Therapeutic decisions in a cohort of patients with idiopathic pulmonary fibrosis: a multicenter, prospective survey from Poland

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Abstract

Background: Pirfenidone and nintedanib are considered as the standard of care in idiopathic pulmonary fibrosis (IPF), but there is no consensus as to which of these two agents should be regarded as first-line treatment.

Objective: To provide real-world data on therapeutic decisions of pulmonary specialists, particularly the choice of the antifibrotic drug in patients with IPF.

Methods: This was a multicenter, prospective survey collecting clinical data of patients with IPF considered as candidates for antifibrotic treatment between September 2019 and December 2020. Clinical characteristics and information on the therapeutic approach were retrieved. Statistical evaluation included multiple logistic regression analysis with stepwise model selection.

Results: Data on 188 patients [74.5% male, median age 73 (interquartile range, 68–78) years] considered for antifibrotic therapy were collected. Treatment was initiated in 138 patients, while 50 patients did not receive an antifibrotic, mainly due to the lack of consent for treatment and IPF severity. Seventy-two patients received pirfenidone and 66 received nintedanib. Dosing protocol ($p < 0.01$) and patient preference ($p = 0.049$) were more frequently associated with the choice of nintedanib, while comorbidity profile ($p = 0.0003$) and concomitant medication use ($p = 0.03$) were more frequently associated with the choice of pirfenidone. Age ($p = 0.002$), lung transfer factor for carbon monoxide ($\text{TL}_{CO}$) ($p = 0.001$), and gastrointestinal bleeding ($p = 0.03$) were significantly associated with the qualification for the antifibrotic treatment.

Conclusion: This real-world prospective study showed that dose protocol and patient preference were more frequently associated with the choice of nintedanib, while the comorbidity profile and concomitant medication use were more frequently associated with the choice of pirfenidone. Age, $\text{TL}_{CO}$, and history of gastrointestinal bleeding were significant factors influencing the decision to initiate antifibrotic therapy.

Keywords: antifibrotic treatment, comorbidities, dosing protocol, nintedanib, pirfenidone

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease with poor prognosis and unknown etiology. The natural history of the disease is characterized by an irreversible, gradual decline of lung function due to lung fibrosis, reduction in exercise tolerance, quality of life, and premature death.1
According to recent estimates, the global prevalence of IPF is 0.33–4.51 per 10,000 persons and varies across geographical regions. The true IPF prevalence is difficult to estimate, as data are strongly dependent on disease definition and diagnostic approach. In Poland, the prevalence of IPF is estimated at 2.51/10,000 persons; however, these estimates need to be updated.

As the etiology of IPF remains elusive, causal treatment cannot be offered to patients affected by the disease. The use of immunomodulatory agents as well as anticoagulants to target some of the suggested mechanisms involved in IPF pathogenesis yielded disappointing results and did not improve survival which is roughly estimated at 3–5 years. It seems, however, that these estimates may no longer reflect the true situation, as we currently witness a rapid evolution of the therapeutic target in IPF, with a shift from an immunomodulatory to antifibrotic approach. Two molecules, pirfenidone and nintedanib, have been shown to slow the progression of IPF and to decelerate the decline of lung function in affected patients.

Pirfenidone suppresses lung fibrosis by reducing fibroblast proliferation, inhibiting collagen production, and reducing the production of profibrogenic mediators. Nintedanib, an oral tyrosine kinase inhibitor with a multipoint mechanism of action, including an inhibitory effect on vascular endothelial growth factor receptors (VEGFR 1–3), platelet-derived growth factor receptors (PDGFR a and b), and fibroblast growth factor receptors (FGFR 1–3), slows the rate of IPF progression and reduces the risk of acute exacerbations of the disease. These two antifibrotics are recognized as an actual standard of pharmacological treatment of IPF, and there are emerging data that they are also effective in other fibrosing interstitial lung diseases (ILDs). Both pirfenidone and nintedanib are available in Poland and are currently fully reimbursed for patients with IPF in the frame of the IPF therapeutic program of the Polish National Health Fund (NHF).

Even though pirfenidone and nintedanib differ in the mechanism of action, to date, there is no convincing data on the superiority of one antifibrotic over the other. Although both agents are regarded as the standard of care in IPF and experts agree that antifibrotics should be initiated upon IPF diagnosis to delay pulmonary function impairment, there is no consensus as to which of them should be regarded as first-line treatment. It is generally agreed that the therapeutic choice should take into account the anticipated endpoints, the safety profile of the drug, comorbidities, coagulation disorders, concomitant treatment, lifestyle (dosing regimen, risk of photosensitization), and patient preference.

The project aimed to provide real-world, prospectively collected data on the therapeutic decisions of pulmonary specialists related to the choice of the antifibrotic drug in patients with IPF.

**Material and methods**

The project was a multicenter, prospective observational study collecting data on IPF patients managed in eight specialized reference centers for pulmonary diseases across Poland between September 2019 and December 2020. All these centers were involved in antifibrotic therapy of patients with IPF in the frame of the NHF therapeutic program. The inclusion and exclusion criteria for the NHF therapeutic program are listed in Supplementary Table 1. The two major inclusion criteria to the study were (1) diagnosis of IPF in accordance with the current guidelines and (2) first dedicated specialist consultation directed at the assessment of eligibility for the IPF treatment program of the NHF and at decision to initiate antifibrotic therapy. Patients who had been previously treated with an antifibrotic were not included in the study.

Prospective clinical data collection included baseline demographic and anthropometric data, data on diagnosis, supplemental oxygen use, pulmonary function test (PFT) results, including spirometry and lung transfer factor for carbon monoxide (TLCO) and 6-min walk test (6MWT). Special emphasis was placed on antiagulation and antiplatelet therapy. Finally, information on the therapeutic approach of pulmonary specialists responsible for IPF patient care was retrieved.

**Statistical analysis**

Statistical analysis was performed using R software for MacOS. Continuous data were presented as mean with standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of data. Variables were compared using the unpaired Student’s t-test, Welch t-test, or the Wilcoxon rank sum test with continuity.
correction, depending on data normality and homogeneity of variance. Categorical data were analyzed by Pearson’s chi-square test or Fisher’s Exact Test according to the assumptions of the tests. Furthermore, multiple logistic regression analysis with stepwise model selection was used to create models to predict which factors were taken into account in qualification to antifibrotic treatment and, if so, which drug was used for the treatment. The models were further evaluated by area under the receiving operating characteristic curve (AUROC) analysis. A \( p \) value < 0.05 was considered significant.

**Results**

**Patient characteristics**

One hundred eighty-eight patients with IPF were considered as potential candidates for antifibrotic therapy within the NHF therapeutic program in the study period. The median age was 73 (IQR, 68–78) years and 74.5% of the patients were males. At the time of qualification for antifibrotic treatment, 47% of the patients were ex-smokers, while 32% were still actively smoking. The median time of symptom duration preceding IPF diagnosis was 12 (IQR, 8.5–32.5) months. In 85.6% of the patients, IPF was diagnosed on a definite usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) after exclusion of other potential causes of pulmonary fibrosis. In 7.4% of the patients, the diagnosis was established based on a probable UIP pattern on HRCT in the appropriate clinical context, following a multidisciplinary team discussion. The definite IPF diagnosis in the remaining 7.0% of the patients was based on the combination of both HRCT and lung biopsy findings (Figure 1). The basic characteristics of the patients are listed in Table 1.

The most frequent comorbidities were arterial hypertension (59%), coronary artery disease (35.6%), heart failure (19.7%), atrial fibrillation (13.3%), gastroesophageal reflux disease (27.7%), diabetes mellitus (25.5%), asthma (5.3%) and chronic obstructive pulmonary disease (4.2%). In addition, at the time of enrollment, three patients were diagnosed with lung cancer.

Twenty-six patients (13.8%) had been receiving anticoagulative therapy; among these, 13 (6.9%) and 12 (6.4%) patients were treated with novel oral anticoagulants (NOAC) and vitamin K antagonists (VKA), respectively. One patient was treated with enoxaparine. Seventy-four (39.4%) patients had been on antiplatelet treatment: 65 (34.6%) on acetylsalicylic acid alone, 5 (2.7%) on clopidogrel alone, while 4 (2.1%) patients had been using double antiplatelet treatment with both acetylsalicylic acid (ASA) and clopidogrel.

**Comparison of patients who were qualified versus disqualified from antifibrotic therapy**

In total, 155 patients were included into the NHF therapeutic program and received an antifibrotic agent. This accounted for 82% of all IPF patients considered as potential candidates for antifibrotic treatment over the study period. The mean interval from diagnosis to treatment onset was 4 (IQR, 1–12) months.

Patients who did not receive antifibrotic treatment (33/188, 17.6%) were significantly older, presented with a worse renal function, and had a more advanced IPF as assessed by the gender, age, physiology index (GAP index), mMRC score, and TLCO (Table 2).

**Reasons for exclusion from antifibrotic treatment**

The most frequent reasons for disqualification from antifibrotic treatment indicated by the respiratory physicians were as follows: need for further observation of the patient before initiating therapy (\( n = 11, 33.3\% \)), lack of patient consent for treatment mainly caused by anxiety related to potential adverse events (\( n = 11, 33.3\% \)), TLCO \( \leq 30\% \) pred. (\( n = 9, 27.3\% \)), FVC \( \leq 50\% \) pred. (\( n = 1 \)), and inability to perform pulmonary function tests due to dyspnea and fatigue (\( n = 1 \)) (Figure 1). Advanced age and comorbidities were also mentioned as causes for disqualification (\( n = 5, 15.2\% \) and \( n = 4, 12.1\% \), respectively). Normal FVC and TLCO were indicated as the reason for disqualification in two patients.

**Comparison of patients who started treatment with pirfenidone versus patients who started treatment with nintedanib**

Of the 138 patients who received antifibrotic therapy, 72 (52.7%) were offered treatment with pirfenidone and 66 (47.8%) with nintedanib. Patients who were offered nintedanib were
significantly younger and had a lower GAP score. No other significant differences were found in terms of demographic data as well as pulmonary function (Table 3).

Patients who received nintedanib less frequently reported a history of myocardial infarction or ischemic heart disease than patients who were treated with pirfenidone: 8 (11.1%) versus 19 (28.8%), \( p = 0.009 \); and 18 (25.0%) versus 30 (45.5%), \( p = 0.01 \), respectively. The incidence of other vascular diseases, renal function impairment, liver diseases, diabetes mellitus, benign prostate hypertrophy, depression, history of malignancy, or lung diseases other than IPF was similar in both groups. Three patients who were offered nintedanib (4.5%) had been diagnosed with lung cancer prior to the initiation of antifibrotic treatment, while such a diagnosis was not noted in the group of patients qualified for pirfenidone.

**Figure 1.** Flow chart presenting of a simplified pathway of IPF diagnosis, patient inclusion, and the choice of antifibrotic therapy in the investigated cohort. IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary team discussion; NHF, National Health Fund; UIP, usual interstitial pneumonia.

*Surgical lung biopsy \( n = 8 \), transbronchial lung cryobiopsy \( n = 5 \).

*Several reasons for disqualification may coexist in the same patient.

*Waiting for therapeutic decision due to formal reasons associated with NHF regulations.

**Choice of the antifibrotic drug**

The results of the physician survey revealed some differences in the factors that influenced the choice of the antifibrotic drug for first-line treatment (Figure 2). Dosing protocol and patient preference were more frequently associated with the choice of nintedanib (\( p < 0.01 \) and \( p = 0.049 \), respectively). The comorbidity profile of the patient and concomitant medication use were more frequently associated with the choice of pirfenidone (\( p = 0.0003 \) and \( p = 0.03 \), respectively). The impact of concomitant medication use mainly applied to anticoagulation and antiplatelet therapy. Anticoagulative treatment was significantly more frequent in patients qualified for pirfenidone compared with those treated with nintedanib (\( p < 0.01 \) and \( p = 0.049 \), respectively). The comorbidity profile of the patient and concomitant medication use were more frequently associated with the choice of pirfenidone (\( p = 0.0003 \) and \( p = 0.03 \), respectively). The impact of concomitant medication use mainly applied to anticoagulation and antiplatelet therapy. Anticoagulative treatment was significantly more frequent in patients qualified for pirfenidone compared with those treated with nintedanib: 9 (12.5%) versus 3 (4.5%) patients, respectively, \( p = 0.07 \). This was also the case for antiplatelet therapy which was applied in 33 (45.8%) patients treated with...
pirfenidone and 22 (33.3%) patients treated with nintedanib ($p = 0.02$).

The physician’s own experience with the antifibrotic agent was also mentioned as an important factor in the choice of treatment ($67/72$, 93.1% of patients treated with pirfenidone and of $59/66$, 89.4% patients treated with nintedanib); however, this was not related to a more frequent choice of one drug over the other.

Multiple logistic regression analysis revealed that age ($p = 0.002$), $TL_{CO}$ expressed as percent of predicted value ($p = 0.001$), and gastrointestinal bleeding ($p = 0.03$) were significantly associated with the decision on the qualification for antifibrotic treatment (Table 4). Time from diagnosis ($p = 0.008$), profile of comorbidities ($p = 0.007$), and dose protocol ($p < 0.0001$) were associated with the choice of drug in antifibrotic therapy (Table 5). AUROC analyses showed good fitness of the models to the data.

### Discussion

Our physician survey study showed that in a Polish cohort of patients with IPF, the decision to initiate antifibrotic treatment was mainly affected by patient age, lung transfer factor, and a history of gastrointestinal bleeding, while the choice of the antifibrotic agent was affected by patient comorbidities, dosing protocol, and time from diagnosis. Dosing protocol and patient preference were related to the choice of nintedanib, while patient comorbidity profile and concomitant medication use (anticoagulative and antiplatelet therapy in particular) was associated with the choice of pirfenidone. Although own experience with the drug was indicated as an important factor in the choice of treatment, it was not related to a more frequent choice of one drug over the other. Disease severity and lack of consent to treatment were the two major causes for not initiating antifibrotic treatment in the investigated cohort of IPF patients.

Although there have been a substantial number of studies comparing pirfenidone and nintedanib with regard to different outcome measures, adverse effects, treatment discontinuation rate, and cost of treatment, we were not able to find prospective studies on the strategy in first-line antifibrotic therapy. Therefore, to our knowledge, this is the first prospective real-world study in IPF patients specifically designed to analyze factors associated with decision making on initiation of antifibrotic therapy and those affecting the choice of antifibrotic agent. Guidelines on IPF diagnosis and treatment recommend both the use of either pirfenidone or nintedanib and emphasize the need of considering the anticipated endpoint, expected benefit, patient comorbidities, drug interactions, and safety profile in the drug choice. Nintedanib has been shown to reduce the risk of acute IPF exacerbations, slow the dynamics of FVC decline and to improve quality of life, while pirfenidone decelerates FVC and 6MWT decline and improves progression-free survival. A recent retrospective study in a cohort of 840 patients treated with pirfenidone and 713 patients receiving nintedanib did not demonstrate significant differences in all-cause 1- and 2-year mortality and respiratory-related hospitalizations. A comparable 2-year mortality for the two agents was

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**Table 1.** Basic characteristics of the investigated cohort of patients with IPF considered for antifibrotic treatment ($n = 188$).

| Parameter                        | Value                      |
|----------------------------------|----------------------------|
| Age, years                       | 73 (68–78)                 |
| BMI, kg/m²                       | 27.86 (25–30.9)            |
| $TL_{CO}$, % predicted           | 53.76 (17.63)              |
| FVC, % predicted                 | 88.18 (21.48)              |
| GAP score, points                | 3 [3–4]                    |
| Pack-years, n                    | 25 [15–40]                 |
| $SpO_2$ [room air], %            | 95 [94–96]                 |
| 6MWD, meters                     | 427 [118] [$n = 135$]      |
| $SpO_2$ decrease in 6MWT, %      | 5 [3–8.5] [$n = 135$]      |
| mMRC                            | 1 [1–2] [$n = 164$]        |

6MWD, 6-min walk distance; 6MWT, 6-min walk test; BMI, body mass index; FVC, forced vital capacity; GAP, gender, age, physiology index; IPF, idiopathic pulmonary fibrosis; mMRC, modified Medical Research Council scale for dyspnea; $SpO_2$, blood oxygen saturation measured by pulse oximetry; $TL_{CO}$, lung transfer factor for carbon monoxide.

Data presented as median and interquartile range or mean with standard deviation where applicable. The numbers in the square brackets following the respective variable show the number of patients with available data. If no bracket was added, data availability was 90–100%.
also shown in another study. It is noteworthy that the authors of this real-life study did not find significant difference in mortality between patients who were treated with either of the antifibrotics and those who did not receive treatment. Therefore, it seems that mortality may not be a relevant factor affecting the choice of the initial antifibrotic. On the contrary, the other mentioned outcomes may appear elusive for the patient. Indeed, two small studies showed differences between physicians and patients in the choice pattern; physicians tended to choose pirfenidone more often than nintedanib (59.1 versus 40.9% and 60.0% versus 36.4%, respectively), while nintedanib was selected more frequently than pirfenidone by the patients (62.1% versus 37.9% and 45.5% versus 11.1%, respectively). The physicians’ choice of pirfenidone as reported by Hayton et al. was mainly motivated by anticoagulant therapy, angina, liver disease, and own preference, while in the study by Kaur et al., by history of diarrhea, history of coronary artery disease, and a longer safety record. These results are similar to our observations in which the physician-led decision on pirfenidone was motivated by concomitant diseases and concomitant medication use, what mainly applied to anticoagulative and antiplatelet treatment. Furthermore, dosing protocol was one of the most important reasons for choosing nintedanib both in our study and in the two studies mentioned above. Although both pirfenidone and nintedanib may produce a number of drug interactions mainly

| Parameter                        | Qualified for treatment, n = 155 | Did not receive treatment, n = 33 | p value |
|----------------------------------|-----------------------------------|-----------------------------------|---------|
| Age, years                       | 72 [67–77]                        | 78 [72–84]                        | 0.001   |
| BMI, kg/m²                        | 27.9 [25.0–31.1]                  | 27.0 [24.5–30]                    | 0.45    |
| Chronic kidney disease stage (KDOQI) | 2 [1.75–2]                       | 3.5 [3–4]                        | 0.006   |
| TLCO, % predicted                | 56.1 [16.48]                      | 42.9 [19]                         | 0.0006  |
| FVC, % predicted                 | 88.0 [20.9]                       | 89.1 [24.6]                       | 0.8     |
| GAP score, points                | 3 [3–4]                           | 4 [3–5]                           | 0.01    |
| NYHA stage                       | 2 [1–2]                           | 2 [1.5–3]                         | 0.12    |
| Pack-years, n                    | 20 [15–39]                        | 25 [20–40]                        | 0.35    |
| SpO₂ (room air), %               | 95 [94–96.5]                      | 95 [93–96]                        | 0.26    |
| Time from diagnosis, months      | 4 [1–12]                          | 0 [0–4]                           | 0.003   |
| 6MWD, meters                     | 432 [114]                         | 395 [145]                         | 0.34    |
| SpO₂ decrease in 6MWT            | 5 [3–8]                           | 6.5 [3–11]                        | 0.33    |
| mMRC                             | 1 [1–2]                           | 2 [1–3]                           | 0.01    |
| History of gastrointestinal bleeding n (%) | 1 [0.5]                      | 5 [3]                            | <0.001  |

6MWD, 6-min walk distance; 6MWT, 6-min walk test; BMI, body mass index; FVC, forced vital capacity; GAP, gender, age, physiology index; IPF, idiopathic pulmonary fibrosis; KDOQI, Kidney Disease Outcomes Quality Initiative; mMRC, modified Medical Research Council scale for dyspnea; SpO₂, blood oxygen saturation measured by pulse oximetry; TLCO, lung transfer factor for carbon monoxide.

Data presented as median and interquartile range or mean with standard deviation where applicable. The numbers in the square brackets following the respective variable show the number of patients with available data. If no bracket was added, data availability was 90–100%.
driven by disruption of the cytochrome P450 metabolic pathway in the liver, the most widely discussed aspect of antifibrotic treatment in the context of concomitant medication is the simultaneous use of nintedanib and anticoagulative and antiplatelet agents. Due to inhibition of PDGF and VEGF, both of which are important regulators of angiogenesis, nintedanib may be associated with increased risk of bleeding. Hence, patients receiving anticoagulative treatment were not included in registration studies. Data from the EMPIRE Registry showed that although bleeding episodes occurred more often in patients receiving nintedanib than patients receiving pirfenidone, the incidence of bleeding was low (136.9 per 10,000 patient-years). Reports based on the Global Pharmacovigilance Database estimate bleeding incidence at 368 per 10,000 patient-years with the vast majority of events being mild. In our study, patients on anticoagulative treatment were more than twice less likely to receive nintedanib than pirfenidone. This is in accordance with earlier findings. In an analysis of 703 patients from the American Pulmonary Fibrosis Foundation Patient Registry, Holtze et al. found that anticoagulant use was associated with the selection of pirfenidone for IPF treatment [odds ratio (OR) = 2.51]. Interestingly, although our results showed that history of gastrointestinal bleeding negatively affected the decision to initiate any antifibrotic therapy, the only patient with gastrointestinal bleeding in the past qualified for treatment received nintedanib and not pirfenidone. This observation is difficult to interpret as it concerns a single patient in the whole group.

Table 3. Comparison of basic clinical data of patients with IPF qualified for treatment with pirfenidone and for nintedanib.

| Parameter                               | Pirfenidone, n = 66 | Nintedanib, n = 72 | p value |
|-----------------------------------------|---------------------|--------------------|---------|
| Age, years                              | 73 (69–78)          | 72 (64–75)         | 0.02    |
| BMI, kg/m²                               | 27.7 (25.0–30.0)    | 27.0 (25.6–30.0)   | 0.96    |
| GAP score, points                       | 3.5 (3–4)           | 3 (3–4)            | 0.04    |
| NYHA stage                              | 2 (1–2)             | 1 (1–2)            | 0.14    |
| Pack-years, n                           | 20 (9.5–30)         | 20 (0–40)          | 0.98    |
| SpO₂ [room air], %                      | 95 (93–96)          | 95 (94–97)         | 0.29    |
| Time from diagnosis to start of treatment [months] | 2.5 (0–7)          | 5.5 (2–13.5)      | 0.008   |
| mMRC, points                            | 1 (1–2)             | 1 (1–2)            | 0.44    |
| TLCO, % predicted                       | 53 (13)             | 57 (18)            | 0.17    |
| FVC, % predicted                        | 87.6 (20.3)         | 87.4 (21.7)        | 0.97    |
| 6MWD, meters                            | 422 (126) [n = 50]  | 446 (109) [n = 54] | 0.32    |
| SpO₂ decrease in 6MWT, %                | 4.5 (3–7.75) [n = 50] | 6.5 (4–9.75) [n = 54] | 0.19    |
| History of gastrointestinal bleeding, n (%) | 0 (0)               | 1 (0.7)            | 1.00    |

6MWD, 6-min walk distance; 6MWT, 6-min walk test; BMI, body mass index; FVC, forced vital capacity; GAP, gender, age, physiology index; IPF, idiopathic pulmonary fibrosis; mMRC, modified Medical Research Council scale for dyspnea; NYHA, New York Heart Association stage for heart failure; SpO₂, blood oxygen saturation measured by pulse oximetry; TLCO, lung transfer factor for carbon monoxide.

Data presented as median and interquartile range or mean with standard deviation where applicable. The numbers in the square brackets following the respective variable show the number of patients with available data. If no bracket was added, data availability was 90–100%.
Despite the increasing awareness of IPF, delay in disease diagnosis is not uncommon. However, in the absence of contraindications, antifibrotic therapy should be initiated once IPF diagnosis is established, and early start of treatment is advocated. In this context, the reported time interval between the diagnosis and initiating treatment in our cohort may raise concern. A certain delay, however, was also reported in other studies. The list of factors delaying early initiation of treatment includes a ‘wait-and-watch’ strategy, treatment risk–benefit ratio considerations, limited physician experience with IPF patient management, and local drug reimbursement regulations. In the setting of treatment within the frame of the Polish NHF therapeutic program, the relatively long time interval between diagnosis and treatment may also be attributed to formal issues associated with inclusion to the program. This includes the qualification process, registration to the program, waiting list for a visit in an authorized pulmonology center, and, finally, waiting for the arrival of the prescribed medication to the dedicated pulmonology center. Perhaps such an institutionalized manner of medication distribution needs to be modified in order to facilitate earlier start of antifibrotic treatment and thus improve its
effectiveness. On the contrary, in Poland, the NHF provides full reimbursement of antifibrotic therapy in patients with the diagnosis of IPF, therefore the choice of the antifibrotic agent is not biased by costs of treatment.

There are two major limitations of our study. First, this was a survey study, therefore by definition, the quality of the acquired data could not be objectively verified. Nevertheless, all the participating institutions are pulmonology reference centers with a wide experience in research and therefore, we believe that maximal effort had been made to provide reliable data. Second, our results may be biased by the local NHF restrictions for antifibrotic prescription, that is, the inclusion/exclusion criteria for the NHF program for IPF treatment. Considering the differences in the regulations across countries, our findings need not necessarily reflect the general situation in decision making on IPF treatment and this should be taken into account in comparative analyses of therapeutic approach in affected patients.

**Conclusion**

Our study showed that patient age, lung transfer factor, and a history of gastrointestinal bleeding are the main factors affecting the decision to start antifibrotic treatment in patients with IPF. Dosing protocol and patient preference were related to the choice of nintedanib, while patient comorbidity profile and concomitant medication use (anticoagulative and antiplatelet therapy in particular) were associated with the choice of pirfenidone. The two most important causes for disqualification from antifibrotic treatment were lack of patient consent to treatment and advanced disease.

**Declarations**

**Ethics approval and consent to participate**

The study was approved by the Institutional Review Board of the Medical University of Warsaw (AKBE/211/2019). All patients signed an informed consent to participate in the study.

**Consent for publication**

All authors of the study accepted this publication.

**Author contributions**

**Katarzyna Górska**: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – original draft.

**Marta Maskey-Warzęchowska**: Conceptualization; Investigation; Resources; Writing – original draft.

**Małgorzata Barnaś**: Conceptualization; Data curation; Investigation; Writing – original draft.

**Adam Białas**: Formal analysis; Software; Writing – review & editing.

**Adam Barczyk**: Investigation; Writing – review & editing.

**Hanna Jagielska-Len**: Investigation; Writing – review & editing.

**Ewa Jassem**: Investigation; Writing – review & editing.

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**Table 5. Results of logistic regression: choice of drug in antifibrotic therapy.**

| Coefficient                  | Estimate | OR   | 95% CI         | p value |
|------------------------------|----------|------|----------------|---------|
| Intercept                    | 0.91     | 2.5  | 1.28–4.88      | 0.008   |
| Time from diagnosis          | −0.05    | 0.95 | 0.92–0.99      | 0.007   |
| Finger clubbing              | −1.55    | 0.21 | 0.06–0.73      | 0.01    |
| Profile of comorbid diseases | 1.31     | 3.7  | 1.43–9.58      | 0.007   |
| Dosing protocol              | −3.02    | 0.05 | 0.02–0.16      | <0.0001 |
| AUROC                        | 0.87     |      | 0.81–0.93      |         |

AUROC, area under the receiving operating characteristic curve; CI, confidence interval; OR, odds ratio.
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**Competing interests**

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Availability of data and materials
The data that support the findings of this study are available from the authors upon reasonable request.

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