The Effectiveness of Selexipag in PAH Patients With and Without Associated Connective Tissue Disease Comorbidity in United States

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BACKGROUND

- Pulmonary arterial hypertension (PAH) is often a complication of patients with connective tissue diseases (CTD).
- Several studies have indicated that patients with PAH associated CTD (PAH-CTD) have poorer outcomes, worse survival, and treatment is less effective compared to patients with idiopathic PAH.[1,2]
- Prostacyclin pathway agents (PPAs) play an important role in the treatment of PAH.[3]
- However, the use of PPAs may become problematic due to their requirement for paternal administration which can result in potentially fatal catheter-associated complications.
- Recently introduced oral PPAs, including selexipag, have resulted in delaying PAH disease progression.[4,5,6]
- In a post-hoc analysis of the GRIPHON trial, the efficacy and safety of selexipag in patients with CTD-associated PAH was consistent with that observed in the overall population.
- There is limited information regarding the clinical outcomes and healthcare costs associated with selexipag use among PAH patients with CTD.
- This study aimed to assess the impact of selexipag treatment in patients with CTD-associated PAH and PAH not associated with CTD in real-world clinical practice.

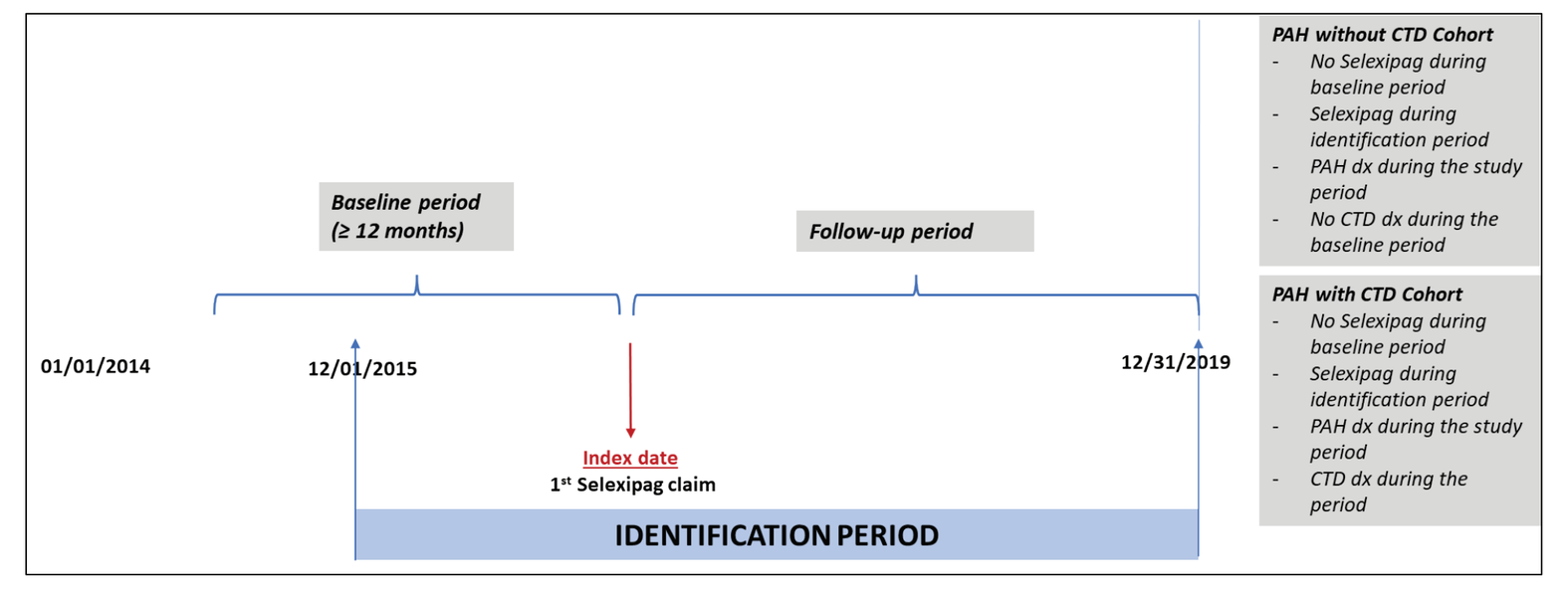
OBJECTIVE

This study evaluated the impact of selexipag on clinical outcomes, including hospitalization, disease progression, health care utilization and medical costs, in PAH patients with and without CTD.

METHODS

This is a retrospective database study using the Optum deidentified Clinformatics® Data Mart database from 01JAN2014-31DEC2019 (study period). The identification period ranged from 01JAN2015-31DEC2019 (Figure 1).

Figure 1. Study Design



CTD: connective tissue diseases; PAH: pulmonary arterial hypertension

Selection criteria:

Patients were included (Figure 2) in the study if they met the following:

- ≥1 pharmacy claim for selexipag during the identification period; the first selexipag claim date during the identification period was defined as the index date.
- ≥1 PH/PAH diagnosis claim (ICD-9-CM: 416.0, 416.8 or ICD-10-CM: I27.0, I27.2, I27.89) in the inpatient or emergency room (ER) setting OR ≥2 PH/PAH diagnosis claims on separate days in the outpatient setting during the study period. The first diagnosis claim date for PH/PAH was defined as the first observed PAH diagnosis date.
- Continuous health plan enrollment was required for ≥12 months prior to the index date with no minimum requirement for the follow-up period.
- ≥18 years of age as of index date.
- Study Cohorts
  - **PAH with CTD Cohort (PAH-CTD):** PAH patients with claim for CTD conditions (SSc: ICD-9-CM: 710.1; ICD-10-CM: M34; SLE: ICD-9-CM: 517.8, 710.0 or ICD-10-CM: M32; Sicca syndrome: ICD-9-CM: 517.8, 710.2 or ICD-10-CM: M35.0; dermatomyositis or polymyositis: ICD-9-CM: 710.3, 710.4 or ICD-10-CM: M33; mixed CTD: ICD-9-CM: 710.8, 710.9 or ICD-10-CM: M35.1 or M36.8) any time during the study period.
  - **PAH without CTD Cohort (PAH non-CTD):** PAH patients without claim for CTD conditions any time during the study period.
- No evidence of claims for selexipag, other prostacyclin pathway agents (treprostinil, epoprostenol and iloprost), chronic thrombo-embolic pulmonary hypertension (CTEPH), lung transplant or balloon atrial septostomy during the baseline period.

Study Variables

- Patient demographics, including age, gender, and geographic region were captured during the 12-month baseline period.
- Charlson Comorbidity Index (CCI) score, individual comorbidities, baseline all-cause and PAH-related healthcare utilizations during the 12-month baseline period were reported.

METHODS - cont'd

Study Outcomes

The following outcomes were captured for the follow-up period:

- Time to first all-cause hospitalization
- Time to first PAH-related hospitalization
- Time to disease progression

  Time to disease progression was defined as time from the index date to earliest of any of the following during the follow-up period:
  - Initiation of parenteral prostanoids treatment was defined the date of the first prescription of IV/SC prostanoids e.g., epoprostenol, treprostinil.
  - Date of all cause death,
  - Lung transplant claim date,
  - Balloon atrial septostomy claim date,
  - PAH-related hospitalization claim date, OR
  - PAH-related ER visit claim date.
- All-cause and PAH-related healthcare utilization
- All-cause and PAH-related healthcare costs

Statistical Analysis

- **Descriptive Analysis Plan:** All study variables were analyzed descriptively, mean, standard deviation, median, and range were provided for continuous variables. Counts and percentages were reported for categorical variables.
- **Multivariate Analysis Plan:** The Cox proportional hazards model was used to examine time to PAH-related hospitalization, time to all- cause hospitalization and time to disease progression. Generalized linear models (GLMs) were performed to compare healthcare costs and utilization between the PAH-CTD and PAH non-CTD cohorts prescribed selexipag.

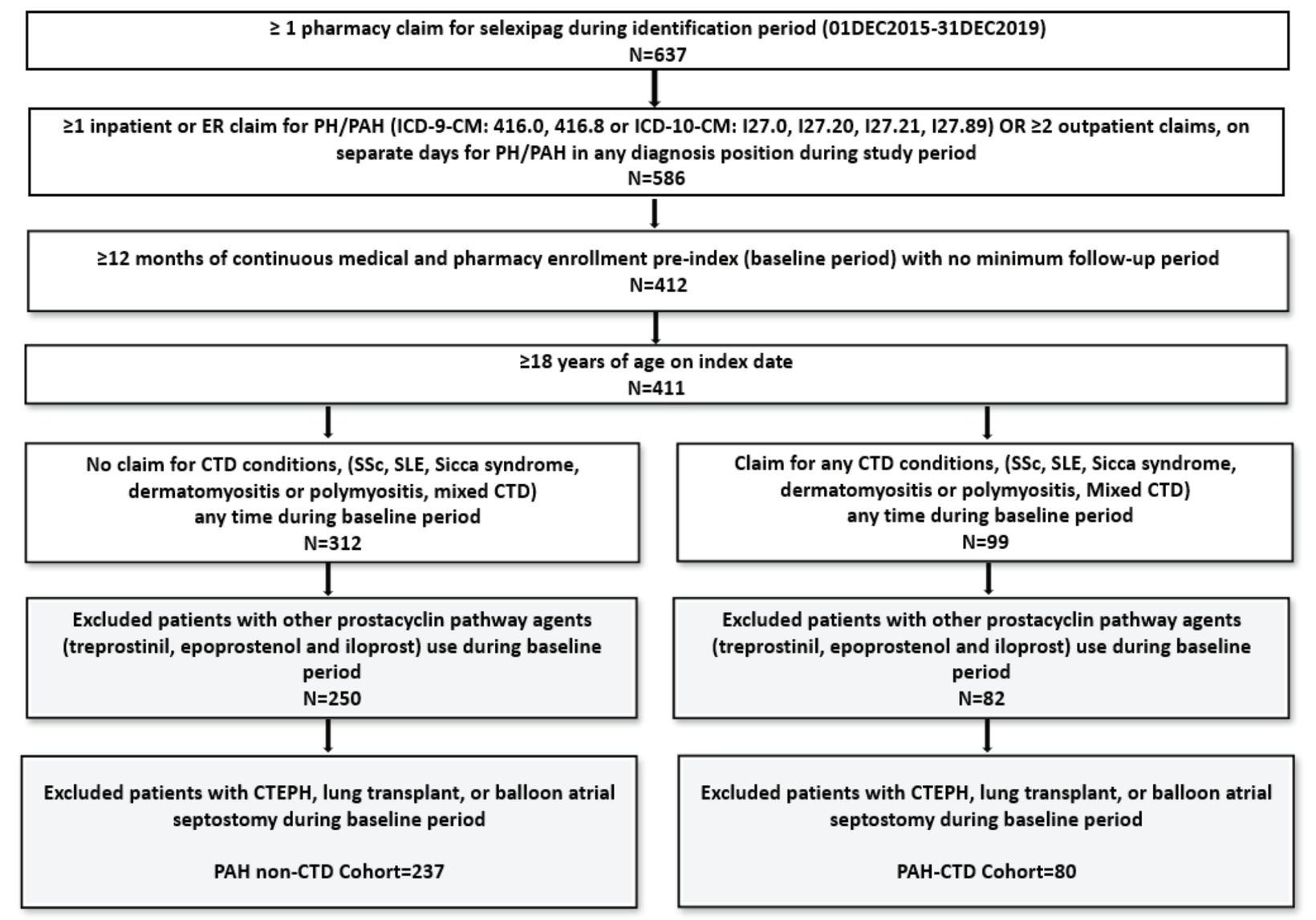
RESULTS

Descriptive Results

After applying all the selection criteria, 237 PAH-CTD and 80 PAH non-CTD patients prescribed selexipag were identified (Figure 2).

- Patients with PAH-CTD were younger than the PAH non-CTD cohort (62.7 vs 64.8 years respectively), consisted of proportionately more females (PAH-CTD=82.5% vs PAH non-CTD=72.0%) and resided in the South US region (PAH-CTD=47.5% vs PAH non-CTD=53.2%).
- Patients with PAH-CTD had a lower mean CCI score compared to those with PAH and without CTD (2.26 and 3.06, respectively). (Table 1)

Figure 2. Patient Flow Diagram



CTD: connective tissue diseases; CTEPH: chronic thromboembolic pulmonary hypertension; ER: emergency room; OR: odds ratio; PAH: pulmonary arterial hypertension; SLE: systemic lupus erythematosus; SSc: systemic sclerosis

Table 1. Descriptive Baseline Characteristics of PAH-CTD and PAH non-CTD Patients who were Prescribed Selexipag

	PAH Non-CTD Cohort	PAH-CTD Cohort	P-value
	N/Mean (%/SD)	N/Mean (%/SD)	
Age (years)	64.8 (13.4)	62.7 (12.5)	0.221
Age Group (years)			
18-44	21 (8.9%)	7 (8.8%)	0.976
45-54	27 (11.4%)	13 (16.3%)	0.258
55-64	51 (21.5%)	22 (27.5%)	0.272
65-74	74 (31.2%)	22 (27.5%)	0.531
>=75	64 (27.0%)	16 (20.0%)	0.212
Gender			
Male	66 (27.8%)	14 (17.5%)	0.065
Female	171 (72.2%)	66 (82.5%)	0.065
US Geographic Region			
Northeast	26 (11.0%)	7 (8.8%)	0.574
North Central	35 (14.8%)	11 (13.7%)	0.823
South	126 (53.2%)	38 (47.5%)	0.381
West and Other	49 (21.1%)	24 (30.0%)	0.087
Charlson Comorbidity Index (CCI) Score			
Mean CCI score	3.1 (2.5)	2.3 (2.2)	0.013*
Baseline All-cause Health Care Utilization			
Patients with an inpatient visit	118 (49.8%)	47 (58.8%)	0.165
Patients with outpatient visit			
Patients with an ER visit	147 (62.0%)	57 (71.3%)	0.136
Patients with an outpatient office visit	236 (99.6%)	80 (100%)	0.561
Patients with another outpatient visit	237 (100%)	80 (100%)	-
Length of stay for all inpatient visits (days)	0.71 (1.85)	0.58 (1.19)	0.479
Number of inpatient visits	0.09 (0.15)	0.10 (0.13)	0.619
Number of outpatient visits	4.62 (2.87)	5.84 (3.47)	0.006*
Number of ER visits	0.15 (0.20)	0.18 (0.22)	0.263
Number of outpatient office visits	1.29 (0.76)	1.55 (0.76)	0.010*
Number of other outpatient visits	3.18 (2.33)	4.11 (3.02)	0.013
Baseline All-cause Health Care Costs			
Inpatient hospitalization costs	$3,048 ($5553)	$4,054 ($7638)	0.281
Outpatient costs	$2,248 ($3060)	$3,085 ($3286)	0.039*
Outpatient ER costs	$289 ($548)	$326 ($417)	0.532
Outpatient office costs	$166 ($104)	$206 ($102)	0.003*
Other outpatient costs	$1,793 ($2,929)	$2,553 ($3,197)	0.051
Total medical costs (inpatient + outpatient)	$5,297 ($6826)	$7,139 ($8594)	0.084

Note: Baseline healthcare utilization and costs were computed per patient per month (PPPM).

*Significant p-values

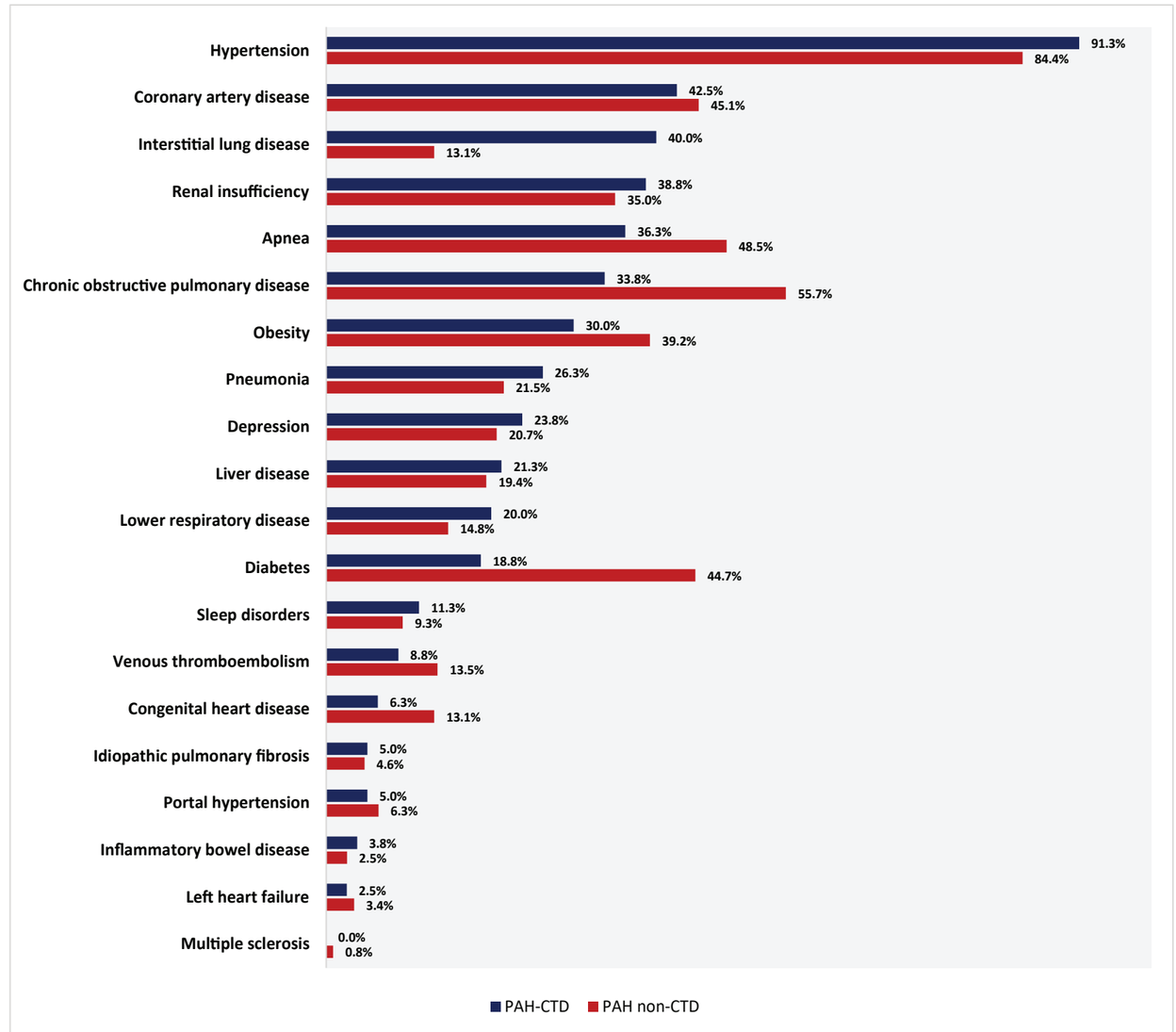
CCI: Charlson comorbidity index; CTD: connective tissue diseases; ER: emergency room; OR: odds ratio; PAH: pulmonary arterial hypertension; SD: standard deviation.

- Hypertension (PAH-CTD=91.25% vs PAH non-CTD=84.39%), dyspnea (PAH-CTD=91.25% vs PAH non-CTD=85.65%), and chronic obstructive pulmonary disease (COPD) (PAH-CTD=33.75% vs PAH-non CTD=55.70%) were the most common comorbidities among PAH patients with both cohorts.

RESULTS - cont'd

- The PAH-CTD cohort had a higher proportion of patients with interstitial lung disease (ILD) (PAH-CTD=40.0% vs PAH-non CTD=13.08%) during the 12-month baseline period. (Figure 3)
- The PAH-CTD cohort had a higher proportion of patients with ≥1 inpatient visit during the baseline period (PAH-CTD = 58.8% vs PAH non-CTD = 49.8%) and shorter length of stay for all inpatient visits (PAH-CTD = 0.58 days vs PAH non-CTD = 0.71 days).
- The PAH-CTD cohort had higher average total medical all-cause health care costs vs the PAH non-CTD cohort during the 12-month baseline period ($7,139 vs $5,297, respectively).

Figure 3. Baseline Comorbidities Among PAH-CTD and PAH non-CTD Cohorts



CTD: connective tissue diseases; PAH: pulmonary arterial hypertension

Unadjusted Outcomes

- PAH-CTD patients had a mean follow-up time of 231 days vs 224 days for PAH non-CTD patients.
- A higher proportion of patients with PAH and CTD had PAH-related hospitalization during the follow-up period vs those without CTD (PAH-CTD = 32.5% vs PAH non-CTD = 26.2%; p=0.274).
- The mean time to PAH-related hospitalization was similar among the PAH-CTD and PAH non-CTD cohorts prescribed selexipag (PAH-CTD = 175 days vs PAH non-CTD = 194 days; p=0.556).
- Patients with PAH-CTD had higher proportion of all-cause hospitalization during the follow-up period compared to those without CTD (PAH-CTD = 36.3% vs PAH non-CTD = 28.3%; p=0.179).
- The mean time to all-cause hospitalization was similar for both cohorts prescribed selexipag (PAH-CTD = 182 days vs PAH non-CTD = 170 days; p=0.661).
- A higher proportion of patients in the PAH-CTD cohort had disease progression during follow-up vs the PAH non-CTD cohort (PAH-CTD = 56.3% vs PAH non-CTD = 47.3%; p=0.164).
- Mean time to disease progression was observed to be lower among patients in the PAH-CTD cohort vs PAH non-CTD cohort; however, the results were not significant (PAH-CTD = 88 days vs PAH non-CTD = 110 days; p=0.450). (Table 2)

Table 2. Unadjusted Outcomes for PAH-CTD and PAH non-CTD Cohorts Prescribed Selexipag

	PAH Non-CTD	PAH-CTD	P-value*
	N/Mean (%/SD)	N/Mean (%/SD)	
Follow-up, Mean (days)	224 (243)	231 (306)	
PAH-related hospitalization			
Patients with All-cause hospitalization	67 (28.3%)	29 (36.3%)	0.179
Time to all-cause hospitalization (days)	170 (204)	182 (242)	0.66
All-cause hospitalization			
Patients with PAH-related hospitalization	62 (26.2%)	26 (32.5%)	0.274
Time to PAH-related hospitalization (days)	175 (206)	194 (271)	0.556
Disease Progression			
Patients with disease progression	112 (47.3%)	45 (56.3%)	0.164
Time to disease progression (days)	110 (195)	88 (234)	0.45

CTD: connective tissue diseases; PAH: pulmonary arterial hypertension

Multivariate Results

- **PAH-related Hospitalization:** After adjusting for potential confounders, there was no statistically significant difference in time to PAH-related hospitalization between patients with PAH-CTD and PAH non-CTD patients prescribed selexipag (hazard ratio [HR]=1.37; 95% CI=0.67-1.90, p-value=0.6410). (Table 3)
- **All-cause Hospitalization:** After adjusting for baseline demographic and clinical characteristics, there was no statistically significant difference in the time to all-cause hospitalization between patients with PAH with vs without CTD prescribed selexipag (HR=1.09; 95% CI=0.71-1.28, p-value=0.7650). (Table 3)
- **Disease Progression:** After adjusting for baseline demographic and clinical characteristics, there was no statistically significant difference in time to disease progression (HR=1.14; 95% CI=0.76-1.75, p-value=0.5220) between PAH patients with or without CTD. (Table 3)
- Patients with higher baseline CCI score and higher baseline outpatient visits were associated with higher risk of PAH-related hospitalization, all-cause hospitalization, and disease progression. Presence of ILD was associated with the risk of all-cause hospitalization and disease progression (all-cause hospitalization: HR=1.77; p=0.028; disease progression: HR=1.70; p=0.006) among the population.

Table 3. Time to PAH-related Hospitalization, All-cause Hospitalization, and Disease Progression Among Patients with PAH with and without CTD who were Prescribed Selexipag

	HR (95%CI)	P-value
Time to PAH-related hospitalization (days)	1.13 (0.67-1.90)	0.641
Time to All-cause hospitalization (days)	1.09 (0.64-1.88)	0.744
Time to disease progression (days)	1.14 (0.76-1.72)	0.522

CI: confidence interval; CTD: connective tissue diseases; HR: hazard ratio; PAH: pulmonary arterial hypertension

Healthcare Utilization and Costs

- After adjusting for baseline demographic and clinical characteristics, the PAH-CTD cohort incurred higher total all-cause medical costs PPPM compared to the PAH non-CTD cohort (PAH-CTD=$6,312 vs PAH non-CTD=$4,663; p=0.047).
- After adjusting for baseline demographic and clinical characteristics, no statistically significant difference in total PAH-related medical costs PPPM was found among between the cohorts (PAH-CTD=$2,568 vs PAH non-CTD=$2,059; p=0.156). (Table 4)

Table 4. Adjusted Healthcare Costs and Utilization for PAH Patients With and Without CTD Prescribed Selexipag

	PAH non-CTD	PAH-CTD	P-Value*
	N/Mean	N/Mean	
All-cause Health Care Utilization			
Length of stay for all inpatient visits (days)	0.65	0.79	0.6495
Number of inpatient visits	0.14	0.09	0.2953
Number of outpatient visits	4.46	5	0.1495
Number of pharmacy claims	4.7	4.93	0.4632
All-cause Health Care Costs			
Inpatient hospitalization costs	$2,398	$3,064	0.1526
Outpatient cost	$1,843	$2,403	0.0655
Total medical costs (inpatient + outpatient)	$4,663	$6,312	0.0469
PAH related Health Care Utilization			
Length of stay for all inpatient visits (days)	0.57	0.73	0.576
Number of inpatient visits	0.12	0.08	0.3133
Number of outpatient visits	1.67	2.12	0.063
Number of pharmacy claims	2.08	2.05	0.8909
PAH related Health Care Costs			
Inpatient hospitalization costs	$939	$1,153	0.2537
Outpatient cost	$828	$1,104	0.0492
Total medical costs (inpatient + outpatient)	$2,059	$2,568	0.1563

CTD: connective tissue diseases; PAH: pulmonary arterial hypertension

LIMITATIONS

- As with all observational retrospective analyses, there are several important limitations associated with claims databases. The presence of a claim for a filled prescription does not indicate that the medication was consumed or taken as prescribed.
- PAH medication or other medications that were administered in the inpatient settings are not captured in the database and therefore could not be measured and included in the analyses.
- The death information, after 2013, may be incomplete as it was no longer a mandatory requirement for states to report on the death data.
- Also, the Optum database does not report actual paid costs. It reports a 'standardized cost' figure that is related to allowable charges and should not be interpreted as the cost of services or medications.
- Despite adjusting for potential confounders, unmeasured confounders such as disease severity, hemodynamics, and functional class may impact the results.
- The lack of specificity of ICD codes in the World Health Organization PAH clinical classification may underestimate or overestimate the PAH diagnosis.

CONCLUSIONS

In this real-world study, the risk of all-cause hospitalization, PAH-related hospitalization and disease progression did not significantly differ among PAH patients with CTD compared to PAH patients without CTD comorbidities who were prescribed selexipag, indicating that regardless of the presence of CTD comorbidities in PAH patients, selexipag therapy may provide similar clinical benefits for both patient groups.

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Disclosures

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