Characteristics of Patients,Treatment Patterns and Medication Adherence and Persistence among Patients with Pulmonary Arterial Hypertension in a Large US Health Plan

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Background

- Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterized by restricted blood flow through the pulmonary arterial circulation, increased pulmonary vascular resistance and, frequently, right heart failure.
- In the US and Europe, the incidence and prevalence are difficult to assess, but range from 2.4-10 and 15-60 million, respectively, as seen in the REVEAL and FRENCH registries.[1, 2]
- PAH patients present with multiple comorbidities, including systemic hypertension (SHTN), diabetes, sleep apnea, renal insufficiency, and ischemic heart disease.[3]
- The treatment for PAH has evolved as several new medications have recently been approved. Thus, more information is needed on characteristics of PAH patients and treatment patterns.

Objective

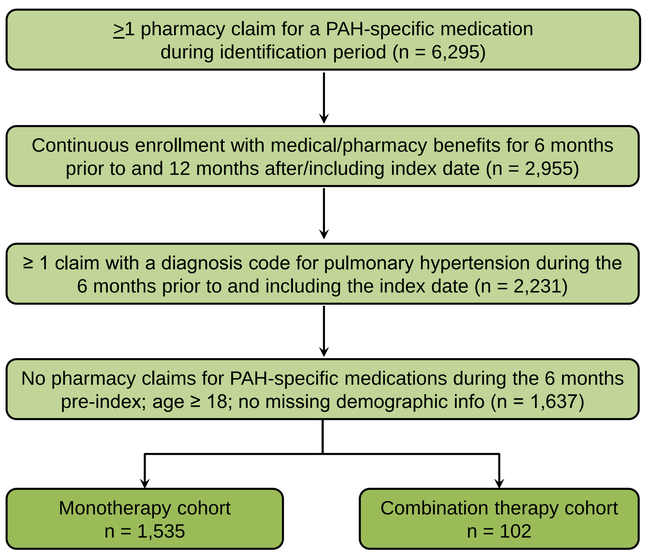
- This study examined patient characteristics and PAH-specific treatment patterns, including medication adherence and persistence, in a large, representative US health plan.

Methods

Study Design

- This retrospective study used administrative claims data to identify patients diagnosed with pulmonary hypertension who were treated with an approved PAH-specific medication between January 2010 and March 2015.
- Index date: date of first claim for a PAH-specific medication
  - Endothelin receptor antagonists (ERAs [ambrisentan, bosentan, macitentan])
  - Phosphodiesterase type 5 inhibitors (PDE-5Is [sildenafil, tadalafil])
  - Prostacyclins (epoprostenol, iloprost, treprostinil) and selective prostacyclin IP receptor agonist (selexipag)
  - Soluble guanylate cyclase stimulator (sGCS [riociguat])
- Inclusion criteria and sample selection are shown in Fig. 1.
- Study cohort assignments (Fig. 1) were based on the number of pharmacy claims for PAH-specific medications within 30 days of the index date.
  - Monotherapy: claims for only 1 PAH-specific drug class
  - Combination therapy: claims for > 1 PAH-specific drug class
- Index regimen: PAH-specific medications and classes filled during the 30 days starting with the index date
  - Second regimen: the subsequent regimen for patients whose regimen was modified during the study
- Patients were followed until health plan disenrollment or study end (31 March 2016).

Figure 1. Inclusion criteria and study sample



Study measures

- Patient characteristics were assessed during the 6 months prior to the index date (baseline period).
- Between-cohort differences in patient characteristics were analyzed using Student's *t* test, a chi-square test, and/or Fisher's exact test, as appropriate.
- Outcomes were assessed during the variable follow-up period of at least 12 months after the index date.
  - Discontinuation of therapy (a gap in therapy of ≥ 90 days)
  - Modification from index regimen (a fill for a new PAH-specific medication)
  - Adherence (proportion of days covered [PDC])
  - Persistence (months to discontinuation/modification of therapy)

Results

Study sample and baseline characteristics

- 1,637 patients met all study criteria and were included (1,535 monotherapy, 102 combination therapy; Fig. 1).
- Baseline patient characteristics (Table 1)
  - The study population was predominantly female (63.7%), mean (standard deviation [SD]) age was 65.3 (13.8) years and 54.4% were enrolled in a Medicare Advantage plan.
  - Mean (SD) follow-up duration was 2.5 (1.2) years with 53.7% followed for > 2 years and 12.7% for > 4 years.
  - Mean Charlson comorbidity score was 3.3. Most common comorbidities were lower respiratory disease (91.6%), SHTN (80.5%), lipid metabolism disorders (55.2%), other connective tissue diseases (42.6%), type 2 diabetes (39.2%), and sleep apnea (37.2%).

Table 1. Baseline patient characteristics

Characteristic	Total (n=1,637)	Monotherapy (n=1,535)	Combination therapy (n=102)	P-value
Age, mean (SD)	65.3 (13.8)	**65.7 (13.7)**	**59.1 (14.2)**	**< 0.001**
Female, n (%)	1,043 (63.7)	**963 (62.7)**	**80 (78.4)**	**0.001**
Insurance type, n (%)				
Commercial	746 (45.6)	**684 (44.6)**	**62 (60.8)**	**0.001**
Medicare	891 (54.4)	**851 (55.4)**	**40 (39.2)**	**0.001**
Years of follow-up, mean (SD)	2.5 (1.2)	2.5 (1.2)	2.4 (1.2)	0.429
Charlson comorbidity score mean (SD)	3.3 (2.0)	3.3 (2.0)	3.4 (2.0)	0.865
Common comorbidities, n (%)				
Lower respiratory disease[a]	1,500 (91.6)	1,404 (91.5)	96 (94.1)	0.349
Systemic hypertension[b]	1,318 (80.5)	1,236 (80.5)	82 (80.4)	0.975
Lipid metabolism disorder[a]	903 (55.2)	854 (55.6)	49 (48.0)	0.135
Connective tissue disease[a]	698 (42.6)	653 (42.5)	45 (44.1)	0.755
Type 2 diabetes[b]	641 (39.2)	609 (39.7)	32 (31.4)	0.096
Sleep apnea[b]	609 (37.2)	**581 (37.9)**	**28 (27.5)**	**0.035**
Respiratory failure/insufficiency[a]	521 (31.8)	487 (31.7)	34 (33.3)	0.736
Thyroid disease[b]	381 (23.3)	353 (23.0)	28 (27.5)	0.303
Depression[b]	218 (13.3)	199 (13.0)	19 (18.6)	0.103

[a]Defined using AHRQ Clinical Classifications Software.
[b]Identified from ICD-9-CM codes on claims during the baseline period.
SD, standard deviation.

Medication regimens

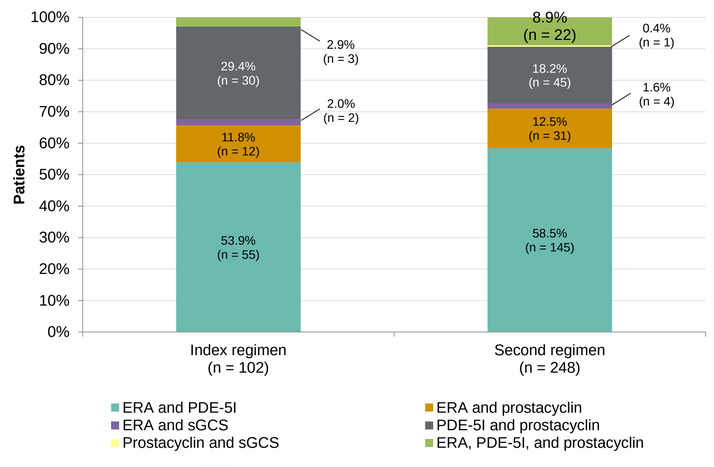
- Most patients (1,535/1,637, 93.8%) initiated treatment with monotherapy (Table 2).
- The proportion of patients treated with combination therapy increased from 6.2% (102/1,637) in the index regimen to 42.7% (248/581) in the second regimen.
- Medication classes used in index and second-regimen therapies
  - PDE-5Is, ERAs, and prostacyclins were used in 70.0% (sildenafil 69%; tadalafil 34%); 26.8% (ambrisentan 51%, bosentan 42%, macitentan 13%); and 8.1% (treprostinil 55%, epoprostenol 43%, iloprost 8%) of index treatment regimens, respectively.
  - Use of ERAs (index regimen, 26.8% vs second regimen, 50.4%) and prostacyclins (index regimen, 8.1% vs second regimen, 22.4%) increased from the index regimen to the second regimen, but remained similar for PDE-5Is (index regimen, 70.0% vs second regimen, 70.7%).
- 284/1,535 patients (18.5%) who initiated treatment with monotherapy later switched to combination therapy.
- The most common combination therapy was ERA plus PDE-5I (index regimen, 53.9%; second regimen, 58.5%; Fig. 2).
- Of the 386/1,637 patients who began combination therapy during the study, most (55.4%) did so within 6 months of the index date.

Table 2. Index and second-regimen therapies by cohort

Medication class, n (%)	Index regimen			Second regimen		
	Total (n=1,637)	Monotherapy (n=1,535)	Combination therapy (n=102)	Total (n=581)	Index monotherapy (n=545)	Index combination therapy (n=36)
ERA	439 (26.8)	367 (23.9)	72 (70.6)	293 (50.4)	264 (48.4)	29 (80.6)
PDE-5I	1,145 (70.0)	1,057 (68.9)	88 (86.3)	411 (70.7)	383 (70.3)	28 (77.8)
Prostacyc./ IPRA	133 (8.1)	88 (5.7)	45 (44.1)	130 (22.4)	102 (18.7)	28 (77.8)
sGCS	25 (1.5)	23 (1.5)	2 (2.0)	17 (2.9)	17 (3.1)	0 (0.0)

ERA, endothelin receptor antagonist; IPRA, prostaglandin IP receptor agonist; PDE-5I, phosphodiesterase type 5 inhibitor; prostacyc., prostacyclin; sGCS, soluble guanylate cyclase stimulator.

Figure 2. Medication classes used in combination therapies, by regimen*



*Percentages may not sum to 100% because of rounding.

Results (continued)

Medication adherence, persistence, and discontinuation

- ERAs were associated with higher adherence (mean [SD] PDC = 0.8 [0.4] vs 0.6 [0.4], p < 0.001; Fig. 3) and persistence (9.5 [10.8] months vs 7.5 [8.6] months, p < 0.01) than PDE-5Is.
- Combination therapies were associated with greater persistence than monotherapies (mean [SD] = 11.7 [11.1] months vs 7.4 [8.8] months, p < 0.01).
- Of patients who discontinued (n = 443) or modified (n = 581) their index regimen, 78.9% did so within 1 year (mean [SD] persistence = 7.6 [9.0] months, median = 4.0 months).
- At 1 year, the probability of continuing the index regimen was 50.3% overall; however, patients who initiated monotherapy were less likely to remain on their index regimen than those who initiated combination therapy (49.2% vs 68.3%; Fig. 4).

Figure 3. Medication adherence (PDC) by cohort

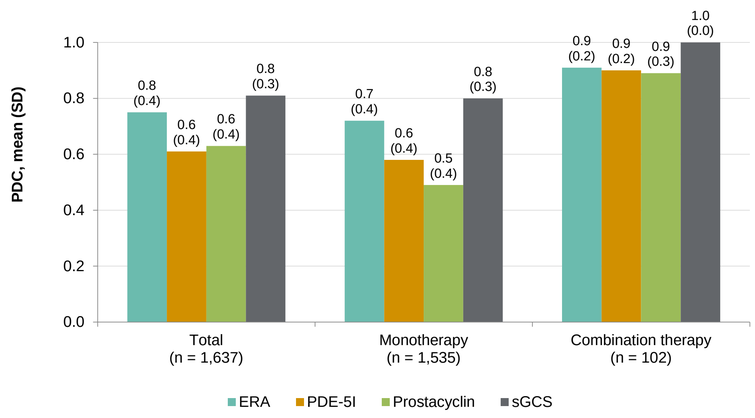
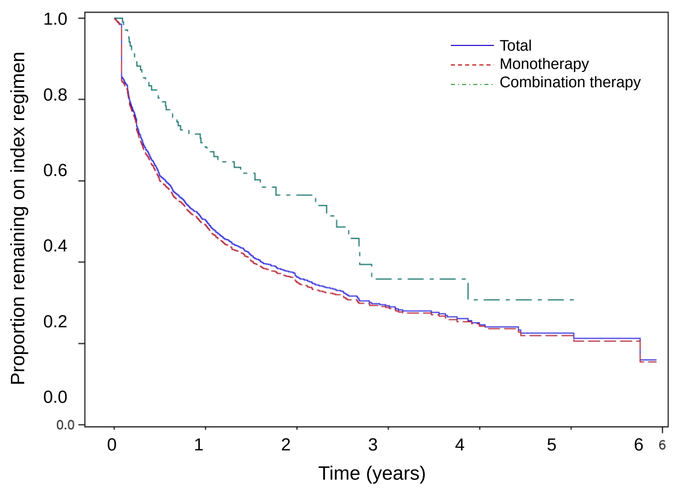


Figure 4. Kaplan–Meier analysis of time to discontinuation or modification of the index regimen



	Patients at risk					
	0 years	1 year	2 years	3 years	4 years	5 years
Total	1,637	724	277	117	47	17
Monotherapy	1,535	663	252	108	41	16
Comb. therapy	102	61	25	9	6	1

Limitations

- This study was conducted in a large US managed care population and may not be generalizable to other populations.
- Because the ICD-9-CM did not have a unique code for PAH, patients were identified with an algorithm using diagnostic and pharmacy codes, which may have affected the sensitivity of the identification algorithm in some cases.
- Medications provided as part of a clinical trial may not be accounted for in claims data.
- Not all therapies were available for the duration of the study; some were approved during the patient identification period, and the selective prostacyclin IP receptor agonist was approved after the study period had ended.

Conclusions

- The majority of PAH patients initiated with monotherapy treatment, most commonly PDE5is, which demonstrated lower adherence and persistence than ERAs. Use of combination therapies increased in the second regimen, which were associated with higher adherence and persistence than monotherapies.
- In this large, US claims-based study, the majority of patients maintained consistent health plan coverage for > 2 years following PAH therapy initiation.
- Therapy adjustments to the initial regimen occurred early, and in the majority of patients, suggesting that patients were not meeting a low-risk profile. This underscores the importance of adhering to guidelines which recommend using multi-parameter risk assessments.[3]

References

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