
# Venous Thromboembolism


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# Overview

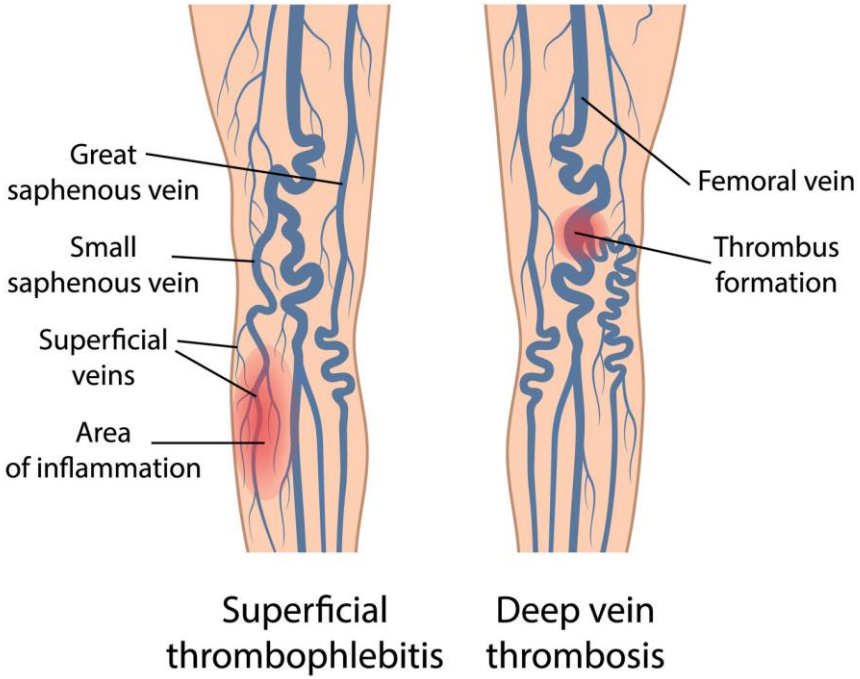
- Types
- Incidence
- Diagnosis
- Initial Anticoagulation
- Provoked vs Unprovoked
- Duration of Anticoagulation
- Secondary Prophylaxis
- Additional Considerations
- Practice Cases

# Types of VTE

- VTE = venous thromboembolism
- DVT = deep vein thrombosis
- PE = pulmonary embolism
- CVST = central venous sinus thrombosis
- Splanchnic thrombosis
  - PVT = portal vein thrombosis
  - Renal vein thrombosis
  - Mesenteric vein thrombosis
- Superficial vein thrombosis → not grouped w/ VTE

# Superficial vs Deep

- LE superficial veins
  - Greater saphenous
  - Lesser saphenous
- UE superficial veins
  - Cephalic
  - Basilic




https://veininstitute.com/blog/varicose-veins-and-the-risk-for-blood-clots

# How common is VTE?

- General population prevalence of VTE 0.1-0.2%
  - Prevalence = 1-2/1000 in their lifetime

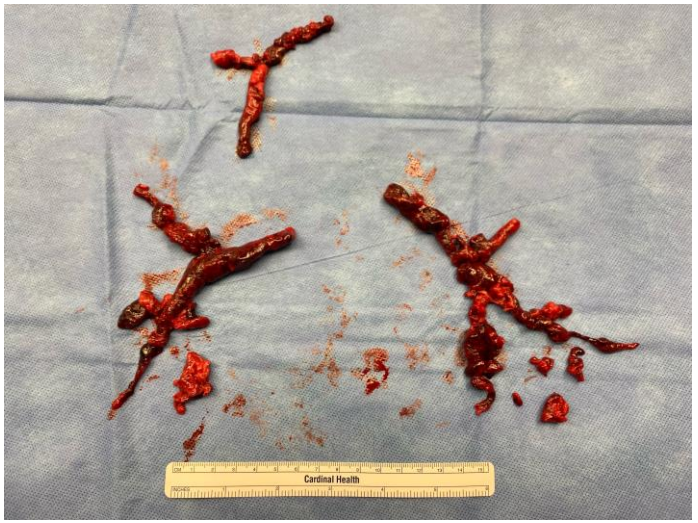



Photo credit: Nathaniel Langer, MD MSc

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# Diagnosis: Wells Score for DVT

**Table 1. Clinical Model for Predicting the Pretest Probability of Deep-Vein Thrombosis.***

| Clinical Characteristic | Score |
|---|---|
| Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment) | 1 |
| Paralysis, paresis, or recent plaster immobilization of the lower extremities | 1 |
| Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia | 1 |
| Localized tenderness along the distribution of the deep venous system | 1 |
| Entire leg swollen | 1 |
| Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity) | 1 |
| Pitting edema confined to the symptomatic leg | 1 |
| Collateral superficial veins (nonvaricose) | 1 |
| Previously documented deep-vein thrombosis | 1 |
| Alternative diagnosis at least as likely as deep-vein thrombosis | –2 |

* A score of two or higher indicates that the probability of deep-vein thrombosis is likely; a score of less than two indicates that the probability of deep-vein thrombosis is unlikely. In patients with symptoms in both legs, the more symptomatic leg is used.

1 point or less → ~3% have a DVT

Then get a d-dimer to rule out

D-dimer NOT appropriate if

- 2 or more points
- Known cause of elevation present
  - e.g. recent surgery, pregnancy

Wells et al 1997; Wells et al 2003

# Diagnosis: Wells Criteria for PE

**Table 1.** Clinical Decision Rule*

| Variable | Points |
|---|---|
| Clinical signs and symptoms of deep vein thrombosis (minimum of leg swelling and pain with palpation of the deep veins) | 3.0 |
| Alternative diagnosis less likely than pulmonary embolism | 3.0 |
| Heart rate >100/min | 1.5 |
| Immobilization (>3 d) or surgery in the previous 4 wk | 1.5 |
| Previous pulmonary embolism or deep vein thrombosis | 1.5 |
| Hemoptysis | 1.0 |
| Malignancy (receiving treatment, treated in the last 6 mo or palliative) | 1.0 |

*Clinical probability of pulmonary embolism unlikely: 4 or less points; clinical probability of pulmonary embolism likely: more than 4 points. Source: Wells et al.[3]

If score <4, then d-dimer can rule out

Again, don't get a d-dimer if known reason for a positive

Wells et al 2000; van Belle et al 2006

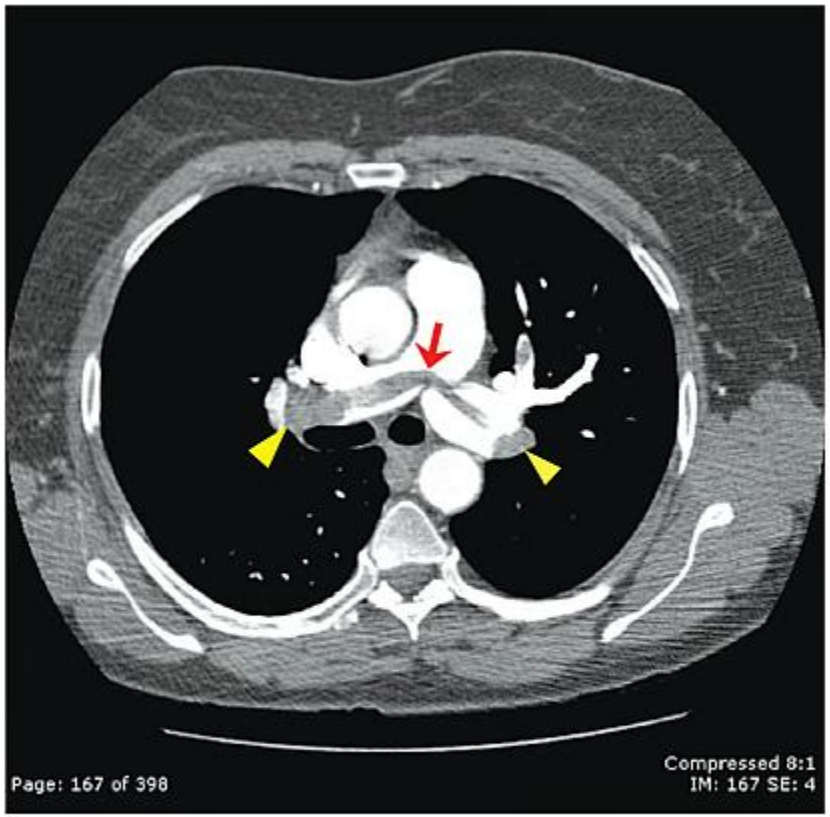
# Lower Extremity Ultrasound

- aka LENIs = Lower extremity non-invasive
- Incompressible = filled with clot
- Echogenicity can inform acute vs chronic

https://www.cuh.nhs.uk/our-services/surgery/vascular-studies-unit/ultrasound-scan-of-your-leg-veins-deep-vein-thrombosisdvt-scan/

# CT Chest for PE

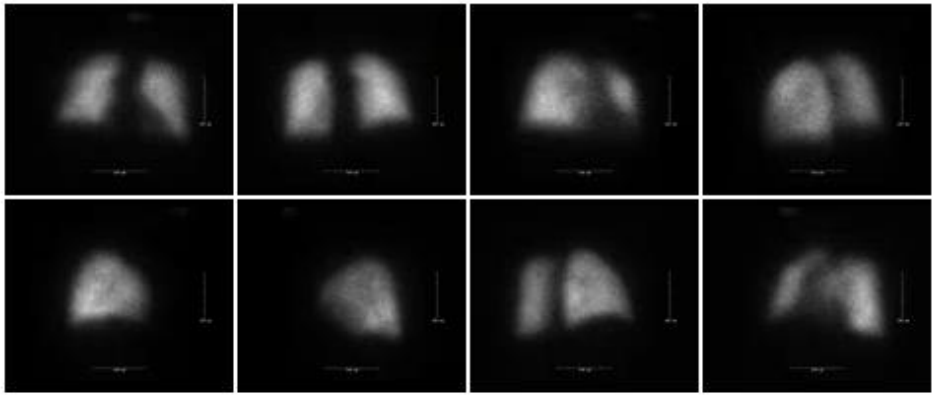
- Contrast is time for pulmonary arterial bed
  - Earlier vs regular contrast timing for systemic circulation



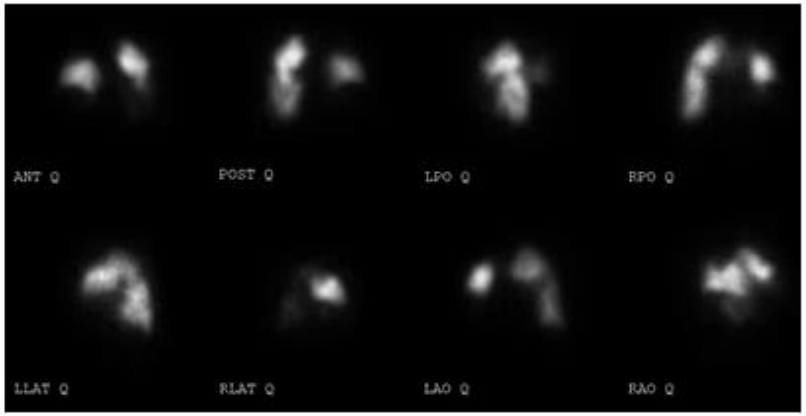
# V/Q Scan

- Ventilation vs perfusion
- High/Intermediate/Low probability
  - Requires a normal CXR
- More sensitive for distal clots
- Less radiation
- Less widely available

Normal



Large perfusion defects

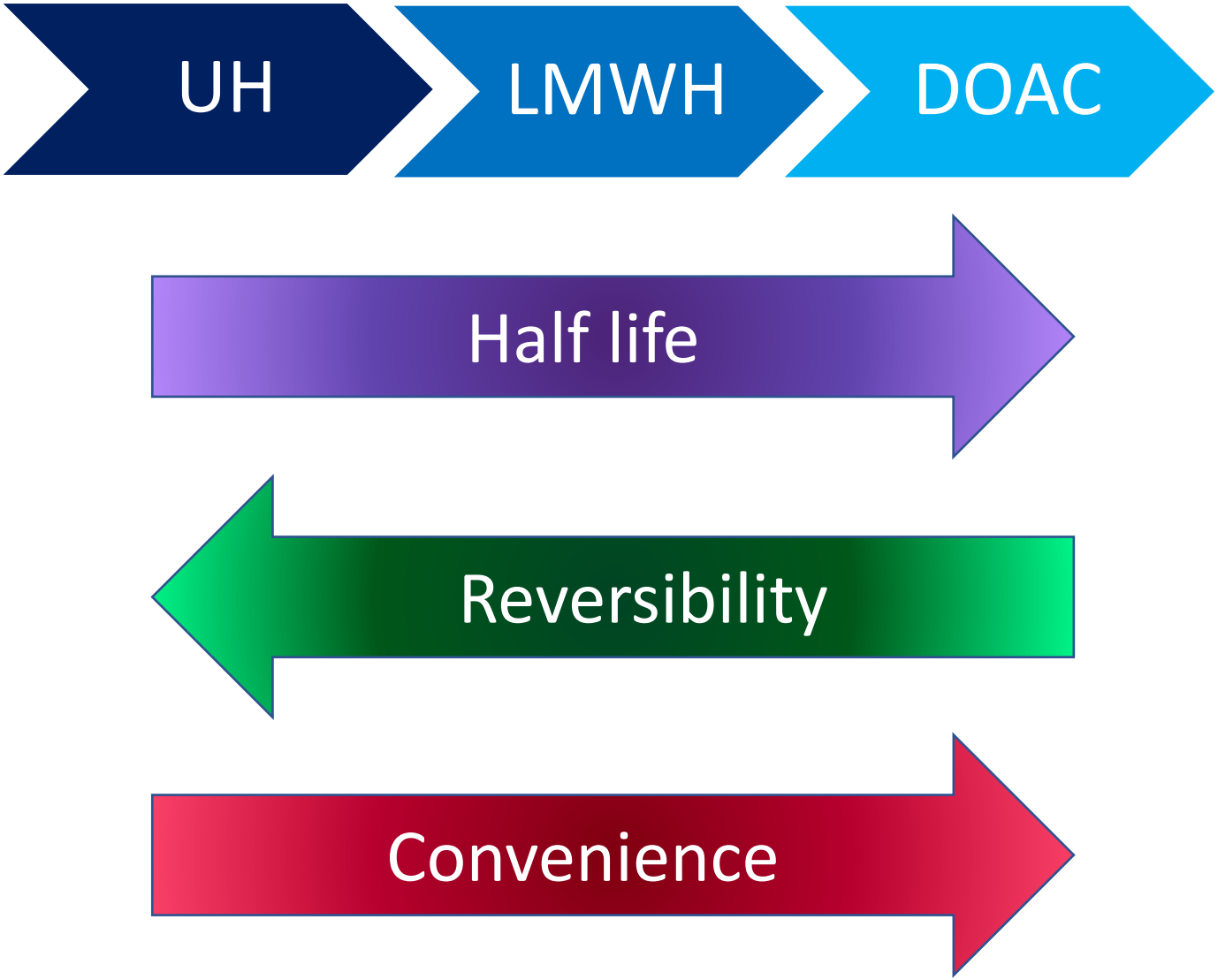



https://hcp.cteph.com/hcp/diagnosis/v-q-scan

# Picking Initial Anticoagulation

- Considerations
  - Stable or unstable?
  - Inpatient or outpatient?
  - What's the bleeding risk?

- Agents
  - Unfractionated heparin (UH)
  - Low molecular weight heparin (LMWH)
  - Direct oral anticoagulant (DOAC):
    - Xa inhibitor: apixaban, rivaroxaban, (edoxaban)
    - Direct thrombin inhibitor: dabigatran
  - Thrombolytics: tPA



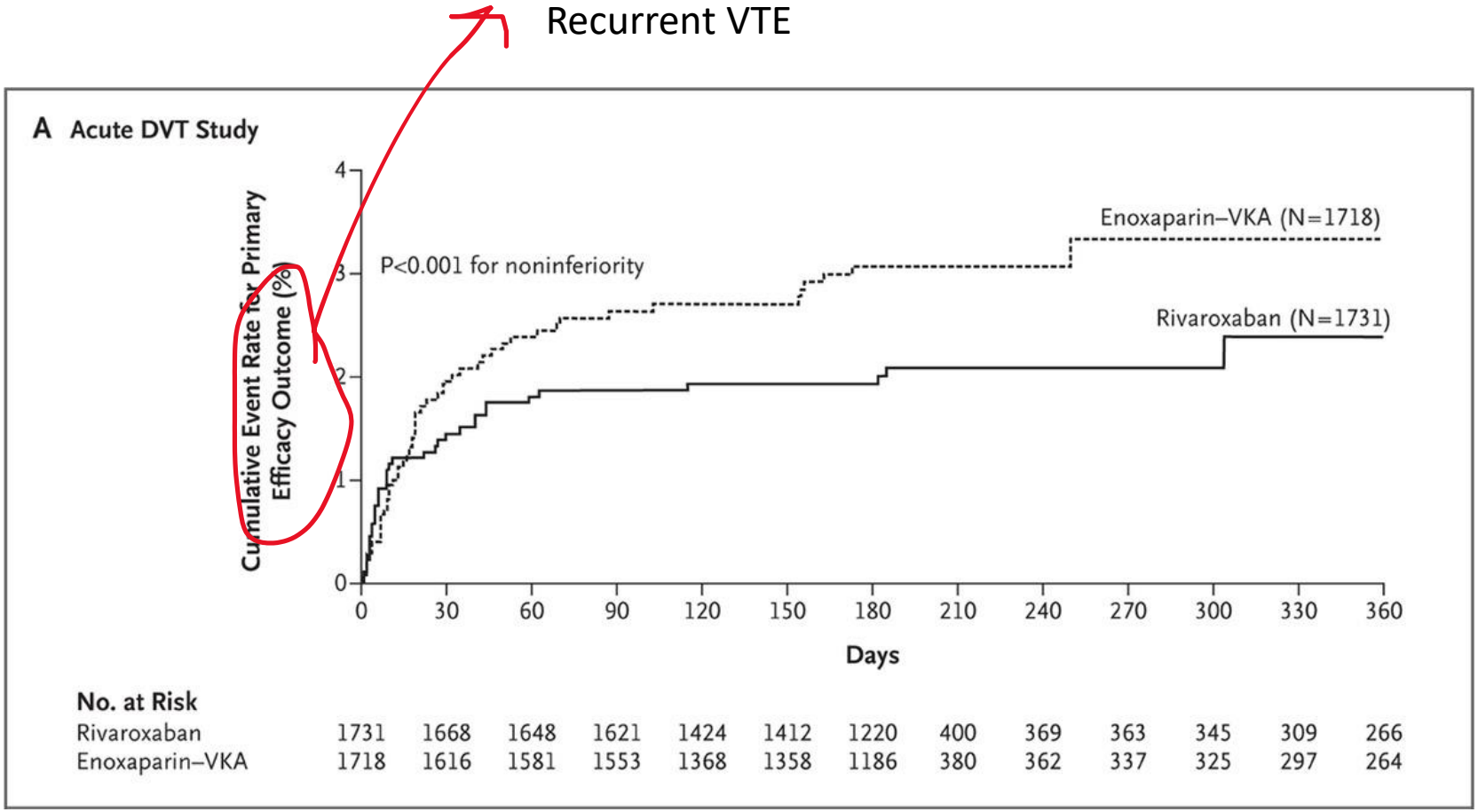
# Downsides to starting w/ UH

- Less reliable onset
  - May take several adjustments before therapeutic
- Ties up an IV
- Frequent lab checks
- Delay of discharge

# Warfarin

- NEVER the first agent for VTE
  - Needs a bridge
- Reserved for
  - Advanced CKD
  - Antiphospholipid syndrome
  - Inability to afford DOAC
  - (Mechanical heart valves)
- Highly reversible

# EINSTEIN: Rivaroxaban for DVT




Buller et al 2012

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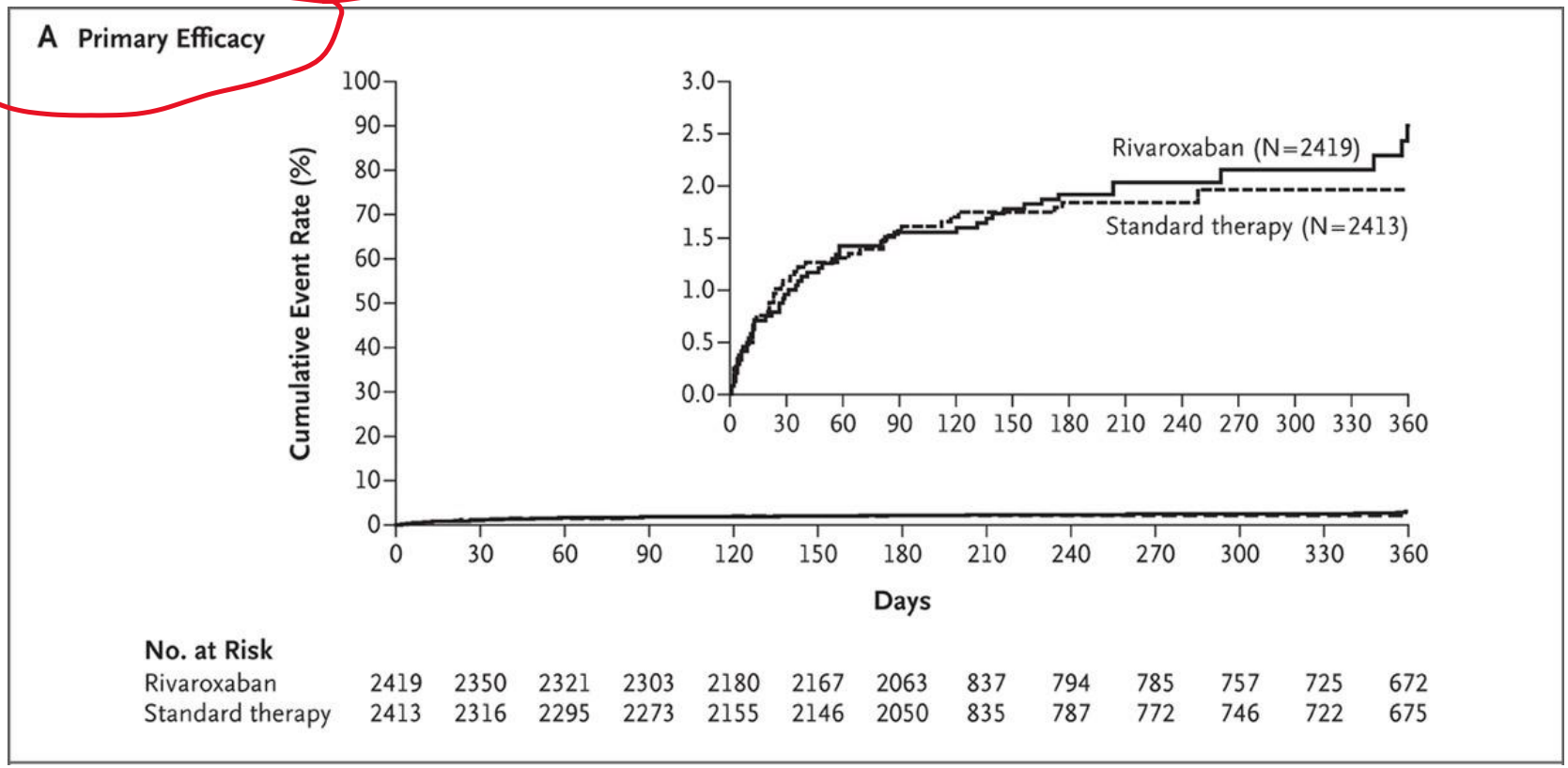
# EINSTEIN-PE: Rivaroxaban for PE

Recurrent VTE




P=0.003 for non-inferiority

Buller et al 2012

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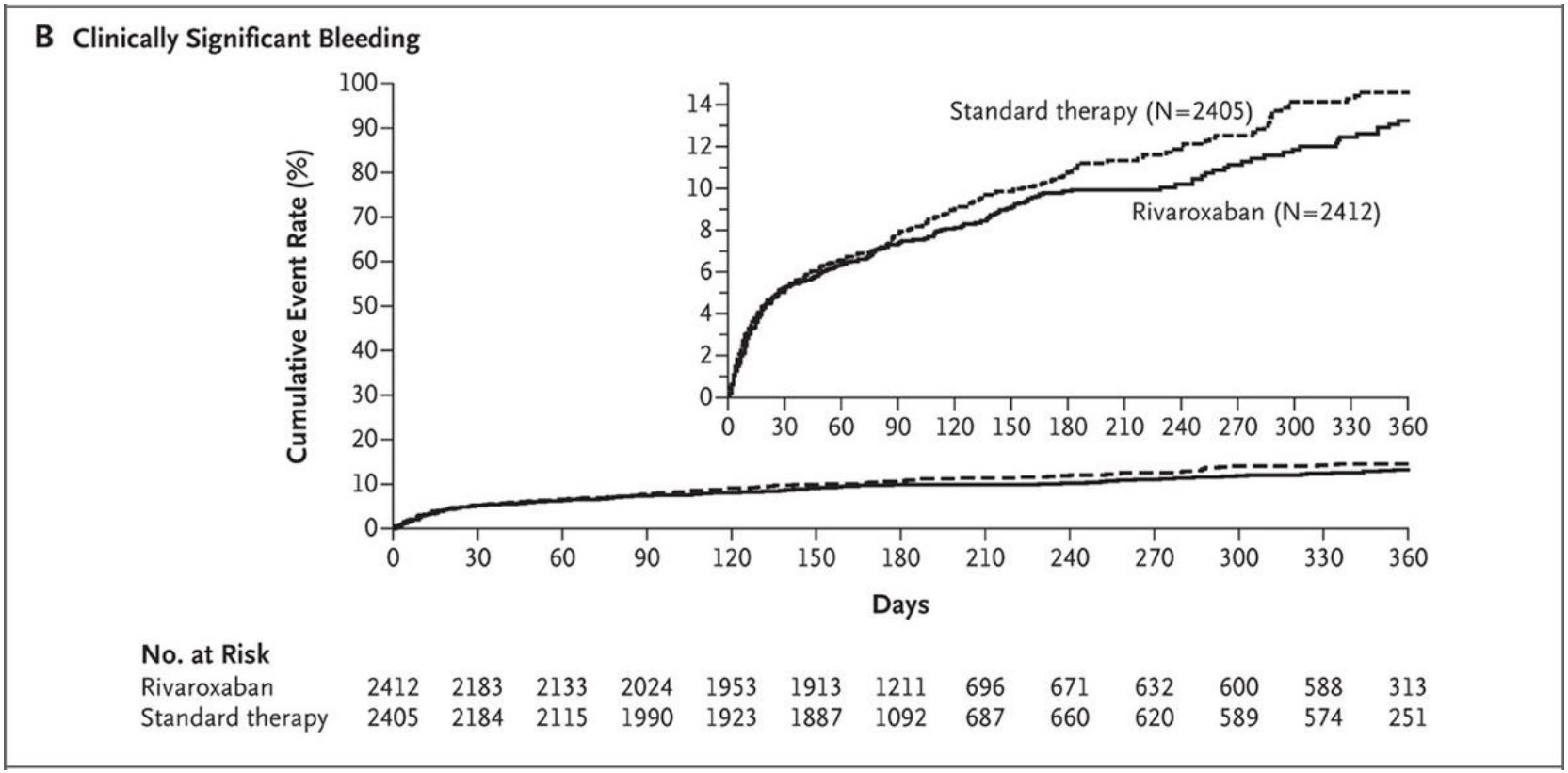
# EINSTEIN-PE: Rivaroxaban for PE




P=0.23

Buller et al 2012

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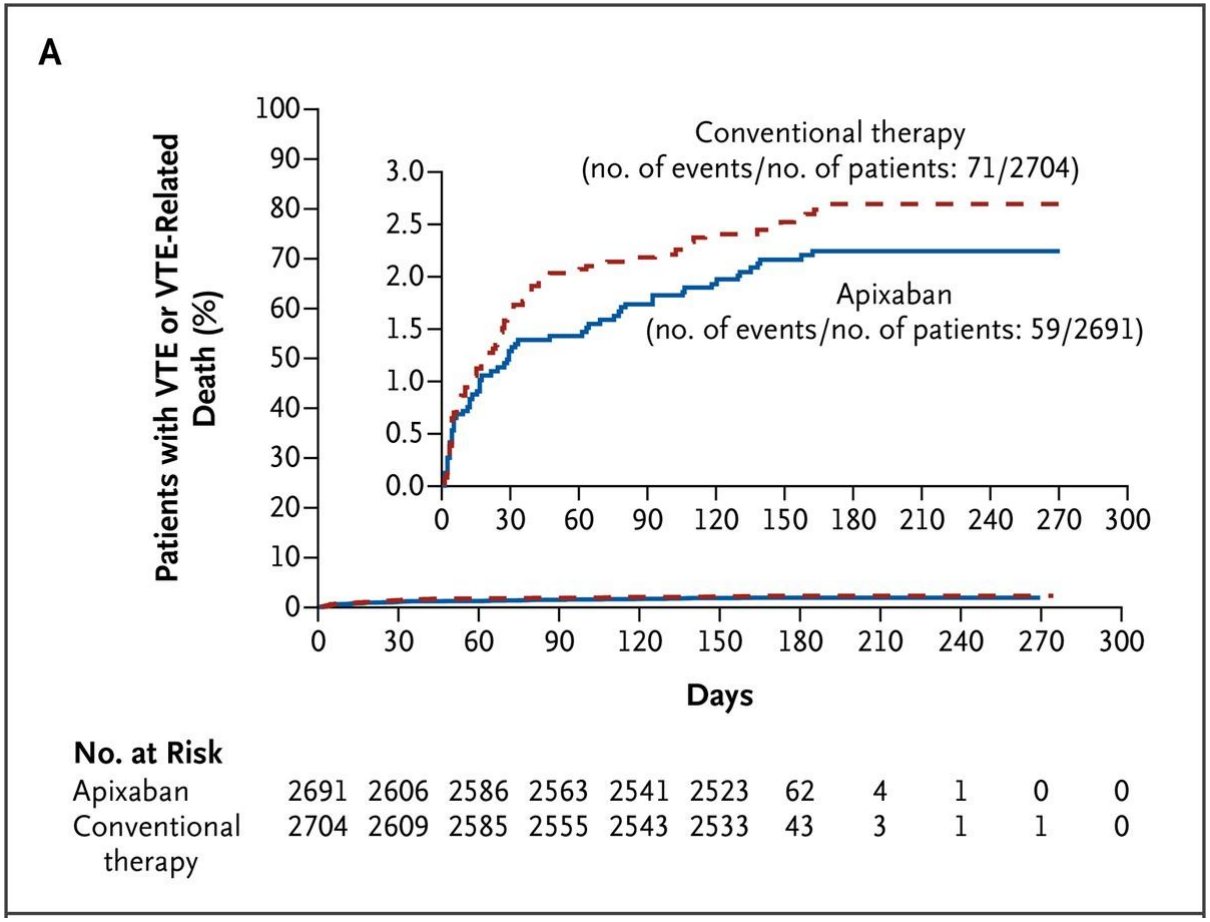
# AMPLIFY: Apixaban for VTE




P<0.001 for non-inferiority

Agnelli et al 2013a

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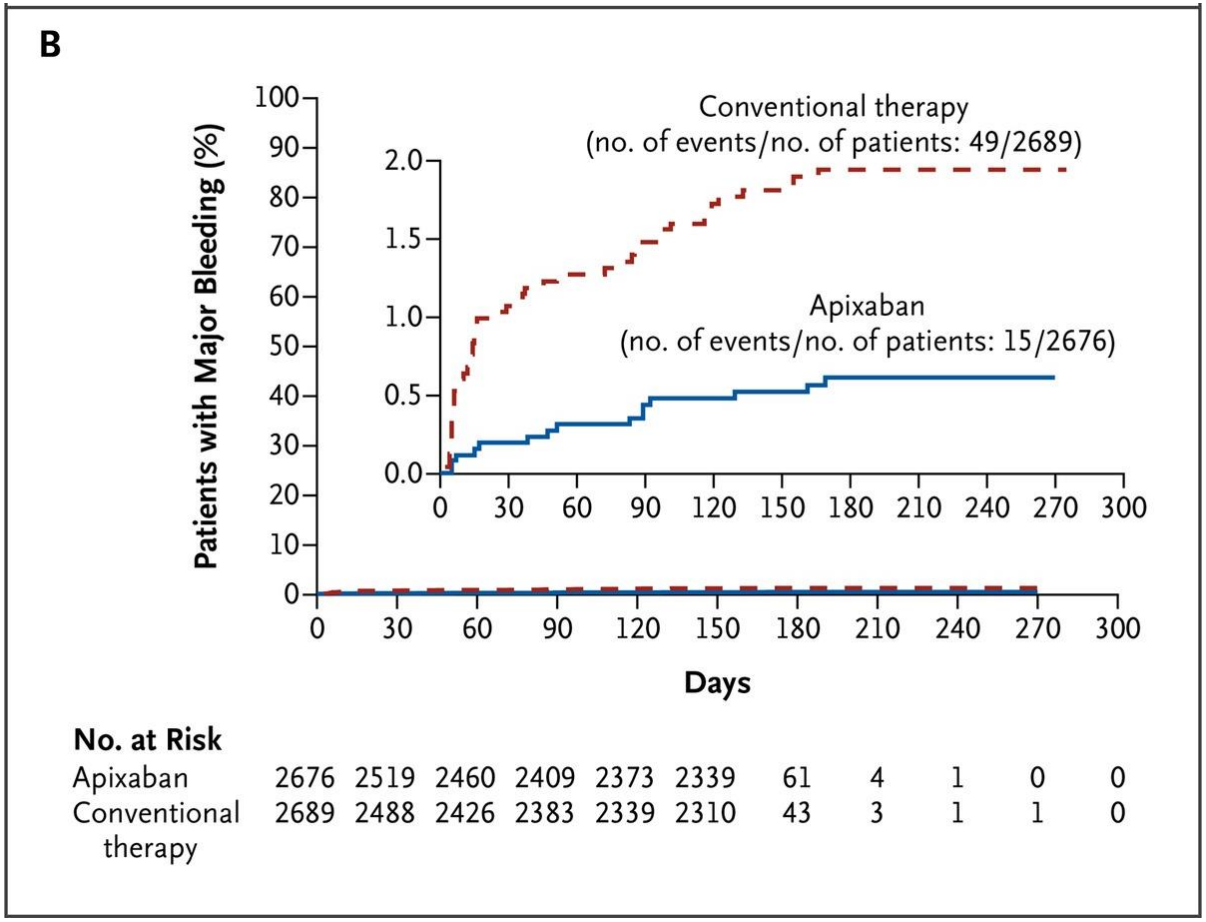
# AMPLIFY: Apixaban for VTE




P<0.001 for superiority

Agnelli et al 2013a

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# Provoked vs Unprovoked Clots

- Provoked: temporal relationship to a temporary cause
  - We know "why" this happened now (at least partly)
  - The patient isn't at the same risk all the time
  - e.g. major surgery, trauma, immobilization, pregnancy & OCPs, cancer
- Unprovoked: no good "why"
  - The patient *likely* remains at the same risk for another event


https://www.freepik.com/free-vector/opened-surprise-gift-box_1311240.htm#query=surprise&position=1&from_view=keyword&track=sph

# Implications for Duration

Risk isn't there all the time

=

Don't anticoagulate all the time

# Provoked VTE Management

- Anticoagulate PAST when transient risk factor is done
- Don’t anticoagulate forever
  - Ongoing cancer is exception
- Usually 3 vs 6 months

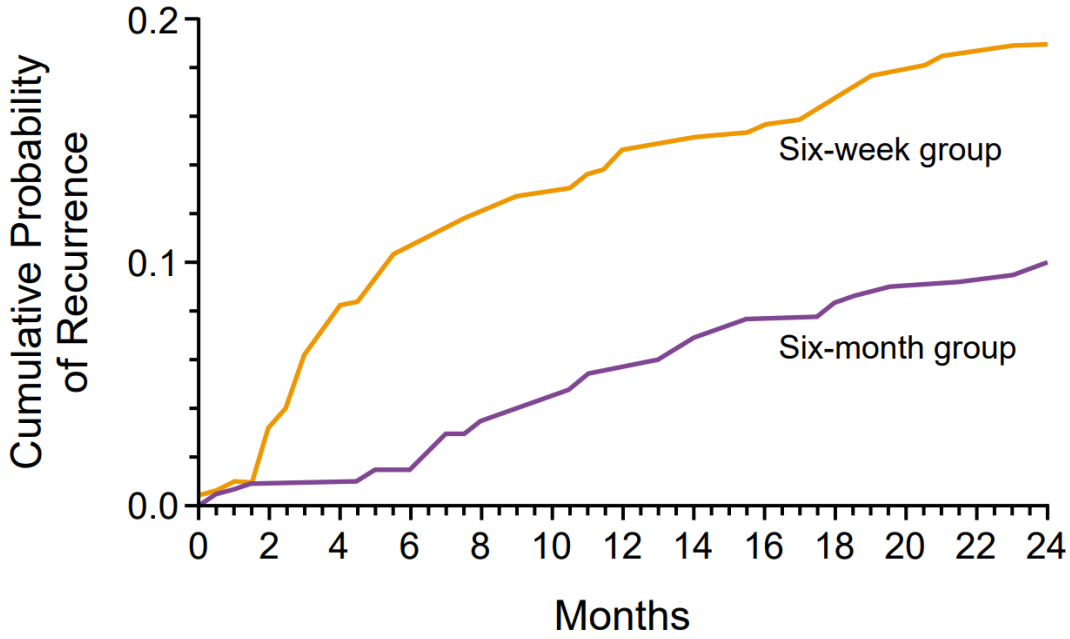
# 4 weeks vs 3 months for *proximal DVT*

- 8.6% vs 0.1% additional VTE in months 2 & 3
- Actually screened OUT the high risk by impedance plethysmography

Levine et al 1995

# 6 weeks vs 6 months for *VTE*

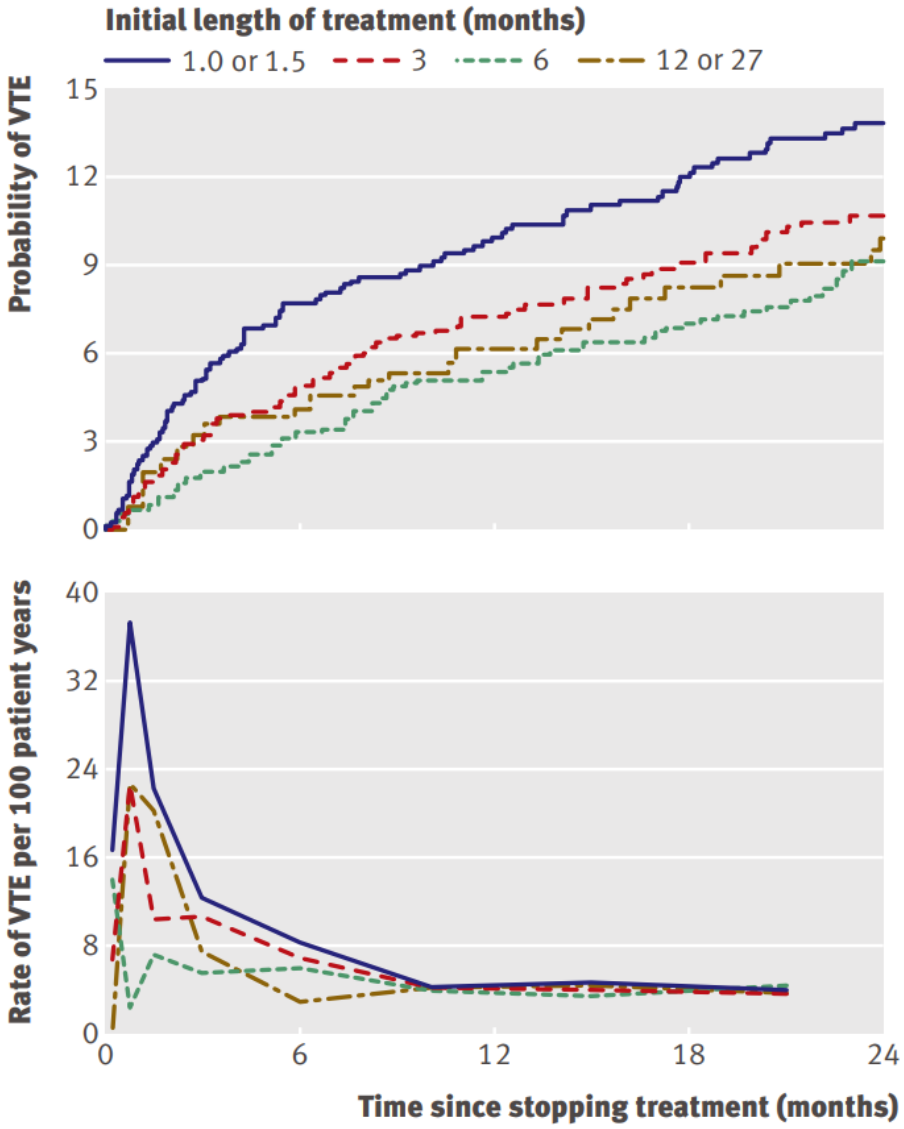
- Provoked or unprovoked
- 18.1% vs 9.5% recurrence w/i 2 year
- Curves parallel after 6 months




Schulman et al 1995

# Importance of time to heal

- Metanalysis of 7 studies of recurrence after first VTE
- >= 3 months lowers rate of recurrent in first 6 months
- Rates are high long term for unprovoked clot




Boutitie et al 2011

# Do you need to rescan?

- Studies of duration did not
- Ongoing symptoms?
- Implications of residual thrombosis?

# Chronic clot: not the best name

- Scar
  - Doesn't dissolve
  - Doesn't embolize
  - Low risk to extend

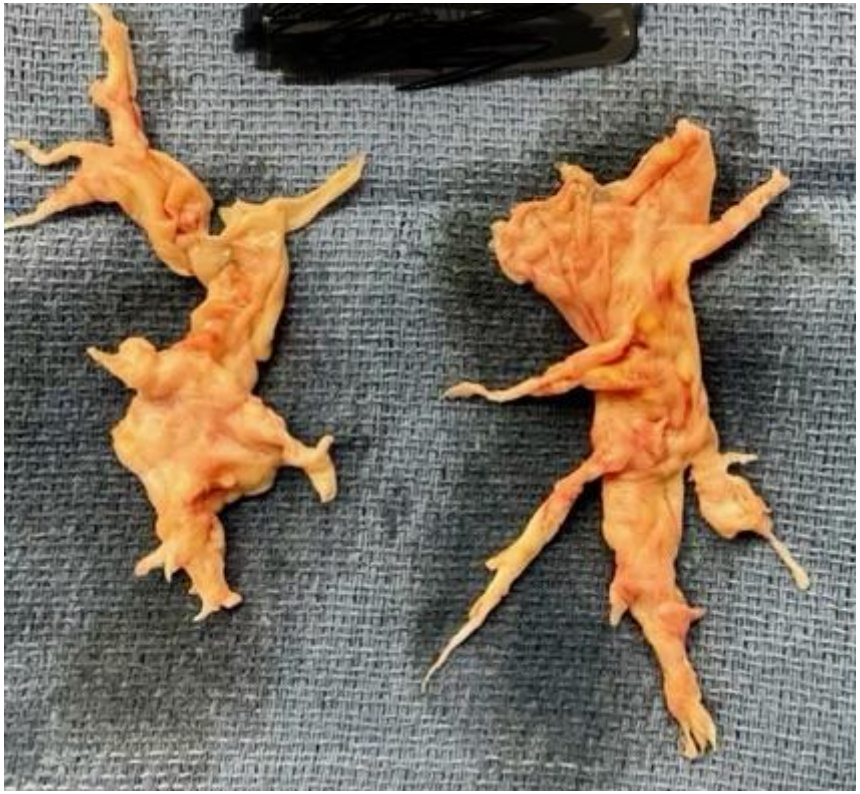
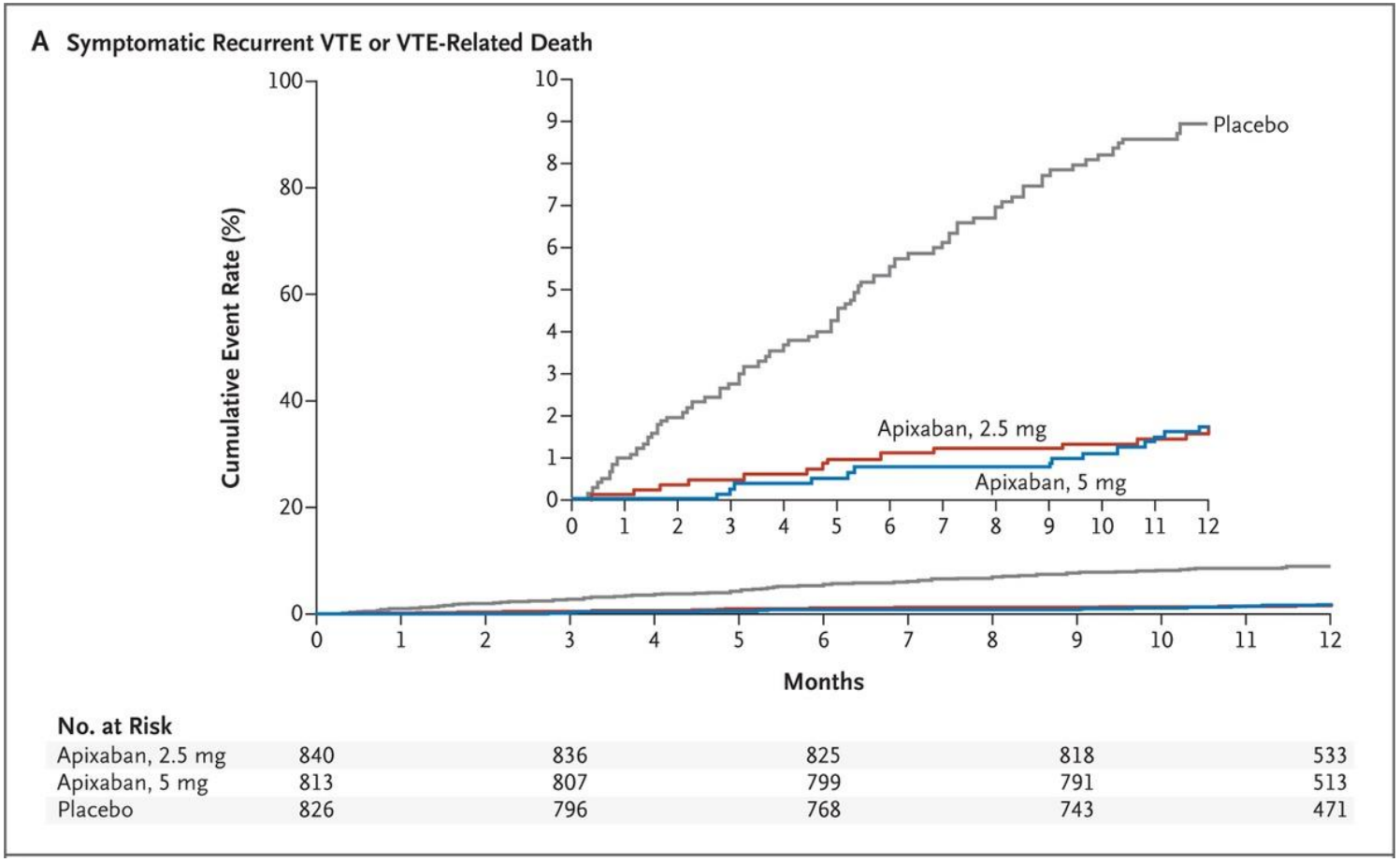


Photo credit: Nathaniel Langer, MD MSc

# Secondary Prophylaxis

- Continuous?
- With provocations?
  - Travel
  - Pregnancy
  - OCPs & high risk meds
  - Surgery

# AMPLIFY-Extend




P<0.001 for both comparisons

Agnelli et al 2013b

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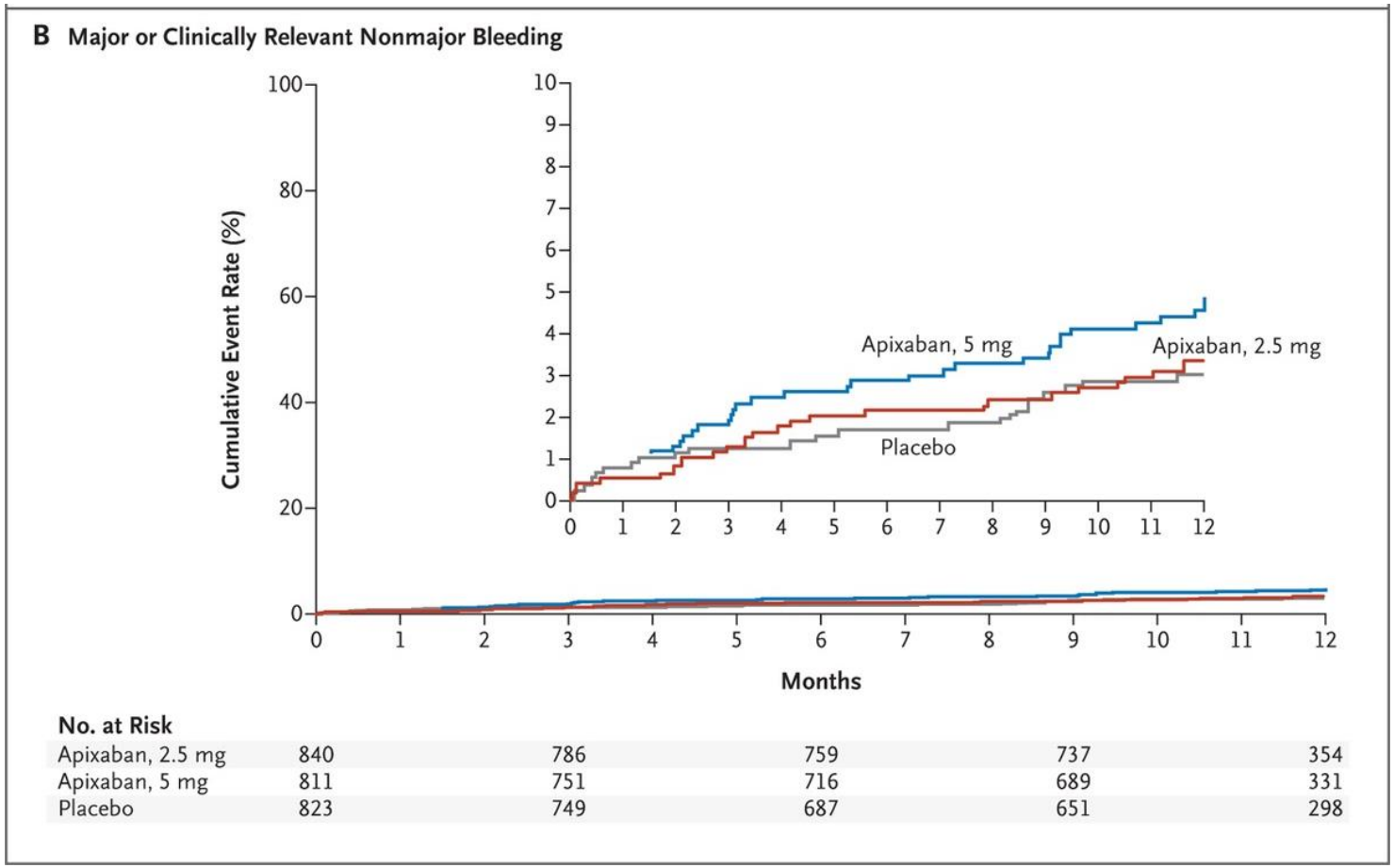
# AMPLIFY-Extend




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Apixaban, 2.5 mg | 840 | 786 | 759 | 737 | 354 |
| Apixaban, 5 mg | 811 | 751 | 716 | 689 | 331 |
| Placebo | 823 | 749 | 687 | 651 | 298 |

Agnelli et al 2013b

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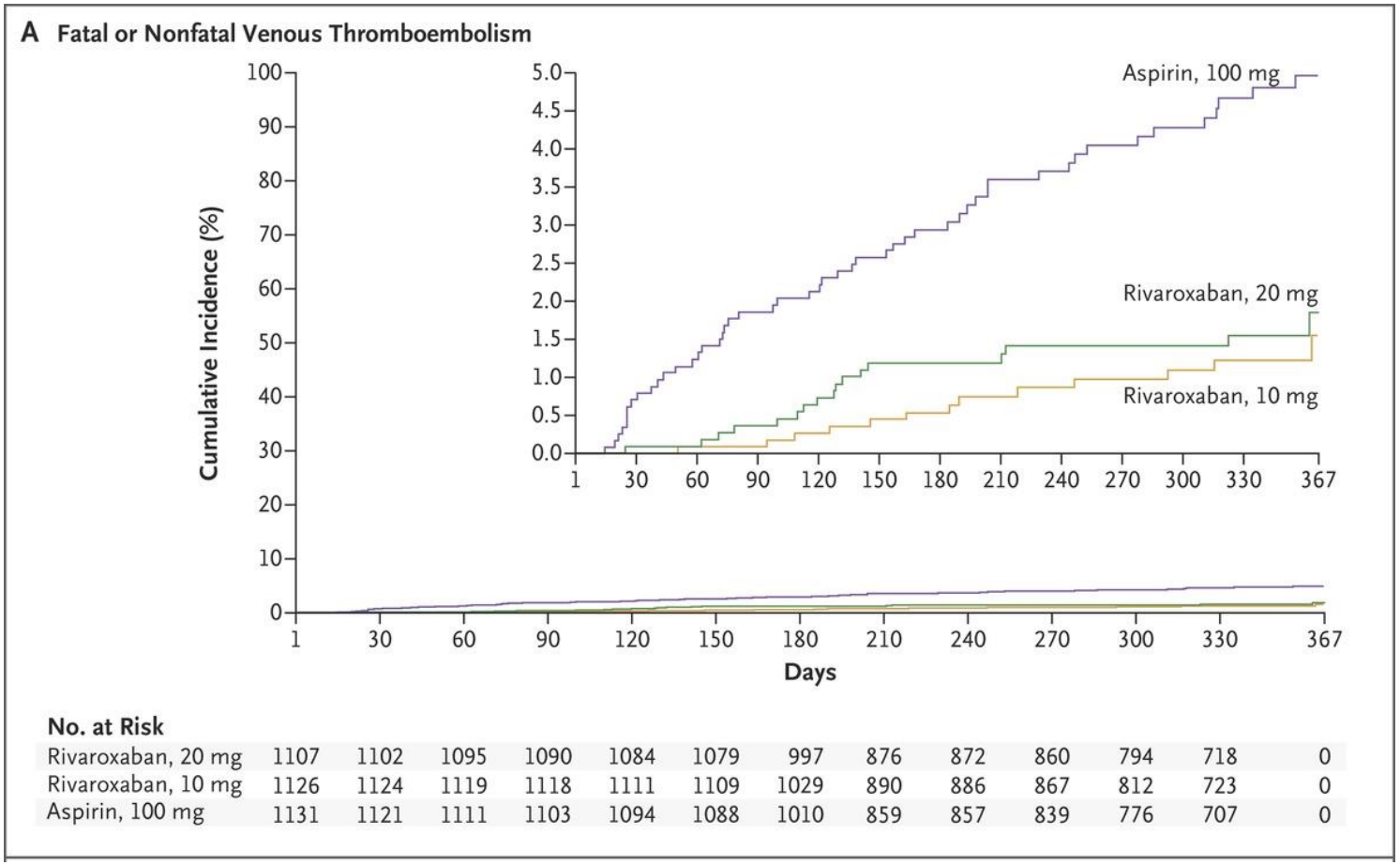
# EINSTEIN-Choice




P<0.001 for both comparisons

Weitz et al 2017

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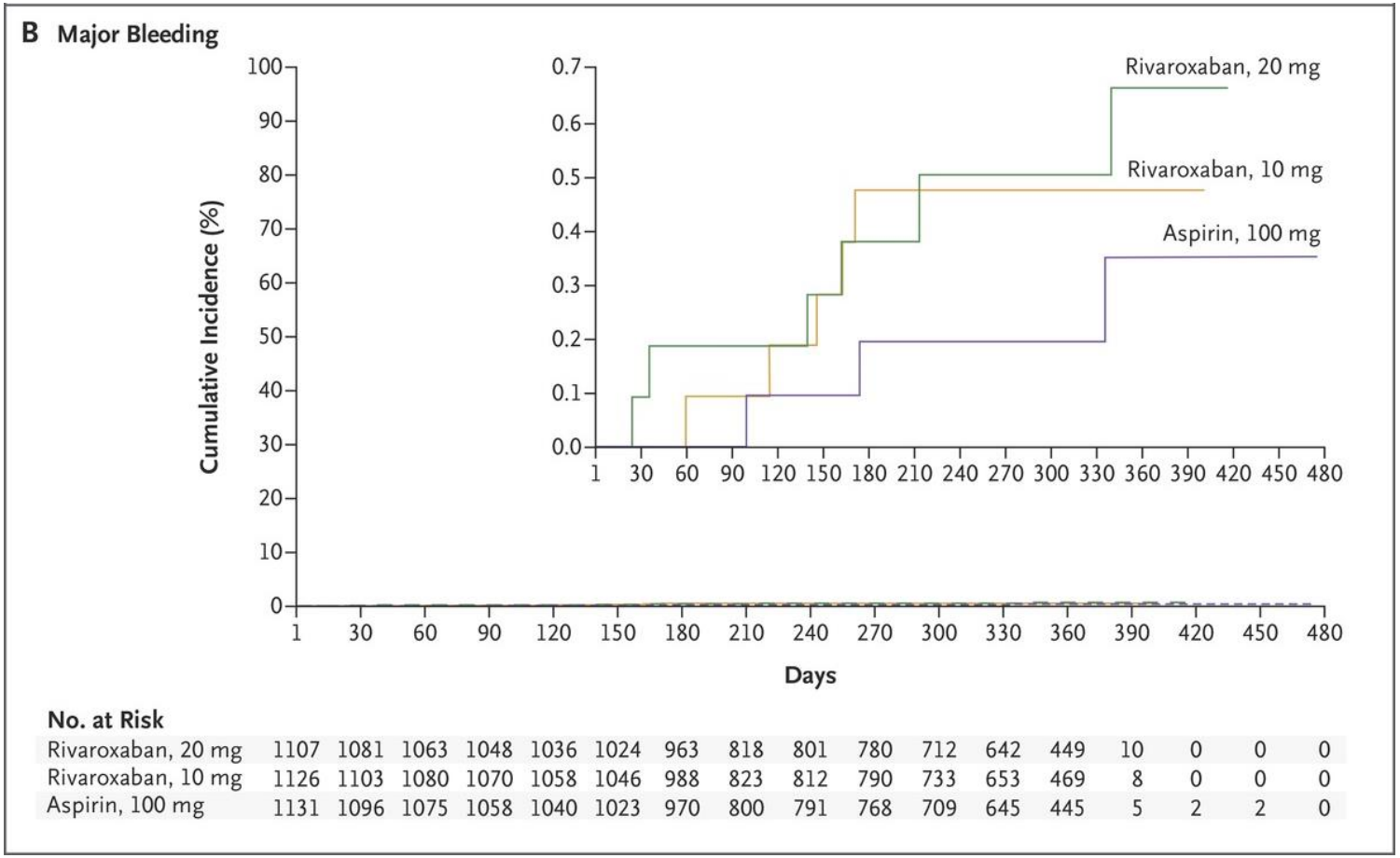
# EINSTEIN-Choice




**No. at Risk**

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rivaroxaban, 20 mg | 1107 | 1081 | 1063 | 1048 | 1036 | 1024 | 963 | 818 | 801 | 780 | 712 | 642 | 449 | 10 | 0 | 0 | 0 |
| Rivaroxaban, 10 mg | 1126 | 1103 | 1080 | 1070 | 1058 | 1046 | 988 | 823 | 812 | 790 | 733 | 653 | 469 | 8 | 0 | 0 | 0 |
| Aspirin, 100 mg | 1131 | 1096 | 1075 | 1058 | 1040 | 1023 | 970 | 800 | 791 | 768 | 709 | 645 | 445 | 5 | 2 | 2 | 0 |

Weitz et al 2017

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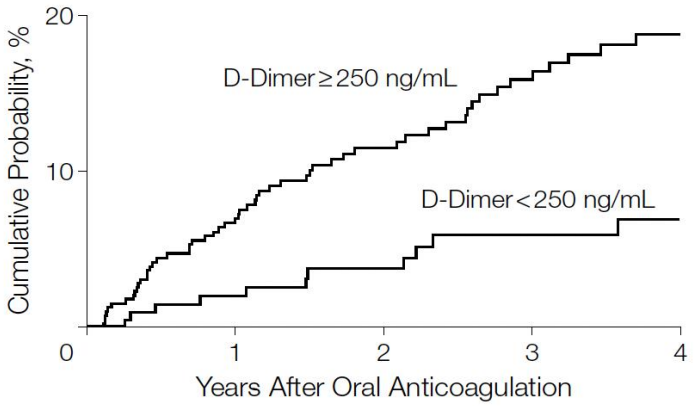
# D-dimer risk stratification

**Figure.** Kaplan-Meier Method Estimates of the Risk of Recurrent VTE According to the Plasma Level of D-Dimer




| No. at Risk D-Dimer | | | | | |
|---|---|---|---|---|---|
| ≥250 ng/mL | 401 | 324 | 230 | 162 | 117 |
| <250 ng/mL | 209 | 182 | 142 | 102 | 85 |

The probability of recurrent venous thromboembolism (VTE) was lower among patients with D-dimer levels of less than 250 ng/mL than among patients with higher levels ($P = .001$ by the Wilcoxon rank sum test and log-rank test).

Eichinger et al 2003

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# D-dimer in the modern era

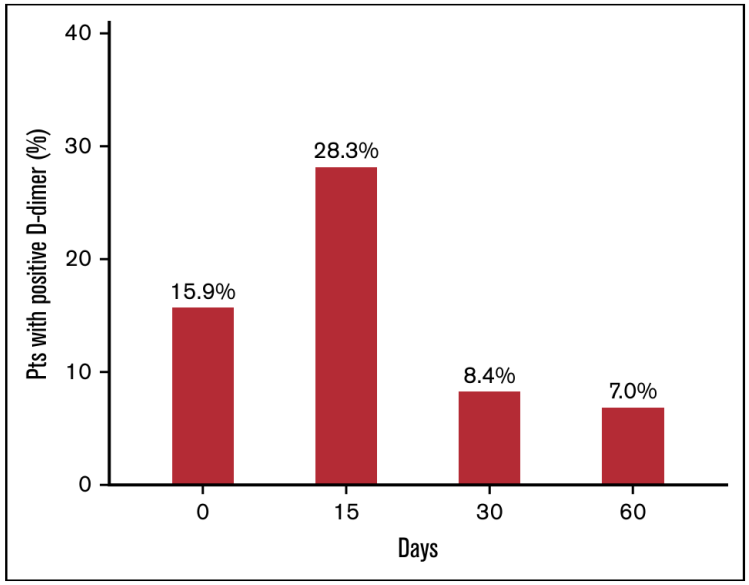


**Figure 2. Prevalence of first-time-ever positive D-dimer result (above the predefined cutoff levels) in the investigated study population at the serial measurement during (0) and days after anticoagulation withdrawal.** The percentages are calculated vs the total number of patients tested.

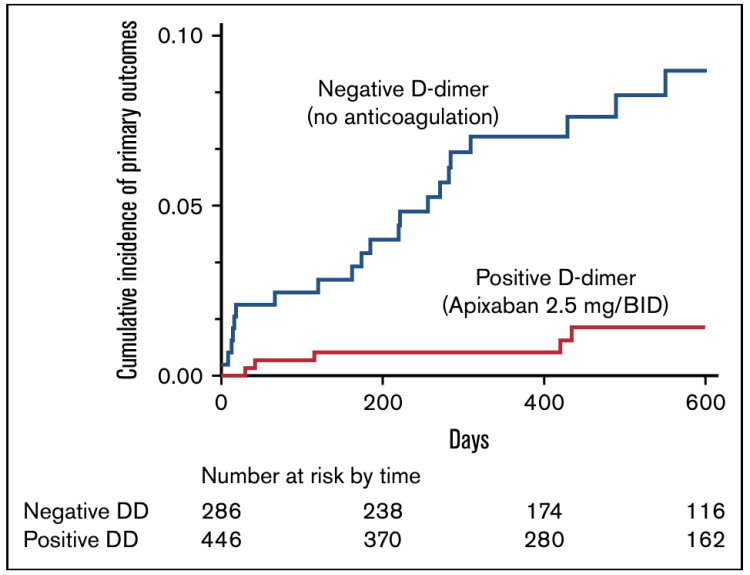


**Figure 3. The Kaplan-Meier cumulative event rates for the primary outcomes in patients receiving low-dose apixaban (dotted line) for positive D-dimer and in patients with persistently negative D-dimer in whom anticoagulation was definitively stopped (continuous line).**

Palareti et al 2022

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# Anticoagulation summary

- Apixaban or rivaroxaban for most
- 3-6 months of therapeutic anticoagulation, then
  - Provoked: stop
  - Unprovoked: reduce dose
    - Can consider d/c, d-dimer risk stratification

# Additional Considerations

# Massive vs Submassive

**Table 2**

**American Heart Association Definitions of Massive, Submassive, and Low-Risk PE and Associated Mortality**

| PE Classification | Definition | Mortality |
|---|---|---|
| Massive | Acute PE with sustained hypotension (< 90 mm Hg systolic) > 15 minutes or requiring inotropic support | 25%–65% (62) |
| Submassive | Systolic pressure > 90 mm Hg and either: (a) RV dysfunction (CT, BNP/proBNP, ECG changes) or (b) myocardial necrosis (elevated troponins) | 3% (20) |
| Low risk | Absence of hypotension, RV dysfunction, and myocardial necrosis | <1% (20) |

Note.—BNP = brain natriuretic peptide, ECG = electrocardiography.

Sista et al 2017

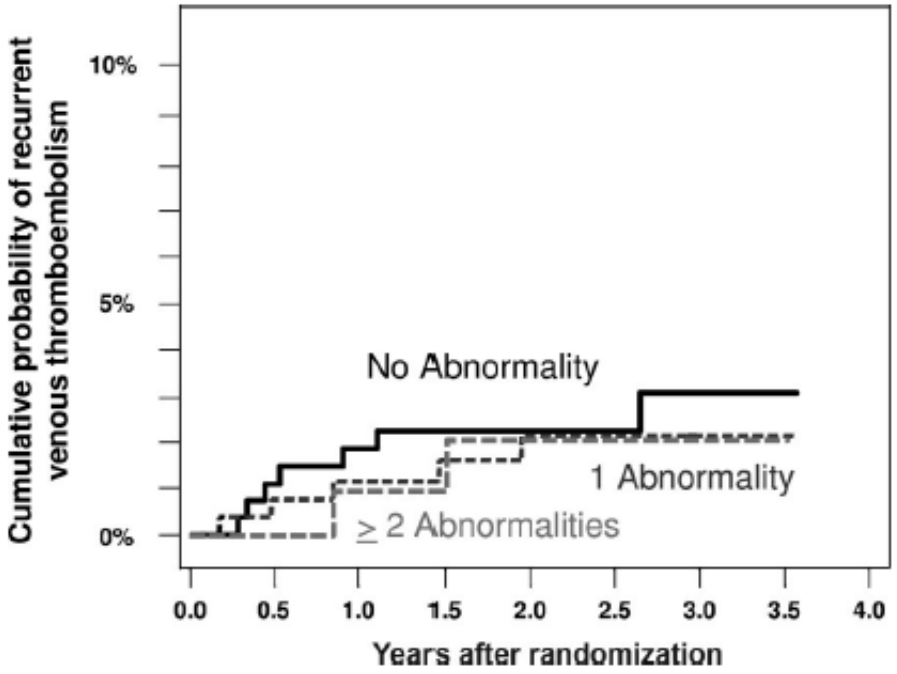
# Screening for malignancy

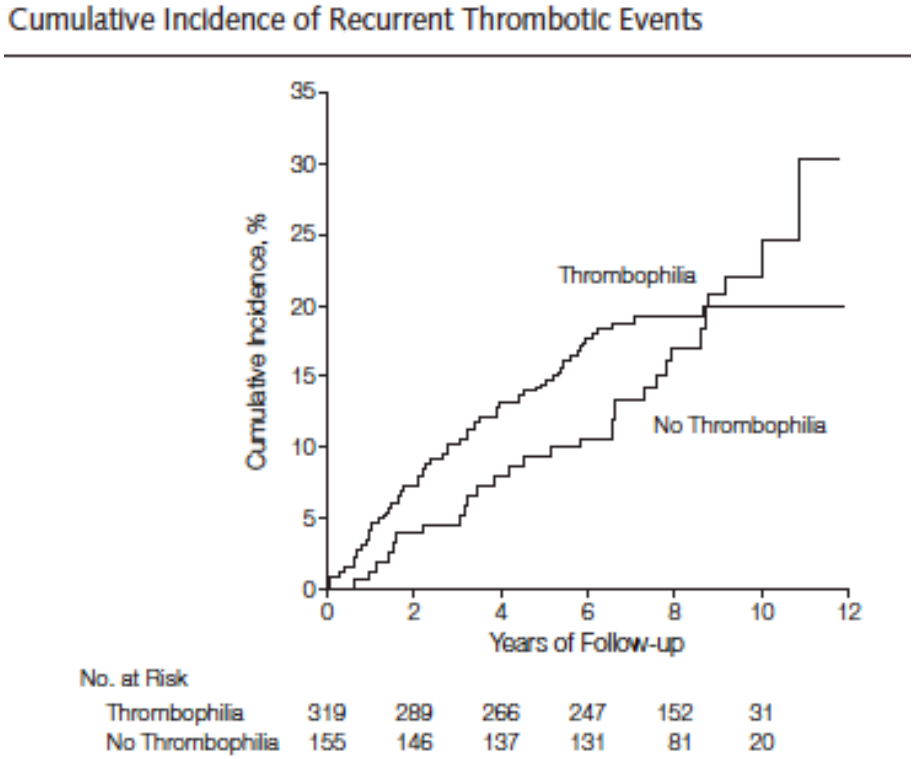
- "Unprovoked" VTE associated w/
  - ~6% malignancy discovered concurrently
  - Up to 10% malignancy discovered w/i 1 year
- Do:
  - Already indicated age-appropriate cancer screening
  - Symptom driven-testing
- Don't: pan-scan
  - CT abdomen/pelvis doesn't improve identification

Carrier et al 2008; Carrier et al 2015

# Hypercoagulability Work Ups

- ASH Choosing Wisely Guideline: No for provoked
- Doesn't predict recurrence for unprovoked




Kearon et al 2008; Christiansen et al 2005; Baglin et al 2003

# What's the downside?

- Cost
- False positives: Protein C, Protein S, Antithrombin
- Mismanagement
  - False reassurance
  - Unnecessary anticoagulation
  - Withholding of other care

# IVC filters rarely help

- ASH Choosing Wisely Guideline: No if anticoagulated
- If on anticoagulation, only prevents asymptomatic PE
- Increases rate of DVT
- Often get forgotten
  - Make a concrete plan for removal

Decousus et al 1998

# Cases

Let’s put it all together

# Case 1

52-year-old woman has worsening Right lower extremity swelling 10 days after a right knee replacement for osteoarthritis

- Should you order a d-dimer?
- What should you order?
- Ultrasound shows a DVT
- What medication do you start?
- How long should she be anticoagulated for?
- Is any other testing needed?

# Case 2

43-year-old man has rapid onset chest pain. Work has been quite stressful recently & he is worried he might get laid off, but he is otherwise well. His heart rate is 90; BP normal. There is no leg swelling or pain.

- Should you order a d-dimer?
- D-dimer is 1200 (significantly elevated)
- What should you order?
- CT PE shows two segmental PEs. Ultrasound shows a Left DVT.

# Case 2 continued

43-year-old man has rapid onset chest pain... His heart rate is 90; BP normal. CT PE shows two segmental PEs. Ultrasound shows a Left DVT.

- What medication do you start?
- Does he need an IVC filter?
- How long should he be *therapeutically* anticoagulated for?
- Is any other testing needed?

# Case 2 continued some more

43-year-old man has rapid onset chest pain... two segmental PEs & a Left DVT... He is therapeutically anticoagulated with a rivaroxaban for 6 months

- What should you do now? What are the options?
- He has a strong preference to be off anticoagulation. Rivaroxaban held. What now?
- D-dimer is 700 after 4 weeks.
- What is his risk of recurrence?
- He opts to resume rivaroxaban at prophylactic dose

# Case 3

21-year-old woman has sudden onset shortness of breath and presents to the ED. She noticed right leg pain a few days ago and some of her shoes don't fit. Her only medication is combined oral contraceptives started 2 months ago. Her heart rate is 110; BP 96/50.

- Should you order a d-dimer?
- What should you order?
- CT PE shows a left PA PE. Ultrasound shows a Right DVT.

# Case 3 continued

21-year-old woman has a left PA PE & right DVT. Her only medication is combined oral contraceptives started 2 months ago. HR 110; BP 96/50.

- What medication do you start?
- Do you need more imaging or labs?
- Does she need an IVC filter?
- Any other medication changes?
- She stabilizes and is treated with apixaban for 6 months, then stops.

# Case 3 continued some more

21-year-old woman has a left PA PE & right DVT. Her only medication is combined oral contraceptives started 2 months ago. HR 110; BP 96/50. She stabilizes and is treated with apixaban for 6 months, then stops. She switches to a progesterone only form of contraception.

- Any future precautions?

# Questions?

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