Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Current Management

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CLINICAL CLASSIFICATION OF PH

1. Pulmonary Arterial Hypertension

1.1 Idiopathic PAH
1.2 PAH with vasoreactivity
1.3 Heritable PAH
1.4 Drugs and toxins induced
1.5 Associated with:
- 1.5.1 Connective tissue disease
- 1.5.2 HIV infection
- 1.5.3 Portal hypertension
- 1.5.4 Congenital heart disease
- 1.5.5 Schistosomiasis

1.6 PAH with overt signs of venous/capillaries (PVOD/PCH) involvement

2. PH due to left heart disease

2.1 PH due to heart failure with preserved E.F
2.2 PH due to heart failure with reduced E.F
2.3 Valvular heart disease

3. PH due to lung diseases and/or hypoxia

3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease

4. PH due to pulmonary artery obstruction

4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions

5. PH with unclear mechanisms

5.1 Haematologic disorders
5.2 Systemic disorders
5.3 Others

G Simonneau, D Montani et *al. Eur Respir J 2018*

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

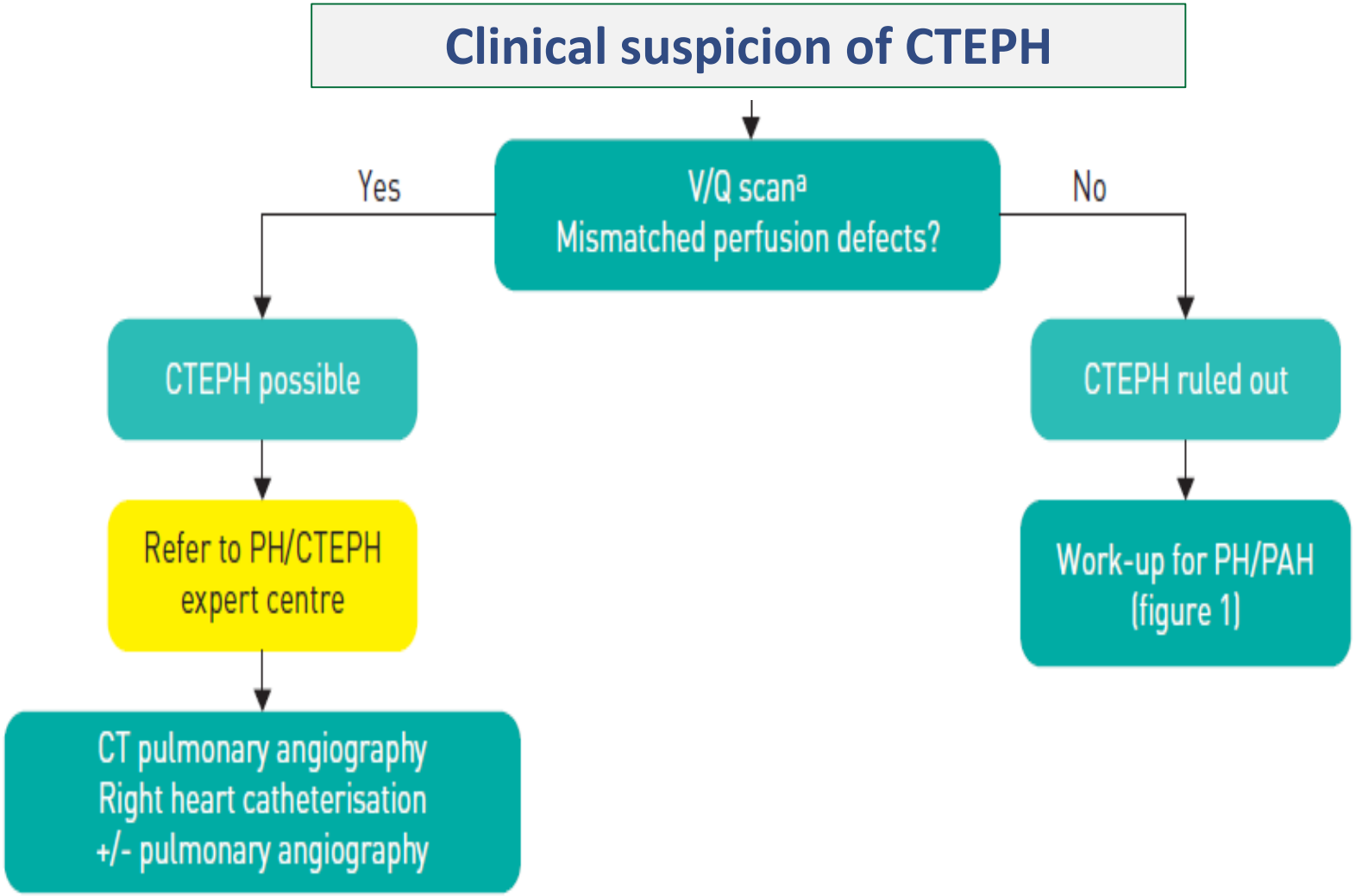
- CTEPH is a form of PH caused by non resolving thromboembolism of pulmonary arteries after at least 3 months of anticoagulation

- Incidence of CTEPH after an acute PE is around 2%

- It is a relatively frequent cause of PH, with 400 to 600 new cases a year in the french PH network

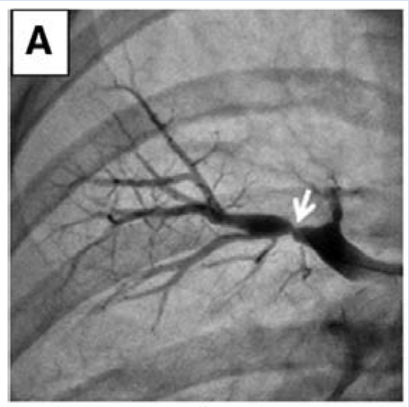
ESC/ERS Guidelines of Pulmonary Hypertension

CTEPH Diagnostic

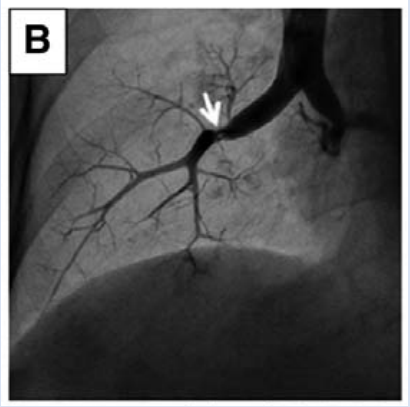


Pulmonary (selective) angiography

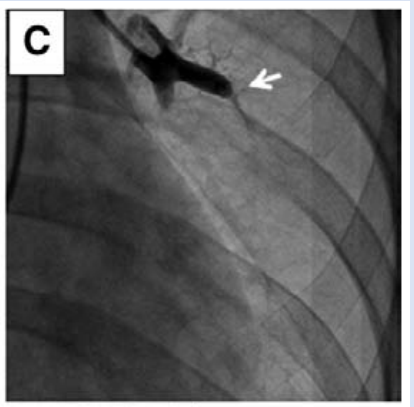
- Gold standard
- Typical findings[1,2]
  - Pouching
  - Webs or bands with or without post-stenotic dilation
  - Wall irregularities
  - Abrupt narrowing
  - Total occlusion of segmental or larger branches



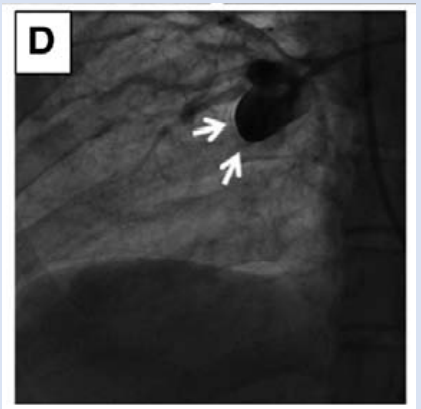
A. Ring-like stenosis lesion



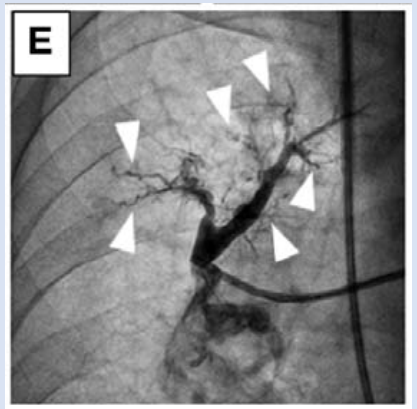
B. Web lesion



C. Subtotal lesion



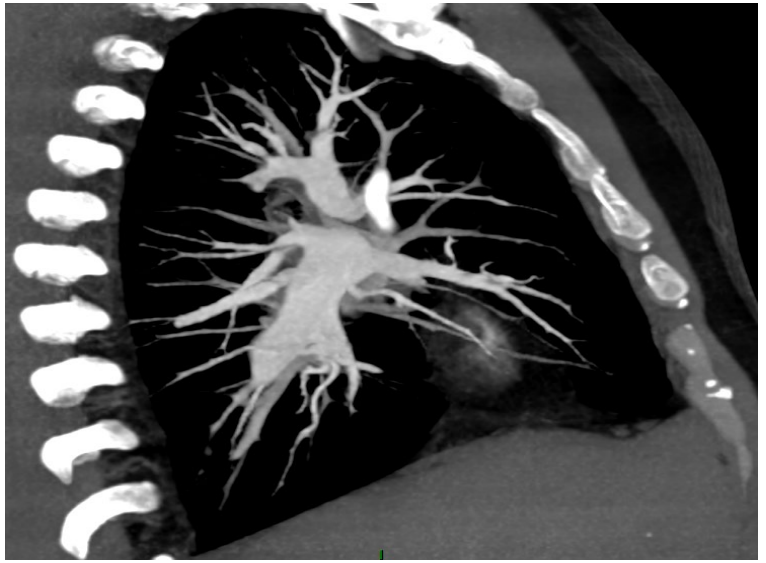
D. Total occlusion lesion

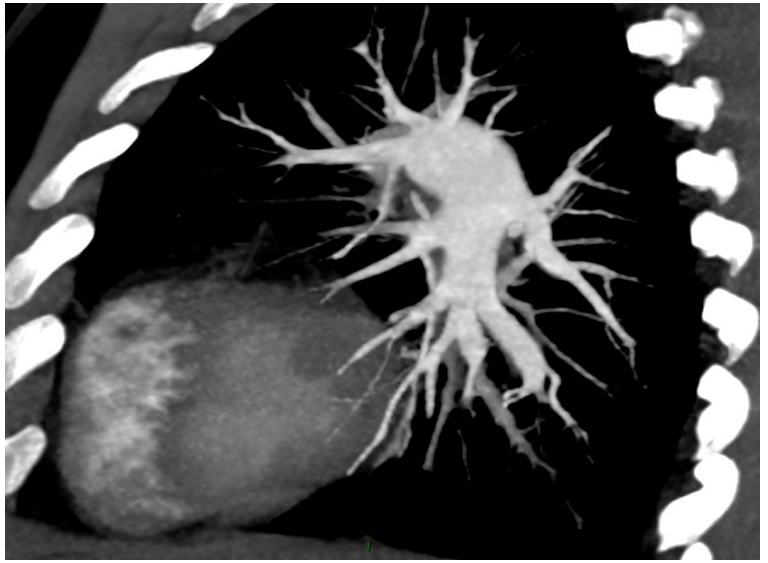


E. Tortuous lesion[3]

1. Nicod P *et al. Ann Intern Med* 1987;107:565–8. 2. Auger WR *et al. Radiology* 1992;182:393–8. 3. Kawakami T *et al. Circ Cardiovasc Interv* 2016;9:e003318.

CT pulmonary angiogram with bi-planar reconstruction





Natural history of CTEPH

Acute PE

↓

Incomplete resolution and organization of thrombi

↓

Stenosis/occlusion of pulmonary arteries

↓

***Micro-vessel vasculopathy* due to shear stress ('IPAH-like')**

↓

Progressive increase in pulmonary vascular resistance

Right heart dysfunction and symptomatic CTEPH

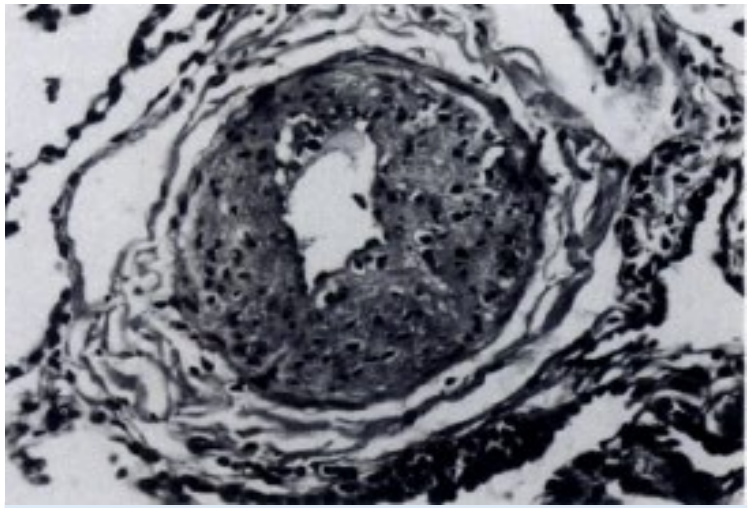
Rationale for using PAH targeted therapies in CTEPH

Method

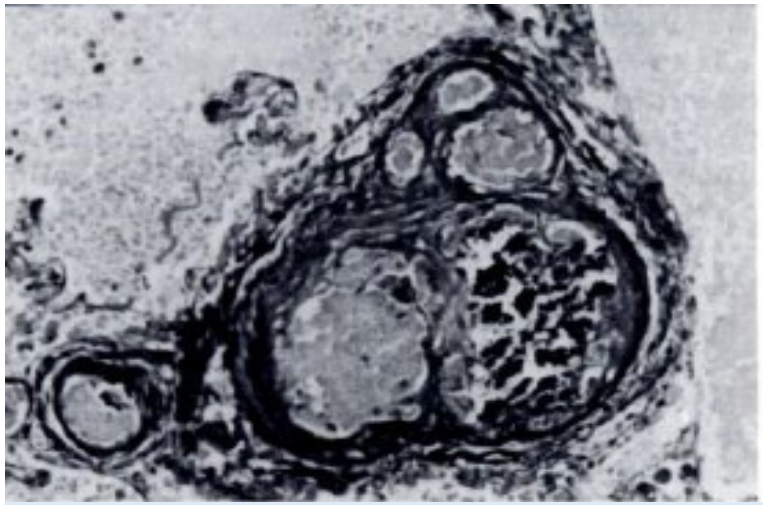
- Lung tissue obtained from patients with CTEPH by biopsy (n=15) or at autopsy (n=16)

Pathological examination indicated that IPAH cannot be differentiated from CTEPH on the basis of histological findings in small pulmonary arteries(0.5 mm)

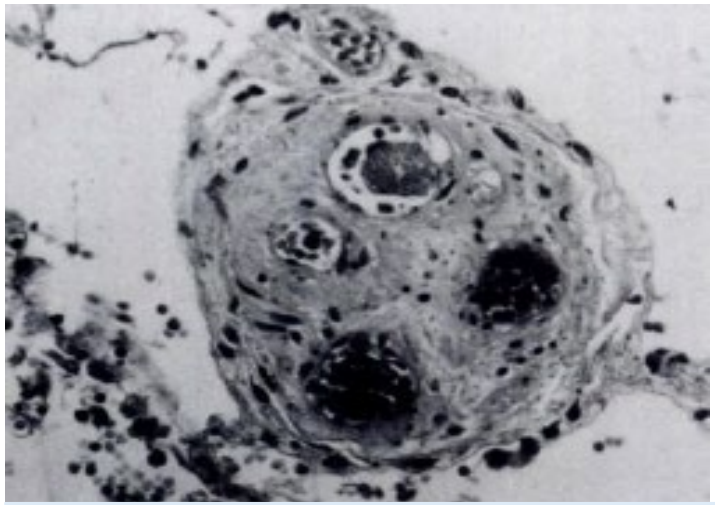
Small-vessel disease histopathology is similar in CTEPH and PAH



Intimal fibromuscular proliferation



Plexiform lesions



Thrombotic lesions

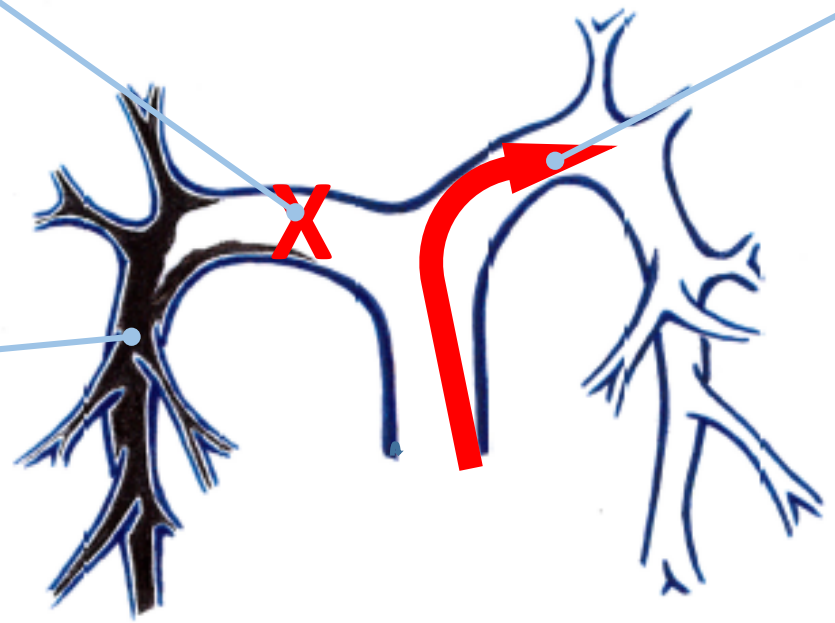
Moser KM, Bloor CM. *Chest* 1993.

Mechanisms inducing small-vessel disease in CTEPH

Shear stress-inducing vasculopathy of small pulmonary arteries

1 Right pulmonary artery totally obstructed by a proximal organized clot

2 No pulmonary blood flow on right-hand side



3 Overall pulmonary blood flow redistributed to left-hand side

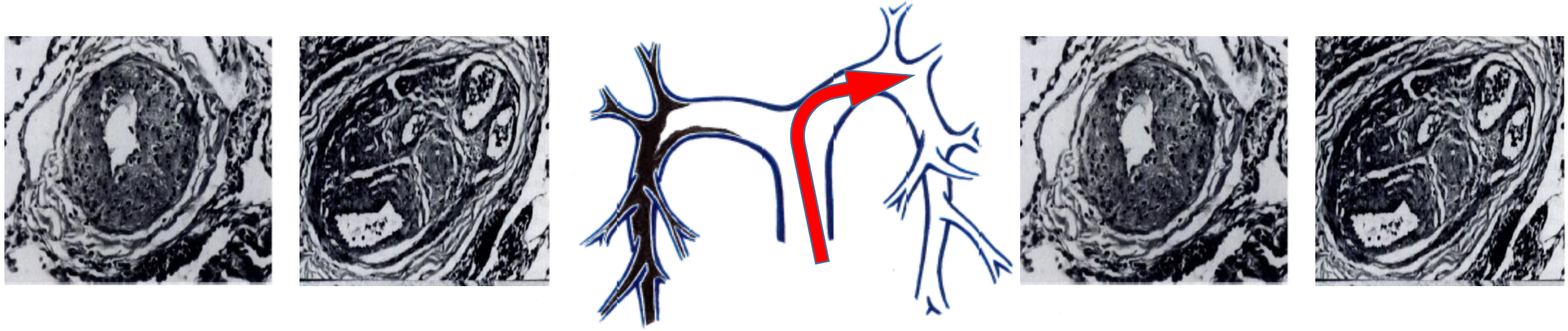
4 High flow and high pressure in left lung

5 Endothelial shear stress and proliferation of small pulmonary artery wall

Pulmonary Vascular Lesions Occurring in Patients With Chronic Major Vessel Thromboembolic Pulmonary Hypertension*

Kenneth M. Moser, M.D., F.C.C.P.; and Colin M. Bloor, M.D.

Chest 1993;103:685–92.

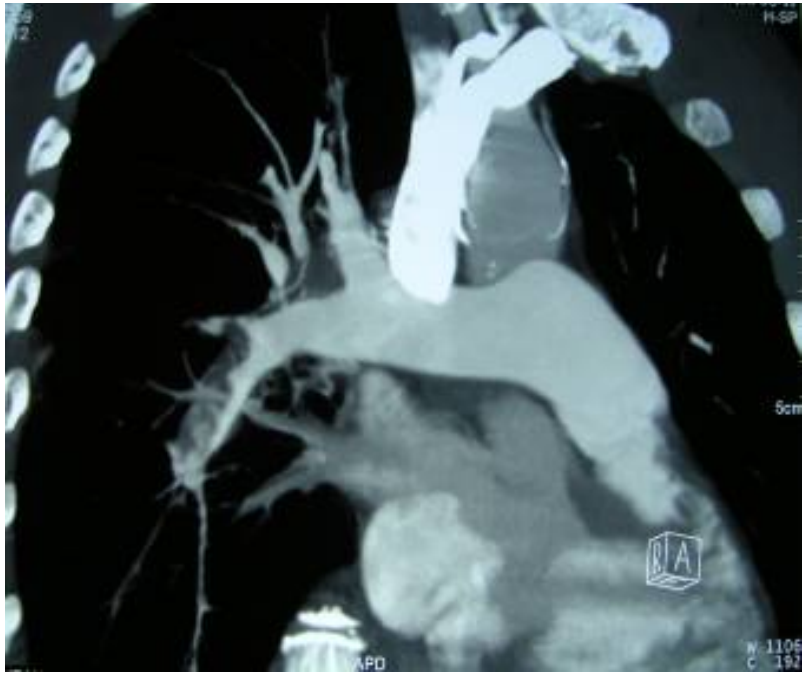


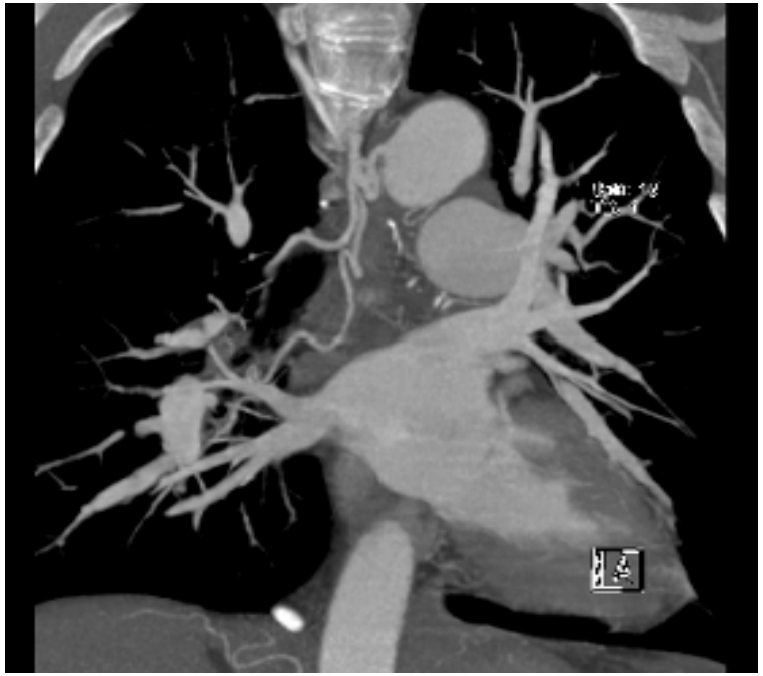
*"….the pulmonary hypertensive lesions, including plexogenic lesions, occurred not only in lung regions served by open proximal vessels – and therefore exposed to pulmonary hypertension – but **also in lung regions distal to completely obstructed and partially obstructed proximal vessels**, as previously noted by others. Data from experimental animals have documented that similar lesions develop distal to ligated pulmonary arteries. The mechanisms responsible remain obscure."*

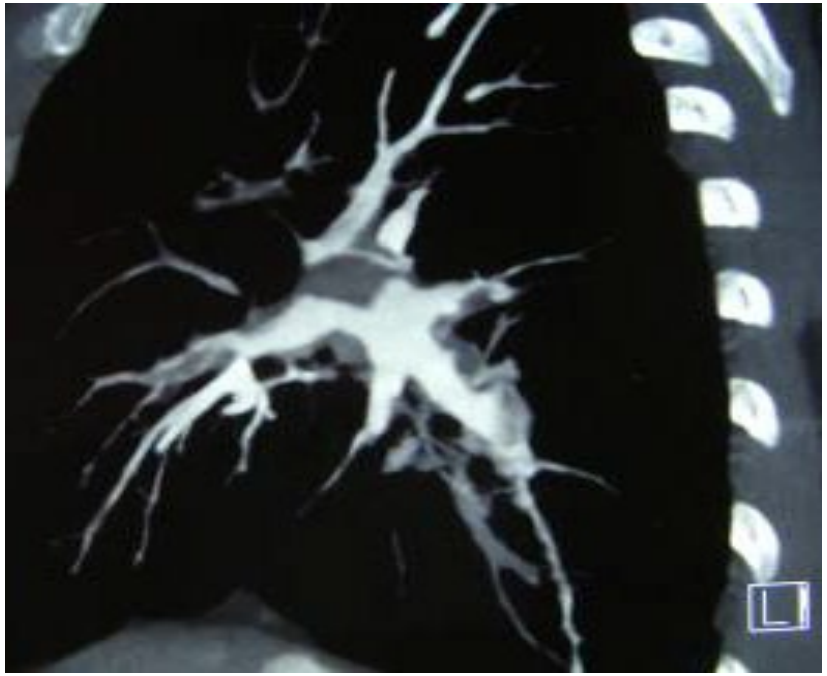
Moser KM, Bloor CM. *Chest* 1993;103:685–92.

Mechanisms inducing small-vessel disease in CTEPH

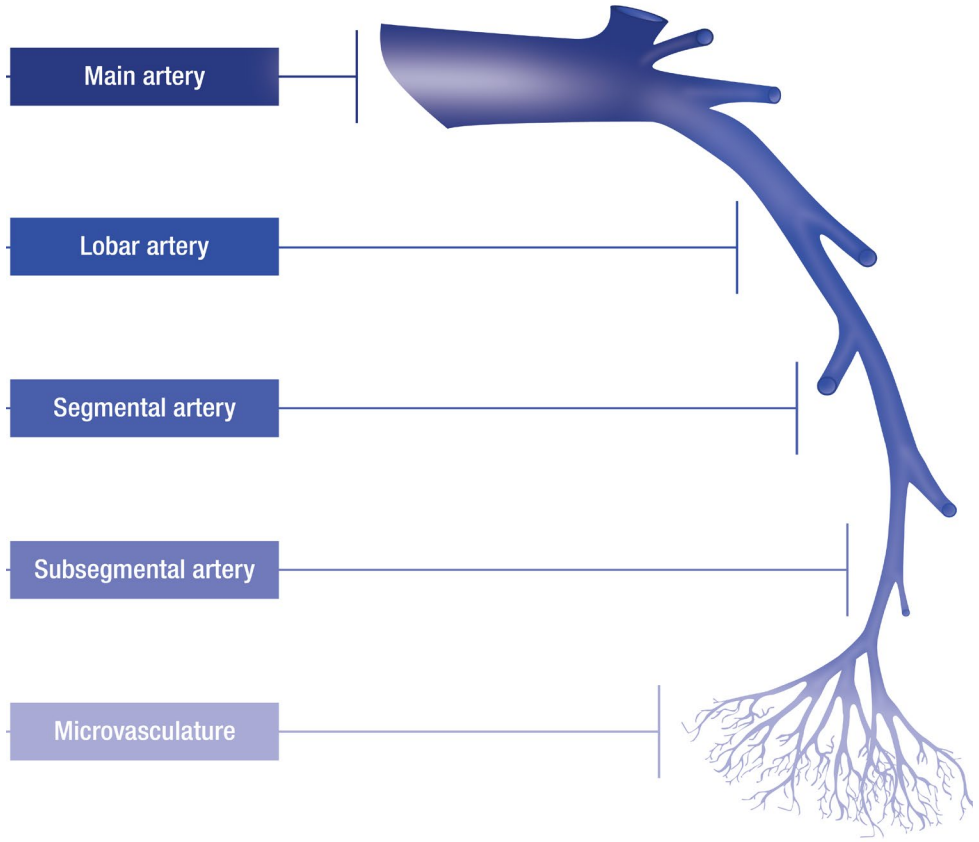
Development of microvasculopathy is also a consequence of exposure of the pulmonary artery circulation to the high-pressure systemic circulation due to the development of anastomoses between bronchial arteries and pulmonary arterial circulation

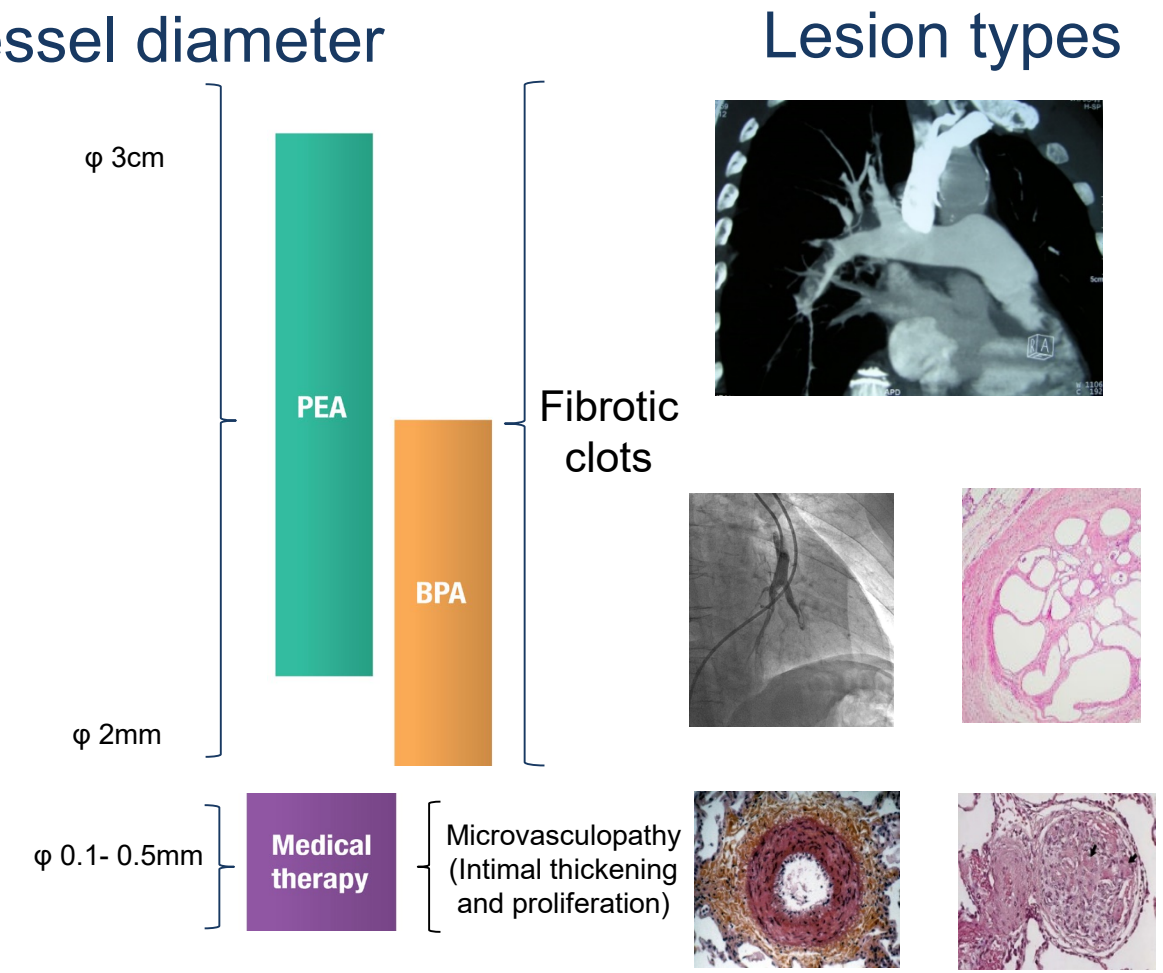






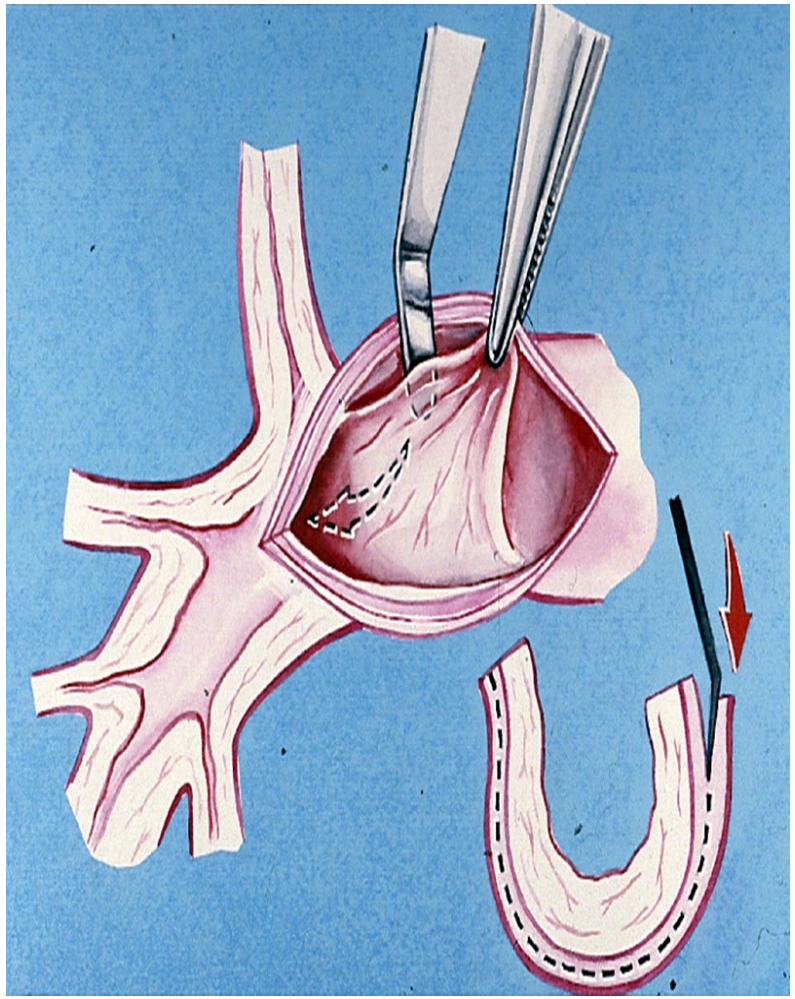
Site of action surgery(PEA), Angioplasty (BPA) and PAH drugs (today only Riociguat approved)

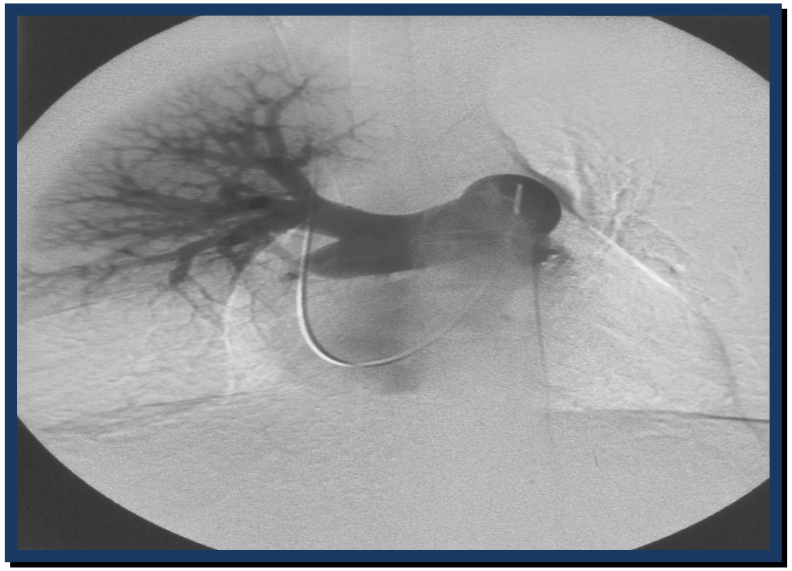




Madani M, Ogo T and Simonneau G, *Eur Respir Rev* 2017

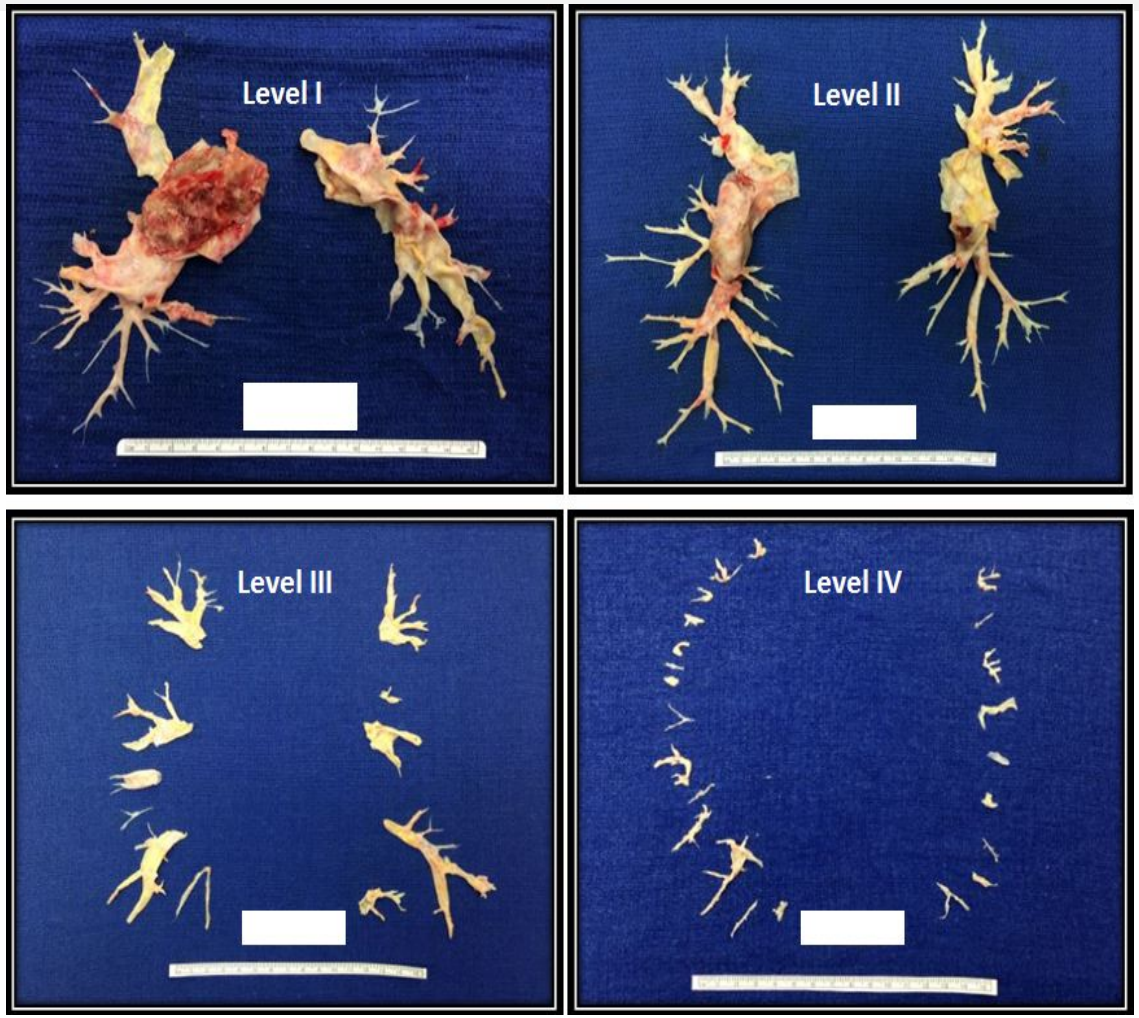
Pulmonary endarterectomy remains the treatment of choice of proximal diseases in the absence of contraindication





Pulmonary Endarterectomy is the gold standard treatment for operable patients

PVR (dyn·s·cm^{-5}) from 1169 to 294



PVR(dyn·s·cm^{-5}) from1290 to 204

PVR(dyn·s·cm^{-5}) from 858 to 365

PVR(dyn·s·cm^{-5}) 527 to 188

M Madani et al . Ann Thorax Surg 2012

Pulmonary Endarterectomy is the gold standard treatment for operable patients

PVR 1169 to 294

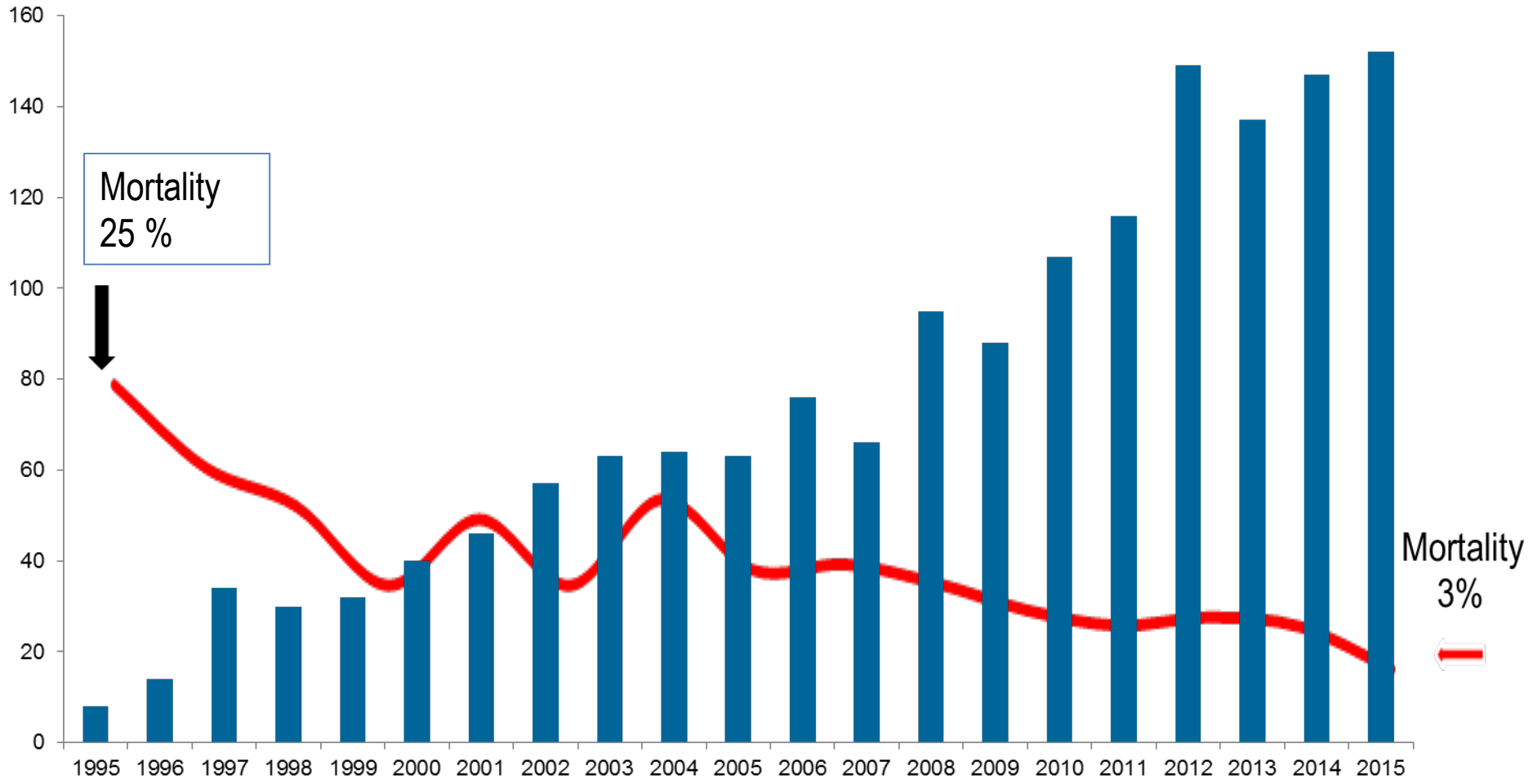
PVR 1290 to 204

PVR 858 to 365

PVR 527 to 188

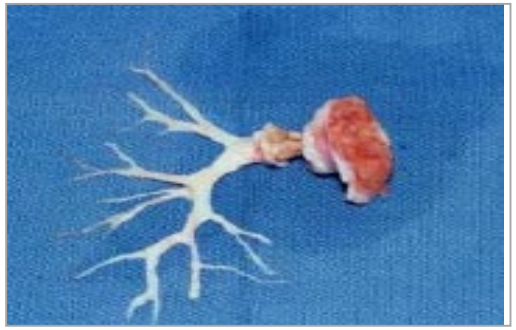
M Madani et al . Ann Thorax Surg 2012

1577 Pulmonary endarterectomies
Paris Sud University (1995-2015)

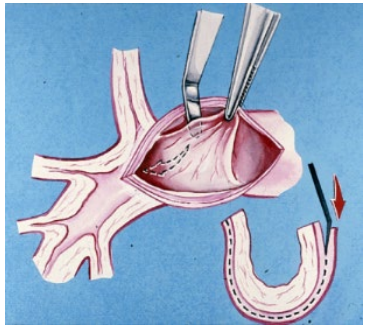


Different therapeutic strategies according to the type and the localisation of vascular lesions

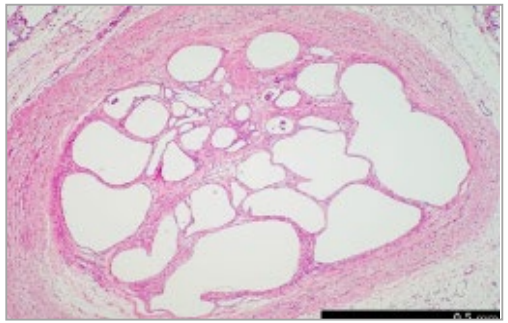
Proximal fibrotic lesions:
Main, lobar, segmental pulmonary arteries



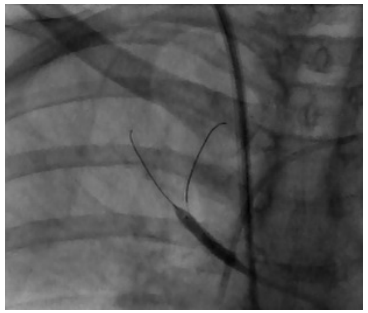
PEA



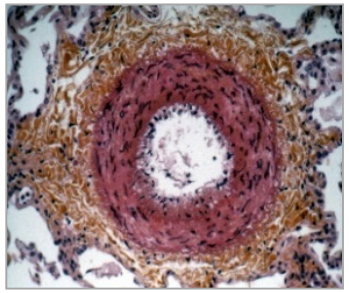
Distal fibrotic lesions:
Sub-segmental and more distal PA up to 3 mm diameter

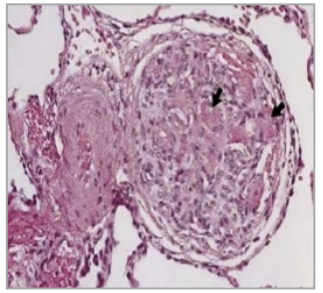


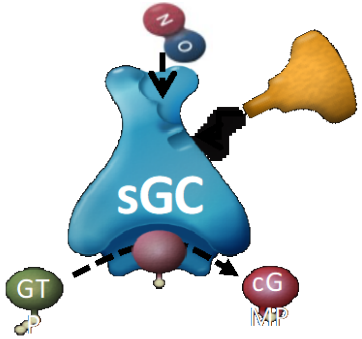
BPA



Small vessels disease (similar to those found in IPAH):
Thickening of small PA wall (0.1 to 0.5 mm diameter)







Med. Rx. (*Riociguat*)

Balloon pulmonary angioplasty for inoperable CTEPH

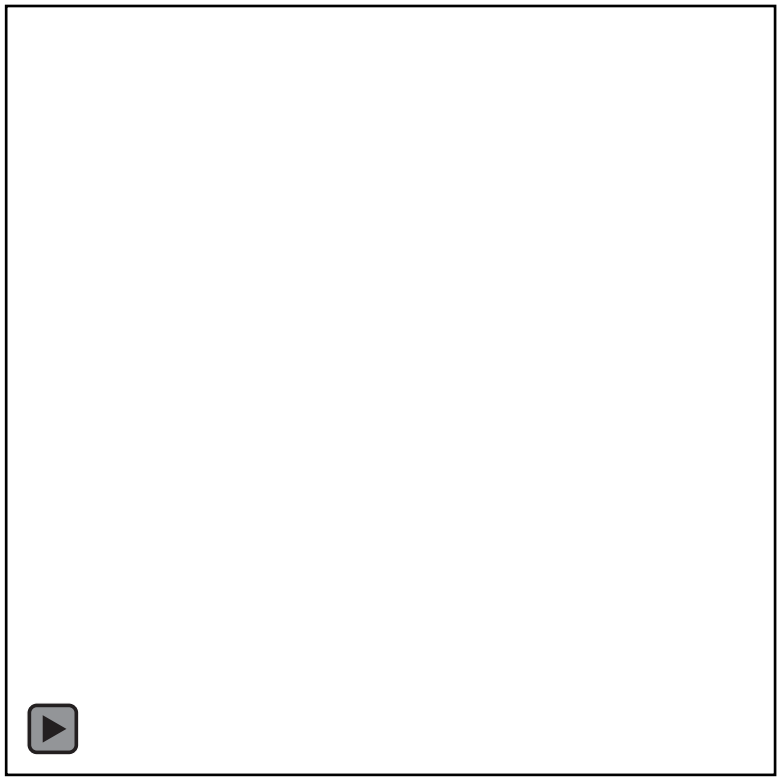
- BPA was first developed for treating PA congenital stenosis [1]
- A 1st case series of 18 patients from USA was reported in 2001[2] with a treatment effect less than those obtained with PEA and with a high rate of severe complications
- Over the last 10 years , several centers in Japan (Okayama, Osaka, 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[3]

1.Lock HE et al . Circulation 1983. 2. Feinstein JA et al . Circulation 2001.
3.A Ogawa & H Matsubara. Reviews in Medicine 2015.

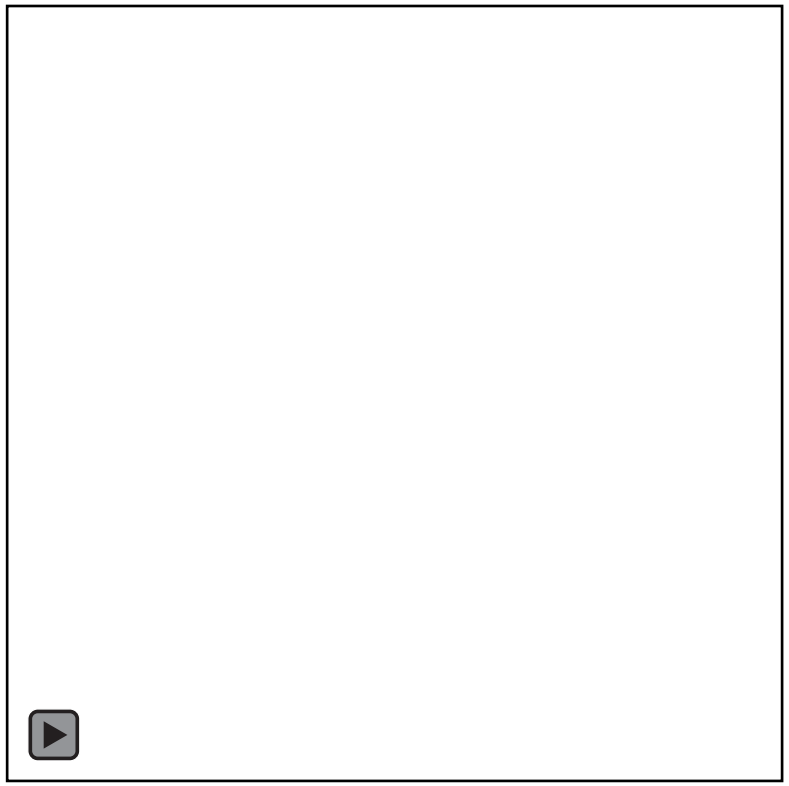
Balloon Pulmonary Angioplasty (BPA)

(To be effective need to target around 12 segmental PA in 6 sessions)

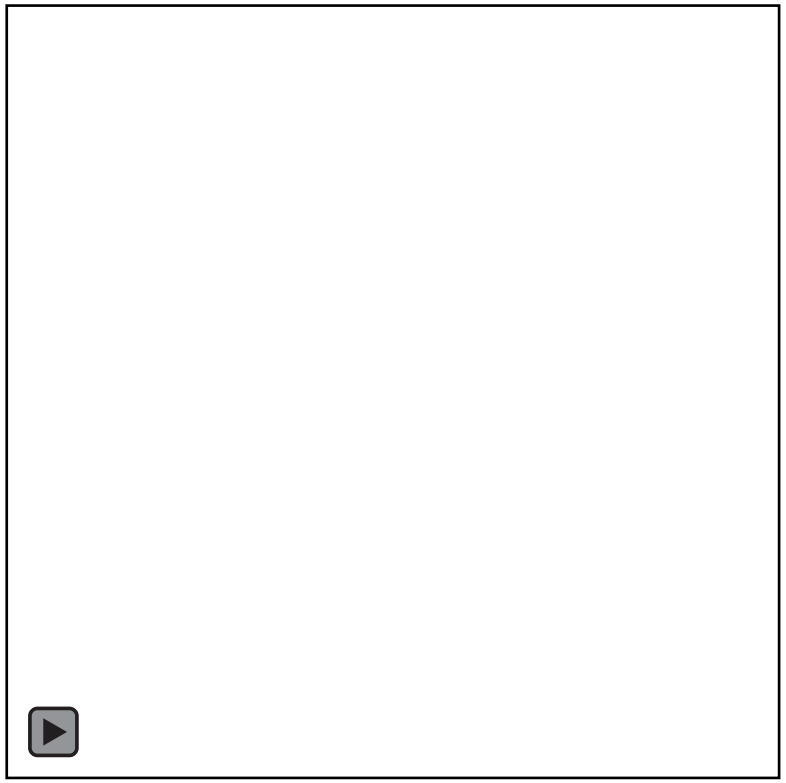
Selective angio



Balloon dilatation



After dilatation



Balloon Pulmonary Angioplasty (BPA) in CTEPH : the Japanese experience

Hemodynamic results

	N	Before BPA PVR	After BPA PVR	Treatment effect
Mizoguchi 2012	68	942±367	327±151	-65%
Sugimura 2012	12	672±236	310±73	-54%
Fukui 2014	20	889±365	490±201	-45%
Taniguchi 2014	29	763±308	284±128	-63%

Mizoguchi H, Circ Cardiovasc Interv 2012; Sugimura K, Circ J 2012;; Fukui S, Eur Respir J 2014; Taniguchi Y et al, EuroIntervention 2014

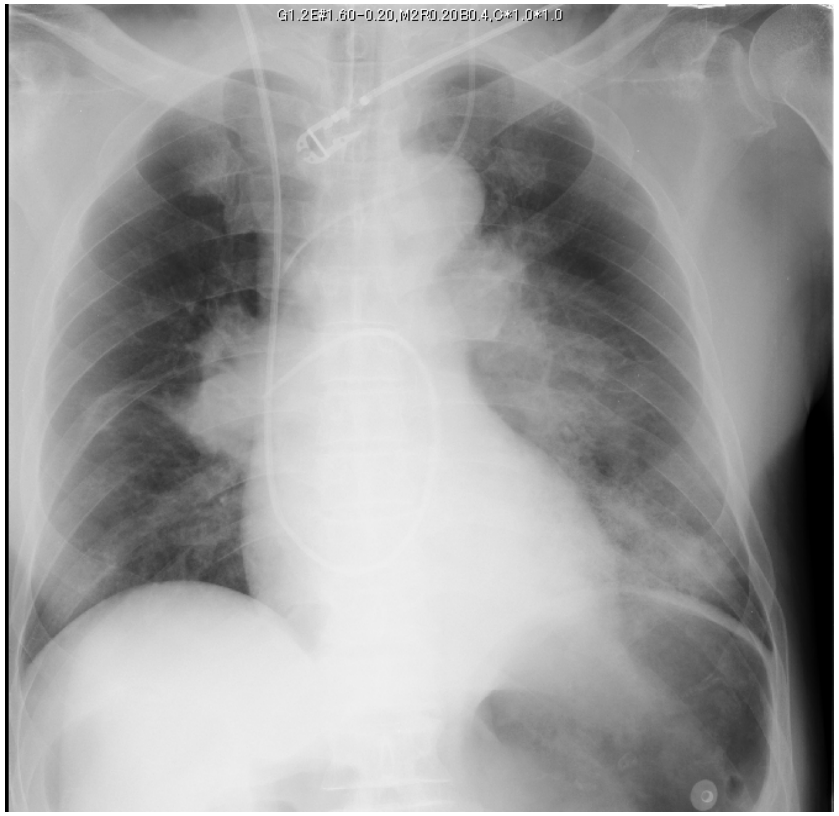
BPA: Safety

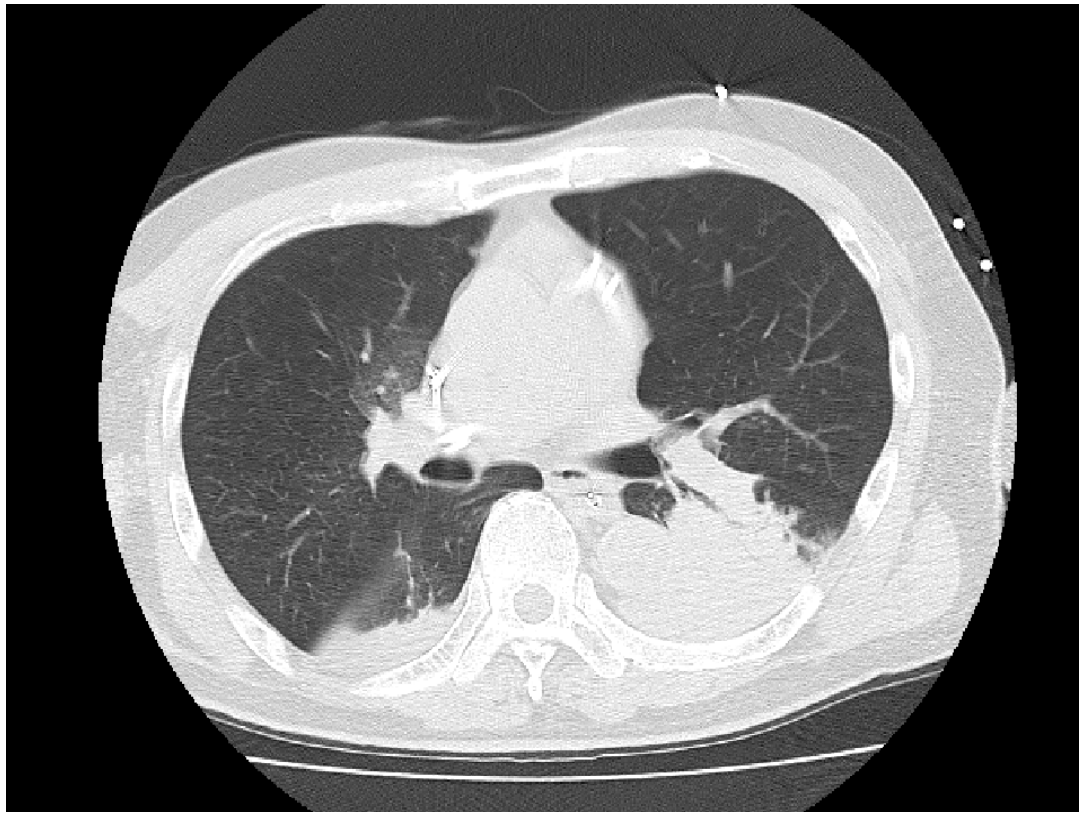
- Complications relatively frequent 10% of sessions and 38% of patients
- Mortality between 0% and 5%
- Main complications are pulmonary artery injuries :PA ruptures, PA dissection, PA perforations leading to lung injury with or without hemoptysis (2)
- There is a correlation between the rate of complications & hemodynamic severity (1)

	lung injury +	*lung injury -*	***p***
PAPm *(mmHg)*	**42 (38-50)**	**33(28-41)**	**0,0001**
RVP*(UW)*	**9,2(7-14,6)**	**6,1(3,9-8,7)**	**0,0001**

1. Inami et al, International Journal cardiology 2013 2. Imani et al, JACC cardiovascular intervention, 2015

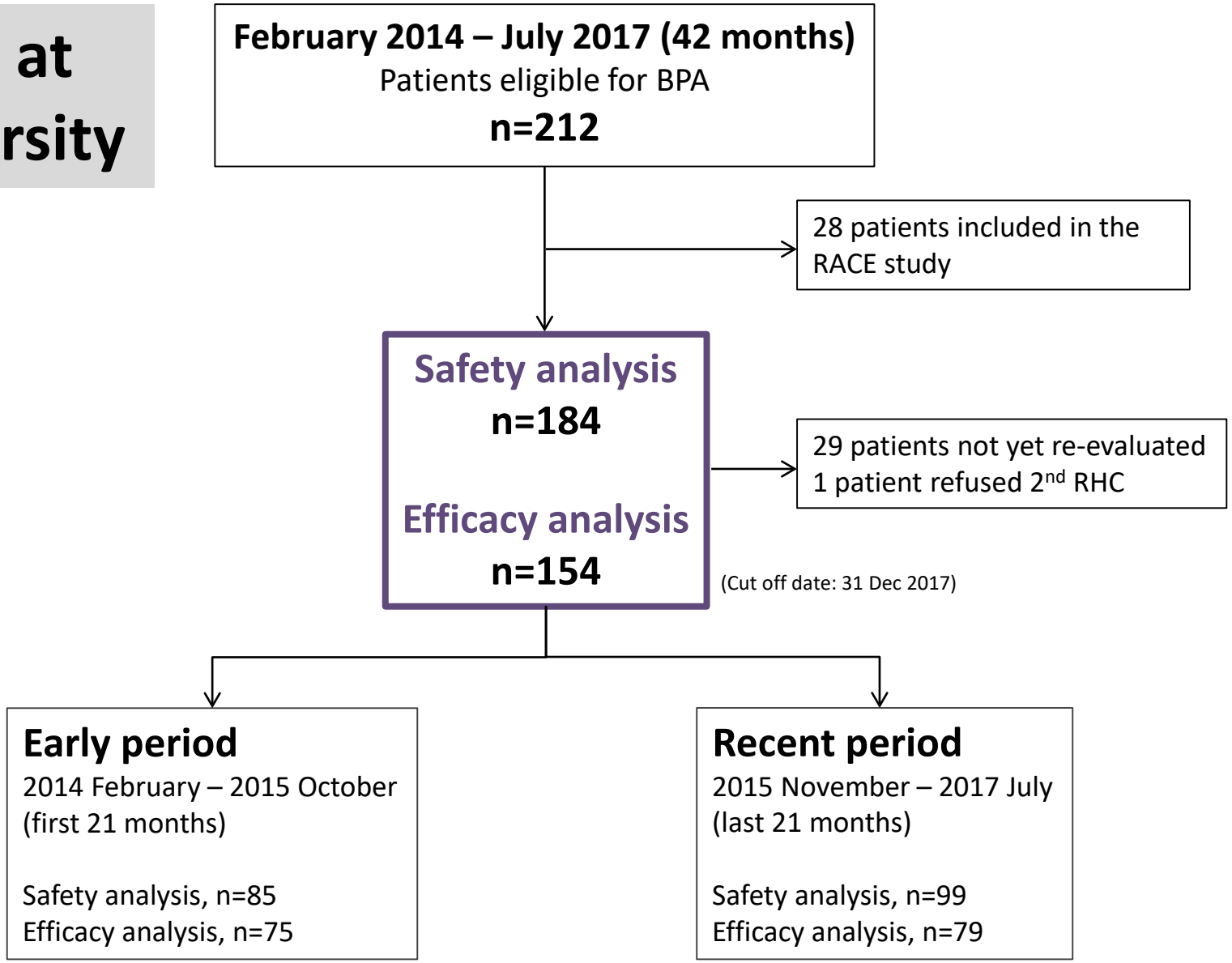
lung injury after BPA





- Characterised by localised and dense lung opacities on CT SCAN
- Immediatly or few hours after BPA
- Severity highly variable
- With or without hemoptysis

BPA experience at Paris Sud University



Patients Characteristics (n=184)

Mean age: 63±14 **Male/female ratio 51%**

Pulmonary hypertension therapy	
sGC stimulator (n, %)	59 (32.1)
ERA (n, %)	73 (39.7)
PDE5-I (n, %)	47 (25.5)
Prostacyclin analog (n, %)	13 (7.1)
Number of medications (none/single/double/triple) (%)	38.0 / 26.6 / 28.3 / 7.1
Indication for BPA	
Clot inaccessibility (n, %)	149 (81.0)
Low risk/benefit ratio for PEA (n, %)	13 (7.0)
Refusal of PEA (n, %)	2 (1.1)
Post-PEA (n, %)	15 (8.2)
Other (n, %)	5 (2.7)

Safety results in 184 patients

Events per session	Total (n=1006)	Early period (n=444)	Recent period (n=562)	p value*
Overall complications (n, %)	113 (11.2)	70 (15.8)	43 (7.7)	< 0.001
Lung injury (n, %)	92 (9.1)	59 (13.3)	33 (5.9)	< 0.001
Mild / Moderate	36 (3.6)	13 (2.9)	23 (4.1)	0.394
Severe	56 (5.6)	46 (10.4)	10 (1.8)	< 0.001
Hemoptysis (n, %)	71 (7.1)	36 (8.1)	35 (6.2)	0.266
Pulmonary artery perforation (n, %)	28 (2.8)	16 (3.6)	12 (2.1)	0.179
Pulmonary artery dissection (n, %)	19 (1.9)	9 (2.0)	10 (1.8)	0.774
Renal dysfunction (n, %)	2 (0.2)	2 (0.5)	0 (0.0)	0.195

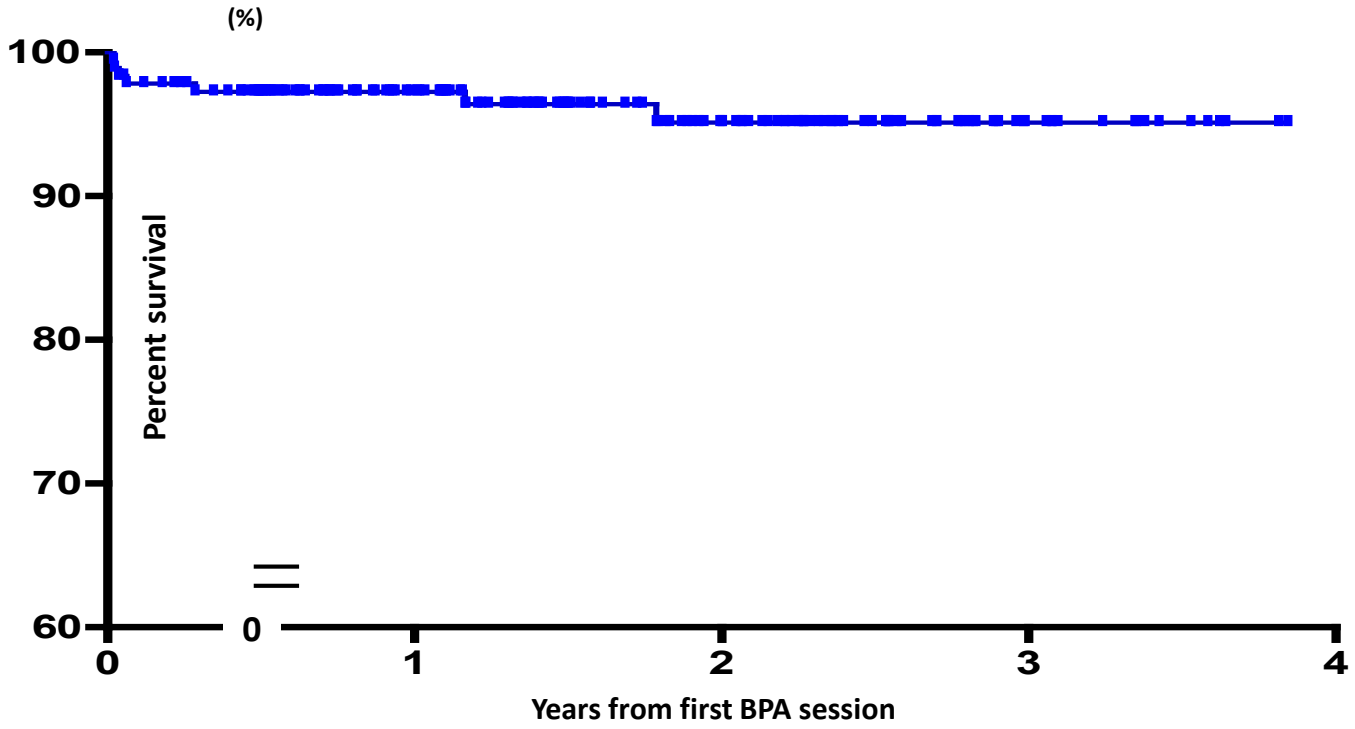
Efficacy results in 154 patients

Variables	Total (n=154)		
	Before	p value	After
Characteristics			
NYHA FC (I,II / III,IV) (%)	35.3 / 64.7	< 0.001	78.7 / 21.3
6MWD (m)	396 ± 120	< 0.001	441 ± 104
PaO2 (mmHg)	65.0 ± 9.0	< 0.001	73.3 ± 12.0
Hemodynamics			
Mean PAP (mmHg)	43.9 ± 9.5	< 0.001	31.6 ± 9.0
Mean RAP (mmHg)	8.1 ± 3.8	< 0.001	6.3 ± 2.8
PAWP (mmHg)	9.6 ± 3.4	0.050	10.3 ± 3.5
Cardiac Index (L/min/m^2)	2.68 ± 0.60	< 0.001	3.07 ± 0.75
PVR (dynes.s.cm^{-5})	604 ± 226	< 0.001	329 ± 177
SvO2 (%)	62.6 ± 7.4	< 0.001	67.9 ± 7.3
% decrease of mean PAP (%)			**-26.1 ± 21.3**
% decrease of PVR (%)			**-42.7 ± 27.4**

Efficacy results in 154 patients

	Early period (n=75)			Recent period (n=79)			*P value
	Before	p value	After*	Before	p value	After*	
Mean PAP (mmHg)	44.3 ± 9.8	< 0.001	33.8 ± 9.8	43.6 ± 9.1	< 0.001	29.5 ± 7.7	0.003
Mean RAP (mmHg)	8.0 ± 3.7	0.010	6.6 ± 2.9	8.2 ± 3.8	< 0.001	6.0 ± 2.7	0.149
PAWP (mmHg)	9.8 ± 3.5	0.176	10.4 ± 3.8	9.4 ± 3.2	0.160	10.1 ± 3.3	0.524
Cardiac Index (L/min/m^2)	2.62 ± 0.58	< 0.001	2.96 ± 0.80	2.73 ± 0.62	< 0.001	3.18 ± 0.68	0.062
PVR (dynes.s.cm^{-5})	607 ± 218	< 0.001	371 ± 188	601 ± 236	< 0.001	289 ± 157	0.004
SvO2 (%)	62.9 ± 7.5	< 0.001	67.3 ± 8.1	62.4 ± 7.3	< 0.001	68.5 ± 6.4	0.353
% decrease of mean PAP (%)			-21.9 ± 21.5			-30.1 ± 20.4	0.017
% decrease of PVR (%)			-36.5 ± 29.1			-48.6 ± 24.5	0.006

BPA Survival

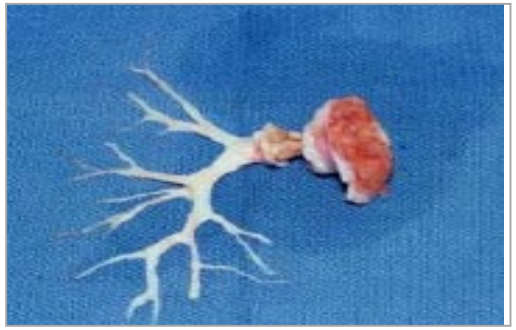


Patients at risk	184	126	65	17

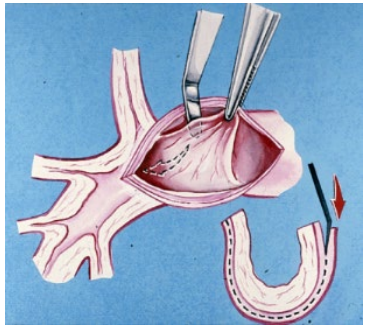
7 deaths among the 184 Patients (3-8%)
4 related to the procedure (2.2%) 3.5% (1st period) and 1% (2nd period)
No deaths over the last year

Different therapeutic strategies according to the type and the localisation of vascular lesions

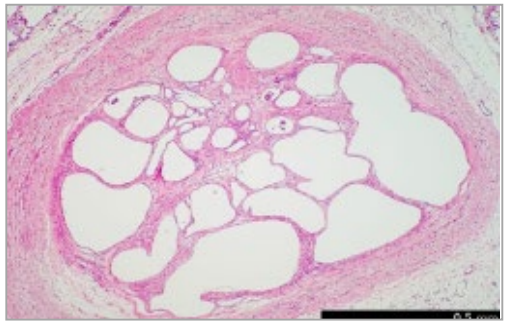
Proximal fibrotic lesions:
Main, lobar, segmental pulmonary arteries



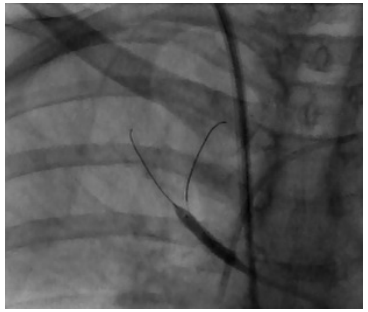
PEA



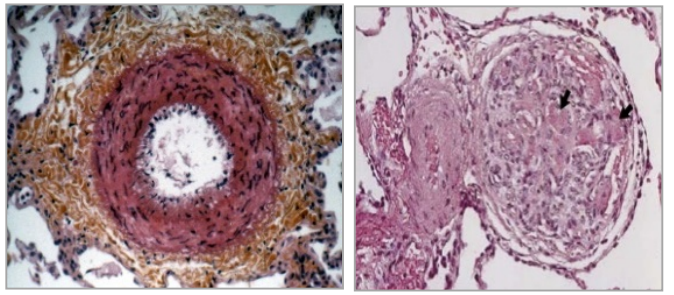
Distal fibrotic lesions:
Sub-segmental and more distal PA up to 3 mm diameter

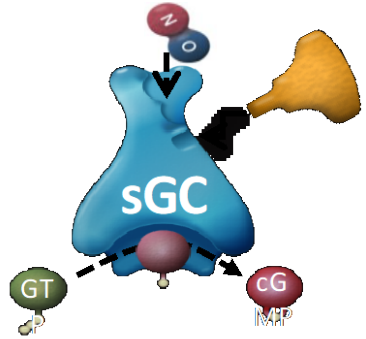


BPA



Small vessels disease (similar to those found in IPAH): Thickening of small PA wall(0.1 to 0.5 mm diameter)



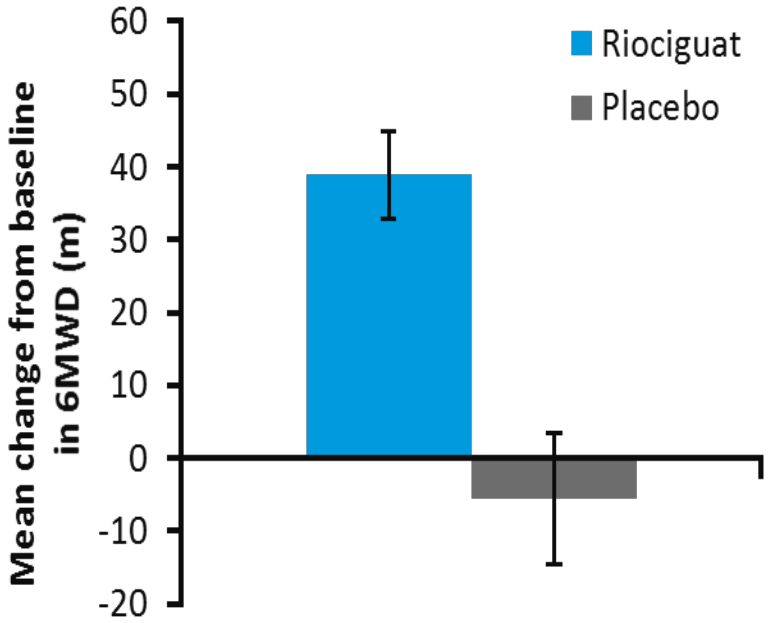


Med. Rx. (*Riociguat*)

Efficacy of Riociguat in non operable CTEPH and persistent PH after PEA assessed at week 16 (overall population: 173 Riociguat/88 Placebo)

Primary endpoint

+46 m *p*<0.001
(95% CI: 25–67 m)



Secondary efficacy end-points (hemodynamic and biomarkers)

Parameter	Riociguat		Placebo		Placebo-corrected LS-mean difference	Riociguat vs placebo; p-value
	Baseline	change from baseline	Baseline	change from baseline		
PVR (dyn·s·cm^{-5})	791	-223 (-28%)	834	-9 (-1%)	-226	<0.0001
mPAP (mmHg)	47.1	-3.9 (-8%)	48.9	-0.5 (-1%)	-3.8	0.0002
CI (L/min/m^2)	2.52	+0.54 (+21%)	2.49	-0.02 (-1%)	+0.56	<0.0001
NT-proBNP (ng/L)	1027	-198 (-19%)	1228	+232 (+19%)	-432	<0.0001

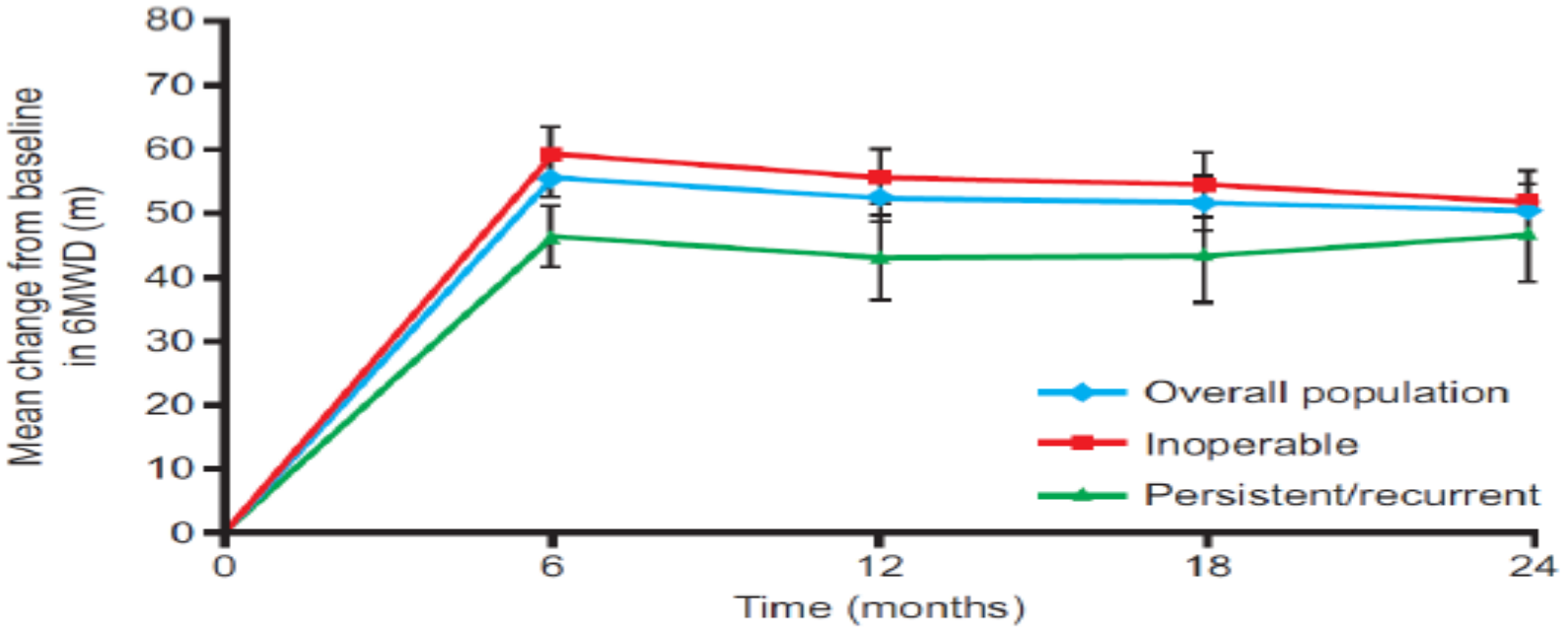
Ghofrani HA, *et al.* N Engl J Med 2013

Riociguat was well tolerated with a good safety profile

Adverse event (treatment-emergent)	Riociguat n=173	Placebo n=88
Ten most frequently reported AEs		
Headache	43 (25%)	12 (14%)
Dizziness	39 (23%)	11 (13%)
Peripheral edema	27 (16%)	18 (21%)
Cough	9 (5%)	16 (18%)
Nasopharyngitis	26 (15%)	8 (9%)
Dyspnea	8 (5%)	12 (14%)
Nausea	19 (11%)	7 (8%)
Diarrhea	17 (10%)	4 (5%)
Vomiting	17 (10%)	3 (3%)
AEs of special interest		
Hypotension	16 (9%)	3 (3%)
Syncope	4 (2%)	3 (3%)

Ghofrani HA, *et al.* N Engl J Med 2013

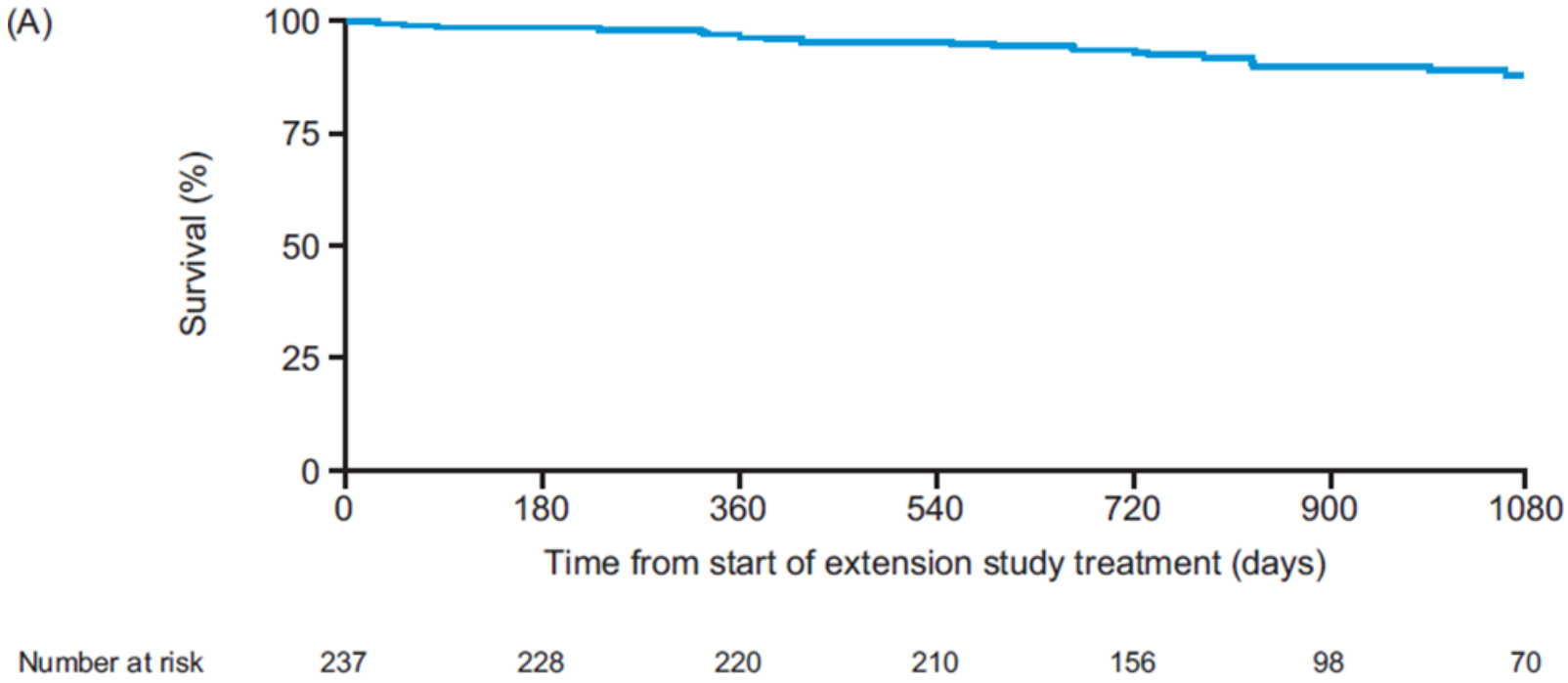
Improvements in 6MWD were sustained over 2 years of riociguat treatment in CHEST-2



Mean 6MWD absolute values (m)				
351	408	404	407	407
346	408	405	407	407
363	407	403	405	405
Number of patients				
237	218	209	199	162
172	158	154	146	119
65	60	55	53	43

Simonneau G *et al*. Lancet Respir Med. 2016

Survival in CHEST-2



- The estimated survival rate was 97% (95% CI 93–98) at 1 year and 93% (95% CI 89–96) at 2 years

Simonneau G *et al*. Lancet Respir Med. 2016

Frequency of AEs per 100 patient-years in Chest-2

AEs, n (rate per 100 patient-years)[a]	CHEST-1	CHEST-2
	Riociguat (n=173)	Total (n=237)
Any AE	889 (1732.5)	2081 (550.9)
5 most frequent AEs in CHEST-2		
Nasopharyngitis	29 (56.5)	86 (22.8)
Dizziness	57 (111.1)	61 (16.2)
Peripheral edema	30 (58.5)	61 (16.2)
Upper respiratory tract infection	11 (21.4)	40 (10.6)
Diarrhea	27 (52.6)	39 (10.3)
Dyspnea	9 (17.5)	39 (10.3)
AEs of special interest		
Syncope	4 (7.8)	22 (5.8)
Hypotension[b]	16 (31.2)	17 (4.5)
Other AEs of interest		
Hemoptysis	4 (7.8)	10 (2.7)

Simonneau G *et al*. Lancet Respir Med. 2016

Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study

Lancet Respir Med 2017

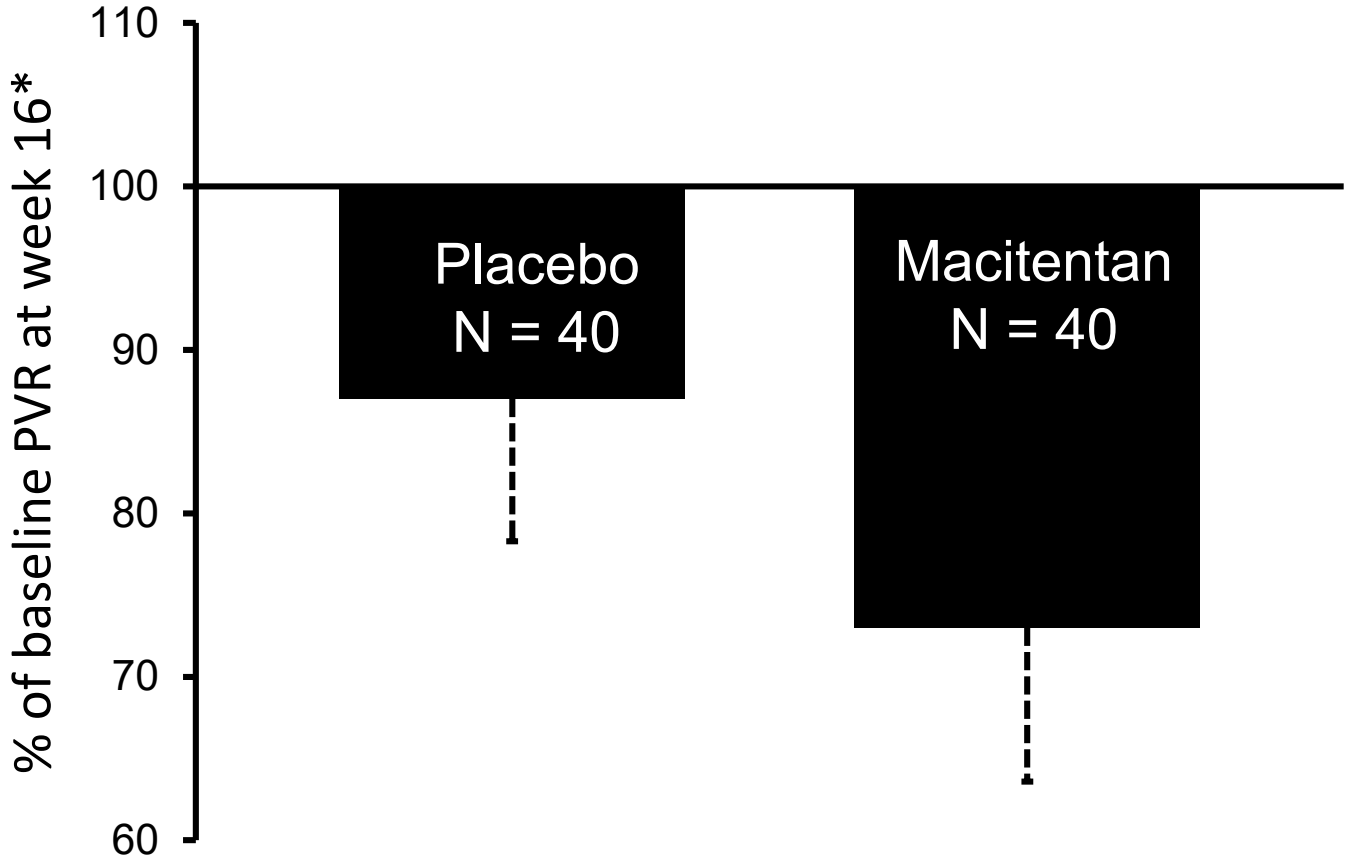
*Hossein-Ardeschir Ghofrani, Gérald Simonneau, Andrea M D'Armini, Peter Fedullo, Luke S Howard, Xavier Jaïs, David P Jenkins, Zhi-Cheng Jing, Michael M Madani, Nicolas Martin, Eckhard Mayer, Kelly Papadakis, Dominik Richard, Nick H Kim, on behalf of the MERIT study investigators**

- Multicentre, double-blind, randomised, placebo-controlled phase 2 study
- To evaluate the efficacy and safety of macitentan in patients with inoperable CTEPH
- Inoperability was confirmed by independent pre-inclusion adjudication
- Treatment with PDE-5i and/or inhaled/oral prostanoid at baseline was allowed for patients in WHO FC III and IV
- Primary endpoint : Change in PVR from baseline to week 16
- Main Secondary endpoint : Change in 6MWD from baseline to week 24

Primary endpoint – Change in PVR at week 16

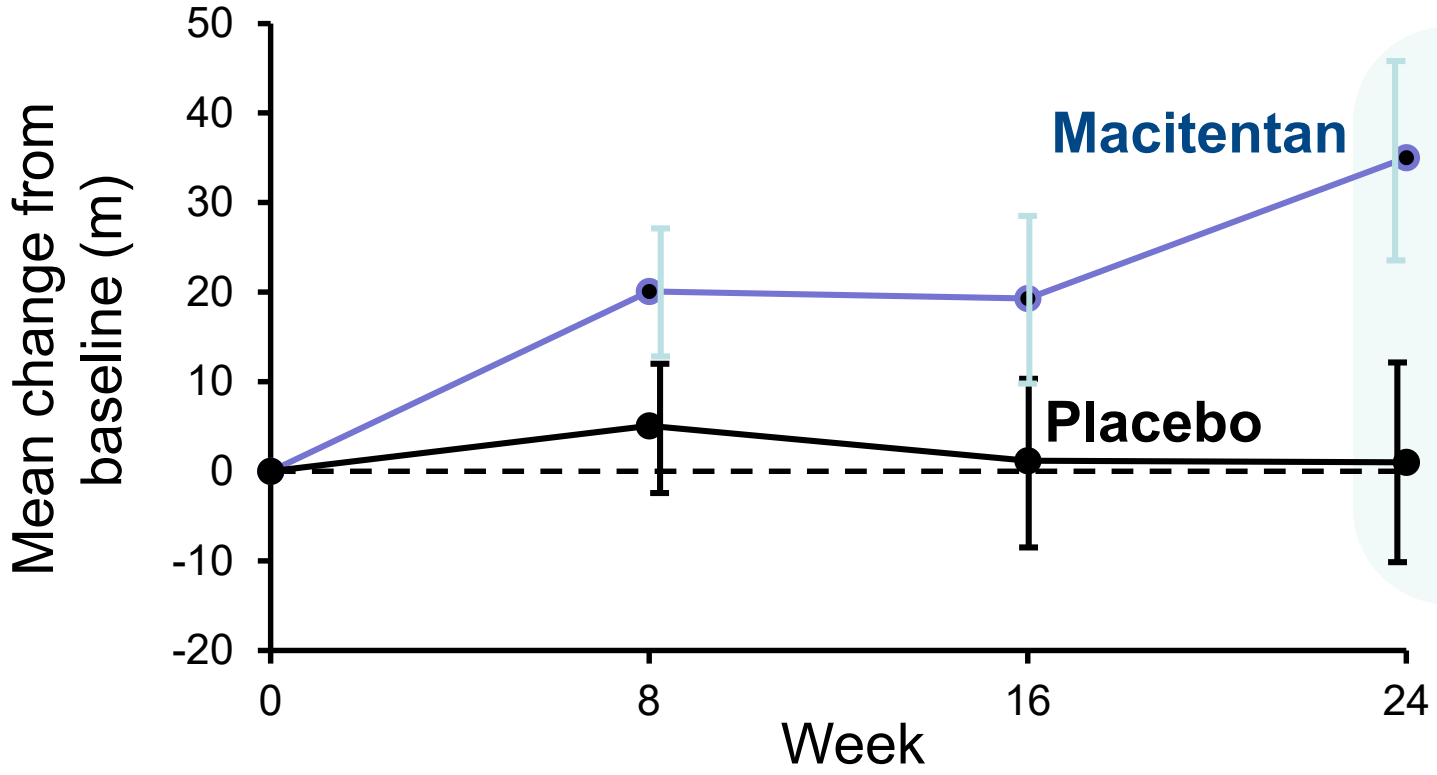
Macitentan vs placebo: PVR reduction 16%

Ratio of geometric means (95% CL): 0.84 (0.70, 0.99), **P=0.04**



*Geometric mean plus 95% CL

Secondary endpoint – Change in 6MWD at week 24



No. of patients				
	40	40	40	40
	40	40	40	40

Treatment effect (95% CL): 34.0 m (2.9, 65.2), P=0.03

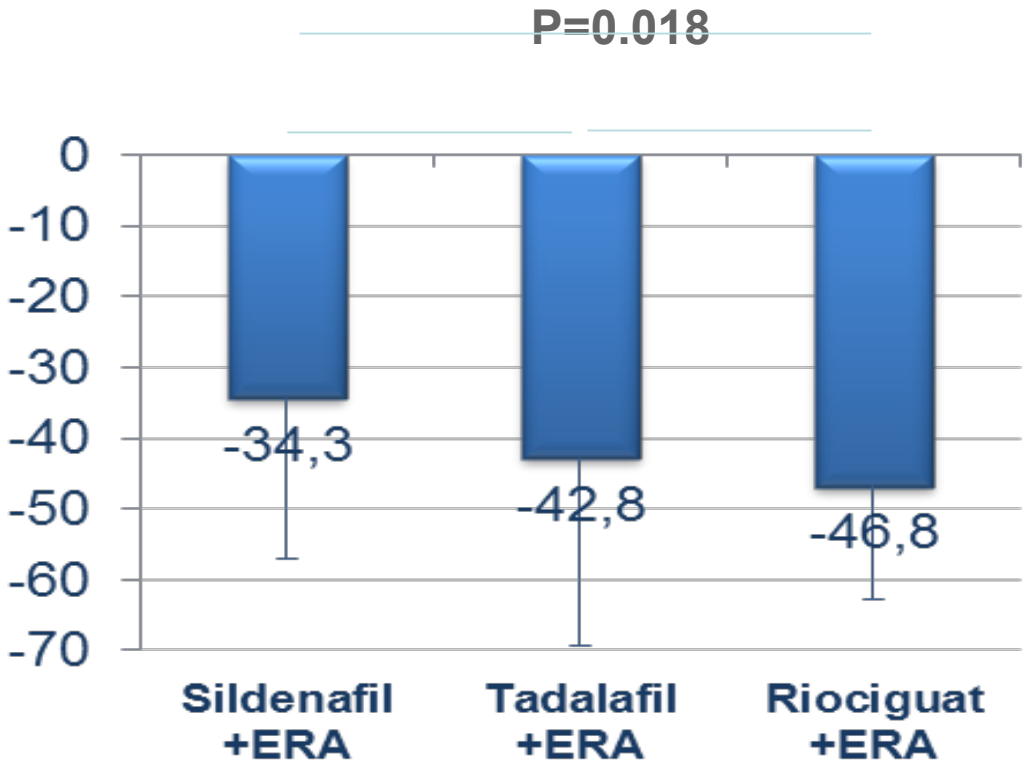
Consistent treatment effect with or without baseline PAH therapy*
- Yes: 32.4 m (-7.0, 71.7)
- No: 37.8 m (-19.7, 95.4)

*Interaction P value: 0.88

Initial combination therapy in inoperable CTEPH: *French experience*

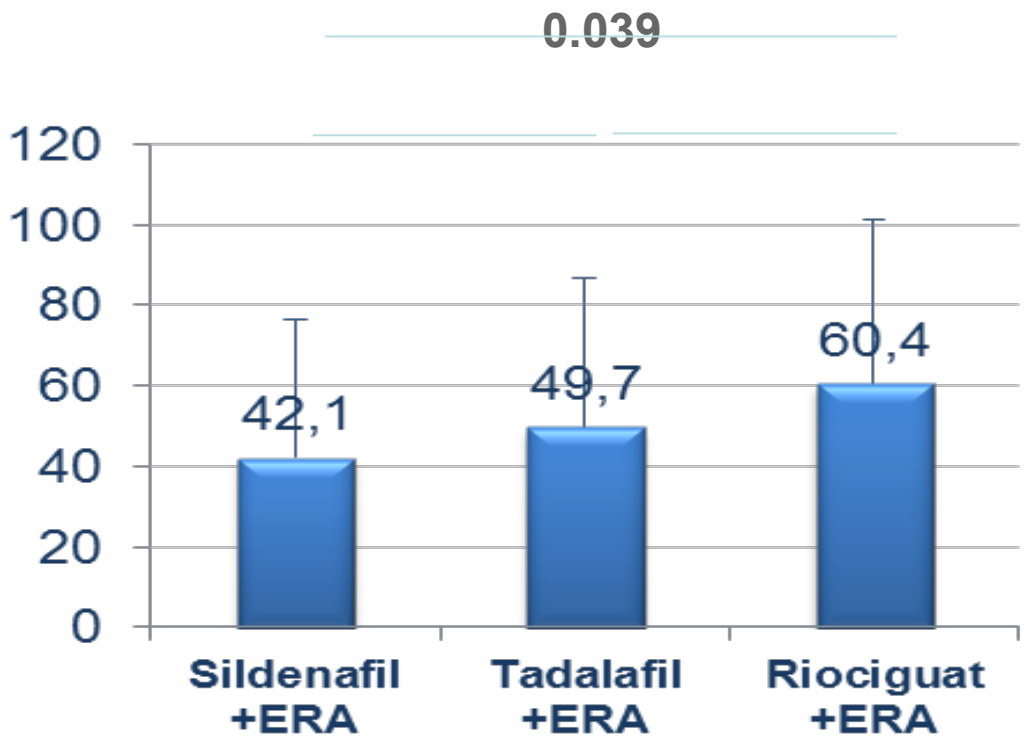
Sildenafil + ERA n=61 - Tadalafil + ERA n=3 - Riociguat + ERA n=25

% decrease of PVR (%)



* P value, one-way ANOVA

% improve of CI (%)



Gabrielly M, *et al*. ERS (abstract)2018

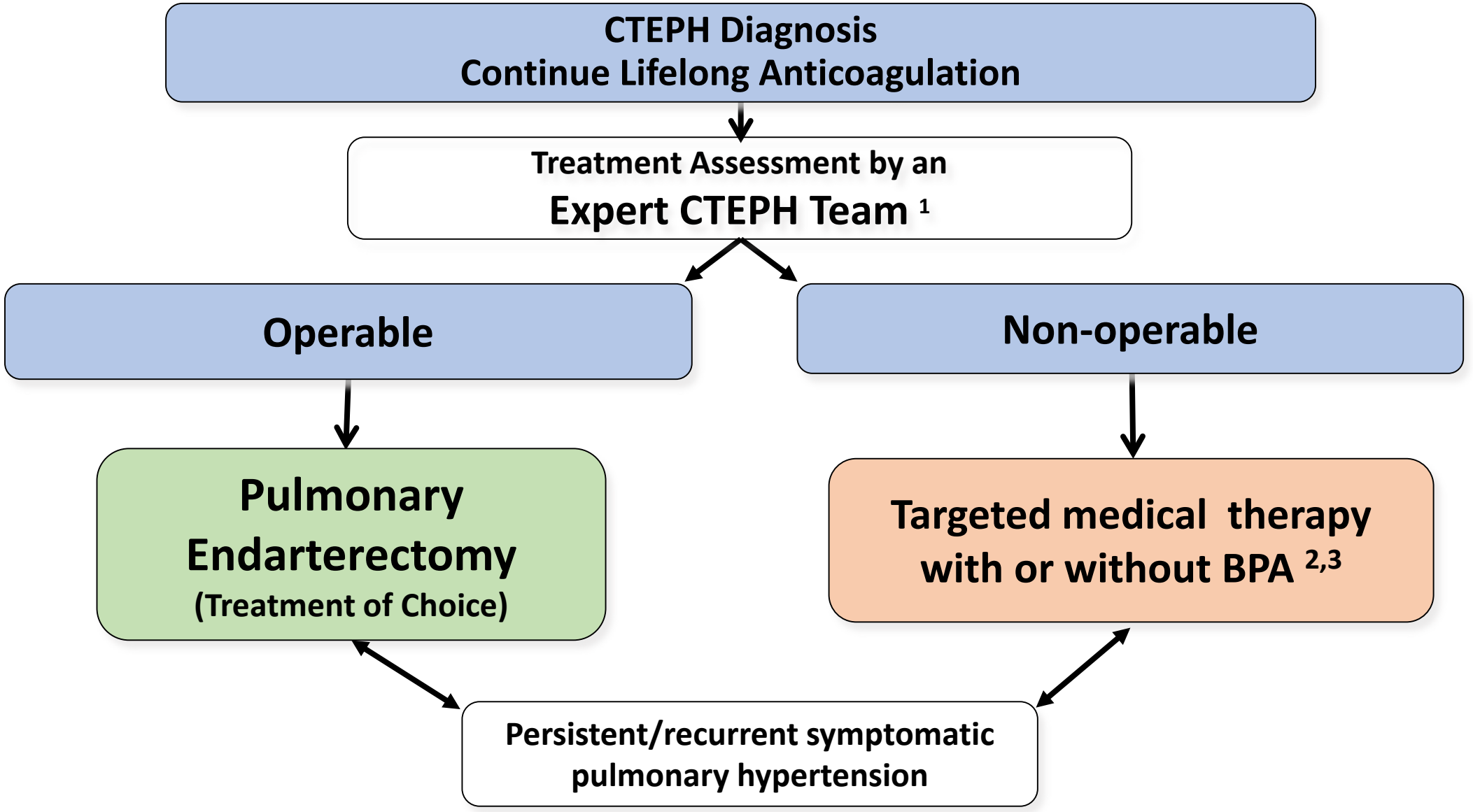
Current management of CTEPH : Summary

- **In operable CTEPH** (50 to 60% of cases) Pulmonary endarterectomy (PEA) remains the gold standard treatment with a post-operative mortality rate of 3% in expert centers. Riociguat is effective for the treatment of residual PH after PEA

- **In non operable CTEPH**

  - Riociguat is the only approved drug with a good safety profil
  - There is growing evidence that BPA is very effective, however it is time consuming and frequently associated with some complications, sometimes severe.The respective role of Riociguat and BPA remains to be properly evaluated (Race study completed)

Today we are entering a new era for the management of CTEPH with the possibility to combine in many patients PEA, BPA and medical therapy



[1] Multidisciplinary: PEA/PTE surgeon, PH expert, BPA interventionalist, and radiologist

N Kim et al. Eur respir J 2018