Evidence on treatment of IPAH

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SR pulmonary medicine

DEFINITION

Definition	Hemodynamic characteristics
PH	mPAP > 20 mmHg
Pre-capillary	mPAP > 20mmHg, PAWP ≤ 15mmHg, PVR > 2WU
Post-Capillary (isolated)	mPAP > 20mmHg, PAWP > 15mmHg, PVR ≤2WU
Combined Pre & Post	mPAP > 20mmHg, PAWP > 15mmHg, PVR > 2WU
Exercise PH	mPAP/ CO slope between rest & exercise > 3mm Hg/L/min

GROUP 1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable[a]
- 1.3 Associated with drugs and toxins[a]
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

GROUP 2 PH associated with left heart disease
- 2.1 Heart failure:
  - 2.1.1 with preserved ejection fraction
  - 2.1.2 with reduced or mildly reduced ejection fraction[b]
- 2.2 Valvular heart disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

GROUP 3 PH associated with lung diseases and/or hypoxia
- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (*e.g.* high altitude)
- 3.6 Developmental lung disorders

GROUP 4 PH associated with pulmonary artery obstructions
- 4.1 Chronic thrombo-embolic PH
- 4.2 Other pulmonary artery obstructions[c]

GROUP 5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders[d]
- 5.2 Systemic disorders[e]
- 5.3 Metabolic disorders[f]
- 5.4 Chronic renal failure with or without haemodialysis
- 5.5 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis

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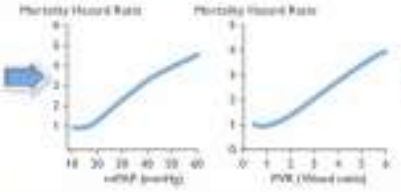
Pulmonary hypertension

Prevalence

1% Global population

Pulmonary congestion in post-capillary PH

Pulmonary vascular disease / obstruction in pre-capillary PH



Right heart failure

Clinical Classification

Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				?
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematologic disorders • Systemic disorders

Prevalence

Rare	Very common	Common	Rare	Rare
				

Therapeutic Strategies

Medical therapy • PAH drugs • CCB in responders **Lung transplantation**	**IpcPH:** • Treatment of LHD* **CpcPH:** • Treatment of LHD* • Potentially: PAH drugs (trials)	**PH-lung disease:** • Optimized care of underlying lung disease **Severe PH:** • Potentially: PAH drugs (trials)	**Surgical therapy:** • PEA **Interventional:** • BPA **Medical therapy:** • PH drugs	**Optimized treatment of underlying disease** • Potentially: PAH drugs (trials)

Diagnostic tool	Characteristic findings/features	Group 1 (PAH)
5.1.1 Clinical presentation	Clinical features	Variable age, but young, female patients may be predominantly affected[a] [161] Clinical presentation depends on associated conditions and phenotype See section 5.1.1
	Oxygen requirement for hypoxaemia	Uncommon, except for conditions with low DLCO or right-to-left shunting
5.1.3 Chest radiography		RA/RV/PA size ↑ Pruning of peripheral vessels
5.1.4 Pulmonary function tests and ABG	Spirometry/PFT impairment	Normal or mildly impaired
	DLCO	Normal or mild-to-moderately reduced (low DLCO in SSc-PAH, PVOD, and some IPAH phenotypes)
	Arterial blood gas	
	PaO_2	Normal or reduced
	$PaCO_2$	Reduced
5.1.5 Echocardiography		Signs of PH (increased sPAP, enlarged RA/RV) Congenital heart defects may be present See section 5.1.5
5.1.6 Lung scintigraphy	Planar – SPECT V/Q	Normal or matched
5.1.7 Chest CT		Signs of PH or PVOD See section 5.1.7
5.1.11 Cardiopulmonary exercise testing		High VE/VCO_2 slope Low $PETCO_2$, decreasing during exercise No EOV
5.1.12 Right heart catheterization		Pre-capillary PH

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Initial evaluation

Suspected cases → Echocardiography → RHC

Measured variables	
Right atrial pressure, mean (RAP)	2–6 mmHg
Pulmonary artery pressure, systolic (sPAP)	15–30 mmHg
Pulmonary artery pressure, diastolic (dPAP)	4–12 mmHg
Pulmonary artery pressure, mean (mPAP)	8–20 mmHg
Pulmonary arterial wedge pressure, mean (PAWP)	≤15 mmHg
Cardiac output (CO)	4–8 L/min
Mixed venous oxygen saturation (SvO_2)[a]	65–80%
Arterial oxygen saturation (SaO_2)	95–100%
Systemic blood pressure	120/80 mmHg
Calculated parameters	
Pulmonary vascular resistance (PVR)[b]	0.3–2.0 WU
Pulmonary vascular resistance index (PVRI)	3–3.5 WU m^2
Total pulmonary resistance (TPR)[c]	<3 WU
Cardiac index (CI)	2.5–4.0 L/min/m^2
Stroke volume (SV)	60–100 mL
Stroke volume index (SVI)	33–47 mL/m^2
Pulmonary arterial compliance (PAC)[d]	>2.3 mL/mmHg

WU, Wood units. [a]Derived from blood sample taken from the pulmonary artery; compartmental oximetry to exclude an intracardiac shunt is recommended when SvO2 0.75%. [b]PVR, (mPAP−PAWP)/CO. [c]TPR, mPAP/CO. [d]PAC, SV/(sPAP−dPAP).

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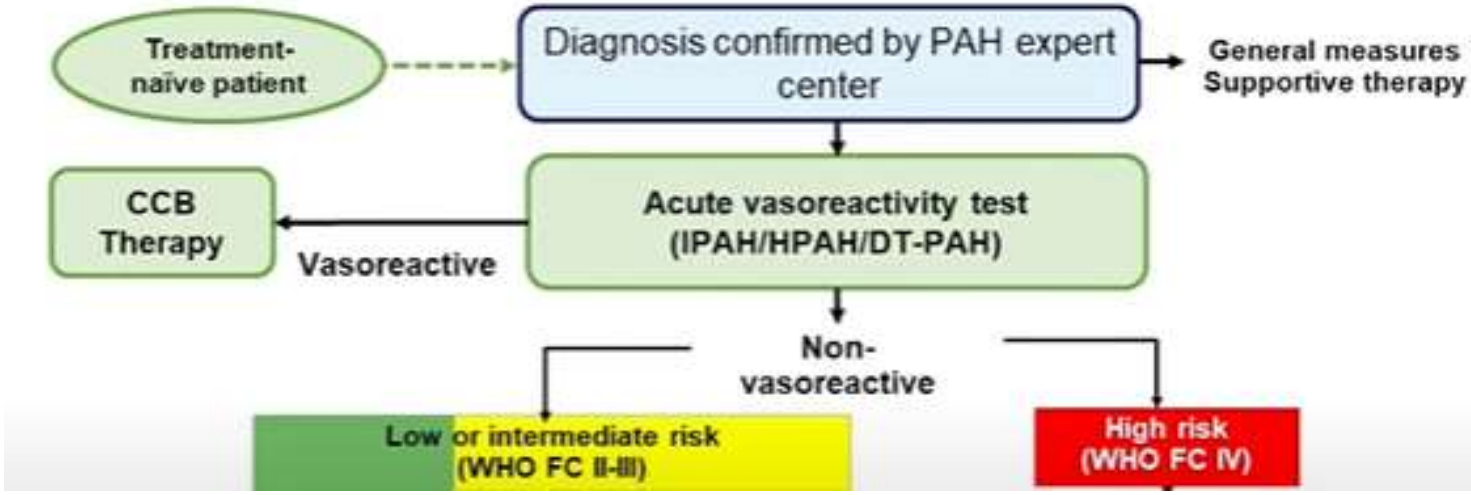
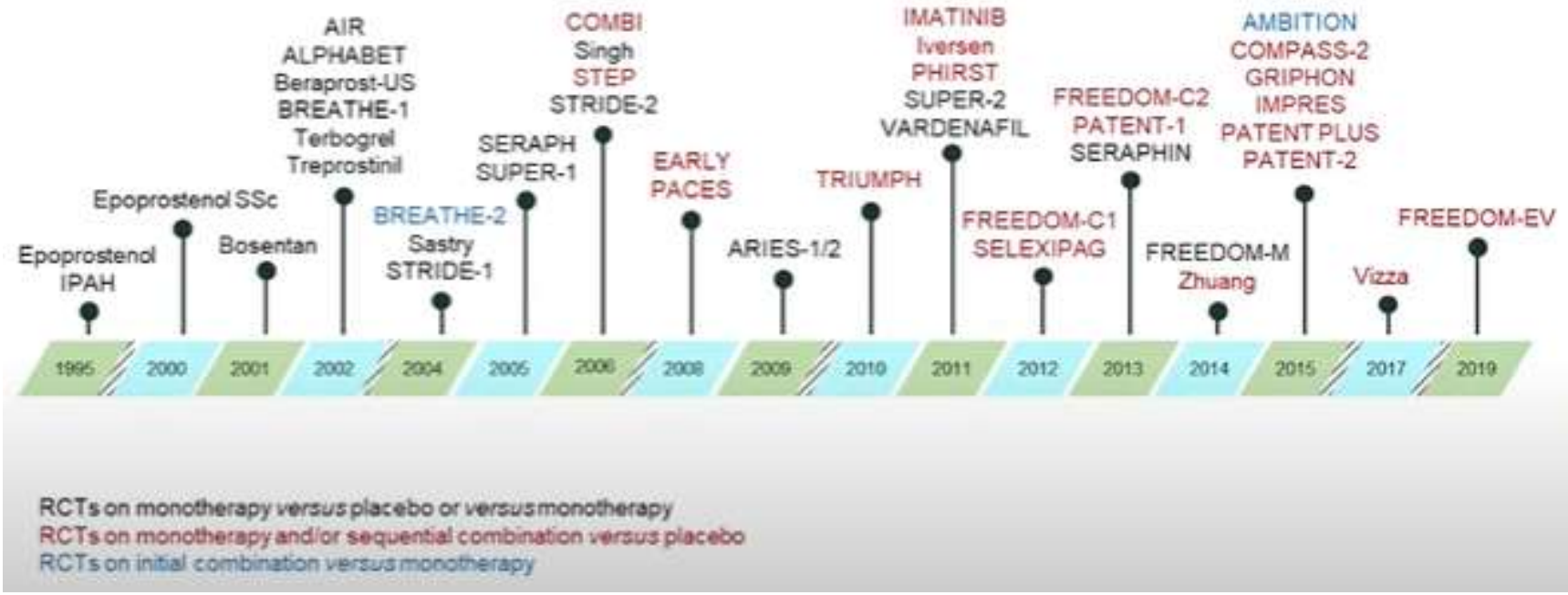

Treatment-naïve patient
Diagnosis confirmed by PAH expert center
General measures
Supportive therapy
CCB Therapy
Vasoreactive
Acute vasoreactivity test (IPAH/HPAH/DT-PAH)
Non-vasoreactive
Low or intermediate risk (WHO FC II-III)
High risk (WHO FC IV)

PAH specific therapy


Epoprostenol IPAH
Epoprostenol SSc
Bosentan
AIR
ALPHABET
Beraprost-US
BREATHE-1
Terbogrel
Treprostinil
BREATHE-2
Sastry
STRIDE-1
SERAPH
SUPER-1
COMBI
Singh
STEP
STRIDE-2
EARLY
PACES
ARIES-1/2
TRIUMPH
IMATINIB
Iversen
PHIRST
SUPER-2
VARDENAFIL
FREEDOM-C1
SELEXIPAG
FREEDOM-C2
PATENT-1
SERAPHIN
FREEDOM-M
Zhuang
AMBITION
COMPASS-2
GRIPHON
IMPRES
PATENT PLUS
PATENT-2
Vizza
FREEDOM-EV
1995
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RCTs on monotherapy versus placebo or versus monotherapy
RCTs on monotherapy and/or sequential combination versus placebo
RCTs on initial combination versus monotherapy

Vasoreactive testing

- Vasoreactive responders eligible for high dose CCB
- Recommended in patients with IPAH, HPAH, or DPAH
- A positive acute response is defined as a reduction in mPAP by $\geqslant$10 mmHg to reach an absolute value $\leqslant$40 mmHg, with increased or unchanged CO
- Done with inhaled iloprost or nitric oxide. Epoprostenol takes a longer time.

Compound	Route	Half-life	Dosage	Duration
Nitric oxide [129]	inh	15–30 s	10–20 p.p.m.	5–10 min[a]
Iloprost [130, 131]	inh	30 min	5–10 µg[b]	10–15 min[c]
Epoprostenol [129]	i.v.	3 min	2–12 ng/kg/min	10 min[d]

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Recommendations	Class[a]	Level[b]
Right heart catheterisation (RHC)		
RHC is recommended to confirm the diagnosis of PH (especially PAH or CTEPH), and to support treatment decisions [25, 26]	I	B
In patients with suspected or known PH, it is recommended to perform RHC in experienced centres [125]	I	C
It is recommended that RHC comprises a complete set of haemodynamics and is performed following standardized protocols [25, 26, 145]	I	C
Vasoreactivity testing		
Vasoreactivity testing is recommended in patients with I/H/DPAH to detect patients who can be treated with high doses of a CCB [129, 146]	I	B
It is recommended that vasoreactivity testing is performed at PH centres	I	C
It is recommended to consider a positive response to vasoreactivity testing by a reduction in mPAP $\geqslant$10 mmHg to reach an absolute value of mPAP $\leqslant$40 mmHg with an increased or unchanged CO[c] [129]	I	C
Inhaled nitric oxide, inhaled iloprost, or i.v. epoprostenol are recommended for performing vasoreactivity testing [129–132]	I	C
Vasoreactivity testing, for identifying candidates for CCB therapy, is not recommended in patients with PAH other than I/H/DPAH, and in PH groups 2, 3, 4, and 5 [124, 129]	III	C

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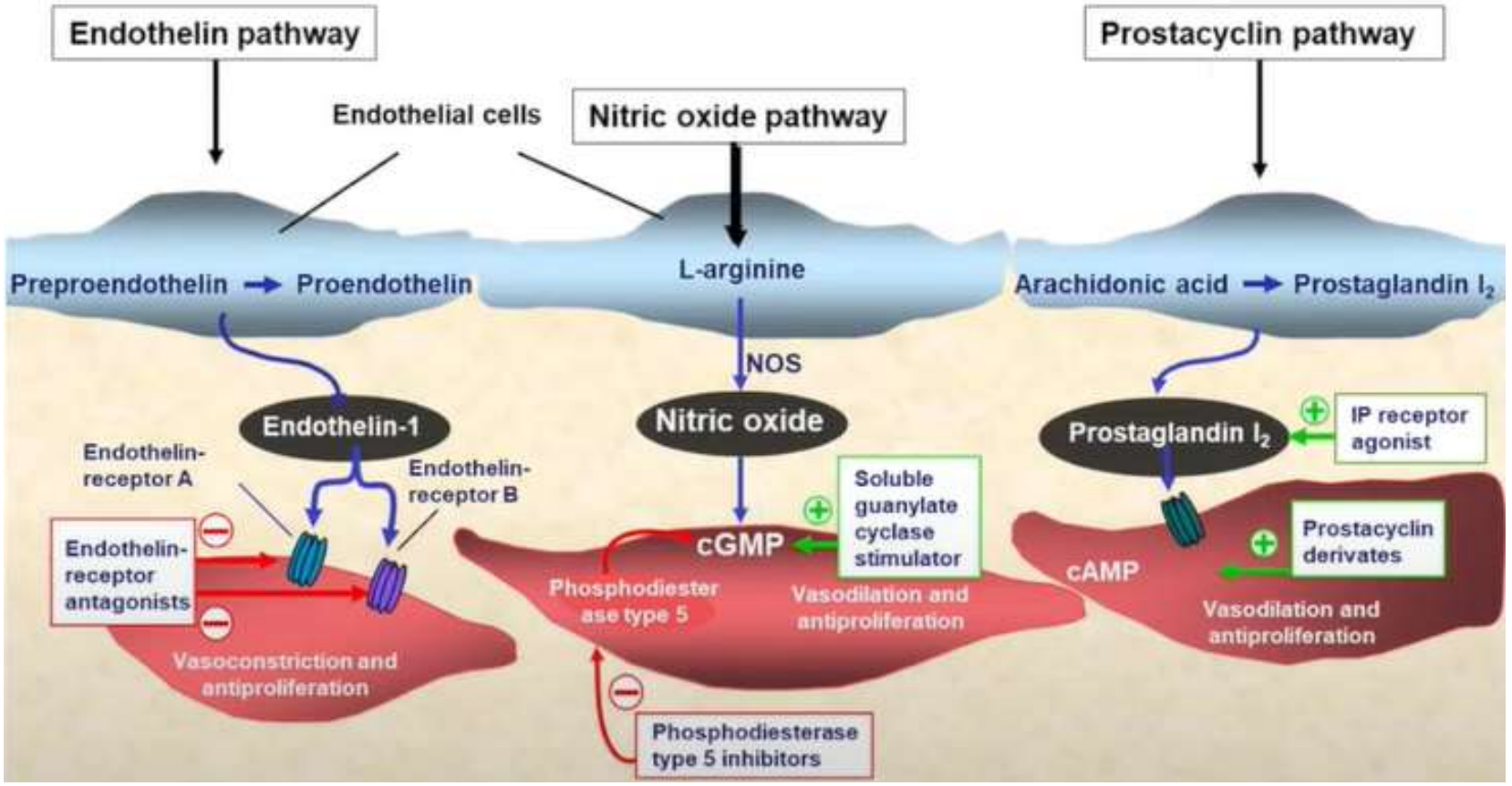

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WHO – Functional Class

Class	Description[a]
WHO-FC I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
WHO-FC II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
WHO-FC III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
WHO-FC IV	Patients with PH with an inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

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Risk assessment at diagnosis

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>440 m	165–440 m	<165 m
CPET	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	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics	RAP <8 mmHg CI ⩾2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 $L/min/m^2$ SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%

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4 Strata risk assessment tool for follow up

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

- Need for 4 strata risk stratification in follow up came from the observation that most of the patients (60-70%) in follow up fell into the intermediate risk category and the mortality ranged from 5 - 20% which was a large interval to ignore.
- Observed 1-year mortality rates in the four risk strata were 0–3%, 2–7%, 9–19%, and >20%
- This risk stratification was large derived from SPAHR (swedish registry) and evidence was largely supported from the observation that these variables had the highest risk/prognostic prediction. Similar observation was derived from other studies like COMPERA, US - REVEAL, & French FPHR

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Recommendations	Class[a]	Level[b]
It is recommended to evaluate disease severity in patients with PAH with a panel of data derived from clinical assessment, exercise tests, biochemical markers, echocardiography, and haemodynamic evaluations [212, 213, 216, 249, 292, 293, 295, 296, 302, 307]	I	B
Achieving and maintaining a low-risk profile on optimised medical therapy is recommended as a treatment goal in patients with PAH [210, 212, 213, 216, 298, 300, 303, 309, 310]	I	B
For risk stratification at the time of diagnosis, the use of a three-strata model (low, intermediate, and high risk) is recommended, taking into account all available data, including haemodynamics [292, 293, 295]	I	B
For risk stratification during follow-up, the use of a four-strata model (low, intermediate-low, intermediate-high, and high risk) based on WHO-FC, 6MWD, and BNP/NT-proBNP is recommended, with additional variables taken into account as necessary [280, 308]	I	B

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Parameters to evaluate periodically

- Clinical evaluation including ABG & pulse oximetry
- WHO functional class
- Exercise capacity – 6MWT/6MWD
- Echocardiography
- BNP/NT-pro BNP and other lab parameter like LFT/RFT/CBC.
- ***HR-QOL questionnaire – PAHSYMPACT/CAMPHOR***
- ***CPET / RHC - should be considered if resources permit***

General measures

Recommendations	Class[a]	Level[b]
General measures		
Supervised exercise training is recommended in patients with PAH under medical therapy [314, 315, 317]	I	A
Psychosocial support is recommended in patients with PAH	I	C
Immunization of patients with PAH against SARS-CoV-2, influenza, and *Streptococcus pneumoniae* is recommended	I	C
Diuretic treatment is recommended in patients with PAH with signs of RV failure and fluid retention	I	C
Long-term oxygen therapy is recommended in patients with PAH whose arterial blood oxygen pressure is <8 kPa (60 mmHg)[c]	I	C
In the presence of iron-deficiency anaemia, correction of iron status is recommended in patients with PAH	I	C
In the absence of anaemia, iron repletion may be considered in patients with PAH with iron deficiency	IIb	C
Anticoagulation is not generally recommended in patients with PAH but may be considered on an individual basis	IIb	C
The use of ACEis, ARBs, ARNIs, SGLT-2is, beta-blockers, or ivabradine is not recommended in patients with PAH unless required by comorbidities (*i.e.* high blood pressure, coronary artery disease, left HF, or arrhythmias)	III	C
Special circumstances		
In-flight oxygen administration is recommended for patients using oxygen or whose arterial blood oxygen pressure is <8 kPa (60 mmHg) at sea level	I	C
For interventions requiring anaesthesia, multidisciplinary consultation at a PH centre to assess risk and benefit should be considered	IIa	C

Supervised Exercise programme

ESC European Society of Cardiology
European Heart Journal (2021) 42, 2284–2295
doi:10.1093/eurheartj/ehaa696
CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial

Ekkehard Grünig[1*†], Alison MacKenzie[2†], Andrew J. Peacock[2],

- Evaluate efficacy and safety of exercise training in patients with PAH and CTEPH
- 129 enrolled (PAH n = 98; CTEPH n = 18)
- mPAP 46.6 ± 15.1 mmHg, WHO – FC II (53%), III (46%)
- Primary endpoint, change of 6MWD , significantly improved by 34.1 ± 8.3 m in the training group (95% CI, 18-51 m; P < 0.0001)
- Secondary – improved QOL, WHOFC, and peak oxygen consumption.

Grünig E etal., Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial. Eur Heart J. 2021 Jun 14;

Anticoagulation

- Data from COMPERA , European registry in which survival rates of patients with IPAH and other forms of PAH were compared by the use of anticoagulation
- Anticoagulation was used in 66% of 800 patients with IPAH and in 43% of 483 patients with other forms of PAH
- Vitamin K antagonists, heparins, and novel oral anticoagulation, but not platelet inhibitors
- In patients with IPAH, there was a significantly better 3-year survival (P=0.006) in patients on anticoagulation compared with patients who never received anticoagulation. survival difference at 3 years remained statistically significant (P=0.017)

Olsson KM etal., Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation. 2014 Jan 7

Circulation

Effect of Warfarin Treatment on Survival of Patients With Pulmonary Arterial Hypertension (PAH) in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL)

Ioana R. Preston, Kari E. Roberts, Dave P. Miller, Ginny P. Sen, Mona Selej,

- The effect of warfarin anticoagulation on survival in IPAH and SSc-PAH patients enrolled in Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), a longitudinal registry of group I PAH
- Patients who initiated warfarin for 1 year on study (n=187) were matched 1:1 with patients never on warfarin
- No survival difference with warfarin in IPAH patients (adjusted hazard ratio, 1.37; P=0.21) or in SSc-PAH patients (adjusted hazard ratio, 1.60; P=0.15)
- SSC-PAH patients on warfarin had increased mortality

Preston IR etal., Effect of Warfarin Treatment on Survival of Patients With Pulmonary Arterial Hypertension (PAH) in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL). Circulation. 2015 Dec 22

THROMBOSIS RESEARCH

Can anticoagulants improve the survival rate for patients with idiopathic pulmonary arterial hypertension? A systematic review and meta-analysis

Peijie Wang [1] • Liu Hu [1] • Yin Yin • ... Hongjie Zheng • Junhang Zhang • Yun Li •

- Systematic review and a random-effects meta-analysis
- 8 studies with a total of 1812 patients with IPAH
- Use of anticoagulants did not significantly decrease mortality risk (P = 0.07, HR = 0.77, 95% CI [0.58, 1.02])
- Anticoagulants performed no significant advantages with the use of PAH-specific therapies (P = 0.82, HR = 0.95, 95% CI [0.63, 1.44])

Wang P etal., Can anticoagulants improve the survival rate for patients with idiopathic pulmonary arterial hypertension? A systematic review and meta-analysis. Thromb Res. 2020 Dec

Other general measures

- Oxygen administration reduces PVR and improves exercise tolerance in patients with PAH where indicated
- Most patients with PAH have minor degrees of arterial hypoxaemia at rest
- PaO2 is < 8kPa or SPO2 < 92%, O2 supplementation for target PaO2 8kPA
- Nocturnal supplementation if there is desaturation during sleep
- For travel hypobaric hypoxia may induce arterial hypoxaemia, additional hypoxic pulmonary vasoconstriction, and increased RV load in PAH
- In-flight oxygen administration is advised for patients using oxygen at sea level and for those with PaO2 <92%
- Fluids and diuretics have to be titrated to prevent low preload and renal back pressure, fluid retention and edema may be a s/e of PAH specific therapy.

CCB for vasoreactive patients

Recommendations	Class[a]	Level[b]
High doses of CCBs are recommended in patients with IPAH, HPAH, or DPAH who are responders to acute vasoreactivity testing	I	C
Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is recommended in patients with IPAH, HPAH, or DPAH treated with high doses of CCBs	I	C
Continuing high doses of CCBs is recommended in patients with IPAH, HPAH, or DPAH in WHO-FC I or II with marked haemodynamic improvement (mPAP <30 mmHg and PVR <4 WU)	I	C
Initiating PAH therapy is recommended in patients who remain in WHO-FC III or IV or those without marked haemodynamic improvement after high doses of CCBs	I	C
In patients with a positive vasoreactivity test but insufficient long-term response to CCBs who require additional PAH therapy, continuation of CCB therapy should be considered	IIa	C
CCBs are not recommended in patients without a vasoreactivity study or non-responders, unless prescribed for other indications (*e.g.* Raynaud's phenomenon)	III	C

	Starting dose	Target dose
Calcium channel blockers		
Amlodipine	5 mg o.d.	15–30 mg o.d.[a]
Diltiazem	60 mg b.i.d.[b]	120–360 mg b.i.d.[b]
Felodipine	5 mg o.d.	15–30 mg o.d.[a]
Nifedipine	10 mg t.i.d.	20–60 mg b.i.d. or t.i.d.

The NEW ENGLAND JOURNAL of MEDICINE

The Effect of High Doses of Calcium-Channel Blockers on Survival in Primary Pulmonary Hypertension

Stuart Rich, M.D., Elizabeth Kaufmann, R.N., and Paul S. Levy, Sc.D.

- 64 patients of primary pullmonary hypertension treated with high doses of CCB
- Survival was compared with patients who did not respond and with patients enrolled in the NIH Registry on Primary Pulmonary Hypertension
- 17 patients responded , nifedipine and diltiazem were used
- After five years, 94 percent of the patients who responded (16 of 17) were alive, vs 55 percent of the patients who did not respond (26 of 47, P = 0.003)

Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med. 1992 Jul 9

Circulation
Volume 111, Issue 23, 14 June 2005; Pages 3105-3111
https://doi.org/10.1161/CIRCULATIONAHA.104.488486

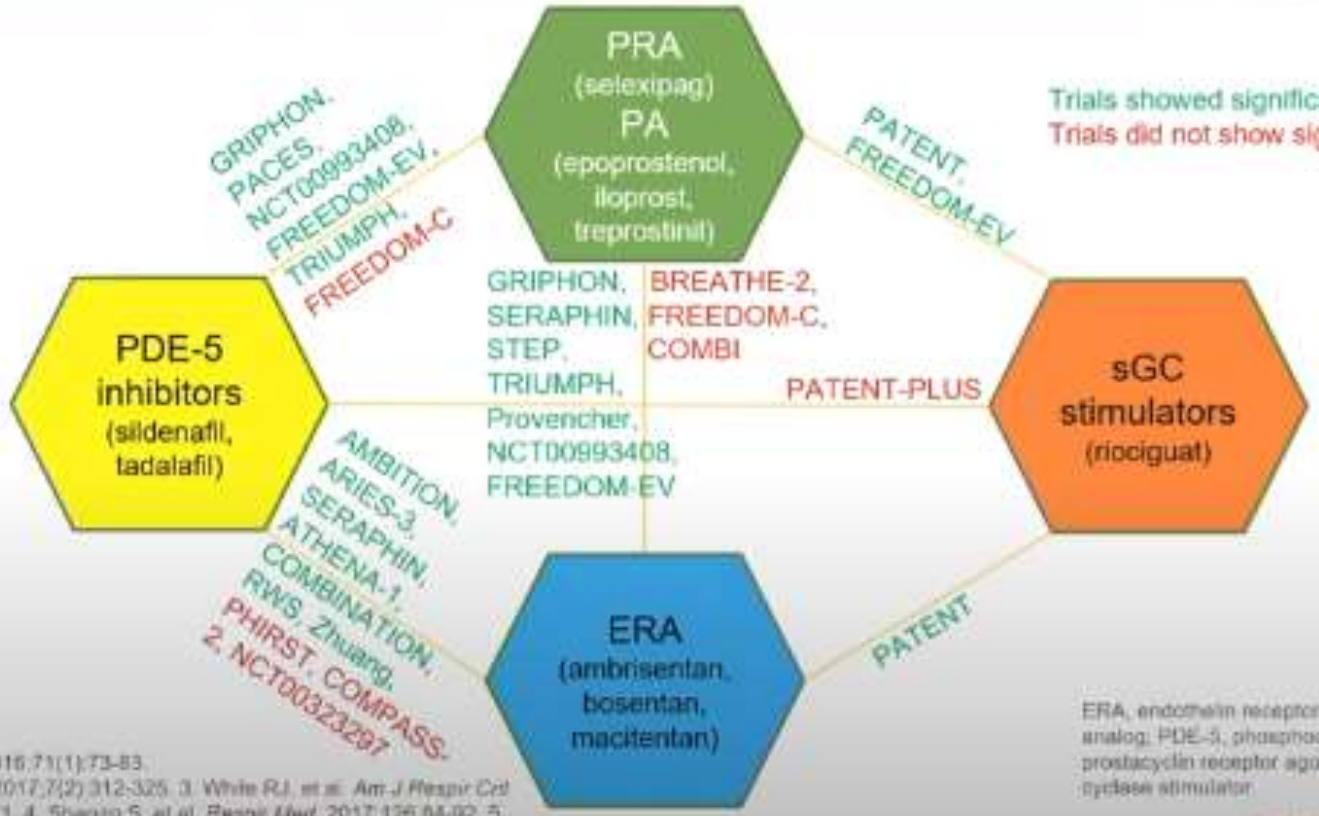
HYPERTENSION

Long-Term Response to Calcium Channel Blockers in Idiopathic Pulmonary Arterial Hypertension

- Acute pulmonary vasodilator testing with epoprostenol or nitric oxide was performed in 557 IPAH patients
- 70 patients who displayed acute pulmonary vasoreactivity & received CCB therapy, only 38 showed long-term improvement
- After 7.0±4.1 years, all but 1 long-term CCB responders were alive in NYHA class I or II, with a sustained hemodynamic improvement
- Group of patients who failed on CCB, the 5-year survival rate was 48%
- Diltiazem or nifedipine (amlodipine in 2 patients)
- Only baseline Svo_2 and PVR levels reached during acute vasodilator testing were associated with long-term CCB therapy success

Sitbon O etal., Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005 Jun 14

Benefit in Clinical Trials: PAH-specific Medications Added to Background or Upfront Combination Therapy



ERA, endothelin receptor antagonists; PA, prostacyclin analog; PDE-5, phosphodiesterase type 5; PRA, prostacyclin receptor agonist; sGC, soluble guanylate cyclase stimulator.

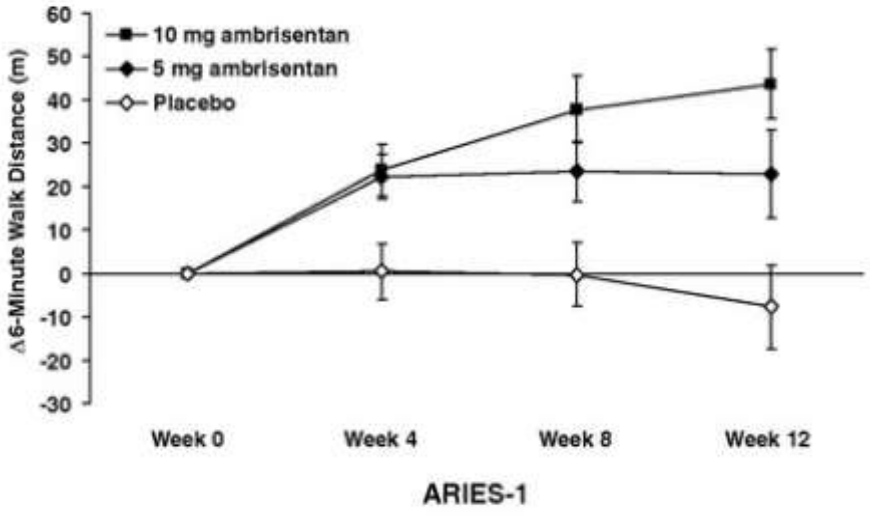
1. Humbert M, et al. *Thorax*. 2016;71(1):73-83. 2. Lajoie AC, et al. *Pulm Circ*. 2017;7(2):312-325. 3. White RJ, et al. *Am J Respir Crit Care Med*. 2020;201(6):707-771. 4. Shapiro S, et al. *Respir Med*. 2017;126:84-92. 5. Badesch DB, et al. *Cardiovasc Ther*. 2012;30(2):93-99. 6. Provencher S, et al. *Eur Heart J*. 2006;27:589-595. 7. Dardi F, et al. *Eur Respir J*. 2015;46:414–421.

Endothelin receptor antagonist

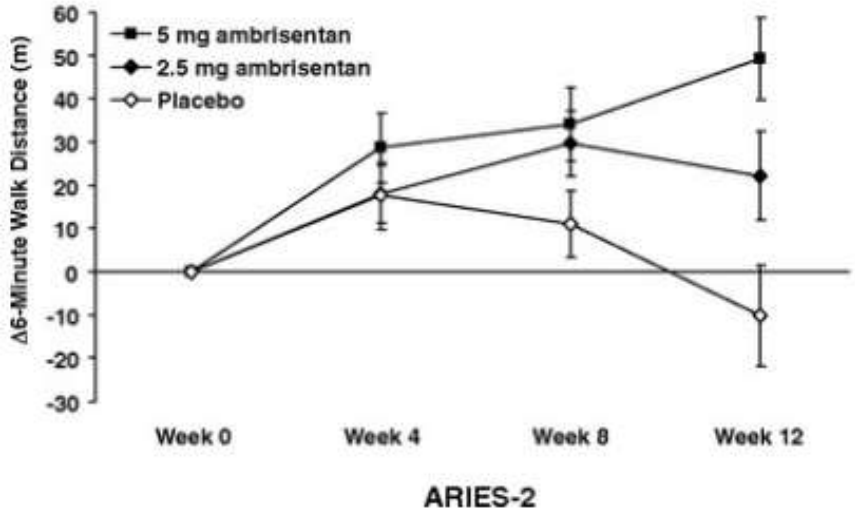
ARIES 1 & 2

- Double-blind, placebo-controlled studies that randomized 202 and 192 patients with pulmonary arterial hypertension, respectively, to placebo or ambrisentan
- PH – idiopathic (60-65%) or associated with connective tissue disease, HIV infection, or anorexigen use
- 6-minute walk distance <150 or >450 m were excluded
- ARIES-1, 5 or 10 mg; ARIES-2, 2.5 or 5 mg , orally once daily for 12 weeks
- Primary : primary end point for each study was change in 6-MWD
- Secondary : Clinical worsening, WHO-FC , Short Form-36 Health Survey score, Borg dyspnea score, and BNP

Galiè N etal., Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation. 2008 Jun 10



ARIES-1



ARIES-2

- 6MWD increased in all ambrisentan groups

  31 m (P=0.008) and 51 m (P<0.001) in ARIES-1 for 5 and 10 mg

  32 m (P=0.022) and 59 m (P<0.001) in ARIES-2 for 2.5 and 5 mg
- Improvements in time to clinical worsening (ARIES-2), WHO-FC (ARIES-1), Short Form-36 score (ARIES-2), Borg dyspnea score (both studies), and BNP (both studies) were observed
- Transaminitis < 3x UNL with ambrisentan
- 280 patients completing 48 weeks of treatment with ambrisentan , 6MWD improved by 39 mtr

ARIES 3

- 224 patients with PH due to idiopathic and familial PAH (31%), CTD(18%), chronic hypoxemia (22%), CTEPH(13%), or other etiologies (16%) were enrolled
- Around 90% patients in WHO FC 2 & 3
- 53% of patients received stable background PAH therapies (sildenafil 41%)
- 5 mg ambrisentan once daily for 24 weeks
- 24 weeks of therapy, an increase in 6MWD (+21 m; 95% CI: 12–29) and a decrease in BNP (–26%; 95% CI: –34 to –16%)
- Increases in 6MWD were not observed in several non-Group 1 PH subpopulations

Badesch DB, etal.,ARIES-3 Study Group. ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. Cardiovasc Ther. 2012 Apr;30

The NEW ENGLAND JOURNAL of MEDICINE

Bosentan Therapy for Pulmonary Arterial Hypertension

Lewis J. Rubin, M.D., David B. Badesch, M.D., Robyn J. Barst, M.D., Nazzareno Galiè, M.D., Carol M. Black, M.D., Anne Keogh, M.D., Tomas Pulido, M.D., Adaani Frost, M.D., Sébastien Roux, M.D., Isabelle Leconte, Ph.D., Michael Landzberg, M.D., and Gérald Simonneau, M.D. for the Bosentan Randomized Trial of Endothelin Antagonist Therapy Study Group

- Double-blind, placebo-controlled study, 213 patients with PH (primary {70%} or CTD)
- >90% WHO FC 3 , some WHO FC 4
- Placebo VS Bosentan (62.5 BD x 4weeks → 125/250mg BD for 12 weeks)
- At 16 weeks mean difference between the placebo group and the combined bosentan groups was 44 m (95 percent CI 21 to 67; P<0.001)
- Improved the Borg dyspnea index, WHO functional class and increased the time to clinical worsening

Rubin LJ, etal.,Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002 Mar 21

In post marketing surveillance 4,623 patients who were naïve to treatment and received Bosentan, 352 had elevated AST/ALT, corresponding to a crude incidence of 7.6%

Bosentan was discontinued due to elevated AST/ALT in 150 (3.2%)

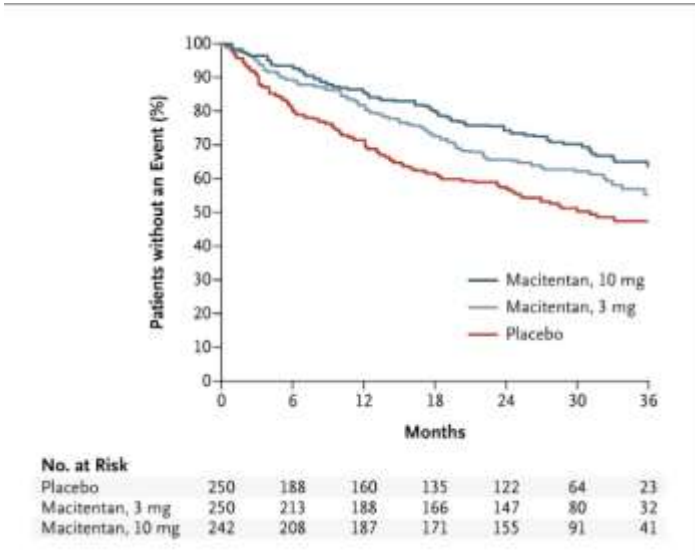
Bosentan has significant pharmacological interactions : hormonal contraceptives unreliable and also lowers serum levels of warfarin, sildenafil, and tadalafil.

Humbert M etal., . Results of European post-marketing surveillance of bosentan in pulmonary hypertension. Eur Respir J. 2007 Aug;30

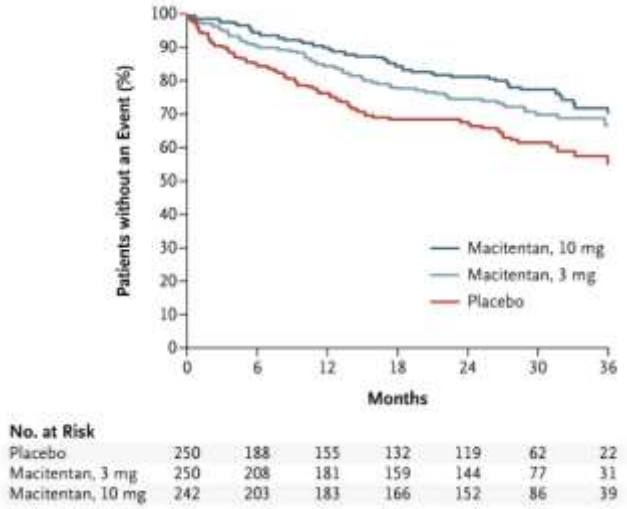
Seraphin

- Patients with PAH with WHO functional class II–IV. (N= 742, IPAH 404=55%)
- Randomized 1:1:1 to placebo (*n* = 250), macitentan 3 mg (*n* = 250) or macitentan 10 mg (*n* = 242) once daily
- 64% of all patients were receiving concomitant treatment with oral phosphodiesterase type 5 inhibitors (61.4%) or oral/inhaled prostanoids (5.4%)
- Primary: time from the initiation of treatment to the 1st occurrence of death/ atrial septostomy/ lung Tx / treatment with IV or SC prostanoids, or worsening of PAH
- Macitentan 3 mg, risk of primary endpoint was reduced by 30% ($p = 0.0108$)
- Macitentan 10 mg reduced the risk of primary end point by 45% ($p < 0.0001$)
- Primary end point occurred in 46.4%, 38.0%, and 31.4% of the patients
- Transaminitis less but anemia is a significant s/e.

Pulido T etal., SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013 Aug 29



Effect of Macitentan on the Composite Primary End Point of a First Event Related to Pulmonary Arterial Hypertension or Death from Any Cause



Effect of Macitentan on the Composite Secondary End Point of Death Due to Pulmonary Arterial Hypertension or Hospitalization for Pulmonary Arterial Hypertension as a First Event.

REPAIR Trial

- REPAIR was a 52-week, open-label, single-arm, multicenter, phase 4 study evaluating the effect of macitentan 10 mg, with or without PDE5i, on RV remodeling and function and cardiopulmonary hemodynamics
- Primary endpoints were: change from baseline to week 26 in RV stroke volume, determined by CMR; and PVR, determined by RHC
- Efficacy measures were assessed for all patients with baseline and week-26 data for both primary endpoints
- At a prespecified interim analysis in 42 patients, both primary endpoints were met, enrollment was stopped, and the study was declared positive
- At final analysis (n=71), RV stroke volume increased by 12 mL (96% confidence level: 8.4-15.6 mL; $P<0.0001$) and PVR decreased by 38% (99% confidence level: 31%-44%; $P<0.0001$) at week 26
- Significant positive changes were also observed in secondary and exploratory CMR (RV and left ventricular), hemodynamic, and functional endpoints at week 26
- Improvements in CMR RV and LV variables and functional parameters were maintained at week 52

Macitentan treatment in patients with PAH resulted in significant and clinically-relevant improvements in RV function and structure and cardiopulmonary hemodynamics

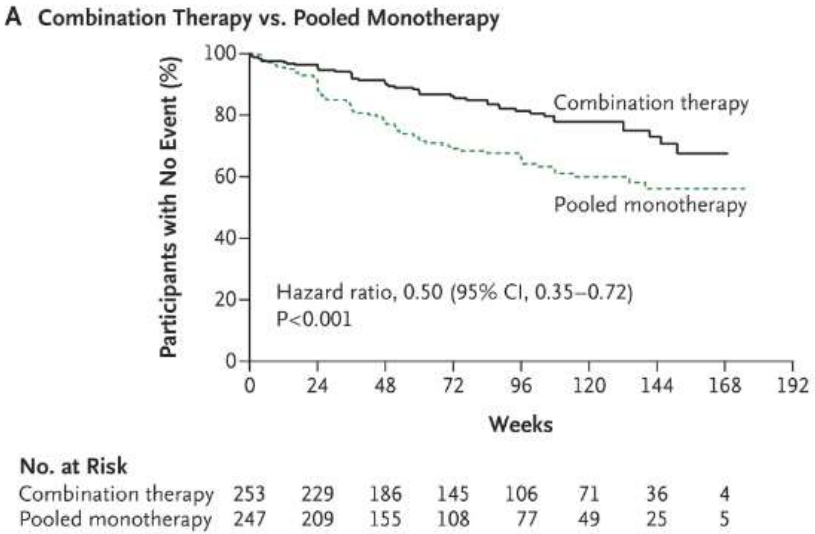
Vonk Noordegraaf A, etal., The REPAIR Study: Effects of Macitentan on RV Structure and Function in Pulmonary Arterial Hypertension. JACC Cardiovasc Imaging. 2022 Feb

Ambition

- 2:1:1 ratio, treatment naïve PAH patients with WHO – FC 2-4 to receive initial combination therapy with 10 mg of ambrisentan plus 40 mg of tadalafil (n=253), 10 mg of ambrisentan plus placebo(n= 126), or 40 mg of tadalafil plus placebo(n=121). IPAH patients were 50-57% patients in each group
- Primary end point : first occurrence of a composite of death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response.
- Primary end-point event occurred in 18%, 34%, and 28% of the participants in these groups, respectively, and in 31% of the pooled-monotherapy group
- Hazard ratio for the primary end point in the combination-therapy group vs the pooled-monotherapy group was 0.50 (95% confidence interval [CI], 0.35 to 0.72; P<0.001).

Galiè Net al., AMBITION Investigators. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. N Engl J Med. 2015 Aug 27;373(9)

Combination therapy



1. NTproBNP reduction (mean change, -67.2% vs. -50.4%; P<0.001)
2. Clinical response (39% vs. 29%; odds ratio, 1.56 [95% CI, 1.05 to 2.32]; P=0.03)
3. 6MWD better (48.9 vs 23.8)

Galiè Net al., AMBITION Investigators. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. N Engl J Med. 2015 Aug 27;373(9)

PDE5 inhibitors

- PDE5 inhibitors sildenafil and tadalafil block the degradation of cGMP, which mediates vasodilation and is produced by nitric oxide-dependent soluble guanylate cyclase. therapeutic efficacy is driven and limited by native nitric oxide availability, which is already diminished in PAH.
- Riociguat acts by directly stimulating soluble guanylate cyclase, independent of endogenous nitric oxide, to enhance production of cGMP

The NEW ENGLAND JOURNAL of MEDICINE

Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension

Nazzareno Galiè, M.D., Hossein A. Ghofrani, M.D., Adam Torbicki, M.D., Robyn J. Barst, M.D., Lewis J. Rubin, M.D., David Badesch, M.D., Thomas Fleming, Ph.D., Tamiza Parpia, Ph.D., Gary Burgess, M.D., Angelo Branzi, M.D., Friedrich Grimminger, M.D., Marcin Kurzyna, M.D., et al., for the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group

- Double-blind, placebo-controlled study, n=278, placebo vs sildenafil (20, 40, or 80 mg) orally three times daily for 12 weeks
- PAH (idiopathic(65%) or associated with CTD or with repaired congenital systemic-to-pulmonary shunts. 90% patients in WHO FC 2 & 3
- Primary : change from baseline to week 12 in 6WMD
- Secondary : change in mPAP and WHO-FC and the incidence of clinical worsening
- 6MWD : 45 m , 46 m , and 50 m for 20, 40 and 80 mg of sildenafil, respectively ($P<0.001$) at the end of 1 yr 51mtr
- Reduced mPAP, improved WHO-FC
- Side effects : flushing, dyspepsia, and diarrhea

Galiè N etal., Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005 Nov 17

PACES

- 16-week, double-blind, placebo-controlled, parallel-group study in 41 centers in 11 countries , 123 in the placebo group and 133 in the sildenafil group
- 267 patients with pulmonary arterial hypertension (idiopathic, associated anorexigen use or CTD, or corrected CHD) who were receiving long-term intravenous epoprostenol therapy
- long-term intravenous epoprostenol therapy + placebo or sildenafil, 20 mg three times daily, titrated to 40 mg and 80 mg three times daily, as tolerated, at 4-week intervals
- primary : change in exercise by 6MWD
- secondary : hemodynamic measurements, time to clinical worsening, and Borg dyspnea score

Simonneau G etal., Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. Ann Intern Med. 2008 Oct 21

With sildenafil addition :

1) In patients with baseline 6MWD >325 mtr more pronounced effects. Placebo adjusted changes increase of 28.8 meters (95% CI, 13.9 to 43.8 meters)

2) Greater change in mPAP by -3.8 mm Hg (CI, -5.6 to -2.1 mm Hg)

3) cardiac output by 0.9 L/min (CI, 0.5 to 1.2 L/min)

4) longer time to clinical worsening and Smaller proportion of patients experiencing a worsening event in the sildenafil group (0.062) than in the placebo group (0.195) by week 16 (P = 0.002)

5) Health-related quality of life also improved in patients who received combined therapy compared with those who received epoprostenol monotherapy

6) No change in Borg score

PACES - 2

PACES 2 : PACES 1 patients followed for 3 years on sildenafil 80mg TID dose

- 6MWD improved or to have been maintained in 59%, 44%, and 33% of patients at 1,2, and 3 years
- WHO FC improved or to have been maintained in 73%, 59%, and 46%.
- PACES-1 baseline 6MWD < 325 meters without 6MWD improvement during the first 20 weeks of sildenafil treatment subsequently had poorer survival.
- At 3 years, 66% of patients were known to be alive, 24% were known to have died, and 10% were lost to follow-up

Simonneau Getal., Long-term sildenafil added to intravenous epoprostenol in patients with pulmonary arterial hypertension. J Heart Lung Transplant. 2014 Jul;

Circulation
Volume 119, Issue 22, 9 June 2009; Pages 2894-2903
https://doi.org/10.1161/CIRCULATIONAHA.108.839274

HYPERTENSION

Tadalafil Therapy for Pulmonary Arterial Hypertension

- 16-week, double-blind, placebo-controlled study, PAH patients, treatment naïve or on bosentan therapy. placebo or tadalafil 2.5, 10, 20, or 40 mg orally OD.
- 405 patients with PH (idiopathic 55-66%) , >95% patients WHO FC 2 & 3
- Primary : change from baseline to week 16 in 6MWD
- Secondary : WHO-FC, clinical worsening, and health-related quality of life
- Only the 40-mg group met the level of statistical significance ($P<0.01$)
- Treatment effect was 33 m (95% confidence interval, 15 to 50 m)
- Tadalafil 40 mg improved the time to clinical worsening ($P=0.041$), incidence of clinical worsening (68% relative risk reduction; $P=0.038$), and health-related quality of life, change in WHO-FC not significant

Galiè N, etal.,Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009 Jun 9

Riociguat evidence

Trial and year	Participants	Result
PATENT-1 (2013)	443 patients with Group 1 PH	6MWDT 36m better vs placebo
PATENT-2 (2015)	324 patients with Group 1 PH	PATENT-1 study results of 12 wks maintained @ 1 yr
PATENT PLUS (2015)	Sildenafil + Riociguat/placebo	Sildenafil + Riociguat is contraindiacted
RESPITE (2017)	51 patients with group 1 PH	6MWDT 31 mtr better
REPLACE (2021)	224 patients with group 1 PH on background PDE5 inhibitor with intermediate risk of 1-year mortality	-Switching from PDE5 inhibitor to riociguat safe
SETOUCHI-PH (On-going)	Primary end point is change in PVR in patients on macitentan and either riociguat or selexipag	Now recruiting…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Riociguat for the Treatment of Pulmonary Arterial Hypertension

Hossein-Ardeschir Ghofrani, M.D., Nazzareno Galiè, M.D., Friedrich Grimminger, M.D., Ekkehard Grünig, M.D., Marc Humbert, M.D., Zhi-Cheng Jing, M.D., Anne M. Keogh, M.D., David Langleben, M.D., Michael Ochan Kilama, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., and Lewis J. Rubin, M.D. for the PATENT-1 Study Group*

- Phase 3, double-blind study, n=443 (61% idiopathic), placebo vs riociguat
- > 90% patients in WHO FC 2 & 3
- Treatment naïve / ERA/ non iv prostanoids
- Primary : change in 6MWD at 12 weeks
- Secondary : NT PRO BNP, WHO-FC, time to clinical worsening,PVR, Borg scale, QOL score
- Least-squares mean difference 6MWD, 36 m; 95% confidence interval, 20 to 52; P<0.001)
- Improvement in NT PRO BNP, WHO-FC, time to clinical worsening, PVR, Borg scale

Ghofrani HA etal.,PATENT-1 Study Group. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med. 2013 Jul 25

Patent plus

- Patients receiving sildenafil (20 mg three times daily) were randomised to placebo or riociguat (up to 2.5 mg three times daily) for 12 weeks
- 80% patients in Riociguat group WHO FC 2/3 , 100% in placebo group WHO FC 2/3
- In the long term extension there was significant hypotension in the combination group
- No favourable effects on exploratory clinical parameters, including haemodynamics and exercise capacity
- Concomitant use of riociguat with phosphodiesterase-5 inhibitors is therefore contraindicated

Galiè N etal., PATENT PLUS: a blinded, randomised and extension study of riociguat plus sildenafil in pulmonary arterial hypertension. Eur Respir J. 2015 May;45

Respite

- 24-week, open-label, multicentre, uncontrolled study
- Patients who did not achieve treatment goal with PDE5i were enrolled
- PDE5i were kept on hold for 2 days and riociguat started
- 61 patients enrolled, 51 (84%) completed RESPITE
- 50 (82%) were receiving concomitant ERA
- WHO-FC III, with 6MWD 165–440 m, CI <3.0 $L \cdot min^{-1} \cdot m^{-2}$ and PVR >400 $dyn \cdot s \cdot cm^{-5}$
- At week 24,

1. Mean ± SD 6MWD had increased by 31±63 m
2. NT-proBNP decreased by 347±1235 $pg \cdot mL^{-1}$
3. WHO FC improved in 28 patients (54%)

Hoeper MM etal., RESPITE: switching to riociguat in pulmonary arterial hypertension patients with inadequate response to phosphodiesterase-5 inhibitors. Eur Respir J. 2017 Sep

Riociguat clinical Effects Studied in Patients with Insufficient Treatment responses to PDE5 inhibitors (RESPITE) - hypothesis – *there is reduced NO availability in PAH* – sGC stimulator like riociguat may have better effects then PDE – 5 i. those who failed sildenafil/tadalafil were given Riociguat and there was improvement of 6MWD by 31 mtr. Limitations were small sample size, trial design and 52% subjects having side effects.

THE LANCET
Respiratory Medicine

Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial

- Assess the effects of switching to Riociguat from PDE5i therapy versus continued PDE5i therapy in patients with PAH at *intermediate risk of 1-year mortality (WHO FC 3)*
- PDE5I with or without ERA, either continuing PDE5i vs switching to Riociguat
- 226 patients were randomly assigned to the riociguat group (n=111) or to the PDE5i group (n=115)
- Primary : absence of clinical worsening, improvements in at least 2 of 3 variables (6MWD, WHO functional class, and Nt-proBNP)

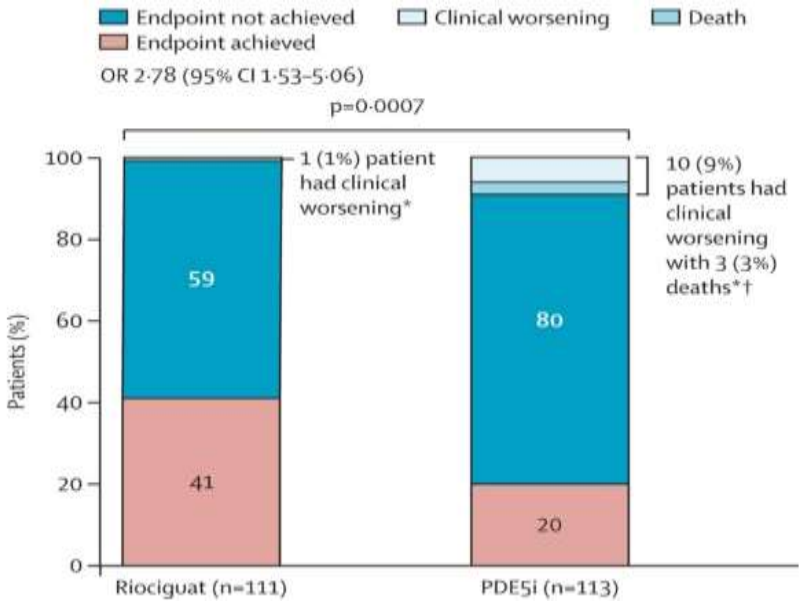
Hoeper MM etal., REPLACE investigators. Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial. Lancet Respir Med. 2021 Jun;9

	Prior PDE5i monotherapy			Prior PDE5i + ERA		
	Riociguat (n=32)	PDE5i (n=32)	Mean difference (95% CI)	Riociguat (n=79)	PDE5i (n=81)	Mean difference (95% CI)
6MWD, m						
Baseline	357 (56)	366 (67)	—	381 (60)	367 (61)	—
Week 24	403 (110)	368 (97)	—	413 (90)	386 (86)	—
Change	+46 (84)	+2 (65)	+44 (7; 81)	+33 (58)	+19 (68)	+14 (-6; 34)
NT-proBNP, *pg/mL*						
Baseline	889 (1293)[a]	1219 (2118)	—	609 (730)[b]	965 (1552)	—
Week 24	658 (944)	1137 (1919)	—	567 (862)	1111 (2349)	—
Change	-211 (601)[a]	-82 (1282)	-129 (-635; 377)	-39 (500)[b]	+146 (1264)	-185 (-485; 116)
WHO FC I/II/III/IV/V						
Week 24, %	3/34/63/0/0	3/16/75/3/3	-0.28 (-0.59; 0.02)	3/44/51/3/0	2/22/70/4/1[d]	-0.26 (-0.45; -0.07)
Improvement, n (%)	12 (38)	6 (19)	—	37 (47)	20 (25)	—
Clinical worsening events, n (%)	0 (0)	4 (13)	—	1 (1)	6 (7)	—

Data are expressed as mean (standard deviation) unless otherwise specified.
[a]n=31. [b]n=77. [c]All patients were in WHO FC III at baseline. WHO FCV indicates patients who died. Data are last observation carried forward.
[d]One patient in WHO FCIII at last visit died later.

REPLACE was a prospective, randomized, controlled, open-label, Phase 4 study in patients with PAH at intermediate risk despite PDE-5i therapy.

Meyer GMB, et al. *ATS* 2021. Hoeper MM, et al. *Lancet Respir Med.* 2021 Mar 24:S2213-2600(20)30532-4.



- Primary endpoint was met by 45 (41%) of 111 patients in the riociguat group and 23 (20%) of 113 patients in the PDE5i group; odds ratio [OR] 2·78 (95% CI 1·53-5·06; p=0·0007)
- Clinical worsening in 1 patient in riociguat vs 10 in PDE5i group, hospitalisation due to worsening PAH [n=9]; disease progression [n=1]; OR 0·10 [0·01-0·73]; p=0·0047

Prostacyclins

The NEW ENGLAND JOURNAL of MEDICINE

A Comparison of Continuous Intravenous Epoprostenol (Prostacyclin) with Conventional Therapy for Primary Pulmonary Hypertension

- Conventional therapy alone (anticoagulants, oral vasodilators, diuretic agents, cardiac glycosides, and supplemental oxygen) vs iv epoprostenol + conventional therapy
- NYHA 3 (around 75%) and NYHA 4 (around 25%)
- 41 patients were randomly assigned to receive epoprostenol plus conventional therapy, and 40 patients were randomly assigned to receive conventional therapy alone
- Improved 6MWD in epoprostenol group (362 m at 12 weeks vs. 315 m at base line) vs decrease in conventional therapy alone (204 m at 12 weeks vs. 270 m at base line) $P<0.002$
- changes in mPAP and change in PVR was also significant in the epoprostenol group

Barst RJ etal., Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996 Feb 1

McLaughlin VV etal., 2002

- Observed survival with epoprostenol therapy at 1, 2, and 3 years was 87.8%, 76.3%, and 62.8%
- Significantly greater than the expected survival of 58.9%, 46.3%, and 35.4% based on historical data

Sitbon O etal., 2002

- Survival in PPH depends on the severity at baseline, as well as the three-month response to therapy
- History of right-sided heart failure, NYHA functional class IV, 6-min WT <or=250 m , RAP >or=12 mm Hg, and mPAP <65 mm Hg – poor outcome indicators

McLaughlin VV etal., Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation. 2002 Sep 17

Sitbon O, etal.,Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol. 2002 Aug 21

The NEW ENGLAND JOURNAL of MEDICINE

Inhaled Iloprost for Severe Pulmonary Hypertension

Horst Olschewski, M.D., Gerald Simonneau, M.D., Nazzareno Galiè, M.D., Timothy Higenbottam, M.D., Robert Naeije, M.D., Lewis J. Rubin, M.D., Sylvia Nikkho, M.D., Rudolf Speich, M.D., Marius M. Hoeper, M.D., Jürgen Behr, M.D., Jörg Winkler, M.D., Olivier Sitbon, M.D., et al., for the Aerosolized Iloprost Randomized Study Group*

- Comparison between daily inhalations of 2.5 or 5.0 µg of iloprost (six or nine times per day; median inhaled dose, 30 µg per day) with inhalation of placebo
- 203 total patients including 102 primary PAH (51 randomised to each group)
- Primary : improved FC by 1 or improved 6WMD by 10%
- End point was met by 16.8 percent of the patients receiving iloprost, as compared with 4.9 percent of the patients receiving placebo (P=0.007)
- After 12 weeks , increase in 6MWD 36.4 m in the iloprost group as a whole (P=0.004) and of 58.8 m in the subgroup of patients with primary pulmonary hypertension

Olschewski H etal., Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002 Aug

Triumph

- Inhaled trepostinil (upto 54 mcg) vs placebo in PAH patients on sildenafil / Bosentan (70%) with NYHA 3 or 4 & 6MWD of 200-450 mtr
- 135 out of total 235 patients were IPAH or familial PH
- Between-treatment median difference in change from baseline in peak 6MWD was 19 m at week 6 (p = 0.0001) and 20 m at week 12 (p = 0.0004)
- Nt pro BNP levels improved
- There were no improvements in other secondary end points, including time to clinical worsening, Borg Dyspnea Score, NYHA functional class, and PAH signs and symptoms

McLaughlin VV etal., Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol. 2010 May 4

Freedom EV

- Double-blind study, randomly allocated 690 participants (1:1 ratio) with PAH to receive placebo or oral treprostinil in addition to background therapy (PDE5 inhibitor or SGC stimulator) / ERA alone
- Mostly WHO FC 2 & 3 (>95%)
- Clinical worsening occurred in 26% of the oral treprostinil group compared with 36% of placebo participants.
- WHO – FC, Borg dyspnea score & Nt- pro BNP, all favored oral treprostinil treatment at Week 24 and beyond.
- Oral treprostinil-assigned participants had a substantially higher mortality risk at baseline but achieved a lower risk profile from Study Weeks 12-60.

White RJ et al., Combination Therapy with Oral Treprostinil for Pulmonary Arterial Hypertension. A Double-Blind Placebo-controlled Clinical Trial. Am J Respir Crit Care Med. 2020 Mar 15;201(6)

Freedom C1 Chest 2012	**Oral treprostinil in the treatment of PAH with a concomitant ERA and/or PDE - 5 inhibitor**	**Change from baseline 6MWD at week 16 was 11 m (P = .07)**	**Higher dose of trepostinil – higher change in 6MWD**
Freedom C2 CHEST 2013	Oral treprostinil in the treatment of PAH with a concomitant ERA and/or PDE - 5 inhibitor	Median difference in 6MWD at week 16 was 10.0 m (95% CI, -2 to 22 m; P = .089)	Oral treprostinil to background ERA and PDE-5I therapy did not improve exercise capacity

Griphon study

- Double blind, selexipag vs placebo (n = 1156, 55% IPAH, >95% WHO FC 2 & 3)
- Treatment naïve or ERA or PDE5i or both
- primary end point was a composite of death from any cause or a complication related to pulmonary arterial hypertension up to the end of the treatment period
- primary end-point event occurred in 397 patients--41.6% of those in the placebo group and 27.0% of those in the selexipag group (hazard ratio in the selexipag group as compared with the placebo group, 0.60; 99% confidence interval, 0.46 to 0.78; P<0.001
- Disease progression and hospitalization accounted for 81.9% of the events

Sitbon O etal., GRIPHON Investigators. Selexipag for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med. 2015 Dec 24

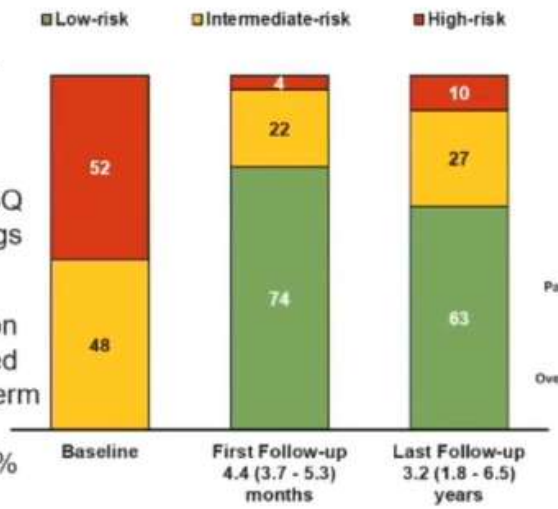
- Effect of selexipag was similar in both the treatment naïve and in patients on treatment
- There was no difference in mortality (105 in placebo group and 100 in selexipag)
- **Results From the Phase III GRIPHON Study**
- categorized post hoc into a time from diagnosis of ≤ 6 months and > 6 months at randomization
- ≤ 6 months in 34.9% and > 6 months in 65.1% of patients
- selexipag reduced the risk of morbidity/mortality in patients with a time from diagnosis of ≤ 6 months and > 6 months, with a more pronounced effect in newly diagnosed patients (hazard ratio, 0.45 [95% CI, 0.33-0.63] and 0.74 [95% CI, 0.57-0.96], respectively; P = .0219 for interaction).

Gaine S etal., Relationship Between Time From Diagnosis and Morbidity/Mortality in Pulmonary Arterial Hypertension: Results From the Phase III GRIPHON Study. Chest. 2021 Jul;160

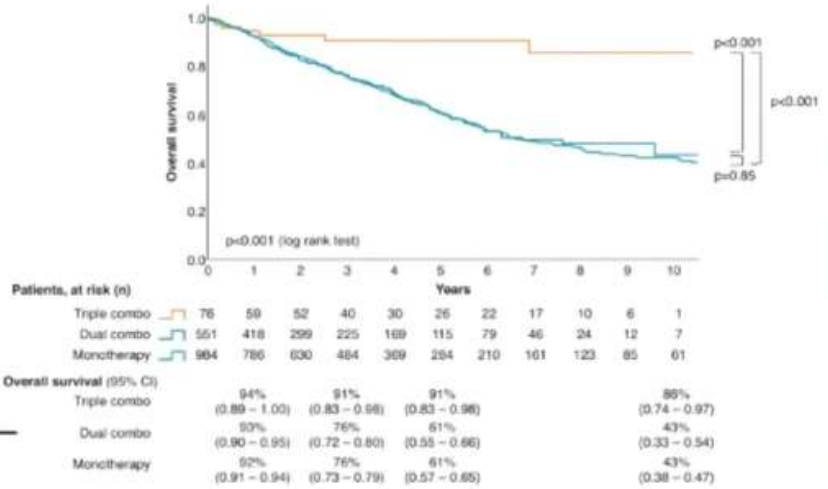
Long-Term Outcomes with Triple Combination Therapy in PAH

- Retrospective study using the French PH registry (n=1611) in newly diagnosed non-vasoreactive PAH patients and those initiated with a combination of IV or SQ PGI_2 and two oral drugs (ERAs and PDE-5i)
- Initial triple combination therapy was associated with favourable long-term outcomes with a 10-year survival of 86%

Risk status



Survival by Initial Treatment Strategy



ERA, endothelin receptor antagonists; IV, intravenous; PDE5i, phosphodiesterase-5 inhibitor; PGI_2, prostacyclin (also called prostaglandin I2); SQ, subcutaneous. Boucly A, et al. ERS 2020. Nr3970; Boucly A, et al. *Am J Respir Crit Care Med.* 2021;204(7):842-854.

TRITON

- Initial triple (macitentan, tadalafil, and selexipag) versus initial double (macitentan, tadalafil, and placebo) oral therapy in newly diagnosed, treatment-naive patients with PAH. (n=123 and n=124)
- 46% patients were idiopathic PH with WHO FC 3 0r 4 in 80% patients
- primary endpoint was change in pulmonary vascular resistance (PVR) at week 26.
- No difference in both groups with change in PVR, Nt pro BNP, 6MWD
- Risk for disease progression (to end of main observation period) was reduced with initial triple versus initial double therapy (hazard ratio: 0.59; 95% confidence interval: 0.32-1.09)

Chin KM etal., Three- Versus Two-Drug Therapy for Patients With Newly Diagnosed Pulmonary Arterial Hypertension. J Am Coll Cardiol. 2021 Oct 5

Summary vaso reactive

Recommendations	Class[a]	Level[b]
High doses of CCBs are recommended in patients with IPAH, HPAH, or DPAH who are responders to acute vasoreactivity testing	I	C
Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is recommended in patients with IPAH, HPAH, or DPAH treated with high doses of CCBs	I	C
Continuing high doses of CCBs is recommended in patients with IPAH, HPAH, or DPAH in WHO-FC I or II with marked haemodynamic improvement (mPAP <30 mmHg and PVR <4 WU)	I	C
Initiating PAH therapy is recommended in patients who remain in WHO-FC III or IV or those without marked haemodynamic improvement after high doses of CCBs	I	C
In patients with a positive vasoreactivity test but insufficient long-term response to CCBs who require additional PAH therapy, continuation of CCB therapy should be considered	IIa	C
CCBs are not recommended in patients without a vasoreactivity study or non-responders, unless prescribed for other indications (*e.g.* Raynaud's phenomenon)	III	C

Summary – non vaso reactive

- PAH specific therapy + general measures
- As per 3 strata risk stratification :

1) For low or intermediate risk → upfront dual oral therapy (ERA/ambrisentan + PDE5i/tadalafil) as per **Ambition & Triton trial .**

Ambition trial *showed benefit* with dual combination therapy in mortality, exercise capacity, NtproBNP levels, hospitalisation and progression. It also showed better clinical response.

Triton showed *no better response* in upfront triple therapy (macitentan, tadalafil, and selexipag) vs dual therapy (macitentan, tadalafil, and selexipag). 6MWD and decrease in PVR was similar

Recommendations	GRADE Quality of evidence	Strength of recommendation	Class[b]	Level[c]
Recommendations for initial therapy				
In patients with IPAH/HPAH/DPAH who present at low or intermediate risk of death, initial combination therapy with a PDE5i and an ERA is recommended [166]	Low	Conditional	I	B

2) High risk : upfront triple therapy including injectable prostacyclin should be started. The evidence comes from the French registry which showed overall mortality benefit.

Also a pilot study by *Sitbon O etal* published in ERJ 2014 : newly diagnosed NYHA FC III/IV PAH patients (n=19) initiated on upfront triple combination therapy (intravenous epoprostenol, bosentan and sildenafil). 18 patients showed improvement in 6MWD, RAP,mPAP, CI, svo2. 17 patient improved to FC 1 or 2.

Recommendations	Class[b]	Level[c]
Recommendations for initial therapy		
In patients with IPAH/HPAH/DPAH who present at high risk of death, initial combination therapy with a PDE5i, an ERA, and i.v./s.c. prostacyclin analogues should be considered[d]	IIa	C

Sitbon O, etal., Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. Eur Respir J. 2014 Jun;

- For follow up : 4 risk strata tool should be used.
- During follow up following recommendations should be utilised for treatment decision

i) In patients who achieve a low-risk status with their initial PAH therapy, continuation of treatment is recommended.

ii) In patients who are at intermediate–low risk despite receiving ERA/PDE5i therapy, adding selexipag should be considered to reduce the risk of clinical worsening. In these patients, switching from PDE5i to riociguat may also be considered. (**Griphon /Replace**)

iii) In patients who are at intermediate–high or high risk while receiving oral therapies, the addition of i.v. epoprostenol or i.v./s.c. treprostinil and referral for LTx evaluation should be considered . If adding i.v./s.c. prostacyclin analogues is unfeasible, adding selexipag or switching from PDE5i to riociguat may be considered .

Seraphin

Griphon

Freedom EV

Vizza

Recommendations	Class[a]	Level[b]
General recommendation for sequential combination therapy		
It is recommended to base treatment escalations on risk assessment and general treatment strategies (see Figure 9)	I	C
Evidence from studies with a composite morbidity/mortality endpoint as primary outcome measure		
Addition of macitentan to PDE5is or oral/inhaled prostacyclin analogues is recommended to reduce the risk of morbidity/mortality events [167, 168, 437]	I	B
Addition of selexipag to ERAs[c] and/or PDE5is is recommended to reduce the risk of morbidity/mortality events [418, 419]	I	B
Addition of oral treprostinil to ERA or PDE5i/riociguat monotherapy is recommended to reduce the risk of morbidity/mortality events [412, 413, 415]	I	B
Addition of bosentan to sildenafil is not recommended to reduce the risk of morbidity/mortality events [419]	III	B

PACES -----→

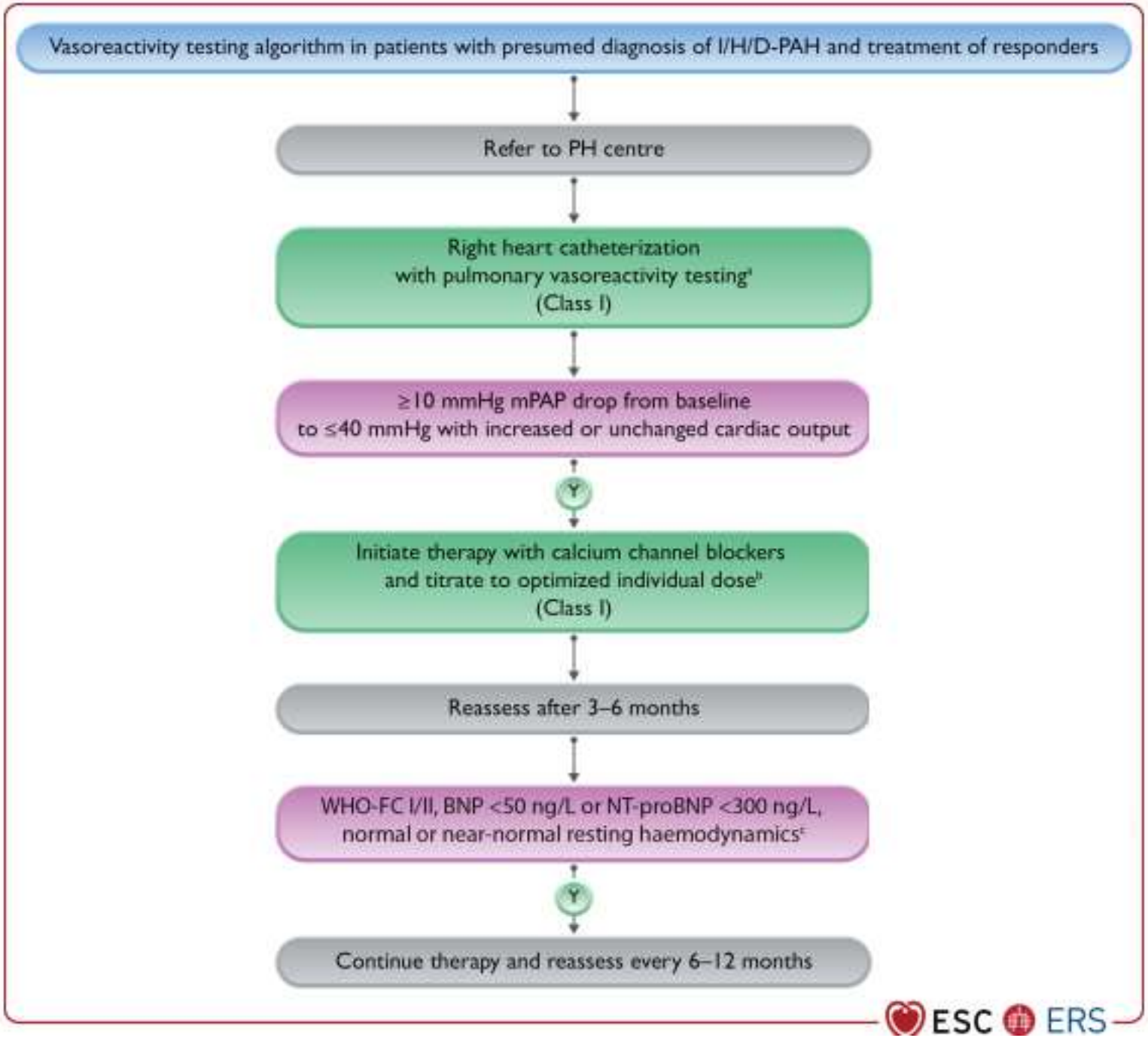
Triumph---- →

Patent 1 /2→

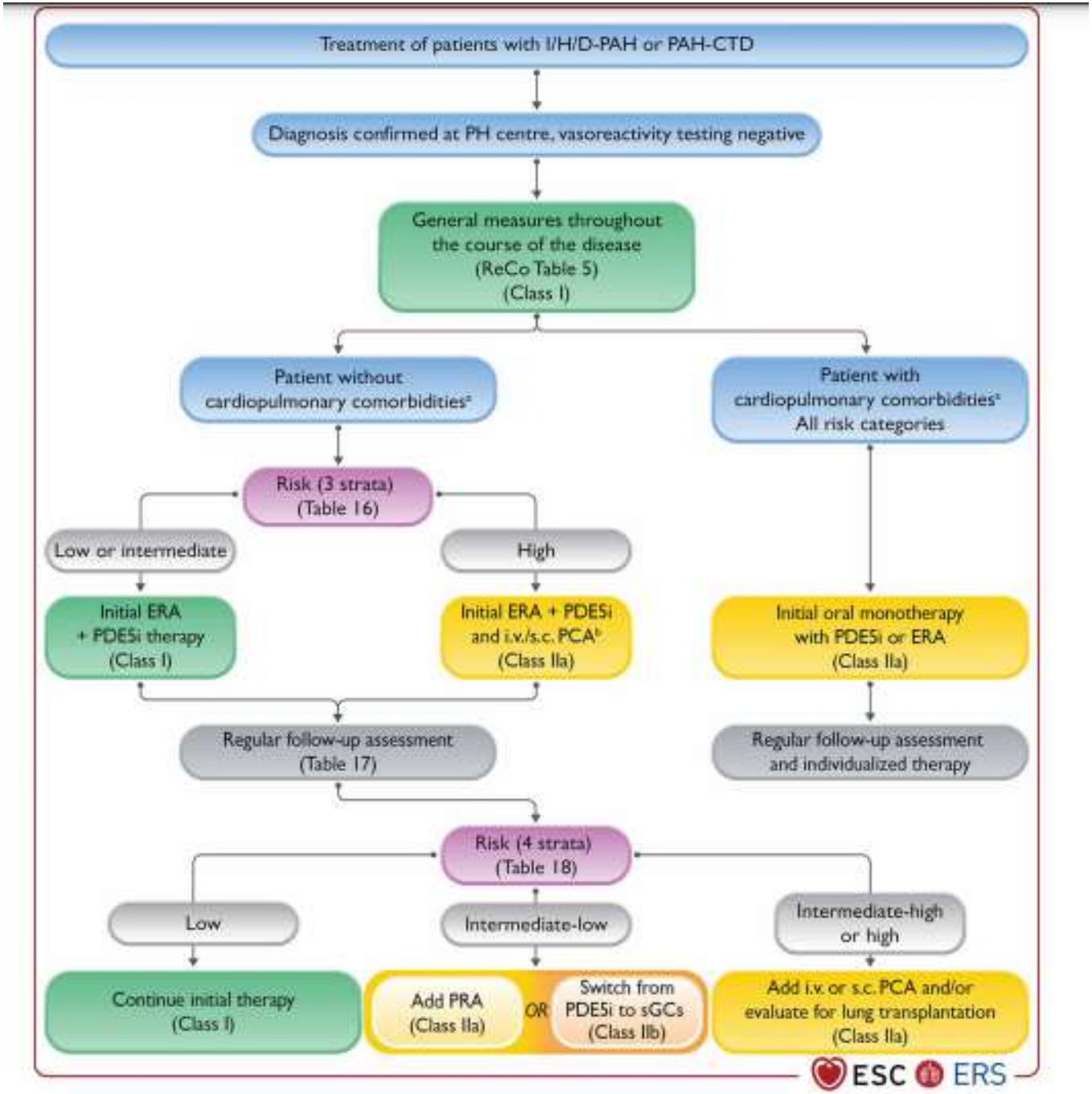
Phirst -------→

Aries 3 ---- →

Recommendations	Class[a]	Level[b]
Evidence from studies with change in 6MWD as primary outcome measure		
Addition of sildenafil to epoprostenol is recommended to improve exercise capacity [392, 438]	I	B
Addition of inhaled treprostinil to sildenafil or bosentan monotherapy should be considered to improve exercise capacity [411, 439]	IIa	B
Addition of riociguat to bosentan should be considered to improve exercise capacity [395, 440]	IIa	B
Addition of tadalafil to bosentan may be considered to improve exercise capacity [393]	IIb	C
Addition of inhaled iloprost to bosentan may be considered to improve exercise capacity [441, 442]	IIb	B
Addition of ambrisentan to sildenafil may be considered to improve exercise capacity [443]	IIb	C
Addition of bosentan to sildenafil may be considered to improve exercise capacity [419, 444]	IIb	C
Addition of sildenafil to bosentan may be considered to improve exercise capacity [444–446]	IIb	C
Other sequential double- or triple-combination therapies may be considered to improve exercise capacity and/or alleviate PH symptoms	IIb	C
Evidence from studies with safety of combination therapy as primary outcome measure		
Combining riociguat and PDE5is is not recommended[d] [389]	III	B



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

	Starting dose	Target dose
Calcium channel blockers		
Amlodipine	5 mg o.d.	15–30 mg o.d.[a]
Diltiazem	60 mg b.i.d.[b]	120–360 mg b.i.d.[b]
Felodipine	5 mg o.d.	15–30 mg o.d.[a]
Nifedipine	10 mg t.i.d.	20–60 mg b.i.d. or t.i.d.
Endothelin receptor antagonists (oral administration)		
Ambrisentan	5 mg o.d.	10 mg o.d.
Bosentan	62.5 mg b.i.d.	125 mg b.i.d.
Macitentan	10 mg o.d.	10 mg o.d.
Phosphodiesterase 5 inhibitors (oral administration)		
Sildenafil	20 mg t.i.d.	20 mg t.i.d.[c]
Tadalafil	20 or 40 mg o.d.	40 mg o.d.
Prostacyclin analogues (oral administration)		
Beraprost sodium	20 µg t.i.d.	Maximum tolerated dose up to 40 µg t.i.d.
Beraprost extended release	60 µg b.i.d.	Maximum tolerated dose up to 180 µg b.i.d.
Treprostinil	0.25 mg b.i.d. or 0.125 mg t.i.d.	Maximum tolerated dose
Prostacyclin receptor agonist (oral administration)		
Selexipag	200 µg b.i.d.	Maximum tolerated dose up to 1600 µg b.i.d.
Soluble guanylate cyclase stimulator (oral administration)		
Riociguat[d]	1 mg t.i.d.	2.5 mg t.i.d.
Prostacyclin analogues (inhaled administration)		
Iloprost[e]	2.5 µg 6–9 times per day	5.0 µg 6–9 times per day
Treprostinil[e]	18 µg 4 times per day	54–72 µg 4 times per day
Prostacyclin analogues (i.v. or s.c. administration)		
Epoprostenol i.v.	2 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 16–30 ng/kg/min, with wide individual variability
Treprostinil s.c. or i.v.	1.25 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 25–60 ng/kg/min, with wide individual variability

PAH with cardiopulmonary comorbidities

- Elderly patients diagnosed with IPAH, with two noted phenotypes.
- Elderly females , left heart type, with HFpEF risk factors but pre capillary PH, low mortality comapred to the cardiopulmonary phenotype
- Elderly males, cardiopulmonary type, hypoxemic, smokers with LHD risk factors

Recommendations	Class[b]	Level[c]
Recommendations for initial therapy		
In patients with IPAH/HPAH/DPAH and cardiopulmonary comorbidities, initial monotherapy with a PDE5i or an ERA should be considered	IIa	C
Recommendations for treatment decisions during follow-up		
In patients with IPAH/HPAH/DPAH with cardiopulmonary comorbidities who present at intermediate or high risk of death while receiving PDE5i or ERA monotherapy, additional PAH medications may be considered on an individual basis	IIb	C

Surgical management

- Baloon atrial septostomy, implantable devices and Potts shunt (between left PA and aorta) – complex procedures and rarely performed
- Pulmonary artery denervation – Trophy1 trial, which included 23 patients undergoing intravascular ultrasound pulmonary artery denervation. Data is limited and not available in most centres. (***TIVUS***)
- Post surgical :

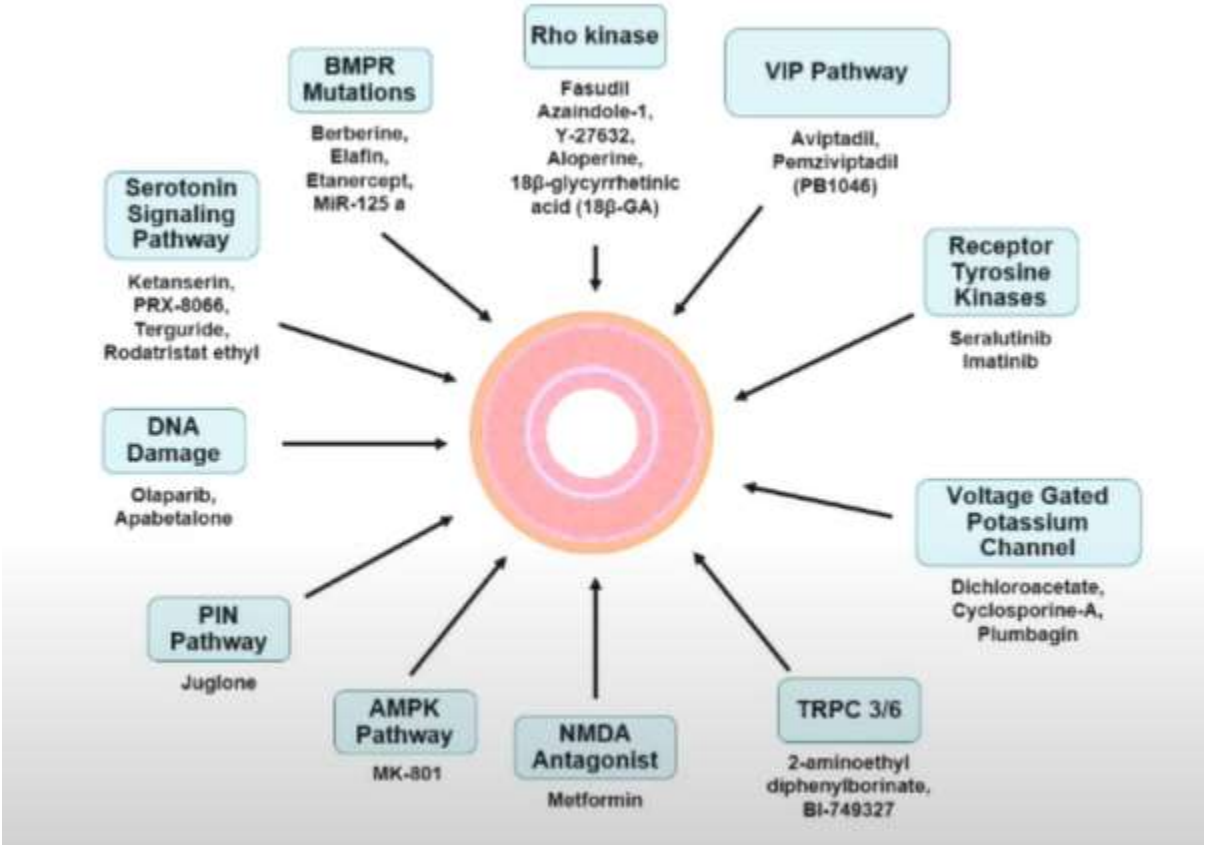
1. 42 ± 63 m (p = 0.02) increase in 6MWD
2. no procedure-related serious adverse events
3. reduction in PVR at 4- or 6-month follow-up was 94 ± 151 dyn·s·cm^{-5}

Lung transplant in PAH

- Inadequate response to combination treatment
- Mortality due to disease per se > mortality due to transplant
- ESC/ERS intermediate–high or high risk
- Both lung / Heart + lung transplant
- Only 3% of total transplant Sx for PAH etiology

Referral
Potentially eligible patients for whom LTx might be an option in case of treatment failure
ESC/ERS intermediate–high or high risk or REVEAL risk score >7 on appropriate PAH medication
Progressive disease or recent hospitalization for worsening PAH
Need for i.v. or s.c. prostacyclin therapy
Known or suspected high-risk variants, such as PVOD or PCH, systemic sclerosis, or large and progressive pulmonary artery aneurysms
Signs of secondary liver or kidney dysfunction due to PAH or other potentially life-threatening complications, such as recurrent haemoptysis
Listing
Patient has been fully evaluated and prepared for transplantation
ESC/ERS high risk or REVEAL risk score >10 on appropriate PAH medication, usually including i.v. or s.c. prostacyclin analogues
Progressive hypoxaemia, especially in patients with PVOD or PCH
Progressive, but not end-stage liver or kidney dysfunction due to PAH, or life-threatening haemoptysis

Additional new therapeutic strategy



Novel targets			Potential drugs
Gene factors and molecule signaling pathways	Regulation of BMPR-II signaling	Restoration of BMPR-II signaling	Berberine; Puerarin; Ataluren
		Micro-RNAs	MiR-20a antagomir; MiR-125a-5p
		BMP ligands	Chloroquine; Hydroxychloroquine; FK506 (tacrolimus)
	Activation of apelinergic pathway		(Pyr1)apelin-13; MM07; Elabela/toddler
	Inhibition of RhoA/Rhokinase signaling		Fasudil; Azaindole-1; 18β-GA (18β-glycyrrhetinic acid); Statins

Novel targets		Potential drugs
Gene factors and molecule signaling pathways (continued)	Inhibition of tyrosine kinase/PDGF pathway	Imatinib; GB-002
	Epigenetic target and DNA damage	Apicidin; Olaparib
	Inhibition of MRP4	MK571; AAV1.shMRP4
	Other targets: KCNK3; aquaporin 1; SOX17; BOLA3	/
	Smooth muscle proliferation	Selenoprotein P; Celastramycin

Novel targets		Potential drugs
Metabolism, ion channel, and endocrine	Correction of mitochondrial abnormalities	Trimetazidine; Ranolazine
	Inhibition of insulin hyposecretion and resistance	Liraglutide; Metformin; Thiazolidinediones
	Reduction of oxidative stress	GS-444,217; Blueberries or dimethylarginine Dimethylaminohydrolase; CXA-10
	Reversal of iron deficiency	Intravenous iron infusion; Oral iron supplement
	Modulation of ion channel (TMEM16A)	Benzbromarone
	Regulation of estrogen level	Anastrozole
Immune regulation	Anti-inflammation and immunosuppression	Anti-TNFα immunotherapy; TGF-β antagonist; Rituximab; Tocilizumab; Rapamycin; Everolimus
	Vaccination based on ET-1 signaling	ETRQB-002
	Anti-inflammation	PB1046

Sotatercept

- It is proposed to act by rebalancing between pro and anti proliferative pathways and thereby altering the vascular remodelling seen in PAH
- Novel 1st in class fusion protein comprising of extracellular domain of Activin receptor type 2 A linked to Fc domain of human IgG1
- In animal models sotatercept inhibited cell proliferation, promoted apoptosis, and alleviated inflammation in the vessel walls, leading to reverse remodeling and restoration of vessel patency
- **STELLAR, SPECTRA, HYPERION , ZENITH & PULSAR trial**

Stellar phase 3

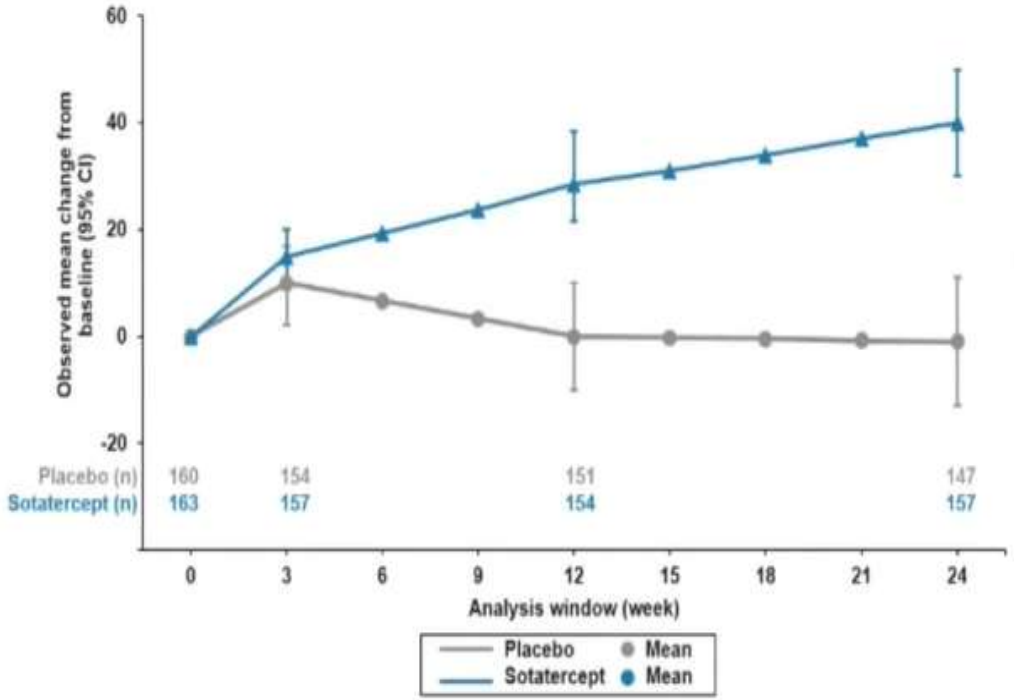
- PAH patients with WHO-FC 2/3 on stable background therapy
- Background therapy : triple 61%, double 35%, mono 5%. (infusion prostacyclin 40%)
- Idiopathic 58% , heritable, drug-induced, CTD –associated, or after shunt correction
- 163 patients to receive sotatercept s/c q3weekly and 160 to receive placebo
- Patients on completion will be eligible to roll into SOTERIA trial (**A Long-term Follow-up Study of Sotatercept for PAH Treatment)**

Stellar phase 3

Primary Endpoint: Change from Baseline in 6MWD at Week 24

	Placebo (N=160)	Sotatercept (N=163)
Observed mean change from baseline (95% CI)*	-1.4 (-13.2 to 10.3)	40.1 (29.9 to 50.2)
Hodges-Lehmann location shift (95% CI)†		40.8 (27.5 to 54.1)
Wilcoxon p-value‡		<0.001

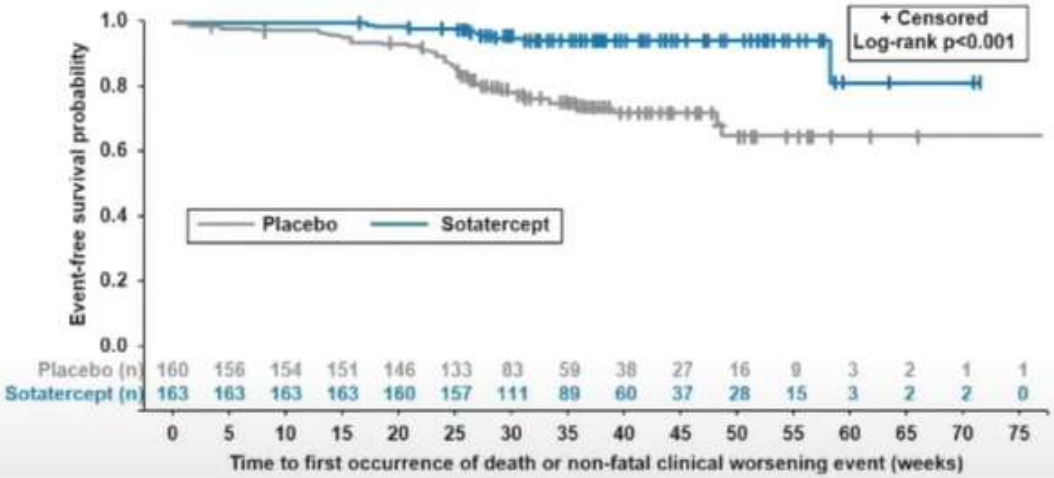
*No imputation of missing data.
†Hodges-Lehmann location shift (95% CI) represents the location shift from placebo estimate (median of the differences in change from baseline at week 24 [sotatercept vs. placebo])
‡From the aligned rank stratified Wilcoxon test with randomization factors as strata.



Time to First Occurrence of Death or Non-Fatal Clinical Worsening Event (TTCW)

	Placebo (N=160)	Sotatercept (N=163)
Total number of patients who died or experienced at least one clinical worsening event, n (%)	42 (26.3)	9 (5.5)
Assessment of first occurrence of death or non-fatal clinical worsening event*:		
Death as first event	6 (3.8)	2 (1.2)
Worsening-related listing for lung or heart-lung transplant	1 (0.6)	1 (0.6)
Need to initiate rescue therapy or need to increase dose of infusion prostacyclin by 10% or more	17 (10.6)	2 (1.2)
Need for atrial septostomy	0	0
PAH-related hospitalization (24 hours)	7 (4.4)	0
Deterioration of PAH	15 (9.4)	4 (2.5)

*Dates and times of reported adverse events were used by the adjudication committee to determine death or first non-fatal clinical worsening event. Patients could have more than one assessment for their first occurrence of non-fatal clinical worsening event or death. A single patient could have more than one non-fatal clinical worsening event but was only counted once for the time to event analysis.



After a median follow-up of 32.7 weeks across the treatment groups, the hazard ratio in the sotatercept group as compared with the placebo group was 0.16 (95% CI: 0.08 to0.35).

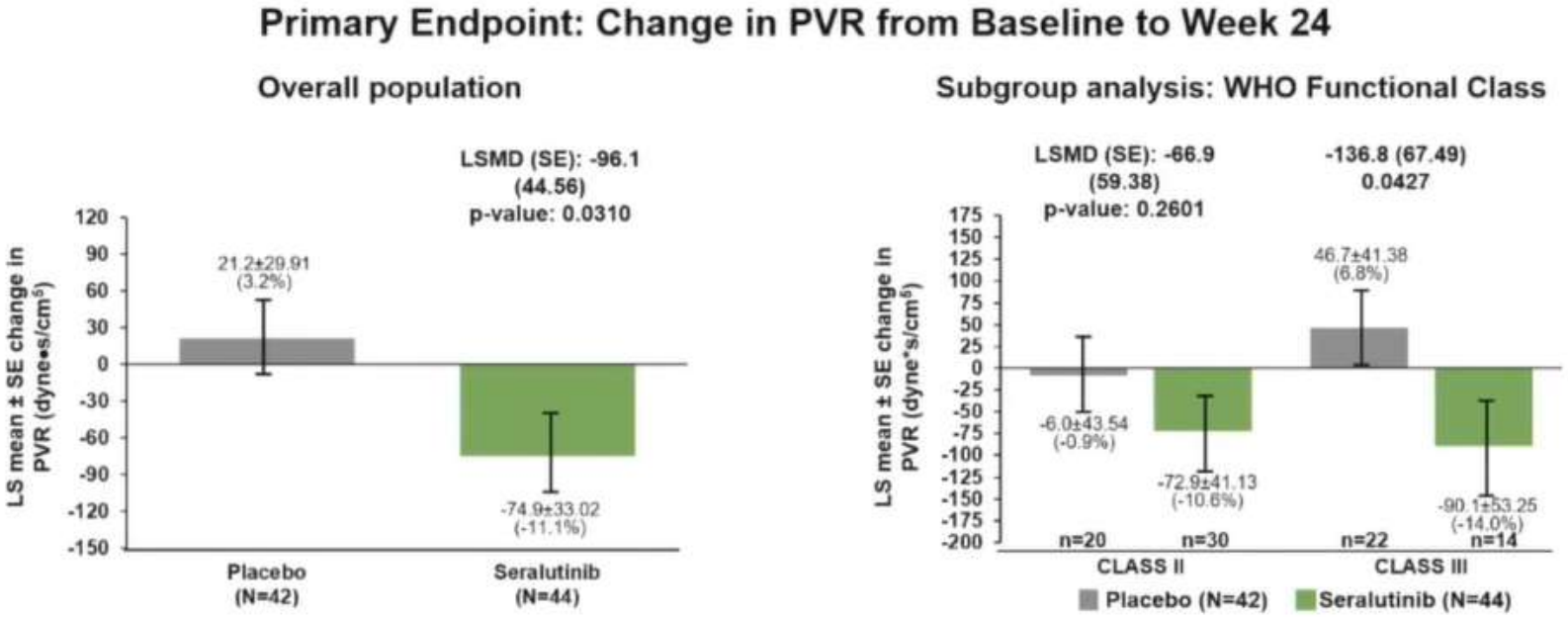
Overall Summary of Safety: Cumulative results through data cut-off date[a]

Number of patients with any	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)
TEAEs of interest[b]	72 (45.0)	97 (59.5)
Bleeding events	25 (15.6)	52 (31.9)
Telangiectasia	6 (3.8)	23 (14.1)
Increased Hb (increased hematocrit, increased RBC count)	0	10 (6.1)
Thrombocytopenia	5 (3.1)	14 (8.6)
Increased blood pressure	1 (0.6)	7 (4.3)
TEAEs with incidence ≥10% in one or more treatment groups		
Epistaxis	3 (1.9)	33 (20.2)
Telangiectasia	6 (3.8)	23 (14.1)
Dizziness	7 (4.4)	24 (14.7)

Seralutinib – Torrey Study

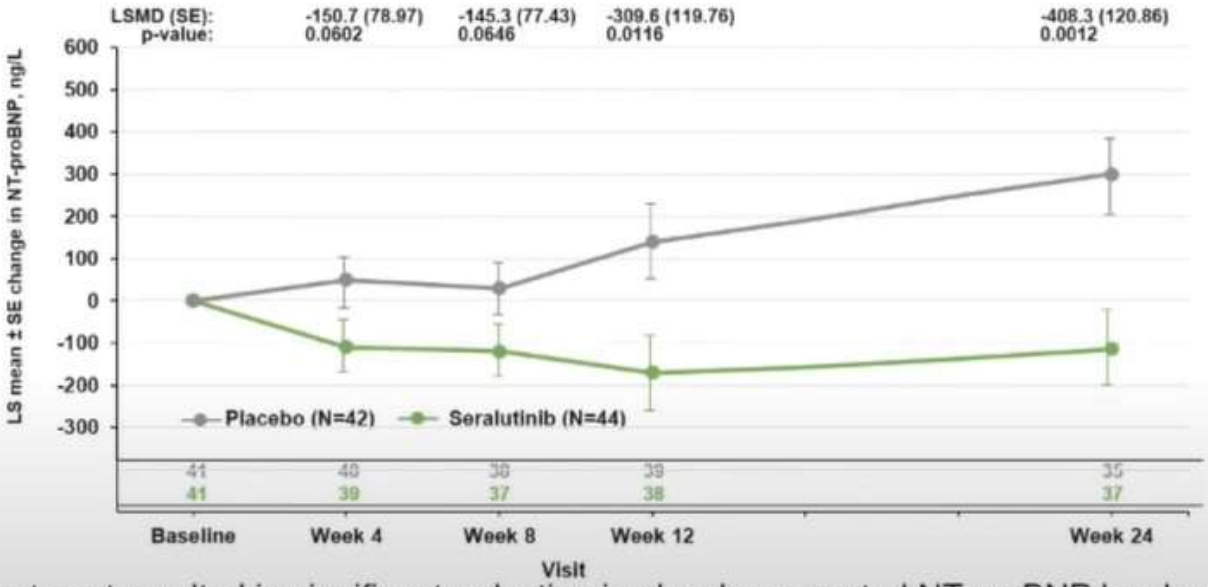
- Platelet-derived growth factor receptor (PDGFR) α/β, colony stimulating factor 1 receptor (CSF1R), and stem cell factor receptor (c-KIT) pathways may be aberrant in PAH patients
- Seralutinib is an inhibitor of PDGFRα/β, CSF1R, and c-KIT delivered via inhalation
- WHO Group 1 Pulmonary Hypertension who are classified as FC II or III
- 80 patients
- Primary : change from baseline to Week 24 in PVR by RHC

Seralutinib – Torrey Study



- In the overall population, seralutinib significantly reduced PVR at Week 24 vs placebo (14.3%, p=0.0310) (**A**)
- Seralutinib displayed a trend toward slightly greater PVR reductions in FC III patients (**B**)

Change in NT-proBNP



- Seralutinib treatment resulted in significant reduction in placebo corrected NT-proBNP levels at Week 12 (-309.6 ng/L, p=0.0116) and Week 24 (-408.3 ng/L, p=0.012)

IMPRES

- Imatinib in IPAH
- Patients with pulmonary vascular resistance ≥ 800 dyne·s·cm symptomatic on ≥ 2 PAH therapies
- Primary outcome was change in 6-minute walk distance
- After 24 weeks, the mean placebo-corrected treatment effect on 6-minute walk distance was 32 m, (95% confidence interval, 12-52; P=0.002)
- Pulmonary vascular resistance decreased by 379 dyne·s·cm
- Functional class, time to clinical worsening, and mortality – no difference
- Serious adverse events and discontinuations were more frequent with imatinib than placebo

Hoeper Mmetal., Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation. 2013 Mar 12;127(10):1128-38. doi: 10.1161/CIRCULATIONAHA.112.000765. Epub 2013 Feb 12.

Inhaled drugs

Inhaled Trepostinil	Inhaled imatinib	Inhaled seralutinib
Breeze – phase 1 study (DPI)	IMPAHCT – phase 2b	
INSPIRE – open label study		
Liposomal suspension – phase 3		
Trepostinil palmitil inhalation powder - pro drug		

RT234 Vardenafil inhalation for PAH

- Inhaled therapy for SOS use to improve exercise tolerance and to relieve episodic symptoms
- Rapid reduction in PVR which is sustained for around 60 mins.
- Currently recruiting patients for phase 2b trial

Vizza

- IPAH & CTD-PH
- taking bosentan (stable dose for ≥3 months) were randomized (1:1) to sildenafil or placebo
- primary endpoint was change from baseline in 6-min walk distance (6MWD) at week 12
- Sildenafil, in addition to stable (≥3 months) bosentan therapy, had no benefit over placebo for 12-week change from baseline in 6MWD

Thank you