Nintedanib, Pirfenidone and Pirfenidone Versus Nintedanib: A Systematic Review And Meta-Analysis

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Research Article

Keywords: IPF, mortality, Nintedanib, Pirfenidone

Posted Date: June 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-589439/v1

Abstract

Background: Patients with idiopathic pulmonary fibrosis have a poor overall prognosis. Only nintedanib and pirfenidone have been shown to reduce mortality.

Objective: This systematic review and meta-analysis aims to assess the efficacy of nintedanib, pirfenidone, and pirfenidone vs nintedanib on patient important outcomes.

Methods: Randomized trials were retrieved from MEDLINE, Cochrane, and EMBASE. The primary outcome was mortality. The secondary outcomes included change in FVC, acute exacerbations and hospitalizations and adverse drug effects leading to discontinuation. We used an inverse variance random effects meta-analysis method to calculate pooled relative risk (RR), standardized mean difference (SMD) and mean difference (MD).

Results: A total of 13 studies were included. Both nintedanib [RR 0.63 (0.47,0.85); moderate certainty] and pirfenidone [RR 0.68 (0.47,0.99); moderate certainty] probably reduce all-cause mortality when compared to placebo, but only nintedanib [SMD 0.47 (0.34, 0.60); high certainty] reduces change in FVC. Nintedanib [RR 0.69 (0.48,0.99); moderate certainty],but not pirfenidone probably reduces acute exacerbations or hospitalizations compared to placebo. Compared with placebo, neither nintedanib nor pirfenidone increased risk of drug discontinuation due to adverse effect but there is probably risk of patient drug discontinuation with pirfenidone compared to nintedanib [RR 4.34 (1.72 to 10.98); moderate certainty].

Conclusion: Both nintedanib and pirfenidone probably reduce all-cause mortality. Nintedanib is probably more tolerable to pirfenidone in regard to compliance and may be more effective than pirfenidone in reducing mortality rate and in slowing disease progression. Larger head to head randomized trials are needed.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a form of chronic progressive lung disease of unknown origin.[1,2] The cause is unknown, but likely results from a complex interplay between genetic and environmental factors. The prognosis for IPF patients is unfavourable, with median survival time from diagnosis ranging from 2–4 years.[1]

Pharmacologic treatment aims to slow disease progression.[3] Current guidelines on IPF treatment recommend the use of nintedanib and pirfenidone.[4] Both nintedanib and pirfenidone have been shown to reduce the rate of FVC decline and mortality in IPF patients. Several other studies have investigated these first-line treatments.[5] It is unclear whether there is relative superiority of one or the other in clinical practice.

This systematic review and meta-analysis looked at the efficacy of nintedanib, pirfenidone, and pirfenidone vs nintedanib. Patient important outcomes include all-cause mortality, change in forced vital capacity (FVC), acute exacerbations and hospitalizations, as well as adverse effects leading to drug discontinuation.

Methods

This review is registered on Open Science Framework (OSF). We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) to structure our manuscript.

Search strategy

We conducted a systematic literature review of randomized controlled studies conducted up to April 2021. The databases selected were relevant to the review topic and types of eligible studies. Eligible studies including randomized controlled trials that included treatment with nintedanib or pirfenidone versus placebo or pirfenidone versus nintedanib (vice versa). We developed the electronic search in the bibliographic database MEDLINE in consultation with a professional librarian. We translated the search into EMBASE, Cochrane Library Central/SR, and Clinicaltrials.gov. Supplementary file 1 and 2 have the search strategy.

Eligibility criteria

We included all bibliographic records screened if the population included in the study were adults > = 18 years of age diagnosed with IPF, and the intervention had to include either nintedanib versus placebo, pirfenidone versus placebo or nintedanib versus pirfenidone (vice versa).

The studies included phase 2 or 3 randomized trials (RT). This was chosen to include the highest quality evidence for a research question of this nature.

Data management & selection process

We used COVIDENCE, a systematic review web platform, to screen abstracts. Duplicates were removed prior to uploading using a reference manager. We formed two independent teams to use COVIDENCE to screen titles and abstracts independently and in duplicate for inclusion based on the PICOS design. Title abstracts were screened by 3 independent teams. After screening, full texts were obtained and assessed for eligibility after being uploaded to COVIDENCE by the same three teams. Discrepancies in screening at both stages were resolved through consensus mediation.

Data collection process & data outcomes

We extracted data using a modified version of Cochrane's template data collection form for intervention reviews of RCTs.

Outcomes and prioritization

The primary outcomes included all cause mortality, standardized mean change in FVC, hospitalizations and exacerbations, as well as adverse events leading to discontinuation.

Risk of bias in individual studies

For each included trial, the same three teams used a revision of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2.0) to give a rating to trials.[6] We rated the evidence using the following scale: at i) low risk of bias, ii) some concerns (probably low risk of bias) iii) some concerns (probably high risk of bias) or iv) high risk of bias, across the following domains: bias arising from the randomisation process; bias owing to departures from the intended intervention; bias from missing outcome data; bias in measurement of the outcome; bias in selection of the reported results, and including deviations from the registered protocol. Reviewers resolved discrepancies by discussion and, when not possible, with adjudication. See supplementary file 3 for details on our RoB tool.

Data synthesis

We performed an inverse variance meta-analysis using a random effect model, reporting 95% CI. We reported relative risk for our dichotomous outcomes and either mean difference (MD) or standardized mean differences (SMD) for our continuous outcomes. We chose standardized mean differences because FVC was calculated either as change in mL or percent change predicted. We investigated the heterogeneity by the I^2 statistic according to which values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity levels, respectively. We did not assess publication bias because the number of studies included was less than 10. For studies in which participants were rerandomized, we included in the primary analysis but included a sensitivity analysis in the supplementary material. We used RevMan for all analysis.[7]

Confidence in evidence

We assessed the certainty of the evidence with the grading of recommendations assessment, development and evaluation (GRADE), using a minimally contextualized framework. For mortality, 2% reduction was selected as minimally important. We used a standardized mean change of 0.25 as minimally important for our continuous outcomes for mixed mL and percent predicted FVC measurements. For only change in mL, we used a cut off of a 100 mL as minimally important. For acute exacerbations, we used 5% as minimally important and 20% for adverse effects leading to discontinuation. The GRADE approach involves separate grading of quality of evidence for each patient-important outcome followed by determining an overall quality of evidence across outcomes. Two reviewers rated each domain for each comparison separately and resolved discrepancies by consensus. We rated the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias, and imprecision.

Results

Study selection

Our search strategy included 2628 records initially and we excluded 1095 from the total for duplication. Therefore, 1533 remained for screening. A total of 50 studies were selected for full text review and 13 randomized controlled trials were included for the systematic review and meta-analysis. See Fig. 1 for the complete PRISMA diagram.

Study characteristics

Thirteen studies reported on outcomes of interest, including randomized 4415 IPF patients. The age and sex of the particiants were similar across all studies, usually older males over the age of sixty. Pulmonary function results were similar across studies. Table 1 has more details on the study characteristics.[8–18]

Table 1. Basic characteristics of randomized trials across outcomes.

Year	Study	Country	Trial registration number
2006	Azuma	Japan	NR
2019	Flaherty	USA, Argentina, Belgium, Canada, Chile, China, France, Germany, Italy, Japan, Republic of Korea, Poland, Russain Federation, Spain, UK	NCT029991
2019	Khalil	Canada	NCT025385
2014	King	Australia, Brazil, Croatia, Israel, Mexico, New Zealand, Peru, Singapore, United States	NCT013662
2020	Lancaster	USA, Canada, Turkey	NR
2019	Maher	Australia,Belgium,Czech Republic, Finland, France, Germany, Hungary, Japan,Poland, Korea,Spain, UK, USA	NCT027884
2011	CAPACITY 2	USA,Italy,Germany,France,UK	NCT002877
2011	CAPACITY 1	USA,Italy,Germany,France,UK	NCT002877
2014	IMPULSIS 2	USA,Canada,chile,china,finland,france,germany,greece,india,japan,korea,mexico,portugal,netherlands,russia,spain,turkey	NCT013354
2014	IMPULSIS 1	USA,Australia,Belgium,China, Czech Republic, France,Germany, India,Ireland,Israel, Italy, Japan,UK,	NCT013354
2011	Richeldi	Argentina, Australia , Belgium , Brazil , Bulgaria, Canada , Chile, China, Czech Republic, France , Germany , Greece, hungry, Ireland, Italy, Korea, Mexico, Netherlands, Portugal, Russia, South Africa , Spain, Taiwan, Turkey, UK	NCT005146
2009	Taniguchi	Japan	NR
2018	Vancheri	USA, Canada	NCT025796

Risk of bias

Most studies were not rated at high risk of bias. One study was at risk of bias due to the randomization process, two due to deviations of the intended interventions, one due to bias in the measurement of the outcome, and one for bias in selection of reported results. Figure 2 has more detail on the risk of bias.

All cause mortality

Six trials reported on mortality for nintedanib. Pooled results of 2633 patients shows that nintedanib reduces all-cause mortality in IPF patients when compared to placebo, [RR 0.63 (0.47,0.85)], $I^2 = 0$; moderate certainty], using a 2% reduction as minimally important. Forest plot 1 and Table 2 has more details.[8–18]

Table 2
Summary of findings Nintedanib compared to Placebo for Idiopathic pulmonary fibrosis patients

Patient or population: Idiopathic pulmonary fibrosis patients

Intervention: Nintedanib

Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect	№ of participants	Certainty of the evidence
	Risk with Placebo	**Risk with Nintedanib**	(95% CI)	(studies)	(GRADE)
Mortality	78 per 1,000	**49 per 1,000** (37 to 66)	**RR 0.63** (0.47 to 0.85)	2633 (6 RCTs)	⨁⨁⨁◯ MODERATE [a]
FVC	-	SMD **0.34 SD higher** (0.34 higher to 0.51 higher)	-	2491 (6 RCTs)	⨁⨁⨁⨁ HIGH
Acute exacerbations and hospitalizations	110 per 1,000	**76 per 1,000** (53 to 109)	**RR 0.69** (0.48 to 0.99)	2611 (6 RCTs)	⨁⨁⨁⨁ HIGH
Adverse effects leading to drug discontinuation	115 per 1,000	**142 per 1,000** (89 to 225)	**RR 1.23** (0.77 to 1.95)	2409 (5 RCTs)	⨁⨁⨁⨁ HIGH

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR**: Risk ratio; **SMD**: Standardised mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The upper bound of the confidence intervals is less than a 2% reduction in mortality.

Five studies reported on mortality for pirfenidone. Pooled results of 836 patients show that pirfenidone probably reduces all-cause mortality when compared to placebo [RR 0.68 (0.47,0.99)], $I^2 = 0$; moderate certainty], using a 2% reduction as minimally important. Forest plot 2 and Table 3 has more details.

Table 3
Summary of findings for Pirfenidone compared to Placebo for IPF patients

Patient or population: IPF patients

Intervention: Pirfenidone

Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect	№ of participants	Certainty of the evidence	Comments
	Risk with Placebo	**Risk with Pirfenidone**	(95% CI)	(studies)	(GRADE)	
Mortality	80 per 1,000	**55 per 1,000** (38 to 79)	**RR 0.68** (0.47 to 0.99)	1746 (5 RCTs)	⨁⨁⨁◯ MODERATE [a]	
FVC	-	SMD **0.21 SD higher** (0.07 higher to 0.36 higher)	-	1480 (4 RCTs)	⨁⨁⨁◯ MODERATE [b]	
Acute exacerbations and hospitalizations	20 per 1,000	**27 per 1,000** (11 to 63)	**RR 1.36** (0.58 to 3.20)	953 (4 RCTs)	⨁⨁⨁⨁ HIGH	
Adverse effects leading to drug discontinuation	66 per 1,000	**84 per 1,000** (54 to 130)	**RR 1.28** (0.83 to 1.98)	2046 (4 RCTs)	⨁⨁⨁⨁ HIGH	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR**: Risk ratio; **SMD**: Standardised mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The upper bound of the CI is less than a 2% reduction in mortality.

b. The upper bound is greater than the pre-specified value of clinical significance but the lower bound is much less.

Two studies reported on mortality for pirfenidone versus nintedanib. Pooled results from 140 patients show that there may be no mortality benefit for pirfenidone versus nintedanib, [RR 0.98 (0.14,6.70), $I^2 = 0$; low certainty, using a 2% reduction in mortality as minimally important. Forest plot 3 and Table 4 has more details.

Table 4
Summary of findings Pirfenidone compared to Nintedanib for IPF patients

Patient or population: IPF patients **Intervention: Pirfenidone** **Comparison: Nintedanib**					
Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect	№ of participants	Certainty of the evidence
	Risk with Nintedanib	**Risk with Pirfenidone**	(95% CI)	(studies)	(GRADE)
Mortality	29 per 1,000	**28 per 1,000** (4 to 194)	**RR 0.98** (0.14 to 6.70)	140 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b]
FVC	The mean FVC was **0** mL	MD **34.37 mL lower** (163.02 lower to 94.29 higher)	-	123 (2 RCTs)	⨁⨁◯◯ LOW [a,b]
Acute exacerbation and hospitalization	15 per 1,000	**23 per 1,000** (3 to 180)	**RR 1.56** (0.20 to 12.09)	136 (2 RCTs)	⨁⨁◯◯ LOW [a,b]
Adverse effects leading to drug discontinuation	104 per 1,000	**453 per 1,000** (180 to 1,000)	**RR 4.34** (1.72 to 10.98)	136 (2 RCTs)	⨁⨁⨁◯ MODERATE [a,c]
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: Confidence interval; **RR**: Risk ratio; **MD**: Mean difference					
GRADE Working Group grades of evidence **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					
Explanations					
a. Both trials were rated at high risk of bias.					
b. The lower bound includes significant benefit and the upper bound contains significant harm.					
c. The lower bound would be less than 20% discontinuation rate.					

Pulmonary function testing

Six studies reported on FVC in the nintedanib group. Pooled results from 2611 patients found that nintedanib was associated with a significantly smaller change in FVC when compared to placebo [SMD 0.42 (0.34, 0.51), I^2 = 0%; high certainty], using a SMD of 0.25 as minimally important. Forest plot 4 and Table 2 has more details.[8–18]

Four studies reported on change in FVC for pirfenidone. Pooled results from 1517 patients show that pirfenidone probably did not reduce the change in FVC when compared to placebo [SMD 0.21 (0.07,0.36), I^2 = 43%; moderate certainty] using SMD 0.25 as minimally important. Forest plot 5 and Table 3 has more details.

Two studies reported on change in FVC for pirfenidone versus nintedanib. Pooled results from 123 patients show that pirfenidone may not be associated with a greater change in FVC when compared to nintedanib [MD -34.37mL (-163, 94,29), I^2 = 79%; low certainty], using MD 100 mL as minimally important. Forest plot 6 and Table 4 has more details.

Pulmonary function testing

Six studies reported on acute exacerbations and hospitalizations for nintedanib. Pooled results from 2611 patients show that nintedanib does not reduce acute exacerbations in IPF patients and all-cause hospitalizations when compared to placebo, [RR 0.69 (0.48,0.99), I^2 = 3; high certainty]], using a 5% reduction as minimally important. Forest plot 7 and Table 2 has more details.

Four trials reported on acute exacerbations and hospitalizations. Pooled results from 950 patients show that pirfenidone did not reduce acute exacerbations or hospitalizations when compared to placebo [RR 1.36 (0.56,3.20), I^2 = 0; high certainty], using 5% reduction as minimally important. Forest plot 8 and Table 3 has more details.

Two trials reported on acute exacerbations and all-cause hospitalizations outcome. Pooled results from 69 patients found there may be no benefit for pirfenidone versus nintedanib, [RR 1.56 (0.20 ,12.09), I^2 = 0; low certainty]. Forest plot 9 and Table 4 has more details.

Adverse events leading to drug discontinuation

Five studies reported on adverse effects leading to drug discontinuation for nintedanib. Pooled results from 2409 patients found no risk of discontinuation of nintedanib compared to placebo, [RR 1.23 (0.77, 1.95), I^2 = 76%; high certainty], using a minimally important difference of 20%. Forest plot 10 and summary of findings Table 2 has more details.

Four studies reported on adverse effects leading to drug discontinuation for pirfenidone. Pooled results from 2046 patients show that there is no risk of drug discontinuation with pirfenidone compared to placebo, [RR 1.28 (0.83, 1.98), I = 39%; high certainty], using a minimally important difference of 20%. Forest plot 11 and Table 3 has more details.

Two studies reported on adverse effects leading to drug discontinuation for pirfenidone versus nintedanib. Pooled results from 136 patients show pirfenidone probably increases the risk of drug discontinuation due to adverse effects when compared to nintedanib, [RR 4.34 (1.72 to 10.98), I^2 = 0; moderate certainty] using a minimally important difference of 20%. Forest plot 12 and Table 4 has more details.

Discussion

Main findings

Our review presents the most up-to-date and highest certainty evidence on the evidence of nintedanib, pirfenidone, and pirfenidone versus nintedanib therapy for IPF patients. We found that both nintedanib and pirfenidone reduce mortality, but nintedanib improved lung function more than pirfenidone. Neither nintedanib or pirfenidone were effective at reducing acute exacerbations or hospitalizations, but nintedanib approached minimally important differences compared to pirfenidone. Compared with placebo, neither patients taking nintedanib or pirfenidone were at risk of drug discontinuation due to adverse effects, but when compared to one another, there was a significant risk of patients discontinuation of pirfenidone compared to nintedanib.

Relation to previous findings

Our findings of direct comparison showed nintedanib and pirfenidone were both more efficacious versus placebo in reducing mortality, and disease progression. This aligns with several SR's and MA's which have similarly reported the efficacy of nintedanib and pirfenidone in reducing mortality and disease progression in IPF patients.[19–22] Although in our analysis, FVC did not meet minimal important difference for change in FVC, it was approaching significance.

Both medications are currently given a conditional recommendation to use in IPF patients. There has not been a definitive randomized controlled trial that shows the relative efficacy of one or the other. In terms of safety and adherence, an open label study comparing the safety and tolerability of nintedanib and pirfenidone showed that nintedanib was associated with more treatment associated adverse effects leading to discontinuation. This is contrary to our findings. However, this study only included patients who already tolerated pirfenidone, which may have biased the results in favour of pirfenidone.[23]

Our findings suggest that nintedanib is more efficacious on a number of fronts. In terms of mortality, there is a greater absolute reduction with nintedanib, as well as improvement of lung function. Drug safety and tolerability are important considerations in patient treatment, and our findings for adverse effects leading to discontinuation, combined with mortality, improvement of lung function and acute exacerbations and hospitalizations, strongly suggest that nintedanib is more efficacious and tolerable for patients with IPF.

Larger head to head trials should be considered to determine the true point estimate of effects in patient important outcomes.

Strengths and limitations

The strengths of this review include our comprehensive search strategy, data screening and extraction in duplicate, rigorous assessment of risk of bias of trials, and use of the GRADE approach in reporting the certainty in the evidence. Additionally, our review includes studies containing direct, head-to-head trials between nintedanib and pirfenidone, rather than use of purely indirect comparisons seen in past reviews

This study has several limitations that should be recognized. There were some differences between studies included in our review, with not all studies measuring all the outcomes, and we were not able to evaluate other important outcomes in our meta-analysis, such as 6-minute walk test, diffusion capacity for carbon monoxide, or quality of life indices. Additionally, there was some variation across studies in treatment duration and follow-up time, preventing inference on long-term outcomes.

Conclusion

This meta-analysis provides the most comprehensive summary to date of the evidence on nintedanib, pirfenidone, and pirfenidone versus nintedanib treatment for IPF patients. We found that nintedanib was probably more efficacious in most patient important outcomes analyzed and likely more tolerable. Larger randomized trials are needed to confirm this.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Data requests can be made to the corresponding author

Competing interests: None

Funding: None

Authors' contributions: TP is the main author. He designed the study, the collection methods and supervised all aspects of the study. He performed all the analytics and wrote the first draft of the manuscript. JM developed the initial search strategy, helped collect data and supervised data collection. MK, SC, RH, MZ, WH, and JS collected the data, performed the risk of bias assessment and helped write the manuscript. JT helped manage references, write and copy-edit the paper and create tables. DZ and AJ supervised the project and provided statistical consultation. The authors have all read and approved the current manuscript.

Acknowledgements: None

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Supplemental Data

Supplementary files 1, 2 & 3 are not available with this version.

Figures

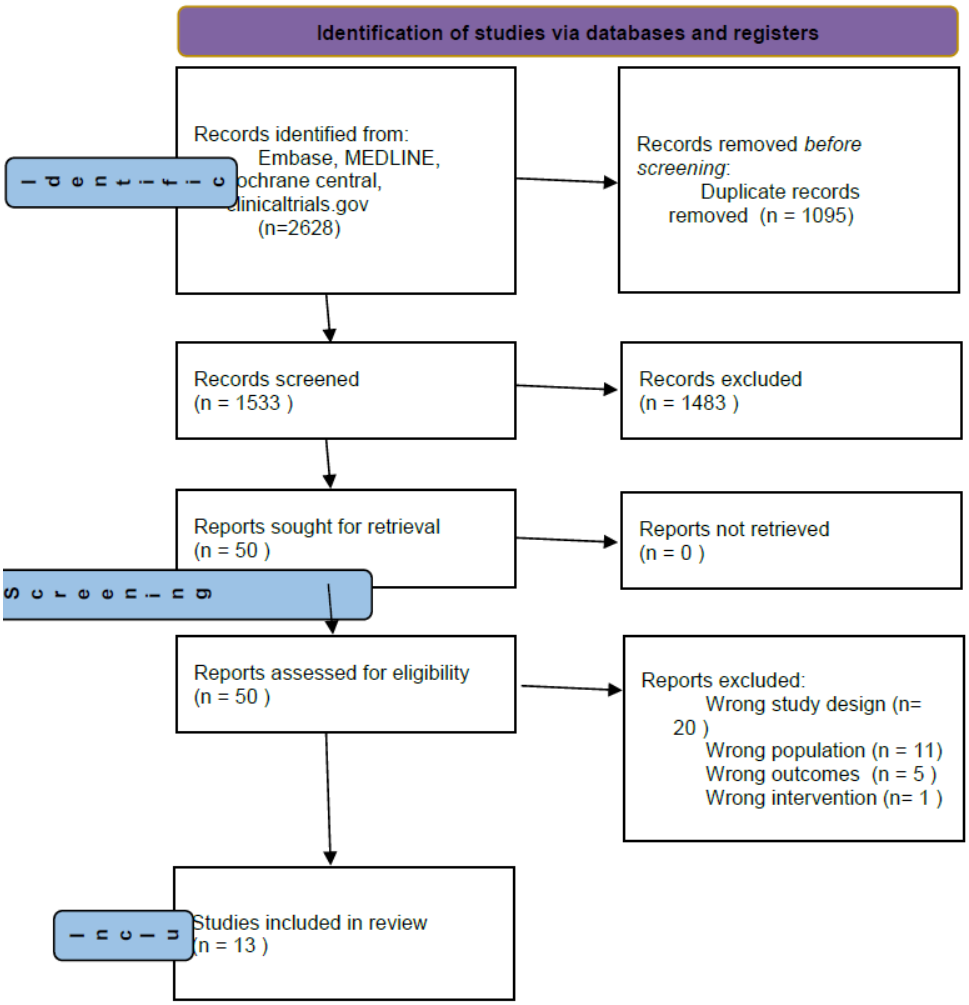

Figure 1

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

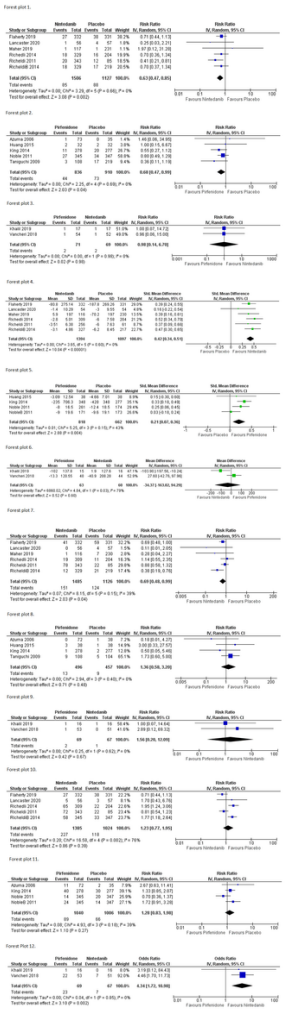

Figure 2

Forest plot 1. Forest plot for nintedanib versus placebo for all-cause mortality Forest plot 2. Forest plot for pirfenidone versus placebo for all-cause mortality Forest plot 3. Forest plot for pirfenidone versus nintedanib for all-cause mortality Forest plot 4. Forest plot for nintendanib versus placebo for pulmonary function testing Forest plot 5. Forest plot for pirfenidone versus placebo for pulmonary function testing Forest plot 6. Forest plot for pirfenidone versus nintedanib for pulmonary function testing Forest plot 7. Forest plot for nintedanib versus placebo for acute exacerbation and all-cause hospitalization Forest plot 8. Forest plot for pirfenidone versus placebo for acute exacerbation and all-cause hospitalization Forest plot 9. Forest plot for pirfenidone versus nintedanib for acute exacerbations and all-cause hospitalizations Forest plot 10. Forest plot for nintedanib versus placebo for adverse events leading to drug continuation Forest plot 11. Forest plot for pirfenidone versus placebo for adverse effects leading to drug discontinuation Forest Plot 12. Forest plot for pirfenidone versus nintedanib for adverse effects leading to drug discontinuation

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020checklist.docx