CHEST

Risk Reduction and Right Heart Reverse Remodeling by Upfront Triple Combination Therapy in Pulmonary Arterial Hypertension

Michele D'Alto, MD, PhD; Roberto Badagliacca, MD, PhD; Paola Argiento, MD, PhD; Emanuele Romeo, MD, PhD; Andrea Farro, MD; Silvia Papa, MD; Berardo Sarubbi, MD, PhD; Maria Giovanna Russo, MD; Carmine Dario Vizza, MD, PhD; Paolo Golino, MD, PhD; and Robert Naeije, MD, PhD

BACKGROUND: Combinations of therapies are currently recommended for patients with severe pulmonary arterial hypertension (PAH), and excellent results have been reported with triple upfront combination of these drugs. We evaluated the effects of this approach on right ventricular (RV) function and outcome in patients with severe PAH.

METHODS: Twenty-one patients (age, 44 ± 15 years) with newly diagnosed high-risk idiopathic PAH that was nonreversible by the inhalation of nitric oxide were treated upfront with a combination of ambrisentan, tadalafil, and subcutaneous treprostinil between 2014 and 2018. Clinical evaluation, World Health Organization functional class, 6-min walk distance, biomarkers, echocardiography, and right-sided heart catheterization data were recorded at baseline and during follow-up.

RESULTS: At a median follow-up of 2 years, all patients were still alive. The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management score decreased from 10 ± 1 to 5 ± 1, right-sided atrial pressure decreased from 13 ± 3 to 5 ± 2 mm Hg, mean pulmonary artery pressure decreased from 60 ± 9 to 42 ± 5 mm Hg, pulmonary vascular resistance (PVR) decreased from 16.4 ± 4.4 to 5.5 ± 1.3 Wood units, N-terminal pro-brain natriuretic peptide decreased from 3,379 ± 1,921 to 498 ± 223 pg/mL, and World Health Organization functional class decreased from 3.4 ± 0.5 to 2.0 ± 0.4 (all $P < .001$). Cardiac index increased from 1.8 ± 0.3 to 3.5 ± 0.8 L/min/m^2 and 6-min walk distance increased from 158 ± 130 to 431 ± 66 m (both $P < .001$). Echocardiography showed decreased right-sided atrial and RV areas, improved left ventricular eccentricity index, and increased fractional area change (all $P < .001$) in proportion to treatment-induced decrease in PVR.

CONCLUSIONS: Triple upfront combination therapy with ambrisentan, tadalafil, and subcutaneous treprostinil in severe nonreversible PAH is associated with considerable clinical and hemodynamic improvement and right-sided heart reverse remodeling.

CHEST 2020; 157(2):376-383

KEY WORDS: heart remodeling; pulmonary arterial hypertension; triple combination therapy

FOR EDITORIAL COMMENT, SEE PAGE 251

ABBREVIATIONS: 6MWD = 6-min walk distance; CO = cardiac output; FAC = fractional area change; LV = left ventricular; mPAP = mean pulmonary artery pressure; NO = nitric oxide; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; REVEAL = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; RHRR = right-sided heart reverse remodeling; RV = right ventricular; RVEDA = right ventricular end-diastolic area; WHO = World Health Organization

AFFILIATIONS: From the Department of Cardiology (Drs D'Alto, Argiento, Romeo, Farro, Sarubbi, Russo, and Golino), Monaldi Hospital - "L. Vanvitelli" University, Naples, Italy; the Department of

It has been increasingly recognized that right ventricular (RV) function is the major determinant of symptoms and outcome in patients with pulmonary arterial hypertension (PAH).[1] The time course of RV function and structure adaptation and eventual failure in the presence of increased pulmonary vascular resistance (PVR) is now being understood. As reviewed, the right ventricle basically adapts to increased afterload by increased contractility to preserve its coupling to the pulmonary circulation, and when this homeometric adaptation gets exhausted, a heterometric adaptation by increased dimensions comes into play to preserve cardiac output (CO) at the price of eventual systemic congestion.[2,3] Therefore, RV dilatation leads to right-sided heart failure, and its reversal would be expected to improve symptoms and prognosis in PAH. Evidence that this can be achieved by current therapies is scarce. Echocardiographic findings of right-sided heart reverse remodeling (RHRR) as determined by decreased right-sided atrial and RV surface areas together with decreased left ventricular (LV) eccentricity index have been shown in one study to be associated with a markedly improved survival in idiopathic PAH.[4] However, this survival benefit was achieved in no more than 18% of the patients under a single drug regimen with addition of a second drug in case of clinical deterioration as was recommended at that time.[5] It has been shown that a combination of two drugs increases the likelihood of RHRR in proportion to decreased PVR.[6,7] Initial or early combination of two drugs is currently recommended for the treatment of PAH.[8]

An even more aggressive treatment with upfront combination of three drugs targeting different pathways in severe idiopathic PAH has been reported in a preliminary study to be associated with a marked decrease in PVR and persistent improvement of functional class, exercise capacity, and survival.[9] We hypothesized that these favorable effects might be accounted for by improved RV structure and function.

Methods

This was a retrospective study conducted in treatment-naive adult patients with severe idiopathic PAH admitted to two Italian centers (Monaldi Hospital in Naples and La Sapienza University in Rome) between January 2014 and December 2018. The study was approved by the local institutional review board (No. 842/16).

All patients underwent a step-by-step diagnostic workup including a reversibility test by inhaled nitric oxide (NO) according to current guidelines.[10] Echocardiographic data were acquired by dedicated cardiologists using commercially available equipment. Standard M-mode, two-dimensional, and Doppler images were obtained as previously reported[7] and in accordance with the American Society of Echocardiography guidelines.[11] Right-sided heart catheterization was performed without sedation by dedicated cardiologists. Measurements of right atrial pressure, pulmonary artery pressure (PAP), and pulmonary artery wedge pressure were obtained at end-expiration. The zero level was set at the midthoracic level. Blood samples for measuring mixed venous oxygen saturation were drawn. CO was measured by thermodilution using an average of at least three measurements. PVR was calculated as the difference between mean pulmonary artery pressure (mPAP) and pulmonary artery wedge pressure divided by CO.

Twenty-one patients were treated with an upfront combination of ambrisentan, tadalafil, and subcutaneous treprostinil. Ambrisentan and tadalafil were administered according to the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial protocol[12]: ambrisentan 5 mg daily, uptitrated to 10 mg at week 8, and tadalafil 20 mg daily, uptitrated to 40 mg at week 4. A continuous infusion of subcutaneous treprostinil using a portable infusion pump (CADD-MS 3 Ambulatory Infusion Pump; Smiths Medical ASD, Inc) was initiated at 2 ng/kg/min with the dose increased by 2 ng/kg/min every 8 to 12 h. After 5 days and once a treprostinil dose of 10 ng/kg/min had been reached, the patients were discharged. Treprostinil was further uptitrated by 2 ng/kg/min every week depending on the patient's tolerance. A matched control cohort of 31 treatment-naïve patients with nonreversible idiopathic PAH receiving oral monotherapy (bosentan: n = 12 [39%]; ambrisentan: n = 6 [19%]; sildenafil: n = 8 [26%]; tadalafil: n = 5 [16%]) as standard of care at that time was extracted from a previously reported retrospective multicenter series.[7]

Clinical status was assessed by World Health Organization (WHO) functional class, 6-min walk distance (6MWD), and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level. The simplified Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) risk score, which incorporates both positive and negative predictors of survival and includes a total of 11 parameters comprising 13 components (seven from etiology and physical examination, and six from diagnostic tests) was used for risk stratification at baseline and during follow-up.[13]

All patients were followed every three months in the outpatient clinic. A complete reassessment including clinical examination, 6MWD, NT-proBNP level, echocardiography, and right-sided heart catheterization was obtained after 12 ± 4 months of treatment.

Cardiology (Drs Badagliacca, Papa, and Vizza), La Sapienza University, Rome, Italy; and the Department of Pathophysiology (Dr Naeije), Free University of Brussels, Brussels, Belgium.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: Michele D'Alto, MD, PhD, Department of Cardiology, Monaldi Hospital - "L. Vanvitelli" University, piazzale E. Ruggieri 1, 80128, Naples, Italy; e-mail: mic.dalto@tin.it

DOI: https://doi.org/10.1016/j.chest.2019.09.009

Statistical Analysis

Data are presented as mean ± SD unless otherwise indicated. Changes in 6MWD, NT-proBNP level, echocardiographic variables, and hemodynamics from baseline to 12-month follow-up were evaluated using paired-samples Student t test for continuous variables. Differences with $P < .05$ were considered significant. To assess the relations between 6MWD, right ventricular end-diastolic area (RVEDA), RV fractional area change (FAC), and PVR changes during follow-up, both linear and nonlinear regression models were fitted, comparing predictive accuracy by means of r^2. A quadratic model was identified as the most accurate. Details of the quadratic model are reported, including corresponding r^2 values, P values, and regression equations. Linear regression analysis was performed to assess the relationship between RVEDA and REVEAL 2.0 changes during follow-up, and expressed as a Pearson correlation coefficient.

Results

Demographics, clinical characteristics, biomarkers, and hemodynamics of the 21 patients treated with upfront triple combination of targeted therapies (and 31 monotherapy historical control subjects used for comparison) are reported in Table 1. The patients were severely ill, with nine of 21 patients with WHO functional class IV and 12 of 21 patients with WHO functional class III. All patients had a REVEAL Registry risk score ≥ 9. The main echocardiographic and hemodynamic features of these patients at baseline and 12-month follow-up are shown in Tables 2 and 3. All patients were alive at the end of follow-up (24 ± 14 months; range, 8-53 months).

During follow-up, four of 21 patients (19%) had mild-to-moderate peripheral edema, two of 21 patients (10%) had nasal congestion, and three of 21 patients (14%) had flushing. No patient had liver aspartate and alanine aminotransferase elevations more than three times the upper limit of normal during the follow-up. Overall, all but one of the 21 patients reached the full dose of ambrisentan and tadalafil (10 and 40 mg daily, respectively). The treprostinil dose at the end of follow-up was 45 ± 17 ng/kg/min (range, 26-92 ng/kg/min). No patient discontinued oral or subcutaneous combination therapy because of side effects.

At the 24-month follow-up reevaluation, all patients improved their WHO functional class. Notably, 19 of 21 patients (90%) reached WHO functional class I or II.

TABLE 1] Demographics, Clinical Characteristics, Biomarkers, and Hemodynamics at Baseline in Triple Upfront Therapy Group and Historical Cohort (Monotherapy)

Variable	Triple Upfront (n = 21)	Historical Cohort (Monotherapy) (n = 31)
Sex		
Female	16 (76)	22 (71)
Male	5 (24)	9 (29)
Age, y	44 ± 15	50 ± 13
WHO functional class		
I	0 (0)	0 (0)
II	0 (0)	0 (0)
III	12 (57)	28 (90.4)
IV	9 (43)	3 (9.6)
NT-proBNP, pg/mL	3,379 ± 1,921	NA
6MWD, m	158 ± 130	310 ± 102
REVEAL Registry risk score	10 ± 1	NA
Hemodynamics		
RAP, mm Hg	13 ± 3	8 ± 4
mPAP, mm Hg	60 ± 9	55 ± 11
PAWP, mm Hg	8 ± 2	9 ± 3
Cardiac index, L/min/m^2	1.8 ± 0.3	2.4 ± 0.5
PVR, WU	16.4 ± 4.4	11.3 ± 4.8

Values are expressed as mean ± SD or No. (%). 6MWD = 6-min walk distance; mPAP = mean pulmonary artery pressure; NA = not available; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; REVEAL = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; WHO = World Health Organization; WU = Wood units.

TABLE 2] Hemodynamics at Baseline and 24-Month Follow-Up

Variable	Baseline	Follow-Up	Change (%)	*P* Value
RAP, mm Hg	13 ± 3	5 ± 2	−8 (−62)	< .001
mPAP, mm Hg	60 ± 9	42 ± 5	−18 (−30)	< .001
PAWP, mm Hg	8 ± 2	9 ± 3	1 (12)	.545
Cardiac input, L/min/m^2	1.8 ± 0.3	3.5 ± 0.8	1.7 (94)	< .001
PVR, WU	16.4 ± 4.4	5.5 ± 1.3	−10.9 (−69)	< .001
Svo_2, %	56 ± 6	70 ± 7	14 (25)	< .001

Values are expressed as mean ± SD or as otherwise indicated. Svo_2 = mixed venous oxygen saturation. See Table 1 legend for expansion of other abbreviations.

The REVEAL Registry risk score was reduced in all patients: 17 of 21 patients (81%) reached the low-risk category and three of 21 patients (19%) reached the intermediate-risk category at the end of follow-up. The 6MWD increased by 273 m (from 158 ± 130 to 431 ± 66 m, $P < .001$) and NT-proBNP levels decreased (from 3,379 ± 1,921 to 498 ± 223 pg/mL; $P < .001$).

Echocardiography showed improved RV function and structure. In particular, the right-sided atrial area decreased by 28%, the RV end-diastolic and end-systolic areas decreased by 29% and 43%, respectively, the RV FAC increased by 63%, and the LV eccentricity index decreased by 20%. RHRR was achieved in all patients. An exemplative case is displayed in Figure 1.

Right-sided heart catheterization showed a decrease in right atrial pressure, mPAP, and PVR by 62%, 30%, and 69%, respectively, and an increase in the cardiac index by 94%.

The decreased RV dimensions and REVEAL Registry score, and the increase in 6MWD, were correlated with the decrease in PVR (all $P < .001$). Individual changes in RVEDA and RV FAC as a function of percent decrease in PVR are shown in Figures 2 and 3, with 31 monotherapy historical control subjects. Markedly more reverse remodeling in relation to more important decreases in PVR was observed in patients treated with triple upfront combination therapy.

There were no significant correlations between changes in RV dimensions or FACs and changes in the REVEAL Registry score. This is illustrated in Figure 4, which shows the relationships between changes in RVEDA and REVEAL Registry scores in patients with decreased PVR of either ≤ 60% or > 60% (linear model: $r = 0.29$, $r^2 = 0.09$, $P = .19$, $y = -1.8 - 0.29x$).

Discussion

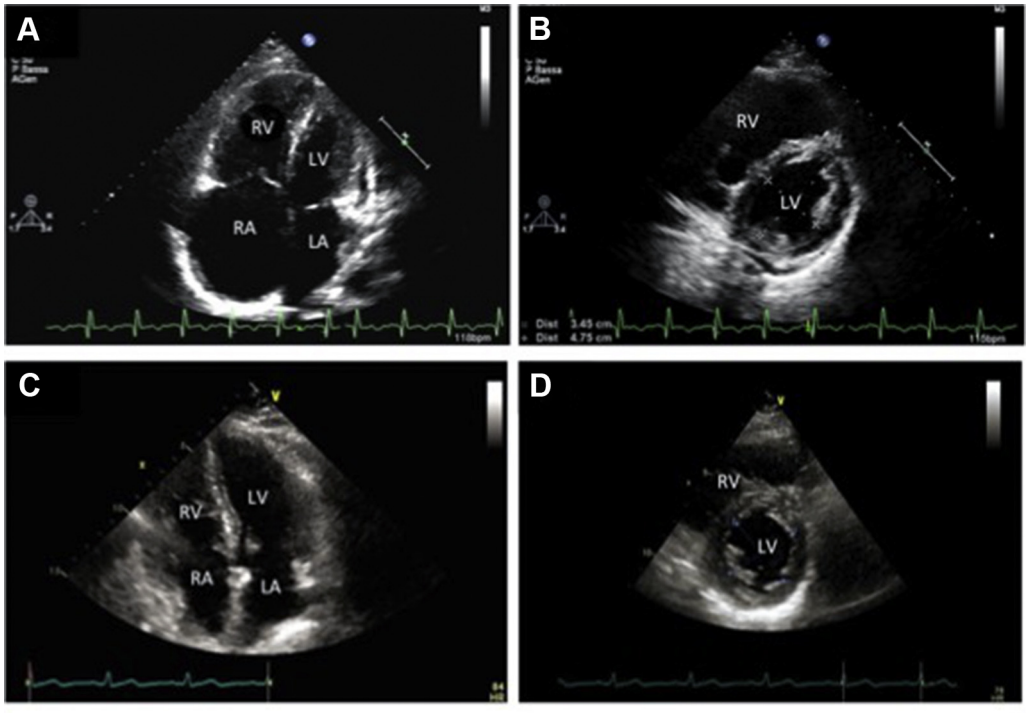
The results show considerable functional and hemodynamic improvement with RHRR and a markedly reduced risk after an average of 2 years of straight-on triple combination therapy with ambrisentan, tadalafil, and treprostinil in patients with severe idiopathic PAH.

There has been a tendency for earlier combinations of targeted therapies in PAH because clinical improvement and survival with single use of these drugs remain insufficient.[5,8,10] Although parenteral prostacyclins have always been the preferred option for patients with WHO functional class IV, treatment is otherwise started with one or two oral drugs targeting endothelin or NO signaling pathways depending on risk assessment, with a parenteral prostacyclin eventually added.[8] For this purpose, patients are commonly categorized in low,

TABLE 3] Echocardiographic Features at Baseline and 24-Month Follow-Up

Variable	Baseline	Follow-Up	Change (%)	*P* Value
Right-sided atrial area, cm^2	29 ± 3	21 ± 2	−8 (−28)	< .001
RV end-diastolic area, cm^2	28 ± 2	20 ± 3	−8 (−29)	< .001
RV end-systolic area, cm^2	21 ± 2	12 ± 2	−9 (−43)	< .001
Fractional area change, %	27 ± 4	40 ± 5	13 (63)	< .001
LV eccentricity index	1.5 ± 0.1	1.2 ± 0.1	−0.3 (−20)	< .001

Values are expressed as mean ± SD or as otherwise indicated. LV = left ventricular; RV = right ventricular.



	Baseline	Follow-up
PVR (WU)	17.9	6.1
RVEDA (cm^2)	26	17
RVESA (cm^2)	19	10
LV-EI	1.5	1.1
REVEAL 2.0	11	7

Figure 1 – *A-D, Typical right ventricular reverse remodeling after triple upfront therapy. Four-chamber and short-axis echocardiographic views at baseline (A and B) and at the end of follow-up (C and D). LA = left atrium; LV = left ventricle; LV-EI = left ventricular eccentricity index; PVR = pulmonary vascular resistance; RA = right atrium; REVEAL 2.0 = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management 2.0 risk score; RV = right ventricle; RVEDA = right ventricular end-diastolic area; RVESA = right ventricular end-systolic area; WU = Wood units.*

intermediate, or high risk of 1-year mortality based on risk assessment scores.[8] The rationale for risk assessment-guided therapies in PAH is that reversal to a lower risk category brings the patient back to the associated survival prediction. Data have been accumulating that this assumption is correct.

The most commonly used risk scoring system in PAH introduced in the 2016 European Society of Cardiology and European Respiratory Society guidelines[10] is based on 14 variables covering clinical assessment, hemodynamic measurements, imaging, exercise testing, and NT-proBNP levels. This risk scoring system was validated a posteriori in registries with extraction of eight,[14] six,[15] and three[16] variables, depending on local accessibility. In the meantime, the REVEAL Registry allowed for a prospective validation of an 11-parameter and 13-component score, including functional class, BP, heart rate, 6MWD, brain natriuretic peptide level, lung function tests, hemodynamics, and pericardial effusion.[13] The most recent version of this score used in the present study was shown to be superior to European Respiratory Society and European Society of Cardiology guideline-derived scores for risk discrimination.[13] Of note, echocardiography was part of the European Respiratory Society and European Society of Cardiology guideline risk assessment in only one study[14] and is part of the REVEAL Registry score,[13] but with only pericardial effusion combined with right-sided atrial area and pericardial effusion alone, respectively.

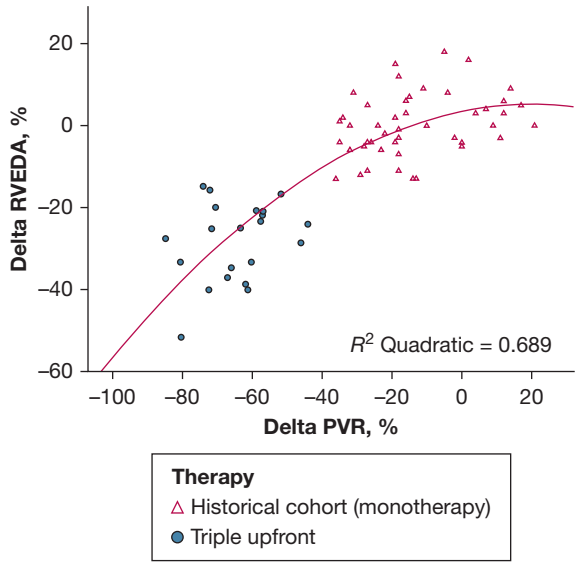


Figure 2 – *Correlation between changes in RVEDA and PVR at follow-up: Δ RVEDA vs Δ PVR (quadratic model: $R^2 = 0.69$, $P = .0001$). Δ RVEDA vs Δ PVR (quadratic model: $R^2 = 0.69$, $P = .0001$; $y = 3.46 + 0.17x - 0.004x^2$). Circles indicate the triple upfront combination therapy, and triangles indicate the oral monotherapy cohort derived from a previous study.[7] Markedly more reverse remodeling in relation to more important decrease in PVR was observed in patients treated with triple upfront combination therapy. See Figure 1 legend for expansion of abbreviations.*

Although all these scores are indirectly affected by the adequacy of RV function adaptation to afterload, none of them included measurements of RV

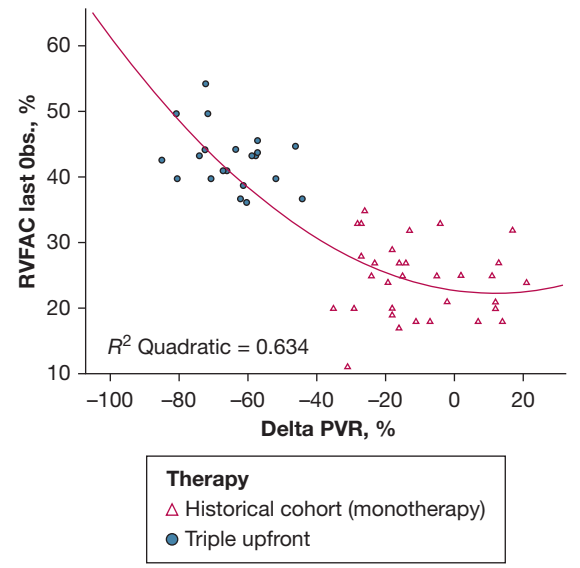


Figure 3 – *Correlation between changes in RVFAC and PVR at follow-up: Δ RVFAC vs Δ PVR (quadratic model: $r^2 = 0.63$, $P = .0001$; $y = 22.8 - 0.08x + 0.003x^2$). Circles indicate the triple upfront combination therapy, and triangles indicate the oral monotherapy cohort derived from a previous study.[7] Markedly better recovery of RVFAC in relation to more important decrease in PVR was observed in patients treated with triple upfront combination therapy. Obs. = observed; RVFAC = right ventricular fractional area change. See Figure 1 legend for expansion of other abbreviation.*

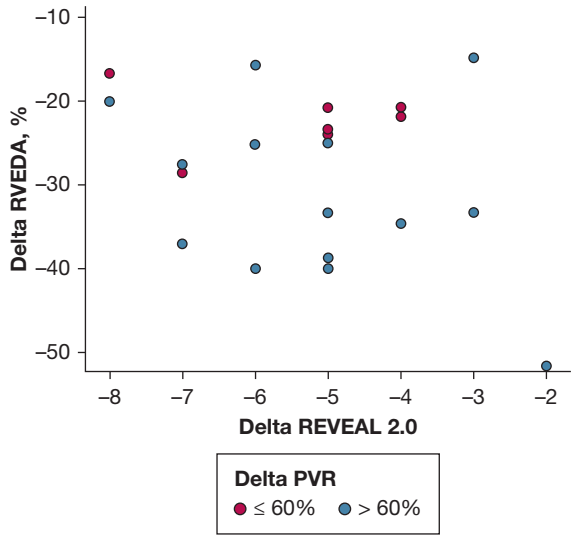


Figure 4 – *Relationships between changes in RVEDA and REVEAL Registry score in patients with decreased PVR of either ≤ 60% or > 60% (linear model: $r = 0.29$, $R^2 = 0.09$, $P = .19$; $y = -1.8 - 0.29x$). Patients with < 60% and > 60% reduction in PVR are reported in the same scatterplot (red circles and blue circles, respectively). Changes in RVEDA were not significantly correlated with changes in the REVEAL Registry score. See Figure 1 legend for expansion of abbreviations.*

dimensions necessary for a diagnosis of right-sided heart failure.[2,3]

Beyond the strategy of stepwise reinforcement of targeted therapies with use of risk scores,[8] Sitbon et al[9] applied a more aggressive triple upfront combination of bosentan, sildenafil, and intravenous epoprostenol in a small preliminary study of 19 patients with severe idiopathic PAH in WHO functional class III and IV. This approach resulted in an unprecedented functional improvement because 17 of these patients improved to WHO functional class I or II, improved the 6MWD by an average of 235 m, decreased mPAP by 20 mm Hg, and had a 67% decrease in PVR at the first follow-up evaluation after 4 months. These favorable effects were sustained during a median follow-up of 32 months in 18 patients (one patient underwent lung transplantation soon after being initiated on triple upfront combination therapy).[9] In the present study, a triple upfront combination of ambrisentan, tadalafil, and subcutaneous treprostinil in patients with severe idiopathic PAH produced strikingly similar results, with sustained improvement in functional state and exercise capacity (273 m in 6MWD), a fall in mPAP (−18 mm Hg), and a decrease in PVR (by 69%). Both studies, although small, show that upfront triple combination of drugs targeting endothelin, NO, and prostacyclin pathways allows for a clinical and hemodynamic improvement in severe PAH that is not observed with one or two of these drugs in combination. Interestingly, within-class

pharmacologic characteristics of drugs do not appear to matter to the results achieved by the triple upfront combination strategy in idiopathic PAH.

In this study, similar to Sitbon et al,[9] inhaled NO was associated with trivial changes in pulmonary hemodynamics; therefore, the patients were diagnosed as nonresponders in agreement with current guidelines.[5,10] Triple upfront combination of targeted therapies was nonetheless associated with decreases in PVR, surpassing the reported effects of inhaled NO in so-called responders, in whom PVR decreased by 40% to 45%.[17,18] The first reversible idiopathic PAH reported by Dresdale et al[19] in 1954 had a 67% decrease in PVR with injection of the alpha receptor blocking agent priscoline directly into the pulmonary artery. The mechanisms of major reversibility of PVR obtained by triple upfront combination of targeted therapies in nonacutely reversible idiopathic PAH are not known.

Right-sided heart failure with clinical picture of a combination of decreased CO (first at exercise and eventually at rest) and systemic congestion is necessarily associated with increased RV dimensions.[1-3] This RV remodeling may occur while PVR and 6MWD are still preserved, but yields a very poor prognosis.[20,21]

The idea to evaluate the effects of PAH therapies alone or in combination on right-sided heart dimensions is not new. van Wolferen et al[22] showed that addition of sildenafil to bosentan in 15 patients with PAH improved RV ejection fraction and decreased RV mass, but with no significant change in RV end-diastolic volume as assessed by MRI. These effects of RV dimensions and function appear small compared with those of upfront triple combination therapy in the present study, which decreased RV surface areas by 30% to 40% and increased FAC, the two-dimensional echocardiographic surrogate of ejection fraction by some 60%.

Reversal of right-sided heart dilatation as defined at two-dimensional echocardiography by the combination of decreased right-sided atrial and RV areas and LV eccentricity index is associated with an excellent long-term survival and quality of life, but is achievable in only a minority of patients under monotherapy or stepwise additions to initial monotherapy.[5] This was further confirmed by a multicenter MRI study, which showed no significant changes in RV volumes and mass and only a slight 5% improvement in ejection fraction in 91 patients with PAH, most of whom were on monotherapy.[23]

RHRR is more constantly obtained by a combination of drugs, preferably with a parenteral prostacyclin, in relation to decreased PVR.[6,7] The likelihood of RHRR is a sigmoid function of decreased PVR, with $>$ 50% RHRR observed when PVR decreases by $>$ 50%. In the present study, triple upfront combination of targeted therapies decreased PVR on average by 69%, and RHRR was obtained in all patients. RHRR was associated with a REVEAL Registry score down to $<$ 6, resulting in excellent survival. However, there was no significant correlation between changes in right heart dimensions and changes in REVEAL Registry scores, indirectly supporting the notion of added value of simple echocardiographic imaging of the right side of the heart in PAH risk assessment.

This study, although small, retrospective, and limited to severe idiopathic PAH, showed that reverse remodeling of the right ventricle can be achieved in a substantial proportion of patients treated by upfront combination triple therapy targeting endothelin, NO, and prostacyclin pathways.

Acknowledgments

Author contributions: M. D. and R. B. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including any adverse effects. M. D., R. B., and R. N. contributed to the study design, data analysis, and interpretation. P. A., E. R., A. F., S. P., B. S., and M. G. R. contributed to data analysis and interpretation. M. D., R. B., and R. N. contributed to writing of the manuscript. C. D. V. and P. G. contributed to critical revision of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: M. D. received fees for participating in advisory boards and received benefits (travel and accommodation for scientific meetings) from Actelion, Bayer, Dompè, GSK, MSD, and United Therapeutics. R. B. received fees for speaking activities and advisory committees from Bayer, Dompe, GSK, Ferrer, Galenica, MSD, and United Therapeutics. C. D. V. has received fees as a speaker in sponsored symposium, has received fees for participating in advisory boards, and has received benefits (travel and accommodation for scientific meetings) from Actelion, Bayer, GSK, MSD, and United Therapeutics. R. N. has provided consultancy services, research grants, and membership of scientific advisory boards for AOP Orphan Pharmaceuticals, Actelion, Reata, and Lung Biotechnology Corp. None declared (P. A., E. R., A. F., S. P., B. S., M. G. R., P. G.).

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

1. Galiè N, Palazzini M, Manes A. Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses. *Eur Heart J*. 2010;31(17):2080-2086.
2. Vonk Noordegraaf A, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. *Eur Respir J*. 2019;53(1):1801900.
3. Sanz J, Sánchez-Quintana D, Bossone E, Bogaard HJ, Naeije R. Anatomy, function, and dysfunction of the right ventricle: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;73(12):1463-1482.
4. Badagliacca R, Poscia R, Pezzuto B, et al. Prognostic relevance of right heart reverse remodeling in idiopathic pulmonary arterial hypertension. *J Heart Lung Transplant*. 2018;37(17):195-205.
5. 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(20):2493-2537.
6. van de Veerdonk MC, Huis In T Veld AE, Marcus JT, et al. Upfront combination therapy reduces right ventricular volumes in pulmonary arterial hypertension. *Eur Respir J*. 2017;49(6):1700007.
7. Badagliacca R, Raina A, Ghio S, et al. Influence of various therapeutic strategies on right ventricular morphology, function and hemodynamics in pulmonary arterial hypertension. *J Heart Lung Transplant*. 2018;37(3):365-375.
8. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J*. 2019;53(1):1801889.
9. Sitbon O, Jais X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J*. 2014;43(6):1691-1697.
10. Galiè N, Humbert M, Vachiery JL, et al. 2015 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(1):67-119.
11. Lang RM, Badano LP, Mor-Avi V, et al. Recommendation for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-270.
12. Galiè N, Barbera GA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373(9):834-844.
13. Benza RL, Gomberg-Maitland M, Elliott CG, et al. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL Risk Score Calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. *Chest*. 2019;156(2):323-337.
14. Kylhammar D, Kjellström B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J*. 2018;39(47):4175-4181.
15. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J*. 2017;50(2):1700740.
16. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J*. 2017;50(2):1700889.
17. Sitbon O, Humbert M, Jagot JL, et al. Inhaled nitric oxide as a screening agent for safely identifying responders to oral calcium-channel blockers in primary pulmonary hypertension. *Eur Respir J*. 1998;12(2):265-270.
18. Sitbon O, Humbert M, Jaïs X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation*. 2005;111(23):3105-3111.
19. Dresdale DT, Mitchom RJ, Schultz M. Recent studies in primary pulmonary hypertension, including pharmacodynamic observations on pulmonary vascular resistance. *Bull N Y Med Acad*. 1954;30(3):195-207.
20. Vonk Noordegraaf A, Haddad F, Bogaard HJ, Hassoun PM. Noninvasive imaging in the assessment of the cardiopulmonary vascular unit. *Circulation*. 2015;131(10):899-915.
21. 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(4):1063-1071.
22. van Wolferen SA, Boonstra A, Marcus JT, et al. Right ventricular reverse remodelling after sildenafil in pulmonary arterial hypertension. *Heart*. 2006;92(12):1860-1861.
23. 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(1):107-114.