Management of Venous Thromboembolism

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TEACHING AFFILIATE

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Disclosures

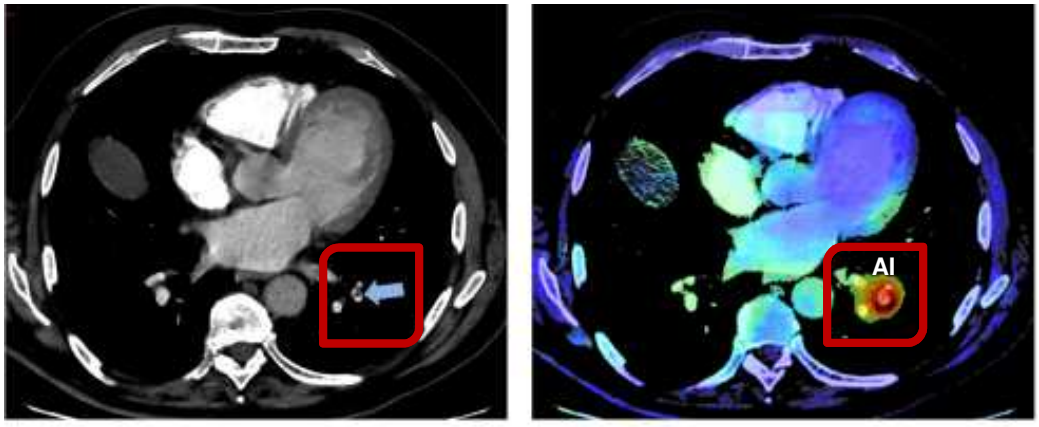
Research Support:

- Bayer; BMS; Boston Scientific EKOS; Janssen; NHLBI

Consultant:

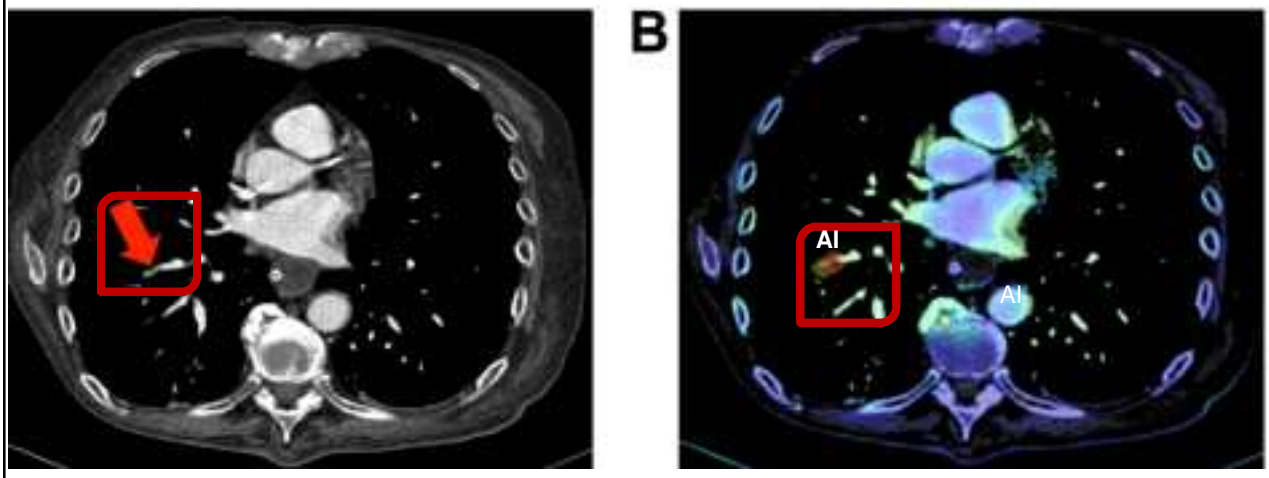
- None

AI for Chest CT Pulmonary Angiogram

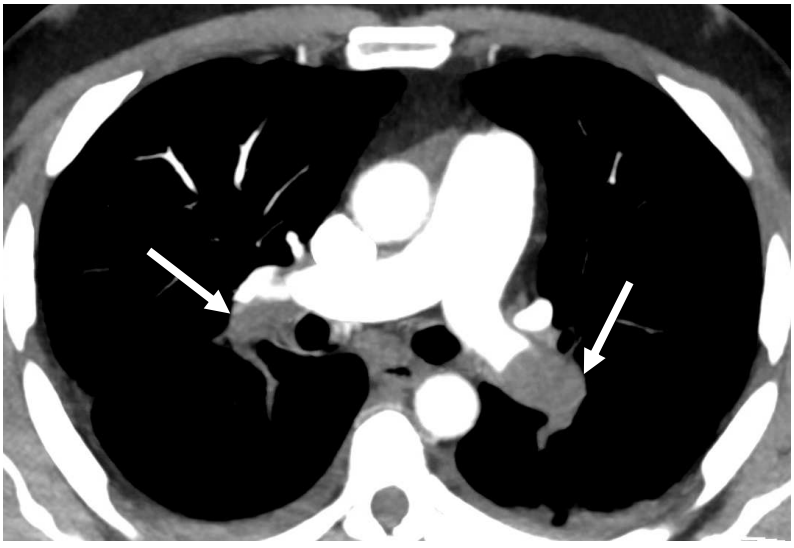


(Ben Cheikh A. European Radiology 2022; March 22)

AI for Chest CT Pulmonary Angiogram



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



FATAL SADDLE PE: 41 y.o. woman with sudden collapse

Itinerary

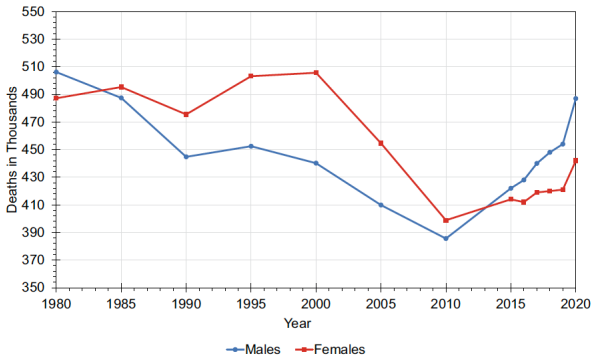
1) Epidemiology
2) Pathophysiology
3) Post Thrombotic Syndrome
4) Anticoagulation, Primarily DOACs
5) Optimal Duration of Anticoagulation
6) Advanced Therapies: Beyond Heparin

Epidemiology

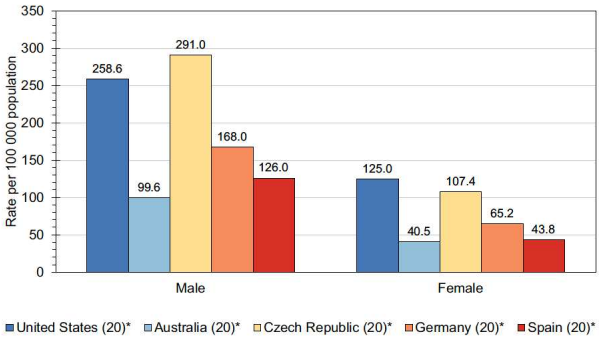
Primary VTE Prevention

1) AHA Guidelines for exercise: at least 30 minutes per day for at least 6 days per week
2) Stay well hydrated (ideally, 2 L/day of water or Gatorade)
3) Heart-healthy lifestyle (e.g., no cigarettes)
4) Prevent or treat known triggers of VTE
   (e.g., obesity (BMI $\geq$ 30)

CVD Deaths in the US 1980 - 2020

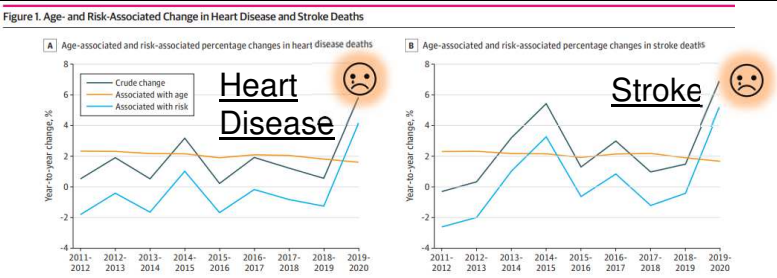


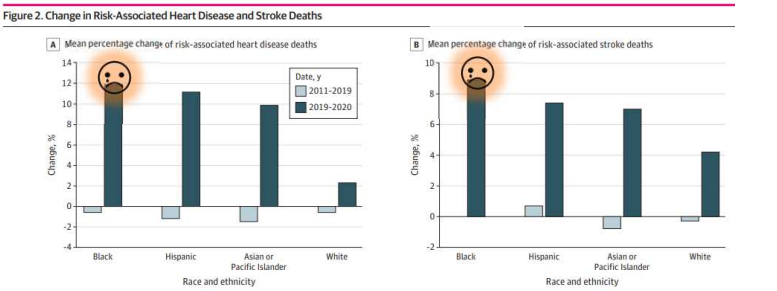
CVD Death Rates in 2020



Tsao et al AHA Heart Disease & Stroke Statistics Circulation. 2023;147:e93–e621

2019-2020: Increased Heart Disease and Stroke Deaths



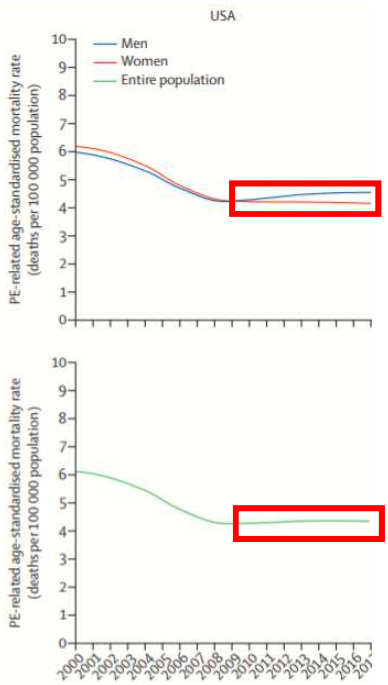


(JAMA Network Open 2022; March 23)

PE-Related Age-Adjusted Mortality in USA

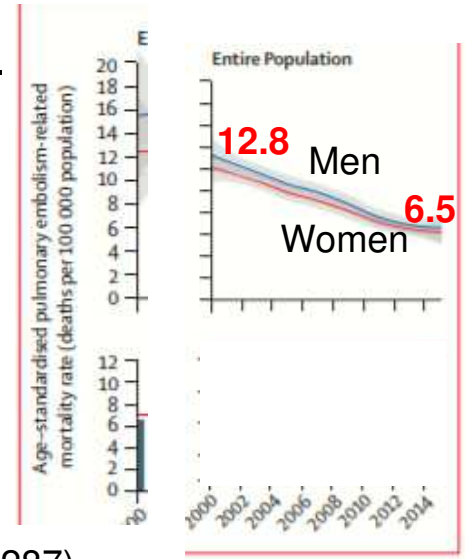
U.S. Mortality reduction in PE stopped in 2010, especially in men.

(Barco S. Lancet Respir Med 2021; 9: 33-42)



Trends in PE Mortality in Europe and Asia

A continuous decrease in PE mortality from 2000 to 2015

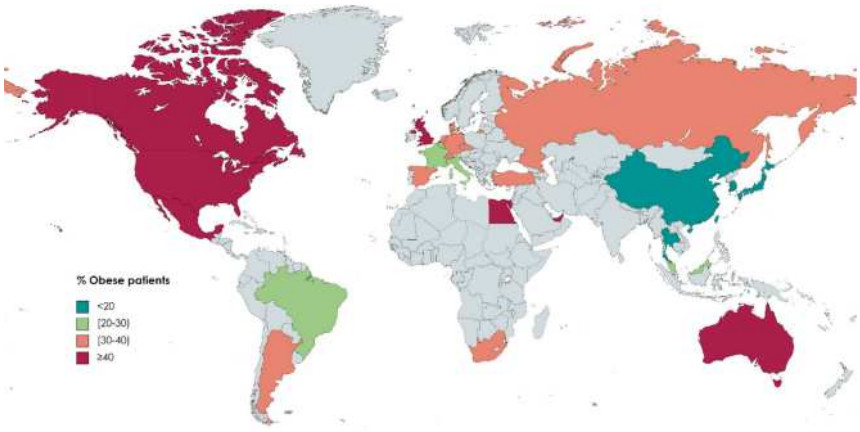


(Barco S. Lancet Respir Med 2020; 8: 277-287)

Impact of Obesity

- Affects 41% of U.S. adults
- An excess of $174 Billion healthcare expenses/yr
- New meds: up to 15% to 20% weight loss
- New meds: X20 expensive as older meds
- Treat and Reduce Obesity Act: seeks to expand Medicare Coverage of Antiobesity meds

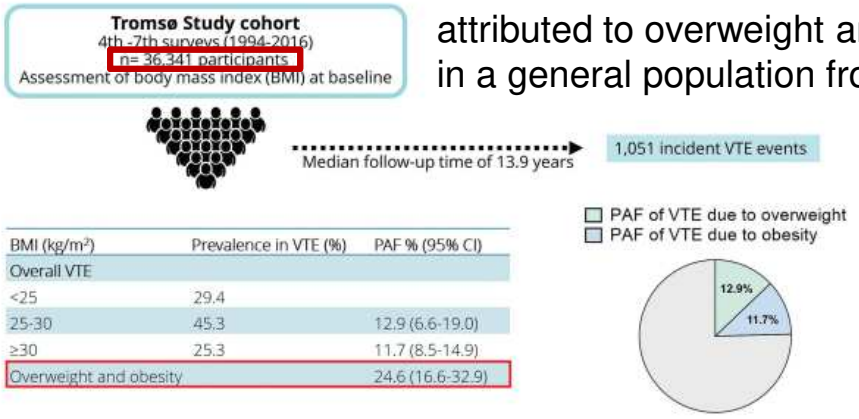
Distribution of Obese Patients according to Country



J Thromb Haemost 2021; 19: 3031–3043.

VTE Attributed to Overweight/ Obesity: Norway

25% of all VTE events can be attributed to overweight and obesity in a general population from Norway

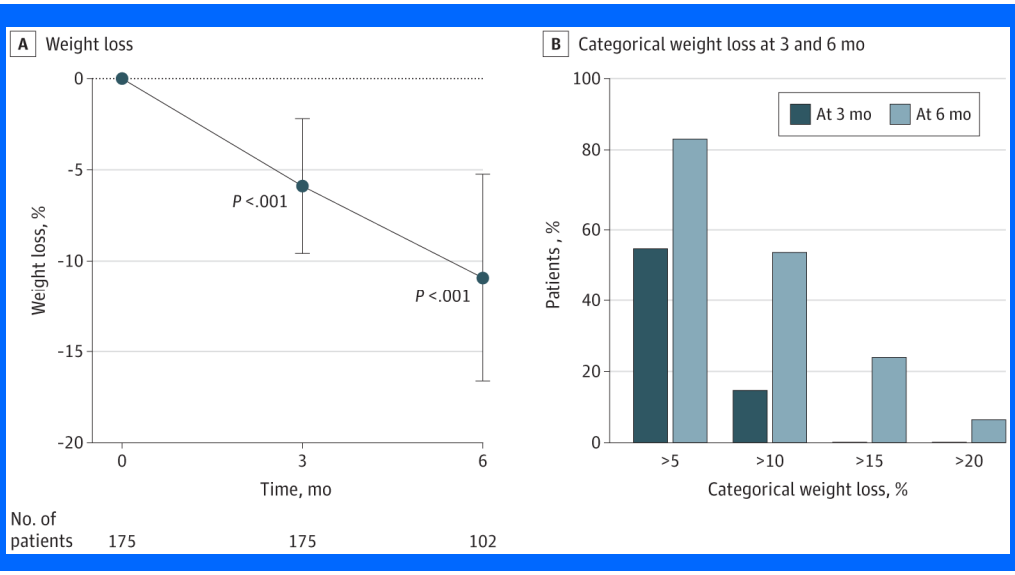


BMI (kg/m²)	Prevalence in VTE (%)	PAF % (95% CI)
Overall VTE		
<25	29.4	
25-30	45.3	12.9 (6.6-19.0)
≥30	25.3	11.7 (8.5-14.9)
Overweight and obesity		24.6 (16.6-32.9)

Visual summary. Population attributable fraction (PAF) of venous thromboembolism (VTE) due to overweight and obesity - The Tromsø Study.

Thrombosis and Haemostasis 2023; August 7

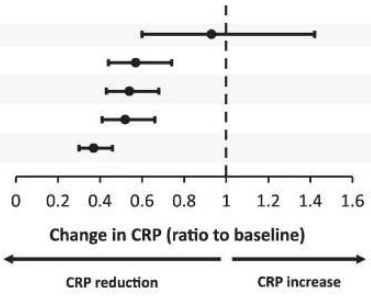
Semaglutide: Weight Loss at 3 and 6 Months



Ghusn W. JAMA Netw Open 2022; Sep 1

Relationship between weight loss with semaglutide and change in inflammation

Subgroup	Semaglutide 2.4 mg *n*	Change from baseline to week 52 (95% CI)	*P* value for trend
On-treatment data			
Body weight decrease			
<5%	14	0.9 (0.6, 1.4)	
≥5–<10%	40	0.6 (0.4, 0.7)	
≥10–<15%	48	0.5 (0.4, 0.7)	0.0003
≥15–<20%	45	0.5 (0.4, 0.7)	
≥20%	56	0.4 (0.3, 0.5)	



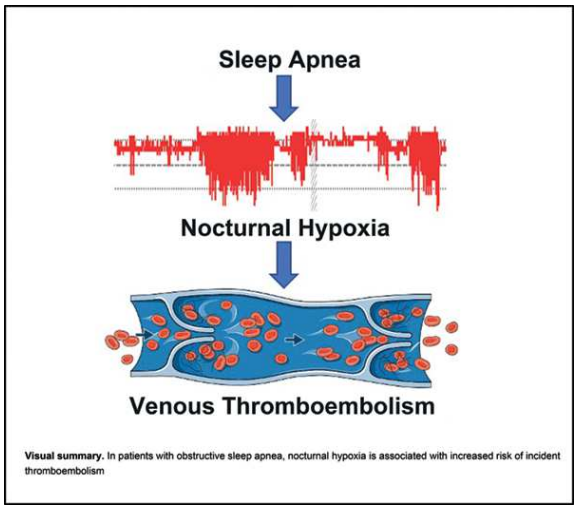
Nature Medicine 2023; August 27

Pathophysiology

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

SLEEP

What Is the Association Between Obstructive Sleep Apnea (OSA) and Venous Thromboembolism (VTE)?

CHEST

STUDY DESIGN

- **Retrospective cohort** of adult patients undergoing baseline PSG in a **large multihospital system**

7/2004

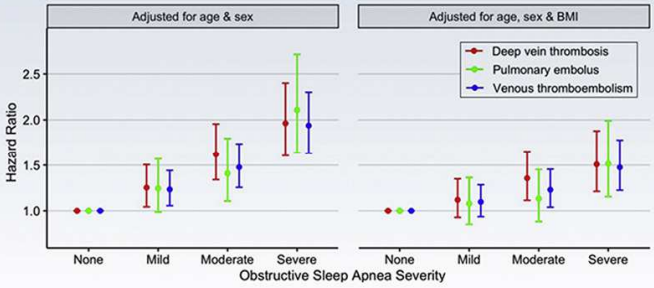
31,309 patients

1, 791 VTE events

12/2018

RESULTS

Risk of Thrombosis and Nocturnal Hypoxemia

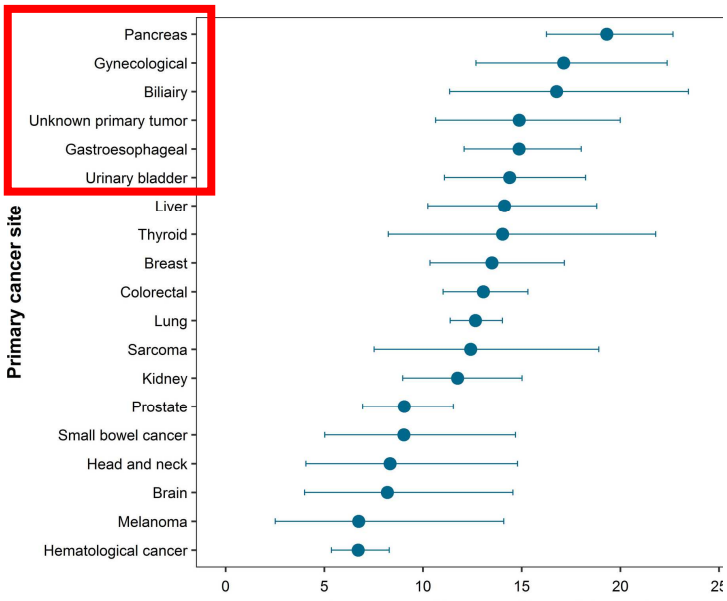


- Patients with >50% sleep time spent with saturations <90% are at increased VTE risk compared to those without nocturnal hypoxemia (HR 1.48, 95% CI 1.16-1.69)

Prolonged nocturnal hypoxemia is independently associated with incident VTE over longitudinal follow up.

Genuardi MV, et al. *CHEST* April 2022 | @journal_CHEST | https://doi.org/10.1016/j.chest.2021.12.630

Cancer Sites in PE Patients



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

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

Post Thrombotic Syndrome

Post Thrombotic Syndrome

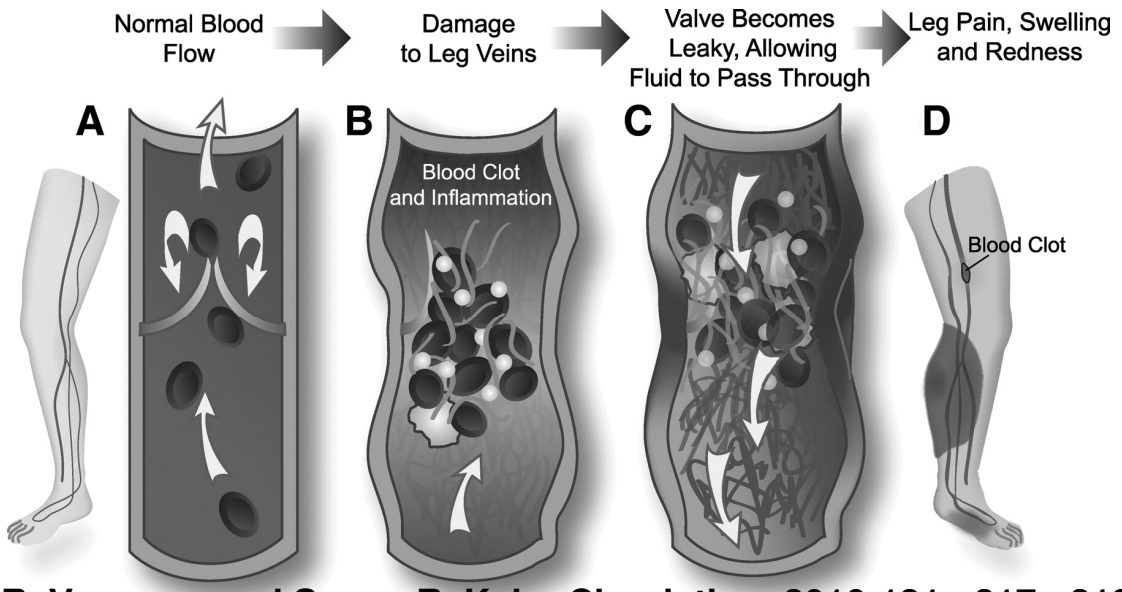
- Diagnosed clinically in patients with chronic venous insufficiency and a DVT ≥ 3 months previously
- Within two years after a DVT, 20–50% of patients will develop post thrombotic syndrome
- PTS: the main determinant of QOL after DVT
- PTS after a first distal DVT is less common than after a first proximal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

Post Thrombotic Syndrome (PTS)

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



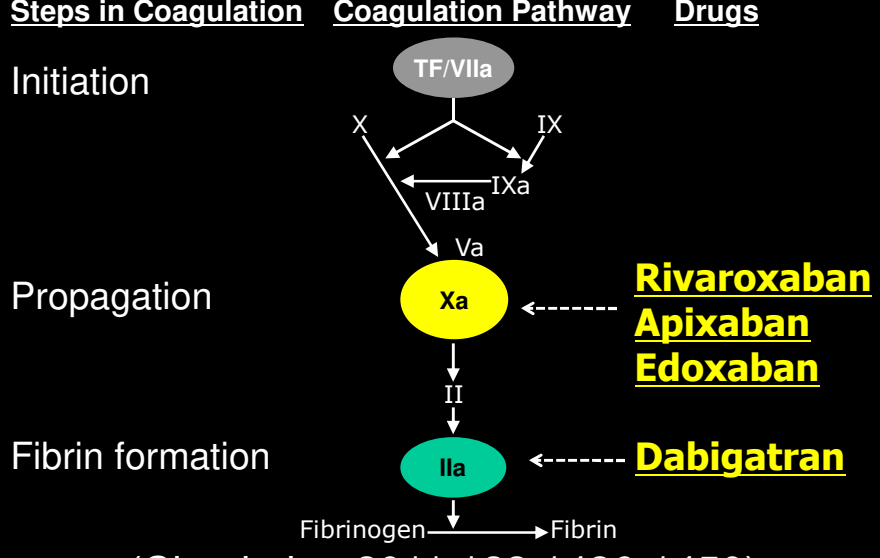
(Sara R. Vazquez, and Susan R. Kahn Circulation. 2010;121:e217-e219)

Post Thrombotic Chronic Venous Ulcers: Decrease Quality of Life

VTE Management Strategy

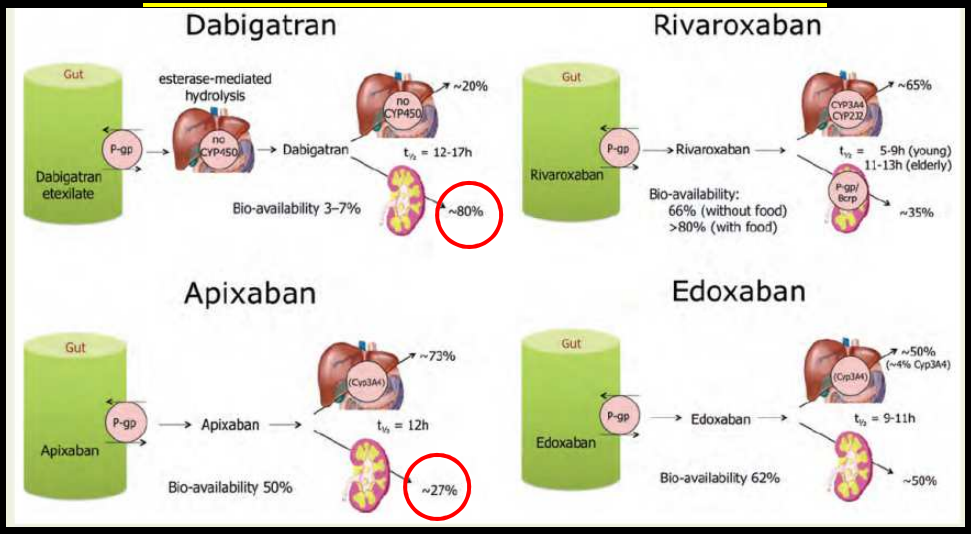
Anticoagulants: Primarily DOACs

DOACS: SITES OF ACTION



(Circulation 2011;123:1436-1450)

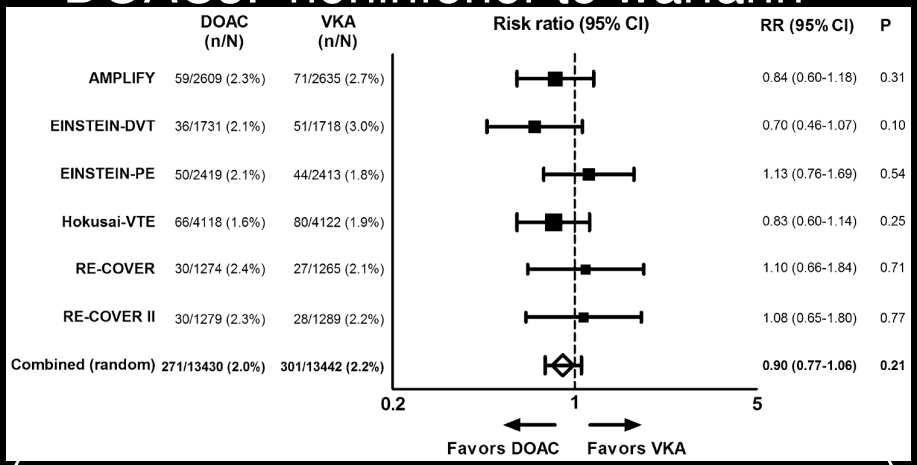
DOACS DIFFER IN LIVER AND KIDNEY METABOLISM



(Europace 2013; 15: 625-651)

ACUTE VTE TREATMENT: DOAC EFFICACY

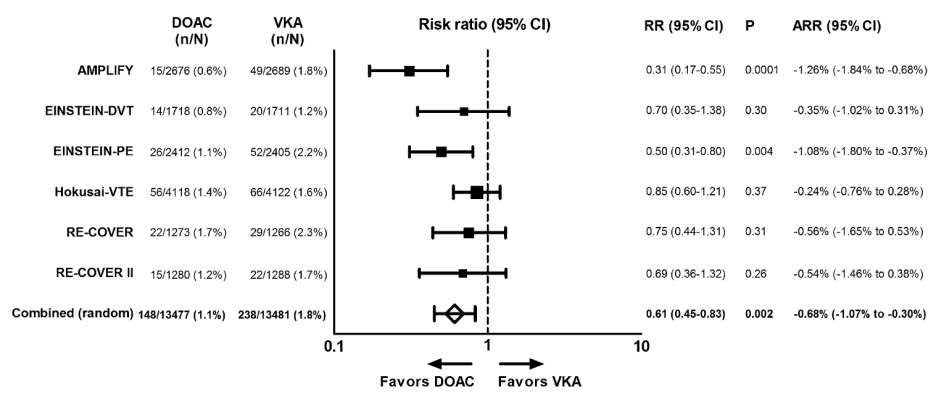
DOACs: noninferior to warfarin



(van Es N, et al. Blood 2014; 124: 1968-1975)

ACUTE VTE TREATMENT: DOAC SAFETY (N=27,235)

DOACs: 39% lower major bleeding



(van Es N, et al. Blood 2014; 124: 1968-1975)

Medicare Patient Copays

Drugs Selected for Price "Negotiations"

- 1. **Eliquis**, for preventing strokes and blood clots, from Bristol Myers Squibb and Pfizer
- 2. **Jardiance**, for diabetes and heart failure, from Boehringer Ingelheim and Eli Lilly
- 3. **Xarelto**, for preventing strokes and blood clots, from Johnson & Johnson
- 4. **Januvia**, for diabetes, from Merck
- 5. **Farxiga**, for diabetes, heart failure and chronic kidney disease, from AstraZeneca
- 6. **Entresto**, for heart failure, from Novartis

Inflation Reduction Act: Medicare

- Eliquis, taken by 3.7 million beneficiaries, has a monthly sticker price of about $400
- Company opt out: 1) Can't sell to Medicare patients, or 2) Can sell but pay a 95% tax per sale
- The program overall (2026) is projected to save the government $98.5 billion over a decade
- $35 monthly cap for copays on insulin (2025)
- $2,000 annual cap for copays (2025)

Inflation Reduction Act: Medicare

Six pharmaceutical manufacturers —

Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Johnson & Johnson, and Merck —

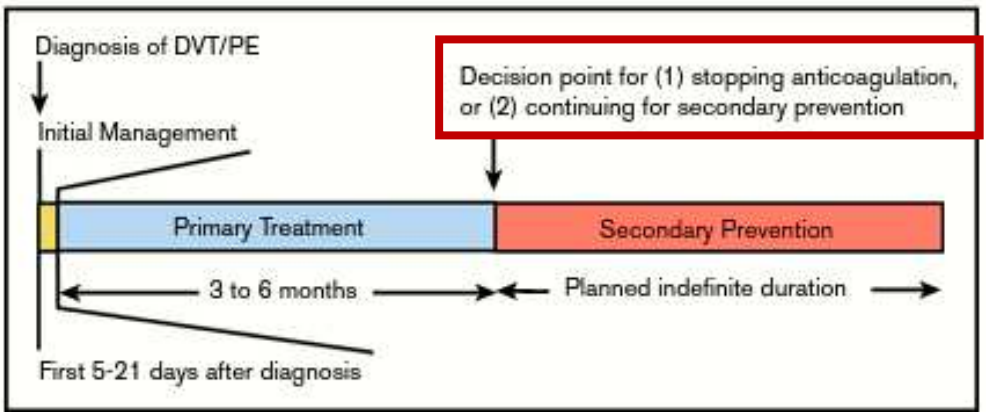
have taken the Biden administration to court in an attempt to block the negotiation program

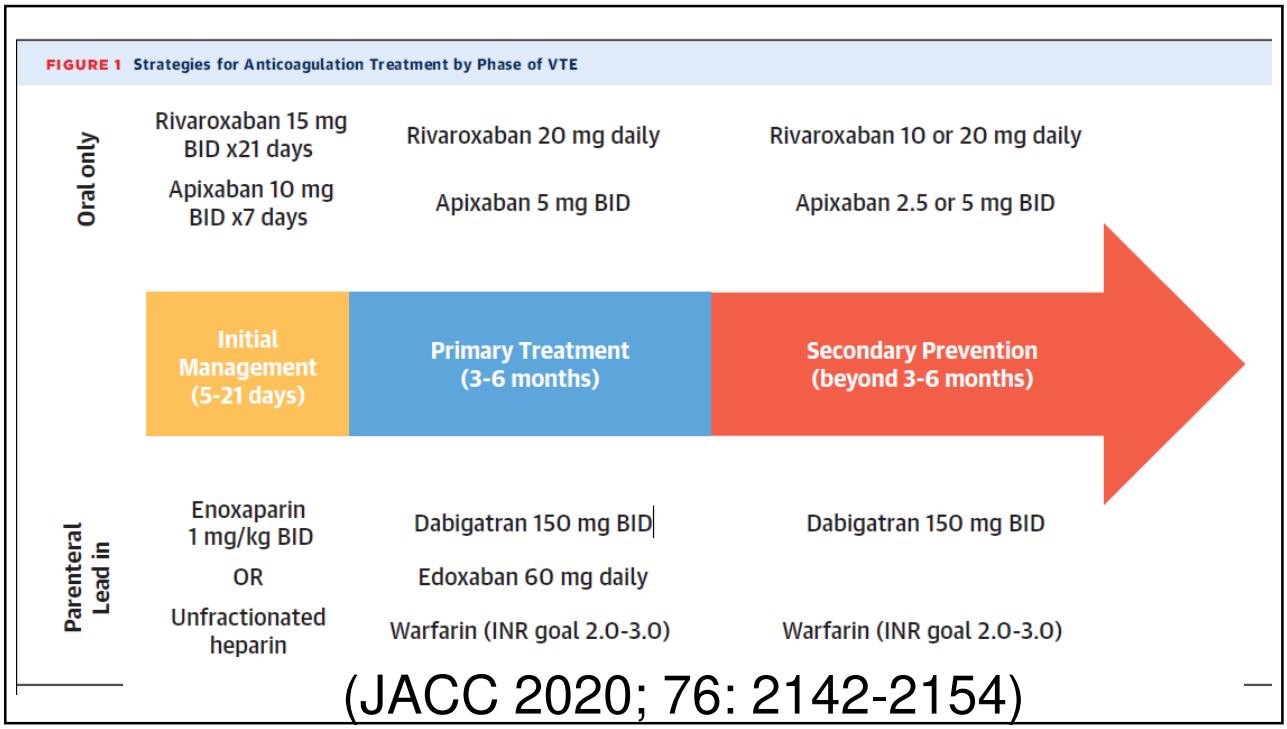
CAN DOACS REPLACE LMWH MONOTHERAPY IN CANCER PATIENTS WITH VTE?

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)

Optimal Duration of Anticoagulation: The Most Controversial Question in PE Management



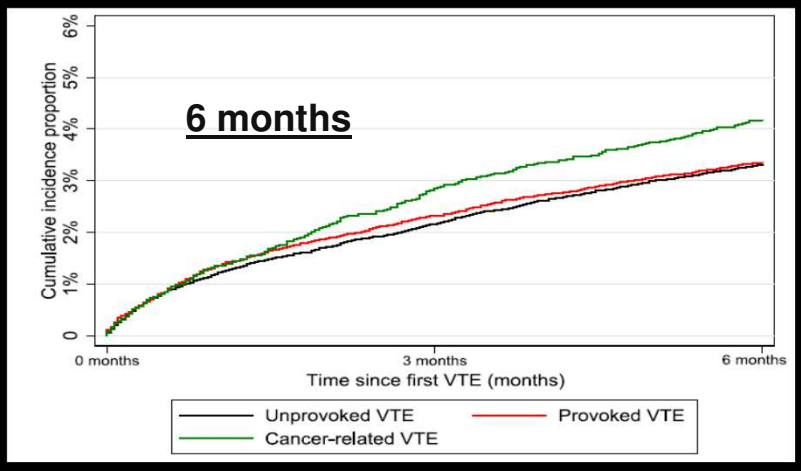


(JACC 2020; 76: 2142-2154)

OPTIMAL DURATION OF ANTICOAGULATION:

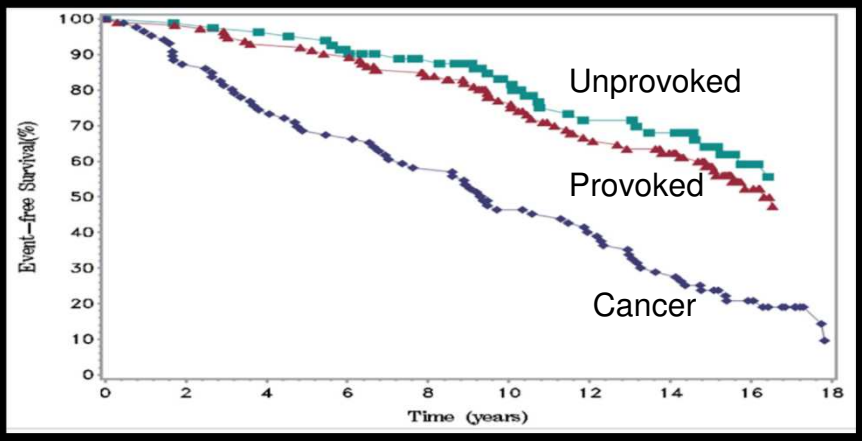
Requiem or double-down on "Provoked" versus "Unprovoked" VTE?

Risk of Recurrent VTE: Danish Cohort Study (N=73,993) 6 Months



(Albertsen IE. Am J Med 2018; 131: 1067-1074)

VTE Subtype: Event-Free Survival Framingham Heart Study (N=9,754)



(Puurunen MK. Thromb Res 2016; 145: 27-33)

Unprovoked VTE: Risk of Recurrence after Discontinuing Anticoagulation (N=7,515)

Years after D/C Anticoagulation	% Recurrence
1	10%
2	16%
5	25%
10	36%

(Khan F. BMJ 2019;366:l4363 | doi: 10.1136/bmj.l4363)

ASH 2020 VTE Guidelines re: Duration of Anticoagulation

"Patients with DVT and/or PE provoked by a transient risk factor typically do not require antithrombotic therapy after completion of primary treatment."

ESC PE Guidelines

"**Terminology such as '<u>provoked</u>' vs. '<u>unprovoked</u>' PE/ VTE is no longer supported by the Guidelines**, as it is **potentially misleading** and **not helpful for decision-making** regarding the duration of anticoagulation."

(ESC PE Guidelines. European Heart Journal 2020; 41: 543-603)

ESC: Anticoagulation Duration

"Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and:

1) No identifiable risk factor
2) A persistent risk factor
3) A minor transient or reversible risk factor"

(ESC PE Guidelines. European Heart Journal 2020; 41: 543-603)

New York Cardiovascular Symposium DECEMBER 11 - 12, 2021
AMERICAN COLLEGE of CARDIOLOGY
JOIN THE CONVERSATION: #NYCVS

ESC PE Guidelines: Risk of Recurrence

Risk of Recurrence	Risk Factors for Index VTE	Examples
Low (<3%/ year)	Transient, reversible factors; >10-fold increased risk of index VTE	Major surgery Major trauma
Intermediate (3% to 8%/ year)	Transient, reversible factors; ≤10-fold increased risk of index VTE	Minor surgery Hospitalized with acute medical illness Pregnancy/ estrogens Long-haul flight
	Persistent risk factors	IBD; Autoimmune Disease
	No identifiable risk factor	
High (>8%/ year)		Active cancer Antiphospholipid syndrome

(ESC PE Guidelines. European Heart Journal 2020; 41: 543-603)

VTE-PREDICT to predict risks of recurrent VTE, bleeding and individual benefits, and harms of extended anticoagulation

Development

Competing risk-adjusted models for
- Recurrent VTE
- Clinically relevant bleeding

were derived in combined individual patient data (n = 15,141)

Bleeding Risk Study, Hokusai-VTE, RE-MEDY, RE-SONATE, PREFER in VTE Registry

Validation

External validation (n = 59,257) showed agreement between predicted and observed risks up to 5 years

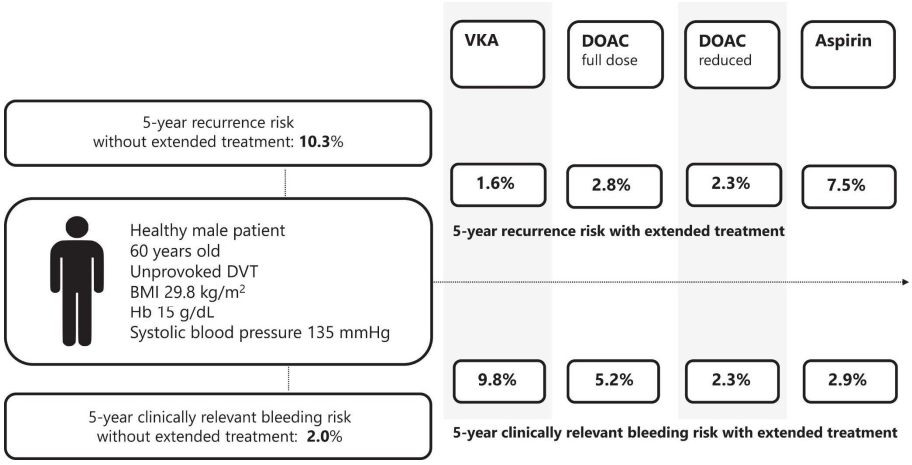
Danish VTE Cohort, EINSTEIN-CHOICE, GARFIELD-VTE, Tromsø study, MEGA study

Key features of the VTE-PREDICT risk score

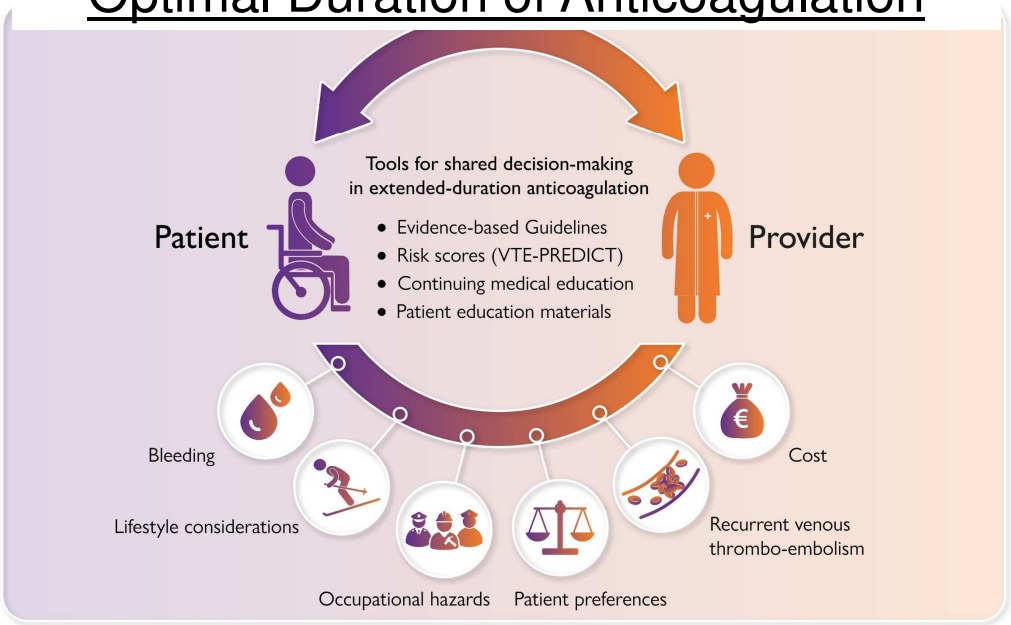
- Suitable for all adult patients with VTE without active cancer for whom the decision to stop or continue anticoagulation is yet to be made
- Uses 14 simple, readily available patient characteristics
- Available worldwide through https://vtepredict.com

Eur Heart J, Volume 44, Issue 14, 7 April 2023, Pages 1245–1247

Example of VTE-Predict



Optimal Duration of Anticoagulation



Eur Heart J, Volume 44, Issue 14, 7 April 2023, Pages 1245–1247

OPTIMAL DURATION OF ANTICOAGULATION:

Who Do You Side with???

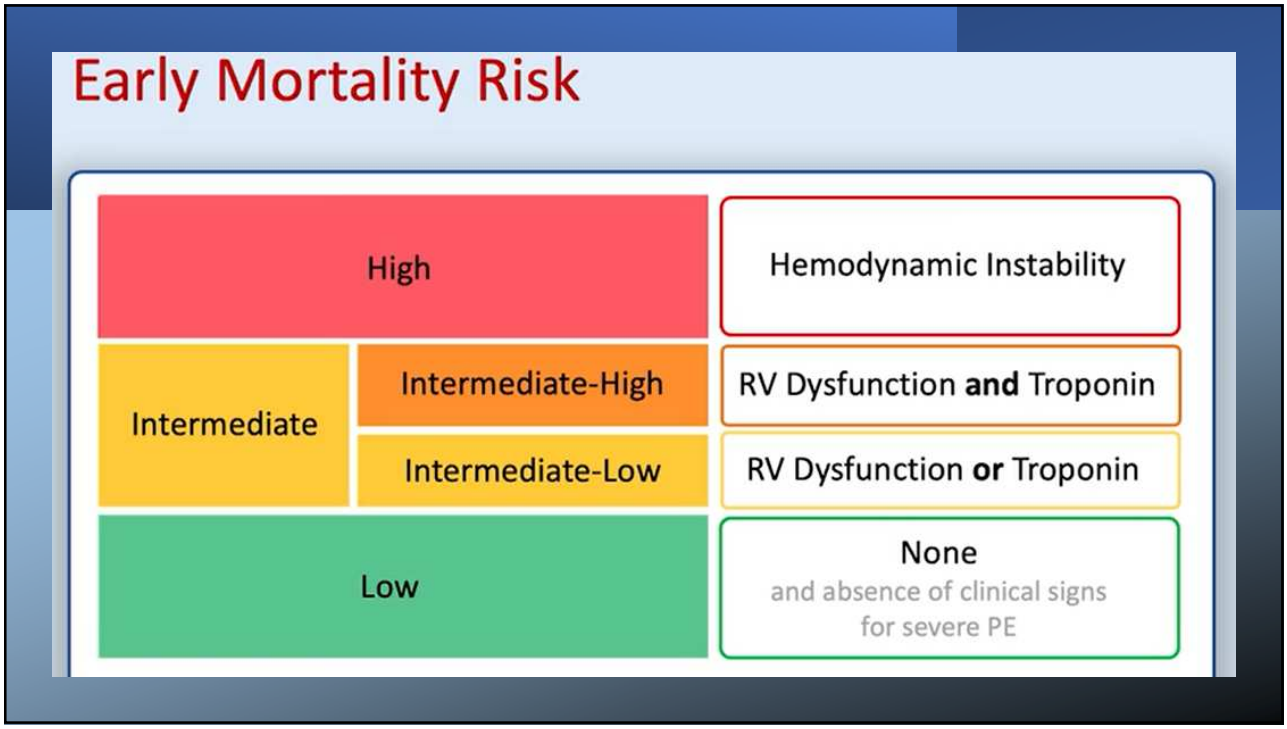
1) American Society of Hematology

2) European Society of Cardiology

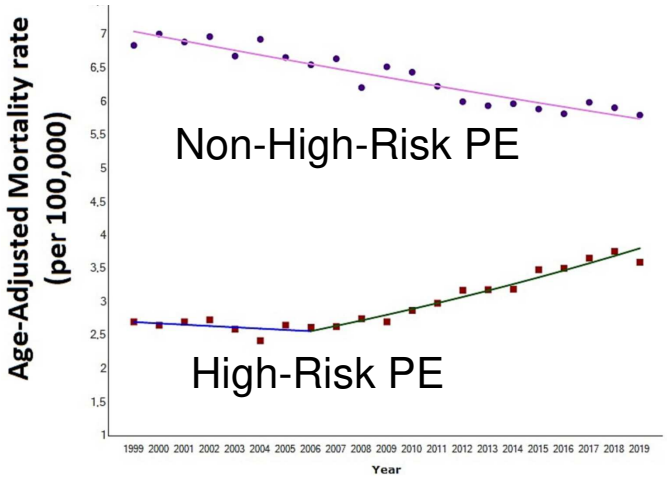
Please Vote

Advanced PE Management

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

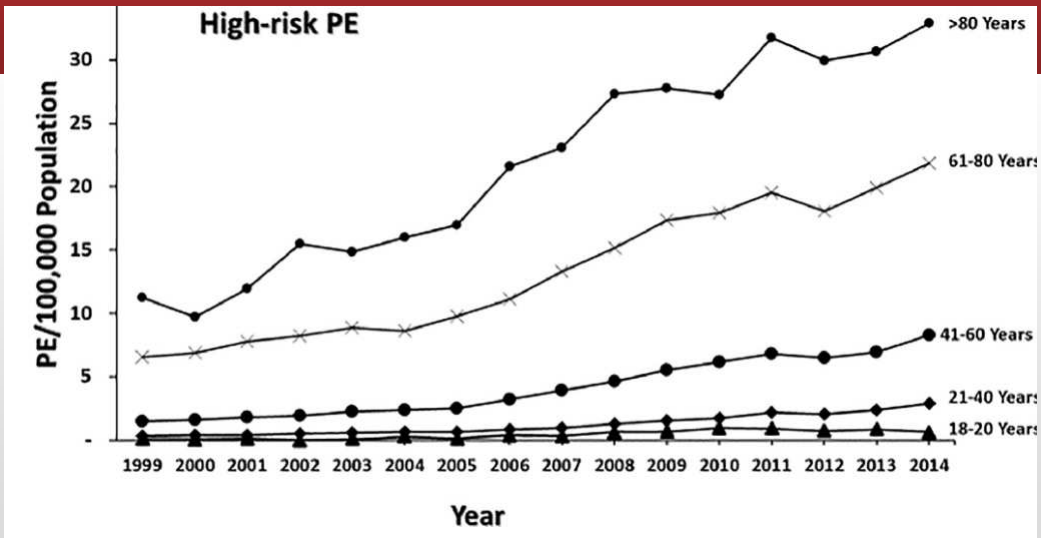


Time Trends in PE Mortality: Non-High Risk vs High-Risk PE



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

High-Risk PE: Age



(Am J Med 2021; 134: 621-625)

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

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.

Options for Reperfusion

- Systemic (via peripheral vein) thrombolysis
- Catheter-directed thrombolysis
- Ultrasound-facilitated catheter-directed thrombolysis
- Mechanical catheter thrombectomy (no thrombolysis)
- Surgical pulmonary embolectomy

AHA: Factors Favoring PE Reperfusion Rx

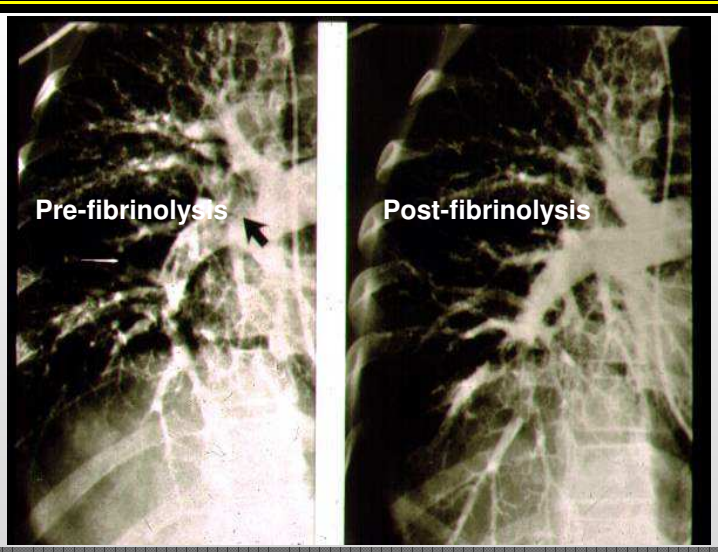
- Lack of improvement/ deterioration
- Clinical distress
- Clot-in-transit
- Severe/ persistent RV strain
- Low cardiac output
- Persistent hypoxia

(Circulation 2019; epubl October 4)

When Should We Initiate Systemic Thrombolysis?

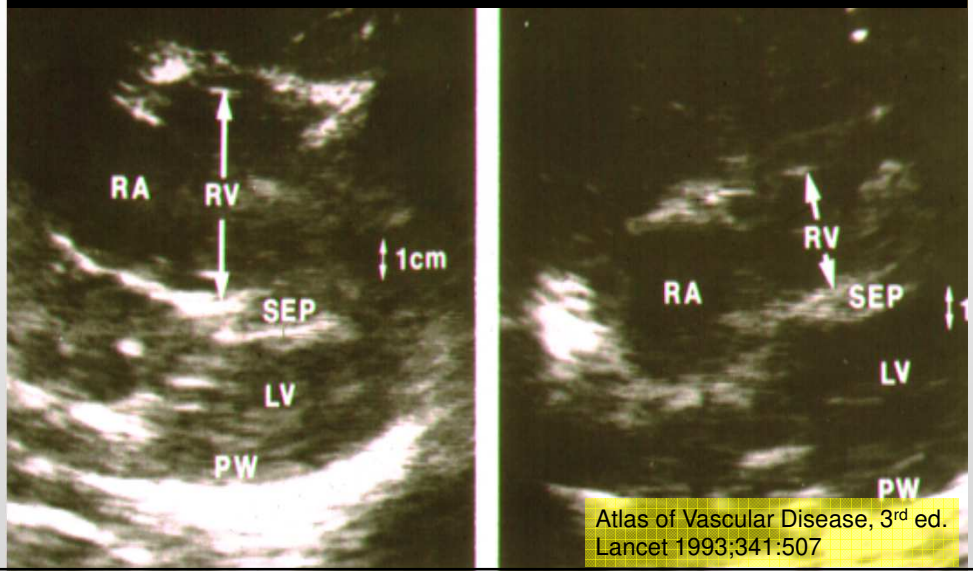
1) The patient is too critically ill to transfer
2) You're moonlighting as the only doctor on duty in the hospital
3) The patient appears young and healthy except for the PE
4) It's not possible to mobilize IR, cardiology, or cardiac surgeon in a timely way

THROMBOLYSIS IN SUBMASSIVE PE: RAPID ANGIOGRAPHIC IMPROVEMENT



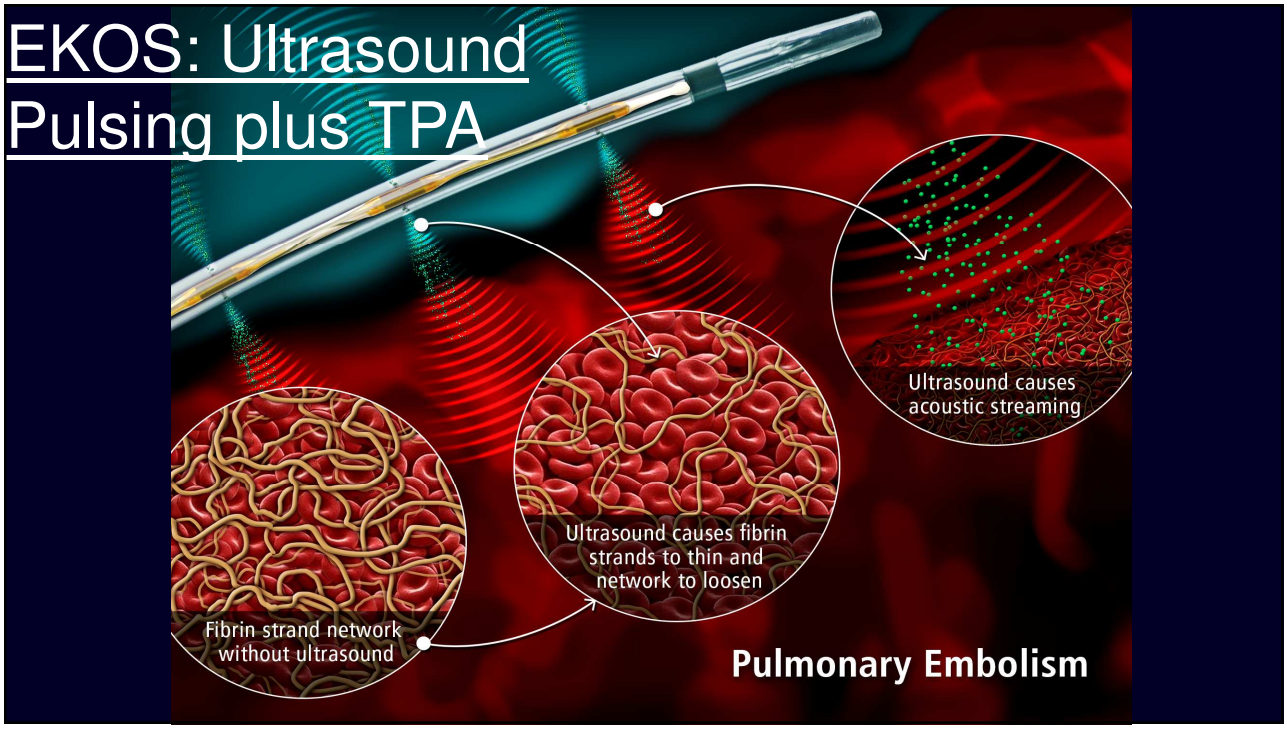
Atlas of Vascular Disease, 3rd ed.

THROMBOLYSIS IN SUBMASSIVE PE: RAPID RV AND ECHOCARDIOGRAPHIC IMPROVEMENT



Atlas of Vascular Disease, 3rd ed.
Lancet 1993;341:507

EKOS: Ultrasound Pulsing plus TPA



Simultaneous Publication In *EuroIntervention*

PERIPHERAL INTERVENTIONS
CLINICAL RESEARCH

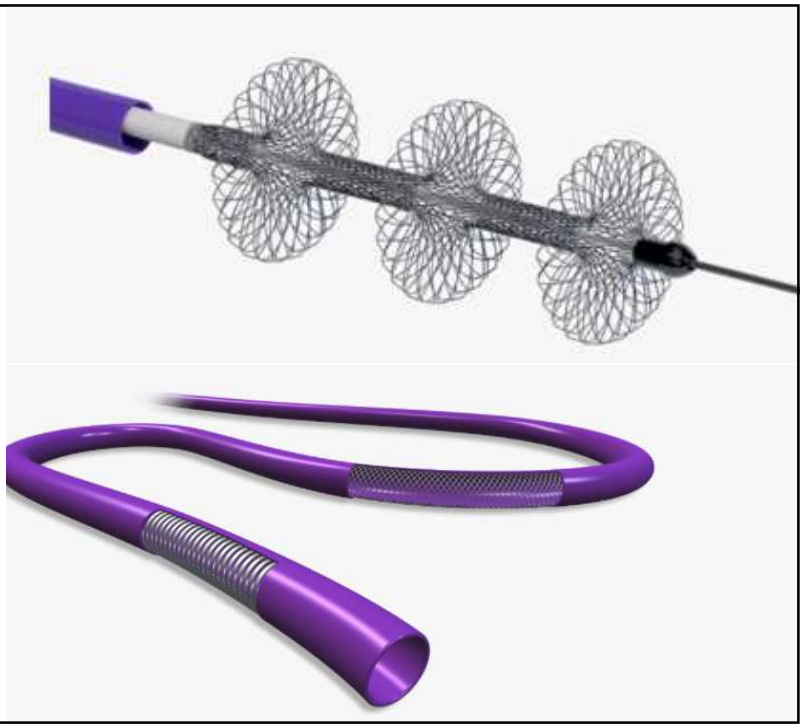
Acute Outcomes for the Full US Cohort of the FLASH Mechanical Thrombectomy Registry in Pulmonary Embolism

Catalin Toma[1]*, MD; Wissam A. Jaber[2], MD; Mitchell D. Weinberg[3], MD, MBA; Matthew C. Bunte[4], MD, MS; Sameer Khandhar[5], MD; Brian Stegman[6], MD; Sreedevi Gondi[7], MD; Jeffrey Chambers[8], MD; Rohit Amin[9], MD; Daniel A. Leung[10], MD; Herman Kado[11], MD; Michael A. Brown[12], MD; Michael G. Sarosi[13], MD; Ambarish P. Bhat[14], MD; Jordan Castle[15], MD; Michael Savin[16], MD; Gary Siskin[17], MD; Michael Rosenberg[18], MD; Christina Fanola[19], MD, MSc; James M. Horowitz[20], MD; Jeffrey S. Pollak[21], MD, for the FLASH Investigators

EuroIntervention 2022;17:1-1 published online

CRF TCT

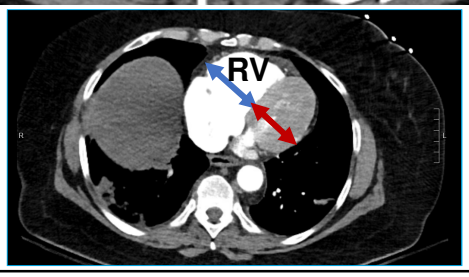
FlowTriever: 20F—No TPA



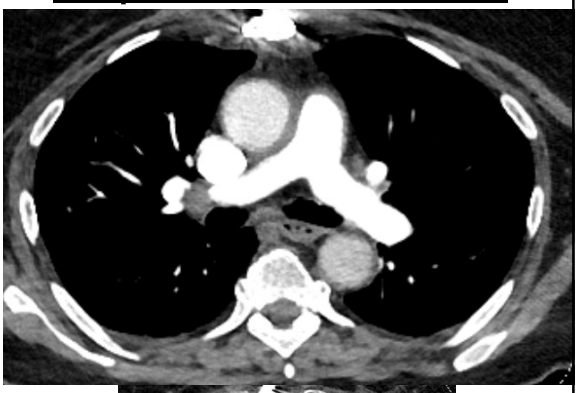
BWH FlowTriever Pulmonary Embolectomy #1—Drs. Bergmark and Shah

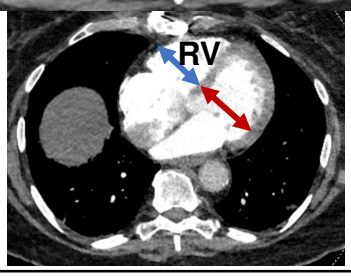
SURGICAL EMBOLECTOMY AT BWH: SURGEON'S CELL PHONE

July 23, 2020

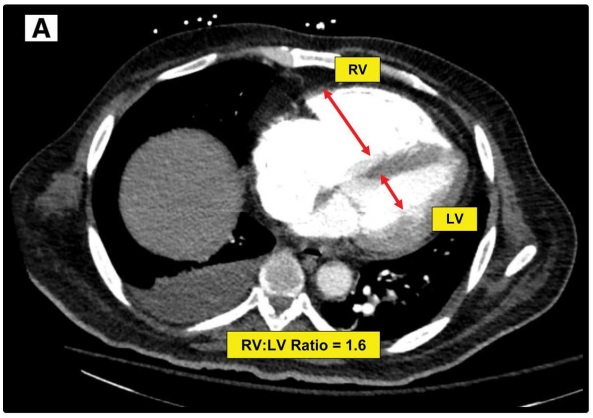


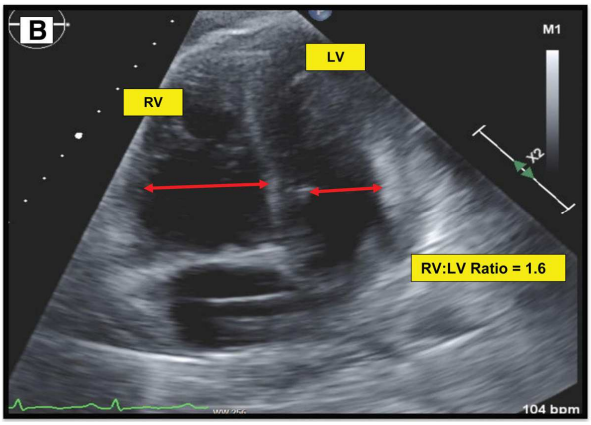
September 1, 2020





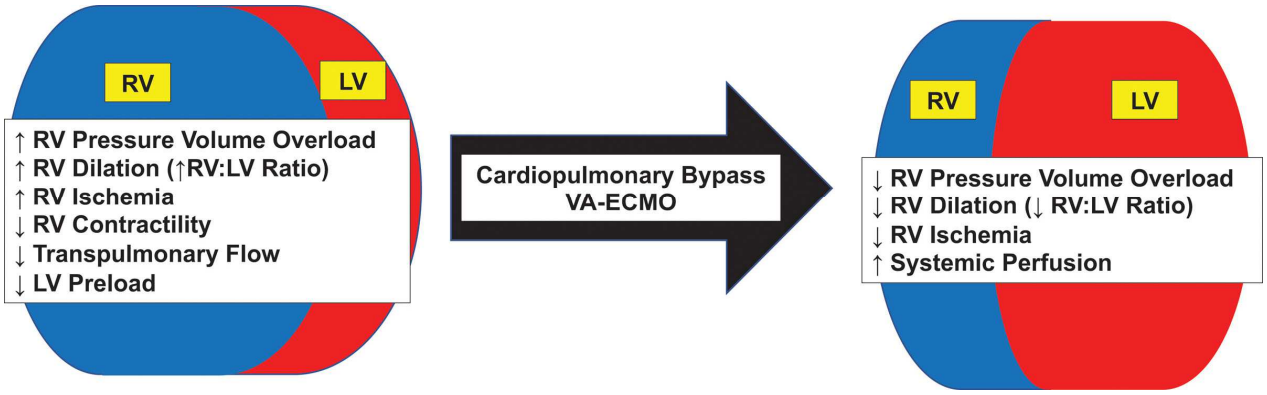
Acute RV Dilation with PE: CT and TTE





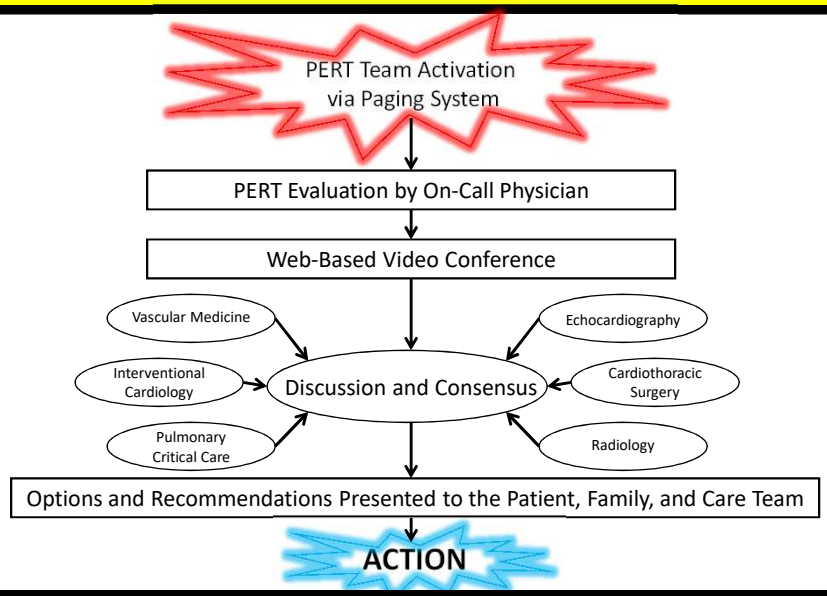
Circulation 2023; Jan 23. 147: e628–e647. AHA Scientific Statement

Beneficial Effects of CPB and VA-ECMO on Biventricular Function



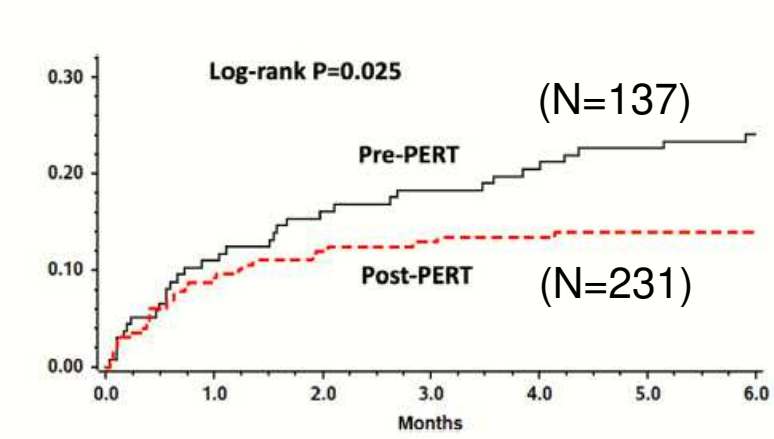
Circulation 2023; Jan 23. 147: e628–e647. AHA Scientific Statement

PE RESPONSE TEAM (PERT)



(Dudzinski D, Piazza G. Circulation 2016; 133: 98-103)

Effect of a PERT on Patient Mortality



(Wright C. Am J Cardiol 2021; 161: 102-107)

Take Home Points

- Prevent or treat known triggers of VTE
- DOACs: More convenient and fewer bleeding complications than warfarin
- Optimal duration of anticoagulation:
  try VTE-PREDICT
- Advanced therapy:
  Systemic lysis
  Catheter-based therapy—with or without TPA
  Surgical embolectomy, ECMO

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- ESC Guidelines for acute pulmonary embolism. Eur Heart J 2020; 41: 543-603
- Piazza G. Registry of Thromboembolic Complications in patients with COVID-19. JACC 2020; 76: 2060-2072
- Chopard R. Lower Extremity VTE. JAMA 2020; 324: 1765-1776
- Goldhaber SZ. ECMO and Surgical Embolectomy. JACC 2020; 76: 912-915