ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Influence of various therapeutic strategies on right ventricular morphology, function and hemodynamics in pulmonary arterial hypertension

Roberto Badagliacca, MD, PhD,[a] Amresh Raina, MD,[b] Stefano Ghio, MD,[c] Michele D'Alto, MD,[d] Marco Confalonieri, MD,[e] Michele Correale, MD,[f] Marco Corda, MD,[g] Giuseppe Paciocco, MD,[h] Carlo Lombardi, MD,[i] Massimiliano Mulè, MD,[j] Roberto Poscia, MD,[a] Laura Scelsi, MD,[c] Paola Argiento, MD,[d] Susanna Sciomer, MD,[a] Raymond L. Benza, MD,[b] and Carmine Dario Vizza, MD[a]

From the [a]Department of Cardiovascular and Respiratory Science, Sapienza University of Rome, Rome, Italy; [b]Cardiovascular Institute, Allegheny General Hospital, Pittsburgh, Pennsylvania, USA; [c]Department of Cardiology, Fondazione IRCCS Policlinico San Matteo–University of Pavia, Pavia, Pavia, Italy; [d]Department of Cardiology, Monaldi Hospital–Second University of Naples, Naples, Italy; [e]Pneumology Unit, Ospedali Riuniti di Trieste, Trieste, Italy; [f]Cardiologia–UTIC Universitaria Ospedali Riuniti di Foggia, Foggia, Italy; [g]Azienda Ospedaliera "G. Brotzu" San Michele, Cagliari, Italy; [h]Dipartimento Cardio-Toraco-Vascolare, Clinica Pneumologica, Azienda Ospedaliera San Gerardo, Monza, Italy; [i]Cardiologia, Università degli studi di Brescia, Brescia, Italy; and the [j]Ferrarotto Hospital, Catania, Italy.

KEYWORDS:
echocardiography;
pulmonary arterial hypertension;
right ventricular morphology;
right ventricular systolic function;
upfront therapy

BACKGROUND: In idiopathic pulmonary arterial hypertension (IPAH) treatment goals include improving right ventricular (RV) function, hemodynamics and symptoms to move patients to a low-risk category for adverse clinical outcomes. No data are available on the effect of upfront combination therapy on RV improvement as compared with monotherapy. The aim of this study was to evaluate echocardiographic RV morphology and function in patients affected by IPAH and treated with different strategies.

METHODS: Sixty-nine consecutive, treatment-naive IPAH patients treated with first-line upfront combination therapy at 10 centers were retrospectively evaluated and compared with 2 matched cohorts treated with monotherapy after short-term follow-up. Evaluation included clinical, hemodynamic and echocardiographic parameters.

RESULTS: At 155 ± 65 days after baseline evaluation, patients in the oral+prostanoid group (Group 1) had the most clinical and hemodynamic improvement compared with the double oral group (Group 2), the oral monotherapy group (Group 3) and the prostanoid monotherapy group (Group 4). The more extensive reduction of pulmonary vascular resistance in Groups 1, 2 and 4 was associated with significant improvement in all RV echocardiographic parameters compared with Group 3. Considering the number of patients who reached the target goals suggested by established guidelines, 8 of 27 (29.6%) and 7 of 42 (16.7%) patients in Groups 1 and 2, respectively, achieved low-risk status, as compared with 2 of 69 (2.8%) and 6 of 27 (22.2%) in Groups 3 and 4, respectively.

Reprint requests: Roberto Badagliacca, MD, PhD, Department of Cardiovascular and Respiratory Science I, School of Medicine, Sapienza University of Rome, Policlinico Umberto I, Viale del Policlinico 155, 00161 Rome, Italy. Telephone: +39 0649979016. Fax: +390649979060.
E-mail address: roberto.badagliacca@uniroma1.it

1053-2498/$ - see front matter
https://doi.org/10.1016/j.healun.2017.08.009

CONCLUSIONS: In advanced treatment-naive IPAH patients, an upfront combination therapy strategy seems to significantly improve hemodynamics and RV morphology and function compared with oral monotherapy. The most significant results seem to be achieved with prostanoids plus oral drug, whereas the use of the double oral combination and prostanoids as monotherapy seem to produce similar results.
J Heart Lung Transplant 2018;37:365–375

Idiopathic pulmonary arterial hypertension (IPAH) is a rare disease, characterized by a progressive increase in pulmonary vascular resistance (PVR) leading to right heart failure.[1,2] Although the prognosis of IPAH has improved in the last decade, we are far from a cure, with long-term morbidity/mortality rates still unsatisfactory. At diagnosis, the majority of treatment-naive patients present with an intermediate risk of clinical worsening or death.[3] Right ventricular (RV) maladaptation to increased after-load represents the main determinant for prognosis and is characterized over time by an increase in RV dimensions and a decrease in systolic function.[4,5] New guidelines suggest 2 alternative approaches for intermediate-risk patients, leaving it to the clinician's discretion as to whether to initiate traditional monotherapy or an upfront combination therapy.[3] No data are available on the effect of an upfront combination therapy strategy on RV morphologic and functional improvement, compared with monotherapy, especially when also considering use of parenteral prostanoids in the upfront combination strategy. Furthermore, no data are available comparing the 2 different approaches in achieving the target goals suggested by the established guidelines.

The present study tried to approach this problem evaluating the hemodynamic profile and RV improvement, assessed by echocardiography, in naïve IPAH patients treated with two different approaches: monotherapy and upfront combination therapy, including parenteral prostanoid as a possible upfront combination.

Methods

Study population

In this study we retrospectively evaluated 69 consecutive, treatment-naive IPAH patients followed at 9 centers from the Italian Pulmonary Hypertension NETwork (iPHNET) and 1 center from the United States (Allegheny General Hospital, Pittsburgh, PA). The study period was from January 2011 to July 2015 and the patients were treated with first-line upfront combination therapy. The choice of specific drugs used in the upfront combination patients was based on usual clinical practices at each center and included endothelin receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE5i) and parenteral prostanoids. Titration regimen of parenteral prostanoid was based on patients' tolerance and all centers complied with the concept of higher dosing to reach significant effects. Upfront combination therapy was defined as 2 drugs from different classes initiated within 3 weeks of each other and maintained throughout the duration of the study period. Similar therapeutic strategies have evolved over the years in the same way at each center, as the iPHNET meets periodically at regional and national meetings. All centers had a common follow-up strategy according to the suggested assessment and timing highlighted by guidelines established by European Society of Cardiology/European Respiratory Society (ESC/ERS) collaboration.[3]

The diagnosis of IPAH was defined and confirmed by the ESC/ERS[3] to exclude secondary causes while conforming to the hemodynamic profile of pre-capillary pulmonary hypertension (i.e., mean pulmonary artery pressure [mPAP] $\geq$25 mm Hg, pulmonary wedge pressure [PWP] $<$15 mm Hg, PVR $\geq$240 dynes/s/cm^5).

Baseline evaluation included medical history, physical examination, a non-encouraged 6-minute walk test (6MWT), right heart catheterization (RHC) and echocardiographic assessment.

Patients with an acute vasodilator response at the time of diagnosis were excluded.

Patients' risk assessment was defined as low, intermediate or high, according to most of the variables suggested by the current guidelines[3] (intermediate risk for World Health Organization [WHO] Functional Class III, 6MWT 165 to 440 meters, right atrial pressure [RAP] 8 to 14 mm Hg, cardiac index (CI) 2.0 to 2.4 liters/min/m^2, right atrial area 18 to 26 cm^2 and no or minimal pericardial effusion; low and high risk: below and above these values, respectively).

A historical group of 69 treatment-naive IPAH patients matched for age, gender, WHO functional class, 6MWT and hemodynamic baseline parameters, treated with oral monotherapy before 2012, were used for comparative analysis and selected from all centers. International guidelines available at that time[6] were less insistent on use of earlier combinations of drugs and parenteral prostanoids than the 2015 update.

Another historical group of 27 treatment-naive, matched IPAH patients treated with parenteral prostanoids before 2012 was used for comparative analysis to exclude that parenteral prostanoids, per se, could explain the results observed in the upfront combination group.

This retrospective study complies with the Declaration of Helsinki and was approved by the local institutional review boards for human studies of each center (Protocol No. 42412 for Europe, Protocol RC-5841 for the USA).

Right heart catheterization

Hemodynamic evaluation was done with the standard technique. Pressures were measured from the mid-chest position with a fluid-filled catheter and pressure transducer, recording the average values over 3 respiratory cycles, according to a common protocol highlighted by guidelines.[3] Cardiac output (CO) was measured by the thermodilution technique (American Edwards Laboratories, Santa Ana, CA), and PVR was calculated with the formula: PVR = (mPAP – PWP) / CO.

Echocardiographic assessment

The most common standard practice echocardiographic parameters used in diagnostic work-up and follow-up of PAH patients were evaluated. Baseline echocardiographic studies were performed

1 week from RHC, before starting specific treatment. All echocardiographic data were acquired by dedicated operators, with the patient in the left lateral decubitus position using commercially available equipment. Standard M-mode, 2-dimensional and Doppler images were obtained during breath-hold at end-expiration and measurements were obtained from the mean of 3 consecutive beats, according to American Society of Echocardiography guidelines.[6] The echocardiograms were read retrospectively specifically for this study and all centers participating were in compliance with the international guidelines.[7] The following standard parameters and derived measures were considered in the analysis: right atrial area (RA area); RV end-diastolic area (RVEDA); RV end-systolic area (RVESA); RV fractional area percent change [RVFAC = (RVEDA – RVESA) / RVEDA × 100]; tricuspid annular plane systolic excursion (TAPSE); left ventricular systolic and diastolic eccentricity index (LV-EIs and LV-EId, respectively); and presence of pericardial effusion. Tricuspid regurgitation was semi-quantitatively graded considering the regurgitant jet area at color Doppler imaging. The transmitral flow velocity curve was obtained by pulsed Doppler imaging, positioning the sample volume between the tips of the mitral leaflets. E- and A-wave peak velocities and ratio of early transmitral flow velocity to atrial flow velocity were also measured.

Three centers were randomly selected for variability evaluation and the widest values reported in the study. Intra- and interobserver variability data were as follows: RVEDA: intraobserver 0.18 ± 0.66 (95% confidence interval [CI] –1.09 to 1.45), interobserver 0.15 ± 1.08 (95% CI –2.07 to 2.37); RVESA: intraobserver 0.16 ± 0.50 (95% CI –0.77 to 1.09), interobserver 0.05 ± 0.55 (95% CI –1.10 to 1.20); LV-EId: intraobserver 0.00 ± 0.07 (95% CI –0.13 to 0.13), interobserver –0.02 ± 0.08 (95% CI –0.18 to 0.14); LV-EIs: intraobserver –0.01 ± 0.04 (95% CI –0.06 to 0.04), interobserver 0.01 ± 0.11 (95% CI –0.18 to 0.20); RA area: intraobserver 0.01 ± 0.44 (95% CI –0.86 to 0.88), interobserver 0.22 ± 1.07 (95% CI –1.62 to 2.06); TAPSE: intraobserver 0.20 ± 0.63 (95% CI –1.03 to 1.43), interobserver 0.00 ± 0.67 (95% CI –1.06 to 1.06); LVEDA intraobserver 0.06 ± 0.79 (95% CI –1.52 to 1.64), interobserver –0.07 ± 0.76 (95% CI –1.63 to 1.49); LVESA: intraobserver –0.02 ± 1.32 (95% CI –0.67 to 0.63), interobserver 0.04 ± 0.42 (95% CI –0.79 to 0.87).

Statistical analysis

To compensate for the lack of randomization methods, the nearest neighbor matching method 1:1, by the exact distance, was used to balance the distribution of covariates in the upfront-treated and control groups, diagnosing the quality of the resulting matching through the standardized difference in means (the difference in means of each covariate divided by the standard deviation in the fully treated group). This method was chosen as the most effective method (increased power and decreased bias) for small group sizes.[8]

Continuous data are expressed as mean ± standard deviation, and categorical data are expressed as count and proportion. Two-group comparisons were done with unpaired or paired, 2-tailed *t*-tests for means if the data were normally distributed or with Wilcoxon's rank-sum tests if the data were not normally distributed. Comparisons among disease groups were done with 2-way analysis of variance (ANOVA). If significant differences were found, post-hoc comparisons (Duncan's multiple range test or Scheffé test) were used to determine the statistical significance among groups. Chi-square or Fisher's exact tests were used to analyze the categorical data.

Linear regression analysis was performed to assess the relations between RVEDA, RVFAC and PVR and expressed as Pearson's correlation coefficient.

Intra- and interobserver variability was measured by the Bland–Altman method by 3 clinicians from 3 different centers and was assessed in a randomly selected cohort of 10 patients. The widest values were identified and reported.

All statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY) and STATA version 13 (StataCorp LP, College Station, TX). All statistical tests were 2-sided. $p < 0.05$ was considered statistically significant.

Results

Study population

Sixty-nine consecutive treatment-naive IPAH patients observed at 10 centers were started on upfront combination therapy between January 2011 and July 2015, with a mean interval of 8.0 ± 6.7 (range 1 to 36) months between IPAH diagnosis and initiation of symptoms. The patients were predominantly women (63.8%), with a mean age of 54 ± 15 years. The majority of patients were WHO Functional Class III at diagnosis, with severe pulmonary hypertension and impaired functional capacity. The echocardiographic evaluation at baseline was consistent with a severe RV dilation and systolic dysfunction.

A matched cohort of 69 treatment-naive IPAH patients receiving oral monotherapy (bosentan, $n = 28$, 40.6%; ambrisentan, $n = 14$, 20.3%; sildenafil, $n = 18$, 26.1%; tadalafil, $n = 9$, 13.0%) and a second matched cohort of 27 treatment-naive IPAH patients receiving prostanoids as monotherapy (epoprostenol intravenous [IV], $n = 7$, 25.9%; treprostinil subcutaneous [SC], $n = 20$, 74.1%) were considered for comparative purposes.

Table 1 summarizes the baseline characteristics of the upfront combination-treated group, divided into oral+parenteral prostanoid (Group 1) and double oral combination (Group 2) groups, and the 2 monotherapy matched cohorts, including the oral (Group 3) and prostanoid (Group 4) groups. The 4 groups of patients were similar with regard to demographics and clinical, hemodynamic and echocardiographic profiles.

Short-term follow-up: Clinical condition and exercise capacity

After 155 ± 65 days, all patients in the study had a significant improvement in the WHO functional class compared with baseline (Tables 2 and 3), with improvement to WHO Class II in 77.8% (21 of 27; $p < 0.001$) in Group 1, 78.6% (33 of 42; $p < 0.001$) in Group 2, 52.2% (36 of 69; $p < 0.001$) in Group 3 and 77.7% (21 of 27; $p < 0.001$) in Group 4 (Group 1 vs 2, $p =$ not statistically significant [NS]; Group 1 vs 3, $p = 0.03$; Group 1 vs 4, $p =$ NS; Group 2 vs 3, $p = 0.01$; Group 2 vs 4, $p =$ NS; Group 3 vs 4, $p = 0.02$).

Table 1 Baseline Characteristics of the Upfront Combination Treatment Group (Divided Into Oral+Parenteral Prostanoid [Group 1] and Double Oral Combination [Group 2]) and Compared With 2 Monotherapy Matched Cohorts (Oral [Group 3] and Prostanoids [Group 4])

	Upfront therapy		Monotherapy		
	Group 1 ($n = 27$)	Group 2 ($n = 42$)	Group 3 ($n = 69$)	Group 4 ($n = 27$)	p
Age (years)	53 ± 18	55 ± 14	54 ± 13	54 ± 15	NS
Gender (F:M)	18:9	26:16	42:27	16:11	NS
Height (cm)	163 ± 9	164 ± 11	165 ± 10	166 ± 9	NS
Weight (kg)	68 ± 14	72 ± 15	71 ± 18	68 ± 13	NS
Time symptoms—diagnosis[a]	8.1 ± 4.9	8.0 ± 7.5	10.1 ± 7.4	9.4 ± 3.4	NS
WHO	3.2 ± 0.4	3.1 ± 0.4	3.0 ± 0.6	3.2 ± 0.4	NS
6MWT (m)	306 ± 88	314 ± 104	321 ± 103	322 ± 78	NS
Hemodynamics					
RAP (mm Hg)	10.4 ± 2.2	9.4 ± 4.7	9.1 ± 4.5	9.7 ± 3.6	NS
mPAP (mm Hg)	54.4 ± 11	52.5 ± 9.6	54 ± 13.3	55.4 ± 11.7	NS
CI (l/min/m^2)	2.1 ± 0.5	2.2 ± 0.6	2.2 ± 0.5	2.2 ± 0.5	NS
PVR (WU)	13.4 ± 4.2	12.4 ± 5.9	12.0 ± 5.5	12.8 ± 4.1	NS
Echocardiography					
RVEDA (cm^2	26.6 ± 3.7	27.8 ± 4.4	29.2 ± 6.6	28.6 ± 4.2	NS
RVESA (cm^2	19.0 ± 2.6	20.0 ± 3.6	20.4 ± 5.8	19.9 ± 3.9	NS
RVFAC (%)	28.0 ± 6.8	27.6 ± 7.8	30.3 ± 9.6	30.3 ± 9.2	NS
TAPSE (mm)	15.6 ± 2.4	15.8 ± 4.1	16.4 ± 4.0	16.1 ± 3.5	NS
RA area (cm^2)	27.9 ± 4.5	24.8 ± 7.1	27.6 ± 10	24.9 ± 8.4	NS
TR severe	6 (22.2%)	11 (26.2%)	16 (23.2%)	6 (22.2%)	NS
LVEDA (cm^2)	20.6 ± 3.2	20.4 ± 6.7	21.0 ± 6.4	20.1 ± 5.4	NS
LVESA (cm^2)	10.9 ± 2.5	12.6 ± 4.7	12.7 ± 4.7	11.9 ± 3.8	NS
LV-EId	1.43 ± 0.14	1.52 ± 0.30	1.50 ± 0.34	1.55 ± 0.30	NS
LV-EIs	1.60 ± 0.27	1.68 ± 0.35	1.74 ± 0.43	1.62 ± 0.26	NS
LVEF (%)	61.8 ± 6.2	60.2 ± 8.0	59.2 ± 7.3	61.3 ± 8.2	NS
LA area (cm^2)	15.0 ± 3.1	16.0 ± 5.0	16.3 ± 4.3	15.1 ± 4.1	NS
LV E-PW (cm/s)	0.6 ± 0.2	0.8 ± 0.4	0.6 ± 0.3	0.7 ± 0.4	NS
LV A-PW (cm/s)	0.7 ± 0.2	0.8 ± 0.3	0.8 ± 0.2	0.8 ± 0.2	NS
LV E/A	0.8 ± 0.4	0.9 ± 0.3	0.8 ± 0.4	0.9 ± 0.2	NS
Pericardial effusion	11 (40.7%)	16 (38.1%)	25 (36.2%)	10 (37.0%)	NS
Bosentan			28 (40.6%)		
Ambrisentan			14 (20.3%)		
Sildenafil			18 (26.1%)		
Tadalafil			9 (13.0%)		
Treprostinil SC				20 (74.1%)	
Epoprostenol IV				7 (25.9%)	
ERA + PDE5i					
Ambrisentan + tadalfil		15 (21.7%)			
Ambrisentan + sildenafil		4 (5.9%)			
Bosentan + tadalafil		9 (13.0%)			
Bosentan + sildenafil		7 (10.1%)			
Macitentan + tadalafil		5 (7.2%)			
Macitentan + sildenafil		2 (2.9%)			
Prostanoid + oral					
Treprostinil SC + tadalafil	11 (15.9%)				
Treprostinil SC + ambrisentan	6 (8.7%)				
Treprostinil SC + bosentan	3 (4.4%)				
Epoprostenol IV + tadalafil	4 (5.9%)				
Epoprostenol IV + bosentan	2 (2.9%)				
Iloprost I + ambrisentan	1 (1.4%)				

6MWT, non-encouraged 6-minute walk test; CI, cardiac index; ERA, endothelin receptor antagonist; I, inhaled; IV, intravenous; LV-EId, left ventricular end-diastolic eccentricity index; LV-EIs, left ventricular end-systolic eccentricity index; LVEDA, left ventricular end-diastolic area; LVESA, left ventricular end-systolic area; LVEF, left ventricular ejection fraction; LV E wave PW, pulsed-wave left ventricular E wave; LV A-PW, pulsed-wave left ventricular A-wave; mPAP, mean pulmonary arterial pressure; PDE5i, phosphodiesterase-5 inhibitor; PVR, pulmonary vascular resistance; RA area, right atrium area; RAP, mean right atrial pressure; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; TAPSE, tricupid annular plane systolic excursion; TR severe, severe tricuspid regurgitation; SC, subcutaneous; WHO, World Health Organization.

[a]Time from onset of symptoms to diagnosis (months).

Table 2 Changes in Clinical, Hemodynamic and Echocardiographic Parameters From Baseline to Short-term Follow-up in Groups 1, 2 and 3

	Upfront therapy								Monotherapy				Groups (155 ± 65 days)		
	Group 1				Group 2				Group 3				3 vs 1	3 vs 2	1 vs 2
	Baseline	155 ± 65 days	Δ	*p*	Baseline	155 ± 65 days	Δ	*p*	Baseline	155 ± 65 days	Δ	*p*	*p*	*p*	*P*
WHO	3.2 ± 0.4	2.3 ± 0.5	−0.9 ± 0.4	0.000	3.1 ± 0.4	2.2 ± 0.4	−0.9 ± 0.5	0.000	3.0 ± 0.6	2.5 ± 0.6	−0.4 ± 0.6	0.000	0.037	0.003	NS
6MWT (m)	306 ± 88	408 ± 87	101 ± 52	0.000	314 ± 104	363 ± 121	56 ± 53	0.000	321 ± 103	348 ± 123	26 ± 48	0.000	0.001	0.007	0.001
Hemodynamics															
RAP (mm Hg)	10.4 ± 2.2	6.1 ± 3.1	−4.1 ± 2.4	0.000	9.5±4.7	7.2 ± 3.8	−2.4 ± 4.2	0.000	9.1 ± 4.6	7.9 ± 4.1	−1.1 ± 4.1	0.014	0.000	NS	0.01
mPAP (mm Hg)	54.4 ± 11	38.4 ± 8.9	−15.6 ± 10.8	0.000	52.5 ± 9.6	43 ± 11	−10.4 ± 10.8	0.000	54 ± 13.3	51.3 ± 13.2	−3.3 ± 5.3	0.000	0.000	0.001	NS
CI (l/min/m^2)	2.1 ± 0.5	2.7 ± 0.2	0.6 ± 0.5	0.000	2.2 ± 0.6	2.8 ± 0.6	0.7 ± 0.6	0.000	2.2 ± 0.5	2.5 ± 0.5	0.3 ± 0.3	0.000	0.002	0.004	NS
PVR (UW)	13.4 ± 4.2	6.2 ± 2.4	−6.8 ± 2.8	0.000	12.4 ± 5.9	7.3 ± 3.0	−5.8 ± 4.5	0.000	12.0 ± 5.5	10.7 ± 5.5	−1.8 ± 2.5	0.000	0.000	0.001	0.04
Echocardiography															
RVEDA (cm^2)	26.6 ± 3.7	20.0 ± 4.2	−6.8 ± 4.4	0.000	27.8 ± 4.4	23.5 ± 5.7	−4.3 ± 3.8	0.000	29.0 ± 7.0	29.2 ± 7.0	−0.3 ± 3.5	NS	0.000	0.000	0.015
RVESA (cm^2)	19.0 ± 2.6	11.1 ± 2.7	−7.9 ± 3.4	0.000	20.0 ± 3.6	14.7 ± 4.5	−5.3 ± 3.5	0.000	20.2 ± 6.0	20.4 ± 6	−0.1 ± 4.2	NS	0.000	0.000	0.001
RVFAC (%)	28.0 ± 6.8	43.0 ± 7.7	15.6 ± 5.2	0.000	27.6 ± 7.8	36.9 ± 10.2	9.2 ± 7.4	0.000	30.4 ± 9.6	30.2 ± 9.2	0.0 ± 7.7	NS	0.000	0.002	0.014
TAPSE (mm)	15.6 ± 2.4	22.2 ± 3.4	6.3 ± 2.7	0.000	16 ± 4.0	18.9 ± 4.2	3.1 ± 4.1	0.000	16.4 ± 4.0	17.4 ± 4.3	0.6 ± 4.8	0.015	0.000	0,009	0.001
RA area (cm^2)	27.9 ± 4.5	20.1 ± 5.2	−7.4 ± 4.6	0.000	24.8 ± 7.1	20.9 ± 6.0	−2.6 ± 5.6	0.000	27.6 ± 10	27.1 ± 8.9	−0.4 ± 3.8	NS	0.000	0.000	0.001
TR severe	6 (22.2)	1 (3.7%)		0.001	11 (26.2%)	3 (7.1%)		0.001	16 (23.2%)	13 (19.1%)		NS	0.003	0.003	NS
LVEDA (cm^2)	20.6 ± 3.2	21.6 ± 3.2	1.0 ± 1.4	0.004	20.4 ± 6.7	21.8 ± 6.9	1.4 ± 3.1	0.016	21.0 ± 6.4	21.2 ± 6.1	0.1 ± 1.9	NS	NS	NS	NS
LVESA (cm^2)	10.9 ± 2.5	11.3 ± 2.0	0.5 ± 1.5	NS	12.6 ± 4.7	13.3 ± 5.7	0.7 ± 2.4	NS	12.7 ± 4.7	12.9 ± 4.8	0.3 ± 1.5	NS	NS	NS	NS
LV-EId	1.43 ± 0.14	1.13 ± 0.09	−0.3 ± 0.1	0.000	1.52 ± 0.30	1.26 ± 0.26	−0.18 ± 0.42	0.000	1.50 ± 0.34	1.49 ± 0.39	−0.01 ± 0.2	NS	0.000	0.002	0.027
LV-EIs	1.60 ± 0.27	1.20 ± 0.13	−0.4 ± 0.2	0.000	1.68 ± 0.35	1.34 ± 0.26	−0.24 ± 0.51	0.000	1.74 ± 0.43	1.68 ± 0.48	−0.16 ± 3.9	0.045	0.000	0.000	0.014
LVEF (%)	61.8 ± 6.2	61.6 ± 5.8	−0.1 ± 2.5	NS	60.2 ± 8.0	62.6 ± 8.5	2.4 ± 5.9	NS	59.2 ± 7.3	60.3 ± 7.2	0.5 ± 5.1	NS	NS	NS	NS
LA area, (cm^2)	15.0 ± 3.1	15.2 ± 3.4	0.0 ± 1.0	NS	15.9 ± 5.0	15.9 ± 4.7	0.6 ± 2.4	NS	16.3 ± 4.3	16.2.2 ± 4.3	0.1 ± 3.0	NS	NS	NS	NS
LV E-PW (cm/s)	0.62 ± 0.2	0.76 ± 0.2	0.13 ± 0.1	0.000	0.75 ± 0.4	0.88 ± 0.4	0.12 ± 0.2	0.011	0.61 ± 0.3	0.65 ± 0.3	0.04 ± 0.2	NS	0.02	0.02	NS
LV A-PW (cm/s)	0.66 ± 0.2	0.70 ± 0.1	0.04 ± 0.1	0.015	0.78 ± 0.3	0.86 ± 0.2	0.08 ± 0.2	0.048	0.75 ± 0.2	0.78 ± 0.2	0.03 ± 0.1	NS	NS	NS	NS
LV E/A	1.0 ± 0.4	1.15 ± 0.4	0.12 ± 0.2	0.013	0.9 ± 0.3	1.0 ± 0.3	0.05 ± 0.3	NS	0.82 ± 0.4	0.82 ± 0.3	0.0 ± 0.2	NS	0.03	0.03	NS
Pericardial effusion	11 (40.7%)	1 (3.7%)		0.001	16 (38.1%)	6 (14.3%)		0.002	25 (36.2%)	22 (31.9%)		NS	0.001	0.001	0.001

6MWT: non-encouraged 6-minute walk test; CI, cardiac index; ERA, endothelin receptor antagonist; LV A-PW, pulsed-wave left ventricular A-wave; LV E-PW, pulsed-wave left ventricular E-wave; LV-EId, left ventricular end-diastolic eccentricity index; LV-EIs, left ventricular end-systolic eccentricity index; LVEDA, left ventricular end-diastolic area; LVEF, left ventricular ejection fraction; LVESA, left ventricular end-systolic area; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RA area, right atrium area; RAP, mean right atrial pressure; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; TAPSE, tricupid annular plane systolic excursion; TR severe, severe tricuspid regurgitation; PDE5i, phosphodiesterase-5 inhibitor; WHO, World Health Organization.

Table 3 Changes in Clinical, Hemodynamic and Echocardiographic Parameters From Baseline to Short-term Follow-up in Group 4

	Group 4				Groups (*p*-values)		
	Baseline	155 ± 65 days	Δ	*p*	1 vs 4	2 vs 4	3 vs 4
WHO	3.2 ± 0.4	2.2 ± 0.6	−0.9 ± 0.4	0.000	NS	NS	0.02
6MWT (m)	322 ± 78	371 ± 89	48 ± 26	0.000	0.001	NS	0.004
Hemodynamics							
RAP (mm Hg)	9.7 ± 3.6	6.5 ± 2.3	−3.3 ± 3.9	0.000	NS	NS	0.001
mPAP (mm Hg)	55.4 ± 11.7	43.8 ± 8.6	−11.5 ± 13	0.000	NS	NS	0.000
CI (l/min/m^2)	2.2 ± 0.5	2.7 ± 0.4	0.5 ± 0.4	0.000	NS	NS	0.002
PVR (UW)	12.8 ± 4.1	7.4 ± 3.2	−5.2 ± 1.2	0.000	0.02	NS	0.001
Echocardiography							
RVEDA (cm^2)	28.6 ± 4.2	23.4 ± 4.2	−5.2 ± 3.5	0.000	0.01	NS	0.000
RVESA (cm^2)	19.9 ± 3.9	14.9 ± 3.3	−5.8 ± 3.7	0.000	0.001	NS	0.000
RVFAC (%)	30.3 ± 9.2	36.3 ± 9.5	6.0 ± 6.1	0.000	0.01	NS	0.000
TAPSE (mm)	16.1 ±3.5	19.3 ± 3.8	3.1 ± 2.8	0.000	0.001	NS	0.000
RA area (cm$^{2)}$	24.9 ± 8.4	21.5 ± 7.5	−3.1 ± 3.9	0.000	0.001	NS	0.000
TR severe	6 (22.2%)	2 (8.7%)		0.004	NS	NS	0.003
LVEDA (cm^2)	20.1 ± 5.4	20.1 ± 5.3	0.04 ± 0.5	NS	NS	NS	NS
LVESA (cm^2)	11.9 ± 3.8	11.9 ± 4.2	−0.02 ± 0.7	NS	NS	NS	NS
LV-EId	1.55 ± 0.3	1.38 ± 0.3	−0.11 ± 0.3	0.000	0.01	NS	0.002
LV-EIs	1.62 ± 0.2	1.42 ± 0.3	−0.13 ± 0.3	0.000	0.01	NS	NS
LVEF (%)	61.3 ± 8.2	61.8 ± 6.8	0.20 ± 0.8	NS	NS	NS	NS
LA area cm^2)	15.1 ± 4	15.3 ± 3.8	0.2 ± 0.8	NS	NS	NS	NS
LV E-PW (cm/s)	0.7 ± 0.4	0.7 ± 0.4	0.05 ± 0.1	NS	0.02	NS	NS
LV A-PW (cm/s)	0.8 ± 0.2	0.8 ± 0.2	0.03 ± 0.1	NS	NS	NS	NS
LV E/A	0.9 ± 0.2	0.8 ± 0.2	0.07 ± 0.2	NS	0.02	NS	NS
Pericardial effusion	10 (37.0%)	3 (11.1%)		0.001	0.001	NS	0.001

6MWT: non-encouraged 6-minute walk test; CI, cardiac index; ERA, endothelin receptor antagonist; LV A-PW, pulsed-wave left ventricular A-wave; LV E-PW, pulsed-wave left ventricular E-wave; LV-EId, left ventricular end-diastolic eccentricity index; LV-EIs, left ventricular end-systolic eccentricity index; LVEDA, left ventricular end-diastolic area; LVEF, left ventricular ejection fraction; LVESA, left ventricular end-systolic area; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RA area, right atrium area; RAP, mean right atrial pressure; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; TAPSE, tricupid annular plane systolic excursion; TR severe, severe tricuspid regurgitation; PDE5i, phosphodiesterase 5 inhibitor; WHO, World Health Organization.

Similarly, the 6MWT distance improved significantly by 101 ± 52 meters ($p = 0.0001$) in Group 1 and 56 ± 53 m ($p = 0.0001$) in Group 2, compared with a more modest change of 26 ± 48 meters ($p = 0.0001$) in the oral monotherapy group (Group 1 vs 2, $p = 0.001$; Group 1 vs 3, $p = 0.001$; Group 2 vs 3, $p = 0.007$).

Interestingly, the 6MWT distance improved by 48 ± 26 meters ($p = 0.0001$) in Group 4, similarly to Group 2 (Group 1 vs 4, $p = 0.001$; Group 2 vs 4, $p =$ NS; Group 3 vs 4, $p = 0.004$).

All patients tolerated combination therapies well and none of the patients had to discontinue the treatment regimen.

Short-term follow-up: Hemodynamic and RV morphology and function

All patients underwent echocardiographic assessment after 155 ± 65 days from the initiation of therapy. Invasive hemodynamic data were also available for 136 of 138 (98.5%) patients.

Changes in the hemodynamic and echocardiographic parameters from baseline to short-term follow-up were compared between Groups 1, 2 and 3 (Table 2). Patients in Group 1 had the greatest hemodynamic improvement overall compared with patients in Groups 2 or 3. For example, although all 3 groups demonstrated a significant reduction in right atrial pressure (RAP), Group 1 patients showed a more robust improvement compared with the others (Groups 2 and 3). Similarly, cardiac index (CI) increased significantly in all patients, but patients with the upfront combination approach had a more prominent increase compared with the oral monotherapy approach, without reaching significance between Groups 1 and 2. Importantly, Group 1 and Group 2 showed 50% and 39.8% reductions of PVR, respectively, compared with a 14.7% reduction in Group 3.

The mean dose of prostanoid reached at 155 ± 65 days in Group 1 was 36 ± 14 ng/kg/min (range 15 to 56 ng/kg/min) with epoprostenol IV and 42 ± 10 ng/kg/min with treprostinil SC (range 14 to 58 ng/kg/min). Importantly, none of the patients treated with upfront combination therapy developed a hemodynamic and clinical pattern of high-output cardiac failure.

Interestingly, hemodynamic improvement in Group 4 was similar to that in Group 2, with a reduction of 3.3 ± 3.9 mm Hg in RAP (Group 1 vs 4, $p =$ NS; Group 2 vs 4, $p =$ NS; Group 3 vs 4, $p = 0.001$), an increase of 0.58 ± 0.42 liters/min/m^2 in CI (Group 1 vs 4, $p =$ NS; Group

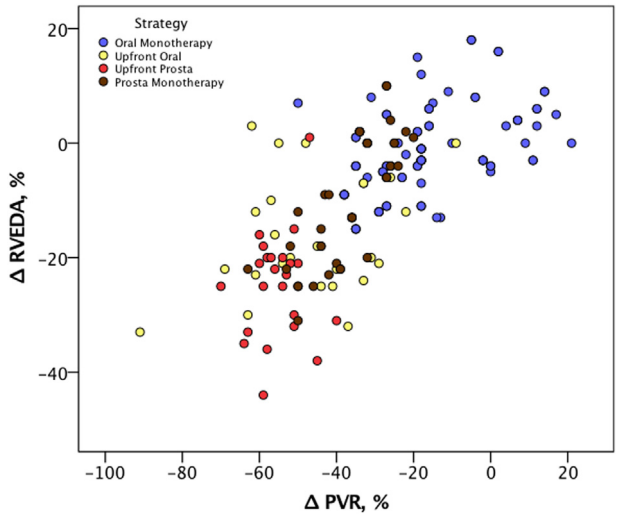

Figure 1 Correlation between the changes in RVEDA and PVR at short-term follow-up: ΔRVEDA vs ΔPVR (quadratic model: $r^2 = 0.49$, $p = 0.0001$, $y = 2.6 + 0.27x - 0.0023 \times 2$; linear model: $r^2 = 0.48$, $p = 0.0001$, $y = 3.43 + 0.40x$). Patients treated with oral monotherapy, prostanoid monotherapy, upfront oral combination and upfront oral plus prostanoid are reported in the same scatterplot (blue circles, brown circles, yellow circles and red circles, respectively). RVEDA, right ventricular end-diastolic area; PVR, pulmonary vascular resistance.

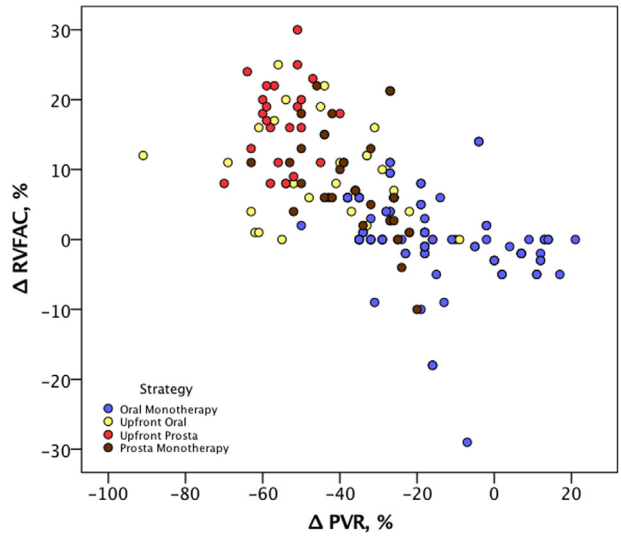

Figure 2 Correlation between the changes in RVFAC and PVR at short-term follow-up: ΔRVFAC vs ΔPVR (quadratic model: $r^2 = 0.40$, $p = 0.0001$, $y = 2.01 - 0.22x - 0.0007 \times 2$; linear model: $r^2 = 0.40$, $p = 0.0001$, $y = -2.22 - 0.263x$). Patients treated with oral monotherapy, prostanoid monotherapy, upfront oral combination and upfront oral plus prostanoid are reported in the same scatterplot (blue, brown, yellow and red circles, respectively). RVFAC, right ventricular fractional area change; PVR, pulmonary vascular resistance.

2 vs 4, p = NS; Group 3 vs 4, $p = 0.002$) and a decrease of 5.2 ± 1.2 Wood units (WU) (38.4%) in PVR (Group 1 vs 4, $p = 0.02$; Group 2 vs 4, p = NS; Group 3 vs 4, $p = 0.001$). These results were reached with a mean dose of 34 ± 12 ng/kg/min for epoprostenol IV (range 16 to 52 ng/kg/min) and 40 ± 8 ng/kg/min for treprostinil SC (range 15 to 56 ng/kg/min).

The more extensive reduction of PVR in Group 1 and 2 was associated with significant improvement in all morphologic and functional echocardiographic parameters compared with Group 3. Figures 1 and 2 reflect the relationship between RV morphologic (RVEDA) and functional changes (RVFAC) with respect to after-load reduction (PVR). Treatment effects are clearly clustered following their management strategies. Patients treated with the upfront combination strategy (Groups 1 and 2) and with prostanoid monotherapy (Group 4) are clustered at the bottom left (Figure 1) and upper left (Figure 2) of the remodeling/PVR relationship, indicating a significant improvement in RV morphology and function. Conversely, those patients treated with the oral monotherapy approach (Group 3) remain around the middle, indicating poor improvement in RV conditions. Group 4 patients showed a significant improvement in right heart morphologic and functional parameters, similar to Group 2 and significantly less pronounced than Group 1 (Table 3). Figure 3 shows an example of significant right heart morphologic and functional improvement in a patient treated with upfront combination therapy (Group 1).RVFAC was chosen over TAPSE for systolic function description as allows for a clearer and more continuous distribution of patients with respect to after-load, not presenting a floor effect in case of severe RV dysfunction[9] and the influence by the overall heart motion.[10]

Therapeutic strategy and risk profile

We analyzed the effect of the different strategies, upfront combination compared with monotherapy, in achieveing a low-risk clinical profile, compatible with a good long-term prognosis. Most variables suggested by the current guidelines were considered for the analysis: WHO Functional Class I/II; 6MWT distance >440 meters; RAP <8 mm Hg; CI ≥2.5 liters/min/m^2; RA area <18 cm^2; and the absence of pericardial effusion.

At baseline, 16 (59.3%) and 11 (40.7%) patients in Group 1, 25 (59.5%) and 17 (40.5%) in Group 2, 51 (73.9%) and 18 (26.1%) in Group 3 and 15 (55.5%) and 12 (44.4%) in Group 4 had an intermediate- and high-risk profile, respectively (p = NS, between groups).

Among high-risk patients, 8 (72.7%) and 3 (27.3) moved to an intermediate- and low-risk profile in Group 1, respectively; 11 (64.7%) and 5 (29.4%) moved to an intermediate- and low-risk profile, respectively, whereas 1 (5.9%) remained unchanged in Group 2; 10 (55.6%) had no change in their risk profile and 8 (44.4%) moved to an intermediate risk in Group 3; 8 (61.5%) and 4 (30.8%) moved to an intermediate- and low-risk profile, respectively, whereas 1 (7.7%) remained unchanged in Group 4 (Group 1 vs 2, $p < 0.05$; Group 1 vs 3, $p = 0.001$; Group 1 vs 4, $p < 0.05$; Group 2 vs 3, $p = 0.001$; Group 2 vs 4, p = NS; Group 3 vs 4, $p = 0.001$) (Figure 4).

Among intermediate-risk patients, 11 (68.7%) and 5 (31.3%) patients in Group 1, 23 (92%) and 2 (8.0%) in Group 2, 49 (96%) and 2 (4.0%) in Group 3 and 12 (85.7%) and 2 (14.3%) in Group 4 remained unchanged and moved to a low-risk profile, respectively (Group 1 vs 2, $p < 0.05$; Group 1 vs 3, $p = 0.001$; Group 1 vs 4, $p < 0.05$; Group 2 vs 3, $p = 0.001$; Group 2 vs 4, p = NS; Group 3 vs 4, $p = 0.001$).

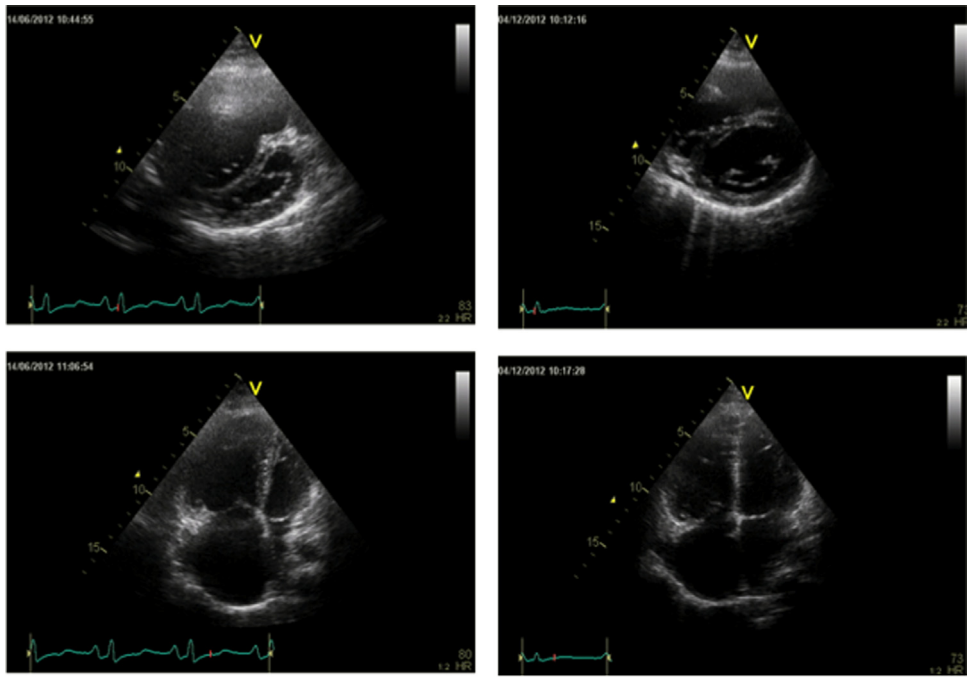

Figure 3 RV morphology by echocardiographic evaluation, at diagnosis and after 6-month treatment, in an IPAH-naive patient treated with upfront combination therapy (parenteral prostanoid plus oral drug). (A) Baseline evaluation: extreme RV dilation associated with LV compression. (B) Six-month evaluation: significant reduction in RV size associated with LV decompression. RV, right ventricular; LV, left ventricular; IPAH, idiopathic pulmonary arterial hypertension.

Interestingly, overall number of patients who reached those target goals (clinical, functional capacity, hemodynamic and echocardiographic imaging) was 8 of 27 (29.6%) in Group 1, 7 of 42 (16.7%) in Group 2, 2 of 69 (2.8%) in Group 3 and 6 of 27 (22.2%) in Group 4 (Figure 5).

Discussion

The present study seems to support the concept that upfront combination therapy may provide more pronounced hemodynamic, RV morphologic and functional improvement compared with the oral monotherapy strategy, suggesting that a combination of parenteral prostanoid plus oral drug could lead to better results than oral combination therapy. This concept is particularly true for advanced IPAH patients with an intermediate- or high-risk profile at diagnosis, such as those in the current study population.

The population studied here included patients with demographic and clinical profiles similar to those of typical incident IPAH patients reported in recent international registries[11,12] with severe pulmonary hypertension, low CI, advanced WHO functional class and reduced functional capacity.

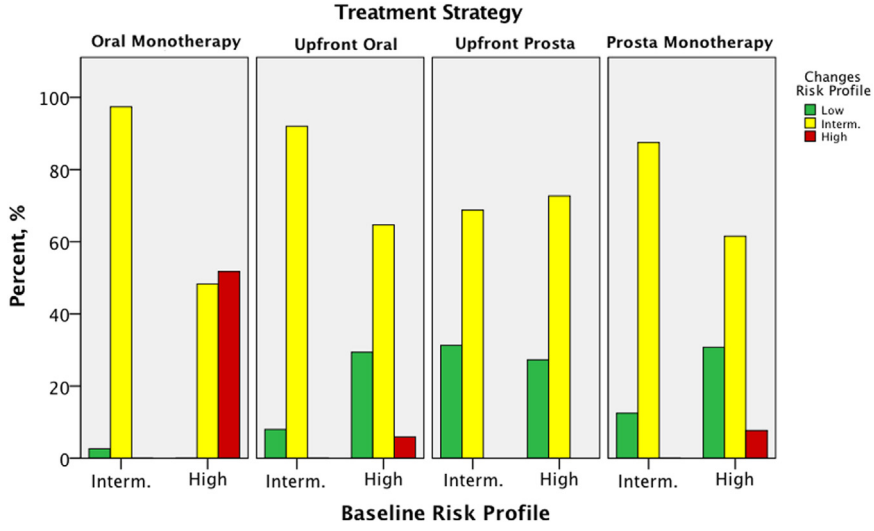

Figure 4 Changes in patients' risk profile at baseline and follow-up, in each group of treatment strategy (Group 1: upfront combination oral plus prostanoid; Group 2: upfront oral combination; Group 3: oral monotherapy; Group 4: parenteral prostanoid monotherapy). The columns represent the percentage of patients with low-risk (green column), intermediate-risk (yellow column) and high-risk (red column) profile at follow-up evaluation, based on their baseline risk profile (*x*-axis).

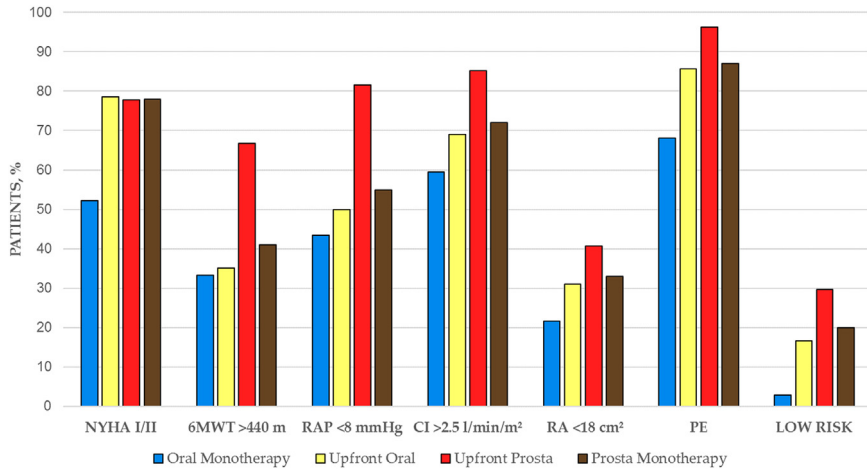

Figure 5 The histogram shows the different patients' percentage in each group of treatments (Group 1: upfront combination oral plus prostanoid, red column; Group 2: upfront oral combination, yellow column; Group 3: oral monotherapy, blue column; Group 4: parenteral prostanoid monotherapy, brown column) achieving the target goals highlighted by guidelines (WHO Class I or II, 6MWT >440 meters, RAP <8 mm Hg, CI ≥2.5 liters/min/m^2, RA area <18 cm^2, no PE). WHO, World Health Organization functional class; 6MWT, 6-minute walk test; RAP, right atrial pressure; CI, cardiac index; RA area, right atrium area; PE, pericardial effusion.

In our study, all treatment strategies were able to improve CI, but the upfront combination with prostanoid plus oral drug decreased PVR to a greater extent when compared with the other strategies. These results are in agreement with those of Sitbon et al in high-risk PAH patients, showing greater improvement in PVR with the upfront combination epoprostenol plus oral drug compared with epoprostenol alone.[13,14] Notably, the reduction of PVR observed by Sitbon et al after 3 to 4 months of epoprostenol monotherapy was similar to that seen in our Group 4. Thus, as the main pathophysiology-driven mechanism for RV dysfunction is represented by after-load mismatch,[15] it is not surprising that the treatment strategies associated with more pronounced reduction in PVR led to significant improvement in all echocardiographically derived morphologic and functional parameters, including RA area, LV-EI and pericardial effusion, widely known to be of prognostic significance. Consequently, a greater number of patients started on upfront prostanoid plus oral drug achieved a low-risk profile compared with the others. Interestingly, patients treated with the upfront double oral combination and those treated with prostanoid monotherapy had similar improvement in their risk profile, with an intermediate response between oral monotherapy and prostanoid combination.

However, as only 35.7% of patients in the double oral group were on the ambrisentan plus tadalafil combination suggested by the AMBITION study,[16] we cannot exclude the possibility of a more pronounced effect with the latter combination compared with the others. On the other hand, as only 52% of patients on parenteral prostanoids were also taking PDE5i, whether a substantial additional impact on the findings could be possible, as the PACES study would suggest when a PDE5i is associated with parenteral prostanoids,[17] may not be concluded from our results.

A more pronounced improvement in WHO functional class was observed among all treated groups, compared with randomized, controlled trials[18–24] and the AMBITION study.[16] Although a possible explanation may arise from an interpretation bias on patient's clinical condition by unblinded physicians, we cannot exclude that, in a pure after-load mismatch model, as our IPAH patients, the hemodynamic improvement may translate more easily in WHO class improvement, in agreement with the previous observation by Kemp et al for patients treated with upfront combination therapy.[13] Indeed, in randomized, controlled trials,[16,18–24] >30% of patients enrolled were those with connective tissue disease–related PAH, where the systemic disease may explain the mismatch between the hemodynamics and the functional improvement.

In our study, targeted monotherapy with oral approved drugs, such as ERA and PD5i, was able to improve WHO functional class and 6MWT distance, increase CI and reduce PVR to a similar degree to that seen in the randomized, controlled trials that established the efficacy of those treatments.[18–24] Nevertheless, our results indicate that only a few patients in this approach were able to achieve a recommended target goal. This is the first report describing patients' risk profiles after oral monotherapy and highlights that mild after-load reduction, as observed after 4 to 6 months of oral monotherapy, may lead to a low probability of reversing right heart dilation and substantially improving RV systolic function, thus not significantly changing patients' clinical risk profile. To our knowledge, no study using echocardiographic or magnetic resonance imaging (MRI) evaluation has ever reported a significant improvement in right heart size and function after short- or long-term monotherapy. Indeed, echocardiographic indices have been used in sub-studies of randomized, controlled trials in attempts to demonstrate improvement in RV morphology and function after oral monotherapy. The findings showed very minor effects on RV end-diastolic volume, LV-EI and ratio of RV to LV surface area.[25,26] The EURO-MR prospective study[27] reported effects of targeted monotherapies on cardiac MRI-derived indices of RV structure and function in PAH patients. The investigators did not find significant changes in RV volume and only mild

changes in RV ejection fraction, but within the limits of agreement of interobserver variability measurements.

Other single-center studies, based on echocardiographic or MRI evaluation, showed no effect on RV volume and ejection fraction after oral monotherapy.[28–30]

Recent findings by van de Veerdonk et al[31] showed that disease progression and mortality are preceded by changes in RV dimension and by a decrease in RV systolic function, even in stable patients, highlighting the importance of RV imaging evaluation during patients' follow-up.

Thus, as the oral monotherapy approach is associated with only limited changes in pulmonary hemodynamics and seems unable to significantly improve RV morphologic and functional parameters in these advanced patients, we cannot exclude the possibility that monotherapy, despite demonstrating improved exercise capacity and reduced hospitalization rates in clinical trials, may simply delay clinical events in the long term.

Study limitations

The lack of randomization is the major limitation of our study, as the arbitrary decision on which treatment was adopted in the individual patients may have influenced the results (and different criteria may have been adopted at different centers). However, randomization is used to ensure balance of the covariates between the treated and control groups, and matching methods are used to replicate this as much as possible for observational (non-randomized) data.[8] After all, our results, in terms of clinical and hemodynamic data, are in agreement with those reported by previous international randomized trials, supporting the hypothesis that, despite an absence of randomization, the matching method used in our study was sufficient for our purposes. Indeed, no randomized, prospective studies on the effects of different treatment strategies on RV structure and function have ever been done, despite the recognized importance of the RV for patients' prognosis.

A second limitation arises from the absence of a central core laboratory for echocardiography measurements. Nevertheless, to minimize interobserver variability, all centers participating in the study complied with international guidelines and were well known from the literature for echocardiographic studies, allowing the adoption of a common protocol (echocardiography guidelines). Three centers were randomly selected for interobserver variability evaluation, and the widest values were reported in the study. This may have been the result of a more conservative approach to avoid the possibility that a difference between 2 treatment groups may result from interobserver variability instead of different treatment regimen effects. In this way any inaccuracy and imprecision introduced by the measurements would be against the upfront treatment effects.

Finally, as all the centers involved in the study were dedicated PH centers, all but 10 patients in the upfront combination group had the complete set of hemodynamic and echocardiographic data recorded. We repeated the analysis excluding those patients with incomplete data, but the results did not differ.

In conclusion, in treatment-naive IPAH patients, an upfront combination therapy strategy seems to significantly improve hemodynamics and RV morphology and function compared with oral monotherapy. The most significant results seem to be achieved with prostanoids plus oral drug, whereas the double oral combination and prostanoids as monotherapy seem to produce similar intermediate results. Finally, our study suggests that intermediate- and high-risk patients may be undertreated with an oral monotherapy approach.

Disclosure statement

Badagliacca R and Vizza CD have received fees as speakers and scientific consultants from Bayer, Dompè, GlaxoSmithKline, MSD, and United Therapeutics; Ghio S has received consulting fees from MSD and GlaxoSmithKline; D'Alto M has received consulting fees and invitation to scientific events from Bayer, MSD, Dompè, and GlaxoSmithKline; Mulè M has received consulting fees and invitation to scientific events from Actelion Pharmaceuticals Ltd, Bayer, Dompè, GlaxoSmithKline, and MSD; Raina A, Confalonieri M, Correale M, Corda M, Paciocco G, Lombardi C, Poscia R, Argiento P, Sciomer S, Benza RL: none declared.

References

1. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. Circulation 2006;114:1417-31.
2. Voelkel NF, Quaife RA, Leinwand LA, et al. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. Circulation 2006;114:1883-91.
3. Galiè N, Humbert M, Vachiery J-L, et al. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
4. Vonk-Noordegraaf A, Haddad F, Chin KM, et al. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. J Am Coll Cardiol 2013;62(suppl):D22-33.
5. Badagliacca R, Poscia R, Pezzuto B, et al. Right ventricular remodeling in idiopathic pulmonary arterial hypertension: adaptive versus maladaptive morphology. J Heart Lung Transplant 2015;34:395-403.
6. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493-537.
7. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713.
8. Stuart EA. Matching methods for causal inference: a review and a look forward. Stat Sci 2010;25:1-21.

9. Mauritz GJ, Kind T, Marcus JT, et al. Progressive changes in right ventricular geometric shortening and long-term survival in pulmonary arterial hypertension. Chest 2012;141:935-43.
10. Giusca S, Dambrauskaite V, Scheurwegs C, et al. Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring. Heart 2010;96:281-8.
11. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164-72.
12. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010;122:156-63.
13. Kemp K, Savale L, O'Callaghan DS, et al. Usefulness of first-line combination therapy with epoprostenol and bosentan in pulmonary arterial hypertension: an observational study. J Heart Lung Transplant 2012;31:150-8.
14. Sitbon O, Jaïs X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. Eur Respir J 2014;43:1691-7.
15. Vonk-Noordegraaf A, Haddad F, Chin KM, et al. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. J Am Coll Cardiol 2013;62(suppl):D22-33.
16. Galiè N, Barberà JA, Frost AE, et al. initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834-44.
17. Simonneau G, Rubin LJ, Galiè N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. Ann Intern Med 2008;149:521-30.
18. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelinreceptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001;358:1119-23.
19. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896-903.
20. Galiè N, Rubin LJ, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet 2008;371:2093-100.
21. Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension. Results of the ambrisentan in pulmonary arterial hypertension, randomized, doubleblind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117:3010-9.
22. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353:2148-57.
23. Sastry BKS, Narasimhan C, Reddy NK, et al. Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. J Am Coll Cardiol 2004;43:1149-53.
24. Galiè N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009;119:2894-903.
25. Hinderliter AL, Willis PW IV, Barst RJ, et al. Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension. Circulation 1997;95:1479-86.
26. Galiè N, Hinderliter AL, Torbicki A, et al. Effects of the oral endothelin-receptor antagonist bosentan on echocardiographic and Doppler measures in patients with pulmonary arterial hypertension. J Am Coll Cardiol 2003;41:1380-6.
27. Peacock AJ, Crawley S, McLure L, et al. Changes in right ventricular function measured by cardiac magnetic resonance imaging in patients receiving pulmonary arterial hypertension-targeted therapy: the EURO-MR Study. Circ Cardiovasc Imaging 2014;7:107-14.
28. van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011;58:2511-9.
29. Chin KM, Kingman M, de Lemos JA, et al. Changes in right ventricular structure and function assessed using cardiac magnetic resonance imaging in bosentan-treated patients with pulmonary arterial hypertension. Am J Cardiol 2008;101:1669-72.
30. Duffels MGJ, Hardziyenka M, Surie S, et al. Duration of right ventricular contraction predicts the efficacy of bosentan treatment in patients with pulmonary hypertension. Eur J Echocardiogr 2009;10:433-8.
31. van de Veerdonk MC, Marcus JT, Westerhof N, et al. Signs of right ventricular deterioration in clinically stable patients with pulmonary arterial hypertension. Chest 2015;147:1063-71.