MILLIMAN RESEARCH REPORT

Pulmonary Arterial Hypertension in the Commercial Population

An analysis of patient characteristics, treatment patterns, and costs

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Table of Contents

Executive Summary

Pulmonary arterial hypertension (PAH) is a progressive disease that can cause ventricular failure and death. Current therapies can improve the odds of survival, though no cure exists. While there are no standards of treatment for PAH, most patients are treated with a drug in the endothelin receptor antagonist (ERA) class. ERAs can be taken with or without a drug in the class of phosphodiesterase inhibitors (PDE 5 inhibitors), with combination therapy becoming more common as the disease progresses. Other classes of PAH drugs include soluble guanylate cyclases (sGCs) and Prostacyclin-related drugs. While PDE 5 inhibitors and sGCs may be used to treat conditions other than PAH, ERAs and Prostacyclin-related drugs are almost solely prescribed for PAH. In this study, we identified the cohort of PAH patients as those using ERA or Prostacyclin-related drugs.

We analyzed a large administrative database comprised of commercial health insurance claims (i.e. insurance not funded by public sources) for the years 2013 to 2016. We identified over 900 people with ERA and/or Prostacyclin use for which we analyzed their drug persistence, treatment patterns, healthcare spending, and comorbid conditions. Our analysis found that the PAH population includes patients with diverse resource utilization as exhibited by considerable variations in treatments patterns and allowed spending levels. In particular:

- We identified a total of 911 adult PAH patients on either an ERA or Prostacyclin drug during the years 2013-2016, which translates into a prevalence rate of 4 PAH patients per 100,000 members.
- On average, PAH patients have over five comorbidities. PAH's high prevalence of multiple comorbidities adds to the cost burden for patients and payers.
- The average PAH patient in our study incurred over $18,000 of allowed spending per month (or annualized spending of over $200,000).
- There is no typical PAH treatment pattern. We identified a wide range of PAH treatment patterns, with about 70% of the patients following one of the five most common patterns.
- About 70% of patients in our study were adherent to their ERA drug after three years of treatment. We observed minimal intra-class switching for ERA patients. About 17% of these patients added a Prostacyclin, on average, 220 days after initiating therapy with an ERA.

This report was commissioned by Actelion Pharmaceuticals, which manufactures drugs used to treat PAH. The findings reflect the research of the authors; Milliman does not intend to endorse any product or organization. If this report is reproduced, it should be reproduced in its entirety, as sections taken out of context can be misleading. As with any economic or actuarial analysis, it is not possible to capture all factors that may be significant. Because we present national average data, the findings should be interpreted carefully before they are applied to any particular situation. One of the coauthors, Gabriela Dieguez, is a member of the American Academy of Actuaries and meets its qualification standards for this work.

Findings of the Longitudinal Analysis (2013-2016)

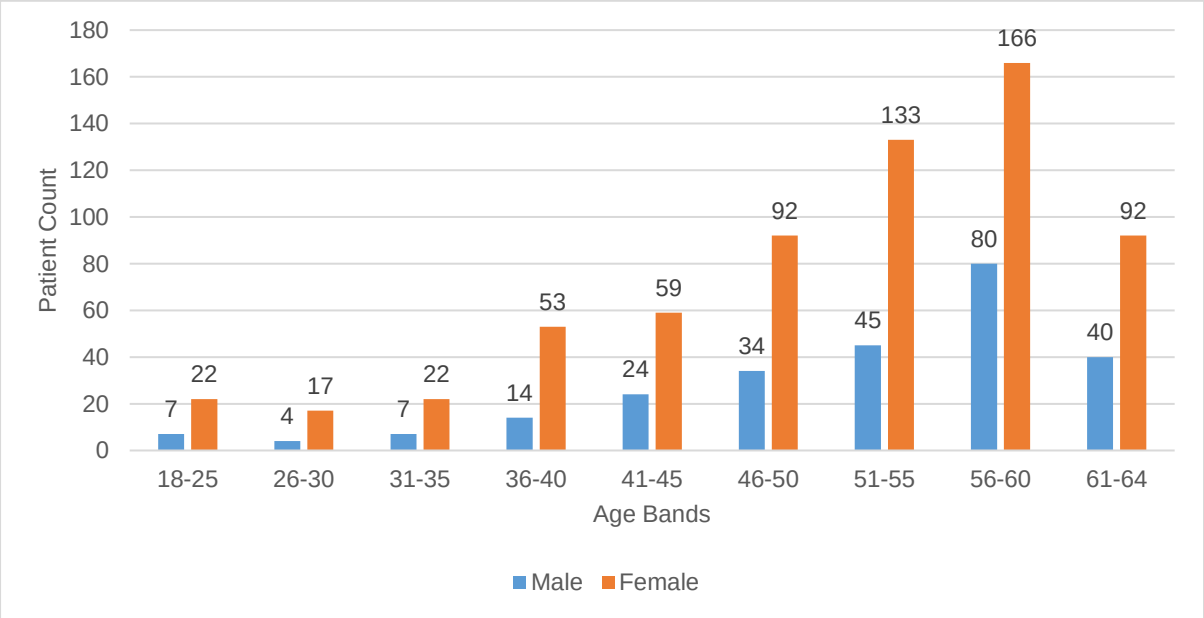
We examined the comorbidities, drug treatment patterns, and allowed costs (which include both patient out-of-pocket and payer costs) of commercially insured PAH patients in the years prior to and following the initial PAH therapy. We defined PAH patients as those using drugs we deemed specific to treating PAH (or "index drugs", ERAs and Prostacyclin-related drugs, in all modes of delivery). Patients were then indexed based on the date of their first fill (or "index" date) of an index drug. In this approach, we excluded PDE 5 inhibitors and SGCs from our definition of index drugs, and incorporated a 90-day clean period to reflect first time index PAH drug use.

POPULATION CHARACTERISTICS

We identified a total of 911 adult patients having received an index PAH drug during the years 2013-2016 with 90 days of coverage prior to their index PAH drug. The population identified was 72% female patients compared to 28% male patients. The average age at index was 50.3 for female patients, compared to 51.7 for male patients.

Figure 1 shows the distribution of PAH patients by age band. In general, PAH patients are more likely indexed with their first PAH drug after their 40th birthday for both male and female patients. The 56-60 age band contains the most patients (80/255 male patients and 166/656 female patients).

FIGURE 1: AGE / GENDER DISTRIBUTION OF PAH PATIENTS*



Sources: Milliman's analysis of MarketScan Commercial databases (2013-2016)
Note: Age of patient at the year of their index PAH script

COMMORBIDITIES

PAH is associated with a high prevalence of multiple comorbidities. Figure 2 shows the top 15 comorbidities among PAH patients in our study. As expected, the most frequent comorbidity is congestive heart failure (95%). Other common comorbidities were chronic obstructive pulmonary disease and asthma (43%), cardio-respiratory failure and shock or respiratory arrest (43%), fibrosis of lung and other lung disorders (32%) and any form of diabetes (30%). We note that diagnosis codes are not always present in administrative claims data, and therefore actual comorbidities may be understated.

FIGURE 2: TOP 15 COMMON COMMORBIDITIES FOR PAH PATIENTS

Comorbidities	% PAH Patients
Congestive Heart Failure	95%
Chronic Obstructive Pulmonary Disease, Including Bronchiectasis; or Asthma	43%
Cardio-Respiratory Failure and Shock, Including Respiratory Distress Syndromes; or Respiratory Arrest	43%
Fibrosis of Lung and Other Lung Disorders	32%
Diabetes with Chronic Complications; or Diabetes without Complication; or Diabetes with Acute Complications; or Amyloidosis, Porphyria, and Other Metabolic Disorders	30%
Rheumatoid Arthritis and Specified Autoimmune Disorders (includes Scleroderma)	27%
Specified Heart Arrhythmias	22%
Systemic Lupus Erythematosus and Other Autoimmune Disorders	19%
Septicemia, Sepsis, Systemic Inflammatory Response Syndrome/Shock	18%
Pulmonary Embolism and Deep Vein Thrombosis	18%
Coagulation Defects and Other Specified Hematological Disorders	13%
Heart Infection/Inflammation, Except Rheumatic	12%
Atrial and Ventricular Septal Defects, Patent Ductus Arteriosus, and Other Congenital Heart/Circulatory Disorders	10%
Major Depressive and Bipolar Disorders	9%
Protein-Calorie Malnutrition	8%

Sources: Milliman's analysis of MarketScan Commercial databases (2013-2016)

TREATMENT PATTERNS

We grouped PAH drugs by class and divided patients into treatment patterns based on their first script, regardless of whether that script was for an index PAH drug (ERA or Prostacyclin) or non-index PAH drug (PDE5 and sGC). We observed that:

- There is no "typical" PAH treatment pattern. We identified a wide range of PAH treatment patterns and summarized the most common in Figure 3.
    - About 70% of patients in our study followed one of the five most common treatment patterns
- Patients that start on Prostacyclin are more likely to stay on monotherapy (36.3%) than patients that start on an ERA (28.5%).
- ERA patients were slightly more likely to start therapy with an ERA (54.5%) than with a PDE5 or sGC (45.5%).
- We found minimal to no intra-class switching for ERA patients – for the most part, patients stay adherent to their index PAH therapy. About 17% of patients added a Prostacyclin, on average, 220 days after initiating therapy with an ERA.

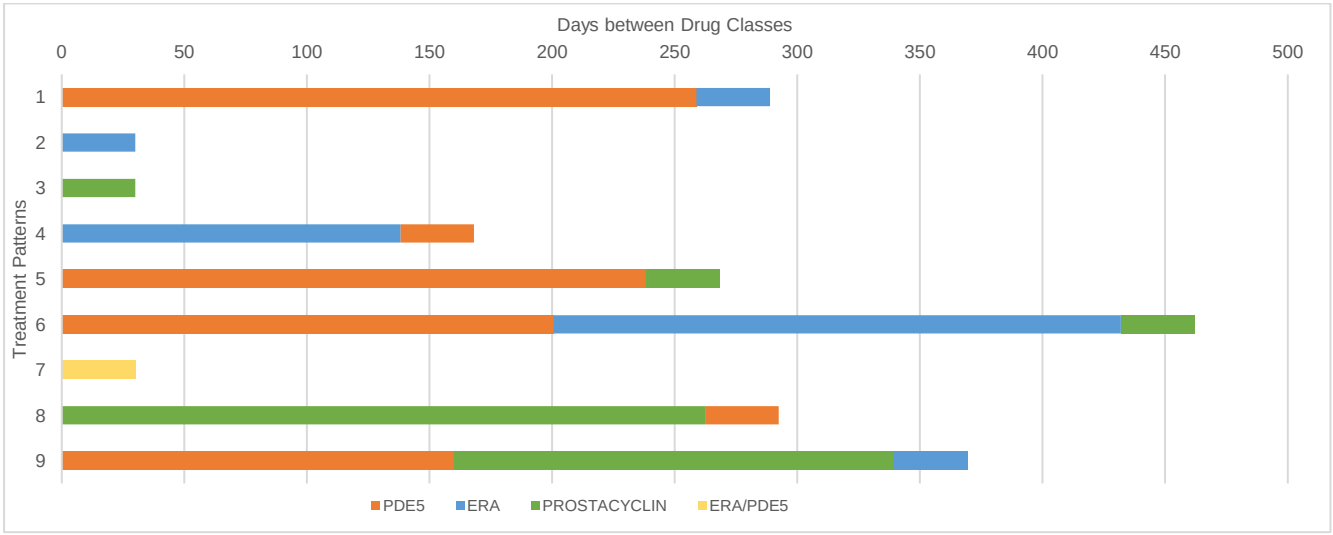
FIGURE 3: PAH TREATMENT PATTERNS

Treatment Pattern	1st PAH Drug	2nd PAH Drug	3rd PAH Drug	Patient Count	% PAH Patients	% Female
1	PDE5	ERA		219	24%	68%
2	ERA			188	21%	75%
3	Prostacyclin			91	10%	73%
4	ERA	PDE5		71	8%	68%
5	PDE5	Prostacyclin		61	7%	66%
6	PDE5	ERA	Prostacyclin	50	5%	84%
7	ERA/PDE5			44	5%	75%
8	Prostacyclin	PDE5		23	3%	83%
9	PDE5	Prostacyclin	ERA	20	2%	80%
All other treatment patterns				144	16%	72%
All PAH patients				**911**	**100%**	**72%**

Sources: Milliman's analysis of MarketScan Commercial databases (2013-2016)

Figure 4 presents the time elapsed between the first, second, and third therapies for the treatment patterns listed above. Patients who started treatment with an index PAH drug tended to spend an average of 195 or more days with that drug before adding another drug such as PDE5 or SGCs (see treatment patterns 4 and 8). However, patients who started on PDE5 drugs spent an average of 240 days on the drug before transitioning to either ERA or Prostacyclin (see treatment patterns 1, 5, 6, and 9).

FIGURE 4: AVERAGE TIME BETWEEN DRUG CLASSES



Sources: Milliman's analysis of MarketScan Commercial databases (2013-2016)

HEALTHCARE COSTS AND THE RELATIVE HEALTH STATUS OF PAH PATIENTS

Figure 5 shows allowed spending (amounts a payer have negotiated for covered health care services) per patient per month (PPPM) for PAH patients with different treatment patterns. Allowed costs include physician-administered Prostacyclin drugs (medical claims with HCPCS codes) and self-administered PAH drugs, in addition to all other medical and prescription drug services. We trended 2014 and 2015 amounts for two years and one year, respectively, to reflect 2016 spending levels. On average, patients that start their index PAH drug therapy with Prostacyclin have higher total monthly costs ($22,757 per patient per month (PPPM)) than patients that start with an ERA ($16,810 PPPM).

Also shown in Figure 5 is the average risk score of the patients included in each of the different treatment patterns. Risk scores are based on the U.S. Department of Health and Human Services hierarchical condition category (HHS-HCC) concurrent risk adjustment model for a silver metal plan for 2016. The risk adjustment model is used in the individual and small group markets to predict costs for the year based on medical conditions coded in that year. Generally, higher risk scores mean higher costs. As shown in Figure 5, the treatment patterns with relatively higher average risk scores have high allowed PPPM costs.

FIGURE 5: ALLOWED MONTHLY COSTS PER PATIENT AND RISK SCORES, BY TREATMENT PATTERN

Prior PAH Drug	Index PAH drug	Subsequent PAH Drug	Average Risk Score	Average Monthly Costs	PAH Patient Count	% of PAH Patients
	ERA		11.9	$ 15,914	188	21%
	ERA	PDE5	15.9	$ 15,759	71	8%
	ERA/PDE5		15.7	$ 27,927	44	5%
Other ERA without prior PAH drug			14.9	$ 25,589	57	6%
PDE5	ERA		13.9	$ 13,131	219	24%
PDE5	ERA	Prostacyclin	16.9	$ 20,514	50	5%
Other ERA with prior PAH drug			15.3	$ 19,754	31	3%
	Prostacyclin		11.8	$ 19,267	91	10%
	Prostacyclin	PDE5	14.0	$ 26,788	23	3%
Other Prostacyclin without prior PAH drug			16.7	$ 23,968	48	5%
PDE5	Prostacyclin		21.1	$ 20,131	61	7%
PDE5	Prostacyclin	ERA	20.5	$ 25,122	20	2%
Other Prostacyclin with prior PAH drug			22.1	$ 38,492	8	1%
All PAH patients			**15.0**	**$ 18,329**	**911**	**100%**

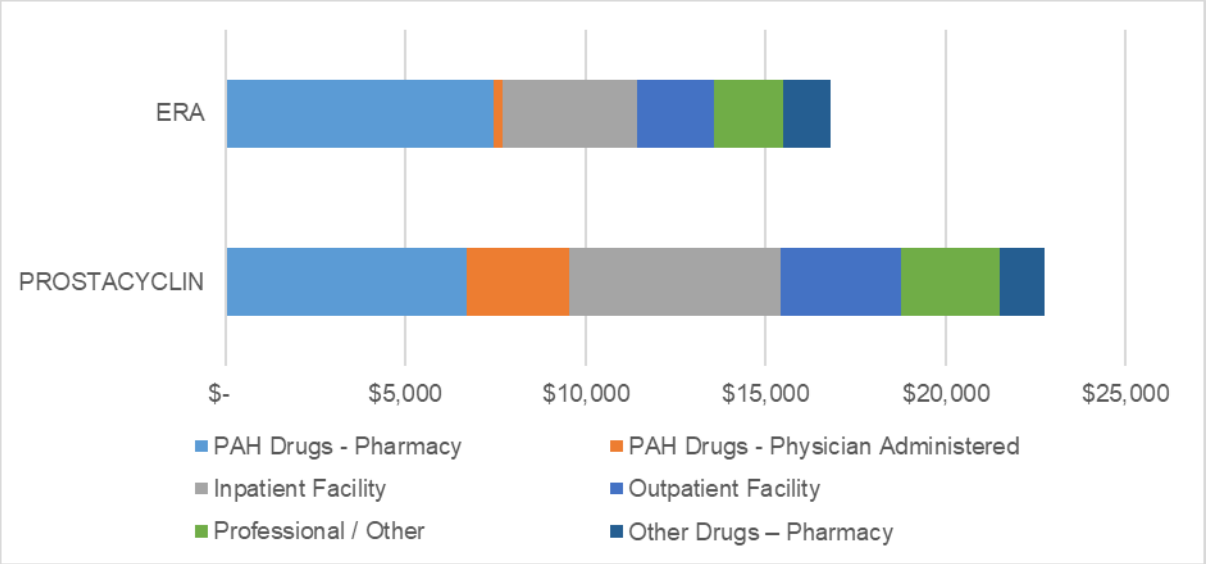
Sources: Milliman's analysis of MarketScan Commercial databases (2013-2016)
Notes:

- Out of the 911 PAH patients identified, 857 had risk scores in the 2016 HHS model. Average risk scores reflect the member month weighted average of the 857 patients' 2016 HCC silver risk scores.
- Average costs per patient per month (PPPM) include costs for all healthcare service, not just the cost of PAH drugs.

Patients indexed with ERA and Prostacyclin and that continue on monotherapy for the duration of our study have respectively an average risk score of 11.9 and 11.8. Those patients are less likely to have severe conditions (HCC factor >10) such as cardio respiratory failure. Patients indexed with ERA who added a PDE5 or those who went from a PDE5 to an ERA have a higher average risk score within the 13.9 to 15.9 range. This category of patients had either more comorbidities or more severe conditions. However, patients who moved from other PAH drugs to Prostacyclin had higher risk scores, on average, ranging from 14.0 to 22.1, which denotes a combination of severe conditions leading the drug switch.

Figure 6 shows the distribution of allowed cost by service categories for ERA and Prostacyclin indexed patients. Medical costs are significantly higher for patients indexed with Prostacyclin compared to ERA (Inpatient: Prostacyclin $5,882, ERA $3,760; Outpatient: Prostacyclin $3,324, ERA $2,129; Professional: Prostacyclin $2,731, ERA $1,878). However, pharmacy PAH costs are higher for ERA indexed patients ($7,446 PPPM) compared to Prostacyclin ($6,704 PPPM). PAH infused drug costs are significantly higher for Prostacyclin indexed patients ($2,835 PPPM) compared to ERA ($223 PPPM).

FIGURE 6: ALLOWED MONTHLY COSTS PER PATIENT, BY SERVICE CATEGORY AND INDEX PAH DRUG CLASS

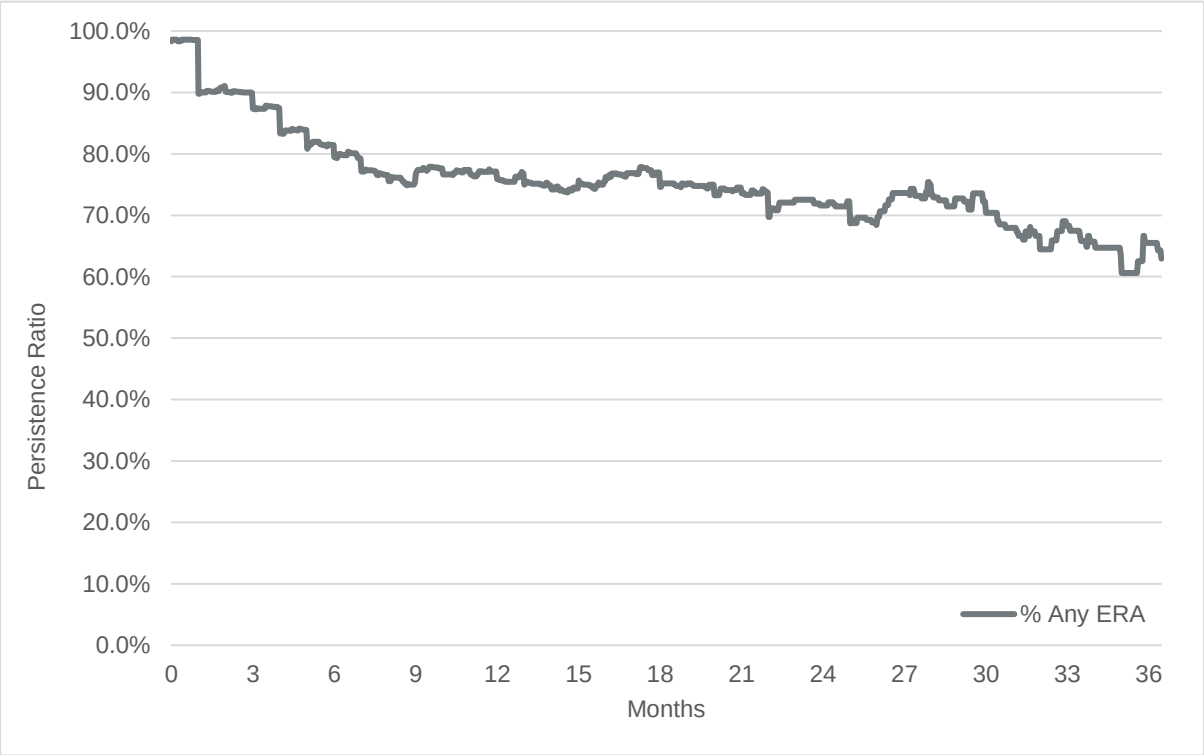


Sources: Milliman's analysis of MarketScan Commercial databases (2013-2016)
Note: We included SNF costs with Professional / Other. SNF costs are very low for PAH patients: $29 PPPM for Prostacyclin starters and $36 PPPM for ERA starters.

TREATMENT PERSISTENCE FOR ERA PATIENTS

We measured treatment persistence for PAH patients whose first script in the study period was an ERA. The persistence curve shown in Figure 7 illustrates the extent to which PAH patients on an ERA are filling their prescriptions on a regular basis. Each point on the curve represents the ratio of the number of patients in possession of a day supply of ERA to the number of patients with coverage on a given day.

FIGURE 7: ERA TREATMENT PERSISTENCE FOR PAH PATIENTS, IN MONTHS SINCE FIRST SCRIPT



Sources: Milliman's analysis of MarketScan Commercial databases (2013-2016)

Figure 7 shows that persistence for ERA patients drops to 90% after one month. This drop in persistence is likely related to a subset of patients who start ERA therapy with a 30-day prescription and then choose not to continue treatment, either stopping treatment entirely or switching to another drug class. Persistence of ERA therapy for patients decreases slightly over time, averaging about 60% after 36 months.

Implications for Payers

A longitudinal analyses of a large administrative claims database such as this one can help commercial payers understand the treatment patterns, disease progression, and cost burden of PAH and its impairments. While PAH is an irreversible, life-threatening condition that gets worse over time, existing treatments can help alleviate symptoms and improve the patient's quality of life.

The results from this study indicate the following:

- There is no typical treatment pathway for PAH patients. We identified 46 treatment pathways in the commercial population, which is reflective of the patient experience – each patient's treatment pathway is heavily dependent on their disease progression and their prescribing physician.
- PAH patients have multiple comorbidities. We observed high prevalence of comorbid conditions such as congestive heart failure (95%), chronic obstructive pulmonary disease and asthma (43%), cardio-respiratory failure and shock or respiratory arrest (43%), fibrosis of lung and other lung disorders (32%) and any form of diabetes (30%) leading to higher cost and utilization in PAH indexed patients.
- The cost burden of PAH is significant, with the average patient spending over $18,000 per month. Less than half (about 45%) of that spending is directly related to PAH therapies, and about one third is accounted for facility charges for services provided either on an inpatient or outpatient basis.

Methodology and data sources

Published studies examining PAH treatment patterns have consistent findings in terms of prevalence, patient characteristics, comorbidities, and cost burden of the disease. However, study design and patient identification varies widely across these studies, although the majority focus only on adults 18 years or older. More recent publications required patients to have more than one pharmacy claim or outpatient procedure (physician-administered infusion) for any PAH related treatment (ERA, PDE5 Prostacyclin or sGCs).

The choice of which PAH treatment to include also differs across studies. Some studies excluded patients who began their treatment with Prostacyclin because those patients tend to be more severe with higher utilization and cost[1], while some studies included patients with at least one or two procedures for a right heart catheterization (RHC)[1]. In order to get a more precise cohort some studies required a diagnosis for pulmonary hypertension (PH)[2] in addition to a pharmacy claim for any PAH related drug. Once patients are identified and indexed, coverage requirements vary significantly between studies. Before index enrollment fluctuates from 180 days to 90 days in the baseline period and the follow-up period ranges from 0 to 365 days.

Existing International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes are not sufficiently specific to distinguish PAH from other related conditions. Therefore, prior studies focused on the PAH population have used a variety of approaches and different combinations of claims-based evidence to identify PAH patients from administrative databases. Some of these approaches include identification of diagnosis codes for pulmonary hypertension, evidence of right heart catheterization, and claims for drugs used to treat PAH.

INDENTIFYING PAH PATIENTS

We identified unique PAH patients as those taking an index PAH drug in 2013, 2014, 2015, or 2016. Index PAH drugs include ERAs and Prostacyclin related drugs regardless of modes of delivery, but exclude PDE5 inhibitors and sGCs. Compared to other studies which included all drug classes, we opted for a higher specificity by selecting only ERA and Prostacyclin in order to exclude patient using PDE5 and sGCs for Erectile Deficiency (ED).

INDEXING THE FIRST PAH DRUG

For each PAH patient in our study, we determined the date of the first script for an index PAH drug. We excluded any patient under the age of 18, and those without 90 days of exposure before their first index PAH script. We examined the characteristics and experience of PAH patients before and after their first index PAH drug script. The steps of our analysis are described below.

FIGURE 8: STUDY DESIGN DESCRIPTION

	Member/PAH Patient Count			
Development of PAH Study Population	**2013**	**2014**	**2015**	**2016**
A. MarketScan	44,200,738	47,691,866	28,638,524	28,189,383
B. Data quality	41,734,661	44,930,914	26,533,689	26,406,201
C. Age<65 in 2016	39,328,411	42,942,910	25,688,152	25,908,337
D. Non-capitated plan	38,414,308	39,244,999	24,722,647	25,197,375
E. 2013-2016 PAH patients identified with 1+ ERA or Prostacyclin drug claim	1,236	1,281	1,063	1,146
E1. Patients aged 18+ at index with 3 months of coverage prior to 1st PAH-specific drug claim	**204**	**279**	**192**	**236**

Sources: Milliman's analysis of MarketScan databases (2013-2016)

[1] Charles D, B. M., Burak A, O. M., Howard M, L. M., Ellen, R. M., Leslie B, M. M., Gregory, L. M., & James R, W. M. (2018). *Treatment Patterns and Associated Health Care Costs Before and After Treatment Initiation Among Pulmonary Arterial Hypertension Patients in the United States.* Journal of Managed Care & Specialty Pharmacy.

[2] Sikirica, M., Iorga, S. R., Bancroft, T., & Potash, J. (2014). The economic burden of pulmonary arterial hypertension (PAH) in the US on payers and patients. Eden Prairie, MN: BMC Health Services Research.

RECONGIZING TREATMENT PATTERNS

We used a recursive approach to identify the various treatment patterns. Once we identified the first instance of a class for each patient, we removed any recurring fill of the same drug before looking for the next class in their treatment. We use this approach to identify the 1st, 2nd, and 3rd drug taken during the treatment.

ESTIMATING RISK SCORES AND COMORBIDITIES

Risk scores were calculated using the 2016 plan year HHS-HCC risk adjustment model. The HHS-HCC risk adjustment model utilizes member demographics and diagnoses to predict medical expenditures, and is used in the individual and small group markets to indicate the relative health status of a member. We report the HHS-HCC risk scores for silver plans, the most popular in this market. The HHS-HHC model is concurrent[3] and uses 264 HCCs and 100 grouped HCCs.

MEASURING PERSISTENCE OF PATIENTS ON ERA THERAPY

For each patient indexed with an ERA and no prior PAH drug use, we flagged each day in which the patient had a script and each day in which the patient had insurance (both medical and prescription drug) coverage. We constructed persistence curves showing the variation over time of the ratio of patients with a script to patients with coverage.

One limitation of pharmacy data is that we can only observe when the prescription was filled but not when the patient actually used the drug. A patient could fill a prescription early, hold onto the drug, and start it later. To account for this variation we applied a 30-day grace period when calculating persistence.

DATA SOURCES

We used Truven's Health Analytics MarketScan® Commercial Databases (2013-2016) for this study. MarketScan databases contain all paid claims generated for millions of commercially insured lives. The 2016 MarketScan database currently contains about 28 million lives. The MarketScan database represents the inpatient and outpatient healthcare service use of individuals nationwide who are covered by the benefit plans of large employers, health plans, government, and public organizations. The data include diagnosis codes, procedure codes, DRG codes, and NDC codes along with site of service information and the amounts paid by commercial insurers. The MarketScan database links paid claims and encounter data to detailed patient information across sites, types of providers, and over time. The annual medical database includes private sector health data from approximately 100 payers.

Please note that the contributors to MarketScan may vary from year to year; therefore, whether a member continues in the database depends on the member continuing coverage in a health plan that continues to contribute its data to MarketScan. A member may not appear in MarketScan because the member has terminated or switched coverage or because the member's health plan has stopped contributing.

[3] Concurrent models use current year information to predict current year cost

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