Pulmonary Circulation and Right Ventricular Function
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

EUROPEAN HEART HOUSE

Pulmonary Hypertension:
Challenging The 2015 PH Guidelines and annual G6 meeting

Friday 14 – Saturday 15 October 2016

Course Directors:
N. Galiè (IT), G. Simonneau (FR)

CTEPH – comments and proposals

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Disclosures

- Irene Lang has relationships with the following: AOP Orphan Pharmaceuticals, Actelion, AstraZeneca, Bayer Pharma AG, Cordis, GSK, Medtronic, MSD, Pfizer, Sanofi, Servier, and United Therapeutics
  - In addition to being an investigator in trials involving these companies, relationships include consultancy, research grants, and membership of scientific advisory boards

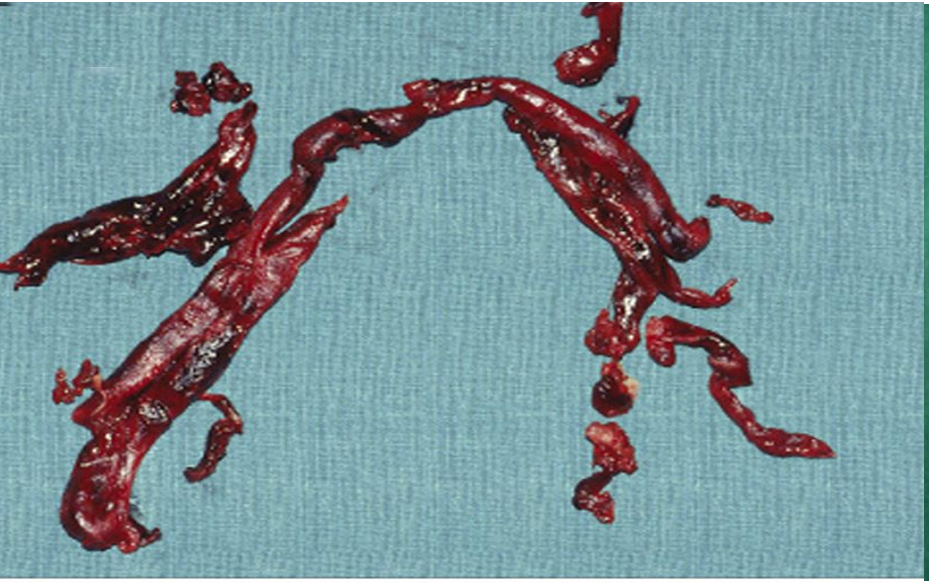
Comprehensive clinical classification

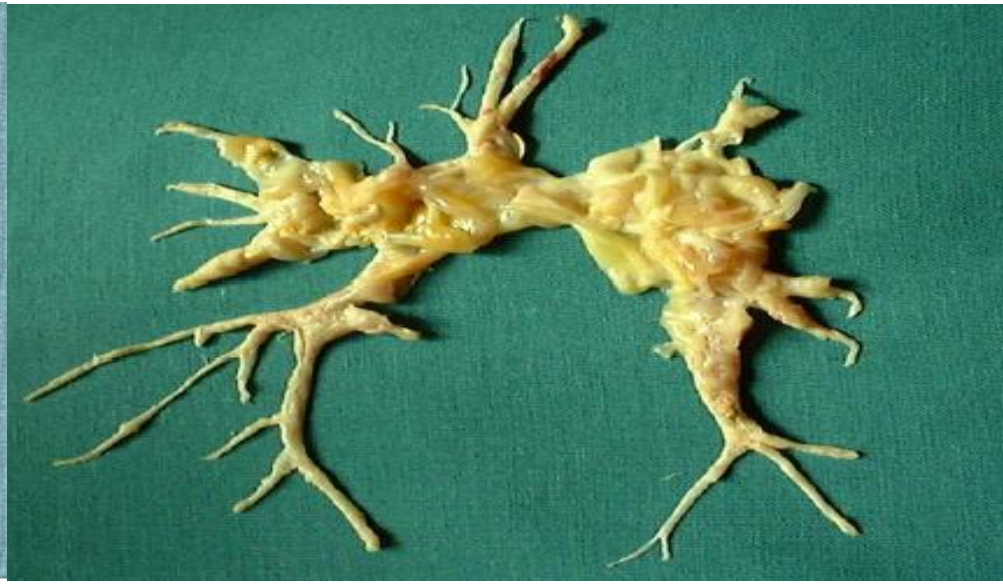
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

Galié N, Humbert M, et al, *Eur Heart J*. 2016 Jan 1;37(1):67-119.

Acute PE and CTEPH





Acute PE

CTEPH

Risk factors for CTEPH versus iPAH

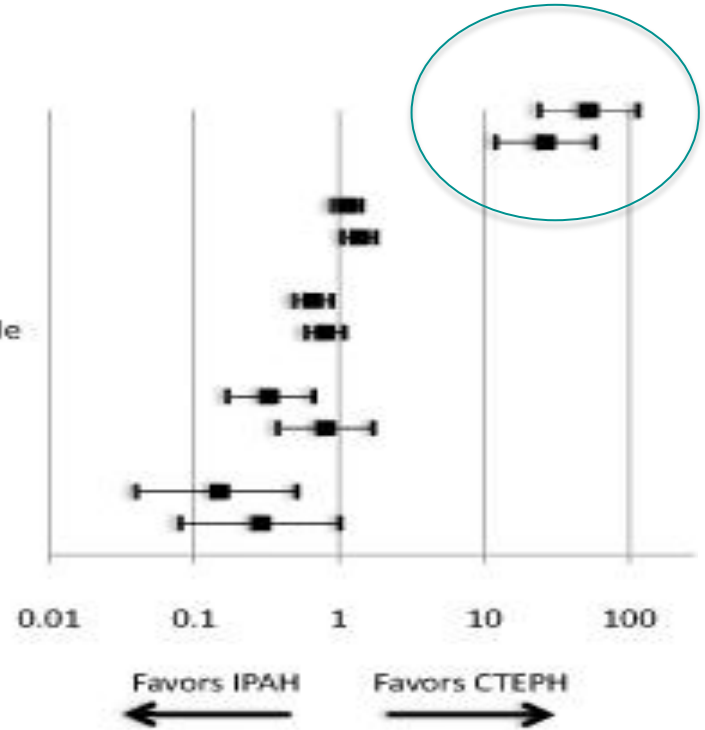
Clinical history of acute VTE - operable
Clinical history of acute VTE - non-operable

Age per 10 years - operable
Age per 10 years - non-operable

Mean pulmonary arterial pressure per 10 mm Hg - operable
Mean pulmonary arterial pressure per 10 mm Hg - non-operable

Gender (Female) - operable
Gender (Female) - non-operable

Diabetes mellitus - operable
Diabetes mellitus - non-operable



Lang I et al. *Thrombosis & Haemostasis* 2013; 110: 83-91

Does acute PE beget chronic thromboembol pulmonary hypertension?

reference	Number of patients with acute pulmonary embolism	Average observat time in months aft the acute event	Cumulative incidence of CTEPH %
Long-term outcomes in acute pulmonary thromboembolism: the incidence of chronic thromboembolic pulmonary hypertension and associated risk factors {Korkmaz, 2012}	325	16.3	4.6
Echocardiographic assessment of pulmonary arterial pressure in the follow-up of patients with pulmonary embolism {Otero, 2011}	744	14	8.3
Incidence of symptomatic and asymptomatic chronic thromboembolic pulmonary hypertension] {Marti, 2010}	110	24	9.1
Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism {Klok, 2010}	877	34	0.57
Active search for chronic thromboembolic pulmonary hypertension does not appear indicated after acute pulmonary embolism {Surie, 2010}	110	36	2.7
Incidence of recurrent venous thromboembolism and of chronic thromboembolic pulmonary hypertension in patients after a first episode of pulmonary embolism {Poli, 2010}	239	36	0.4
Prevalence Of Chronic Thrombo-embolic Pulmonary Hypertension After Acute Pulmonary Embolism : A Prospective Multicenter Study {Sanchez, 2010}	700	26	4.7
Incidence of chronic pulmonary hypertension in patients with previous pulmonary embolism {Dentali, 2009}	91	6-12	8.8
Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism {Becattini, 2006}	259	46	1.0
Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after acute pulmonary embolism {Miniati, 2006}	834	25	1.0
Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism {Pengo, 2004}	314	94.3	3.8
Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis {Ribeiro, 1999}	78	12	5.0

CT-Signs of CTEPH at the time of the acute PE

	CTEPH + (n=7)	CTEPH – (n=99)
Organised mural thrombi, yes / no, (%)	6 (86) / 1(14)	20 (20) / 79 (80)
Arterial webs or bands, yes / no, (%)	4 (57) / 3 (43)	3 (3) / 96 (97)
Dilated bronchial arteries, yes / no, (%)	1 (25) / 3 (75)1	13 (13) / 76 (87)
Mosaic parenchymal perfusion pattern, yes / no, (%)	6 (86) / 1 (14)	27 (27) / 70 (73)
Presence of at least two CT signs, yes / no, (%)	7 (100) / 0 (0)	19 (19) / 80 (81)

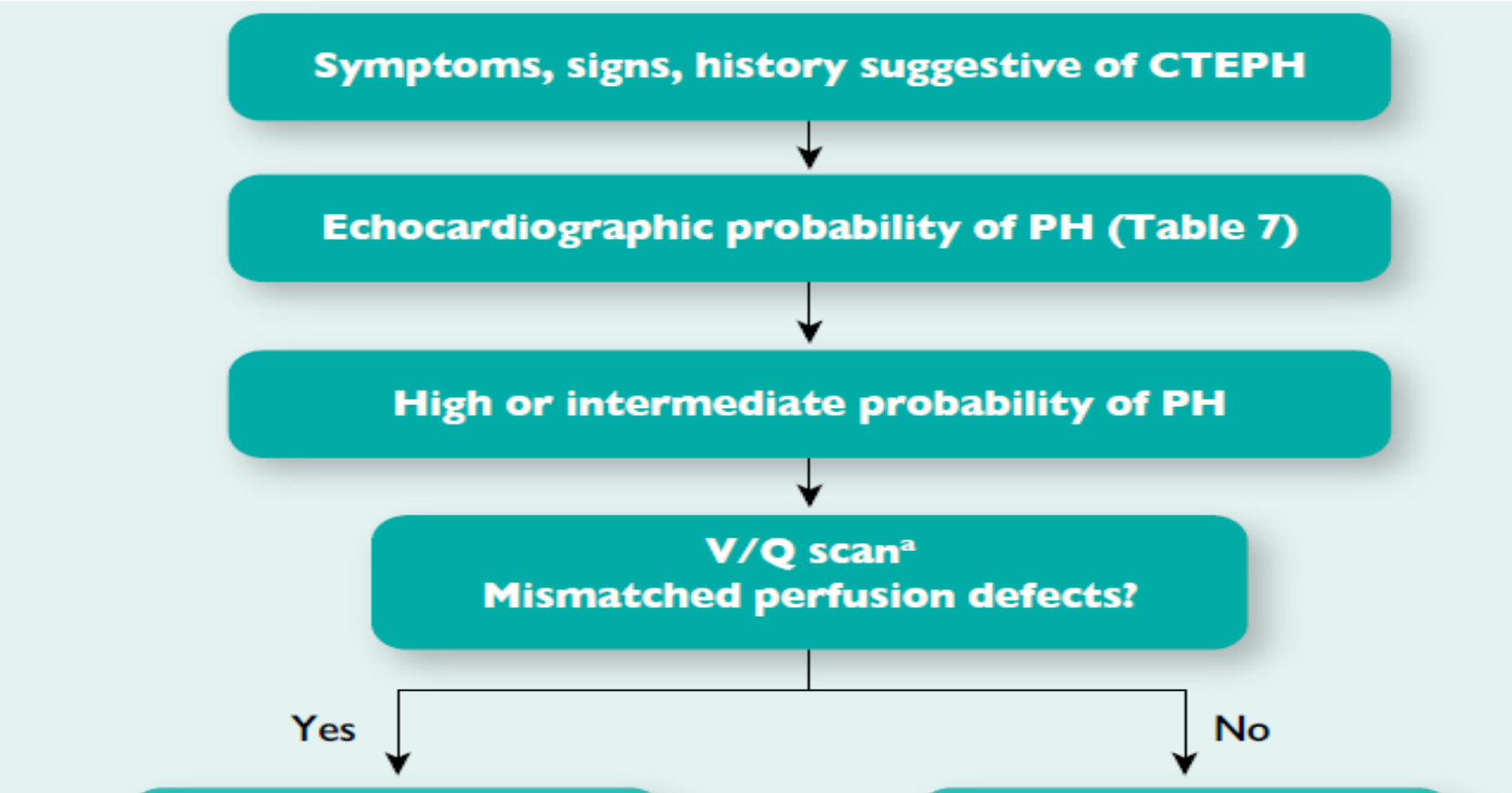
[1]Due to the quality of injections in bronchial arteries, this sign was interpretable in only 4 out the 7 CT.

Guérin L, et al. *Thromb Haemost.* 2014 Sep 2;112(3):598-605.

Comment/Proposal 1 – CTEPH disease concepts

- The reported history of acute PE in >75% of CTEPH cases may be an overestimation
- CTEPH is not ruled out by the absence of a history of VTE.

Diagnostic algorithm



Diagnostic management according to echocardiographic probability of PH in patients with symptoms compatible with PH, with or without risk factors for PAH or CTEPH

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[c]	Class[a]	Level[b]
Low	Alternative diagnosis should be considered	IIa	C
Intermediate	Alternative diagnosis, echo follow-up, should be considered	IIa	C
	Further investigation of PH may be considered[d]	IIb	
High	Further investigation of PH (including RHC[d]) is recommended	I	C
Echocardiographic probability of PH	**With risk factors or associated conditions for PAH or CTEPH[c]**	**Class[a]**	**Level[b]**
Low	Echo follow-up should be considered	IIa	C
Intermediate	Further assessment of PH including RHC should be considered[c]	IIa	B
High	Further investigation of PH[d] including RHC is recommended	I	C

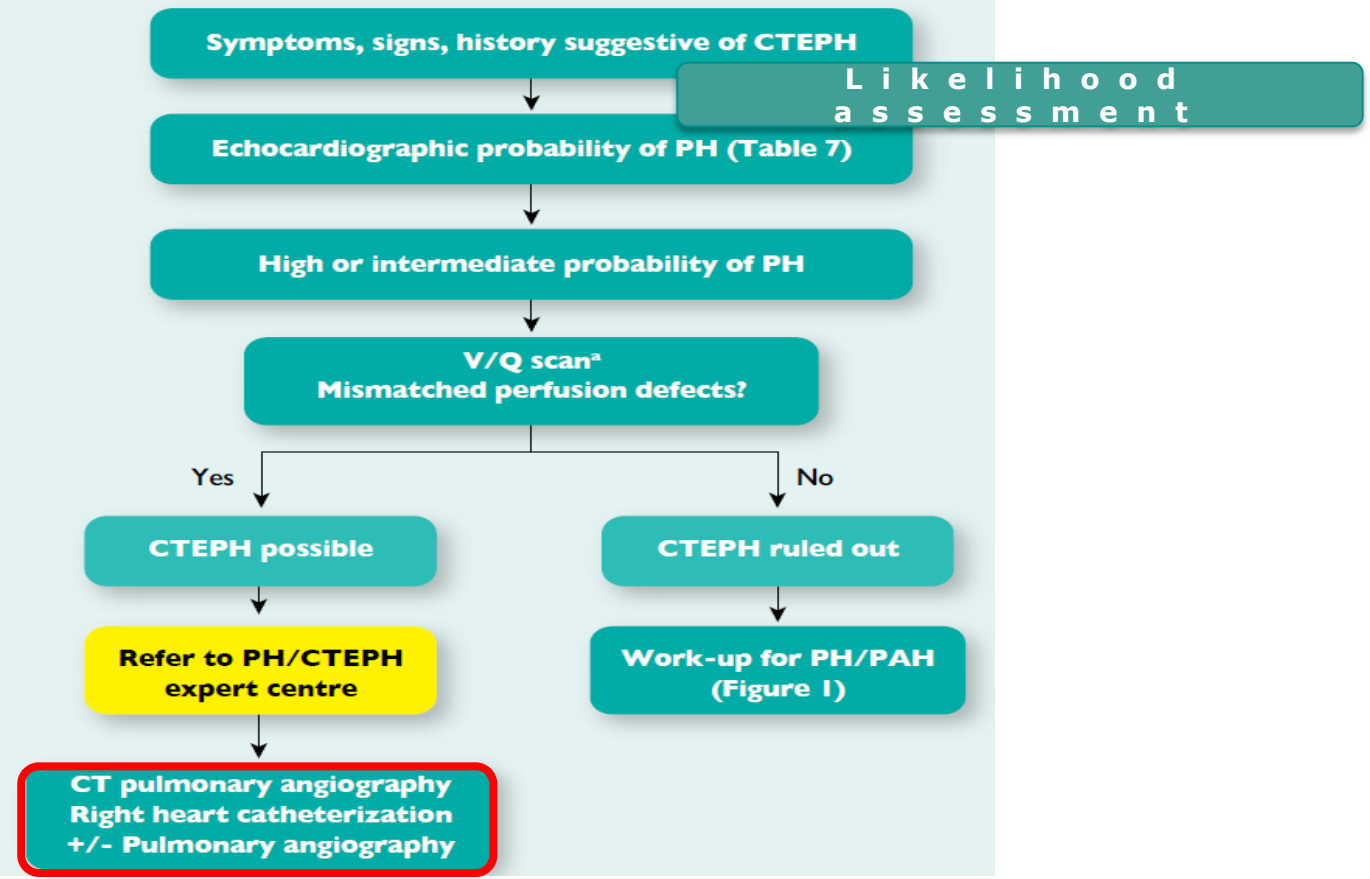
Galié N, Humbert M, et al, *Eur Heart J*. 2016 Jan 1;37(1):67-119.

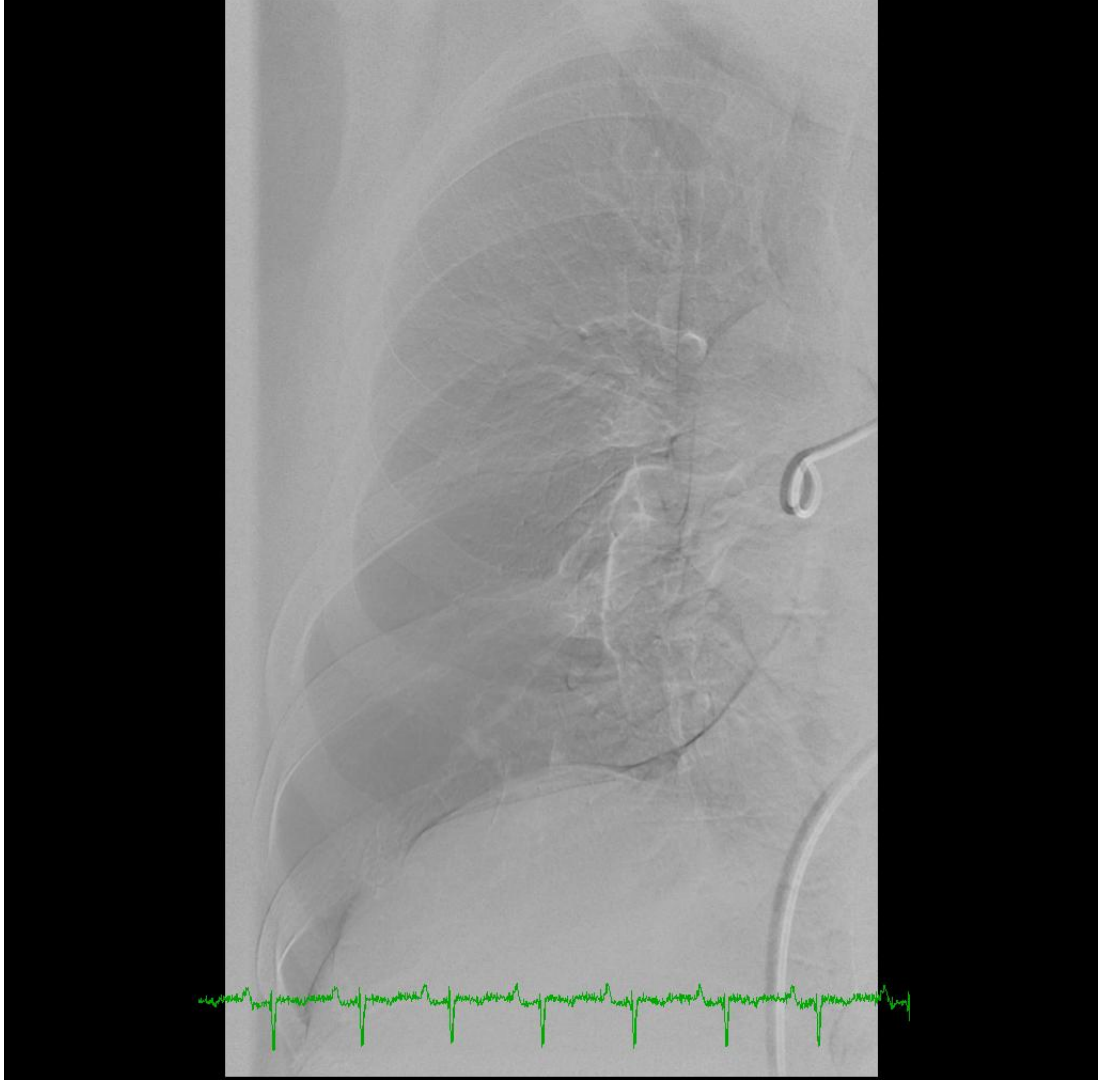
CTEPH Associated Conditions

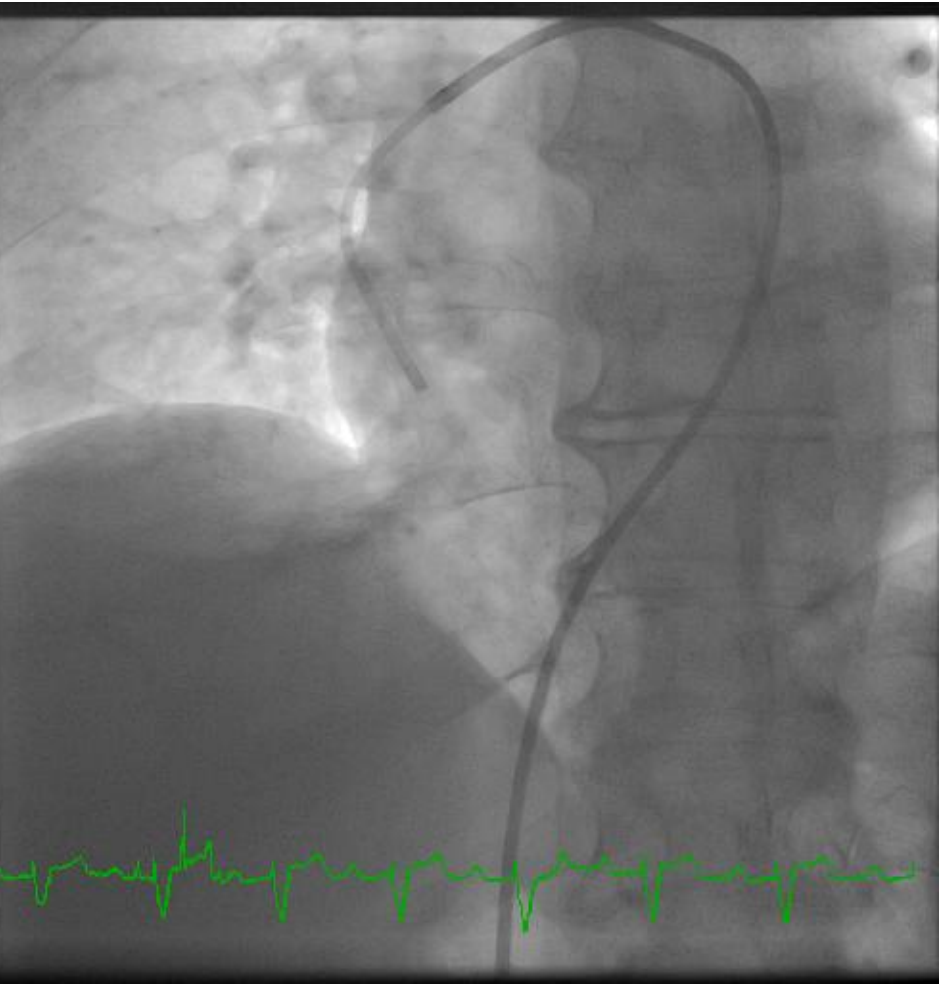
Associated condition	OR
VA shunt/infected leads [1, 2]	13.00 [2.5-129] and 76.4 [7.67-10350.62]
Splenectomy [1, 2, 3]	13.00 [2.7-127] and 17.87 [1.56-2438]
Recurrent VTE [1]	14.4 [5.40-43.08]
Thyroid replacement therapy [1]	6.1 [2.73-15.05]
Previous VTE [1]	4.52 [2.35-9.12]
Antiphospholipid antibodies /LA [1]	4.20 [1.56-12.21]
Survived cancer [1]	3.76 [1.47-10.43]
Inflammatory bowel disease [1, 2]	3.19 [0.74-16.03]
Blood groups non-0 [1,4]	2.09 [1.12-3.94]
Fibrinogen Aα Thr312Ala polymorphism [5]	1.68 [1.13-2.49]
HLA-B*5201 (Japan) [6]	2.14 [1.29-3.55]
HLA-DPB1*0202 (Japan) [6]	3.41 [1.71-6.74]

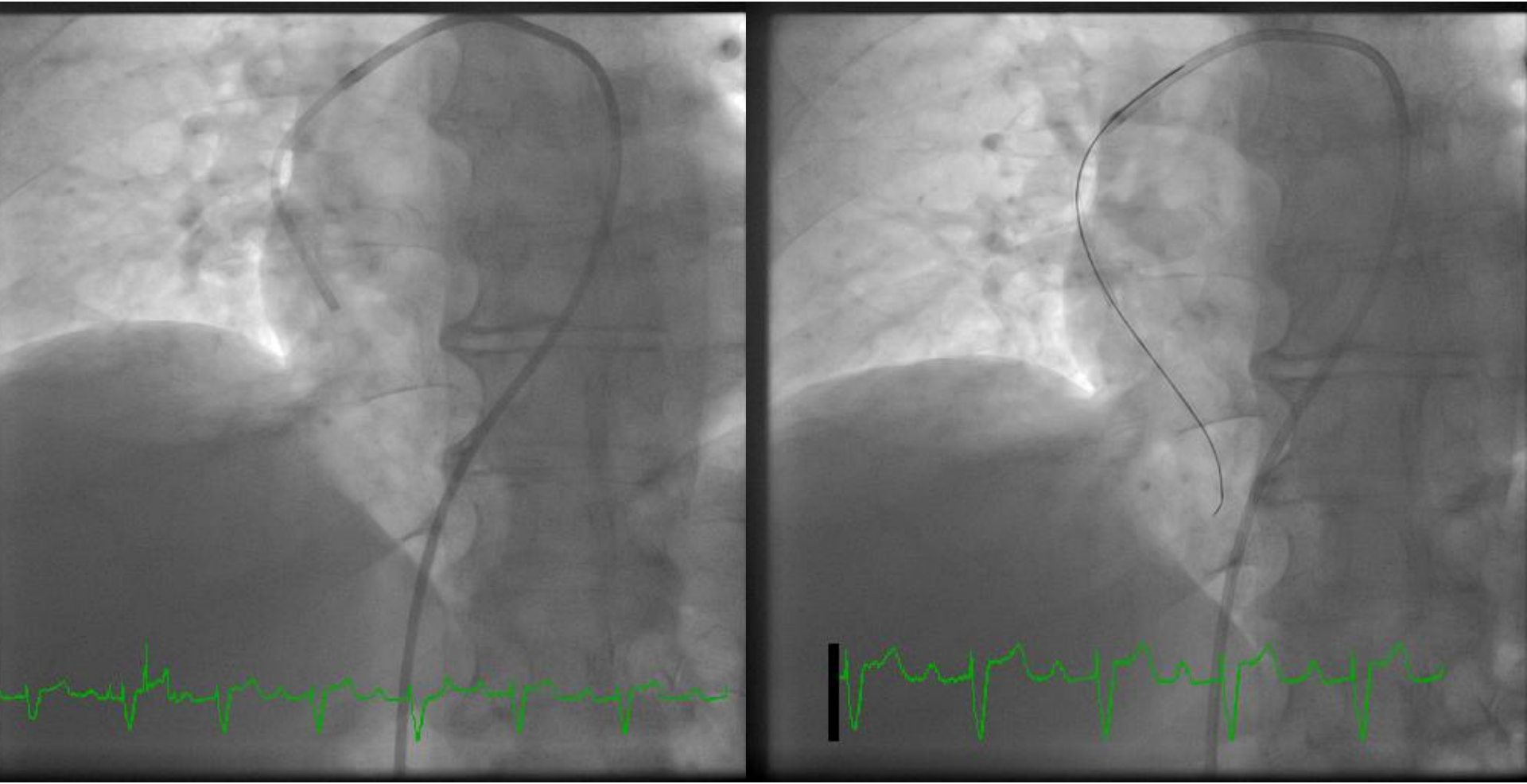
1 Bonderman D and Lang IM, *et al*. *ERJ* 2009; 33: 325-3
2 Bonderman D et al *Thromb Haemost.* 2005;93:512-516
3 Jais et al *Thorax.* 2005;60:1031-1034
4 Bonderman D et al *Thromb Haemost.* 2003;90:372-376
5 Suntharalingam J et al. *Eur Respir J.* 2008;31:736-741
6 Tanabe N et al *Eur Respir J.* 2005;25:131-138.

Diagnostic algorithm









Comment/Proposal 2 – diagnosis

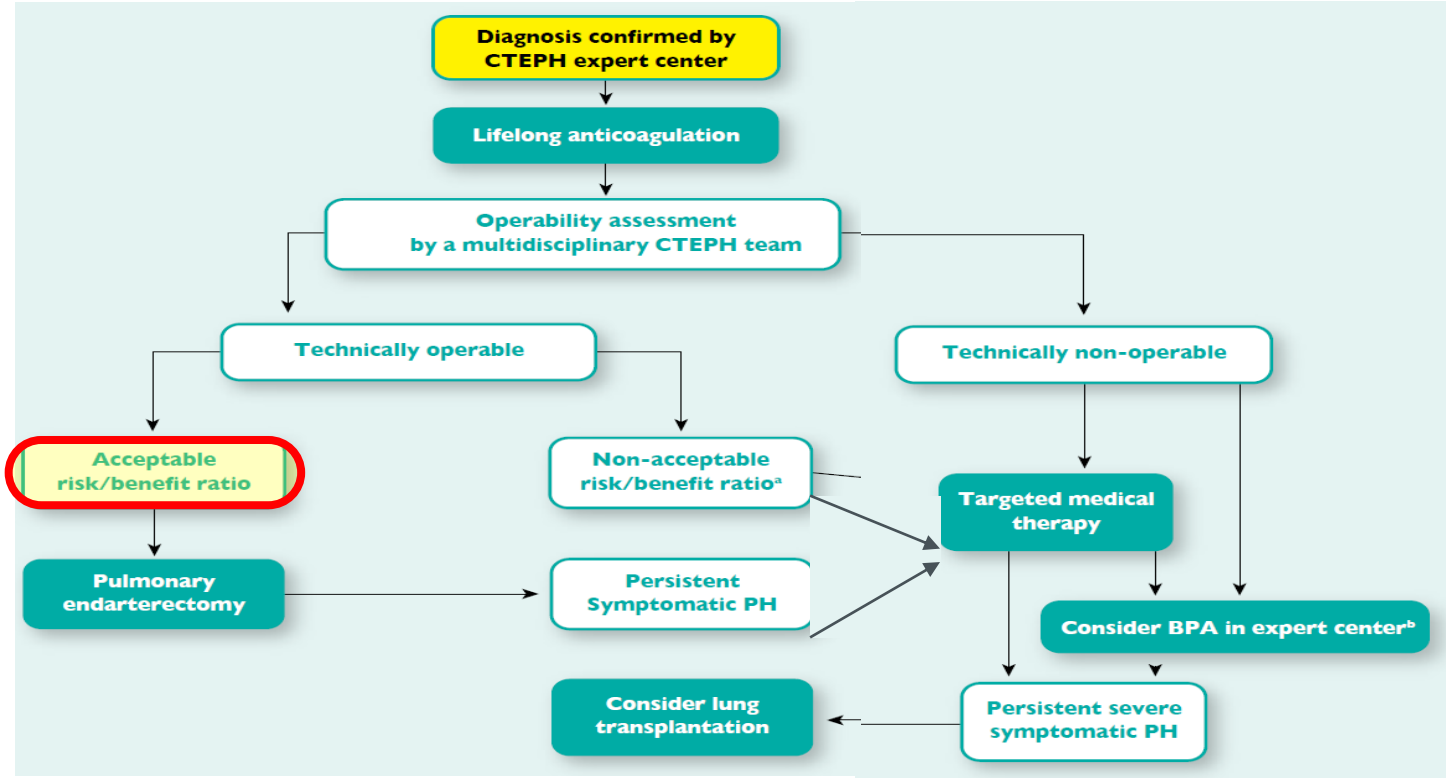
- Clinical likelihood should be actively evaluated, for example splenectomy is a definitive cause for CTEPH
- In the diagnostic work-up for CTEPH an invasive pulmonary angiogram should become mandatory.
- In doubt, selective pulmonary angiography with direct injection should be performed.

CTEPH treatment options

	PEA	Medical treatment	Angioplasty
Experience	>8500 cases Multiple publications	CHEST-1 and CHEST-2	~350 documented cases (>1300 procedures)
Indication	Operable CTEPH	Non-operable and persistent/recurrent PH	Non-operated disease (not established for cases with previous PEA)
Pros	Accepted standard, reproducible results, recommended in guidelines, potentially curative	Entirely non-invasive	Percutaneous procedure according to interventional standards
Cons	Invasive surgical procedure	Life-long treatment, evidence currently based on a single positive trial	Emerging technique, comparative trials lacking, not established outside of Japan.

Lang IM and Madani M. *Circulation.* 2014 Aug 5;130(6):508-18.

Treatment algorithm



Galié N, Humbert M, et al, *Eur Heart J*. 2016 Jan 1;37(1):67-119.

CTEPH Risk Assessment - surgery

	Low Risk (All criteria)	Intermediate Risk (1 criterion)	High Risk (1 criterion)	Prohibitive Risk (1 criterion)
STS PROM	< 4%	4-8%	> 8%	> 50% risk of death/major morbidity at 1 year
Frailty	None	1 index (mild)	≥ 2 indices (mod-severe)	
Major Organ System Compromise	None	1 organ system	≤ 2 organ systems	≥ 3 organ systems
Procedure-specific Impediment	None	Possible	Possible	Severe

Nishimura RA et al. *J Thorac Cardiovasc Surg*. 2014 Jul;148(1):e1-e132.

Limited frailty evaluation

- Grip strength
- Gait speed
  - Walking as geriatric vital sign
  - History of falls
- ADL assessment
  - iADL assessment
- Cognitive Assessment
- BMI

- No frailty
  - = able to perform all ADL
  - Performs 5MWT in < 6 seconds
- Mild frailty
  - unable to perform 1 ADL
  - unable to perform 5MWT in < 6 seconds
- Severe frailty
  - unable to perform ≥ 2 ADL

Arnett DK et al *Circulation*. 2014 Oct 28;130(18):1662-7.

CTEPH Risk Assessment -

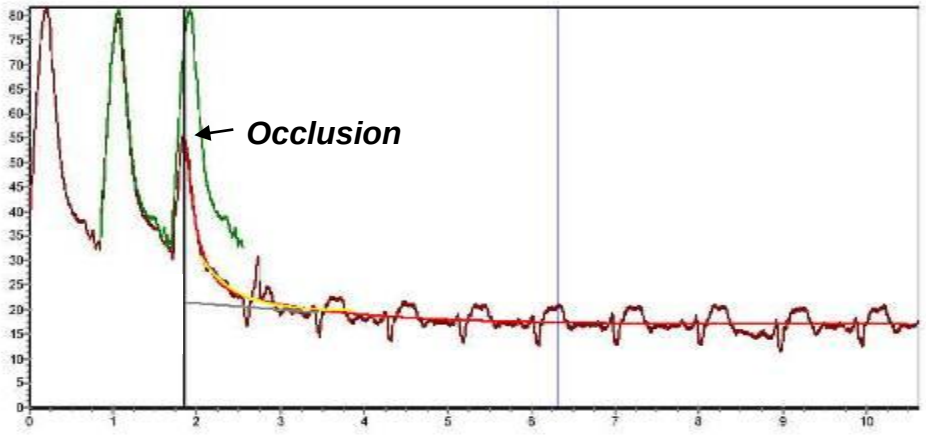
CTEPH Chronic Thromboembolic Pulmonary Hypertension REGISTRY

Determinants of prognosis	operated	Not operated
dialysis-dependent renal failure	HR, 11.52; 95% CI, 1.42–93.48; *P*=0.0221	
bridging therapy with PAH drugs	HR, 2.62; 95% CI, 1.30–5.28; *P*=0.0072	
need for additional cardiac procedures	HR, 3.10; 95% CI, 1.54–6.24; *P*=0.0015	
History of acute VTE	HR, 0.48; 0.24–0.97; *P*=0.0413	
Preoperative mPAP	HR, 0.67; 0.47–0.94; *P*=0.0226	
NYHA class	HR, 4.16; 95% CI, 1.49–11.62; *P*=0.0065	HR, 4.76; 95% CI, 1.76–12.88; *P*=0.0021
History of cancer	HR, 3.02; 95% CI, 1.36–6.69; *P*=0.0065	HR, 2.15; 95% CI, 1.18–3.94; *P*=0.0129
increased RAP	HR, 1.34; 95% CI, 0.95–1.90; *P*=0.0992	HR, 1.50; 95% CI, 1.20–1.88; *P*=0.0004
coronary disease		HR, 1.81; 95% CI, 1.00–3.28; *P*=0.0492
left heart failure		HR, 1.98; 95% CI, 1.02–3.83; *P*=0.0440
chronic obstructive pulmonary disease		HR, 2.14; 95% CI, 1.22–3.73; *P*=0.0075

Delcroix M et al. *Circulation* 2016 Mar 1;133(9):859-71.

CTEPH Risk Assessment

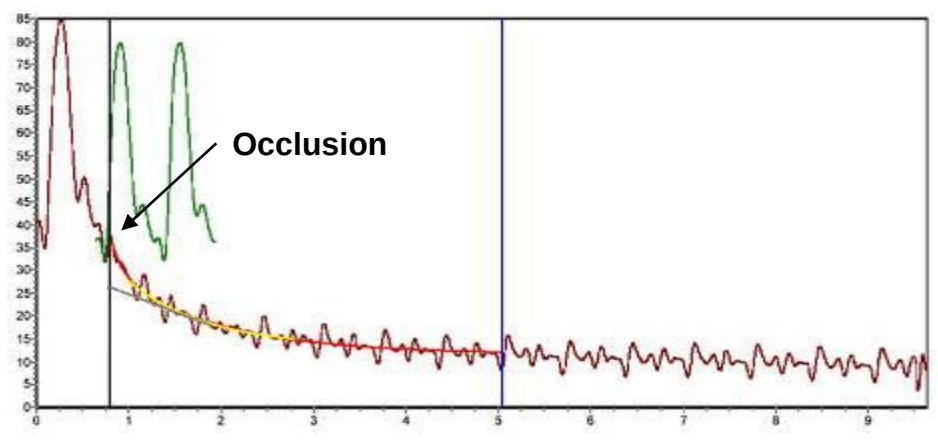
Pulmonary Artery Occlusion Waveform Analysis



Patient 1 -- Rup 81%

Pre-op
Ppa 81/33 (**50**)
fPP 0.96

Post-op
Ppa 31/11 (**21**)
ΔR 66% rel



Patient 2 – Rup 52%

Pre-op
Ppa 84/33 (**53**)
fPP 0.96

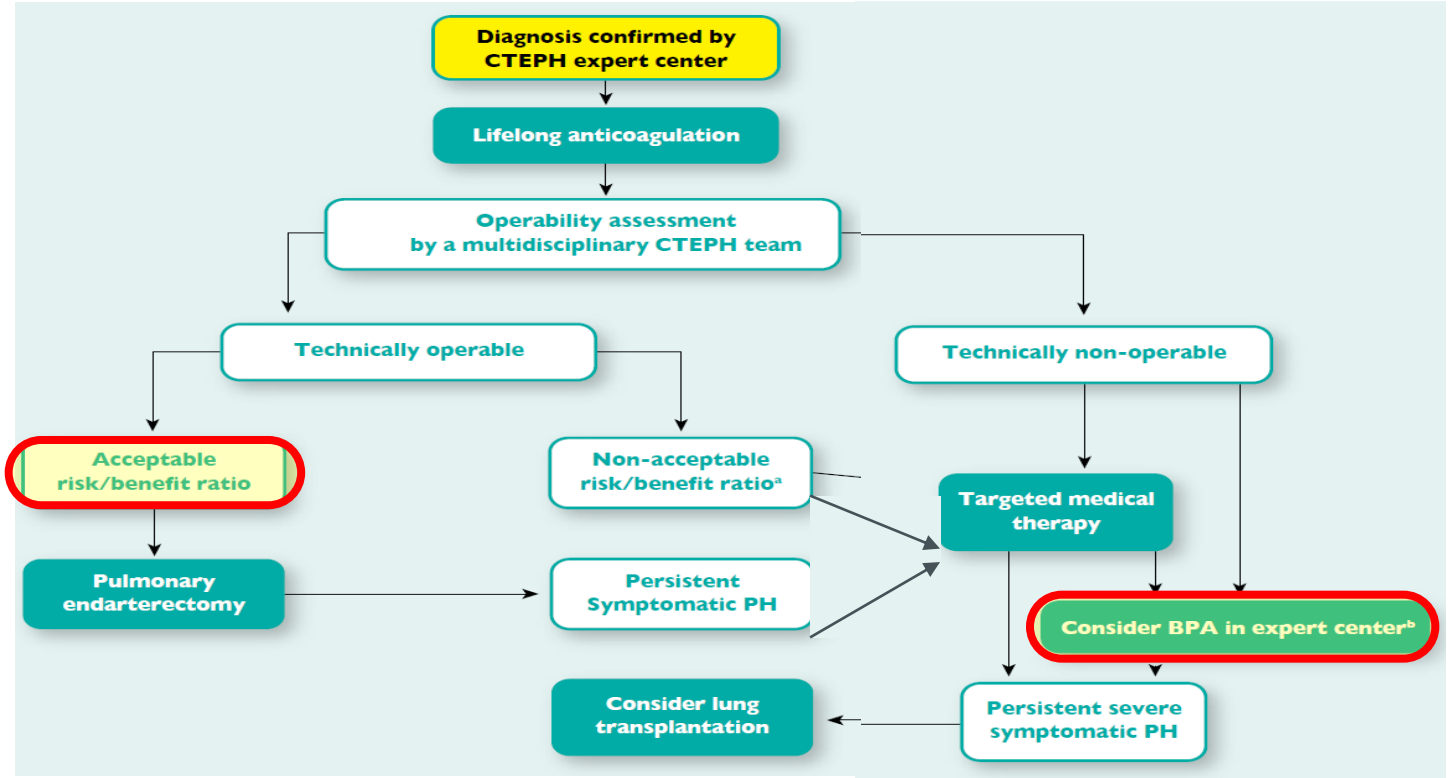
Post-op
Ppa 86/33 (**52**)
ΔR 26% rel

Kim NH, *et al. Circulation* 2004;109:18-22.

Comment/Proposal 3 – treatment decisions

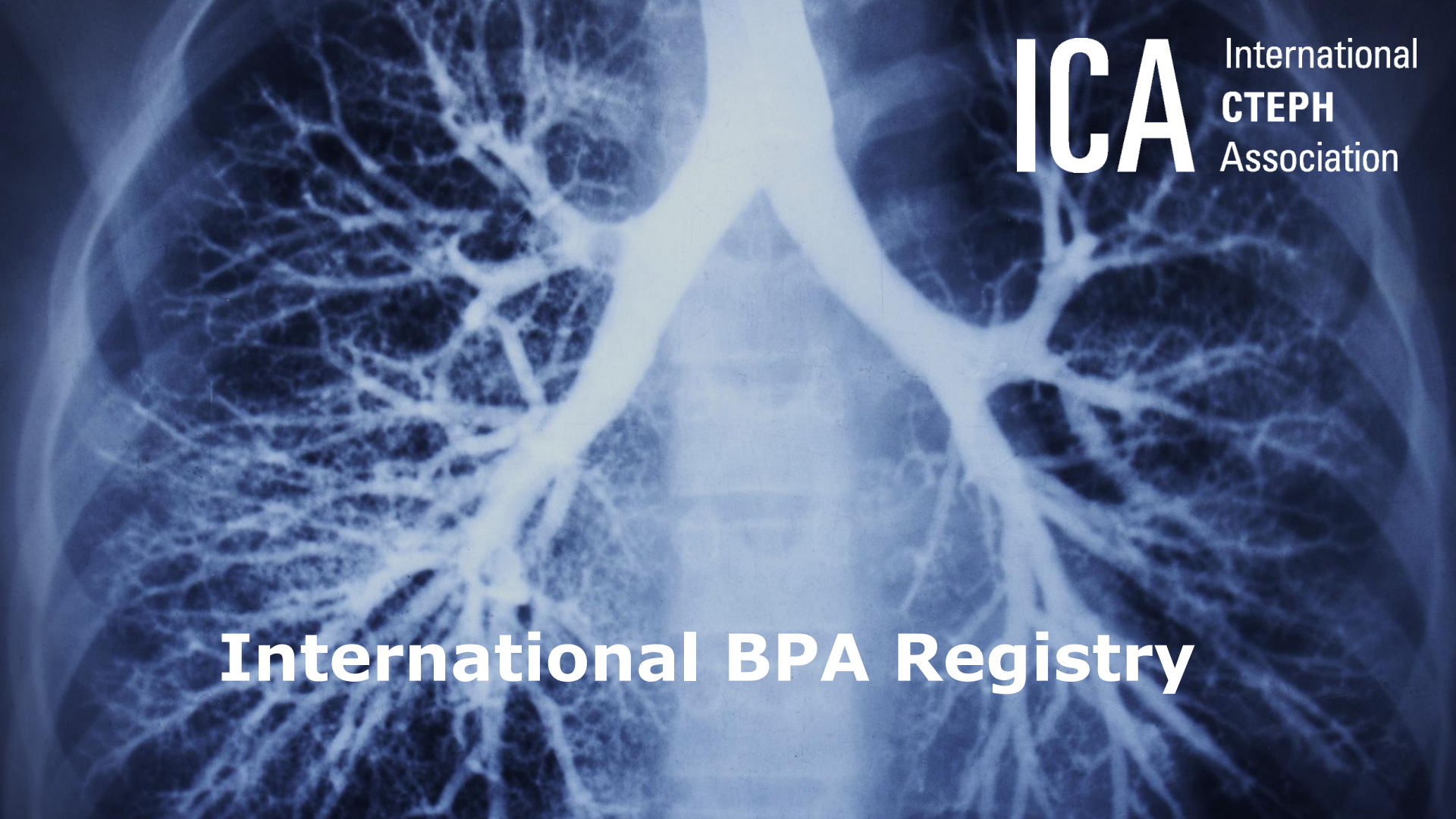
- Risk assessment should be performed prior to a CTEPH treatment decision
  - A surgical risk score including frailty assessment
  - CTEPH disease inherent risk
  - Vascular physiology – upstream resistance

Treatment algorithm



IIb,C

Galié N, Humbert M, et al, *Eur Heart J*. 2016 Jan 1;37(1):67-119.


ICA
International
CTEPH
Association
International BPA Registry

Key facts

Title	International BPA Registry
Sponsor	International CTEPH Association
Registry design	4-year prospective registry with 24 months recruitment and 24 months follow-up time
Principal investigator	Prof Nick H. Kim, San Diego, USA
Principal co-investigator	Prof Irene Lang, Vienna, Austria
Goal	Analyze consecutive BPA cases for the treatment of CTEPH from the leading international CTEPH teams
Financial support	Bayer AG
Target site number	15–20 sites from Europe, North America and Japan
Target patient number	500 (max. 40 per site)

Registry objectives

- **Primary objective**
  - Efficacy of BPA
  - Safety of BPA
  - Assess change of mPAP and PVR from baseline

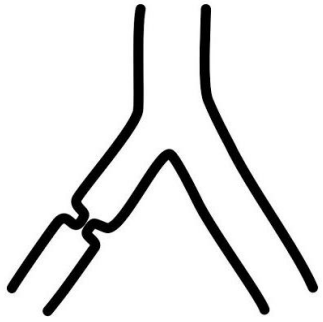
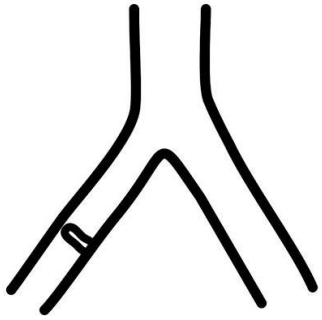
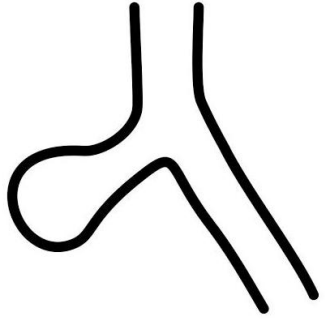
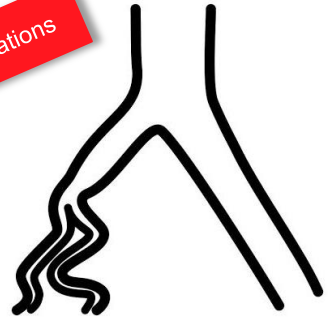
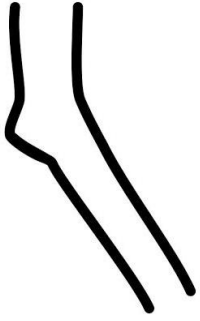
- **Secondary objectives**
  - Compare and contrast BPA patient selection process
  - Compare and contrast BPA techniques
  - Track and analyze BPA complications

Numbers and distribution of pulmonary thromboembolic lesions (500 procedures for 97pts)

Lesion type	A	B	C	D	E
Description	Ring-like	Web	Subtotal	Pouching	Tortuous
Number, n	248	1235	342	67	44
Bifurcation lesion, n (%)	248 (100)	1092 (88.4)	301 (88.0)	61 (91.0)	0 (0)
Distribution (upper/middle or lingular/lower)					
Right lung, n	103/7/46	215/172/367	64/42/118	6/16/24	5/3/9
Left lung, n	29/0/63	61/22/398	13/6/99	0/2/19	6/1/20
Success, n (%)	248 (100)	1219 (98.7)	296 (86.5)*	35 (52.2)†	28 (63.6)
Complication, n (%)	4 (1.6)	27 (2.2)	53 (15.5)*	4 (6.0)	19 (43.2)
Type of complication					
Balloon injury, n	3	7	5	0	0
Wire injury/perforation, n	0	12	41	4	19
Dissection of vessels, n	1	8	7	0	0

Courtesy Prof. Hiromi Matsubara

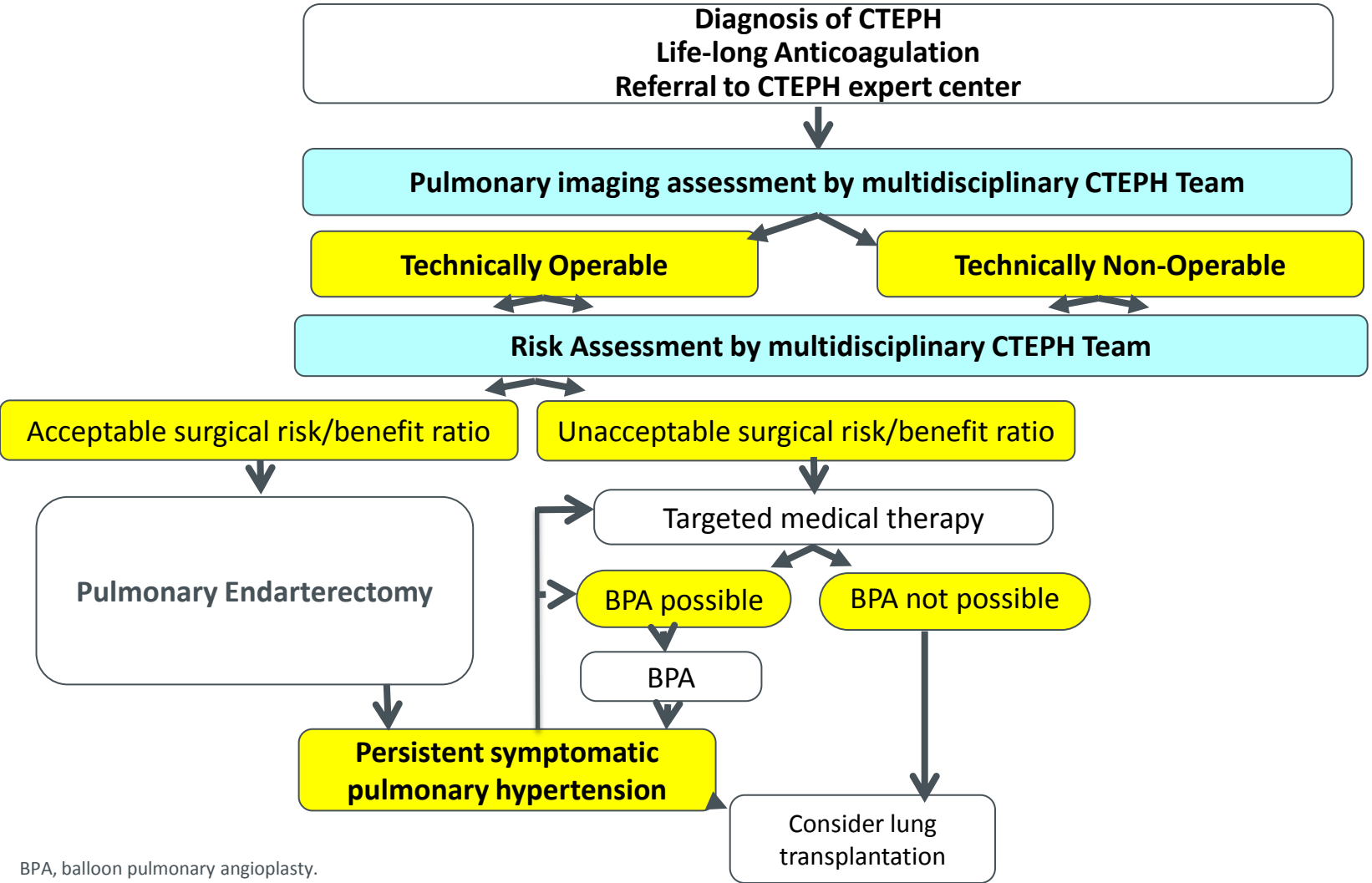
Assessing BPA risk: Lesion classification

	Ring-like stenosis	Web	Subtotal occlusion	Total occlusion
Proximal			Most complications 	
Distal		Most complications 		

Comment/Proposal 4 - BPA

- More than 500 patients have undergone BPA in Europe
- BPA is effective: mPAP decreased by 23%, PVR by 38% and CO increased by 17%
- Complication rates are between 1 and 10% of cases
- A European BPA registry is under way and much needed
- Lesion classification for establishment of a risk score matters

Tx Algorithm 2018-2020



BPA, balloon pulmonary angioplasty.

Thank you for your attention!