Chronic Thromboembolic Pulmonary Hypertension (CTEPH

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Disclosures

Consultant
-Alnylam
-J&J
-Bayer
-United Therapeutics

Pulmonary Hypertension is a Disease of the Lung and Heart

Pulmonary hypertension (PH) has many different etiologies

PH typically leads to an increase in pulmonary vascular resistance (PVR) and high blood pressure in the lungs

The right side of the heart has to work harder to pump blood through the narrowed arteries

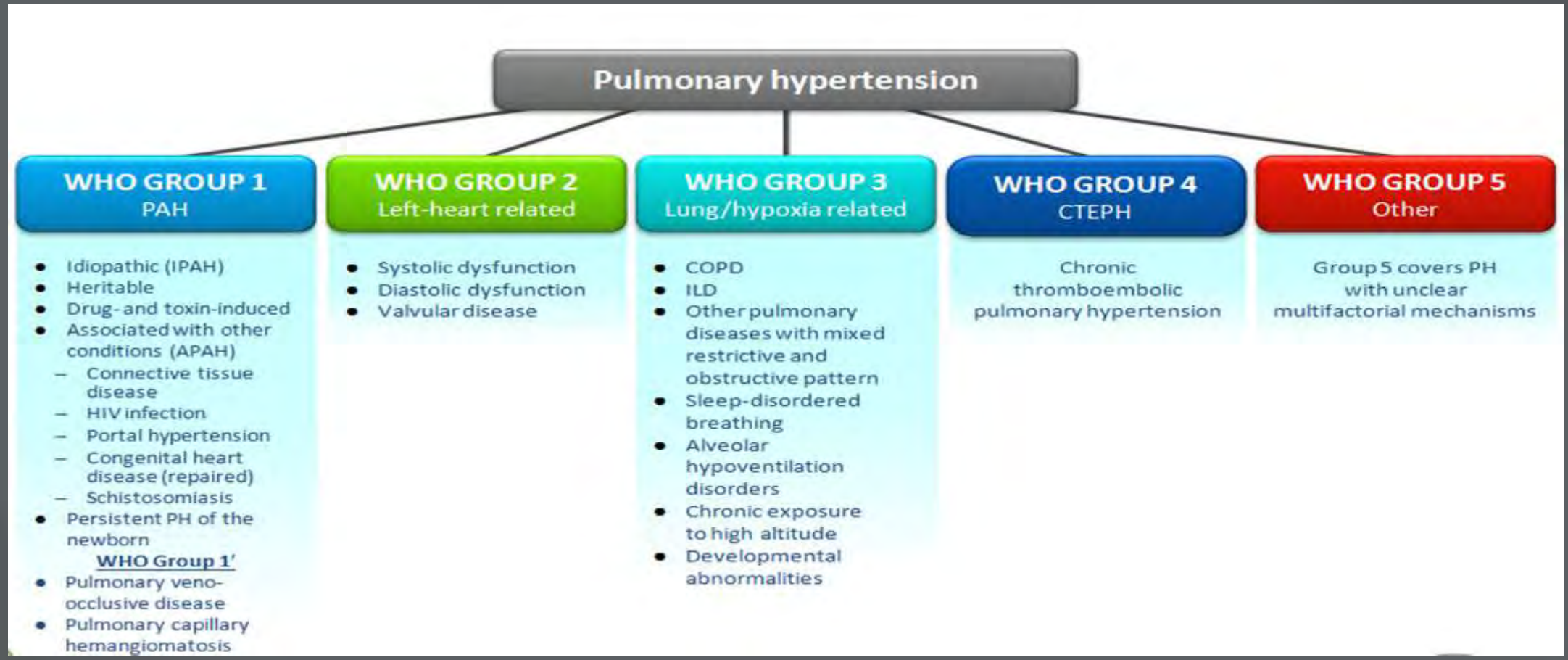
Eventually, the right heart becomes enlarged and consequently is less able to pump blood through the lungs …

… leading to heart failure and death

Galiè et al. *Eur Heart J*. 2009;30:2493–2537. McLaughlin VV et al. *J Am Coll Cardiol*. 2009;53;1573–1619. Rosenblum WD. *Cardiol Rev*. 2010;18:58–63. Rosenkranz S. *Clin Res Cardiol*. 2007;96:527–541.

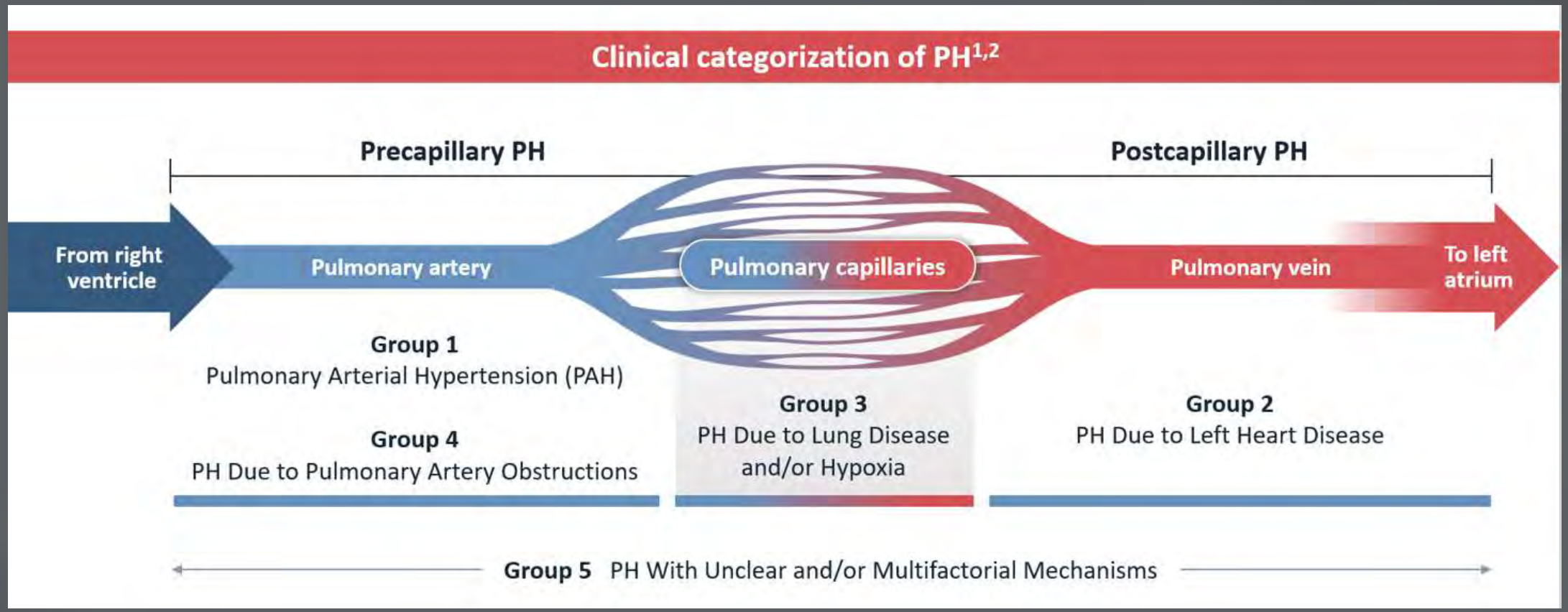
Pulmonary Hypertension is a rapidly progressive, ultimately fatal condition

PH is classified into Five Groups



CTEPH, chronic thromboembolic pulmonary hypertension; **COPD**, chronic obstructive pulmonary disease; **ILD**, interstitial lung disease; **HIV**, human immunodeficiency virus. Simonneau G et al. *J Am Coll Cardiol*. 2009;54(1 suppl):S43–S54.

PH is Categorized Based on its Underlying Cause



References: 1. Simonneau G, et al. *Eur Respir J.* 2019;53(1):1801913. **2.** Kumar N, et al. Pulmonary hypertension. In: *Teaching Rounds: A Visual Aid to Teaching Internal Medicine Pearls on the Wards.* New York, NY: McGraw-Hill Education; 2016.

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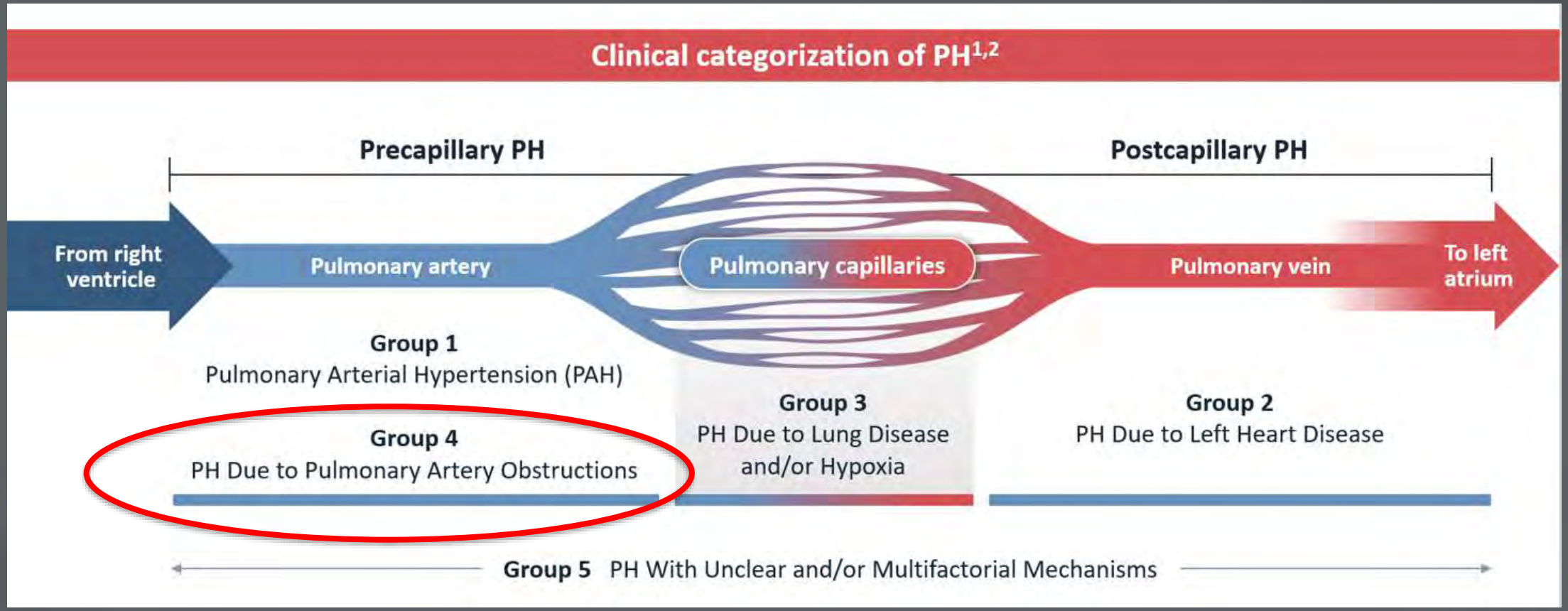

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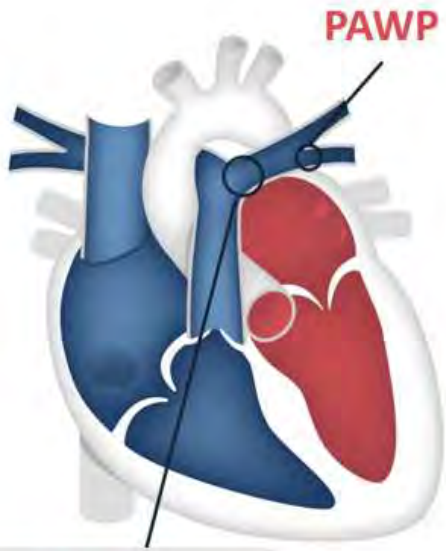
Hemodynamic Definition of PH

Normal mPAP
8-16 mmHg at rest

PH
mPAP > 20 mmHg at rest

The Hemodynamic Definition of Precapillary PH has Changed Over Time



mPAP
Upper limit of normal[1]:
~20 mm Hg

PVR
Upper limit of normal[2]:
~2 WU

2015
ESC/ERS definition[1]
mPAP ≥25 mm Hg (at rest)
PAWP ≤15 mm Hg
PVR >3 WU (Group 1 only)

2022
ESC/ERS definition[2]
mPAP >20 mm Hg (at rest)
PAWP ≤15 mm Hg
PVR >2 WU

Timeline

2018
WSPH definition[3]
mPAP >20 mm Hg (at rest)
PAWP ≤15 mm Hg
PVR ≥3 WU

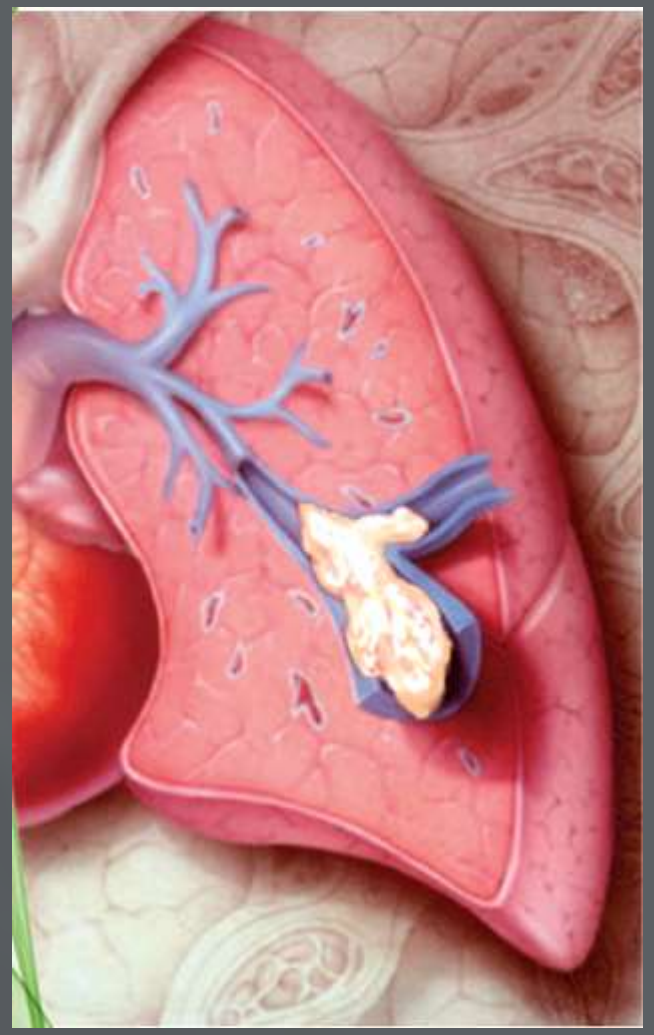
ESC/ERS=European Society of Cardiology/European Respiratory Society; WSPH=World Symposium on Pulmonary Hypertension; WU=Wood units.

References: 1. Galiè N, et al. *Eur Heart J.* 2016;37(1):67-119. **2.** Humbert M, et al. *Eur Heart J.* 2022;43(38):3618-3731. **3.** Simonneau G, et al. *Eur Respir J.* 2019;53(1):1801913.

CTEPH: *Introduction*

- CTEPH is an important cause of PH that is commonly considered to be the consequence of an episode of acute PE
- Following acute PE, unresolved residual thrombus becomes organized and fibrosed, leading to ongoing obstruction to pulmonary blood flow
- Untreated (even on anticoagulation), this leads to progressive PH, RV dysfunction and death
- “ Honeymoon period” after acute PE

What is CTEPH

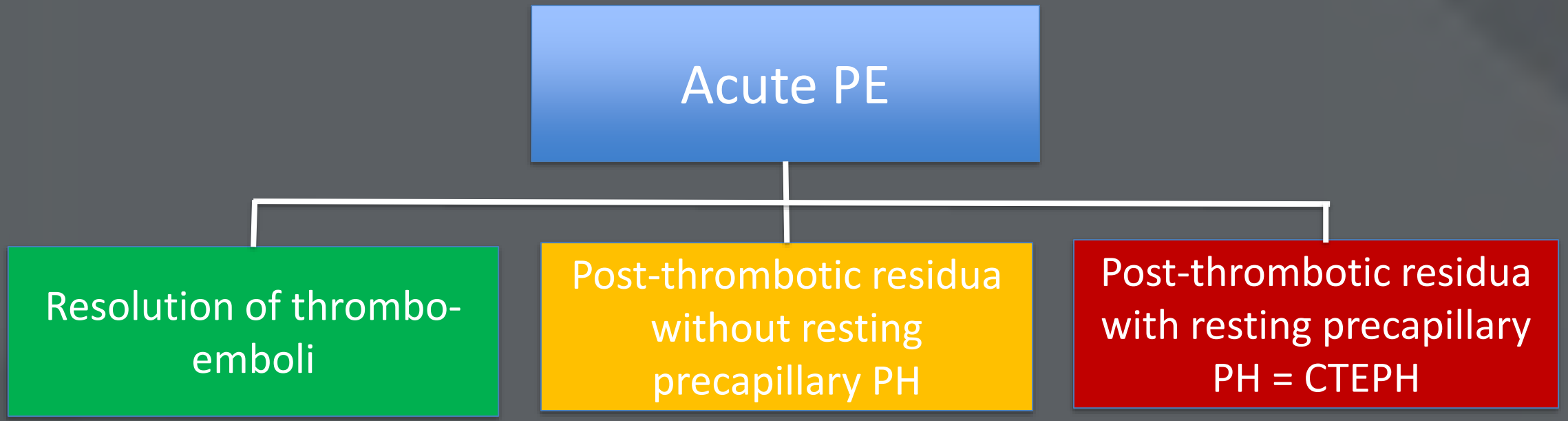


- Vascular disorder characterized by:
  - Organized thrombotic obstructions in the pulmonary arteries
- It may include small-vessel vasculopathy that is indistinguishable from idiopathic PAH

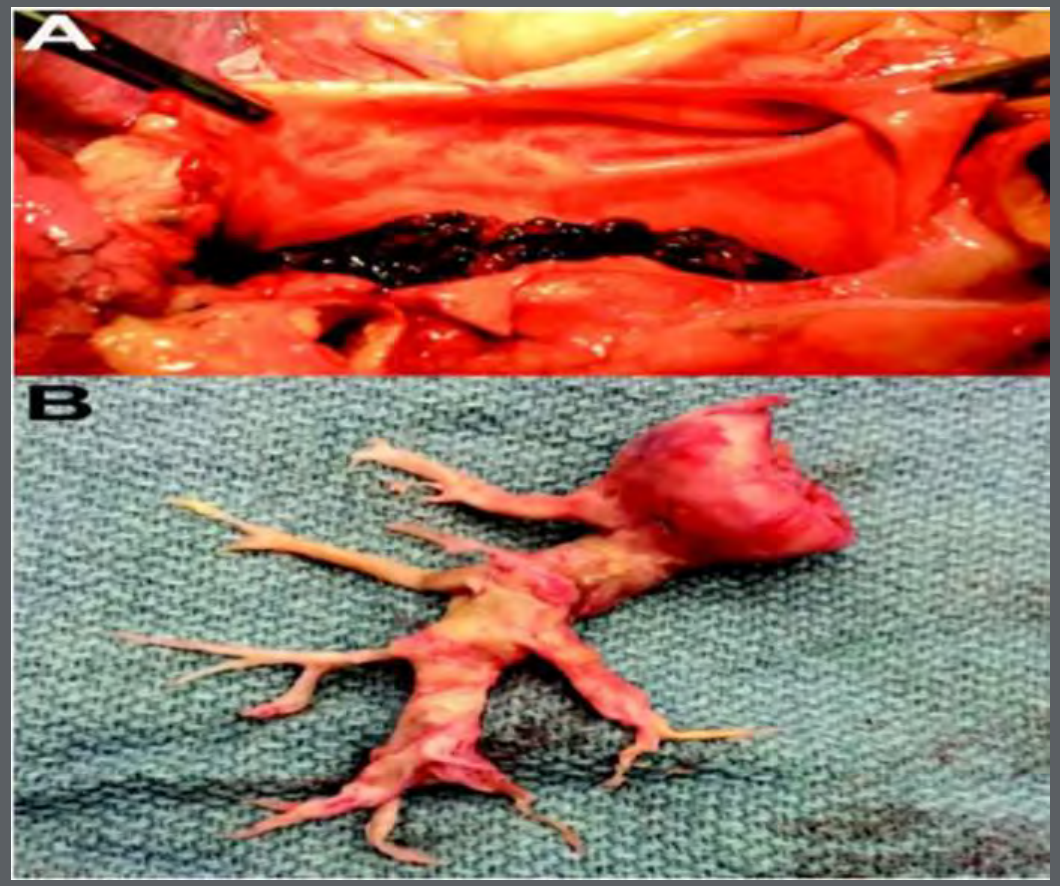
- Defined by the following observations after 3 months of effective anticoagulation:
  - mPAP >20 mmHg
  - Mismatched perfusion defects

Galiè et al. *Eur Heart J*. 2009;30:2493–2537. Jaff et al. *Circulation*. 2011;123:1788–1830. Lang IM et al. *N Engl J Med*. 2004;350:2236–2238. McLaughlin VV et al. *Circulation*. 2009;119:2250–2294. Wilkens et al. *Int J Cardiol*. 2011;154S S54–S60.

Etiopathogeneis



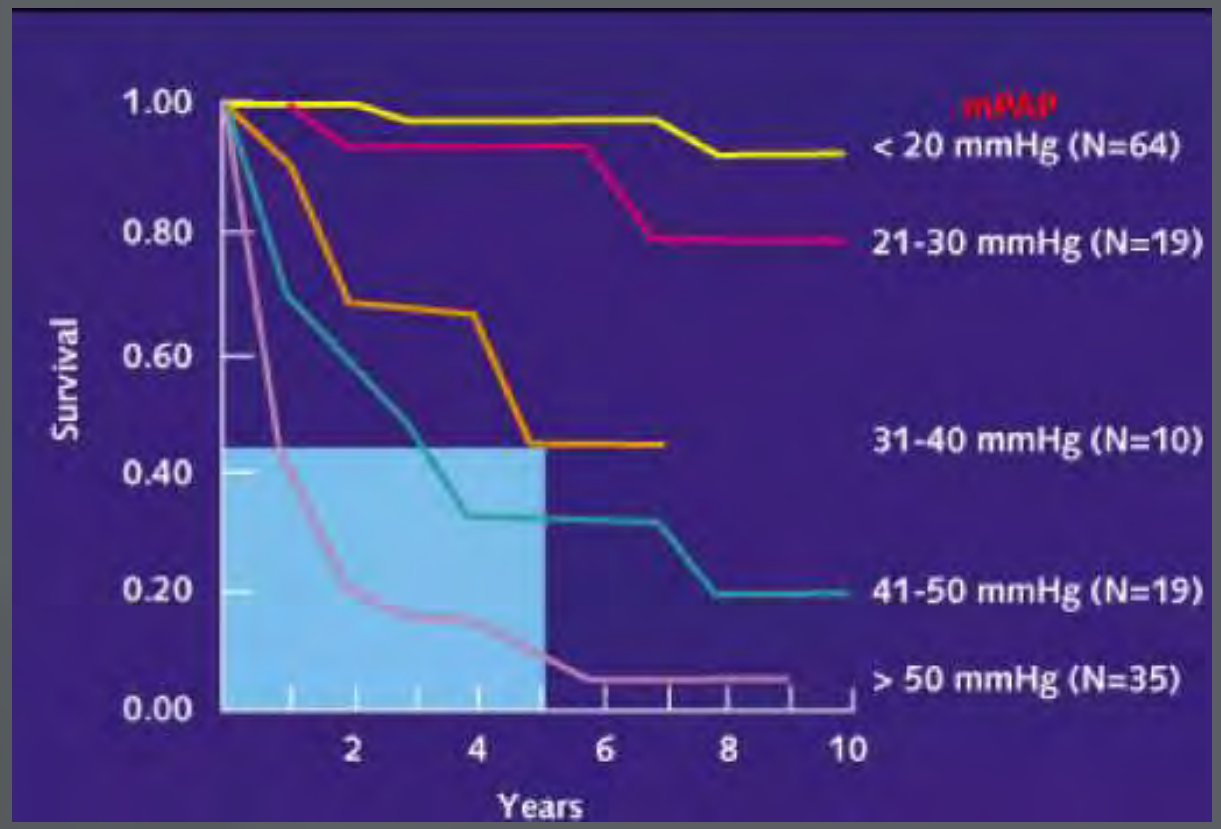
CTEPH *Introduction*



Vascular obstructive lesion in acute PE (A) versus CTEPH (B)

Matthews DT, Hemnes AR. Pulmonary Circ 2016; 6(2): 145-154

CTEPH: Survival without treatment



mPAP 31-40 mmHg – 5 years survival 45%
mPAP 41-50 mmHg – 5 years survival 33%
mPAP > 50 mmHg – 5 years survival 14%

Riedel et al, Chest 1982; 81: 151
Lewczuk et al, Chest 2001; 119: 818

Epidemiology

- Each year, approximately 600,000 individuals in the US have an acute PE
- Estimated incidence of CTEPH, after acute PE 0.5-4.0%
- The true incidence may be underestimated
- Based on a registry (2007-2009) including 679 patients from 16 European countries and Canada, histroy of acute PE was reported in nearly 75% of patients

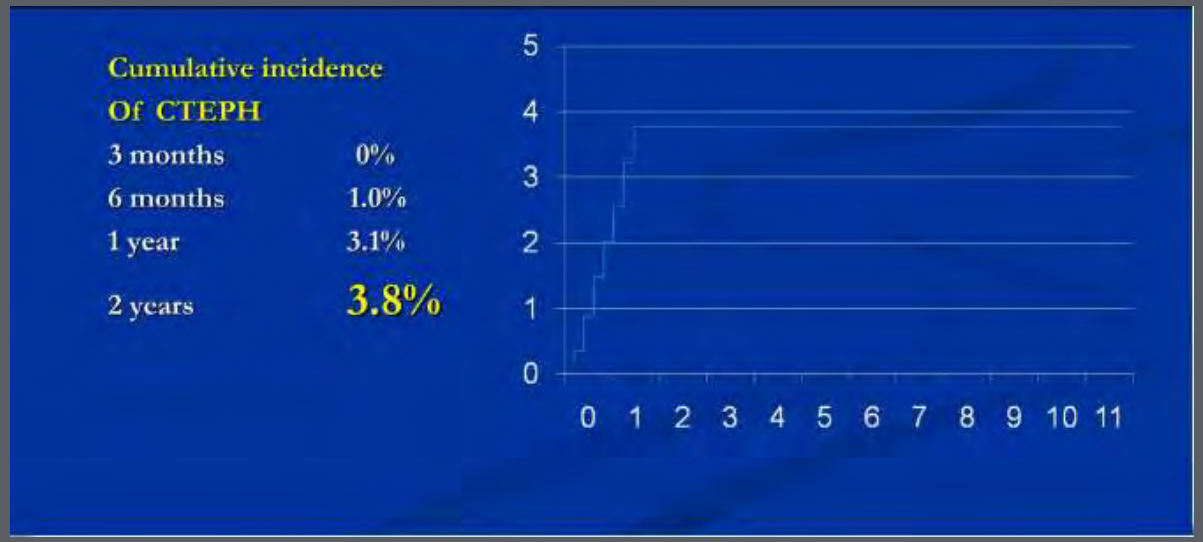
Incidence of CTEPH after Episode of PE

Each year in the US, the annual number of new CTEPH cases is between 500 and 2500

Tapson VF, Humbert M Proc Am Thorac Soc 2006;3:564-567

Incidence of CTEPH after First Episode of PE

- In a prospective study follow-up study including 314 patients with PE, incidence of CTEPH was 3.8% within 2 years after a first episode of symptomatic PE
- 7/223 patients (5 patients in NYHA class II, 2 patients in NYHA class III
- None of the remaining patients developed CTEPH after 2 years



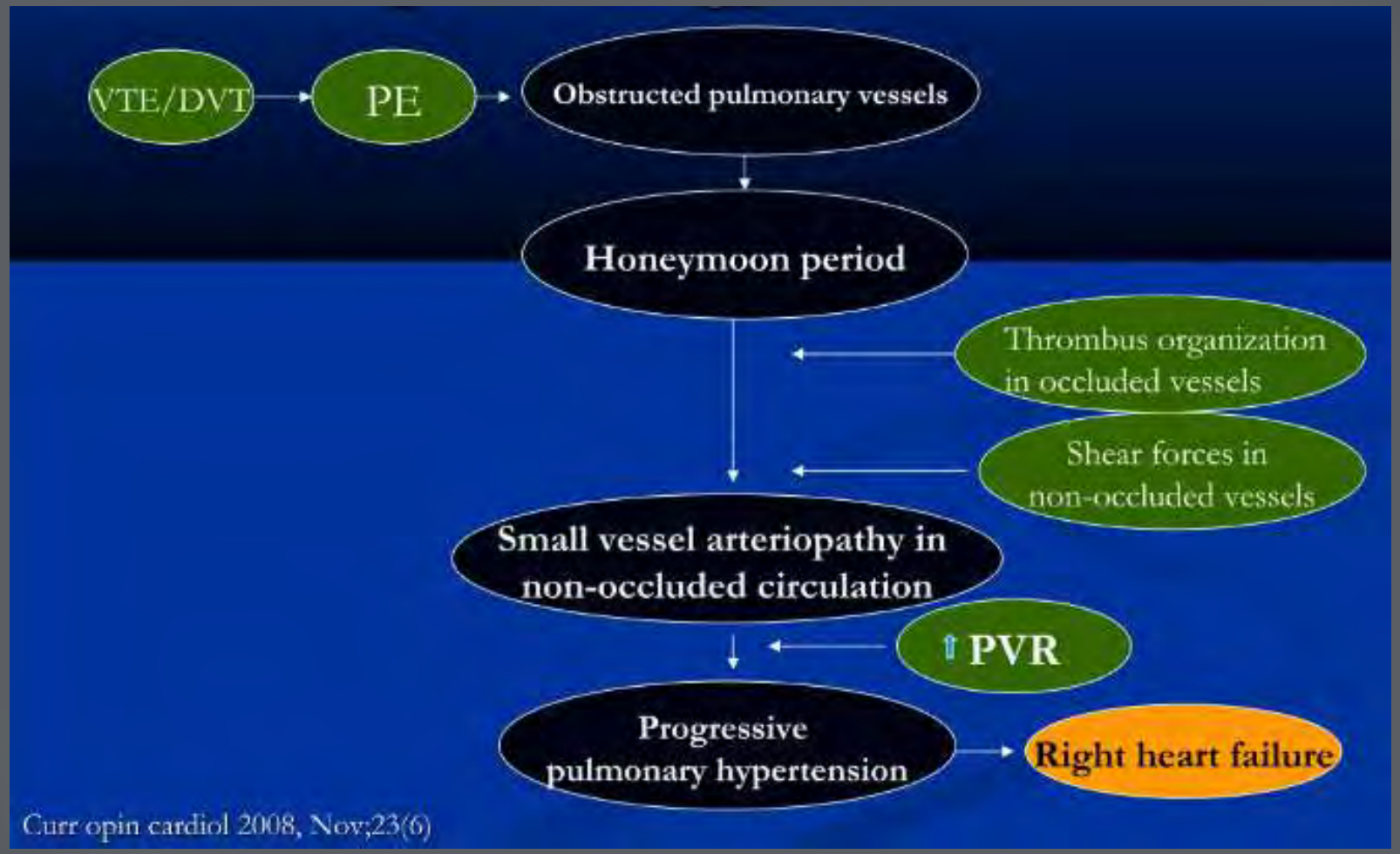
Pengo V, et al. N Engl J Med. 2004; 350:2257-64

Proposed annual incidence of CTEPH in USA

DIAGNOSED PE	600,000
CTEPH	25,000

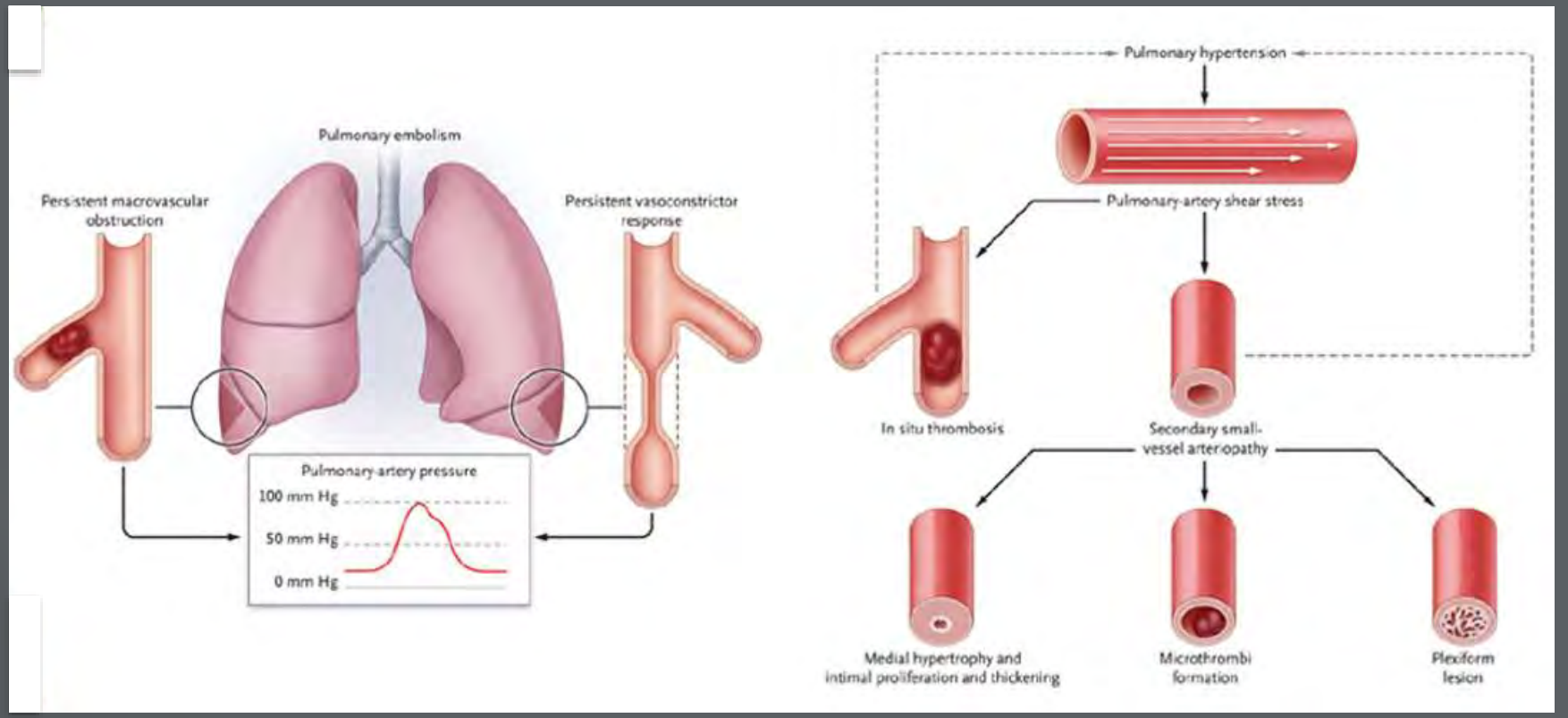
Pengo V, et al. N Engl J Med. 2004; 350:2257-64

Pathophysiology of CTEPH



CETPH Pathogenesis

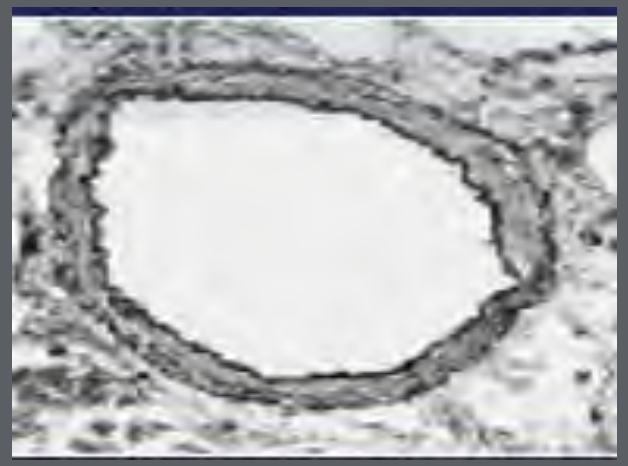
- CTEPH results from persistent macrovascular obstruction and a vasoconstrictor response that lead to a secondary small vessel arteriopathy.
- Reductions in the pulmonary diameter due to thrombosis and vasoconstriction result in adverse vascular remodeling

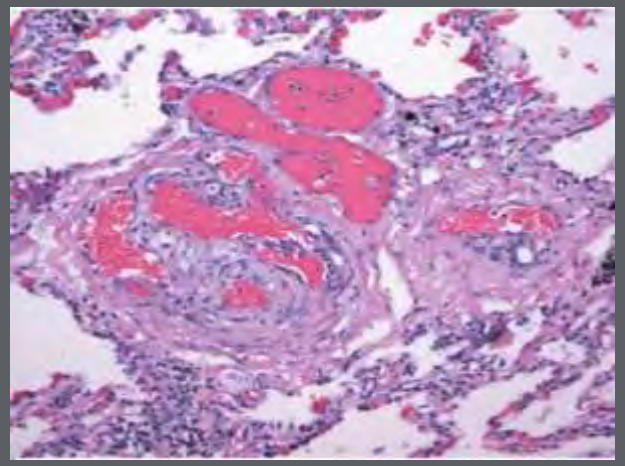


Piazza et al NEJM 2011; 364:351-60

CTEPH: Histopathological Paradox

Tissue/vessels distal to occluded segment: normal
Distal vessel distal to patent pulmonary arterial segment- small vessel abnormalities





Definition of CTEPH

- Hemodynamic measurements:
  - mPAP ≥ 20 mmHg
  - PWP ≤ 15 mmHg
  - PVR > 2 WU
- Chronic and organized thrombi/emboli in the pulmonary arteries (main, lobar, segmental, subsegmental)
- After at least 3 months of effective anticoagulation

CTEPH

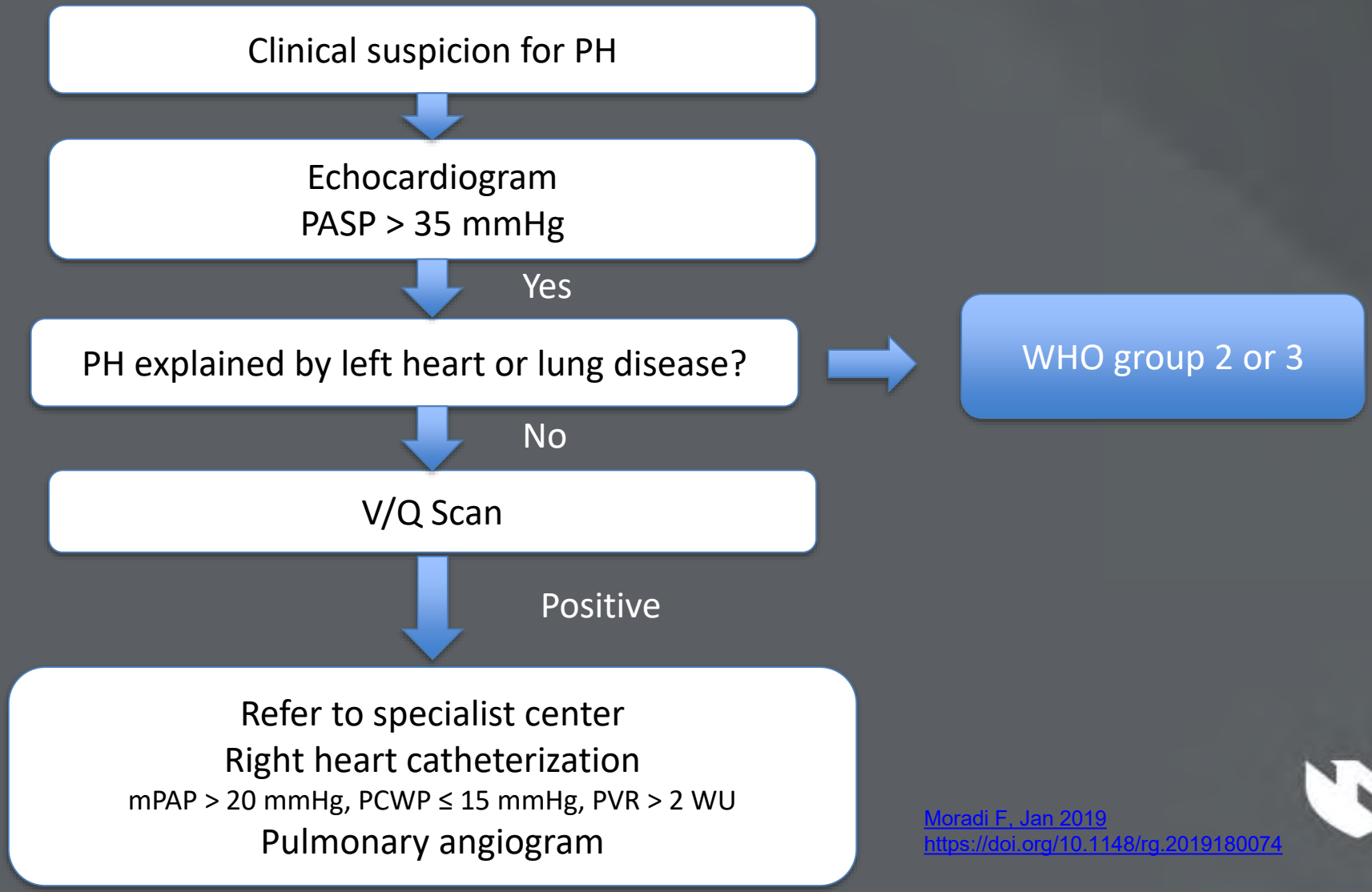
- Incidence 0.5 to 4% after symptomatic PE
- Underdiagnosis
- In Europe, both genders are equally affected, whereas mostly women in Japan
- Median age is 63 years
- Median time of 14 months between symptom onset and diagnosis
- Only PH group that is potentially curable by pulmonary endarterectomy (PEA)
  - PEA is the only curative treatment

Hoeper MM, Rubin LJ CTEPH. Circulation 2006

CTEPH: *Risk Factors*

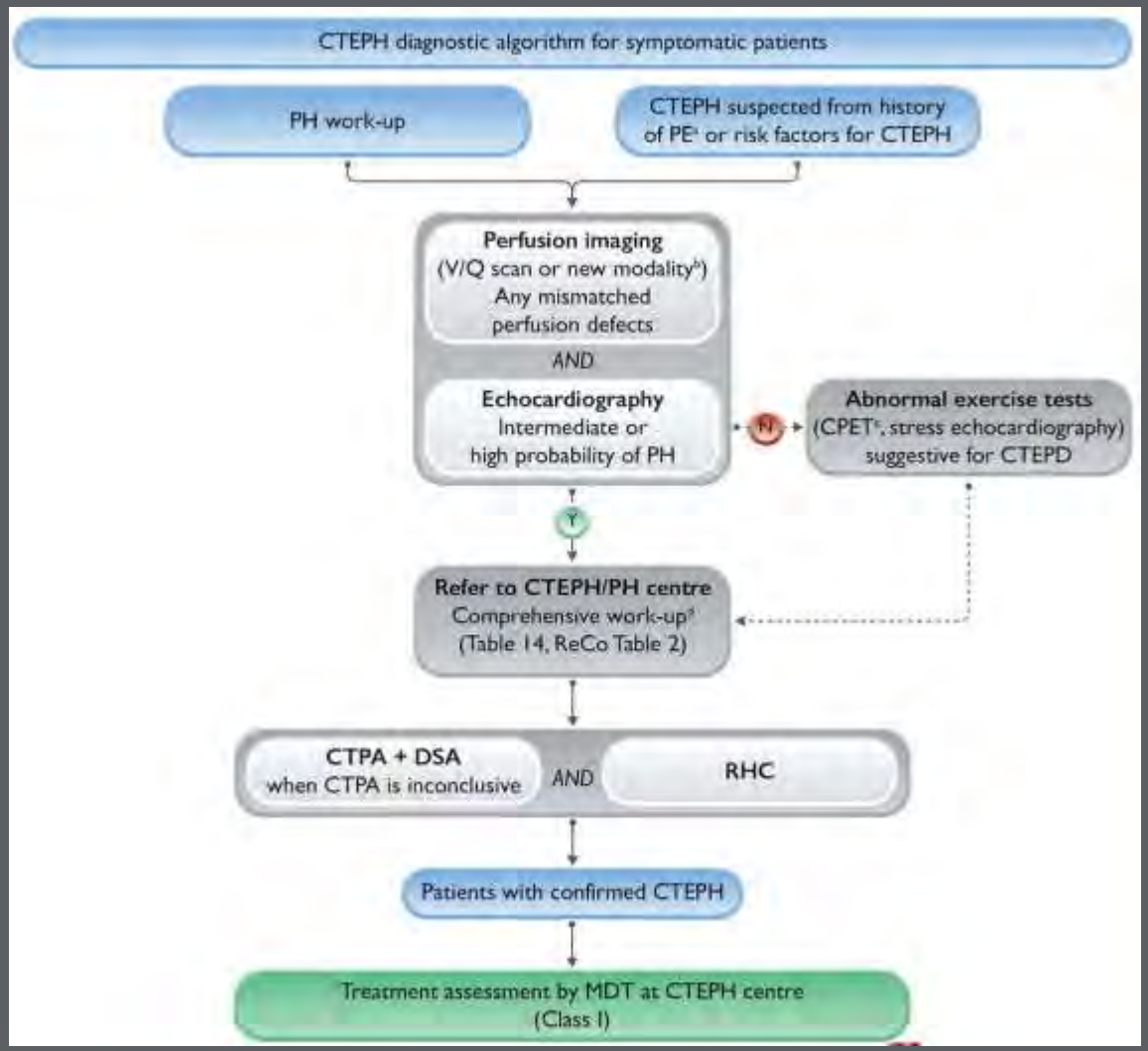
- PE
- Ventriculoatrial shunt
- Infected pacemaker
- Splenectomy
- Cancer
- Antiphospholipid antibodies (in 20% of CTEPH pts)
- High levels of factor VIII (in 41% of CTEPH pts)
- ABO blood groups other than O
  - Non O blood type CTEPH vs PAH (88 vs. 56%)
- Elevated Lp (a)
  - CTEPH vs. PAH vs. Control (26.6 vs. 9.6 vs. 7.2 mg/dL)
- Protein C,S & fctor V Leiden deficiencies <1% of pts with CTEPH

Approach for diagnosing CTEPH



Moradi F, Jan 2019
https://doi.org/10.1148/rg.2019180074

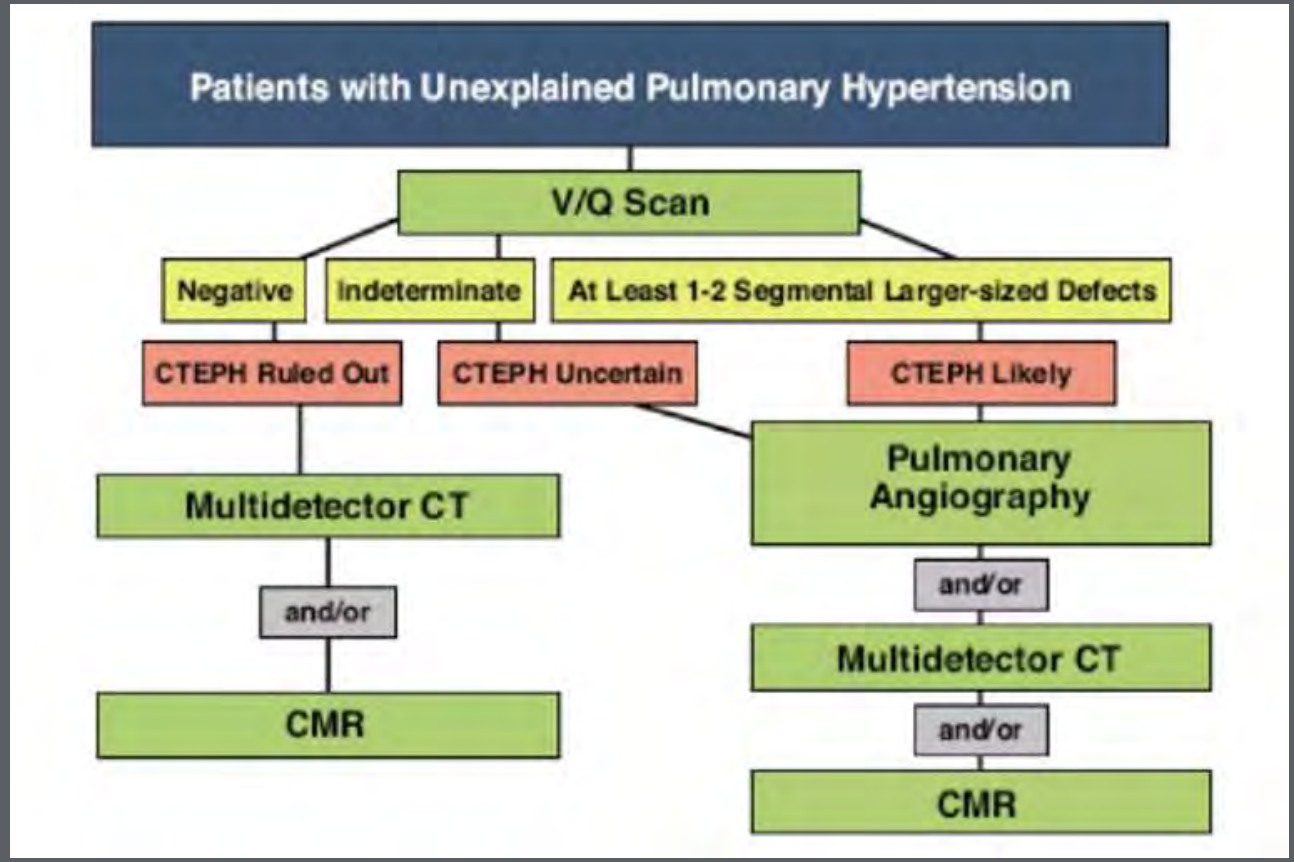
Diagnostic strategy in CTEPH



CPET=cardiopulmonary exercise test
CTPA computed tomography pulmonary angiography
DSA digital substraction angiography
MDT multidisciplinary team

Humbert M et al 2022 ESC/ERS Guidelines for the diagnosis and treatment of PH European Respiratory Journal 2022; DOI: 10.1183/13993003.00879-2022

CTEPH *Diagnostic Imaging Algorithm*



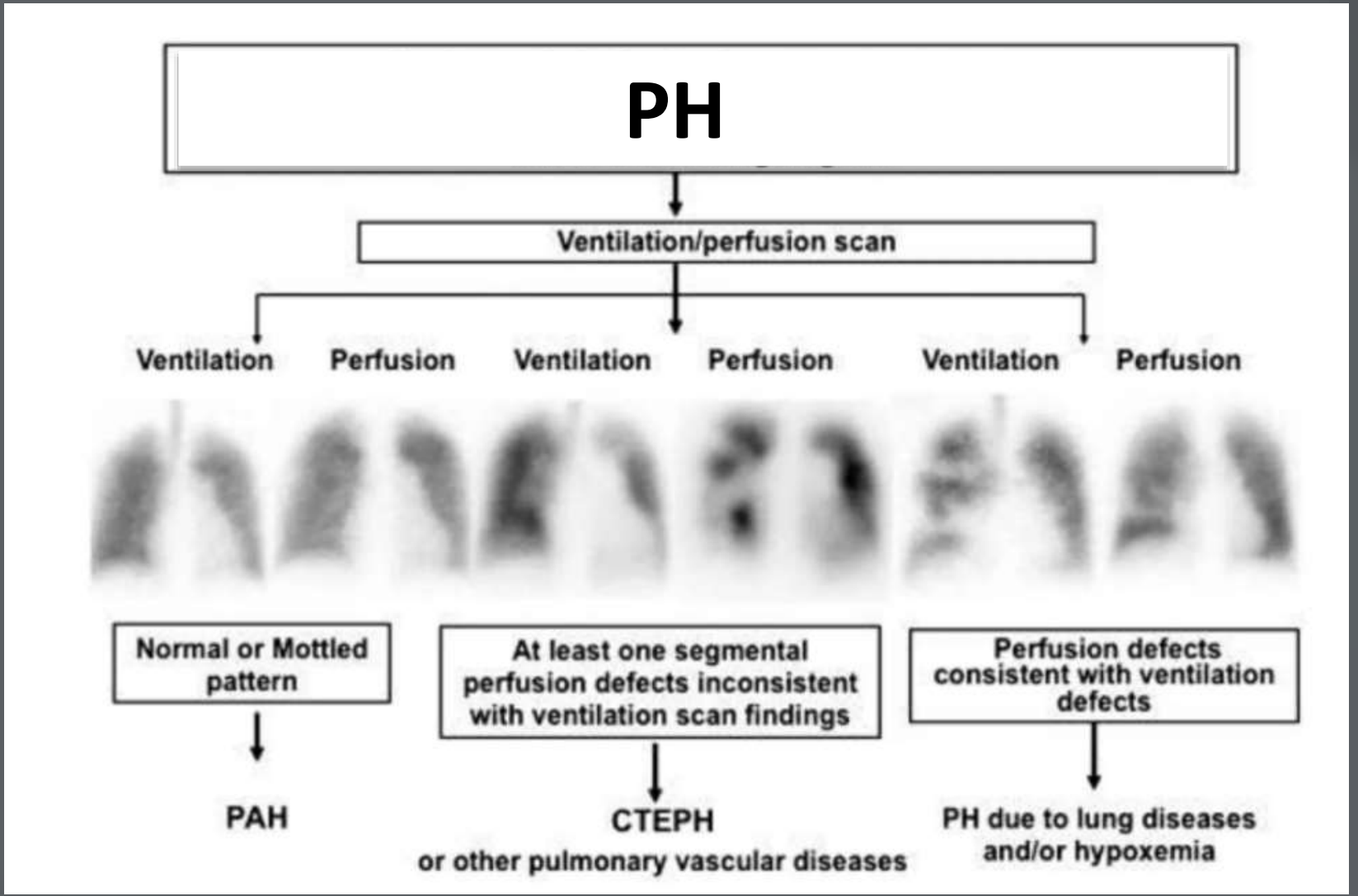
Lang et al JACC CardiovascularImaging 2010; 3:1287

Ventilation/Perfusion (V/Q) Scan

- In CTEPH, at least one segmental or larger mismatched ventilation-perfusion defects are present
- In Idiopathic PAH, perfusion scans are usually normal
- Cannot localize the extent of the disease
- Cannot determine surgical accessibility

- Conditions indistinguishable from CTEPH in V/Q
  - Extrinsic vascular compression from mediastinal adenopathy of fibrosis
  - Primary pulmonary vascular tumors (ie Angiosarcom)
  - Pulmonary veno-occlusive disease
  - Large vessel pulmonary vasculitis

V/Q Scan in CTEPH



Tanabe N et al Respiratory Investigation 2013; 51(3):134-146

Ventilation-Perfusion (V/Q) Scintigraphy is more Sensitive than CT Pulmonary Angiogram (CTPA) for the Diagnosis of CTEPH

		V/Q			CTPA	
	Group	Low probability	Intermediate probability	High probability	Negative	Positive
CTEPH	A (*n* = 78)	2	1	75	38	40
No CTEPH	B (*n* = 149)	134	7	8	148	1

	Scintigraphy		
Indicator	V/Q (1)*	V/Q (2)†	CTPA
Sensitivity (%)	97.4	96.2	51.3
Specificity (%)	90	94.6	99.3
Accuracy (%)	92.5	95.2	82.8
NPV (%)	98.5	97.9	79.7
PPV (%)	83.5	90.3	97.6

Intermediate-High High

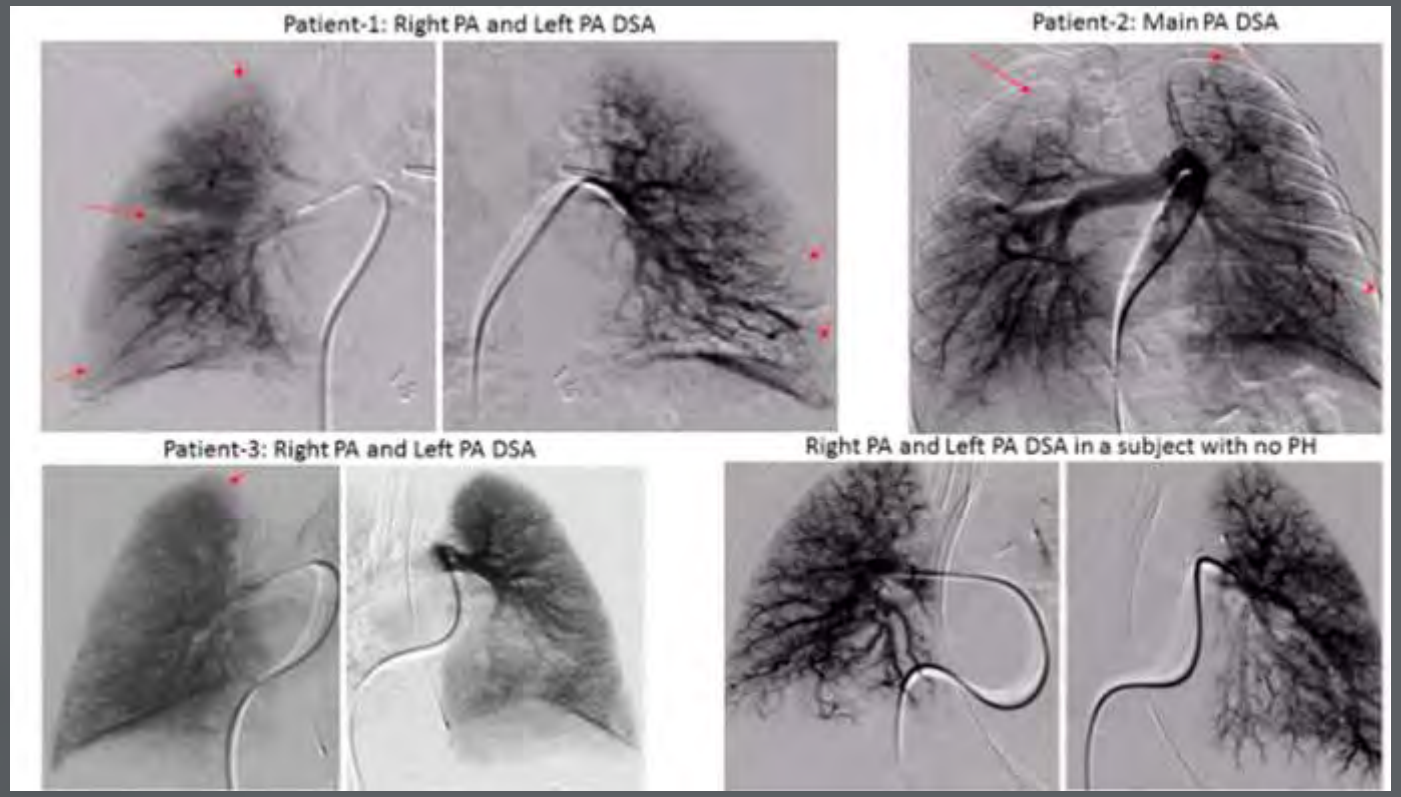
Nina Tunariu1, Simon J.R. et al
J Nucl Med 2007; 48:680–684

CTEPH CTA, MRI, and Imaging

- CTA Sensitivity of 51% compared with > 96% sensitivity of V/Q Scan
- With CTA filling defects are often not seen
- MRI is inferior to CT
- A normal V/Q scan virtually rules out CTEPH
- A normal CTA or MRI does not rule out a diagnosis of CTEPH

Pulmonary Angiograqphy

Definitive for the diagnosis and assessment of surgically correctable CTEPH or PBA
Safe, even with severe PH
Findings include webs, abrupt vascular cut-offs, ring-like stenoses, pouches

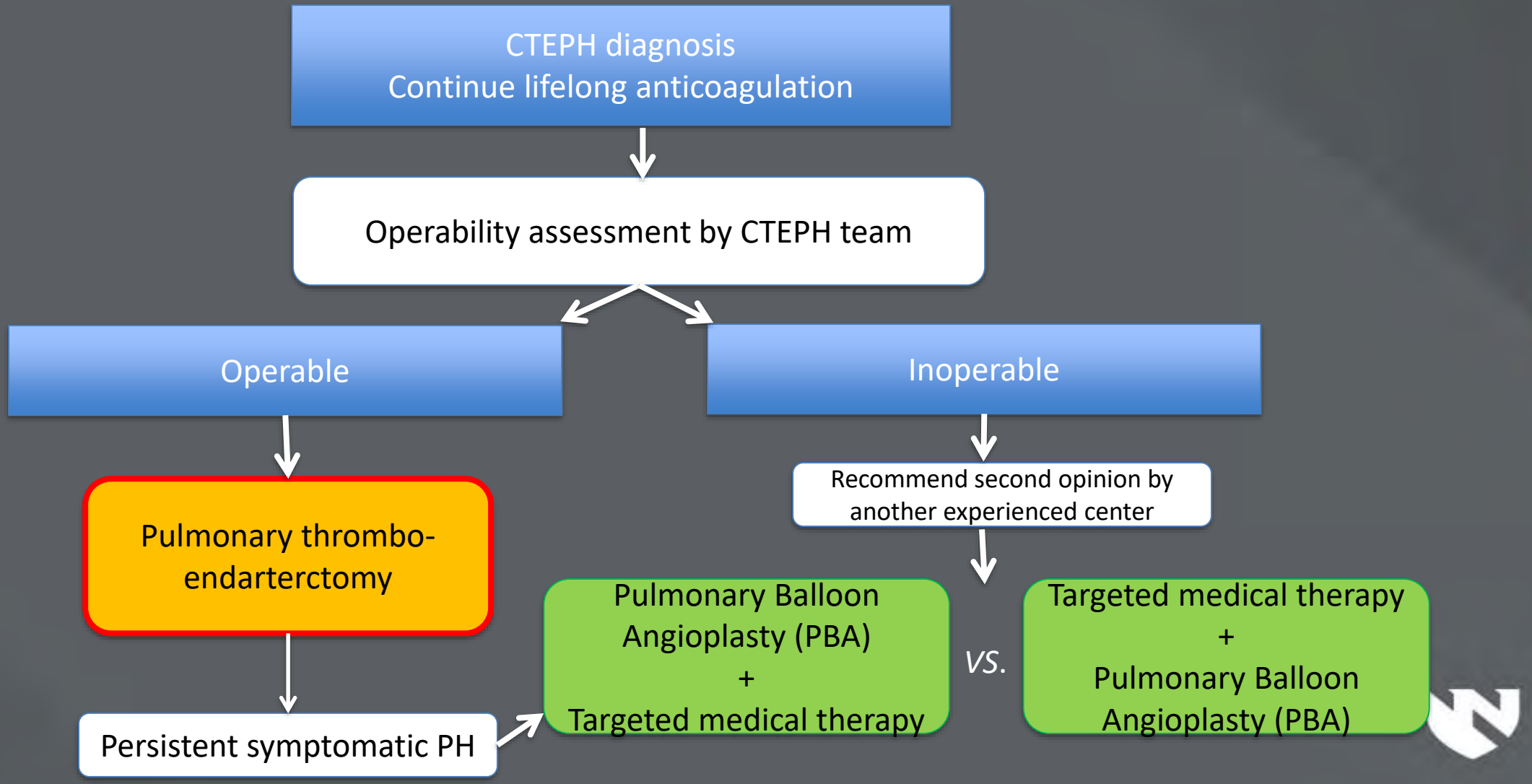


CTEPH rules

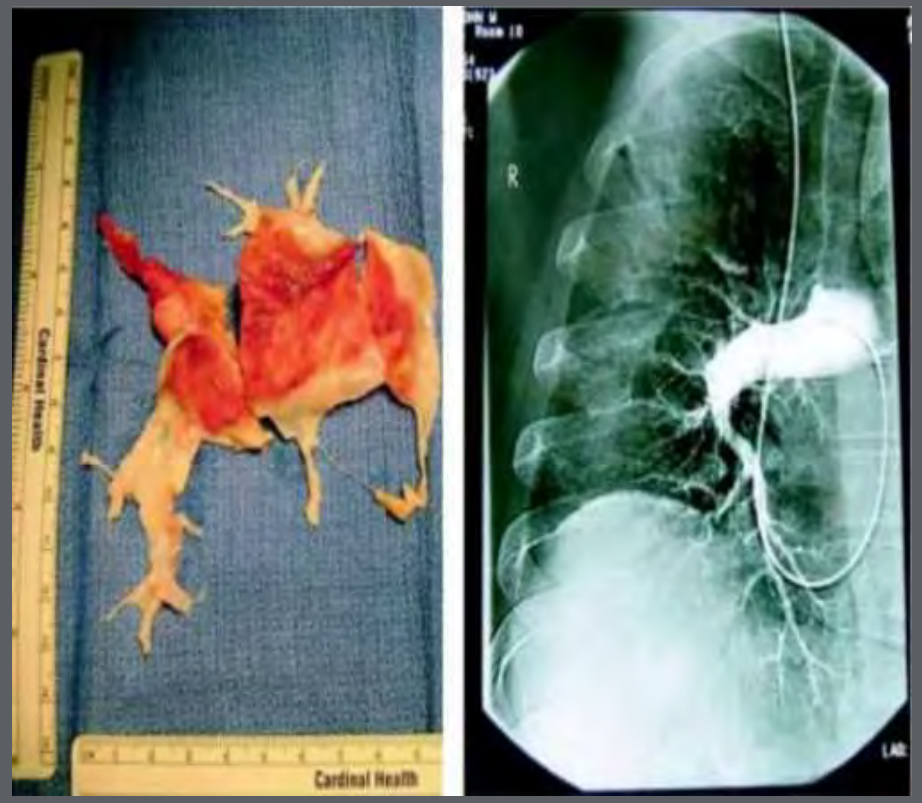
- A normal V/Q Scan virtually rules out CTEPH
- A normal CTA doe not rule put a diagnosis of CTEPH
- Right heart catheterization

  mPA > 20 mmHg, PW < 15 mmHg, PVR > 2 WU
- Pulmonary angiogram

CETPH Management Algorithm



Pulmonary Endarterectomy (PEA)



PEA cast and corresponding pulmonary angiogram

McNeil K, Dunning J. Heart 2007;93(9):1152-58

Pulmonary Endarterectomy (PEA)

- PEA is the only curative treatment
- Pioneered at UCSD (San Diego): > 3000 cases of PEA
- Periprocedural mortality <2% to 5%
- Decision should be made by a CTEPH team (cardologist, pulmonologist, CT surgeon and radiologist)
- Should not be considered non-operable if not reviewed by at least 2 independent experienced PEA surgeons
- Reverse pulmonary vascular remodeling can occur
- Recurrent CTEPH after successful PEA is extremely rare

Pulmonary Endarterectomy (PEA)

- PEA is also considered in patients who have normal or nearly normal pulmonary hemodynamics at rest but in whom significant PH develops during exercise (Chronic thrombo-embolic pulmonary disease (CTEPD))
- No surgery for distal disease (sub-segmental)
- Occurrence of reperfusion lung injury due to loss of endothelial integrity
- Pulmonary (non-cardiogenic) edema to severe diffuse alveolar damage

Predictors of Surgical Sucess

- Prior history of pulmonary embolism and/or DVT
- “Honeymoon period” (period of months between acute embolic event and clinical symptoms of CTEPH
- Angiographic lesions located proximally in pulmonary arteries or lobar branches
- Correlation between PVR and anatomic obstruction
- Immediate postoperative PVR < 7.3 WU had better long-term outcomes than PVR > 7.3 WU

Balloon Pulmonary Angioplasty (BPA)

- The first series of balloon pulmonary angioplasty (BPA) was reported nearly 20 years ago by Feinstein et al. The technique has subsequently been refined in multiple centres in Japan and is now rapidly being adopted in Europe and the US

- BPA is an alternative therapy in selected patients who have inoperable disease due to distal surgically inaccessible disease or persistent or recurrent PH after PEA

- Successful BPA may reduce PA pressures, improve blood flow distribution and decrease RV afterload in CTEPH patients

Balloon Pulmonary Angioplasty (BPA)

- Meta-analysis suggested superiority of BPA when compared to riociguat (23 clinical trials including 1454 patients (631 with PBA vs 823 on riociguat) with greater improvements in exercise tolerance and pulmonary hemodynamics except for cardiac output [1]
- RACE trial included 124 patients randomised 1:1 to either BPA or riociguat. After 6 months PVR fell by 60% in the BPA group and 32% in the medical therapy group ($p<0.001$) [2]
- The secondary endpoints change in mPAP, mean right atrial pressure, N-terminal pro-brain natriuretic peptide (NT-proBNP) and functional class (FC) showed greater improvement in the BPA group, although 6-minute walking distance (6MWD) was not significantly different between the two groups [2]

1. Wang W. et al.. Clin Cardiol 2019;42:741–52
2. Bosworth T. Balloon pulmonary angioplasty beats riociguat in randomized CTEPH trial. MDedge News 18 October 201

Balloon Pulmonary Angioplasty (BPA)

- Mortality 0-5.6%
- Reperfusion pulmonary injury or lung hemorrhage (2-23%) can be a fatal complication
- PA dissection or perforation 0-6.4%
- Limit dilatation to no more than 2-3 vessels per sitting
- IVUS and OCT to ensure that the maximal size is not >60-90% of the original size of the vessel diameter

Balloon Pulmonary Angioplasty (BPA)

- Mizoguchi et al performed BPA in 68 inoperable CTEPH
- All patients showed significant improvements in PAP, BNP levels and functional exercise capacity
- 66 patients were alive at 2.2 ± 1.4 years
- Follow-up at 1 year conformed improved angiographic appearance of the pulmonary arteries

Circ Cardiovasc Interv 2012; 5:748-55

Medical therapy

- CTEPH is inoperable in as many as 50% of cases
- Around 10-15% patients do not respond to PEA
- Patients left untreated have a poor prognosis
- Anticoagulation therapy should be continued for life
- Only one therapy approved by FDA for inoperable and post-operative patient with persistent PH: Riociguat
- IVC filter placement is not mandatory because of origin of clot may be other sites
- Riociguat, met the primary end point for nonoperable CTEPH or persistent/recurrent PH after PEA
- In the CTREPH trial, sc trepostinil conformed improvement in exercise capacity, hemodynamics and QOL at 6 months

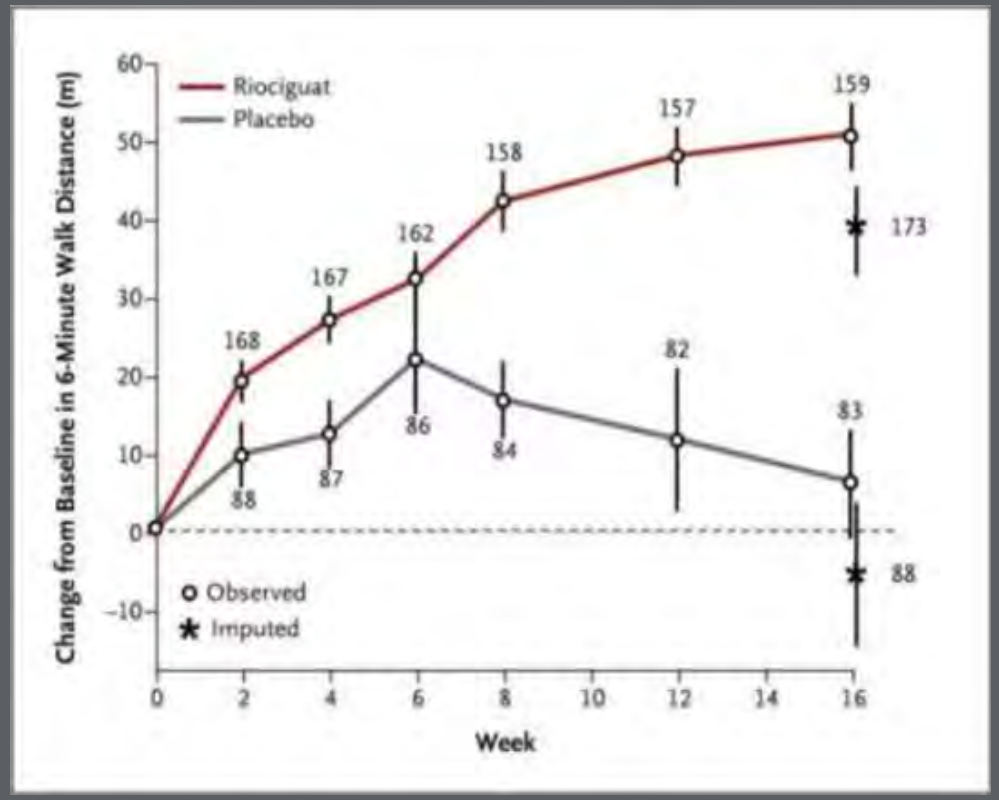
Indication for Medical Therapy

- Where there is inoperable distal disease or co-morbidities that make PEA a high-risk option:
- As a therapeutic bridge to PEA
- Patients with persistent or residual PH after PEA

When Medical therapy in CTEPH

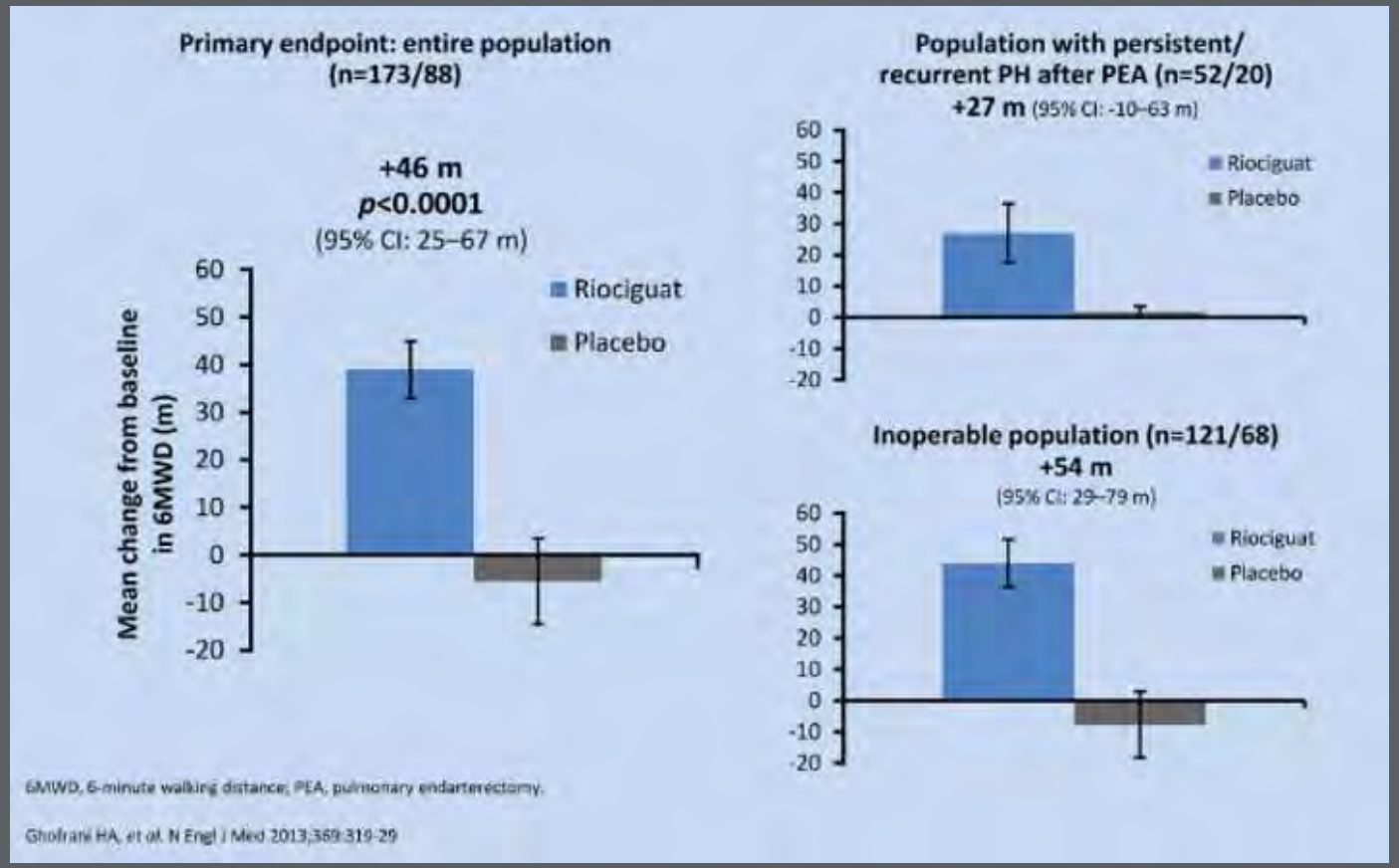
- Cannot do PEA
  - distal disease
  - too many or too severe co-morbidities (severe restrictive or obstructive lung disease)
  - Persistent PH or recurrent PE post PEA
  - Bridge to PEA (i.e too high PVR)

Medical therapy: *Riociguat*



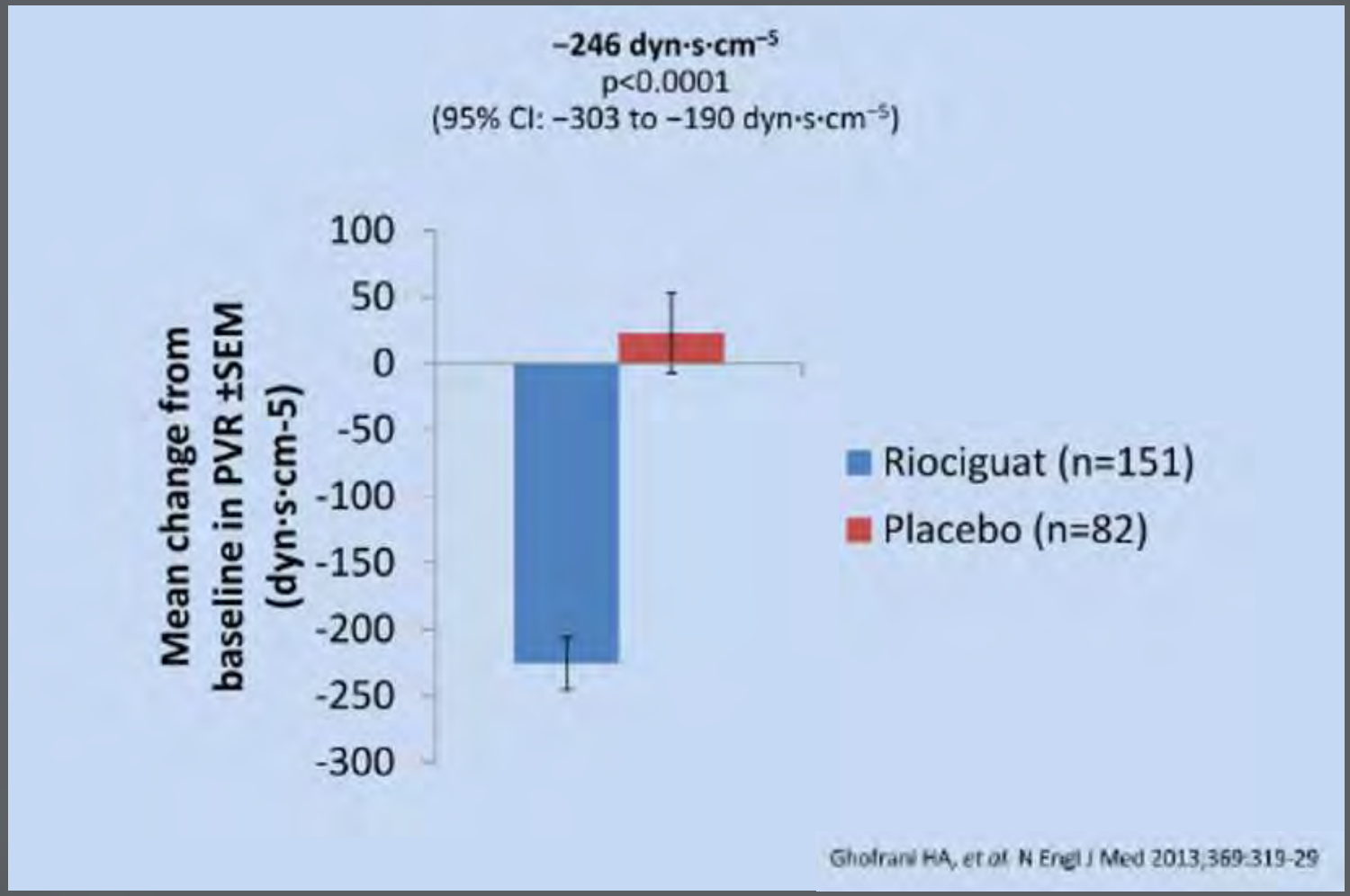
Ghofrani HA et al. NEJM 2013;369:319-29

Medical therapy: *Riociguat*

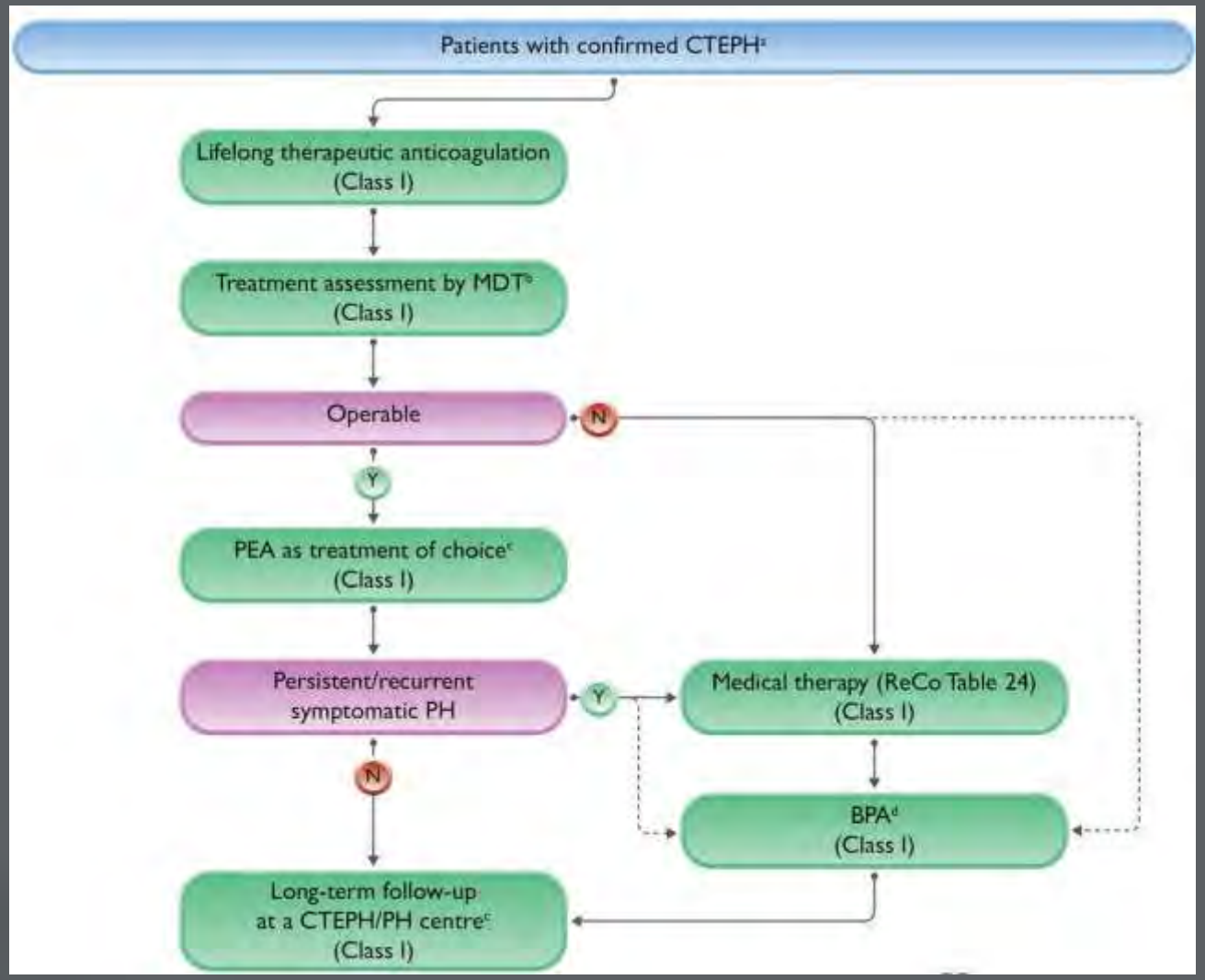


Medical therapy: *Riociguat in CHEST-1*

Riociguat significantly improved PVR

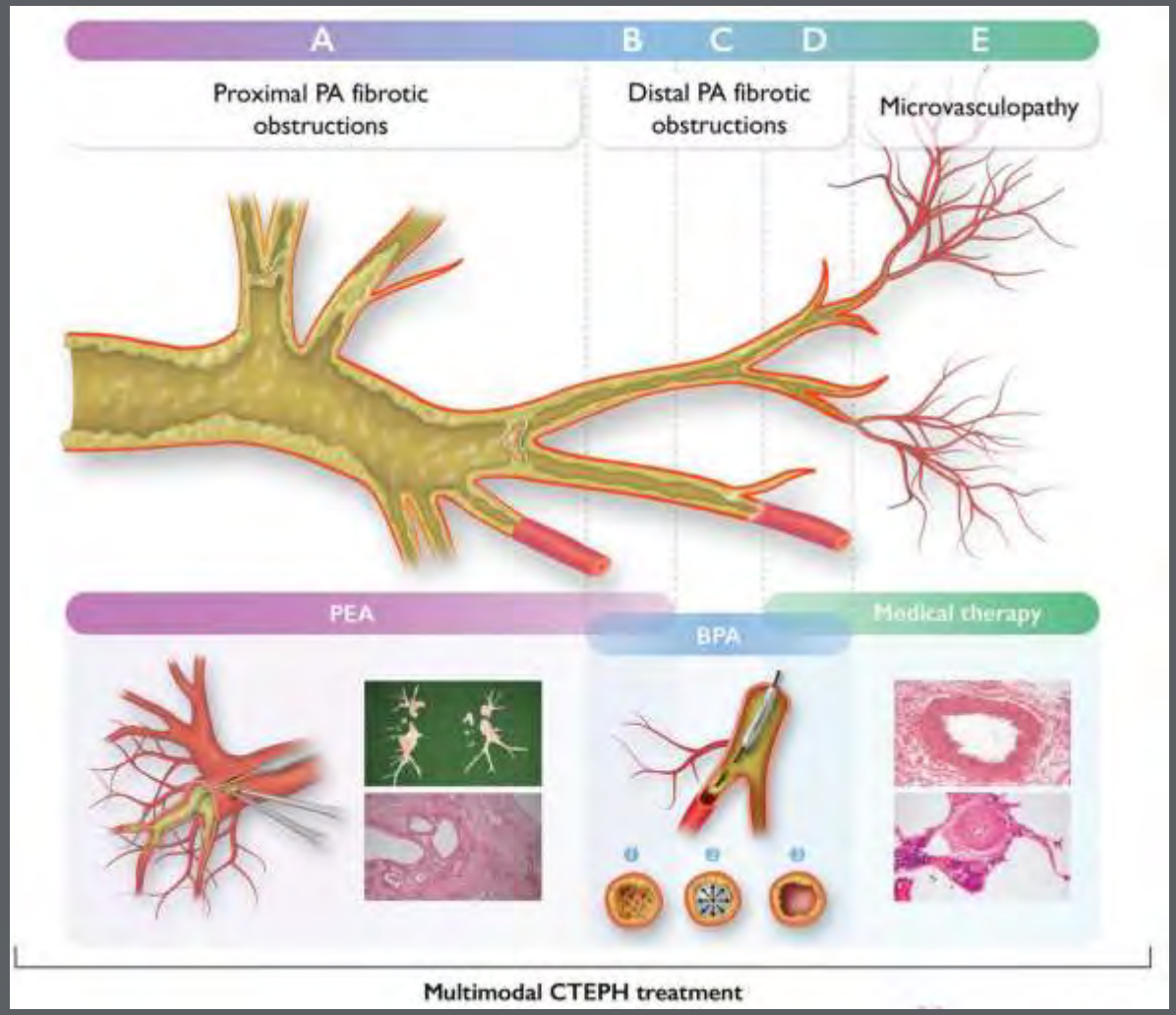


Management strategy in CTEPH



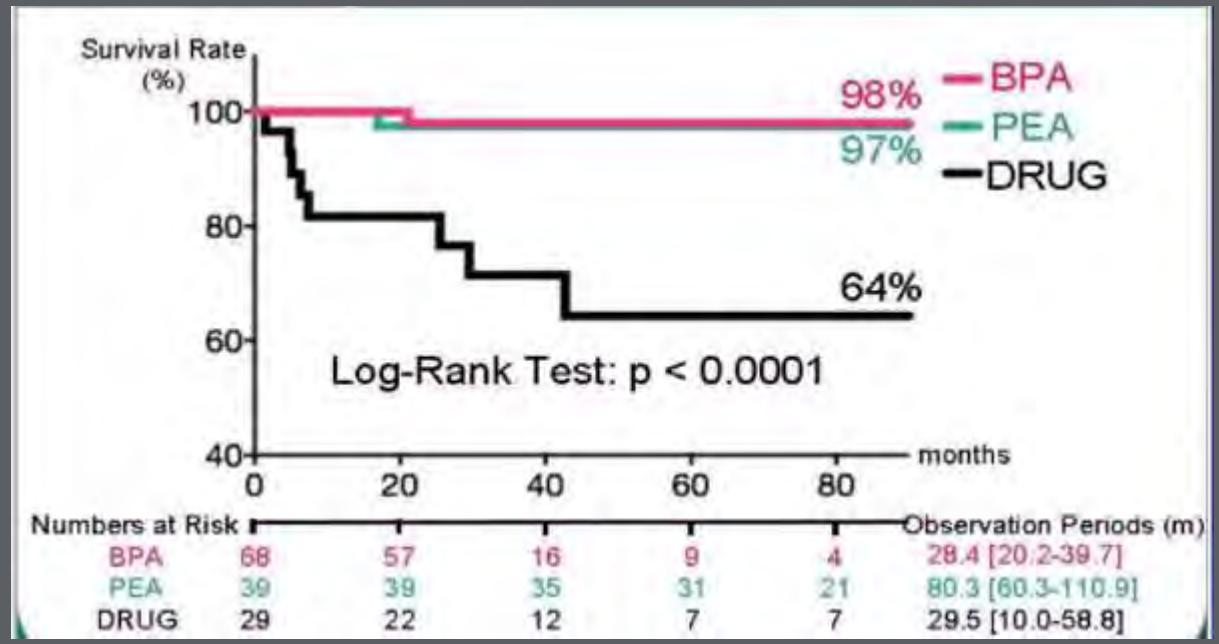
Humbert M et al 2022 ESC/ERS Guidelines for the diagnosis and treatment of PH European Respiratory Journal 2022; DOI: 10.1183/13993003.00879-2022

Overlap in treatments/multimodality approaches in CTEPH



Humbert M et al 2022 ESC/ERS Guidelines for the diagnosis and treatment of PH European Respiratory Journal 2022; DOI: 10.1183/13993003.00879-2022

CTEPH:
PEA *vs.* PBA *vs.* medical therapy



Inami T, Kataoka M, Shimura N et al ESC Congress 2013

Conclusions (1)

- CTEPH is an important complication of acute PE
- V/Q Scan scan is key in the diagnosis of CTEPH
- Normal V/Q Scan rules out the diagnosis of CTEPH
- PEA should be considered in every CTEPH patient as the first line treatment option in patients with CTEPH
- A complete bilateral PEA remains the best option and may cure the disease
- PBA should be considered if the patient is not PEA candidate

Conclusions (2)

- Anticoagulation therapy should be continued for life
- Riociguat for non operable CTEPH and persistent/recurrent PH after PEA
- More research is needed to understand the mechanisms of fibrotic vascular remoduling seen in CTEPH

Thank you

Q & A

Back-up slides

PH Is a Rapidly Progressive, Ultimately Fatal Condition

Pulmonary Hypertension

WHO GROUP 1 PAH	WHO GROUP 2 Left-heart related	WHO GROUP 3 Lung/hypoxia related	WHO GROUP 4 CTEPH
Based on a sample of 194 patients followed between 1981 and 1988, median survival was estimated at 2.8 years (IPAH)[1]	In a study of 379 patients referred to a single center between 1992 and 1998, patients with Group 2 PH had 7× higher mortality than left-sided heart failure alone[2]	5-year survival rate in study of 84 total COPD patients was 36% in those with PH *vs* 62% in patients without PH[3] In a study of 79 IPF patients, the 6.5-year mortality rate was 60% among those with PH *vs* 30% in patients with IPF alone[4]	Mean survival 6.8 years without surgical treatment in a study of 48 Japanese patients[5]

CTEPH, chronic thromboembolic pulmonary hypertension; **IPF**, idiopathic pulmonary fibrosis; **[I]P[A]H**, [idiopathic] pulmonary [arterial] hypertension; **WHO**, World Health Organization. *Sources*: [1]D'Alonzo et al. *Ann Intern Med*. 1991;115:343–349. [2]Ghio et al. *J Am Coll Cardiol*. 2001;37:183–188. [3]Oswald-Mamosser et al. *Chest*. 1995;107:1193–1198. [4]Lettieri et al. *Chest*. 2006;129:746–752. [5]Kunieda et al. *Intern Med*. 1999;38:543–546.

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Table 2: Overview of Studies Reporting Clinical and Biomarker Response to Balloon Pulmonary Angioplasty

Author	n	Sessions/ Patient	Women (%)	Follow-up (months)	Pre-BPA FC I/II (%)	Post-BPA FC I/II (%)	Pre-BPA 6MWD (m)*	Post-BPA 6MWD (m)*	Pre-BPA NT-proBNP/ BNP (ng/l)*	Post-BPA NT-proBNP/ BNP (ng/l)*
Feinstein et al. 2001[12]	18	2.7	NR	34	0	88	209	497	NR	NR
Inami et al. 2014[43]	103	3.4	80	14	13	NR	360 (280–430)	420 (350–510)	95 (42–270)	34 (16–59)
Kinutani et al. 2016[44]	28	3	68	NR	29	96	303.0 ± 92	395 ± 124	160 ± 233	26.1 ± 30.5
Tatabe et al. 2016[23]	35	3.5	74	15	63	100	408 ± 181	482 ± 146	252 ± 237	34 ± 23
Ogo et al. 2016[22]	80	4.8	73	12	4	NR	372 ± 124	470 ± 99	227 ± 282	48 ± 57
Aoki et al. 2017[46]	77	5	82	38	68	NR	380 ± 138	486 ± 112	55.8 (25–219)	25 (16–50)
Olsson et al. 2017[17]	56	5	56	14	16	71	358 ± 108	391 ± 108	504 (233–1,676)	242 (109–555)
Yamasaki et al. 2017[47]	20	2.7	80	5	10	79	396 ± 120	441 ± 104	NR	NR
Ogawa et al. 2017[25]	380	4.6	70	18	19	96	318 ± 122	401 ± 105	240 ± 334	43 ± 76
Kreichbaum et al. 2018[28]	51	5	55	6	4	88	375 (281–446)	NR	821 (153–1872)	257 (115–508)
Brenot et al. 2019[30]	184	5.5	49	18	36	79	396 ± 120	441 ± 104	NR	NR
Hoole et al. 2020[18]	30	3	27	3	20	90	366 ± 107	440 ± 104	442 (168–1,607)	202 (155–447)
Velazquez et al. 2019[29]	46	3.4	70	15	12	88	395 ± 112	468 ± 103	1,233 ± 1,327	255 ± 318
Siennicka et al. 2019[31]	58	4.4	57	22	19	55	342 ± 142	NR	3,005 ± 4,650	NR
van Thor et al. 2020[36]	38	4.5	61	6	63	89	374 ± 124	422 ± 125	195 (96–1,812)	154 (71–387)

**Data are presented as mean ± SD or median (IQR). 6MWD = 6-minute walking distance; BPA= balloon pulmonary angioplasty; FC = functional class; NT-proBNP = N-terminal pro-brain natriuretic peptide; NR = not reported.*

Table 4: Overview of Studies Reporting Details of Complications Associated with Balloon Pulmonary Angioplasty

Author and Year	N	Sessions	Mortality	AE Rate	Wire Injury	PA Dissection or Perforation	Embolisation or Stent	Reperfusion or Lung Haemorrhage	Other
Feinstein et al. 2001[17]	18	47	5.6%	47%	2%	2%	2%	23%	Femoral pseudoaneurysm × 3
Ogo et al. 2016[22]	80	385	0%	16%	7.5%	0.3%	1.5%	4.7%	Haemoptysis 4.7%, Contrast allergy × 8
Ogawa et al. 2017[25]	380	1,408	2.6%	36.3%	NR	3.4%	1.3%	17.8%	Haemoptysis 14%, intubation × 17, ECMO × 9
Velazquez et al. 2019[29]	46	156	2.1%	28%	2.4%	6.4%	0.6%	5.8%	Haemoptysis 12.8%, intubation + ECMO × 1
Brenot et al. 2019[30]	184	1,006	2.2%	11.2%	NR	3.7%	0.6%	9.1%	Haemoptysis 7.1%, NIV 3%, intubation with/ without ECMO × 4
Hoole et al. 2020[18]	30	95	0%	10.5%	3.2%	NR	1%	3.2%	Haemoptyisis 5%, femoral pseudoaneurysm × 2
Maschke et al. 2019[32]	67	266	0%	10.9%	NR	1.1%	0%	2.2%	Haemoptysis 3%, dry cough 4.1%, atrial tachycardia × 1
Godinas et al. 2019[35]	18	91	0%	12%	3%	0%	1%	2%	Arrhythmia × 2, stress cardiomyopathy × 1
van Thor et al. 2020[36]	38	172	0%	12%	8%	1.5%	0%	0%	Conduction disturbance/ arrhythmia 1.5%

AE = adverse event; ECMO = extracorporeal membrane oxygenation; NIV non-invasive ventilation; NR = not reported; PA = pulmonary artery.