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Aaron W. Trammell, M.D. Date

The Influence of Pulmonary Vasodilator Therapy on Outcomes in Veterans with Pulmonary Hypertension Due to Left Heart Disease

By

Aaron W. Trammell

Master of Science

Clinical Research

C. Michael Hart, M.D.

Advisor

Mitchel Klein, Ph.D.

Committee Member

Laura Plantinga, Ph.D.

Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.

Dean of the James T. Laney School of Graduate Studies

_____

Date

The Influence of Pulmonary Vasodilator Therapy on Outcomes in Veterans with Pulmonary Hypertension Due to Left Heart Disease

By

Aaron W. Trammell

M.D., UNC-Chapel Hill, 2008

Advisor: C. Michael Hart, M.D.

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ABSTRACT

The Influence of Pulmonary Vasodilator Therapy on Outcomes in Veterans with Pulmonary Hypertension Due to Left Heart Disease

By: Aaron W. Trammell

Background: Pulmonary hypertension (PH) is a state of elevated blood pressure in the pulmonary circulation, which increases morbidity and mortality regardless of underlying etiology and is most common in patients with left-sided heart disease. While pulmonary vasodilator therapies are effective for pulmonary arterial hypertension (PAH; "PAH-targeted therapy"), benefit in PH due to left-sided heart disease (PH-LHD) is relatively understudied. We hypothesized that PAH-targeted therapy is used in a small proportion of veterans with PH-LHD and has no impact on survival.

Methods: We utilized national data from the Veterans Health Administration Corporate Data Warehouse to identify a cohort of veterans with PH diagnosed between 01/01/2003 and 09/30/2015. We extracted data on demographics, comorbidities, diagnostic evaluation, use of PAH-targeted therapy and death. By using comorbid conditions, we identified the subtype of PH. The propensity for PAH-targeted therapy use was evaluated in multivariable logistic regression models. The effect of treatment on death was estimated using multivariable Cox proportional hazards analyses using covariates, using propensity score, and using propensity matching to account for confounding by indication of the treatment effect.

Results: We identified 110,564 veterans diagnosed with PH during the study period. Patients were mostly male (96%), had median age 70.2 years, and had median follow-up of 2.85 years. Left heart disease was the only comorbidity associated with PH in 16%. Of veterans with PH-LHD, 2.9% received treatment with PAH-targeted therapy and had a median time from PH diagnosis to death of 5.21 years compared to 3.88 years in veterans never treated with PAH-targeted therapy; unadjusted hazard ratio 0.74, 95% confidence interval: 0.65, 0.82. No benefit of PAH-targeted therapy on risk of death was observed when adjusted for confounding covariates or propensity score.

Conclusions: Using administrative and clinical data of veterans receiving care in the Veterans Health Affairs system, we identified a large cohort with PH, many of whom have PH-LHD. We showed that PAH-targeted therapy is used in a minority of patients with PH-LHD and has no effect on survival when accounting for baseline differences between treated and untreated subjects. Further investigation into whether this therapy is associated with other benefits or risks, such as difference in hospitalization frequency, is warranted.

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INTRODUCTION

Pulmonary hypertension (PH) is a physiologic state of elevated blood pressure in the pulmonary circulation, mainly manifest in patients as shortness of breath, swelling, poor exertion tolerance, heart palpitations, and sometimes syncope or sudden death. It is not a disease itself, but a condition that results from others. A rise in the pressure of blood flowing through the lungs may result from increased flow through the lungs, increased resistance to blood flow through the lungs, or from increased pressure in the left heart. Regardless of the underlying cause, PH causes undue strain of the right ventricle of the heart, which ultimately leads to right ventricular failure and death. Due to this effect, the presence of PH from any underlying disease is a marker of increased morbidity and mortality. Based on the pathophysiologic principles and conditions known to cause PH, clinicians classify PH into five separate subtypes. Existing registries and clinical trials have predominantly studied one subtype: pulmonary arterial hypertension (PAH), a primary vascular disease of the lung that is now treated with medications that target the pulmonary vessels. These PAH-targeted therapies decrease resistance to pulmonary blood flow, thereby easing strain on the right ventricle of the heart and relieving the adverse effects of the condition. However, with an annual incidence in the U.S. of two cases per million adults, the healthcare burden of PAH is dwarfed by PH due to other causes, which are far more common. PH due to underlying left-sided heart disease (PH-LHD) is the most common subtype of PH in the U.S., but, lacking evidence for a best treatment approach to PH-LHD, PAH-targeted therapies are sometimes employed as default due to their benefit in PAH. While PH-LHD subjects may develop progressive failure of the right ventricle as seen in PAH, it is unclear whether medications targeting the pulmonary

vascular bed have an effect in PH-LHD. Thus, a major knowledge gap for clinicians who treat patients with PH is whether therapies that are known to be effective for PAH have any benefit in the larger population of patients with PH-LHD. While based on sound physiologic principles, current practice lacks prospective evidence from clinical trials and there are no large registries of PH-LHD from which to draw conclusions. The frequency and efficacy of the practice of using PAH-targeted therapy in other conditions, especially PH-LHD, warrant evaluation.

The Veterans Health Administration (VHA) cares for a large population of veterans with cardiopulmonary disease, thus PH-LHD is thought to be enriched in the veteran population. Clinical, pharmacy and administrative data on care received by veterans from the VHA is available for research use. We designed a retrospective longitudinal cohort study of PH-LHD subjects to identify subjects with PH and assess the frequency and effect of PAH-targeted therapy use. As no existing cohort was available, we identified veterans diagnosed with PH by diagnosis codes used in clinical care and billing purposes. In those veterans, we obtained baseline demographics, comorbid conditions, diagnostic procedures, and pertinent laboratory data. We utilized those data to classify veterans by PH subtype based on comorbid conditions and to estimate the frequency with which PAH-targeted therapies are used in those with PH-LHD. Utilizing Cox proportional hazards modeling, we estimated the association of use of PAH-targeted treatment with time from PH diagnosis until death. We utilized multivariable adjustment with baseline covariates, adjustments based on probability of PAH-targeted therapy use (propensity score), and propensity-matched analyses to estimate the independent effect of these therapies on survival in veterans with PH-LHD.

BACKGROUND

Pulmonary hypertension (PH) is a physiologic state of having elevated pulmonary artery pressure. This rise in pressure above normal develops secondary to one or more of a heterogeneous group of underlying conditions (1). A clinical classification system is used, that categorizes patients with PH into one of five subtypes or "Groups." These groups are based on the underlying pathophysiology of disease causing PH. Arguably the most notable subtype, pulmonary arterial hypertension (PAH; Group 1) is an intrinsic pulmonary vascular disease with an estimated prevalence of 10-25 cases per million adults in U.S. and European registry studies, and 14 FDA-approved therapeutic options (2, 3). PAH is differentiated from the other subtypes of PH which may be secondary to left heart disease (PH-LHD; Group 2), parenchymal lung disease (Group 3), chronic thromboembolism (Group 4), or other unclear or multifactorial mechanisms (Group 5) (1). Unfortunately, therapies that are effective for treating PAH have no established efficacy, and thus are not recommended for treatment of these more common forms of PH (2, 4).

PH-LHD (Group 2) makes up a large proportion of patients referred to specialists who manage patients with PH and is accepted as the most common subtype of PH in the United States (3, 5-8). Advanced left heart disease, such as systolic and diastolic left heart failure, are complicated by PH in up to 75-80% of cases (9-11), and the high morbidity and mortality associated with PH leaves physicians without therapeutic options. Current guidelines acknowledge that pulmonary vasodilator therapies approved for use in PAH have sound rationale for benefit in PH-LHD, but recommend only management of the underlying left heart disease and "expert assessment" of PH (2, 6).

However, there are several reasons why real-world practice may deviate from these recommendations. First, PH-LHD is often misclassified as PAH in patients referred to PH treatment centers (8). About one-third of patients referred without a clear cause of PH are ultimately diagnosed with PH-LHD, some of whom have already been on therapy for PAH (8). Even when PH-LHD is the presumed diagnosis, PAH-approved therapy was noted to be prescribed to some patients in a survey of U.S. PH referral centers (12). It is unclear whether this practice is intentional off-label prescribing or due to the perception that PH-LHD and PAH exist as a spectrum or concomitantly, which are additional justifications for PAH-approved therapy use in these patients. Regardless of reason, it is not clear which patients with PH-LHD are treated with PAH-approved therapy in clinical practice, nor are the benefits or harms of this approach to management clear.

The Veterans Health Administration (VHA) has one of the largest resources of administrative and healthcare data available (13). Because of the increased incidence of chronic left-sided heart disease in veterans and higher prevalence of risk factors for other cardiopulmonary diseases (14-16), we expected sufficient sample size of veterans with PH, especially PH-LHD, to evaluate important questions regarding non-PAH forms of PH. We utilized nationwide VHA data from January 1, 2003, to September 30, 2016, to investigate the subtypes of PH seen in veterans, measure the proportion of PH-LHD patients who are treated with PAH-approved therapies , and evaluate the effect of that therapy on survival.

METHODS

Overview

We performed a retrospective cohort study of veterans who received medical care within the VHA system and were diagnosed with PH between January 1, 2003, and September 30, 2015 (Figure 1). This study was designed to test the hypotheses that therapies approved for PAH do not improve survival in PH-LHD. The first major aim of the study was to identify a cohort of veterans diagnosed with PH within the national VHA system and assess the distribution of PH subtypes in this population. The second aim was to identify the clinical characteristics and overall survival from time of PH diagnosis of those veterans with PH. The third major aim was to assess the frequency with which PAH-targeted therapies are used in veterans with PH-LHD and estimate their independent effect on survival. Approval for the study was obtained from Emory University's Institutional Review Board and Atlanta VA Medical Center's Research & Development Committee.

Data Sources

Data for the analyses were from the VHA Corporate Data Warehouse (CDW) obtained through Veterans Administrations Informatics and Computing Infrastructure (VINCI). VINCI is a secure computing environment enabling researcher access to broad datasets including CDW and facilitates data analysis. The CDW includes >16 years of longitudinal data on >22.3 million veterans (13). Data include medical and administrative information from within the VHA system as well as data on some medical care obtained by enrolled veterans outside the VHA system.

Study Population

Adult veterans with data available in the CDW were eligible for inclusion. Subjects were included if a diagnosis of PH by *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis code—including 416.0, 416.2, 416.8, 416.9—was first entered during the inclusion period, defined as January 1, 2003, through September 30, 2015. The inclusion period's end was chosen to coincide with the major change in VHA operations from using *ICD-9* diagnosis codes to using the more recent *International Classification of Diseases, Tenth Revision, ICD-10*. Patients were excluded if they were not a veteran, were less than 18 years of age at the time of possible cohort entry, or if an *ICD-9* code for PH was used and stored in CDW at any point prior to January 1, 2003. Data are available in CDW beginning with fiscal year 1999. Follow-up data including date of first hospitalization and date of death were extracted for the duration of the inclusion period and through one additional year (through September 30, 2016), the end of the full study period. Follow-up was administratively censored at the end of this study period, or when the patient was no longer actively followed in the VHA system. This was determined by using data stored in CDW that records veterans' last healthcare utilization date (e.g. clinic visit, pharmacy event, physical therapy appointment, radiology exam).

Definition of the cohort and measured covariates

Pulmonary hypertension was identified by *ICD-9* diagnosis code as described above. Because diagnosis codes may be improperly used to "rule out" diagnoses, patients were excluded if the *ICD-9* code for PH did not 1) appear at least once on an inpatient claim, or 2) appear on at least 2 outpatient records/claims separated by at least 30 days during the study period (17). For each veteran in the cohort, the subtype of PH was classified based on comorbid diagnoses utilizing a modification of the currently accepted

clinical classification of PH (Table 1) (1). For instance, if an *ICD-9* code indicating systolic heart failure (428.8x) were present, the patient was categorized as Group 2 PH (PH-LHD), while if an *ICD-9* code for idiopathic pulmonary fibrosis (516.31) were present, the patient was categorized as Group 3 PH (PH due to lung diseases and/or hypoxemia). Because some patients have *ICD-9* codes spanning more than one clinical classification grouping (e.g. *ICD-9* codes for both systolic heart failure and idiopathic pulmonary fibrosis), we classified such patients as "Multiple causes, unclassifiable PH," which is not part of the clinical classification of PH (1), but was needed due to the nature of the current study. The use of administrative diagnosis codes to classify subtypes of PH for epidemiologic study has been applied in the past (18) and the method used in this study is minimally adapted.

Selected covariates available within the national CDW were collected based on review of existing literature and suspicion of playing a role in the development, progression, and/or outcome of PH-LHD. The covariates included demographic information, comorbid conditions, medication use, and measures of PH disease severity, as well as the outcome of interest.

Exposure of interest

The exposure of interest in the current study was whether included patients received PAH-targeted therapy. PAH-targeted therapies included those approved by the FDA for use in PAH (sildenafil, tadalafil, riociguat, bosentan, ambrisentan, macitentan, treprostinil administered by various routes, epoprostenol, and selexipag). These medications span three pharmacologic classes and were considered individually, by pharmacologic class, and as a whole. We identified receipt of these medications through

use of VA pharmacy domain within the CDW dataset. This domain includes all medications ordered and dispensed within the VHA, the date of order, date of dispensation, and complete prescription information including medication dose, instructions and days' supply dispensed. Medications prescribed and filled outside the VHA system and utilized by veterans at the time of VHA encounters are also available, but with less detail (e.g. dates dispensed). For analyses, the use of PAH-targeted therapy was defined as a binary variable—ever vs never on any PAH-targeted therapy. In separate analyses, PAH-targeted therapy was considered as a time-varying covariate—on vs off PAH-targeted therapy. For those analyses, being on two or more agents was considered the same as being on a single PAH-targeted therapy.

Outcome

Death data are available within CDW's Vital Status Files. The Vital Status Files collate death data from several sources including deaths in VA facilities, VA benefits claims, Social Security Administration, and Centers for Medicare & Medicaid Services. The CDW Vital Status Files have been validated against the National Death Index with a sensitivity of 98.3% and specificity of 99.8% (19). The National Death Index is the gold standard source for mortality data in the U.S. The beginning of the risk period for time to outcome analysis was the date of PH diagnosis, unless otherwise specified.

Statistical analyses

All statistical analyses were performed utilizing SAS Enterprise Guide software, Version 7.1 (SAS Institute, Cary, NC). Continuous variables are reported as means and standard deviation (SD) or median with interquartile ranges (IQRs). Categorical variables are reported as percentages unless otherwise noted. Comparisons of covariates between

groups were made by chi-square test or *t* test as appropriate. Variables displaying strongly non-normal distribution (e.g. levels of brain natriuretic peptide) were transformed and parametric tests were utilized for multivariable analysis. The primary outcome of time to death was assessed by Cox proportional hazards models (see more details below) with results presented as hazard ratios with 95% confidence intervals (CI). *P* values were calculated as two-sided and considered statistically significant when $P < 0.05$.

Predictors of receiving PAH-targeted therapy

Patients treated with PAH-targeted therapy were anticipated to differ from those never treated due to confounding by indication. We evaluated this suspicion through the use of propensity scores (20). For this procedure, we used logistic regression with an outcome of ever receiving any PAH-targeted therapy and 29 predictor variables that would be generally available to the clinician at the time of PH diagnosis and decision to pursue treatment. Because logistic regression methods exclude cases with missing data for any covariate, we evaluated missingness for the included variables and found that several laboratory values had missingness >3%. For those variables (all continuous), we established quartiles. For propensity score modeling, those variables were entered as categorical by quartiles with a separate category for missing using standard logistic regression. The resulting estimated probabilities for PAH-targeted therapy (propensity scores) were used as deciles. We separately performed propensity score matching using the PROC PSMATCH procedure. PROC PSMATCH was uses propensity scores to perform propensity matching without replacement using the greedy nearest-neighbor

strategy with inverse weighting (21). Treated patients were matched using this method to up to 10 untreated patients (i.e. 1:10).

Analysis of mortality in veterans with PH-LHD

We utilized date of initial PH diagnosis and date of death with censoring to estimate survival in veterans with PH-LHD. For the analysis, we utilized several approaches. First, we performed Cox proportional hazards regression analysis to generate unadjusted and adjusted hazard ratios for death (Figure 2, Model 1; primary analysis). The adjusted hazard ratios were generated using separate multivariable Cox proportional hazards regression using 1) clinically important covariates, 2) the propensity score decile as a categorical predictor, and 3) the full set of covariates used in the development of the propensity score (full model). Because treatment did not always begin at the time of PH diagnosis, and could be discontinuous after treatment was begun, we allowed PAH-targeted therapy to vary with time (Figure 2, Model 2). Specifically, we used counting process data format with start/stop dates for each use of PAH-targeted therapy based on available pharmacy data. For this analysis, we used the robust sandwich method to estimate the covariance matrix. Additionally, we analyzed the cohort of propensity-matched treated and untreated patients (Figure 2, Model 3).

Missing data

Data were missing for some variables. No variable used in the analysis had a high degree of missingness (>10%). With variables with modest rate of missingness (3-10%), we chose to categorize data and including a category for missing data. For variables with <3% missing values, we used complete case analysis.

RESULTS

Study Population Characteristics

From an estimated 22 million unique veterans with data available in the VHA CDW, a total of 205,147 had an *ICD-9* diagnosis code for PH used during their VHA care. Of these, 94,583 were excluded based on inclusion and exclusion criteria (Figure 3) and did not contribute to analyses or results. The most frequent exclusion was because the *ICD-9* diagnosis code was not utilized for ≥ 30 days as an outpatient or ever used as an inpatient. The remaining 110,564 patients constituted the overall cohort available for analyses. The cohort was predominantly male (n=106,629, 96.4%), overweight or obese (68.2%) and had a median age of 70.2 years (interquartile range [IQR], 62.1–79.6) (Table 2).

Of the 110,564 patients in our cohort, 8.0% (n=8,839) had Group 1 PAH and 16.1% (n=17,831) had Group 2 PH/PH-LHD (Table 2). The majority of patients (57.6%, n=63,641) had comorbid conditions that could indicate inclusion in more than one PH subgroup and were thus were unclassifiable. Other comorbidities that would not directly indicate a specific form of PH were also common in the cohort with left heart disease, diabetes, chronic obstructive pulmonary disease (COPD), and chronic kidney disease being most common. The majority of patients had evaluation with echocardiogram and CT chest imaging. However, heart catheterization procedures occurred in less than 10% of patients.

Baseline Characteristics and Survival in Veterans with PH-LHD

Veterans with PH-LHD, compared to PH due to other causes, were older, more commonly male, more likely to have comorbid renal disease, and had higher values for

brain natriuretic peptide (BNP) (Table 3). Median follow-up after PH-LHD diagnosis was 3.00 years [IQR 1.15–5.85]. Of the 17,831 veterans with PH-LHD, 11,973 (67.2%) died during study follow-up. The survival from diagnosis of PH-LHD to death was a median of 3.91 years (95% CI: 3.82, 4.01) (Figure 4).

Characteristics Associated with Mortality and the Effect of PAH-Targeted Therapy in PH-LHD

As in the overall cohort of patients with PH, there were significant associations of baseline characteristics with risk of death. Treatment with PAH-targeted therapy occurred in 511 (2.9 %) patients with PH-LHD. The large majority who were treated with PAH-targeted therapy received PDE5-inhibitors (data not shown). Patients who were treated had a median duration of 3.8 months between the initial *ICD-9* diagnosis code for PH and start of treatment. Unadjusted survival from the time of diagnosis differed between treated and untreated patients. The median survival from diagnosis was 5.21 years in treated patients and 3.88 years in untreated patients (Figure 5). Without adjustment, the use of PAH-targeted therapy was associated with a 26% lower risk of death (95% CI: 18%, 35%) (Table 4). Adjusting for age and gender resulted in an estimated null effect of treatment with PAH-targeted therapy on death.

Because of the perceived likelihood of confounding by indication in the use of PAH-targeted therapy, several analyses using propensity scores were performed. Twenty-nine variables were utilized in logistic regression model of probability of being ever treated with PAH-targeted therapy (versus never treated). The two groups (treated versus not treated) varied in almost all covariates (Table 2). Because some patients lacked complete data on all 29 covariates, 413/511 treated and 14,641/17,302 untreated were

included in the propensity score model. The c-statistic for the propensity model was 0.780.

Multivariable Cox proportional hazards regression of PAH-targeted therapy on risk of death incorporating the absolute propensity score or propensity score decile resulted in a null effect of treatment (Table 4). Similar findings were obtained with all baseline covariates directly included in the multivariable model (full model), without using the derived propensity score.

Because patients were not necessarily treated at the time of diagnosis, PAH-targeted therapy was also considered as a time-varying covariate in the analysis. Unadjusted for other covariates, being on therapy was associated with a 20% increased (95% CI: 15%, 25%) risk of death. This finding of increased risk of death remained and was greater when adjusting for propensity score decile. These findings may be related to the selective use of PAH-targeted therapies in later stages of disease, when adverse outcomes such as death would be more likely.

In a separate attempt to address confounding, we created a sub-cohort of patients in which treated patients were matched to untreated patients based on propensity score using inverse weighting and a 1:10 ratio with greedy matching method. Because of incomplete overlap in propensity score between treated and untreated patients, not all treated patients could be matched, and not all that were matched could be matched to 10 untreated patients. Thus, 406 treated patients were matched to 3,758 untreated patients. An example of the effect of adjusting for propensity score, and comparing matched patients on the difference between groups is demonstrated in Figure 6. A separate proportional hazards Cox analysis was performed in this propensity-matched cohort.

Unadjusted, there was no evidence of an effect of PAH-targeted therapy on death in the matched cohort.

Treatment with PAH-Targeted Therapies in the Overall Cohort with PH

Within the overall cohort, 4.3% of patients (n=4,723) were treated with PAH-targeted therapies. There were statistically significant differences in most measured variables (Table 2) between treated and untreated patients. Most notably, patients who received PAH-targeted therapies were younger (median age 65.9 vs 70.4 years, $P < 0.0001$) and of a non-white race. Of the guideline-recommended (2) studies for evaluation of a patient with PH, treated patients were more likely to have had each of the studies than untreated patients, except for echocardiogram (78.0% of treated, 86.9% of untreated patients).

Bivariable Analysis of Factors Associated with Mortality in the Overall Cohort with PH

Of the 110,564 veterans with PH in our cohort, 71,045 (64.3%) died during the study period. Median survival by Kaplan-Meier method was 3.88 years (95% CI: 3.84, 3.92) (Figure 7). In bivariable analyses of all patients with PH, there were significant associations of age, gender, and PH subtype with survival by Cox proportional hazards modeling (Table 5). Each 10-year increase in the age at which a diagnosis of PH was made, was associated with a 46% increase in risk of death. Male sex was associated with a 73% higher risk (HR 1.73, 95% CI: 1.65, 1.82) compared to female. Males with PH had a median survival of 3.81 years (95% CI: 3.77, 3.85) while females with PH had a median survival of 7.05 years (95% CI: 6.60, 7.46). Survival also varied by the subtype of PH (Table 5 and Figure 4). Group 1 PAH, which included 8,839 patients, had a median survival of 8.35 years (95% CI: 8.09, 8.64). Group 2 PH-LHD and Group 3 PH due to

lung disease each had worse survival than PAH with median survival of 3.91 years (95% CI 3.82, 4.01) and 5.41 years (95% CI: 5.41, 5.27), respectively. Notably, patients with PH due to multiple causes (e.g. had comorbid conditions included in two separate PH subtypes) had poorest survival. Median survival in that group was 3.02 years (95% CI: 2.98, 3.07).

DISCUSSION

We have developed a retrospective longitudinal cohort of veterans receiving care in the VHA system and diagnosed with pulmonary hypertension. Our cohort, with a total of 110,564 patients, is the largest of its type reported. Due to the nature of the VHA's population of veteran patients, our cohort is predominantly male (96.4%) and includes patients that are on average older than reported registries of pulmonary hypertension. Most registries of PH include predominantly or exclusively patients with the subtype Group 1 PAH with the largest having approximately 3,500 patients (3, 22). In contrast, our cohort is a rich resource for the study of patients with significant comorbidities and PH due to other causes. For example, many comorbid conditions that do not directly cause PH, but may influence a patient's disease course, were very common. Over half of patients carried a diagnosis of chronic kidney disease. Similarly, diabetes mellitus was diagnosed in the majority. Some diseases that are known to be associated with PH were uncommon in our cohort. For example, HIV was present in 0.8%, and connective tissue disease in 7.3%. Our cohort contains a large number of patients with diagnosed chronic left-sided heart disease and/or chronic lung disease. Chronic left-sided heart disease and chronic lung disease are well known to contribute to PH and either can cause PH in isolation of other causes. In our cohort, the majority had comorbid diagnoses of both chronic left-sided heart disease and chronic lung diseases. In fact, 58% were unable to be specifically classified into a PH subtype based on their comorbid conditions due to multiplicity. These patients were not analyzed in detail, but were noted in unadjusted analysis to have worse survival than any of the traditional PH subgroups.

There were 17,831 veterans that were diagnosed with PH during our cohort entry period who only had comorbid left-sided heart disease as a potential cause of their PH, and so were classified as PH-LHD subtype. Veterans with PH were also commonly found to have comorbid lung disease as the only potential cause of PH (n=18,382). Patients with PH due to chronic left-sided heart or lung disease are not the usual target of PAH-targeted therapies; by definition they do not have confirmed PAH and PAH-targeted therapies have no established efficacy in non-PAH forms of PH. Guidelines do not recommend use of PAH-targeted therapies in these subtypes (2). Regardless, some patients with these types are treated in the clinical setting even in expert PAH treatment centers (12). Our cohort demonstrates that only a minority of veterans with non-PAH forms of PH receive PAH-targeted therapies (4.2% in our cohort) in the VHA system. It is unknown how frequent this therapy is utilized in other settings, but it is suspected to be utilized more frequently than what we found in veterans cared for in VHA facilities. This may suggest that the use of national formularies, established pharmacy protocols, and the oversight of clinical pharmacists may reduce the frequency of off-label therapy.

In 17,831 veterans with PH-LHD, 511 (2.9%) were treated with PAH-targeted therapy. Those patients who were treated differed in baseline demographics compared to those untreated. Most notably, treated patients were younger. They were diagnosed with PH at median age 65.1 (IQR 57.6–75.5), while those never treated were diagnosed with PH at median age 73.1 (IQR 62.4–82.1). Without correction for baseline differences, we observed an average benefit of PAH-targeted therapy (HR 0.74, 95% CI: 0.65, 0.82). However, with adjustment for baseline difference using various methods, no effect of therapy was seen (Table 4). This is not surprising overall as even in the subtype PAH,

where these treatments have proven benefit and FDA-approval, a survival benefit has rarely been demonstrated in prospective clinical trials (2, 4). Rather, those studies, with increasing enrollment have demonstrated improved outcome in terms of endpoints that assess morbidity rather than mortality. For example, the two most recent clinical trials leading to approval of new PAH-targeted therapy were that for macitentan and selexipag (23, 24). Those studies enrolled 742 and 1,156 patients, respectively. Both studies used composite outcome design with one element of the composite being mortality. Neither study demonstrated a survival difference between groups treated with the agent under study. The outcome of both studies were driven by "clinical worsening" of pulmonary hypertension, most frequently indicated by hospitalization. In contrast to this retrospective study, the majority of patients in those two studies were on additional "background" PAH-targeted therapies. In the present retrospective analysis, we analyzed patients based on having any PAH-targeted therapy versus none.

Furthermore, our study's retrospective nature demonstrated that clinical decision making differs markedly from randomized trials as evidenced by differences in all baseline characteristics between patients who received and did not receive PAH-targeted therapies. These potential confounding factors were found to be the major determinant of death, rather than the use of PAH-targeted therapy itself. Most notably, subjects with PH-LHD who were treated with PAH-targeted therapy were several years younger on average than those who were not treated. This difference in age accounted for the difference in outcome seen (demonstrated in a model including only age and treatment as predictors). Clinicians' experience treating these younger patients may reinforce their biased opinion that PAH-targeted therapies improve disease risk. However, when we

analyzed PAH-targeted therapy as a time-varying covariate, we demonstrated that when patients with PH-LHD are treated (some time after their PH-LHD diagnosis), their risk of death is significantly higher than not being on therapy. Our time-varying treatment may be influenced by lead-time bias, as subjects in the later stages of a disease are more likely to have adverse outcome(s). Alternatively, this may demonstrate that when these therapies are used, clinicians are doing so in subjects who are destined to have a near term poor outcome, e.g. it is "too little, too late".

Our study was a retrospective analysis of data collected for clinical and administrative use and has several important limitations. First, our study relied on *ICD-9* codes for determining whether patients had PH and to which subtype they best fit. While this is an inherent limitation that may result in misclassification bias, it allowed us to capture a larger cohort for analysis and the captured cohort resembled those in previously published single-center studies (25, 26). Second, the veterans in our cohort were evaluated and treated in the course of routine clinical care and thus, our exposure of interest, PAH-targeted therapy, could be influenced by confounding by indication. To address this, we matched patients on their propensity for treatment using data ondemographics, laboratory measures, the evaluation studies that a patient had, and their comorbidities which may influence a physicians' tendency to utilize PAH-targeted therapy. This approach allows patients who were treated and untreated to be "leveled" in their underlying likelihood of receiving PAH-targeted therapy, based on observed covariates. However, we cannot assure that additional variables not available in our dataset influenced treatment decisions and biased the outcomes reported here. In addition to residual confounding between treated and untreated patients, there is the possibility for

misclassification between patients treated and untreated. The majority of data in our dataset regarding PAH-targeted therapy was available in our source dataset in patients treated at VHA facilities and receiving medications from VHA pharmacies. However, some patients (e.g. those with private payer insurance) may receive PAH-targeted treatment outside the VHA system and could be misclassified in the exposure of interest. If the misclassification were nondifferential with respect to PAH-targeted therapy and mortality, this would be expected to bias our results towards the null. A third limitation regards uncertainty on PH disease severity. An important part of PH patient assessment is that of disease severity (2, 6). We were unable to account for disease severity by the most commonly used clinical criteria—NYHA/WHO functional classification—as it was not available in our source dataset. Additionally, right heart catheterization is a means to confirm and measure the severity of PH. This invasive test is often performed at VHA centers and we were able to assess for whether it had been performed, but were unable to include data from the study itself. Manual chart review would allow inclusion of that data, but are impractical in a dataset the size presented here. Fourth, our main outcome was death, which could possibly be misrepresented. While death has been shown to be accurately captured in VHA datasets (19) we were unable to use additional data sources to confirm dates of death. Lastly, our study may not be generalizable to other populations of patients with PH. Because our study included only veterans receiving care in the VHA system, it may not apply to other veterans, or non-veterans. Additionally, our cohort was predominantly male, so interpretation and application of our findings to females should be done with caution. Despite limitations, this cohort is a valuable tool for ongoing study of pulmonary hypertension, especially that due to comorbid heart or lung disease.

In conclusion, we have demonstrated that the VHA system cares for a large number of patients with PH, many of whom have PH-LHD as the underlying subtype. PAH-targeted therapy was used infrequently in this retrospective cohort study, suggesting that it was applied to a highly selected population. Our analyses of the effect of this therapy suggest that the population in which it is used has a lower risk of death, but we observed no independent association between PAH-targeted therapy. Further study of PAH-targeted therapy should be performed to assess additional relevant patient-oriented outcomes including frequency of hospitalization. Additionally, patients with PH due to lung disease or due to multiple causes is common in veterans, carries a high risk of mortality, and should be evaluated further in this retrospective dataset.

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TABLES / FIGURES

Table 1: Schema for classification of pulmonary hypertension in veterans by *ICD-9* diagnosis code usage.

PH Grouping Designation	**Included *ICD-9* Codes**
Group 1, PAH	416.0, 416.8, 416.9 (Excluded if meeting any of the below)
Group 2, PH due to left heart disease	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx
Group 3, PH due to lung diseases and/or hypoxemia	490.xx–496.xx, 500.xx–508.xx, 515.xx, 516.xx, 517.1, 517.2, 327.23
Group 4, chronic thromboembolic PH	416.2
Group 5, PH with unclear multifactorial mechanisms	282.0x, 282.4x, 282.6x, 271.xx, 272.7
Multiple causes, unclassifiable	Patients with ICD-9 diagnosis codes included in more than 1 of Groups 2, 3, 4, and/or 5 above

ICD-9 codes of 416.0, 416.2, 416.8, 416.9 were required to be present for inclusion.

PAH, pulmonary arterial hypertension; PH, pulmonary hypertension

Table 2. Characteristics of U.S. veterans with pulmonary hypertension receiving care in the Veteran Health Administration system, 01/01/2003-09/30/2015.

Clinical variable	Full cohort	PAH-targeted therapy	
N	110,564	Yes, 4,723	No, 105,841
Age, median [IQR]	70.2 [62.1–79.6]	65.9 [59.2–75.0]	70.4 [62.2–79.8]
Gender, N (%)			
Male	106,629 (96.4%)	4,464 (94.5%)	102,165 (96.5%)
Female	3,933 (3.6%)	259 (5.5%)	3,674 (3.5%)
Unknown / Missing	2 (0.0%)	0 (0.0%)	2 (0.0%)
Race, N (%)			
Black	18,211 (16.5%)	930 (19.7%)	17,281 (16.3%)
White	81,265 (73.5%)	3,227 (68.3%)	78,038 (73.7%)
Other race	2,119 (1.9%)	112 (2.4%)	2,007 (1.9%)
Race missing	8,969 (8.1%)	454 (9.6%)	8,515 (8.1%)
BMI, median [IQR], kg/m^2	29.1 [24.8–34.8]	29.4 [25.5–34.4]	29.1 [24.8–34.9]
BMI classification, N (%)			
Underweight	2,834 (2.6%)	60 (1.3%)	2,774 (2.6%)
Normal	23,632 (21.4%)	915 (19.4%)	22,717 (21.5%)
Overweight	29,247 (26.5%)	1,317 (27.9%)	27,930 (26.4%)
Obese	46,086 (41.7%)	2,034 (43.1%)	44,052 (41.6%)
Follow-up, median [IQR], years	2.9 [1.2–5.5]	3.3 [1.7–5.6]	2.8 [1.1–5.5]
Studies within 1 year of diagnosis, N (%)			
Echocardiogram	95,636 (86.5%)	3,682 (78.0%)	91,954 (86.9%)
Chest CT	60,717 (54.9%)	2,881 (61.0%)	57,836 (54.6%)
V/Q imaging scan	12,667 (11.5%)	1,096 (23.2%)	11,571 (10.9%)
Pulmonary function testing	57,136 (51.68%)	2,957 (62.6%)	54,179 (51.2%)
Left heart catheterization	8,646 (7.8%)	467 (9.9%)	8,179 (7.7%)
Right heart catheterization	8,341 (7.5%)	875 (18.5%)	7,466 (7.1%)
Six minute walk test	6,489 (5.9%)	698 (14.8%)	5,791 (5.5%)
Selected comorbidities, N (%)			
Left heart disease	86,444 (78.2%)	3,375 (71.5%)	83,069 (78.5%)
Diabetes	61,309 (55.5%)	2,469 (52.3%)	58,840 (55.6%)
COPD	72,501 (65.6%)	3,145 (66.6%)	69,356 (65.5%)
Interstitial lung disease	13,032 (11.8%)	1,089 (23.1%)	11,943 (11.3%)
HIV	861 (0.8%)	68 (1.4%)	793 (0.8%)
Liver cirrhosis	21,307 (19.3%)	1,028 (21.8%)	20,279 (19.2%)
Chronic kidney disease	63,033 (57.0%)	2,382 (50.4%)	60,651 (57.3%)
Connective tissue disease	8,117 (7.3%)	623 (13.2%)	7,494 (7.1%)
Lab data, median [IQR]			
BNP (pg/mL)	497 [164–1,462]	411 [136–1,117]	501 [165–1,476]
Creatinine (mg/dL)	1.2 [0.9–1.5]	1.2 [0.9–1.4]	1.2 [0.9–1.5]
Sodium (mEq/L)	139 [136–141]	139 [137–141]	139 [136–141]
PH subtype, N (%)			
Group 1 PAH	8,839 (8.0%)	455 (9.6%)	8,384 (7.9%)
Group 2 PH-LHD	17,831 (16.1%)	511 (10.8%)	17,320 (16.4%)
Group 3 PH, lung disease	18,382 (16.6%)	1,177 (24.9%)	17,205 (16.3%)
Group 4 CTEPH	1,562 (1.4%)	51 (1.1%)	1,511 (1.4%)
Group 5 miscellaneous PH	309 (0.3%)	31 (0.7%)	278 (0.3%)
PH with multiple causes	63,641 (57.6%)	2,498 (52.9%)	61,143 (57.8%)

P values are calculated by two sample *t* tests or Chi-square tests as appropriate and are corrected for multiple comparisons. Two-sided *P* value calculated as alpha=0.05. *P* value was <0.0001 for all variables listed in the table. BMI, body mass index; IQR, interquartile range; V/Q, ventilation-perfusion nuclear scintigraphy; COPD, chronic obstructive pulmonary disease; BNP, brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension due to left heart disease; CTEPH, chronic thromboembolic pulmonary hypertension. BMI is reported as kg/m^2 and classified by accepted standards: Underweight BMI is less than 18.5, normal BMI is 18.5 to 24.9, overweight BMI is 25 to 29.9, and obese is BMI 30 or higher.

Table 3. Characteristics of U.S. veterans (2003-2015) with pulmonary hypertension due to left-sided heart disease, compared to all veterans with pulmonary hypertension.

	Overall Cohort (n=110,564)	**PH-LHD (n=17,831)**	***P* Value**
Age at PH Diagnosis			<0.0001
Median [IQR]	70.2 [62.1–79.6]	72.8 [62.2–82.0]	
Mean (±SD)	70.4 (±11.6)	71.8 (±12.4)	
Gender, N (%)			<0.0001
Male	106,629 (96.4%)	17,311 (97.1%)	
Female	3,933 (3.6%)	520 (2.9%)	
Race, N (%)			<0.0001
Black	18,211 (16.5%)	3,740 (21.0%)	
White	81,265 (73.5%)	12,178 (68.3%)	
Other race	2,119 (1.9%)	361 (2.0%)	
Race missing	8,969 (8.1%)	1,552 (8.7%)	
BMI, median [IQR], kg/m^2	29.1 [24.8–34.8]	28.2 [24.6–32.7]	<0.0001
BMI classification, N (%)			<0.0001
Underweight	2,834 (2.6%)	273 (1.5%)	
Normal	23,632 (21.4%)	4,289 (24.1%)	
Overweight	29,247 (26.5%)	5,585 (31.3%)	
Obese	46,086 (41.7%)	6,279 (35.2%)	
BMI missing	8,765 (7.9%)	1,405 (7.9%)	
Lab data, median [IQR]			
Baseline BNP (pg/mL)	497 [164–1,462]	883 [350–2,395]	<0.0001
Baseline creatinine (mg/dL)	1.2 [0.9–1.5]	1.3 [1.0–1.8]	<0.0001
Baseline sodium (mEq/L)	139 [136–141]	139 [136–141]	<0.0001
Selected comorbidities, N (%)			
Diabetes mellitus	61,309 (55.5%)	10,356 (58.1%)	<0.0001
Liver disease	21,307 (19.3%)	3,477 (19.5%)	0.40
Renal disease	63,033 (57.0%)	11,917 (66.8%)	<0.0001
Follow-up, median [IQR], years	2.8 [1.2–5.5]	3.0 [1.2–5.9]	<0.0001
Outcome			
Follow-up, yr, median [IQR]			
Death during follow-up, N (%)	71,045 (64.3%)	11,973 (67.2%)	<0.0001
Hosp (events/yr), median [IQR]	0.5 [0.0–1.8]	0.5 [0.0–1.8]	<0.0001
Hosp (events/yr), mean (±SD)	1.8 (±4.7)	1.9 (±4.7)	<0.0001

Comparisons are between patients with PH-LHD and all those with other forms of PH. *P* values are calculated by two sample *t* tests or Chi-square tests and corrected for multiple comparisons. Two-sided *P* value calculated as alpha=0.05. *P* value was <0.0001 for all variables listed in the table except history of liver disease (*P*=0.40). Abbreviations are the same as those in Table 2.

Table 4. Effect of PAH-targeted treatment vs. no treatment on death in veterans with PH-LHD.

Effect of Treatment	Death during follow up		
	Hazard Ratio	95% CI	P-value
PH-LHD total cohort			
Unadjusted	0.74	[0.65, 0.82]	<.0001
Adjusted (age, gender)	0.91	[0.80, 1.03]	0.13
Adjusted (all PS covariates)	1.03	[0.91, 1.16]	0.69
Adjusted (PS, continuous variable)	1.01	[0.89, 1.15]	0.86
Adjusted (stratified by PS decile)	1.02	[0.89, 1.16]	0.81
Time-varying, unadjusted	1.20	[1.15, 1.25]	<.0001
Time-varying, stratified by PS decile	1.46	[1.27, 1.68]	<.0001
PH-LHD matched cohort			
PS-matched (1:10)	0.96	[0.77, 1.19]	0.71

CI, confidence interval; PS, propensity score

Table 5: Hazard ratio for death for selected covariates, all veterans with PH.

Covariate	Death during follow up		
	Hazard Ratio	95% CI	*P* value
Gender (Male vs Female)	1.73	[1.65, 1.82]	<.0001
Age (each 10 y)	1.46	[1.45, 1.47]	<.0001
PH Group			
Group 1 PAH	Reference		
PH-LHD (vs Group 1 PAH)	2.02	[1.95, 2.09]	<.0001
PH-LHD (adj for gender, age)	1.96	[1.89, 2.03]	<.0001
Group 3 PH, lung disease	1.53	[1.47, 1.58]	<.0001
Group 4 CTEPH	0.75	[0.68, 0.83]	<.0001
Group 5 miscellaneous PH	0.91	[0.76, 1.08]	0.27
PH with multiple causes	2.49	[2.41, 2.57]	<.0001
Ever use PAH-targeted therapy	0.88	[0.85, 0.92]	<.0001

CI, confidence interval; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension due to left heart disease; PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension.

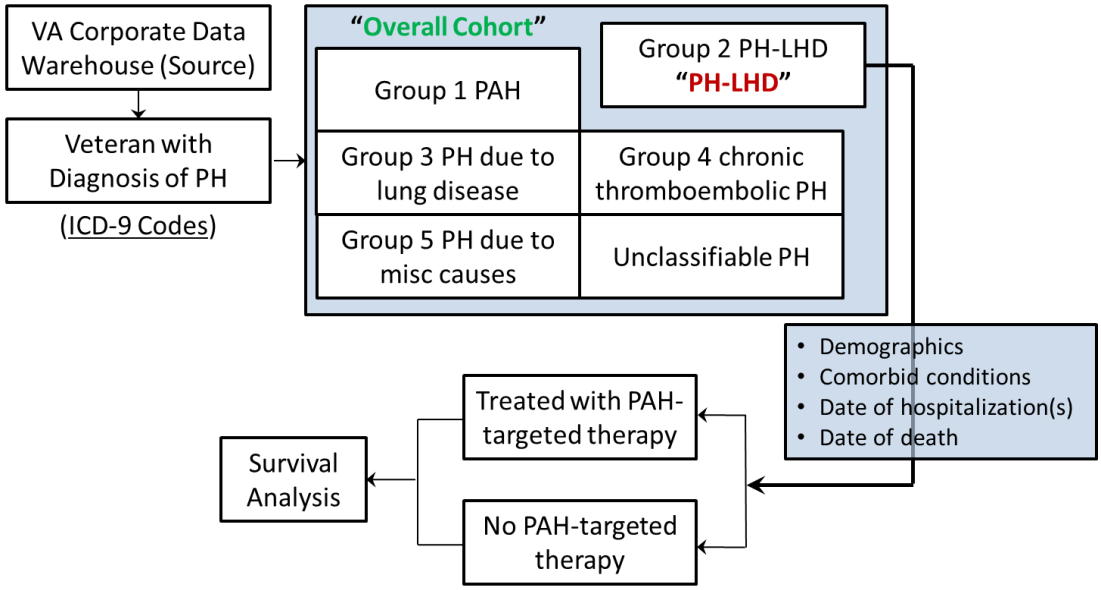


Figure 1. Study diagram of retrospective cohort study to evaluate subtypes, treatment and outcome of veterans with pulmonary hypertension. PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; misc, miscellaneous.

Models for regression are stated:

Model 1: $h(t) = h_0(t)\exp(\beta_1 \text{Predictor} + \sum(\gamma_i \text{Covariate}_i))$

Model 2: $h(t) = h_0(t)\exp(\beta_1 \text{Treat} + \sum(\gamma_i \text{Covariate}_i))$

Model 3: $h_g(t) = h_{0g}(t)\exp(\beta_1 \text{Treat})$ where $g = \text{Match}_i$, i 1 to 406)

Figure 2. Models for Cox proportional hazards analysis.

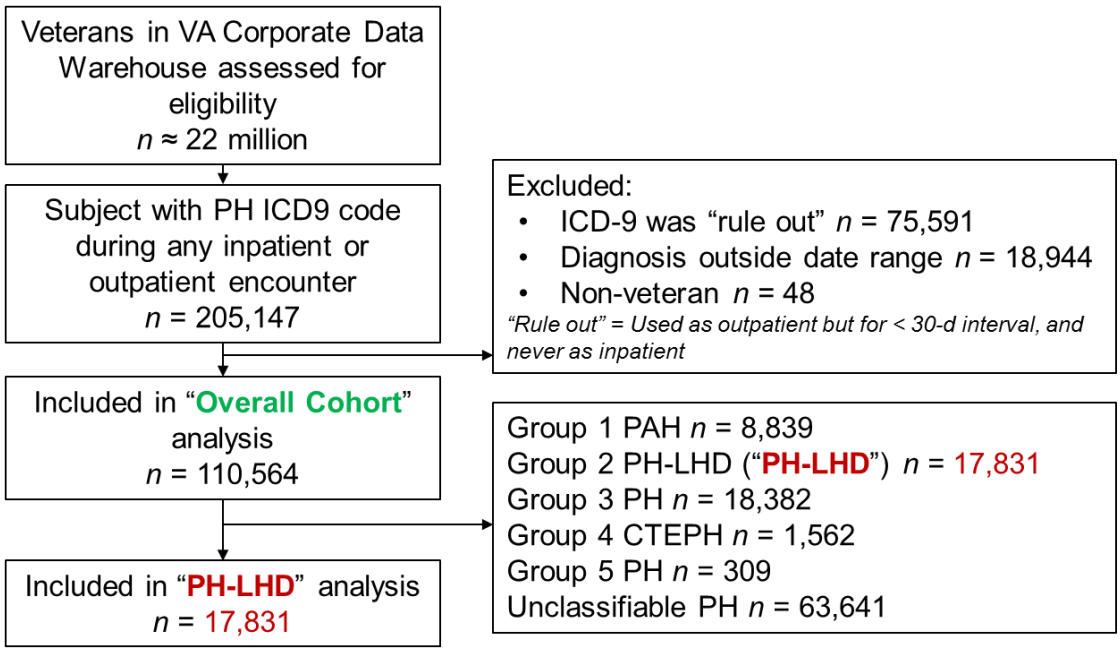
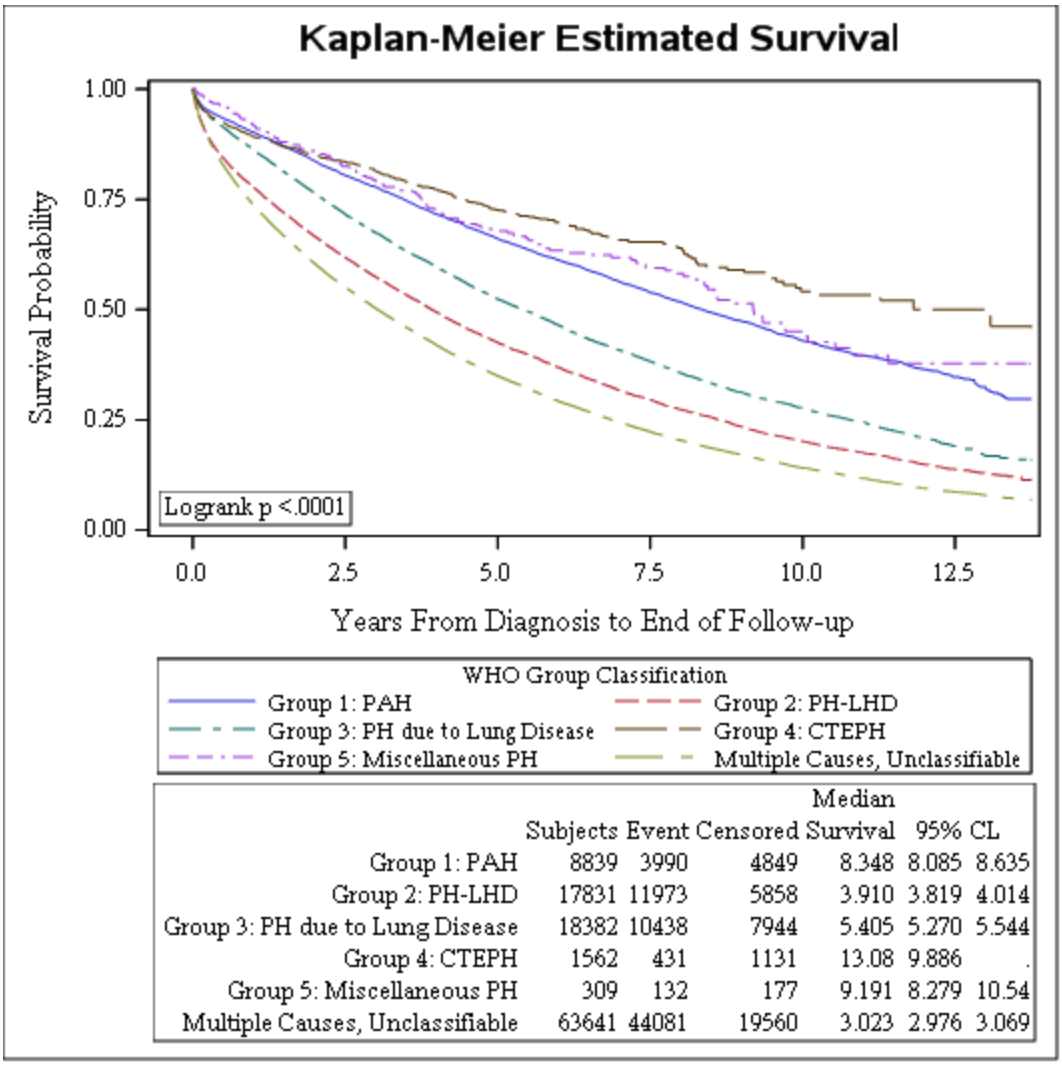


Figure 3. Cohort flow diagram for study.



	Subjects	Event	Censored	Median Survival	95% CL	
Group 1: PAH	8839	3990	4849	8.348	8.085	8.635
Group 2: PH-LHD	17831	11973	5858	3.910	3.819	4.014
Group 3: PH due to Lung Disease	18382	10438	7944	5.405	5.270	5.544
Group 4: CTEPH	1562	431	1131	13.08	9.886	.
Group 5: Miscellaneous PH	309	132	177	9.191	8.279	10.54
Multiple Causes, Unclassifiable	63641	44081	19560	3.023	2.976	3.069

Figure 4. Kaplan-Meier survival curve for veterans with pulmonary hypertension, stratified by subtype, unadjusted.

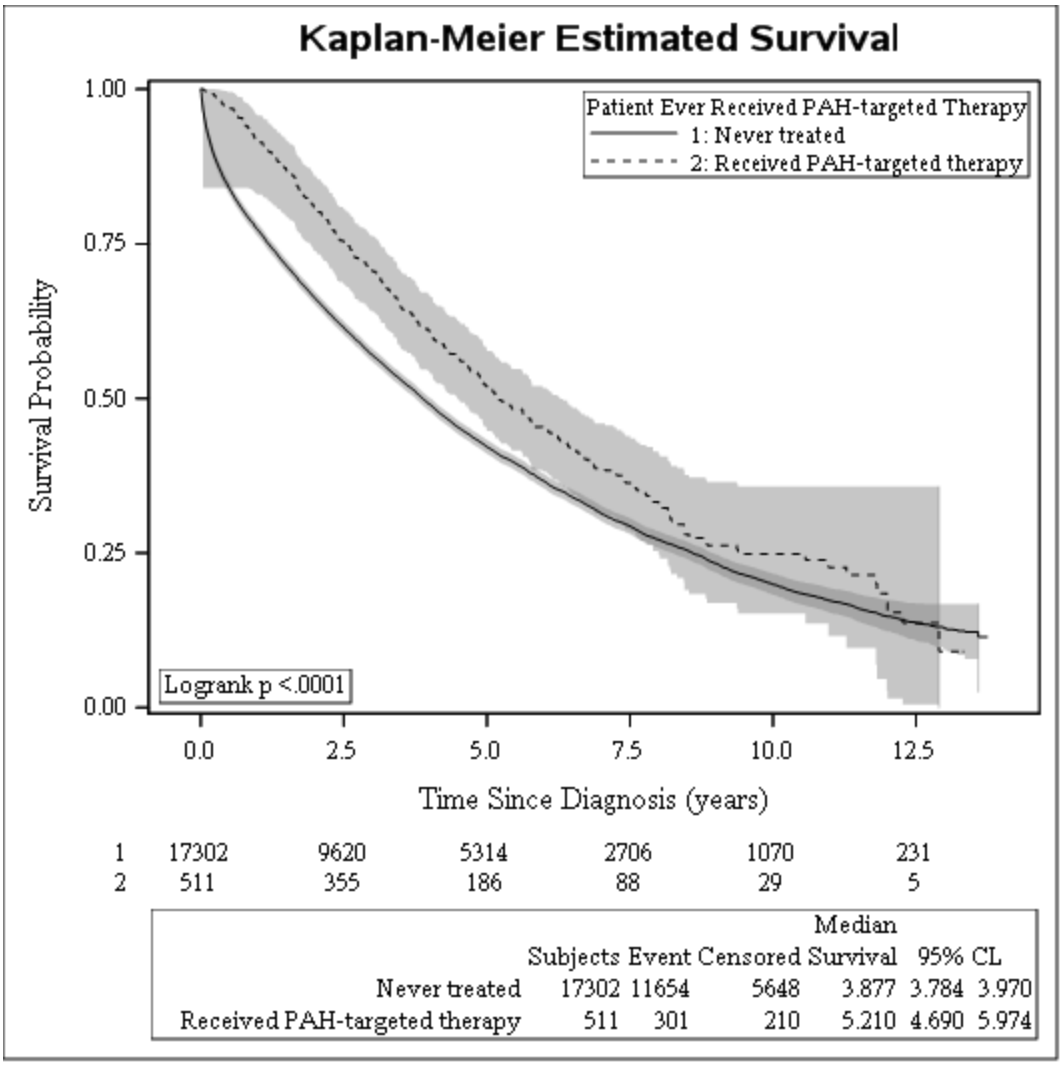


Figure 5: Kaplan-Meier survival curve for veterans with pulmonary hypertension due to left heart disease, stratified by treatment status, unadjusted.

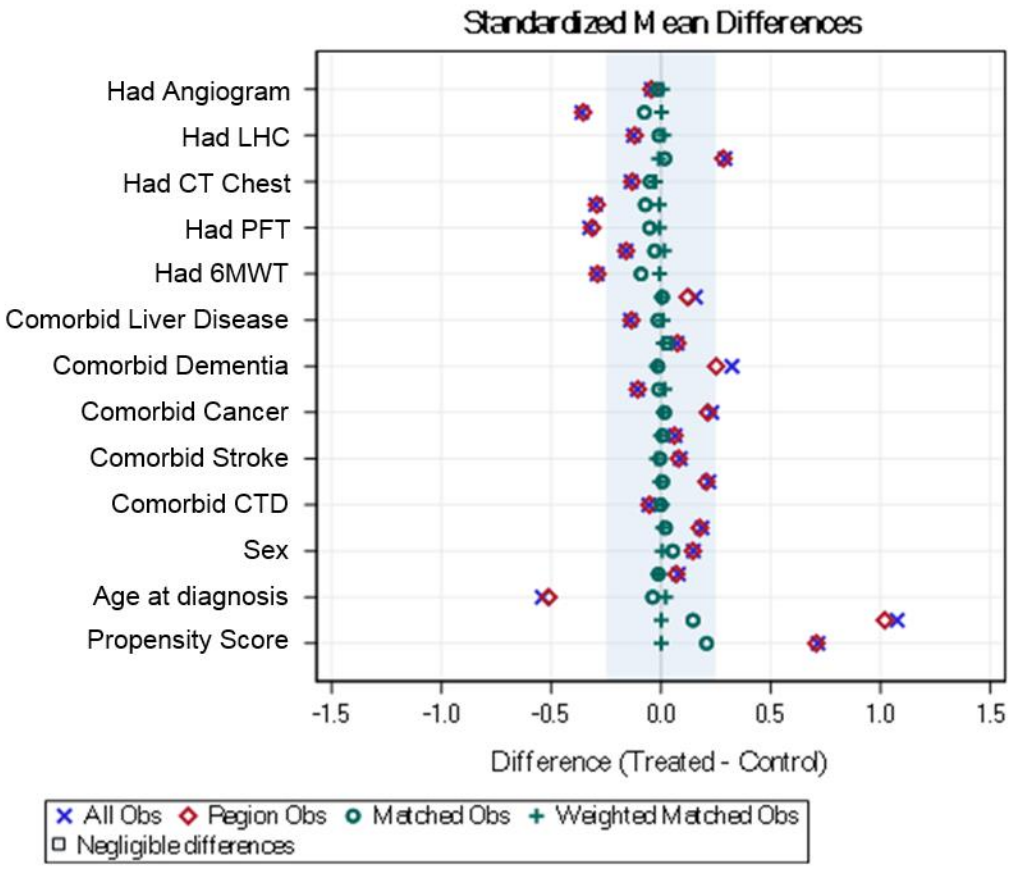


Figure 6: Differences between treated and untreated patients and effect on balancing of selected covariates by propensity matching.

Mean differences are given between treated and untreated observations. Comparisons are represented in the figure for all observations in the propensity analysis (blue x), those within a region of compatibility (red triangle), between matched observations (green circle) and matched observations with inverse weighting (green plus). The region of compatibility is defined as the region of propensity score overlap between treated and untreated subjects. Treated subjects with propensity scores higher than any untreated subjects, and untreated subjects with propensity scores lower than any treated subjects are excluded. LHC indicates left heart catheterization; PFT, pulmonary function testing; CTD, connective tissue disease.

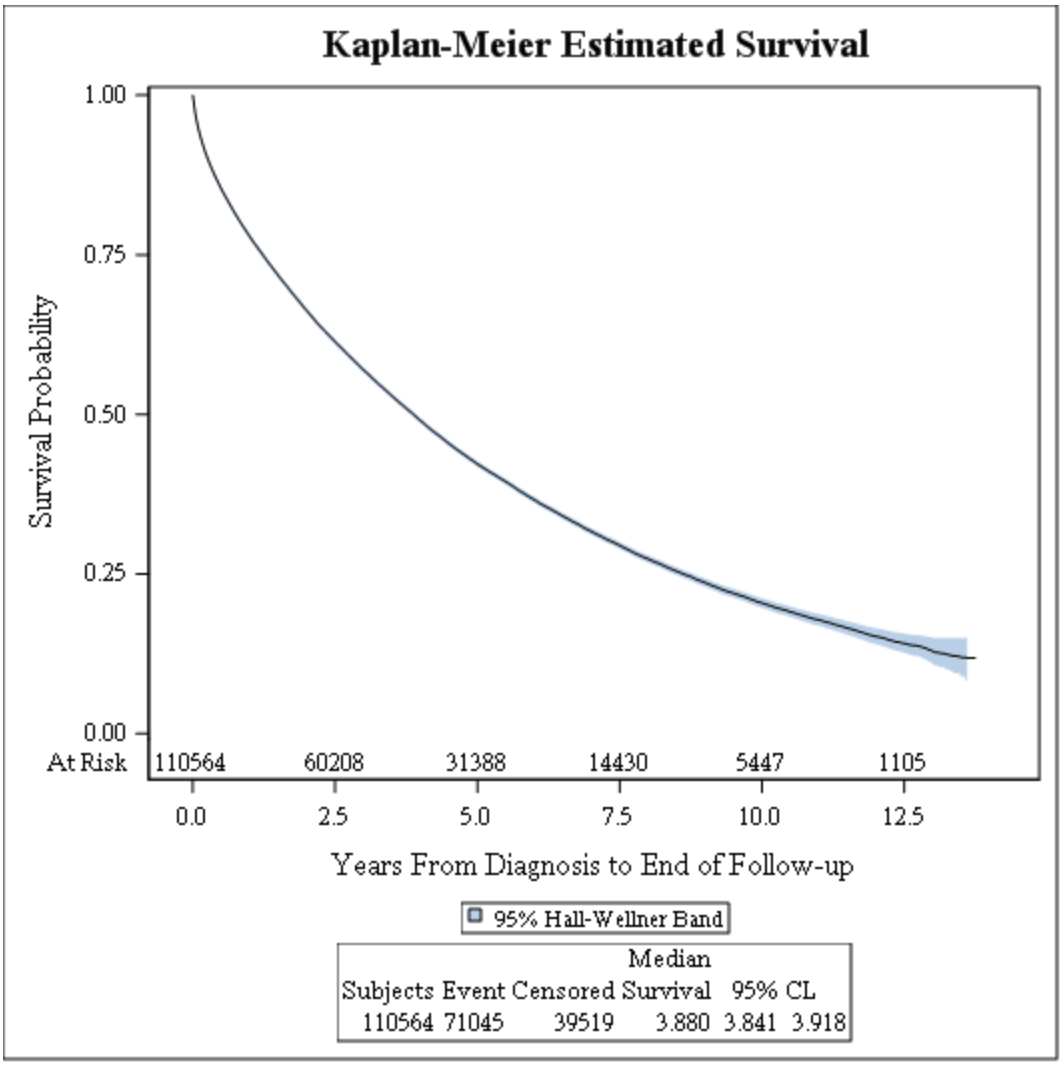


Figure 7. Kaplan-Meier survival curve for veterans with pulmonary hypertension diagnosed between 01/01/2003 and 09/30/2015 and receiving care in the VHA system.

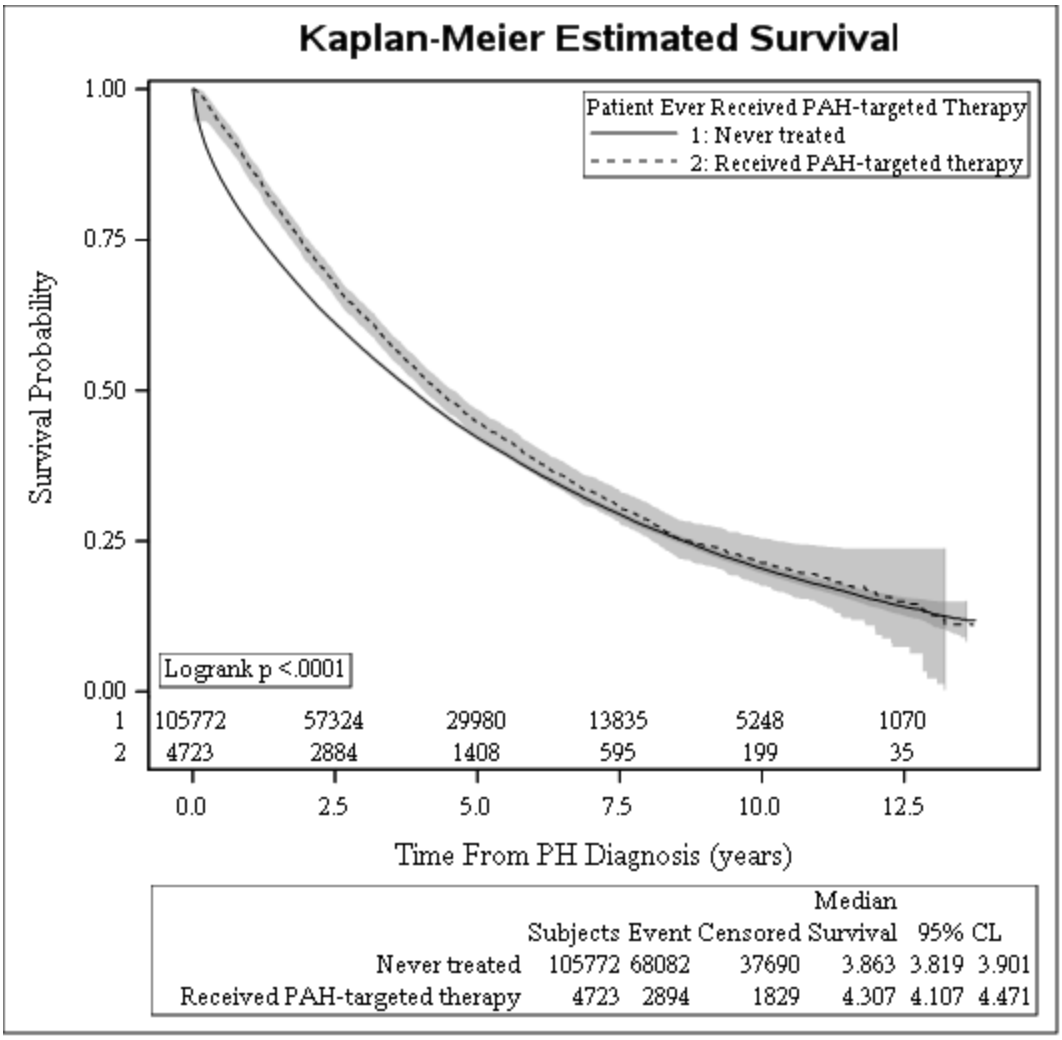


Figure 8: Kaplan-Meier survival curve for veterans with pulmonary hypertension, stratified by treatment status, unadjusted. Includes all veterans with PH.