Received: 1 March 2021 | Accepted: 1 July 2021

DOI: 10.1111/resp.14116

ORIGINAL ARTICLE

Official Journal of the Asian Pacific Society of Respirology
Respirology APSR WILEY

Outcomes of patients with advanced idiopathic pulmonary fibrosis treated with nintedanib or pirfenidone in a real-world multicentre cohort

Michael T. Durheim[1,2,3] | Elisabeth Bendstrup[4] | Lisa Carlson[5] | Eva M. Sutinen[6,7] | Charlotte Hyldgaard[8] | Dimitrios Kalafatis[5] | Marjukka Myllärniemi[6,7] | C. Magnus Sköld[5,9] | Tone Sjåheim[1]

[1]Department of Respiratory Medicine, Oslo University Hospital – Rikshospitalet, Oslo, Norway

[2]Institute for Clinical Medicine, University of Oslo, Oslo, Norway

[3]Division of Pulmonary, Allergy and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina, USA

[4]Center for Rare Lung Disease, Department of Respiratory Diseases and Allergy, Aarhus University, Aarhus, Denmark

[5]Department of Respiratory Medicine and Allergy, Karolinska University Hospital, Stockholm, Sweden

[6]Department of Pulmonary Medicine, Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland

[7]Individualized Drug Therapy Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland

[8]Diagnostic Center, Silkeborg Regional Hospital, Silkeborg, Denmark

[9]Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

Correspondence
Michael T. Durheim, Department of Respiratory Medicine, Oslo University Hospital – Rikshospitalet, Postboks 4950 Nydalen, 0424 Oslo, Norway.
Email: michael.durheim@medisin.uio.no

Funding information
Academy of Finland; Boehringer Ingelheim; F. Hoffmann-La Roche; Hjärt-Lungfonden; Norwegian Respiratory Society; Nummela Sanatorium Foundation for Medical Research; Paul and Ragna Nyberg Foundation; Sigrid Juséliuksen Säätiö; Helsinki University Hospital; Roche; Karolinska University Hospital; Karolinska Institutet; InterMune/Roche

Associate Editor: Francesco Bonella **Senior Editor:** Chris Grainge

Abstract

Background and objective: Antifibrotic therapy with nintedanib or pirfenidone slows disease progression and reduces mortality in patients with idiopathic pulmonary fibrosis (IPF). However, patients with advanced IPF, as defined by forced vital capacity (FVC) < 50% and/or diffusion capacity for carbon monoxide (DLCO) < 30% of predicted, have not been included in randomized trials, and the outcomes of such patients who initiate treatment are not well understood. We determined lung function, disease progression and mortality outcomes following initiation of antifibrotic therapy in patients with advanced IPF at the time of treatment initiation compared to those with mild–moderate IPF.

Methods: We included 502 patients enrolled in IPF registries from four Nordic countries. Linear mixed models were used to assess change in FVC and DLCO over time. Cox proportional hazards models were used to assess transplant-free survival and progression- and transplant-free survival.

Results: Of 502 patients, 66 (13%) had advanced IPF. Annual change in FVC was −125 ml (95% CI −163, −87) among patients with mild–moderate IPF, and +28 ml (95% CI −96, +152) among those with advanced IPF. Advanced IPF at treatment initiation was associated with poorer transplant-free survival (hazard ratio [HR] 2.39 [95% CI 1.66, 3.43]) and progression- and transplant-free survival (HR 1.60 [95% CI 1.15, 2.23]).

Conclusion: In a broadly representative IPF population, patients with advanced IPF at the initiation of antifibrotic therapy did not have greater lung function decline over time compared with those with mild–moderate IPF, but had substantially higher mortality. Prospective studies are needed to determine the effect of antifibrotic therapy in patients with advanced IPF.

KEYWORDS
advanced idiopathic pulmonary fibrosis, antifibrotic therapy, interstitial lung disease, mortality, nintedanib, pirfenidone, transplant-free survival

INTRODUCTION

Treatment of idiopathic pulmonary fibrosis (IPF) with pirfenidone or nintedanib reduces loss of lung function over time.[1,2] Randomized trials have excluded patients with forced vital capacity (FVC) < 50% of predicted and/or diffusion capacity for carbon monoxide (DLCO) < 30% of predicted, but in practice many patients receiving antifibrotic treatment have more severe lung function impairment.[3] Outcomes in such patients have been assessed primarily in follow-up analyses of clinical trials[4] or in post-marketing studies,[5] in which treatment appears to benefit patients with advanced IPF. However, such patients remain a highly selected group, in that they have survived an initial study observation period and thus cannot be assumed to represent patients with severe lung function impairment at the start of treatment.

FVC and DLCO at a given timepoint are predictive of mortality in IPF,[6,7] but do not necessarily predict future trajectory of lung function.[8,9] A substantial minority of patients with IPF are not treated with antifibrotic drugs,[10] likely related to limited or uncertain benefit,[11] patient preference or limitations on reimbursement. In summary, patients, clinicians and health care authorities may reasonably share uncertainty about the benefits of initiating treatment when lung function impairment is already severe.

We leveraged registry data from four Nordic countries to assess change in lung function and transplant-free survival among patients with advanced IPF at treatment initiation, defined as FVC < 50% of predicted and/or DLCO < 30% of predicted, compared with patients with mild to moderate IPF.

SUMMARY AT A GLANCE

Patients with advanced idiopathic pulmonary fibrosis (IPF) have not been included in randomized trials of nintedanib or pirfenidone, but are often treated with these drugs. We show that in a real-world setting, patients with severe compared to mild–moderate IPF may not have lung function decline during treatment, but show substantially greater mortality.

METHODS

We performed a retrospective cohort study using four interstitial lung disease registries: the Swedish IPF registry,[12,13] the Aarhus University Hospital IPF registry,[14] the FinnishIPF registry,[15] and the Oslo University Hospital ILD registry (Tables S1 and S2 in the Supporting Information). All included consecutively evaluated patients with IPF. Of note, the Oslo University Hospital registry initially included only patients who were treated with antifibrotic therapy.

We included patients with IPF who initiated treatment with nintedanib or pirfenidone from August 2011 to November 2019. Multidisciplinary discussion is standard in the diagnosis of IPF at all participating centres, and diagnosis was based on consensus guidelines.[16,17] Patients were classified as having 'advanced IPF' if their FVC was less than 50% of predicted, and/or DLCO less than 30% of predicted, at the time treatment with nintedanib or pirfenidone was initiated (Table S3 in the Supporting Information). Patients who were unable to perform the DLCO manoeuvre were also classified as advanced IPF.[6] Patients with both FVC ≥ 50% of predicted and DLCO ≥ 30% of predicted were classified as having 'mild–moderate IPF' (Figure 1). The FVC and DLCO measurements performed closest to the date of treatment initiation were considered the baseline values for classification. Patients with no lung function measurements within 30 days of treatment initiation were not included (Figure 1). The date of treatment initiation was considered time zero for all longitudinal and survival analyses.

The primary outcomes were estimated annual rate of change in FVC from zero to one year following antifibrotic therapy initiation, based on a repeated measures approach as described below, and transplant-free survival. Ascertainment of death was based on complete national registries in each country, as described in greater detail in Appendix S1 in the Supporting Information. All deaths, including patients listed for and awaiting lung transplantation, were included. Secondary outcomes included change in DLCO from zero to one year, and progression- and transplant-free survival. For the latter outcome, disease progression was defined as a 10% relative decline in the % predicted value for FVC. All available follow-up data were used for time-to-event outcomes. Longitudinal analyses of FVC and DLCO were limited to 15 months of follow-up due to the paucity of available measurements beyond that period.

Descriptive statistics are presented as mean (SD) or *n* (%). Baseline characteristics were compared using two-sample *t*-tests or chi-square tests, except for time from IPF diagnosis to treatment initiation which was compared with a Kruskal–Wallis test due to non-linear distribution. Linear mixed models were used to assess change in lung function over time, with a random intercept and slope to account for each patient's baseline value and within-subject correlation, respectively. Such models accommodate missing data without imputation provided that missingness is non-informative. We included fixed effects for time from treatment initiation, comparison group (advanced vs. mild–moderate IPF) and their interaction, as well as gender and age at treatment initiation. Patient height was also included in the models assessing FVC in litres. All covariates were selected *a priori* based on their known associations with outcomes in IPF, or because they were essential to interpreting FVC values in millilitres (in the case of the height covariate). An unstructured covariance matrix was used to account for the irregular and variable timing of lung function measurements both within and among patients.

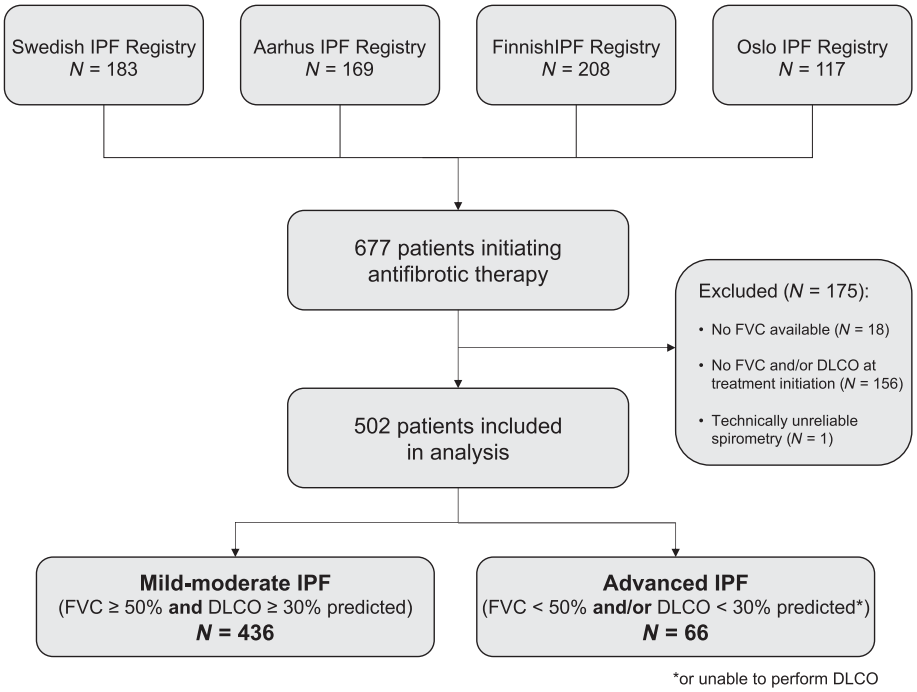

FIGURE 1 Study cohort. Patients who initiated antifibrotic therapy were included in one of the four idiopathic pulmonary fibrosis (IPF) registries, and classified as having mild–moderate or advanced IPF based on forced vital capacity and diffusion capacity for carbon monoxide (DLCO) at the time of treatment initiation. Patients who could not perform the DLCO manoeuvre were classified as advanced IPF, and patients with missing lung function data at treatment initiation for other or unknown reasons were excluded

TABLE 1 Patient characteristics at the initiation of antifibrotic therapy

	Mild–moderate IPF	Advanced IPF	
	$n = 436$	$n = 66$	*p*-Value
Age at treatment initiation (years)	70 (8)	70 (8)	0.805
Time from diagnosis to treatment initiation (days [median, IQR[a]])	62 (7–330)	66 (3–414)	0.746
Smoking status ($n = 374$[b])			0.569
Never	86 (27)	12 (23)	
Former	222 (69)	40 (75)	
Current	13 (4)	1 (2)	
Female	105 (24)	11 (17)	0.183
FVC (L)	2.88 (0.79)	2.08 (0.74)	<0.001
FVC (% predicted)	77 (17)	55 (20)	<0.001
DLCO (% predicted)[c]	49 (12)	31 (12)	<0.001
Pirfenidone	279 (65)	40 (61)	0.439
Nintedanib	147 (35)	26 (39)	0.439

Note: Results presented as mean (SD) or *n* (%) unless otherwise indicated. *p*-Values from two-sample *t*-tests or chi-square tests unless otherwise indicated.
Abbreviations: DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range.
[a]Presented as median (IQR) due to non-normal distribution. *p*-Value from Kruskal–Wallis rank test.
[b]Smoking status not available in FinnishIPF patients.
[c]Twelve patients with advanced IPF could not perform the DLCO manoeuvre. These values were not imputed.

The Kaplan–Meier estimator and Cox proportional hazards models were used to compare time-to-event outcomes. Adjusted models included age and gender *a priori* based on their known associations with outcomes in IPF.[6] All Cox models were also stratified by the enrolling centre, to account for potential differences in patient population or management patterns.

Statistical analyses were performed with STATA version 16.1 (College Station, TX, USA).

RESULTS

Of 502 included patients, 66 (13%) had advanced IPF at initiation of nintedanib or pirfenidone treatment, with FVC < 50% of predicted and/or DLCO < 30% of predicted. The proportion of patients treated with nintedanib versus pirfenidone appeared to be similar between those with advance and mild–moderate IPF (Table 1).

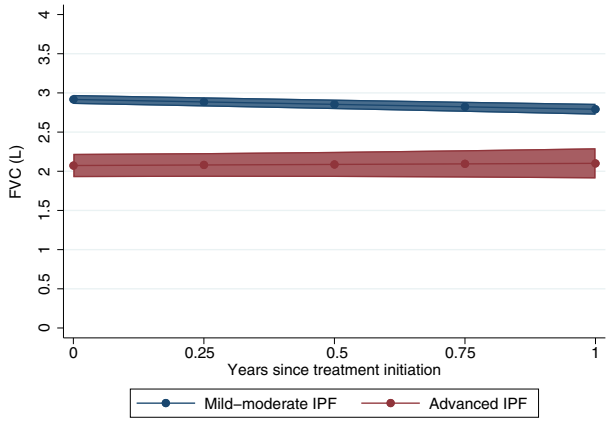

FIGURE 2 Change in forced vital capacity (FVC) following the initiation of antifibrotic therapy. Lines represent the estimated rate of change in FVC over time based on a linear mixed model including time, age at treatment initiation, height, comparison group (advanced vs. mild–moderate idiopathic pulmonary fibrosis) and group-by-time interaction. Shaded areas represent 95% CI

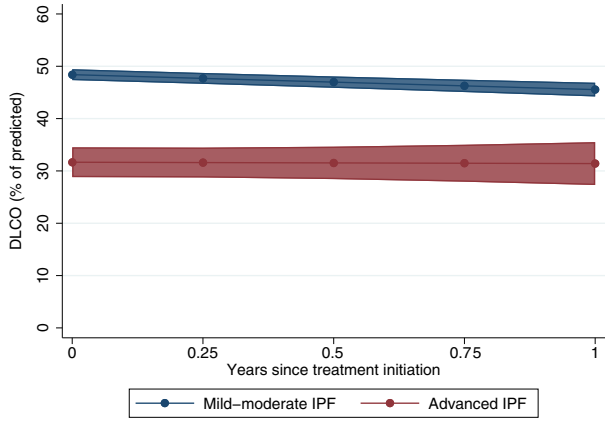

FIGURE 3 Change in diffusion capacity for carbon monoxide (DLCO) following the initiation of antifibrotic therapy. Lines represent the estimated rate of change in DLCO (% predicted) over time based on a linear mixed model including time, age at treatment initiation, height, comparison group (advanced vs. mild–moderate idiopathic pulmonary fibrosis) and group-by-time interaction. Shaded areas represent 95% CI

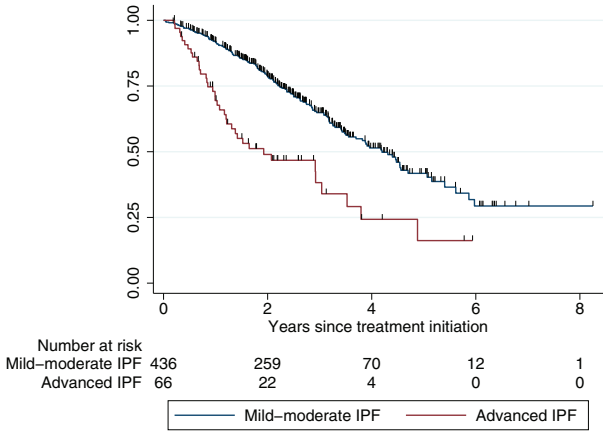

FIGURE 4 Transplant-free survival from the initiation of antifibrotic therapy

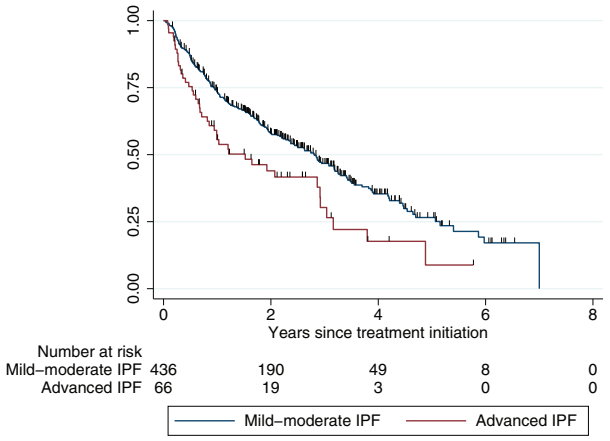

FIGURE 5 Progression- and transplant-free survival from the initiation of antifibrotic therapy. Progression defined as 10% relative decline in the % predicted value for forced vital capacity

The estimated annual change in FVC was −125 ml (95% CI −163, −87) among patients with mild–moderate IPF and +28 ml (95% CI −96, +152) among patients with advanced IPF (Figure 2). The group-by-time interaction ($p = 0.021$) suggested that the rate of change in FVC over time among advanced IPF patients differed from the rate of change among mild–moderate IPF patients.

The annual rate of change in DLCO (% predicted) was −2.9% (95% CI −3.8, −1.9) among patients with mild–moderate IPF, and −0.3% (95% CI −3.6, +3.1) among patients with advanced IPF (Figure 3). The group-by-time interaction ($p = 0.145$) suggested that the rates of change did not differ by group.

Median follow-up time was 2.2 years. During the study period, 137 (31%) patients with mild–moderate IPF died and 22 (5%) were transplanted, whereas 32 (48%) patients with advanced IPF died and five (8%) were transplanted. Median transplant-free survival was 1.9 years among patients with advanced IPF, and 4.2 years among those with mild–moderate IPF (log-rank $p < 0.001$) (Figure 4). The risk of death or transplant was more than twice as high for patients with advanced IPF (hazard ratio [HR] 2.39 [95% CI 1.66, 3.43], $p < 0.001$). After adjustment for age at treatment initiation and gender, advanced IPF at treatment initiation remained associated with a similar increase in risk of death (HR 2.41 [95% CI 1.67, 3.47], $p < 0.001$).

Median time to disease progression, transplant or death was 1.5 years among patients with advanced IPF compared with 2.8 years among those with mild–moderate IPF (log-rank $p = 0.003$; Figure 5). The risk of disease progression, transplant or death was just over 50% greater among patients with advanced IPF (HR 1.60 [95% CI 1.15, 2.23], $p = 0.005$). After adjustment for age at treatment initiation and gender, advanced IPF was similarly associated with risk of disease progression, transplant or death (HR 1.62 [95%

CI 1.16, 2.27], $p = 0.004$). These differences appeared to be primarily driven by mortality rather than disease progression (Figure S1 in the Supporting Information).

DISCUSSION

Our study demonstrates that in a large, multicentre cohort treated with nintedanib or pirfenidone, FVC decreases substantially over time among patients with mild–moderate IPF at the time of treatment initiation, but remains more stable among patients with advanced IPF. By contrast, patients with advanced IPF had substantially poorer transplant-free survival than those with mild–moderate IPF.

Interestingly, we did not observe FVC decline at the group level among treated patients with advanced IPF, in contrast to those with more moderate disease severity at treatment onset. This may be due to a partial floor effect on FVC, limiting the measurable further decline that can be detected among patients with poor baseline lung function. Any interpretation of lung function outcomes in IPF must take into account that the measurements themselves become increasingly difficult for patients with more advanced disease. Indeed, inability to perform the DLCO manoeuvre is an established prognostic factor,[6] and even spirometry may be difficult among the most advanced patients.

Annual decline in FVC among patients with mild–moderate IPF in our study was nominally greater than that of actively treated patients in INPULSIS,[2] but less than those in the placebo groups. This likely reflects the less selected patient population in our registry-based study compared with a narrowly defined clinical trial population. Annual FVC decline in ASCEND[1] was greater in both arms, although this is related in part to the imputation strategy used in that trial. Interestingly, FVC over time in the advanced IPF patients in our study was more stable than in similar patients from the post-authorization INPULSIS-ON study, in which patients with FVC < 50% predicted at the start of follow-up had an annual FVC decline of −62 ml/year.[5]

By contrast with lung function outcomes, mortality in our study was substantially higher for patients with advanced IPF at the time of treatment onset compared with patients with mild–moderate IPF. Mortality has been reported as substantially lower in a small group of patients with advanced IPF who were enrolled in ASCEND and CAPACITY due to decline in lung function between screening and randomization[18]; this difference again likely reflects the more selected patient population enrolled in trials. Median survival in mild–moderate IPF, while approximately twice as long as in advanced IPF, was still just over 4 years in our cohort, highlighting the poor prognosis even among treated patients with mild–moderate disease as conventionally defined.

Although international guidelines do not differentiate advanced IPF from less advanced disease with respect to antifibrotic therapy,[19] the decision to treat patients with advanced disease is less certain, including in the Nordic countries.[20] In practice, however, patients with advanced IPF are commonly treated with nintedanib or pirfenidone, with as many as one in five treated patients having FVC and/or DLCO values below the thresholds for inclusion in trials.[3] Existing insights into the outcomes of such patients have come largely from secondary analyses of clinical trials or from open-label post-authorization studies. In ASCEND, outcomes of patients who experienced a 10% relative decline in FVC during the trial were analysed during a subsequent defined follow-up period, and appeared to have continued benefit from pirfenidone compared to placebo.[4] Patients with 'baseline' FVC < 50% of predicted in RECAP, which followed up patients who had completed ASCEND and CAPACITY, had a similar FVC trajectory compared with patients with better preserved FVC at baseline.[21] In INPULSIS-ON, 41 (6%) patients had an FVC < 50% at baseline.[5] It is notable that in all of these prior studies, patients had been followed up from the time of enrolment in the parent clinical trial. By contrast, our study included patients with advanced IPF at the start of treatment, who would not have been eligible for enrolment in trials. As such, our results may be less subject to survivor bias.

In the absence of clinical trials focusing specifically on advanced patients, observational data may still inform the expectations of clinicians and especially patients when considering the risks and benefits of treatment. In addition, our findings may inform future study design if randomized trials are pursued in patients with more advanced IPF. For example, FVC may be neither the most relevant outcome to affected patients nor the most efficient for detecting the effect of an intervention. Historically, mortality as a primary endpoint in IPF clinical trials has been viewed as impractical due to the low event rate in trial populations and accordingly large sample sizes required,[22] but if a more broadly representative IPF population is combined with a composite event-driven outcome incorporating both mortality and disease progression, such a strategy may not be impossible.

Our study has several limitations. Most importantly, while our primary aim was to describe outcomes of patients with advanced IPF who initiate antifibrotic treatment, the lack of an untreated comparator group precludes us from estimating a treatment effect. Estimating a treatment effect using observational data requires accounting for confounding to a degree that was not possible using the available data; furthermore, the Oslo University Hospital registry in particular was originally developed as a treatment-specific registry, limiting the ability to include a representative untreated group.

Second, because of differences in data collection among the registries, we could not assess the impact of comorbidities. Concomitant emphysema in particular may be associated with low DLCO relative to FVC, and with more modest loss of FVC over time, but nonetheless high mortality risk—in other words, the pattern observed in the advanced IPF patients in our study. The impact of concomitant emphysema on outcomes in advanced IPF warrants

further investigation. We were also unable to account for abdominal obesity; while development or reduction of obesity over time could confound change in FVC over time for a given patient, our primary intent in classification at baseline was to mirror lung function criteria used in previous clinical trials in IPF, which did not adjust for body weight or BMI. Furthermore, BMI in previous reports from portions of our cohort has been similar to in the general population.[12,15]

Finally, for similar reasons, we cannot report on hospital admissions or acute exacerbations, specific causes of death or safety outcomes apart from mortality. There is an unmet need to characterize the effect of antifibrotic therapy on acute exacerbations and hospital admissions in particular, as treatment appears to impact such outcomes in clinical trial populations.[2,23]

In conclusion, in a broadly representative population of over 500 patients with IPF from four Nordic countries, we have demonstrated that patients with advanced IPF at the time of treatment initiation have more stable lung function during follow-up, but substantially greater risk of mortality, compared with patients with mild–moderate IPF. There is a need for prospective studies specifically designed to determine the effect of antifibrotic therapy in patients with advanced IPF.

ACKNOWLEDGEMENTS

The authors thank all participants and physicians, study nurses and other clinical staff who are involved and contribute to the Swedish IPF registry, FinnishIPF registry, Oslo University Hospital IPF registry and Aarhus University Hospital IPF registry. Eva M. Sutinen and Marjukka Myllärniemi acknowledge the Finnish IPF Consortium (U. Hodgson, R. Kaarteenaho, A. Böök, E. R. Salomaa, S. Saarelainen, H. Kankaanranta and M. Purokivi).

Research funding: Michael T. Durheim was supported by a grant from the Norwegian Respiratory Society and an unrestricted grant from Boehringer Ingelheim. The Oslo University Hospital and Aarhus IPF registries have been supported by unrestricted grants from Boehringer Ingelheim and InterMune/Roche. Research based on the Swedish IPF registry is supported by grants from the Swedish Heart-Lung Foundation, Karolinska Institutet, Karolinska University Hospital and Paul and Ragna Nyberg Foundation, and by investigator-initiated grants from Roche and Boehringer Ingelheim. The FinnishIPF registry is supported by the Academy of Finland, Sigrid Juselius Foundation, Helsinki University Hospital—a governmental grant for health and sciences research, the Nummela Sanatorium Foundation for Medical Research and Boehringer Ingelheim.

AUTHOR CONTRIBUTIONS

Michael Durheim: Conceptualization; data curation; formal analysis; funding acquisition; methodology; project administration; writing - original draft. **Elisabeth Bendstrup:** Conceptualization; data curation; project administration; writing-review & editing. **Lisa Carlson:** Data curation; writing-review & editing. **Eva Sutinen:** Data curation; writing-review & editing. **Charlotte Hyldgaard:** Data curation; writing-review & editing. **Dimitrios Kalafatis:** Data curation; writing-review & editing. **Marjukka Myllärniemi:** Conceptualization; funding acquisition; project administration; writing-review & editing. **Magnus Sköld:** Conceptualization; funding acquisition; project administration; writing-review & editing. **Tone Sjåheim:** Conceptualization; data curation; funding acquisition; project administration; writing-review & editing.

CONFLICT OF INTEREST

Michael T. Durheim reports consulting and lecture fees from Boehringer Ingelheim and Roche, outside the current study, and that an immediate family member is a full-time employee of Boehringer Ingelheim who has played no role in this study or its funding. Elisabeth Bendstrup reports unrestricted grants, consulting and lecture fees from Roche, Boehringer Ingelheim and Galapagos, outside the current study. C. Magnus Sköld reports advisory board participation and lecture fees from Boehringer Ingelheim, Roche and InterMune, and research grants from Boehringer Ingelheim and Roche, outside the current study. Tone Sjåheim reports lecture fees from Boehringer Ingelheim and Roche, outside the current study.

HUMAN ETHICS APPROVAL DECLARATION

The study was approved by the relevant ethics committees at all participating institutions. A waiver of informed consent was obtained for the Oslo University Hospital registry and the Aarhus University Hospital registry; patients from the remaining two cohorts provided written informed consent.

ORCID

Michael T. Durheim https://orcid.org/0000-0002-4186-5698

REFERENCES

1. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370:2083–92.
2. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.
3. Salisbury ML, Conoscenti CS, Culver DA, Yow E, Neely ML, Bender S, et al. Antifibrotic drug use in patients with IPF: data from the IPF-PRO registry. Ann Am Thorac Soc. 2020;17:1413–23.
4. Nathan SD, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, et al. Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. Thorax. 2016;71:429–35.
5. Wuyts WA, Kolb M, Stowasser S, Stansen W, Huggins JT, Raghu G. First data on efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis and forced vital capacity of </=50% of predicted value. Lung. 2016;194:739–43.
6. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012;156:684–91.

7. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;184:459–66.
8. Salisbury ML, Xia M, Zhou Y, Murray S, Tayob N, Brown KK, et al. Idiopathic pulmonary fibrosis: gender-age-physiology index stage for predicting future lung function decline. Chest. 2016;149:491–8.
9. Schmidt SL, Tayob N, Han MK, Zappala C, Kervitsky D, Murray S, et al. Predicting pulmonary fibrosis disease course from past trends in pulmonary function. Chest. 2014;145:579–85.
10. Maher TM, Strek ME. Antifibrotic therapy for idiopathic pulmonary fibrosis: time to treat. Respir Res. 2019;20:205.
11. Caminati A, Cassandro R, Torre O, Harari S. Severe idiopathic pulmonary fibrosis: what can be done? Eur Respir Rev. 2017;26:170047.
12. Ferrara G, Carlson L, Palm A, Einarsson J, Olivesten C, Skold M. Idiopathic pulmonary fibrosis in Sweden: report from the first year of activity of the Swedish IPF-Registry. Eur Clin Respir J. 2016;3:31090.
13. Gao J, Kalafatis D, Carlson L, Pesonen IHA, Li CX, Wheelock A, et al. Baseline characteristics and survival of patients of idiopathic pulmonary fibrosis: a longitudinal analysis of the Swedish IPF Registry. Respir Res. 2021;22:40.
14. Hyldgaard C, Moller J, Bendstrup E. Changes in management of idiopathic pulmonary fibrosis: impact on disease severity and mortality. Eur Clin Respir J. 2020;7:1807682.
15. Kaunisto J, Salomaa ER, Hodgson U, Kaarteenaho R, Kankaanranta H, Koli K, et al. Demographics and survival of patients with idiopathic pulmonary fibrosis in the FinnishIPF registry. ERJ Open Res. 2019;5:00170–2018.
16. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, 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.
17. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198:e44–68.
18. Nathan SD, Costabel U, Albera C, Behr J, Wuyts WA, Kirchgaessler KU, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment. Respir Med. 2019;153:44–51.
19. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192:e3–e19.
20. Skold CM, Bendstrup E, Myllarniemi M, Gudmundsson G, Sjaheim T, Hilberg O, et al. Treatment of idiopathic pulmonary fibrosis: a position paper from a Nordic expert group. J Intern Med. 2017;281:149–66.
21. Maher TM, Lancaster LH, Jouneau S, Morrison L, Lederer DJ, Molina-Molina M, et al. Pirfenidone treatment in individuals with idiopathic pulmonary fibrosis: impact of timing of treatment initiation. Ann Am Thorac Soc. 2019;16:927–30.
22. King TE Jr, Albera C, Bradford WZ, Costabel U, du Bois RM, Leff JA, et al. All-cause mortality rate in patients with idiopathic pulmonary fibrosis. Implications for the design and execution of clinical trials. Am J Respir Crit Care Med. 2014;189:825–31.
23. Ley B, Swigris J, Day BM, Stauffer JL, Raimundo K, Chou W, et al. Pirfenidone reduces respiratory-related hospitalizations in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2017;196:756–61.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Durheim MT, Bendstrup E, Carlson L, Sutinen EM, Hyldgaard C, Kalafatis D, et al. Outcomes of patients with advanced idiopathic pulmonary fibrosis treated with nintedanib or pirfenidone in a real-world multicentre cohort. Respirology. 2021;26:982–8. https://doi.org/10.1111/resp.14116