

# **Chronic Thromboembolic Pulmonary Hypertension**

Fellows Core Curriculum February 17, 2017

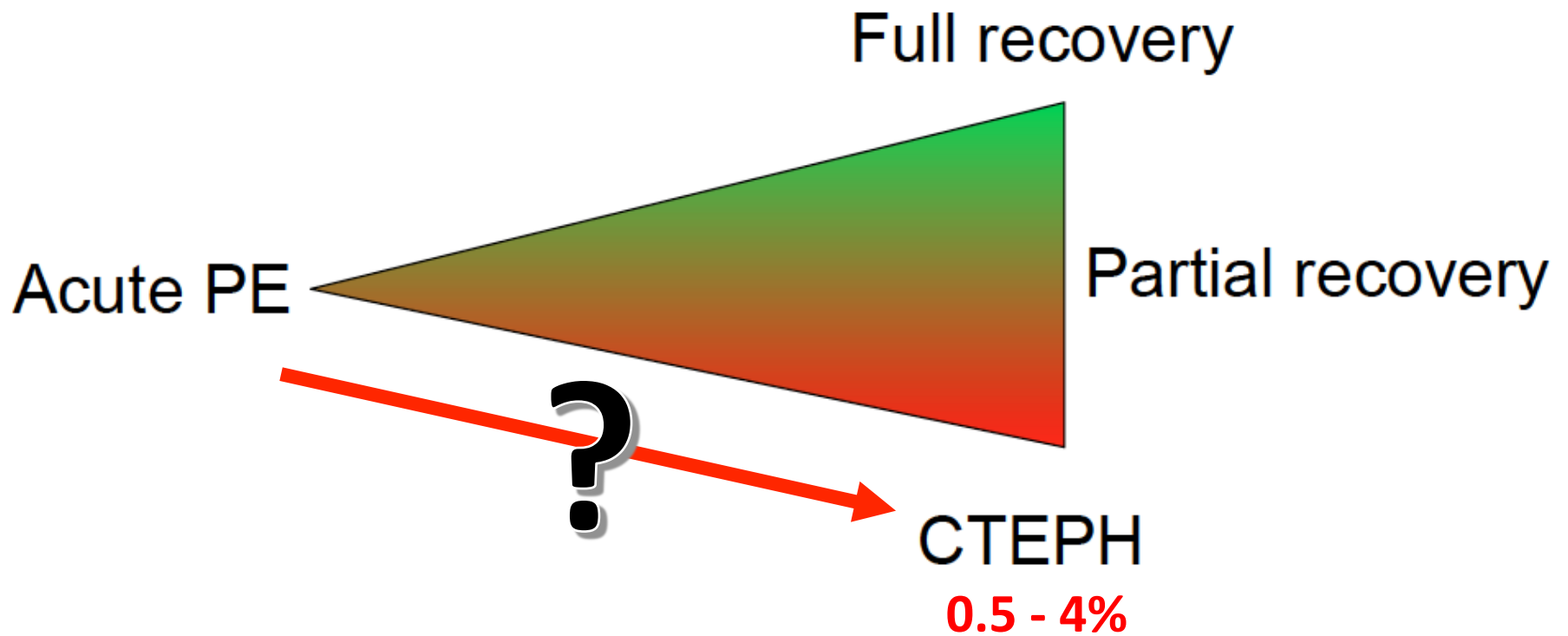
Quyên Nguyễn

Belinda Rivera-Lebron

# What is CTEPH?

Persistent thromboemboli after acute PE  
+  
Pulmonary hypertension

# PE Natural History



# Objectives

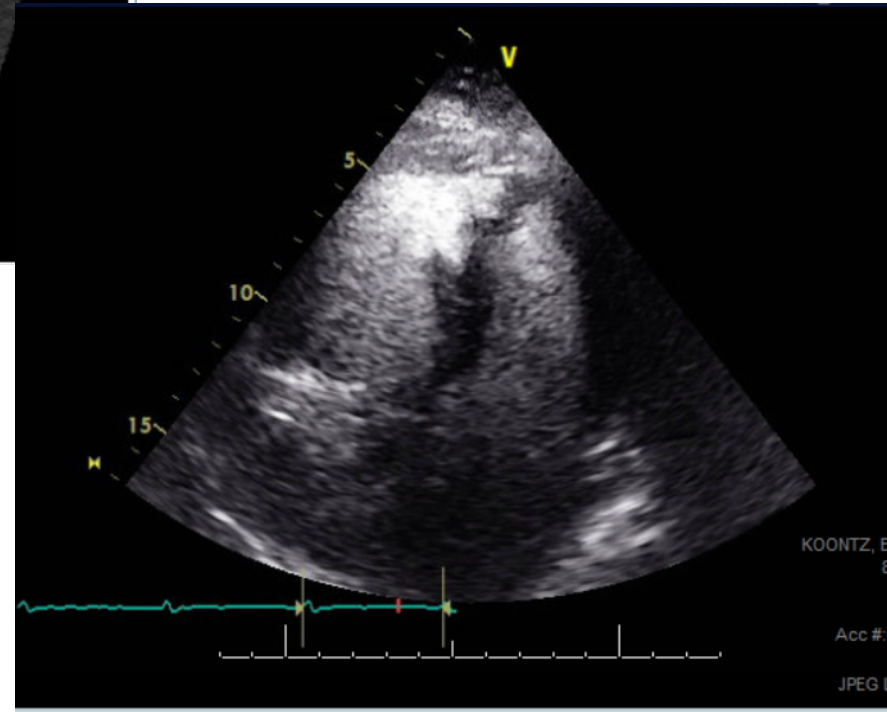
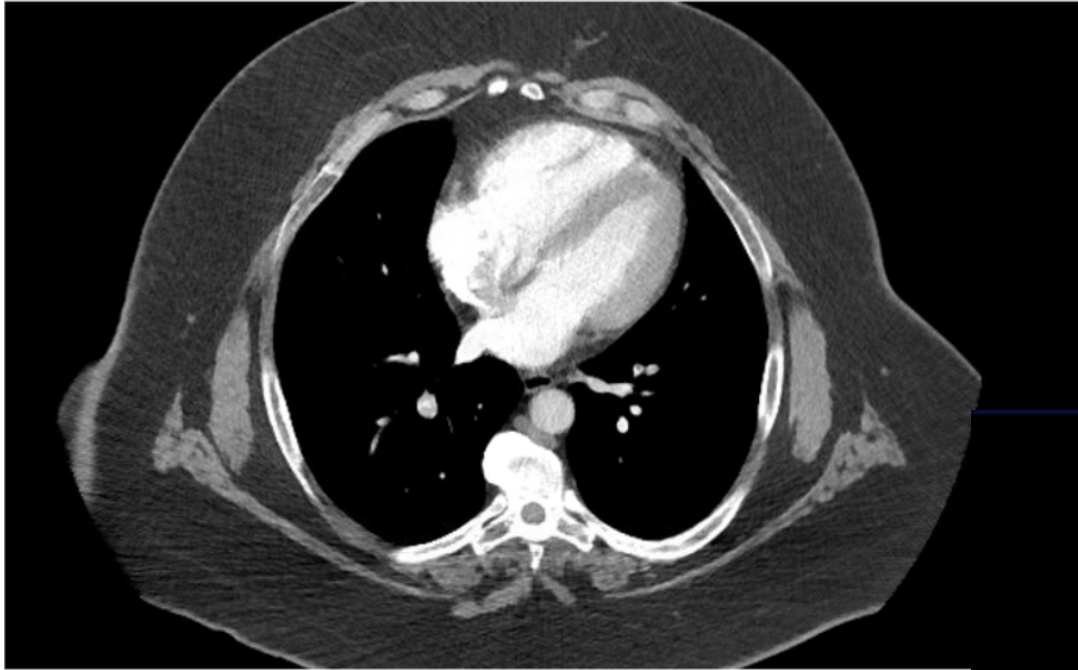
- Explore the outcomes of acute PE
- Use specific tests to assess cardiopulmonary impairments after PE
- Develop an algorithm for when and how to diagnose CTEPH after PE
- Discuss management options for CTEPH



Ms. BK

- 44 yr old morbidly obese female
- BMI 63
- Hx OSA on CPAP
- 3 days of worsening DOE
- dx PE at OSH by CTA
- Presyncope, no syncope
- +troponin and BNP, large RV
- PESI 86, sPESI 1 = class III intermediate risk
- Remained hemodynamically stable
- No thrombolytic therapy
- UFH -> warfarin

# CTA + Echo



Why did I get a clot?



Will

**How long will it take for the clots to go away?**

Will I need to have a lot of frequent tests after I leave the hospital?

**Will I have any long term problems from this?**

When can I go back to work?

What are my activity restrictions?

Am I at risk for another clot?

**What kind of follow up am I going to need?**

How long will it take for the clots to go away?



Thrombus Resolution

\$100

\$200

\$300

\$400



After acute PE, at what time point is  
50% of clot resolved?

**2-4 weeks**

Serial angiograms and V/Q scans in patients diagnosed with PE and treated with heparin

Time after Rx	% Resolution
2 hours	Negligible
24 hours	10%
7 days	40%
2-4 weeks	50%

Dong et al. Cochrane Database Syst Rev 2009

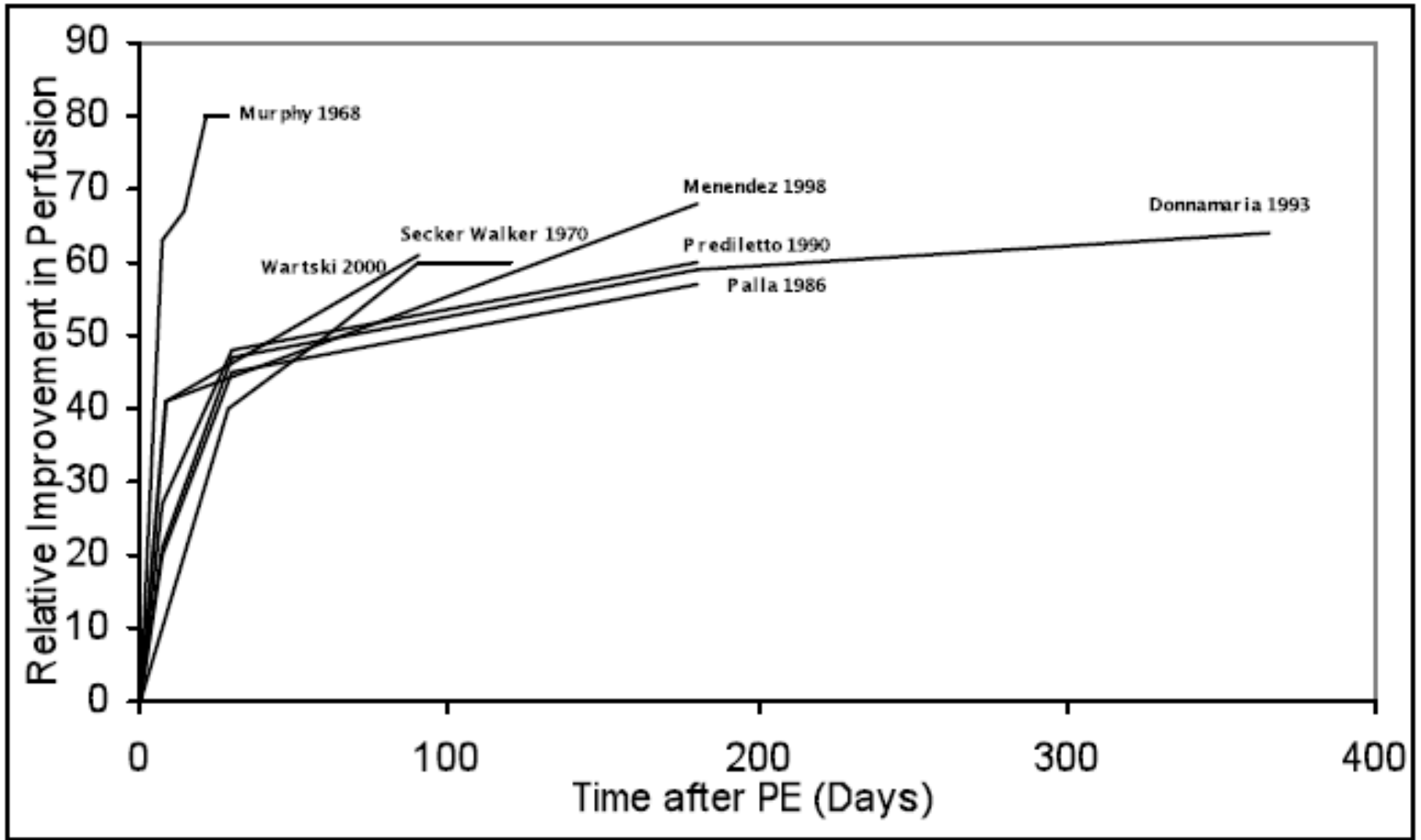
**What % of patients achieve complete resolution of thrombus, after 12 months of anticoagulation for PE ?**

**65-92%**

Study	n	Time of follow up	Imaging Test	% patients with resolution
Alonso-Martinez 2012	166	4.5 mo	CTA	74%
Cosmi 2011	80	9 mo	CT	85%
	93		Lung perfusion	72%
Stein 2010	79	28 d	CTA	81%
Miniati 2006	320	1 yr	Lung perfusion	65%
Golpe 2012	91	6 mo	CTA	80%
Sanchez 2010	254	12 mo	V/Q	71%
Korknaz 2012	121	3 mo	CTA	52%
	146	6 mo		73%
	159	12 mo		92%
Aghayev 2013	111	1 yr	CTA	77%
Kaczynska 2008	55	6 mo	CT or lung perfusion	30%
Wartski 2000	157	3 mo	Lung perfusion	34%

After an acute PE, when does the patient's thrombus resolution rate plateau?

**3 months**



**SPECIAL  
ROUND**

# What are the risk factors for incomplete thrombus resolution (despite anticoagulation)?

**Large thrombus size**

**Central location**

**Older age**

**Longer time between symptoms and diagnosis of PE**

**Prior history of VTE**



# Take home message

- Bulk of clot resolves early (before 6 months).
- Residual clot more than 12 months out likely represent permanent fibrous scars.

# Acute PE



Remodeling of thrombus

Resistance to fibrinolysis

Abnormal endothelial cell behavior

Mesenchymal cell-mediated remodeling

Lack of neovascularization

## Organized scar



No single biological cause of CTEPH

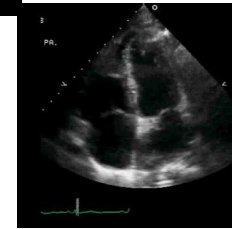
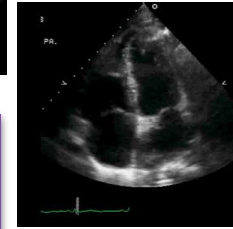
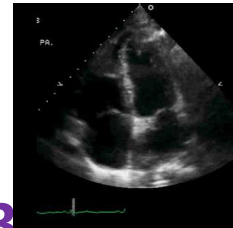
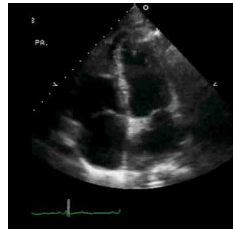
Difficult to predict who will progress

Small vessel reaction

RV dysfunction

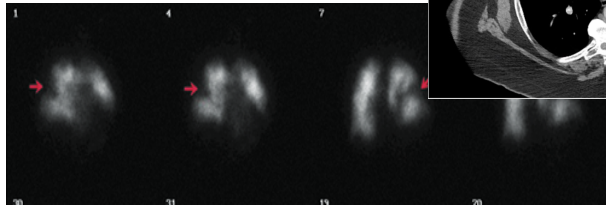
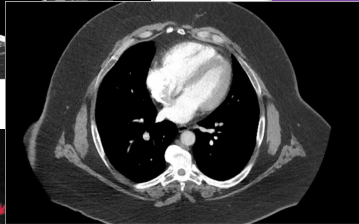
# PH

Acute PE



25-35%

Organized  
scar



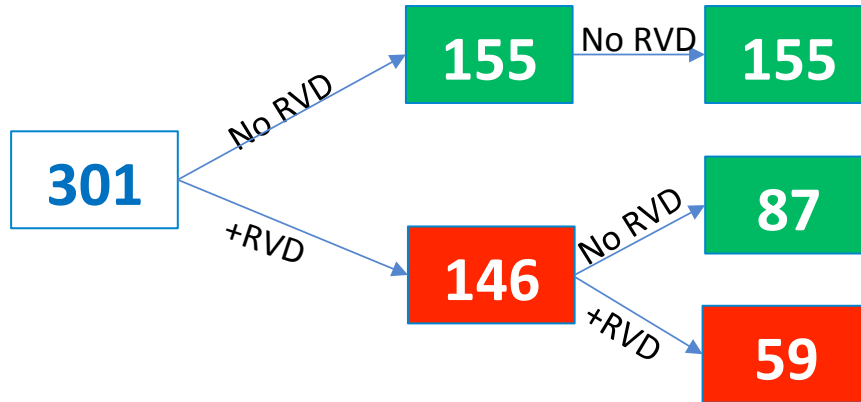
1-4%

PH

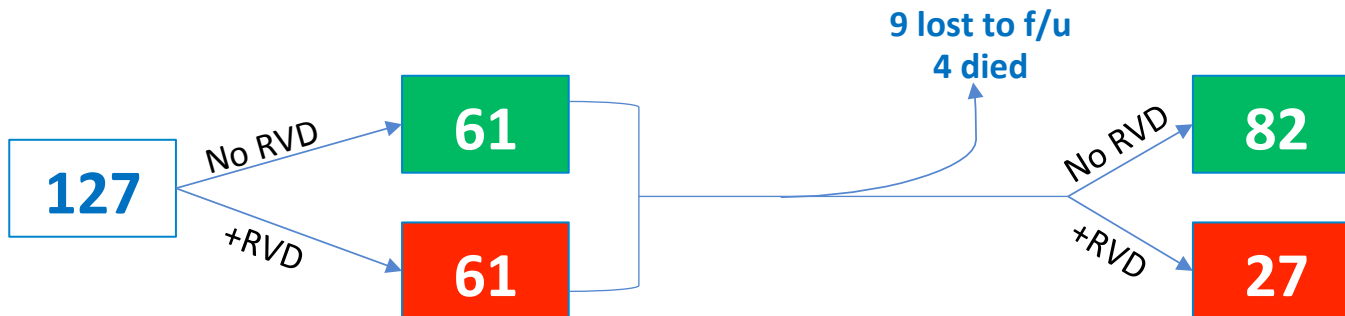
Admission

11-13d

6 mos



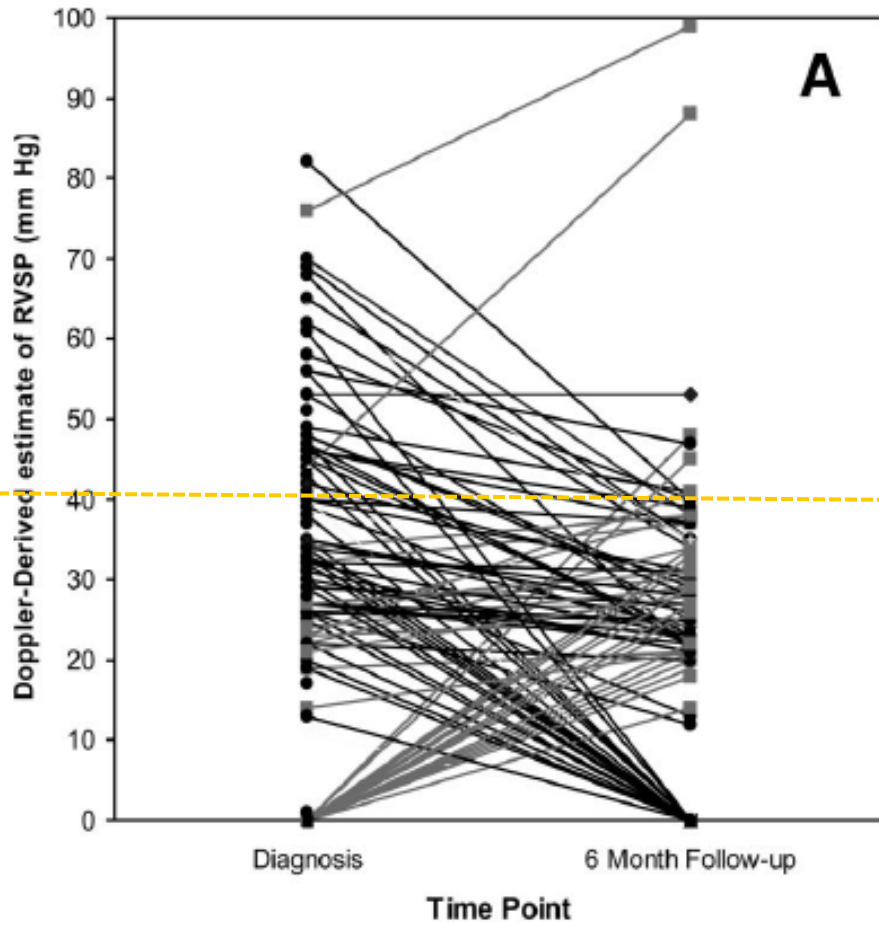
Grifoni et al – acute PE



Stevinson et al – acute non massive PE

Heparin only

Heparin + tPA



# Take home message

- Hemodynamic normalization occurs in majority of patients
- A minority of patients actually get worse

Will I have any long term problems from this?



\$200

\$400

cont

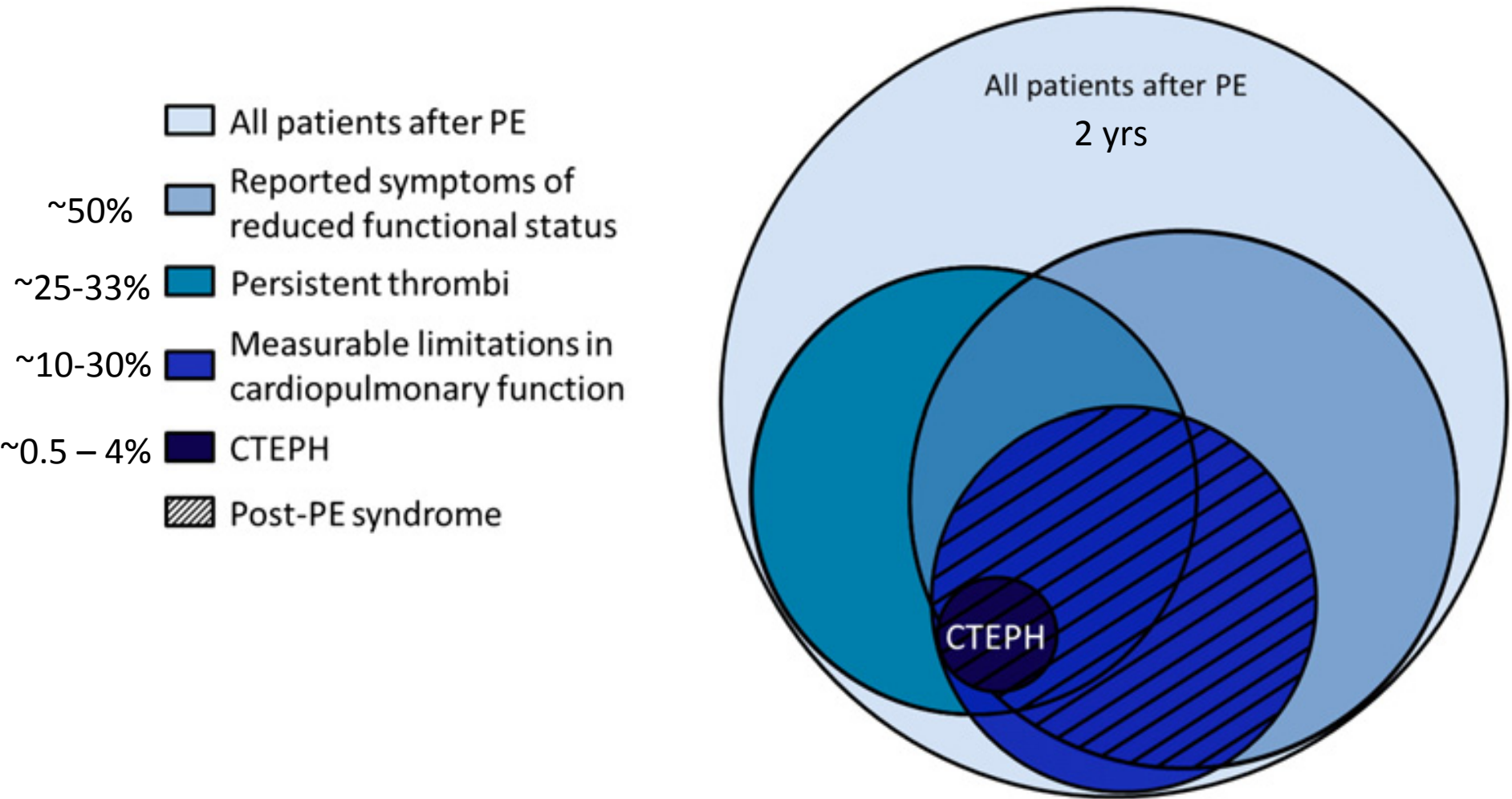
**TRUE OR FALSE:**

**Up to 3 years after adequately treated PE, more than half of patients report poor physical performance.**

**TRUE**



# Long term consequences of PE



back

**DAILY  
DOUBLE**

Which of the following is a risk factor for CTEPH in Ms. BK?

- A. Submassive PE
- B. 1<sup>st</sup> PE
- C. Unprovoked PE
- D. A + C

**C. Unprovoked PE**

**Table 1. Risk Factors for Chronic Thromboembolic Pulmonary Hypertension.**

**Factors specific to pulmonary embolism**

Recurrent or unprovoked pulmonary embolism

Large perfusion defects when pulmonary embolism detected

Young or old age when pulmonary embolism detected

Pulmonary-artery systolic pressure >50 mm Hg at initial manifestation of pulmonary embolism

Persistent pulmonary hypertension on echocardiography performed 6 mo after acute pulmonary embolism detected

**Chronic medical conditions**

Infected surgical cardiac shunts or pacemaker or defibrillator leads

Postsplenectomy

Chronic inflammatory disorders

Thyroid-replacement therapy

Cancer

**Thrombotic factors**

Lupus anticoagulant or antiphospholipid antibodies

Increased levels of factor VIII

Dysfibrinogenemia

**Genetic factors**

ABO blood groups other than O

HLA polymorphisms

Abnormal endogenous fibrinolysis

Pengo. NEJM 2004  
Wilkins. Intern J Cardiology 2011  
Fedullo. AJRCCM 2011  
Piazza. NEJM

# Take home message

- The interplay of anatomic, hemodynamic, and functional outcomes after PE is complex.
- Many patients will continue to be impaired in some way after acute PE.



Ms. BK

- 6 months after acute submassive PE
- BMI still > 60
- Improved dyspnea but clearly worse than before clot
- Dyspnea after several yards flat ground
- Cannot exercise
- Hypercoagulability labs negative
- Continues on warfarin

**How would you evaluate her  
dyspnea?**

# Reasons to screen for CTEPH

- Fatal if untreated
  - 10% 5 yr-survival mPAP > 50
- Cure is possible
  - Pulmonary thromboendarctectomy
  - Medical therapy available
- Incidence underestimated
  - PE underrecognized
  - Studies only include pts with documented PE
  - 25-40% pts with CTEPH lack dx of DVT/PE



What kind of testing am I going to need for this?



\$600

\$800

cont

What is the best test to screen for  
CTEPH?

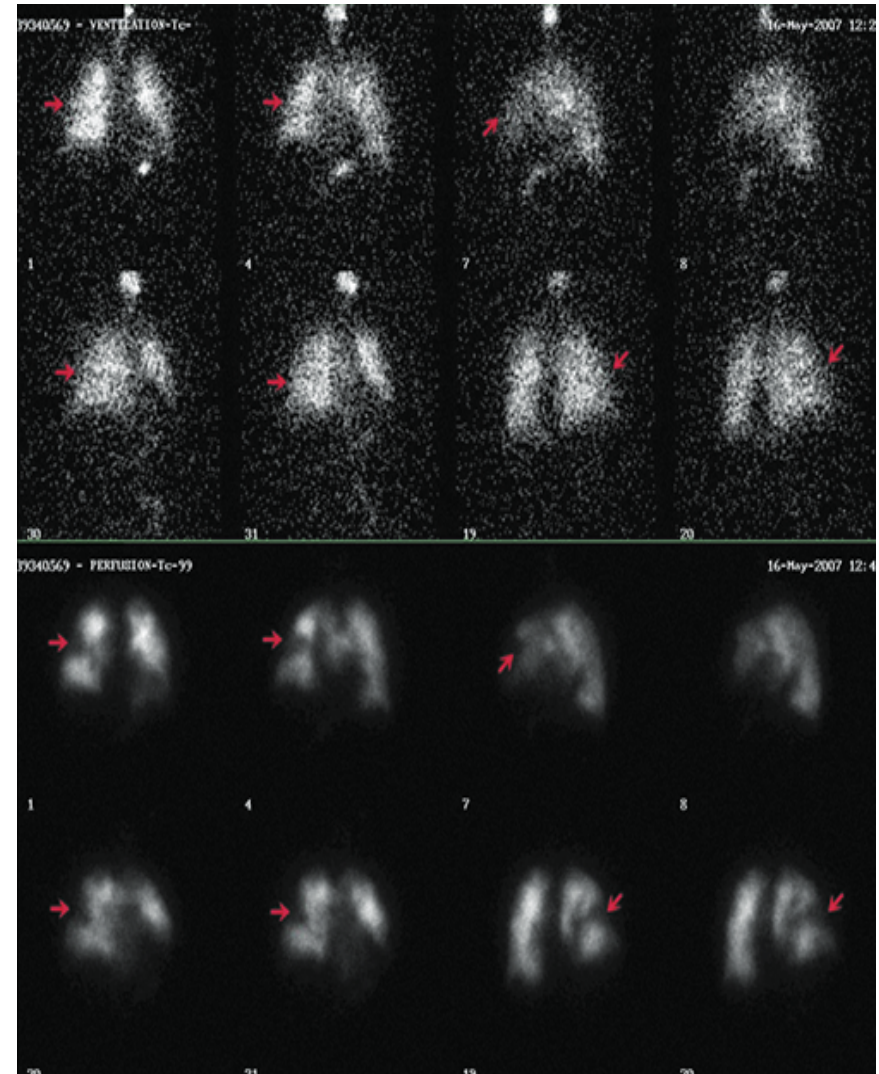
V/Q scan

# V/Q scan more sensitive than CTA

- use to screen for CTEPH

N = 227	VQ scan	CTA
Sens	<b>97%</b>	51%
Spec	94%	99%
PPV	90%	98%
NPV	98%	80%

Gold standard = pulmonary angiogram



Tunariu. J Nucl Med 2007

back

**Besides imaging which demonstrates at least one perfusion defect, what additional test must be performed to confirm a diagnosis of CTEPH?**

**RHC**

# CTEPH Diagnosis

- > 3 mo post-PE
- mPAP  $\geq$  25 & PCWP  $\leq$  15
- At least 1 perfusion defect on V/Q scan or segmental defect in CTA or PA gram

# When and how would you screen her for CTEPH?

UPMC post acute PE follow up

After 3 mo anticoagulation:

- Echo
- V/Q scan
  - Low Prob → CTEPH ruled out
  - Interm Prob → CTEPH uncertain
  - High Prob → CTEPH likely → RHC



Mr. CT

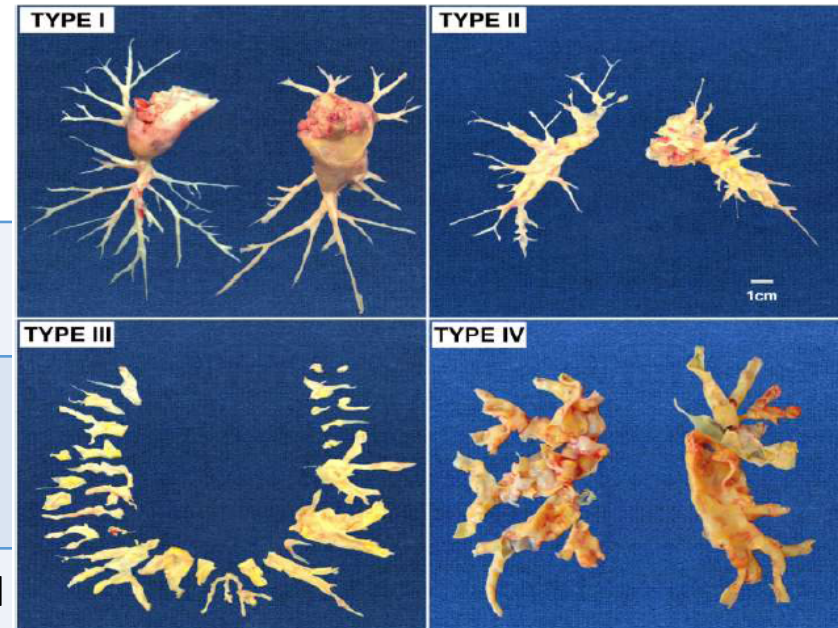
- 41 yr old morbidly obese male
- BMI 43
- Hx antiphospholipid antibody
- Hx recurrent VTE, PE at ages 14, 27, 31
- Chronic AC but interruptions
- Can still perform work on dairy farm (milks cows)
- Last 6 months progressive DOE, can't climb 1 flight of stairs
- 6MWD 260 meters, sat 92%→76%

# Treatment of choice:

## Pulmonary thromboendarterectomy

- PTE can be curative
- Factors influencing PTE

<b>Anatomical considerations</b>	Central, accessible clot Assess by dedicated CTA
<b>Comorbidities</b>	LV dysfunction, renal disease, pulmonary disease, CVA, immunosuppression
<b>Hemodynamics</b>	higher incidence of residual PAH w/ PVR > 5
<b>Center experience</b>	UCSD 160 cases/yr UPMC 10-15 cases/yr
<b>Technical considerations</b>	median sternotomy, other thoracic surgeries

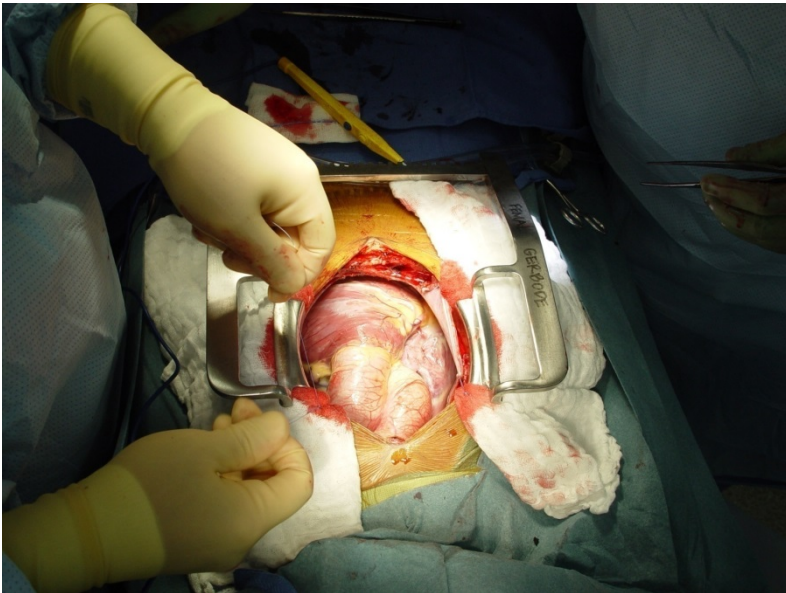




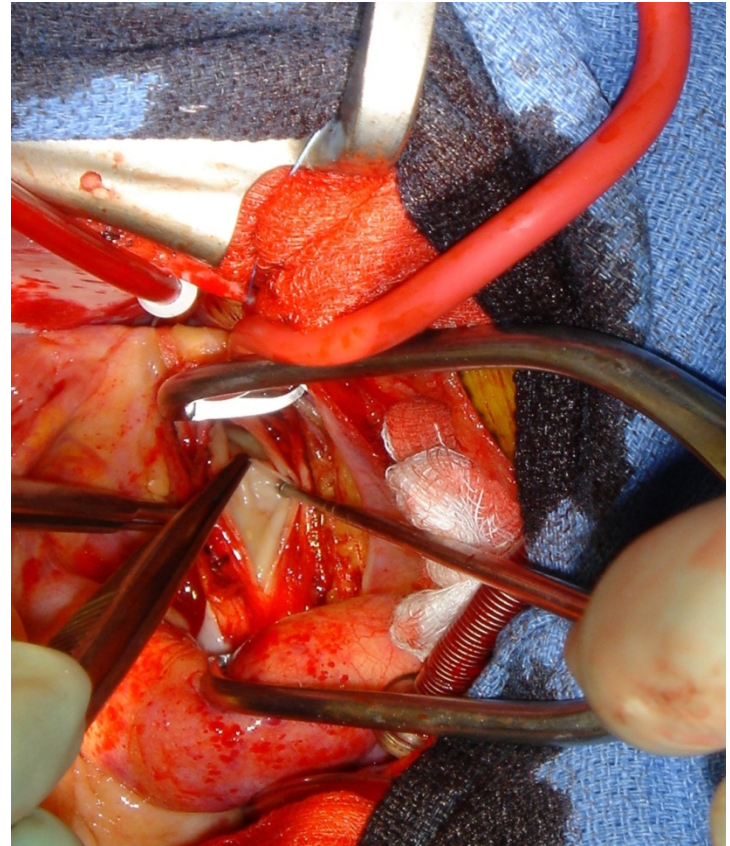
# PTE

- Pre-op everyone gets IVC filter
- Median sternotomy → cardiopulmonary bypass → hypothermic circulatory arrest at 20° (20 min on-10min off to minimize neuro damage and back-bleeding from bronchial A to PA anastomosis)
- Mortality 4-5% (except if PVR > 12, mortality 10%)

## Median sternotomy



## Rt PA endarterectomy



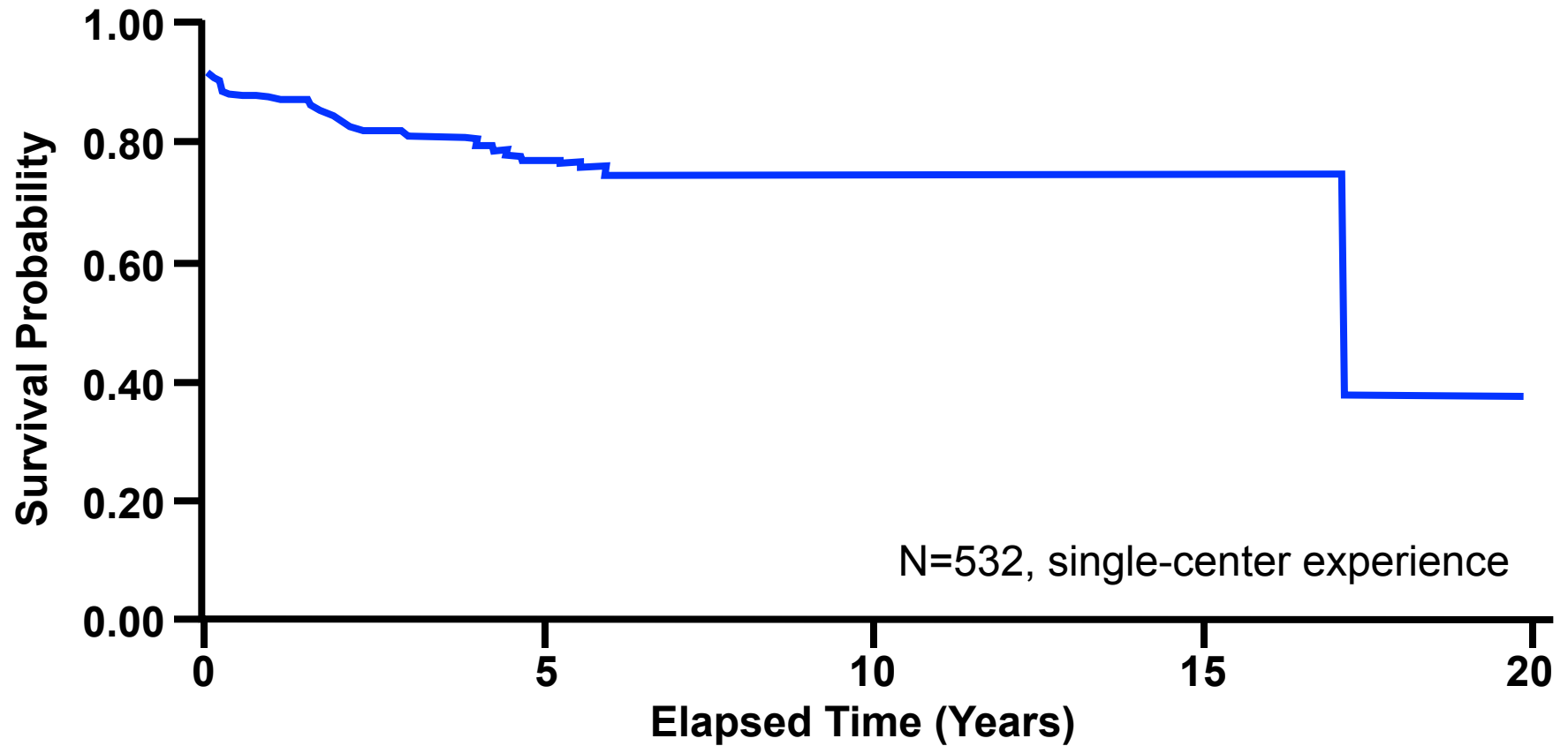
Pre-op



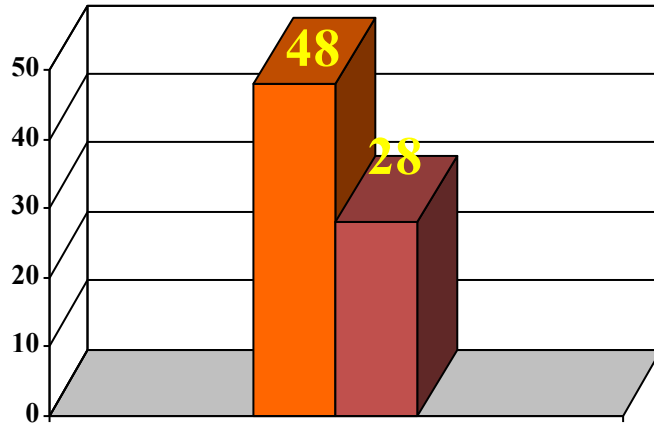
Post-op



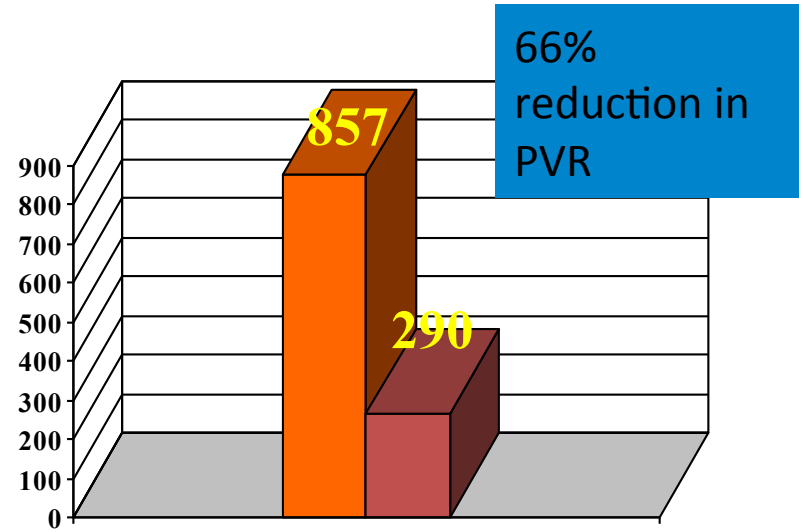
# Survival After Successful PTE



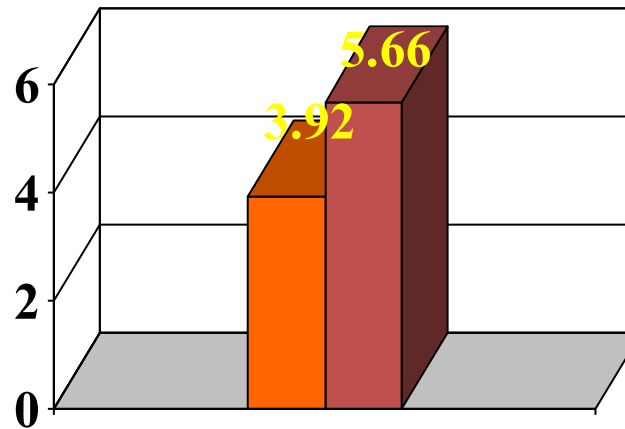
# Hemodynamics After PTE



Mean PA (mm Hg)

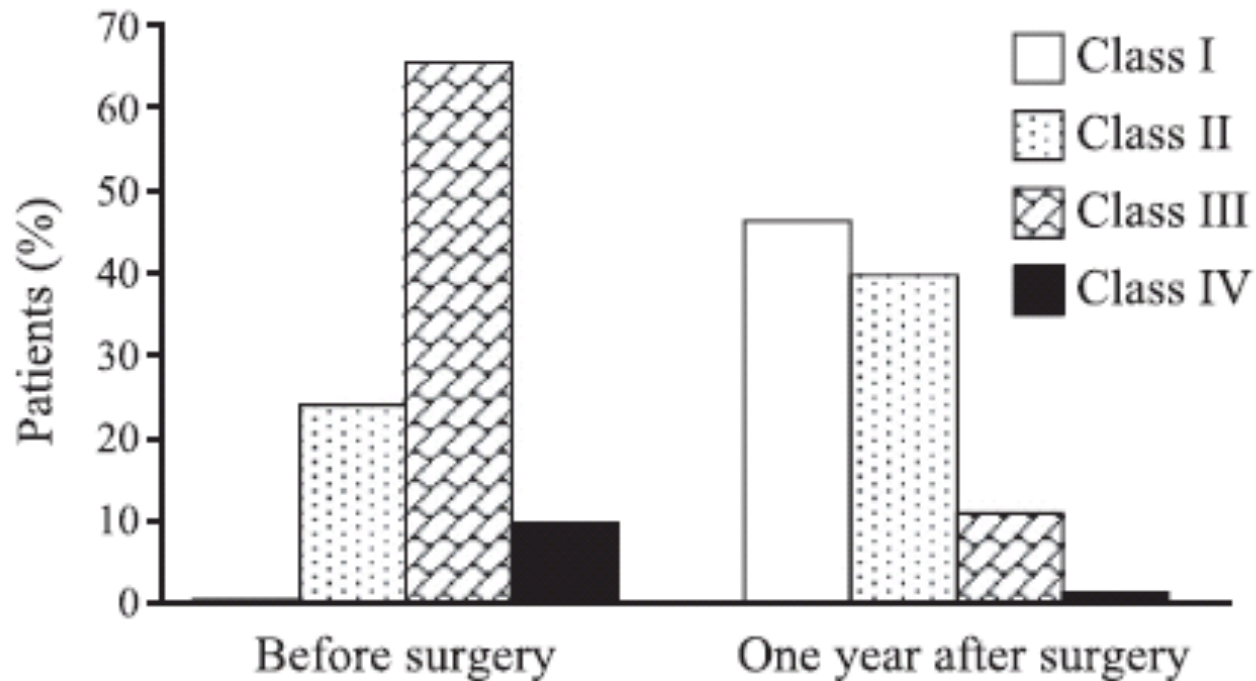


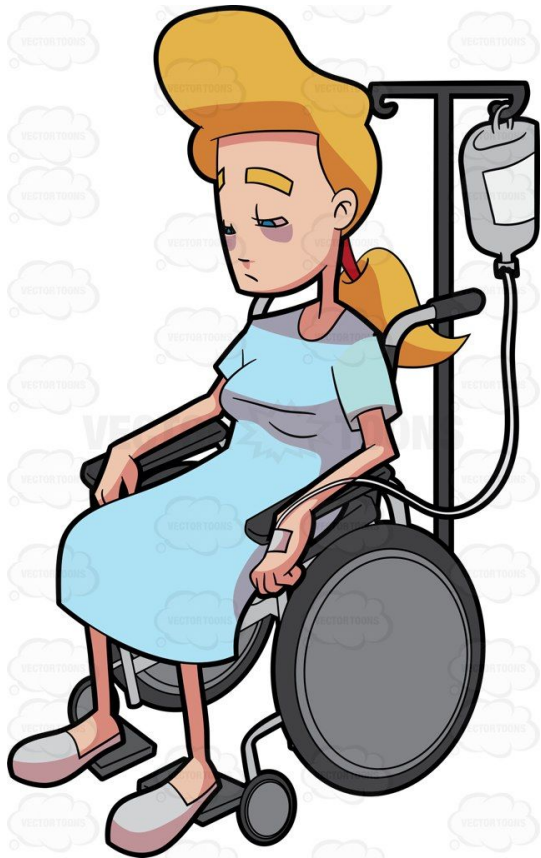
PVR (dynes/sec/cm-5)



C.O. (Lit/min)

# NYHA Functional Pre and Post-PTE





Ms. JS

- 31 yr old F
- Hx TVR 2013 for endocarditis
- Recurrent admissions for RV failure ->
- Dx CTEPH
- Went to Temple for PTE 8/2016
- No significant post-op complications
- Discharged on sildenafil
- Still with some dyspnea on exertion but improved

CT 5/2016 – RLL chronic

V/Q 5/2016 – RUL, RLL

RHC:

	Pre PTE	Post PTE
RA	15	20
PA (s/d/m)	84/33 (50)	76/32 (47)
PCWP	2	17
CO	4.7	5
PVR	10.2	5.8

# Persistent Pulmonary Hypertension

- 5-35% have persistent PH post-PTE
- Why?
  - Surgically inaccessible disease
  - Distal vasculopathy
  
- Medical therapy for PH

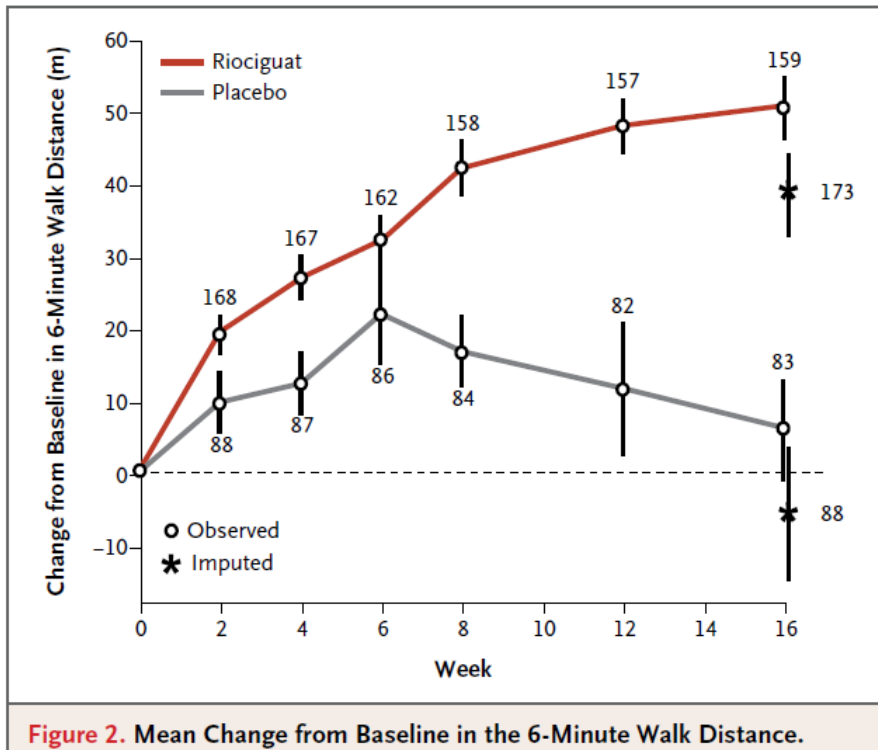


# Medical treatment

**Table 1** Short-Term (3 to 6 Months) Effects of Medical Treatment in CTEPH

	First Author (Ref. #), Year	Study Design	Duration	n	NYHA	6MWD*	Effect	PVR	Effect
Epoprostenol (IV)	Cabrol et al. (48), 2007	-	3 months	23	III-IV	280 ± 112	66	(T) 29 ± 7†	-21%
Treprostinil (SC)	Skoro-Sajer et al. (49), 2007	-	6 months	25	III-IV	260 ± 111	59	924 ± 347	-13%
Iloprost (inh)	Olschewski et al. (50), 2002	RCT	3 months	57	III-IV	NA	NS	NA	NS
Sildenafil (PO)	Ghofrani et al. (51), 2003	-	6 months	12	NA	312 ± 30	54	1,935 ± 228‡	-30%
Sildenafil (PO)	Reichenberger et al. (52), 2007	-	3 months	104	II-IV	310 ± 11	51	863 ± 38	-12%
Sildenafil (PO)	Suntharalingam et al. (53), 2008	RCT	3 months	19	II-III	339 ± 58	18 (NS)	734 ± 363	-27%
Bosentan (PO)	Hoeper et al. (54), 2005	-	3 months	19	II-IV	340 ± 102	73	914 ± 329	-33%
Bosentan (PO)	Hughes et al. (55), 2005	-	3 months	20	II-IV	262 ± 106	45	(T) 1,165 ± 392	-21%
Bosentan (PO)	Bonderman et al. (56), 2005	-	6 months	16	II-IV	299 ± 131	92	712 ± 213	NA
Bosentan (PO)	Seyfarth et al. (57), 2007	-	6 months	12	III	319 ± 85	72	1,008 ± 428	NA
Bosentan (PO)	Jais et al. (58), 2008	RCT	4 months	157	II-IV	342 ± 84	2 (NS)	783 (703-861)	-24%
Riociguat (PO)	Ghofrani et al. (59), 2010	-	3 months	41	II-III	390 (330-441)	55	691 (533-844)	-29%
Riociguat (PO)	Ghofrani et al. (60), 2013	RCT	4 months	261	II-IV	347 ± 80	46	787 ± 422	-31%

# Riociguat (Adempas<sup>®</sup>)



- CHEST-1 Trial
- N = 261, 16 wks
  - Inoperable 72%
  - Post-op 28%
- ↑ 6MWD 46 m
- ↓ PVR by 2.8 WU
- ↓ NT-pro BNP
- ↓ WHO class
- No  $\Delta$  time-to-clinical-worsening

# Take Home Message

- Riociguat for persistent PH after PTE or non-operable disease
- Lifelong anticoagulation
- Do NOT deprive a patient of a life-saving procedure for medical management trial!

# Summary



- After acute PE, most patients have anatomic and functional resolution
- CTEPH is rare consequence (1-4%) but high M&M, so have high index of clinical suspicion!
- Diagnosis:
  - Screening: V/Q scan
  - Confirmatory: RHC +/- PA gram
- Treatment: Pulmonary thromboendarterectomy (can be curative!)
- If inoperable or PH post-surgery: Riociguat