Macitentan and phosphodiesterase-5 inhibitor as monotherapy or in combination in newly diagnosed patients with pulmonary arterial hypertension: A pooled analysis

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Introduction

- Initial combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 inhibitor (PDE5i) is guideline-recommended as standard of care in patients with pulmonary arterial hypertension (PAH) with low or intermediate risk and no cardiopulmonary comorbidities[1]
- This recommendation was based on the AMBITION and TRITON studies; however,[2,3] there remains a lack of data on the effect of initial combination therapy on survival outcomes

Objective

- To compare time to all-cause mortality between early macitentan and PDE5i combination therapy versus either as monotherapy

Methods

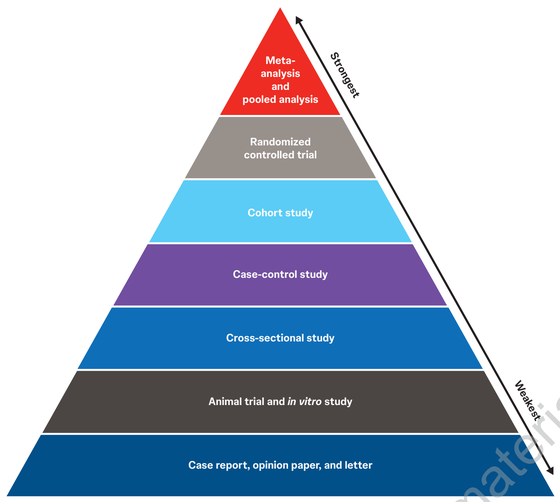
Patient selection and cohort definitions

- This post-hoc, retrospective analysis pooled long-term patient-level data (with a planned follow-up time ≥1 year) from randomized controlled trials (RCTs) and observational registries that had prospective all-cause mortality data available from adults with incident PAH who initiated macitentan 10 mg or PDE5i monotherapy or macitentan plus PDE5i combination
- This encompassed all randomized patients from the SERAPHIN, GRIPHON, and TRITON RCTs, all participants in the REPAIR study safety dataset, and all enrolled patients in the REVEAL, OPUS, and EXPOSURE registries who met the following criteria:
  - ≥18 years of age (at index date) with a recent (i.e., within 6 months of index date) diagnosis of PAH (World Health Organization [WHO] Group 1 pulmonary hypertension)
  - Those from observational registries were required to have undergone at least one follow-up visit
- Patients were excluded if they were receiving intravenous, subcutaneous, inhaled, or oral prostacyclin pathway agents, soluble guanylate cyclase stimulators, or an ERA other than macitentan at index date
  - Patients who had started any PAH-specific therapy >6 months before index date and those who died before index date were also excluded
- Patients were divided into three cohorts according to treatment:
  - (i) Combination therapy: macitentan and PDE5i were both received at index date, or one of these was received at index date and the second was initiated within the following 30 days; no other PAH-specific therapies were added within a 30-day time window from index date
  - (ii) Macitentan monotherapy: only macitentan was received at index date and no other PAH-specific therapies were added within a 30-day time window from index date
  - (iii) PDE5i monotherapy: only PDE5i was received at index date and no other PAH-specific therapies were added within a 30-day time window from index date
- The primary analysis focused on a 30-day window for all studies (except EXPOSURE) to account for access differences by region, which captured patients whose macitentan and PDE5i treatment started on the same day and those undergoing rapid sequential therapy
- Further details for the RCTs/registries included in this study can be found in **Table 1**, and an overview of where pooled analysis fits into evidence-based practice is shown in **Figure 1**

Statistical analysis

- Two strategies were utilized to account for intercurrent events, defined as discontinuation of macitentan or PDE5i treatment during the study, or the start of a new PAH therapy at any time
  - A treatment policy (TP) strategy used all data regardless of whether an intercurrent event had occurred, similar to an intent-to-treat strategy
- In a while on treatment (WOT) strategy, data were censored as soon as an intercurrent event was experienced
- Subgroup analyses using the TP strategy were performed according to PDE5i received (tadalafil or sildenafil), within new users (i.e., subgroup of patients who received their assigned therapy at index), and among patients from observational registries (i.e., using registry data only)
- Since all analyses were exploratory, no multiplicity adjustments were made, and p values were generated for descriptive purposes only
- Missing data for baseline characteristics were imputed, resulting in the creation of 57 imputed datasets
- For each imputed dataset, propensity score (PS) methods were used to balance key demographic and disease characteristics (see **Table 2**) in the monotherapy cohorts to match those of the combination cohort
- Trimming (i.e., excluding patients in regions of non-overlap) was conducted, resulting in 57 PS analysis sets
- Weighted hazard ratios (HRs) were computed from weighted Cox regression models for each imputed dataset and were pooled
- Weighted Kaplan–Meier estimates and corresponding 95% confidence intervals (CIs) were computed at 6-monthly timepoints for each imputed dataset and were pooled

Figure 1. Hierarchy of scientific evidence



Results

Study population

- In total, 2201 patients with newly (within 6 months) diagnosed PAH from four clinical trials[4] and three registries[5] met inclusion criteria and were included in the primary analysis
  - Most data were extracted from the OPUS (39%) and EXPOSURE (36%) registries (**Table 1**)

Table 1. Data sources and number of patients included in the pooled analysis, according to treatment cohort (primary analysis)

Pooled analysis population, n (%)				
Study	**Macitentan 10 mg + PDE5i combination therapy**	**Macitentan 10 mg monotherapy**	**PDE5i monotherapy**	**Total**
Clinical trials[4]				
SERAPHIN (NCT00660179)	23 (3)	34 (5)	21 (3)	78 (4)
GRIPHON (NCT01106014)	N/A[a]	N/A[a]	50 (6)	50 (2)
TRITON (NCT02558231)	118 (16)	–	–	118 (5)
REPAIR (NCT02310672)	42 (6)	18 (3)	–	60 (3)
Observational registry studies[5]				
REVEAL (NCT00370214)	N/A[a]	N/A[a]	238 (30)	238 (11)
OPUS (NCT02126943)	456 (60)	413 (63)	–	869 (39)
EXPOSURE (EUPAS19085)	115 (15)	189 (29)	484 (61)	788 (36)
Total newly diagnosed patients with PAH, n	**754**	**654**	**793**	**2201**

Patients receiving intravenous, subcutaneous, inhaled, or oral prostanoids, soluble guanylate cyclase stimulators, or an ERA other than macitentan at index date were excluded from the analysis.
[a]Macitentan data were not collected in GRIPHON or REVEAL as it was not commercially available at the time these studies were conducted.
ERA, endothelin receptor antagonist; **N/A**, not applicable; **n**, number; **PAH**, pulmonary arterial hypertension; **PDE5i**, phosphodiesterase-5 inhibitor; **PH**, pulmonary hypertension; **RV**, right ventricular.

- Treatment cohorts comprised combination therapy (n=754) of macitentan plus PDE5i (421 tadalafil, 324 sildenafil, and 9 other), macitentan monotherapy (n=654), and PDE5i monotherapy (n=793; 301 tadalafil, 490 sildenafil, and 2 other)
- After weighting, baseline demographic and clinical characteristics for the primary analysis population were broadly similar between treatment cohorts
  - There were slight differences between cohorts in age, sex, race, and PAH etiology (**Table 2**)
- Patients in the combination and PDE5i cohorts tended to have more severe WHO functional class and pulmonary vascular resistance than those in the macitentan cohort; diuretic use was higher for patients in the combination cohort versus either of the monotherapy cohorts; more patients in the PDE5i cohort had underlying hypertension; and underlying renal insufficiency was more prevalent in the combination and macitentan cohorts
  - Data were similar after weighting (**Table 2**)

Table 2. Unweighted patient characteristics at baseline according to treatment cohort in the primary analysis

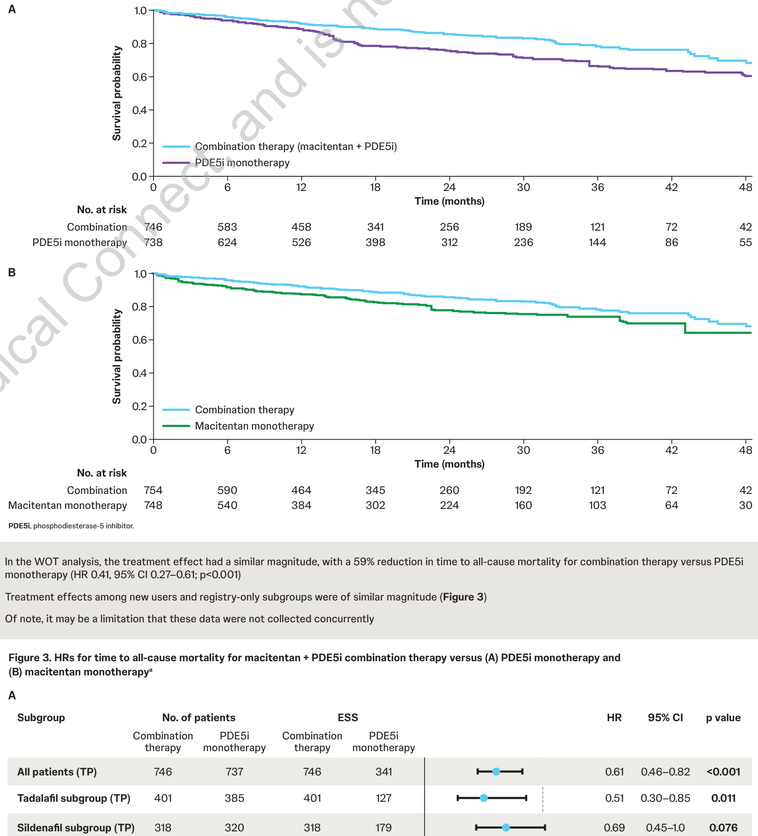
	Macitentan + PDE5i combination therapy (n=754)	Macitentan monotherapy (n=645)	PDE5i monotherapy (n=786)
Age, years	57.6 (15.06)	62.8 (13.94)	59.1 (16.82)
Male sex	205 (27.2)	169 (26.2)	260 (33.0)
PAH etiology			
Idiopathic PAH	397 (52.6)	384 (59.6)	444 (56.5)
CVD-CTD	223 (29.6)	194 (30.1)	183 (23.3)
Other	134 (17.8)	66 (10.2)	159 (20.2)
WHO FC			
I	32 (4.3)	48 (7.5)	25 (3.1)
II	175 (23.2)	223 (34.7)	209 (26.5)
III	497 (65.9)	351 (54.5)	493 (62.7)
IV	50 (6.6)	21 (3.3)	60 (7.6)
6-MWD, m	305.8 (124.52)	306.9 (128.44)	310.5 (130.75)
mPAP, mmHg	49.4 (12.63)	41.6 (12.37)	46.8 (13.25)
PVR, dyn•s•cm^{-5}	832.8 (397.88)	639.8 (375.90)	770.3 (469.56)
Cardiac index, L/min/m^2	2.4 (0.82)	2.6 (0.85)	2.5 (0.90)
mRAP, mmHg	9.6 (6.34)	9.3 (5.49)	9.2 (5.98)
Heart rate, bpm	81.3 (14.27)	78.0 (14.50)	79.8 (14.97)
BMI, kg/m^2	28.7 (6.81)	30.0 (7.33)	28.0 (6.65)
Non-PH medication			
Diuretics	441 (58.5)	255 (39.6)	173 (22.0)
Ongoing comorbidities			
Diabetes mellitus	154 (20.4)	147 (22.7)	175 (22.2)
Hypertension	221 (29.3)	213 (33.1)	343 (43.7)
Renal insufficiency	51 (6.8)	25 (3.9)	15 (1.9)

Data are presented as mean ± standard deviation, or n (%).
Note: Weighted results will be presented in the manuscript.
6-MWD, 6-minute walking distance; **BMI**, body mass index; **CTD**, connective tissue disease; **CVD**, cardiovascular disease; **FC**, functional class; **mPAP**, mean pulmonary arterial pressure; **mRAP**, mean right artrial pressure; **n**, number of imputed datasets; **PAH**, pulmonary arterial hypertension; **PDE5i**, phosphodiesterase-5 inhibitor; **PH**, pulmonary hypertension; **PSA**, propensity score analysis; **PVR**, pulmonary vascular resistance; **SD(%)**, number and percentages of absolute standardized differences >0.2; **WHO**, World Health Organization.

Time to all-cause mortality

- Early macitentan and PDE5i was associated with a 39% risk reduction of all-cause mortality versus PDE5i monotherapy (HR 0.61 [95% CI 0.46–0.82]) and a 32% risk reduction versus macitentan monotherapy (HR 0.68 [95% CI 0.48–0.95]) (**Figure 2**)
- Treatment effects were more pronounced when macitentan was combined with tadalafil (49–43%; HR 0.51 [95% CI 0.30–0.85] and HR 0.57 [95% CI 0.37–0.88], respectively) versus sildenafil (31–26%; HR 0.69 [95% CI 0.45–1.04] and HR 0.74 [95% CI 0.46–1.17], respectively) (**Figure 3**)

Figure 2. Kaplan–Meier estimates for all-cause mortality (A) macitentan + PDE5i combination therapy versus PDE5i monotherapy and (B) macitentan combination therapy versus macitentan monotherapy[a]



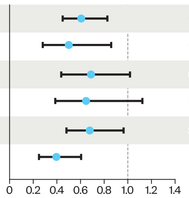
PDE5i, phosphodiesterase-5 inhibitor.

- In the WOT analysis, the treatment effect had a similar magnitude, with a 59% reduction in time to all-cause mortality for combination therapy versus PDE5i monotherapy (HR 0.41, 95% CI 0.27–0.61; p<0.001)
- Treatment effects among new users and registry-only subgroups were of similar magnitude (**Figure 3**)
- Of note, it may be a limitation that these data were not collected concurrently

Figure 3. HRs for time to all-cause mortality for macitentan + PDE5i combination therapy versus (A) PDE5i monotherapy and (B) macitentan monotherapy[a]

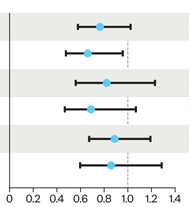
A

Subgroup	No. of patients		ESS		HR	95% CI	p value
	Combination therapy	PDE5i monotherapy	Combination therapy	PDE5i monotherapy			
All patients (TP)	746	737	746	341	0.61	0.46–0.82	**<0.001**
Tadalafil subgroup (TP)	401	385	401	127	0.51	0.30–0.85	**0.011**
Sildenafil subgroup (TP)	318	320	318	179	0.69	0.45–1.0	**0.076**
New users only (TP)	301	310	301	178	0.65	0.40–1.1	**0.081**
Registry only (TP)	546	548	546	261	0.68	0.49–0.95	**0.024**
All patients (WOT)	746	737	746	341	0.41	0.27–0.61	**<0.001**



B

Subgroup	No. of patients		ESS		HR	95% CI	p value
	Combination therapy	Macitentan monotherapy	Combination therapy	Macitentan monotherapy			
All patients (TP)	754	748	754	294	0.68	0.37–0.95	**0.026**
Tadalafil subgroup (TP)	421	426	421	242	0.57	0.37–0.88	**0.011**
Sildenafil subgroup (TP)	324	336	324	232	0.74	0.46–1.17	**0.194**
New users only (TP)	322	333	322	195	0.60	0.36–1.00	**0.051**
Registry only (TP)	562	570	562	296	0.81	0.58–1.13	**0.216**
All patients (WOT)	754	748	754	294	0.78	0.50–1.23	**0.283**



CI, confidence interval; **ESS**, effective sample size; **HR**, hazard ratio; **PDE5i**, phosphodiesterase-5 inhibitor; **PSA**, propensity score analysis; **TP**, treatment policy; **WOT**, while on treatment.

[a]Note: For macitentan + PDE5i combination therapy and monotherapy unweighted groups: all patients were assigned a weight of 1; n is the average rounded to full integer of the number of patients after trimming over the 57 PSAs. For monotherapy weighted groups: patients were reweighted to balance the characteristics between the monotherapy cohort and the combination therapy cohort; n is the average rounded to full integer of the sum of these weights over the 57 PSAs. ESS represents the size of an unweighted sample with approximately the same amount of precision as the weighted sample under consideration.

Conclusions

- **This pooled analysis of 2201 patients from clinical trials and observational registries may indicate a survival benefit of early, including upfront, combination therapy with macitentan 10 mg plus PDE5i on all-cause mortality compared to PDE5i monotherapy or macitentan monotherapy in patients newly diagnosed with PAH**
- **These results add to the growing evidence base supporting ERA plus PDE5i combination therapy in newly diagnosed patients with PAH**

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Disclosures

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