Overview of the Evaluation and Management of Venous Thromboembolism (VTE) for the PCP

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Beth Israel Lahey Health

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Educational Objectives -- Evaluation and Management of VTE: One should…

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1. …understand and be able to implement recent evidence-based recommendations for the evaluation of venous thromboembolic disease (VTE)
2. …understand and be able to implement recent evidence-based recommendations for the treatment of venous thromboembolic disease (VTE)
3. …be able to differentiate among currently available anticoagulant medications and their uses and relative risks
4. …understand and be able to implement management recommendations in several special cases of VTE
5. …have an overview of the evolving understanding of issues of hypercoagulability with COVID infection and vaccines

Evaluation and Treatment of VTE for the PCP: Overview of the session…

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1. Review current guidelines from authoritative sources for the evaluation and treatment of patients with VTE
2. Explore specific management guidelines through case-based discussion and audience participation questions
3. Review available agents and recommendations for their use
4. Special cases
5. Brief overview of hypercoagulability related to COVID infection and/or immunization
6. Q and A

I have no relationship with any pharmaceutical or medical device company and I have no conflicts of interest to report.

--James J. Heffernan, MD, MPH

Audience Participation: Poll Everywhere

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Send text → JAMESHEFFERN812

To → 22333

What was the cause of death of Dr. A. Trousseau?

A. Laudanum overdose
B. Gastric cancer 6 months after development of VTE
C. Trampled by horses in a tragic carriage accident
D. Tertiary lues (syphilis)

Case #1

The visiting nurse for a 67 year old man calls to report tachycardia and malaise. Patient underwent R THR 5 weeks previously. He received warfarin as VTE prophylaxis for 3 weeks through rehab (target INR 1.5 per ortho at OSH). He was treated at home a week ago for pyelonephritis with resolution of symptoms, but developed a burning sensation of his feet on ciprofloxacin and was switched to TMP/SMX. He has had tachycardia, DOE and malaise for the last 3 days. He is asked to come to clinic.

PMH: childhood polio, atrophied L leg. PE after R TKR

Examination: P 110 at rest, 130 with minimal exertion. BP 114/74. RR 24. O2 sat 95%. Lungs clear. Cor regular, hyperdynamic. Legs without edema or calf tenderness. Normal mental status.

Case #1 (cont.)

What is your estimate of the clinical likelihood of PE?

A. Low

B. Intermediate

C. High

Calculator: Pulmonary embolism Wells score

- [ ] Symptoms of DVT (3 points)
- [x] No alternative diagnosis better explains the illness (3 points)
- [x] Tachycardia with pulse >100 (1.5 points)
- [x] Immobilization (>=3 days) or surgery in the previous four weeks (1.5 points)
- [x] Prior history of DVT or pulmonary embolism (1.5 points)
- [ ] Presence of hemoptysis (1 point)
- [ ] Presence of malignancy (1 point)

Total Criteria Point Count: 7.5

Reset Form

Pulmonary Embolism Risk Score Interpretation

Score >6:	High probability
Score >=2 and <=6:	Moderate probability
Score <2:	Low Probability

Back to Case #1…

What factor warrants immediate consideration of thrombolytic therapy in a patient with PE?

A. Elevated troponin and/or pro-BNP
B. S1-Q3-T3 on ECG
C. Hypotension
D. Right heart strain on echocardiogram

Pulmonary Embolism Severity Index (PESI)

Clinical Feature	Points
Age	**67**
Male gender	**10**
History of cancer	30
Heart failure	10
Chronic lung disease	10
Pulse ≥ 110	**20**
SBP < 100	30
RR ≥ 30	20
Temperature < 36 C	20
Altered mental status	60
Art. O2sat < 90%	20

Class	Points
I	< 66
II	66-85
III	**86-105**
IV	106-125
V	> 125

LOW RISK = Class I, II

HIGH RISK = Class III, IV, V

Case #1 (cont.)

Due to concerns over PE, the patient is sent to the ED where CTA demonstrates PEs in all lobes. ProBNP is 324 (0-229). Trop negative. ECG normal but for rate.

What is the most strongly recommended anticoagulant regimen for this patient?

A. IV UFH/warfarin
B. SC LMWH or fondaparinux/warfarin
C. LMWH or UFH acutely, followed by edoxaban for 3 mos
D. Rivaroxaban or apixaban, acutely and for 3 mos

Evaluation and Treatment of VTE: The changing landscape…

Evaluation:

1. Confirmed value in use of clinical decision rules (or gestalt) to assess pretest likelihood
2. Application of Pulmonary Embolism Exclusion Criteria (PERC) to short-circuit need for further evaluation in cases of low clinical pretest likelihood
3. Integration of clinical decision rules with high-sensitivity d-dimer when indicated
4. Imaging directly for high pretest likelihood cases

Treatment:

1. Limit thrombolysis to cases of significant hemodynamic compromise
   - Systemic thrombolysis for PE w/ major hemodynamic effects
   - Catheter-directed thrombolysis for severe, compromising DVT
2. General preference for DOACs over other modalities in most instances of VTE
3. More circumscribed use of treatment extended beyond 3 months

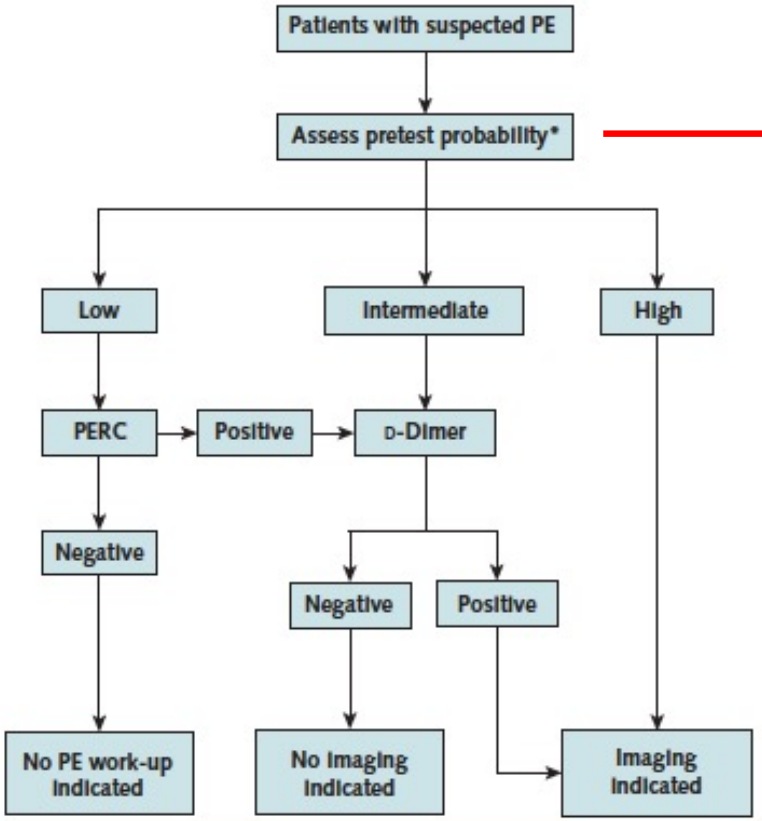
Evaluation of patients with suspected/possible acute venous thromboembolism…

Evaluation of Patients With Suspected Acute PE: Best Practice Advice From the Clinical Guidelines Committee of the ACP

1. Use validated clinical prediction rules to estimate pretest probability.
2. No not obtain d-dimer measurements or imaging studies in patients with low pretest probability of PE and meet all Pulmonary Embolism Rule-Out Criteria.
3. Obtain a high-sensitivity d-dimer measurements as the initial diagnostic test in patients with an intermediate pretest probability of PE or in patients with a low pretest probability who do not meet all Pulmonary Embolism Rule-Out Criteria; do not use imaging studies as the initial test in patients with a low or intermediate pretest probability of PE.
4. Use age-adjusted d-dimer thresholds (age x 10 ng/mL rather than a generic 500 ng/mL) in patients older than 50 to determine whether imaging is warranted.
5. Do not obtain imaging studies in patients with a d-dimer level below the age-adjusted cutoff.
6. Obtain imaging with CT pulmonary angiography (CTPA) in patients with high pretest probability of PE; reserve ventilation-perfusion scans for patients unable to receive CTPA; do not obtain a d-dimer measurement in patients with a high pretest probability of PE.

(*Ann Intern Med*. 2015;163:701-11.)

Figure 1. Pathway for the evaluation of patients with suspected PE.



PE = pulmonary embolism; PERC = Pulmonary Embolism Rule-Out Criteria.
* Using either a clinical decision tool or gestalt.

- Wells prediction rule (PE)
- Geneva score, revised
- Clinical gestalt

(*Ann Intern Med*. 2015;163:701-11.)

Assessing pre-test likelihood of PE: Wells Prediction Rule

Appendix Table 1. Wells Prediction Rule for Pretest Probability of PE*

Clinical Characteristic	Score	Simplified Score
Previous PE or DVT	1.5	1
Heart rate >100 beats/min	1.5	1
Recent surgery or immobilization	1.5	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Hemoptysis	1	1
Cancer	1	1
	Pretest probability: 0–1: Low 2–6: Intermediate ≥7: High Dichotomized score: ≤4: PE unlikely (low) >4: PE likely (high)	Pretest probability: ≤1: PE unlikely (low) >1: PE likely (high)

DVT = deep venous thrombosis; PE = pulmonary embolism.
* Information from references 34 and 35.

(*Ann Intern Med*. 2015;163:701-11.)

Assessing pre-test likelihood of PE: Revised Geneva Score

Appendix Table 2. Revised Geneva Score for Predicting Pretest Probability of PE*

Clinical Characteristic	Score	Simplified Score
Age >65 y	1	1
Previous PE or DVT	3	1
Surgery (under general anesthesia) or fracture of the lower limbs in the past month	2	1
Cancer (solid or hematologic; currently active or considered cured for <1 y)	2	1
Unilateral lower-limb pain	3	1
Hemoptysis	2	1
Heart rate		
75–94 beats/min	3	1
≥95 beats/min	5	2
Pain on deep venous palpation of lower limb and unilateral edema	4	1
	Pretest probability: <4: Low 4–10: Intermediate >10: High	Pretest probability: ≤2: Unlikely (low) >2: Likely (high)

DVT = deep venous thrombosis; PE = pulmonary embolism.
* Information from references 36 and 37.

(*Ann Intern Med*. 2015;163:701-11.)

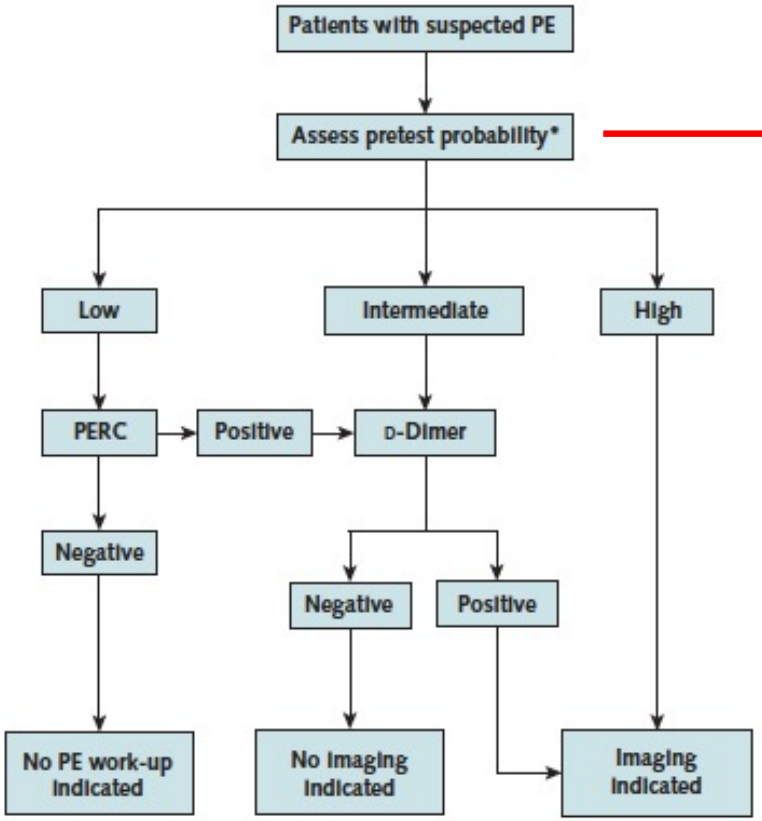
Table 1. Pulmonary Embolism Rule-Out Criteria for Predicting Probability of Pulmonary Embolism in Patients With Low Pretest Probability*

Clinical Characteristic	Meets Criterion	Does Not Meet Criterion
Age <50 y	0	1
Initial heart rate <100 beats/min	0	1
Initial oxygen saturation >94% on room air	0	1
No unilateral leg swelling	0	1
No hemoptysis	0	1
No surgery or trauma within 4 wk	0	1
No history of venous thromboembolism	0	1
No estrogen use	0	1
	Pretest probability with score of 0 is <1%	

* Information from reference 46.

(*Ann Emerg Med*. 2004;44:490-502.)

Figure 1. Pathway for the evaluation of patients with suspected PE.



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- Wells prediction rule (PE)
- Geneva score, revised
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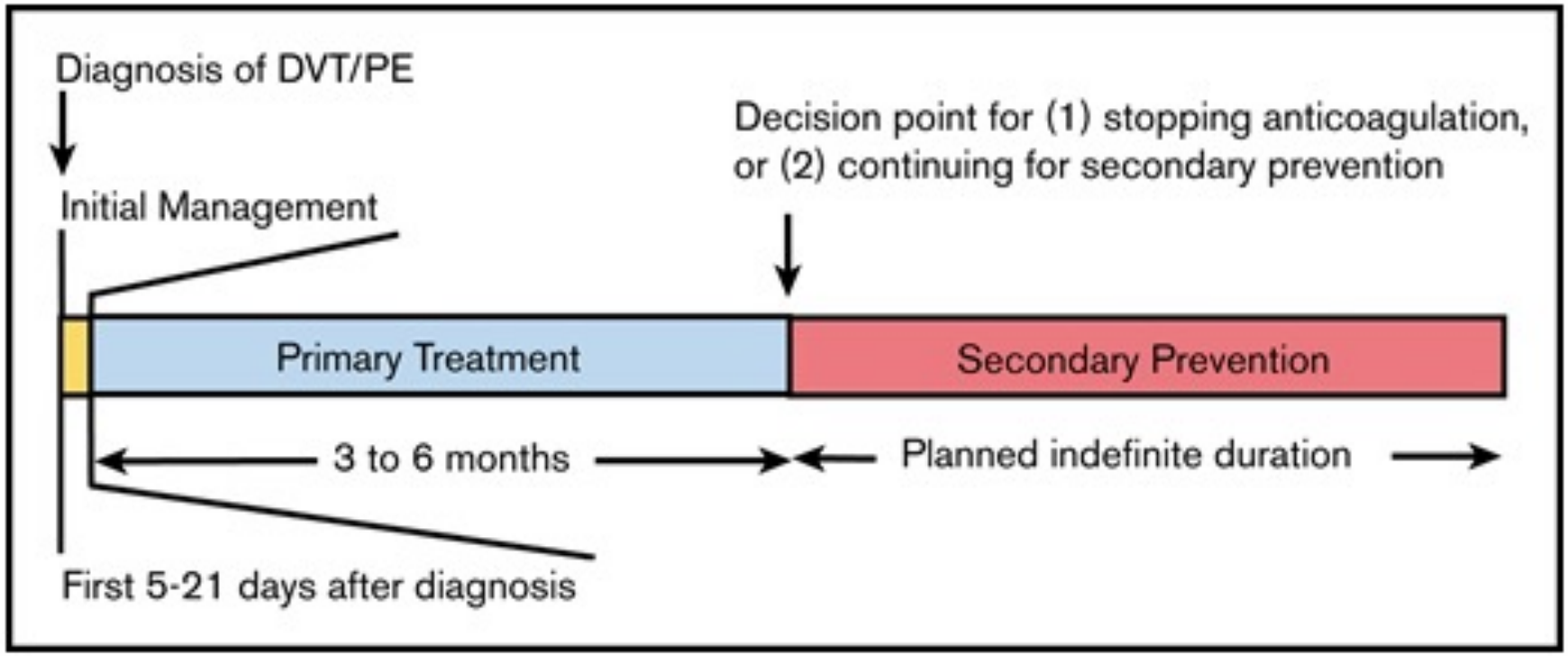
(*Ann Intern Med*. 2015;163:701-11.)

Treatment of patients with acute venous thromboembolism…



(Blood Adv (2020) 4 (19): 4693–4738.)

In the beginning…

…there was heparin

…and warfarin

VTE: Traditional Anticoagulants

Unfractionated heparin

- Acts primarily to inhibit factor Xa and thrombin
  - Xa:IIa inhibition = 1:1
- Administered SC or IV

Warfarin

- Vitamin K antagonist
- Major action in depleting factors II, VII, IX, X
- Early procoagulant effect by impairing synthesis of proteins C and S
- Complex interactions with other medications and foods

VTE: The old “new” agents

Low molecular weight heparins (Xa:IIa inhib. = 2:1)

- **Enoxaparin sodium**
- **Dalteparin sodium**
- Ardeparin sodium
- Tinzaparin sodium

Direct thrombin inhibitors

- **Argatroban**
- Lepirudin, **desirudin**
- **Bivalirudin**

Factor Xa inhibitor

- **Fondaparinux** – pentasaccharide; indirect Xa inhibitor – catalyzes Xa inactivation by AT

VTE: The new “new” kids on the block…

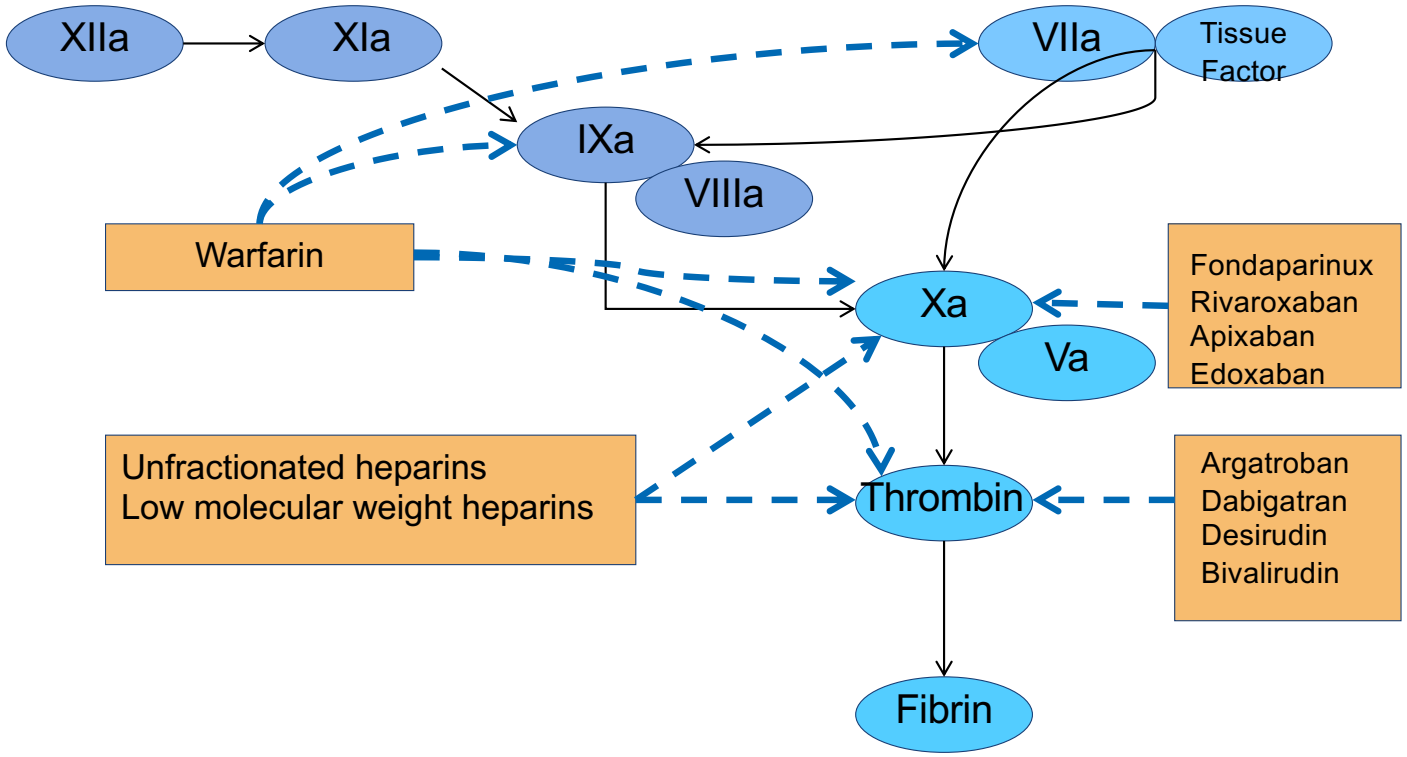
Direct thrombin inhibitor

- Dabigatran

Factor Xa inhibitors

- Rivaroxaban
- Apixaban
- Edoxaban

The Clotting Cascade and Sites of Action of Anticoagulant Medications



CLINICAL GUIDELINES | OCTOBER 2, 2020

American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism

Thomas L. Ortel, Ignacio Neumann, Walter Ageno, Rebecca Beyth, Nathan P. Clark, Adam Cuker, Barbara A. Hutten, Michael R. Jaff, Veena Manja, Sam Schulman, Caitlin Thurston, Suresh Vedantham, Peter Verhamme, Daniel M. Witt, Ivan D. Florez, Ariel Izcovich, Robby Nieuwlaat, Stephanie Ross, Holger J. Schünemann, Wojtek Wiercioch, Yuan Zhang, Yuqing Zhang

Blood Adv (2020) 4 (19): 4693–4738.

- Well-organized set of 28 evidence-based recommendations on treatment of VTE from ASH
- Organized as summary section with easy drill-down on individual recommendations
- Strong recommendations:
  - Use of thrombolytic therapy in patients with PE and hemodynamic compromise
  - INR range 2.0-3.0 for patients with VTE who use VKA for secondary prophylaxis
  - Indefinite anticoagulation for patients with recurrent unprovoked VTE
- Conditional recommendations:
  - Preference for home treatment over hospital-based treatment for patients with uncomplicated PE or DVT at low risk for complications
  - Preference for DOACs over VKA for primary treatment of VTE

Antithrombotic Therapy for VTE Disease

Second Update of the CHEST Guideline and Expert Panel Report

Scott M. Stevens, MD; Scott C. Woller, MD; Lisa Baumann Kreuziger, MD; Henri Bounameaux, MD; Kevin Doerschug, MD; Geert-Jan Geersing, MD, PhD; Menno V. Huisman, MD; Clive Kearon, MD, PhD; Christopher S. King, MD; Andrew J. Knighton, PhD; Erica Lake, MLS; Susan Murin, MD; Janine R. E. Vintch, MD; Philip S. Wells, MD; and Lisa K. Moores, MD

CHEST 2021; 160(6):e545-e608

- Most recent iteration of ACCP VTE management guidelines
  - Second update to 9th edition (2012); 1st full edition 36 years ago
- Includes 29 guidance statements covering aspects of antithrombotic management of VTE from initial management through secondary prevention and risk reduction of postthrombotic syndrome
  - 13 guidance statements graded as “strong” recommendations
  - 8 guidance statements substantially modified since 2016
  - 4 new guidance statements since 2016
- Comparison of individual guidance statements with other VTE mgt. guidelines

Practice Guideline > Chest. 2021 Dec;160(6):2247-2259. doi: 10.1016/j.chest.2021.07.056.
Epub 2021 Aug 2.

Executive Summary: Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report

Scott M Stevens [1], Scott C Woller [2], Lisa Baumann Kreuziger [3], Henri Bounameaux [4], Kevin Doerschug [5], Geert-Jan Geersing [6], Menno V Huisman [7], Clive Kearon [8], Christopher S King [9], Andrew J Knighton [10], Erica Lake [11], Susan Murin [12], Janine R E Vintch [13], Philip S Wells [14], Lisa K Moores [15]

DOACs: Practical considerations in treating VTE…

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- All carry black box warnings about increased risk of thrombotic event with discontinuation and epidural/spinal hematoma risk with neuraxial anesthesia and LP
- Dabigatran and edoxaban require acute rx w/ LMWH/UFH
- Rivaroxaban to be taken with food (15 and 20 mg dosages)
- Apixaban and dabigatran taken bid for all uses
- Edoxaban and rivaroxaban (after acute rx of VTE) taken qd
- On FDA approval, dabigatran, rivaroxaban and edoxaban were rated as category C in pregnancy; apixaban was rated as category B
- Evolving evidence of most favorable profile – efficacy and safety – for apixaban over others
- Possible increased cardiovascular complications with dabigatran
- Varied insurance coverage and cost to patients

Cl

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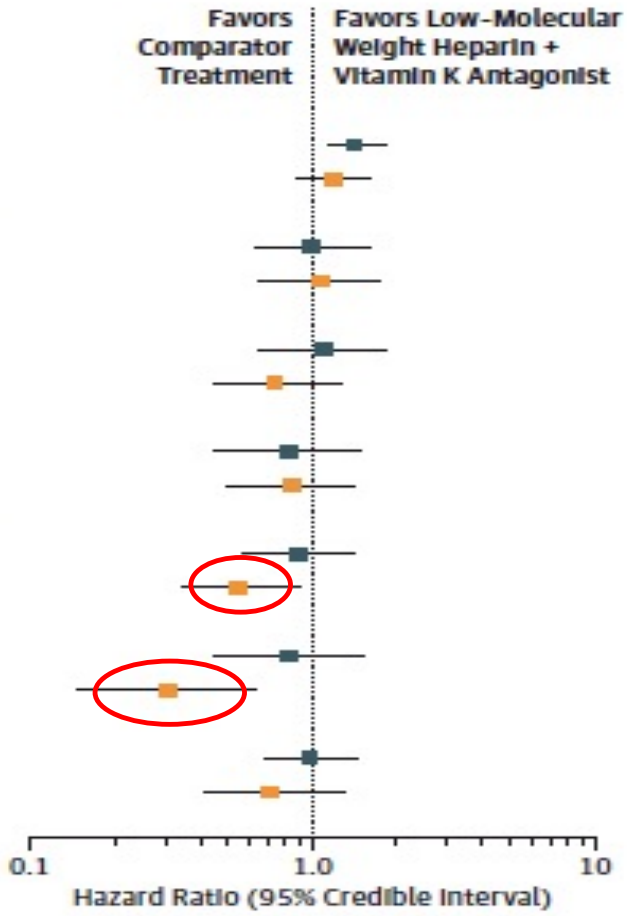
Figure 3. Network Meta-analysis Comparing Low-Molecular-Weight Heparin–Vitamin K Antagonist Combination for Recurrent Venous Thromboembolism and Major Bleeding

A Recurrent venous thromboembolism and major bleeding

Comparator Treatment	Hazard Ratio (95% Credible Interval)
Unfractionated heparin + vitamin K antagonist	
Recurrent VTE	1.42 (1.15-1.80)
Major bleeding	1.19 (0.90-1.58)
Fondaparinux + vitamin K antagonist	
Recurrent VTE	1.01 (0.65-1.62)
Major bleeding	1.07 (0.65-1.70)
Low-molecular-weight heparin + dabigatran	
Recurrent VTE	1.11 (0.67-1.80)
Major bleeding	0.74 (0.46-1.26)
Low-molecular-weight heparin + edoxaban	
Recurrent VTE	0.83 (0.46-1.49)
Major bleeding	0.84 (0.51-1.39)
Rivaroxaban	
Recurrent VTE	0.90 (0.57-1.41)
Major bleeding	0.55 (0.35-0.89)
Apixaban	
Recurrent VTE	0.84 (0.46-1.51)
Major bleeding	0.31 (0.15-0.62)
Low-molecular-weight heparin alone	
Recurrent VTE	0.99 (0.70-1.42)
Major bleeding	0.71 (0.42-1.31)



Severe Bleeding Risks of DOACs in Prevention and Treatment of VTE

- Network meta-analysis of 31 RCTs (76,641 patients)
- For **treatment of VTE**, risk of major bleeding significantly lower for apixaban than for dabigatran (OR 2.10, 95% CI 1.07-4.12) and edoxaban (OR 2.64, 95% CI 1.36-5.15)
- Safety ranking (highest to lowest):
  - Major bleeding: apixaban > rivaroxaban > dabigatran > edoxaban > VKAs
  - GI bleeding: apixaban > rivaroxaban > edoxaban > VKAs > dabigatran
  - Intracranial bleeding: rivaroxaban > edoxaban > dabigatran > apixaban > VKAs
  - Fatal bleeding: edoxaban > rivaroxaban > dabigatran > apixaban > VKAs
- For **prevention of VTE**, risk of major bleeding significantly lower for apixaban than for rivaroxaban (OR 2.14, 95% CI 1.02-4.52)

(*Eur J Vasc Endovasc Surg*. 2021)

Case #2

You are called to see a 26 year old woman for suspicion of lymphedenitis who presented with groin pain. She is G2P1 and pregnant at 30 weeks gestation, admitted to Ob/Gyn. She has had mild, bilateral pedal edema late each day for the past month, but an otherwise uncomplicated pregnancy. Her earlier pregancy and delivery were uncomplicated. She owns a cat.

Exam: well-appearing; P 84; BP 100/63; T 99.0; lungs clear; cor regular; soft abdomen with gravid uterus; firmness/tenderness in femoral triangle with no obvious abnormal lymph nodes; 1+ bilateral pedal edema; no calf tenderness.

Case #2 (cont.)

You are concerned about DVT and alternative diagnoses and advise imaging.

Which side is affected?

A. Left

B. Right

C. How the &#!* should I know?

D. Both

VTE in Pregnancy

6 to 15-fold increase of VTE during pregnancy and the immediate postpartum period over non-pregnant controls

- Two-thirds of cases occur antepartum, distributed across all trimesters

Leading cause of maternal mortality (27%)

DVT in pregnancy is found in the left leg in > 85% of cases and in proximal veins only in 70%

- Virchow's triad: hypercoagulability, compression of left iliac vein and venous webs are putative basis for this predisposition

Isolated iliac vein involvement at onset in 17% of cases

- Risk for *phlegmasia cerulea dolens* with progression/extension

Warfarin largely contraindicated as treatment option

- Fetal loss/hemorrhage, embryopathy and neurologic abnormalities

The LEFt Clinical Prediction Rule for DVT in Pregnancy

Cross-sectional study of 194 pregnant women with suspected DVT

Three variables found to be highly predictive of DVT in pregnancy

1. Left leg symptoms (L)
2. Calf circumference difference > 2 cm (E)
3. First trimester presentation (Ft)

Number of Variables	Prevalence of DVT (%)
0	0
1	16
≥ 2	58

Ann Intern Med. 2009;151:85-92

Treatment of Pregnancy Related VTE

- Prefer LMWH over UFH for treatment and prophylaxis of VTE in pregnancy
- Continue treatment 6 weeks after delivery
- For women on anticoagulation with VKA who become pregnant, switch to LMWH
- Limit use of fondaparinux and parenteral direct thrombin inhibitors to those with severe allergic reactions to heparin (HIT)
- Avoid the use of DOACs in pregnant women
  - Apixaban: Category B; other DOACs: Category C
- In breastfeeding women, continue UFH, LMWH, warfarin, danaparoid or r-hirudin if needed clinically
- In breastfeeding women, use alternative agents rather than fondaparinux, oral direct thrombin inhibitors and oral Xa inhibitors

Risk of

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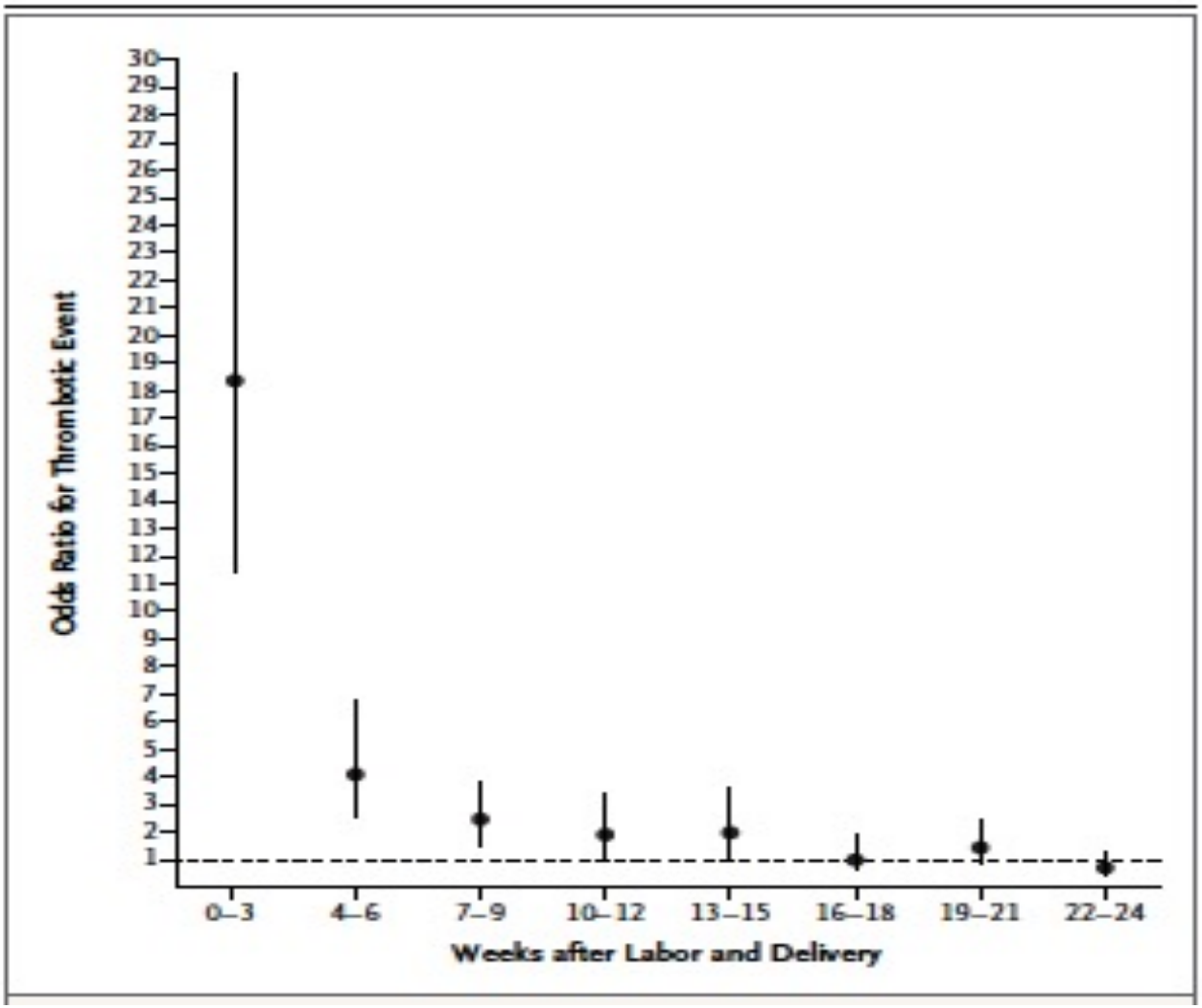
Risk of a ssessed among 1,

- Cases id

Risk grea out to > 12 weeks



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Case #3

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A 69 year old retired carpenter presents to be seen for right leg pain and swelling. He has just returned from a short vacation in the Bahamas. Before he left on vacation he had noted tenderness and swelling above and behind the right medial malleolus. He is very active at baseline and reports likely trauma to the site of tenderness. While away, the area of tenderness and local swelling has extended proximally, now at/above the knee medially. He is otherwise well.

Exam: Well-appearing; P 60; BP 108/62; striking, palpable cord along the course of the right greater saphenous vein – indurated, 1 cm diameter; 1-2+ ankle and foot swelling

Case #3 (cont.)

You make a clinical diagnosis of superficial thrombophlebitis of the right greater saphenous vein and order duplex ultrasound. This confirms SVT along a 20 cm segment of the saphenous vein, with the upper extent around the tibial plateau. There is no evidence of associated DVT.

Which of the following regimens has been best validated in treating this clinical presentation?

A. Enoxaparin 40 mg SC qd X 12 days
B. Fondaparinux 2.5 mg SC daily x 45 days
C. Warfarin 1 mg orally daily X 21 days
D. Indomethicin 50 mg orally BID with leg compression X 21 days
E. Rivaroxaban 10 mg PO qd X 45 days

Management of Lower Extremity Superficial Vein Thrombosis (SVT)

Consider risks of extension and complications

- 4% PE; 10% proximal DVT; 13% distal DVT at presentation with > 5 cm SVT

Patients with SVT extending above the knee → ultrasonography to exclude DVT

- If DVT identified, treat according to DVT protocol

For SVT alone involving vein segment > 5 cm

- Preferred treatment → fondaparinux 2.5 mg SC qd X 45 days
  - CALISTO study - NEJM 2010;363:122-32
- LMWH at prophylactic dosage is reasonable alternative
  - STENOX study - Arch Intern Med. 2003; 163:1657-63
- Rivaroxaban 10 mg PO qd shown to be non-inferior to fondaparinux
  - SURPRISE study – Lancet Haematol. 2017;4:e105-13

Surgical therapy associated with higher rates of VTE than treatment with anticoagulation

Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report (2021)

- With acute, isolated distal DVT without severe symptoms or risks for extension → serial imaging (weekly X 2) over immediate anticoagulation
  - If thrombus extends within calf or proximally on serial imaging → full anticoagulation
- With subsegmental PE and no proximal DVT and low risk of recurrent PE → surveillance
  - Recent evidence has shown higher than anticipated recurrence rate (3.1% at 90 days)

(*Ann Intern Med*. 2022;175:29-35.)

- Treat patients with incidentally noted, asymptomatic PE with standard anticoagulation
- Treat cerebral vein/sinus thrombosis with LMWH for at least 3 months
- Use anticoagulation alone over interventional therapy for acute proximal DVT of leg
  - Consideration of thrombolytic therapy for limb threatening DVT
- Treat acute PE associated with hypotension in patients not at high risk for bleeding with systemically-administered thrombolytic therapy; otherwise, use anticoagulation alone

Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report (2021) (cont.)

- In selected patients with acute PE who deteriorate on anticoagulation (drop in BP, rising pulse, worsening gas exchange, signs of inadequate perfusion, worsening RV function, increasing biomarkers) → systemic thrombolytic therapy if bleeding risk is acceptable
- Preference for systemically administered thrombolytic therapy over central catheter-delivered thrombolysis in patients with acute PE who warrant thrombolysis
  - In patients with acute PE and hypotension plus high bleeding risk or failed systemic thrombolysis or shock → catheter-directed thrombolysis
- Do not use IVC filter in addition to anticoagulation in patients with acute DVT
  - Use IVC filter only in patients with proximal DVT and a contraindication to anticoagulation
- Outpatient treatment over hospitalization for low-risk PE, provided access to medications, ability to access care and home circumstances are adequate
- In patients with PE or DVT → apixaban, dabigatran, edoxaban or rivaroxaban over VKA treatment

Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report (2021) (cont.)

- For cancer-associated VTE → apixaban, edoxaban or rivaroxaban over LMWH
  - Increased bleeding risk with edoxaban and rivaroxaban (but not apixaban) in patients with luminal GI malignancies
- For antiphospholipid-antibody associated VTE → VKA w/ INR 2.5 over DOAC
- For SVT of the leg at increased risk of progression → anticoagulation X 45 days
  - Fondaparinux 2.5 mg daily as first choice; rivaroxaban 10 mg daily as reasonable alternative

Duration of treatment phase of anticoagulation

- 3-month standard; then assess need of extended-phase therapy
- Do not extend treatment if VTE diagnosed in setting of major or minor transient risk factor
- In absence of transient provoking factory or if persistent risk factor → offer extended phase anticoagulation with a DOAC
  - Use VKA if unable to receive a DOAC

Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report (2021) (cont.)

- In patients offered extended-phase therapy → reduced-dose apixaban or rivaroxaban over aspirin or no therapy
- In patients with unprovoked proximal DVT or PE who are stopping anticoagulation → aspirin if no contraindication
- Do not routinely use compression stockings to prevent post-thrombotic syndrome in patients with acute DVT
  - Reasonable to consider use to ameliorate leg symptoms

Overview of COVID-19 Related Hypercoagulability and Clotting Events

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- Hypercoagulability associated with COVID infection noted early in pandemic
  - VTE in 14.1% of COVID-19 infected patients (22.7% among COVID-19 patients in ICUs)
- Putative mechanisms:
  1. Endothelial injury/endothelitis, complement activation, catheters, SIRS mediators….
  2. Stasis in acutely ill patients, especially in ICU
  3. Changes in procoagulants
- Events correlate, generally, with severity of disease, but noted less frequently over time
- Clinical experience: VTE >> arterial thrombosis; microvascular thrombosis
- Common lab abnormalities: Elevated d-dimer and fibrinogen; normal or mildly prolonged PT and aPTT; platelet count variable – mildly elevated, normal or mildly decreased
- Management:
  1. Thromboprophylaxis for all patients hospitalized w/ COVID
  2. Treat established VTE w/ standard measures
  3. No routine thromboprophylaxis or aspirin use for outpatient COVID infection

Thromboembolic Complications Associated with COVID Vaccines: Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)

- Seen in patients receiving adenoviral vector COVID vaccines
  - AstraZenaca/Oxford/Serum Institute of India vaccine (ChAdOx1 nCoV-19)
  - Janssen/Johnson & Johnson vaccine (Ad26.COV2.S)
- Caused by IgG antibodies that recognize PF4 bound to platelets, resulting in platelet activation
  - Likely 2-hit requirement: (1) neoantigen formation; (2) systemic inflammatory response
- Epidemiology: Rare – 1/26,000 (AZ) to 1/263,000 (JJ); median age 48; M/F = 45%/55%
- Clinical features: Onset of process 5-10 days after vaccination with clinical identification 5-30 days after vaccination; +/- flu-like illness; thrombocytopenia; thrombosis
- Sites of thrombosis: (1) cerebral vein/dural sinus; (2) splanchnic vein; (3) adrenal vein; (4) DVT/PE; (5) arterial events (stroke, limb ischemia, MI)
- Management: (1) anticoagulation; (2) IVIG; (3) plasma exchange (refractory cases)
- Prognosis: Mortality rate 22% in largest case series, worse w/ CVT, more severe hemostatic abnormalities

Management of Acute Upper Extremity DVT

Initial evaluation of suspected UEDVT → duplex U/S

- If negative, further testing with d-dimer, serial DUS or venographic-based imaging (traditional, CT or MR)

Preference for anticoagulation over thrombolysis

- LMWH or fondaparinux preferred over IV/SC UFH
- No controlled trials using DOACs; moderate real-world experience with DOACs suggests benefit and safety, with partial or complete recanalization in patients w/o cancer and w/o central lines
- Thrombolysis most likely to benefit patients with – severe symptoms, heavy proximal clot burden, symptoms < 14 days, good functional status, life expectancy > 1 year, low bleeding risk

In patients with UEDVT associated with a central venous catheter, OK to maintain catheter if needed

- Maintain anticoagulation as long as catheter is in place and for three months after removal

In UEDVT not associated with a catheter or with cancer, continue anticoagulation for 3 months

Screening for Occult Cancer in Patients with Unprovoked VTE

- Systematic review/meta-analysis of individual patient data (n = 2,316 patients from 10 studies)
- 12-month period prevalence of cancer after VTE diagnosis was 5.2% (95% C.I., 4.1% to 6.5%)
  - Higher in patients with more extensive screening initially (OR 2.0, 1.2-3.4) but not at 12 months (OR 1.4, .89-2.1)
  - Cancer prevalence increased linearly with age -- (OR 7.1, 3.1-16) in patients > 50 compared with those < 40

(Ann Intern Med. 2017;167:410-7.)

VTE Update: Selected References (1/3)

Evaluation

- *Ann Intern Med*. 2015;163:701-11. – Best-practice advice from ACP

Comprehensive treatment guidelines

- *Blood Adv.* 2020;4:4693–4738. – American Society of Hematology 2020 treatment guidelines
- *Chest.* 2021; 160(6):e545-e608 – Comprehensive guideline and expert panel report update
- *Chest.* 2021;160:2247-59 – Executive summary of #2

Management of lower extremity superficial venous thrombosis (SVT)

- CALISTO study – *N Engl J Med.* 2010;363:122-32 - fondaparinux
- STENOX study - *Arch Intern Med*. 2003; 163:1657-63 - LMWH
- SURPRISE study – *Lancet Haematol*. 2017;4:e105-13 - rivaroxaban

VTE Update: Selected References (2/3)

VTE complicating pregnancy

- Ginsberg JS, Brill-Edwards P, Burrows RF et al**. Venous thrombosis during pregnancy: leg and trimester of presentation**. *Thromb Haemost* 1992;67:519-20.
- Chan WS, Spencer FA, Ginsberg JS. **Anatomic distribution of deep vein thrombosis in pregnancy**. *CMAJ.* 2010;182:657-60.
- Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO; American College of Chest Physicians. **VTE, thrombophilia, antithrombotic therapy, and pregnancy**: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012 Feb;141(2 Suppl):e691S-736S.
- Chan WS, Lee A, Spencer FA, Crowther M, Rodger M, Ramsay T, Ginsberg JS. **Predicting deep venous thrombosis in pregnancy: out in "LEFt" field?** *Ann Intern Me*d. 2009 Jul 21;151(2):85-92.
- Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MS. **Risk of a thrombotic event after the 6-week postpartum period**. *N Engl J Med*. 2014 Apr 3;370(14):1307-15.

VTE Update: Selected References (3/3)

Hypercoagulability and anticoagulation in patients with COVID-19 infection

- *Res Pract Throm Haemost.* 2020;4:1178-91. – Systematic review/meta-analysis of 66 studies
- *N Engl J Med.* 2021;385:777-89. – Heparin in critically ill patients
- *N Engl J Med.* 2021;385:790-802. -- Heparin in noncritically ill patients

Thrombosis with Thrombocytopenia Syndrome After COVID-19 Vaccination

- *Ann Intern Med*. 2022;175:513-22. – US experience (case series from VAERS) 12/20-8/21
- *Ann Intern Med.* 2022;175:604-5. – Editorial w/ excellent discussion of HIT, VITT and TTS.