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 death¹
- The European Society of Cardiology/European Respiratory Society 2022 guidelines recommend treatment for PAH based on a patient's 1-year risk of
- 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 comorbidities²
- 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)

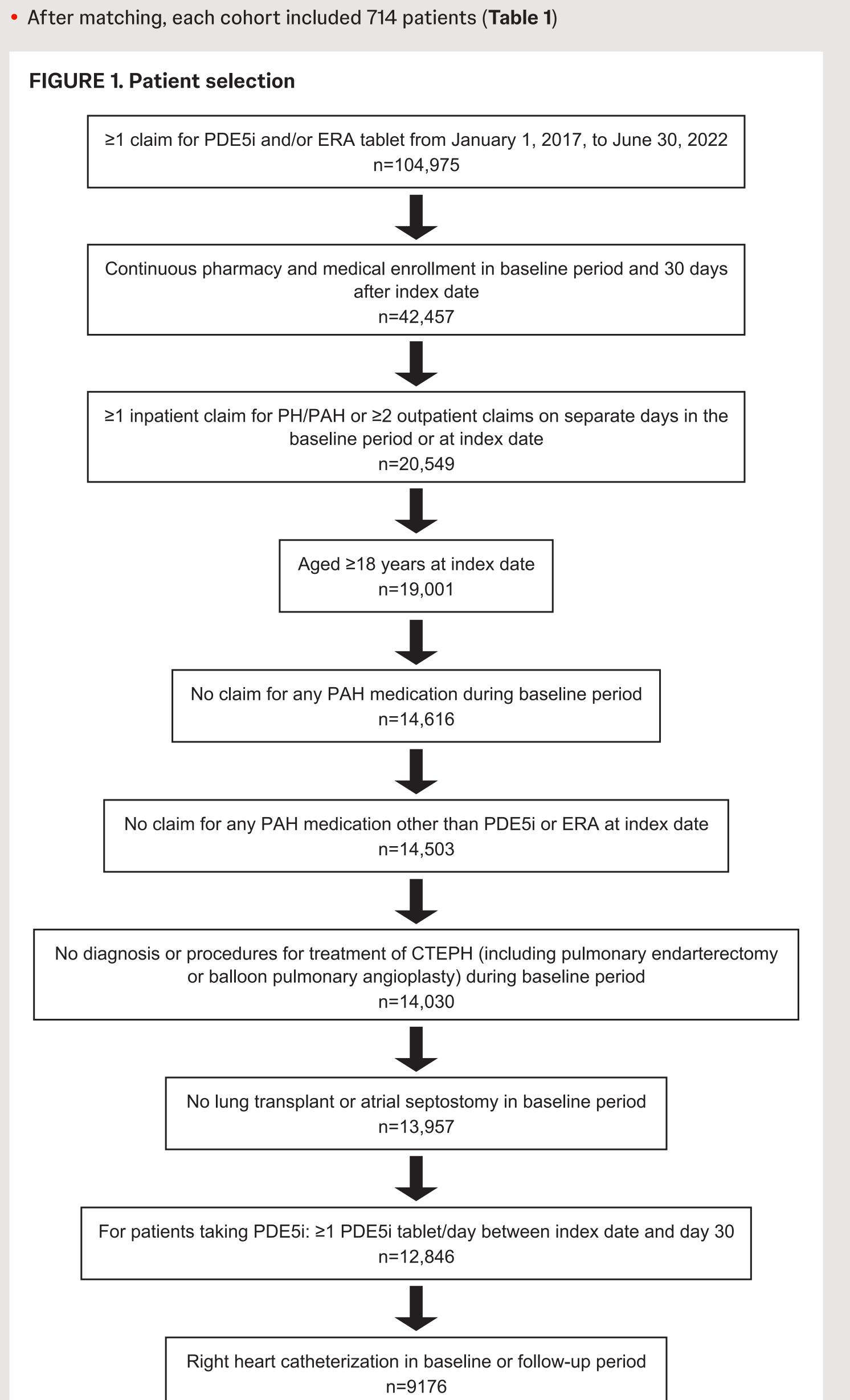


TABLE 1. Baseline demographic and clinical characteristics (matched cohorts)

	Dual combination therapy (n=714)	PDE5i monotherapy (n=714)	ERA monotherapy (n=714)	<i>P</i> -value ^a	<i>P</i> -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)	_	- 6
Insurance type, n (%)				0.69	0.82
Commercial	225 (31.5)	206 (28.9)	221 (31.0)	-	<u> </u>
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) PDE5i use in first 30 days, n (%)	4.2 (2.9)	4.6 (2.9)	4.1 (2.8)	<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	O	O	1 (0.1)	_	_
Ambrisentan + macitentan	3 (0.4)	0	0	_	_
^a Comparison of dual combin	ation therapy and PDE5	i monotherapy cohorts.			

Comparison of dual combination therapy and ERA monotherapy cohorts.

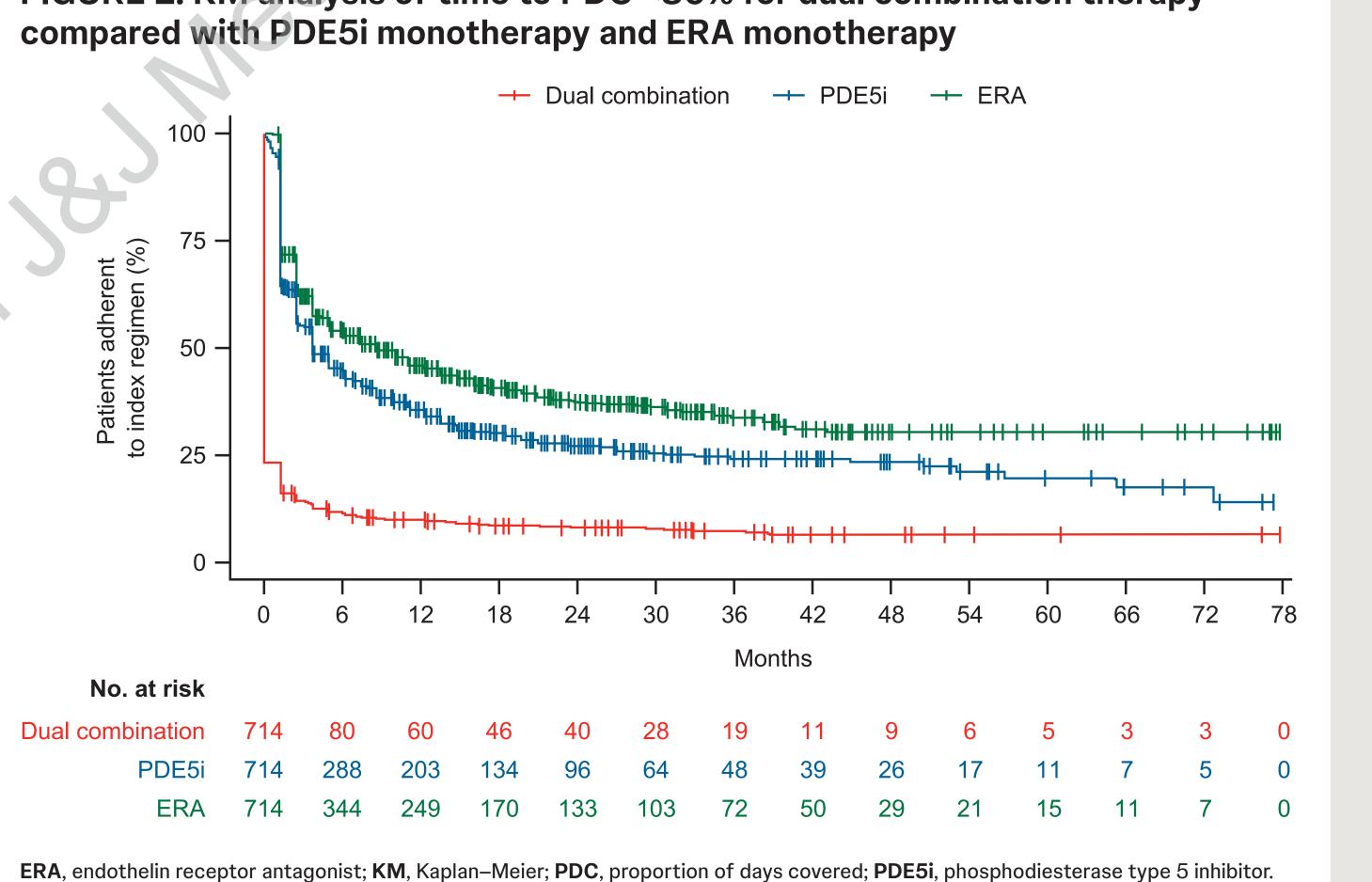
SD, standard deviation

CCI, Charlson Comorbidity Index; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase type 5 inhibitor

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



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

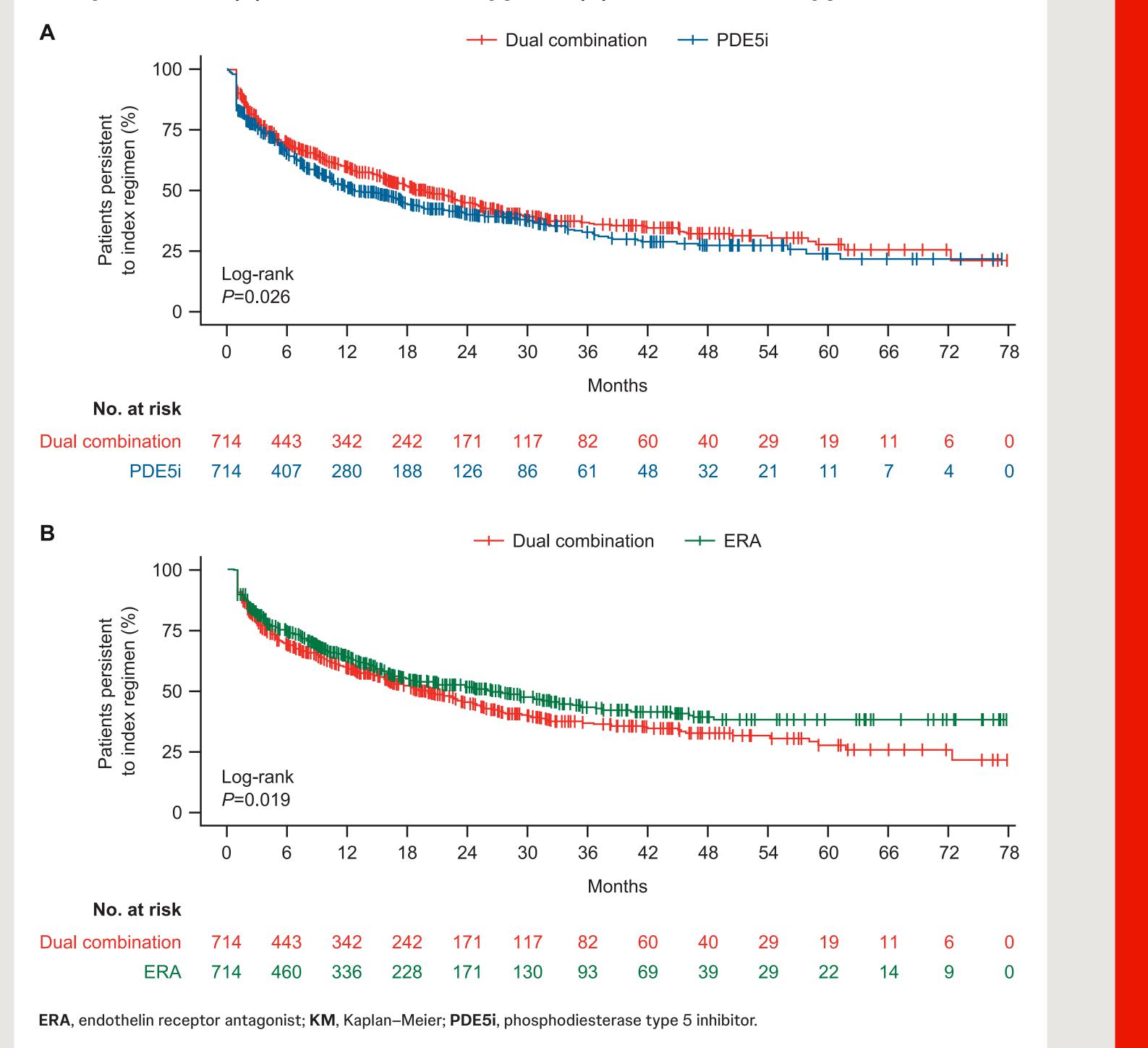
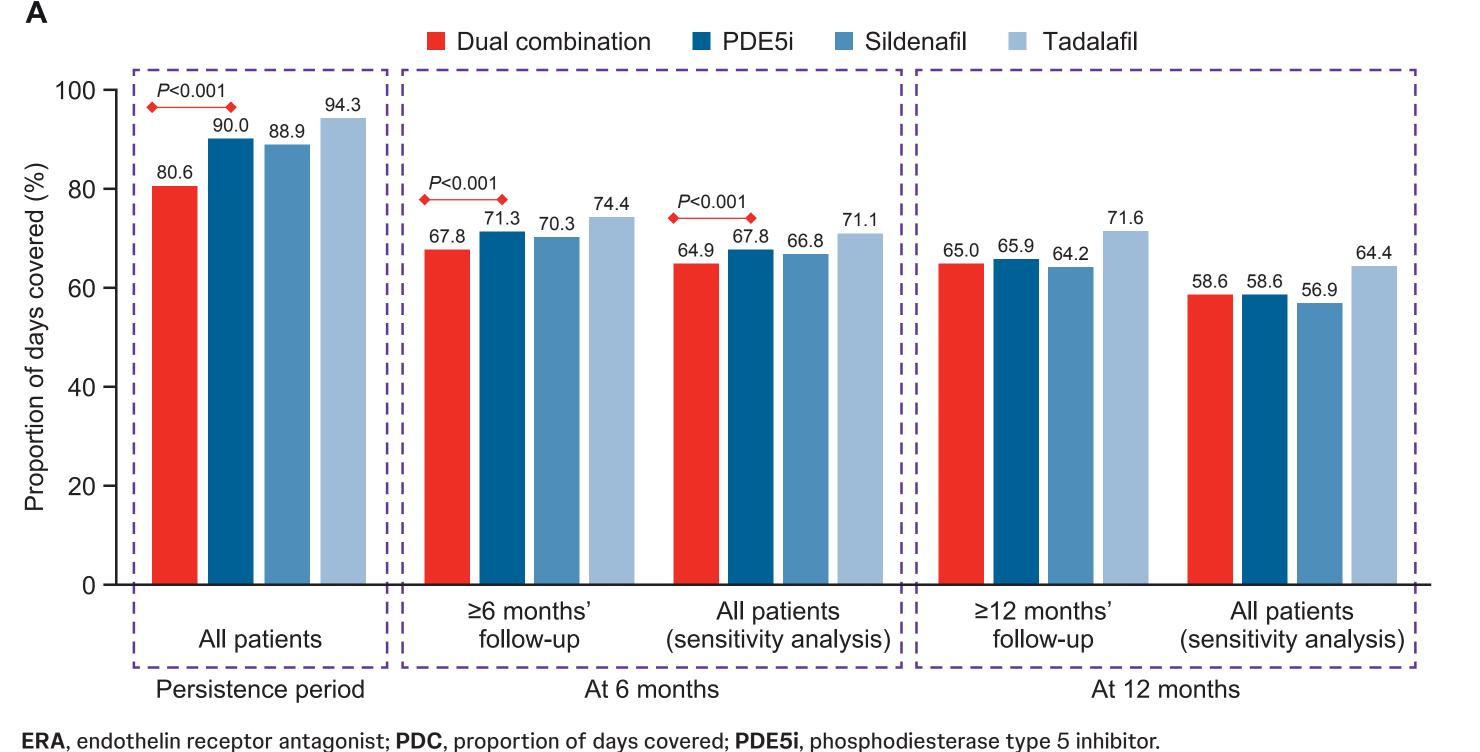
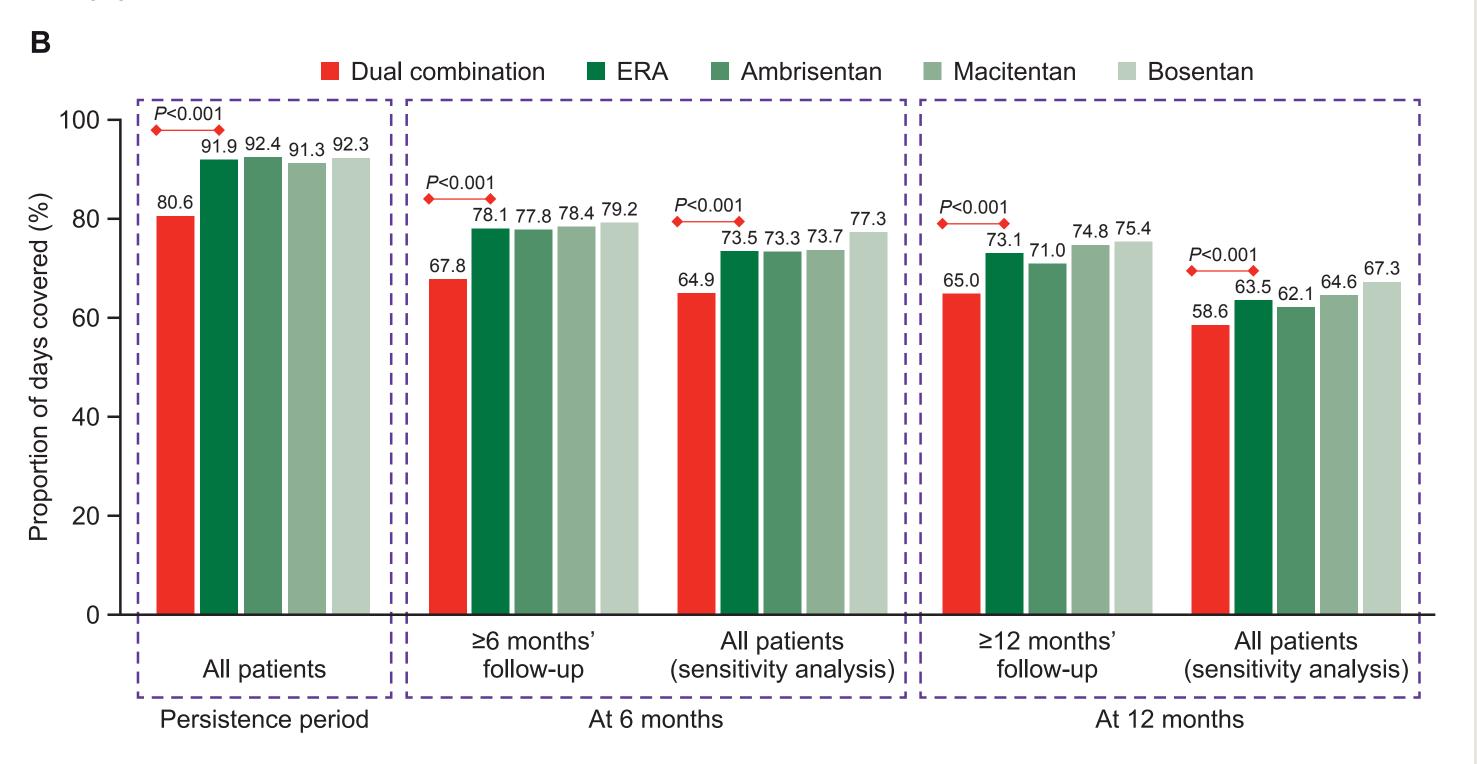


FIGURE 3. Mean PDC overall, at 6 months (among patients with ≥6 months of follow-up and all patients), and at 12 months (among patients with ≥12 months of follow-up and all patients) for dual combination therapy compared with (A) PDE5i monotherapy and (B) ERA monotherapy





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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Pulmonary Hypertension



PDE5i, phosphodiesterase type 5 inhibitor; PH, pulmonary hypertension.

CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension