ESC HEART FAILURE
ESC Heart Failure 2024; **11**: 1540–1552
Published online 15 January 2024 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14611

ORIGINAL ARTICLE

Impact of rapid sequential combination therapy on distinct haemodynamic measures in newly diagnosed pulmonary arterial hypertension

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Abstract

Aims In pulmonary arterial hypertension (PAH), upfront combination therapy with ERA and PDE5i is associated with a reduction in morbidity and mortality events and improves standard haemodynamics, but data remain limited. Aims of this study were (i) to capture detailed haemodynamic effects of rapid sequential dual combination therapy in patients with newly diagnosed PAH; (ii) to monitor the impact of treatment initiation on clinical variables and patients' risk status, and (iii) to compare the treatment effect in patients with 'classical PAH' and 'PAH with co-morbidities'.

Methods Fifty patients (median age 57 [42–71] years, 66% female) with newly diagnosed PAH (76% idiopathic) were treated with a PD5i/sGC-S or ERA, followed by addition of the respective other drug class within 4 weeks. All patients underwent repeat right heart catheterization (RHC) during early follow-up.

Results At early repeat RHC (7 ± 2 months), there were substantial reductions in mean pulmonary artery pressure (mPAP: 52.2 ± 13.5 to 39.0 ± 10.6 mmHg; −25.3%), and pulmonary vascular resistance (PVR: 12.1 ± 5.7 to 5.8 ± 3.1 WU; −52.1%), and an increase in cardiac index (2.1 ± 0.4 to 2.7 ± 0.7 mL/min/m^2; +32.2%) (all $P < 0.05$). Haemodynamic improvements correlated with improved clinical parameters including 6-min walking distance (336 ± 315 to 389 ± 120 m), NTproBNP levels (1.712 ± 2.024 to 506 ± 550 ng/L, both $P < 0.05$) and WHO-FC at 12 months, resulting in improved risk status, and were found in patients with few (n = 37) or multiple cardiovascular co-morbidities (BMI > 30 kg/m^2, hypertension, diabetes, coronary artery disease [≥3]; n = 13), albeit baseline PVR in PAH patients with multiple co-morbidities was lower (9.3 ± 4.4 vs. 13.1 ± 5.9 WU) and PVR reduction less pronounced compared with those with few co-morbidities (−42.7% vs. −54.7%). However, comprehensive haemodynamic assessment considering further variables of prognostic relevance such as stroke volume index and pulmonary artery compliance showed similar improvements among the two groups (SVI: +50.0% vs. +49.2%; PA_C: 91.7% vs. 100.0%). Finally, the 4-strata risk assessment approach was better able to capture treatment response as compared with other approaches, particularly in patients with co-morbidities.

Conclusions Rapid sequential combination therapy with PDE5i/sGC-S and ERA substantially ameliorates cardiopulmonary haemodynamics at early follow-up in patients without, and to a lesser extent, with cardiovascular co-morbidities. This occurs in line with improvements of clinical parameters and risk status.

Keywords Combination therapy; Endothelin receptor antagonist; Haemodynamics; Phosphodiesterase type 5 inhibitor; Pulmonary arterial hypertension (PAH)

Received: 7 June 2023; Revised: 16 October 2023; Accepted: 16 November 2023
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Introduction

The establishment of targeted therapies has markedly improved the morbidity and mortality of patients with pulmonary arterial hypertension (PAH).[1,2] Available therapies target the nitric oxide (NO), endothelin, and prostacyclin pathways, and their combined use was shown to provide additive effects.[3–5] Hence, targeting several pathways at once appears be of clinical benefit for affected patients.

Several randomized controlled trials have demonstrated, that the addition of specific compounds in patients who were already on PAH therapies targeting other pathways improved clinical outcomes.[6–9] In particular, the AMBITION study provided evidence, that initial combination therapy with an endothelin receptor antagonist (ERA), ambrisentan, and a phosphodiesterase type 5 inhibitor (PDE5i), tadalafil, was superior to monotherapy with either compound in preventing morbidity/mortality events and improving exercise capacity.[9] Based on this evidence, the most recent expert recommendations for the treatment of PAH and updated guidelines highlight the role of upfront dual oral combination therapy with an ERA and a PDE5i for the majority of patients with newly diagnosed PAH.[10,11] Further studies also demonstrated haemodynamic benefit, as this treatment strategy was able to reduce pulmonary vascular resistance (PVR) by approximately 50%.[12,13] However, more detailed data on haemodynamics and in different PAH phenotypes remain scarce. In this context, a recent study evaluating the prognostic value of haemodynamic variables during repeat right heart catheterization revealed that stroke volume index (SVI) and right atrial pressure (RAP) are the strongest predictors of outcome in treated PAH patients.[14]

In addition to haemodynamics, multi-modal risk assessment as proposed by the ESC/ERS guidelines[11] provides important prognostic information at the time of diagnosis using the 3-strata approach,[15–18] and particularly during early follow-up after treatment initiation using the 4-strata approach.[19,20] Data from the French PH network (FPHN) aimed at identifying patients with a particularly low mortality risk by capturing the number of low-risk variables in a 4-criteria (including invasive haemodynamics) and a 3-criteria (non-invasive) approach.[17] Both the ESC/ERS 3-strata and 4-strata approaches as well as both FPHN approaches showed that improvement of the risk profile to a 'low-risk' status was associated with better outcomes.[15–20]

Although the diagnosis of PAH is based on clear haemodynamic criteria defining pre-capillary PH,[11,21–23] registry data have shown a substantial change in phenotype over time.[24–27] In contrast to younger (mostly female) patients with no or few cardiovascular co-morbidities (now termed 'classical PAH'), the majority of patients that are nowadays diagnosed with PAH are at advanced age and harbour multiple cardiovascular risk factors ('PAH with co-morbidities'). The latter patients were not eligible in the AMBITION study,[9] so that evidence for the efficacy/superiority and tolerability of upfront combination therapy is lacking in this subgroup of patients.

Aims of this study were (i) to capture in detail the haemodynamic effects of rapid sequential dual oral combination therapy in patients with newly diagnosed PAH who underwent repeat right heart catheterization during early follow-up, (ii) to monitor the impact of treatment initiation on clinical variables and patients' risk status, and (iii) to compare the treatment effect in patients with 'classical PAH' and 'PAH with co-morbidities'.

Methods

Patients, treatment strategy, and follow-up

We analysed 50 consecutive patients with newly diagnosed PAH in WHO-FC II or III, in whom the diagnosis was confirmed by right heart catheterization (RHC) between December 2014 and August 2021, and who were treated with dual oral combination therapy with a PDE5i (sildenafil 20 mg tid; tadalafil 40 mg once daily) or sGC-stimulator (riociguat 1.5–2.5 mg tid) and an ERA (macitentan 10 mg once daily; ambrisentan 5 or 10 mg once daily). The 'rapid sequential' approach was defined by initiation of therapy with one drug class at the time of diagnosis, and addition of the respective other drug class within 4 weeks (*Figure* S1). All patients who tolerated dual oral combination therapy for at least 6 months and underwent repeat RHC during early follow-up were eligible for the analysis. According to recent recommendations,[27,28] patients were sub-categorized as 'classical PAH' (younger patients with no more than 2 cardiovascular risk factors) and 'PAH with co-morbidities' (elderly patients with ≥3 cardiovascular risk factors). Risk factors included essential hypertension, diabetes mellitus, obesity (BMI $>$ 30 kg/m^2), and a history of coronary artery disease.[9] Patients with a 'high risk' profile (according to ESC/ERS guidelines[11]) who were eligible for combination therapy including parenteral prostanoids and thus received such therapy were excluded.

Assessment of cardiopulmonary haemodynamics

The diagnosis of PAH was confirmed by RHC in all patients. For the present analysis, the pressure tracings of all patients were analysed in a standardized and blinded manner, according to current guidelines and recommendations.[11,21,22] All pressure values were measured at end-expiration (means from three cardiac cycles; in patients with atrial fibrillation, means from five cardiac cycles). As per standardized RHC protocol, the pressure transducer was routinely placed at the mid-thoracic level. Treatable PH was defined by a mean PAP of ≥25 mmHg, and post-capillary PH was defined by a PAWP $>$15 mmHg (mean value integrating the v-wave) at

end-expiration under resting conditions.[11,21,22,29] RHC also included the measurement of cardiac output (CO), cardiac index (CI), mixed venous oxygen saturation (SvO_2), and calculation of the transpulmonary pressure gradient (TPG = PAPm − PAWP), diastolic pressure gradient (DPG = PAPd − PAWP), PA compliance (PA_C = stroke volume/[PAPs − PAPd]), pulmonary vascular resistance (PVR = [PAPm − PAWP]/CO), stroke volume index (SVI), RV stroke work index (RVSWI = SVI*[mPAP − RAP] *0.0136), and pulmonary artery pulsatility index (PAPi = [PAPs − PAPd]/RAP). All pressure gradients were calculated using end-expiratory values.

Exclusion of significant lung disease and pulmonary embolism

Significant chronic lung disease was routinely ruled out by spirometry (FVC > 60% predicted; FEV1 > 60% predicted) and CT lung scan (absence of significant parenchymal abnormalities), and chronic thromboembolic PH was excluded by ventilation/perfusion scan in all patients, according to current guidelines.[11]

Echocardiography

Transthoracic echocardiography was performed using the Philips iE 33 system (Philips GmbH, Hamburg, Germany), equipped with a 2.5 MHz transducer. Specific assessments of right heart morphology and function included right atrial area, right ventricular end-diastolic diameter (RVEDD), tricuspid annular plane systolic excursion (TAPSE), and tricuspid regurgitation velocity (TRV). The systolic tricuspid pressure gradient ($\Delta P_{max}TV$) was calculated from TRV by the modified Bernoulli equation, and PA systolic pressure (PASP) was estimated as the sum of $\Delta P_{max}TV$ and estimated right atrial pressure. Additionally, the TAPSE/PASP ratio was calculated as a non-invasive index of RV-PA coupling.[30,31] Significant left-sided valvular disease (≥moderate) was ruled out by Doppler echocardiography. All measurements were performed according to current guidelines.[32]

Six-minute walking test

Exercise capacity was evaluated by the 6-min walk test, which was standardized according to the guidelines of the American Thoracic Society.[33] All subjects were made familiar with the test prior to the first measurement, and were then used to perform it at their routine follow-up visits.

NTproBNP serum levels

NTproBNP serum levels were measured by the Elecsys proBNP II Test (Roche Diagnostics GmbH, Mannheim, Germany); normal values are age-adjusted, but the overall cut-off value is <125 ng/L.

Risk assessment

Risk assessment was performed according to the ESC/ERS guidelines for the diagnosis and treatment of PH,[11] utilizing different methodologies: (i) Overall risk assessment by the 3-strata approach ('low', 'intermediate', 'high' risk status): Patients were categorized as 'Low risk', 'Intermediate risk', or 'High risk' according to cut-off values for WHO-FC, 6MWD, NTproBNP, right atrial area, mean right atrial pressure, pericardial effusion, CI, SVI and SvO_2 defined in the ESC/ERS guidelines.[11] Each variable was graded from 1 to 3 where 1 = 'Low risk', 2 = 'Intermediate risk', and 3 = 'High risk'. If a 6-min walking test (6MWT) 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[15,16]; (ii) Overall risk assessment by the 4-strata approach, according to cut-off values for WHO-FC, 6MWD, and NTproBNP defined in the ESC/ERS guidelines.[11] Each variable was graded from 1 to 4 where 1 = 'Low risk', 2 = 'Intermediate-low risk', and 3 = 'Intermediate-high risk', and 4 = 'High risk'.[19,20] The points were summed up, divided by the number of denominators, and rounded to the next integer to determine individual risk. (iii) Risk assessment by the French approach (three non-invasive criteria: WHO-FC, 6MWD and NTproBNP, and four criteria including invasive: WHO-FC, 6MWD, RAP, and CI).[17]

Risk assessment by either strategy was performed at baseline (i.e. at the time of PAH diagnosis) and at the time of re-evaluation.[15–20] To consider patients' age, risk stratification was performed separately for various age groups (18–45, 46–64, 65–74, ≥75 years) as previously analysed in the SPAHR registry.

Statistical analysis

Qualitative variables at baseline were summarized using count and percentage. We compared distributions of qualitative variables by Fisher's exact test. The distributions of quantitative variables at baseline were summarized by means ± standard deviation (SD) or medians (Q1, Q3) as indicated. Values of quantitative variables (i.e. before and after treatment) were described by means ± SD or medians (Q1, Q3) and tested using the paired t-test at two-sided significance level 5%. *P*-values

<0.05 were considered statistically significant, though no adjustment for multiple testing was done. In case of missing values, last observation carried forward was used. Calculations were done in Excel (Microsoft Corp., Redmond, WA) and SPSS Statistics (IBM Corp., Armonk, NY).

Results

Patient characteristics

Demographics, patient characteristics at baseline, co-morbidities and concomitant medications are listed in *Table 1*. The majority of patients were diagnosed with idiopathic PAH. Compared with patients with 'classical PAH', those with 'PAH with co-morbidities' were significantly older and—based on the definition—had more cardiovascular co-morbidities.

Patient disposition is depicted in *Figure S2*. Patients received the combination of an ERA (macitentan *n* = 41; ambrisentan *n* = 9) and a PDE5i (tadalafil *n* = 40, sildenafil *n* = 8) or sGC-S (riociguat *n* = 2) within 4 weeks.

Impact of rapid sequential combination therapy on cardiopulmonary haemodynamics at early follow-up

Baseline invasive haemodynamic assessment and repeat RHC performed at 7 ± 2 months revealed that upon treatment initiation, there was a marked improvement of cardiopulmonary haemodynamics as compared with baseline values (*Table 2*). The changes of the most relevant haemodynamic variables are depicted in *Figure 1*. These included significant reductions of PAPm, PVR, and RAP, and substantial increases of CI, SVI, and PA_C. In fact, PVR was reduced by 52.1% in all patients, and by even 54.7% in patients with 'classical PAH'. In patients with 'PAH with co-morbidities', the baseline PVR was significantly lower as compared with those with 'classical PAH' (9.3 ± 4.4 vs. 13.1 ± 5.9 WU), but was still significantly reduced by 42.7% in response to dual oral combination therapy. Interestingly, when considering the haemodynamic variables that most strongly predict survival in treated PAH patients such as CI, RAP, SVI and PA_C, the treatment response was almost identical in patients with 'classical PAH' and those with 'PAH with co-morbidities' (*Figure 1*).

Improvement of clinical and echocardiographic variables

In line with haemodynamic improvement, we found robust enhancement of clinical variables during the whole observation period up to 12 months. In the whole cohort, this included a net improvement of the 6MWD by 33, 47, and 53 m, and a mean reduction of NTproBNP levels by 43.8%, 72.8%, and 70.4% at 3, 6, and 12 months, respectively, as well as a decline in WHO-FC at all time-points (*Table 3*). While the baseline 6MWD was substantially lower in patients with 'PAH with co-morbidities', the net increase was comparable among these patients and those with 'classical PAH'. Similar improvements in NTproBNP and WHO-FC were observed in both subgroups. Re-evaluation by echocardiography revealed slight reductions of right heart dimensions and PAP, moderately enhanced TAPSE, and a significant improvement of the TAPSE/PASP ratio in both subgroups (*Table 4*).

Table 1 Demographics, patient baseline characteristics, co-morbidities, and cardiovascular risk factors in 50 patients with newly diagnosed pulmonary arterial hypertension (PAH) undergoing rapid sequential combination therapy

	All (*n* = 50)	Classical PAH (*n* = 37)	PAH with co-morbidities (*n* = 13)	*P*-value
Patient characteristics				
Age, years (means ± SD)	54.5 ± 18.9	49.8 ± 18.9	67.8 ± 10.7	<0.001
Age, years (median, Q1–Q3)	57 (42–71)	50 (30–68)	68 (65–76)	<0.001
Gender, m/f (%)	34/66	30/70	46/54	0.3219
Type of PAH:				
Idiopathic, *n* (%)	38 (76.0%)	27 (73.0%)	11 (84.6%)	0.480
Hereditary, *n* (%)	2 (4.0%)	2 (5.1%)	0 (0.0%)	1
Drug-induced, *n* (%)	2 (4.0%)	1 (2.6%)	1 (9.1%)	0.456
Connective tissue disease, *n* (%)	7 (14.0%)	6 (15.4%)	1 (9.1%)	0.660
Congenital heart disease, *n* (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
HIV, *n* (%)	1 (2.0%)	1 (2.6%)	0 (0.0%)	1
Other, *n* (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Co-morbidities/CV risk factors				
Hypertension, *n* (%)	29 (58.0%)	17 (46.0%)	12 (92.3%)	0.004
Diabetes, *n* (%)	12 (24.0%)	3 (8.1%)	9 (69.2%)	<0.001
Dyslipidaemia, *n* (%)	9 (18.0%)	3 (8.1%)	6 (46.2%)	0.006
CAD, *n* (%)	7 (14.0%)	2 (5.4%)	5 (38.5%)	0.009
BMI > 30 kg/m^2, *n* (%)	17 (34.0%)	8 (20.5%)	9 (69.2%)	0.005

Distributions of qualitative variables were compared by the Fisher's exact test.
BMI, body mass index; CAD, coronary artery disease; CV, cardiovascular; PAH, pulmonary arterial hypertension.

Table 2 Pulmonary haemodynamics as assessed by right heart catheterization at baseline and at early follow-up

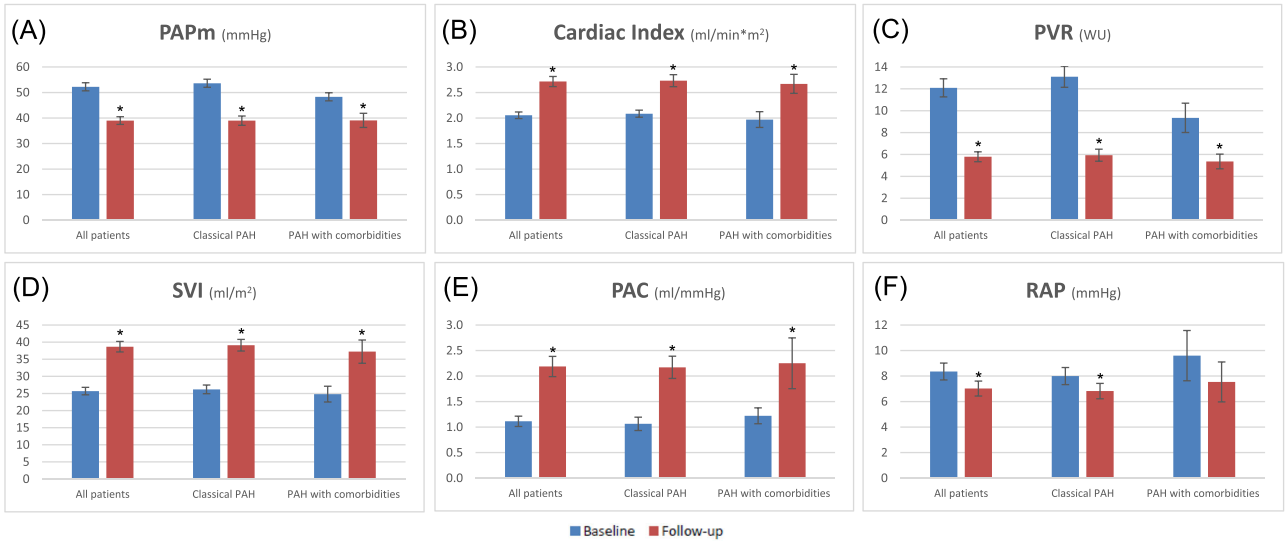
	Baseline	Follow-up
All (n = 50)		
Systolic PAP, mmHg	82.0 ± 21.0	62.3 ± 18.0*
Diastolic PAP, mmHg	32.8 ± 10.0	23.6 ± 7.7*
Mean PAP, mmHg	52.2 ± 13.5	39.0 ± 10.6*
PAWP[#], mmHg	10.0 ± 3.2	11.9 ± 4.4*
RAP, mmHg	8.4 ± 4.4	7.0 ± 4.0
CO, L/min	3.9 ± 1.0	5.0 ± 1.5*
CI, L/min/m^2	2.1 ± 0.4	2.7 ± 0.7*
TPG, mmHg	42.0 ± 13.8	27.2 ± 9.9*
DPG, mmHg	23.7 ± 11.1	11.8 ± 6.9*
Heart rate, b.p.m.	83.6 ± 18.4	72.2 ± 12.6*
Stroke volume Index, (mL/m^2/beat)	25.7 ± 7.1	38.7 ± 9.9*
PVR, WU	12.1 ± 5.7	5.8 ± 3.1*
PA_C, mL/mmHg	1.1 ± 0.6	2.2 ± 1.3*
PAPi	8.0 ± 7.8	7.8 ± 7.0
RV stroke work index, g/m^2/beat	15.3 ± 5.3	16.1 ± 4.8
SvO_2, %	58.4 ± 12.6	66.4 ± 6.5*
Classical PAH (n = 37)		
Systolic PAP, mmHg	84.3 ± 22.0	62.4 ± 19.2*
Diastolic PAP, mmHg	33.8 ± 10.4	23.8 ± 8.2*
Mean PAP, mmHg	53.6 ± 13.7	39.0 ± 11.2*
PAWP[a], mmHg	9.4 ± 3.0	12.0 ± 3.5*
RAP, mmHg	8.0 ± 4.0	6.8 ± 3.6
CO, L/min	3.8 ± 0.9	4.9 ± 1.6*
CI, L/min/m^2	2.1 ± 0.4	2.7 ± 0.7*
TPG, mmHg	43.8 ± 14.0	27.1 ± 10.4*
DPG, mmHg	25.3 ± 11.1	11.9 ± 7.4*
Heart rate, b.p.m.	84.7 ± 20.1	72.1 ± 12.9*
Stroke volume index, mL/m^2/beat	26.2 ± 7.0	39.1 ± 9.8*
PVR, WU	13.1 ± 5.9	5.9 ± 3.6*
PA_C, mL/mmHg	1.1 ± 0.7	2.2 ± 1.3*
PAPi	8.5 ± 8.7	7.1 ± 4.4
RV stroke work index, g/m^2/beat	16.1 ± 5.7	16.6 ± 5.2
SvO_2, %	57.9 ± 13.5	66.7 ± 6.5*
PAH with co-morbidities (n = 13)		
Systolic PAP, mmHg	75.7 ± 17.1	62.2 ± 14.7*
Diastolic PAP, mmHg	30.1 ± 8.6	23.0 ± 6.1*
Mean PAP, mmHg	48.3 ± 12.6	39.1 ± 9.2*
PAWP[#], mmHg	11.5 ± 3.6	11.5 ± 6.6
RAP, mmHg	9.6 ± 5.6	7.5 ± 5.0
CO, L/min	4.1 ± 1.1	5.5 ± 1.4*
CI, L/min/m^2	2.0 ± 0.5	2.7 ± 0.6*
TPG, mmHg	36.9 ± 12.6	27.4 ± 8.5*
DPG, mmHg	19.1 ± 10.2	11.5 ± 5.2*
Heart rate, b.p.m.	80.9 ± 14.1	72.6 ± 12.2*
Stroke volume index, (mL/m^2/beat)	24.8 ± 7.9	37.2 ± 10.7*
PVR, WU	9.3 ± 4.4	5.4 ± 2.1*
PA_C, mL/mmHg	1.2 ± 0.6	2.3 ± 1.5*
PAPi	6.3 ± 3.4	9.8 ± 11.4
RV stroke work index, g/m^2/beat	13.7 ± 2.6	14.8 ± 3.2
SvO_2, %	60.2 ± 9.5	65.5 ± 6.7*

Data represent means ± SD.
CI, cardiac index; CO, cadiac output; DPG, diastolic pressure gradient, PA_C, pulmonary artery compliance; PAP, pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; TPG, transpulmonary pressure gradient.
[a]If no reliable PAWP could be measured, left ventricular end-diastolic pressure (LVEDP) was measured instead and used for calculation of TPG and PVR.
*$P < 0.05$.

Changes in risk assessment upon treatment initiation

In order to capture the impact of targeted PAH therapy on patients' individual risk, we applied the 3-strata risk assessment strategy proposed by the ESC/ERS guidelines,[11] utilizing two different methods of analysis.[15–18] When using the SPAHR method, we found an improved risk status at 6 months in the whole cohort and in particular in younger patients, but to a much lesser extent in elderly patients, presumably those with co-morbidities (*Figure 2*). The FPHN method considers the number of variables defining a 'low-

Figure 1 Improvement of key pulmonary haemodynamics from baseline to early follow-up as assessed by repeat right heart catheterization. Data represent mean values ± SEM. PAC, pulmonary artery compliance; PAPm, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVI, stroke volume index.



risk' status only (4 and 3 criteria approaches). Both the 4 criteria approach, which requires repeat RHC, and the 3 criteria approach, which considers non-invasive measures only (WHO-FC, 6MWD, and NTproBNP), showed an improvement of the risk status in the whole cohort a well as both subgroups. However, patients with 'PAH with co-morbidities' were less likely to reach the thresholds defining 'low risk', and thus had fewer 'low-risk' variables both at baseline and during follow-up (*Figure 3A* and *3B*). Finally, we also used the 4-strata risk assessment strategy proposed by the ESC/ERS guidelines.[11,19,20] This approach appeared more sensitive to capture treatment responses as compared with the 3-strata approach, particularly between 'intermediate-high' and 'intermediate-low' risk, and particularly in patients with co-morbidities (*Figure 4*). Of note, when considering invasive haemodynamics recommended in the updated ESC/ERS guidelines only (CI, RAP, and SVI), 57% of patients with 'classical PAH' and 54% of those with 'PAH with co-morbidities' reached a 'low-risk' profile for CI (≥2.5 L/min*m^2), with corresponding numbers for RAP (<8 mmHg) of 54% and 46% and for SVI (>38 mL/m^2) of 51% and 38%, respectively.

Safety and tolerability of pulmonary arterial hypertension targeted therapy

The medication was well tolerated in all analysed patients. Adverse events included the typical side effects of ERAs and PDE5i such as headache, nasal congestion, flushing, whereas we did not observe clinically relevant systemic hypotension. Liver enzymes (GOT and GPT), haemoglobin levels, and renal function (GFR) remained largely unchanged at 3, 6, and 12 months (*Table 3*).

Discussion

The data presented herein indicate that (i) patients with PAH exhibit substantial improvement of cardiopulmonary haemodynamics upon initiation of rapid sequential combination therapy with PDE5i/sGC-S and ERA (reduction of PVR; improvements in CI, SVI, and PAC); (ii) haemodynamic improvements correlated with improved clinical parameters that are prognostically relevant, resulting in improved risk status; and (iii) haemodynamic and clinical improvements were found in patients with 'classical PAH', and—albeit to a lesser extent—in those with 'PAH with co-morbidities'.

In PAH, early dual oral combination therapy represents the standard of care for the majority of patients,[10,11] and initial combination therapy with tadalafil and ambrisentan was shown to be superior to monotherapy with either compound in patients with 'classical PAH'.[9] While the current recommendations are primarily based on RCTs utilizing composite morbidity/mortality endpoints, the impact of such a treatment strategy on cardiopulmonary haemodynamics remained largely unknown. The TRITON and OPTIMA studies showed a significant reduction in PVR upon initiation of upfront combination therapy with an ERA (macitentan) and a PDE5i.[12,13] However, a comprehensive haemodynamic analysis including further parameters that are known to predict

Table 3 Clinical variables and laboratory values at baseline and during follow-up

	Baseline	3 months	6 months	12 months
All (n = 50)				
WHO-FC	3.0 ± 0.5	2.6 ± 0.5*	2.4 ± 0.5*	2.3 ± 0.5*
6MWD, m (mean)	336 ± 135	369 ± 132*	383 ± 123*	389 ± 121*
6MWD, m (median)	347 (236–247)	383 (279–460)*	368 (287–466)*	368 (317–459)*
NTproBNP, ng/mL (mean)	1712 ± 2025	963 ± 1206*	465 ± 469*	506 ± 550*
NTproBNP, ng/mL (median)	760 (392–2311)	462 (204–1110)*	279 (125–617)*	269 (109–645)*
Creatinine, mg/dL	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	1.1 ± 0.3
Haemoglobin, g/dL	14.0 ± 2.2	13.2 ± 2.1*	13.1 ± 2.1*	13.4 ± 2.1*
GOT, U/L	34.7 ± 20.5	26.4 ± 8.5*	23.9 ± 7.8*	25.5 ± 12.9*
GPT, U/L	29.6 ± 22.1	20.0 ± 14.2*	17.6 ± 12.3*	19.4 ± 15.4*
Uric acid, mg/dL	7.8 ± 2.5	6.9 ± 2.4*	6.5 ± 2.2*	6.6 ± 2.3*
eGFR, mL/min/1.73 m^2	75.9 ± 27.8	77.7 ± 29.1	79.3 ± 30.0	76.2 ± 29.3
CRP, mg/L	6.9 ± 8.2	5.7 ± 8.2	4.8 ± 6.9	6.7 ± 10.9
Classical PAH (n = 37)				
WHO-FC	3.0 ± 0.5	2.6 ± 0.5*	2.4 ± 0.5*	2.2 ± 0.5*
6MWD, m (mean)	362 ± 139	391 ± 133	406 ± 128*	414 ± 129*
6MWD, m (median)	381 (256–471)	386 (282–466)	414 (321–471)*	414 (336–476)*
NTproBNP, ng/mL (mean)	1748 ± 2010	954 ± 1283*	425 ± 461*	458 ± 560*
NTproBNP, ng/mL (median)	831 (311–2341)	432 (156–1068)*	255 (107–591)*	231 (101–600)*
Creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	1.0 ± 0.3
Haemoglobin, g/dL	13.7 ± 2.3	12.9 ± 2.1*	12.9 ± 2.1*	13.1 ± 2.1*
GOT, U/L	37.0 ± 22.2	27.1 ± 7.9*	25.5 ± 8.2*	26.9 ± 14.5*
GPT, U/L	32.9 ± 23.9	21.3 ± 14.9*	19.6 ± 13.4*	21.5 ± 17.2*
Uric acid, mg/dL	7.6 ± 2.6	6.5 ± 2.1*	6.0 ± 1.8*	6.3 ± 2.1*
eGFR, mL/min/1.73 m^2	79.6 ± 26.5	83.2 ± 27.6	85.7 ± 27.8	80.9 ± 28.9
CRP, mg/L	6.5 ± 8.1	5.8 ± 8.5	4.2 ± 5.5	6.7 ± 11.4
PAH with co-morbidities (n = 13)				
WHO-FC	3.0 ± 0.6	2.5 ± 0.5*	2.5 ± 0.5*	2.5 ± 0.5*
6MWD, m (mean)	269 ± 93	305 ± 106	321 ± 83*	322 ± 55*
6MWD, m (median)	286 (209–337)	304 (281–396)	344 (276–368)*	344 (309–368)*
NTproBNP, ng/mL (mean)	1619 ± 2058	989 ± 962	573 ± 476	640 ± 499
NTproBNP, ng/mL (median)	544 (433–1469)	544 (272–1439)	367 (259–1000)	443 (257–1039)
Creatinine, mg/dL	1.1 ± 0.4	1.1 ± 0.5	1.2 ± 0.4	1.2 ± 0.3
Haemoglobin, g/dL	15.1 ± 1.4	14.4 ± 1.5*	14.2 ± 2.0*	14.5 ± 1.7
GOT, U/L	28.2 ± 9.0	25.6 ± 10.5*	20.0 ± 5.1*	22.2 ± 4.9*
GPT, U/L	20.1 ± 11.4	18.6 ± 12.1	12.9 ± 6.3*	14.4 ± 5.7*
Uric acid, mg/dL	8.0 ± 1.8	7.9 ± 2.7	8.0 ± 2.5	7.7 ± 2.4
eGFR, mL/min/1.73 m^2	64.7 ± 24.8	61.9 ± 22.5	60.3 ± 25.3	62.0 ± 23.1
CRP, mg/L	8.7 ± 8.6	5.3 ± 7.2	6.5 ± 9.6	6.7 ± 9.3

6MWD; 6-min walk distance; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; NTproBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, WHO functional class.
*$P < 0.05$.

survival is currently lacking. In addition, the value of targeted PAH therapies in elderly patients with 'PAH with co-morbidities' appears questionable and represents a current matter of debate.[26–28]

While PAH is defined by an elevated PAPm,[21,22] reductions of this haemodynamic variable by targeted therapies were not associated with improved outcome. Most RCTs evaluating the efficacy of PAH therapies have demonstrated only modest reductions of PAPm, at least in the context of monotherapy or sequential combination therapy (previous works [1–5], reviewed in Vizza et al.[35]). More recent studies evaluating PAH targeted therapies such as macitentan, selexipag, or the combination of ambrisentan and tadalafil, utilized composite clinical endpoints and have demonstrated marked reductions in morbidity/mortality events, particularly in the context of combination therapy.[6,7,9] A 'landmark analysis' of the GRIPHON and SERENADE studies revealed that morbidity events were strong predictors of mortality in both trials,[34] and registry data have shown that initial up-front combination therapy (dual, triple) was associated with a better long-term survival rate over monotherapy.[36] However, haemodynamic data obtained from repeat RHC were not available in any of these studies, and data on haemodynamic improvement remained sparse. In particular, it remained unclear which impact the proposed standard of care for the majority of patients with PAH—dual oral combination therapy—has on multiple haemodynamic variables. When performing repeat RHC at early follow-up, the patients reported herein exhibited substantial improvements after initiating ERA and PDE5i or sGC-S, particularly a reduction of PVR of approximately 50%. The magnitude of this haemodynamic improvement by two oral drugs may be considered quite remarkable, should provide the basis for the reduction of morbidity/mortality events observed in RCTs,[6,7,9] and is in

Table 4 Echocardiographic variables at baseline and during follow-up

All (n = 50)	Baseline	3 months	6 months	12 months
RA area, cm^2	22.6 ± 7.3	22.7 ± 7.2	21.7 ± 7.5	20.9 ± 7.8*
RVEDD, mm	44.3 ± 8.6	43.9 ± 8.3	42.3 ± 7.8*	42.7 ± 8.9
PASP, mmHg	83.8 ± 21.5	69.7 ± 20.5*	61.3 ± 17.6*	59.8 ± 20.2*
TAPSE, mm	19.1 ± 5.3	20.6 ± 5.4*	20.5 ± 5.0	21.3 ± 4.3*
TAPSE/PASP, mm/mmHg	0.26 ± 0.11	0.34 ± 0.15*	0.37 ± 0.16*	0.42 ± 0.23*
LVEDD, mm	40.1 ± 5.7	42.5 ± 5.5*	42.4 ± 5.7*	42.6 ± 6.2*
LVEF, %	62.3 ± 11.4	62.0 ± 11.1	61.7 ± 11.0	61.3 ± 10.8
Classical PAH (n = 37)				
RA area, cm^2	22.2 ± 7.8	22.7 ± 8.1	21.6 ± 8.3	20.4 ± 8.6*
RVEDD, mm	45.1 ± 8.5	44.1 ± 8.2	42.4 ± 7.4*	42.9 ± 8.9
PASP, mmHg	84.9 ± 22.7	71.1 ± 20.9*	61.9 ± 16.6*	62.8 ± 20.2*
TAPSE, mm	19.7 ± 4.8	20.6 ± 5.3*	20.3 ± 5.1	21.2 ± 4.3
TAPSE/PASP, mm/mmHg	0.25 ± 0.12	0.33 ± 0.16*	0.36 ± 0.16*	0.38 ± 0.16*
LVEDD, mm	39.8 ± 5.9	41.8 ± 5.7 *	41.9 ± 5.7*	41.8 ± 6.4
LVEF, %	62.7 ± 11.5	62.6 ± 11.5	62.1 ± 11.4	61.4 ± 11.1
PAH with co-morbidities (n = 13)				
RA area, cm^2	23.7 ± 5.6	22.8 ± 4.0	22.0 ± 4.2	22.1 ± 4.1
RVEDD, mm	42.4 ± 8.7	43.5 ± 8.5	41.9 ± 8.8	42.1 ± 9.0
PASP, mmHg	80.8 ± 17.2	65.3 ± 18.8*	59.7 ± 20.2*	51.0 ± 17.2*
TAPSE, mm	17.7 ± 6.2	20.3 ± 5.6	21.3 ± 4.4	21.7 ± 4.2*
TAPSE/PASP, mm/mmHg	0.24 ± 0.11	0.35 ± 0.12*	0.40 ± 0.16*	0.55 ± 0.35*
LVEDD, mm	41.0 ± 5.3	44.2 ± 4.5*	43.6 ± 5.4	45.0 ± 5.0*
LVEF, %	61.3 ± 11.2	60.4 ± 9.7	61.0 ± 9.7	61.1 ± 10.0

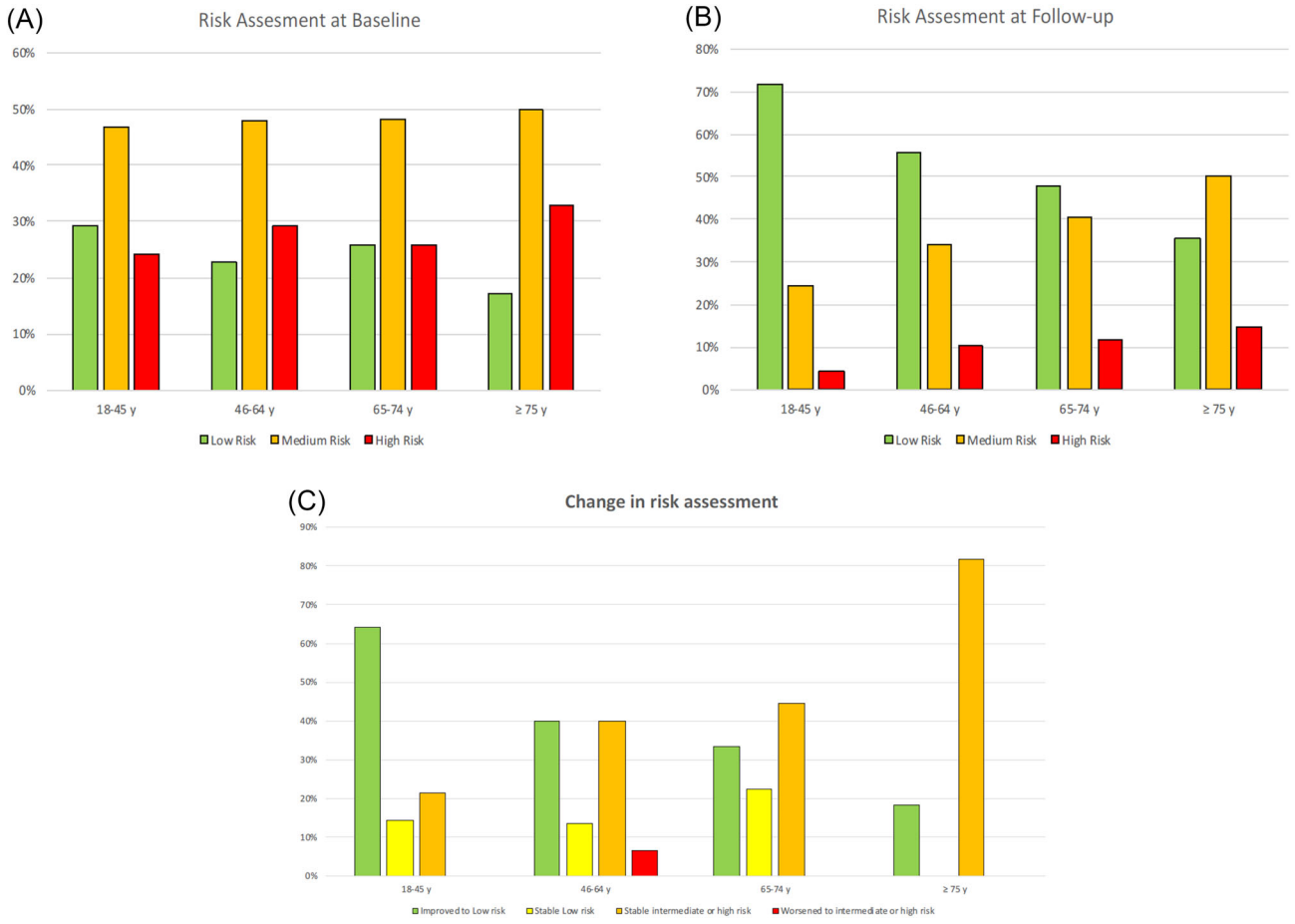
LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; RA, right atrium, RVEDD, right ventricular end-diastolic diameter; TAPSE, tricuspid annular plane systolic excursion.
*$P < 0.05$.

line with other recent studies,[12,13] showing a somewhat larger reduction in PVR when compared recent data from Italy.[37] Additionally, we show substantial improvements of further haemodynamic parameters considered for risk assessment in the updated guidelines such as CI and SVI, as well as PA_C.[11] Adding the second drug with a delay of 4 weeks (rapid sequential combination therapy) did not ameliorate the treatment effect when compared with other studies, but allows judgement about response to therapy and potential side effects of individual components of combination therapy.

The marked reduction of PVR by combination therapy observed in our patients is in line with the above studies,[12,13,37] and retrospective analyses from the FPHN demonstrating haemodynamic benefit in patients with severe and advanced PAH considered at high risk at the time of diagnosis who received upfront triple combination therapy including a parenteral prostanoid, which translated into better outcomes versus monotherapy.[36,38] These data indicate that haemodynamics can be substantially improved initially by aggressive treatment regimen even in patients with advanced disease. Nevertheless, the time and specific compound used for intensification of therapy may be crucial. A post-hoc analysis of the GRIPHON trial has shown that among pre-treated patients already on a PDE5i and ERA, the benefit of additional selexipag versus placebo tended to be even more pronounced in patients with less symptom burden (WHO-FC II) as compared with those in WHO-FC III.[39] Similar findings were reported from the AMBITION study, where the impact of initial combination therapy on the risk of both clinical failure events and PAH-associated hospitalizations was also more pronounced in PAH patients in WHO-FC II.[40] In this context, a recent study revealed that addition of even a parenteral prostanoid, intravenous treprostinil, in patients on background targeted PAH therapies displaying an insufficient response to non-parenteral treatments, led to improvement to a 'low risk' status and favourable outcome in a subset (19%) of patients, whereas the majority of patients remained at intermediate or high risk, which was associated with high mortality.[41] These data indicate that timely escalation during the early course of the disease may be crucially important, and failure to reach a low-risk profile should prompt timely listing for lung transplantation in appropriate candidates.

In a haemodynamic sub-study of the SERAPHIN trial, macitentan—the predominant ERA utilized in our cohort—led to improvements of PAPm, CI, and PVR at 6 months, irrespective of WHO-FC and PAH background therapy.[42] Reaching the haemodynamic and NTproBNP threshold levels defining a low risk status according to ESC/ERS guidelines (CI $>$ 2.5 L/min/m^2, RAP $<$8 mmHg, NTproBNP $<$750 fmol/mL) was associated with a lower risk of morbidity/mortality events,[42] and the predictive value of NTproBNP thresholds was recently underscored in a analysis from the GRIPHON trial.[43] In the present study, the combination of ERA and PDE5i or sGC-S as the initial treatment regimen led to even much greater improvements in these variables, further supporting such a treatment strategy. Moreover, when interpreting and judging about haemodynamic improvement in PAH it is crucial to consider the most relevant variables. Weatherald and

Figure 2 Risk stratification according to the ESC/ERS guidelines 3-strata approach,[11] utilizing the SPAHR methodology of analysis.[15] Data are shown according to patients' age. (A) Risk assessment at baseline. (B) Risk assessment at follow-up (6 months). (C) Changes in risk assessment between baseline and follow-up.



co-workers have recently shown that SVI and RAP represent the strongest predictors of transplant-free survival in treated PAH patients undergoing repeat RHC,[14] and other studies highlighted the role of PA_C in this context.[44] Importantly, we found substantial improvements in both SVI and PA_C, and these were almost identical in the subgroups of patients with 'classical PAH' and those with 'PAH with co-morbidities'. When considering echocardiographic variables, the absolute changes in PASP and TAPSE were modest, but the TAPSE/PASP ratio, representing an index of RV-PA coupling,[30,31] improved substantially in both subgroups. The prognostic impact of such changes has recently been confirmed.[45] Taken together, the magnitude of changes and the values reached upon initiation of rapid sequential combination therapy in the patients reported herein appear of major clinical relevance.

In our series, haemodynamic improvement upon initiation of rapid sequential combination therapy was associated with considerable improvement of patients' risk status. A recent analysis from the SPAHR registry demonstrated that upon initiation of PAH therapy, a 'low risk' status was achieved only in younger individuals, whereas the risk status remained largely unchanged in elderly PAH patients, presumably with multiple co-morbidities,[26] indicating that elderly patients in whom co-morbidities may be present, do not sufficiently respond to PAH targeted therapies. This is in contrast to findings from the COMPERA registry where subjects with 'classical PAH' (here termed 'typical PAH') and those with ≥3 LHD-associated co-morbidities ('atypical PAH') showed similar improvements in 6MWD, BNP/NTproBNP levels, and WHO-FC,[28] albeit starting at lower baseline values and not reaching the same threshold levels. When we performed risk assessment and monitored the changes in risk status upon treatment initiation, we also found that elderly patients were less likely to improve their risk status to reach an overall low-risk profile when utilizing the 3-strata approach. However, the 4-strata approach appeared much better able to capture treatment responses in both phenotypes (see *Figure 4*), and 'intermediate-low' risk may be a reachable and relevant treatment goal in PAH patients with co-morbidities.[46]

Figure 3 Risk stratification according to the ESC/ERS guidelines,[11] utilizing the FNPH methodology of analysis which focusses on low risk criteria only.[15] (A) Analysis based on the course of 4 criteria (including RHC) at baseline and 6 months of follow-up. (B) Analysis based on the course of 3 criteria (non-invasive) at baseline and 6 months of follow-up.

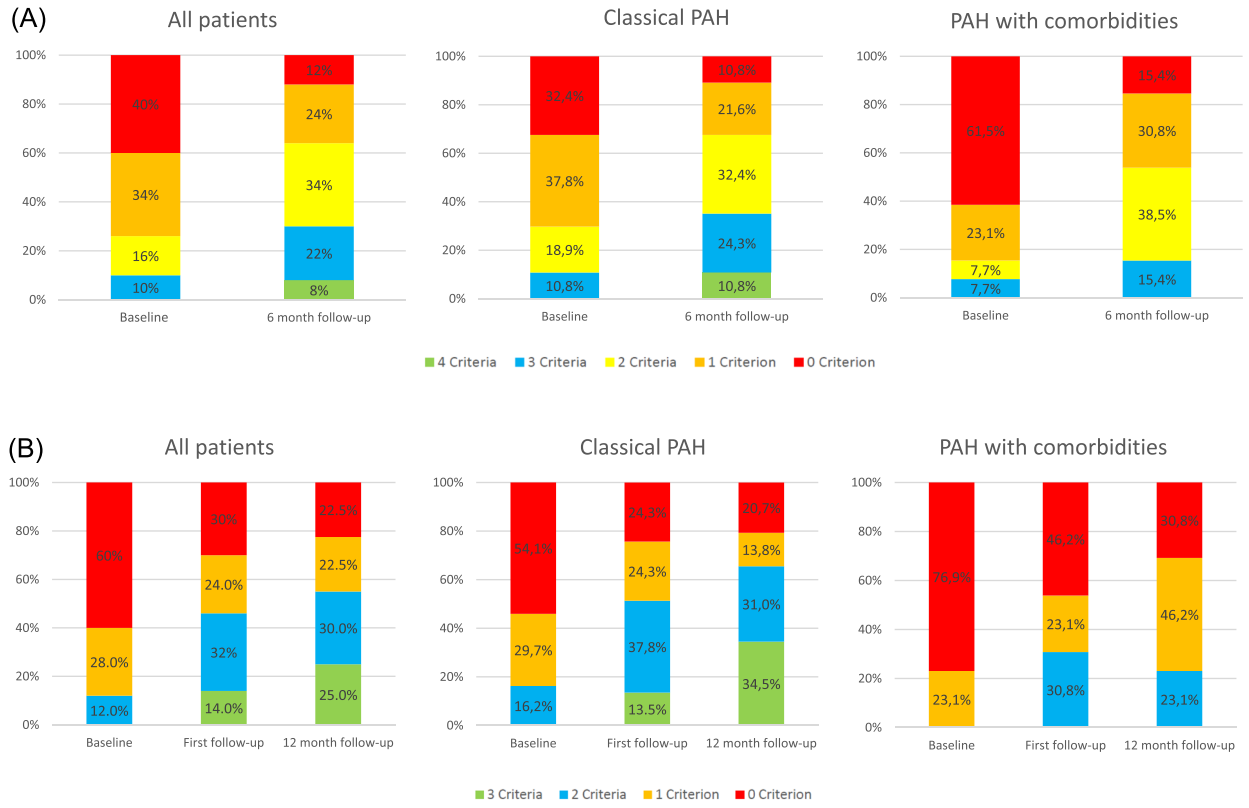
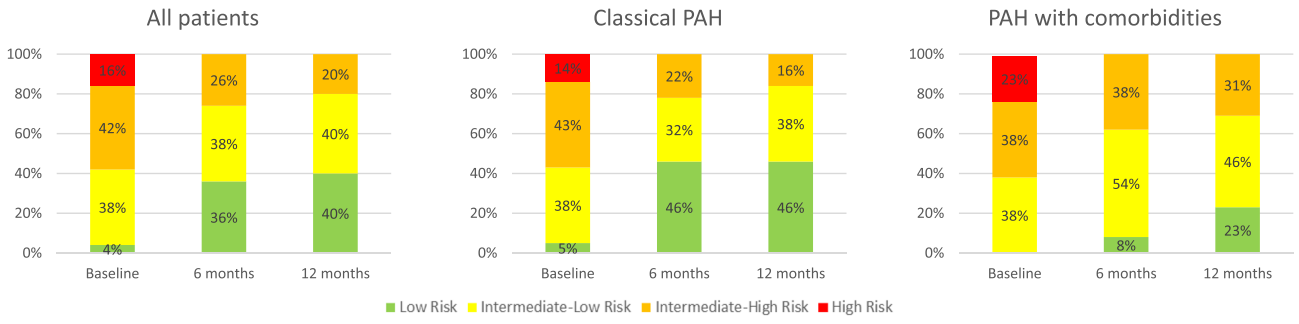


Figure 4 Risk stratification according to the ESC/ERS guidelines 4-strata approach at baseline, 6 and 12 months of follow-up.[11]



Furthermore, we observed significant improvements in both subgroups when applying the FNPH approach, particularly when including haemodynamic variables. In fact, invasive haemodynamics were best able to capture the treatment response in patients with 'PAH with co-morbidities', whereas 6MWD and WHO-FC may be influenced and limited by co-morbidities themselves. The consideration of the TAPSE/PASP ratio may help to overcome limitations in this context.[45] This highlights the importance of the methodology used when performing risk assessment and judging upon the treatment response particularly in elderly PAH patients with co-morbidities. In any case, comprehensive risk assessment will inform decision making for further escalation and optimization of targeted PAH therapy.[11,47]

Limitations

Limitations include the limited number of patients, the single center approach, the last observation carried forward approach for missing data, lack of a control group, and open-label therapy, which may result in a bias towards overestimation of the treatment effect. However, given the magnitude of the observed changes, particularly with regard to invasive haemodynamics and NTproBNP levels (which are less prone to investigator bias), our data should have captured the true magnitude of the treatment effect. Most patients received a combination of macitentan and tadalafil. The low number of patients with other drug combinations prevents the analysis of differences in therapeutic response.

Conclusions

In summary, our data shows that rapid sequential combination therapy with ERA and PDE5i/sGC-S initiated in patients with newly diagnosed PAH substantially improves multiple prognostically relevant pulmonary haemodynamics (including PVR, CI, SVI, PA_C, and RAP) at early follow-up. This was consistent with improvements in clinical variables and risk status in patients without, and to a lesser extent, with cardiovascular risk factors.

Acknowledgements

The technical support provided by Linda Nikel, Jasmin Rudolph, Julia Fund, and Susanne Rölle-Höhne is greatly acknowledged. This manuscript contains parts of a doctoral thesis by Phillip Nattmann and Patrycja Stafiej. This study was supported in part by a research grant from Actelion Pharmaceuticals.

Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest

Tilmann Kramer: Remunerations for lectures from Actelion. Felix Gerhardt: Remunerations for lectures from Actelion, Bayer, GSK, and United Therapeutics; grants to institution from Actelion, Bayer, Novartis, and United Therapeutics. Daniel Dumitrescu: Remunerations for lectures and/or consultancy from Actelion, Bayer, GSK, MSD, Novartis, Servier, and Vifor. Christopher Hohmann: Personal fees from MSD and Pfizer, lecture fees from Actelion, travel grants from Actelion, Bayer, Orion Pharma, and MSD. Stephan Rosenkranz: Remunerations for lectures and/or consultancy from Abbott, Acceleron, Actelion, Aerovate, Altavant, AOP, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, Ferrer, Gossamer, MSD, Novartis, Pfizer, United Therapeutics, and Vifor; grants to institution from Actelion, AstraZeneca, Bayer, and Janssen. The rest of the authors have nothing to disclose.

Supporting information

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

Figure S1. Schematic depicting the flow of 50 patients with a new diagnosis of PAH undergoing rapid sequential combination therapy with PDE5i and ERA, including index RHC, repeat RHC, and non-invasive follow-up variables up to 12 months.
Figure S2. Subject distribution and treatment pattern of patients with newly diagnosed PAH, and eligibility for the current analysis. DOCT, double oral combination therapy.

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