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RESEARCH ARTICLE

Initial combination therapy with macitentan and tadalafil in patients with pulmonary arterial hypertension, with and without cardiac comorbidities

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Aims According to current guidelines, initial monotherapy should be considered for pulmonary arterial hypertension (PAH) patients with cardiopulmonary comorbidities. This analysis of combined data from the TRITON and REPAIR clinical trials, assesses efficacy and safety of initial double combination therapy in patients without vs. with 1–2 cardiac comorbidities.

Methods and results Data were combined for patients from TRITON (NCT02558231) and REPAIR (NCT02310672) on initial macitentan and tadalafil double combination therapy (overall set, $n = 148$) and two subgroups defined as patients without cardiac comorbidities ($n = 62$) and those with 1–2 cardiac comorbidities ($n = 78$). Patients with ≥3 comorbidities were excluded from these studies. For the overall set, the median (Q1–Q3) duration of combined macitentan and tadalafil exposure was 513.0 (364.0–778.0) days, and was similar between subgroups. Change from baseline to Week 26 for pulmonary vascular resistance was −55% and −50% for patients without and with 1–2 cardiac comorbidities, respectively; marked improvements in other hemodynamic and functional parameters were also observed, although functional parameters improved to a lesser extent in patients with comorbidities. At Week 26, the majority of patients had improved PAH risk status, according to the non-invasive four-strata and REVEAL Lite 2.0 methods. The safety profile of initial macitentan plus tadalafil combination therapy was consistent with the known profiles of the two drugs, and similar between the subgroups.

Conclusions Initial double combination therapy with macitentan plus tadalafil is efficacious in patients with PAH with 1–2 cardiac comorbidities and those without, with similar safety and tolerability profiles between the two groups.

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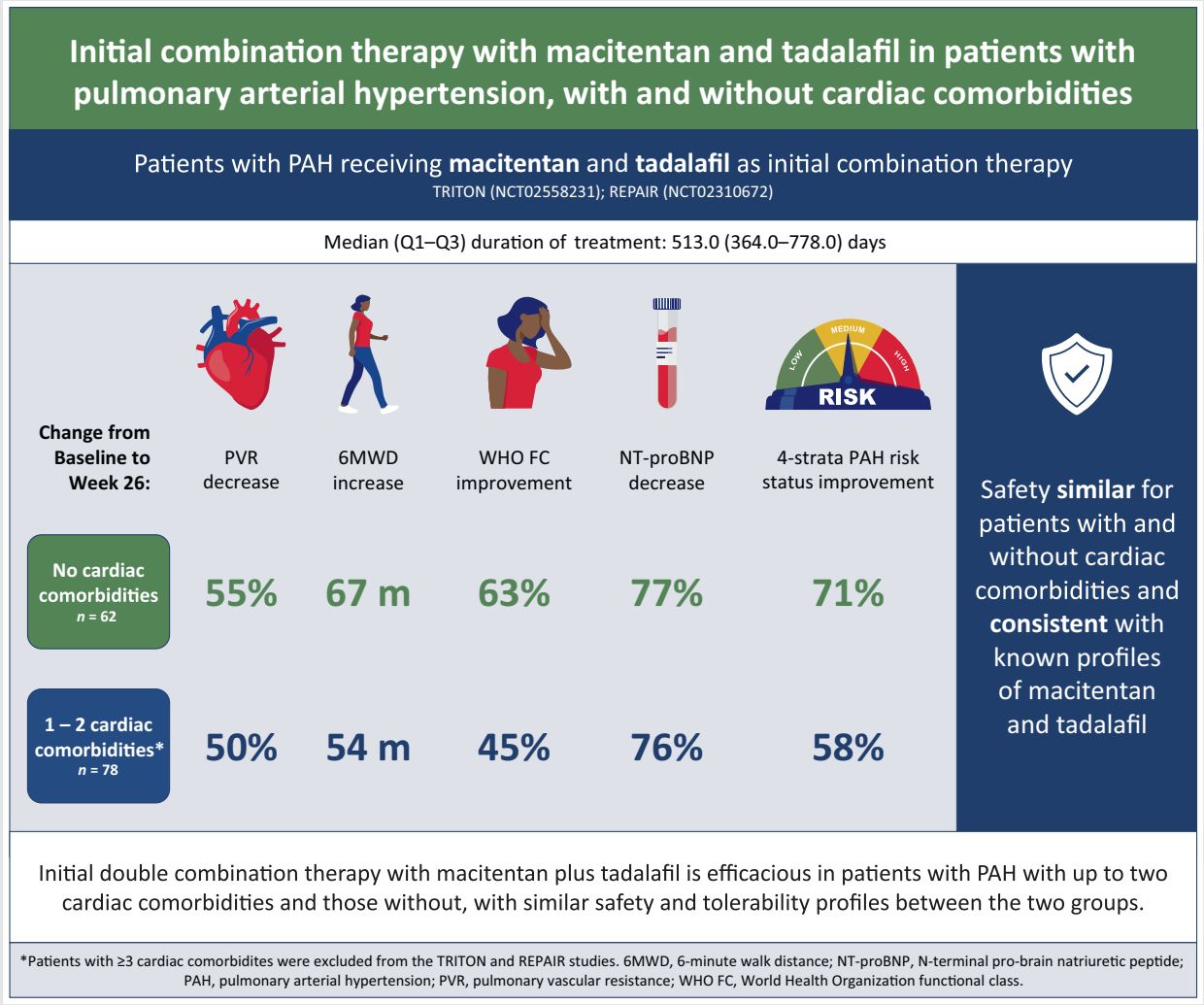
Graphical Abstract



Initial macitentan and tadalafil combination therapy in pulmonary arterial hypertension (PAH) patients with or without cardiac comorbidities. 6MWD, 6-min walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; WHO FC, World Health Organization functional class.

Keywords Pulmonary arterial hypertension • Risk stratification • Cardiac comorbidities • Macitentan • Tadalafil • Initial double combination therapy

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by detrimental remodelling of the pulmonary vasculature that can lead to death due to right heart failure.[1,2] Current therapies for patients with PAH have advanced substantially in the last decade, with the benefit of initial double combination therapy with an endothelin receptor antagonist (ERA) and phosphodiesterase 5 inhibitor (PDE5i) shown in several studies[3–7]; however, in real-world clinical practice many patients are initiated and maintained on monotherapy.[8–11]

Registry data show that the profile of PAH patients has changed over the years, with patients now older and presenting with more cardiopulmonary comorbidities.[12–16] Within the context of a PAH diagnosis, cardiac comorbidities have been defined as conditions associated with an increased risk of left ventricular diastolic

dysfunction, including obesity, hypertension, diabetes mellitus, and coronary heart disease. Pulmonary comorbidities include signs of mild parenchymal lung disease and a low diffusing capacity of the lungs for carbon monoxide (DLCO; <45% of the predicted value).[1,2]

According to current guidelines, initial monotherapy with a PDE5i or ERA should be considered for PAH patients with cardiopulmonary comorbidities, and treatment escalations may be considered on an individual basis, citing limited data to support the use of initial combination therapy in these patients.[1,2] While this stepwise approach may particularly resonate for older patients with a high cardiopulmonary comorbidity burden, the question remains whether a more aggressive treatment strategy with initial combination therapy would be beneficial for younger patients with a lower comorbidity burden. Data on the safety, tolerability and effectiveness of combination therapy in these patients are therefore needed.

Patients with pulmonary or a high number (≥3) of cardiac comorbidities are now largely excluded from randomized controlled trials (RCTs).[3,5] In contrast, patients with a lower number of cardiac comorbidities (1–2) have been included in most PAH RCTs, although comorbidity status has not been the focus of the trials. This post-hoc analysis combines data from the TRITON[5] and REPAIR[17] trials for patients who received macitentan and tadalafil as initial double combination therapy to assess the efficacy and safety of this treatment regimen in patients with PAH with and without cardiac comorbidities.

Methods

Study designs

The study designs for TRITON (NCT02558231) and REPAIR (NCT02310672) have been described previously[5,17]; key elements are summarized in online supplementary *Table S1*. Both studies were conducted in compliance with the Declaration of Helsinki, the protocols were approved by institutional review boards/independent ethics committee at each study site and written informed consent was obtained from all patients. Briefly, TRITON was a multicenter, double-blind, randomized, phase 3b study; eligible patients were PAH treatment-naïve adults with a 6-min walk distance (6MWD) ≥50 m and a pulmonary vascular resistance (PVR) ≥6 Wood units (WU). Patients were treated with either initial triple oral therapy (macitentan, tadalafil, and selexipag) or initial double oral therapy (macitentan, tadalafil, and placebo). REPAIR was a multicenter, single-arm, open-label, 52-week, phase 4 study; eligible patients were adults in World Health Organization functional class (WHO FC) I–III, with a 6MWD of ≥150 m and who were either treatment-naïve or receiving a stable background PDE5i for at least 3 months prior to screening. Patients in REPAIR were treated with macitentan, with physicians having the option to additionally initiate a PDE5i within 14 days. For patients in both studies, PAH diagnosis was required by confirmatory right heart catheterization (RHC). Patients with a high cardiopulmonary comorbidity burden were excluded from both TRITON and REPAIR, as were patients with DLCO <40%; the relevant exclusion criteria for both studies are outlined in online supplementary *Table S2*. Data from the OPTIMA study, an open-label, single-arm, phase 4 study of PAH treatment-naïve patients initiating macitentan and tadalafil[7] (study details described in online supplementary *Table S1*), were used as a reference cohort for PAH risk status analyses.

Patient selection for combined analysis

Patients receiving macitentan and tadalafil combination therapy in the TRITON and REPAIR studies were included in this analysis. For TRITON, this included patients in the double oral therapy group who were treated with macitentan 10 mg, tadalafil 40 mg and placebo. For REPAIR, this included patients who newly initiated tadalafil up to 14 days after initiation of macitentan 10 mg.

Analysis sets

The TRITON/REPAIR combined analysis sets comprised the overall set, patients without cardiac comorbidities and patients with 1–2 cardiac comorbidities at screening. Cardiac comorbidities comprised those described in the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines,[1,2] and were defined as obesity (body mass index >30 kg/m^2), history of essential hypertension, diabetes mellitus, and history of coronary heart disease. Patients with a medical history of mild parenchymal lung disease were excluded from the no cardiac comorbidities cohort. The preferred terms used to define each comorbidity are listed in online supplementary *Table S3*.

Outcomes and assessments

Efficacy assessments included the change from baseline to Week 26 (the timepoint used for the primary endpoint analysis for both TRITON and REPAIR) in PVR and other hemodynamic variables, and the functional parameters 6MWD, N-terminal pro-brain natriuretic peptide (NT-proBNP) and WHO FC. Changes in PVR and NT-proBNP were expressed as the Week 26 to baseline ratio. Subgroup analyses by age, sex, WHO FC, and PAH etiology were conducted for continuous variables PVR, NT-proBNP, and 6MWD.

Safety assessments included treatment-emergent adverse events (AEs) with onset during the macitentan and tadalafil combination treatment exposure. This constituted the time between initiation of the second drug and discontinuation of either drug plus 30 days, or, if earlier, Week 52 plus 30 days for REPAIR, or the end of the main observation period for TRITON. Serious AEs (SAEs), AEs leading to macitentan or tadalafil discontinuation, AEs leading to death, and AEs of special interest (AESI) (combined terms for edema, anemia, hypotension and liver events) were also described.

Pulmonary arterial hypertension risk status was assessed using the non-invasive three-strata method[18–20] at baseline, and change in risk status from baseline to Week 26 (TRITON and REPAIR) or Week 16 (OPTIMA) was assessed using the non-invasive four-strata[10,20] and the REVEAL Lite 2.0[21] methods. Detailed methodologies are provided in online supplementary *Table S4*.

Statistical analyses

For PVR and NT-proBNP, the ratio of Week 26 vs. baseline parameter was log transformed and analyzed using an adjusted analysis of covariance (ANCOVA) model with 95% confidence interval (CI) with factors for region (North America vs. Rest of World) and baseline WHO FC, and a covariate for log baseline parameter. The mean change (95% CI) from baseline (log transformed) was estimated based on the model and the geometric mean ratio (vs. baseline) and CI were obtained by exponentiation. For 6MWD and hemodynamic variables, the change from baseline to Week 26 was analyzed using an ANCOVA with factors for region (North America vs. Rest of World) and baseline WHO FC,

and a covariate for the baseline parameter. Missing post-baseline values were imputed using the last observation carried forward (LOCF). All analyses were performed post-hoc and are therefore exploratory in nature.

Results

Patient disposition

The overall analysis set comprised 148 patients who received initial macitentan and tadalafil combination therapy: 127 patients from TRITON and 21 patients from REPAIR (online supplementary *Figure S1*). From the overall set, 78 patients ($n = 73$ from TRITON and $n = 5$ from REPAIR) had 1–2 cardiac comorbidities at screening. Patients with ≥3 cardiac comorbidities at screening were excluded from TRITON and none of the patients included from REPAIR had ≥3 cardiac comorbidities. In total, there were 70 patients without cardiac comorbidities; however, to avoid including patients with a potential pulmonary phenotype, eight patients with a medical history of mild parenchymal lung disease were excluded from this cohort. The subgroup of patients without cardiac comorbidities therefore consisted of 62 patients ($n = 47$ from TRITON and $n = 15$ from REPAIR).

Patient demographics and characteristics

Patient demographics and baseline characteristics are outlined in *Table 1*. The majority of patients in the overall set were white, female, with idiopathic PAH and in WHO FC III. The median (Q1–Q3) time from PAH diagnosis was 13.0 (6.0–26.0) days for the overall set, and was similar between the comorbidity subgroups. The median age for patients without and with 1–2 cardiac comorbidities was 44.5 vs. 55.5 years, respectively. The number of comorbidities categorized by age is presented in online supplementary *Figure S2*. For patients without and with 1–2 cardiac comorbidities, 80.6% vs. 71.8% were female, the mean 6MWD was 387.6 vs. 331.2 m, respectively, and a similar hemodynamic profile was observed between the two subgroups (*Table 1*). Concomitant medications at baseline are outlined in online supplementary *Table S5*. For patients with cardiac comorbidities, the most common were hypertension and obesity; combinations of cardiac comorbidities are detailed in *Table 2*.

At baseline, most patients in the overall set were at intermediate risk using the three-strata approach (75.7%); 26.4% were at intermediate-low and 54.7% were at intermediate-high risk using the four-strata risk method. In contrast, patients were predominantly classified as high risk (54.1%) according to the REVEAL Lite 2.0 method. The proportions of patients in each risk category for the three- and four-strata methods were similar irrespective of comorbidity status. More patients in the 1–2 cardiac comorbidities subgroup were in the high-risk REVEAL Lite 2.0 category compared to patients without cardiac comorbidities (62.8% vs. 45.2%, respectively).

Outcomes

Hemodynamic improvements from baseline to Week 26 were observed across both subgroups, including a PVR reduction of 53%, 55% and 50% for patients in the overall set, and those without or with 1–2 cardiac comorbidities, respectively (*Table 3*, *Figure 1A*). From baseline to Week 26, the change in heart rate was −7.6, −8.6 and −6.6 bpm and the change in systolic blood pressure was −1.2, −0.4 and −0.7 mmHg for patients in the overall set, and those without or with 1–2 cardiac comorbidities, respectively (*Table 3*). Improvements in clinical parameters from baseline to Week 26 were also observed, with NT-proBNP reductions of 75%, 77% and 76%, and 6MWD increases of 56.8, 66.7 and 53.5 m, for patients in the overall set, and those without or with 1–2 cardiac comorbidities, respectively (*Table 3*, *Figure 1B,C*). In further analyses of PVR, 6MWD and NT-proBNP according to subgroups of age, sex, WHO FC and PAH etiology, changes were also consistent with those in the overall set (*Figure 1*), with the exception of 6MWD, where patients ≥65 years improved to a lesser extent than those <65 years (*Figure 1C*). Improvements in WHO FC from baseline to Week 26 were observed for 52.7%, 62.9% and 44.9% of patients in the overall set, and those without or with 1–2 cardiac comorbidities, respectively (*Table 3*).

Risk status

When change in risk status from baseline to Week 26 was assessed using the four-strata and REVEAL Lite 2.0 methods, the majority of patients in the overall set either improved (64.2% and 55.4%, respectively) or maintained (30.4% and 42.6%, respectively) risk category at Week 26 (online supplementary *Figure S3*). A higher proportion of patients without cardiac comorbidities improved risk status vs. those with 1–2 cardiac comorbidities (four-strata: 71.0% vs. 57.7% improved, 22.6% vs. 37.2% maintained; REVEAL Lite 2.0: 64.5% vs. 51.3% improved, 33.9% vs. 46.2% maintained) (online supplementary *Figure S3*). For both risk assessment methods, few patients worsened in risk status from baseline to Week 26, irrespective of comorbidity status (online supplementary *Figure S3*). These data for change in PAH risk status were consistent with observations from the OPTIMA study used as a reference cohort (four-strata: 52.2% improved, 37.0% maintained; REVEAL Lite 2.0: 50% improved, 50% maintained) (online supplementary *Figure S4*).

Safety

Macitentan and tadalafil exposure is detailed in *Table 4*. The median (Q1–Q3) duration of combined macitentan and tadalafil exposure was 513.0 (364.0–778.0) days, 498.0 (365.0–687.0) and 554.0 (362.0–814.0) for patients in the overall set, and in patients with no cardiac comorbidities or 1–2 cardiac comorbidities, respectively. Most (93.9%) patients in this analysis experienced at least one AE, with similar proportions between the subgroups (*Table 4*). The most common AEs reported for both patients with 1–2 cardiac comorbidities and those without cardiac comorbidities were headache, peripheral edema and diarrhea (*Table 4*). SAEs were experienced by 32.1% patients with 1–2 cardiac comorbidities and 22.6% of patients without cardiac comorbidities (*Table 4*). In patients with 1–2 cardiac comorbidities and those without cardiac comorbidities, AESI of edema were reported for 47.4% and 40.3% and AESI of anemia were reported for 11.5% and 16.1%,

Table 1 Demographics and baseline characteristics

	Overall set ($n = 148$)[a]	Patients without cardiac comorbidities ($n = 62$)	Patients with 1–2 cardiac comorbidities ($n = 78$)
Age, years, median (Q1–Q3)	50.5 (38.0–63.0)	44.5 (33.0–53.0)	55.5 (48.0–66.0)
Female sex, *n* (%)	111 (75.0)	50 (80.6)	56 (71.8)
Body mass index, kg/m^2, mean (SD)	27.0 (5.4)	24.6 (3.5)	29.3 (5.6)
Race, *n* (%)			
White	124 (83.8)	52 (83.9)	65 (83.3)
Black/African American	5 (3.4)	0	5 (6.4)
Asian	5 (3.4)	3 (4.8)	2 (2.6)
Other	3 (2.0)	1 (1.6)	2 (2.6)
Not collected/missing	11 (7.4)	6 (9.7)	4 (5.1)
Geographical region, *n* (%)			
North America (USA or Canada)	73 (49.3)	24 (38.7)	43 (55.1)
Rest of World	75 (50.7)	38 (61.3)	35 (44.9)
PAH etiology, *n* (%)			
Idiopathic	79 (53.4)	34 (54.8)	44 (56.4)
Heritable	9 (6.1)	6 (9.7)	3 (3.8)
Drug- and/or toxin-induced	9 (6.1)	5 (8.1)	4 (5.1)
Associated with:			
Connective tissue disease	44 (29.7)	14 (22.6)	24 (30.8)
HIV	5 (3.4)	3 (4.8)	1 (1.3)
Congenital heart disease	2 (1.4)	0	2 (2.6)
Time from PAH diagnosis[b], *n*	127	47	73
Days, median (Q1–Q3)	13.0 (6.0–26.0)	12.0 (7.0–20.0)	13.0 (5.0–26.0)
6MWD, *n*	145	61	76
m, mean (SD)	356.4 (120.9)	387.6 (120.2)	331.2 (116.6)
WHO FC[c], *n* (%)			
I	1 (0.7)	1 (1.6)	0
II	28 (18.9)	13 (21.0)	14 (17.9)
III	114 (77.0)	46 (74.2)	61 (78.2)
IV	5 (3.4)	2 (3.2)	3 (3.8)
NT-proBNP level, *n*	146	60	78
ng/L, mean (SD)	1937.4 (2104.2)	1906.4 (2177.5)	1905.1 (1844.1)
Hemodynamic variables			
Pulmonary vascular resistance, WU, mean (SD)	12.4 (4.5)	12.9 (4.9)	11.9 (3.9)
Mean pulmonary arterial pressure, mmHg, mean (SD)	53.0 (11.5)	54.1 (12.4)	52.5 (10.4)
Mean right atrial pressure[d], mmHg, mean (SD)	8.0 (4.2)	7.6 (4.0)	8.2 (4.3)
Pulmonary arterial wedge pressure[e], mmHg, mean (SD)	8.5 (3.2)	8.6 (3.0)	8.4 (3.4)
Cardiac index, L/min/m^2, mean (SD)	2.1 (0.6)	2.2 (0.6)	2.1 (0.6)
Heart rate, bpm, mean (SD)	83.0 (12.7)	84.3 (13.2)	82.8 (12.1)
Systolic blood pressure, mmHg, mean (SD)	117.2 (14.5)	113.5 (13.6)	120.5 (14.5)
eGFR, ml/min/1.73 m^2, mean (SD)	81.3 (21.2)	87.5 (20.1)	75.7 (20.9)
Cardiac comorbidities, *n* (%)			
History of essential hypertension	57 (38.5)	0	57 (73.1)
Obesity (BMI >30 kg/m^2)	36 (24.3)	0	36 (46.2)
Diabetes mellitus	11 (7.4)	0	11 (14.1)
History of coronary heart disease	11 (7.4)	0	11 (14.1)
Pulmonary comorbidities, *n* (%)			
Mild parenchymal lung disease	21 (14.2)	0	13 (16.7)
Baseline risk category, *n* (%)			
Three-strata[18–20]			
Low	20 (13.5)	10 (16.1)	8 (10.3)
Intermediate	112 (75.7)	46 (74.2)	61 (78.2)
High	11 (7.4)	3 (4.8)	7 (9.0)
Missing	5 (3.4)	3 (4.8)	2 (2.6)

Table 1 (Continued)

	Overall set ($n = 148$)[a]	Patients without cardiac comorbidities ($n = 62$)	Patients with 1–2 cardiac comorbidities ($n = 78$)
Four-strata[10,20]			
Low	12 (8.1)	6 (9.7)	6 (7.7)
Intermediate-low	39 (26.4)	17 (27.4)	17 (21.8)
Intermediate-high	81 (54.7)	33 (53.2)	46 (59.0)
High	11 (7.4)	3 (4.8)	7 (9.0)
Missing	5 (3.4)	3 (4.8)	2 (2.6)
REVEAL Lite 2.0[21]			
Low	37 (25.0)	15 (24.2)	18 (23.1)
Intermediate	30 (20.3)	19 (30.6)	10 (12.8)
High	80 (54.1)	28 (45.2)	49 (62.8)
Missing	1 (0.7)	0	1 (1.3)

6MWD, 6-min walk distance; BMI, body mass index; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; Q1-Q3, interquartile range; SD, standard deviation; WHO FC, World Health Organization functional class; WU, Wood units.
[a]Includes eight patients with pulmonary comorbidities and no cardiac comorbidities who were excluded from the subgroups.
[b]Data available for TRITON only; for REPAIR only the year of diagnosis was reported.
[c]As per electronic case report form.
[d]Overall set: $n = 147$; patients with cardiac comorbidities: $n = 77$.
[e]Overall set: $n = 141$; patients without comorbidities: $n = 60$; patients with cardiac comorbidities: $n = 74$.

Table 2 Cardiac comorbidity combinations at baseline

	Overall set ($n = 148$)[a]	Patients without cardiac comorbidities ($n = 62$)	Patients with 1–2 cardiac comorbidities ($n = 78$)
Patients with ≥1 cardiac comorbidity, *n* (%)	78 (52.7)	0	78 (100)
Essential hypertension	57 (38.5)	0	57 (73.1)
Obesity (BMI >30 kg/m^2)	36 (24.3)	0	36 (46.2)
Diabetes mellitus	11 (7.4)	0	11 (14.1)
Coronary heart disease	11 (7.4)	0	11 (14.1)
Combinations of cardiac comorbidities,[b] *n* (%)			
Hypertension only	25 (16.9)	0	25 (32.1)
Obesity only	13 (8.8)	0	13 (16.7)
Diabetes mellitus only	3 (2.0)	0	3 (3.8)
Coronary heart disease only	2 (1.4)	0	2 (2.6)
Obesity and hypertension	21 (14.2)	0	21 (26.9)
Hypertension and coronary heart disease	6 (4.1)	0	6 (7.7)
Diabetes mellitus and hypertension	3 (2.0)	0	3 (3.8)
Diabetes mellitus and coronary heart disease	3 (2.0)	0	3 (3.8)
Obesity and diabetes mellitus and hypertension[c]	2 (1.4)	0	2 (2.6)

BMI, body mass index.
[a]Includes eight patients with pulmonary comorbidities and no cardiac comorbidities who were excluded from the subgroups.
[b]No patients had the combinations of diabetes mellitus and obesity or coronary heart disease and obesity.
[c]Includes two patients in TRITON with a recorded BMI ≤30 kg/m^2 at screening and a BMI >30 kg/m^2 at baseline (i.e. at randomization).

respectively (online supplementary *Table S6*). There were 9 (6.1%) patients who died, including 6 (7.7%) patients with 1–2 cardiac comorbidities and 2 (3.2%) patients without cardiac comorbidities (AEs leading to death during the treatment emergent period are available in online supplementary *Table S6*).

Over the entire observation period, the proportions of patients that discontinued macitentan (19.4–23.1%) and discontinued tadalafil (17.7–19.2%) were similar across subgroups (*Table 4*). For patients with 1–2 cardiac comorbidities, the majority who discontinued macitentan (17/18) or tadalafil (12/15) did so within 1 year, whereas the majority of patients without cardiac comorbidities discontinued the drugs after 1 year (9/12 for macitentan and 7/11 for tadalafil). Macitentan discontinuations due to an AE were higher for patients with 1–2 cardiac comorbidities vs. those without (14.1% vs. 8.1%), while tadalafil discontinuations due to an AE were similar between the subgroups (7.7% vs. 6.5%).

Table 3 Change from baseline to Week 26 in hemodynamic and functional parameters

	Overall set ($n = 148$)[a]			Patients without cardiac comorbidities ($n = 62$)			Patients with 1–2 cardiac comorbidities ($n = 78$)		
Hemodynamic parameters									
	n	**Baseline, mean (SD)**	**Ratio[b], geometric mean (95% CI)**	***n***	**Baseline, mean (SD)**	**Ratio[b], geometric mean (95% CI)**	***n***	**Baseline, mean (SD)**	**Ratio[b], geometric mean (95% CI)**
PVR, WU	148	12.4 (4.5)	0.47 (0.43, 0.51)	62	12.9 (4.9)	0.45 (0.41, 0.50)	78	11.9 (3.9)	0.50 (0.44, 0.57)
	n	**Baseline, mean (SD)**	**Change[c], LS mean (95% CI)**	***n***	**Baseline, mean (SD)**	**Change[c], LS mean (95% CI)**	***n***	**Baseline, mean (SD)**	**Change[c], LS mean (95% CI)**
mPAP, mmHg	148	53.0 (11.5)	−13.2 (−14.8, −11.6)	62	54.1 (12.4)	−14.6 (−16.8, −12.3)	78	52.5 (10.4)	−11.6 (−13.9, −9.3)
mRAP, mmHg	147	8.0 (4.2)	−1.7 (−2.3, −1.0)	62	7.6 (4.0)	−1.6 (−2.6, −0.6)	77	8.2 (4.3)	−1.8 (−2.8, −0.8)
PAWP, mmHg	141	8.5 (3.2)	1.1 (0.4, 1.8)	60	8.6 (3.0)	0.89 (−0.13, 1.9)	74	8.4 (3.4)	1.2 (0.1, 2.2)
Cardiac index, L/min/m^2	148	2.1 (0.6)	0.82 (0.68, 0.97)	62	2.2 (0.6)	0.82 (0.64, 1.01)	78	2.1 (0.6)	0.85 (0.61, 1.09)
Heart rate, bpm	148	83.0 (12.7)	−7.6 (−9.9, −5.2)	62	84.3 (13.2)	−8.6 (−11.8, −5.4)	78	82.8 (12.1)	−6.6 (−10.3, −2.9)
SBP, mmHg	148	117.2 (14.5)	−1.2 (−3.6, 1.2)	62	113.5 (13.6)	−0.4 (−3.8, 3.1)	78	120.5 (14.5)	−0.7 (−4.3, 2.9)
Functional parameters									
	n	**Baseline, mean (SD)**	**Ratio[b], geometric mean (95% CI)**	***n***	**Baseline, mean (SD)**	**Ratio[b], geometric mean (95% CI)**	***n***	**Baseline, mean (SD)**	**Ratio[b], geometric mean (95% CI)**
NT-proBNP, ng/L	146	1937.4 (2104.2)	0.25 (0.20, 0.33)	60	1906.4 (2177.5)	0.23 (0.16, 0.33)	78	1905.1 (1844.1)	0.24 (0.17, 0.34)
	n	**Baseline, mean (SD)**	**Change[c], LS mean (95% CI)**	***n***	**Baseline, mean (SD)**	**Change[c], LS mean (95% CI)**	***n***	**Baseline, mean (SD)**	**Change[c], LS mean (95% CI)**
6MWD, m	145	356.4 (120.9)	56.8 (41.5, 72.1)	61	387.6 (120.2)	66.7 (45.2, 88.2)	76	331.2 (116.6)	53.5 (29.8, 77.2)
eGFR, ml/min/1.73 m^2	148	81.3 (21.2)	6.2 (3.6, 8.8)	62	87.5 (20.1)	7.9 (4.3, 11.6)	78	75.7 (20.9)	5.8 (1.9, 9.6)
	n	**Baseline, *n* (%)**	**Change, *n* (%)**	***n***	**Baseline, *n* (%)**	**Change, *n* (%)**	***n***	**Baseline, *n* (%)**	**Change, *n* (%)**
WHO FC	148	I: 1 (0.7) II: 28 (18.9) III: 114 (77.0) IV: 5 (3.4)	3 (2.0) worsened 67 (45.3) unchanged 78 (52.7) improved	62	I: 1 (1.6) II: 13 (21.0) III: 46 (74.2) IV: 2 (3.2)	1 (1.6) worsened 22 (35.5) unchanged 39 (62.9) improved	78	I: 0 II: 14 (17.9) III: 61 (78.2) IV: 3 (3.8)	2 (2.6) worsened 41 (52.6) unchanged 35 (44.9) improved

6MWD, 6-min walk distance; ANCOVA, analysis of covariance; CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; SD, standard deviation; WHO FC, World Health Organization functional class; WU, Wood units.

[a]Includes eight patients with pulmonary comorbidities and no cardiac comorbidities who were excluded from the subgroups.

[b]Adjusted change using an ANCOVA model with factors for region and baseline WHO FC and a covariate for baseline parameter.

[c]From ANCOVA model on parameter change from baseline with factors for region and baseline WHO FC, and a covariate for baseline parameter.

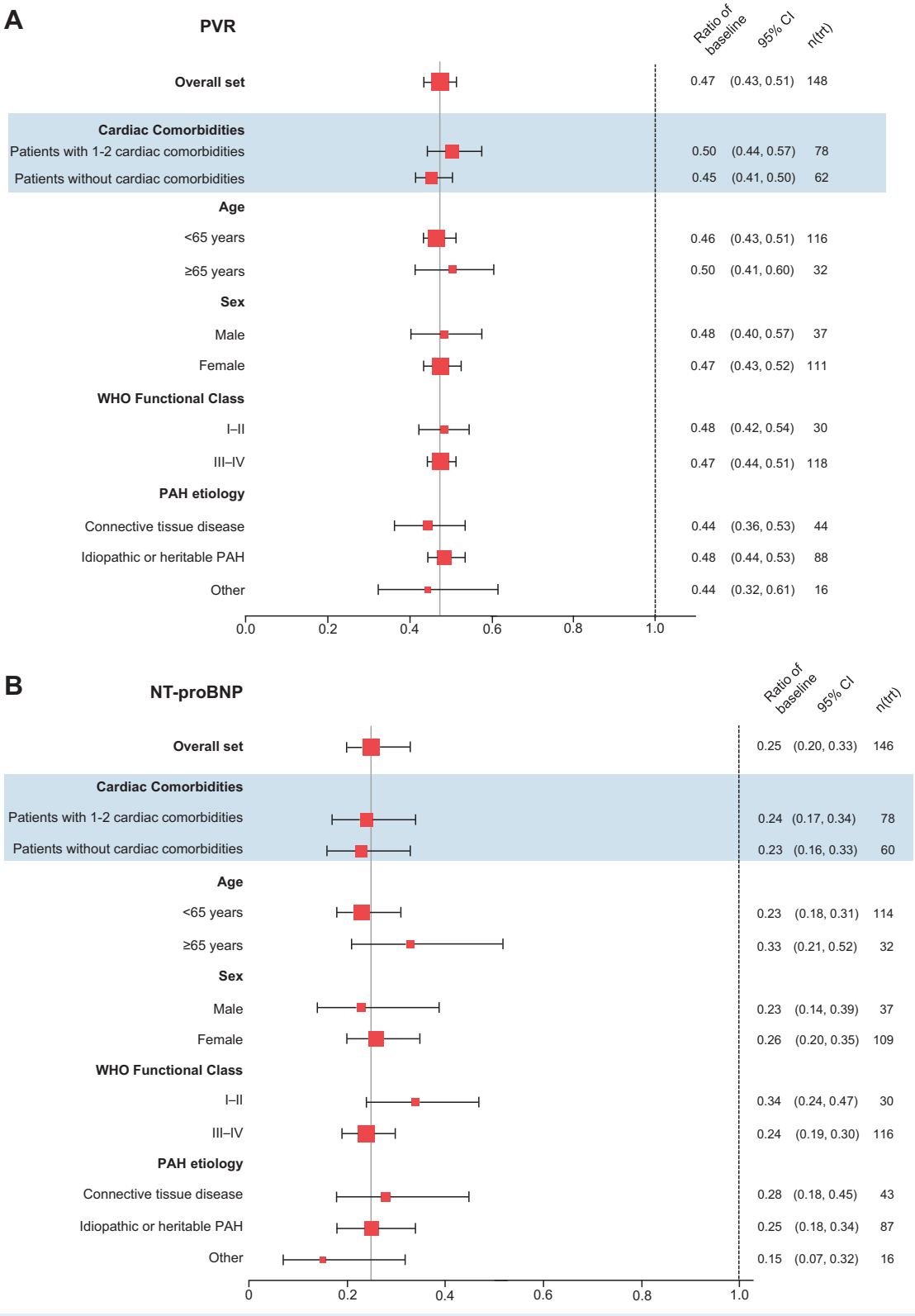


Figure 1 Continued

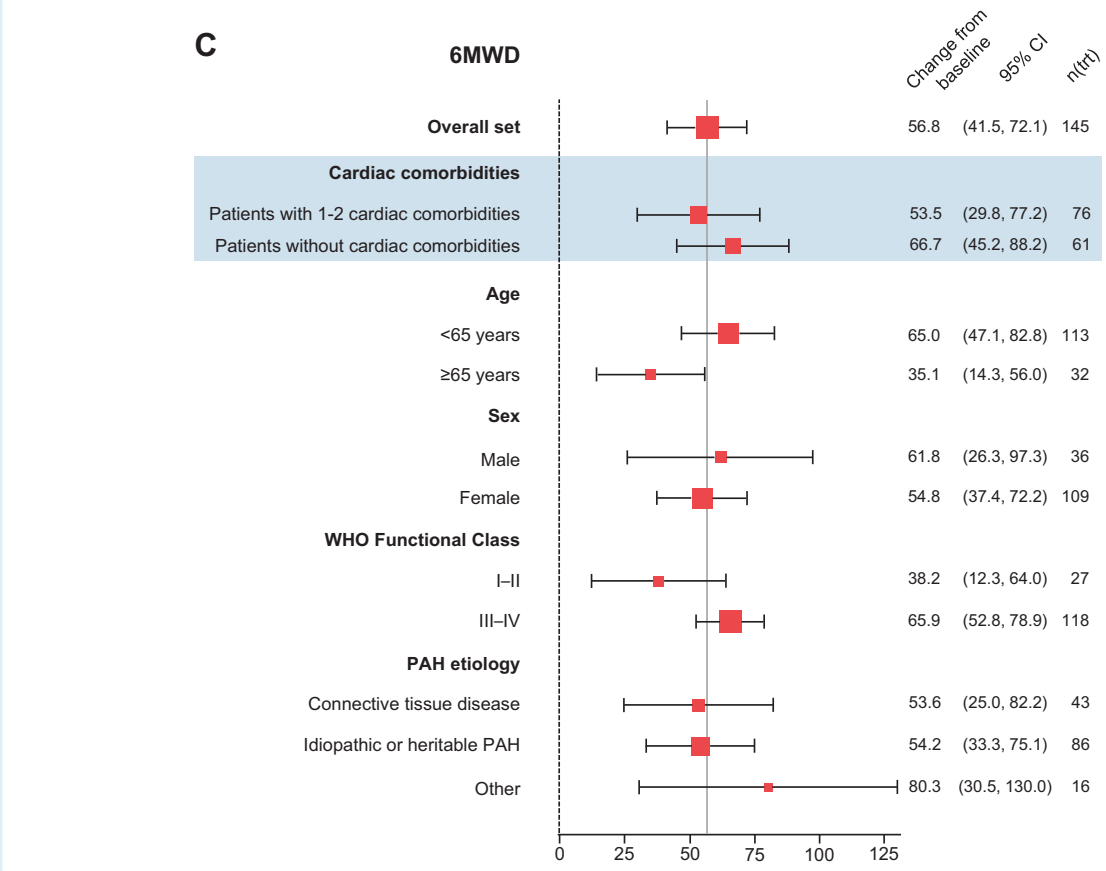


Figure 1 Forest plots of change from baseline to Week 26 in pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP) and 6-min walk distance (6MWD). (*A*) PVR: ratio of baseline at Week 26; (*B*) NT-proBNP: ratio of baseline at Week 26; (*C*) 6MWD: change from baseline to Week 26. For PVR and NT-proBNP, ratios are expressed as the geometric mean ratio. For 6MWD, change from baseline to Week 26 is expressed as the least squares mean. CI, confidence interval; *n*(trt), number of patients receiving initial macitentan and tadalafil combination therapy; PAH, pulmonary arterial hypertension; WHO FC, World Health Organization functional class.

There were no trends with respect to the types of AEs leading to discontinuation of either drug; further breakdowns of AEs are provided in online supplementary *Tables S6* and *S7*.

Discussion

These analyses show that initial double oral combination therapy with macitentan and tadalafil is effective, safe and well-tolerated in PAH patients including in those with 1–2 cardiac comorbidities (*Graphical Abstract*). Marked improvement in hemodynamic parameters, and clinically relevant improvements in 6MWD and NT-proBNP were observed, regardless of comorbidity status. Almost all patients in both subgroups had improved or unchanged WHO FC and PAH risk status, although this occurred to a slightly higher extent in patients without cardiac comorbidities.

There has been an evolution in the demographics of PAH patients, towards an older population that present with a hemodynamic profile of pre-capillary pulmonary hypertension (PH) (e.g. a pulmonary arterial wedge pressure ≤15 mmHg; and PVR >3 WU), but also have cardiac or pulmonary comorbidities.[12–16] For such patients, differentiating PAH (Group 1 PH) from Group 2 and Group 3 PH can be challenging, especially when they have borderline hemodynamics. Taking into account this risk and the limited evidence on combination therapy in patients with cardiopulmonary comorbidities in general, and initial combination therapy in particular, the treatment algorithm outlined in the current ESC/ERS PH guidelines recommends a conservative approach of initial monotherapy.[1,2] However, it is still imperative that these patients with PAH receive optimal therapy and are not left undertreated. Due to the restrictive eligibility criteria of TRITON and REPAIR, patients in these studies represented a 'true' PAH population.[5,17] Still, over half of these patients representing the classical PAH phenotype had 1–2 cardiac comorbidities.

In this post-hoc analysis of TRITON and REPAIR, initial treatment with macitentan and tadalafil combination therapy led to improvements in hemodynamic parameters, NT-proBNP, 6MWD and WHO FC regardless of cardiac comorbidity status, although the extent of improvement in functional parameters was somewhat less in patients with comorbidities. Consistent with this and the results using the OPTIMA dataset,[7] the majority of patients in all subgroups improved risk category from baseline to Week

Table 4 Exposure to study drugs, adverse events and discontinuations over the observation period

	Overall set ($n = 148$)[a]	Patients without cardiac comorbidities ($n = 62$)	Patients with 1–2 cardiac comorbidities ($n = 78$)
Exposure, days, median (Q1–Q3)			
Macitentan	520.0 (368.0–778.0)	498.0 (365.0–687.0)	563.5 (369.0–814.0)
Tadalafil	528.5 (368.0–782.5)	498.0 (365.0–712.0)	567.5 (368.0–814.0)
Combination	513.0 (364.0–778.0)	498.0 (365.0–687.0)	554.0 (362.0–814.0)
Patients with ≥1 AE, *n* (%)	139 (93.9)	57 (91.9)	74 (94.9)
Most common AEs[b], *n* (%)			
Headache	86 (58.1)	39 (62.9)	42 (53.8)
Peripheral edema	51 (34.5)	18 (29.0)	29 (37.2)
Diarrhea	43 (29.1)	16 (25.8)	23 (29.5)
Nausea	34 (23.0)	11 (17.7)	20 (25.6)
Dizziness	29 (19.6)	13 (21.0)	14 (17.9)
Nasal congestion	25 (16.9)	10 (16.1)	11 (14.1)
Nasopharyngitis	25 (16.9)	13 (21.0)	11 (14.1)
Dyspnea	24 (16.2)	9 (14.5)	15 (19.2)
Flushing	24 (16.2)	14 (22.6)	8 (10.3)
Myalgia	24 (16.2)	11 (17.7)	12 (15.4)
Back pain	22 (14.9)	11 (17.7)	11 (14.1)
Fatigue	21 (14.2)	7 (11.3)	14 (17.9)
Pain in extremity	21 (14.2)	11 (17.7)	10 (12.8)
Cough	20 (13.5)	7 (11.3)	13 (16.7)
Gastroesophageal reflux disease	19 (12.8)	5 (8.1)	14 (17.9)
Arthralgia	18 (12.2)	4 (6.5)	12 (15.4)
Dyspepsia	18 (12.2)	9 (14.5)	9 (11.5)
Upper respiratory tract infection	18 (12.2)	6 (9.7)	10 (12.8)
Vomiting	18 (12.2)	9 (14.5)	7 (9.0)
Pyrexia	14 (9.5)	10 (16.1)	3 (3.8)
Jaw pain	14 (9.5)	8 (12.9)	5 (6.4)
Epistaxis	14 (9.5)	3 (4.8)	9 (11.5)
Hypokalemia	13 (8.8)	2 (3.2)	10 (12.8)
Patients with ≥1 serious AE, *n* (%)	41 (27.7)	14 (22.6)	25 (32.1)
Most common serious AEs[c], *n* (%)			
Right ventricular failure	7 (4.7)	2 (3.2)	5 (6.4)
Pulmonary arterial hypertension	6 (4.1)	3 (4.8)	2 (2.6)
Acute respiratory failure	4 (2.7)	0	3 (3.8)
Pneumonia	3 (2.0)	0	3 (3.8)
Pulmonary veno-occlusive disease	3 (2.0)	1 (1.6)	2 (2.6)
Syncope	3 (2.0)	1 (1.6)	1 (1.3)
Anemia	2 (1.4)	0	2 (2.6)
Bronchitis	2 (1.4)	0	2 (2.6)
Gastrointestinal hemorrhage	2 (1.4)	0	2 (2.6)
Pericardial effusion	2 (1.4)	0	2 (2.6)
Vomiting	2 (1.4)	0	2 (2.6)
Pneumonia aspiration	2 (1.4)	2 (3.2)	0
Patients discontinuing macitentan, *n* (%)	33 (22.3)	12 (19.4)	18 (23.1)
Patients with ≥1 AE leading to macitentan discontinuation, *n* (%)	18 (12.2)	5 (8.1)	11 (14.1)
Patients discontinuing tadalafil, *n* (%)	27 (18.2)	11 (17.7)	15 (19.2)
Patients with ≥1 AE leading to tadalafil discontinuation, *n* (%)	10 (6.8)	4 (6.5)	6 (7.7)

AE, adverse event; Q1-Q3, interquartile range.
Reported exposure is from initiation of the second study drug in the macitentan and tadalafil combination to the earliest of the last dose of combination, or the end of the main observation period in TRITON/Week 52 in REPAIR. Treatment-emergent AEs with onset during the macitentan and tadalafil combination treatment exposure period.
[a]Includes eight patients with pulmonary comorbidities and no cardiac comorbidities who were excluded from the subgroups.
[b]Occurred in ≥10% of patients in any group.
[c]Occurred in ≥2% of patients in any group.

26 using both the non-invasive four-strata[10,20] and REVEAL Lite 2.0[21] methods, although a smaller proportion of patients with cardiac comorbidities achieved a low-risk status. This is perhaps not unexpected, given the degree of baseline functional impairment and older age of these patients, although they were still much younger than those with cardiac comorbidities reported in disease registries.[12,22] Comorbidity burden has been strongly linked to age, with older (≥65 years) PAH patients having substantially more comorbidities than younger patients.[22,23] Our data also show a trend towards a greater number of comorbidities with older age. That the observed differences in functional outcomes between patients with and without cardiac comorbidities may be largely attributable to age is supported by subgroup analyses of 6MWD, where older patients (≥65 years) appeared to do less well; however, PVR and NT-proBNP by age showed improvements that were consistent with the overall set. These data suggest that 6MWD and change in PAH risk status may not be suitable measures to evaluate older patients. A recent study suggested that the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio may serve as a replacement for 6MWD for risk assessment in PAH,[24] which could be a more appropriate benchmark for older and/or comorbid patients. Given the correlation between age and comorbidity status, large, dedicated studies will be required to clarify the contribution of each with respect to outcome measures.

The benefits of PAH therapy observed in this analysis for patients with cardiac comorbidities are in line with results from other studies. Treatment effects of initial combination therapy with ambrisentan and tadalafil vs. pooled monotherapy were directionally the same, but lower in magnitude, in patients excluded from the primary analysis set, the majority of whom had cardiac comorbidities, in a post-hoc analysis of the AMBITION trial.[25] A post-hoc analysis of the GRIPHON study showed a similar treatment effect of selexipag vs. placebo on reduction of morbidity/mortality in patients with and without comorbidities; more than 75% of patients were on background PAH therapy.[26] In terms of real-world data, analyses of the COMPERA registry demonstrated a beneficial, albeit attenuated, PAH-specific treatment response in NT-proBNP, WHO FC, and 6MWD for patients with up to four cardiac comorbidities, compared to those without.[22] However, the comorbid patients were much older and were more often receiving monotherapy, which may account for some of the observed differences in outcomes.[22] A recent analysis of the iPHNET database reported that all patients showed improvements in PVR and risk status following initial combination therapy, although the magnitude of these changes was again smaller in patients with cardiac comorbidities.[27]

The duration of exposure to both macitentan and tadalafil combination therapy and the individual drugs in this analysis was longer in patients with 1–2 cardiac comorbidities than those without comorbidities. The proportion of patients experiencing an AE was similar for patients with 1–2 cardiac comorbidities and those without such comorbidities, with the most common AEs reported for both subgroups being headache, peripheral edema and diarrhea. Not unexpectedly, events of edema were higher for patients with comorbidities vs. those without (peripheral edema, 37.2% vs. 29.0%; grouped terms for edema 47.4% vs. 40.3%). In addition, AEs of nausea, cough, gastroesophageal reflux disease, arthralgia, epistaxis, and hypokalemia were more common (≥5% difference between subgroups) in patients with 1–2 cardiac comorbidities, while AEs of headache, nasopharyngitis, flushing, pyrexia, and jaw pain were more common in patients without cardiac comorbidities.

The proportions of patients discontinuing either macitentan or tadalafil for any reason over the entire observation period were similar for patients across comorbidity subgroups. However, compared to patients without comorbidities, a higher proportion of patients with 1–2 cardiac comorbidities discontinued the drugs within 1 year vs. greater than 1 year (21.8% vs. 4.8% for macitentan and 15.4% vs. 6.5% for tadalafil). In an analysis of data from the COMPERA registry, a higher proportion of patients with 1–2 cardiac comorbidities were also observed to have discontinued an ERA within 1 year compared to those without (12.7% vs. 3.8%), but PDE5i discontinuations were similar between the groups (9.1% vs. 7.2%).[22] Such differences in patterns of discontinuations may be accounted for by differences in age between the two populations (56 years in this analysis vs. 73 years in COMPERA). A large proportion of patients in the COMPERA analysis discontinued ERA treatment due to edema[22]; however, in this analysis of TRITON/REPAIR there was no clear pattern of AEs leading to discontinuation of either macitentan or tadalafil. The trend for higher AE-related discontinuation of PAH treatment with increasing numbers of cardiac comorbidities was also observed in a post-hoc analysis of AMBITION, where patients excluded from the primary analysis (the majority due to presence of ≥3 cardiovascular risk factors) were more likely to end ambrisentan + tadalafil treatment due to an AE than patients included in the primary analysis set (33% vs. 14%).[25] Together these data indicate that the safety and tolerability profiles of initial macitentan plus tadalafil combination therapy were consistent between the comorbidity subgroups and with the known profiles of the two drugs.

For clinicians managing PAH patients, the information provided herein on the risks/benefits of early double combination therapy in patients who are diagnosed with PAH, but have some cardiac comorbidities, should be helpful. It is important to acknowledge that comorbidity burden cannot be measured by simply counting the number of comorbidities; information on severity, duration and controlled/not controlled status, must also be considered. The TRITON and REPAIR studies did not collect information specific to the severity or management of the comorbidities, or how they changed over time; such information is needed to fully understand the impact of comorbidities on outcomes. Until now, this has also been the case for other clinical trials and registries, which have not been systematically collecting these data and this remains a significant evidence gap.

Limitations of this analysis include its post-hoc nature, that the classification of comorbidities was based on number only and did not include assessments of severity or control, and that the study population does not represent the full spectrum of patients with comorbidities, as those with multiple (≥3) cardiac comorbidities were excluded from the TRITON/REPAIR trials. As the patient population represents only those eligible for a clinical trial, further analyses of patients with comorbidities in the real-world, clinical setting are needed.

Conclusions

This post-hoc analysis shows that initial combination therapy with macitentan plus tadalafil is efficacious in patients with PAH with up to two cardiac comorbidities and those without, with similar safety and tolerability profiles between the two subgroups.

Supplementary Information

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

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