Stratégies thérapeutiques de l'HTP thromboembolique chronique

Xavier JAÏS

Centre de Référence de l'Hypertension Pulmonaire – Service de Pneumologie
Hôpital Universitaire de Bicêtre – INSERM UMR S999 – Université Paris-Sud
Le Kremlin-Bicêtre – France

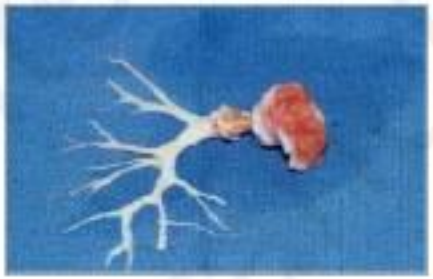
Disclosure Statement of Financial Interest

I currently have, or have had over the last three years, financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company:

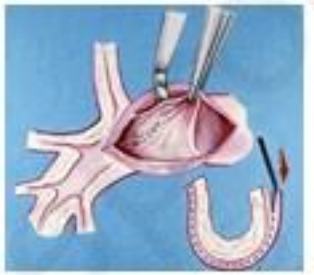
Financial Relationship	Companies
Grant /	Actelion Pharmaceuticals
Research Support /	Bayer HealthCare
Consulting Fees /	GlaxoSmithKline
Honoraria	Merck

Tailored management of CTEPH according to the type of lesions

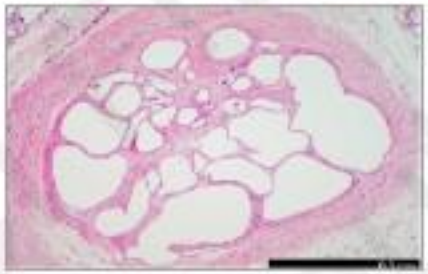
Proximal fibrotic lesions:
Main, lobar, segmental pulmonary arteries



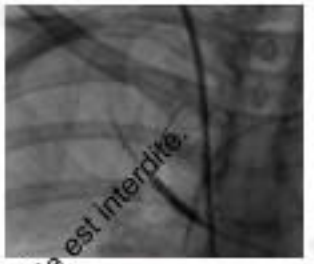
PEA



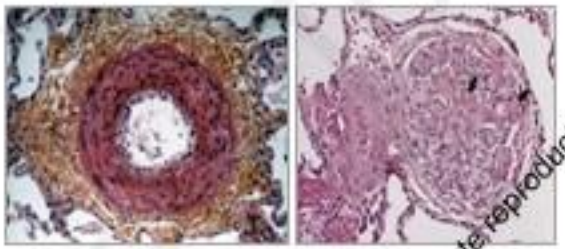
Distal fibrotic lesions:
Sub-segmental and more distal PA up to 3 mm diameter



BPA

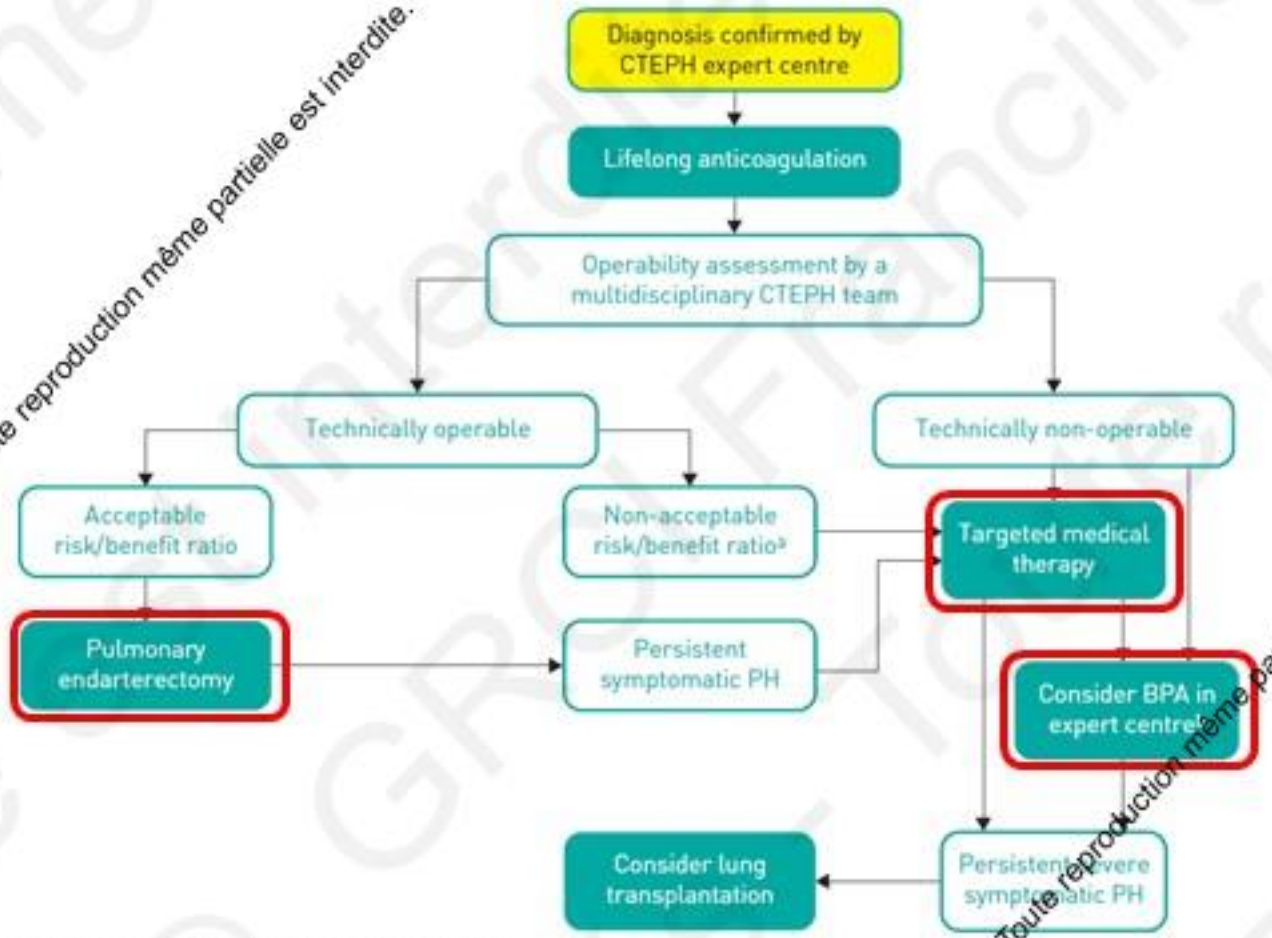


Small vessels disease (similar to those found in IPAH):
Thickening of small PA wall (0.1 to 0.5 mm diameter)



Med. Rx. (*Riociguat*)

CTEPH Treatment Algorithm (2015 ESC/ERS guidelines)



Galiè N, Humbert M, *et al. Eur Respir J* 2015 & *Eur Heart J* 2016.

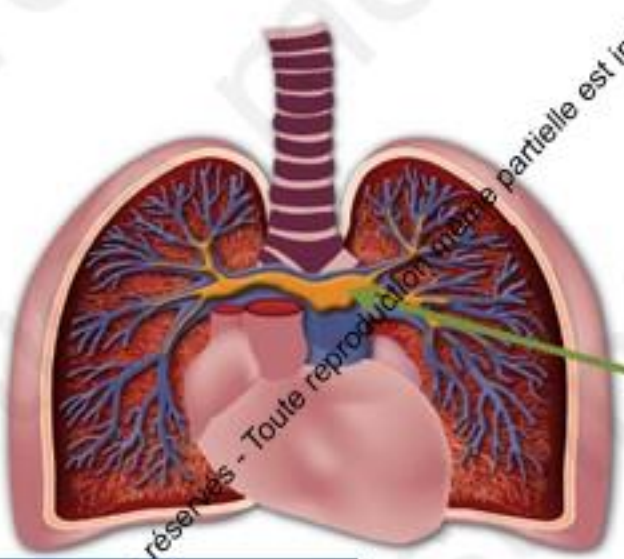
BPA= balloon pulmonary angioplasty

Combining different treatment modalities in CTEPH

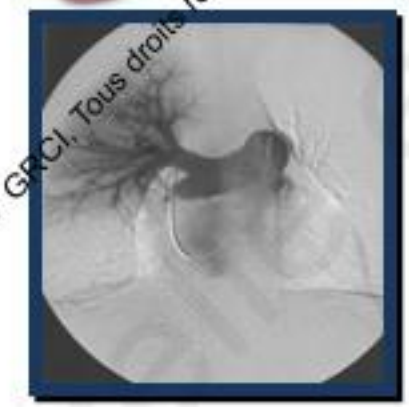
- Current modalities for the treatment of CTEPH
  - Surgery (PEA)
  - Angioplasty (BPA)
  - Medical therapy (PAH-targeted drugs)

- Combined modalities
  - PEA + medical treatment
    - before surgery ("bridging therapy")
    - after surgery ("persistent PH")
  - BPA + medical treatment
  - PEA + BPA

Pulmonary endarterectomy (PEA) is the treatment of choice for operable patients with CTEPH



Organized thrombotic material



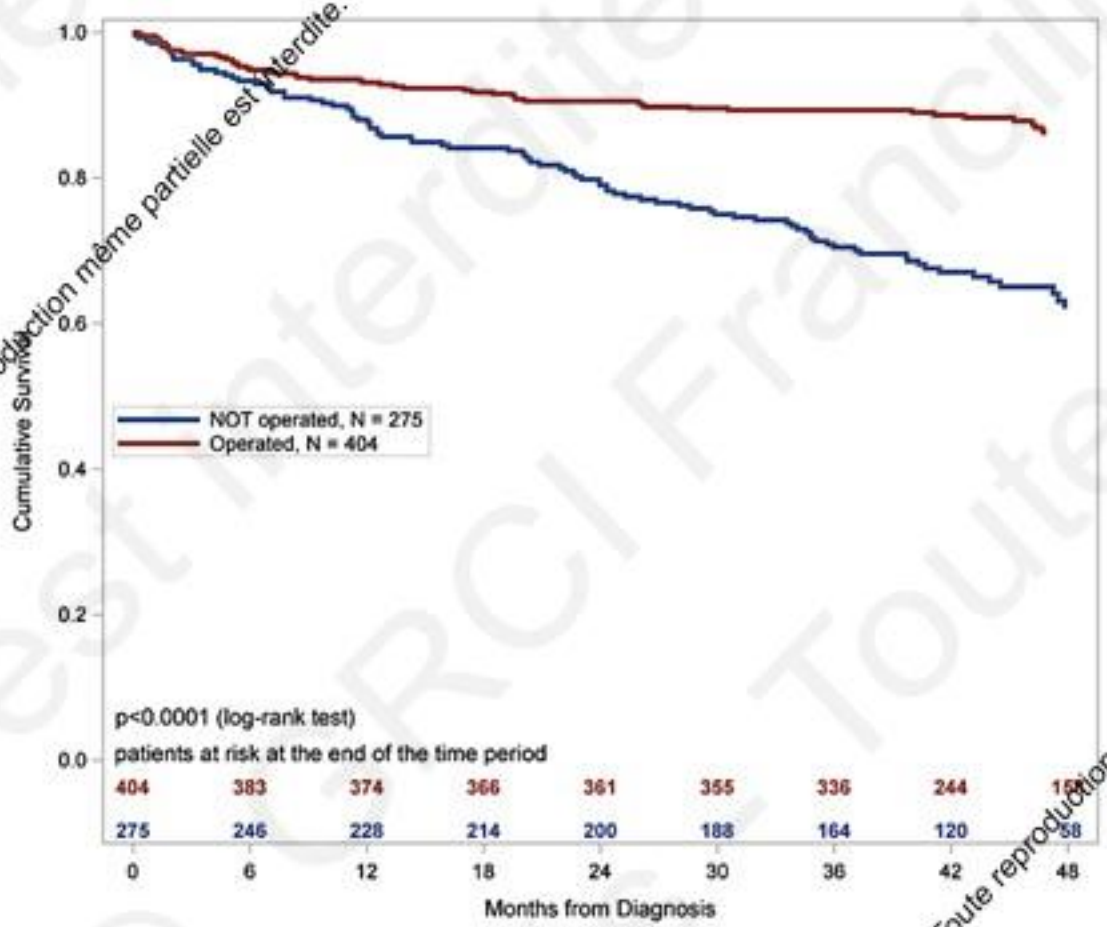
- Presence of proximal lesions
- Good correlation between obstruction and level of PVR
- No comorbidities

Thistlethwaite PA *et al. J Thorac Cardiovasc Surg* 2002.
Dartevelle P *et al. Eur Respir J* 2004.
Jamieson SW *et al. Ann Thorac Surg* 2003.

PEA outcomes: major haemodynamic improvement

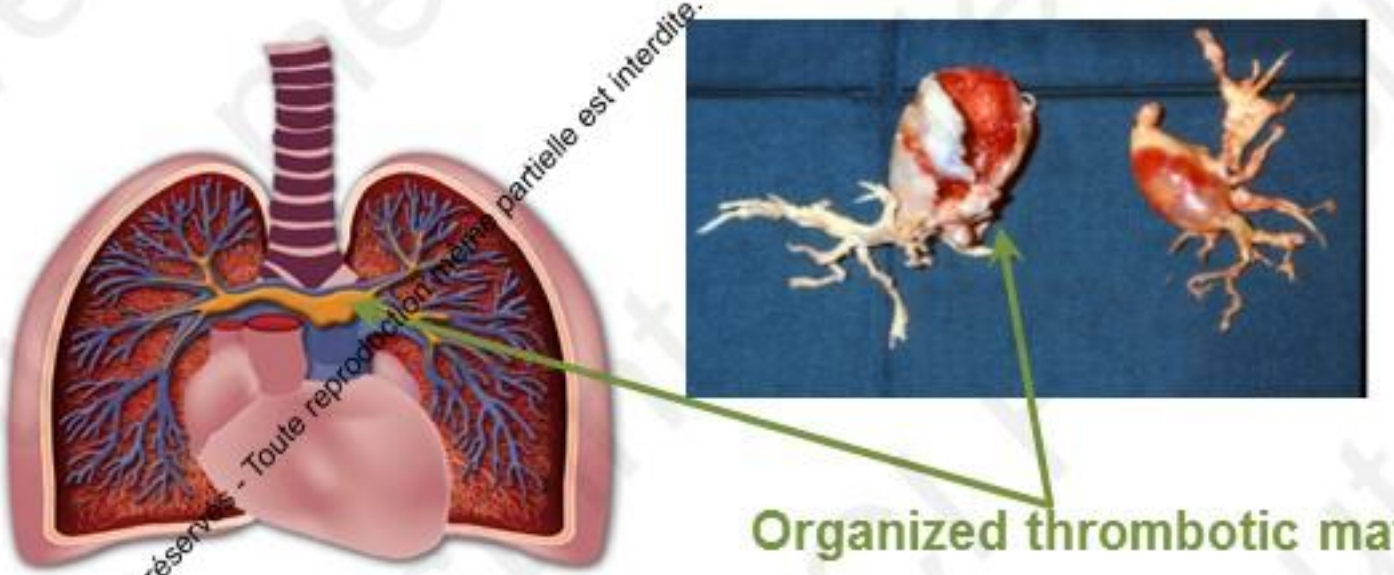
Study	N	Before PEA PVR (dyn.s.cm^{-5})	After PEA PVR (dyn.s.cm^{-5})	Treatment effect
Corsico AG, et al. *AJRCCM* 2008	157	1140	349	-69%
Freed DH *JTCVS* 2011	314	805	301	-63%
Madani MM *Ann Thorac Surg* 2012	500	719	253	-65%
Mayer E *JTCVS* 2012	386	698	235	-66%
Skoro-Sajer N *Thorax* 2014	110	770	280	-64%
Cannon JE *Circulation* 2016	880	830	317	-62%

Survival in operated and not-operated CTEPH patients



Delcroix M, *et al. Circulation.* 2016;133:859-71.

Pulmonary endarterectomy (PEA) is the treatment of choice for operable patients with CTEPH



- Peri-operative mortality <5% in experienced centers but increasing when pre-operative PVR> 800-1200 dyn.s.cm^{-5} (1,2)
- 35–40% are not amenable for PEA (distal lesions, comorbidities)
- Some patients have persistent PH after PEA

(1) Dartevelle P, *et al. Eur Respir J 2004;* (2) Mayer E, *et al. J Thorac Cardiovasc Surg 2011;* (3) Pepke-Zaba J, *et al. Circulation* 2011.

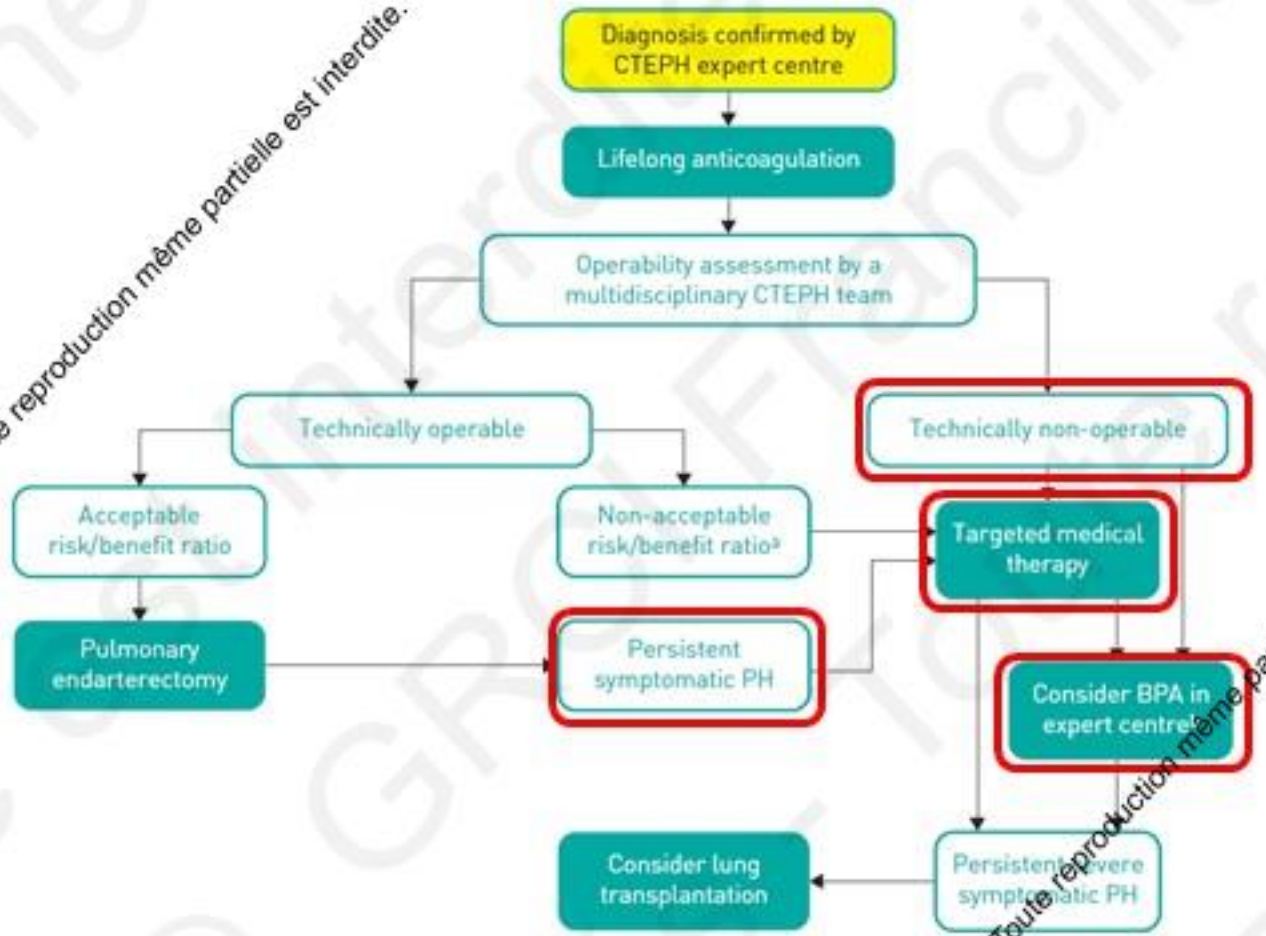
Persistent / residual PH following PEA

- 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 dyn.s.cm^{-5} end ICU	**6%**
Skoro-Sayer N, *Circulation* 2009	103	PVR >550 dyn.s.cm^{-5} end ICU	**14%**
Corsico AG, *Am J Respir Crit Care Med* 2008	157	PVR >500 dyn.s.cm^{-5} at 4	**24%**

CTEPH Treatment Algorithm (2015 ESC/ERS guidelines)

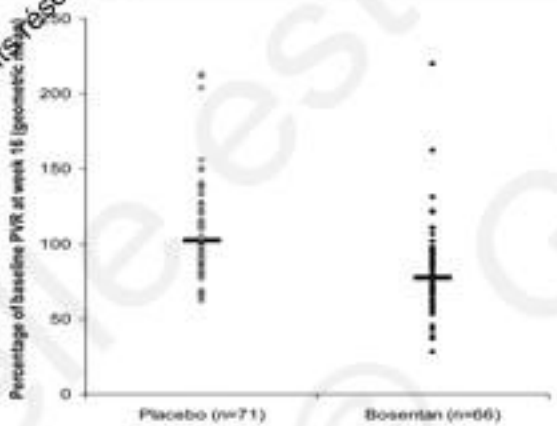


Galiè N, Humbert M, *et al. Eur Respir J* 2015 & *Eur Heart J* 2016.

BPA= balloon pulmonary angioplasty

RCT with bosentan in CTEPH

	Treatment	Patients (n)	Study duration	Primary endpoint	Secondary endpoints
BENEFIT	Bosentan *vs* placebo	157 Inoperable (n=113) Persistent PH after PEA (n=44)	16 wks	**Δ PVR -24%** (p=0.0001) **Δ 6-MWD +2.2 m** (p=0.54)	**Positive**: TPR; CI; Borg scale; Δ NT-pro-BNP **Negative**: FC; TTCW; QoL (SF-36)

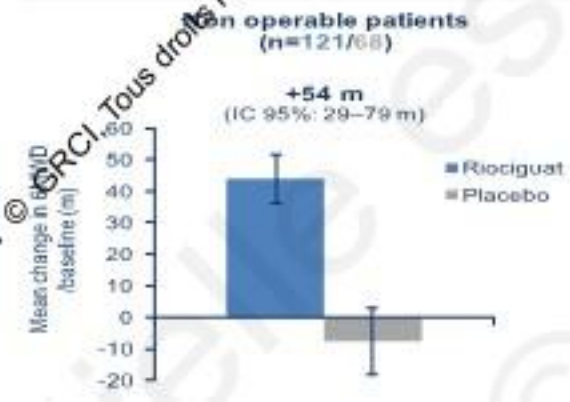


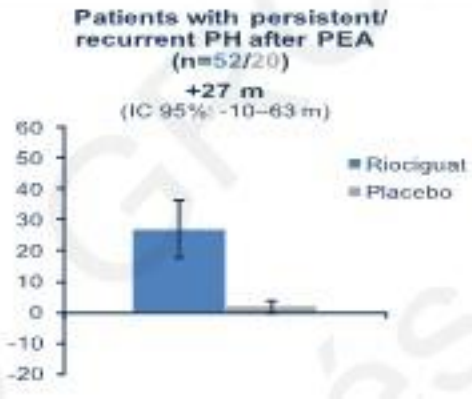
FC: Functional class; 6-MWD: 6-min walk distance; CI: Cardiac Index; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; QoL: Quality of Life; TPR: Total Pulmonary Resistance pulmonaire; PVR: Pulmonary Vascular Resistance; TTCW: Time to clinical worsening

Jaïs X, *et al. J Am Coll Cardiol* 2008.

RCT with riociguat in CTEPH

	Treatment	Patients (n)	Study duration	Primary endpoint	Secondary endpoints
CHEST	Riociguat *vs* placebo	261 Inoperable (n=189) Persistent PH after PEA (n=72)	16 wks	**Δ 6MWD +46 M (95%CI: 25–67m)** **(p<0.0001)**	**Positive**: PVR; NT-pro-BNP; FC; Borg scale; QoL (ED-Q5) **Negative**: TTCW; QoL (LPH)





FC: Functional class; 6-MWD: 6-min walk distance; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; QoL: Quality of Life; PVR: Pulmonary Vascular Resistance; TTCW: Time to clinical worsening; LPH: Living with PH questionnaire; ED-Q5: EuroQol five-dimensions questionnaire.

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

RCT with macitentan in CTEPH

	Treatment	Patients (n)	Study duration	Primary endpoint	Secondary endpoints
MERIT-1	Macitentan* *vs* placebo*	80 All Inoperable	24 wks	**Δ PVR at week 16** **-16%** **(p=0.04)**	**Positive**: **Δ 6MWD at week 24** **+34 M (p=0.03)** ΔCI at week 16; Δ NT-pro-BNP at week 24 **Negative**: FC; Borg scale

*At baseline, 61% of patients were receiving PAH targeted therapy:

- 96% were on PDE-5i
- 24% were on oral /inhaled prostanoids

FC: Functional class; 6-MWD: 6-min walk distance; CI: Cardiac Index; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; PVR: Pulmonary Vascular Resistance.

Ghofrani HA, *et al. Lancet Respir Med* 2017.

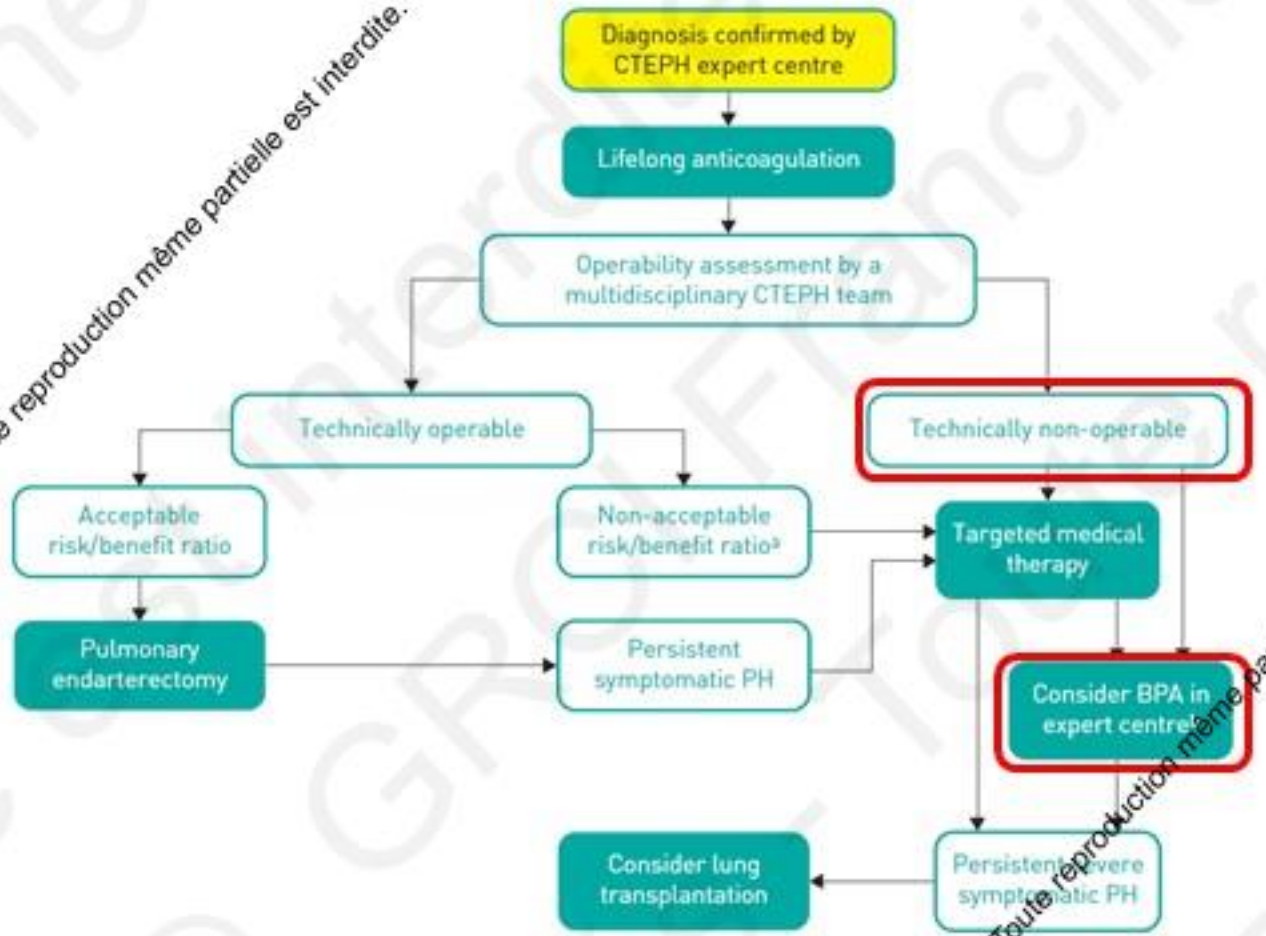
Randomized controlled trials (RCTs) in inoperable CTEPH or persistent PH after surgery

Study	Drug	Patients (n)	Inoperable / Persistent PH post PEA (%)	Study duration	Primary endpoint	Primary EP met	Secondary EP met
BENEFIT	Bosentan[1]	157	72 / 28	16 weeks	6-MWD PVR	No **Yes**	(TTCW) No
-	Sildenafil[2]	19	53 / 47	12 weeks	6-MWD	No	(PVR) **Yes**
CHEST-1	Riociguat[3]	261	72 / 28	16 weeks	6-MWD	**Yes**	(PVR) **Yes** (TTCW) No
MERIT-1	Macitentan[4]	80	100 / 0	24 weeks	PVR	**Yes**	(6-MWD) **Yes**

- 4 RCTs showed beneficial effects of PAH medications on hemodynamics in inoperable CTEPH but only 2 demonstrated an improvement in 6-MWD (MERIT-1 and CHEST-1)
- No effect on TTCW
- Only one approved medical therapy (riociguat) for inoperable CTEPH or residual postoperative PH

(1) Jaïs X *et al. J Am Coll Cardiol* 2008. (2) Suntharalingam J *et al. Chest* 2008. (3) Ghofrani HA *et al. NEJM* 2013. (4) Ghofrani HA *et al. Am J Respir Crit Care Med* 2017.

CTEPH Treatment Algorithm (2015 ESC/ERS guidelines)



Galiè N, Humbert M, *et al. Eur Respir J* 2015 & *Eur Heart J* 2016.

BPA= balloon pulmonary angioplasty

Balloon pulmonary angioplasty (BPA) series

Author	Year	Study	Patients (n)	Medical treatment before BPA
Kataoka	2012	Prospective	29	100%
Mizoguchi	2012	Observational	68	100%
Andreassen	2013	Observational	20	10%
Inami	2014	Retrospective	136	85%
Taniguchi	2014	Retrospective	29	100%
Fukui	2014	Retrospective	20	75%
Aoki	2016	Prospective	24	92%
Roik	2016	Prospective	11	66%
Inami	2016	Retrospective	170	91%
Kurzyna	2017	Observational	56	100%
Ogo	2017	Retrospective	80	61%
Ogawa	2017	Retrospective	308	72%

Kataoka M, *et al. Circ Cardiovasc Interv* 2012;5:756–62. Mizoguchi H, *et al. Circ Cardiovasc Interv* 2012;5:748–55. Andreassen AK, *et al. Heart* 2013;99:1415–20. Inami T, *et al. PLoS One* 2014;9:e94587. Taniguchi Y, *et al. EuroIntervention* 2014;10:518-25. Fukui S, *et al. Eur Respir J* 2014;43:1396–402. Aoki T, *et al. Circ J* 2016;80:2227–34. Roik M, *et al. Int J Cardiol* 2016;203:228-35. Inami T, *et al. Circulation* 2016;134:2030–2. Kurzyna M, *et al. Kardiologia Polska* 2017;75:645–54. Ogo T, et al. Eur J Radiol 2017;89:270–6. Ogawa A, *et al. Circ Cardiovasc Qual Outcomes* 2017;10:e004029.

Haemodynamic effects of BPA

	N	Before BPA PVR (dyn.s.cm^{-5})	After BPA PVR (dyn.s.cm^{-5})	Treatment effect
Mizoguchi, 2012	38	942±367	327±151	-65%
Sugimura, 2012	12	672±236	310±73	-54%
Andreassen, 2013	20	704±320	472±288	-33%
Fukui, 2014	20	889±365	490±201	-45%
Taniguchi, 2014	29	763±308	284±128	-63%
Aoki, 2016	24	517	268	-48%
Ogawa, 2017	308	854±451	360±223	-58%

Mizoguchi H *et al, Circ Cardiovasc Interv* 2012; Sugimura K *et al, Circ J* 2012; Andreassen AK *et al, Heart* 2013; Fukui S *et al, Eur Respir J* 2014; Taniguchi Y *et al, EuroIntervention* 2014; Aoki T *et al, Circ J* 2016; Ogawa A, *et al. Circ Cardiovasc Qual Outcomes* 2017;10:e004029.

Complications of BPA

- Complications after BPA are frequent (10% of sessions and 38% of patients)
- Main complications are pulmonary artery injuries: PA ruptures, PA dissection, PA perforations, Pulmonary injury (mortality≈1%)
- Correlation between the rate of complications and hemodynamic severity

Imani et al (1)	*Pulmonary injury* +	*Pulmonary injury* -	*p*
mPAP *(mmHg)*	42 (38-50)	33 (28-41)	0,0001
PVR *(WU)*	9,2 (7-14,6)	6,1 (3,9-8,7)	0,0001
CI *(L/min/m²)*	2,5 (1,9-2,7)	2,6 (2,4-3,3)	0,006

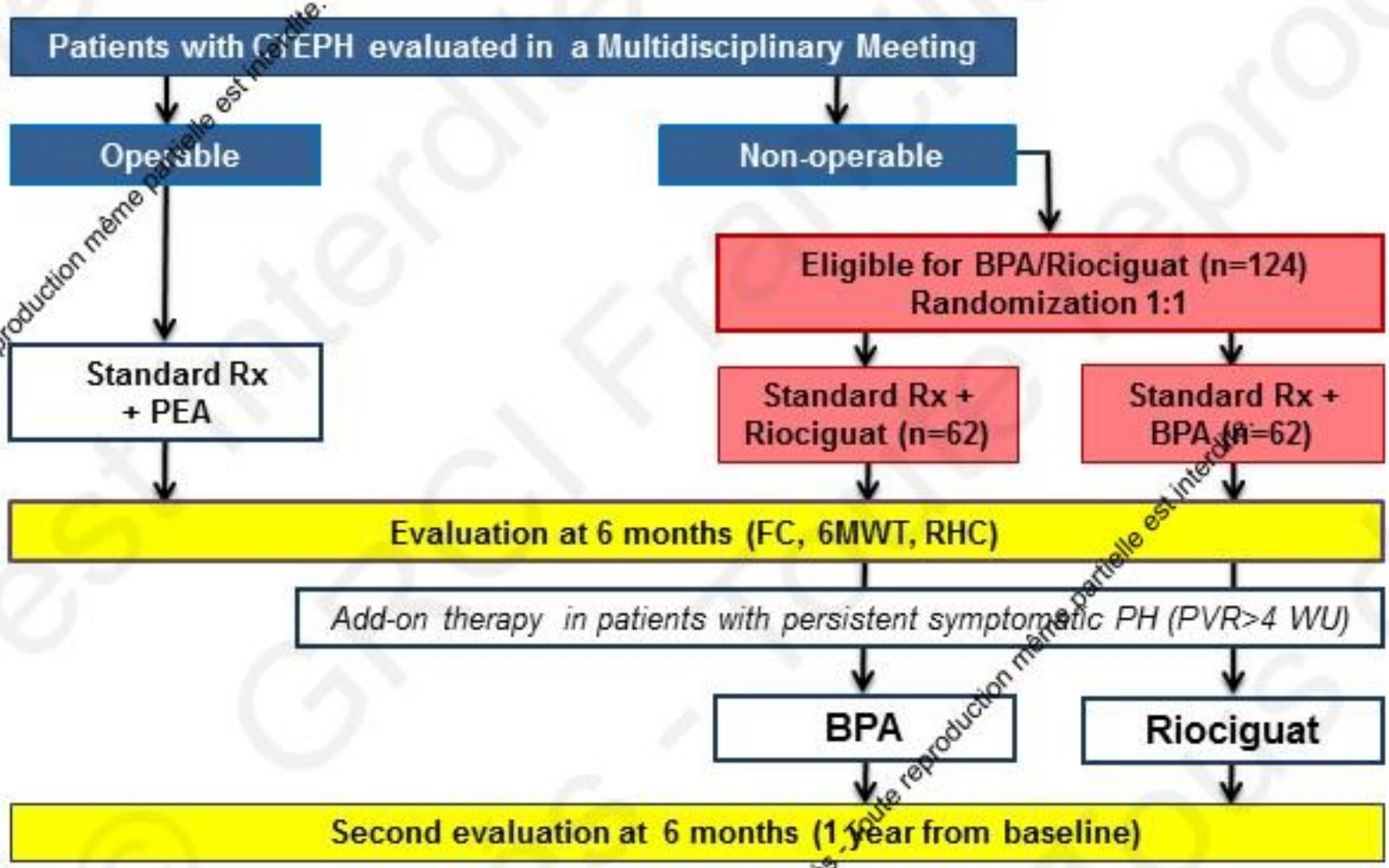
(1) Inami T *et al, Int J Cardiol* 2016; (2) Inami T *et al, JACC Cardiovasc Interv 2015.*

Toute reproduction même partielle est interdite.

RACE study: Riociguat *vs* balloon pulmonary Angioplasty in non-operable Chronic thromboEmbolic pulmonary hypertension

- Multicenter open-label, randomized, parallel groups study to assess the efficacy and safety of riociguat *vs* BPA in patients with inoperable CTEPH
- 20 PH centres in France / 2 BPA centres
- Primary endpoint
  - Change in PVR at week 26 expressed as a percentage of baseline value
- Hypothesis
  - Decrease by 50% in BPA group and 30% in riociguat group
  - 62 newly diagnosed treatment-naïve patients in each group
- Inclusion period: 3 years

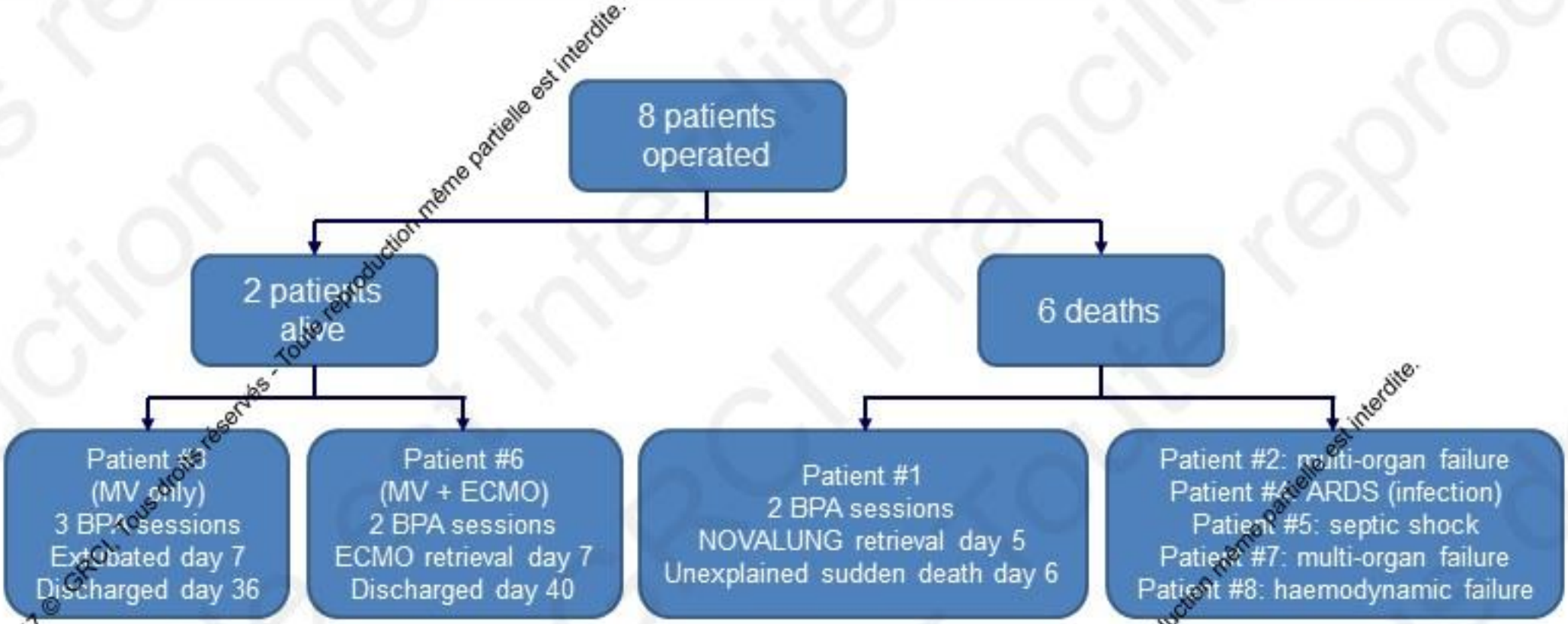
RACE: Study design



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

Rescue BPA after PEA

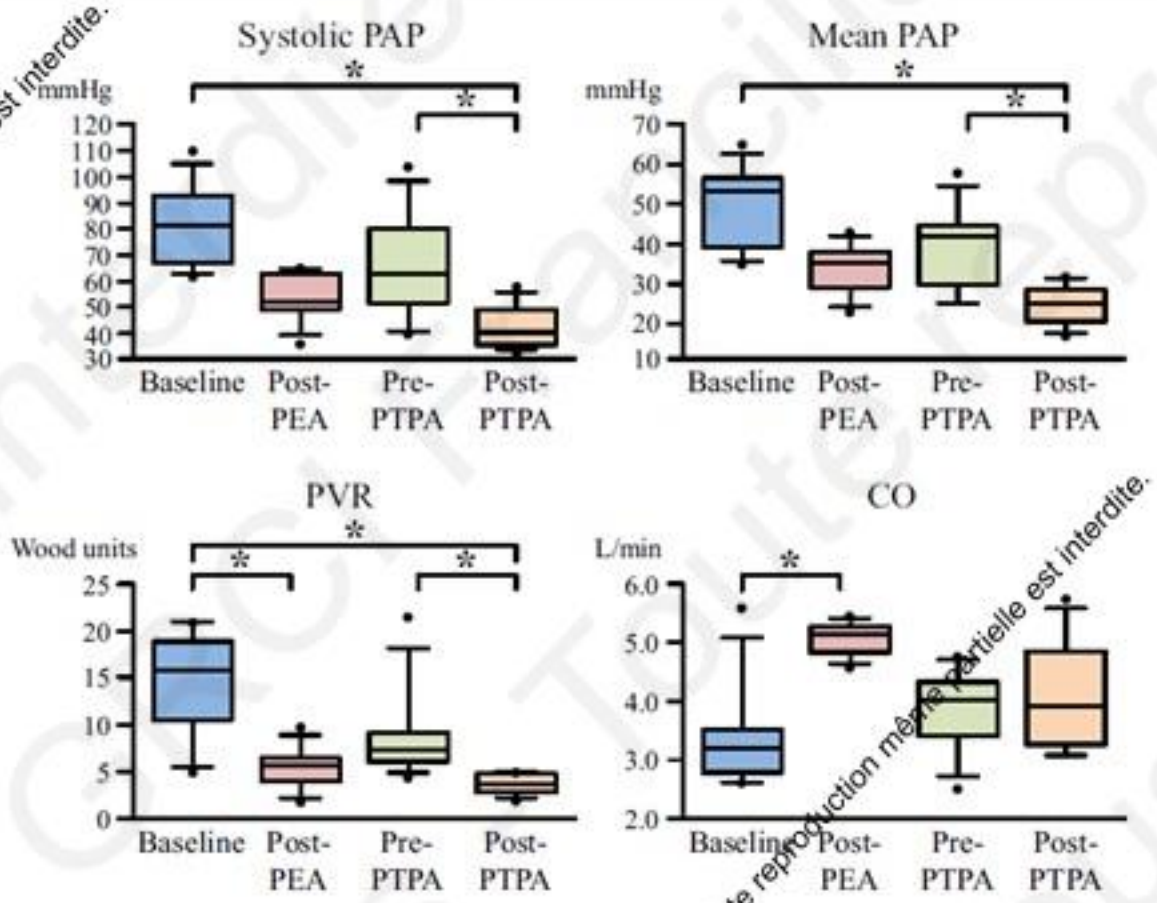
Paris-Sud University – Marie Lannelongue Hospital experience (n=8)



Slide courtesy of Philippe Brenot – Presented at International CTEPH Conference 2017, Leuven, Belgium.

BPA a long time after PEA

- n= 9
- 4.1 (2.7-7.9) years after PEA



Shimura N *et al. Int J Cardiol* 2015.

Conclusion

- Surgery (PEA) remains the treatment of choice in operable cases.
  - Increased mortality when PVR are elevated (> 800 dyn.s.cm^{-5})
  - Persistent PH is frequent after surgery
- Medical therapy must be considered in non operable CTEPH or in persistent PH after surgery (riociguat is the only agent approved).
- Balloon pulmonary angioplasty is an appealing technique
  - Medical therapy as a bridge to BPA is widely used despite the absence of RCTs. The RACE study will provide important data.
  - The role of combination of PEA and BPA is more questionable
    - After PEA, "Rescue BPA" immediately after surgery has poor prognosis
    - In contrast, the results of BPA long time after PEA are very encouraging