THROMBOEMBOLISM Q & A 2019

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Objectives

- Approach to subsegmental PE, calf vein DVT and superficial vein thrombosis
- Determine duration of anticoagulation for VTE
- Review options for secondary prevention of VTE
- Manage anticoagulation in recurrent VTE
- Choose appropriate DOAC for VTE
- Role of thrombophilia work up

Resources

- AC Forum clinical guidance-VTE, splancnic vein, reversal etc. https://acforum.org/web/education-guidance.php
- University of Washington Anticoagulation http://depts.washington.edu/anticoag/home

Subsegmental PE

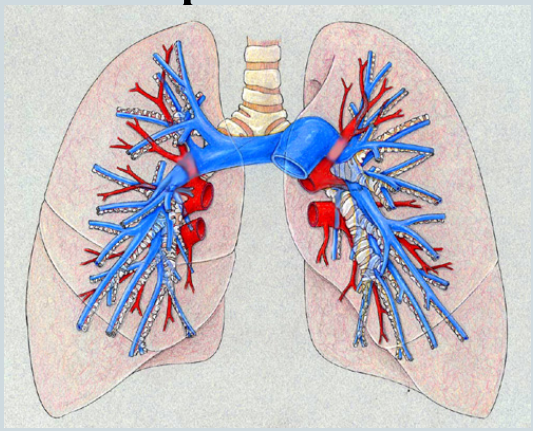
A 77 yo man had undergoes colectomy for recurrent bleeding from diverticulosis. On POD # 3 he becomes tachycardic to the 110s. WBC is elevated.The surgical team orders an abdominal CT which shows a fluid collection concerning for early abscess. It also shows an isolated RLL subsegmental PE. A dedicated CTa shows a single isolated RLL subsegmenral PE. Do you anticoagulate this patient?

a) Sure, it is a PE.
b) No this is incidental. Let's pretend we don't know it is there

Isolated Subsegmental PE

Definition: PE shown on CT angiography that occurred in a subsegmental branch but no larger order of vessels. The subsegmental PE may involve one or more than one subsegmental branch

Identification of ISSPE has tripled over past decade



Isolated Subsegmental PE

Anticoagulant treatment for subsegmental pulmonary embolism

Hugo HB Yoo[1], Thais HAT Queluz[1], Regina El Dib[2]

[1]Department of Internal Medicine, Botucatu Medical School, UNESP - Univ Estadual Paulista, Botucatu, Brazil. [2]Department o Anaesthesiology, Botucatu Medical School, UNESP - Univ Estadual Paulista, Botucatu, Brazil

Contact address: Hugo HB Yoo, Department of Internal Medicine, Botucatu Medical School, UNESP - Univ Estadual Paulista, Distrito de Rubiao Junior, s/n, Campus de Botucatu, Botucatu, Sao Paulo, 18618-970, Brazil. hugo@fmb.unesp.br.

Editorial group: Cochrane Vascular Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2016.
Review content assessed as up-to-date: 15 December 2015.

Citation: Yoo HHB, Queluz THAT, El Dib R. Anticoagulant treatment for subsegmental pulmonary embolism. *Cochrane Databas of Systematic Reviews* 2016, Issue 1. Art. No.: CD010222. DOI: 10.1002/14651858.CD010222.pub3.

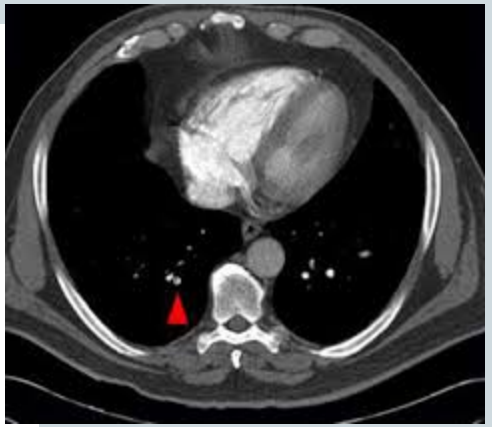
Summary of main results

There is currently no evidence from randomised controlled trials to assess the effectiveness and safety of anticoagulation therapy versus no intervention in patients with isolated subsegmental pulmonary embolism (SSPE) or incidental SSPE.

Isolated Subsegmental PE

Whether to Anticoagulate Subsegmental PE

***19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation** (Grade 2C) **or (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C).



IS IT REAL?
ISSPE is more likely to be TRUE if….good quality scan, mult defects, centrally located, d-dimer elevated, seen on mult cuts, patient symptomatic vs incidental;high pretest prob of PE
Get u/s of bilateral lower extrem (upper if CVC)
Consider risk of recurrence-higher if not post op; immobile; active cancer
IF high bleed risk –don't AC: get serial u/s

Kearon et al. Chest. 2016;149(2):315-352.

Subsegmental PE

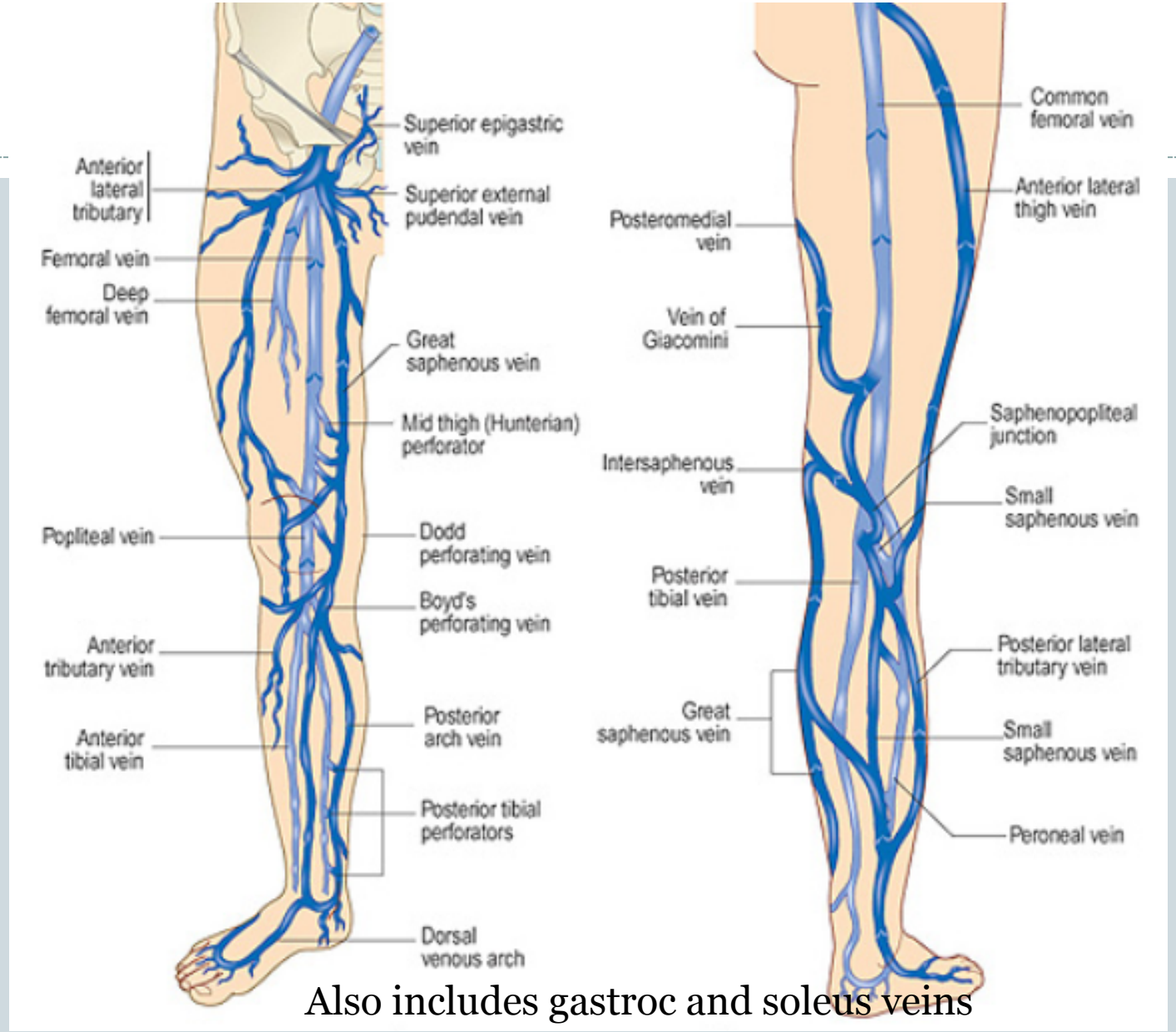
A 77 yo man had undergoes colectomy for recurrent bleeding from diverticulosis. On POD # 3 he becomes tachycardic to the 110s. WBC is elevated.The surgical team orders an abdominal CT which shows a fluid collection concerning for early abscess. It also shows an isolated RLL subsegmental PE. A dedicated CTa shows a single isolated RLL subsegmenral PE. Do you anticoagulate this patient?

a) Sure, it is a PE.
b) No this is incidental. Lets pretend we don't know it is there

Calf Vein DVT

A 37 year old man presents with right calf pain one week after being kicked in calf during a soccer game. On exam right calf is 2 cm> left. U/S shows thrombosis in the peroneal vein. What anticoagulation regimen do you recommend?

1. Rivaroxaban 15 mg BID x 21 days then 20 mg daily to complete 3 months of therapy
2. Prophylactic dosing of LMWH or DOAC
3. No anticoagulation, return in one week for repeat ultrasound of lower extremity.
4. Um, is that a deep vein? ♪

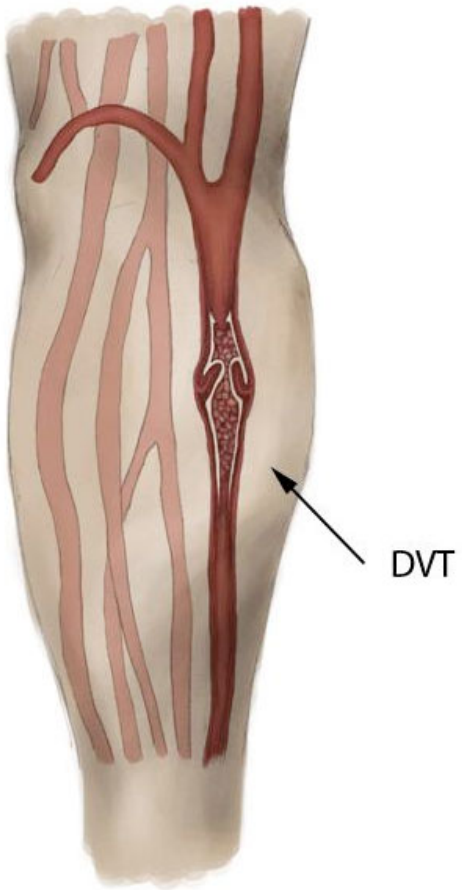


Also includes gastroc and soleus veins

Calf Vein DVT-CHEST 2016

Whether and How to Anticoagulate Isolated Distal DVT

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



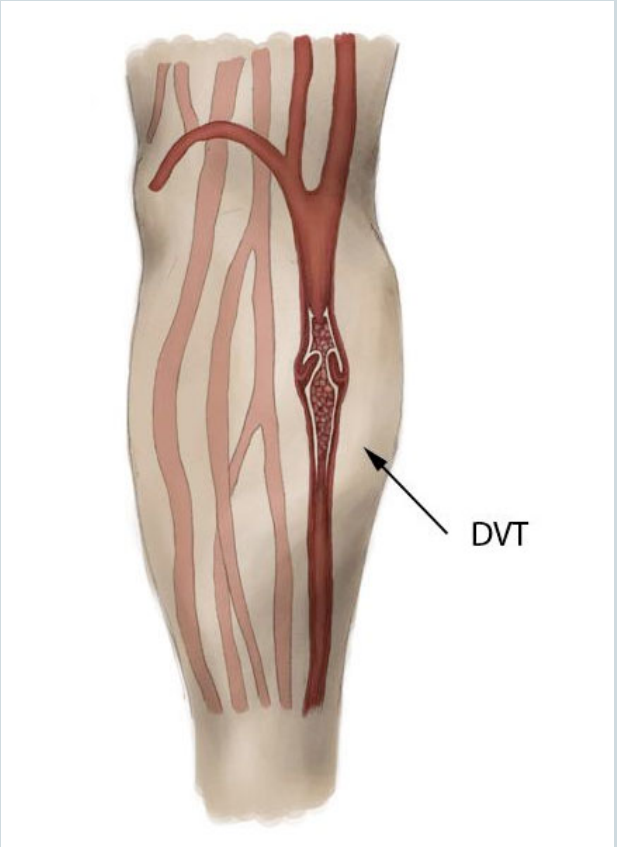
Risk factors for extension: d-dimer +, extensive thrombosis close to proximal veins; active cancer, prior VTE, inpatient

Kearon et al. Chest. 2016;149(2):315-352.

Calf Vein DVT-CHEST 2016

AC Forum clinical guidance

We suggest treatment of distal DVT with anticoagulation versus observation. We suggest a duration of therapy 3 months.



Streiff MB et al. *J Thromb Thrombolysis*. 2016;41:32-67..

Calf Vein DVT

Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial

Marc Righini, Jean-Philippe Galanaud, Hervé Guenneguez, Dominique Brisot, Antoine Diard, Pascale Faisse, Marie-Thérèse Barrellier, Claudine Hamel-Desnos, Christine Jurus, Olivier Pichot, Myriam Martin, Lucia Mazzolai, Clarisse Choquenet, Sandrine Accassat, Helia Robert-Ebadi, Marc Carrier, Grégoire Le Gal, Bernadette Mermilllod, Jean-Pierre Laroche, Henri Bounameaux, Arnaud Perrier, Susan R Kahn, Isabelle Quere

Summary

Background The efficacy and safety of anticoagulant treatment is not established for patients with acute symptomatic deep vein thrombosis (DVT) of the calf. We aimed to assess whether therapeutic anticoagulation is superior to placebo in patients with

Methods In thi
cancer or previo
medical centre

Lancet Haematol 2016; 3: e556–62

- 1st DVT, no cancer, outpatient only
- 6 weeks LMWH and GCS vs placebo and GCS
- U/S at 3-7 days and 42 days
- Outcome progression to proximal DVT or PE
- No difference in VTE (3% v 5%), increased risk of bleeding (4% v 0%)

Righini et al. Lancet Haematol 2016;3: e556–62

Calf Vein DVT

A 37 year old man presents with right calf pain on week after being kicked in calf during a soccer game. On exam right calf is 2 cm> left. U/S shows thrombosis in the peroneal vein. What anticoagulation regimen do you recommend?

1. Rivaroxaban 15 mg BID x 21 days then 20 mg daily to complete 3 months of therapy
2. Prophylactic dosing of LMWH or DOAC
3. No anticoagulation, return in one week for repeat ultrasound of lower extremity.
4. Um, is that a deep vein? ♪

Superficial Vein Thrombosis

A 55 year old woman presents with painful swelling over anterior left thigh. On exam she has a palpable cord concerning for SVT. She has an u/s which shows thrombosis of the greater saphenous vein extending from the calf proximally and terminating 6 cm from the deep femoral vein. What do you recommend?

a. Prophylactic fondaparinux
b. Prophylactic rivaroxaban
c. Full dose DOAC or warfarin
d. NSAIDS and ice

Superficial Vein Thrombosis –CHEST Guidelines

- Factors that favor the use of AC : extensive SVT; above the knee, close to saphenofemoral junction; severe symptoms; involvement of the greater saphenous vein; history of VTE or SVT; active cancer; recent surgery
- In patients with superficial vein thrombosis of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B).

CALISTO TRIAL- fonda vs placebo
Primary outcome 1% vs 6%

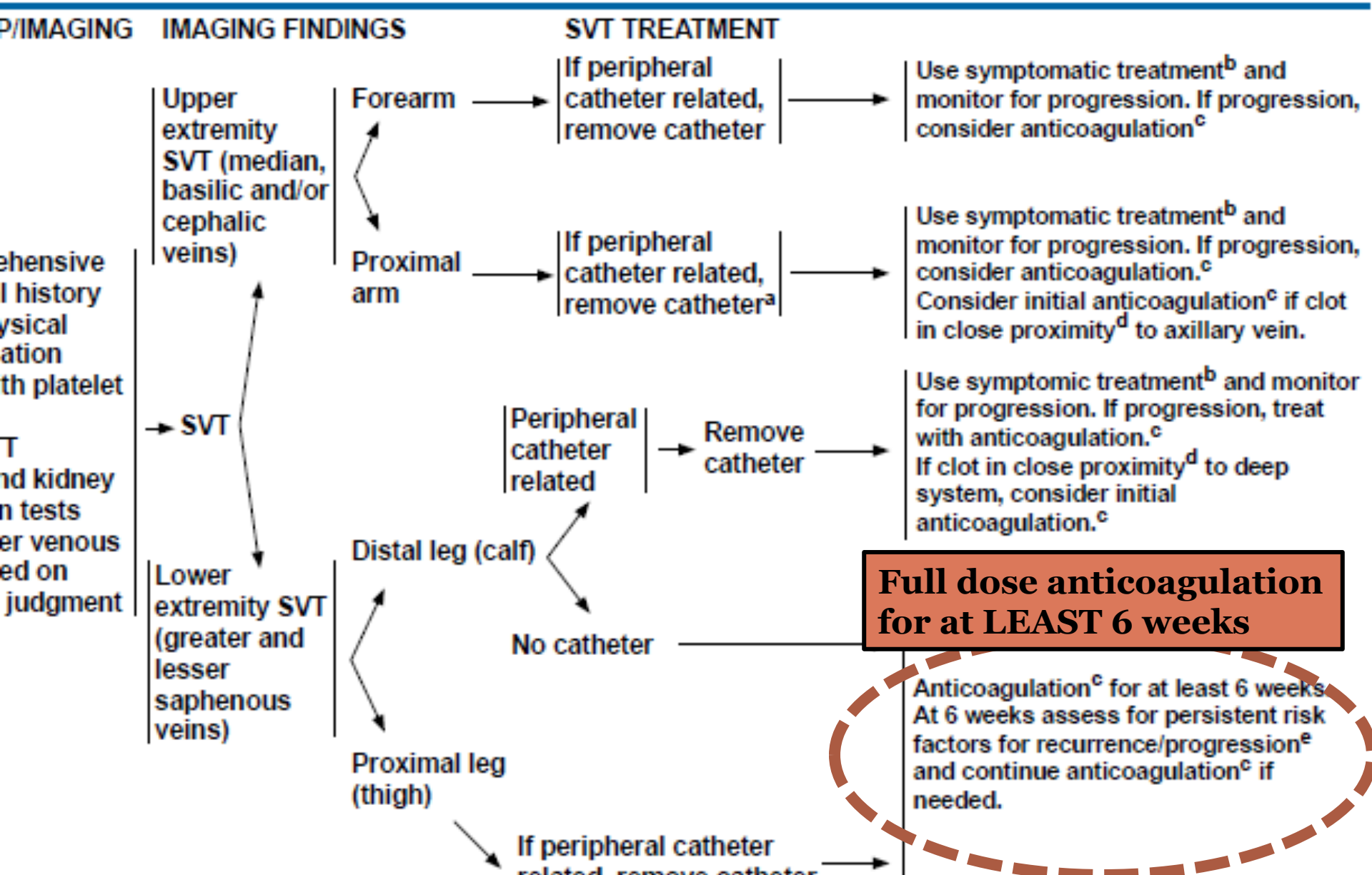
Kearon C et al. *Chest*. 2012

Superficial Vein Thrombosis

Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 2b trial

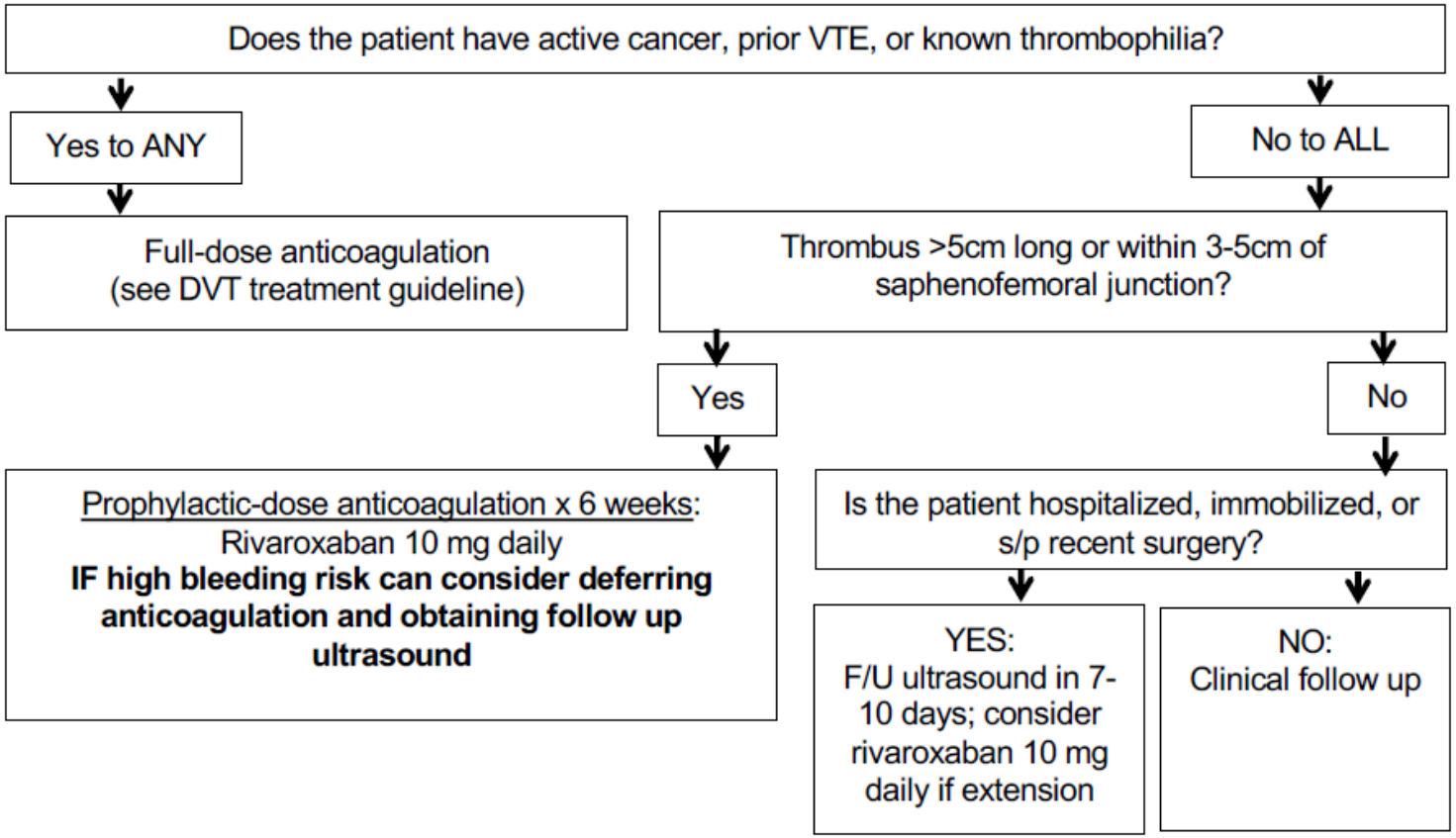
- >400 pts symptomatic SVT riva 10 mg v fonda 2.5mg
- Symptomatic above the knee SVT of at least ≥ 5 cm length + other risk factor (>65 , male,hx VTE , cancer, autoimmune disease, non-varicose veins)
- No difference in primary efficacy outcome
- After 6 weeks 7% recurrence risk in high risk patients (v 1.2% in CALISTO)

NCCN Guidelines Version 1.2017
Acute Superficial Vein Thrombosis (SVT)



Guide to management of superficial venous thrombosis of lower extremity

SFVAMC Anticoagulation and Thrombosis Service – Updated 6.2019



Kearon et al. CHEST 2016; 149(2):315-352; Decousus N Engl J Med 2010;363:1222-32; Bayer-Westendorf Lancet Haematol 2017; 4: e105–13

Superficial Vein Thrombosis

A 55 year old woman presents with painful palpable swelling over anterior left thigh. On exam she has a palpable cord concerning for SVT. She has an u/s which shows thrombosis of the greater saphenous vein extending from the calf proximally and terminating 2 cm from the deep femoral vein. What anticoagulant regimen do you recommend?

a. Prophylactic fondaparinux
b. Prophylactic rivaroxaban
c. Full dose DOAC or warfarin
d. Nsaids and ice

Duration of Anticoagulation for VTE

A 57 year old man presents with unprovoked PE. He has no other PMHx. He is started on rivaroxaban. How long should he remain on anticoagulation?

1) One year

2) 6 months

3) 3 months

4) Indefinitely

Risk of VTE Recurrence After Anticoagulation Is Stopped

Characteristic	Recurrence at 1 yr	Recurrence at 5 yr
Major provoked (transient)	1%	3%
Minor provoked (transient)	5%	15%
Unprovoked	10%	30%
Cancer	20%	—

~20% in those with medically provoked VTE

Major transient risk factors

Major surgery, trauma

Minor transient risk factors

Pregnancy, minor surgery, long-haul air travel, immobilization, medical illness

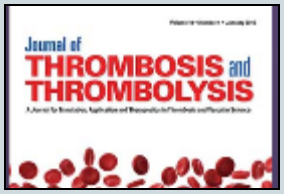
Nontransient risk factors

Active cancer, severe thrombophilia, inflammatory bowel disease

Kearon C et al. *Blood*. 2014;123(12):1794-1801.

2. Heit JA. *Nat Rev Cardiol*. 2015;12(8):464-474.

Duration of Anticoagulation for VTE: 2016 CHEST and AC Forum Guidelines/Guidance



Indication	CHEST 2016[1]	AC Forum 2016[2]
1st provoked VTE	3 mo	3 mo (surgical)[a] ≥3 mo (medical)
1st unprovoked VTE	Extended[b]	Extended
2nd unprovoked VTE	Extended[b]	Extended
VTE + cancer	Extended[b]	Extended

[a]Unless risk factors for recurrence persist

[b]No scheduled stop date, unless high bleeding risk.

Kearon C et al. *Chest*. 2016;149(2):315-352. Streiff MB et al. *J Thromb Thrombolysis*. 2016;41:32-67.

ESC PE Guidelines-Duration of Therapy

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]	DURATION OF AC
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	≥ 3 months
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	Suggest indefinite
	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	Recommend indefinite

Konstantinedes et al. Eur Heart J. 2019;Epub ahead of print.

VTE and Bleeding Risk: 2016 CHEST Guideline

Risk of Major Bleeding After 3 Mo of Anticoagulation, %/y			
	Low *(0 risk factors)*	**Moderate** *(1 risk factor)*	**High** *(≥2 risk factors)*
Baseline risk	0.3	0.6	≥2.5
Increased risk	0.5	1.0	≥4.0
Total risk	0.8	1.6	≥6.5

Risk Factors for Bleeding with Anticoagulation

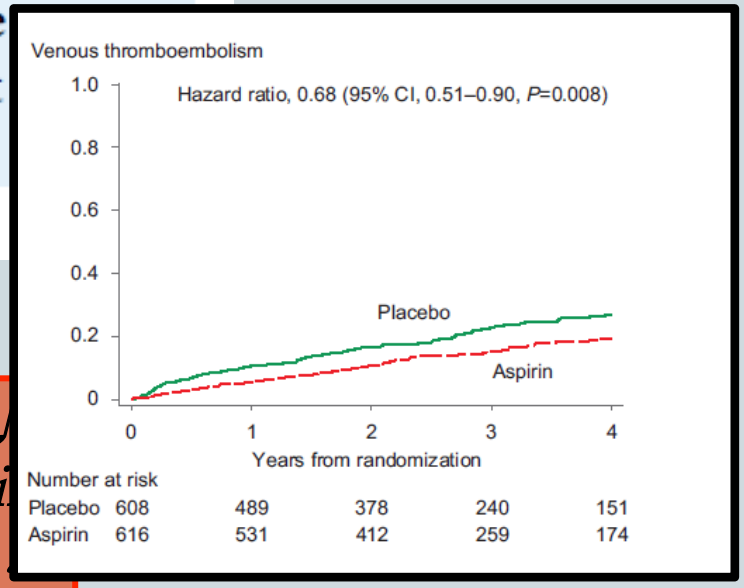
- **Age >65 y**
- **Age >75 y**
- **Previous bleeding**
- **Cancer**
- **Renal or hepatic failure**
- **Thrombocytopenia**
- **Previous stroke**
- **Diabetes**
- **Anemia**
- **Antiplatelet therapy**
- **Poor anticoagulation control**
- **Recent surgery**
- **Frequent falls**
- **Alcohol abuse**
- **NSAID use**

Reprinted from *Chest*, 149(2), Kearon C et al, Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report, 315-352, with permission from the American College of Chest Physicians.

ASA for Secondary VTE Prevention

Aspirin for Extended Treatment of VTE

***12. In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we aspirin over no aspirin to prevent recurrent** (Grade 2C).



ASA is not considered a reasonable alternative to anticoagulant therapy i patients who want extended duration therapy♪

Simes et al. Circulation. 2014;130:1062-1071.)

ORIGINAL ARTICLE

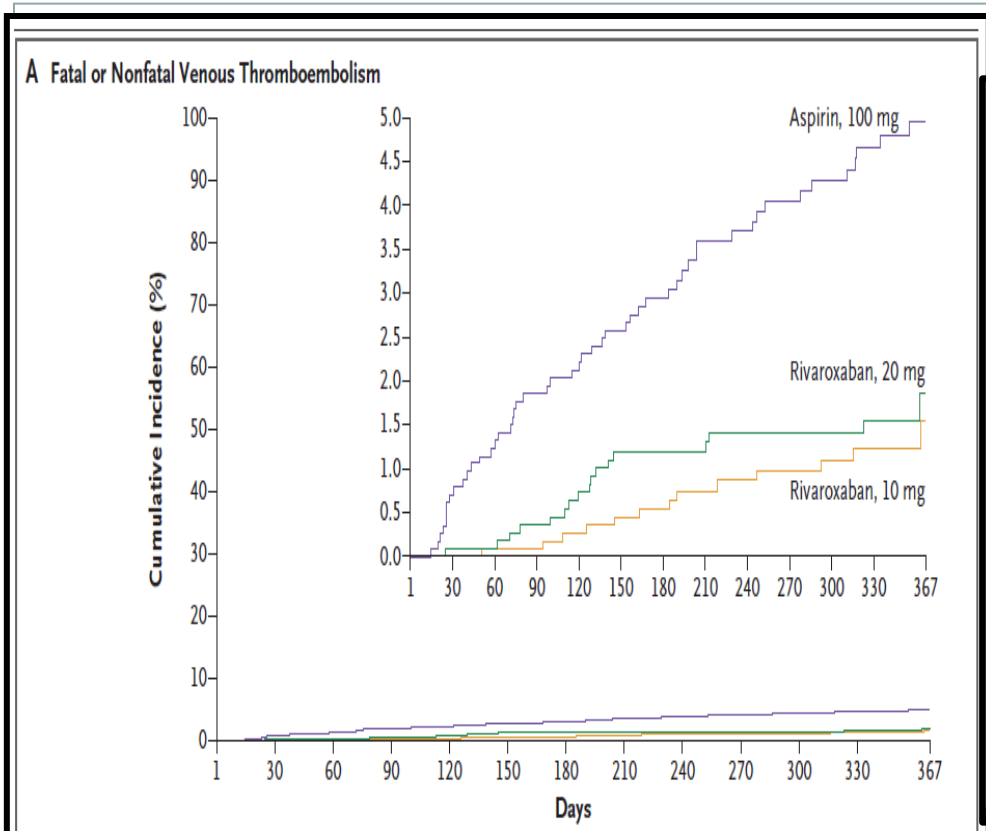
Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

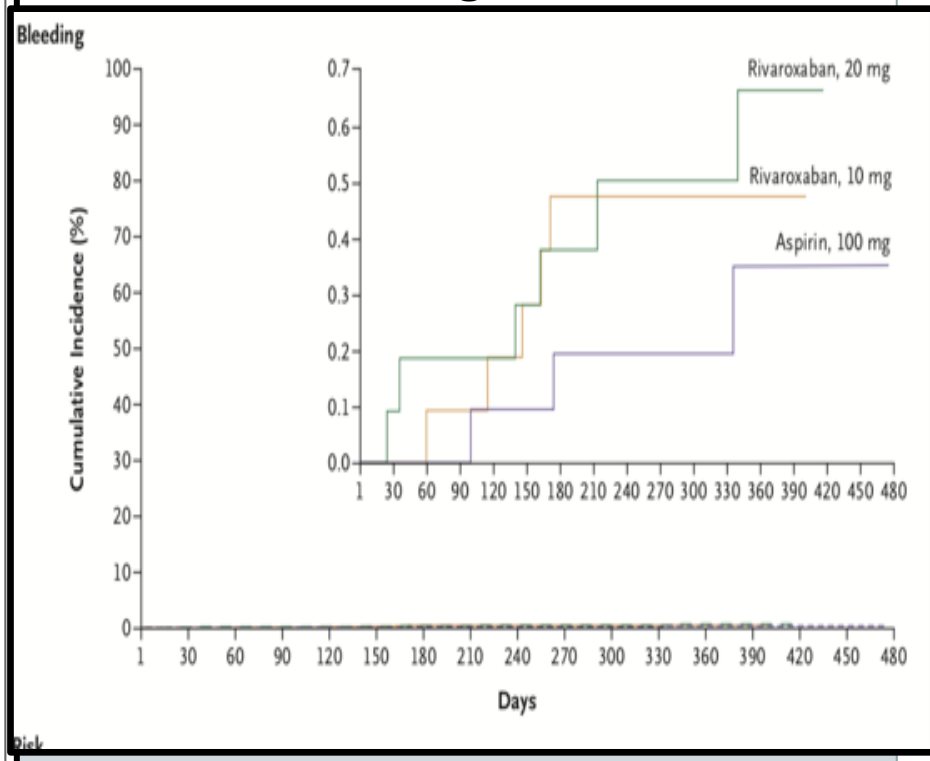
J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

- After 6-12 months of anticoagulation for VTE
- Provoked (~60%) or unprovoked (~40%)
- Clinical equipose about indefinite AC therapy
- One year follow up

Weitz et al. N Engl J Med March 2017

Weitz et al. N Engl J Med March 2017





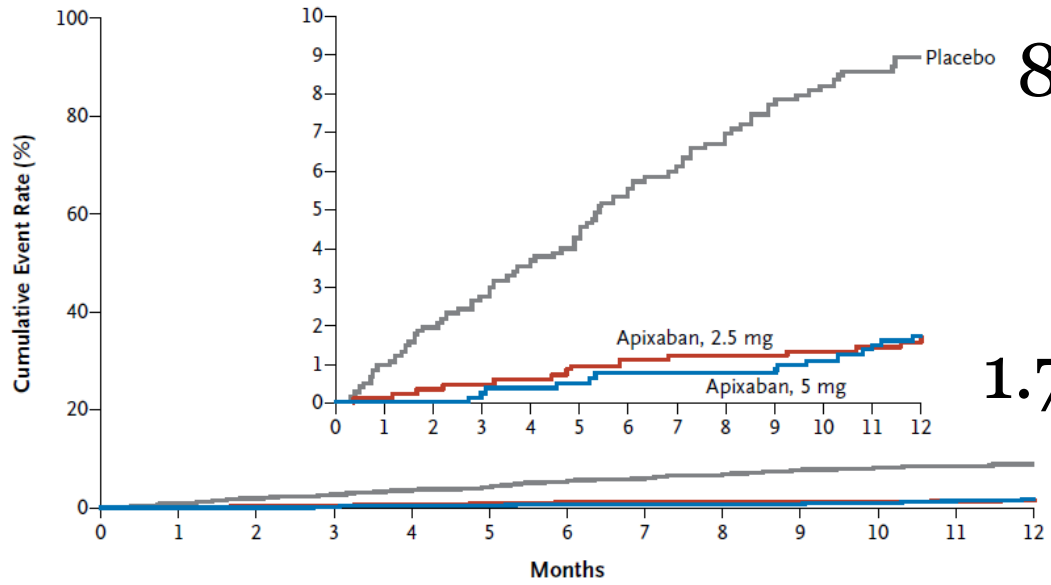
	All	Provoked VTE	Recurrent VTE	BLEED
Rivaroxaban 20 mg	1.5%	1.4%	1.5%	3.3%
Rivaroxaban 10 mg	1.2%	0.9%	1.0%	2.4%
ASA 81 mg	4.4%	3.6%	8.8%	2.0%

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 21, 2013 VOL. 368 NO. 8

Apixaban for Extended Treatment of Venous Thromboembolism

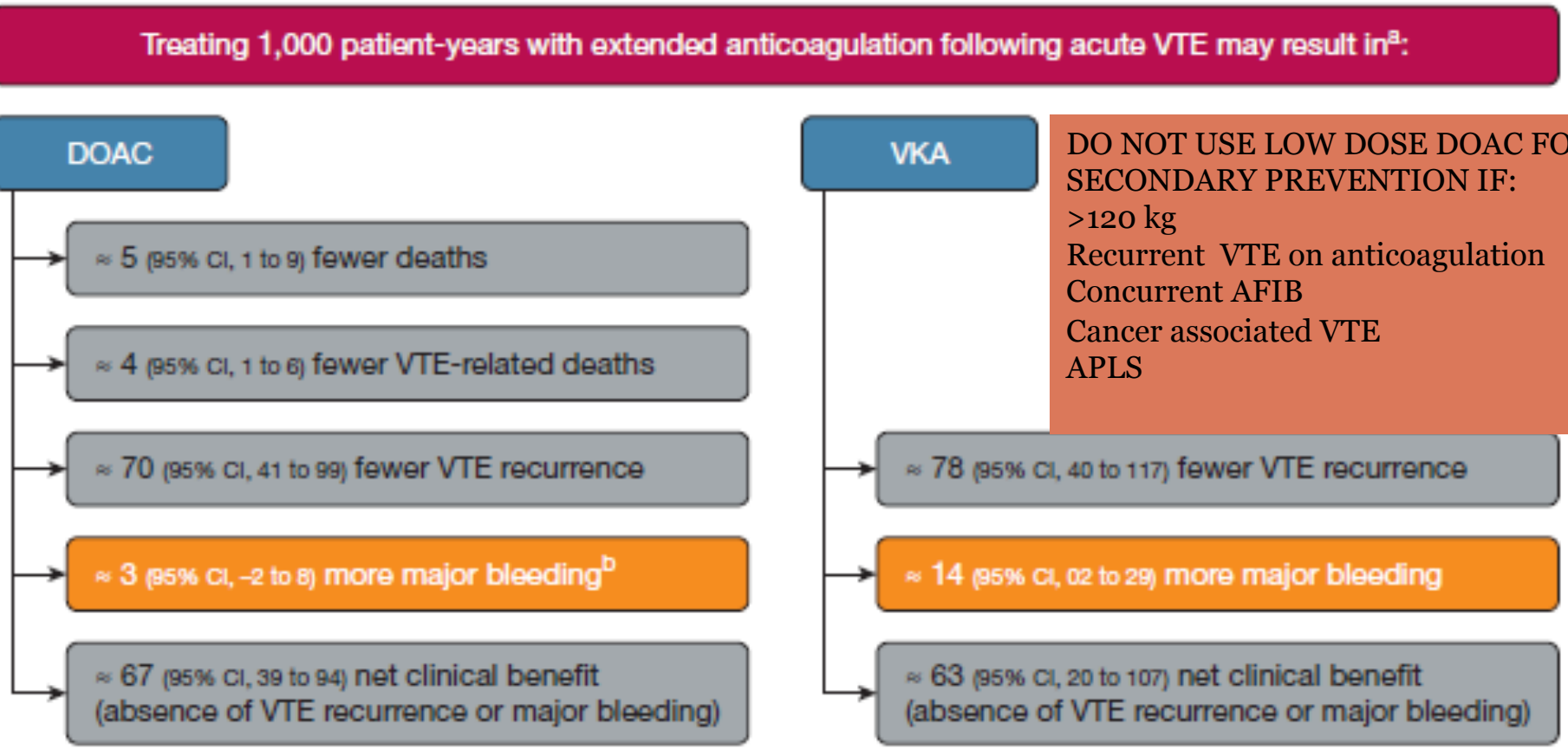
Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*



8.8%

1.7%

Agnelli etal
NEJM 2013



DO NOT USE LOW DOSE DOAC FOR SECONDARY PREVENTION IF:
>120 kg
Recurrent VTE on anticoagulation
Concurrent AFIB
Cancer associated VTE
APLS

Mai V et al CHEST 2019

UNPROVOKED VTE

- All patients get 3-6 months of FULL intensity anticoagulation for VTE
- At 3-6 months determine candidacy for secondary prevention
- ~50% will develop recurrent VTE if off anticoagulation
- Case fatality rate of VTE is ~4% in all comers but closer to 9% in those who present with PE
- Case fatality rate of bleeding is ~10%
- Case by case decision…consider continuation in all if not

Secondary Prevention Options	Do not use dose reduced DOAC:
Low dose DOAC***	Obesity
Full dose anticoagulation	Cancer
ASA	Recurrent VTE on AC

Duration of Anticoagulation for VTE

A 57 year old man presents with unprovoked PE. He has no other PMHx. He is started on rivaroxaban. How long should he remain on anticoagulation?

1) One year

2) 6 months

3) 3 months

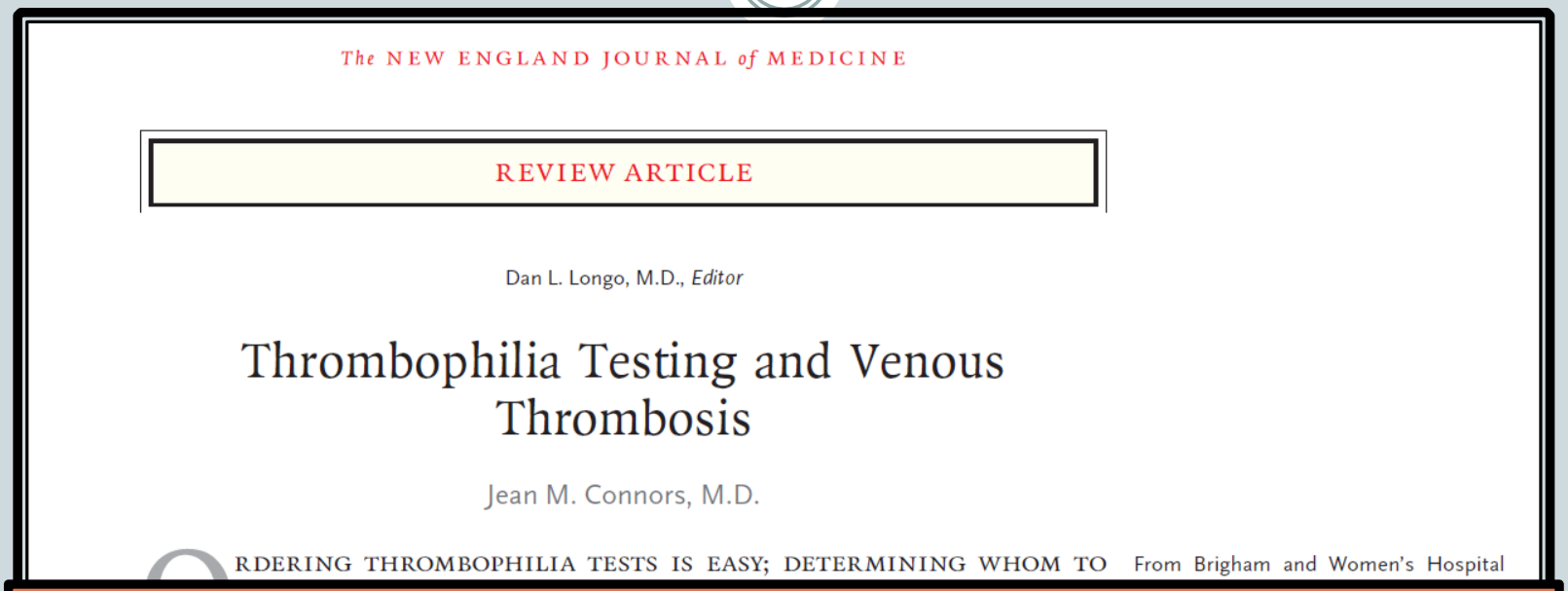
4) Indefinitely

Thrombophilia Testing

Should he have a thrombophilia work up for this unprovoked VTE event?

- Yes
- No

Thrombophilia Testing



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Thrombophilia Testing and Venous Thrombosis

Jean M. Connors, M.D.

RDERING THROMBOPHILIA TESTS IS EASY; DETERMINING WHOM TO

From Brigham and Women's Hospital

No current guidance/.guidelines
EXCEPT ASH Choosing Wisely Campaign-"do not test in provoked VTE"
Results of thrombophilia testing should RARELY affect clinical decisions about VTE treatment-no strong influence on recurrence risk beyond stratification based on clinical presentation
Can help explain "why"
Can be of interest to family members
Current tests are insufficient for identifying inherited VTE risk

Who should we suspect harbors thrombophilia?

Table 1. 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, combination oral contraceptives, or immobility) 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†

* The antiphospholipid syndrome must also be considered, but it is not inherited.
† Patients with splanchnic-vein VTE should be assessed for myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria.

UNPROVOKED THROMBOSIS IN YOUNG PATIENT THINK ABOUT:

- PROTEIN C, S, ANTITHROMBIN DEFICIENCY→OFTEN POSITIVE FAMILY HISTORY
- FACTORV LEIDEN MUTATION AND PROTHROMBIN GENE MUTATION -Northern european descent
- APLS-PRIMARY OR SECONDARY (lupus)
- MAY THURNERS SYNDROME- ILIAC VEIN COMPRESSIOJN SYNDROME…LEFT LOWER EXTREM VENOUS COMPRESSION-LEFT ILIAC VEIN COMPRESSED BY RIGHT ILIAC ARTERY
- UPPER EXTREMITY DVT-PAGET SCHROEDERS SYNDROME-THORACIC OUTLET SYNDROME WITH VENOUS COMPRESSION
- NEPHROTIC SYNDROME
- IBD
- PNH
- PREGNANCY, IVF
- CANCER (less likely < 50 yo)

VENOUS AND ARTERIAL THROMBOSIS

- APLS
- PFO-with paradoxical embolism
- HYPERHOMOCYSTIENEMIA
- SICKLE CELL
- P VERA
- PNH
- HIT
- CANCER
- DIC
- Beurgers disease
- Hyperviscosity-MGUS, MM

Thrombophilia Tests

Table 3. Thrombophilia Tests and Prevalence of Risk Factors.*

Thrombophilia Type	Assay	Prevalence
Inherited		
Increased procoagulant activity (common)		
Factor V Leiden	APCR and PCR	White, 5.0% Hispanic, 2.2% Black, 1.2% Native American, 1.2% Asian, 0.4%
Prothrombin gene mutation	PCR	White, 3%
Decreased anticoagulant activity (uncommon)		
Protein C	Activity assay	<0.5%
Protein S	Activity assay	<0.5%
Antithrombin	Activity assay	<0.5%
Acquired		
Lupus anticoagulants†	In vitro clotting assay: PTT-LA, dRVVT, silica clotting time ELISA: ACL IgG and IgM, beta-2 glycoprotein 1 IgG and IgM	Overall, 0–5% Patients with VTE, 10–12% Patients with SLE, 35%

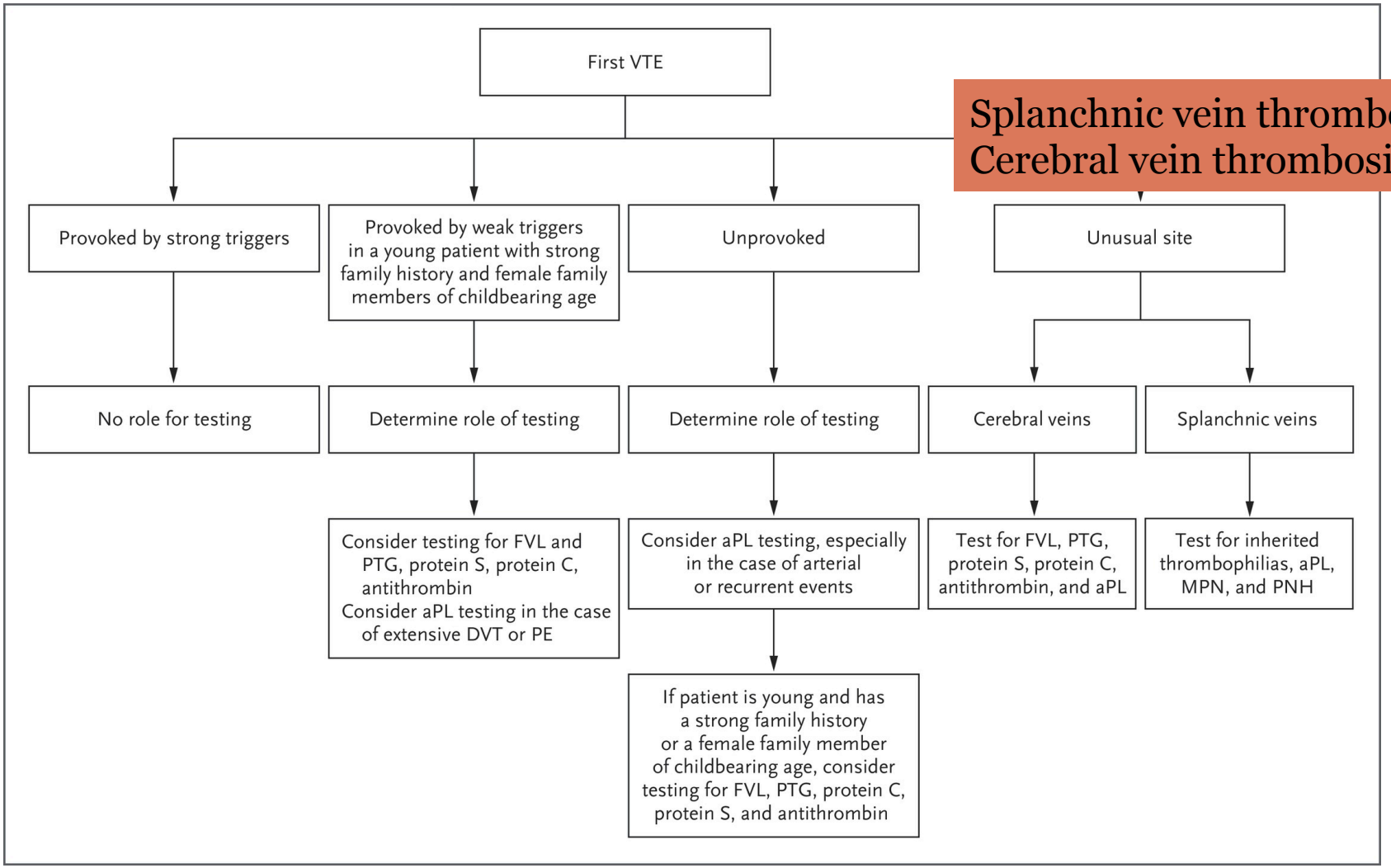
Summary of Recommendations Regarding Testing for Thrombophilia.

Table 2. Summary of Recommendations Regarding Testing for Thrombophilia.*

Recommendation	Explanation
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
Do not test if VTE is provoked by strong risk factors	Strong risk factors are major trauma, major surgery, immobility, major illness
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
Identify goals of testing	Identify goals in order to aid decision making regarding future VTE prophylaxis, to guide testing of family members (especially regarding risk associated with COC or pregnancy in female family members), and to determine cause (especially for severe VTE, fatal VTE in family members, or VTE in an unusual location); test results alone should not be used for decision making regarding duration of anticoagulant therapy

* COC denotes combination oral contraceptives, DOAC direct oral anticoagulant, LMWH low-molecular-weight heparin, UFH unfractionated heparin, and VKA vitamin K antagonist.

Algorithm for Selecting Patients with a First Venous Thromboembolism (VTE) for Thrombophilia Testing.



Splanchnic vein thrombosis
Cerebral vein thrombosis

IMPACT OF ANTICOAGULATION & THROMBOSIS ON THROMBOPHILIA LABS

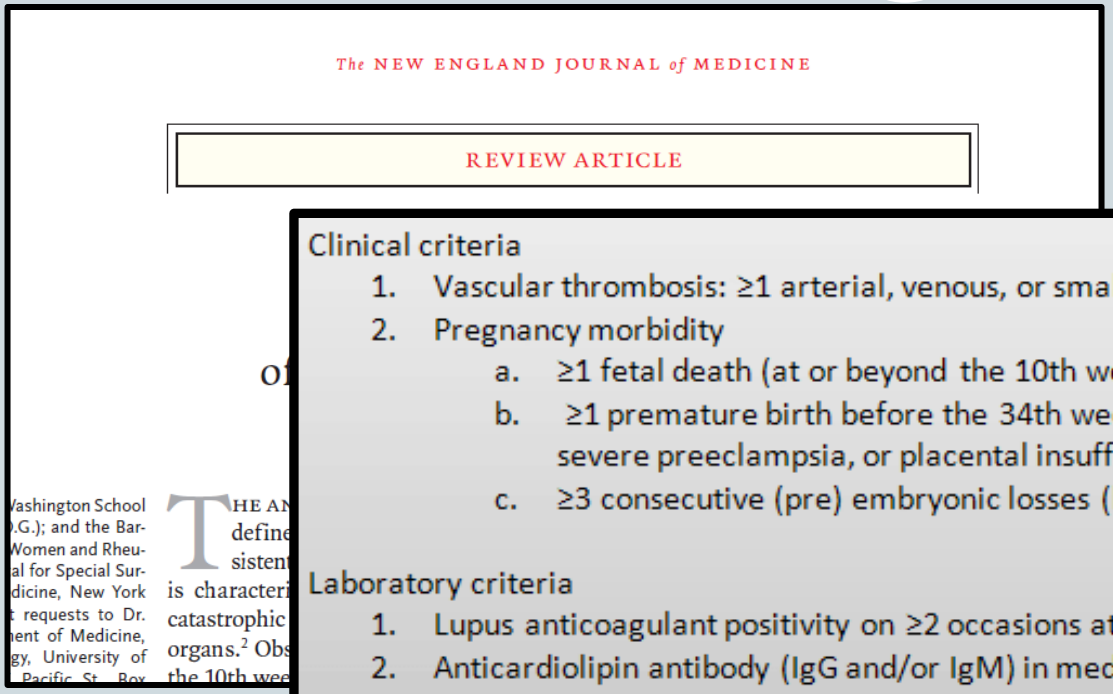
	ACUTE THROMBOSIS	WARFARIN	HEPARIN	DOAC
PROTEIN C,PROTEIN S	↓ (FALSE POSITIVE)	↓ (FALSE POSITIVE)	NO EFFECT	FALSE NORAML
ANTITHROMBIN	↓ (FALSE POSITIVE)	↑ (FASLE NEGATIVE)	↓ (FALSE POSITIVE)	FALSE NORMAL
LUPUS ANTICOAGULANT	NO EFFECT	FALSE POSITVE	FALSE POSITIVE	FASLE POSITIVE
B2GP1, Acl ABS	NO EFFECT	NO EFFECT	NO EFFECT	NO EFFECT
FACTOR V LEIDEN	NO EFFECT	NO EFFECT	NO EFFECT	NO EFFECT
PROTHROMBIN GENE MUTATION	NO EFFECT	NO EFFECT	NO EFFECT	NO EFFECT

DEFER TESTING (3-6 MOS)

RARELY WE SEND APLS ACUTELYIF STRONG SUSPICION

CAN SEND FLV/PTG BUT IN HETEROZYGOUS FORM NOT IMPORTANT

Antiphospholipid Antibody Syndrome


The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Clinical criteria

1. Vascular thrombosis: ≥1 arterial, venous, or small vessel thrombosis.
2. Pregnancy morbidity
   a. ≥1 fetal death (at or beyond the 10th week of gestation)
   b. ≥1 premature birth before the 34th week of gestation because of eclampsia, severe preeclampsia, or placental insufficiency
   c. ≥3 consecutive (pre) embryonic losses (before the 10th week of gestation)

Laboratory criteria

1. Lupus anticoagulant positivity on ≥2 occasions at least 12 weeks apart.
2. Anticardiolipin antibody (IgG and/or IgM) in medium or high titer (i.e., >40, or above the 99th percentile), on two or more occasions at least 12 weeks apart.
3. Anti-β2-glycoprotein-I antibody (IgG and/or IgM) in medium or high titer (i.e., above the 99th percentile) on two or more occasions at least 12 weeks apart.

Definite APS is present if at least one of the clinical criteria and one of the laboratory criteria are met

Antiphospholipid Antibody Syndrome

- WHY- risk of recurrence off AC much higher; at risk for arterial disease, bridge therapy; DOACs generally avoided
- WHO- arterial and venous events, unexpected arterial events, recurrent thrombosis ON anticoagulation, underlying autoimmune d/o, prolonged aPTT
- WHAT-send Lupus anticoagulant, Beta 2 glycoprotein antibodies and anticardiolipin antibodies (IgG & Ig M)
- WHEN-LAC-don't do it on anticoagulation; antibodies you can send anytime
- IF POSITIVE-
  - must repeat in 12 weeks-high rate of transient positivity
  - LAC most predicative of 1st and recurrent VTE, triple positives at highest risk

Thrombophilia Testing

Should he have a thrombophilia work up for this unprovoked VTE event?

- Yes
- No

VTE Recurrence on Anticoagulation

A 65 year old man with unprovoked PE that occurred 3 months ago develops SOB and chest pain and is found to have recurrent PE. He is on warfarin. His INR is 2.0. What anticoagulation regimen do you recommend now?♪

A) rivaroxaban♪

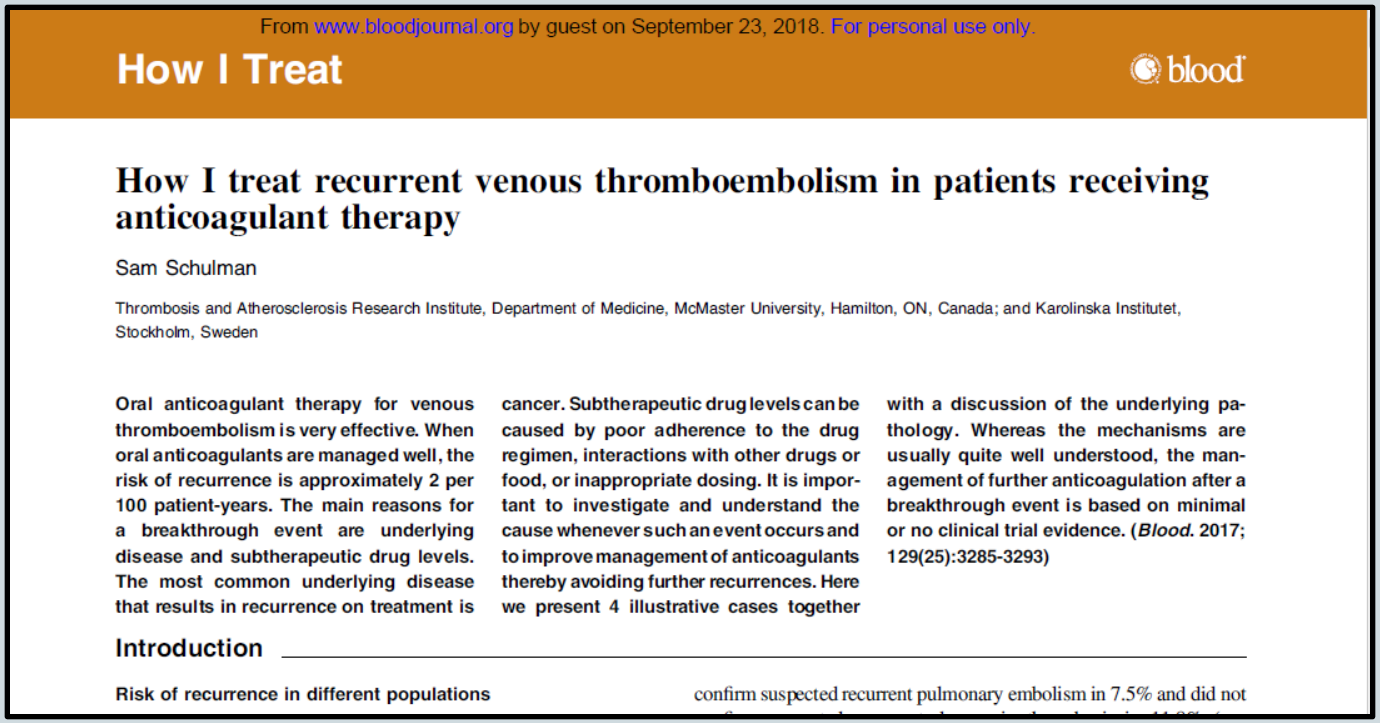
B) warfarin with goal inr 3-4♪

C) IVC filter♪

D) Low molecular weight heparin♪

E) Honestly, why me?♪

VTE Recurrence on Anticoagulation



How I Treat

blood

How I treat recurrent venous thromboembolism in patients receiving anticoagulant therapy

Sam Schulman

Thrombosis and Atherosclerosis Research Institute, Department of Medicine, McMaster University, Hamilton, ON, Canada; and Karolinska Institutet, Stockholm, Sweden

Oral anticoagulant therapy for venous thromboembolism is very effective. When oral anticoagulants are managed well, the risk of recurrence is approximately 2 per 100 patient-years. The main reasons for a breakthrough event are underlying disease and subtherapeutic drug levels. The most common underlying disease that results in recurrence on treatment is cancer. Subtherapeutic drug levels can be caused by poor adherence to the drug regimen, interactions with other drugs or food, or inappropriate dosing. It is important to investigate and understand the cause whenever such an event occurs and to improve management of anticoagulants thereby avoiding further recurrences. Here we present 4 illustrative cases together with a discussion of the underlying pathology. Whereas the mechanisms are usually quite well understood, the management of further anticoagulation after a breakthrough event is based on minimal or no clinical trial evidence. (*Blood.* 2017; 129(25):3285-3293)

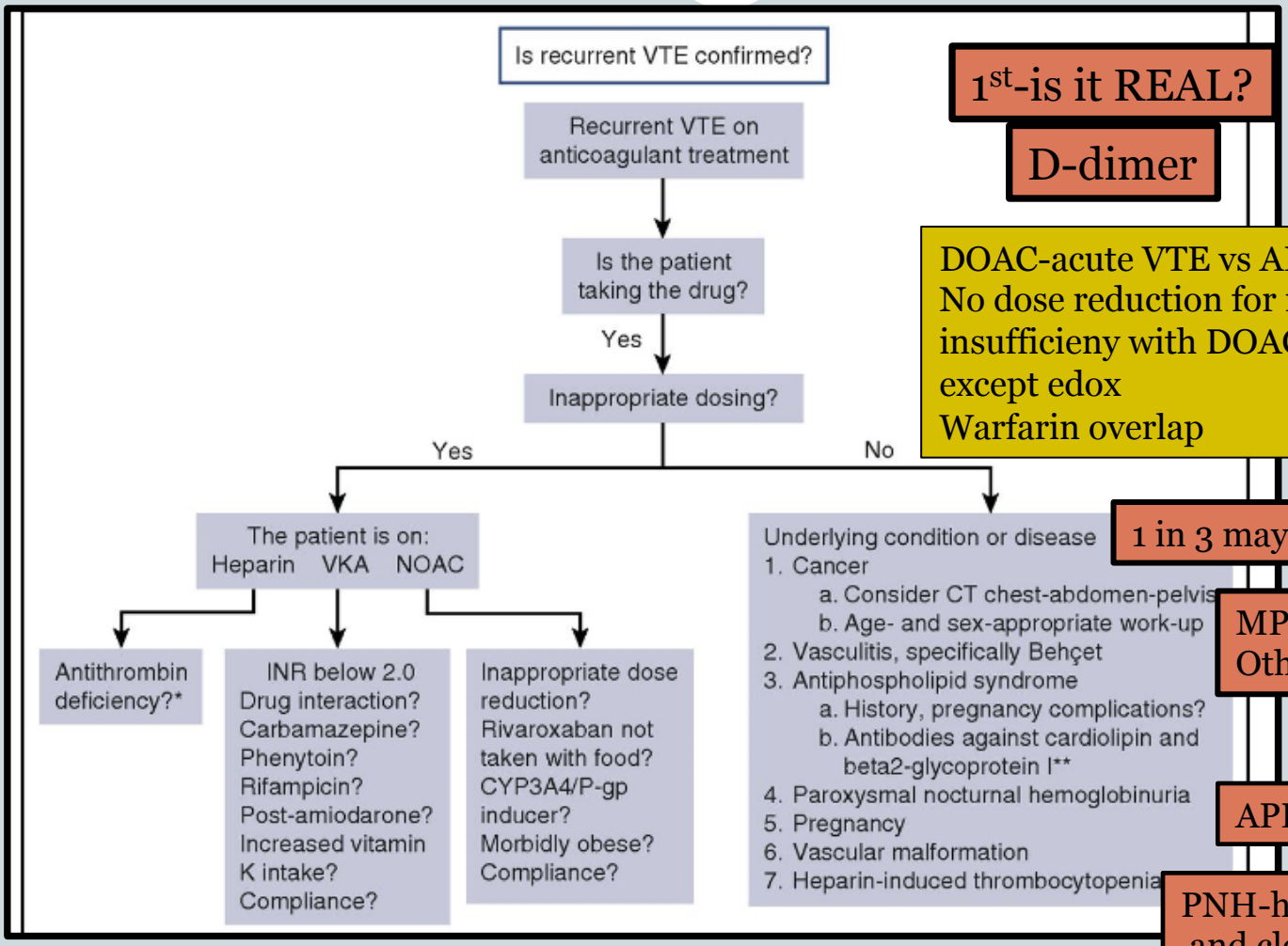
Introduction

Risk of recurrence in different populations

confirm suspected recurrent pulmonary embolism in 7.5% and did not

Shulman Blood 2017

VTE Recurrence on Anticoagulation



1st-is it REAL?

D-dimer

DOAC-acute VTE vs AFIB
No dose reduction for renal insufficieny with DOAC except edox
Warfarin overlap

1 in 3 may have cancer

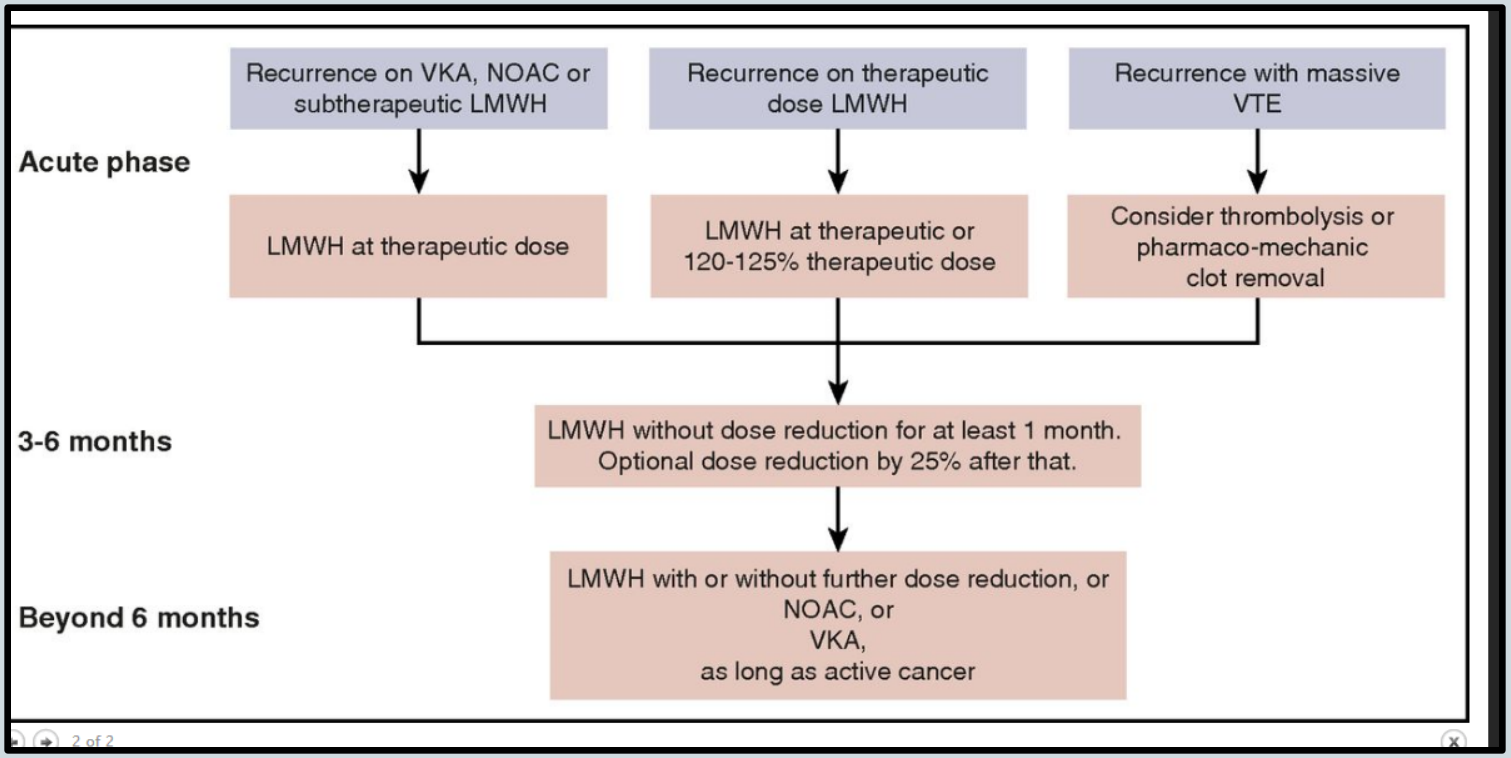
MPO-JAK 2
Other exon mutations

APLS-beware the INR

PNH-hemolysis cytopenias and clots in weird places

Shulman Blood 2017

VTE Recurrence on Anticoagulation



NOTICE-NO MENTION OF IVC FILTER!

Shulman Blood 2017

CHEST 2016:VTE Recurrence While on AC

Anticoagulant Therapy

***29. In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily** (Grade 2C).

***30. In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third** (Grade 2C).

Anticoagulation in Recurrent VTE in APLS

- Increase INR to 3-3.5
- Add ASA to usual intensity warfarin?
- Add statin
- Consider hydroxychloroquine
- LMWH-case reports:some good, some not so good
- Fondaparinux-limited data

VTE Recurrence on Anticoagulation

A 65 year old man with unprovoked PE that occurred 3 months ago develops SOB and chest pain and is found to have recurrent PE. He is on warfarin. His INR is 2.0. What anticoagulation regimen do you recommend now?♪

A) rivaroxaban♪

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C) IVC filter♪

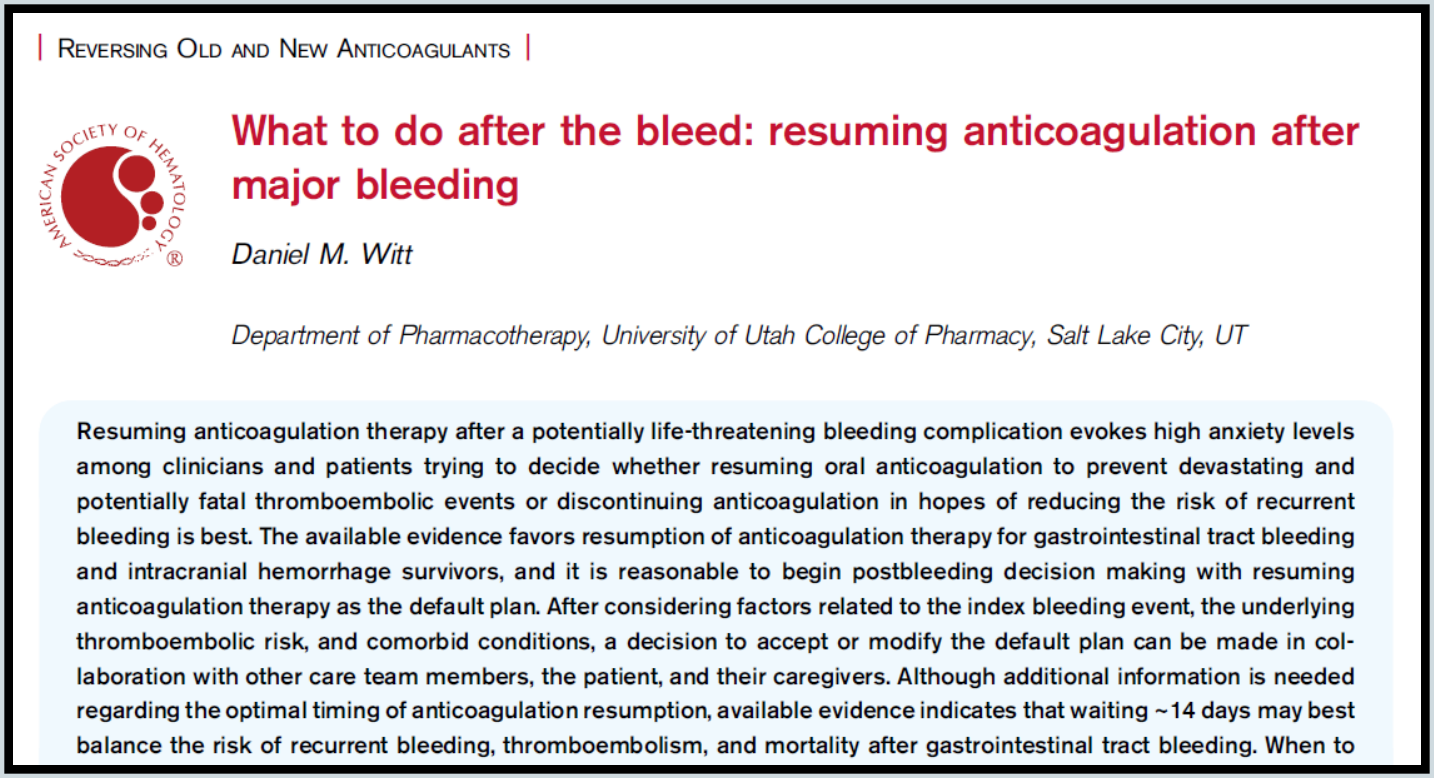
D) Low molecular weight heparin♪

What To Do After the Bleed

76 y/o man with CAD (NSTEMI 2006), AFIB CHADS-Vasc=4 on warfarin and ASA is admitted with UGIB. INR is 3.0. He requires 3u PRBCs, vit K and FFP. EGD shows peptic ulcer disease. He is started on high dose PPI therapy, bx for H Pylori done. When should his anticoagulation be restarted?

a) Never
b) In two weeks
c) In three months
d) Let the primary provider deal with this one

What To Do After the Bleed



REVERSING OLD AND NEW ANTICOAGULANTS

What to do after the bleed: resuming anticoagulation after major bleeding

Daniel M. Witt

Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, UT

Resuming anticoagulation therapy after a potentially life-threatening bleeding complication evokes high anxiety levels among clinicians and patients trying to decide whether resuming oral anticoagulation to prevent devastating and potentially fatal thromboembolic events or discontinuing anticoagulation in hopes of reducing the risk of recurrent bleeding is best. The available evidence favors resumption of anticoagulation therapy for gastrointestinal tract bleeding and intracranial hemorrhage survivors, and it is reasonable to begin postbleeding decision making with resuming anticoagulation therapy as the default plan. After considering factors related to the index bleeding event, the underlying thromboembolic risk, and comorbid conditions, a decision to accept or modify the default plan can be made in collaboration with other care team members, the patient, and their caregivers. Although additional information is needed regarding the optimal timing of anticoagulation resumption, available evidence indicates that waiting ~14 days may best balance the risk of recurrent bleeding, thromboembolism, and mortality after gastrointestinal tract bleeding. When to

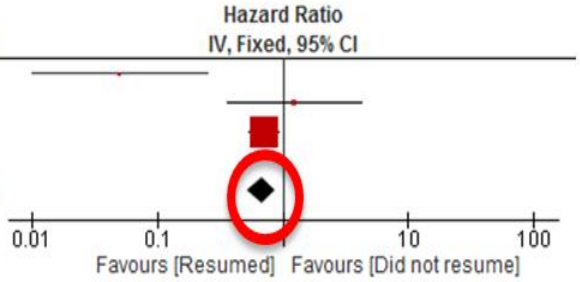
Witt Hematology 2016

Gastrointestinal Tract Bleeding

Overall mortality

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Witt 2012	-2.9957	0.8212	2.6%	0.05 [0.01, 0.25]
Nieto 2008	0.2151	0.631	4.5%	1.24 [0.36, 4.27]
Qureshi 2014	-0.3444	0.1387	92.9%	0.71 [0.54, 0.93]
Total (95% CI)			**100.0%**	**0.68 [0.52, 0.88]**

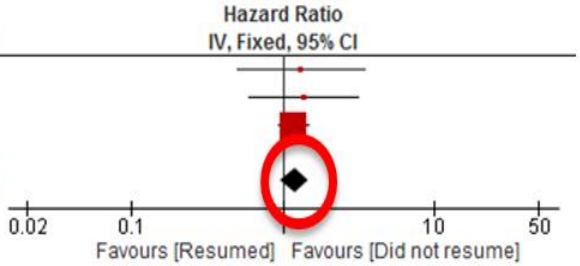
Heterogeneity: $Chi^2 = 11.10$, $df = 2$ ($P = 0.004$); $I^2 = 82\%$
Test for overall effect: $Z = 2.91$ ($P = 0.004$)



Recurrent bleeding

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Witt 2012	0.2776	0.4953	4.9%	1.32 [0.50, 3.48]
Nieto 2008	0.3221	0.425	6.6%	1.38 [0.60, 3.17]
Qureshi 2014	0.1655	0.116	88.5%	1.18 [0.94, 1.48]
Total (95% CI)			**100.0%**	**1.20 [0.97, 1.48]**

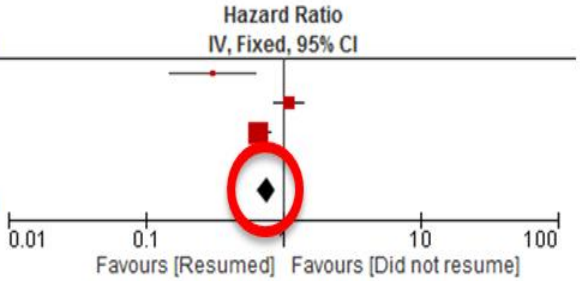
Heterogeneity: $Chi^2 = 0.17$, $df = 2$ ($P = 0.92$); $I^2 = 0\%$
Test for overall effect: $Z = 1.66$ ($P = 0.10$)



Thromboembolism

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Witt 2012	-1.1712	0.3704	3.9%	0.31 [0.15, 0.64]
Nieto 2008	0.0953	0.1315	31.3%	1.10 [0.85, 1.42]
Qureshi 2014	-0.4005	0.0915	64.7%	0.67 [0.56, 0.80]
Total (95% CI)			**100.0%**	**0.76 [0.66, 0.88]**

Heterogeneity: $Chi^2 = 15.67$, $df = 2$ ($P = 0.0004$); $I^2 = 87\%$
Test for overall effect: $Z = 3.74$ ($P = 0.0002$)

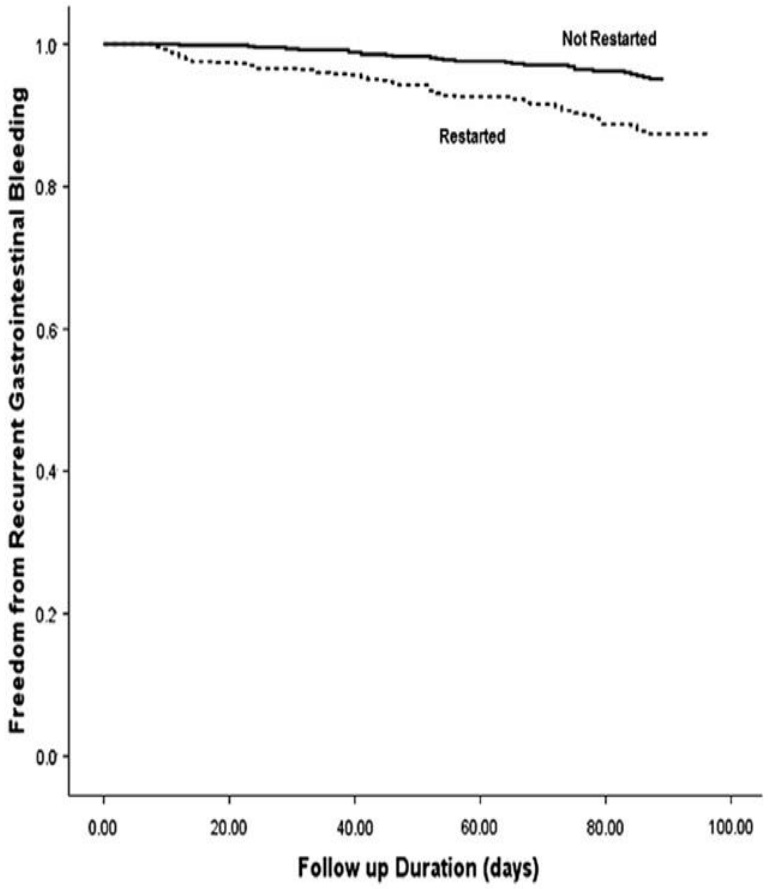


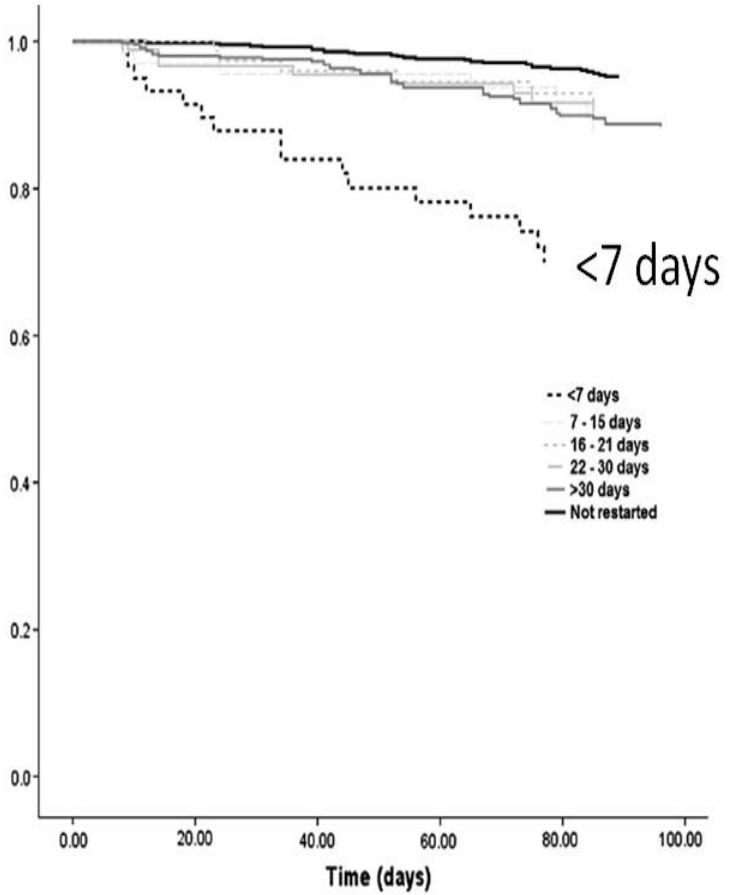
Thromb Haemost 114:819

Gastrointestinal Tract Bleeding

Time-to-event adjusted analyses performed to find an association of restarting warfarin and recurrent GIB, arterial thromboembolism, and mortality.

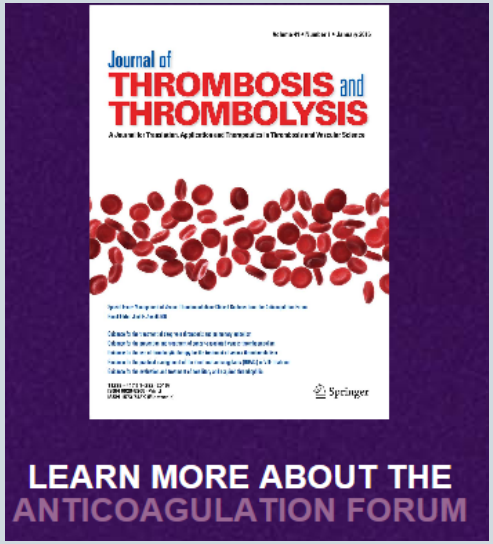
Recurrent GI Bleeding





Am J Card 113:662

AC FORUM Clinical Guidance Antithrombotic Therapy for VTE



"IN THE EVENT OF GI BLEED WE SUGGEST WAITING AT LEAST 7 DAYS WITHOUT EVIDENCE OF ACTIVE BLEEDING AND AFTER ENDOSCOPIC TX BEFORE REINITIATING AC"

GIBs: DOACs vs Warfarin

Table 2

GIBs in studies on patients with AF : DOACs vs warfarin.

Data from: Connolly et al. N Engl J Med 2009;361:1139–1151; Patel et al. N Engl J Med 2011;365:883–891; Granger et al. N Engl J Med 2011;365:981–992; Giugliano et al. N Engl J Med 2013;369(22):2093-104.

	DOAC			Warfarin			DOAC/W (years-pts %)	RR (95% CI) GIB DOAC/W
	GI events (n)	Life-threatening GI events (n)	Total pts. (n)	GI events (n)	Life-threatening GI events (n)	Total pts. (n)		
Dabigatran 110 mg twice daily arm	133	67	6015	120	57	6022	1.12/1.02	1.10 (0.86–1.41) p: 0.43
Dabigatran 150 mg twice daily arm	182	94	6076	120	57	6022	1.51/1.02	1.50 (1.19–1.89) p < 0.001
Rivaroxaban 20 mg once daily arm	224	52 (1 fatal event)	7111	154	47 (5 fatal events)	7125	2.00/1.24	1.46 (1.117–1.902) p < 0.001
Apixaban 5 mg twice daily arm	105	ND	9088	119	ND	9052	0.76/0.86	0.879 (0.624–1.238) p = 0.33
Edoxaban 30 mg once daily arm	129	ND	7002	190	ND	7012	0.82/1.23	0.67 (0.53–0.83) p < 0.001
Edoxaban 60 mg once daily arm	232	ND	7012	190	ND	7012	1.23/1.51	1.23 (1.02–1.50) p = 0.03

ND: not determined.

Di Minno et al. Blood Reviews 2015.

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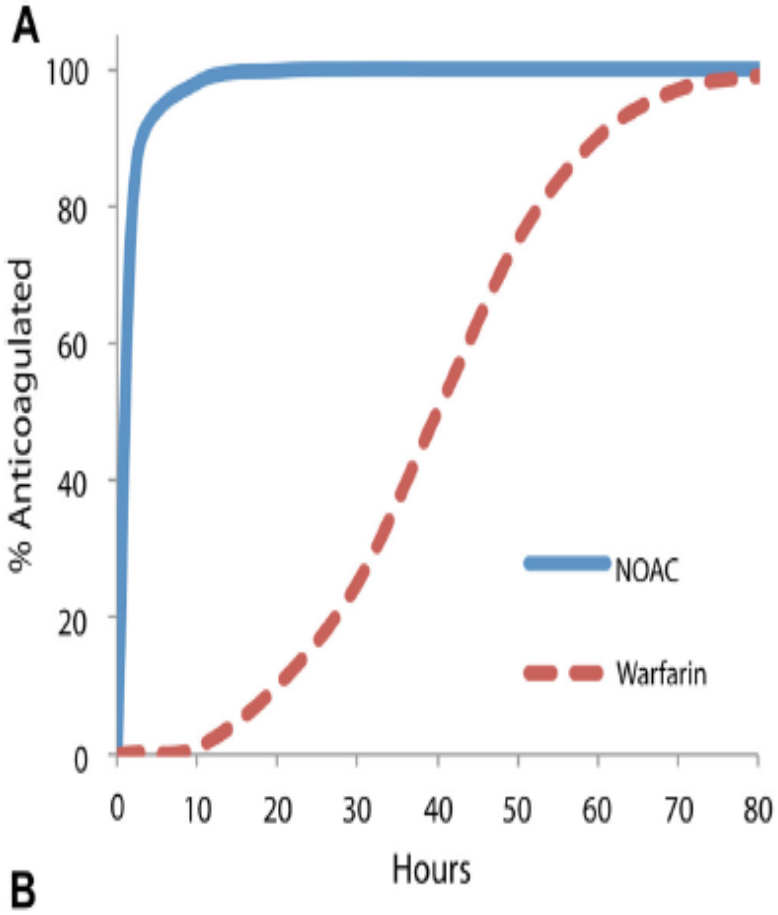
ND: not determined.

Di Minno et al. Blood Reviews 2015.

Resumption of DOACs



Anticoagulation **FULLY** therapeutic within *1-2 hours*

Only dabigatran has a reversal agent

Considerations After GIB on AC

- Reassess risk benefit of anticoagulation
  secondary prevention of VTE therapy, low CHADS-vasc
- Assess risk of rebleeding from source
  identifiable source, treatable lesion?
- Take steps to decrease risk of bleeding related to AC regimen
- Reconsider need for antiplatelet therapy
  if warfarin-was INR in range, is control good?
  spurious elevation in INR or poor TTR→DOAC
  increase INR monitoring->home POC INR?
- If ongoing strong indication for AC determine best time to restart therapy in multidisciplinary meeting with proceduralist - *Remember DOAC immediately active*

What To Do After the Bleed

76 y/o man with CAD (NSTEMI 2006), AFIB CHADS-Vasc=4 on warfarin and ASA is admitted with UGIB. INR is 3.0. He requires 3u PRBC. He has peptic ulcer disease. He is on PPI therapy, bx for H Pylori. When should anticoagulation be restarted?

a) Never
b) In two weeks
c) In three months
d) Let the primary provider deal with this one

"Two weeks may provide the best balance among GI bleed recurrence , thromboembolism and mortality""

DOAC selection, dosing, monitoring

Mr. M is an 80 year old man with CHF, HTN, CKD, and acute unprovoked PE. He has a remote history of GI bleed from gastritis. He is on a PPI. He does not want to use warfarin and is interested in a "new" blood thinner. Which DOAC do you choose for him?

Table 1. Comparison of Warfarin and DOACs

	Warfarin[8]	Dabigatran[7]	Rivaroxaban[3,9]	Apixaban[4,10]	Edoxaban[6,11]
Target	Vitamin K epoxide reductase	Free and clot-bound thrombin	Factor Xa	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No	No
Bioavailability	>95%	6.5%	>80%	50%	62%
Metabolism	Hepatic; primarily metabolized by CYP2C9; also metabolized by	Renal; 80% renally excreted unchanged; not a substrate of	1/3 excreted renally unchanged; 2/3 metabolized by CYP3A4 and	Hepatic; 73% metabolized to inactive metabolites	Stays largely unchanged; minimally metabolized by hepatic CYP450 pathway; substrate of P-gp
Plasma protein binding	97%	34%-35%	~92%-95%	87%	55%
Half-life					10-14
Elimination					50% renal, 50% biliary and fecal
Peak effect (h)	72-96	2	2-4	3-4	1-2

Abbreviations: CYP1A2, cytochrome P-450 1A2; CYP2C9, cytochrome P-450 2C9; CYP2J2, cytochrome P-450 2J2; CYP3A4, cytochrome P-450 3A4; CYP450, cytochrome P-450; DOAC, direct oral anticoagulant; P-gp, P-glycoprotein 1.

TAKE HOME POINT #1 Check the renal function!!!

TAKE HOME POINT #2 note short half lives- don't miss a dose

Standard dosing of direct oral anticoagulants

Anticoagulant	Nonvalvular AF - stroke prophylaxis*	VTE treatment¶	VTE primary prophylaxis^Δ
Dabigatran (Pradaxa)	150 mg twice daily	Parenteral anticoagulation for 5 to 10 days; then dabigatran 150 mg twice daily	110 mg for the first day, then 220 mg once daily
Apixaban (Eliquis)	5 mg twice daily	10 mg twice daily for one week, then	2.5 mg twice daily
Rivaroxaban (Xarelto)	20 mg once daily with the evening meal	15 mg twice daily with food for three weeks; then 20 mg once daily with food	10 mg once daily, with or without food

TAKE HOME POINT #3 DOSING FOR VTE NOT THE SAME AS AFIB AND NO RENAL ADJUSTMENT FOR RIVA AND APIX

SAFETY

- GIB- apixaban< dabigatran< warfarin< rivaroxaban
- ICH-DOACS< warfarin
- Renal clearance-apixaban< rivaroxaban< dabigatran

TAKE HOME POINT #4 APIXABAN WINS BEST IN SAFETY

DOAC selection, dosing, monitoring

Mr. M is an 80 year old man with CHF, HTN, CKD, and new non valvular AFIB. SCr = 1.4 mg/dL, Wt 70 kg. He has a remote history of GI bleed from gastritis. He is on a PPI. He does not want to use warfarin and is interested in a "new" blood thinner. Which DOAC do you choose for him?

DOAC Selection in NVAF

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
MOA	FIIa inh	FXa inh	FXa inh	FXa inh
Admin	BID swallow whole	QD *w/ meal*	BID	QD
Renal elimination	~80%	~1/3	~1/4	~1/2
Drug Interactions	P-gp	CYP3A4/ P-gp	CYP3A4/ P-gp	P-gp
Other	No pill box	-	-	Avoid in CrCl >95 ml/min in AFIB

DOAC Selection in NVAF

	DABI	RIVA	APIX	EDOX
FDA Approval Trial vs. WARF	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE
Eff: CVA, SEE	Superior	Noninferior	Superior	Noninferior
Saf: Maj bleed	Similar	Similar	Superior	Superior
ICH	Superior	Superior	Superior	Superior
GI bleed	Worse	Worse	Similar	Worse
Mortality	Favorable	Favorable	Superior	Favorable
Bleeds in elderly subgroup ≥75 yrs	Trend of more major bleed	Trend of more CR bleed	Less bleed	Less major, more GI bleed

Appropriate NVAF DOAC Dosing

	DABI	RIVA	APIX	EDOX
Regular dosing	150 mg BID	20 mg QD	5 mg BID	60 mg QD (CrCl ≤95)
Reduced dosing	75 mg BID	15 mg QD	2.5 mg BID	30 mg QD
Indications for lower dose:	-CrCl 15-30 ml/min -CrCl 30-50 ml/min +DDI	-CrCl 15-50 ml/min	-2 or more: -SCr ≥1.5 -Wt ≤60 kg -Age ≥80 y	-CrCl 15-50 ml/min
Studied clinically	NO	Not CrCl <30	Not CrCl <25	Not CrCl <30 /min

TAKE HOME POINT #5 there is adjustment for renal function for AFIB indications.Use appropriate dose according to PI

DOAC selection, dosing, monitoring

Mr. M is an 80 year old man with CHF, HTN, CKD, and new non valvular AFIB. SCr = 1.4 mg/dL, Wt 70 kg. He has a remote history of GI bleed from gastritis. He is on a PPI. He does not want to use warfarin and is interested in a "new" blood thinner. Which DOAC do you choose for him?

DOACS in AFIB Selection

- Overall, DOACs perform in most aspects as good or in some cases better than warfarin
  - ***Renal function***
    - Avoid dabigatran in patients with significant impairment or fluctuating or borderline renal function
    - Avoid edoxaban in patients with very good renal function (CrCl >95 ml/min)
    - High bleed risk / GI bleed history or high risk –consider apixaban
  - Drug interactions may guide selection

DOAC selection, dosing, monitoring

Mr. M is an 80 year old man with CHF, HTN, CKD, and new AF. SCr = 1.4 mg/dL, Wt 70 kg. He has a remote history of GI bleed from gastritis. He is on a PPI. He does not want to use warfarin and is interested in a "new" blood thinner. Which DOAC do you choose for him?

- *CHA2DS2-VASc Score = 4; high risk*
- *CrCl ~42 ml/min*
- *You recommend apixaban 5 mg BID*

GO TO WARFARIN INSTEAD OF DOAC IF:

- Valvular AFIB
- Mechanical heart valves
- APLS
- ?Dialysis and CrCl < 25 ml/min
- ?LV thrombus
- ? Extremes of weight?