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# INFLUENCE OF VARIOUS THERAPEUTIC STRATEGIES ON RIGHT VENTRICULAR MORPHOLOGY, FUNCTION AND HEMODYNAMICS IN PULMONARY ARTERIAL HYPERTENSION

**Short title:** PAH and right ventricular adaptation

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[c], MD; Paola Argiento, MD[d]; Susanna Sciomer, MD[a]; Raymond L. Benza, MD[b]; Carmine Dario Vizza, MD[a]

[a]Dept. of Cardiovascular and Respiratory Science - Sapienza University of Rome, Italy

[b]Cardiovascular Institute, Allegheny General Hospital, Pittsburgh, Pennsylvania, USA

[c]Dept. of Cardiology, Fondazione IRCCS Policlinico San Matteo - University of Pavia, Italy

[d]Dept. of Cardiology, Monaldi Hospital - Second University of Naples, Italy

[e]Pneumology Unit, Ospedali Riuniti di Trieste, Italy

[f]Cardiologia-UTIC Universitaria Ospedali Riuniti di 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, Italy

[j]Ferrarotto Hospital, Catania, Italy

**Address for correspondence:** Roberto Badagliacca, MD, PhD, Dept. of Cardiovascular and Respiratory Science, I School of Medicine, Sapienza University of Rome, Policlinico Umberto I, Viale del Policlinico 155 - 00161 Rome, Italy. roberto.badagliacca@uniroma1.it

**ABSTRACT**

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, compared with monotherapy. The aim of the present study is to evaluate echocardiographic RV morphology and function in patients affected by IPAH 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 two matched cohorts treated with monotherapy after short-term follow-up. Evaluation included clinical, hemodynamic and echocardiographic parameters.

Results. After 155±65 days from baseline evaluation, patients in the oral+prostanoid group (Group 1) experienced the most important 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 Group 1, 2 and 4 was associated with a significant improvement in all RV echocardiographic parameters compared with Group 3. Considering the number of patients who reached the target-goals suggested by guidelines, 8/27 (29.6%) and 7/42 (16.7%) patients in Group 1 and 2, respectively, achieved low risk status compared with 2/69 (2.8%) and 6/27 (22.2%) in Group 3 and 4, respectively.

Conclusions. In advanced treatment-naïve 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, while double oral combination and prostanoids as monotherapy seem to produce similar results.

**Keywords:** pulmonary arterial hypertension, right ventricular morphology, right ventricular systolic function, echocardiography, upfront therapy.

**ABBREVIATIONS LIST**

6MWT: 6-minute walk test

CI: cardiac index

CO: cardiac output

ERA: endothelin receptor antagonists

IPAH: idiopathic pulmonary arterial hypertension

LV: left ventricular

LV-EId: left ventricular diastolic eccentricity index

LV-EIs: left ventricular systolic eccentricity index

mPAP: mean pulmonary artery pressure

MRI: magnetic resonance imaging

PAH: pulmonary arterial hypertension

PDE5i: phosphodiesterase-5 inhibitors

PVR: pulmonary vascular resistance

PWP: pulmonary wedge pressure

RA: right atrium

RAP: right atrial pressure

RHC: right heart catheterization

RV: right ventricular

RVEDA: RV end-diastolic area

RVESA: RV end-systolic area

RVFAC: RV fractional area change

TAPSE: tricuspid annular plane systolic excursion

WHO: World Health Organization

**INTRODUCTION**

Idiopathic pulmonary arterial hypertension (IPAH) is a rare disease characterized by a progressive increase of 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 morbi-mortality rates still unsatisfactory. At diagnosis, the majority of treatment-naïve patients present at intermediate risk of clinical worsening or death.[3] Right ventricular (RV) maladaptation to increased afterload represents the main determinant of patients' prognosis and is characterized over time by an increase in RV dimensions and a decrease in systolic function.[4,5] New guidelines suggest two alternative approaches for intermediate-risk patients, leaving it up the clinician's discretion whether to initiate traditional monotherapy or an upfront combination therapy to these patients.[3] No data are available on the effect of an upfront combination therapy strategy on RV morphological and functional improvement, compared with monotherapy especially when considering parenteral prostanoids in the upfront combination strategy. Furthermore, no data are available comparing the two different approaches in achieving the target-goals suggested by guidelines.

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

## METHODS

### Study population

The study retrospectively evaluated 69 consecutive treatment-naive IPAH patients followed at nine centers from the italian Pulmonary Hypertension NETwork (iPHNET) and one center from the United States (Allegheny General Hospital, Pittsburgh, Pennsylvania), between January 2011 and July 2015 and treated with first-line upfront combination therapy. The choice of specific drugs used in upfront combination was based on the usual clinical practice at each center and included endothelin receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE5i) and parenteral prostanoids. Titration regimen of parenteral prostanoid was based on patient's tolerance and all centers were compliant with the concept of high dosage to reach significant effects. Upfront combination therapy was defined as two drugs from different classes initiated within three weeks of each other and maintained throughout the duration of the study period. Similar therapeutic strategies have been evolved during the years in the same way in each center as this group meets periodically in regional and national meetings. All centers had a common follow-up strategy according to the suggested assessment and timing highlighted by ESC/ERS Guidelines.[3]

The diagnosis of IPAH was defined and confirmed according to the recent European guidelines[3] to exclude secondary causes and conforming to the hemodynamic profile showing precapillary pulmonary hypertension (mean pulmonary artery pressure-mPAP ≥ 25 mmHg, pulmonary wedge pressure-PWP <15 mmHg, pulmonary vascular resistance-PVR >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 and high according to most of the variables suggested by the current guidelines (3): intermediate risk for WHO functional class III, 6MWT 165-440m, right atrial pressure-RAP 8-14mmHg, cardiac index-CI 2.0-2.4 l/min/$m^2$, right atrial area 18-26 $cm^2$, and no or minimal pericardial effusion; low and high risk, below and above the previous 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 was used for comparative analysis and selected from all centers. International guidelines available at that time[6] were less insistent on earlier combinations of drugs and parenteral prostanoids utilization than their 2015 update.

Another historical group of 27 treatment-naive matched IPAH patients treated with parenteral prostanoid 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 n. 42412 for Europe; Protocol RC-5841 for USA).

**Right heart catheterization**

Hemodynamic evaluation was made with standard technique. Pressures were measured from the mid-chest position with a fluid-filled catheter and pressure transducer, recording the average values over three 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 pulmonary vascular resistance (PVR) was calculated with the formula PVR=(mPAP-PWP)/CO.

**Echocardiographic assessment**

The most common standard-practice echo-parameters used in diagnostic work-up and follow-up of PAH patients have been evaluated in the present study.

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, 2D and Doppler images were obtained during breath hold at end expiration and measurements were obtained from the mean of 3 consecutive beats in accordance with the American Society of Echocardiography Guidelines.[7] The echocardiograms were read retrospectively specifically for this study and all centers participating to the study were compliant to international guidelines.[6] 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 change % [RVFAC=(RVEDA - RVESA)/RVEDA x 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 semiquantitatively 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 the ratio of early transmitral flow velocity to atrial flow velocity were measured.

Three centers were randomly selected for variability evaluation and the widest values reported in the study. Intraobserver and interobserver variability are reported as following: RVEDA intraobserver 0.18 ± 0.66 (95% confidence interval [CI]: -1.09 to 1.45), interobserver 0.15 ± 1.08 (95% confidence interval [CI]: -2.07 to 2.37); RVESA intraobserver 0.16 ± 0.50 (95% confidence interval [CI]: -0.77 to 1.09), interobserver 0.05 ± 0.55 (95% confidence interval [CI]: -1.10 to 1.20); LV-EId intraobserver 0.00 ± 0.07 (95% confidence interval [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% confidence interval [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% confidence interval [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% confidence interval [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% confidence interval [CI]: -1.52 to 1.64), interobserver -0.07 ± 0.76 (95% confidence interval [CI]: -1.63 to 1.49); LVESA intraobserver -0.02 ± 1.32 (95% confidence interval [CI]: -0.67 to 0.63), interobserver 0.04 ± 0.42 (95% confidence interval [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 full treated group). This method was chosen as the most effective method (increased power and decreased bias) for small groups sizes.[8]

Continuous data are expressed as mean ± standard deviation, and categorical data are expressed as counts and proportions. Two-group comparisons were done with unpaired or paired, two-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 group were made by using two-way analysis of variance (ANOVA). If significant differences were found, post-hoc comparisons (Duncan's multiple range test, 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 a Pearson correlation coefficient.

Intraobserver and interobserver variability has been measured by the Bland-Altman method by three clinicians from three different centers and has been assessed in a randomly selected cohort of 10 patients. The widest values have been reported in the text.

All statistical analyses were performed using SPSS software (version 20.0, IBM) and Stata 13 (StataCorp, College Station, TX, USA). All statistical tests were 2-sided, and a p value <0.05 was considered statistically significant.



## RESULTS

### Study population

Sixty-nine consecutive treatment-naïve 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 months (range 1 to 36 months) between IPAH diagnosis and initiation of symptoms. The patients were predominantly females (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 dilatation 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 i.v., n. 7, 25.9%; Treprostinil s.c., n. 20, 74.1%) were considered for comparative purposes.

Table 1 summarizes the baseline characteristics of the upfront combination treated-group, divided in oral plus parenteral prostanoid (Group 1) and double oral combination (Group 2), and the two monotherapy matched cohorts, oral (Group 3) and prostanoids (Group 4). The four groups of patients were similar for the demographic, clinical, hemodynamic and echocardiographic profile.

**Short-term follow-up: clinical condition and exercise capacity**

After 155 ± 65 days, all patients in the study experienced a significant improvement in the WHO functional class compared to baseline (Table 2 and 3) with improvement to WHO class II in 77.8% (21/27; p<0.001) in Group 1, 78.6% (33/42; p<0.001) in Group 2, 52.2% (36/69; p<0.001) in Group 3 and 77.7% (21/27; p<0.001) in Group 4 (Group 1 vs 2, p=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).

Similarly, six-minute walk distance significantly improved by 101 ± 52 m (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 m (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, 6MW distance improved by 48 ± 26 m (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 needed to withdraw the treatment regimen.

**Short-term follow-up: hemodynamic and RV morphology and function**

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

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

The mean dosage of prostanoid reached at 155 ± 65 days in Group 1 was 36 ± 14 ng/kg/min (range 15-56 ng/kg/min) with epoprostenol i.v. and 42 ± 10 ng/kg/min with treprostinil s.c. (range 14-58 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, the hemodynamic improvement experienced by Group 4 was similar to Group 2, with – 3.3 ± 3.9 mmHg reduction in RAP (Group 1 vs 4, p=ns; Group 2 vs 4, p=ns; Group 3 vs 4, p=0.001), + 0.58 ± 0.42 l/min/$m^2$ increase in CI (Group 1 vs 4, p=ns; Group 2 vs 4, p=ns; Group 3 vs 4, p=0.002), and – 5.2 ± 1.2 WU (-38.4%) reduction 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 dosage of 34 ± 12 ng/kg/min for epoprostenol i.v. (range 16-52 ng/kg/min) and 40 ± 8 ng/kg/min for treprostinil s.c (range 15-56 ng/kg/min).

The more extensive reduction of PVR in Group 1 and 2 was associated with a significant improvements in all morphological and functional echocardiographic parameters compared with Group 3. Figures 1 and 2 reflect the relationship between RV morphological (RVEDA) and functional changes (RVFAC) with respect to afterload reduction (PVR). Treatment effects are clearly clustered following their management strategies. Patients treated with the upfront combination strategy (Group 1 and 2) and with prostanoid monotherapy (Group 4) are clustered to 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 morphological 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 morphological and functional improvement in a patient treated with upfront combination therapy (Group 1).

RVFAC was chosen over TAPSE for systolic function description as allows a more clear and continuous distribution of patients in respect of afterload, 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 different strategies, upfront combination compared with monotherapy, in achieveing the low-risk clinical profile, compatible with a good long-term prognosis. Most of the variables suggested by the current guidelines were considered for the analysis: WHO functional class I/II, 6MW distance > 440 m, RAP < 8 mmHg, CI ≥ 2.5 l/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%), 18 (26.1%) in Group 3, 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, while 1 (5.9%) remained unchanged in Group 2; 10 (55.6%) unchanged 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, while 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%) in Group 1, 23 (92%) and 2 (8.0%) in Group 2, 49 (96%) and 2 (4.0%) in Group 3, 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).

Interestingly, overall the number of patients who reached those target-goals (clinical, functional capacity, hemodynamic and echo-imaging) was 8/27 (29.6%) in Group 1, 7/42 (16.7%) in Group 2 and 2/69 (2.8%) in Group 3, 6/27 (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 morphological and functional improvement compared with the oral monotherapy strategy, suggesting that a combination parenteral prostanoid plus oral drug could reach better results than oral combination therapy. This concept is particularly true for advanced IPAH patients with an intermediate and high-risk profile at diagnosis, as the current study population.

Our population includes patients with a demographic and clinical profile similar to a typical incident IPAH patients, as reported in recent international registries[11,12] with severe pulmonary hypertension, low CI, advanced WHO functional class and reduced functional capacity.

In the present study, all treatment strategies were able to improve CI, but the upfront combination with prostanoid plus oral drug decreased PVR to a larger extent compared with the other strategies. These results are in agreement with the study 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 3-4 months of epoprostenol monotherapy was similar to the improvement shown in our Group 4. Thus, as the main pathophysiologic-driven mechanism for RV dysfunction is represented by afterload mismatch, 15 it is not surprising that the treatment strategies associated with more pronunced reduction in PVR have reached a significant improvement of all echocardiographic-derived morphologic and functional parameters, including RA area, LV-EI and pericardial effusion, widely known to be of prognostic significance. As a consequence, 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 followed the Ambrisentan plus Tadalafil combination suggested by the AMBITION study,[16]we cannot exclude a more pronounced effect with the latter combination compared with others. On the other hand, as only 52% of patients on parenteral prostanoids were combined with PDE5i, whether a substantial additional impact on the findings could be possible, as the PACES study would suggest when a PDE5i is associated to parenteral prostanoids,[17] may not be claimed from the present study.

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 afterload mismatch model, as our IPAH patients, the hemodynamic improvement may translate more easily in WHO class improvement, in agreement with the previous observation of Kemp et al for patients treated with upfront combination therapy. Indeed, in randomized controlled trials[16,18-24] more than 30% of patients enrolled are connective tissue disease related PAH, where the systemic disease may explain the mismatch between the hemodynamic and the functional improvement.

In our study, targeted monotherapy with oral approved drugs, as ERA and PD5i, was able to improve WHO functional class and 6-minute walk distance, increase CI and reduce PVR to a similar magnitude seen in randomized controlled trials that established the efficacy of those treatments.[18-24] Nevertheless, our results indicate that only a few patients with this approach were able to achieve a recommended target-goal. These is the first report describing patient's risk profile after oral monotherapy and highlights that mild afterload reduction, as observed after 4 to 6 months of oral monotherapy, may provide low probability of reversing right heart dilatation and substantially improving right vetricular systolic function, thus not significantly changing patient's clinical risk profile. To our knowledge, no previous study based on echocardiographic or magnetic

resonance imaging (MRI) evaluation has ever reported a significant improvement of right heart size and function after short-term or long-term monotherapy. Indeed, echocardiographic indices have been used in substudies of randomized controlled trials, trying to demonstrate improvement of RV morphology and function after oral monotherapy. These have shown very small effects on RV end-diastolic volume, LV-EI and the ratio of RV to LV surface areas.[25,26] The EURO-MR prospective study 27 reported previously the effects of targeted monotherapies on cardiac MRI-derived indices of RV structure and function in PAH patients. The authors did not find significant changes in RV volumes 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 monotherapies.[28–30]

Recent findings by van de Veerdonk et al[31] showed that disease progression and mortality are preceded by changes in RV dimensions and 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 morphological and functional parameters in such advanced patients, we cannot exclude that monotherapy although it has demonstrated to improve exercise capacity and reduce hospitalization rates in clinical trials, may just delay clinical events in the long-term.

## STUDY LIMITATIONS

The lack of randomization is the major limitation of the 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 in different centers). However, as 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 (nonrandomized) data.[8] After all, our results in terms of clinical and hemodynamic data are in agreement with those reported by international randomized trials, supporting the hypothesis that despite the absence of randomization, the matching method used in the present study was acceptable enough 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 lab for echo-measurements. Nevertheless, to minimize interobserver variability all centers participating to the study were compliant to international guidelines and well known from the literature for echo-studies, allowing the adoption of a common protocol (echo guidelines). Three centers were randomly selected for interobserver variability evaluation and the widest values reported in the study. This may result in a more conservative approach to avoid that a difference between two treatment groups may result from interobserver variability instead of different treatment-regimen effects. In this way any inaccuracy and imprecision introduced by the measurements were 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 the hemodynamic and echocardiographic data recorded. We have repeated the analysis excluding those patients with incomplete data without finding different results.

## CONCLUSIONS

In treatment-naïve 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, while double oral combination and prostanoids as monotherapy seem to produce similar intermediate results. Finally, our study suggests that intermediate and high risk patients may result undertreated from an oral monotherapy approach.

**Conflict of interest statement -** Badagliacca R and Vizza CD have received personal fees from GSK, UT, Dompé, Bayer, MSD, outside the submitted work.

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FIGURE LEGENDS

Figure 1. Correlation between the changes in RVEDA and PVR at short-term follow-up: Δ RVEDA versus Δ PVR (quadratic model: r2=0.49, p=0.0001, y=2.6+0.27x-0.0023x2; linear model: r2=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).

LEGEND – 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: Δ RVFAC versus Δ PVR (quadratic model: r2=0.40, p=0.0001, y=2.01+-0.22x-0.0007x2; linear model: r2=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 circles, brown circles, yellow circles and red circles, respectively).

LEGEND – RVFAC: right ventricular fractional area change; PVR: pulmonary vascular resistance.

Figure 3. RV morphology by echocardiographic evaluation, at diagnosis and after 6-month treatment, in an IPAH naïve 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.

LEGEND – RV: right ventricular; LV: left ventricular; IPAH: idiopathic pulmonary arterial hypertension.

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 (green column), intermediate (yellow column) and high-risk profile (red column) 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 I-II; 6MWT >440 m; RAP < 8 mmHg; CI ( 2.5 l/min/m2; RA area <18 cm2; no PE).

LEGEND – WHO: functional class; 6MWT: six-minute walk test; RAP: right atrial pressure; CI: cardiac index; RA area: right atrium area; PE: pericardial effusion.

| | *Upfront Therapy* | | *Monotherapy* | | |
|---|---|---|---|---|---|
| | **Group 1** | **Group 2** | **Group 3** | **Group 4** | **p** |
| | **n. 27** | **n.42** | **n.69** | **n.27** | |
| **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** | 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, mmHg | 10.4±2.2 | 9.4±4.7 | 9.1±4.5 | 9.7±3.6 | NS |
| mPAP, mmHg | 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 wave PW, cm/s | 0.6±0.2 | 0.8±0.4 | 0.6±0.3 | 0.7±0.4 | NS |
| LV A wave 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 s.c. | 20 (74.1%) |
| Epoprostenol i.v. | 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 s.c.- Tadalafil | 11 (15.9%) |
| Treprostinil s.c.- Ambrisentan | 6 (8.7%) |
| Treprostinil s.c. – Bosentan | 3 (4.4%) |
| Epoprostenol i.v. – Tadalafil | 4 (5.9%) |
| Epoprostenol i.v. - Bosentan | 2 (2.9%) |
| Iloprost i. - Ambrisentan | 1 (1.4%) |

**Table 1.** Baseline characteristics of the upfront combination treated-group, divided in oral plus parenteral prostanoid (Group 1) and double oral combination (Group 2), compared with the two monotherapy matched cohorts, oral (Group 3) and prostanoids (Group 4).

*WHO*: World Health Organization; *6MWT*: non-encouraged 6-minute walk test; *mPAP*: mean pulmonary arterial pressure; *RAP*: mean right atrial pressure; *CI*: cardiac index; *PVR*: pulmonary vascular resistance; *RA area*: right atrium area; *RVEDA*: right ventricular end-diastolic area; *RVESA*: right ventricular end-systolic area; *RVFAC*: right ventricular fractional area change; *TAPSE*: tricupid anular plane systolic excursion; *TR severe*: severe tricuspid regurgitation; *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 wave PW*: pulsed wave left ventricular A wave; *ERA*: endothelin receptor antagonist; *PDE5i*: phosphodiesterase 5 inhibitor; *s.c.*: subcutaneous; *i.v.*: intravenous; *i.*: inhaled; *Time symptoms-diagnosis:* time from symptoms onset to diagnosis (months).

| | *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, mmHg | 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, mmHg | 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, | 26.6± | 20.0 | -6.8± | 0.00 | 27.8 | 23.5 | -4.3± | 0.00 | 29.0± | 29.2 | -0.3± | N | 0.00 | 0.00 | 0.01 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $cm^2$ | 3.7 | ±4.2 | 4.4 | 0 | ±4.4 | ±5.7 | 3.8 | 0 | 7.0 | ±7.0 | 3.5 | S | 0 | 0 | 5 |
| RVESA, $cm^2$ | 19.0± 2.6 | 11.1 ±2.7 | - 7.9± 3.4 | 0. 000 0 | 20.0 ±3.6 | 14.7 ±4.5 | - 5.3± 3.5 | 0. 000 0 | 20.2 ±6.0 | 20.4 ±6 | - 0.1± 4.2 | N S | 0. 000 0 | 0. 000 0 | 0. 001 |
| RVFAC, % | 28.0± 6.8 | 43.0 ±7.7 | 15.6 ±5.2 | 0. 000 0 | 27.6 ±7.8 | 36.9 ±10. 2 | 9.2± 7.4 | 0. 000 0 | 30.4 ±9.6 | 30.2 ±9.2 | 0.0± 7.7 | N S | 0. 000 0 | 0. 002 | 0. 014 |
| TAPSE, mm | 15.6± 2.4 | 22.2 ±3.4 | 6.3± 2.7 | 0. 000 0 | 16±4 .0 | 18.9 ±4.2 | 3.1± 4.1 | 0. 000 0 | 16.4± 4.0 | 17.4 ±4.3 | 0.6± 4.8 | 0. 015 | 0. 000 0 | 0, 009 | 0. 001 |
| RA Area, $cm^2$ | 27.9± 4.5 | 20.1 ±5.2 | - 7.4± 4.6 | 0. 000 0 | 24.8 ±7.1 | 20.9 ±6.0 | - 2.6± 5.6 | 0. 000 0 | 27.6± 10 | 27.1 ±8.9 | - 0.4± 3.8 | N S | 0. 000 0 | 0. 000 0 | 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 %) | | N S | 0. 003 | 0. 003 | N S |
| 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 | N S | N S | N S | N S |
| LVESA, $cm^2$ | 10.9± 2.5 | 11.3 ±2.0 | 0.5± 1.5 | N S | 12.6 ±4.7 | 13.3 ±5.7 | 0.7± 2.4 | N S | 12.7± 4.7 | 12.9 ±4.8 | 0.3± 1.5 | N S | N S | N S | N S |
| LV-EId | 1.43± 0.14 | 1.13 ±0.0 9 | - 0.3± 0.1 | 0. 000 0 | 1.52 ±0.3 0 | 1.26 ±0.2 6 | - 0.18 ±0.4 2 | 0. 000 0 | 1.50± 0.34 | 1.49 ±0.3 9 | - 0.01 ±0.2 | N S | 0. 000 0 | 0. 002 | 0. 027 |
| LV-EIs | 1.60± 0.27 | 1.20 ±0.1 3 | - 0.4± 0,2 | 0. 000 0 | 1.68 ±0.3 5 | 1.34 ±0.2 6 | - 0.24 ±0.5 1 | 0. 000 0 | 1.74± 0.43 | 1.68 ±0.4 8 | - 0.16 ±3.9 | 0. 045 | 0. 000 0 | 0. 000 0 | 0. 014 |
| LVEF, % | 61.8± 6.2 | 61.6 ±5.8 | - 0.1± 2.5 | N S | 60.2 ±8.0 | 62.6 ±8.5 | 2.4± 5.9 | N S | 59.2± 7.3 | 60.3 ±7.2 | 0.5± 5.1 | N S | N S | N S | N S |
| LA area, $cm^2$ | 15.0± 3.1 | 15.2 ±3.4 | 0.0± 1.0 | N S | 15.9 ±5.0 | 15.9 ±4.7 | 0.6± 2.4 | N S | 16.3± 4.3 | 16.2 2±4. 3 | 0.1± 3.0 | N S | N S | N S | N S |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LV E wave 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 wave 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 |

**Table 2.** Changes in clinical, hemodynamic and echocardiographic parameters from baseline to short-term follow-up in Group1, 2 and 3.

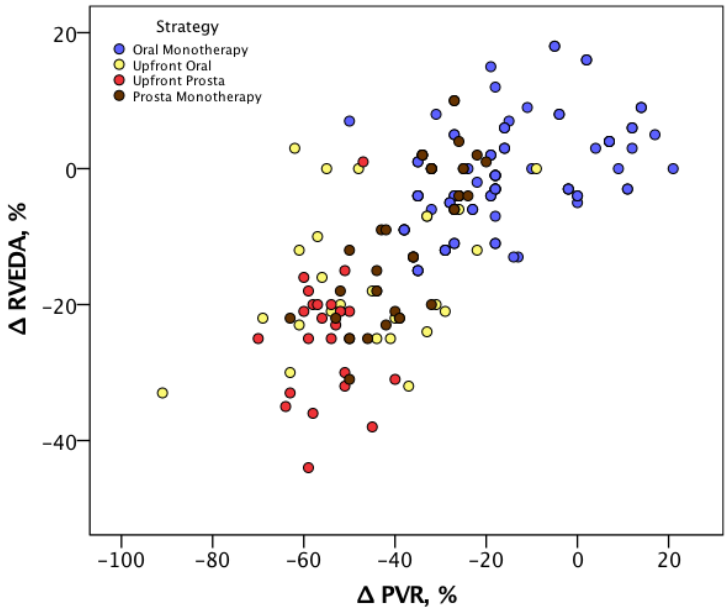
*WHO*: World Health Organization; *6MWT*: non-encouraged 6-minute walk test; *mPAP*: mean pulmonary arterial pressure; *RAP*: mean right atrial pressure; *CI*: cardiac index; *PVR*: pulmonary vascular resistance; *RA* area: right atrium area; *RVEDA*: right ventricular end-diastolic area; *RVESA*: right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

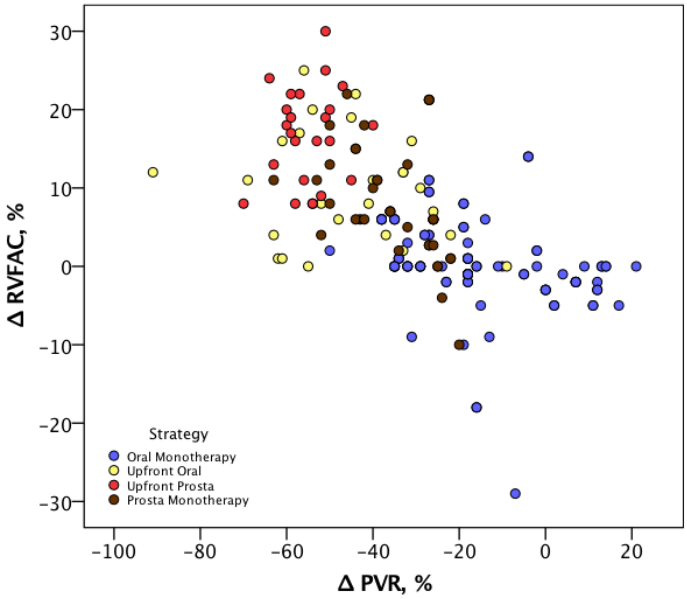
| | GROUP 4 | | | | GROUPS | | |
|---|---|---|---|---|---|---|---|
| | *Baseline* | *155±65 days* | *Δ* | p | **1 vs 4** p | **2 vs 4** p | **3 vs 4** p |
| **WHO** | 3.2±0.4 | 2.2±0.6 | -0.9±0.4 | 0.000 | NS | NS | 0.02 |
| **6MWT, m** | 322±78 | 371±89 | 48±26 | 0.000 | 0.001 | NS | 0.004 |
| **Hemodynamics** | | | | | | | |
| RAP, mmHg | 9.7±3.6 | 6.5±2.3 | -3.3±3.9 | 0.000 | NS | NS | 0.001 |
| mPAP, mmHg | 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 |

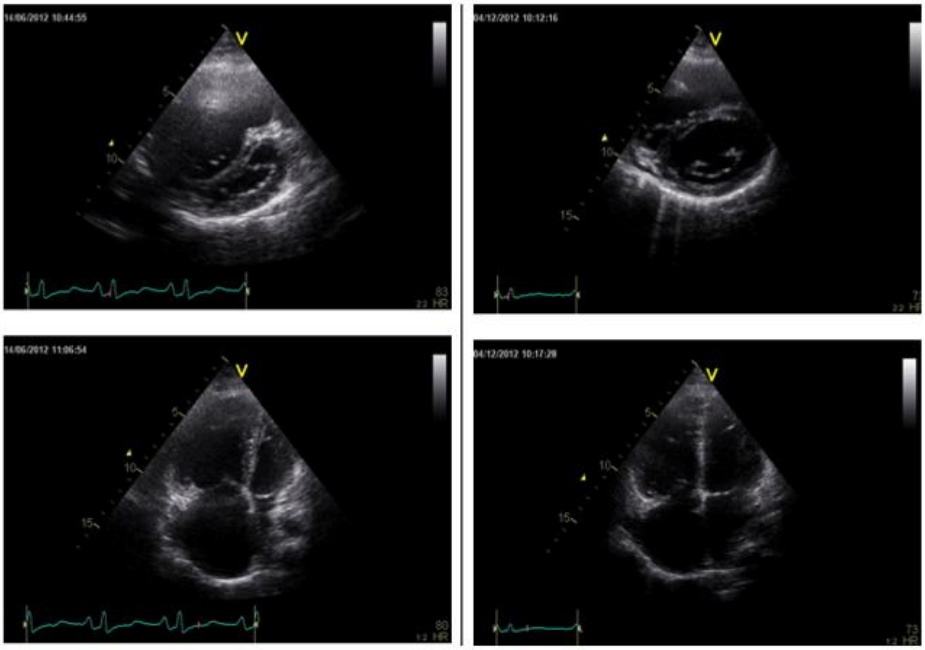
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| LV-EId | 1.55±0.3 | 1.38±0.3 | -0.11±0.3 | 0.000 | 0.01 | NS | 0.002 |
| LV-EIs | 1.62±0.2 | 1.42±0.3 | -0.13±0.3 | 0.000 | 0.01 | NS | NS |
| LVEF, % | 61.3±8.2 | 61.8±6.8 | 0.20±0.8 | NS | NS | NS | NS |
| LA area, $cm^2$ | 15.1±4 | 15.3±3.8 | 0.2±0.8 | NS | NS | NS | NS |
| LV E wave PW, cm/s | 0.7±0.4 | 0.7±0.4 | 0.05±0.1 | NS | 0.02 | NS | NS |
| LV A wave 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 |

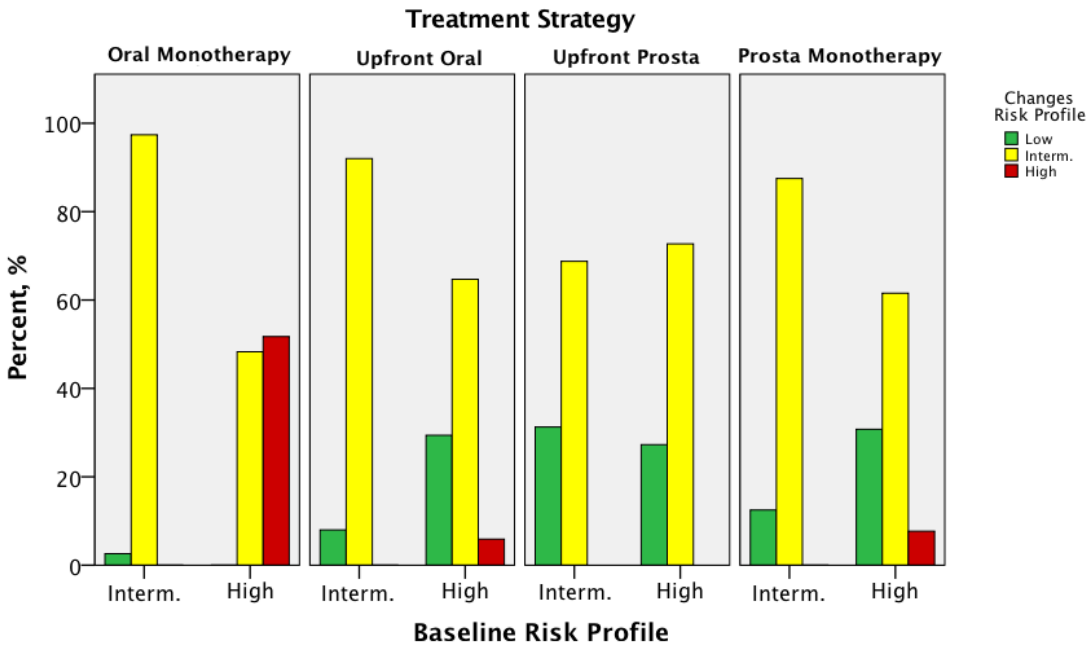
**Table 3.** Changes in clinical, hemodynamic and echocardiographic parameters from baseline to short-term follow-up in Group 4.

*WHO*: World Health Organization; *6MWT*: non-encouraged 6-minute walk test; *mPAP*: mean pulmonary arterial pressure; *RAP*: mean right atrial pressure; *CI*: cardiac index; *PVR*: pulmonary vascular resistance; *RA* area: right atrium area; *RVEDA*: right ventricular end-diastolic area; *RVESA*: right ventricular end-systolic area; *RVFAC*: right ventricular fractional area change; *TAPSE*: tricupid anular plane systolic excursion; *TR* severe: severe tricuspid regurgitation; *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 wave PW*: pulsed wave left ventricular A wave.






Treatment Strategy
Oral Monotherapy
Upfront Oral
Upfront Prosta
Prosta Monotherapy
Changes Risk Profile
Low
Interm.
High
Percent, %
100
80
60
40
20
0
Interm.
High
Baseline Risk Profile