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

# Thrombosis and Anticoagulation

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- Clinical focus: Thrombosis and Vascular Medicine
- Research focus: Thrombosis

# DISCLOSURES

**Research Grants:** BMS/Pfizer, Janssen, Alexion, Bayer, Amgen, BSC, NIH Esperion, 1R01HL164717-01

**Advisory Role:** BSC, Amgen, BCRI, PERC, NAMSA, BMS, Janssen, Regeneron

# OBJECTIVES

1. Review the epidemiology and pathophysiology of VTE
2. Discuss the risk stratification of PE and DVT
3. Apply evidence- and pathophysiology-based strategies to manage PE patients

# Association Between Black Race, Clinical Severity, and Management of PE

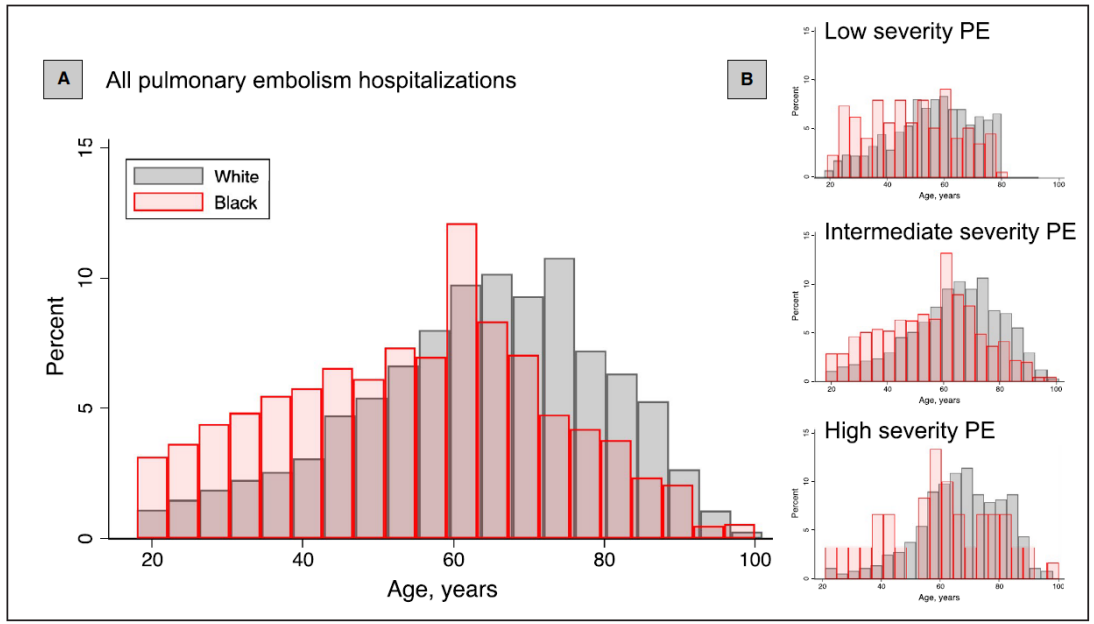



Figure 2. Age of hospitalization for pulmonary embolism by age, per classification for severity in the full cohort.

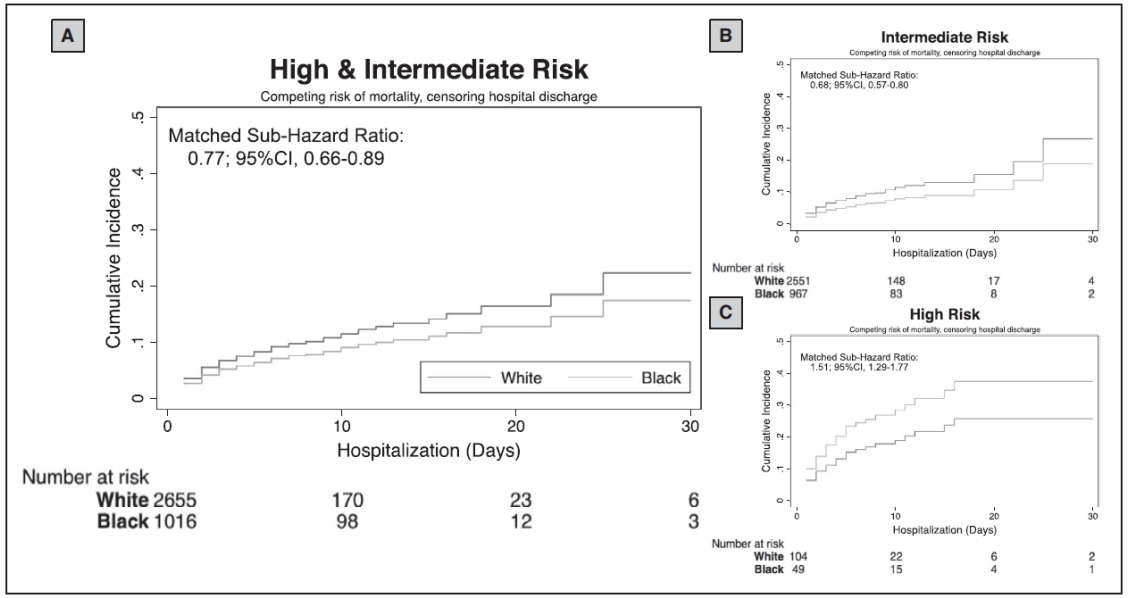
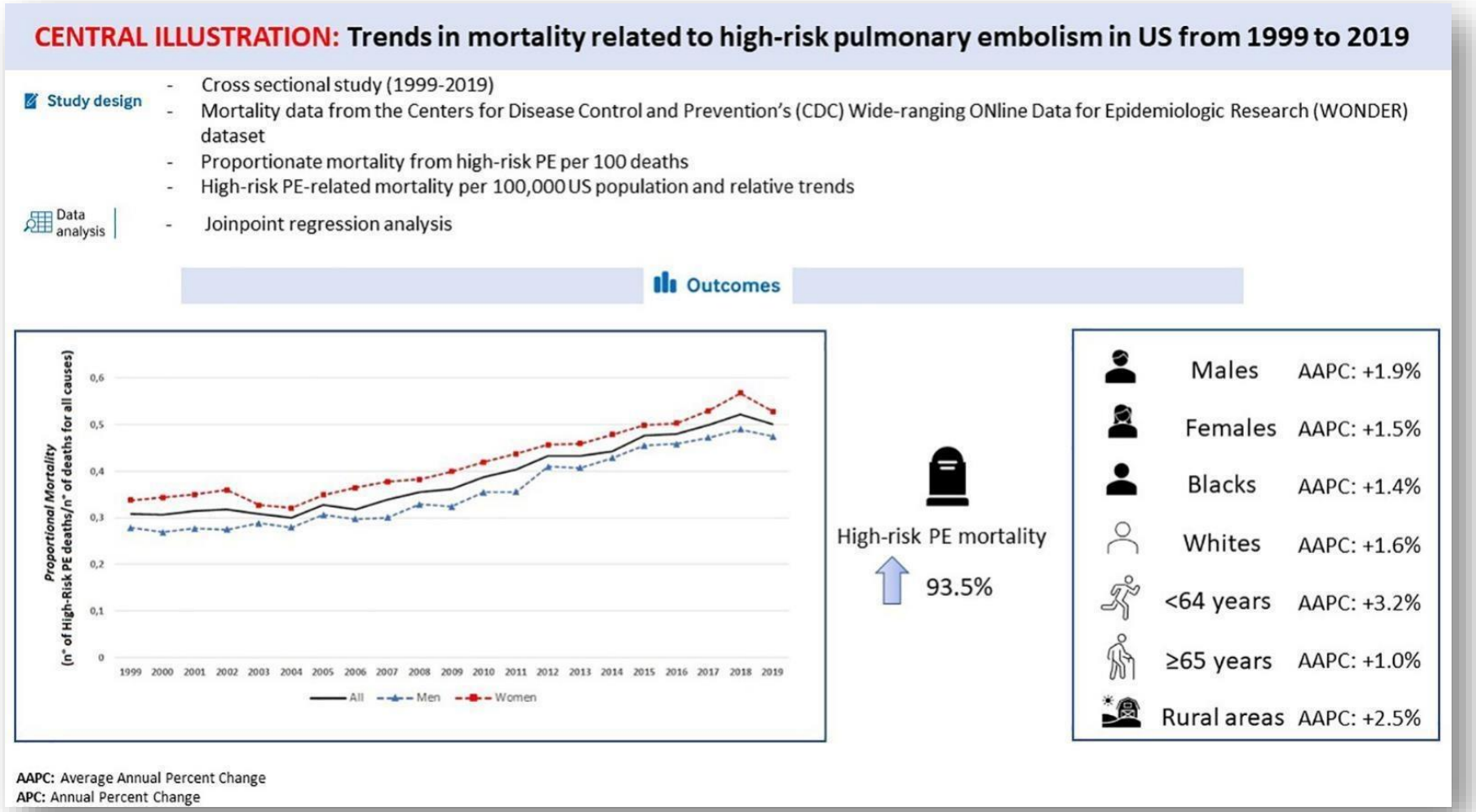



Figure 4. Cumulative hazard of the risk of in-hospital procedures overall among intermediate and high-severity pulmonary embolisms in the matched cohort together (A) and separately (B and C).



Phillips AR, et al. J Am Heart Assoc. 2021;10:e021818

# US Mortality Trends in Patients with High-Risk PE






Zuin M, et al. Thromb Res. 2023;228:72

# US Mortality Trends in Early Adults with PE

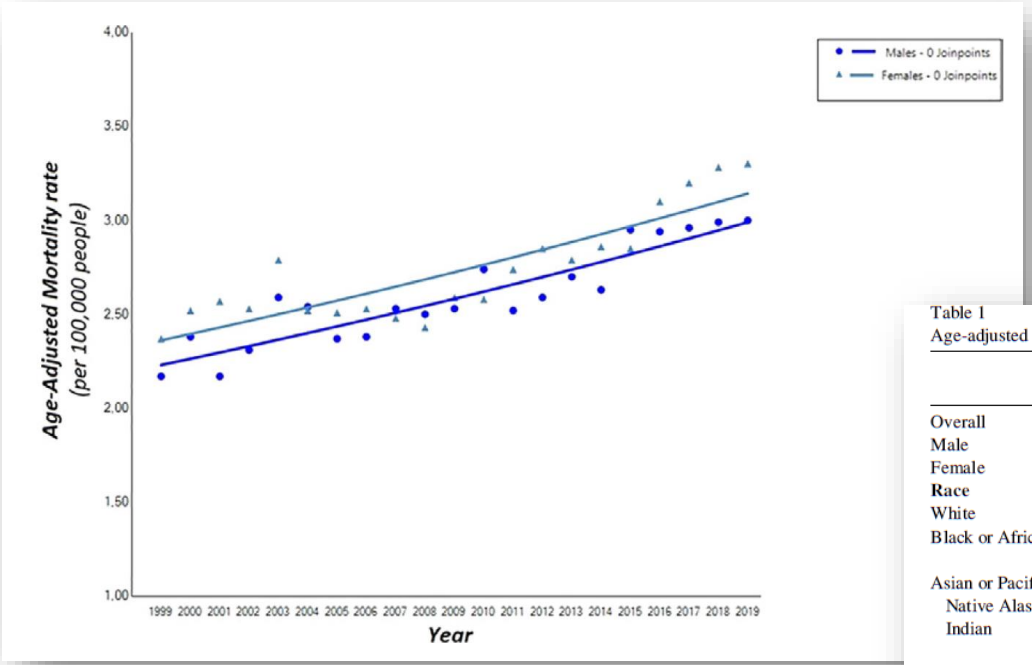



Table 1
Age-adjusted mortality rate trend in early adults with pulmonary embolism (25-44 years), 1999-2019, stratified by gender and race/ethnicity

| | AAMR 1999 (95% CI) | AAMR 2019 (95% CI) | AAPC; (95% CI), p | Number of Joinpoints | Period 1 [years] APC; (95% CI), p | APC - period 2 [years] APC; (95% CI), p | p |
|---|---|---|---|---|---|---|---|
| Overall | 2.27 (2.17 to 2.37) | 3.20 (3.13 to 3.31) | 1.4; (1.1 to 1.7), p<0.001 | 0 | - | - | - |
| Male | 2.17 (2.03 to 2.31) | 3.00 (2.83 to 3.16) | 1.5; (1.2 to 1.8), p<0.001 | 0 | - | - | 0.058 |
| Female | 2.37 (2.22 to 2.52) | 3.36 (3.18 to 3.54) | 1.4;(1.0 to 1.9), p<0.001 | 0 | - | - | |
| **Race** | | | | | | | |
| White | 1.86 (1.76−1.96) | 2.74 (2.61−2.87) | 1.7; (1.4 to 2.0), p<0.001 | 0 | - | - | White vs Blacks: p=0.002 |
| Black or African American | 5.72 (5.27−6.17) | 6.74 (6.27−7.21) | 0.7; (0.3 to 1.0), p<0.001 | 1 | [1999−2007] −0.3; (−1.0 to 0.5), p=0.44 | [2007−2019] 1.3; (0.9 to 1.7), p<0.001 | White vs Asian/Pacific Islander and Alaska/American Indian: p<0.001 Blacks vs Asian/Pacific Islander and Alaska/American Indian: p= 0.003 |
| Asian or Pacific Islander and Native Alaska/American Indian | 0.61 (0.41 to 0.89) | 1.14 (0.92 to 1.40) | 2.5; (1.6 to 3.4), p<0.001 | 0 | - | - | |
| **Ethnicity** | | | | | | | |
| Latinx/Hispanic | 1.14 (0.93−1.35) | 1.71 (1.51−1.91) | 1.7; (0.6 to 3.0), p=0.003 | 1 | [1999−2010] −0.9; (−2.3. to 0.6), p=0.23 | [2010 to 2019] 5.0; (2.9 to 7.2), p<0.001 | - |

AAMR = age-adjusted mortality rate, expressed as deaths per 100.000 population; AAPC = average annual percent change; APC = annual percent change.

Zuin M, et al. Am J Cardiol. 2023;202:169

# When Innovation Fails: Barriers to Health Equity

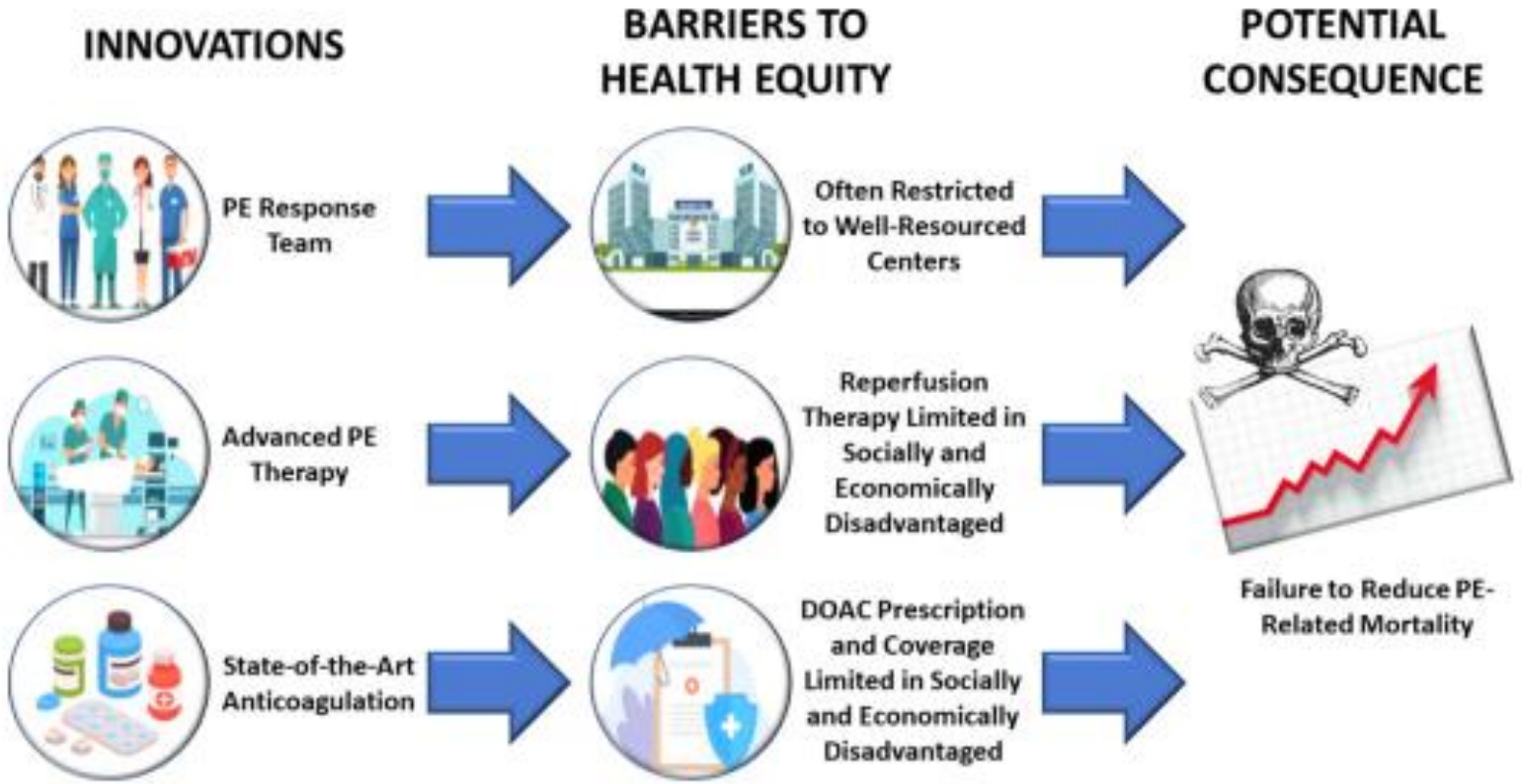
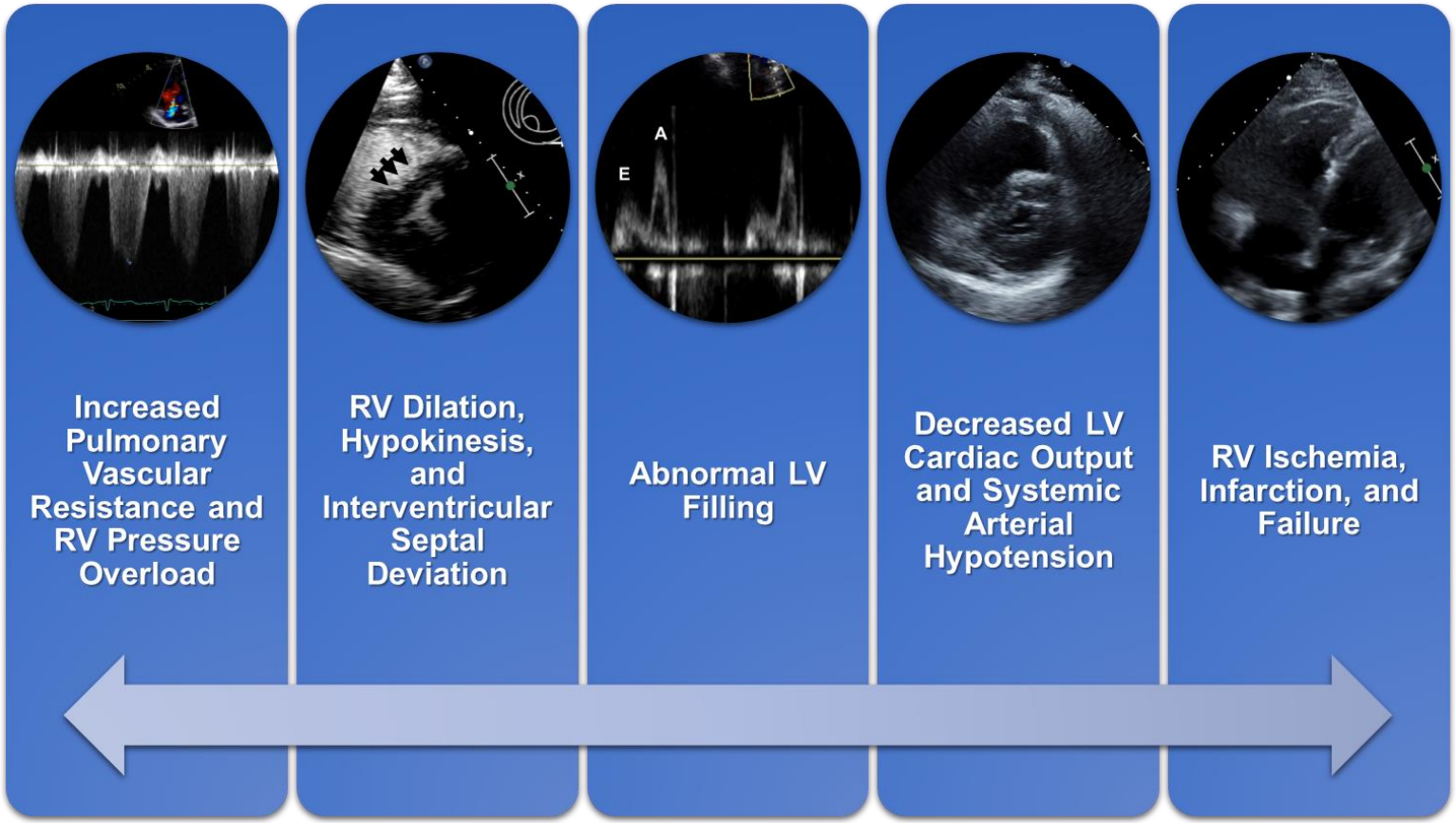
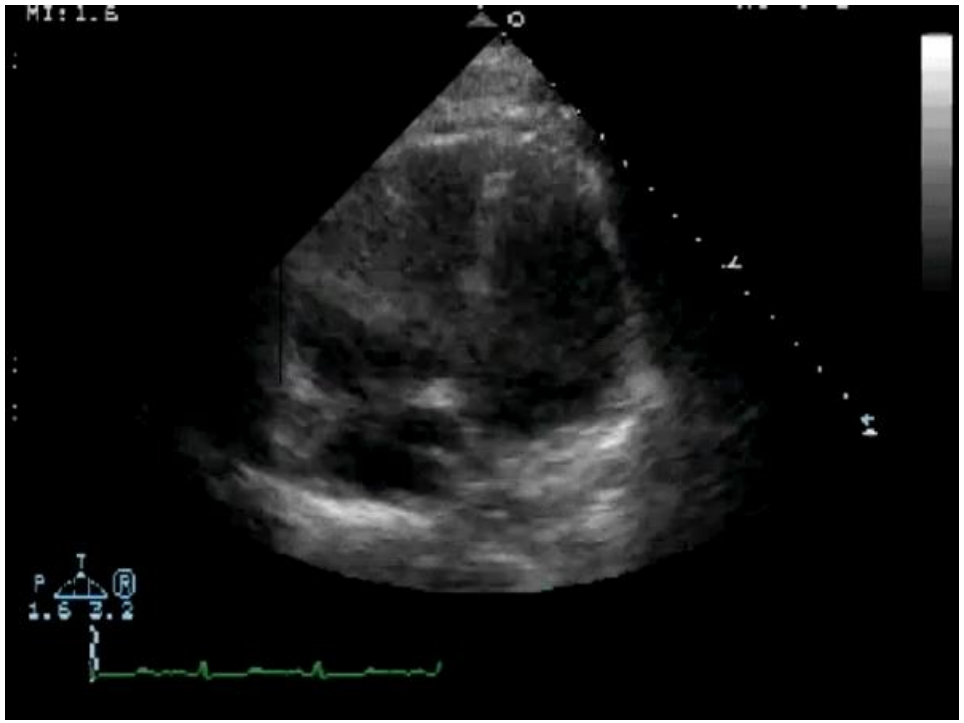



FIGURE Health equity barriers to innovation in pulmonary embolism clinical care and failure to reduce mortality. DOAC, direct oral anticoagulant; PE, pulmonary embolism.

Piazza G. J Thromb Haemost. 2024;22:1838

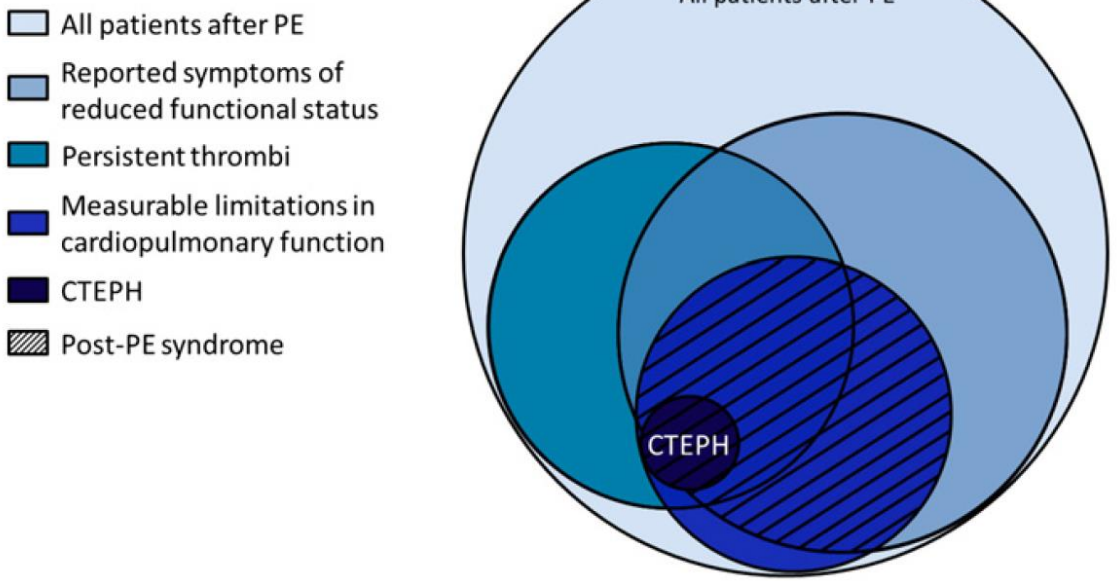
# Pathophysiology of PE

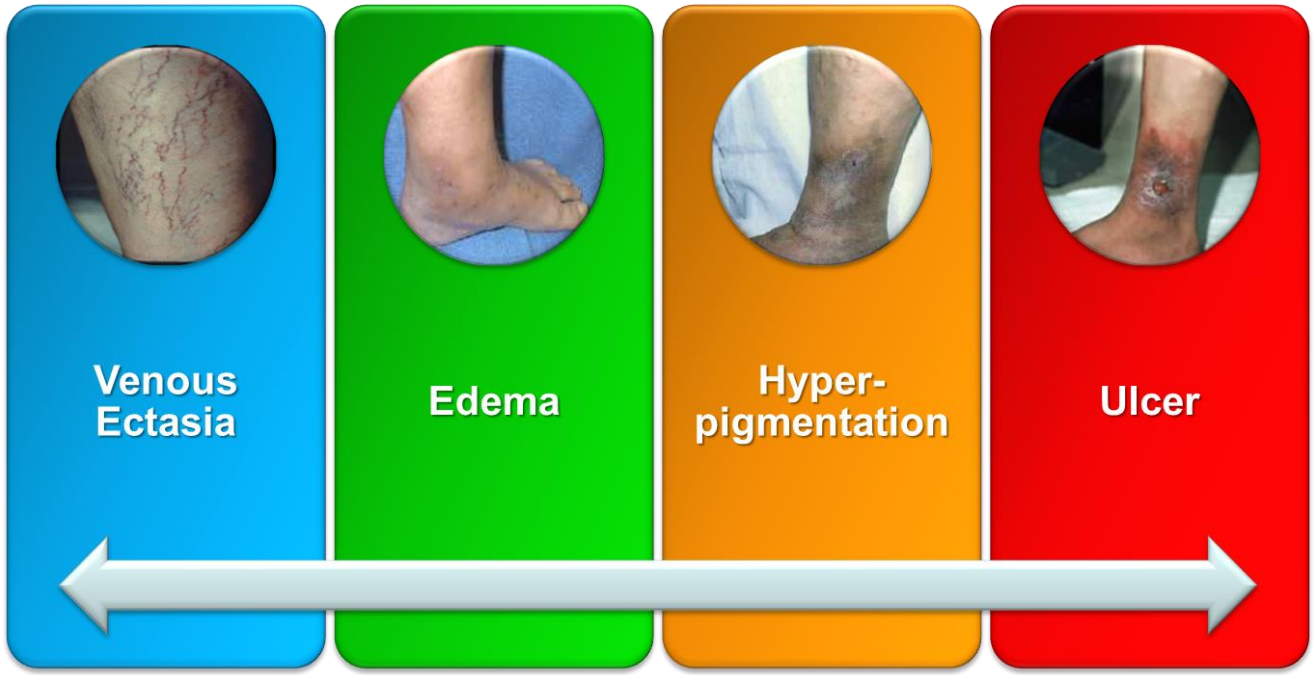


Piazza G. J Am Coll Cardiol. 2020;76:2117

# Long-Term Complications of PE and DVT




Klok FA, et al. Blood Reviews 2014; 28: 221 [10]

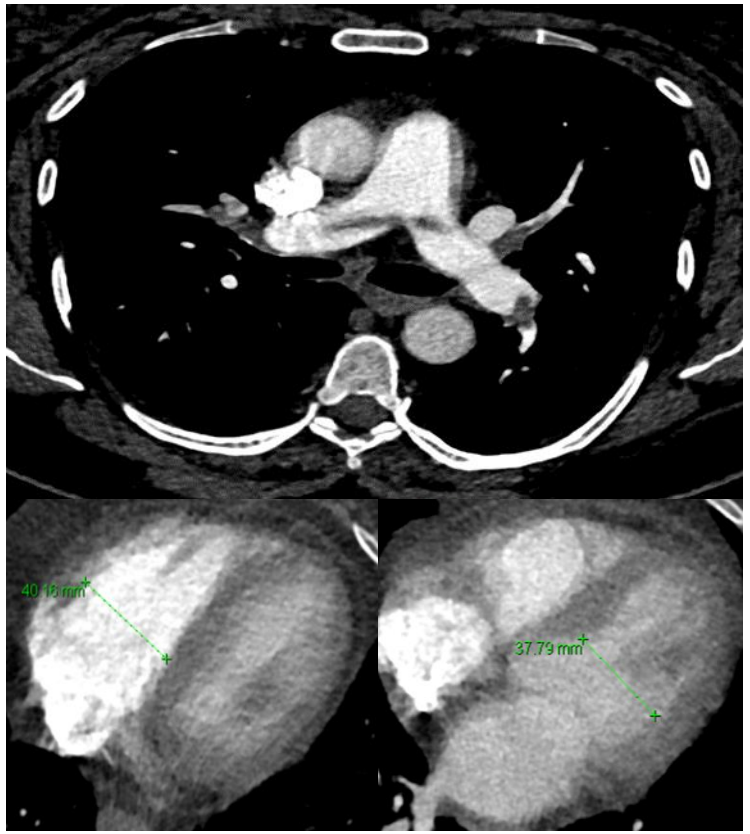
# Case No. 1

A 78-year-old man with colon cancer status post colectomy presents with sudden onset pleuritic pain, dyspnea, and right ankle edema.

He is tachycardic to 118 bpm, normotensive at 100/62 mmHg, and hypoxemic with an $O_2$ saturation of 90% on room air.

His high sensitivity cardiac troponin T is increased.

He undergoes chest CT angiography to assess for PE.



# Question No. 1

In which risk category would you place this patient?

a) Low-risk PE
b) Intermediate-low-risk PE
c) Intermediate-high-risk PE
d) High-risk PE

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In which risk category would you place this patient?

a) Low-risk PE
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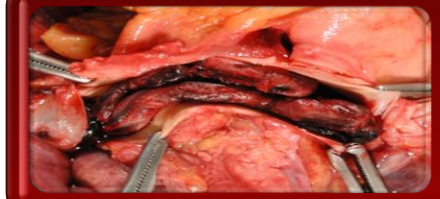
c) Intermediate-high-risk PE
d) High-risk PE

Explanation: normal systemic blood pressure and two markers of RV dysfunction distinguishes intermediate-high-risk PE.

# Spectrum of Disease

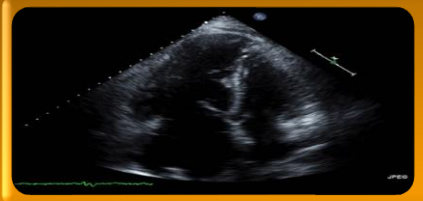


## High-Risk (Massive) PE (~5%)

- Hypotension, syncope, cardiogenic shock, cardiac arrest
- Respiratory failure
- Often fatal if aggressive care not instituted

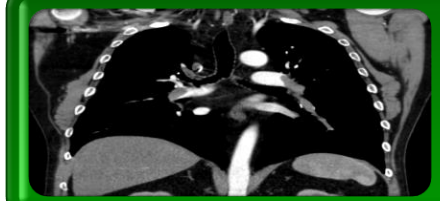
## Catastrophic PE (<1%)

- “Super-massive PE”
- Refractory cardiogenic shock
- Ongoing CPR



## Intermediate-Risk (Submassive) PE (~25%)

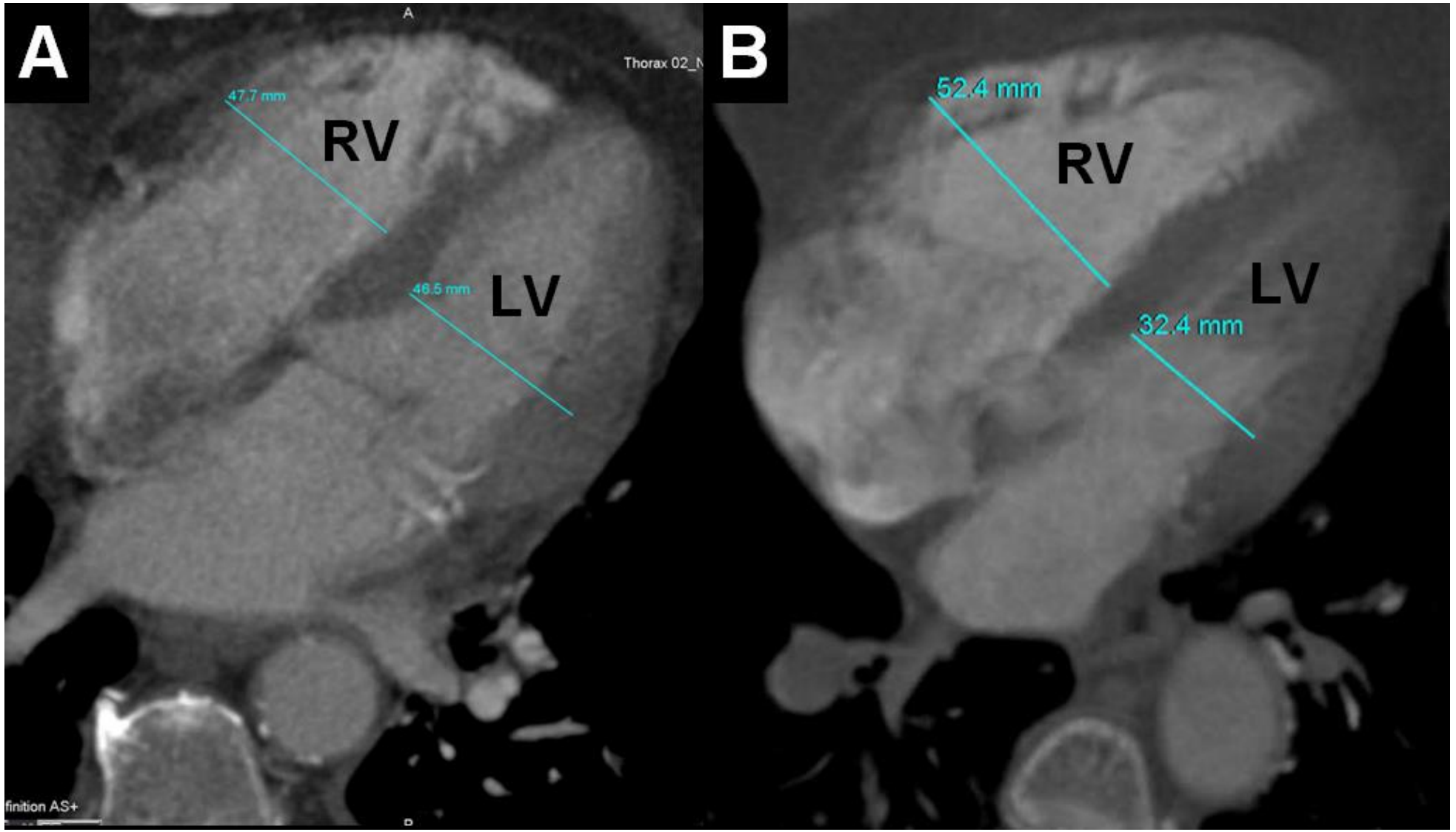
- Normotensive
- Right ventricular (RV) dysfunction is present
- Increased risk of adverse outcomes



## Low-Risk PE (~70%)

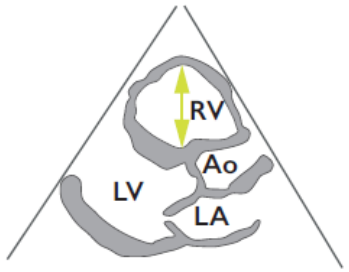
- Normotensive
- Normal RV function
- Excellent prognosis with anticoagulation alone

# RV Enlargement on CT Predicts Increased 30-Day Mortality

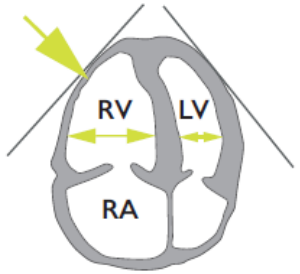



Schoepf UJ, et al. Circulation 2004;110:3276

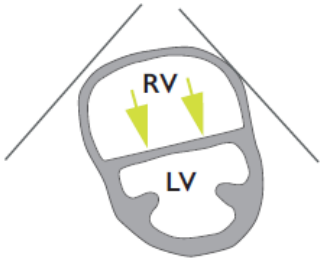
# Echocardiographic Assessment of RV in PE



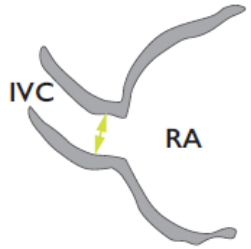

**A.** Enlarged right ventricle, parasternal long axis view



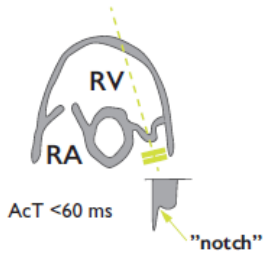

**B.** Dilated RV with basal RV/LV ratio >1.0, and McConnell sign (arrow), four chamber view

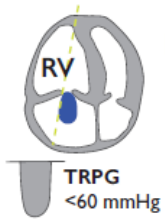



**C.** Flattened intraventricle septum (arrows) parasternal short axis view

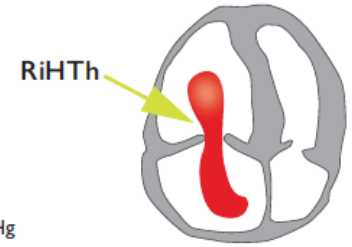



**D.** Distended inferior vena cava with diminished inspiratory collapsibility, subcostal view

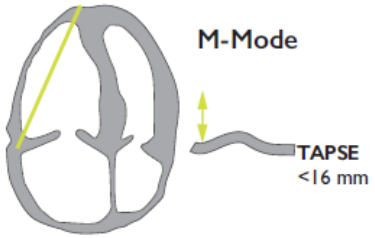


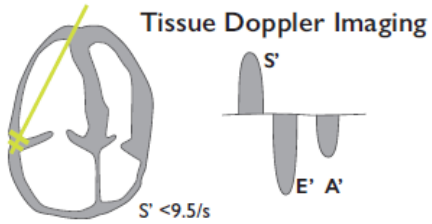

**E.** 60/60 sign: coexistence of acceleration time of pulmonary ejection <60 ms and midsystolic "notch" with mildy elevated (<60 mmHg) peak systolic gradient at the tricuspic valve




**F.** Right heart mobile thrombus detected in right heart cavities (arrow)




**G.** Decreased tricuspid annular plane systolic excursion (TAPSE) measured with M-Mode (<16 mm)




**H.** Decreased peak systolic (S') velocity of tricuspid annulus (<9.5 cm/s)

Konstantinides SV, et al. Eur Heart J. 2019; 00:1

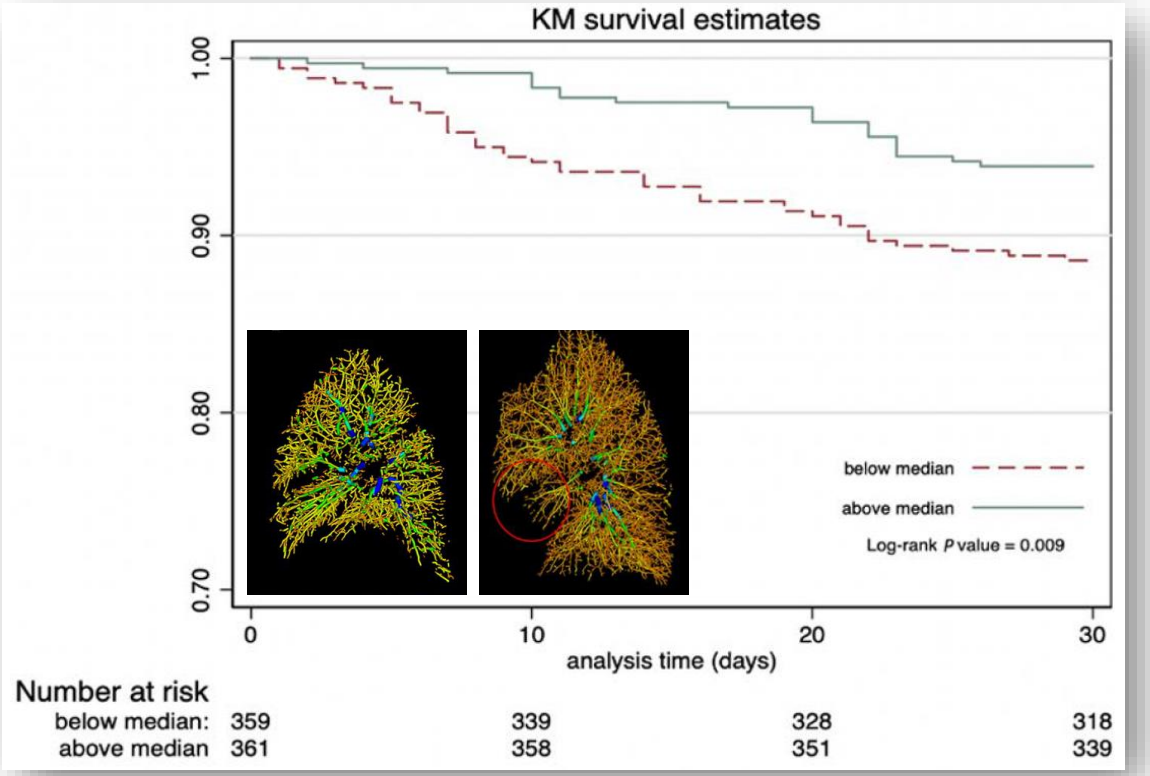
# Clot-Burden: PE Outcomes

| Variable | Survivors ($n = 596$) | Deceased Patients ($n = 39$) | *P* Value |
|---|---|---|---|
| No. of PEs* | 2.0 (3.1 ± 3.1) | 2.0 (2.5 ± 2.1) | .247 |
| Proximal level of PE† | | | |
| Mediastinal PA | 172 (28.8) | 10 (25.6) | — |
| Lobar PA | 145 (24.3) | 6 (15.4) | .520 |
| Segmental PA | 183 (30.7) | 19 (48.7) | .152 |
| Subsegmental PA | 96 (16.1) | 4 (10.2) | .582 |
| Qanadli score (%)* | 12.5 (17.0 ± 15.9) | 7.5 (17.1 ± 19.6) | .995 |
| Mastora score (%)* | 5.1 (10.4 ± 13.1) | 3.2 (11.4 ± 17.1) | .659 |
| Blood clot volume ($mm^3$)* | 927.3 (3556.4 ± 6598.3) | 630.4 (3211.8 ± 679.7) | .750 |

**Table 4. Cox Proportional Hazard Model Assessing the Hazard Ratio of a Reduction in Small Venous Blood Volume With 30- and 90-Day Mortality After Adjusting for Age, Sex, Lung Volume, Small Arterial Blood Volume, Abnormal RV:LV Ratio, and Presence of Cancer**

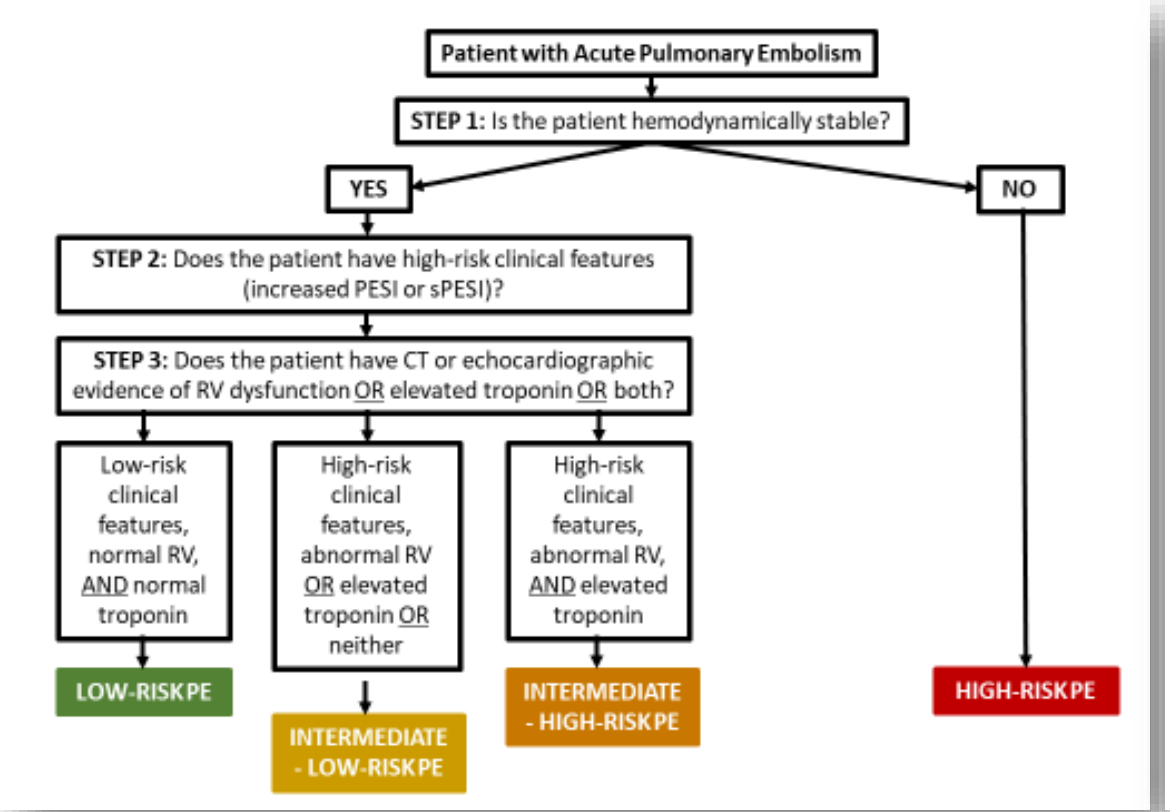
| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| Mortality | HR | CI | *P* value | HR | CI | *P* value |
| 30-day | 1.47 | 0.95–2.32 | 0.08 | 2.52 | 1.51–4.45 | <0.001 |
| 90-day | 1.06 | 0.68–1.33 | 0.77 | 1.66 | 1.10–2.50 | 0.016 |

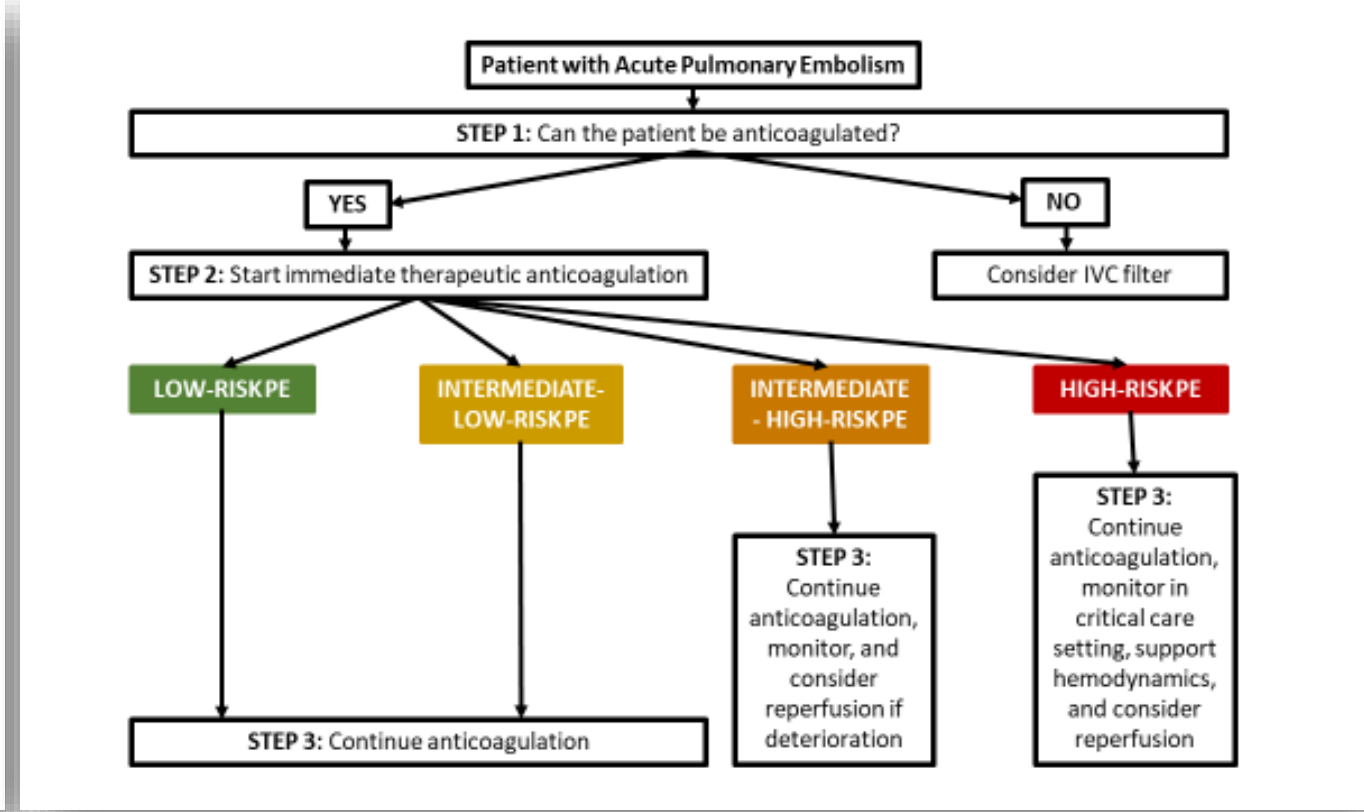
Hazard ratios reported here are per 1 SD (17.84 mL) decrease in small venous volume. HR indicates hazard ratio; LV, left ventricle; and RV, right ventricle.




Furlan A, et al. Radiology. 2012;265:283-293
Minhas J, et al. Circ Cardiovasc Imaging. 2021;14:e012347

# Risk Stratification for PE



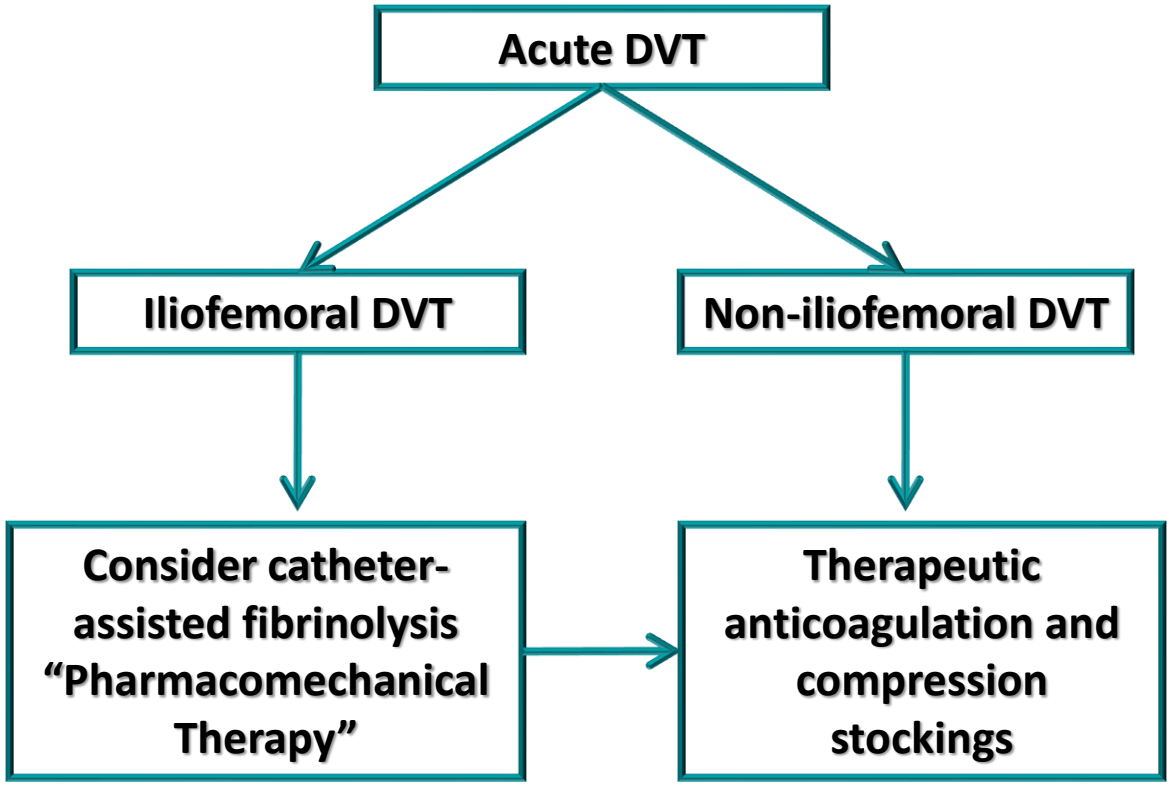

Piazza G. J Am Coll Cardiol. 2020;76:2117

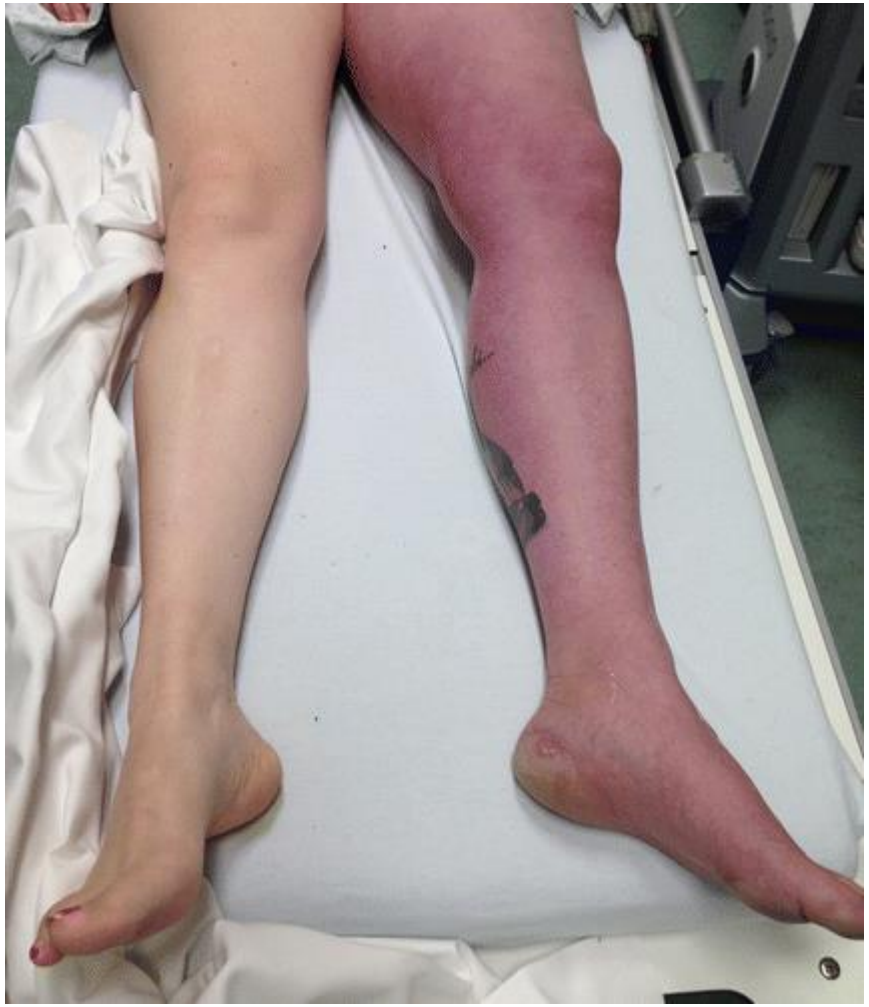
# Risk Stratification Recommendations

| ✓ Suggested ⚠ Not Addressed ✗ Not Recommended | ESC/ ERS [2] | PERT [12] | CHEST [13] | AHA [14] | ASH [15] | NICE [20] |
|---|---|---|---|---|---|---|
| Recommendation for risk stratification | ✓ | ✓ | ⚠ a | ✓ | ⚠ | ⚠ |
| Definition provided for low-risk PE | ✓ | ✓ | ✓ | ✓ | ✓ | ⚠ |
| Definition provided for intermediate-risk (submassive) PE | ✓ | ✓ | ⚠ | ✓ | ✓ | ⚠ |
| Definition provided for intermediate-low risk PE | ✓ | ✓ | ⚠ | ⚠ | ⚠ | ⚠ |
| Definition provided for intermediate-high risk PE | ✓ | ✓ | ⚠ | ⚠ | ⚠ | ⚠ |
| Definition provided for PE deterioration | ⚠ | ✓ | ✓ | ⚠ | ⚠ | ⚠ |
| Definition provided for high-risk (massive) PE | ✓ | ✓ | ✓ | ✓ | ✓ | ⚠ |
| Early discharge or entirely home-based care for low-risk PE | ✓ c | ✓ | ✓ | ⚠ b | ✓ | ✓ |
| Use of a multidisciplinary PERT | ✓ | ✓ | ⚠ | ⚠ b | ⚠ d | ✓ |

Zuin M, et al. J Am Coll Cardiol. 2024;84:1561

# Risk Stratification for Acute DVT



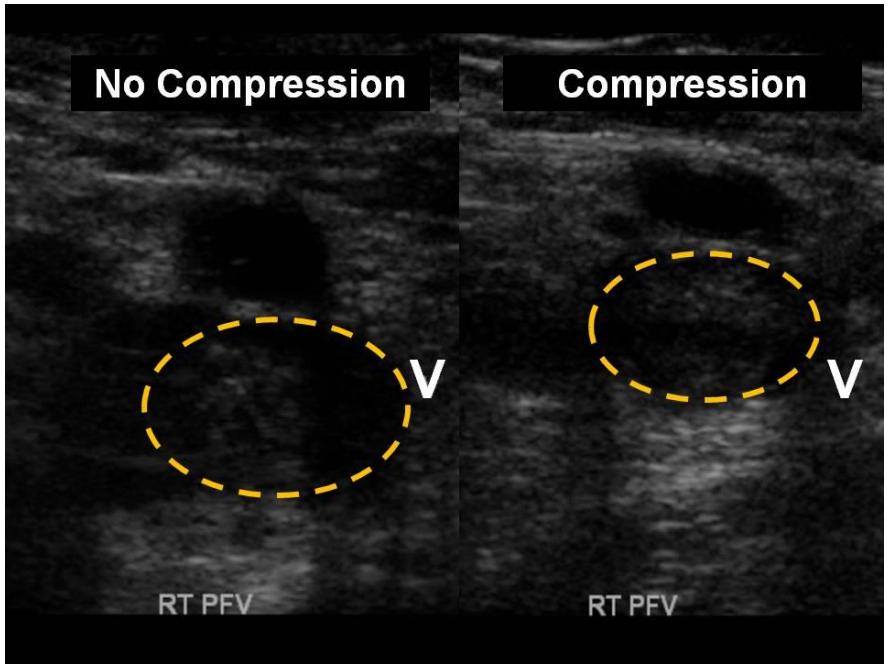
https://econtent.hogrefe.com/doi/10.1024/0301-1526/a000894

# Case No. 2

A 39-year-old woman with obesity, type 2 diabetes, and hypertension presents with right leg edema and pain 1 week after cholecystectomy for gallstones.

She admits to being quite sedentary post-operatively and has mostly been binge-watching her favorite streaming shows.

Venous ultrasound demonstrates right femoral DVT.



# Question No. 2

Which of the following is the most appropriate next step in management?

a) Start enoxaparin 120 mg twice daily
b) Start dabigatran 150 mg twice daily
c) Start rivaroxaban 15 mg twice daily for 3 weeks then switch to 20 mg daily
d) Start edoxaban 90 mg once daily
e) Start apixaban 2.5 mg twice daily

# Question No. 2

Which of the following is the most appropriate next step in management?

a) Start enoxaparin 120 mg twice daily
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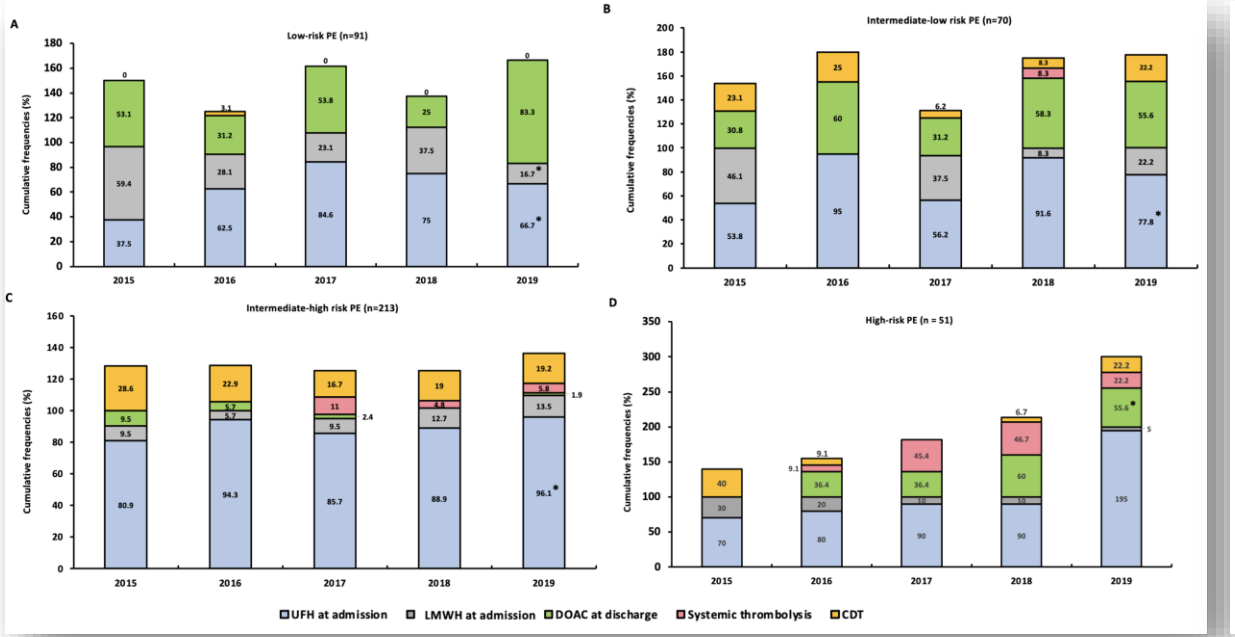
c) Start rivaroxaban 15 mg twice daily for 3 weeks then switch to 20 mg daily
d) Start edoxaban 90 mg once daily
e) Start apixaban 2.5 mg twice daily

Explanation: Rivaroxaban 15 mg twice daily for 3 weeks then 20 mg daily is the only correct FDA-approved regimen listed for acute DVT.

# Immediate Anticoagulation for PE: Lessons from PE Response Team Registries



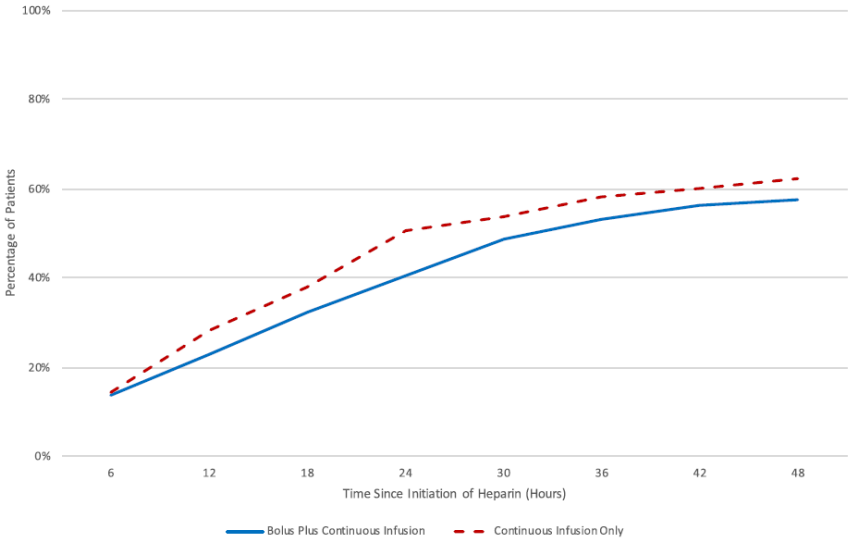
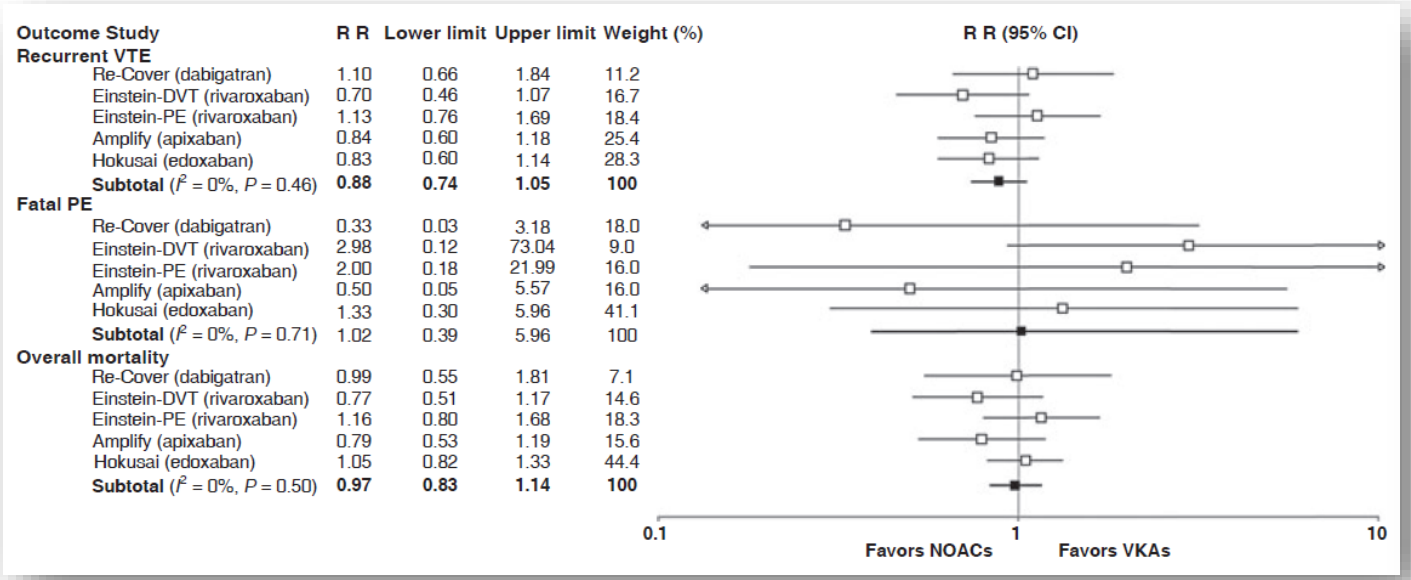




**Figure 5** Percentage of patients in each dosing group who have ever had a therapeutic aPTT value over time. aPTT = activated partial thromboplastin time.

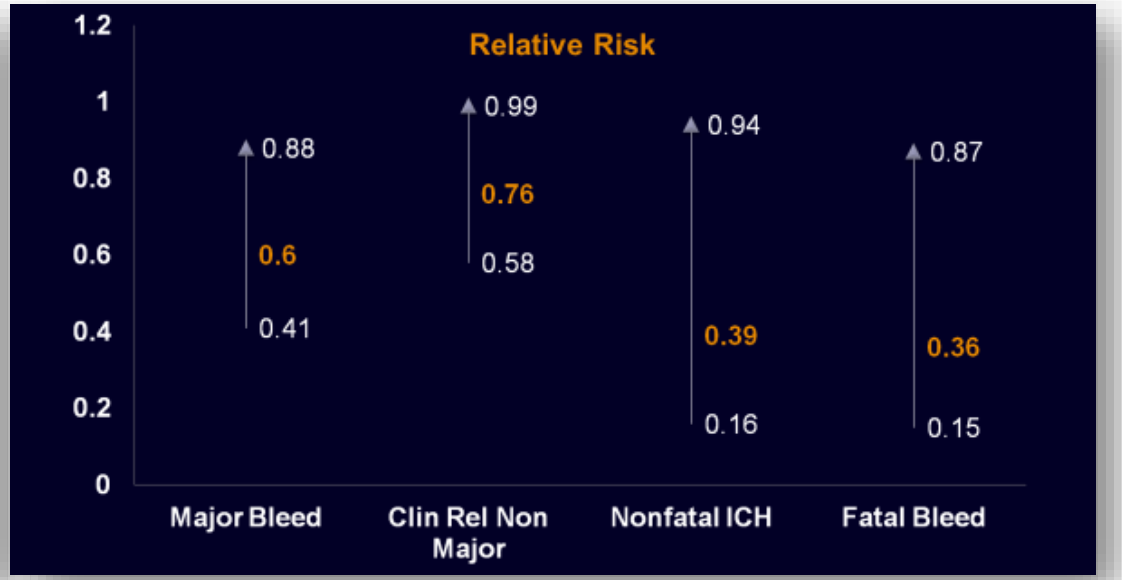

Chopard R, et al. J Thromb Thrombolysis. 2022;54:449
Prucnal CK, et al. Acad Emerg Med. 2020;27:117

# Efficacy and Safety of DOACs for VTE Treatment: Meta-Analysis



| Outcome Study | R R | Lower limit | Upper limit | Weight (%) |
|---|---|---|---|---|
| **Recurrent VTE** | | | | |
| Re-Cover (dabigatran) | 1.10 | 0.66 | 1.84 | 11.2 |
| Einstein-DVT (rivaroxaban) | 0.70 | 0.46 | 1.07 | 16.7 |
| Einstein-PE (rivaroxaban) | 1.13 | 0.76 | 1.69 | 18.4 |
| Amplify (apixaban) | 0.84 | 0.60 | 1.18 | 25.4 |
| Hokusai (edoxaban) | 0.83 | 0.60 | 1.14 | 28.3 |
| **Subtotal** ($I^2$ = 0%, $P$ = 0.46) | **0.88** | **0.74** | **1.05** | **100** |
| **Fatal PE** | | | | |
| Re-Cover (dabigatran) | 0.33 | 0.03 | 3.18 | 18.0 |
| Einstein-DVT (rivaroxaban) | 2.98 | 0.12 | 73.04 | 9.0 |
| Einstein-PE (rivaroxaban) | 2.00 | 0.18 | 21.99 | 16.0 |
| Amplify (apixaban) | 0.50 | 0.05 | 5.57 | 16.0 |
| Hokusai (edoxaban) | 1.33 | 0.30 | 5.96 | 41.1 |
| **Subtotal** ($I^2$ = 0%, $P$ = 0.71) | 1.02 | 0.39 | 5.96 | 100 |
| **Overall mortality** | | | | |
| Re-Cover (dabigatran) | 0.99 | 0.55 | 1.81 | 7.1 |
| Einstein-DVT (rivaroxaban) | 0.77 | 0.51 | 1.17 | 14.6 |
| Einstein-PE (rivaroxaban) | 1.16 | 0.80 | 1.68 | 18.3 |
| Amplify (apixaban) | 0.79 | 0.53 | 1.19 | 15.6 |
| Hokusai (edoxaban) | 1.05 | 0.82 | 1.33 | 44.4 |
| **Subtotal** ($I^2$ = 0%, $P$ = 0.50) | **0.97** | **0.83** | **1.14** | **100** |





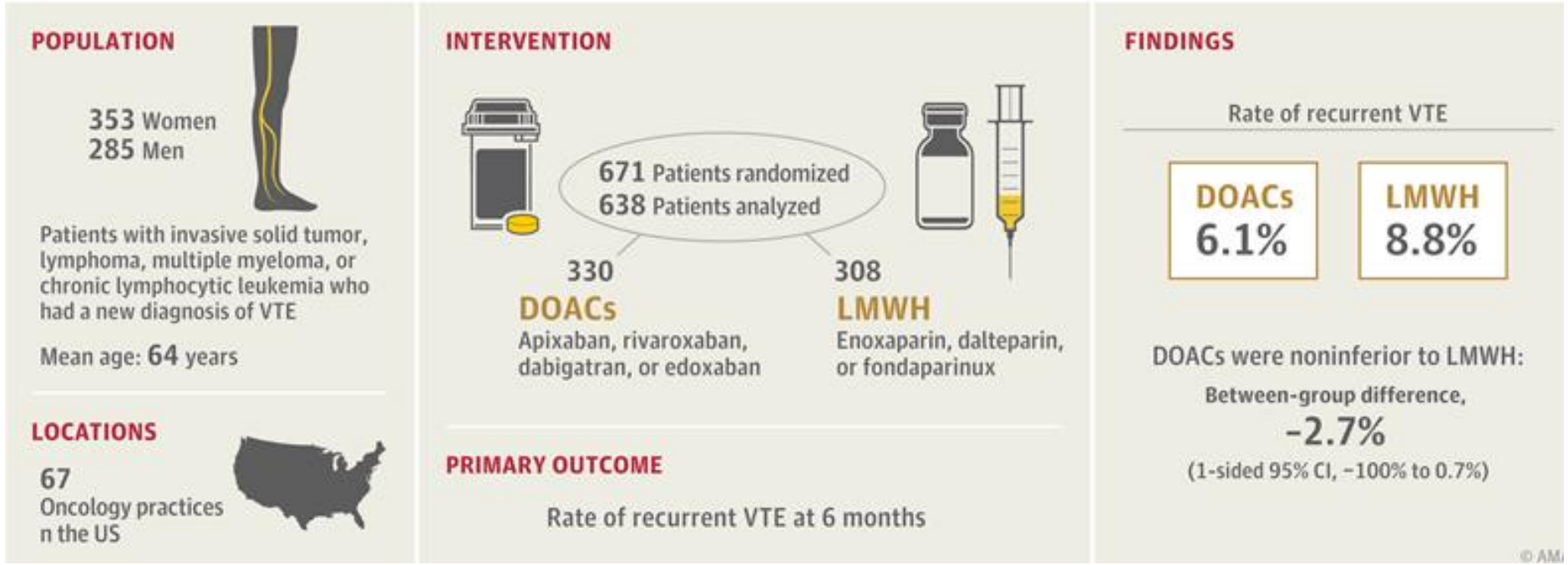

van der Hulle T, et al. J Thromb Haemost. 2014;12:320

# Comparative effectiveness DOAC vs LMWH for VTE in cancer

## CANVAS Pragmatic Trial

**QUESTION** Among patients with cancer and a venous thromboembolism (VTE) event, are direct oral anticoagulants (DOACs) noninferior to low-molecular-weight heparin (LMWH) for preventing recurrent VTE events?

**CONCLUSION** Among adults with cancer and VTE, DOACs were noninferior to LMWH for preventing recurrent VTE over 6-month follow-up.




Schrag D, et al. JAMA. 2023;329:1924

# Anticoagulation for Acute PE: Evidence-Based Guideline Recommendations

✓ Suggested ⚠ Not addressed ✗ Not recommended

| | ESC/ERS [2] | PERT [12] | CHEST [13] | AHA [14] | ASH [16] | NICE [20] |
|---|---|---|---|---|---|---|
| **Therapeutic anticoagulation should be initiated while awaiting diagnostic results if the pretest probability of PE is intermediate or high and the bleeding risk is low** | ✓ | ✓ | ⚠ | ✓ | ⚠ | ✓ a |
| **Therapeutic anticoagulation should be given to all patients with confirmed PE who do not have a contraindication** | ✓ | ✓ | ✓ | ✓ b | ✓ | ✓ |
| **Immediate anticoagulant choice in high-risk PE if advanced therapies are considered: unfractionated heparin** | ✓ | ✓ | ⚠ | ⚠ | ⚠ | ✓ |
| **Immediate anticoagulant in intermediate-high risk PE not requiring advanced therapies: LMWH or DOAC (unless contraindications)** | ✓ | ⚠ | ⚠ | ⚠ | ✓ e | ✓ |
| **Immediate anticoagulant choice in low-risk PE: DOAC (unless contraindications)** | ✓ | ✓ | ⚠ | ⚠ | ✓ e | ✓ |
| **Immediate anticoagulant choice in patients with HIT or a history of HIT: parenteral direct thrombin inhibitor or fondaparinux** | ✓ c | ⚠ | ⚠ | ✓ d | ✓ f | ⚠ |
| **For oral anticoagulation in the treatment phase of PE, DOAC is recommended over VKA unless there is severe kidney disease, concomitant use of interacting drugs, or antiphospholipid syndrome** | ✓ d | ✓ | ✓ | ⚠ | ✓ | ✓ |

a. If PE unlikely, but D-dimer cannot be offered within 4 hours, NICE 2020 guidelines recommend interim anticoagulation while awaiting results
b. Therapeutic anticoagulation with LMWH, IV/SC heparin, or fondaparinux is recommended for all patients with confirmed PE.
c. No preference for parenteral or oral anticoagulation for intermediate or low-risk PE in the formal recommendations; LMWH or fondaparinux preferred over UFH.
d. Recommends danaparoid, lepirudin, argatroban or bivalirudin; ESC 2019 recommends fondaparinux if allergy or adverse reaction to LMWH
e. ASH does not differentiate the choice of agents based on acuity of care
f. ASH provides specific comments on the management of HIT in VTE into a dedicated guidelines [18]

Zuin M, et al. J Am Coll Cardiol. 2024;84:1561

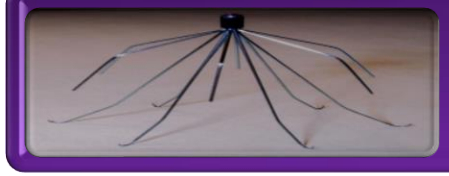
# Advanced Therapies

**Fibrinolysis**

**Catheter-Directed Therapy**

**Surgical Embolectomy**

**Mechanical Circulatory Support**



**IVC Filter**

# Advanced Therapies for Acute PE: Evidence-Based Guideline Recommendations

✓ Suggested ⚠ Not addressed ✗ Not recommended

| | ESC/ERS [2] | PERT [12] | CHEST [13] | AHA [10, 14] | ASH [16] | NICE [20] |
|---|---|---|---|---|---|---|
| **Systemic fibrinolysis in hemodynamically unstable PE patients** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Systemic fibrinolysis in hemodynamically stable experiencing hemodynamic and/or respiratory worsening** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Reduced dose systemic fibrinolysis** | ✗ | ✓ b | ⚠ | ⚠ | ⚠ | ⚠ |
| **Routine use of systemic fibrinolysis in hemodynamically stable PE patients** | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Surgical embolectomy in hemodynamically unstable PE patients** | ✓ | ✓ | ⚠ | ⚠ | ⚠ | ✓ e |
| **CDIs in hemodynamically unstable PE patients in whom systemic fibrinolysis has failed or is contraindicated** | ✓ | ✓ | ✓ | ✓ | ✓ c | ⚠ f |
| **CDIs in hemodynamically stable experiencing hemodynamic and/or respiratory worsening** | ✓ | ✓ | ✓ | ✓ | ⚠ d | ⚠ f |
| **Extracorporeal Membrane Oxygenation (ECMO)** | ✓ a | ✓ | ⚠ | ⚠ | ⚠ | ⚠ |

a. ECMO may be considered in combination with surgical embolectomy or catheter-directed therapies in patients with refractory cardiogenic shock.
b. In high-risk patients with relative contraindications to systemic fibrinolysis
c. In centers with the appropriate infrastructure, clinical staff, and procedural experience
d. Prefer systemic fibrinolysis and perform close cardiovascular monitoring to promptly identify the development of hemodynamic compromise.
e. Surgical thrombectomy may occasionally be performed for patients with a life-threatening PE
f. Catheter-based embolectomy should only be used within the confines of research protocols due the absence of adequate supporting clinical trials

Zuin M, et al. J Am Coll Cardiol. 2024;84:1561

# Systemic Fibrinolysis

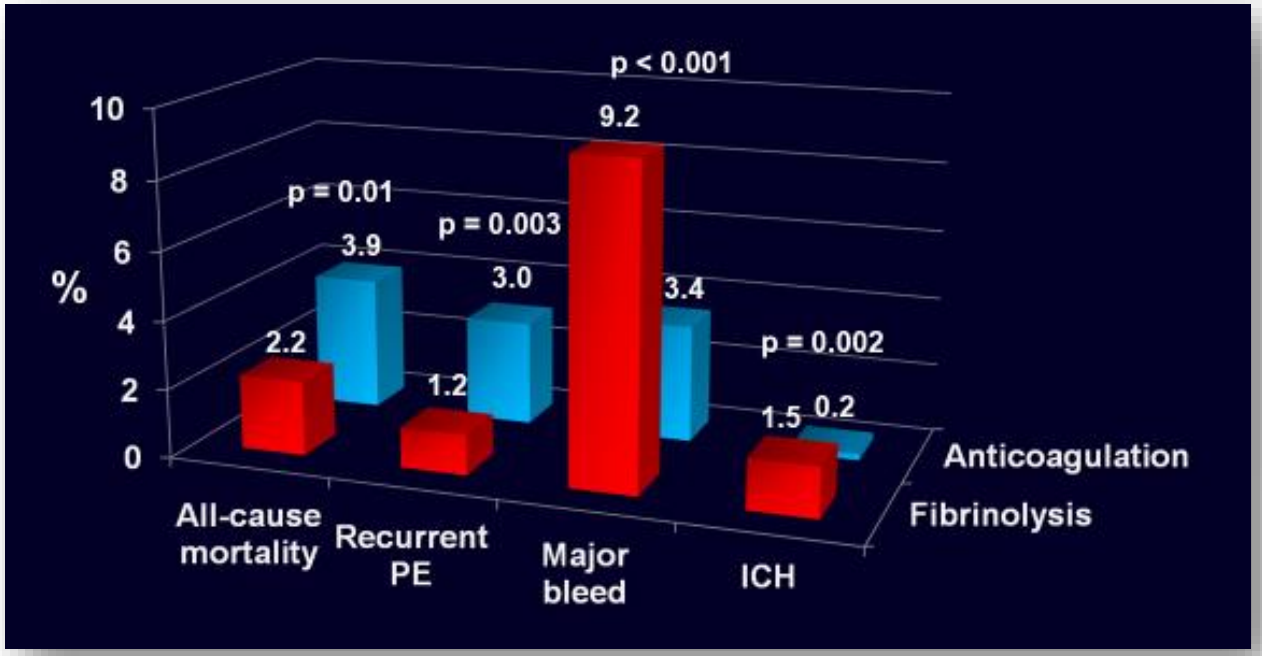
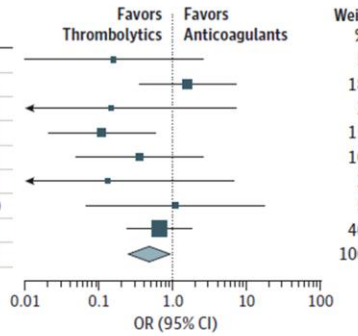



Figure 3. Odds of Mortality in Patients With Intermediate-Risk Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation

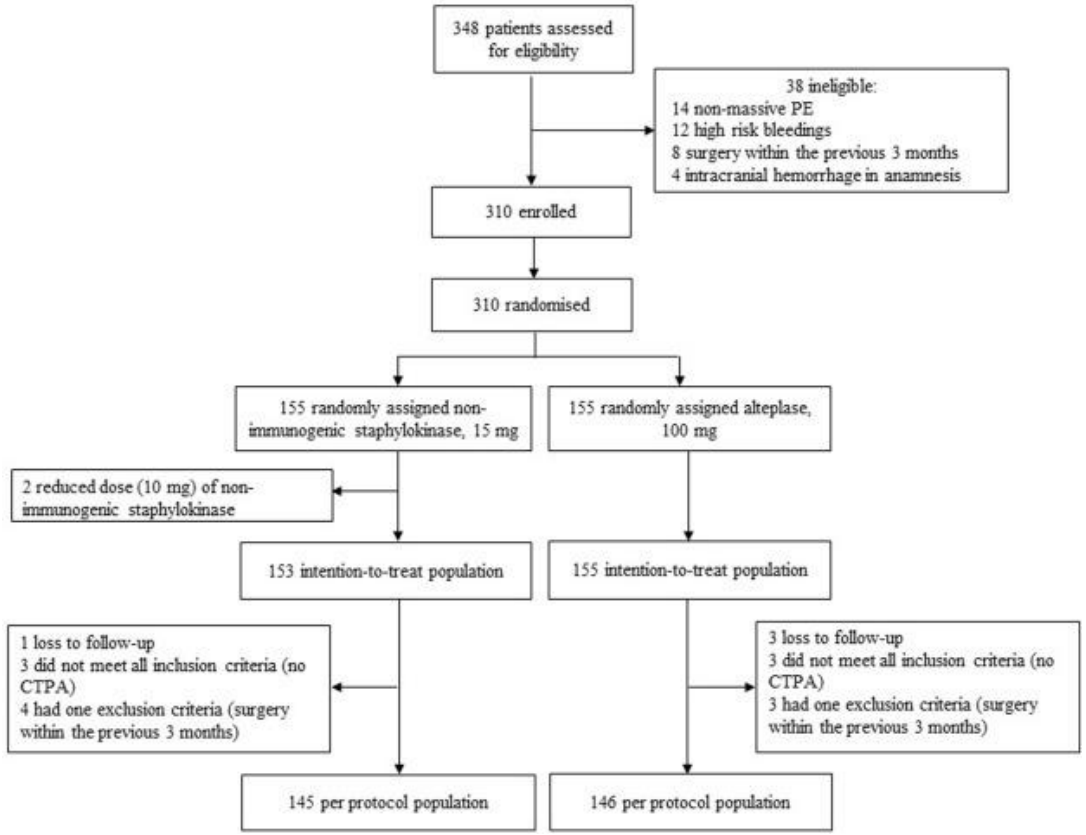
| Source | Thrombolytics No. of Events | Thrombolytics No. of Patients | Anticoagulants No. of Events | Anticoagulants No. of Patients | OR (95% CI) | Weight, % |
|---|---|---|---|---|---|---|
| Goldhaber et al,[2] 1993 | 0 | 46 | 2 | 55 | 0.16 (0.01-2.57) | 5.3 |
| Konstantinides et al,[3] 2002 | 4 | 118 | 3 | 138 | 1.58 (0.35-7.09) | 18.4 |
| TIPES,[29] 2010 | 0 | 28 | 1 | 30 | 0.14 (0.00-7.31) | 2.7 |
| Fasullo et al,[11] 2011 | 0 | 37 | 6 | 35 | 0.11 (0.02-0.58) | 15.1 |
| MOPETT,[10] 2012 | 1 | 61 | 3 | 60 | 0.35 (0.05-2.57) | 10.5 |
| ULTIMA,[30] 2013 | 0 | 30 | 1 | 29 | 0.13 (0.00-6.59) | 2.7 |
| TOPCOAT,[9] 2014 | 1 | 40 | 1 | 43 | 1.08 (0.07-17.53) | 5.3 |
| PEITHO,[8] 2014 | 6 | 506 | 9 | 499 | 0.66 (0.24-1.82) | 40.0 |
| Total | 12 | 866 | 26 | 889 | 0.48 (0.25-0.92) | 100.0 |

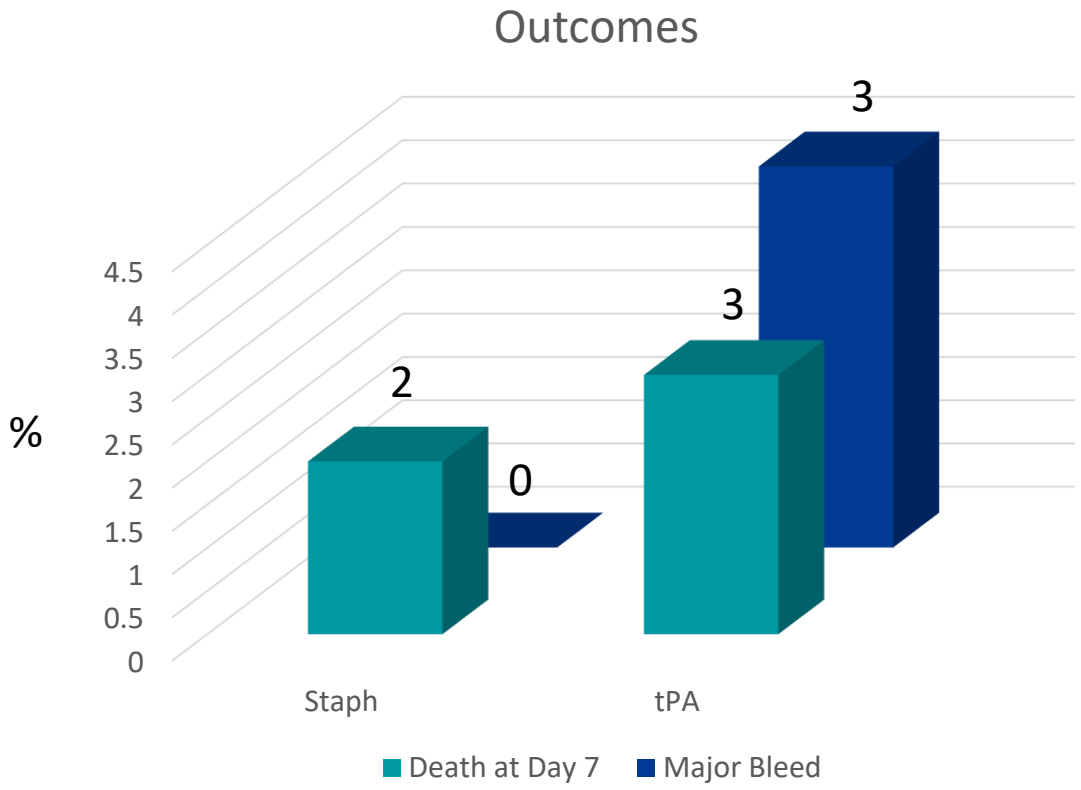
Heterogeneity: $\chi^2_7 = 7.63$; $P = .37$; $I^2 = 8\%$
Overall effect: $z = 2.22$; $P = .03$




Chatterjee S, et al. JAMA 2014;311:2414

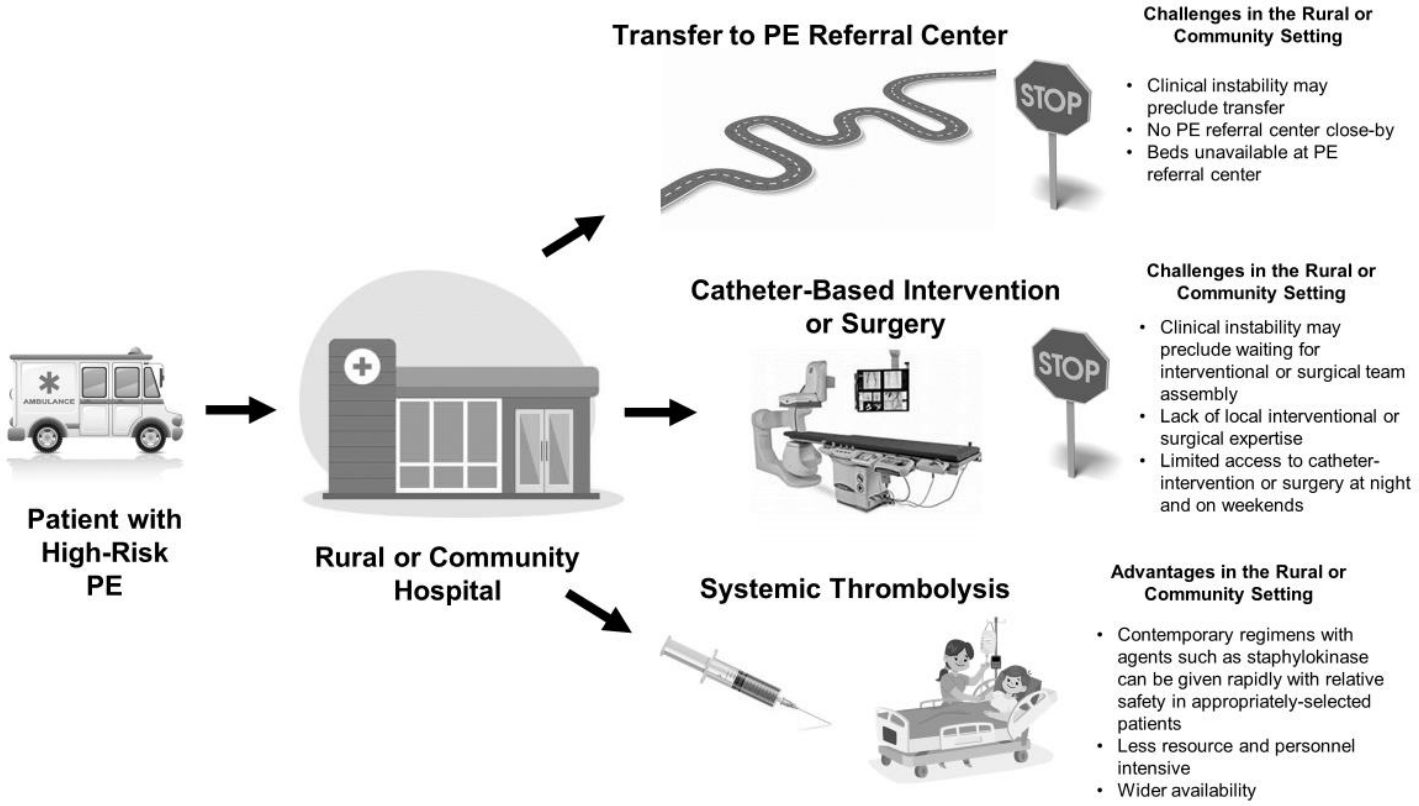
# FORPE: Non-immunogenic Recombinant Staphylokinase versus Alteplase for High-Risk PE



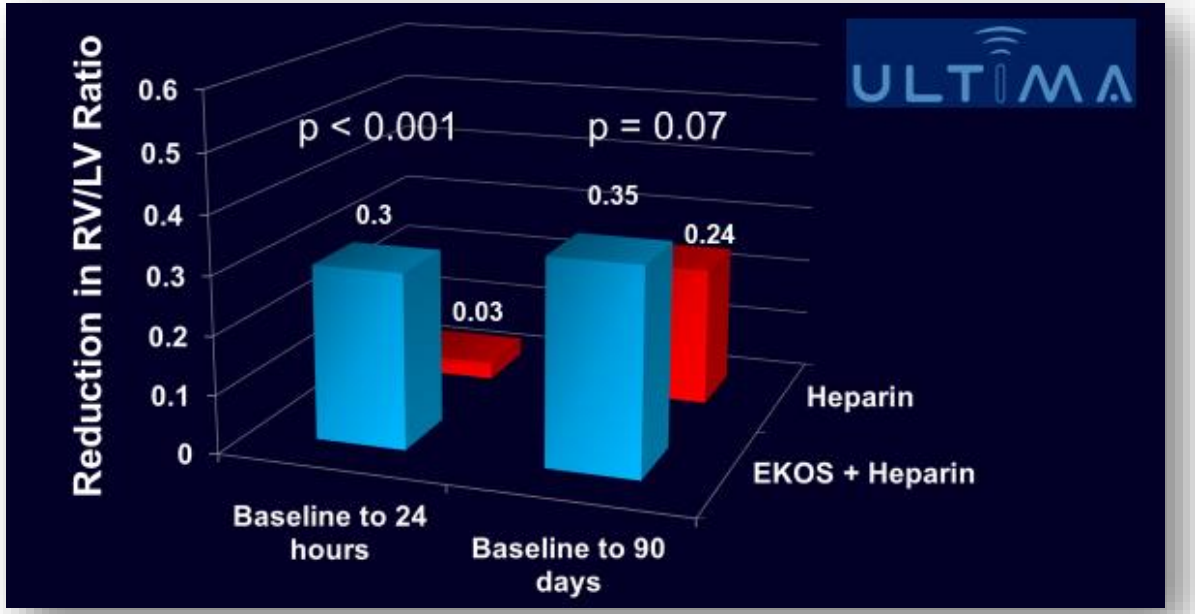

Kirienko AI, et al. J Thromb Haemost. 2025;23:657

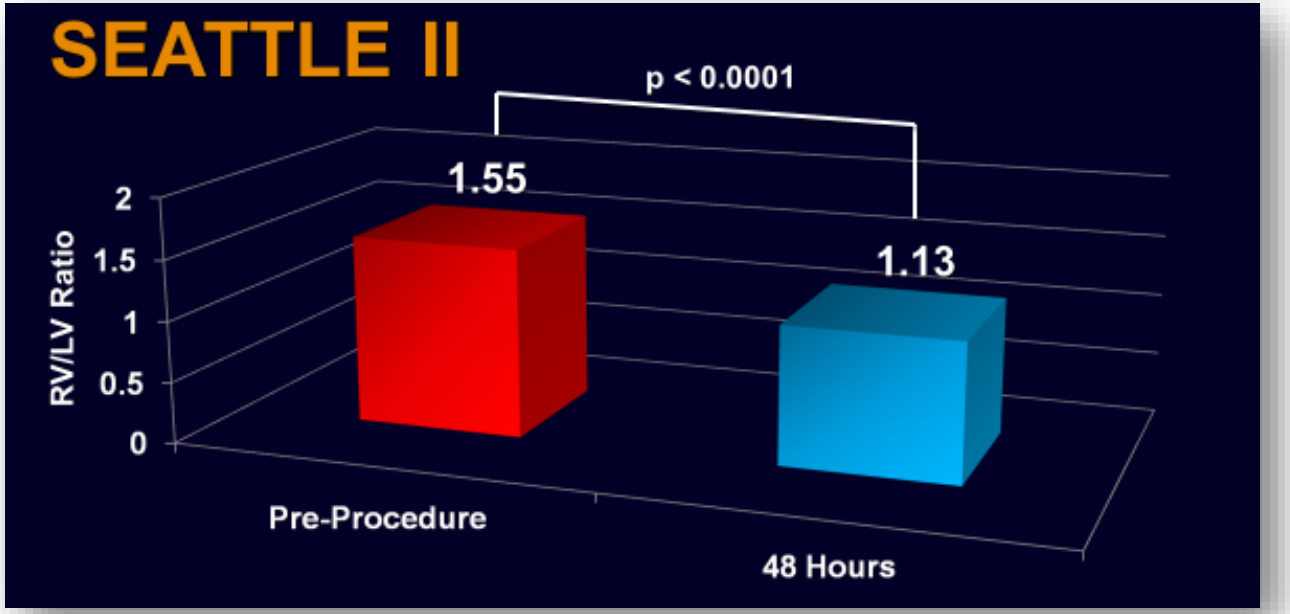
# Systemic Fibrinolysis: A Role in Today's Landscape




Henkin S, Piazza G. J Thromb Haemost. 2025; in press.

# Ultrasound-Facilitated Catheter-Directed Fibrinolysis



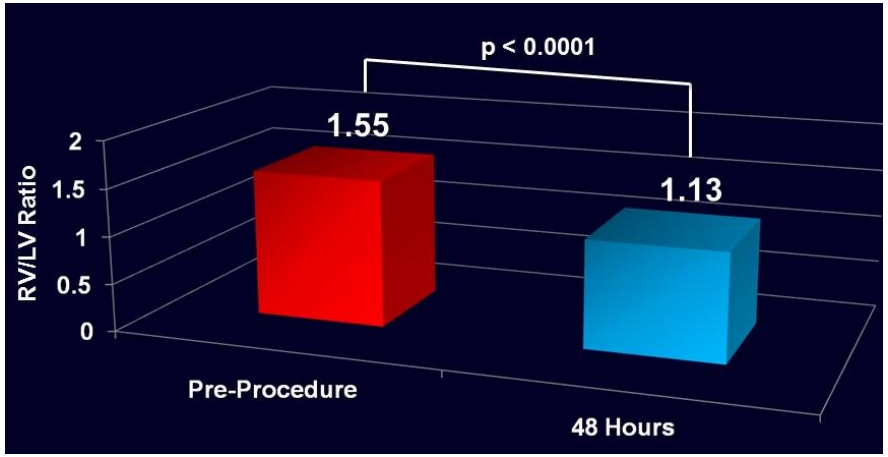

Kucher N, et al. Circulation 2014;129:479
Piazza G, et al. JACC Cardiovasc Interv. 2015;8:1382

# Overcoming the Hurdle of Intracranial Hemorrhage

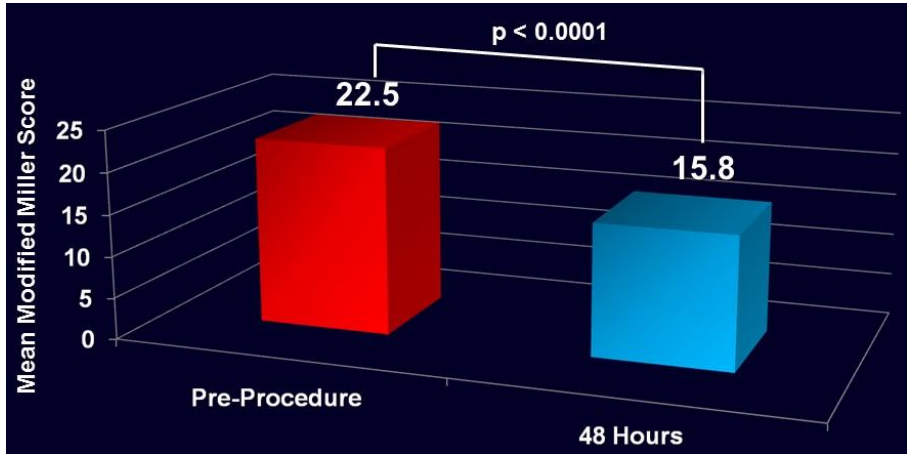
| Study | Intracranial Hemorrhage (Fibrinolysis Group) |
|---|---|
| **ICOPER** (Goldhaber SZ, et al. 1999) | 9/304 (3.0%) |
| **PEITHO** (Meyer G, et al. 2014) | 10/506 (2.0%) |
| **ULTIMA** (Kucher N, et al. 2013) | 0/30 (0%) |
| **SEATTLE II** (Piazza G, et al. 2015) | 0/150 (0%) |

# The SEATTLE II Paradox

Change in RV/LV Diameter Ratio




Change in Angiographic Obstruction

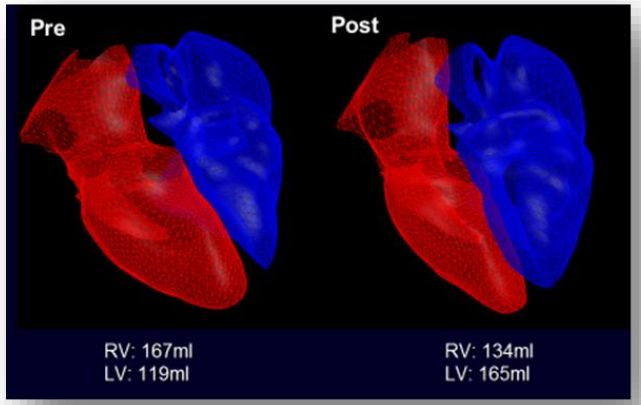


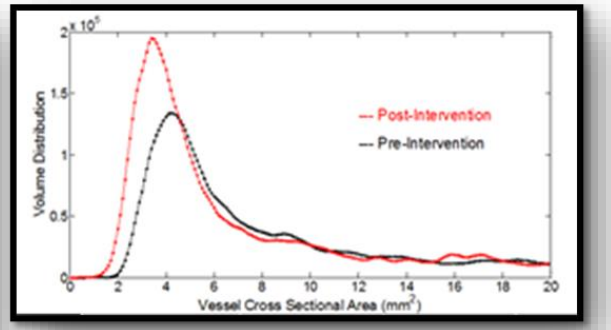

While most patients have normalization of RV size on chest CT, the average observed reduction in angiographic obstruction (modified Miller score) is only 30%.

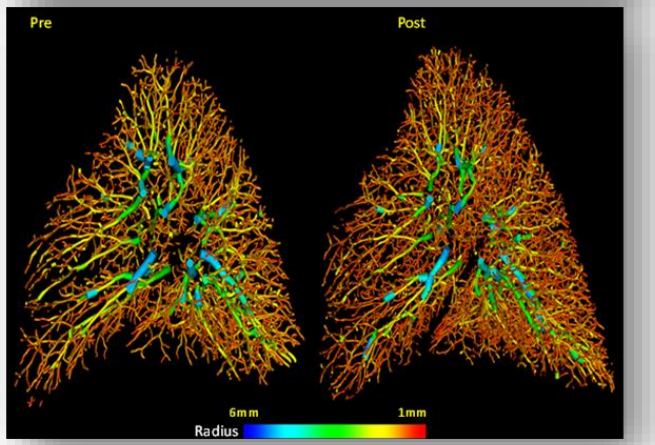
This paradox suggests that symptomatic improvement and reduction in RV size may be achieved by mechanisms in addition to reduction in proximal pulmonary artery obstruction.

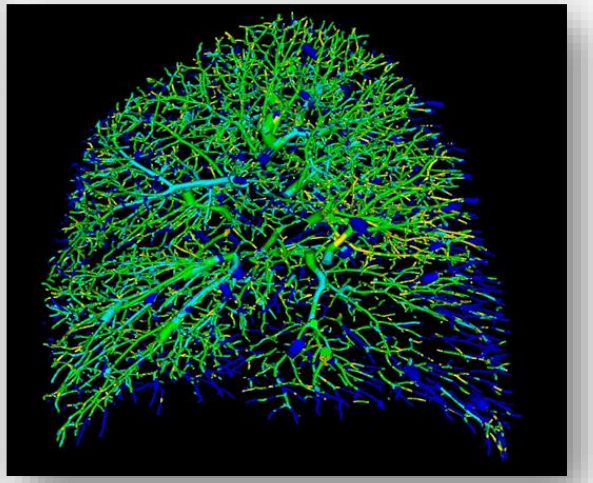
Piazza G, et al. JACC Cardiovasc Interv. 2015;8:1382

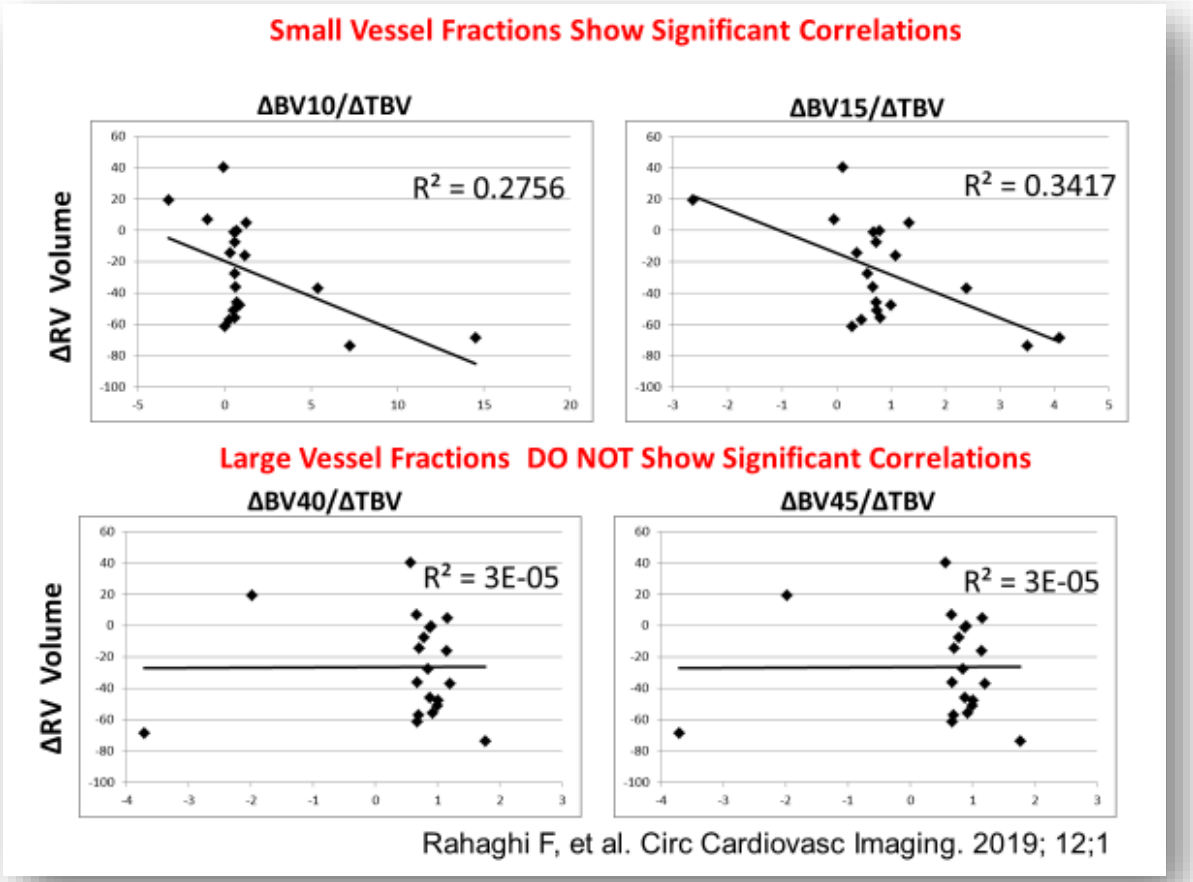
# SEATTLE-3D: Correlating the Change in RV Volume to Vascular Response



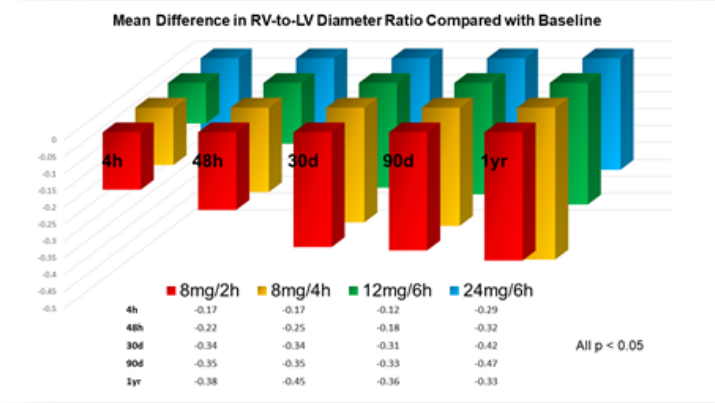



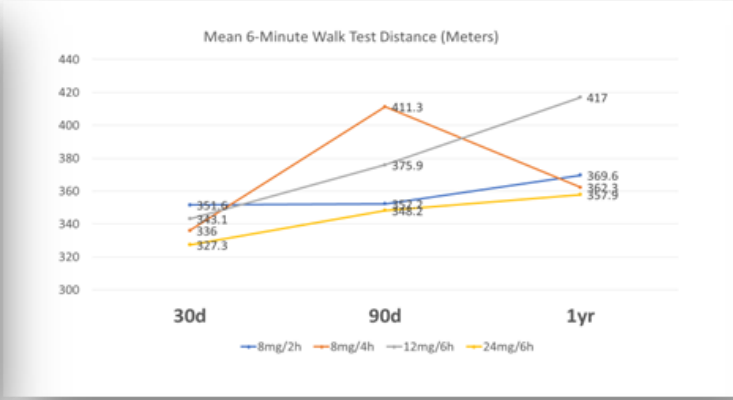



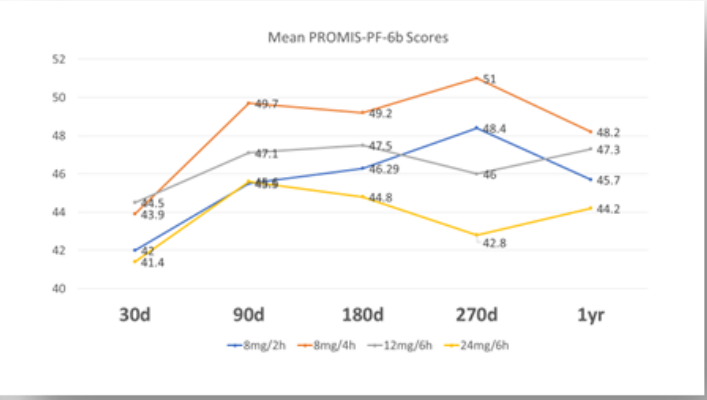



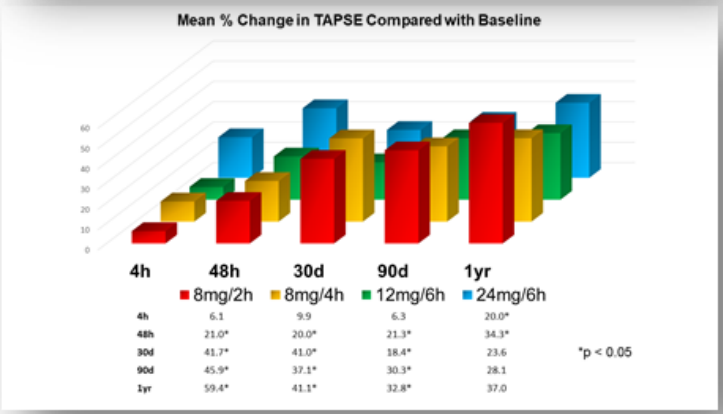


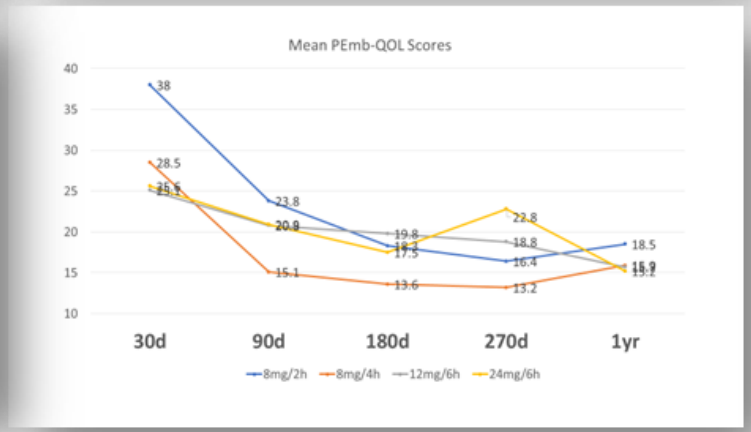
# OPTALYSE-PE: Long-Term Recovery

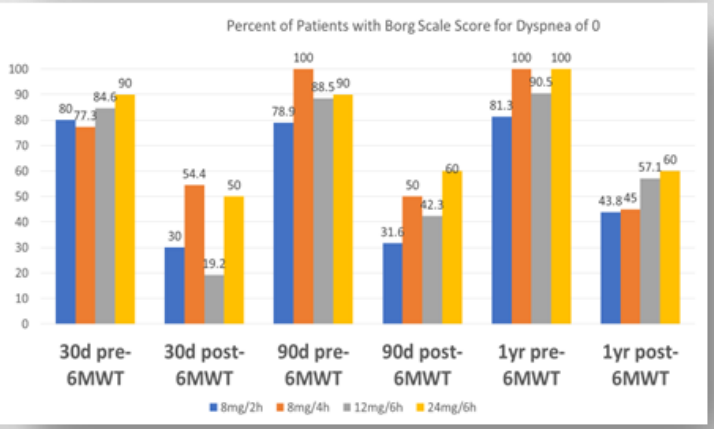


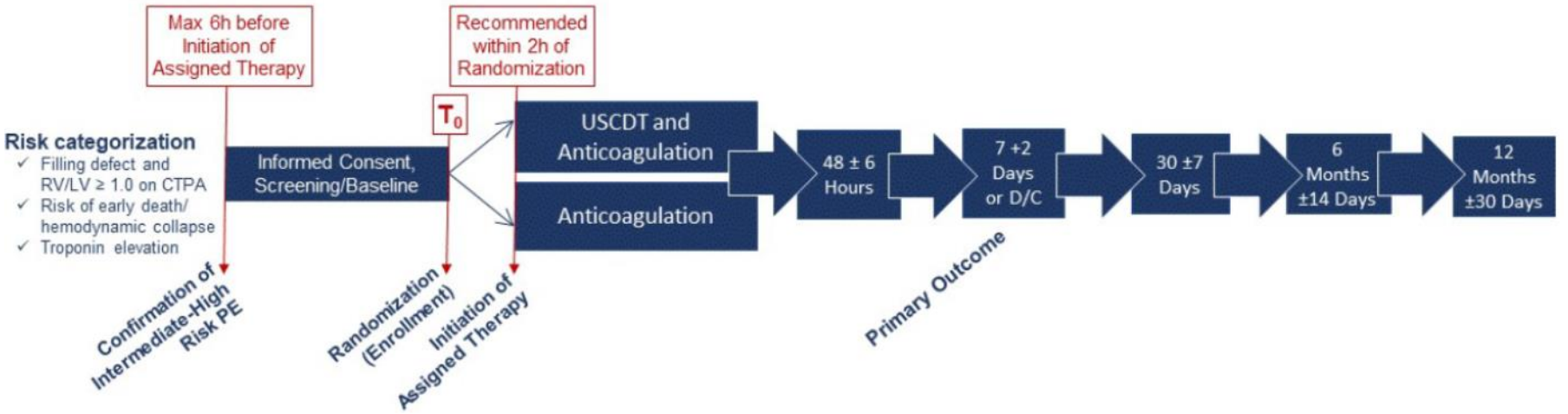




Piazza G, et al. Circ Cardiovasc Interv. 2020; 13:e009012

# HI-PEITHO: Randomized Controlled Trial

A randomized trial of ultrasound-facilitated, catheter-directed, thrombolysis versus anticoagulation
for acute intermediate-high risk pulmonary embolism:

The HIgher-risk Pulmonary Embolism THrOmbolysis study (HI-PEITHO)

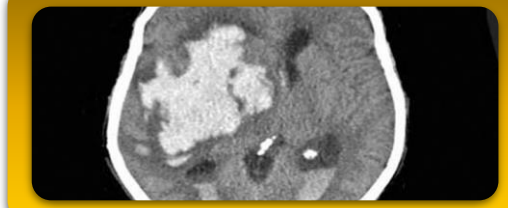



ENROLLING NOW!

# KNOCOUT-PE Prospective Cohort: Safety in 489 Real-World Patients Undergoing US-Facilitated CDT

**Major Bleeding**

- 1.8% (comparable to mechanical thrombectomy)



**Intracranial Hemorrhage**

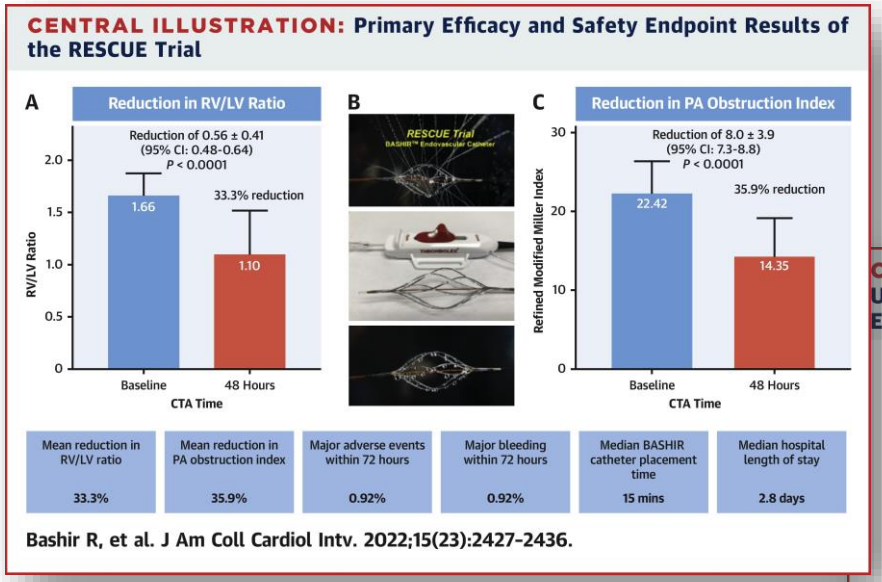
- 0%

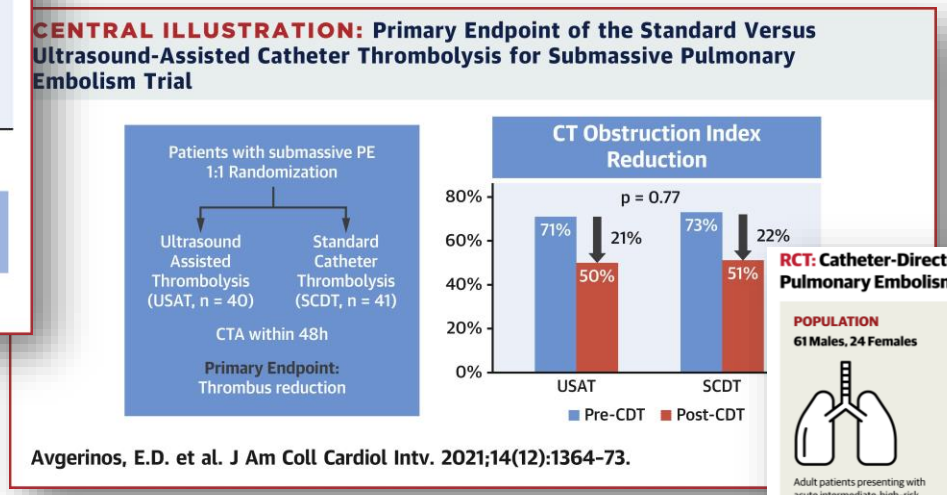
**Access Site Bleed**

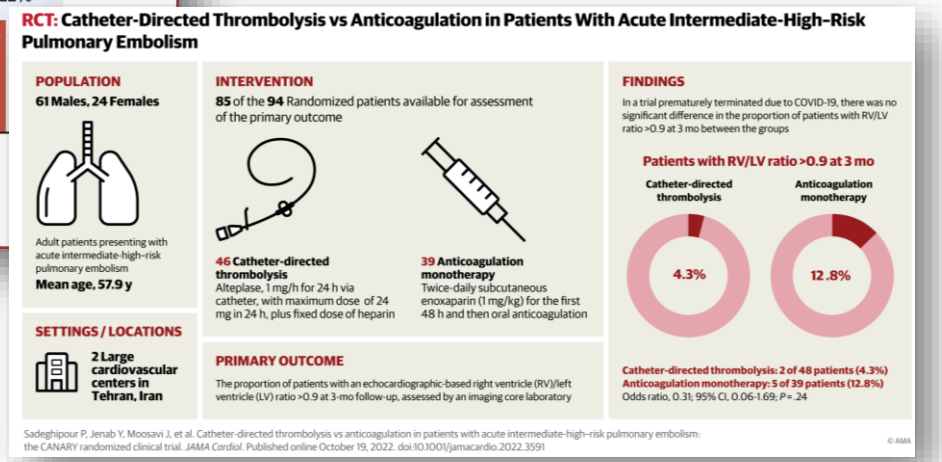
- 0.8%

Sterling K, et al. Circ Cardiovasc Interv. 2024 Jan 24:e013448

# RESCUE, SUNSET sPE, and CANARY: CDT Trials



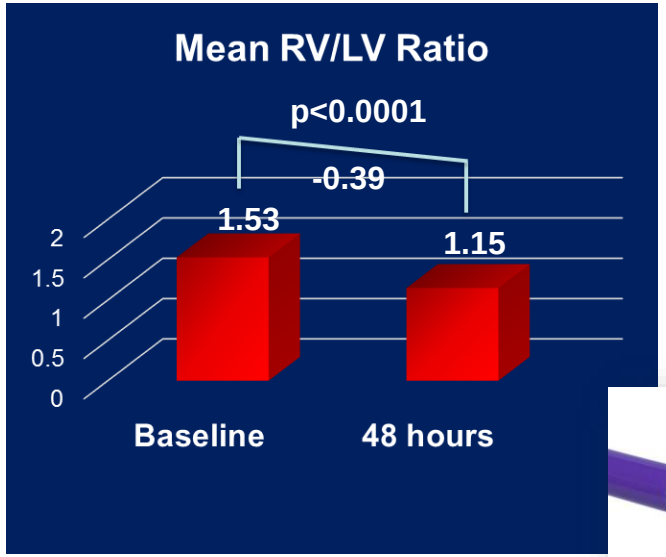
# Aspiration Embolectomy with the FlowTriever: FLARE

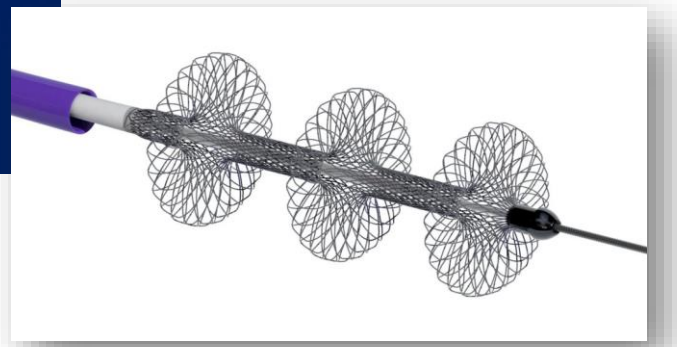
Prospective, multicenter, single-arm study evaluating the FlowTriever System in 106 patients with acute PE.

Patients with proximal PE and RV/LV ratio≥0.9 were eligible to participate.

3.8% rate of major adverse events.

PEERLESS 2 will provide more data.



Tu T, et al. JACC: Cardiovasc Interv. 2019;12:859

# Mechanical Thrombectomy in High-Risk PE: FLAME Registry

**Table 1. Demographics, Medical History, and Clinical Presentation**

| | FlowTriever arm (n=53) | Context arm (n=61) |
|---|---|---|
| Age, y | 64.8±15.3 | 61.6±13.9 |
| Female | 26 (49.1%) | 35 (57.4%) |
| BMI, kg/m² | 32.2±6.1 | 33.9±8.5 |
| Race | | |
| American Indian or Alaskan Native | 0 (0.0%) | 0 (0.0%) |
| Asian | 0 (0.0%) | 0 (0.0%) |
| Black or African American | 16 (30.2%) | 40 (65.6%) |
| Native Hawaiian or Pacific Islander | 0 (0.0%) | 0 (0.0%) |
| White | 33 (62.3%) | 18 (29.5%) |
| Other | 0 (0.0%) | 1 (1.6%) |
| Not provided | 4 (7.5%) | 2 (3.3%) |
| Clinical presentation at admission or time of high-risk PE diagnosis | | |
| SCAI shock stage* | | |
| A | 2 (3.8%) | 1 (1.6%) |
| B | 11 (20.8%) | 6 (9.8%) |
| C | 29 (54.7%) | 22 (36.1%) |
| D | 5 (9.4%) | 12 (19.7%) |
| E | 6 (11.3%) | 20 (32.8%) |
| Systolic BP, mm Hg | 97.4±21.4 n=49 | 93.5±33.4 n=59 |
| Diastolic BP, mm Hg | 65.5±14.7 n=49 | 57.8±23.5 n=59 |
| Heart rate, bpm | 99.9±22.6 n=48 | 103.1±29.4 n=58 |
| Tachycardia, >100 bpm | 29 (54.7%) | 34 (55.7%) |

**Table 2. Primary End Point in the FlowTriever Arm**

| | FlowTriever arm (n=53) | Performance goal |
|---|---|---|
| Primary end point* | 9 (17.0%†; 8.1%–9.8%) | 32.0% |

**CONCLUSIONS:** Among patients selected for mechanical thrombectomy with the FlowTriever System, a significantly lower associated rate of in-hospital adverse clinical outcomes was observed compared with a prespecified performance goal, primarily driven by low all-cause mortality of 1.9%.

Silver MJ, et al. Circ Cardiovasc Interv. 2023;16:e013406

# Ultrasound-Facilitated, Catheter-Based Fibrinolysis vs Mechanical Thrombectomy

## REAL-PE

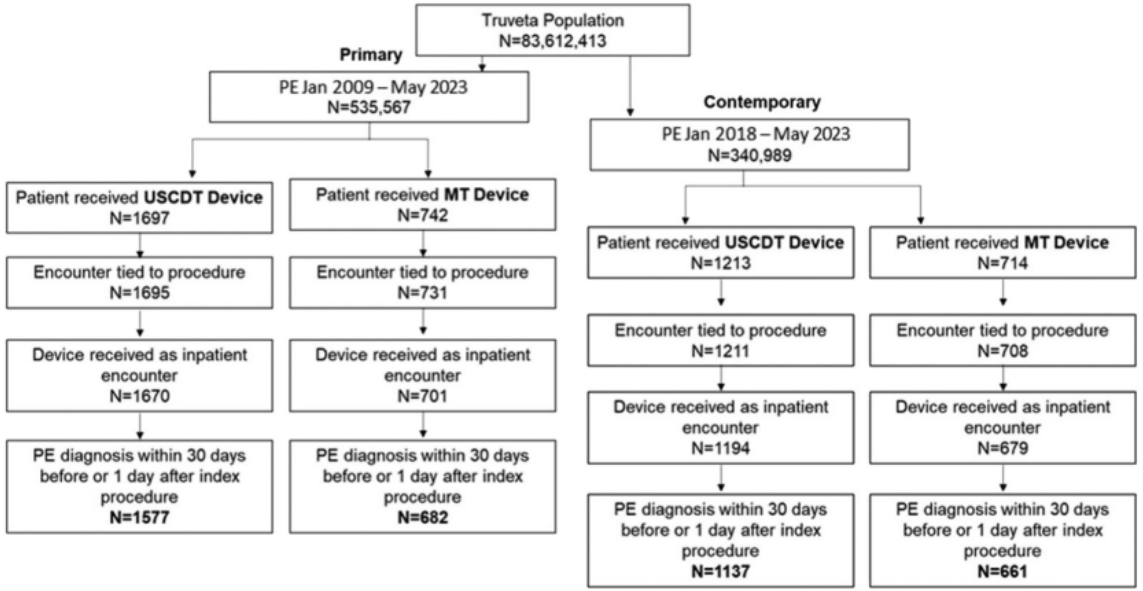



**Figure 1.**
Patient flowchart for inclusion in the primary and contemporary cohorts.

| | Primary (2009-2023) | | | Contemporary (2018-2023) | | |
|---|---|---|---|---|---|---|
| | p-value | USCDT | MT | p-value | USCDT | MT |
| Transfusion 7 days | <0.0001 | 30 (1.9%) | 40 (5.9%) | <0.0001 | 22 (1.9%) | 39 (5.9%) |
| Hgb decrease >2 | <0.0001 | 842 (53.4%) | 460 (67.4%) | <0.0001 | 580 (51.0%) | 444 (67.2%) |
| Hgb decrease >5 | <0.0001 | 233 (14.8%) | 154 (22.6%) | <0.0001 | 154 (13.5%) | 150 (22.7%) |
| Major Bleed Dx Code | 0.137 | 180 (11.4%) | 93 (13.6%) | 0.0207 | 114 (10.0%) | 90 (13.6%) |
| ISTH Major Bleed | 0.0018 | 195 (12.4%) | 118 (17.3%) | 0.0002 | 125 (11.0%) | 114 (17.2%) |
| BARC3B Major Bleed | 0.019 | 186 (11.8%) | 105 (15.4%) | 0.0024 | 120 (10.6%) | 102 (15.4%) |

Monteleone P, et al. JSCAI. 2023; in press

# PEERLESS: No Difference in Clinical Outcomes

## Trial design

### Eligibility criteria

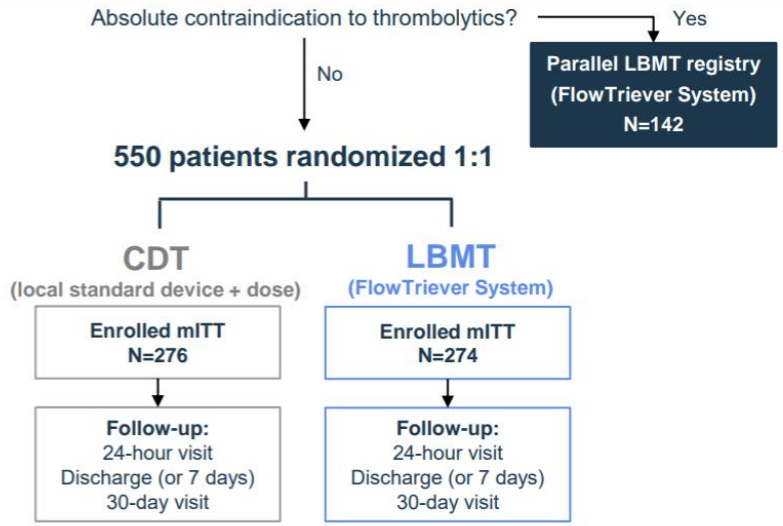
**Inclusion**

- SBP > 90 mmHg + central clot + RV dysfunction
- Symptom onset within 14 days
- Intervention planned within 72 hours
- + ≥ 1 additional clinical risk factor
  - Elevated cardiac troponin
  - History of heart failure
  - History of chronic lung disease
  - Heart rate ≥ 110 bpm
  - SBP < 100 mmHg
  - RR ≥ 30 breaths per min
  - Oxygen saturation < 90%
  - Syncope related to PE
  - Elevated lactate

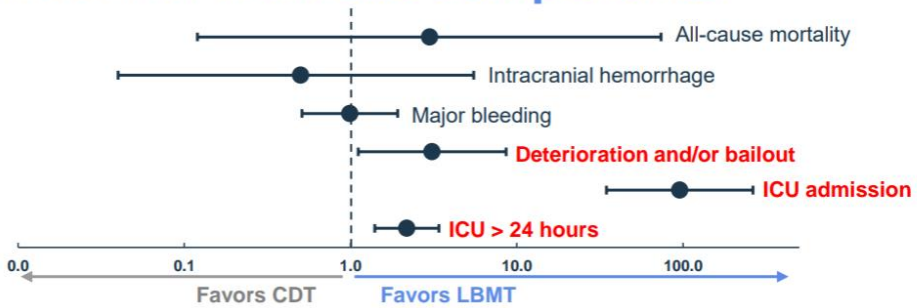
**Exclusion**

- Unable to receive AC
- Right heart clot in transit
- Life expectancy < 30 days
- CTEPH/CTED
- sPAP ≥ 70 mmHg on invasive hemodynamics

### Treatment and follow-up




## Results: Win ratio components




| | CDT events | LBMT events | Odds ratio [95% CI] | *P* value |
|---|---|---|---|---|
| **All-cause mortality** | 1 (0.4) | 0 (0.0) | 2.99 [0.12–73.70] | 1.00 |
| **Intracranial hemorrhage** | 1 (0.4) | 2 (0.7) | 0.50 [0.04–5.51] | 0.62 |
| **Major bleeding** | 19 (6.9) | 19 (6.9) | 0.99 [0.51–1.92] | 1.00 |
| **Clinical deterioration and/or escalation to bailout therapy** | 15 (5.4) | 5 (1.8) | 3.09 [1.11–8.63] | **0.038** |
| **Postprocedural ICU admission** | 272 (98.6) | 114 (41.6) | 95.4 [34.6–263.6] | **< 0.001** |
| ICU stay > 24 hours* | 178 (65.4) | 53 (46.5) | 2.18 [1.40–3.40] | **< 0.001** |

**Removing escalation to bailout patients (because of bias against CDT), there is no statistical difference (LBMT vs. CDT: 4 vs 10 patients; Fisher's Exact 0.17).**

Jaber W, et al. Circulation. 2024; epub ahead of print

# PEERLESS: No Difference in Major Bleeding

## Bleeding events through discharge / 7 days

| | CDT N = 276 | LBMT N = 274 | *P* value |
|---|---|---|---|
| **Major bleeding (ISTH)** | **19 (6.9)** | **19 (6.9)** | 1.00 |
| **Adjudicated reasons for major bleeding** | | | |
| Fatal bleeding* | 1 (0.4) | 0 (0) | |
| Symptomatic bleeding in a critical area or organ‡ | 2 (0.7) | 2 (0.7) | |
| Intracranial hemorrhage† | 1 | 2 | |
| Hemarthrosis | 1 | 0 | |
| Hgb drop ≥ 2 g/dL (1.24 mmol/L) and/or transfusion ≥ 2 units | 16 (5.8) | 17 (6.2) | |
| Access site source | 10 | 8 | |
| Transfusions administered | 8 | 1 | |
| # units transfused | 3.3 ± 1.8 | 2.0 | |
| **Clinically relevant non-major bleeding events‡** | 9 (3.3) | 7 (2.6) | 0.80 |
| **Minor bleeding events‡** | 1 (0.4) | 6 (2.2) | 0.07 |

Jaber W, et al. Circulation. 2024; epub ahead of print[45]

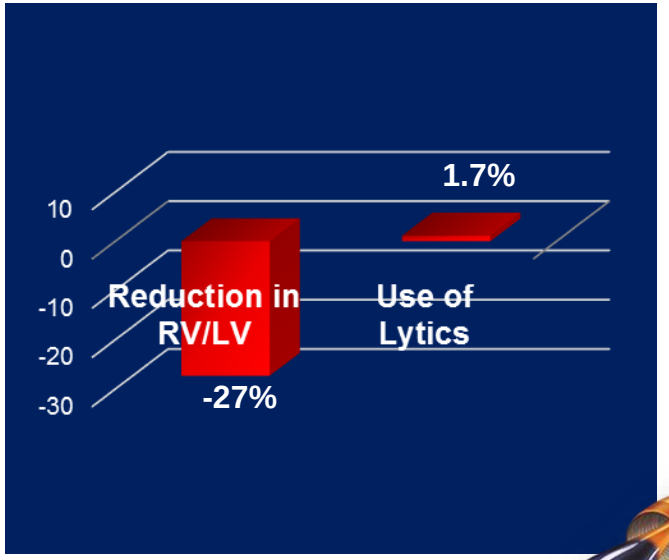
# Thrombus Aspiration for Acute PE: EXTRACT-PE

Prospective, multicenter, single-arm study evaluating the Indigo Aspiration System in 119 patients with acute PE.

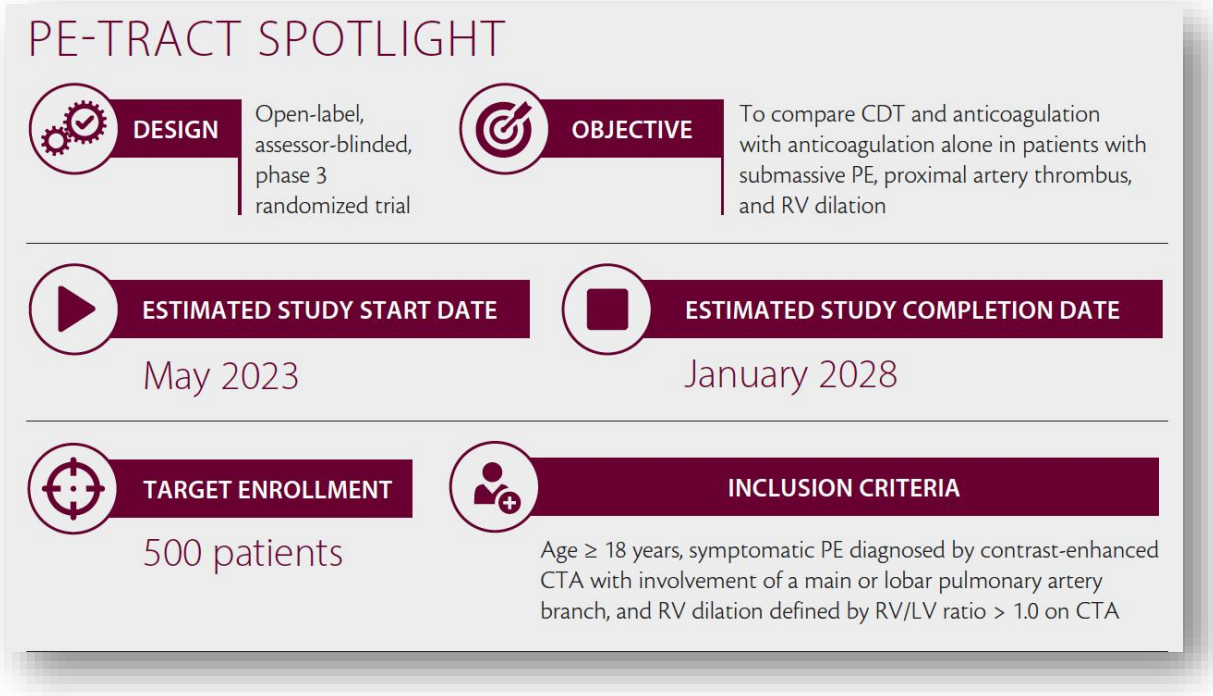
Patients with proximal PE and RV/LV ratio≥0.9 were eligible to participate.

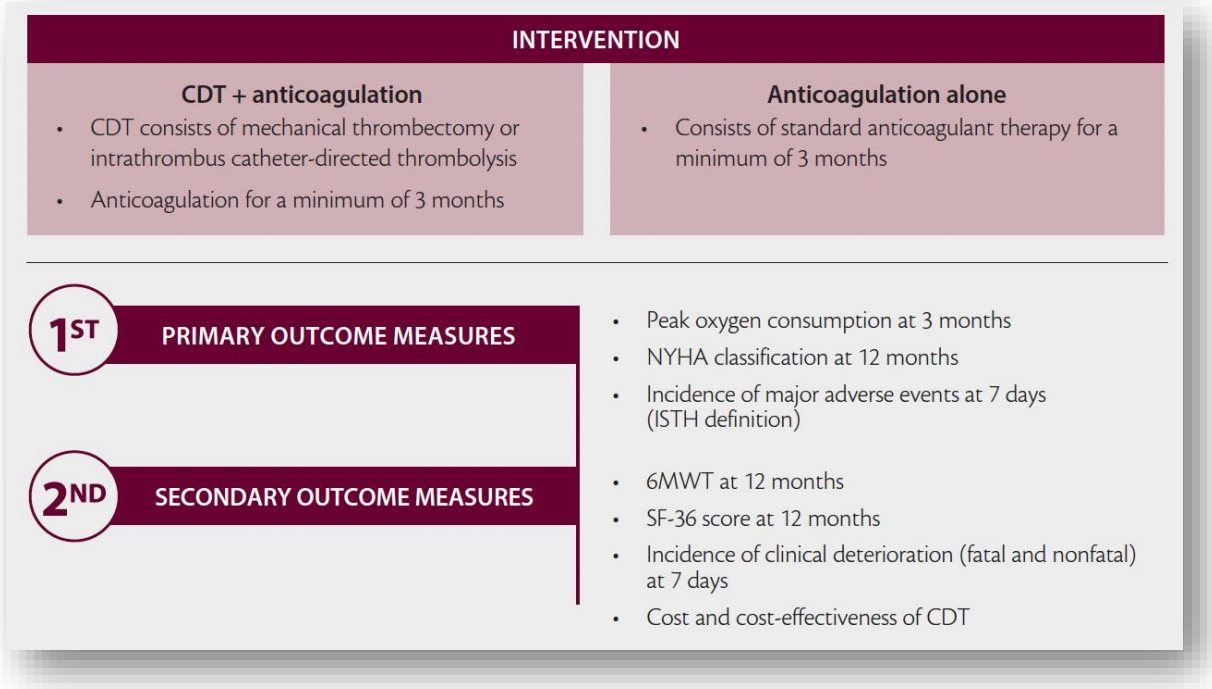
1.7% rate of major adverse events.

STRIKE-PE and STORM-PE will provide more data.



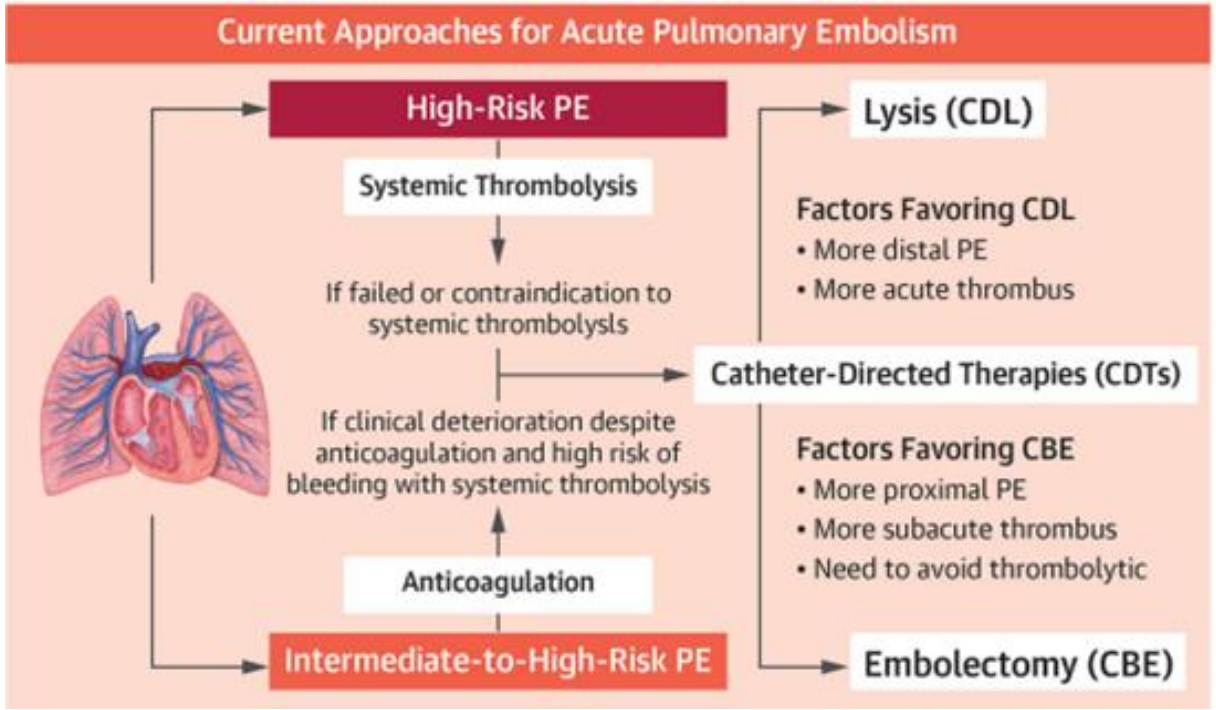

# PE-TRACT: An NIH-Funded Trial

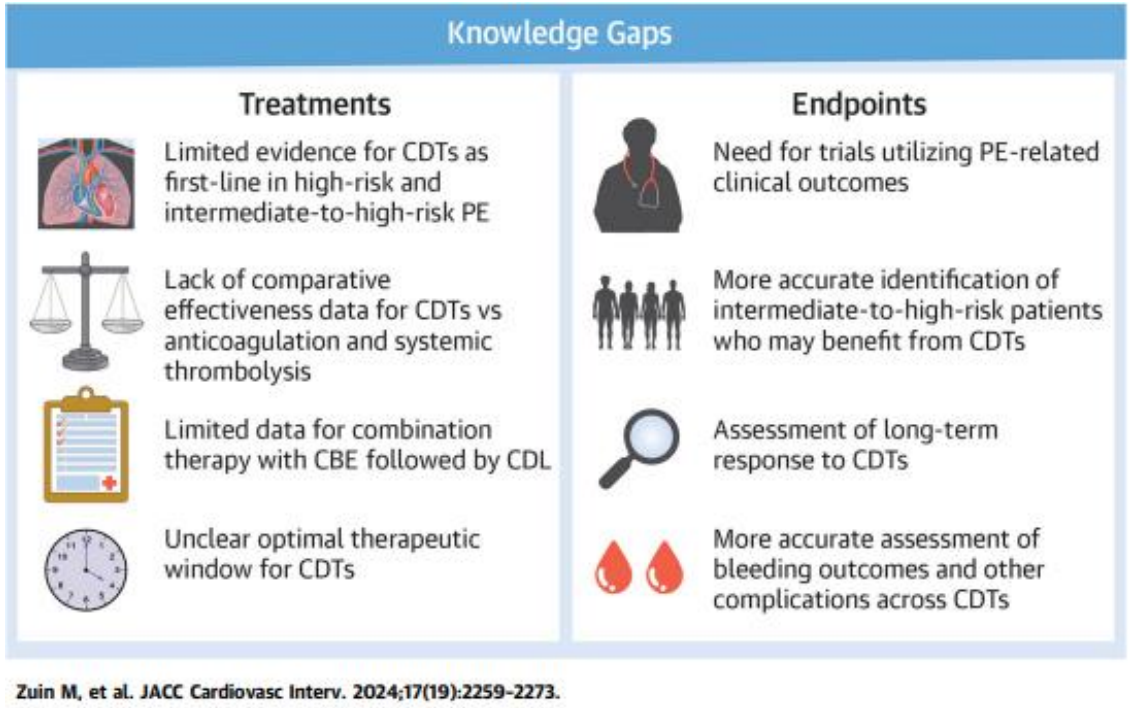



https://evtoday.com/articles/2021-july/the-importance-of-the-pe-tract-trial

# Current Approaches to Catheter-Based Therapy



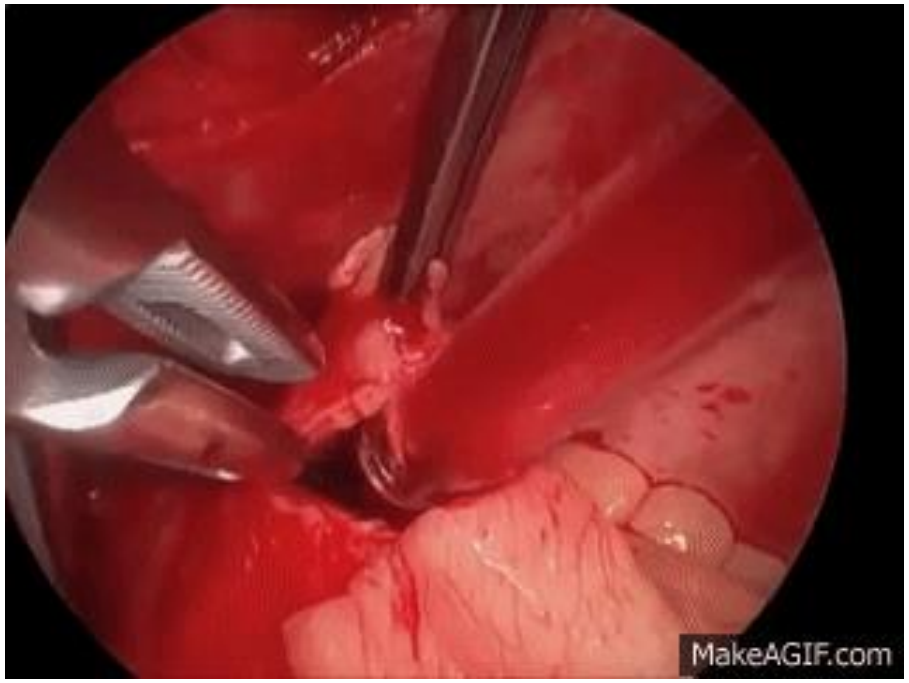

Zuin M, et al. JACC Cardiovasc Interv. 2024;17(19):2259-2273.

# Surgical Embolectomy

**TABLE 2. Indications for surgical embolectomy (n = 47)**

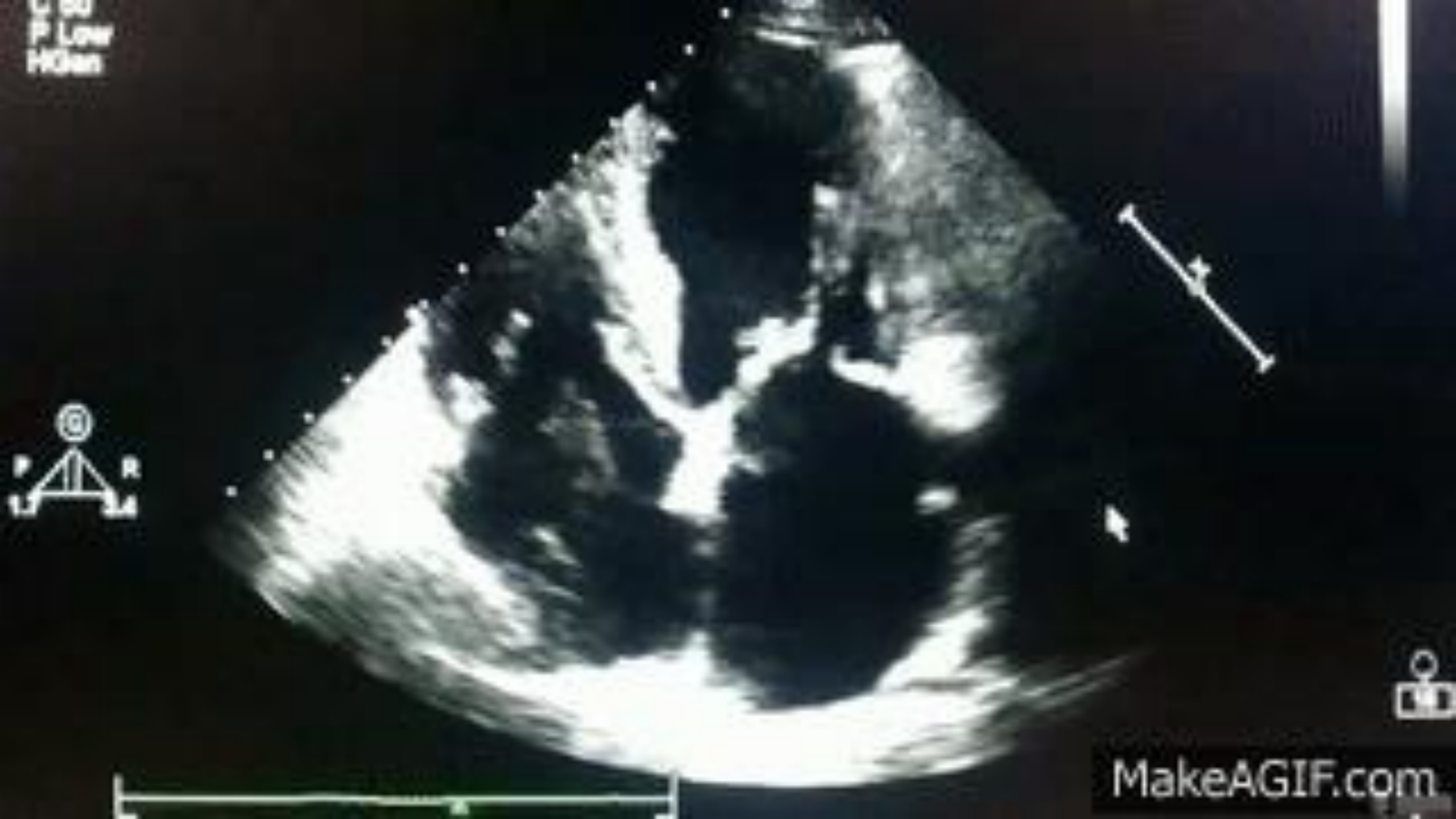
| Indication | N (%) |
|---|---|
| Contraindications to thrombolysis | 21 (45%) |
| Recent surgical intervention | 10 (21%) |
| Active bleeding | 3 (6%) |
| Stroke | 4 (9%) |
| Other | 4 (9%) |
| Failed medical treatment | 5 (10%) |
| Failure of thrombolytics | 4 (9%) |
| Failure of catheter embolectomy | 1 (2%) |
| Large RA-RV thrombus | 5 (10%) |
| RV hemodynamic dysfunction | 15 (32%) |
| Large PFO | 1 (2%) |

*RA-RV*, Right atrium–right ventricle; *PFO*, patent foramen ovale.




**Surgical embolectomy requires a median sternotomy and cardiopulmonary bypass.**

Leacche M, et al. J Thorac Cardiovasc Surg 2005;129:1018
https://www.youtube.com/watch?v=SzsQWIMYbN8

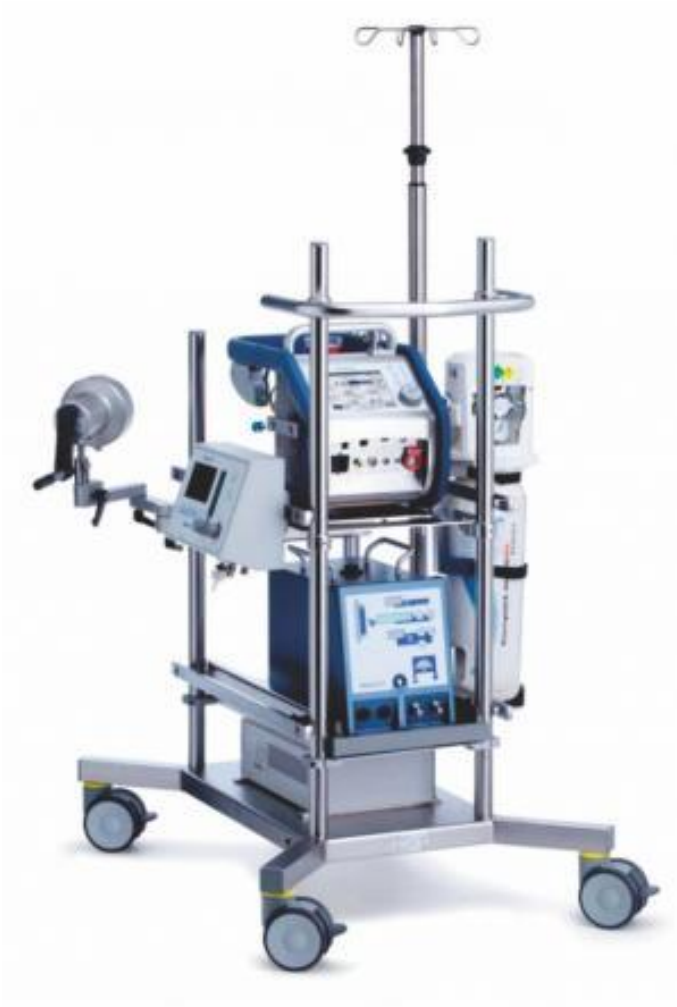

MakeAGIF.com

# ECMO for Catastrophic PE

20 years of case reports and series of PE patients treated with ECMO demonstrate 70% survival.

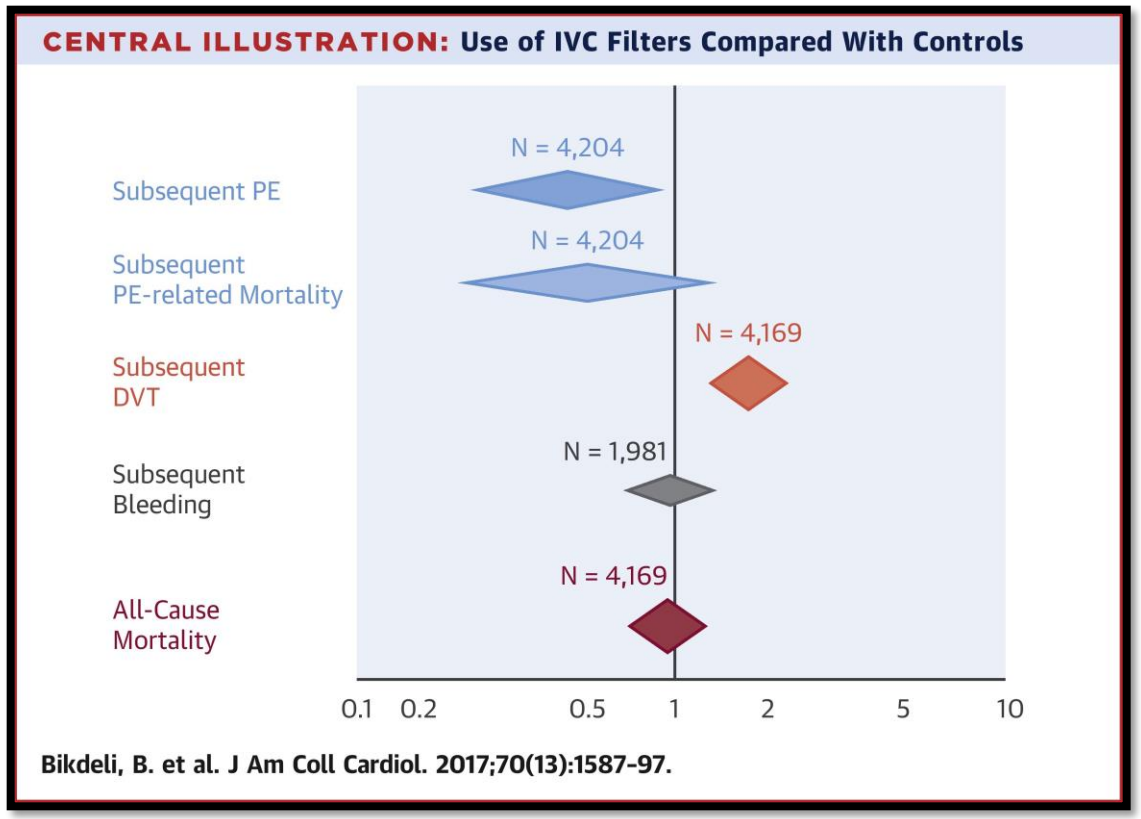
Survival rates are similar whether ECMO was used alone or with another advanced therapy.

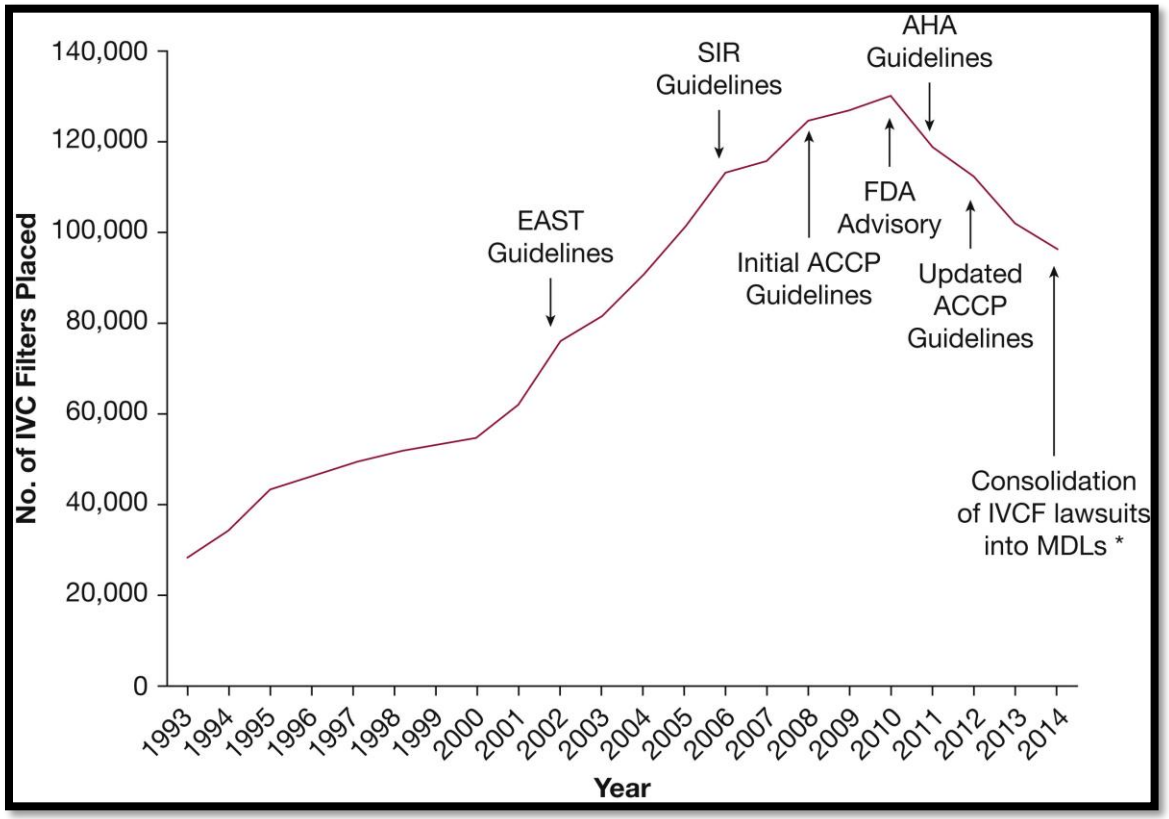
Veno-arterial (VA) ECMO has been used effectively to bridge to surgical or catheter embolectomy or simply to “buy time.”



Yusuf HO, et al. Perfusion 2015;30:611

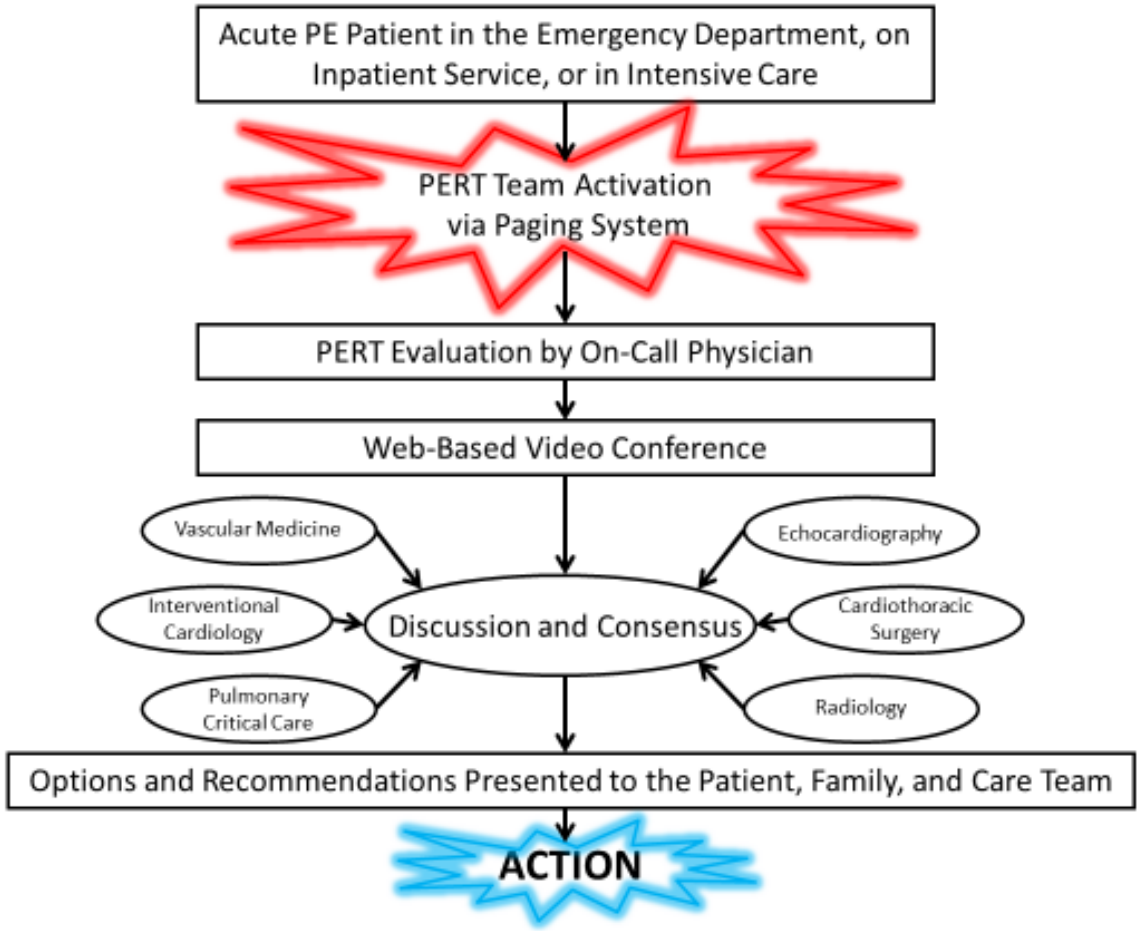
# Inferior Vena Cava Filters




Bikdeli B, et al. J Am Coll Cardiol. 2017;70:1587
Ahmed O, et al. CHEST. 2017;151:1402

# PE Response Teams

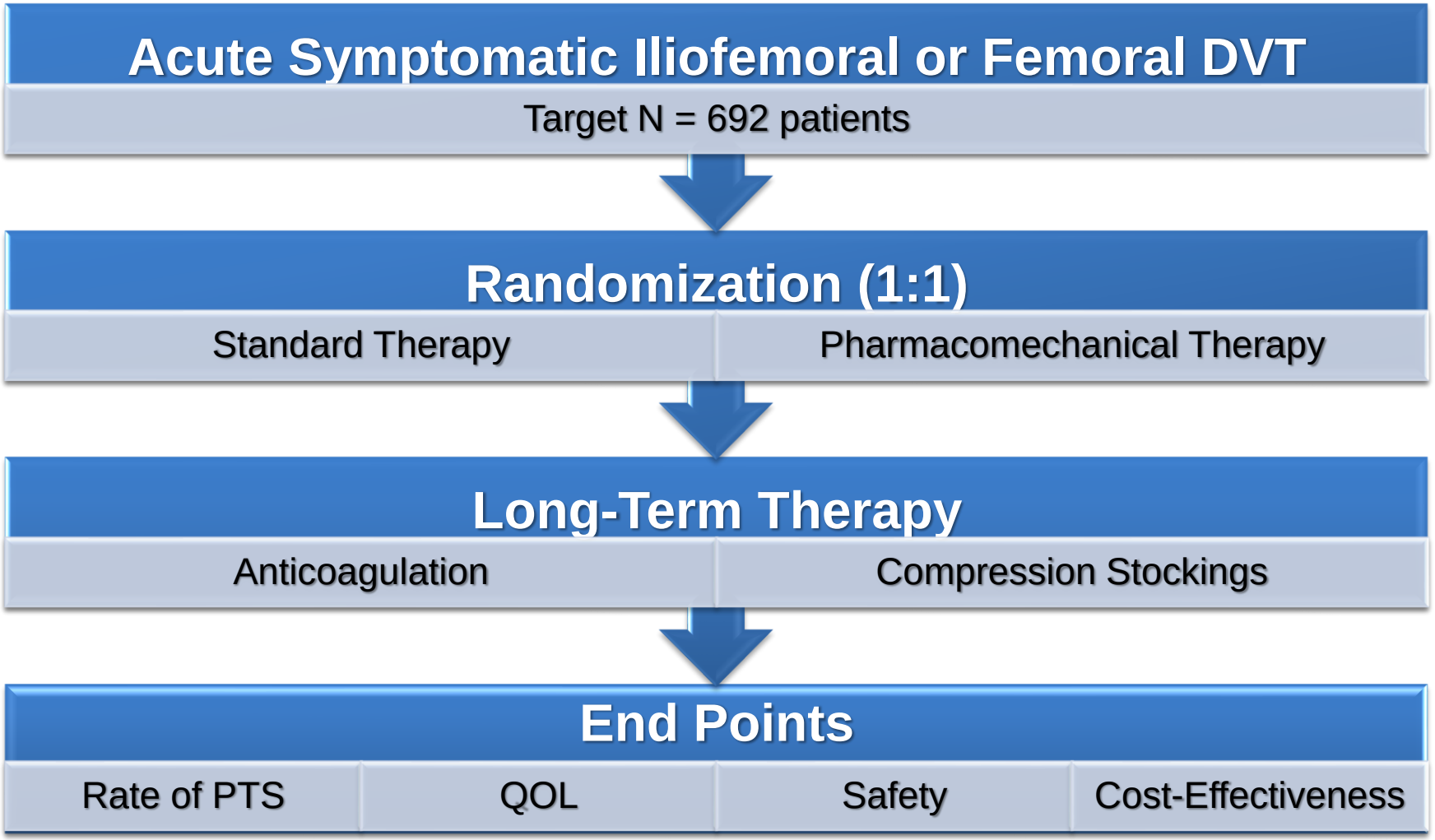



**6.8 Recommendations for multidisciplinary pulmonary embolism teams**

| Recommendation | Class[a] | Level[b] |
|---|---|---|
| Set-up of a multidisciplinary team and a programme for the management of high- and (in selected cases) intermediate-risk PE should be considered, depending on the resources and expertise available in each hospital. | IIa | C |

Konstantinides SV, et al. Eur Heart J. 2019; 00:1

# ATTRACT Trial: Pharmacomechanical Therapy for Iliofemoral and Femoral DVT




http://www.attract.wustl.edu/dvt-study-overview

# Pharmacomechanical Therapy for DVT: ATTRACT

| Outcome | Pharmacomechanical N=336 | No-Pharmacomechanical N=355 | p-value |
|---|---|---|---|
| Major bleeding (10 days) | 1.7% | 0.3% | 0.049 |
| Any bleeding (10 days) | 4.5% | 1.7% | 0.034 |
| Fatal bleeding | 0 | 0 | |
| Intracranial hemorrhage | 0 | 0 | |

| Outcome (24 months) | Pharmacomechanical N=336 | No-Pharmacomechanical N=355 | p-value |
|---|---|---|---|
| Any PTS | 46.7% | 48.2% | 0.56 |
| Recurrent VTE | 12.5% | 8.5% | 0.09 |
| SF-36 (Overall QOL) | 11.8 | 10.1 | 0.37 |
| VEINES (Venous QOL) | 27.7 | 23.5 | 0.08 |
| Moderate or Severe PTS | Overall 17.9% Iliofemoral 18.4% Femoral-popliteal 17.1% | Overall 23.7% Iliofemoral 28.2% Femoral-popliteal 18.1% | 0.035 |

Vedantham S, et al. N Engl J Med 2017; 377:2240

# Case No. 3

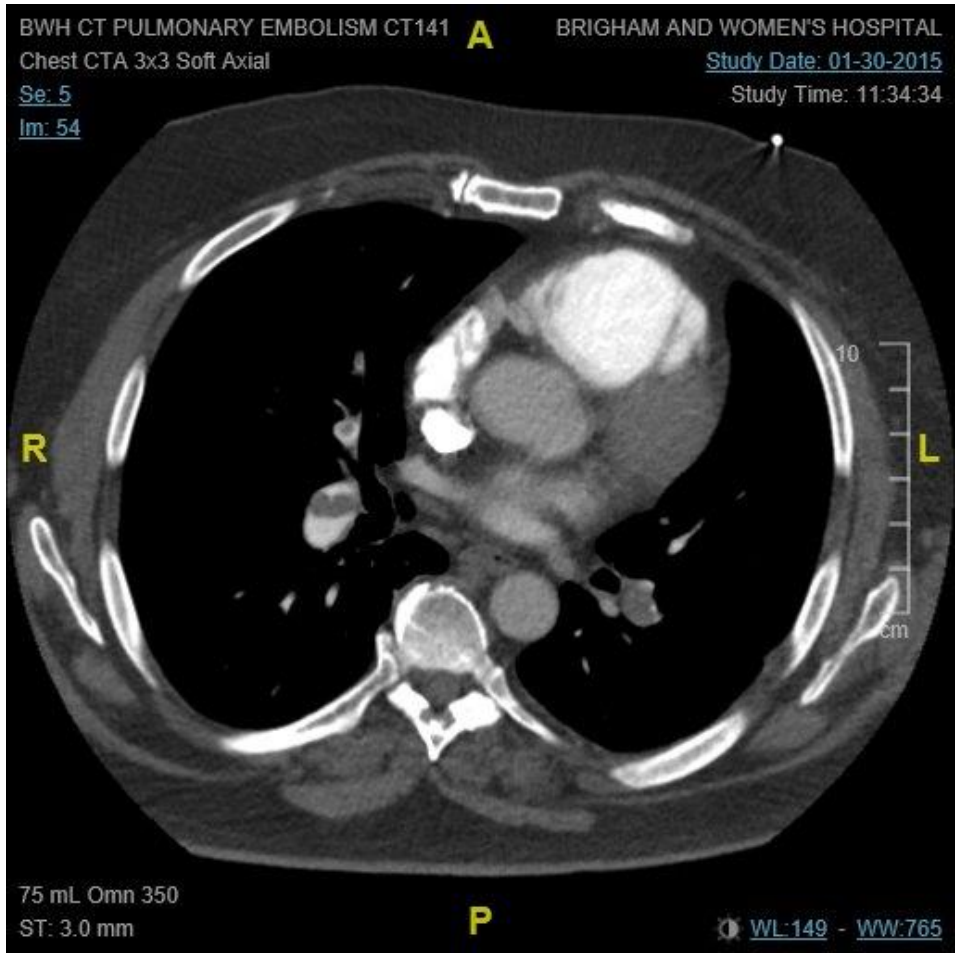
A 82-year-old man with obesity, coronary artery disease, and carotid artery disease presents with right-sided pleuritic pain and dyspnea.

He denies any recent trauma, surgery, or immobility.

His heart rate is 108 bpm, blood pressure 148/72 mmHg, and $O_2$ saturation 89% on room air.

His high sensitivity cardiac troponin T is normal.

He undergoes CT angiography.



# Question No. 3

The patient is admitted and started on heparin with a goal PTT of 60-80 seconds. He improves steadily and is ready for discharge 4 days later. Which is the preferred regimen for oral anticoagulation in this patient?

a) Warfarin with an INR target of 2-3 for 12 months then 1.5-2 thereafter
b) Apixaban 5 mg twice daily for 6 months and then 2.5 mg twice daily indefinitely
c) Dabigatran 150 mg twice daily for 6 months and then 75 mg twice daily indefinitely
d) Enoxaparin 120 mg twice daily indefinitely

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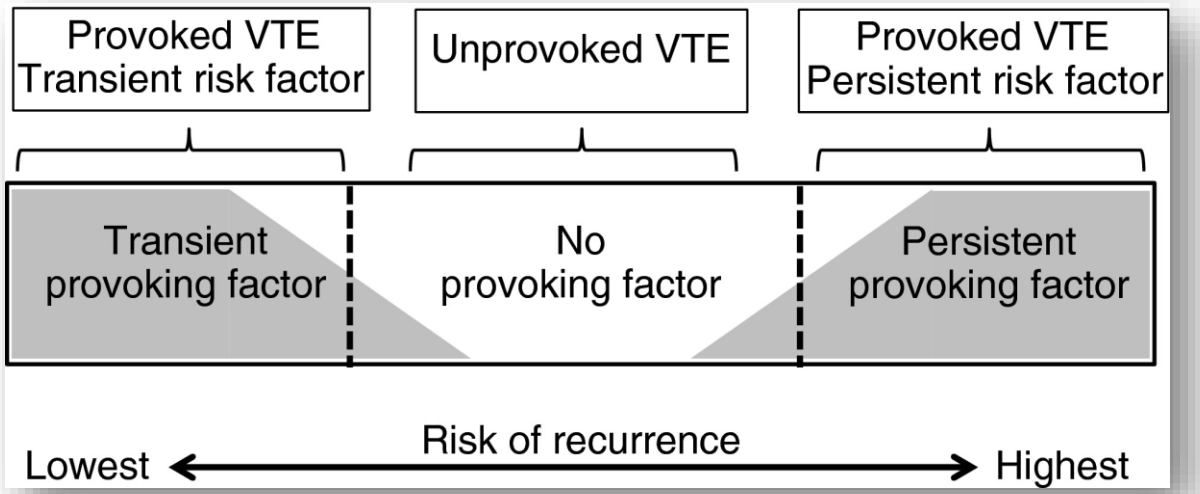
d) Enoxaparin 120 mg twice daily indefinitely

Explanation: For unprovoked VTE, indefinite duration anticoagulation is recommended. Low-intensity apixaban offers the best safety and efficacy of the options given for this patient.

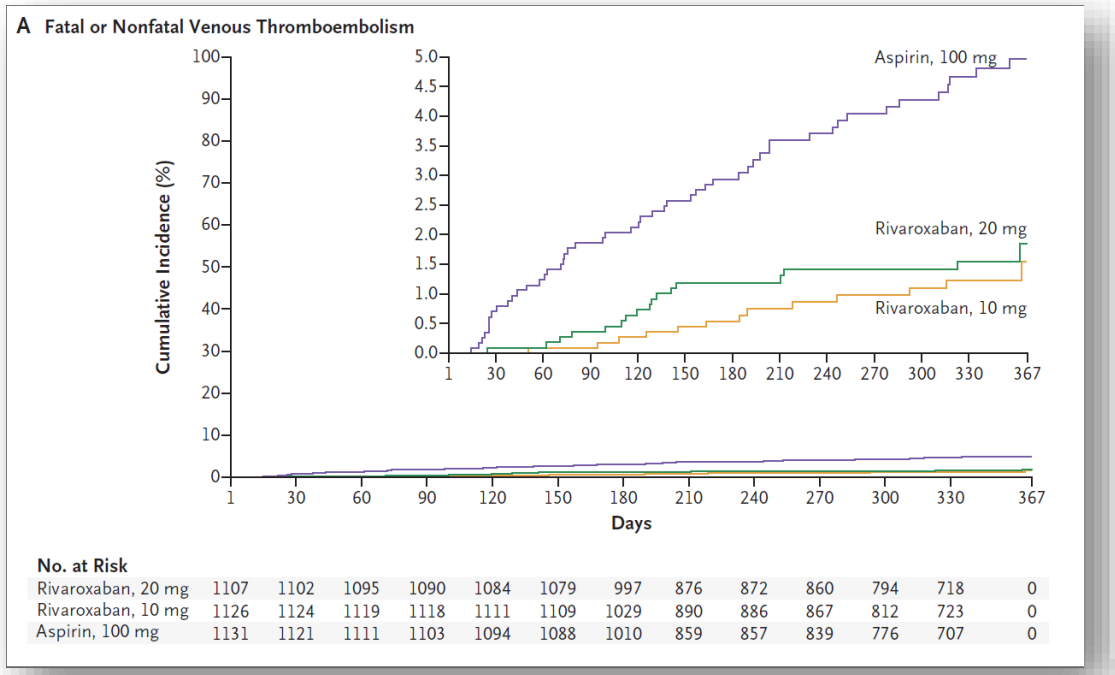
# Risk of Recurrence: ISTH and ESC Guidelines

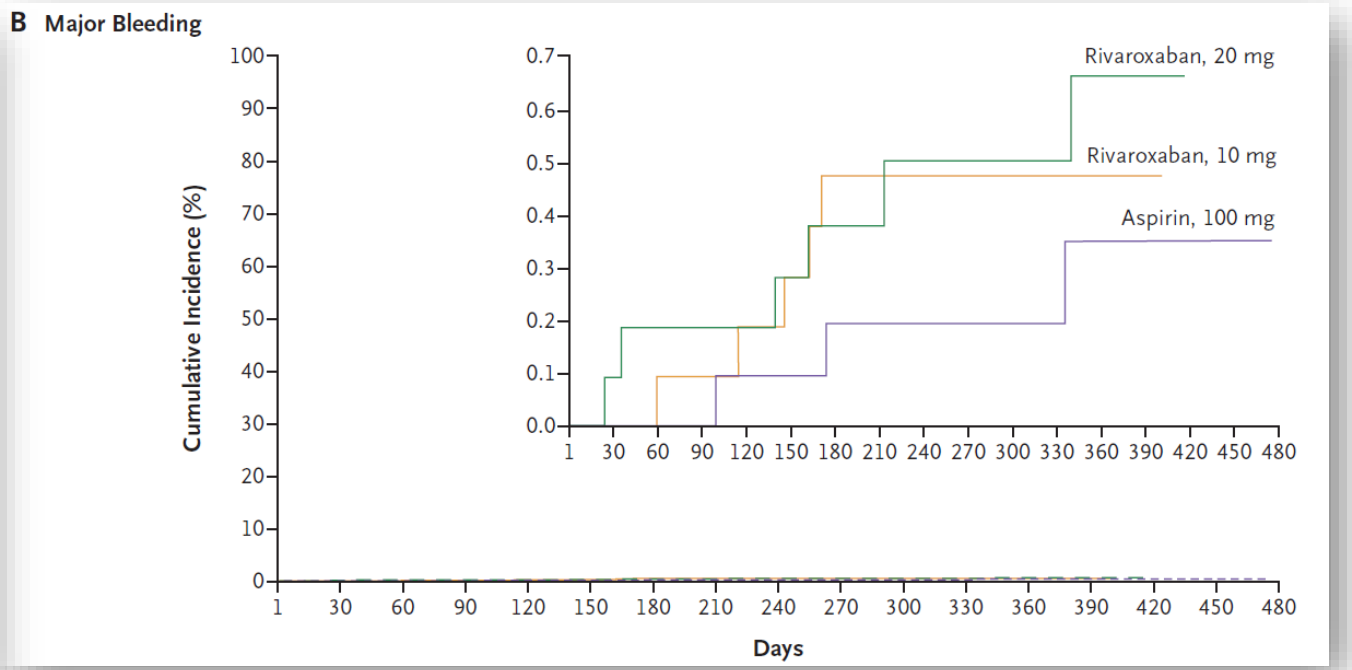



| Estimated risk for long-term recurrence[a] | Risk factor category for index PE[b] | Examples[b] |
|---|---|---|
| Low (<3% per year) | Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor) | • Surgery with general anaesthesia for >30 min<br>• Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness<br>• Trauma with fractures |
| Intermediate (3–8% per year) | Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE | • Minor surgery (general anaesthesia for <30 min)<br>• Admission to hospital for <3 days with an acute illness<br>• Oestrogen therapy/contraception<br>• Pregnancy or puerperium<br>• Confined to bed out of hospital for ≥3 days with an acute illness<br>• Leg injury (without fracture) associated with reduced mobility for ≥3 days<br>• Long-haul flight |
| | Non-malignant persistent risk factors | • Inflammatory bowel disease<br>• Active autoimmune disease |
| | No identifiable risk factor | |
| High (>8% per year) | | • Active cancer<br>• One or more previous episodes of VTE in the absence of a major transient or reversible factor<br>• Antiphospholipid antibody syndrome |

Kearon C, et al. J Thromb Haemost 2016; 14: 1480
Konstantinides SV, et al. Eur Heart J. 2019; 00:1

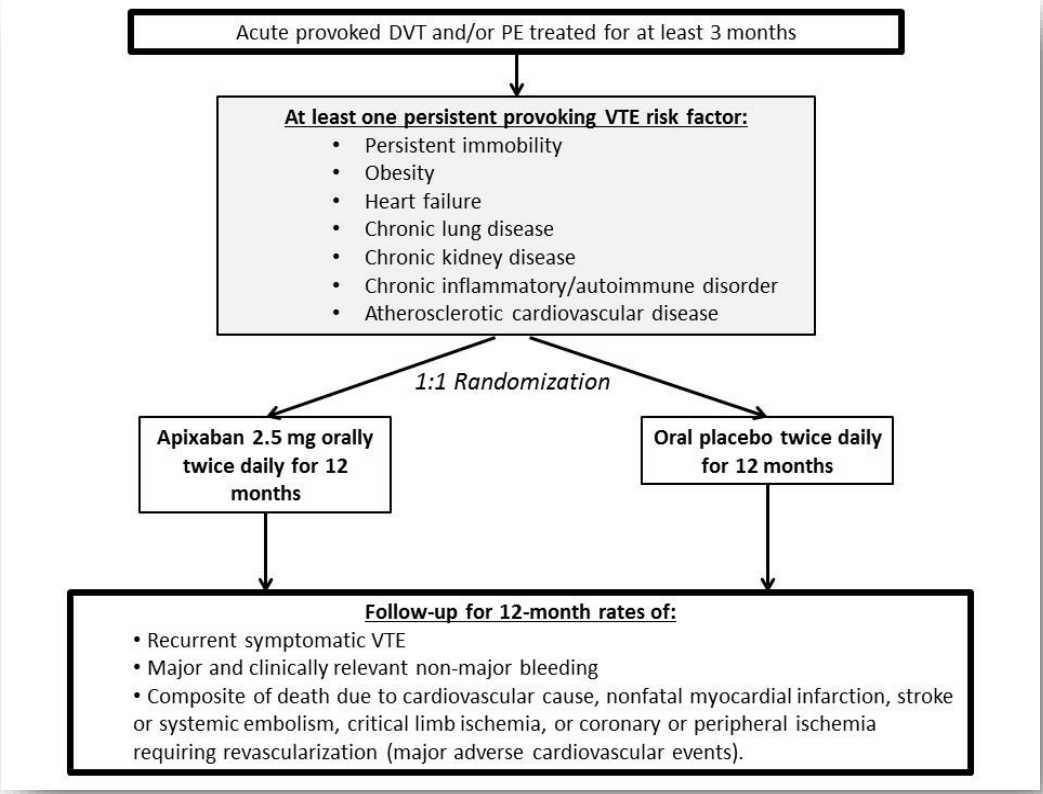
# Extended Secondary Prevention for All VTE: EINSTEIN CHOICE

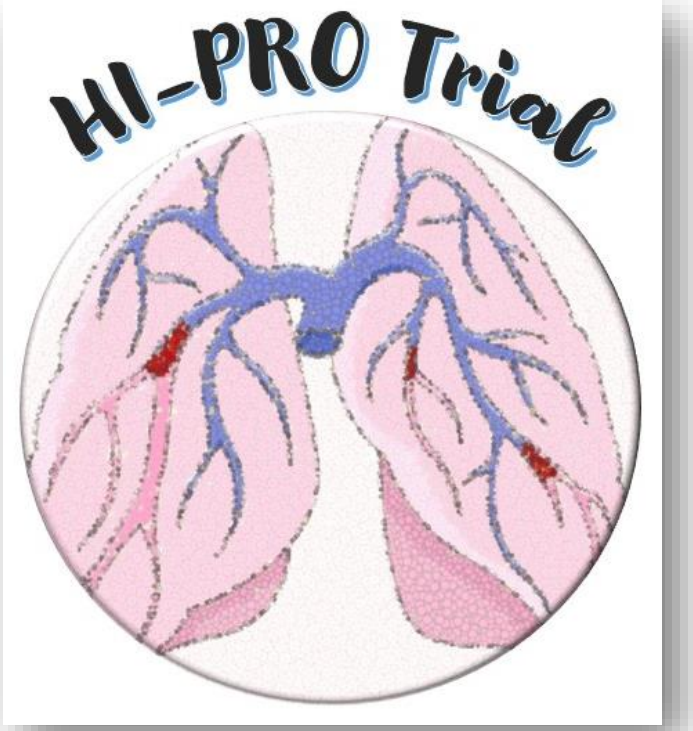



Weitz JI, et al. N Engl J Med 2017;376:1211

# HI-PRO Trial: 600 High-Risk Patients with Provoked VTE




Bikdeli B, et al. Thromb Haemost. 2022;122:1061

# Shared Decision-Making: Patient Preferences and Attitudes Toward Bleeding and VTE Recurrence

Cost
Lifestyle Implications
Concern for Bleeding

Limited Therapy

Concern for VTE Recurrence

Extended Therapy

# Bleeding Risk Must Be Part of the Equation

## The VTE-BLEED Score

### Introduction

The VTE-BLEED score was developed to identify patients on anticoagulation for VTED and who were at increased risk of bleeding. The original study was based on a *post-hoc* analysis of patients enrolled in various trials evaluating Dabigatran [a direct Thrombin inhibitor] versus standard treatment with Warfarin and subsequent studies have evaluated patients on Rivaroxaban [a direct Factor Xa inhibitor].

The algorithm is summarised below:

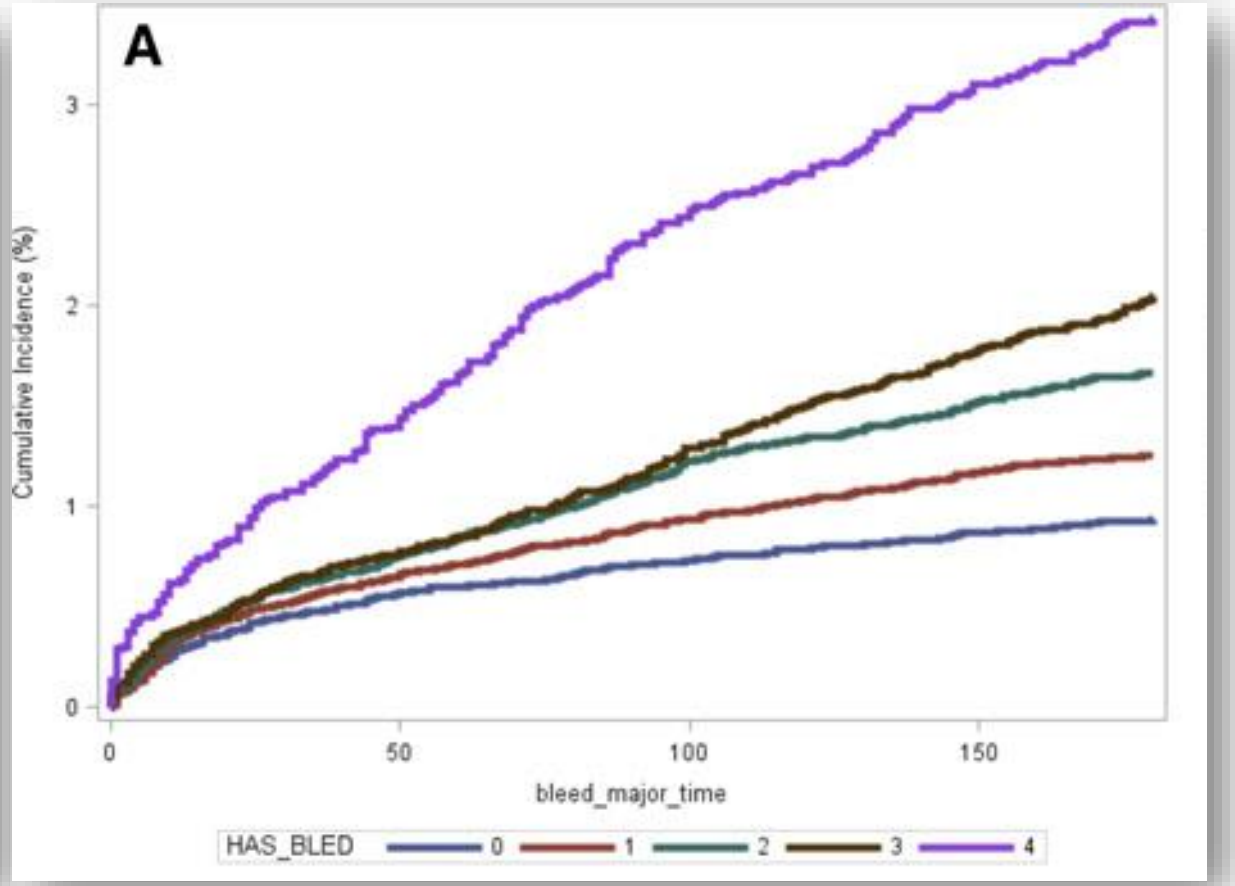
**The VTE Bleed Score:**

**Select Criteria:**

| | | |
|---|---|---|
| **Active Cancer** | | |
| ○ | Yes | 2 Points |
| **Male Patient with Uncontrolled Hypertension** **[Systolic BP ≥140mm Hg]** | | |
| ○ | Yes | 1 Point |
| **Anaemia** **[Hb <130g/L Men. Hb <120g/L Women]** | | |
| ○ | Yes | 1.5 Points |
| **History of Bleeding** **[Major or non-major clinically relevant bleeding]** | | |
| ○ | Yes | 1.5 Points |
| **Renal Dysfunction** **[CrCl 30-60ml/min]** | | |
| ○ | Yes | 1.5 Points |
| **Age ≥60 yrs** | | |
| ○ | Yes | 1.5 Points |

| | |
|---|---|
| **Score** **[Max score 9]** | |

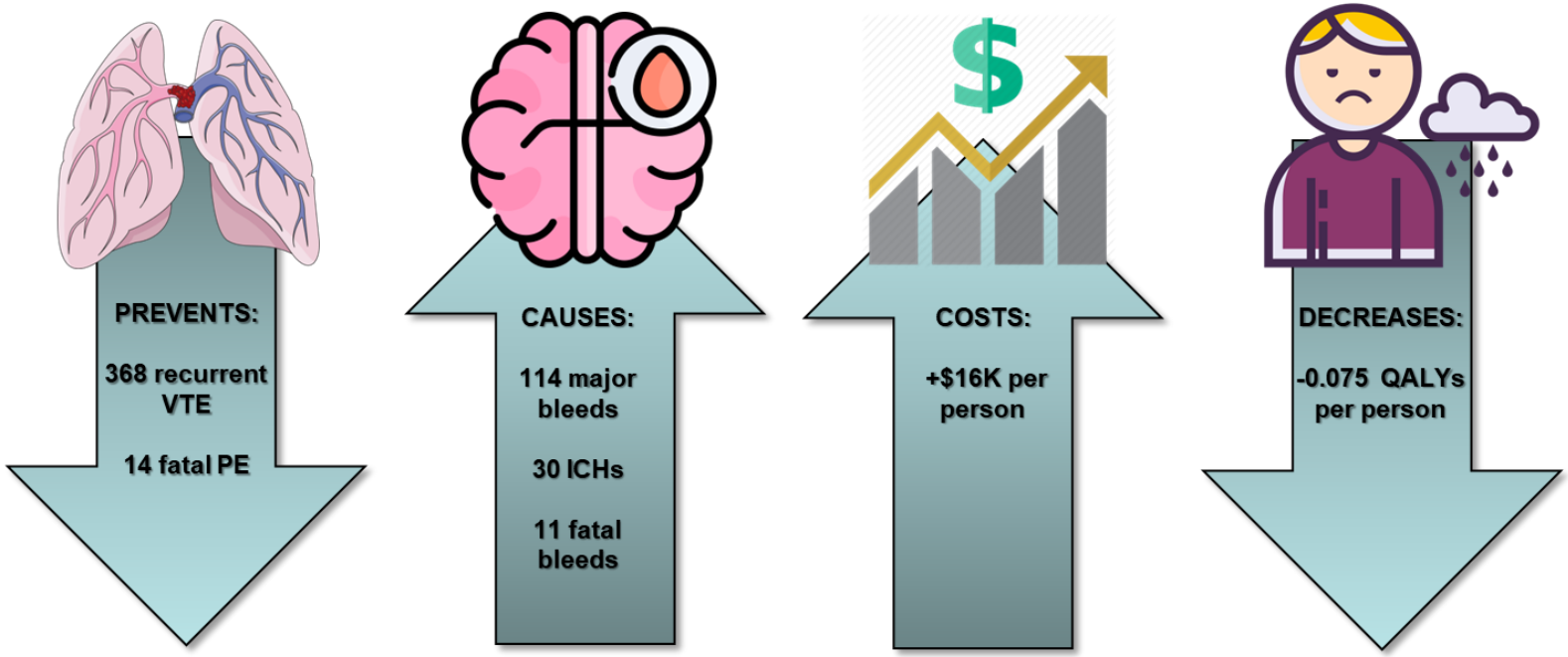
| **VTE-BLEED Score** | |
|---|---|
| **<2** | Low bleeding risk |
| **≥2** | High bleeding risk |




Klok FA, et al. Br J Haematol. 2018; 183: 457
Brown JD, et al. JAHA. 2018; 7: e007901

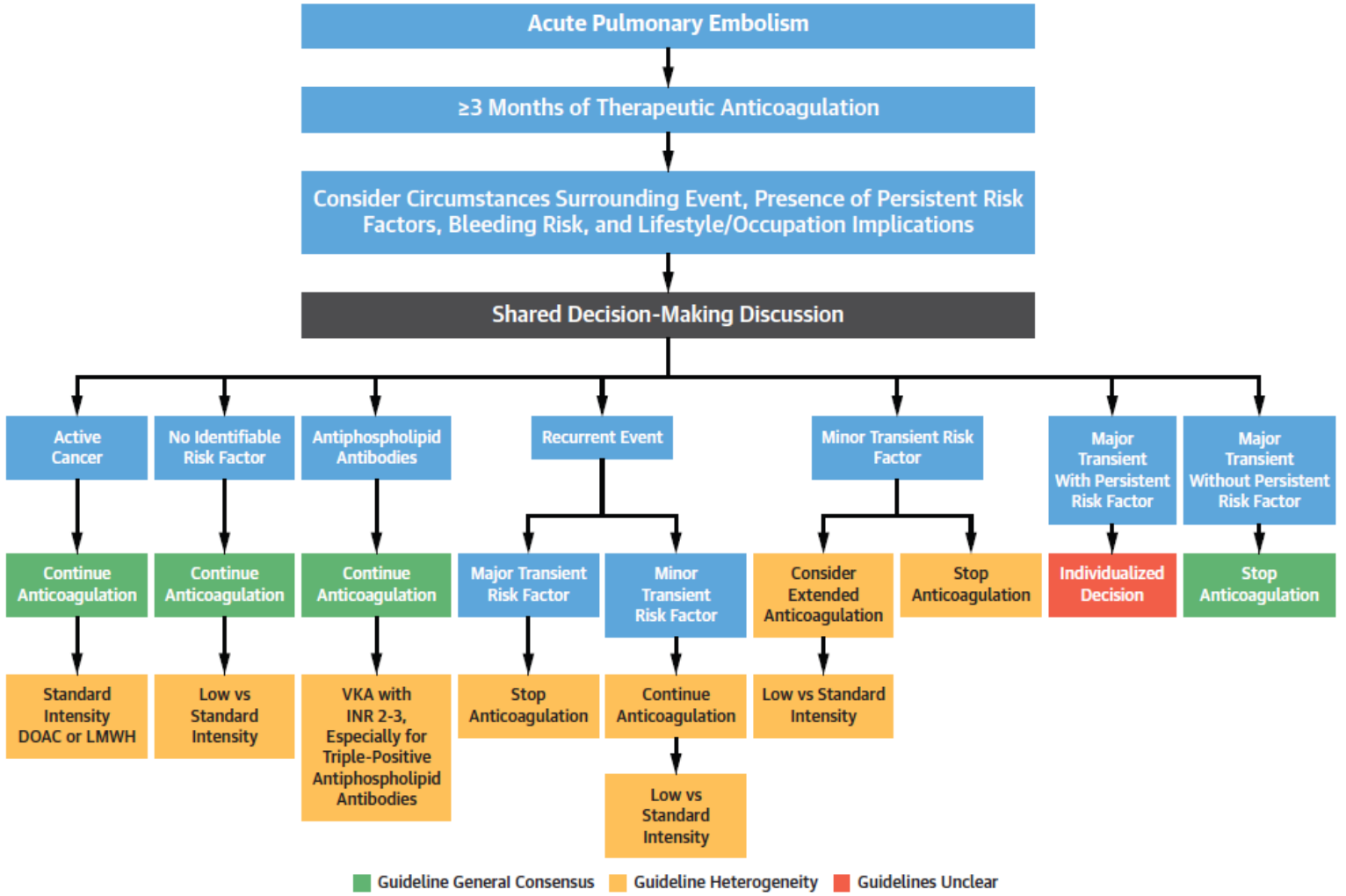
# A Cautionary Note on Indefinite Anticoagulation: A Canadian Cost-Effectiveness Study

In a hypothetical cohort of 1000 patients with a first unprovoked VTE, indefinite vs. time-limited anticoagulation




Khan F, et al. Ann Intern Med. 2023;176:949

# Optimal Duration of Anticoagulation: Guideline-Based Care






Zuin M, et al. J Am Coll Cardiol. 2024;84:1561

# Follow-Up Care for PE

✓ Suggested ⚠ Not addressed ✗ Not recommended

| | ESC/ERS [2] | PERT [12] | CHEST [13] | AHA [14] | ASH [15] | NICE [20] |
|---|---|---|---|---|---|---|
| **Routine re-evaluation of patients at 3-6 months after the index PE event** | ✓ | ✓ | ⚠ | ⚠ | ⚠ | ⚠ |
| **TTE and or V/Q scan in patients with persistent otherwise unexplained dyspnea and/or exercise intolerance after 3 months [b]** | ✓ | ✓ | ⚠ | ✓ [a] | ⚠ | ⚠ |
| **Refer symptomatic patients with PH and/or mismatched perfusion defects at V/Q scan to a referral center for CTEPH** | ✓ | ✓ | ⚠ | ✓ | ⚠ | ⚠ |

a. After 6 weeks to evaluate persistent pulmonary hypertension
b. Preference of imaging is generally based on center's expertise and resources availability

Zuin M, et al. J Am Coll Cardiol. 2024;84:1561

# Lifestyle Modification

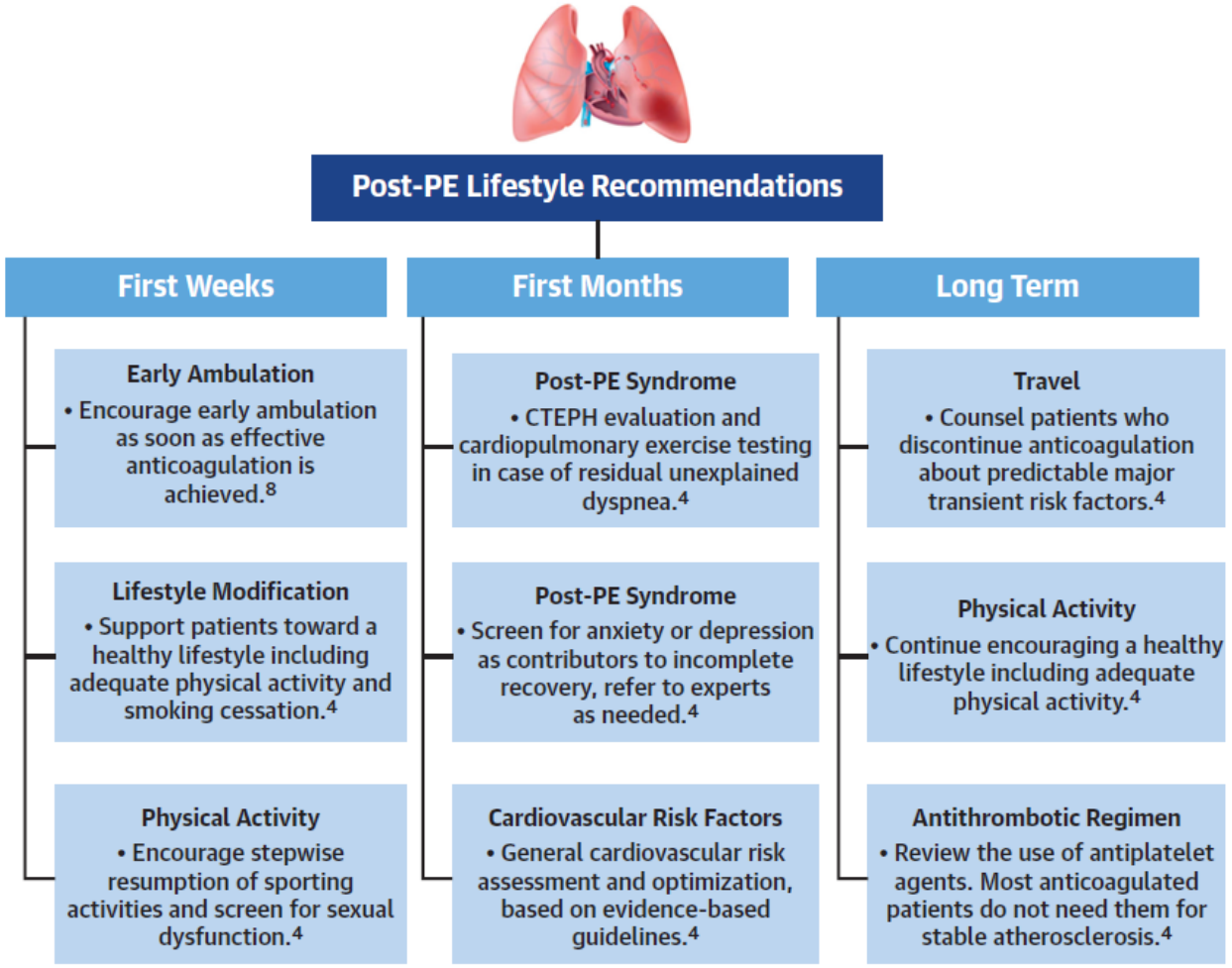
Suggested | Not addressed | Not recommended

| | ESC/ERS [2] | PERT [12] | CHEST [13] | AHA [14] | ASH [16] | NICE [20] |
|---|---|---|---|---|---|---|
| **Smoking Cessation** | ✓ a | ⚠ | ⚠ | ⚠ | ⚠ | ⚠ |
| **Diet** | ✓ a | ⚠ | ⚠ | ⚠ | ⚠ | ⚠ |
| **Weight loss strategy for overweight/obesity** | ⚠ | ⚠ | ⚠ | ⚠ | ⚠ | ⚠ |
| **Return to work** | ⚠ | ⚠ | ⚠ | ⚠ | ⚠ | ⚠ |
| **Physical activity/exercise** | ✓ a | ⚠ | ⚠ | ⚠ | ⚠ | ⚠ |
| **Participation in sexual activity** | ⚠ | ⚠ | ⚠ | ⚠ | ⚠ | ⚠ |

a. The ESC Guideline text stated "work collaboratively with patients using behavioral frameworks and motivational interviewing, to identify and modify associated risk factors (smoking cessation, diet, physical activity, and exercise.

Zuin M, et al. J Am Coll Cardiol. 2024;84:1561

# Lifestyle Modification




Zuin M, et al. J Am Coll Cardiol. 2024;84:1561

# KEY TAKE HOME POINTS

1. Risk stratification is critical to identify VTE patients who may benefit from advanced therapy.

2. Selection of advanced therapies depends on assessment of the patient's risk of adverse outcomes and major bleeding.

3. Determining the optimal anticoagulation regimen should consider risk of recurrence, risk of bleeding, and patient preference.

# REFERENCES


Chopard R, Albertsen IE, Piazza G. Diagnosis and Treatment of Lower Extremity Venous Thromboembolism: A Review. JAMA. 2020;324:1765-1776.

Piazza G. Advanced Management of Intermediate- and High-Risk Pulmonary Embolism: JACC Focus Seminar. J Am Coll Cardiol. 2020;76:2117-2127.

Zuin M, et al. International Clinical Practice Guideline Recommendations for Acute Pulmonary Embolism: Harmony, Dissonance, and Silence. J Am Coll Cardiol. 2024;84:1561-1577.

Konstantinides SV, et al. 2019 ESC Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism Developed in Collaboration With the European Respiratory Society (ERS): The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2020; 00:1