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Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry

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ABSTRACT After introduction of the new international guidelines on idiopathic pulmonary fibrosis (IPF) in 2011, we investigated clinical management practices for patients with IPF according to physicians' diagnoses.

A prospective, multicenter, noninterventional study with comprehensive quality measures including on-site source data verification was performed in Germany.

502 consecutive patients (171 newly diagnosed, 331 prevalent; mean±SD age 68.7±9.4 years, 77.9% males) with a mean disease duration of 2.3±3.5 years were enrolled. IPF diagnosis was based on clinical assessments and high-resolution computed tomography (HRCT) in 90.2%, and on surgical lung biopsy combined with histology in 34.1% (lavage in 61.8%). The median 6-min walk distance was 320 m (mean 268±200 m). The mean forced vital capacity was 72±20% pred and diffusing capacity of the lung for carbon monoxide was 35±15% pred. No drugs were administered in 17.9%, oral steroids in 23.7%, N-acetylcysteine in 33.7%, pirfenidone in 44.2% and other drugs in 4.6% of patients. Only 2.8% of the cohort was listed for lung transplantation.

IPF patients were diagnosed in line with the new guidelines. They had more severe disease than those enrolled in recent randomised controlled trials. In addition to HRCT, the frequency of lung biopsies was surprisingly high. Treatment patterns varied substantially.



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This largest published registry of IPF patients shows surprising disease severity and treatment variation <http://ow.ly/JbWRn>

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Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause that is limited to the lungs [1]. The disease is characterised by progressive worsening of lung function and carries a prognosis that is worse than that of many cancers. According to revised guidelines of the European Respiratory Society (ERS), the American Thoracic Society (ATS) and other societies [1], revised in 2011, and an update of the ATS/ERS classification of idiopathic interstitial pneumonias in 2013 [2], the diagnosis of IPF requires exclusion of other known causes of interstitial lung disease (ILD), the presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to SLB, and specific combinations of HRCT and SLB patterns in patients subjected to SLB. IPF predominantly presents in older individuals, with preponderance in men and previous or current smokers. Patients typically have unexplained, chronic and worsening exertional dyspnoea, and commonly exhibit unproductive cough, bibasilar inspiratory crackles and finger clubbing.

Currently, substantial efforts are being made to investigate the efficacy and safety of new drugs for IPF in controlled clinical trials [3]. Meanwhile, however, observational data on the characteristics of patients with IPF outside clinical studies, their management under clinical practice conditions and their long-term outcomes are sparse. In repeated calls for action to establish IPF registries, various authors underlined that improved management of this disease is dependent on better understanding of its epidemiology and diagnostic spectrum, and an analysis of outcomes from emerging therapies [4–6].

Registry data can serve further purposes; for example, they can complement the data from RCTs, provide much-needed information on drug utilisation (of particular importance during the introduction of new therapies) and evaluate to what extent guidelines are followed in practice [7, 8].

The contemporary Investigating Significant Health Trends in Idiopathic Pulmonary Fibrosis (INSIGHTS-IPF) registry was implemented to prospectively and comprehensively assess the characteristics, diagnostic procedures, treatment patterns, quality of life and long-term outcomes of patients with IPF under clinical practice conditions in Germany. Here, the baseline data of a large cohort of >500 patients, which in contrast to clinical trials were not pre-selected, is presented.

Methods

The rationale and design of the INSIGHTS-IPF registry have been described previously in detail [9, 10]. In short, INSIGHTS-IPF is a multicentre, noninterventional study (registry) that documents patients with IPF in routine care. The study was initiated in November 2012 and continues to enrol patients (www.clinicaltrials.gov identifier number NCT01695408).

The study materials were approved by the Ethics Committee of the Medical Faculty, Technical University of Dresden, Dresden, Germany, on September 15, 2012, and by further local ethics committees as per local requirements. The Gesellschaft für Wissenschaftstransfer (GWT-TUD GmbH), a 100% subsidiary of the Technical University of Dresden, sponsored the study. The study was designed and is being supervised by an interdisciplinary steering committee (see author list).

In order to ensure adequate patient numbers per centre and high quality of data, the focus of the study is on specialised lung centres or practices. Currently, 19 pulmonary specialist centres in all parts of Germany are entering data into the registry.

Patients are eligible for documentation if they are aged ≥ 18 years, have IPF diagnosed by a physician who follows current international or German national guidelines, and have provided written informed consent. To avoid selection of patients and, thus, violation of the “real-life” principle, no explicit noneligibility criteria were defined. Patients were included in a consecutive manner at each site in order to avoid selection bias.

At baseline, data on demographics, risk factors and comorbidities are collected. Detailed information on IPF as defined in our study is comprised of disease history, diagnostic procedures, and prior and current drug and non-drug treatment. At follow-up visits, every 6 ± 3 months, events such as hospitalisation, disease exacerbation or death are recorded, as well as current management practice.

Predicted percentage values for lung function were calculated on the basis of lung function test results, according to the following established formulas: for total lung capacity and diffusing capacity of the lung for carbon monoxide (DLCO), formulas by CRAPO *et al.* [11] from 1981 were used; for inspiratory vital capacity (IVC), the formula by QUANJER *et al.* [12] from 1993 was used; and for forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and FEV1/FVC, formulas by QUANJER and co-workers [12, 13] from 1993 and 2012 were applied. In terms of reference values, between 1978 and 2009, no secular trends were observed, and differences between datasets comprising >1000 subjects were small [14].

Further, in yearly intervals, patient-related outcomes are being documented, including the San Diego Shortness of Breath Questionnaire [15, 16] and the St George's Respiratory Questionnaire (SGRQ) [17]. Scores on the latter range from 0 to 100, with higher scores indicating more limitations (suggested minimally important difference for patients with IPF has been estimated at 5–8 points) [18].

The GAP point-scoring system (GAP index) is a clinical prediction tool for the prognosis of patients with IPF using gender, age, and two lung physiology variables, FVC and DLCO. Patients were categorised as stage I, II or III, corresponding to an estimated 1-year mortality of 6%, 16% and 39%, respectively [19].

Data collection and statistical analysis

Data collection is performed using an Internet-based case report form (electronic case report form) with automated plausibility checks. On-site monitoring with source data verification is performed in $\geq 20\%$ of centres.

Sample size was determined by feasibility aspects and no formal sample size calculation was made. The study uses a non-probability sampling approach.

Categorical data are displayed as absolute and relative frequencies. For continuously distributed data, data following an approximately normal distribution are reported as mean and standard deviation; otherwise, median and interquartile range (IQR) are shown. The analysis was mainly performed descriptively. Characteristics of patients who were enrolled in INSIGHTS-IPF were compared with those in randomised controlled clinical trials (table S1) by a Chi-squared test for categorical variables and a t-test for continuously distributed variables. Data were analysed with STATA 12.1 (StataCorp, College Station, TX, USA).

Results

At interim analysis database lock (October 27, 2014), 19 centres had entered data for 502 patients. All results reported in this article were entered at the time of inclusion of the patients (baseline visit).

Demographics

Baseline characteristics are presented in table 1. All but two patients were Caucasian (99.6%). Substantially more men than women were documented (77.9% *versus* 22.1%) and patients were predominantly older (mean age 68.7 years). In accordance with the age pattern, the majority of patients were retired (80.0%).

Risk factors and comorbidities

Environmental exposure was reported in 136 patients (27.1% of total). Among those, types of exposure included asbestos in 56 patients, metal dusts in 25, raising birds in 19, wood dusts in 16 and solvents in

TABLE 1 Patient characteristics and risk factors in the total cohort by idiopathic pulmonary fibrosis (IPF) disease duration

	Patients	Total cohort	Subgroups		
			Prevalent IPF [#]	Incident IPF [†]	p-value
Patients		502	331	171	
Males	502	391 (77.9)	243 (73.4)	148 (86.6)	0.001
Age years	502	68.7 $\pm$ 9.4	67.5 $\pm$ 9.8	71.0 $\pm$ 8.0	<0.001
Body mass index kg·m⁻²	502	27.6 $\pm$ 4.1	27.4 $\pm$ 4.2	28.2 $\pm$ 3.8	0.048
Smoking status	502				
Never		195 (38.8)	140 (42.3)	55 (32.2)	0.087
Previous		302 (60.2)	188 (56.8)	114 (66.7)	
Current		5 (1.0)	3 (0.9)	2 (1.2)	
6-min walk distance m	502	267.6 $\pm$ 199.7	266.7 $\pm$ 198.7	269.4 $\pm$ 202.1	0.886
Symptom duration months	458	46.9 $\pm$ 52.5	57.6 $\pm$ 54.4	27.2 $\pm$ 42.3	<0.001
Disease duration months	498	27.6 $\pm$ 41.9	41.3 $\pm$ 46.2	1.4 $\pm$ 2.0	0.036
Risk factors	502				
Environmental exposure		136 (27.1)	80 (24.2)	56 (32.8)	0.028
Gastro-oesophageal reflux		148 (29.5)	106 (32.0)	42 (24.6)	0.136
Genetic predisposition		20 (4.0)	13 (3.9)	7 (4.1)	0.887
Exposure to drugs associated with IPF		8 (1.6)	5 (1.5)	3 (1.8)	0.309

Data are presented as n, n (%) or mean $\pm$ SD, unless otherwise stated. [#]: duration since diagnosis ≥ 6 months; [†]: duration since diagnosis <6 months.

18. Interestingly, IPF occurred, on average, 21.3 years after smoking cessation and only 1.0% of the patients were current smokers.

As shown in figure 1, comorbidities were frequent, particularly overweight/obesity (47.8%/26.5%). Pulmonary hypertension was suspected on transthoracic echocardiography in 86 (17.2%) patients; however, the results of right heart catheterisation from 52 of these patients confirmed pulmonary hypertension in 27 (52%) patients only, pre-capillary pulmonary hypertension in 21 (40.4%) and post-capillary pulmonary hypertension in six (11.5%) patients.

On the GAP score, which allows prognostic stratification of patients (n=348 with all necessary values), 21.8% were in stage I, 56.9% in stage II and 21.3% in stage III.

IPF characteristics

On average, the first symptoms had occurred 3.9 ± 4.4 years before inclusion in the registry. Patients' median age at onset of first symptom was 66.3 years (IQR 58–73 years) and age of IPF diagnosis was 68.4 years (IQR 60–74 years). In categorical terms, 26.7% of our patients were newly diagnosed (within 6 months; “incident IPF”) and in 73.3%, disease duration was ≥ 6 months (“prevalent cases”).

Current IPF symptoms are shown in figure 2. Dyspnoea (85.9%), cough (74.7%) and bibasilar crackles (79.0%) were the most frequently reported signs or symptoms. When evaluating the linkage of clubbing and crackles with lung function and exercise capacity, no clear association was found. However, patients with the absence of both clubbing and crackles compared with those with presence of both findings, had significantly higher % predicted FVC values and a trend to higher 6-min walk distance values but about the same DLCO value (table S2).

Diagnostic procedures

Lung function tests

Lung function tests were a standard procedure and reported in 496 (98.8%) patients in the 12 months before baseline and results were current (performed 1.1 ± 6.2 months before enrolment). Mean FVC was 72 ± 20 % pred, mean IVC was 72 ± 20 % pred and mean DLCO was 35 ± 15 % pred (table 2).

Confirmatory procedures for the IPF diagnosis are shown in figure 3. Multidisciplinary discussion (MDD) was the diagnostic basis in 108 (21.8%) patients.

High-resolution computed tomography

Diagnosis was based on HRCT in 452 (90.2%) patients. HRCT findings in 447 patients showed the following patterns, according to current ATS/ERS criteria [1]: UIP pattern in 75.6% of patients, possible UIP in 23.7% and no UIP pattern in 0.7%.

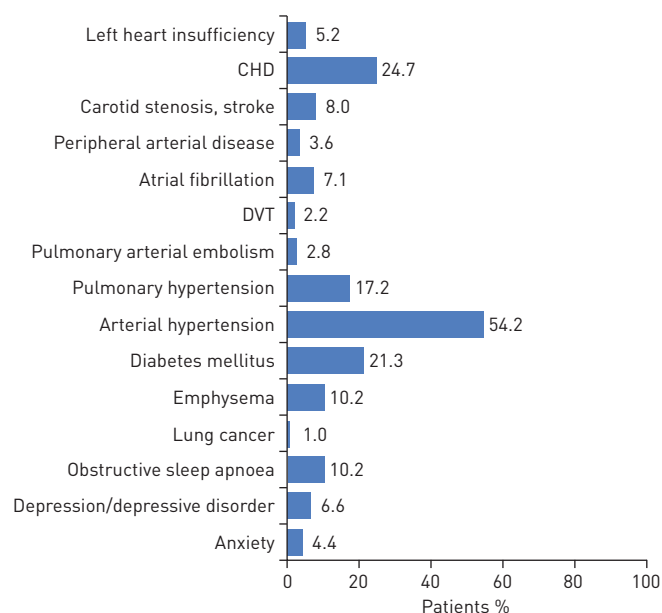


FIGURE 1 Comorbidities at baseline. CHD: coronary heart disease; DVT: deep venous thrombosis.

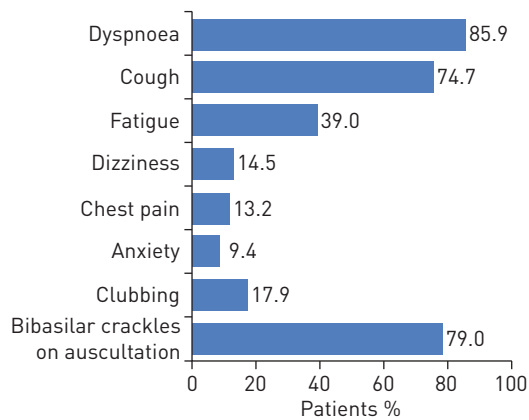


FIGURE 2 Symptoms indicative of idiopathic pulmonary fibrosis at baseline.

Surgical lung biopsy

In order to obtain adequate lung specimen, histology was performed in 171 (34.1%) patients with a median of 1.6 years (IQR 0.3–3.5 years) before enrolment. In 170 patients (one without data), according to current ATS/ERS criteria [1], the following patterns were seen: UIP pattern in 141 (82.9%) patients, probable UIP pattern in 14 (8.2%) patients, possible UIP pattern in 12 (7.1%) patients and no UIP pattern in three (1.8%) patients.

The combination of HRCT and biopsy was available in 154 patients (table 3). In this group, the following HRCT patterns were reported: UIP in 62.8% and possible UIP in 37.2%. There was no patient with an inconsistent UIP pattern. The great majority of these cases (144 patients, 93.5%) had a definitive IPF diagnosis, while eight patients were diagnosed with probable IPF (no patient with a possible IPF diagnosis). In these patients, the diagnosis was based on MDD in 16.7% (24 out of 144) and 12.5% (one out of eight), respectively (table S3).

Out of 293 patients in whom IPF diagnosis was based on HRCT and clinical assessment alone, 49 (16.7%) showed a possible UIP pattern on HRCT. Among those, eight (16.3%) patients had a diagnosis based on MDD.

Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) was performed in 310 (61.8%) out of 502 patients.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was undertaken by 138 patients with a mean maximal oxygen uptake of $16.8 \pm 5.2 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$.

TABLE 2 Lung function in the total cohort and by IPF disease duration

Parameter	Patients n	Total cohort	Subgroups		
			Prevalent IPF [#]	Incident IPF [†]	p-value
Patients n		502	331	171	
Total lung capacity L	469	4.4±1.4	4.4±1.5	4.6±1.2	0.228
Total lung capacity % pred	469	70.2±21.1	69.4±24.0	71.8±14.3	0.378
Inspiratory vital capacity L	440	2.6±0.9	2.6±0.9	2.7±0.8	0.638
Inspiratory vital capacity % pred	440	72.2±20.0	71.9±20.4	72.8±19.3	0.584
FVC L	447	2.6±0.8	2.5±0.9	2.6±0.8	0.584
FVC % pred	447	72.2±20.6	71.7±19.7	73.7±19.3	0.346
FEV₁ L	485	2.2±0.7	2.2±0.7	2.2±0.6	0.334
FEV₁ % pred	485	74.7±19.8	73.5±20.2	76.9±18.7	0.068
FEV₁/FVC	447	0.9±0.1	0.9±0.1	0.9±0.1	0.361
FEV₁/FVC % pred	447	112.3±11.9	111.6±11.8	113.6±12.1	0.098
D_{co} mL·min⁻¹·mmHg⁻¹	408	10.4±4.9	10.2±4.4	11.0±5.6	0.089
D_{co} % pred	408	35.5±15.5	34.4±14.1	37.7±17.6	0.041
PAO₂ mmHg	461	67.8±11.7	67.2±12.4	68.9±10.2	0.158
PACO₂ % pred	461	38.9±6.2	39.5±6.8	37.6±4.4	0.001

Data are presented as n or mean±SD. FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; D_{co}: diffusing capacity of the lung for carbon monoxide; PAO₂: alveolar oxygen tension; PACO₂: alveolar carbon dioxide tension. [#]: duration since diagnosis ≥6 months; [†]: duration since diagnosis <6 months.

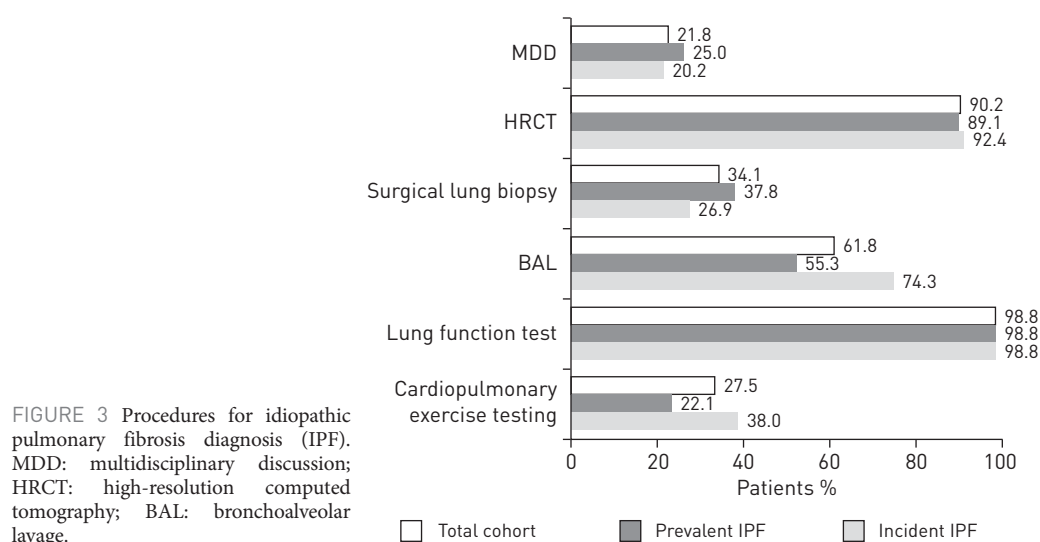


FIGURE 3 Procedures for idiopathic pulmonary fibrosis diagnosis (IPF). MDD: multidisciplinary discussion; HRCT: high-resolution computed tomography; BAL: bronchoalveolar lavage.

6-min walking test

The 6-min walking test was performed in all 502 patients, with a median walking distance of 320 m (268 ± 200 m).

Prior and current therapy

Previous therapy for IPF (undergone before entry of the patient into the registry) and current treatment are displayed in figure 4, and included the following: no drugs in 17.9%; oral steroids in 26.1% (as monotherapy in 6.8%); NAC in 33.7% (as monotherapy in 12.0%, as triple therapy with azathioprine and steroids in 1.4%); pirfenidone in 44.2% (as monotherapy in 26.7%, in combination with NAC in 10.4% and in combination with prednisone in 6.2%); other drugs in 4.6%; anticoagulation irrespective of indication in 20.5%; and long-term oxygen in 33.1%.

Hospitalisation

Within the last 12 months prior to the inclusion visit, 42.9% of patients were hospitalised due to IPF or related events, 3.9% were hospitalised due to events not related to IPF, 9.2% were admitted to emergency departments and 4.5% underwent pulmonary rehabilitation.

Overall judgment

In physicians' overall judgment, 36.3% had stable disease, 30.9% had slow progression, 11.2% had rapid progression and in 21.7% of cases, no judgment was considered possible.

Candidates for lung transplantation

A total of 169 (33.7%) patients were aged <66 years and 99 (58.6%) were potential candidates for lung transplantation based on disease severity (FVC <50% pred and/or DLCO <40% pred). Only 14 patients (2.8%), however, were listed for lung transplantation.

TABLE 3 High-resolution computed tomography (HRCT) and surgical biopsy results by usual interstitial pneumonia (UIP) pattern

Surgical lung biopsy	HRCT			
	UIP	Possible UIP pattern	Inconsistent with UIP pattern	No results
UIP definite	84	42	0	2
UIP probable	9	5	0	0
UIP possible	4	8	0	0
Definitely not UIP	0	2	0	0
No results	0	0	0	1
Not performed	241	49	3	3

Data are presented as n. Combination of HRCT and biopsy was analysable for 154 patients. Missing information on UIP was noted in three cases.

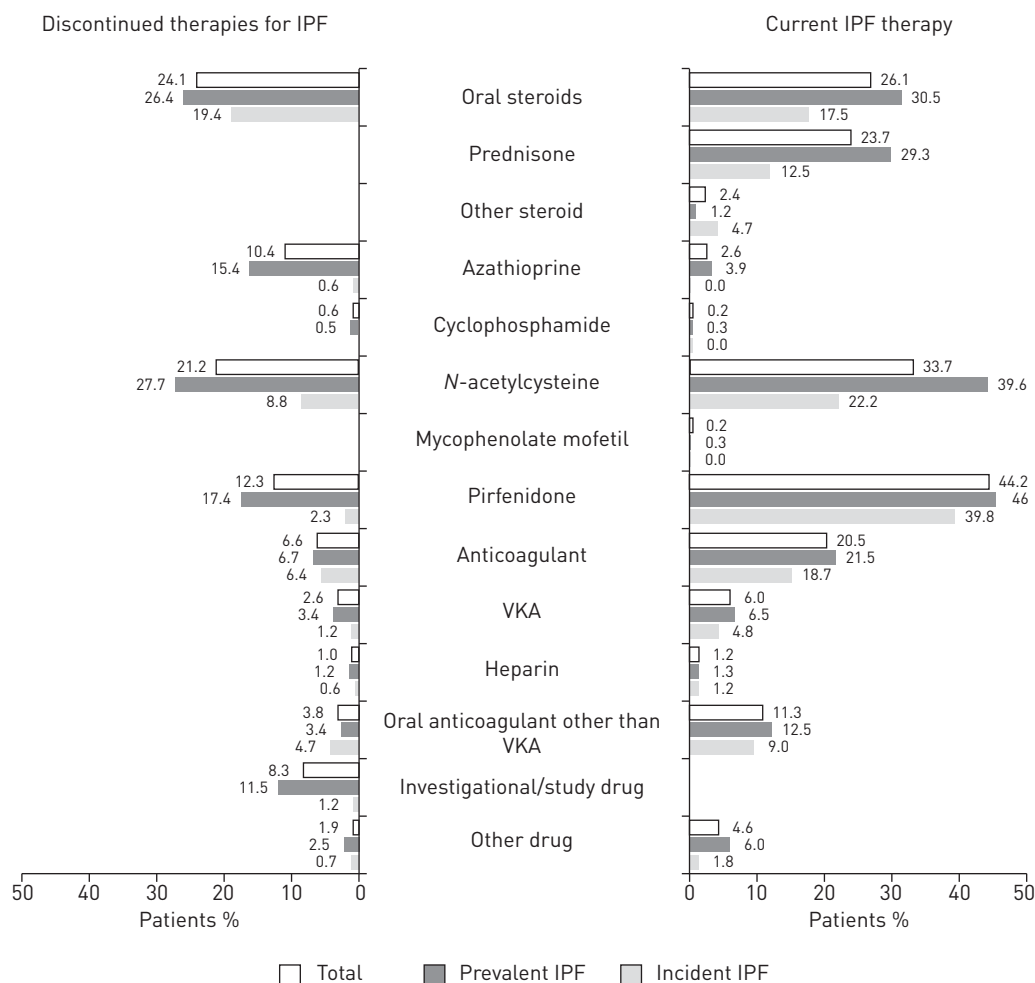


FIGURE 4 Previous and current drug treatment for idiopathic pulmonary fibrosis (IPF). VKA: vitamin-K antagonist.

Ancillary comparisons

Incident versus prevalent IPF

In the comparison between 331 patients with a known diagnosis of IPF for at least 6 months (prevalent cases) and newly diagnosed patients (<6 months; “incident cases”), the incident group was significantly older (71.0 *versus* 67.5 years), had higher proportions of male patients (86.6% *versus* 73.4%) and patients receiving steroids (12.9% *versus* 29.3%), and had a higher *DLCO* (37.7% *versus* 17.6% pred) (table 1).

Comparisons with RCTs

Table S1 presents a comparison of patient demographics, clinical characteristics, lung function test results and symptoms according to the SGRQ between INSIGHTS-IPF and the INPULSIS-1 [20], INPULSIS-2 [20], ASCEND [21] and PANTHER-NAC [22] studies. Patients in INSIGHTS-IPF were the same age as patients in ASCEND and PANTHER, but were older than those in the two INPULSIS studies. Furthermore, INSIGHTS-IPF patients had a longer disease duration than the patients in any of the RCTs, and a much lower 6-min walk distance than the patients in the ASCEND and PANTHER studies (no values from INPULSIS available). Lung function parameters were worse in INSIGHTS-IPF (*e.g.* *DLCO* of 36% *versus* 43–48% pred in the RCTs; FEV₁/FVC of 77% *versus* 81–84% pred in the RCTs). With respect to the SGRQ, INSIGHTS-IPF patients had higher scores, indicating more severe disease (48 *versus* 40 points in the RCTs).

Patient with lymphocytosis

Of the 278 patients for whom lymphocyte values were obtained at entry, 31 had lymphocytes >30% and 247 had lymphocytes ≤30%. There were no statistical differences between the subgroups, with the exception of current steroid treatment (32.3% *versus* 13.8%) and the alveolar oxygen tension (64.5% *versus* 10.1%; table S4). Only four out of 310 patients with lavage results (1.1%) had eosinophils >20% in the fluid.

Patients with versus without IPF medication at baseline

For this ancillary analysis, IPF medication was defined very comprehensively, as any of the following: prednisone, other steroid, azathioprine, cyclophosphamide, mycophenolate mofetil, NAC, pirfenidone, other drugs for IPF treatment, or prophylactic or therapeutic anticoagulation. The number of patients receiving none of this medication at baseline was 90 (17.9%). Patients receiving IPF medication *versus* those receiving no IPF medication had a statistically significantly longer symptom duration (51.2 *versus* 28.4 months), lower DLCO (34.2% *versus* 41.3% pred) and a lower FVC (2.1% *versus* 2.3% pred). Thus, treated patients, compared with those not receiving IPF medication, had longer disease duration and more severe disease (table S5).

Discussion

INSIGHTS-IPF, currently documenting one of the largest IPF cohorts in Europe, uses a comprehensive protocol for data collection, which fulfils current standards [6]. The registry is of particular interest as it investigates the management, response and characteristics of patients after the introduction of the revised ERS/ATS/Latin American Thoracic Society/Japanese Respiratory Society guidelines on IPF in 2011 [1], and their adaptations in Germany [23]. These guidelines were based on a strict, evidence-based procedure (in contrast to the old guidelines [24], which were mainly driven by expert opinion [25]). They introduced a new IPF definition with the need to recognise the specific pattern of UIP on HRCT images of the lungs and/or in the SLB specimens obtained from patients in the appropriate clinical setting. Therefore, datasets collected before 2011 on IPF patients as diagnosed using major and minor criteria as defined in the 2000 ATS/ERS IPF guidelines [24] are of lesser value.

Notably, physicians' individual diagnoses of IPF, which were not necessarily in line with definitions according to the new guidelines, were the eligibility criteria in the study. Nonetheless, the criteria appear to have been adopted early after their introduction: Nine out of 10 patients in our study had an IPF diagnosis based on clinical assessment combined with HRCT and in all but two patients, a definitive/possible UIP pattern was noted (75.6%/23.7%). Only eight patients had probable disease. Thus, the present registry represents a robust dataset of confirmed IPF patients in line with the new definition. It is notable that additional histological analysis from surgical lung biopsies was reported in 34.1% of patients, even in those with a definitive UIP pattern on HRCT. According to the current ERS/ATS guidelines, this intervention is no longer required to make a diagnosis of IPF in patients with definitive HRCT features of UIP, and should be avoided in these patients due to a significant risk for morbidity and mortality in this fragile patient population. In line with this reasoning, we already observed a decline in the frequency of surgical lung biopsies in the incident patients compared with the prevalent group, which was diagnosed earlier. Interestingly, 61.8% of patients received BAL as an adjunctive test, *i.e.* the majority of patients. The aforementioned international IPF guidelines state that BAL cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority. In contrast, the German adaptation of the guidelines [23] (in line with other European national guidelines) recommends performing BAL to exclude differential diagnoses [26].

Overall, the characteristics of patients in INSIGHTS-IPF differed from those in current clinical studies (see four RCT examples in table S1). While ethnicity and sex distribution were generally similar, interestingly, 6-min walk distance was lower in our registry (mean 268 m) than in the RCTs. FVC was similar to PANTHER-NAC, higher than in ASCEND, and lower than in INPULSIS-1 and INPULSIS-2. Furthermore, the % pred DLCO and other lung function parameters indicated more severe disease in the INSIGHTS-IPF cohort. The SGRQ was highest in INSIGHTS-IPF as well, indicating more severe disease with a clinically relevant difference (defined as >5 points) compared with the RCTs [18]. Patients were highly symptomatic and, as expected, dyspnoea was the leading symptom, being present in 85.9% of patients. Bibasilar, inspiratory crackles (dry or "velcro"-type in quality), which have been discussed as an easy and early "screening" method for IPF diagnosis [27, 28], were noted in only 79.0% of patients, and digital clubbing was reported in only 17.9% of patients, which is considerably less often than in previous studies (25–50%) [29, 30]. While we believe this to be a true finding, as expert centres were involved in this study, the absence of crackles and of clubbing might, alternatively, reflect a lack of documentation, as a reflection of the perceived higher importance of technical findings like HRCT.

As for baseline characteristics, the percentage of patients who never smoked was higher in INSIGHTS-IPF (39%) than in any of the RCTs and the rate of current smokers was also much lower (INSIGHTS-IPF 1% *versus* 2–7% in RCTs). In the present cohort, IPF occurred about two decades after smoking cessation, which is in line with a patient survey in the USA [31]. This remarkable finding may indicate the existence of a delayed reaction pattern, which may also be relevant for other exposures like organic dusts or metal dust.

A high rate of comorbidities was documented, illustrating the difficulty of treating this vulnerable patient group. This underscores the need for more intense research on the main comorbidities; in particular,

cardiovascular diseases, diabetes, pulmonary hypertension, emphysema and reflux. More individualised treatment approaches may be needed to address patient needs.

In the comparison between incident and prevalent IPF patients, significant differences were noted for age, sex distribution, steroid use and DLCO. These differences must be considered with caution, as the group composition depends on an arbitrary time criterion, and immortal time/survival bias and other selection bias may have had substantial influence.

With respect to treatment, overall approaches for IPF have changed substantially in the last decade in the USA [32] and probably also in Europe. In INSIGHTS-IPF, one out of every six patients did not receive any specific drug for IPF at all. These patients did not differ from those in treatment with respect to demographics but had shorter disease duration and less severe disease by lung function parameters. It appears that in selected cases, physicians follow a “wait and see” strategy before the initiation of treatment. While this is in line with current guidelines [1, 23], it remains unknown whether this strategy is still acceptable, given the availability of therapies and the unpredictable natural course of the disease in individual patients. Another reason for not treating might be that, according to current guidelines, no particular drug received a strong recommendation. The most frequently used drug in our registry was pirfenidone, which is currently the only approved agent for IPF treatment in Europe and which has been marketed in Germany since October 2011. Current international guidelines weakly recommend against use of this drug [1] but after thorough discussion of the data available at the time of creation of the German guidelines, it received a weak positive recommendation [23]. Nintedanib, a multi-tyrosine kinase inhibitor, was used in a small subset of patients, which reflects the treatment preferences in specialist centres that were allowed to document patients in the open-label, nonblinded periods of clinical studies. With the availability of the results of the ASCEND pirfenidone study and the INPULSIS-1 and INPULSIS-2 nintedanib studies, the US Food and Drug Administration has already approved both drugs for the whole spectrum of IPF, labelling both drugs as “breakthrough therapies”. The European Medicines Agency has also delivered a positive opinion for nintedanib for the treatment of IPF and approval is expected soon. Consequently, it can be expected that the drug utilisation pattern will change in the next few months in practice and, thus, in our registry.

The rate of steroid use was high despite the fact that international guidelines discourage this. Reasons are speculative, but may include treatment of dry cough, previous exacerbations or difficulty in tapering off therapy. A similar pattern in the use of steroids has been described in the RCTs and in a survey of French pulmonologists [33].

Nearly a third of patients (31.2%) in the INSIGHTS-IPF registry were treated with combination therapy, most frequently including pirfenidone. The combination of prednisone, azathioprine and NAC triple therapy, as investigated in PANTHER-IPF, was compromised by excess deaths, more hospitalisations and a higher prevalence of serious adverse events. This triple therapy, which was the standard of care until 2012, when the PANTHER-IPF study revealed the potential harm of this regimen for IPF patients, was only used in seven patients and, thus, was in line with current recommendations, which allows this therapy in patients who had stabilised or improved under this regime [34]. NAC combined with pirfenidone was often used despite the absence of supportive data; we expect that in view of the negative results of the PANTHER-NAC study, this combination will be abandoned.

Long-term oxygen therapy was more frequently used in INSIGHTS-IPF (31%) than in the CAPACITY study arms (17–28%), again indicating, on average, more severe disease in real clinical practice settings.

It was noteworthy that, though approximately one in five patients (19.7%) were potential candidates for lung transplantation (considering age and lung function), only 3% were actually listed. Considering the strong recommendation for lung transplantation in appropriate patients with IPF [1], the reasons for this surprising finding need to be explored.

Methodological considerations

The current INSIGHTS-IPF registry is prospective and recruits consecutive patients, thus limiting selection bias. It applies various measures for quality assurance, the most important being systematic plausibility checks as well as on-site monitoring with systematic comparisons between study data and patient files [10, 35].

The main limitations of this study are those inherent to any registry. Given that this is an observational, nonrandomised study, different biases can obscure any true causal association [36]. Clinical decisions of the treating physicians may assign patients to different drugs based on disease severity, disease duration, presence of comorbidities and other factors. This can potentially introduce allocation or channelling bias and confound the association between treatment and outcomes. In our registry, there is no re-evaluation of patients, which may result in some inclusion of patients with overlapping diagnoses, such as fibrosing nonspecific interstitial pneumonia or other causes of a UIP pattern on HRCT and/or SLB. However, as

mainly specialist ILD centres are involved, the quality of diagnoses should be high, and indeed is based on HRCT and biopsy in the great majority of cases. Still, the inclusion of only ILD expert centres might not reflect the true picture of IPF management in Germany. In addition, extrapolation of the results to other, especially non-European, countries may be limited by other factors; for example, the German guidelines differ in some aspects from the international guidelines. Drug therapy may differ as well, especially with regards to pirfenidone, due to its early license in Germany. Derivation of nationwide epidemiological data on the true incidence and prevalence of IPF is not a part of the study, but the registry will provide representative data on the practice of IPF specialist centres and large pulmonary hospitals (referral centres), in which many of the known IPF patients are treated.

In conclusion, first, the present registry suggests that patients with IPF have more severe disease than patients in recent RCTs. Second, in addition to HRCT, biopsies are often taken, which could indicate overdiagnosis of patients, at least in the past. Third, treatment approaches vary substantially. As expected, an important part of the treatment armamentarium is the newly introduced drug pirfenidone. The variety of drugs used for IPF and their combinations indicate uncertainty in identifying individualised optimal treatment approaches for stable patients, severely compromised patients or those with significant comorbidities. Finally, lung transplantation was not commonly considered as a treatment option.

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Results based on a smaller sample were presented at the meetings of the ATS in San Diego, CA, USA, on May 18, 2014, and of the ERS in Munich, Germany, on September 8, 2014.

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References

- 1 Raghu G, Collard HR, Egan JJ, *et al.* 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.
- 2 Travis WD, Costabel U, Hansell DM, *et al.* An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733–748.
- 3 Antoniou KM, Margaritopoulos GA, Siafakas NM. Pharmacological treatment of idiopathic pulmonary fibrosis: from the past to the future. *Eur Respir Rev* 2013; 22: 281–291.
- 4 Wilson JW, du Bois RM, King TE Jr. Challenges in pulmonary fibrosis: 8 – the need for an international registry for idiopathic pulmonary fibrosis. *Thorax* 2008; 63: 285–287.

- 5 Blackwell TS, Tager AM, Borok Z, *et al.* Future directions in idiopathic pulmonary fibrosis research. An NHLBI workshop report. *Am J Respir Crit Care Med* 2014; 189: 214–222.
- 6 Ryerson CJ, Corte TJ, Collard HR, *et al.* A global registry for idiopathic pulmonary fibrosis: the time is now. *Eur Respir J* 2014; 44: 273–276.
- 7 Alpert JS. Are data from clinical registries of any value? *Eur Heart J* 2000; 21: 1399–1401.
- 8 Gitt AK, Bueno H, Danchin N, *et al.* The role of cardiac registries in evidence-based medicine. *Eur Heart J* 2010; 31: 525–529.
- 9 Behr J, Hoepfer MM, Kreuter M, *et al.* Charakteristika und Versorgung der idiopathischen Lungenfibrose. Rationale für das INSIGHTS-IPF-Register. [Characteristics and management of idiopathic pulmonary fibrosis: INSIGHTS-IPF registry.] *Dtsch Med Wochenschr* 2012; 137: 2586–2588.
- 10 Behr J, Hoepfer M, Kreuter M, *et al.* Investigating significant health trends in idiopathic pulmonary fibrosis (INSIGHTS-IPF): rationale, aims and design of a nationwide prospective registry. *BMJ Open Respir Res* 2014; 1: e000010.
- 11 Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981; 123: 659–664.
- 12 Quanjer PH, Tammeling GJ, Cotes JE, *et al.* Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 6: Suppl. 16, 5–40.
- 13 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
- 14 Quanjer PH, Stocks J, Cole TJ, *et al.* Influence of secular trends and sample size on reference equations for lung function tests. *Eur Respir J* 2011; 37: 658–664.
- 15 Ries AL. Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. *COPD* 2005; 2: 105–110.
- 16 Kupferberg DH, Kaplan RM, Slymen DJ, *et al.* Minimal clinically important difference for the UCSD shortness of breath questionnaire. *J Cardiopulm Rehabil* 2005; 25: 370–377.
- 17 Ringbaek T, Martinez G, Lange P. A comparison of the assessment of quality of life with CAT, CCQ, and SGRQ in COPD patients participating in pulmonary rehabilitation. *COPD* 2012; 9: 12–15.
- 18 Swigris JJ, Brown KK, Behr J, *et al.* The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. *Respir Med* 2010; 104: 296–304.
- 19 Ley B, Ryerson CJ, Vittinghoff E, *et al.* A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med* 2012; 156: 684–691.
- 20 Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.
- 21 King TE Jr, Bradford WZ, Castro-Bernardini S, *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2083–2092.
- 22 Martinez FJ, de Andrade JA, Anstrom KJ, *et al.* Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2093–2101.
- 23 Behr J, Günther A, Ammenwerth W, *et al.* S2K-Leitlinie zur Diagnostik und Therapie der idiopathischen Lungenfibrose. [German guideline for diagnosis and management of idiopathic pulmonary fibrosis.] *Pneumologie* 2013; 67: 81–111.
- 24 Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000; 161: 646–664.
- 25 Raghu G. Idiopathic pulmonary fibrosis: guidelines for diagnosis and clinical management have advanced from consensus-based in 2000 to evidence-based in 2011. *Eur Respir J* 2011; 37: 743–746.
- 26 Ohshimo S, Bonella F, Cui A, *et al.* Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009; 179: 1043–1047.
- 27 American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002; 165: 277–304.
- 28 Cottin V, Cordier JF. Velcro crackles: the key for early diagnosis of idiopathic pulmonary fibrosis? *Eur Respir J* 2012; 40: 519–521.
- 29 Johnston ID, Prescott RJ, Chalmers JC, *et al.* British Thoracic Society study of cryptogenic fibrosing alveolitis: current presentation and initial management. Fibrosing Alveolitis Subcommittee of the Research Committee of the British Thoracic Society. *Thorax* 1997; 52: 38–44.
- 30 Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival. *Thorax* 1980; 35: 171–180.
- 31 Collard HR, Tino G, Noble PW, *et al.* Patient experiences with pulmonary fibrosis. *Respir Med* 2007; 101: 1350–1354.
- 32 Peikert T, Daniels CE, Beebe TJ, *et al.* Assessment of current practice in the diagnosis and therapy of idiopathic pulmonary fibrosis. *Respir Med* 2008; 102: 1342–1348.
- 33 Cottin V, Cadranel J, Crestani B, *et al.* Management of idiopathic pulmonary fibrosis in France: a survey of 1244 pulmonologists. *Respir Med* 2014; 108: 195–202.
- 34 Wells AU, Behr J, Costabel U, *et al.* Triple therapy in idiopathic pulmonary fibrosis: an alarming press release. *Eur Respir J* 2012; 39: 805–806.
- 35 Epstein M. Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Saf* 2005; 14: 589–595.
- 36 Delgado-Rodriguez M, Llorca J. Bias. *J Epidemiol Community Health* 2004; 58: 635–641.