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Project thesis

# Effects of antifibrotic therapy with nintedanib or pirfenidone on mortality and other clinical endpoints in IPF: a systematic review

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# Abstract

## Background

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease with a short median survival time ranging from 2-5 years, emphasizing the urgent need for effective treatments. Nintedanib and pirfenidone are established therapies for IPF, based on their ability to slow decline in lung function as measured by forced vital capacity (FVC). However, their impact on mortality, acute exacerbations, and side effects, directly affecting patient experiences, remains unclear.

## Purpose

This systematic review aims to summarize the effects of nintedanib and pirfenidone on mortality, acute exacerbations, and side effects in patients with IPF.

## Method

A PubMed search yielded 2,079 articles related to IPF and the two therapies. After initial screening and use of exclusion criteria, 11 articles were found to be relevant. Exclusion criteria included articles older than 2010, studies focusing on subgroups of patients with IPF and articles including drugs other than nintedanib and/or pirfenidone. Articles not published in widely recognized databases, such as PubMed, were also excluded.

## Results

Individual trials showed no significant reduction in all-cause mortality associated with nintedanib or pirfenidone compared to placebo. Pooled analyses suggested a potential reduction in all-cause mortality with antifibrotic therapy. Pirfenidone did not significantly improve IPF-specific mortality, and nintedanib did not reduce respiratory-related deaths. With respect to acute exacerbations, pirfenidone trials reported no significant reduction, while nintedanib trials had mixed results. Nintedanib may reduce acute exacerbations, especially at higher doses. Both therapies caused mild to moderate side effects. The adverse effects of pirfenidone were often dose-dependent and included primarily gastrointestinal symptoms and skin problems. Nintedanib primarily led to diarrhea, occasionally requiring discontinuation. Both drugs caused elevated liver enzyme (transaminase) levels in a small minority of patients, manageable without severe complications.

## Conclusion

In conclusion, while nintedanib and pirfenidone demonstrate a reduction in all-cause mortality and a slowing of FVC decline in IPF patients, their impact on IPF-specific and respiratory-related mortality, as well as on acute exacerbations (particularly for pirfenidone), is more limited. Moreover, the adverse event profiles, including gastrointestinal issues, skin disorders, and liver enzyme elevations, although mild to moderate, further complicate their use. Side effects such as photosensitivity and persistent diarrhea can significantly impair quality of life, potentially overshadowing the benefits of reduced FVC decline. Therefore, individual treatment decisions must be informed by a comprehensive and balanced understanding of benefits and risks of these drugs.

# CONTENTS

# Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease characterized by progressive scarring of the lung parenchyma, without identifiable cause (1,2). IPF is associated with chronic dyspnea and cough, and almost invariably with progressive respiratory failure (1,2). Prognosis is variable but generally poor, with median survival times ranging from 2-5 years (1–7), highlighting the urgent need for effective treatment options.

There are currently two available pharmacologic therapies for IPF: nintedanib and pirfenidone. Both of these drugs were approved primarily based on their demonstrated effect on reducing the decline in forced vital capacity (FVC) in multiple randomized controlled trials (3,7–10). FVC is a relevant outcome measure in IPF because it is practical, reproducible, and significantly associated with mortality among patients with IPF (11). FVC is also a physiologically appropriate measure of the restrictive ventilatory defect that characterizes IPF and other forms of pulmonary fibrosis (12). While total lung capacity (TLC) as measured by plethysmography is considered the ultimate measure of restrictive lung physiology, FVC is simpler and more practical as a serially measured clinical trial endpoint and reflects its use in longitudinal monitoring of patients with IPF in clinical practice.

In short, FVC has been commonly used as a *surrogate endpoint* in clinical trials in IPF, due to its relationship with disease pathophysiology and, crucially, to its established association with mortality, the clinical endpoint presumably of ultimate importance to patients. While it may be intuitive to suggest simply using mortality as the primary endpoint of clinical trials, mortality has not been a practical primary endpoint, likely because the more stable subset of IPF patients who tend to participate in trials have relatively lower mortality risk than the IPF population at large; this lower mortality risk would require prohibitively large sample sizes (13,14).

Despite the demonstrated effects of nintedanib and pirfenidone on slowing the reduction in FVC, these drugs are not curative, and the overall prognosis for IPF remains poor. Moreover, despite the established association between FVC and mortality, FVC is not a truly clinical outcome directly experienced by patients; accordingly, it is crucial to understand whether these drugs demonstrably improve clinical outcomes of direct importance to patients, such as mortality, acute clinical worsening events, and side effects or adverse events.

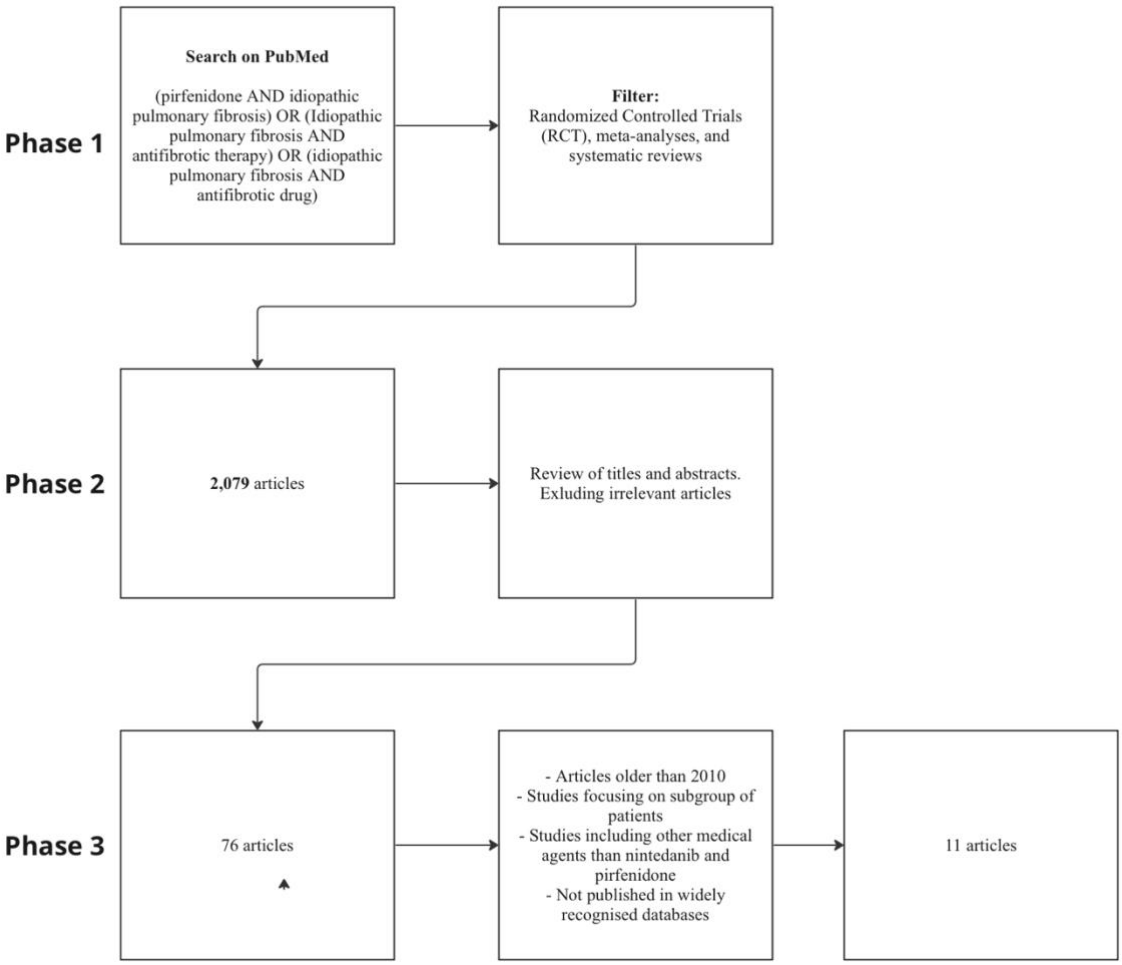
While mortality and adverse effects are common endpoints assessed in investigational drug studies, acute exacerbations is a term used more specifically in the context of IPF. Acute exacerbations are episodes of acute clinical worsening that abruptly interrupt periods of stability (15,16). These episodes manifest as a decline in lung function, often accompanied by symptoms like worsened shortness of breath and cough (15,16). Many such acute episodes occur without a clear external trigger such as infections, pulmonary embolism or cardiovascular events (15). Diagnostic tests, including high-resolution CT imaging, often reveal new areas of lung damage (15). Unfortunately, there are no well-documented treatment options for acute exacerbations of IPF, and the prognosis remains poor, with high mortality rates reported within short time periods following these episodes (15). Given the impact of acute exacerbations on the progression and outcome of IPF, it is especially pertinent to assess the documented effects of approved antifibrotic medications on these clinical events.

In response to these uncertainties, this systematic review aims to provide a detailed overview of the effects of pirfenidone and nintedanib on mortality, acute exacerbations, and side effects in patients with IPF.

## Methods

The formulation of the research question was guided by the PICO model, an instrumental framework for refining questions and facilitating a more structured literature search. PICO is an acronym representing Population, Intervention, Comparison, and Outcome. In this specific context, the population comprises patients diagnosed with IPF. The intervention under investigation is the use of nintedanib or pirfenidone. The comparison involves antifibrotic treatment against a placebo group. Finally, the outcomes of interest are mortality, acute exacerbations, and adverse events. This structured approach is crucial in delineating the parameters of the study, thereby ensuring a focused and comprehensive exploration of the relevant literature.

A PubMed search was performed using the terms (nintedanib and idiopathic pulmonary fibrosis) OR (pirfenidone AND idiopathic pulmonary fibrosis) OR (Idiopathic pulmonary fibrosis AND antifibrotic therapy) OR (idiopathic pulmonary fibrosis AND antifibrotic drug). Results were filtered for Randomized Controlled Trials (RCTs), meta-analyses, and systematic reviews, obtaining 2,079 results initially. After reviewing the titles and abstracts of the articles, those not relevant to the research question and endpoints of this review were filtered out, resulting in 76 articles being shortlisted. Upon closer examination of these articles, using exclusion criteria, 11 articles were found to be relevant. Exclusion criteria included articles older than 2010, studies focusing on subgroups of patients with IPF and articles including drugs other than nintedanib and pirfenidone. Articles not published in widely recognized databases, such as PubMed, were also excluded.


Phase 1
Search on PubMed
(pirfenidone AND idiopathic pulmonary fibrosis) OR (Idiopathic pulmonary fibrosis AND antifibrotic therapy) OR (idiopathic pulmonary fibrosis AND antifibrotic drug)
Filter:
Randomized Controlled Trials (RCT), meta-analyses, and systematic reviews
Phase 2
2,079 articles
Review of titles and abstracts. Exluding irrelevant articles
Phase 3
76 articles
- Articles older than 2010
- Studies focusing on subgroup of patients
- Studies including other medical agents than nintedanib and pirfenidone
- Not published in widely recognised databases
11 articles

| Study Title | Author(s) | Year | Study Design |
|---|---|---|---|
| Pirfenidone in idiopathic pulmonary fibrosis | H. Taniguchi et al. | 2010 | Phase 3 RCT |
| Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY) | P.W. Noble et al. | 2011 | Two identical phase 3, concurrent 72-week RCTs (004 & 006) |
| Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis (TOMORROW) | L. Richeldi et al. | 2011 | Phase 2 RCT |
| A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (ASCEND) | T.E. King et al. | 2014 | 52-week Phase 3 RCT |
| Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis (INPULSIS) | L. Richeldi et al. | 2014 | Two parallel 52-week Phase 3 studies (INPULSIS-1 and INPULSIS-2) |
| Safety, tolerability and appropriate use of nintedanib in idiopathic pulmonary fibrosis. | T.J. Corte et al. | 2015 | Pooled analysis |
| Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS® trials | L. Richeldi et al. | 2016 | Pooled analysis and meta-analysis of TOMORROW trial and INPULSIS Trials |
| Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis | S.D. Nathan et al. | 2017 | Meta-analysis and pooled analysis of CAPACITY, ASCEND, Shionogi Phase 2, and Shionogi Phase 3 |

| Study Title | Author(s) | Year | Study Design |
|---|---|---|---|
| Cardiovascular safety of nintedanib in subgroups by cardiovascular risk at baseline in the TOMORROW and INPULSIS trials | I. Noth et al. | 2019 | Pooled analysis |
| Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis | T. Petnak et al. | 2021 | Systematic review and meta-analysis of 26 articles (8 RCT and 18 cohort studies) |
| Efficacy and safety of pirfenidone in the treatment of idiopathic pulmonary fibrosis: a systematic review and meta-analysis of randomised controlled trials | W. Wu et al. | 2021 | Systematic review and meta-analysis of RCTs |

# Mortality

## All-cause mortality

Antifibrotic treatment did not have a significant impact on all-cause mortality when comparing the treatment groups to the placebo groups in any of the individual randomized controlled trials (RCTs) (3,7–9,17).

In the RCTs, pirfenidone did not significantly affect all-cause mortality when compared to placebo (3,7,9). The 72-week CAPACITY trials (7), comprising two identical, concurrent trials (004 and 006), each with a pirfenidone group and a placebo group, examined the effect of pirfenidone on mortality as an exploratory endpoint. In the pooled population, the HR for overall all-cause mortality was 0.77 (95% CI 0.47-1.28), with an associated p-value of 0.315, indicating no statistically significant reduction in all-cause mortality risk with pirfenidone treatment (7). A similar result was observed in the 52-week phase 3 ASCEND RCT by King et al. (9), showing no significant difference in all-cause mortality between the treatment and placebo groups. However, a prespecified pooled analysis of data from both the ASCEND and CAPACITY studies indicated a significant reduction in the risk of death from any cause in the pirfenidone group compared to placebo (HR 0.52, 95% CI, 0.31-0.87, p=0.01) (9).

In a phase 3 study by Taniguchi et al. (3), the efficacy and safety of pirfenidone in Japanese patients were investigated. In this study, the participants were divided into three groups: One group receiving up to 1800 mg pirfenidone per day, a low-dose group receiving a maximum of 1200 mg/day, and a third placebo group (3). While mortality was not a standalone endpoint, the study did evaluate progression-free survival time as a secondary endpoint. Disease progression in this context was defined by either death or a ≥10% decline in FVC from baseline, thereby incorporating mortality into this endpoint (3). Using a log-rank test, the study found no significant difference in progression-free survival between either of the treatment groups and placebo (3).

In a separate study by Nathan et al. (18) a pooled analysis was conducted using data from the CAPACITY and ASCEND trials to assess the effect of pirfenidone on all-cause mortality. Additionally, these trials, along with the Shinogi Phase 2 and Shinogi Phase 3 trials, were included in a random-effects meta-analysis (18). The pooled analysis included studies with similar protocols, such that datasets could simply be combined; by contrast, the meta-analysis was necessary when including the additional studies, which had differences in study population, in- and exclusion criteria, and study protocol that precluded simply pooling the datasets (18). Across these studies, a total of 1578 patients were analysed (809 in the pirfenidone group and 769 in the placebo group), with different mortality outcomes, including all-cause mortality being examined at weeks 52, 72, and 120 (18).

In general, the individual studies favored pirfenidone, showing a significantly lower risk of all-cause mortality in the treatment group compared to the placebo (18). However, at the end of follow-up, only meta-analyses showed a significantly lower risk associated with pirfenidone (18).

The pooled analysis demonstrated a significant benefit of pirfenidone over placebo in terms of all-cause mortality, with an HR of 0.52 (95% CI 0.31-0.87, p=0.0107) at 52 weeks and an HR of 0.63 (95% CI 0.41-0.98, p=0.0404) at 72 weeks (18). However, by the end of follow-up, the difference in all-cause mortality rates between the pirfenidone and placebo groups were non-significant in the pooled analysis (18). However, in the random-effects meta-analyses, which included the Japanese trials, the p-value of 0.0346 still favored pirfenidone with a HR of 0.65 (18).

The INPULSIS trials (8), consisting of two concurrent 52-week phase 3 studies (INPULSIS-1 and INPULSIS-2), aimed to assess the efficacy and safety of administering 150 mg of nintedanib twice daily versus placebo. Within these studies, all-cause mortality was a secondary endpoint (8). Notably, nintedanib did not lead to a significant reduction in the risk of all-cause mortality among patients with IPF when compared to placebo, with a hazard ratio (HR) of 0.7 (95% CI, 0.43-1.12, p=0.14) (8). Additionally, the TOMORROW study (17), a phase 2 randomized controlled trial, explored the effects of different doses of nintedanib over a 12-month period. This study involved four groups, each receiving varying doses of nintedanib, and their outcomes were compared with those of a placebo group (17). In the TOMORROW study (17), there were no significant differences in death from any cause between any of the four active treatment groups and the placebo group. This observation is further corroborated by a pooled analysis conducted by Richeldi et al. (19) which utilized data from both the TOMORROW study and the INPULSIS trials. This analysis, along with a subsequent meta-analysis, confirmed the lack of a significant difference in all-cause mortality between the treatment groups receiving nintedanib and the placebo groups (19).

A systematic review and meta-analysis conducted by Petnak et al. (10) examined the effect of antifibrotic therapy on mortality and the risk of acute exacerbations. The study included a total of 26 articles, consisting of eight randomized controlled trials (RCTs) and 18 cohort studies (10). By combining the data for pirfenidone and nintedanib, the pooled results demonstrated that the use of antifibrotic agents was associated with a significantly lower risk of all-cause mortality compared to placebo, with a pooled risk ratio (RR) of 0.55 (95% CI, 0.45-0.66; I^2=82%) (10). Subgroup analyses were performed to explore potential variations, and the findings across the subgroup analyses consistently favored antifibrotic treatment over placebo in terms of reducing the risk of all-cause mortality (10).

## IPF-related mortality

IPF-related mortality was only specifically assessed in studies examining pirfenidone. The findings on IPF-related mortality in the RCTs mirrored the trend seen in all-cause mortality. Neither the CAPACITY (7) nor the ASCEND (9) studies individually demonstrated a significant difference in IPF-related mortality rates when comparing pirfenidone to placebo groups. However, a prespecified pooled analysis of data from both studies revealed a notable reduction in IPF-related mortality (HR 0.32, 95% CI 0.14-0.76, p=0.006) (10).

## Death from respiratory cause

Death from respiratory cause was only specifically examined in the nintedanib studies, and not in the pirfenidone studies. Death from respiratory causes was examined in both the INPULSIS trials (8) and the pooled and meta-analysis conducted by Richeldi et al. (20). The findings from both studies showed no significant difference in deaths from respiratory causes when using nintedanib compared to placebo (8,19).

# Discussion - The Effect of Pirfenidone and Nintedanib on Mortality in IPF Treatment

Regarding mortality endpoints, the primary focus in this review is on endpoints analyzed under an intention to treat (ITT) principle, meaning that patients were classified based on the treatment group to which they were originally randomized, regardless of whether they in fact remained on the allocated treatment for the duration of the study protocol. The outcomes analyzed under the “intention to treat”perspective are all-cause mortality, respiratory-related mortality, and IPF-related mortality. This approach ensures that the results reflect the realistic application of these medications across a broad patient population. Endpoints such as on-treatment mortality or treatment-emergent mortality have been excluded from this analysis. On-treatment mortality endpoints may not fully align with an ITT analysis, as they only consider patients who continue with the treatment and exclude those who discontinue it, which can introduce bias and potentially reduce the generalizability of the findings.

Randomized controlled trials (RCTs) for both pirfenidone and nintedanib, such as the CAPACITY (7), ASCEND (9), and INPULSIS trials (8), did not demonstrate a significant impact on all-cause mortality. These findings, while methodologically robust, might have been limited by smaller sample sizes and shorter treatment durations. These limitations potentially underpowered the studies to detect significant mortality benefits.

Pooled- and meta-analyses represent an opportunity to better understand the potential of these medications to impact mortality and other clinical outcomes. For instance, the prespecified pooled analysis of the CAPACITY and ASCEND trials found a significant reduction in all-cause mortality with pirfenidone, an observation not evident in the individual trials. (9) This highlights the ability of larger datasets to enhance the statistical power necessary to detect significant effects that might be missed in smaller, individual studies. Again, it is important to critically appraise the relatively simpler pooled analysis approach, with respect to the homogeneity of the patient populations and study treatment protocols; provided enough similarities, the pooled approach yields aggregate results that are simple to interpret, but enough differences in patient populations and/or treatment protocols give rise to the need for more methodologically complex meta-analyses, which are designed to account for such differences.

The meta-analysis conducted by Nathan et al. (18) which incorporated additional trials from Japan, offered more substantial evidence supporting the mortality benefits of pirfenidone. However, it is important to note that these findings showed inconsistency towards the end of the follow-up period.(18) While the pooled analysis incorporating both the ASCEND and CAPACITY studies did not yield significant results at the end of the study, the meta-analysis which also included two Japanese trials, maintained its significance (18). The potential advantages of meta-analysis, therefore, include both increasing sample size and statistical power, but also providing a more heterogenous overall study population with regard to demographics, disease characteristics and study design, thus potentially more representative of that seen in clinical practice.

Turning our attention to nintedanib, the INPULSIS (8) and TOMORROW (17) trials had similar trends as observed with pirfenidone in the CAPACITY trials (7). While individual studies did not show statistically significant mortality benefits, the meta-analysis by Petnak et al. (10) suggested a reduced risk of all-cause mortality with use of antifibrotic therapy. This pattern reinforces the idea that antifibrotic agents, when their effects are aggregated over larger populations, might confer a survival benefit.

Even though the results from the meta-analysis by Petnak et al. (10) are promising, it is important to note that the study included both RCTs and cohort studies. RCTs, considered the gold standard in treatment efficacy evaluation, minimize treatment bias and confounding due to their design. However, their strict inclusion criteria can sometimes limit the generalizability of the results to a broader patient population. On the other hand, observational studies, though more prone to biases like selection bias and confounding, often offer a wider representation of the real-world setting, including a more diverse patient demographic. This difference in design and inherent biases between RCTs and observational studies necessitates cautious interpretation when these study types are combined in a meta-analysis.

While pirfenidone and nintedanib showed some tendency to reduce all-cause mortality in larger studies, their impact on IPF-specific mortality and death from respiratory causes is less clear. IPF-related mortality was examined in the pirfenidone studies, while death from respiratory cause was examined in the nintedanib studies. Yet, only the prespecified pooled analysis in the ASCEND study (9) found a significant reduction in IPF-related mortality associated with pirfenidone. The remaining studies, both for pirfenidone and nintedanib, found no difference in IPF-related mortality or respiratory-related mortality between the antifibrotic treatment and the placebo groups (7,9,17,19). While there is some evidence of reduced all-cause mortality, it is more unclear if the antifibrotic therapies have an impact on IPF-related mortality. While theoretically a drug intervention could impact all-cause but not disease-specific mortality if it has benefits outside of direct effect on the disease, in this case there is no other biologically suspected mechanism for benefit of these drugs in IPF; as such, it seems likely that the smaller observed effects on IPF-specific mortality may be related to the lower event rates (and therefore reduced statistical power) associated with the more specific endpoint definition.

In any case, studies to date suggest that pooled- and/or meta-analyses are necessary to demonstrate a benefit of antifibrotic therapy on mortality outcomes in IPF. This raises an important consideration regarding the magnitude of the effects of these medications, especially on IPF-related and respiratory-related mortality. Given that larger studies are required to confirm whether these drugs impact IPF-related mortality, it is likely that any such effect is likely to be subtle, at least over a relatively short follow-up period.

## Acute exacarbations

In the CAPACITY trials examining pirfenidone, one secondary endpoint was the worsening of IPF. This worsening was specifically defined as the time to either acute exacerbation, death, lung transplantation, or hospital admission for respiratory issues (7). The term "acute IPF exacerbation"was clearly defined in the trial protocol and is detailed in *Table 1*. Notably, the trials showed no significant difference between the treatment groups and the placebo groups with respect to time to worsening of IPF (7).

In contrast, in their systematic review and meta-analysis of RCTs, Wu et al. (20) assessed acute exacerbations as a standalone endpoint. Such exacerbations were characterized by an unexplained worsening of dyspnea within the previous 30 days in patients already diagnosed with IPF or a similar worsening occurring concurrently with the time of diagnosis of IPF (20). This worsening was associated with the appearance of new bilateral ground-glass opacities or consolidation that other causes could not account for (20). In their meta-analysis, four RCTs were used to calculate the risk ratio for acute exacerbations in patients treated with pirfenidone compared to placebo (20). The study found that there was no significant difference on the incidence of acute exacerbations when using pirfenidone compared to placebo (20).

In the INPULSIS trials on nintedanib, the “time to the first acute exacerbation”was one of the pre-specified secondary endpoints (8). The criteria used to define acute exacerbations in this study can be seen in Table 2. The effects of Nintedanib on acute exacerbations in patients with IPF were inconsistent across these trials. While INPULSIS-1 showed no significant impact of nintedanib on time to the first acute exacerbation, a significant reduction was observed in INPULSIS-2 (8). Furthermore, a prespecified pooled analysis from these trials showed no significant effect of nintedanib on this endpoint. This stands in contrast to the prespecified sensitivity analysis, which was based on centrally adjudicated acute exacerbations rather than local investigator reported events, and which showed reduced time to the first acute exacerbation associated with nintedanib (8). Based on these results, while there is inconsistency in the outcomes between the individual studies, the sensitivity analysis does provide some indication that Nintedanib might have a beneficial effect in reducing time to the first acute exacerbation in IPF patients.

In the phase 2 RCT, known as the TOMORROW study (17), four different doses of nintedanib were investigated over a 12-month period. Patients were assigned to one of the following regimens: 50 mg once daily, 50 mg twice daily, 10 mg twice daily, or 150 mg twice daily. These were compared to a placebo group (17). Within this study, nintedanib did not show a significant benefit in reducing the incidence of acute exacerbations in the group receiving doses up to 100 mg twice daily. However, for the group administered 150 mg twice daily, the incidence of acute exacerbations was reduced by 84% with a risk ratio of 0.16 and a CI of 0.03-0.7 (17).

When the data from TOMORROW and INPULSIS trial were pooled, the hazard ratio for time to first exacerbation favored nintedanib with an HR of 0.53 (95% CI, 0.34-0.83, p=0.0047) (19). In this study, the criteria for an acute exacerbation was defined as in the INPULSIS trials (19).

The previously mentioned study by Petnak et al. (10) investigated the impact of antifibrotic therapy on both acute exacerbations and mortality. In their systematic review and meta-analysis, seven of the 26 included articles were used to conduct a meta-analysis specifically focusing on the effect of antifibrotic therapy on acute exacerbations (10). Four of the seven included studies were RCTs, and three were retrospective cohort studies (10). The pooled analysis including both the RCTs and the cohort studies, found that there was a statistically

significant reduction in the risk of acute exacerbations of 37%, when treated with antifibrotic drugs compared to placebo (10). The effectiveness of antifibrotic treatment in reducing the risk of acute exacerbations was supported by the subgroup analyses (10). The RCTs showed an RR of 0.58(95% CI, 0.38-0.89;$I^2$=11%), and the cohort studies showed an RR of 0.65(95% CI, 0.53-0.79;$I^2$=0%) (10). The pooled analysis did not distinguish between nintedanib and pirfenidone. In subgroup analyses of these two drugs, only nintedanib demonstrated a statistically significant reduction in the relative risk of acute exacerbations compared to placebo (10). Although pirfenidone showed a 43% reduction in risk compared to placebo, this result was not statistically significant (10).

These findings highlight the potential benefits of antifibrotic therapies, specifically nintedanib, in reducing the risk of acute exacerbations in IPF patients. Although pirfenidone appears to offer some risk reduction, results to date have not been statistically significant.

*Table 1*

| **Acute IPF Exacerbation definition in the CAPACITY trial (7)**<br>Within a 4-week period a patient must develop evidence of all of the following criteria: |
|---|
| 1) Worsening of Pa O2 (≥8mm Hg drop from most recent pre-worsening value) |
| 2) Clinically significant worsening of dyspnea |
| 3) New, superimposed ground-glass opacities on HRCT in ≥1 lobe |
| 4) All other causes such as cardiac, thromboembolic, aspiration or infectious processes have been ruled out |

*Table 2*

| **Acute exacerbation**<br><br>*Definition from INPULSIS trials (found in the protocol)(8)* |
|---|
| **Otherwise unexplained clinical features within one month, including all of the following:**<br><br>o Unexplained worsening or development of dyspnea within 30 days.<br>o New diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit.<br>o Exclusion of infection as per routine clinical practice and microbiological studies.<br>o Exclusion of alternative causes as per routine clinical practice, including the following:<br>o Left heart failure<br>Pulmonary embolism<br>Identifiable cause of acute lung injury |

## Discussion - The effect of pirfenidone and nintedanib on acute exacerbations in IPF

Taken together, data on the potential effect of antifibrotic therapy on risk of acute exacerbations are inconsistent. The systematic review and meta-analysis by Petknak et al. (10) serves as a foundational reference in understanding the impact of antifibrotic therapy on acute exacerbations. The pooled analysis demonstrated a statistically significant 37% reduction in the risk of acute exacerbations when treated with antifibrotic drugs compared to placebo (10). This effect was consistent across subgroup analyses, highlighting the potential efficacy of antifibrotic therapy. However, a closer examination reveals that only nintedanib showed a statistically significant risk reduction compared to placebo (10). The apparent risk reduction by pirfenidone, though promising, lacked statistical significance (10). Similarly, pirfenidone failed to demonstrate a significant benefit in acute exacerbations in both the CAPACITY trials (7) and the meta-analysis of four RCTs by Wu et al. (21).

A crucial consideration in interpreting these findings is the specification of endpoints. The CAPACITY trials (7) evaluated the effect of pirfenidone on worsening of IPF, defined as the time to either acute exacerbation, death, lung transplantation, or hospital admission for respiratory issues (7). This approach, while methodologically sound, complicates the task of discerning the specific impact of pirfenidone on acute exacerbations. Indeed, the trial found no difference in the time to worsening of IPF between treatment and placebo groups(7). This consideration also applies to the study by Petnak et al. (10). The RCTs of pirfenidone in this meta-analysis examined “acute worsening,”whereas those of nintedanib assessed “acute exacerbations (10). The term “acute worsening”is broader and may dilute the capacity to pinpoint the specific effect on acute exacerbations, emphasizing the need for caution when combining studies for pirfenidone and nintedanib. However, the meta-analysis by Wu et al. (20), which defined acute exacerbations more precisely as “unexplained worsening of dyspnea within the previous 30 days in patients already diagnosed with IPF or those with a concurrent diagnosis of IPF,”still found no significant difference between the treatment and placebo groups (20). This suggests that pirfenidone may not have a beneficial effect on the rate of acute exacerbations.

In contrast to the pirfenidone studies, the INPULSIS trials (8) specifically considered "time to the first acute exacerbation,"offering a clearer understanding of the effect of the drug on IPF-related exacerbations. However, the results were inconsistent between the two studies. While INPULSIS-1 showed no significant benefits, INPULSIS-2 observed a significant reduction in this endpoint (8). The inconsistency highlights the uncertainty of drug effects on acute exacerbation events in IPF and suggests the possibility of variability in patient responses or other influencing factors not accounted for in the study design.

Furthermore, a prespecified pooled analysis from these trials showed no significant effect of nintedanib on this endpoint (8). In contrast, a prespecified sensitivity analysis suggested that nintedanib significantly reduced the time to the first acute exacerbation in patients with IPF (8). This finding is particularly interesting as it may provide a closer approximation of the true effect of nintedanib on narrowly defined acute exacerbations. In the sensitivity analysis, all patients with reported acute exacerbations by site investigators were reassessed by a blinded adjudication committee (8). The committee reviewed the reported cases of acute exacerbations to evaluate whether the reported cases met the criteria for this endpoint (8). By excluding cases that did not met the criteria for acute exacerbations, the sensitivity analysis provides more robust evidence on the effect of nintedanib on the time to acute exacerbations. However, if the effect of nintedanib on acute exacerbation had been larger, the pooled analysis would likely also have been statistically significant. This discrepancy may suggest that the effect, if present, is modest.

In the INPULSIS trials (8) the patients received 150 mg of nintedanib twice daily in both INPULSIS-1 and INPULSIS-2 meaning that the effect of nintedanib on the different endpoints were only examined for this specific dose. In contrast to this, the TOMORROW study (17) investigated four different doses of nintedanib over a 12-month period. Insights from the TOMORROW study indicated significant efficacy only in the highest dosage group of nintedanib, suggesting a dose-dependent effect (17). Strengthening the argument for the role of nintedanib in acute exacerbations, the combined data from TOMORROW and INPULSIS trials, as reported by Richeldi et al. (19) indicated a significant reduction in time to the first exacerbation with nintedanib.

In conclusion, nintedanib appears to be associated with a small but somewhat inconsistent reduction in risk of acute exacerbations, with effects seen most prominently in pooled analyses (10,17,19). For pirfenidone, however, the results are less promising, suggesting no effect of pirfenidone on acute exacerbations (7,10,20), although evaluation of pirfenidone studies is made more complicated by acute exacerbations being less narrowly defined or included as part of composite endpoints.

# Adverse events

## Pirfenidone

In the CAPACITY trials (7), a significant majority of patients (98%) reported experiencing at least one treatment-emergent adverse event. A treatment-emergent adverse event was defined as adverse events that occurred in patients who were administered pirfenidone at a dose of 2403mg/day in study 004 or 006, and with an incidence that was at least 1.5 times greater than that in patients who received placebo (7). In the 004 study, 87 patients were assigned to 1197 mg pirfenidone per day, and 174 patients were assigned to 2403 mg/day (7). In the 006 study, all patients in the pirfenidone group were assigned to 2403 mg pirfenidone per day.(7) The adverse events most commonly reported by those administered 2403 mg/day of pirfenidone included gastrointestinal events, skin disorders and dizziness (7). Gastrointestinal events included nausea, dyspepsia, vomiting and anorexia. Skin disorders included rash and photosensitivity reactions (7). The adverse events were considered to be of mild to moderate severity, and dose-response relationships were observed (7).

In the group of patients receiving pirfenidone, there was an increased incidence of specific laboratory abnormalities, including hyperglycemia, hyponatremia, hypophosphatemia, and lymphopenia, in comparison to the placebo group (7). However, these abnormalities were not associated with any notable clinical consequences (7). In addition, a higher percentage of patients in the pirfenidone group showed elevated levels of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), at more than three times the upper limit of normal, compared to the placebo group (7). Despite this, these elevations were reversible and not associated with significant adverse clinical outcomes (7).

The observations in the ASCEND study by King. et al (9) were similar to those of the CAPACITY trials (7). Gastrointestinal and skin-related adverse events were more frequent in the group treated with pirfenidone compared to the placebo group (9). The severity of these events were considered mild to moderate and also without significant sequelae (9).

Serious adverse events are defined as events immediately life-threatening, fatal, require or prolong hospitalization, or are otherwise medically significant. In the ASCEND study by King. et al (9), 19.8% in the pirfenidone group and 24.9% in the placebo group experienced such events, which included the worsening of IPF as a serious adverse event. However, worsening of idiopathic pulmonary fibrosis was also a defined efficacy endpoint in this study, and when excluded as a serious adverse event, the percentage of patients with serious adverse events was 18.7% in the pirfenidone group and 20.2% in the placebo group (9).

Elevated levels of ALT or AST were also observed in this study, among 2.9% of patients in the pirfenidone group and 0.7% in the placebo group (9). The elevations in liver enzymes were reversible and without clinically significant consequences (9). In total, serious adverse events and deaths were observed more in the placebo group compared to the pirfenidone group (9).

In the systematic review and meta-analysis of RCTs on pirfenidone conducted by Wu et al. (20), it was found that skin-related adverse events, such as photosensitivity, were similarly frequent in both the pirfenidone and placebo groups, with a relative risk (RR) of 1.04 (95% CI, 0.95-1.14, p=0.38, I2=37%). However, the overall risk of experiencing any adverse events was significantly higher in the pirfenidone group, with a 3.89 times increased risk compared to the placebo group (95% CI, 2.09-7.24, p<0.0001) (20).

In the phase 3 trial conducted by Taniguchi et al. (3) patients were categorized into high-dose, low-dose, and placebo groups. The study found that photosensitivity was a notably common adverse event, especially in the high-dose pirfenidone group (3). Approximately 51% of patients in the high-dose group and 53% in the low-dose group experienced photosensitivity, compared to 22.4% in the placebo group (3). This difference was statistically significant ($p<0.01$) between the high-dose and placebo groups. However, there was no significant difference in photosensitivity between the high and low-dose groups (3). Other adverse events such as asteatotic eczema, anorexia, abdominal discomfort, dizziness, nasopharyngitis, and upper respiratory tract infections also showed significant differences between the pirfenidone and placebo groups (3). Notably, the high-dose group exhibited a higher incidence of anorexia, dizziness, and increased gamma-GTP levels, whereas the low-dose group showed a higher occurrence of asteatotic eczema, abdominal discomfort, and decreased white blood cell counts compared to the placebo group (3).

## Nintedanib

In both INPULSIS-1 and INPULSIS-2 trials (8), diarrhea was the most common side effect observed among participants taking nintedanib, with the majority experiencing mild to moderate intensity. This side effect led a small percentage (around 4.5%) of participants to stop taking the medication prematurely in each study (8). The studies showed a similar rate of serious adverse events between the nintedanib and placebo groups (8). Furthermore, a slightly higher percentage of participants in the nintedanib groups experienced elevated liver enzyme levels compared to those in the placebo groups (8). Infrequent events included myocardial infarctions, with a small number occurring in both nintedanib and placebo groups, resulting in a few fatalities (8).

In the study conducted by Richeldi et al. (19) there was a notable rate of early treatment discontinuation due to adverse events among patients using nintedanib (20.6%) compared to those on a placebo (15.0%). Diarrhea stood out as the main adverse event for nintedanib users, with 61.5% reporting it, in contrast to 17.9% of placebo users (19). This led 5.3% of patients on nintedanib to discontinue treatment early, compared to 0.2% on placebo (19). Both groups had a similar rate of experiencing at least one serious adverse event (30.0% for nintedanib users and 30.1% for placebo users) (19).

In the TOMORROW study (17), the incidence of adverse events was consistent across all groups, including serious adverse events. However, the group that received 150 mg of nintedanib twice daily showed a lower percentage of serious adverse events (27.1%) compared to the placebo group (30.6%) (17). The 150 mg group also had the highest discontinuation rate due to adverse effects (30.6%), with the most common reasons being diarrhea, nausea, and vomiting (17). Within this group, 4.7% experienced serious gastrointestinal issues and 5.9% encountered severe gastrointestinal problems, particularly diarrhea, compared to none in the placebo group (17).

The study also found a decline in fatal adverse events as the dosage of nintedanib increased (17). In the active-treatment groups, the number of fatalities was, in ascending order of dosage: 10, 4, 5, and 1, while the placebo group had 12 deaths (17).

In the study, 7.1% of patients receiving 150 mg of nintedanib 1120 twice daily exhibited notable increases in liver enzymes, AST and ALT, reaching at least triple the upper normal limit which was evaluated as clinically significant elevations (17). This was also observed in one patient each in the groups taking 100 mg and 50 mg twice daily (17). In contrast, no such elevations were reported in patients taking 50 mg once daily or in the placebo group (17). Interestingly, these elevated liver enzyme levels either returned to normal or decreased with ongoing treatment, a reduction in dosage, or cessation of the drug (17). The abnormal liver function test results lead to discontinued medication in only two patients (17).

In a study conducted by Corte et al. (21), pooled data were used to assess how adverse events were managed during the 52-week INPULSIS trials (21). In this study, a higher percentage of patients treated with nintedanib (95.5%) experienced adverse events compared to those on the placebo (89.6%) (21). The incidence of serious adverse events was similar between the nintedanib (30.4%) and placebo (30.0%) groups (21). Notably, diarrhea was the most commonly reported adverse event in the nintedanib group, affecting 62.4% of patients, while only 18.4% of placebo patients experienced it (21). Most cases of diarrhea were of mild or moderate intensity (21).

When looking at specific details of diarrhea events, the majority of patients had fewer than four extra stools per day, with watery bowel movements being the most common description (21). Diarrhea led to permanent dose reduction or interruption of treatment in some cases, but for the majority of patients with diarrhea adverse events, the symptoms resolved without needing a dose reduction (21).

Other adverse events were nausea, vomiting and increased liver enzymes. Adverse events like nausea and vomiting were mild to moderate. With respect to liver enzymes, the majority of the patients returned to normal values by the end of treatment (21).

Adverse events like bleeding, epistaxis, contusions and gastrointestinal perforations were reported, but were either very seldom or occurred with similar frequency in the treatment and placebo groups; as such, their causal association with nintedanib is uncertain (21). This also seems to apply to "cardiac disorder adverse events". For fatal cardiac disorder adverse events, there was a 0.5% occurrence in the nintedanib group and 1.4% in the placebo group (21). Similarly, the nintedanib group also witnessed fewer serious cardiac disorder adverse events compared to the placebo group (21). While these differences are slight and favor nintedanib, a deeper examination of cardiac-related adverse events unveils some noteworthy distinctions. Using MedDRA, the Medical Dictionary for Regulatory Activities, which provides a standardized platform for consistent regulatory communication in medical research (22), the data indicates a potential elevation in events like myocardial infarction in the nintedanib group (2.7%) compared to the placebo group (1.2%) (21). Nonetheless, a smaller proportion of patients in the nintedanib group (1.6%) compared to placebo (3.1%) experienced events categorized as other ischemic heart disease (21).

## Discussion - The adverse effects of nintedanib and pirfenidone in treating IPF

Adverse events, while not always directly causing fatalities, can significantly impact the quality of life, drug adherence, and the overall therapeutic experience of patients.
For pirfenidone, gastrointestinal events, skin disorders, and dizziness seem to be the most frequently reported adverse outcomes (3,7,9). Notably, these events are often of mild to moderate severity, indicating that, while uncomfortable or distressing, they might not be immediately life-threatening (7,9). The high prevalence of photosensitivity across trials, especially in the high-dose group, resonates with the idea of dose-response relationships (3). It should also be noted that photosensivity was most frequent in older studies, and that this observation led to focus on skin protective measures in later trials, where skin-related side effects were less frequent.

Interestingly, elevations in liver enzymes were reversible and without serious clinical consequences (7,9). This indicates that while pirfenidone carries a risk of hepatic toxicity, it is not likely to result in overt hepatic dysfunction or failure, provided that abnormal results are discovered in a timely fashion and appropriate steps (i.e. reduction or discontinuation of the drug) are taken. Indeed, monitoring of liver enzymes is considered part of standard care for IPF patients treated with pirfenidone in clinical practice.

For nintedanib, diarrhea prominently stands out as the major adverse event (8,17,21,23). The fact that it led to medication discontinuation in a few cases in some studies underpins the impact it could have on drug adherence and, consequently, on treatment efficacy. Elevated liver enzyme levels, as for pirfenidone, surfaced in nintedanib-treated patients. Yet, similar to pirfenidone, these elevations, while warranting monitoring, have not directly translated to severe hepatic dysfunction provided appropriate reduction or discontinuation of nintedanib in response (17,21).

When weighing the adverse events of antifibrotic therapy against the potential benefits, it is imperative to consider the overarching therapeutic objectives. Both drugs have shown efficacy in slowing the decline in FVC, a relevant metric indicative of lung function

preservation (3,7–10). This slowed decline, when evaluated against mild to moderate adverse events, makes a compelling case for the use of these drugs, especially in a progressive disease such as IPF. However, it is important to recognize the individual variability in tolerating these adverse events. For some, photosensitivity or persistent diarrhea might be distressing enough to reconsider therapy, while others might deem them manageable. In conclusion, while the adverse events associated with pirfenidone and nintedanib are noteworthy, they are largely mild to moderate and reversible. Balancing the reduced FVC decline against these adverse events, the benefits might outweigh the risks. Still, it is essential for clinicians to adopt a patient-centric approach, ensuring that the patient is well-informed and comfortable with the potential adverse events.

## Concluding remarks

In this systematic review, the aim was to explore the effect of nintedanib and pirfenidone on mortality, acute exacerbations, and the profile of adverse events of these antifibrotic therapies.

The findings in this review present a complex landscape. Both nintedanib and pirfenidone have shown a tendency to reduce all-cause mortality in pooled and meta-analyses. However, their impact on IPF-specific and respiratory-related mortality is less clear. The studies included in this review did not demonstrate significant benefits for these endpoints. This observation indicates potential constraints in the statistical power of the included studies. In particular, occurrences of IPF-related mortality were by definition more infrequent than occurrences of mortality of any cause.

Furthermore, the studies included in this review demonstrated that nintedanib likely has a significant beneficial impact on acute exacerbations. For pirfenidone, on the other hand, the studies failed to demonstrate significant benefit in reducing acute exacerbations.

While the effects of antifibrotic therapies on these clinical outcomes are modest and somewhat variable, their adverse event profiles are primarily confined to gastrointestinal symptoms, skin disorders, and elevated liver enzymes. These side effects are generally of mild to moderate severity and are often reversible upon discontinuing treatment. Consequently, the side effects initially do not seem to outweigh the benefits of these therapies, especially considering that both nintedanib and pirfenidone have been shown to slow the decline in FVC. However, it is crucial to recognize that a decrease in FVC is not a direct clinical outcome experienced by patients, which emphasizes the importance of mortality and acute exacerbations as patient-centered clinical outcomes. In some cases, adverse events like photosensitivity or persistent diarrhea may be distressing enough to outweigh the benefits of a reduced decline in FVC and modest effects on mortality and acute exacerbations. At the same time, there exist no other therapies shown to reduce disease progression in IPF. Ideally, a comprehensive and balanced understanding of benefits and risks will help patients and their physicians make informed decisions about treatment with nintedanib and pirfenidone.

# Literature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