Upfront combination therapy reduces right ventricular volumes in pulmonary arterial hypertension

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ABSTRACT In pulmonary arterial hypertension (PAH), upfront combination therapy is associated with better clinical outcomes and a greater reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP) than monotherapy. NT-proBNP levels reflect right ventricular (RV) wall stress, which increases when the right ventricle dilates. This study explored the impact of upfront combination therapy on RV volumes compared with monotherapy in PAH patients.

This retrospective study involved 80 incident PAH patients (New York Heart Association class II and III) who were treated with upfront combination therapy (n=35) (*i.e.* endothelin receptor antagonists (ERAs) plus phosphodiesterase-5-inhibitors (PDE5Is)) or monotherapy (n=45) (*i.e.* either ERAs or PDE5Is). All patients underwent right-sided heart catheterisation and cardiac magnetic resonance imaging at baseline and after 1-year follow-up.

Combination therapy resulted in more significant reductions in pulmonary vascular resistance and pulmonary pressures than monotherapy. NT-proBNP was decreased by ∼77% in the combination therapy group compared with a ∼51% reduction after monotherapy ($p<0.001$). RV volumes and calculated RV wall stress improved after combination therapy (both $p<0.001$) but remained unchanged after monotherapy (both p=NS). RV ejection fraction improved more in the combination therapy group than in the monotherapy group ($p<0.001$).

In PAH patients, upfront combination therapy was associated with improved RV volumes.

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Introduction

Pulmonary arterial hypertension (PAH) is characterised by abnormal pulmonary vascular remodelling resulting in chronic pressure overload of the right ventricle and ultimately the development of right ventricular (RV) failure and death [1, 2]. The general treatment goal in patients with PAH is to reduce the load on the right ventricle in order to accomplish favourable RV adaptation, stable RV function and low mortality rates [3, 4]. Treatment of PAH patients within New York Heart Association (NYHA) functional class II or III comprises either (1) initial single-agent therapy with endothelin receptor antagonists (ERAs) or phosphodiesterase-5-inhibitors (PDE5Is), or (2) the application of both agents (*i.e.* upfront combination therapy) [3]. Recently, it was shown in the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial that upfront oral combination therapy resulted in a longer time to clinical failure and a greater reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP) compared with upfront monotherapy [5]. Since changes in NT-proBNP reflect changes in RV wall stress [6, 7], these findings may be explained by either a reduction in pulmonary pressures or by more favourable RV remodelling. Indeed, it was recently observed that pulmonary pressures dropped significantly after upfront combination therapy [8]. However, to date, changes in RV volumes and wall thickness after combination therapy have not yet been explored. This could be of importance because RV dilatation is among the strongest predictors of mortality in PAH patients [9] and is an important determinant of RV wall stress [10]. Previous studies have demonstrated that although monotherapy leads to a decrease in pulmonary vascular resistance (PVR), it does not affect RV dilatation, and consequently RV wall stress remains high [11–15]. Based on the observation that NT-proBNP decreases more in the combination treatment group [5], we hypothesised that upfront combination therapy not only results in a greater decrease in PVR but will also lead to improvements in RV volumes, thereby reducing RV wall stress.

Therefore, the aim of the present study was to assess the therapeutic effects of upfront oral combination therapy on RV volumes in NYHA class II or III patients with idiopathic PAH (IPAH), heritable PAH (HPAH) or drug- and toxin-induced PAH (DPAH). PAH patients treated with upfront oral monotherapy were used as a control group.

Methods

Study design and patient selection

This study retrospectively analysed data from an ongoing prospective registry of newly diagnosed PAH patients admitted to the VU University Medical Center, Amsterdam, who routinely underwent right-sided heart catheterisation (RHC), cardiac magnetic resonance imaging (CMR), six-minute walk testing and blood sampling. Because the Medical Ethics Review Committee of the VU University Medical Center did not consider the study to fall within the scope of the Medical Research Involving Human Subjects (WMO) (approval number 2012288), an informed consent statement was not obtained.

Inclusion criteria for the present study were: (1) newly diagnosed patients with IPAH, HPAH or DPAH, (2) age ⩾18 years, (3) NYHA functional class II or III, (4) the use of oral PAH-specific medication consisting of ERA or PDE5I applied as either upfront monotherapy or dual combination therapy (*i.e.* initiated directly after diagnosis), (5) RHC and CMR performed at baseline and after 1 year of follow-up. Patients with a positive acute vasodilator challenge and/or patients treated with calcium channel blockers [3] were excluded from the analysis. Patients meeting the inclusion criteria were enrolled between August 2002 and July 2015, and totalled 114 patients. RHC and CMR were performed within a median time interval of 2 days. Nine patients died during the first year of follow-up and were excluded (two of these patients had received upfront combination therapy and seven had been treated with monotherapy). Nine of the 105 patients were excluded because of treatment with calcium channel blockers. In addition, 16 patients had no or insufficient CMR assessment at 1 year follow-up and could therefore not be included. In total, 80 patients fulfilled the study criteria and were included in the present study (figure 1). Thirty-five patients treated with upfront combination therapy were compared with 45 patients who received upfront monotherapy.

Treatment regimens

Application of PAH-targeted medical therapies was performed in line with the guidelines and according to the availability in the Netherlands. Since August 2002 and 2005, ERA (ambrisentan, bosentan, macitentan or sitaxentan) and PDE5I (sildenafil or tadalafil), respectively, have been available in the Netherlands. Patients were treated with upfront oral monotherapy (ERA or PDE5I) or upfront dual combination therapy (ERA plus PDE5I). Upfront monotherapy was defined as the application of one type of drug, initiated directly after diagnosis. Upfront combination therapy implies the application of two types of drugs (ERA plus PDE5I), both started at the exact same time point after diagnosis and up-titrated in the following 4–8 weeks. The treating physician decided which specific type of ERA or PDE5I was to be applied and whether a patient should receive upfront monotherapy or combination therapy.

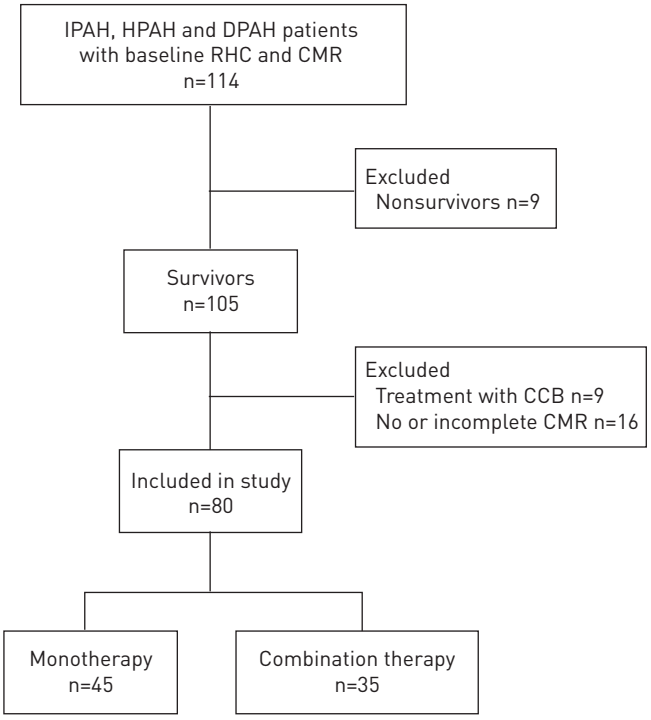

FIGURE 1 Study profile. CCB: calcium channel blockers; CMR: cardiac magnetic resonance imaging; DPAH: drug- and toxin-induced pulmonary arterial hypertension; HPAH: heritable pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; RHC: right-sided heart catheterisation.

Dosing regimens were as follows: bosentan 62.5 mg twice daily, increasing to 125 mg twice daily after 4 weeks; ambrisentan 5 mg once daily, increasing up to 10 mg once daily if necessary; macitentan 10 mg once daily without further up-titration; sitaxentan 100 mg daily; sildenafil 20 mg three times daily; tadalafil 20 mg once daily, up-titrated up to 40 mg once daily after 1 week.

All patients received anticoagulants, diuretics and oxygen therapy if needed. During follow-up, some patients went through one or multiple treatment regimens.

Assessments

Right-sided heart catheterisation

Haemodynamic assessment was performed with a 7F balloon-tipped flow-directed Swan-Ganz catheter (131HF7, Baxter Healthcare Corp, Irvine, CA, USA), inserted *via* the jugular or femoral vein during continuous electrocardiographic monitoring. The following parameters were measured: mean pulmonary arterial pressure (mPAP), right atrial pressure, pulmonary arterial wedge pressure (PAWP), heart rate and mixed venous oxygen saturation. Cardiac output (CO) was measured using the Fick method or thermodilution method. PVR was calculated as 80×(mPAP−PAWP)/CO. CO was indexed to body surface area (BSA), shown as cardiac index (CI).

Cardiac magnetic resonance imaging

CMR was performed on a Siemens 1.5-Tesla Sonata or 1.5-Tesla Avanto scanner (Siemens Medical Solutions, Erlangen, Germany), equipped with a 6-element phased-array receiver coil. Electrocardiographic-gated cine magnetic resonance (MR) imaging was performed using a balanced steady-state precession pulse sequence during repeated inspiratory breath-holds. CMR data acquisition was acquired according to our standard protocol [16]. After recording several localiser images, a variety of short-axis images covering the ventricles from base to apex were obtained with a typical slice thickness of 5 mm and an interslice gap of 5 mm.

The short-axis images were post-processed by a blinded observer who analysed the ventricular volumes and mass using a MASS software package (MEDIS, Medical Imaging Systems, Leiden, the Netherlands). On end-diastolic images (first cine MR image after the R-wave trigger) and end-systolic images (cine MR image with visually the smallest cavity area), endocardial and epicardial contours of the right ventricle and left ventricle (LV) were obtained by manual tracing. Papillary muscles and trabeculae were included as part

of the ventricular wall mass. Ventricular volumes were calculated using Simpson's rule. Stroke volume (SV) was calculated as end-diastolic volume (EDV) minus end-systolic volume (ESV). Right ventricular ejection fraction (RVEF) was calculated according to the following equation: (SV/EDV)×100%. For mass calculation, the myocardial volume was multiplied by the specific density of the heart (1.05 g·cm^{-3}) [17]. The relative ventricular wall thickness was calculated as the ratio of RV mass divided by the EDV [18]. Volume and mass measurements were indexed to BSA. RV end-systolic wall stress was calculated according to LaPlace's law (RV end-systolic wall stress=0.5×RV systolic pressure×RV end-systolic radius/RV end-systolic wall thickness), as explained previously [7, 19].

Six-minute walk test

The six-minute walking test (6MWT) was performed according to the American Thoracic Society guidelines [20].

Blood sampling

Since November 2002, N-terminal pro-brain natriuretic peptide (NT-proBNP) measurements have become part of our routine clinical assessment. NT-proBNP plasma levels were analysed using the Elecsys 1010 electrochemiluminescence immunoassay (Roche Diagnostics, Almere, the Netherlands), as described previously [21].

Statistical analysis

Statistical analyses were carried out using SPSS version 22 software (SPSS Inc., Chicago, IL, USA) or Prism 5 for Windows (GraphPad Software Inc., San Diego, CA, USA). A p-value <0.05 was considered statistically significant. Data are presented as mean±standard deviation for continuous variables and absolute for categorical variables, unless stated otherwise. Variables were log-transformed in cases of a non-normal distribution. Differences in baseline variables between patients treated with mono- or combination therapy were calculated using independent t-tests. Within-group differences in baseline and follow-up parameters were tested with paired t-tests. The changes in clinical parameters, haemodynamics and RV structure and function during follow-up were compared between the monotherapy and combination therapy group using linear regression analysis. This analysis was repeated with co-variate correction for differences in baseline values between groups (PVR). Correction for multiple testing was not applied because of our predefined study hypothesis and selected number of outcome parameters.

Results

Patient characteristics

Mean age of the total study population was 49±17 years; 75% were female and the majority of patients had IPAH (85%). There were no differences between the monotherapy and combination therapy groups with regard to age, gender, type of diagnosis, or NYHA class (table 1). Patients who received upfront combination therapy had a higher PVR and lower CI at baseline than patients initiated on monotherapy. No differences were found between the two groups with respect to NT-proBNP, exercise capacity or CMR RV parameters (table 2).

Follow-up measurements

The median time between baseline and follow-up measurements was 12 months (interquartile range 12–14 months). Both treatment regimens were associated with improvements in exercise capacity, NYHA class, haemodynamics and CMR variables after 1 year of follow-up (table 2, figures 2–4). The change in six-minute walk distance was greater in the combination group than in the monotherapy group (p=0.041). Furthermore, NT-proBNP levels decreased more in patients treated with combination therapy than in those who received monotherapy (p=0.001) (figure 2).

Both treatment groups showed a significant decrease in PVR, but the magnitude of decrease was larger in the upfront combination therapy group (combination *versus* monotherapy: p for change <0.001). MPAP decreased after combination therapy, but remained unchanged after monotherapy. Both groups showed a similar change in CI (p=0.071) (figure 3). RVEF improved more in the combination therapy group than in the monotherapy group (p<0.001). The mean change in right ventricular end-diastolic volume (RVEDV) was −5±16 mL·m^{-2} after combination therapy and 3±16 mL·m^{-2} after monotherapy (p for difference between groups=0.038). Patients who had received combination therapy had a more significant decrease in right ventricular end-systolic volume (RVESV) than patients who had received monotherapy (mean change: −13±17 mL·m^{-2} *versus* −1±15 mL·m^{-2}; p=0.002) (figure 4). RV mass remained unchanged after monotherapy but decreased after combination therapy. The relative wall thickness of the right ventricle was unaltered in both treatment groups (table 2).

TABLE 1 Baseline characteristics

Variable	Total cohort	Monotherapy	Combination therapy	p-value
Subjects n	80	45	35	
Female	60 (75)	34 (76)	26 (74)	0.896
Age years	49±17	49±17	50±19	0.803
Diagnosis				0.103
Idiopathic PAH	68 (85)	40 (89)	28 (80)	
Heritable PAH	10 (13)	3 (7)	7 (20)	
Drugs/toxins PAH	2 (3)	2 (4)	0	
NYHA class				0.067
II	24 (30)	16 (36)	6 (17)	
III	56 (70)	29 (64)	29 (83)	
BSA m^2	1.9±0.2	1.9±0.2	1.9±0.7	0.939
Comorbidities				0.158
Diabetes mellitus	3 (4)	1 (2)	2 (6)	
Systemic hypertension	14 (18)	5 (11)	9 (26)	
Coronary artery disease	3 (4)	1 (2)	2 (6)	
Medical therapy				
ERA		34 (76)	35 (100)	
Ambrisentan	20 (17)	6 (13)	14	
Bosentan	42 (37)	22 (5)	20[#]	
Macitentan	4 (3)	3 (7)	1	
Sitaxentan	3 (3)	3 (7)	0	
PDE5I		11 (24)	35 (100)	
Sildenafil	31 (27)	9 (20)	22	
Tadalafil	15 (13)	2 (4)	13	
Renal function				
Creatinine $\mu mol \cdot L^{-1}$	84±23	86±27	81±18	0.340

Data are presented as as mean±SD or n (%), unless otherwise stated. PAH: pulmonary arterial hypertension; NYHA: New York Heart Association; BSA: body surface area; ERA: endothelin receptor antagonist; PDE5I: phosphodiesterase-5-inhibitor. [#]: One patient did not tolerate the full dosage of bosentan and therefore received a lower dose of 62.5 mg twice daily. All other patients were treated with full dosage of ERA and/or PDE5I.

The relative change in PVR was significantly correlated to the absolute change in RVEF after combination therapy (R=−0.60; p<0.001). In contrast, we did not find a significant correlation between the change in PVR and RVEF after monotherapy (p>0.05). Strikingly, RVEF decreased by >3% [9] in only two out of 35 patients after initiation of combination therapy, and one of these two patients did not show an improved PVR either. In eight out of 45 patients (18%) in the monotherapy group, RVEF decreased by >3% despite therapy (figure 5).

In the monotherapy group, we did not find different therapeutic effects between the patients treated with ERA monotherapy and the patients treated with PDE5I (p>0.05 for all parameters).

However, even after correction for baseline differences in PVR, we found significant differences in haemodynamics, CMR parameters and NT-proBNP between the combination therapy group and monotherapy group, except for RVEDV and RV mass (table S1).

Treatment strategies

In the group of patients initiated on monotherapy, one patient switched from ERA (bosentan) to PDE5I (sildenafil; after 4 months) owing to liver enzyme abnormalities. All other patients in the upfront monotherapy group received and tolerated the full dosage of ERA or PDE5I. In the combination therapy group, one patient did not tolerate the full dosage of the combined treatment of bosentan plus sildenafil owing to liver enzyme abnormalities; therefore, the dosage of bosentan was kept constant at 62.5 mg twice daily. All other patients in the combination therapy group were treated with full-dosage ERA plus PDE5I.

In the monotherapy group, eight patients (18%) were treated with sequential combination therapy (n=7 initiated on ERA and n=1 initiated on PDE5I) owing to lack of clinical improvement after upfront monotherapy (median time 5 months; IQR 5–6 months). In the group of patients initiated on dual combination therapy, treatment was switched to sequential triple therapy (*i.e.* by adding prostacyclin) in

TABLE 2 Differences in clinical parameters at baseline and during follow-up

Variables	Monotherapy[#]			Combination therapy[¶]			p-value for baseline difference between groups	B[§]	95% CI (B)	p-value for change during follow-up[+]
	Baseline	1-year FU	Mean change	Baseline	1-year FU	Mean change				
RHC										
mPAP mmHg	54±11	53±18	−3±10	56±17	43±12	−11 ±13***	0.675	−7.5	−12.5 to −2.5	**0.004**
RAP mmHg	8±4	7±4	−1±5	8±5	5±4	−3±5**	0.761	−1.0	−4.2 to 0.3	0.084
PVR dyn·s·cm^{-5}	705 (485–998)	574 (347–867)	−162 ±300**	950 (383–1046)	393 (294–514)	−426 ±344***	**0.045**	−0.001	−0.001 to −0.0001	<**0.001**
PAWP mmHg	9±4	8±4	−1±5	8±3	8±4	0±3	0.624	0.3	−1.6 to 2.2	0.739
CI L·min^{-1}·m^{-2}	2.6±0.8	3.2±1.2	0.7 ±1.2**	2.3±0,5	3.4±0.9	1.1±0.9***	**0.032**	0.5	−0.0 to 1.0	0.071
Heart rate bpm	79±18	79±13	−2±17	80±14	74±10	−7±14***	0.769	−5.1	−12.1 to 1.8	0.147
S_{vO_2} %	66±7	66±9	0±8	63±8	70±5	6±7***	0.102	6.6	3.0 to 10.3	**0.001**
CMR variables										
RVEDV mL·m^{-2}	79±20	82±22	3±16	81±25	76±25	−5±16	0.703	−7.6	−14.9 to −0.5	**0.038**
RVESV mL·m^{-2}	51±19	51±23	−1±15	55±25	43±22	−13 ±17***	0.381	−11.9	−19.2 to −4.6	**0.002**
RV mass g·m^{-2}	51±13	50±15	0±11	52±15	46±14	−6±15**	0.759	−6.3	−12.1 to −0.6	**0.032**
Relative RV wall thickness	0.66±0.18	0.64 ±0.17	−0.02 ±0.16	0.69±0.25	0.65 ±0.28	−0.04 ±0.26	0.506	0.0	−0.1 – 0.1	0.072
RVEF %	36±11	40±14	4±9**	34±12	47±13	13±11***	0.319	8.9	4.4 to 13.4	<**0.001**
LVEDV mL·m^{-2}	46±13	51±14	5±8***	44±10	53±12	9±12***	0.367	4.2	−0.3 to 8.7	0.066
LVESV mL·m^{-2}	17±8	19±8	1±7	18±7	18±6	0±7	0.691	−1.1	−4.1 to 1.9	0.478
LV mass g·m^{-2}	55±14	57±11	2±9*	54±9	57±11	4±9*	0.749	1.3	−2.7 to 5.3	0.517
SV mL·m^{-2}	29±8	33±11	4±6***	26±6	35±7	9±8***	0.074	5.0	1.7 to 8.2	**0.003**
LVEF %	63±10	66±10	3±10*	60±10	66±7	6±10**	0.160	3.4	−1.0 to 7.9	0.130
RV wall stress kPA	12±4	11±4	−1±4	13±5	9±4	−4±5***	0.273	−2.8	−4.6 to −0.9	**0.003**
NT-proBNP ng·L^{-1}	741 (159–2392)	408 (98–1915)	−365 ±1610*	950 (624–1050)	218 (87–572)	−1203 ±1057***	0.121	−0.1	−0.2 to −0.04	**0.001**
6MWD m	411±106	446±115	27±95*	409±119	475±114	70±75***	0.948	42.2	1.7 to 82.8	**0.041**

Data are presented as mean±SD or median (IQR), unless otherwise stated. [#]: n=45; [¶]: n=35; [+]: p-value for the difference in change in variables between groups during follow-up without correction for baseline co-variates; [§]: B represents the regression coefficient for the difference in variable change between groups without correction for baseline co-variates. Within-group differences between baseline and follow-up variables are indicated by *: p<0.05; **: p<0.01; ***: p<0.001. NT-proBNP was measured in 71 patients and values were log-transformed before testing. FU: follow-up; RHC: right-sided heart catheterisation; mPAP: mean pulmonary arterial pressure; RAP: right atrial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure; CI: cardiac index; S_{vO_2}: mixed venous oxygen saturation; CMR: cardiac magnetic resonance imaging; RVEDV: right ventricular end diastolic volume; RVESV: right ventricular end-systolic volume; RV: right ventricle; RVEF: right ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LV: left ventricle; SV: stroke volume; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; 6MWD: six-minute walk distance. Values presented in bold are statistically significant.

three patients after 3, 8 and 10 months, respectively, owing to clinical worsening (*i.e.* deterioration into NYHA class IV). In table S2, an analysis is provided of the data after exclusion of the eight patients from the monotherapy group and the three patients from the combination therapy who had switched therapy during the 12 months of follow-up. The remaining 37 patients of the upfront monotherapy group showed differences in haemodynamics, NT-proBNP and CMR parameters compared with the 32 patients in the upfront combination therapy group. The results from table S2 are comparable to those shown in table 1 and table S1.

Discussion

In the present study, we showed – in NYHA class II and III PAH patients – that treatment with upfront combination therapy ERA plus PDE5I is associated with significant reductions in PVR and pulmonary pressures and resulted in improved RV volumes and function. Compared with combination therapy, upfront monotherapy was associated with smaller decreases in RV afterload, and RV volumes remained unchanged.

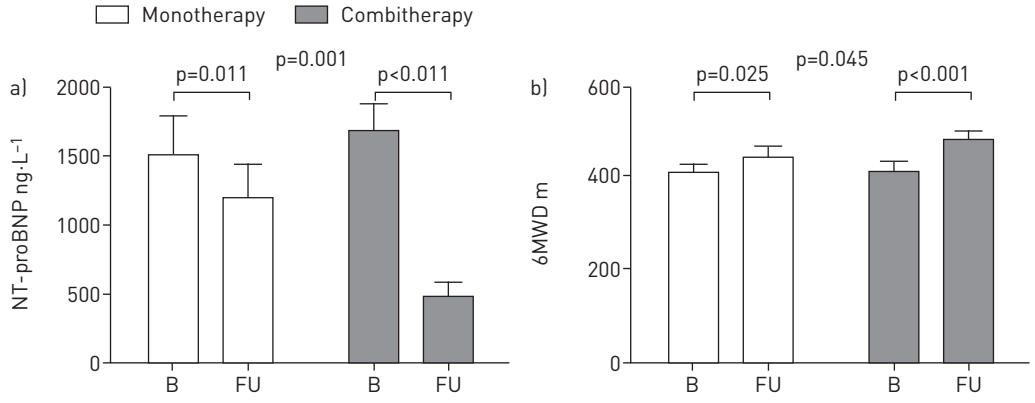

FIGURE 2 a) The decrease in N-terminal pro-brain natriuretic peptide (NT-proBNP) was greater in the upfront combination therapy group (grey bars) than in the monotherapy group (white bars). b) The six-minute walk distance (6MWD) improved in both groups. Data are presented as mean±SEM. B: baseline; FU: follow-up.

Effects of combination therapy on RV afterload

In accordance with earlier studies [22], we found statistically significant reductions in PVR after single-agent therapy, but the PVR change was modest (~19%) and mPAP was not significantly reduced. In contrast, we showed that PVR dropped by ~59% after upfront oral combination therapy. These results are in agreement with former studies showing a ~45–70% decrease in PVR after upfront therapy of ERA plus PDE5I [8] or ERA plus prostacyclins [23, 24]. Importantly, the decrease in PVR after combination therapy was not only accompanied by normalisation of the CO but also by a ~23% reduction in mPAP. This RV unloading was accompanied by subsequent improvements in RV remodelling and function. In fact, a progressive deterioration in RVEF was found in only two patients treated with upfront combination therapy.

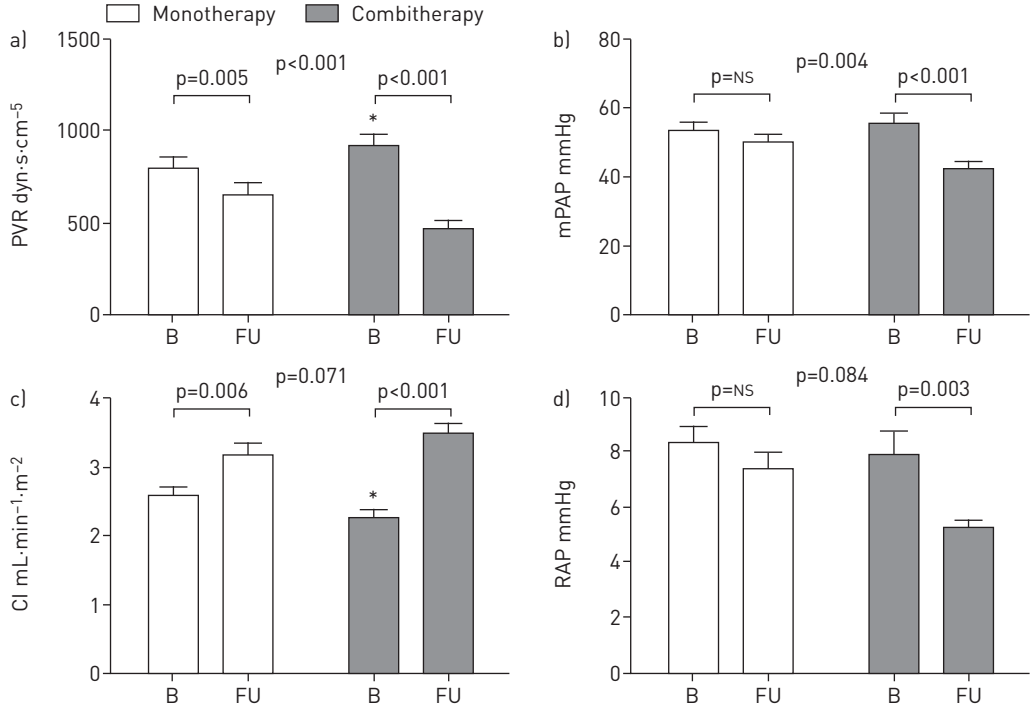

FIGURE 3 Patients treated with upfront combination therapy (grey bars) showed greater improvements in (a) pulmonary vascular resistance (PVR) and (b) mean pulmonary arterial pressure (mPAP) than patients receiving upfront monotherapy (white bars). Both patients groups showed normalisation of the cardiac index (CI) (c). Right atrial pressure (RAP) (d) remained unchanged after monotherapy and improved after combination therapy. Data are presented as mean±SEM. *: p<0.05 for baseline difference between the mono and combination therapy groups. B: baseline; FU: follow-up; NS: nonsignificant.

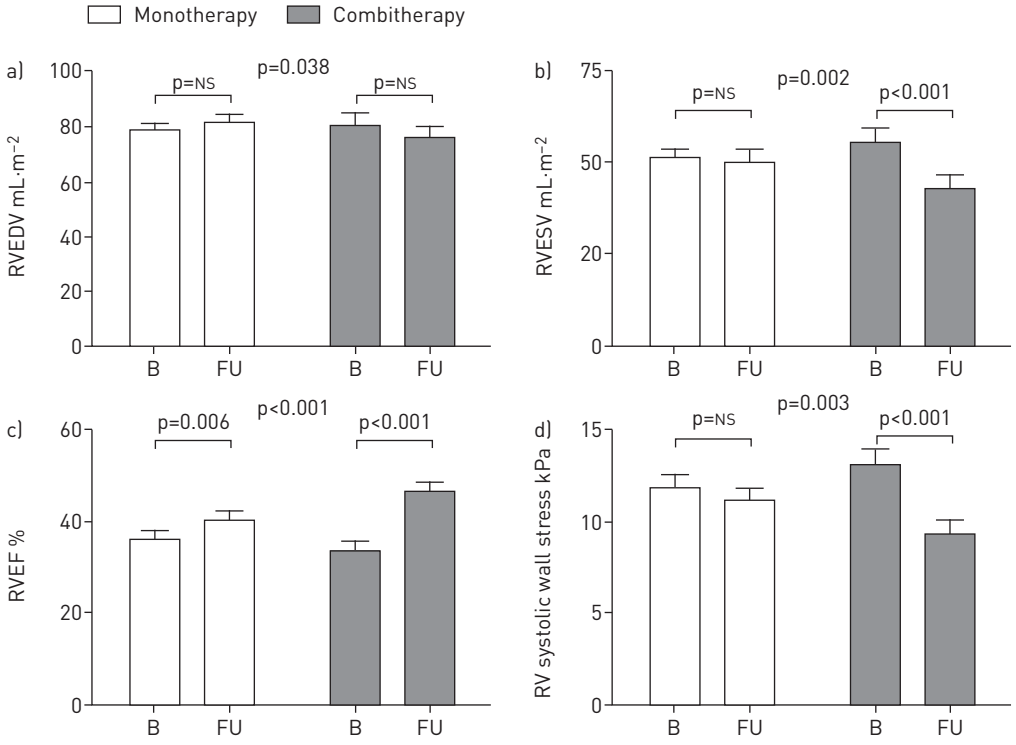

FIGURE 4 Neither monotherapy (white bars) nor combination therapy (grey bars) resulted in an improvement in right ventricular end-diastolic volume (RVEDV) (a). Right ventricular end-systolic volume (RVESV) (b) and right ventricular (RV) wall stress (d) decreased after combination therapy but remained unaltered after monotherapy. The increase in right ventricular ejection fraction (RVEF) (c) was greater after combination therapy than after monotherapy. Data are presented as mean±SEM. B: baseline; FU: follow-up; NS: nonsignificant.

Effects of upfront combination therapy on RV volumes

The most important finding of the present study was that RVESV decreased significantly after upfront combination therapy. Of note, a decrease in RVESV was accompanied by a stable RVEDV, and consequently stroke volume was improved after combination treatment.

In line with previous studies, we showed that RV volumes remain unchanged after upfront monotherapy [11–15]. Moreover, it has been shown that RV volumes do not alter after combination therapy when

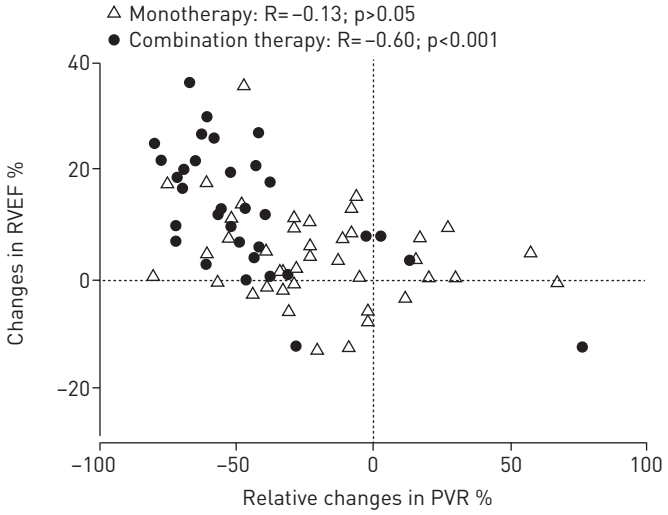

FIGURE 5 The relative changes in pulmonary vascular resistance (PVR) were correlated with the changes in right ventricular ejection fraction (RVEF) after upfront combination therapy (black circles) but not after upfront monotherapy (open triangles).

applied sequentially during follow-up [12]. Our findings are of major clinical relevance since RV dilatation is one of the most important prognostic predictors in patients with PAH [25, 26] and is a sensitive parameter for monitoring patients during follow-up [18]. In addition, and in line with earlier studies [11], we found that changes in RV mass are relatively small after medical treatment. Small changes in RV mass with concomitant large reductions in RV volumes after combination therapy contribute to a more favourable concentric RV remodelling pattern which is associated with better survival [27, 28].

Possible mechanisms for improved RV adaptation and function after upfront combination therapy

In this study, we evaluated the relationship between NT-proBNP, RV afterload and RV remodelling in PAH patients receiving combination therapy. In accordance with the results from the AMBITION trial [5] and other studies [8, 29], we observed a ~77% reduction in NT-proBNP after upfront combination therapy. The magnitude of the decrease in NT-proBNP was significantly larger after combination therapy than after monotherapy. These findings are not only of prognostic relevance [30, 31] but also of physiological interest since NT-proBNP is considered a surrogate marker of RV wall stress [21, 32]. According to LaPlace's law, ventricular wall stress can be reduced by either reducing intraluminal pressures, decreasing chamber radius, or increasing wall thickness [19]. In the present study, we showed that combination therapy resulted in significant reductions in both PVR and RV pressures, leading to a considerable decrease in intraluminal RV volumes and smaller changes in RV wall thickness. As a consequence, the calculated RV end-systolic wall stress dropped significantly. In contrast, after monotherapy pulmonary pressures, RV volumes and mass were unchanged, and thereafter in the monotherapy group, RV wall stress remained high. We showed that the changes in RV pressures and volumes after medical treatment were the most important contributors to changes in RV wall stress, and are summarised in figure 6. Our findings are of clinical importance since a decreased RV wall stress positively affects myocardial perfusion and oxygen demand [36, 37] and may therefore contribute to the reversal of progressive RV dysfunction. This is supported by the large and clinically relevant increase in RVEF observed after combination therapy [9]. Moreover, we observed a significant relationship between

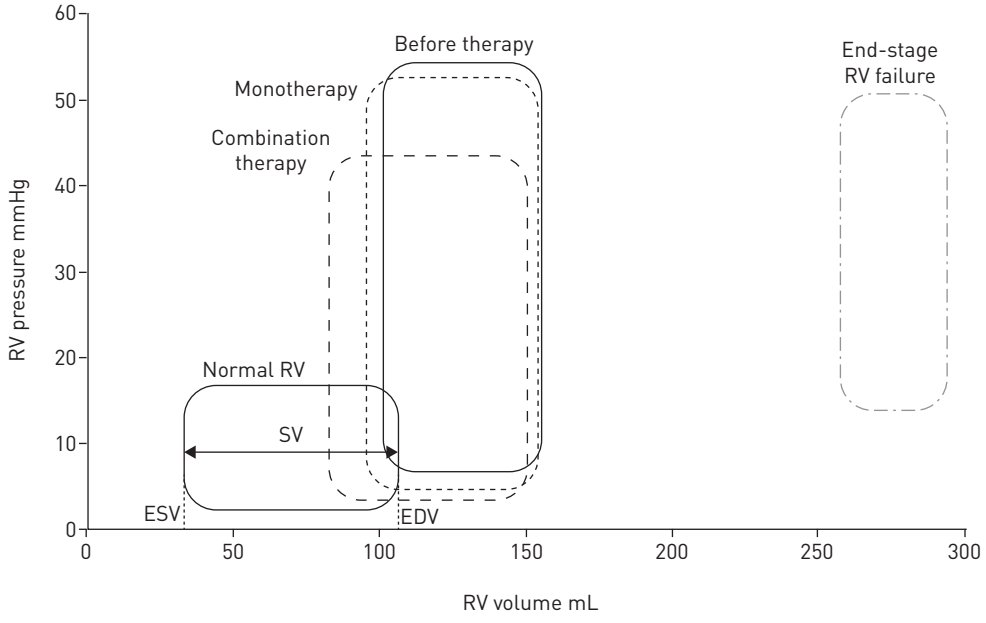

FIGURE 6 Schematic pressure–volume relationships that summarise the effects of upfront monotherapy (-----) and combination therapy (– – –) in patients with pulmonary arterial hypertension (PAH) (—). Compared with control subjects (Normal RV) [33, 34], PAH patients showed increased right ventricular (RV) pressures and right ventricular end-systolic volume (RVESV). After monotherapy, RV pressures were modestly reduced but right ventricular end-diastolic volume (RVEDV) and RVESV remained unchanged. Importantly, upfront combination therapy was associated with significant reductions in both RV pressures and RVESV. Because RV pressures and volumes are main contributors to RV wall stress, the calculated ventricular systolic wall stress will be lowered after combination therapy but remains high after monotherapy. The pressure–volume loop of end-stage RV failure (·–·) is included for comparison. In cases of RV failure, RV pressures are comparable to other stages of RV dysfunction, though RV volumes are massively increased [18, 35]. Of note, stroke work (*i.e.* area within one pressure–volume loop) is increased in PAH patients compared with controls but depresses with the development of RV failure. EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume.

the changes in PVR and RVEF after combination therapy, but did not find such a relationship after monotherapy. These results demonstrate that in cases where there is a sufficient decrease in RV afterload, reversal of RV dysfunction is guaranteed and "right ventricle - arterial coupling" will be preserved [38], whereas smaller changes in PVR do not necessarily lead to improved RV function. In addition to a reduced afterload and potential direct RV therapeutic effects, other intrinsic RV factors could also play a role in a more favourable RV adaptation response following combination therapy [39].

Clinical implications

We have shown – in patients with PAH – that upfront oral combination therapy, in contrast to upfront monotherapy, is associated with a significant reduction in the main determinants of wall stress – namely, RV volumes and mPAP. Since progressive RV dilation and increased RV wall stress precede ultimate disease progression and are major contributing factors that drive the right ventricle into failure [6, 18], the results of this retrospective analysis suggest that the vicious circle leading to the development of RV failure might be interrupted by aggressive upfront medical treatment in all patients. In addition, the favourable RV therapeutic effects observed in this study also raise the question as to whether prognosis can be improved by a goal-oriented strategy specifically directed at improving RV remodelling and function.

Limitations

The present study has the limitations of a retrospective analysis. The treatment strategy was non-controlled and rather reflects the therapeutic choice of the treating physician. However, our study reflected the treatment strategy that is generally accepted in clinical care and is supported by official guidelines [3]. Furthermore, the therapeutic effects on haemodynamics and NT-proBNP observed after both upfront monotherapy and combination therapy correspond to earlier prospective studies indicating that our results reflect "real world" therapeutic responses [5, 29] In addition, our study may be biased by the lengthy inclusion period – from 2002 to 2015 – while only monotherapy was available before 2005. Yet, we would like to emphasise that the present study was not aimed at measuring treatment efficacy. Patients receiving upfront combination therapy were slightly more compromised at baseline than patients treated with monotherapy. However, we limited this potential bias by correcting for differences in baseline characteristics.

Conclusions

We showed – in NYHA class II and III PAH patients – that treatment with upfront combination therapy of an ERA plus a PDE5I is associated with significant reductions in RV volumes. This was accompanied by reduced NT-proBNP levels and a relief of the calculated RV wall stress.

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