Evolution of management guideline for pulmonary hypertension

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2020년 폐고혈압 진료지침

Korean guideline for diagnosis and treatment of pulmonary hypertension

대한심장학회
대한결핵 및 호흡기학회

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Hemodynamic Definition of PH and PAH

PH Mean PAP ≥25 mm Hg

PAH Mean PAP ≥25 mm Hg *plus*
PAWP ≤15 mm Hg
PVR > 3 Wood units

Hemodynamic profiles in PH

PAP= CO * PVR + LA pressure

Increased CO

Left to right shunt (VSD, ASD, PDA)
Liver cirrhosis
Hyperthyroidism
Anemia
ESRD
Etc.

PAH = precapillary PH

Pulmonary venous hypertension (PVH) = postcapillary PH

폐고혈압의 혈역학적 분류

정의	특징	폐고혈압 임상군
모세혈관전 폐고혈압 (Pre-capillary PH)	mPAP ≥ 25 mmHg PAWP ≤ 15 mmHg	1, 3, 4, 5
모세혈관후 폐고혈압 (Post-capillary PH)	mPAP ≥ 25 mmHg PAWP > 15 mmHg	
국한된 모세혈관후 폐고혈압 (Isolated post-capillary PH; IpcPH)	+ DPG < 7 mmHg and/or PVR ≤ 3 WU	2, 5
복합 모세혈관전후 폐고혈압 (Combined pre- and post-capillary PH; CpcPH)	+ DPG ≥ 7 mmHg and/or PVR > 3 WU	2, 5

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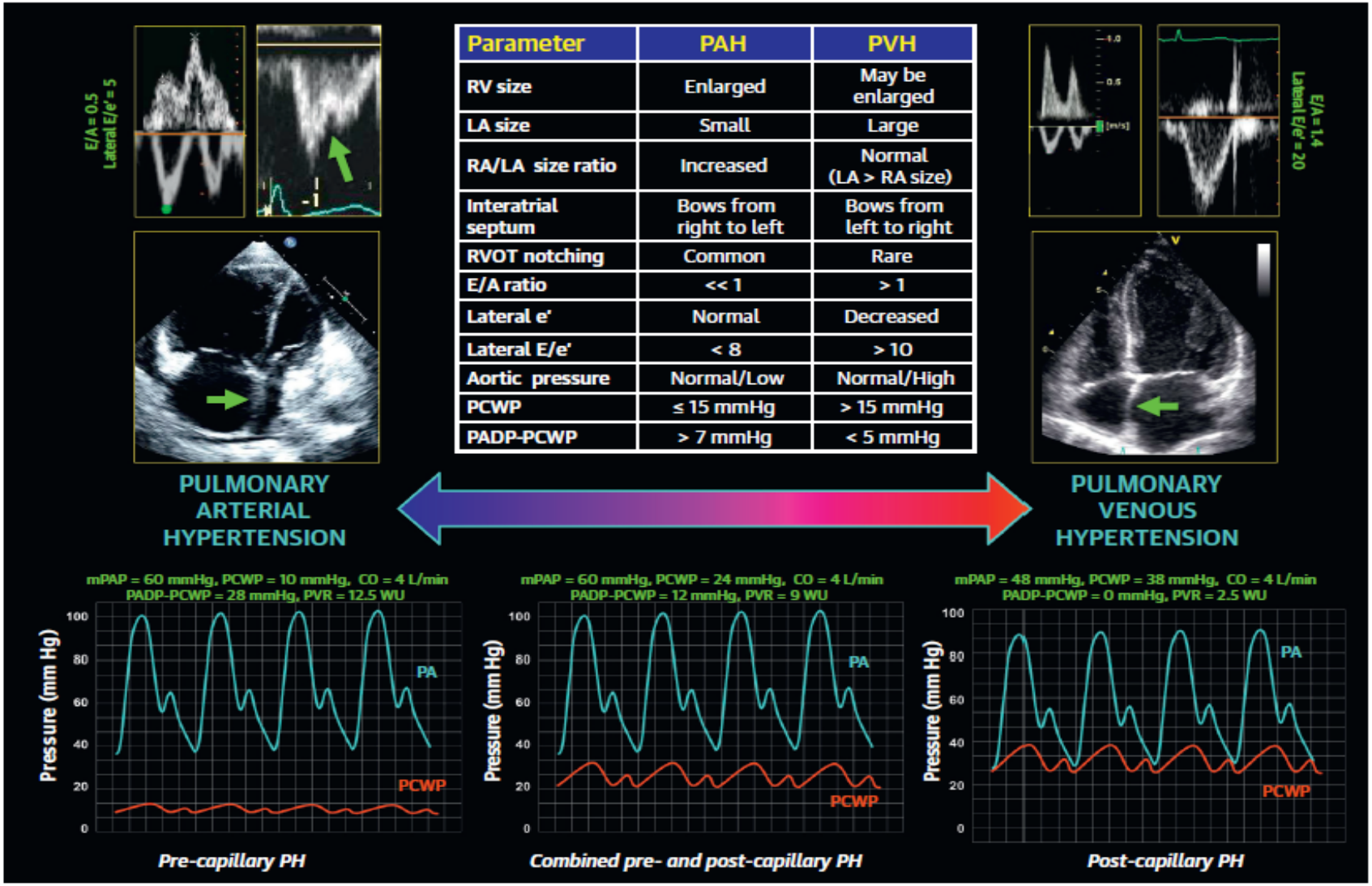
PAH vs PVH



Parameter	PAH	PVH
RV size	Enlarged	May be enlarged
LA size	Small	Large
RA/LA size ratio	Increased	Normal (LA > RA size)
Interatrial septum	Bows from right to left	Bows from left to right
RVOT notching	Common	Rare
E/A ratio	<< 1	> 1
Lateral e'	Normal	Decreased
Lateral E/e'	< 8	> 10
Aortic pressure	Normal/Low	Normal/High
PCWP	≤ 15 mmHg	> 15 mmHg
PADP-PCWP	> 7 mmHg	< 5 mmHg

McLaughlin VV et al. J Am Coll Cardiol 2015;65:1976–97

폐고혈압의 임상적 분류

1. 폐동맥고혈압

1.1 특발폐동맥고혈압

1.2 유전폐동맥고혈압

1.3 약물 및 독소 유발 폐동맥고혈압

1.4 질환과 관련된 폐동맥고혈압

- 1.4.1 결합조직병
- 1.4.2 사람면역결핍바이러스감염
- 1.4.3 간문맥고혈압
- 1.4.4 선천심장병
- 1.4.5 주혈흡충증

1.5 칼슘통로차단제에 장기간 반응을 보이는 폐동맥고혈압

1.6 정맥침범(폐정맥폐쇄질환: pulmonary veno-occlusive disease)/모세혈관침범(폐모세혈관종증: pulmonary capillary hemangiomatosis)의 명확한 소견을 보이는 폐동맥고혈압

1.7 신생아의 지속적 폐고혈압증후군

2. 좌심장질환으로 인한 폐고혈압

2.1 박출률보존심부전으로 인한 폐고혈압

2.2 박출률저하심부전으로 인한 폐고혈압

2.3 심장판막질환

2.4 모세혈관 후 폐고혈압을 일으키는 선천/후천 심혈관계 질환

3. 폐질환이나 저산소증으로 인한 폐고혈압

3.1 폐쇄폐질환

3.2 제한폐질환

3.3 제한/폐쇄 형태가 혼합된 타 폐질환

3.4 폐질환이 없는 저산소증

3.5 발달폐질환

4. 폐동맥폐쇄로 인한 폐고혈압

4.1 만성혈전색전폐고혈압

4.2 타 폐동맥 폐쇄

5. 불명확하거나 다인자 요인들에 의한 폐고혈압

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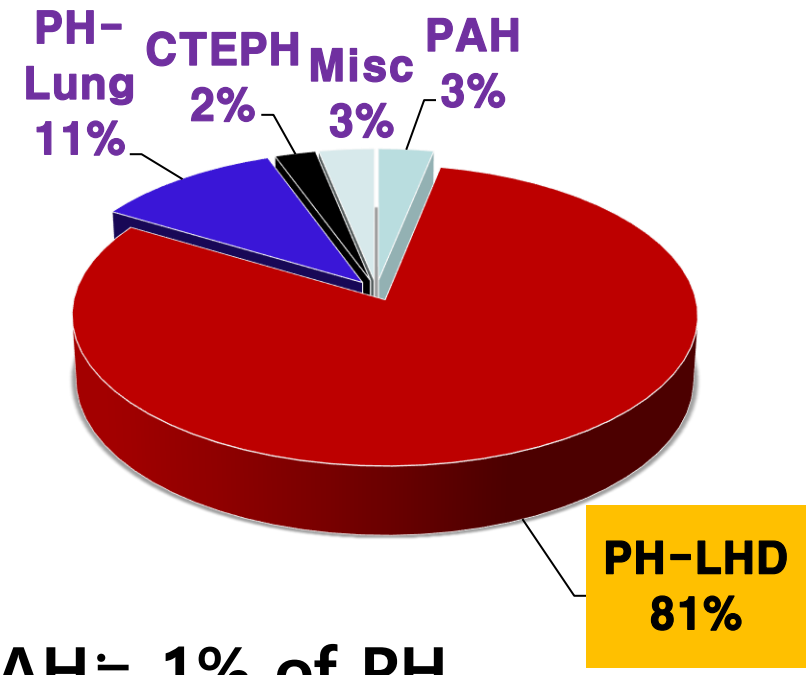
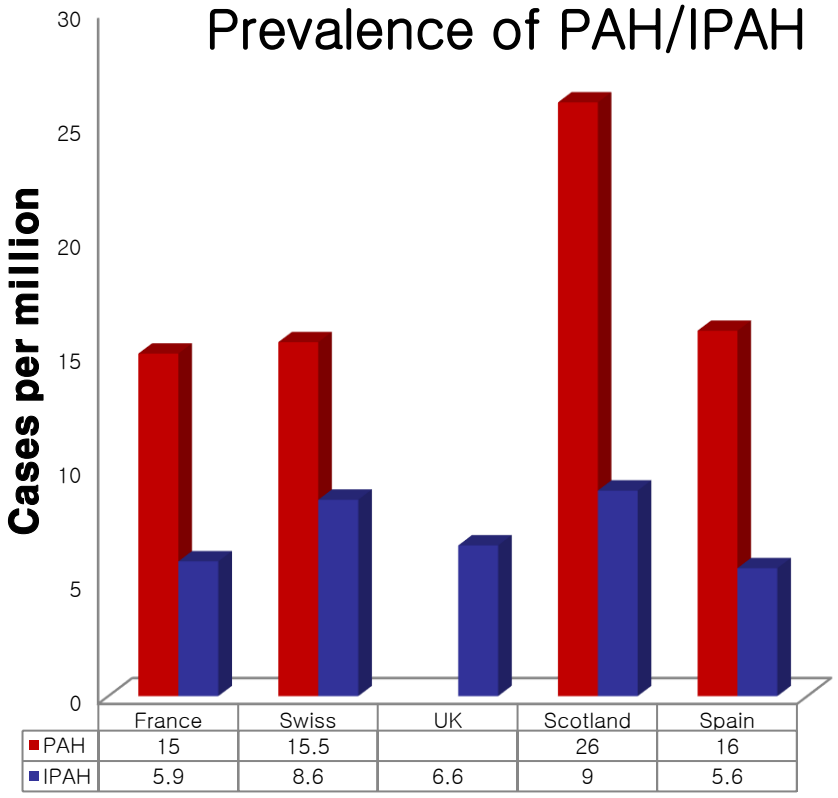
IPAH is “orphan disease”



IPAH≒ 1% of PH



Strange G,et al. Heart (2012)

PAH in South Korea

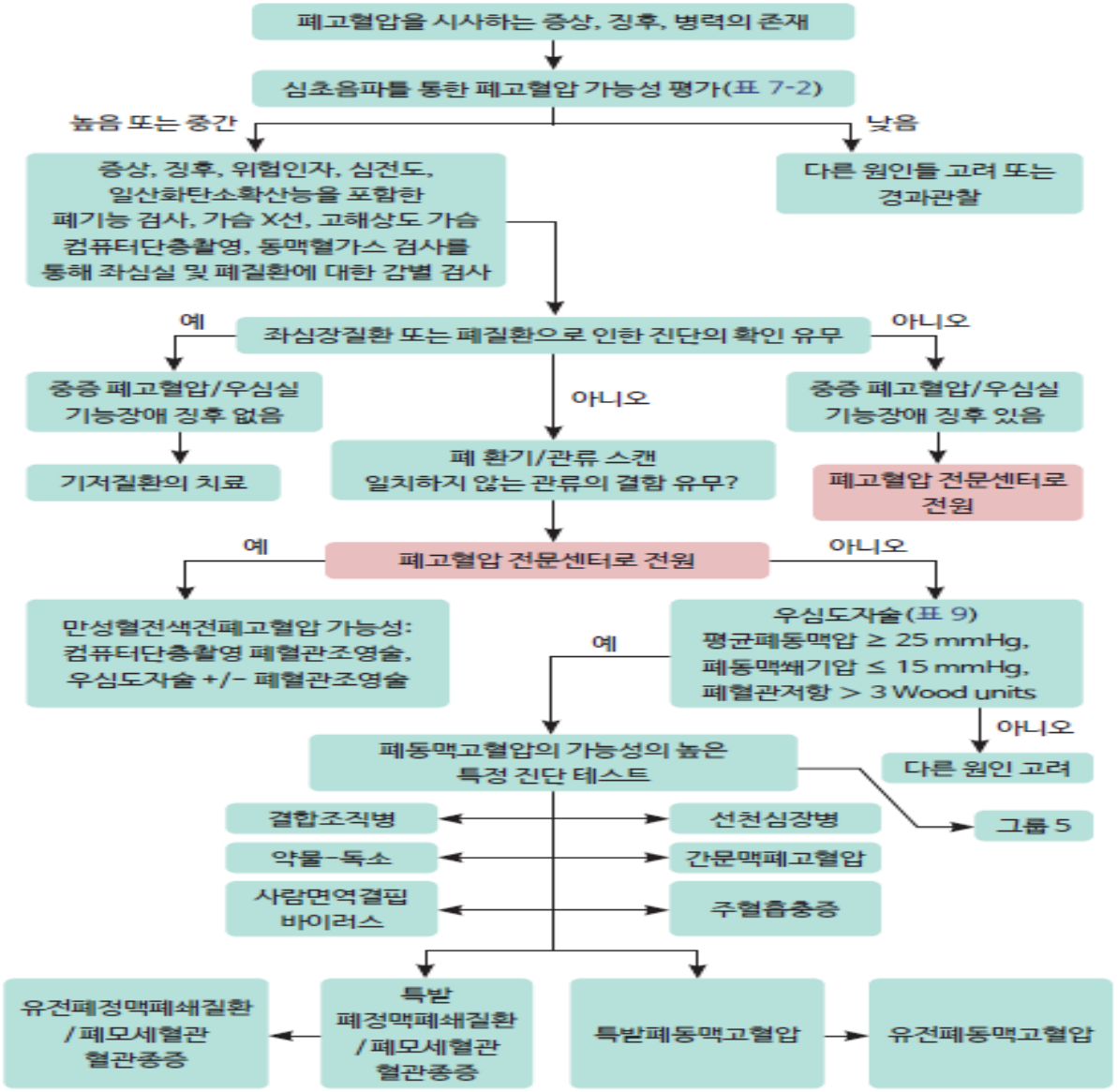
PAH incidence : 4.84 patients /1 million people/year

IPAH (51.6%) , CHD-PAH (25.8%), CTD-PAH (17.2%)

	All patients	IPAH group	APAH group	P-value	APAH-CHD	APAH-CTD-SSc	APAH-CTD-SLE	APAH-CTD-other
Patients, n (%)	1307 (100.0)	674 (51.6)	633 (48.4)		337 (53.2)	90 (14.2)	135 (21.3)	71 (11.2)
Age	44±13	48±12	41±12	<0.001	40±12	50±10	38±11	43±12
Female sex, n (%)	906 (69.3)	409 (60.7)	497 (78.5)	<0.0001	218 (64.7)	86 (95.6)	133 (98.5)	60 (84.5)
Comorbidity								
HTN, n (%)	392 (30.0)	285 (42.3)	107 (16.9)	<0.0001	44 (13.1)	18 (20.0)	34 (25.2)	11 (15.5)
DM, n (%)	76 (5.8)	55(8.2)	21 (3.3)	0.0002	10 (3.0)	5 (5.6)	3 (2.2)	3 (4.2)
Renal failure (CKD), n (%)	32 (2.5)	22 (3.3)	10 (1.6)	0.0489	1 (0.3)	3 (3.3)	9 6.7)	0 (0.0)
Arrhythmia, n (%)	81 (6.2)	46 (6.8)	35 (5.5)	0.3316	1 (0.3)	0 (0.0)	1 (0.7)	2 (2.8)
TIA or stroke, n (%)	29 (2.2)	19 (2.8)	10 (1.6)	0.1285	7 (2.1)	0 (0.0)	2 (1.58)	1 (1.4)
Follow-up duration (year)	2.7±2.2	2.3±2.0	3.1±2.4	<0.0001	3.1±2.4	3.0±2.3	3.4±2.5	3.2±2.4

Song SJ, et al. PLoS ONE 13(12):e0209148

Diagnostic algorithm of PH



Echo

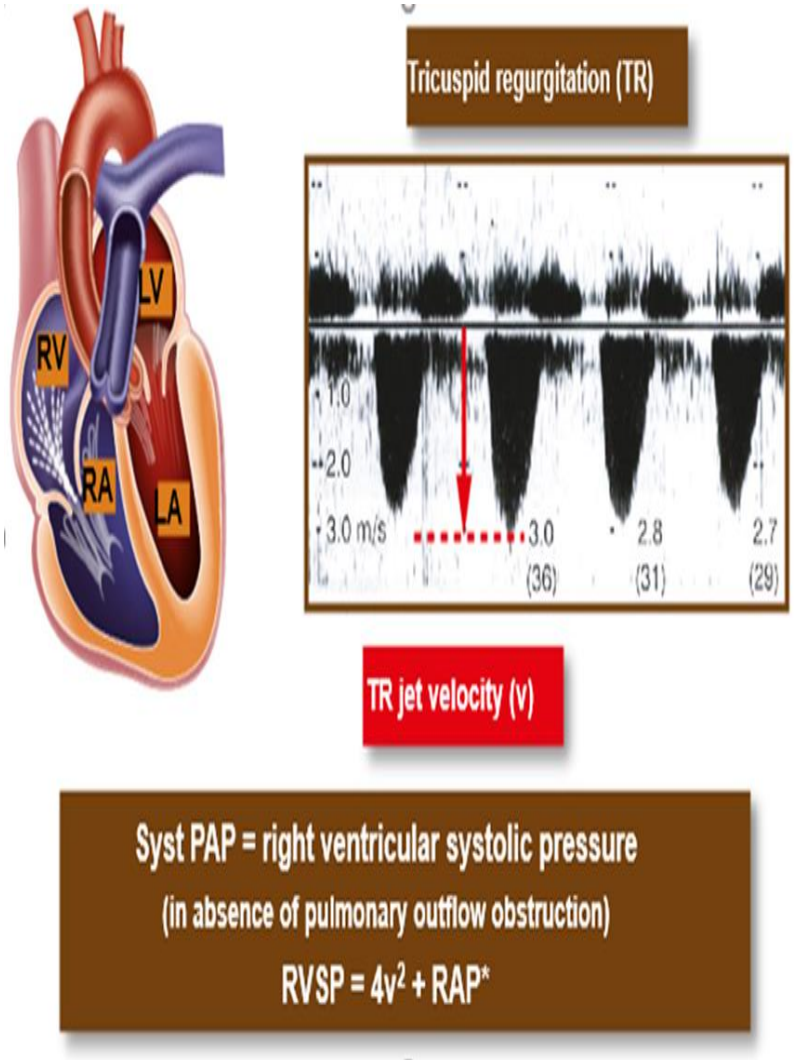
↓

V/Q scan

↓

RHC

Echocardiographic probability of PH

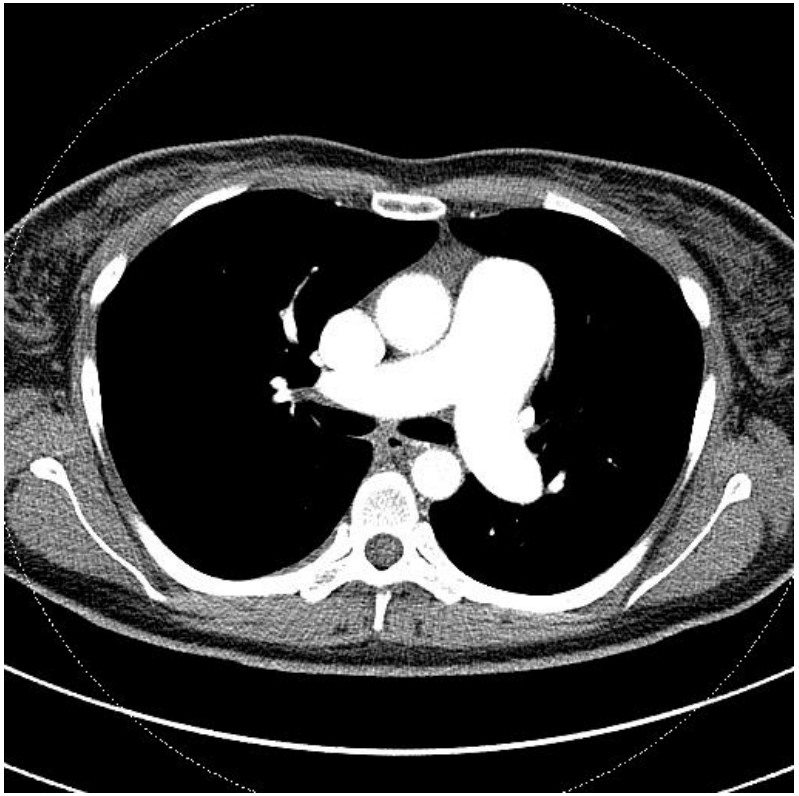


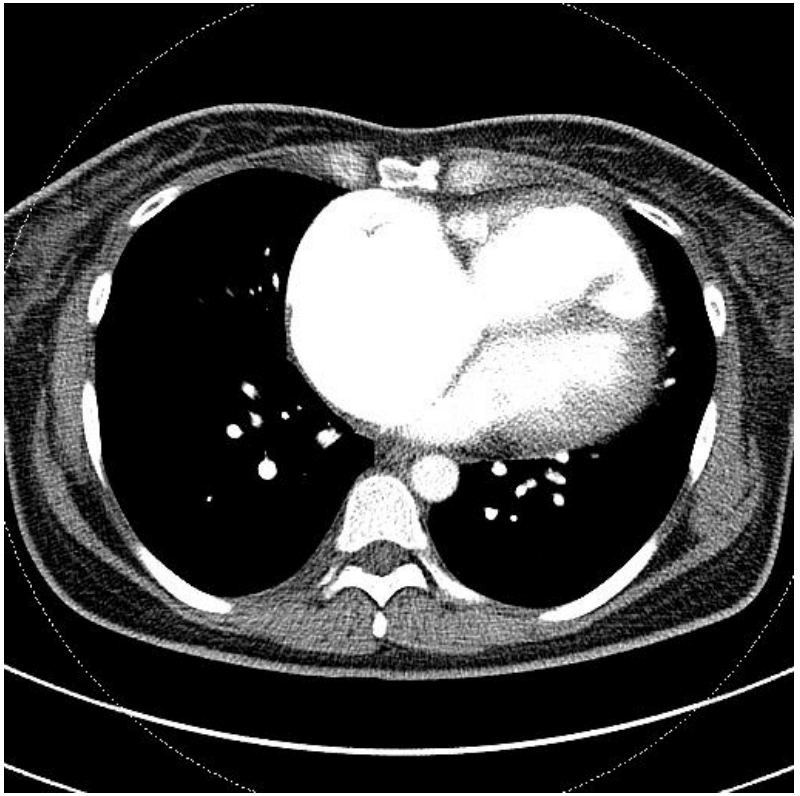
① 최대 삼첨판역류속도 (m/s)	② 심초음파검사에서 '①' 이외에 다른 '폐고혈압 징후'의 유무[a]	③ 폐고혈압 가능성
≤ 2.8 또는 측정이 안됨	없음	낮음
≤ 2.8 또는 측정이 안됨	있음	중간
2.9~3.4	없음	
2.9~3.4	있음	높음
> 3.4	필요하지 않음	

Other Echo ‘PH sign’

A: 심실[a]	B: 폐동맥[a]	C: 하대정맥과 우심방[a]
우심실/좌심실 기저부의 직경 비율 > 1.0	우심실 유출로 도플러 속도증가 시간(acceleration time) < 105 msec 및/또는 수축기 중 도플러 신호 패임(midsystolic notching)	하대정맥 직경 > 21 mm 및 호흡시 하대정맥 직경감소(심호흡시 < 50% 또는 안정 호흡시 < 20%)
폐고혈압으로 인한 우심실 압력 상승으로 심실중격이 좌심실 쪽으로 눌림(수축기 및/또는 이완기 시 좌심실 편심률(eccentricity) 지수 > 1.1)	초기 이완기 폐동맥판막 역류 혈류속도 > 2.2 m/sec	우심방면적(수축기 말) > 18 cm^2
	폐동맥 직경 > 25 mm	

Chest CT of IPAH patient





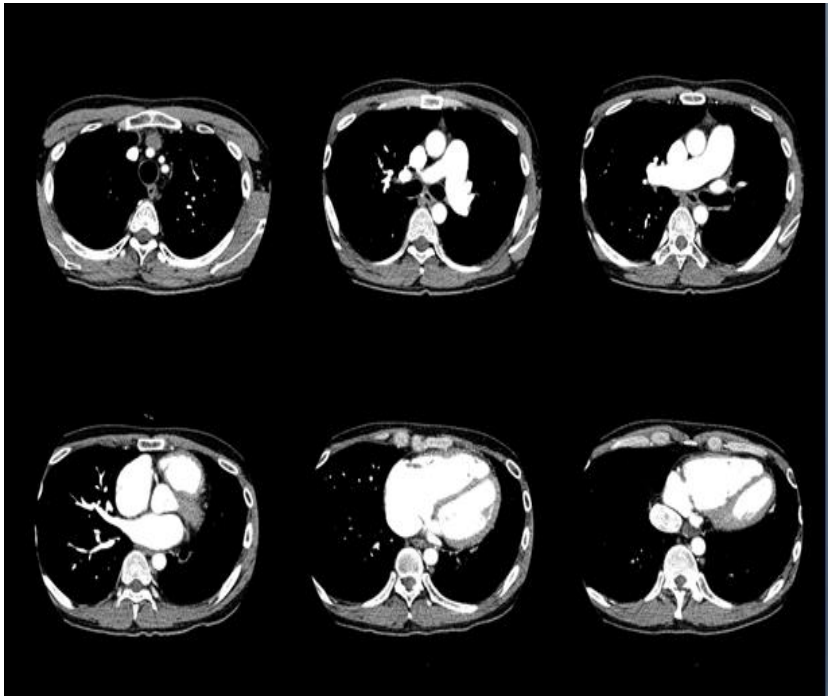
V/Q scan vs CTPA in CTEPH

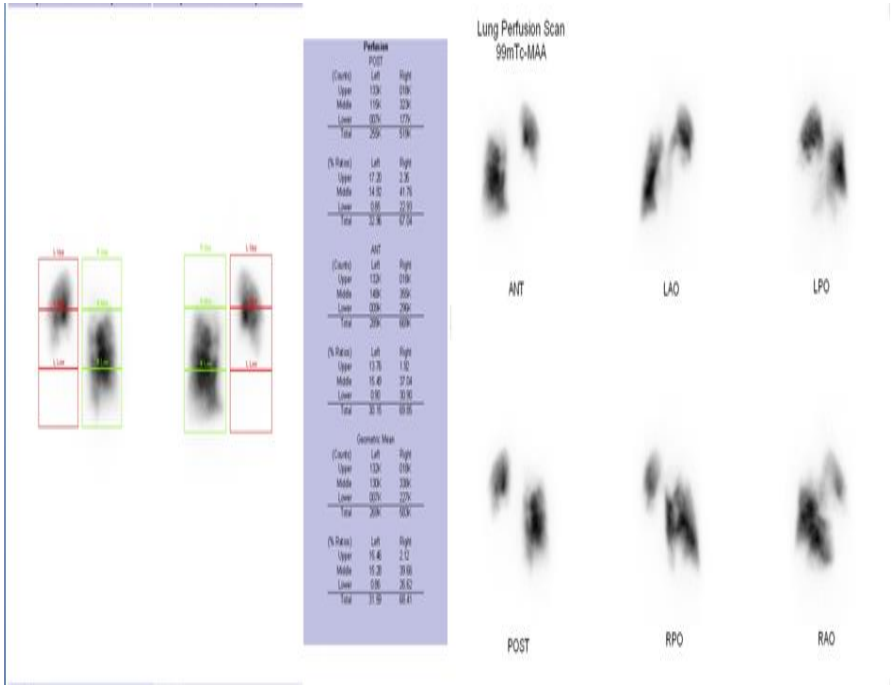
	Scintigraphy		CTPA
	V/Q (1)*	V/Q (2)#	
Sensitivity (%)	**97.4**	**96.2**	**51.3**
Specificity (%)	90	94.6	99.3
Accuracy (%)	92.5	95.2	82.8
NPV (%)	**98.5**	**97.9**	**79.7**
PPV (%)	83.5	90.3	97.6

* Intermediate with high-probability scans as indicative of CTEPH.
# Only high-probability scans as indicative of CTEPH.

J Nucl Med 2007; 48:680–684

V/Q scan vs CTPA in CTEPH

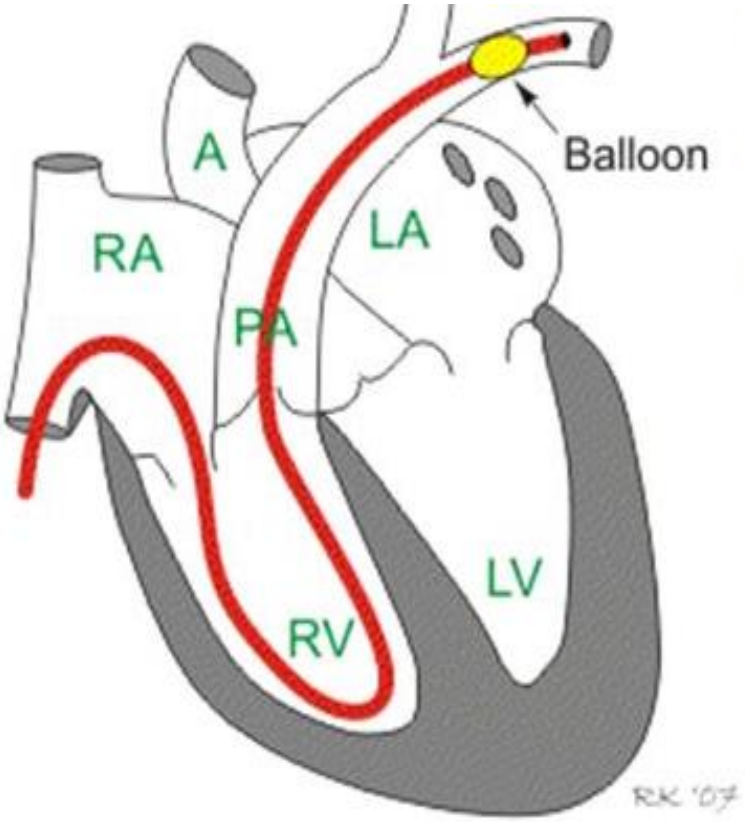




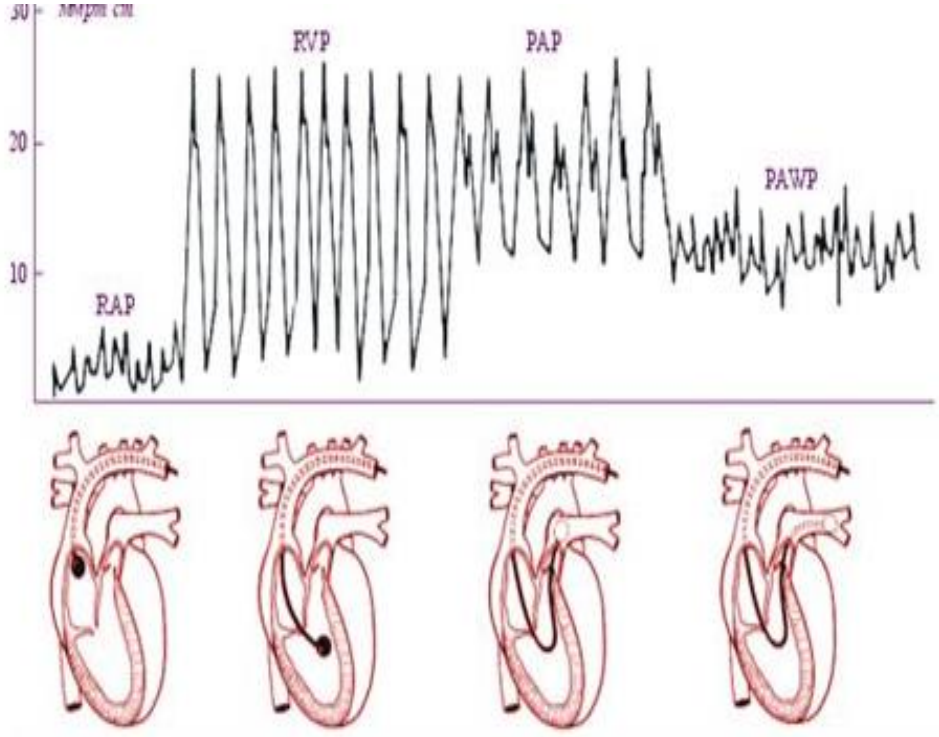
Right heart catheterization

1. 폐고혈압 확진 및 분류
2. 치료 방법 및 약제 선택
3. 폐고혈압 중증도 평가

폐동맥압 측정



Balloon-tipped, Swan-Ganz catheter for measuring pulmonary capillary wedge pressure (PCWP).

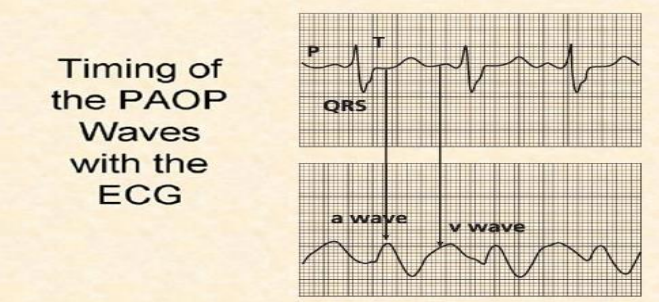


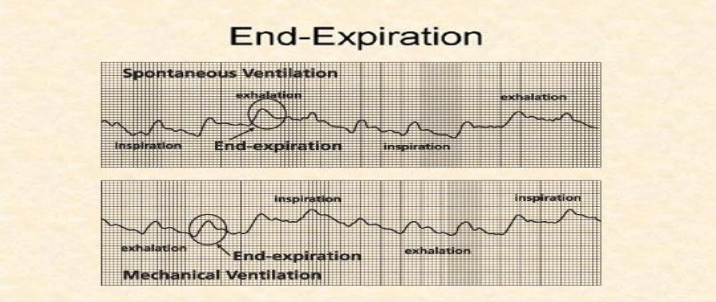
CVP = RAP = RVEDP

PCWP = LAP = LVEDP

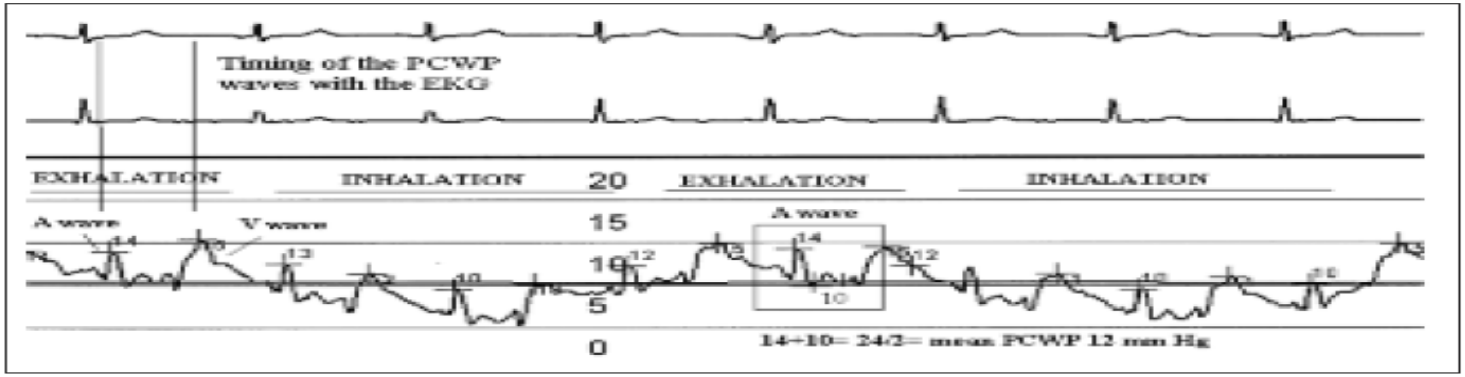
Measurement of PCWP

1) **Identification of the A wave during exhalation**
(right before the beginning of the pressure decline)





2) **Average the top and bottom values of the A wave**



Measurement of cardiac output

❖ **Fick method**

$$CO\ (L/m) = \frac{\text{oxygen consumption (mL } O_2\text{/m)}}{\text{arteriovenous oxygen difference (mL of } O_2\text{/L)}}$$

- **Direct Fick method: gold standard method**
- **Indirect Fick method: inaccurate estimate of O_2 consumption**

❖ **Thermo-dilution method**

- At least 3 measurements within 10% of each other
- limitations in severe TR and congenital heart defect
- must be performed by trained personel

Indirect Fick vs Thermodilution

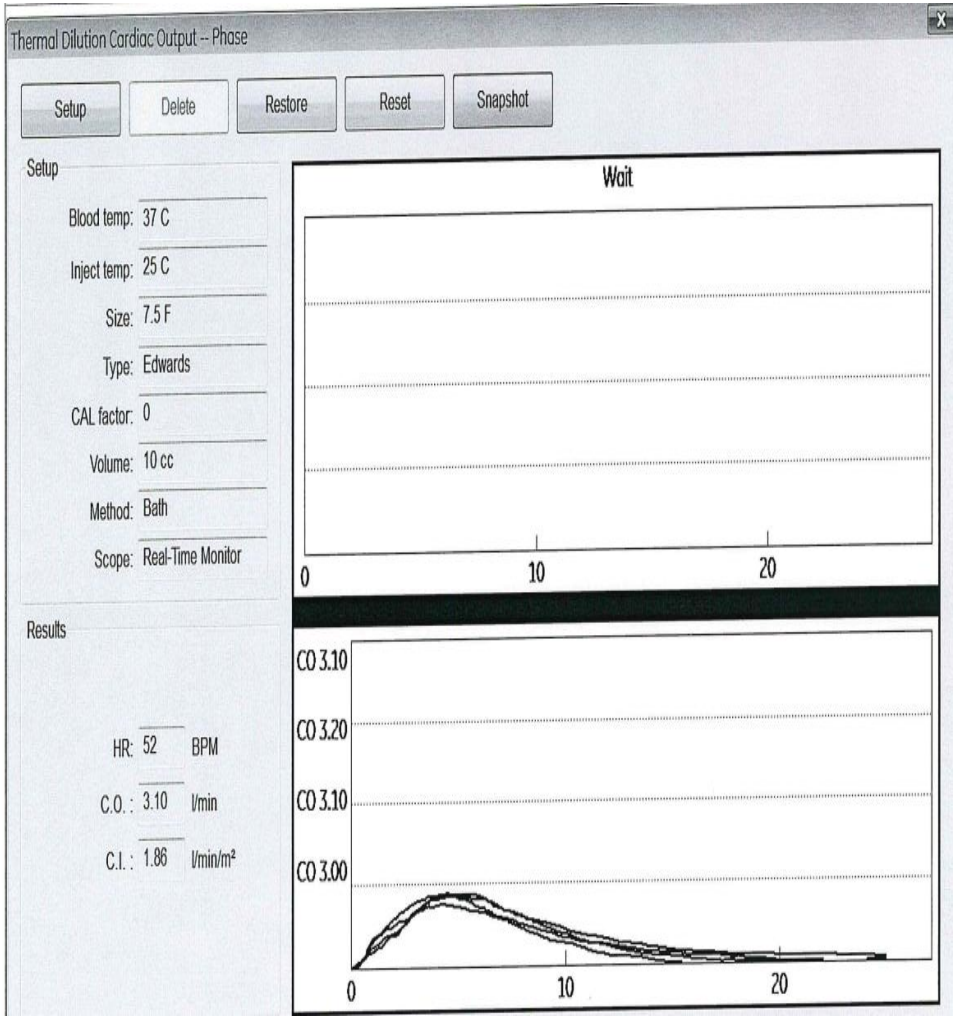
Fick method

Flow

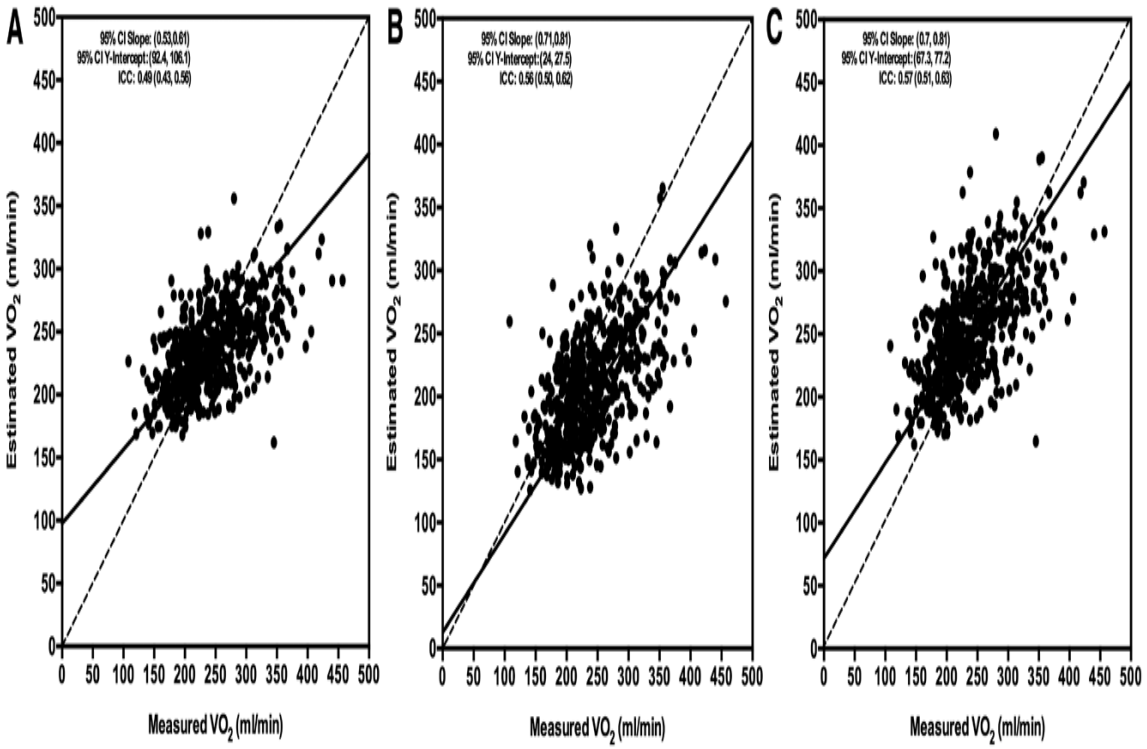
PBF(Qp) (L/min)	4.30	#DIV/0!
SBF(Qs) (L/min)	4.19	#DIV/0!
Cardaic Index (L/min/M^2)	2.51	#DIV/0!
Qp/Qs	1.03	#DIV/0!

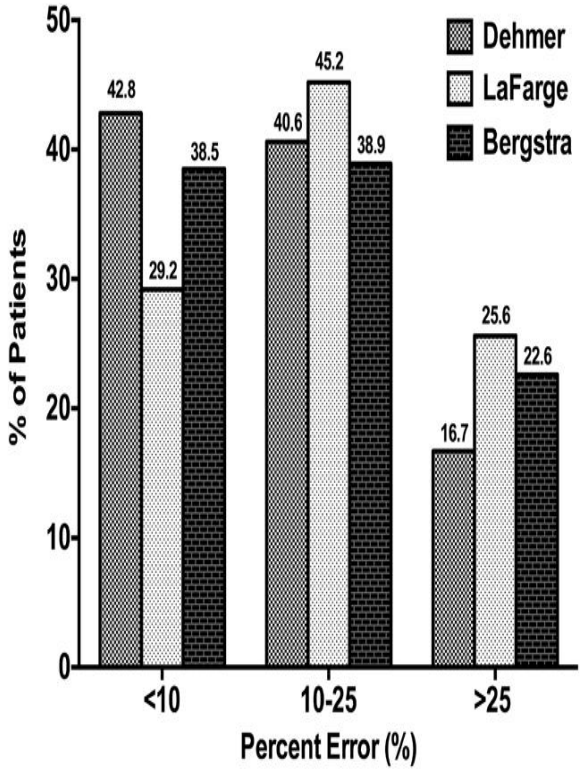
Resistance

PVR (Wood units)	7.21	#DIV/0!
SVR (Wood units)	17.67	#DIV/0!
PVRI (dyn s $cm^{-5}m^{-2}$)	963.81	#DIV/0!
SVRI (dyn s $cm^{-5}m^{-2}$)	2361.26	#DIV/0!
Rp/Rs	0.41	#DIV/0!



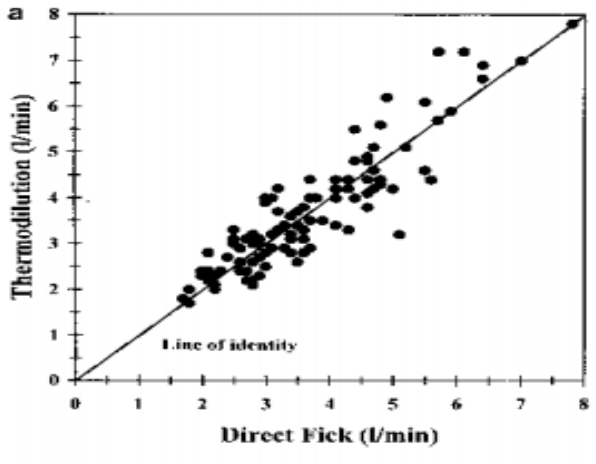
Inaccuracy of Estimated Resting Oxygen Uptake

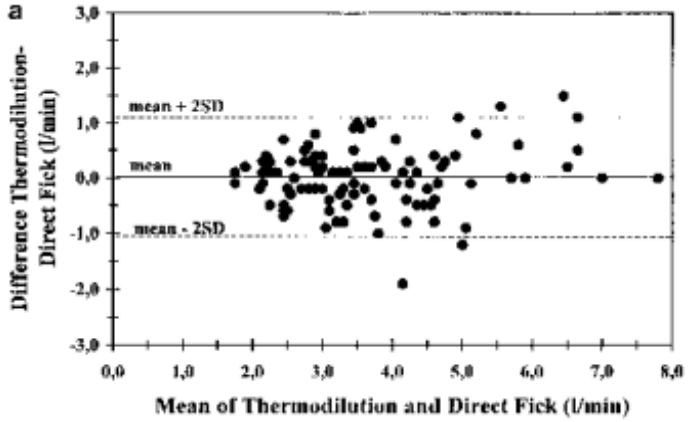


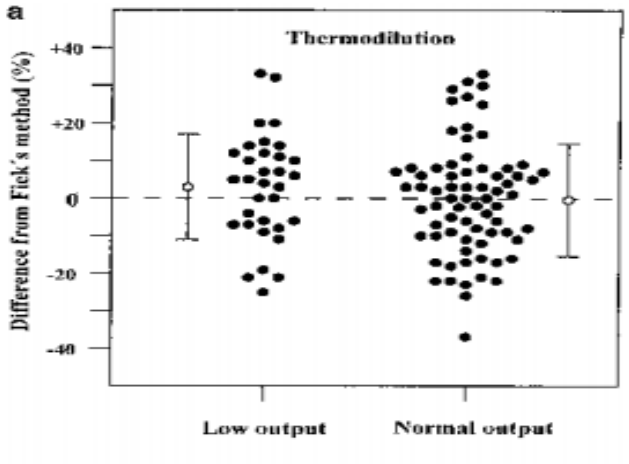


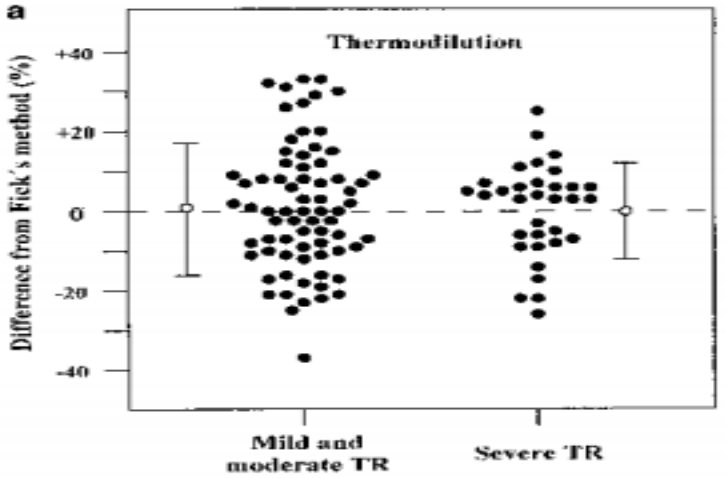
Narang N, et al. Circulation. 2014;129:203-210

Measurement of CO in PH: Thermodilution









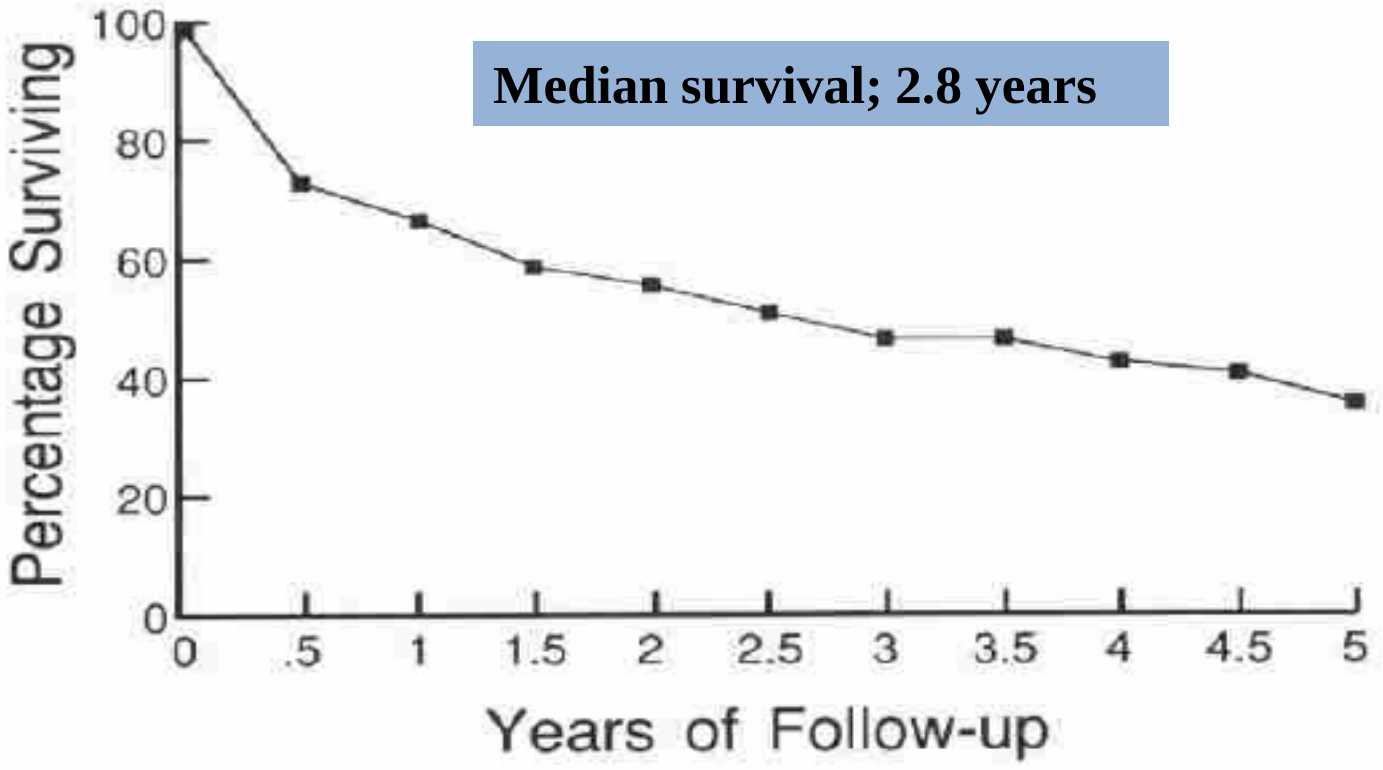
Hoeper et al. AJRCCM1999;160:535–541

1993 ACCP consensus statement on PPH

- **There is no cure for PPH, nor is there a therapeutic approach** which is uniformly accepted or successful.
- General measure : avoid aggravating factors of PPH.
- Supplemental oxygen therapy
- Cardiac glycosides and diuretics
- **Anticoagulation therapy**
- **Vasodilators (nifedipine, diltiazem, postacycline, PGE1)**
- Atrial septostomy
- Lung transplantation; Heart-lung or double lung

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

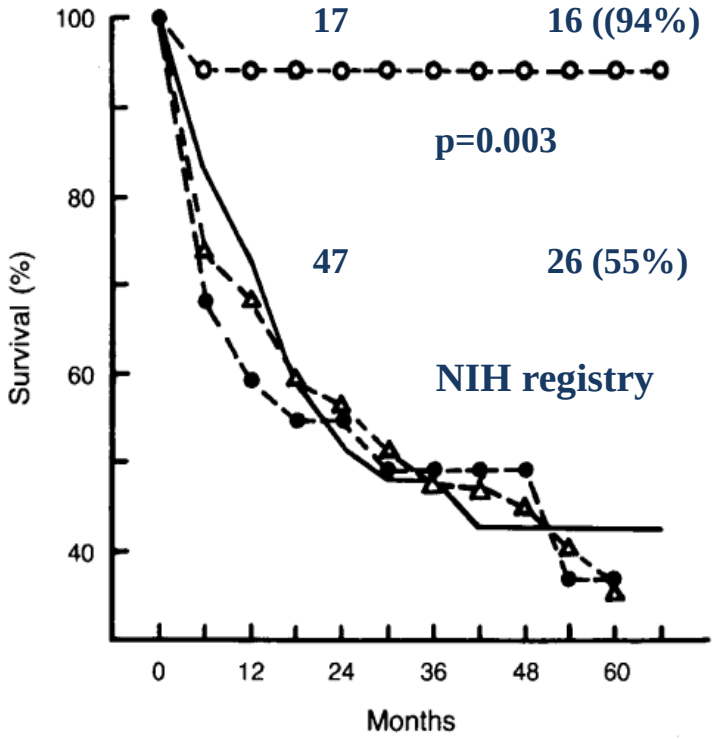
- **NIH registry (1981-1985 to 1988), 194 patients with IPAH**



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

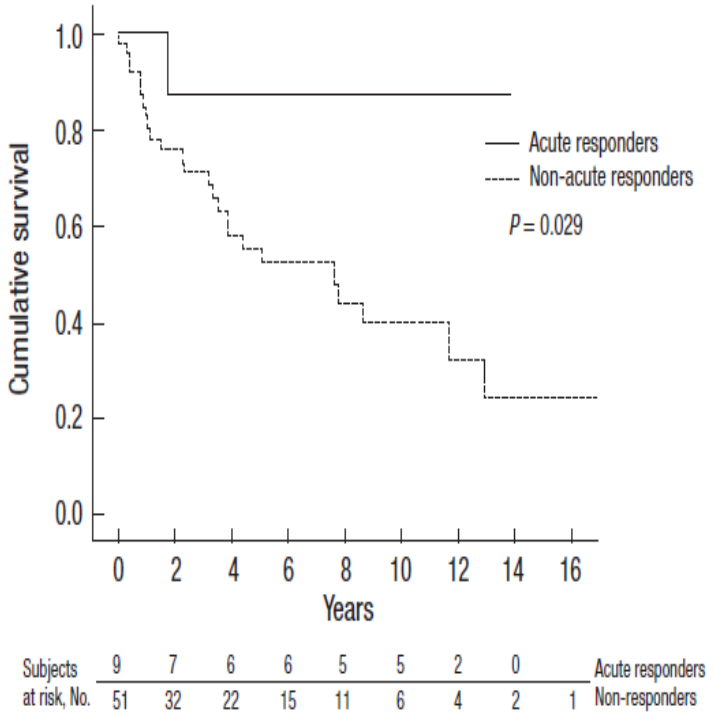
Calcium channel blockers on survival in PPH

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

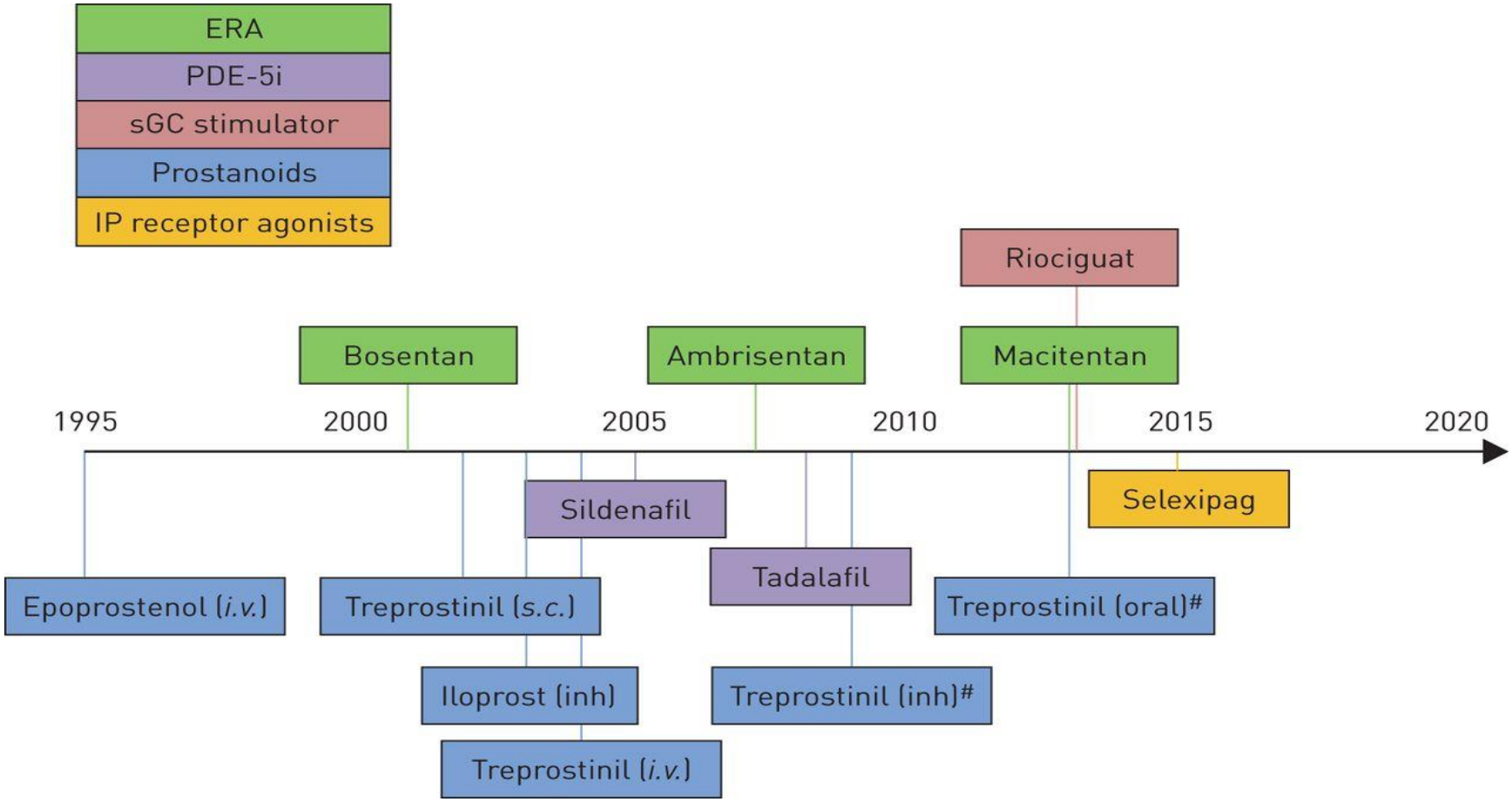
Acute vasodilator testing

- **Indication: All IPAH patients**

- **Agent for acute vasodilator testing**
  iNO, inhaled iloprost, IV epoprostenol, IV adenosine

- **Definition of positive vasodilator response**
  1. Fall in mPAP ≥ 10 mmHg and
  2. mPAP ≤ 40 mmHg and
  3. with an increased or unchanged cardiac outcome

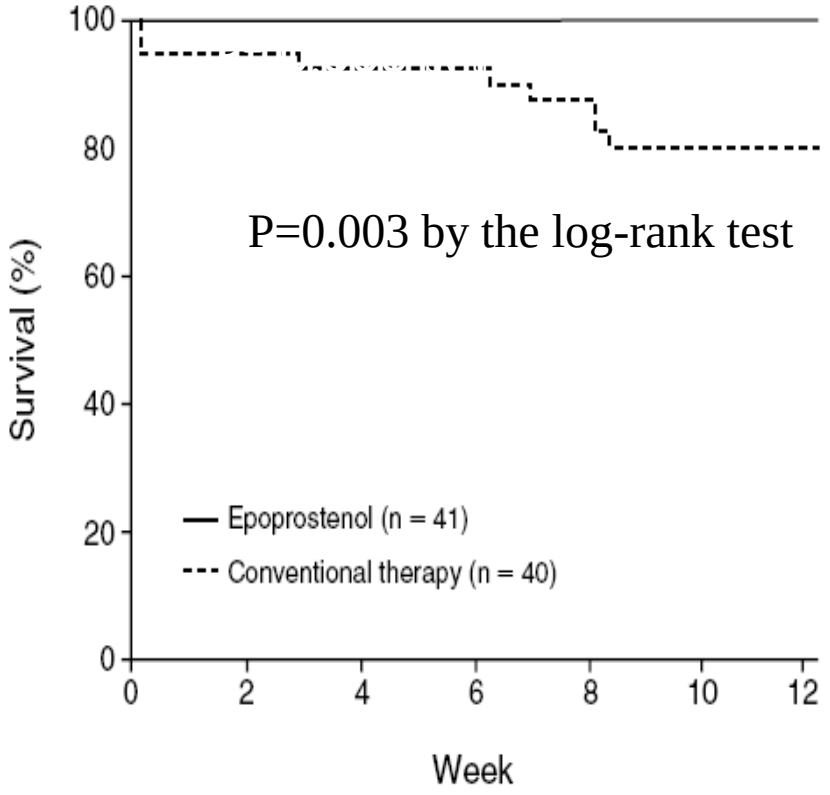
Approved PAH targeting agent



Continuous intravenous epoprostenol for primary pulmonary hypertension

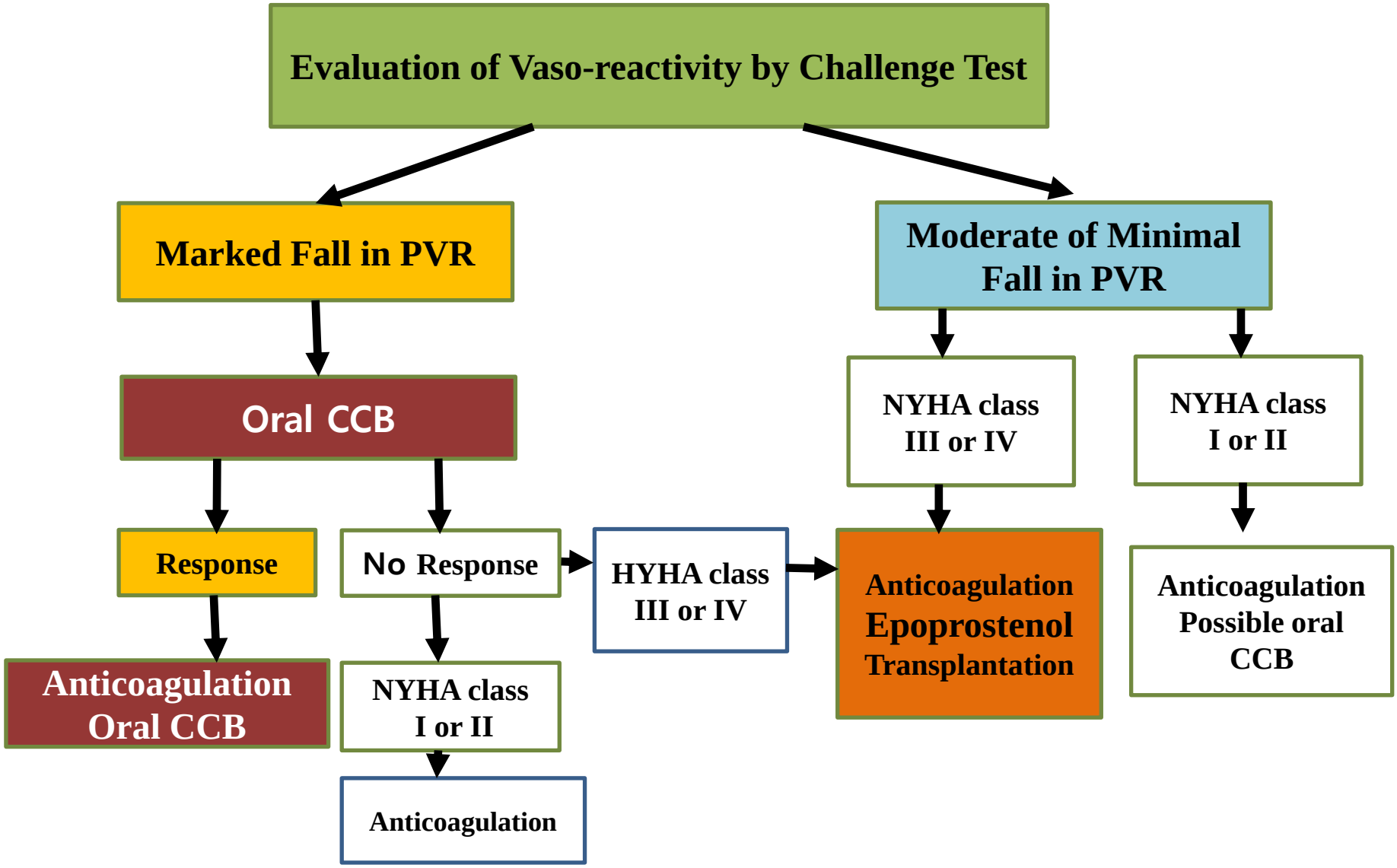
- **12 week open-label** prospective, randomized, multicenter trial, **PPH-FC III, IV**

- **6 min-walk distance ↑**
- **Quality of life ↑**
- **Hemodynamics**
  mean PAP ↓
  cardiac index ↑
  PVR ↓
- **Survival ↑**



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

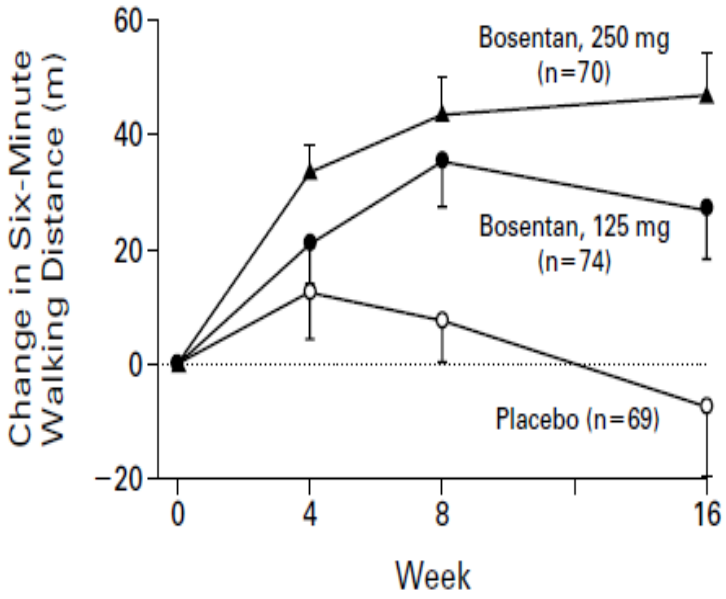
1997 algorithm for the management of PPH

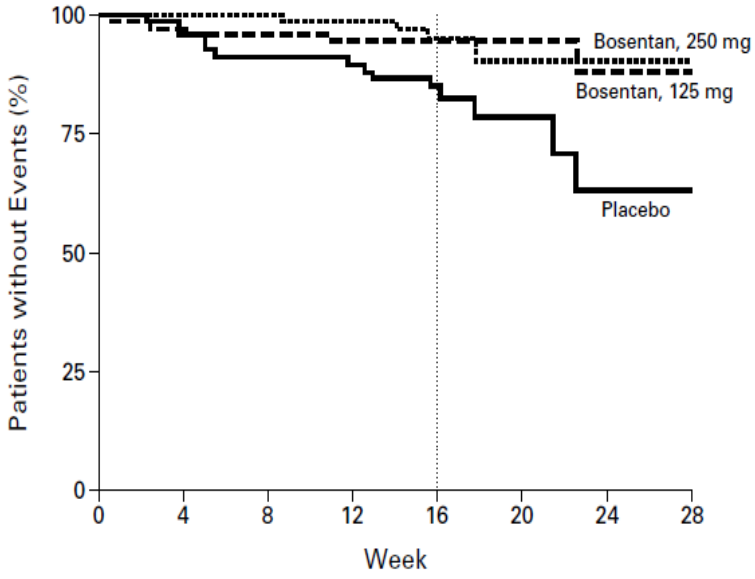


Rubin LJ. N Engl J Med 1997;336:111-117

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

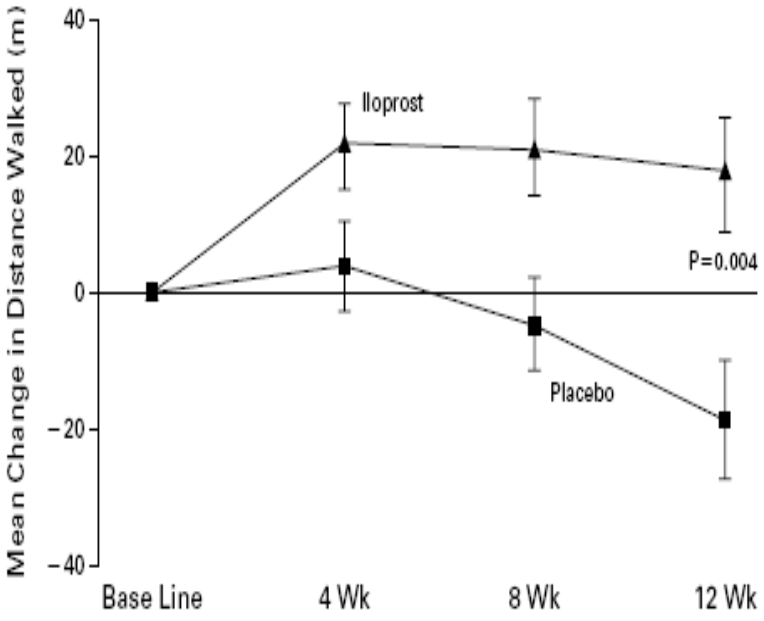
Inhaled iloprost for PAH: AIR study

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)

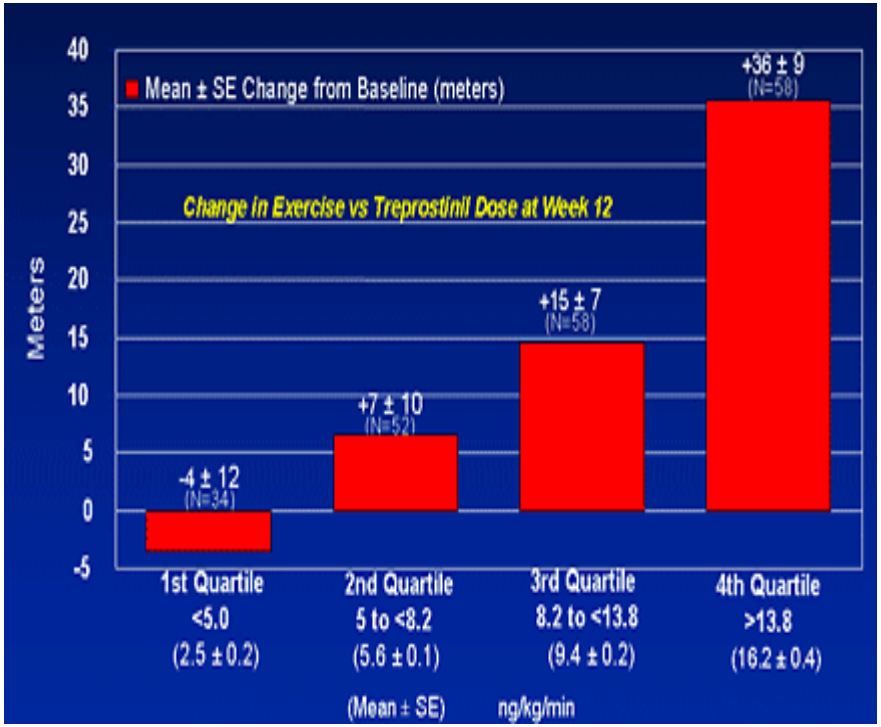
FC II (25/28), III (190/192), IV (18/16)

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

Exercise capacity
; Δ6MWD 16 m (p=0.006)

-> **Greater in the sicker and dose-related.**

Improvement in hemodynamics And dyspnea score

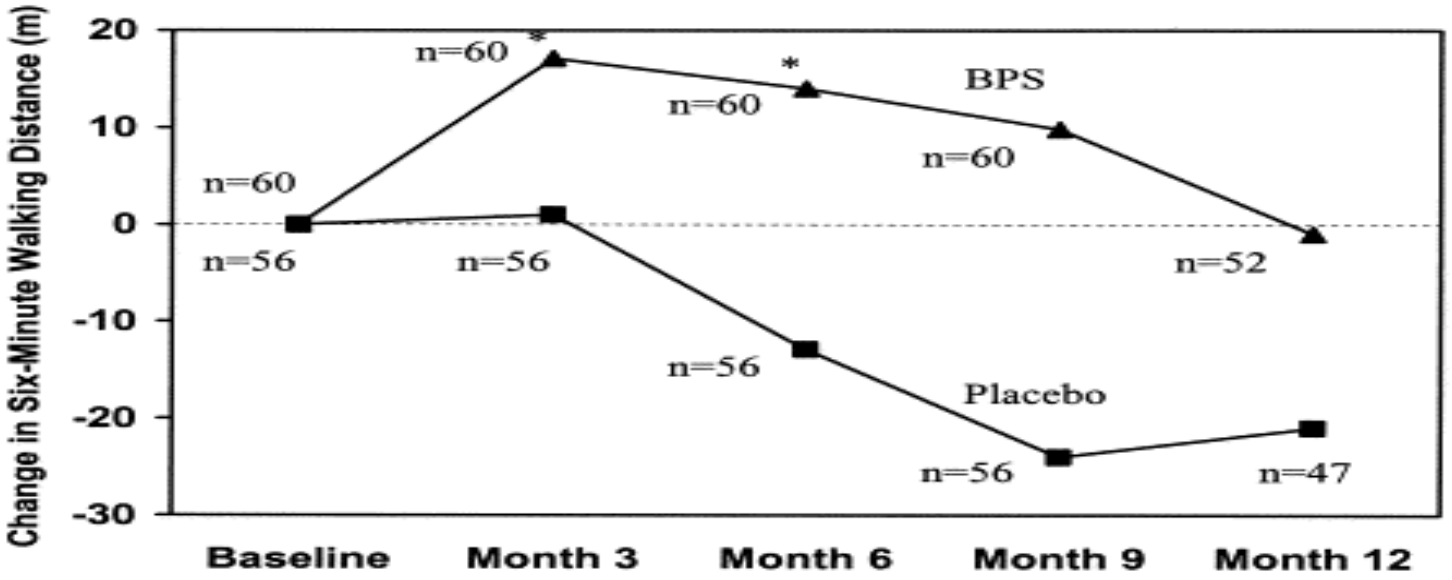


Simonneau G, et al. Am J Respir Crit Care Med Vol 2002; 165: 800–804.

Beraprost for PAH

- **Chemically stable, orally active**
  - Start 20 μg by mouth 4 times a day; increase in increments of 20 μg 4 times a day if tolerated

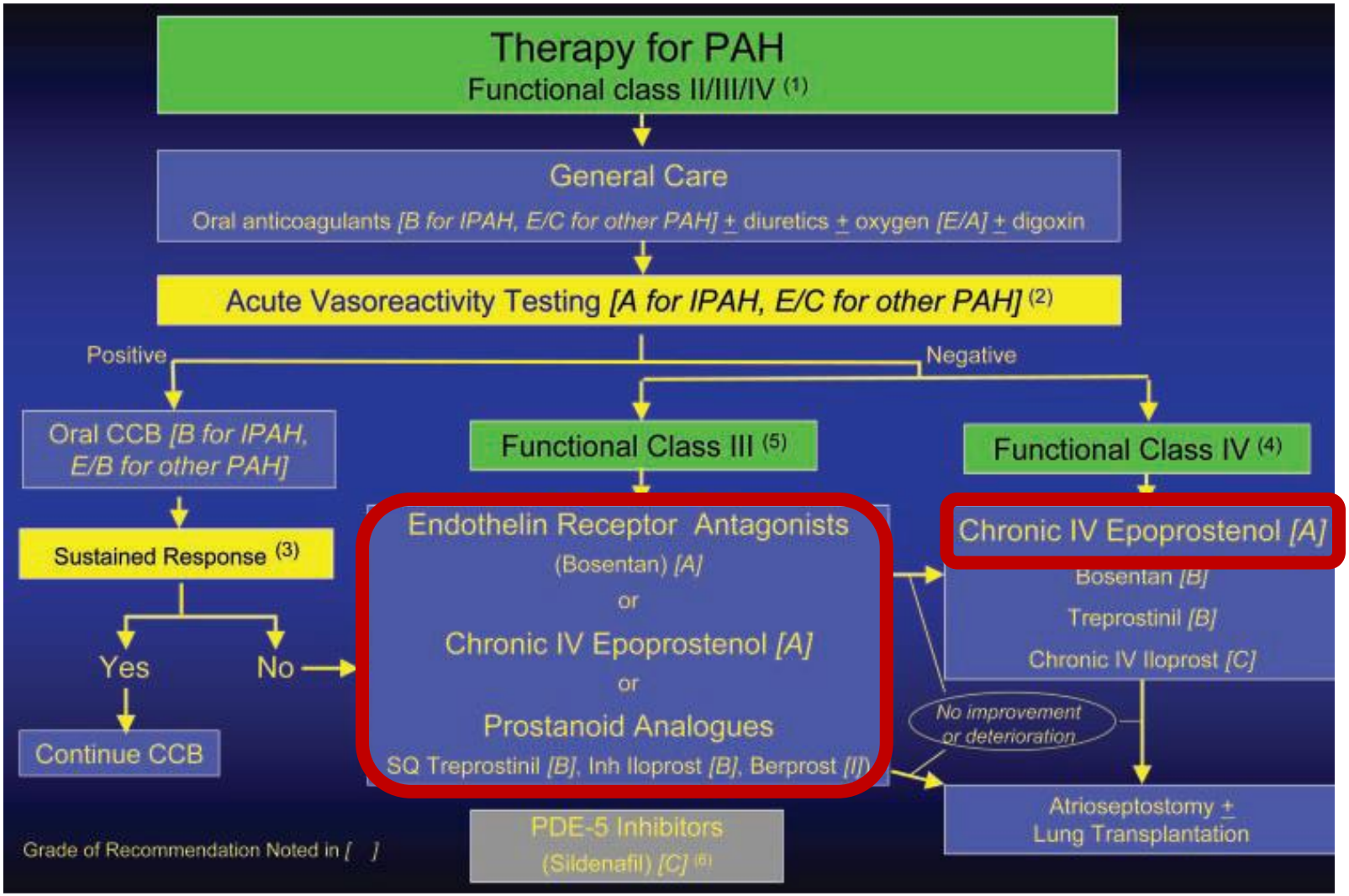
*** 12-month double-blind, randomized, placebo-controlled trial**



➢ **No significant improvement in dyspnea, functional class, survival**

Barst et al., J Am Coll Cardiol 2003; 41:2119-2125

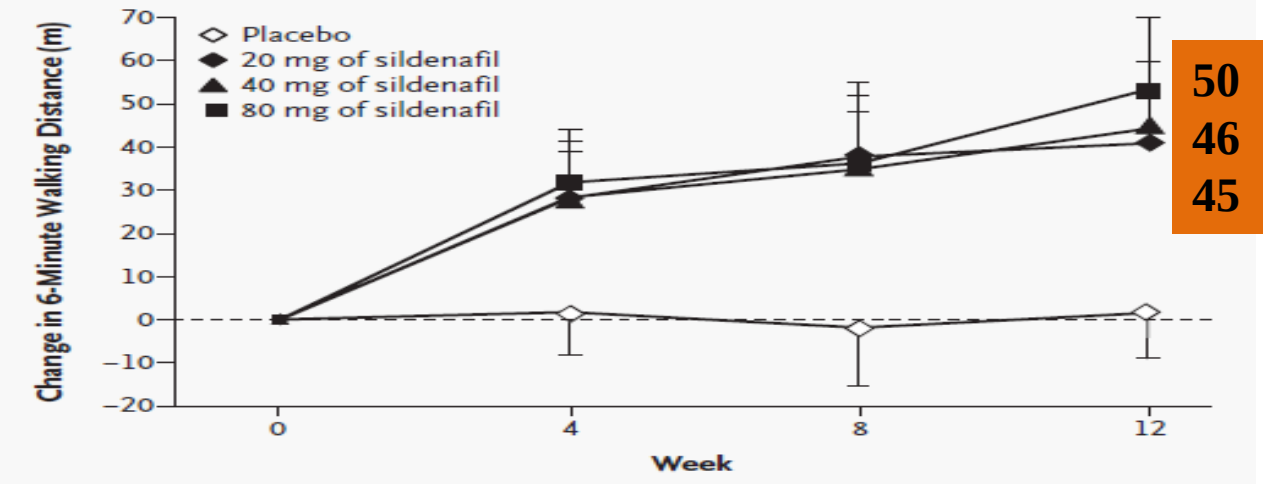
ACCP 2004 guidelines for PAH



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%)**

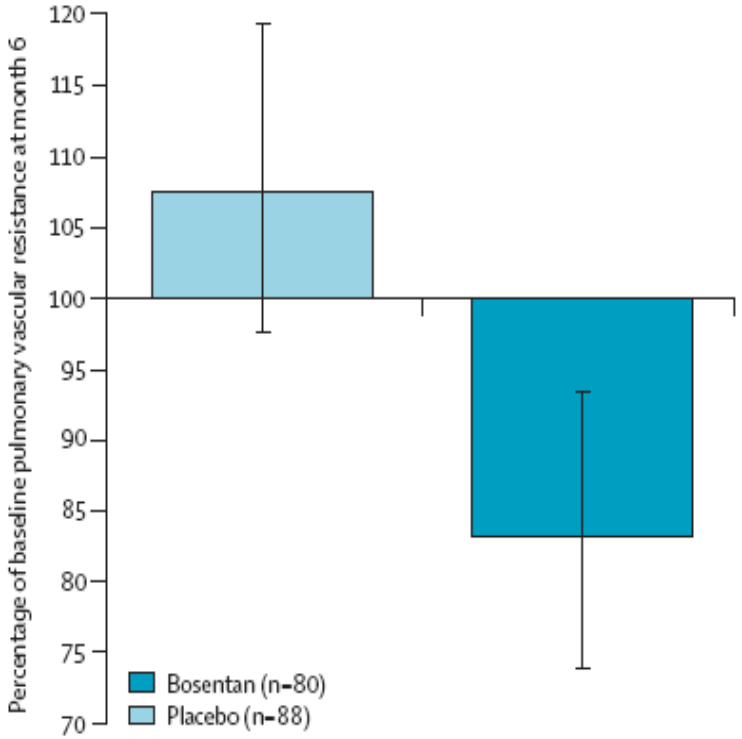


Variable	Placebo (N=65)	Sildenafil					
		20 mg (N=65)	P Value	40 mg (N=63)	P Value	80 mg (N=65)	P Value
Heart rate — beats/minute	−1.3 (−4.1 to 1.4)	−3.7 (−5.9 to −1.4)	0.18	−3.3 (−5.5 to −1.0)	0.27	−4.7 (−7.3 to −2.2)	0.05
Mean pulmonary artery pressure — mm Hg	0.6 (−0.8 to 2.0)	−2.1 (−4.3 to 0.0).	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

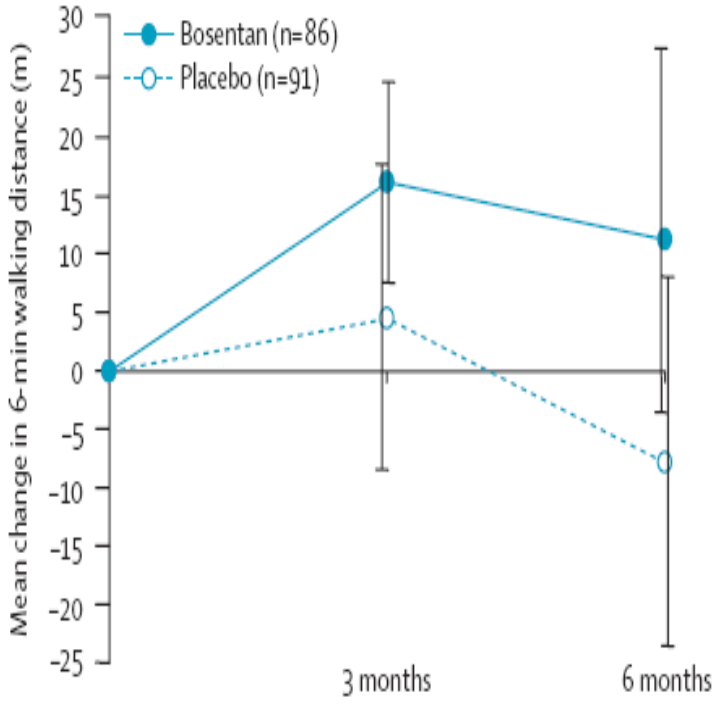
Galie N, et al. N Engl J Med 2005;353:2148-57.

Bosentan treatment in patients with mildly symptomatic PAH; EARLY study

Patients : 185 patients with FC-II PAH (IPAH, PAH-CTD, PAH-CHD, PAH-HIV)
Primary endpoint : change in PVR & 6MWD after 6 month



Treatment effect −22·6%, p=0.0001

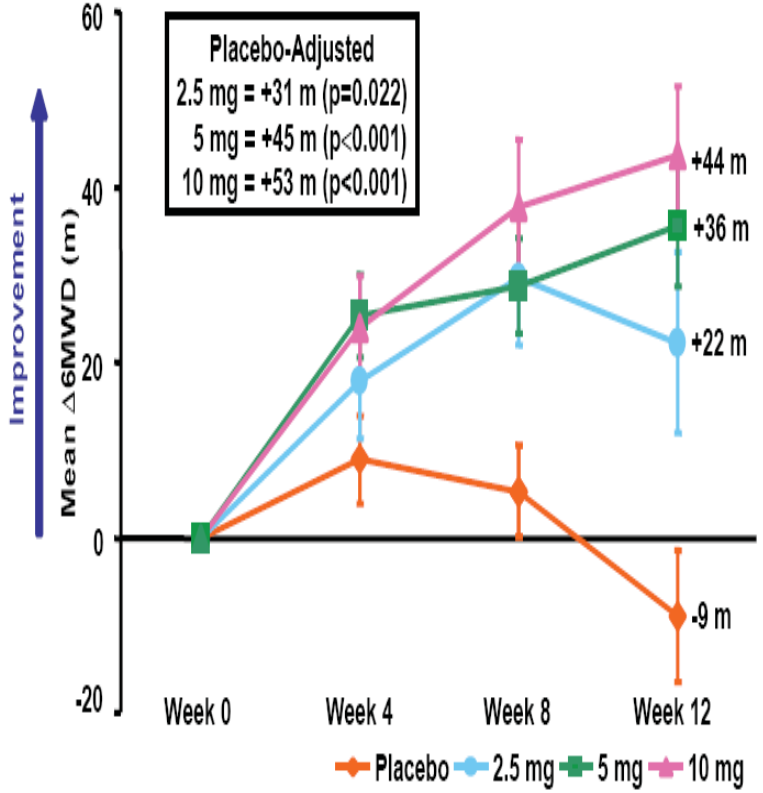


treatment effect of 19.1 m (p=0.075)

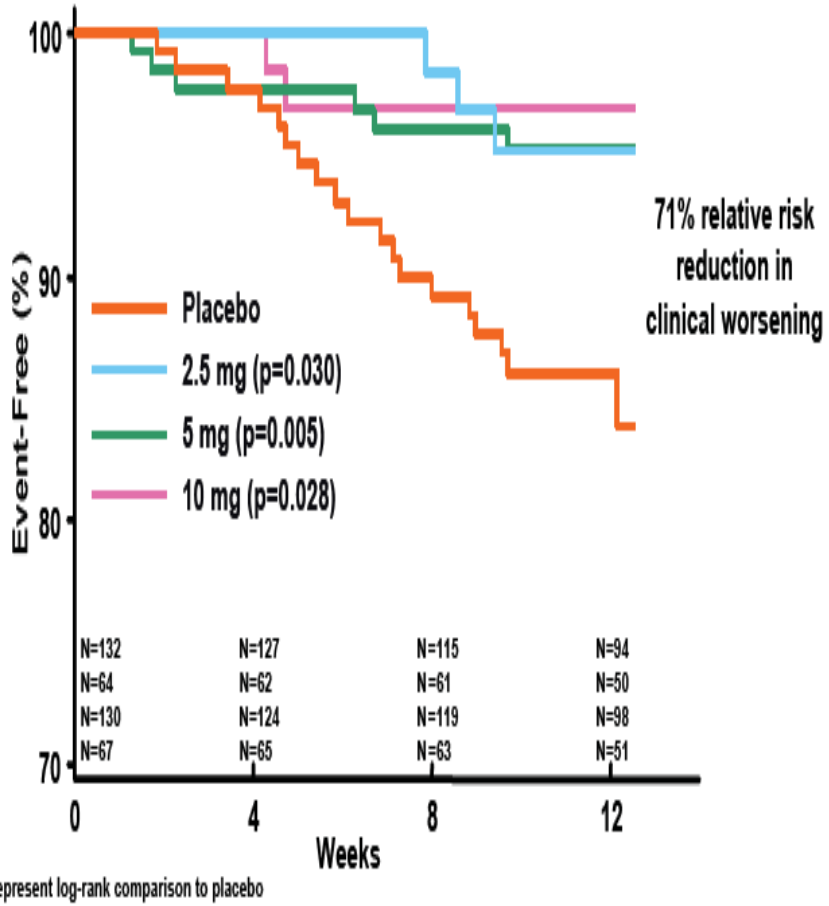
Galie et al. Lancet 2008; 371: 2093–100

Ambrisentan for PAH: ARIES 1, 2

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



Mean ± standard error
Wilcoxon rank sum test stratified by PAH etiology and study

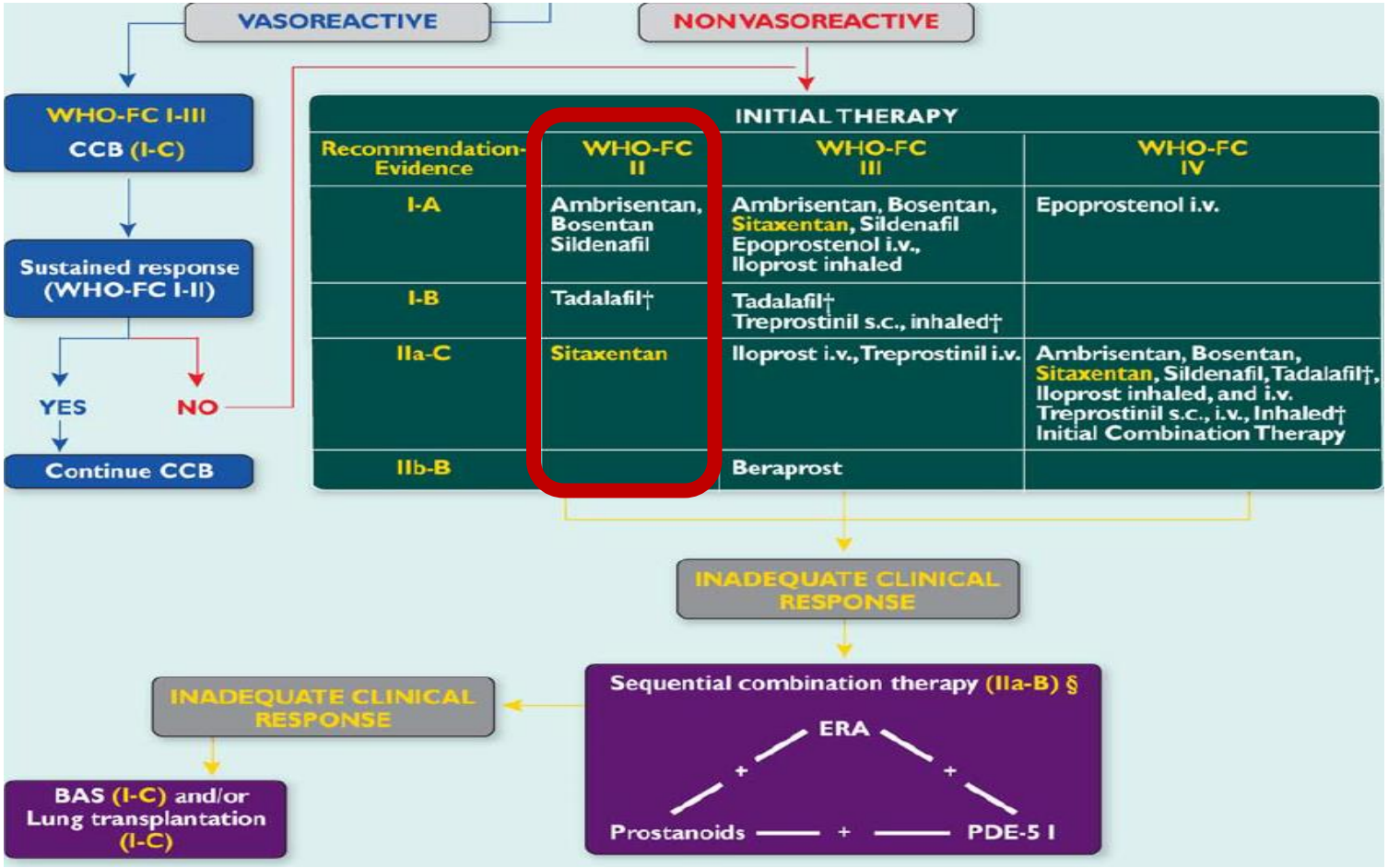


P-values represent log-rank comparison to placebo

Galie N, et al. Circulation. 2008;117:3010-3019

ESC/ERS 2009 guidelines for PH

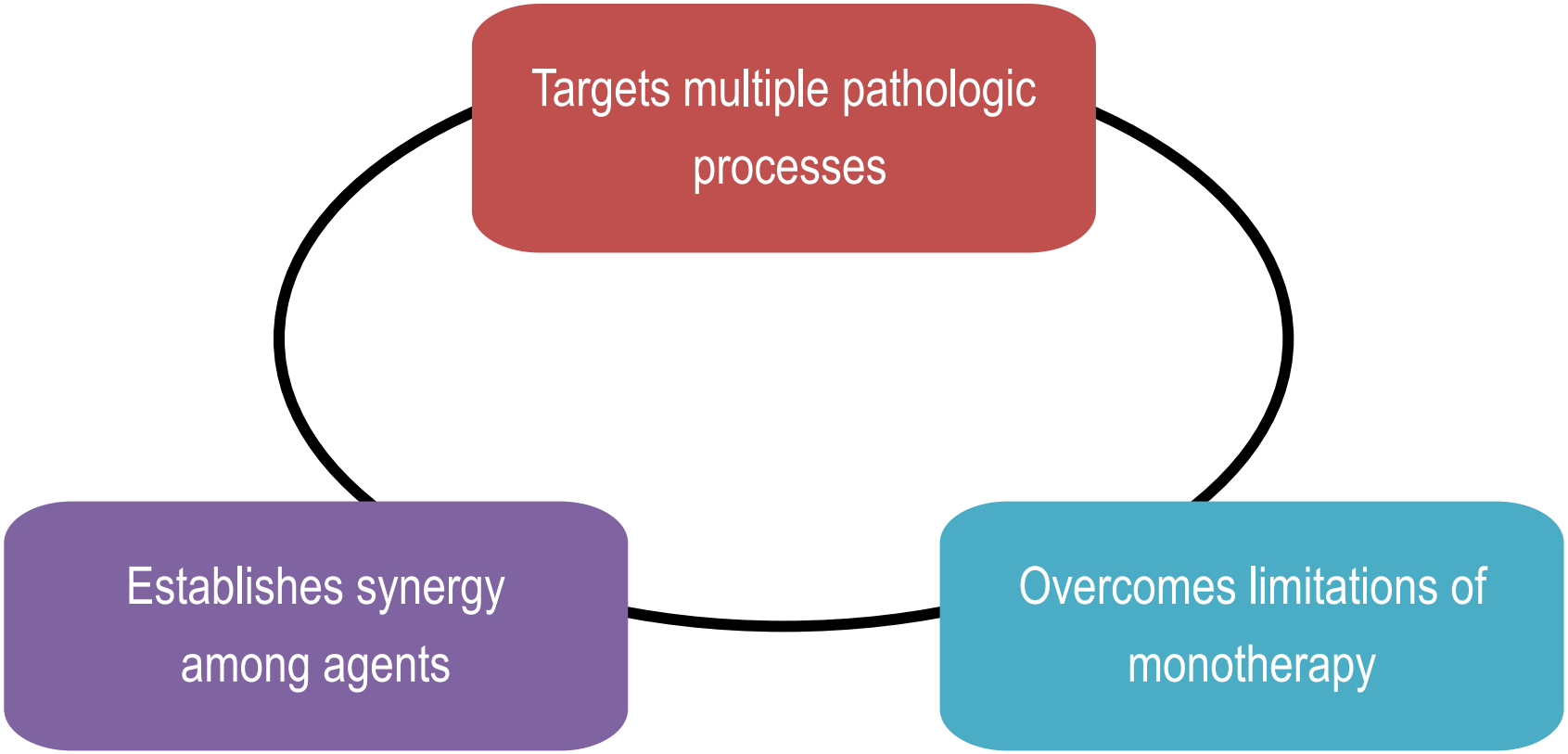
- **PAH target agent for WHO-FC II**
- **Sequential combination**



European Heart Journal (2009) 30, 2493–2537

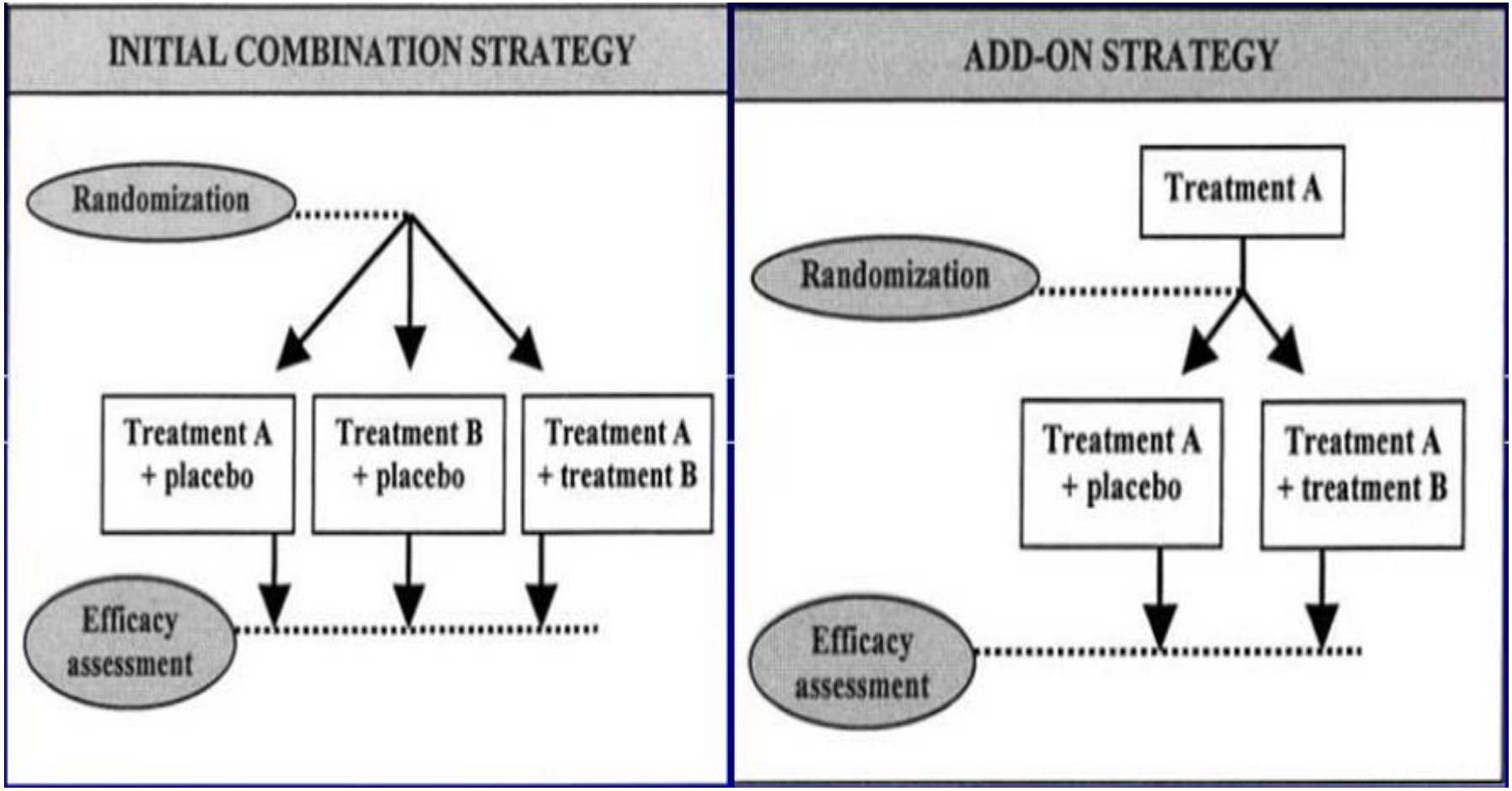
The rationale for combination therapy

- None of the available treatment options cures PAH and the **disease will eventually progress despite active treatment**.



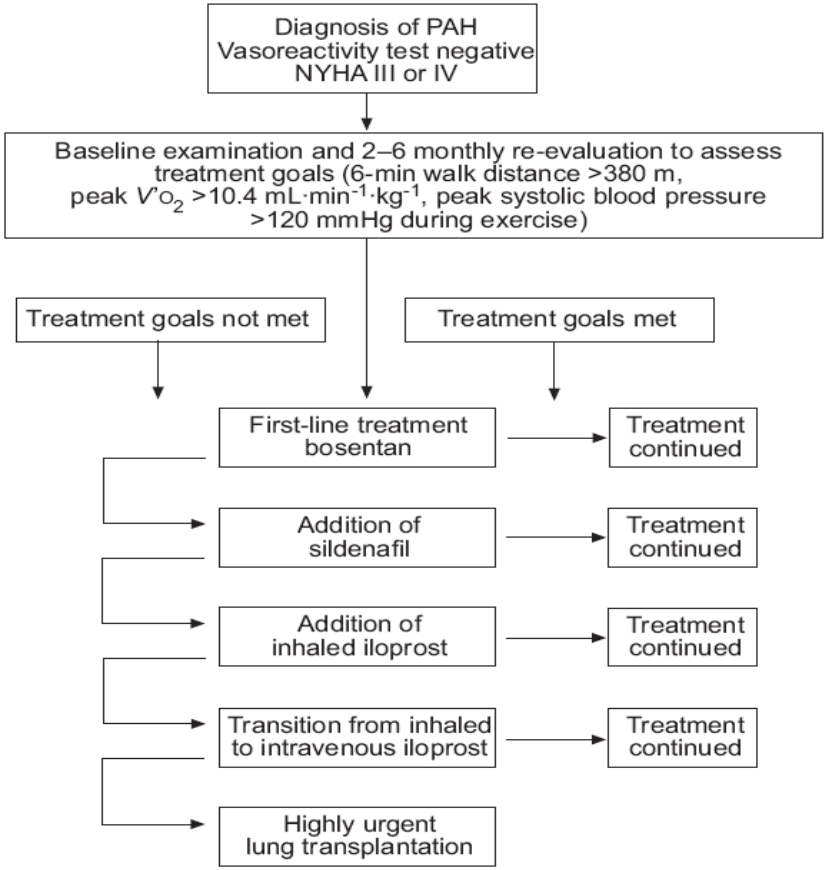
Ghofrani HA, et al. Eur Respir Rev. 2014;23:469-475.

Strategies for the evaluation of combination therapy



Provencher et al. Chest 2005;128;622S-628S

Goal-oriented treatment and combination therapy for PAH



Treatment goals:

1) 6MWD > 380m

2) Peak VO2 > 10.4 mL/min/kg

3) peak systolic BP > 120mmHg during exercise

Double combination 51 (43%)

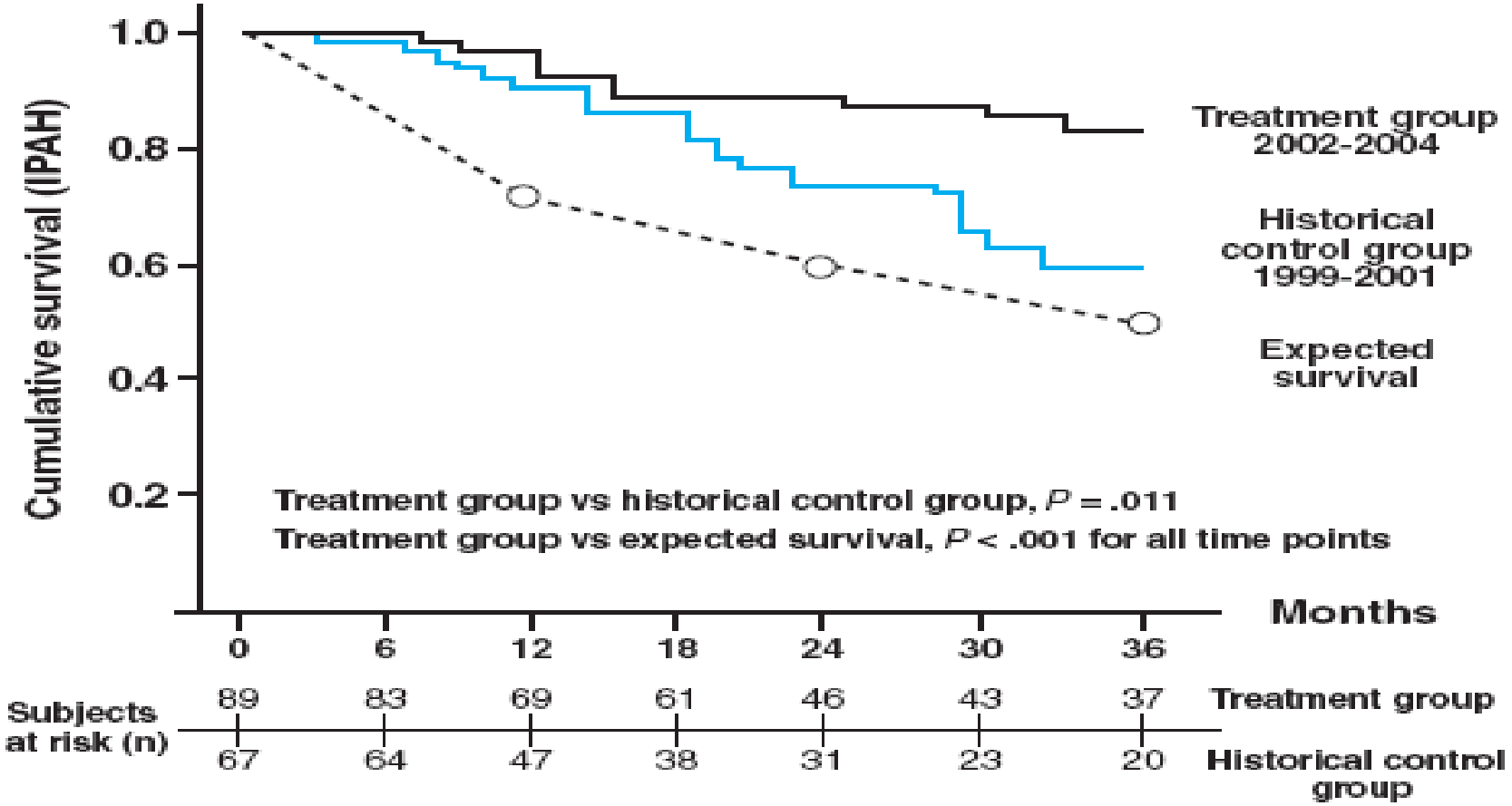
Triple combination 19 (16%)

IV iloprost 5 (4%)

Transplantation 1

Eur Respir J 2005; 26: 858–863

Survival of patients with IPAH with a goal-oriented treatment strategy



Eur Respir J 2005; 26: 858–863

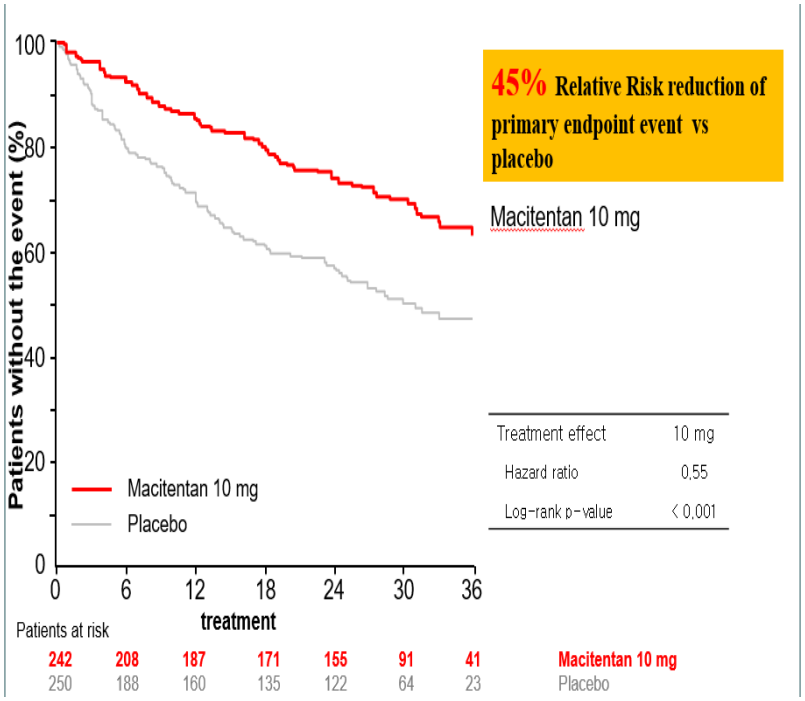
Sequential combination therapy in SERAPHIN trial

	Placebo (n = 250)	Macitentan 3 mg (n = 250)	Macitentan 10 mg (n = 242)	All patients (n = 742)
Background PAH therapy, n (%)				
Yes	**154 (61.8)**	**163 (65.7)**	**154 (63.6)**	**471 (63.7)**
Phosphodiesterase-5 inhibitors	**150 (60.2)**	**154 (62.1)**	**150 (62.0)**	**454 (61.4)**
Oral/inhaled prostanoids	**7 (2.8)**	**18 (7.3)**	**15 (6.2)**	**40 (5.4)**
No	**95 (38.2)**	**85 (34.3)**	**88 (36.4)**	**268 (36.3)**

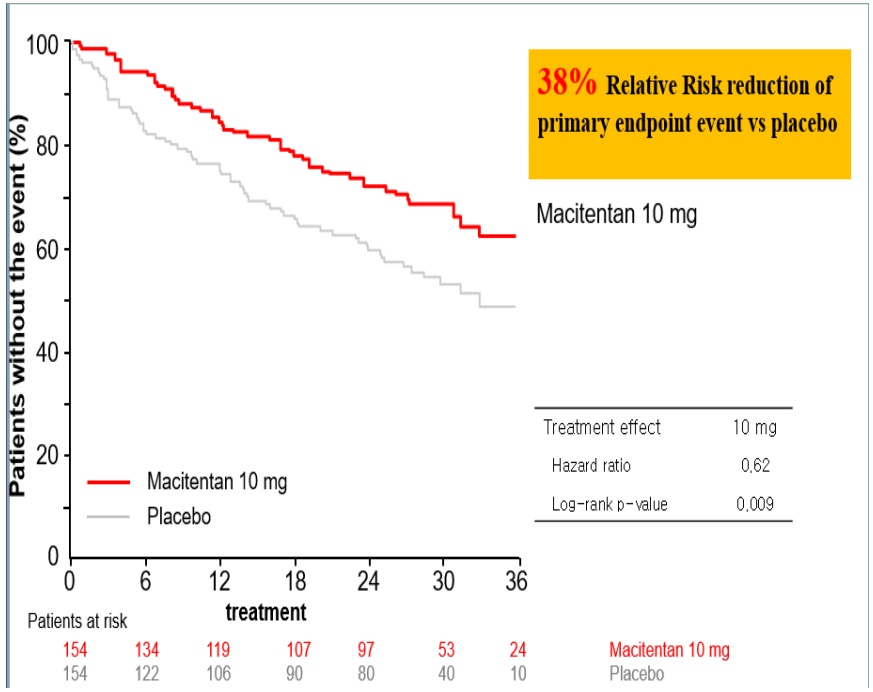
N Engl J Med 2013;369:809-18

Primary endpoint: Morbidity and Mortality

All patients

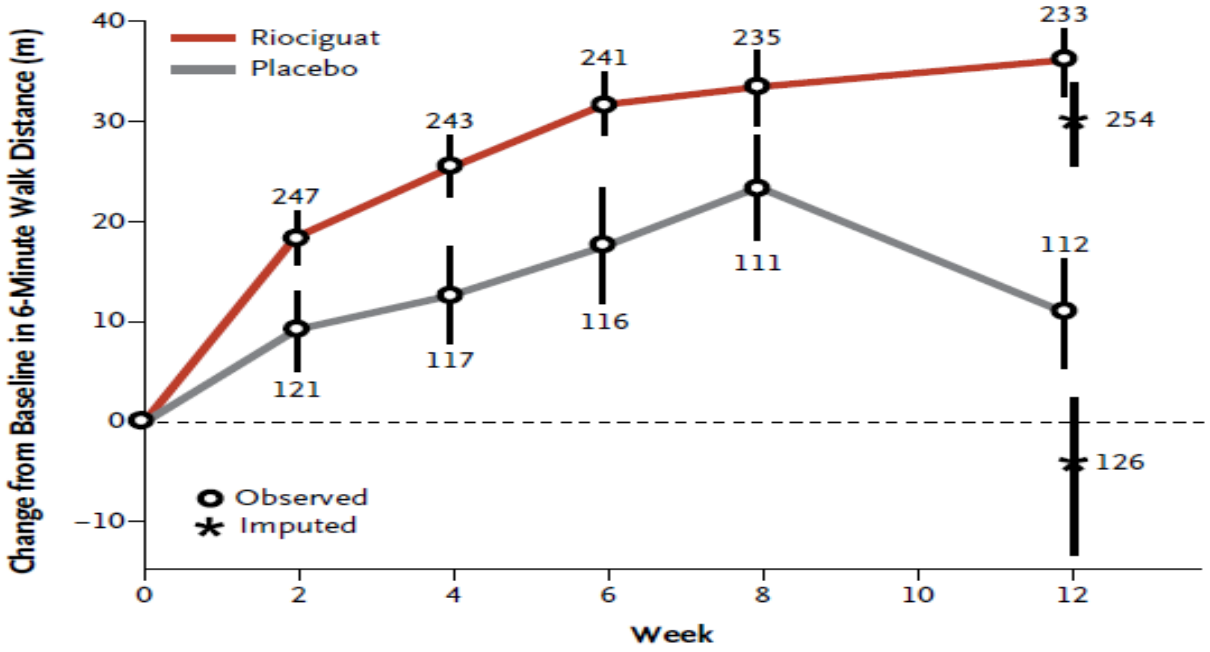


Patients with background Therapy



N Engl J Med 2013;369:809-18

Sequential combination therapy in Patent-1 trial



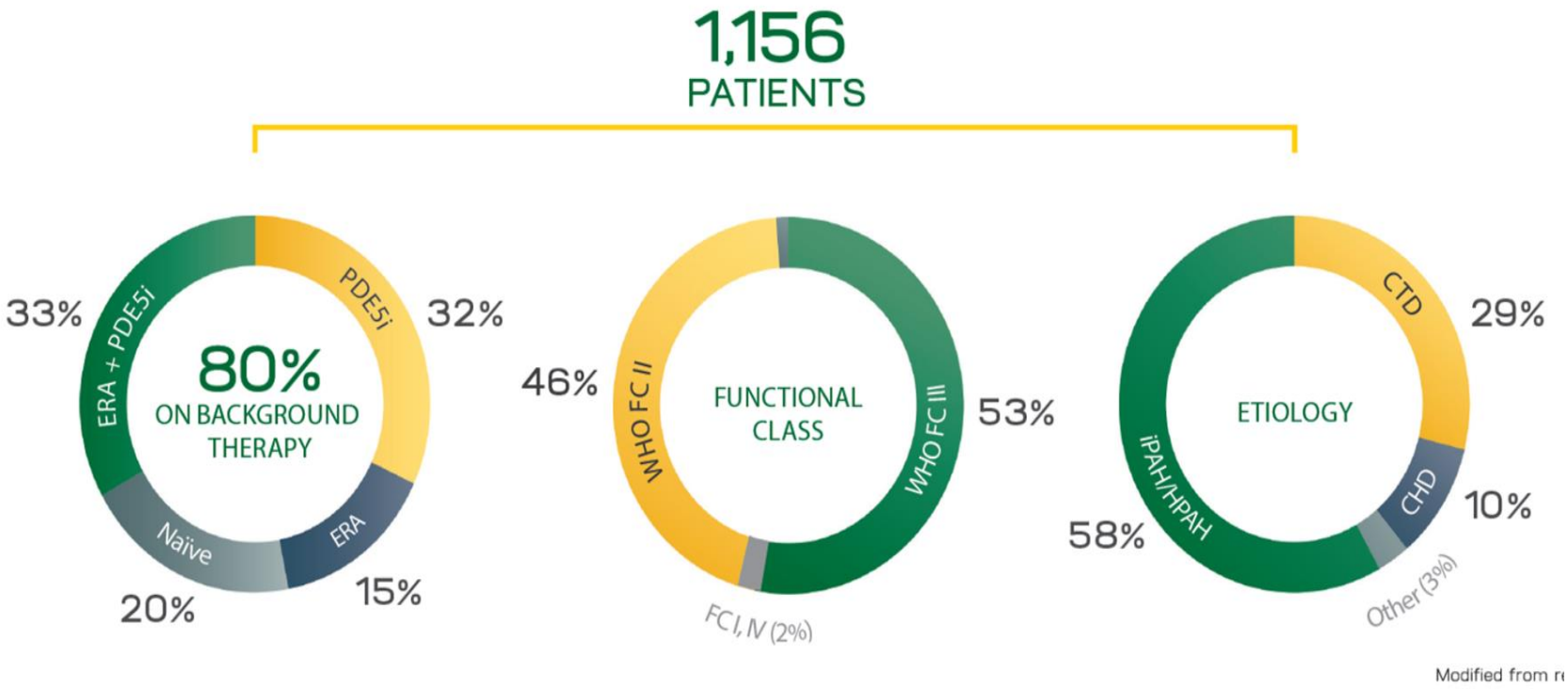
Baseline variable	No. of patients	Placebo	Riociguat	LS-mean treatment difference in change in 6MWD, m (95% CI)
		Change in 6MWD (m)		
Baseline therapy				
Treatment-naïve	189	-6	32	38 (16–60)
Pretreated	191	-5	27	34 (11–56)
Pretreated – ERA	167	0	23	24 (1–48)
Pretreated – prostanoid	24	-49	56	106 (38–173)

Ghofrani HA, et al. N Engl J Med 2013;369:330-40.

Sequential combination therapy in GRIPHON trial

The safety and efficacy of UPTRAVI in patients with PAH was established in the GRIPHON, phase 3 trial.

Patient characteristics at baseline: background therapy, FC, etiology



Modified from r

ERA; endothelin receptor antagonist, PDE-5i; phosphodiesterase type 5 inhibitor, iPAH; idiopathic PAH, hPAH; heritable PAH, CTD-PAH; PAH associated with connective tissue disease, CHD-PAH; PAH associated with congenital heart disease / # PAH associated with corrected-congenital shunts

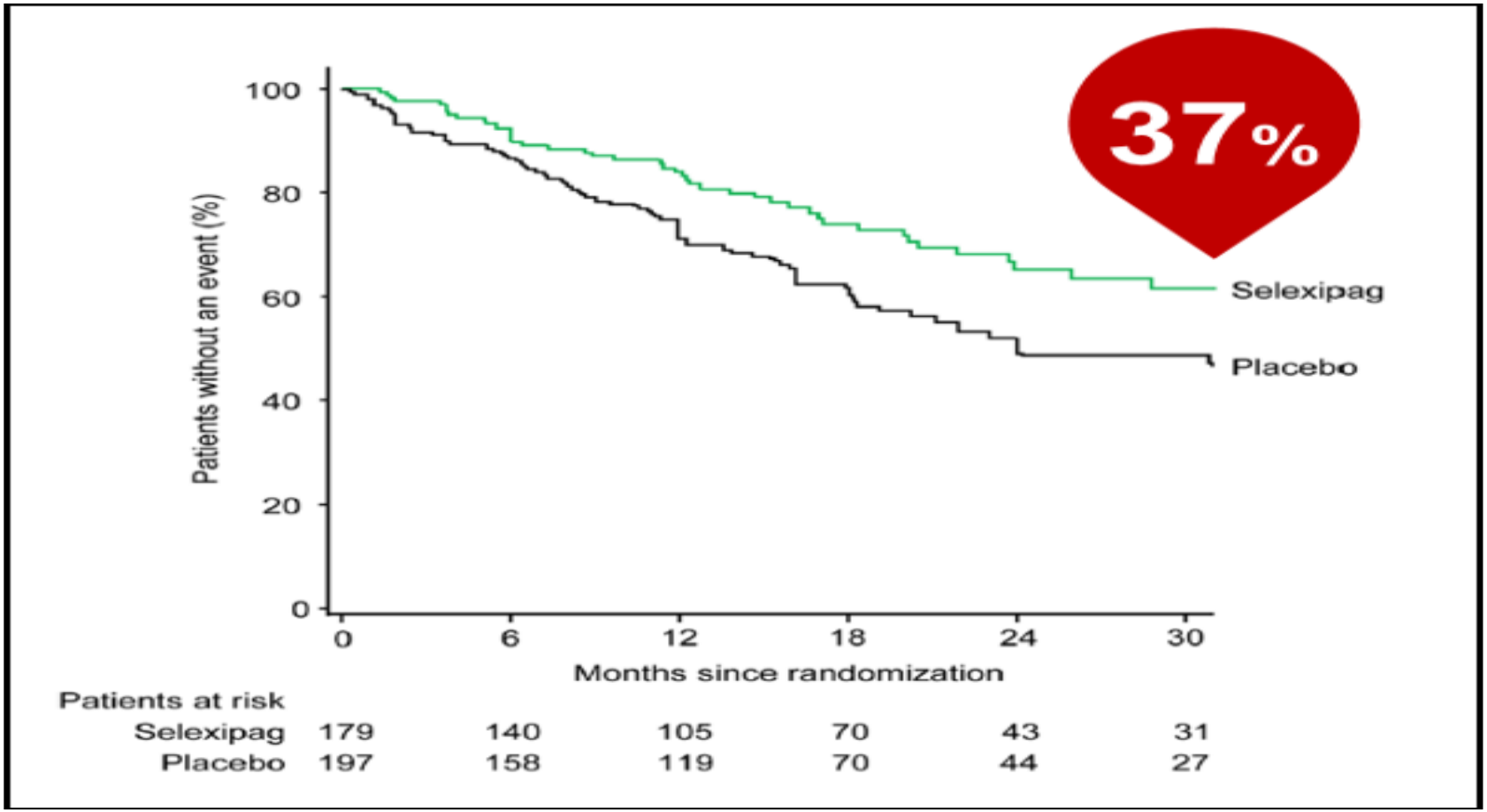
Modified from Sitbon O, et al. N Engl J Med. 2015 Dec 24;373(26):2522-33

GRIPHON study : Primary endpoints

Primary endpoint events = first events only, *n* (%)	Placebo *n* = 582	Selexipag *n* = 574	Selexipag vs. placebo	
	Number of patients (%)		HR (95% CI)	*p*-value‡
All primary endpoint events	242 (41.6)	155 (27.0)	**0.60 (0.46-0.78)**	<0.001
Hospitalization for PAH worsening	109 (18.7)	78 (13.6)		
Disease progression	100 (17.2)	38 (6.6)		
Death (all causes)	18 (3.1)	28 (4.9)		
Initiation of parenteral prostanoid or chronic O_2 therapy for PAH worseni ng	13 (2.2)	10 (1.7)		
PAH worsening resulting in need for lung transplantation or balloon atrial septostomy	2 (0.3)	1 (0.2)		

Modified from Sitbon O, et al. N Engl J Med. 2015 Dec 24;373(26):2522-33

Triple combination therapy: Time to first morbidity or mortality

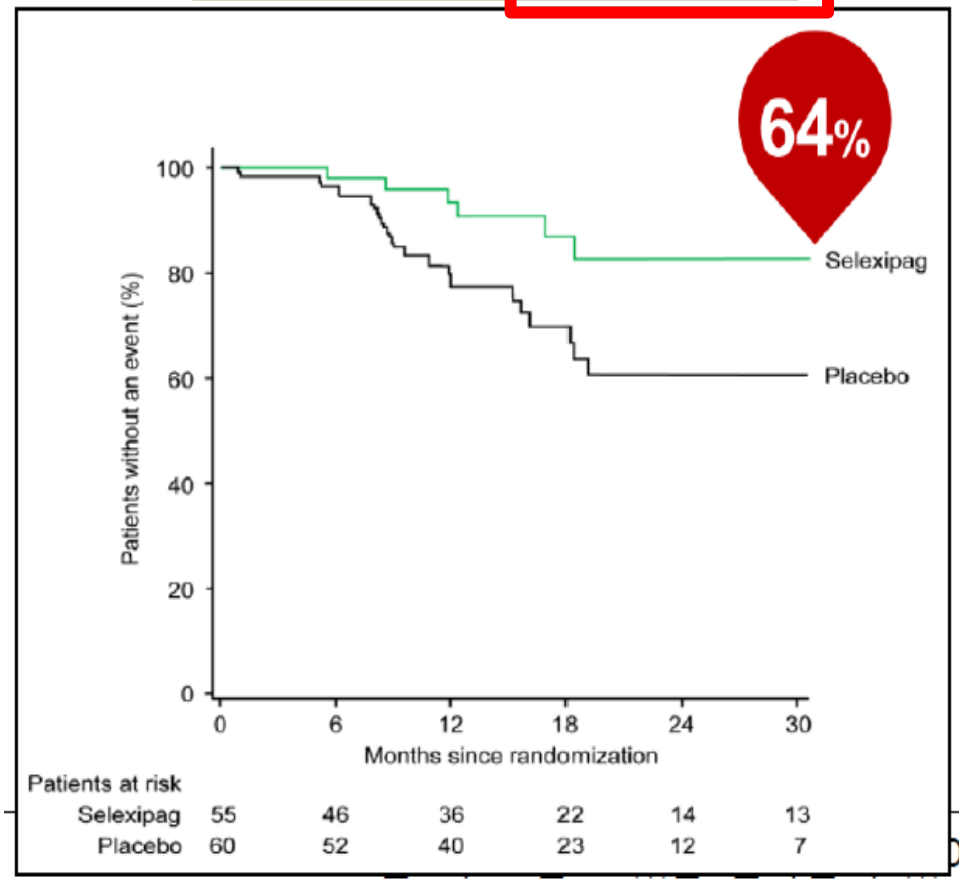


J. Gerry Coghlan , et al. Am J Cardiovasc Drugs 2018, 18;37-47

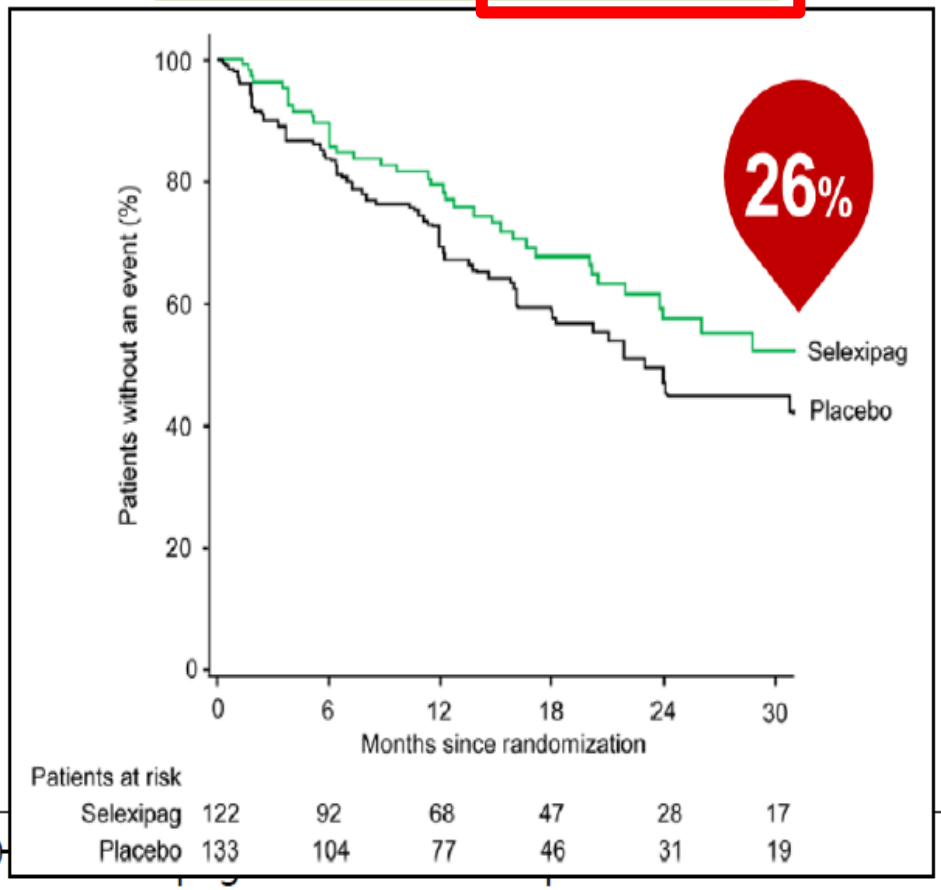
Triple combination therapy:
The earlier, the better

Results

Patients with WHO FC II at baseline



Patients with WHO FC III at baseline



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

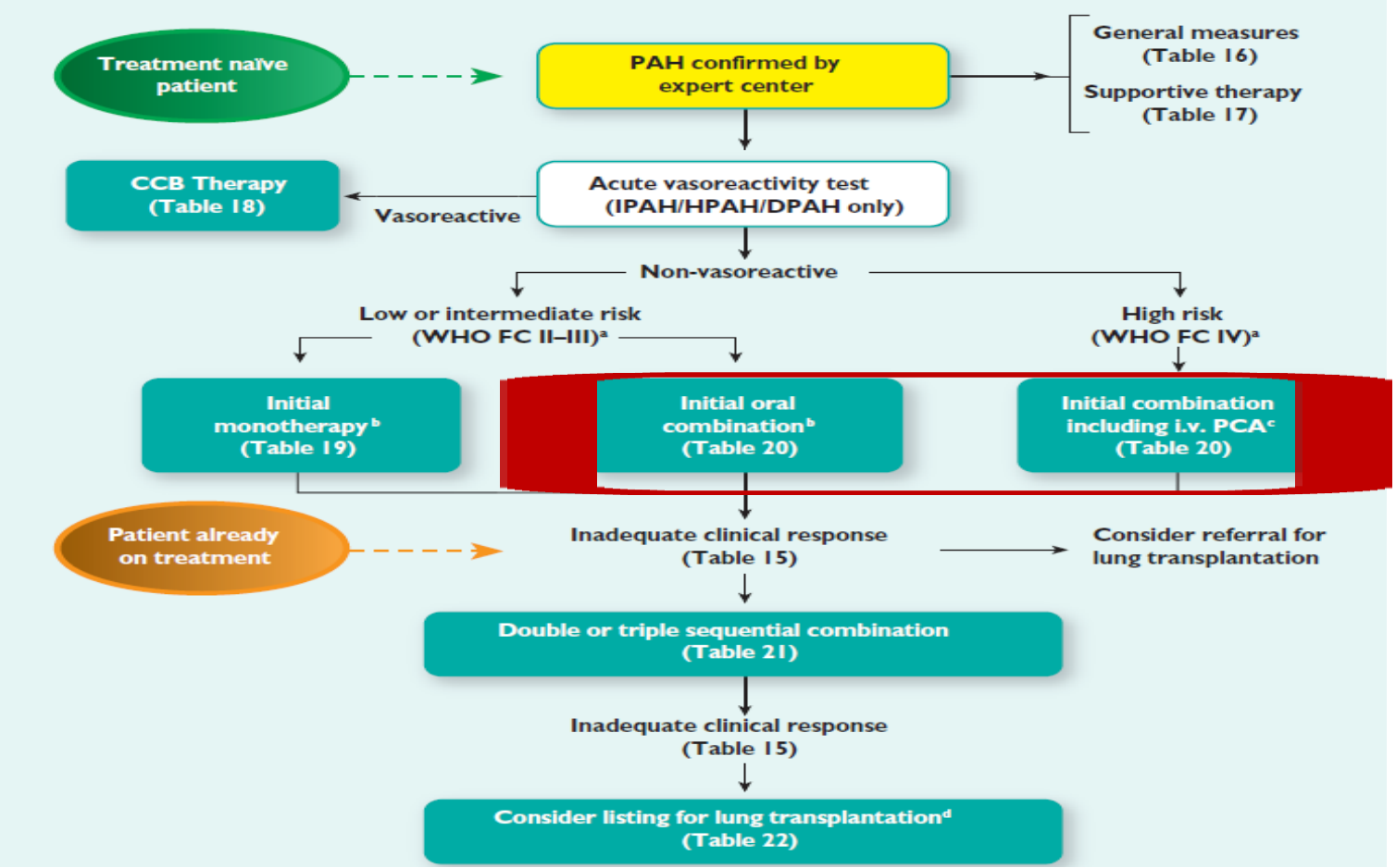
Sequential combination therapy for PAH

조치/치료	권고 수준 - 근거 수준					
	WHO-FC II		WHO-FC III		WHO-FC IV	
실데나필 – '마시센탄' 추가	I	B	I	B	IIb	C
보센탄 – '리오시구앗' 추가	I	B	I	B	IIb	C
엔도텔린 수용체 길항제 및/또는 포스포디에스터라제-5억제제 – '셀렉시팍' 추가	I	B	I	B	IIb	C
에포프로스테놀 – '실데나필' 추가	–	–	I	B	IIa	B
실데나필 또는 보센탄 – '트레프로스티닐 흡입제' 추가	IIa	B	IIa	B	IIa	C
보센탄 – '일로프로스트 흡입제' 추가	IIb	B	IIb	B	IIb	C
보센탄 – '타다라필' 추가	IIa	C	IIa	C	IIa	C
실데나필 – '암브리센탄' 추가	IIb	C	IIb	C	IIb	C
에포프로스테놀 –'보센탄' 추가	–	–	IIb	C	IIb	C
실데나필 – '보센탄' 추가	IIb	C	IIb	C	IIb	C
보센탄 –'실데나필' 추가	IIb	C	IIb	C	IIb	C
기타 2제 병용치료	IIb	C	IIb	C	IIb	C
기타 3제 병용치료	IIb	C	IIb	C	IIb	C
실데나필 또는 다른 포스포디에스터라제-5억제제 – '리오시구앗' 추가	III	B	III	B	III	B

Korean guideline for diagnosis and treatment of pulmonary hypertension. 2020

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

예후 결정요인[a] (1년 추정 사망률)		저위험도 < 5%	중간 위험도 5~10%	고위험도 >10%
우심부전의 임상증상		없음	없음	있음
증상의 진행		없음	느림	빠름
실신		없음	간헐적인 실신[b]	반복되는 실신[c]
WHO 기능등급		I, II	III	IV
6분 보행거리		> 440 m	165~440 m	< 165 m
심폐운동검사	Peak VO_2	> 15 mL/min/kg (> 65% pred.)	11~15 mL/min/kg (35~65% pred.)	< 11 mL/min/kg (< 35% pred.)
	VE/CO_2 slope	< 36	36~44.9	≥ 45
BNP/ NT-proBNP	BNP	< 50 ng/L	50~300 ng/L	> 300 ng/L
	NT-proBNP	< 300 ng/L	300~1,400 ng/L	> 1,400 ng/L
영상(심초음파, 심장 자기공명영상)	우심방면적	< 18 cm^2	18~26 cm^2	> 26 cm^2
	심장막삼출	없음	없거나 미미함	있음
혈역학지표	우심방압	< 8 mmHg	8~14 mmHg	> 14 mmHg
	심박출량지수 (CI)	≥ 2.5 L/min/m^2	2.0~2.4 L/min/m^2	< 2.0 L/min/m^2
	SvO_2	> 65%	60~65%	< 60%

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Simplified risk assessment in PAH

예후 결정요인[a] (1년 추정 사망률)		저위험도 < 5%	중간 위험도 5~10%	고위험도 > 10%
		적어도 3개 이상의 저위험도 지표들이 있고, 고위험도 지표가 하나도 없는 경우	지표들이 저위험 또는 고위험의 범주에 들지 않을 경우	심박출량지수나 SvO_2를 포함하는 적어도 2개 이상의 고위험도 지표들이 있는 경우
WHO 기능등급		I, II	III	IV
6분 보행거리		> 440 m	165~440 m	< 165 m
BNP/ NT-proBNP	BNP	< 50 ng/L	50~300 ng/L	> 300 ng/L
	NT-proBNP	< 300 ng/L	300~1,400 ng/L	> 1,400 ng/L
혈역학 지표	우심방압	< 8 mmHg	8~14 mmHg	> 14 mmHg
	심박출량지수 (CI)	≥ 2.5 L/min/m^2	2.0~2.4 L/min/m^2	< 2.0 L/min/m^2
	SvO_2	> 65%	60~65%	< 60%

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폐동맥고혈압의 중증도 및 치료에 대한 임상적 반응 평가

권고사항	권고 수준	근거 수준
임상적 평가, 운동능력 검사, 생화학적 지표, 심초음파검사, 혈역학적 평가를 통해 폐동맥고혈압 환자의 중증도를 평가하는 것이 필요하다(표 12-1, 12-2, 표 13).	I	C
안정적인 환자에게는 3~6개월마다 정기적으로 추적검사를 시행하는 것이 권고된다(표 13).	I	C
저위험도 상태(표 12-1, 12-2)에 도달하고 유지하는 것이 폐동맥고혈압 환자에게 적절한 치료이다.	I	C
중간 위험도 상태(표 12-1, 12-2)에 도달 또는 유지되는 것은 대부분의 환자에게 불충분한 치료이다.	IIa	C

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Initial (Upfront) combination therapy: Ambrisentan+Tadalafil

End Point	Combination-Therapy Group (N=253)	Pooled-Monotherapy Group (N=247)	Ambrisentan-Monotherapy Group (N=126)	Tadalafil-Monotherapy Group (N=121)
Primary end point				
First event of clinical failure — no. of participants (%)	46 (18)	77 (31)	43 (34)	34 (28)
Death	9 (4)	8 (3)	2 (2)	6 (5)
Hospitalization for worsening pulmonary arterial hypertension	10 (4)	30 (12)	18 (14)	12 (10)
Disease progression	10 (4)	16 (6)	12 (10)	4 (3)
Unsatisfactory long-term clinical response	17 (7)	23 (9)	11 (9)	12 (10)
Hazard ratio, combination therapy vs. monotherapy (95% CI)	Reference	0.50 (0.35 to 0.72)	0.48 (0.31 to 0.72)	0.53 (0.34 to 0.83)
P value	—	<0.001	<0.001	0.005

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

Initial combination therapy for PAH

조치/치료	권고 수준 - 근거 수준					
	WHO-FC II		WHO-FC III		WHO-FC IV	
암브리센탄 + 타다라필[a]	I	B	I	B	IIb	C
그 외 엔도텔린 수용체 길항제 + 포스포디에스터라제-5억제제	IIa	C	IIa	C	IIa	C
보센탄 + 실데나필 + I.V. 에포프로스테놀	–	–	IIa	C	IIa	C
보센탄 + I.V. 에포프로스테놀	–	–	IIa	C	IIa	C
그 외 엔도텔린 수용체 길항제 또는 포스포디에스터라제-5억제제 + S.C. 트레프로스티닐			IIa	C	IIa	C
그 외 엔도텔린 수용체 길항제 또는 포스포디에스터라제-5억제제 + 그 외 I.V. 프로스타사이클린			IIa	C	IIa	C

[a] 임상시험의 1차 평가목표(임상적 실패까지의 소요 시간 또는 모든 원인으로 인한 사망률 감소)가 입증된 무작위 대조군 연구

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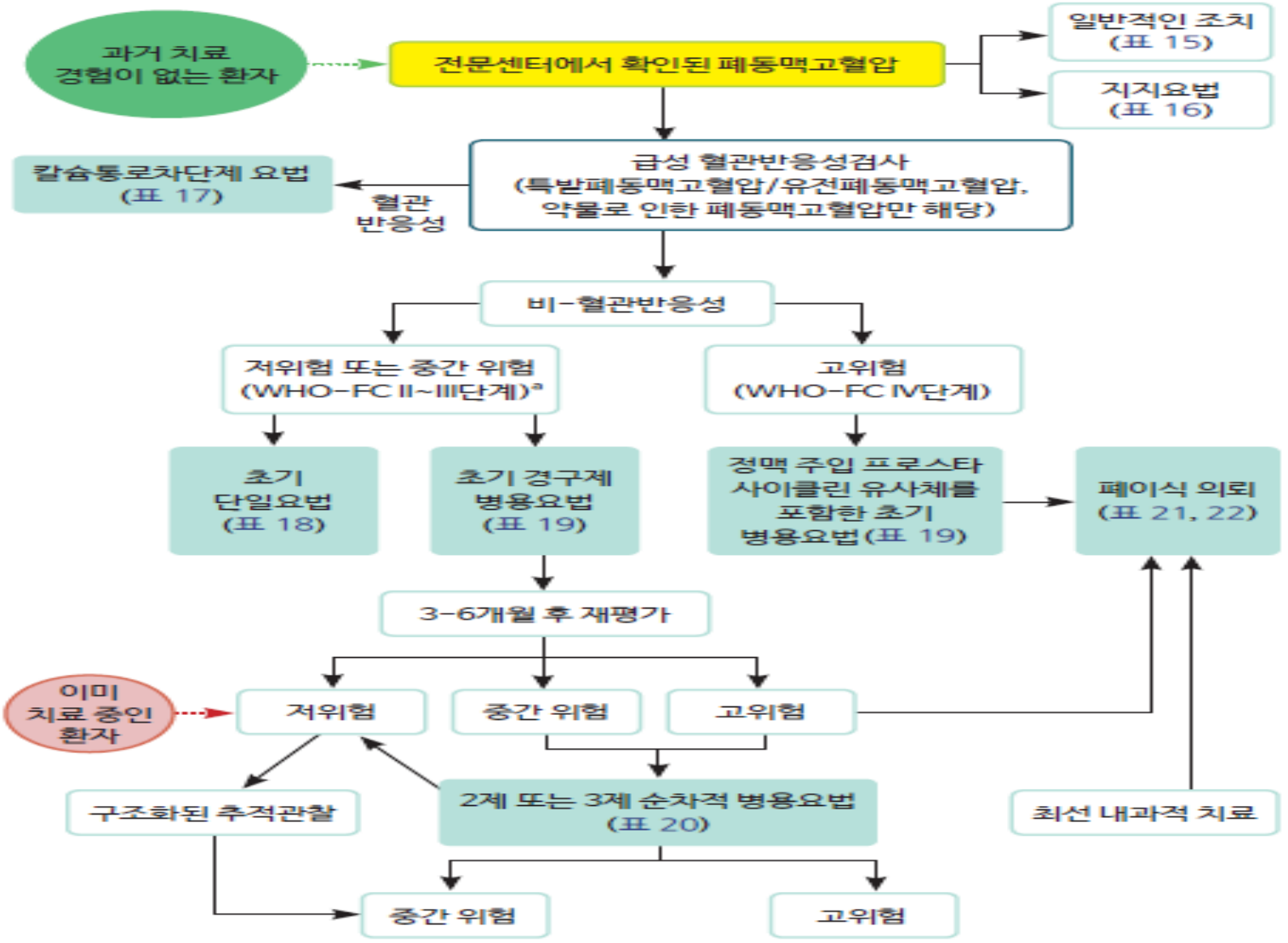
폐고혈압의 치료 알고리즘



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Lung transplantation

□ 응급도 0	– 입원한 환자로 다음 한 가지 이상 해당하는 경우 □ 호흡부전증으로 인공호흡기(Intubation ventilator)를 부착 중인 환자 □ 체외막형 심폐기를 가동 중인 환자
□ 응급도 1	(60일마다 재등록하며 검사 결과는 검사 시점과 상관없이 인정한다) – 다음 한 가지 이상 해당하여야 한다. 1) 산소 투여 없이 측정한 동맥혈 가스 검사상 PaO_2 < 55 mmHg 2) 평균 폐동맥압 > 65 mmHg, 또는 평균 우심방압 > 15 mmHg 3) 심박출량 지표 < 2 L/min/m^2 인 경우 4) 동맥혈가스분석에서 PCO_2 ≥ 80 mmHg인 경우 5) 입원 환자 중 고유량비강캐뉼라(highflow nasal cannula) 30 L FiO_2 ≥ 0.6으로 2주 이상 유지 중인 경우(유지 중에만 인정)
□ 응급도 2	– 다음 한 가지 이상 해당하여야 한다. (등록 시점 30일 이내의 검사 결과로 등록할 수 있으며 180일마다 연장할 수 있다. 검사 결과는 처음 등록 시점 검사 결과만으로 연장이 가능하다.) 1) 폐기능검사에서 1초 강제호기량(FEV1) < 25% 2) 산소 없이 측정한 동맥혈 가스 분석에서 PaO_2 < 60 mmHg 3) 평균우심방압이 10~15 mmHg인 경우 4) 평균 폐동맥압이 55~65 mmHg인 경우 5) 심박출량지표 < 2~2.5 L/min/m^2 인 경우 6) 동맥혈가스분석에서 70 mmHg ≤ PCO_2 < 80 mmHg인 경우 7) DLCO < 30% 인 경우

Take home messages

- **Diagnosis of PH: Echo -> V/Q scan -> RHC**
- **Most common cause of PH: PH due to left heart disease**
- **Treatment of IPAH : based on acute vasodilator test**
  risk stratification
- **PAH target agents: Prostanoids,**
  Endothelin receptor antagonists,
  PDE-5 inhibitors
- **Initial combination treatment**