Management of Pulmonary Embolism

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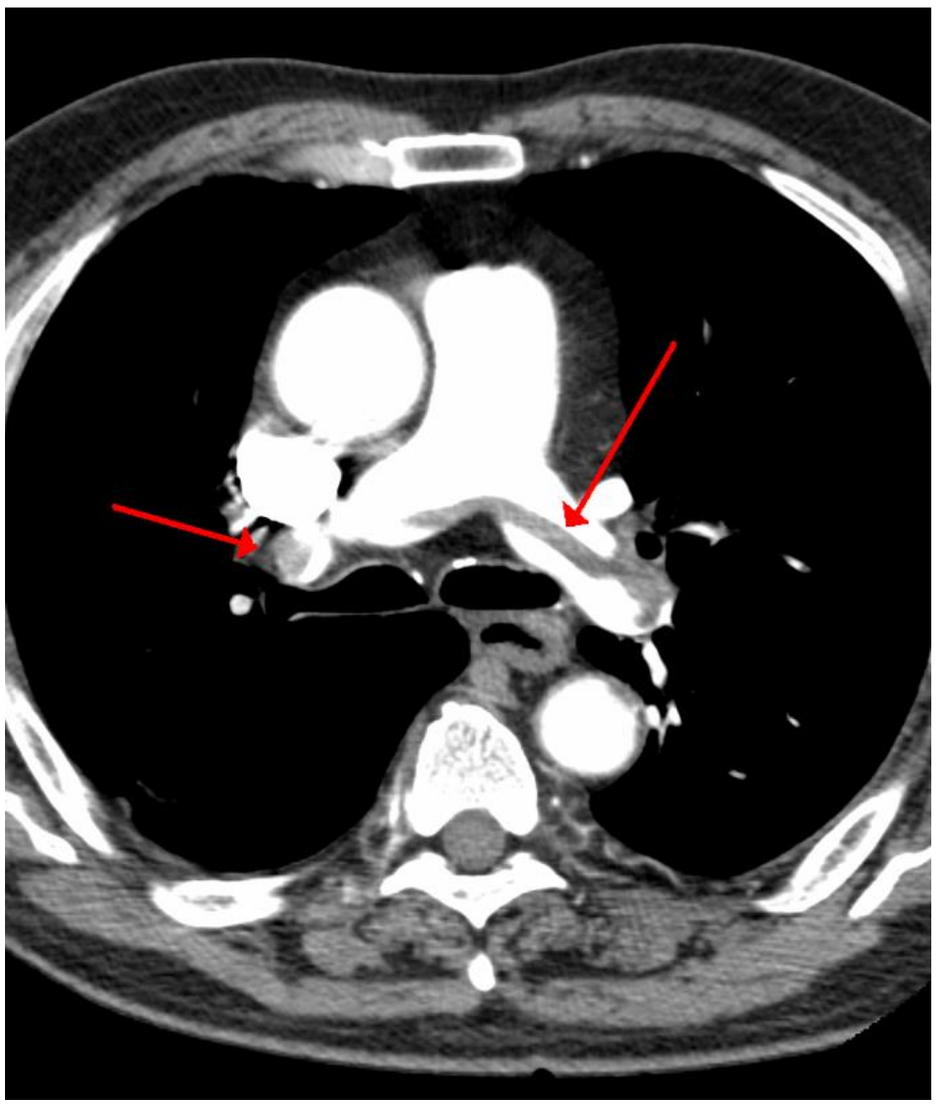
- I have no conflicts of interest to report.

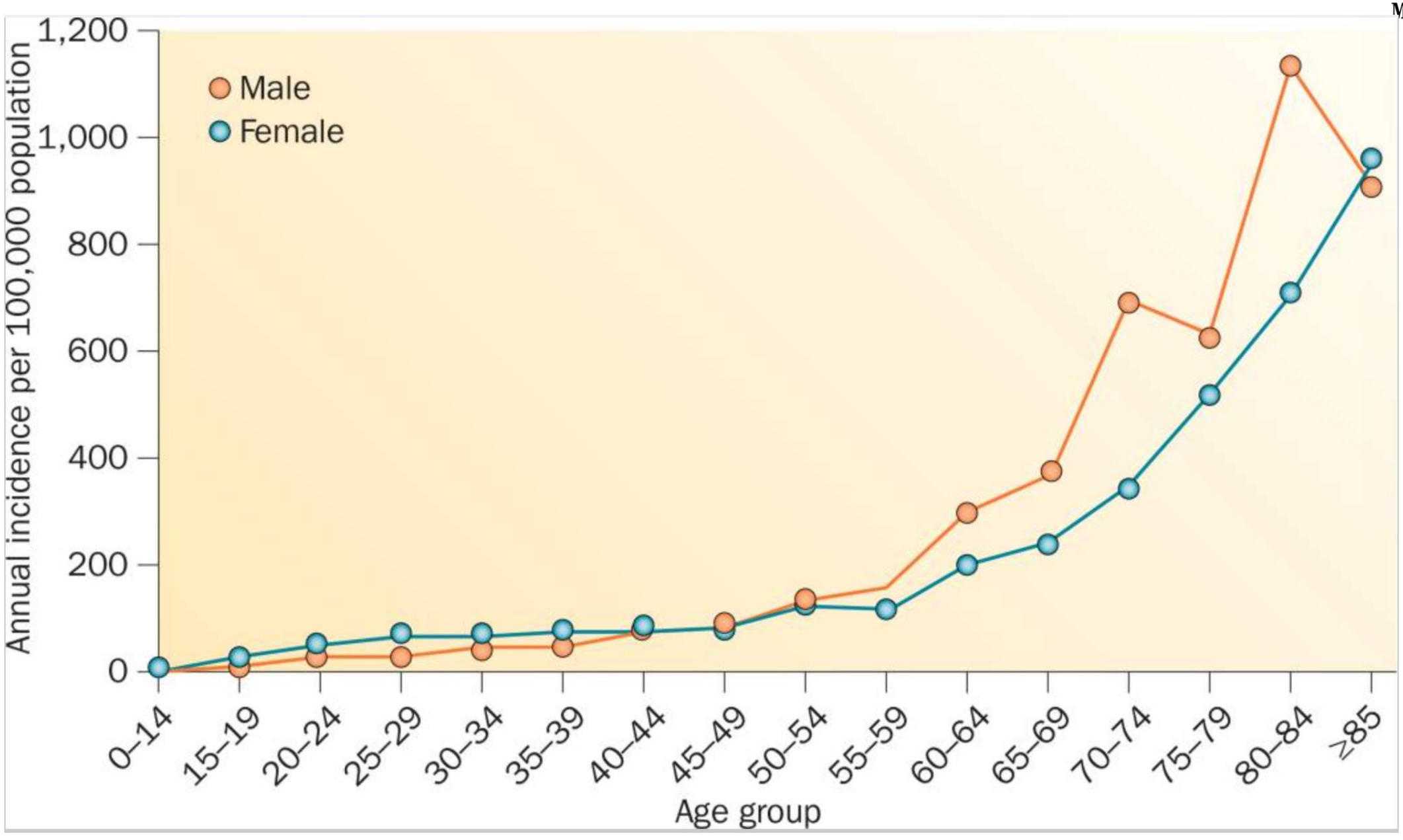
VTE Overview

- VTE introduction:
  - How do we prevent this in people at risk?
  - How do we diagnosis this?
- **How do we treat this?**



VTE Pathogenesis

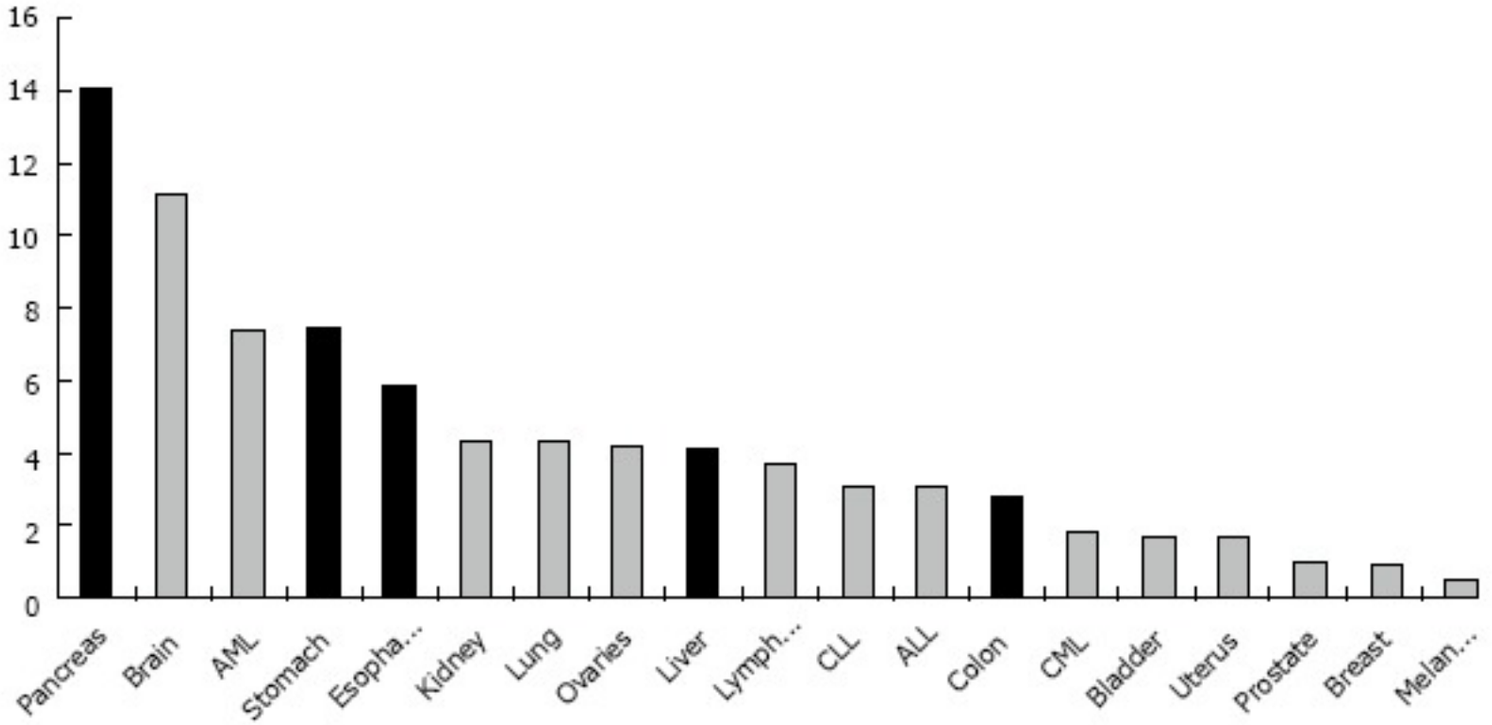
- Virchow's triad (stasis, endothelial injury, hypercoagulability)
- Acute Death (for PE):
  - 10% sudden death
  - untreated -> 20-30% mortality
- (DVT) - Clot propogation, Embolization: 15%
- Recurrence
- Post-phlebitic syndrome, CTEPH



Epidemiology of venous thromboembolism

John A. Heit

Nat Rev Cardiol. 2015 Aug; 12(8): 464–474.



Venous thromboembolic event-risk according to different cancer entities (modified from Wun et al[5] 2009). VTE-Incidence in the first year after cancer diagnosis (all stages) California Cancer Registry 1993-1999 (Patient Hospital Discharge Dataset). VTE: Venous thromboembolism event.

World J Gastrointest Oncol. 2016 Mar 15; 8(3): 258–270.
Published online 2016 Mar 15. doi: 10.4251/wjgo.v8.i3.258

PMCID: PMC4789611

Primary prevention and treatment of venous thromboembolic events in patients with gastrointestinal cancers - Review

Clinical Characteristics of Patients with Acute Pulmonary Embolism: Data from PIOPED II

	PE No Prior CPD N= 127-133 n (%)	No PE No Prior CPD N= 361-366 n (%)	PE All Patients N= 184-191 n (%)	No PE All Patients N= 622-632 n (%)
Dyspnea				
Dyspnea (rest or exertion)	97 (73)	248 (68)	151 (79)	459 (73)
Dyspnea (at rest) #	73 (55)	167 (46)	117 (61)	338 (54)
Dyspnea (exertion only) #	21 (16)	73 (20)	31 (16)	111 (18)
Orthopnea (≥2-pillow)	37 (28)	88 (24)	69 (36)	220 (35)
Pleuritic pain	58 (44)	207 (57) ^	89 (47)	376 (59) ^
Chest pain (not pleuritic)	25 (19)	80 (22)	33 (17)	130 (21)
Cough	45 (34)	103 (28)	82 (43)	248 (39)
Wheezing	27 (21)	66 (18)	58 (31)	193 (31)
Calf or thigh swelling	52 (41)	62 (17) ^^	72 (39)	126 (20) ^^
Calf and thigh swelling	9 (7)	14 (4)	15 (8)	35 (6)
Calf or thigh pain	56 (44)	83 (23) ^^	78 (42)	156 (25) ^^
Calf and thigh pain	22 (17)	24 (7) ^^	30 (16)	61 (10) ^^^

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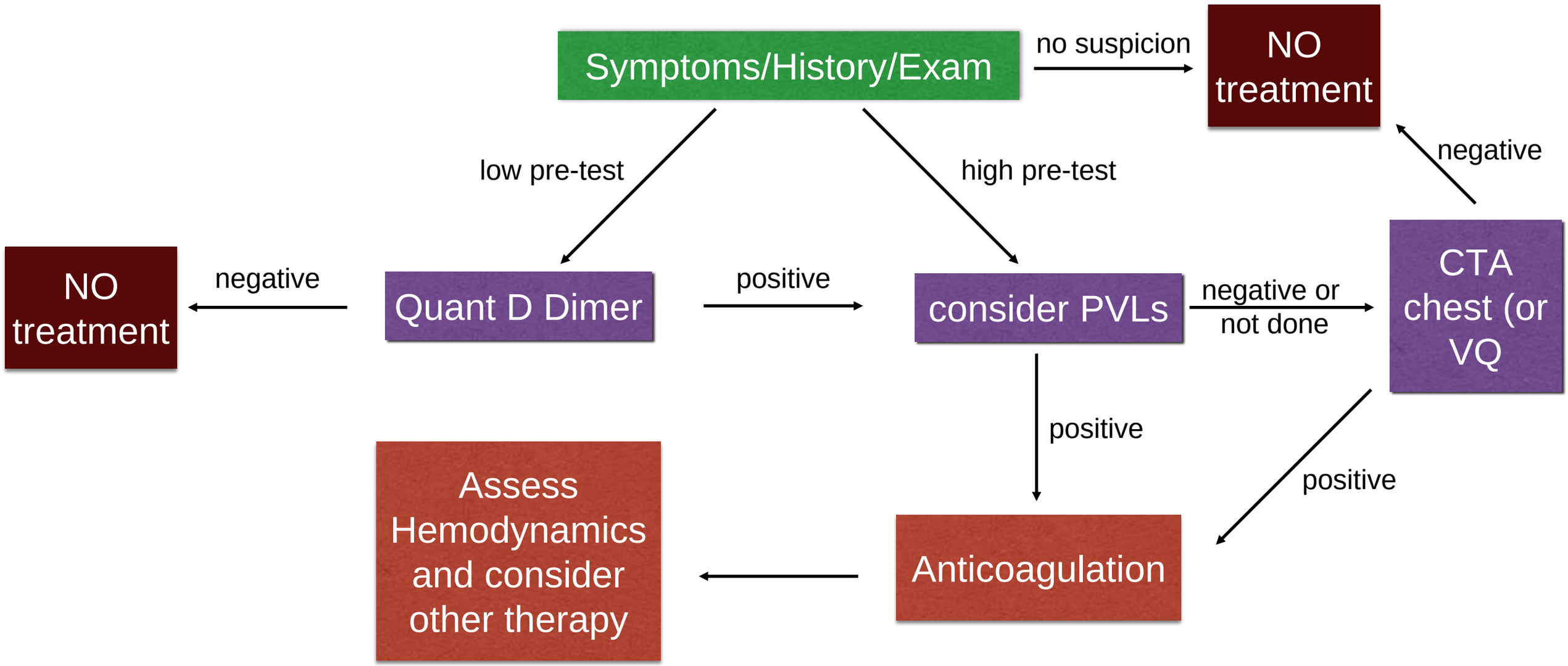
Table 1. Model for Determining the Clinical Probability of Pulmonary Embolism, According to the Wells Score.*

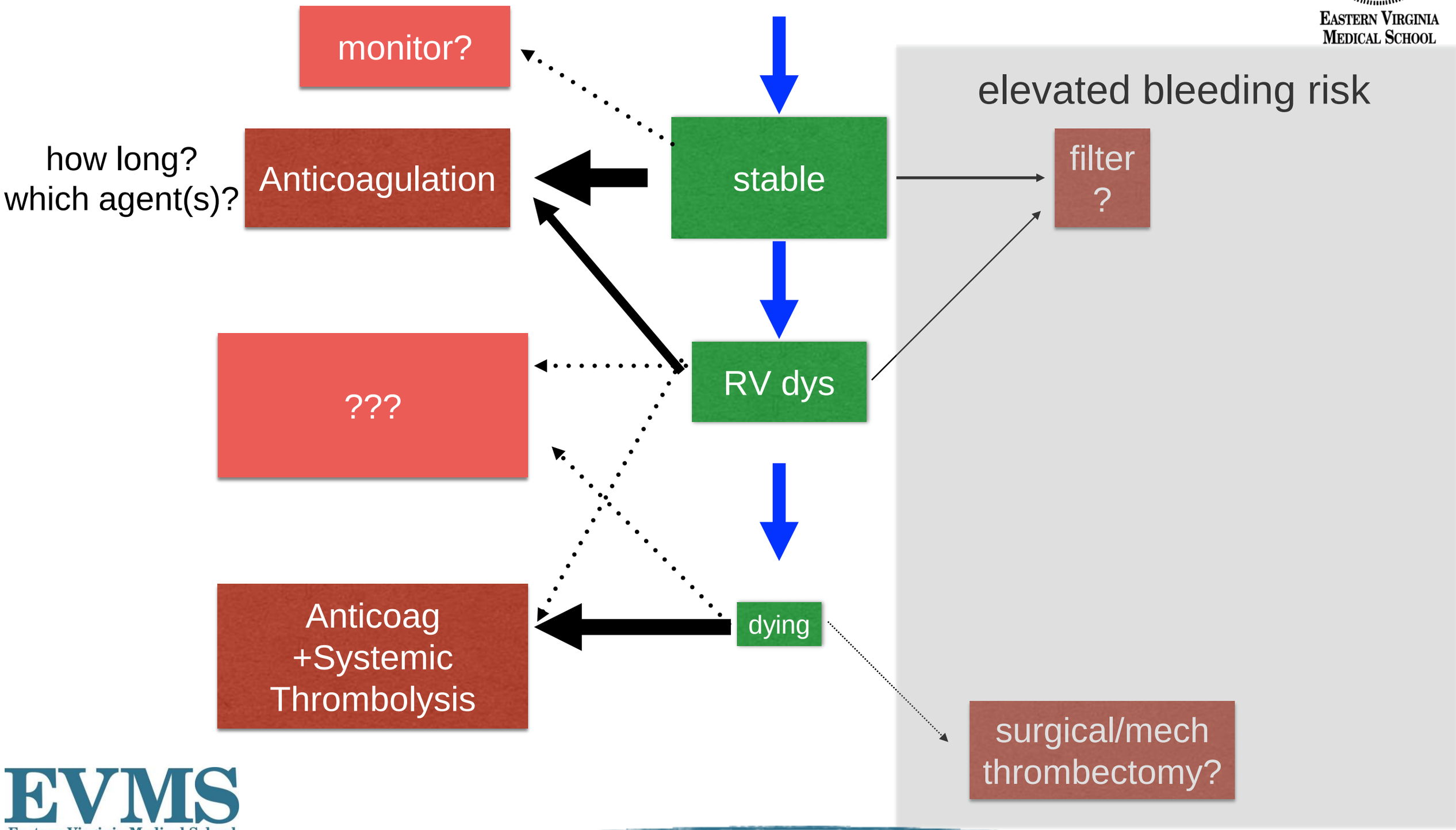
Clinical Feature	Score
Clinical signs and symptoms of DVT (objectively measured leg swelling and pain with palpation in the deep-vein system)	3.0
Heart rate >100 beats/min	1.5
Immobilization for ≥3 consecutive days (bed rest except to go to bathroom) or surgery in previous 4 weeks	1.5
Previous objectively diagnosed pulmonary embolism or DVT	1.5
Hemoptysis	1.0
Cancer (with treatment within past 6 mo or palliative treatment)	1.0
Pulmonary embolism likely or more likely than alternative diagnoses (on the basis of history, physical examination, chest radiography, ECG, and blood tests)	3.0

* Data are from Wells et al.[24] The condition of patients is scored according to the following criteria: less than 2.0, low probability; 2.0 to 6.0, moderate probability; and more than 6.0, high probability. DVT denotes deep venous thrombosis, and ECG electrocardiography.

PE Diagnostic Approach



PE Acute Therapeutic Approach



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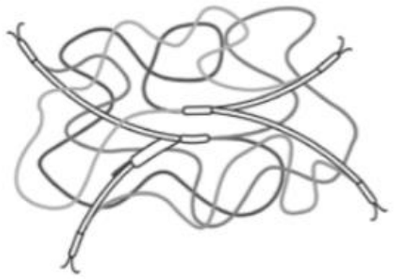

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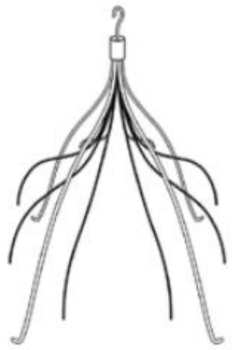

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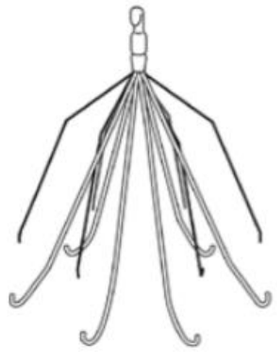

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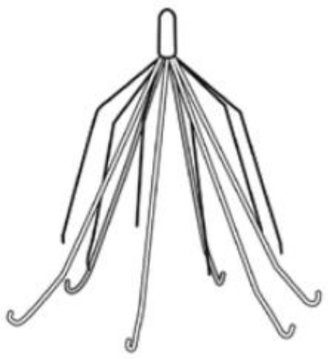

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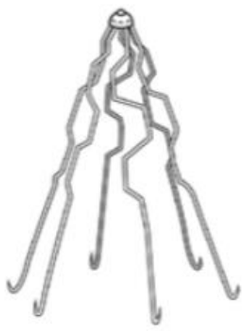

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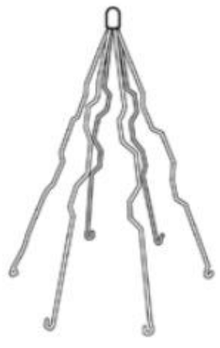

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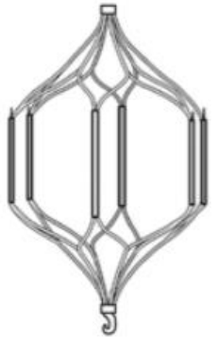

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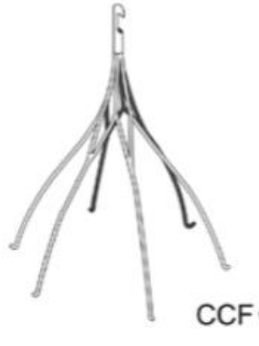
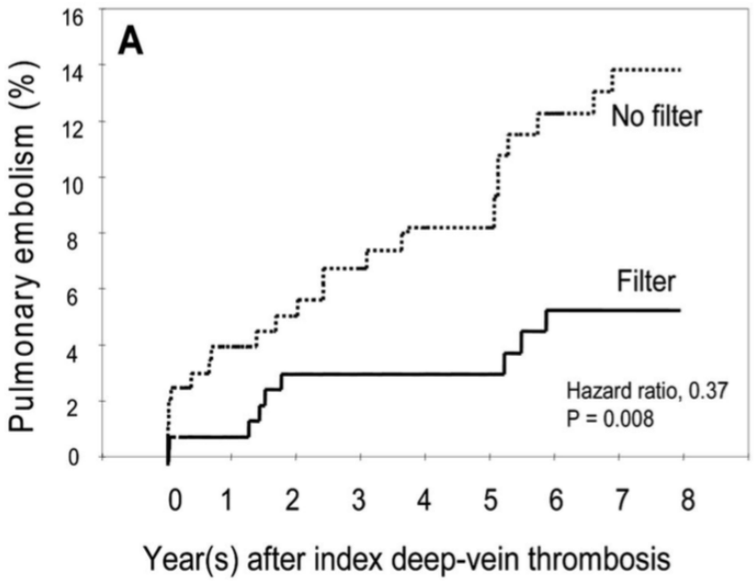
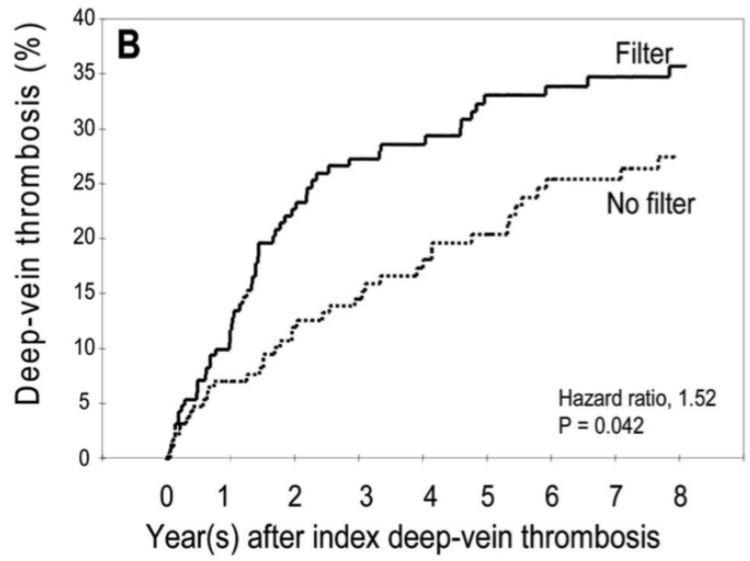
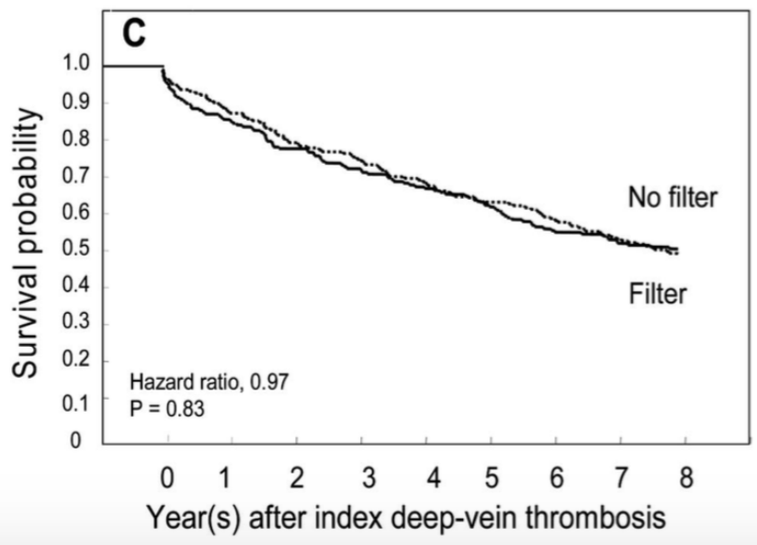


IVC Filter



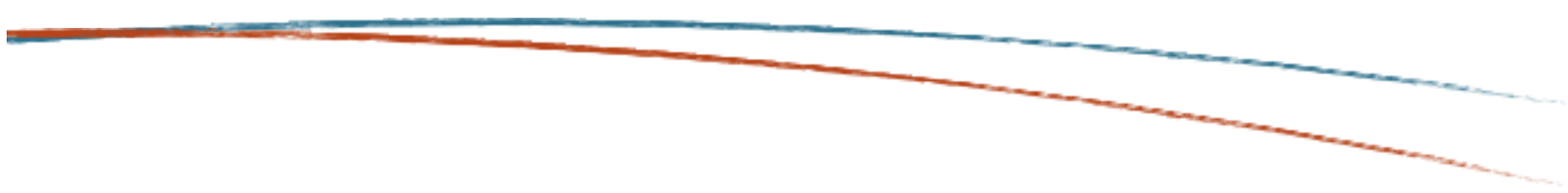




Eight-Year Follow-Up of Patients With Permanent Vena Cava Filters in the Prevention of Pulmonary Embolism

The PREPIC (Prévention du Risque d'Embolie Pulmonaire par Interruption Cave) Randomized Study

The PREPIC Study Group*



IVC Filter

Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism: A Randomized Clinical Trial

Patrick Mismetti, MD, PhD1,2,3; Silvy Laporte, MS, PhD2,3; Olivier Pellerin, MD, MSc4,5; Pierre-Vladimir Ennezat, MD, PhD6; Francis Couturaud, MD, PhD7; Antoine Elias, MD, PhD8; Nicolas Falvo, MD9; Nicolas Meneveau, MD, PhD10; Isabelle Quere, MD, PhD11; Pierre-Marie Roy, MD, PhD12,13; Olivier Sanchez, MD, PhD14; Jeannot Schmidt, MD, PhD15,16; Christophe Seinturier, MD17; Marie-Antoinette Sevestre, MD18; Jean-Paul Beregi, MD, PhD19; Bernard Tardy, MD, PhD20,21; Philippe Lacroix, MD22; Emilie Presles, MSc3; Alain Leizorovicz, MD23; Hervé Decousus, MD24; Fabrice-Guy Barral, MD25,26; Guy Meyer, MD13 ; for the PREPIC2 Study Group

[+] Author Affiliations

JAMA. 2015;313(16):1627-1635. doi:10.1001/jama.2015.3780.

IVC Filter

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Table 3. Clinical Outcomes For Patients With at Least 1 Event in the PREPIC2 Trial

Clinical Outcomes	Group, No. With Events (%)		Relative Risk, % (95% CI)	*P* Value[b]
	Filter (n = 200)[a]	Control (n = 199)		
At 3 Months				
Recurrent pulmonary embolism (primary efficacy outcome)[c]	6 (3.0)	3 (1.5)	2.00 (0.51-7.89)	.50
Fatal	6 (3.0)	2 (1.0)		
Nonfatal	0 (0.0)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	1 (0.5)	1.00 (0.06-15.9)	>.99
Recurrent venous thromboembolism	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.36
Major bleeding	8 (4.0)	10 (5.0)	0.80 (0.32-1.98)	.63
Death	15 (7.5)	12 (6.0)	1.25 (0.60-2.60)	.55
At 6 Months				
Recurrent pulmonary embolism[c]	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.54
Fatal	6 (3.0)	3 (1.5)		
Nonfatal	1 (0.5)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	2 (1.0)	0.50 (0.05-5.47)	>.99
Recurrent venous thromboembolism	8 (4.0)	6 (3.0)	1.33 (0.47-3.77)	.59
Major bleeding	13 (6.5)	15 (7.5)	0.87 (0.42-1.77)	.69
Death	21 (10.6)	15 (7.5)	1.40 (0.74-2.64)	.29

[a] One patient in the filter group was lost to follow-up and was considered as missing in the analysis.

[b] Fisher exact test. Patients who died, with no event recorded before death, were considered as having experienced no event.

[c] The cumulative rates of events at 3 months were 3.0% in the filter group and 1.5% in the control groups when estimated using the Kaplan-Meier method, censoring data on patients who died or were lost to follow-up; hazard ratio (HR), 2.02 (95% CI, 0.51-8.09). Corresponding figures at 6 months were 3.5% in the filter group and 2.0% in the control group; HR, 1.78 (95% CI, 0.52-6.09). Similar efficacy results were observed when considering in the filter group only patients who had actually received a filter: pulmonary embolism recurrence was observed in 4 of 193 patients (2.1%) in the filter group and 3 of 199 patients (1.5%) in the control group (relative risk with filter, 1.37 [95% CI, 0.31-6.06]; *P* = .72).

IVC Filter

- Consider if you **cannot** anticoagulate.

● Severe bleeding diathesis
● Platelet count <50,000/microL
● Recent, planned, or emergent surgery/procedure
● Major trauma
● Active bleeding
● History of intracranial hemorrhage
● Intracranial or spinal tumors
● Large abdominal aortic aneurysm with concurrent severe hypertension
● Stable aortic dissection

PE or Proximal DVT - IVC Filter Now
Distal DVT - consider serial US

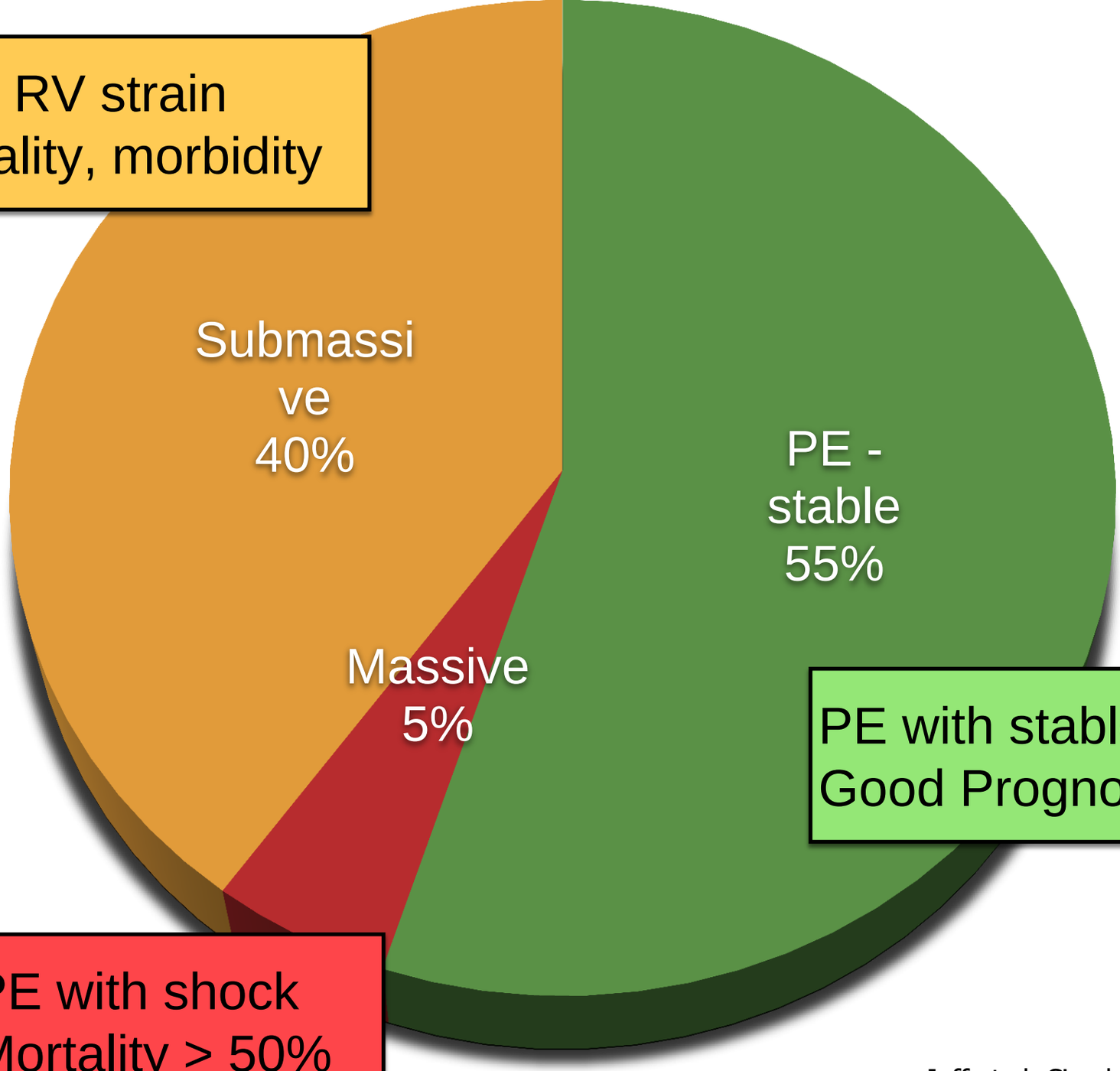
Anticoagulation

- If high suspicion of PE in a sick patient, anticoagulate while figuring it out.

- **For lobar or > PEs, all patients who can be anti-coagulated should be.**

- If hemodynamically stable (no RV strain) and no clot in transition, then anticoagulation alone is sufficient.

PE, normal BP, RV strain
Increased mortality, morbidity



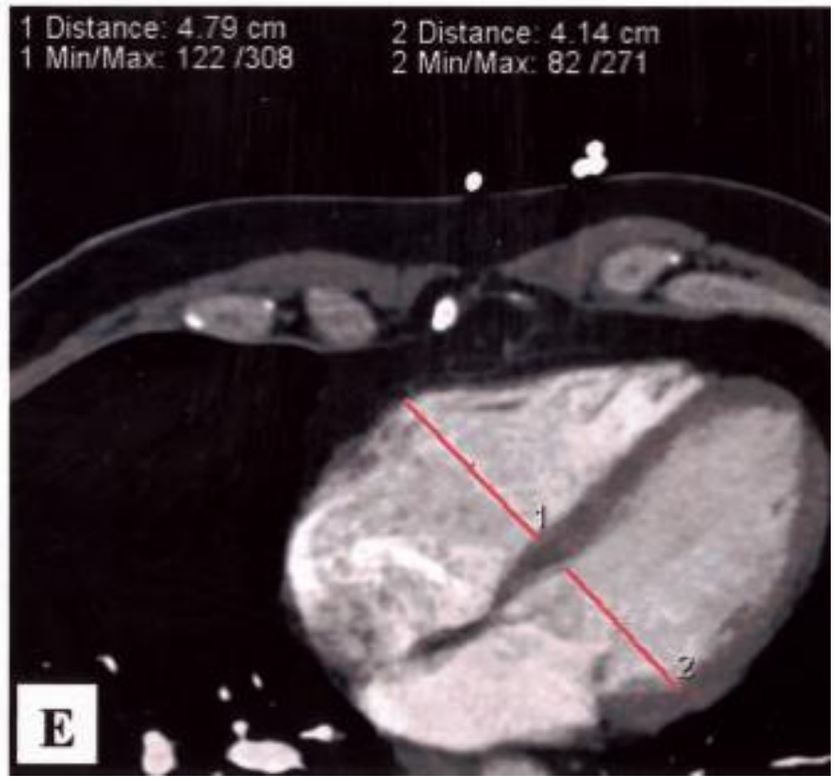
PE with stable hemodynamics:
Good Prognosis

PE with shock
Mortality > 50%

Jaff et al. Circulation 2011;123(16):1788-1830.
Goldhaber et al. Lancet. 1999;353(9162):1386-9.
Quiroz et al. Circulation (2004);109;2401-2404
Frémont, Chest 2008; 133;558-362
Schoef, Circ 2004; 110:3276-3280
Kucher, Arch Intern Med 2005; 165:1777-1781

Should we treat Submassive PE differently?

- RV/LV ratio > 0.9 is an independent risk factor for mortality
- Persistent RV dysfunction at d/c:
  - 8 fold risk of recurrent, symptomatic PE
  - 4 fold risk of mortality



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Schoef, Circ 2004; 110:3276-3280
Kucher, Arch Intern Med 2005; 165:1777-1781
Grifoni, Arch Intern Med. 2006 Oct 23;166(19):2151-6.

Systemic Thrombolysis

- Obstructive Shock is a widely accepted indication for systemic thrombolysis. (ACCP Guidelines)

- Has been proposed for:

  - RV dysfunction

  - Respiratory Failure

  - Extensive Clot Burden

  - RA or RV thrombus

  - Patent Foramen Ovale

***22. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy** (Grade 1B).

***23. In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy** (Grade 2C).

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus Empen, M.D., Ana Franca, M.D., Nazzareno Galiè, M.D., Annette Geibel, M.D., Samuel Z. Goldhaber, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian Kupatt, M.D., Nils Kucher, M.D., Irene M. Lang, M.D., Mareike Lankeit, M.D., Nicolas Meneveau, M.D., Ph.D., Gerard Pacouret, M.D., Massimiliano Palazzini, M.D., Antoniu Petris, M.D., Ph.D., Piotr Pruszczyk, M.D., Matteo Rugolotto, M.D., Aldo Salvi, M.D., Sebastian Schellong, M.D., Mustapha Sebbane, M.D., Bozena Sobkowicz, M.D., Branislav S. Stefanovic, M.D., Ph.D., Holger Thiele, M.D., Adam Torbicki, M.D., Franck Verschuren, M.D., Ph.D., and Stavros V. Konstantinides, M.D., for the PEITHO Investigators*

PEITHO

- Not in shock
- AND RV dysfunction: RV ED diameter > 30mm, R/L ED diameter > 0.9, RV hypokinesis, Tricuspid Sys Velocity > 2.6 m/s
- AND positive troponin (trop T > 0.01)
- Tenectoplase 30 to 50mg vs. placebo
- 7 day composite outcome of hemodynamic compromise or death.

Table 3. Efficacy Outcomes.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12
Fatal	0	3 (0.6)		
Nonfatal	1 (0.2)	2 (0.4)		
Other in-hospital complications and procedures — no. (%)				
Mechanical ventilation	8 (1.6)	15 (3.0)		
Surgical embolectomy	1 (0.2)	2 (0.4)		
Catheter thrombus fragmentation	1 (0.2)	0 (0.0)		
Vena cava interruption	5 (1.0)	1 (0.2)		
Thrombolytic treatment other than study medication	4 (0.8)	23 (4.6)		
Death from any cause between randomization and day 30 — no. (%)	12 (2.4)	16 (3.2)	0.73 (0.34–1.57)	0.42
Patient still hospitalized at day 30 — no. (%)	59 (11.7)	50 (10.0)		
Rehospitalization between randomization and day 30 — no. (%)	22 (4.4)	15 (3.0)		

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Table 4. Safety Outcomes in the Intention-to-Treat Population.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
	no. (%)			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7	12 (2.4)	1 (0.2)	12.10 (1.57–93.39)	0.003
Ischemic stroke	2 (0.4)	0		
Hemorrhagic stroke‡	10 (2.0)	1 (0.2)		
Serious adverse events between randomization and day 30	55 (10.9)	59 (11.8)	0.91 (0.62–1.34)	0.63

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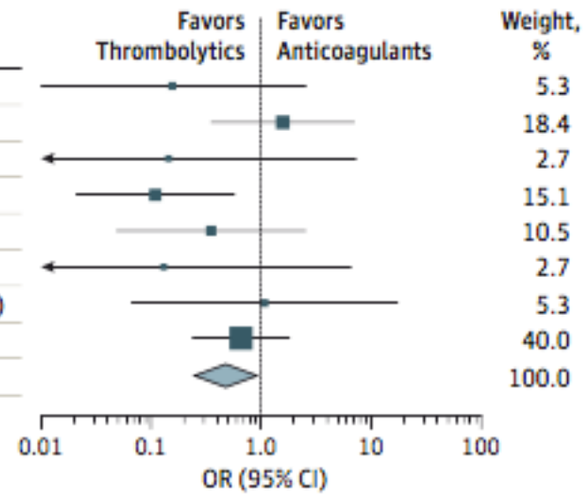
Figure 3. Odds of Mortality in Patients With Intermediate-Risk Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation

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: $z = 2.22$; $P = .03$



Evaluated using the Peto method of meta-analysis. The standard practice in meta-analysis of odds ratios (ORs) and risk ratios is to exclude studies from the meta-analysis where there are no events in either group.[13] A 0-cell or continuity correction was not used based on recommendations regarding calculation of a Peto OR for studies with 0 events in only 1 group.[13] MOPETT indicates Moderate Pulmonary Embolism Treated with Thrombolysis trial; PEITHO, Pulmonary Embolism Thrombolysis trial; TIPES, Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT, Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism trial.

JAMA. 2014 Jun 18;311(23):2414-21. doi: 10.1001/jama.2014.5990.

Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis.

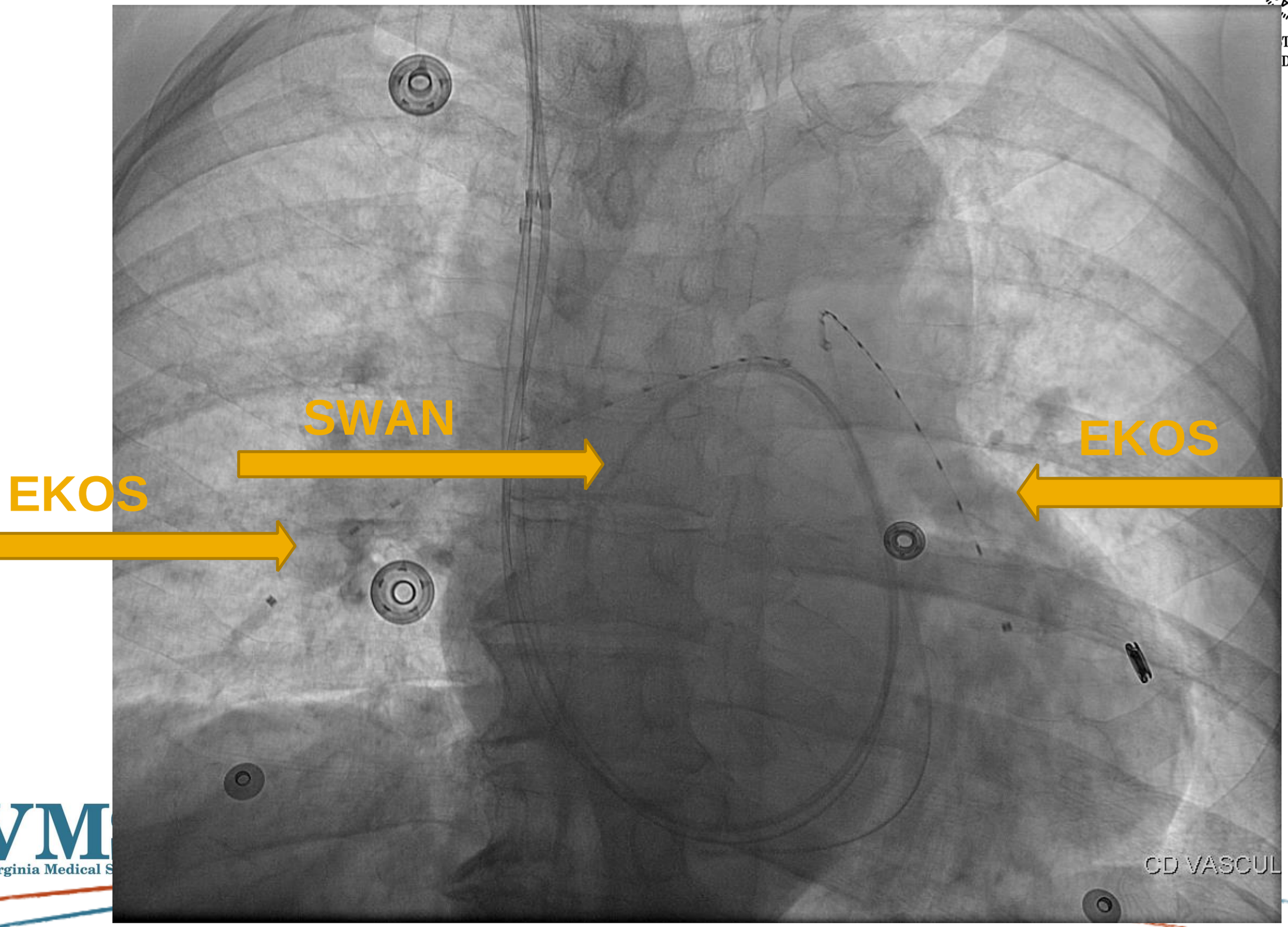
Thrombolytics

- Accepted as therapy in massive PE with shock.
- 1/2 systemic dose tPA appears to have similar efficacy
- higher bleeding rates may result from TNKase and/or elevated PTTs in setting of thrombolytic use.
- Patient selection is critical

Catheter Directed Thrombolysis

***24. In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over CDT** (Grade 2C).

Remarks: Patients who have a higher risk of bleeding with systemic thrombolytic therapy and who have access to the expertise and resources required to do CDT are likely to choose CDT over systemic thrombolytic therapy.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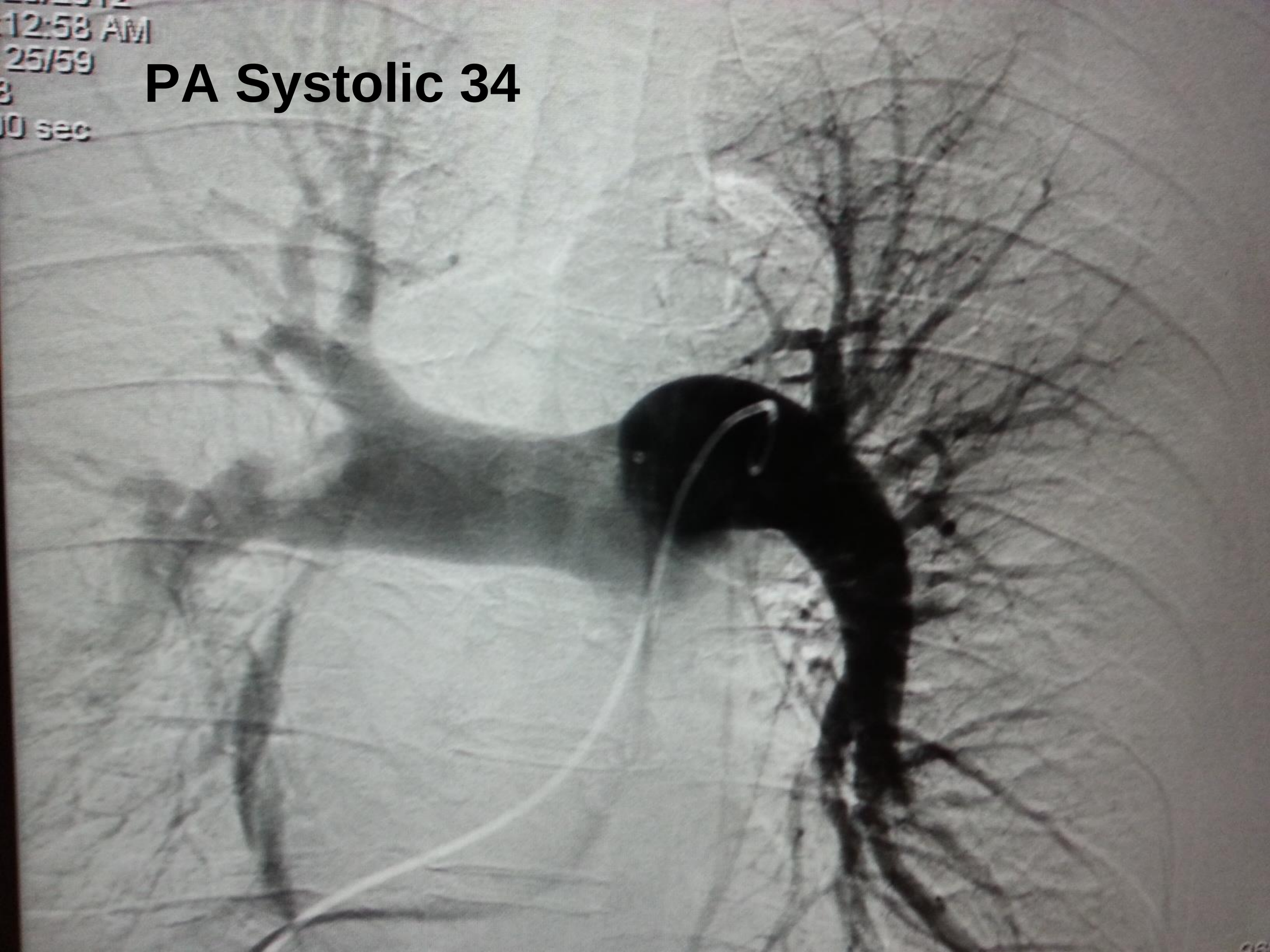


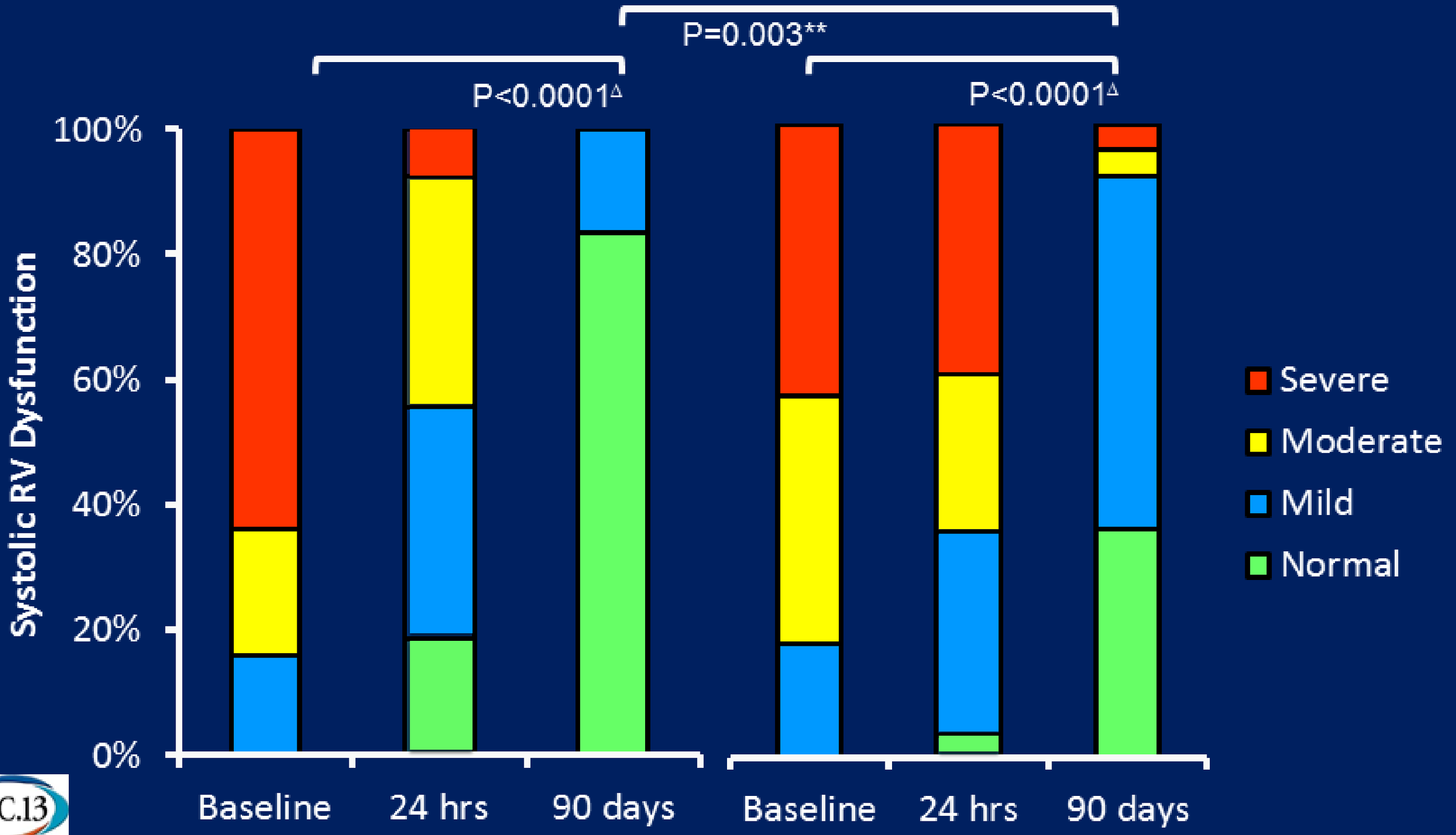
POD #1

- TPA administered at 1mg/hr/catheter
- Low dose heparin in each sheath
- Swan PA pressures monitored until resolution of PA hypertension
- Fibrinogen, PTT, CBC and hemodynamics monitored for signs/symptoms of bleeding

Ultima Trial

- Low dose (<20mg tpa)
- Multicenter, randomized controlled trial
- Ultrasound assisted catheter-directed thrombolysis
- Acute symptomatic PE confirmed by CT
- RV/LV ratio >1 on echo (normal is 0.6)

Systolic RV dysfunction



**Two-sided exact Mantel-Haenzel test

Δ Wilcoxon rank sum test

Catheter Directed Thrombolysis

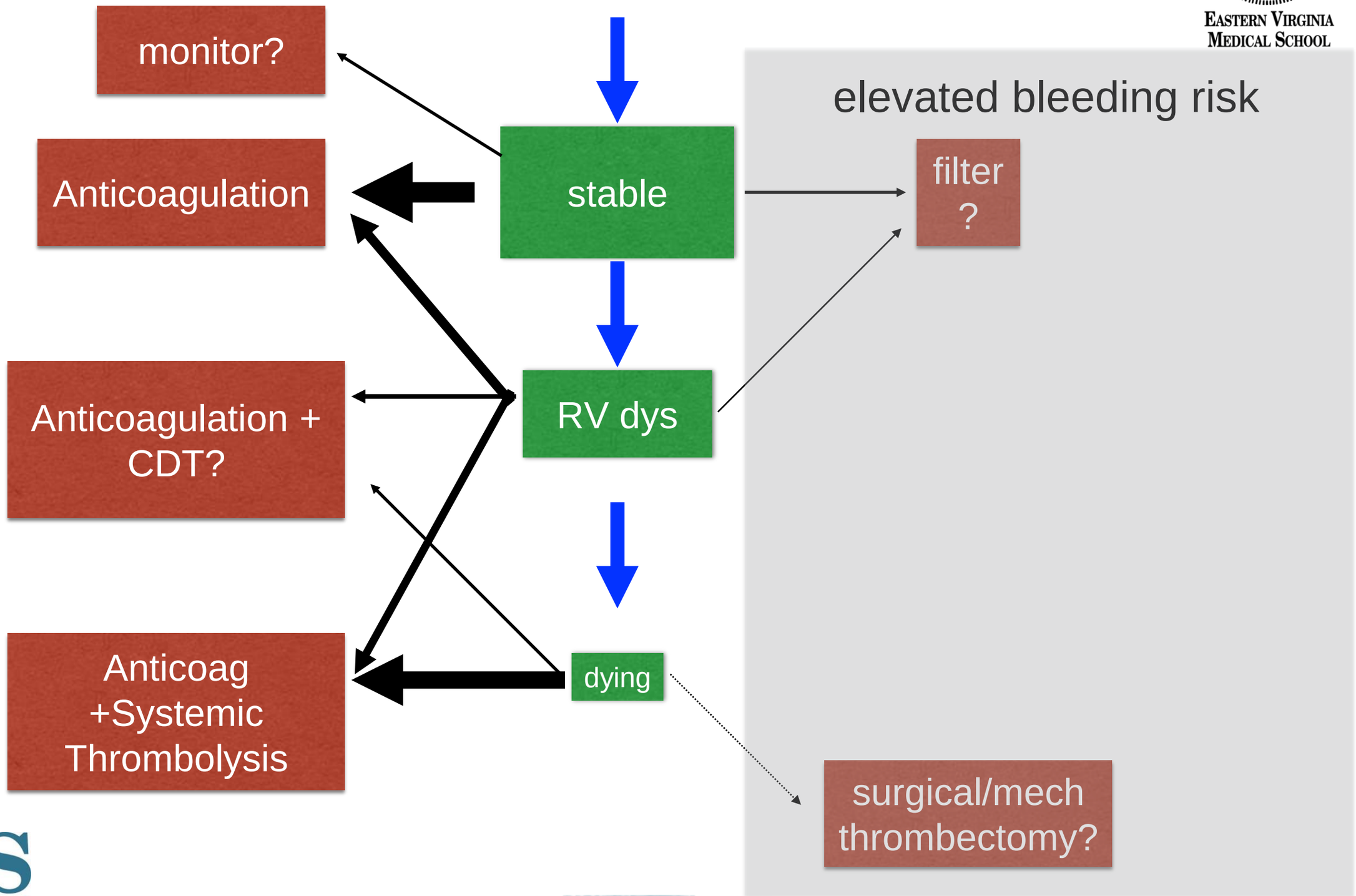
- Superior hemodynamic response versus anticoagulation alone

- Significantly lower dose of TPA (15mg to 40mg versus 50mg-100mg) over a longer period of time (12 hours versus 2 hours)

- Potential for lower risk of adverse events and improved efficacy

- Based on safety data and theoretical benefit, may see this performed more frequently at capable centers.

PE Acute Therapeutic Approach



Summary

- Anticoagulation alone in most cases. NOACs are preferred in many cases.

- Lytics appear to have a role in submassive/massive PE. *Patient selection is critical*. The agent, dose, mode of delivery, and overall anticoagulation protocol may influence patient outcomes.