

University of Pavia - School of Medicine
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Cardiac Surgery Unit - Chronic Thromboembolic Pulmonary Hypertension Centre
Pavia, Italy



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XI edizione PLACE–Platform of Laboratories for Advances in Cardiac Experience

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IPERTENSIONE POLMONARE: TRA INCERTEZZE E DUBBI

Ipertensione Polmonare Cronica Tromboembolica: terapia multimodale personalizzata per ogni singolo paziente



GENERAL CONSIDERATIONS

CTEPH is a two-cause disease

- Mechanical obstruction → PEA and BPA are the therapeutic options
- Microvascular disease (Eisenmenger-like syndrome) → specific medical therapy

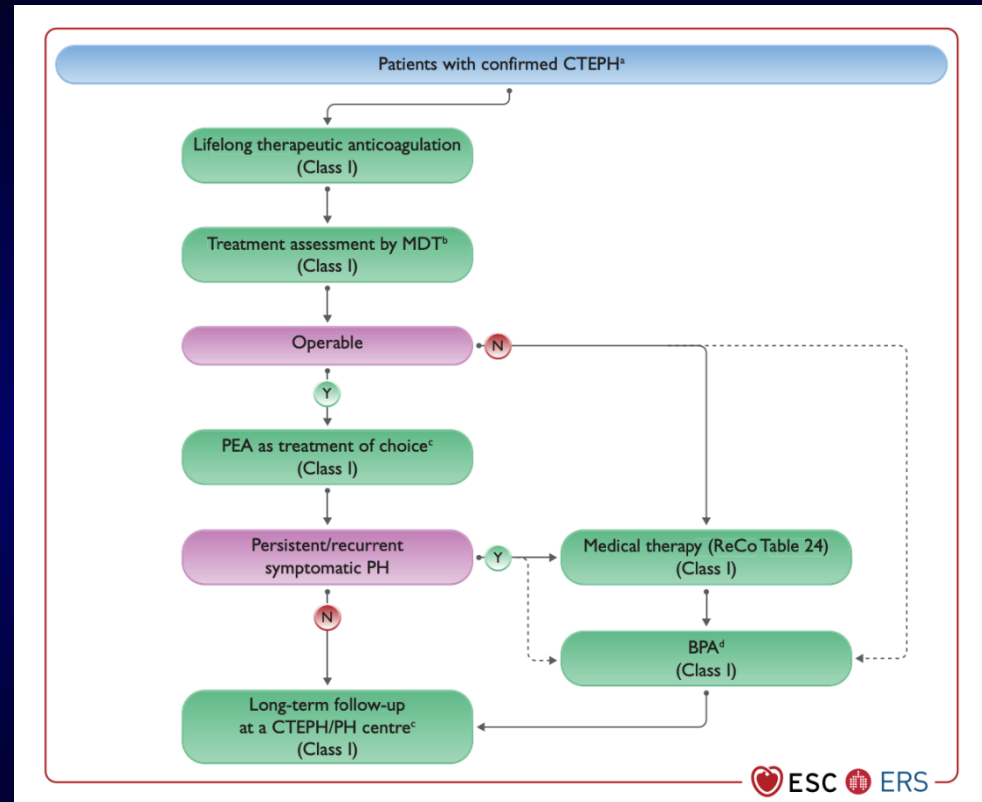
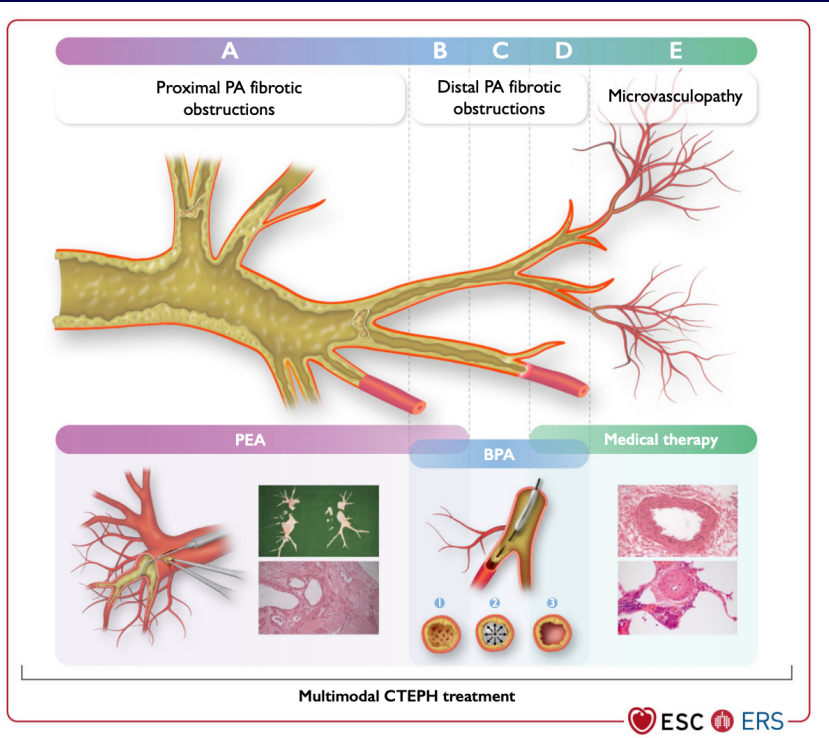


TREATMENT FOLLOWING GUIDELINES

MULTIMODAL APPROACH

10.2. Therapy

The CTEPH treatment algorithm includes a multimodal approach of combinations of pulmonary endarterectomy (PEA), BPA, and medical therapies to target the mixed anatomical lesions: proximal, distal, and microvasculopathy, respectively ([Figures 14 and 15](#)).



TREATMENT FOLLOWING GUIDELINES

MULTIMODAL APPROACH

10.2.1. Surgical treatment

Surgical PEA is the treatment of choice for patients with accessible PA lesions.¹⁰² As surgery may normalize pulmonary haemodynamics (65% decrease in PVR)⁷⁶⁶ and functional capacity, an expert multidisciplinary team including an experienced PEA surgeon (on-site or closely collaborating) is mandatory for evaluating operability and deciding final treatment.¹⁰²

PEA is recommended as the treatment of choice for patients with CTEPH and fibrotic obstructions within pulmonary arteries accessible by surgery^{54,102}

I

B



TREATMENT FOLLOWING GUIDELINES

MULTIMODAL APPROACH

10.2.3. Interventional treatment

Balloon pulmonary angioplasty (*Figure 15*) has become an established treatment for selected patients with inoperable CTEPH or persistent/recurrent PH after PEA, improving haemodynamics (PVR decrease 49–66%), right heart function, and exercise capacity.^{781–794} Long-term outcomes are promising, but evidence is still scarce.⁷⁹⁵

BPA is recommended in patients who are technically inoperable or have residual PH after PEA and distal obstructions amenable to

BPA^{54,102,783,784,789,793,798,811}

I

B



TREATMENT FOLLOWING GUIDELINES

MULTIMODAL APPROACH

10.2.2. Medical therapy

To manage the microvascular component of CTEPH ([Figure 15](#)), medical therapies have been used off-label based on uncontrolled studies and/or regional approvals.

Riociguat is recommended for symptomatic patients with inoperable CTEPH or persistent/recurrent PH after PEA⁷⁷⁵

I

B

persistent/recurrent PH after PEA.⁷⁷⁵ Riociguat, after 16 weeks of therapy, improved

Treprostinil s.c. may be considered in patients in WHO-FC III–IV who have inoperable CTEPH or persistent/recurrent PH after PEA⁷⁷⁶

IIb

B

Conclusions: MACiTEPH was discontinued for futility, as no treatment effect on 6MWD (primary endpoint) was observed. Despite the higher discontinuation rate in the macitentan 75 mg group, no unexpected safety signals were observed in CTEPH patients.

placebo at 16 and 24 weeks, respectively. A phase 3 RCT is ongoing to evaluate the safety and efficacy of macitentan 75 mg in inoperable or persistent/recurrent CTEPH (NCT04271475).

MACiTEPH



TREATMENT FOLLOWING GUIDELINES

MULTIMODAL APPROACH

Other medical therapies—PDE5is (e.g. sildenafil) and ERAs (e.g. bosentan)—have been used off-label, as their efficacy in inoperable CTEPH has not been proven by RCTs or registry data.^{769,778,779} However, oral combination therapy, including PDE5is and ERAs, is common practice in patients with CTEPH with severe haemodynamic compromise.⁷⁸⁰

Off-label use of drugs approved for PAH may be considered in symptomatic patients who have inoperable CTEPH^{55,777–779,801}

IIb

B

In patients with inoperable CTEPH, a combination of sGC stimulator/PDE5i, ERA,⁷⁷⁷ or parenteral prostacyclin analogues⁷⁷⁶ may be considered

IIb

C

AGENZIA ITALIANA DEL FARMACO

COMMISSIONE CONSULTIVA TECNICO SCIENTIFICA

DETERMINAZIONE 12 febbraio 2013

Inserimento del medicinale **bosentan** nell'elenco dei medicinali erogabili a totale carico del Servizio Sanitario Nazionale ai sensi della legge 23 dicembre 1996, n. 648, per il *trattamento dell'ipertensione Polmonare Cronica Tromboembolica (IPCTE) inoperabile mediante intervento chirurgico di Endoarteriectomia Polmonare (EAP), IPCTE persistente dopo intervento chirurgico di EAP inefficace o recidiva di IPCTE dopo intervento chirurgico di EAP efficace ma non ripetibile.*



EVALUATION PROCESS

DIFFERENT STEPS

- PEA's assessment
- Specific medical therapy
- BPA's assessment

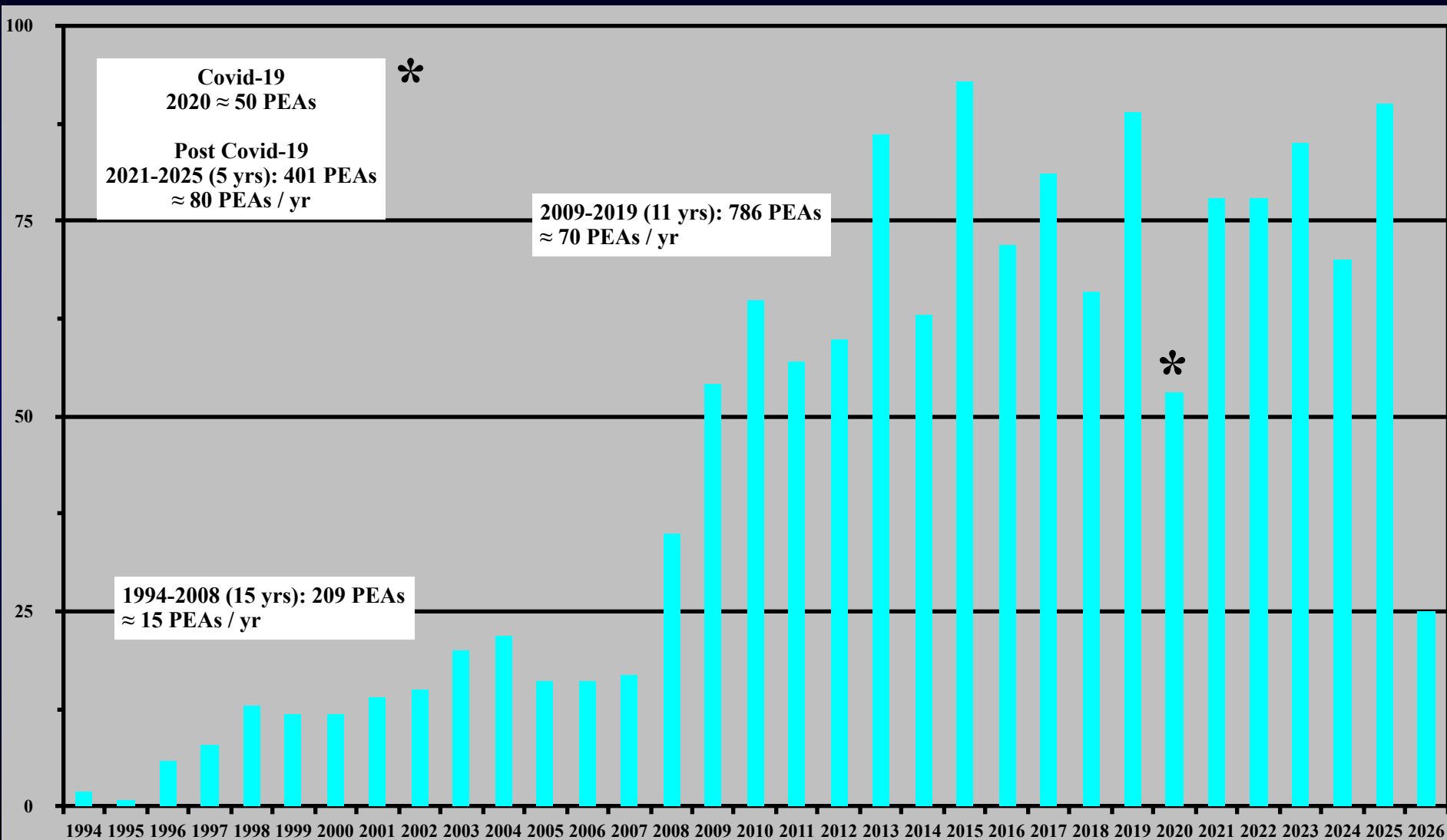


OUR PROGRAM

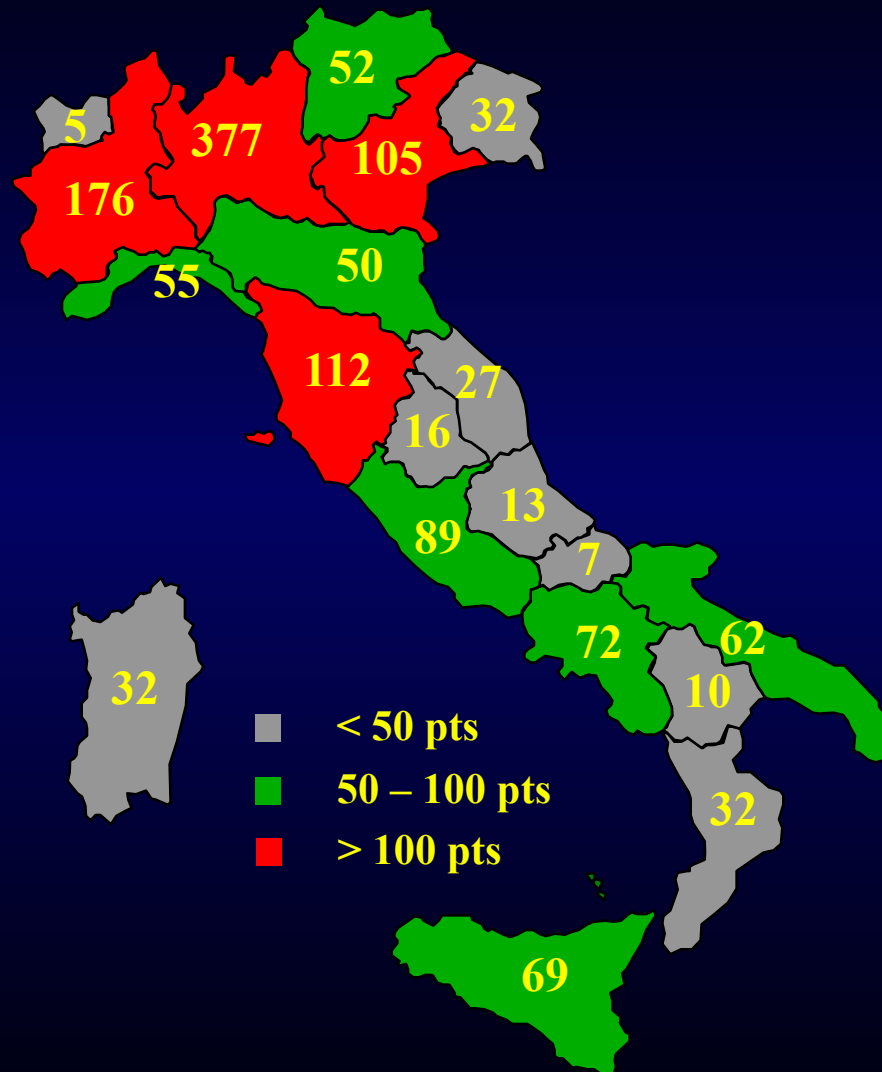
- National and international referral program
- Begin: April 1994
- April 2026: 1474 PEAs performed

AMOUNT OF PATIENTS

1474 PEAs



PATIENTS' REFERRAL

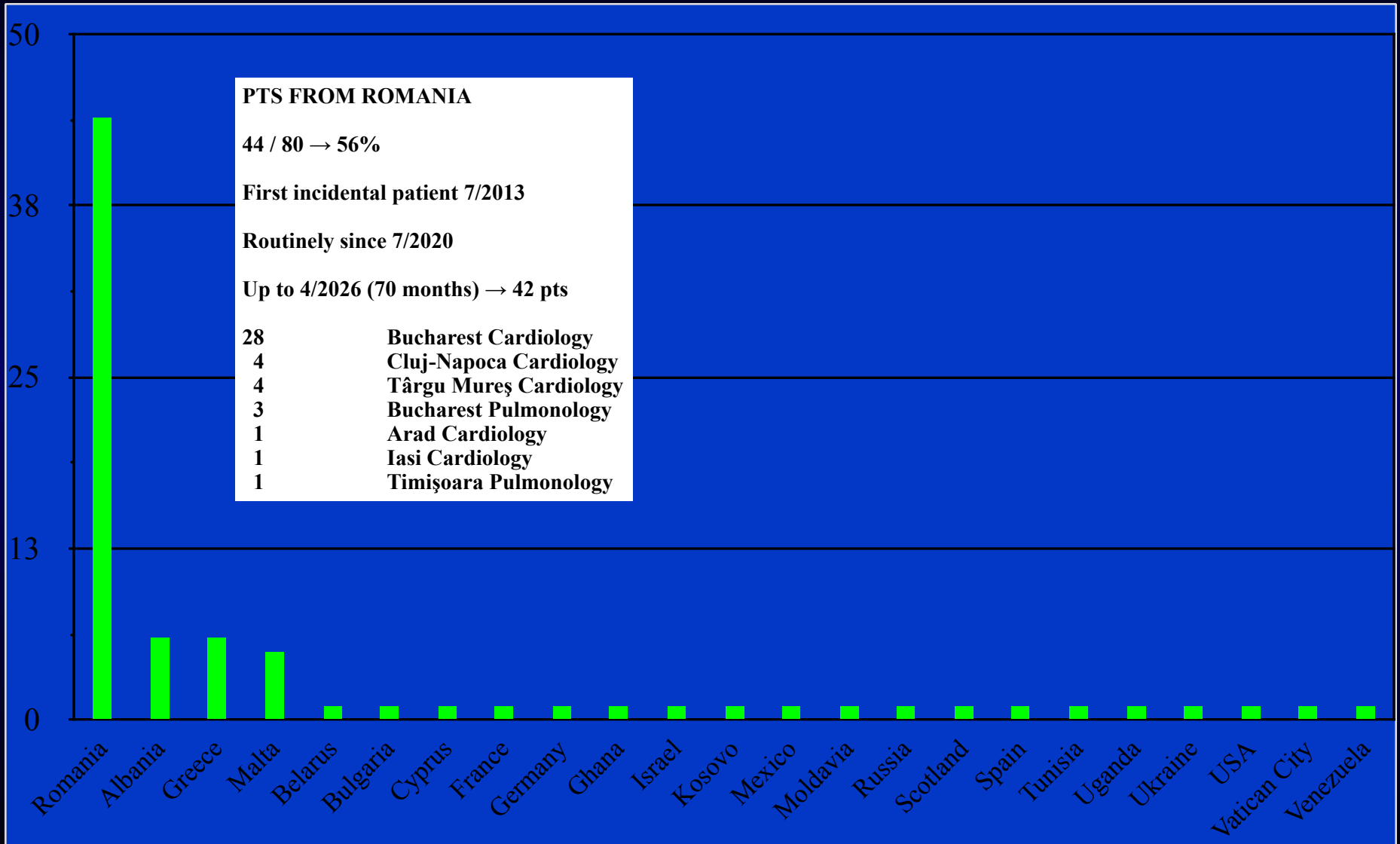


FROM 4/1994 TO 4/2026
1394 PEAs

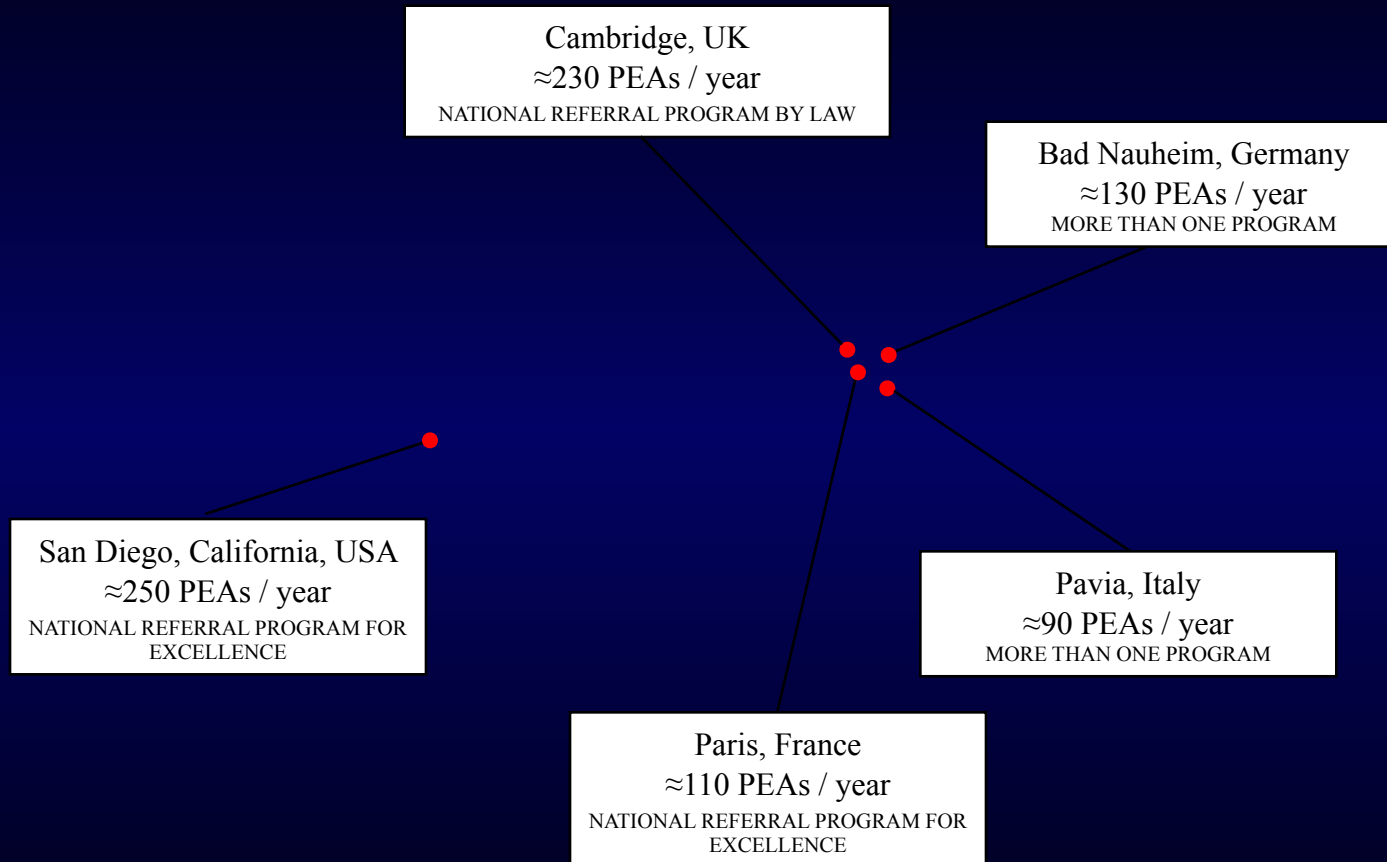
LOMBARDY vs. OTHERS
27% vs. 73%

OUTSIDE ITALY PATIENTS' REFERRAL

FROM 10/2001 TO 4/2026 - 80 PEAs



MAIN WORLD PEA CENTERS



GENERAL CONSIDERATIONS

Better diagnosis → more evaluated patients at a earlier stage

Better treatment → more operated patients with better results



INDICATIONS FOR SURGERY

NYHA FUNCTIONAL CLASS

ACQUIRED CARDIOVASCULAR DISEASE

(J Thorac Cardiovasc Surg 2011;141:702-10)

Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry

Eckhard Mayer, MD,^a David Jenkins, FRCS,^b Jaroslav J. Jaap Klok, MD,^c Bart Meyns, MD,^f Lars Bo Ilkjaer, MD,^g Irene Lang, MD,^h Joanna Pepke-Zaba, MD,^b Gerald Sir

Study Design

This prospective registry was designed to include newly diagnosed (≤ 6 months) consecutive patients with CTEPH in participating centers in Europe and Canada, from February 2007 to January 2009. The registry proto-

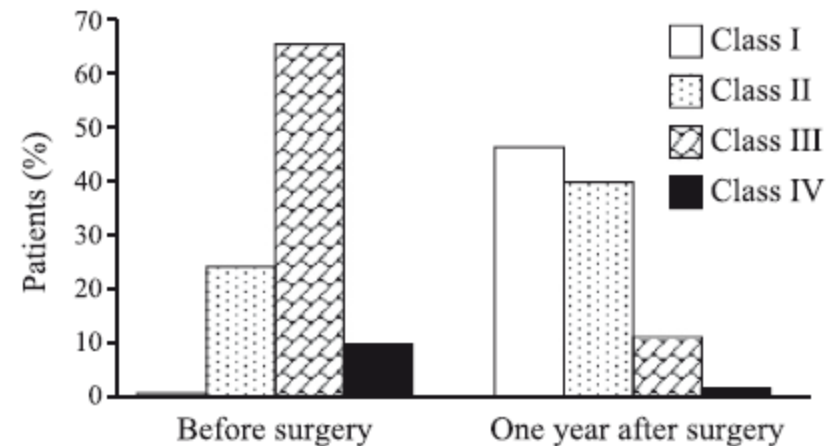


FIGURE 1. NYHA functional class before surgery and within 1 year after surgery (n = 221).

NYHA FUNCTIONAL CLASS

	INTERNATIONAL REGISTRY 2007-2008	PAVIA 2007-2008	PAVIA 2017-2018
II	25%	5%	19%
III	65%	50%	56%
IV	10%	45%	25%



NYHA FUNCTIONAL CLASS

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; Soren Mellekjaer, MD; Jerzy Lewczuk, MD; Iveta Simkova, MD; Joan A. Barbera, MD; Marc de Perrot, MD; Marius M. Hoeper, MD; Sean Gaine, MD; Rudolf Speich, MD; Miguel A. Gomez-Sanchez, MD; Gabor Kovacs, MD; Xavier Jais, MD; David Ambroz, MD; Carmen Treacy, BSc; Marco Morsolini, MD; David Jenkins, MD; Jaroslav Lindner MD; Philippe Dartevelle, MD; Eckhard Mayer, MD; Gerald Simonneau, MD

Circulation. 2016;133:859-871



NYHA FUNCTIONAL CLASS

NYHA class IV is one of the most important predictor of death increasing mortality by 4 to 5 times

Table 4. Independent Correlates of Mortality for Operated and Not-Operated Patients						
Covariate	Operated (n=346)			Not-Operated (n=219)		
	HR	95% CI	P Value	HR	95% CI	P Value
NYHA class III vs I-II				2.43	1.00–5.89	0.0489
NYHA class IV vs I-II	4.16	1.49–11.62	0.0065	4.76	1.76–12.88	0.0021

Circulation. 2016;133:859-871



SPECIFIC THERAPY BEFORE PEA?

ACCORDING TO GUIDELINES

10.2.4. Multimodal treatment

Multimodal therapy including surgery, medication, and intervention is offered to selected patients with CTEPH (*Figure 15*).¹⁰²

Using medical therapy in patients with high pre-operative PVR to improve pulmonary haemodynamics before PEA is common practice but still controversial, as it is felt to delay timely surgical referral and therefore definitive treatment.^{801–803}



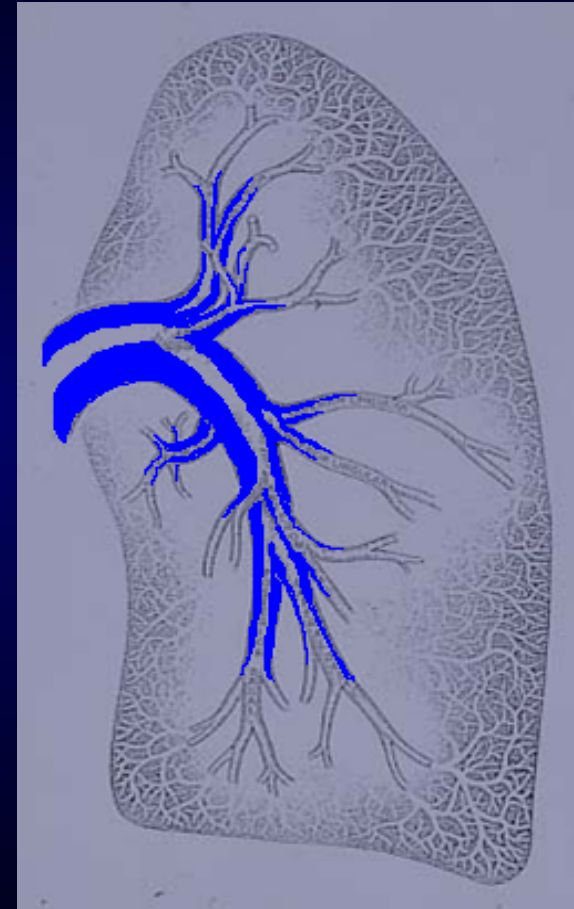
GENERAL CONSIDERATIONS

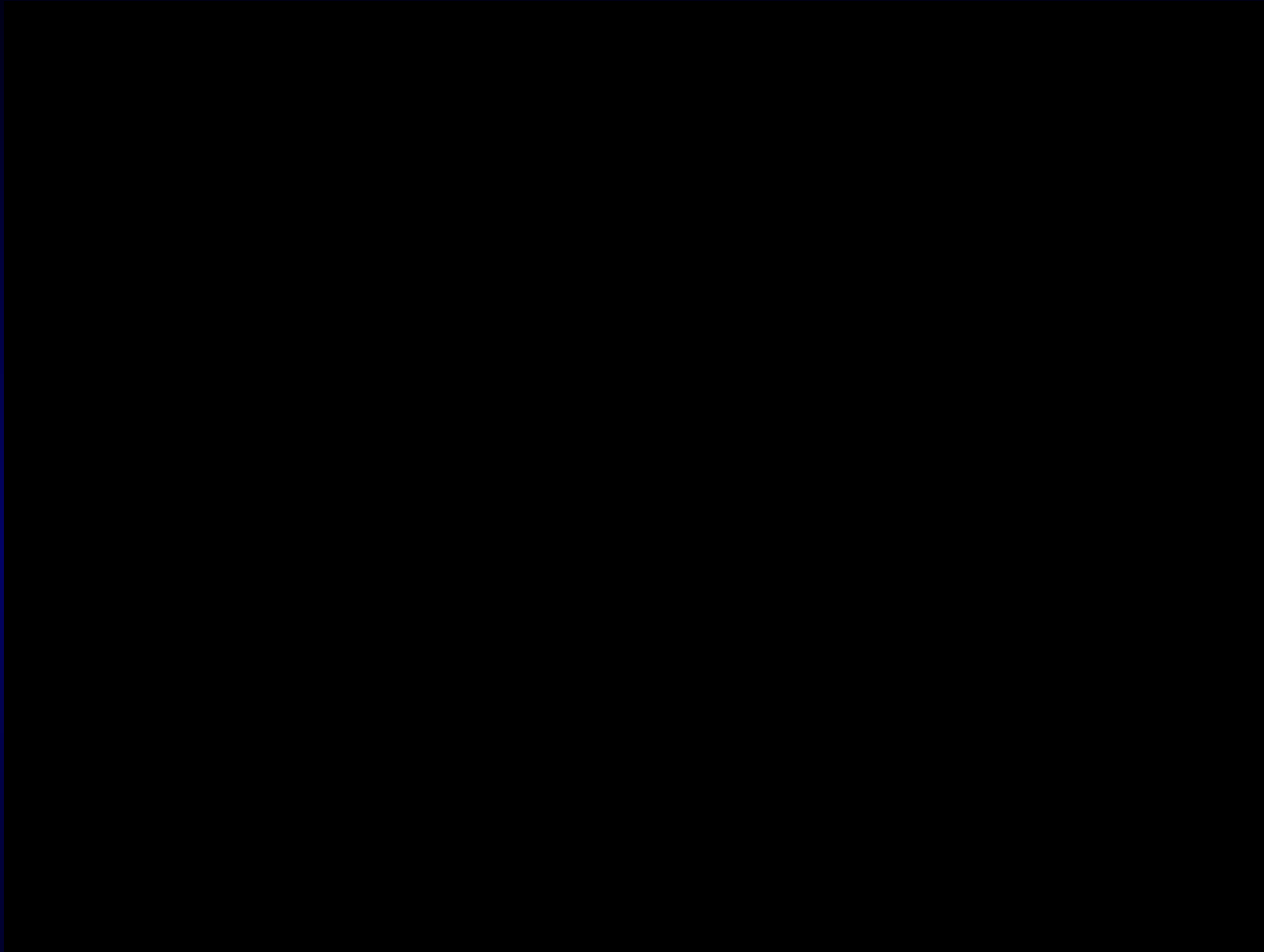
Better diagnosis → more evaluated patients at a earlier stage

Better treatment → more operated patients with better results



PROXIMAL LESIONS





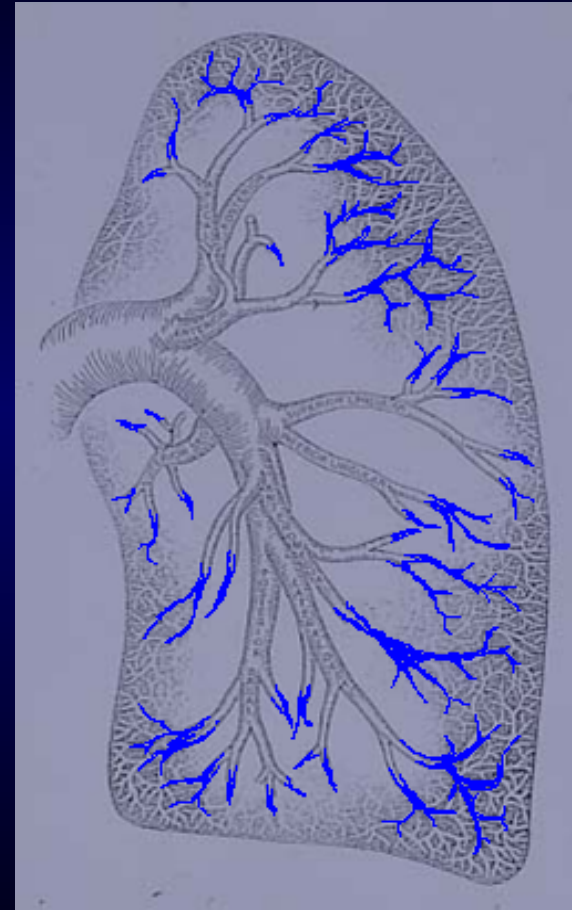
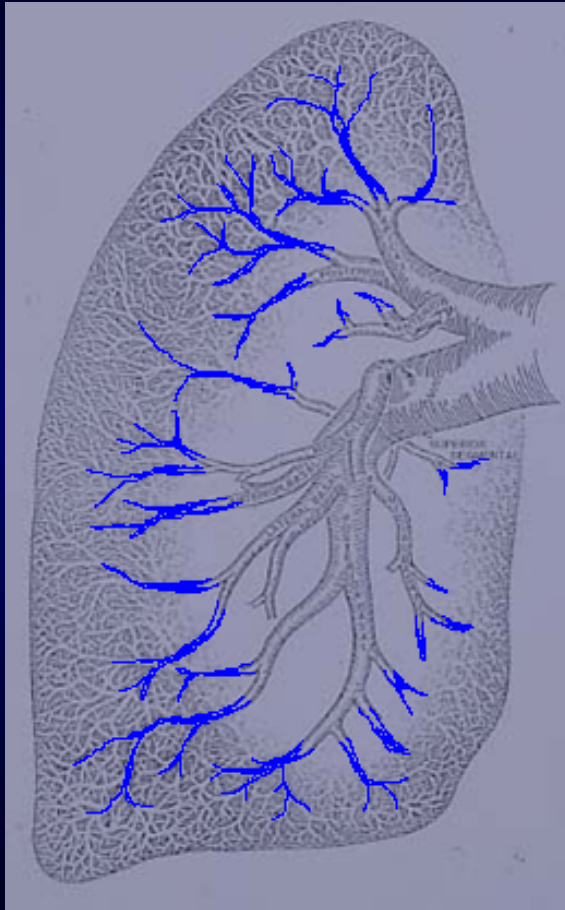
PROXIMAL SURGICAL SPECIMENS

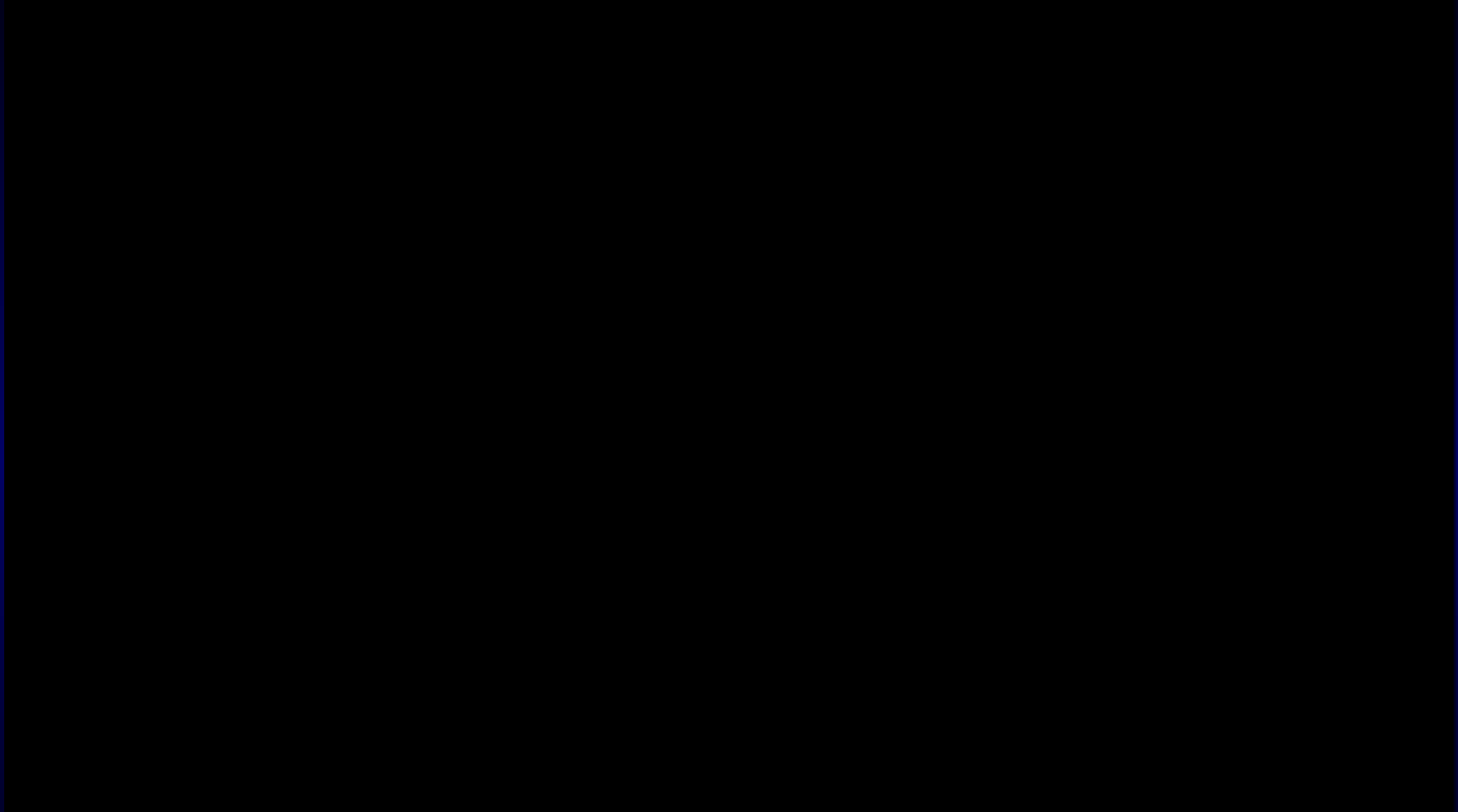
mPAP	43	→	20	(-53%)
CO	3.3	→	6.9	(+109%)
PVR	994	→	220	(-78%)



mPAP	50	→	25	(-50%)
CO	2.6	→	4.4	(+69%)
PVR	1385	→	364	(-74%)

DISTAL LESIONS





CORRECT ARTERIAL DISSECTION PLANE

Reverse Ariadne's thread

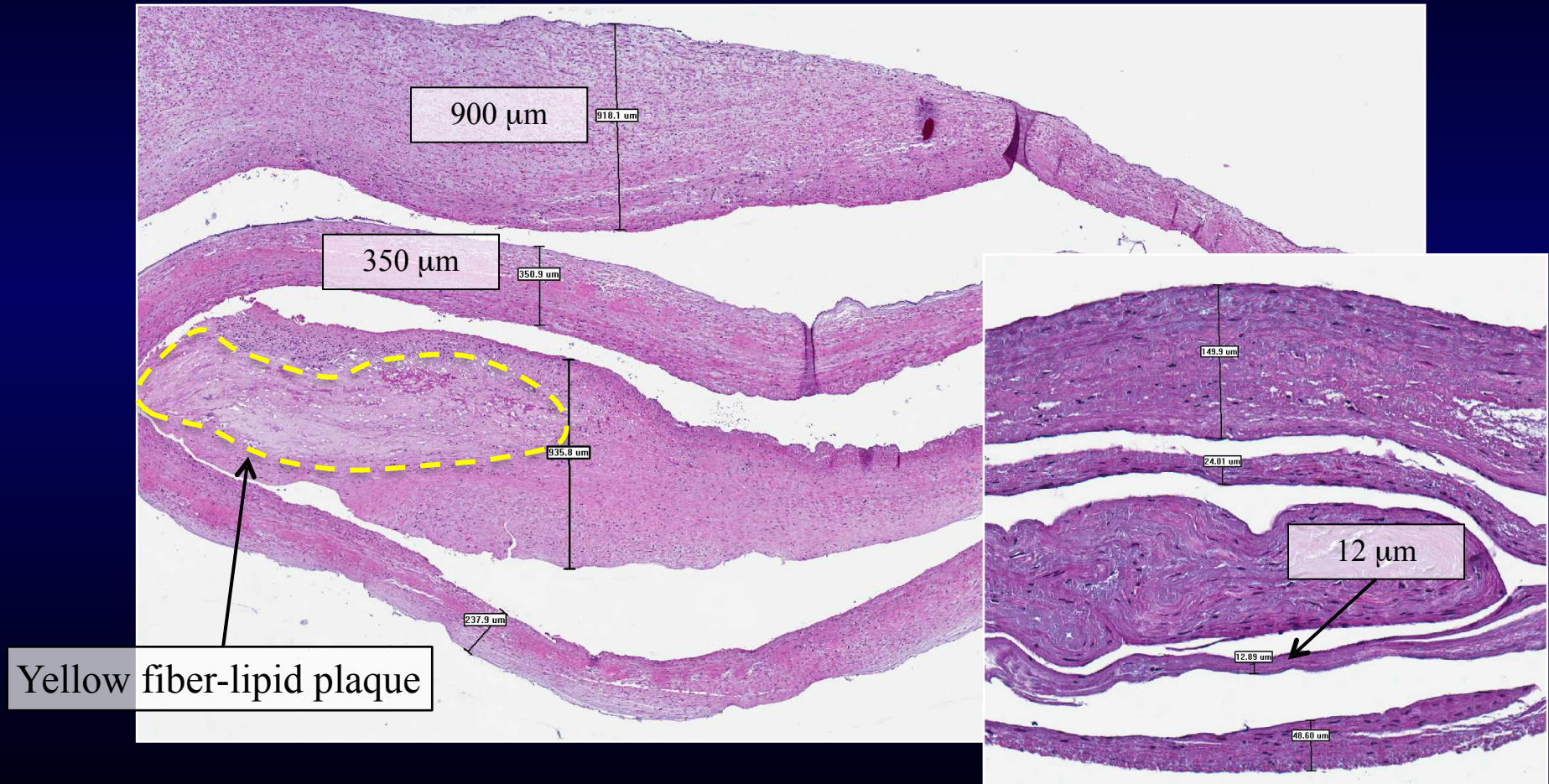


SURGICAL SPECIMENS



TRICKS AND TIPS

Proximal dissection for the clearance of distal obstructions



TRICKS AND TIPS

Proximal dissection for the clearance of distal obstructions



Sample



DISTAL LESIONS

D'Armini et al

Acquired Cardiovascular Disease

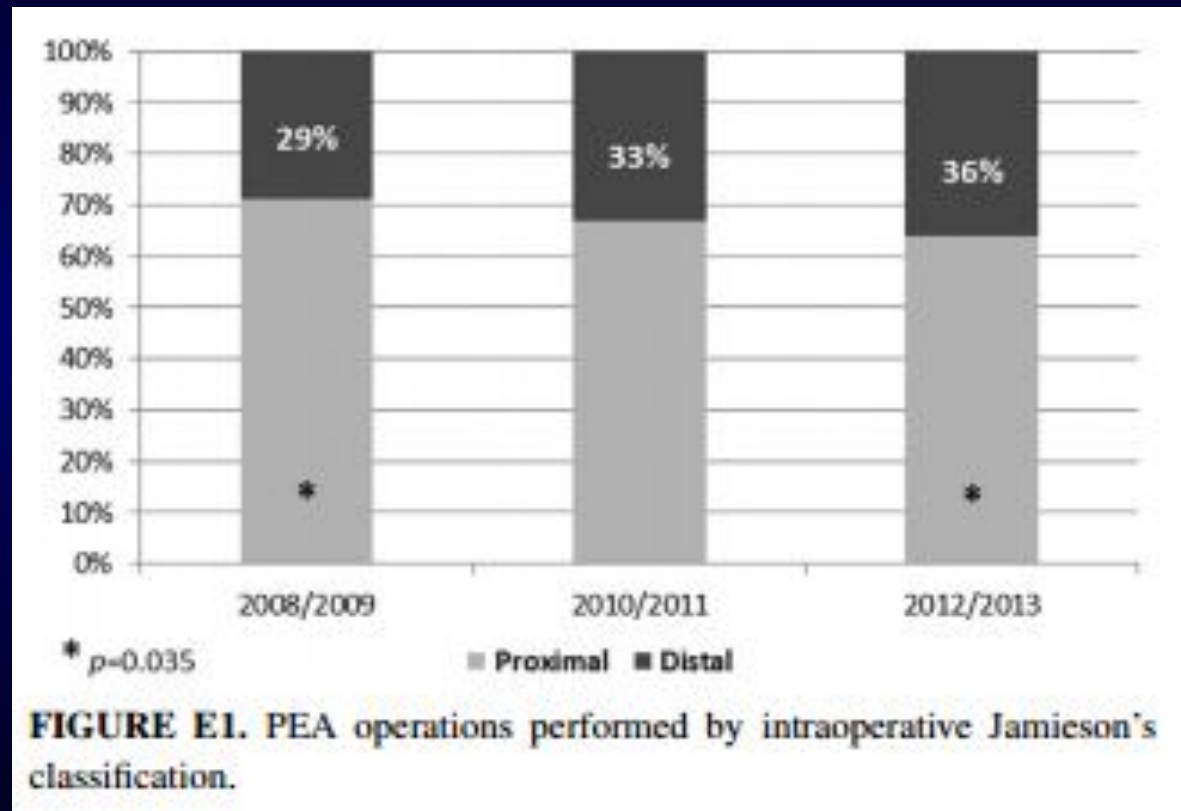
Pulmonary endarterectomy for distal chronic thromboembolic pulmonary hypertension

Andrea M. D'Armini, MD,^{a,b} Marco Morsolini, MD, PhD,^a Gabriella Mattiucci, MD,^{a,b}
Valentina Grazioli, MD,^{a,b} Maurizio Pin, MD,^b Adele Valentini, MD,^c Giuseppe Silvaggio, MD,^b
Catherine Klersy, MD, MSc,^d and Roberto Dore, MD^c

(J Thorac Cardiovasc Surg 2014;148:1005-12)



DISTAL LESIONS



DISTAL LESIONS

TABLE 3. Hemodynamic time course after pulmonary endarterectomy

	Proximal	Distal
Mean pulmonary arterial pressure (mm Hg)		
Preoperative	44 ± 10	46 ± 11
At discharge	22 ± 7	24 ± 6
3-mo follow-up	24 ± 9	25 ± 7
12-mo follow-up	23 ± 7	24 ± 8
<i>P</i> value*	<.001	<.001
PVR (dyne·s·cm ⁻⁵)		
Preoperative	876 ± 392	926 ± 337
At discharge	251 ± 146	295 ± 161
3-mo follow-up	270 ± 175	300 ± 139
12-mo follow-up	243 ± 115	300 ± 224
<i>P</i> value*	<.001	<.001
Cardiac output (L/min)		
Preoperative	3.9 ± 1.3	3.7 ± 1.2
At discharge	5.0 ± 1.2	4.7 ± 1.2
3-mo follow-up	5.2 ± 1.1	5.0 ± 1.2
12-mo follow-up	5.0 ± 1.1	4.7 ± 1.0
<i>P</i> value*	<.001	<.001

PVR, Pulmonary vascular resistance. *Each time point versus preoperative. Test of interaction: *P* = .975 (mean pulmonary arterial pressure); *P* = .777 (*PVR*); *P* = .825 (cardiac output).



DISTAL LESIONS

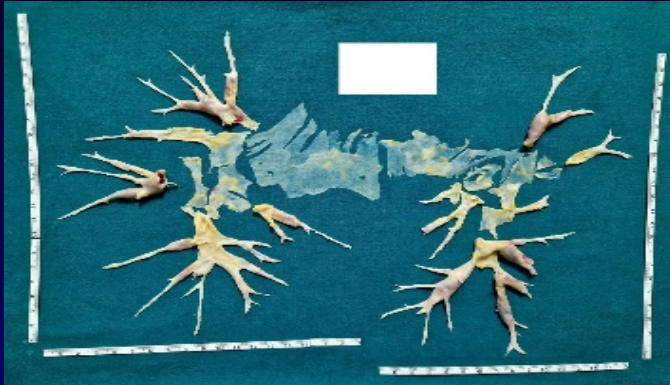
TABLE 4. Partial pressure of oxygen in arterial blood, modified Bruce exercise test, and 6-minute walking distance time course after pulmonary endarterectomy

	Proximal	Distal
Arterial partial pressure of oxygen (mm Hg)		
Preoperative	65 ± 12	66 ± 11
3-mo follow-up	82 ± 13	80 ± 11
12-mo follow-up	80 ± 11	80 ± 11
<i>P</i> value*	<.001	<.001
Modified Bruce exercise test (m)		
Preoperative	51 (0-143)	52 (0-102)
3-mo follow-up	495 (182-658)	435 (143-586)
12-mo follow-up	520 (261-709)	474 (225-620)
<i>P</i> value*	<.001	<.001
6-min walking distance (m)		
Preoperative	277 ± 118	289 ± 112
3-mo follow-up	391 ± 118	398 ± 107
12-mo follow-up	389 ± 118	396 ± 112
<i>P</i> value*	<.001	<.001

*Each time point versus preoperative. Test of interaction: *P* = .317 (partial pressure of oxygen in arterial blood); *P* = .205 (modified Bruce exercise test); *P* = .962 (6-min walking distance).



TREATED BRANCHES



75 TREATED BRANCHES



59 TREATED BRANCHES



63 TREATED BRANCHES

**IT IS IMPORTANT THE
NUMBER OF TREATED
BRANCHES?**



PULMONARY ENDARTERECTOMY IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION: RELATIONSHIP BETWEEN TREATED BRANCHES AND OUTCOME

Int J Cardiol 2023 Apr 15;377:124-130



BACKGROUND

In patients with CTEPH undergoing PEA it is important to minimize residual obstructions, in order to achieve low postoperative pulmonary vascular resistances and better clinical results



METHODS

In 564 consecutive CTEPH pts undergoing PEA the count of the number of treated branches was performed directly on the surgical specimens

Post-operative FUP visits were scheduled at 3 months and 12 months after surgery including right heart catheterization and modified Bruce test



ANALYSIS OF PEA SPECIMENT

Surgical specimen of a patient with a Jamieson 1 disease. A total of 32 branches were treated in the right lung and 29 in the left lung. The arrows indicate how 5 treated branches were counted in the middle lobe of the right lung

S= superior lobe, M = middle lobe, I = inferior lobe, L = lingula



POPULATION

The population was divided into tertiles based on the number of treated branches

Group 1	from 4 to 30 treated branches	194 patients
Group 2	from 31 to 43 treated branches	190 patients
Group 3	from 44 to 100 treated branches	180 patients



MPAP AT 3 AND 12 MONTHS AFTER PEA



PVR AT 3 AND 12 MONTHS AFTER PEA



LONG-TERM SURVIVAL



PATIENTS SUITABLE FOR BPA

DIFFERENT SUBGROUPS

- Technically inoperable
- Excessive comorbidities (distal lesions)
- Refuse PEA (distal lesions)
- Post-PEA non suitable of redo-PEA

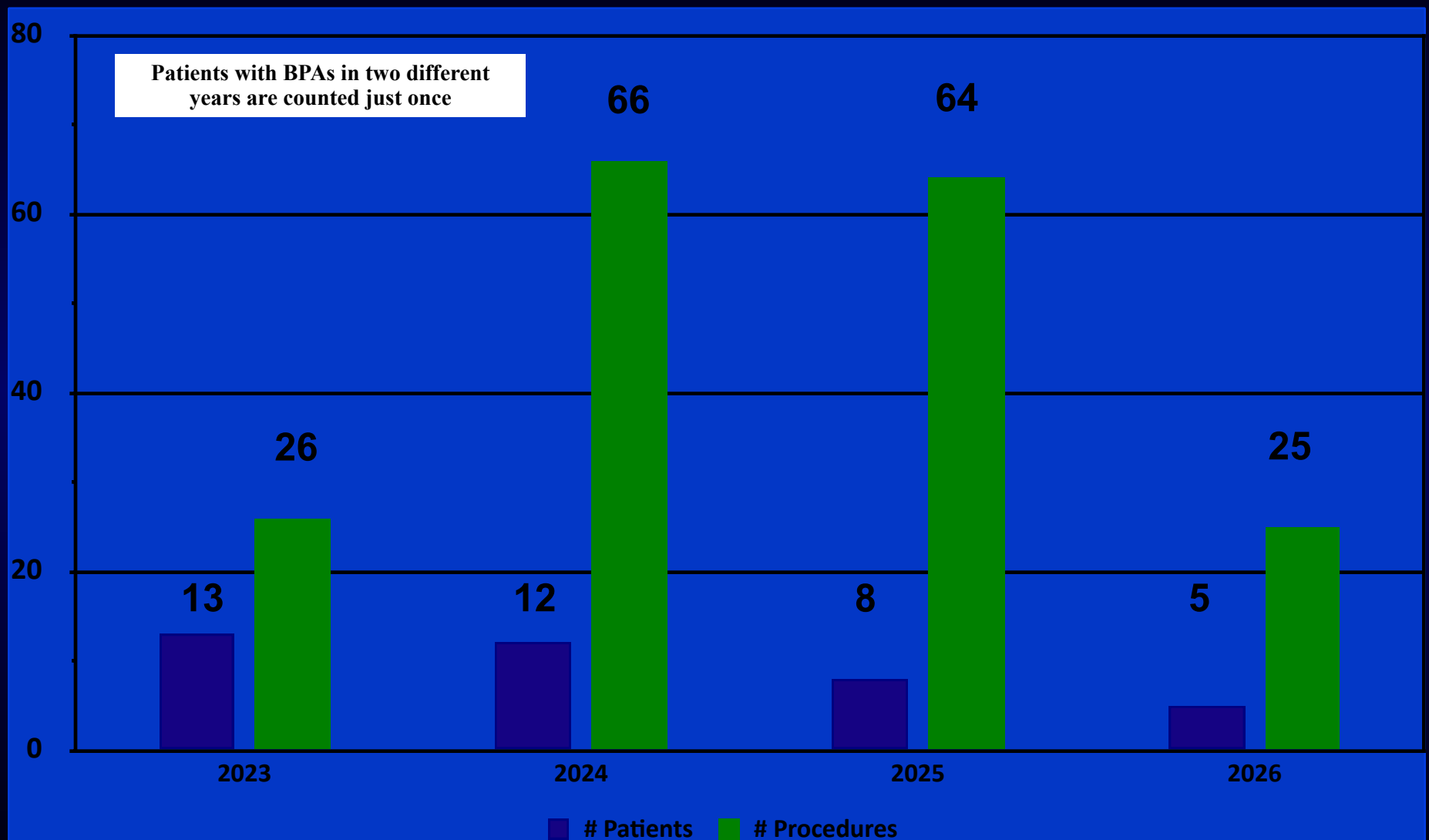


OUR BPA's PROGRAM

- National and International referral program
- Begin: March 2023
- May 2026: 38 pts with 181 BPAs performed

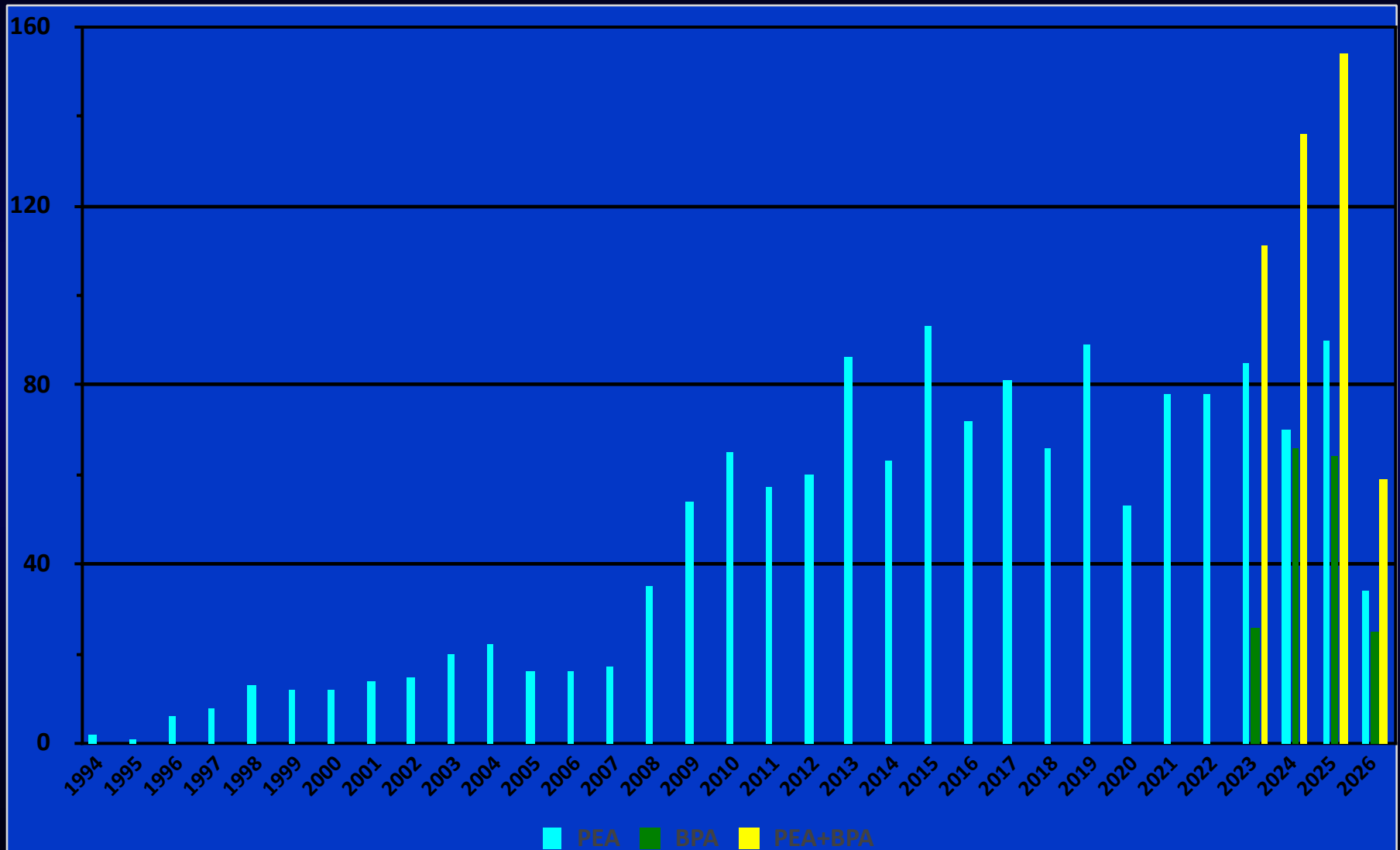
BPA: PATIENTS & PROCEDURES

38 & 181



PEA AND BPA / YEAR

1483 PEAs & 181 BPAs



BPA PROCEDURE

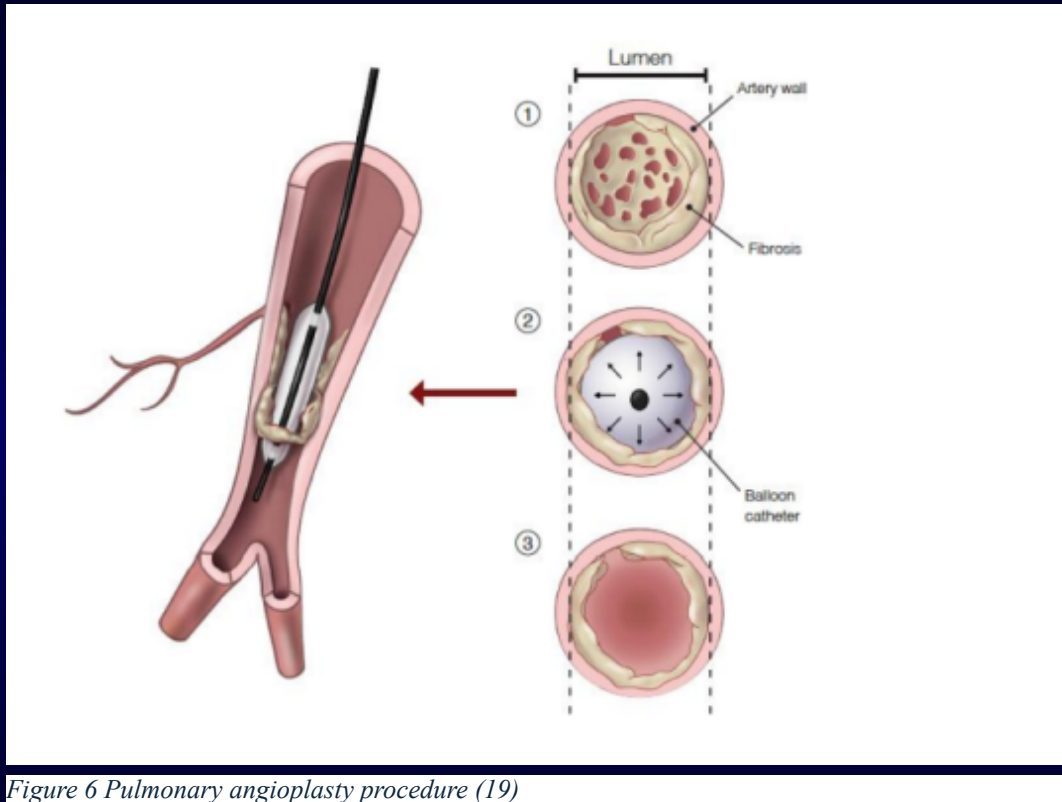


Figure 6 Pulmonary angioplasty procedure (19)

- performed via **femoral or jugular vein** using **6, 7, or 8 French catheters**
- **segmental angiography** to precisely localize the lesions
- balloons from **2 mm to 6 mm** are inflated between **4 and 14 atm**

BPA PROCEDURE

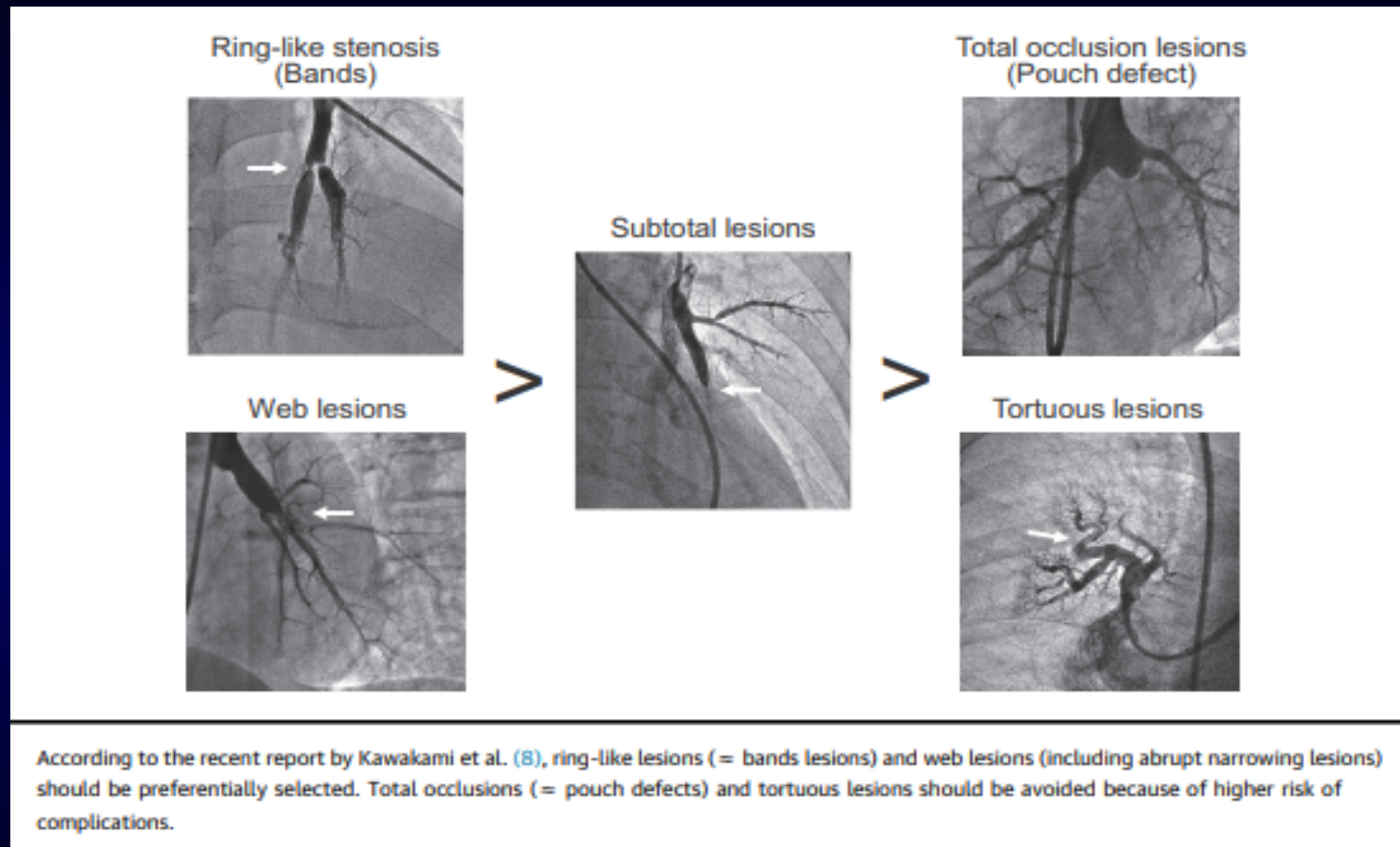


Figure 7 Representative angiograms showing favorable versus unfavorable anatomy of angioplasty

BPA PROCEDURE

- Procedural complications include vessel rupture or dissection, hemoptysis, reperfusion edema, and pulmonary parenchymal hemorrhage
- Maximum one or two lobes should be treated per session
- Two sessions in 10 days, revaluation after three months following procedure, till a total of 10 sessions

SPECIFIC THERAPY BEFORE BPA?

According to guidelines

The recommendation on the use of medical therapy before interventional therapy in patients with CTEPH who are considered inoperable but candidates for BPA is based on PICO question IV ([Supplementary Data, Section 10.2](#)). The included evidence suggests that pre-treatment improves pulmonary haemodynamics and safety of the procedure. This is confirmed by the clinical experience of Task Force members. However, due to the low certainty of the evidence, the recommendation is conditional.

PICO : Should patients with CTEPH who are considered inoperable but candidates for BPA receive medical therapy before interventional therapy is initiated?

Recommendations	GRADE		Class	Level
	Quality of evidence	Strength of recommendation		
In patients with CTEPH who are candidates for BPA, medical therapy should be considered prior to the intervention	Very low	Conditional	Ila	B

10.2. PICO question IV: Should patients with chronic thrombo-embolic pulmonary hypertension who are considered inoperable but candidates for balloon pulmonary angioplasty receive medical therapy before interventional therapy is initiated?

See the following sections for search strategy ([13.4](#)), PRISMA diagram ([14.4](#)), GDT evidence profile ([15.4](#)), and Evidence to Decision table ([16.4](#)).

10.2.1. Conclusions

10.2.1.1. Recommendations

In patients with CTEPH who are candidates for balloon pulmonary angioplasty (BPA), medical therapy should be considered prior to the intervention (conditional recommendation, very low quality of evidence).

SPECIFIC THERAPY BEFORE BPA?

According to literature

Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (RACE): a multicentre, phase 3, open-label, randomised controlled trial and ancillary follow-up study

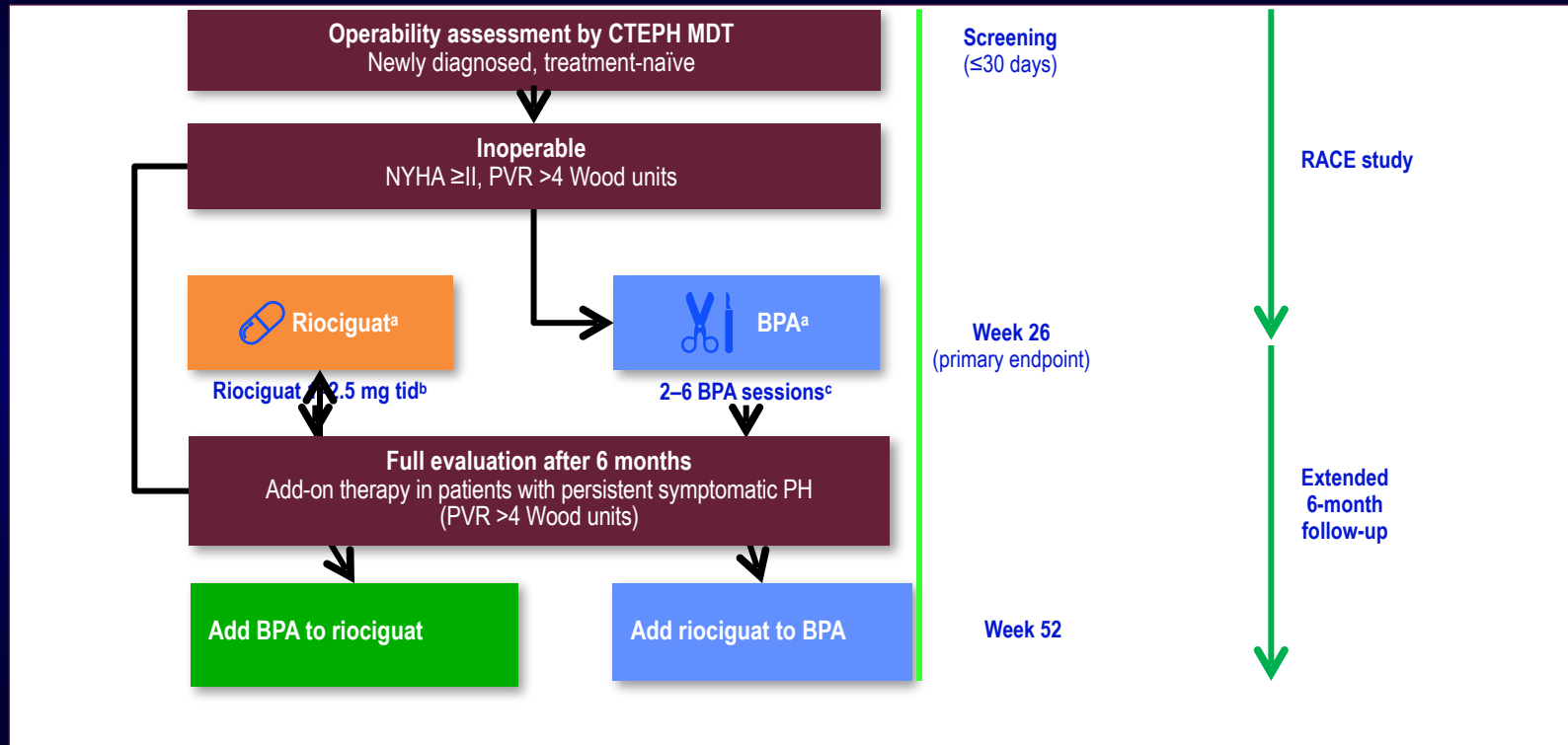
Xavier Jaïs¹, Philippe Brenot², Hélène Bouvaist³, Mitja Jevnikar⁴, Matthieu Canuet⁵, Céline Chabanne⁶, Ari Chaouat⁷, Vincent Cottin⁸, Pascal De Groote⁹, Nicolas Favrolt¹⁰, Delphine Horeau-Langlard¹¹, Pascal Magro¹², Laurent Savale⁴, Grégoire Prévot¹³, Sébastien Renard¹⁴, Olivier Sitbon⁴, Florence Parent⁴, Romain Trésorier¹⁵, Cécile Tromeur¹⁶, Céline Piedvache¹⁷, Lamiae Grimaldi¹⁸, Elie Fadel¹⁹, David Montani⁴, Marc Humbert⁴, Gérald Simonneau⁴

Clinical Trial > [Lancet Respir Med.](#) 2022 Oct;10(10):961-971.

doi: 10.1016/S2213-2600(22)00214-4. Epub 2022 Aug 1.

SPECIFIC THERAPY BEFORE BPA?

According to literature



SPECIFIC THERAPY BEFORE BPA?

According to literature

Interpretation: At week 26, pulmonary vascular resistance reduction was more pronounced with BPA than with riociguat, but treatment-related serious adverse events were more common with BPA. The finding of fewer BPA-related serious adverse events among patients who were pretreated with riociguat in the follow-up study compared with those who received BPA as first-line treatment points to the potential benefits of a multimodality approach to treatment in patients with inoperable CTEPH. Further studies are needed to explore the effects of sequential treatment combining one or two medications and BPA in patients with inoperable CTEPH.

Thank you for your attention

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