PHARMACOLOGIC MANAGEMENT OF PULMONARY HYPERTENSION OTHER THAN IDIOPATHIC CATEGORY

DM Seminar

13.11.2021

OUTLINE

- Introduction
- PH-LHD
- CLD-PH
- CTEPH-PH
- GROUP 1-PH
- GROUP 5-PH
- Summary

PULMONARY HYPERTENSION

- Pulmonary hypertension is defined as a mean pulmonary arterial pressure (mPAP) greater than 20 mm Hg at rest as per the Sixth World Symposium on Pulmonary Hypertension in 2018

- This cut-off was determined after analyzing 1187 patients from 47 studies, the cut-off is independent of sex and ethnicity and slightly affected by age and posture

- In defining pre-capillary PH, Pulmonary vascular resistance[PVR] is taken into account and >3 WU is set as an arbitrary cut-off

Kovacs et al. *ERS* 34.4 (2009): 888-894

HEMODYNAMIC DEFINITIONS OF PULMONARY HYPERTENSION (PH)

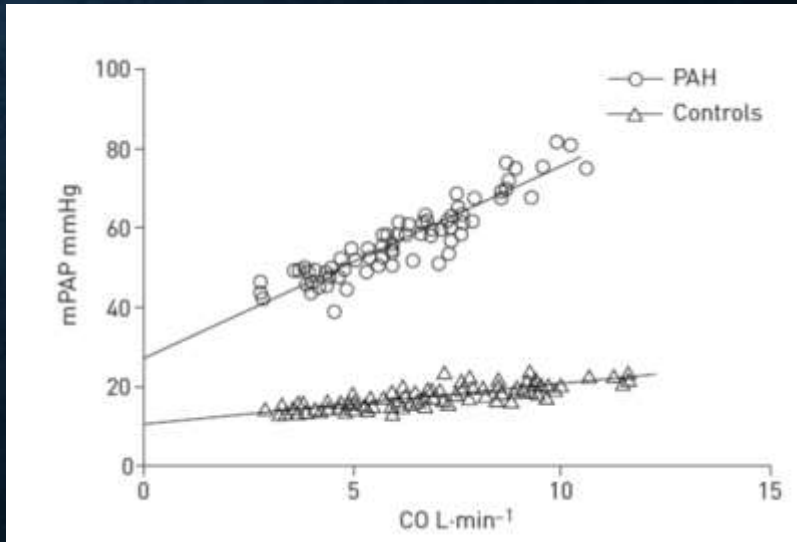
Definitions	Characteristics	Clinical groups
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR ⩾3 WU	1, 3, 4 and 5
Isolated post-capillary PH (IpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR <3 WU	2 and 5
Combined pre- and post-capillary PH (CpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩾3 WU	2 and 5

Simonneau et al. *ERJ* 53.1 (2019).

Simonneau, Gérald, et al. *ERJ* 53.1 (2019)

COMPONENT OF EXERCISE

- A rise in resting PH pressure is a late event in the natural history of PVDs, because of microvascular “reserves”
- PAP rises only when ⩾50% of the microcirculation has been lost
- Multipoint mPAP–CO
- In general, mPAP rises by ⩾1 mmHg per litre of CO in normal subjects; PVD patients have a rise of ⩾3 mmHg per litre of CO, reflecting increased resistance
- Impractical as a clinical routine
- Difficult to define what is normal and abnormal



Simonneau, Gérald, et al. *ERJ* 53.1 (2019)

EVALUATION OF PULMONARY HYPERTENSION

- History and physical examination
- Blood tests
- PFTs
- 6MWT [minimal clinically important difference- 30 metres]
- CPET
- Nocturnal oximetry and sleep testing
- ECG and 2D ECHO
- CMR
- VQ scan
- CT chest
- RHC

Simonneau, Gérald, et al. *ERJ* 53.1 (2019)

PH DUE TO LEFT HEART DISEASE[PH-LHD]

- PH-LHD is the most common cause of PH
- PH-LHD- IpcPH and CpcPH
- Outdated terms now- pulmonary venous hypertension, out-of-proportion PH, mixed PH, and passive versus reactive PH
- Genetic predisposition in CpcPH
- Transpulmonary gradient (TPG) >12 mmHg
- Diastolic pressure gradient (DPG) ≥7 mmHg

Christelle et al. *Journal of AHA* (2021): e020633

IPCPH-ETIOLOGIES

- HFrEF
- HFmrEF
- HFpEF
- Valvular heart disease
- Cardiomyopathies
- Arrythmias

Christelle et al. *Journal of AHA* (2021): e020633

WHEN TO SUSPECT PH-LHD

- Heart disease + loud P2 or a parasternal heave, echo estimated PASP exceeds 35 mmHg, or cardiac imaging suggests right ventricular (RV) or right atrial dilation, RV dysfunction, moderate to severe tricuspid regurgitation, or interventricular septal flattening
- RHC is indicated if any one of the following is present
- Evidence of right ventricular (RV) dysfunction - include RV dilation, RV free wall hypokinesis, or interventricular septal flattening
- The cause of PH is unclear or more than one cause is suspected
- Advanced HF therapies are being considered

Lteif, Christelle et al. *Journal of AHA* (2021): e020633

Clinical and Biological Insights Into Combined Post- and Pre-Capillary Pulmonary Hypertension

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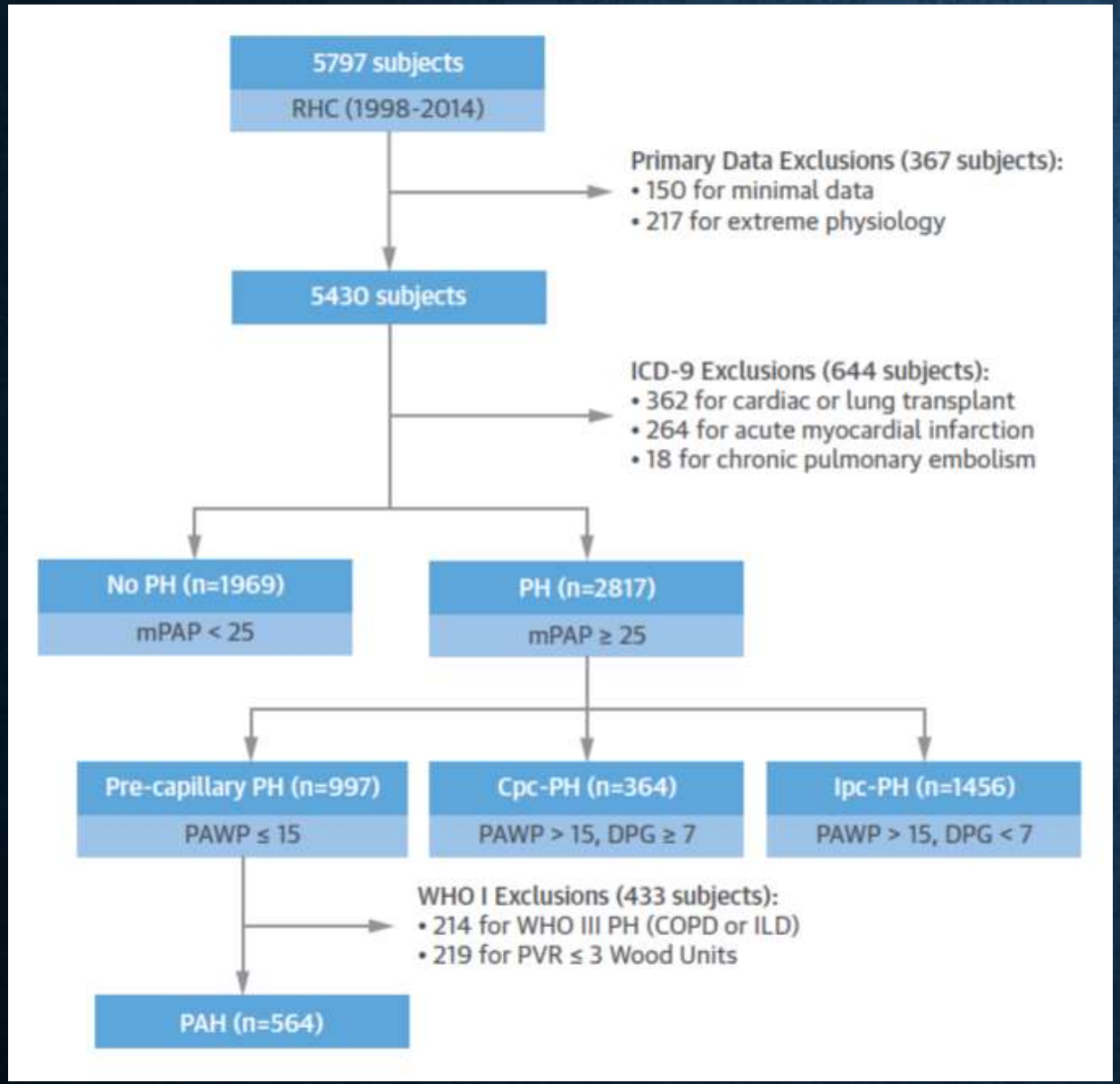
ABSTRACT

BACKGROUND Pulmonary hypertension (PH) is a common and morbid complication of left heart disease with 2 subtypes: isolated post-capillary pulmonary hypertension (Ipc-PH) and combined post-capillary and pre-capillary pulmonary hypertension (Cpc-PH). Little is known about the clinical or physiological characteristics



- Whole exome was done in 297 patients
- Tissue specific gene expression profiles was done in 447 patients

	PAH (n = 564)	Cpc-PH (n = 364)	Ipc-PH (n = 1,456)
Age, yrs	55 ± 15	56 ± 14	62 ± 14*
Female	69†	49	43*
BMI, kg/m^2 (n = 1,909)	29 ± 7†	32 ± 9	31 ± 8
Race			
White	78	72	83*
Black	17	21	13*
Other	5	7	4*
Comorbidities			
Hypertension	64†	80	85
Diabetes mellitus	24†	49	49
Obesity	35†	54	48
CAD	45†	66	81*
COPD	0†	16	14
ILD	0†	9	3*
OSA	7†	15	14
Anemia	34†	51	61*
ASD	8	6	5
Atrial fibrillation	18†	32	45*
Valvular disease	7	9	8
Heart failure	50†	65	64
Lupus	4†	1	1
Scleroderma	11†	3	<1

Medications			
Anticoagulant agents	38	38	38
Lipid-lowering medications	27†	42	55*
CCBs	15	15	16
Beta-blockers	22†	43	51*
ACE inhibitors	20	25	31*
ARBs	7†	15	13
Diuretic agents	58†	72	73
ERAs	11†	3	<1*
PDE5 inhibitors	10†	6	2*
Prostacyclins	13†	4	<1*
Laboratory tests			
BNP, pg/ml (n = 1,691)	637 ± 894†	970 ± 1,216	945 ± 1,125
GFR, ml/min/1.73 m^2 (n = 2,347)	68 ± 25†	65 ± 34	61 ± 29
Hemoglobin, g/dl (n = 2,333)	13.6 ± 2.2†	12.7 ± 2.3	12.1 ± 2.1*
Glycosylated hemoglobin, % (n = 1,364)	6.3 ± 1.4†	6.7 ± 1.6	6.5 ± 1.4*

	N	PAH (n = 484)	Cpc-PH (n = 312)	Ipc-PH (n = 1,222)
LVEDD, cm	1,996	4.3 ± 1.1*	5.2 ± 1.4	5.4 ± 1.2†
LVESD, cm	1,947	2.9 ± 1.2*	4.0 ± 1.7	4.1 ± 1.5†
LV IVS thickness, mm	1,730	11 ± 3*	12 ± 3	12 ± 3
LA diameter, cm	1,935	3.9 ± 0.8*	4.5 ± 0.9	4.7 ± 0.8†
LV ejection fraction, %	1,991	51 ± 12*	42 ± 19	40 ± 19
LV mass index, g/m^2	1,644	86 ± 41*	113 ± 51	124 ± 47†
LVH	1,975	23*	33	35
LAE	1,935	40*	69	78*

	N	PAH (n = 564)	Cpc-PH (n = 364)	Ipc-PH (n = 1,456)
Heart rate, beats/min	1,318	78 ± 14*	82 ± 16	76 ± 16†
Systolic BP, mm Hg	2,167	126 ± 24	128 ± 26	126 ± 26
Diastolic BP, mm Hg	2,125	76 ± 16	76 ± 13	70 ± 14†
Mean RA pressure, mm Hg	2,200	8 ± 5*	14 ± 7	12 ± 6†
Systolic PA pressure, mm Hg	2,293	72 ± 23	69 ± 20	53 ± 13†
Diastolic PA pressure, mm Hg	2,294	29 ± 11*	34 ± 8	23 ± 6†
Mean PA pressure, mm Hg	2,293	45 ± 14*	47 ± 11	36 ± 8†
PAWP, mm Hg	2,187	9 ± 4*	22 ± 5	24 ± 6†
DPG, mm Hg	2,147	19 ± 12*	12 ± 6	-1 ± 5†
Transpulmonary gradient, mm Hg	2,146	35 ± 15*	25 ± 10	12 ± 5†
PVR, Wood units	2,175	8.6 ± 5.0*	5.8 ± 3.2	2.6 ± 1.6†
Cardiac index, l/min/m^2	2,018	2.5 ± 0.8	2.5 ± 0.8	2.7 ± 0.9†
Stroke volume, ml	1,105	60 ± 24	64 ± 30	71 ± 30†
PA oxygen saturation, %	2,051	64 ± 9*	61 ± 10	63 ± 10†
Pulmonary arterial compliance, ml/mm Hg	1,036	1.6 ± 1.0*	2.4 ± 1.8	2.7 ± 1.7†
RC time, s	1,013	0.67 ± 0.22*	0.61 ± 0.28	0.37 ± 0.19†

OUTCOMES

- the risk of death was no different in patients with Cpc-PH versus patients with Ipc-PH (hazard ratio [HR]: 1.14; 95% CI: 0.96 to 1.35; p-0.15)
- Significant Gene Ontology Groups identified for the 141 genes associated with Cpc-PH and PAH compared with Ipc-PH control subjects

Gene
PARVB, FLII, SSH3, SYNE2, LIMCH1, MYO9B, MACF1, MYH11
ROPN1B, MOSPD3, FLG, RPSA, CCDC108, COL4A3, COL11A2, COL18A1, LAMA5, MYH11
COL18A1, COL4A3, COL11A2, FREM1, LAMA5
COL18A1, COL4A3, FREM1, LAMA5
SHMT1, ALDH1L1
UTP14C, RPSA
HLA-DPA1, HLA-DPB1

MANAGEMENT

- Adequate treatment of LHD can reduce the mPAP and is shown to have mortality benefit
- Beta blockers, ACE inhibitors, ARBs, SGLT-2 inhibitors, ARNIs, Spironolactone, Diuretics– HFrEF
- SGLT-2 inhibitors and co-morbidity management – HFpEF
- Device therapy

PAH TARGETED DRUGS-ERA

Study	Drug	Population	Primary outcome	Result
REACH-I trial [2005] [n=370]	Bosentan 500mg BD – 26 weeks	NYHA III-IV LVEF<35% 6MWT >375m	Death, hospitalization, NYHA class change	Terminated early due to **liver toxicity**
ENABLE trial [2002] [n=1613]	Bosentan 125mg BD	NYHA III-IV LVEF<35% 6MWT >375m	Clinical status at 9 months	**No improvement**, increased fluid retention
Kaluski et al [2008] [n=94]	Bosentan 125mg BD	NYHA III-IV LVEF<35% SPAP>40 mmHg	SPAP at 20 weeks	**No significant improvement**
MELODY-1 trial [2018] [n=94]	Macitentan 10mg OD- 12 weeks	CpcHF NYHA-II or III LVEF>30%	Fluid retention and NYHA class change	**More fluid retention**
HEAT trial [2002] [n=157]	Darusentan 30,100,300mg OD- 3 weeks	NYHA III LVEF<35% PAWP>12 mmHg CI<2.6L/min/m2	CI PAWP	Mild improvement in CI after 3 weeks of treatment
EARTH trial [2004] [n=642]	Drausentan 10mg to 300mg OD – 24 weeks	NYHA II-III LVEF<35%	LVEF	**No significant improvement at 6 months**

PAH TARGETED DRUGS-PDE5 INHIBITORS

Study	Drug	Population	Primary outcome	Result
Lewis et al [n=34] [2007]	Sildenafil 25 mg TDS to 75mg TDS-12 weeks	LVEF<40% NYHA-II-IV mPAP>25 mmHg	VO2	**Improvement of VO2 at peak exercise**
Behling et al [n=19] [2008]	Sildenafil 50mg TDS-4weeks	LVEF<40%	CPET parameters Echo-SPAP Pleth derived forearm blood flow	Decrease in SPAP
Guazzi et al [n=44] [2011]	Sildenafil 50mg TDS	LVEF>50% SPAP-40mmHg	Pulmonary hemodynamics RV performance	**Significant improvements**
Guazzi et al [n=44] [2011]	Sildenafil 50mg TDS	HF with mild to moderate PH[Mpap-25-35] EOB	EOB changes Hemodynamic measurements	**Improvements in EOB, mPAP, PAWP and PVR**
RELAX study [n=216] [2013]	Sildenafil 20mg TDS-12 weeks f/b 60mg TDS-12 weeks	NYHA II-IV NT-ProBNP>400	Change in peak oxygen consumption after 24 weeks	No improvement
Hoendermis et al [n=52] [2015]	Sildenafil 60mg TDS-12 weeks	mPAP>25 mmHg PAWP>15mmHg LVEF>45%	mPAP change	No improvement
SIOVAC study [n=200] [2018]	Sildenafil 40mg TDS-24 weeks	mPAP>30mmHg HF stable, valvular heart disease corrected	Death HF hospitalization NYHA class	Worsening of clinical outcomes

PAH TARGETED DRUGS- SGC STIMULATORS

Study	Drug	Population	Primary outcome	Result
LEPHT trial [phase IIb] [n=201] [2013]	Riociguat 0.5, 1, 2 mg TDS-16 weeks	LVEF<40% mPAP>25mmHg	Changes in mPAP	**No improvement**
DILATE 1 trial [n=39] [2014]	Riociguat 0.5, 1, 2 mg OD-16 weeks	LVEF<40% mPAP>25mmHg PAWP>15mmHg	Changes in mPAP	**No improvement**
SOCRATES-REDUCED study [n=456] [2015]	Vericiguat 1.25, 2.5, 5 10 mg OD-12 weeks	LVEF<45%	Changes in NT-ProBNP	**No improvement**
SOCRATES-PRESERVED study [n=477] [2017]	Vericiguat 1.25, 2.5, 5 10 mg OD-12 weeks	LVEF<45%	Changes in NT-ProBNP	**No improvement**
VICTORIA [n=5050] [2020]	Vericiguat 10 mg OD	NYHA II-IV LVEF <45% Elevated NT levels	Death First hospitalization	**Reduction in primary outcome event** **Increased incidence of anemia and syncopal events**

OTHER DRUGS

- FIRST study[1997] - IV Epoprostenol – terminated early due to decreased survival
- HELP trial [2021] – IV Levosimendan - exercise-PCWP- No improvement but increased 6MWD [n=36]
- Oral sodium nitrite- pending
- Mirabegron- pending
- Pulmonary artery denervation[PADN]- catheter based technique, successful in animal studies, PHASE II trial in humans began in September 2017

LVAD

Study	Sample size	Inclusion	End points	Hemodynamic results
Zimpfer et al [2007]	35 patients	HTPL candidates with PH	PVR	**PVR was significantly reduced** regardless of continuous or pulsatile LVAD device
Mikus et al [2011]	145 patients	HTPL candidates with CpcPH and IpcPH	mPAP, PVR, TPG	**mPAP, PVR, and TPG was decreased significantly**
Kumarsinghe et al [2018]	24 patients	HTPL candidates with CpcPH	TPG, PVR, and all-cause mortality	**TPG and PVR was improved** with continuous flow LVAD, No difference in mortality

MITRACLIPS AND CARDIOMEMS

Study	Sample size	Inclusion	End points	Hemodynamic results
Abraham WT et al [2011]	550 cases	NYHA III irrespective of LVEF	HF hospitalisation	37% reduction of HF hospitalizations at 15 months
EVEREST II trial [2012]	78 cases	Symptomatic severe MR	NYHA class, MR grade, LVESV, LVEDV, and 12-month mortality	Decreased MR grade, LVEDV, and LVESV, suggestive of LV reverse remodeling, no mortality benefit
Stone GW et al [2018]	614 cases [medical vs mitraclip]	Symptomatic severe MR	HF hospitalization and all-cause mortality	Reduction in hospitalization and all-cause mortality
Hunlich M et al [2018]	70 cases [CARDIOMEMS]	Severe MR with PH-LHD	TR, sPAP, and TAPSE	Improvement in TR, sPAP, and TAPSE

PH-LHD

- PAH specific therapies are generally not recommended in this group
- PDE-5 inhibitors have shown some benefit, however use with caution when combined with other heart failure medications
- Device therapies do improve pulmonary hemodynamics but are not indicated solely to target a reduction of PAP
- CARDIOMEMS-HF system is a unique personalised PAP monitor that can guide diuretic therapy

PH DUE TO LUNG DISEASE AND/OR HYPOXEMIA

- Obstructive lung disease (eg, chronic obstructive pulmonary disease or bronchiectasis)
- Restrictive lung disease (eg, interstitial lung disease, kyphoscoliosis)
- Other lung disease with mixed obstruction and restriction (eg, pulmonary fibrosis with emphysema)
- Hypoxia without lung disease (eg, high altitude, sleep-disordered breathing, obesity hypoventilation)
- Developmental lung disorders (eg, bronchopulmonary dysplasia, congenital lobar emphysema)

GENERAL MEASURES

- Treatment of associated condition
- Conventional and supportive therapies
- Exercise, cessation of smoking, vaccination
- Oxygen
- Diuretics

RHC-WHEN TO DO?

- Patients with CLD when significant PH is suspected and the patient's management will likely be influenced by RHC results [referral for transplantation, inclusion in clinical trials, treatment of unmasked LV dysfunction, or compassionate use of therapy]

- RHC may be considered when clinical worsening, progressive exercise limitation and/or gas exchange abnormalities are not deemed attributable to ventilatory impairment or an accurate prognostic assessment is deemed sufficiently important

Nathan, Steven D., et al. *ERJ* 53.1 (2019).

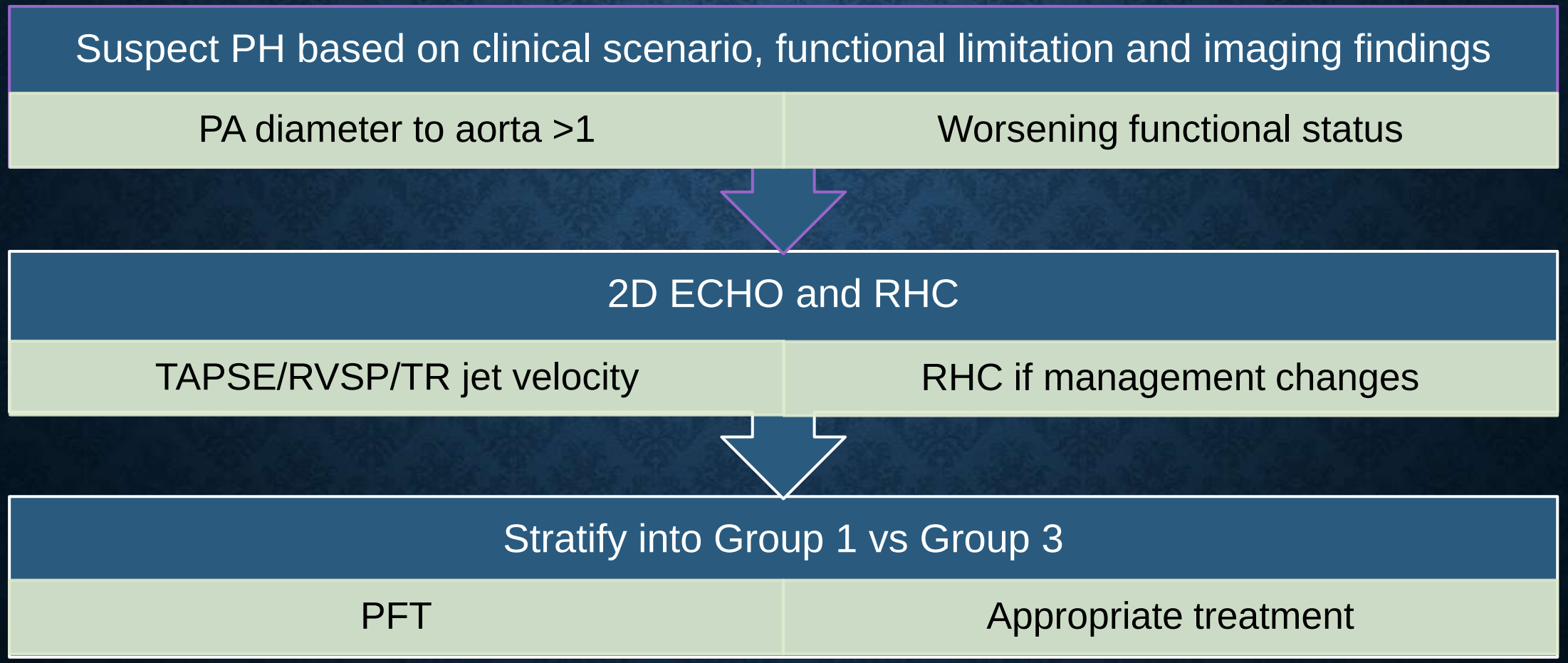
CLD-PH

- A floating average over several breaths is suggested to measure mean pressures- exaggerated variations in pressures in intrathoracic pressures in a breath cycle
- Definition is as follows

CLD *without* PH: mPAP < 21 mm Hg, or mPAP 21–24 mm Hg with PVR < 3 WU
CLD *with* PH: mPAP 25–34 mm Hg, or mPAP 21–24 mm Hg with PVR ≥ 3 WU
CLD *with severe* PH: mPAP ≥ 35 mm Hg, or mPAP ≥ 25 mm Hg with low cardiac index (<2.0 L/min/m^2).

Nathan, Steven D., et al. *ERJ* 53.1 (2019).

APPROACH TO CLD-PH



COPD

- Assessment of PH should be carried out in a stable patient, not during exacerbations
- ECHO has a sensitivity of 85% and specificity of 55% when compared to RHC in PH-Group 3
- PH was usually mild and moderate
- Less than 4% has a mean PAP of more than 35mmHg in COPD cases
- Those who are detected not to have PH, tend to develop PH with disease progression
- In patients with PH, severity correlates with development of PH

Arcasoy, Selim M., et al. AJRCCM167.5 (2003): 735-740.

PH SPECIFIC THERAPIES-COPD

Study	Infusion and dose	Inclusion	End points	Hemodynamic results
Naeije et al [1982] [n=26] ATS	$PgE_{1,}$ 0.02-0.04 µg/kg/min	Decompensated COPD	Cardiac index TO2[Oxygen delivery to tissues]	Improvement in CI and TO2 **No improvement** in vascular pressures Increased side effects
Archer et al [1996] [n=16] CHEST	$PGI_{2,}$ 2 to 12 ng/kg/min	Acute respiratory failure in COPD	PVR PaO2	Tachyphylaxis within 24 hours **Increased side effects** Decrease in PaO2
Dernaika et al [2009] [n=10]	Nebulized Iloprost 2.5-5µg	FEV1<65% FEV1/FVC<70% RV morphological changes + RVSP>35 mmHg	D[A–a]O2 Ve/VCO2 Ve/VO2 6MWT DLCO	**Decreased Ve** **6MWT improvement [35m]** **Narrowing of D[A–a]O2**

Study	Drug	Inclusion	End points	Hemodynamic results
Blanco et al [2010] [n=20] ATS	Sildenafil [20 vs 40 mg] –single dose	COPD PH proven by RHC	mPAP at rest and exercise PaO2 V/Q relationship	Decrease in mPAP No change in PaO2 and V/Q
Rao et al [2011] [n=33]	Sildenafil 20 mg TDS- 12 weeks	GOLD III–IV Echo: sPAP >40 mmHg	6MWD sPAP	**6MWT- increased by190 m** Decrease in sPAP
Blanco et al [2013] [n=60] ATS	Sildenafil 20 mg or placebo 3 times daily- 3 months	RHC-mPAP ⩾25 mmHg; Echo-sPAP ⩾35 mmHg	Exercise endurance time	**No improvement**
Goudie et al [2014] [n=120]	Tadalafil 10 mg OD-12 weeks	COPD PH-Echo	6MWD, sPAP, QoL, BNP, SaO2	**No improvement**
Vitulo et al [2016] [n=28]	Sildenafil 20 mg TDS- 16 weeks	RHC-mPAP >35 mmHg (if FEV1 <30%), mPAP ⩾30 mmHg (if FEV1 ⩾30%)	PVR, CI, BODE scores, QoL	PVR reduced Improved CI, BODE scores and QoL
Stolz et al [2008] [n=30]	Bosentan 125 mg BD- 12 weeks	GOLD III–IV Echo diagnosed PH	6MWD QOL	**6MWD- no change** **Worsened hypoxaemia** and health-related QoL

ILD

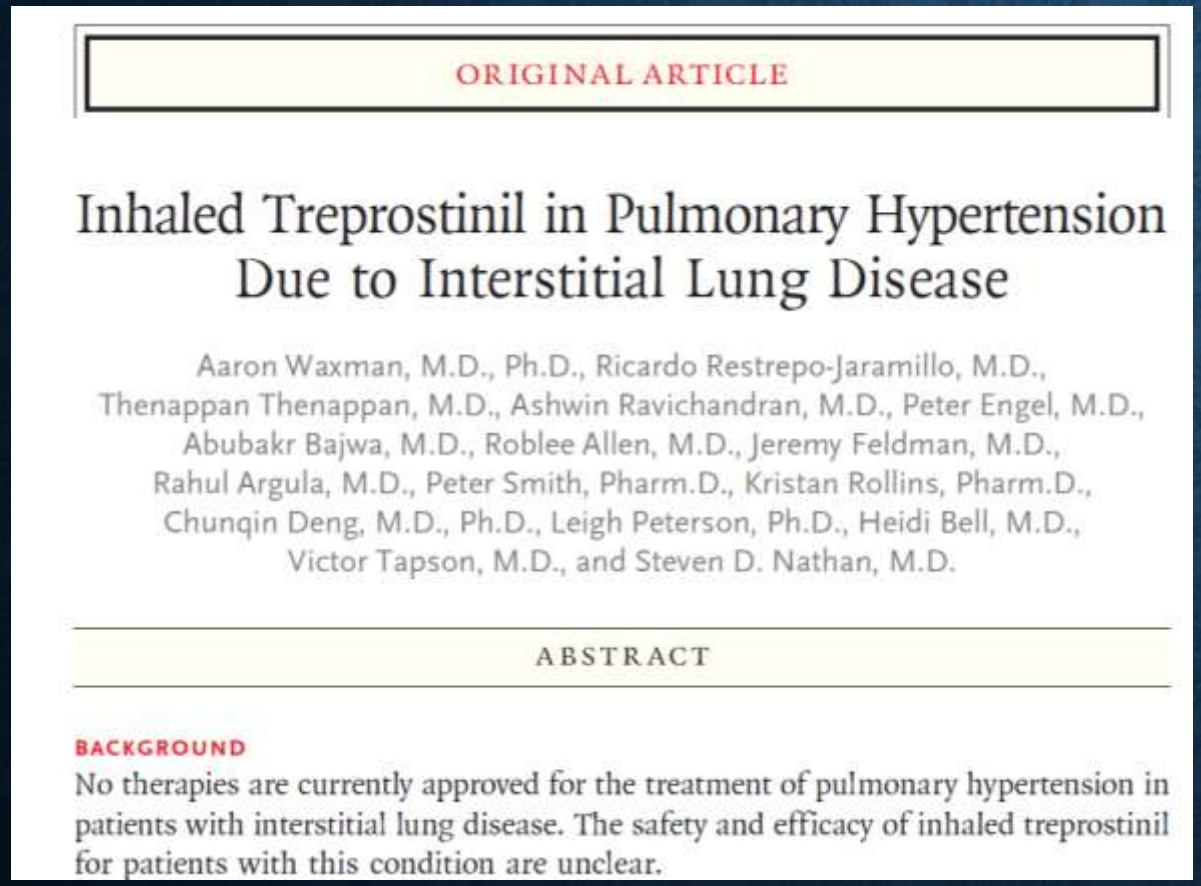
- Most of the data in literature emanates from IPF
- PH incidence increases as severity of IPF increases
- There is limited correlation with between PH severity and lung function impairment or high-resolution CT fibrosis score [distinct gene signatures have been observed in IPF-PH lungs]
- CPFE- PH is a significant contributor to functional limitation and mortality

Mejía, Mayra, et al. *Chest* 136.1 (2009): 10-15
Nathan, Steven D., et al. *ERJ* 53.1 (2019).

ILD

Study	Drug	Inclusion	End points	Hemodynamic results
Zisman et al [2010][n=180]	Sildenafil 20mg TDS-12-24 weeks	IPF [DLCO<35%]	6MWD	**No improvement**
Han et al [2013][n=119]	Sildenafil 20mg TDS-12 weeks	IPF and RVD	6MWD	Reduced decline in treatment arm
Hoeper et al [2015][n=133]	PDE-5 monotherapy-13 weeks	IIP [mPAP>25]	6MWD	Improvement
BUILD-3 trial [2011][n=616]	Bosentan 62.5 to 125mg BD- 3years	IPF	Time to IPF worsening or death	**No improvement**
ARTEMIS-IPF trial[2013][n=492]	Ambrisentan 10mg OD vs placebo	IPF	Time to IPF worsening, hospitalization or death	**Terminated early**
RISE-IIP [2019][n=147]	Riociguat 0.5-2.5mg TDS	IIP [mPAP>25 mmHg]	6MWD	**Terminated early**
Saggar et al [2014] [n=15]	SC/IV Treprostinil	ILD [mPAP>25 mmHg and PVR>3WU]	Hemodynamic parameters	mPAP decreased PVR decreased CI increased
PULSE INO [2020] [N=41]	30 µg/kg inhaled NO -8 weeks	ILD [mPAP>25 mmHg and PVR>3WU]	MVPA	Improved actigraphy

ILD-INCREASE TRIAL



ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

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ABSTRACT

BACKGROUND

No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. The safety and efficacy of inhaled treprostinil for patients with this condition are unclear.

- Inhaled Treprostinil VS Placebo
- n=326
- NEJM Jan 2021
- 72 microgram QID
- IIP-40%, CPFE-25%, CTD-ILD-25%, chronic HP-6%
- Diagnosis was made on CT [not biopsy]
- 80% were not on anti-fibrotics
- **Improved 6MWD** [+21 m in the treatment arm and -10m in the placebo arm
- **Decrease in mean NT-proBNP**

SLEEP DISORDERD BREATHING AND HYPOXIA

- PH is usually mild in this group of patients
- Nasal CPAP reduced PASP from 29 to 24 mmHg after 12 weeks of therapy
- Effect was highest in patients with higher PASP at baseline
- Surgical methods of weight loss also improved pulmonary hemodynamics
- Pharmacotherapy has not been evaluated

Arias, Miguel A., et al. *ERJ* 27.9 (2006): 1106-1113

GROUP 3-APPROACH

Disease	Approach
COPD	No PH specific therapies
ILD	No PH specific therapies ?Inhaled Iloprost
Sleep disordered breathing	No PH specific therapies

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)

- Pulmonary thromboendarterectomy (PTE) is the only potentially curative therapy
- Patients not suitable candidates for PTE
- have persistent pulmonary hypertension (PH) after PTE
- A bridge to PTE [uncommon]

PTE-SUITABLE OR NOT

- Is there significant hemodynamic or exercise impairment? [>3 WU with or without exercise] [3-15 WU]
- Are the chronic thromboemboli accessible to surgery? [DSPA>CTPA-MRPA] [Proximal disease more amenable than distal]
- What is the anticipated postoperative hemodynamic outcome? [Weaning from cardiopulmonary bypass and ventilation]
- Are there comorbid conditions affecting surgical candidacy?
- Are there patient preferences that impact the decision?

Piazza et al NEJM 364.4 (2011): 351-360
Fedullo, Peter, et al. AJRCCM 183.12 (2011): 1605-1613

PH-SPECIFIC THERAPIES

- **NYHA class I** – Supportive management and regular follow up

- **NYHA class II-III** – Riociguat is the preferred drug in this category [CHEST 1 and CHEST 2 study]
- ERAs are an acceptable second option
- PDE5 inhibitors have not shown any benefit
- Initiation with dual therapy has not shown better outcomes when compared to monotherapy

- **NYHA IV**- Parenteral prostanoids

ORIGINAL ARTICLE

Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

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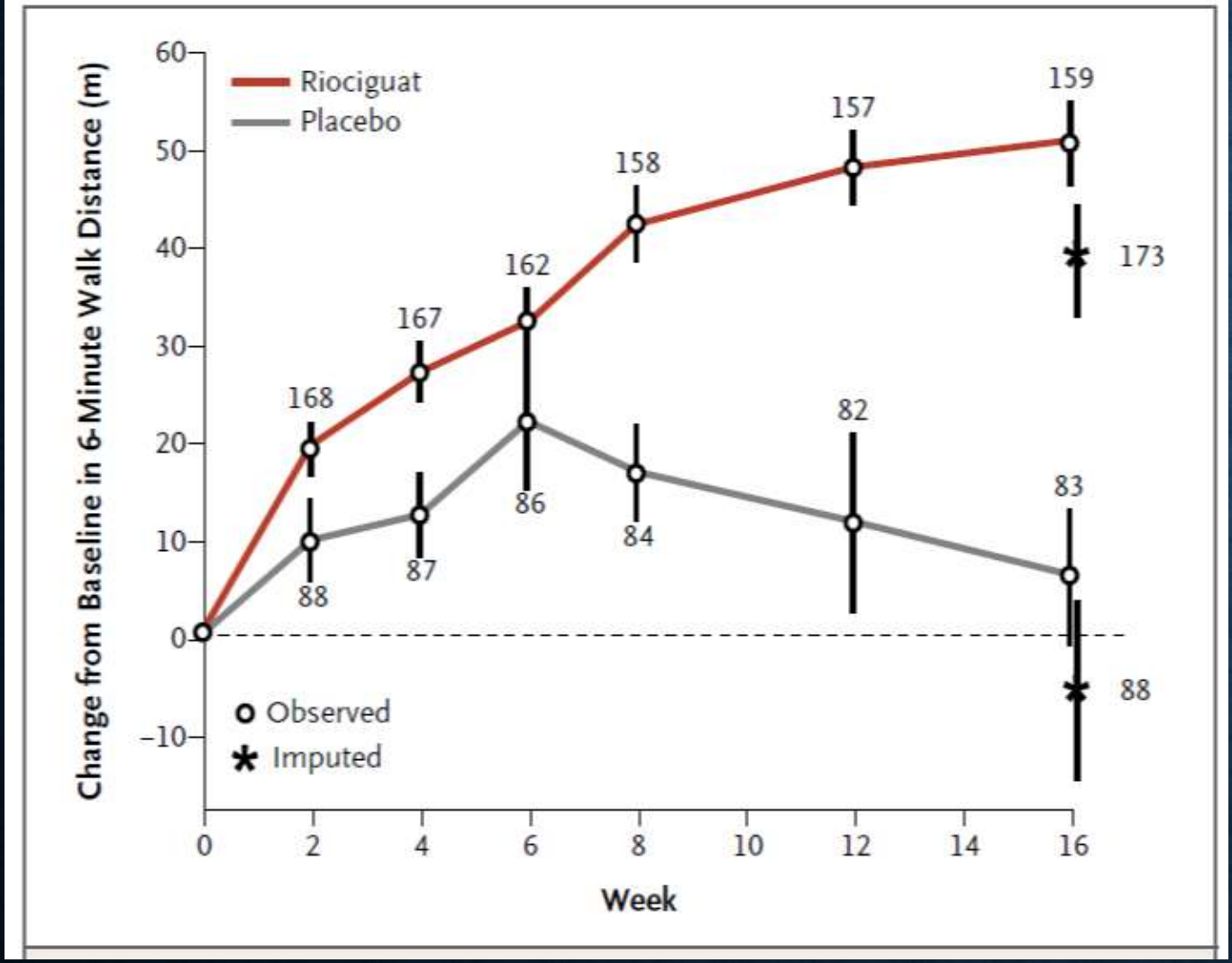
ABSTRACT

BACKGROUND

Riociguat, a member of a new class of compounds (soluble guanylate cyclase stimulators), has been shown in previous clinical studies to be beneficial in the treatment of chronic thromboembolic pulmonary hypertension.

- phase 3, multicenter, randomized, double-blind, placebo-controlled study
- 261 patients
- To receive placebo or riociguat
- The primary end point was 6MWD



6MWD had increased by a mean of **39 m** in the riociguat group, as compared with a mean decrease of **6 m** in the placebo group (least-squares mean difference, **46 m**; 95% confidence interval [CI], 25 to 67; P<0.001)

Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2)

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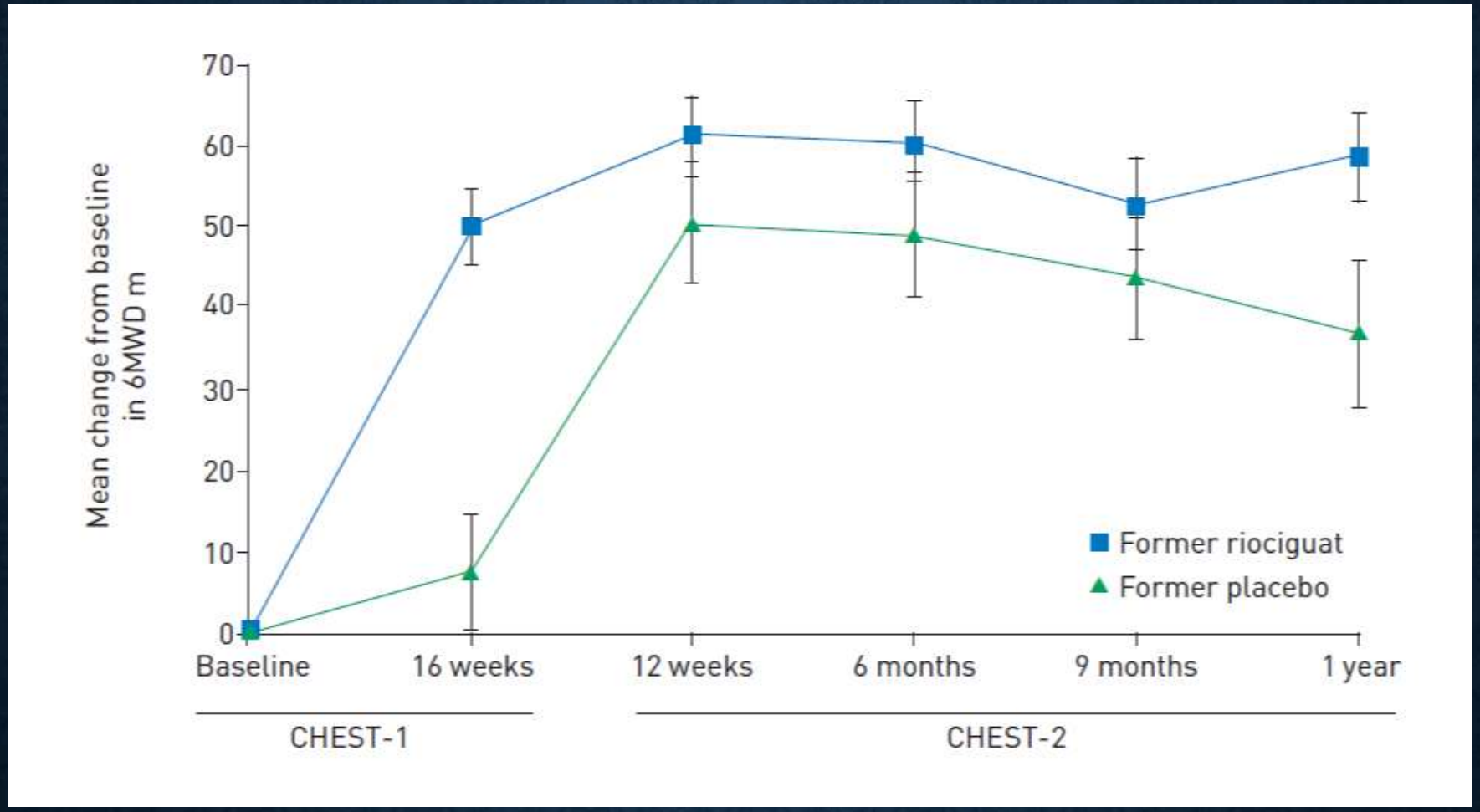
114 patients in Riociguat group were followed up from CHEST 1 study



CHEST 1 study participants were followed up for 1 year and found to have persistent Improvement in 6MWD
Improvement in NT-proBNP levels and Borg dyspnea scale

CTD RELATED PH

- CTD-ILD with pulmonary hypertension are at a greater risk of mortality when compared with those that do not develop PH
- PH is known to occur in a lot of ILDs most notably in systemic sclerosis
- Immunosuppression is a key part in managing CTDs

Comparison of Treatment Response in Idiopathic and Connective Tissue Disease–associated Pulmonary Arterial Hypertension

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Abstract

Rationale: Studies suggest that patients with connective tissue disease–associated pulmonary arterial hypertension (CTD-PAH) have a poorer treatment response to therapies for PAH compared with patients with idiopathic PAH (IPAH), but individual

Measurements and Main Results: The study sample included 827 participants with CTD-PAH and 1,935 with IPAH from 11 RCTs. Patients with CTD-PAH had less improvement in 6MWD when assigned to active treatment versus placebo compared with patients with IPAH (difference in treatment effect on Δ6MWD in CTD-PAH vs. IPAH, −17.3 m; 90% confidence interval, −31.3 to −3.3; *P* for

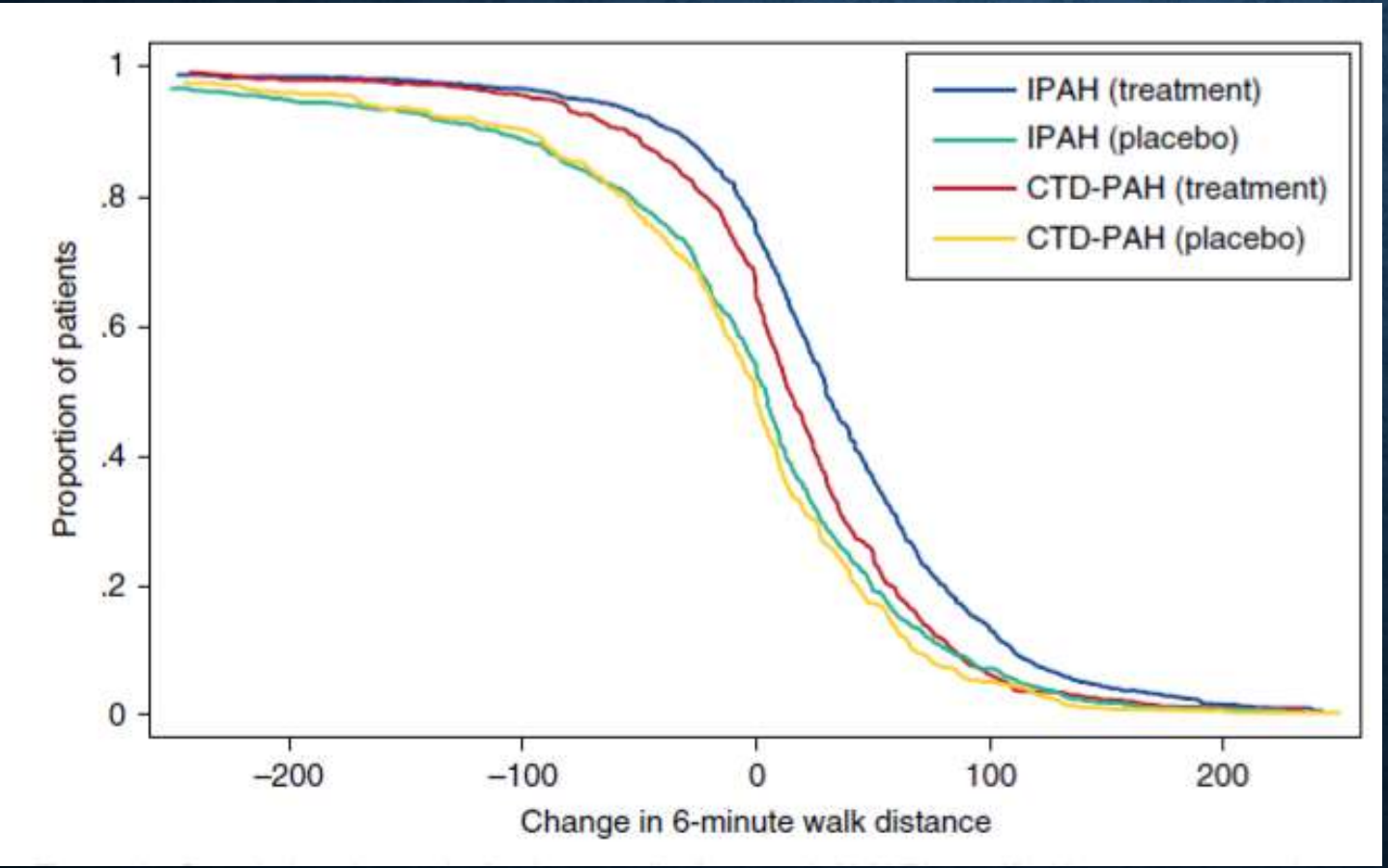
Ambrisentan (ARIES-1 and ARIES-2)
Bosentan (BREATHE-1)
Iloprost (AIR)
Macitentan (SERAPHIN)
Riociguat (PATENT-1)
Sildenafil (SUPER)
Sitaxsentan (STRIDE-1, STRIDE-2, and STRIDE-4)
subcutaneous Treprostinil

2000-2013

PATIENT POPULATION AND DRUG

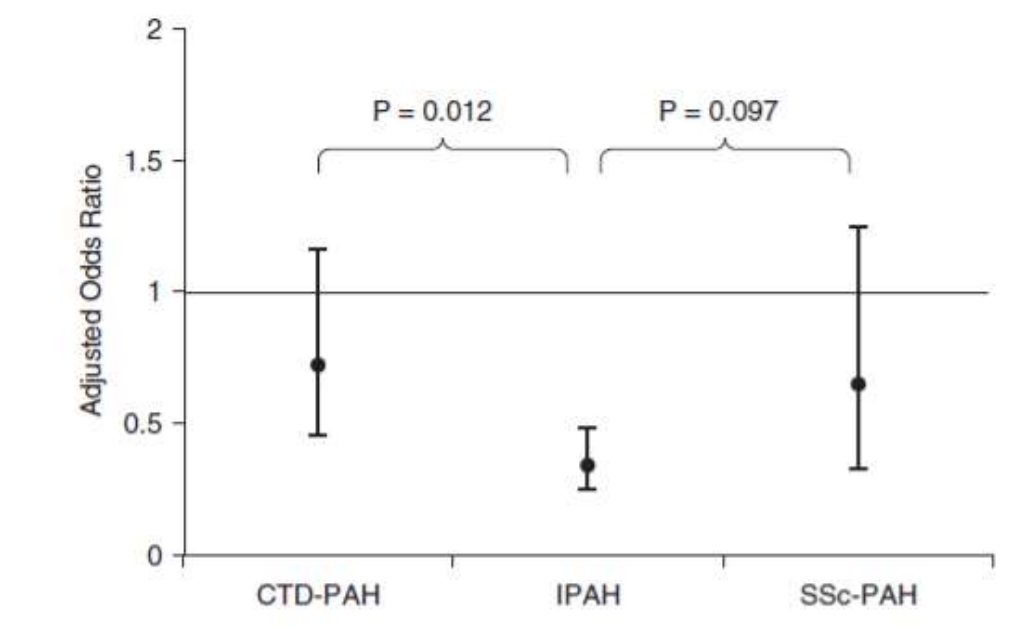
- 2,762 patients -827 with CTD-PAH and 1,935 with IPAH
- 465 (56%) had SSc (limited or diffuse cutaneous SSc)
- 121 (15%) had SLE
- 86 (10%) had mixed CTD
- 79 (10%) had Sjogren's syndrome
- 17 (2%) had an overlap syndrome
- 59 (7%) had another CTD
- Most of the trials were studies of ERAs - 1,614 [59%] participants

	CTD-PAH (*n* = 827)	IPAH (*n* = 1,935)	Difference-in-Difference (90% CI)	*P* Value for Interaction
Change in 6-minute-walk on active treatment, m	9.6	30.1		
Change in 6-minute-walk on placebo, m	−13.5	−10.3		
Treatment – Placebo, m	23.1	40.4	−17.3 (−31.3 to −3.3)	0.043



Improvement in 6MWT in CTD ILD and IPAH

CLINICAL WORSENING OR DEATH



- 117[13%] vs 260[14%] – Clinical worsening
- 28[3%] vs 55[3%]- death
- IPAH-active treatment reduced the risk of clinical worsening compared with placebo (OR, 0.34; 95% CI, 0.25–0.48)
- No difference was seen among patients with CTD-PAH (OR, 0.72; 95% CI, 0.45–1.16; p for interaction = 0.012)
- Patients with CTD-ILD were at a higher risk of death when compared to IPAH (OR, 1.95; 95% CI,1.27–3.02; P = 0.011)

Review

Comparison between the efficacy of combination therapy and monotherapy in connective tissue disease associated pulmonary arterial hypertension: a systematic review and meta-analysis

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ABSTRACT

Objective. *Although the efficacy of combined treatment targeting pulmonary arterial hypertension (PAH) has been suggested to be preferable, the comparative efficacy of combination therapy versus monotherapy in connec-*

Introduction

Despite advances in diagnosis and treatment in recent decades, pulmonary arterial hypertension (PAH) remains an important cause of morbidity and mortality worldwide. Pathophysiologically, PAH is characterised by a progres-

- Prospective RCTs assessing the efficacy of PAH-target combination therapy compared with background monotherapy in adult patients with CTD-PAH
- Reported the clinical outcomes of interest
- Follow-up duration was at least 12 weeks
- Specific therapies for PAH

STUDIES INCLUDED

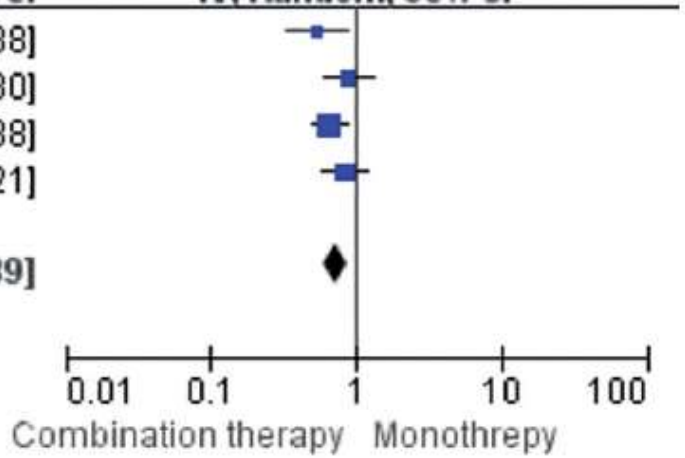
Study	CTD/All[%]	Follow-up	Baseline Therapy	Therapeutic arm	Primary outcome
PATENT-1/2 [2016]	111/ 443 [26%]	12 weeks – 2 years	ERAs	Riociguat	6MWD
AMBITION [2016]	187/500[37%] 118(SSc-PAH)	79 weeks	Ambrisentan or Tadalafil	Ambrisentan or Tadalafil	**Clinical failure**
COMPASS-2 [2015]	88/334[26%]	16 weeks	Sildenafil	Bosentan	**Clinical failure**
GRIPHON [2015]	334/1156 [29%]	71 weeks	ERA or PDE 5 or both	Selexipag	**Clinical failure**
SERAPHIN [2013]	224/742[30%]	6 months	ERA, Non parenteral prostaglandins	Macitentan	**Clinical failure**
PHIRST [2011]	19/87[22%]	16 weeks	Bosentan	Tadalafil	6MWD

Clinical outcome

Study or Subgroup	Combination therapy Events	Total	Monotherapy Events	Total	Weight	Risk Ratio IV, Random, 95% CI
AMBITION, 2016	20	103	30	84	15.1%	0.54 [0.33, 0.88]
COMPASS-2, 2015	22	43	26	45	23.2%	0.89 [0.60, 1.30]
GRIPHON, 2015	48	167	73	167	36.4%	0.66 [0.49, 0.88]
SERAPHIN, 2013	46	143	31	81	25.3%	0.84 [0.58, 1.21]
Total (95% CI)		**456**		**377**	**100.0%**	**0.73 [0.60, 0.89]**
Total events	136		160			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.43$, $df = 3$ ($P = 0.33$); $I^2 = 13\%$

Test for overall effect: $Z = 3.15$ ($P = 0.002$)

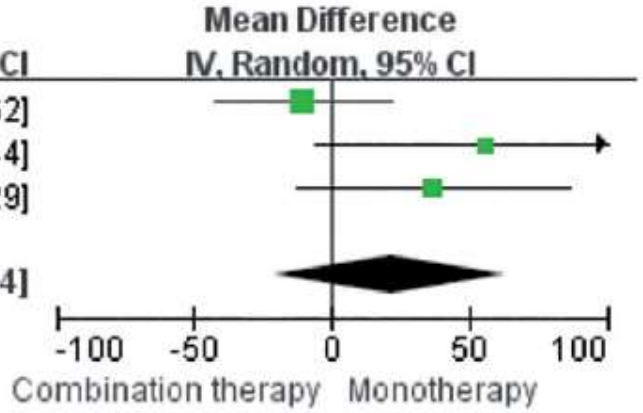


6MWT

Study or Subgroup	Combination therapy Mean	SD	Total	Monotherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
AMBITION, 2016	19.7	96.8	103	30.3	122.7	84	42.8%	-10.60 [-42.82, 21.62]
PATENT-1/2, 2016	17	50	46	-39	118	15	25.6%	56.00 [-5.44, 117.44]
PHIRST, 2011	37.9	47.3	19	1.3	64.8	8	31.7%	36.60 [-13.09, 86.29]
Total (95% CI)			**168**			**107**	**100.0%**	**21.38 [-20.38, 63.14]**

Heterogeneity: $Tau^2 = 791.38$; $Chi^2 = 4.80$, $df = 2$ ($P = 0.09$); $I^2 = 58\%$

Test for overall effect: $Z = 1.00$ ($P = 0.32$)



SSC-PH PHENOTYPES

- SSc-PVOD - Meets haemodynamic criteria for PAH but radiological and clinical features of PVOD
- SSc-PH-LHD - mPAP ⩾20 mmHg, PAWP >15 mmHg
- SSc-IpcPH - mPAP ⩾20 mmHg, PAWP >15 mmHg, PVR <3 WU
- SSc-CpcPH - mPAP ⩾20 mmHg, PAWP >15 mmHg, PVR ⩾3 WU
- SSc-PH-HFpEF - SSc-PH-LHD due to heart failure with preserved ejection fraction
- SSc-PH-HFrEF - SSc-PH-LHD due to heart failure with reduced ejection fraction
- SSc-PH-ILD - mPAP ⩾20 mmHg, PAWP ⩽15 mmHg, PVR ⩾3 WU in the presence of significant ILD (often defined as HRCT showing >20% fibrotic lung involvement and/or FVC <70% predicted)

Haque, Ashraful, et al. *ERR* 30.161 (2021)

CTD-PH APPROACH

- Clinical history and physical examination
- 2D ECHO
- PFT, 6MWT
- Improvement with immunosuppression
- RHC – Individualize the components contributing to overall PH [Group 2, 3 and 4]
- Treatment like IPAH

DRUG/TOXIN INDUCED PH

Definite	Possible
Aminorex Fenfluramine Dexfenfluramine Benfluorex Methamphetamines Dasatinib Toxic rapeseed oil	Cocaine Phenylpropanolamine L-tryptophan St. John's wort Amphetamines Interferon-α, interferon-β Alkylating agents Bosutinib Direct-acting antiviral agents for hepatitis C (e.g., sofosbuvir) Leflunomide Indirubin (Chinese herb Qing-Dai)

Simonneau, Gérald, et al. *ERJ* 53.1 (2019)

PVOD-PCH

- **NYHA class I** – Supportive management and regular follow up

- **NYHA class II-III** –ERA or PDE5 inhibitors have shown benefit in hemodynamic parameters
- Initiation with dual therapy is not recommended upfront due to side effects

- **NYHA IV**- Parenteral prostanoids- caution of fatal pulmonary edema

Montani et al 87.4 (2008): 220-233

HIV-PH

- Exact prevalence of HIV is not known
- People infected for longer than 8-10 years are known to develop PH
- With ART, PH is increasing in this group of patients
- HIV gp120 protein is known to stimulate Endothelin-1, Tat downregulates BMPR2 and Nef protein induces plexiform changes
- HIV associated PH behaves similar to IPAH
- Diagnosis of exclusion

TREATMENT

- Antiretroviral therapy [ART] – is known to reduce pulmonary artery pressures when compared to monotherapy or no therapy
- Supportive care
- PH specific therapy in HIV patients, evidence is limited
- Avoid CCBs, hypotension and drug interaction are key issues
- Bosentan was tried in 59 patients and improvement in exercise capacity, PVR and functional status persistent at 2.5 years [drug interaction with Ritonavir and cobicistat]
- PDE5 inhibitors have not been evaluated in RCTs

Zuber, Jean-Philippe, et al. *Clinical inf disease* 38.8 (2004): 1178-1185.
Pal, Jyotirmoy, et al. *Journal of IMA* 111.12 (2013): 845-6.

SCD-PH

- PH is usually multifactorial in SCD
- Endothelial injury from recurrent sickling, acute and chronic inflammation, hypercoagulability and thrombosis, chronic intravascular hemolysis, and altered bioavailability of the potent vasodilator nitric oxide (NO) along with heart failure
- Screening for pulmonary hypertension is recommended
- History is misleading usually
- 2D ECHO – once in 8-18 years and regularly in 1-3 years thereafter

Klings, Elizabeth S.,et al. *AJRCCM* 189.6 (2014): 727-740

RISK FACTORS FOR MORTALITY

- Increased tricuspid regurgitant jet velocity (TRV) measured by Doppler Echocardiography [>2.5 m/sec]
- Increased serum N-terminal pro–brain natriuretic peptide (NT-pro-BNP) level [>160pg/ml]
- Pulmonary hypertension measured by RHC [mPAP>25 mmHg]

Klings, Elizabeth S., et al. *AJRCCM* 189.6 (2014): 727-740.

TREATMENT

- Hydroxyurea
- Chronic transfusion therapy
- Anticoagulation
- PH specific therapy

ATS RECOMMENDATIONS 2013

SCD clinical scenario	Recommendation	Level of evidence
Elevated TRV alone or Elevated NT-pro-BNP alone	Recommendations are **against** targeted PAH therapy	Strong recommendation, moderate-quality evidence
Most patients with SCD who have RHC-confirmed PH	Recommendations are **against** targeted PAH therapy	Strong recommendation, moderate-quality evidence
Select patients with SCD who have RHC-confirmed marked elevation of their PVR, normal PAWP and symptomatic	a **trial** of either a prostacyclin agonist or an ERA	weak recommendation, very low-quality evidence
Select patients with SCD who have RHC-confirmed marked elevation of their PVR, normal PAWP and symptomatic	we recommend **against** phosphodiesterase-5 inhibitor therapy as a first-line agent	Strong recommendation, moderate-quality evidence

OTHER HEMATOLOGIC DISORDERS

- Beta Thalassemia
- Myeloproliferative disorders
- Dasatinib
- Bosutinib
- No trials of PH specific therapies are available

SARCOIDOSIS ASSOCIATED-PH [SAPH]

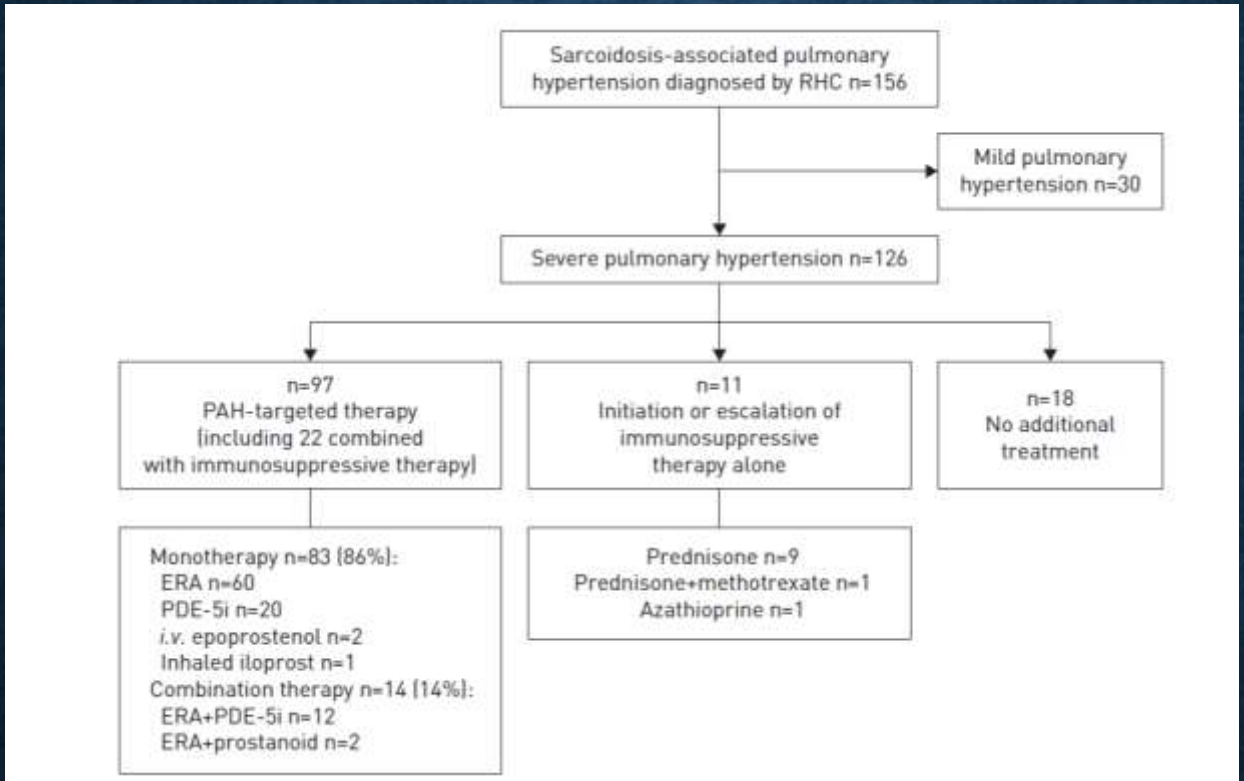
- Fibrosis-associated remodelling and obliteration of pulmonary vessels, extrinsic compression of central pulmonary vessels by lymphadenopathy or mediastinal fibrosis, pulmonary veno-occlusive-like lesions, granulomatous involvement of pulmonary vessels, left ventricular dysfunction, and portopulmonary hypertension
- Sarcoidosis-PH portends a poor prognosis

Nunes, Hilario, et al. *Thorax* 61.1 (2006): 68-74.

SARCOIDOSIS

Study	Drug	Inclusion	End points	Hemodynamic results
Barnett et al [2009] [n=22]	Sildenafil [9] Bosentan [12] Epoprostenol [1] -11 months	Stage IV disease Moderate restriction on PFT PH by ECHO	NYHA class 6MWD mPAP	**Improvement** in all parameters
Baughman et al [2014] [n=39]	Bosentan – 16 weeks	mPAP ⩾25 mmHg, NYHA FC II or III	Hemodynamic parameters	**PVR decreased** **mPAP decreased** 6MWD- no change
Bonham et al [2015] [n=46]	Epoprostenol[7] treprostinil[6] ERA [12] PDE5i [20] - variable	Biopsy proven pulmonary sarcoidosis mPAP>25 mmHg	Retrospective study	Improved CI/CO ratio and decreased PVR in 10 patients on
Boucly et al [2017] [n=126]	Monotherapy and combination therapy +/- immunosuppressants	PH Sarcoidosis	NYHA class Hemodynamic parameters	**Improvement in both**

MPAP>25 OR 25-34 WITH CI<2.5
68 WERE ON LTOT AT BASELINE



Bosentan (n=54)
Ambrisentan (n=6)
Sildenafil (n=15)
Tadalafil [n=5]
Epoprostenol [n=2]
inhaled Iloprost[n=1]
bosentan and sildenafil (n=8)
bosentan and tadalafil (n=1)

Ambrisentan and sildenafil (n=2)
Ambrisentan and tadalafil (n=1)
Bosentan and IV Epoprostenol (n=1)
Bosentan and SC Treprostinil (n=1)

	Baseline	First follow-up visit[¶]	Difference	p-value
WHO/NYHA functional class I–II/III/IV	11/52/18	26/45/10		0.01
6MWD m	311±127	324±138	+13 m	0.33
RAP mmHg	7±4	6±4	−14%	0.007
mPAP mmHg	48±9	42±11	−13%	<0.00001
Cardiac index $L \cdot min^{-1} \cdot m^{-1}$	2.6±0.8	2.9±0.8	+12%	<0.00001
PVR Wood units	9.7±4.4	6.9±3.0	−29%	<0.00001

- 81 Patients were followed up at 4-6 months of duration, rest were either taken up for transplant, lost to follow up or died
- **Short term improvement** in hemodynamic parameters was observed
- Long term outcomes of the patients at 28 months is also available
- **No improvement in 6MWD** was observed at this point
- 11 patients had received only immunosuppression and improvement in hemodynamics was seen in two patients who had extrinsic compression of Pulmonary artery
- Long term improvements were not seen mainly due to extrapulmonary disease

PLCH AND LAM

- **PLCH**- 29 consecutive patients were enrolled in the study who had PLCH and PH confirmed by RHC
- 12 patients were given PH-specific therapies and all were followed up till 5 years
- Improved mPAP and PVR in 12 cases and a better trend towards mortality
- No worse oxygenation

- **LAM**- 20 patients were given PH-specific therapies [Bosentan or Sildenafil] and a decrease in hemodynamic parameters was observed but not in terms of functional status

Le Pavec, Jérôme, et al. *Chest* 142.5 (2012): 1150-1157
Cottin, Vincent, et al. *ERJ* 40.3 (2012): 630-640

OTHER SYSTEMIC DISORDERS

- Gauchers disease
- GSDs
- Neurofibromatosis-1
- Chronic renal failure [transplantation helps reversing PH]
- Fibrosing mediastinitis [Bypass the obstruction or stenting helps reversing PH]
- PH specific therapies have not been evaluated yet

SUMMARY

Diseases	PH specific therapy
Group 2	No PH specific therapy
Group 3	No PH specific therapy
Group 4	Surgery > Riociguat
CTD-PH	RHC, if IPAH is predominant – PH specific therapy
Sarcoidosis-PH	RHC, if IPAH is predominant – PH specific therapy
SSC-PH	RHC, if IPAH is predominant – PH specific therapy
SCD-PH	Transfusion, anticoagulation, hydroxyurea, RHC-Trial of prostacyclin analogue or ERA
HIV-PH	ART, Bosentan improved hemodynamic parameters
PLCH and LAM-PH	Not enough data available
Toxin and Drug induced PH	Withdrawal of the drug and reassess again

THANK YOU…