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Comparative Long-Term Effectiveness of Nintedanib and Pirfenidone in Idiopathic Pulmonary Fibrosis: A Systematic Literature Review

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ABSTRACT

Introduction: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease. Pirfenidone and nintedanib slow progression, but no head-to-head randomized trials have tested their long-term effectiveness, particularly in real-world and advanced disease.

Objective: To synthesize and appraise the long-term comparative effectiveness and safety of nintedanib versus pirfenidone in IPF.

Methods: We conducted a systematic review (PubMed, Embase, Cochrane CENTRAL; to March 2025) of studies ≥12 months in adults with IPF. Outcomes included forced vital capacity (FVC) decline, mortality, exacerbations, hospitalizations, adverse events, and quality of life. Risk of bias was assessed with Cochrane RoB 2.0, Newcastle–Ottawa Scale, and AMSTAR-2.

Results: Fourteen studies met criteria. Both agents reduced annual FVC decline by ~50% versus placebo. Long-term extensions showed sustained effects: pirfenidone ~141–150 mL/year and nintedanib ~125 mL/year. A post hoc analysis (CleanUP-IPF) favored nintedanib at 12 months for FVC (+106 mL; 95% CI, 34–178), a difference that diminished by 24 months. Mortality and exacerbation rates were broadly comparable. Safety profiles differed: pirfenidone more often produced gastrointestinal and cutaneous events; nintedanib was associated with diarrhea and transaminase elevations.

Conclusions: Evidence supports broadly comparable long-term efficacy of pirfenidone and nintedanib in IPF, with distinct tolerability profiles that may guide individualized selection. Real-world data corroborate benefits in advanced disease and comorbidity. The absence of direct randomized comparisons limits certainty; adequately powered head-to-head RCTs and biomarker-guided treatment strategies are needed.

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Abbreviations
FVC = Forced Vital Capacity
OR = Odds Ratio
HR = Hazard Ratio
plac = placebo.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease (ILD) of unknown etiology characterized by aberrant wound healing and excessive deposition of extracellular matrix, leading to irreversible scarring of the lung parenchyma. It typically affects individuals over the age of 60, with a higher incidence in men and former smokers. The global prevalence of IPF ranges from 14 to 63 cases per 100,000 persons depending on diagnostic criteria and geographic location, and its incidence appears to be rising due to aging populations and improved diagnostic awareness [1].

The clinical course of IPF is marked by a relentless decline in pulmonary function, most notably in forced vital capacity (FVC), which serves as the primary surrogate endpoint in clinical trials. Declines in FVC are strongly correlated with increased mortality. The median survival from diagnosis is approximately 3 to 5 years, which is worse than many cancers [2].

Historically, management options were limited to palliative measures such as oxygen therapy and lung transplantation for eligible patients. No pharmacological interventions demonstrated a clear survival benefit until the approval of two antifibrotic

agents: pirfenidone and nintedanib. Pirfenidone, an oral pyridone compound with antifibrotic, anti-inflammatory, and antioxidant properties, was shown in the CAPACITY and ASCEND phase III trials to significantly reduce FVC decline and improve progression-free survival compared to placebo [3]. Nintedanib, a tyrosine kinase inhibitor targeting pathways involved in fibrogenesis (VEGF, FGF, and PDGF receptors), was evaluated in the INPULSIS and TOMORROW trials, demonstrating a similar ability to reduce the annual rate of FVC loss and potential benefits in reducing acute exacerbations [4].

The approval of these therapies marked a pivotal shift in the treatment paradigm of IPF, offering patients disease-modifying options that decelerate pulmonary decline, delay symptom progression, and may extend survival.

Despite the individual efficacy of both nintedanib and pirfenidone being well-established, no randomized head-to-head clinical trials have been conducted to directly compare their long-term effects. This absence of direct comparison introduces uncertainty in selecting the optimal treatment for individual patients. Instead, evidence has been pieced together from network meta-analyses, post-hoc comparative analyses, and real-world studies, all of which inherently carry limitations such as selection bias, heterogeneity in patient populations, and differences in study design.

Both agents have been shown to reduce the annual FVC decline by approximately 110–120 mL compared to placebo in their respective pivotal trials, suggesting similar short-term efficacy. A 2015 Bayesian network meta-analysis including major IPF trials concluded that there were no statistically significant differences between nintedanib and pirfenidone in terms of FVC preservation or one-year mortality risk [5].

However, the long-term comparative effectiveness (beyond one year) remains uncertain, especially in terms of real-world durability, adverse event profiles, and quality-of-life outcomes. Additionally, clinical trials often exclude patients with advanced disease (e.g., FVC <50% predicted, DLCO <30%) or significant comorbidities (such as emphysema, pulmonary hypertension, or cardiovascular disease). These patients, however, make up a substantial proportion of those encountered in everyday practice.

Emerging observational data, such as from the INPULSIS-ON and RECAP open-label extensions, suggest that both drugs maintain their efficacy and tolerability beyond 2–4 years. Yet, discrepancies exist between trials and registries, and it is unclear whether treatment benefits remain comparable over extended follow-up, particularly in frail or polymorbid patients [6,7].

In this context, clinicians must often choose between pirfenidone and nintedanib based on factors other than efficacy, such as the patient's tolerance to gastrointestinal side effects, liver function status, pill burden, drug-drug interactions, and patient preference. Further comparative research, especially in underrepresented patient populations, remains a critical unmet need to optimize personalized treatment strategies.

Given the converging lines of evidence, we hypothesize that nintedanib and pirfenidone offer comparable long-term efficacy in slowing pulmonary function decline in patients with IPF, with differences, if any, likely to be minor and potentially influenced by patient-specific factors such as tolerability and comorbidity profiles. Furthermore, we postulate that both antifibrotic agents retain their clinical benefits over extended periods (>1 year), making them viable long-term treatment options in routine practice. This hypothesis, if supported, would reinforce current clinical guidelines that recommend either agent based on individualized considerations rather than presumed efficacy differences.

The objective of this systematic review is to synthesize and critically evaluate the available long-term data on the efficacy and tolerability of nintedanib and pirfenidone in IPF. By integrating evidence from clinical trials, long-term extension studies, and real-world cohorts, we aim to clarify whether meaningful differences exist between these two treatments in terms of pulmonary function preservation, exacerbation rates, survival, and safety outcomes. Our goal is to inform clinical decision-making by providing an evidence-based, comparative appraisal of these agents across diverse patient populations and timeframes.

Methods

Study Design

This study was designed as a systematic review of the literature to compare the long-term effectiveness of the antifibrotic agents nintedanib and pirfenidone in patients diagnosed with idiopathic pulmonary fibrosis (IPF).

Eligibility Criteria

Types of Studies

We included randomized controlled trials (RCTs), open-label extensions, and observational studies (prospective or retrospective cohorts) that evaluated the long-term use (≥12 months) of nintedanib or pirfenidone in IPF. Network meta-analyses and adjusted indirect comparisons were also considered if they provided comparative data on the two drugs.

Types of Participants

Studies involving adult patients (≥18 years) with a clinical and radiological diagnosis of IPF, confirmed using consensus guidelines (e.g., ATS/ERS/JRS/ALAT), were included. Patients with varying degrees of disease severity and comorbidities (e.g., emphysema, pulmonary hypertension) were eligible.

Types of Interventions

The interventions of interest were

- Pirfenidone, administered at approved dosages (e.g., 2403 mg/day)
- Nintedanib, administered at 300 mg/day (150 mg twice daily)

Types of Outcomes

Primary Outcomes

- Annual decline in Forced Vital Capacity (FVC) (in mL/year or % predicted)
- All-cause mortality over a follow-up of at least one year

Secondary Outcomes

- Incidence of acute exacerbations
- Time to disease progression or progression-free survival
- Rate of hospitalizations
- Adverse events leading to treatment discontinuation
- Health-related quality of life (e.g., SGRQ, UCSD SOBQ)

Search Methods for Identification of Studies

Electronic Searches

We systematically searched the following databases from inception to March 2025:

- PubMed/MEDLINE

- Embase
- Cochrane Central Register of Controlled Trials (CENTRAL)
- ClinicalTrials.gov
- Web of Science

The search strategy combined terms related to the disease and interventions, such as:
"Idiopathic pulmonary fibrosis" OR "IPF" AND ("nintedanib" OR "pirfenidone") AND ("long-term" OR "12 months" OR "1 year" OR "extended follow-up") AND ("randomized" OR "observational" OR "extension").

Searching Other Resources
We reviewed reference lists of included articles, conference abstracts, and regulatory agency reports (e.g., EMA, FDA) for additional studies. Grey literature and ongoing trials were identified via ClinicalTrials.gov and EU Clinical Trials Register.

Data Collection and Analysis
Selection of Studies
Two reviewers independently screened titles and abstracts. Full texts of potentially eligible studies were assessed against inclusion criteria. Discrepancies were resolved by discussion or by involving a third reviewer.

Data Extraction and Management
A Standardized Data Extraction form was Used to Collect Data on
- Study characteristics (author, year, design, sample size)
- Patient demographics and baseline lung function
- Details of antifibrotic treatment (dose, duration)
- Outcome measures (FVC decline, mortality, exacerbations)
- Adverse event profiles and discontinuation rates

Data were entered into a pre-piloted Excel spreadsheet and cross-checked for accuracy.

Risk of Bias Assessment
We Assessed the Methodological Quality Using:
- Cochrane Risk of Bias 2.0 tool for RCTs
- Newcastle-Ottawa Scale (NOS) for observational studies
- AMSTAR-2 for any included meta-analyses

Each study was evaluated independently by two reviewers.

Bias Control Strategy
Handling Missing Data
We extracted and reported available data as presented. If data were missing or unclear, we contacted the study authors. Sensitivity analyses were planned to assess the potential impact of missing outcome data.

Reporting Bias Assessment
Publication bias was assessed visually using funnel plots and, where possible, with Egger's regression test for meta-analytic outcomes.

Synthesis of Results
Results were presented in a narrative synthesis, structured by outcome type and antifibrotic agent.

Results
As shown in the PRISMA flow diagram (Figure 1), our database searches initially yielded 731 records. After removing 89 duplicates, 642 unique records remained and were screened by title and abstract, leading to the exclusion of 604 records. We then retrieved and assessed the full text of the 38 remaining reports; all were available for review. Following full-text evaluation, 24 reports were excluded—18 because their design did not meet our criteria and 6 because their populations were ineligible—resulting in 14 studies included in the final review.

Clinical Trial Findings on the Long-Term Efficacy of Pirfenidone and Nintedanib, Their Indirect Comparison, and Evidence in Special Populations (Patients with Advanced Disease and Relevant Comorbidities) (Table 1).

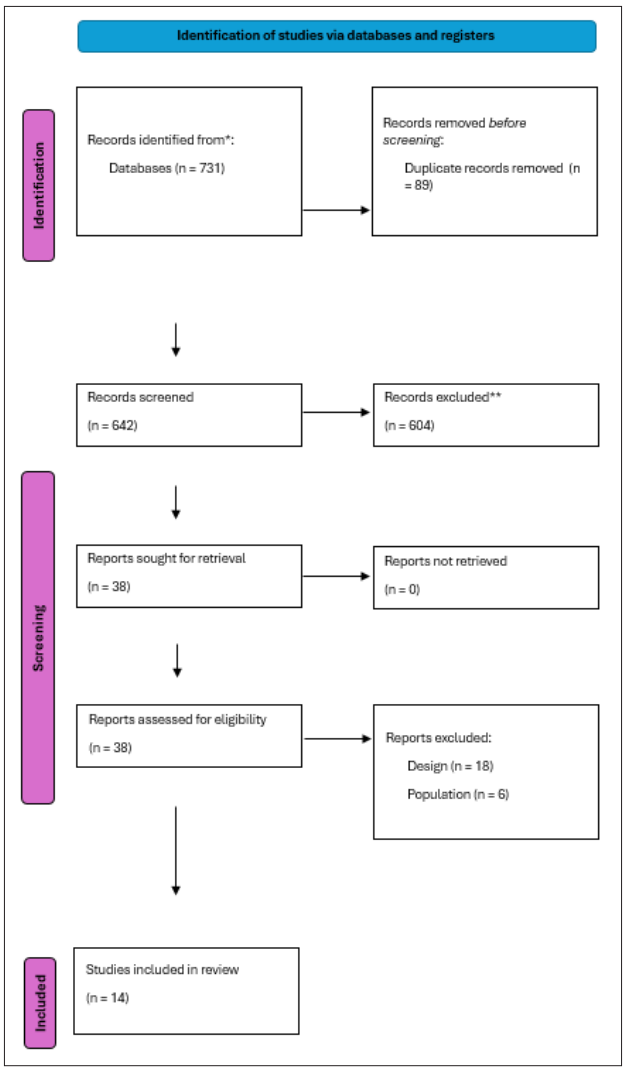

Figure 1: PRISMA Flow Diagram

Table 1: Comparison of Key Efficacy and Safety Outcomes of Pirfenidone vs. Nintedanib in IPF, based on Clinical Trials and Meta-Analyses

Outcome (52 weeks)	Pirfenidone	Nintedanib
Mean FVC decline vs. placebo	–120 mL (smaller drop vs. placebo). Placebo: approx. –260 mL (8)	–110 mL (smaller drop vs. placebo). Placebo: approx. –220 mL (8)
Patients with ≥10% FVC decline or death	Significant reduction (OR ~0.58 vs. placebo) (8)	Trend toward reduction (OR ~0.65 vs. placebo; p ≈ 0.08) (8)
Annual mortality (vs. placebo)	3–4% (pirfenidone) vs. 7–8% (placebo) – lower with pirfenidone (HR ~0.52) (8)	5–7% (nintedanib) vs. 8–10% (placebo); non-significant difference (HR ~0.70) (8)
Risk of acute exacerbation	↓ Incidence in some studies (e.g., fewer hospitalizations) (11)	↓ Significant in pooled analysis (HR ~0.5) (11)
Long-term FVC decline rate	~150 mL/year (in open-label extension) (15)	~125 mL/year (in open-label extension) (6)
Common adverse effects	Nausea, dyspepsia, anorexia; photosensitive skin rashes (10)	Diarrhea, nausea; elevated liver transaminases (6)

Note: Both drugs similarly reduce the annual decline in lung function and show favorable trends in exacerbation and mortality outcomes (without direct comparison between them in RCTs). Differences in adverse events may influence treatment choice in clinical practice.

Long-Term Efficacy of Antifibrotic Agents in IPF

Numerous randomized clinical trials have confirmed that both pirfenidone and nintedanib reduce the annual rate of decline in forced vital capacity (FVC) by approximately 50% compared to placebo [8,9]. FVC is the standard measure of IPF progression, as accelerated FVC decline is associated with increased mortality. The main efficacy results are summarized below [10]:

- **Pirfenidone vs. Placebo:** In the CAPACITY and ASCEND phase III studies, pirfenidone significantly reduced pulmonary function deterioration. Pooled data showed that at 1 year, the mean FVC decline was lower with pirfenidone than with placebo (difference of approximately 0.12 L) [8,9]. Additionally, a lower proportion of patients treated with pirfenidone experienced an FVC %predicted decline of ≥10% or death at 52 weeks. Pirfenidone prolonged the time to disease progression (progression-free survival) compared to placebo. In a combined analysis of ASCEND + CAPACITY, pirfenidone reduced the relative risk of 1-year mortality by approximately 48% (HR = 0.52; 95% CI: 0.31–0.87) [11]. A trend toward fewer acute exacerbations and hospitalizations was also observed with pirfenidone. Importantly, pirfenidone does not restore lost lung function but slows the decline in FVC and reduces 1-year mortality [12].
- **Nintedanib vs. Placebo:** The phase III INPULSIS-1 and -2 trials demonstrated that nintedanib significantly reduces the annual rate of FVC decline compared to placebo (e.g., in INPULSIS, annual FVC loss was ~–114 mL with nintedanib vs. –240 mL with placebo) [8,9]. The absolute FVC difference after 1 year between nintedanib and placebo is similar to that of pirfenidone (~0.11 L) [8,9]. Regarding clinical events, the effect on acute exacerbations was not statistically significant in individual trials (one of the INPULSIS trials showed fewer exacerbations with nintedanib, the other did not); however, in a pooled analysis (including phase II TOMORROW), nintedanib reduced the risk of first acute exacerbation by ~47% (HR = 0.53; 95% CI: 0.34–0.83) [13]. One-year mortality was lower with nintedanib than with placebo in the trials, but the sample sizes did not allow statistical significance (HR = 0.70; 95% CI: 0.32–1.55). Nonetheless, a post-hoc analysis showed reduced mortality with nintedanib treatment (HR = 0.57; p = 0.027) [8,9]. In summary, nintedanib slows functional progression of IPF similarly to pirfenidone and may reduce exacerbation events.

Long-Term Effectiveness (>1 year)

Since IPF is a progressive disease, it is crucial to assess whether the benefit persists beyond 52 weeks. Both drugs have open-label extension data and long-term follow-up studies:

- **Long-Term Pirfenidone:** In the open-label RECAP extension (patients who completed the pivotal trials), pirfenidone maintained a consistent safety profile over up to ~5 years of follow-up [14]. The annual rate of FVC decline in patients continuously treated with pirfenidone was ~140–150 mL/year on average, in both advanced and non-advanced disease [15]. This rate is substantially lower than the historically expected rate without treatment (e.g., >200–250 mL/year). Observationally, "real-world" patients treated with pirfenidone show a 3-year survival rate of ~73%, significantly higher than historical cohorts without access to antifibrotics (absolute survival benefit of ~30% at 3 years) [16]. This benefit was observed even among patients with comorbidities and more severe disease, who were typically excluded from trials.
- **Long-Term Nintedanib:** In the INPULSIS-ON open-label extension study, over 90% of INPULSIS patients continued with nintedanib for up to ~4 years. The median total exposure to nintedanib was 44.7 months (range ~1–5.7 years) [6]. Results showed that the annual rate of FVC decline remained consistent with prolonged treatment (approximately –125 mL/year in the extension), similar to what was observed in the first year, with no evidence of loss of efficacy. In terms of safety, no new signals emerged: the most frequent adverse effects continued to be diarrhea (GI event reported at ~60–70 per 100 patient-years) and manageable liver enzyme elevations. There was a low discontinuation rate due to adverse effects over long periods [9]. These data suggest that nintedanib's benefit persists over time, with a predictable safety profile.

Direct Comparison Between Nintedanib and Pirfenidone

No head-to-head clinical trials (direct comparative studies) of pirfenidone versus nintedanib in IPF have been conducted. However, indirect comparisons (network meta-analyses) and post-hoc cohort analyses allow for the inference of similarities and differences:

- **Network Meta-Analysis:** A Bayesian analysis that included 9 trials (up to 2015) indirectly compared pirfenidone and nintedanib. It concluded that both drugs have equivalent efficacy in slowing FVC loss and found no significant evidence of differences between them. For example, pirfenidone

and nintedanib both showed very similar magnitudes of FVC preservation at 1 year versus placebo (~0.11–0.12 L). Similarly, no clear difference in 1-year mortality was detectable between the two according to this model [8]. These findings support the clinical perception that antifibrotic efficacy is comparable.

- **Post-Hoc Analysis of the CleanUP-IPF Study:** Recently, a pragmatic study (CleanUP-IPF) allowed patients with IPF to receive either antifibrotic; from that cohort, which was randomized to another intervention, adjusted outcomes were compared between pirfenidone users (n=264) and nintedanib users (n=143). At 12 months, patients on nintedanib had slightly better FVC than those on pirfenidone (mean difference +106 mL; 95% CI: 34–178 mL), suggesting a slightly slower decline with nintedanib during that period. However, this difference diminished after 24 months of follow-up, indicating that pulmonary function curves converge over the longer term. Importantly, there were no significant differences in overall survival or respiratory hospitalizations between the two groups in this adjusted analysis. These findings (not derived from a direct randomized assignment) should be interpreted cautiously, but they align with the notion that neither drug has shown clear superiority in hard outcomes [17].
- **Other Comparative Outcomes:** Both drugs appear to contribute to improved long-term survival in IPF, although with nuances. Pirfenidone showed a significant reduction in 1-year mortality versus placebo in combined analyses, while nintedanib showed only a trend (possibly due to sample size). In longer-term follow-up and observational studies, both pirfenidone and nintedanib are associated with greater survival than the natural history of the disease. For example, in a national cohort in France, patients on nintedanib had slightly lower mortality than those on pirfenidone over ~1 year of follow-up, although with a higher risk of exacerbations, suggesting population differences more than drug effect [11]. Essentially, there is no conclusive evidence that one drug prolongs life more than the other; both appear to provide benefit.
- **Tolerability and Adherence Profile:** The toxicities differ slightly and may guide individual choice. Pirfenidone commonly causes gastrointestinal effects (nausea, dyspepsia, anorexia) and skin reactions (photosensitive rash), whereas nintedanib primarily causes diarrhea (often manageable with loperamide) and elevated liver enzymes [6,10]. In trials, discontinuation rates were comparable between the two treatments and reasonably low. A real-world study found no significant difference in the proportion of patients discontinuing pirfenidone vs. nintedanib after one year [18]. However, in clinical practice, some patient's intolerant to one antifibrotic may tolerate the other, meaning adverse event experience can individualize treatment choice. In a French analysis, nintedanib had a lower discontinuation risk than pirfenidone (HR 0.7), possibly due to tolerance differences, although pirfenidone showed lower mortality risk in that cohort [6,10]. In summary, comparative long-term efficacy is similar, so factors such as comorbidities, interactions, patient preferences, and side-effect tolerance guide therapeutic decision-making.

Impact on Specific Populations

The following is a review of the evidence regarding the effects of pirfenidone and nintedanib in patient subgroups, particularly those with more advanced disease or relevant comorbidities, since these populations are often underrepresented in clinical trials but are common in clinical practice.

Patients with Advanced vs. Mild Disease

Pivotal IPF trials generally included patients with moderately preserved lung function (e.g., FVC ≥ 50% and DLCO ≥ 30–35%), excluding very advanced IPF [15]. However, subsequent analyses have assessed whether antifibrotic therapies are equally beneficial in more severe IPF:

- **Pirfenidone in Advanced IPF:** A post-hoc analysis combining data from six studies (including ASCEND, CAPACITY, and others) compared advanced patients (typically defined as FVC <50% or DLCO <35%) to non-advanced patients in terms of response to pirfenidone. It was observed that pirfenidone significantly reduced FVC decline versus placebo in both advanced and non-advanced patients. The magnitude of effect was similar in both subgroups (e.g., the annual rate of FVC decline with pirfenidone was ~–141 mL in advanced patients vs. –153 mL in non-advanced, both clearly better than placebo). Likewise, 1-year mortality was numerically lower with pirfenidone than with placebo in both groups. These findings underscore that patients with severe IPF also benefit from pirfenidone, leading to the expansion of its approval in Europe to include "advanced" IPF [15]. In fact, observational studies report stabilization or slowing of lung function decline in patients with severely impaired IPF who receive pirfenidone, even improving symptoms such as dyspnea in GAP stage II/III [12].
- **Nintedanib in Advanced IPF:** Although nintedanib trials had similar inclusion criteria, subgroup analyses suggest equivalent results across different severities. For instance, in patients with mild IPF (FVC >90% predicted) at baseline, the rate of untreated FVC decline is comparable to that of more moderate IPF, and nintedanib confers the same relative benefit in both cases. In other words, nintedanib is effective even in very early IPF, where deterioration occurs insidiously. Conversely, in advanced IPF, studies such as INSTAGE included patients with DLCO <35% (indicative of severe disease with possible pulmonary hypertension); all received nintedanib (± sildenafil). The results confirmed that nintedanib is safe and can be administered in severe disease, with signs of similar functional benefit, although the main focus was on quality-of-life symptoms [19]. Overall, no data suggest that nintedanib's antifibrotic effect diminishes in advanced cases; it is presumed to continue slowing fibrosis even in later stages.

Patients with Comorbidities (Emphysema, Pulmonary Hypertension, etc.)

The typical IPF population is older and often presents with comorbidities (coexisting conditions) such as smoking-related emphysema, group 3 pulmonary hypertension, gastroesophageal reflux disease, cardiovascular disease, sleep apnea, diabetes, among others [20]. These conditions can affect IPF progression and raise treatment considerations:

IPF with Emphysema (CPFE Syndrome)

Between 10–30% of patients with IPF have associated pulmonary emphysema (particularly smokers), a condition known as combined pulmonary fibrosis and emphysema (CPFE) syndrome. Since emphysema can independently reduce FVC, it was important to assess whether antifibrotics were effective in this subgroup. A subgroup analysis of the INPULSIS trials examined patients with IPF who had mild-to-moderate radiological emphysema: no difference was found in the magnitude of nintedanib's effect on

FVC regardless of emphysema presence [13]. That is, the reduction in pulmonary decline with nintedanib was consistent even in the presence of emphysema. Although no specific RCT data exist for pirfenidone in CPFE, clinical evidence suggests pirfenidone is also beneficial in IPF with emphysema. Retrospective studies indicate that patients with CPFE treated with antifibrotics show slower progression than the natural history, and guidelines recommend not withholding antifibrotics in patients with concurrent emphysema. In conclusion, the presence of emphysema does not negate the indication for antifibrotics, although functional assessment must be carefully interpreted (FVC may not fully reflect severity due to increased air volume from emphysema).

IPF with Pulmonary Hypertension (PH)

Group 3 pulmonary hypertension is a common comorbidity in advanced IPF (due to capillary destruction and hypoxic vasoconstriction). Although severe PH is associated with a poor prognosis, antifibrotic therapy remains essential for treating the underlying fibrosis. The INSTAGE (nintedanib ± sildenafil) and SPIPF (pirfenidone ± sildenafil) trials assessed adding vasodilator therapy for PH [15]. Results showed that adding sildenafil did not improve FVC decline compared to antifibrotic alone, although in SPIPF it did improve quality of life and dyspnea in patients with very low DLCO. This suggests that antifibrotic treatment alone provides the main antifibrotic benefit even in the presence of PH, while PH-specific drugs may be considered as symptomatic adjuncts in selected cases (e.g., if there is disproportionate dyspnea due to PH). In summary, patients with IPF and pulmonary hypertension should receive antifibrotics; PH is not a contraindication, although closer monitoring is required (e.g., nintedanib may increase bleeding risk in patients with severe PH, but no significantly higher rates of major hemorrhagic events were observed in studies) [6].

Other Comorbidities (Cardiovascular, Metabolic, etc.)

Approximately 30–50% of patients with IPF have cardiovascular (e.g., coronary artery disease, heart failure) or metabolic comorbidities. In the CleanUP-IPF study analyses, for example, a notable proportion had a history of ischemic heart disease. Neither antifibrotic showed a loss of efficacy in patients with cardiac history; in fact, after adjusting for these variables, efficacy results remained consistent [17]. However, interaction and risk considerations are important: nintedanib, being a mild antiangiogenic agent, requires caution in patients on antiplatelets/anticoagulants (possible increased bleeding risk) and periodic monitoring of liver function [6]. Pirfenidone may cause idiosyncratic hepatotoxicity, so liver enzymes must also be monitored. Advanced age per se does not reduce the benefit: studies indicate similar efficacy regardless of age or sex, although in very elderly patients, comorbidities and frailty necessitate careful monitoring of adverse effects [10].

Risk of Bias Evaluation

Risk of bias was low across most domains for the two systematic reviews, whereas they judged at high risk for study eligibility criteria, data collection and appraisal, and synthesis and findings, with some concerns in identification and selection of studies (Table 2) [8,10,20]. In the clinical trials assessed by RoB-2, all four studies showed low risk arising from the randomization process and deviations from assignment to intervention, but concerns or high risk emerged for deviations related to adherence, missing outcome data, measurement of the outcome, and selection of reported results—culminating in an overall judgment of some concerns for the first three trials and high risk for Costabel U (2017) (Table 3) [6,9,14,19]. Finally, all seven observational and post-hoc analyses scored eight or nine stars on the Newcastle–Ottawa Scale—reflecting low risk of bias in selection, comparability, and outcome domains (Table 4).

Table 2: Risk of Bias Evaluation (Systematic Review Studies) (ROBIS)

Domain	Fleetwood K 2017	Man RK 2024	Caminati et al. 2019
Study Eligibility Criteria	Low	Low	High
Identification and Selection of Studies	Low	Low	Some concerns
Data Collection and Study Appraisal	Low	Low	High
Synthesis and Finding	Low	Low	High

Table 3: Risk of Bias Evaluation (Clinical Trial Studies) (RoB-2)

Domain	Crestani et al 2019	Song JW, 2020	Kolb M 2017	Costabel U, 2017
Bias arising from the randomization process	Low	Low	Low	Low
Bias due to deviations from intended interventions (effect of assignment to intervention)	Low	Low	Low	Low
Bias due to deviations from intended interventions (effect of adhering to intervention)	Some concerns	Some concerns	High	High
Bias due to missing outcome data	Some concerns	Some concerns	Some concerns	Some concerns
Bias in measurement of the outcome	Low	Low	Low	High
Bias in selection of the reported result	Some concerns	Some concerns	Some concerns	Low
Overall risk of bias	Some concerns	Some concerns	Some concerns	High

Table 4: Risk of Bias Evaluation (Observational Studies/Post-hoc Analysis). Newcastle-Ottawa Scale (NOS)

Domain (Stars)	Belhassen et al. (2021)	Nathan et al. (2019)	Richeldi et al. (2016)	Behr et al, 2023	Margaritopoulos et al., (2018)	Kim et al., (2024)	Cerri et al., (2019)
Selection	4	4	4	4	3	3	4
Comparability	2	2	2	2	2	2	2
Outcome	3	3	3	3	3	3	3
Overall	9 (Low risk)	9 (Low risk)	9 (Low risk)	9 (Low risk)	8 (Low risk)	8 (Low risk)	9 (Low risk)

Discussion

This systematic review confirms that both nintedanib and pirfenidone significantly reduce the rate of decline in forced vital capacity (FVC) over both short- and long-term follow-up in patients with IPF. Despite the absence of head-to-head randomized trials, indirect comparisons and real-world data indicate that their efficacy in preserving lung function, reducing exacerbation rates, and potentially extending survival is clinically and statistically comparable over extended periods. Differences in adverse event profiles, however, may influence treatment selection based on individual patient characteristics.

The efficacy of pirfenidone and nintedanib in slowing the progression of idiopathic pulmonary fibrosis (IPF) has been demonstrated in several pivotal clinical trials. In the ASCEND trial, pirfenidone significantly reduced the proportion of patients experiencing a ≥10% decline in forced vital capacity (FVC) or death at 52 weeks compared to placebo (16.5% vs. 31.8%; $p<0.001$), indicating a 47.9% relative reduction in disease progression [21]. Similarly, the INPULSIS trials showed that nintedanib reduced the annual rate of FVC decline by approximately 50% compared to placebo, with mean differences of 125.3 mL/year in INPULSIS-1 and 93.7 mL/year in INPULSIS-2 [22].

Long-term extension studies have confirmed the sustained efficacy of both drugs. The RECAP study demonstrated that pirfenidone maintained its effect on slowing FVC decline over extended periods, with mean annual declines of 141.5 mL in patients with advanced IPF and 153.5 mL in those with non-advanced disease [15]. Similarly, the INPULSIS-ON study reported that nintedanib continued to slow FVC decline over long-term treatment, with an annual rate of decline of approximately 125 mL/year [23].

A post hoc analysis of the CleanUP-IPF trial suggested a marginal advantage in FVC preservation with nintedanib over pirfenidone at 12 months (mean difference: 106 mL; 95% CI: 34–178 mL). However, this difference was attenuated by 24 months, indicating that the long-term efficacy of both drugs converges over time [24].

While both antifibrotic agents are effective in slowing disease progression, some differences have been observed in specific outcomes. A pooled analysis of pirfenidone trials reported a significant reduction in all-cause mortality at 52 weeks compared to placebo (hazard ratio [HR]: 0.52; 95% CI: 0.31–0.87; $p=0.0107$) [25]. In contrast, a pooled analysis of nintedanib trials showed a significant reduction in the risk of first acute exacerbation (HR: 0.53; 95% CI: 0.34–0.83; $p=0.0047$) [13].

Real-world studies have highlighted differences in tolerability profiles. For instance, a study reported higher discontinuation rates due to adverse events with nintedanib compared to pirfenidone (48.98% vs. 27.80%; $p<0.001$), with diarrhea being the most common side effect for both drugs [26]. However, other studies have found similar discontinuation rates between the two treatments, suggesting that tolerability may vary across populations and clinical settings [27].

In terms of patient subgroups, both drugs have shown efficacy in patients with varying degrees of disease severity. The RECAP study indicated that pirfenidone's effect on FVC decline was consistent across patients with advanced and non-advanced IPF [15]. Similarly, nintedanib has been effective in patients with severe lung function impairment, demonstrating its utility across a broad spectrum of IPF patients [28].

Overall, while both pirfenidone and nintedanib are effective in managing IPF, differences in specific outcomes and tolerability profiles may influence treatment decisions. These nuances underscore the importance of individualized patient care and the need for further head-to-head comparative studies.

A key strength of this review is its comprehensive integration of evidence from randomized trials, extension studies, and real-world data, offering a robust comparative framework. We also included special populations (e.g., patients with comorbidities or advanced disease), often excluded from RCTs but common in clinical practice.

However, limitations must be acknowledged. No direct head-to-head RCT exists, so conclusions are reliant on indirect comparisons prone to confounding. Furthermore, heterogeneity in outcome reporting, population characteristics, and study designs complicates meta-analytic synthesis. Lastly, publication bias and data missingness in observational studies could influence the generalizability of our findings, despite low assessed risk of bias in most domains.

Given the comparable efficacy, treatment selection should be individualized, considering patient-specific factors such as tolerance, comorbidities, pill burden, and lifestyle preferences. Both antifibrotics represent viable, durable options for long-term IPF management. From a policy perspective, health systems should ensure equitable access to both agents to support personalized care.

Future research should prioritize head-to-head randomized trials or large-scale pragmatic studies in real-world settings. Specific attention should be given to frail, elderly, and polymorbid populations, who remain underrepresented yet highly prevalent. Biomarker-driven approaches may also enhance therapy personalization in the future.

Conclusions

This systematic review supports the conclusion that nintedanib and pirfenidone offer equivalent long-term benefits in terms of preserving pulmonary function, reducing disease progression, and potentially improving survival in IPF. While minor differences in tolerability and short-term clinical endpoints exist, these should inform rather than dictate treatment selection. Optimizing IPF

outcomes hinges not on identifying a "superior" agent, but on tailoring antifibrotic therapy to the clinical profile and preferences of individual patients.

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