New Drugs for Blood Clots: Implications for Myeloprolierative Neoplasms (MPN)

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Objectives

- Epidemiology of venous thromboembolism (VTE)
  - How common is it?
- What symptoms are typically associated with VTE and stroke?
- How is VTE diagnosed?
- What drugs are available to treat clots?
- What are the new drugs available to treat VTE?
- Do they have a role in managing VTE in patients with cancer?
- Implications for myeloproliferative neoplasms

Epidemiology of venous thromboembolism (how common is it)?

Population	Thrombosis (venous/arterial)
General	0.1 to 1% (venous)
Solid organ (pancreas, lung etc)	10 to 30%
Myeloproliferative Neoplasms	
PV	12 to 39%
ET	10 to 29%
Myelofibrosis	13%

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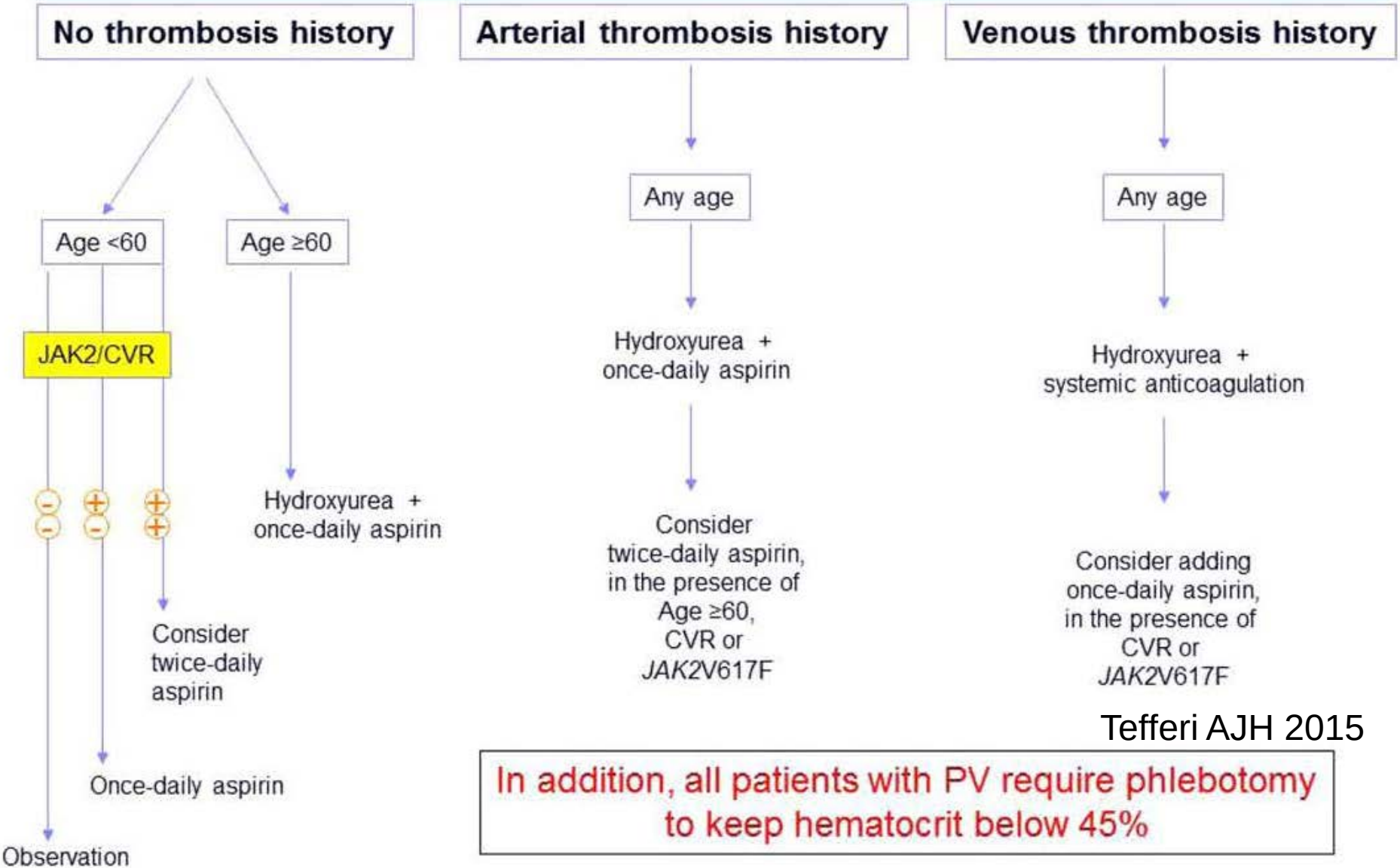
Contemporary treatment algorithm in essential thrombocythemia and polycythemia vera



Tefferi AJH 2015

In addition, all patients with PV require phlebotomy to keep hematocrit below 45%

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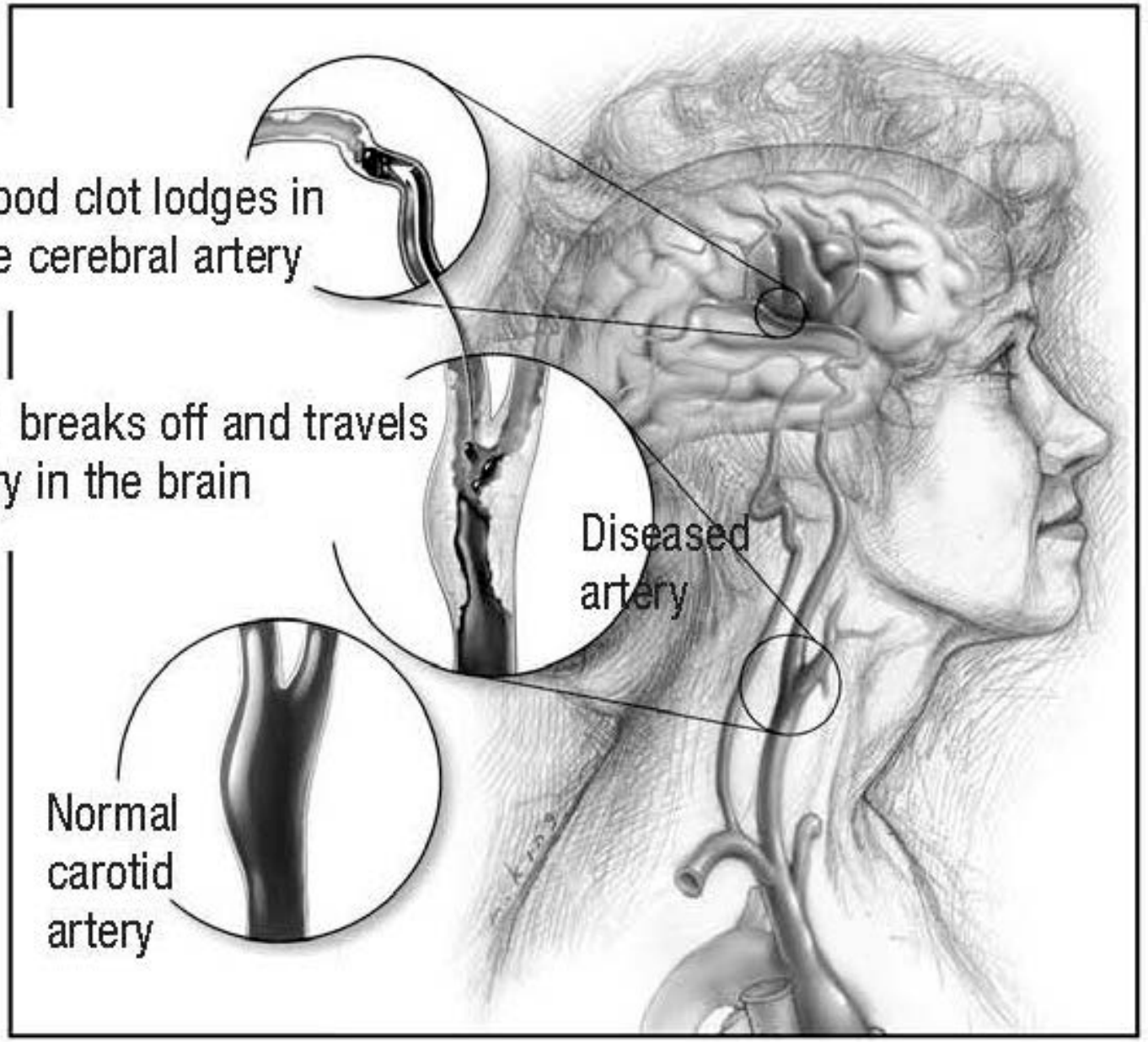
What symptoms are associated with venous thrombosis and stroke?

Weakness, Paralysis, visual changes



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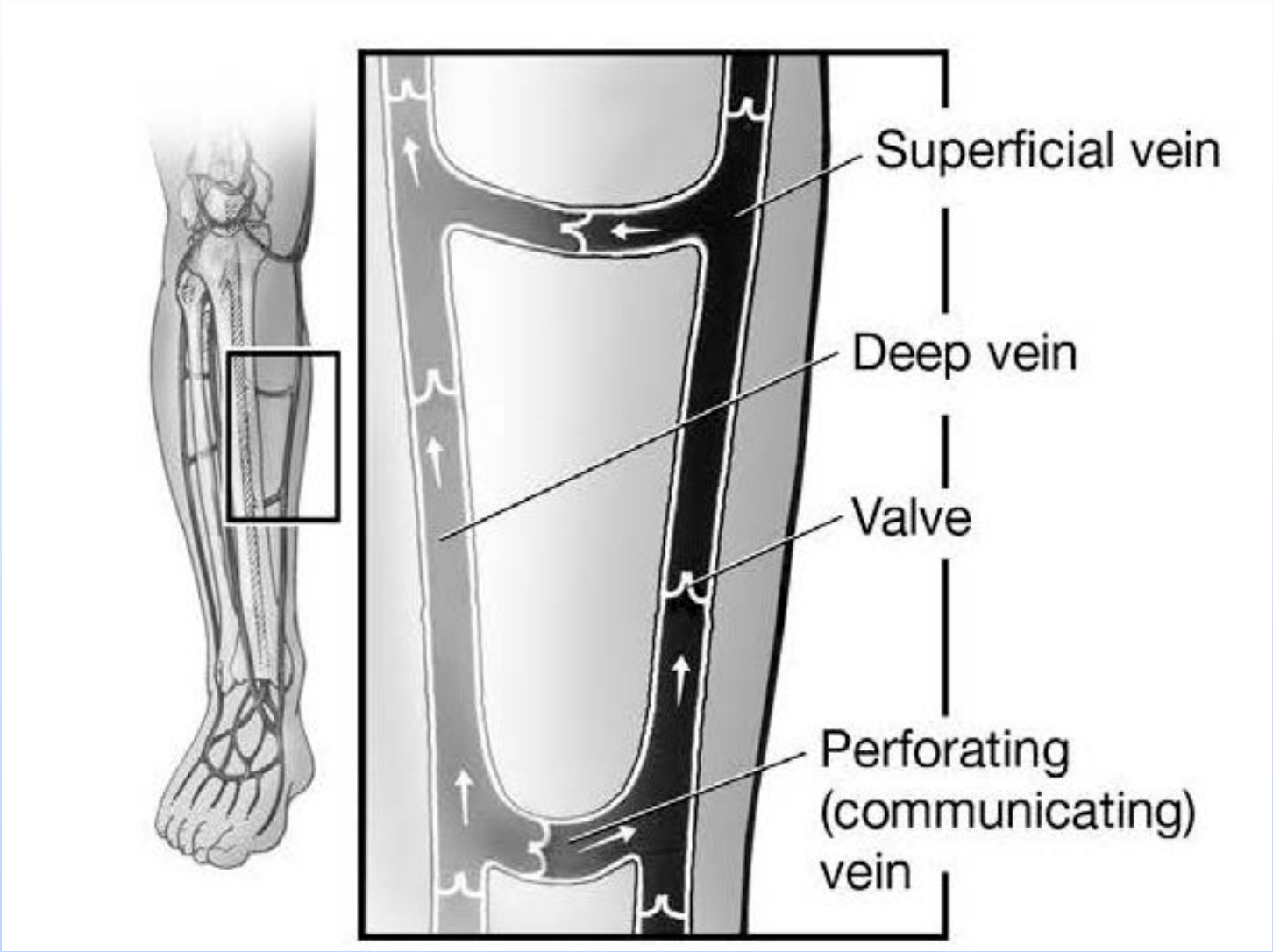
Deep vein thrombosis



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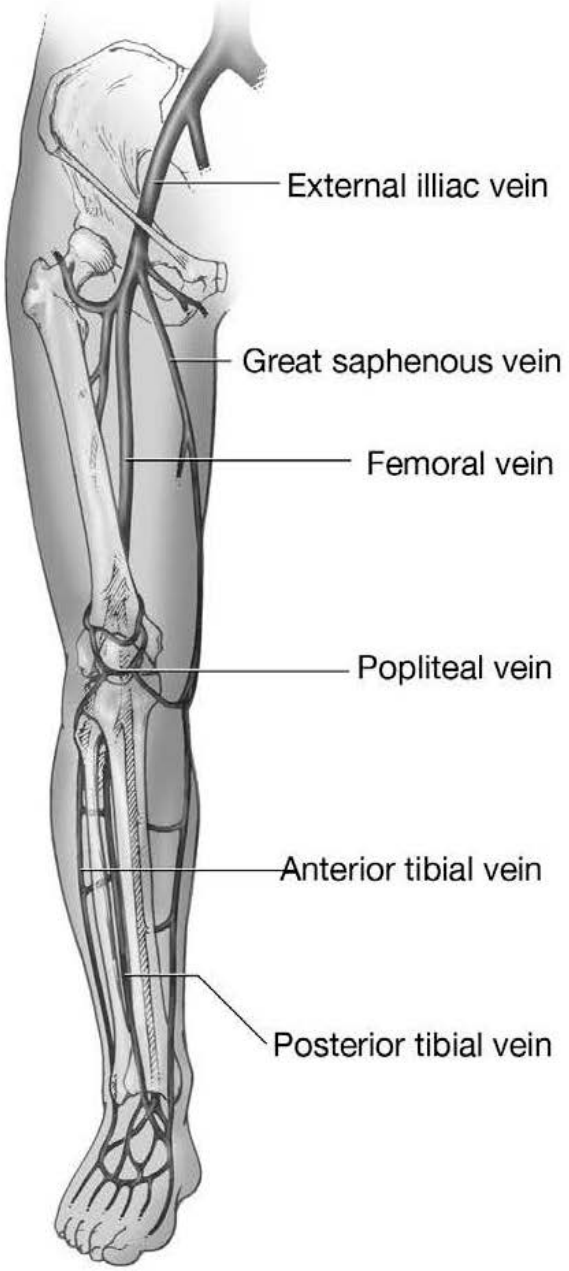
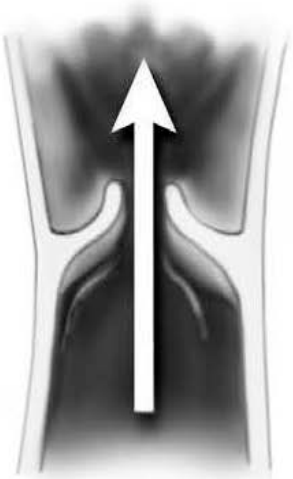
Deep vein thrombosis





Surrounding muscle squeezes vein, pushing blood up through valve.

When surrounding muscle relaxes, valve closes, stopping backflow of blood.

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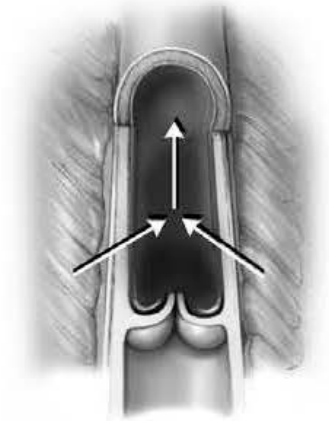
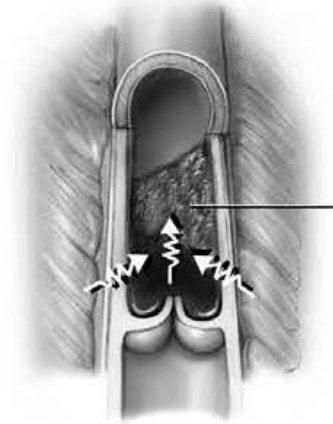
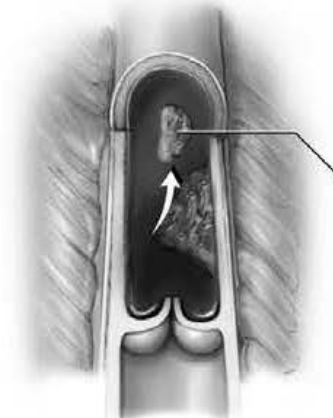


a. Normal blood flow in a deep vein



b. Deep vein thrombosis (DVT)

A clot (thrombus) may block veins and prevent blood flow from nearby muscle.

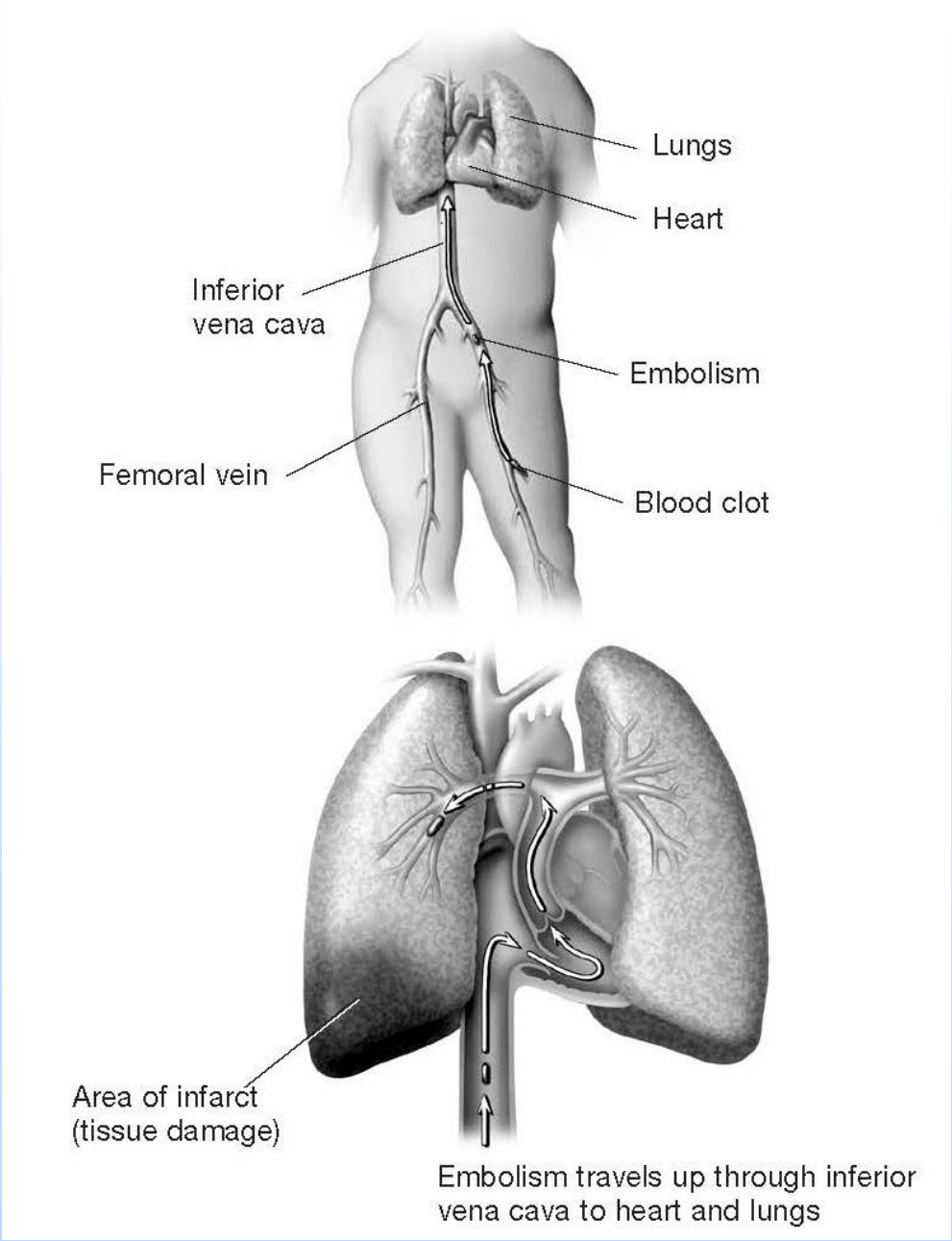


c. Venous thromboembolism

Part of the clot may dislodge and be carried to other areas of the body.

Swelling with or without pain

Pulmonary Embolism



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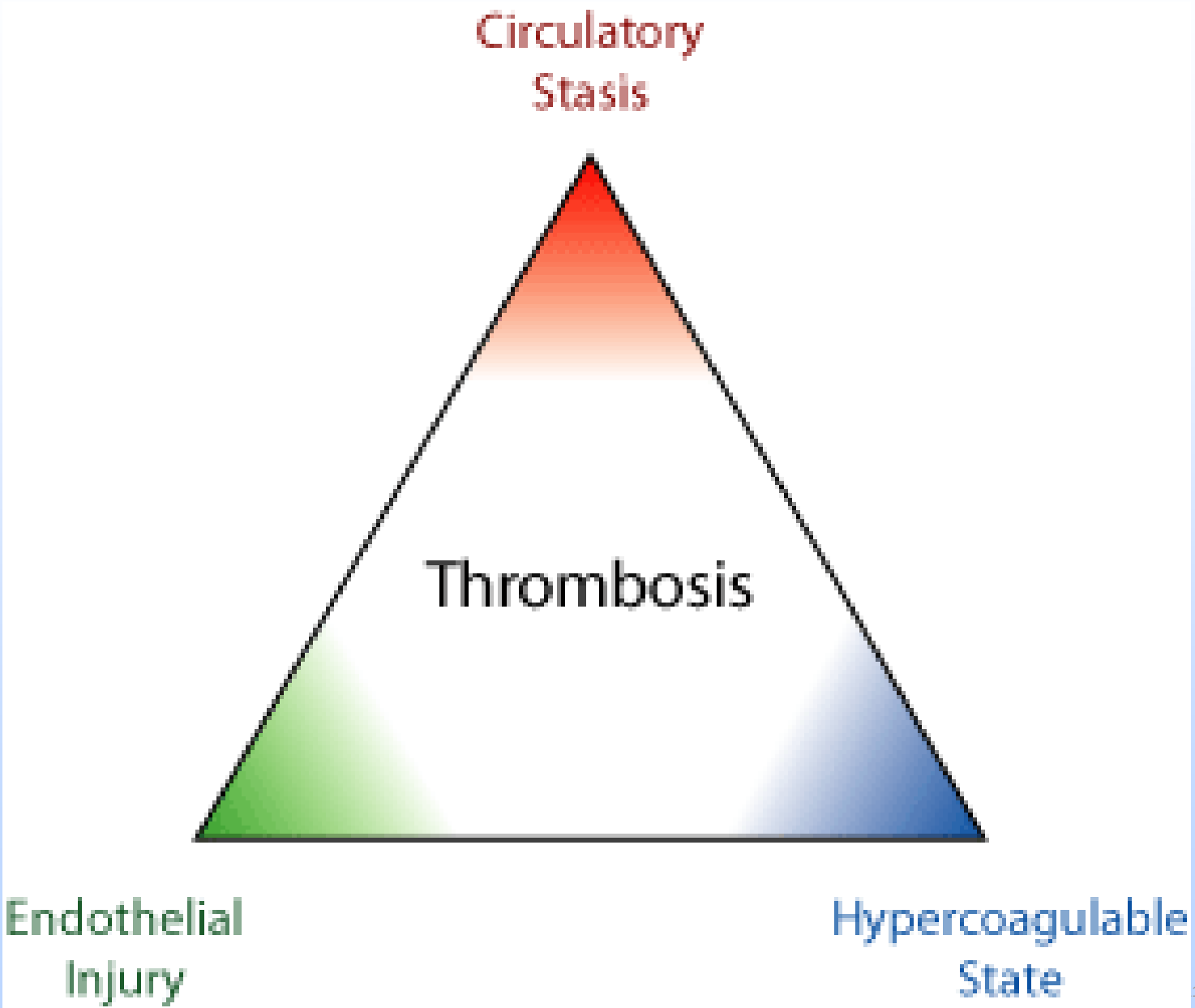
How do blood clots form?

Virchow's Triad



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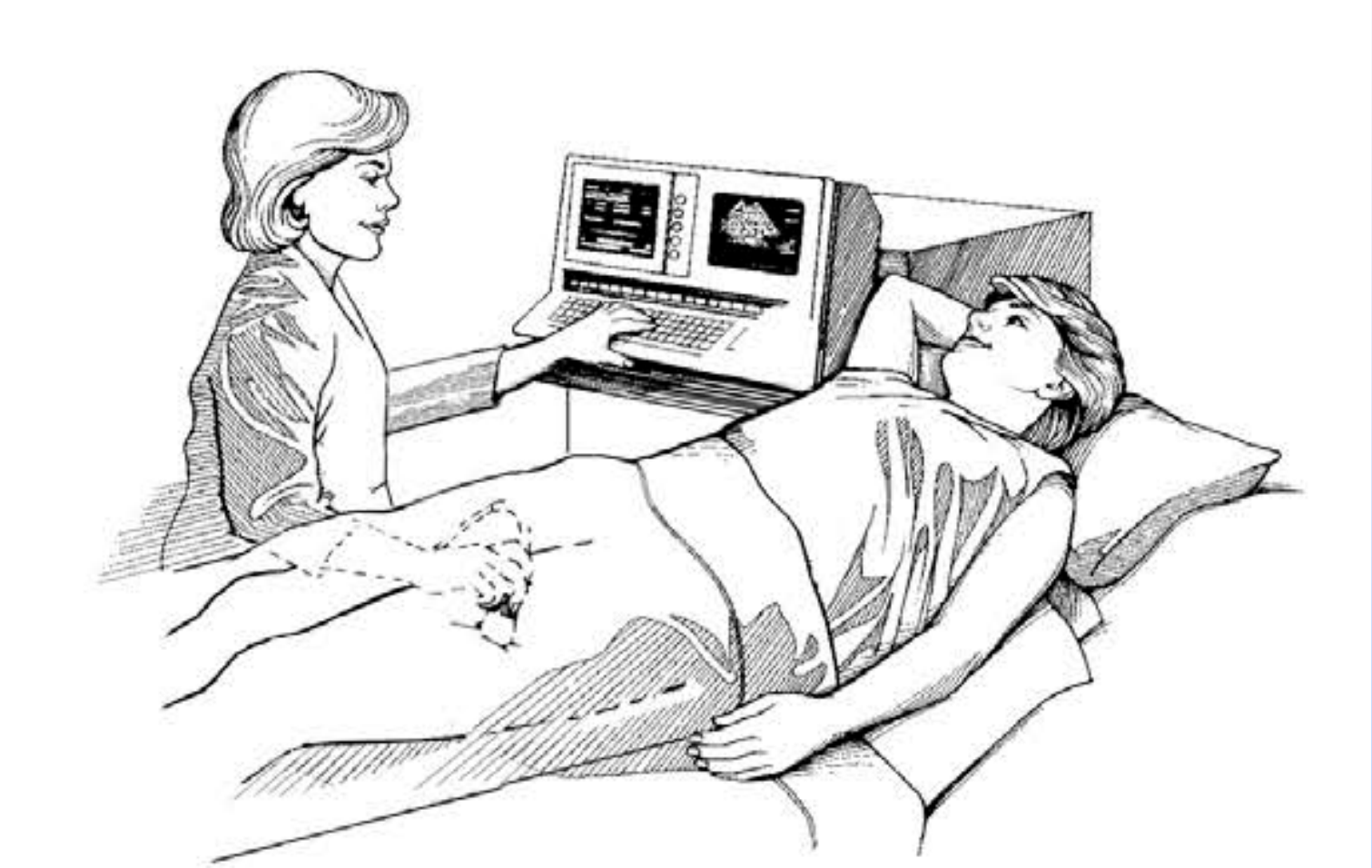
How is VTE and stroke diagnosed?

Duplex Ultrasound: deep vein thrombosis



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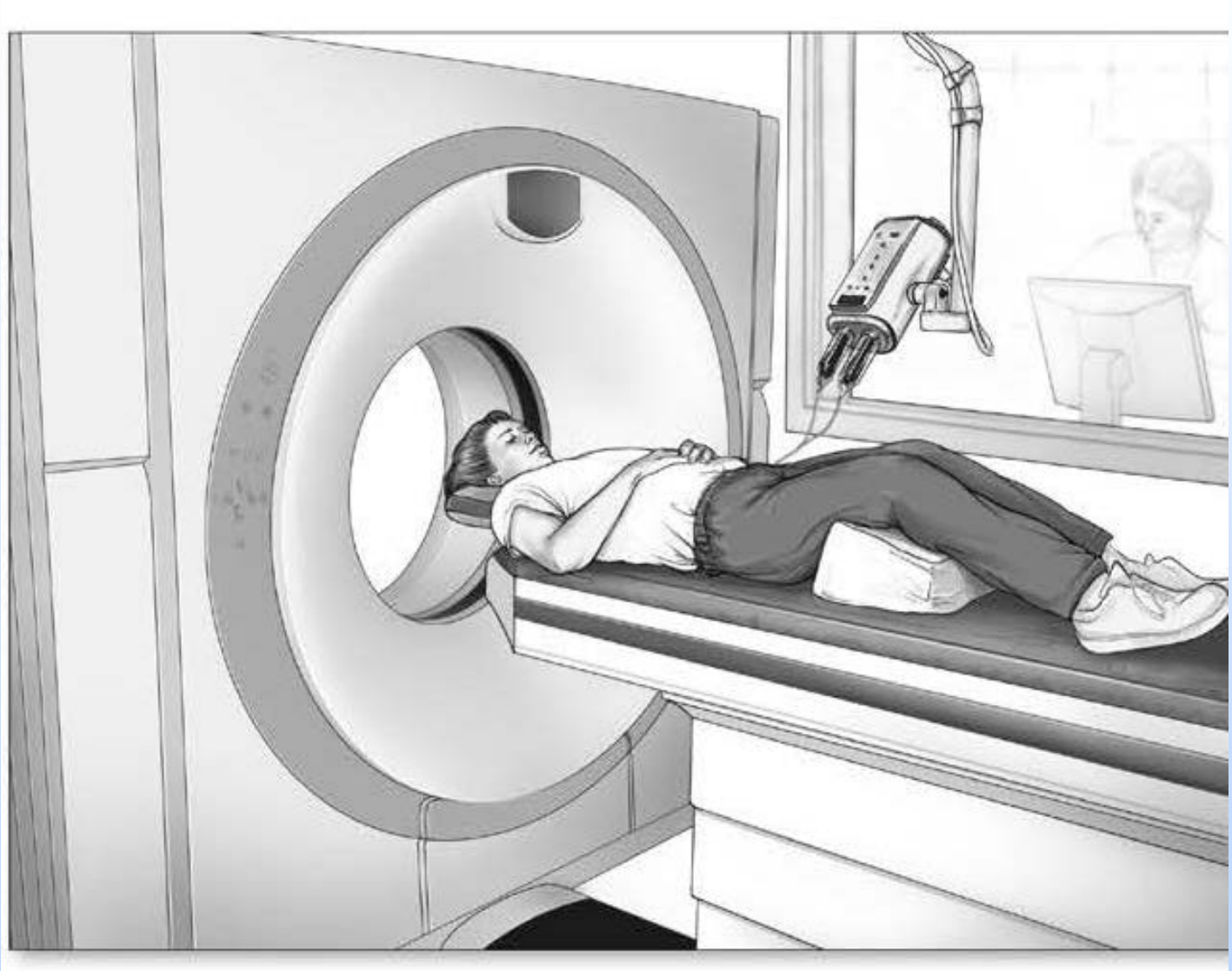
CT Scan: pumonary embolism



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CT scan or MRI

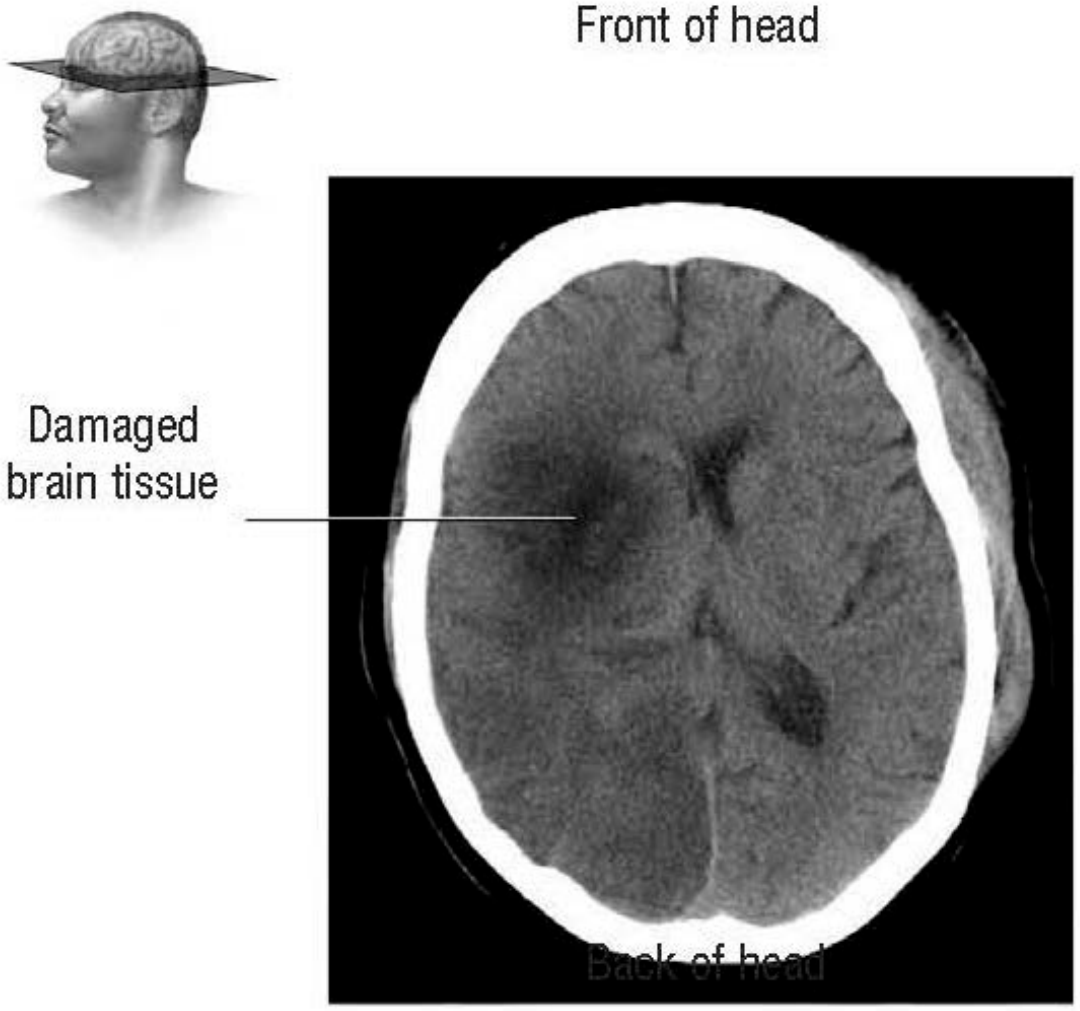

Figure 6. Darker area on head CT scan shows brain tissue damaged by stroke.

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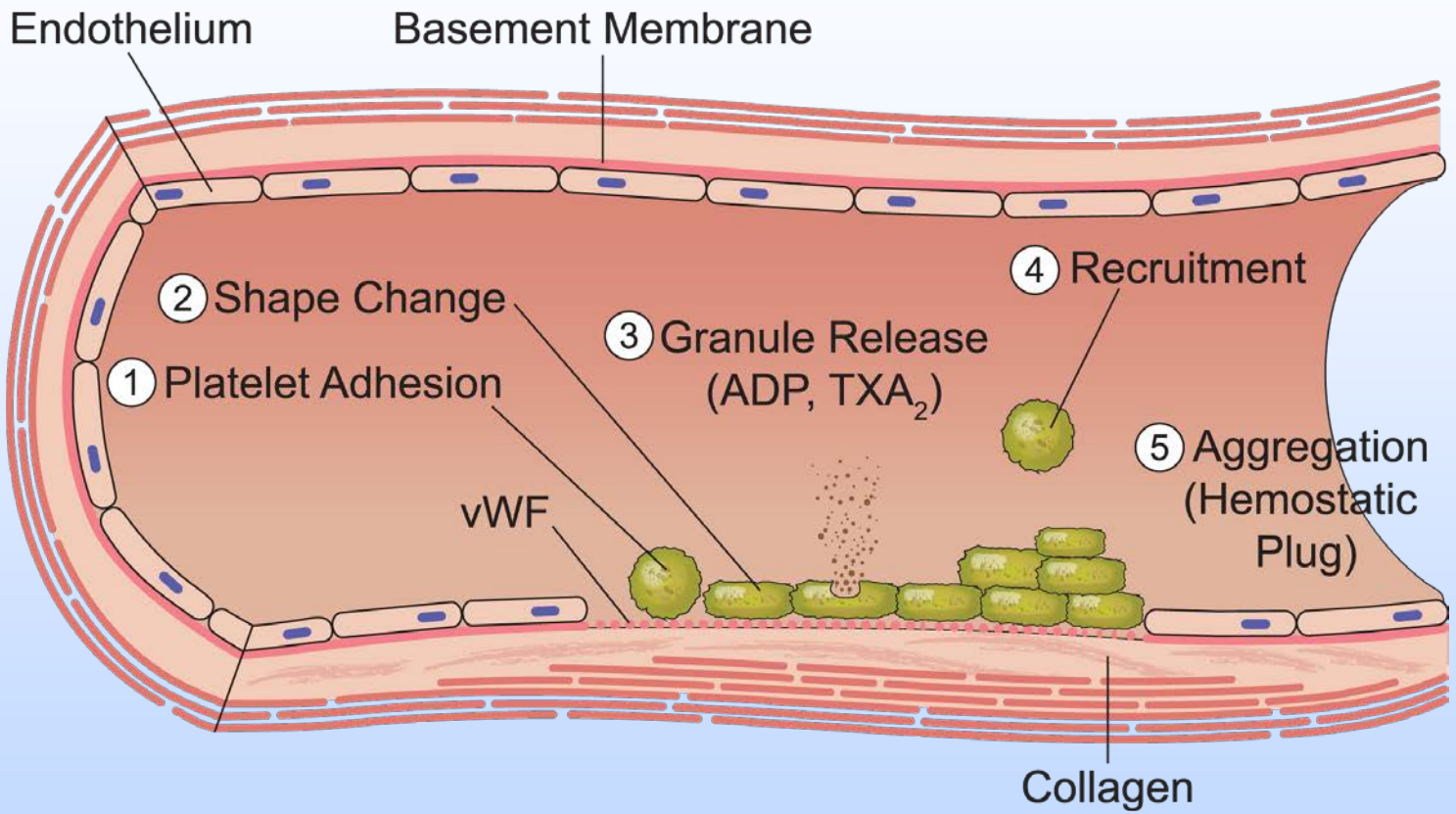
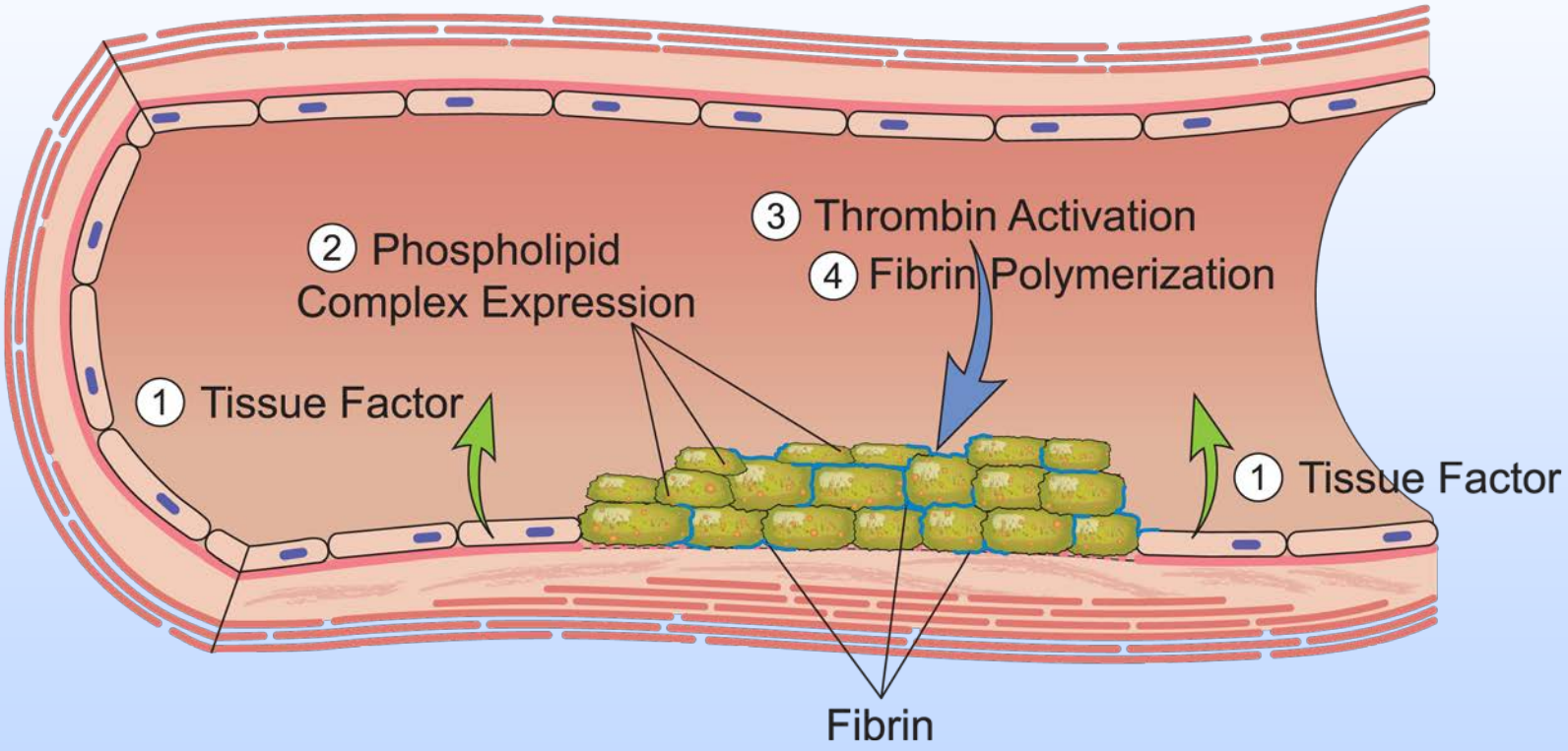
What drugs are available to treat/prevent blood clots?

How do blood clots form?

Primary Hemostasis: platelet plug formation



Secondary Hemostasis: clot formation



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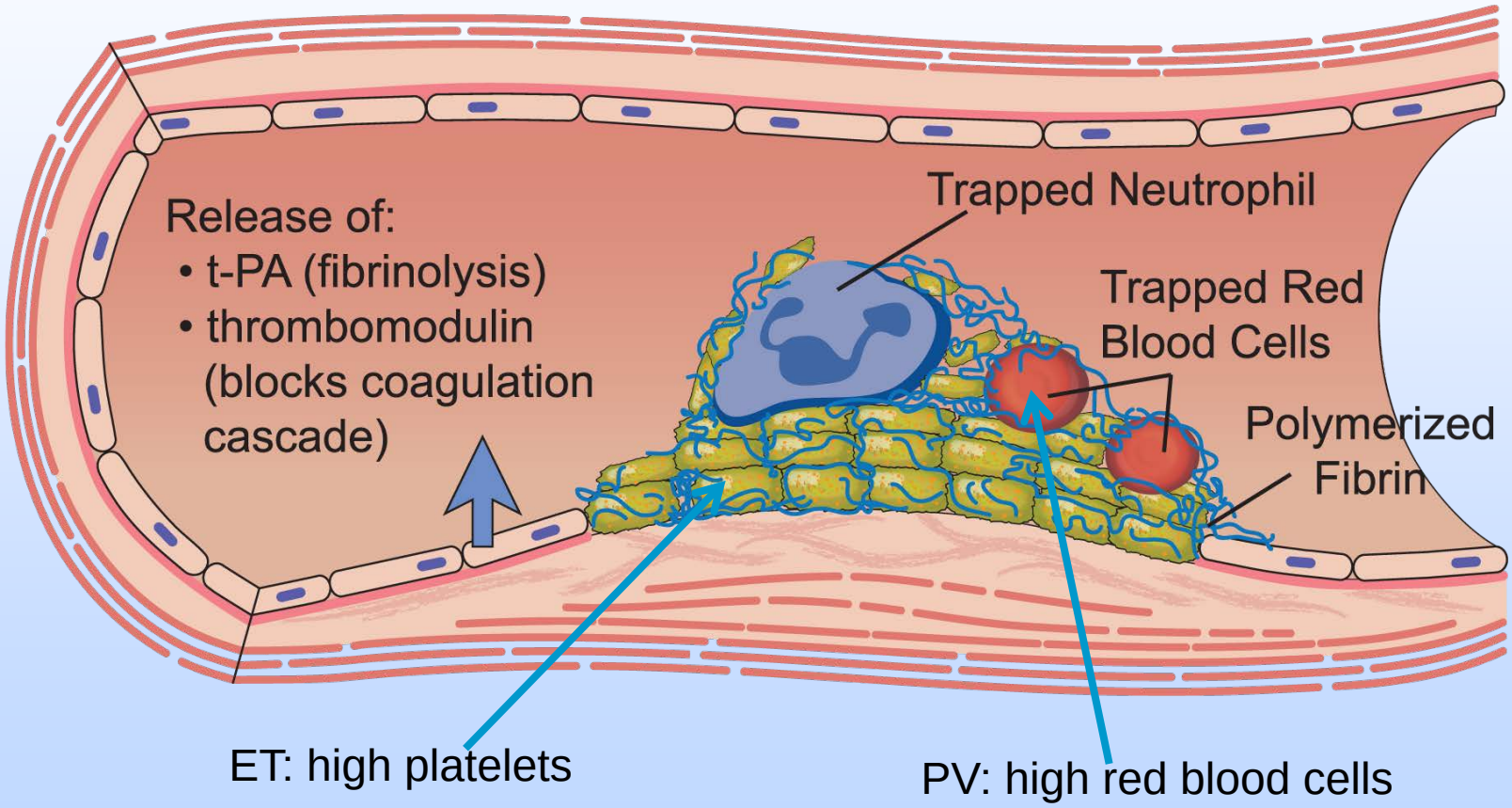
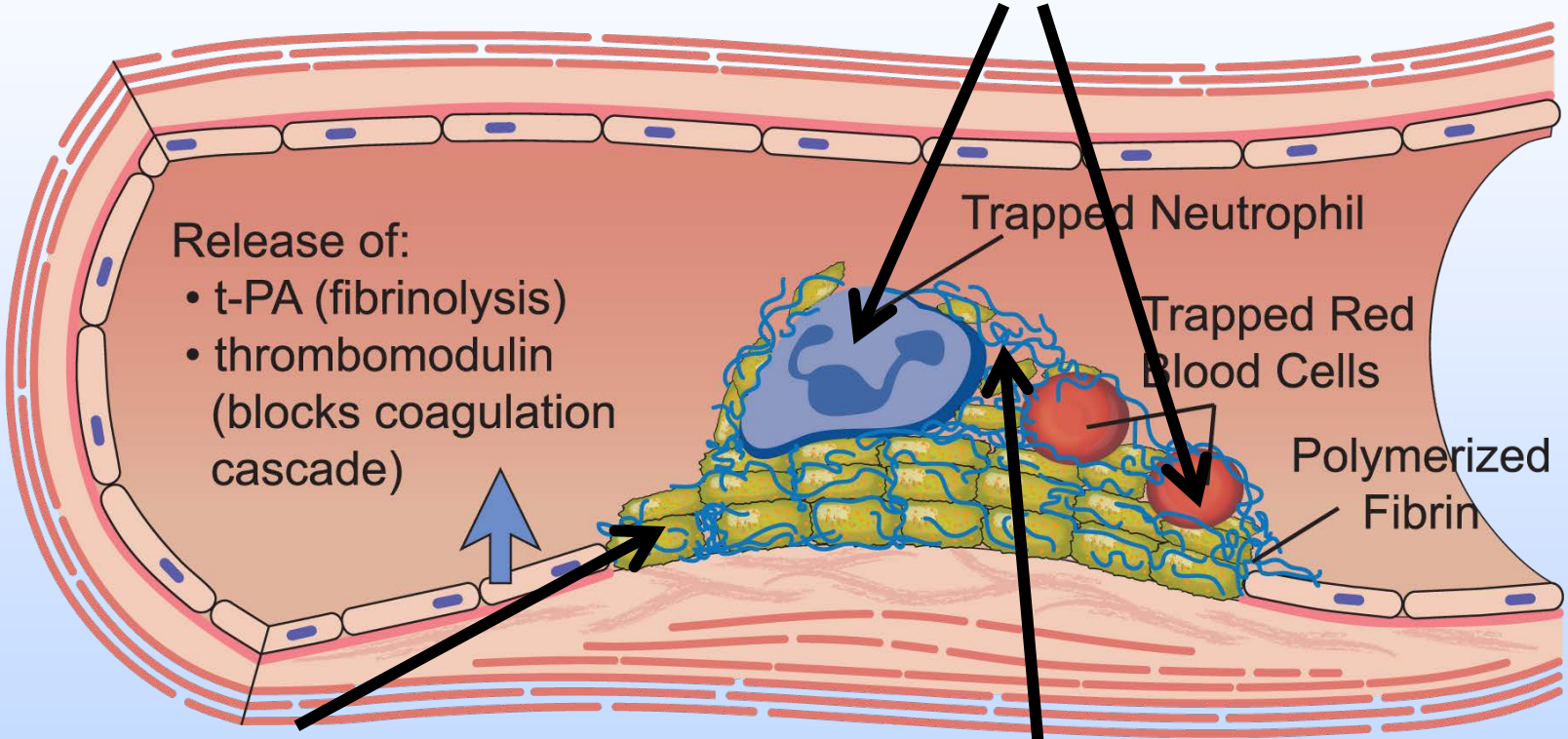
Thrombus/Antithrombotic/Fibrinolytic Events: remodeling of clot



Thrombus/Antithrombotic/Fibrinolytic Events

Hydrea ± phlebotomy



Anti-platelet agents:
Aspirin, clopidogrel (Plavix)

Anti-coagulants:
warfarin

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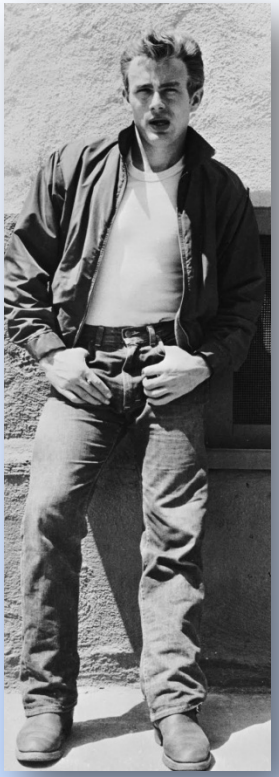
What are the new drugs available to treat VTE?

The good news: currently, choosing anticoagulants is like buying jeans!

Then



Size?

Now

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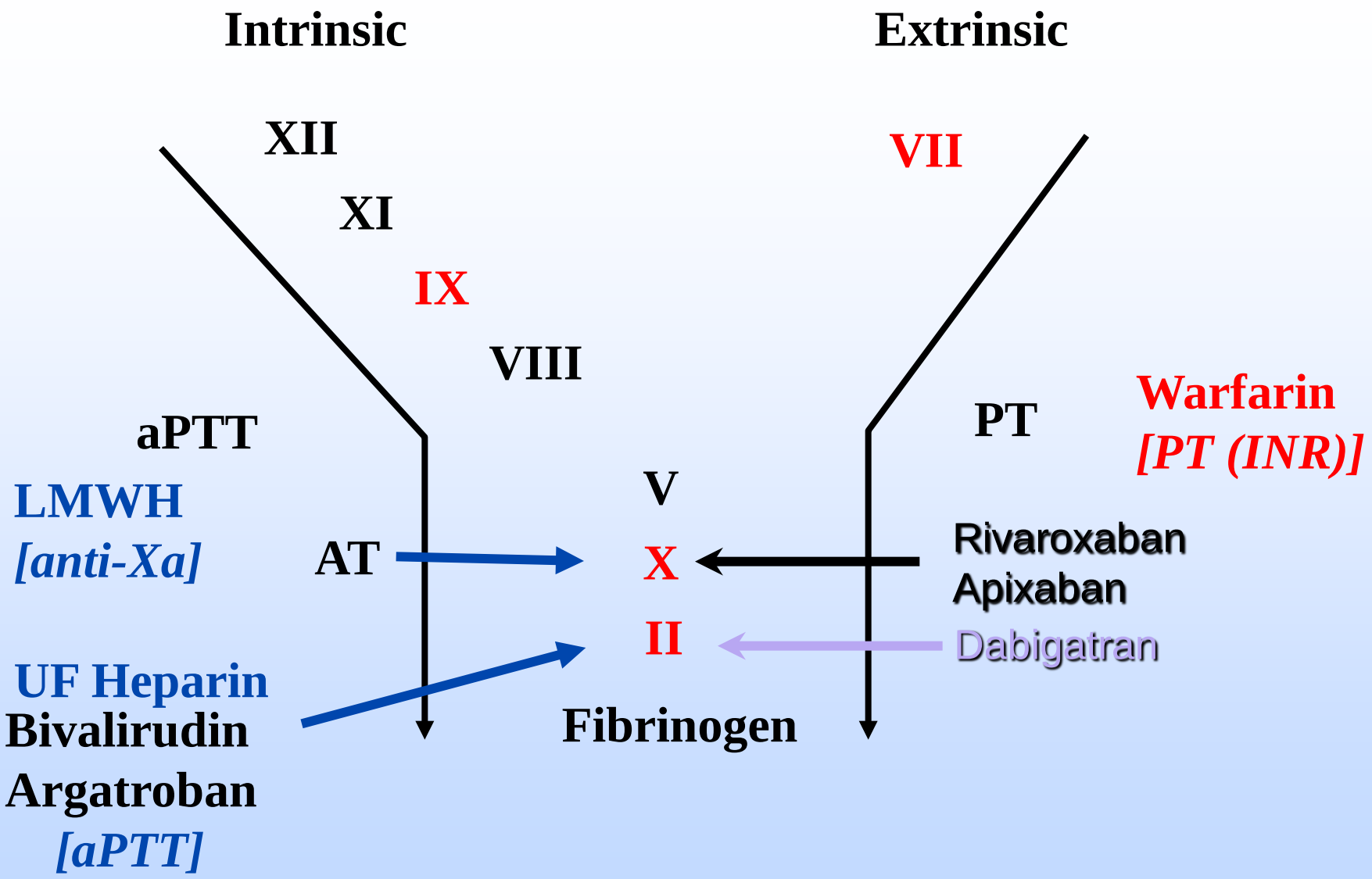
Courtesy Dr McBane

Anti-thrombotics: Antiplatelet agents & Anticoagulants

- Injectable (IV or subcutaneous [SC])
  - Heparin (IV)
  - Low molecular weight heparin (SC)
    - Enoxaparin (Lovenox)
    - Dalteparin (Fragmin)
    - Tinzaparin
- Pills:
  - Warfarin (Coumadin, Jantoven)
    - Interfere with vitamin K
    - Reduces manufacture of vitamin K dependent clotting factor proteins
  - Newer anticoagulants:
    - Directly inhibit clotting factor proteins



Sites of action and [monitoring] of anti-thrombotic agents

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What are the new drugs available to treat VTE? Direct acting anticoagulants

- Direct factor Xa inhibitors
  - Rivaroxaban
  - Apixaban
  - Edoxaban
- Direct thrombin (factor II) inhibitors
  - dabigatran

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Do they have a role in managing VTE in patients with cancer?

Efficacy and safety

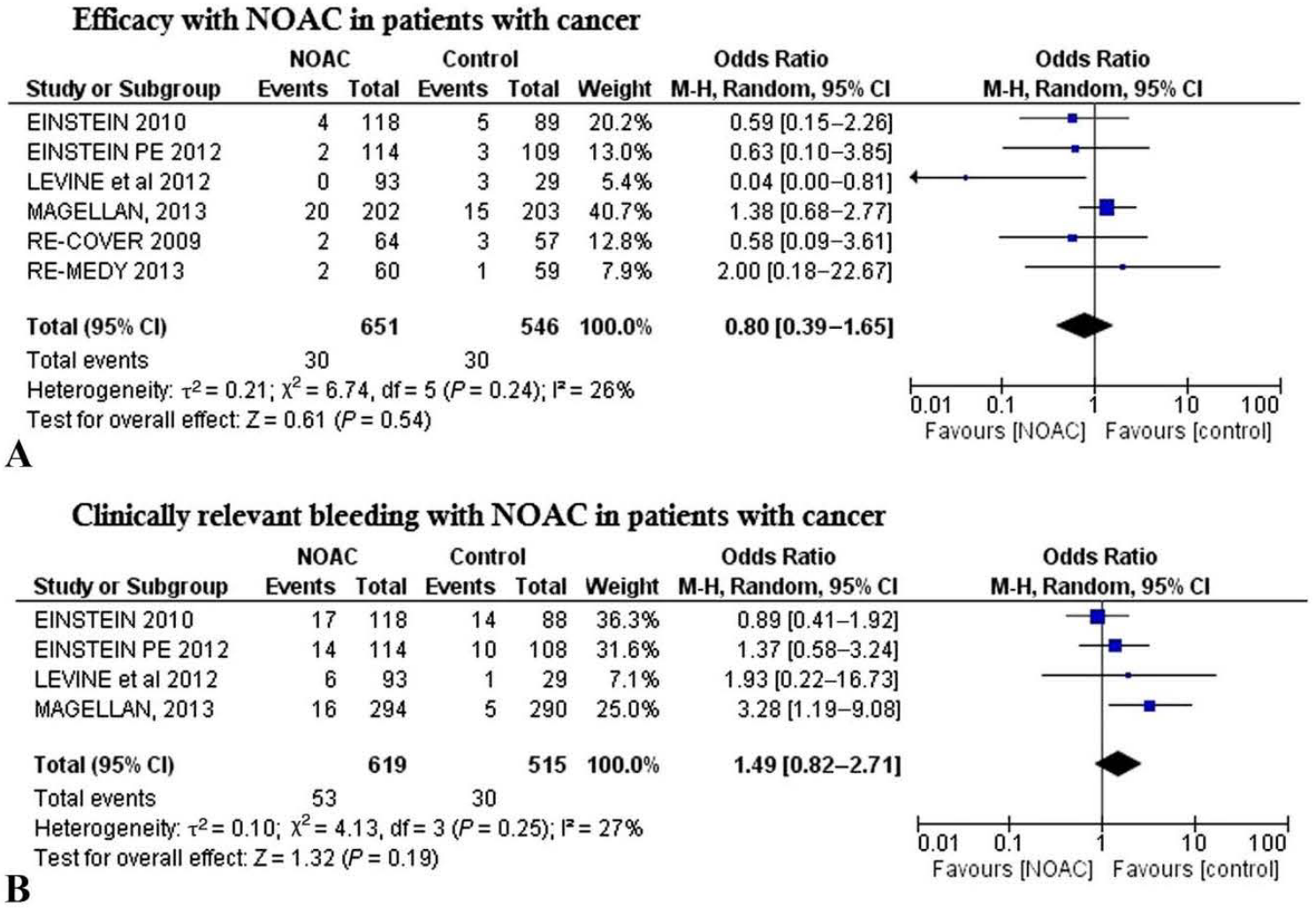

FIGURE 2. Efficacy (A) and safety (B) of NOAC in patients with cancer.

Sardar P et al 2014

Conclusion

- Preliminary results showed that NOAs are non-inferior to the current standard anticoagulant therapy.
- However, large scale randomized controlled trials specifically targeted cancer patients are needed.

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How do they compare to standard treatment with warfarin?

- Atrial fibrillation trials
  - As safe and effective as warfarin for prevention of stroke
- Deep vein thrombosis treatment trials
  - As safe as and as effective as warfarin for treatment of deep vein thrombosis and pulmonary embolism
- What about treatment of stroke?
  - No clinical data

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VTE treatment in solid organ malignancy

- Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE *(ASCO Guideline)*

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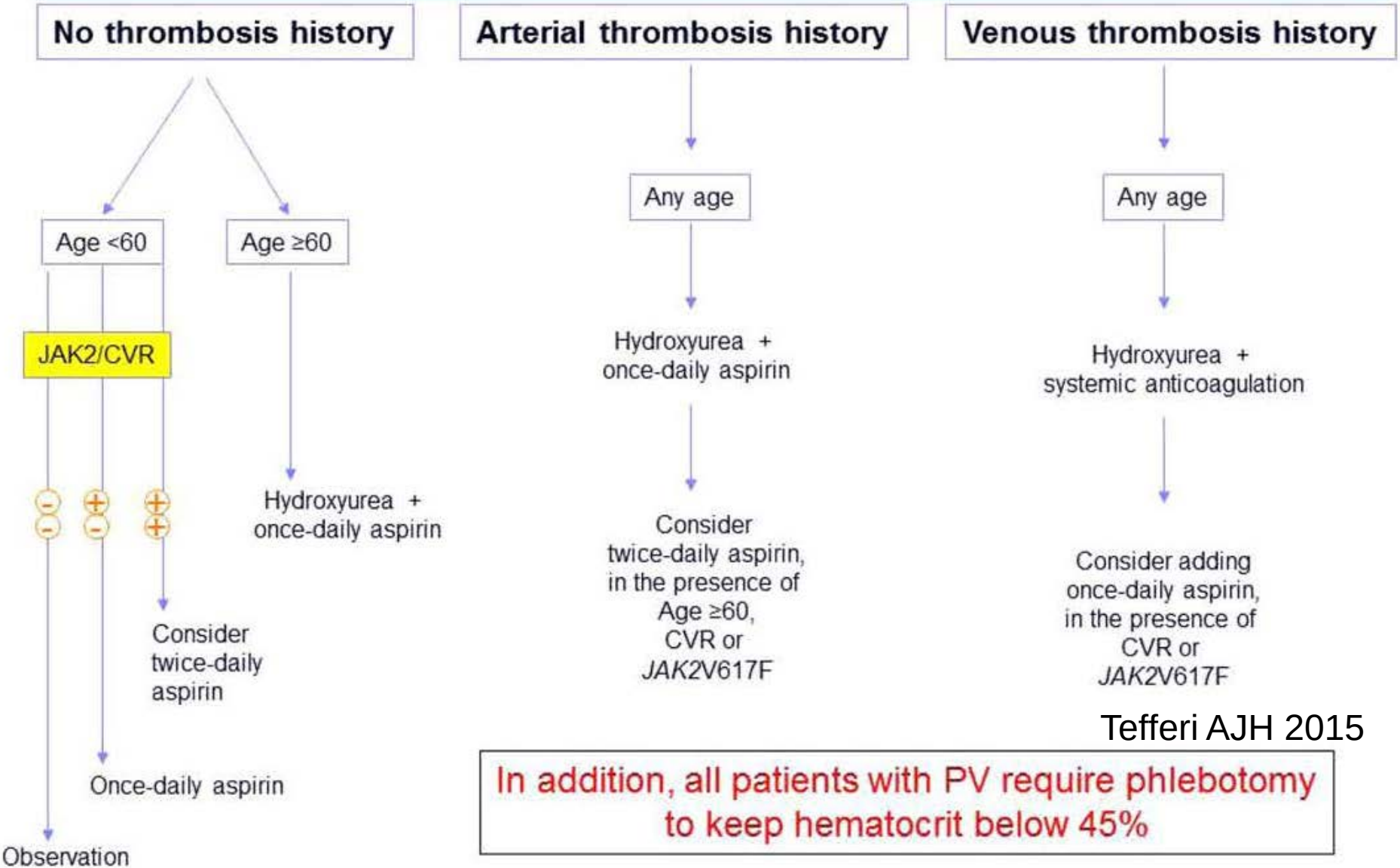
Lymann GH et al J Clin Oncol 31:2189-2204.

Implications for myeloproliferative neoplasms

- Currently no role in management of stroke associated with MPN
  - High risk patients: aspirin
  - Control of modifiable risk factors
    - Smoking, cholesterol, exercise
- Role in management of venous thrombosis is not defined
  - Follow standard approach to prevention and management

Contemporary treatment algorithm in essential thrombocythemia and polycythemia vera



Tefferi AJH 2015

In addition, all patients with PV require phlebotomy to keep hematocrit below 45%

When would I consider using a novel agent?

- Stroke: antiplatelet agents
- Venous thrombosis:
  - Initiate standard management for VTE
    - Heparin and warfarin
- If warfarin management is difficult or fails
  - Difficult to control INR
  - INR outside of therapeutic range more often
  - Recurrent thrombosis despite therapeutic INRs

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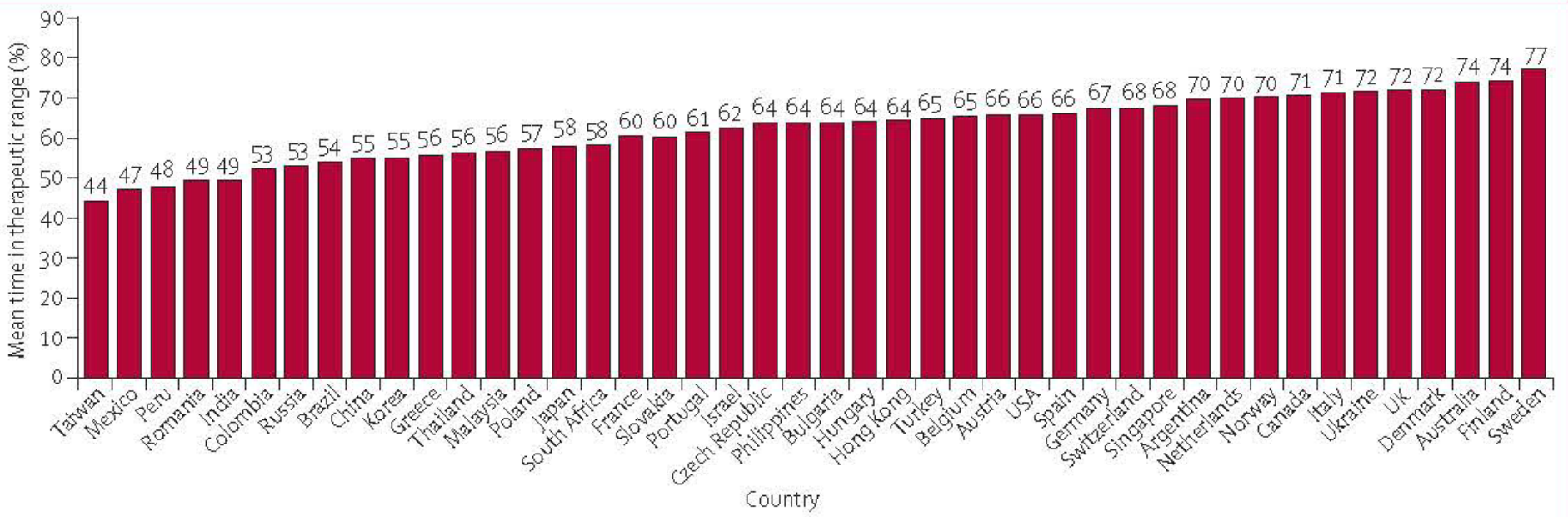
Time in Therapeutic Range (INR target 2-3)



Wallentin Lancet 2010

When would I consider using a novel agent?

- Tailor to specific situation (individualized approach)
  - Status of kidneys
  - Other medications that may interact
- Clinical trials in patients with MPN are needed

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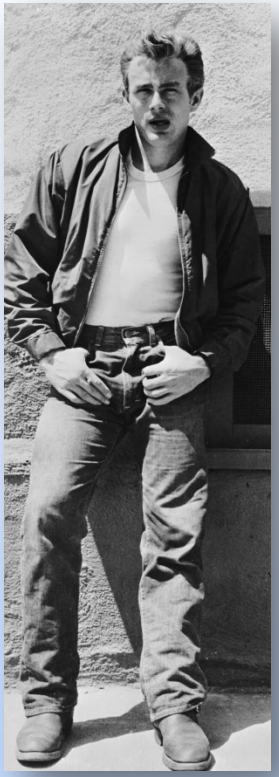
The good news: currently, choosing anticoagulants is like buying jeans!

Then



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Thank you for your attention

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