Current management of
Chronic Thromboembolic Pulmonary Hypertension

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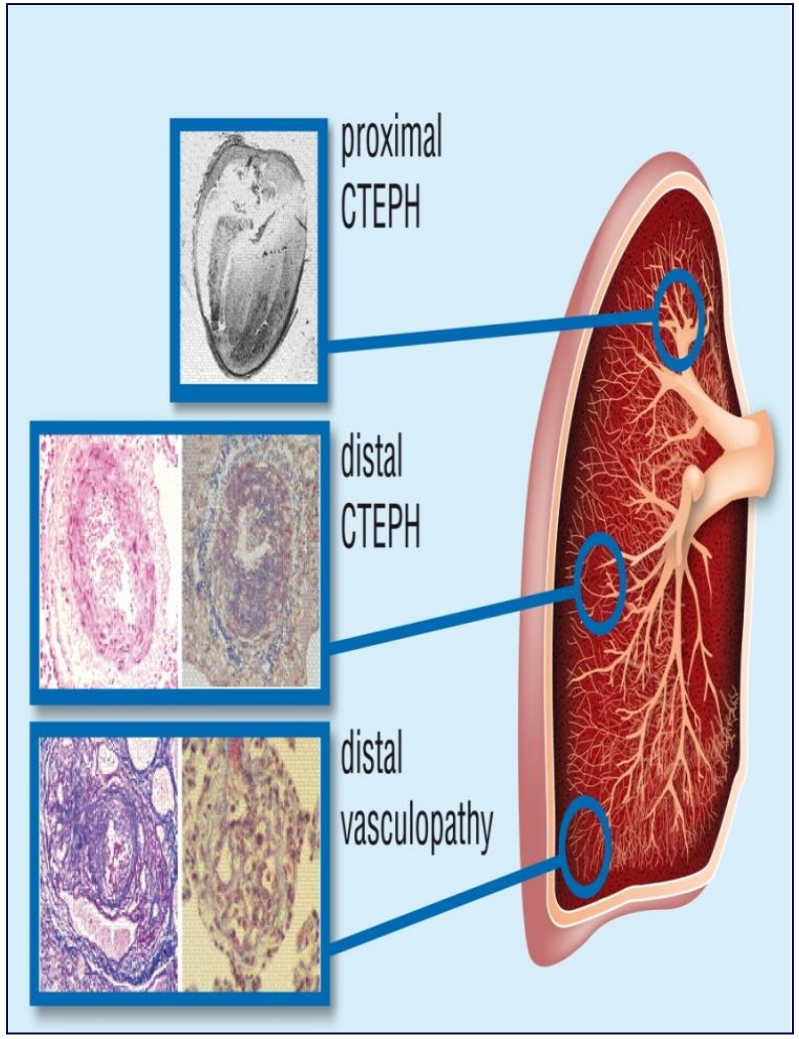
Antoine-Béclère Bicêtre Paul-Brousse

Marie Lannelongue

Centre Chirurgical

Mechanisms of pulmonary hypertension in CTEPH



- Obstruction of proximal pulmonary arteries (main, lobar,segmental) by organized fibrotic clots surgically accessible by **PEA**
- Obstruction of more distal pulmonary arteries (subsegmental…) by fibrotic clots surgically non accessible when isolated : **a role for BPA**
- Distal pulmonary vasculopathy with histological findings similar to IPAH : **a role for PAH specific therapies**

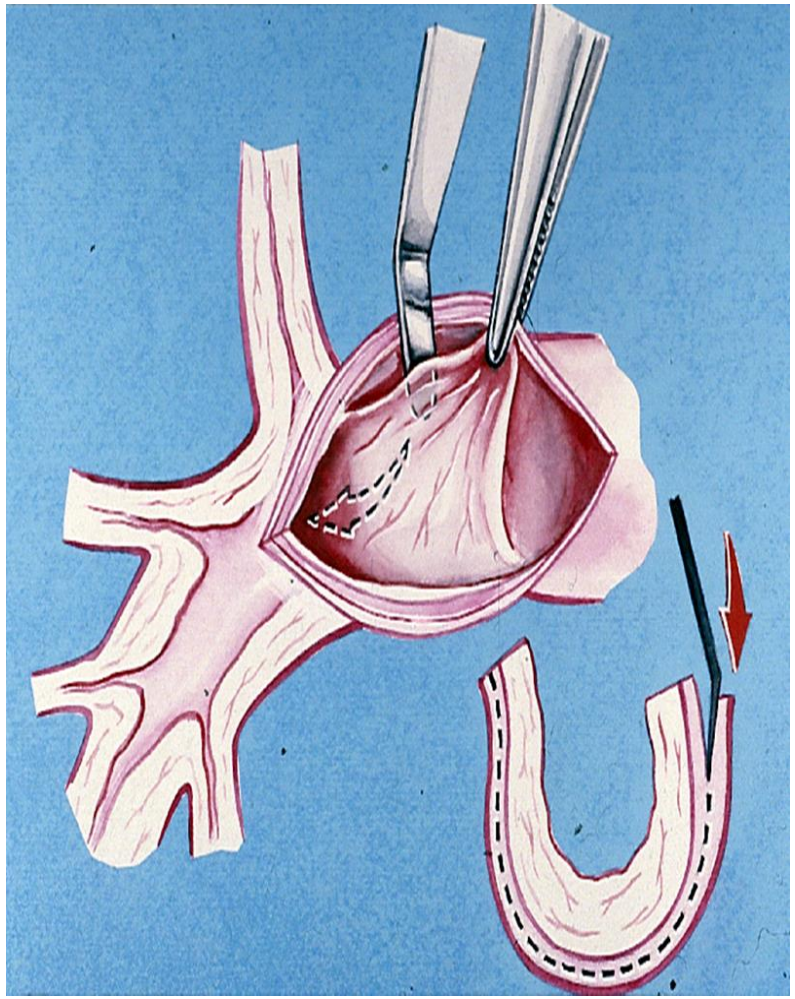
Chronic thromboembolic pulmonary Hypertension is at the crossroads with the development of novel treatment options*

- **In operable CTEPH, Pulmonary endarterectomy (PEA)** remains the gold standard treatment (60%)

- **in non noperable CTEPH, alternative treament options are emerging**
  - **Riociguat*****, a stimulator of the soluble guanylate cyclase is the 1st drug approved for the treatment of CTEPH
  - **Balloon pulmonary angioplasty (BPA):** Recent results from Japanese groups are very impressive******

*Hoeper M, Eur respir j 2014. **Madani M et al, Ann Th Surg 2012
***Ghofrani A et al, New Engl J Med 2013. ****Sugimura K et al Circ J 2012

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



Pulmonary Endarterectomy: Recent Changes in a Single Institution's Experience of More Than 2,700 Patients

Ann Thorac Surg 2012;94:97–103

Michael M. Madani, MD, William R. Auger, MD, Victor Pretorius, MD, Naohide Sakakibara, MD, Kim M. Kerr, MD, Nick H. Kim, MD, Peter F. Fedullo, MD, and Stuart W. Jamieson, MD

Divisions of Cardiovascular and Thoracic Surgery and Pulmonary and Critical Care Medicine, University of California San Diego Health Center, San Diego, California

- Retrospective analysis of 1,500 patients with CTEPH who underwent Pulmonary Endarterectomy at USCD

  - Group 1: 1000 patients operated between 1999 & 2006
  - Group 2: 500 patients operated between 2006 & 2010

Pulmonary Endarterectomy: Recent Changes in a Single Institution's Experience of More Than 2,700 Patients

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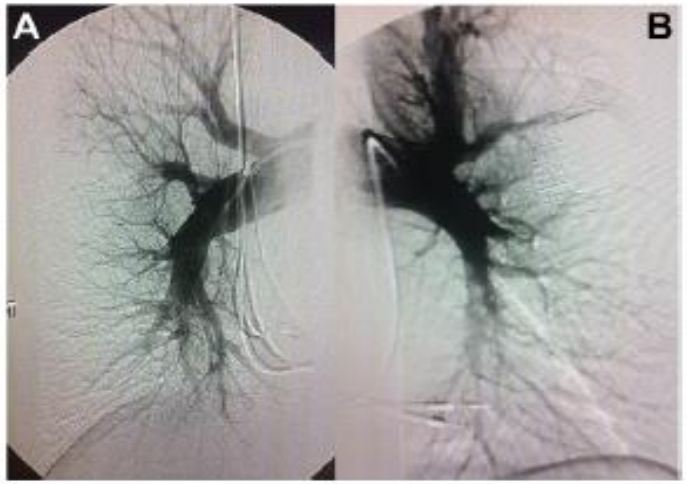
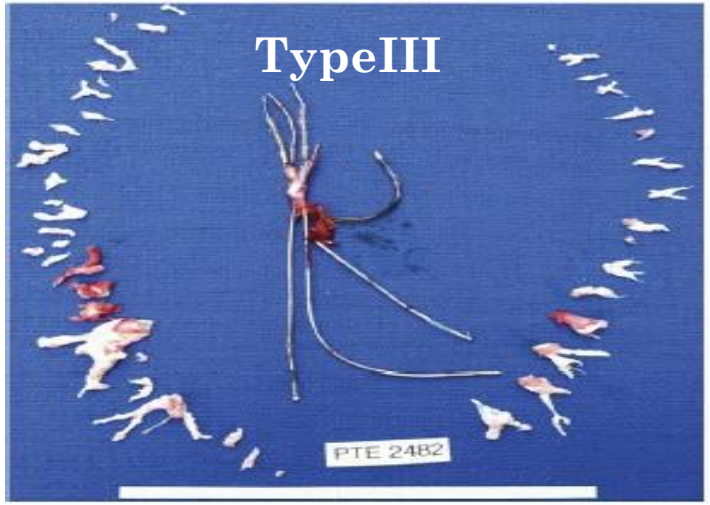
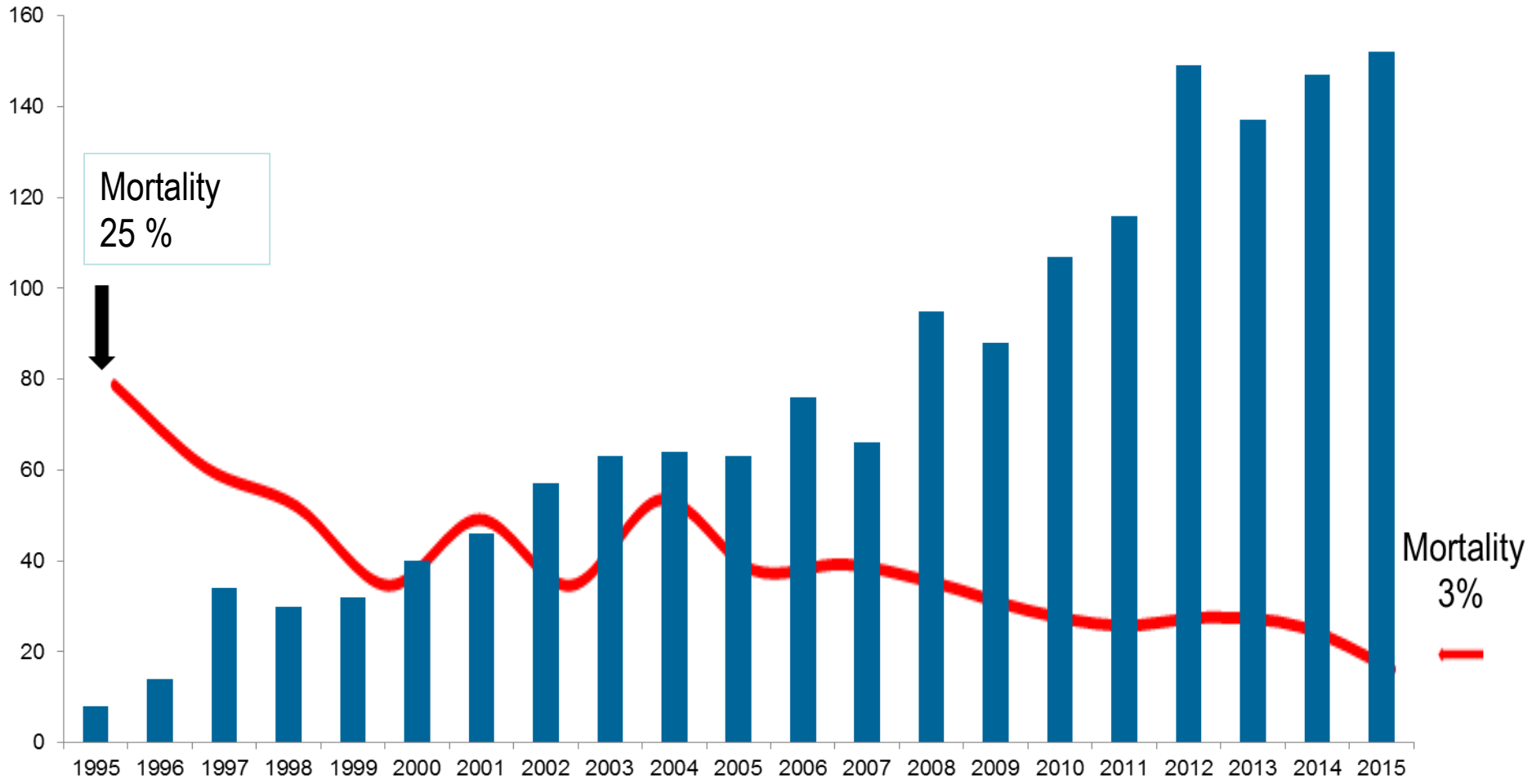




Variable		Group 1 (n = 1,000)	Group 2 (n = 500)	*p* Value
Type I	] Proximal	100 (10.0)	60 (12.0)	0.2491
Type II		520 (52.0)	190 (38.0)	< 0.001[b]
Type III	More distal	275 (27.5)	197 (39.4)	< 0.001[b]
Type IV	PAH	87 (8.7)	38 (7.6)	0.4897
PVR (dynes/sec/cm^{-5})				
Preoperative		861.2 ± 446.2	719.0 ± 383.2	< 0.001[a]
Postoperative		294.8 ± 204.2	253.4 ± 148.6	< 0.001[a]
Intra-hospital mortality		**5,2%**	**2,2%**	**<0.001**

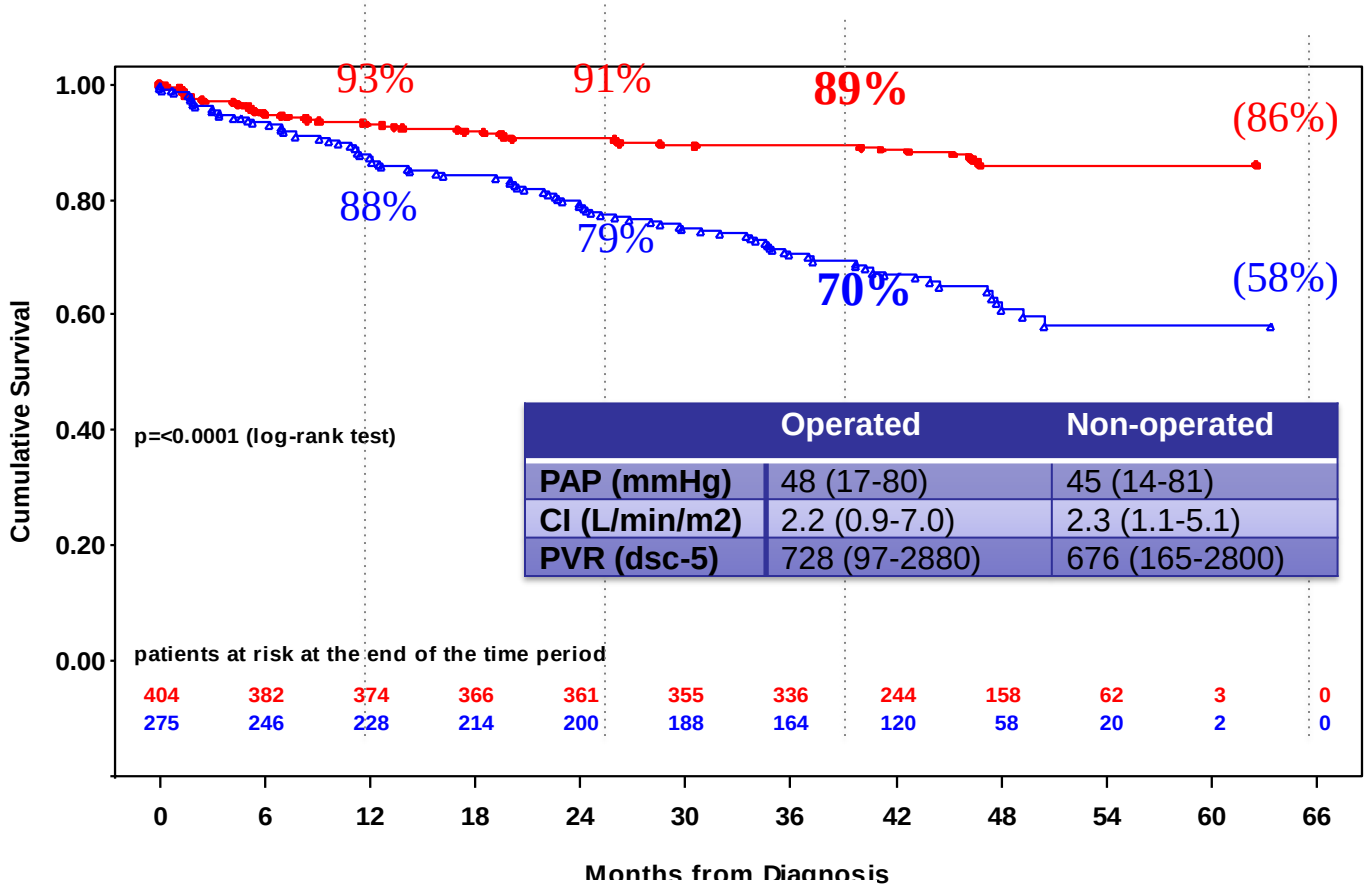
1577 Pulmonary endarterectomies
Paris Sud University (1995-2015)



Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension

Results From an International Prospective Registry

Marion Delcroix, MD; Irene Lang, MD; Joanna Pepke-Zaba, MD; Pavel Jansa, MD; Andrea M. D'Armini, MD; Repke Snijder, MD; Paul Bresser, MD; Adam Torbicki, MD; Sören Mellemkjaer, MD; Jerzy Lewczuk, MD; Iveta Simkova, MD; Joan A. Barberà, MD; Marc de Perrot, MD; Marius M. Hoeper, MD; Sean Gaine, MD; Rudolf Speich, MD; Miguel A. Gomez-Sanchez, MD; Gabor Kovacs, MD; Xavier Jaïs, MD; David Ambroz, MD; Carmen Treacy, BSc; Marco Morsolini, MD; David Jenkins, MD; Jaroslav Lindner MD; Philippe Dartevelle, MD; Eckhard Mayer, MD; Gérald Simonneau, MD



	Operated	Non-operated
PAP (mmHg)	48 (17-80)	45 (14-81)
CI (L/min/m2)	2.2 (0.9-7.0)	2.3 (1.1-5.1)
PVR (dsc-5)	728 (97-2880)	676 (165-2800)

Surgery (PEA) n=404

Medical Tt ERA/PDE5i N=275

Circulation 2016

Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

Hossein-Ardeschir Ghofrani, M.D., Andrea M. D'Armini, M.D., Friedrich Grimminger, M.D., Marius M. Hoeper, M.D., Pavel Jansa, M.D., Nick H. Kim, M.D., Eckhard Mayer, M.D., Gerald Simonneau, M.D., Martin R. Wilkins, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., Gerrit Weimann, M.D., and Chen Wang, M.D., for the CHEST-1 Study Group*

New Engl J Med 2013

Inclusion criteria in CHEST-1

- Patients with CTEPH adjudicated to be technically inoperable or with persistent PH after PEA
- Age 18–80 years
- 6MWD at baseline 150–450 m
- PVR >300 dyn·sec·cm^{-5} and mPAP ≥25 mmHg

Patients excluded if treated with ERAs, prostacyclin analogs, PDE5i, and/or NO donors within 3 months prior to study entry

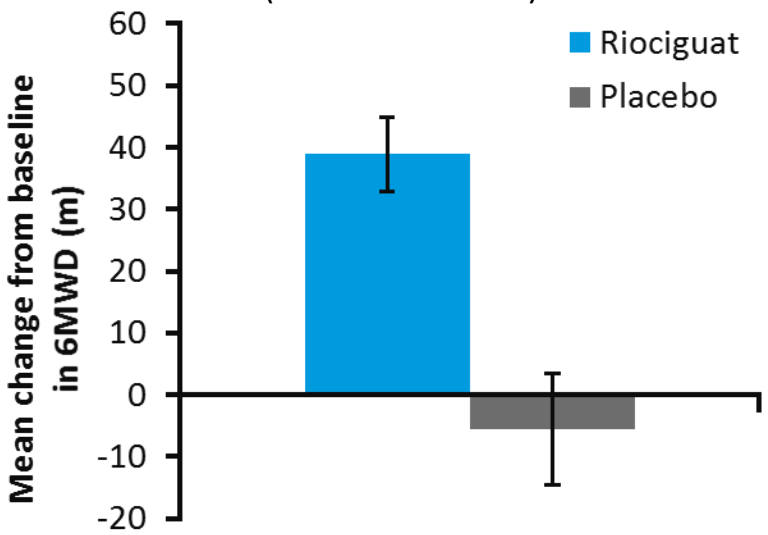
Maximum Dose allowed : Riociguat 2.5 mg TID

Primary end point at week 16

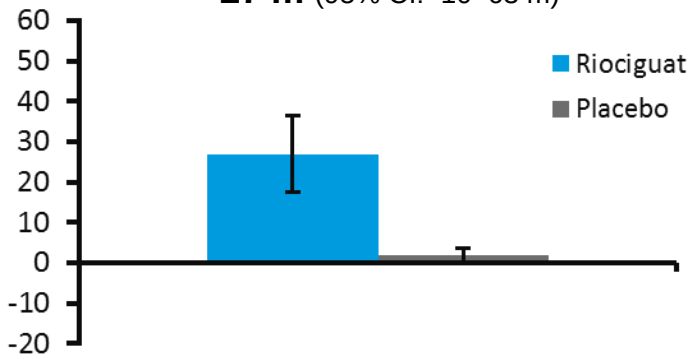
CHEST
Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial
Riociguat

Primary endpoint: entire population (n=173/88)

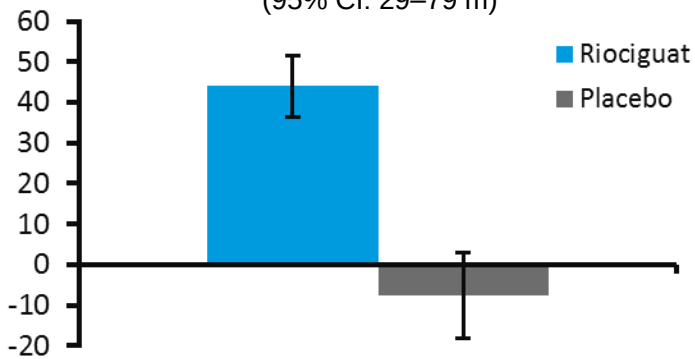
+46 m
***p*<0.001**
(95% CI: 25–67 m)



Population with persistent/ recurrent PH after PEA (n=52/20)
+27 m (95% CI: -10–63 m)



Inoperable population (n=121/68)
+54 m
(95% CI: 29–79 m)



6MWD, 6-minute walking distance; PEA, pulmonary endarterectomy.

Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

Significant and meaningful improvement of cardiopulmonary hemodynamics and biomarkers

Parameter	Riociguat		Placebo		Placebo-corrected LS-mean difference	Riociguat vs placebo; p-value
	Baseline	Mean change from baseline	Baseline	Mean change from baseline		
PVR ($dyn \cdot s \cdot cm^{-5}$)	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**

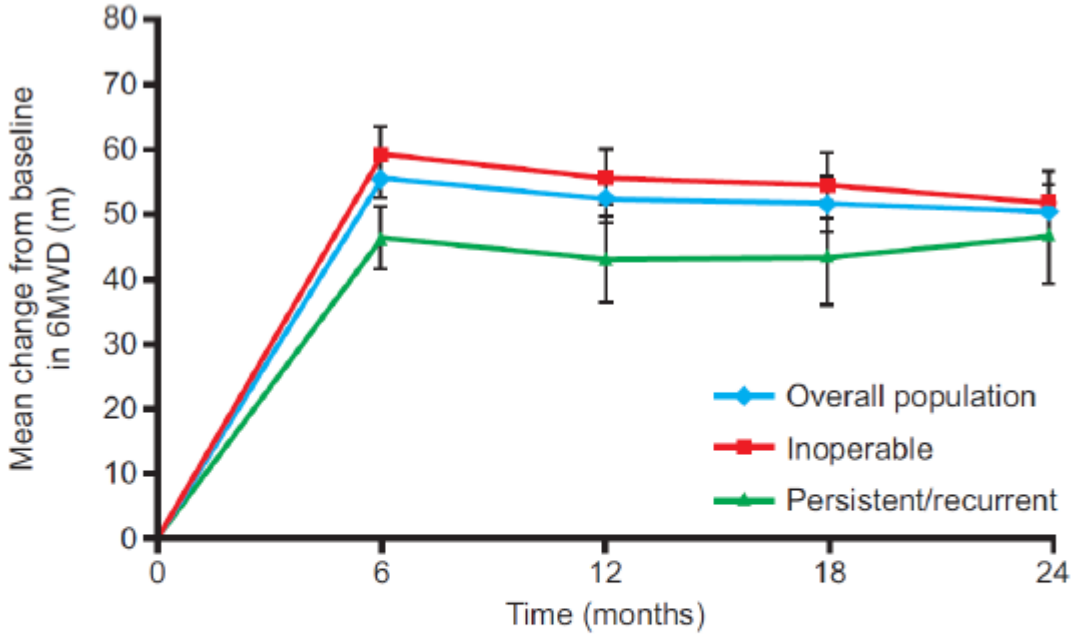
CI, cardiac index

Long-term outcomes in patients treated with Riociguat for chronic thromboembolic pulmonary hypertension: Data from the CHEST-2 open-label, long-term extension trial

Gérald Simonneau, Andrea M D'Armini, Hossein-Ardeschir Ghofrani, Friedrich Grimminger, Pavel Jansa, Nick H Kim, Eckhard Mayer, Tomas Pulido, Chen Wang, Pablo Colorado, Arno Fritsch, Christian Meier, Sylvia Nikkho and Marius M Hoeper

Lancet Respir Med. 2016

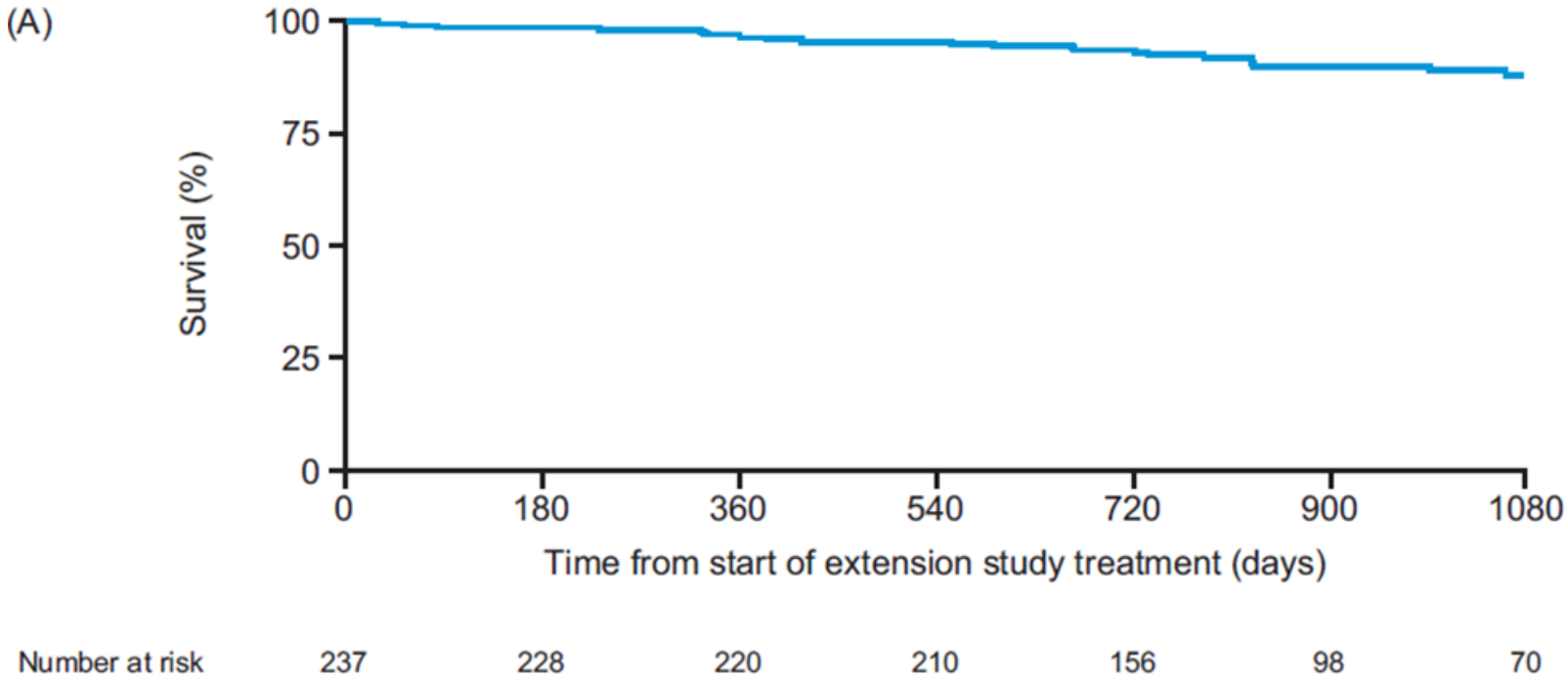
Mean change from baseline in 6MWD in CHEST-2



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

Data shown are observed values, mean±SEM.
6MWD = 6-minute walking distance; SEM = standard error of the mean
Simonneau G *et al.* Lancet Respir Med. 2016 Apr 8. pii: S2213-2600(16)30022-4. doi: 10.1016/S2213-2600(16)30022-4. Supplementary appendix

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 Apr 8. pii: S2213-2600(16)30022-4. doi: 10.1016/S2213-2600(16)30022-4

Frequency of AEs per 100 patient-years

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)

[a]Total number of events are shown; a patient may have had more than 1 event

[b]Defined by systolic blood pressure <90 mmHg

CHEST-2 data cut-off March 2013; mean treatment duration was 582 days

Simonneau G *et al. Eur Respir J* 2015;45:1293–302.

MERIT: Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension

MERIT-1:

- To evaluate the safety, tolerability and efficacy of macitentan in 78 inoperable CTEPH
- Primary Outcome Measure:
  - PVR at rest at Week 16 expressed as percent of baseline PVR at rest
- Secondary Outcome Measures

Results:

- Significant 16% reduction in PVR at Week 16 with macitentan compared with placebo ($p = 0.04$)
- Significant effect on 6MWD at Week 24: +34.0 m with macitentan compared with placebo ($p = 0.03$)
- Observed efficacy was consistent across all sub-groups, including patients receiving background PAH-specific therapy at baseline (61%), including PDE-5 inhibitors (59%)

Clinicaltrials.gov; NCT02021292.
Actelion Press Release, 7 Nov 2016.

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) 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

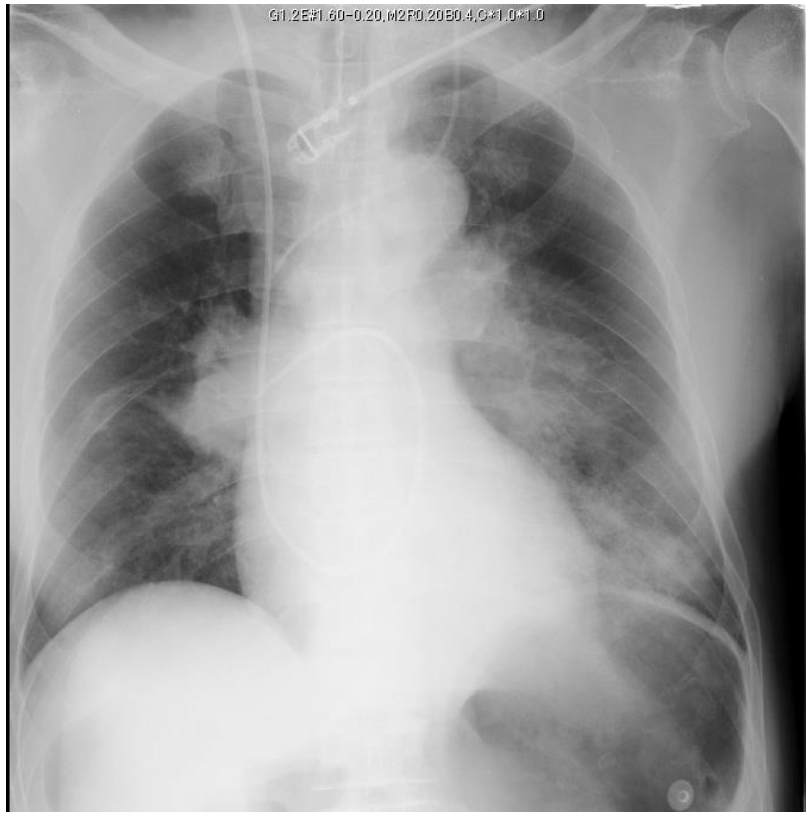
BPA: Safety

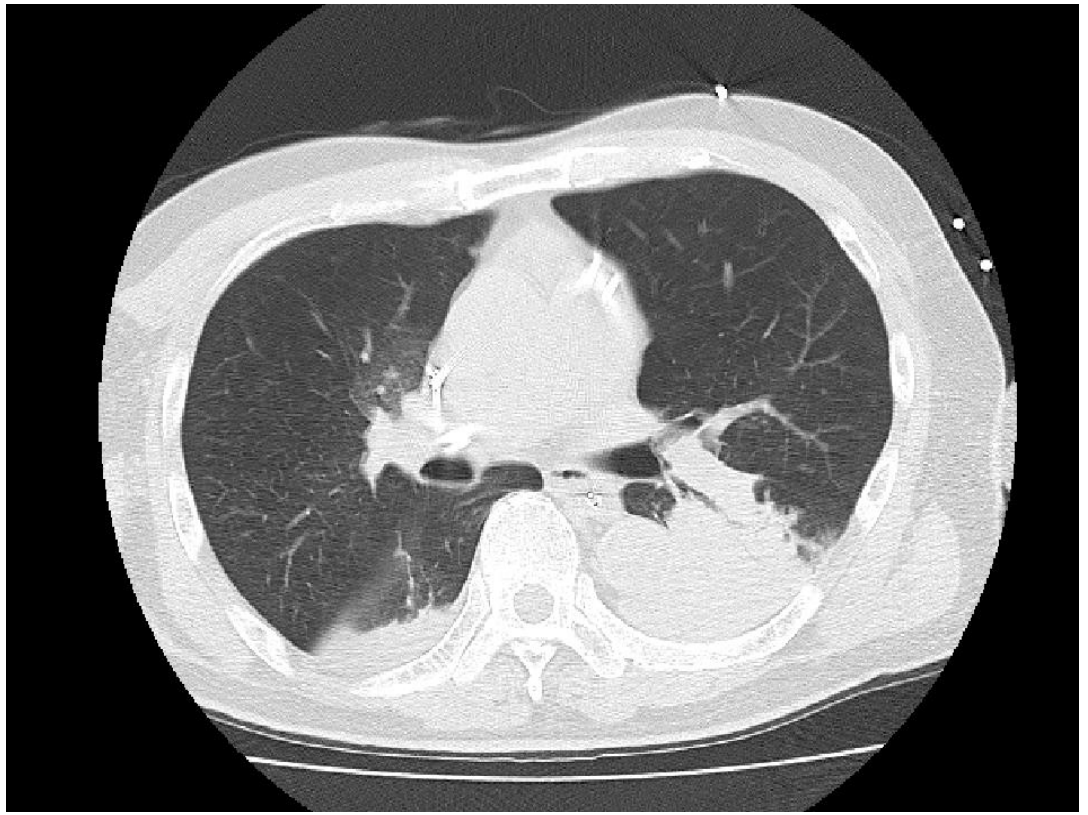
- Relatively frequent 10% of sessions and 38% of patients (1)
- Mortalty between 0% and 5%
- Main complications are pulmonary artery injuries :PA ruptures, PA dissection, PA perforations,reperfusion lung injury (2)
- Correlation between the rate of complications & hemodynamic severity (1)

	Reperfusion lung injury +	***Reperfusion 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
IC *(L/min/m²)*	2,5(1,9-2,7)	2,6(2,4-3,3)	0,006

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

Reperfusion lung injury





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

Success & complication rate of BPA according to morphology of chronic thromboembolic lesions

Novel Angiographic Classification of Each Vascular Lesion in Chronic Thromboembolic Pulmonary Hypertension Based on Selective Angiogram and Results of Balloon Pulmonary Angioplasty

- Between 2004 & 2012 the Okayama center enrolled 97 patients undrgoing BPA for CTEPH Were analyzed 500 consecutive procedures (1936 lesions)

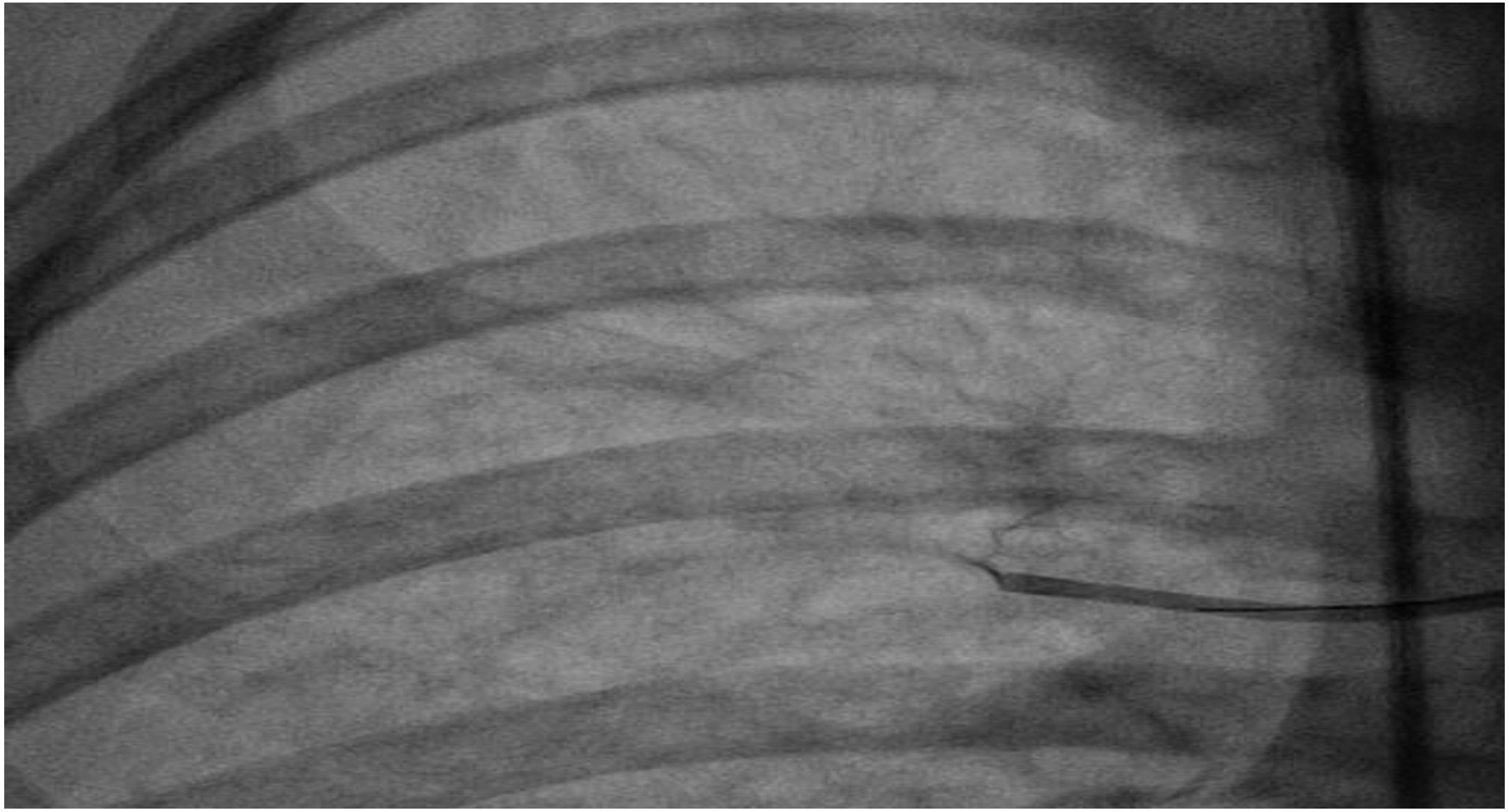
- Lesions were classified Type A: Ring-like stenosis lesions. Type B: web lesions Type C: subtotal occlusion Type D: total occlusion lesion. Type E: Tortuous lesions

- Complications: Balloon injury, wire injury/perforation, vessel dissection Hemoptysis, Lung injury (hypoxemia + lung opacities) and deaths

- Success rate in passing the guidewire across the lesion and delivering the balloon cath to the lesion and clinical and hemodymamic improvement

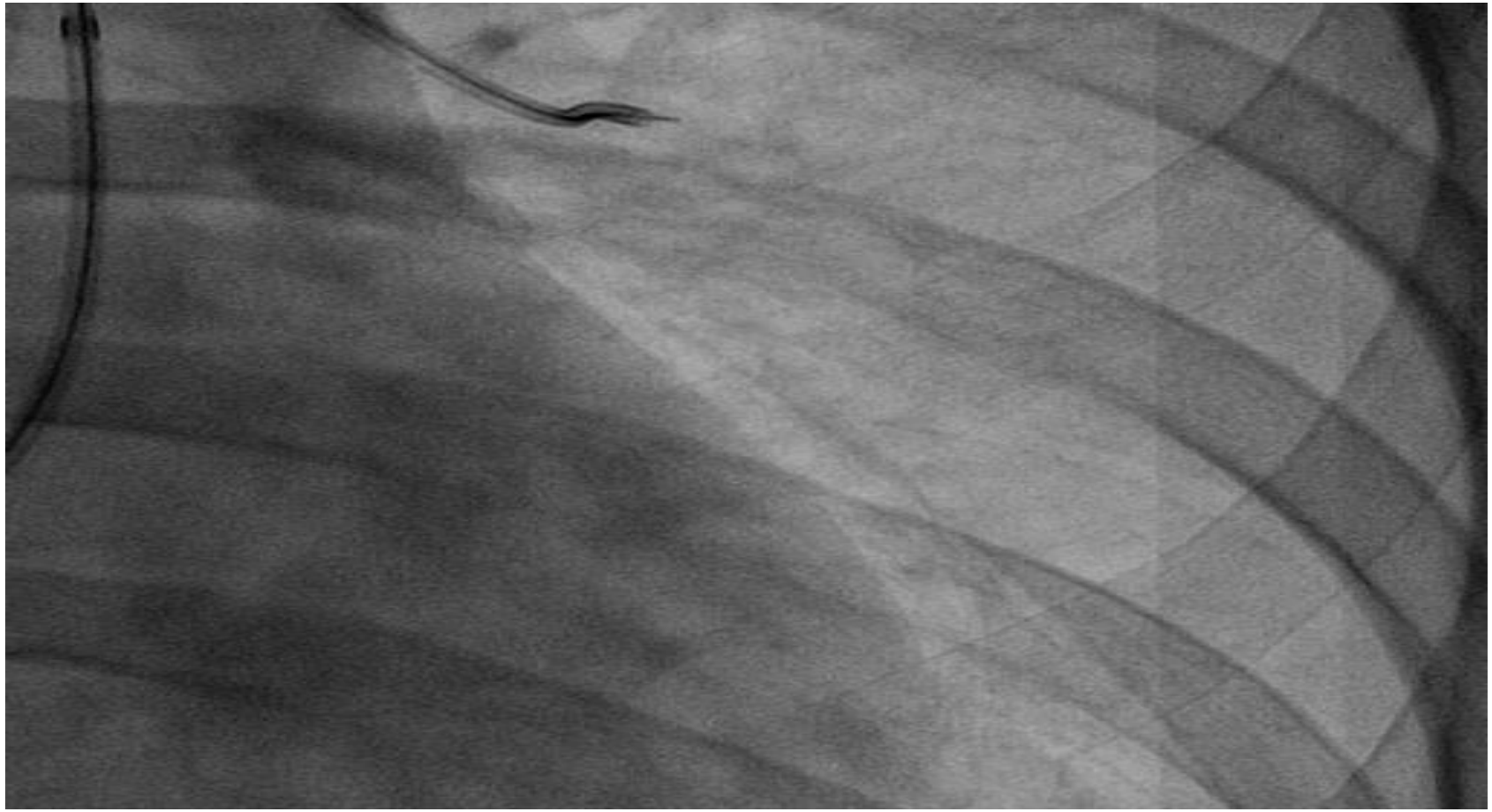
T Kawakami et al. Circ Cardiovasc Interv 2016

A: Ring-like stenosis lesions (12%) success 100% Complications 1.6%

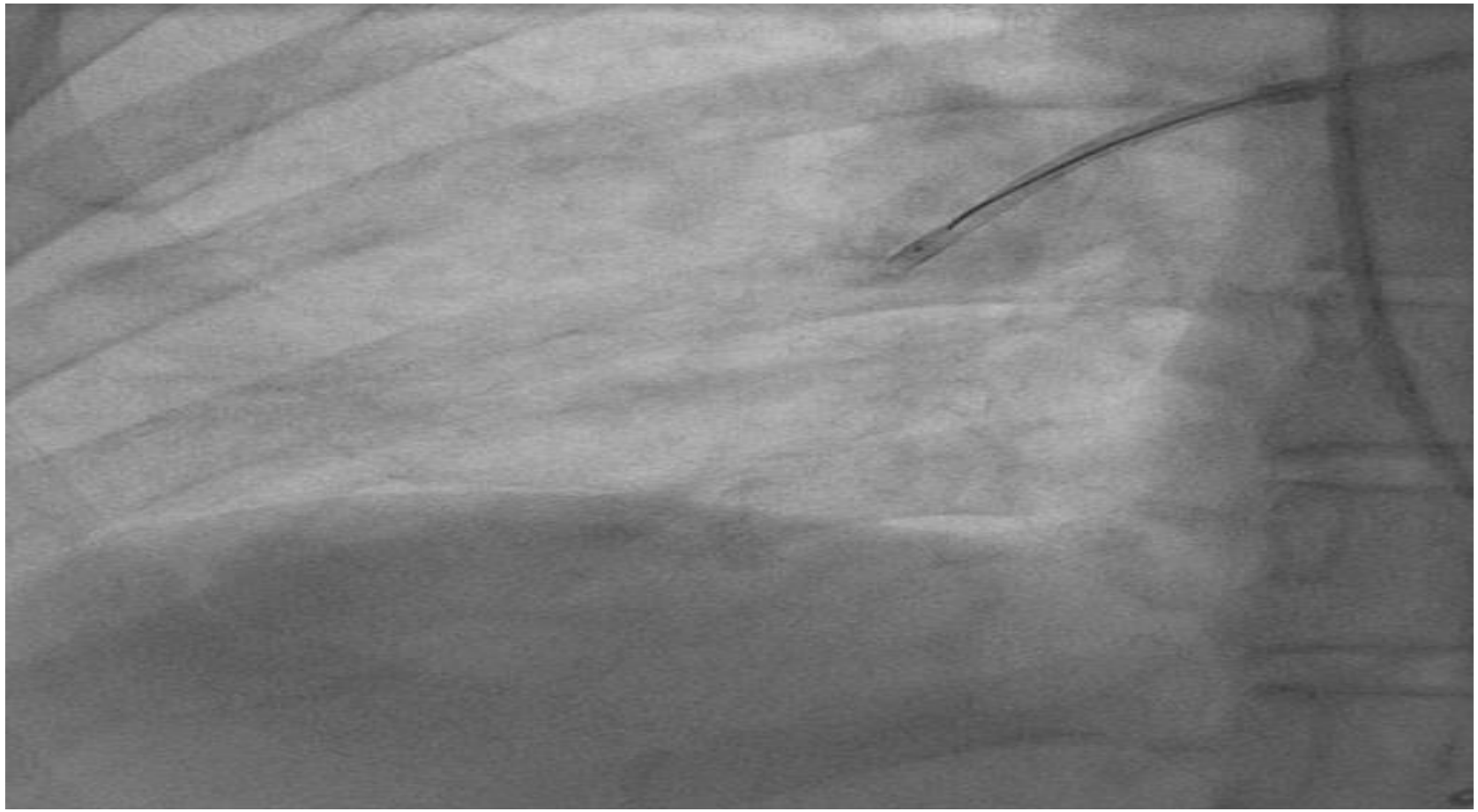


B: Web lesions (60%) success 98.7% Complications 2.2%

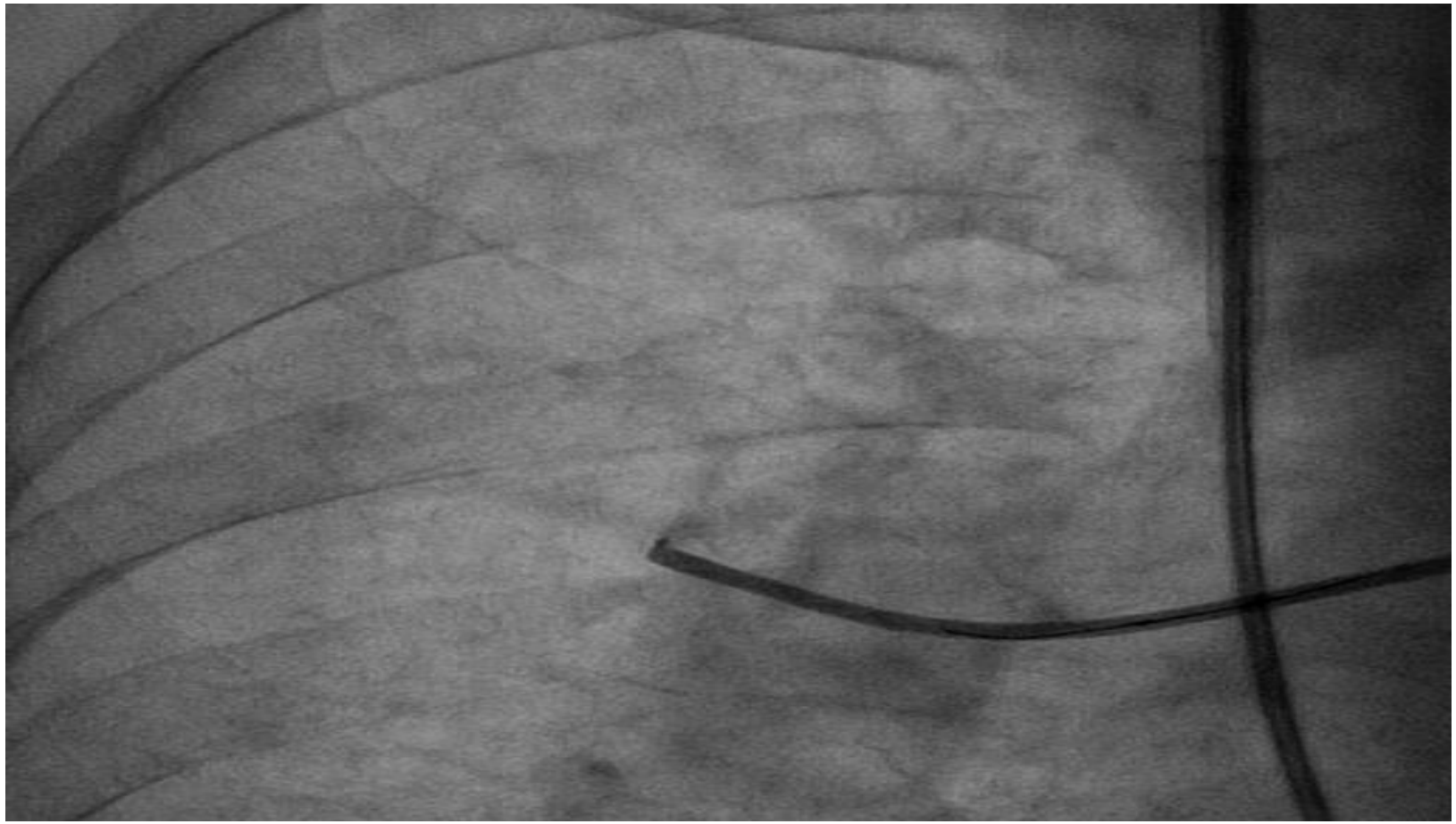
C:Subtotal occlusion lesions (28%) success 86.5% Complications16%



D:total occlusion lesions (4%) success 56.5% Complications 6%



E: Tortuous lesions (6%) success 63.5% Complications 43%



BPA at Paris Sud University : Patient's Selection

- **Weekly multidiciplinary meeting**

  ➢Cardiothoracic surgeons experienced in PEA (E Fadel, S Mussot, O Mercier)
  ➢Cardiologists experienced in BPA (Ph Brenot, C Garcia, B Gerardin)
  ➢Pneumologists experienced in PH (X Jais, M Humbert, G Simonneau,,,,,,,,)
  ➢Radiologists experienced in Pulmonary vascular imag. (O Planché, A Rangeard)

- **BPA Proposed in :**

  ➢Inoperable CTEPH due to distal disease
  ➢Inoperable CTEPH due co-morbidities
  ➢ Recurent/ persistent pulmonary hypertension after PEA
  ➢(*Rescue therapy immediatly after failure of PEA)*

BPA at Paris Sud University Since feb 2014 to july 2016)

136 Patients (748 sessions), Mean age 63 yo, 54% male

Risk Factors for CTEPH

Splenectomy	13%
PAC for chemotherapy	10%
Haematologic disorders	8%
Antiphosoholipids AB syndrome	4%
Pace-maker	2%

Indications for BPA

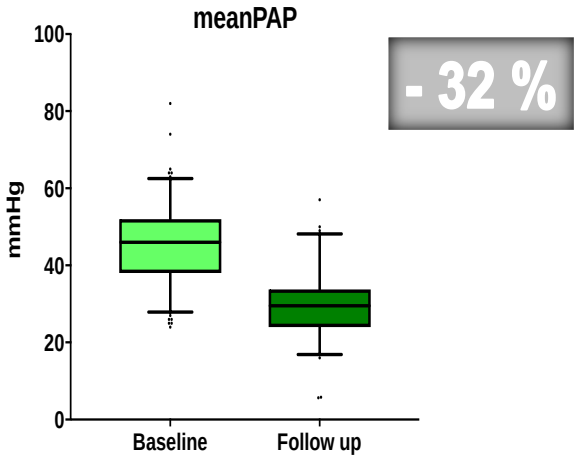
Distal disease	66%
Co-morbidities	23%
Persistent/recurrent CTEPH after PEA	5,5%
Before BPA in severe patients	1%
(Rescue therapy after failure of PEA)	*5%*

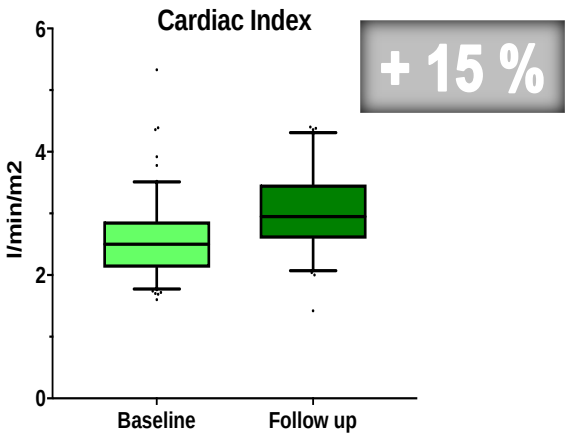
BPA at Paris Sud University
Safety data in 136 patients and 748 sessions (5.5 per patients)

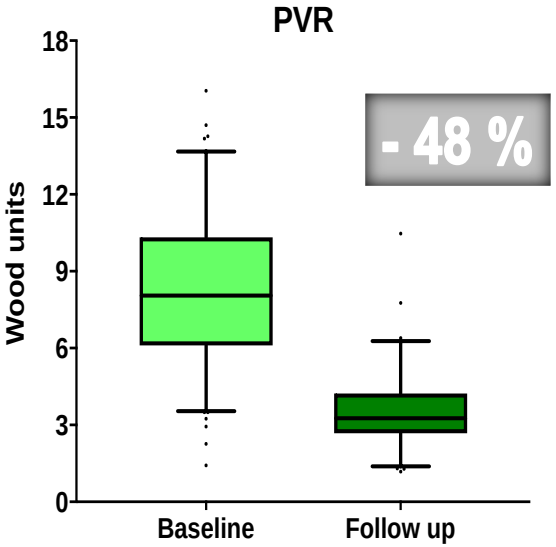
Complications	N	% sessions	% patients	Management
Hemoptysis	38	5%	25%	2 bronchial arteries embolizations
PA dissection	12	1.5%	10%	6 stents
Reperfusion lung injury	41	6%	30%	Nasal O2 18% Non Invasive Ventilation12% Invasive Ventilation 2%
Deaths related to BPA	4	0.4%	3 %	Reperfusion lung injury
Others *(Renal insuf., Infection, puncture sitet*	7	1%	5%	

BPA at Paris Sud University
Efficacy data in 75 patients with a mean follow-up of 7.7 months

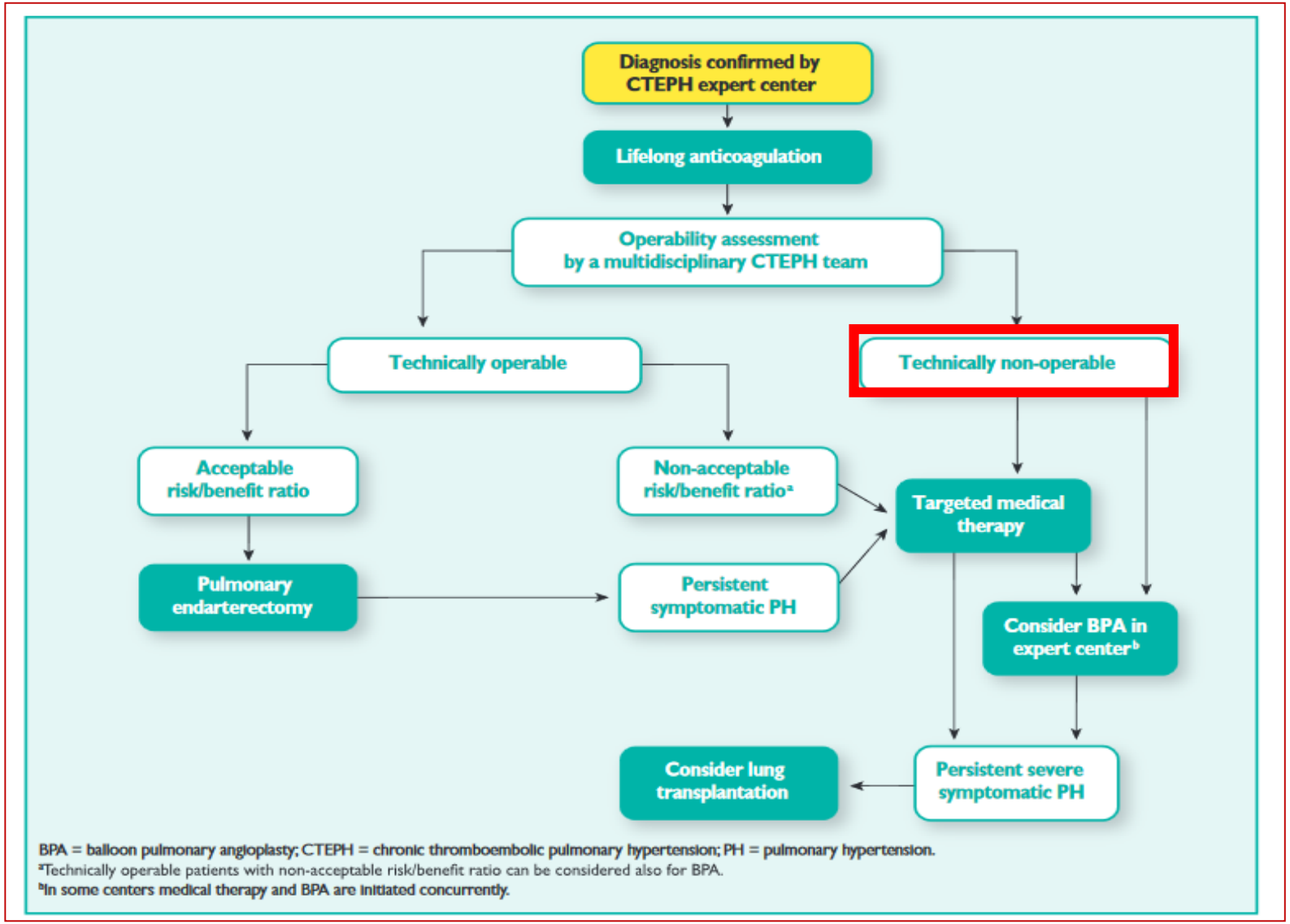
	Baseline	Follow-up	*p*-value
Mean RAP(mmHg)	8 ± 3	6 ± 4	*0,063*
Mean PAP (mmHg)	44 ± 10	30 ± 9	< *0.001*
Cardiac index (L/min/m²)	2.6 ± 0,6	3.0 ± 0,6	< *0.001*
PVR (UW)	7.6 ± 3,0	3.6 ± 1,5	< *0.001*





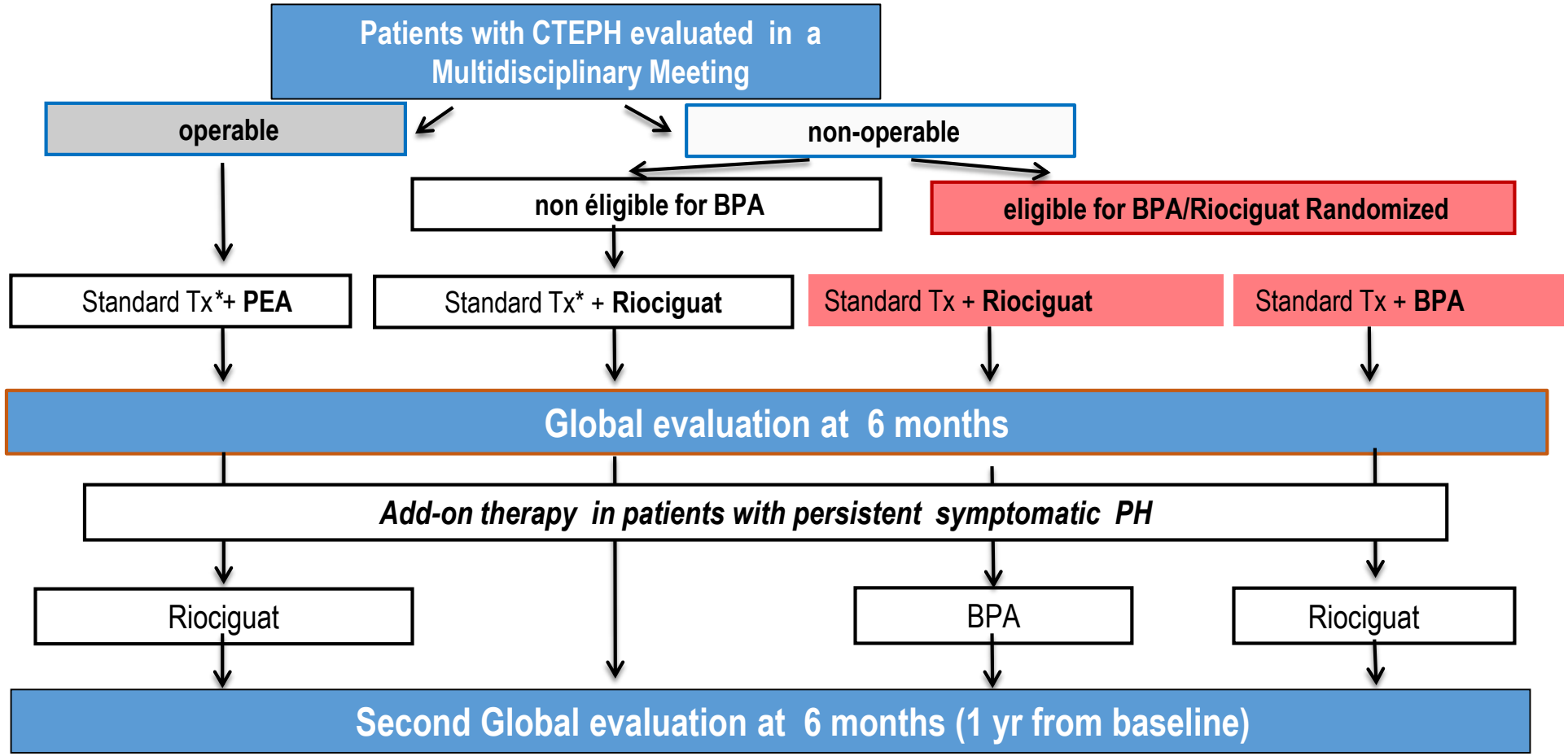


Current management of CTEPH
Recent Guidelines



ESC/ERS Guidelines 2015

RACE Study "**R**iociguat versus balloon pulmonary **A**ngioplasty in non-operable **CTEPH**



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 and a dramatic post-operative improvement. **Riociguat** is effective for the treatment of residual PH after PEA, its role as a bridge to PEA needs to be properly evaluated
- **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 is frequently associated with some complications, sometimes severe
- The respective role of Riociguat and BPA remains to be properly evaluated

Today we are entering a new era for the management of CTEPH

with the possibility to combine in many patients PEA, BPA andmedical therapy

International CTEPH Conference 2017

June 9 – 10, 2017 Leuven, Belgium

www.icc2017.be

NICE

February 27-28
March 1, 2018

WORLD SYMPOSIUM ON PULMONARY HYPERTENSION