Management of PAH

Puneet Saxena

Introduction

- Early identification and treatment
- Advanced disease may be less responsive to therapy
- Principles of management of PAH cannot be extrapolated to other forms of PH

Outline

- Definition and Classification
- Diagnosis
- Vasoreactivity Testing
- Assessment of severity
- Treatment
  - General measures
  - Supportive therapy
  - Advanced therapy
- Recent advances

Definition & Classification

Diagnostic Criteria

- PH is defined as an increase in mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest as assessed by right heart catheterization (RHC).

- PAH is defined as a subgroup of PH with:
  - PAWP ≤15 mmHg with PVR > 3 Wood units
  - Chronic lung diseases and other causes of hypoxemia are mild or absent
  - Venous thromboembolic disease is absent
  - Certain miscellaneous disorders are absent, including systemic disorders (eg, sarcoidosis), hematologic disorders (eg, myeloproliferative diseases), and metabolic disorders (eg, glycogen storage disease).

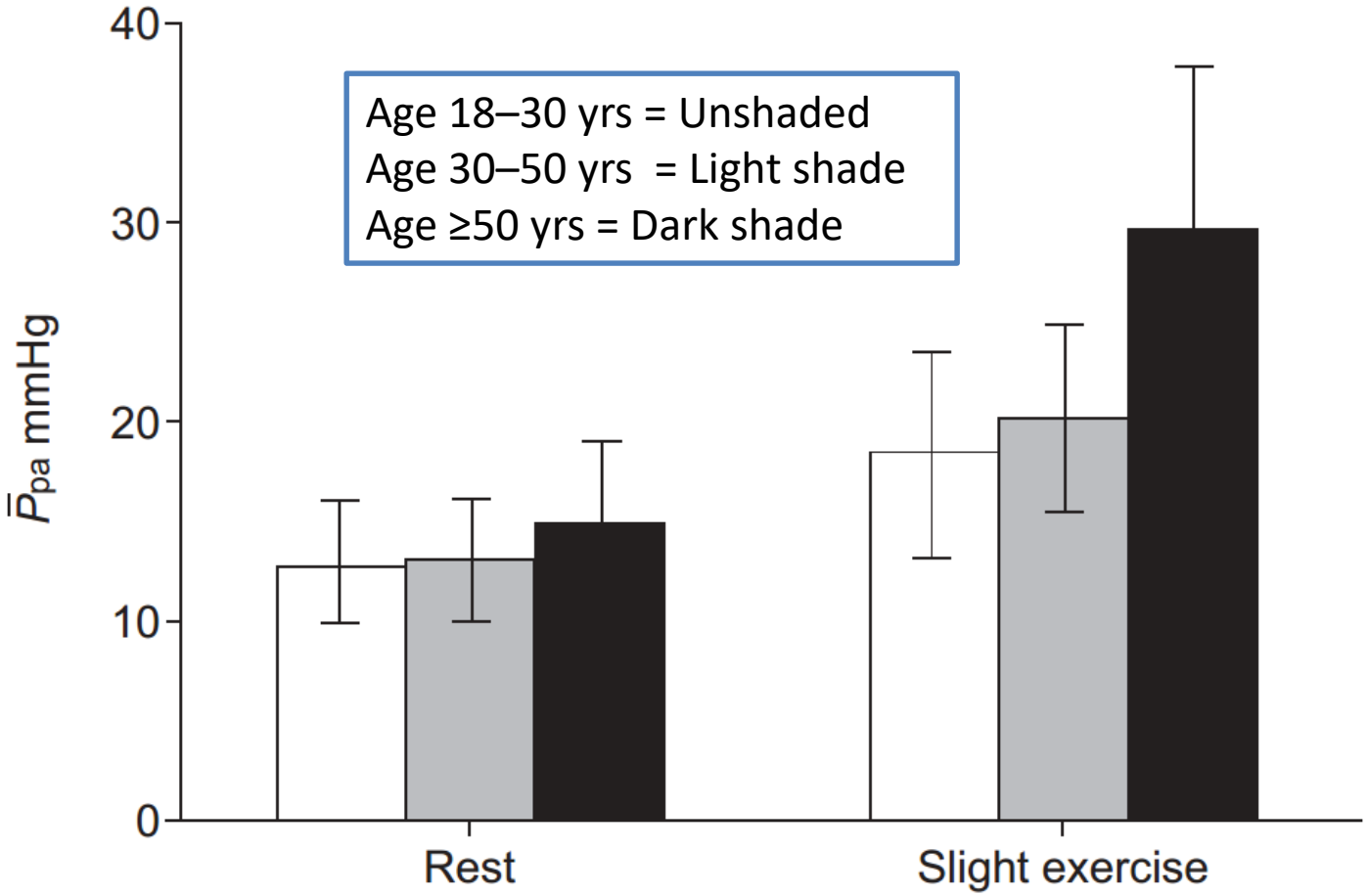
Galie`N et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal (2016) 37, 67–119

Borderline PAH?

- Systematic review of 47 studies describing 72 healthy populations (1187 patients)
  - Normal resting PAPm: 14 ± 3.3 mmHg
  - Upper limit of normal (ULN = Mean + 2SD): 20.6 mmHg

Kovacs G et al. Eur Respir J 2009; 34: 888–894

PH on exercise?



Kovacs G et al. Eur Respir J 2009; 34: 888–894

Group 1. PAH

1.1 Idiopathic

1.2 Heritable
- 1.2.1 BMPR2 mutation
- 1.2.2 Other mutations

1.3 Drugs and toxins induced

1.4 Associated with:
- 1.4.1 CTD
- 1.4.2 HIV
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart disease
- 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1'.1 Idiopathic

1'.2 Heritable
- 1'.2.1 EIF2AK4 mutation
- 1'.2.2 Other mutations

1'.3 Drugs, toxins and radiation induced

1'.4 Associated with:
- 1'.4.1 CTD
- 1'.4.2 HIV

1". Persistent pulmonary hypertension of the newborn

ESC/ERS Guidelines 2016

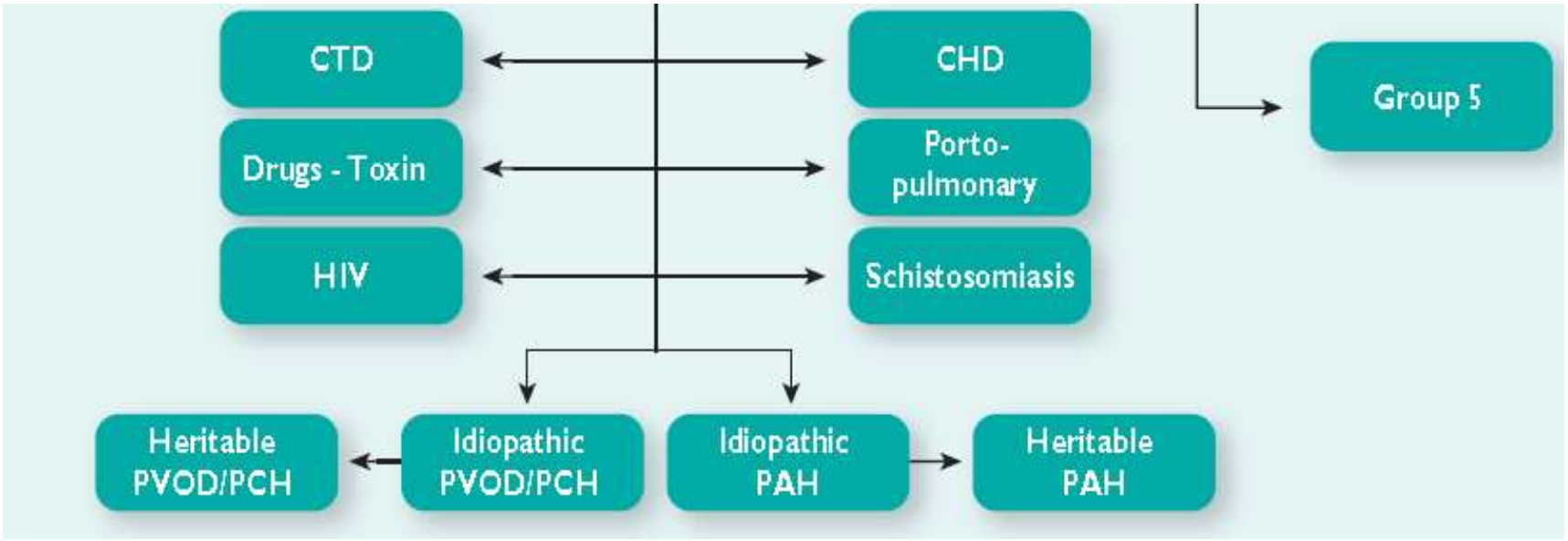
Diagnosis of PAH

Registry	Age, yrs		Female, %	
	PAH	IPAH	PAH	IPAH
U.S. NIH (1991, 1987)	NA	36 ± 15	NA	63
U.S. PHC (2010)	48 ± 14	45 ± 14	77	75
Scottish-SMR (2007)	52 ± 12	49 ± 11	70	62
French (2006, 2010)	50 ± 15	52 ± 15	65	62
Chinese (2007)	NA	36 ± 12	NA	71
U.S. REVEAL (2006-9)	50 ± 14	50 ± 15	80	83
Spanish (2012)	45 ± 17	46 ± 18	71	73
UK (2012)	NA	50 ± 17	NA	70
New Chinese registry(2011-12)	36 ± 13	38 ± 13	70	70
Mayo (2011)	52 ± 15	52 ± 15	75	76
Compera (2013)	NA	65 ± 15	NA	60

Diagnosis of PAH

Rule out Gp 2-5

RHC - mPAP 25 mmHg, PAWP≤ 15 mmHg, PVR >3 Wood units

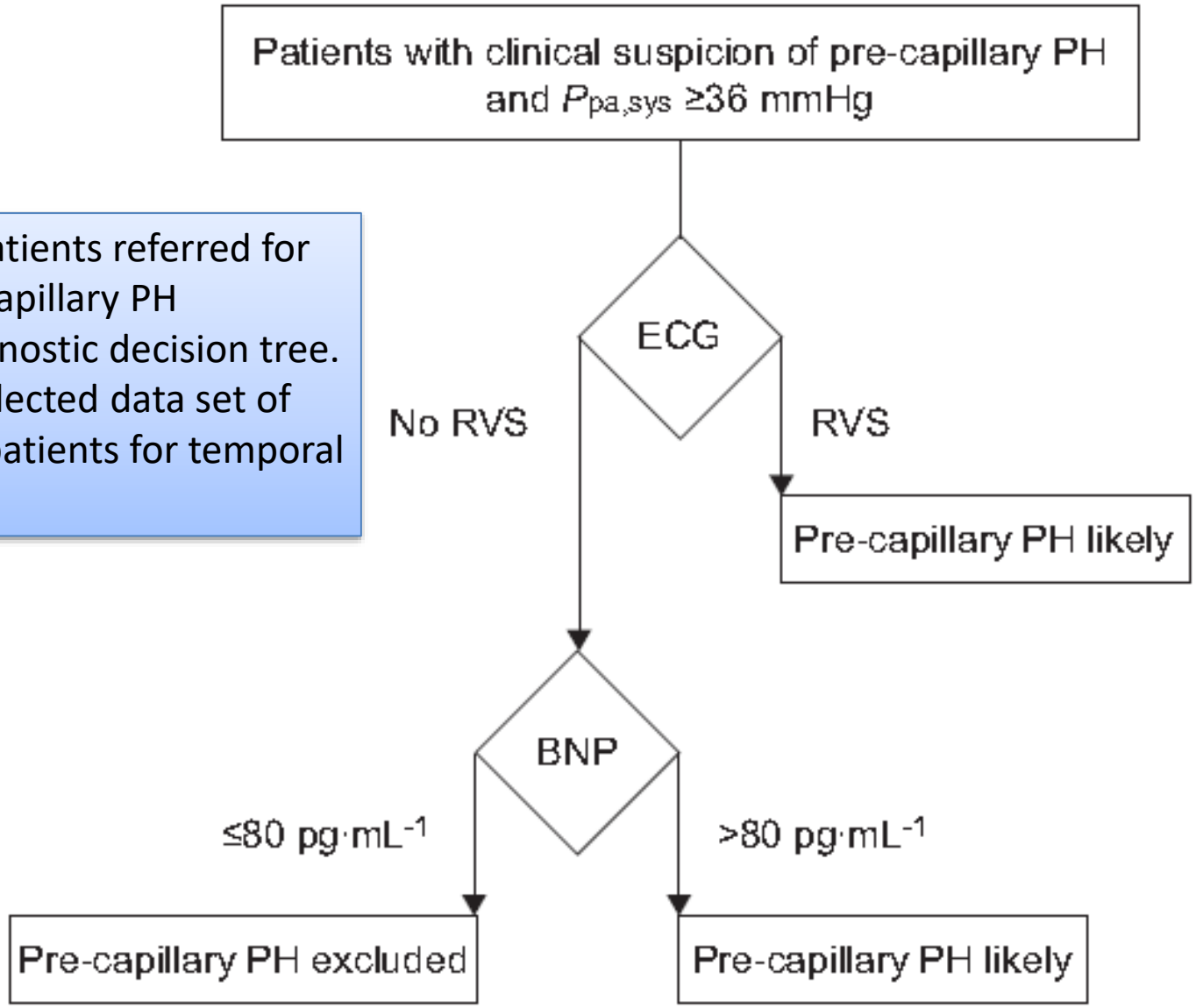


ECG

- Normal ECG does not exclude the diagnosis
- Abnormal ECG is more likely in severe rather than mild PH
- P pulmonale, RAD, RVH, RV strain, RBBB and QTc prolongation
- Prolongation of the QRS complex and QTc suggest severe disease. *(Int J Cardiol. 2013)*

Galie`N et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal (2016) 37, 67–119

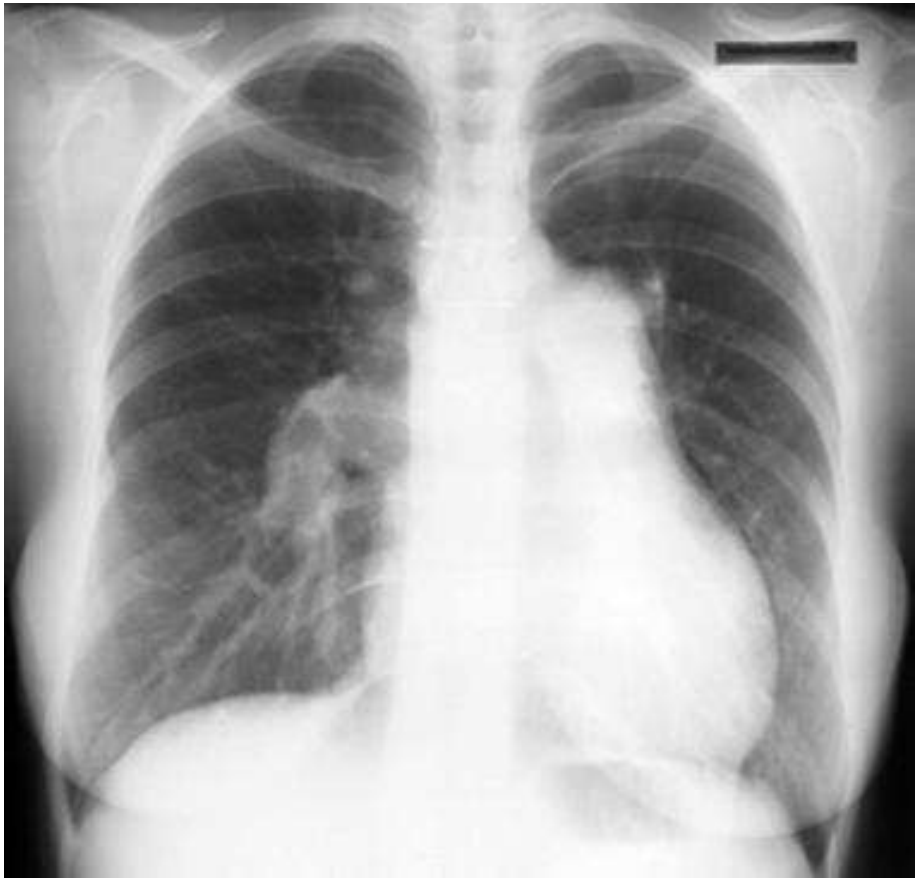
- Data from 251 patients referred for suspicion of pre-capillary PH
- Noninvasive diagnostic decision tree.
- Prospectively collected data set of 121 consecutive patients for temporal validation.



Bonderman D et al. Int J Cardiol 2013;167:669–676.

CXR

- Abnormal in 90% pts at diagnosis
- May suggest Gp 3/2
- May distinguish arterial and venous PH
- degree of PH does not correlate with the extent of radiographic abnormalities



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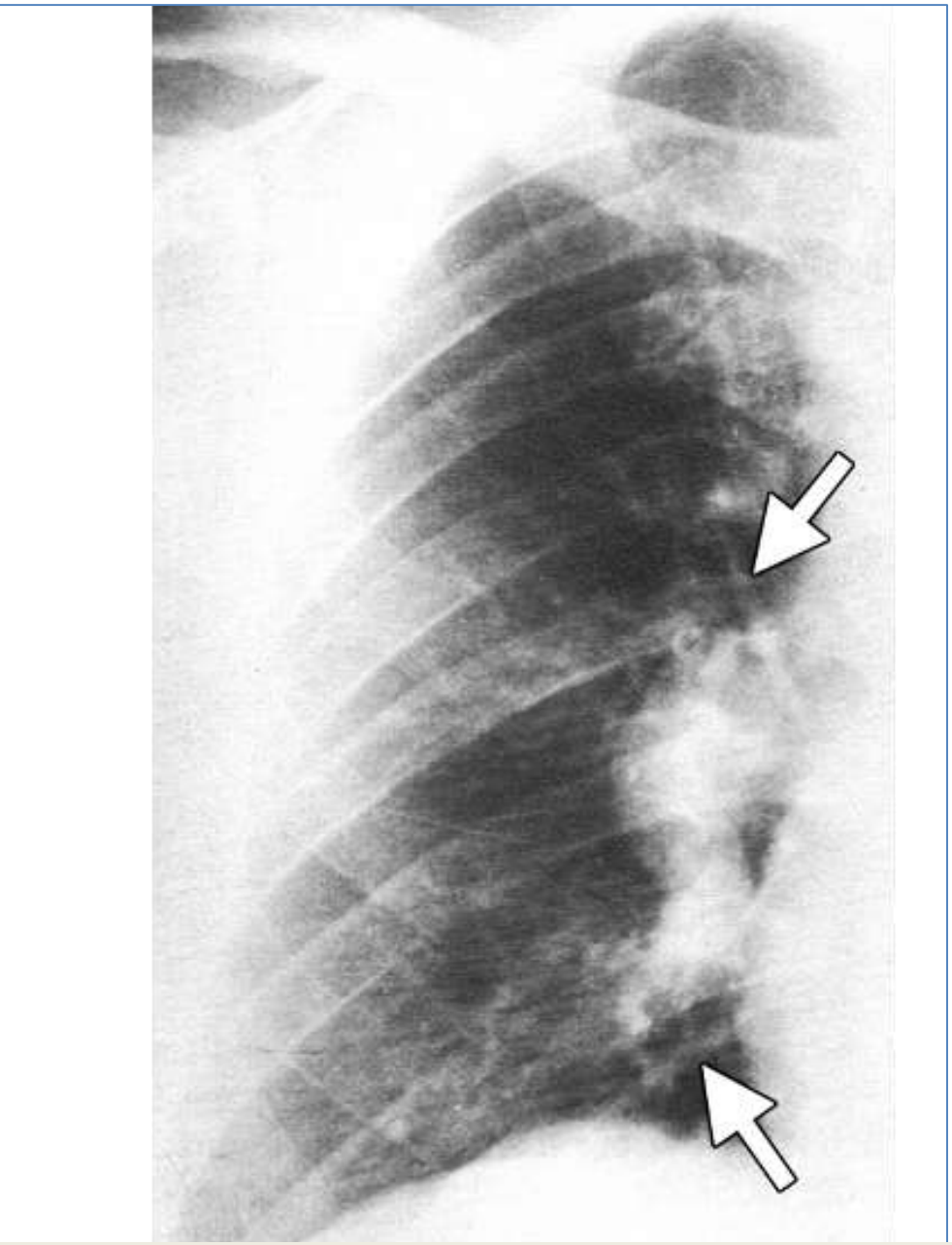
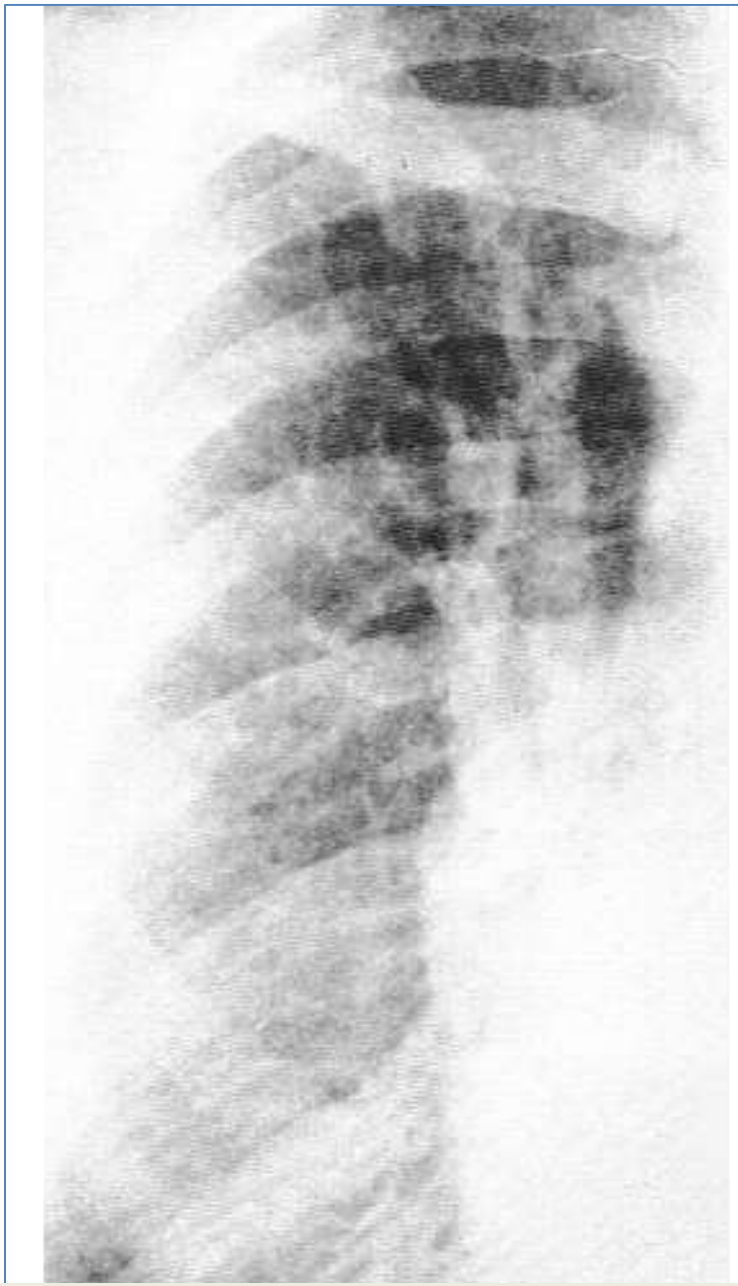




Milne EN. Forgotten gold in diagnosing pulmonary hypertension: the plain chest radiograph. Radiographics 2012

PFT and ABG

- Usually mild to moderate reduction of lung volumes
- Most have reduced DLCO
  - <45% predicted associated with a poor outcome
- Although obstruction is unusual, peripheral airway obstruction can be detected
- PaO2 remains normal or is only slightly lower
- PaCO2 is decreased
  - independent marker of mortality

Hoepper et al. Eur Respir J 2007; 29: 944–950

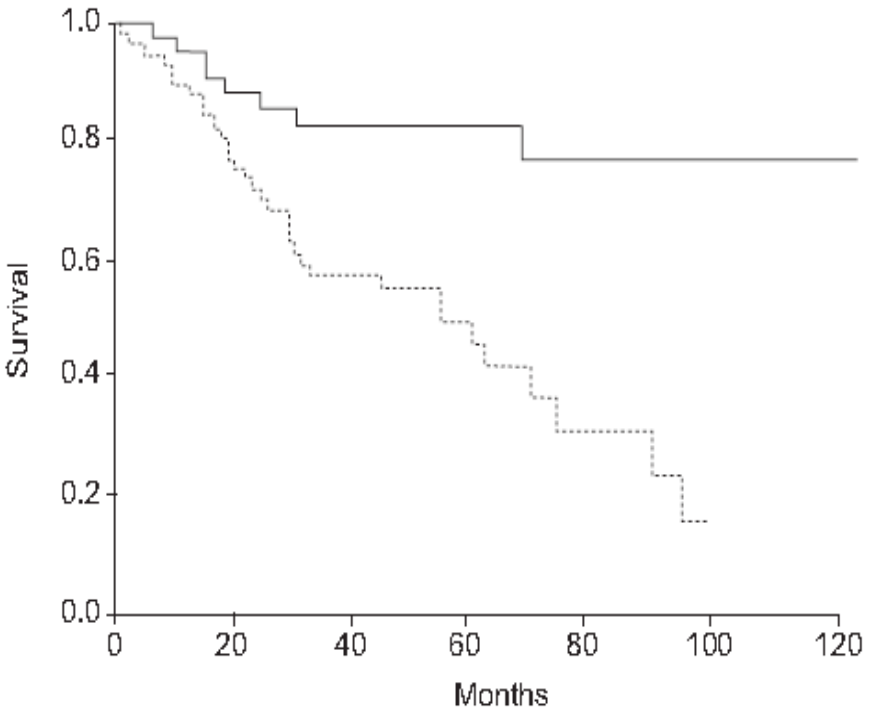
Eur Respir J 2007; 29: 944–950
DOI: 10.1183/09031936.00134506

Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension

M.M. Hoeper, M.W. Pletz, H. Golpon and T. Welte

- 12-yr retrospective analysis assessing blood gases, haemodynamics, exercise variables and survival in 101 patients with IPAH

Independent variable	OR (95% CI)	p-value
6MWD	1.007 (1.003–1.011)	<0.001
RAP	0.873 (0.805–0.947)	0.001
mPAP	0.984 (0.954–1.014)	0.292
Cardiac index	2.591 (1.075–6.241)	0.034
PVR	0.999 (0.998–1.000)	0.040
Sv_1O_2	1.057 (1.007–1.109)	0.025
Pa_1O_2		
At baseline	1.025 (0.996–1.056)	0.097
At 3 months	1.020 (0.991–1.049)	0.176
Pa_1CO_2		
At baseline	1.191 (1.058–1.341)	0.004
At 3 months	1.449 (1.242–1.690)	<0.001



ECHO

Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

ESC guidelines 2015

Echocardiographic signs in addition to TR velocity measurement

Ventricles	Pulmonary artery	IVC and right atrium
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the Interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2m/sec	Right atrial area (end-systole) >18 cm2
	PA diameter >25 mm	

Echocardiographic signs from at least two different categories from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension

CTPA

- Increased PA diameter (≥29 mm)
  - Sens 0.79, sp 0.83
- Pulm:ascending aorta diameter ratio ≥1.0
  - Sens 0.74, sp 0.81
- Segmental artery:bronchus >1 : 1 in 3-4 lobes

- May give clues for alternative diagnosis

Firdaus et al. Lung. 2016; 194(5): 813–819.

Right heart catheterization

- Morbidity -1.1% and mortality -0.055%
- LHC may be done simultaneously when left heart disease is suspected
- Pressure measurements should be made in the PA, PA wedge position, RV and RA
- Blood samples for oximetry should be taken from the high superior vena cava, IVC and PA
- CO should be measured using thermodilution or the direct Fick method
- Derived variables should include transpulmonary pressure gradient (TPG) and PVR

ESC/ERS 2015

Recommendations	Class[a]	Level[b]
RHC is recommended to confirm the diagnosis of pulmonary arterial hypertension (group 1) and to support treatment decisions	I	C
In patients with PH, it is recommended to perform RHC in expert centres (see section 12) as it is technically demanding and may be associated with serious complications	I	B
RHC should be considered in pulmonary arterial hypertension (group 1) to assess the treatment effect of drugs (Table 16)	IIa	C
RHC is recommended in patients with congenital cardiac shunts to support decisions on correction (Table 24)	I	C

Recommendations	Class[a]	Level[b]
RHC is recommended in patients with PH due to left heart disease (group 2) or lung disease (group 3) if organ transplantation is considered	I	C
When measurement of PAWP is unreliable, left heart catheterization should be considered to measure LVEDP	IIa	C
RHC may be considered in patients with suspected PH and left heart disease or lung disease to assist in the differential diagnosis and support treatment decisions	IIb	C
RHC is indicated in patients with CTEPH (group 4) to confirm the diagnosis and support treatment decisions	I	C

ESC/ERS 2015

Vasoreactivity testing

- IPAH, HPAH or drug-induced PAH
- Vasodilator - Inhaled nitric oxide (NO) at 10–20 parts per million (ppm)
  - i.v. epoprostenol
  - i.v. Adenosine
  - inhaled iloprost

- Positive acute response - a reduction of the mPAP ≥10 mmHg to reach an absolute value of mPAP ≤40 mmHg with an increased or unchanged CO
- 10% of patients with IPAH will meet these criteria

ESC/ERS 2015

Assessment of severity

- WHO-FC -one of the most powerful predictors of survival
- Echo – vital follow-up tool
  - Estimated PAPs at rest is usually not prognostic and not relevant for therapeutic decision making
  - Speckle tracking improves the quantification of RV function
  - Echo during exercise provides additional information on RV function
- RHC –Important prognostic information
  - RA pressure, CI and SvO2 are the most robust indicators
  - PAPm provides little prognostic information
  - uncertainties around the optimal timing of follow-up RHC

CMR

- More accurate for the assessment of RV morphology and function than echo
- Also allows measurement of stroke volume and CO
- CMR prognostic markers
  - increased RV volume
  - reduced LV volume
  - reduced RV ejection fraction
  - reduced stroke volume
- Follow-up CMR studies may have utility in the long-term management of PAH by identifying RV failure prior to the development of clinical features

Swift AJ et al. Prognostic value of cardiovascular magnetic resonance imaging measurements corrected for age and sex in idiopathic pulmonary arterial hypertension. Circ Cardiovasc Imaging 2014;7:100–106.

Exercise Capacity

- 6MWT most widely used
  - Absolute values, but not changes in 6MWD, provide prognostic information
  - No single threshold that is applicable for all patients
  - Peripheral O2 measurements and heart rate response, BORG scale await confirmation

- CPET
  - low end-tidal partial pressure of carbon dioxide (pCO2)
  - High ventilator equivalents for carbon dioxide (VE/VCO2)
  - low oxygen pulse (VO2/HR)
  - low peak oxygen uptake (peak VO2)
  - peak VO_2 is most widely used for therapeutic decision making

Biochemical markers

- markers of vascular dysfunction
  - asymmetric dimethylarginine (ADMA), endothelin-1, angiopoeitins, von Willebrand factor
- markers of inflammation
  - C-reactive protein, interleukin 6, chemokines
- markers of myocardial stress
  - ANP, BNP/ NT-proBNP, troponins
- markers of low COand/or tissue hypoxia
  - pCO2, uric acid, growth differentiation factor 15 (GDF15), osteopontin
- markers of secondary organ damage
  - Creatinine, bilirubin

BNP

- BNP appears to have a slightly tighter correlation with pulmonary haemodynamics and is less affected by kidney function

- NT-proBNP seems to be a stronger predictor of prognosis

Leuchte HH, et al. N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension. Chest 2007;131: 402–409

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 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	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%

Achievement/maintenance of a low-risk profile is recommended as an adequate treatment response for patients with PAH

ESC/ERS 2015

Suggested assessment and timing for the follow-up of patients with PAH

	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+	+	+
Basic lab[b]	+	+	+	+	+
Extended lab[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[f]	+[e]	+[e]

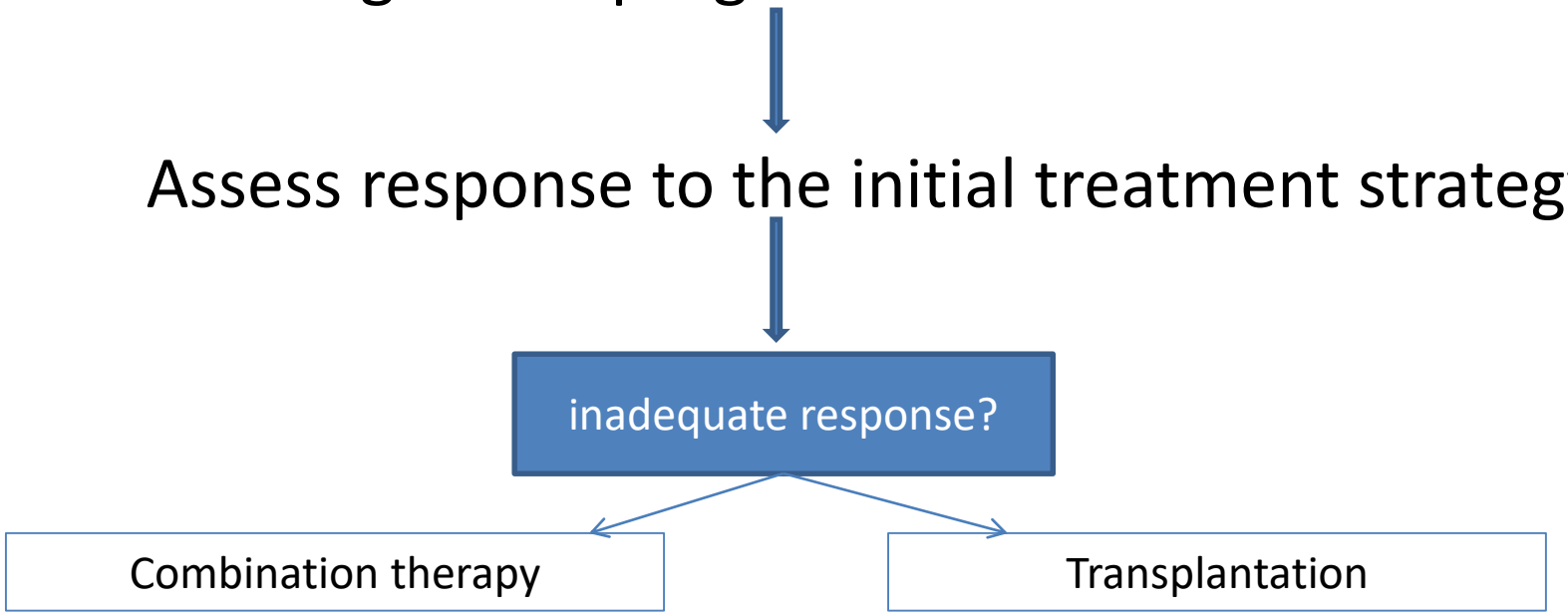
ESC/ERS 2015

Treatment of PAH - Initial approach

- General measures
  - Physical activity and supervised rehabilitation
  - Pregnancy, birth control and post-menopausal hormonal therapy
  - Infection prevention
  - Psychosocial support
  - Adherence to treatments
  - Genetic counselling
- Supportive therapy (oral anticoagulants, diuretics, O2, digoxin)
- Referral to expert centres
- Acute vasoreactivity testing for the indication of chronic CCB therapy

Treatment of PAH – Advanced therapy

- High-dose CCB in vasoreactive patients
- Drugs approved for PAH in non-vasoreactive patients according to the prognostic risk



General Measures

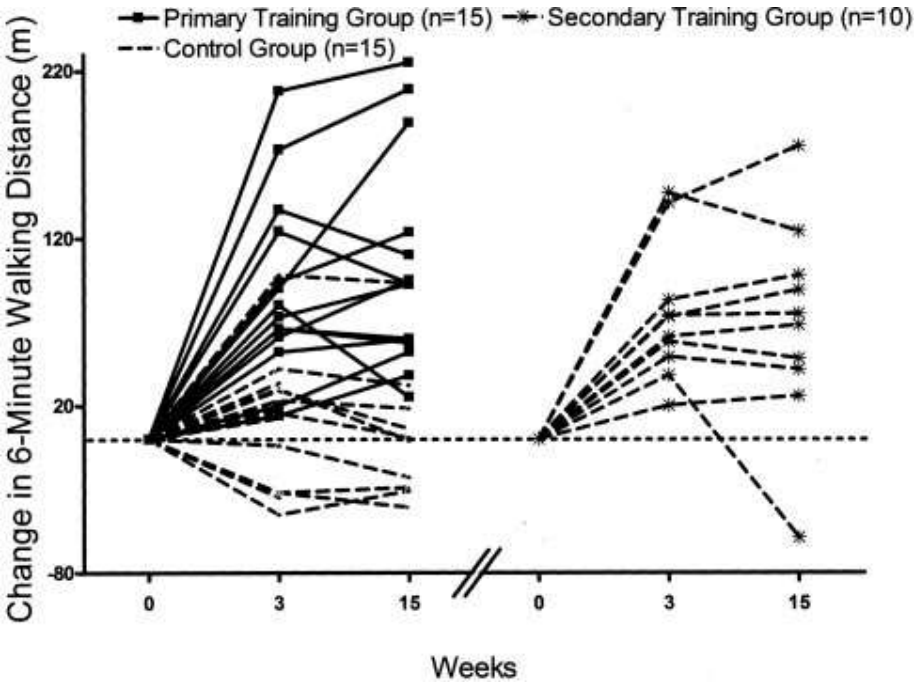
Recommendations	Class	Level
PAH patients should avoid pregnancy	I	C
Immunization against influenza and pneumococcal infection	I	C
Psychosocial support	I	C
Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy	IIa	B
In-flight O2 administration should be considered for patients in WHO-FC III and IV and those with PaO2 consistently <60 mmHg	IIa	C
In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible	IIa	C
Excessive physical activity that leads to distressing symptoms is not recommended	III	C

Physical activity and supervised rehabilitation

- Prospective randomized study to evaluate the effects of exercise and respiratory training in patients with severe symptomatic PH
- 30 patients with PH
  - 21 women; mean age, 50 yrs; PAPm, 50mm Hg; mean WHOclass, 2.9; PAH, n23; CTEPH, n7
- On stable disease-targeted medication
- Randomly assigned to a control (n15) and a primary training (n15) group
- Primary end points
  - changes from baseline to wk 15 in 6MWD
  - Scores of the Short Form Health Survey quality-of-life questionnaire

Mereles D et al. Circulation. 2006;114:1482-1489

- At wk 15, patients in the primary and secondary training groups had an improved 6MWD
  - mean difference between the control and the primary training group was 111 m (95% CI, 65 to 139 m; *P0.001)*
- Exercise training was well tolerated and improved scores of quality of life, WHO functional class, peak oxygen consumption, oxygen consumption at the anaerobic threshold, and achieved workload.
- PAPs at rest did not change significantly after 15 weeks of exercise and respiratory training (from 61±18 to 54±18 mm Hg) within the training group.

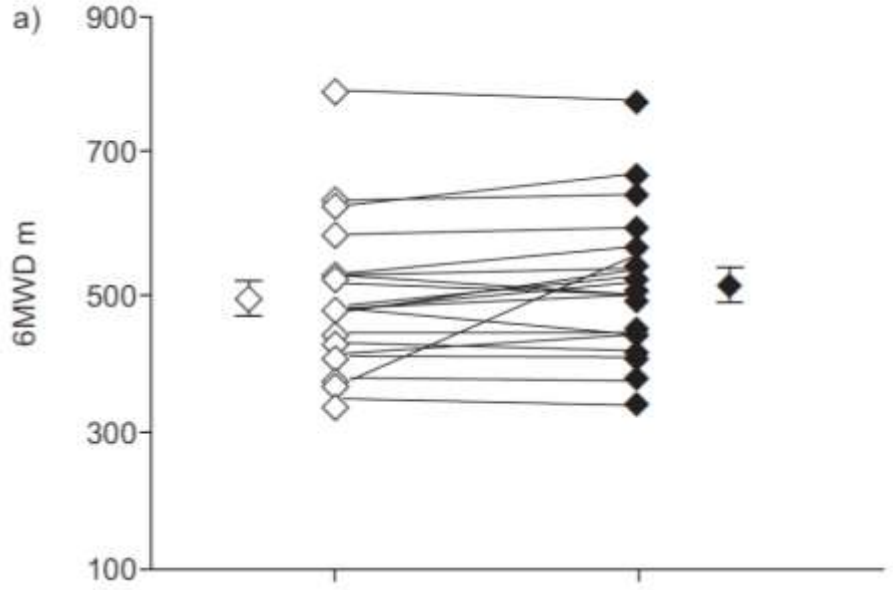


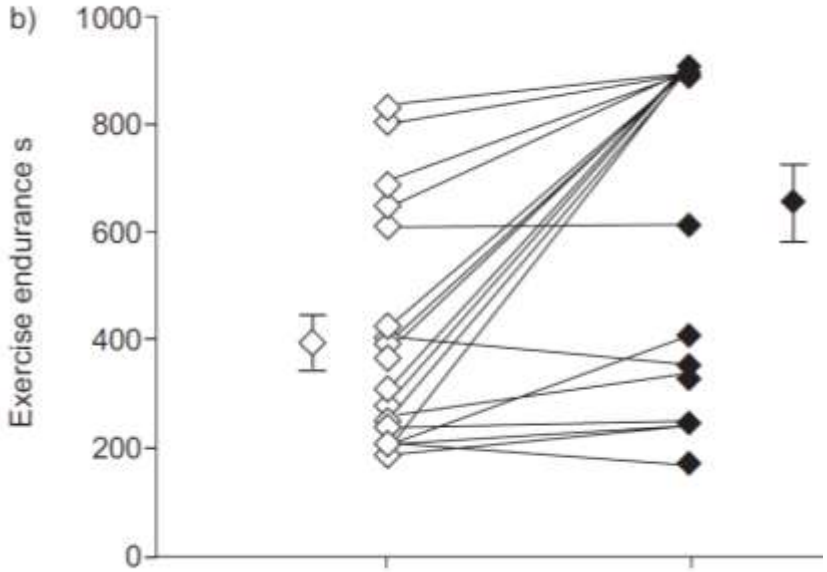
Mereles D et al. Circulation. 2006;114:1482-1489

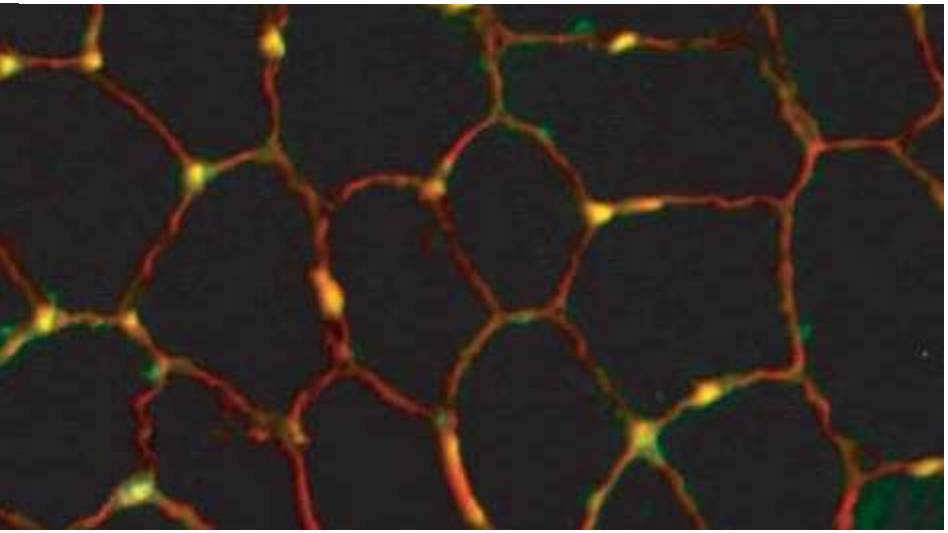
Effects of exercise training in patients with IPAH

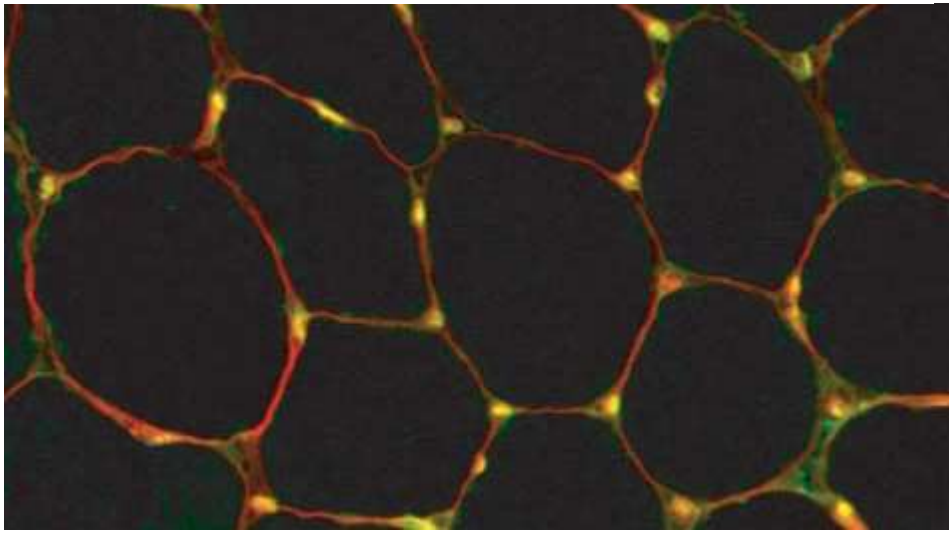
- 19 clinically stable iPAH patients (NYHA II-III) underwent a supervised exercise training programme for the duration of 12 weeks.
- Maximal capacity, endurance capacity and quadriceps function were assessed at baseline and after 12 weeks.
- In 12 patients, serial quadriceps muscle biopsies were obtained

de Man FS et al. Eur Respir J. 2009;34(3):669-75









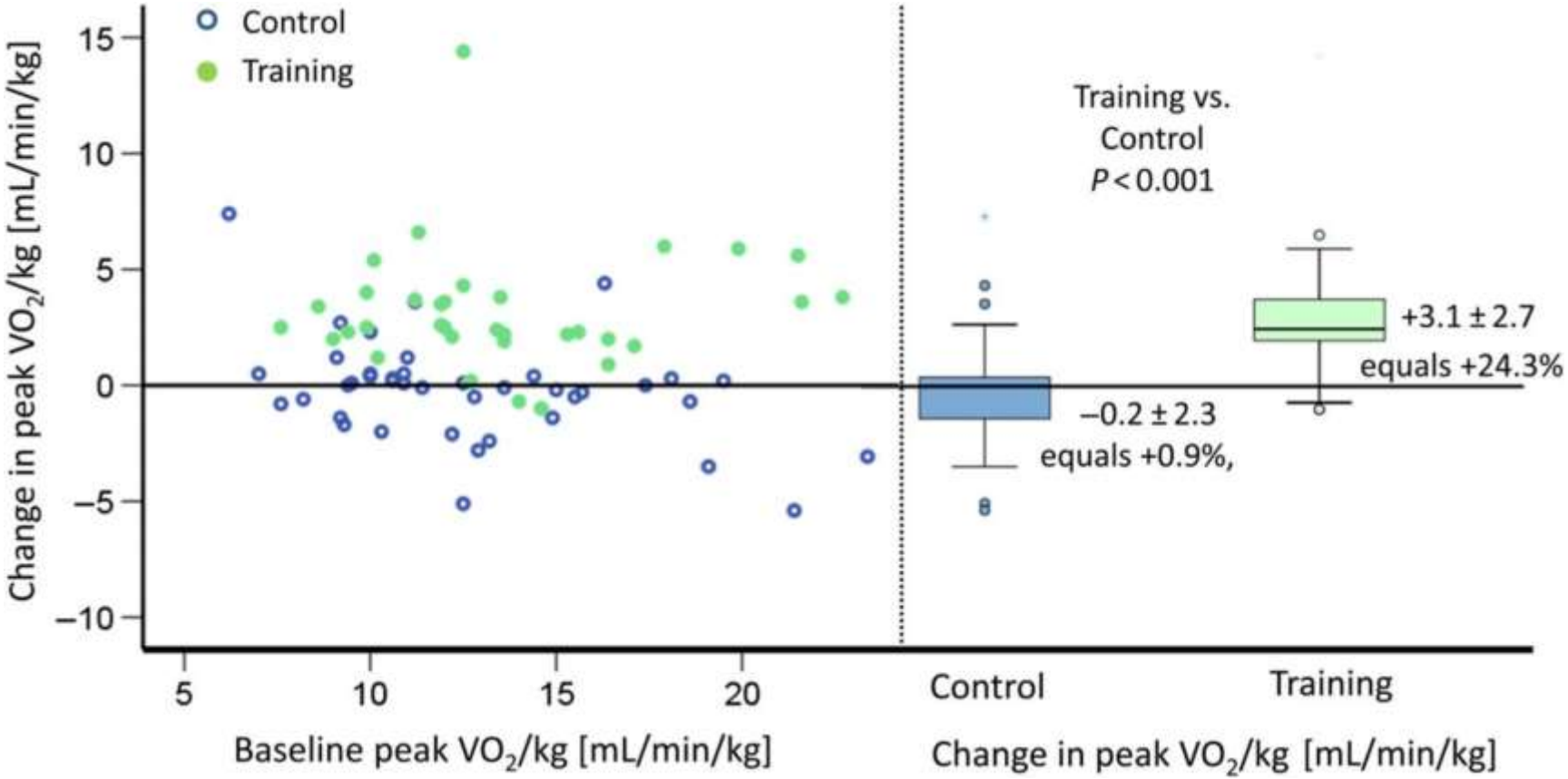
red: cell membrane of the quadriceps myocytes; yellow: capillaries

de Man FS et al. Eur Respir J. 2009;34(3):669-75

Exercise training improves peak oxygen consumption and haemodynamics in patients with severe PAH and inoperable CTEPH: a prospective, RCT

- 87 patients (54% female, 56 ± 15 years, 84% WHO-FC III/IV, 53% combination therapy) on stable disease-targeted medication were randomly assigned to a control and training group
- Non-invasive assessments and right heart catheterization at rest and during exercise were performed at baseline and after 15 weeks.
- Primary endpoint was the change in peak VO_2 /kg. Secondary endpoints included changes in haemodynamics.

Nicola Ehlken et al. Eur Heart J (2015) 37 (1): 35-44.



Nicola Ehlken et al. Eur Heart J (2015) 37 (1): 35-44.

Exercise-based rehabilitation programmes for pulmonary hypertension (Review)

- 6 RCTs, pooled data from 5
- Study duration ranged from 3 to 15 weeks
- Both inpatient- and outpatient based rehabilitation that incorporated both upper and lower limb exercise

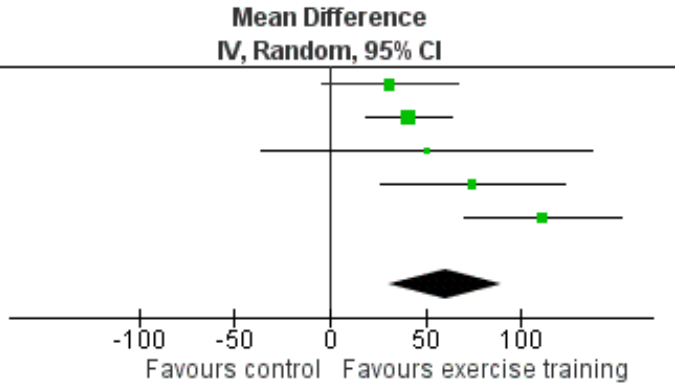
- Mean 6MWD following exercise training 60.12 m higher
  - n = 165, 5 RCTs, low-quality evidence; minimal important difference 30 m
- Mean peak VO_2 2.4 ml/kg/minute higher
  - n = 145, 4 RCTs, low quality evidence
- Mean peak power 16.4 W higher
  - n = 145, 4 RCTs, lowquality evidence
- Mean change in HRQoL (SF-36 physical component) 4.63 points higher
  - n = 33, 2 RCTs, low-quality evidence
- SF-36 mental component 4.17 points higher
  - n = 33; 2 RCTs, low-quality evidence

Morris NR et al. Cochrane Database Syst Rev. 2017 Jan 19;1:CD011285

Exercise-based rehabilitation programmes for pulmonary hypertension (Review)

Study or Subgroup	Exercise rehabilitation Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chan 2013	43	46	13	12	46.6	13	23.1%	31.00 [-4.59, 66.59]
Ehlken 2016	29	53	38	-12	46	41	28.9%	41.00 [19.04, 62.96]
Ganderton 2013	55.4	95.5	5	5	22.6	5	9.0%	50.40 [-35.62, 136.42]
Ley 2013	91	66.2	10	16.9	39.8	10	18.3%	74.10 [26.23, 121.97]
Mereles 2006	96	61	15	-15	54	15	20.8%	111.00 [69.77, 152.23]
Total (95% CI)			**81**			**84**	**100.0%**	**60.12 [30.17, 90.07]**

Heterogeneity: $Tau^2 = 681.52$; $Chi^2 = 10.97$, df = 4 (P = 0.03); $I^2 = 64\%$
Test for overall effect: Z = 3.93 (P < 0.0001)



- Supervised exercise-based rehabilitation is likely to be safe for people with PH who are stable on medical therapy
- Can lead to meaningful improvements in exercise capacity
- Clinical importance of improvements in HRQoL is less clear

Morris NR et al. Cochrane Database Syst Rev. 2017 Jan 19;1:CD011285

Lacunae

- Optimal method of exercise rehabilitation
- Intensity and duration of the training
- Characteristics of the supervision
- Mechanisms for the improvement of symptoms, exercise and functional capacity
- Effects on prognosis and survival

Pregnancy, birth control and post-menopausal hormonal therapy

- Pregnancy remains associated with a substantial mortality rate in PAH (upto 56%)
- Barrier contraceptives – unpredictable effect
- Progesterone-only pill preferable
  - ERAs can reduce the efficacy of OCPs
- Intra-uterine coils may cause vaso-vagal rxn
- Safety of post-menopausal HRT - unclear

Thorne S et al. J Fam Plann Reprod Health Care 2006;32:75–81

Pregnancy outcomes in pulmonary arterial hypertension in the modern management era

- Multinational, prospective registry to examine the contemporary outcome of pregnancies in patients with PAH
- 3-yr period; 13 participating centres; 26 pregnancies
- 3 (12%) females died (had uncontrolled PAH)
- 1 (4%) developed right heart failure requiring urgent heart–lung transplantation
- 8 eight abortions; 2spontaneous and 6induced
- 16 (62%) pregnancies were successful
  - These females had well controlled PAH
  - 8 were long-term responders to CCBs

Jaïs X et al. Eur Respir J. 2012;40(4):881-5

Supportive therapies

Recommendations	Class	Level
Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention	I	C
Continuous LTOT is recommended in PAH patients when PaO2is consistently <60 mmHg	I	C
Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of Anorexigens	IIb	C
Correction of anaemia and/or iron status may be considered in PAH patients	IIb	C
The use of ACEI/ARB/beta-blockers and ivabradine is not recommended in patients with PAH unless required by co-morbidities (i.e. HTN, CAD or left HF)	III	C

Diuretics

- No good study investigating choice of diuretics in PAH patients
- Many experts add an aldosterone antagonists such as spironolactone
- Torsemide may be better than Frusemide – more consistent results

•*Cohn JN. Optimal diuretic therapy for heart failure. Am J Med.2001;111:577*
•*Murray, M.D. et al. Open-label randomized trial of torsemide compared with furosemide in patients with heart failure. Am J Med. 2001; 111: 513–520*

Oral Anticoagulants

- High prevalence of vascular thrombotic lesions at postmortem examination in patients with IPAH *(Fuster V. Circulation 1984)*
- Abnormalities in coagulation and fibrinolytic pathways have also been reported *(Herve P. Clin Chest Med 2001, Hoeper MM. Eur Respir J 1998, Huber K. Am J Respir Crit Care Med 1994)*
- Non-specific factors - heart failure and immobility
- Used in 50-85% patients in US/European registries

•*Benza RL et al. \REVEAL registry. Chest. 2012;142(2):448–456.*
•*Hoeper MM et al. COMPERA registry. Int J Cardiol. 2013;168(2):871–880.*

Warfarin in PAH – meta-analysis

- No RCTs found
- 9 cohort studies were selected (2 prospective)
- 31% mortality risk reduction with warfarin (HR = 0.69, CI 0.57-0.82)
- "Pooled results from cohort studies suggest a survival benefit, but the moderate study quality, the high risk of publication bias, and the methodological limitations inherent in the analysis of observational studies preclude a definite conclusion."
- Need for quality RCT

Caldeira et al. Canadian Journal of Cardiology 30 (2014)

Recommendations on Warfarin

- Recommended in all patients with IPAH, HPAH and PAH due to anorexigens
- However should be used with caution in patients with hemoptysis or bleeding
- Also interactions with other PAH specific drugs must be kept in mind
- DOAs are not yet validated
  - Risk of bio-accumulation

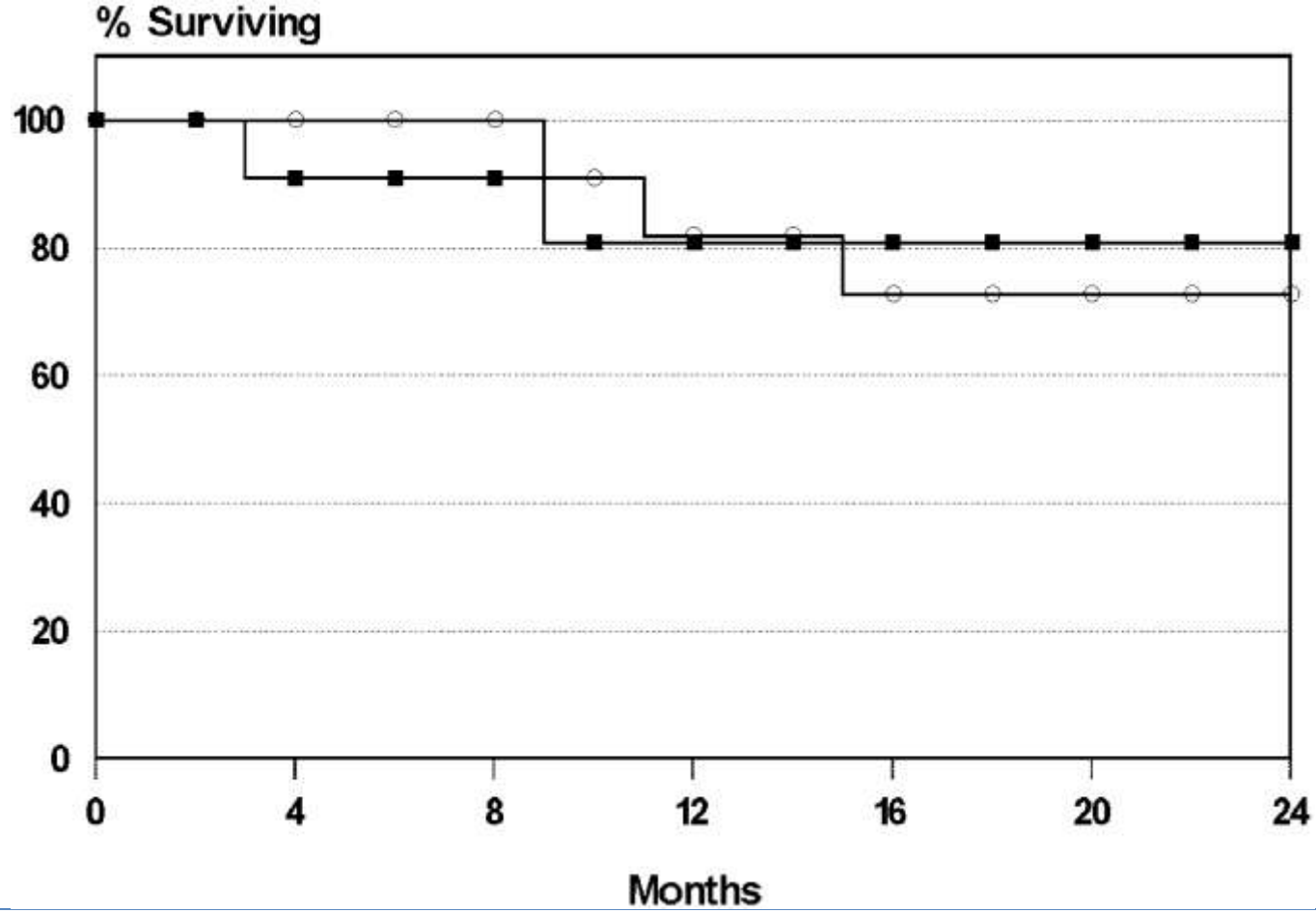
  (Gabriel L et al. Respiration. 2016;91(4):307-15)

ESC 2015

Oxygen therapy

- Oxygen: sO2< 90% or pO2<60 should receive supplemental oxygen
- Demonstrated to reduce the PVR in patients with PAH
- No randomised data to suggest that LTOT is beneficial
- Data extrapolated from evidence in COPD

NOT in Eisenmenger Syndrome



- Kaplan-Meier survival estimates for patients with Eisenmenger Syndrome receiving nocturnal oxygen therapy (open circles) and for those in the control group (closed squares).
- Mean survival estimates are 20.73 mo (95% confidence intervals [CI] 17.48 to 23.97) and 20.77 months (95% CI 16.69 to 24.85), respectively (chi-square log-rank 0.08, p = NS).

Sandoval J et al. Am J Respir Crit Care Med 2001;164:1682–1687

Other supportive therapies

- Digoxin - shown to improve CO acutely in IPAH, although its efficacy is unknown when administered chronically *(Rich S, Chest 1998)*

- ACEI/ARB, β-blockers, ivabradine – No evidence

- Iron supplementation
  - Fe deficiency common - 43% in IPAH, 46% in SSc-PAH, 56% in Eisenmenger syndrome
    (Ruiter. Eur Respir J 2011, Ruiter. Rheumatology 2014, Rhodes CJ. J Am Coll Cardiol 2011, Van De Bruaene A. Eur Heart J 2011)
  - May be associated with reduced exercise capacity, and higher mortality, independent of the presence or severity of anaemia *(Broberg CS. J Am Coll Cardiol 2006, Rhodes CJ. J Am Coll Cardiol 2011)*
  - Fe supplementation may improve exercise capacity and QoL (Viethen T. Int J Cardiol 2014)

Advanced/Targeted Therapy

CCBs

- Nifedipine and Diltiazem MC used > Amlodipine
- Verapamil avoided d/t negative inotropic effect
- HR > 100 → Ditiazem
- HR < 100 → Nifedipine/Amlodipine
- High dose CCBs required:
  - Nifedipine 120-240 mg/d
  - Diltiazem 240-720 mg/d
  - Amlodipine upto 20 mg/d

Taichman, Ornelas et al. CHEST 2014
McLaughlin, Archer et al. Circulation 2009

CCBs

Rich et al. NEJM 1992

- 17/64 patients (26%) had acute pulmonary vasoreactivity (20% decrease in mPAP and PVR)
- Responders received CCBs: At 5 yrs CCB group had 94% survival compared with 55% in non-responders (p=0.003)

Sitbon et al. Circulation 2005.

- Retrospective study: 70/557 (12.6%) showed vasoreactivity and got CCB
- Only 38/70 (7% of total) had response to CCB
- CCB responders had better baseline NYHA Class, longer 6MWD and hemodynamic variables
- Also showed significant survival benefit (98% v 48%)

CCB responder group had reached a lower mPAP (<40 mmHg) and lower PVR on vasodilator testing when compared to CCB non-responder group

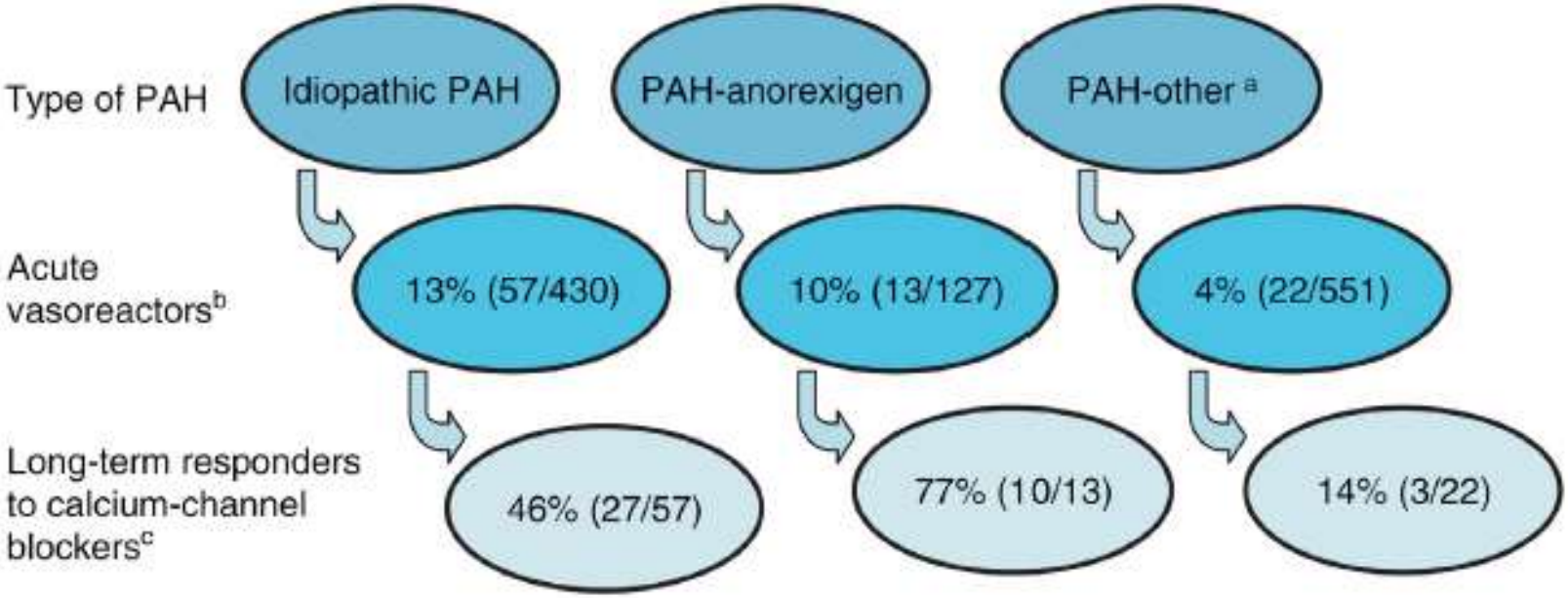


Figure 4. Breakdown of long-term responders to calcium channel blocker (CCB) monotherapy amongst those who are acutely vasoreactive, by type of PAH (data adopted from Sitbon et al. (2004)

Fallah. Global Journal of Health Science 2015

Factors predicting response to CCBs

TABLE 5. Odds Ratios for Variables Associated With Treatment Success on Long-Term CCB for Acute Responders (Univariate Analysis)

	Dichotomy/Median	Odds Ratio	95% CI	*P*
Baseline clinical variables				
Age, y	<42.8	2.18	0.83–5.75	0.115
History of RHF	No	3.48	0.95–12.68	0.059
NYHA functional class	II/III-IV	3.02	1.13–8.13	0.028
Hemodynamic variables measured at baseline				
Mean RAP, mm Hg	<7	2.36	0.89–6.21	0.083
Mean PAP, mm Hg	<56	3.02	1.13–8.13	0.028
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	>2.5	3.21	1.20–8.54	0.015
PVR, Wood units	<11.5	4.24	1.55–11.49	0.005
Svo_2, %	>65	19.18	5.73–64.25	<0.0001
Variables achieved during acute vasodilator testing				
Mean PAP, mm Hg	<37	6.13	2.11–17.86	0.0009
Fall in mean PAP, %	>31	7.35	2.54–21.28	0.0002
PVR, Wood units	<6.7	7.35	2.54–21.28	0.0002
Fall in PVR, %	>45	3.27	1.22–8.77	0.018

RHF indicates right heart failure; RAP, right atrial pressure.

Sitbon et al. Circulation 2005.

CCBs: Use with Caution!

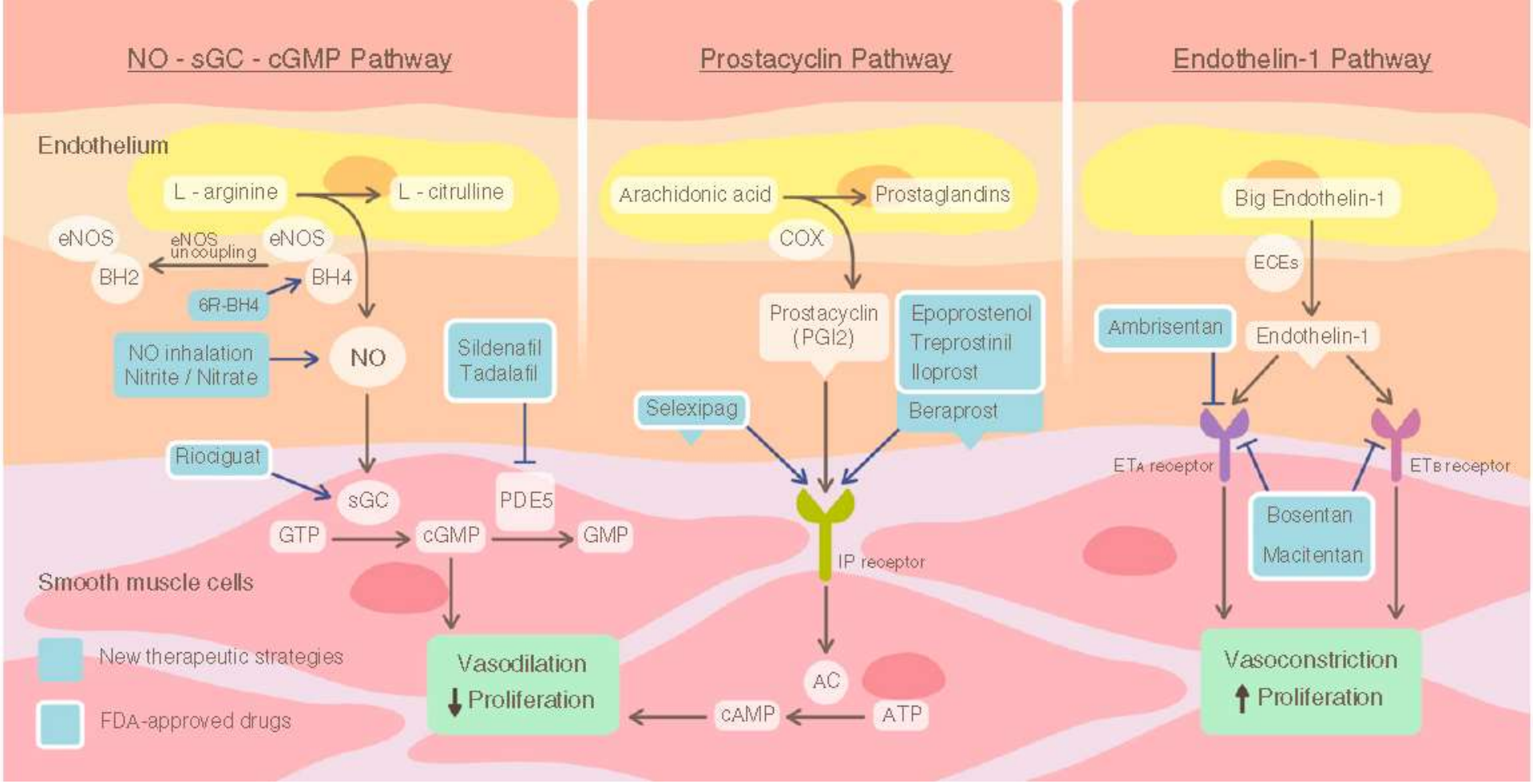
- Start with low dose and titrate upwards
- Edema
- Hypotension
- Reflex tachycardia → RV ischaemia
- Increasing CCB doses in patients who are not vasoreactive may be fatal
- As 93% patients are not likely to respond → Should not be used without vasoreactivity testing

Taichman, Ornelas et al. CHEST 2014

ESC 2015 recommendations

- High doses of CCBs are recommended in patients with IPAH, HPAH and DPAH who are responders to acute vasoreactivity testing (1C)
- Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) (1C)
- Continuation recommended in patients in WHO-FC I or II with marked haemodynamic improvement (near normalization) (1C)

Specific PAH Therapy



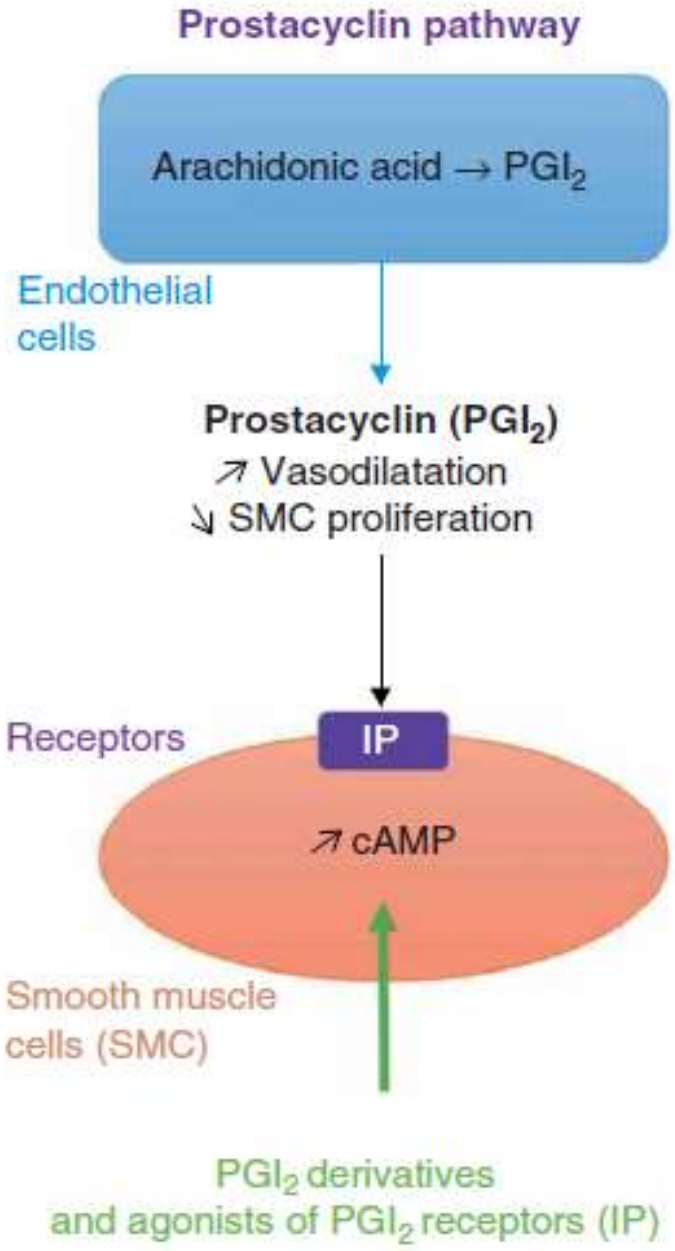
6R-BH4 = sapropterin dihydrochloride, tetrahydrobiopterin
AC = adenylyl cyclase
BH2 = dihydrobiopterin
BH4 = tetrahydrobiopterin

Gladwin MT. Am J Respir Crit Care Med; 195(1):1–16

Prostanoids

- Prostacyclin(PGI_2) – endogenous eicosanoid produced by endothelial cells.
- Epoprostenol is the synthetic equivalent of prostacyclin, and treprostinil and iloprost are both stable synthetic analogs
- Deficiency of prostacyclin activity identified as an important part of the pathobiology of PAH.
- Loss of expression of prostacyclin synthase also been observed in lung tissue of PAH patients.

Agarwal R *et al. AHJ 2011*



Epoprostenol
Treprostenil
Iloprost
Beraprost
Selexipag

Perrin et al. Expert Opin. Pharmacother. 2015

Prostanoids - Mechanism of Action

- Results in smooth-muscle relaxation with vasodilation
- Targets pathologic vascular remodeling observed in PAH
- Anti-proliferative, inhibition of platelet aggregation, anti-inflammatory, and augmentation of ventricular inotropy

LeVarge. Therapeutics and Clinical Risk Management 2015

Prostanoids – Dosing and administration

Drug	Preparation	Administration	Dosage
Epoprostenol GM (glycine-mannitol FLOLAN) 0.5 mg 1.5 mg lyophilised powder	Reconstituted solutions stable for up to 8 hrs. May be stored for up to 40 hrs refrigerated at 2°C to 8°C.	Continuous IV infusion via central line with ambulatory infusion pump	Start at 2 ng/kg/min (titrate upward 3-7 days) Mean dose: 12 wks = 11 ng/kg/min 1 yr = 21 ng/kg/min 1 ½ yr = 35 ng/kg/min
Epoprostenol AS (arginine-sucrose VELETRI) 0.5 mg 1.5 mg lyophilised powder	Reconstituted solutions stable for up to 48 hrs. May be stored for up to 8 days refrigerated at 2°C to 8°C.	do	do EPITOME-2 Trial 2014

Not to be exposed to direct sunlight

Prostanoids – Dosing and administration (contd)

Drug	Preparation	Administration	Dosage
Iloprost – Inhaled (VENTAVIS) 10 mcg/ml = 2.5 mcg 20 mcg/ml = 5 mcg	No dilution required	Oral inhalation via ultrasonic nebuliser	2.5-5 mcg per dose 6 to 9 times/day
Treprostenil – Inhaled (TYVASO) 1.74 mg/2.9 ml	No dilution required. One ampoule to be changed every 24 hrs.	Oral inhalation via Tyvaso Inhalational System	3-9 breaths per session (18-54 mcg) 4 times/day
Treprostenil - IV/SC (REMODULIN)	With sterile water: storage upto 4 hrs at room temp and 24 hrs refrigerated. With diluent: Maybe stored upto 14 days. Administer within 48 hrs	Continuous IV/SC infusion with ambulatory infusion pump	1.25 ng/kg/min and titrate upward *Dosage of 40ng/kg/min a/w improved survival
Treprostenil – Oral (ORENITRAM)	-	-	0.25 mg bd and increase 3-4 days *Mean dose 3.4 mg bd

Epoprostenol – Landmark Trial

- 12 week prospective randomized open label trial (epoprostenol vs standard care)
- IPAH, NYHA Class III/IV, n = 81 (41 Epoprostenol)
- 1^{o} outcome: mean 6MWD increased by 32 m in epoprostenol group (decrease by 25 m in std Rx)
- Other statistically significant outcomes:
  - Only randomised PAH trial to show improved survival
  - Improvement in hemodynamic parameters, FC, QoL and dyspnea scores

Barst et al. NEJM 1996

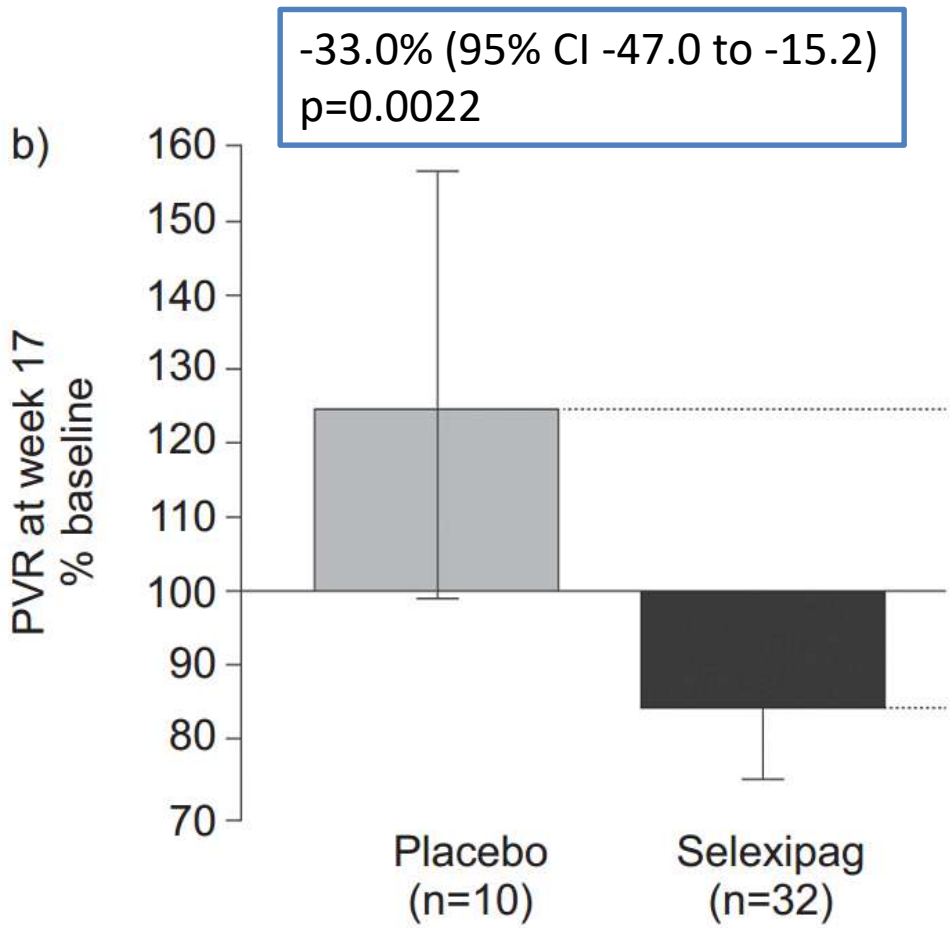
Drug(s) tested	Study	N	Weeks	Background therapy	Primary endpoint	Main Results
Beraprost	ALPHABET	130	12	No	6MWD	6MWD improved Haemodynamics not improved
	Barst	116	52	No	CW	CW not improved
Epoprostenol	Rubin	23	12	No	6MWD	6MWD improved Haemodynamics improved
	Barst	81	12	No	6MWD	6MWD improved Haemodynamics improved Survival improved
	Badesch	111	12	No	6MWD	6MWD improved
Inhaled Iloprost	AIR	203	12	No	6MWD & FC	6MWD & WHO-FC improved Haemodynamics improved at peak
	STEP	67	12	Bosentan	6MWD	6MWD improved (P = 0.051) TTCW improved
	COMBI	40	12	Bosentan	6MWD	Terminated for futility 6MWD not improved No clinical improvement

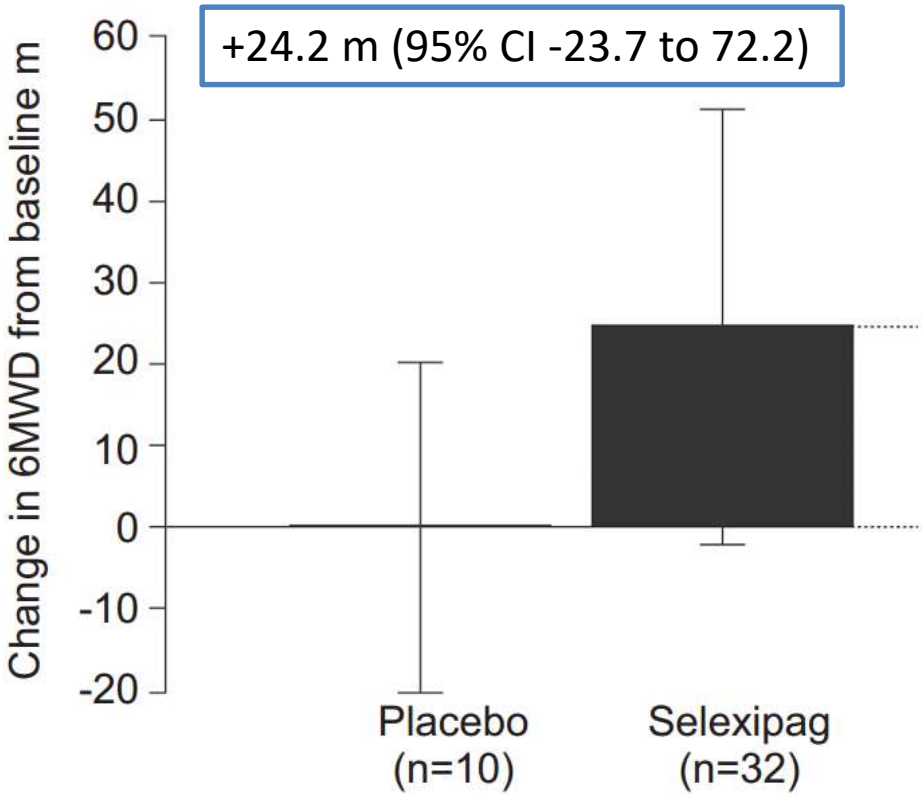
Drug(s) tested	Study	N	Weeks	Background therapy	Primary endpoint	Main Results
Treprostinil	SC-Pivotal study	470	12	No	6MWD	6MWD improved Haemodynamics improved Pain at infusion site
	Inhal TRIUMPH	235	12	Bosentan or Sildenafil	6MWD	6MWD improvement (+20 m at peak, +12 m at trough) TTCW not improved
	PO-Freedom M	185	16	No	6MWD	6MWD improvement (+26 m at peak, +17 m at trough) TTCW not improved
	PO-Freedom C1	354	16	ERA and/or PDE-5i	6MWD	6MWD not improved TTCW not improved
	PO-Freedom C2	310	16	ERA and/or PDE-5i	6MWD	6MWD not improved TTCW not improved
Selexipag	Phase-2	43	17	ERA and/or PDE-5i	PVR	PVR improved 6MWD not improved
	GRIPHON	1156	74	ERA and/or PDE-5i	Composite	TTCW improved

Beraprost

Galie` N, et al. J Am Coll Cardiol 2002	Barst RJ et al. J Am Coll Cardiol 2003
• 130 patients with PAH • Randomized to the maximal tolerated dose of beraprost (median dose 80 µg qid) or to placebo for 12 wks • Primary end point – 6MWD • Difference between groups in the mean change of 6MWD- 25.1 m (95% CI: 1.8 to 48.3, p = 0.036)	• 116 patients • Randomized to the maximal tolerated dose of beraprost (median dose 120 µg qid) or to placebo for 12 months • Primary end point was disease progression; i.e., death, transplantation, epoprostenol rescue, or >25% decrease in peak oxygen consumption (VO_2) • Benefecial effects observed at 6 months but attenuated by 12 months

Selexipag





Simonneau G et al. Eur Respir J. 2012 Oct;40(4):874-80

Griphon Study

- Event-driven, phase 3, randomized, double-blind, placebo-controlled trial
- 1156 patients; individualised doses
- Background therapy allowed
- Primary end point- composite of death from any cause or a complication related to PAH
- Risk of the primary composite end point significantly lower with selexipag than with placebo (by 40%)

Sitbon et al. N Engl J Med 2015;373:2522-33.

Adverse events with prostacyclins

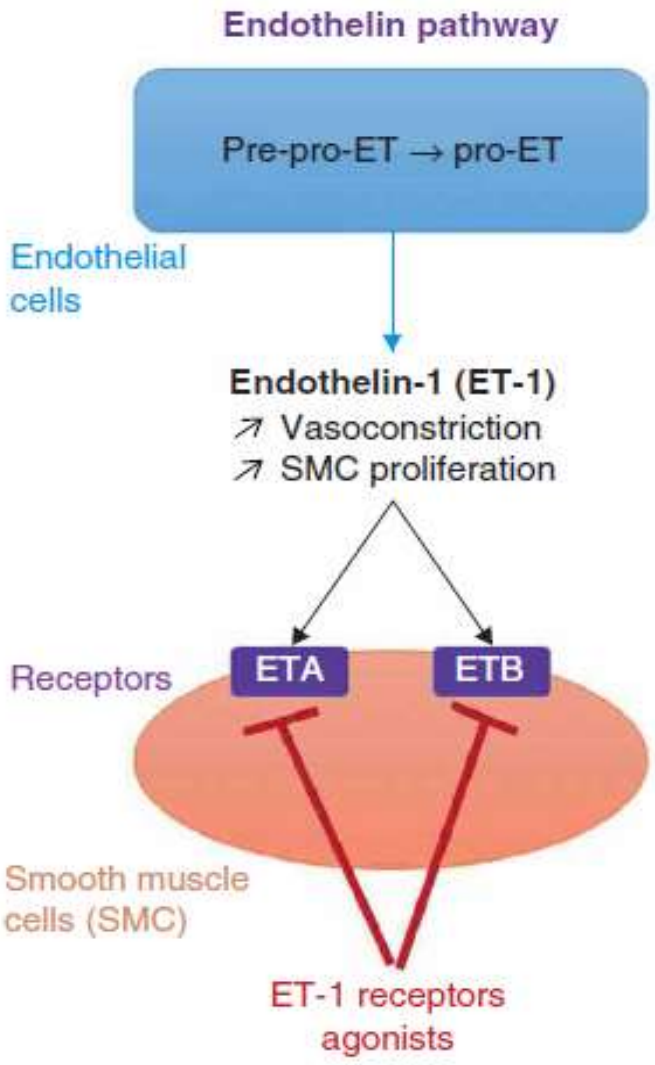
Drug Related

- Flushing
- Headache
- Diarrhea
- Nausea/Vomiting
- Jaw pain
- Flu-like symptoms
- Syncope/hypotension
- Cough
  (with inhaled)

Catheter Related

- Sepsis
- Thrombosis
- Bleeding
- Drug interruption and rebound PAH
- Paradoxical embolism

Endothelin pathway



Perrin et al. Expert Opin. Pharmacother. 2015

Endothelin receptor antagonists

- ET-1 → potent vasoconstrictor that promotes smooth muscle proliferation and contributes to disease progression in PAH.
- ET-1 levels increased in PAH, levels correlate with PVR in IPAH.
- 2 receptors, endothelin-A (ETA) and endothelin-B (ETB).
- ETA receptors, found on smooth muscle cells only, induce vasoconstriction and cellular proliferation.
- ETB receptors on smooth muscle cells, when activated, also stimulate vasoconstriction; **however, ETB receptors on endothelial cells have the counter-effect of vasodilation and clearance of ET-1**.
- Whether selective ETA receptor antagonism offers greater benefit in PAH? – Inconclusive data

Agarwal R et al. AHJ 2011

Comparison of ERAs

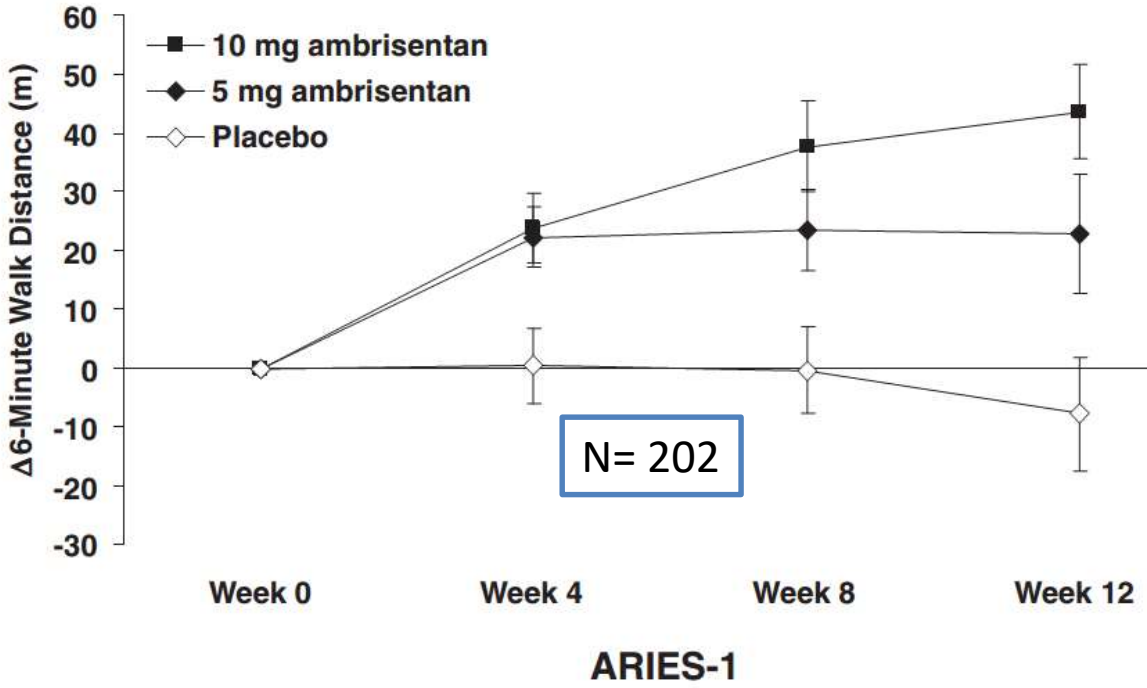
Drug	Dose	Selectivity	Main Adverse Affects	Interactions	Monitoring
Bosentan BOSENTAS/ LUPIBOSE Rs 110: 62.5 mg	Initially 62.5 mg bd, If LFT normal increase to 125 mg bd	Non-selective	Transaminitis, Teratogenic, Edema, Anemia	Glyburide, Cyclosporine, CYP450 inhibitors/inducers	Monthly LFT, Monthly pregnancy testing
Ambrisentan AMBRICAN/ ENDOBLOC Rs 140: 5mg Rs 230: 10mg	5 mg to 10 mg od	ET-A	<Transaminitis, Teratogenic, Nasal congestion, edema, Anemia	Cyclosporine, CYP450 inhibitors/inducers	Monthly pregnancy testing
Macitentan	10 mg od	Non-selective	do	do	

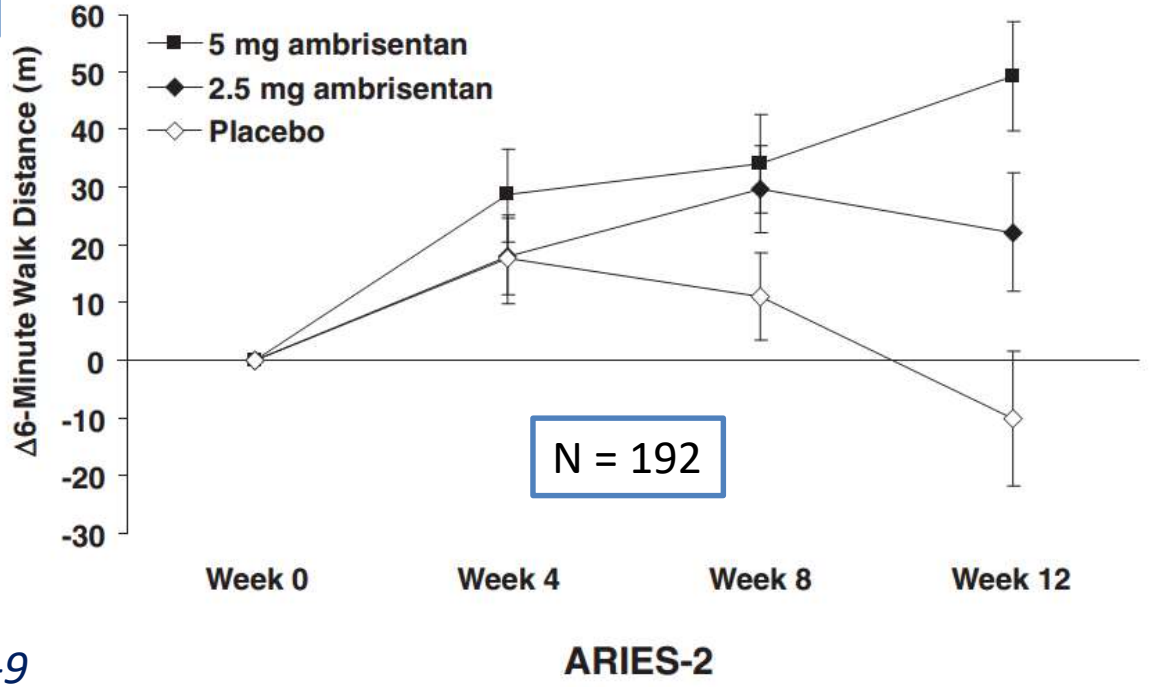
Sitaxsentan withdrawn after reports of ALF

Drug(s) tested	Study	No of pts	Duration (weeks)	Background therapy	Primary endpoint	Main Results
Ambrisentan	ARIES-1	202	12	No	6MWD	6MWD improved TTCW not improved
	ARIES-2	192	12	No	6MWD	6MWD improved TTCW improved
Bosentan	Study-351	32	12	No	6MWD	6MWD improved TTCW improved
	Breathe-1	213	16	No	6MWD	6MWD improved TTCW improved
	Early	185	24	No or CCB(41%)Sildenafil (16%)	PVR, 6MWD	PVR improved, TTCW improved, 6MWD not improved
	BREATHE-5	54	12	No	SaO2, PVR	PVR improved, 6MWD improved
	Compass-2	334	99	Sildenafil	TTCW	TTCW not improved 6MWD improved, NT-proBNP improved
Macitentan	Seraphin	742	115	No, or Sildenafil or Inh Iloprost	TTCW	TTCW improved in monotherapy and combination

ARIES 1 & 2: Ambrisentan

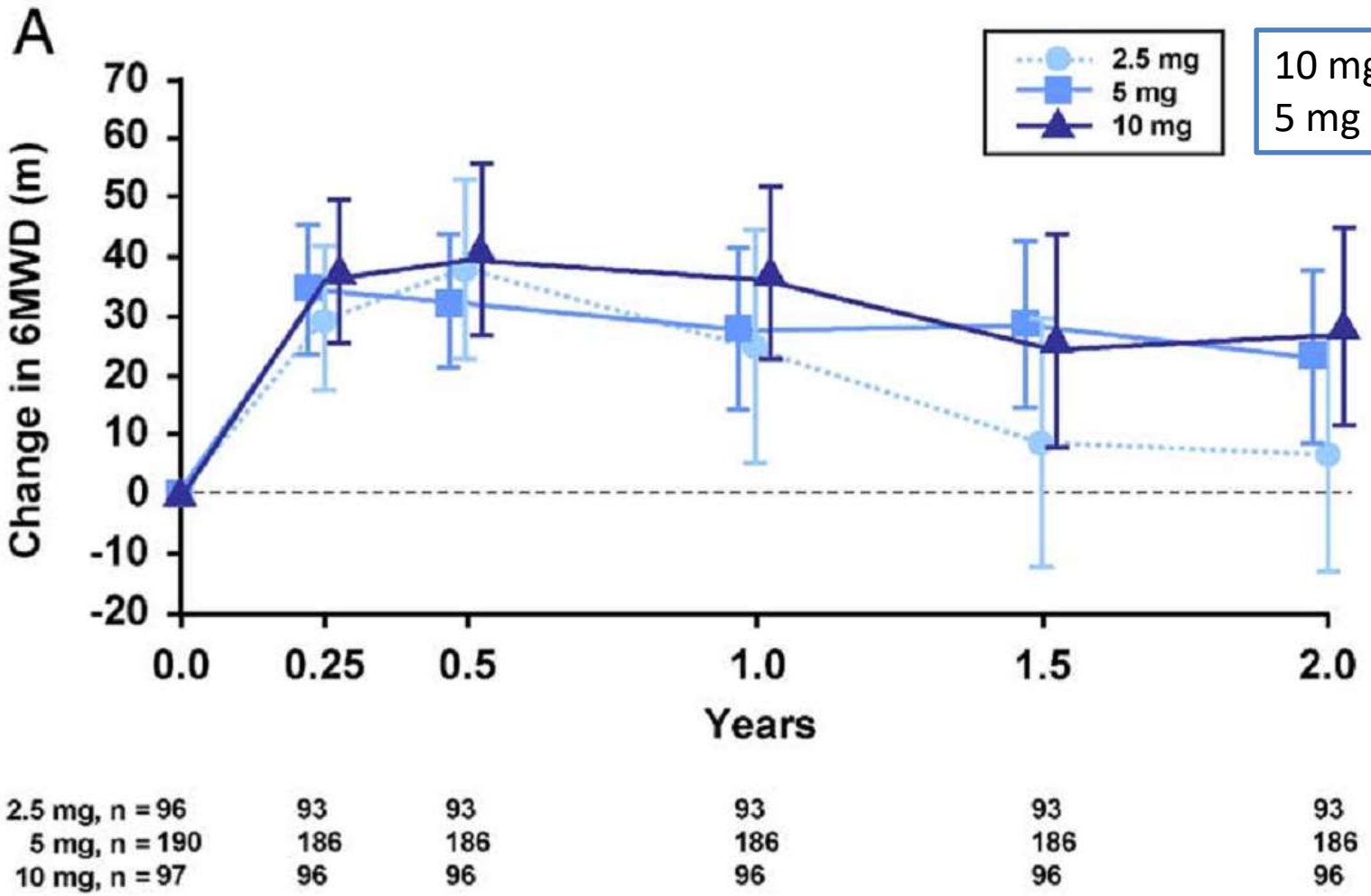
All WHO FC included, but consisted predominantly of WHO FC II, III





Circulation. 2008 Jun 10;117(23):3010-9

ARIES extension

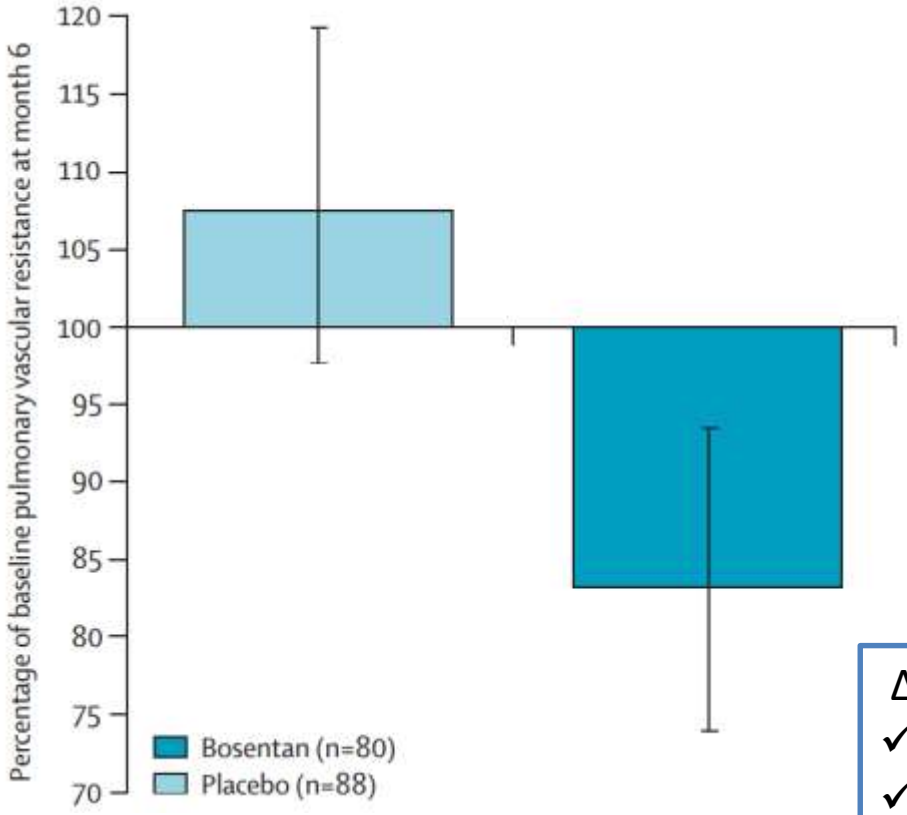


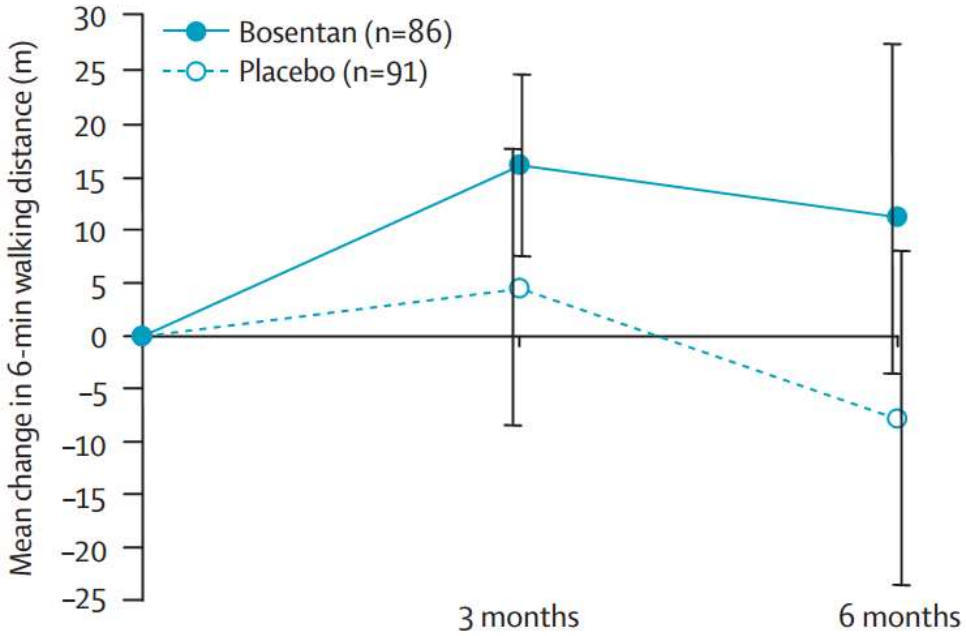
10 mg = 28 m
5 mg = 23 m

Dyspnea scores improved in 5mg & 10 mg, Survival better when compared with NIH registry

Oudiz et al.J Am Coll Cardiol. 2009

EARLY: Bosentan in WHO FC II





Δ6MWD = 19 m, p=ns
✓FC improvement
✓Time to CW improved
✓nT-BNP

N = 185

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

Macitentan – SERAPHIN trial

- Multicentre, double blind RCT, n=742
- 250 = placebo, 250 = 3 mg, 242 = 10 mg
- Group 1, NYHA class II or III
- 61% PDE-5, 5% prostanoids as additional Rx
- Follow-up for 2 yrs
- Primary outcome = composite of mortality and morbidity

Pulido et al. NEJM 2013

Table 2. Primary and Secondary End Points for Events Related to Pulmonary Arterial Hypertension and Death.*

End Point	Placebo (N=250)	Macitentan, 3 mg (N=250)	Macitentan, 10 mg (N=242)	Macitentan, 3 mg, vs. Placebo		Macitentan, 10 mg, vs. Placebo	
				Hazard Ratio (97.5% CI)	P Value	Hazard Ratio (97.5% CI)	P Value
	number of patients (percent)						
Event related to PAH or death as the first event							
All events	116 (46.4)	95 (38.0)	76 (31.4)	0.70 (0.52–0.96)	0.01	0.55 (0.32–0.76)	<0.001
Worsening of PAH	93 (37.2)	72 (28.8)	59 (24.4)				
Death from any cause†	17 (6.8)	21 (8.4)	16 (6.6)				
Prostanoid initiation	6 (2.4)	1 (0.4)	1 (0.4)				
Lung transplantation	0	1 (0.4)	0				
Death due to PAH or hospitalization for PAH as the first event							
All events	84 (33.6)	65 (26.0)	50 (20.7)	0.67 (0.46–0.97)	0.01	0.50 (0.34–0.75)	<0.001
Hospitalization for PAH	79 (31.6)	56 (22.4)	45 (18.6)				
Death due to PAH‡	5 (2.0)	9 (3.6)	5 (2.1)				
Death from any cause	19 (7.6)	21 (8.4)	14 (5.8)	0.97 (0.48–1.98)	0.92	0.64 (0.29–1.42)	0.20
Death due to PAH§	14 (5.6)	14 (5.6)	7 (2.9)	0.87 (0.37–2.04)	0.72	0.44 (0.16–1.25)	0.07
Death from any cause by the end of the study¶	44 (17.6)	47 (18.8)	35 (14.5)	1.05 (0.65–1.67)	0.83	0.77 (0.46–1.28)	0.25

Treatment effect maintained across subgroups including those receiving background therapy

Other outcomes and status

- 6MWD (vs placebo): 3 mg-16.8m, 10 mg-22m
- Significant change in FC (20 and 22% resp)
- Better cardiac hemodynamics at 6 months
- ADR: Headache, anemia (4.3% in 10mg arm), nasal congestion
- 10 mg received FDA approval in October 2013

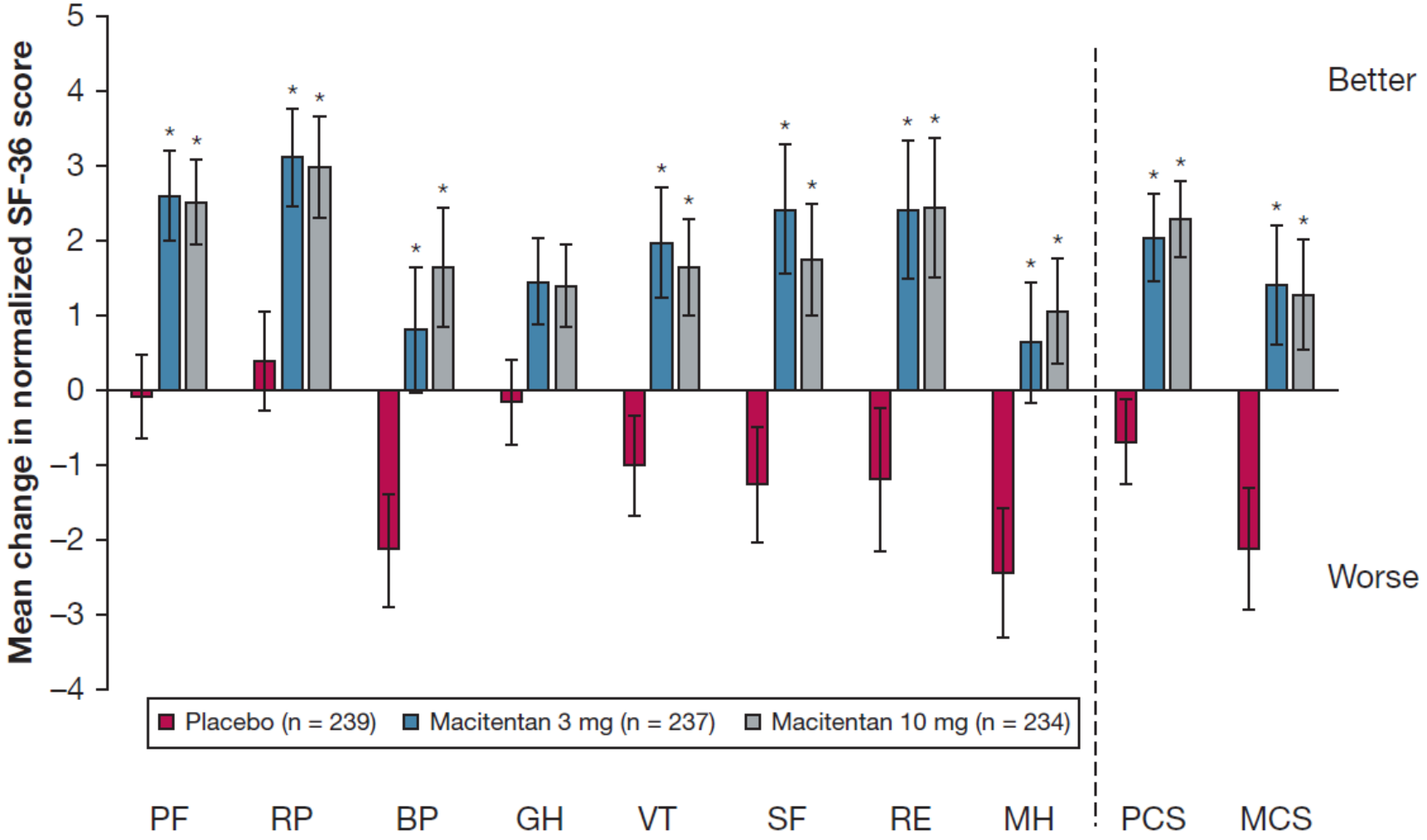
CHEST

Macitentan Improves Health-Related Quality of Life for Patients With Pulmonary Arterial Hypertension

Results From the Randomized Controlled SERAPHIN Trial

- To evaluate the effect of macitentan on
- HRQoL
- SF-36 at baseline, at month 6 and month 12, and at the end of treatment (EOT)
- Time to a clinically meaningful deterioration in the PCS and MCS scores
- Associations between baseline PCS/MCS scores and time to morbidity/mortality events

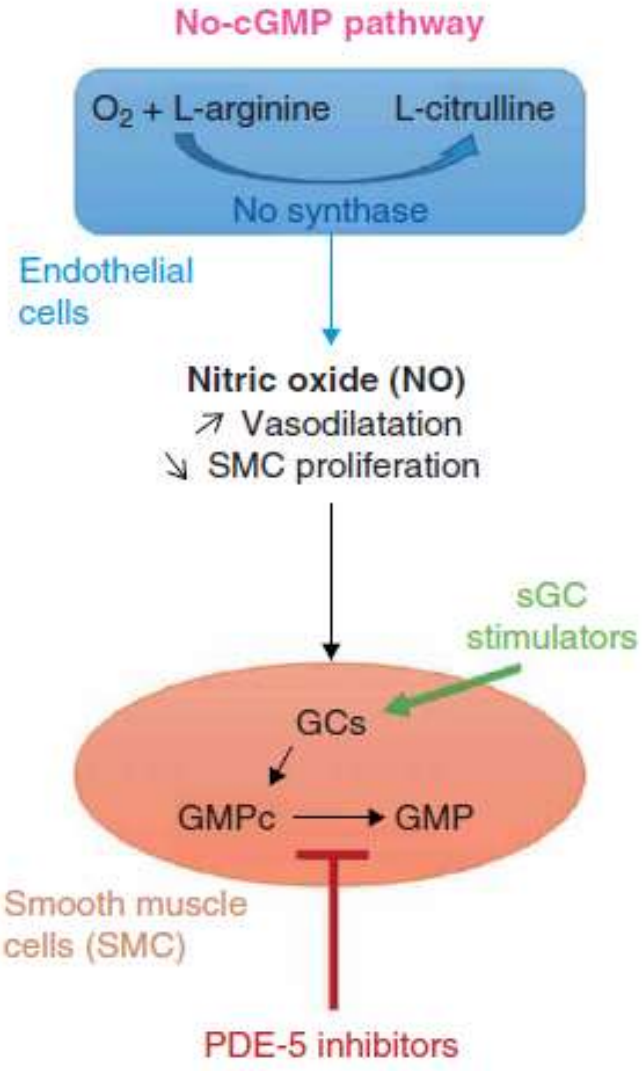
CHEST 2017; 151(1):106-118



- At month 6, macitentan 10 mg significantly improved seven of eight SF-36 domains and the PCS and MCS scores vs placebo
- Macitentan 10 mg significantly reduced the risk of a three-point or greater deterioration in
  - PCS (hazard ratio [HR], 0.60; 95% CI, 0.47-0.76; P < .0001)
  - MCS scores (HR, 0.76; 95% CI, 0.61-0.95; P ¼ .0173)

CHEST 2017; 151(1):106-118

PDE-5 inhibitors - mechanism



Perrin et al. Expert Opin. Pharmacother. 2015

PDE-5 inhibitors - mechanism

- NO → vasodilator, antiproliferative, and antithrombotic.
- Its activity is mediated by second messenger, cGMP.
- cGMP rapidly degraded by PDE-5 isoenzyme.
- PDE-5 inhibition thus acts to enhance cGMP levels and prolong its vasodilating effects.
- Increased myocardial PDE-5 expression, facilitated by pressure-overloaded myocytes, in the hypertrophied RV
- PDE5 inhibitors may directly target RV function and acutely improve contractility in RV failure patients who express elevated PDE5 levels.

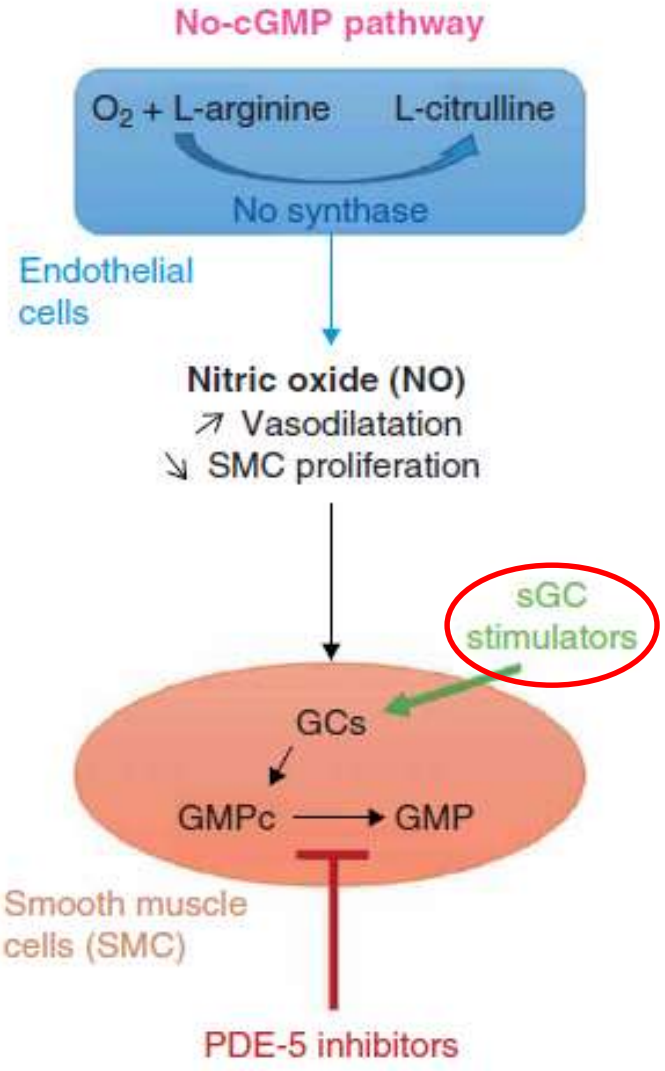
Agarwal R et al. AHJ 2011

Comparison of PDE-5 inhibitors

Drug	Dose	Main Adverse Affects	Interactions	Contraindications
Sildenafil	Only 20 mg TDS FDA approved (higher doses used off-label)	Flushing, dyspepsia, myalgia, visual changes, epistaxis, nasal congestion, headache	Concomitant nitrates avoided (hypotension), Cyp450 inhibitors	MI in past 3 months, hypotension, AION
Tadalafil	40 mg OD	do	do	do
Vardenafil	5mg BD	do	do	do

Drug(s) tested	Study	N	Weeks	Background therapy	Primary endpoint	Main Results
Riociguat	PATENT	443	12	No, or bosentan, or prostanoids	6MWD	6MWD improved Haemodynamics improved
	PATENT PLUS	30	18	Sildenafil	Supine SBP	Terminated for excess of SAE
Sildenafil	SUPER-I	277	12	No	6MWD	6MWD improved TTCW not improved
	Sastry	22	12	No	TT	TT improved
	Singh	20	6	No	6MWD	6MWD improved
	PACES	264	16	Epoprostenol	6MWD	6MWD improved, TTCW and hemodynamics improved
	Iversen	20	12	Bosentan	6MWD	6MWD not improved
	Pfizer study	103	12	Bosentan	6MWD	6MWD not improved
Tadalafil	PHIRST	405	16	No, or Bosentan (54%)	6MWD	6MWD improved (In bosentan treated patients +23 m, 95% CI -2 to 48 m) TTCW improved
Vardenafil	EVALUATION	66	12	No	6MWD	6MWD improved, TTCW improved

Guanylyl cyclase activator - Riociguat



Perrin et al. Expert Opin. Pharmacother. 2015

Guanylyl cyclase activator - Riociguat

- Soluble guanylyl cyclase stimulator → increases cGMP levels → Vasodilation
- Pyrimidine derivative
- First-in-its class drug
- Good oral bioavailability
- T ½ = 5-10 hrs
- Dose = 1-2.5 mg tds

- MC adverse effects:

  Hypotension, syncope, transaminitis, supraventricular tachycardia, edema, headache, nasal congestion, neck pain
- Dose to be reduced by 0.5-1 mg in case of ADR

Meis et al. Expert Opin. Pharmacother. 2015

RCTs with Riociguat

Study	n	Population	6MWD Improvement (compared to placebo)	Death/Clinical Worsening	FC change	QoL	Hemodynamics	Serious Adverse Events
Ghofrani 2013 (PATENT)	443	Grp 1 PAH, NYHA II,III>IV	36m at 12 wks, 55m at 24 wks (p=.001), NYHA III/IV had more benefit	Y	Y	N	Y	Hypotension (10%, p=.005))
Ghofrani 2013 (CHEST-1)	261	CTEPH, NYH II or III	46m at 12 wks, (p=.001)	N	Y	Y (Dyspnea scores also improved)	Y	do

Guanylate cyclase stimulators for pulmonary hypertension (Cochrane review)

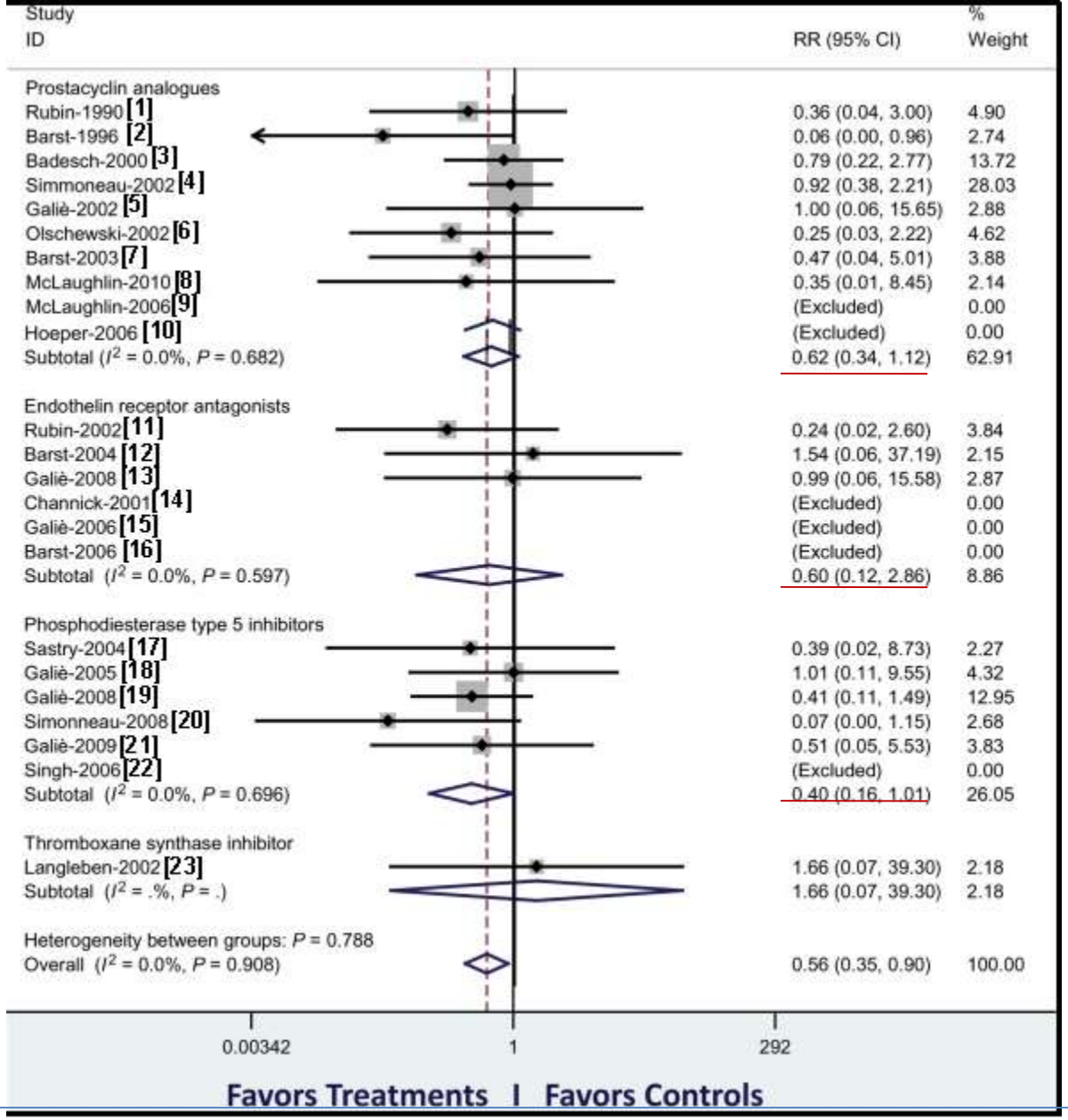
- 5 trials involving 962 participants are included
- short duration (< 16 weeks)
- Mean difference increase in 6MWD of 30.13 metres (95% CI 5.29 to 54.96; participants = 659; studies = 3)
  - On subgroup analysis, for PAH there was no effect noted (6MWD; MD 11.91 metres, 95% CI -44.92 to 68.75; participants = 398; studies = 2)
  - when participants receiving PDE5i were excluded, sGC stimulators increased 6MWD by a MD of 36 m

Cochrane Database Syst Rev. 2016 Aug 2;(8):CD011205.

PATENT 2

- Long term extension arm – open labelled
- 396 patients
  - 197 riociguat monotherapy
  - 199 combination therapy
- significant association between overall survival with
  - 6MWD - p=0·0006
  - NT-proBNP concentration – p= 0·0225
  - WHO FC p= 0·0191
- Riociguat well tolerated; improvement in parameters persisted at 2 yrs

Eur Respir J. 2015 May;45(5):1303-13. Epub 2015 Jan 22
Lancet Respir Med. 2016;4(5):361



Summary of RCTs Testing the Effect of Prostacyclin Replacement Therapy, PDE5i, and ERAs on Mortality in PAH

Maron et al. doi:10.1001/jamacardio.2016.4471

New drugs

- Inhaled VIP
- TKIs (PDGF inhibitors)
- Serotonin antagonists
- Rho kinase inhibitors
- VEGFR inhibitors
- Angiopoietin-1 inhibitors
- Elastase inhibitors
- Mitochondrial modulators

Galie` N, et al. J Am Coll Cardiol. 2016 ;62(12):1101-2

Other modalities

- Gene therapy
- Stem-cell therapy
  - effective in the monocrotaline rat model
- PA denervation by a radiofrequency ablation catheter

Galie` N, et al. J Am Coll Cardiol. 2016 ;62(12):1101-2

PADN1 Study

- 21 patients with IPAH
  - 13 patients received the PADN procedure
  - 8 control group
- PADN was performed at the bifurcation of the main PA, and at the ostial right and left PA
- Primary endpoints -change of PAP, TEI, and 6MWT at 3 months
- Results
  - PAPm (from 55±5 mm Hg to 36±5 mm Hg, $p < 0.01$)
  - 6MWT (from 324±21 m to 491±38 m, $p < 0.006$)
  - Tei index (from 0.7±0.04 to 0.50±0.04, $p < 0.001$)

Chen SL. J Am Coll Cardiol 2013;62: 1092–1100.

Combination therapy for PAH

- Strong rationale for combining drugs as different drugs act on different pathways
- Beyond a simple additive effect, certain combinations may also have a synergistic action (eg Sildenafil and prostanoid/Selective ETRA)
- REVEAL registry – 52% pts on combination Rx
- The general treatment paradigm has been to add drugs sequentially
- In an early open-label trial using a step-wise goal-directed approach, sildenafil and iloprost added sequentially after 1st line therapy with bosentan (n=123) showed significant benefit

Hoeper et al. Eur Respir J 2005; 26: 858–863

Sequential vs. upfront combination

- Retrospective analysis of 97 patients with newly diagnosed PAH (86% FC class III-IV)
- Explored initial dual oral combination treatment with
  - bosentan plus sildenafil (n=61)
  - bosentan plus tadalafil (n=17)
  - ambrisentan plus tadalafil (n=11)
  - ambrisentan plus sildenafil (n=8)
- significant improvements in FC, exercise capacity, dyspnoea and haemodynamic indices after 4 months
- Overall survival rates were 97%, 94% and 83% at 1, 2 and 3 years, respectively

Sitbon O et al. Initial dual oral combination therapy in pulmonary arterial hypertension. Eur Respir J. 2016 Jun;47(6):1727-36

Drug(s) tested	Study	No of pts	Duration (weeks)	Background therapy	Primary endpoint	Main Results
Epoprostenol vs epoprostenol + bosentan	BREATHE -2	33	12	No	PVR	PVR not improved 6MWD not improved
Ambrisentan or Tadalafil vs ambrisentan + tadalafil	AMBITION	500	78	No	TTCW	TTCF improved 6MWD improved

BREATHE-2: Bosentan + IV epoprostenol

ABSTRACT: The efficacy and safety of combining bosentan, an orally active dual endothelin receptor antagonist and epoprostenol, a continuously infused prostaglandin, in the treatment of pulmonary arterial hypertension (PAH) was investigated.

In this double-blind, placebo-controlled prospective study, 33 patients with PAH started epoprostenol treatment (2 $ng \cdot kg^{-1}min^{-1}$ starting dose, up to 14 ± 2 $ng \cdot kg^{-1}min^{-1}$ at week 16) and were randomised for 16 weeks in a 2:1 ratio to bosentan (62.5 mg *b.i.d* for 4 weeks then 125 mg *b.i.d*) or placebo.

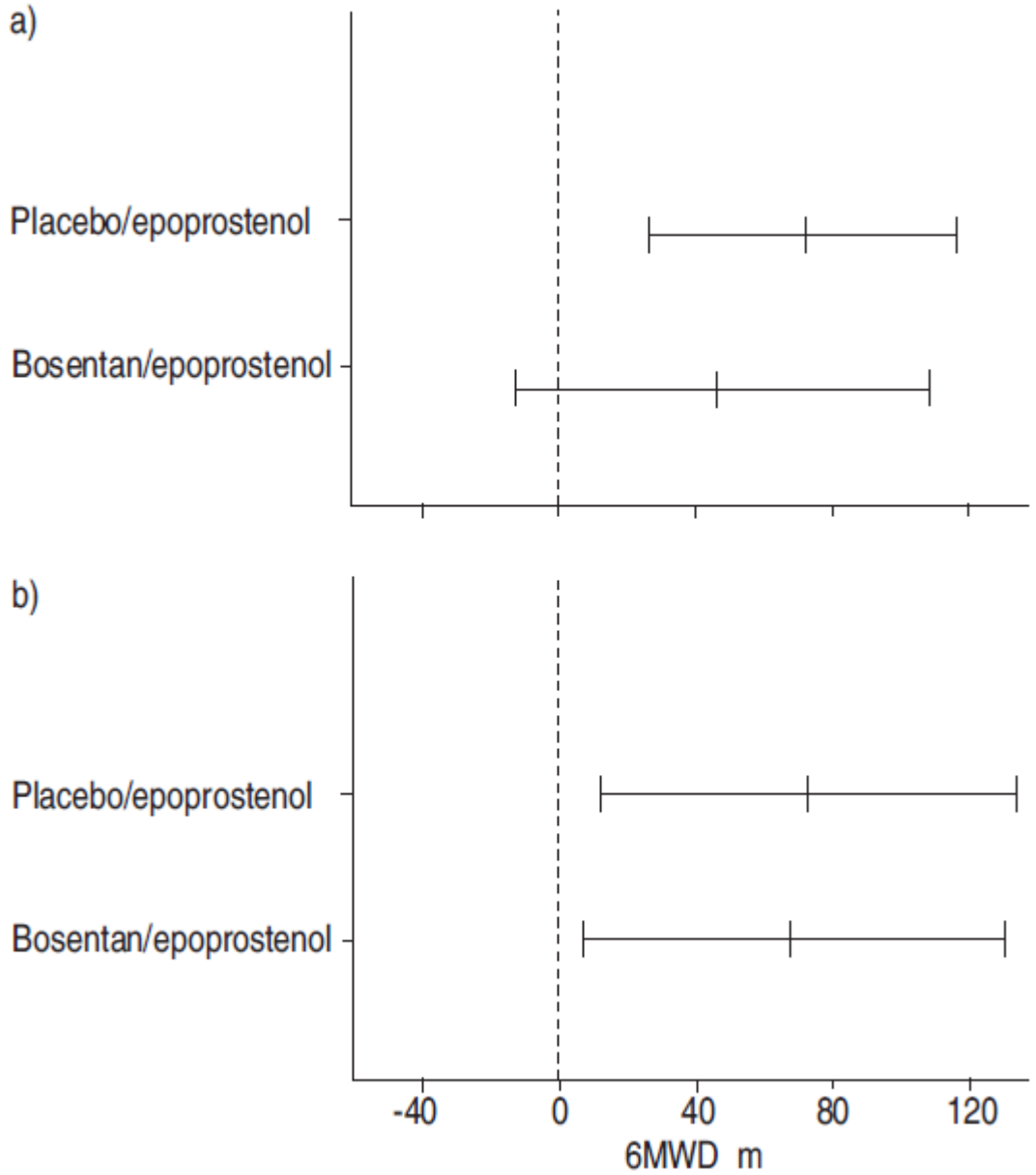
Haemodynamics, exercise capacity and functional class improved in both groups at week 16. In the combination treatment group, there was a trend for a greater (although nonsignificant) improvement in all measured haemodynamic parameters. There were four withdrawals in the bosentan/epoprostenol group (two deaths due to cardiopulmonary failure, one clinical worsening, and one adverse event) and one withdrawal in the placebo/epoprostenol group (adverse event).

This study showed a trend but no statistical significance towards haemodynamics or clinical improvement due to the combination of bosentan and epoprostenol therapy in patients with pulmonary arterial hypertension. Several cases of early and late major complications were reported. Additional information is needed to evaluate the risk/benefit ratio of combined bosentan-epoprostenol therapy in pulmonary arterial hypertension.

Eur Respir J 2004; 24: 353–359.

Humbert et al. Eur Respir J 2004

BREATHE-2: Bosentan + IV epoprostenol



Baseline

Week 16

COMBI Trial: Iloprost + Bosentan

ABSTRACT: Addition of inhaled iloprost to bosentan may have beneficial effects in patients with idiopathic pulmonary arterial hypertension (IPAH). A multicentre, open, randomised, controlled trial was performed to assess the safety and efficacy of inhaled iloprost in patients with IPAH who had already been treated with bosentan.

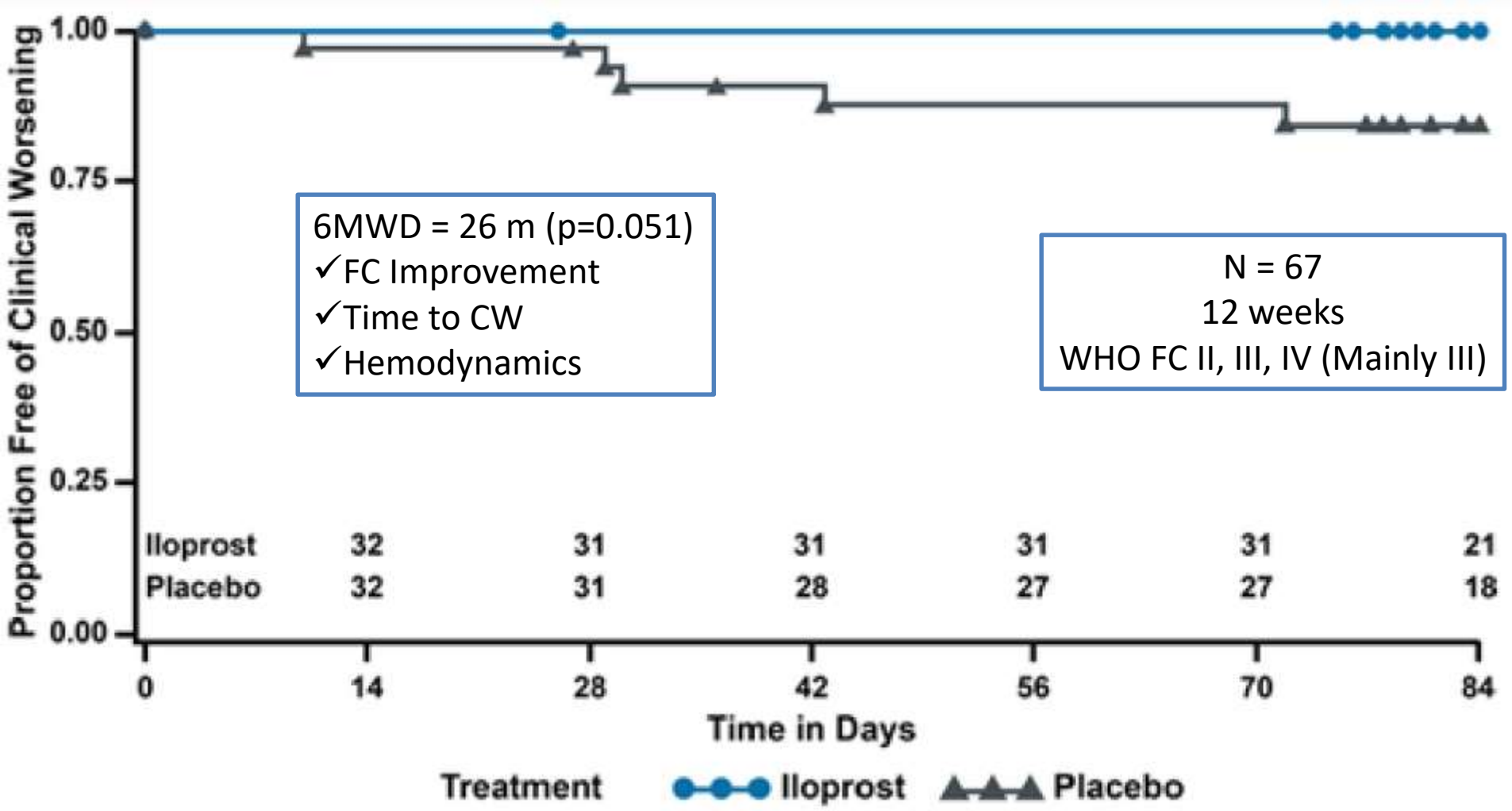
The trial was terminated early after a futility analysis predicted failure with respect to the predetermined sample size. At that time, 40 patients were randomised to receive either bosentan alone (control group) or bosentan plus inhaled iloprost (combination group) for a 12-week period.

The primary end-point, change in 6-min walking distance, was not met (mean changes +1 m and -9 m in the control and combination group, respectively). These results may have been skewed by three outliers in the iloprost group who presented with severe clinical worsening. None of the secondary end-points including functional class, peak oxygen uptake, and time to clinical worsening differed significantly between groups.

The current study failed to show a positive effect of adding inhaled iloprost to bosentan in idiopathic pulmonary arterial hypertension patients. Further studies involving larger sample sizes and long-term follow-up are needed to determine the efficacy of adding inhaled iloprost to bosentan in patients with idiopathic pulmonary arterial hypertension.

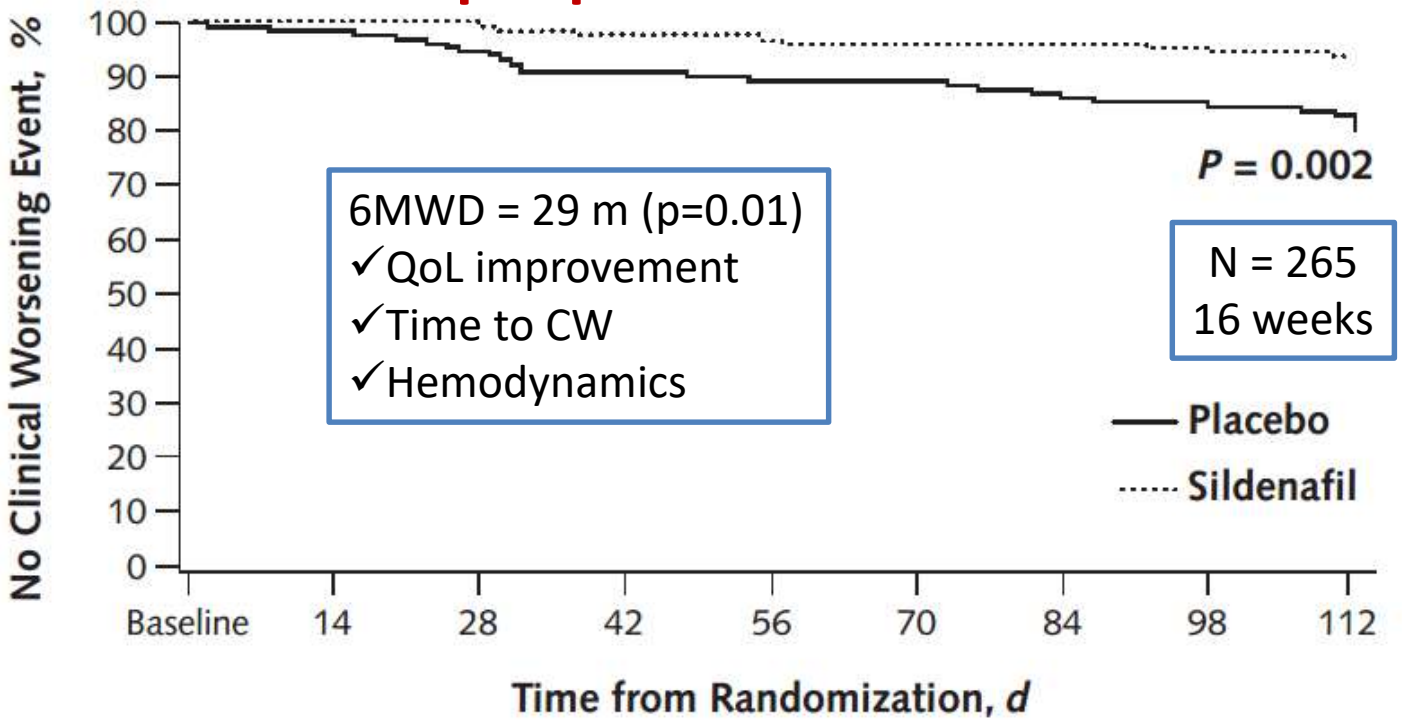
Hoeper et al. Eur Respir J 2006

STEP trial: Addition of Inhaled Iloprost to Bosentan



McLaughlin et al Am J Respir Crit Care Med. 2006

PACES: Addition of sildenafil to epoprostenol



6MWD = 29 m (p=0.01)
✓QoL improvement
✓Time to CW
✓Hemodynamics

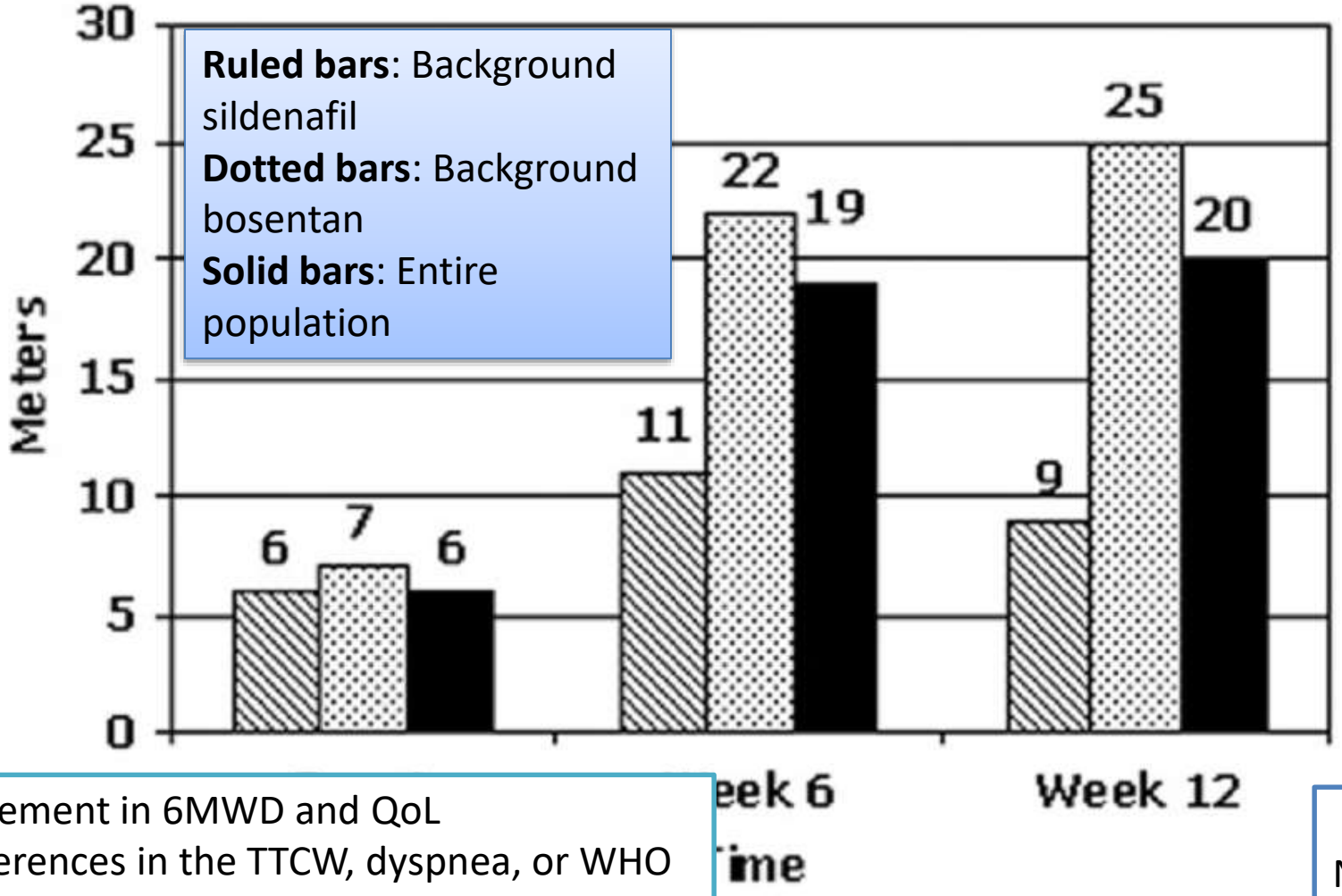
N = 265
16 weeks

Treatment	Persons at Risk (Censored), *n*				
	Baseline	Day 28*	Day 56†	Day 84‡	Day 112§
Epoprostenol + placebo	131	123 (1)	116 (0)	111 (2)	70 (36)
Epoprostenol + sildenafil	134	134 (0)	128 (2)	125 (2)	78 (44)

All WHO FC included, but predominantly II, III

Simonneau et al. Ann Intern Med. 2008

TRIUMPH I: Addition of inhaled treprostinil to oral therapy



Improvement in 6MWD and QoL
No differences in the TTCW, dyspnea, or WHO FC

N = 235
NYHA III/IV

McLaughlin VV et al. J Am Coll Cardiol. 2010 May 4;55(18):1915-22

Tadalafil + Bosentan in PHIRST: 6MWD

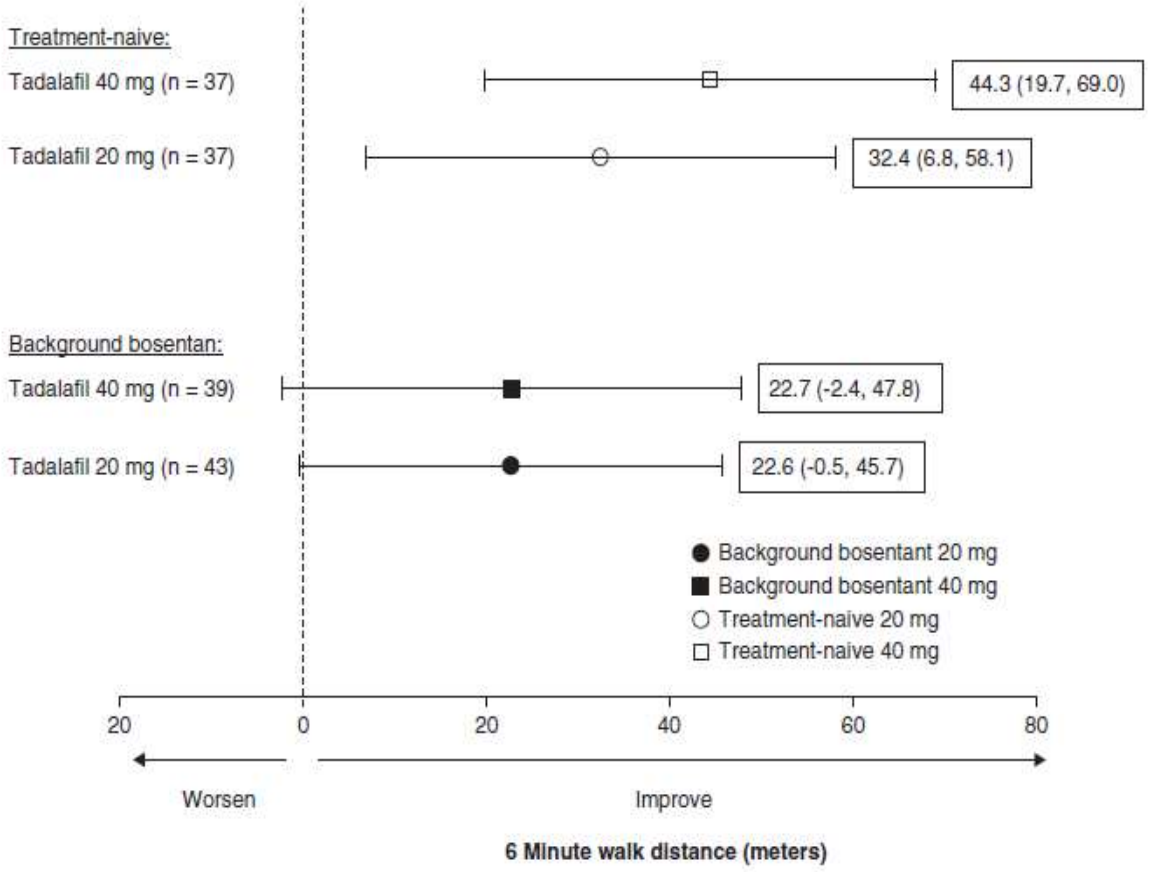


Figure 1. Placebo-adjusted treatment differences in 6-min walk distance (meters) from baseline to week 16 by bosentan use.

Tadalafil + Bosentan in PHIRST: clinical worsening

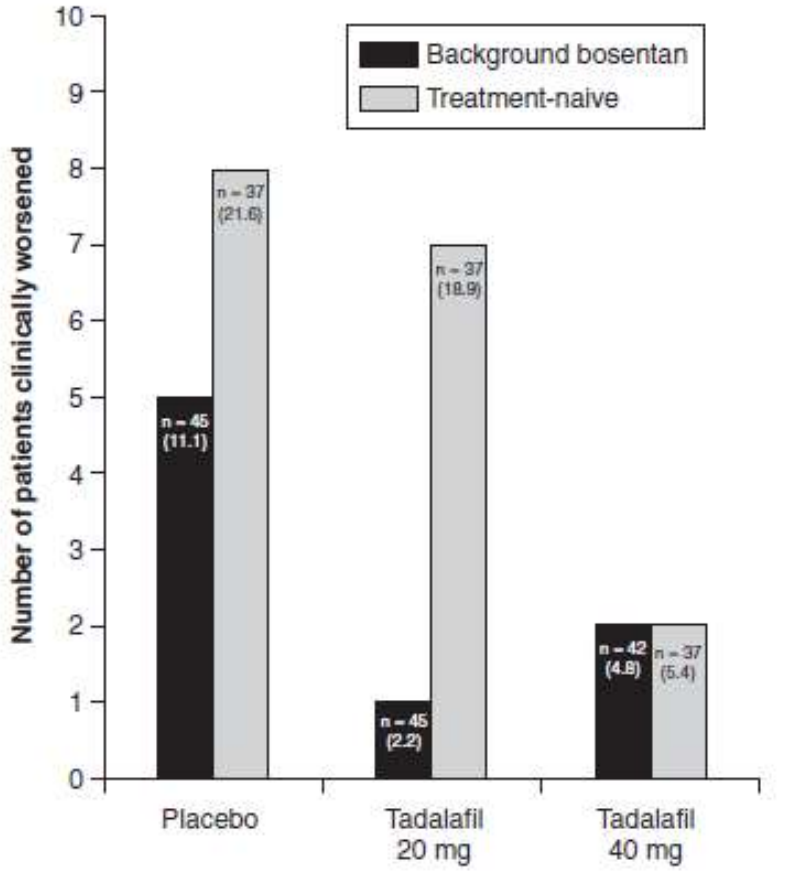


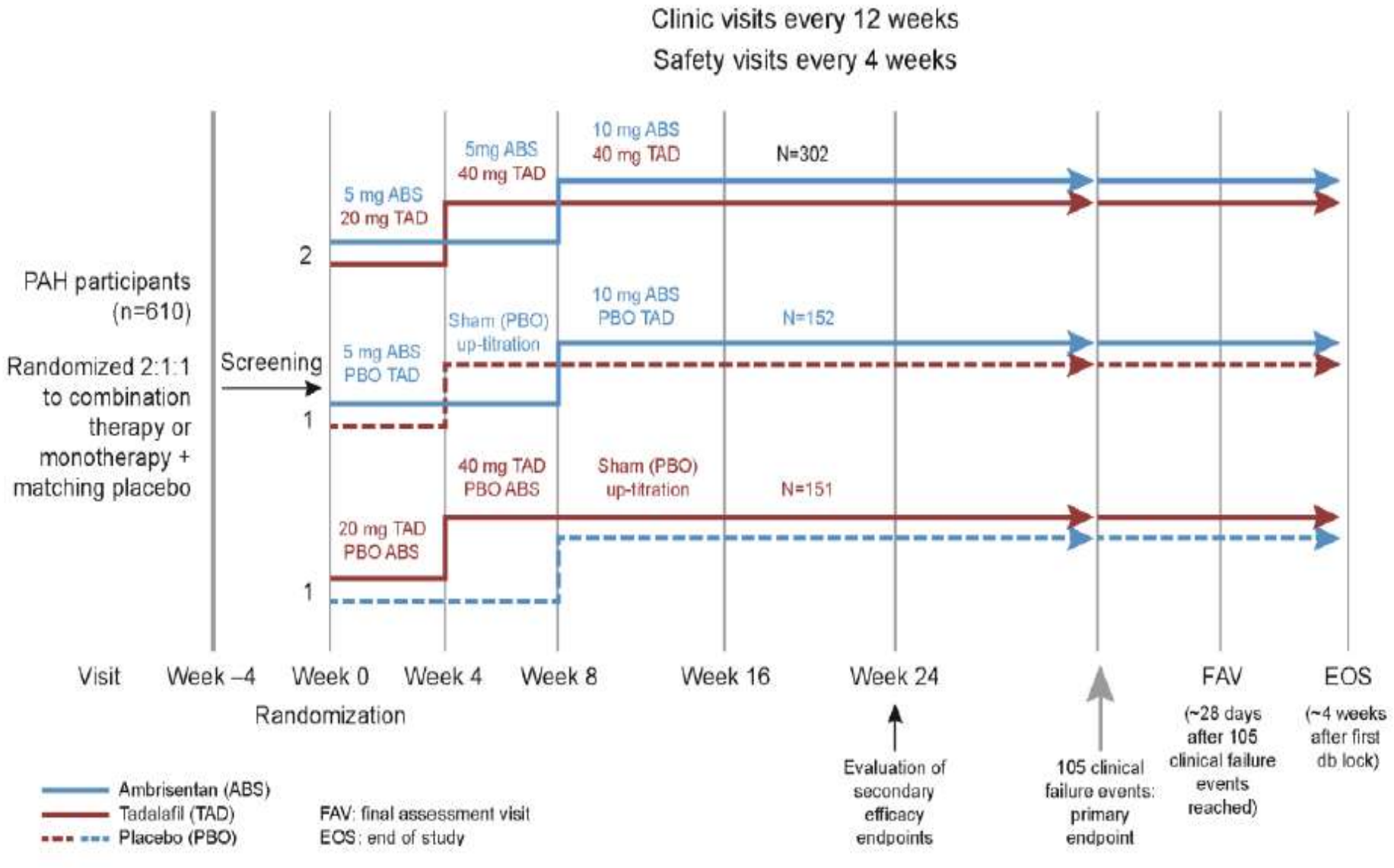
Figure 2. Clinical worsening by bosentan use and tadalafil treatment subgroup.

AMBITION trial

- Multicenter, randomized, double-blind, phase 3 trial, n=500
- 126 pts = Ambrisentan 10 mg monotherapy
- 121 pts = Tadalafil 40 mg monotherapy
- 253 pts = Combination
- Follow-up 517 days
- Group I PAH
- NYHA II (30%), III (70%)

Galie et al. NEJM. Aug 2015

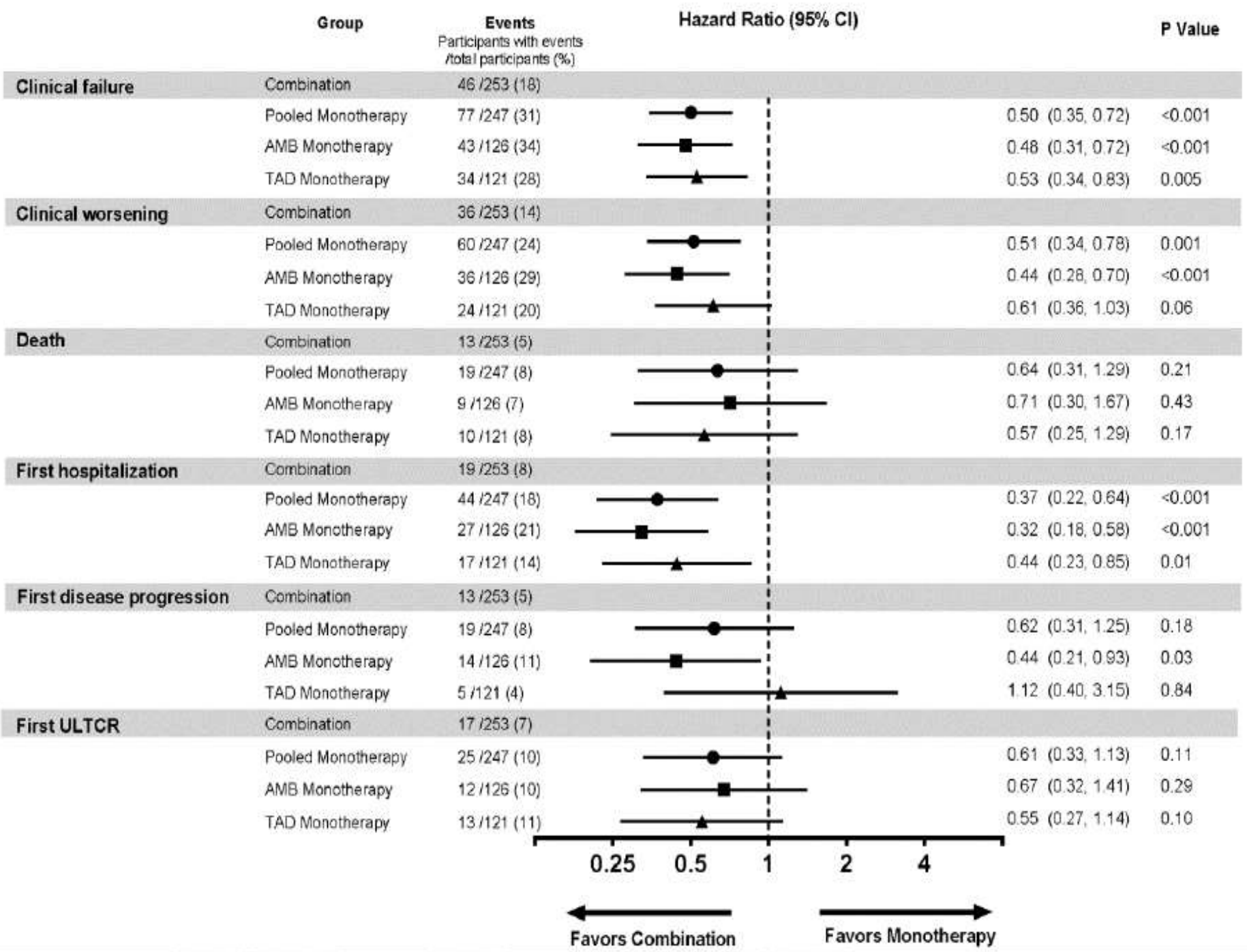
Study Design



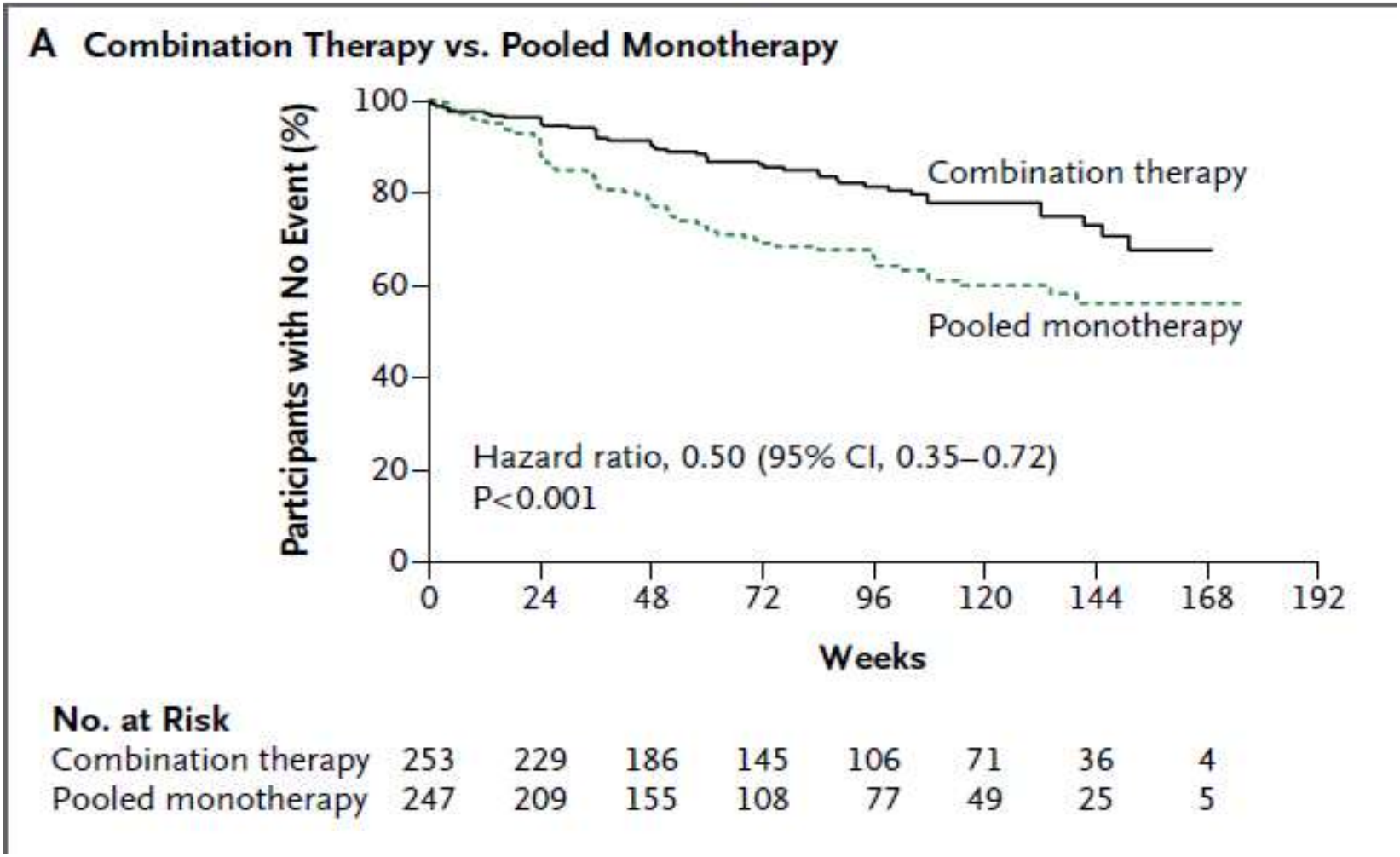
Results

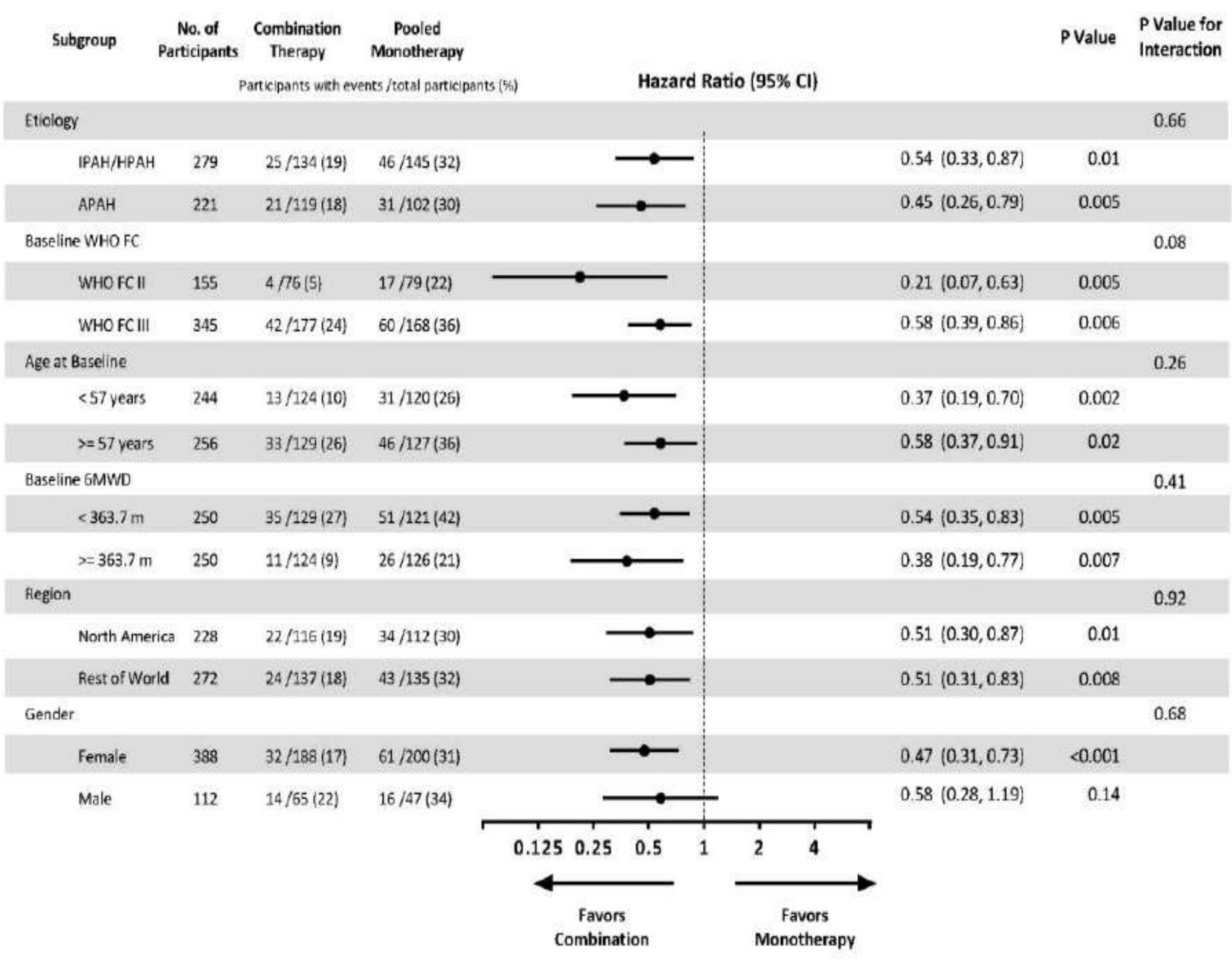
Table 4. Primary and Secondary Efficacy End Points.*

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


Group
Events
Participants with events /total participants (%)
Hazard Ratio (95% CI)
P Value
Clinical failure
Combination 46 /253 (18)
Pooled Monotherapy 77 /247 (31) 0.50 (0.35, 0.72) <0.001
AMB Monotherapy 43 /126 (34) 0.48 (0.31, 0.72) <0.001
TAD Monotherapy 34 /121 (28) 0.53 (0.34, 0.83) 0.005
Clinical worsening
Combination 36 /253 (14)
Pooled Monotherapy 60 /247 (24) 0.51 (0.34, 0.78) 0.001
AMB Monotherapy 36 /126 (29) 0.44 (0.28, 0.70) <0.001
TAD Monotherapy 24 /121 (20) 0.61 (0.36, 1.03) 0.06
Death
Combination 13 /253 (5)
Pooled Monotherapy 19 /247 (8) 0.64 (0.31, 1.29) 0.21
AMB Monotherapy 9 /126 (7) 0.71 (0.30, 1.67) 0.43
TAD Monotherapy 10 /121 (8) 0.57 (0.25, 1.29) 0.17
First hospitalization
Combination 19 /253 (8)
Pooled Monotherapy 44 /247 (18) 0.37 (0.22, 0.64) <0.001
AMB Monotherapy 27 /126 (21) 0.32 (0.18, 0.58) <0.001
TAD Monotherapy 17 /121 (14) 0.44 (0.23, 0.85) 0.01
First disease progression
Combination 13 /253 (5)
Pooled Monotherapy 19 /247 (8) 0.62 (0.31, 1.25) 0.18
AMB Monotherapy 14 /126 (11) 0.44 (0.21, 0.93) 0.03
TAD Monotherapy 5 /121 (4) 1.12 (0.40, 3.15) 0.84
First ULTCR
Combination 17 /253 (7)
Pooled Monotherapy 25 /247 (10) 0.61 (0.33, 1.13) 0.11
AMB Monotherapy 12 /126 (10) 0.67 (0.32, 1.41) 0.29
TAD Monotherapy 13 /121 (11) 0.55 (0.27, 1.14) 0.10
0.25
0.5
1
2
4
Favors Combination
Favors Monotherapy

Kaplan–Meier Curves for the Probability of a First Adjudicated Primary End-Point Event.




Subgroup
No. of Participants
Combination Therapy
Pooled Monotherapy
Participants with events /total participants (%)
Hazard Ratio (95% CI)
P Value
P Value for Interaction
Etiology 0.66
IPAH/HPAH 279 25 /134 (19) 46 /145 (32) 0.54 (0.33, 0.87) 0.01
APAH 221 21 /119 (18) 31 /102 (30) 0.45 (0.26, 0.79) 0.005
Baseline WHO FC 0.08
WHO FC II 155 4 /76 (5) 17 /79 (22) 0.21 (0.07, 0.63) 0.005
WHO FC III 345 42 /177 (24) 60 /168 (36) 0.58 (0.39, 0.86) 0.006
Age at Baseline 0.26
< 57 years 244 13 /124 (10) 31 /120 (26) 0.37 (0.19, 0.70) 0.002
>= 57 years 256 33 /129 (26) 46 /127 (36) 0.58 (0.37, 0.91) 0.02
Baseline 6MWD 0.41
< 363.7 m 250 35 /129 (27) 51 /121 (42) 0.54 (0.35, 0.83) 0.005
>= 363.7 m 250 11 /124 (9) 26 /126 (21) 0.38 (0.19, 0.77) 0.007
Region 0.92
North America 228 22 /116 (19) 34 /112 (30) 0.51 (0.30, 0.87) 0.01
Rest of World 272 24 /137 (18) 43 /135 (32) 0.51 (0.31, 0.83) 0.008
Gender 0.68
Female 388 32 /188 (17) 61 /200 (31) 0.47 (0.31, 0.73) <0.001
Male 112 14 /65 (22) 16 /47 (34) 0.58 (0.28, 1.19) 0.14
0.125 0.25 0.5 1 2 4
Favors Combination
Favors Monotherapy

Secondary end points

Secondary end points	Combination	Pooled Monotherapy	Ambrisentan	Tadalafil
NT-proBNP level†				
Percentage change in geometric mean from baseline to week 24	−67.2	−50.4	−56.2	−43.8
P value	Reference	<0.001	0.01	<0.001
Satisfactory clinical response at week 24 — no. of participants/total no. (%)‡				
Yes	91/234 (39)	66/226 (29)	35/113 (31)	31/113 (27)
No	143/234 (61)	160/226 (71)	78/113 (69)	82/113 (73)
Unknown	19/253 (8)	21/247 (9)	13/126 (10)	8/121 (7)
Odds ratio, combination therapy vs. monotherapy (95% CI)	Reference	1.56 (1.05 to 2.32)	1.42 (0.88 to 2.31)	1.72 (1.05 to 2.83)
P value	—	0.03	0.15	0.03
6-Minute walk distance — m§				
Median (IQR) change from baseline to week 24	48.98 (4.63 to 85.75)	23.80 (−12.25 to 64.53)	27.00 (−14.00 to 63.25)	22.70 (−8.25 to 66.00)
P value	Reference	<0.001	<0.001	0.003
Change in WHO functional class at week 24 — no. of participants/total no. (%)§				
Improved	94/252 (37)	81/244 (33)	42/124 (34)	39/120 (33)
No change	146/252 (58)	147/244 (60)	73/124 (59)	74/120 (62)
Deteriorated	12/252 (5)	16/244 (7)	9/124 (7)	7/120 (6)
P value	Reference	0.24	0.30	0.36

Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study

- Newly diagnosed NYHA FC III/IV PAH patients
- IV epoprostenol, bosentan and sildenafil
- N=19
- Retrospectively from a prospective registry
- Significant improvements in 6MWD and haemodynamics after 4 months in 18 pts ($p<0.01$)
  - 17 had improved to NYHA FC I or II

Sitbon O et al. Eur Respir J 2014; 43

Comparative Effectiveness of Pharmacologic Interventions for Pulmonary Arterial Hypertension
A Systematic Review and Network Meta-Analysis

- 31 RCTs
  - 29 two-arm trials comparing active intervention to placebo
  - 1 two-arm trial comparing active agents against each other
  - one three-arm trial comparing combination therapy of two active agents against each of the agents as monotherapy

Jain S et al. Chest 2017; 151(1):90-105

Efficacy in reducing clinical worsening as risk ratio (95% CI)	Efficacy in improving functional status as risk ratio (95% CI)							
	ERA	1.02 (0.70-1.50)	0.89 (0.48-1.65)	**0.31 (0.14-0.70)**	1.10 (0.56-2.17)	0.89 (0.55-1.45)	1.01 (0.56-1.82)	**1.56 (1.22-2.00)**
	1.37 (0.86-2.18)	PDE5i	0.87 (0.45-1.68)	**0.30 (0.13-0.71)**	1.08 (0.52-2.24)	0.87 (0.53-1.42)	0.98 (0.51-1.88)	**1.53 (1.06-2.19)**
	0.71 (0.39-1.29)	**0.52 (0.27-1.00)**	PO/ INH Prostanoid	**0.35 (0.13-0.89)**	1.24 (0.52-2.94)	1.01 (0.47-2.15)	1.13 (0.52-2.50)	1.76 (0.99-3.13)
	–	–	–	IV/ SC Prostanoid	**3.57 (1.31-9.77)**	**2.89 (1.14-7.32)**	**3.26 (1.27-8.41)**	**5.06 (2.32-11.04)**
	2.85 (0.66-12.31)	2.09 (0.47-9.20)	4.02 (0.91-17.68)	–	Riociguat	0.81 (0.36-1.83)	0.91 (0.40-2.09)	1.42 (0.75-2.66)
	1.98 (1.10-3.59)	1.45 (0.79-2.66)	**2.79 (1.26-6.20)**	–	0.70 (0.15-3.29)	ERA + PDE5i	1.13 (0.54-2.37)	**1.75 (1.05-2.92)**
	0.82 (0.42-1.60)	0.60 (0.29-1.22)	1.15 (0.56-2.35)	–	0.29 (0.06-1.30)	**0.41 (0.18-0.97)**	Selexipag	1.55 (0.91-2.66)
	0.53 (0.36-0.78)	**0.39 (0.24-0.62)**	0.75 (0.47-1.19)	–	**0.19 (0.05-0.76)**	**0.27 (0.14-0.52)**	0.65 (0.38-1.12)	Placebo

Jain S et al. Chest 2017; 151(1):90-105

Results

- Riociguat, ERA, PDE5i, and ERA +PDE5i compared with placebo associated with significant reduction in risk of CW
  - Riociguat had the strongest effect (single study)
- IV/SC prostanoids, ERA, PDE5i, and ERA + PDE5i associated with significant improvement in WHO FC and 6MWD compared with placebo
- ERA + PDE5i associated with a lower likelihood of PAH-related hospitalization (single study)
- none of the studied agents was associated with reduced mortality
- PO/INH prostanoids and selexipag were more likely to be discontinued secondary to adverse events

Jain S et al. Chest 2017; 151(1):90-105

RECOMMENDATIONS FOR EFFICACY OF INITIAL DRUG COMBINATION THERAPY

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C

RECOMMENDATIONS FOR EFFICACY OF SEQUENTIAL DRUG COMBINATION THERAPY

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Macitentan added to sildenafil[d]	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag[e] added to ERA and/or PDE-5i[d]	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	–	–	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C
Bosentan added to epoprostenol	–	–	IIb	C	IIb	C
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C
Other double combinations	IIb	C	IIb	C	IIb	C
Other triple combinations	IIb	C	IIb	C	IIb	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

Balloon atrial septostomy

- Inter-atrial R-L shunt can decompress the right heart chambers and increase LV preload and CO
- improves systemic O_2 transport
- decreases sympathetic hyperactivity
- benefit in WHO-FC IV with RHF refractory to medical therapy or with severe syncopal symptoms
- Bridge to Lung Tx
- No mortality benefit

Lung Transplantation

- NYHA Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids.
- Cardiac index ≤ 2 liters/min/m2.
- Mean right atrial pressure ≥ 15 mm Hg.
- 6-minute walk test ≤ 350 m.
- Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure (renal failure, increasing bilirubin, brain natriuretic peptide, or recurrent ascites)
- survival is increased to 52– 75% at 5 years and to 45–66% at 10 years

Weill et al. ISHLT consensus guidelines. January 2015

Lung Tx only or Heart-lung Tx?

- Isolated bilateral lung transplantation is associated with comparable or better results than heart-lung transplantation

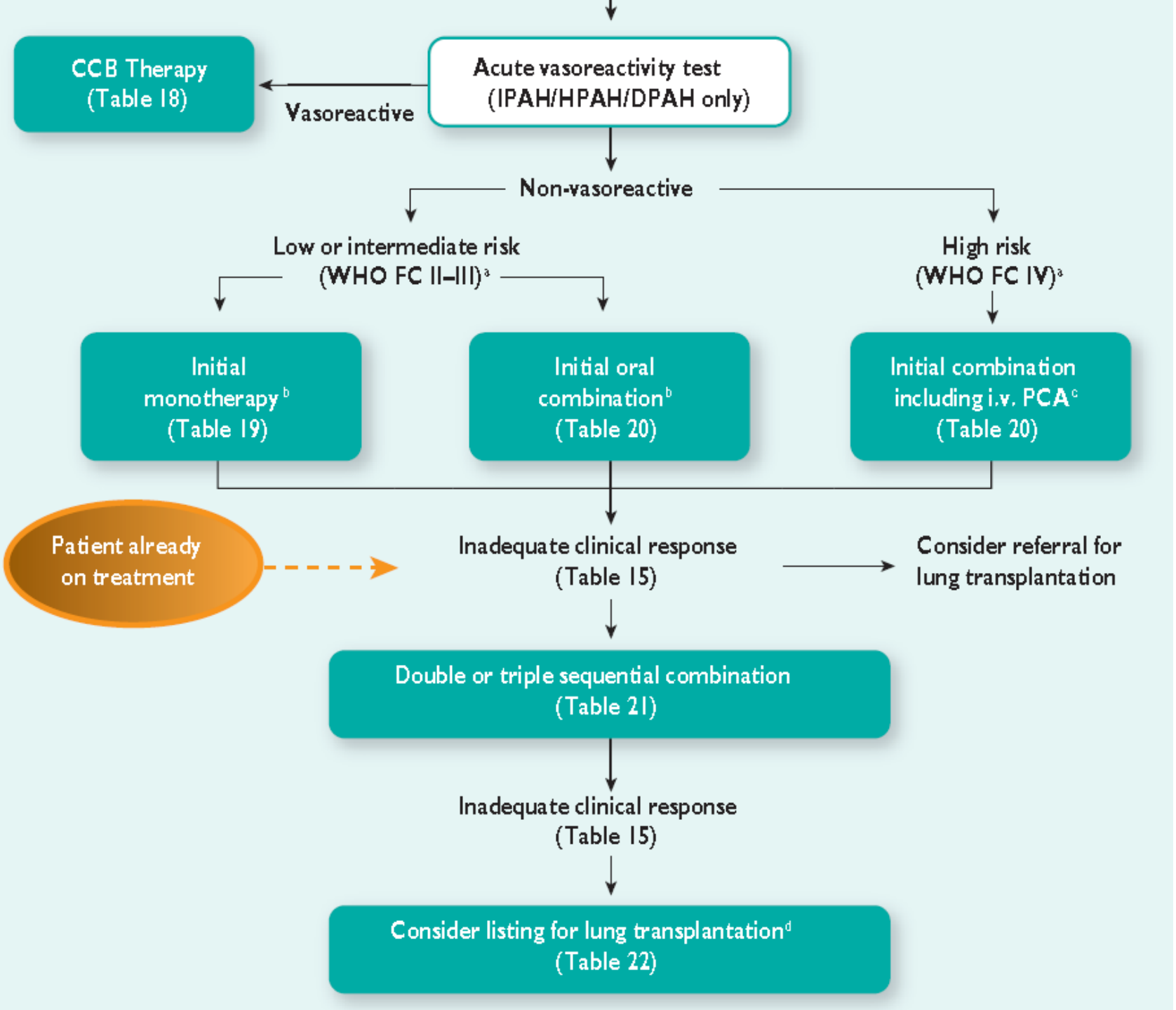
- Patients with irreversible myocardial dysfunction or congenital defects with irreparable defects of the valves or chambers in conjunction with intrinsic lung disease or severe PAH are considered for heart-lung transplantation

Weill et al. ISHLT consensus guidelines. January 2015

Recommendations for efficacy of ICU management, balloon atrial septostomy and lung transplantation

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Hospitalization in ICU is recommended in PH patients with high heart rate (>110 beats/ min), low blood pressure (systolic blood pressure <90 mmHg), low urine output and rising lactate levels due or not due to co-morbidities	–	–	–	–	I	C

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Inotropic support is recommended in hypotensive patients			I	C	I	C
Lung transplantation is recommended soon after inadequate clinical response on maximal medical therapy	–	–	I	C	I	C
BAS may be considered where available after failure of maximal medical therapy	–	–	IIb	C	IIb	C


CCB Therapy
(Table 18)
Vasoreactive
Acute vasoreactivity test
(IPAH/HPAH/DPAH only)
Non-vasoreactive
Low or intermediate risk
(WHO FC II–III)[a]
High risk
(WHO FC IV)[a]
Initial
monotherapy[b]
(Table 19)
Initial oral
combination[b]
(Table 20)
Initial combination
including i.v. PCA[c]
(Table 20)
Patient already
on treatment
Inadequate clinical response
(Table 15)
Consider referral for
lung transplantation
Double or triple sequential combination
(Table 21)
Inadequate clinical response
(Table 15)
Consider listing for lung transplantation[d]
(Table 22)

PAH associated with Adult Congenital Heart Disease

- Better survival than IPAH
- Some patients may have Gp 2 or 3 PAH
- No prospective data available on the usefulness of vasoreactivity testing, closure test or lung biopsy for operability assessment
- Closure contraindicated in Eisenmenger syndrome
- Closure useless in patients with small/coincidental defects

PAH associated with congenital heart disease

1. Eisenmenger's syndrome
2. 2. PAH associated with prevalent systemic-to-pulmonary shunts
   - Correctable
   - Non-correctable
3. PAH with small/coincidental defects

   VSD <1 cm and ASD<2 cm; closing contraindicated
4. PAH after defect correction

Galie`N et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal (2016) 37, 67–119

Recommendations for correction of CHD with prevalent systemic-to-pulmonary shunts

PVRi ($WU \cdot m^2$)	PVR (WU)	Correctable
<4	<2.3	Yes
>8	>4.6	No
4-8	2.3-4.6	Individualise

Medical mgt

- Data scarce
- Recommended to avoid strenuous exercise
- Pregnancy discouraged
- LTOT may improve symptoms, but not survival
- Oral anticoagulation – individualise
- CCBs not recommended
- Bosentan is recommended in WHO-FC III patients with Eisenmenger syndrome (IB)
- Other ERAs, PDE-5is and prostanoids should be considered in patients with Eisenmenger syndrome

PAH in CTD

- Prevalence of haemodynamically proven precapillary PH in SSc - 5 to 12%
- Prognosis worse than IPAH
- Same treatment algorithm as IPAH
- Resting echocardiography as a screening test in asymptomatic patients with SSc
- Annual screening -echo, DLCO and biomarkers
- RHC in all cases of suspected PAH
- OAC – individualise; CCBs not useful

Porto-pulmonary HTN

- ECHO– symptomatic and Tx candidates
- RHC recommended in all suspected cases
- Higher CI and a lower PVR than IPAH
- Mortality risk at least as high as in IPAH
- Treatment algorithm same
- Anticoagulation not recommended
- Beta-blockers avoided; Bosentan avoided
- Liver Tx in selected patients responding well to PAH therapy; C/I in severe PAH

PAH associated with HIV

Recommendations	Class	Level
Echocardiographic screening in asymptomatic HIV pts to detect PH is not recommended	III	C
Same treatment algorithm used for patients with PAH should be considered, taking into consideration co-morbidities and drug–drug interactions	IIa	C
Anticoagulation is not recommended because of a lack of data on the efficacy:risk ratio	III	C
CCBs not recommended	III	C

Prognostic markers in PAH

Lower	Determinants of Risk	Higher
No	**Clinical Evidence of RV Failure**	Yes
Gradual	**Progression**	Rapid
II, III	**WHO Class**	IV
Longer (>400 m)	**6 Minute Walk Distance**	Shorter (<300 m)
Minimally elevated	**BNP**	Very elevated
Minimal RV Dysfunction	**Echocardiographic Findings**	Pericardial Effusion Significant RV Dysfunction
Normal/Near normal RAP and CI	**Hemodynamics**	High RAP, Low CI

ACCF-AHA Expert Consensus. J Am Coll Cardiol 2009;53:1573– 619

Take Home message

- No approved therapy for PAH shown to prevent progression of the underlying pulmonary vascular disease - PAH remains an incurable disease
- Correct diagnosis (PAH and group) and ruling out treatable causes is must
- Stepwise approach to Rx based on WHO FC
- Rational combination therapy maybe helpful in those with progressive disease
- Lung Tx for those symptomatic despite maximal Rx

Available in India

Generic	Brand	Price
Ambrisentan 5mg	Endobloc 5	145
Ambrisentan 10mg	Endobloc 10	235
Bosentan 62.5mg	Bosentas/Lupibose 62.5mg	69
Bosentan 125mg	Bosentas/ Lupibose 125mg	110
Sildenafil 20mg	Assurans/Vasosure	15
Tadalafil 20mg	Pulmopres	25

THANK YOU