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Survival and course of lung function in the presence or absence of antifibrotic treatment in patients with idiopathic pulmonary fibrosis: long-term results of the INSIGHTS-IPF registry

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Key Words: lung fibrosis, outcomes, survival, observational, antifibrotic agents

Abstract:

Rationale. There is a paucity of observational data on antifibrotic therapy for idiopathic pulmonary fibrosis (IPF).
Objective. We aimed to assess the course of disease of IPF patients with and without antifibrotic therapy under real-life conditions.
Methods. We analysed data from a non-interventional, prospective cohort study of consecutively enrolled IPF patients from 20 ILD expert centres in Germany. Data quality was ensured by automated plausibility checks, on-site monitoring, and source data verification. Propensity scores were applied to account for known differences in baseline characteristics between patients with and without antifibrotic therapy.
Results. Among the 588 patients suitable for analysis, the mean age was 69.8±9.1 years, and 81.0% were males. The mean duration of disease since diagnosis was 1.8±3.4 years. The mean % predicted value at baseline for forced vital capacity (FVC) and diffusion capacity (DLCO) were 68.6±18.8 and 37.8±18.5, respectively.
During a mean follow-up of 1.2±0.7 years, 194 (33.0%) patients died. The one-year and two-year survival rates were 87% vs. 46% and 62% vs. 21%, respectively, for patients with vs. without antifibrotic therapy. The risk of death was 37% lower in patients with antifibrotic therapy (HR=0.63, 95%CI: 0.45; 0.87; p=0.005). The results were robust (and remained statistically significant) on multivariable analysis. Overall decline of FVC and DLco was slow and did not differ significantly between patients with or without antifibrotic therapy.
Conclusions. Survival was significantly higher in IPF patients with antifibrotic therapy, but the course of lung function parameters was similar in patients with and without antifibrotic therapy. This suggests that in clinical practice premature mortality of IPF patients eventually occurs despite stable measurements for FVC and DLco.

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Methods. We analysed data from a non-interventional, prospective cohort study of consecutively enrolled IPF patients from 20 ILD expert centres in Germany. Data quality was ensured by automated plausibility checks, on-site monitoring, and source data verification. Propensity scores were applied to account for known differences in baseline characteristics between patients with and without antifibrotic therapy.

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Word count abstract: 267 words

Key words: Lung fibrosis, outcomes, survival, adjustment, observational, pirfenidone, nintedanib, antifibrotic therapy

Background

Idiopathic pulmonary fibrosis (IPF) is a severe respiratory disease characterised by progressive scarring of the lung, leading to respiratory failure and death within 3-5 years from diagnosis.[1] Effective treatments are still limited. The antifibrotic treatments pirfenidone and nintedanib have been shown to slow disease progression as measured by annual rate of decline in forced vital capacity (FVC),[2] but their effect on lung function and survival under clinical practice conditions warrants further exploration.

As randomised controlled studies on antifibrotic treatments have limitations in terms of their generalizability due to patient selection/exclusion and duration of follow-up, observational data in unselected IPF patients are needed to provide a more comprehensive picture. A number of registries have been initiated in various countries to provide such real-life data,[3-8] but their follow-up is limited to 1-2 years only.

The database of the INSIGHTS-IPF registry, one of the largest IPF registries worldwide, offers the opportunity to analyse the course of disease and long-term effectiveness of antifibrotic therapy in IPF. The aims of the present analysis were (1) to describe and compare cohorts of patients with and without antifibrotic therapy, (2) to assess the correlation between antifibrotic drug use and lung function, and (3) to test the correlation between antifibrotic drug use and survival.

Methods

Design and parameters. The INSIGHTS-IPF (“Investigating significant health trends in idiopathic pulmonary fibrosis”) registry is a nationwide, investigator-initiated observational study. The registry has been continuously enrolling consecutive incident and prevalent patients in routine clinical care across 20 pulmonary specialist centres in Germany since November 2012. Patients ≥18 years of age with a study-site diagnosis of IPF according to the 2011 ATS/ERS/JRS/ALAT IPF guideline[9] after provision of written informed consent can be enrolled, with no explicit exclusion criteria. The registry’s structure, methodology, and regulatory aspects, as well as a detailed description of the baseline characteristics of the patient cohort, have been reported previously.[10-12] The study has been approved by the ethics committee at the Technical University of Dresden and various local ethical committees. All patients provided informed consent before their data were documented in the registry. The ClinTrials.gov identifier is NCT01695408.

Data were collected at enrolment (baseline) and at subsequent 6- to 12-month intervals. At each follow-up visit, all clinical events, including hospitalisation and acute exacerbations (as judged by the treating physician), as well as deaths that occurred during the study period, were recorded by each site. At each visit, if available, a range of routine pulmonary function tests were documented, including forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO), the forced expiratory volume in 1 s (FEV1), and six-minute walk distance (6MWD). The gender, age, and physiology (GAP) index was calculated based on available data.[13]

The treating physician was requested to judge the overall clinical course of IPF at baseline and each follow-up visit by the categories: stable disease, slow progression, rapid progression, no judgement possible. Physiologic changes between baseline and 2-year follow-up were categorized as stable if FVC did not change or was improved by ≥5%; as a moderate decrease if decreased by >5-10%; or as a significant decrease if decreased by >10%.

Quality measures. All data were collected using a standardised internet-based case report form (eCRF) with secure electronic data transfer to the central database. Quality measures included automated plausibility checks at data entry, statistical checks on data quality (focusing on missing values and outliers) as well as on-site monitoring and source data verification performed in the majority of centres (over 70%).

Data analysis. Data were summarised by descriptive statistics including means and standard deviations and absolute and relative frequencies at baseline and each subsequent follow-up assessment. Data analysis comprised the period between the first documentation in the registry in December 2012 until the data cut-off point in December 2018. The analyses follow the intention to treat principle, which means that each patient with at least one dose of antifibrotic therapy is assigned to the treatment group.

The entire observation period was considered for each patient in the registry in order to compare outcomes, in terms of mortality and pulmonary function test results, between patients who were treated with antifibrotic therapy and those who were not. Patients in the registry who had never been treated with an antifibrotic therapy were assigned to the control group. The first observation in that group was the registry enrolment visit. Patients who started an antifibrotic therapy before enrolment into the registry (start of more than 10 days before, e.g. as participant in a clinical study) were excluded because of the non-availability of clinical data at treatment start. The data were divided into individual treatment episodes for patients who started pirfenidone and/or nintedanib during the observation period. For these patients, the first observation was the initial treatment visit. If a patient was treated with pirfenidone and nintedanib (in sequence) during follow-up, then two treatment episodes were assigned (one for each drug) for the pulmonary function and 6MWD tests at the corresponding time point. In contrast, the risk of mortality was analysed for the last available antifibrotic treatment episode in patients who were treated with pirfenidone followed by nintedanib, or vice versa, during follow-up. All patients with a follow-up period of at least 3 months were included in the analyses. In addition, a follow-up interval of 2 years was considered. The primary analysis for lung function tests and 6MWD is based on the observed values in the registry. Since the number of missing values in lung function tests (FVC: baseline 4.5%, follow-up 20.7%; DLCO: baseline 16.2%, follow-up 31.9%) and 6MWD (baseline 14.1%, follow-up 57.3%) were substantial, we applied the technique of multiple imputation for those variables to estimate the missing values as sensitivity analyses. Patients with a missing lung function test tended to be on a less severe disease course compared to patients with available lung function test. Preliminary analyses showed that mortality, age, and comorbidities were associated with the absence of the considered variables. Therefore, the first sensitivity analysis used an imputation model including the predictor variables age, sex, number of comorbidities, IPF duration, mortality, antifibrotic therapy, and the lung function and 6MWD results from the prior visit. The number of imputations was set to 10. As a second sensitivity analysis, the last observation carried forward method for lung function and 6MWD was used as well. The third sensitivity analysis used the imputation of missing values by the worst possible value (FVC, DLCO, and 6MWD of 0) for patients who died.

Propensity score. INSIGHTS-IPF is an observational study and thus allocation to treatment was not randomly assigned. Consequently, various patient characteristics at baseline may be imbalanced, possibly leading to biased results and conclusions. The standard approach to deal with this problem is to model the probability of treatment assignment by the physician (propensity score) based on the clinical characteristics at treatment start in order to balance the characteristics of the two considered groups of patients. [14,15,16] The propensity score was estimated by a logistic regression model that included the covariates sex, age, smoking status, number of comorbid diseases, IPF disease duration, FVC % predicted, 6MWD, concomitant therapy with steroids, and the global assessment of the disease course by the physician at baseline. A weight value (inverse probability of treatment weighting, IPTW) was calculated for each patient based on the propensity score. [17] All statistical comparisons between patients with and without antifibrotic therapy were weighted to balance the to groups regarding the clinical characteristics at treatment start.

In the primary analysis, the course of the pulmonary function (FVC% and DLCO% predicted) and 6MWD tests were analysed by weighted linear mixed models to account for the possibility of two treatment episodes for a single patient (additional cluster variable) and the longitudinal study design based on the observed values. An interaction term treatment x time was included into the weighted linear mixed models to test for differences in change in the three considered parameters by treatment. Secondary analyses of lung function and 6MWD included the imputed data, which employed two imputation methods: last-observation-carried-forward and worst-case imputation. The risk of mortality was analysed by a multivariable Cox proportional hazard model weighted by the propensity score. The proportional-hazards assumption was tested on the basis of Schoenfeld residuals after fitting the Cox regression model.

Data were analysed with STATA 12.1 (StataCorp LP. Stata Statistical Software: Release 12. College Station, TX, USA).

Results

A total of 588 patients were deemed suitable for the present analysis. The mean age of the study population was 69.8 years, with a large male preponderance (81.0%). The mean duration of symptoms before the baseline visit was 3.5 ± 4.2 years and the mean time between diagnosis and study enrolment was 1.8 ± 3.4 years. Fifty eight percent of the patients had disease duration of less than 12 months and 47% of less than 6 months. The mean Borg Dyspnea score was 2.2 ± 2.4, and the GAP index stages were as follows: Stage I in 20.4% of the patients, Stage II in 49.9% of the patients, and Stage III in 29.7% of the patients. In terms of lung function parameters at baseline, the mean predicted FVC was 68.6% ± 18.8 and the mean predicted DLCO was 37.8% ± 18.5. Health-related quality of life as measured on the 100-point visual analogue scale was 59.6 ± 23.6. As current therapy at baseline, prednisone was reported in 23.6% and N-acetylcysteine in 25.5% of patients.

The mean follow-up time was 1.2 ± 0.7 years (maximum of two years) for the total sample, 1.2 ± 0.5 years for patients under antifibrotic therapy, and 1.0 ± 0.7 years for patients who had never been treated with antifibrotic therapy. A total of 334 treatment episodes under antifibrotic therapy (168 pirfenidone, 166 nintedanib) were reported for 298 patients in our registry, resulting in 36 patients (12 %) with two episodes. Among these, pirfenidone was the first antifibrotic drug in 29 patients. Seven patients switched from pirfenidone to nintedanib within 3 months after discontinuation of pirfenidone; the other 22 patients started nintedanib on average 13 months after discontinuation of pirfenidone (Table 1).

Generalized linear mixed models were used to analyse the pulmonary function and 6MWD tests. These models included all antifibrotic therapy treatment episodes, and were based on the observed values. During the 2 years of follow-up, mean predicted FVC% remained almost stable (Figure 1A, β for change in follow-up=-0.42, 95%CI: -1.44 to 0.60, p=0.416), with no significant differences between the two groups (β for time x therapy= -0.65, 95%CI: -1.82 to 0.52, p=0.274). Predicted DLCO showed a similar course in both groups (Figure 1B), with no significant decline in DLCO (β for change in follow-up =-1.05, 95%CI: -2.40 to 0.30, p=0.127) in follow-up and no significant differences between the two groups (β for time x therapy= -0.40, 95%CI: -2.56 to 1.77, p=0.721). Results for the 6MWD test were available in 89% of patients at baseline; however, this measurement was compromised by a high rate of missing data during follow-up. There was no statistically significant difference in the course of 6MWD results over time (β for change in follow-up = -14.8, 95%CI: -25.6, 4.1, p=0.076), considering the observed values. The primary analysis was repeated in patients with disease duration of less than or equal to 12 months at enrolment (prevalent patients, Figure 1: second column). A slightly better course of FVC %, DLCO %, and 6MWD was observed in patients with antifibrotic therapy; however, the difference was not statistically significant. The sensitivity analyses using imputed data and data obtained by the LOCF approach resulted in comparable results to those of the primary analysis. If an FVC % of 0 was imputed in patients who died during follow-up, patients never on antifibrotic therapy tended to have a slightly, but not significantly, stronger FVC decline. The decline in DLCO was worse in patients with antifibrotic treatment, although when imputation of the worst individual value was implemented, there were no significant differences between groups.

The risk of mortality was analysed for the last available treatment episode in patients who were treated with pirfenidone (n=139) and nintedanib (n=159) in follow-up. A total of 194 (33.0%) patients died during follow-up. A total of 79 (41%) patients died of IPF related reasons (20% by respiratory failure, and 8% by respiratory infection/pneumonia), followed by complicating comorbidity (8%) and other causes not related to IPF (9%). The reason of death was unknown for 71 (37%) patients.

Overall mortality was substantially lower in patients treated with antifibrotic therapy. The risk of death for any reason was 37% lower in patients with antifibrotic therapy compared with those without such therapy (HR = 0.63, 95%CI: 0.45; 0.87; p=0.005, Figure 1). This result was robust (and remained statistically significant) on multivariable analysis, as reported in Table 2. Analysis for both antifibrotic drugs approved for treating IPF, nintedanib and pirfenidone, revealed no statistically significant difference in overall mortality between the two drugs (HR for pirfenidone versus nintedanib = 1.39, 95%CI: 0.87 – 2.22, p=0.164).
In patients treated with antifibrotics the risk of IPF-related death was not (statistically significantly) lower compared to patients without such therapy (HR = 0.75, 95%CI: 0.45; 1.25; p=0.266), while the risk of death for unknown reason was 56% lower in patients with antifibrotics (HR = 0.44, 95%CI: 0.26; 0.75; p=0.003). Due to the lower numbers of events in this sub-group analysis this result should be interpreted with caution.

We tested the hypothesis whether survival differs between patients with stable FVC (i.e. 10% decline or less during follow-up) compared to patients with worsening of FVC of more than 10% during follow-up, regardless of therapy. The risk of mortality was slightly higher in such patients with disease progression compared to stable IPF patients (HR = 1.34, 95%CI: 0.89 – 2.02, p=0.163). This result was confirmed while adjusting for the effect for antifibrotic treatment.

The risk of mortality was additionally analyzed in patients with disease duration of less than 12 months prior to study enrollment. The risk of death in the subsample of incident patients was 64% lower in patients treated with antifibrotic therapy compared to controls (HR = 0.44, 95%CI: 0.25; 0.78; p=0.003). The result was confirmed in multivariable analysis.

Discussion

The present analysis of the large and contemporary INSIGHTS-IPF registry indicates that patients on antifibrotic therapy appear to survive significantly longer than IPF patients without antifibrotic therapy. The lower overall mortality risk in the patients treated with antifibrotic medication was mainly driven by patients with unknown reason of death. The statistically nonsignificant relationship between antifibrotic therapy and IPF-related deaths might be due to the low number of recorded IPF-related deaths (79. 4% of deaths).

Compared with the recently published observational data from the EurIPF registry, patients in INSIGHTS-IPF were nearly identical in terms of TLC % predicted (70.0% vs 71.2%), FVC % predicted (68.4% versus 68.3%), and FEV_1 % predicted (110% versus 111%), while DLCO % predicted was lower in our study (42.1% versus 37.8%).[9] A subset of IPF patients with long-term follow up within the EurIPF registry were analysed by Kaplan-Meier analysis (without propensity score matching) in correlation with the date of first IPF diagnosis. The analysis of this subset found that median survival on antifibrotic drugs was 123.1 months (censored cases inclusive, range 84– 162 months), compared with a median survival of 68.3 months in patients treated with any other medication including immunosuppressive therapies (censored cases inclusive, range 54–83 months). Functional follow-up data from the EurIPF registry were not reported. Another difference between our data and those of the EurIPF registry, besides the larger number of patients and the statistics applied in our cohort, is the fact that pirfenidone was used in the vast majority (83%) of the EurIPF registry cohort while in our study population nintedanib and pirfenidone where almost equally distributed, slightly favouring nintedanib (53.3%).

Interestingly, we observed a similar, stable course of lung function parameters (FVC and DLCO) over time in both groups, with and without antifibrotic therapy, while overall mortality was considerably higher in the group not treated with antifibrotics. At first glance, our data could provide basis for a hypothesis that stable physiological measurements like FVC and DLco alone may not provide a safeguard against premature mortality in IPF. Lung function measurements every 6 to 12 months is common practice and thus employed in our registry. However, such measurements may be less sensitive to detect differences in the course of IPF compared to highly standardized serial measurements at shorter intervals which are commonly applied in clinical trials. Moreover, missing lung function data may have contributed to blunt differences of the slope of FVC and DLco decline between patients with and without antifibrotic therapy. In this context, it is noteworthy that hospital-based FVC measurements, compared with unsupervised daily home measurements, have been suggested to be less sensitive in detecting progression of fibrosis and in predicting subsequent prognosis.[10] However, a recent clinical treatment trial using daily home spirometry for the primary endpoint also revealed potential technical and practical obstacles associated with this methodology. [20]

The phenomenon of emphysema blunting the decline of FVC in both groups may have contributed to this observation, but the prevalence of emphysema as reported by the investigators was low in both groups. The higher preponderance of steroid-treated patients in the group not treated with antifibrotics may also be considered to potentially contribute to a higher mortality in this group. However, the mean prednisone dosage in our study - given to a quarter of patients in our - study was 14 mg/d. In the INPULSIS study the maximum dose was 15mg/day and in the ASCEND study, prednisone was only allowed if given for another indication.[11, 12] Nonetheless, we cannot exclude that unbalanced steroid-medication has contributed to the observed difference. Finally, antioxidant drugs (NAC) were less commonly used in the antifibrotic therapy arm. The impact of these drugs on prognosis is still under discussion and thus a bias cannot be fully excluded.[13, 14] In consideration of all the limitations our data should be taken as a signal of caution that stability of FVC and DLco may not always protect from premature mortality in the absence of antifibrotic therapy in a fatal disease like IPF. The common practice, still widely used, of withholding antifibrotic therapy from physiologically stable IPF patients may therefore set these patients on a path of increased risk of dying.[15]

Another important aspect of our study is the fact that all patients were enrolled solely based on investigator judgement. The patients enrolled were, therefore, a cohort which included all the imponderabilities of diagnosis in this complex disease which occur in daily practice. The observed difference in survival in favour of antifibrotic therapy is, therefore, an important argument for the clinical application of these drugs, even though a causative argument cannot be made from our study. This observation is, therefore in accordance with recent clinical trials showing that antifibrotic therapies are effective in progressive fibrotic interstitial lung diseases other than IPF.[20,26,27]

Our data do not identify a cause for the difference in overall mortality between patients with and without antifibrotic therapy. However, one can speculate that acute exacerbation may have contributed substantially to this difference.

A number of limitations need to be taken into consideration when interpreting the findings. The major limitation of this study is that patients with existing (prevalent) and newly diagnosed (incident) IPF were documented which may potentially cause lead time bias regarding mortality. This is especially important since time to diagnosis was approximately one year longer in the never-treated population, which could indicate a “healthy survivor effect”.[16]

Further, there was no randomization between the group of patients who had never been treated with an antifibrotic therapy and patients who were treated with an antifibrotic drug. To account for bias by indication, we calculated a propensity score to estimate the probability of being treated with an antifibrotic drug in our registry based on clinical characteristics. However, there may exist unmeasured variables that cannot be included in the propensity score model that may have impacted the association between antifibrotic therapy and mortality. Furthermore, accompanying therapies such as anti-oxidant or anti-acid therapy may have impacted the results of our analysis. We also had to account for a high proportion of missing values in the pulmonary function tests and in the 6MWD test in the follow-up data, which could have affected our results. The fact that only ILD specialty centers participated in the INSIGHTS-IPF Registry may limit the generalizability of our study.

In conclusion, we were able to demonstrate a significant lower all-cause mortality in IPF patients treated with antifibrotic drugs when compared to a matched cohort of IPF patients not treated with antifibrotic drugs. Moreover, our analysis provides the basis for a hypothesis that stability of lung function parameters over time, especially FVC and DLco, in untreated IPF patients may be misleading as our data indicate that stability of these parameters probably do not protect from premature death.

Declarations

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Ethics approval and consent to participate

The study materials were approved by the Ethics Committee of the Medical Faculty, Technical University of Dresden (EK 255082012), and by further local ethic committees as per local requirements.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

JB received grants from Boehringer Ingelheim, and personal fees for consultation or lectures from Actelion, Bayer, Boehringer-Ingelheim, and Roche. He is member of the national and international IPF guideline committee; AP reports grants and personal fees from Roche/InterMune, grants and personal fees from Boehringer Ingelheim, outside the submitted work; HuWi reports personal fees from Boehringer Ingelheim, and personal fees from Roche, outside the submitted work; MC reports honoraria for lectures from Boehringer Ingelheim Pharma GmbH and Roche Pharma, and for serving on advisory boards from Boehringer Ingelheim, outside the submitted work; DP reports personal fees outside the submitted work from Actelion, Bayer, Boehringer Ingelheim, Sanofi, Biogen, Shield and MSD; DS reports personal fees from Boehringer Ingelheim, Roche, outside the submitted work; SV reports personal fees from Boehringer Ingelheim, personal fees from Roche Pharma, personal fees from Actelion Pharma, grants and personal fees from Novartis Pharma, personal fees from Berlin Chemie, and personal fees from Astra, outside the submitted work; HeWi reports personal fees from Boehringer, personal fees from Roche, during the conduct of the study;

personal fees from Bayer, personal fees from Biotest, personal fees from Actelion, personal fees from GSK, and personal fees from Pfizer, outside the submitted work; CN reports honoraria for lectures and serving on advisory boards from Boehringer Ingelheim and Roche Pharma; SA reports case payments from Boehringer Ingelheim, during the conduct of the study; personal fees from Boehringer Ingelheim, and personal fees from Roche, outside the submitted work; SG reports personal fees from Boehringer Ingelheim, personal fees from Roche Pharma, personal fees from Actelion Pharma, grants and personal fees from Novartis Pharma, personal fees from Berlin Chemie, and personal fees from Astra, all outside the submitted work; TW reports grants from Boehringer, during the conduct of the study; TB reports grants from German Center for Lung Research (DZL), personal fees for consultation or lecture from Roche, AstraZeneca, Chiesi, GSK, and Novartis outside the submitted work; MK reports grants and personal fees from Roche/InterMune, grants and personal fees from Boehringer Ingelheim, outside the submitted work.

All other authors declare that they have no competing interests.

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Table 1. Characteristics of patients, in the total analysed cohort and by presence or absence of antifibrotic treatment

	Total n=588	Never been treated with antifibrotic therapy n=290	Treated with antifibrotic therapy n=298
Male sex; n(%)	476 (81.0)	230 (79.3)	246 (82.6)
Age; mean (SD), p50	69.8 (9.1); 72	70.3 (9.4); 73	69.2 (8.8); 71
Body Mass Index in kg/m²; mean (SD), p50	27.6 (4.1); 27.2	26.9 (4.1); 26.3	28.2 (4.0); 27.7
underweight (BMI<18.5); n (%)	1 (0.2)	1 (0.3)	0 (0.0)
normal weight (18.5 ≤ BMI ≤ 25); n (%)	153 (26.0)	93 (32.1)	60 (20.1)
overweight(25 < BMI ≤ 30); n (%)	291 (49.5)	133 (45.9)	158 (53.0)
obesity (BMI>30); n (%)	143 (24.3)	63 (21.7)	80 (26.9)
Never smoked; n(%)	205 (34.9)	96 (33.1)	109 (36.6)
Ex-smoker; n(%)	372 (63.3)	189 (65.2)	183 (61.4)
Number of comorbidities; mean ± SD	1.7 (1.5); 2	1.8 (1.5); 2	1.7 (1.4); 2
Symptom duration; mean (SD), p50	3.5 (4.2); 2.2	3.5 (4.7); 2.2	3.4 (3.8); 2.1
Age at symptom onset; mean (SD), p50	66.1 (10.5); 68.0	66.4 (11.3); 69.0	65.9 (9.8); 67.7
Age at diagnosis; mean (SD), p50	68.0 (10.0); 70.0	68.1 (10.7); 70.6	68.0 (9.2); 69.9
6-minute walk distance; mean (SD), p50	278.5 (193.9); 330	257.6 (188.7); 300	297.8 (197.1); 360
Borg index; mean (SD), p50	2.2 (2.4); 1	2.2 (2.5); 1	2.2 (2.2); 1
Current therapy			
Prednisone, n (%)	139 (23.6)	86 (29.7)	53 (17.8)
Other steroids, n (%)	11 (1.9)	2 (0.7)	9 (3.0)
Azathioprine, n (%)	14 (2.4)	10 (3.5)	4 (1.3)
Cyclophosphamide, n (%)	1 (0.2)	0 (0.0)	1 (0.3)
Mycophenolate mofetil, n (%)	1 (0.2)	1 (0.3)	0 (0.0)
N-Acetylcysteine, n (%)	150 (25.5)	101 (34.8)	49 (16.4)
Antifibrotic therapy, n (%)	298 (50.7)	0 (0.0)	298 (100.0)
Patients on oxygen therapy	157 (26.7)	86 (29.7)	71 (23.3)
Environmental exposure	199 (33.8)	86 (29.7)	113 (37.9)
Gastro-oesophageal reflux	162 (27.6)	81 (27.9)	81 (27.2)
Family history of ILD	27 (4.6)	20 (6.9)	7 (2.4)
Exposure to drugs	21 (3.6)	9 (3.1)	12 (4.0)
GAP index, n(%)			

Stage I	115 (20.4)	56 (20.4)	59 (20.3)
Stage II	282 (49.9)	128 (46.6)	154 (53.1)
Stage III	168 (29.7)	91 (33.1)	77 (26.6)
Lung function test			
Total Lung Capacity, % predicted; mean (SD), p50	71.0 (20.5); 70.5	71.5 (25.7); 69.7	70.5 (14.2); 71.1
Inspiratory Vital Capacity, % predicted; mean (SD), p50	73.2 (20.4); 74.1	70.8 (22.2); 71.8	75.4 (18.4); 76.4
FVC, % predicted; mean (SD), p50	68.6 (18.8); 70.2	66.8 (19.8); 67.9	70.4 (17.5); 71.5
FEV_1, % predicted; mean (SD), p50	76.1 (19.7); 76.8	74.1 (20.7); 74.4	77.9 (18.6); 78.4
FEV_1: FVC, % predicted; mean (SD), p50	110.9 (11.7); 111.2	111.6 (12.2); 111.9	110.3 (11.2); 110.8
DLCO, % predicted; mean (SD), p50	37.8 (18.5); 35.5	37.6 (20.2); 35.5	38.0 (16.9); 35.2
Health-related quality of life, EQ5D; mean (SD), p50	59.6 (23.6); 60	58.0 (24.1); 60	61.2 (23.1); 65

P50 = median; SD = standard deviation

Table 2. Risk of mortality estimated by a multivariable Cox regression model

	HR	P value	95% CI
Antifibrotic therapy	0.66	0.016	0.47 ; 0.93
Age	1.09	<0.001	1.07 ; 1.12
Female sex	0.71	0.116	0.47 ; 1.09
IPF disease duration	0.96	0.005	0.94 ; 0.99
Any comorbid disease	1.05	0.821	0.69 ; 1.60
FVC % predicted	0.96	<0.001	0.95 ; 0.98
Overall physician's judgement of clinical course of IPF:			
stable disease	1.00		
slow progression	1.41	0.102	0.93 ; 2.12
rapid progression	2.69	0.002	1.45 ; 4.97

Hazard Ratio (HR) for 1 year change in age and IPF disease duration, HR for 1% change in FVC% predicted.

Figure 1: Change in FVC % predicted (A), DLCO % predicted (B), and 6-minute walking distance (6MWD; C) over the 2-year follow-up (β (interaction term time x therapy) = estimated difference in change during 2-year follow-up in the considered parameter between patients with and without antifibrotic therapy)

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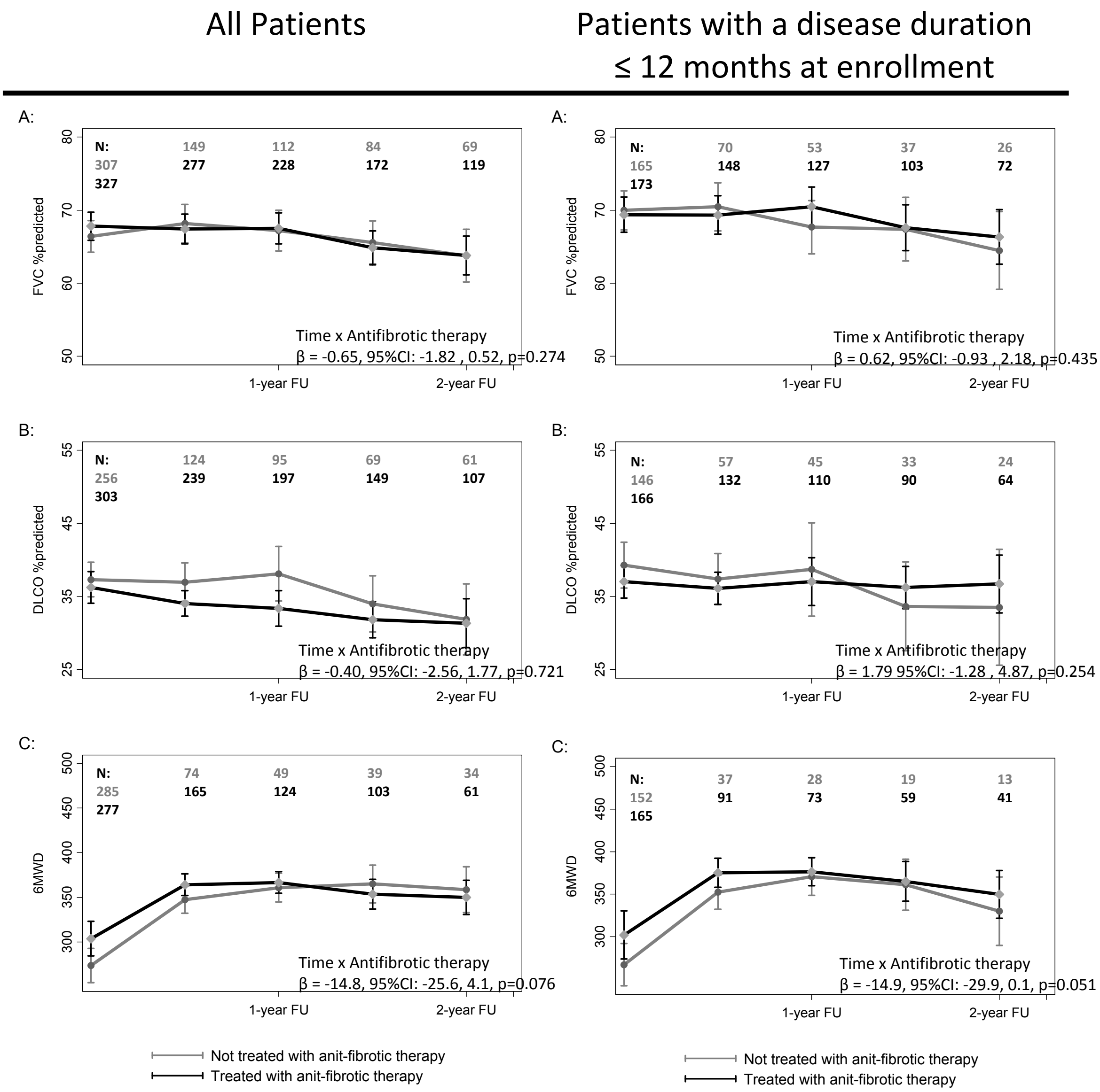
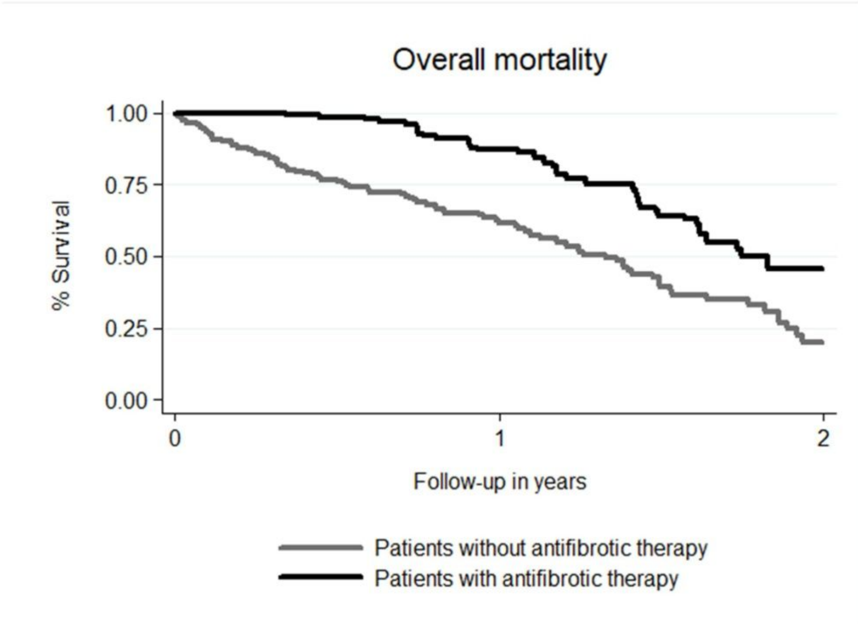


Figure 2: Risk of mortality within 2 years by antifibrotic treatment (by propensity score weighted Kaplan-Meier survival curves).



Number of patients at risk

With antifibrotic therapy	281	129	57
No antifibrotic therapy	252	139	93

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Survival and course of lung function in the presence or absence of antifibrotic treatment in patients with idiopathic pulmonary fibrosis: long-term results of the INSIGHTS-IPF registry

Running title: IPF long-term outcomes on antifibrotic treatment
9.23 Interstitial Lung Disease

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Abstract

Rationale. There is a paucity of observational data on antifibrotic therapy for idiopathic pulmonary fibrosis (IPF).

Objective. We aimed to assess the course of disease of IPF patients with and without antifibrotic therapy under real-life conditions.

Methods. We analysed data from a non-interventional, prospective cohort study of consecutively enrolled IPF patients from 20 ILD expert centres in Germany. Data quality was ensured by automated plausibility checks, on-site monitoring, and source data verification. Propensity scores were applied to account for known differences in baseline characteristics between patients with and without antifibrotic therapy.

Results. Among the 588 patients suitable for analysis, the mean age was 69.8±9.1 years, and 81.0% were males. The mean duration of disease since diagnosis was 1.8±3.4 years. The mean % predicted value at baseline for forced vital capacity (FVC) and diffusion capacity (DLCO) were 68.6±18.8 and 37.8±18.5, respectively.

During a mean follow-up of 1.2±0.7 years, 194 (33.0%) patients died. The one-year and two-year survival rates were 87% vs. 46% and 62% vs. 21%, respectively, for patients with vs. without antifibrotic therapy. The risk of death was 37% lower in patients with antifibrotic therapy (HR=0.63, 95%CI: 0.45; 0.87; p=0.005). The results were robust (and remained statistically significant) on multivariable analysis. Overall decline of FVC and DLco was slow and did not differ significantly between patients with or without antifibrotic therapy.

Conclusions. Survival was significantly higher in IPF patients with antifibrotic therapy, but the course of lung function parameters was similar in patients with and without antifibrotic therapy. This suggests that in clinical practice premature mortality of IPF patients eventually occurs despite stable measurements for FVC and DLco.

Word count abstract: 267 words

hat gelöscht: AT

hat gelöscht: Patients on antifibrotic therapy

hat gelöscht: in the decline of FVC and DL_{CO} compared with patients without….

hat gelöscht: functional stability of lung function as measured by change of FVC and DLCO over time may not represent a safeguard against premature mortality of IPF in clinical practice.

Key words: Lung fibrosis, outcomes, survival, adjustment, observational, pirfenidone, nintedanib, antifibrotic therapy

Background

Idiopathic pulmonary fibrosis (IPF) is a severe respiratory disease characterised by progressive scarring of the lung, leading to respiratory failure and death within 3-5 years from diagnosis.[1] Effective treatments are still limited. The antifibrotic treatments pirfenidone and nintedanib have been shown to slow disease progression as measured by annual rate of decline in forced vital capacity (FVC),[2] but their effect on lung function and survival under clinical practice conditions warrants further exploration.

Feldfunktion geändert

Feldfunktion geändert

As randomised controlled studies on antifibrotic treatments have limitations in terms of their generalizability due to patient selection/exclusion and duration of follow-up, observational data in unselected IPF patients are needed to provide a more comprehensive picture. A number of registries have been initiated in various countries to provide such real-life data,[3-8] but their follow-up is limited to 1-2 years only.

Feldfunktion geändert

The database of the INSIGHTS-IPF registry, one of the largest IPF registries worldwide, offers the opportunity to analyse the course of disease and long-term effectiveness of antifibrotic therapy in IPF. The aims of the present analysis were (1) to describe and compare cohorts of patients with and without antifibrotic therapy, (2) to assess the correlation between antifibrotic drug use and lung function, and (3) to test the correlation between antifibrotic drug use and survival.

Methods

Design and parameters. The INSIGHTS-IPF ("Investigating significant health trends in idiopathic pulmonary fibrosis") registry is a nationwide, investigator-initiated observational study. The registry has been continuously enrolling consecutive incident and prevalent patients in routine clinical care across 20 pulmonary specialist centres in Germany since November 2012. Patients ≥18 years of age with a study-site diagnosis of IPF according to the 2011 ATS/ERS/JRS/ALAT IPF guideline[9] after provision of written informed consent can be enrolled, with no explicit exclusion criteria. The registry's structure, methodology, and regulatory aspects, as well as a detailed description of the baseline characteristics of the patient cohort, have been reported previously.[10-12] The study has been approved by the ethics committee at the Technical University of Dresden and various local ethical committees. All patients provided informed consent before their data were documented in the registry. The ClinTrials.gov identifier is NCT01695408.

Data were collected at enrolment (baseline) and at subsequent 6- to 12-month intervals. At each follow-up visit, all clinical events, including hospitalisation and acute exacerbations (as judged by the treating physician), as well as deaths that occurred during the study period, were recorded by each site. At each visit, if available, a range of routine pulmonary function tests were documented, including forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO), the forced expiratory volume in 1 s (FEV1), and six-minute walk distance (6MWD). The gender, age, and physiology (GAP) index was calculated based on available data.[13]

The treating physician was requested to judge the overall clinical course of IPF at baseline and each follow-up visit by the categories: stable disease, slow progression, rapid progression, no judgement possible. Physiologic changes between baseline and 2-year follow-up were categorized as stable if FVC did not change or was improved by ≥5%; as a moderate decrease if decreased by >5-10%; or as a significant decrease if decreased by >10%.

Quality measures. All data were collected using a standardised internet-based case report form (eCRF) with secure electronic data transfer to the central database. Quality measures included automated plausibility checks at data entry, statistical checks on data quality (focusing on missing values and outliers) as well as on-site monitoring and source data verification performed in the majority of centres (over 70%).

Data analysis. Data were summarised by descriptive statistics including means and standard deviations and absolute and relative frequencies at baseline and each subsequent follow-up assessment. Data analysis comprised the period between the first documentation in the registry in December 2012 until the data cut-off point in December 2018. The analyses follow the intention to treat principle, which means that each patient with at least one dose of antifibrotic therapy is assigned to the treatment group.

The entire observation period was considered for each patient in the registry in order to compare outcomes, in terms of mortality and pulmonary function test results, between patients who were treated with antifibrotic therapy and those who were not. Patients in the registry who had never been treated with an antifibrotic therapy were assigned to the control group. The first observation in that group was the registry enrolment visit. Patients who started an antifibrotic therapy before enrolment into the registry (start of more than 10 days before, e.g. as participant in a clinical study) were excluded because of the non-availability of clinical data at treatment start. The data were divided into individual treatment episodes for patients who started pirfenidone and/or nintedanib during the observation period. For these patients, the first observation was the initial treatment visit. If a patient was treated with pirfenidone and nintedanib (in sequence) during follow-up, then two treatment episodes were assigned (one for each drug) for the pulmonary function and 6MWD tests at the corresponding time point. In contrast, the risk of mortality was analysed for the last available antifibrotic treatment episode in patients who were treated with pirfenidone followed by nintedanib, or vice versa, during follow-up. All patients with a follow-up period of at least 3 months were included in the analyses. In addition, a follow-up interval of 2 years was considered. The primary analysis for lung function tests and 6MWD is based on the observed values in the registry. Since the number of missing values in lung function tests (FVC: baseline 4.5%, follow-up 20.7%; DLCO: baseline 16.2%, follow-up 31.9%) and 6MWD (baseline 14.1%, follow-up 57.3%) were substantial, we applied the technique of multiple imputation for those variables to estimate the missing values as sensitivity analyses. Patients with a missing lung function test tended to be on a less severe disease course compared to patients with available lung function test. Preliminary analyses showed that mortality, age, and comorbidities were associated with the absence of the considered variables. Therefore, the first sensitivity analysis used an imputation model including the predictor variables age, sex, number of comorbidities, IPF duration, mortality, antifibrotic therapy, and the lung function and 6MWD results from the prior visit. The number of imputations was set to 10. As a second sensitivity analysis, the last observation carried forward method for lung function and 6MWD was used as well. The third sensitivity analysis used the imputation of missing values by the worst possible value (FVC, DLCO, and 6MWD of 0) for patients who died.

hat gelöscht: rather high

Propensity score. INSIGHTS-IPF is an observational study and thus allocation to treatment was not randomly assigned. Consequently, various patient characteristics at baseline may be imbalanced, possibly leading to biased results and conclusions. The standard approach to deal with this problem is to model the probability of treatment assignment by the physician (propensity score) based on the clinical characteristics at treatment start in order to balance the characteristics of the two considered groups of patients. [14,15,16] The propensity score was estimated by a logistic regression model that included the covariates sex, age, smoking status, number of comorbid diseases, IPF disease duration, FVC % predicted, 6MWD, concomitant therapy with steroids, and the global assessment of the disease course by the physician at

hat gelöscht: As such, the allocation to treatment was not assigned at random such as in a randomized controlled trial. In an observational study without randomization, various patient characteristics at baseline may be imbalanced, leading to biased results and conclusions.

baseline. A weight value (inverse probability of treatment weighting, IPTW) was calculated for each patient based on the propensity score. [17] All statistical comparisons between patients with and without antifibrotic therapy were weighted to balance the to groups regarding the clinical characteristics at treatment start.

In the primary analysis, the course of the pulmonary function (FVC% and DLCO% predicted) and 6MWD tests were analysed by weighted linear mixed models to account for the possibility of two treatment episodes for a single patient (additional cluster variable) and the longitudinal study design based on the observed values. An interaction term treatment x time was included into the weighted linear mixed models to test for differences in change in the three considered parameters by treatment. Secondary analyses of lung function and 6MWD included the imputed data, which employed two imputation methods: last-observation-carried-forward and worst-case imputation. The risk of mortality was analysed by a multivariable Cox proportional hazard model weighted by the propensity score. The proportional-hazards assumption was tested on the basis of Schoenfeld residuals after fitting the Cox regression model.

Data were analysed with STATA 12.1 (StataCorp LP. Stata Statistical Software: Release 12. College Station, TX, USA).

Results

A total of 588 patients were deemed suitable for the present analysis. The mean age of the study population was 69.8 years, with a large male preponderance (81.0%). The mean duration of symptoms before the baseline visit was 3.5 ± 4.2 years and the mean time between diagnosis and study enrolment was 1.8 ± 3.4 years. Fifty eight percent of the patients had disease duration of less than 12 months and 47% of less than 6 months. The mean Borg Dyspnea score was 2.2 ± 2.4, and the GAP index stages were as follows: Stage I in 20.4% of the patients, Stage II in 49.9% of the patients, and Stage III in 29.7% of the patients. In terms of lung function parameters at baseline, the mean predicted FVC was 68.6% ± 18.8 and the mean predicted DLCO was 37.8% ± 18.5. Health-related quality of life as measured on the 100-point visual analogue scale was 59.6 ± 23.6. As current therapy at baseline, prednisone was reported in 23.6% and N-acetylcysteine in 25.5% of patients.

The mean follow-up time was 1.2 ± 0.7 years (maximum of two years) for the total sample, 1.2 ± 0.5 years for patients under antifibrotic therapy, and 1.0 ± 0.7 years for patients who had never been treated with antifibrotic therapy. A total of 334 treatment episodes under antifibrotic therapy (168 pirfenidone, 166 nintedanib) were reported for 298 patients in our registry, resulting in 36 patients (12 %) with two episodes. Among these, pirfenidone was the first antifibrotic drug in 29 patients. Seven patients switched from pirfenidone to nintedanib within 3 months after discontinuation of pirfenidone; the other 22 patients started nintedanib on average 13 months after discontinuation of pirfenidone (Table 1).

Generalized linear mixed models were used to analyse the pulmonary function and 6MWD tests. These models included all antifibrotic therapy treatment episodes, and were based on the observed values. During the 2 years of follow-up, mean predicted FVC% remained almost stable (Figure 1A, β for change in follow-up=-0.42, 95%CI: -1.44 to 0.60, p=0.416), with no significant differences between the two groups (β for time x therapy= -0.65, 95%CI: -1.82 to 0.52, p=0.274). Predicted DLCO showed a similar course in both groups (Figure 1B), with no significant decline in DLCO (β for change in follow-up =-1.05, 95%CI: -2.40 to 0.30, p=0.127) in follow-up and no significant differences between the two groups (β for time x therapy= -0.40, 95%CI: -2.56 to 1.77, p=0.721). Results for the 6MWD test were available in 89% of patients at baseline; however, this measurement was compromised by a high rate of missing data during follow-up. There was no statistically significant difference in the course of 6MWD results over time (β for change in follow-up = -14.8, 95%CI: -25.6, 4.1, p=0.076), considering the observed values. The primary analysis was repeated in patients with disease duration of less than or equal to 12 months at enrolment (prevalent patients, Figure 1: second column). A slightly better course of FVC %, DLCO %, and 6MWD was observed in patients with antifibrotic therapy; however, the difference was not statistically significant. The sensitivity analyses using imputed data and data obtained by the LOCF approach resulted in comparable results to those of the primary analysis. If an FVC % of 0 was imputed in patients who died during follow-up, patients never on antifibrotic therapy tended to have a slightly, but not significantly, stronger FVC decline. The decline in DLCO was worse in patients with antifibrotic treatment, although when imputation of the worst individual value was implemented, there were no significant differences between groups.

The risk of mortality was analysed for the last available treatment episode in patients who were treated with pirfenidone (n=139) and nintedanib (n=159) in follow-up. A total of 194 (33.0%) patients died during follow-up. A total of 79 (41%) patients died of IPF related reasons (20% by respiratory failure, and 8% by respiratory infection/pneumonia), followed by

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complicating comorbidity (8%) and other causes not related to IPF (9%). The reason of death was unknown for 71 (37%) patients.

Overall mortality was substantially lower in patients treated with antifibrotic therapy. The risk of death for any reason was 37% lower in patients with antifibrotic therapy compared with those without such therapy (HR = 0.63, 95%CI: 0.45; 0.87; p=0.005, Figure 1). This result was robust (and remained statistically significant) on multivariable analysis, as reported in Table 2. Analysis for both antifibrotic drugs approved for treating IPF, nintedanib and pirfenidone, revealed no statistically significant difference in overall mortality between the two drugs (HR for pirfenidone versus nintedanib = 1.39, 95%CI: 0.87 – 2.22, p=0.164). In patients treated with antifibrotics the risk of IPF-related death was not (statistically significantly) lower compared to patient without such therapy (HR = 0.75, 95%CI: 0.45; 1.25; p=0.266), while the risk of death for unknown reason was 56% lower in patients with antifibrotics (HR = 0.44, 95%CI: 0.26; 0.75; p=0.003). Due to the lower numbers of events in this sub-group analysis this result should be interpreted with caution.

We tested the hypothesis whether survival differs between patients with stable FVC (i.e. less than 10 % decline during follow-up) compared to patients with worsening of FVC of more than 10% during follow-up, regardless of therapy. The risk of mortality was slightly higher in such patients with disease progression compared to stable IPF patients (HR = 1.34, 95%CI: 0.89 – 2.02, p=0.163). This result was confirmed while adjusting for the effect for antifibrotic treatment.

The risk of mortality was additionally analyzed in patients with disease duration of less than 12 months prior to study enrollment. The risk of death in the subsample of incident patients was 64% lower in patients treated with antifibrotic therapy compared to controls (HR = 0.44, 95%CI: 0.25; 0.78; p=0.003). The result was confirmed in multivariable analysis.

Discussion

The present analysis of the large and contemporary INSIGHTS-IPF registry indicates that patients on antifibrotic therapy appear to survive significantly longer than IPF patients without antifibrotic therapy. The lower overall mortality risk in the patients treated with antifibrotic medication was mainly driven by patients with unknown reason of death. The statistically non-

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significant relationship between antifibrotic therapy and risk of IPF-related deaths might be due to the low number of recorded IPF-related deaths (79. 4% of deaths).

Compared with the recently published observational data from the EurIPF registry, patients in INSIGHTS-IPF were nearly identical in terms of TLC % predicted (70.0% vs 71.2%), FVC % predicted (68.4% versus 68.3%), and FEV_1 % predicted (110% versus 111%), while DLCO % predicted was lower in our study (42.1% versus 37.8%).[9] A subset of IPF patients with long-term follow up within the EurIPF registry were analysed by Kaplan-Meier analysis (without propensity score matching) in correlation with the date of first IPF diagnosis. The analysis of this subset found that median survival on antifibrotic drugs was 123.1 months (censored cases inclusive, range 84– 162 months), compared with a median survival of 68.3 months in patients treated with any other medication including immunosuppressive therapies (censored cases inclusive, range 54–83 months). Functional follow-up data from the EurIPF registry were not reported. Another difference between our data and those of the EurIPF registry, besides the larger number of patients and the statistics applied in our cohort, is the fact that pirfenidone was used in the vast majority (83%) of the EurIPF registry cohort while in our study population nintedanib and pirfenidone where almost equally distributed, slightly favouring nintedanib (53.3%).

Interestingly, we observed a similar, stable course of lung function parameters (FVC and DLCO) over time in both groups, with and without antifibrotic therapy, while overall mortality was considerably higher in the group not treated with antifibrotics. At first glance, our data could provide basis for a hypothesis that stable physiological measurements like FVC and DLco alone may not provide a safeguard against premature mortality in IPF. Lung function measurements every 6 to 12 months is common practice and thus employed in our registry. However, such measurements may be less sensitive to detect differences in the course of IPF compared to highly standardized serial measurements at shorter intervals which are commonly applied in clinical trials. Moreover, missing lung function data may have contributed to blunt differences of the slope of FVC and DLco decline between patients with and without antifibrotic therapy. In this context, it is noteworthy that hospital-based FVC measurements, compared with unsupervised daily home measurements, have been suggested to be less sensitive in detecting progression of fibrosis and in predicting subsequent prognosis.[10] However, a recent clinical treatment trial using daily home spirometry for the primary endpoint also revealed potential technical and practical obstacles associated with this methodology. [20]

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The phenomenon of emphysema blunting the decline of FVC in both groups may have contributed to this observation, but the prevalence of emphysema as reported by the investigators was low in both groups. The higher preponderance of steroid-treated patients in the group not treated with antifibrotics may also be considered to potentially contribute to a higher mortality in this group. However, the mean prednisone dosage in our study - given to a quarter of patients in our - study was 14 mg/d. In the INPULSIS study the maximum dose was 15mg/day and in the ASCEND study, prednisone was only allowed if given for another indication.[11, 12] Nonetheless, we cannot exclude that unbalanced steroid-medication has contributed to the observed difference. Finally, antioxidant drugs (NAC) were less commonly used in the antifibrotic therapy arm. The impact of these drugs on prognosis is still under discussion and thus a bias cannot be fully excluded.[13, 14] In consideration of all the limitations our data should be taken as a signal of caution that stability of FVC and DLco may not always protect from premature mortality in the absence of antifibrotic therapy in a fatal disease like IPF. The common practice, still widely used, of withholding antifibrotic therapy from physiologically stable IPF patients may therefore set these patients on a path of increased risk of dying.[15]

Another important aspect of our study is the fact that all patients were enrolled solely based on investigator judgement. The patients enrolled were, therefore, a cohort which included all the imponderabilities of diagnosis in this complex disease which occur in daily practice. The observed difference in survival in favour of antifibrotic therapy is, therefore, an important argument for the clinical application of these drugs, even though a causative argument cannot be made from our study. This observation is, therefore in accordance with recent clinical trials showing that antifibrotic therapies are effective in progressive fibrotic interstitial lung diseases other than IPF.[20,26,27]

Our data do not identify a cause for the difference in overall mortality between patients with and without antifibrotic therapy. However, one can speculate that acute exacerbation may have contributed substantially to this difference.

A number of limitations need to be taken into consideration when interpreting the findings. The major limitation of this study is that patients with existing (prevalent) and newly diagnosed (incident) IPF were documented which may potentially cause lead time bias regarding mortality. This is especially important since time to diagnosis was approximately one year longer in the never-treated population, which could indicate a "healthy survivor effect".[16]

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Further, there was no randomization between the group of patients who had never been treated with an antifibrotic therapy and patients who were treated with an antifibrotic drug. To account for bias by indication, we calculated a propensity score to estimate the probability of being treated with an antifibrotic drug in our registry based on clinical characteristics. However, there may exist unmeasured variables that cannot be included in the propensity score model that may have impacted the association between antifibrotic therapy and mortality. Furthermore, accompanying therapies such as anti-oxidant or anti-acid therapy may have impacted the results of our analysis. We also had to account for a high proportion of missing values in the pulmonary function tests and in the 6MWD test in the follow-up data, which could have affected our results. The fact that only ILD specialty centers participated in the INSIGHTS-IPF Registry may limit the generalizability of our study.

In conclusion, we were able to demonstrate a significant lower all-cause mortality in IPF patients treated with antifibrotic drugs when compared to a matched cohort of IPF patients not treated with antifibrotic drugs. Moreover, our analysis provides the basis for a hypothesis that stability of lung function parameters over time, especially FVC and DLco, in untreated IPF patients may be misleading as our data indicate that stability of these parameters probably do not protect from premature death.

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Declarations

Acknowledgements

The authors thank the patients for their participation in the registry.

The authors acknowledge the sustained valuable contribution of Silke Geier (deceased in September 2019) to this registry.

Ethics approval and consent to participate

The study materials were approved by the Ethics Committee of the Medical Faculty, Technical University of Dresden (EK 255082012), and by further local ethic committees as per local requirements.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

JB received grants from Boehringer Ingelheim, and personal fees for consultation or lectures from Actelion, Bayer, Boehringer-Ingelheim, and Roche. He is member of the national and international IPF guideline committee; AP reports grants and personal fees from Roche/InterMune, grants and personal fees from Boehringer Ingelheim, outside the submitted work; HuWi reports personal fees from Boehringer Ingelheim, and personal fees from Roche, outside the submitted work; MC reports honoraria for lectures from Boehringer Ingelheim Pharma GmbH and Roche Pharma, and for serving on advisory boards from Boehringer Ingelheim, outside the submitted work; DP reports personal fees outside the submitted work from Actelion, Bayer, Boehringer Ingelheim, Sanofi, Biogen, Shield and MSD; DS reports personal fees from Boehringer Ingelheim, Roche, outside the submitted work; SV reports personal fees from Boehringer Ingelheim, personal fees from Roche Pharma, personal fees from Actelion Pharma, grants and personal fees from Novartis Pharma, personal fees from Berlin Chemie, and personal fees from Astra, outside the submitted work; HeWi reports personal fees from Boehringer, personal fees from Roche, during the conduct of the study;

personal fees from Bayer, personal fees from Biotest, personal fees from Actelion, personal fees from GSK, and personal fees from Pfizer, outside the submitted work; CN reports honoraria for lectures and serving on advisory boards from Boehringer Ingelheim and Roche Pharma; SA reports case payments from Boehringer Ingelheim, during the conduct of the study; personal fees from Boehringer Ingelheim, and personal fees from Roche, outside the submitted work; SG reports personal fees from Boehringer Ingelheim, personal fees from Roche Pharma, personal fees from Actelion Pharma, grants and personal fees from Novartis Pharma, personal fees from Berlin Chemie, and personal fees from Astra, all outside the submitted work; TW reports grants from Boehringer, during the conduct of the study; TB reports grants from German Center for Lung Research (DZL), personal fees for consultation or lecture from Roche, AstraZeneca, Chiesi, GSK, and Novartis outside the submitted work; MK reports grants and personal fees from Roche/InterMune, grants and personal fees from Boehringer Ingelheim, outside the submitted work.

All other authors declare that they have no competing interests.

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466 **Table 1. Characteristics of patients, in the total analysed cohort and by presence or absence**
467 **of antifibrotic treatment**
468

	Total **n=588**	**Never been treated with antifibrotic therapy** **n=290**	**Treated with antifibrotic therapy** **n=298**
Male sex; n(%)	476 (81.0)	230 (79.3)	246 (82.6)
Age; mean (SD), p50	69.8 (9.1); 72	70.3 (9.4); 73	69.2 (8.8); 71
Body Mass Index in kg/m²; mean (SD), p50	27.6 (4.1); 27.2	26.9 (4.1); 26.3	28.2 (4.0); 27.7
underweight (BMI<18.5); n (%)	1 (0.2)	1 (0.3)	0 (0.0)
normal weight (18.5 ≤ BMI ≤ 25); n (%)	153 (26.0)	93 (32.1)	60 (20.1)
overweight(25 < BMI ≤ 30); n (%)	291 (49.5)	133 (45.9)	158 (53.0)
obesity (BMI>30); n (%)	143 (24.3)	63 (21.7)	80 (26.9)
Never smoked; n(%)	205 (34.9)	96 (33.1)	109 (36.6)
Ex-smoker; n(%)	372 (63.3)	189 (65.2)	183 (61.4)
Number of comorbidities; mean ± SD	1.7 (1.5); 2	1.8 (1.5); 2	1.7 (1.4); 2
Symptom duration; mean (SD), p50	3.5 (4.2); 2.2	3.5 (4.7); 2.2	3.4 (3.8); 2.1
Age at symptom onset; mean (SD), p50	66.1 (10.5); 68.0	66.4 (11.3); 69.0	65.9 (9.8); 67.7
Age at diagnosis; mean (SD), p50	68.0 (10.0); 70.0	68.1 (10.7); 70.6	68.0 (9.2); 69.9
6-minute walk distance; mean (SD), p50	278.5 (193.9); 330	257.6 (188.7); 300	297.8 (197.1); 360
Borg index; mean (SD), p50	2.2 (2.4); 1	2.2 (2.5); 1	2.2 (2.2); 1
Current therapy			
Prednisone, n (%)	139 (23.6)	86 (29.7)	53 (17.8)
Other steroids, n (%)	11 (1.9)	2 (0.7)	9 (3.0)
Azathioprine, n (%)	14 (2.4)	10 (3.5)	4 (1.3)
Cyclophosphamide, n (%)	1 (0.2)	0 (0.0)	1 (0.3)
Mycophenolate mofetil, n (%)	1 (0.2)	1 (0.3)	0 (0.0)
N-Acetylcysteine, n (%)	150 (25.5)	101 (34.8)	49 (16.4)
Antifibrotic therapy, n (%)	298 (50.7)	0 (0.0)	298 (100.0)
Patients on oxygen therapy	157 (26.7)	86 (29.7)	71 (23.3)
Environmental exposure	199 (33.8)	86 (29.7)	113 (37.9)
Gastro-oesophageal reflux	162 (27.6)	81 (27.9)	81 (27.2)
Family history of ILD	27 (4.6)	20 (6.9)	7 (2.4)
Exposure to drugs	21 (3.6)	9 (3.1)	12 (4.0)
GAP index, n(%)			

Stage I	115 (20.4)	56 (20.4)	59 (20.3)
Stage II	282 (49.9)	128 (46.6)	154 (53.1)
Stage III	168 (29.7)	91 (33.1)	77 (26.6)
Lung function test			
Total Lung Capacity, % predicted; mean (SD), p50	71.0 (20.5); 70.5	71.5 (25.7); 69.7	70.5 (14.2); 71.1
Inspiratory Vital Capacity, % predicted; mean (SD), p50	73.2 (20.4); 74.1	70.8 (22.2); 71.8	75.4 (18.4); 76.4
FVC, % predicted; mean (SD), p50	68.6 (18.8); 70.2	66.8 (19.8); 67.9	70.4 (17.5); 71.5
FEV_1, % predicted; mean (SD), p50	76.1 (19.7); 76.8	74.1 (20.7); 74.4	77.9 (18.6); 78.4
FEV_1: FVC, % predicted; mean (SD), p50	110.9 (11.7); 111.2	111.6 (12.2); 111.9	110.3 (11.2); 110.8
DLCO, % predicted; mean (SD), p50	37.8 (18.5); 35.5	37.6 (20.2); 35.5	38.0 (16.9); 35.2
Health-related quality of life, EQ5D; mean (SD), p50	59.6 (23.6); 60	58.0 (24.1); 60	61.2 (23.1); 65

P50 = median; SD = standard deviation

Table 2. Risk of mortality estimated by a multivariable Cox regression model

	HR	P value	95% CI
Antifibrotic therapy	0.66	0.016	0.47 ; 0.93
Age	1.09	<0.001	1.07 ; 1.12
Female sex	0.71	0.116	0.47 ; 1.09
IPF disease duration	0.96	0.005	0.94 ; 0.99
Any comorbid disease	1.05	0.821	0.69 ; 1.60
FVC % predicted	0.96	<0.001	0.95 ; 0.98
Overall physician's judgement of clinical course of IPF:			
stable disease	1.00		
slow progression	1.41	0.102	0.93 ; 2.12
rapid progression	2.69	0.002	1.45 ; 4.97

Hazard Ratio (HR) for 1 year change in age and IPF disease duration, HR for 1% change in FVC% predicted.

Figure 1: Change in FVC % predicted (A), DLCO % predicted (B), and 6-minute walking distance (6MWD; C) over the 2-year follow-up (β (interaction term time x therapy) = estimated difference in change during 2-year follow-up in the considered parameter between patients with and without antifibrotic therapy)

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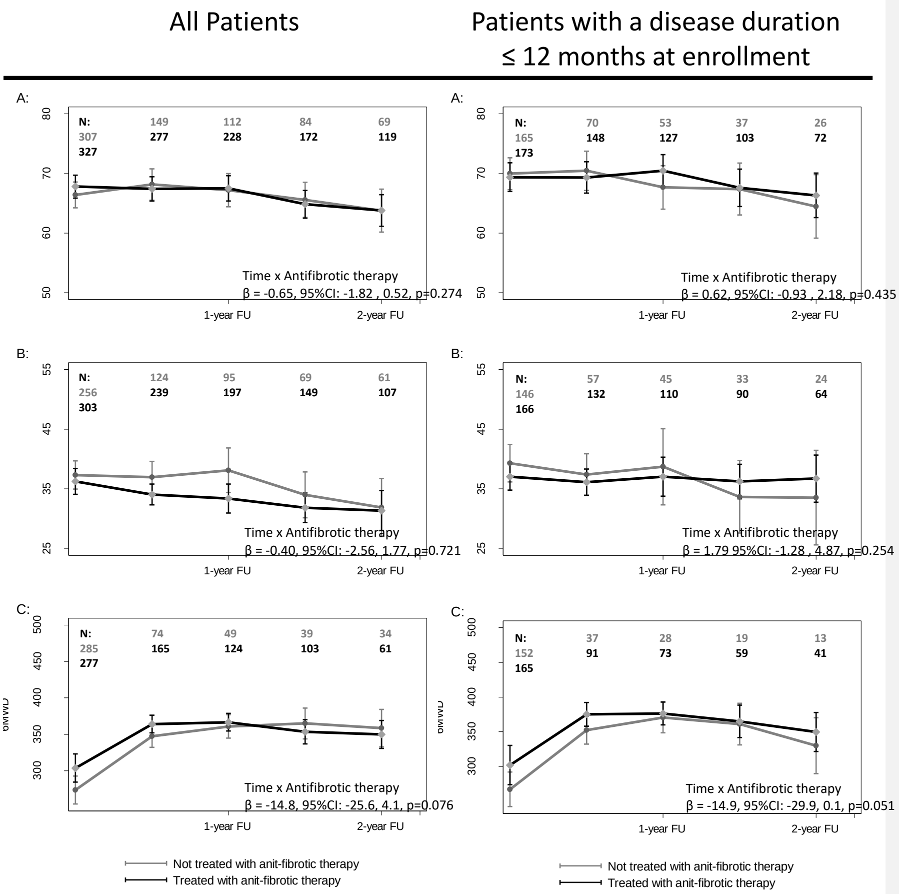
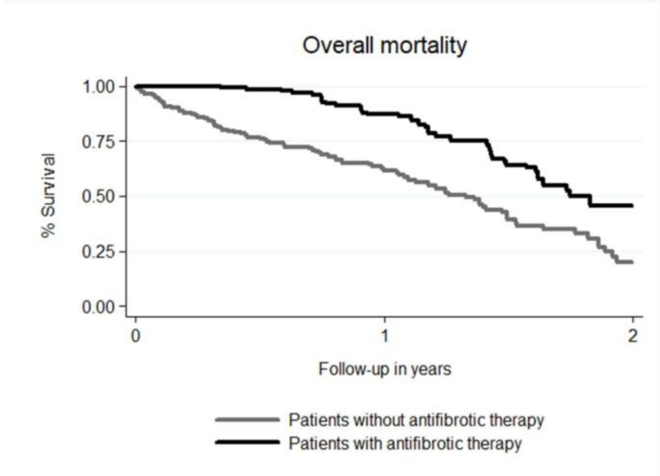


Figure 2: Risk of mortality within 2 years by antifibrotic treatment (by propensity score weighted Kaplan-Meier survival curves).



Number of patients at risk			
With antifibrotic therapy	281	129	57
No antifibrotic therapy	252	139	93

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	n.a.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	4-5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-8
		(b) Indicate number of participants with missing data for each variable of interest	6-8
		(c) Summarise follow-up time (eg, average and total amount)	6

Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	13-15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16-17
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.