

Medical therapy for CTEPH: New data, new horizons

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Learning objectives

Recall the new and emerging data around patient and disease characteristics in order to select the optimal treatment strategy for each individual patient

Interpret new and emerging data for medical therapy and their impact on daily clinical practice

Assess the latest changes to best practice for the care of patients with CTEPH



Overview

CHEST Virtual Congress 2020 (18–21 October)

ERS International Congress 2020 v i r t u a l (6–9 September)

Medical therapy for CTEPH: New data, new horizons



Part 1: Assessment of patients with CTEPH



Part 2: New and emerging data on medical therapies in CTEPH



Part 3: Best practice in the management of CTEPH



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Medical therapy for CTEPH: New data, new horizons

Assessment of patients with CTEPH



Assessment of operability is subjective and challenging

Classification:
preoperative
WHO FC **II–IV**

No PVR threshold or measure of RV dysfunction that can be considered to **preclude PEA**

Advanced age per se is **not a contraindication for surgery**

Surgical accessibility of thrombi in the **main, lobar or segmental pulmonary arteries**

Pre-operative specimen level prediction: Accuracy for PTE



To determine accuracy of pre-operative specimen level prediction in CTEPH prior to PTE



50 patients with CTEPH undergoing PTE



CTEPH physician
Pre-operative prediction of PTE specimen level encompassing all data + imaging



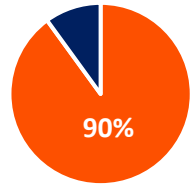
Resected PTE specimens classified using UCSD levels 1 (main) – 4 (subsegmental)

Pre-operative vs surgical findings
Predictions compared with PTE surgeon-defined surgical classification*

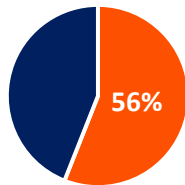
Baseline patient characteristics

Patients with history of previous TEv (%)

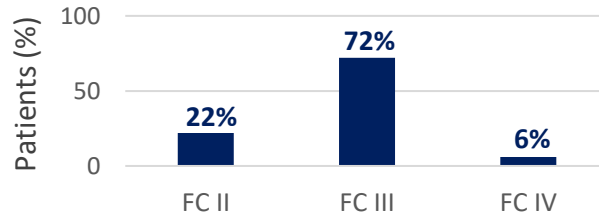
Acute PE



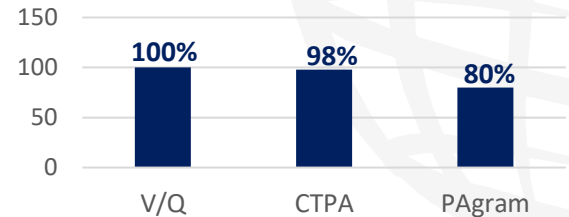
DVT



Functional status: WHO FC



Imaging assessment: modalities



*PTE surgeon blinded to pre-operative predictions.

CTEPH, chronic thromboembolic pulmonary embolism; CTPA, computed tomography pulmonary angiogram; DVT, deep vein thrombosis; FC, Functional Class; PAgram, pulmonary angiogram; PE, pulmonary embolism; PTE, pulmonary thromboendarterectomy; TEv, thromboembolic event; UCSD, University of California, San Diego; V/Q, ventilation-perfusion scan; WHO FC, World Health Organization functional class.

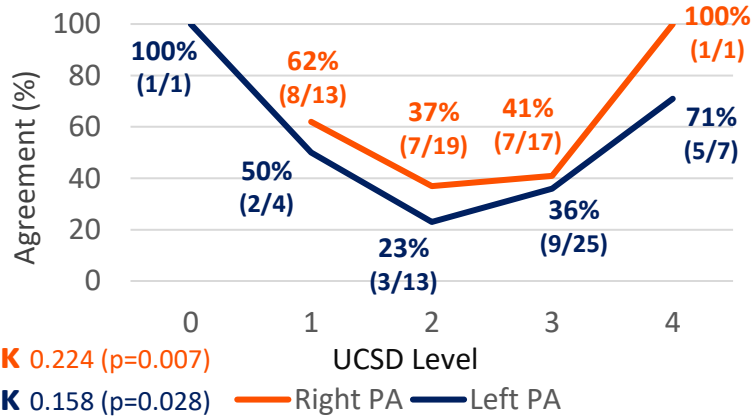
Pirompanich P, et al. Presented at Virtual ERS International Congress, 6–9 September 2020. EPoster #1538.

Pre-operative specimen level prediction: Accuracy for PTE

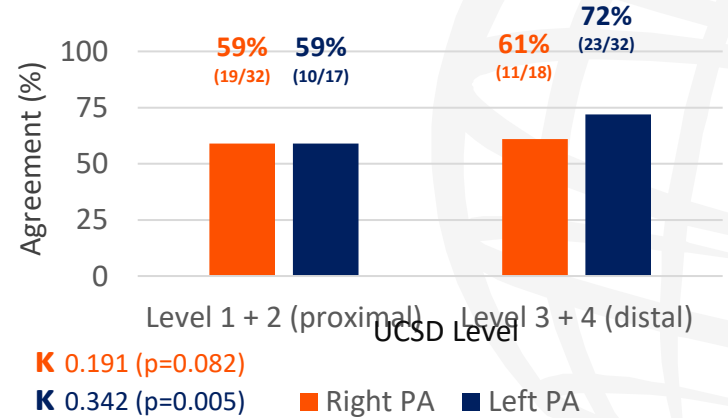


Surgical specimen level cannot be reliably predicted prior to PTE, even with CTEPH diagnostic expertise

Pre- and post-operative concordance: specimen level based on disease level and laterality



Pre- and post-operative concordance: disease level after grouping levels as 'proximal' or 'distal'



Preoperative prediction of surgical specimen level found at PTE has only slight to fair accuracy

CTPA: Predictive value for PEA surgical accessibility



To assess predictive value of radiological classification of disease level by CTPA using surgical classification as a standard of reference



43 patients
with CTEPH undergoing
pre-operative CTPA



Three chest radiologists*
independently assess CTPA



Disease level classified based
on most proximal thrombus



Radiological
and surgical
classification
scoring criteria

LEVEL 1 Main PA

LEVEL 2 Lobar PA

LEVEL 2a Lobar PA

LEVEL 2b Lower lobe basal trunk

LEVEL 3 Segmental PA

LEVEL 4 Subsegmental PA



Proximal disease
Levels 1–2a



Distal disease
Levels 2b–4

*blinded to surgical results.

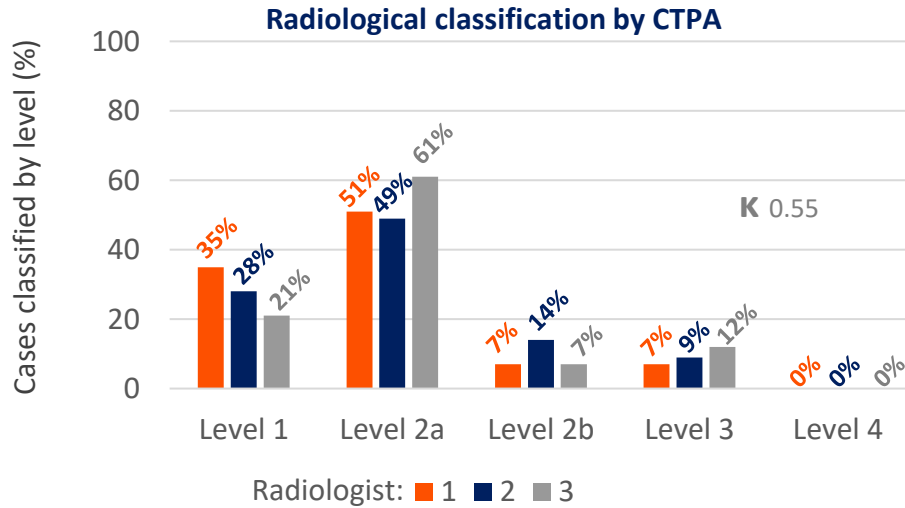
CTEPH, chronic thromboembolic pulmonary embolism; CTPA, computed tomography pulmonary angiogram; PA, pulmonary artery; PEA, pulmonary endarterectomy; PTE, pulmonary thromboendarterectomy.

Frauenfelder T, et al. Presented at Virtual ERS International Congress, 6–9 September 2020. EPoster #1548.

CTPA: Predictive value for PEA surgical accessibility



CTPA highly sensitive to predict 'proximal disease' to inform surgical accessibility in patients with CTEPH



Surgical (Jamieson) vs radiological (CTPA) classification (no. cases)

		-----Right lung-----				-----Left lung-----				
		CTPA				CTPA				
		1	2a	2b	3	1	2a	2b	3	
Jamieson	1	4	6	0	0	1	2	3	1	0
	2	1	9	2	1	2 <td>1</td> <td>8</td> <td>6</td> <td>0</td>	1	8	6	0
	3	0	6	0	4	3 <td>0</td> <td>5</td> <td>0</td> <td>7</td>	0	5	0	7
	4	0	0	0	1	4 <td>0</td> <td>0</td> <td>0</td> <td>1</td>	0	0	0	1



Radiological prediction of surgeon-defined proximal CTEPH was sensitive (92–100%) with a specificity of 24–53%

This imaging-based classification may guide future surgical decision-making surrounding operability of patients with CTEPH

κ, Kappa interobserver agreement value; CTEPH, chronic thromboembolic pulmonary embolism; CTPA, computed tomography pulmonary angiogram; PEA, pulmonary endarterectomy; Frauenfelder T, et al. Presented at Virtual ERS International Congress, 6–9 September 2020. EPoster #1548.



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Medical therapy for CTEPH: new data, new horizons

**New and emerging data on
medical therapies in CTEPH**



Medical therapies in operable and residual CTEPH

Trial	Study drug	Duration (weeks)	Patients (n)	NYHA FC	6MWD (m)	PVR baseline dyn·s·cm ⁻⁵
BENEFIT ¹	Bosentan	16	157	II–IV	342±84	783
CHEST-1 ²	Riociguat	16	261	II–IV	347±80	787±422

Data are presented as n or mean±SD, unless otherwise stated. Both trials had an adjudication process for operability.

6MWD, six-minute walking distance; CTEPH, chronic thromboembolic pulmonary hypertension; NYHA FC, New York Heart Association Functional Class; 6MWD, 6-min walk distance; PVR, pulmonary vascular resistance.

1. Jais X, et al. *J Am Coll Cardiol*. 2008;52:212–2134; 2. Ghofrani HA, et al. *N Engl J Med*. 2013;369:31–329. Table adapted from: Kim NH, et al. *Eur Respir J*. 2019;53:1801915.

Dual ERA + PDE5i therapy pre-PEA in high PVR setting

 Evaluate haemodynamic effects of dual ERA + PDE5i therapy pre-PEA in patients with operable CTEPH and high pre-op PVR

Observational retrospective analysis

 2012–19



21 consecutive patients



Aged 58 (± 16) years

Male (52%)



Most common regimen:

bosentan + riociguat

(n=10)

Inclusion criteria for analysis:

- Operable CTEPH
- PVR >800 dyn.s.cm⁻⁵
- Received dual ERA + PDE5i or riociguat prior to PEA

Pre-PEA evaluation

Improved

- 6MWD: 337 \pm 119 to 380 \pm 98 m (p<0.01)

Decreased

- mPAP: 56 \pm 9 to 47 \pm 9 mmHg (p<0.0001)
- PVR: 1,102 \pm 280 to 622 \pm 171 dyn.s.cm⁻⁵ (p<0.00001)

Post-PEA assessment (n=15)

76% decrease in PVR from baseline:
1,085 \pm 289 to 260 \pm 111 dyn.s.cm⁻⁵ (p<0.05)

6MWD, 6-minute walk distance; CTEPH, chronic thromboembolic hypertension; ERA, endothelin receptor antagonist; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase-5 inhibitor; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; pre-op, PVR, pulmonary vascular resistance.

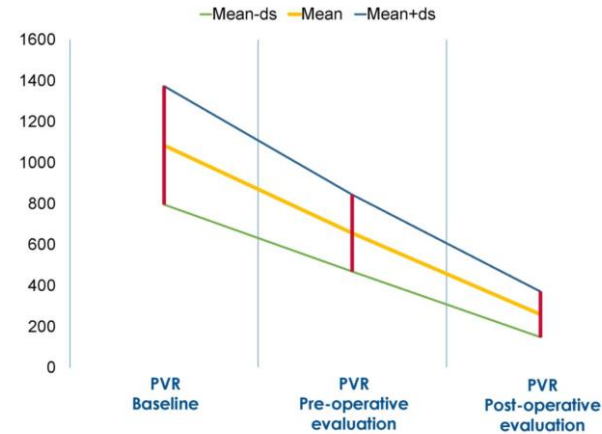
Trigui Y, et al. Presented at Virtual ERS International Congress, 6–9 September 2020. EPoster #1537.

Dual ERA + PDE5i therapy pre-PEA in high PVR setting

Functional and haemodynamic assessments

	Baseline	Pre-op	Post-op	p-value
NYHA FC, n I/II/III/IV	0/1/11/3	2/5/6/2	5/9/1/0	0.013
6MWD, m (n)	321 ±110	376 ±95	411 ±94	0.004
RAP, mmHg	10 ±4	8 ±3	7 ±2	0.1
mPAP, mmHg	56 ±9	49 ±8	28 ±11	0.000055
PAWP, mmHg	8 ±2	10 ±2	11 ±4	0.13
CO ₂ , L/min	3.7 ±0.7	4.8 ±1	5.3 ±1.5	0.00003
CI, L/min/m ²	2.08 ± 0.32	2.74 ±0.45	2.97 ± 0.73	0.000048
PVR, dyn.s.cm ⁻⁵	1,085 ±289	657 ±187	260 ±111	0.00001
SvO ₂ , %	58 ±7	64 ±5	66 ±6	<0.05

PVR evaluation



PVR are expressed in dyn.s.cm⁻⁵. p-value<0.05.



Dual ERA + PDE5i therapy pre-PEA improves pulmonary haemodynamics and exercise capacity in patients with operable CTEPH and high pre-op PVR

6MWD, 6-minute walk distance; CI, cardiac index; CO₂, carbon dioxide; CTEPH, chronic thromboembolic hypertension; ERA, endothelin receptor antagonist; mPAP, mean pulmonary arterial pressure; NYHA FC, New York Heart Association functional class; PAWP, pulmonary arterial wedge pressure; PDE5i, phosphodiesterase-5 inhibitor; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; RAP, right arterial pressure; SvO₂, mixed venous oxygen saturation.

Trigui Y, et al. Presented at Virtual ERS International Congress, 6–9 September 2020. EPoster #1537.

Sequential multimodal therapy pre-PEA in high-risk CTEPH



Assess feasibility of sequential multimodal therapy in patients with operable lesions on one side and contralateral surgically inaccessible lesions and high PVR

Observational retrospective analysis



Feb 2017–June 2019



13 patients



Aged 69 (± 9.4) years

Male (53%)

Cohort clinical profile

- Mixed anatomical lesions
- PVR >800 dyn.s.cm⁻⁵
- BPA on inoperable side; PEA on contralateral lung



6 completed study

Still awaiting PEA (n=3)

Study drop-out (n=4)

Refused surgery (n=2)
Cancer diagnosis (n=2)

4 upfront dual therapy



BOS + RIO
or
BOS + TAD

2 monotherapy



RIO
5 months pre-BPA

BOS, bosentan; BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RIO, riociguat; TAD, tadalafil.

Jevnikar M, et al. Presented at Virtual ERS International Congress, 6–9 September 2020. EPoster #1539.

Sequential multimodal therapy pre-PEA in high-risk CTEPH

 **6**

achieved improvement in NYHA FC and 6MWD in all completing multimodal therapy

Baseline vs post-op assessment



NYHA FC: 3–4 vs FC 1–2

6MWD: 321±34 m vs 398±24 m



Safety

0 deaths
severe peri-op complications

Haemodynamic assessment (n=6)

	Baseline	Post-PAH therapy	Post-BPA	Post-PEA	p-value
mPAP, mmHg	54±7 [37–64]	45.5±8 [30–60]	38.8±11 [29–58]	28±8 [19–41]	0.031
PVR, dyn.s.cm ⁻⁵	960±232 [657–1,510]	729±181 [301–1,023]	397±76 [291–508]	419 ±260 [218–988]	0.031
CI, L/min/m ²	1.93±0.4 [1.53–3.04]	2.91±1.05 [1.98–4.81]	3.4±0.4 [2.6–4.72]	2.69±0.5 [1.62–3.45]	0.016

Sequential multimodal therapy combining medical therapy, BPA and PEA was safe and effective in 6 patients with CTEPH with mixed anatomical lesions and severe PH

6MWD, 6-minute walk distance; BPA, balloon pulmonary angioplasty; CI, confidence interval; CTEPH, chronic thromboembolic hypertension; mPAP, mean pulmonary arterial pressure; NYHA FC, New York Heart Association Functional Class; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

Jevnikar M, et al. Presented at Virtual ERS International Congress, 6–9 September 2020. EPoster #1539.



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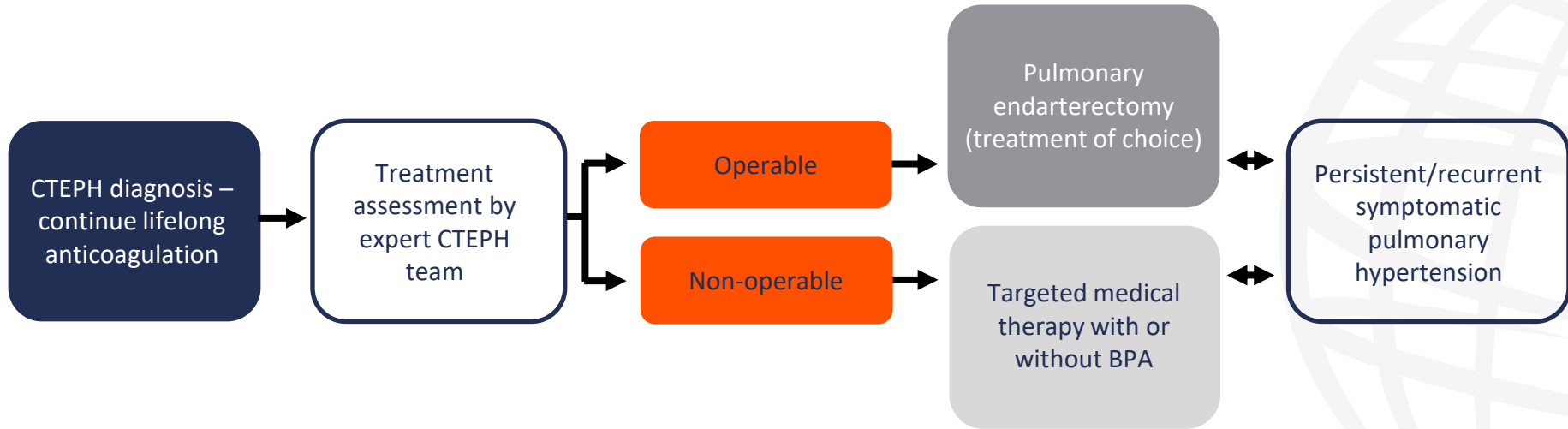
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Medical therapy for CTEPH: New data, new horizons

Best practice in the management of CTEPH



Can we establish a treatment algorithm?



Multidisciplinary: pulmonary endarterectomy surgeon, pulmonary hypertension expert, BPA interventionalist and radiologist.

Treatment assessment may differ depending on the level of expertise.

BPA without medical therapy can be considered in selected cases.

BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension.

Kim NH, et al. *Eur Respir J*. 2019;53:1801915.

Anticoagulant therapy: Guideline adherence (PAH; CTEPH)



Assess adherence to guidelines for anticoagulant therapy in PAH and CTEPH

451 patients



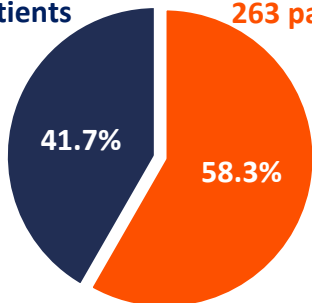
aged 59.7±15 years



57% female

PAH
188 patients

CTEPH
263 patients



Observational study
Single reference centre



Data collection:

- Demographics
- Diagnosis (specific condition)
 - Current treatments
- Indications/contraindications
- for anticoagulation therapy



Nov 2018–April 2019

CTEPH

only
(n=263)

Guidelines

263

100% receiving
anticoagulant
therapy



VKA:
n=218 (83%)



DOAC:
n=45 (17%)

Justification for switch
from VKA to DOAC
n=11

No drug
interaction
n=24

96.2% satisfactory adherence to anticoagulation
guidelines for patients with CTEPH

BPA for CTEPH: The Viennese experience



Assess BPA effectiveness for inoperable CTEPH or persistent PH after PEA in an Austrian population



April 2014–Oct 2019

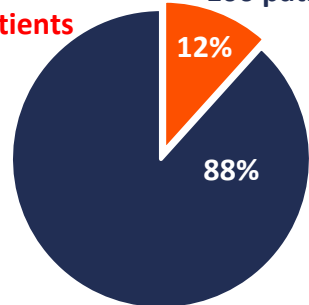
120 patients



Underwent 690
BPA procedures
until Oct 2019

Persistent PH
post-PEA
14 patients

Inoperable CTEPH
106 patients



BPA significantly improved functional and haemodynamic parameters

 **45**
completed BPA
6.8±3.4 procedures

6 persistent PH post-PEA

39 – inoperable CTEPH



Δ mPAP similar

p=0.845

6 persistent PH post-PEA

-33 ± 40%

39 inoperable CTEPH

-29 ± 18%



Safety



Lung injury
in 5.1% of
sessions*

*0.4% severe

Δ Baseline 6 months post last BPA

Significantly improved:

6MWD: 127 (45, 184)

WHO FC: -1 (-2,-1)

Nt-proBNP: -222 (-1,037, -6)



Significantly decreased:

mPAP: -30 ± 21%; p<0.001

PVR: -26 ± 24%; p<0.001



BPA improves symptoms and haemodynamics in patients with CTEPH
BPA is equally effective in persistent PH and inoperable CTEPH