ORIGINAL RESEARCH

Antifibrotic Drug Use in Patients with Idiopathic Pulmonary Fibrosis

Data from the IPF-PRO Registry

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Abstract

Rationale: Two antifibrotic medications, nintedanib and pirfenidone, have been approved for the treatment of idiopathic pulmonary fibrosis (IPF) in the United States. Few data have been published on the use of these medications in clinical practice.

Objectives: To investigate patterns of use of antifibrotic medications in the United States.

Methods: The Idiopathic Pulmonary Fibrosis Prospective Outcomes (IPF-PRO) Registry, a multicenter U.S. registry, has enrolled patients with IPF that was diagnosed or confirmed at the enrolling center in the past 6 months. Data from patients enrolled from June 5, 2014, to March 4, 2018, were used to determine antifibrotic medication use ("treatment") in the enrollment window and in a follow-up window approximately 6 months later. Associations between patient characteristics and treatment status were tested using logistic regression.

Results: Overall, 551 of 782 eligible patients (70.5%) were treated in the enrollment window. Younger age, lower forced vital capacity percentage predicted, oxygen use with activity, worse self-rated health (based on the Short Form 12 or St. George's Respiratory Questionnaire score), referral to the enrolling center by a pulmonologist, use of a lung biopsy in diagnosis, and carrying a diagnosis of IPF to the enrolling center were associated with being treated. Among 534 patients treated at enrollment who had follow-up data, 94.0% remained treated in follow-up. Better self-rated health (based on the Short Form 12 mental component score or EuroQoL score) and not using oxygen with activity at enrollment were associated with continuing treatment in follow-up. Among 172 patients who were untreated at enrollment and had follow-up data, 29.7% started treatment in follow-up. Lower diffusing capacity of the lung for carbon monoxide percentage predicted, a family history of interstitial lung disease, a history of sleep apnea, and a definite diagnosis of IPF at enrollment were associated with starting treatment in follow-up.

Conclusions: The majority of patients in the IPF-PRO Registry were receiving an approved medication for IPF at enrollment. Treatment at enrollment was associated with greater disease severity, more compromised quality of life, and the use of oxygen with activity.

Clinical trial registered with ClinicalTrials.gov (NCT01915511).

Keywords: idiopathic pulmonary fibrosis; interstitial lung disease; treatment; clinical practice patterns

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A complete list of members may be found before the beginning of the References.

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Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease (ILD) characterized by a decline in lung function and high mortality (1). Two antifibrotic drugs, nintedanib and pirfenidone, have been approved for the treatment of IPF. In placebo-controlled clinical trials (2–5), these treatments slowed the progression of IPF, as demonstrated by a reduction in the rate of decline in forced vital capacity (FVC). Pooled data from these trials suggest that these drugs may also improve survival (6, 7). Use of either drug is conditionally recommended in the latest American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) treatment guidelines for IPF, indicating that the majority of individuals would want such a treatment, but many would not, and emphasizing the consideration of patient preferences in decision-making (8).

The IPF Prospective Outcomes (IPF-PRO) Registry (NCT01915511) is a multicenter longitudinal U.S. registry of patients with IPF (9). The IPF-PRO Registry is coordinated by the Duke Clinical Research Institute and funded by Boehringer Ingelheim Pharmaceuticals, Inc, and aims to improve knowledge of the natural history of IPF, its impact on patients, and current practices in its diagnosis and management. The data collected in the registry provide an opportunity to investigate the use of antifibrotic therapies in patients with IPF, allowing a better understanding of prescribing patterns and the factors that may influence them. We used data from the IPF-PRO Registry to investigate antifibrotic drug use at enrollment and during short-term follow-up, associations between patient characteristics at enrollment and antifibrotic drug use at enrollment and during follow-up, and the characteristics of patients treated with antifibrotic drugs in the registry relative to the eligibility criteria used in Phase III trials of nintedanib and pirfenidone.

Methods

The design of the IPF-PRO Registry has been published (9). Patients with IPF that was diagnosed or confirmed at the enrolling center in the past 6 months were eligible provided that they were not listed for lung transplantation or participating in a randomized clinical trial at the time of enrollment (these events were allowed after enrollment). Enrollees are followed prospectively while receiving the usual care, with follow-up data collected approximately every 6 months.

This analysis included patients enrolled between June 5, 2014 (registry inception) and March 4, 2018 (9 mo before data extraction on December 3, 2018, selected to allow for adequate follow-up time in the registry to assess treatment in the follow-up window). Patients in the analysis cohort were defined as "treated" or "untreated" with antifibrotic medication in the "enrollment window" and the "first follow-up window" approximately 6 months later (Table 1). Briefly, if the start and/or stop date for either drug was before or within the first 3 months after enrollment or "yes" was marked for antifibrotic medication use on the enrollment case report form, the patient was treated at enrollment. If medication start and/or stop dates or a "yes" mark on the case report form indicated treatment use between 3 and 8 months after enrollment, the patient was treated in the first follow-up window. Patients with missing data on antifibrotic medication use at enrollment were excluded from all analyses. Patients with missing data on antifibrotic medication use in the first follow-up window were excluded from analyses investigating treatment use after enrollment.

The collection of patient-specific variables in the IPF-PRO Registry has been described (9). Continuous variables are presented as median (25th–75th percentile), and categorical variables are presented as the number (proportion) of participants.

FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}) data were converted to percent-predicted values using the equations published by Hankinson and Crapo, respectively (10, 11). D_{LCO} data were corrected for hemoglobin level using the formula published by Macintyre (12).

Associations between patient characteristics at enrollment and treatment use in the enrollment window and the first follow-up window were examined to determine which characteristics were associated with treatment use at enrollment, which characteristics were associated with continuing treatment in the follow-up interval, and which characteristics were associated with starting treatment during the follow-up interval. Univariable logistic regression models were used, with the untreated group as the reference/comparator. Statistical significance was defined as a P value of less than 0.05. Continuous patient characteristics were assessed for linearity using a lack-of-fit test that compared a linear fit with a nonlinear fit based on a restricted cubic spline with three knots. Variables with missing data from 25% or more of patients were excluded from the inferential analyses. Otherwise, missing data were handled using multiple imputation as follows: the missing data were filled in five times to generate five complete data sets as per the full conditional specification method, the five complete data sets were analyzed using standard statistical analyses, and the results from the five complete datasets were combined to produce the final inferential results.

The proportions of treated and untreated patients in the enrollment

Table 1. Definitions of "treated" and "untreated" with antifibrotic medication in enrollment and first follow-up windows

	In Enrollment Window	In First Follow-Up Window
Treated*	Start date and/or stop date before or ⩽3 mo after enrollment "Yes" for antifibrotic medication use on case report form at enrollment	Stop date 3–8 mo after enrollment Start date ⩽8 mo and stop date missing or >8 mo after enrollment Stop date >8 mo after enrollment and start date missing "Yes" for antifibrotic medication use on case report form 3–8 mo after enrollment
Untreated	No treatment use documented or start date >3 mo after enrollment	No treatment use documented or start date >8 mo after enrollment

*To be counted as treated in either time window, participants needed to meet at least one of the listed criteria (e.g., in the enrollment window, a patient would be counted as treated if the start date and/or stop date for antifibrotic medication was before or within 3 months after enrollment and/or "yes" for antifibrotic medication use was marked on the case report form at enrollment).

window who met key demographic and physiological eligibility criteria for the INPULSIS trials of nintedanib (3) or the CAPACITY (Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes) (4) and ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis) (5) trials of pirfenidone were analyzed descriptively. The proportions of patients who were treated in the enrollment window were assessed by year of enrollment and by site (among sites that enrolled 20 or more patients). To visualize the relationship between patient characteristics and treatment use across sites enrolling 20 or more patients, box plots were created to display site-level medians (for continuous characteristics) and proportions (for categorical characteristics) for each characteristic identified as associated with treatment use at enrollment in the inferential analysis.

Results

Antifibrotic Drug Use at Enrollment

A total of 782 patients were eligible for this analysis after excluding 216 patients who were enrolled after March 4, 2018, and four patients who had missing data on antifibrotic drug use. Of these patients, 551 (70.5%) received antifibrotic medication in the enrollment window (Figure 1). Of the treated patients, 53.2% received pirfenidone alone, 40.7% received nintedanib alone, and 6.2% received both pirfenidone and nintedanib (but not necessarily simultaneously) (Figure 2A). The proportion of patients who were treated in the enrollment window was relatively stable over time (Figure 3A). There was substantial variation in the proportion of patients treated in the enrollment window across sites that enrolled 20 or more patients (Figure 3B).

Patient Characteristics at Enrollment and Treatment Status in the Enrollment Window

Patient characteristics at enrollment by treatment status in the enrollment window are summarized in Table 2. Younger age (odds ratio [OR], 0.87; 95% confidence interval [CI], 0.79–0.97, per 5-yr increase), lower FVC% predicted (OR, 0.91; 95% CI, 0.84–1.00, per 10% increase), oxygen use with activity (OR, 1.55; 95% CI, 1.11–2.16), worse self-rated health based on the Short Form 12 (SF-12) mental component score (OR, 0.82; 95% CI, 0.69–0.97, per 10-point increase) and SF-12 physical component score (OR, 0.84; 95% CI, 0.72–0.97, per 10-point increase), referral to the enrolling center by a pulmonologist (OR, 1.55; 95% CI, 1.14–2.13), carrying a diagnosis of IPF to the enrolling center (OR, 1.45; 95% CI, 1.06–1.98), and use of a lung biopsy in diagnosis (OR, 3.07; 95% CI, 2.00–4.75) were significantly associated with being treated in the enrollment window (Figure 4). The relationship between St. George's Respiratory Questionnaire (SGRQ) total score and treatment use was nonlinear and, as such, was modeled using a two-part linear spline with a knot at 48 points (Figure E1). The odds of being treated increased significantly for every 10-point increase (worsening) in SGRQ total score among patients with a score of less than 48 (OR, 1.25; 95% CI, 1.09–1.44) but not among patients with a score of greater than 48 (OR, 0.87; 95% CI, 0.71–1.06). In a sensitivity analysis that excluded the 19 patients enrolled in the registry before the U.S. Food and Drug Administration approval of antifibrotic drugs on October 15, 2014, the associations between patient characteristics at enrollment and treatment status were consistent with the original analysis (data not shown).

Patient Characteristics at Enrollment by Site

The distributions of patient characteristics associated with treatment use at enrollment were explored among sites that enrolled 20 or more patients (Figure E2). The

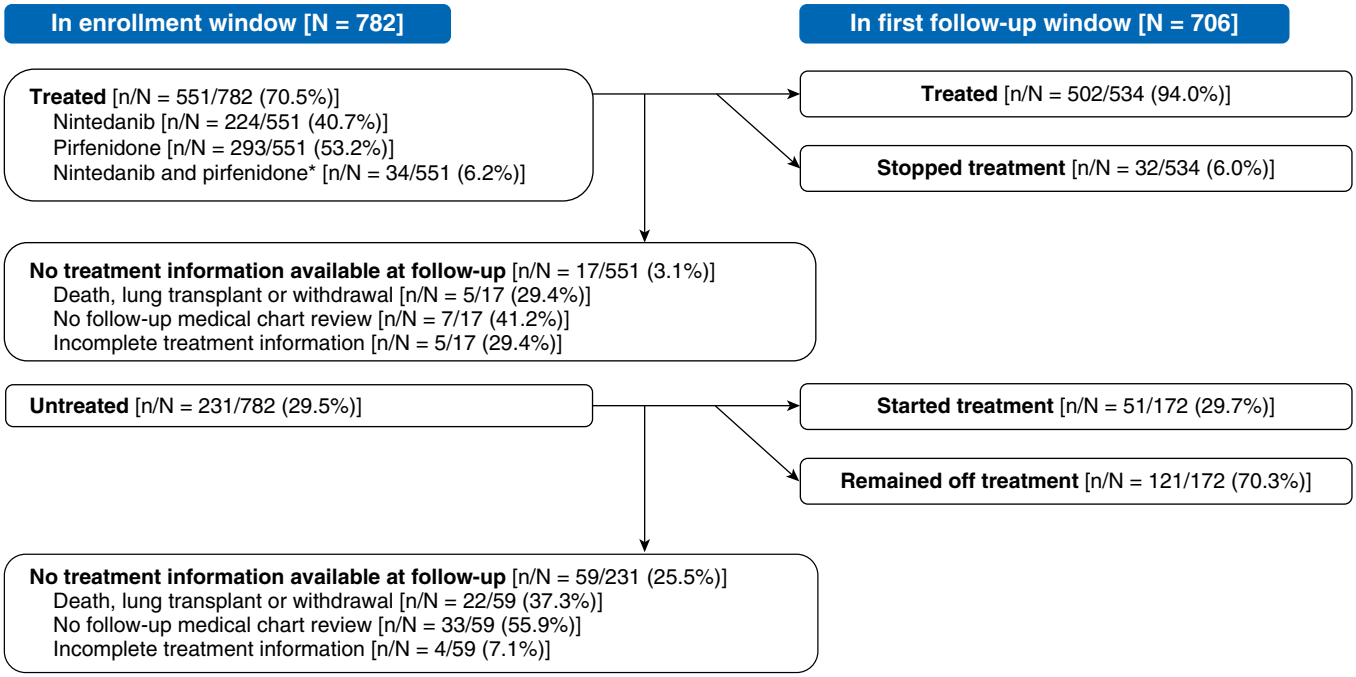

Figure 1. Antifibrotic medication use in enrollment window and first follow-up window. *Not all patients took both treatments simultaneously.

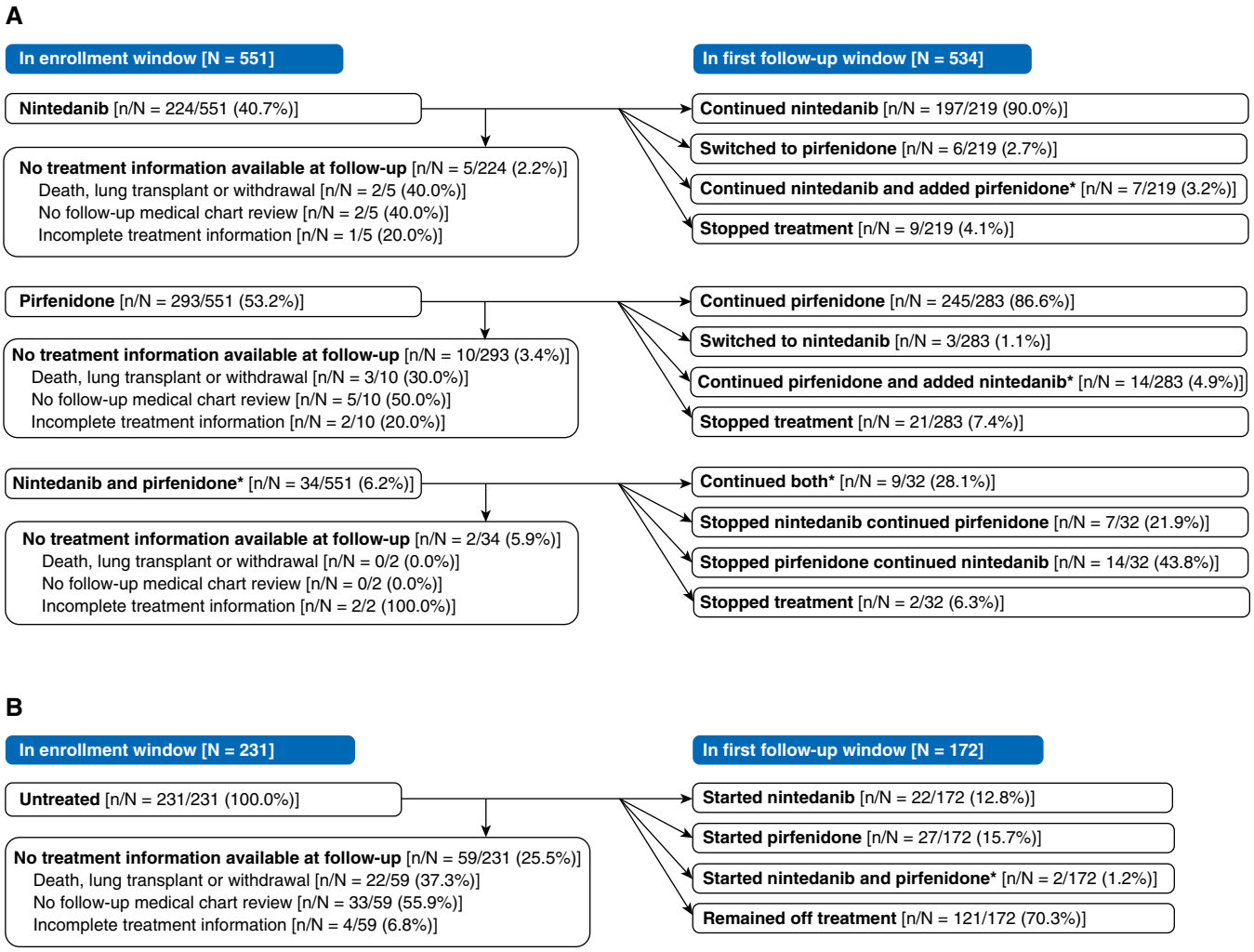

Figure 2. (*A*) Choice of antifibrotic drug in enrollment window and first follow-up window among treated patients at enrollment. (*B*) Choice of antifibrotic drug in first follow-up window among patients untreated at enrollment. *Not all patients took both treatments simultaneously.

interquartile ranges of the site-level proportions of patients who carried a diagnosis of IPF to the enrolling center and of patients using supplemental oxygen with activity, were nearly 20%, whereas the SGRQ total score had an interquartile range of nearly 10 points (on a scale of 0–100 points).

Fulfillment of Eligibility Criteria for INPULSIS, CAPACITY, and ASCEND Trials by Treatment Status in the Enrollment Window

The majority of patients enrolled in the IPF-PRO Registry met the individual eligibility criteria for the INPULSIS, CAPACITY, and ASCEND trials based on age, FVC% predicted, and D_{LCO}% predicted, and the eligibility criteria for ASCEND based on forced expiratory volume in 1 second (FEV_1)/FVC ratio and 6-minute walk distance (Table 3). Individual eligibility criteria that were met by fewer than 75% of patients in the registry included D_{LCO} of 35% predicted or greater and FEV_1/FVC ratio of 0.8 or greater. Approximately 73%, 63%, and 42% of patients who were treated in the enrollment window, respectively, met all the eligibility criteria assessed for the INPULSIS, CAPACITY, and ASCEND trials (Table 3). The proportions of patients who met eligibility criteria were similar in the subgroups of patients who were treated and untreated in the enrollment window (Table 3).

Antifibrotic Drug Use in the First Follow-Up Window

A total of 706 patients had data available on antifibrotic drug use in the first follow-up window (Figure 1). Reasons for unavailable data in the first follow-up window were death, lung transplant or withdrawal from the registry, lack of medical chart review, and incomplete documentation of medication use. Among 534 patients who were treated in the enrollment window and had data available on antifibrotic drug use in the first follow-up window, 502 patients (94.0%) remained treated in the first follow-up window (Figure 1). Most patients received the same treatment in the follow-up window as in the enrollment window (Figure 2A). Among 172 patients who were

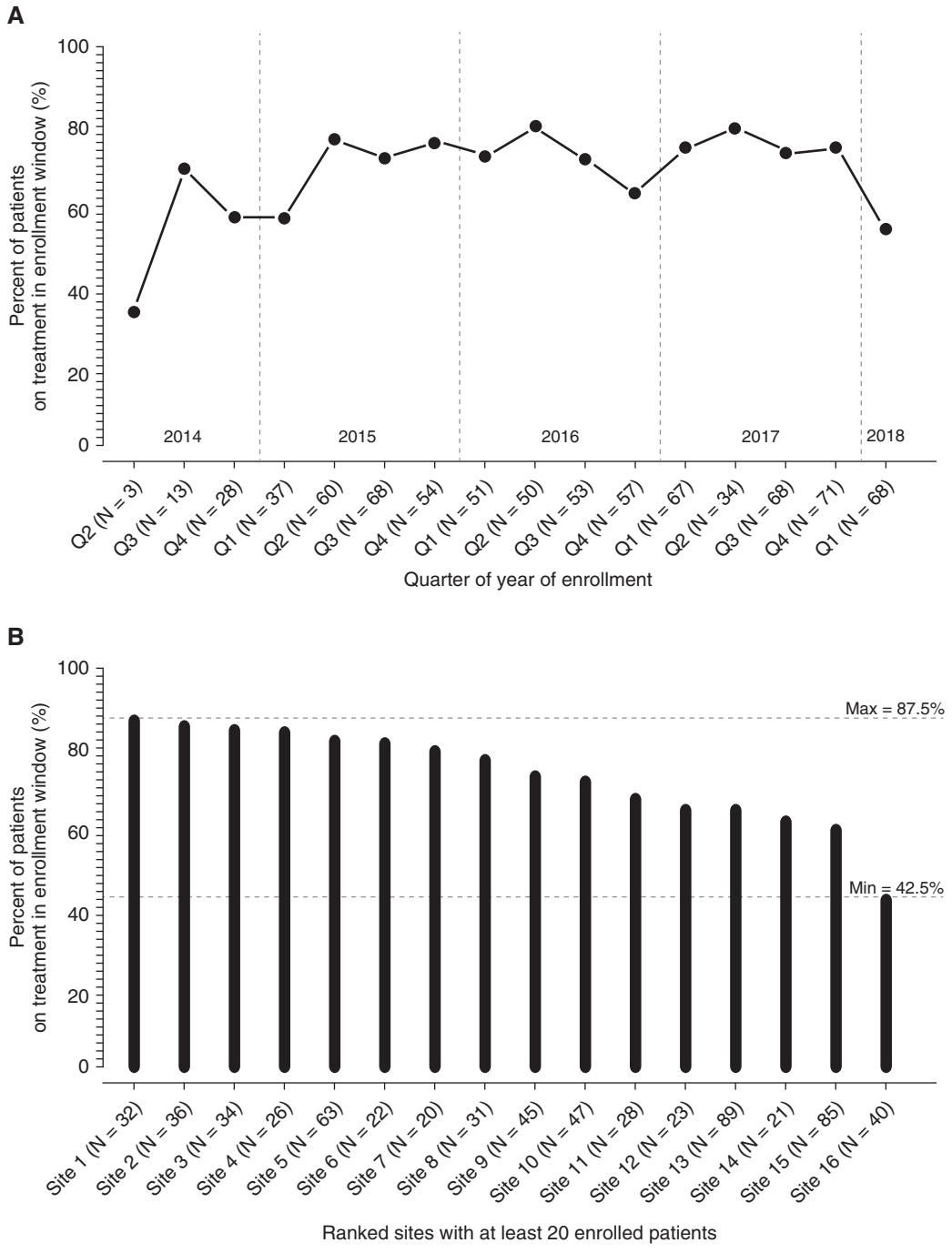

Figure 3. Proportion of patients who received antifibrotic medication in the enrollment window by (*A*) year of enrollment and by (*B*) enrolling center. max = maximum; min = minimum.

untreated in the enrollment window and had data available on antifibrotic drug use in the first follow-up window, 51 patients (29.7%) started treatment in the follow-up window; 22 patients (12.8%) started treatment with nintedanib, 27 patients (15.7%) started treatment with pirfenidone, and two patients (1.2%) started treatment with both nintedanib and pirfenidone (not necessarily simultaneously) (Figure 2B). An interactive Sankey diagram showing antifibrotic drug use in the enrollment and follow-up windows is available at https://www.usscicomms.com/respiratory/salisbury/IPF-PRO-antifibrotic-drug-use.

Patient Characteristics at Enrollment and Treatment Status in the First Follow-Up Window

A summary of patient characteristics at enrollment by treatment status in the first follow-up window among those treated and untreated in the enrollment window are presented in Tables E1 and E2. Among

Table 2. Characteristics of patients at enrollment by antifibrotic medication use in enrollment window

Characteristic	Treated (*n* = 551)		Untreated (*n* = 231)	
	Summary Measure	Missing Data	Summary Measure	Missing Data
Age, yr	70 (65–75)	—	71 (66–76)	—
Sex, M	417 (75.7)	—	166 (71.9)	—
Race, white	514 (95.5)	13 (2.4)	217 (95.6)	4 (1.7)
Body mass index, kg/m^2	29.2 (26.0–32.6)	36 (6.5)	28.7 (25.8–31.4)	17 (7.4)
Weight, kg	85.9 (76.5–98.5)	14 (2.5)	86.2 (74.3–95.5)	8 (3.5)
Current or former smoker	382 (69.6)	2 (0.4)	151 (65.4)	—
FVC, % predicted	69.2 (59.4–79.4)	68 (12.3)	71.0 (61.0–83.0)	29 (12.6)
D_{LCO}, % predicted	41.7 (32.2–50.0)	79 (14.3)	43.9 (33.1–55.4)	36 (15.6)
Oxygen use at rest	112 (20.9)	15 (2.7)	37 (16.3)	4 (1.7)
Oxygen use with activity	197 (36.8)	16 (2.9)	61 (26.9)	4 (1.7)
SGRQ total score*	40.6 (28.0–54.0)	36 (6.5)	35.3 (22.3–50.6)	22 (9.5)
SF-12 mental component score†	53.0 (45.9–58.9)	45 (8.2)	55.3 (47.9–59.4)	27 (11.7)
SF-12 physical component score†	37.9 (30.6–45.7)	45 (8.2)	40.1 (32.5–48.9)	27 (11.7)
CASA-Q cough symptoms domain‡	58.3 (41.7–75.0)	22 (4.0)	58.3 (41.7–75.0)	15 (6.5)
CASA-Q cough impact domain‡	78.1 (59.4–96.9)	22 (4.0)	78.1 (56.3–90.6)	16 (6.9)
EuroQoL score§	0.8 (0.7–1.0)	26 (4.7)	0.8 (0.7–1.0)	16 (6.9)
EuroQoL visual analog scale‖	75 (60–85)	24 (4.4)	79 (67–90)	18 (7.8)
Distance to enrolling center, miles	38.4 (14.9–110.9)	1 (0.2)	28.6 (12.2–78.4)	—
Referred by pulmonologist	361 (65.8)	2 (0.4)	126 (55.3)	3 (1.3)
Prior diagnosis of IPF (before referral to enrolling center)	269 (49.0)	2 (0.4)	92 (40.0)	1 (0.4)
Diagnostic criteria¶		11 (2.0)		1 (0.4)
Definite IPF	373 (69.1)		152 (66.1)	
Probable IPF	119 (22.0)		55 (23.9)	
Possible IPF	48 (8.9)		23 (10.0)	
MDD used in diagnosis	211 (38.7)	6 (1.1)	93 (40.8)	3 (1.3)
Lung biopsy used in diagnosis	163 (29.9)	6 (1.1)	28 (12.3)	3 (1.3)
HRCT used in diagnosis	518 (95.0)	6 (1.1)	222 (97.4)	3 (1.3)
Family history of ILD	101 (19.1)	21 (3.8)	35 (15.7)	8 (3.5)
History of GERD	385 (70.0)	1 (0.2)	159 (68.8)	—
History of sleep apnea	159 (29.0)	3 (0.5)	52 (22.7)	2 (0.9)
History of coronary artery disease	158 (28.8)	3 (0.5)	73 (31.7)	1 (0.4)
History of pulmonary hypertension	42 (7.7)	4 (0.7)	13 (5.7)	2 (0.9)
History of chronic kidney disease	21 (3.8)	5 (0.9)	5 (2.2)	2 (0.9)
Creatinine >2.0 mg/dl	3 (0.8)	191 (34.7)	2 (1.4)	92 (39.8)
History of cirrhosis or chronic liver disease	10 (1.8)	3 (0.5)	4 (1.7)	1 (0.4)
ALT or AST >75 U/L	4 (1.0)	165 (29.9)	3 (2.1)	86 (37.2)
Oral steroid use	67 (13.2)	45 (8.2)	24 (11.4)	21 (9.1)
Anticoagulant use	105 (20.7)	44 (8.0)	42 (20.1)	22 (9.5)

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATS/ERS/JRS/ALAT = American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association; CASA-Q = Cough and Sputum Assessment Questionnaire; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; GERD = gastroesophageal reflux disease; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MDD = multidisciplinary discussion; SF-12 = Short Form 12; SGRQ = St. George's Respiratory Questionnaire.

Data for the summary measures are median (25th–75th percentile) or *n* (% of patients without missing data). Missing data are *n* (%).

*Scores range from 0 to 100; higher scores indicate worse health-related quality of life.

†Scores range from 0 to 100; lower scores indicate worse health.

‡Scores range from 0 to 100; lower scores indicate worse cough.

§Scores range from 0 to 1; lower scores indicate worse health.

‖Scores range from 0 to 100; lower scores indicate worse health.

¶According to 2011 ATS/ERS/JRS/ALAT diagnostic guidelines (13).

patients treated in the enrollment window, better self-rated health based on the EuroQoL score (OR, 1.22; 95% CI, 1.07–1.39, per 0.1-point increase) and not using oxygen with activity (OR, 0.49; 95% CI, 0.24–0.99) at enrollment were significantly associated with continuing treatment in the first follow-up window (Figure E3). The relationship between the SF-12 mental component score and treatment use was nonlinear and, as such, was modeled using a two-part linear spline with a knot at 38 points. The odds of continuing treatment increased significantly for every 10-point increase in the SF-12 mental component score among patients with a score of greater than 38 (OR, 1.07; 95% CI, 1.02–1.13) but not among patients with a score of less than 38 (OR, 0.81; 95% CI, 0.61–1.08). Among patients untreated in the enrollment window, lower D_{LCO}% predicted (OR, 0.86; 95% CI, 0.76–0.97, per 5% increase), a family history of ILD (OR, 2.35; 95% CI, 1.00–5.52), a diagnosis of definite IPF according to the 2011 guidelines (13) (OR, 2.83; 95% CI, 1.33–6.05), and a history of sleep apnea (OR, 2.33; 95% CI, 1.12–4.83) were significantly associated with

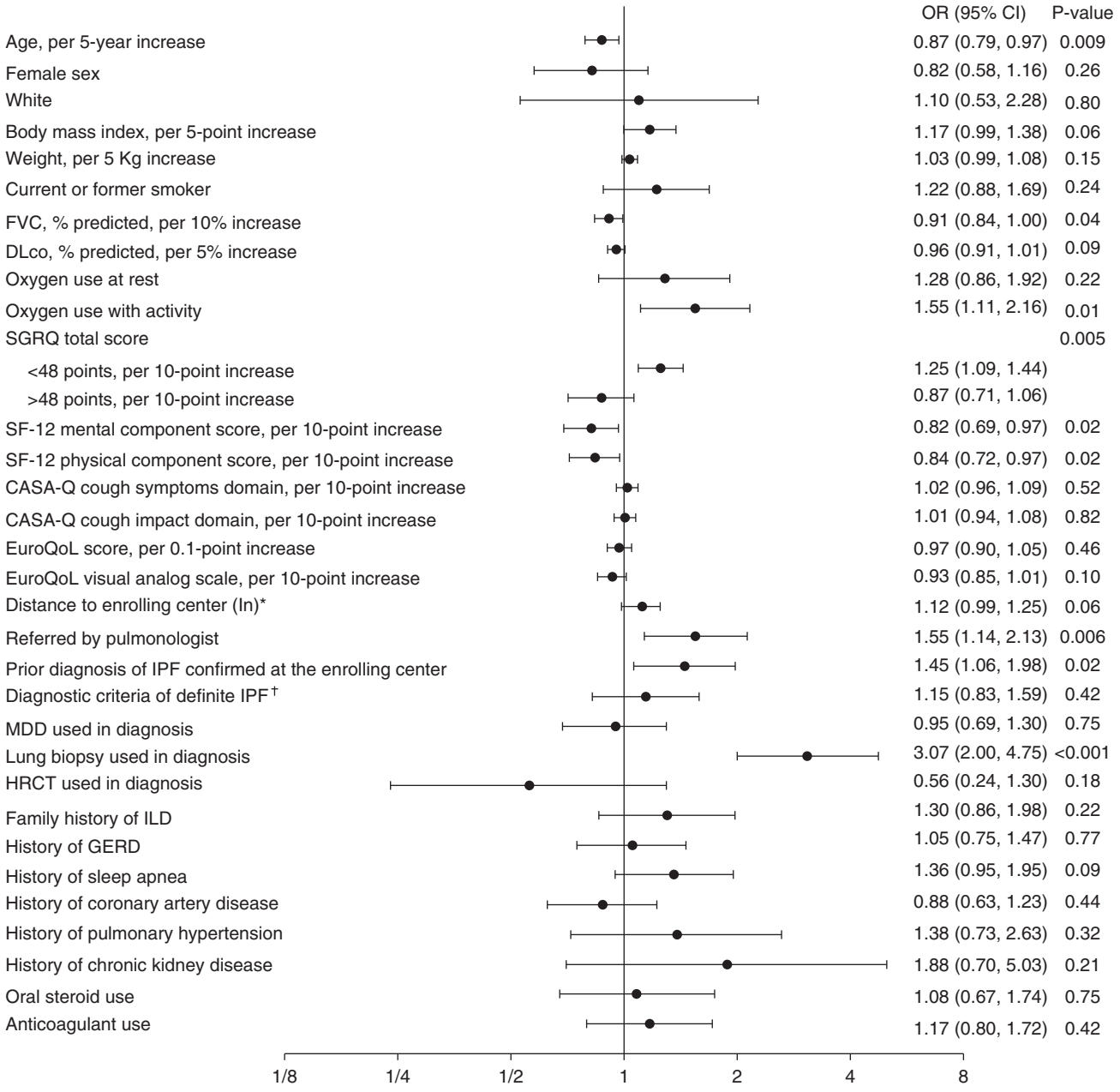

Figure 4. Relationship between patient characteristics at enrollment and antifibrotic medication use in enrollment window. *Natural log of distance in km. †Compared with probable/possible IPF according to 2011 ATS/ERS/JRS/ALAT diagnostic guidelines (13). ATS/ERS/JRS/ALAT = American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association; CASA-Q = Cough and Sputum Assessment Questionnaire; CI = confidence interval; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; GERD = gastroesophageal reflux disease; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MDD = multidisciplinary discussion; OR = odds ratio; SF-12 = Short Form 12; SGRQ = St. George's Respiratory Questionnaire.

starting treatment in the first follow-up window (Figure E4).

Discussion

We investigated the use of antifibrotic medication (nintedanib and/or pirfenidone) among 782 patients with IPF enrolled in the U.S. IPF-PRO Registry. Although the use of antifibrotic medication at the time of enrollment has been studied in several registries (14–20), patient characteristics associated with the treatment decisions at enrollment and during follow-up as well as the variability in treatment use across ILD centers have not been well characterized. We found that the majority of patients enrolled in the IPF-PRO Registry were treated with antifibrotic medication at enrollment and that individuals with more severe disease at enrollment were more likely to be treated. Fewer than 10% of patients treated at enrollment stopped

Table 3. Patients in the IPF-PRO registry who met eligibility criteria for the INPULSIS, CAPACITY, and ASCEND trials by antifibrotic medication in the enrollment window

Inclusion Criterion	Treated (*n* = 551), *n* (% of Patients without Missing Data)	Untreated (*n* = 231), *n* (% of Patients without Missing Data)
Patients meeting each individual inclusion criterion		
Age		
⩾40 yr (INPULSIS)	551 (100.0)	231 (100.0)
40–80 yr (CAPACITY and ASCEND)	521 (94.6)	206 (89.2)
FVC% predicted*		
⩾50% predicted (INPULSIS and CAPACITY)	427 (88.4)	186 (92.1)
50–90% predicted (ASCEND)	371 (76.8)	150 (74.3)
D_{LCO}% predicted†		
30–79% predicted (INPULSIS)	377 (79.9)	158 (81.0)
⩾35% predicted (CAPACITY)	324 (68.6)	139 (71.3)
30–90% predicted (ASCEND)	380 (80.5)	160 (82.1)
FEV_1/FVC‡		
⩾0.7 (INPULSIS)	502 (96.5)	204 (94.0)
⩾0.8 (ASCEND)	351 (67.5)	131 (60.4)
6MWD§		
⩾150 m (ASCEND)	349 (95.9)	118 (93.7)
Patients meeting all the above eligibility criteria		
INPULSIS‖	337 (72.9)	144 (75.4)
CAPACITY‖	291 (63.0)	122 (63.9)
ASCEND¶	135 (41.8)	42 (37.8)

Definition of abbreviations: 6MWD = 6-minute walk distance; ASCEND = Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis; CAPACITY = Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IPF-PRO = Idiopathic Pulmonary Fibrosis Prospective Outcomes.
*Percentages based on *n* = 483 and *n* = 202 in the treated and untreated groups.
†Percentages based on *n* = 472 and *n* = 195 in the treated and untreated groups.
‡Percentages based on *n* = 520 and *n* = 217 in the treated and untreated groups.
§Percentages based on *n* = 364 and *n* = 126 in the treated and untreated groups.
‖Percentages based on *n* = 462 and *n* = 191 in the treated and untreated groups.
¶Percentages based on *n* = 323 and *n* = 111 in the treated and untreated groups.

treatment, and almost 30% of those not initially treated started treatment during the first follow-up window. We identified substantial variation in treatment use across sites. Taken together, these results suggest that a combination of physician and patient preferences may contribute to the variation in treatment practice.

Approximately 70% of patients were receiving an antifibrotic drug at enrollment in the IPF-PRO Registry. This is similar to the proportions of patients with IPF who were treated with antifibrotic medication at enrollment in other registries in the United States (14), Europe (15–17), and Latin America (20), although some reports from Europe document lower use (18, 19). Variation in the proportions of patients treated with antifibrotic medications across these registries could relate to differences in healthcare systems and access to treatment, the types of site at which patients were recruited, the timing of data collection, and the methodology used to recruit patients and analyze treatment status. Similar to previous studies, we found that a younger age (14, 21, 22), a lower FVC and/or lower D_{LCO} (14, 21, 23), and the use of supplemental oxygen (14) were associated with treatment use at the time of enrollment in the IPF-PRO Registry. Only one analysis identified in our literature review found a higher D_{LCO}% predicted in treated patients compared with untreated patients (16). Our analysis also identified the use of a lung biopsy in the diagnostic process to be associated with treatment use at enrollment; we could not identify another registry assessing the relationship between lung biopsy and treatment use.

To date, the relationship between quality of life measures and treatment use has not been thoroughly explored. The INSIGHTS-IPF (Investigating significant health trends in idiopathic pulmonary fibrosis) Registry in Germany found no relationship between several measures of self-rated health and treatment use (19), and an analysis of the Pulmonary Fibrosis Foundation Patient Registry in the United States did not select several quality of life measures for inclusion in a multivariable model explaining treatment use (14). Interestingly, in our analyses, the relationship between the SGRQ total score and antifibrotic drug use at enrollment was not linear; among patients with a SGRQ total score of less than 48 points (i.e., with better self-rated health), an increasing (worsening) score was associated with increased odds of being treated. Among patients with scores above 48, an increasing (worsening) score was not associated with a significant difference in the odds of treatment, but the point estimate suggested that worsening symptoms were associated with decreased odds of treatment. The reasons for this nonlinear relationship are unclear but could suggest that beyond a certain level of health impairment, further worsening no longer impacts patients' treatment acceptance. Alternatively, we may lack the power to detect a significant relationship between treatment and an increasing SGRQ total score among patients

with scores above 48. International surveys have suggested that physicians are less likely to prescribe an antifibrotic drug to patients with IPF whom they regard as having stable or preserved lung function, few symptoms, or good quality of life (24, 25); our findings suggest that these biases may be borne out in practice.

In the IPF-PRO Registry, most of the patients who were treated at enrollment remained treated approximately 6 months later, which is consistent with the results of clinical trials (26, 27) and other real-world studies (28–32). Although patients with worse self-rated health were more likely to be treated at enrollment, better self-rated health (based on the SF-12 mental component score or EuroQoL score) and not using oxygen with activity at enrollment were associated with continuing treatment in the follow-up window. Among patients treated in the enrollment window who had an SF-12 mental component score of greater than 38 (who comprised approximately 90% of the patients), an increasing score (better self-related health) was significantly associated with increased odds of staying on treatment in follow-up. Previous real-world studies have found that patients with IPF who had better health based on a higher FVC% predicted were less likely to discontinue antifibrotic therapy (32–34). Approximately 30% of the patients who were untreated at enrollment had started treatment approximately 6 months later. Characteristics at enrollment that were associated with starting treatment during follow-up included lower D_{LCO}% predicted, a diagnosis of definite IPF, a family history of ILD, and a history of sleep apnea. Patients and physicians participating in the IPF-PRO Registry were not queried on the reasoning behind treatment decisions, but our data lead us to speculate that symptoms and quality of life may contribute to these decisions.

Among sites that enrolled at least 20 patients, we identified variability in the proportion of patients treated at enrollment, and our analysis suggested that several patient characteristics associated with treatment use may vary substantially across sites. Similarly, significant variation was observed in antifibrotic medication prescription across sites in the Pulmonary Fibrosis Foundation Patient Registry, with the differences between sites not being fully explained by patient and site characteristics (14). This suggests that a combination of physician and patient preferences may contribute to variation in antifibrotic drug use.

The INPULSIS, CAPACITY, and ASCEND trials of nintedanib and pirfenidone specified eligibility criteria based on age and lung function (FVC and D_{LCO}) (3–5). The majority of the patients enrolled in the IPF-PRO Registry would have met these individual criteria. In addition, based on mean values at enrollment, the patients enrolled in the IPF-PRO Registry and most other large patient registries in IPF appear to have similar degrees of impairment in FVC and D_{LCO} to the patients enrolled in INPULSIS and ASCEND trials (35). Of note, fewer patients met all of the summarized eligibility criteria for a given trial. It is important to note that there were other eligibility criteria for these trials that could not be assessed based on the data collected in the IPF-PRO Registry.

Strengths of our analyses include the collection of data on antifibrotic drug use from a large population of patients with IPF recruited at over 40 centers. Our analyses also have several limitations. The patient populations enrolled in registries, such as the IPF-PRO Registry, may differ from the general population of patients with IPF; for example, patients who seek referral to expert centers and/or who participate in registries may be more motivated to start and/or to continue treatment. Although we identified factors associated with antifibrotic drug use, we were unable to determine the reasons behind these relationships because patient and physician preferences, access to therapies, and other factors that may impact treatment decisions were not captured. Based on our definition of "treated" at enrollment (which included patients who started drugs before enrollment), survivor bias could have inflated the proportion of patients continuing medication in the 6-month follow-up window (i.e., those already tolerating treatment are more likely to continue it). The duration of antifibrotic treatment use before enrollment was not recorded. Our analyses were not prespecified and so should be considered exploratory. We have not demonstrated a causal association between patient characteristics and treatment initiation. Because the registry is conducted in a real-world setting, there was a degree of missing data and variability in follow-up time. Only one equation for calculation of FVC% predicted and one equation for calculation of D_{LCO}% predicted were used, and different reference equations may have provided different results for the proportions of patients in the registry who met inclusion criteria for the INPULSIS and ASCEND trials based on the cutoffs for FVC and D_{LCO} (36, 37).

In conclusion, data from the IPF-PRO Registry demonstrated that approximately seven in 10 patients with IPF were receiving an antifibrotic therapy at enrollment. Younger age; a greater severity of disease based on lung function, self-rated health status, and use of oxygen; and the use of a lung biopsy in the diagnostic process were associated with treatment at enrollment. Better quality of life and not using oxygen at enrollment were associated with remaining on treatment during the follow-up period, whereas lower D_{LCO}, a family history of ILD, a history of sleep apnea, and a diagnosis of definite IPF were associated with starting treatment in the follow-up period. Further analyses of data from the IPF-PRO Registry will provide additional insights into antifibrotic drug use in patients with IPF. ■

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References

1 Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al*.; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198: e44–e68.

2 Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, *et al*. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011;365:1079–1087.

3 Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, *et al*.; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–2082.

4 Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, *et al*.; CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011;377:1760–1769.

5 King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, *et al*.; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2083–2092.

6 Richeldi L, Cottin V, du Bois RM, Selman M, Kimura T, Bailes Z, *et al*. Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS(®) trials. *Respir Med* 2016;113:74–79.

7 Nathan SD, Albera C, Bradford WZ, Costabel U, Glaspole I, Glassberg MK, *et al*. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. *Lancet Respir Med* 2017;5:33–41.

8 Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, *et al*.; American Thoracic Society; European Respiratory society; Japanese Respiratory Society; Latin American Thoracic Association. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med* 2015;192:e3–e19. [Published erratum appears in *Am J Respir Crit Care Med* 192:644.]

9 O'Brien EC, Durheim MT, Gamerman V, Garfinkel S, Anstrom KJ, Palmer SM, *et al*. Rationale for and design of the Idiopathic Pulmonary Fibrosis-PRospective Outcomes (IPF-PRO) registry. *BMJ Open Respir Res* 2016;3:e000108.

10 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.

11 Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis* 1981;123: 185–189.

12 Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, *et al*. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;26: 720–735.

13 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, *et al*.; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.

14 Holtze CH, Freiheit EA, Limb SL, Stauffer JL, Raimundo K, Pan WT, *et al*. Patient and site characteristics associated with pirfenidone and nintedanib use in the United States; an analysis of idiopathic pulmonary fibrosis patients enrolled in the Pulmonary Fibrosis Foundation Patient Registry. *Respir Res* 2020;21:48.

15 Wuyts WA, Dahlqvist C, Slabbynck H, Schlesser M, Gusbin N, Compere C, *et al*. Baseline clinical characteristics, comorbidities and prescribed medication in a real-world population of patients with idiopathic pulmonary fibrosis: the PROOF registry. *BMJ Open Respir Res* 2018; 5:e000331.

16 Zurkova M, Kriegova E, Kolek V, Lostakova V, Sterclova M, Bartos V, *et al*.; ILD section; IPF registry. Effect of pirfenidone on lung function decline and survival: 5-yr experience from a real-life IPF cohort from the Czech EMPIRE registry. *Respir Res* 2019;20:16.

17 Fernández-Fabrellas E, Molina-Molina M, Soriano JB, Portal JAR, Ancochea J, Valenzuela C, *et al*.; SEPAR-IPF National Registry. Demographic and clinical profile of idiopathic pulmonary fibrosis patients in Spain: the SEPAR National Registry. *Respir Res* 2019;20: 127.

18 Vancheri C, Albera C, Harari S, Pesci A, Poletti V, Rottoli P, *et al*., on behalf of the FIBRONET study group. IPF symptoms' course during a 3-month observation: FIBRONET observational study's preliminary results. Presented at the European Respiratory Society International Congress, September 9–13, 2017, Milan, Italy.

19 Kreuter M, Swigris J, Pittrow D, Geier S, Klotsche J, Prasse A, *et al*. Health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: insights-IPF registry. *Respir Res* 2017;18: 139.

20 Caro FM, Roldán IB, Curbelo P, Kairalla R, Mejía M, Noriega L, *et al*.; on behalf of the REFIPI Group. Treatment of patients with idiopathic pulmonary fibrosis in real-life setting: results from the Latin American Pulmonary Fibrosis Registry REFIPI. *Eur Respir J* 2019;54:PA1730.

21 Pesonen I, Carlson L, Murgia N, Kaarteenaho R, Sköld CM, Myllärniemi M, *et al*. Delay and inequalities in the treatment of idiopathic pulmonary fibrosis: the case of two Nordic countries. *Multidiscip Respir Med* 2018;13:14.

22 Jo HE, Glaspole I, Grainge C, Goh N, Hopkins PM, Moodley Y, *et al*. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. *Eur Respir J* 2017;49:1601592.

23 Behr J, Kreuter M, Hoeper MM, Wirtz H, Klotsche J, Koschel D, *et al*. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. *Eur Respir J* 2015;46:186–196.

24 Maher TM, Molina-Molina M, Russell AM, Bonella F, Jouneau S, Ripamonti E, *et al*. Unmet needs in the treatment of idiopathic pulmonary fibrosis-insights from patient chart review in five European countries. *BMC Pulm Med* 2017;17:124.

25 Maher TM, Swigris JJ, Kreuter M, Wijsenbeek M, Cassidy N, Ireland L, *et al*. Identifying barriers to idiopathic pulmonary fibrosis treatment: a survey of patient and physician views. *Respiration* 2018;96:514–524.

26 Lancaster L, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, *et al*. Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials. *BMJ Open Respir Res* 2016;3:e000105.

27 Lancaster L, Crestani B, Hernandez P, Inoue Y, Wachtlin D, Loaiza L, *et al*. Safety and survival data in patients with idiopathic pulmonary

fibrosis treated with nintedanib: pooled data from six clinical trials. *BMJ Open Respir Res* 2019;6:e000397.
28 Hughes G, Toellner H, Morris H, Leonard C, Chaudhuri N. Real world experiences: pirfenidone and nintedanib are effective and well tolerated treatments for idiopathic pulmonary fibrosis. *J Clin Med* 2016;5:78.
29 Galli JA, Pandya A, Vega-Olivo M, Dass C, Zhao H, Criner GJ. Pirfenidone and nintedanib for pulmonary fibrosis in clinical practice: tolerability and adverse drug reactions. *Respirology* 2017;22: 1171–1178.
30 Brunnemer E, Wälscher J, Tenenbaum S, Hausmanns J, Schulze K, Seiter M, *et al*. Real-world experience with nintedanib in patients with idiopathic pulmonary fibrosis. *Respiration* 2018;95:301–309.
31 Cottin V, Koschel D, Günther A, Albera C, Azuma A, Sköld CM, *et al*. Long-term safety of pirfenidone: results of the prospective, observational PASSPORT study. *ERJ Open Res* 2018;4: 00084-2018.
32 Fletcher SV, Jones MG, Renzoni EA, Parfrey H, Hoyles RK, Spinks K, *et al*. Safety and tolerability of nintedanib for the treatment of idiopathic pulmonary fibrosis in routine UK clinical practice. *ERJ Open Res* 2018;4:00049-02018.
33 Yoon HY, Park S, Kim DS, Song JW. Efficacy and safety of nintedanib in advanced idiopathic pulmonary fibrosis. *Respir Res* 2018;19:203.
34 Costabel U, Albera C, Glassberg MK, Lancaster LH, Wuyts WA, Petzinger U, *et al*. Effect of pirfenidone in patients with more advanced idiopathic pulmonary fibrosis. *Respir Res* 2019;20:55.
35 Culver DA, Behr J, Belperio JA, Corte TJ, de Andrade JA, Flaherty KR, *et al*. Patient registries in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2019;200:160–167.
36 Ward K, Spurr L, Goldman NR, Margaritopoulos GA, Kokosi M, Renzoni E, *et al*. Patient eligibility for anti-fibrotic therapy in idiopathic pulmonary fibrosis can be altered by use of different sets of reference values for calculation of FVC percent predicted. *Respir Med* 2016;120: 131–133.
37 Burgess A, Goon K, Brannan JD, Attia J, Palazzi K, Oldmeadow C, *et al*. Eligibility for anti-fibrotic treatment in idiopathic pulmonary fibrosis depends on the predictive equation used for pulmonary function testing. *Respirology* 2019;24:988–995.