Prior authorization restrictiveness negatively impacts time to receipt of endothelin receptor antagonist therapy for pulmonary arterial hypertension

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Introduction

- Health plan coverage is critical for access to medications and medical care in the United States
- Access to specialty medications often requires prior authorizations (PAs), which can pose significant challenges for patients and escalates the administrative burden for providers[1]
- In a 2022 American Medical Association survey of physicians, 94% of respondents reported a delay in patient care owing to PA[2]
- Time from pulmonary arterial hypertension (PAH) symptom onset to diagnosis is typically at least 2 years, and PAH clinical practice guidelines recommend approaches for diagnosis at an earlier stage when approved therapies may be more effective[3]
- Most PAH therapies require a PA,[4] and this process has the potential to further delay the time to receipt and initiation of medication among patients diagnosed with PAH
- In a meta-analysis of 6 data sets, a PAH treatment delay of 12–16 weeks was associated with a lasting deficit in functional capacity compared with those who initially received treatment, highlighting the necessity for patients to receive prompt treatment following PAH diagnosis[5]

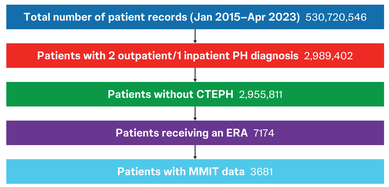
Objective

- The primary objective of this study was to determine the impact of PA restrictiveness on time from PAH medication prescription to medication receipt of endothelin receptor antagonist (ERA) therapy

Methods

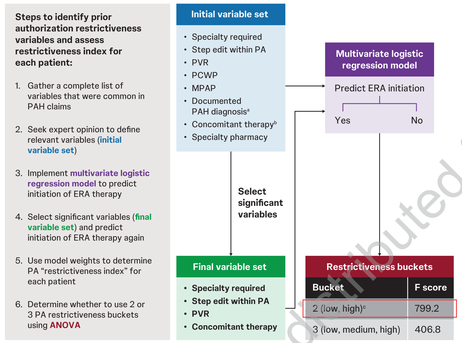
- This retrospective study used Prospection's US open-network claims data and Managed Markets Insight & Technology (MMIT) Payer and Formulary data (Jan 2018–Apr 2023)
- Eligible adult patients had a pulmonary hypertension diagnosis with either 2 outpatient diagnoses on separate days or 1 inpatient diagnosis, and were being treated with an ERA (macitentan, ambrisentan, or bosentan) (**Figure 1**)
  - The index date for each patient was the first PAH treatment prescription date using a lookback period of 6 months of clinical activity leading up to the index date
- Patients were excluded if they had a chronic thromboembolic pulmonary hypertension (CTEPH) diagnosis (ICD-10 code I27.24), had a claim for a CTEPH-related procedure, or a claim for any drug indicated for left heart disease
- PA restrictiveness was based on formulary requirements beyond the label (e.g., specialty prescriber, step edits, pulmonary vascular resistance measurement, and/or concomitant PAH-targeted therapy), with low/high restrictiveness defined as 0/≥1 formulary requirement (**Figure 2**)
  - A complete list of variables was gathered from Prospection claims data and from MMIT policy information; clinical expert opinion was sought to define the initial variable set, which included gender, Elixhauser Comorbidity Index score, treatment strategy, and age
  - The initial variable set was analyzed in a multivariate logistic regression model to identify significant variables and the finalized model was based on variables that remained statistically significant
  - PA restrictiveness was evaluated using ANOVA to determine whether 2 buckets (low vs high restrictiveness) or 3 buckets (low, medium, or high restrictiveness) provided the best stratification based on F score , which is an indicator of predictive performance
- A weighted Cox regression model was used to estimate the association between PA restrictiveness and time to receipt of an ERA, with entropy balancing to account for differences between restrictiveness levels

FIGURE 1. STROBE flow chart



CTEPH, chronic thromboembolic pulmonary hypertension; **ERA**, endothelin receptor antagonist; **MMIT**, Managed Markets Insight & Technology; **PH**, pulmonary hypertension; **STROBE**, Strengthening the Reporting of Observational Studies in Epidemiology.

FIGURE 2. Methodology for determining PA restrictiveness



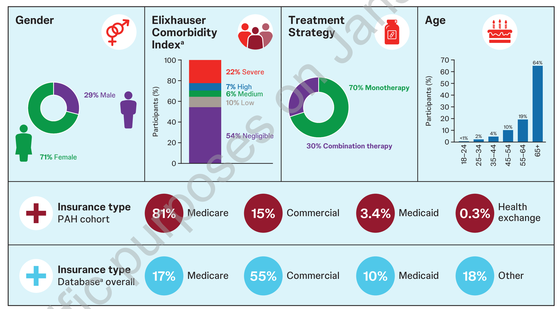
[a]ICD-10 codes I27.0, I27.20, I27.21, or I27.89; or ICD-9 codes 416.0, 416.8, or 416.9. [b]Concomitant medication restrictions were included in the model for any formularies that have restrictions for use with another specific medication. [c]Buckets for low vs high PA restrictiveness were defined as 0/≥1 formulary requirement.
ERA, endothelin receptor antagonist; **MPAP**, mean pulmonary arterial pressure; **PA**, prior authorization; **PAH**, pulmonary arterial hypertension; **PCWP**, pulmonary capillary wedge pressure; **PVR**, pulmonary vascular resistance.

Results

Patient characteristics

- Data were analyzed from 3681 adult patients with PAH receiving an ERA (macitentan, n=2512; ambrisentan, n=1114; or bosentan, n=55)
- Patient demographics and clinical characteristics are described in **Figure 3**
- The majority of patients (71%) were female, had negligible Elixhauser Comorbidity Index scores (54%), were ≥65 years of age (64.4%), had Medicare insurance coverage (81%), and received ERA monotherapy (70%)
- This PAH cohort was more likely to be aged ≥65 years and covered by Medicare than the overall population of patients represented in the claims database (**Figure 3**)

FIGURE 3. Patient demographics and clinical characteristics (n=3681)

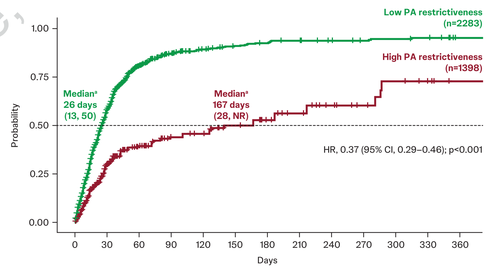


[a]A comprehensive set of 30 comorbidity measures separate from the primary reason for hospitalization.
[b]Prospection's US open-network claims data and Managed Markets Insight & Technology (MMIT) Payer and Formulary data (Jan 2018–Apr 2023).

Time from ERA prescription for PAH to medication receipt

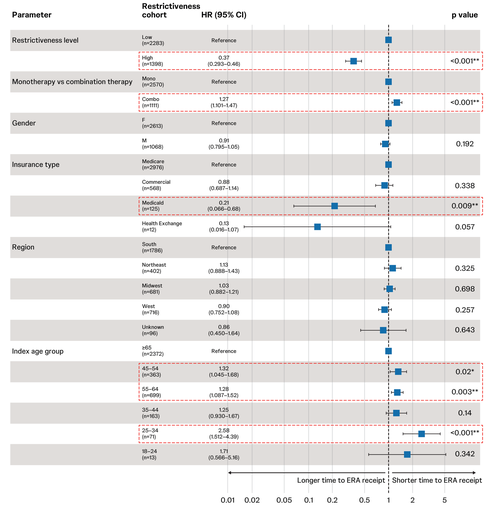
- Restrictiveness was stratified on the basis of 2 buckets based on superior statistical results (F score) compared to 3 buckets
- Median (Q1, Q3) time to receipt of an ERA was 26 (13, 50) days in the low PA restrictiveness cohort versus 167 (28, not reached [NR]) days in the high PA restrictiveness cohort
- Based on a Cox model regression analysis, patients in the high PA restrictiveness cohort (n=1398) were at 63% greater risk of not receiving ERA therapy compared with those in the low PA restrictiveness cohort (n=2283) (p<0.001; **Figure 4**)
- By specific ERA, median (Q1, Q3) time to receipt of an ERA in the high versus low PA restrictiveness cohorts was:
  - 187 (33, NR) versus 27 (14, 50) days for macitentan
  - 72 (19, NR) versus 21 (9, 53) days for ambrisentan
  - 37 (37, 41) versus 29 (11, 34) days for bosentan
- Time to ERA receipt was significantly longer in patients on Medicaid (vs Medicare) and those with severe (vs negligible) Elixhauser Comorbidity Index (**Figure 5**)
- Time to ERA receipt was significantly shorter for patients aged 25–34 and 55–65 years compared with patients aged ≥65 years (**Figure 5**)

FIGURE 4. Time to receipt of ERA medication for PAH, by PA restrictiveness



[a]Median (Q1, Q3) time to receipt of an ERA, in days.
CI, confidence interval; **HR**, hazard ratio; **PA**, prior authorization; **PAH**, pulmonary arterial hypertension; **Q**, quartile.

FIGURE 5. Forest plot showing parameters impacting time to receipt of ERA medication for PAH, by PA restrictiveness[a]



[a]Number of events: 1276; global p-value (log-rank): 2.7×10^{-44}. Events refer to the number of patients that reached the endpoint (receipt of an ERA).
CI, confidence interval; **HR**, hazard ratio.

Limitations

- Owing to the nature of the available claims data used in this analysis, a high proportion of the patients (81%) included in this analysis were covered by Medicare, which covers individuals over the age of 65, and therefore the findings from this analysis may not apply to all age groups; median age at PAH diagnosis among patients in the US TRIO database and the REVEAL and USPHSR registries ranges from 50–53 years[6]
- It is possible the generic versus brand status of individual ERAs contributed to the differences in time to ERA receipt between the high and low PA restrictiveness cohorts
- Right heart catheterization was not required for inclusion in the cohort, and it was not possible to distinguish between PAH and other pulmonary hypertension groups with available ICD codes, so it is possible patients included in this analysis did not have PAH, although the receipt of an ERA increases the likelihood that the analyzed patients had PAH
- The high rate of treatment with monotherapy in this analysis does not comport with clinical guidelines for PAH, and likely reflects real-world use by treaters outside of PAH specialty referral centers; this finding may form the basis for additional analyses evaluating current PAH treatment practices

Conclusions

- Greater PA restrictiveness is associated with longer time to receipt of ERA therapy (176 days high PA restrictiveness vs 26 days low PA restrictiveness) among patients with pulmonary hypertension
- Longer time to ERA receipt may result in treatment abandonment and can detrimentally impact patient outcomes
- Combined with previous studies showing the long-term negative consequences of PAH treatment delays,[5] these findings indicate highly restrictive PA processes lead to delays that are detrimental to patient well-being

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Disclosures

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