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

Hospital Management of PE and DVT

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October 7, 2024

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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- Harvard Medical School
- Medicine Residency @BWH
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- 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:

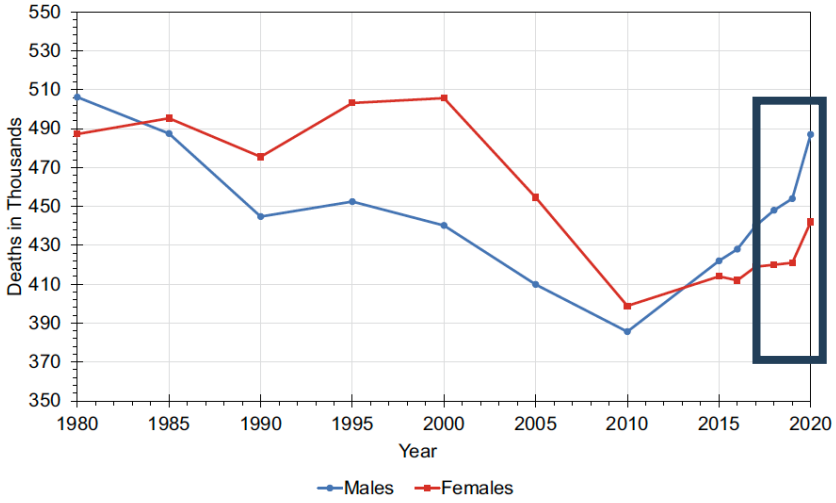
Bayer, BMS, Boston Scientific, Janssen, NHLBI

Consultant Support:
None

Learning Objectives: VTE Update

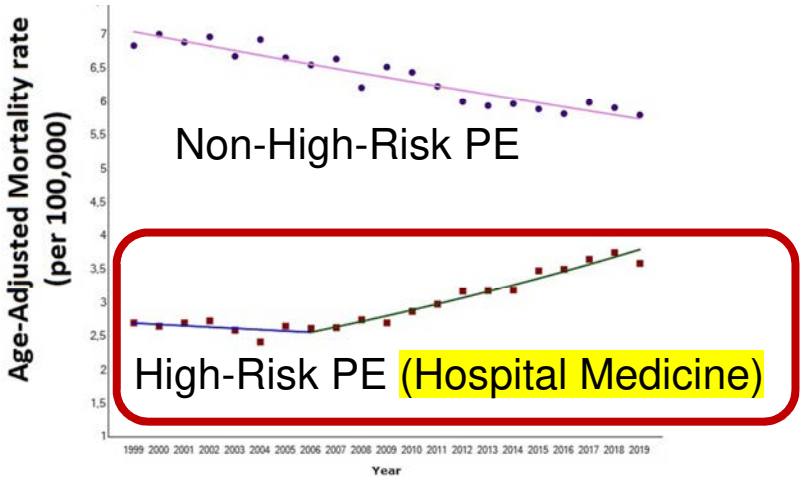
- Epidemiology: Socioeconomic Status/ VTE
- Artificial Intelligence: Diagnosis of PE
- Inflammation-linked conditions trigger VTE
- Post-PE and Post-Phlebitic Syndrome
- DOACs: a) Rivaroxaban vs apixaban
  b) Is warfarin dead?
- Optimal duration of anticoagulation: My approach
- Advanced management of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

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

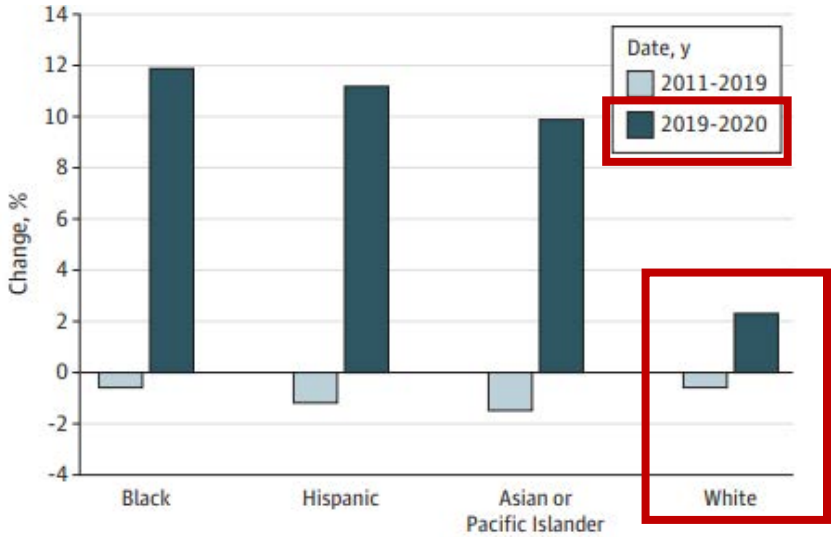


Thrombosis Research, 2023-08-01, Volume 228, Pages 72-80

Epidemiology

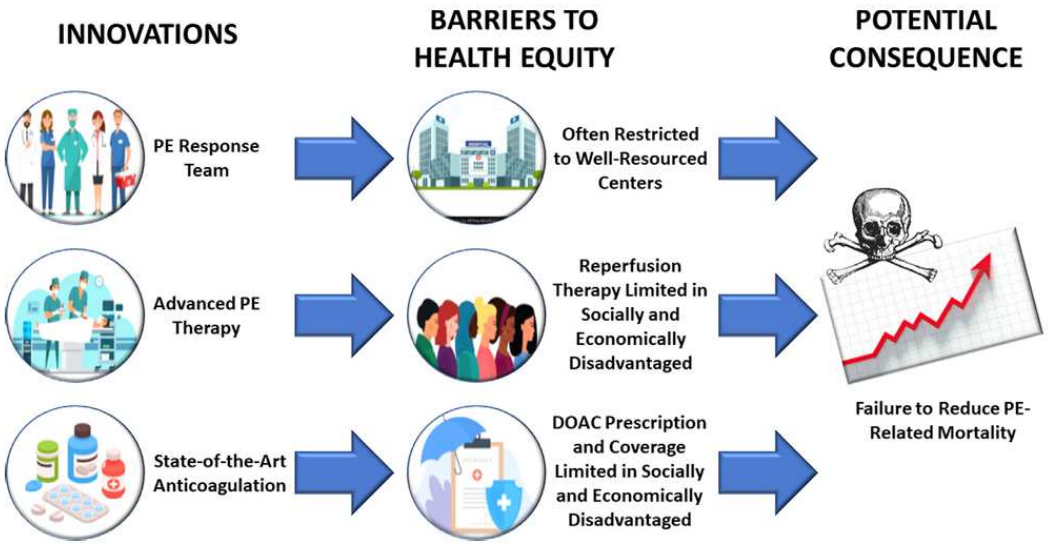
Does Socioeconomic Status Play a Role?

2019-2020: Increased Heart Disease Deaths: Race and Ethnicity



(JAMA Network Open 2022; March 23)

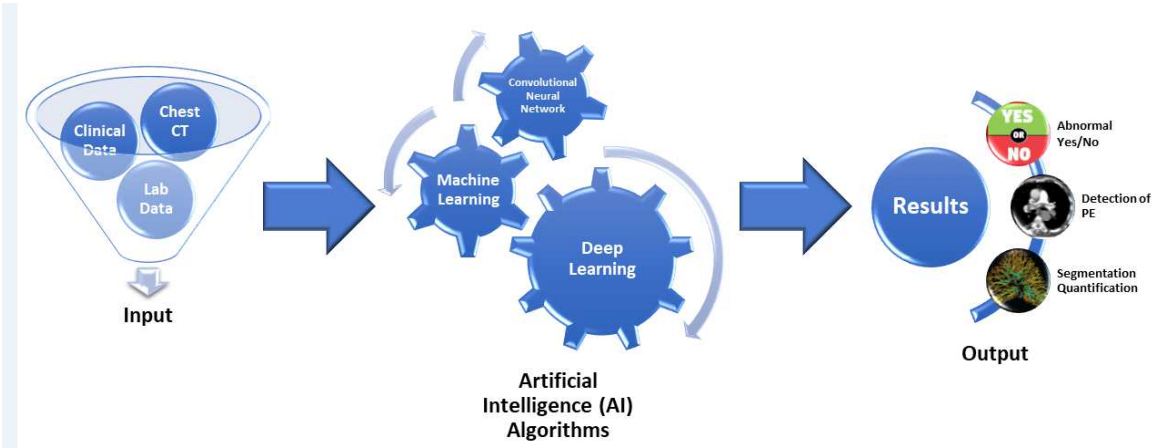
Health Equity Barriers in PE



Piazza G. JTH 2024; 22: 1838-1840

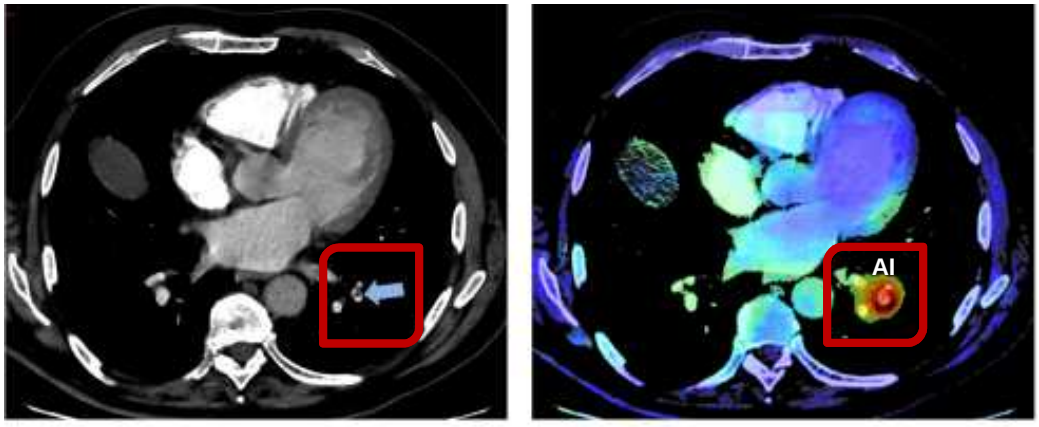
AI-Assisted Diagnosis and Pathophysiology

Artificial Intelligence (AI)-Assisted Diagnosis of PE



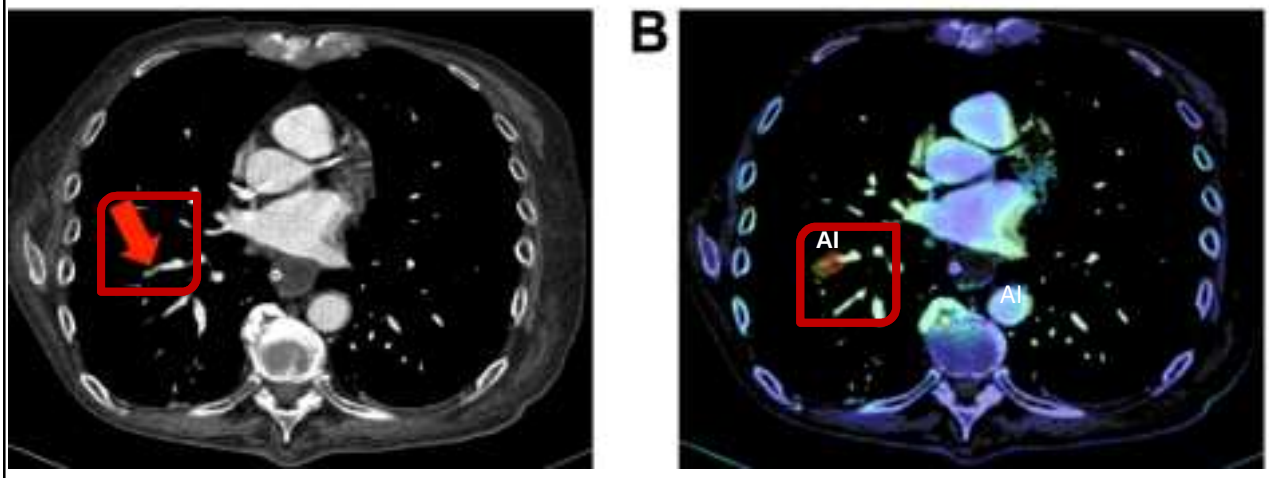
Inputs: chest CT, clinical data, and lab results. Neural networks identify repeating patterns of abnormalities. Natural language processing identifies risk factors, symptoms, and signs to generate clinical probability. Outputs: any abnormality, detection of PE, and localization/ quantification of PE.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

Risk Factors (e.g., inflammation) for VTE and

Tips for Follow-Up

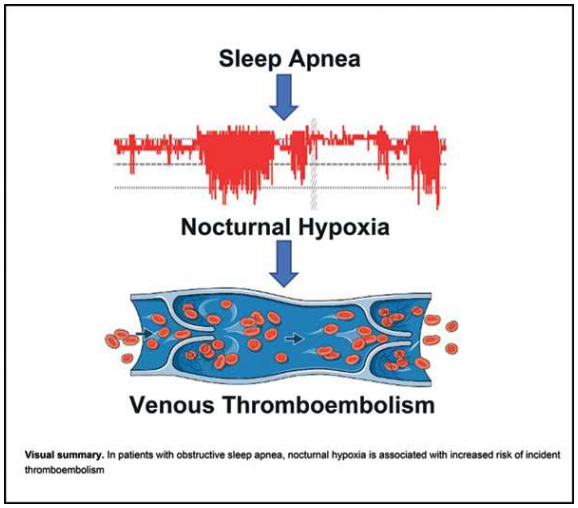
Lab Tests of Hypercoagulability

- 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

Inflammation-Linked Conditions that Can Trigger PE or DVT

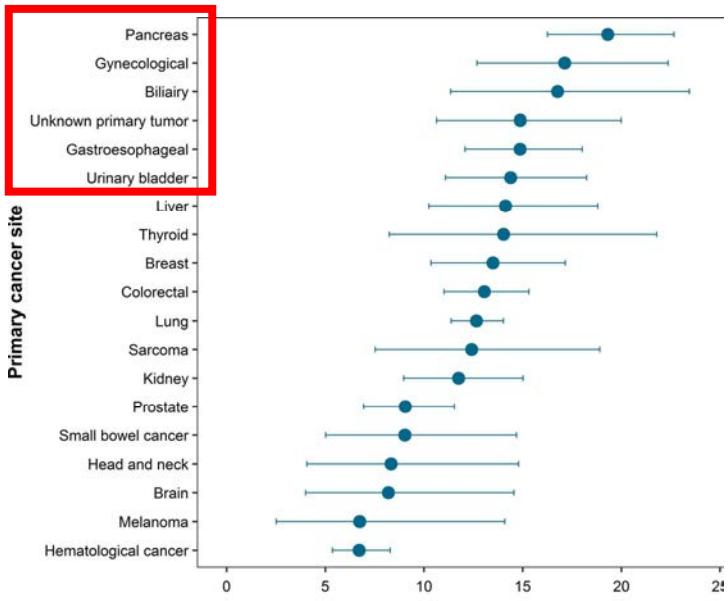
- Ulcerative colitis/ Crohn's disease
- Rheumatoid arthritis/ psoriasis
- Elevated LDL cholesterol or LP(a)
- Obesity/ metabolic syndrome
- Acute coronary syndrome/ stroke
- Pneumonia/ COPD
- Cigarette smoking

In OSA, nocturnal hypoxia is associated with increased VTE



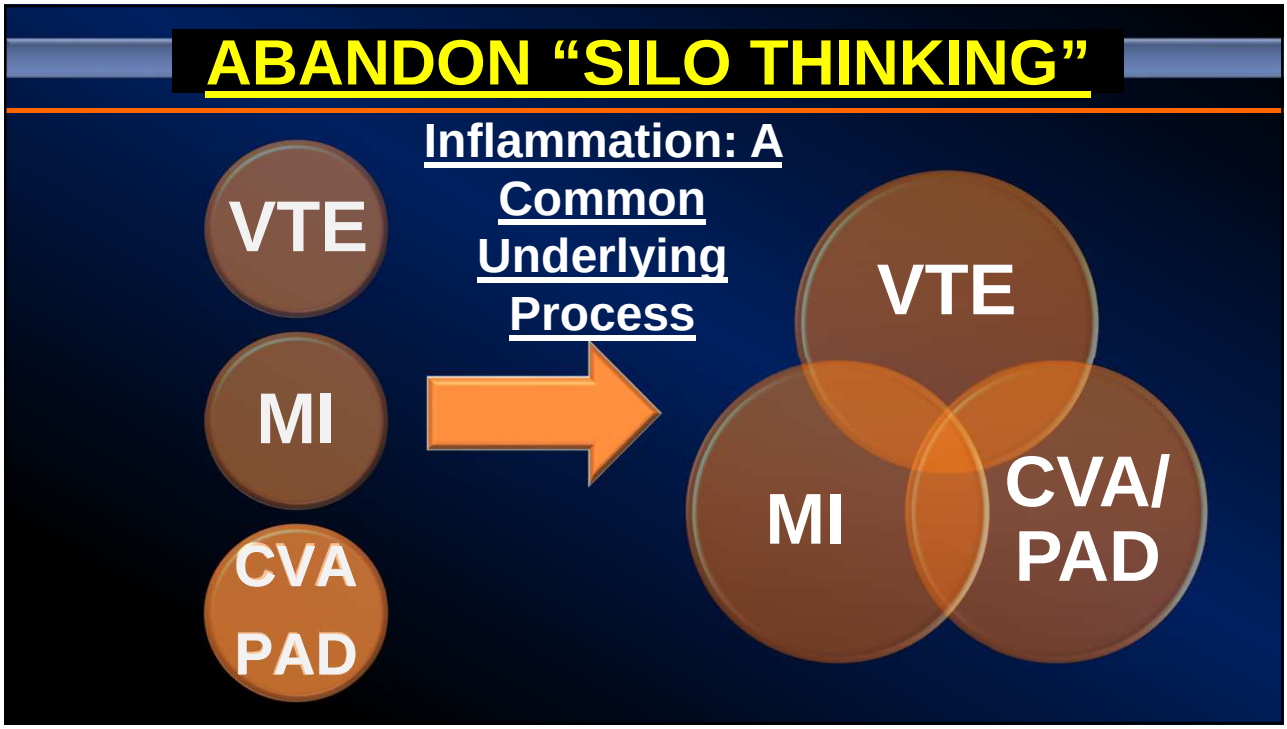
Thromb Haemost 2023; 123: 393-401

Cancer Sites in PE Patients



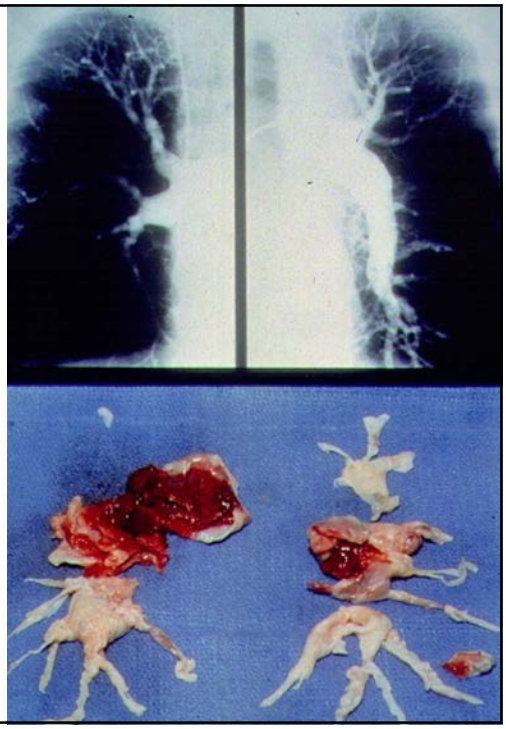
(Gimbel IA. JTH 2021; 19: 1228-1235)

ABANDON "SILO THINKING"



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

Post Phlebitic Syndrome

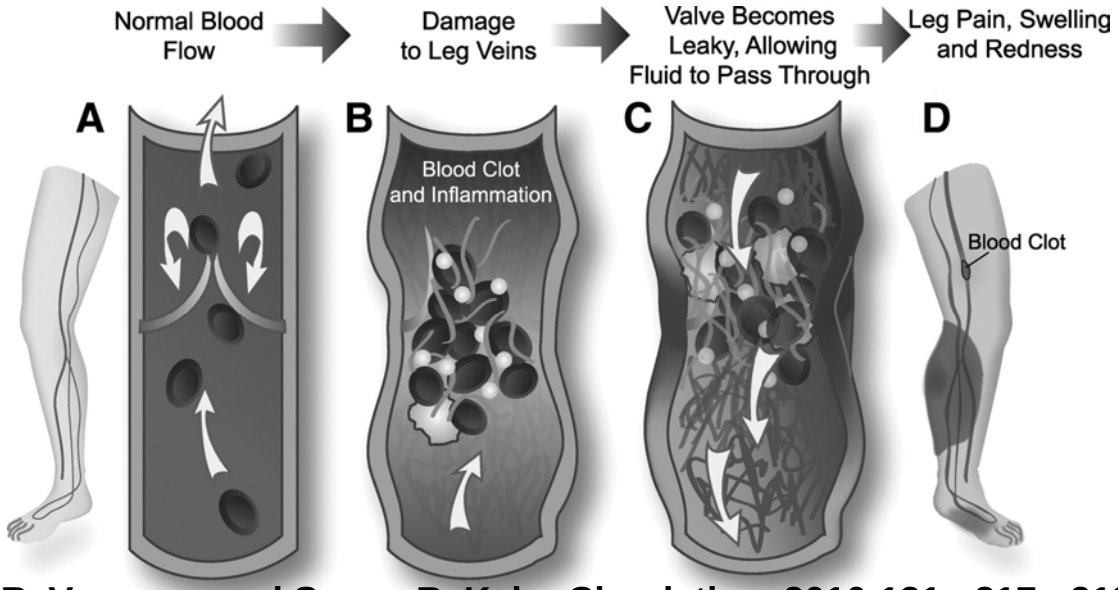
- Diagnosed clinically in patients with chronic venous insufficiency and a DVT ≥ 3 months previously
- Within two years after a DVT, 20–50% of patients will develop post phlebitic syndrome
- PTS: the main determinant of QOL after DVT
- PTS after a first distal DVT is less common than after a first proximal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

Post Thrombotic Syndrome (PTS)

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

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

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

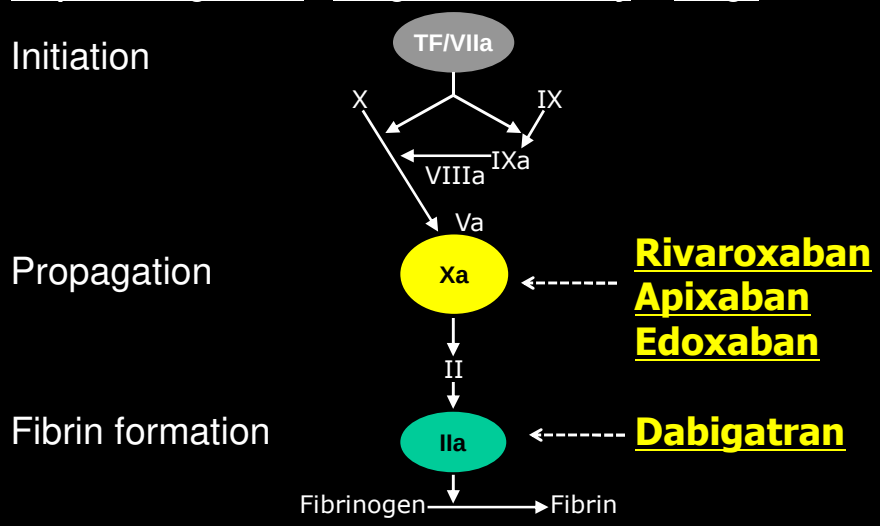
Chronic Edema/ Advanced Pigment Changes

Venous Stasis Ulcer

VTE Management Strategy

- **Rivaroxaban vs apixaban for VTE**
- **Is Warfarin Dead?**

DOACS: SITES OF ACTION



(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
- 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

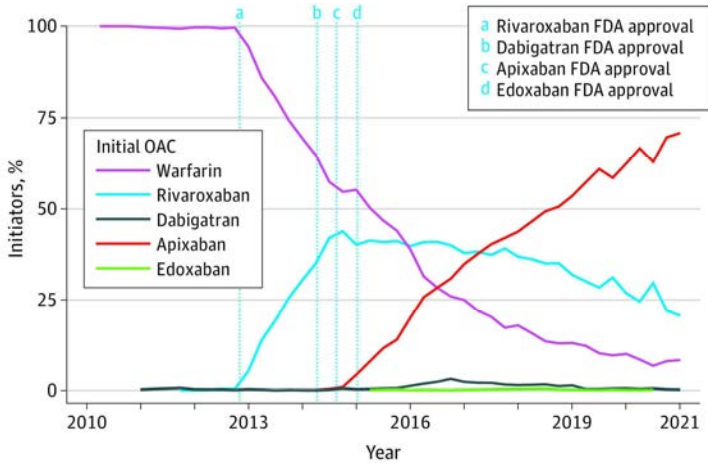
Apixaban

- Third to market
- Excellent efficacy and safety
- Straightforward dosing: either 2.5 mg or 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
- 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)

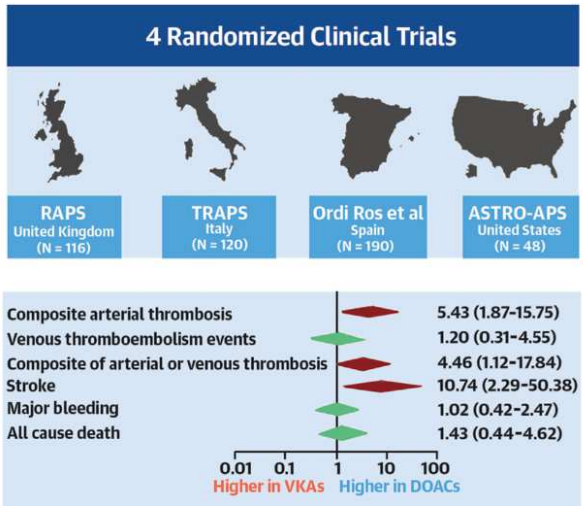
Warfarin: Multiple Problems

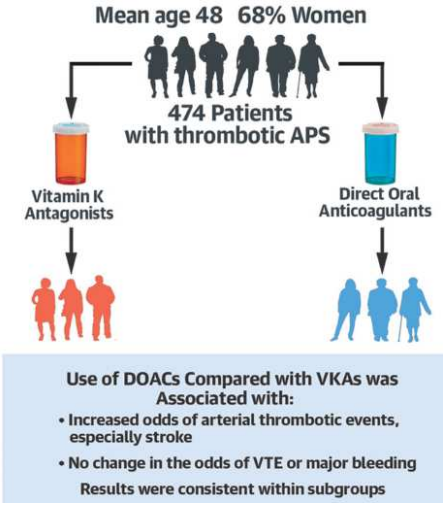
- High rate of major bleeding, even when INR is within the target range of 2.0 to 3.0
- Intracranial bleeds on warfarin: 40% are within the targeted therapeutic range
- More major bleeding compared with DOACs
- Inconvenience: blood draws, dose adjustments
- Hundreds of drug-drug interactions and drug-food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



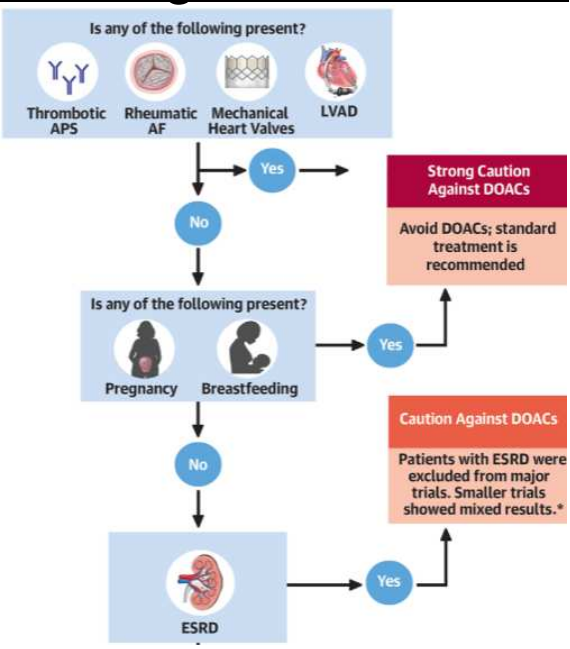


JACC 2023; 81: 16-30

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

Cautions Against DOACs



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

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**

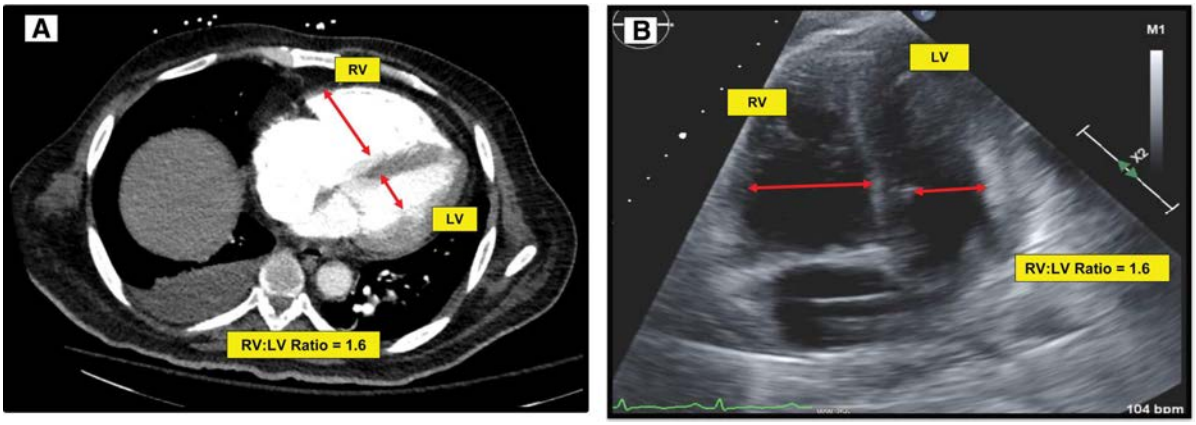
SZG Approach to Duration of VTE Anticoagulation: Queries prior to setting an "End Date"

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



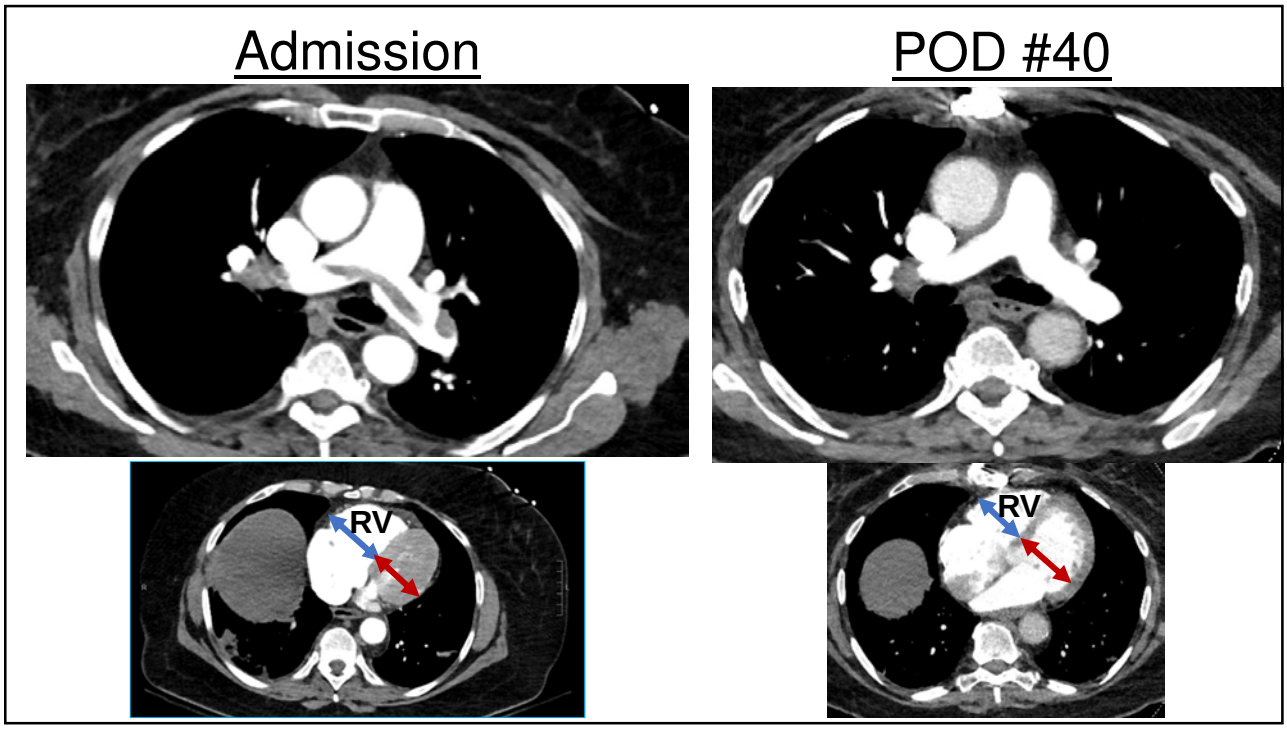
Circulation 2023; Jan 23. 147: e628–e647. AHA Scientific Statement

Options for Reperfusion

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

Factors Favoring PE Reperfusion Rx

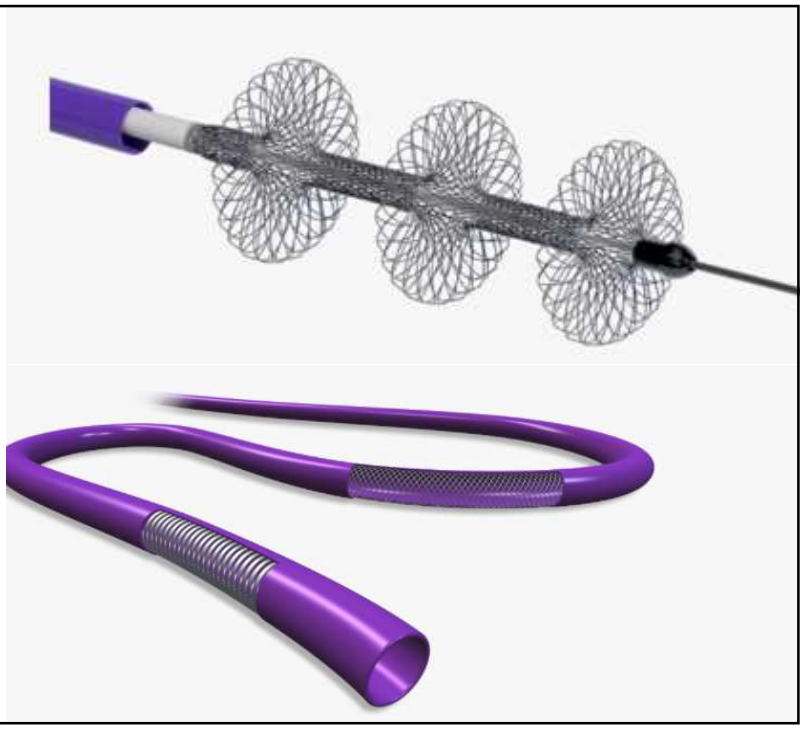
- Hemodynamic instability
- Severe/persistent RV dysfunction
- Lack of improvement/ deterioration
- Persistent hypoxia



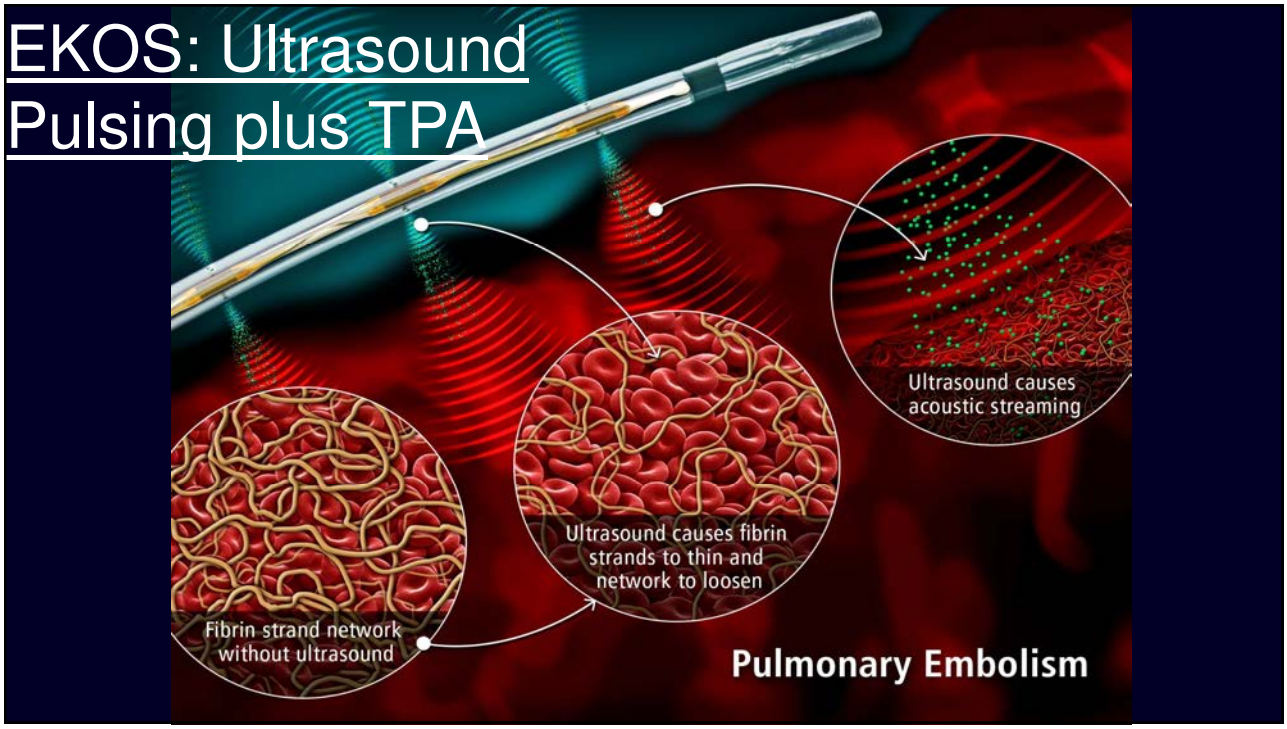
Adjunctive Therapy for Massive PE

- 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

FlowTriever: 20F—No TPA



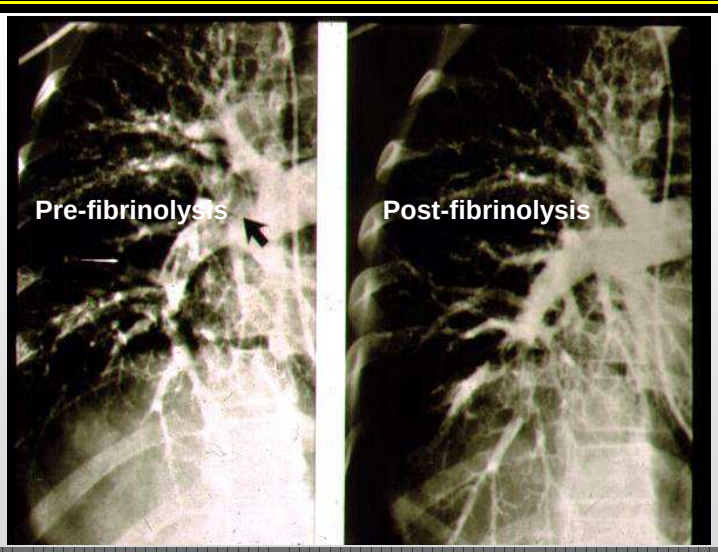
EKOS: Ultrasound Pulsing plus TPA



Systemic Thrombolysis

- Decreases the death rate by 35-50% but 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.
- Consider systemic lysis if:
  - The patient is otherwise young and healthy
  - IR, interventional cardiology, cardiac surgery cannot be mobilized quickly

THROMBOLYSIS IN SUBMASSIVE PE: RAPID ANGIOGRAPHIC IMPROVEMENT



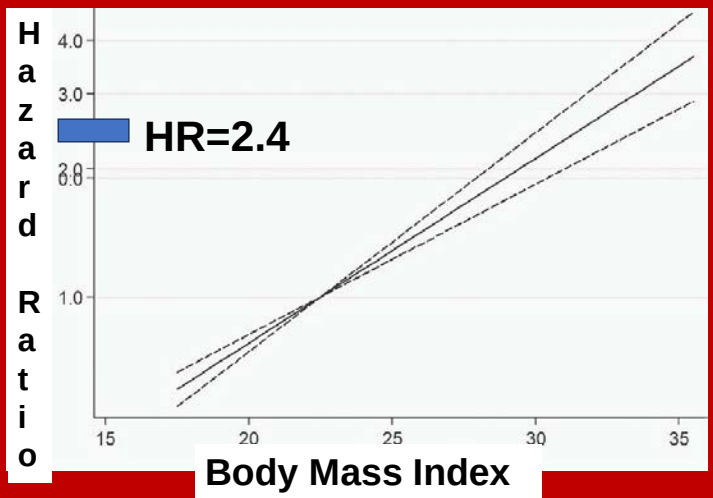
Atlas of Vascular Disease, 3rd ed.

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

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

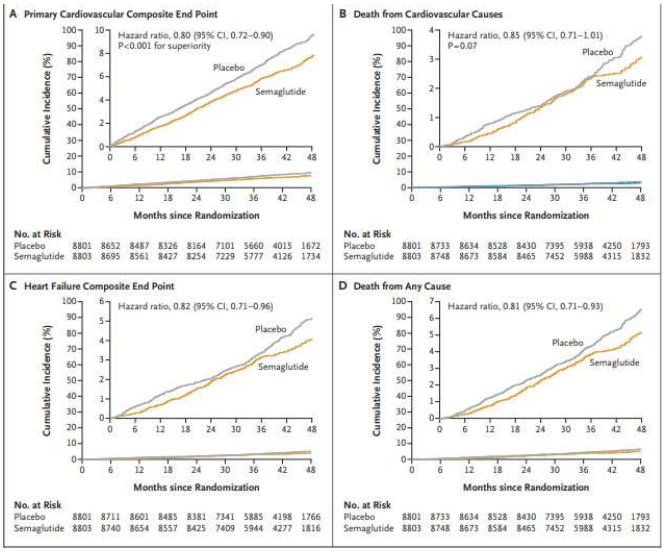
1) **Medicare to Cover Wegovy for Patients at High CV Risk**

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

GLP-1 Physiology

Am Heart J 2020; 229: 61-69

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