Real-world adherence and persistence of upfront therapy in patients with pulmonary arterial hypertension in the United States

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Introduction

- Pulmonary arterial hypertension (PAH) is a rare, progressive disease, which results from elevated pulmonary arterial pressure and leads to right ventricular failure and death[1]
- The European Society of Cardiology/ European Respiratory Society 2022 guidelines recommend treatment for PAH based on a patient's 1-year risk of mortality[2]
  - Upfront combination therapy with a phosphodiesterase type 5 inhibitor (PDE5i) and an endothelin receptor antagonist (ERA) is recommended for low- and intermediate-risk patients without cardiopulmonary comorbidities[2]
- Optimal adherence and persistence to PAH therapies are necessary to improve outcomes; however, adherence to PAH therapy remains a significant challenge[3,4]

Objective

- To characterize adherence and persistence to PAH-specific therapies in patients newly initiating therapy

Methods

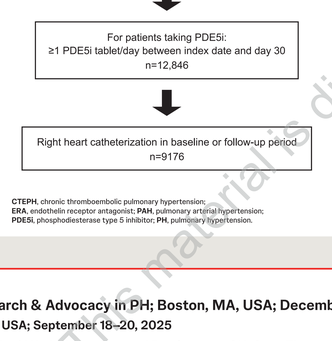
- This retrospective cohort study utilized claims from the Komodo Research Database
- Patients initiating therapy with a PDE5i and/or an ERA were identified using the following inclusion criteria:
  - At least one claim for a PDE5i and/or an ERA from January 1, 2017, to June 30, 2022 (index date)
  - Continuous medical and pharmacy health plan enrollment for ≥12 months prior to and including the index date (baseline period) and ≥30 days after the index date
  - At least one inpatient claim or at least two outpatient claims on two separate days for pulmonary hypertension/PAH
  - Claim for a right heart catheterization
  - Aged ≥18 years at the index date
- Patients with chronic thromboembolic pulmonary hypertension or a history of lung transplantation or atrial septostomy were excluded
- Upfront combination therapy was defined as the second agent started within 30 days of the index date
- Persistence was defined as time from the index date to treatment discontinuation (i.e., a gap in therapy of >60 days)
- Adherence was measured by proportion of days covered (PDC) during the treatment period; non-adherence was defined as PDC <80%
- Propensity score matching was utilized 1:1:1 across treatment groups
- For the sensitivity analysis, adherence was assessed at 6 and 12 months for patients who had a minimum of 6 and 12 months' follow-up, respectively, and for all patients

Results

Patient characteristics

- A total of 9176 patients (6989 PDE5i monotherapy, 1006 ERA monotherapy, and 1181 dual combination therapy) met the study criteria (**Figure 1**)
- After matching, each cohort included 714 patients (**Table 1**)

FIGURE 1: Patient selection



CTEPH, chronic thromboembolic pulmonary hypertension; **ERA**, endothelin receptor antagonist; **PAH**, pulmonary arterial hypertension; **PDE5i**, phosphodiesterase type 5 inhibitor; **PH**, pulmonary hypertension.

TABLE 1: Baseline demographic and clinical characteristics (matched cohorts)

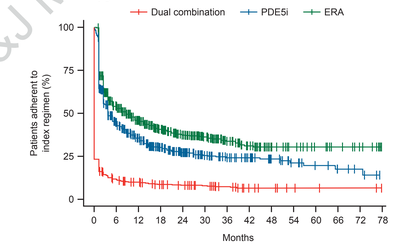
	Dual combination therapy (n=714)	PDE5i monotherapy (n=714)	ERA monotherapy (n=714)	*P*-value[a]	*P*-value[b]
Age, mean (SD), years	57.5 (14.0)	58.9 (13.5)	58.1 (13.8)	0.055	0.41
Female sex, n (%)	536 (75.1)	484 (67.8)	530 (74.2)	0.003	0.76
Race/ ethnicity, n (%)				>0.99	0.88
Asian or Pacific Islander	27 (3.8)	24 (3.4)	29 (4.1)	–	–
Black/African American	156 (21.8)	159 (22.3)	160 (22.4)	–	–
Hispanic/ Latino	102 (14.3)	102 (14.3)	107 (15.0)	–	–
Other	37 (5.2)	39 (5.5)	29 (4.1)	–	–
White	392 (54.9)	390 (54.6)	389 (54.5)	–	–
Geographic region, n (%)				0.11	0.61
Northeast	132 (18.5)	161 (22.5)	130 (18.2)	–	–
South	245 (34.3)	207 (29.0)	266 (37.3)	–	–
Midwest	141 (19.7)	151 (21.1)	127 (17.8)	–	–
West	195 (27.3)	192 (26.9)	188 (26.3)	–	–
Puerto Rico	1 (0.1)	3 (0.4)	3 (0.4)	–	–
Insurance type, n (%)				0.69	0.82
Commercial	225 (31.5)	206 (28.9)	221 (31.0)	–	–
Medicaid	232 (32.5)	243 (34.0)	219 (30.7)	–	–
Medicare	245 (34.3)	250 (35.0)	261 (36.6)	–	–
Medicare medical, Commercial drug	12 (1.7)	15 (2.1)	13 (1.8)	–	–
CCI				0.014	0.62
Mean (SD)	4.2 (2.9)	4.6 (2.9)	4.1 (2.8)	–	–
PDE5i use in first 30 days, n (%)				<0.001	<0.001
Sildenafil	299 (41.9)	566 (79.3)	0	–	–
Tadalafil	403 (56.4)	144 (20.2)	0	–	–
Sildenafil + tadalafil	12 (1.7)	4 (0.6)	0	–	–
ERA use in first 30 days, n (%)				<0.001	<0.001
Ambrisentan	411 (57.6)	0	317 (44.4)	–	–
Bosentan	6 (0.8)	0	22 (3.1)	–	–
Macitentan	294 (41.2)	0	374 (52.4)	–	–
Ambrisentan + bosentan	0	0	1 (0.1)	–	–
Ambrisentan + macitentan	3 (0.4)	0	0	–	–

[a]Comparison of dual combination therapy and PDE5i monotherapy cohorts.
[b]Comparison of dual combination therapy and ERA monotherapy cohorts.
CCI, Charlson Comorbidity Index; **ERA**, endothelin receptor antagonist; **PDE5i**, phosphodiesterase type 5 inhibitor; **SD**, standard deviation.

Adherence

- Overall adherence in terms of mean PDC was 80.6%, 90.0%, and 91.6% for the dual combination therapy, PDE5i monotherapy, and ERA monotherapy cohorts, respectively, with a statistically significant difference between the dual combination therapy cohort and each of the monotherapy cohorts (*P*<0.001 for both comparisons)
- Non-adherence (PDC <80%) was highest with dual combination therapy (35.4% of patients), followed by PDE5i monotherapy (17.1%) and ERA monotherapy (11.9%)
- Median time to PDC <80% was statistically significantly shorter for the dual combination therapy cohort (0.03 months [95% confidence interval {CI}, 0.03–0.03]) than the PDE5i monotherapy (3.71 months [95% CI, 3.71–4.96]) and ERA monotherapy (8.64 months [95% CI, 6.18–11.10]) cohorts (*P*<0.001 for both comparisons) (**Figure 2**)
- Among patients with 6 and 12 months of follow-up, the proportion of those adherent (in terms of mean PDC) at 6 and 12 months, respectively, was lower than the proportion adherent over the entire persistence period (**Figures 3A** and **3B**)

FIGURE 2: KM analysis of time to PDC <80% for dual combination therapy compared with PDE5i monotherapy and ERA monotherapy

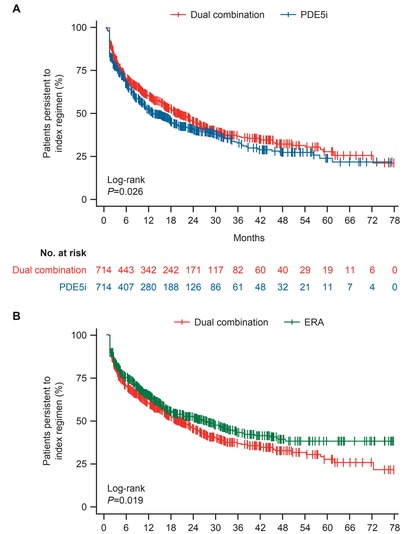


ERA, endothelin receptor antagonist; **KM**, Kaplan–Meier; **PDC**, proportion of days covered; **PDE5i**, phosphodiesterase type 5 inhibitor.

Persistence

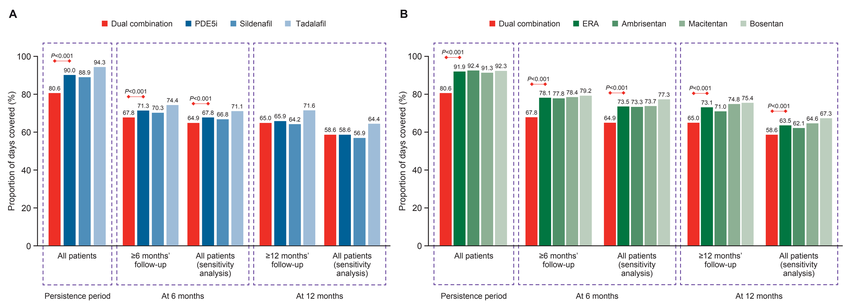
- Median persistence was highest for ERA monotherapy (26.5 months [95% CI, 19.0–33.0]), followed by dual combination therapy (19.8 months [95% CI, 16.6–23.4]) and PDE5i monotherapy (12.9 months [95% CI, 10.8–17.4]) (**Figures 4A** and **4B**)

FIGURE 4: KM analysis of time to discontinuation for dual combination therapy compared with (A) PDE5i monotherapy and (B) ERA monotherapy



ERA, endothelin receptor antagonist; **KM**, Kaplan–Meier; **PDE5i**, phosphodiesterase type 5 inhibitor.

FIGURE 3: Mean PDC overall, at 6 months (among patients with ≥6 months of follow-up and all patients), and at 12 months (among patients with ≥12 months of follow-up and all patients) for dual combination therapy compared with (A) PDE5i monotherapy and (B) ERA monotherapy



ERA, endothelin receptor antagonist; **PDC**, proportion of days covered; **PDE5i**, phosphodiesterase type 5 inhibitor.

Conclusions

- **Adherence to initial PAH therapy is suboptimal, especially with upfront dual combination therapy**
- **Although overall adherence was relatively high in all groups, median time to PDC <80% was significantly shorter for the PDE5i plus ERA combination therapy compared with either monotherapy (*P*<0.001 for both comparisons)**
- **Strategies to improve adherence (i.e., education, medication counseling, and simplified treatment regimens) are crucial to optimizing outcomes**

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