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CONFERENCE

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VASCULAR THERAPIES

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MAY 2-4

Submassive Pulmonary Embolism: There Is a Role for Routine Catheter Directed Therapy

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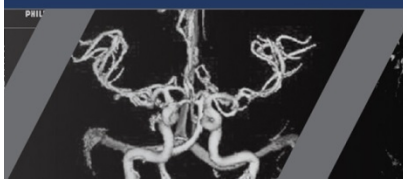
Sentara Vascular Specialists



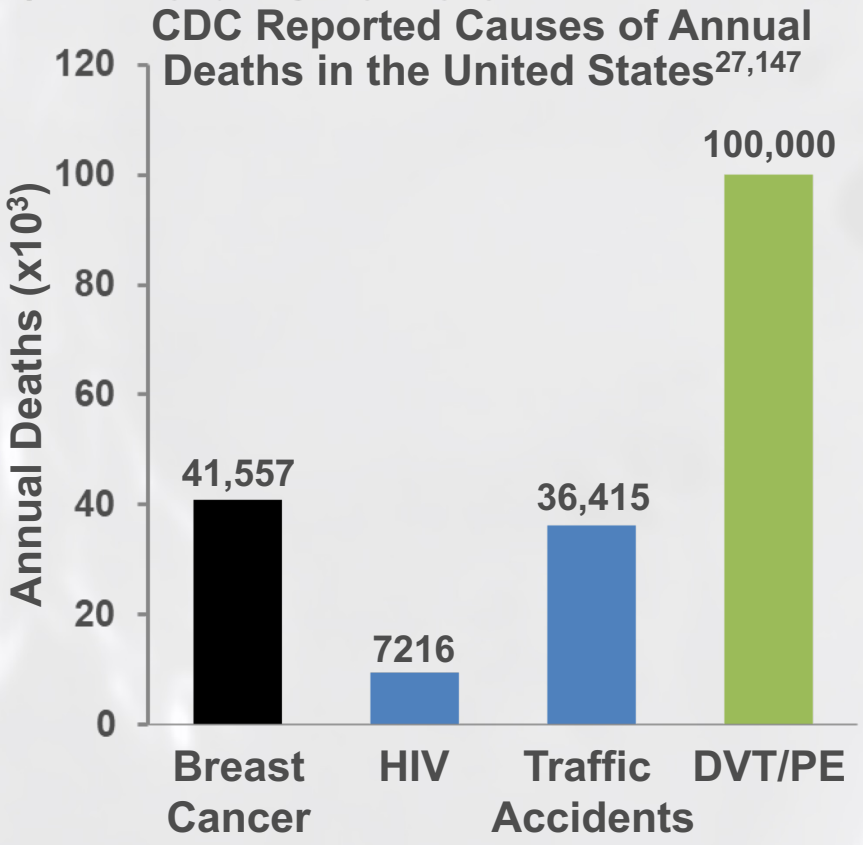
Disclosures

- Local PI
  - Knockout PE
  - Extract PE
- National PI
  - Clout

VTE Is a Major Cause of Morbidity and Mortality With a Significant Economic Burden in the United States

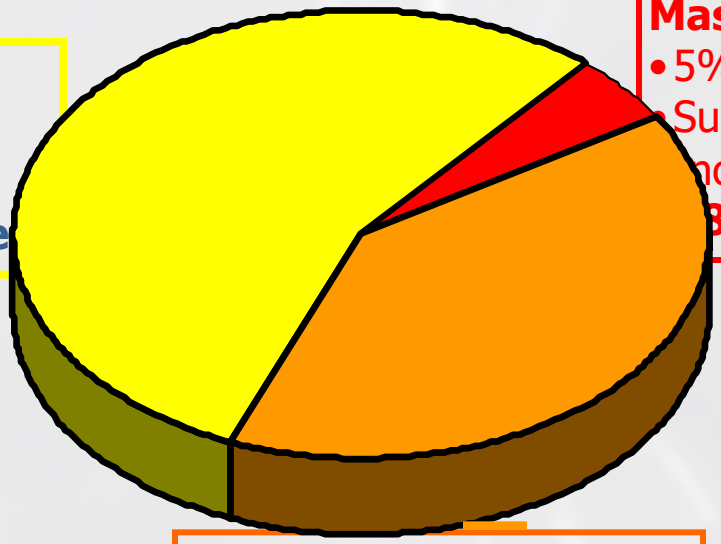
VTE kills more people each year than breast cancer, HIV, and traffic accidents…combined[27,147]

- affected by DVT/PE annually[71]
- ≈550,000 hospitalizations annually in the United States for DVT and/or PE[28]
- Healthcare costs associated with DVT/PE in 2011 were estimated to be up to $10 billion[26]



PE Patient Risk Stratification

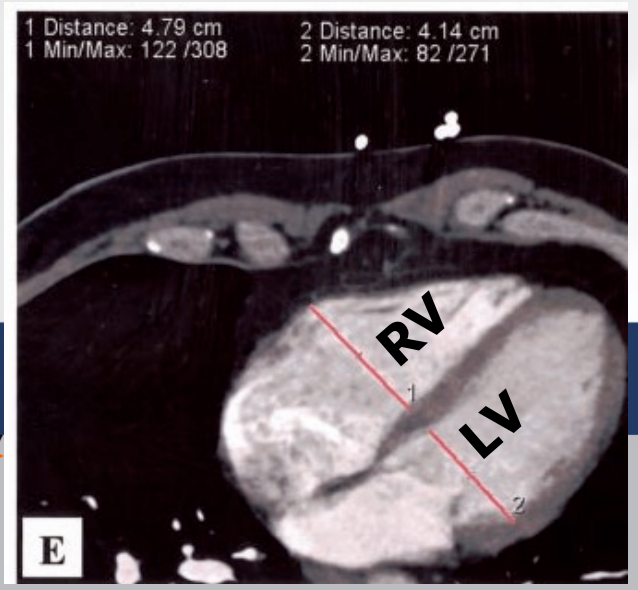
Minor PE
- 55% PE population
- Good prognosis
- **Low mortality rate**



Massive PE
- 5% PE population
- Sustained hypotension
- notropic support
- **3% mortality** @ 3 mo

Submassive PE
- 40% PE population
- Systemic normotension
- **RV dysfunction**
- **22% mortality** @ 3 mo

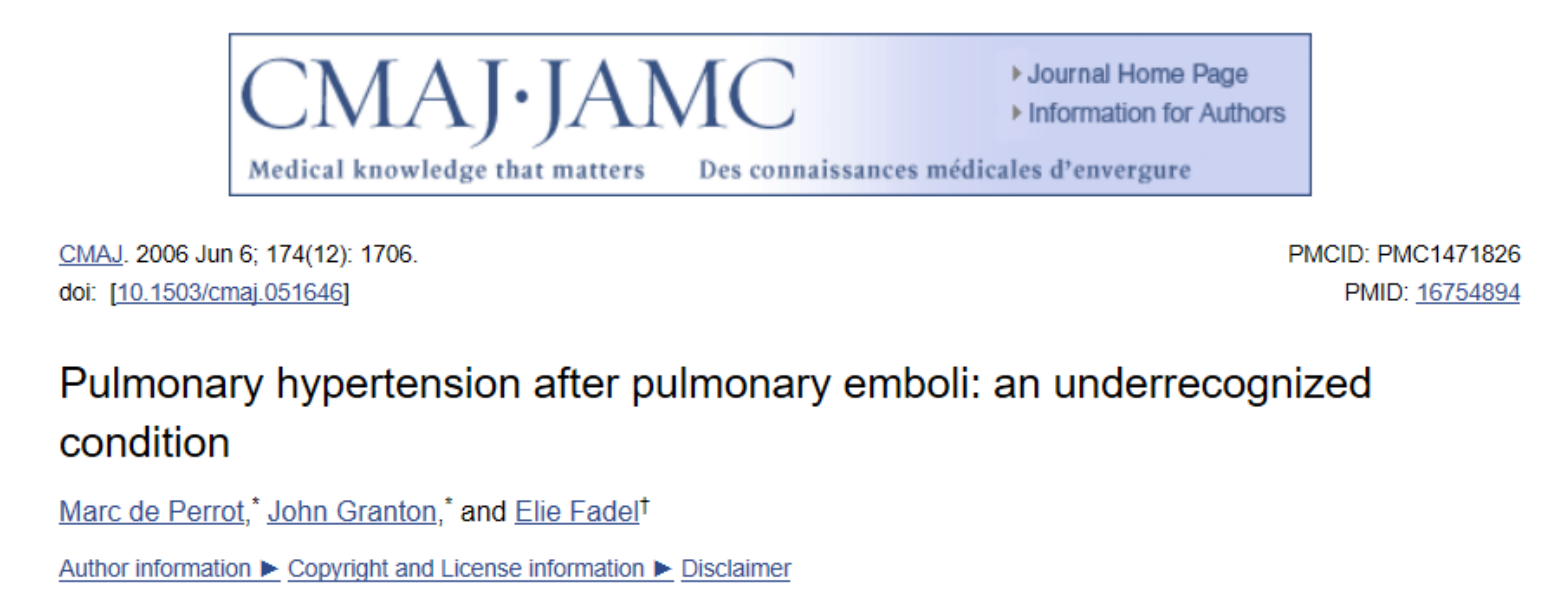
RV/LV ratio



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;558-562
Schoef, Circ 2004; 110:3276-3280
Kucher, Arch Intern Med 2005; 165:1777-1781

Chronic Issues with PE

- 3.8% of 314 consecutive patients who presented with acute pulmonary emboli developed symptomatic pulmonary hypertension within 2 years.



CMAJ·JAMC
Medical knowledge that matters — Des connaissances médicales d'envergure
Journal Home Page
Information for Authors

CMAJ. 2006 Jun 6; 174(12): 1706.
doi: [10.1503/cmaj.051646]
PMCID: PMC1471826
PMID: 16754894

Pulmonary hypertension after pulmonary emboli: an underrecognized condition

Marc de Perrot,* John Granton,* and Elie Fadel†

Chronic Issues with PE

- 7068 patients identified with PE
- Data followed for 2 years post event
- 87% made a claim of PH related symptom
- 7.6% were identified as having PH
- Only 55% of those with a symptom had any imaging work up
- PH may be under recognized after PE

Monitoring for Pulmonary Hypertension Following Pulmonary Embolism: The INFORM Study

Victor F. Tapson, MD,[a] David M. Platt, MD,[b] Fang Xia, PhD,[b] Simon A. Teal, BSc,[c] Margarita de la Orden, MSc,[c] Christine H. Divers, PhD,[b] Carol A. Satler, MD, PhD,[b] Vijay N. Joish, PhD,[b] Richard N. Channick, MD[d]

[a]Division of Pulmonary and Critical Care Medicine, Cedars-Sinai Medical Center, Los Angeles, Calif; [b]Bayer HealthCare Pharmaceuticals, Whippany, NJ; [c]Bayer Pharma AG, Berlin, Germany; [d]Department of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston.

How should we treat PE?

ACCP Guidelines Recommend Extended Anticoagulation for Patients With Unprovoked VTE

- In general, 3 months of anticoagulation therapy is recommended for patients with VTE and extended therapy for unprovoked VTE is suggested for patients with low to moderate bleeding risk

Provoked VTE

3 months

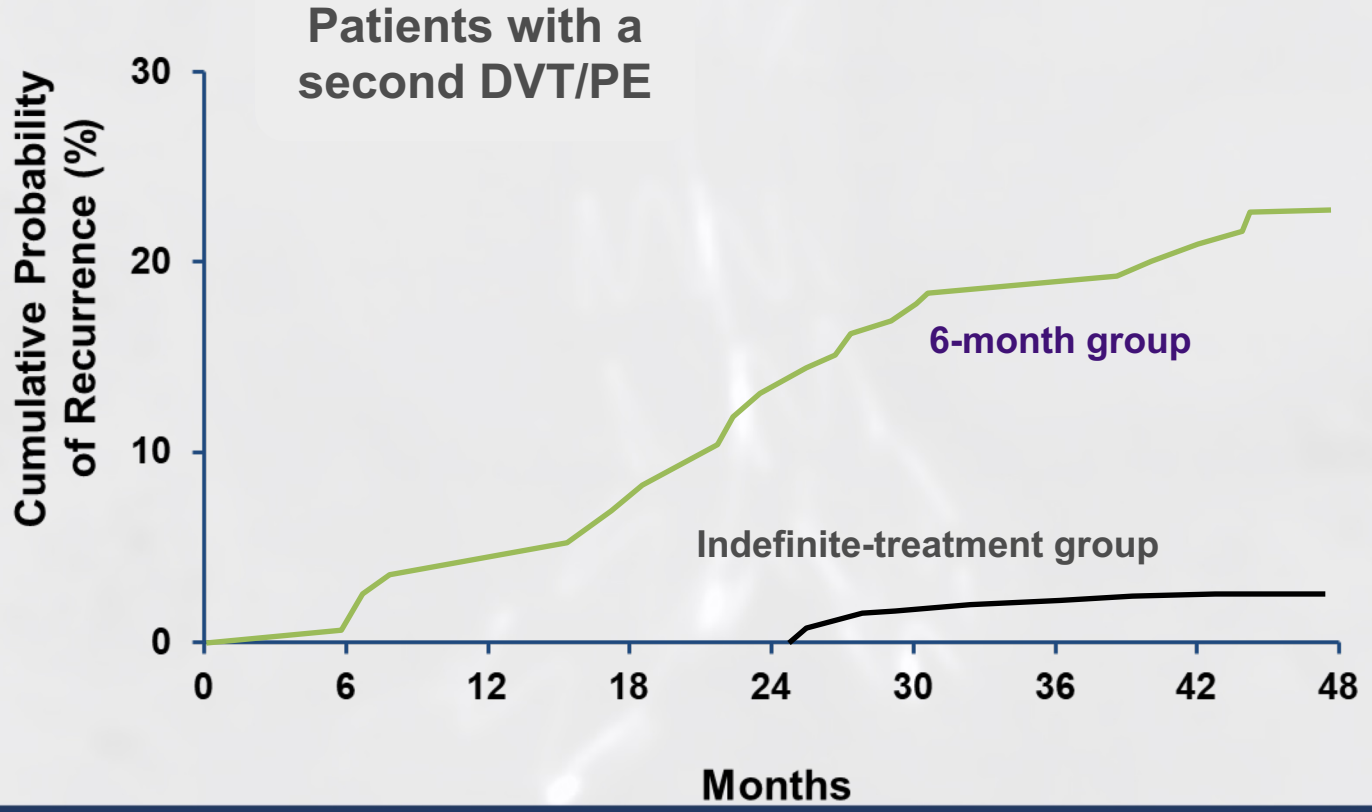
Unprovoked VTE

Reassessment at periodic intervals

Indefinite

- Duration of treatment beyond 3 months is informed by multiple factors, eg, bleeding risk, characteristics of the initial VTE, or other clinical considerations

The DURAC Trial Demonstrated a Continued Risk of Recurrence After Discontinuation of Anticoagulation[135]



Recurrence was significantly higher in patients who discontinued anticoagulation after 6 months of therapy

The PESI and Simplified PESI Are Validated Tools to Identify Low-Risk Patients

Variable	Score	
	PESI	sPESI
Age >80 years	Age in years	1
Male sex	10	0
History of cancer	30	1
History of heart failure	10	1*
History of chronic lung disease	10	
Pulse ≥110 bpm	20	1
Systolic BP <100 mm Hg	30	1
Respiratory rate ≥30 breaths/min	20	0
Temperature <36°C	20	0
Altered mental status†	60	0
SaO_2 <90%‡	20	1

Classification by Total Score		
	PESI	sPESI
Class I	≤65	Low risk=0
Class II	66-85	
Class III	86-105	High risk≥1
Class IV	106-125	
Class V	>125	

*Heart failure or history of chronic lung disease combined into a single category of chronic cardiopulmonary disease. †Disorientation, lethargy, stupor, or coma. ‡With or without the administration of supplemental oxygen.

Outpatient Treatment May Be an Option for Patients With Low-Risk PE

	Outcomes Within 14 days, n (%)			Outcomes Within 90 days, n (%)		
	Outpatient (n=171)	Inpatient (n=168)	*P* Value*	Outpatient (n=171)	Inpatient (n=168)	*P* Value*
Recurrent VTE	0	0	0.003	1 (0.6)	0	0.011
Major bleeding	2 (1.2)	0	0.031	3 (1.8)	0	0.086
Overall mortality	0	0	0.003	1 (0.6)†	1 (0.6)‡	0.005

*P value for noninferiority. †Patient died from accident-related trauma with resultant aortic rupture.
‡Patient died from pneumonia and lung cancer.

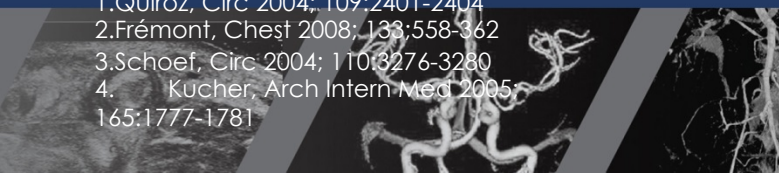

WARNING
THIS SIGN
IS ONLY A
DISTRACTION

What data do we have to support Sub-Massive Pulmonary Embolism Surgical Treatment?

Why Treat Submassive PE?

RV/LV ratio > 0.9 is an independent predictor of mortality[1-4]

1.Quiroz, Circ 2004; 109:2401-2404
2.Frémont, Chest 2008; 133;558-562
3.Schoef, Circ 2004; 110:3276-3280
4. Kucher, Arch Intern Med 2005; 165:1777-1781



Surgical embolectomy has 20% to 30% mortality. Systemic thrombolysis has a high risk of bleeding, including intra-cranial bleed.

CDT uses a lower dose of thrombolytic drug (about 1/3) and is expected to cause less bleeding.

Am Heart J. 1997 Sep;134(3):479-87.

Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate.

Ribeiro A[1], Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfeldt L.

ARCHIVES OF
INTERNAL MEDICINE

ORIGINAL INVESTIGATION

Association of Persistent Right Ventricular Dysfunction at Hospital Discharge After Acute Pulmonary Embolism With Recurrent Thromboembolic Events

Patients with persistent RV dysfunction at discharge:

8 times more likely to have **recurrent PE**
4 times higher in **mortality rate**

than patients with RV dysfunction regressed at discharge[6]

symptomatic, recurrent fatal or nonfatal VTE.

Arch Intern Med. 2006;166:2151-2156

Grifoni, Arch Intern Med 2006; 166:2151-215

Mortality Associated with Right Heart Strain

- proBNP
  - >1000 pg/mL had a high negative predictive value (95% for a complicated course, 100% for death).
  - <600 ng/L indicated uncomplicated outcome in multiple papers.

- Troponin T >0.07 predicted PE mortality, HR 18.1 (P=0.0004). proBNP>7600 ng/L predicted PE mortality, HR 7.3(P=0.007).

- Myoglobin, heart-type fatty acid-binding protein (H-FABP) and D-Dimer were not significant in predicting PE mortality.

Lung. 2015 Oct;193(5):639-51. doi: 10.1007/s00408-015-9752-4. Epub 2015 Jul 2.

Prognostic Value of Biomarkers in Acute Non-massive Pulmonary Embolism: A Systematic Review and Meta-analysis.

Bajaj A[1], Rathor P[2], Sehgal V[3], Kabak B[4], Shetty A[5], Al Masalmeh O[6], Hosur S[7].

Eur Heart J. 2005 Oct;26(20):2166-72. Epub 2005 May 23.

Biomarker-based risk assessment model in acute pulmonary embolism.

Kostrubiec M[1], Pruszczyk P, Bochowicz A, Pacho R, Szulc M, Kaczynska A, Styczynski G, Kuch-Wocial A, Abramczyl Kuczynska K.

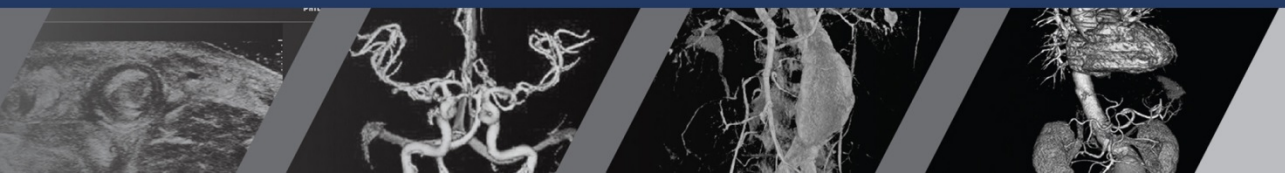
Med Clin (Barc). 2015 Mar 15;144(6):241-6. doi: 10.1016/j.medcli.2013.11.041. Epub 2014 Jun 16.

N-terminal Pro-B type natriuretic peptide as long-term predictor of death after an ac pulmonary embolism.

Alonso-Martínez JL[1], Annicchérico-Sánchez FJ[2], Urbieta-Echezarreta MA[2], Pérez-Ricarte S[2].

Rationale against Systemic

- Systemic PE thrombolysis is associated with a 13% risk of major bleeding and 1.8% risk of intracranial hemorrhage
  - Real world 20% major bleeding and 3% ICH
    - As such, systemic thrombolysis is witheld in 2/3 of patients with massive PE



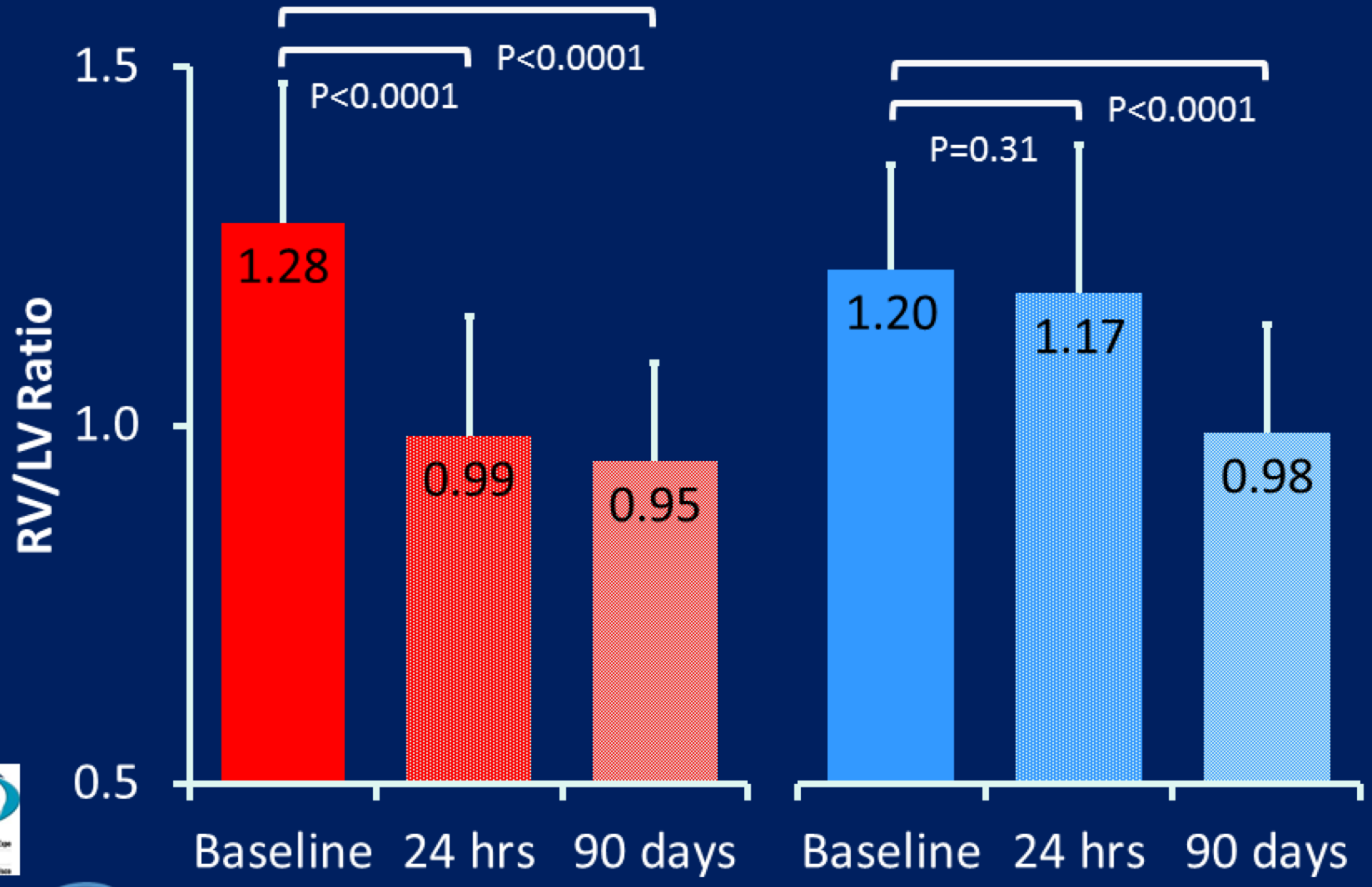
[1]Eur Heart J 2008: 29:2276-2315
[2]Am J Cardiol. 2006;97:127-9
[3]Circulation 2006;113:577-82

What are the results of Catheter Directed Therapy?

Ultima Trial

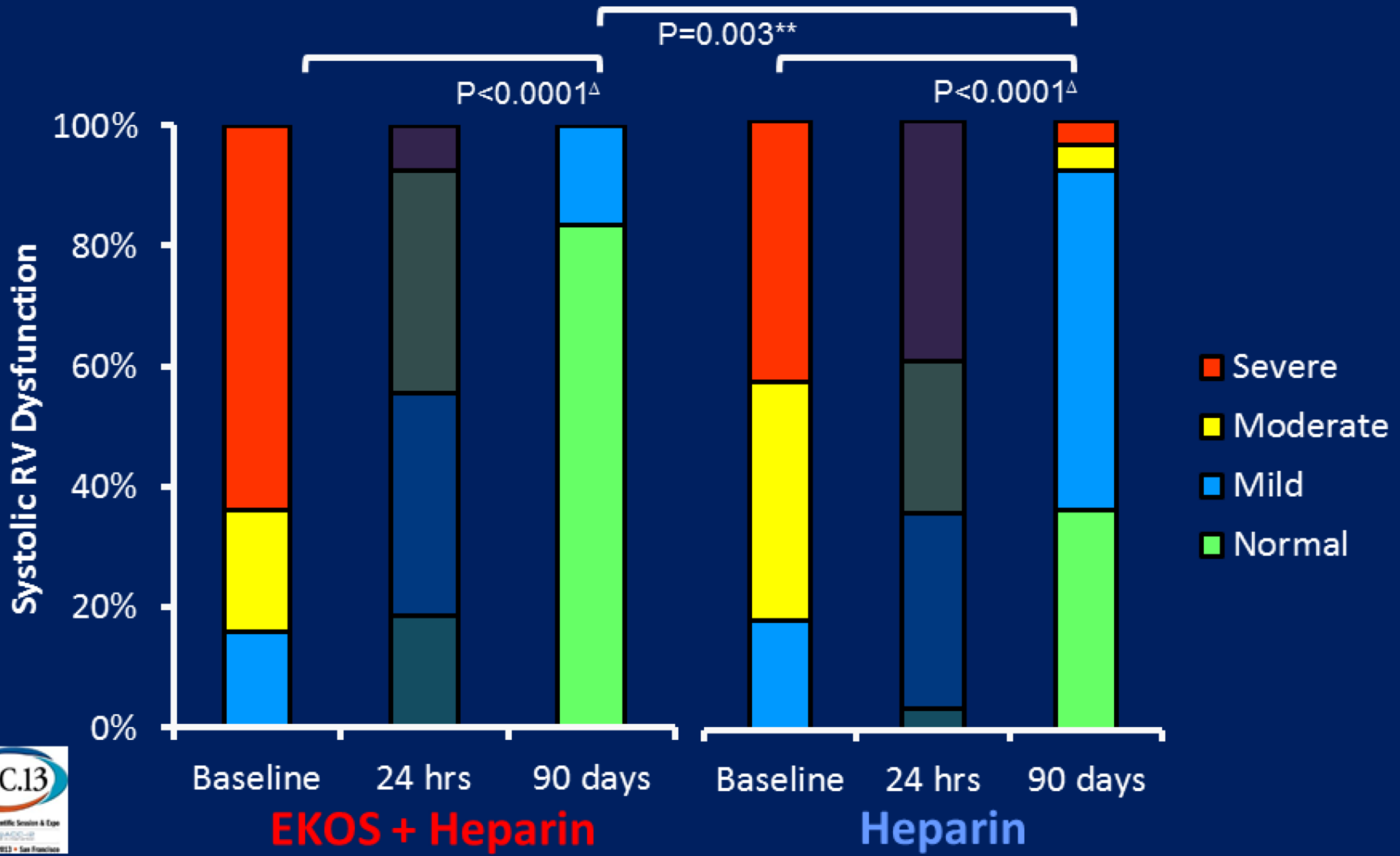
- Multicenter, randomized controlled trial
- Ultrasound assisted catheter directed thrombolysis
- Superior to heparin alone for reversing RV enlargement
- Acute symptomatic PE confirmed by CT
- RV/LV ration >1 on echo (normal is 0.6)

RV/LV ratio (echo)



Kucher 2013

Systolic RV dysfunction



**Two-sided exact Mantel-Haenzel test

Δ Wilcoxon rank sum test

Kucher 2013

Conclusions

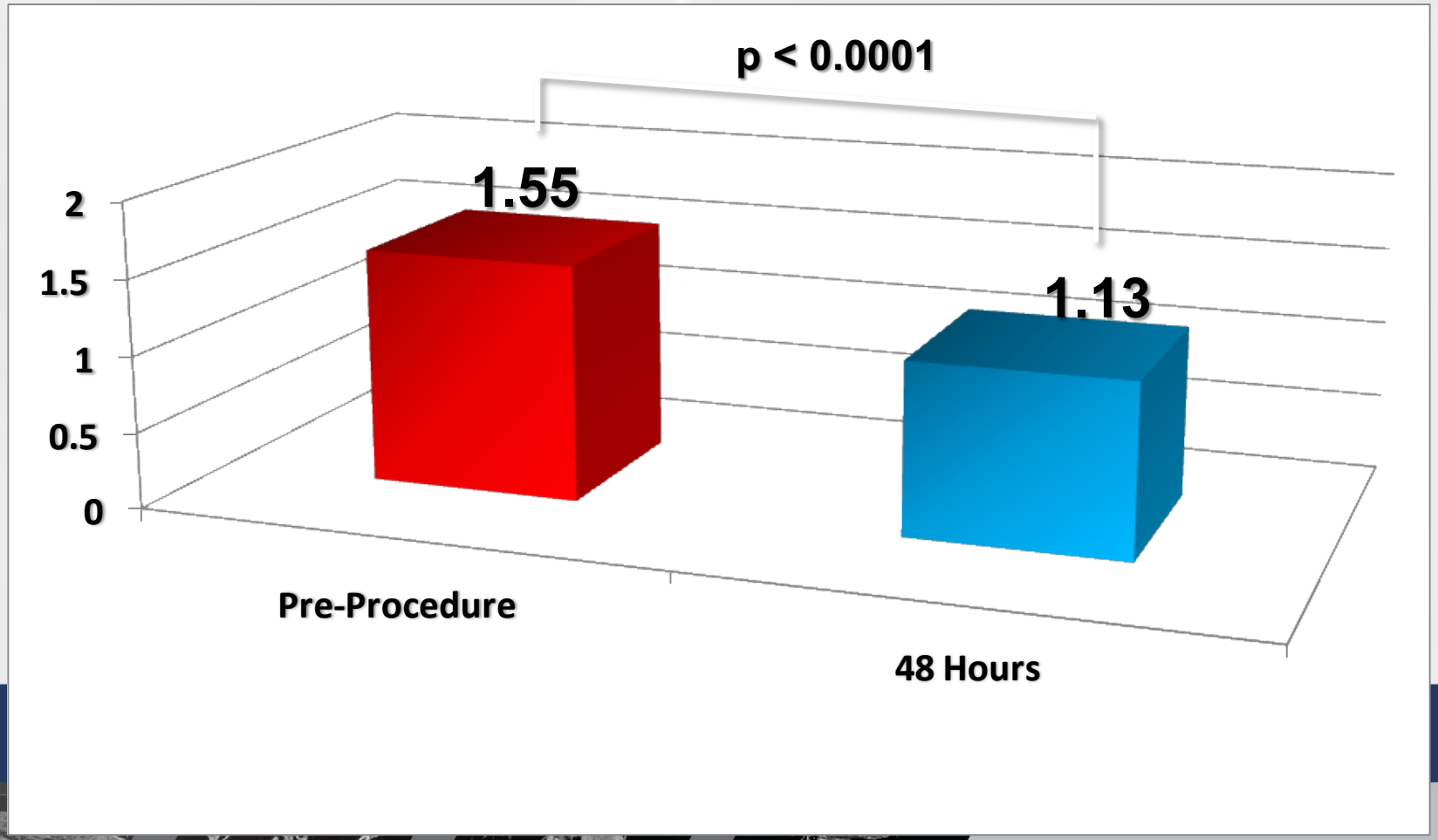
- Catheter directed (ultrasound accelerated) thrombolysis was superior to heparin in reversing right heart dysfunction.
- No increase in bleeding complications
- At 90 days the right heart function is improved with CDT over Heparin

SEATTLE II

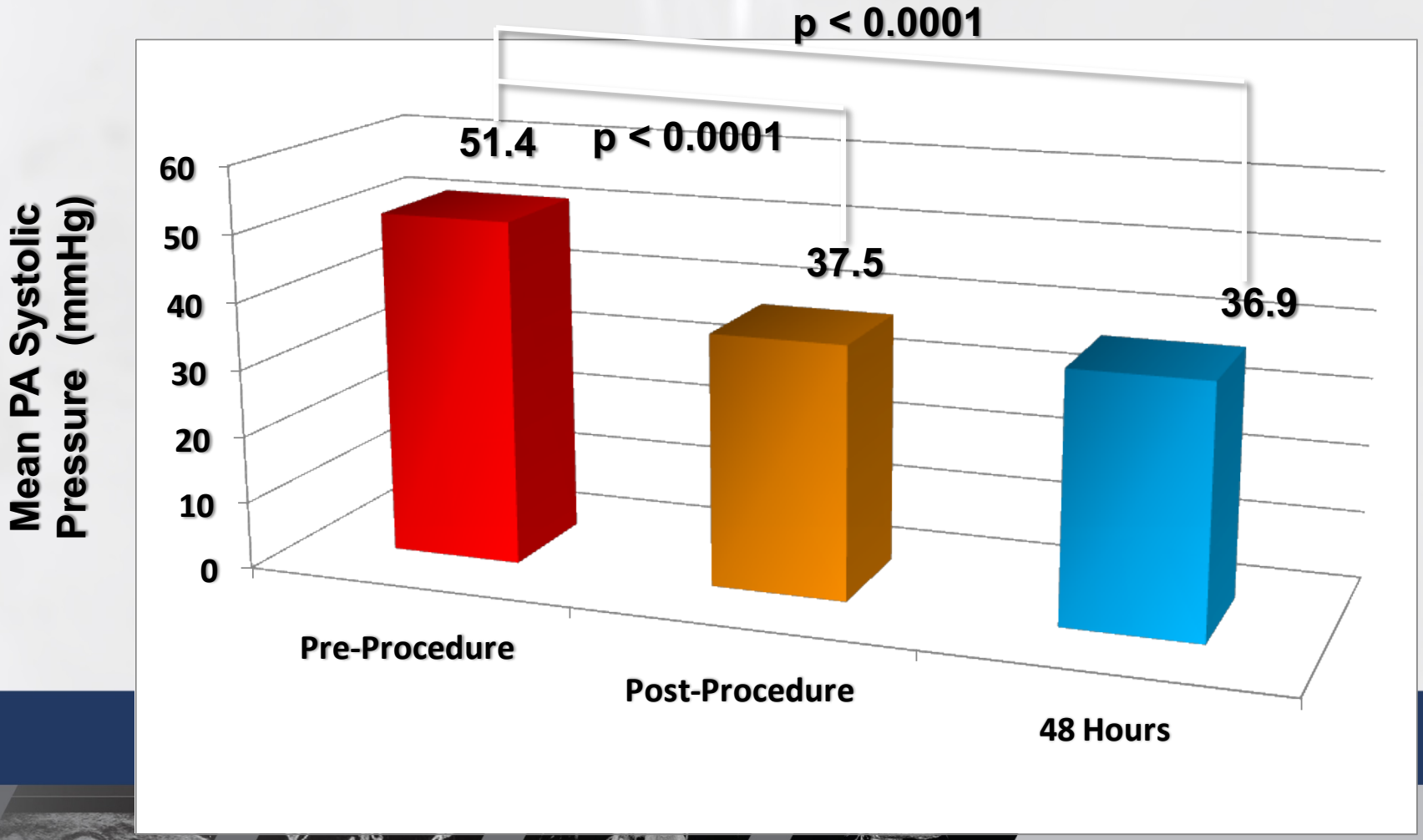
A prospective, single-arm, multicenter trial to:

- Assess the Safety and Efficacy of low dose thrombolytic for acute massive and submassive PE

Outcomes: RV/LV Ratio



Outcomes: PA Systolic Pressure



Meta-analysis suggested thrombolysis was associated with lower mortality for intermediate-risk PE, recurrent PE

Major bleeding was also significantly increased, but not for patients 65 years and younger

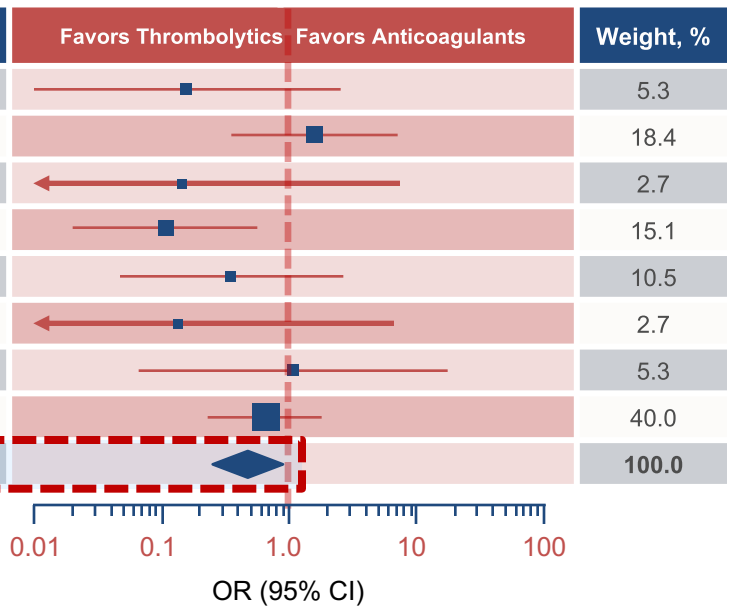
Outcome of Interest (No. of Studies Reporting)	No. of Events/No. of Patients, Absolute Event Rate (%)		No. Needed to Treat or harm	*P* Value
	Thrombolytic Group	Anticoagulant Group		
All-cause mortality (16)	23/1061 (2.17)	41/1054 (3.89)	NNT=59	.01
Major bleeding (16)[a]	98/1061 (9.24)	36/1054 (3.42)	NNH=18	<.001
ICH (15)	15/1024 (1.46)	2/1019 (.19)	NNH=78	.002
Recurrent PE (15)	12/1024 (1.17)	31/1019 (3.04)	NNT=54	.003
Age > 65 y				
All-cause mortality (5)	14/673 (2.08)	24/658 (3.65)	NNT=64	.07
Major bleeding (5) [a]	87/673 (12.93)	27/658 (4.10)	NNH=11	<.001
Age ≤ 65 y				
All-cause mortality (11)	9/388 (2.32)	17/396 (4.29)	NNT=51	.09
Major bleeding (11) [a]	11/388 (2.84)	9/396 (2.27)	NNH=176	.89
Intermediate-risk PE				
All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT=65	.03
Major bleeding (8) [a]	67/866 (7.74)	20/889 (2.25)	NNH=18	<.001

Chatterjee S et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: a Meta-analysis. JAMA 2014; 311(23):2414-2421.

Lysis in submassive PE

Mortality meta-analysis

Source	Thrombolytics # of Events	Thrombolytics # of Patients	Anticoagulants # of Events	Anticoagulants # 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	.66 (0.24-1.82)	40.0
Total	**12**	**866**	**26**	**889**	**.48 (0.25-0.92)**	**100.0**



Heterogeneity: $\chi^2_7 = 7.63$; $P = .37$; $I^2 = 8\%$

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

Intermediate-risk PE				
All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT=65	.03
Major bleeding (8)[a]	67/866 (7.74)	20/889 (2.25)	NNH=18	<.001

Chatterjee S et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: a Meta-analysis. JAMA 2014; 311(23):2414-2421.

Other Data

- Prospective multicenter single arm
- 106 patients at 18 sites
- Proximal PE and RH Strain
- RV/LV ratio decreased from 1.53 to 1.15 at 48 hours

Penumbra Trial

- Extract Pulmonary Embolism
  - Single Arm trial
  - Suction Thrombectomy with Cat-8 Penumbra
  - Measurement of Thrombus Burden and Pressures pre- and post- procedure

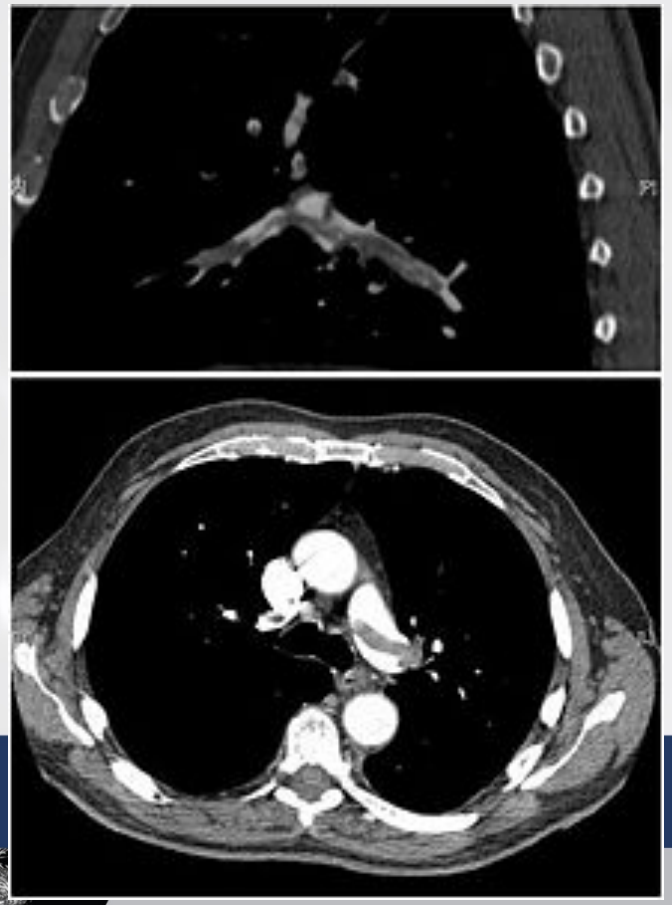
What Would You Do?

WWYD?

- 45 year old female comes to the ER with chest pain and shortness of breath.
- She has had a prior DVT for which she received coumadin for a year.
- She stopped her blood thinner 3 months ago.
- Elective ankle surgery 2 weeks ago.
- HR 105
- BP 100/60
- O2 sat 98% on 2L NC

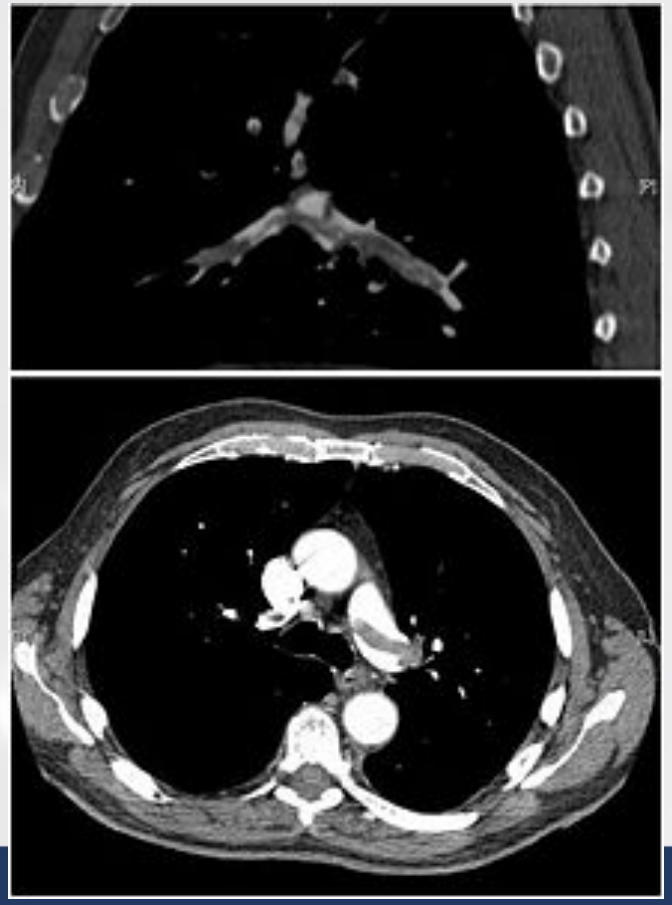
WWYD?

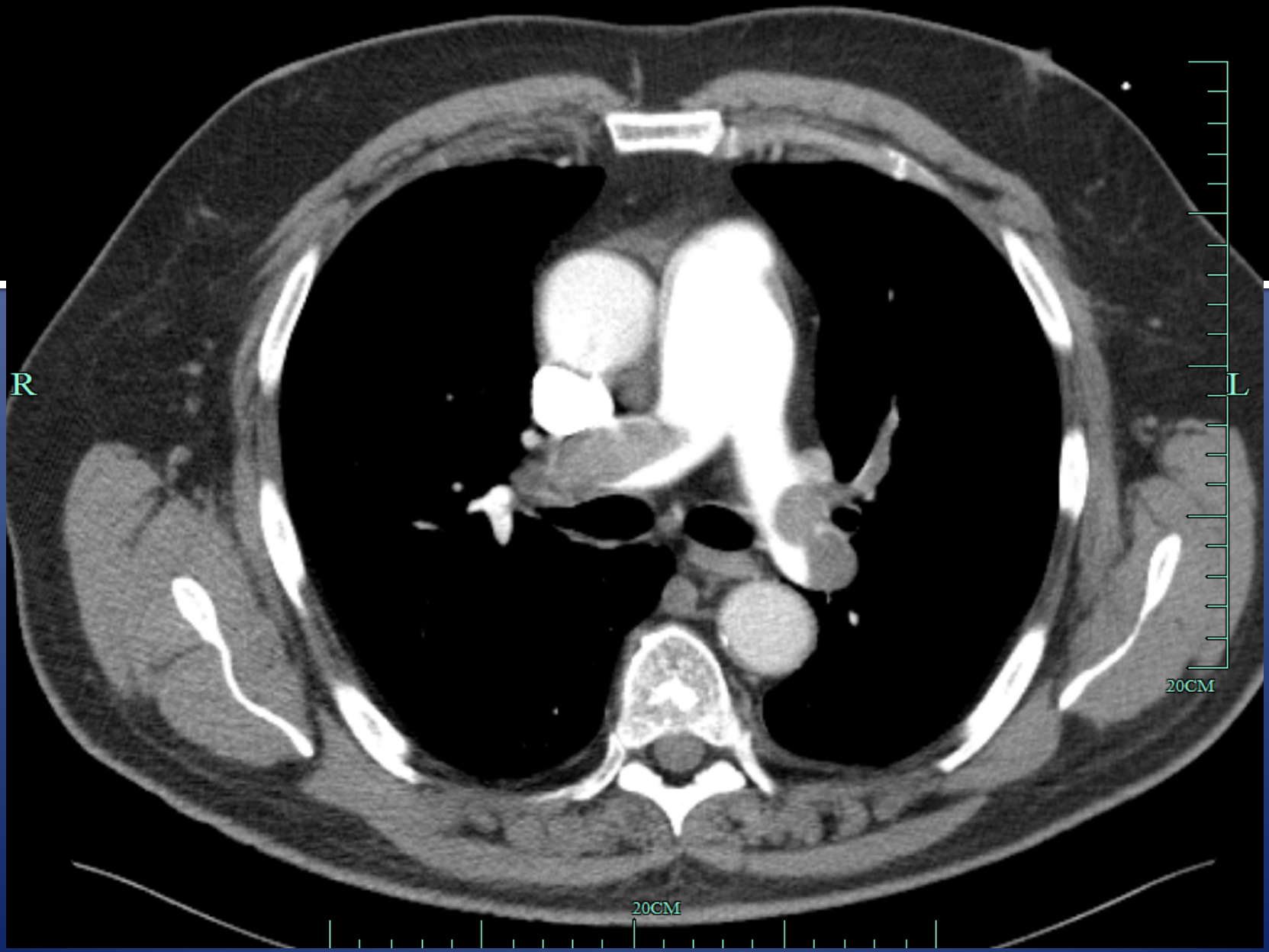
- Echo shows dilated right ventricle
- RV/LV Ratio 1.2
- BNP 3200
- Troponin .5



WWYD?

- What now?
- Who makes the decision?
- How do they make the decision?
- Will the best treatment plan be offered to this patient?

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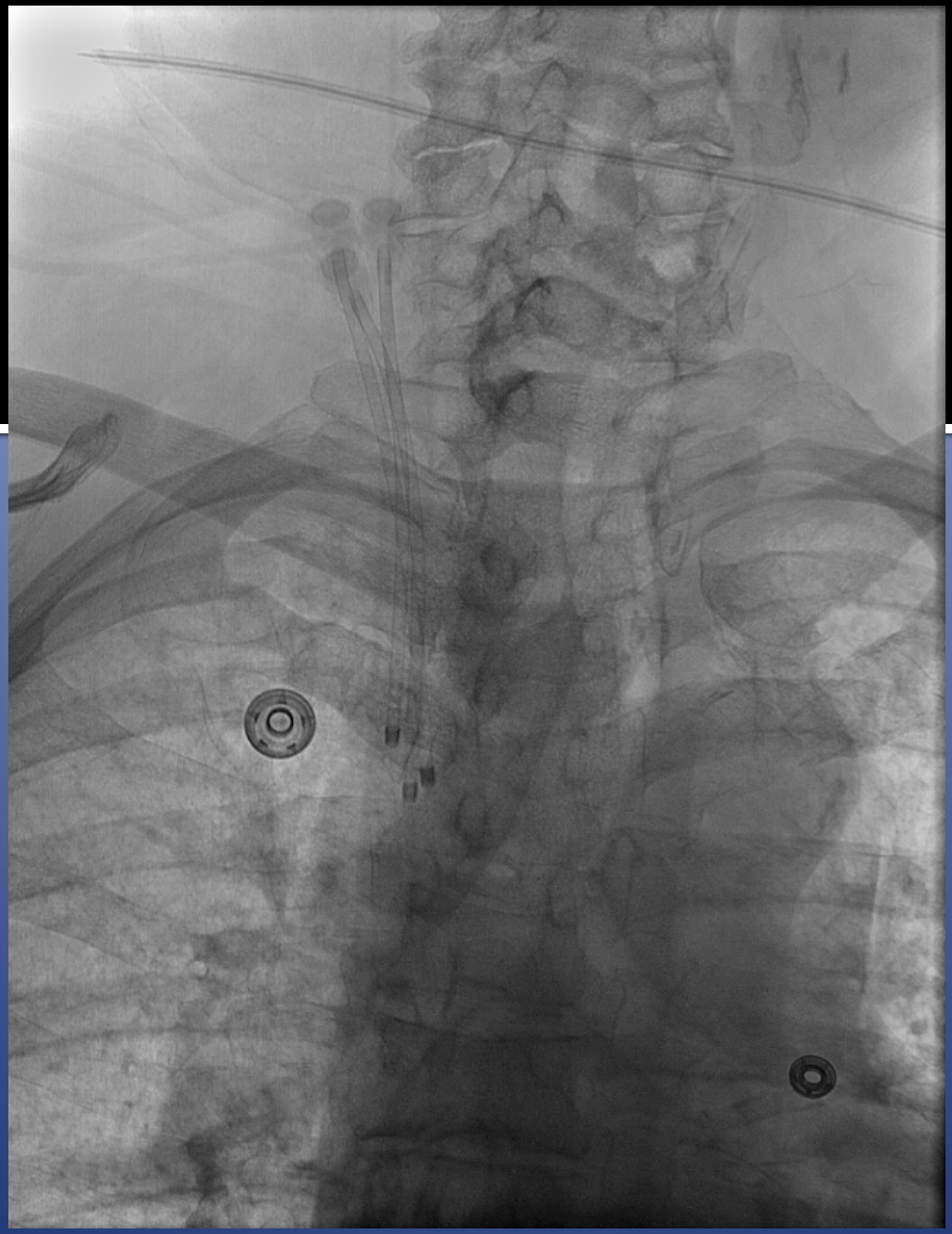

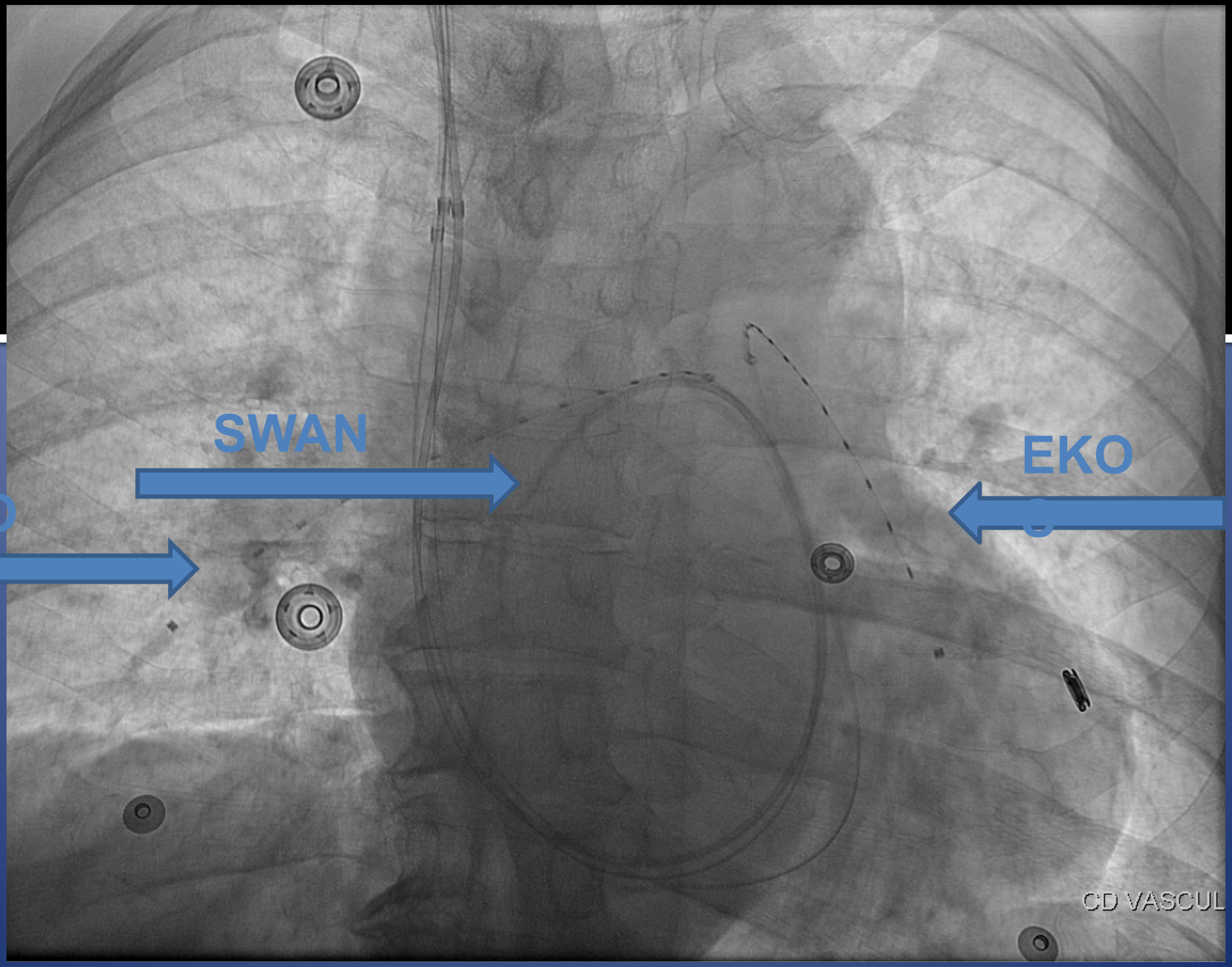
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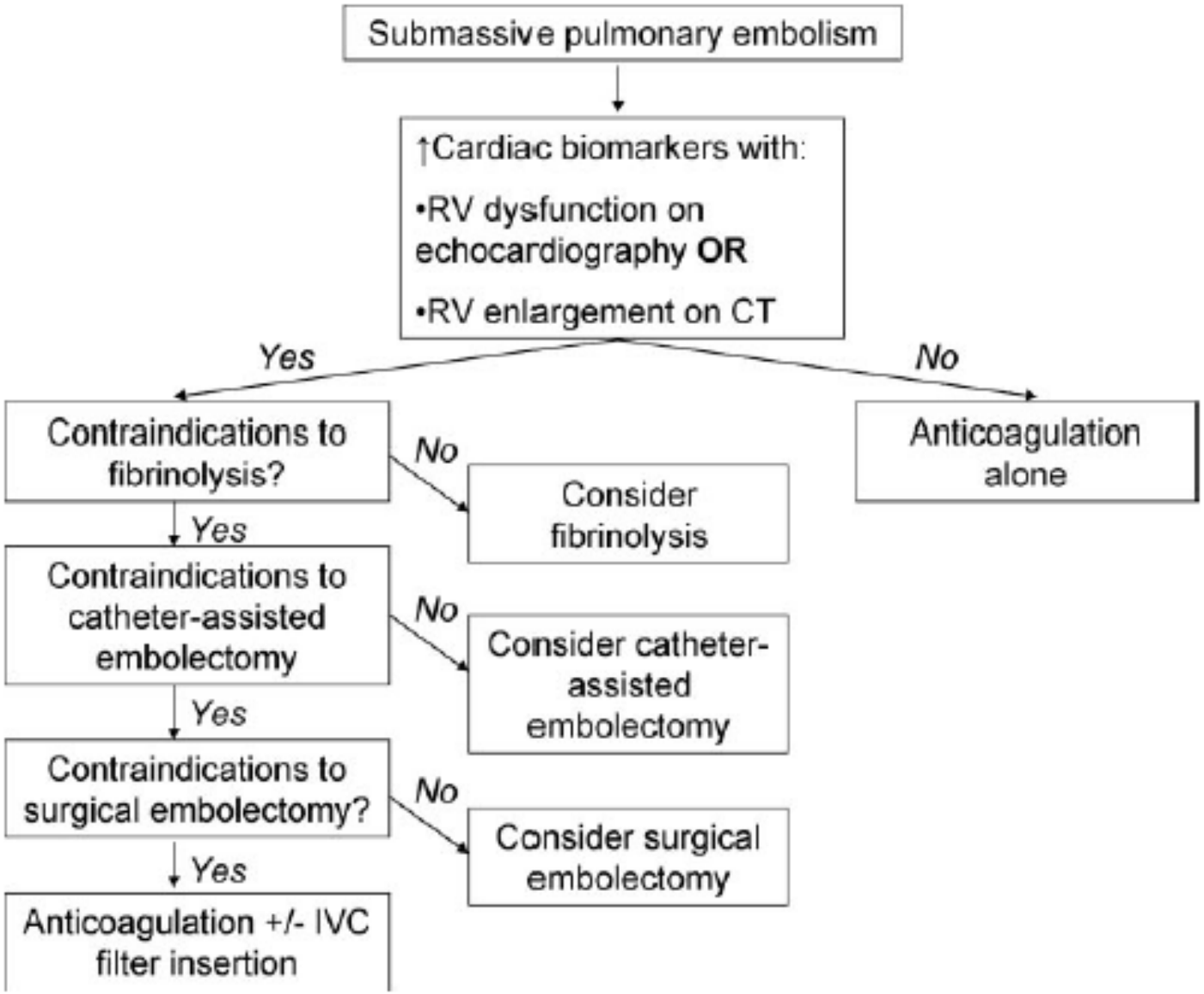
POD #1

- 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

Post Op Care

- Discharge planning
  - Plan for 12 months of anticoagulation
  - Compression stockings 30-40mmHg for two years
  - 72 hour echo to look for resolution of right heart strain
  - 3 month follow up appt. to assess for resolution of right heart strain and symptoms of post thrombotic syndrome

Treatment Algorithm



Conclusion

- Submassive PE is associated with poor long and short term outcomes.
- The reversal of Right Heart Strain leads to better results.
- The routine use of catheter directed therapy in sub-massive PE should improve short and long term outcomes.