

Venous Thromboembolism

Diagnosis and Treatment

MD Perspective

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ACVIM

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Content

1	Diagnosis
2	Treatment
3	Other

Disclosures

- Stago Diagnostics
- Bristol Myers Squibb

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Diagnosis

VTE History

“Curbside”:

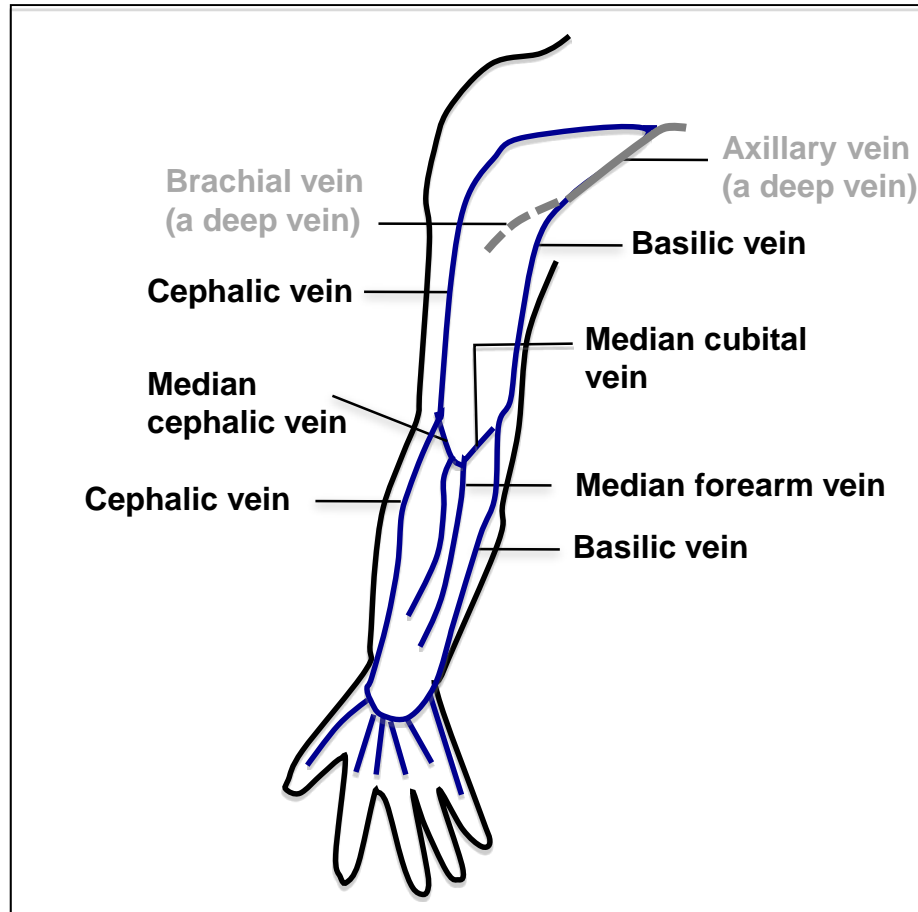
“Quick question: How long would you anticoagulate a 64 year old with a basilic vein DVT after phlebotomy stick?”

Caveat!

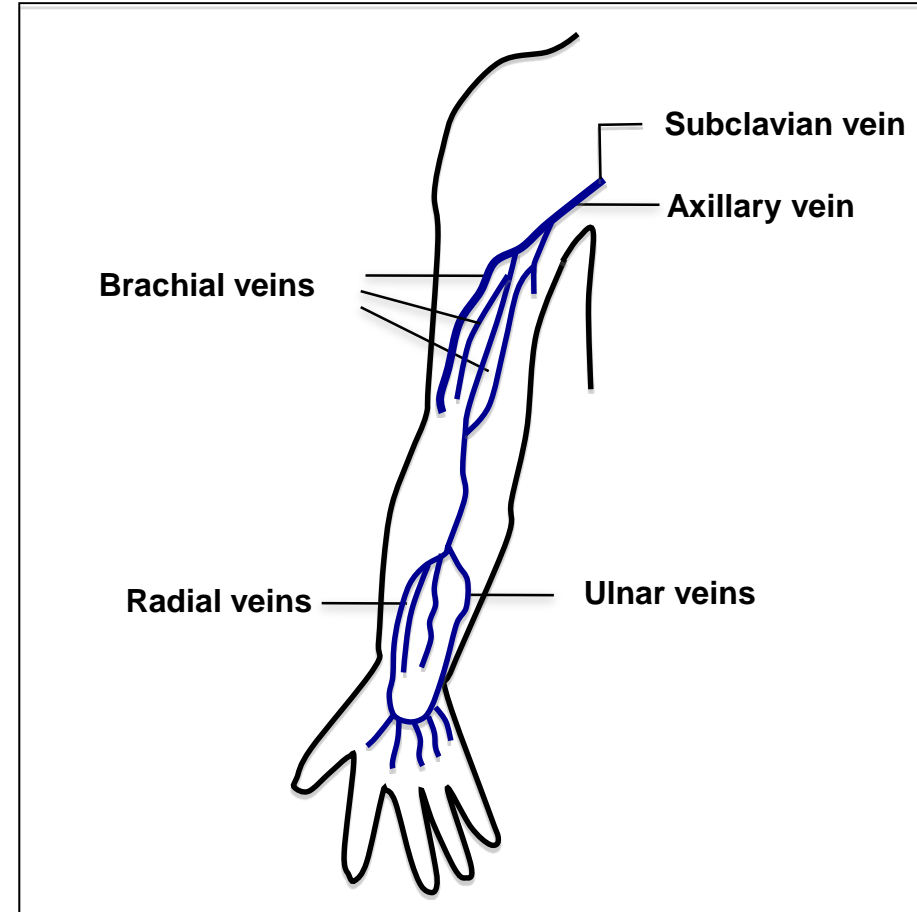
- “Basilic vein” is NOT a deep vein.
- This patient has a superficial thrombophlebitis.

Arm Clots – Basic Anatomy

Superficial Veins



Deep Veins



VTE History

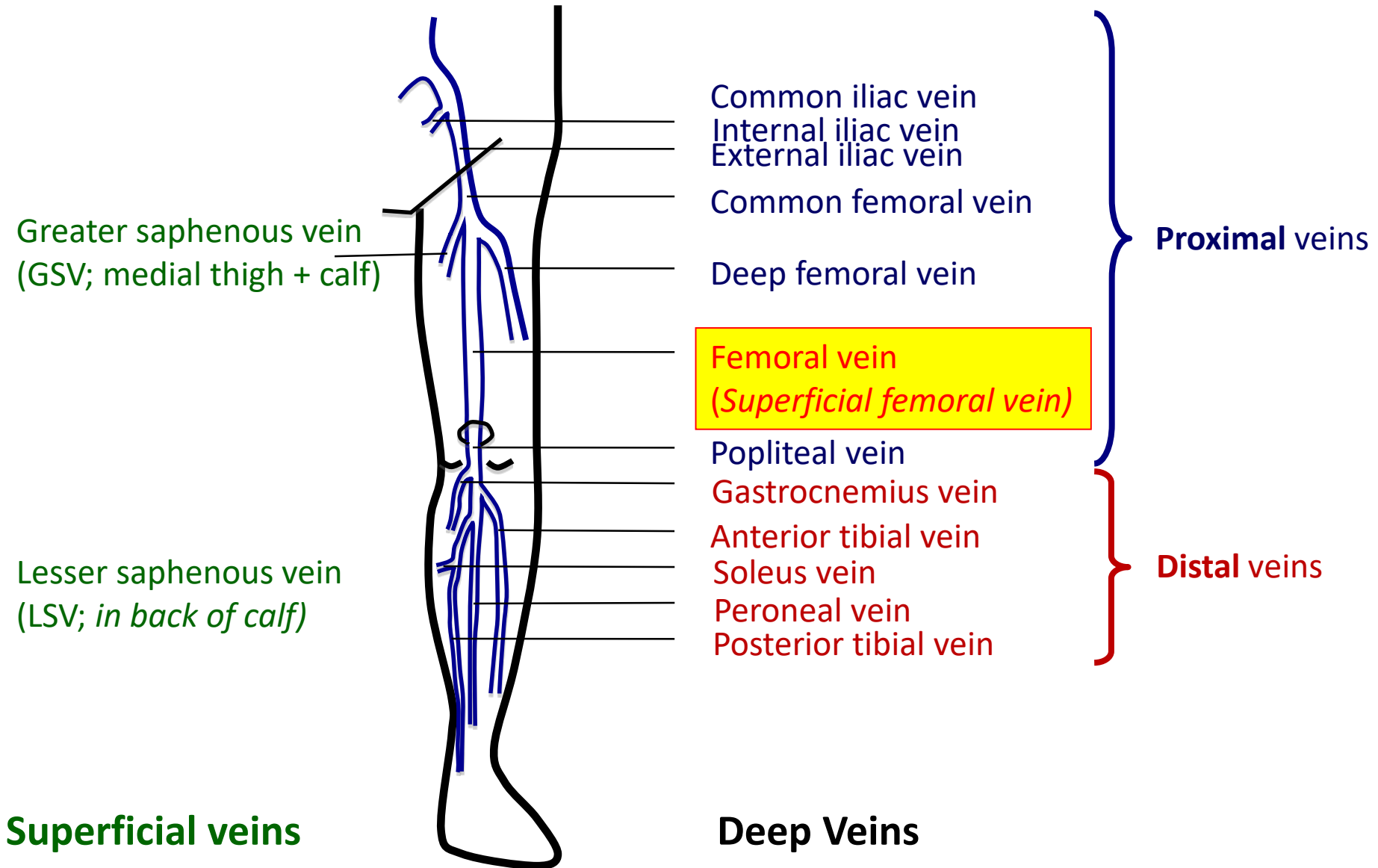
“Curbside”:

“Quick question: Superficial clot in the right leg superficial femoral vein; not very symptomatic. My plan was to observe.”

Caveat!

- “Superficial femoral vein” is NOT a superficial vein.
- This pt has a proximal leg DVT.

Leg Clots – Basic Anatomy

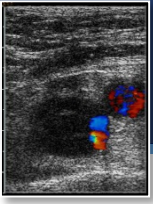


Basics



Teaching point

Know arm and leg venous anatomy



Doppler Ultrasound

Imaging characteristics

Acute" (= days to up to 3 months)

1. Dilated vein
2. "Spongy"
3. Hypo-echoic



"Chronic"

1. Retracted vein
2. Firm clot
3. Hyper-echoic

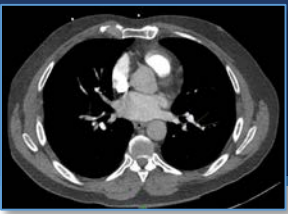
Diagnosing recurrent DVT

- Decision is conglomerate of:
(1) New clinical symptoms, (2) DD, (3) Doppler ultrasound



CT Scans

Question radiology reports!



CT Scans

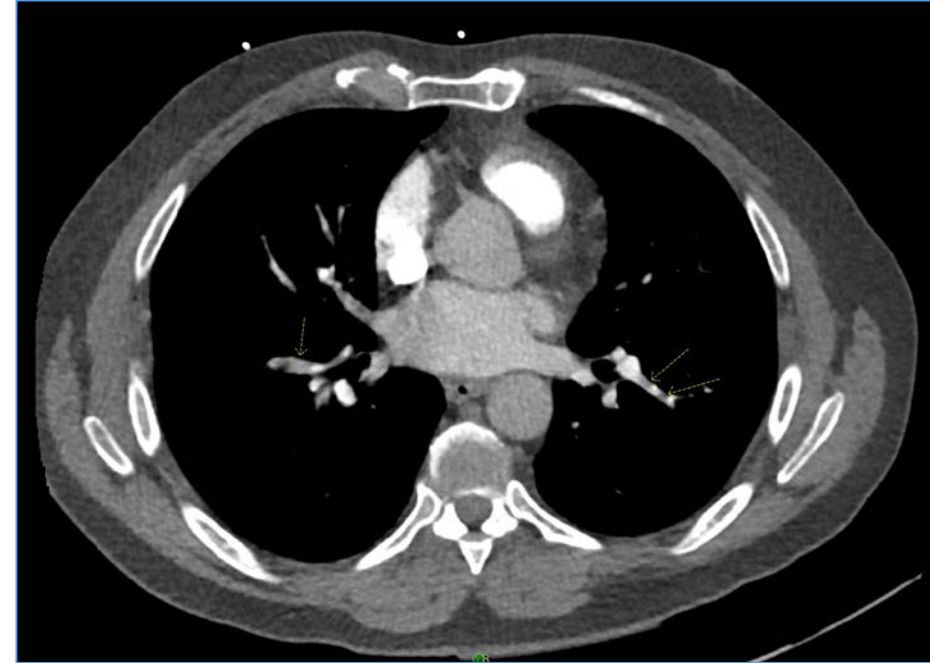
Example

Question radiology reports!

- 60 year old, smoker
- ED with sudden SOB
 - DD-neg
 - CTA: PE
 - Venous Doppler legs neg
- COPD treatment and anticoag.

Q: "How long to anticoagulate?"

A: "Long-term anticoagulation?"



IMPRESSION:

1. Several small acute subsegmental pulmonary emboli in both lower lobes. Overall clot burden is minimal.
2. Pattern of diffuse centrilobular ground-glass attenuation micronodularity throughout the lungs bilaterally. This is likely a manifestation of a smoking related disease such as RB (respiratory bronchiolitis), or if the patient is symptomatic, RB-ILD (respiratory bronchiolitis-interstitial lung disease). If the patient is not a smoker, this can be seen with acute hypersensitivity pneumonitis.
3. Emphysema (ICD10-J43.9).
4. Aortic atherosclerosis (ICD10-I70.0).



CT Scans

Caveats

- If CTA result does NOT match pre-test clinical assessment:
CTA is wrong in ca. 50 % of cases

[Stein P. NEJM 2006;354:2317-27]

- Review CTA with best radiologist - sub-segmental PE
- “Acute” vs “chronic” PE



VQ Scan

- For chronic PE: VQ scan is test of choice
- CTA is insensitive to detect chronic PE (CTEPH)

Caveats

- VQ scan can NOT differentiate between acute and chronic
- VQ abnormalities frequently persist for months
(of 157 PE patients, $\frac{2}{3}$ had VQ abnormality at 3 months)

Imaging



Teaching points

Know limitations of Doppler ultrasound and CTA.

Review imaging with Doppler technician / radiologist.

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Treatment

How Long to Treat?

Conglomerate decision of:

1. VTE Risk Factors

A. ..., B. ..., C. ...



2. Bleeding Risk Factors

A. ..., B. ..., C. ...

3. Patient preference





2022

Recurrence Triangle

How long to treat?

3 months

Long-term

VTE due to major transient risk factor

Woman with VTE on hormones
Non-major transient risk factor

Woman, unprovoked VTE

- DVT
- PE

Man, unprovoked VTE

- DVT
- PE

[Choosing Wisely®;
Hicks LK, et al. *Hematology ASH Education
Program* 2014;2014: 599-603]

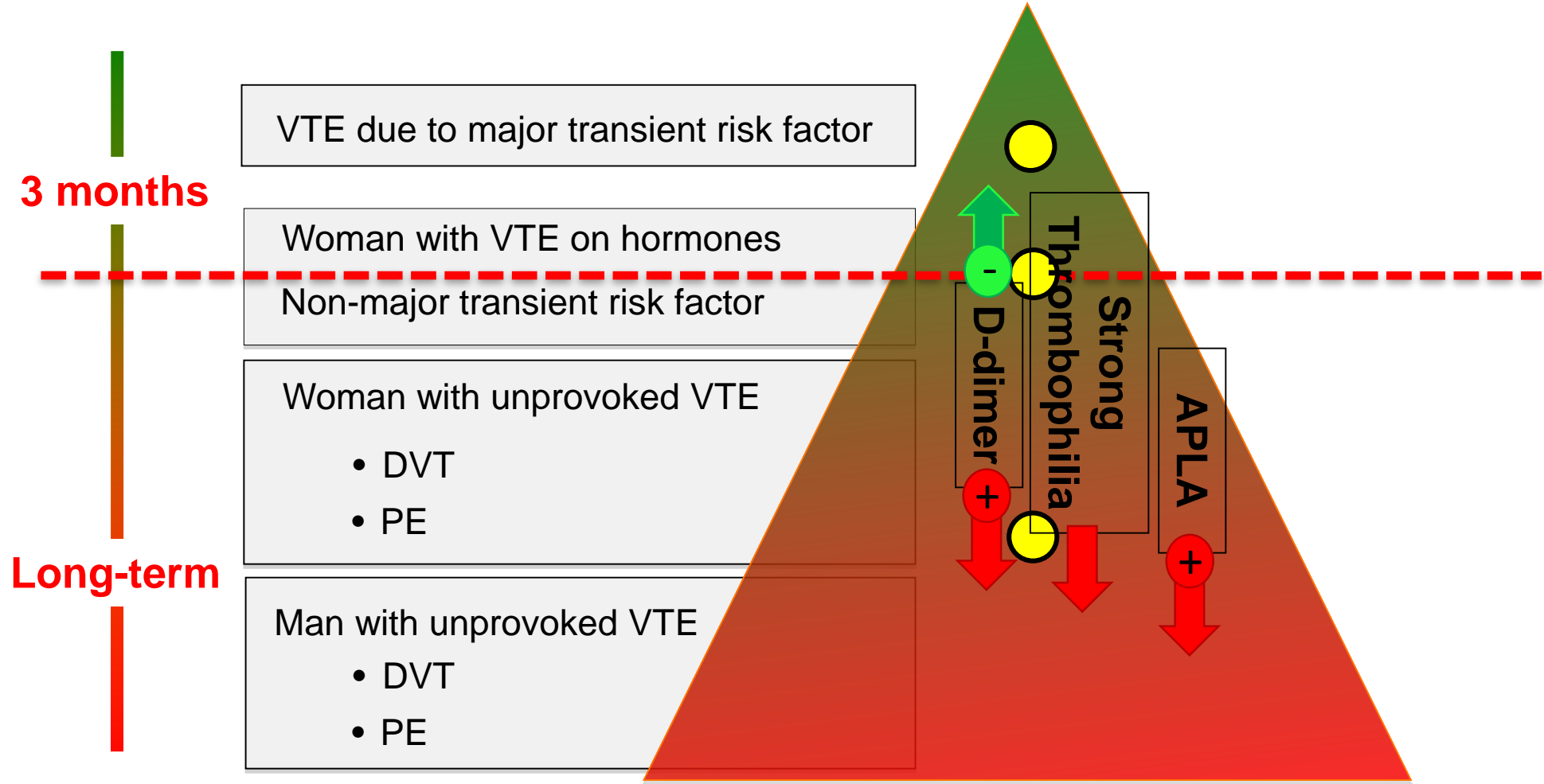


ACCP, AHA, ISTH, BJH
ASH 2020



2022

Recurrence Triangle





2022

Recurrence Triangle

How long to treat?

3 months

Long-term

VTE due to major transient risk factor

Woman with VTE on hormones

Non-major transient risk factor

Woman, unprovoked VTE

- DVT
- PE

Man, unprovoked VTE

- DVT
- PE

Cumulative VTE
Recurrence Rate

1 year

5 years

1 %

3 %

2.7 %²

6 %¹

5 %

15 %

10 %

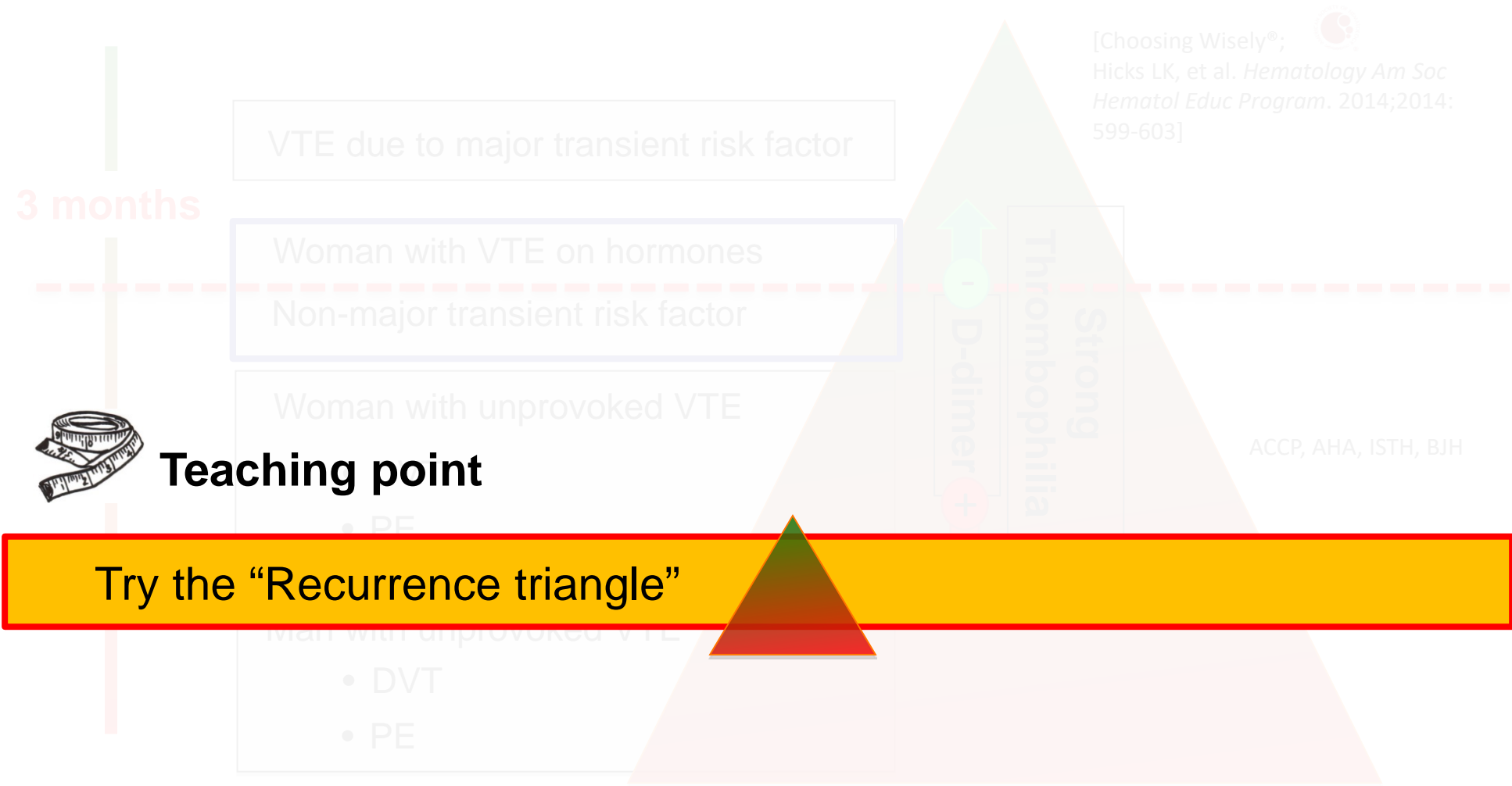
30 %

[Kearon C et al. Blood 2014;123:1794-1801]

¹[Douketis J et al. BMJ 2011;342:d813]

²[Wiegers HMG et al. J Thromb Haemost 2022;20:1158-65]

Recurrence Triangle





Lab Testing

Table 7 Influence of acute thrombosis and anticoagulants on thrombophilia test results

Test	Acute thrombosis	Unfractionated heparin	Low molecular weight heparin	Vitamin K antagonists	DOACs
Factor V Leiden genetic test	Reliable	Reliable	Reliable	Reliable	Reliable
APC resistance assay	Reliable ^a	?? ^a	?? ^b	Reliable ^a	Unreliable ^b
Prothrombin G20210A genetic test	Reliable	Reliable	Reliable	Reliable	Reliable
Protein C activity	?? ^f	Reliable	Reliable	Low	Elevated ^f
Protein C antigen	?? ^f	Reliable	Reliable	Low	Reliable
Protein S activity	May be low	Reliable	Reliable	Low	Elevated ^f
Protein S antigen	May be low	Reliable	Reliable	Low	Reliable
Antithrombin activity	May be low	May be low	May be low	May be elevated ^h	Elevated ^g
Lupus anticoagulant	Accurate ^d	?? ^e	?? ^f	?? ^e	False positive ⁱ
Anticardiolipin antibodies	Accurate ^d	Reliable	Reliable	Reliable	Reliable
Anti- β_2 -glycoprotein-I antibodies	Accurate ^d	Reliable	Reliable	Reliable	Reliable
Homocysteine	Reliable	Reliable	Reliable	Reliable	Reliable



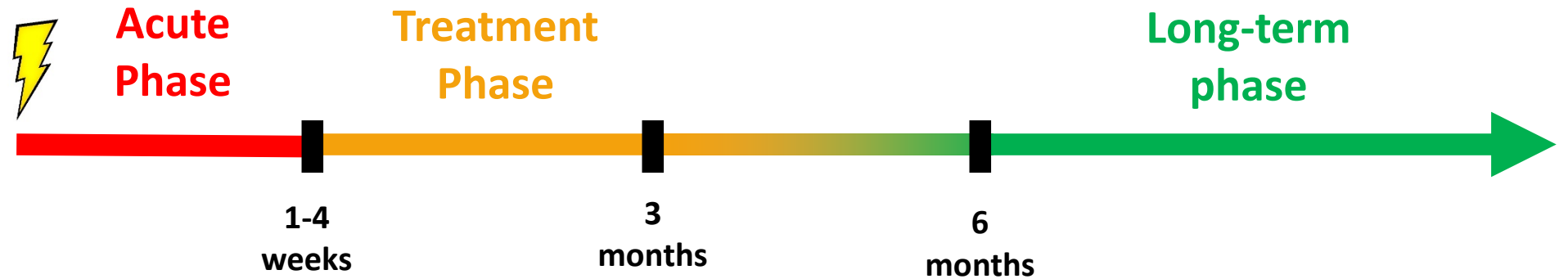
Lab Testing



Teaching points

- Be clear whom to test and when to test
- Be aware of influence of anticoagulants on thrombophilia labs
- APLA tests: Understand what exactly the lab did

DOAC Dosing



Apixaban

7 days

10 mg bid x 7 d

5 mg bid maintenance

2.5 mg bid

Rivaroxaban

3 weeks

15 mg bid x 3 wks

20 mg qd maintenance

10 mg qd

Dabigatran

All the time

150 mg bid all the time

VTE: Apixaban vs Rivaroxaban

- No prospective direct comparison study exist
- One was attempted – terminated 2019 due to poor enrollment (PCORI funded COVET trial).

[ClinicalTrials.gov Identifier: NCT03196349]

How to decide?

- Once daily versus twice daily
- Cost – copay for patient

- Bleeding? Retrospective data suggest some advantage with Apixaban, particularly less **menstrual bleeding**.

[Myers B et al. 2017 Mar;176(5):833-835]

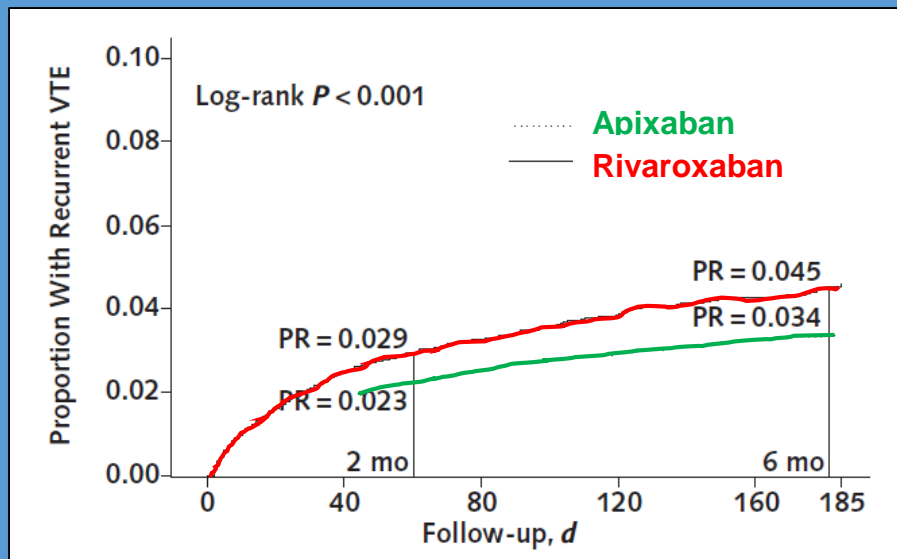
[prospective RAMBLE trial terminated: ClinicalTrials.gov Identifier: NCT02829957]

VTE: Apixaban vs Rivaroxaban

- U.S.-based commercial health care insurance database
- 18,618 (Apixaban) vs. 18,618 (Rivaroxaban); VTE patients

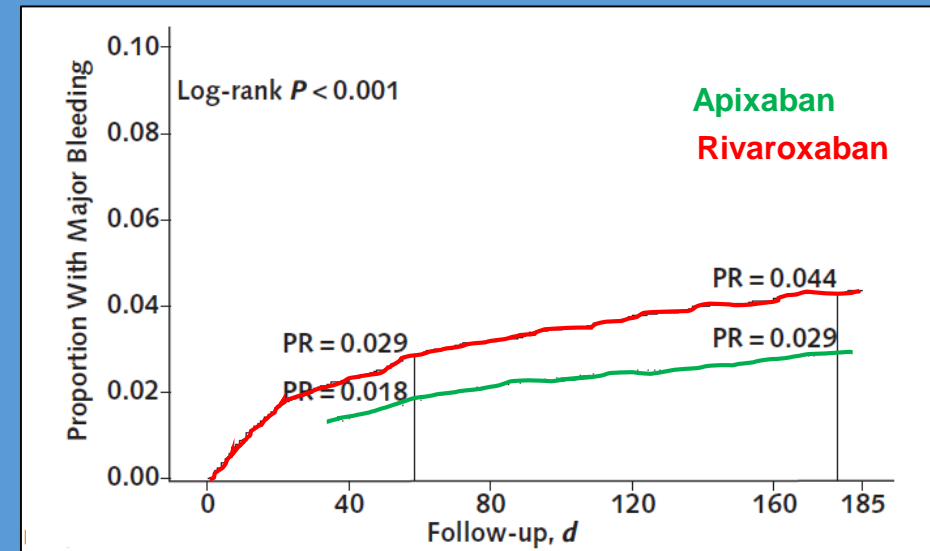


Recurrent VTE



Apix vs Riva: hazard ratio, **0.77** [95% CI, 0.69 to 0.87]

Bleeding (GI and intracranial)

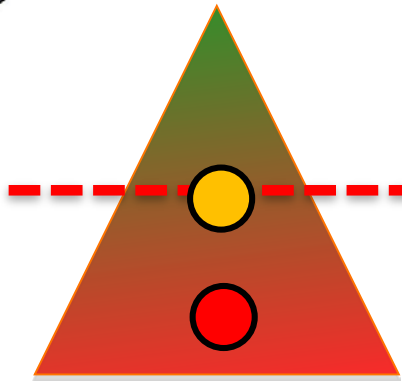


Apix vs Riva: hazard ratio, **0.60** [CI, 0.53 to 0.69]

How Long to Treat?



My Practice



Intermediate dose

Equipoise?

Full dose

Or:

- Elderly
- Lower body weight
- Higher risk bleeding

- Patient's copay?
- Pharma support program available?

Additional Issues

1. Baseline f/u Doppler ultrasound: when stopping anticoagulation.

[Ageno W et al. JTH 2013; 11: 1597–1602]

2. ~~“Residual clot”~~ = Scar tissue

3. “**Long-term**” anticoagulation = extended = lifelong.

However: Re-evaluation every so often (once per year).

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DOACs in Special Populations

Renal Impairment and DOACs

Take-home point

Renal impairment/ hemodialysis:

- Apixaban ok; preferably NOT rivaroxaban (caveat: dosing!)
- *Dosing:*
 - 5 mg bid in the heavier, younger, lower risk bleeding person.
 - 2.5 mg bid in the low-weight, elderly, with comorbidities and higher risk for bleeding person.

[Apixaban package insert 04/2021: https://packageinserts.bms.com/pi/pi_eliquis.pdf. Accessed Jan 19, 2022]

[Rivaroxaban package insert 12/2021: <https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/XARELTO-pi.pdf> Accessed Jan 19, 2022]

Obesity and DOACs

- > 120 kg
- BMI > 40 kg/m²



[Martin K et al. J Thromb Haemost 2016;14:1308-1313]



[Martin K et al J Thromb Haemost. 2021 Aug;19(8):1874-1882]



Obesity and DOACs

Take-home points

- **Severe obesity**

- Up to a BMI 40 kg/m² and weight 120 kg: all DOACs reasonable.
- > 40 kg/m² and > 120 kg: rivaroxaban and apixaban (fewer data) are reasonable.

[Martin K et al J Thromb Haemost. 2021 Aug;19(8):1874-1882]



Obesity and DOACs

Take-home points

- **Severe obesity**

- Up to a BMI 40 kg/m² and weight 120 kg: all DOACs reasonable.
- > 40 kg/m² and > 120 kg: rivaroxaban and apixaban (fewer data) are reasonable.

- **Bariatric surgery:**

- In the acute post-operative phase: parenteral anticoagulant.
- After ≥ 4 weeks, a switch to warfarin or a DOAC may be considered.
- If a DOAC is used: trough level testing.

[Martin K et al J Thromb Haemost. 2021 Aug;19(8):1874-1882]

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Clots in Unusual Locations

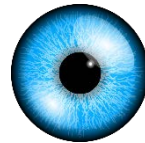
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Cerebral and sinus vein thrombosis

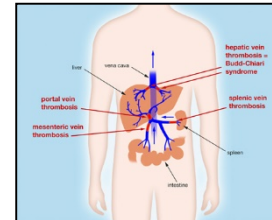


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Retinal vein and artery thromboses



3



Budd-Chiari
Portal vein
Splenic vein
SMV

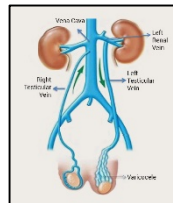
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Renal vein



5

Gonadal vein



<https://www.fatihugmd.com/varicocele>

6

Skin



7

Arterial clots,
unexplained

Work-up and
treatment



Clots in Unusual Locations



1. Define clot (retake history; question diagnosis and imaging report)
2. List VTE risk factors: A...., B...., C....
3. List bleeding risk factors: A...., B...., C....
4. Studies/data are limited on:
 - VTE recurrence
 - Best treatment (Is treatment needed at all? Length of anticoagulation)
 - Role of thrombophilia testing
5. Decisions are almost all based on very weak evidence
6. Therefore: One cannot be dogmatic.
7. If unprovoked: Consider thrombophilia w/u

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Other

DOACs – Interruption for Surgery

	Half-life
Apixaban	ca. 12 hrs
Dabigatran	12–14 hrs
Rivaroxaban	6-13 hrs

[Samuelson BT et al. Chest 2017;151:127-138]

$3 \times t_{1/2} = 36 \text{ hrs (1.5 days)}$

$5 \times t_{1/2} = 60 \text{ hrs (2.5 days)}$

DOACs – Interruption for Surgery

PAUSE trial

DOAC	Surgical Procedure-Associated Bleeding Risk	Preoperative DOAC Interruption Schedule						Postoperative DOAC Resumption Schedule			
		Day -5	Day -4	Day -3	Day -2	Day -1		Day +1	Day +2	Day +3	Day +4
<ul style="list-style-type: none"> Apixaban Rivaroxaban Dabigatran, GFR > 50 mL/min 	High	→			X	X	(No DOAC)	X	X	→	
	Low	→				X				→	
Dabigatran etexilate (CrCl <50 mL/min) ^a	High	→	X	X	X	X	Day of Surgery	X	X	→	
	Low	→			X	X				→	

[Modified from: Douketis JD et al. 2019;179(11):1469-1478. doi:10.1001/jamainternmed.2019.2431]



Recreational Sports



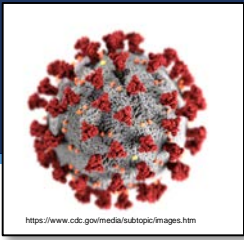
Temporary anticoagulation interruption



Take-home points

$3 \times t_{1/2} = 36 \text{ hrs (1.5 days)}$

$5 \times t_{1/2} = 60 \text{ hrs (2.5 days)}$



COVID Vaccine and VTE Risk

1



[Barda N et al. NEJM2021;385:1078-90]

2



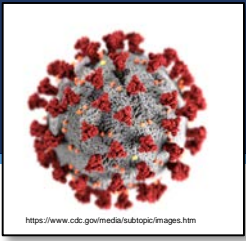
[Klein NP et al. JAMA 2021;326:1390-1399]

3



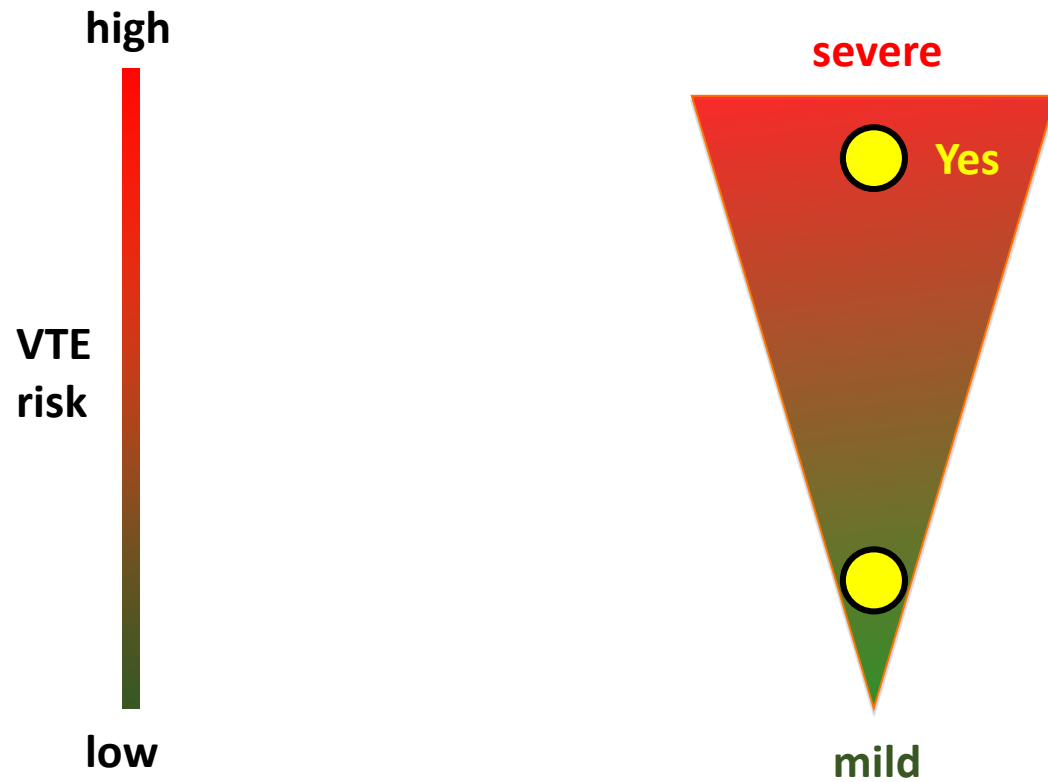
[Houghton DE et al. 2022 Apr 10;10.1111/jth.15725. doi: 10.1111/jth.15725. Online ahead of print]

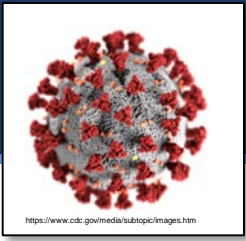
Findings: **NO** increased VTE risk after vaccination



COVID Infection and VTE

COVID infection





COVID Infection and VTE

COVID infection

Individual VTE
risk factors

high

VTE
risk

low

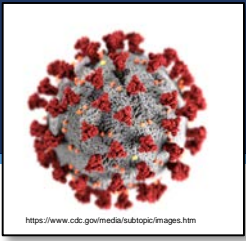
severe

Yes

mild

a lot

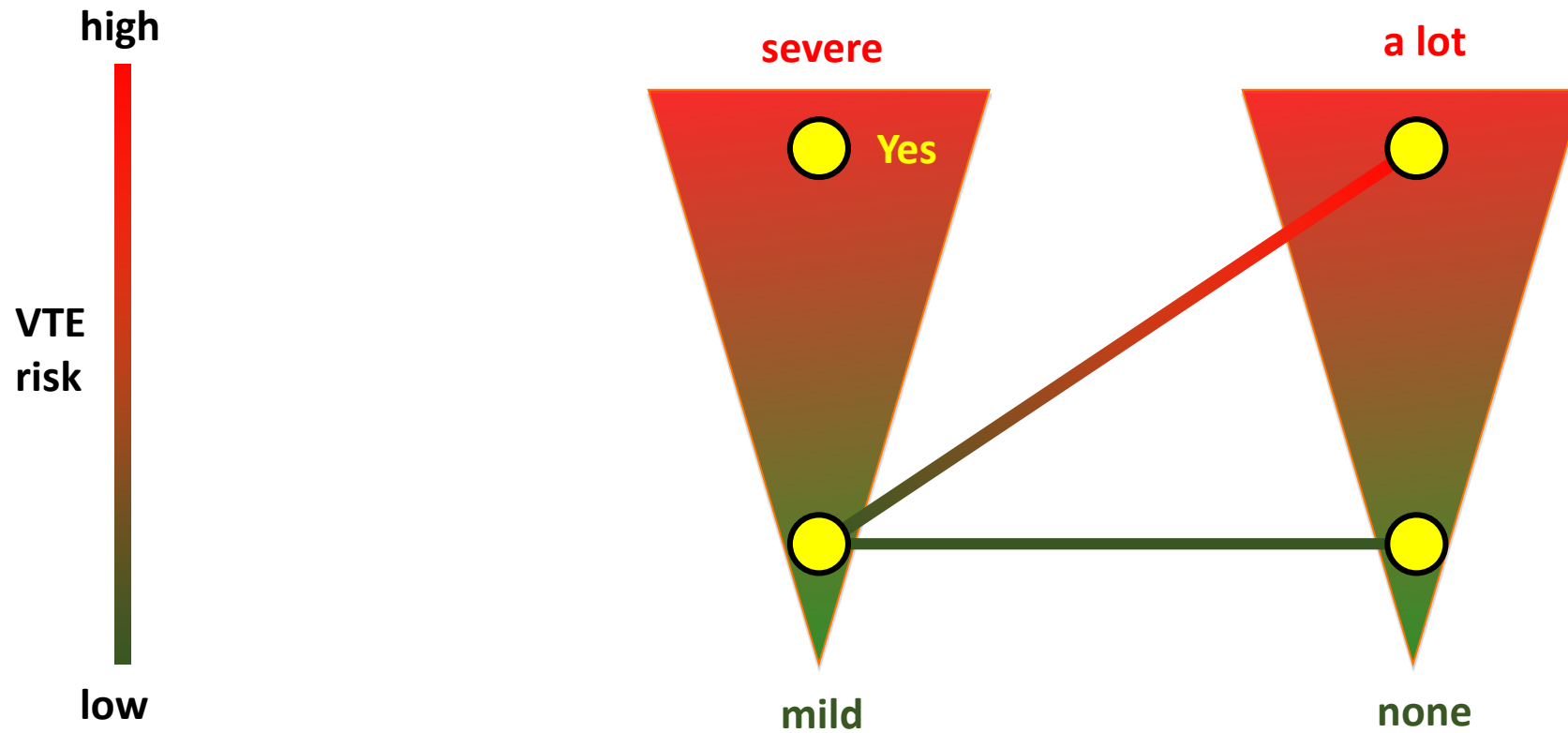
none



COVID Infection and VTE

COVID infection

Individual VTE
risk factors



Finally... and to Recap:

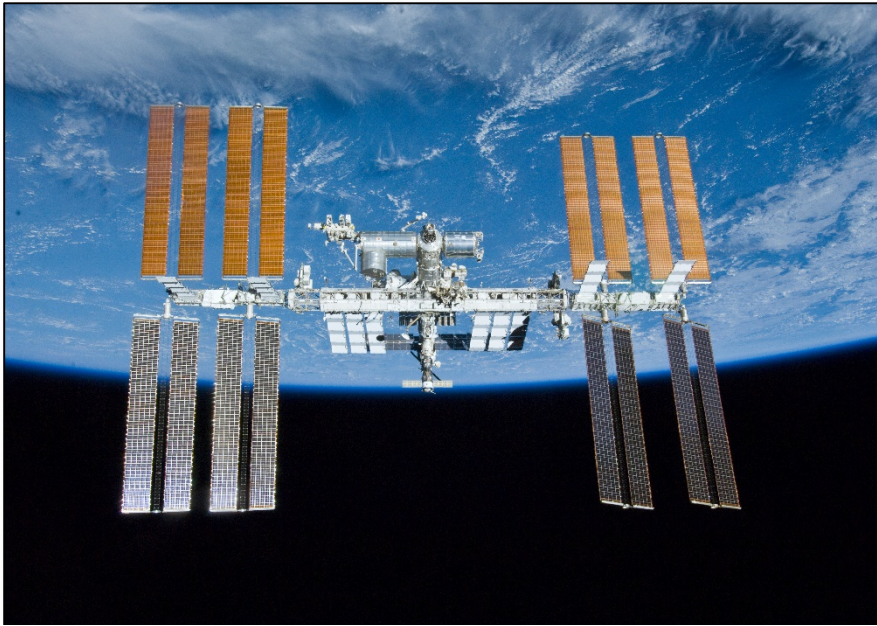


Photo courtesy of NASA



1. Critically review diagnosis
2. Review with best radiologist possible
3. List VTE risk factors: A...; B....; C...
4. List Bleeding risk factors: A...; B...; C...
5. Patient preference



Comments?

Questions?



American Holly, spalted





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