Management of Venous Thromboembolism

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

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S
Department of Medicine

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HARVARD
MEDICAL SCHOOL
TEACHING AFFILIATE

Disclosures

- Research Support:
- Bayer; BMS; Boston Scientific EKOS; Janssen; NHLBI

- Consultant:
- Pfizer

Key Learning Objectives

- Epidemiology—mortality rates, inequities
- DOACs for VTE
- Cancer and VTE
- Optimal duration of anticoagulation
- Management beyond anticoagulation: catheter or surgical embolectomy

Epidemiology/ Healthcare Disparities

2019-2020: Increased Heart Disease and Stroke Deaths

Figure 1. Age- and Risk-Associated Change in Heart Disease and Stroke Deaths

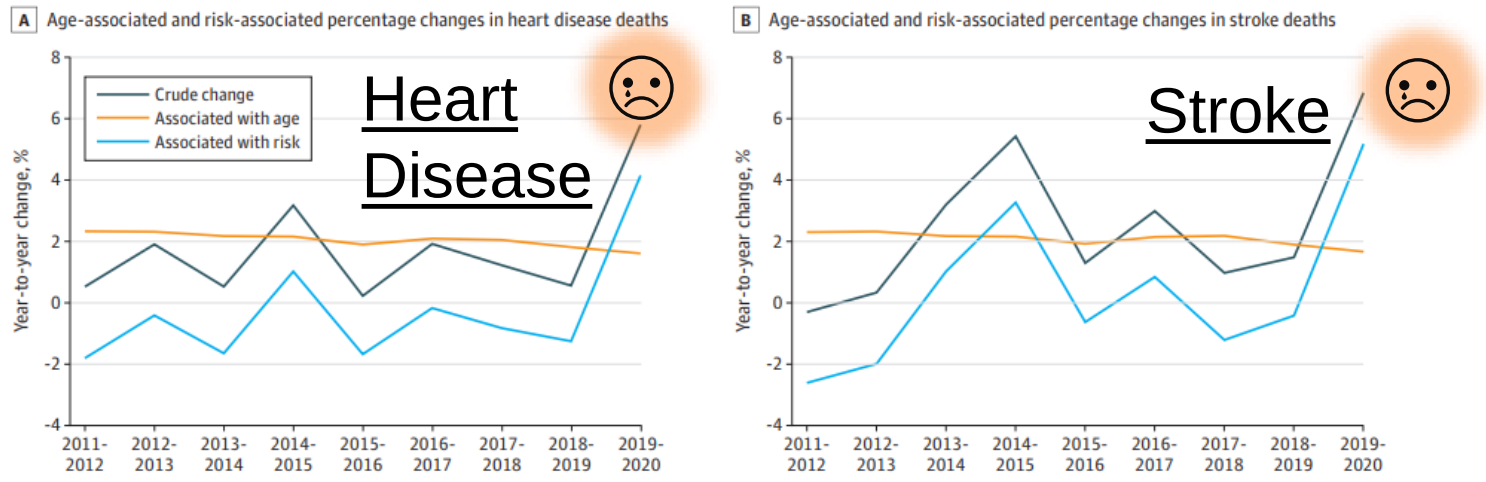
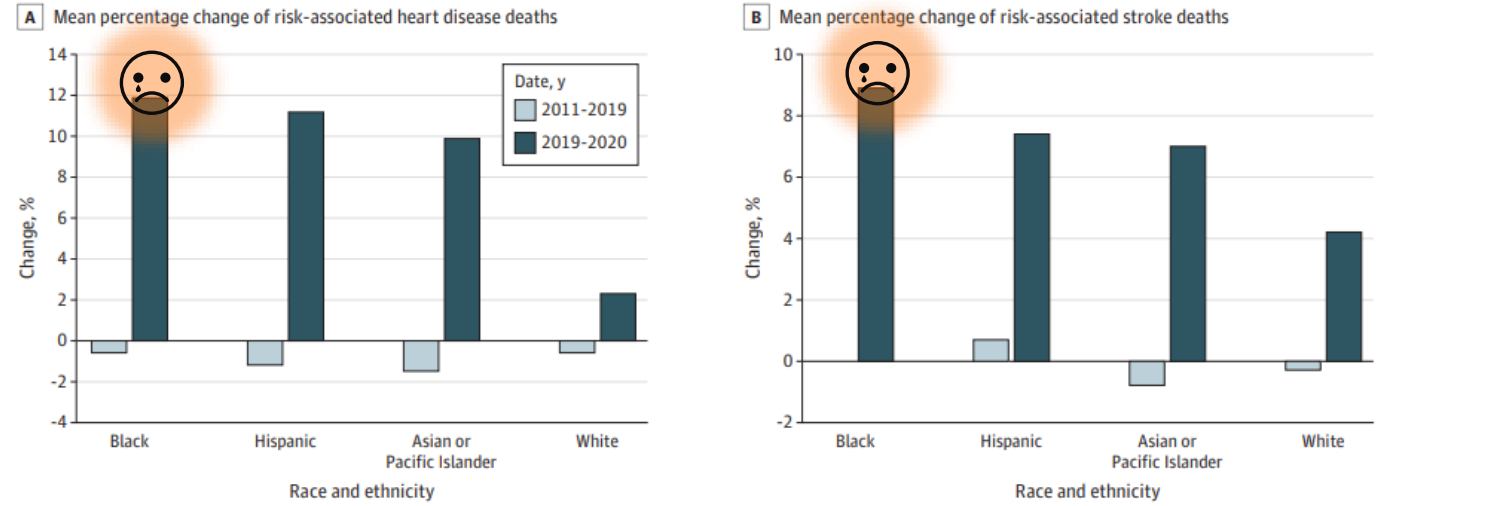


Figure 2. Change in Risk-Associated Heart Disease and Stroke Deaths

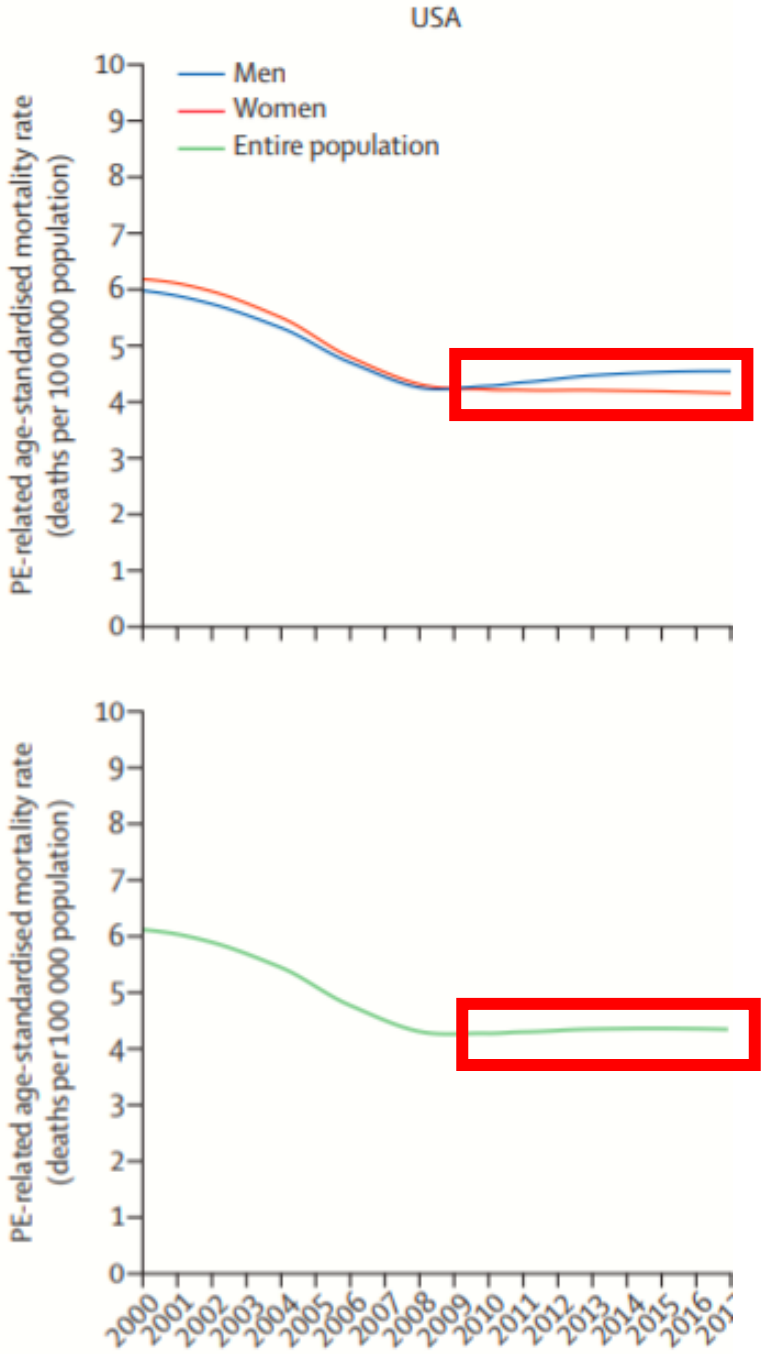


(JAMA Network Open 2022; March 23)

PE-Related Age-Adjusted Mortality in USA

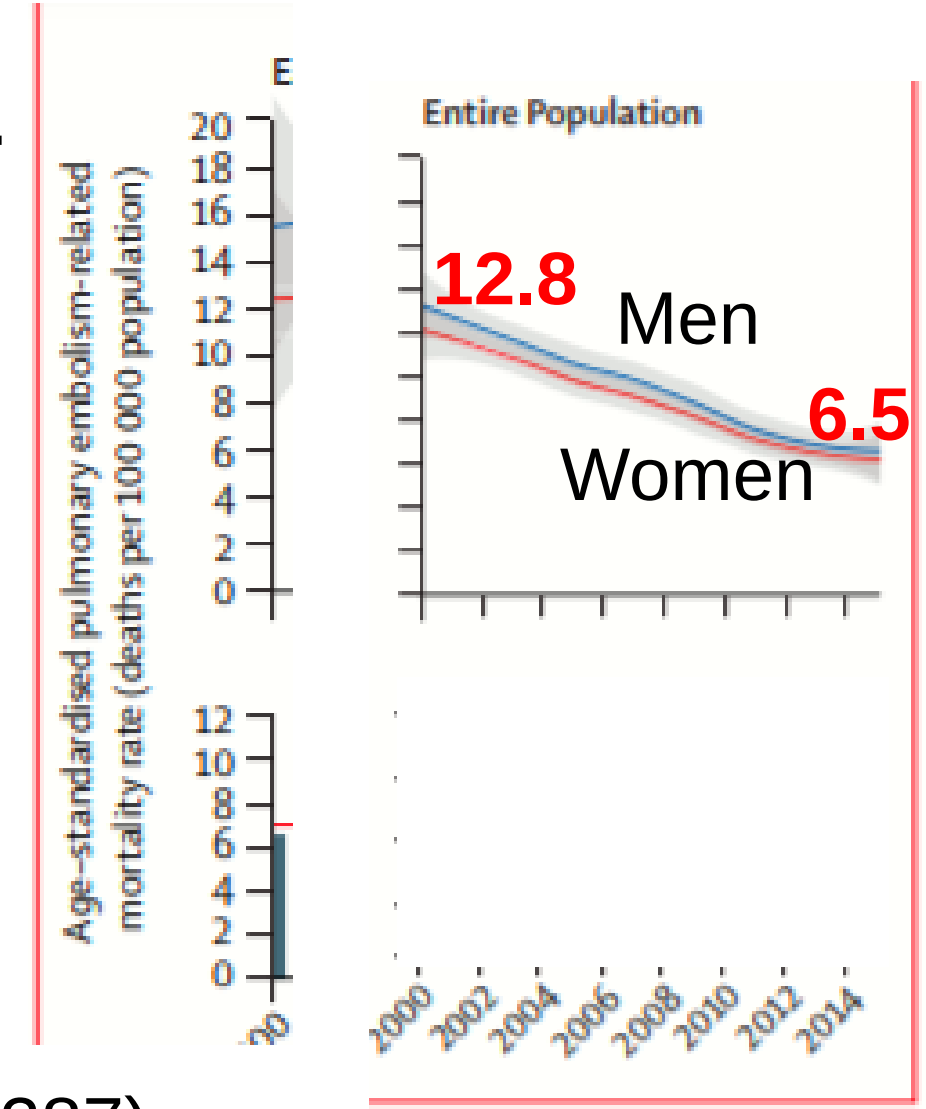
U.S. Mortality reduction in PE stopped in 2010, especially in men.

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



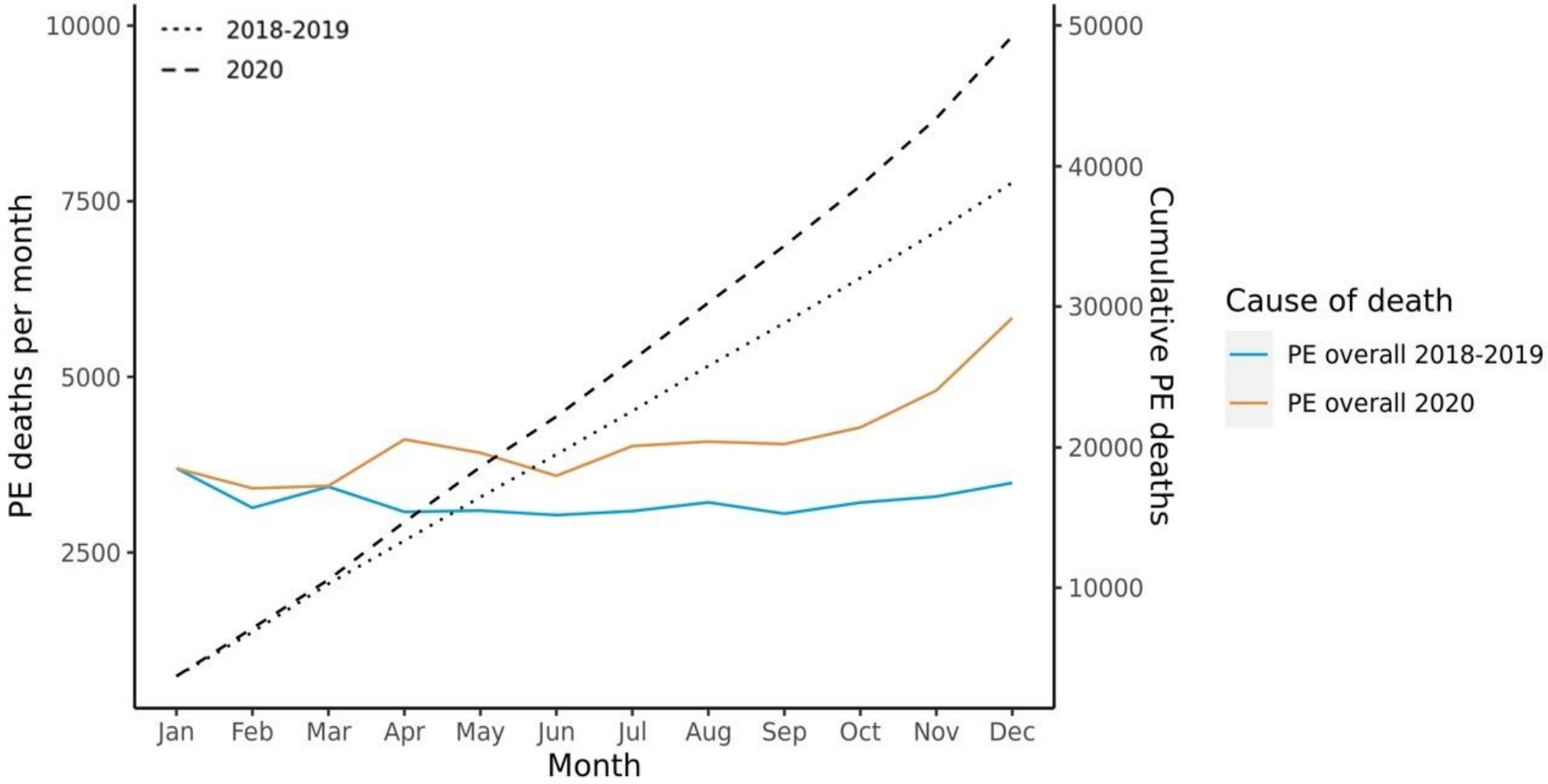
Trends in PE Mortality in Europe and Asia

A continuous decrease in PE mortality from 2000 to 2015



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

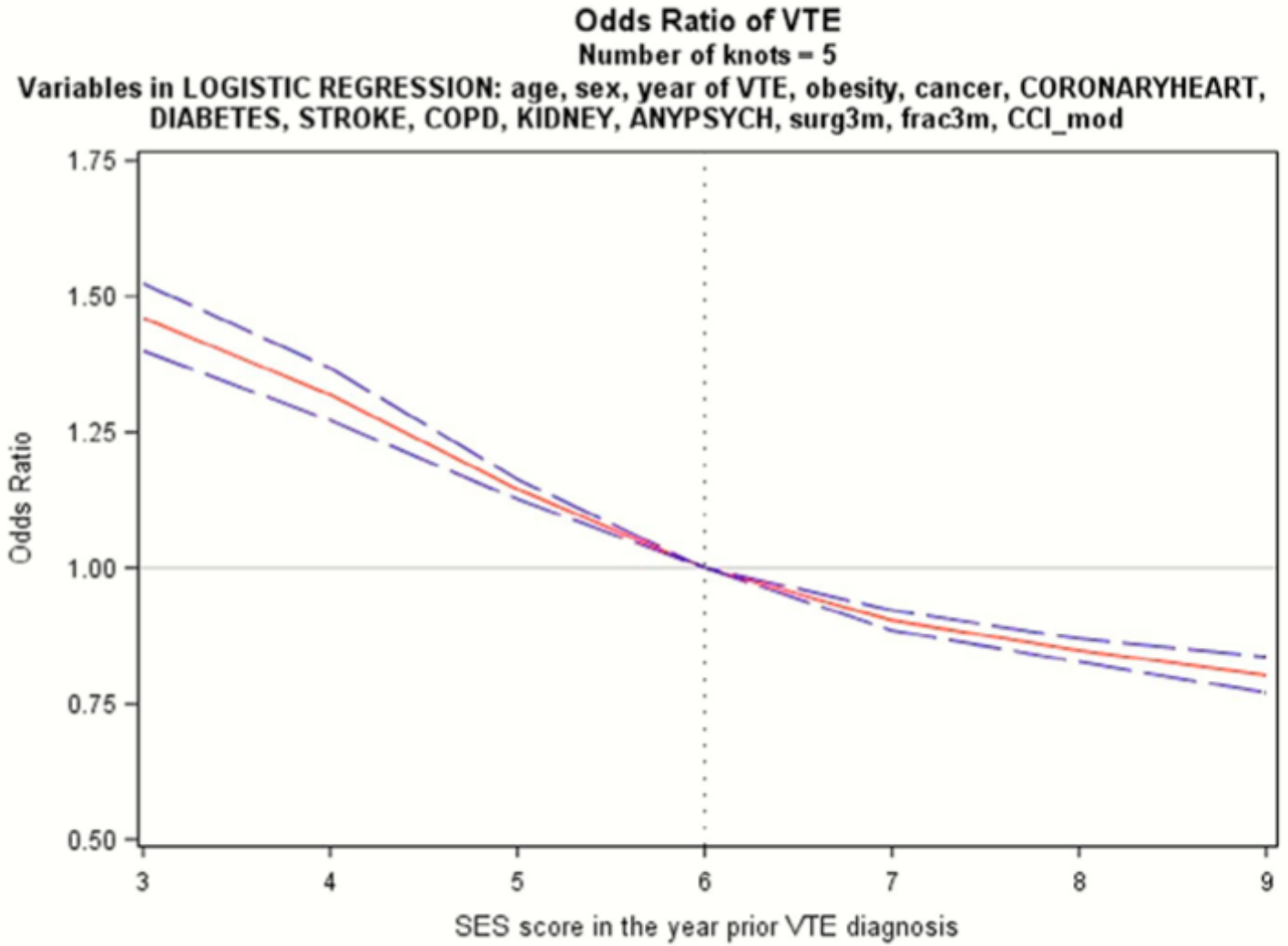
PE Mortality in the U.S.—2018-2020



(Farmakis I…Konstantinides S. CHEST 2023)

Healthcare Disparities

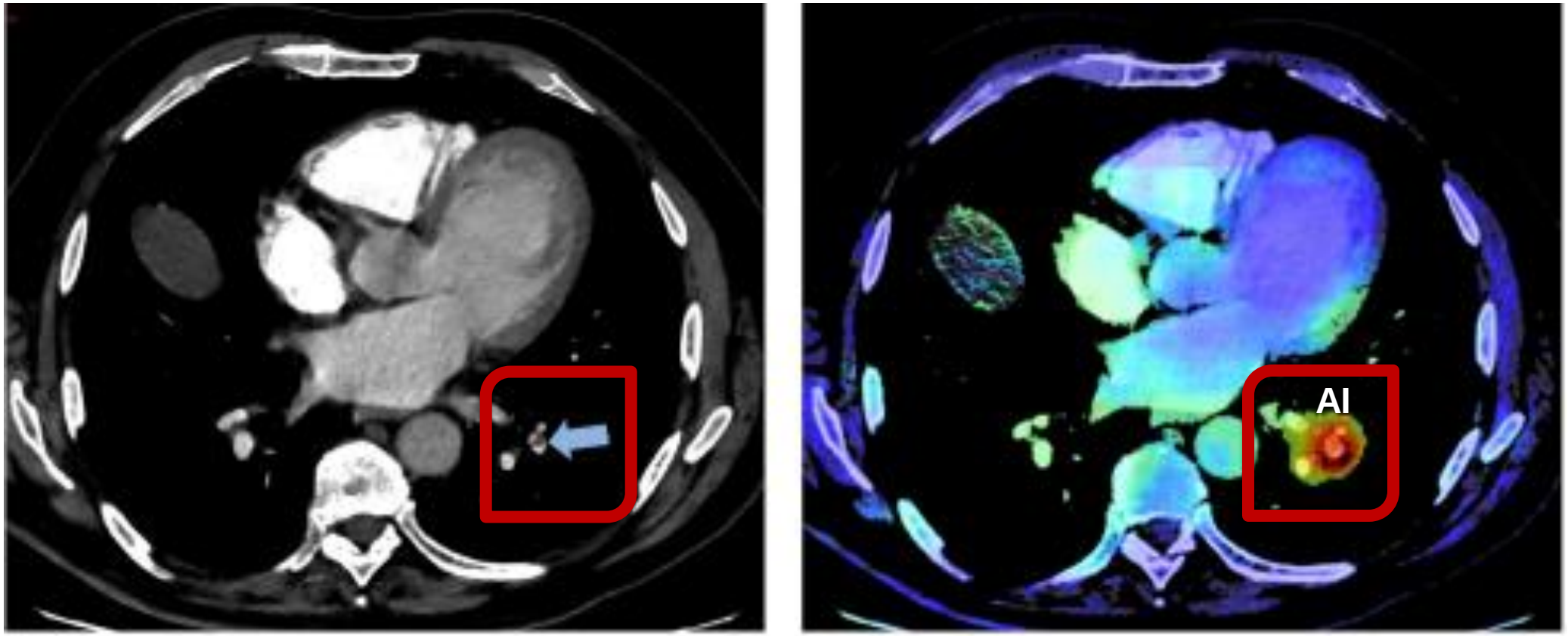
SES Score and Incident VTE (N=51,350)



(Jorgensen H. JTH 2021; 19: 3051-3061)

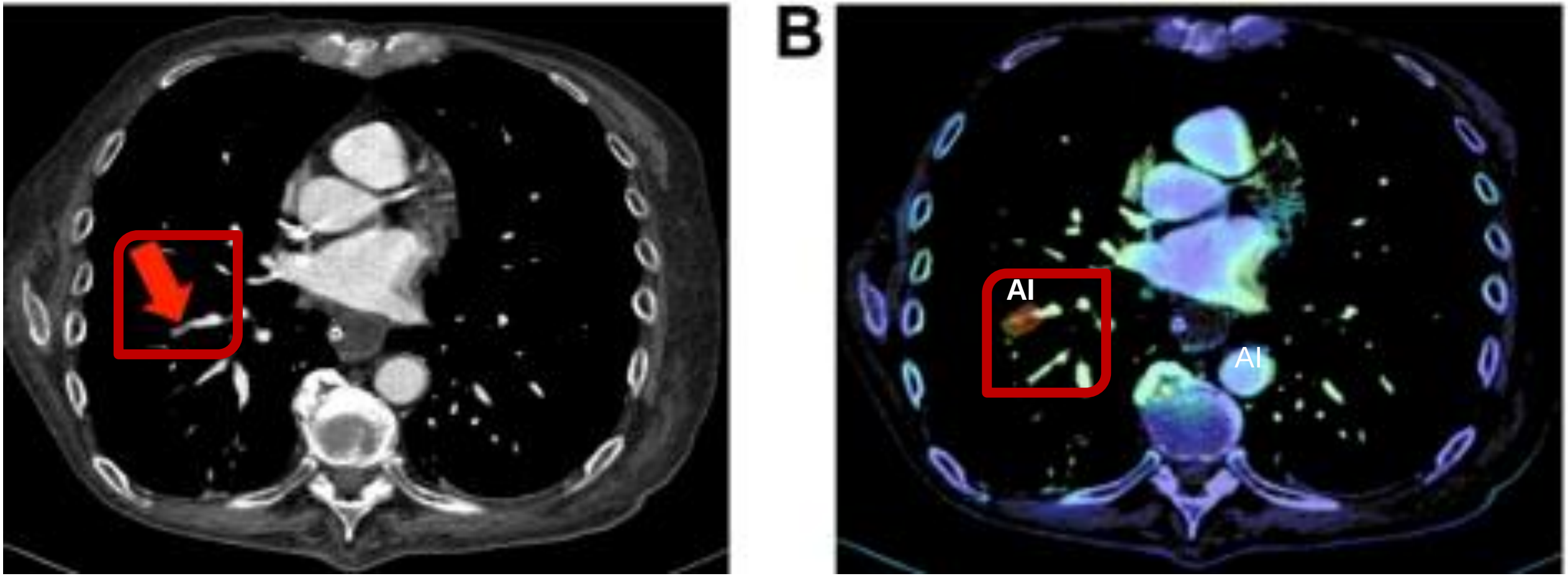
Pathophysiology

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)

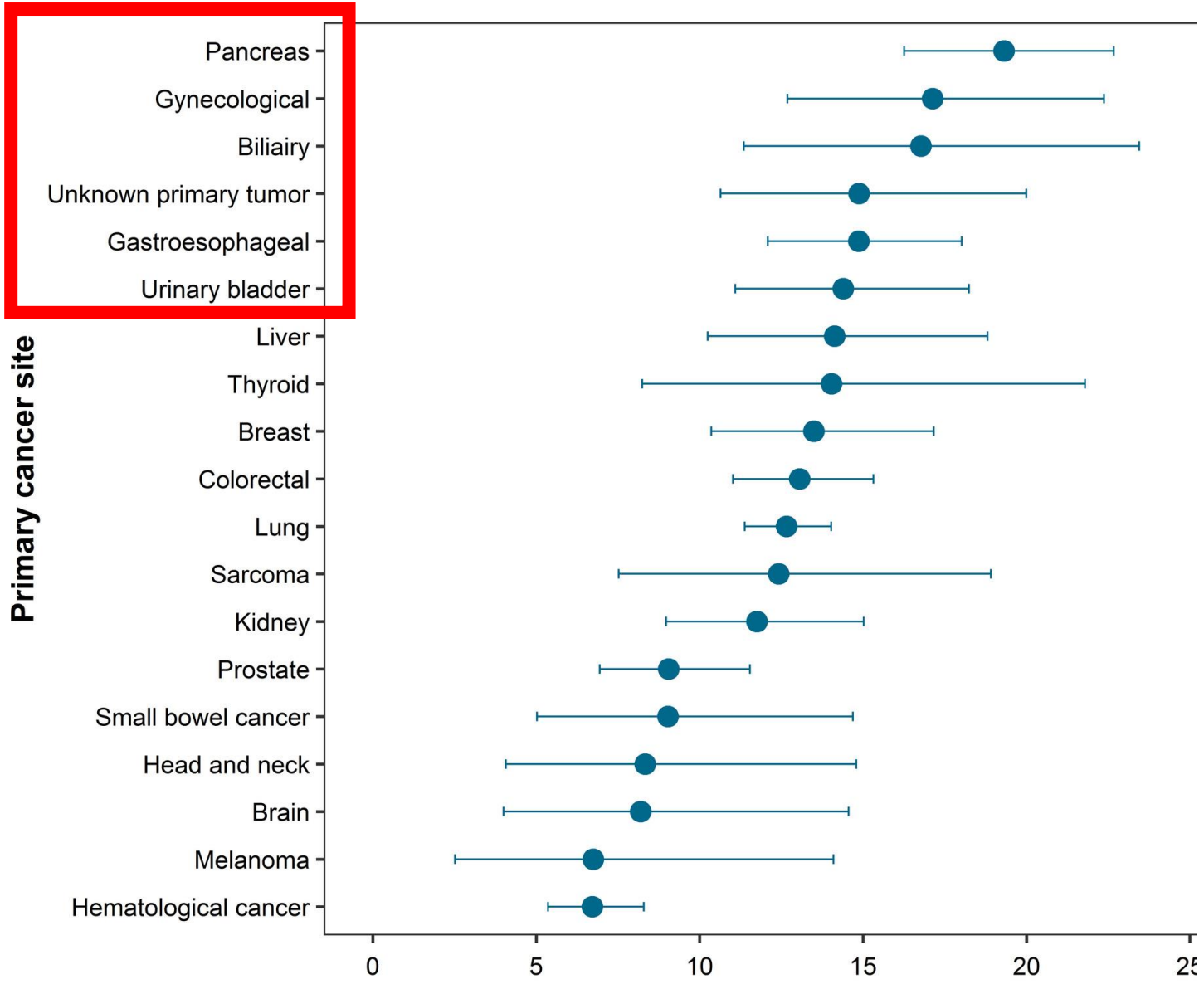
Inflammation-Linked Conditions that Can Trigger PE or DVT

- 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

Cancer Sites in PE Patients



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

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

STUDY DESIGN

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

7/2004

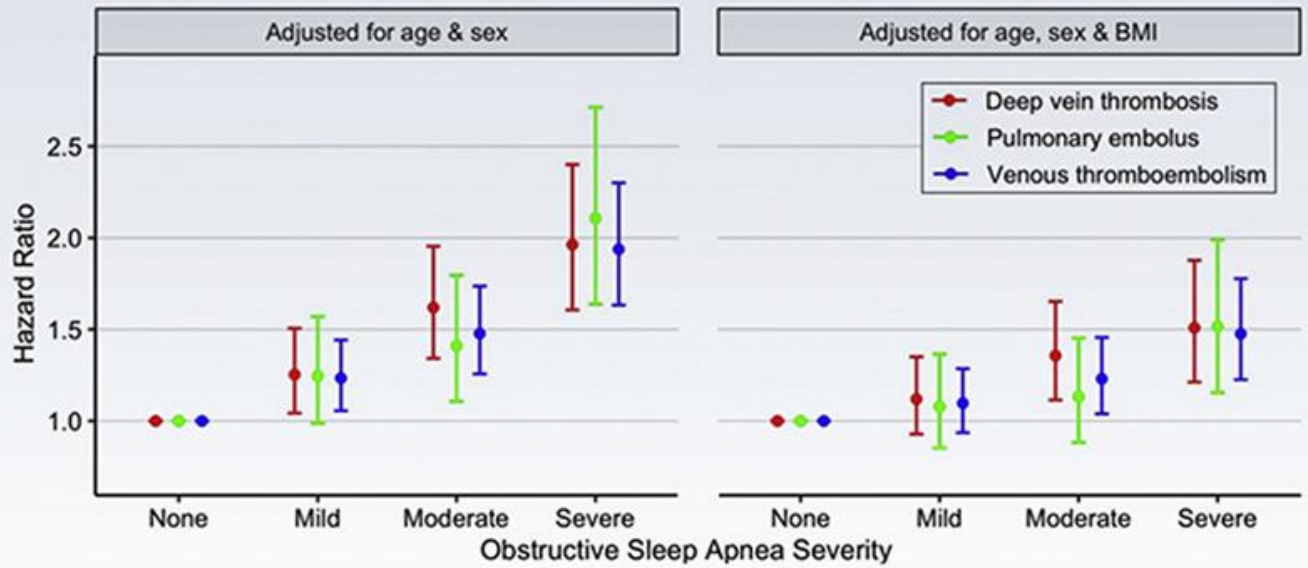
31,309 patients

12/2018

1, 791 VTE events

RESULTS

Risk of Thrombosis and Nocturnal Hypoxemia

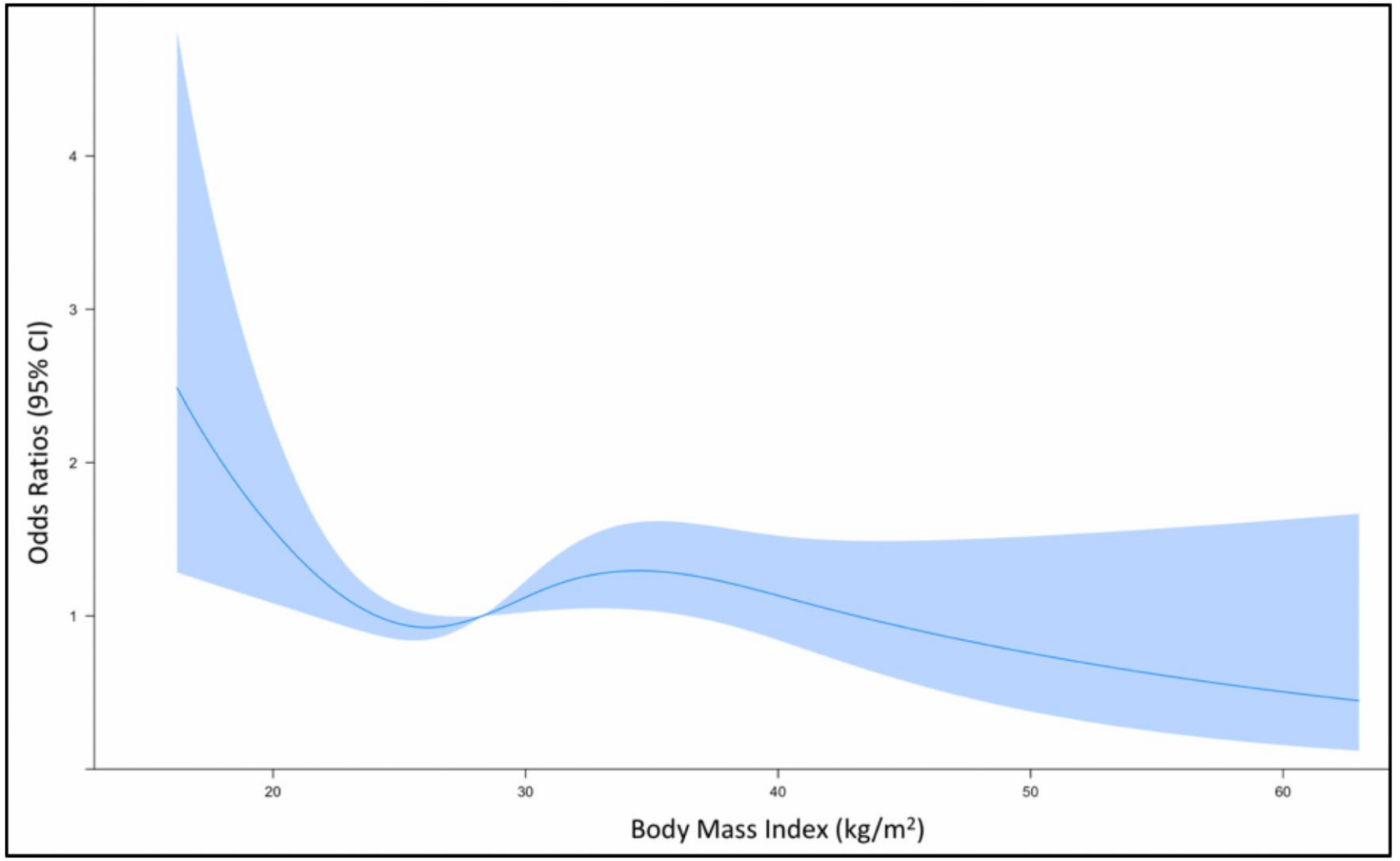


- Patients with >50% sleep time spent with saturations <90% are at increased VTE risk compared to those without nocturnal hypoxemia (HR 1.48, 95% CI 1.16-1.69)

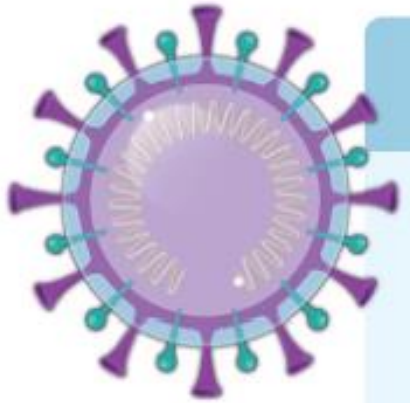
Prolonged nocturnal hypoxemia is independently associated with incident VTE over longitudinal follow up.

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

Inverse Relationship: BMI and VTE



(Kalayci A…Goldhaber SZ. Thromb Res 2022; 211: 63-69)



Sars-COV-2

A

Risk factors

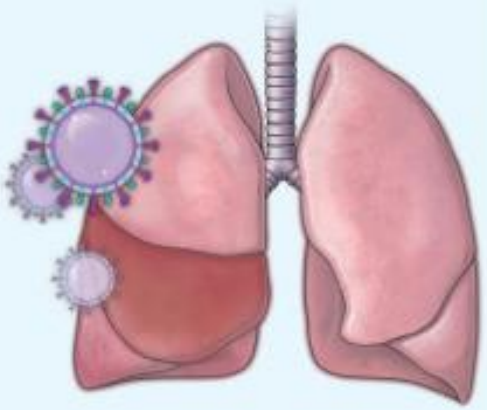
- Acute illness
- Bed-ridden, stasis
- Genetics
- Fever
- Diarrhea
- Sepsis
- Liver injury
- CKD
- COPD
- HF
- Malignancy

Inflammatory response → Endothelial dysfunction Superinfected

Tissue factor
↓TFPI

Lymphopenia

Inflammatory cytokines
↑IL-6, CRP



B

Hemostatic abnormalities

- Pulmonary microthrombi
- Intravascular coagulopathy
- Myocardial injury
- ↑Cardiac biomarkers

- ↑D-dimer, FDPs, PT
- ↓Platelets

C

Clinical outomes

Venous thromboembolism

Myocardial infarction

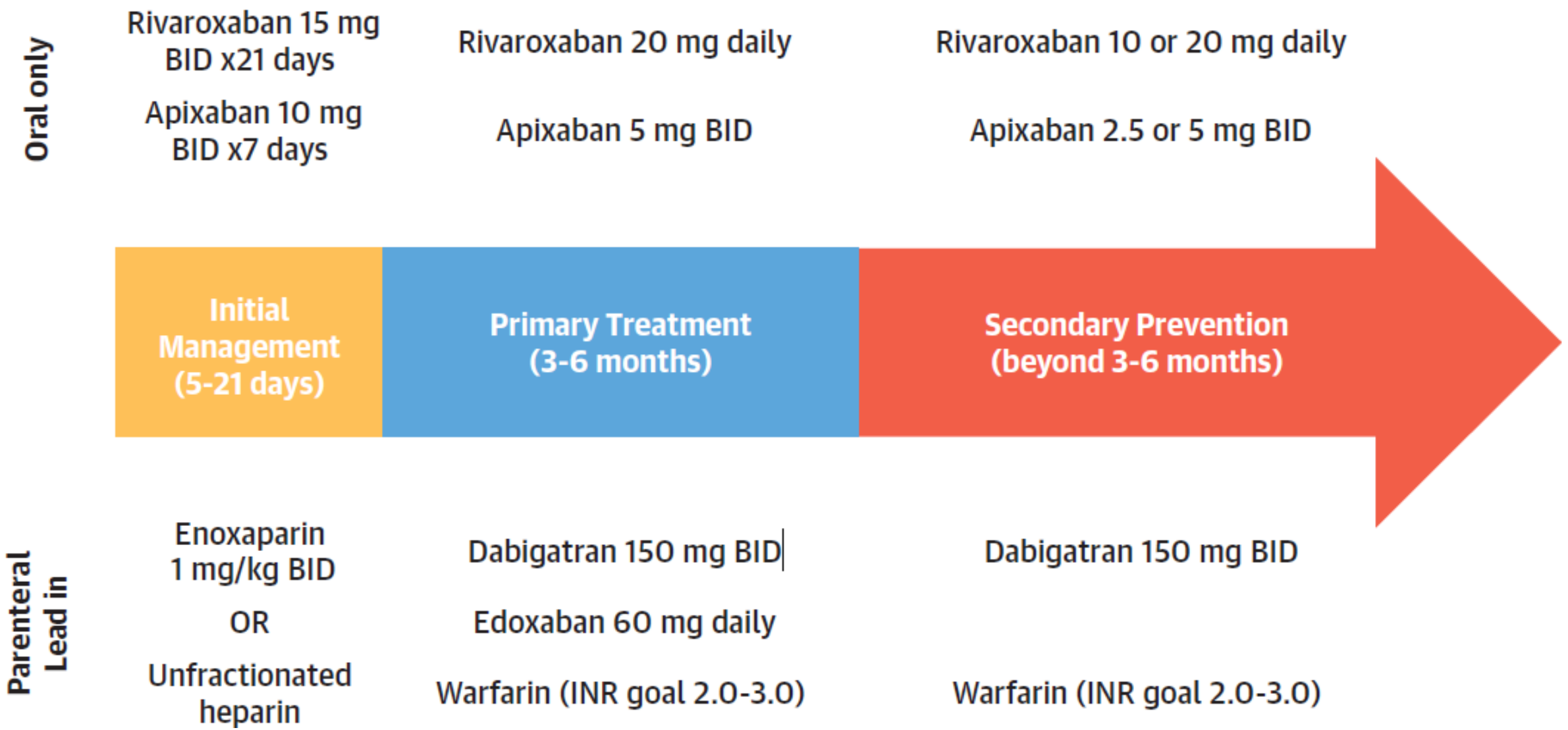
Disseminated intravascular coagulation

DOAC Paradigm To Treat

Pulmonary Embolism and DVT

(Renner E, Barnes G. JACC 2020; 76: 2142-2154)

FIGURE 1 Strategies for Anticoagulation Treatment by Phase of VTE



(JACC 2020; 76: 2142-2154)

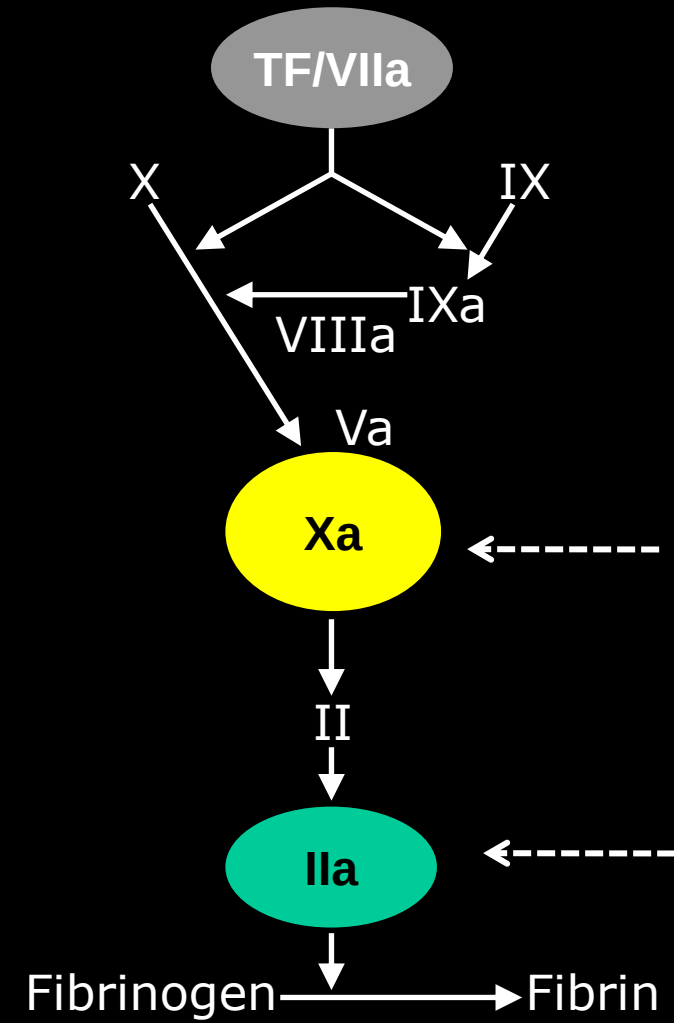
DOACS: Sites of Action

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

Initiation

Propagation

Fibrin formation

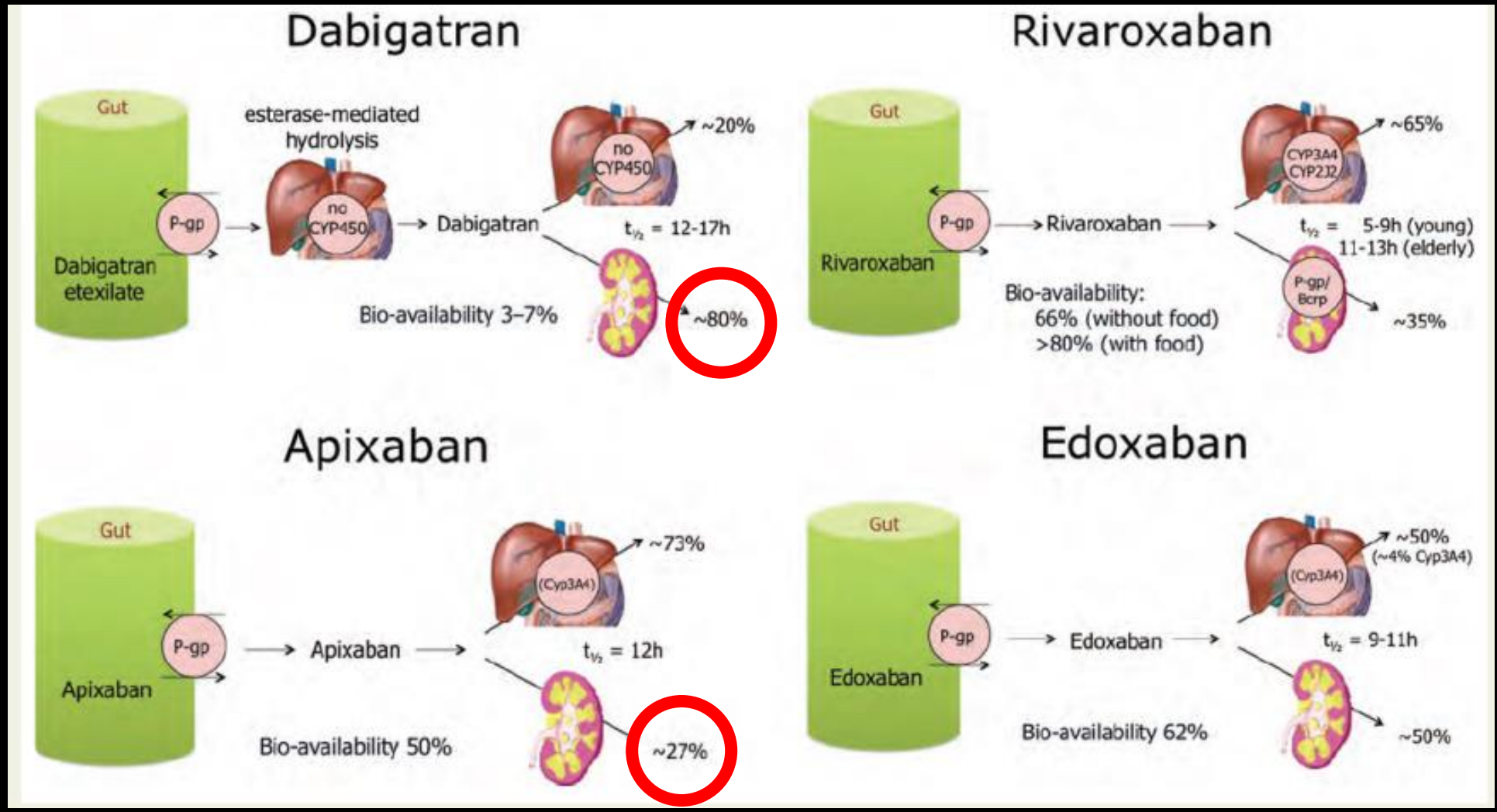


Rivaroxaban
Apixaban
Edoxaban

Dabigatran

(Circulation 2011;123:1436-1450)

DOACS Differ in Liver/ Kidney Metabolism



(Europace 2013; 15: 625-651)

Generic DOAC Is Now Available

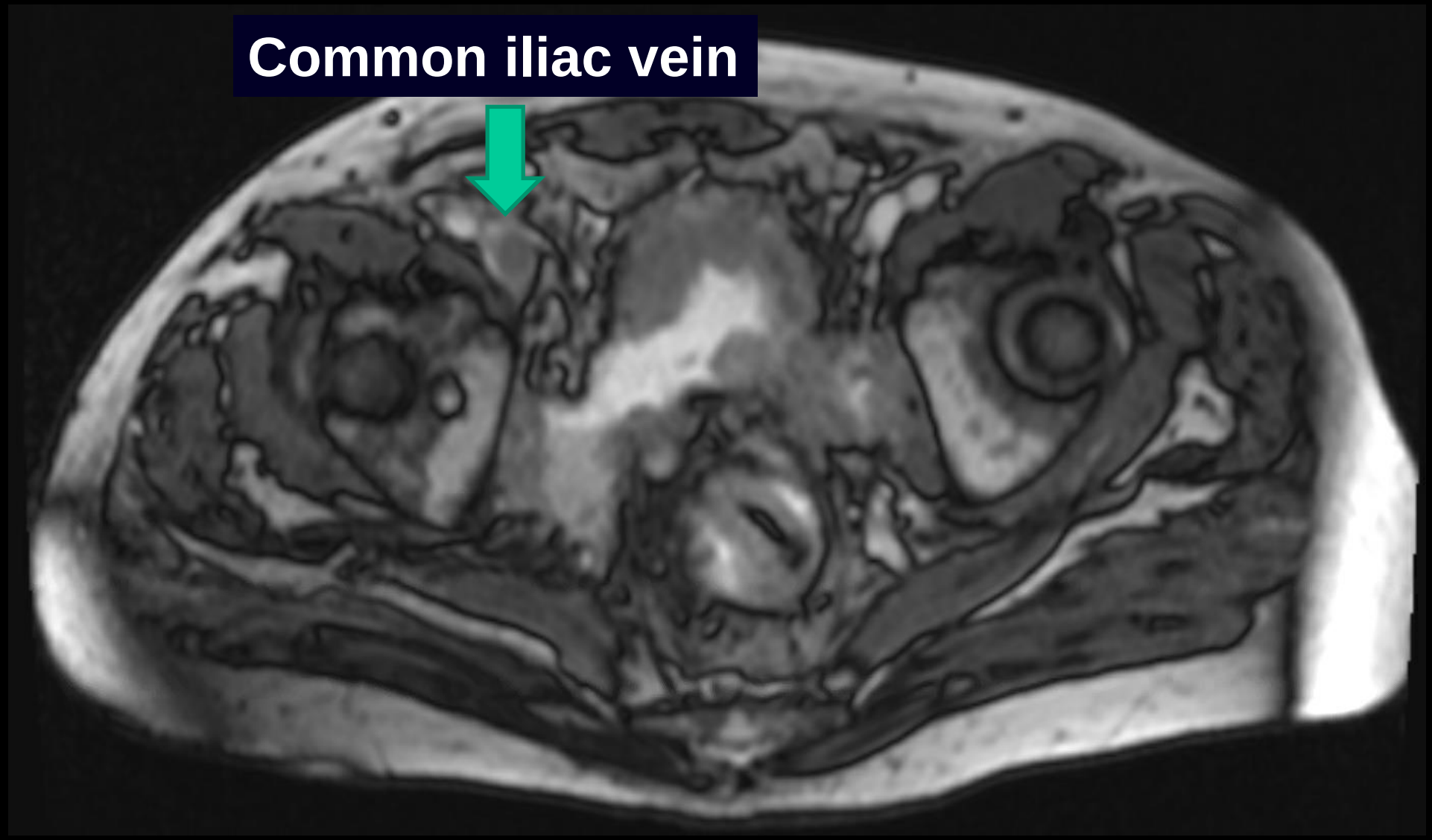
- Dabigatran, introduced by Boehringer Ingelheim in 2010 as “Pradaxa”
- Generic dabigatran, introduced by Camber Pharmaceuticals in 2022
- Pradaxa 150 mg capsule: $6.96
- Camber’s 150 mg capsule: $5.87
- As additional generics are marketed, dabigatran’s price will fall further

CAN DOACS REPLACE LMWH MONOTHERAPY IN CANCER PATIENTS WITH VTE?

CHALLENGES: ANTICOAGULATING CANCER PATIENTS WITH VTE

- Cancer is thrombogenic: High rates of recurrent thrombosis despite anticoagulation
- Cancer chemotherapy: thrombogenic/ thrombocytopenic
- Occult metastases are bleeding sources
- Interactions among anticoagulants and novel chemotherapeutic agents—uncharted territory
- Frailty

60 y.o. Man with Stage IV Bladder Cancer



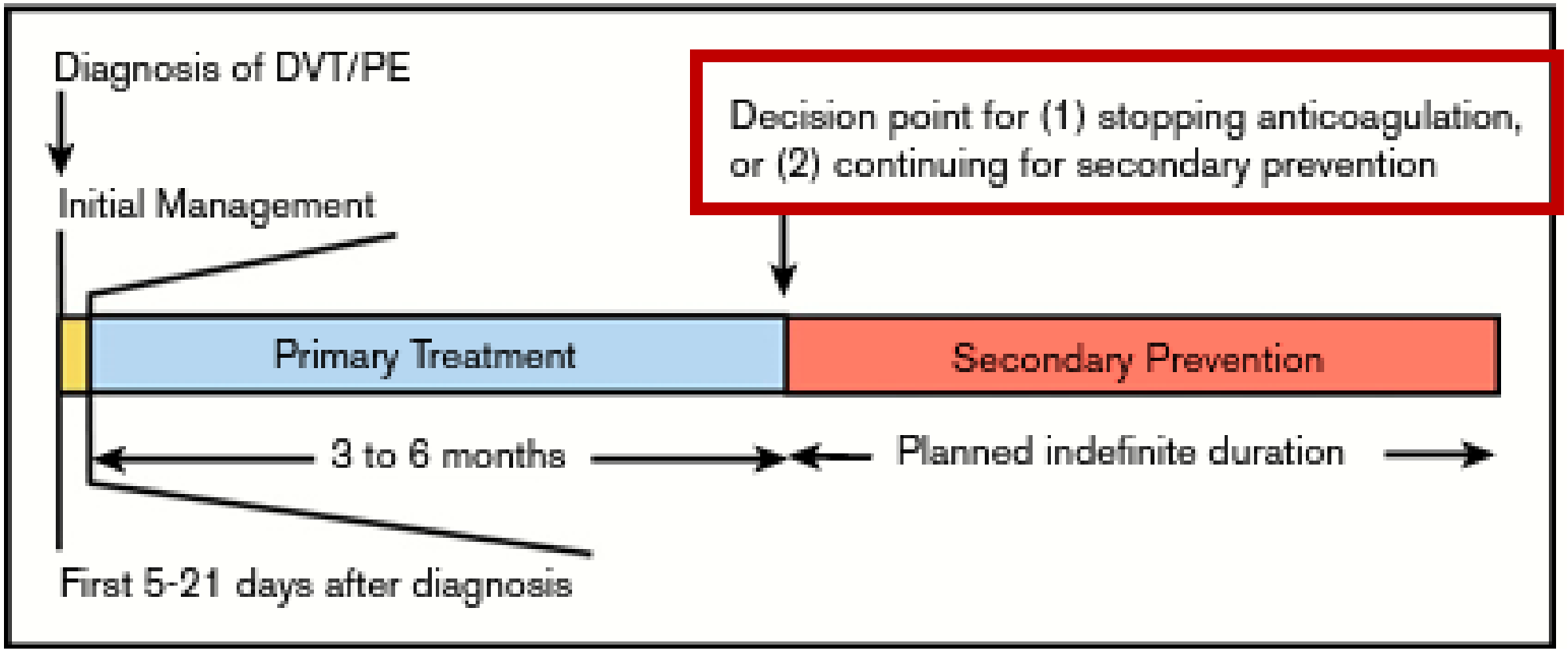
CANCER / ACUTE VTE: DOAC vs. Dalteparin

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)

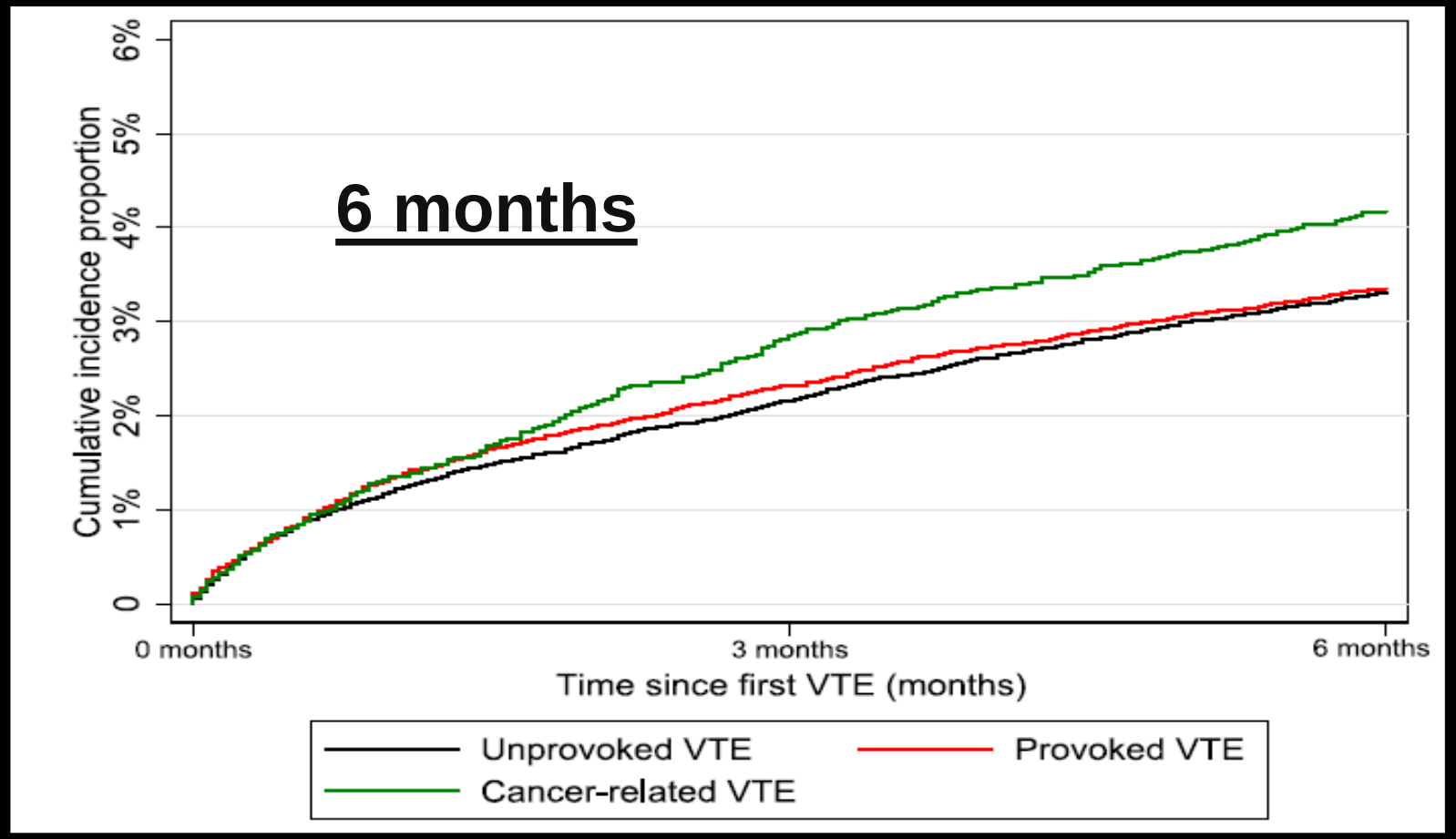
OPTIMAL DURATION OF ANTICOAGULATION:

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

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

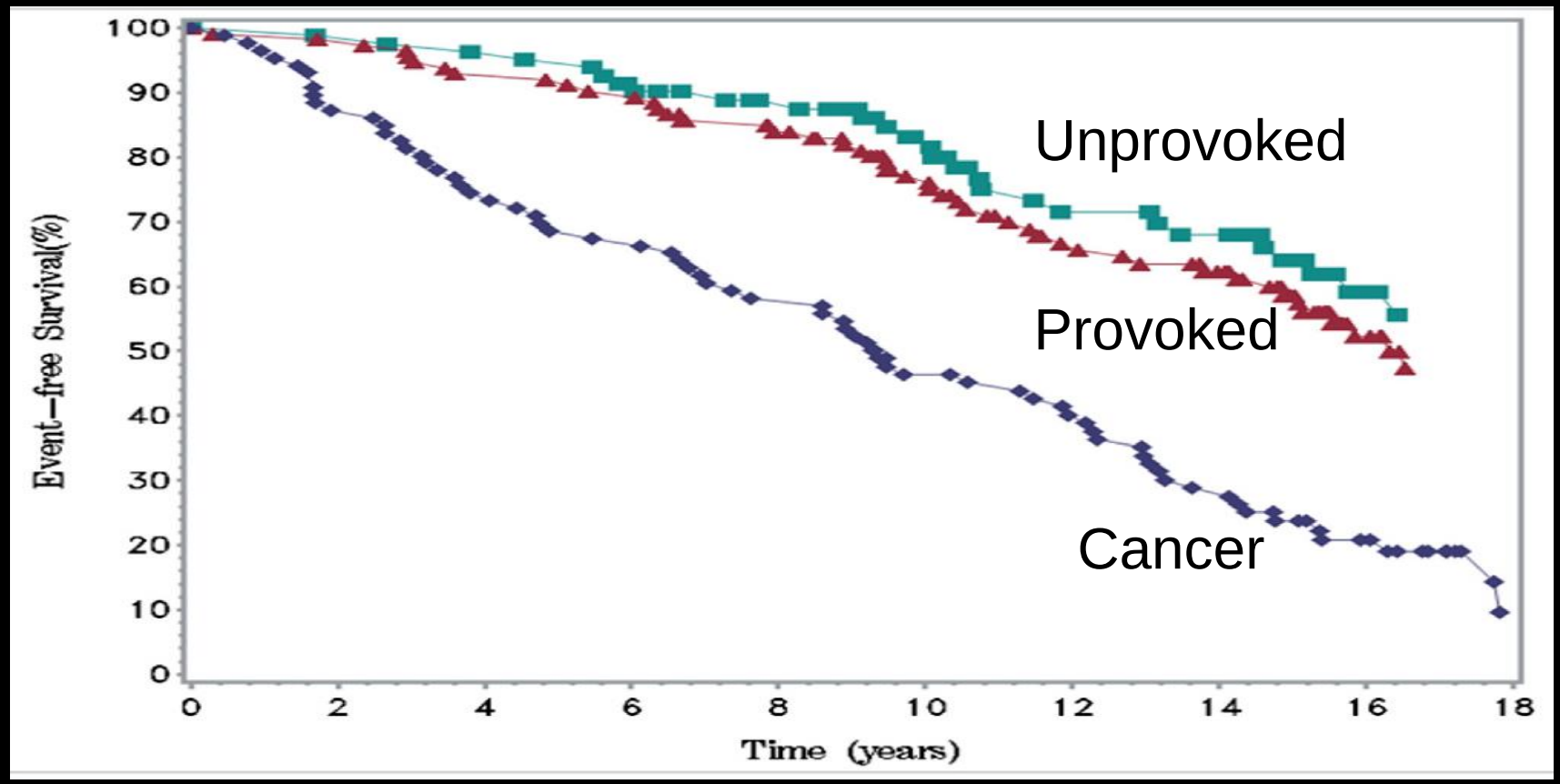


Risk of Recurrent VTE: Danish Cohort Study (N=73,993) 6 Months



(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 ‘provoked’ vs. ‘unprovoked’ 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)

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)

OPTIMAL DURATION OF ANTICOAGULATION:

Who Do You Side with???

1) American Society of Hematology

2) European Society of Cardiology

ADVANCED VTE THERAPY:

BEYOND ANTICOAGULATON

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

AHA: Factors Favoring PE Reperfusion Rx

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

(Circulation 2019; epubl October 4)

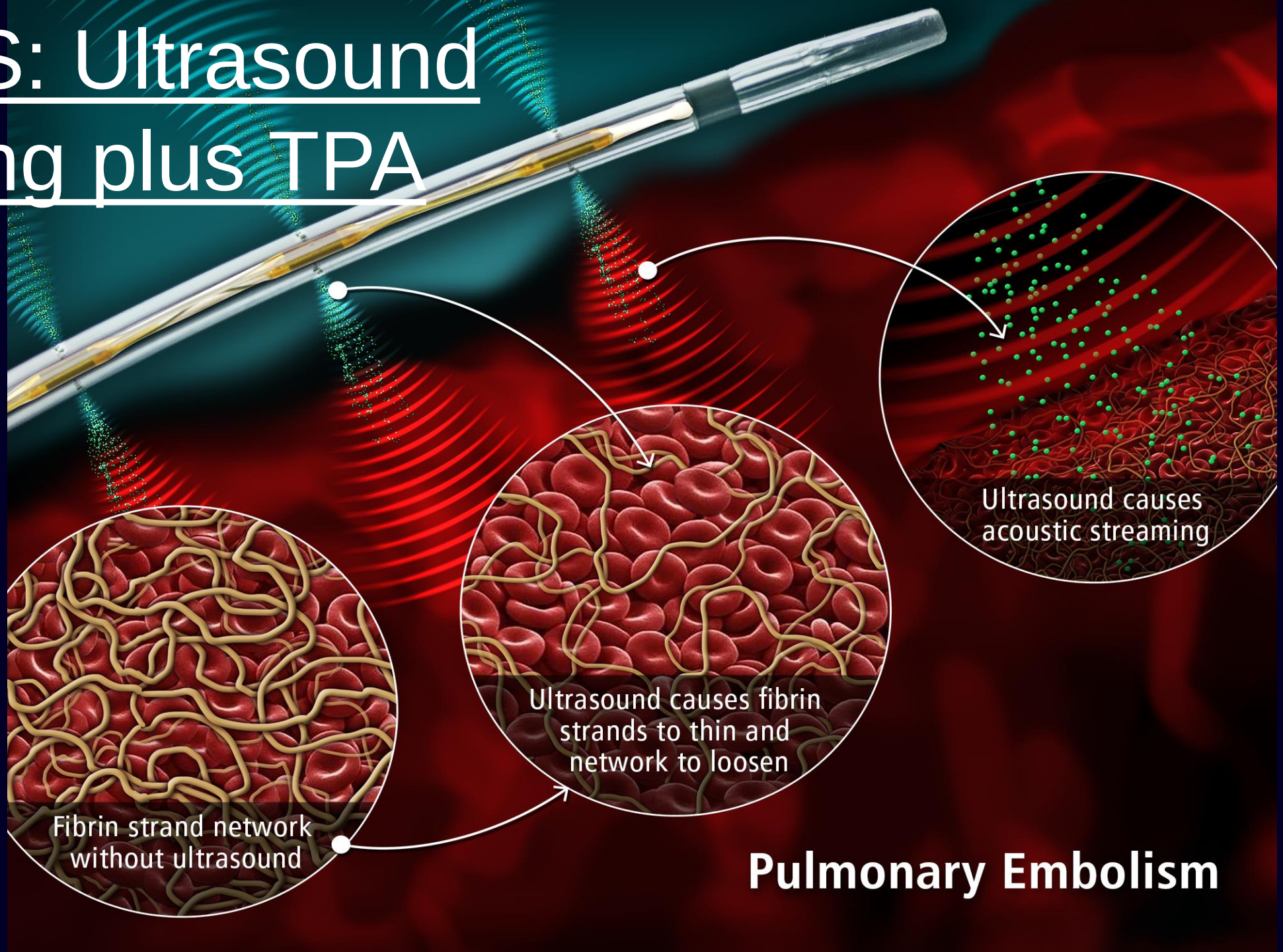
Options for Advanced Therapy in Acute PE

TABLE 1 Options for Advanced Therapy in Acute PE

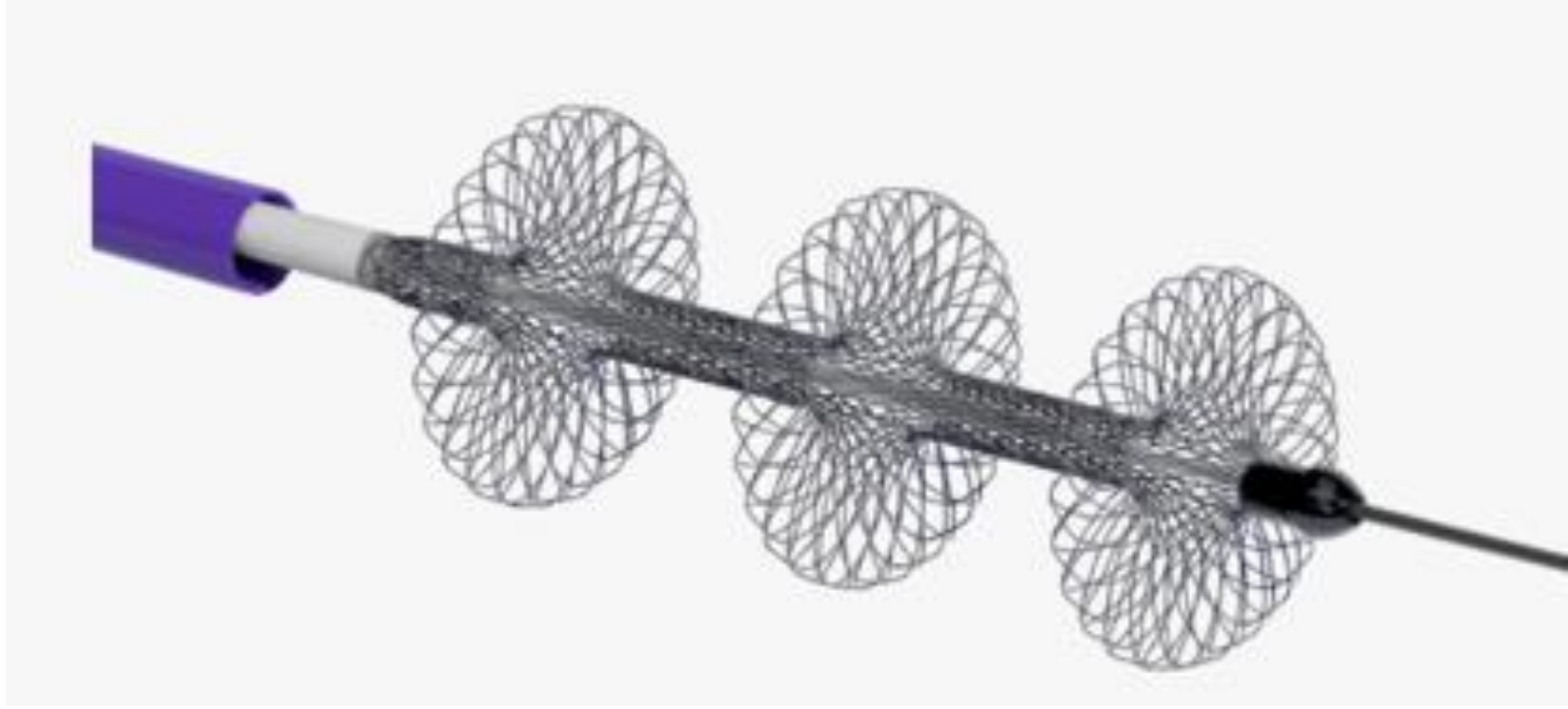
Option	Indications	Advantages	Disadvantages
Systemic fibrinolysis	High- and intermediate-high-risk PE	• Rapid administration • Decreases mortality • Prevents hemodynamic collapse • Expedites RV recovery and symptom relief	• 2%-5% risk of ICH
Catheter-directed therapy	High- and intermediate-high-risk PE	• Expedites RV recovery and symptom relief • Reduced risk of ICH • Option for mechanical embolectomy with some devices	• Limited long-term and comparative data • May take time to mobilize
Surgical embolectomy	High- and intermediate-high-risk PE	• Expedites RV recovery and symptom relief • Reduced risk of ICH • Avoids need for fibrinolysis	• Limited long-term and comparative data • May take time to mobilize • Limited to more centrally located PE
ECMO	Refractory cardiogenic shock	• Supports hemodynamics and oxygenation in patients with refractory shock or hypoxemia	• Limited long-term and comparative data • May take time to mobilize

(Piazza G. JACC 2021; 76: 2117-2127)

EKOS: Ultrasound Pulsing plus TPA



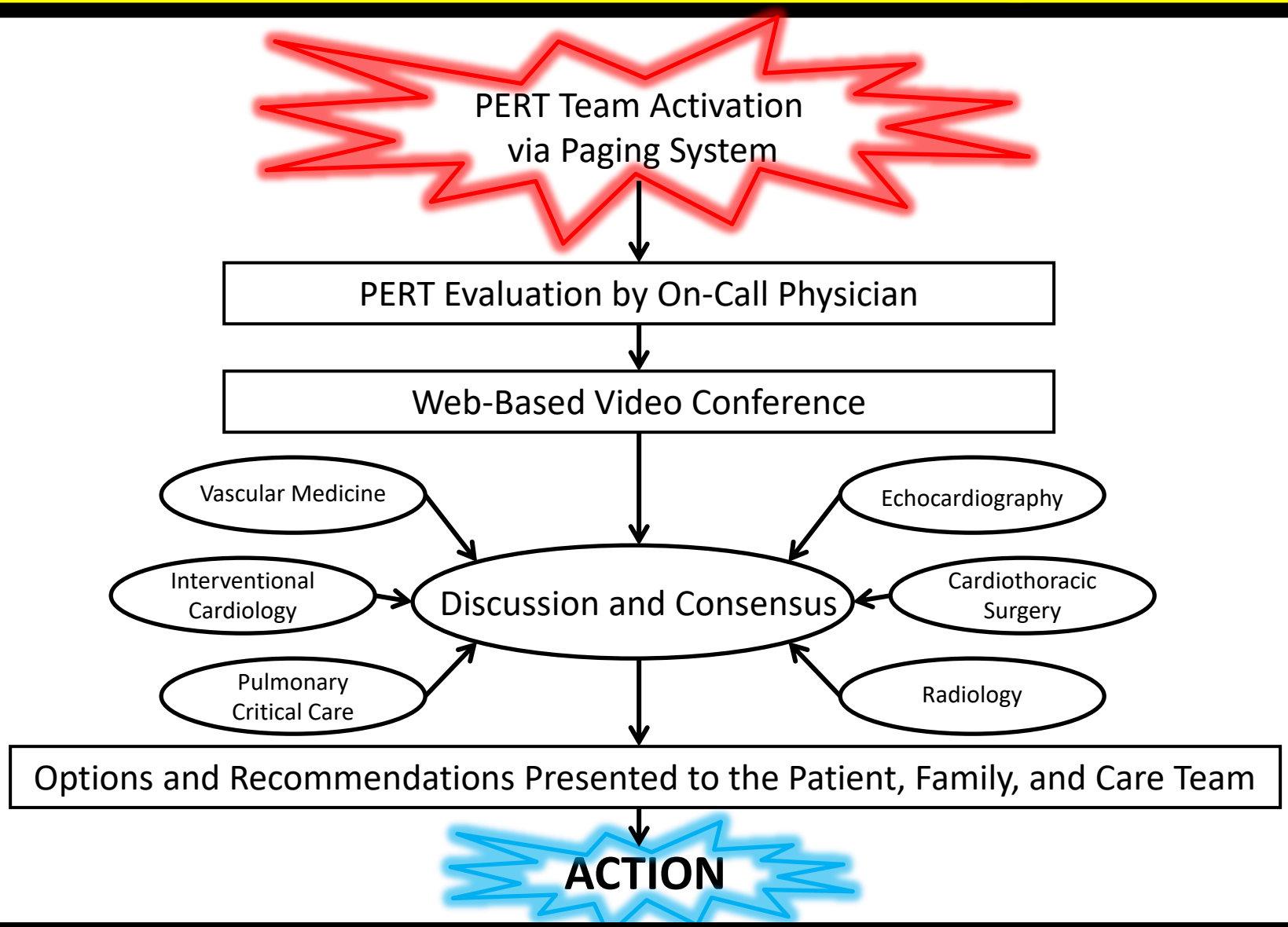
FlowTriever: 20F—No TPA



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

SURGICAL EMBOLECTOMY AT BWH: SURGEON'S CELL PHONE

PE RESPONSE TEAM (PERT)



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

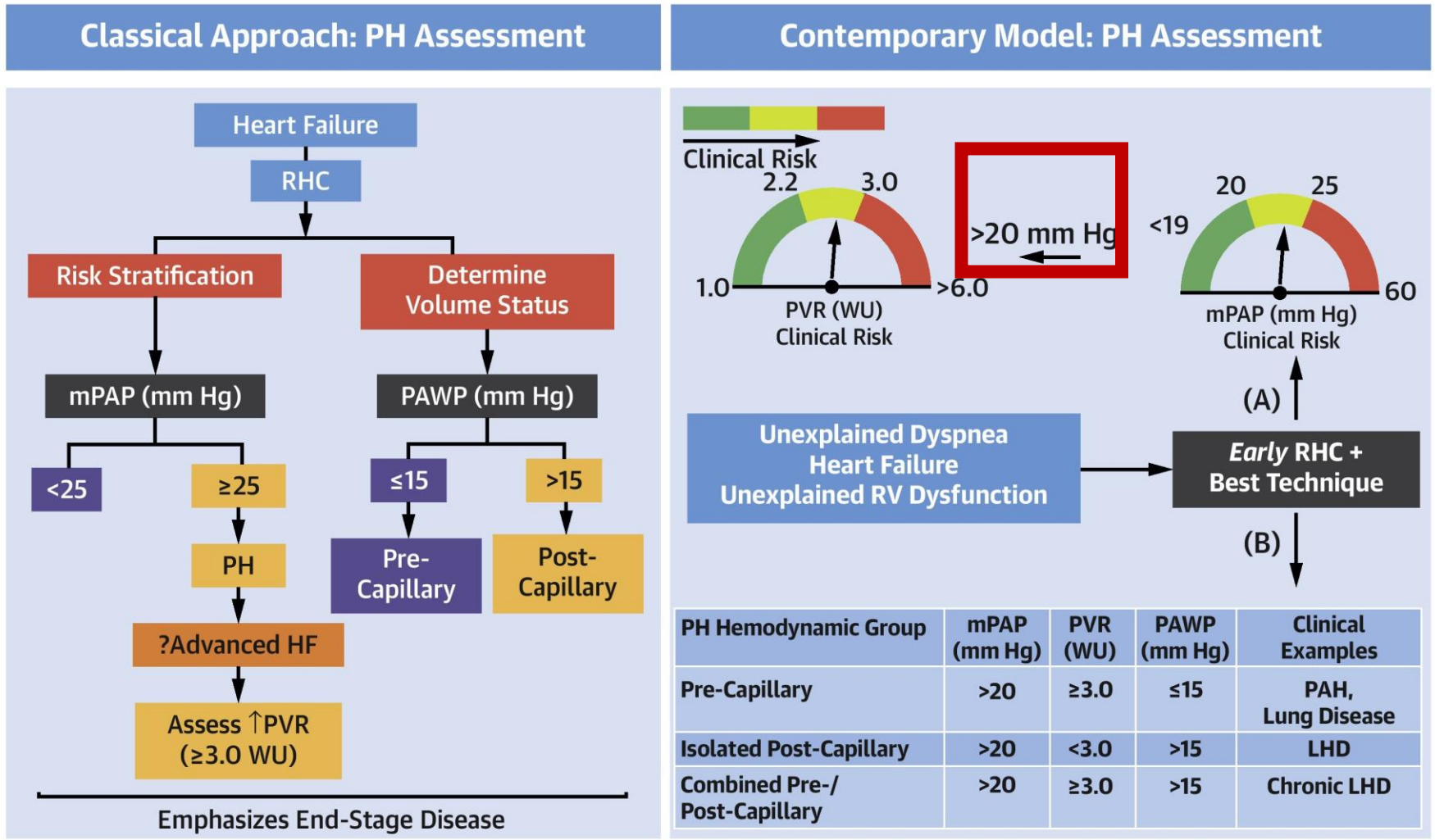
Longitudinal Follow-Up of PE Patients

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).

Are We Underutilizing MR to Assess RV Function after PE?

- MR quantifies RV size, RV function, and regional RV wall motion volumetrically
- No geometric assumptions
- Excellent imaging of RV free wall (often not the case with ECHO)
- No need for IV contrast
- Pretty good quality even with real-time free-breathing (PE patients often can’t breath hold)
- However, ECHO is better than MR for estimating PA pressure

CENTRAL ILLUSTRATION: A Comparison Between Classical and Contemporary Models for Interpreting Hemodynamic Results From Right Heart Catheterization to Classify and Risk Stratify Patients With Pulmonary Hypertension

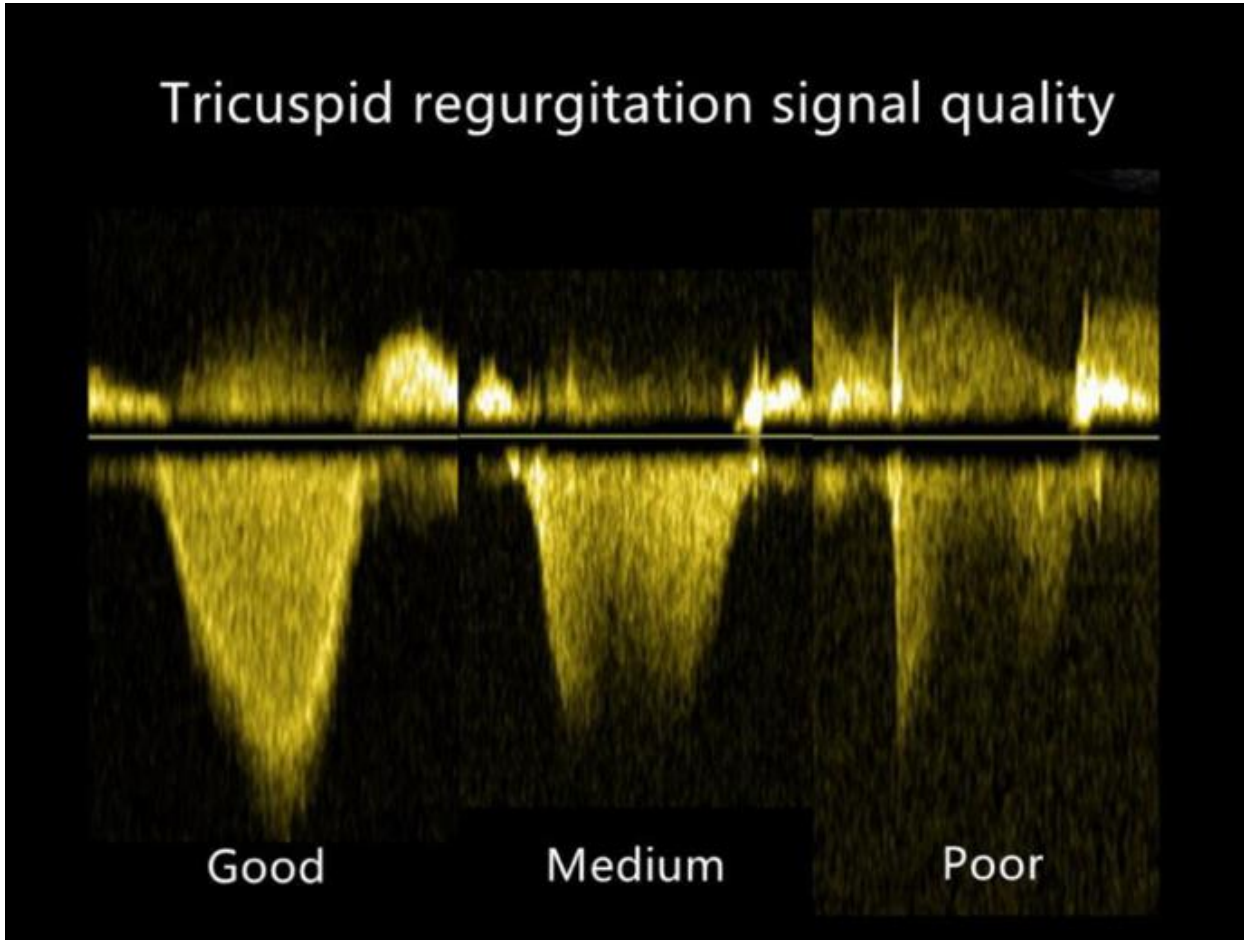


PH Hemodynamic Group	mPAP (mm Hg)	PVR (WU)	PAWP (mm Hg)	Clinical Examples
Pre-Capillary	>20	≥3.0	≤15	PAH, Lung Disease
Isolated Post-Capillary	>20	<3.0	>15	LHD
Combined Pre-/ Post-Capillary	>20	≥3.0	>15	Chronic LHD

Maron, B.A. et al. J Am Coll Cardiol. 2020;76(22):2671-81.

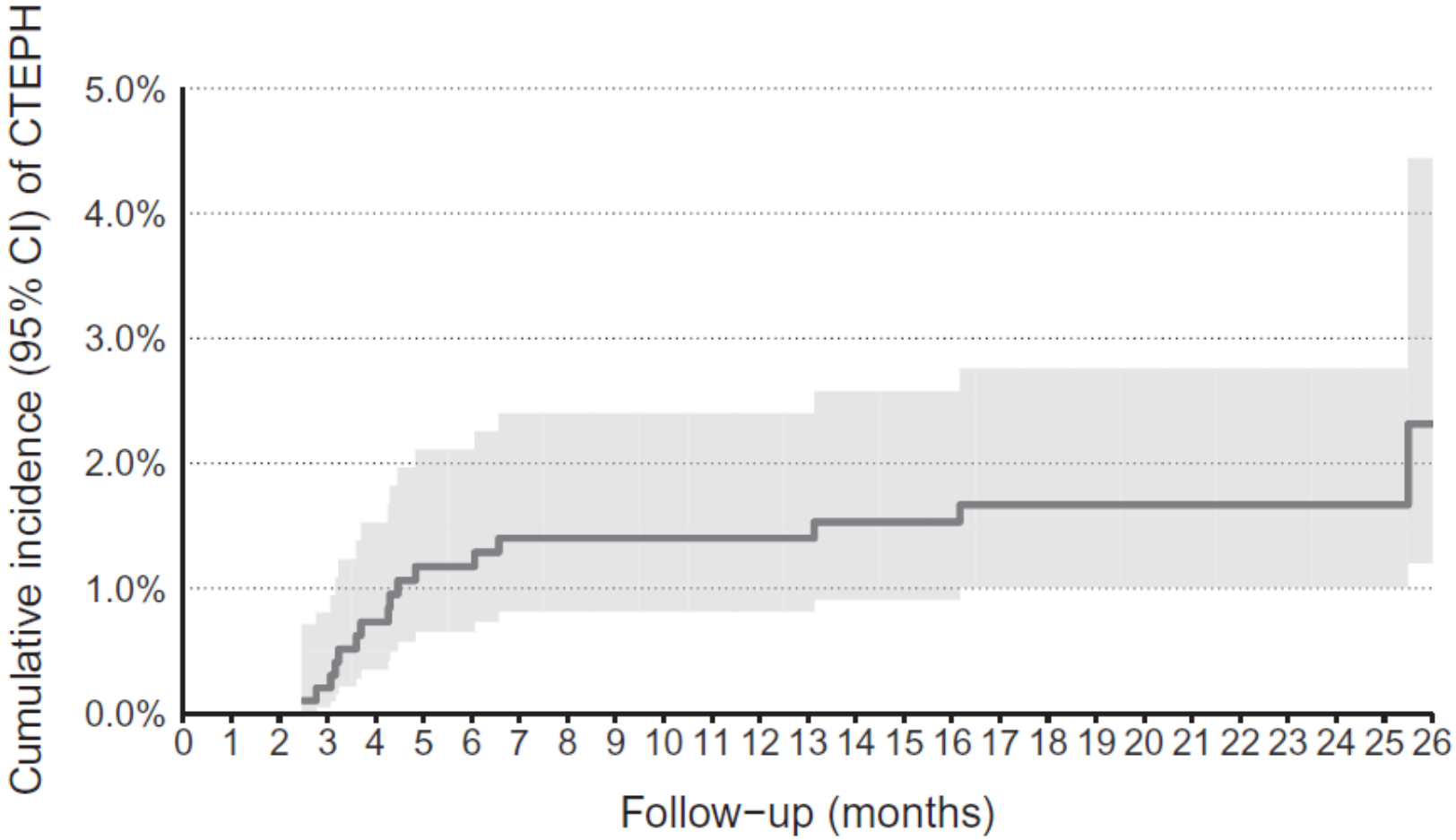
ECHO Estimation of Pulmonary Artery Pressure (N=218)

1) Poor TR signal underestimates sPAP
2) Good TR signal overestimates sPAP in 41% of patients
3) As PH progresses, DE underestimates PAP
4) As PCW increases, ECHO underestimates PAP

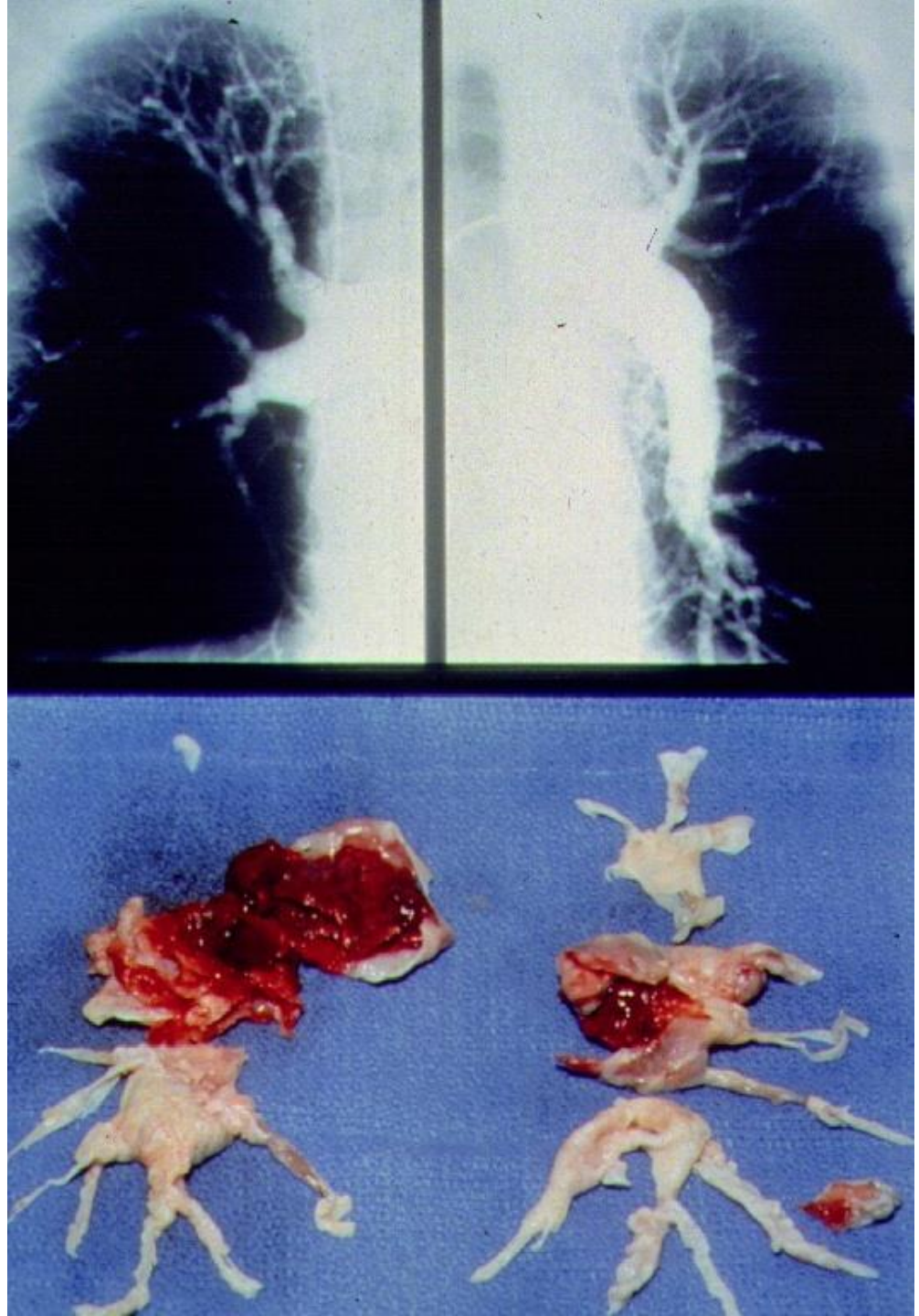


BMC Med Imaging **22,** 91 (May 16, 2022)

CTEPH Incidence (N=1,017)



(European Heart J 2022; April 7)



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

(European Heart Journal 2022; April 7)

Table 2 Study outcomes

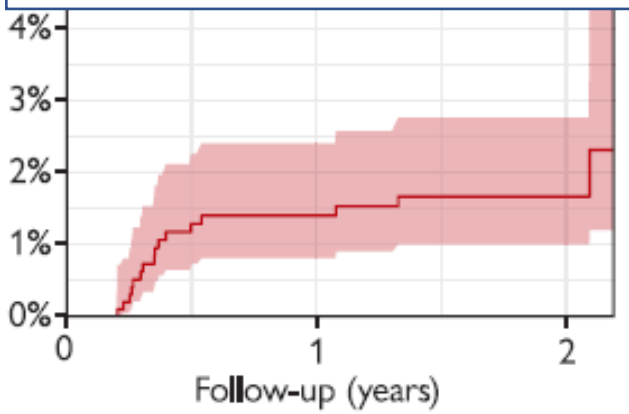
	Evaluable study population $N = 1017$
Co-primary outcomes	
Chronic thromboembolic pulmonary hypertension	
Two-year cumulative incidence (95% CI)	2.3% (1.2–4.4%)
Time to diagnosis (days), median (min-max; IQR)	129 (74–765; 97–186)
Post-pulmonary embolism impairment	Evaluable study population $N = 880$
Two-year cumulative incidence (95% CI)	16.0% (12.8–20.8%)
Visit of first documentation	
3 months	46
12 months	29
24 months	41
Secondary outcomes	
Death from any cause	56 (5.5%)
Cancer	22
Sepsis	5
Respiratory failure	3
Other, n	26
PE recurrence	19 (1.9%)
Major bleeding	87 (8.6%)
Stroke	7 (0.7%)
Re-hospitalization	318 (31%)

CI, confidence interval; IQR, interquartile range; PE, pulmonary embolism.

FOCUS.

CTEPH: 2.3%

PPEI: 16.0%



- Acute PE
- Discharge
- 3 Months
- 12 Months
- 24 Months

← Median time to CTEPH diagnosis

129 days

Cumulative incidence

- CTEPH 2.3% (95% CI 1.2-4.4%)
- PPEI 16.0 % (95% CI 12.8-20.8%)

1098 Patients with acute PE enrolled

1017 Patients analyzed for CTEPH

880 Patients analyzed for PPEI

Echocardiographic criteria

- RV basal diameter
- RA end-systolic area
- TAPSE
- LV eccentricity index
- RA pressure (estimated)
- Tricuspid regurgitant jet velocity
- Pericardial effusion

Clinical, functional or laboratory criteria

- Persistent/worsening symptoms
- Clinical RV failure
- Syncope
- WHO functional class
- Six-minute walking distance
- BNP or NT-proBNP plasms levels
- Cardiopulmonary exercise testing

(European Heart Journal 2022; April 7)

Summary/ Take Home Points

1. Health inequities lead to worse PE outcomes
2. DOACs: assess bleeding risk, liver function, and kidney function
3. Patients with cancer and VTE can often be treated with a DOAC rather than LMWH
4. Consider extended duration AC in most VTE patients rather than a fixed “stop date.”
5. Advanced therapy: systemic thrombolysis, catheter directed therapy with or without thrombolysis, or surgical embolectomy

References

- 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