malignancy, N (%)	46 (75.4)	47 (64.4)	93 (69.4)	0.17[2]
Chemotherapy, N (%)	29 (47.5)	39 (53.4)	68 (50.7)	0.04[2]
Catheter-associated UE-DVT, N (%)	10 (16.4)	16 (21.9)	26 (19.4)	0.42[2]
Malignancy & Catheter, N (%)	9 (14.8)	12 (16.4)	21 (15.7)	0.79[2]
Recent Surgery, N (%)	2 (3.3)	10 (13.7)	12 (9.0)	0.04[2]
Hormonal Therapy, N (%)	1 (1.6)	1 (1.4)	2 (1.5)	0.90[2]
Prior VTE, N (%)	7 (11.7)	14 (19.4)	21 (15.9)	0.22[2]
Time from Diagnosis to Start of Drug (days), mean (SD)	2.5 (6.9)	2.3 (3.7)	2.4 (5.4)	0.02[1]
Outcomes (3 months)				
VTE Recurrence, N (%)	1 (1.6)	0 (0.0)	1 (0.7)	0.27[2]
Major bleeding, N (%)	2 (3.3)	0 (0.0)	2 (1.5)	0.12[2]
Clinically relevant non-major bleeding, N (%)	1 (1.6)	5 (6.8)	6 (4.5)	0.15[2]
Death, N (%)	5 (8.2)	0 (0.0)	5 (3.7)	0.01[2]

[1]Kruskal Wallis [2]Chi-Square

Abbreviations: UE: upper extremity, DVT: deep vein thrombosis, PE: pulmonary emboli, VTE: venous thromboembolism, SD: standard deviation, BMI: body mass index (kg/m^2), CrCl: creatinine clearance

What if it had been a anterior view superficial veins of the upper extremity?



- ✓There are limited data to guide management of upper extremity superficial vein thrombosis and phlebitis of upper extremity veins.
- ✓Fortunately, it appears that pulmonary embolus from superficial vein thrombosis and phlebitis is very rare.
- ✓In those with thrombosis confined to the superficial veins, such as the cephalic or basilic vein, treatment with anticoagulation has not been studied.

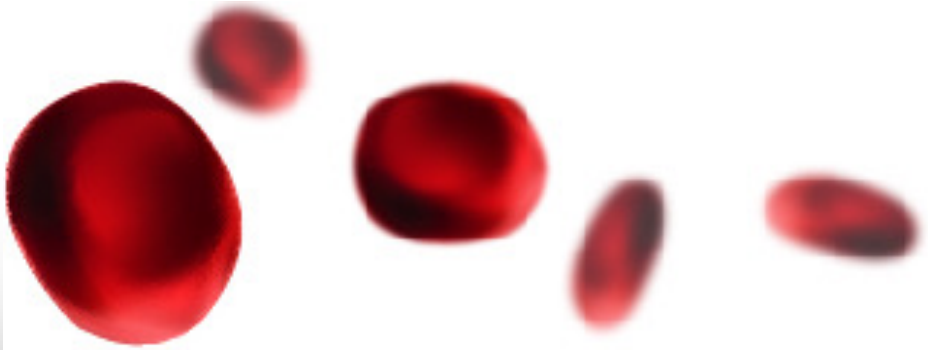
✓The initial management of superficial vein thrombosis and phlebitis related to peripheral intravenous catheters consists of discontinuing the intravenous infusion and **removing the peripheral catheter**.

✓In this situation, anticoagulation with either full dose anticoagulation or less than therapeutic doses of LMWH (e.g. approximately 50% of a treatment dose) to prevent progression of the thrombus while the catheter remains in place is reasonable.

What if is it was a isolated thrombosis of brachial vein?

- ✓There is uncertainty about the need to anticoagulate patients with thrombosis confined to the brachial vein
- ✓The risk of long-term chronic venous sequelae from venous obstruction at this site generally appears to be quite small.
- ✓The ACCP guidelines favor anticoagulation for up to three months if the thrombosis is symptomatic, is associated with malignancy, or the catheter remains in place

Case report

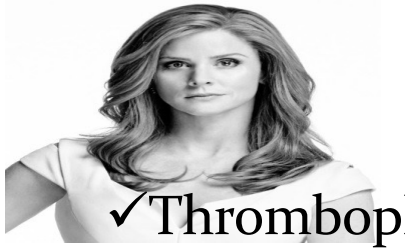


Gupta A, JAMA 2017

Case report

Gupta A, JAMA 2017

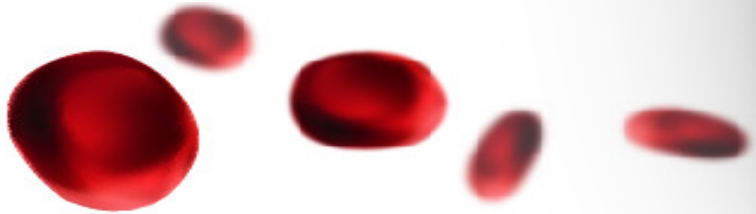
- ✓A 52-year-old woman with hypertension and type 2 diabetes presented with right-sided groin pain after a fall.
- ✓Her medications included lisinopril,pravastatin, andglipizide.
- ✓Examination and imaging findings were consistent with fracture of the right femoral neck and she subsequently underwent successful total hip arthroplasty.
- ✓On postoperative day 4, she developed pain and swelling of the right calf, and duplex ultrasonography demonstrated thrombosis of the right popliteal vein.
- ✓She reported no personal or family history of thrombosis or complications with prior pregnancies, and she was up to date on routine cancer screening.
- ✓Anticoagulation therapy with heparin and warfarin was initiated.



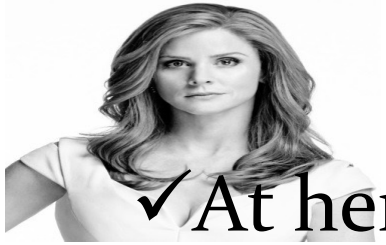
Gupta A, JAMA 2017

- ✓Thrombophilia testing was performed 48 hours later and included factor V Leiden and prothrombin gene mutations, protein C, protein S, and antithrombin activity, and antiphospholipid antibodies (IgG and IgM anticardiolipin, antibeta2 glycoprotein 1, and lupus anticoagulant)

- ✓Results demonstrated decreased activity of proteinC (25%;reference range, 70%-160%), protein S (34%; reference range, 65%-160%), and antithrombin (45%; reference range, 80%-130%).



She was discharged home with warfarin treatment and referred to the hematology clinic for follow-up

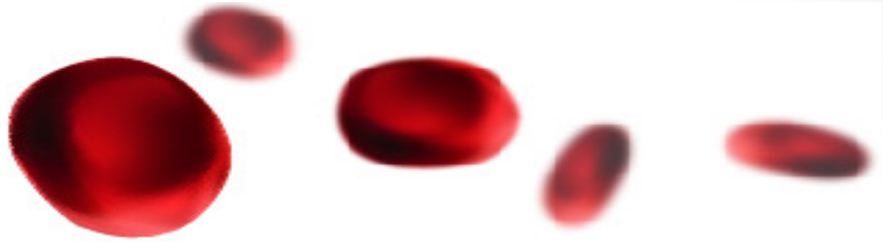


- ✓At her follow-up visit 2 weeks later, she was told that because these laboratory test blood samples had been drawn in the context of a recent thrombus and concurrent anticoagulation therapy, the results were spurious, and 3 months of anticoagulation was advised

- ✓Prior to having these results explained to her in the hematology clinic, the patient experienced significant worry about possibly suffering from rare disorders and the prospect of passing these on to her children. …

Gupta A, JAMA 2017

She remains without recurrent venous thromboembolism (VTE) at 1-year follow-up



Although inherited and acquired thrombophilias are acknowledged to increase the risk of venous thromboembolism

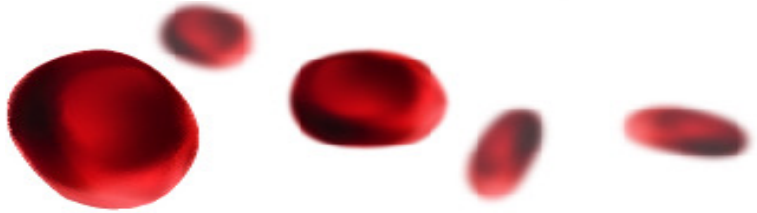
The majority of patients with VTE should not be tested for thrombophilia.

According to Medicare data,280 000 tests for inherited thrombophilia were claimed in 2014, costing an estimated $300 to $670 million, and up to 55% of patients with provoked VTE have been reported to undergo thrombophilia testing

Thrombophilia Type

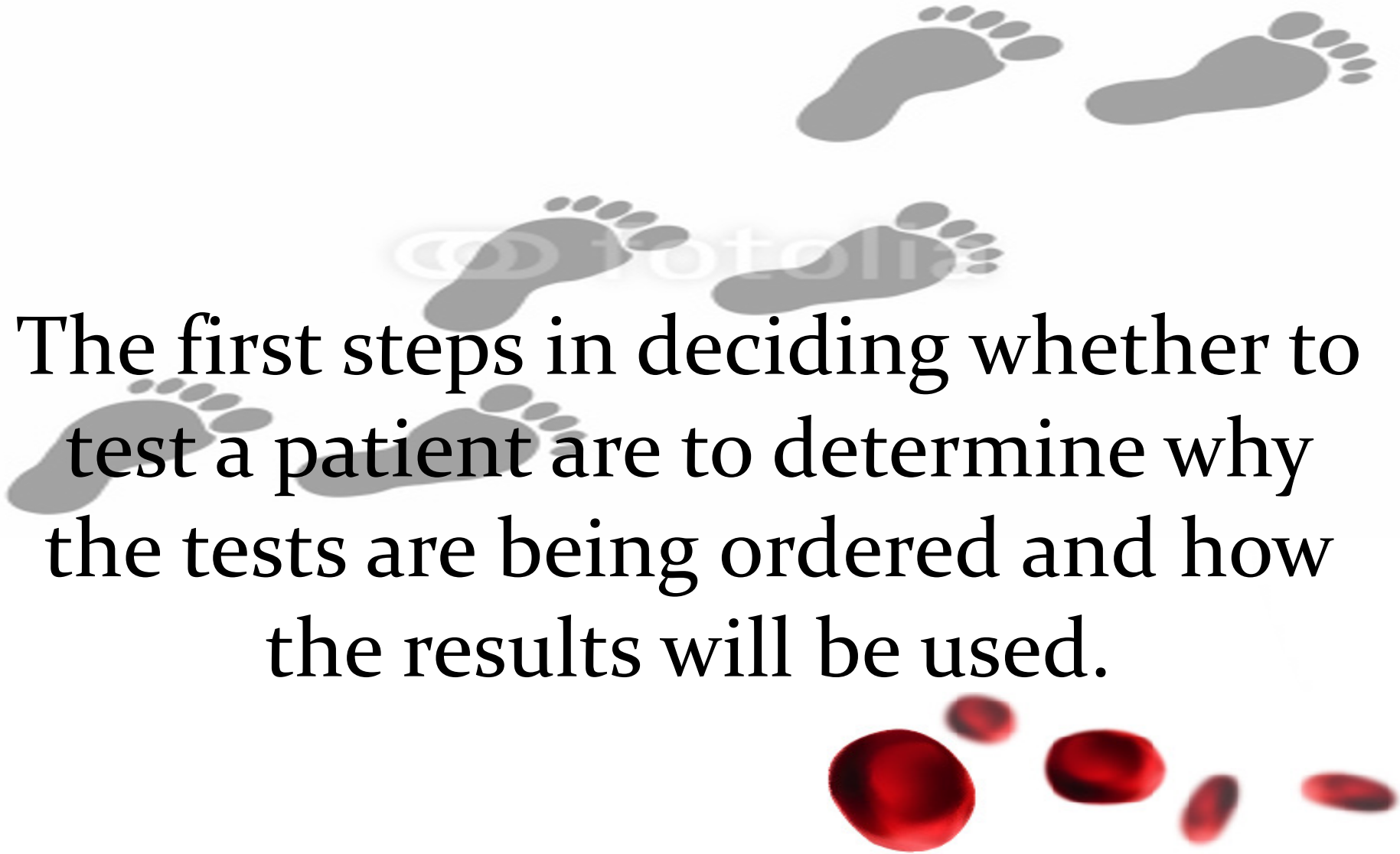
Inherited	
Increased procoagulant activity (common)	Factor V leiden
	Prothrombin gene mutation
Decreased anticoagulant activity (uncommon)	Protein C
	Protein S
	Antithrombin

Acquired
Lupus anticoagulant



Whom to test

How to use the results



The first steps in deciding whether to test a patient are to determine why the tests are being ordered and how the results will be used.

- ✓As the etiology of thrombosis is multifactorial, the presence of a thrombophilic defect is only one of many elements that determine risk
- ✓Test results should not affect decisions about the duration of anticoagulant therapy for the management of VTE
- ✓A negative thrombophilia evaluation is not a sufficient basis to stop anticoagulants following an episode of unprovoked VTE in a patient with low bleeding risk and willingness to continue therapy
- ✓Patients with inherited thrombophilia can often be identified by coagulation experts on the basis of the patient's personal and family history of VTE, even without knowledge of test results

Clinical Characteristics Suggestive of Inherited Thrombophilia in Patients with Venous Thromboembolism (VTE).

- ✓Thrombosis at a young age (<50 yr), especially in association with weak provoking factors (minor surgery, prolonged air travel, combination oral contraceptives,) or unprovoked VTE
- ✓Strong family history of VTE (first-degree family members affected at a young age)
- ✓Recurrent VTE events, especially at a young age
- ✓VTE in unusual sites such as splanchnic or cerebral veins

Secondary prevention following provoked VTE
Should thrombophilia testing be performed to help determine duration of anticoagulation following provoked VTE?

- ✓Of the many factors which predict the risk of recurrent thrombosis after an initial event, the presence of provoking factors is the most important
- ✓A positive thrombophilia evaluation is not a sufficient basis to offer extended anticoagulation following an episode of provoked VTE.

Do not perform thrombophilia testing following an episode of provoked VTE.

Secondary prevention following provoked VTE

Should thrombophilia testing be performed to help determine duration of anticoagulation following unprovoked VTE?

- ✓The absolute risk for recurrent VTE among patients with unprovoked thrombosis is higher than among those with provoked VTE, with 5-year risk approaching 30 % unless extended-duration anticoagulant therapy is provided
- ✓Current guidelines from the American College of Chest Physicians (ACCP) recommend extended duration anticoagulation after unprovoked VTE unless the risk of bleeding is high or this is contrary to the patient's values and preferences.
- ✓Other factors, such as the degree of post-thrombotic symptoms, D dimer levels after a minimum of 3 months of anticoagulant therapy, and residual vein thrombosis may also modify the risk of recurrence

Do not perform thrombophilia testing in patients following an episode of unprovoked VTE.

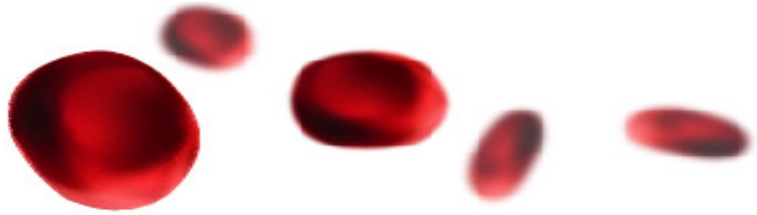
Do not test

Do not test

- ✓Testing for heritable thrombophilia in unselected patients presenting with a first episode of venous thrombosis.
- ✓Do not test if VTE is provoked by strong risk factors
- ✓Testing is not recommended in unselected patients with upper limb venous thrombosis.
- ✓Testing is not recommended in patients with central venous catheter (CVC)-related venous thrombosis.
- ✓Testing is not indicated in patients with retinal vein occlusion.

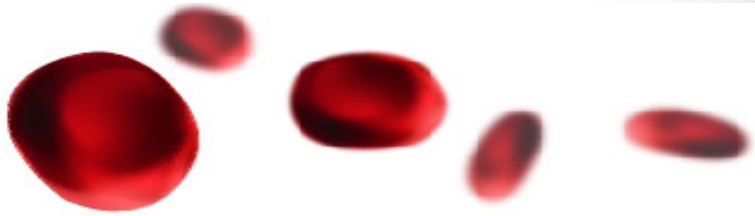
Do not test at time of VTE event

Test at completion of anticoagulant therapy for provoked VTE; for unprovoked VTE, test after treatment for acute event if cessation of anticoagulant therapy is contemplated and test results might change management strategy



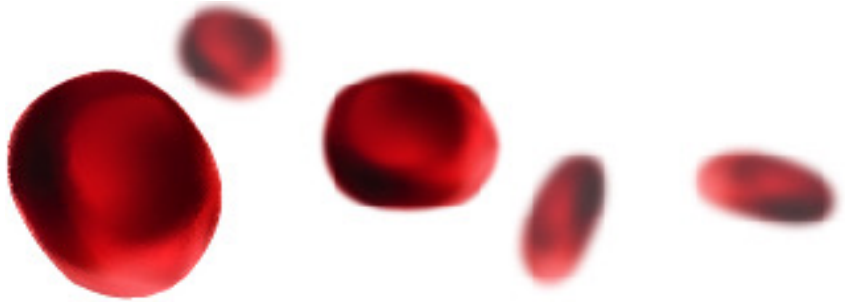
Do not test while patient is receiving anticoagulant therapy

Test when VKA has been stopped for at least 2 wk, DOAC has been stopped for at least 2 days (preferably longer), and UFH or LMWH for antithrombin levels has been stopped for more than 24 hr



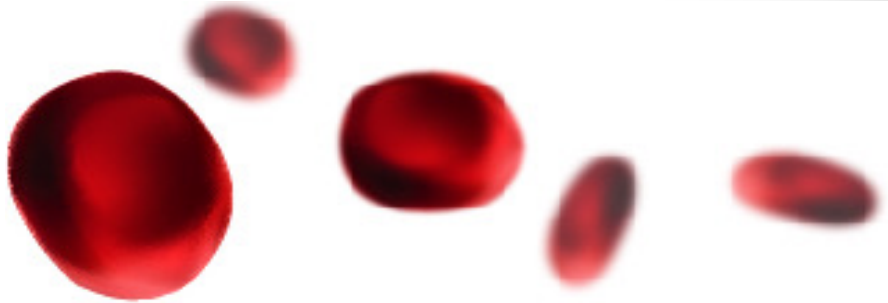
Consider testing

Consider testing in patients in whom VTE occurs at a young age in association with weak provoking factors or a strong family history of VTE or in patients who have recurrent VTE



Repeat testing

There is no benefit in repeating a normal thrombophilia screens. In the event of an abnormal result, requests for confirmatory testing should be limited to the relevant deficiency only.



Known the 4 P:

- Patient selection
- Patient counseling
- Proper test interpretation
- Provision of education and advice

✓ Don't test while the patient is on anticoagulation

✓ Don't test during an acute thrombosis

Ordering thrombophilia tests is easy....

Determining whom to test and how to use the results is not!