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

PE and DVT: A Moving Target

Samuel Z. Goldhaber, MD
Director, Faculty Promotions
Director, Thrombosis Research Group
Cardiovascular Division
Brigham and Women's Hospital
Professor of Medicine
Harvard Medical School

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

November 7, 2024

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Samuel Z. Goldhaber, MD

- 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

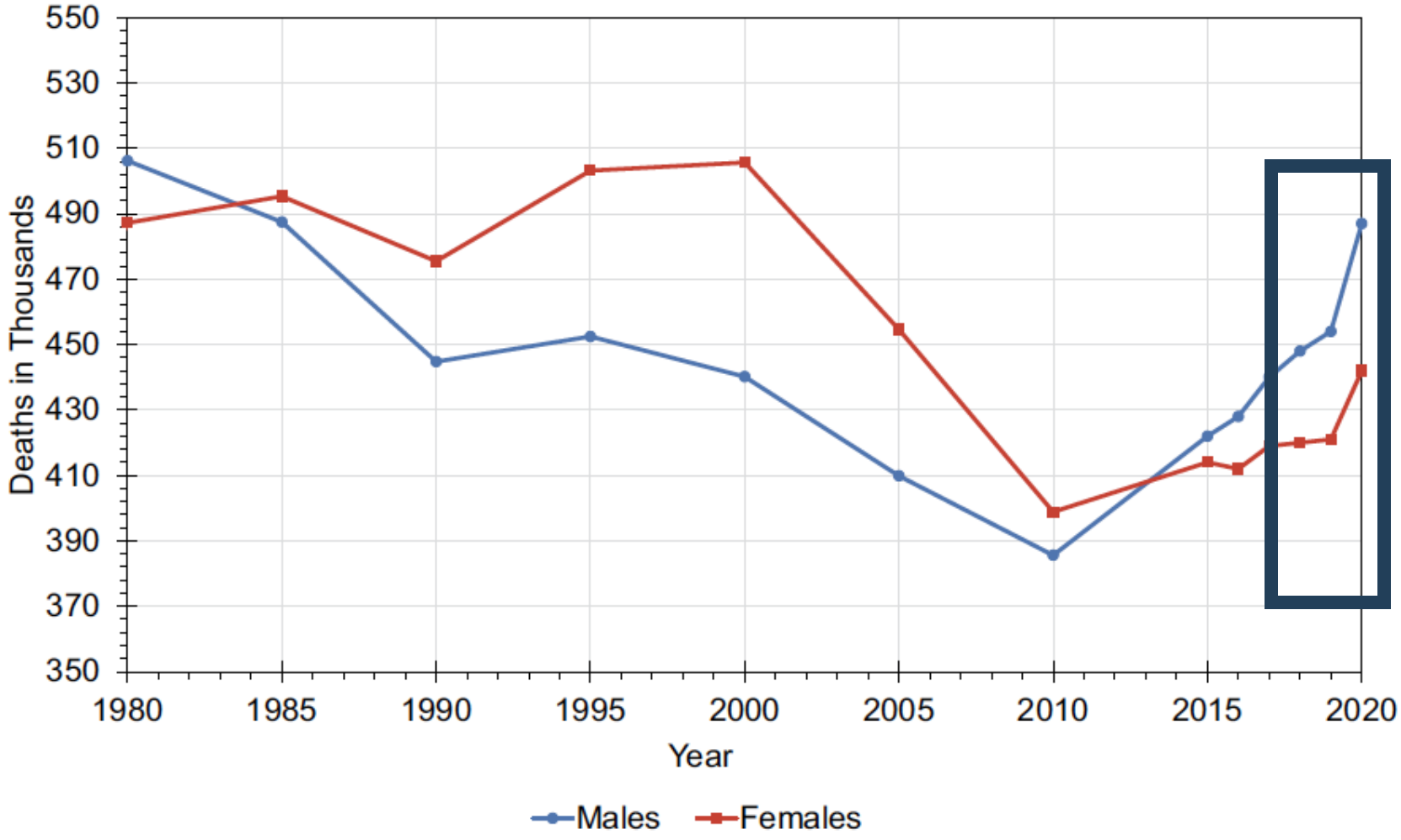
Learning Objectives: VTE Update

- Epidemiology: Socioeconomic Status/ VTE
- Artificial Intelligence: Diagnosis of PE
- Inflammation-linked conditions trigger VTE
- Post-PE and Post-Phlebitic Syndrome
- DOACs: a) Rivaroxaban vs apixaban
  b) Is warfarin dead?
- Optimal duration of anticoagulation: My approach
- Advanced management of high-risk PE
- Prevention: Focus on Obesity

Epidemiology

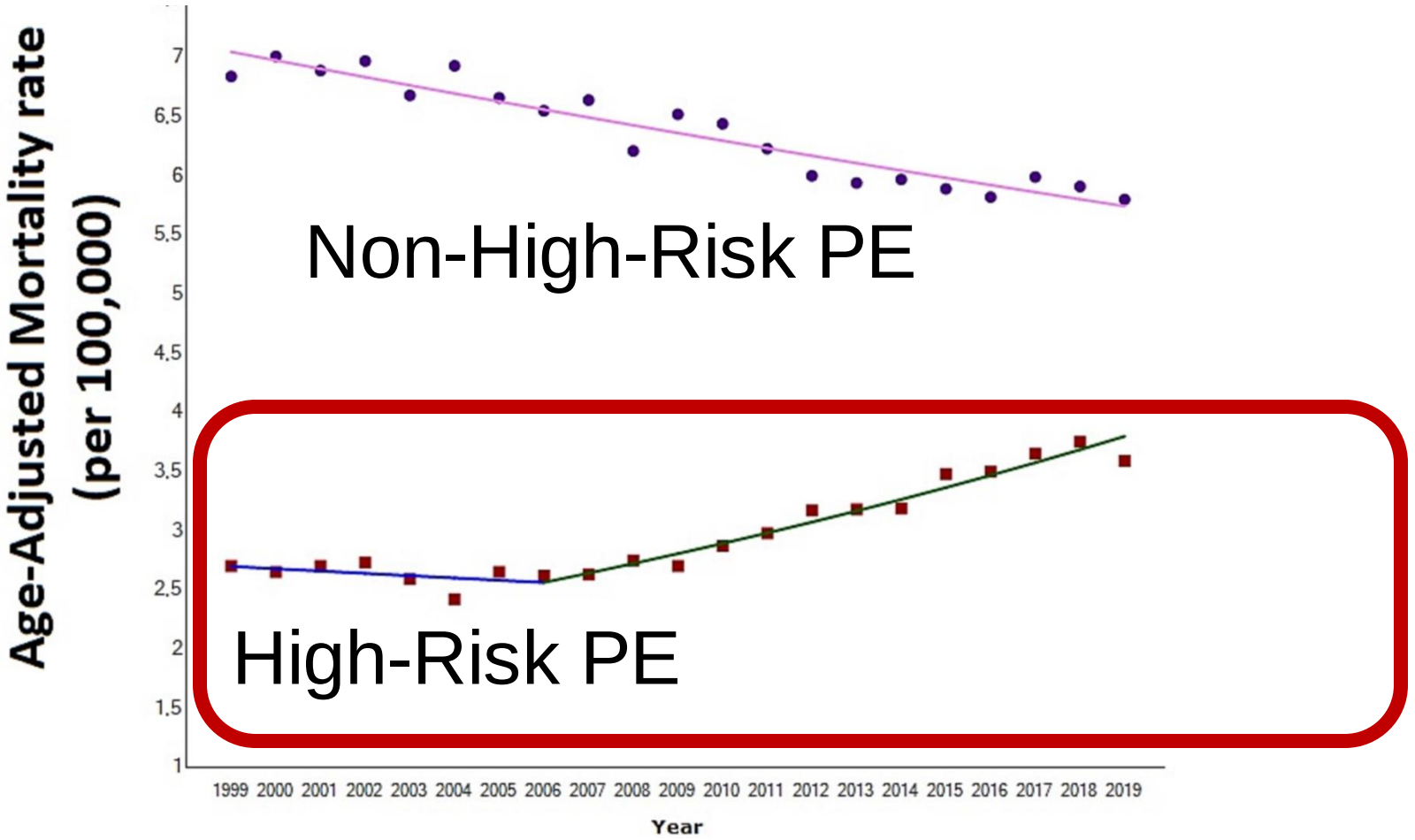
Does Socioeconomic Status Play a Role?

CVD Deaths in the US 1980 - 2020



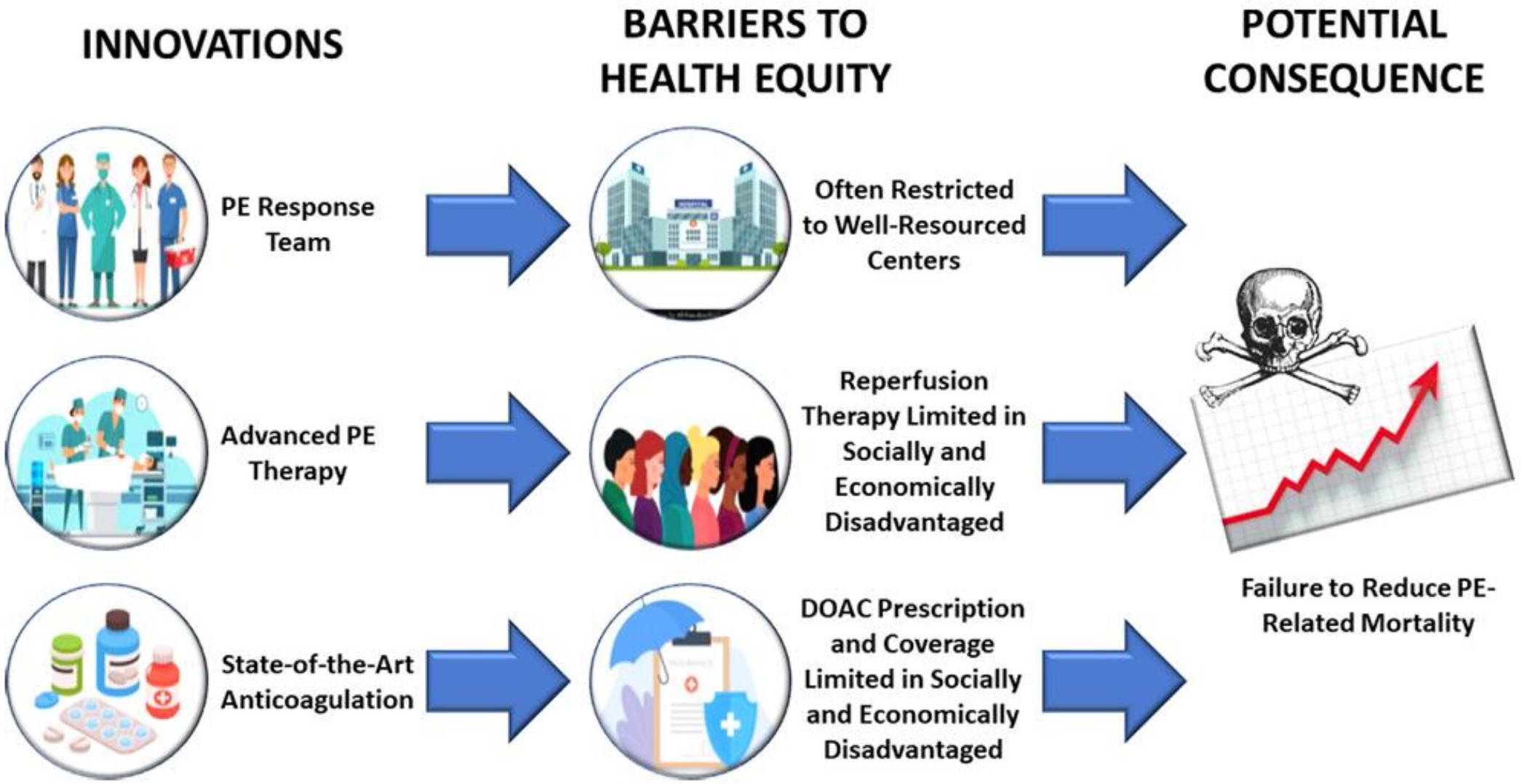
Tsao et al . Circulation 2023; 147: e93–e621

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



Thrombosis Research, 2023-08-01, Volume 228, Pages 72-80

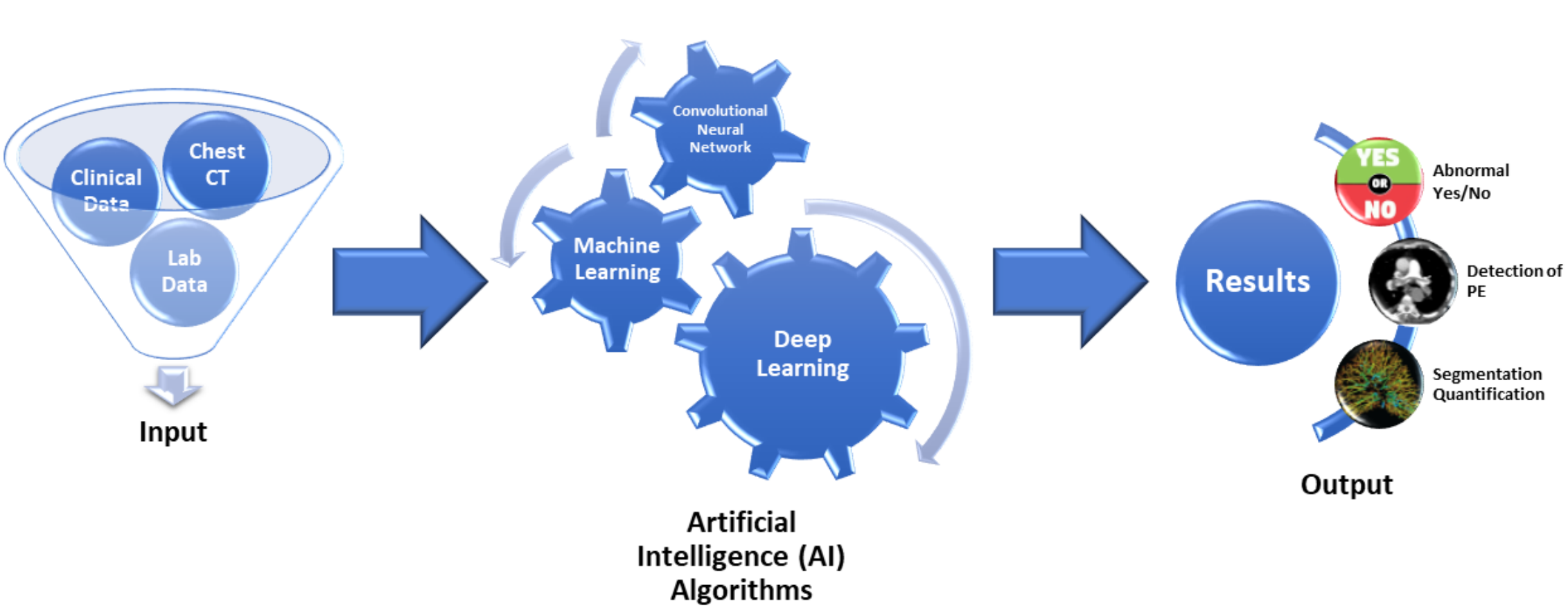
Health Equity Barriers in PE



Piazza G. JTH 2024; 22: 1838-1840

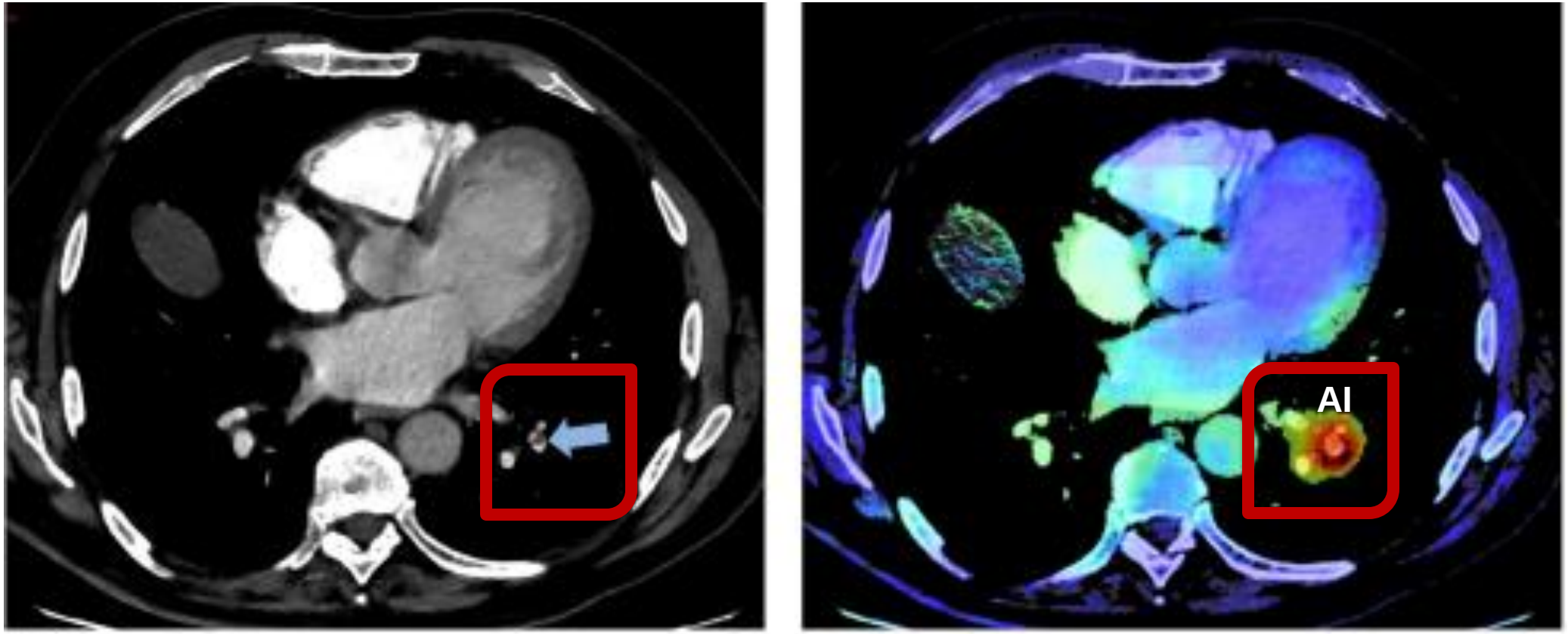
AI-Assisted Chest CT Diagnosis and D-dimer Adjusted for Age > 50 Years

Artificial Intelligence (AI)-Assisted Diagnosis of PE



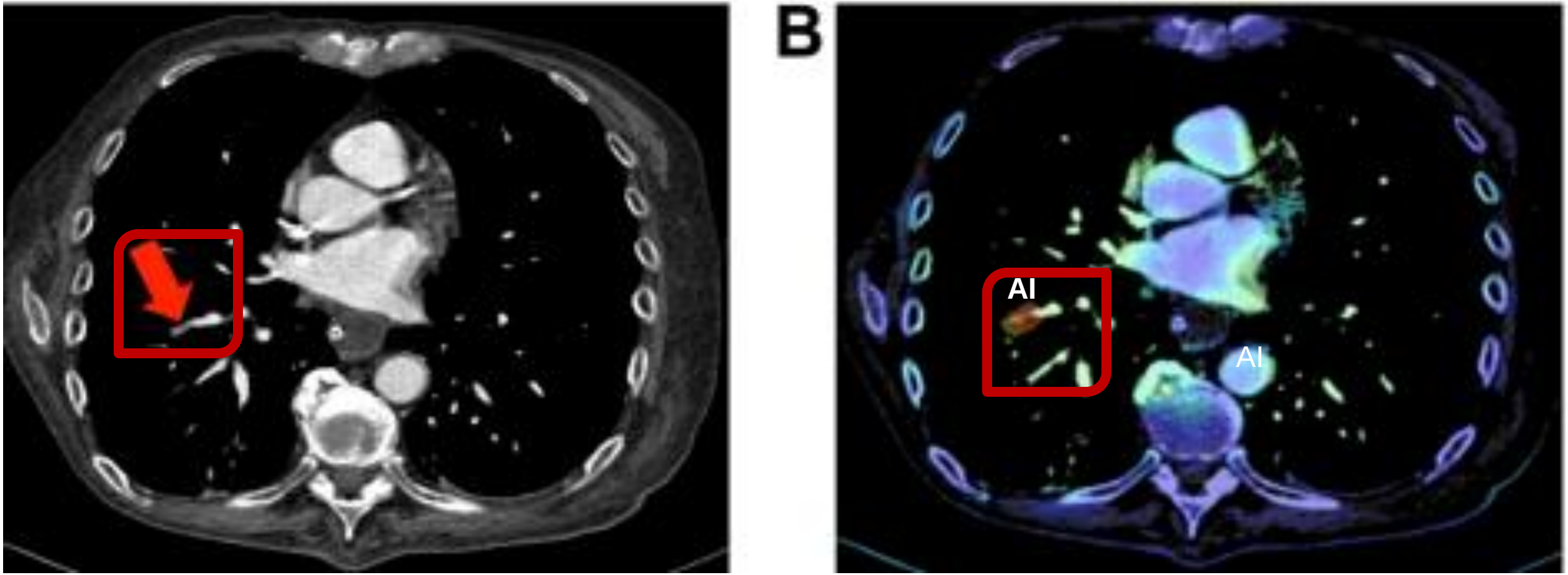
Inputs: chest CT, clinical data, and lab results. Neural networks identify repeating patterns of abnormalities. Natural language processing identifies risk factors, symptoms, and signs to generate clinical probability. Outputs: any abnormality, detection of PE, and localization/ quantification of PE. Courtesy of Gregory Piazza, MD

AI for Chest CT Pulmonary Angiogram



(Ben Cheikh A. European Radiology 2022; March 22)

AI for Chest CT Pulmonary Angiogram



(Ben Cheikh A. European Radiology 2022; March 22)

AGE-ADJUSTED D-DIMER (>50 y.o.)

- (Adjusted for age) D-dimer upper limit of normal in those > 50 y.o. is:

  50 X Age (in years) ng/ml
- Accurate in ADJUST-PE Trial
- 5-times as many negative D-dimer tests in patients > 75 y.o. using this adjusted definition of normal D-dimer

(JAMA 2014; 311: 1117-1124)

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—beware of false positives with heparin or rivaroxaban

VTE Risk Factors

(e.g., inflammation)

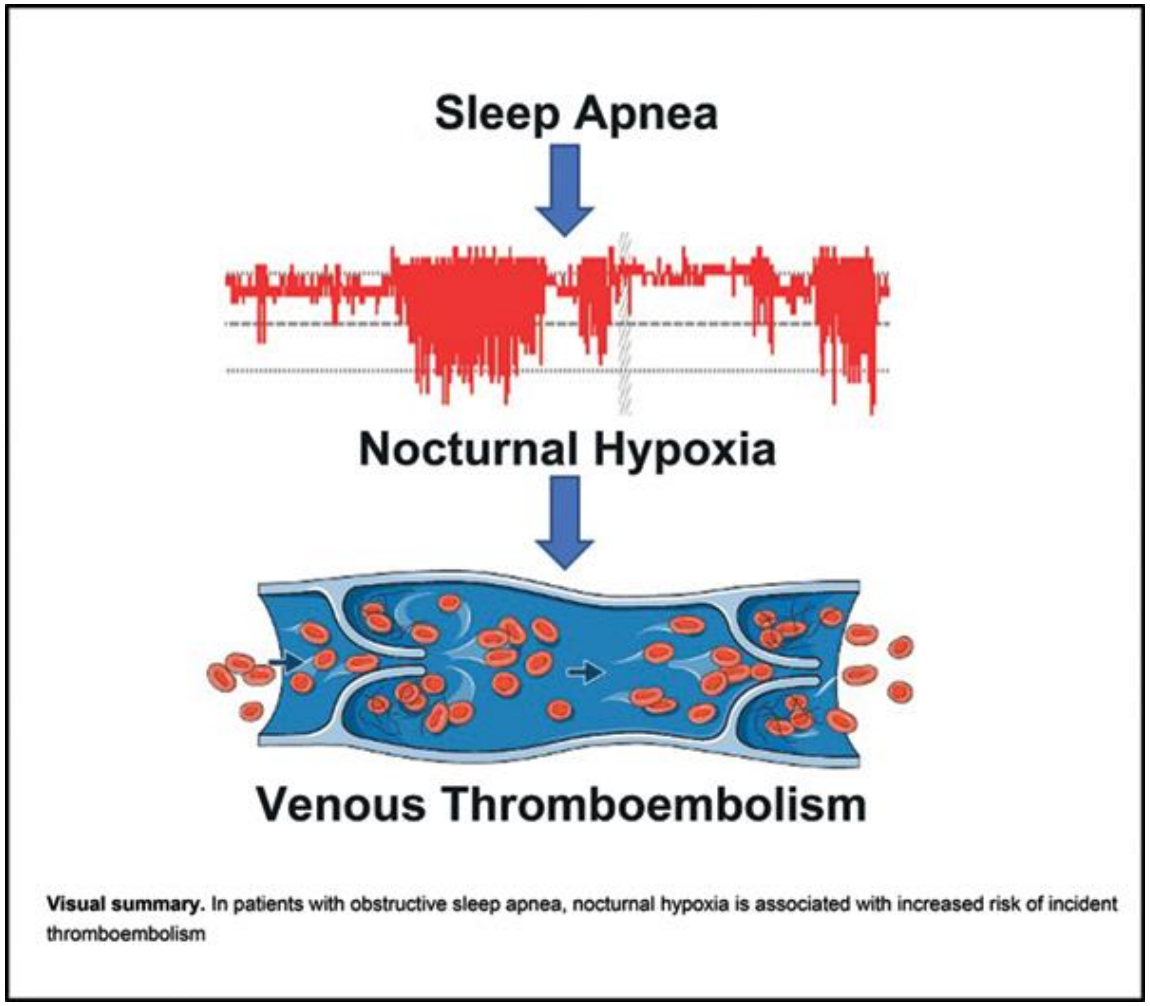
and

Tips for Follow-Up

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

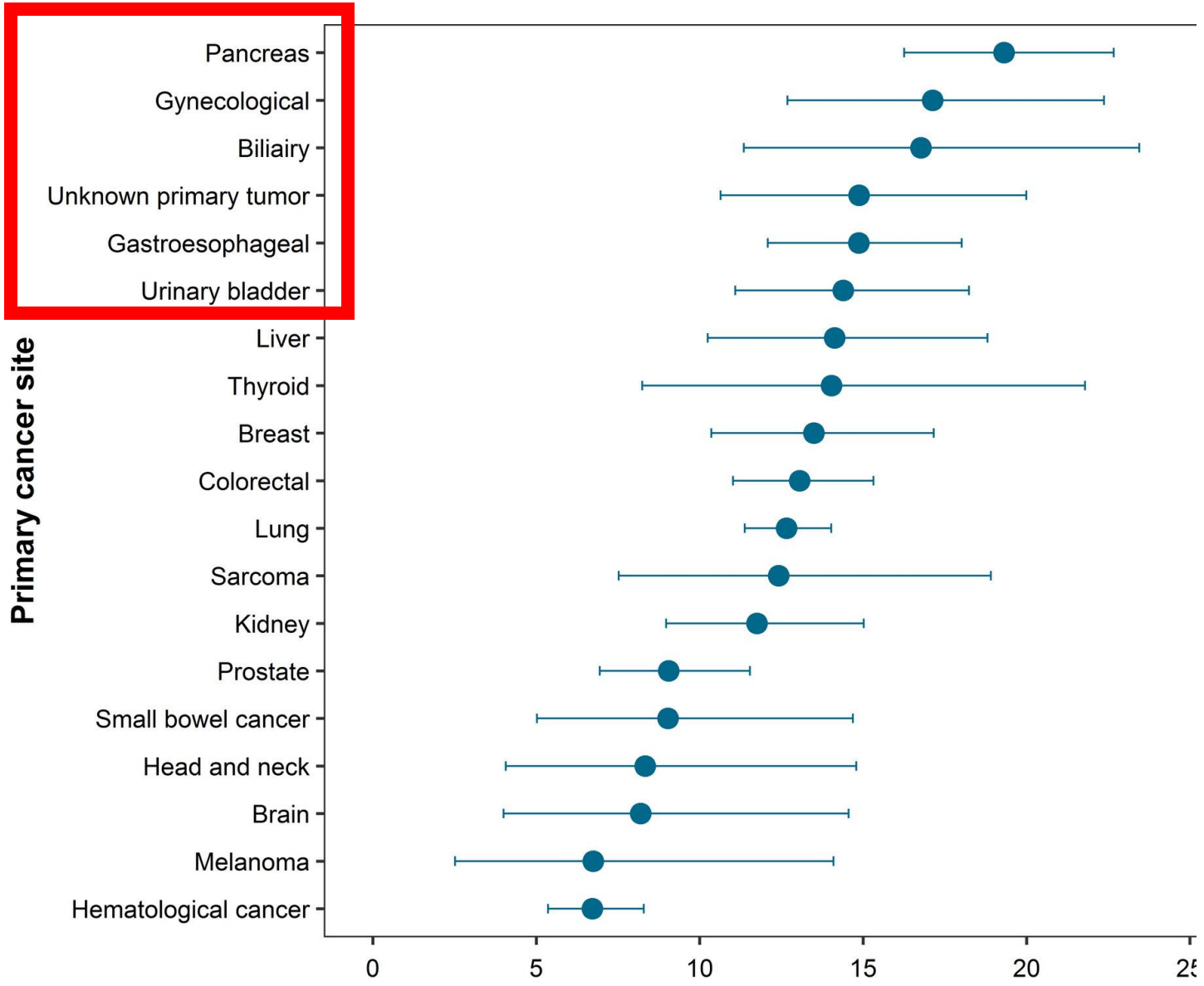
In OSA, nocturnal hypoxia is associated with increased VTE



Visual summary. In patients with obstructive sleep apnea, nocturnal hypoxia is associated with increased risk of incident thromboembolism

Thromb Haemost 2023; 123: 393-401

Cancer Sites in PE Patients



(Gimbel IA. JTH 2021; 19: 1228-1235)

ABANDON "SILO THINKING"

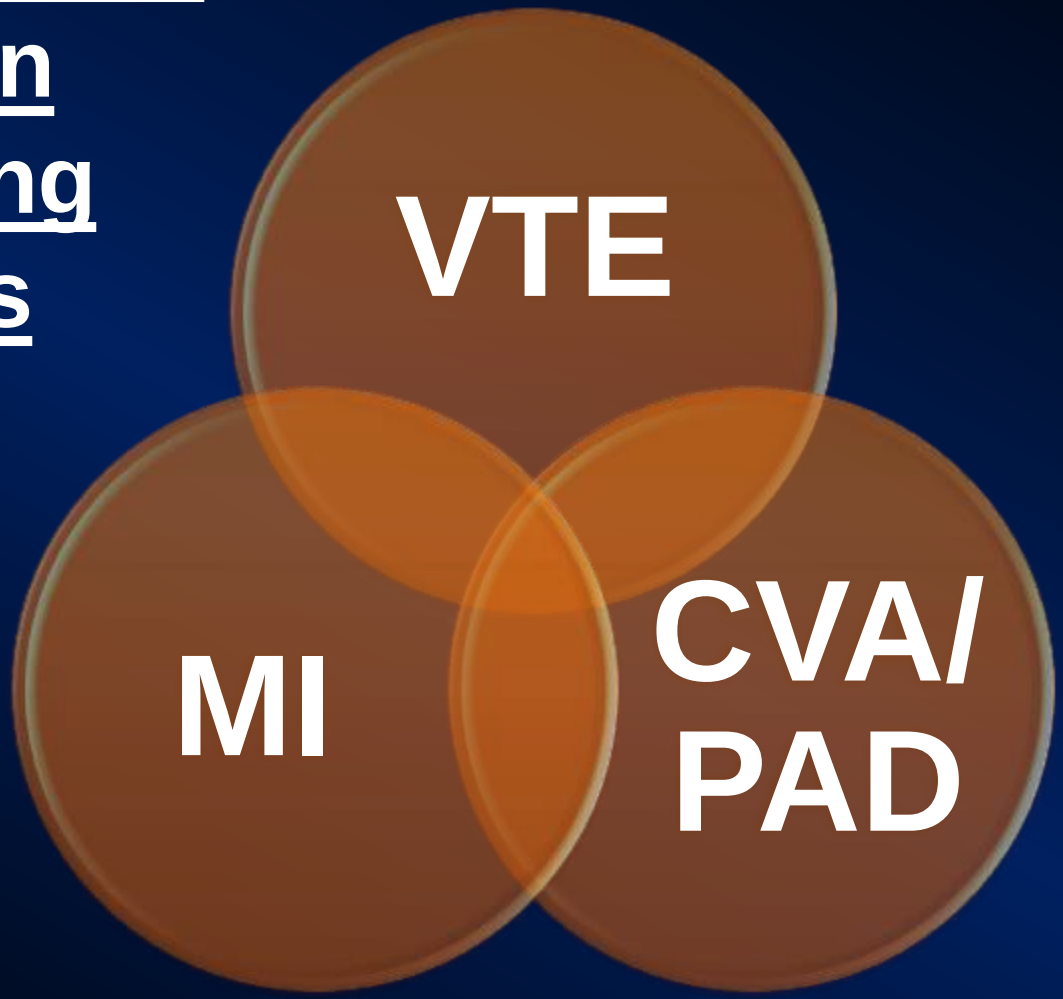
VTE

MI

CVA

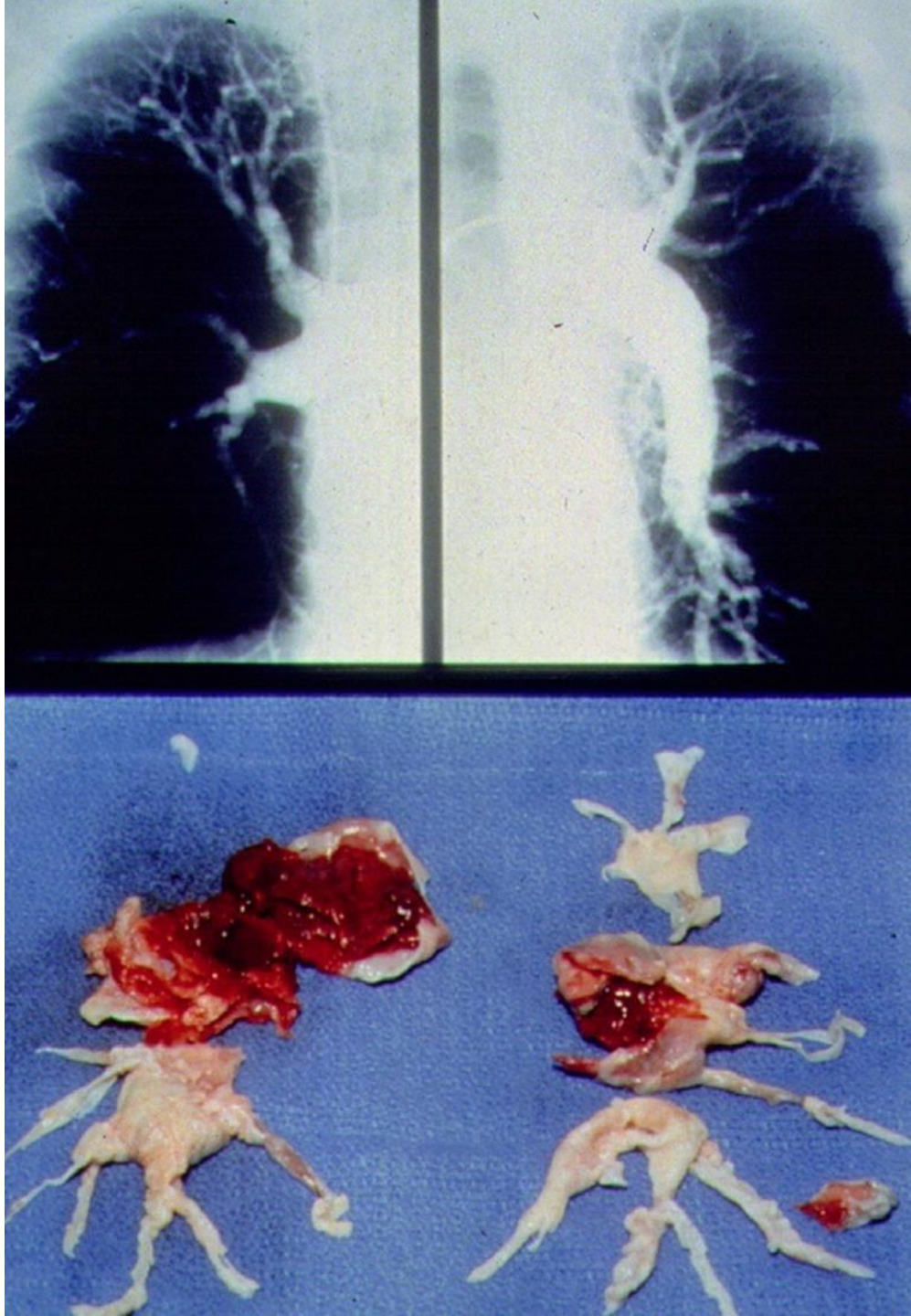
PAD

Inflammation: A Common Underlying Process

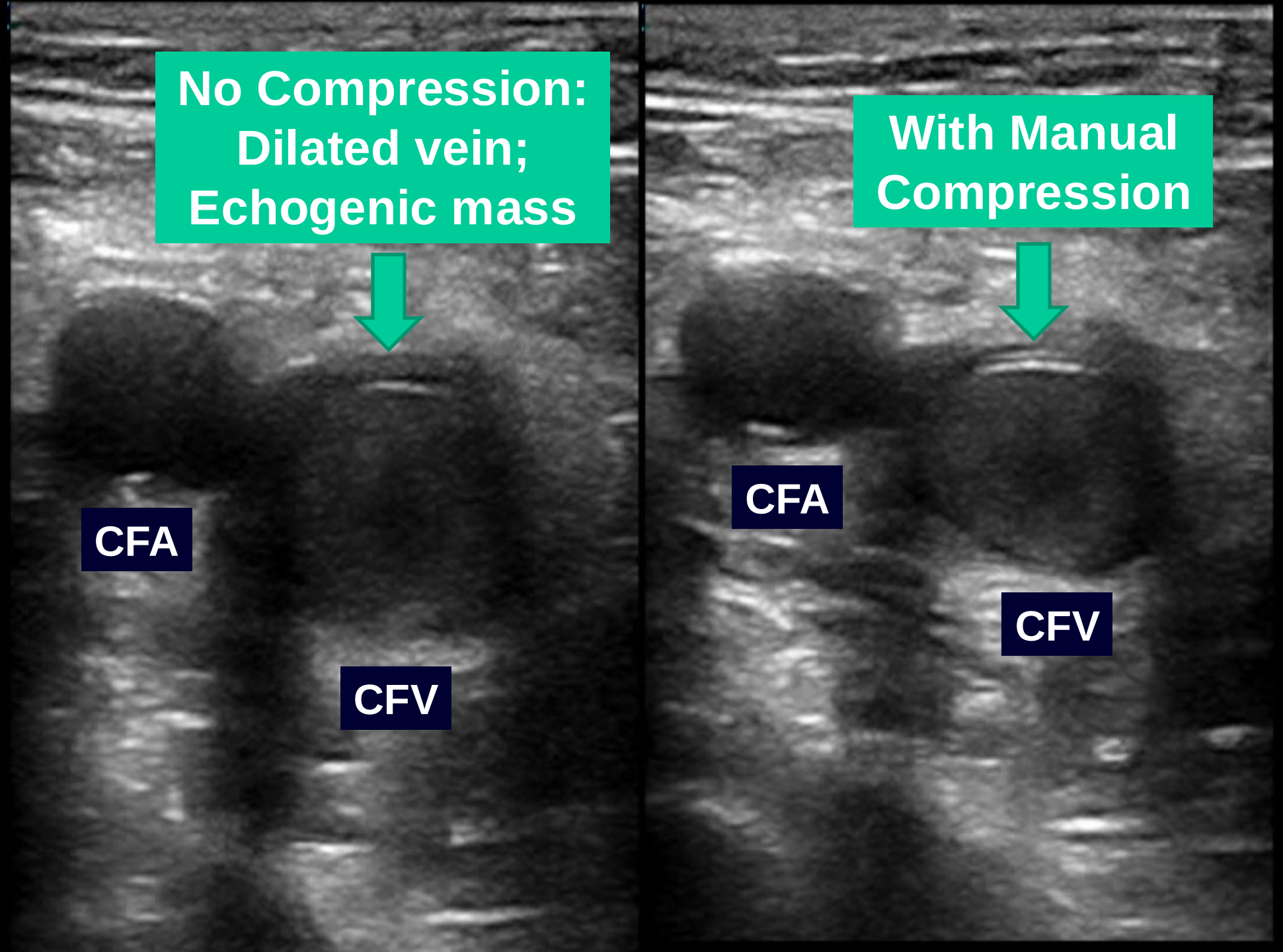


Post-PE impairment (PPEI) is frequent (16%/2 yrs) and associated with death, re-hospitalization (31%), CTEPH, and decreased quality of life.

(European Heart Journal 2022; April 7)



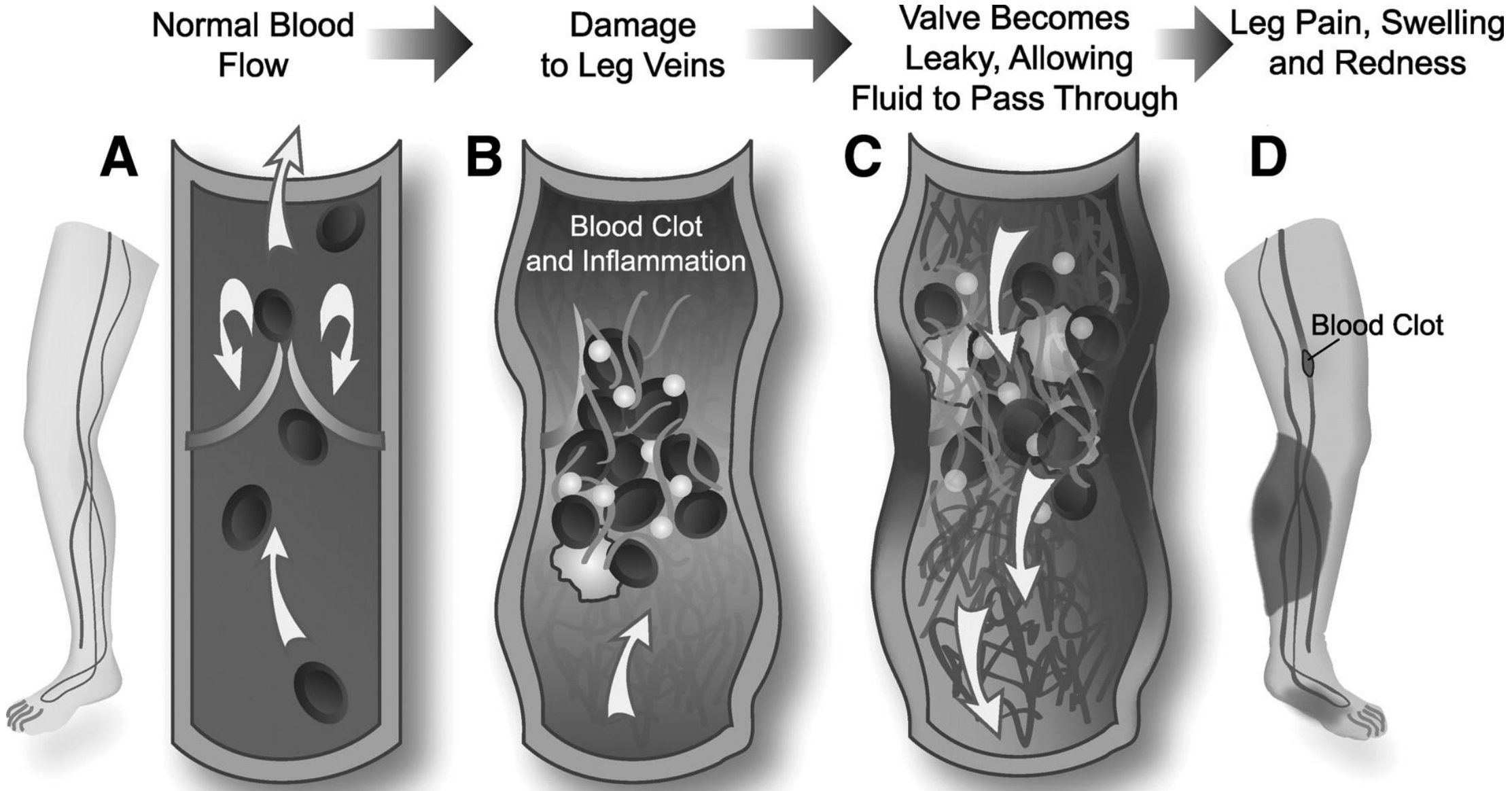
Post Phlebitic Syndrome of the Leg


No Compression:
Dilated vein;
Echogenic mass
CFA
CFV
With Manual
Compression
CFA
CFV

Post Phlebitic Syndrome

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

PTS: Valves in the leg veins become leaky



(Sara R. Vazquez, and Susan R. Kahn Circulation. 2010;121:e217-e219)

PROGRESSION of CHRONIC VENOUS INSUFFICIENCY

Stasis Dermatitis—skin oozing

Chronic Edema/ Advanced Pigment Changes

Venous Stasis Ulcer

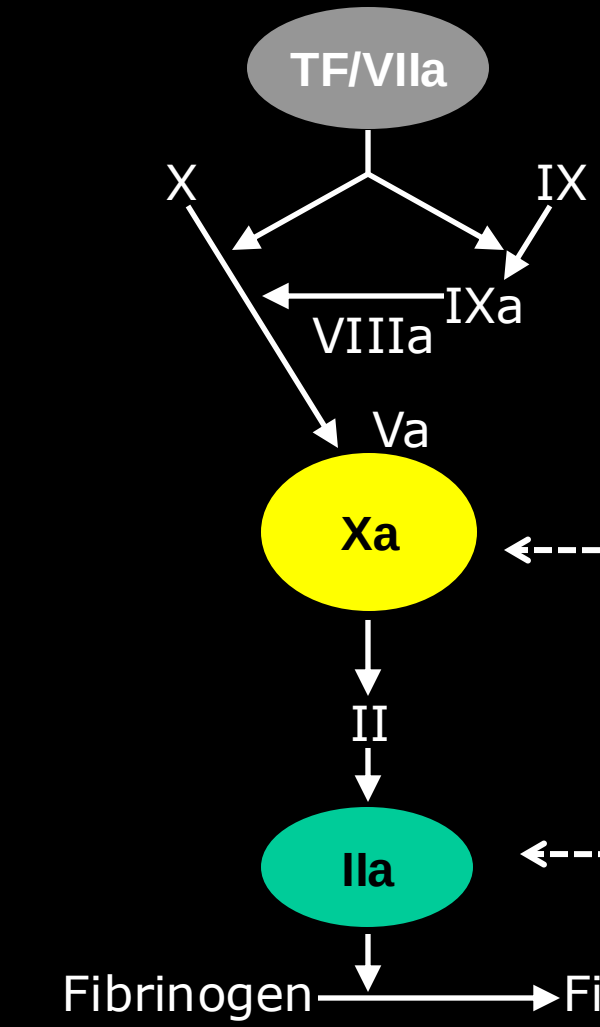
VTE Management Strategy

- Rivaroxaban vs apixaban for VTE
- Is Warfarin Dead?

DOACS: SITES OF ACTION

Steps in Coagulation **Coagulation Pathway** **Drugs**

Initiation



Propagation

Rivaroxaban
Apixaban
Edoxaban

Fibrin formation

Dabigatran

(Circulation 2011;123:1436-1450)

Dabigatran

- First to market
- Poor launch—failure to educate providers that the drug is metabolized by the kidney and that dose reduction or drug avoidance is warranted with CKD 4 and CKD5
- Initially, a wave of hemorrhagic deaths
- Probably the most potent DOAC (SZG)
- Two generic versions are FDA approved

Rivaroxaban

- Second to market
- First DOAC approved for once daily dosing
- The short half-life is probably responsible for a bit less efficacy than the other DOACs
- Take with the dinner meal to prolong half-life
- Can cause severe migraine headaches necessitating head CT scans
- Can cause severe genitourinary bleeding leading to cystoscopy or D&Cs
- Good choice for patients who'll have adherence challenges with BID dosing

Apixaban

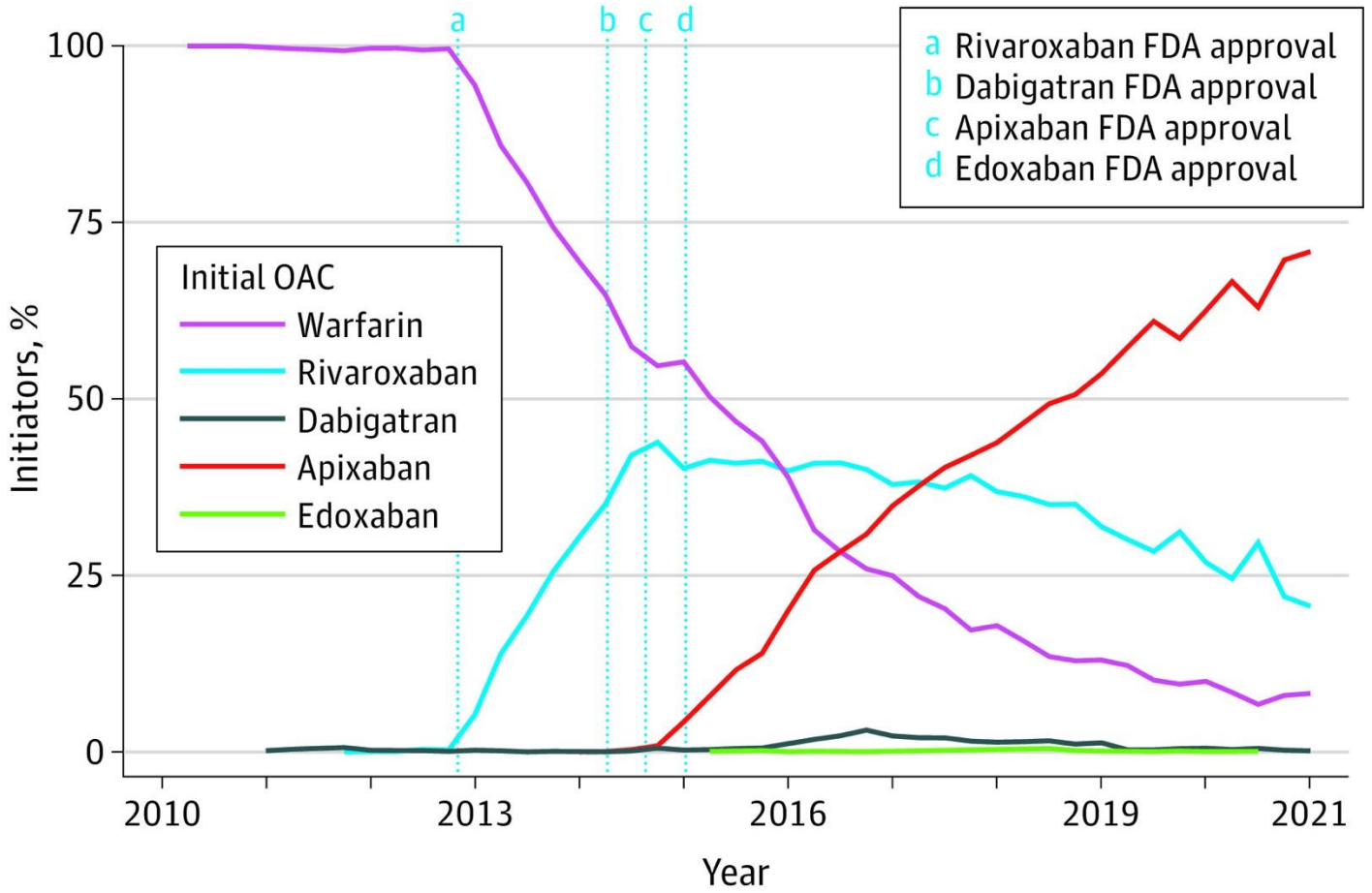
- Third to market
- Excellent efficacy and safety
- Straightforward maintenance dosing:

  usually 5 mg BID
- Help patients remember to take the evening dose (e.g., set alarm on smart phone)
- Manufacturer has remained laser-focused on AF and VTE
- Excels against competitors in prevention and treatment of VTE in oncology patients

Edoxaban

- Fourth (of 4) to market
- Resistance from insurers and formularies to include edoxaban as a DOAC option
- Once daily, with excellent absorption on a full or empty stomach: 60 mg daily (30 mg if CrCl 15-50)
- Effective and well tolerated
- The only DOAC superior to warfarin in preventing recurrent VTE
- Has a niche in treating geriatric patients (15 mg/day rather than 60 mg/day)

Trends in Use of Oral Anticoagulants With VTE in the US, 2010-2020



JAMA Network Open 2023; Mar 1; 6: e234059

Rivaroxaban vs. Apixaban for VTE

	Patients	Person-years	Events	Crude incidence per 100 person-years	Adjusted hazard ratio (95% CI)	p value
Recurrent venous thromboembolism						
Apixaban	3091	861	25	3	0·37 (0·24–0·55)	<0·0001
Rivaroxaban	12 163	3394	254	7	Ref	..
Major bleeding*						
Apixaban	3091	862	28	3	0·54 (0·37–0·82)	0·0031
Rivaroxaban	12 163	3400	188	6	Ref	..
Minor bleeding*						
Apixaban	3091	839	166	20	0·57 (0·48–0·67)	<0·0001
Rivaroxaban	12 163	3186	1082	34	Ref	..

Dawwas GK. Lancet Haematology 2018; Dec 14

CANCER / ACUTE VTE: DOAC vs. Dalteparin

DOAC	Trial Result
Edoxaban (Hokusai)	Better efficacy; Less GI safety; (NEJM 2018)
Rivaroxaban (SELECT-D)	Better efficacy; Less GI safety (J Clin Oncol 2018)
Apixaban* (Caravaggio)	Same efficacy; Same safety (NEJM 2020)

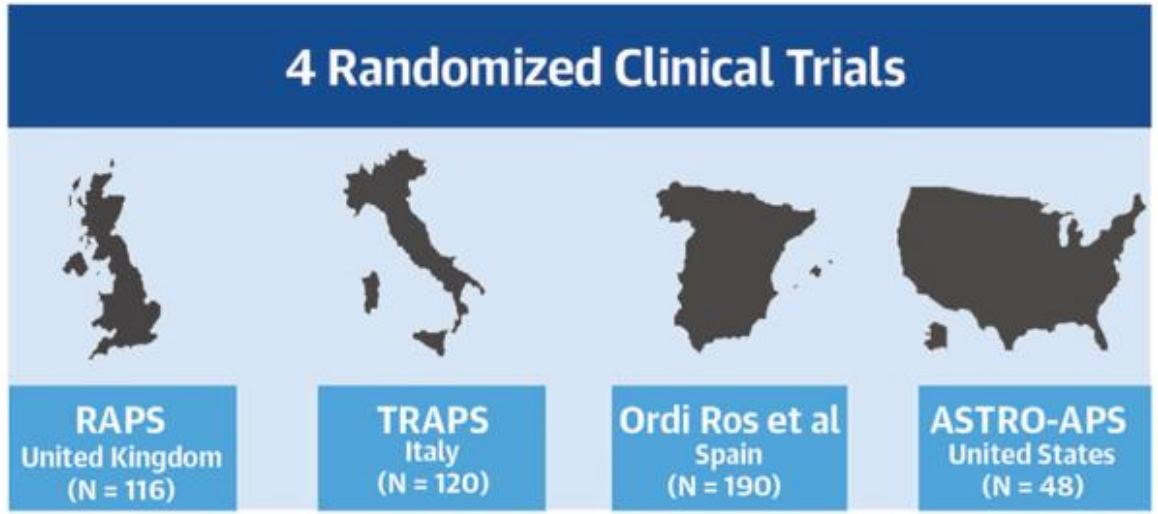
Warfarin: Multiple Problems

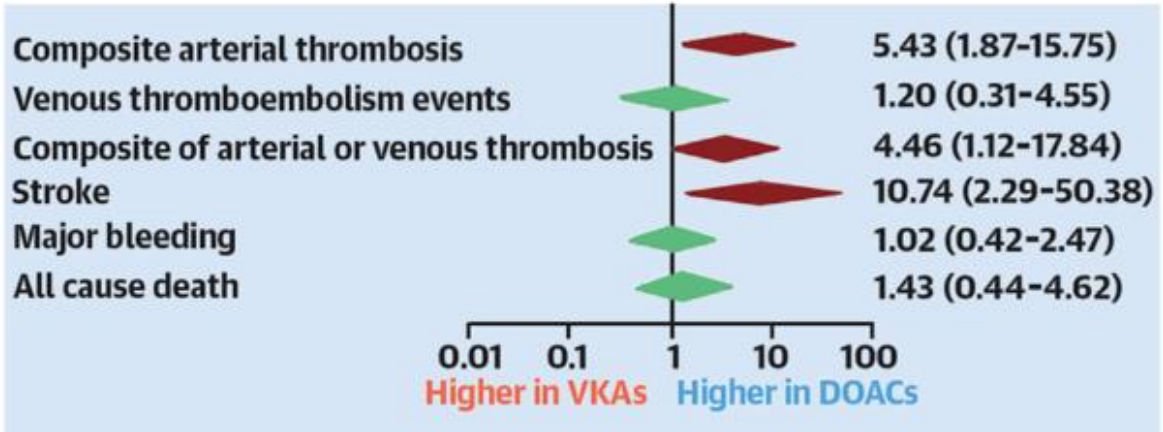
- High rate of major bleeding, even when INR is within the target range of 2.0 to 3.0
- Intracranial bleeds on warfarin: 40% are within the targeted therapeutic range
- More major bleeding compared with DOACs
- Inconvenience: blood draws, dose adjustments
- Hundreds of drug-drug interactions and drug-food interactions, especially with healthy green leafy vegetables

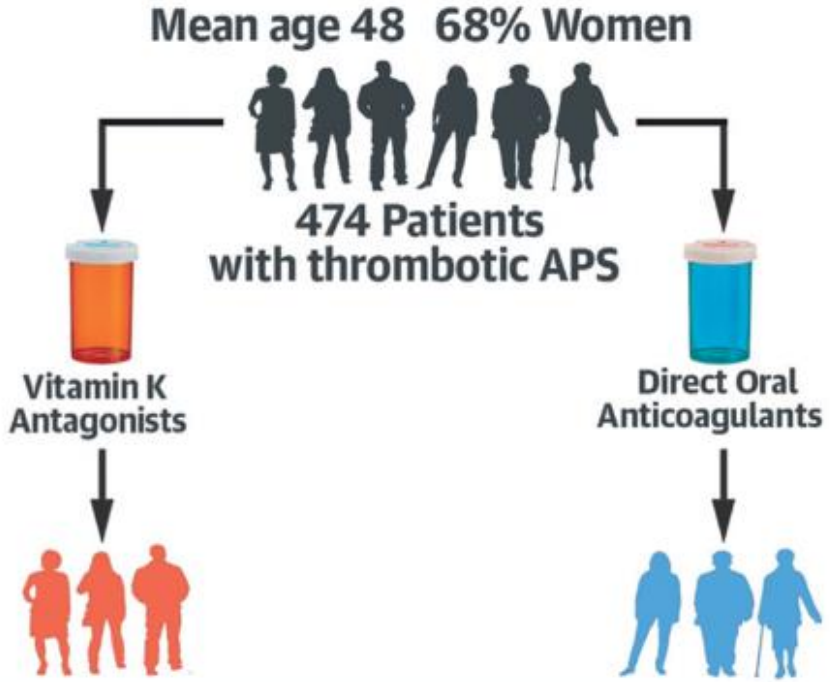
Status of Warfarin

- Coumadin® is no longer manufactured anywhere in the world.
- Coumadin® shares the fate of TWA, the Christmas Tree Shops, Filene's, Jordan Marsh, Oldsmobile
- Does this mean warfarin is dead?

DOACs vs VKAs on Thrombotic APLAS







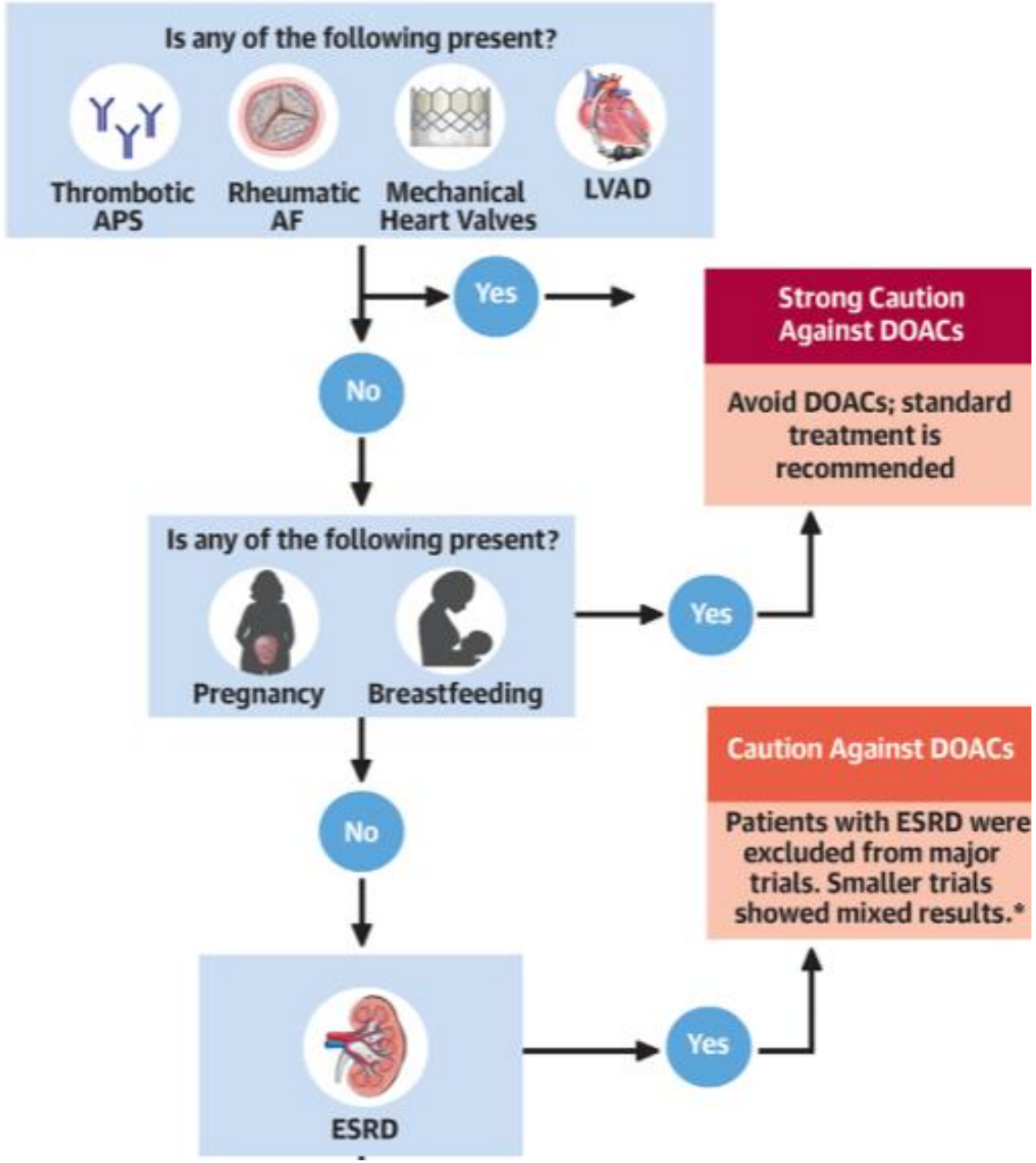
Use of DOACs Compared with VKAs was Associated with:

- Increased odds of arterial thrombotic events, especially stroke
- No change in the odds of VTE or major bleeding

Results were consistent within subgroups

JACC 2023; 81: 16-30

Cautions Against DOACs



Bejjani A, et al. JACC 2024; 83: 444–465

Warfarin: Multiple VTE Indications

- Monitor medication adherence
- Frail and obese patients
- APLAS
- Recurrent VTE or stroke 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

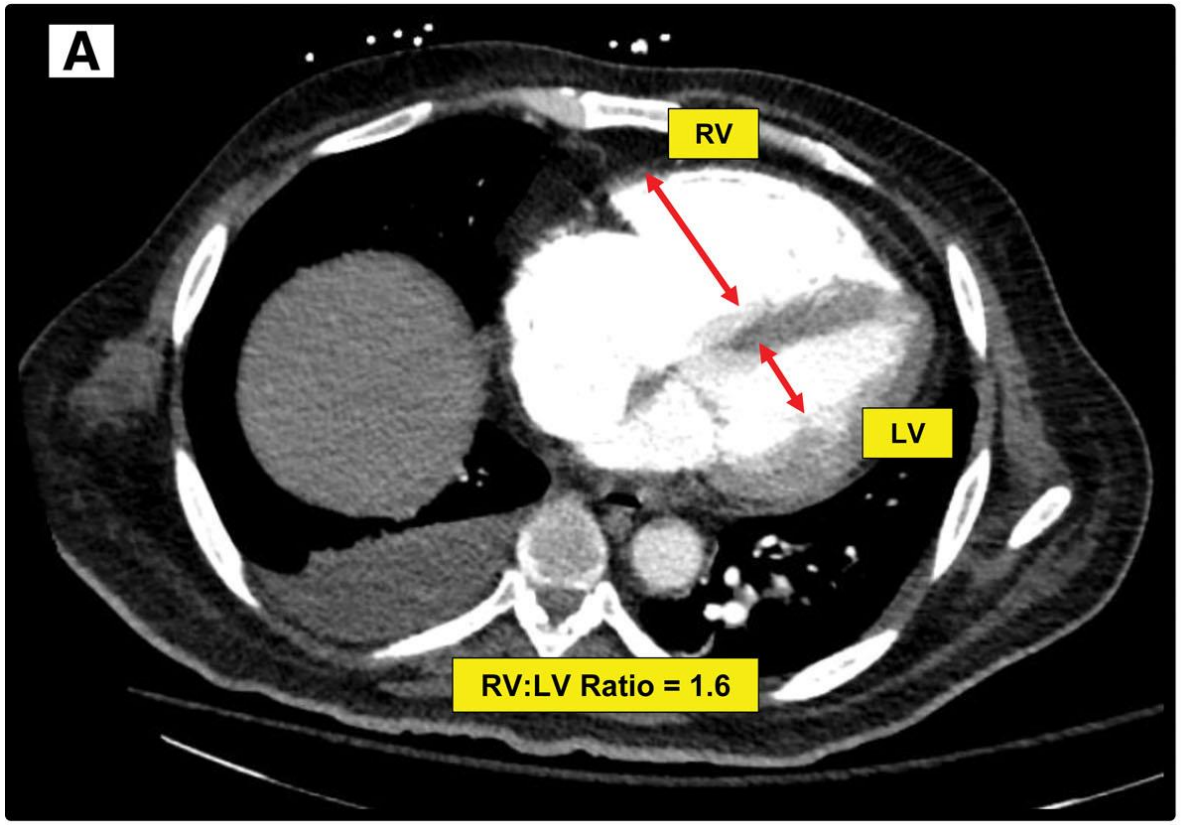
SZG Approach to Duration of VTE Anticoagulation: Queries prior to setting an “End Date”

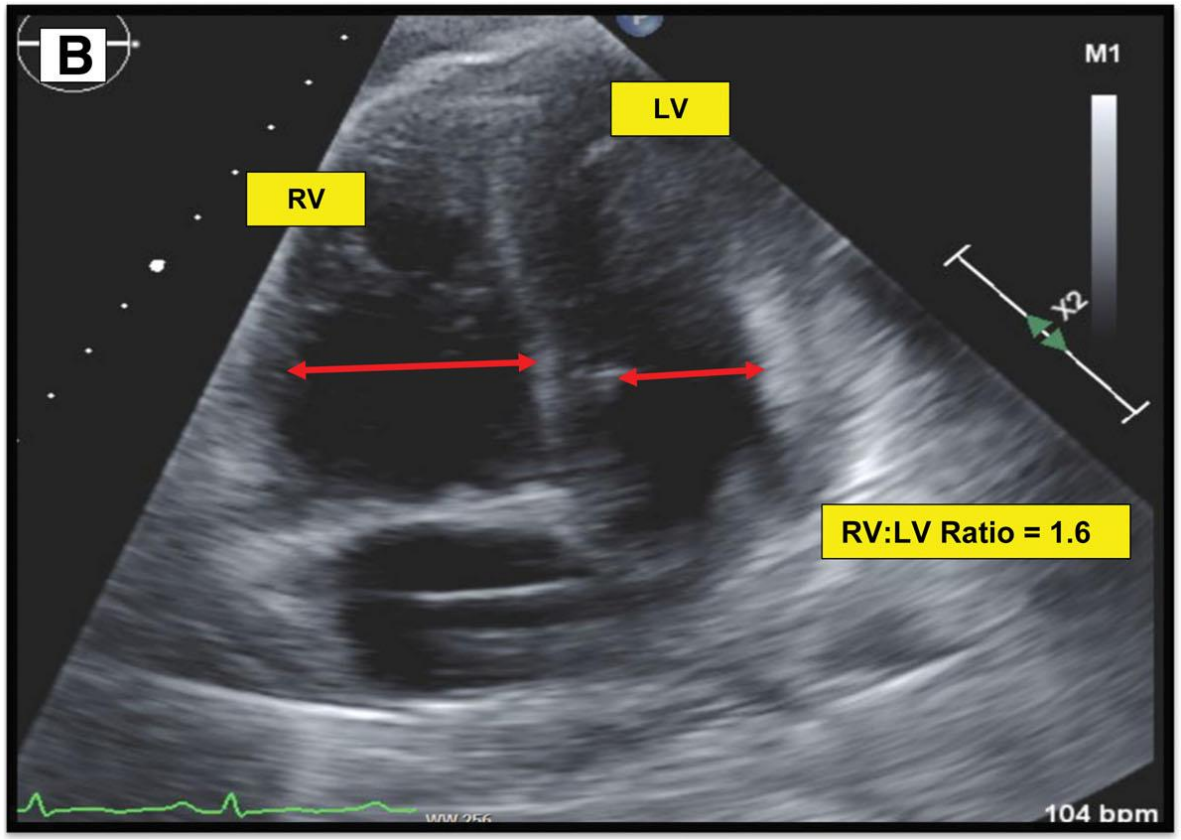
1) Is VTE a surrogate for high risk of MI, stroke, or DM2?—Check LDL-C, A1C, and FH
2) Is there a prior history of PE or DVT?
3) Is there lab evidence of APLAS?
4) Is there active cancer, possibly occult?
5) Are there CV risk factors that can be reversed: obstructive sleep apnea, cigarette smoking, sedentary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

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

Implementation of PE Reperfusion Rx

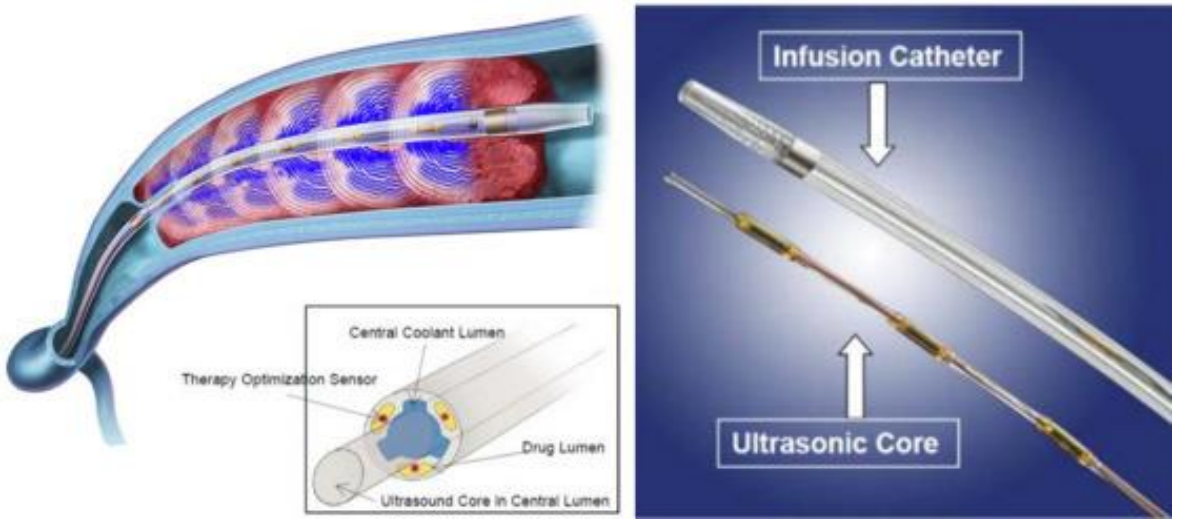
- Hemodynamic instability
- Severe/persistent RV dysfunction
- Lack of improvement/ deterioration
- Persistent hypoxia

Options for Reperfusion

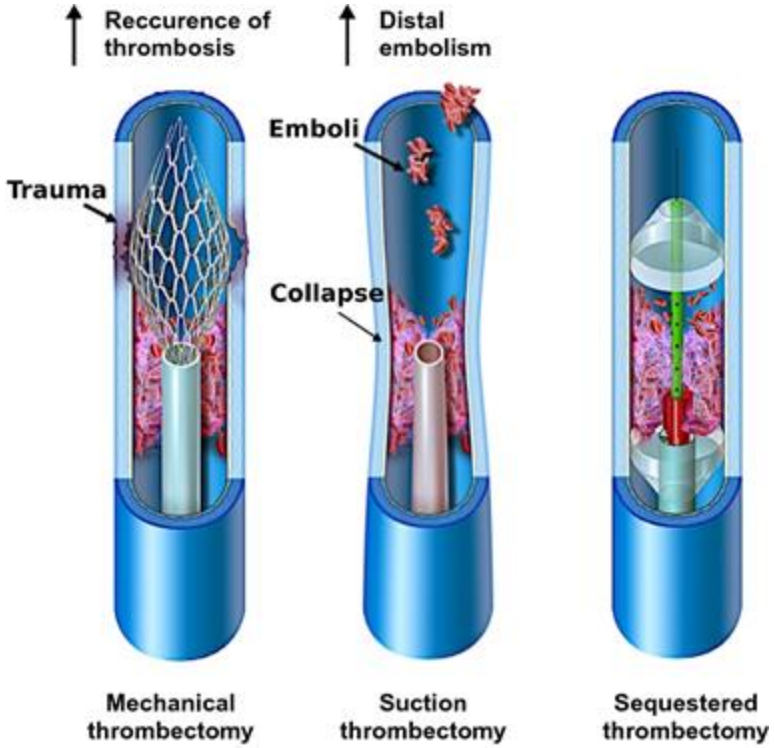
- Catheter-directed thrombectomy with or without low-dose TPA
- Ultrasound-facilitated catheter-directed fibrinolysis with low-dose TPA
- Surgical pulmonary embolectomy +/- ECMO
- Systemic (via peripheral vein) thrombolysis

What is “CDT” or Catheter-Directed Therapy?

Thrombolysis Catheter



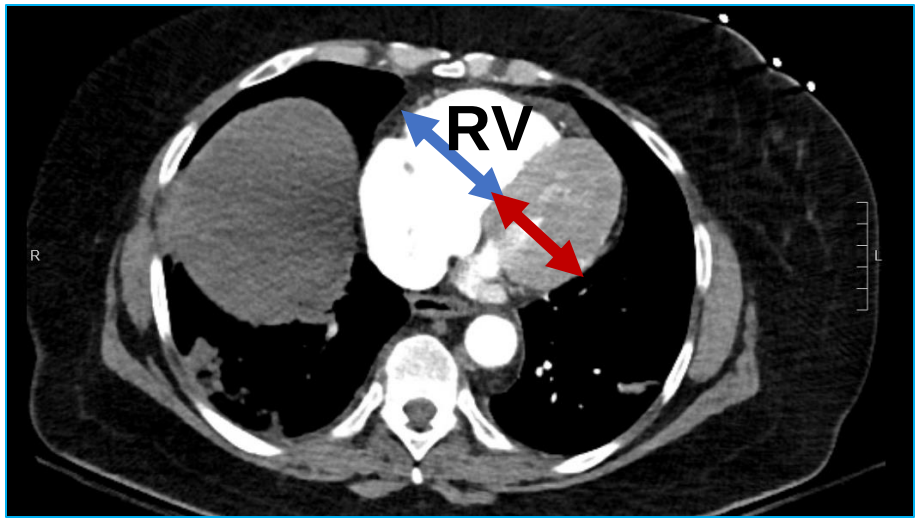
Mechanical Thrombectomy Catheter



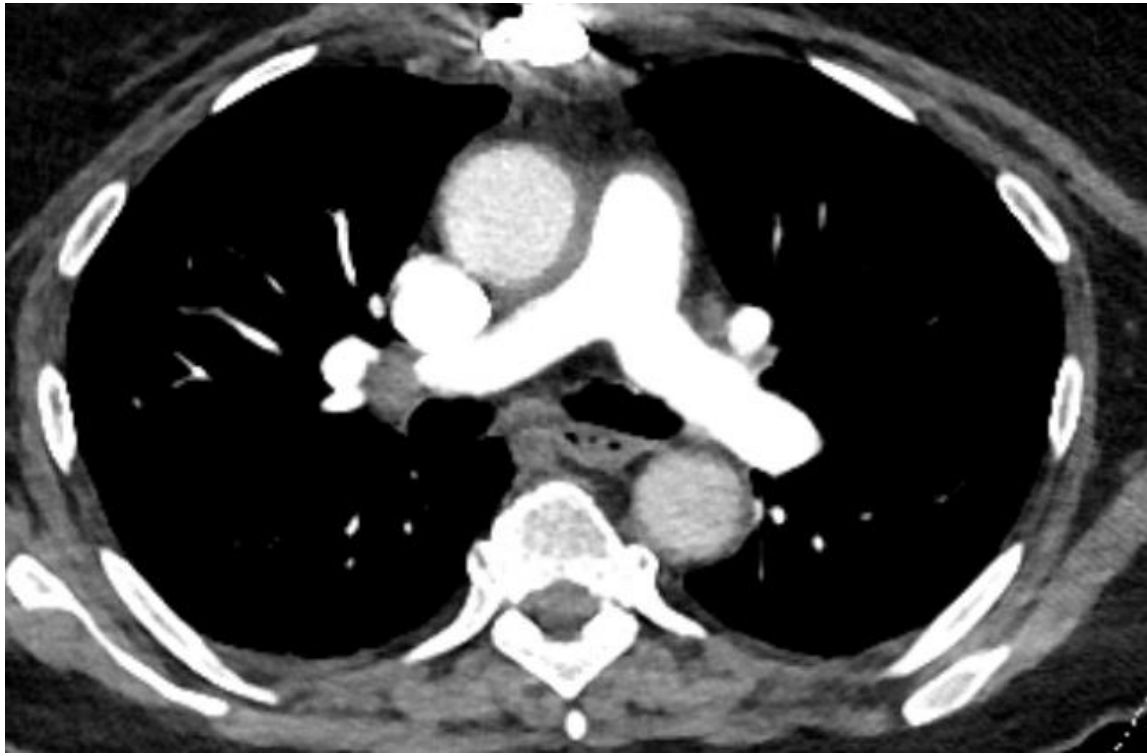
Rousseau Heliyon 2021
Ismail Scientific reports, Inari; Megavac

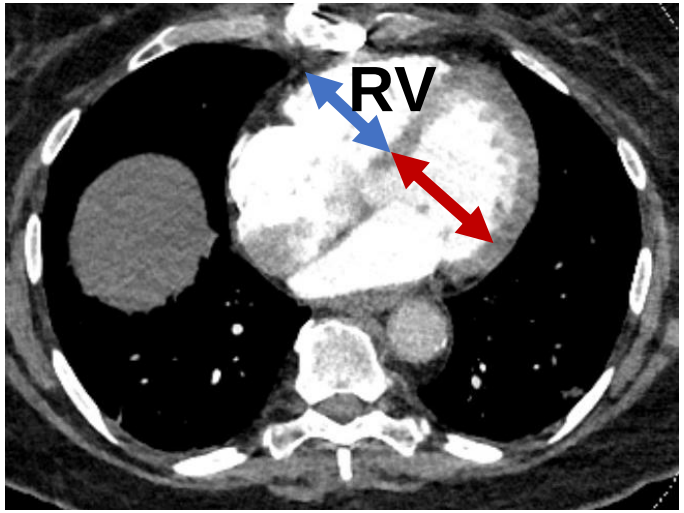
slide courtesy of Dr. Shari Brosnahan

Admission



Embolectomy: POD #40





Adjunctive Therapy for Massive PE

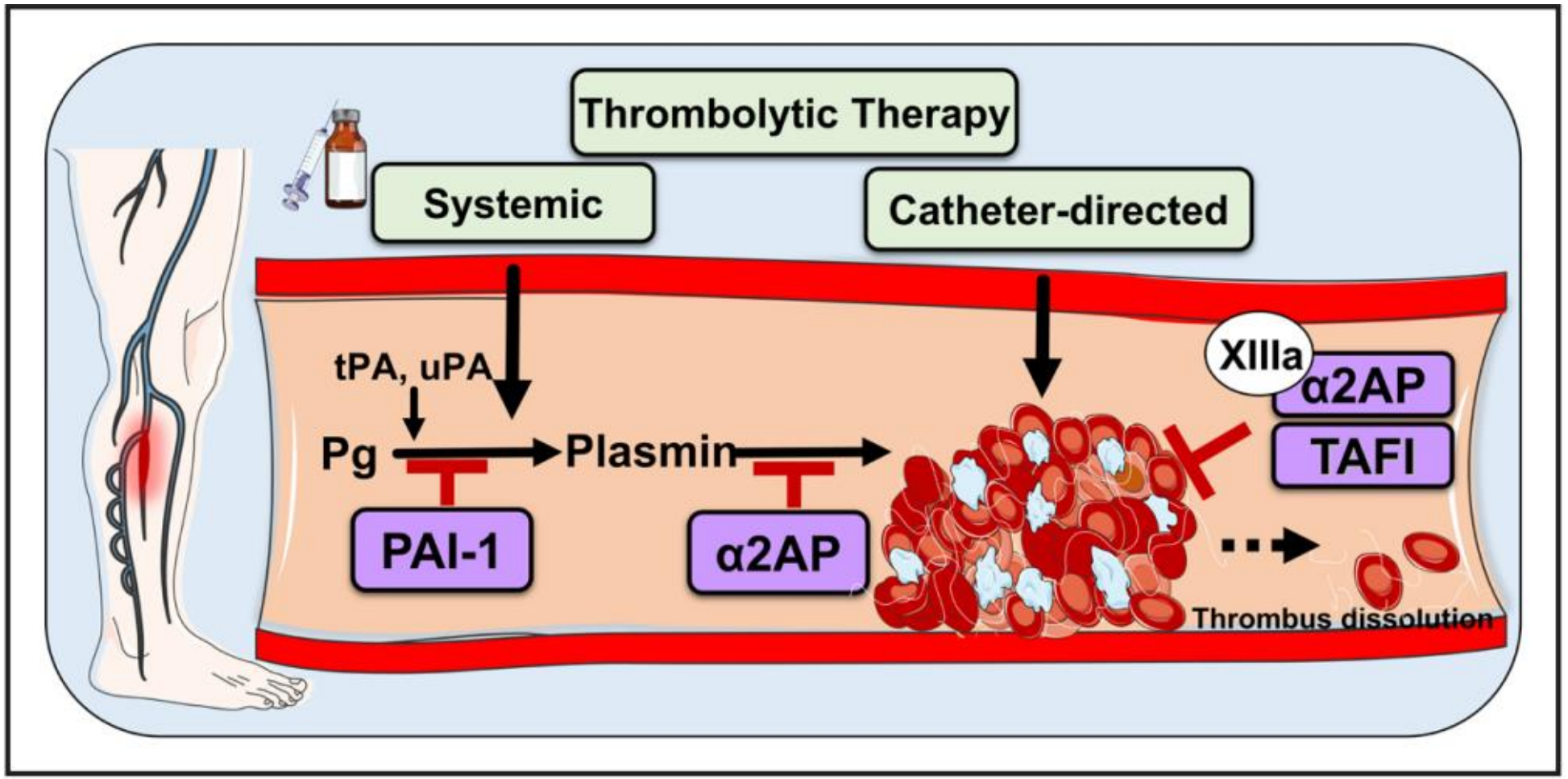
- Ensure excellent oxygenation
- Do not volume load the fragile RV with more than 500 ml to raise the BP
- Low threshold to begin pressors
    1) Norepinephrine
    2) Dobutamine

Targeting Fibrinolytic Inhibition to Treat VTE

- Fibrinolysis is rigidly controlled by endogenous fibrinolysis inhibitors, including α2-antiplasmin, plasminogen activator inhibitor-1, and thrombin-activatable fibrinolysis inhibitor.
- Accelerated, safe, and effective fibrinolysis may be achieved by therapeutically targeting these fibrinolytic inhibitors.

Circulation 2024;150: 884–898

Targeting Fibrinolytic Inhibition to Treat VTE



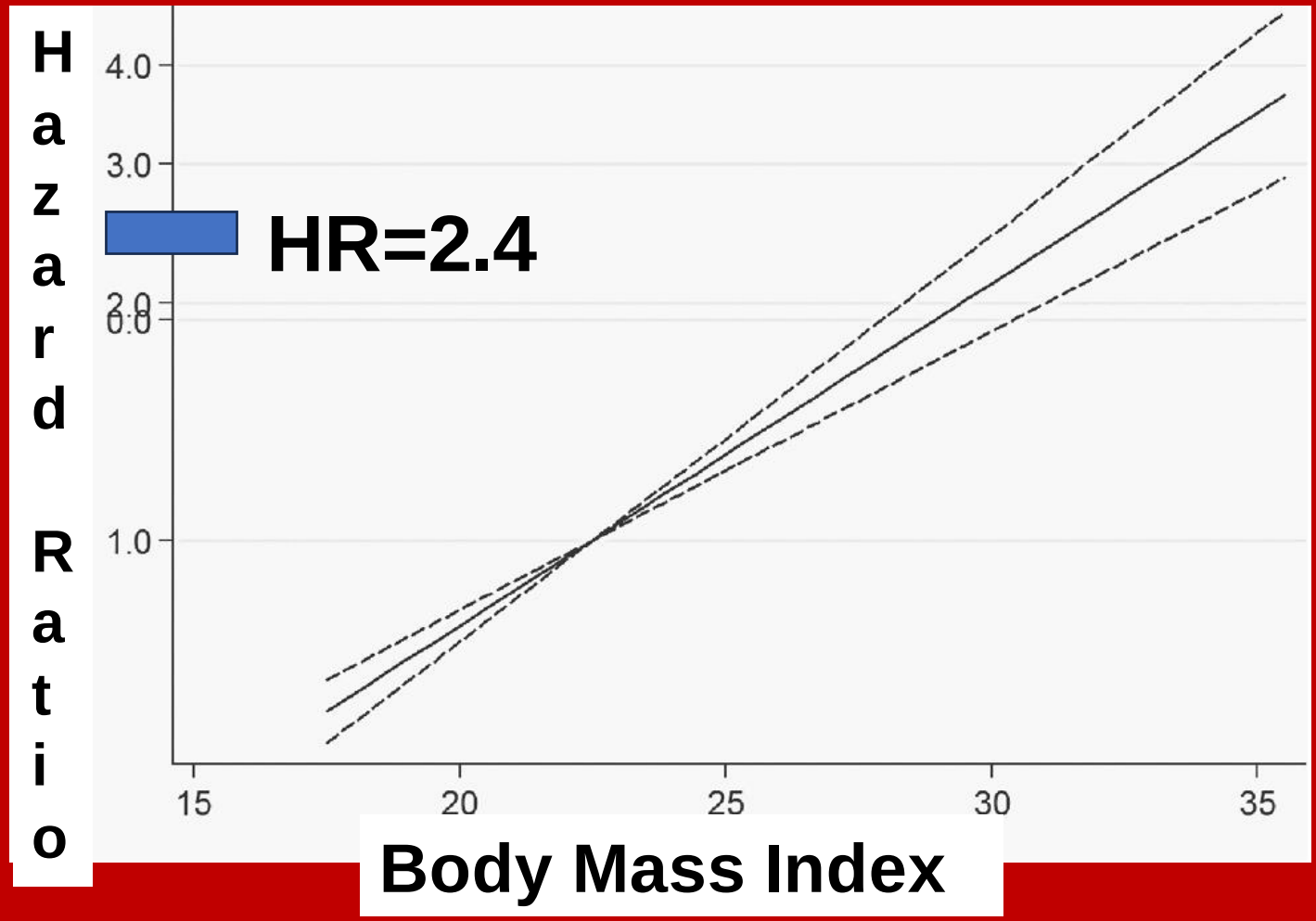
Circulation 2024;150: 884–898

Prevention of PE:

Impact of Obesity and

Weight Management

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



Thrombosis Research 2020; 192: 64-72

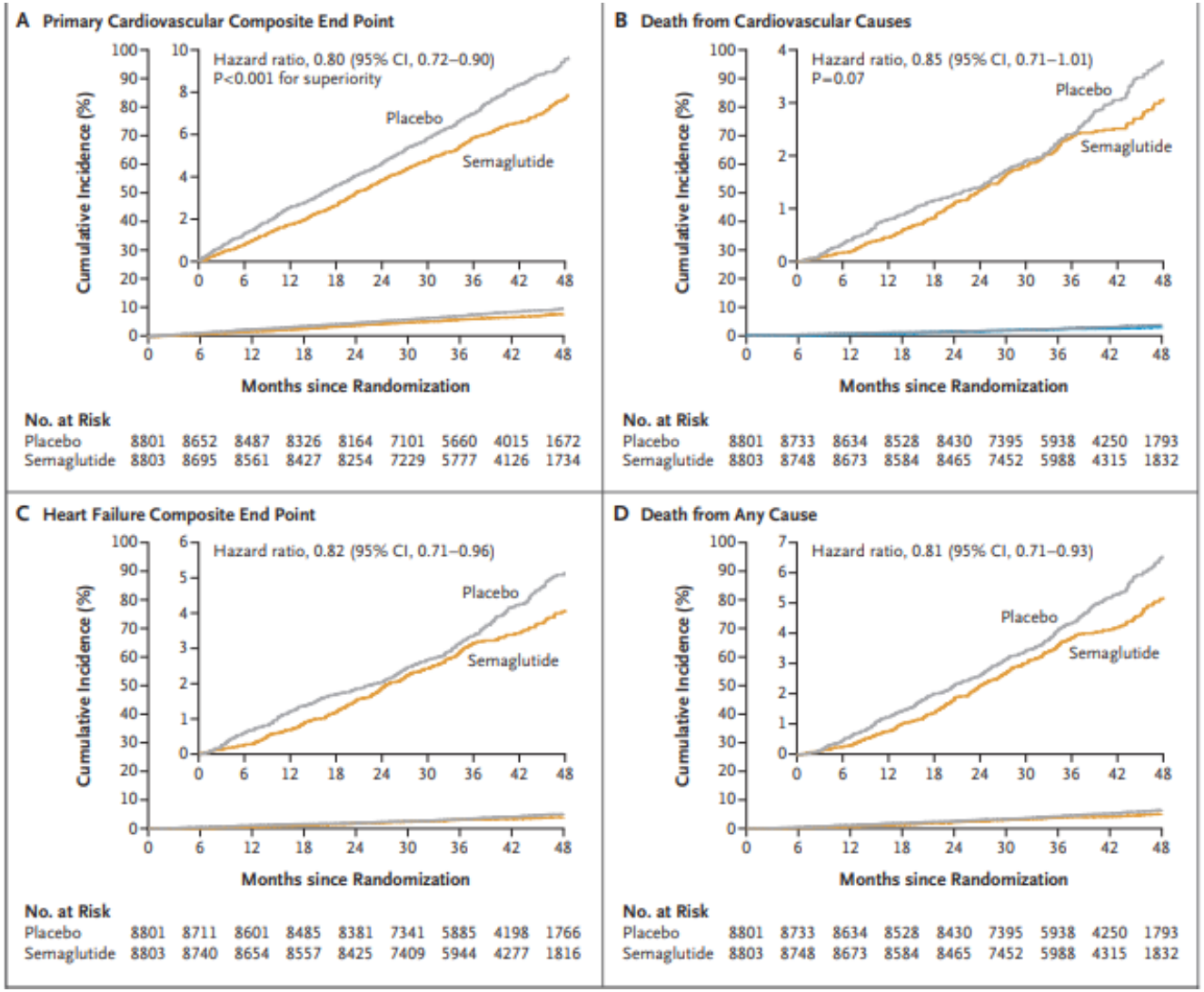
Semaglutide: Generic Name for 3 Drugs with Different Indications/ Dosing

1. WEGOVY—FDA approved for Weight Management and for Reduction of MI and Stroke in Obese Patients; administered SC
2. OZEMPIC—FDA approved for Improving Glycemic Control; administered SC
3. RYBELSUS— FDA approved for Improving Glycemic Control; administered by mouth

1) Medicare to Cover Wegovy for Patients at High CV Risk

2) 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

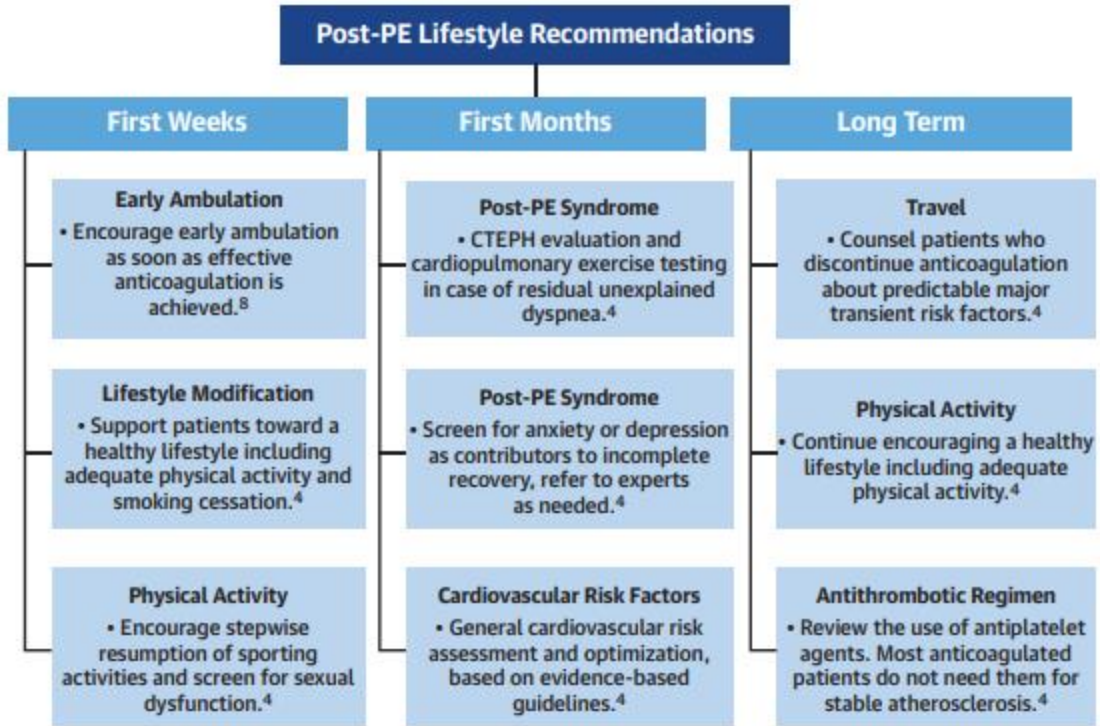
Take Home Points

- Mortality from MI, stroke, and PE: increasing in US
- Inflammation (e.g., psoriasis) increases VTE risk
- Post-PE Impairment: common (16%), lowers QOL
- Apixaban surpasses rivaroxaban: efficacy/ safety
- Warfarin: alive but underutilized
- Optimal duration of anticoagulation: controversial
- Advanced therapy: systemic lysis, catheter-based—with or without TPA, surgical embolectomy, ECMO
- PE prevention by emphasizing Weight Management

References

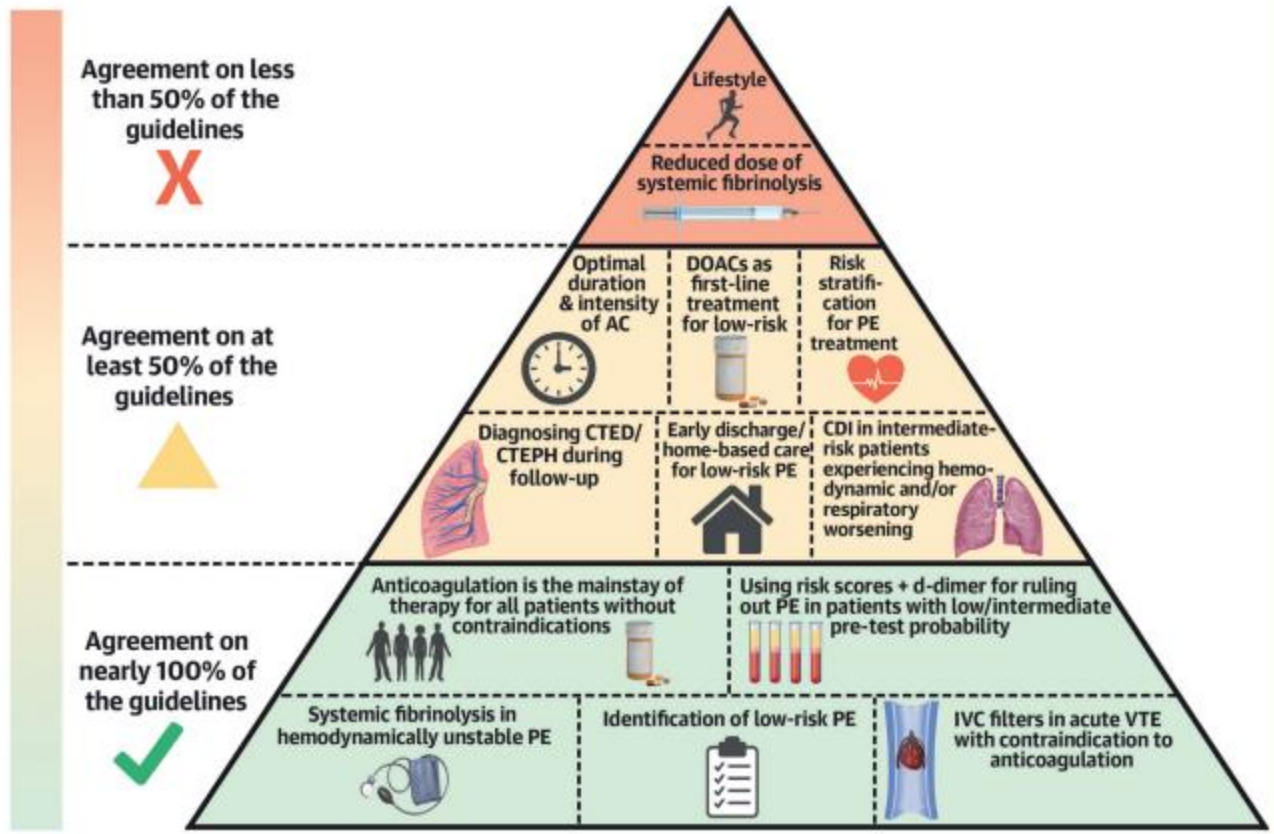
- ESC Guidelines for acute PE. Eur Heart J 2020; 41: 543
- PE and SES. Circ CV Qual Outcomes. 2024;17: e010090
- Apixaban VTE Mortality Reduction. JTH 2023; 21: 953
- Apixaban vs Rivaroxaban. JTH 2024; 57: 453–465
- PE Mortality. Thrombosis Research 2023; 228: 72-80
- Anticoagulation Duration. Eur Heart J 2023; 44: 1245
- SZG. ECMO/ Surgical Embolectomy. JACC 2020; 76: 912
- GLP-1 Physiology: Am Heart J 2020; 229: 61-69
- SELECT RCT: WEGOVY (N=17,604). NEJM 11/11/23
- Bariatric Surgery: JACC 2022; 79:1429-1437

FIGURE 5 Summary of Post-PE Lifestyle Recommendations



Resumption of ambulation is recommended upon starting therapeutic anticoagulation,[72] with activities escalated as tolerated. Lifestyle modifications and cardiovascular risk optimization should be considered both initially and during follow-up visits. Early follow-up should assess symptoms of post-pulmonary embolism (PE) syndrome and consider testing exercise limitations as a sign of for chronic thromboembolic pulmonary hypertension, along with mental health screening. Long-term follow-up should counsel on prophylactic measures if anticoagulation is discontinued, and major surgery is upcoming. Most with stable atherosclerotic cardiovascular disease on anticoagulation likely do not need continued antiplatelet therapy.[57]

CENTRAL ILLUSTRATION **Consensus on Pulmonary Embolism Care Across U.S. and European Guidelines**



Zuin M, et al. JACC. 2024;84(16):1561-1577.

PE remains a major cardiovascular cause of mortality, despite clinical advancements. Clinicians encounter challenges in determining optimal anticoagulant strategies and interventions mainly because of the heterogeneity and uncertainty exhibited across numerous international guidelines. Among these guidelines, general agreement exists on most PE care recommendations, with variability in specifics. There is notable lack of consensus regarding lifestyle and usage of reduced dose of systemic fibrinolysis. AC = anticoagulation; CDI = catheter-directed intervention; CTED = chronic thromboembolic disease; CTEPH = chronic thromboembolic pulmonary hypertension; DOAC = direct oral anticoagulant; IVC = inferior vena cava; PE = pulmonary embolism; VTE = venous thromboembolism.