Comorbidities among patients with pulmonary arterial hypertension in the Time to Therapy Activation and Initial Combination Therapy (TITANIC) study

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Background

- Patients with pulmonary arterial hypertension (PAH) experience long delays in diagnosis (~3 years),[1–3] likely resulting from the low incidence of the disease and non-specific symptoms that can lead to incorrect diagnoses
- Early therapy is essential to optimize patient outcomes in PAH, but the delay in diagnosis means that pulmonary vasculature has already deteriorated by the time treatment commences[4]
- Little is known regarding time to treatment following a PAH diagnosis

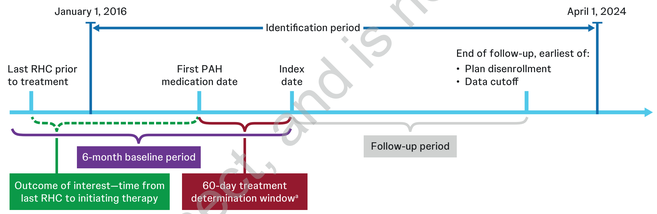
Objective

- To characterize time to treatment and examine how comorbidity burden influences initial treatment regimen choice in real-world US patients with PAH

Methods

- Adults with PAH were identified in the Komodo Health database using claims for right heart catheterization (RHC), pulmonary hypertension diagnostic codes (International Classification of Diseases, 9th Revision, Clinical Modification codes 416.0 and 416.8; International Classification of Diseases, 10th Revision, Clinical Modification codes I27.0, I27.20, I27.21, and I27.89), and PAH medications
- The identification period was January 1, 2016, to April 1, 2024
- To determine the intended initial treatment regimen, a 60-day treatment determination window was implemented following the first PAH medication claim (**Figure 1**)
  - The index date was the 61st day after the first PAH medication
  - The 60-day window was intended to determine if the clinically intended therapeutic regimen was upfront monotherapy, dual therapy, or triple therapy; ≥14 days' overlapping drug use was required to ensure a multidrug therapy regimen was intended (index treatment determination window)
- The baseline period was 6 months prior to the index date and was used to evaluate patient demographics, comorbidities, and Quan-CharIson Comorbidity Index (Quan-CCI) scores
- The outcome studied was the time from the most recent RHC to initiation of PAH therapy, categorized by initial treatment regimen

FIGURE 1: Study design



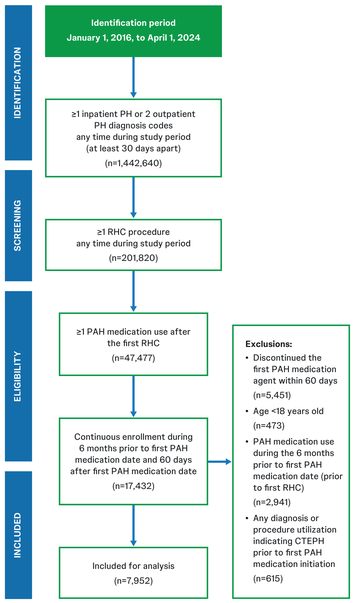
*Selection of a 60-day window to capture treatment intent was based on protocols of trials of upfront combination therapy (AMBITION, dual combination therapy titrated by day 56; TRITON, triple combination therapy initiated by day 18 and titrated by day 84)[5,6]
PAH, pulmonary arterial hypertension; **RHC**, right heart catheterization.

Results

Patient demographics and initial treatment regimen

- In total, 7,952 patients were included (**Figure 2**)
- The median time from the most recent RHC to receipt of the first PAH medication was 43 days (**Figure 3**)
- Most patients (77.7%) initially received monotherapy, with 20.0% and 2.3% receiving upfront dual and triple therapy, respectively (**Figure 3**)
- There was a higher proportion of men in the upfront monotherapy versus the dual and triple therapy cohorts, and patients receiving monotherapy were older on average (**Table 1**)

FIGURE 2: Patient flow diagram

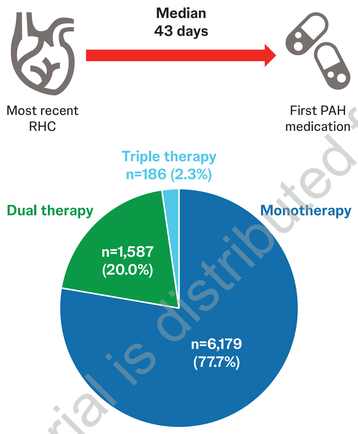


CTEPH, chronic thromboembolic pulmonary hypertension; **PAH**, pulmonary arterial hypertension; **PH**, pulmonary hypertension; **RHC**, right heart catheterization.

Comorbidities during the baseline period

- The mean Quan-CCI score was 3.85 in the monotherapy cohort, 4.02 in the dual therapy cohort, and 4.08 in the triple therapy cohort (**Figure 4A**)
- Cardiac comorbidities were reported in 86.3%, 83.3%, and 88.7% of patients from the monotherapy, dual therapy, and triple therapy cohorts, respectively (**Figure 4B**)
- The frequency of comorbidities varied across the three treatment cohorts (**Table 2**)
  - Patients in the monotherapy cohort had more atrial fibrillation, chronic obstructive pulmonary disease, coronary artery disease, and diabetes compared with those in the dual and triple therapy cohorts
  - Those receiving dual or triple therapy had more dyspnea compared with those receiving monotherapy
  - The triple therapy cohort had more congestive heart failure and heart failure than the monotherapy and dual therapy cohorts
  - Sleep apnea, interstitial lung disease, and obesity had similar frequencies across the cohorts

FIGURE 3: Time to initiation of PAH therapy and regimen received



PAH, pulmonary arterial hypertension; **RHC**, right heart catheterization.

TABLE 1: Baseline demographics

Characteristic	Monotherapy cohort (n=6,179)	Dual therapy cohort (n=1,587)	Triple therapy cohort (n=186)
Age, years, mean (SD)	58.77 (14.5)	54.12 (14.0)	49.44 (13.0)
Age category, n (%)			
18–24 years	96 (1.6)	38 (2.4)	4 (2.2)
25–34 years	306 (5.0)	119 (7.5)	24 (12.9)
35–44 years	654 (10.6)	229 (14.4)	43 (23.1)
45–54 years	1,133 (18.3)	372 (23.4)	44 (23.7)
55–64 years	1,826 (29.6)	483 (30.4)	49 (26.3)
≥65 years	2,164 (35.0)	346 (21.8)	22 (11.8)
Male sex, n (%)	2,007 (32.5)	401 (25.3)	38 (20.4)
Insurance plan type, n (%)[a]			
Commercial	1,949 (31.7)	620 (39.2)	66 (36.5)
Medicaid (including dual)	1,618 (26.3)	541 (34.2)	87 (48.1)
Medicare	2,580 (42.0)	419 (26.5)	28 (15.5)

[a]For monotherapy cohort, n=6,147; for dual therapy cohort, n=1,580; for triple therapy cohort, n=181. **SD**, standard deviation.

TABLE 2: Comorbidities during the baseline period

Comorbidity, n (%)	Monotherapy cohort (n=6,179)	Dual therapy cohort (n=1,587)	Triple therapy cohort (n=186)
Atrial fibrillation	1,180 (19.1)	163 (10.3)	5 (2.7)
Congestive heart failure	4,298 (69.6)	1,153 (72.7)	156 (83.9)
Chronic obstructive pulmonary disease	2,558 (41.4)	564 (35.5)	57 (30.6)
Coronary artery disease	2,005 (32.4)	393 (24.8)	43 (23.1)
Depression	1,351 (21.9)	371 (23.4)	55 (29.6)
Diabetes without chronic complications	2,049 (33.2)	468 (29.5)	48 (25.8)
Diabetes with chronic complications	1,358 (22.0)	254 (16.0)	19 (10.2)
Dyspnea	4,237 (68.6)	1,211 (76.3)	148 (79.6)
Heart failure	4,298 (69.6)	1,153 (72.7)	156 (83.9)
Hypertension	4,866 (78.8)	1,226 (77.3)	151 (81.2)
Idiopathic pulmonary fibrosis	299 (4.8)	53 (3.3)	7 (3.8)
Inflammatory bowel disease	69 (1.1)	20 (1.3)	1 (0.5)
Interstitial lung disease	1,003 (16.2)	238 (15.0)	24 (12.9)
Left heart failure	225 (3.6)	52 (3.3)	8 (4.3)
Lower respiratory disease	580 (9.4)	146 (9.2)	26 (14.0)
Multiple sclerosis	24 (0.4)	10 (0.6)	1 (0.5)
Obesity	2,539 (41.1)	640 (40.3)	82 (44.1)
Pneumonia	1,077 (17.4)	269 (17.0)	34 (18.3)
Sleep apnea	714 (11.6)	173 (10.9)	19 (10.2)
Sleep disorder	638 (10.3)	180 (11.3)	20 (10.8)

Higher frequency with monotherapy | Higher frequency with dual and triple therapy | Higher frequency with triple therapy

FIGURE 4: Quan-CCI scores (A) and cardiac comorbidities (B) during the baseline period

A

B

[a]Cardiac comorbidities assessed were diabetes, obesity, hypertension, and coronary artery disease.
Quan-CCI, Quan-Charlson Comorbidity Index; **SD**, standard deviation.

Conclusions

- **These real-world data demonstrate substantial delays in treatment initiation and highlight distinct comorbidity profiles across PAH treatment cohorts**
- **Patients receiving monotherapy had higher prevalence of atrial fibrillation, chronic obstructive pulmonary disease, coronary artery disease, and diabetes; those receiving triple therapy had more congestive heart failure and heart failure**
- **These findings suggest that comorbidities may influence initial regimen choice, underscoring the need to address comorbidities alongside timely initiation of PAH therapy**
- **An important consideration is that higher comorbidity burden and frequent monotherapy use may reflect treatment of secondary pulmonary hypertension, rather than primary PAH**

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Disclosures

CK is employed by Medical Specialties Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, MA, USA. **CJP** is an employee of Johnson & Johnson, Titusville, NJ, USA; **WT** was an employee during the time this study was conducted. **TP**, **NS**, and **DF** are employed by Beth Israel Deaconess Medical Center, Boston, MA, USA.

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