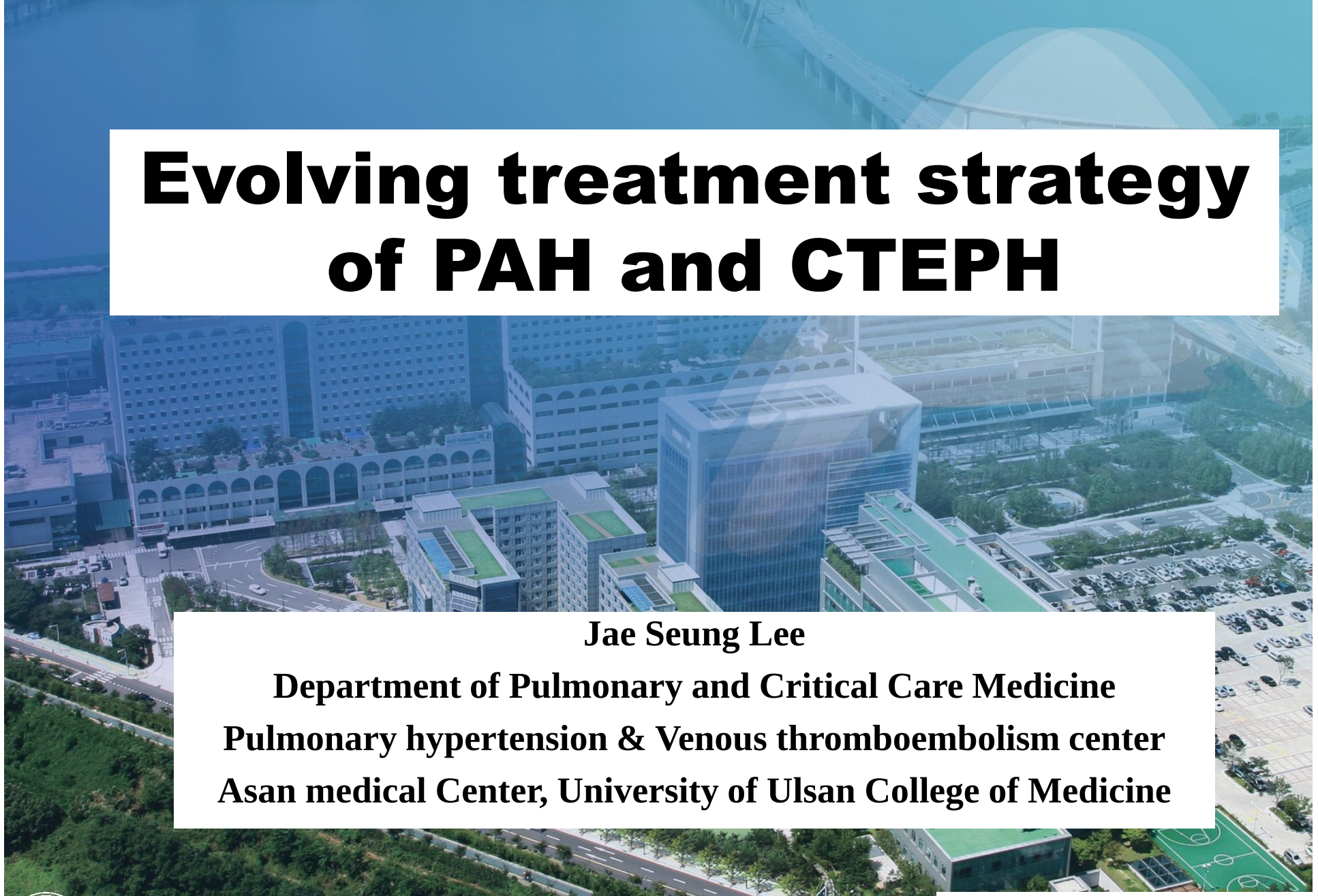
Evolving treatment strategy of PAH and CTEPH



Jae Seung Lee

Department of Pulmonary and Critical Care Medicine

Pulmonary hypertension & Venous thromboembolism center

Asan medical Center, University of Ulsan College of Medicine

서울아산병원
Asan Medical Center

PHT Center
Pulmonary Hypertension & Venous Thrombosis Center
폐고혈압·정맥혈전센터

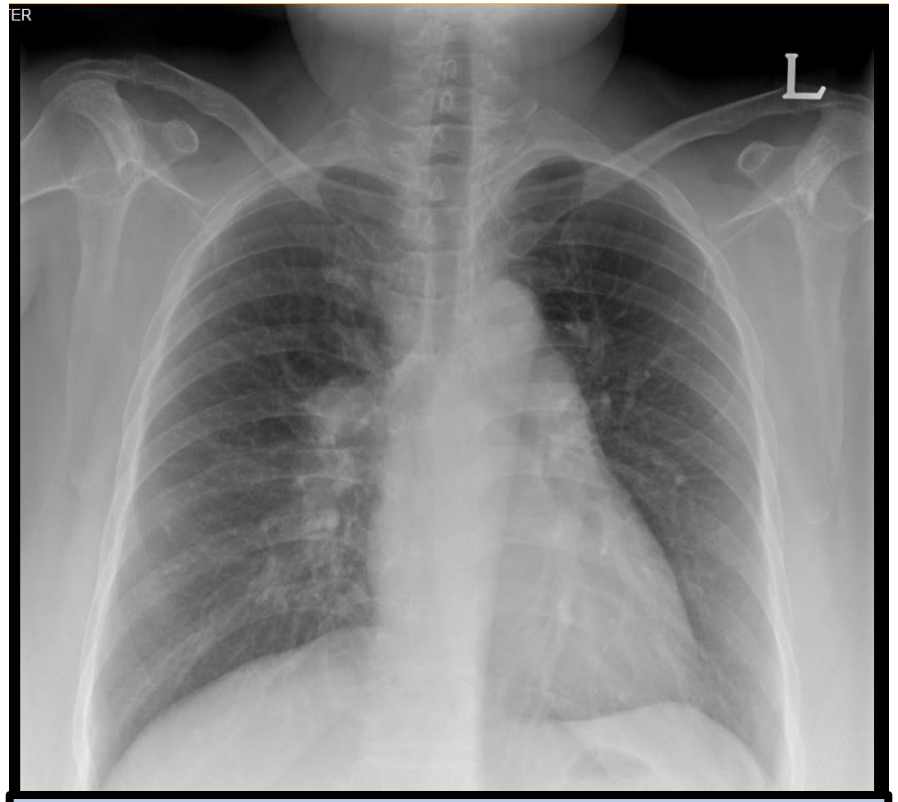
25/F IPAH

C. C : recurrent syncope, 10 times

P. M. Hx. : none

Height 155 weight 92 BMI 38

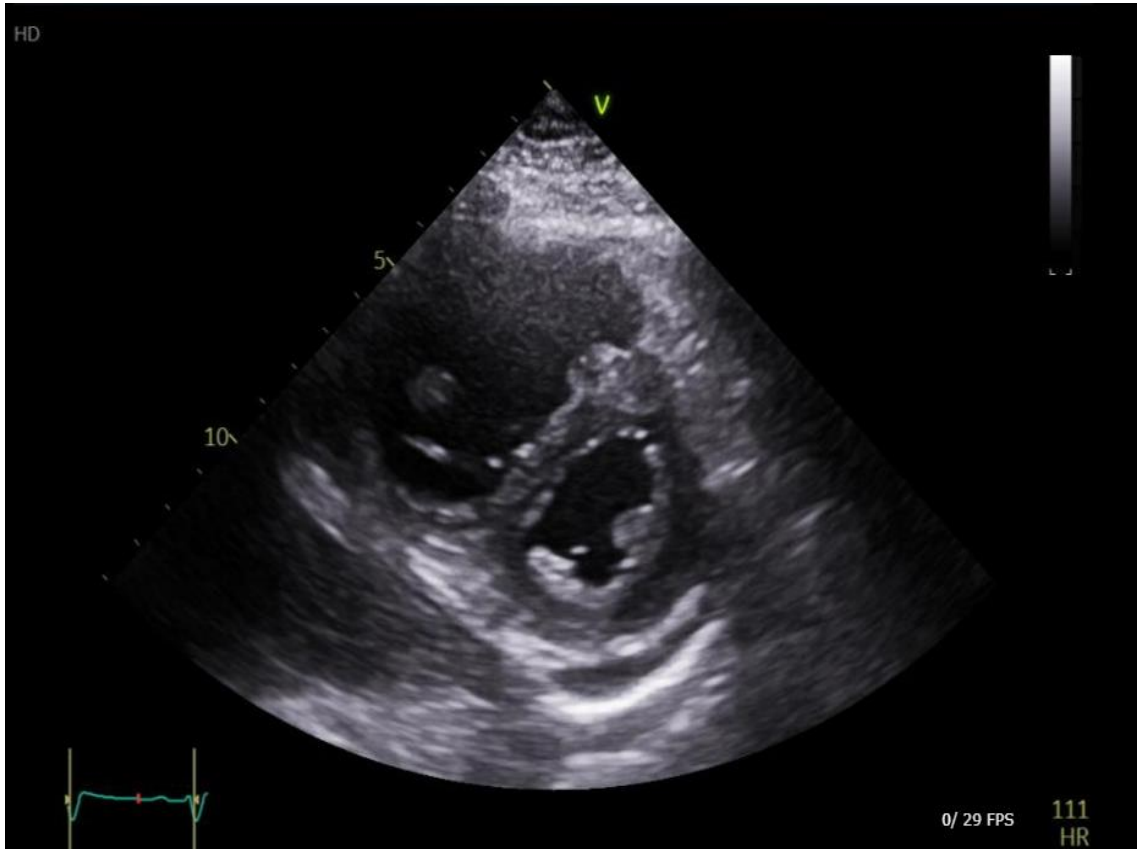
BNP 329 pg/ml

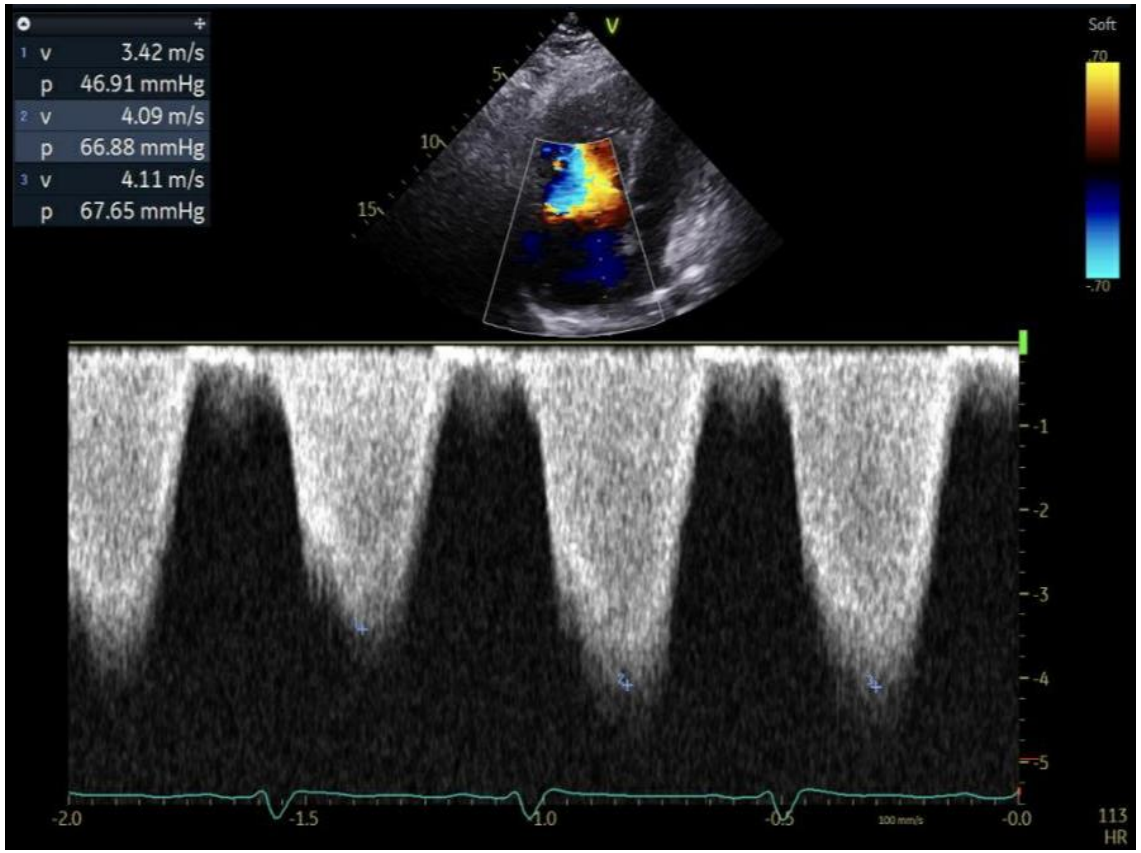


PFT: FVC 71 %pred. FEV_1 72 %pred.
DLco 59 %pred.

6MWT 190m (SpO2 94% -> 94%)

Echocardiography





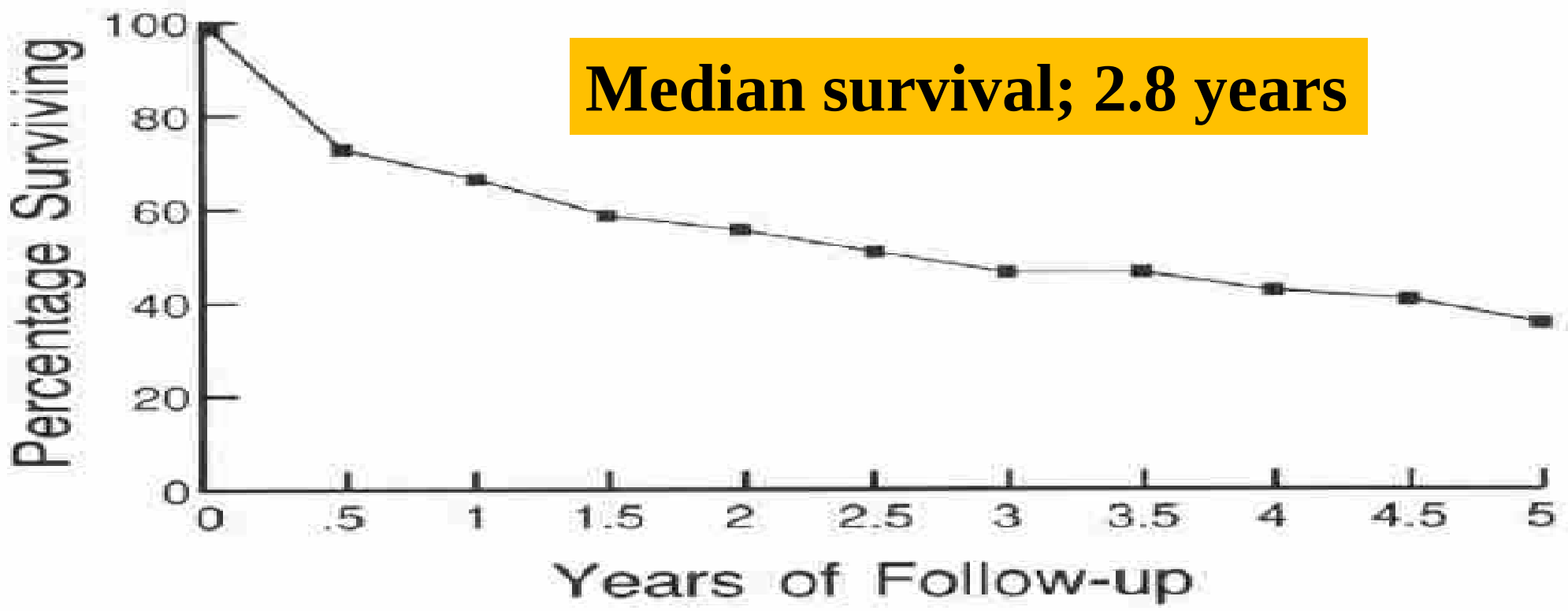
Severe functional TR with severe resting PH and RV dysfunction

25/F IPAH after triple combination treatment (SC treprostinil, macitentan, sildenafil)

Date	2023.12	2024.09
mRAP	**25**	**13**
Mean PAP	**61**	**57**
PCWP	14	13
ScvO2 (%)	52	65.7
CO	**2.5**	**4.7**
PVR (WU)	**18.8**	**9.3**

Survival in patients with IPAH: the era before PAH target agents

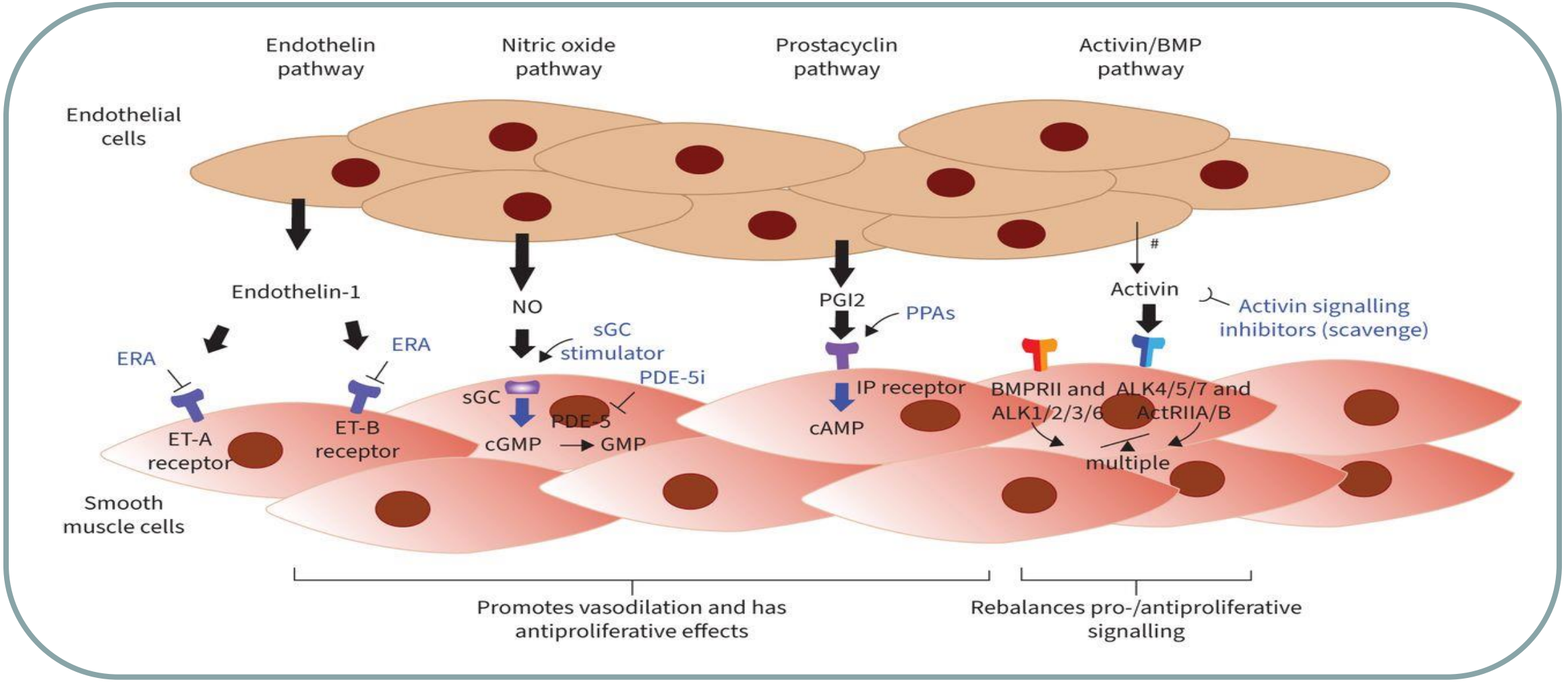
➢NIH registry (1981-1985 to 1988), 194 patients with IPAH



Median survival; 2.8 years

D'Alonzo GE, et al. Ann Internal Med. 1991;115:343-349

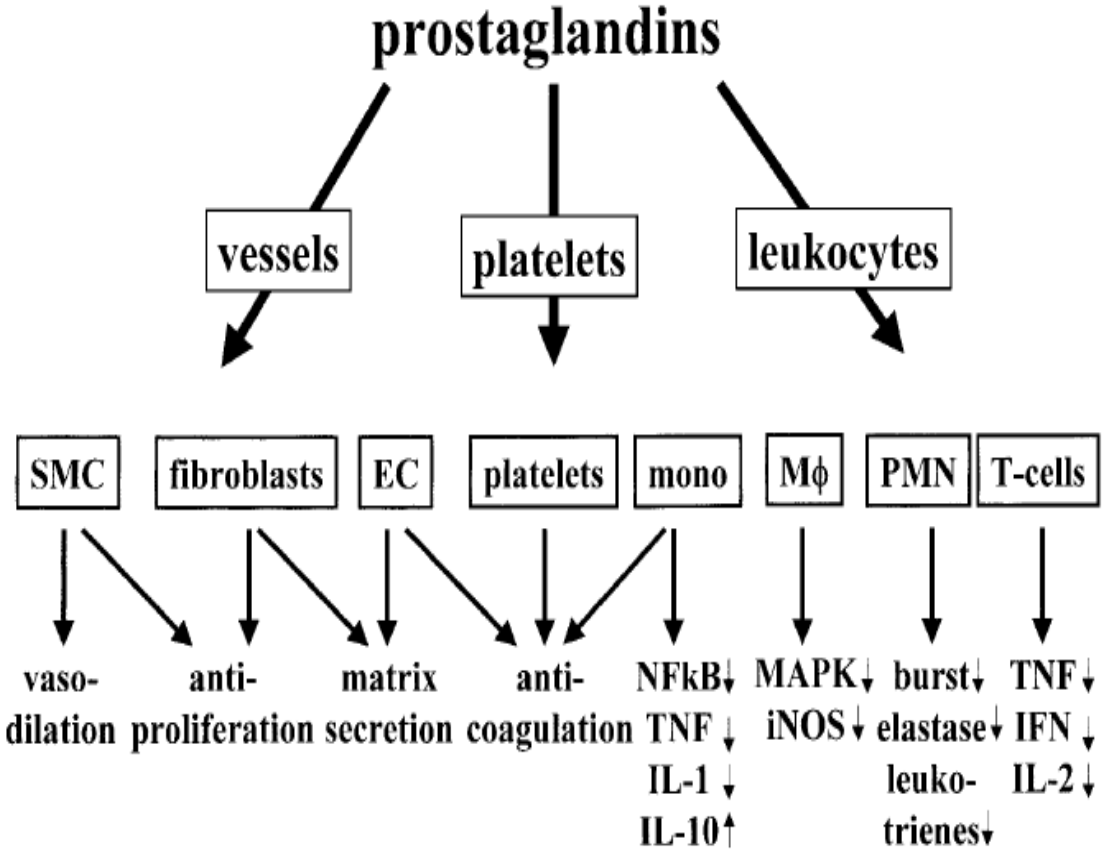
4-pathway drugs for PAH



Chin KM, et al. Eur Respir J 2024; in press: 2401325

Pharmacologic properties of prostacyclins

- Potent vasodilator
- Anti-platelet effect
- Anti-proliferative
- Anti-inflammatory
- Inotropic effect



Olscewski H et al. J Lab Clin Med 2001; 138: 287–297

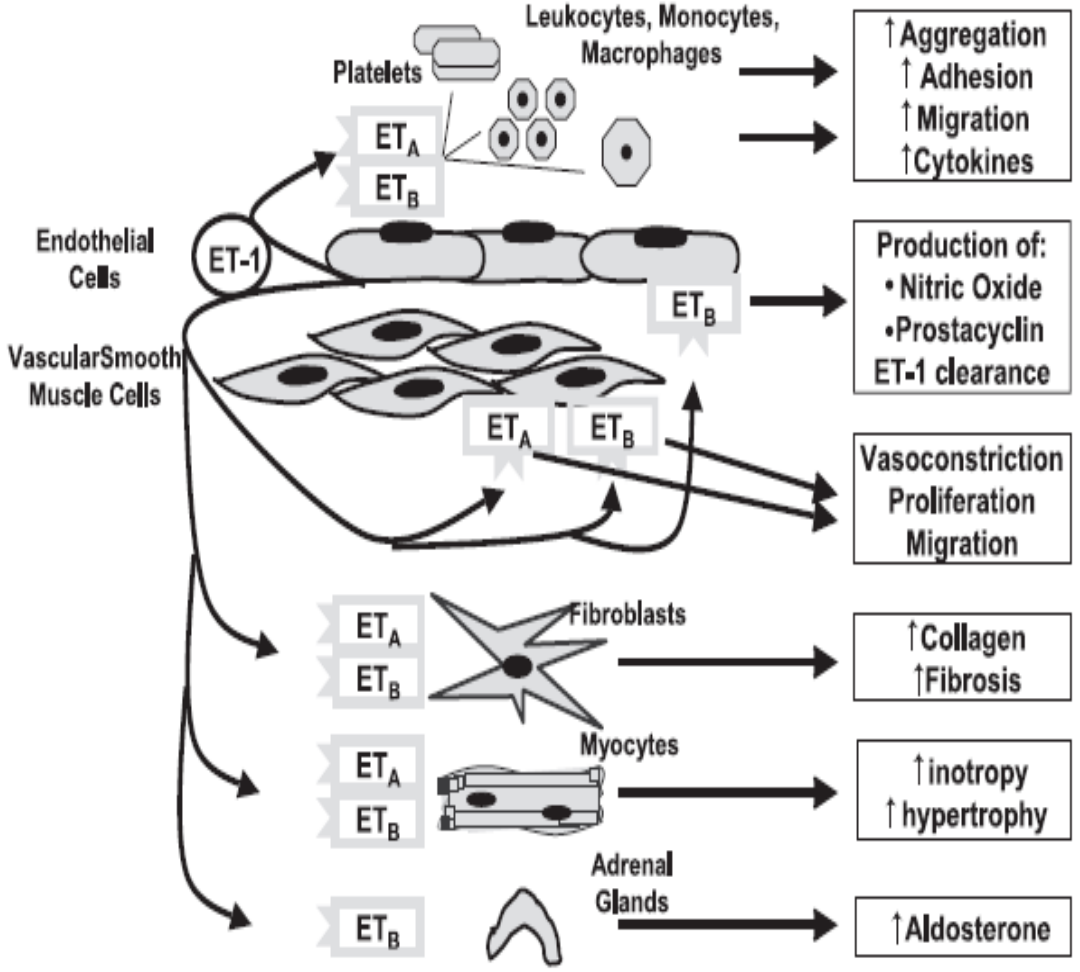
Effects of endothelin

ET_A–mediated effects

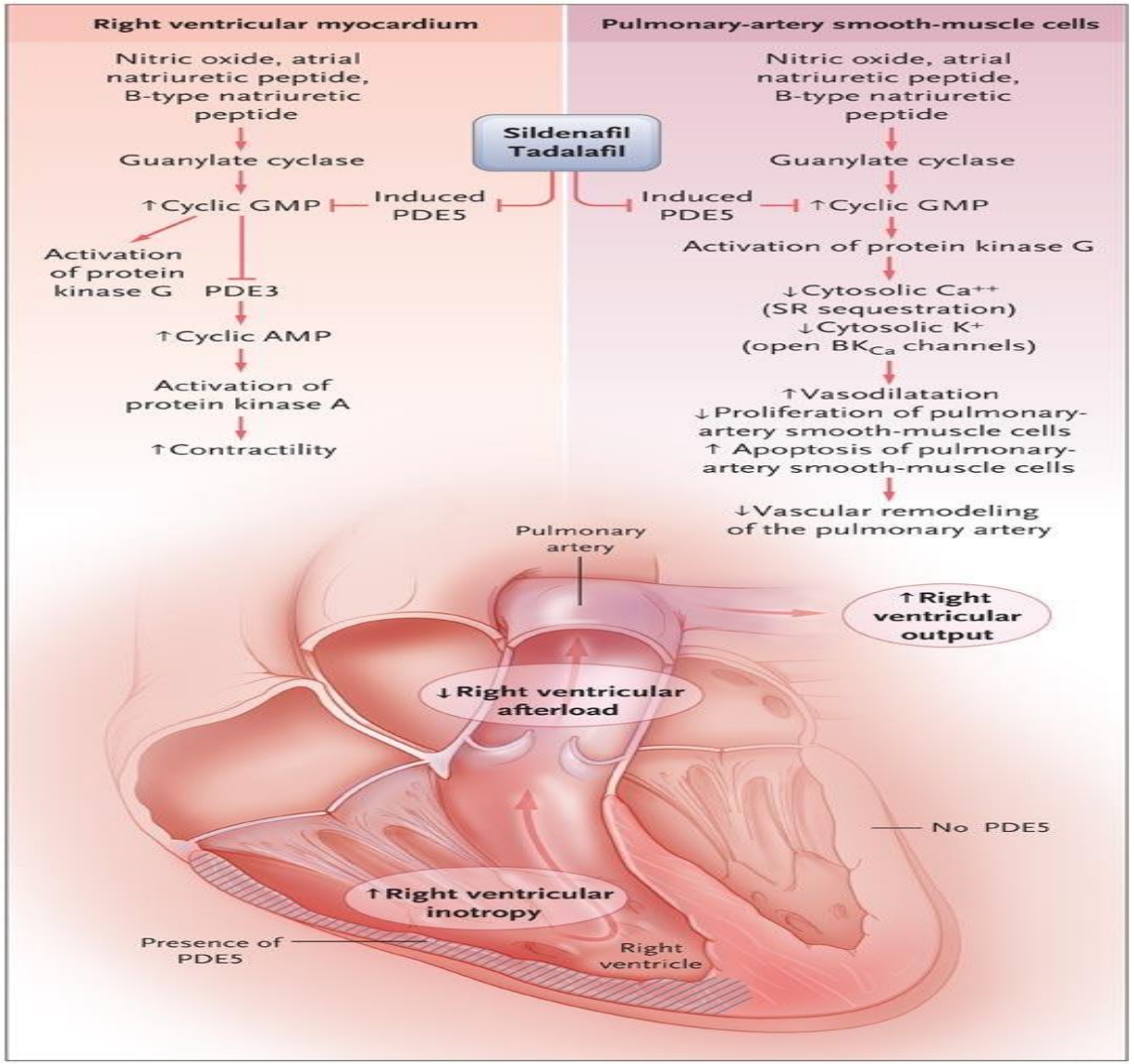
-vasoconstriction
- proliferation, hypertrophy
- cell migration
- fibrosis

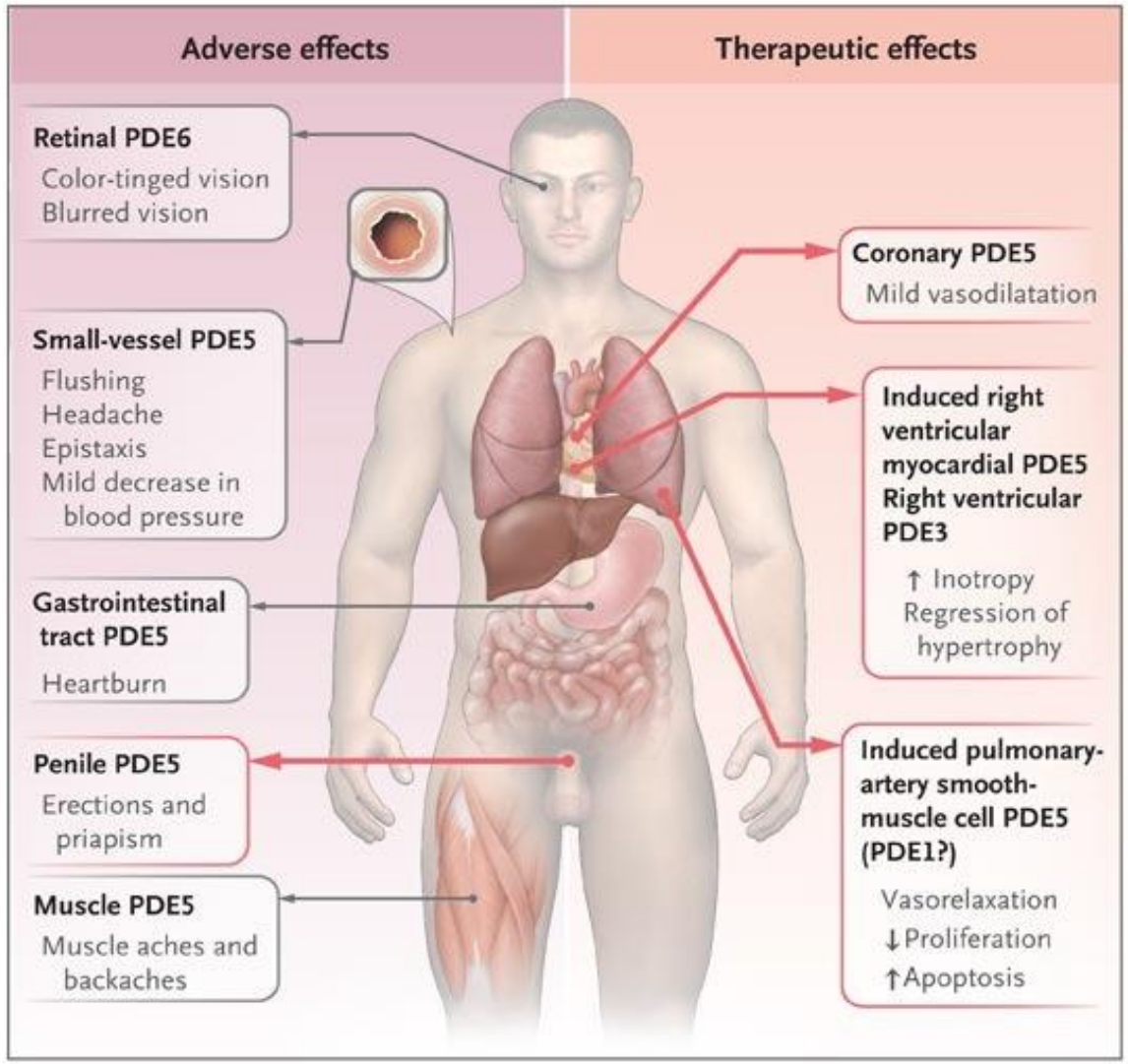
ET_B-mediated effect

- **release of NO and PGI**
- ET-1 clearance
- inhibits ET converting enzyme



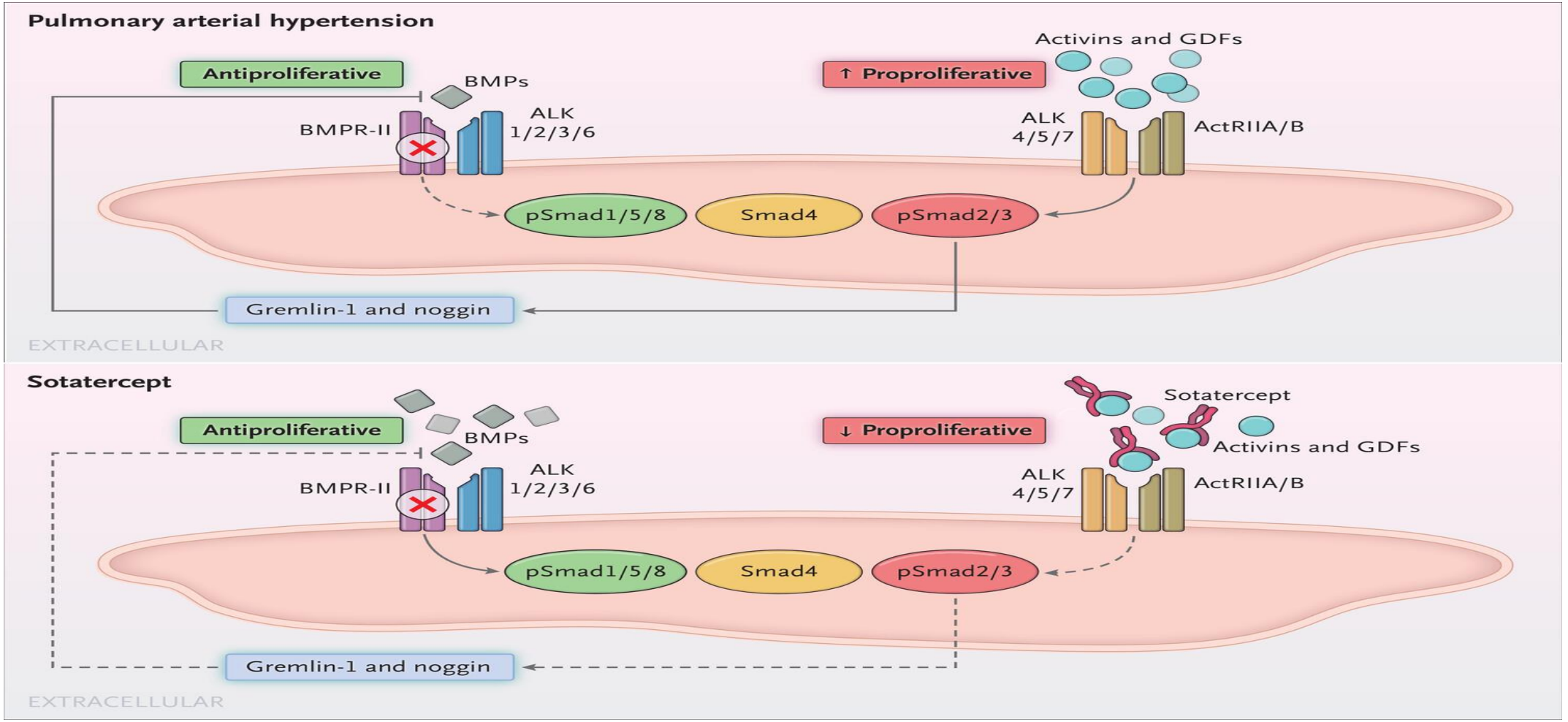
Phosphodiesterase (PDE)-5 Inhibitors for PAH





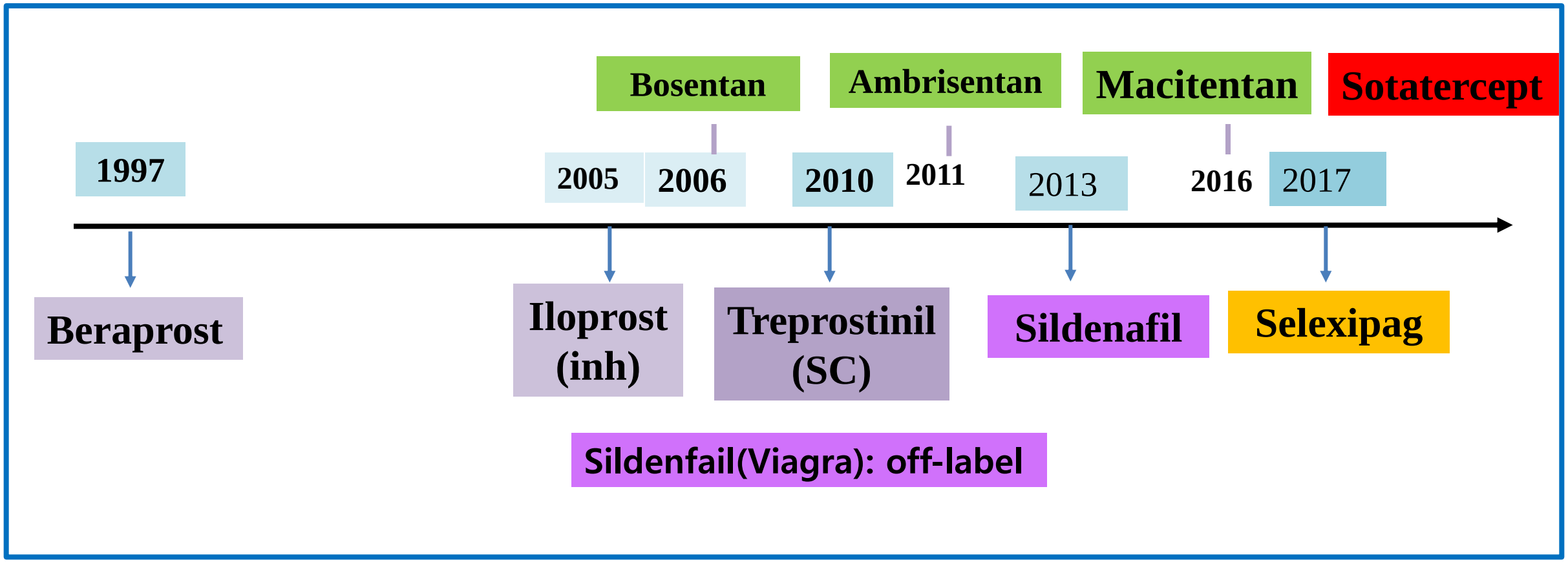
Archer SL, et al. N Engl J Med 2009;361:1864-71

Sotatercept in Acitivin/BMP pathway



Humbert M, et al. N Engl J Med 2021;384:1204-1215

PAH drug approval in South Korea

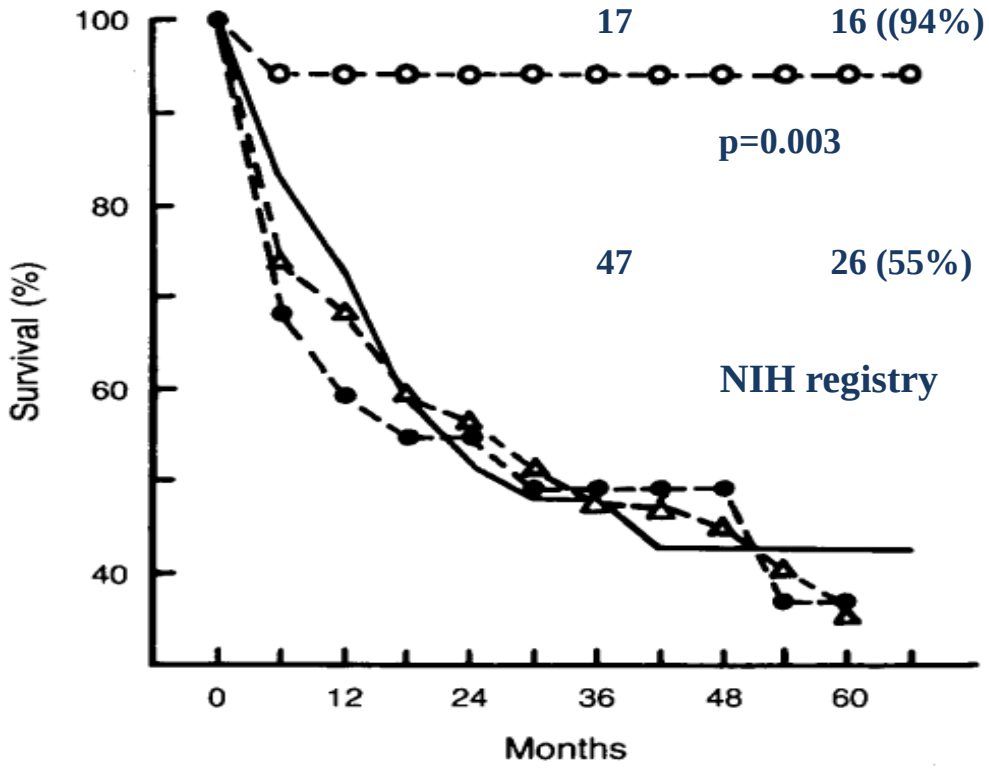


1993 ACCP consensus statement on PPH

- **There is no cure for PPH, nor is there a therapeutic approach** which is uniformly accepted or successful.
- **Anticoagulation therapy**
- **Vasodilators (nifedipine, diltiazem, postacycline, PGE1)**
- Atrial septostomy
- Lung transplantation; Heart-lung or double lung

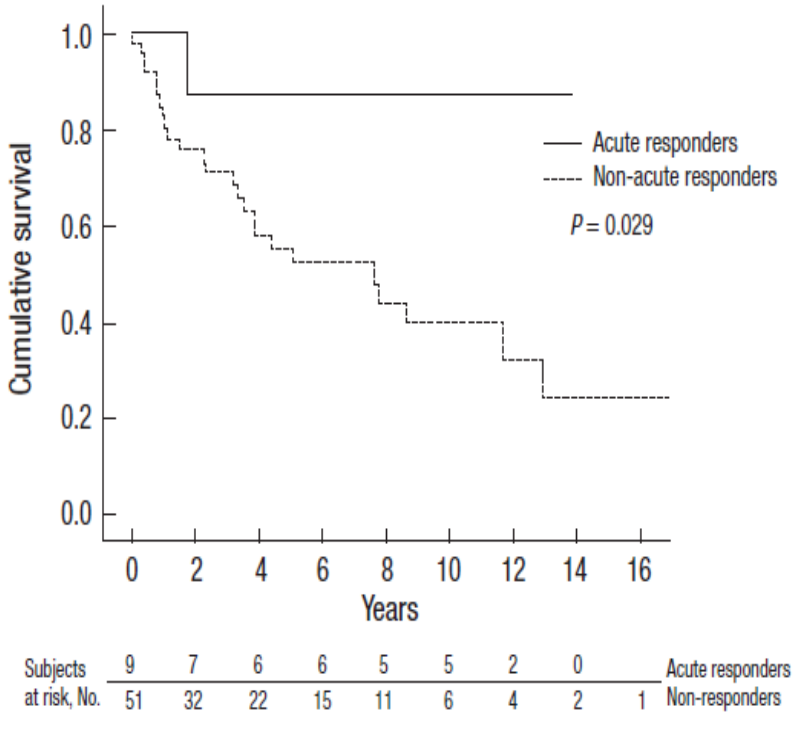
Calcium channel blockers on survival in PPH

64 patients with PPH



Rich et al. N Engl J Med 1992;327:76-81

60 patients with PPH in AMC

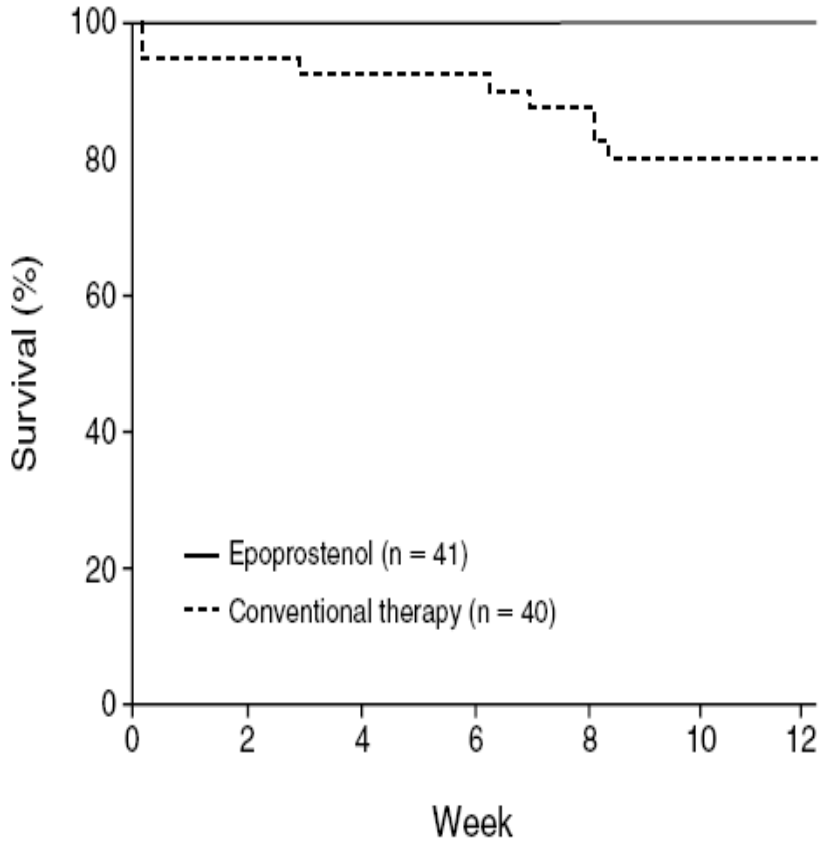


Ahh JH et al. Korean Med Sci 2014; 29: 1665-1671

Epoprostenol

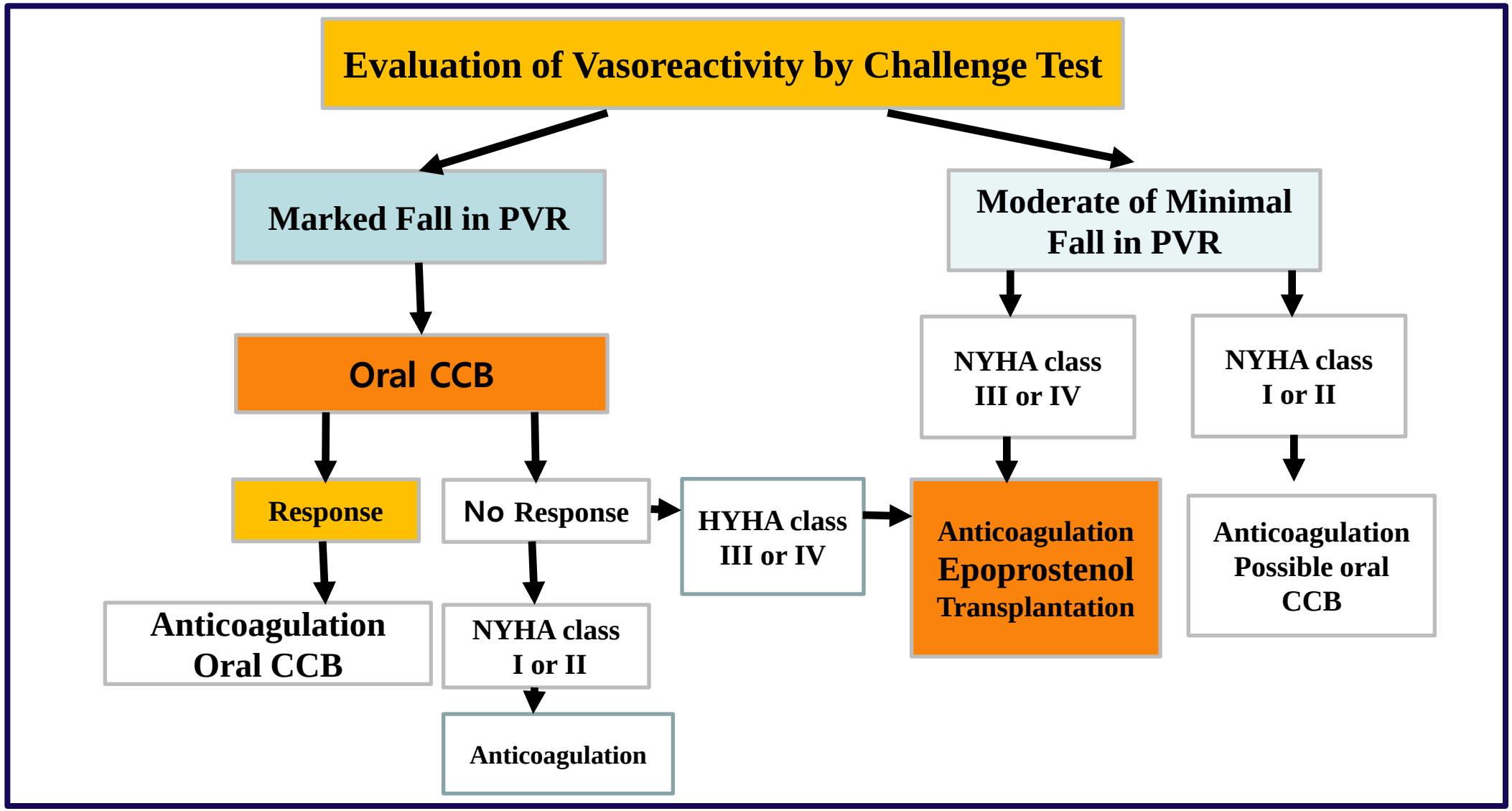
- "Gold standard" for FC IV PAH

- **The only PAH therapy with a survival benefit for patients with PAH that has been demonstrated in a single RCT.**



Barst et al. N Engl J Med 1996;334:296-301

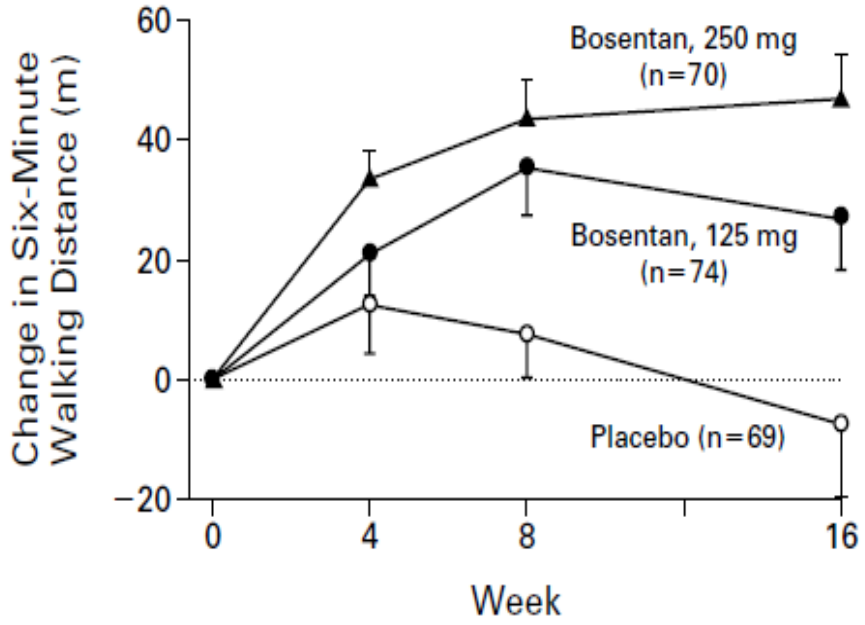
1997 algorithm for the management of PPH

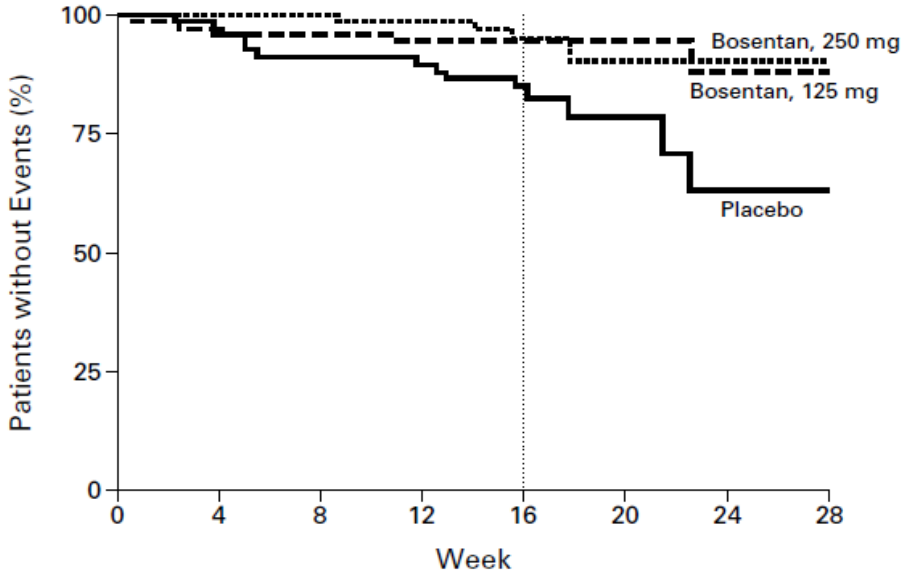


Rubin LJ. N Engl J Med 1997;336:111-117

Bosentan for PAH: BEATHE-1 study

- **12 week** prospective, randomized, multicenter open trial,
- **PAH(PPH, CTD-PAH), FC III, IV**
- **Bosentan improved 6MWD (44m, P<0.001),** Borg dyspnea index and WHO functional class and **increased the time to clinical worsening**.





No. at Risk								
Placebo	69	68	63	62	48	10	7	3
Bosentan, 125 mg	74	72	71	70	55	18	14	7
Bosentan, 250 mg	70	70	70	68	48	13	11	6

Rubin LJ, et al. N Engl J Med 2002;346:896-903

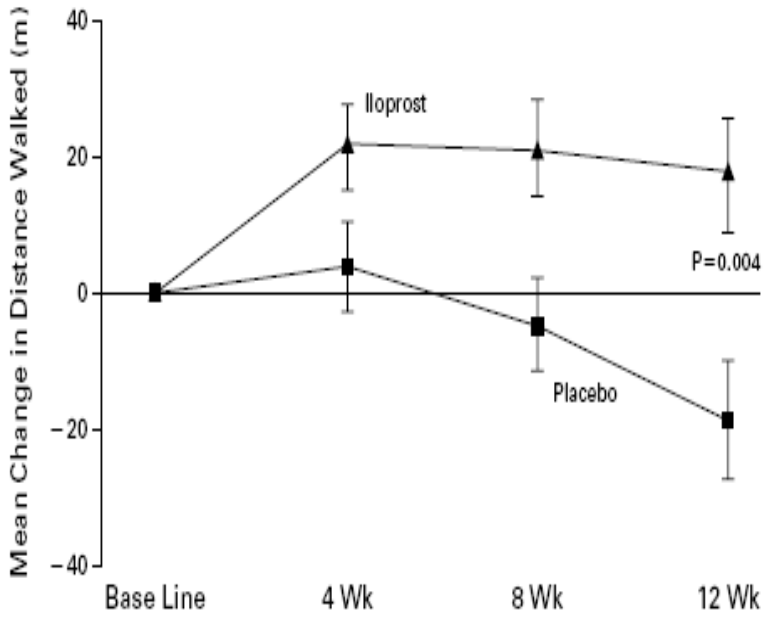
Inhaled iloprost for PAH: AIR study

12 week, double-blind, prospective, randomized, multicenter trial

Inclusion: IPAH (51/51) Drug-PAH (4/5) CTD-PAH (13/22) CTEPH (33/24)
FC-III (60/59) FC IV (41/43)

Primary endpoint: clinical improvement (NYHA class and 6MWD at least 10%)

Result: iloprost 16.8% vs placebo 4.9%, p=0.007



Variable	Iloprost Group			Placebo Group		
	All Patients	Patients with Primary Pulmonary Hypertension	Patients with Nonprimary Pulmonary Hypertension	All Patients	Patients with Primary Pulmonary Hypertension	Patients with Nonprimary Pulmonary Hypertension
	percentage of patients					
Change in NYHA class						
Improved by 2 classes	1.0*	1.9	0.0	0.0	0.0	0.0
Improved by 1 class	23.8*	22.6	25.0	12.7	7.3	19.1
Unchanged	64.4	66.0	62.5	65.7	69.1	61.7
Worsened	5.9	3.8	8.3	7.8	10.9	4.3
Data missing	1.0	1.9	0.0	0.0	0.0	0.0
Noncompletion of study	4.0	3.8	4.2	13.7	12.7	14.9
Death	1.0	1.9	0.0	3.9	3.6	4.3
Other	3.0†	1.9	4.2	9.8‡	9.1	10.6
Change in 6-minute walk distance						
≥10% increase	37.6§	49.1	25.0	25.5	30.9	19.1
<10% increase to <10% decrease	42.6	37.7	47.9	32.4	20.0	46.8
≥10% decrease	13.9	5.7	22.9	25.5	32.7	17.0
Data missing	5.9	7.5	4.2	16.7	16.4	17.0
Combined end point	16.8¶	20.8	12.5	4.9	5.5	4.3

Olschewski H, et al. N Engl J Med 2002;347:322-9

Continuous SC treprositnil in PAH

Inclusion: PPH (134/136), PH with CTD (41/49) or CHD (58/51)

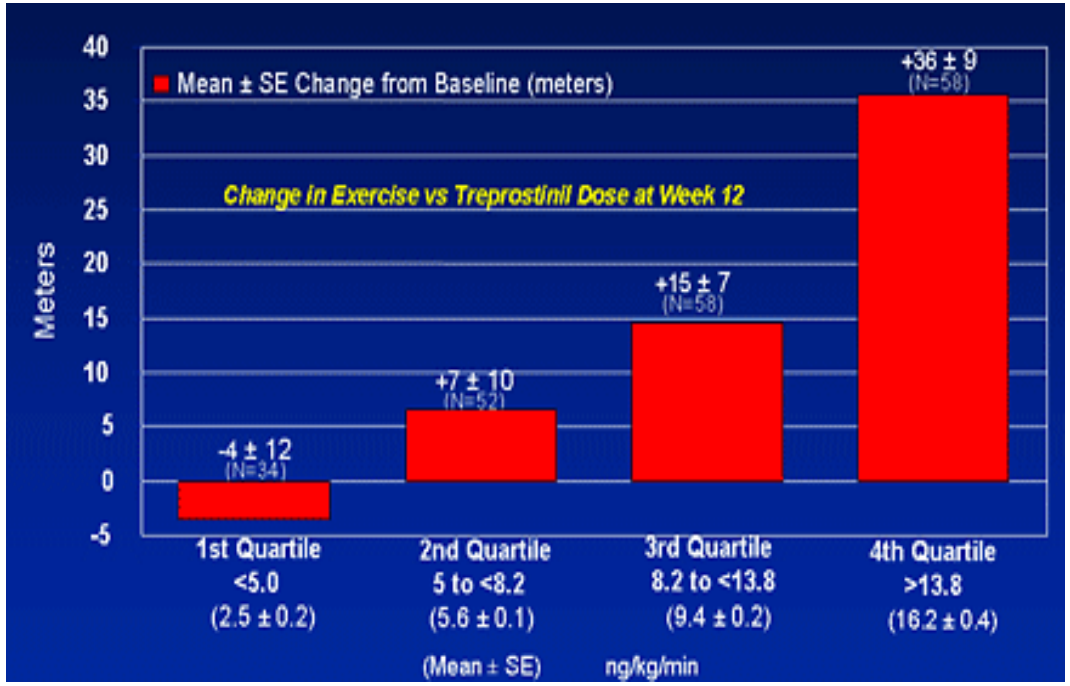
FC II (25/28), III (190/192), IV (18/16)

Design: 12 weeks, double-blind, placebo-controlled multicenter

Exercise capacity

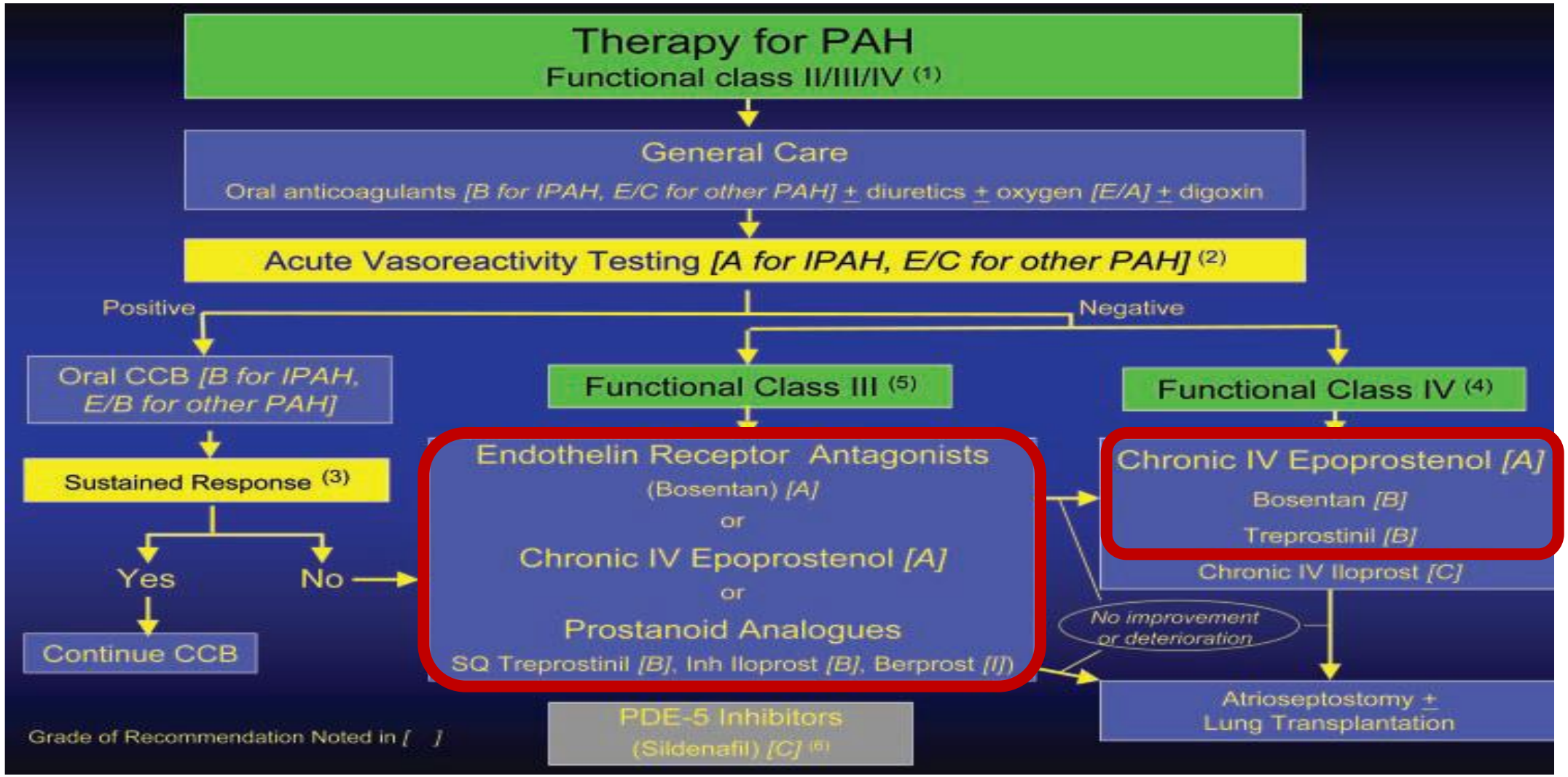
; Δ6MWD 16 m (p=0.006)

Greater in the sicker and dose-related.



Am J Respir Crit Care Med Vol 2002; 165: 800–804,

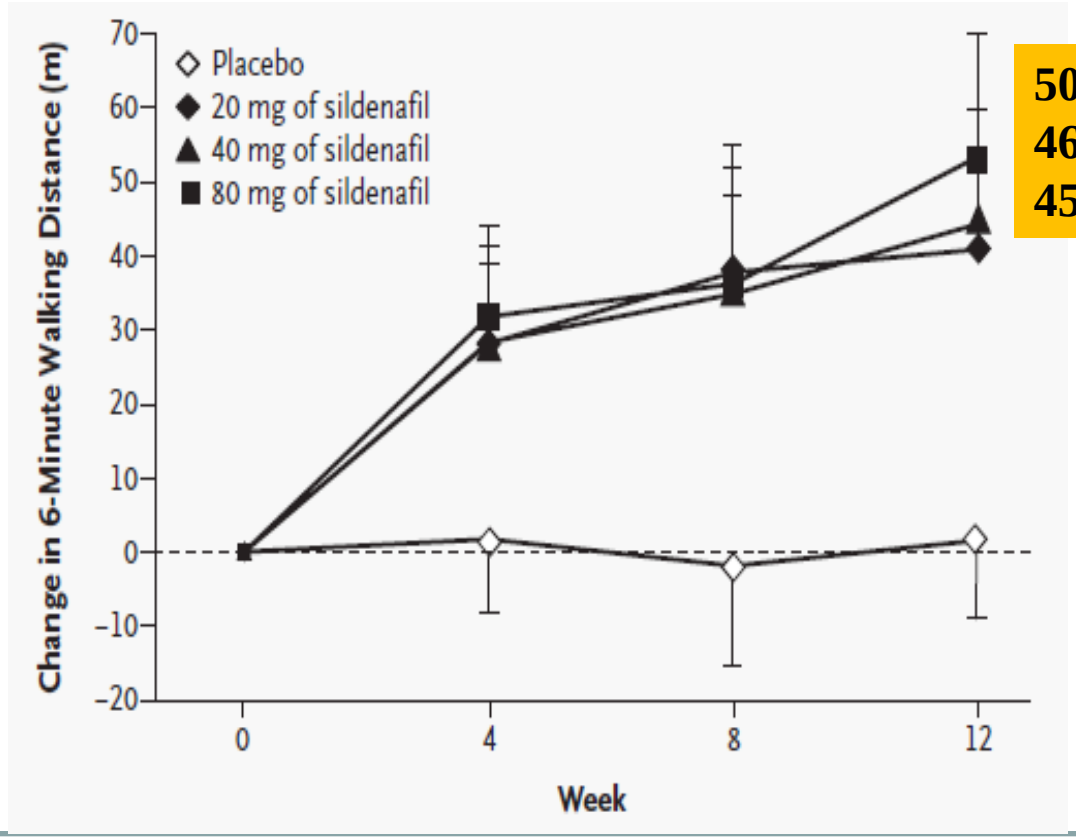
ACCP 2004 guidelines for PAH



CHEST 2004; 126:35S–62S

Sildenafil for PAH: SUPER study

- **12 week, double-blind,** prospective, randomized, multicenter trial
- **PAH(PPH, CTD-PAH, CHD-PAH), FC II (39%), III (58%)**

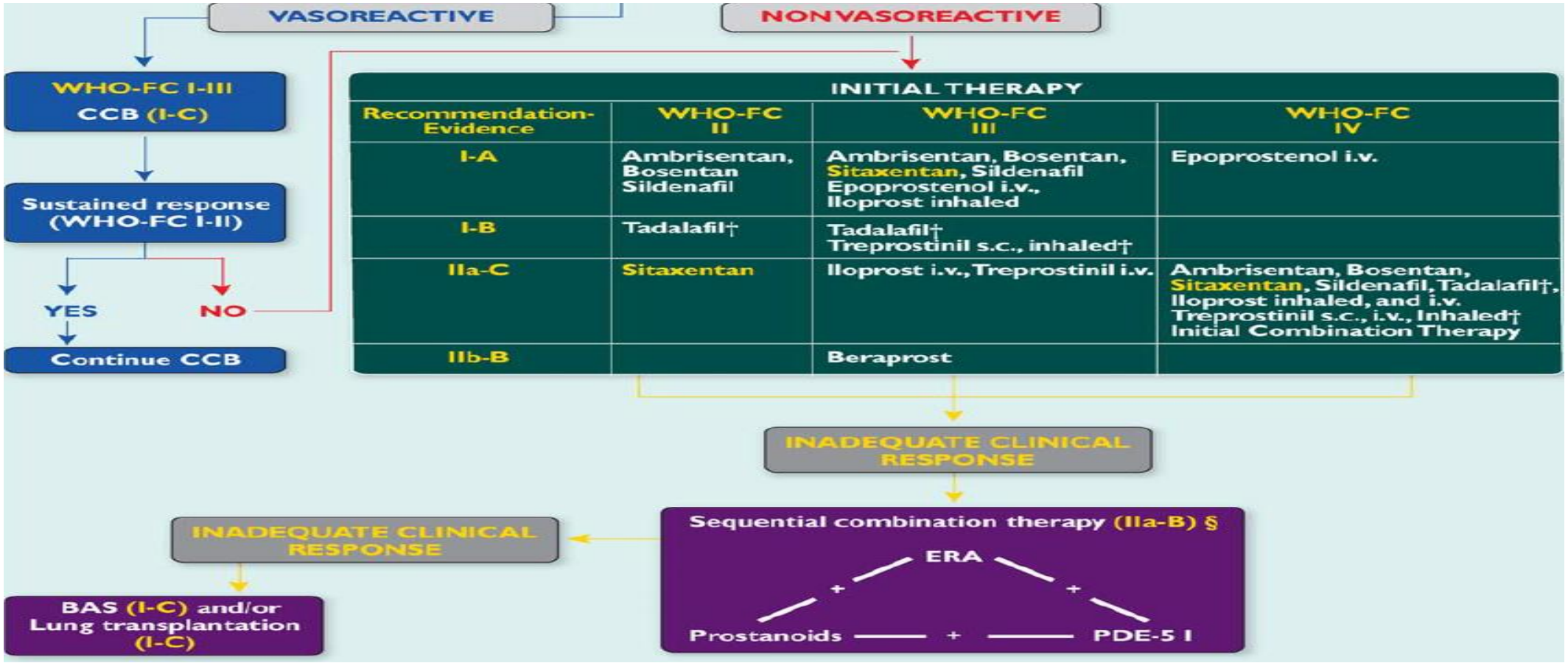


Variable	Placebo (N=65)	Sildenafil					
		20 mg (N=65)	P Value	40 mg (N=63)	P Value	80 mg (N=65)	P Value
Heart rate — beats/minute	-1.3 (-4.1 to 1.4)	-3.7 (-5.9 to -1.4)	0.18	-3.3 (-5.5 to -1.0)	0.27	-4.7 (-7.3 to -2.2)	0.05
Mean pulmonary artery pressure — mm Hg	0.6 (-0.8 to 2.0)	-2.1 (-4.3 to 0.0).	0.04	-2.6 (-4.4 to -0.9)	0.01	-4.7 (-6.7 to -2.8)	<0.001
Cardiac index — liters/min/m²	-0.02 (-0.17 to 0.13)	0.21 (0.04 to 0.8).	0.06	0.24 (0.05 to 0.42)	0.03	0.37 (0.20 to 0.55)	0.001
Pulmonary vascular resistance — dyn·sec·cm⁻⁵	49 (-54 to 153)	-122 (-217 to -27)	0.01	-143 (-218 to -69)	0.01	-261 (-365 to -157)	<0.001
Right atrial pressure — mm Hg	0.3 (-0.9 to 1.5)	-0.8 (-1.9 to 0.3)	0.19	-1.1 (-2.4 to 0.2)	0.10	-1.0 (-2.1 to 0.1)	0.11

Galie N, et al. N Engl J Med 2005;353:2148-57.

ESC/ERS 2009 guidelines for PH

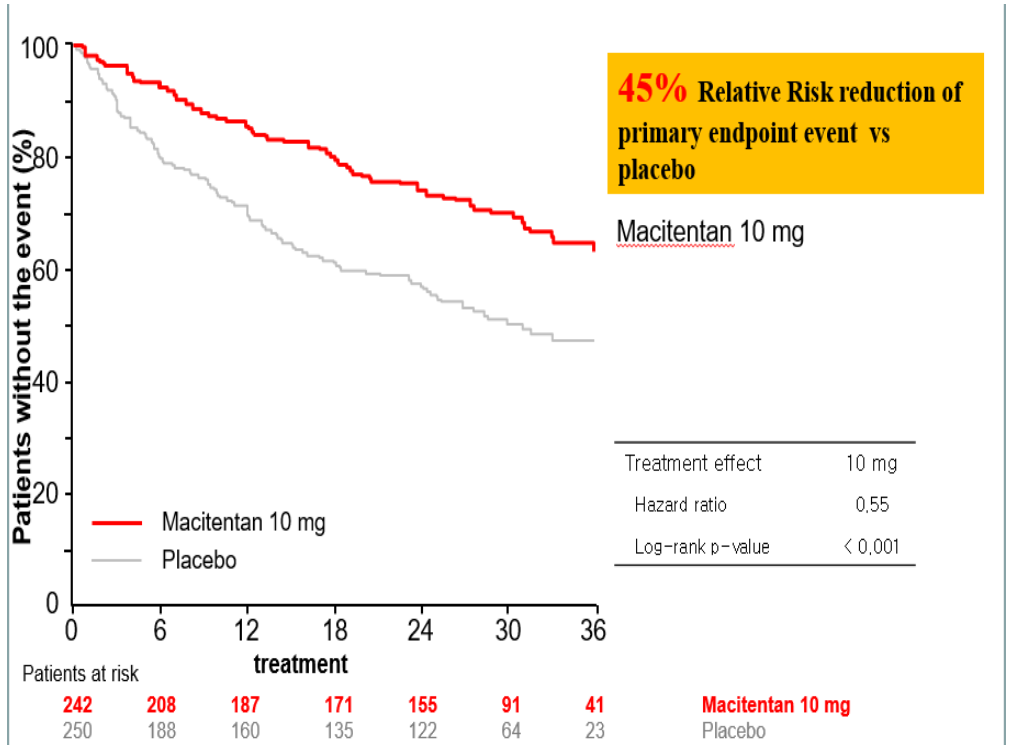
- **PAH target agent for WHO-FC II**
- **Sequential combination**



European Heart Journal (2009) 30, 2493–2537

Sequential combination therapy : macitentan to PDE5i

All patients

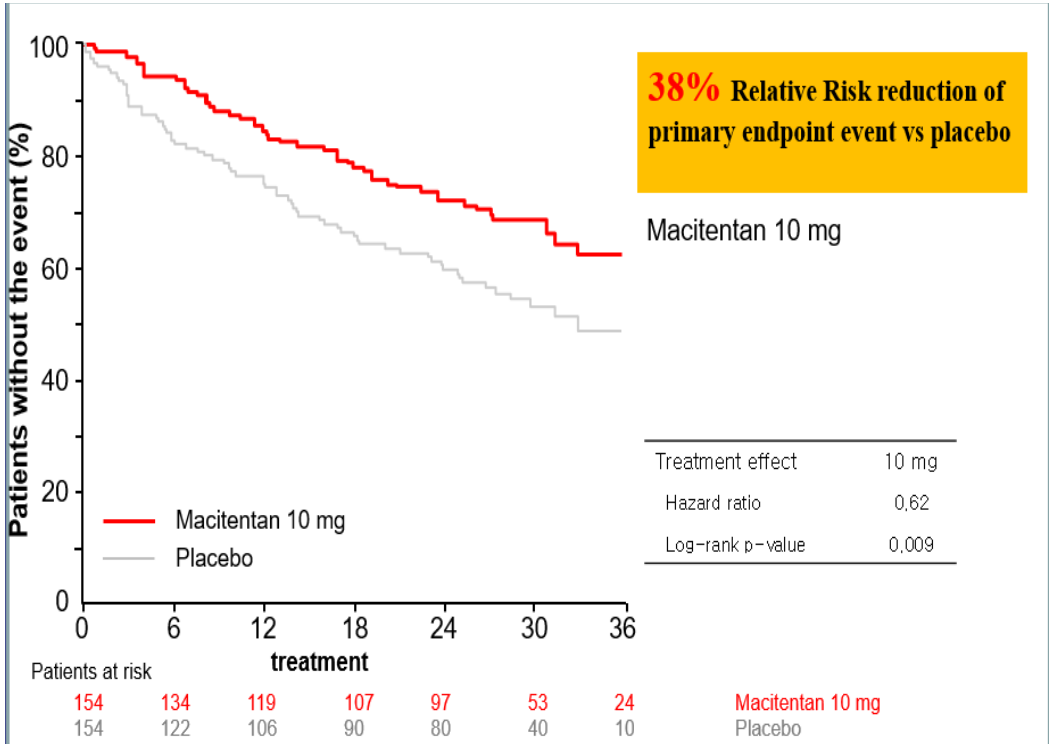


45% Relative Risk reduction of primary endpoint event vs placebo

Macitentan 10 mg

Treatment effect	10 mg
Hazard ratio	0,55
Log-rank p-value	< 0,001

Patients with background Therapy



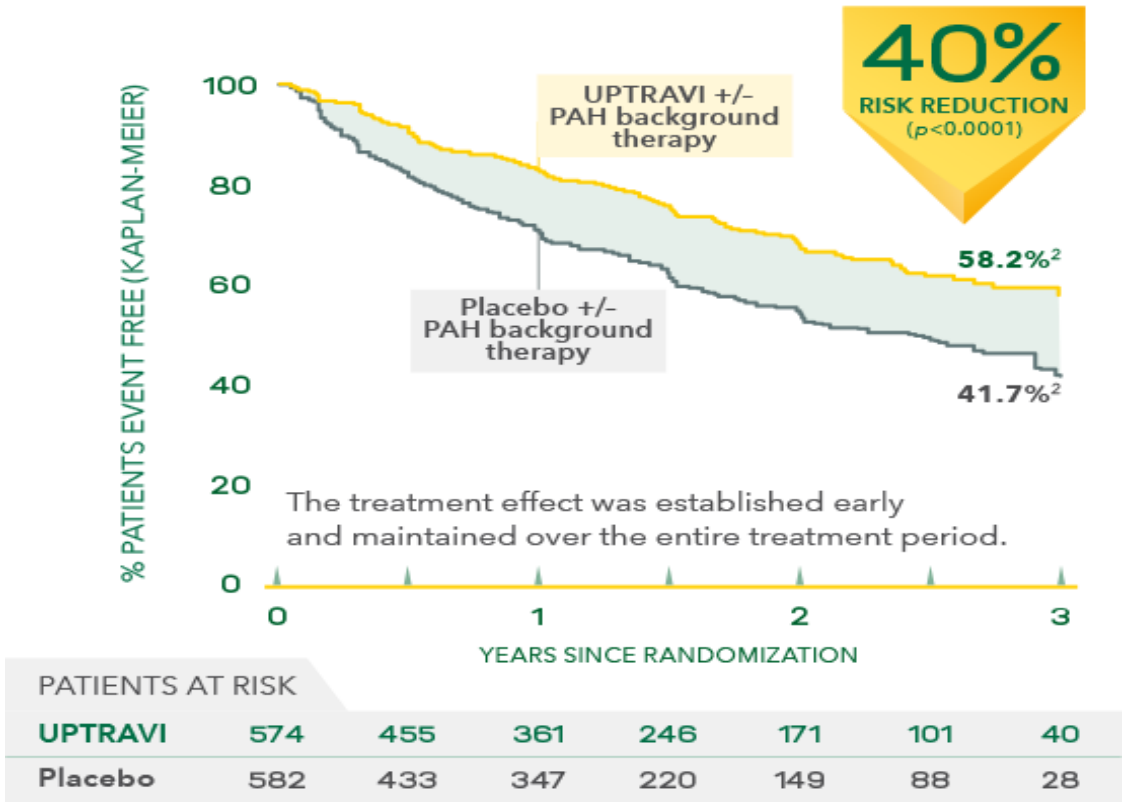
38% Relative Risk reduction of primary endpoint event vs placebo

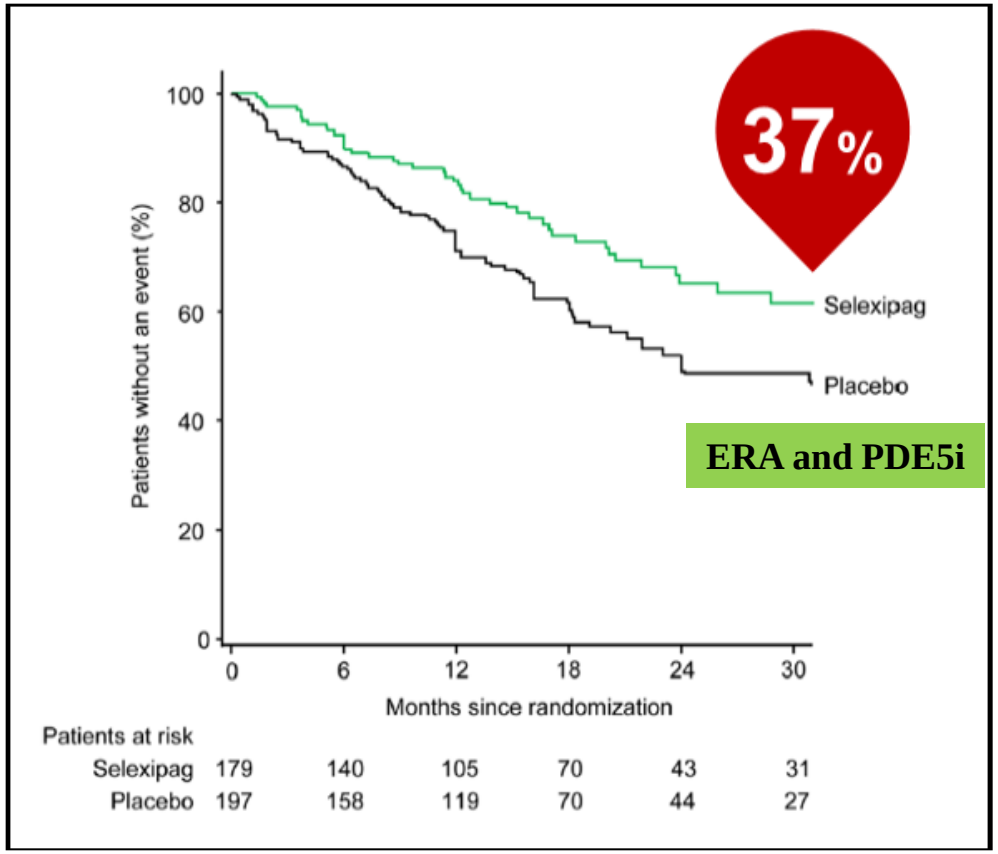
Macitentan 10 mg

Treatment effect	10 mg
Hazard ratio	0,62
Log-rank p-value	0,009

N Engl J Med 2013;369:809-18

Triple combination therapy: selexipag to ERA and PDE5i



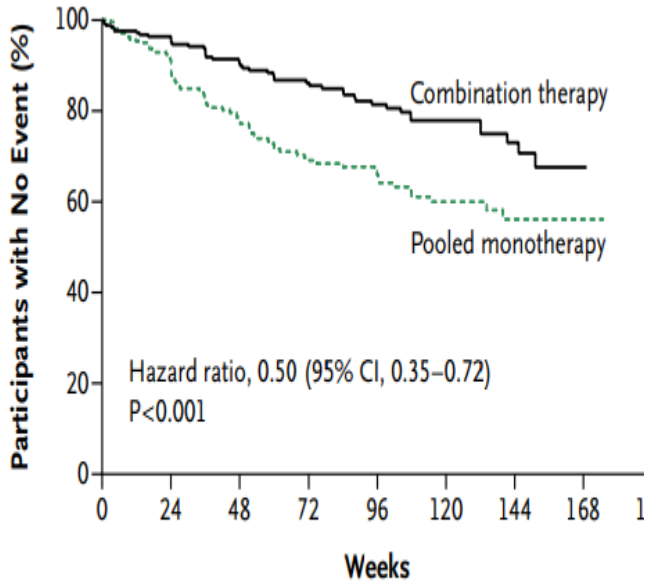


Sitbon O, et al N Engl J Med 2015;373:2522-2533

J. Gerry Coghlan , et al. Am J Cardiovasc Drugs 2018, 18;37-47

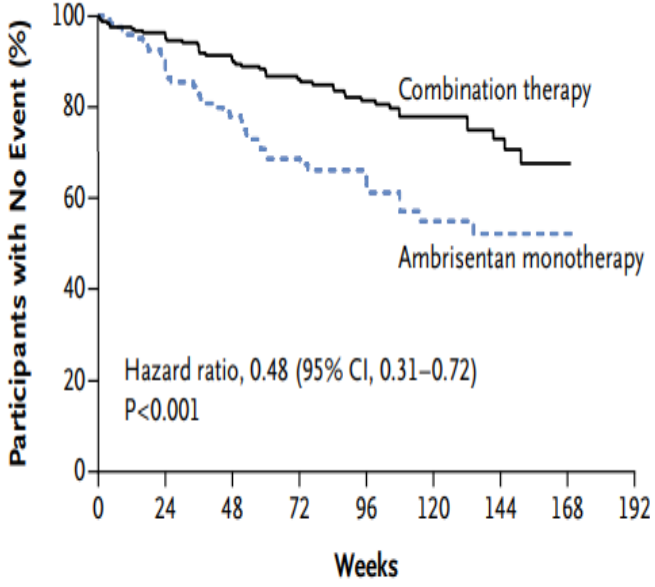
Initial (Upfront) combination therapy: Ambrisentan+Tadalafil

A Combination Therapy vs. Pooled Monotherapy



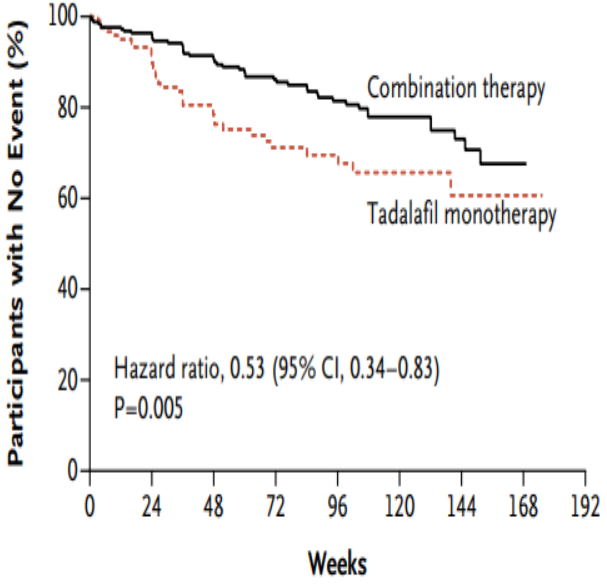
No. at Risk								
Combination therapy	253	229	186	145	106	71	36	4
Pooled monotherapy	247	209	155	108	77	49	25	5

B Combination Therapy vs. Ambrisentan Monotherapy



No. at Risk								
Combination therapy	253	229	186	145	106	71	36	4
Ambrisentan monotherapy	126	104	81	57	39	23	14	3

C Combination Therapy vs. Tadalafil Monotherapy

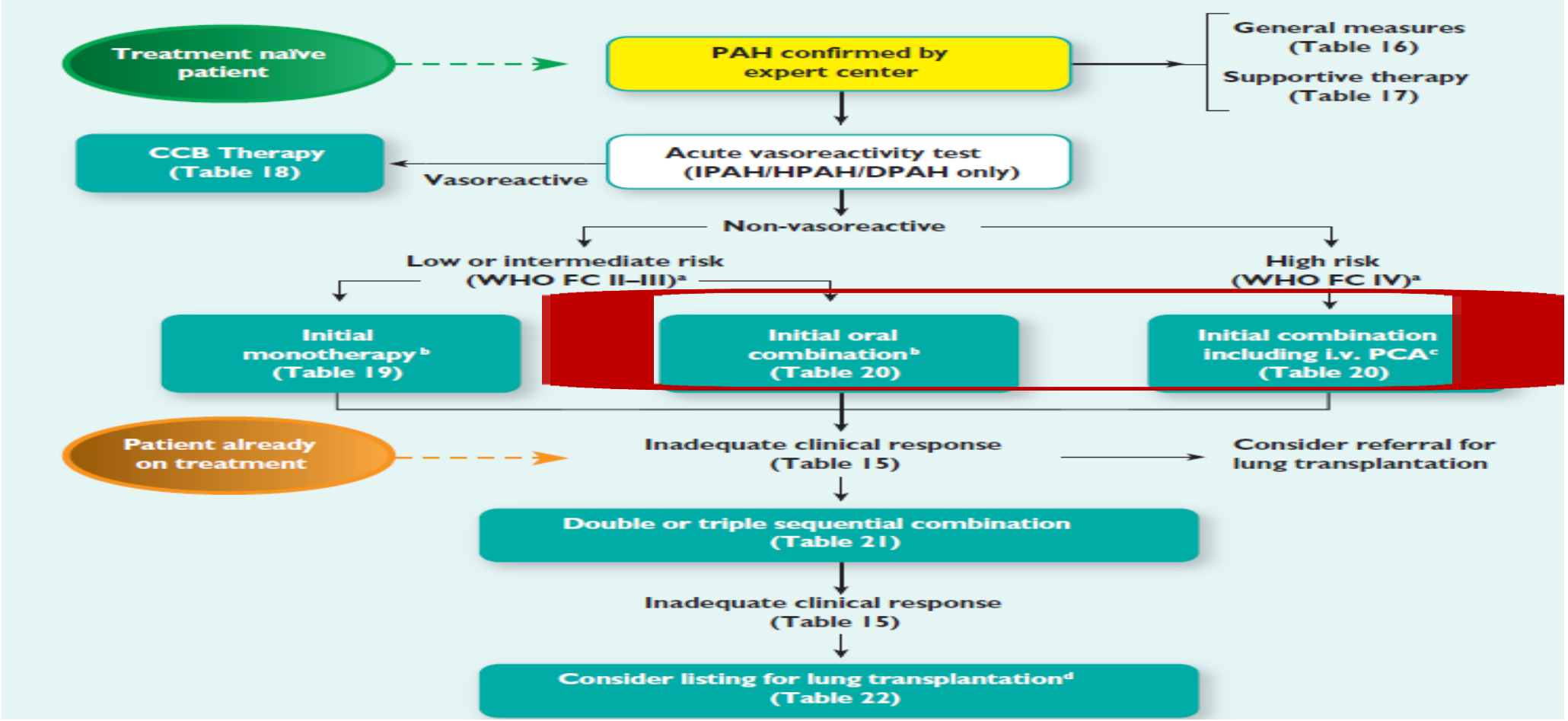


No. at Risk								
Combination therapy	253	229	186	145	106	71	36	4
Tadalafil monotherapy	121	105	74	51	38	26	11	2

Galie N et al. N Engl J Med 2015;373:834-44

ESC/ERS 2015 guidelines for PH

- Initial treatment based on risk stratification
- Initial combination treatment



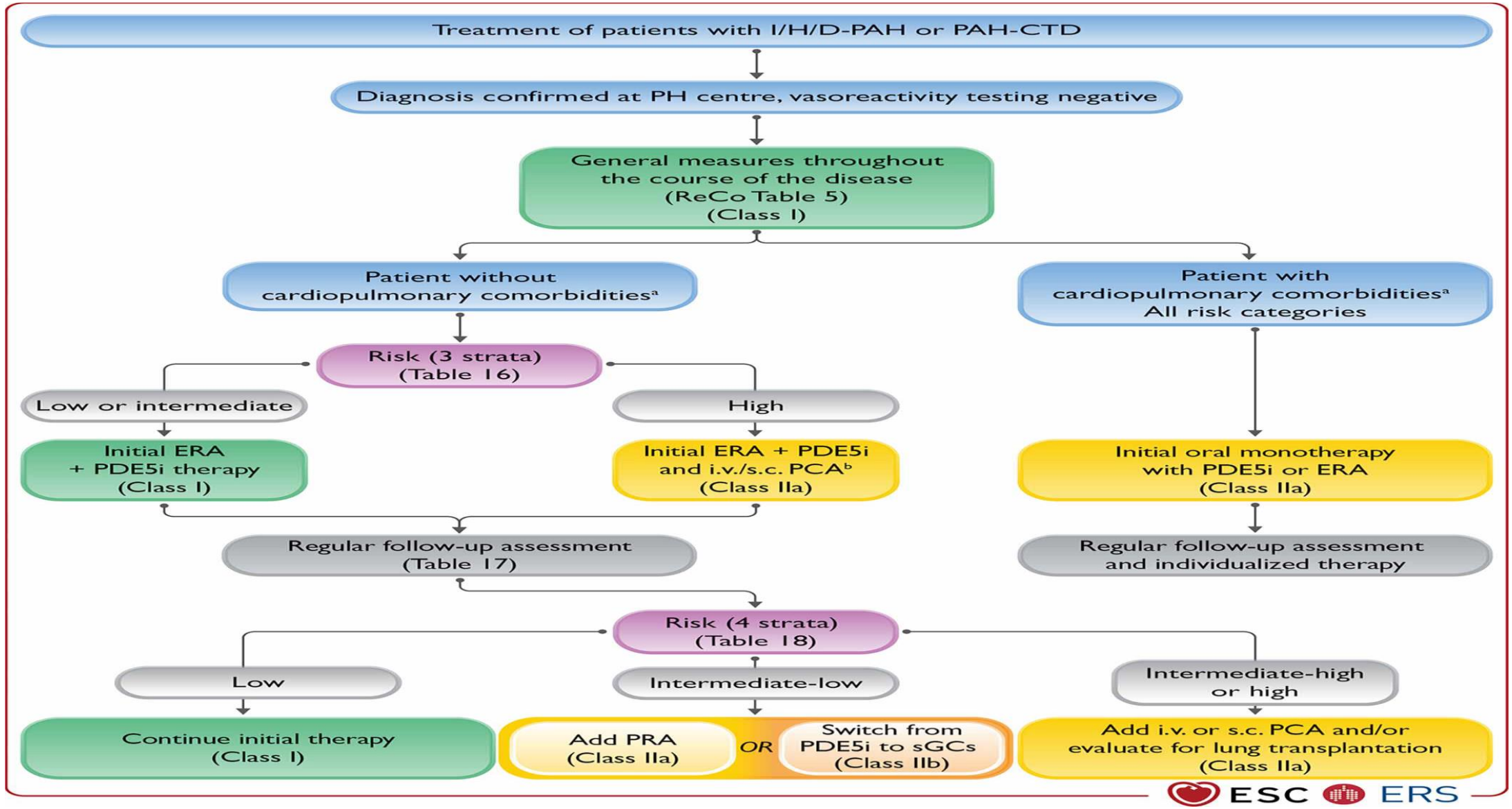
European Heart Journal (2016) 37, 67–119

Risk assessment in PAH

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

2015 ESC/ERS guidelines for PH

ESC/ERS 2022 guidelines for PH



Refined 4-strata risk assessment during f/u

Determinants of prognosis	Low risk	Intermediate-low risk	Intermediate-high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP, ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

2022 ESC/ERS guidelines for PH

Initial combination therapy for patients with idiopathic, heritable, or drug-associated PAH without cardiopulmonary comorbidities

- **Initial combination therapy with ambrisentan and tadalafil is recommended.(IB)**
- **Initial combination therapy with macitentan and tadalafil is recommended. (IB)**
- **Initial combination therapy with other ERAs and PDE5i should be considered. (IIaB)**
- **Initial combination therapy with macitentan, tadalafil, and selexipag is not recommended. (IIIB)**

Rationales for upfront triple combination therapy for intermediate risk

- **Minority of patients (about 30-40%) treated with upfront oral combination therapy reach low-risk status**
- **The timing of therapies matter; treatments are more efficacious early.**
- **Delay in PAH targeted therapy do not "catch up" to their earlier treatment.**
- **Clinical worsening that may trigger escalation is associated with increased mortality.**

Initial triple versus dual oral combination therapy in PAH

TRITON: Multicenter, double-blind, randomized, placebo-controlled, phase 3b study

Newly diagnosed, treatment-naive patients with pulmonary arterial hypertension (PAH)

n = 123	Macitentan 10 mg o.d.	Tadalafil 40 mg o.d.	Selexipag 200-1,600 µg b.i.d.
n = 124	Macitentan 10 mg o.d.	Tadalafil 40 mg o.d.	Placebo 200-1,600 µg b.i.d.

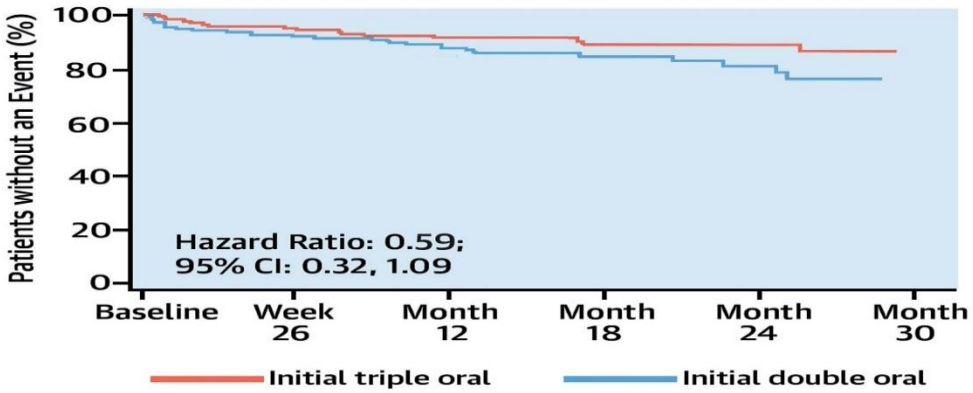
Change from Baseline to Week 26

	Initial triple	Initial double	Treatment effect
Primary Endpoint			
Pulmonary vascular resistance	-54%	-52%	No difference
Secondary Endpoints (Exploratory Analyses)			
6-Minute walk distance	+55 m	+56 m	No difference
NT-proBNP	-74%	-75%	

Time to First Disease Progression Event

Secondary Endpoints (Exploratory Analyses)

41% reduction in risk of disease progression with initial triple oral vs initial double oral combination therapy



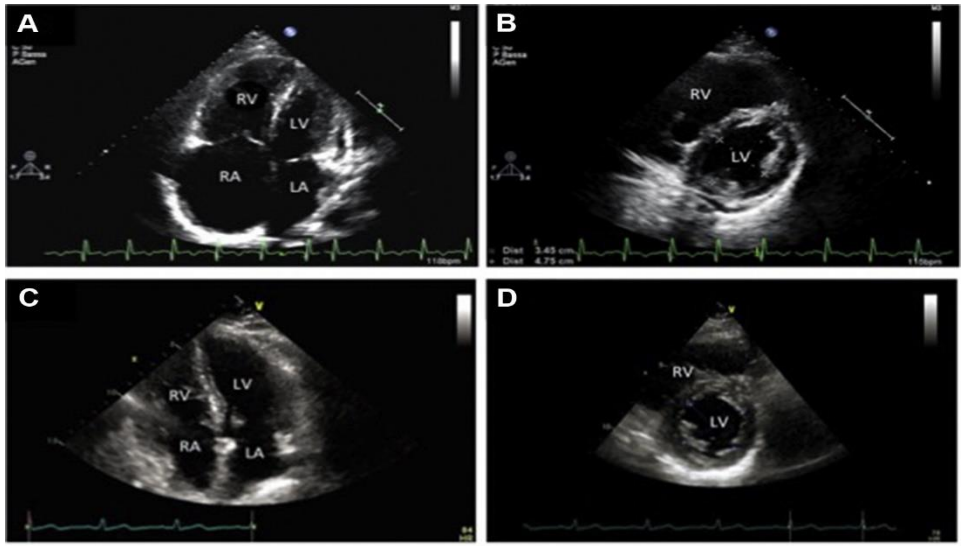
Chin, K.M. et al. J Am Coll Cardiol. 2021;78(14):1393–1403.

Right Heart Reverse Remodeling by Upfront Triple Combination Therapy in PAH

21 patients with newly diagnosed high-risk IPAH were treated upfront with a combination of ambrisentan, tadalafil, and subcutaneous treprostinil

Variable	Baseline	Follow-Up	Change (%)	*P* Value
Right-sided atrial area, cm^2	29 ± 3	21 ± 2	−8 (−28)	< .001
RV end-diastolic area, cm^2	28 ± 2	20 ± 3	−8 (−29)	< .001
RV end-systolic area, cm^2	21 ± 2	12 ± 2	−9 (−43)	< .001
Fractional area change, %	27 ± 4	40 ± 5	13 (63)	< .001
LV eccentricity index	1.5 ± 0.1	1.2 ± 0.1	−0.3 (−20)	< .001

Variable	Baseline	Follow-Up	Change (%)	*P* Value
RAP, mm Hg	13 ± 3	5 ± 2	−8 (−62)	< .001
mPAP, mm Hg	60 ± 9	42 ± 5	−18 (−30)	< .001
PAWP, mm Hg	8 ± 2	9 ± 3	1 (12)	.545
Cardiac input, $L/min/m^2$	1.8 ± 0.3	3.5 ± 0.8	1.7 (94)	< .001
PVR, WU	16.4 ± 4.4	5.5 ± 1.3	−10.9 (−69)	< .001
Svo_2, %	56 ± 6	70 ± 7	14 (25)	< .001

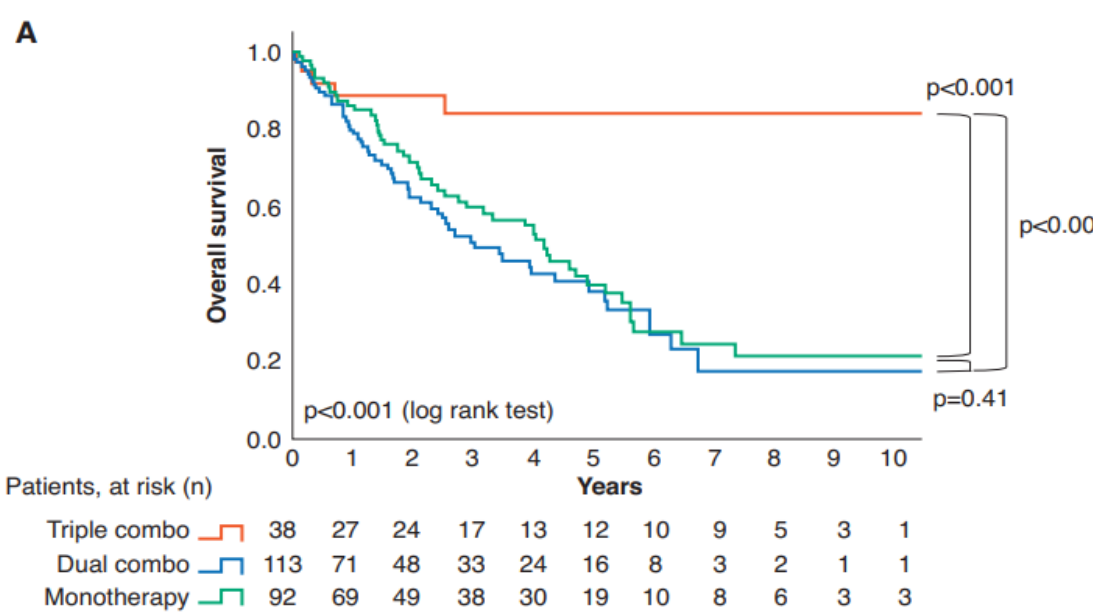


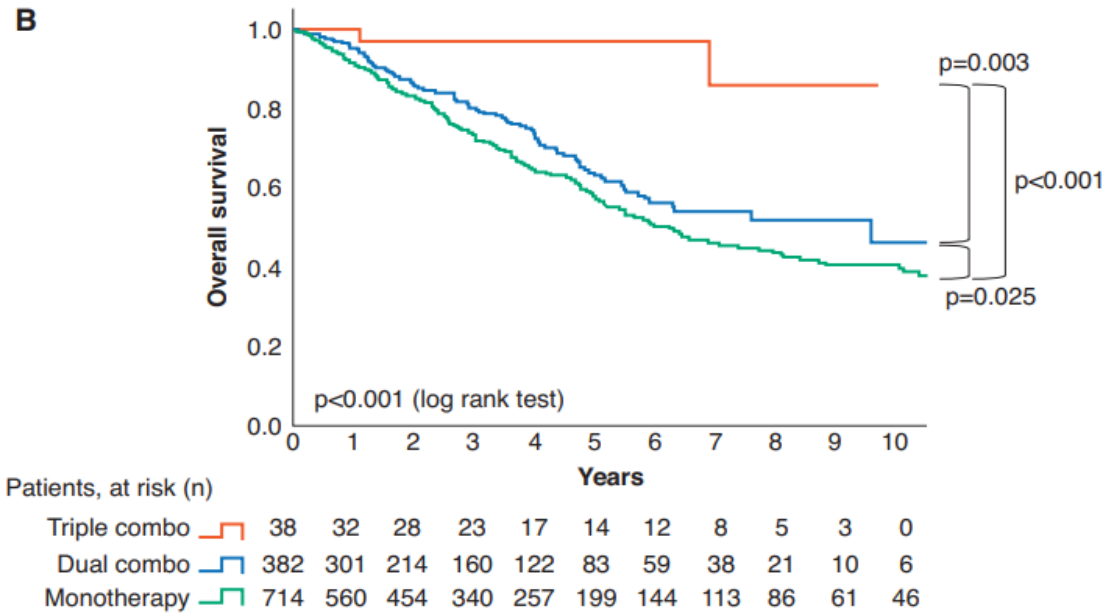
	Baseline	Follow-up
PVR (WU)	17.9	6.1
RVEDA (cm^2)	26	17
RVESA (cm^2)	19	10
LV-EI	1.5	1.1
REVEAL 2.0	11	7

D'Alto M, et al. CHEST 2020; 157(2):376–383

Initial triple-combination therapy with parenteral prostacyclin

- A retrospective analysis of incident patients with idiopathic, heritable, or anorexigen-induced PAH enrolled in **the French Pulmonary Hypertension Registry**





A) Patients with a high-risk status

(B) patients with an intermediate-risk status

Boucly A, et al. Am J Respir Crit Care Med. 2021;204-842-54

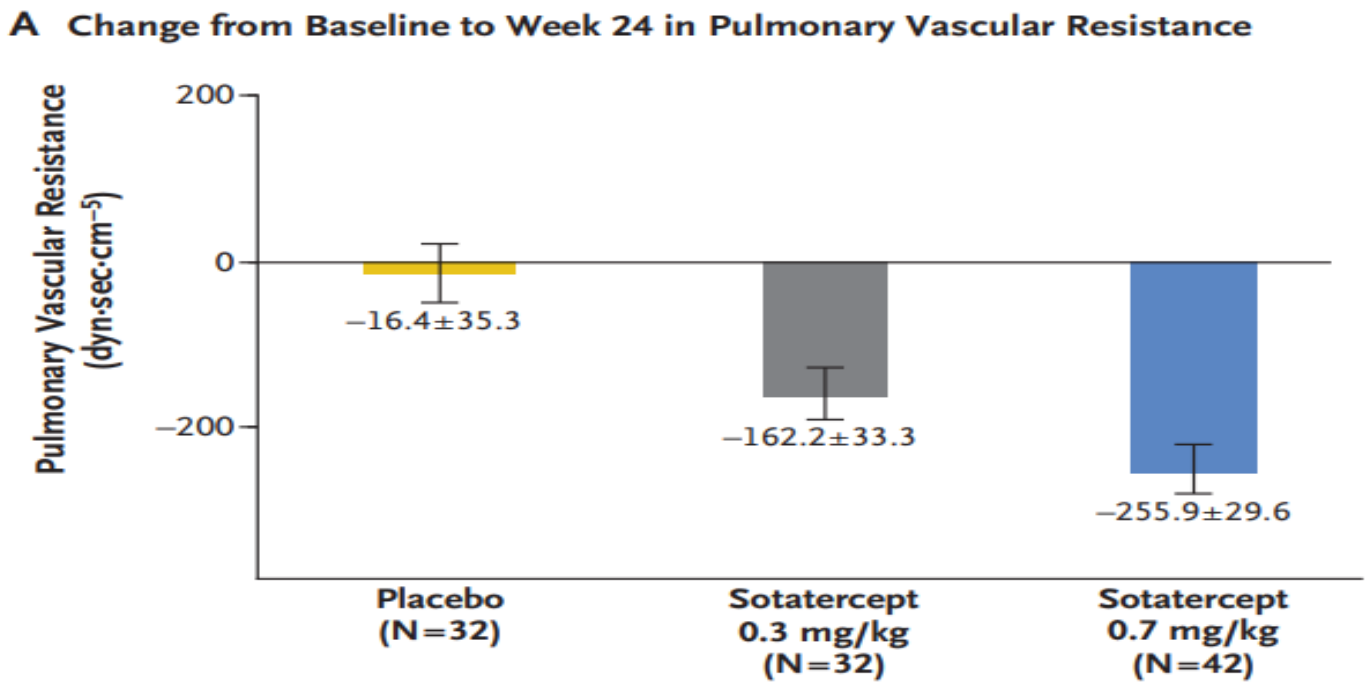
Sotatercept: the PULSAR trial

Inclusion(n=106): **IPAH (58%), Heritable (16%), CTD(17%).** **Drug(7%), CHD (3%)**

FC II (53%), III (47%)

Mono (9%), dual (35%), Triple (56%), IV/SC PCA (37%)

Design: 24 weeks, double-blind, placebo-controlled multicenter



Humbert M, et al. N Engl J Med 2021;384:1204-1215

Sotatercept: the STELLAR trial

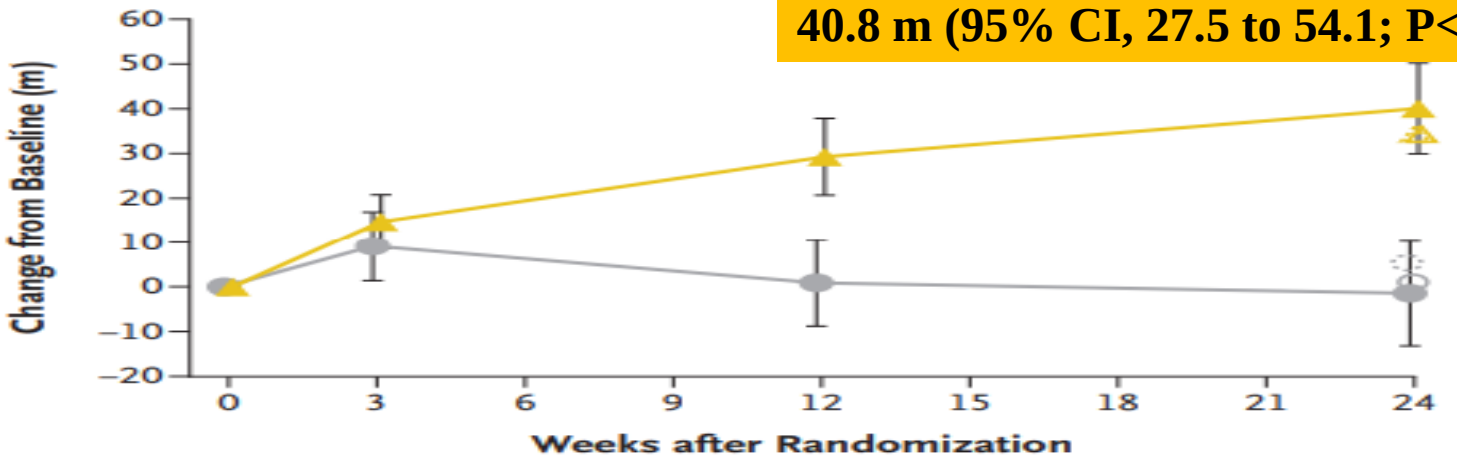
Inclusion(n=323): **IPAH (58%),** Heritable (18%), CTD(15%). Drug(3%), CHD (5%)

FC II (49%), III (51%)

Mono (4%), dual (34%), **Triple (61%), IV/SC PCA (40%)**

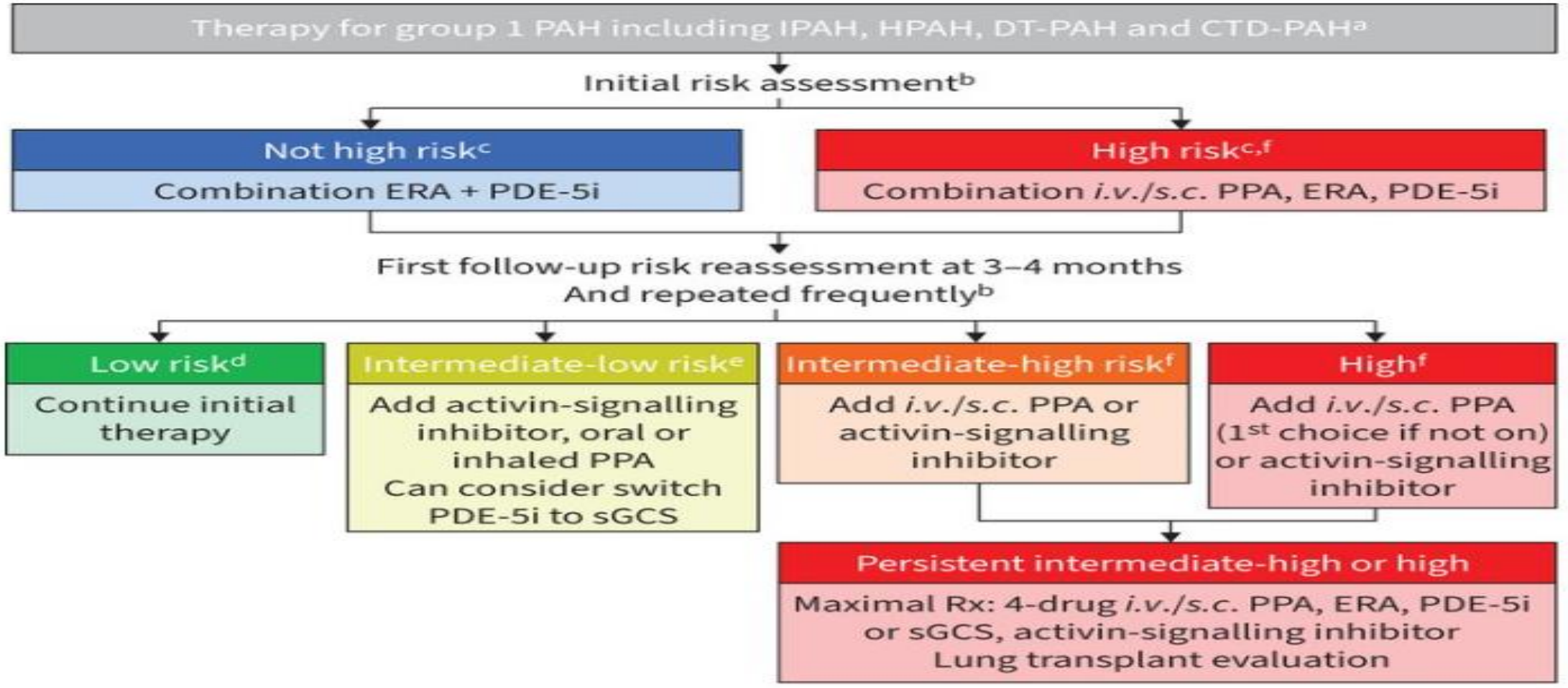
Design: 24 weeks, double-blind, placebo-controlled multicenter

40.8 m (95% CI, 27.5 to 54.1; P<0.001)



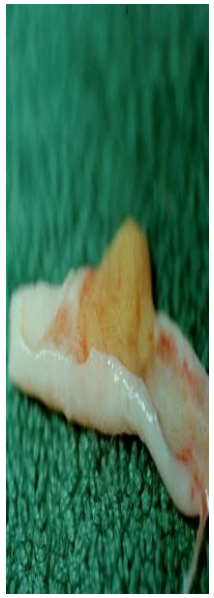
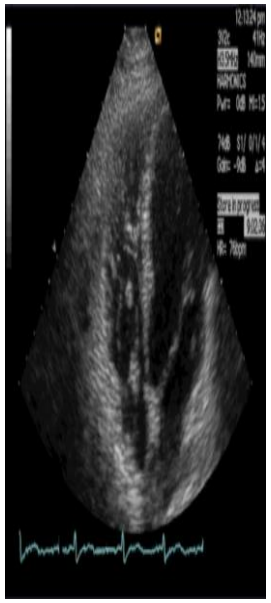
Hoeper MM, et al. N Engl J Med 2023;388:1478-90.

2024 7th World symposium on PH

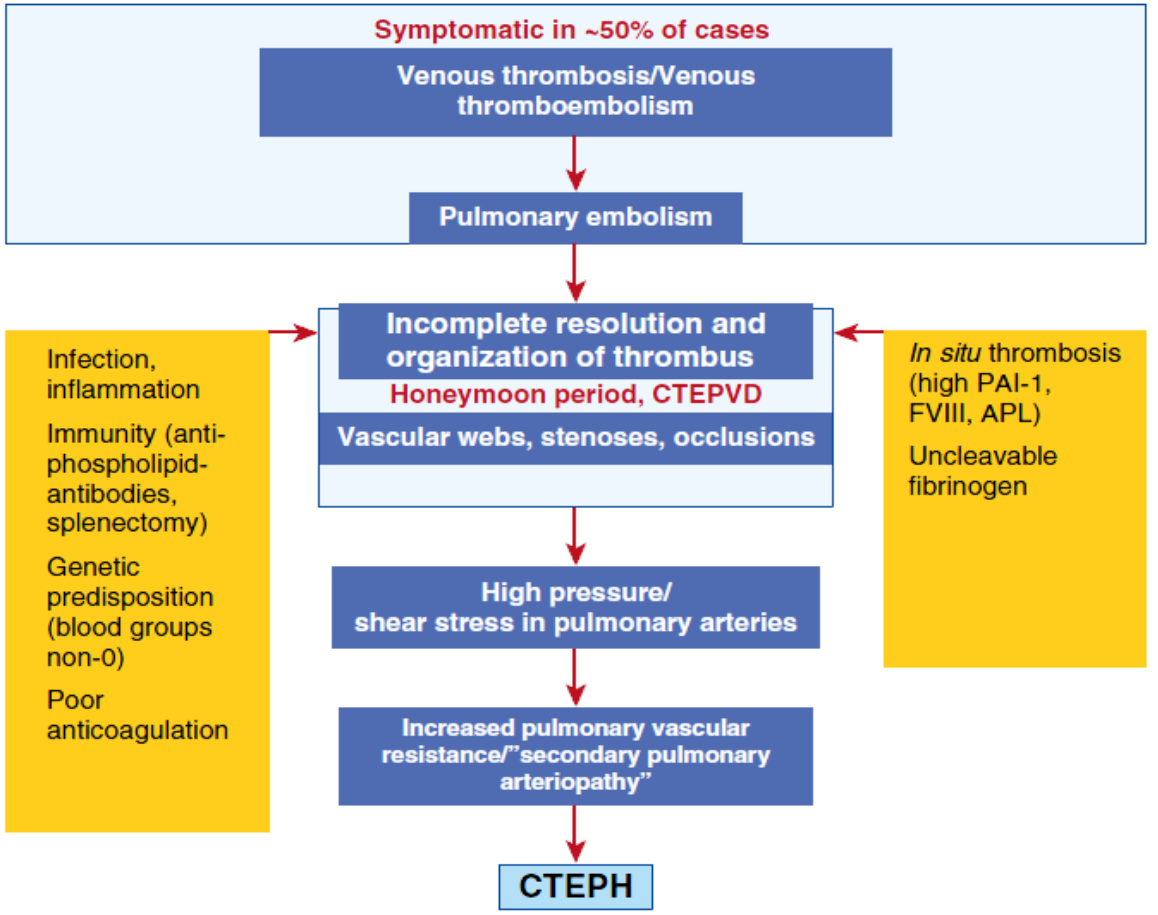


Chin KM, et al. Eur Respir J 2024; in press: 2401325

Chronic thromboembolic pulmonary hypertension (CTEPH)

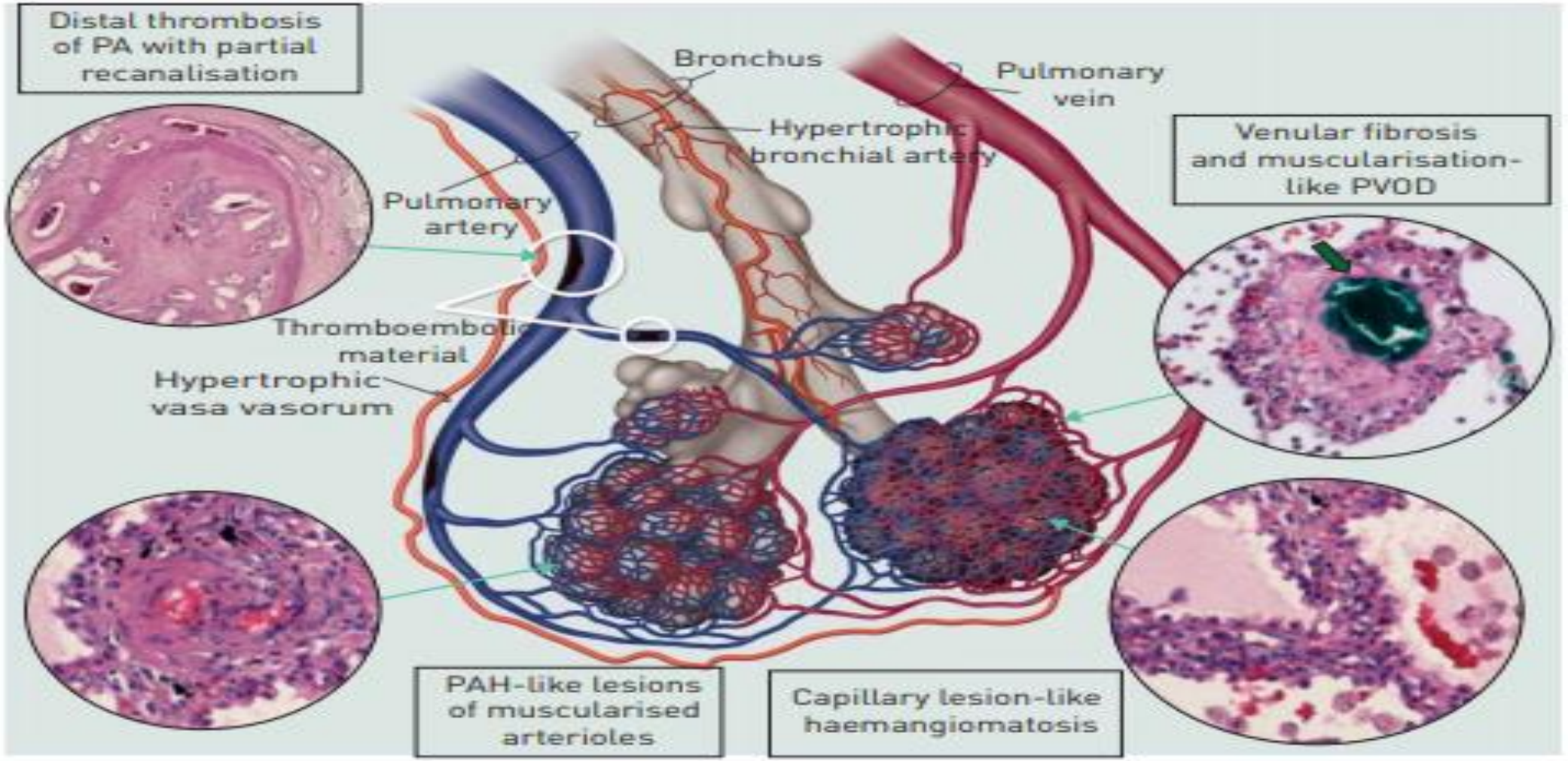



DVT EMBOLUS IN TRANSIT **ACUTE PE** **CTEPH**



Lang I M, , et al. Ann Am Thorac Soc 2016;13:S215-221

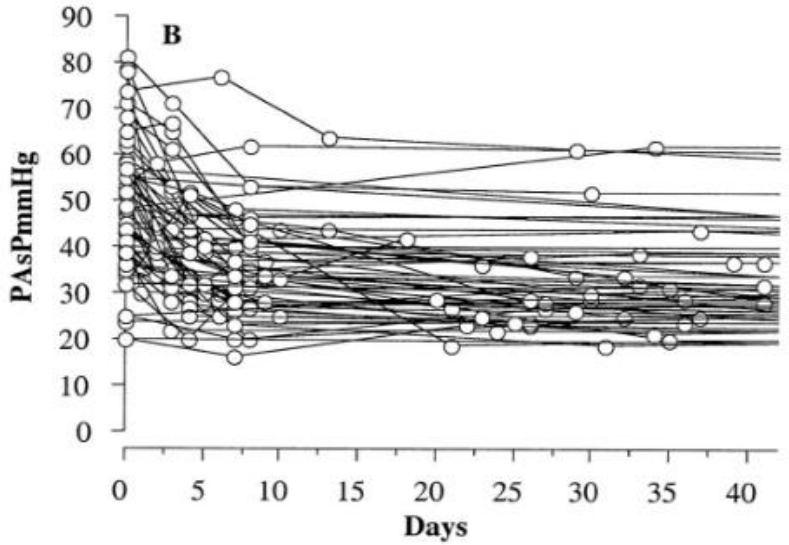
Microvasculopathy in CTEPH

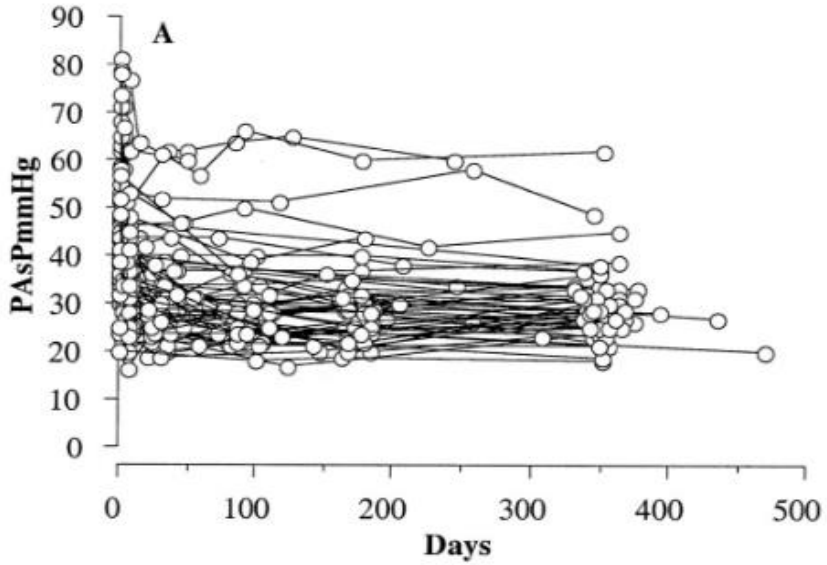


Dorfmuller P, et al. Eur Respir J 2014; 44: 1275–1288

Pulmonary artery systolic pressure after acute PE

Initial dynamic (exponential) phase and a late stable (linear) phase.
The stable phase appeared start **1 month after diagnosis of acute PE**.

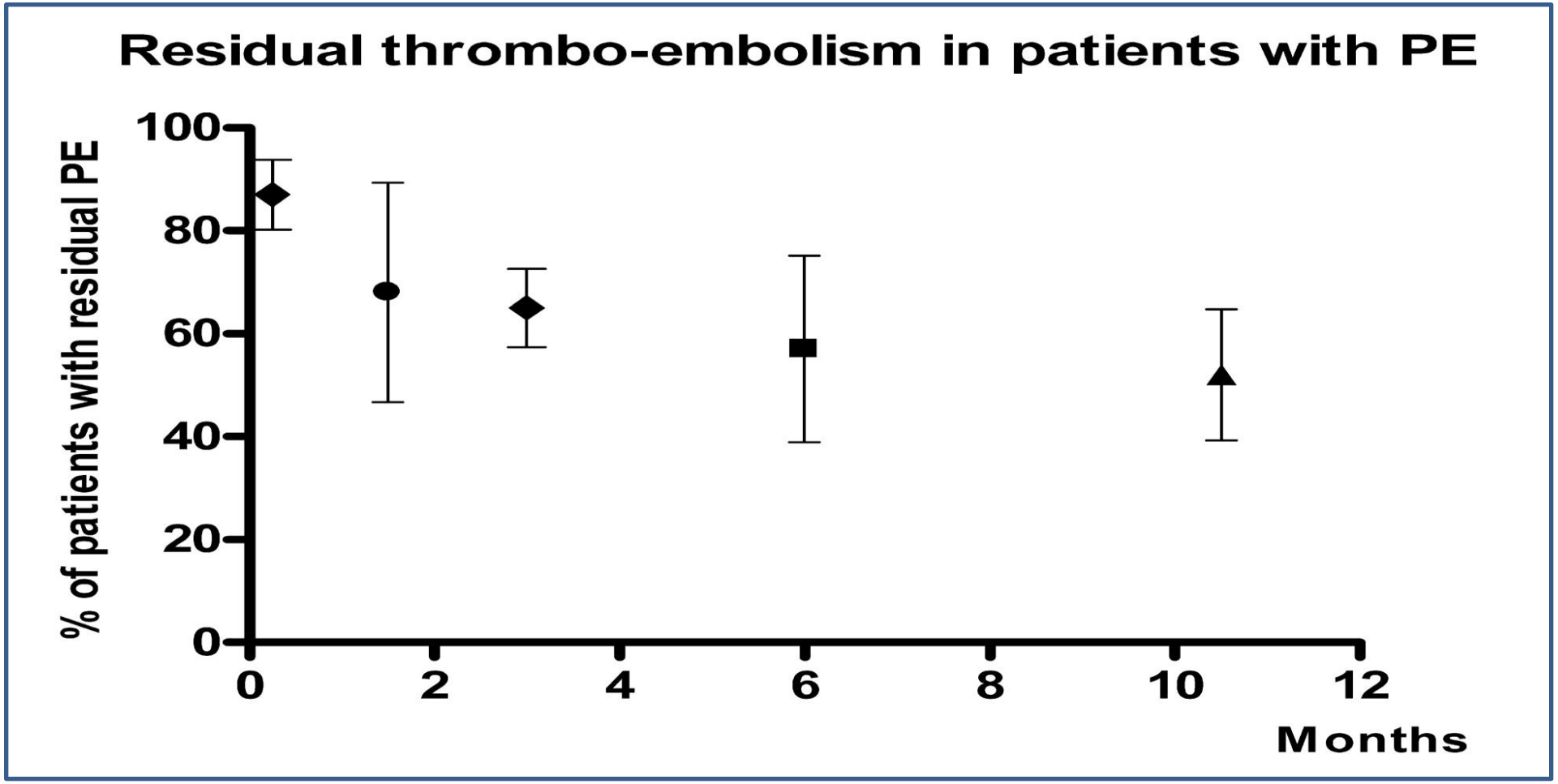




A sPAP of >50 mmHg at the time of diagnosis of acute PE was associated with persistent PH after 1 year.

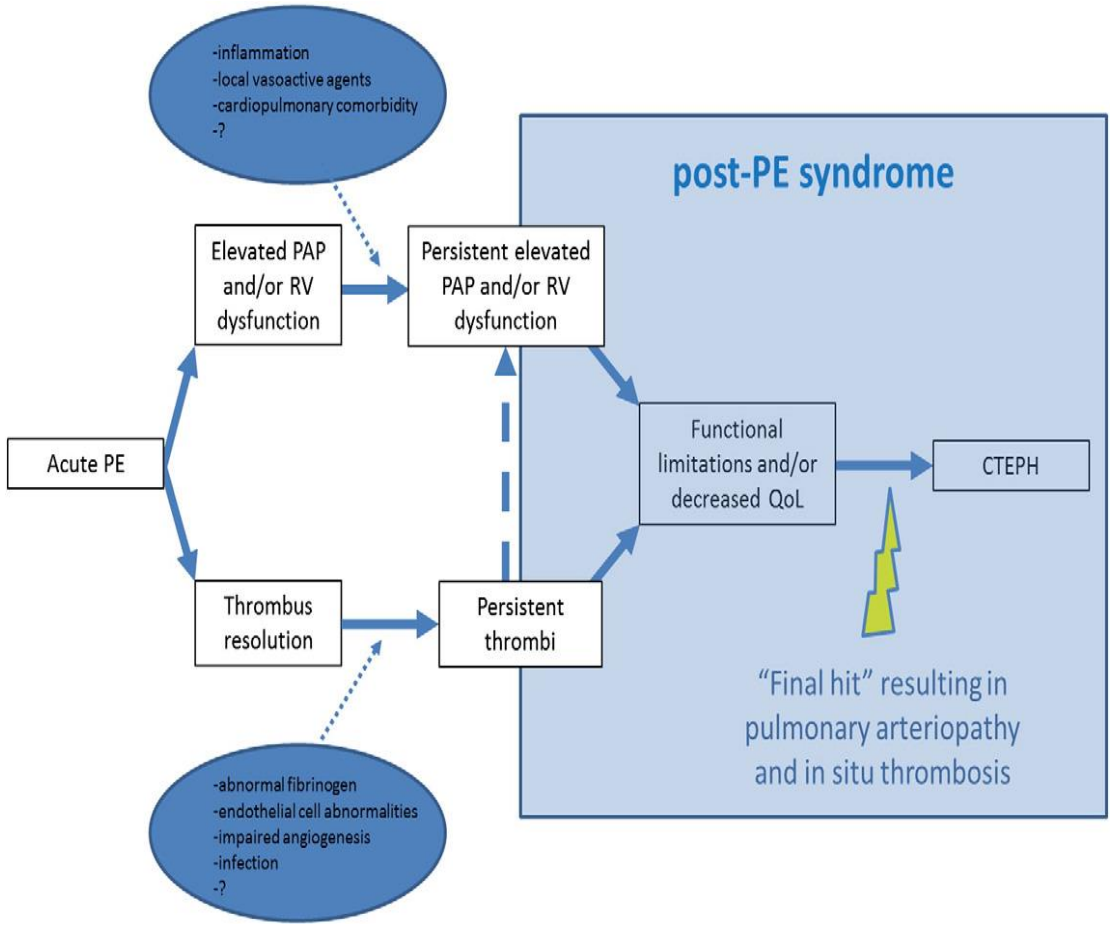
Ribeiro A, et al. Circulation1999 Mar 16;99(10):1325-30

Persistent perfusion defect after Acute PE

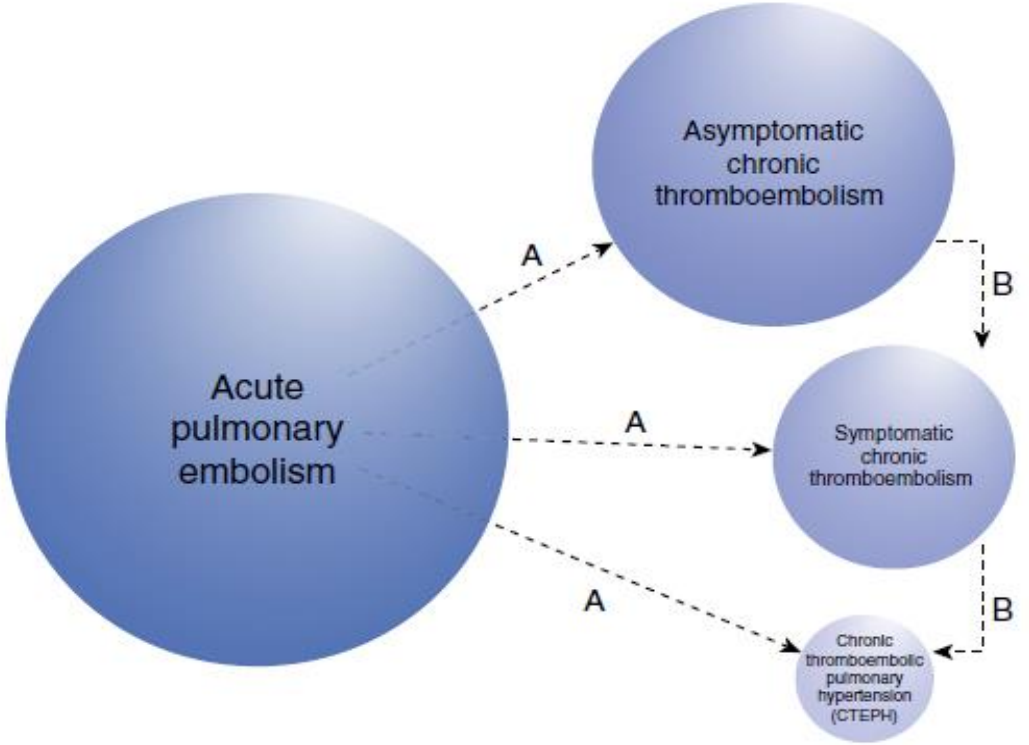


Nijkeuter, M. et al. Chest 2006;129:192-197

The post-PE syndrome, CTEPD and CTEPH



Klok FA, et al. Blood Reviews 28 (2014) 221–226



Kim NH and Simonneau G. Ann Am Thorac Soc 2016;13:S255–258

Case 22/F Acute PE

2022.03.16 acute PTE로 thrombolysis

Family history of VTE: grandfather, father, aunt

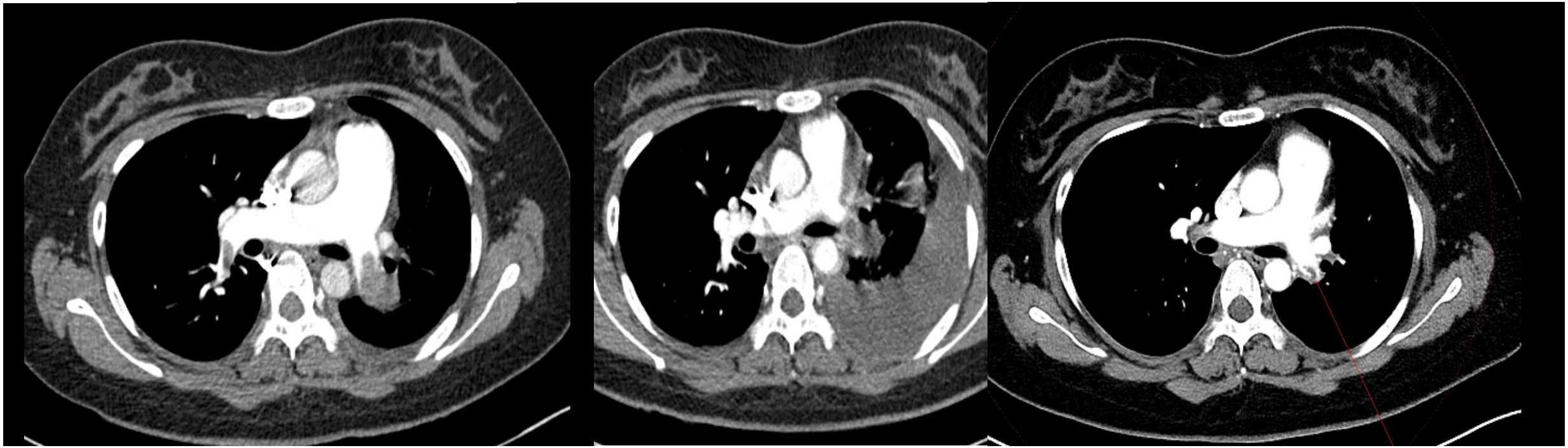
Anti-thrombin 47%

SERPINC1 gene sequencing:

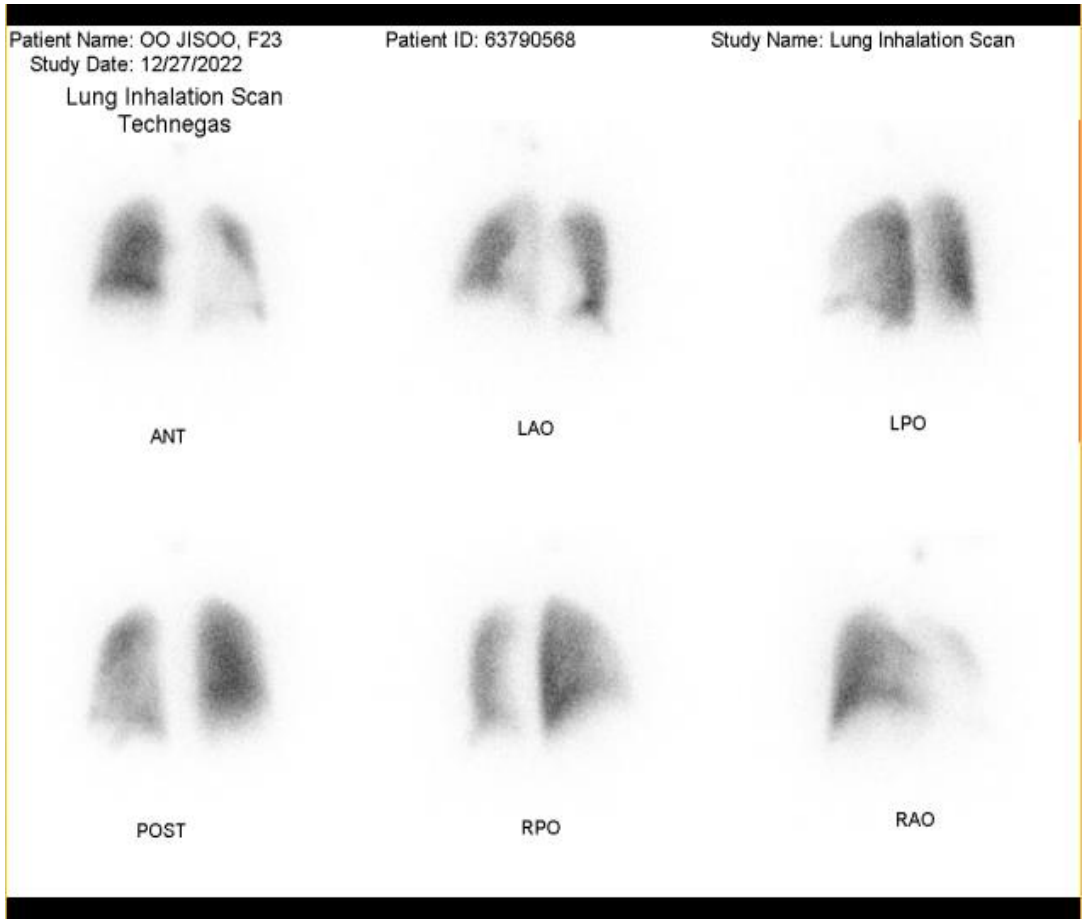
Genetic Variants Observed

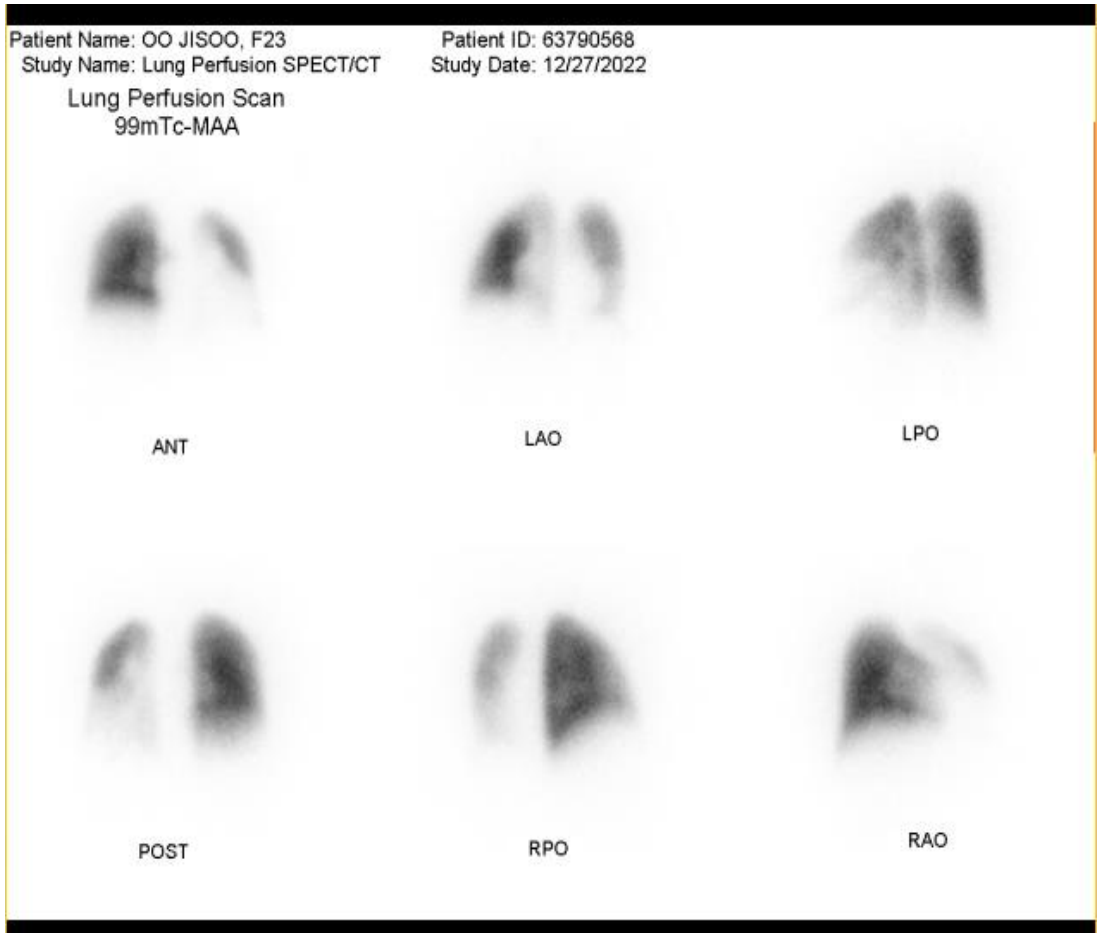
Base Change	AA Change	Designation	Pathogenicity
c.409_414delGTATTT	p.V137_F138del	Heterozygous	Likely pathogenic

2022.03.16 2022.04.02 2022.11



V/Q scan





Large V/Q mismatched perfusion decrease in LLL and LUL lingular division

Case 22/F CTEPD

Echocardiography (2022.07)

1. **Decreased RV free wall contractility**
2. **No evidence of pulmonary hypertension (TRVmax 2.1m/s)**

PFT

FVC 2.23L (57% pred.)

FEV1 2.02L (61% pred.)

DLco: 51% pred. DL/VA 92% pred.

6MWT: 560m (98 -> 91%)

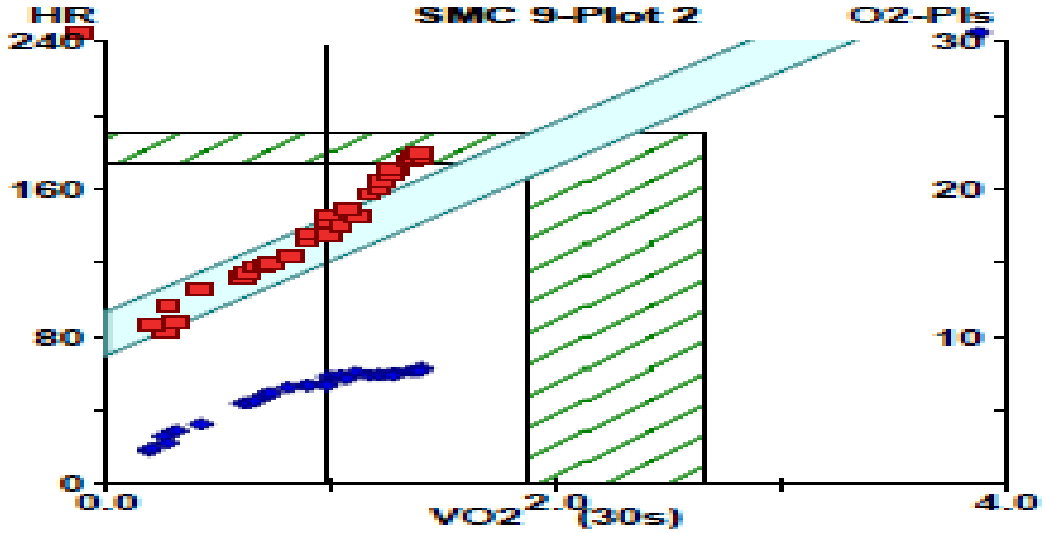
- CPET:

  Work 86W (Borg dyspnea scale 9)

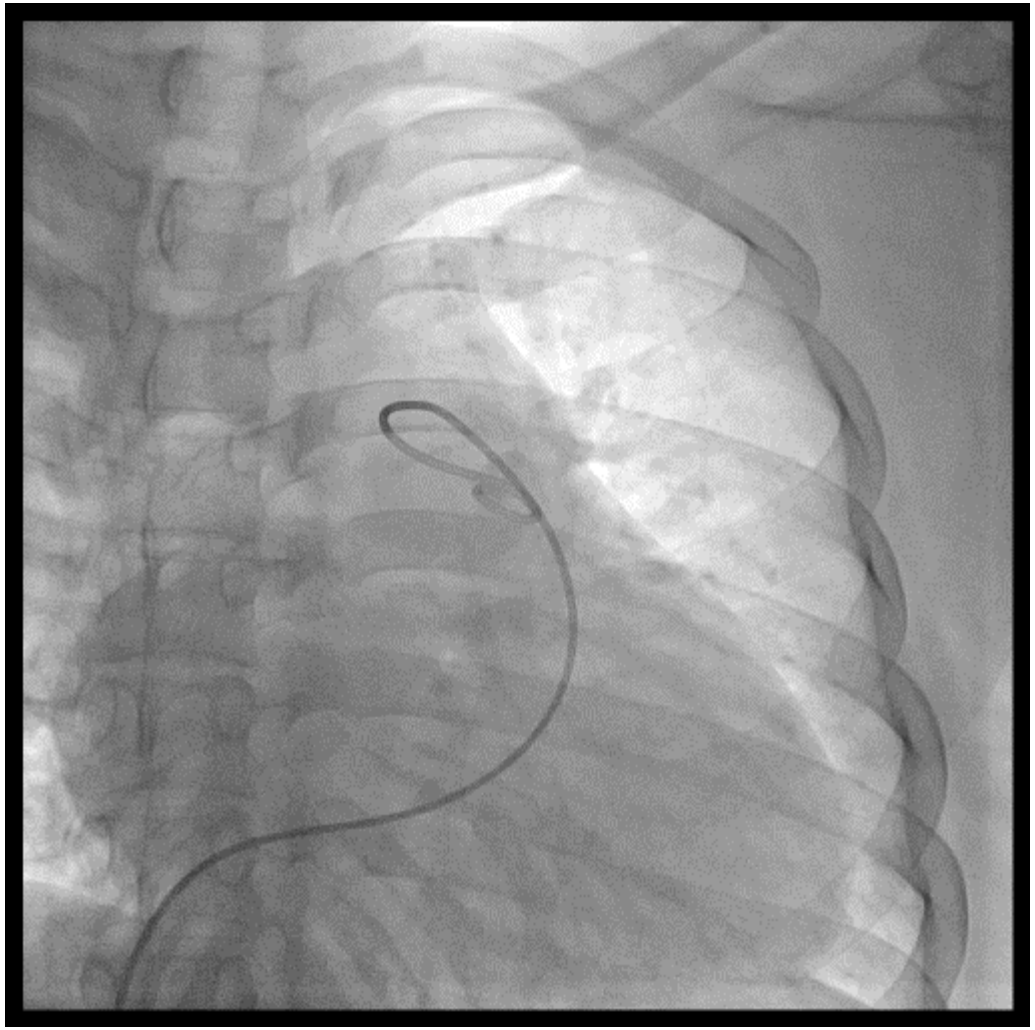
  VO2max 17.8ml/kg/min (54% pred.)

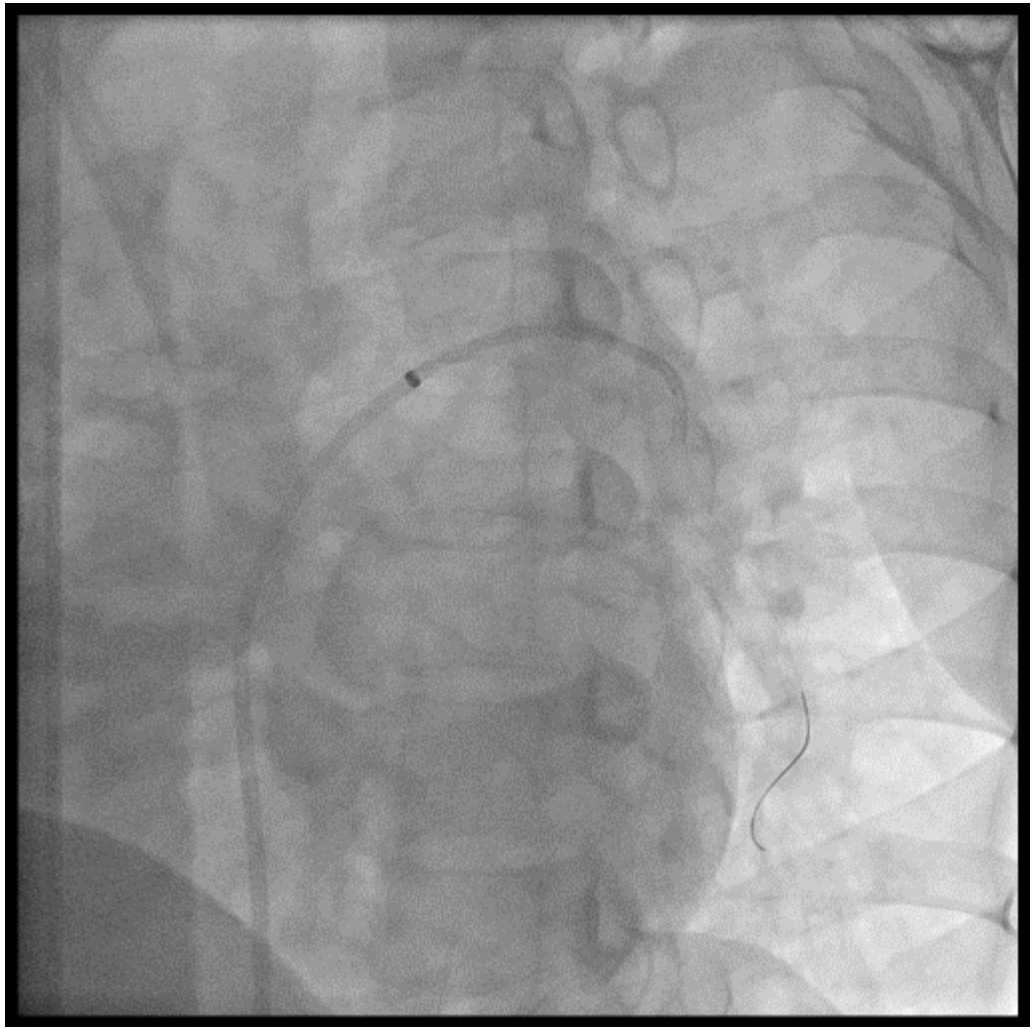
  O2pulse 7.9ml/min (72% pred.)

  SpO2 98 -> 91%

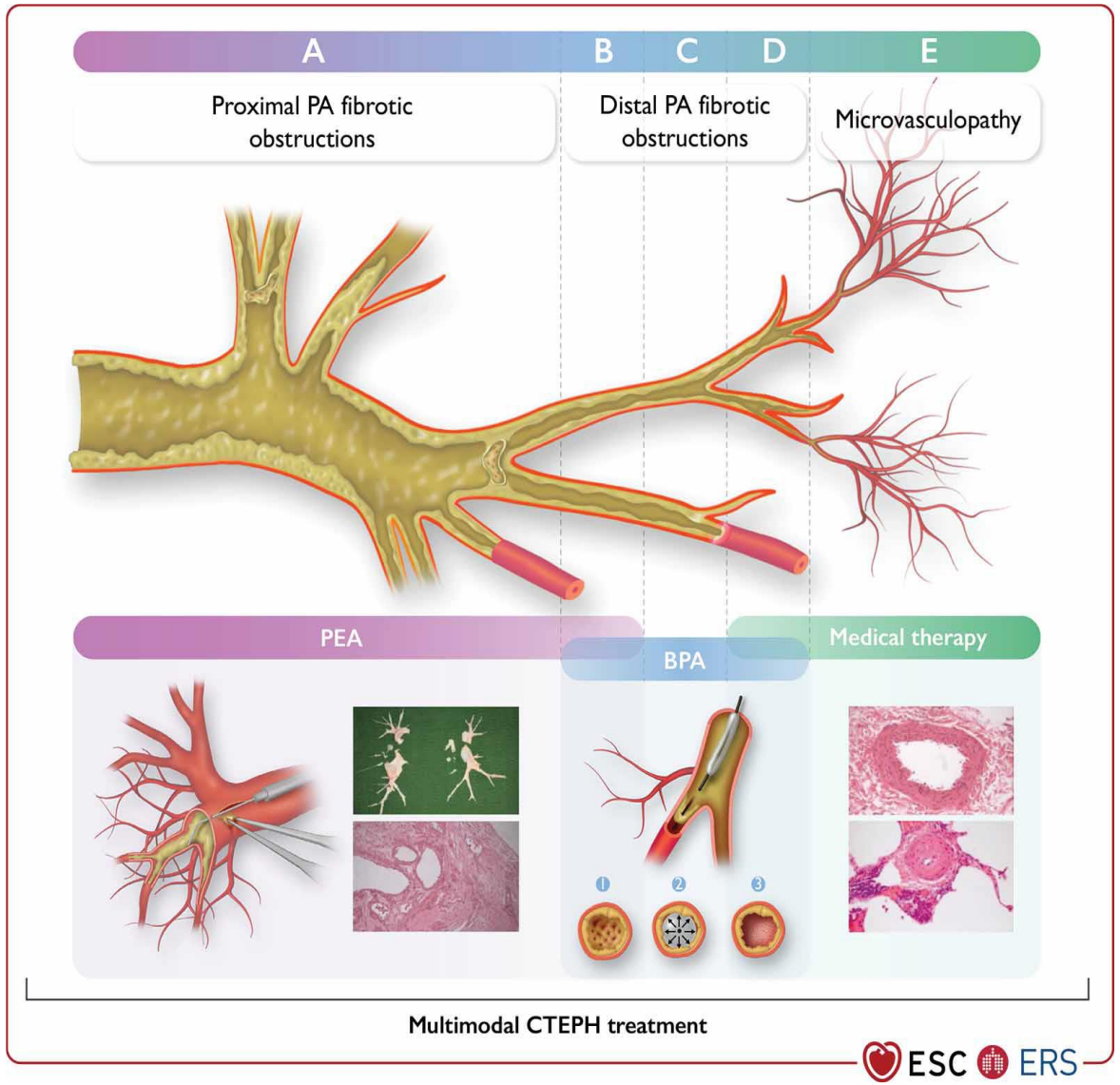


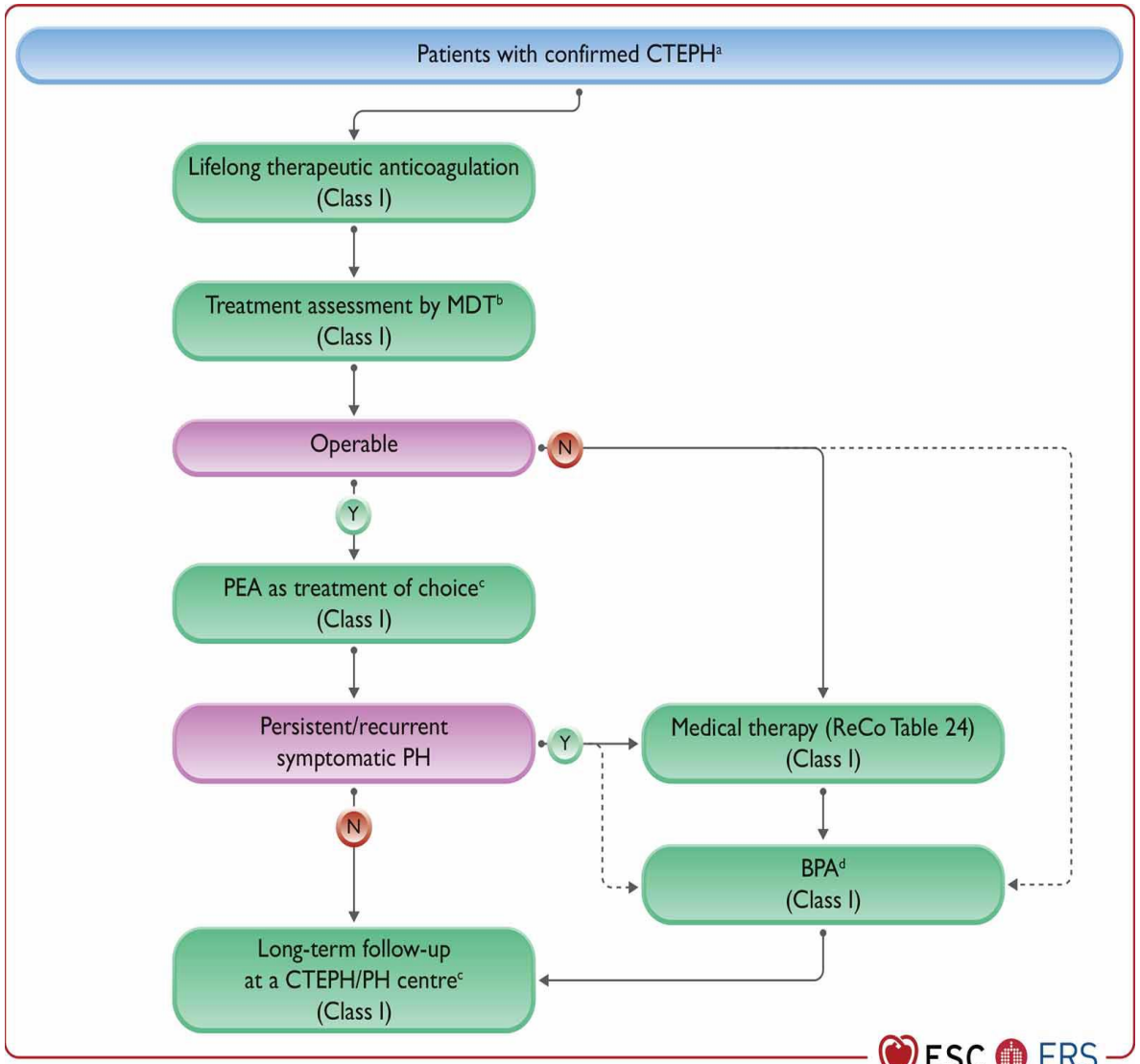
Pulmonary angiography





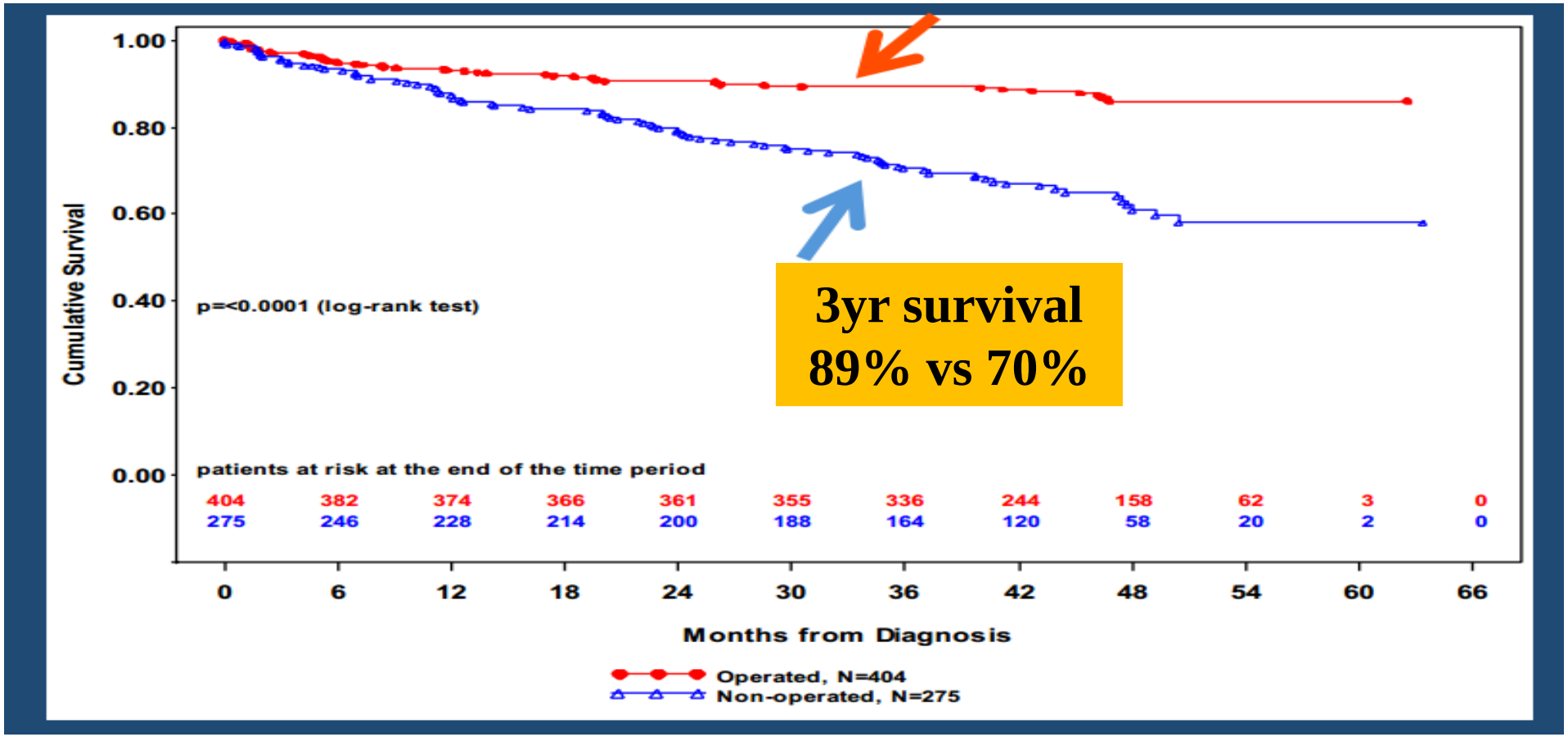
The management options for CTEPH





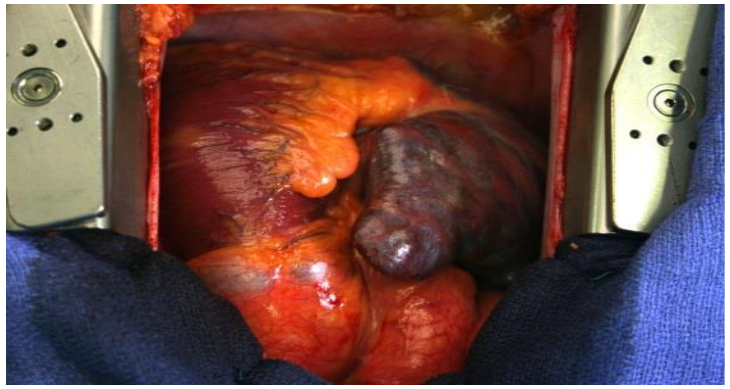
CTEPH: Surgical PH

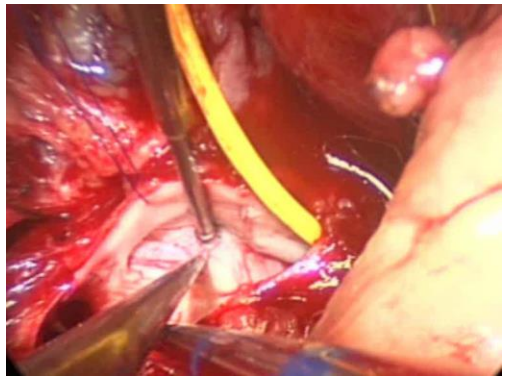
Results From an International Prospective Registry

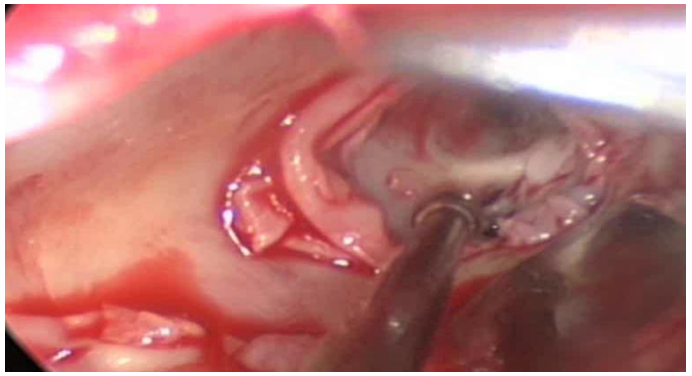


Delcroix M, et al. Circulation. 2016;133:859–871

Pulmonary endarterectomy (PEA)



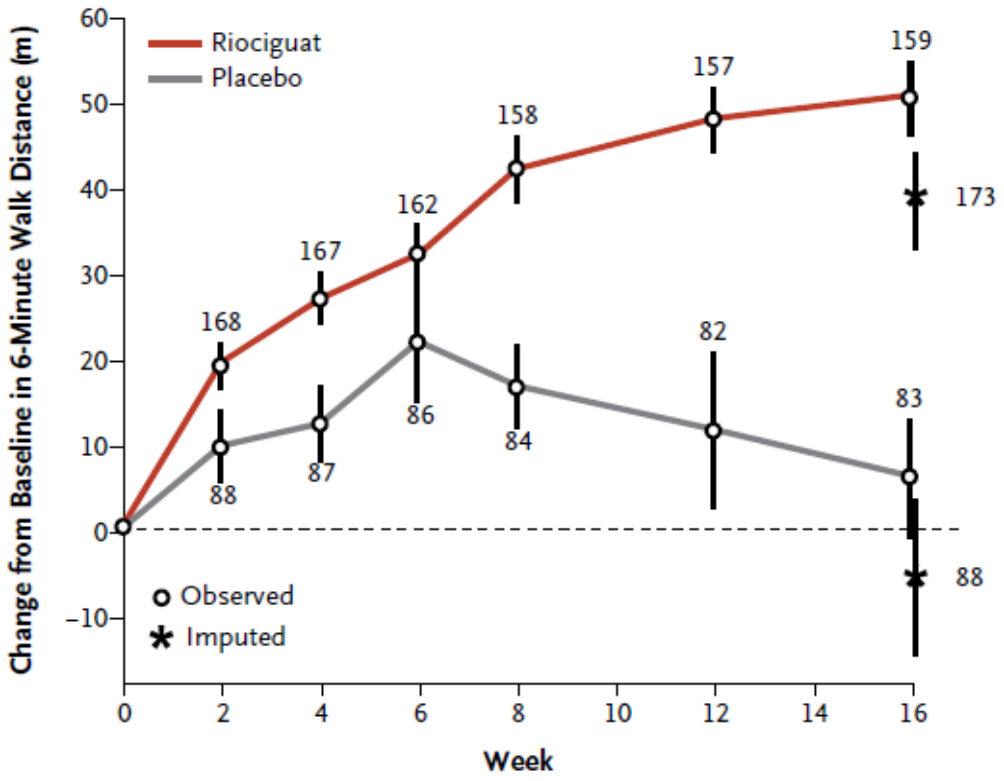




- 정중 흉골절개술
- 인공심폐기 통한 체외순환
- 저체온 (20° C)
- 삼장 정지 (20 분)
- 폐동맥의 혈전 제거 및 내막 박리

Riociguat for CTEPH

Inclusion: Inoperable (189), Post-PEA (72)

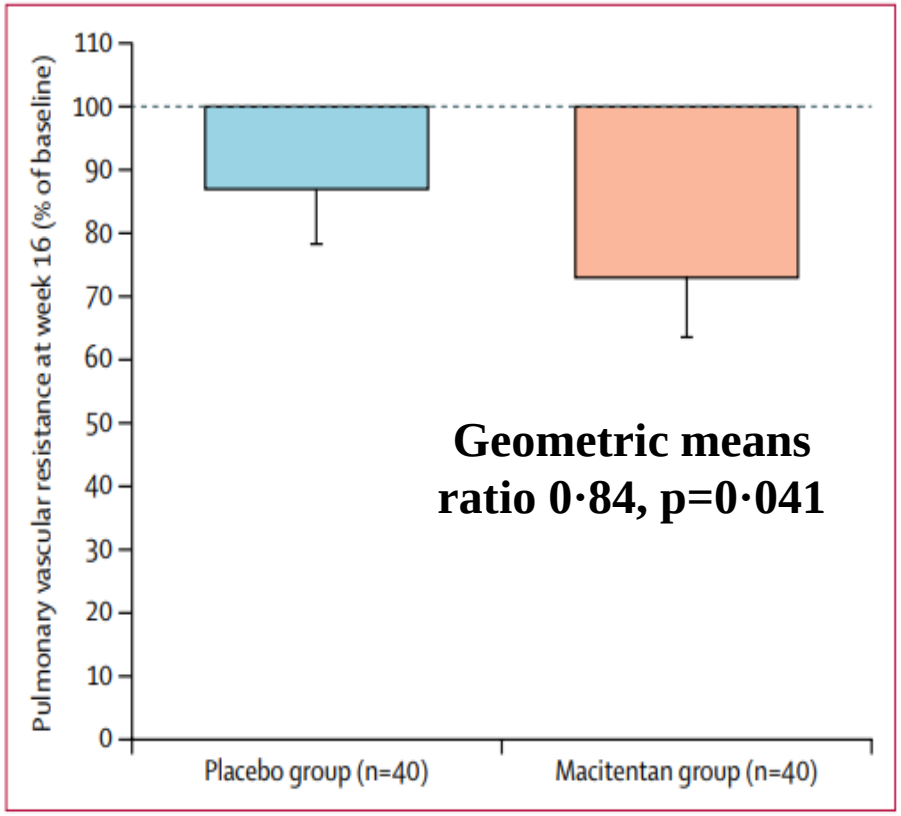


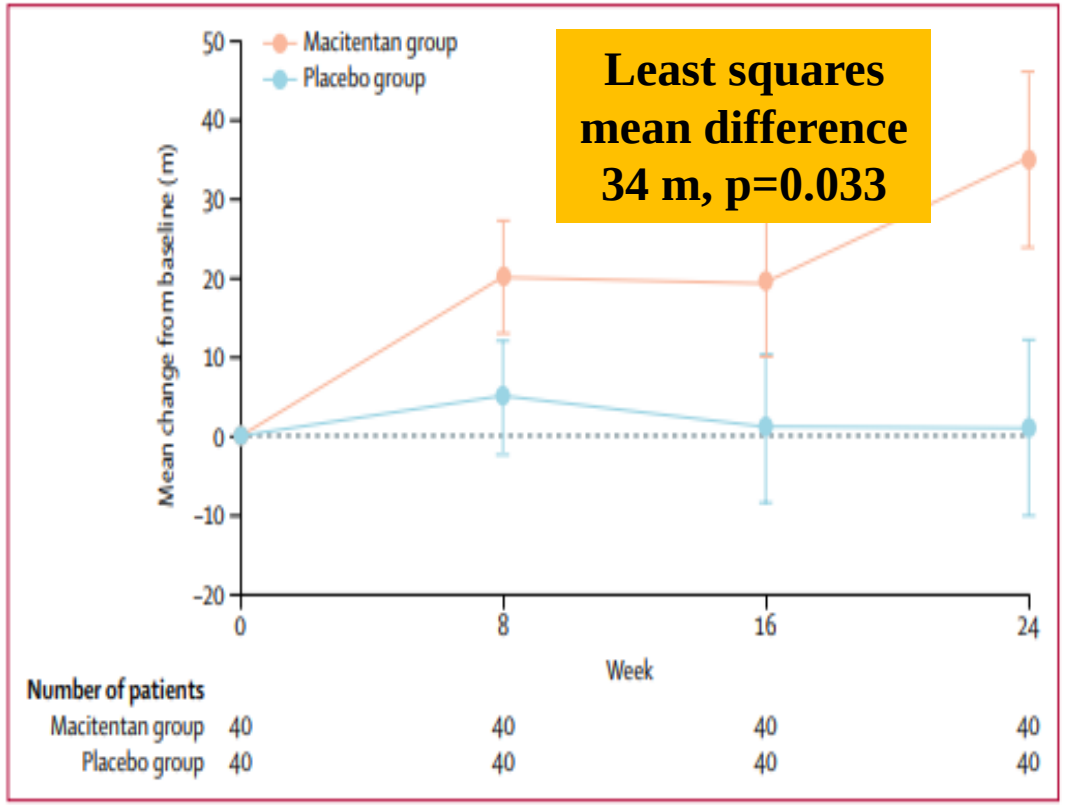
End Point	Placebo			Riociguat			Least-Squares Mean Difference (95% CI)	P Value†
	No. of Patients	Baseline	Change	No. of Patients	Baseline	Change		
Primary end point								
6-Min walk distance (m)‡	88	356±75	−6±84	173	342±82	39±79	46 (25 to 67)	<0.001
Secondary end points								
Pulmonary vascular resistance (dyn·sec·cm^{-5})	82	779±401	23±274	151	791±432	−226±248	−246 (−303 to −190)	<0.001
NT-proBNP (pg/ml)	73	1706±2567	76±1447	150	1508±2338	−291±1717	−444 (−843 to −45)	<0.001
WHO functional class§	87	0 patients in class I, 25 (29%) in class II, 60 (69%) in class III, 2 (2%) in class IV	13 patients (15%) moved to lower class (indicating improvement), 68 (78%) stayed in same class, 6 (7%) moved to higher class	173	3 patients (2%) in class I, 55 (32%) in class II, 107 (62%) in class III, 8 (5%) in class IV	57 patients (33%) moved to lower class (indicating improvement), 107 (62%) stayed in same class, 9 (5%) moved to higher class	—	0.003
Borg dyspnea score¶	88	4±2	0.2±2.4	173	4±2	−0.8±2	—	0.004
EQ-5D score**	87	0.66±0.25	−0.08±0.34	172	0.64±0.24	0.06±0.28	0.13 (0.06 to 0.21)	<0.001

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

Macitentan for inoperable CTEPH: MERIT-1, phase 2, RCT

Inclusion: Treatment naïve (39%), background PAH medication (61%)
Primary endpoint: PVR

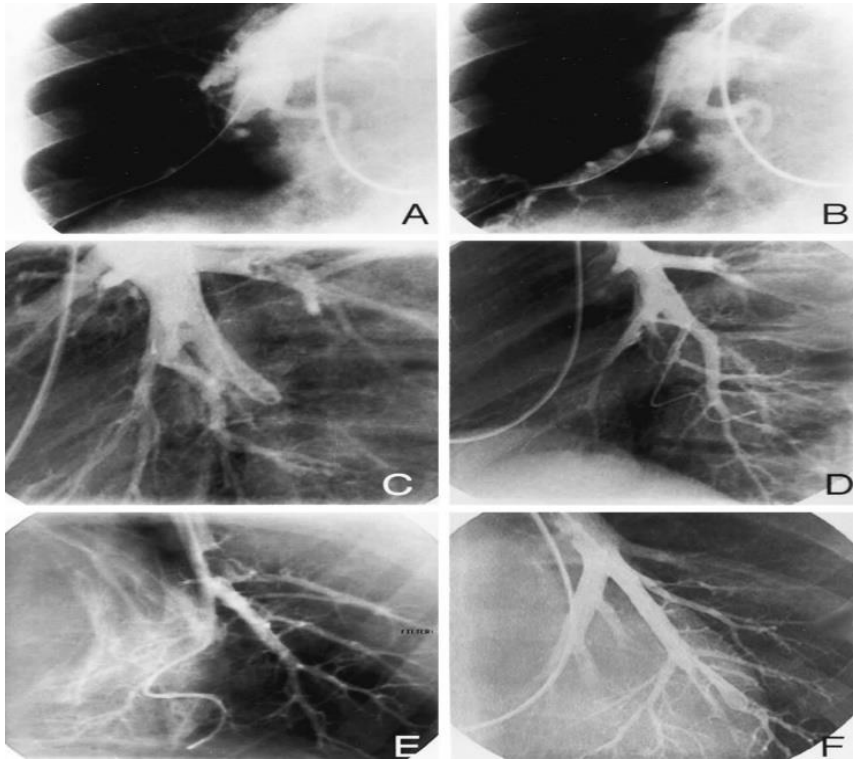




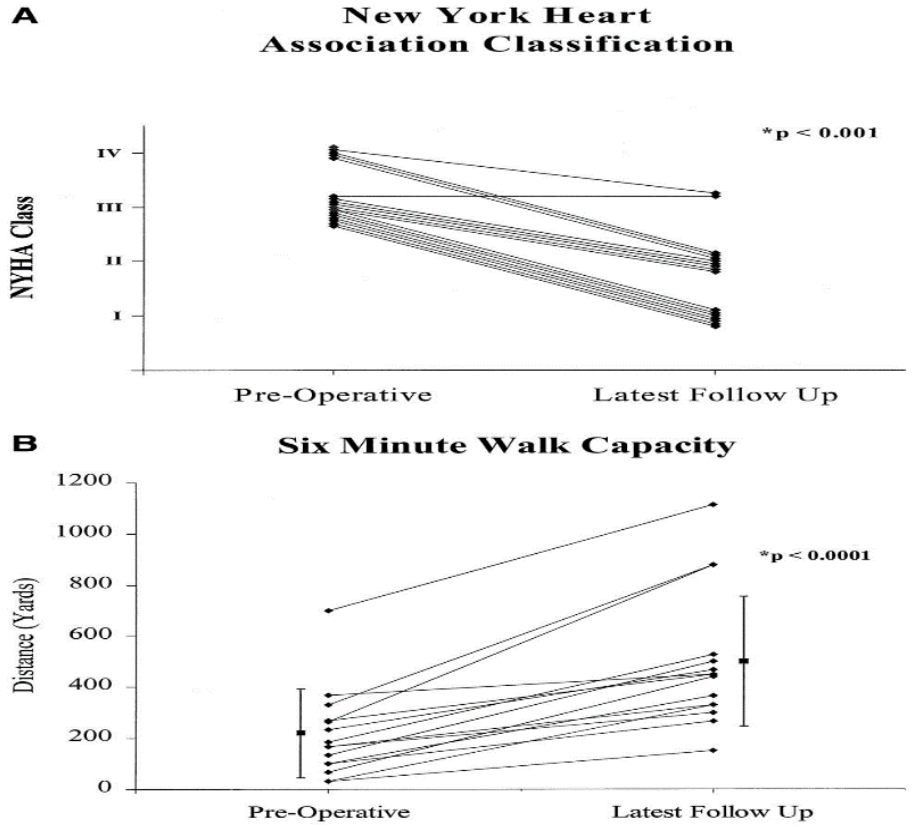
Ghofrani HA, et al. Lancet Respir Med. 2017;5:785–794

Balloon pulmonary angioplasty (BPA)

➢ 18 patients with CTEPH underwent BPA



Average 36 month follow-up



➢ 11 patients developed reperfusion pulmonary edema, 3 patients required mechanical ventilation.
➢ 1 patient died of right heart failure 1 week after BPA.

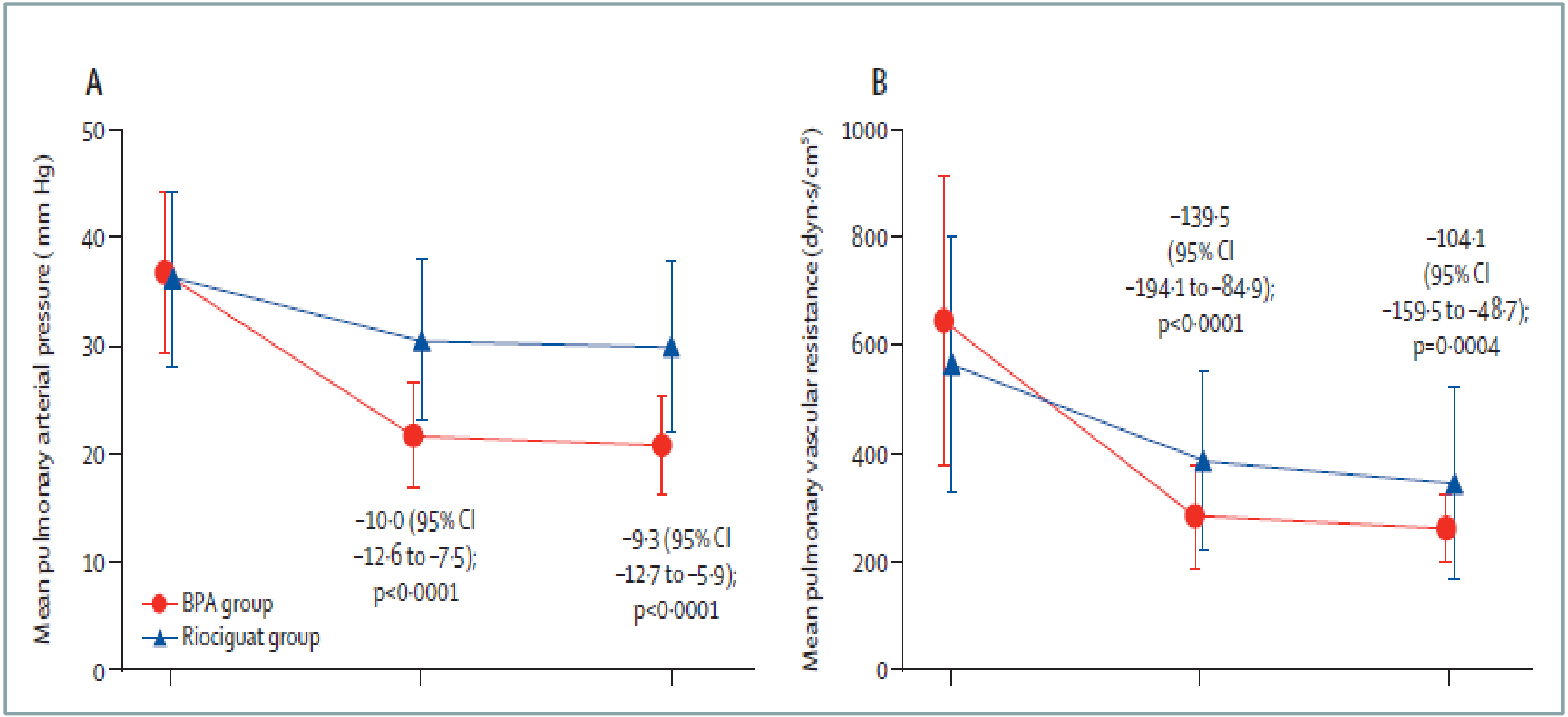
Feinstein JA et al. Circulation. 2001;103:10-13

Long-term outcomes of BPA

First Author, Year Published	Subjects (Country)	Procedures (Total)	Procedures/ Patient	Long-Term Survival
Feinstein et al,[38] 2001	18 (USA)	47	2.6	89% at 34.2 mo
Mizoguchi et al,[41] 2012	68 (Japan)	255	3.8	97% at 2.2 ± 1.4 y
Sugimura et al,[39] 2012	12 (Japan)	NA	5	100% at 12 mo
Andreassen et al,[42] 2013	20 (Norway)	73	3.7	85% at 51 mo
Yanagisawa et al,[70] 2014	70 (Japan)	257	4 (age <65 y)	100% (<65 y)
			3 (age ≥65 y)	96.8% (≥65 y) at 12 mo
Shimura et al,[47] 2015	110 (Japan)	423	3.8	100% at 1.97 y
Inami et al,[45] 2016	170 (Japan)	649	3.8	97.6% at 2.8 y

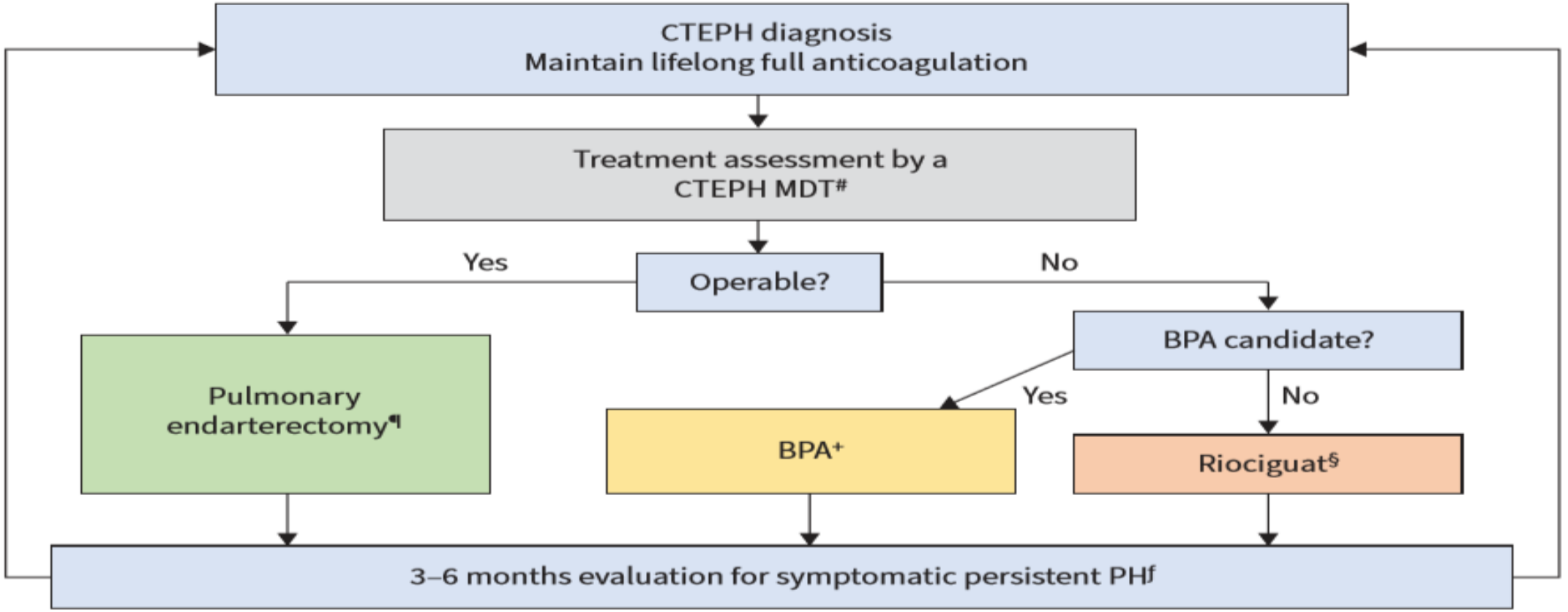
Mahmud E et al. Intervent Cardiol Clin 2018;7:103-117

BPA vs riociguat in operable CTEPH



Kawakami T, et al. Lancet Respir Med 2022; 10: 949–60

2024 7th World symposium on PH



Kim NH, et al Eur Respir J 2024; in press: 2401294

CTEPH multidisciplinary team (MDT)

	Requirements
MDT	PEA surgeon + BPA specialist + PH expert + pulmonary vascular radiologist
PEA centre	⩾20 surgeries per year with post-operative mortality rate <5%, ECMO support
Expert PEA centre	50 surgeries per year with mortality <3%, capable of treating segmental/ subsegmental disease, ECMO support
BPA centre	⩾50 procedures per year with procedure related mortality <3%
Expert BPA centre	>100 procedures per year with mortality <1%, ECMO support
Comprehensive CTEPH centre	Combined PEA + BPA + PH + ECMO expertise available with treatments based on centre MDT

Kim NH, et al. Eur Respir J 2024; in press: 2401294

Take home message

1. **4-pathway drugs for PAH treatment : Prostacycline, NO, endothelin, activin/BMP pathway**
2. **Early dual or triple combination therapy for PAH without comorbidities**
3. **IV/SC prostacyclin pathway agent for “high risk” PAH**
4. **CTEPH treatment: PEA >> BPA > Riociguat with MDT**