ISHLT CTEPH/PAH March 2021
JOURNAL WATCH

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Waxman A, et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease
N Engl J Med 2021;384:325-34.

STUDY HIGHLIGHTS

Background: No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease.

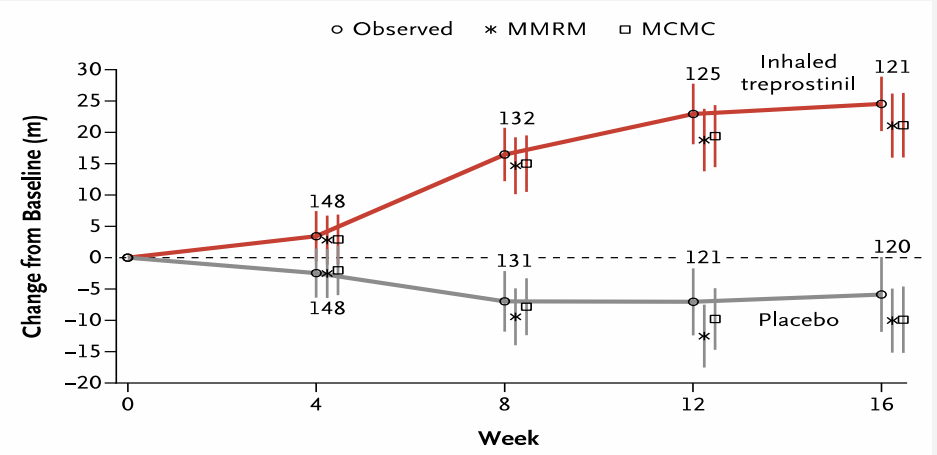
Objective: To evaluate the safety and efficacy of inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease

Design: Multicenter, randomized, double- blind, placebo-controlled trial comparing inhaled treprostinil (up to 12 breaths, total, 72 µg) four times daily vs placebo (1:1 ratio)

Outcomes: Primary endpoints: the change in peak 6-min walk distance from baseline to week 16. Secondary end points: the change in NT-proBNP level at week 16 and the time to clinical worsening

Table 2. Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††



REVIEWER'S COMMENT:

- In patients with PH secondary to ILD, inhaled treprostinil improved 6MWD, NT-proBNP, and time to clinical worsening events
- Serious adverse events were not reported more frequently in the treprostinil group.
- No significant treatment-related changes in pulse oximetry or supplemental oxygen use in either group
- Fewer patients had exacerbations of underlying lung disease in the treprostinil group than in the placebo group (26.4% vs. 38.7%; P=0.02)
- Fewer exacerbations of ILD in the treprostinil group suggests that the pathogenesis of fibrosis in ILD and the mechanisms leading to pulmonary hypertension in ILD are closely intertwined.

LIMITATIONS:

- Short duration of the study
- 21% of the patients discontinued the trial prematurely (before week 16)
- Clinical worsening and exacerbation of ILD were not adjudicated by an independent review committee

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Montani D, et al. Screening for Pulmonary Arterial Hypertension in Adults Carrying a *BMPR2* Mutation

European Respiratory Journal. *2020 Dec 30:2004229.* doi: 10.1183/13993003.04229-2020

STUDY HIGHLIGHTS

PAH due to *BMPR2* mutation carries a worse prognosis than IPAH. What is the risk of PAH occurrence in this subgroup? How can we detect it early to offer timely treatment?

Design: Prospective observational study through the DELPHI-2 study. Asymptomatic carriers of *BMPR2* mutation who were NYHA FC I were clinically assessed for PAH incidence between 2014 and 2016 with option for long term follow up.

Exclusion: Patients with known conditions associated with PAH

Results: 55 patients (26 males) were included. There was a 2.3% annual risk (.99% in men and 3.5% in women) of developing PAH.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Delay between diagnosis and assessment, *months*	71	69	5	6	5
PAH therapies	ERA PDE5i	PDE5i	ERA PDE5i	ERA PDE5i	ERA PDE5i
REVEAL 2.0 Score [16]					
Score at diagnosis	2	3	8	4	5
Score at last follow-up	4 (low risk)	4 (low risk)	5 (low risk)	2 (low risk)	3 (low risk)
ESC/ERS Guidelines [2]					
Signs of right heart failure	No	No	No	No	No
Progression of symptoms	No	No	No	No	No
Syncope	No	No	No	No	No
NYHA functional class	II	I	II	I	II
6MWD, *m*	587	358	454	490	533
CPET: V'O2 at peak, ml/min/Kg (% pred)	..	..	..	15 (81%)	25 (76%)
VE/VCO2 slope				40	32
NT-proBNP, *ng/mL*	96	234	66	92	113
Echocardiography: RA area, cm^2	< 18	< 18	..	< 18	< 18
Pericardial effusion	No	No		No	No
Haemodynamics RAP, *mmHg*	6	7	5	4	11
CI, $L.min^{-1}.m^2$	2·57	2·56	2·83	2·42	2·68
SvO2, *%*	71	68	73	71	71

Potential risk factors: pregnancy (patient 1) and chemotherapy (patients 3 and 4)

REVIEWER'S COMMENTS

In asymptomatic *BMPR2* carriers, the combination of EKG, DLCO, and CPET score can help identify PAH as opposed to echo alone

Exercise PH in this population may be an early marker of pulmonary vascular remodeling. 16.7% of the 12 patients with exercise PH developed PAH in follow up

LIMITATIONS

Cannot exclude that lead-time bias or length-time bias may have contributed to the observed response to oral therapy and maintenance of low- risk status at follow up

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D'Alto M, et al. Hemodynamics and risk assessment 2 years after the initiation of upfront ambrisentan-tadalafil in PAH.

J Heart Lung Transplant. 2020 Dec;39(12):1118-1125.

STUDY HIGHLIGHTS

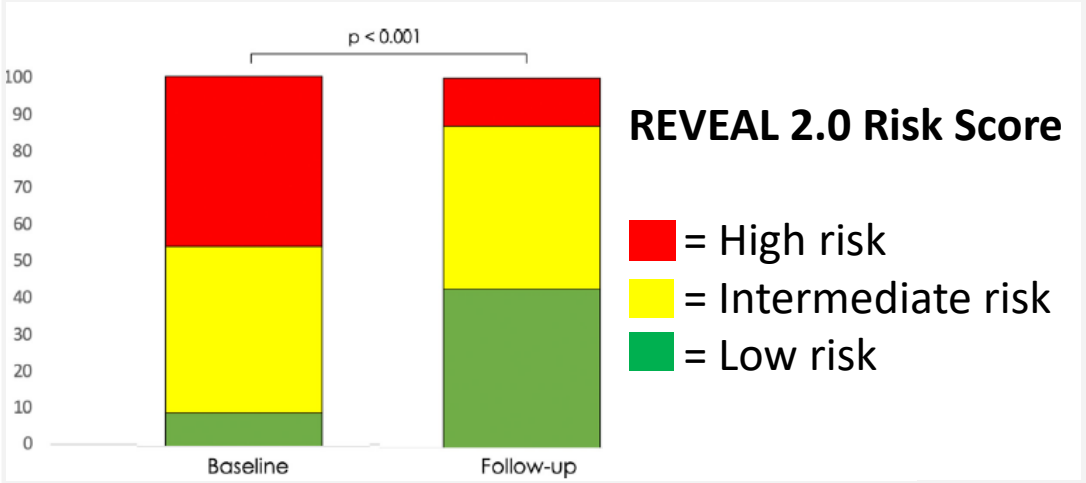
Initial upfront combination therapy with PDE-5i and ERA has become standard of care for PAH. How successful is this therapy after two years of follow-up?

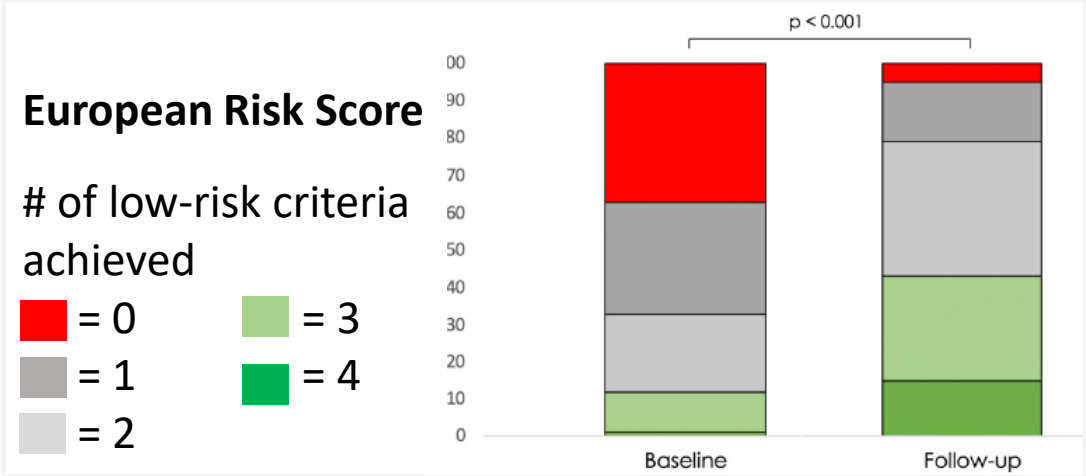
Design: Multicenter retrospective cohort study including centers in the Italian PH network conducted between 2013 and 2018.

Inclusion: Newly-diagnosed, treatment-naïve patients with IPAH, CTD-PHD, CHD-PAH with closed shunt with 24 months of follow-up.

Outcomes: REVEAL 2.0 risk score, European risk score, hemodynamics, WHO FC, 6MWD, NT-proBNP levels.

RESULTS





REVIEWER'S COMMENTS

Less than half of patients had a low-risk status two years after being started on upfront combination therapy.

Patients with a reduction in PVR by >50% or attainment of a normal SVi were more likely to achieve a low-risk status.

LIMITATIONS

- A relatively small number of patients (7 out of 106) had an escalation of therapy to parenteral prostanoid. 22/106 patients were started on inhaled/oral prostanoids during the follow-up period.
- Limited sample size with a geographically restricted population.
- Retrospective analysis with no control group.