Πνευμονική Υπέρταση: τι άλλαξε στο 6ο Παγκόσμιο Συμπόσιο Πνευμονικής Υπέρτασης:

στη θεραπεία της ΧΕΡΗ

Γεωργία Γ. Πίτσιου
Πνευμονολόγος- Εντατικολόγος
Αναπληρώτρια Καθηγήτρια, Τμήμα Ιατρικής ΑΠΘ
Γ.Ν. “Γ.Παπανικολάου”

Conflict of interest

The speaker has received

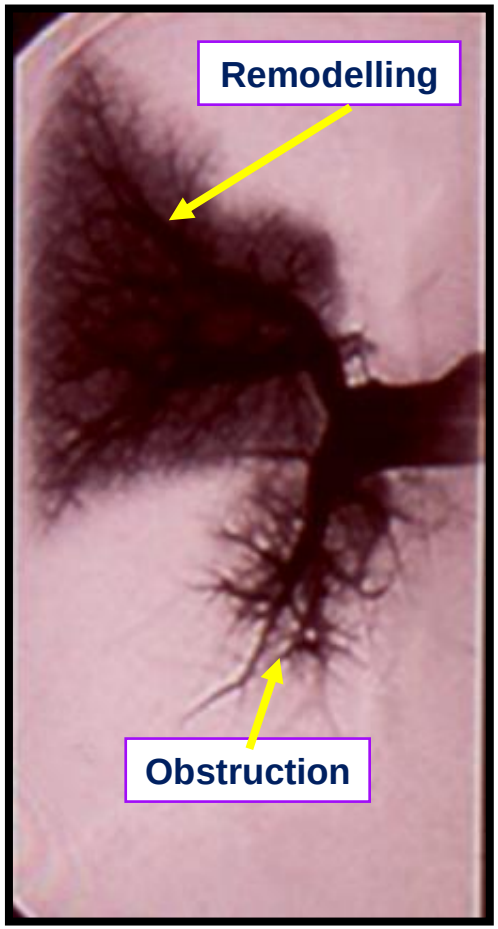
Honoraria for lectures and/or consultancy for Actelion, Bayer, ELPEN, GSK and MSD.

Group	Description
Group 4	**CTEPH & other pulmonary artery obstructions** 4.1 **Chronic thromboembolic pulmonary hypertension (CTEPH)** 4.2 Other pulmonary artery obstructions (Table 6)

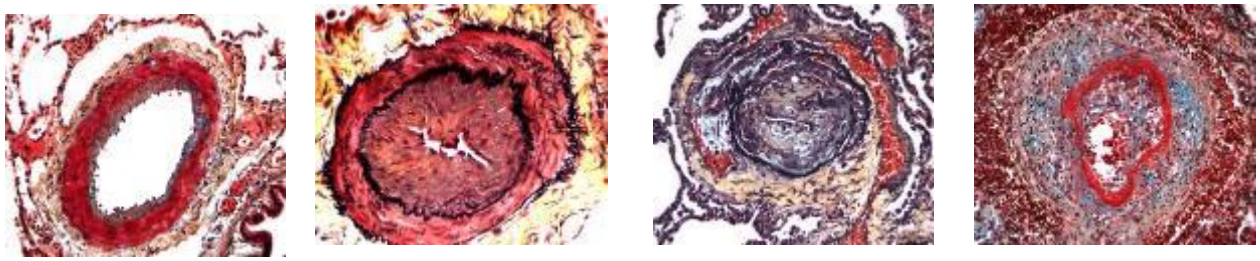
Table 6. Other pulmonary artery obstructions

4.2.1 Sarcoma (high-grade or intermediate-grade) or angiosarcoma	
4.2.2 Other malignant tumors	Renal carcinoma Uterine carcinoma Germ cell tumors of the testis Other tumors
4.2.3 Non malignant tumors	Uterine leiomyoma
4.2.4 Arteritis without connective tissue disease	
4.2.5 Congenital pulmonary artery stenoses	
4.2.6 Parasites	Hydatidosis

Chronic thromboembolic pulmonary hypertension (CTEPH)



- CTEPH is symptomatic PH with persistent perfusion defects after 3-6 months of adequate anticoagulation
- CTEPH is a disease with
  - a mechanical component judged amenable to surgery (**obstruction of elastic PA**)
  - and variable small vessel disease in non-occluded areas (**remodelling in small muscular PA**)



CTEPH PATHOPHYSIOLOGY

- Increased thrombosis[1]
- Deficient fibrinolysis[2]
- Platelet activation[3]
- Inflammation[1,4,5,11]
- Infection[1,6]
- Splenectomy[1,3]
- Activation of EC/SMC[5,7]
- Progenitor cells[8]
- Deficient angiogenesis[9,12]
- Genetics[10]

Unresolving pulmonary emboli

1. Bonderman D *et al. Thromb Haemost* 2005;93:512–6. 2. Morris TA *et al. Am J Resp Crit Care Med* 2006;173:1270–5. 3. Frey MK *et al. J Am Heart Assoc* 2014;3:e000772. 4. Quarck R *et al. J Am Coll Cardiol* 2009;53:1211–8. 5. Wynants M *et al. Eur Resp J* 2012;40:886–94. 6. Bonderman D *et al. Arterioscler Thomb Vasc Biol* 2008;28:678–84. 7. Quarck R *et al. Respir Res* 2012;13:27. 8. Firth AL *et al. Am J Physiol Cell Physiol* 2010;298:C1217–25. 9. Alias S *et al. Arterioscler Thromb Vasc Biol* 2014;34:810–9. 10. Suntharalingam J *et al. Eur Respir J* 2008;31:736–41. 11. Zabini D *et al. Eur Respir J* 2014;44:951–62. 12. Quarck R *et al. Eur Respir J* 2015;46:431–43.

CTED incidence

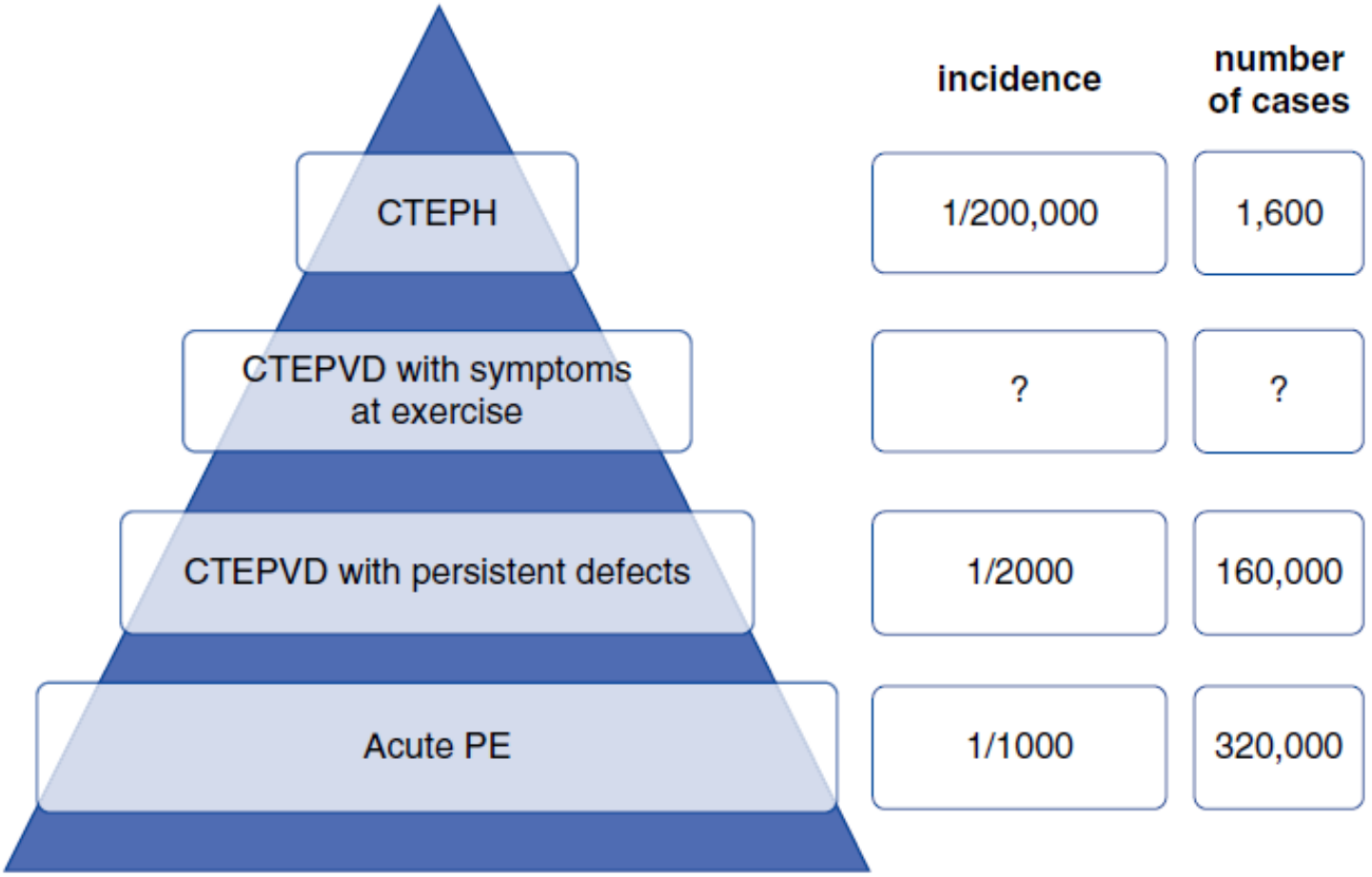


Figure 1. Estimates of the number of new patients with chronic thromboembolic pulmonary hypertension (CTEPH) and chronic thromboembolic pulmonary vascular disease (CTEPVD) per year in the United States. PE = pulmonary embolism.

Delcrois M et al. AnnalsATS 2016

CTEPH-Chronic Thromboembolic Disease (CTED) definitions

TABLE 1 Chronic thromboembolic disease (CTED) compared with chronic thromboembolic pulmonary hypertension (CTEPH)

Diagnostic criteria	CTEPH	CTED
Symptoms	Exercise dyspnoea	Exercise dyspnoea
PH	*Present at rest*	*Absent at rest*
RHC at exercise		*mPAP/CO slope >3 mmHg·L^{-1}·min^{-1}*
***V/Q* scan**	Any mismatched perfusion defect	Any mismatched perfusion defect
Angiography (CTPA or DSA)	Typical findings of CTEPH	Typical findings of CTEPH
CPET		*Excluding ventilatory limitation, deconditioning*
TTE		*Excluding left ventricular myocardial or valvular disease*
Anticoagulation	At least 3 months	At least 3 months

RHC: right heart catheterisation; *V/Q*: ventilation/perfusion; CTPA: computed tomography pulmonary angiogram; DSA: digital subtraction angiogram; CPET: cardiopulmonary exercise test; TTE: transthoracic echocardiogram; mPAP: mean pulmonary arterial pressure; CO: cardiac output.

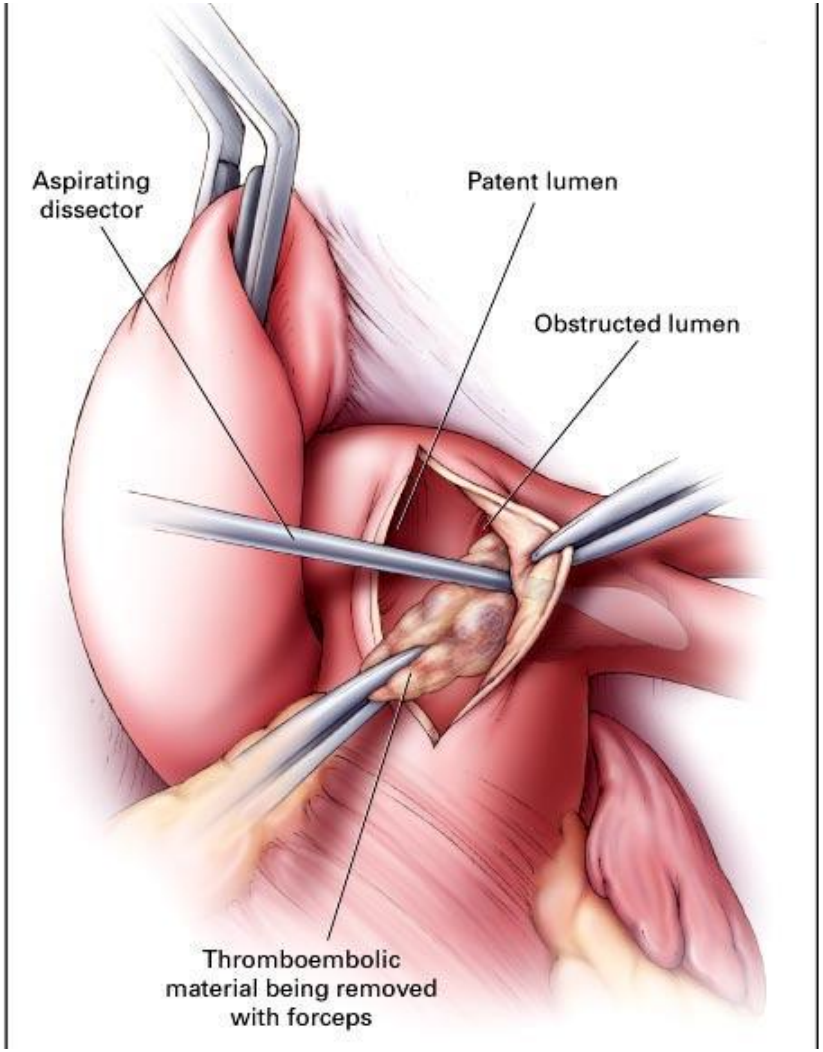
Kim NH et al. ERJ 2018

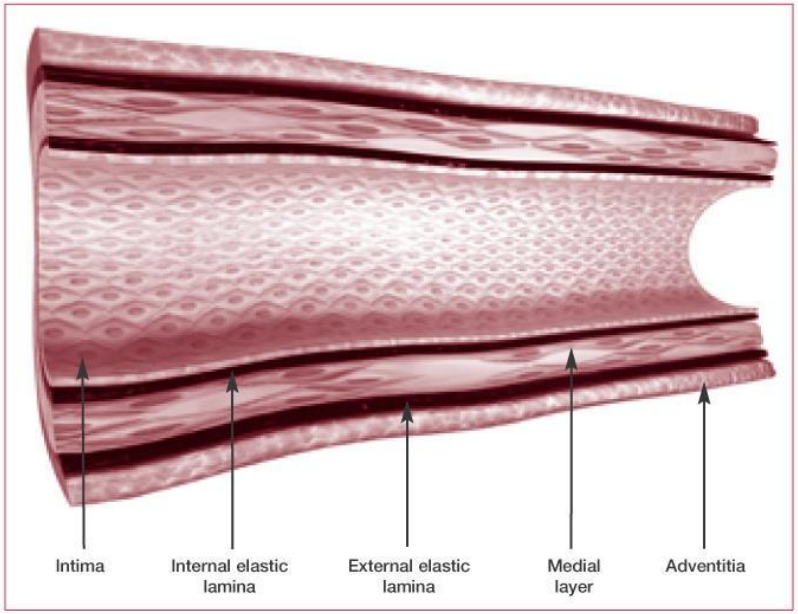
6th WORLD SYMPOSIUM PULMONARY HYPERTENSION

CTEPH management

- **Pulmonary endarterectomy**
- **Balloon Pulmonary Angioplasty**
- **PH-targeted medical therapy**

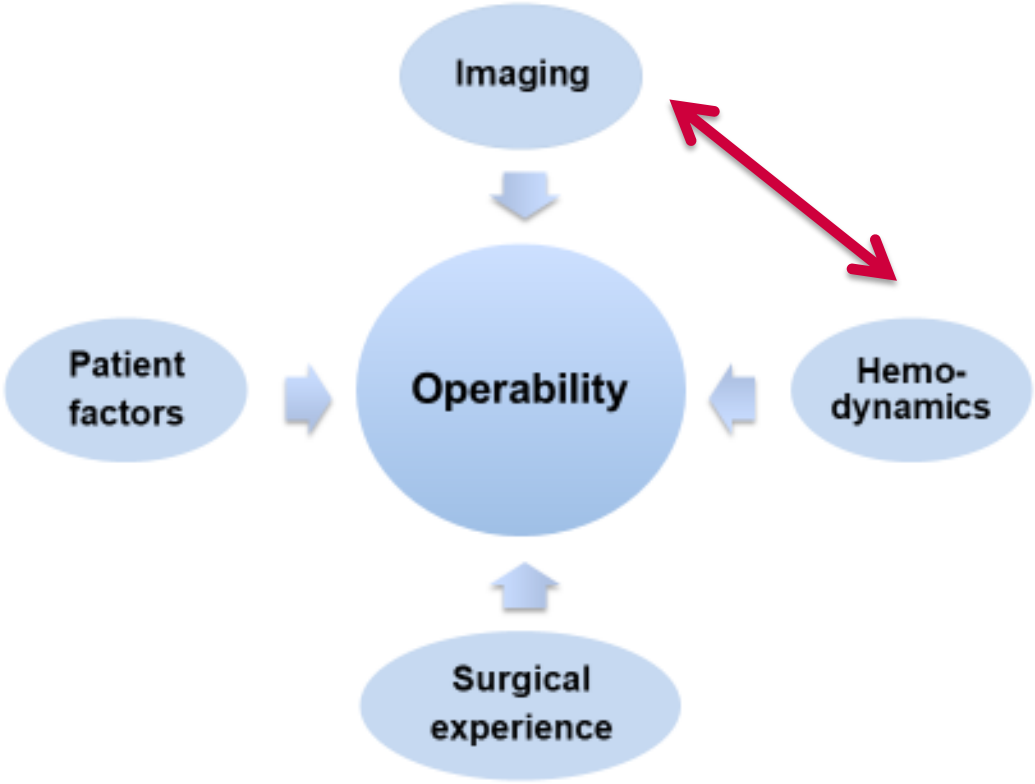
PULMONARY ENDARTERECTOMY





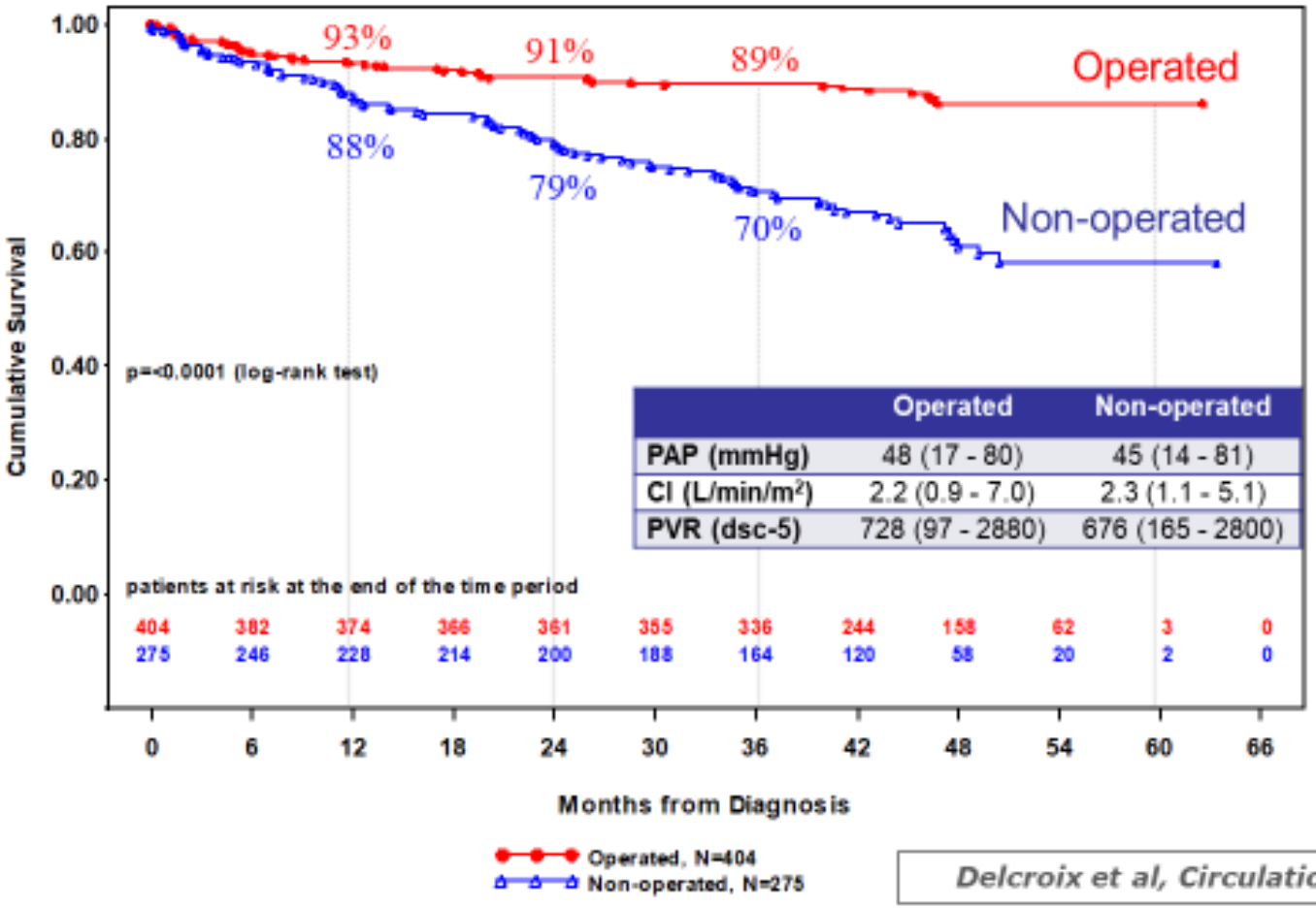
- **Performed during deep hypothermic circulatory arrest**
- **20 mins to complete each PA**
- **Removal of the intraluminal obstruction, intima and a portion of the medial layer of the pulmonary artery**

FROM CTEPH DIAGNOSIS TO OPERABILITY



Kim, *et al. JACC* 2013

KM SURVIVAL ESTIMATES: OPERATED AND NON-OPERATED

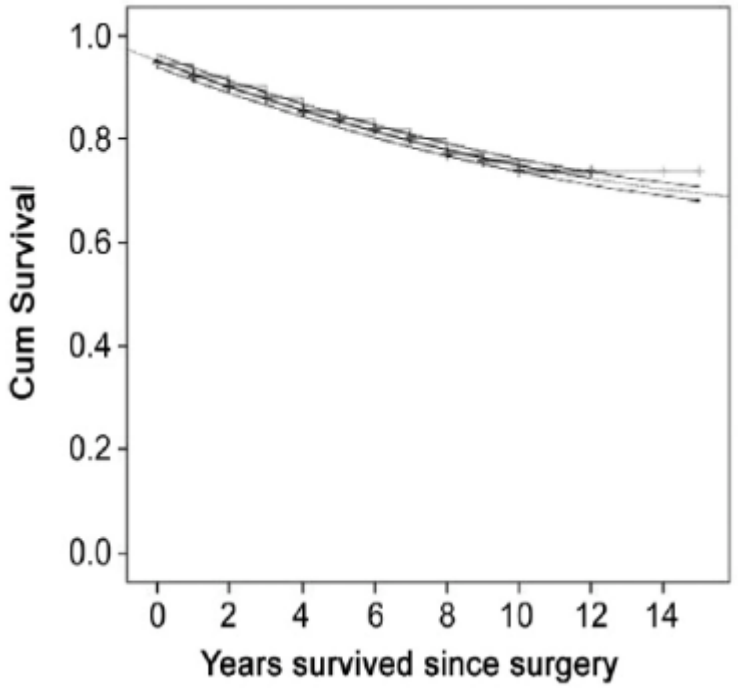


	Operated	Non-operated
PAP (mmHg)	48 (17 - 80)	45 (14 - 81)
CI (L/min/m^2)	2.2 (0.9 - 7.0)	2.3 (1.1 - 5.1)
PVR (dsc-5)	728 (97 - 2880)	676 (165 - 2800)

Delcroix et al, Circulation 2016

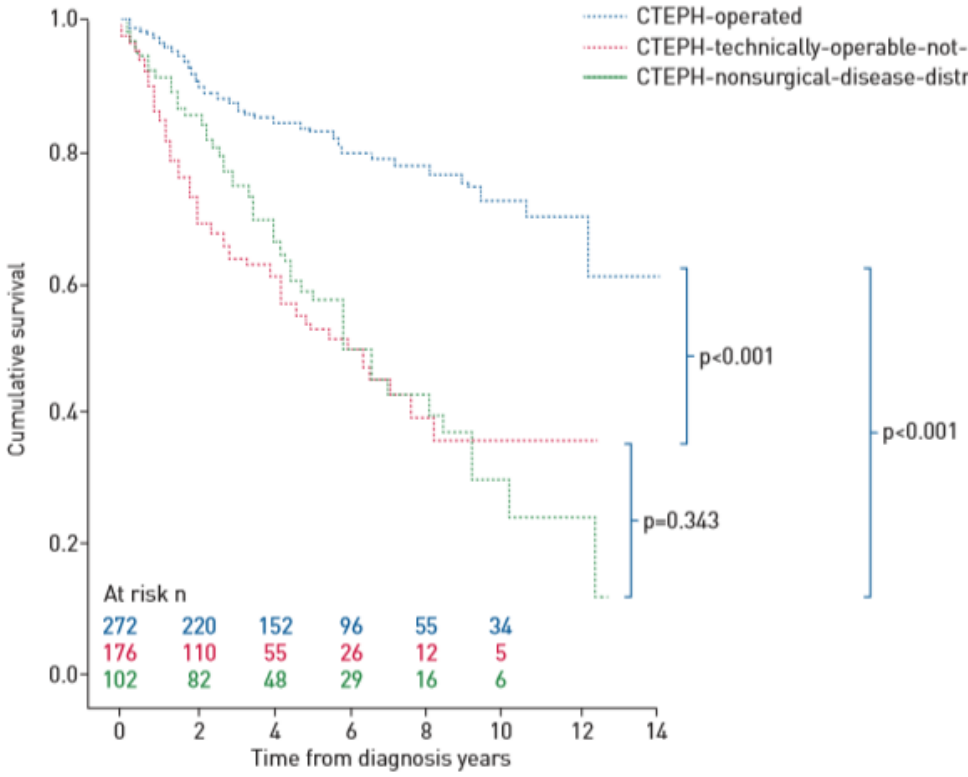
Long term survival data

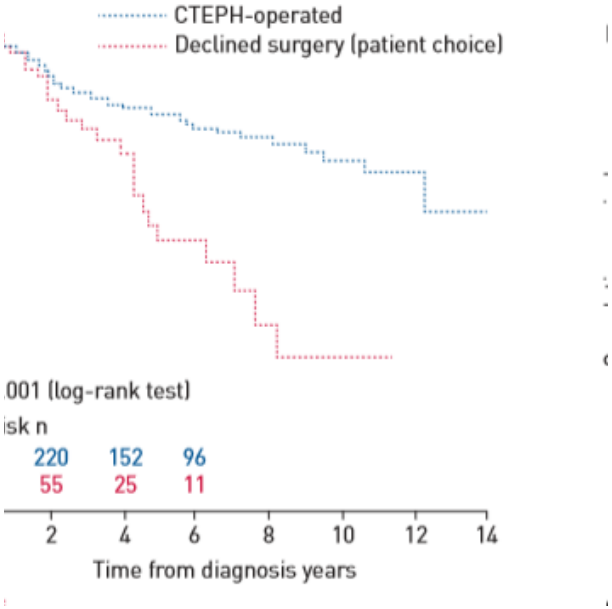
In-hospital mortality 2.2%
10-year-survival 75%



Madani M et al. Ann Thorac Surg 2012;94:97-103

Survival by technical operability and patient choice





Quadery SR et al. ASPIRE registry, ERJ 2018

Benefit/risk assessment for PEA

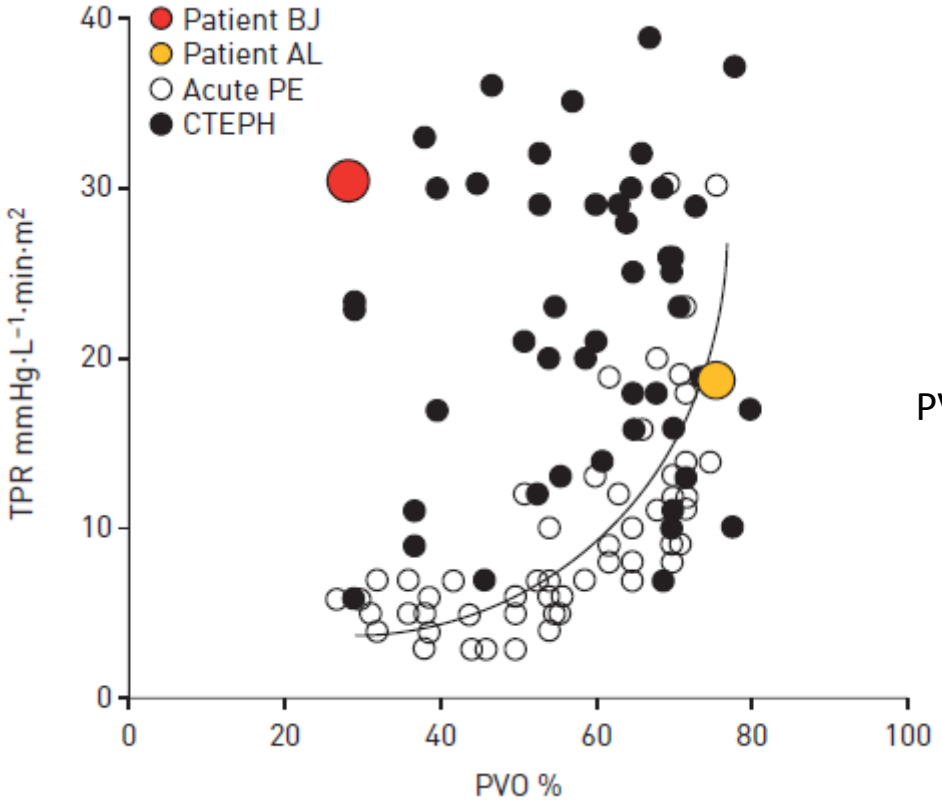
not indications/contraindications

TABLE 2 Favourable risk–benefit assessment for pulmonary endarterectomy

Characteristics	Lower risk with predictable good long-term outcome	Higher risk with less predictable long-term outcome (not contraindications)
History	History of DVT/PE	No history of DVT/PE
Examination	No signs of right heart failure	Signs of right heart failure
Comorbidity	None	Significant concomitant lung or left heart disease
Functional limitation	Functional class II or III	Functional class IV
Imaging	Clear disease concordant on all images	Inconsistency on imaging modalities
Type of disease	Bilateral lower lobe disease	No disease appreciable in lower lobes
Haemodynamics	PVR <1000 dyn·s·cm^{-5}, in proportion to site and number of obstructions on imaging; higher PA pulse pressure	PVR >1200 dyn·s·cm^{-5}, out of proportion to site and number of obstructions on imaging; higher PA diastolic pressure

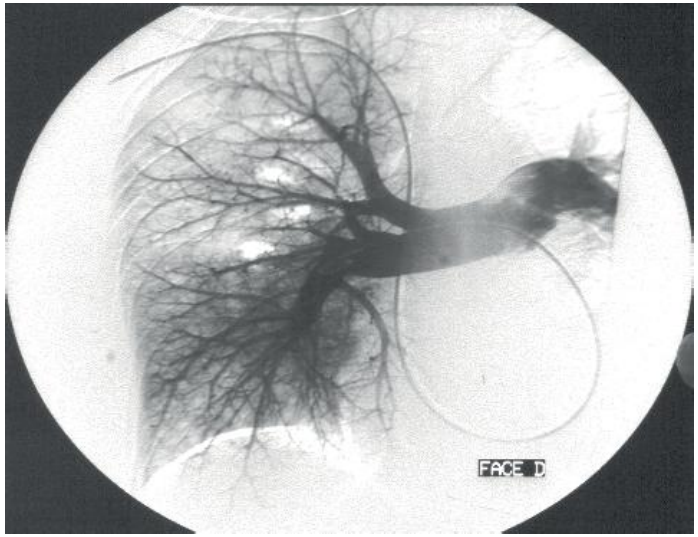
DVT: deep vein thrombosis; PE: pulmonary embolism; PVR: pulmonary vascular resistance; PA: pulmonary artery.

Kim NH et al. ERJ 2018

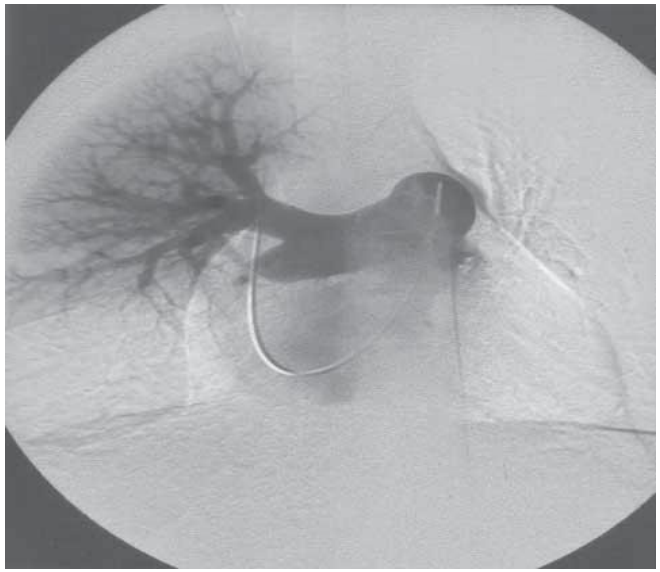


Pulmonary vascular obstruction score%

PVO 35%

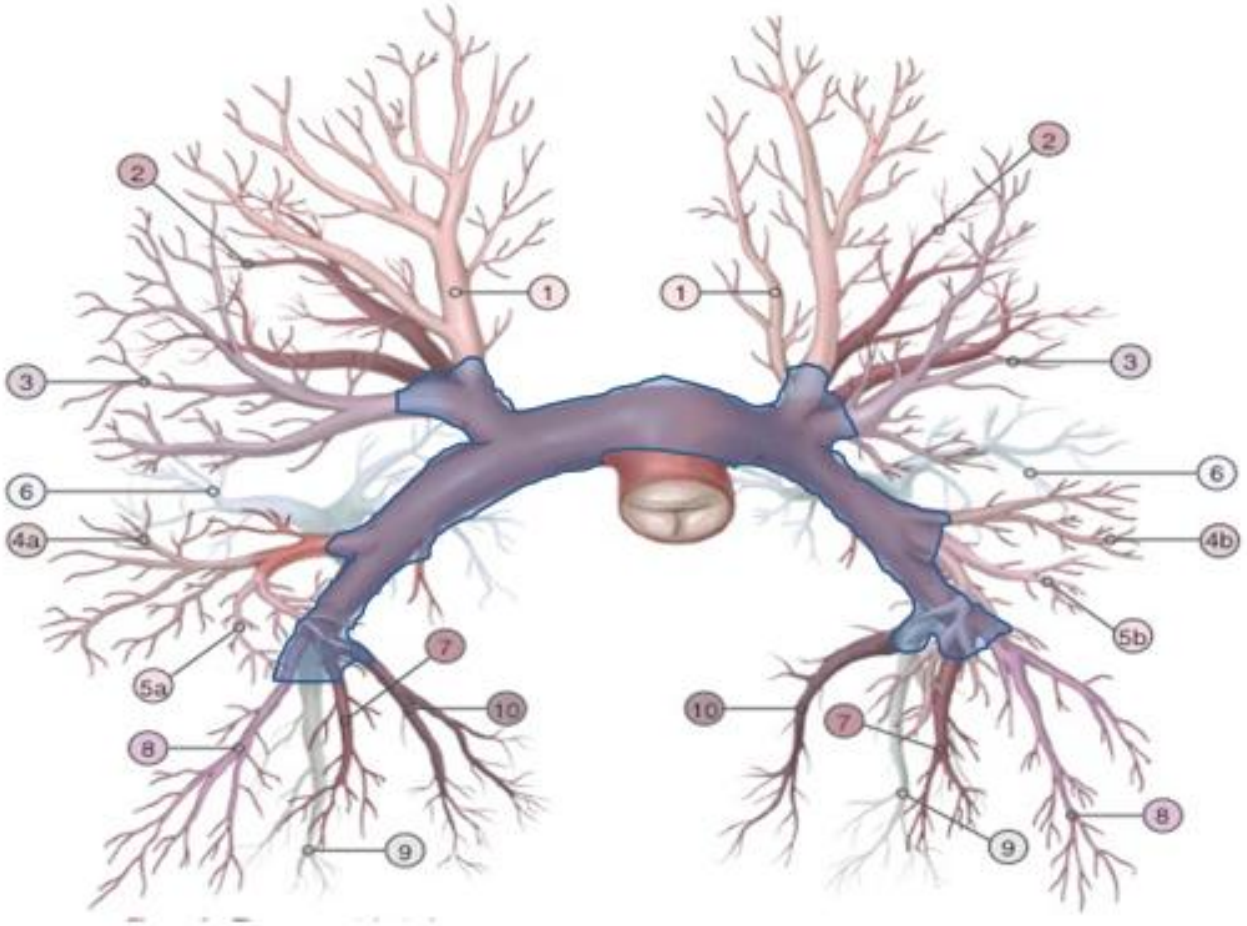


PVO 75%



Azarian R et al. J Nucl Med 1997; 38: 980–983

LIMITS OF OPERABILITY (?)

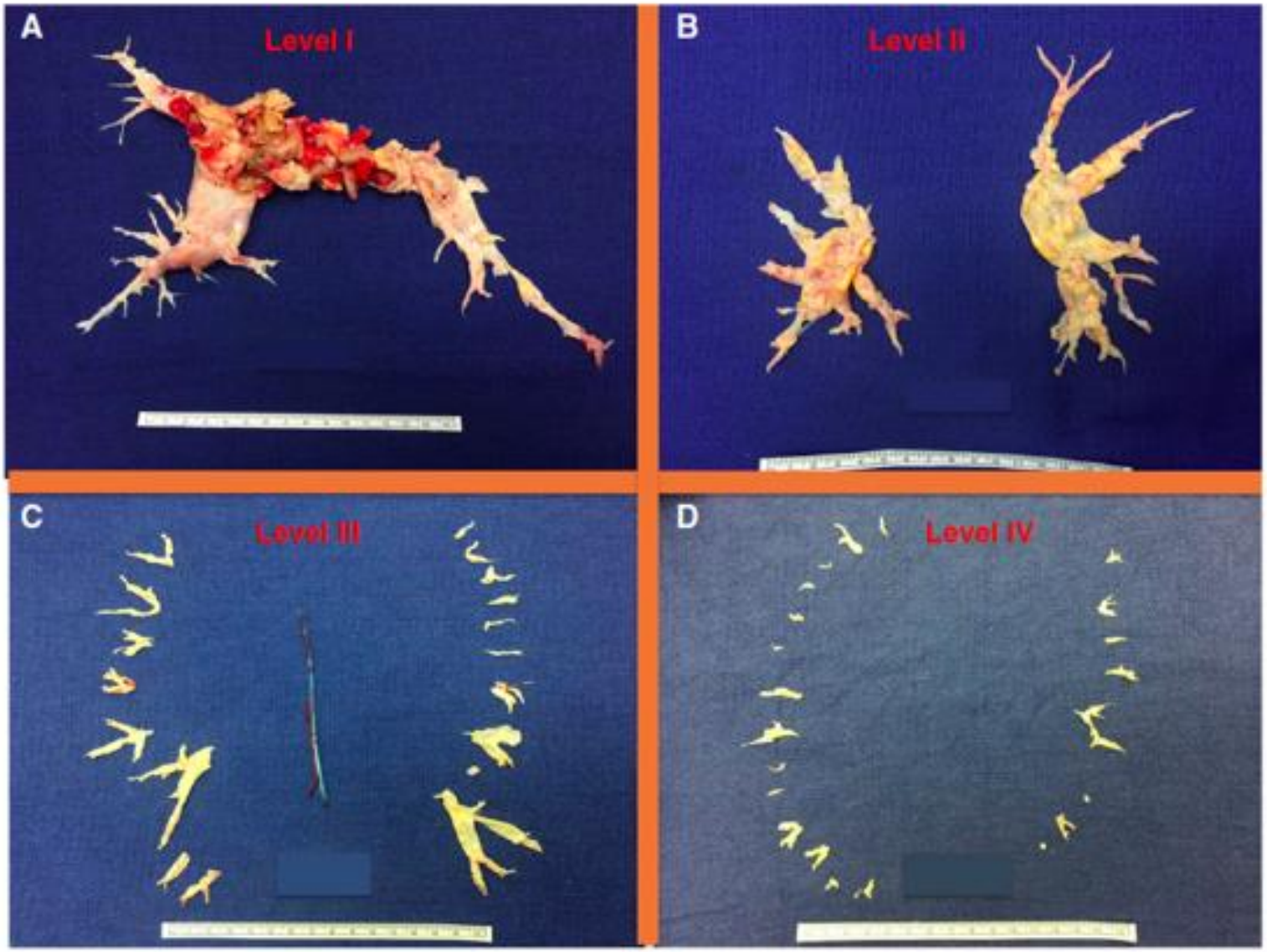


UCSD surgical classification

TABLE 3 University of California San Diego chronic thromboembolism (CTE) surgical classification

Surgical levels	Location of CTE
Level 0	No evidence of thromboembolic disease in either lung
Level I	CTE starting in the main pulmonary arteries
(Level IC)	(Complete occlusion of one main pulmonary artery with CTE)
Level II	CTE starting at the level of lobar arteries or in the main descending pulmonary arteries
Level III	CTE starting at the level of the segmental arteries
Level IV	CTE starting at the level of the subsegmental arteries

Madani M et al. Ann Am Thorac Soc 2016, Kim NH et al. ERJ 2018



Madani et al, Ann ATS 2016

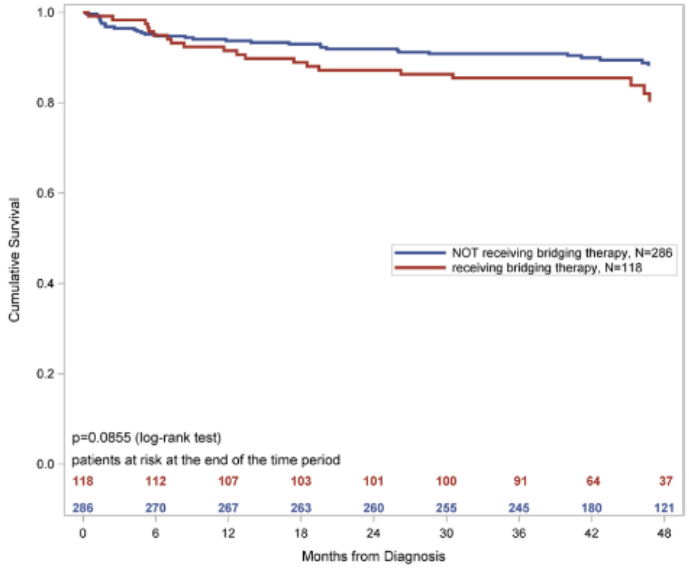
Impact on bridging medical therapy in operable CTEPH

- Registry: worse observed survival

Table 4. Independent Correlates of Mortality for Operated and Not-Operated Patients

	Operated (n=346)			Not-Operated (n=219)		
Covariate	HR	95% CI	*P* Value	HR	95% CI	*P* Value
NYHA class III vs I–II				2.43	1.00–5.89	0.0489
NYHA class IV vs I–II	4.16	1.49–11.62	0.0065	4.76	1.76–12.88	0.0021
RAP	1.34	0.95–1.90	0.0992	1.50	1.20–1.88	0.0004
PAP	0.67	0.47–0.94	0.0226			
History of acute VTE	0.48	0.24–0.97	0.0413			
History of cancer	3.02	1.36–6.69	0.0065	2.15	1.18–3.94	0.0129
Coronary disease/myocardial infarction	–			1.81	1.00–3.28	0.0492
CHF or LV dysfunction	–			1.98	1.02–3.83	0.0440
Dialysis-dependent renal failure	11.52	1.42–93.48	0.0221	–		
COPD	–			2.14	1.22–3.73	0.0075
PAH-targeted therapy started at diagnosis	2.62	1.30–5.28	0.0072	–	–	–
Postoperative PH	3.66	1.72–7.82	0.0008	–	–	–
All other complications	3.82	1.72–8.51	0.0010	–	–	–
Additional cardiac procedure	3.10	1.54–6.24	0.0015	–	–	–

Cox multivariable analysis of operated and not-operated patients, separately. CHF indicates congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LV, left ventricle; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RAP, right atrial pressure; and VTE, venous thromboembolism



Delcroix M et al. Circulation 2016

- PEA bridging study: NCT0327357

Operable patients with high PVR, 1:1 with riociguat or placebo for 3 months

Primary endpoint: change from baseline PVR

Impact of medical therapy before PEA in operable patients

- Retrospective analysis of CTEPH patients referred for PEA to UCSD (2005-2007)
- 31% of patients on PAH-targeted therapy
- Significant delay for referral

	2005		2006		2007	
	n	%	n	%	n	%
Group						
Control	141	80.11	107	68.15	97	62.99
PHT	35	19.89	50	31.85	57	37.01
Medication						
Bosentan	14	40.00	17	34.00	24	42.11
Sildenafil	14	40.00	31	62.00	40	70.18
Epoprostenol	7	20.00	7	14.00	5	8.77

	PHT Group (n=111)	Control Group (n=244)	*P*
Median age, y (IQR)	51 (39–62.5)	52 (37–64)	0.84
Sex, M/F	52/59	121/123	0.63
Median time to referral, mo (IQR)	8.9 (4–13)	4.4 (2.5–7)	<0.01
Anticoagulation	110 (99.1)	240 (98.4)	0.89
Diuretic	65 (58.6)	114 (46.7)	0.04
Spironolactone	24 (21.6)	18 (7.4)	<0.01
Digoxin	16 (14.4)	15 (6.1)	0.01
Dopamine	3 (2.7)	2 (0.8)	0.16

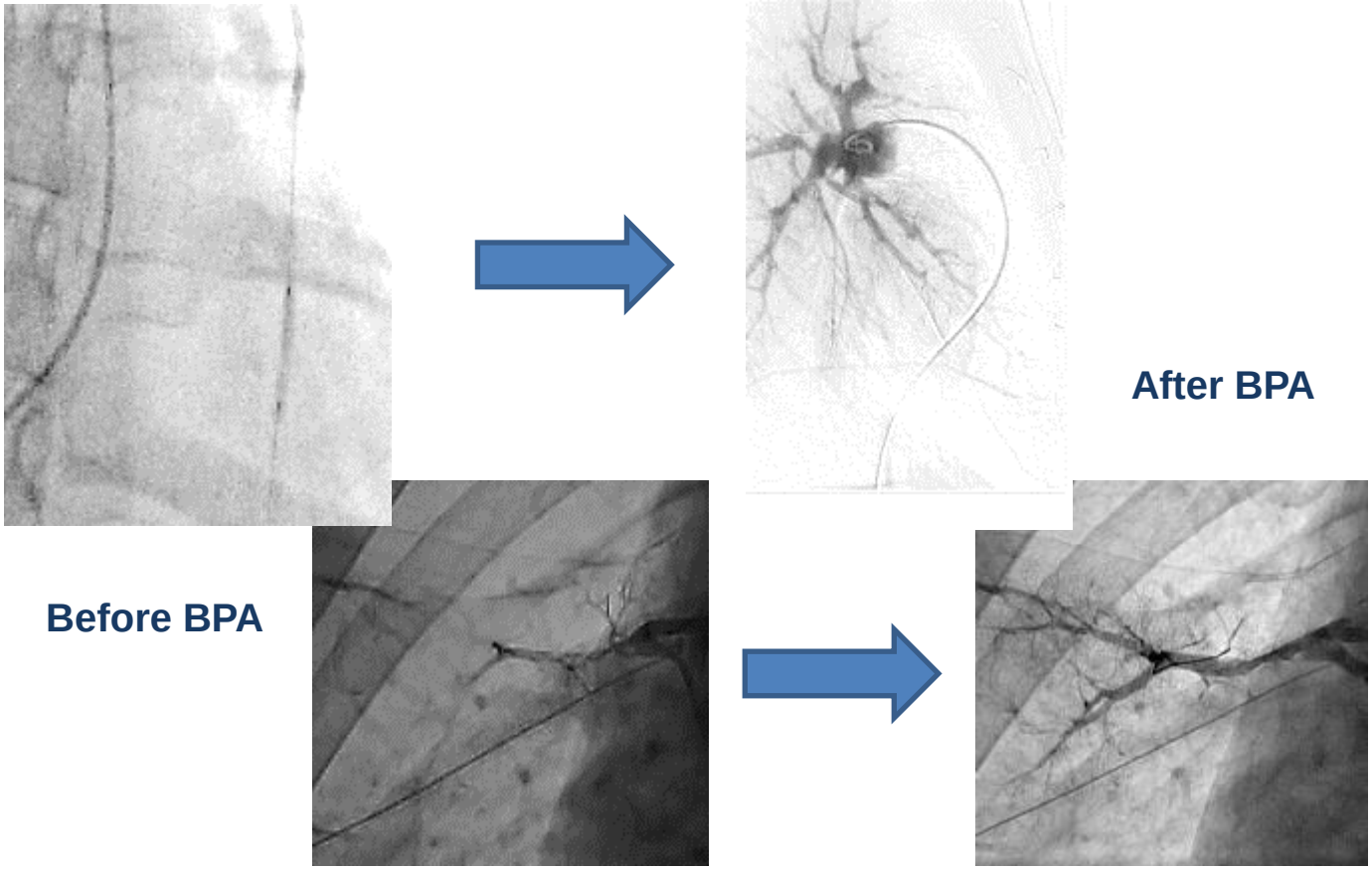
Jensen KW, *et al. Circulation* 2009;120:1248-54.

6th WORLD SYMPOSIUM PULMONARY HYPERTENSION

CTEPH management

- **Pulmonary endarterectomy**
- **Balloon Pulmonary Angioplasty**
- **PH-targeted medical therapy**

Balloon Pulmonary Angioplasty in CTEPH



Balloon Pulmonary Angioplasty for Inoperable CTEPH[a]

- BPA was first developed for treating PA congenital stenosis[b]
- A first case series of 18 patients from the US was reported in 2001 with a treatment effect less than those obtained with PEA, and with a high rate of severe complication[c]
- Over the last 10 years, several centers in Japan (Okayama, Osaka, Kobe, Tokyo, and others) have refined the BPA procedure leading to improvement in efficacy and safety of this treatment option for inoperable patients with CTEPH[d]

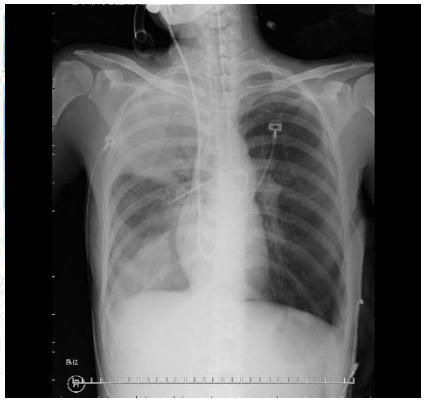
a. Kim NH, et al. *Eur Respir J*. 2018. [Epub ahead of print]; b. Lock JE, et al. *Circulation* 1983;67:962-967; c. Feinstein JA, et al. *Circulation.* 2001;103:10-13; d. Ogawa A, et al. *Front Cardiovasc Med*. 2015;2:4.

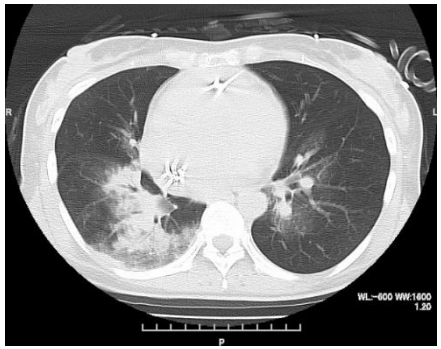
WORLD SYMPOSIUM PULMONARY HYPERTENSION

Improving results with BPA

Study	Year	Study location	Patients	Mean age (yrs)	Study duration (months)	Medical therapy before BPA	Effect in PVR	Lung injury	In-hospital mortality	Long-term outcomes
Feinstein et al.	2001	USA	18	51.8	36	0%	-23% (TPR)	61%	5.6%	89% at 34.2 months
Mizoguchi et al.	2012	Japan	68	62.2	26	100%	-65%	60%	1.5%	97% at 2.2 yr
Kataoka et al.	2012	Japan	29	62.3	6	100%	NR	53%	3.4%	NR
Andreassen et al.	2013	Norway	20	60	51	10%	-33%	35%	10%	85% at 51 months
Fukui et al.	2014	Japan	20	67	12	75%	-45%	0%	0%	NR
Roik et al	2016	Poland	11	76	NR	54%	-48%	18%	0%	NR
Ogo et al.	2017	Japan	80	68	12	61%	-57%	17%	0%	NR
Ogawa et al.	2017	Japan	249	61.5	14	72%	-66%	35%	3%	94.5% at 2 year
Aoki et al.	2017	Japan	77	65	60	96%	-64%	23%	0%	98.4% at 5 year
Olsson et al.	2017	Germany	56	65	14	59% PDE5 inhibitor	-26%	9%	0%	NR
Average			628 (total)	63.3	25.7	72.5	-55%	29%	1.8%	

Classification of BPA complications





During the procedure
Vascular injury[1] with/without hemoptysis
Wire perforation
Balloon over- dilatation
High pressure contrast injection
Vascular dissection
Allergic reaction to contrast
Adverse reaction to conscious sedation/local anesthesia
After the procedure
Lung injury[2] (radiographic opacity with/without hemoptysis, with/without hypoxemia)
Renal dysfunction
Access site problems

Signs of vascular injury: extravasation of contrast, hypoxemia, cough, tachycardia, increased pulmonary arterial pressure
Causes of lung injury: Vascular injury >> Reperfusion lung injury

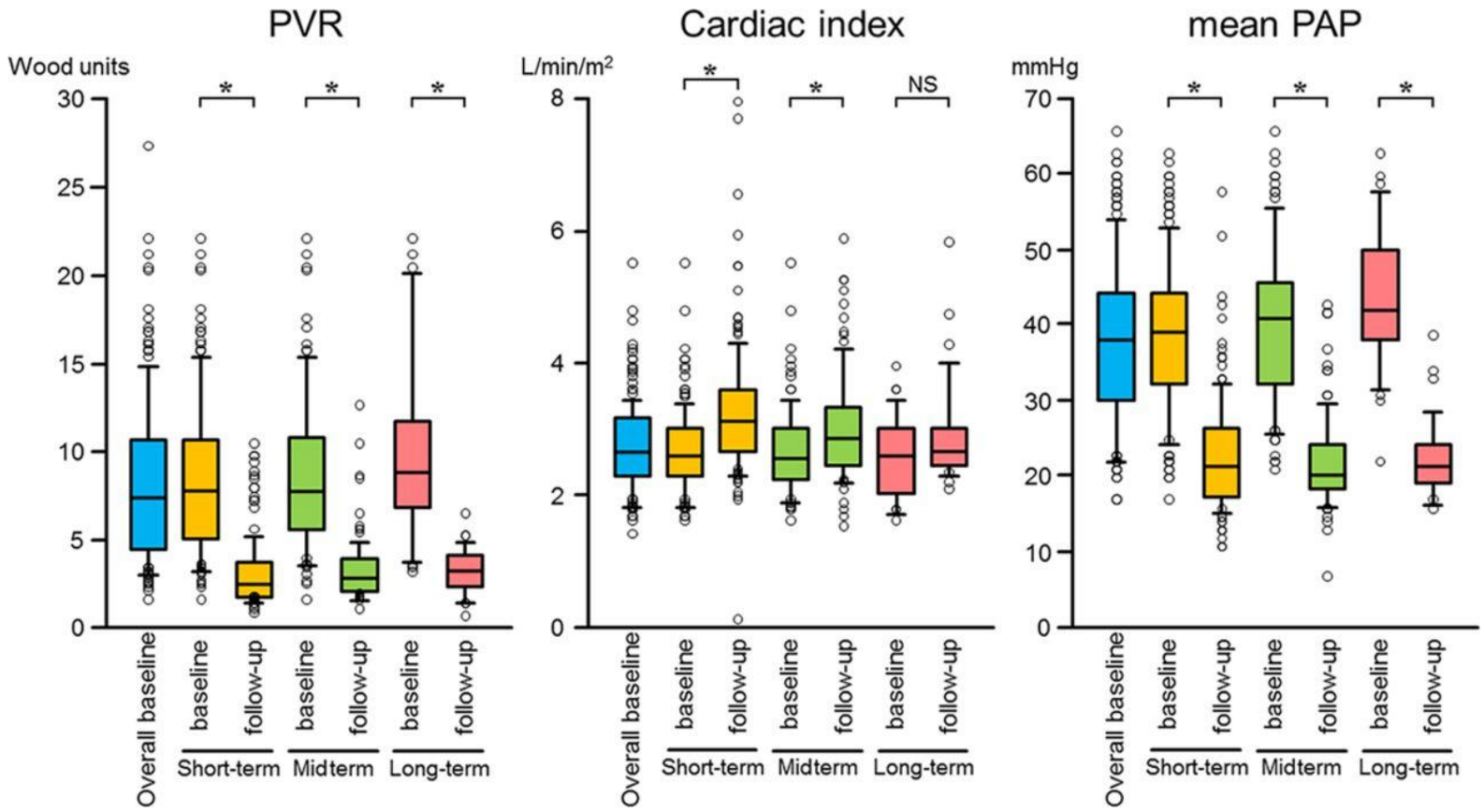
Kim NH et al. ERJ 2018

Advances in BPA therapy

	2013	2018
Publications	3	166
Sites	Japan	International
Patient number	100	>1000
BPA targets	Limited segments	All segments
Procedural risk	High	Lower
Short-term efficacy:		
Expert center	Intermediate	High
Non-expert center	-	Intermediate
Long-term outcome	-	<5 years

Long-Term Outcomes After Percutaneous Transluminal Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension

Takumi Inami, MD*
Masaharu Kataoka, MD*
Ryoji Yanagisawa, MD
Haruhisa Ishiguro, MD
Nobuhiko Shimura, MD
Keiichi Fukuda, MD
Hideaki Yoshino, MD
Toru Satoh, MD



170 pts, 649 sessions

Long-Term Outcomes After Percutaneous Transluminal Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension

Circulation. 2016;134:2030–2032

CTEPH management

- **Pulmonary endarterectomy**
- **Balloon Pulmonary Angioplasty**
- **PH-targeted medical therapy**

Randomized controlled trials (RCTs) in CTEPH

TABLE 5 Pulmonary hypertension-targeted medical therapy randomised controlled trials in chronic thromboembolic pulmonary hypertension

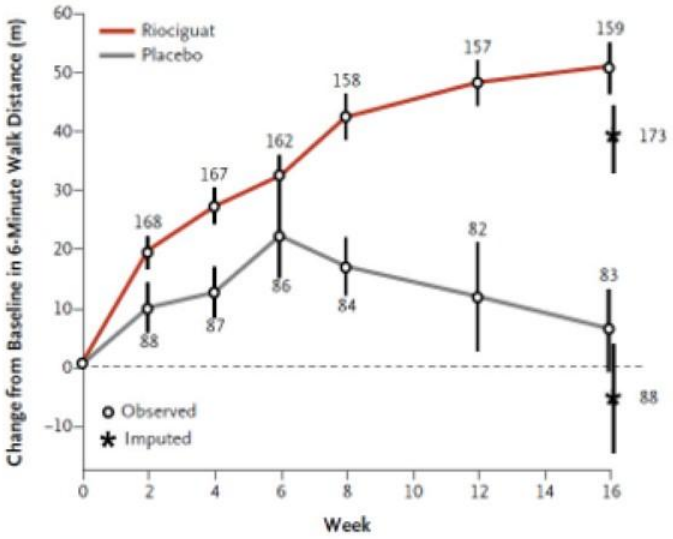
Trial [ref.]	Study drug	Duration weeks	Subjects n	NYHA FC	6MWD m	6MWD effect m	PVR baseline dyn·s·cm^{-5}	PVR effect %
BENEFIT [73]	Bosentan	16	157	II–IV	342±84	+2^{NS}	783 (95% CI 703–861)	−24
CHEST-1 [55]	Riociguat	16	261	II–IV	347±80	+46	787±422	−31
MERIT-1 [74]	Macitentan	16 (24$^{\#}$)	80	II–IV	352±81	+34	957±435	−16

Data are presented as n or mean±SD, unless otherwise stated. NYHA FC: New York Heart Association Functional Class; 6MWD: 6-min walk distance; PVR: pulmonary vascular resistance; NS: non-significant. All three trials had an adjudication process for operability. $^{\#}$: 6MWD measured at 24 weeks.

Kim NH et al. ERJ 2018

CHEST-1

Riociguat for the Treatment of CTEPH

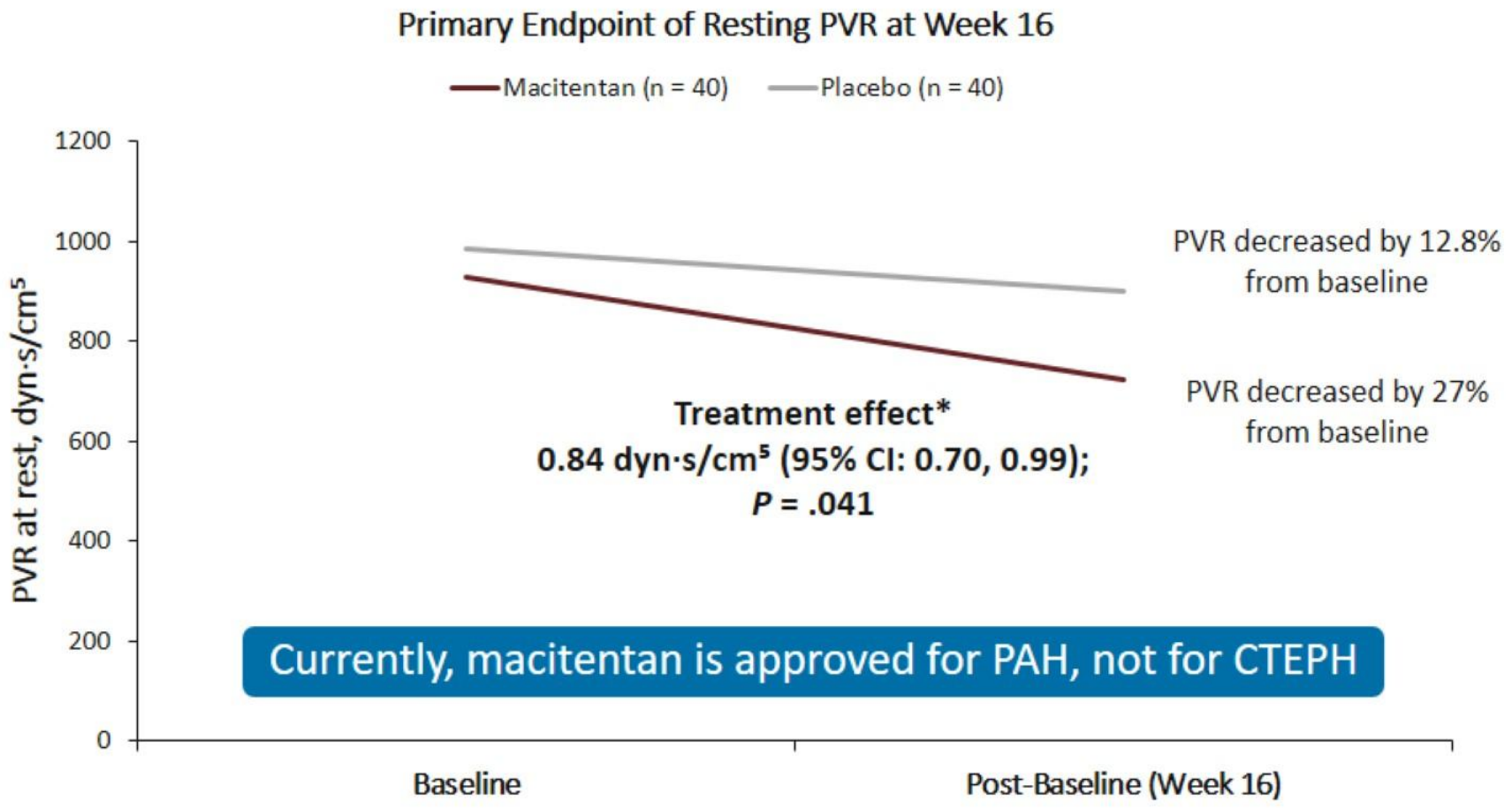


Riociguat approved for the treatment of inoperable CTEPH or residual PH after PEA

End Point	Placebo			Riociguat			P Value
	No. of Patients	Baseline	Change	No. of Patients	Baseline	Change	
Secondary end points							
Pulmonary vascular resistance (dyn·sec·cm^{-5})	82	779±401	23±274	151	791±432	−226±248	<0.001
NT-proBNP (pg/ml)	73	1706±2567	76±1447	150	1508±2338	−291±1717	<0.001
WHO functional class§	87	0 patients in class I, 25 (29%) in class II, 60 (69%) in class III, 2 (2%) in class IV	13 patients (15%) moved to lower class (indicating improvement), 68 (78%) stayed in same class, 6 (7%) moved to higher class	173	3 patients (2%) in class I, 55 (32%) in class II, 107 (62%) in class III, 8 (5%) in class IV	57 patients (33%) moved to lower class (indicating improvement), 107 (62%) stayed in same class, 9 (5%) moved to higher class	0.003

Ghofrani HA, et al. *N Engl J Med*. 2013;369:319-329.

MERIT-1 (Phase 2 Double-Blind Study)
Macitentan in 80 Patients With Inoperable CTEPH



*Expressed as the macitentan:placebo ratio of geometric means (95% CI) was calculated by analysis of covariance on the log transformed week 16 value.

Ghofrani HA, et al. *Lancet Respir Med*. 2017;5:785-794.

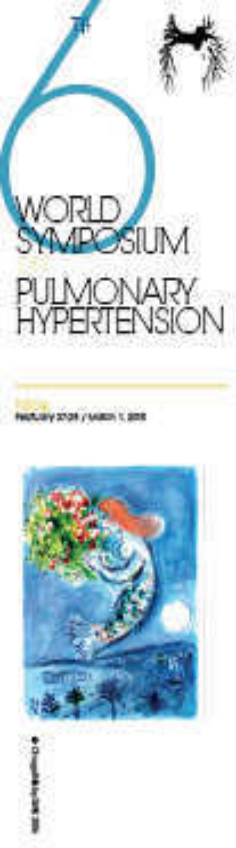
Effects of PH drug therapy on exercise capacity and hemodynamics (RCT)

combination therapy

Study drug (author year)	Duration months	n	NYHA class	6MWD m mean±SD	Effect meters	PVR dyn.s.cm^{-5}	Effect % PVR
Macitentan (Ghofrani 2017)	4 (6$^{\$}$)	80	II - IV	352 ± 81	34	957 ± 435	-16
PDE5 inhib plus Macitentan		49			32		-16

$^{\$}$ *6MWD measured at 6 months*

Ghofrani et al, Lancet Respir Med 2017



Role of medical therapy

Current recommendations

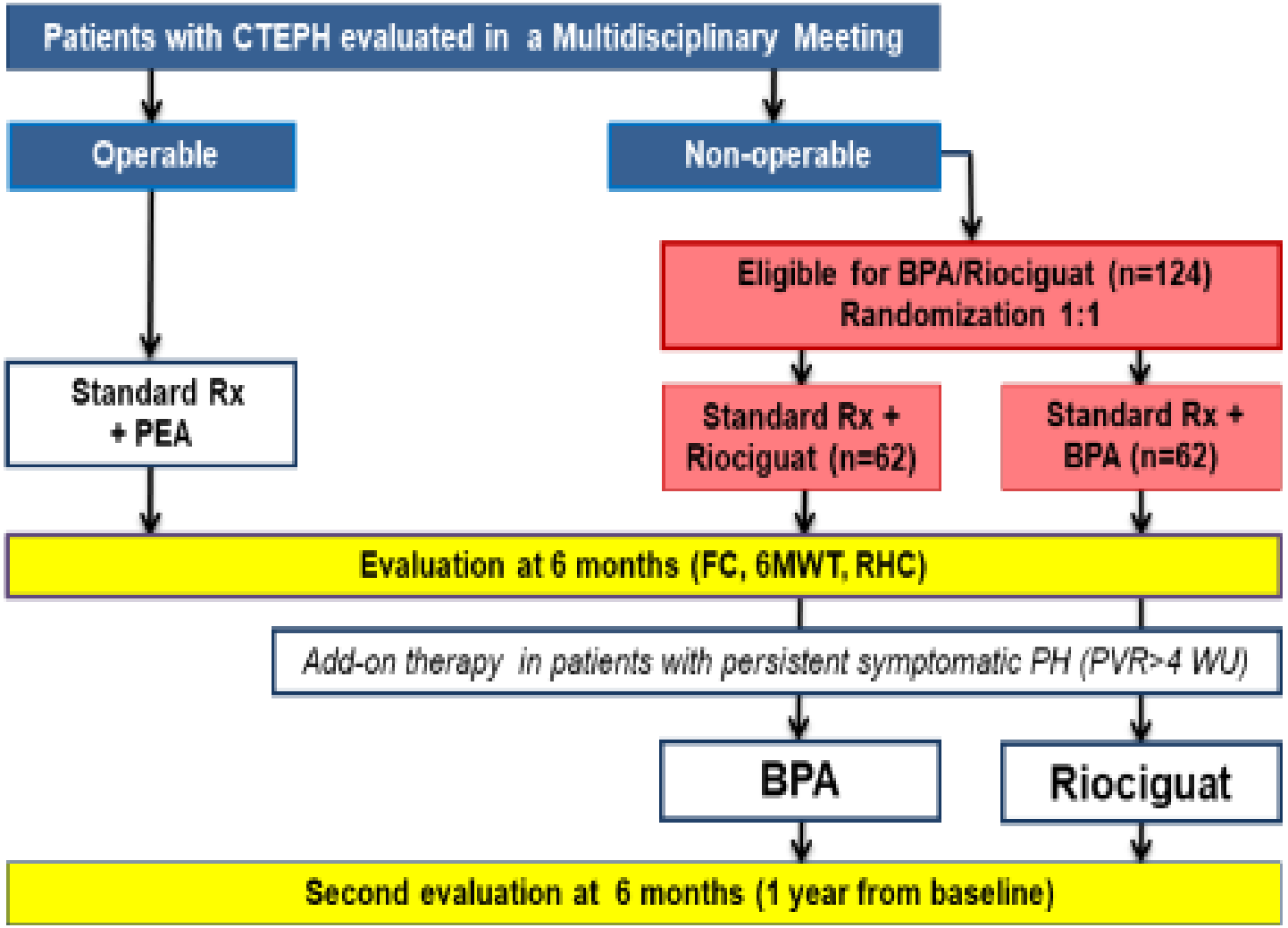
CTEPH subgroups	Recommendations
Technical inoperable	Consider medical therapy* (RCT 1,2)
Persistent/Recurrent	Consider medical therapy* (RCT 1)
Refusing surgery	No data
Medically inoperable	No data
Bridge to PEA	Little data, RCT pending
Bridge to BPA	No RCT data
CTED	No data
All	Anticoagulation lifelong. No RCT

**One currently approved drug, Riociguat*

[1] *Ghofrani et al., NEJM 2013*

[2] *Ghofrani et al. Lancet Respir Med 2017*

RACE: Study design



Standard Rx: VKAediuretics±oxygen;
PEA= pulmonary endarterectomy;
BPA= balloon pulmonary angioplasty

Persistent / recurrent PH following PEA

- Due to incomplete resection, distal vasculopathy, inaccessible lesions, or re-occlusion
- Most important cause of postoperative morbidity and mortality

- No consensus on the definition

Reference	N	Criteria	Prevalence
Mayer E, *J Thorac Cardiovasc Surg* 2011	386	mPAP >25 mmHg end ICU	**17%**
Freed DH, *J Thorac Cardiovasc Surg* 2011	314	mPAP >30 mmHg at 3 mo	**31%**
Madani MM, *Ann Thorac Surg* 2012	500	PVR >500 dyne.s.cm^{-5} end ICU	**6%**
Skoro-Sayer N, *Circulation* 2009	103	PVR >550 dyne.s.cm^{-5} end ICU	**14%**
Corsico AG, *Am J Respir Crit Care Med* 2008	157	PVR >500 dyne.s.cm^{-5} at 4y	**24%**

Potential implications for follow-up after PEA

- 51% of pts have mPAP≥25mmHg when measured by RHC at 3 to 6 months post-PEA

3-6 months after PEA surgery	Therapeutic decision
Haemodynamics normalized	No additional therapy needed (risk of recurrent PH ≈ 1%)
Asymptomatic, mild residual PH after 3-6 months (PAPm <30 mmHg; PVR <425 dyn)	Probably no additional treatment needed
Asymptomatic, moderate-to-severe residual PH (PAPm ≥30 mmHg, PVR ≥425 dyn)	Consider medical therapy, balloon pulmonary angioplasty
Symptomatic, any degree of residual PH	Consider medical therapy, balloon pulmonary angioplasty

Cannon JE et al. Circulation 2016;133:1761-71; Hoeper MM Circulation 2016;133:1731-3

Persistent/Recurrent PH post PEA

Recommendation

- Long term follow-up is important
- Consider treatment reassessment (medical/BPA/redo PEA)

  if symptomatic II-IV and

  mPAP≥25mmHg, PVR≥300dyn.s.cm^{-5} at >6months post PEA

Cannon JE et al. Circulation 2016, Kim NH et al. ERJ 2018

CTEPH Diagnosis
Continue Lifelong Anticoagulation

↓

Treatment Assessment by an Expert CTEPH Team [1,2]

↓

Operable → **Pulmonary Endarterectomy** (Treatment of Choice)

Non-operable → **Targeted medical therapy with or without BPA** [2,3]

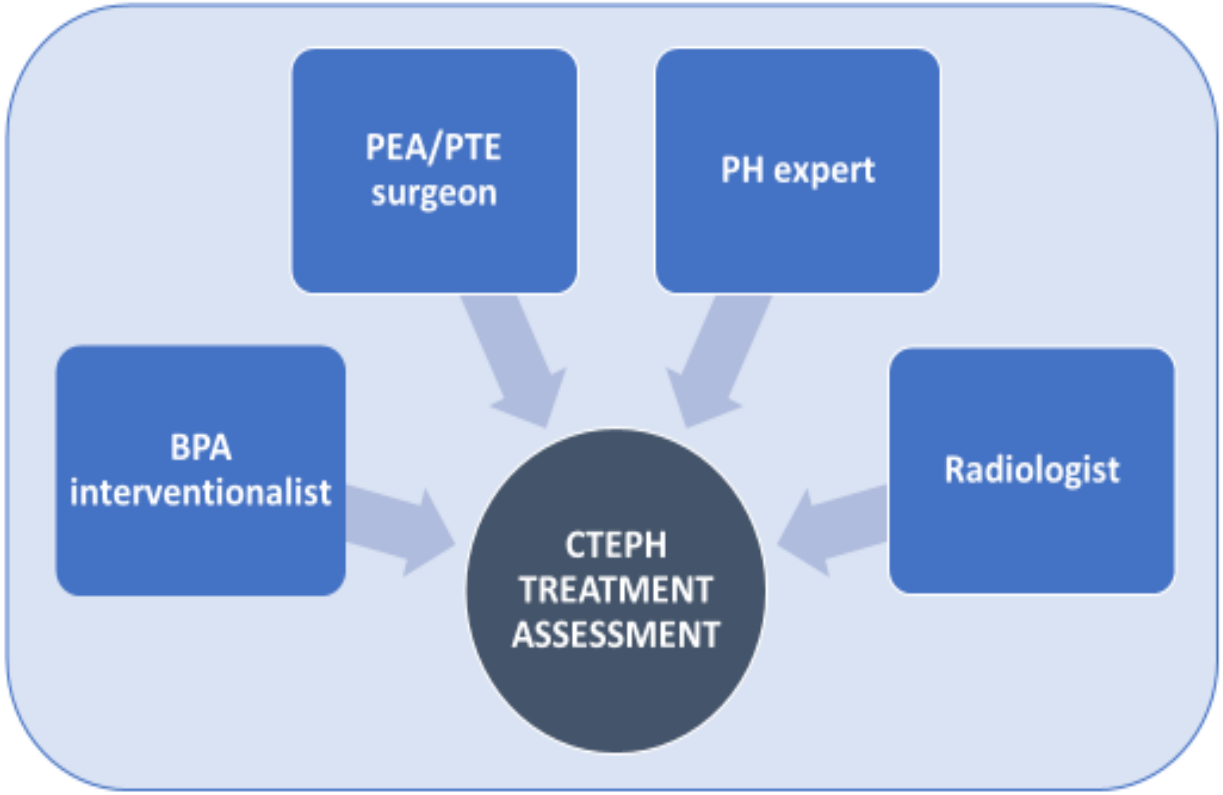
↓

Persistent/recurrent symptomatic pulmonary hypertension

[1] Multidisciplinary: PEA/PTE surgeon, PH expert, BPA interventionalist, and radiologist
[2] Expert center defined: > 50 PEA/PTE, > 100 BPA sessions per year
[3] BPA without medical therapy can be considered in selected cases

6th WSPH Nice 2018

All CTEPH patients should be assessed by a multidisciplinary team



Definition of expert surgical centre

- surgical mortality (<5%)
- surgical volume (more than 50 PEAs per year)
- ability to perform segmental endarterectomy

**evaluate and offer any/all established treatment modalities according to individual need

Jenkins D et al. Eur Respir Rev 2017, Kim NH et al. ERJ 2018

Also valid for CTED management?

Continue Lifelong Anticoagulation

Treatment Assessment by an Expert CTEPH Team [1,2]

Operable

Non-operable

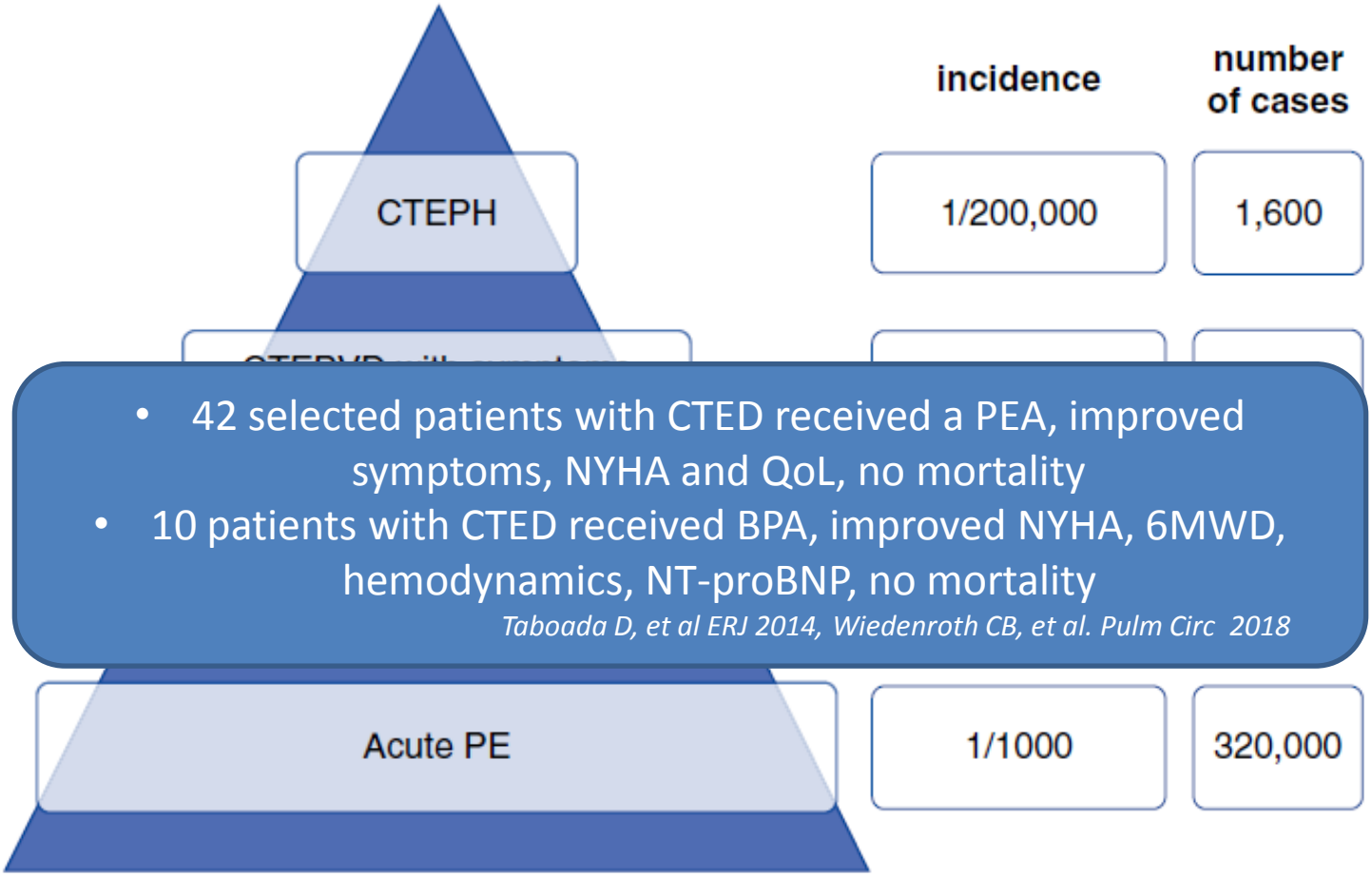
Pulmonary Endarterectomy
(Treatment of Choice)

Targeted medical therapy with or without BPA [2,3]

Persistent/recurrent symptomatic pulmonary hypertension

[1] Multidisciplinary: PEA/PTE surgeon, PH expert, BPA interventionalist, and radiologist
[2] Expert center defined: > 50 PEA/PTE, > 100 BPA sessions per year
[3] BPA without medical therapy can be considered in selected cases

CTED treatment



- 42 selected patients with CTED received a PEA, improved symptoms, NYHA and QoL, no mortality
- 10 patients with CTED received BPA, improved NYHA, 6MWD, hemodynamics, NT-proBNP, no mortality

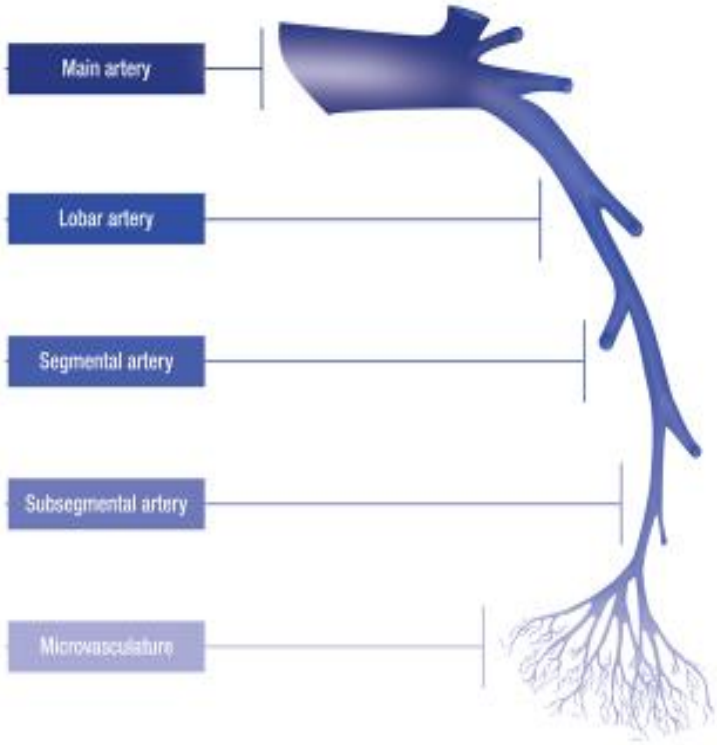
Taboada D, et al ERJ 2014, Wiedenroth CB, et al. Pulm Circ 2018

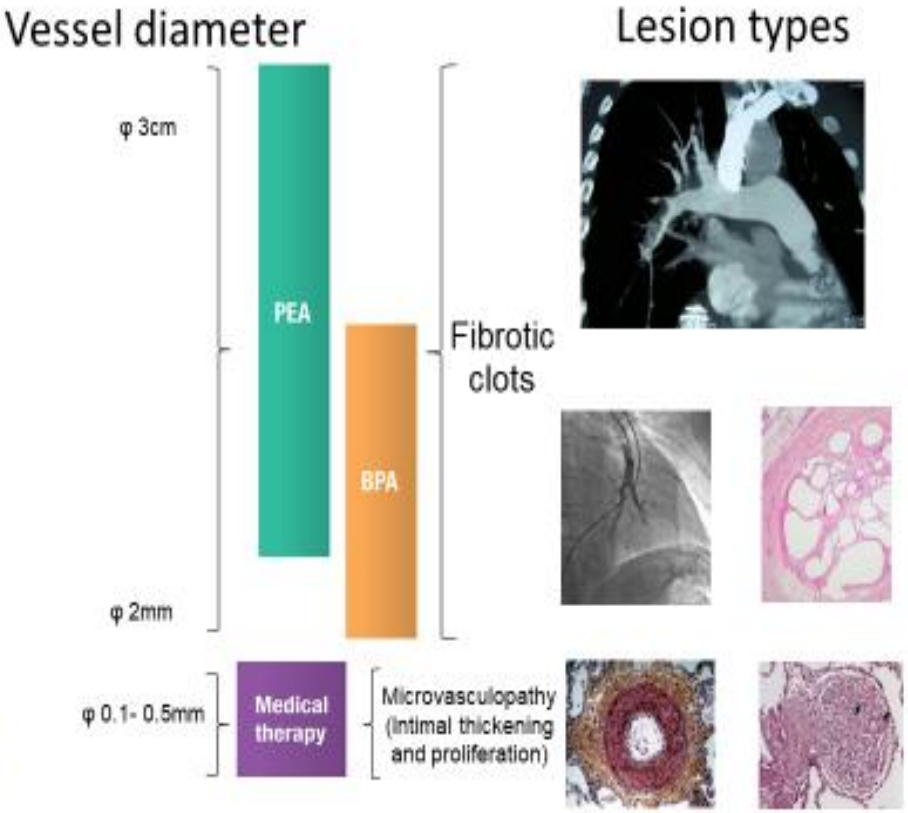
***5% of PEA**

Figure 1. Estimates of the number of new patients with chronic thromboembolic pulmonary hypertension (CTEPH) and chronic thromboembolic pulmonary vascular disease (CTEPVD) per year in the United States. PE = pulmonary embolism.

Delcrois M et al. AnnalsATS 2016

6th WORLD SYMPOSIUM PULMONARY HYPERTENSION





Madani et al, *Eur Respir Rev* 2017

Key-points in CTEPH treatment

- Evidence for excellent long term survival following PEA surgery
- Operability is subjective, but is a key decision as PEA remains the recommended treatment
- Increased evidence for efficacy and reproducibility of BPA with reduction in complications in expert centres
- Riociguat approved for inoperable patients and RCT evidence for benefit of combination therapy with PDE5-i and macitentan
- Some patients will have residual PH, even after effective surgery, and multimodality therapy will be the future of CTEPH treatment


UC San Diego
School of Medicine


UC San Diego Health
Cardiovascular Institute
World Leader in PTE Surgery
Our faculty developed and refined PTE surgery, and we performed our 4,000th procedure in 2019.
Our multidisciplinary team leads the world in the diagnosis and treatment of all forms of CTEPH (chronic thromboembolic pulmonary hypertension) with excellent clinical outcomes.


4000