Profiles and treatment patterns of patients with pulmonary arterial hypertension on monotherapy at experienced centres

Max Wissmüller1,2, Panagiota Xanthouli3,4, Nicola Benjamin3,4, Ekkehard Grünig3,4, Manuel J. Richter4,5, Henning Gali6,7, Hossein Ardeschir Ghofrani4,5, Simon Herkenrath6,7, Dirk Skowasch8, Carmen Pizarro8, Michael Halank9, Christopher Hohmann1,2, Martin Hellmich10, Felix Gerhardt1,2 and Stephan Rosenkranz1,2,11*

1Klinik III für Innere Medizin, Herzzentrum der Universität zu Köln, Kerpener Str. 62, Cologne, 50935, Germany; 2Cologne Cardiovascular Research Center (CCRC), Universität zu Köln, Cologne, Germany; 3Zentrum für pulmonale Hypertonie, Thoraxklinik, Universitätsklinikum Heidelberg und Translational Lung Research Centre, Heidelberg, Germany; 4Deutsches Zentrum für Lungenforschung (DZL), Giessen, Germany; 5Abt. Pneumologie, Medizinische Klinik II, Universitätsklinikum Gießen und Marburg, Universitätsklinik Gießen und Marburg Lung Center (UZLMC), Giessen, Germany; 6Institute for Pneumology, University of Cologne, Solingen, Germany; 7Bethanien Hospital, Clinic of Pneumology and Allergology Center for Sleep Medicine and Respiratory Care, Solingen, Germany; 8Medizinische Klinik II, Universitätsklinikum Bonn, Bonn, Germany; 9Medizinische Klinik I, Universitätsklinik Carl Gustav Carus, TU Dresden, Dresden, Germany; 10Institut für Medizinische Statistik, Informatik und Epidemiologie (IMISE), Universität zu Köln, Cologne, Germany; and 11Center for Molecular Medicine Cologne (CMMC), Universität zu Köln, Cologne, Germany

Abstract

Aims  Guideline recommendations highlight the critical role of combination therapy for the treatment of pulmonary arterial hypertension (PAH). Conversely, registry data demonstrate that a considerable number of PAH patients remain on monotherapy. The reasons for this discrepancy remain elusive. The aim of this study was to assess the patient profiles, treatment patterns, and disease characteristics of patients diagnosed with PAH who were kept on monotherapy at experienced pulmonary hypertension (PH) centres and to capture potential reasons for monotherapy.

Methods and results  We analysed the patient profiles of 182 patients on monotherapy with PAH-targeted drugs, managed at experienced PH expert centres (Cologne, Giessen, Heidelberg, and Dresden). Patients were identified based on their latest follow-up visit and analysed retrospectively from the time of PAH diagnosis to last follow-up. Patients were dichotomized by age, and patient characteristics, treatment patterns, response to therapy, change in risk status, and drug tolerability were recorded during the course of their disease. Patients’ mean age was 69.1 ± 13.1 years at the most recent follow-up (Key Time Point 1) and 64.5 ± 14.9 years at the time of diagnosis (Key Time Point 2). The mean time on monotherapy was 60.7 ± 53.8 months; 35.7/64.3% of patients were male/female. The majority (66.5%) had idiopathic PAH, followed by PAH associated with connective tissue disease (17.0%) and portopulmonary PH (8.2%). Among patients on monotherapy, there were five main clusters: (i) patients with failed escalation attempts mostly because of intolerability (26.9%); (ii) low risk on monotherapy, favourable response, and no reason for escalation (24.2%); (iii) patients with mild PAH (36.3%); (iv) elderly patients with PAH and multiple co-morbidities (38.5%); and (v) patients with associated forms of PAH where the level of evidence for combination therapies is considered low (16.5%). There were substantial differences between patients above or below the median age (68 years). The most frequently used monotherapy for PAH was phosphodiesterase type 5 inhibitors (75.3%).

Conclusions  A considerable number of PAH patients are on monotherapy at large PH expert centres, characterized by specific reasons that justify this kind of treatment. Nevertheless, as comprehensive treatment strategies have shown improved long-term outcomes even in mildly symptomatic patients, each case of monotherapy should be justified.

Keywords  Pulmonary arterial hypertension; Therapy; Monotherapy; Phenotype

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*Correspondence to: Stephan Rosenkranz, Klinik III für Innere Medizin, Herzzentrum der Universität zu Köln, Kerpener Str. 62, 50935 Cologne, Germany. Tel: +49-221-478-32356; Fax: +49-221-478-32355. Email: stephan.rosenkranz@uk-koeln.de

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Introduction

Guideline recommendations highlight the critical role of combination therapy in the treatment of patients with pulmonary arterial (PA) hypertension (PAH). Several randomized controlled trials have demonstrated that adding a targeted PAH drug in patients who are already on background therapy in the context of sequential combination therapy improves the clinical status of patients, as assessed by composite morbidity and mortality endpoints and/or specific PAH parameters. Recently, it was demonstrated in a landmark analysis that the occurrence of morbidity events is highly predictive for all-cause mortality in PAH, supporting the importance of such study endpoints. The AMBITION study provided strong evidence that upfront combination therapy with a phosphodiesterase type 5 inhibitor (PDE5i: tadalafil) and an endothelin receptor antagonist (ERA: ambrisentan) in patients with newly diagnosed PAH is superior to monotherapy with either compound alone in preventing morbidity and mortality events. Further analysis of the AMBITION data indicated that this treatment approach may even improve short-term survival early after diagnosis. Finally, the soluble guanylate cyclase stimulator riociguat was also shown to be beneficial in patients who are pretreated with an ERA or a prostacyclin analogue in the PATENT study, and triple upfront combination therapy including a parenteral prostanooid was particularly efficacious in patients with advanced PAH and severely impaired haemodynamics. Based on this evidence, current guidelines and expert consensus reports recommend combination therapy for the majority of PAH patients.

Despite this scientific evidence and clear guideline recommendations, registry data continuously demonstrate that a fairly large number of PAH patients remain on monotherapy with only one approved PAH drug. This is a potential matter of concern, because such data may indicate that a considerable number of patients appear not to be on optimized therapy in the routine care setting. When considering the multiple treatment options that are available today, the reasons for this phenomenon remain speculative.

Given the current registry data, it appears important to understand the rationale to keep patients on PAH monotherapy in experienced centres. In particular, it is crucial to understand whether monotherapy is used appropriately in this context, as well as to identify potential shortcomings in the ‘real-world’ setting of PAH therapy. It appears critical to capture sufficient data on the patient profile (‘classical PAH’, PAH with co-morbidities), the impact of specific co-morbidities, the drugs of choice, the tolerability of targeted drugs, and the course of the disease in PAH patients on monotherapy. Therefore, the aim of this data analysis was to describe the patient profiles, treatment patterns, response to therapy, change in risk status, and drug tolerability in patients diagnosed with PAH who are on monotherapy in experienced pulmonary hypertension (PH) centres.

Patients and methodology

Patients

Patients with documented PAH who are currently on monotherapy with an ERA OR a PDE5i/riociguat OR a prostanooid/selexipag in experienced German PH centres, including Cologne (and associated centres within the PH network Nordrhein), Giessen, Heidelberg, and Dresden, were identified and analysed in a retrospective fashion. In all patients, PAH was confirmed by right heart catheterization (RHC), and PAH diagnosis was established following guideline recommendations. Acute vasoresponders on monotherapy with calcium channel blocker were excluded. The investigation conforms to the principles outlined in the Declaration of Helsinki. All patients gave written informed consent for the usage of their data for research purposes, and the analysis was approved by the local Ethics Committee of the University of Cologne (Reference 20-1640).

Structured analysis

The starting point of this retrospective analysis was the current situation (last visit), during Q2/2020. Patient data were obtained from the time of diagnosis (initial RHC)/start of therapy to the latest follow-up visit (Figure 1). The difference between time of diagnosis and last visit is defined as the time on PAH therapy. In addition, further follow-up visits were monitored (first follow-up, then 6–12 month intervals, and structured analysis at 6, 12, and 24 months), and efficacy and safety/tolerability as well as risk status were assessed [according to European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines] (Supporting Information, Table S1). In case of a repeat RHC, haemodynamic data were captured, and potential attempts of treatment escalation that may have been terminated because of various reasons (poor tolerability/side effects and lack of efficacy)—thus resulting in monotherapy—were also captured. The cohort was subdivided into patients with an age equal or below the median and those above the median.

In addition, patients were classified as having ‘classical PAH’ (<3 co-morbidities) or ‘PAH with co-morbidities’ (≥3 co-morbidities), according to the AMBITION criteria. Co-morbidities considered were history of essential hypertension, diabetes mellitus (any type), obesity (body mass index ≥30 kg/m²), and history of coronary artery disease.
History or presence of atrial fibrillation and chronic kidney disease (defined as reported ‘renal failure’ or ‘chronic kidney disease’) was also captured.

Right heart catheterization

Pulmonary arterial hypertension was diagnosed by RHC in all patients, and pressure tracings were interpreted by experienced investigators, according to current guidelines. Pre-capillary PH was defined by a mean pulmonary artery pressure (mPAP) ≥25 mmHg and a pulmonary artery wedge pressure (PAWP) ≤15 mmHg. In all analysed patients, pulmonary vascular resistance (PVR) was elevated to >3 Wood units (WU). RHC also included the measurement of cardiac output (CO), mixed venous oxygen saturation (SvO₂), and calculation of the transpulmonary pressure gradient (TPG = PAPm — PAWP), diastolic pressure gradient (DPG = PAPd — PAWP), stroke volume (═CO/heart rate), PA compliance (═stroke volume/PAPs — PAPd), PVR (═[PAPm — PAWP]/CO), and stroke volume index.

Echocardiography

Transthoracic echocardiography was performed at the various centres using standard equipment. Specific assessments of right heart morphology and function included right atrial area, right ventricular (RV) end-diastolic diameter (measured as RV inlet diameter at the four-chamber view), tricuspid annular plane systolic excursion, RV fractional area change, and peak tricuspid regurgitation velocity. The systolic tricuspid pressure gradient (ΔPₘₐₓTV) was calculated from tricuspid regurgitation velocity by the modified Bernoulli equation, and PA systolic pressure was estimated as the sum of ΔPₘₐₓTV and estimated right atrial pressure. Additionally, the tricuspid annular plane systolic excursion/PA systolic pressure ratio was calculated as a non-invasive index of RV–PA coupling. Significant left-sided valvular disease (≥ moderate) was ruled out by Doppler echocardiography. All measurements were performed according to current guidelines.

Exercise capacity

Exercise capacity was evaluated by the 6 min walk test, which was performed in a standardized way in all participating centres, according to the guidelines of the American Thoracic Society.

Pulmonary function testing, computed tomography, and rule out of chronic thrombo-embolic pulmonary hypertension

Significant chronic lung disease was routinely ruled out by spirometry (forced vital capacity >60% predicted; forced expiratory volume in 1 s >60% predicted) and computed tomography lung scan (absence of significant parenchymal abnormalities), and chronic thrombo-embolic PH was excluded by ventilation/perfusion scan in all patients, according to current guidelines.

Risk assessment

Risk assessment was performed according to the ESC/ERS guidelines for the diagnosis and treatment of PH. Patients were categorized as ‘low risk’, ‘intermediate risk’, or ‘high risk’ according to cut-off values for World Health Organization functional class (WHO-FC), 6 min walking distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP), right
atrial area, mean right atrial pressure, pericardial effusion, cardiac index, and \( \text{SvO}_2 \) as defined in the ESC/ERS guidelines.\(^1\) Data were analysed as follows: each variable was graded from 1 to 3 where 1 = ‘low risk’, 2 = ‘intermediate risk’, and 3 = ‘high risk’. If a 6 min walk test was registered as interrupted, it was assigned a grade of 3. Dividing the sum of all grades by the number of available variables for each patient rendered a mean grade. The mean grade was rounded off to the nearest integer, which was used to define the patient’s risk group.\(^16,17\)

Risk assessment was performed at baseline (i.e. at the time of PAH diagnosis) and at the time of re-evaluation.\(^16–19\)

**Statistical analyses**

Qualitative variables were summarized using count and percentage, and quantitative variables using means ± standard deviation. In case of missing values, last observation carried forward was used. Changes in values of quantitative variables (i.e. before and after treatment) were described by means ± standard error and tested using the two-sided paired \( t \)-test. Time-to-event distributions were summarized by the Kaplan–Meier method and compared using the log-rank test. To compare distributions of categorical variables, the \( \chi^2 \) test or Fisher’s exact test was used. \( P \) values <0.05 were considered statistically significant. Calculations were performed in Excel (Microsoft Corp., Redmond, WA) and SPSS Statistics (IBM Corp., Armonk, NY).

**Results**

**Patient profiles of pulmonary arterial hypertension patients on monotherapy**

The data collection was performed at the PH centres of the universities of Cologne (including the PH Network Nordrhein), Giessen, Heidelberg, and Dresden. A total of 182 patients who are currently on monotherapy with PAH-targeted drugs were analysed, representing 29.5% of treated PAH patients in the participating centres. Patient demographics and disease characteristics are displayed in *Table 1*. Patients’ mean age at last follow-up (Key Time Point 1) was 69.1 ± 13.1 years; 117 patients (64.3%) were female. The majority of patients (66.5%) had idiopathic PAH (PAH diagnosis) and at the time of re-evaluation.16

### Table 1 Patient characteristics and phenotypes of PAH patients on monotherapy

| Patient characteristics | All patients \( (n = 182) \) | Younger \( (\leq 68 \text{ years}) \) \( (n = 95) \) | Older \( (> 68 \text{ years}) \) \( (n = 87) \) | \( P \) value\(^a\) |
|-------------------------|-------------------------------|-------------------|-------------------|---------------|
| Age at last follow-up (years) | 69.4 ± 12.9 | 60.4 ± 11.0 | 79.4 ± 4.9 | <0.0001 |
| Female sex, n (%) | 117 (64.3) | 65 (68.4) | 52 (59.8) | - |
| BMI (kg/m\(^2\)) | 27.7 ± 6.4 | 27.4 ± 7.2 | 28.1 ± 5.4 | 0.14 |
| Time since diagnosis (months) | 60.7 ± 53.8 | 85.8 ± 61.1 | 33.2 ± 23.4 | <0.0001 |
| Age at diagnosis (years) | 64.5 ± 14.9 | 53.3 ± 12.0 | 76.7 ± 4.9 | <0.0001 |
| Time on PH therapy (months) | 60.7 ± 53.8 | 85.8 ± 61.1 | 33.2 ± 23.4 | <0.0001 |
| Type of PH | | | | |
| Idiopathic PAH, n (%) | 121 (66.5) | 45 (47.4) | 76 (87.4) | <0.0001 |
| Hereditary PAH, n (%) | 0 (0) | 0 (0) | 0 (0) | 1.0 |
| Drug/toxin-induced PAH, n (%) | 0 (0) | 0 (0) | 0 (0) | 1.0 |
| APAH-CTD, n (%) | 31 (17.0) | 22 (23.2) | 9 (10.3) | 0.029 |
| APAH-CHD, n (%) | 10 (5.5) | 8 (8.4) | 2 (2.3) | 0.10 |
| APAH-HIV, n (%) | 5 (2.7) | 5 (5.3) | 0 (0) | 0.06 |
| Portopulmonary PH, n (%) | 15 (8.2) | 15 (15.8) | 0 (0) | <0.0001 |
| Other, n (%) | 0 (0) | 0 (0) | 0 (0) | 1.0 |
| Co-morbidities | | | | |
| Hypertension, n (%) | 109 (59.9) | 44 (46.3) | 65 (74.7) | 0.001 |
| Diabetes, n (%) | 40 (22.0) | 17 (17.9) | 23 (26.4) | 0.21 |
| Coronary heart disease, n (%) | 62 (34.1) | 16 (16.8) | 46 (52.9) | <0.0001 |
| BMI > 30 kg/m\(^2\), n (%) | 53 (29.1) | 26 (27.4) | 27 (31.0) | 0.63 |
| Atrial fibrillation, n (%) | 50 (27.5) | 12 (12.6) | 38 (43.7) | <0.0001 |
| Dyslipidaemia, n (%) | 23 (12.6) | 11 (11.6) | 12 (13.8) | 0.66 |
| COPD, n (%) | 25 (13.7) | 15 (15.8) | 10 (11.5) | 0.52 |
| Chronic kidney disease, n (%) | 31 (17.0) | 9 (9.5) | 22 (25.3) | 0.0055 |
| PAH phenotype | | | | |
| Classical PAH, n (%) | 112 (61.5) | 70 (73.7) | 42 (48.3) | 0.0005 |
| PAH with co-morbidities, n (%) | 70 (38.5) | 25 (26.3) | 45 (51.7) | 0.0004 |

APAH, associated form of pulmonary arterial hypertension; ASD, atrial septal defect; BMI, body mass index; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

In addition to the whole sample, subgroups of patients above or below the median age (younger) at last follow-up (68 years) and those above the median (older) are shown.

\(^1\)The two older patients with APAH-CHD had a closed ASD.
PAH, followed by PAH associated with connective tissue disease (17.0%) and portopulmonary PH (8.2%). The mean age at the time of diagnosis (Key Time Point 2) was 64.5 ± 14.9 years. PAH diagnosis was established between January 2003 and March 2020, and the mean time from PAH diagnosis to last follow-up (disease duration) was 61.6 ± 54.7 months.

Co-morbidities were present in the majority of patients, and their presence was associated with age. Cardiovascular co-morbidities included systemic hypertension (59.9%), diabetes mellitus (22.0%), coronary artery disease (34.1%), dyslipidaemia (12.6%), and obesity (29.1%) (Table 1); 49 patients (26.9%) had atrial fibrillation. Chronic obstructive pulmonary disease was present as a pulmonary co-morbidity in 25 patients (13.7%), and 29 patients (15.9%) had chronic kidney disease. According to patient phenotyping based on the presence of multiple cardiovascular co-morbidities,\(^5,10,11\) 112 patients (61.5%) were classified as ‘classical PAH’ and 70 patients (38.5%) as ‘PAH with co-morbidities’. Patients’ median age at last follow-up was 68 years. There were substantial differences in co-morbidities in younger vs. older patients (Table 1).

### Cardiopulmonary haemodynamics of pulmonary arterial hypertension patients on monotherapy

Cardiopulmonary haemodynamics at the time of PAH diagnosis had been assessed by RHC, confirming pre-capillary PH in all patients. Their haemodynamic profiles are summarized in Table 2. A subset of patients (n = 84) underwent repeat RHC during follow-up (Supporting Information, Table S2). In these patients, the median time to repeat RHC was 28 months (inter-quartile range 14–73).

At the time of diagnosis (before treatment initiation), there was a wide variety of haemodynamic impairment, but the mean PVR in all patients was only moderately elevated at 6.6 ± 3.3 WU. Although the mean age at diagnosis was quite high, patients clearly had pre-capillary PH (PAWP 10.3 ± 3.6 mmHg), and cardiac index was not severely compromised. Nevertheless, PA compliance was substantially reduced while right atrial pressure was in the normal range, indicating that patients had undergone RHC in a compensated state. Haemodynamic measures were similar in younger and elderly patients.

Data obtained by follow-up RHC (while patients were on monotherapy with a PAH-targeted drug) were available for 84 patients. When focusing on the invasive measures utilized for risk assessment as recommended in the ESC/ERS guidelines,\(^1\) cardiac index (2.7 ± 0.7 L/min-m\(^2\)), right atrial pressure (8.1 ± 4.6 mmHg), and SvO\(_2\) (68.0 ± 8.4%) were all mainly indicative of a low-risk status under therapy. Furthermore, PA compliance and stroke volume index were also higher as compared with baseline assessments and within a range that was suggestive of a favourable outcome.\(^20–22\)

### Treatment pattern

Among the patients on monotherapy with a PAH-targeted drug, the vast majority (75.3%) were on a PDE5i and an

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**Table 2** Cardiopulmonary haemodynamics as assessed by RHC at the time of diagnosis

| All patients | RHC at time of diagnosis (n = 182) |
|-------------|-----------------------------------|
| PAP, systolic (mmHg) | 63.6 ± 18.7 |
| PAP, diastolic (mmHg) | 23.6 ± 7.6 |
| PAP, mean (mmHg) | 38.7 ± 10.6 |
| PAWP (mmHg) | 10.3 ± 3.6 |
| TPG (mmHg) | 28.2 ± 10.9 |
| DPG (mmHg) | 13.2 ± 8.1 |
| Cardiac output (L/min) | 4.6 ± 1.4 |
| Cardiac index (L/min-m\(^2\)) | 2.4 ± 0.7 |
| PVR (WU) | 6.6 ± 3.3 |
| PA compliance (mL/mmHg) | 1.8 ± 0.9 |
| Stroke volume index (mL/m\(^2\)) | 34.2 ± 9.4 |
| RAP (mmHg) | 7.2 ± 4.4 |
| SvO\(_2\) (%) | 66.4 ± 8.3 |

| Younger patients (≤68 years) | RHC at time of diagnosis (n = 95) |
|-----------------------------|----------------------------------|
| PAP, systolic (mmHg) | 65.5 ± 21.8 |
| PAP, diastolic (mmHg) | 25.3 ± 8.5 |
| PAP, mean (mmHg) | 40.5 ± 12.3 |
| PAWP (mmHg) | 9.1 ± 3.5 |
| TPG (mmHg) | 31.2 ± 12.5 |
| DPG (mmHg) | 16.1 ± 8.9 |
| Cardiac output (L/min) | 4.8 ± 1.3 |
| Cardiac index (L/min-m\(^2\)) | 2.5 ± 0.6 |
| PVR (WU) | 7.1 ± 3.9 |
| PA compliance (mL/mmHg) | 2.0 ± 1.1 |
| Stroke volume index (mL/m\(^2\)) | 34.7 ± 8.9 |
| RAP (mmHg) | 6.7 ± 4.8 |
| SvO\(_2\) (%) | 67.0 ± 9.4 |

| Older patients (>68 years) | RHC at time of diagnosis (n = 87) |
|---------------------------|----------------------------------|
| PAP, systolic (mmHg) | 63.3 ± 18.8 |
| PAP, diastolic (mmHg) | 23.5 ± 7.7 |
| PAP, mean (mmHg) | 38.6 ± 10.7 |
| PAWP (mmHg) | 10.2 ± 3.6 |
| TPG (mmHg) | 28.2 ± 10.9 |
| DPG (mmHg) | 13.2 ± 8.1 |
| Cardiac output (L/min) | 4.6 ± 1.4 |
| Cardiac index (L/min-m\(^2\)) | 2.4 ± 0.7 |
| PVR (WU) | 6.6 ± 3.3 |
| PA compliance (mL/mmHg) | 1.8 ± 0.9 |
| Stroke volume index (mL/m\(^2\)) | 34.0 ± 9.5 |
| RAP (mmHg) | 7.2 ± 4.4 |
| SvO\(_2\) (%) | 66.0 ± 9.5 |

DPG, diastolic pressure gradient; PA, pulmonary artery; PAP, pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; SvO\(_2\), mixed venous oxygen saturation; TPG, transpulmonary pressure gradient; WU, Wood units.

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Table 3: Treatment pattern of PAH patients on monotherapy

| Type of PAH monotherapy at last visit | n (%) |
|--------------------------------------|-------|
| Endothelin receptor antagonist        | 31 (17.0) |
| Ambrisentan                          | 6 (3.3) |
| Bosentan                             | 10 (5.5) |
| Macitentan                           | 15 (8.2) |
| Phosphodiesterase type 5 inhibitor   | 137 (75.3) |
| Sildenafil                            | 89 (48.9) |
| Tadalafil                            | 48 (26.4) |
| Soluble guanylate cyclase stimulator | 14 (7.7) |
| Riociguat                            | 14 (7.7) |
| Prostanoid                           | 0 (0) |
| Inhaled iloprost                     | 0 (0) |
| Treprostinil (s.c./i.v.)             | 0 (0) |
| Epoprostenol (i.v.)                  | 0 (0) |
| Prostacyclin receptor agonist        | 0 (0) |
| Selexipag                            | 0 (0) |

Escalation attempts

| No. of patients with escalation attempt | n (%) |
|----------------------------------------|-------|
| 49 (26.9)                              |       |
| 29 (15.9)                              |       |
| 11 (6.0)                               |       |
| 9 (4.9)                                |       |

PAH, pulmonary arterial hypertension. Values for drug classes are in bold.

Main reasons for monotherapy

The main reasons for PAH patients being on monotherapy as reported by the respective centres are summarized in Table 4. The most common cause was co-morbidities (‘atypical PAH’), followed by ‘mild PAH’, satisfactory response, no reason for escalation, and failed escalation attempts where the second or third drugs added were not tolerated. In younger patients, the principal cause for monotherapy was ‘mild PAH’, whereas ‘PAH with co-morbidities’ was the predominant reason in elderly patients (Figure 2 and Table 4).

Table 4: Main reasons for monotherapy as reported by PH centres (n = 182); sum = 100%

| Main reasons for PAH monotherapy at last visit, n (%) | All patients (n = 182) | Younger patients (n = 95) | Older patients (n = 87) | P valuea |
|------------------------------------------------------|------------------------|---------------------------|-------------------------|----------|
| Mild PAH, satisfactory response, no reason for escalation | 49 (26.9)              | 39 (41.1)                 | 10 (11.5)               | <0.0001  |
| Escalation attempt failed (not tolerated)             | 37 (20.3)              | 22 (23.2)                 | 15 (17.2)               | 0.61     |
| Temporary escalation (lack of improvement)           | 6 (3.3)                | 3 (3.2)                   | 3 (3.4)                 | 0.99     |
| Patient denied escalation                            | 3 (1.6)                | 1 (1.1)                   | 2 (2.3)                 | 0.61     |
| Patient non-compliant                                | 1 (0.5)                | 0 (0)                     | 1 (1.1)                 | 0.48     |
| PAH with co-morbidities (‘atypical PAH’)             | 78 (42.9)              | 23 (24.2)                 | 55 (63.2)               | <0.0001  |
| Associated form of PAH (low evidence for combo therapy) | 8 (4.4)                | 7 (7.4)                   | 1 (1.1)                 | 0.066    |

PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

The clinical characteristics of the 182 patients on monotherapy during the course of the disease are summarized in Table 6. Full data sets were available for all patients at last follow-up (Key Time Point 1) and at the time of diagnosis (Key Time Point 2) and for the majority of patients at the other time points (6, 12, and 24 month follow-up). Overall, at the last follow-up visit, a significant number of patients were in the ‘low-risk’ category (24.2%), and the majority of patients were in the ‘intermediate-risk’ group (73.1%). At the time of diagnosis, 81.3% were in the ‘intermediate risk’ and an additional 8.2% in the ‘high-risk’ category, whereas 10.4% showed a ‘low-risk’ profile. Upon treatment initiation with one targeted PAH drug, many of the clinical parameters that were captured improved within the first 6 months, and mostly remained stable thereafter. This resulted in a substantial increase in the proportion of patients classified as ‘low risk’. Nevertheless, the majority of patients did not fulfil the criteria determining a low-risk status, so that additional PAH therapies and a more comprehensive treatment approach may be warranted.
In this context, we observed considerable differences in younger vs. older patients (Supporting Information, Tables S3 and S4). In particular, younger patients had a higher 6MWD and much lower NT-proBNP levels and were much more likely to reach a low-risk status during therapy.

Profi ling of patients on monotherapy at experienced pulmonary hypertension centres—main conditions as reasons for monotherapy

When viewed together, among the patients on monotherapy at experienced centres, there were five main ‘conditions’ that may be viewed as predominant reasons for monotherapy (Figure 3). Patients may be clustered as follows (sum of percentage exceeds 100, because more than one reason may apply to individual patients): (i) escalation attempt conducted but terminated in most cases because of intolerability (26.9%): a total of 78 escalation attempts were conducted in 49 patients. Most escalation attempts were terminated because of side effects/intolerability, which occurred more frequently in older patients diagnosed with PAH who had significant co-morbidities. (ii) Low-risk profile on monotherapy, favourable response, and no reason for escalation (24.2%): these patients mostly had mild to moderate haemodynamic impairment at the time of diagnosis, responded well to therapy, and had a low-risk profile while on monotherapy. Therefore, treating physicians saw no reason to escalate therapy. (iii) Mild PAH (36.3%): in a significant number of patients, there was only mild PAH (mPAP ≤ 30 mmHg and PVR ≤ 5 WU) at the time of diagnosis, which improved upon initiation of PAH-targeted therapy with one drug. In most

Table 5 Treatment escalation attempts by drug class and reasons for their termination

| Drug class    | No. of escalation attempts (n) | Not tolerated (n) | Lack of improvement (n) | Reasons for intolerability                                                                 |
|---------------|-------------------------------|-------------------|-------------------------|------------------------------------------------------------------------------------------------|
| ERA           | 39                            | 36                | 3                       | Nausea, peripheral oedema, muscle pain, syncope, hypotension, hepatotoxicity                   |
| PDE5 inhibitor| 27                            | 24                | 3                       | Abdominal pain, headache, flush, arthralgia, peripheral oedema                                 |
| sGC stimulator| 4                             | 4                 | —                       | Hypotension, dizziness                                                                       |
| Parenteral PCA| 1                             | 1                 | —                       | Nausea, site pain                                                                            |
| Inhaled PCA   | 2                             | 2                 | —                       | Cough, dizziness                                                                             |
| PR agonist    | 3                             | 3                 | —                       | Abdominal pain, nausea, arthralgia                                                            |
| Total         | 76                            | 70                | 6                       |                                                                                               |

ERA, endothelin receptor antagonist; PCA, prostacyclin receptor agonist; PDE5, phosphodiesterase type 5; PR, prostacyclin receptor; sGC, soluble guanylate cyclase.
### Table 6 Clinical variables and risk status during the course of the disease (time of diagnosis, 6, 12, and 24 months after treatment initiation, and last follow-up)—all patients

| Time of Dx (n = 182) | Follow-up 6 months (n = 167) | Follow-up 12 months (n = 163) | Follow-up 24 months (n = 143) | Last follow-up (n = 182) |
|----------------------|-------------------------------|-------------------------------|-------------------------------|--------------------------|
| **Clinical parameters** |                               |                               |                               |                          |
| WHO-FC               | 2.8 ± 0.5                     | 2.6 ± 0.6**                   | 2.5 ± 0.7**                   | 2.5 ± 0.6**              |
| 6MWD (m)             | 345 ± 121                     | 376 ± 104**                   | 374 ± 112**                   | 401 ± 104**              |
| Borg score           | 4.1 ± 2.1                     | 3.5 ± 2.1**                   | 3.5 ± 2.1**                   | 3.6 ± 2.2**              |
| NT-proBNP (ng/mL)    | 1543 ± 2937                   | 1044 ± 2088*                  | 1037 ± 2077*                  | 1089 ± 2819              |
| HR (b.p.m.)          | 75.9 ± 13.2                   | 75.7 ± 13.4                   | 75.5 ± 12.9                   | 73.4 ± 13.1              |
| Systolic BP (mmHg)   | 125 ± 17                      | 122 ± 18*                     | 123 ± 18                      | 120 ± 19                 |
| Diastolic BP (mmHg)  | 75 ± 12                       | 73 ± 11*                      | 72 ± 11**                     | 71 ± 11**                |
| Weight (kg)          | 77.2 ± 18.4                   | 76.4 ± 18.2                   | 76.8 ± 17.7                   | 77.0 ± 14.8              |
| **Echocardiography** |                               |                               |                               |                          |
| RA area (cm²)        | 22.1 ± 8.8                    | 19.9 ± 7.3**                  | 21.1 ± 10.6                   | 19.5 ± 6.3**             |
| RVEDD (mm)           | 32.7 ± 12.7                   | 30.0 ± 12.0**                 | 30.1 ± 12.1**                 | 30.4 ± 11.8**            |
| TAPSE (mm)           | 19.8 ± 5.4                    | 21.3 ± 4.9**                  | 20.8 ± 5.6*                   | 21.7 ± 5.1*              |
| PASP (mmHg)          | 60.3 ± 19.7                   | 51.7 ± 15.9**                 | 51.4 ± 16.6**                 | 54.1 ± 21.0**            |
| **ESC/ERS risk**     |                               |                               |                               |                          |
| Low, n (%)           | 19 (10.4)                     | 39 (23.3)**                   | 41 (25.2)**                   | 45 (31.5)**              |
| Intermediate, n (%)  | 148 (81.3)                    | 123 (73.7)                    | 116 (71.2)*                   | 92 (64.3)**              |
| High, n (%)          | 15 (8.2)                      | 5 (3.0)                       | 6 (3.7)                       | 6 (4.2)                  |
| **Pulmonary function testing** |                               |                               |                               |                          |
| FVC (L)              | 2.7 ± 1.0                     | 2.6 ± 1.1**                   | 2.6 ± 1.1**                   | 2.6 ± 1.1**              |
| FEV1 (L)             | 2.0 ± 0.8                     | 1.9 ± 0.9                     | 1.9 ± 0.9                     | 1.9 ± 0.9                |
| FEV1/FVC (%)         | 73.2 ± 13.1                   | 71.4 ± 11.0**                 | 71.4 ± 11.0**                 | 71.4 ± 11.0**            |
| SO2 (%)              | 91.1 ± 9.6                    | 92.3 ± 8.1                    | 92.3 ± 8.1                    | 92.3 ± 8.1               |

6MWD, 6 min walking distance; BP, blood pressure; Dx, diagnosis; ERS, European Respiratory Society; ESC, European Society of Cardiology; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, heart rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; PASP, pulmonary arterial systolic pressure; RA, right atrial; RVEDD, right ventricular end-diastolic diameter; SO2, oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class.

* \( p < 0.05 \) vs. time of diagnosis.

** \( p < 0.01 \) vs. time of diagnosis.

### Figure 3 Profiling of patients on monotherapy at experienced pulmonary hypertension centres—five main conditions as predominant or contributing reasons for monotherapy (sum of percentage exceeds 100, because more than one reason may apply to individual patients). CHD, congenital heart disease; CTD, connective tissue disease; HIV, human immunodeficiency virus; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; WU, Wood units.
cases, this was associated with improvement of clinical variables, resulting in a low-risk status. Therefore, escalation of therapy was not deemed as indicated by the treating physicians. (iv) ‘Atypical PAH’ or ‘PAH with co-morbidities’ in older patients (38.5%): in many of these patients, treating physicians kept patients on monotherapy for this reason. (v) Specific PAH subgroups/associated forms of Group 1 PH in whom the level of evidence for combination therapy is considered low (16.5%): a subset of 30 patients on monotherapy had specific subtypes of PAH in whom the level of evidence for combination therapies is considered low, such as PAH associated with congenital heart disease (CHD) or connective tissue disease, human immunodeficiency virus (HIV) infection, or portopulmonary hypertension.

Safety and adverse events

Pulmonary arterial hypertension-targeted drugs that patients received as monotherapy were tolerated and did not cause any significant side effects. In patients in whom escalation attempts were terminated because of side effects or intolerability, the respective adverse events were documented and summarized for each drug class in Table 5.

Discussion

In this retrospective study, we analysed the patient characteristics of PAH patients remaining on monotherapy at experienced PH centres. Specifically, we addressed the question which patients are treated with only one drug, although a large body of evidence and guideline recommendations are in favour of combination therapy to treat this potentially deadly disease. We focused our analysis on experienced PH expert centres to largely exclude lack of knowledge/experience as a potential reason to limit PAH management to only one therapy, and to explore the characteristics of PAH patients on monotherapy that are managed by physicians who are experienced in managing this disease. This may explain why the proportion of PAH patients on monotherapy in our cohort (29.5%) is lower when compared with recent registry data.16–19

While there is no unique picture of patients on monotherapy, the majority of individuals with PAH who were kept on monotherapy at experienced centres was characterized by specific reasons that justify this kind of treatment. Patient clusters include those with mild PAH/low-risk profile, elderly patients with multiple co-morbidities, patients with failed escalation attempts mostly because of intolerability, and those with associated forms of PAH where the level of evidence for combination therapies is considered low. The most frequently used monotherapy for PAH was PDE5i, and sildenafil in particular. By contrast, the use of ERA was rather low, and prostanoids or prostacyclin receptor agonists did not play a role.

As a whole, our cohort represents an elderly population (mean age 64.5 ± 14.9 years at diagnosis; 69.4 ± 12.9 years at last follow-up) of prevalent patients, who appeared to be quite stable after a mean time of 60.7 ± 53.8 months on monotherapy. According to recent registry data, this is consistent with real-life data in various parts of Europe, where the age of PAH patients at diagnosis has constantly risen over the years.16–19 Our study design, focusing on alive patients and starting from the last follow-up retrospectively, may have led to selection of a rather stable group of patients. Upon treatment initiation, clinical variables mostly improved within 6 months and remained stable throughout. While the response to therapy was heterogeneous, a subset of patients showed improvement of multiple parameters into a range that is indicative of a low risk.16–19 It should be acknowledged that the subjective assessment of ‘mild PAH’ by providers does not necessarily reflect objective measures of low risk. Patients not responding so well to the first therapy mostly underwent a treatment escalation attempt that may have been unsuccessful because of intolerability to the second therapy, so that patients ended up on monotherapy at the last follow-up visit. However, the details determining ‘intolerability’ remain poorly defined. Given the accumulating evidence for the superiority of combination therapy in multiple PAH phenotypes and even in mildly symptomatic patients2,3,5–8,23–26 it should be considered which side effects may be tolerated and if some of them can be handled.

Aside from ‘vasoresponders’ on high-dose calcium channel blocker therapy, which were excluded from our analysis, the recommendations of the 6th World Symposium on Pulmonary Hypertension suggest that monotherapy may be adequate in the following situations5: (i) long-term treated historical PAH patients with monotherapy (>5–10 years) stable with low-risk profile; (ii) elderly PAH patients (>75 years) with multiple risk factors for heart failure with preserved left ventricular ejection fraction (high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, and obesity), that is, ‘atypical PAH’; (iii) PAH patients with suspicion or high probability of pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis; (iv) patients with PAH associated with HIV infection or portal hypertension or uncorrected CHD (as such patients were not included in randomized controlled trials of initial combination therapy); (v) PAH patients with very mild disease (e.g. WHO-FC I, PVR < 4 WU, mPAP < 30 mmHg, and normal RV at echocardiography); and (vi) combination therapy unavailable or contraindicated (e.g. severe liver disease). When considering these World Symposium on Pulmonary Hypertension recommendations, the patients reported herein for the most part presented with at least one of the earlier criteria.

One aspect may be the distinction between younger PAH patients with ‘typical’ or ‘classical’ PAH from older patients
with ‘atypical PAH’ or ‘PAH with co-morbidities’, because the Cologne Consensus Conference proposed initial dual oral combination therapy as the standard of care in patients with ‘typical PAH’, whereas monotherapy (and potential escalation to sequential combination therapy) was recommended for patients with ‘atypical PAH’. This was based on the solid evidence for the superiority of (upfront) oral combination therapy in patients with ‘typical PAH’,2,3,5 and the lack of evidence for upfront combination therapy in ‘atypical PAH’, because such patients were particularly not considered in the primary analysis set (PAS) of the AMBITION study. However, even when this distinction is considered in registry analyses (COMPERA), and the treatment patterns are analysed in ‘typical’ and ‘atypical PAH’ separately, it turns out that even in ‘typical PAH’, the percentage of patients on combination therapy at 3 and 12 months is rather low (i.e. 17.8% and 44.4%, respectively) and even substantially lower in ‘atypical PAH’ (7.9% and 25.9%, respectively). Therefore, other reasons must have prompted physicians to keep patients on monotherapy. In the present analysis, the majority of patients with ‘typical/classical PAH’ had a reason for being on monotherapy (mild PAH, low risk, and long-term stable with monotherapy). However, the presence of ‘PAH with co-morbidities’ (i.e. ‘atypical PAH’) was mentioned by the treating physicians as a reason for keeping patients on monotherapy in a considerable number of cases, particularly in the older patients.

In this context, it is worthwhile to note that a recent analysis from the AMBITION trial focusing on patients with co-morbidities (EX-PAS group) that were excluded from the PAS indicated that such patients may also benefit from initial combination therapy, albeit to a lesser extent. A post hoc analysis of the GRIPHON study, focusing on the effects of the prostacyclin receptor agonist selexipag in patients with or without multiple cardiovascular risk factors, found similar benefit in both groups. Hence, both of these analyses indicate that PAH patients with ≥3 cardiovascular co-morbidities may also benefit from combination therapy with ERA, PDE5i, and selexipag, indicating that the use of monotherapy in patients with co-morbidities as reported herein must be properly considered. Perception of intolerance to a second drug should not prevent the treating providers from attempting combination therapy, if otherwise deemed appropriate. Nevertheless, in patients with idiopathic PAH from the COMPERA registry, a recent cluster analysis based on age, sex, diffusing capacity for carbon monoxide, smoking status, and presence of co-morbidities (obesity, hypertension, CHD, and diabetes mellitus) identified distinct phenotypes, which differed in clinical presentation, response to therapy, and survival. Specifically, a cluster of younger age and without co-morbidities had a better response to PAH treatment and better outcome when compared with clusters of older patients with co-morbidities, lower diffusing capacity for carbon monoxide, and smoking history. However, there were also differences in the treatment patterns with less combination therapies in the latter groups. The efficacy and safety of PAH therapies in such patients must be further assessed in randomized controlled trials.

The current ESC/ERS guidelines introduced a risk assessment strategy, which was validated independently in three large registries.16–19 These studies consistently found that the risk assessment strategy proved valid both at baseline and at follow-up, works in major PAH subgroups, and provides accurate mortality estimates in patients with PAH. Furthermore, a simplified risk assessment tool that quantifies the number of low-risk criteria present accurately predicted transplant-free survival, and patients with all variables in the low-risk category had excellent survival.18,19 In addition, follow-up haemodynamics were also shown to be predictive of survival in PAH patients who are on targeted therapy.20 Hence, optimizing the individual patient’s risk profile and improving haemodynamic parameters that are predictive of survival (particularly stroke volume index and right atrial pressure) appear as important treatment goals in patients with PAH. Within our cohort, 24.2% were classified as ‘low risk’ at their last follow-up despite being on monotherapy, while the majority of the remaining patients were at ‘intermediate risk’, which is in line with registry data.16–19 Importantly, the percentage of patients reaching a ‘low-risk’ status was much higher in the younger patients as compared with the older ones.

When assessing the impact of age and co-morbidities on risk stratification in idiopathic PAH, recent data from the Swedish registry (SPAHR) indicated that a significant improvement in the individual risk status from baseline to follow-up (median 5 months) was observed in younger patients only, whereas no significant improvement was found in the older patients with co-morbidities. Nevertheless, in COMPERA, there was a similar magnitude of improvement in prognostically relevant clinical variables such as WHO-FC, 6MWD, and BNP/NT-proBNP levels, albeit with substantially lower baseline values and therefore reaching the ‘low-risk’ thresholds to a much lesser extent. Importantly, the improvements of the earlier clinical variables in such patients in COMPERA were observed despite the fact that only few patients were treated with combination therapies. While advanced age and co-morbidities may be the rationale for PAH monotherapy on one hand, there may be potential for further improvement on the other hand. Although combination therapy in PAH was shown to be superior to monotherapy in numerous studies primarily conducted in patients with ‘typical PAH’,17–19 safety issues and drug tolerability are also critical issues in the context of combination therapy that may be of particular relevance in patients with ‘atypical PAH’. Furthermore, the validity of the ESC/ERS risk stratification strategy in older patients with co-morbidities appears questionable. Hence, patient phenotyping in this context may be important for clinical decision making in
terms of monotherapy vs. combination therapy, and further evaluation of risk assessment in co-morbid PAH patients is warranted.

Finally, a subset of our patients had remained on monotherapy because of specific forms of PAH with limited evidence for combination therapy, including those with HIV-associated PAH, portal hypertension, or CHD. However, also in some of these patients, there is emerging and accumulating evidence that combining targeted PAH therapies may be beneficial and safe. This was recently shown for patients with PAH associated with CHD and also for those with portopulmonary hypertension.

Limitations of the study

Limitations of our study include its retrospective nature, the relatively small cohort, and a potential selection bias of patients alive at last follow-up. Data were collected from patient records, and a reporting bias may be present. Because this is a retrospective analysis starting from the last documented follow-up visit, structured capturing of safety and adverse events occurring with specific drug classes or compounds was not possible.

Conclusions

A considerable number of patients with PAH are currently on monotherapy at large German PH expert centres. While this may be considered inadequate in the modern treatment era of PAH, there were specific reasons for keeping patients on monotherapy in the vast majority of cases. Nevertheless, more comprehensive and aggressive treatment strategies have consistently shown better long-term outcomes even in mildly symptomatic patients, so that each case of monotherapy should be justified.

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Conflict of interest

M.W. received remunerations for lectures from Janssen. P.X. received lecture fees from MSD and OMT. N.B. received fees for lectures from Actelion, Bayer, MSD, and Janssen. E.G. reports fees for lectures and/or consultations from Actelion, Bayer, GSK, MSD, Pfizer, and United Therapeutics. M.J.R. received research support from Bayer and United Therapeutics and personal speaker fees from Actelion, Mundipharma, Roche, and OMT. H.G. received fees for lectures/consultancy from Actelion, AstraZeneca, Bayer, BMS, GSK, Janssen-Cilag, Lilly, MSD, Novartis, OMT, Pfizer, and United Therapeutics. H.A.G. reports personal fees and consultancy fees from Actelion, Bayer, GlaxoSmithKline, Novartis, and Pfizer; other fees from Bellerophon Pulse Technologies; and consultancy fees from MSD. S.H. received speaker fees from Janssen, GSK, and MSD and advisory fees from Janssen and MSD. D.S. received honoraria for lectures and consultancy from Actelion and Janssen. C.P. reports honoraria for lectures from Actelion and Janssen. M.H. received remunerations for consultancy and/or lectures from Acceleron, Actelion, AstraZeneca, Bayer, Berlin Chemie, GSK, Janssen, MSD, and Novartis. C.H. received lecture/consultancy fees from Actelion, Bayer, MSD, and Pfizer. F.G. reports remunerations for lectures from Actelion, Bayer, Janssen, and MSD and grants to institution from Actelion, Bayer, and Janssen. S.R. reports remunerations for lectures and/or consultancy from Abbott, Actelion, Arena, Bayer, BMS, Ferrer, Gilead, GSK, MSD, Novartis, Pfizer, and United Therapeutics and grants to institution from Actelion, AstraZeneca, Bayer, Novartis, and United Therapeutics.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Data collection at the various time-points.

Table S2. Cardiopulmonary hemodynamics as assessed by RHC at the time of diagnosis and during follow-up in PAH patients on monotherapy who underwent repeat RHC.

Table S3. Clinical variables and risk status during the course of the disease (time of diagnosis, 6, 12, and 24 months after treatment initiation, and last follow-up) – younger patients (≤68 years); *p < 0.05 vs. time of diagnosis; **p < 0.01 vs. time of diagnosis. BP, blood pressure; Dx, diagnosis; FEV1; FVC, forced vital capacity; HR, heart rate; 6MWD, 6 minute walking distance; PASP, Pulmonary arterial systolic pressure; RA, right atrial; RVEDD, right ventricular end-diastolic diameter; SO2, oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class.
Table S4. Clinical variables and risk status during the course of the disease (time of diagnosis, 6, 12, and 24 months after treatment initiation, and last follow-up) – older patients (>68 years); *p < 0.05 vs. time of diagnosis; **p < 0.01 vs. time of diagnosis. BP, blood pressure; Dx, diagnosis; FEV1, forced vital capacity; HR, heart rate; 6MWD, 6 minute walking distance; PASP, Pulmonary arterial systolic pressure; RA, right atrial; RVEDD, right ventricular end-diastolic diameter; SO2, oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class.

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