



Brigham and Women's Hospital
Founding Member, Mass General Brigham

CHALLENGES IN VTE MANAGEMENT

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- Harvard Medical School
- Medicine Residency @BWH
- CV Medicine Fellowship @BWH
- Director, Faculty Promotions
CV Medicine Division @BWH
- Professor of Medicine @ HMS
 - Clinical focus: Vascular Medicine, Pulmonary Embolism, DVT, Obesity, Autonomic Dysfunction (e.g., POTS)
 - Research focus: Thrombosis

Disclosures

Research Support:

Bayer, BMS, Boston Scientific, Janssen, NHLBI

Consultant Support:

None

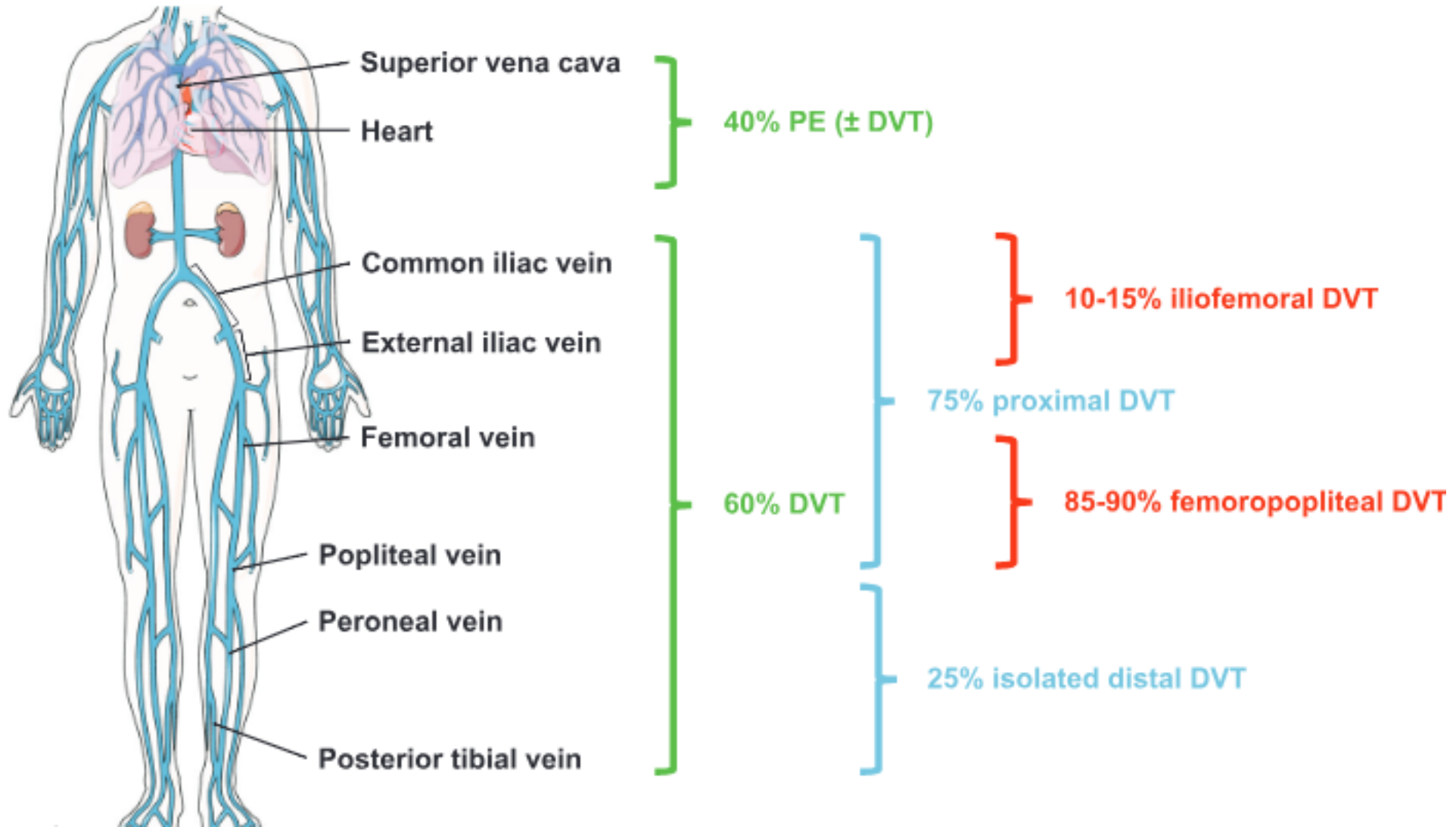
Key Learning Objectives

- Epidemiology and Pathophysiology
- Artificial Intelligence: Diagnosis of PE
- Inflammation-linked conditions trigger VTE
- DOACs: Rivaroxaban vs Apixaban vs Warfarin
- Optimal duration of anticoagulation: My approach
- Advanced management of high-risk PE
- Obesity and VTE

Epidemiology/ Pathophysiology

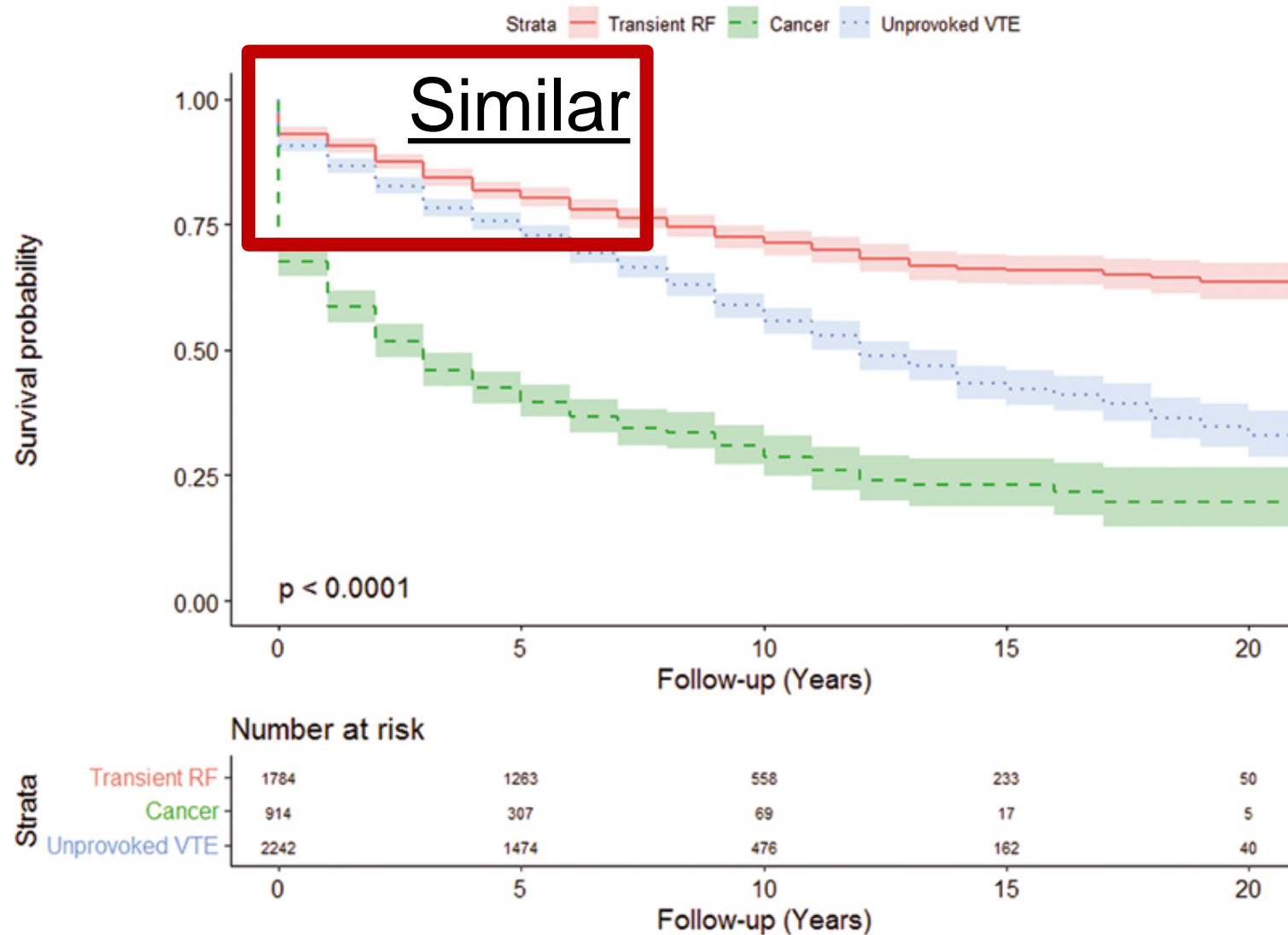
Does Socioeconomic
Status Play a Role?

Anatomical Distribution of VTE



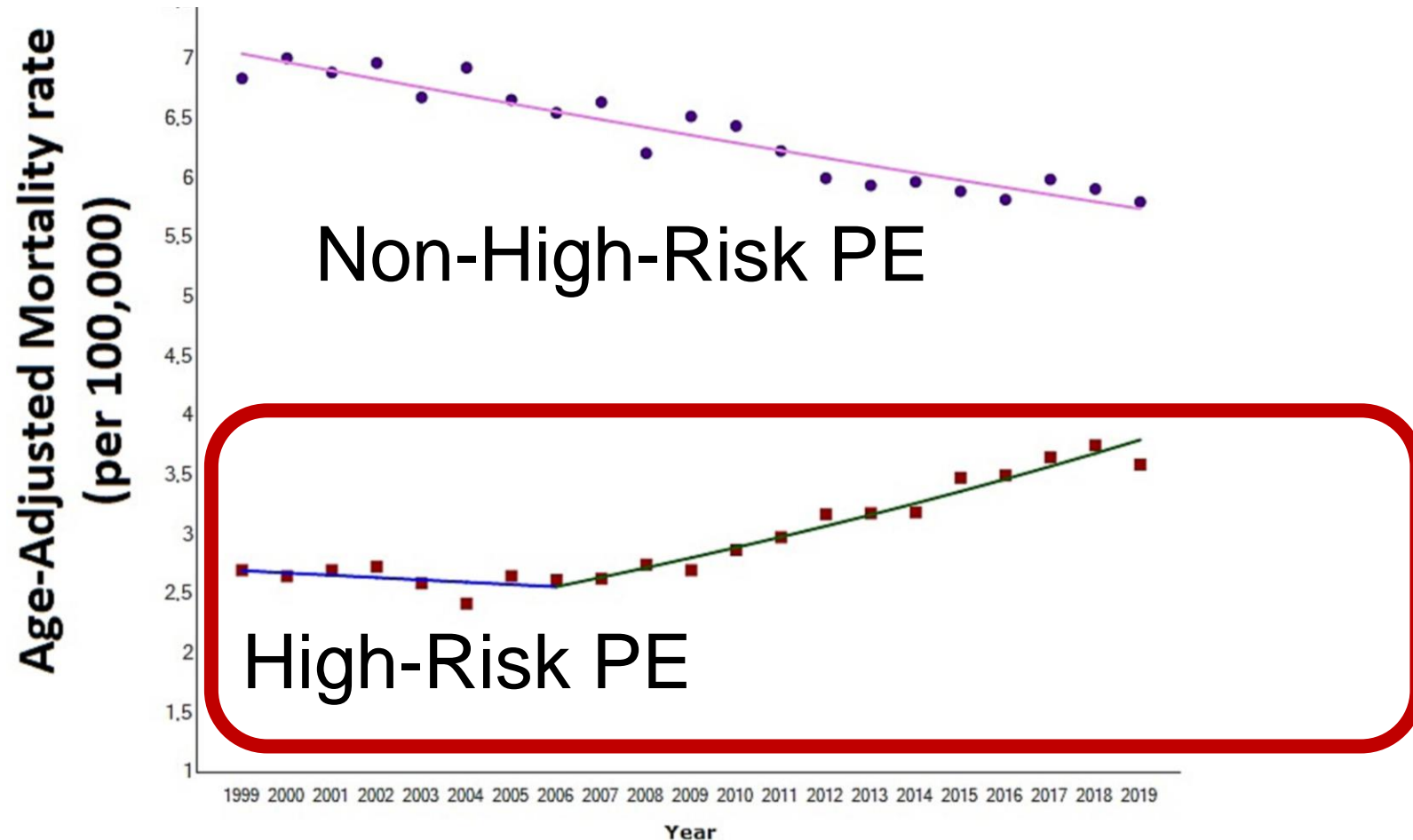
Vasa 2024; 53: 298-307

DVT: Survival Probability (N=4,940)



Semin Thromb Hemost 2022; 48: 465-480

Time Trends in PE Mortality: Non-High Risk vs High-Risk PE

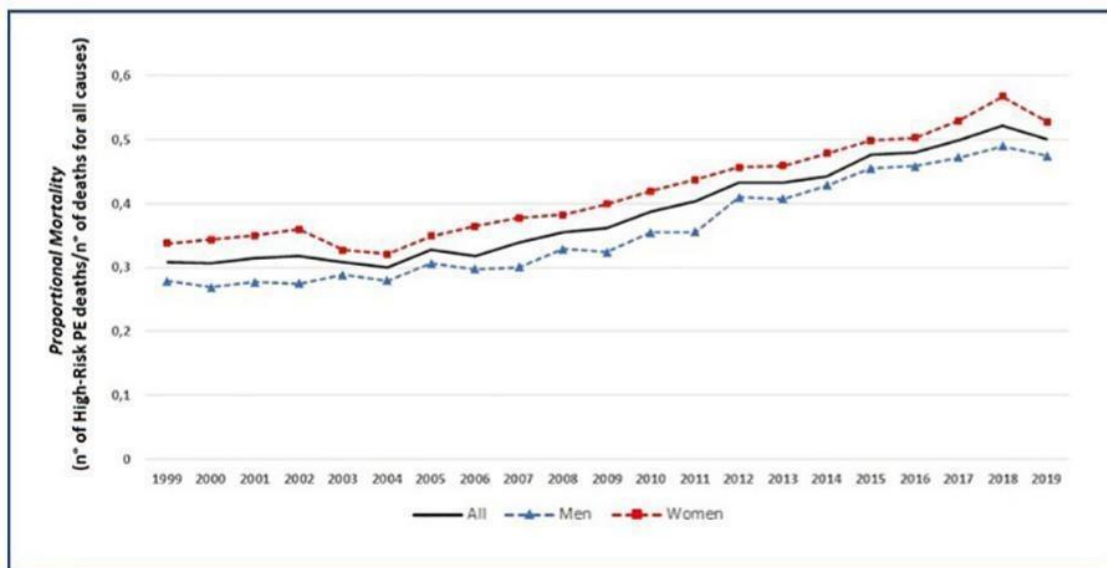


High-Risk PE Mortality: 1999 to 2019

CENTRAL ILLUSTRATION: Trends in mortality related to high-risk pulmonary embolism in US from 1999 to 2019

- Study design**
 - Cross sectional study (1999-2019)
 - Mortality data from the Centers for Disease Control and Prevention's (CDC) Wide-ranging ONline Data for Epidemiologic Research (WONDER) dataset
 - Proportionate mortality from high-risk PE per 100 deaths
 - High-risk PE-related mortality per 100,000 US population and relative trends
- Data analysis**
 - Joinpoint regression analysis

Outcomes

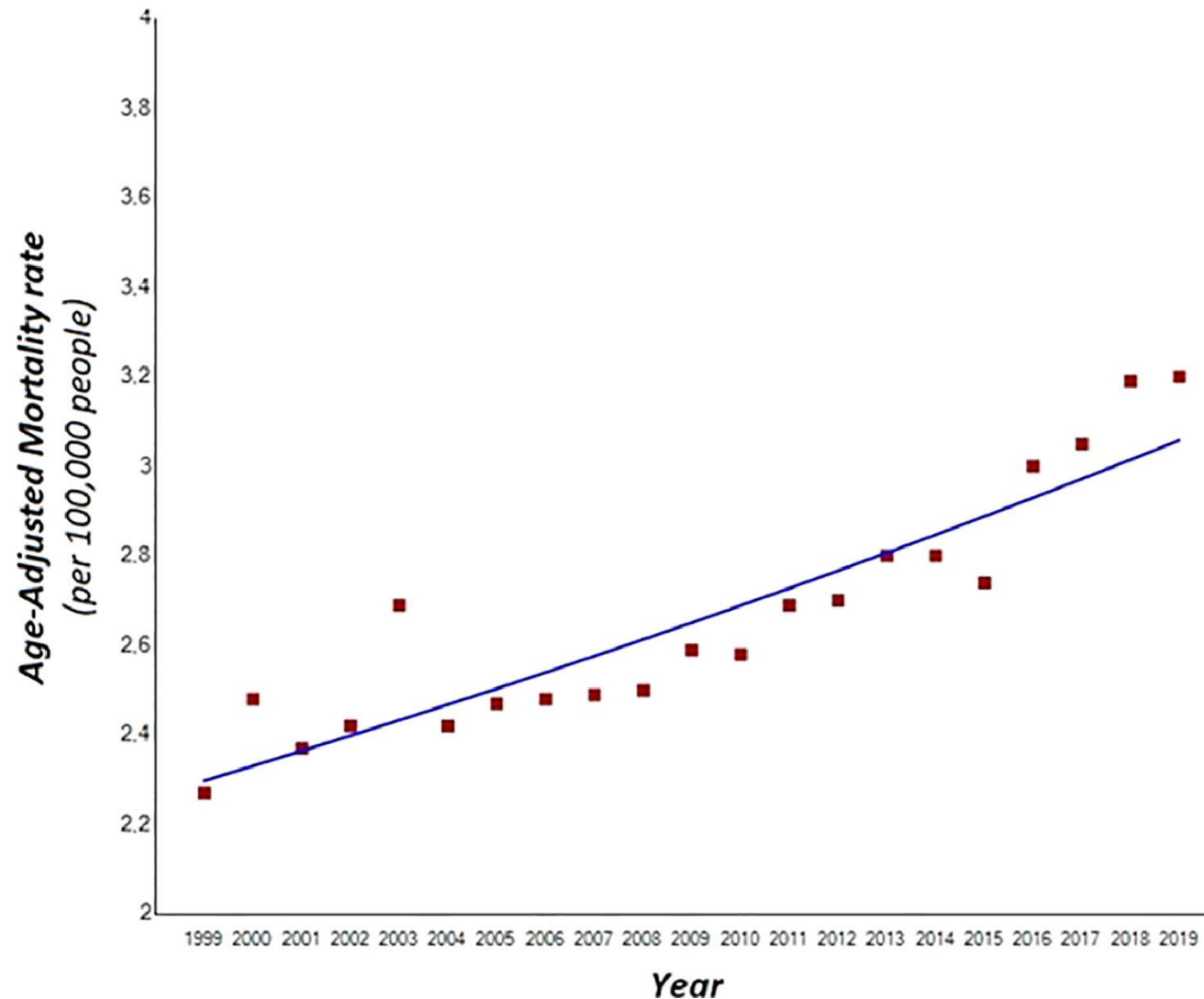


High-risk PE mortality
↑ 93.5%

	Males	AAPC: +1.9%
	Females	AAPC: +1.5%
	Blacks	AAPC: +1.4%
	Whites	AAPC: +1.6%
	<64 years	AAPC: +3.2%
	≥65 years	AAPC: +1.0%
	Rural areas	AAPC: +2.5%

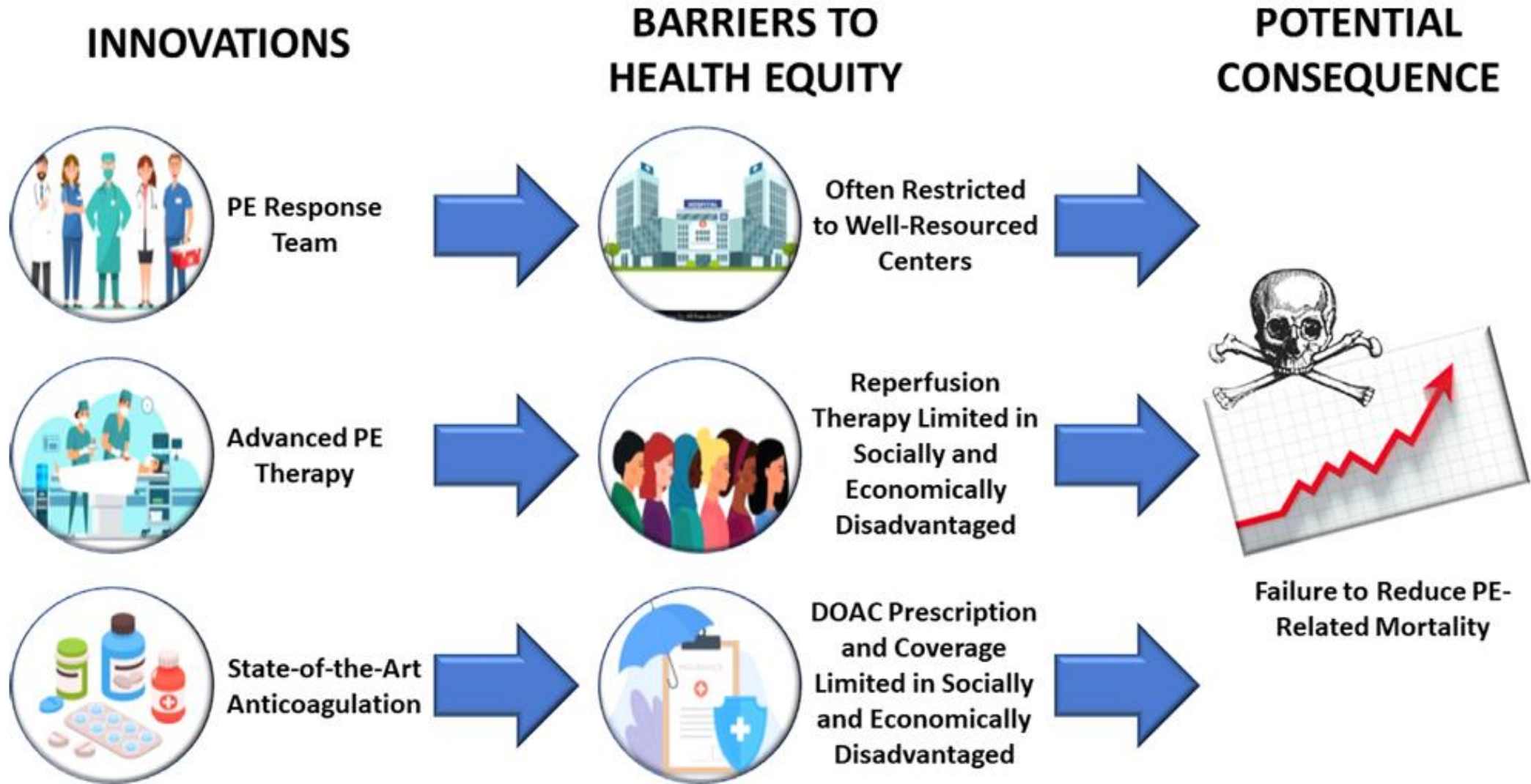
AAPC: Average Annual Percent Change
APC: Annual Percent Change

Mortality Rate from PE, 25-44 y.o., USA



Am J Cardiol 2023; 202: 169-175

Health Equity Barriers in PE



Piazza G. JTH 2024; 22: 1838-1840



Public awareness



Willingness to
seek care



Clinician awareness



More informed diagnostic and
treatment strategies



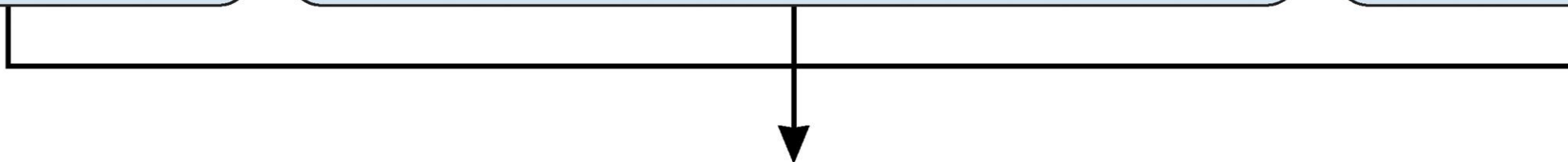
Inclusive research



Policy changes



Access to PE care/
monitoring PE trends



Better outcomes for all PE patients

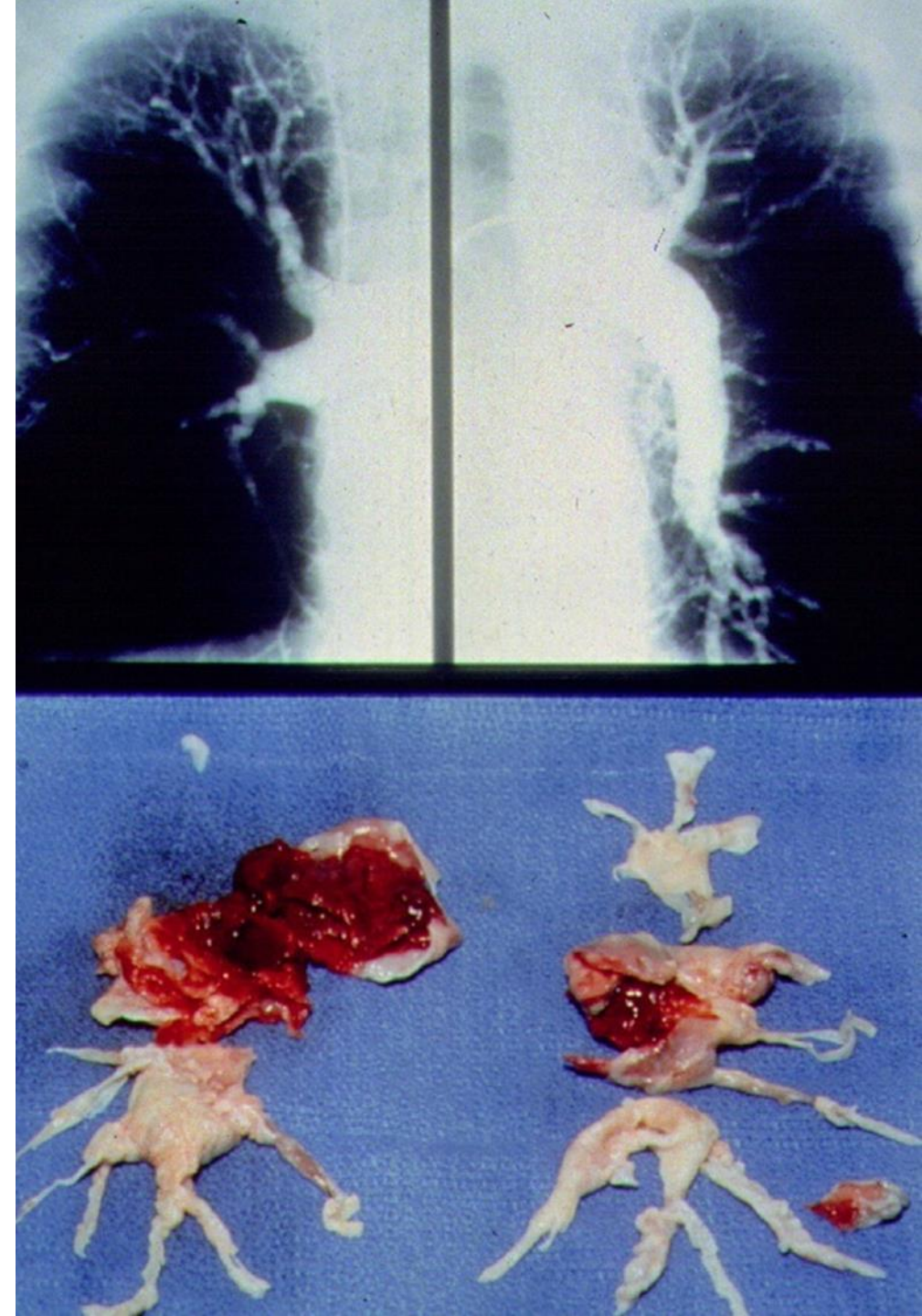
Longitudinal Follow-Up of PE Patients

Follow acute PE patients longitudinally to assess for dyspnea or functional limitation, which may indicate development of post PE impairment (PPEI) or chronic thromboembolic pulmonary hypertension (CTEPH).

(European Heart J 2022; April 7)

Post-PE impairment (PPEI) with persistent dyspnea and incomplete recovery is frequent (16%/2 yrs) and associated with CTEPH, death, re-hospitalization (31%), and decreased quality of life.

(European Heart Journal 2022; April 7)



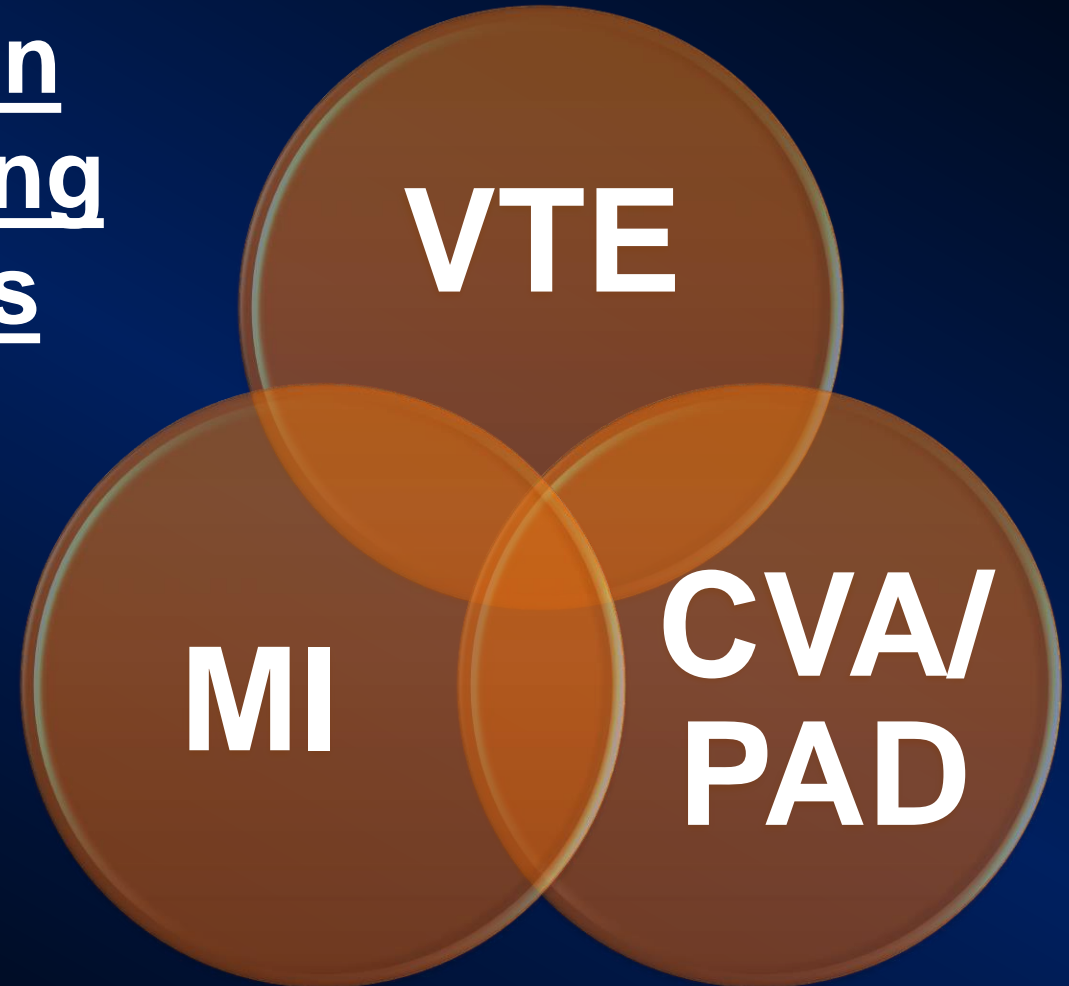
ABANDON “SILO THINKING”

Inflammation: A
Common
Underlying
Process

VTE

MI

CVA
PAD

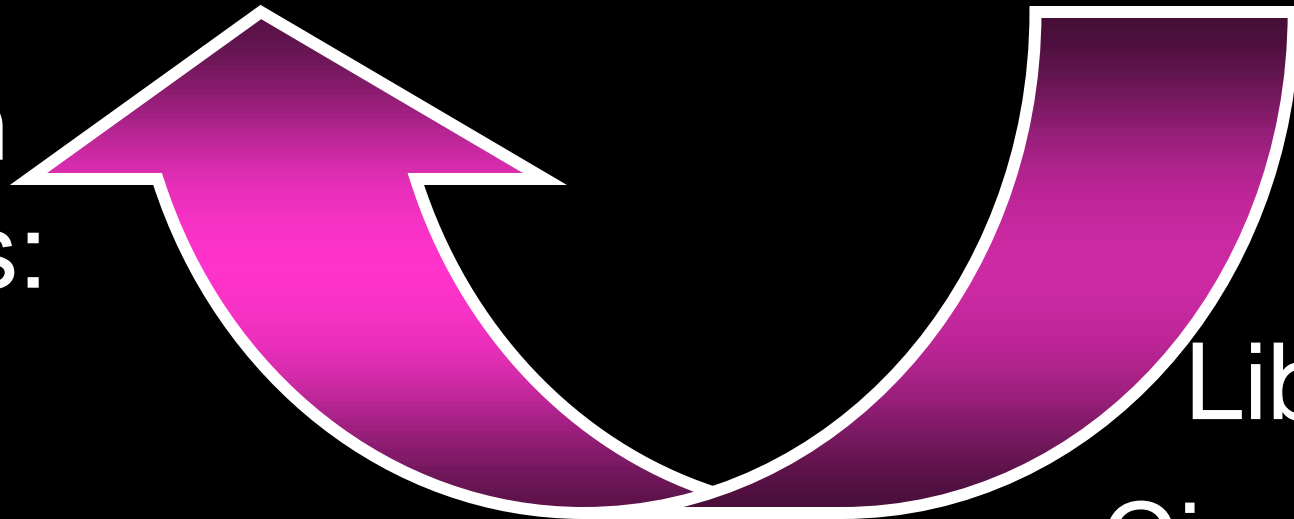


PERSISTENT INFLAMMATION



Inflammation Thrombosis

Inflammation
& Thrombosis:
The Clot
Thickens



Libby & Simon
Circulation 2001

Inflammation-Linked Conditions that Can Trigger PE or DVT

- Ulcerative colitis/ Crohn's disease
- Rheumatoid arthritis/ psoriasis
- Elevated LDL cholesterol or LP(a)
- Obesity/ metabolic syndrome
- Acute coronary syndrome/ stroke
- Pneumonia/ COPD
- Cigarette smoking

Lab Tests of Hypercoagulability

- Genetic: Factor V Leiden; PT Gene Mutation
- Acquired: Lupus Anticoagulant; Anticardiolipin Antibodies; Antiphospholipid Syndrome
- Genetic or Acquired: Deficiencies of antithrombin III, protein C, protein S

VTE Management Strategy

Apixaban vs Rivaroxaban vs Warfarin

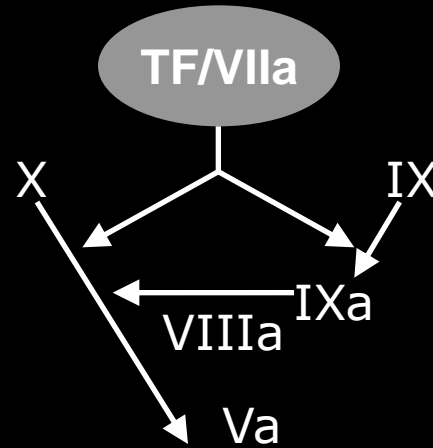
DOACS: SITES OF ACTION

Steps in Coagulation

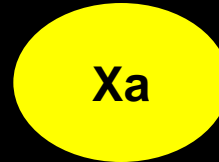
Coagulation Pathway

Drugs

Initiation

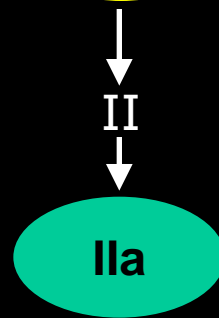


Propagation



Rivaroxaban
Apixaban
Edoxaban

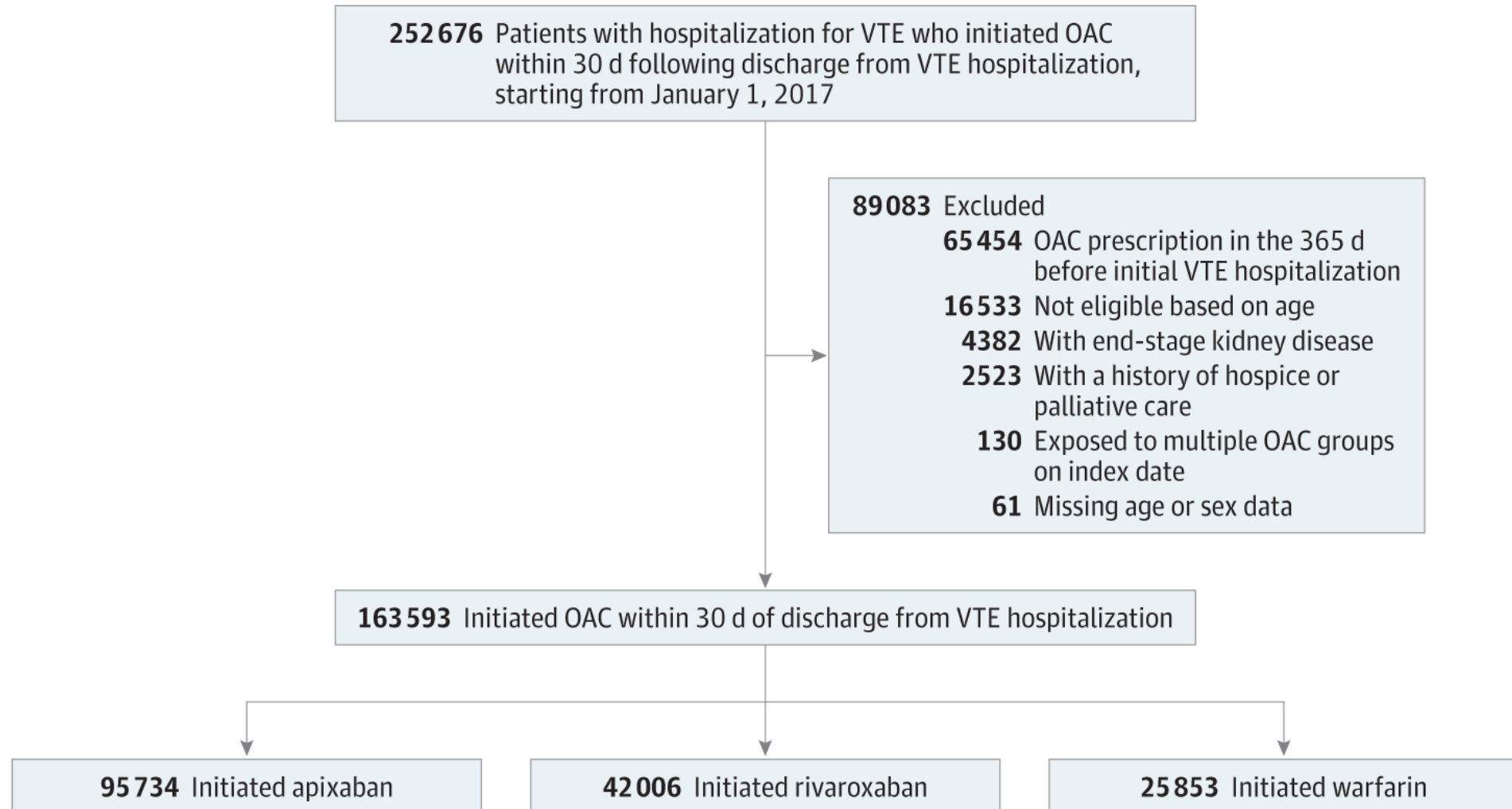
Fibrin formation



Dabigatran

(Circulation 2011;123:1436-1450)

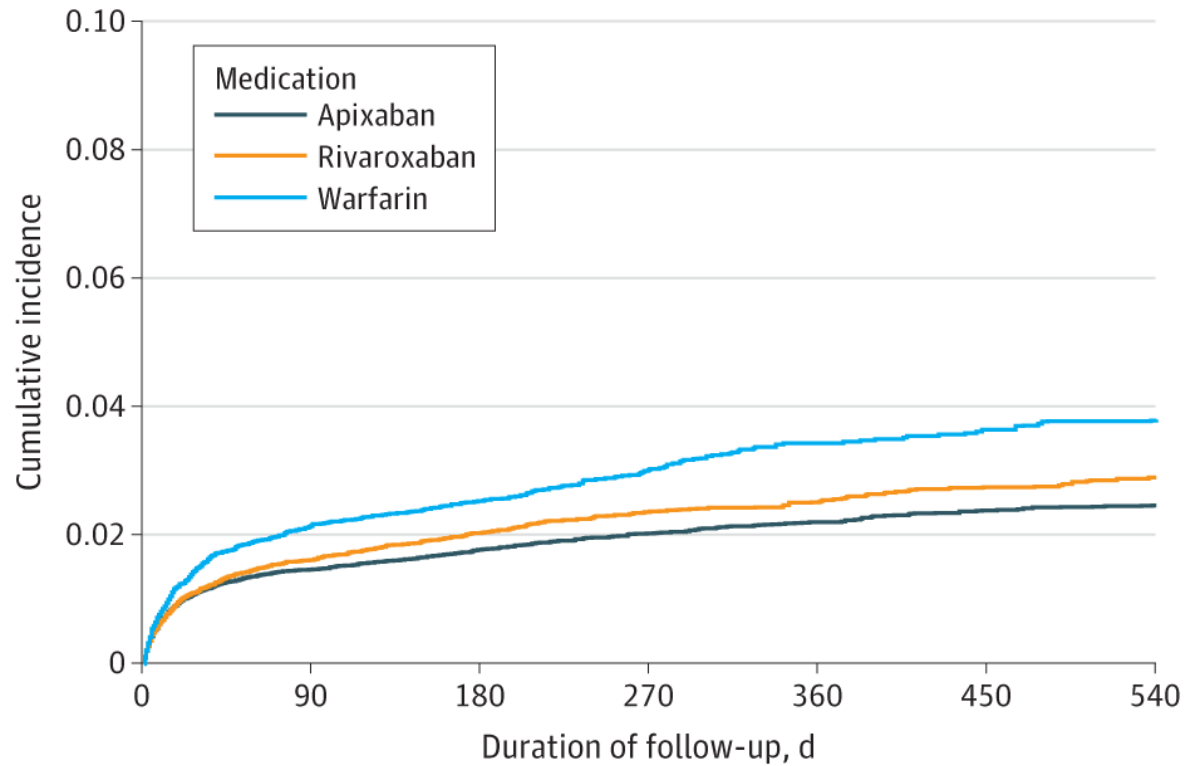
Recurrent VTE and Major Bleeding: Apixaban vs Rivaroxaban vs Warfarin (N=163,593)



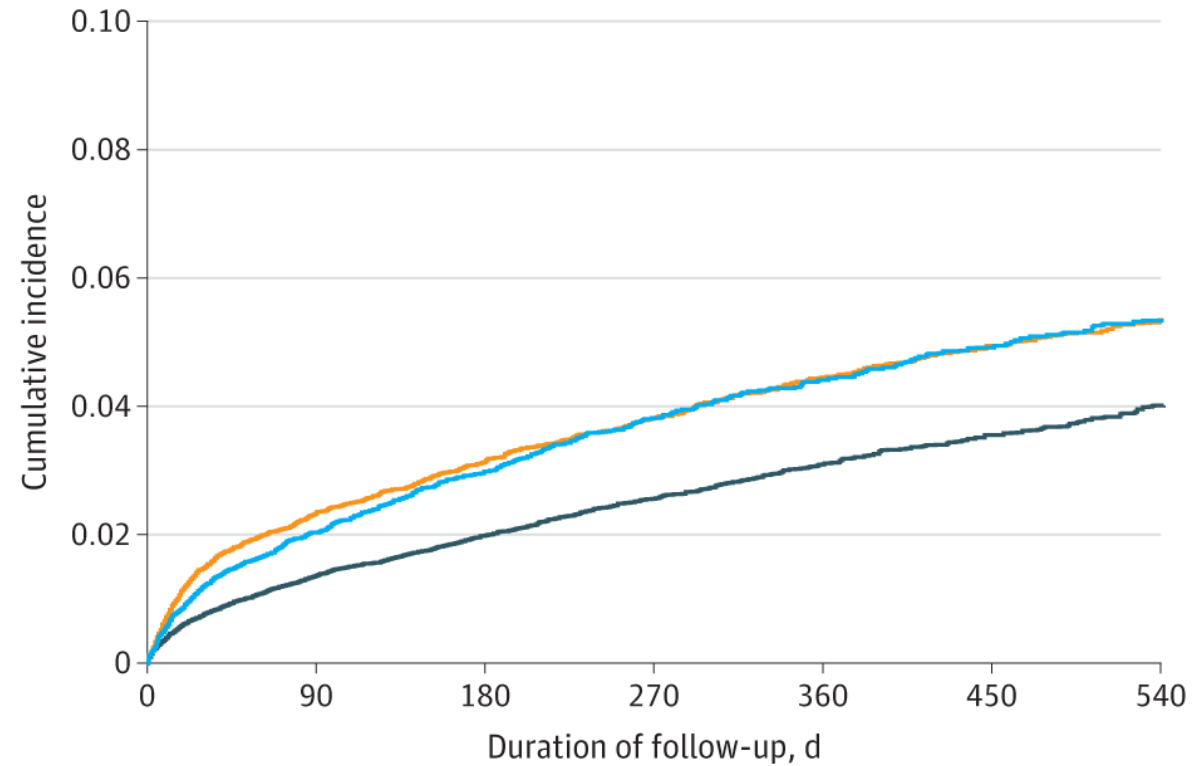
JAMA Internal Medicine 2025; May 12

Recurrent VTE and Major Bleeding: Apixaban vs Rivaroxaban vs Warfarin (N=163,593)

A Hospitalization for recurrent VTE

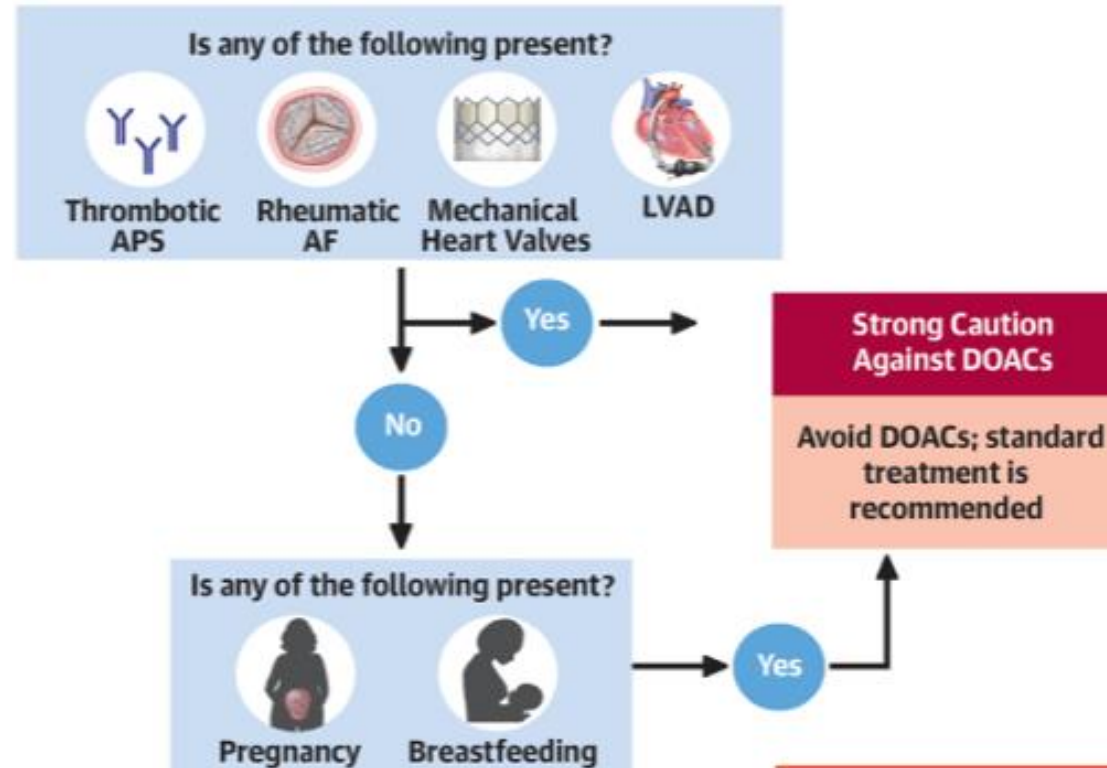


B Hospitalization for major bleeding



JAMA Internal Medicine 2025; May 12

Cautions Against DOACs



Warfarin: Multiple VTE Indications

- Monitor medication adherence
- Frail and obese patients
- APLAS
- Recurrent VTE despite DOAC
- Major bleeding despite DOAC
- Titrate intensity of anticoagulation
 - INR 3.0-4.0—High intensity
 - INR 2.0-3.0—Standard intensity
 - INR 1.5-2.0—Low intensity

Warfarin: Management of Dosing: Tricks of the Trade

- Don't check INR more than twice per week
- Make small, subtle changes in dosing
- Remember to ask about adherence to warfarin
- Caution re: alcohol, NSAIDs, fish oil capsules, turmeric
- Humidify the bedroom at night to prevent nosebleeds
- Prescribe warfarin for 8:00 p.m. nightly
- Low-dose vitamin K to increase INR (counterintuitive)
- BID warfarin dose if total dose exceeds 12 mg

Optimal Duration of Anticoagulation: An Example of Clinical Equipoise

- Is Classifying DVT as “Provoked” versus “Unprovoked” relevant?
ASH: Yes ESC: No
- Does evidence support this classification to determine optimal duration of Rx?
- ASH: Yes ESC: No

SZG Approach to Duration of VTE Anticoagulation:

Queries prior to setting an “End Date”

- 1) Is VTE a surrogate for high risk of MI, stroke, or DM2?—Check LDL-C, A1C, and FH
- 2) Is there a prior history of PE or DVT?
- 3) Is there lab evidence of APLAS?
- 4) Is there active cancer, possibly occult?
- 5) Are there CV risk factors that can be reversed: cigarette smoking, sedentary lifestyle, obesity?

Chronic Venous Insufficiency

(Post-Phlebitic Syndrome)

(Post-Thrombotic Syndrome)

Post Thrombotic Syndrome

- Diagnosed clinically in patients with chronic venous insufficiency and a DVT \geq 3 months previously
- Within two years after a DVT, 20–50% of patients will develop post thrombotic syndrome
- PTS: the main determinant of QOL after DVT
- PTS after a first distal DVT is less common than after a first proximal DVT

Post Thrombotic Syndrome (PTS)

<u>SYMPTOMS</u>	<u>SIGNS</u>
Pain	Edema
Swelling	Telangiectasias
Cramps	Venous Dilatation
Heaviness	Varicose Veins
Fatigue	Redness
Itching	Cyanosis
Paresthesia	Hyperpigmentation

(Kahn SR. Circulation 2014; 130: 1636-1661)

Post Thrombotic Chronic Venous Ulcers: Decrease Quality of Life



Progression of Chronic Venous Insufficiency



**Stasis
Dermatitis—
skin oozing**

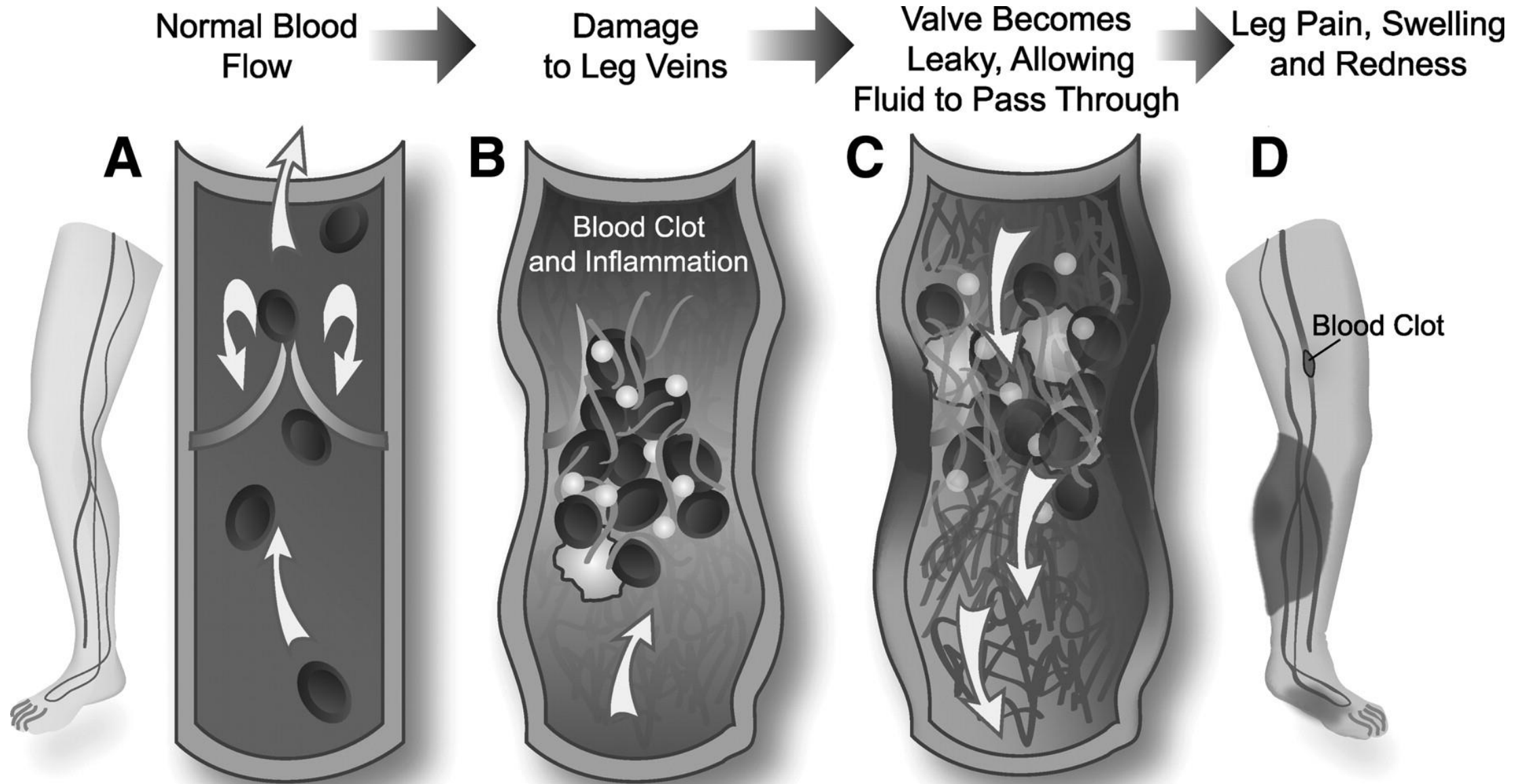


**Chronic Edema/
Advanced
Pigment
Changes**



**Venous Stasis
Ulcer**

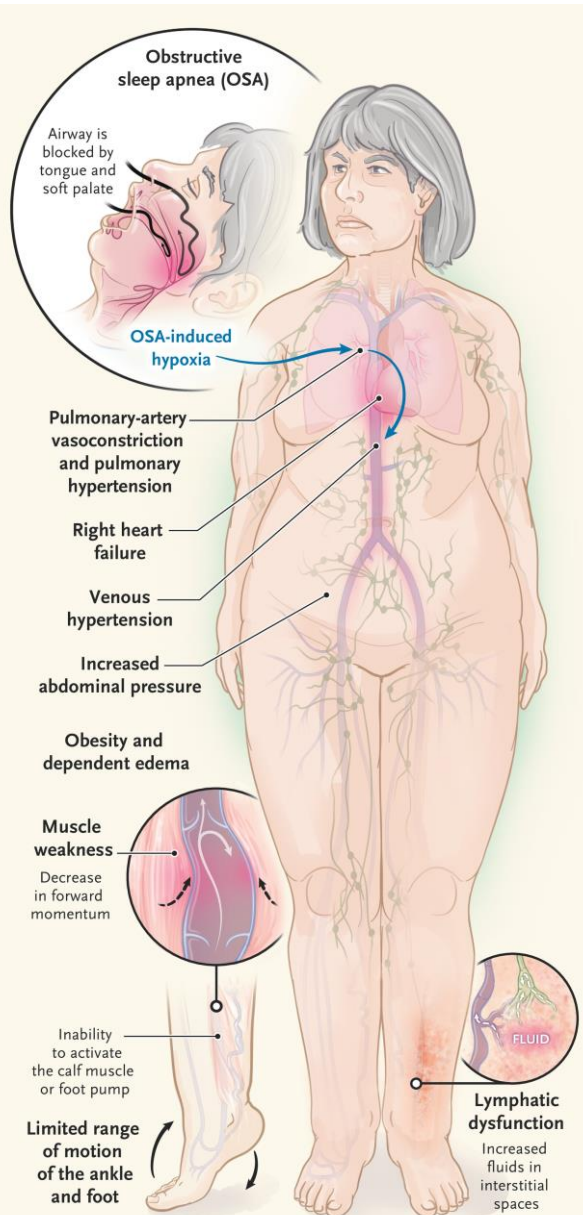
PTS: Valves in the leg veins become leaky



Sara R. Vazquez and Susan R. Kahn *Circulation* 2010; 121: e217-e219

Functional Venous Insufficiency and Venous Hypertension

Functional venous insufficiency:
obstruction of venous return, elevated central pressures (e.g., obesity, OSA, or right heart failure), lymphatic dysfunction, poor calf and foot pump function can lead to venous hypertension, even in the absence of structural venous damage.



NEJM 2024; 391: 2350-2359

Manifestations of Chronic Venous Disease



Venous Ulcer



Weak Calf Muscle;
Dependent Edema



Varicose and
Spider Veins

N Engl J Med 2024; 391: 2350-2359

Dependent Rubor



CCJM 2025; 92: 205-206

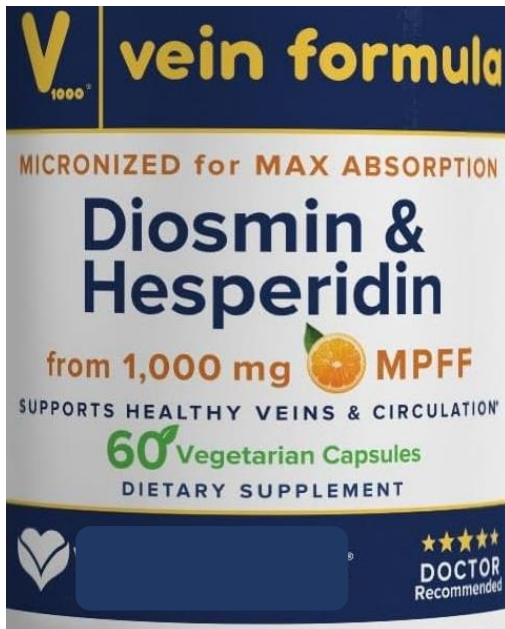
CVI Guideline Recommendations

- Ultrasound is the test of choice to diagnose venous reflux in a patient with CVI
- Compression therapy is the primary treatment option: stockings or CircAid



Guideline Recommendations for CVI

- Intervene surgically if venous reflux extends from above to below the knee
- If surgery isn't feasible, relieve CVI-related leg pain, leg heaviness, night cramps, swelling with: Micronized Purified Flavonoid Fraction (MPFF)



A venotonic and plant-based antioxidant. It improves blood circulation, reduces inflammation, and strengthens blood vessels

NEJM 2024; 391: 2350

Mechanisms: Micronized Purified Flavonoid Fraction (MPFF)

- Over-the-counter medication. Order on Amazon.
- Protects the microcirculation from oxidative stress
- Modulates microvalve function
- Reduces transient venous reflux
- Promotes better valve competence
- These mechanisms collectively reduce leg pain, heaviness, swelling, and improve quality of life

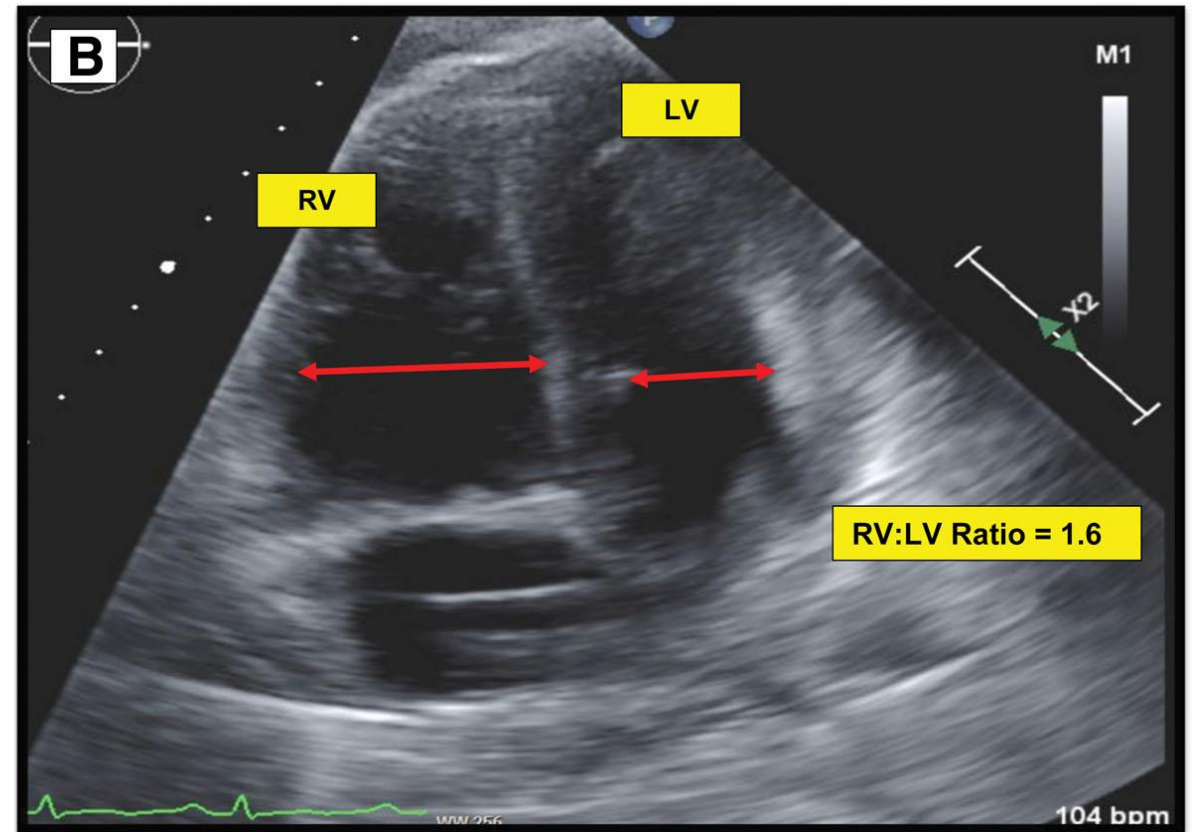
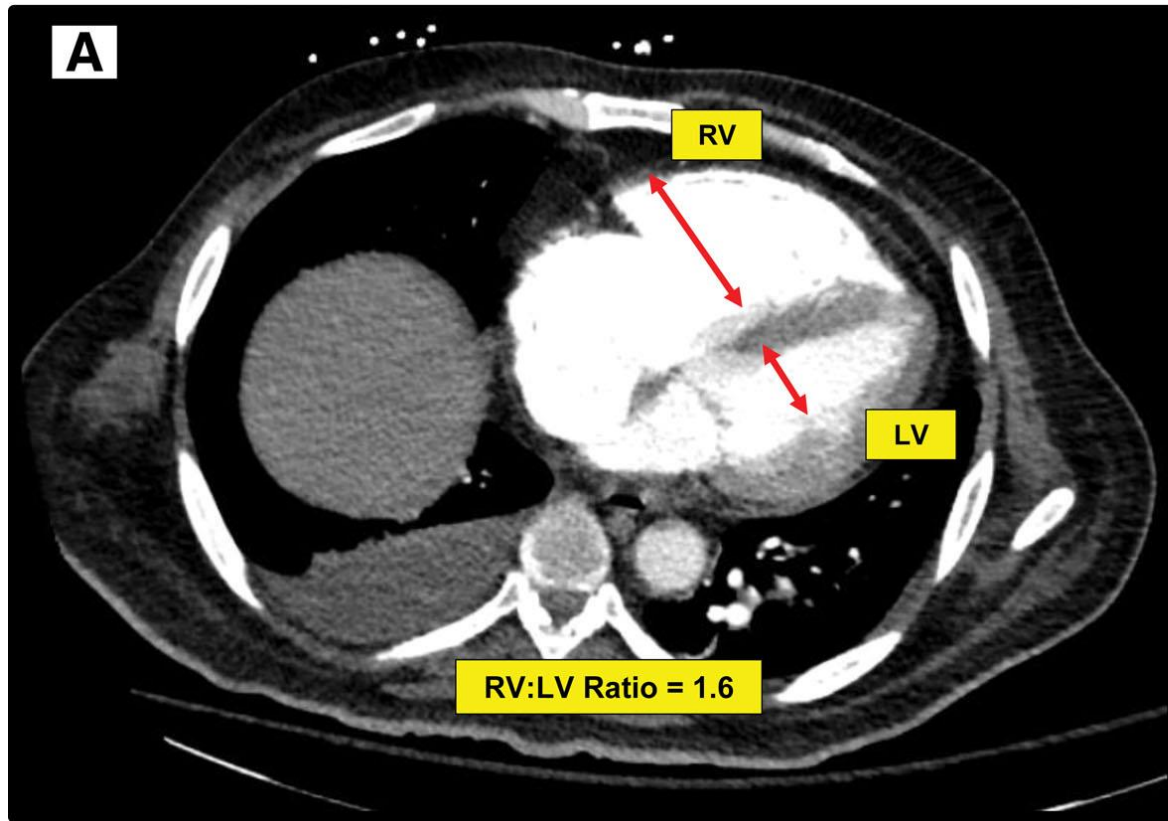
Home Exercises for Leg Swelling

- Ankle Pumps: Perform plantar/ dorsiflexion of the ankle. Curl toes forward in plantar flexion; flex toes toward you in dorsiflexion.
- Ankle Rotations: Perform large ankle circles in both directions.
- Toe Gripping: Curl toes forward; make a fist with your toes in sitting position. Toe-grab a towel on the floor
- Toe Spreading: Spread the toes as much as possible. Alternate with toe gripping,
- Calf Squeezing: Contract the calf muscles.
- Leg Elevation: Keep legs elevated during prolonged sitting. (NEJM 2024; 391: 2350-2359)

Advanced PE Management

Our Tool Kit To Treat PE
When Anticoagulation Alone
Does Not Suffice

Acute RV Dilation with PE: CT and TTE



Circulation 2023; Jan 23. 147: e628–e647. AHA Scientific Statement

Adjunctive Therapy for Massive PE

- Ensure excellent oxygenation and intensive anticoagulation
- Do not volume load the fragile RV with more than 500 ml to raise the BP
- Low threshold to begin pressors
 - 1) Norepinephrine
 - 2) Dobutamine

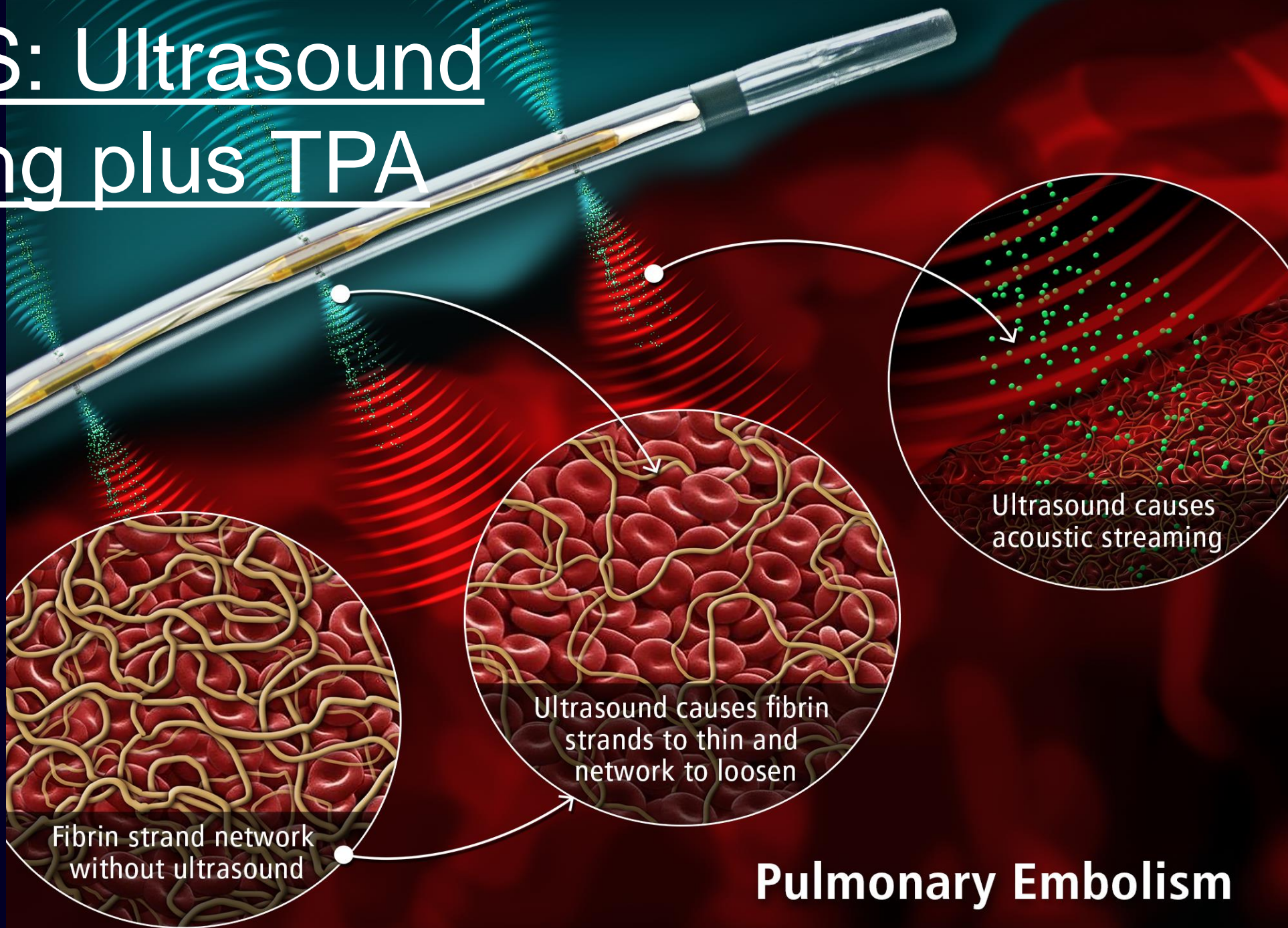
Background

- Hemodynamically unstable PE has an 8-fold higher mortality rate than stable PE.
- In patients with hemodynamically unstable PE, systemic thrombolysis decreases the death rate by 35-50%, but it causes a 2-3% rate of intracranial hemorrhage.
- In 1990, the FDA approved systemic TPA to treat massive PE in a dose of 100 mg as a continuous infusion over 2 hours.

When Should We Initiate Systemic Thrombolysis?

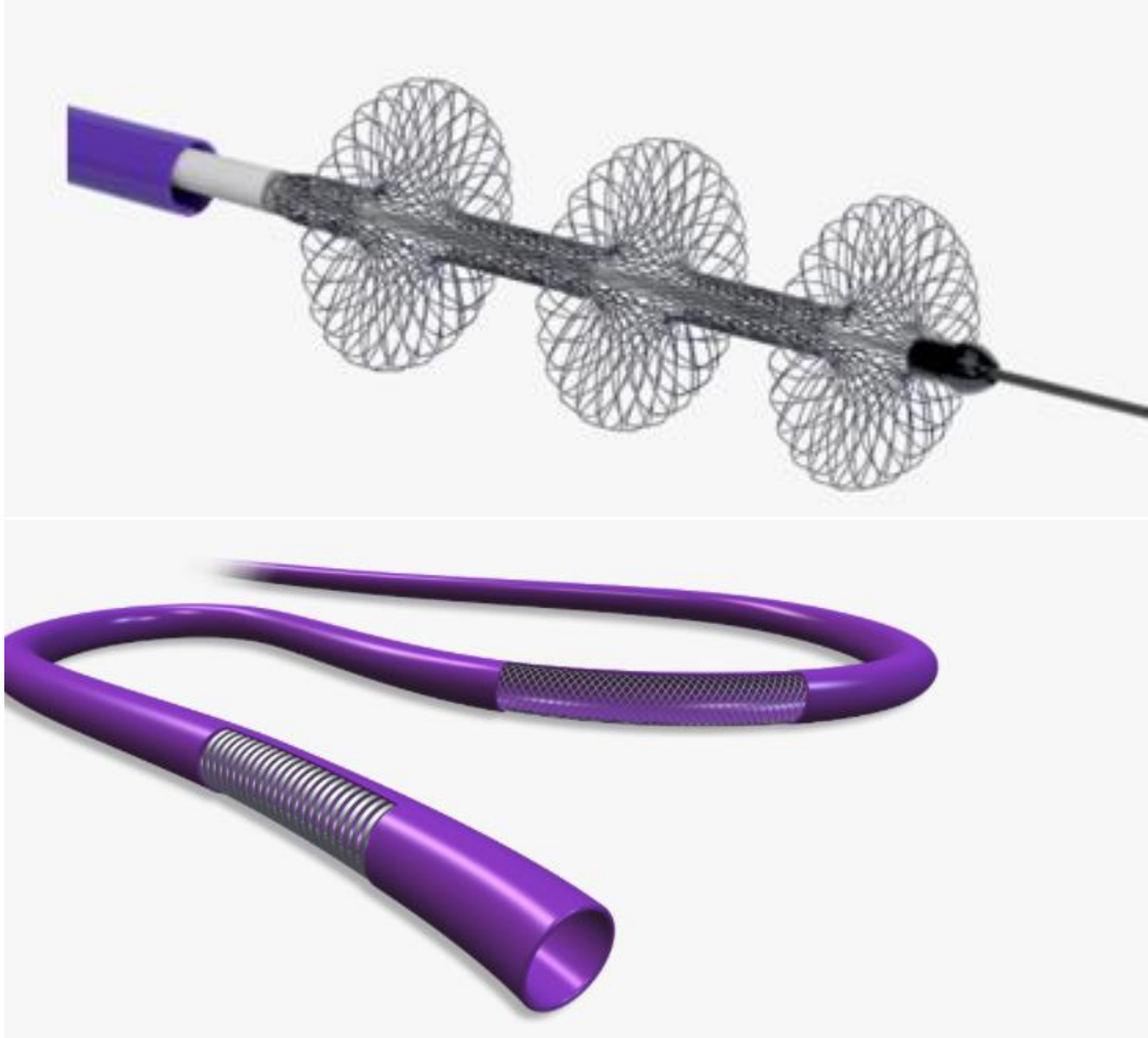
- 1) The patient is too critically ill to transfer
- 2) You're moonlighting as the only doctor on duty in the hospital
- 3) The patient appears young and healthy except for the PE
- 4) It's not possible to mobilize IR, cardiology, or cardiac surgeon in a timely way

EKOS: Ultrasound Pulsing plus TPA



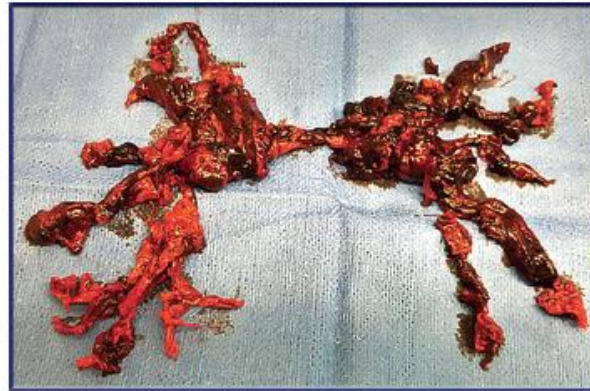
Pulmonary Embolism

FlowTrievers:
20F—No TPA



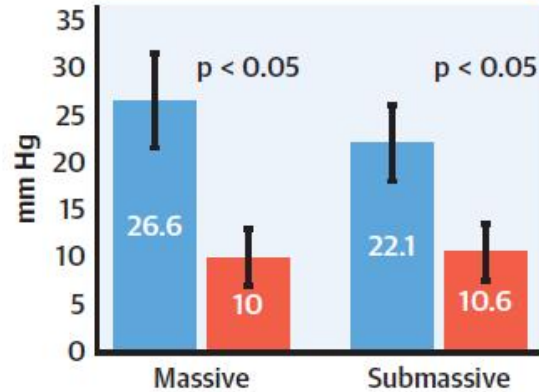
CENTRAL ILLUSTRATION Improvement in Right Ventricular Function After Surgical Management of Acute Pulmonary Embolism

RV Function
after Surgical
Pulmonary
Embolectomy

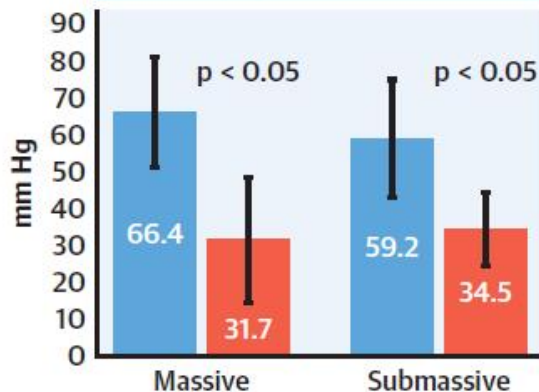


(Goldberg, JB.
JACC 2020;
76: 903-911)

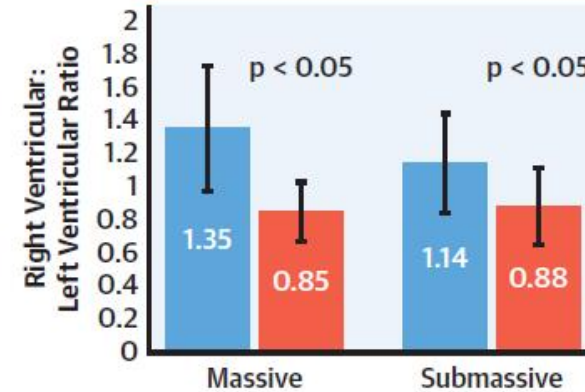
CVP



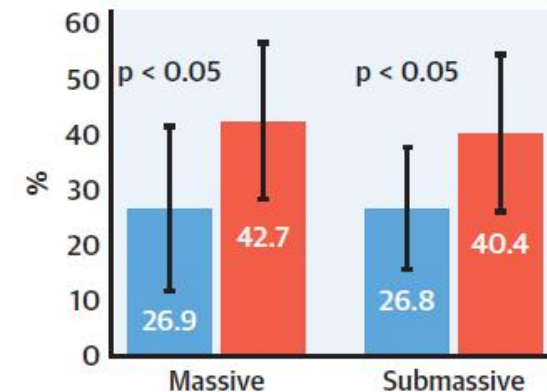
PA_{syst}



RV/LV ratio



RV FAC

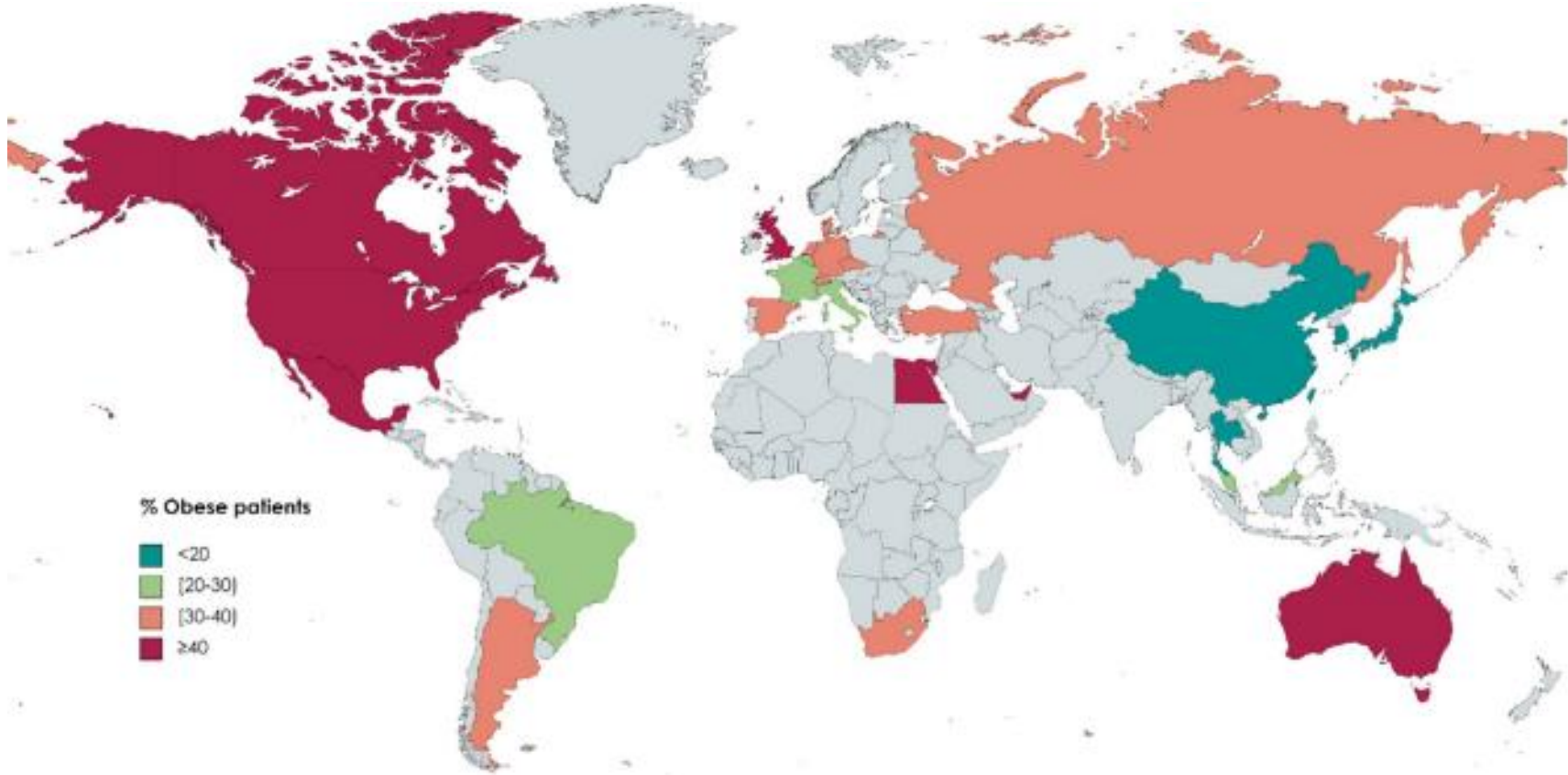


■ Pre-Operative ■ Post-Operative

Impact of Obesity and

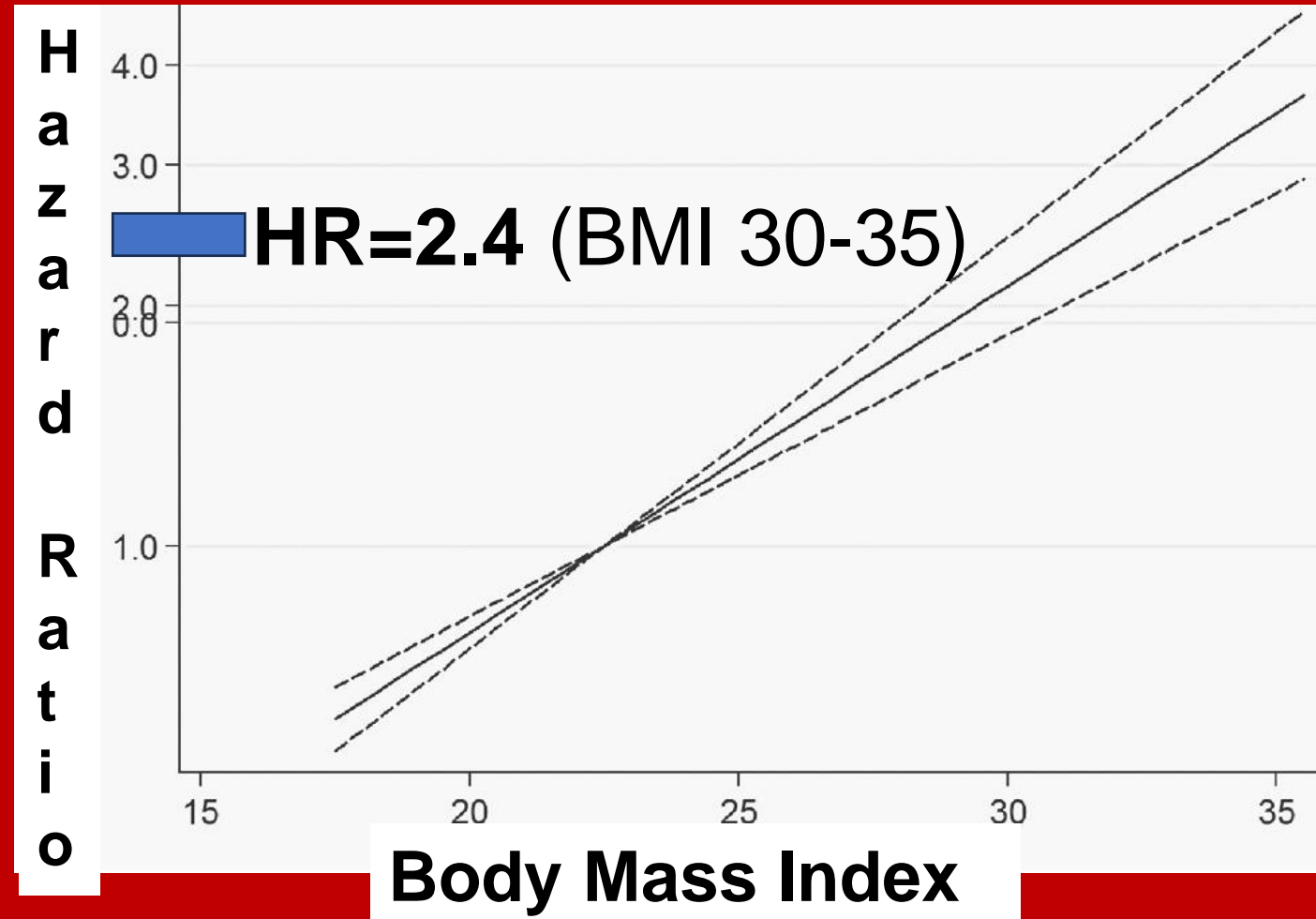
Weight Management

Distribution of Obese Patients according to Country



J Thromb Haemost 2021; 19: 3031–3043.

Hazard Ratio=2.4 for PE in those with Obesity (N=3,910,747)

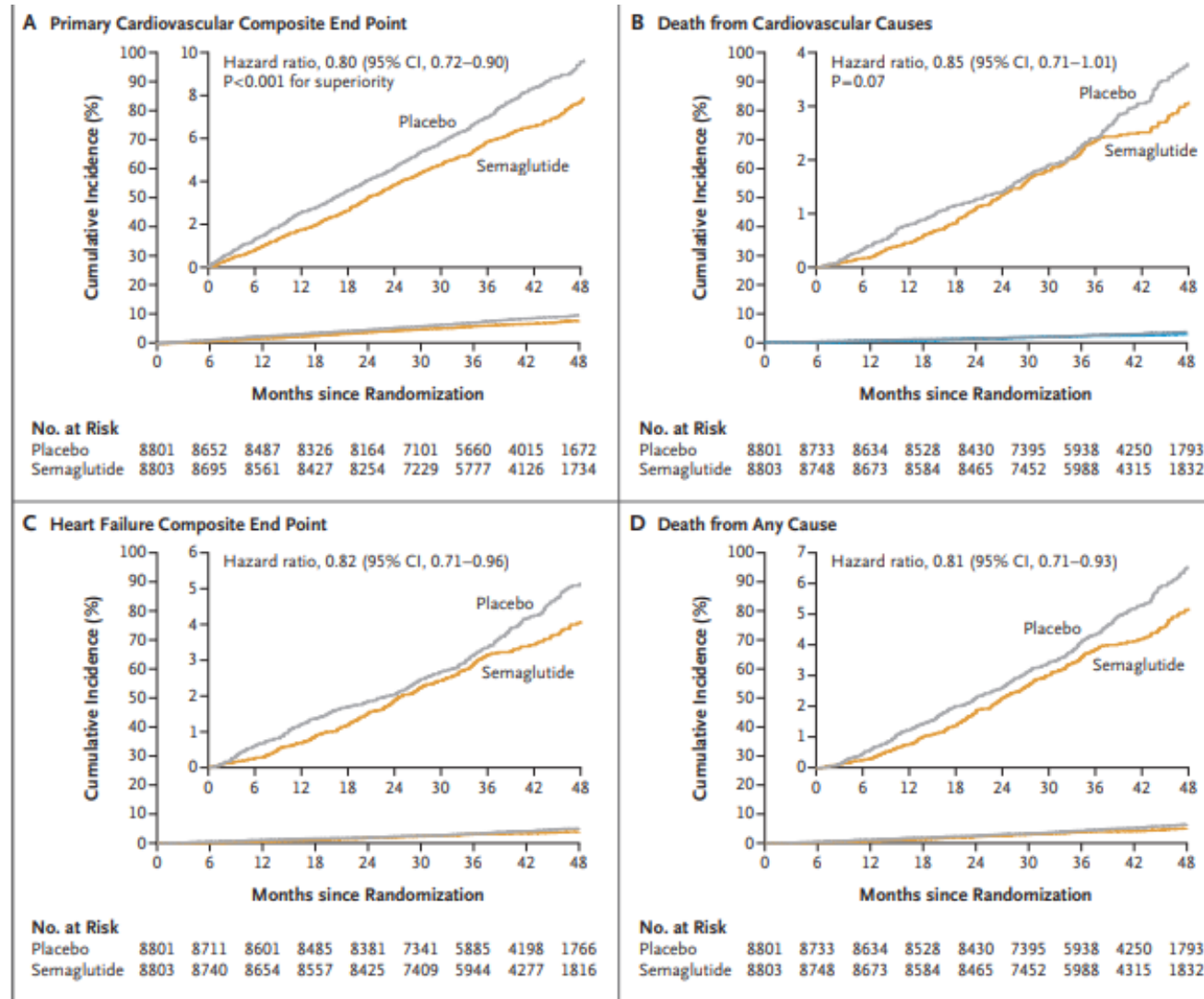


Thrombosis Research 2020; 192: 64-72

Wegovy received FDA approval in March 2024 to reduce the risk of CV events in adults with obesity or overweight



SELECT Trial: WEGOVY RCT (N=17,604)



N Engl J Med 2023;389:2221-2232

Take Home Points

- Mortality from PE: Increasing in US
- Inflammation increases VTE risk
- Post-PE Impairment: Common, decreases QOL
- Apixaban surpasses rivaroxaban: Efficacy/ safety
- Warfarin: Underutilized
- Optimal duration of anticoagulation: controversial
- Advanced therapy: systemic lysis, catheter-based—
with or without TPA, surgical embolectomy, ECMO
- Will weight management with meds decrease VTE?

References

- ESC Guidelines for acute PE. Eur Heart J 2020; 41: 543
- PE Mortality. Thrombosis Research 2023; 228: 72-80
- Anticoagulation Duration. Eur Heart J 2023; 44: 1245
- SELECT RCT: Wegovy. NEJM 2023; November 11
- PE and SES. Circ CV Qual Outcomes. 2024;17: e010090
- Statistics on PE and DVT. Circulation 2024; 149: e849
- Chronic venous insufficiency. NEJM 2024; 391: 2350-59
- Apixaban vs Rivaroxaban vs Warfarin. JAMA Internal Medicine 2025; May 12