



Drug Treatment of Idiopathic Pulmonary Fibrosis

Systematic Review and Network Meta-Analysis

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BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is a form of chronic progressive fibrosing interstitial lung disease of unknown origin. Recently, nintedanib and pirfenidone demonstrated efficacy in slowing disease progression and were approved by the US Food and Drug Administration. Although numerous treatments have been evaluated in IPF, none have shown significant decreases in mortality. The objective of this study was to identify all pharmacologic treatments evaluated for IPF and analyze their efficacy via Bayesian network meta-analysis and pairwise indirect treatment comparisons. This review did not evaluate the effect of steroid therapy.

METHODS: We searched MEDLINE, Embase, and the Cochrane Library for studies published on or before August 2014. Studies were required to contain a randomized evaluation of nonsteroidal drug therapy for treatment of IPF and be published in English. Key outcomes of interest for this analysis were pulmonary function as measured by FVC as well as all-cause and respiratory-specific death. All outcomes were analyzed via a Bayesian framework.

RESULTS: Our review identified 30 eligible studies that evaluated 16 unique treatments. Under both the fixed-effect and random-effect models for respiratory-specific mortality, no treatments performed better than placebo. For all-cause mortality, pirfenidone and nintedanib had effects approaching significance with credible intervals slightly crossing the null under a fixed-effect model. Notably, for respiratory-specific mortality, all-cause mortality, and decline in percent predicted FVC, nintedanib and pirfenidone were virtually indistinguishable and no clear advantage was detected.

CONCLUSIONS: Although two treatments have been approved for IPF on the basis of reduced decline in pulmonary function, neither one has a clear advantage on mortality outcomes.

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ABBREVIATIONS: IPF = idiopathic pulmonary fibrosis; %FVC = percentage of predicted FVC; SUCRA = surface under the cumulative ranking

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Idiopathic pulmonary fibrosis (IPF) is a form of chronic progressive fibrosing interstitial pneumonia of unknown origin.¹ Its prevalence in the United States is believed to be between 14 and 42.7 per 100,000 individuals, depending on how it is defined clinically.^{2,3} Among the Medicare-eligible population the prevalence was estimated to be as high as 494.5 per 100,000 individuals in 2011.⁴ Risk factors for disease include cigarette smoking and gastroesophageal disease.¹ The progression of IPF is generally characterized by a decline in pulmonary function, measured as FVC. Patients with IPF are generally staged according to their percentage of predicted FVC (%FVC) (Table 1). Although the sex, age, and physiology staging method⁵ has been proposed, it is not currently the standard of care.

Many treatments have been evaluated for use in patients with IPF but guideline groups have found insufficient evidence to recommend any of them.¹ In late 2014, two drugs, pirfenidone and nintedanib, were approved for treatment of IPF based largely on their ability to slow disease progression. Pirfenidone is a drug that has been evaluated in numerous clinical trials⁶⁻⁸ including the most recent phase 3-approval trials (PIPF004 and PIPF006). In the PIPF004/6 trials, pirfenidone met its primary end point of absolute change from baseline in %FVC in the PIPF004 trial with a modest effect size of 4.4%. No effect was seen on the primary end point in the PIPF006 trial and neither trial showed a survival benefit.⁹ At the request of the US Food and Drug Administration, the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary

Fibrosis (ASCEND) trial was launched as a confirmatory trial of the PIPF004 and PIPF006 trials. The ASCEND trial showed a reduction in the rate of FVC decline as well as a statistically significant improvement in progression-free survival.¹⁰

Nintedanib is a tyrosine kinase inhibitor originally developed as an anti-vascular agent for oncology indications. Based on the presumed pathogenesis of IPF and involvement of vascular and platelet derived growth factor cell-signaling pathways, nintedanib was tested for efficacy against IPF in the To Improve Pulmonary Fibrosis with BIBF 1120 (TOMORROW),¹¹ INPULSIS-1, and INPULSIS-2 trials.¹² In these trials, nintedanib showed a significant improvement in FVC decline relative to placebo without a significant side-effect profile.

The results of these trials have been incorporated into the most recent clinical guideline for IPF, although no treatment received an unconditional recommendation for use.³ A large number of agents have been evaluated as potential treatments for IPF but direct pairwise comparisons are unavailable. The objective of our study was to identify all treatments that have been evaluated for IPF systematically to conduct a network meta-analysis from a Bayesian perspective. Although a previous network meta-analysis was conducted on this topic,¹³ it was limited to only three agents. In particular, we focused our analysis on the clinical end points of all-cause and respiratory-specific mortality and did not have an a priori limitation on the treatments evaluated.

Materials and Methods

This systematic review and network meta-analysis was designed to evaluate and quantify the efficacy and harms of available pharmacological treatments for IPF. Studies included those that used a randomized design to evaluate the effect of a nonsteroidal drug therapy published in English. Studies that contained a population

that was not exclusively being treated for IPF but included other interstitial pneumonias were excluded. No limitations were placed on the length of follow-up in our initial search, but the primary end point was treatment effect at 1 year. The literature search, abstraction, and analysis were conducted in accordance with standards outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*¹⁴ and PRISMA statements.^{15,16}

Data Sources and Searches

A systematic search was conducted in literature databases including MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials using a search string employed by a previously conducted Cochrane Review to answer the same clinical question (e-Table 1).¹⁷ The search was conducted in October 2014 and no exclusions were placed on the time of publication. Two independent reviewers (W. J. C. and S. H. F.) conducted an abstract review of all records.

Articles that were not excluded at abstract review underwent a full text review for eligibility by the two independent reviewers. Final decisions on exclusion at both the abstract and full text review stages were made by consensus process and any disagreements were resolved by a third senior reviewer.

Data Extraction and Quality Assessment

Data extraction underwent a process similar to inclusion review, with independent abstraction by the two

TABLE 1] Treatment Effect to Placebo

Treatment	Respiratory-Specific Death			All-Cause Death			%FVC Decline \geq 10%		
	FE	RE-V	RE-I	FE	RE-V	RE-I	FE	RE-V	RE-I
Pirfenidone	0.58 (0.33-1.00)	0.51 (0.06-3.76)	0.54 (0.15-1.79)	0.69 (0.45-1.04)	0.65 (0.15-2.75)	0.67 (0.36-1.22)	0.52 (0.41-0.67)	0.50 (0.21-1.04)	0.51 (0.33-0.74)
Nintedanib	0.63 (0.36-1.08)	0.44 (0.05-3.16)	0.52 (0.13-1.65)	0.70 (0.45-1.09)	0.71 (0.13-3.82)	0.71 (0.35-1.44)	0.61 (0.48-0.78)	0.57 (0.20-1.29)	0.58 (0.34-0.89)
Imatinib	0.78 (0.27-2.16)	0.78 (0.06-9.80)	0.80 (0.23-2.68)	1.10 (0.51-2.56)	1.15 (0.30-4.76)	1.11 (0.44-2.86)
NAC	0.68 (0.15-3.62)	0.71 (0.03-16.2)	0.68 (0.08-6.40)	0.84 (0.20-4.50)	0.83 (0.06-14.0)	0.85 (0.17-4.75)
Interferon-gamma-1B	0.97 (0.67-1.40)	0.83 (0.12-5.81)	0.85 (0.27-2.52)	0.98 (0.70-1.39)	0.84 (0.15-4.46)	0.92 (0.47-1.64)
Bosentan	1.72 (0.49-8.33)	1.75 (0.09-33.3)	1.69 (14.3-0.25)	1.02 (0.52-2.08)	0.97 (0.16-5.75)	1.01 (0.43-2.38)
Warfarin	0.77 (0.35-1.72)	0.73 (0.09-5.88)	0.76 (0.20-2.93)	1.04 (0.50-2.22)	0.99 (0.16-6.21)	1.04 (0.43-2.56)
Macitentan	0.47 (0.12-1.83)	0.47 (0.02-8.86)	0.47 (0.06-3.44)	1.18 (0.35-5.00)	1.22 (0.09-16.7)	1.25 (0.30-5.56)
Etanercept	0.89 (0.09-9.31)	0.89 (0.03-32.7)	0.89 (0.06-12.7)	2.00 (0.35-16.7)	2.04 (0.11-50.0)	1.89 (0.28-20.0)
Ambrisentan	2.13 (0.83-6.67)	2.17 (0.12-33.3)	2.22 (0.37-12.5)	2.33 (0.99-6.25)	2.44 (0.21-33.3)	2.38 (0.78-7.69)
AZA	2.17 (0.53-10.0)	1.96 (0.14-33.3)	2.08 (0.31-14.3)	2.63 (0.76-11.1)	2.38 (0.25-25.0)	2.63 (0.63-11.1)
NAC plus AZA	3.70 (0.99-16.7)	4.35 (0.31-100.0)	4.00 (0.66-33.3)	3.23 (0.97-12.5)	3.70 (0.39-50.0)	3.33 (0.89-16.7)
Colchicine	3.45 (0.87-16.7)	3.03 (0.14-100.0)	3.45 (0.66-20.0)

Data are presented as 95% credible interval. AZA = azathioprine; FE = fixed-effects model for network meta-analysis; NAC = *n*-acetylcysteine; %FEV = percentage of predicted FVC; RE-I = random-effects model with informative prior; RE-V = random-effects model with vague prior.

reviewers and final decisions made by consensus process and disagreements resolved by a third senior reviewer. Abstracted characteristics included study features, patient baseline characteristics, and clinical measures. Patient characteristics extracted from each study included age, sex, weight, smoking status, time since diagnosis, percentage that were diagnosed by biopsy, and concomitant medications including percentage that received steroid treatment. Clinical measures extracted from studies included FVC, the ratio of FEV₁ to FVC, diffusion capacity of the lung for carbon monoxide, oxygen saturation, St George Respiratory Questionnaire score, 6-min walk test distance, median survival, median progression-free survival, and respiratory and all-cause mortality. FVC and diffusion capacity of the lung for carbon monoxide measures were captured in both absolute terms and percent predicted values. Whenever possible, pulmonary function test results were extracted at baseline and at final measurement. Study quality was assessed using the Cochrane Risk of Bias Tool,¹⁴ with an additional measure included for overall study quality.

Data Synthesis and Analysis

All data were abstracted independently by two reviewers and reconciled by consensus. Any disagreement was resolved by a third senior reviewer. The primary end point of our assessment was the impact of treatments on respiratory and all-cause mortality, which was assessed via OR. Both fixed-effect and random-effects models were applied for event data. Our analysis used a Bayesian framework and we used informative priors for the random-effects model. Informative variance priors were assigned using estimates of heterogeneity from previous meta-analyses.¹⁸ In addition, the random-effects model was run with vague priors as a sensitivity analysis to assess the robustness of our results. We evaluated heterogeneity using the Brooks-Gelman-Rubin method and by assessing whether Monte-Carlo error was less than 5% of the SD of the models' effect estimates as well as between-study variance.¹⁹ To assess systematic differences in effect modifiers among studies, the posterior mean deviance of individual points in the inconsistency model was plotted against their posterior mean deviance in the consistency model to identify evidence loops in the treatment network when evidence was inconsistent. The methods of this inconsistency plot have been described extensively elsewhere.²⁰

In addition, as each chain of the Monte-Carlo cycle ranks treatments in order of their calculated effect sizes, these ranks are captured and then reported as the

percentage of simulations in which each treatment ranks relative to other treatments. Results of this treatment ranking were captured as a surface under the cumulative ranking (SUCRA) line for each treatment as well as a rankogram, which presents a stacked bar chart with each bar representing a rank and the area of that bar representing the percentage of simulation for which each treatment has that rank. The SUCRA values for all analyzed treatments were pulled for each model. The methods and a more detailed description of the SUCRA and rankogram are described elsewhere.²¹ The SUCRA method provides a probability that each treatment ranks first on each model. For a hypothetical treatment that always ranks first, it will have a SUCRA of 1, and for a treatment that always ranks 0 it will have a SUCRA of 0. Thus the results of the SUCRA model will indicate the likelihood that a treatment is the most preferred, with higher values indicating a greater likelihood for benefit. The SUCRA values for all treatments under a given model do not necessarily sum to 1.

Our analysis focused on risk of death as well as pulmonary function as measured by FVC. FVC can be measured on either an absolute scale as the total volume of air expelled in liters or on a relative scale as the percentage predicted for an adult of the same height and age without disease. %FVC therefore ranges on a scale from zero to 100. Although a difference for %FVC of as little as 2% to 6% has been estimated to be the minimal clinically important difference,²² many trials report patients who have a drop in %FVC of $\geq 10\%$. This converts the continuous %FVC to a binary event. For our analysis we considered both %FVC and the proportion of patients whose %FVC was reduced by $\geq 10\%$. Continuous pulmonary outcomes were analyzed via standardized mean difference.

Software

The network meta-analysis was conducted in WinBUGS (BUGS [Bayesian inference Using Gibbs Sampling] project). Analysis for event data was conducted in NetMetaXL (Cornerstone Research Group), which provides a Microsoft Excel interface for the WinBUGS platform.²³ Analysis of continuous outcomes was performed using the WinBUGS software package and a previously validated statistical model by Agapova et al.²⁴

Results

Our literature review identified 1,168 studies, 30 of which ultimately qualified for inclusion in our review (Fig 1). The most common reasons for exclusion

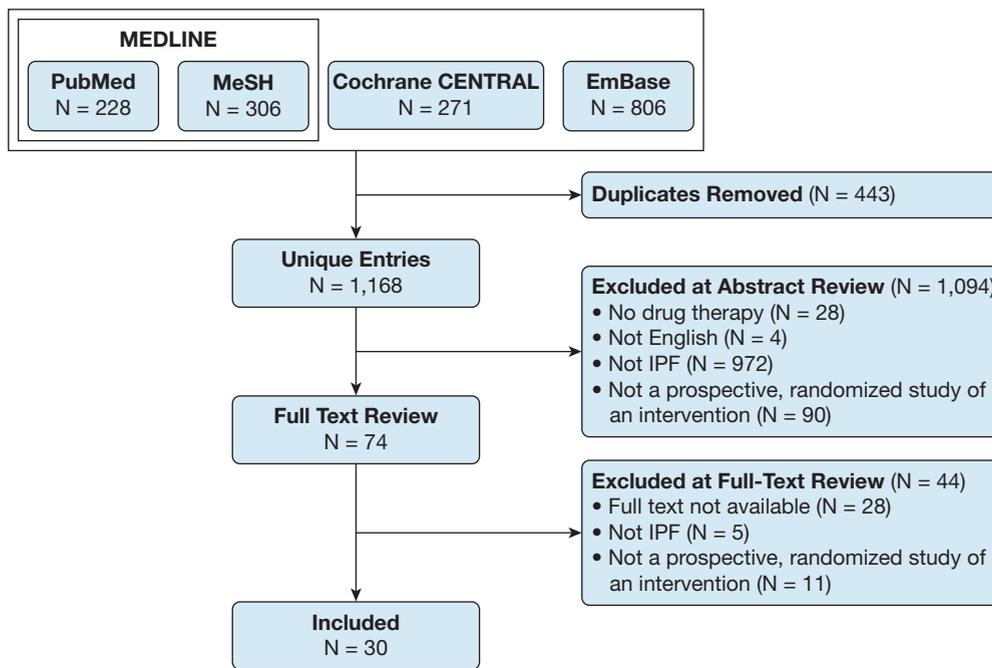


Figure 1 – Search results are shown. IPF = idiopathic pulmonary fibrosis.

included the use of a population that was not being treated exclusively for IPF and the lack of prospective, randomized design. The 30 studies that were included represent 16 treatments, 6,865 patients with IPF, and approximately 7,305 person-years of observation time. This allowed us to create 100, 66, and six pairwise comparisons for the outcomes of all-cause death, respiratory-specific death, and %FVC, respectively.

Network and Study Characteristics

Among the 30 studies were 16 unique treatments. The most commonly studied medications were interferon-gamma 1B, nintedanib, and pirfenidone (Fig 2). Ultimately all analyses focused on studies that reported outcomes at 1 year. In addition, of all outcomes gathered, only %FVC, all-cause mortality, and respiratory-specific mortality were reported consistently across enough studies to allow for pooling of results. Among included studies, the most common comparator was placebo, and the study size ranged dramatically. Studies did not vary significantly in terms of clinical or demographic characteristics (e-Table 2A). Mean age of participants ranged in age from 54 to 71 years and were predominantly male and current or former smokers. In addition, risk of bias in these studies was low (Fig 3, e-Table 3). Two studies, that of Douglas et al²⁵ and Sildenafil Trial of Exercise Performance in Idiopathic

Pulmonary Fibrosis (STEP-IPF),²⁶ were excluded from the final analysis since their length of follow-up was too short to allow for pooling with other trials. Ziesche et al²⁷ did not report outcomes included in this analysis and was also excluded. All other trials were relatively consistent in terms of reporting of mortality and respiratory end points (e-Table 2B).

Outcomes

The primary outcomes of interest for this analysis were all-cause and respiratory-specific death. These end points were reported by the vast majority of trials. Under the fixed-effects model for respiratory-specific mortality, three treatments (pirfenidone, nintedanib, and warfarin) showed a significant treatment advantage over *n*-acetylcysteine and azathioprine combination therapy (Fig 4A, e-Table 4). No other treatments showed a significant effect and none performed better than placebo (Table 1). Under the random-effects model with an informative prior, no pairwise comparison showed a significant effect. For all-cause mortality, dual therapy with *n*-acetylcysteine and azathioprine performed similarly poorly (Fig 4B, e-Table 5). Pirfenidone and nintedanib had effects approaching significance, with credible intervals slightly crossing the null under a fixed-effects model. Notably, for both respiratory-specific and all-cause mortality, nintedanib and pirfenidone were virtually indistinguishable. For both of these outcomes,

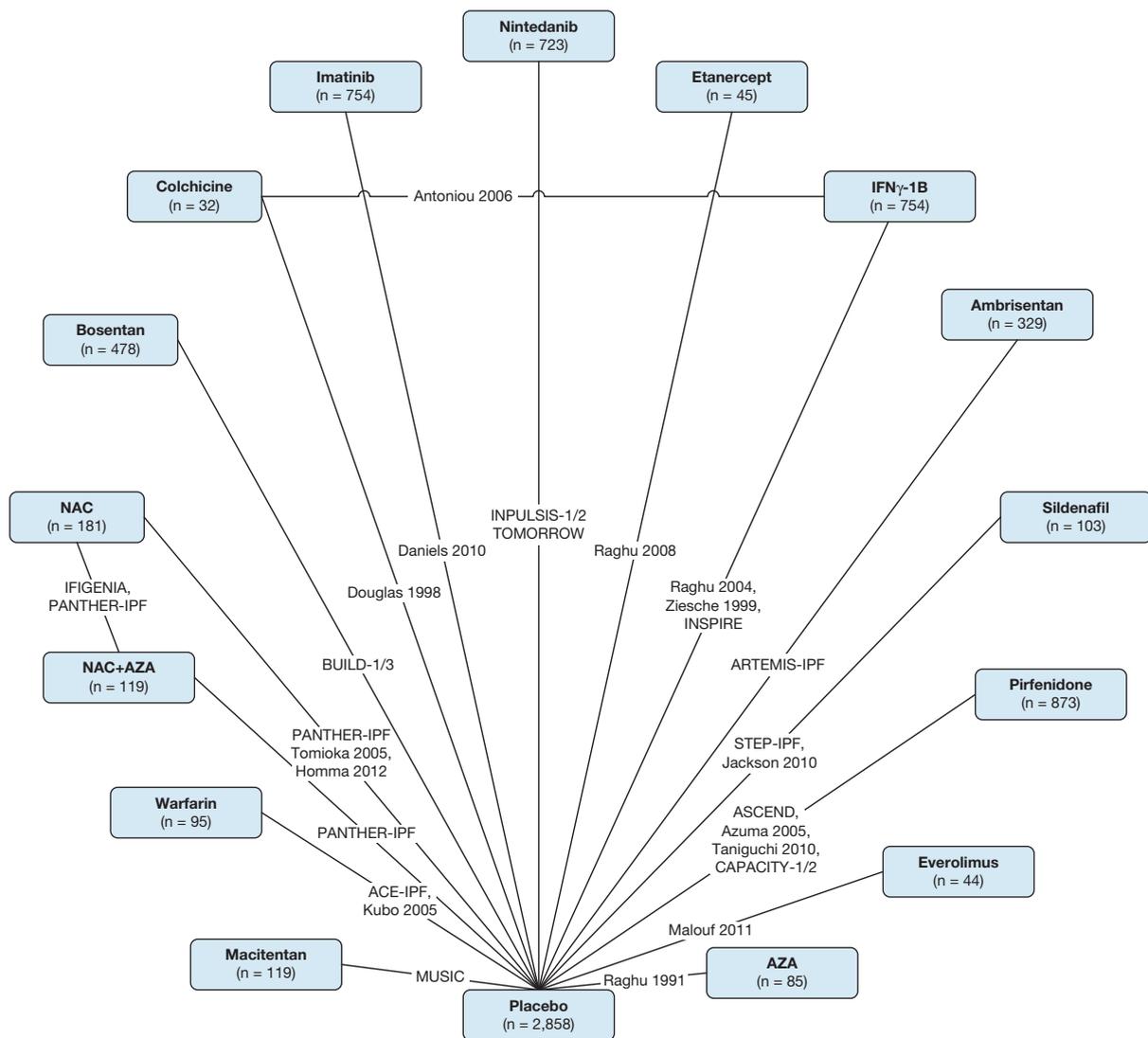


Figure 2 - Network of included medications. AZA = azathioprine; IFN = interferon; NAC = n-acetylcysteine. See Figure 1 legend for expansion of other abbreviation.

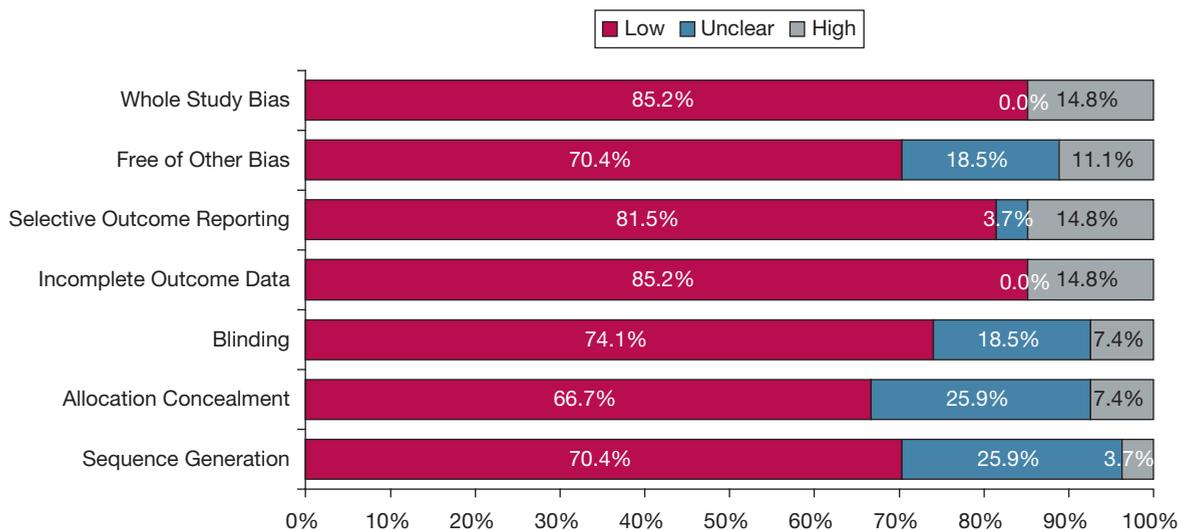


Figure 3 - Risk of bias among studies is demonstrated.

A

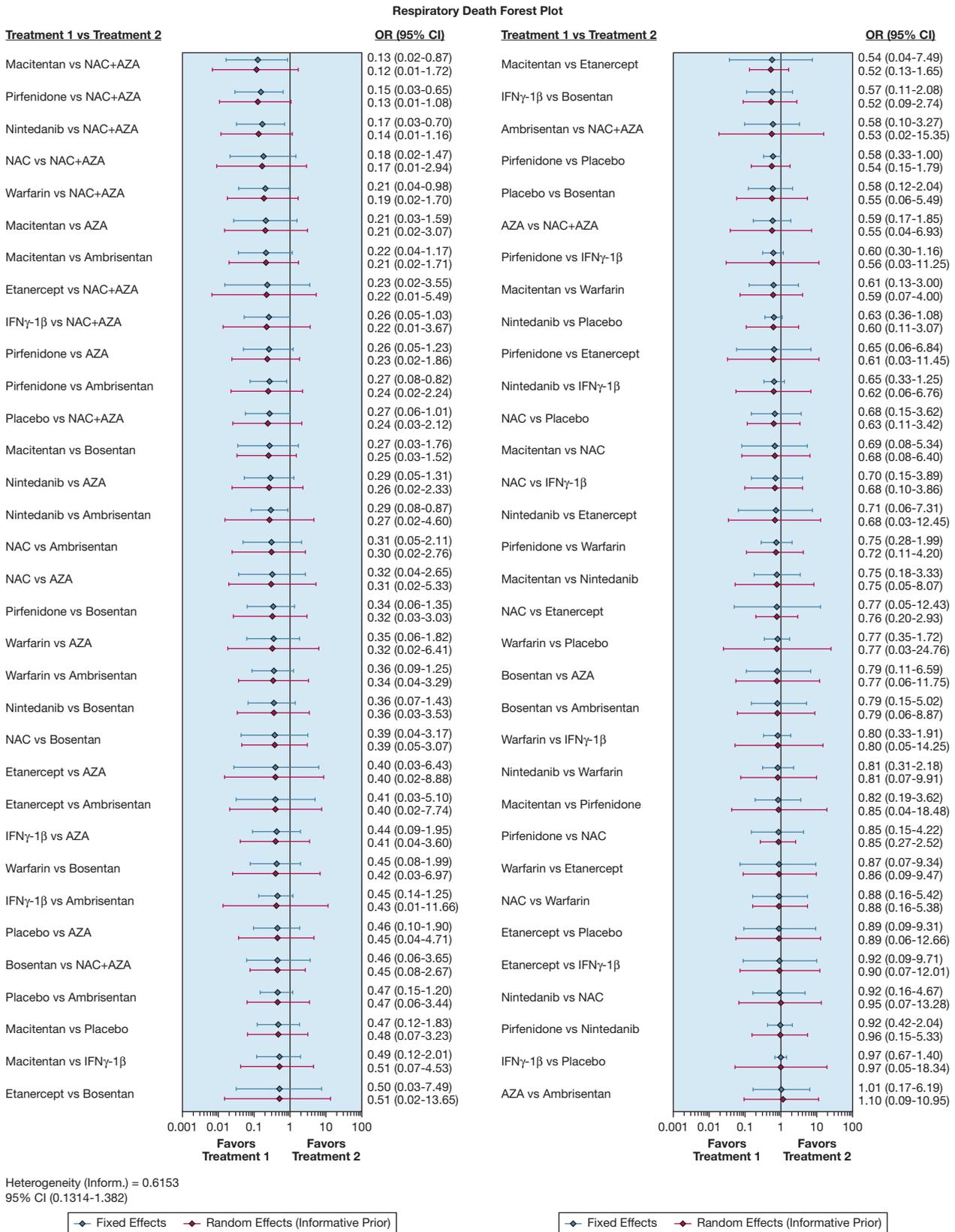


Figure 4 – Forest plot of results of network meta-analysis for all possible pairwise drug comparisons. A, Pairwise comparisons of respiratory-specific cause of death. B, Pairwise comparisons of all cause death. C, Pairwise comparisons of %FVC decline by $\geq 10\%$ over the course of the trial. Not all studies reported all end points so these figures represent possible comparisons based on available data. See Figure 2 legend for expansion of abbreviations.

B

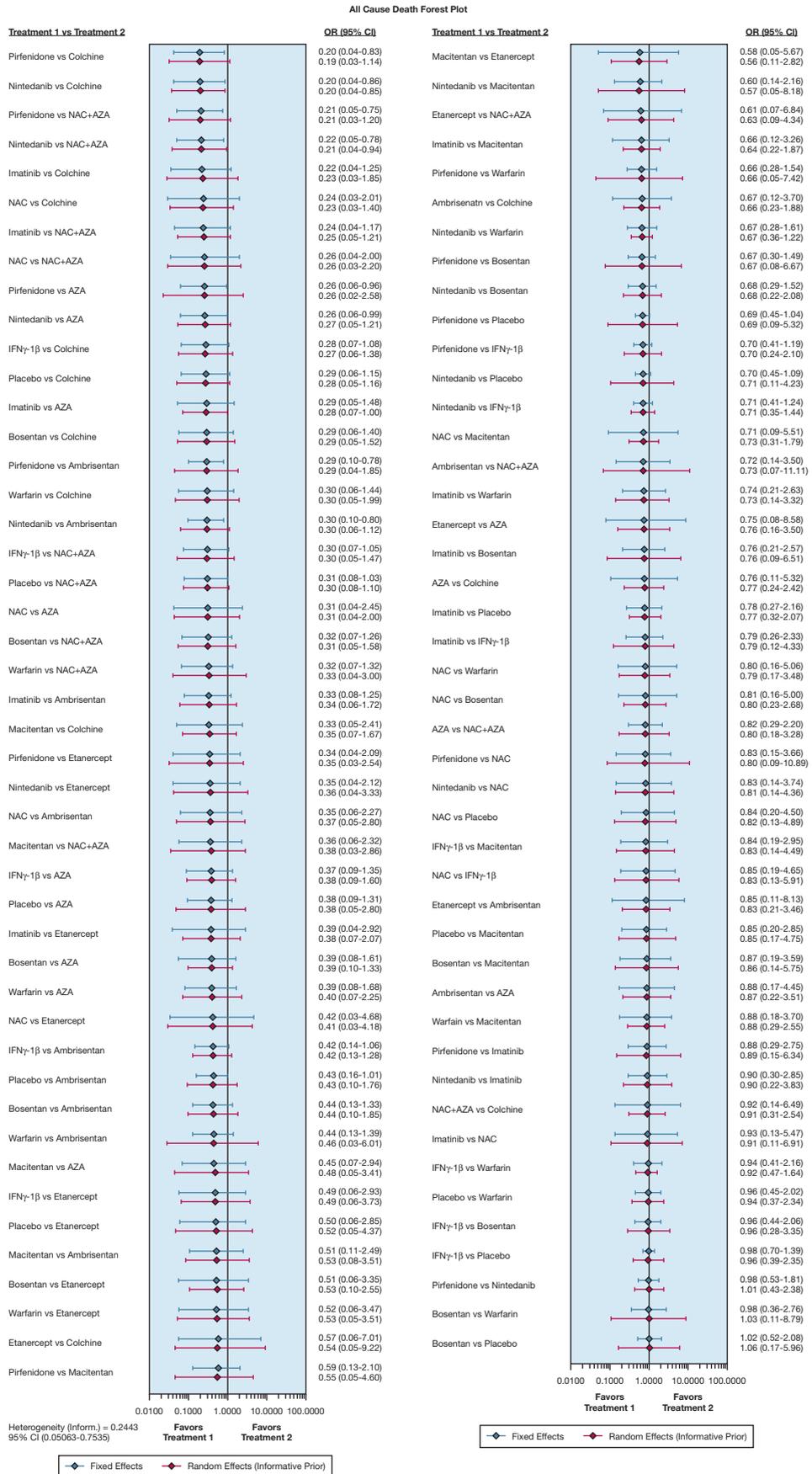


Figure 4 - Continued

C

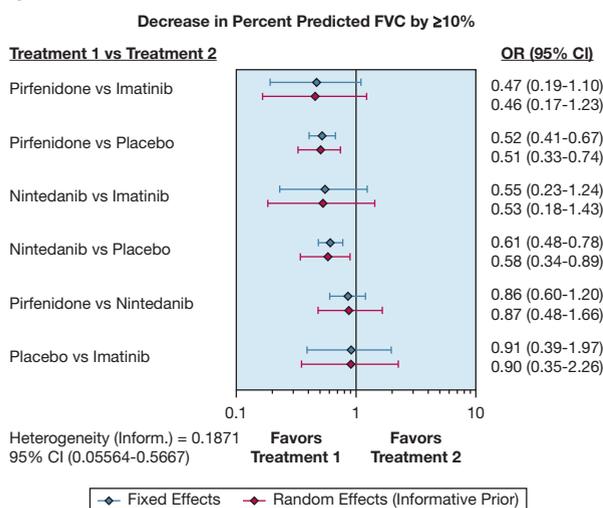


Figure 4 – Continued

our sensitivity analysis showed virtually no difference with the use of a vague rather than informative prior.

Although all trials reported some measure of pulmonary function, the end points used were highly variable among studies. The most consistently reported outcomes were respiratory-specific and all-cause mortality, which allowed for a large number of comparisons among treatments. Reporting of FVC varied among trials. Absolute change in FVC and %FVC were not reported in a sufficient number of trials to

allow for reliable interpretation. Many of the more recent trials have adopted the binary outcome of %FVC decline >10%. Use of this outcome allowed for comparison of many of the most commonly used treatments. Both respiratory-specific and all-cause mortality showed significant uncertainty; only a limited number of comparisons demonstrated a significantly different impact on measures of mortality (Fig 4, e-Tables 4 and 5).

Analysis of change in %FVC from baseline showed a great deal of uncertainty, as evidenced by the large confidence intervals (e-Table 6). When evaluated as %FVC decline ≥10%, the evidence becomes much more interpretable (Fig 4C, e-Table 7). Whereas pirfenidone and nintedanib both show significant improvement over placebo (Table 1), their benefit relative to each other is still unclear.

Because of the large number of treatments evaluated, we also evaluated the SUCRA values, which give a sense of the likelihood of each treatment being preferred (Table 2). Relative ranking SUCRA values for respiratory-specific mortality show a likely benefit for treatment of patients with pirfenidone and nintedanib. These same trends are reflected in all-cause mortality and %FVC decline ≥10%. Interestingly, macitentan performed well for all-cause mortality. These trends were reflected in the treatment rankings based on SUCRA values (e-Figs 2-4).

TABLE 2] Surface Under the Cumulative Ranking

Treatment	Respiratory-Specific Death			All-Cause Death			%FVC Decline ≥10%		
	FE	RE-V	RE-I	FE	RE-V	RE-I	FE	RE-V	RE-I
Pirfenidone	0.8165	0.6954	0.7896	0.7911	0.6789	0.7315	0.9261	0.8302	0.8816
Nintedanib	0.803	0.6628	0.7618	0.7549	0.7146	0.7493	0.7026	0.7271	0.7299
Imatinib	0.7031	0.6182	0.6861	0.1688	0.2201	0.1883
NAC	0.647	0.5851	0.6325	0.658	0.5748	0.6139
Interferon-gamma-1B	0.5791	0.618	0.6258	0.5045	0.5483	0.5554
Bosentan	0.5668	0.5596	0.5661	0.296	0.3733	0.3379
Placebo	0.5618	0.5498	0.5578	0.4758	0.4844	0.475	0.2026	0.2226	0.2002
Warfarin	0.5559	0.5498	0.5664	0.6338	0.582	0.6003
Macitentan	0.5009	0.4988	0.4819	0.8	0.6671	0.7337
Etanercept	0.3256	0.3678	0.314	0.553	0.5231	0.5374
Ambrisentan	0.2166	0.3206	0.2419	0.2009	0.322	0.2541
AZA	0.2138	0.3334	0.226	0.2432	0.3467	0.2886
NAC plus AZA	0.1472	0.221	0.1968	0.08872	0.1848	0.1229
Colchine	0.1468	0.2929	0.1583

See Table 1 legend for expansion of abbreviations.

Consistency and Heterogeneity

Both models for mortality as well as %FVC and mortality showed good convergence. Models for mortality showed strong consistency of results (e-Fig 1), which suggests a minimal difference in effect modifiers between groups. I^2 statistics were 0.62, 0.24, and 0.19 for respiratory death, all-cause death and %FVC decline $\geq 10\%$, respectively. These values suggest that heterogeneity was not too great to limit quantitative pooling.

Conclusions

To our knowledge, this study presents the most comprehensive review to date of available medical treatments for IPF. Although other high-quality meta-analyses have been published, they are limited because either they are not current and therefore do not include newer therapies¹⁷ or they limit their analysis to a small number of treatments.¹³ The availability of rigorously studied and Food and Drug Administration-approved treatments for IPF is a great advance for patients diagnosed with IPF. Our analysis confirms that compared with numerous other treatments studied for IPF, pirfenidone and nintedanib slow the rate of disease progression, as measured by the rate of FVC decline over 1 year in patients enrolled in clinical trials. Although nintedanib and pirfenidone reduce the risk of decline in pulmonary function for patients with IPF, their impact on long-term mortality remains unclear. Although reliance on surrogate end points for the approval of these agents allows treatments to reach patients faster, it can often be misleading.²⁸ In the case of IPF, a rare condition with high disease burden, the risk of using a surrogate end point may be worth the benefit of providing treatment to patients. However, the improvement in pulmonary function seen with these treatments has not yet translated into improvements in mortality risk. Although this is an area of debate,

the most recent findings suggest that FVC may be a correlate rather than a reliable surrogate.

Our analysis also highlights the lack of uniform reporting of pulmonary function in studies on IPF. With so many available measures of pulmonary function, the development of uniform and consistent standards for reporting will be essential for a comparison of treatments.

Our analysis has several notable limitations which should be acknowledged. First, although a number of treatments have been evaluated for IPF, the variability in reporting of trial results limited the number of analyses we were able to perform. In addition, although our strong results for consistency suggest that the impact of heterogeneity was minimal, pooling trials from such a broad range of treatments and populations published over such a long period may present some limitations. In fact, some key differences in the trial's inclusion and exclusion criteria make it difficult to extrapolate them to the community of patients with IPF at large.²⁹

Pirfenidone and nintedanib were approved based on their impact on pulmonary function tests in patients with IPF. Our network meta-analysis confirms that effect but also highlights the limited data on the final clinical end points of mortality. Ultimately, this highlights the need for greater understanding of the long-term consequences of treatment with these agents, which may be available only after more use of these treatments in clinical practice. In addition, although the results of this network meta-analysis provide an insight into the IPF treatment trials, our findings should not be extrapolated to treatment recommendations, and such recommendations are deferred to clinical practice guidelines and evidence-based guidelines.

Acknowledgments

Author contributions: B. E. D., S. H. F., and W. J. C. had access to all data for the complete review. B. E. D. and W. J. C. take responsibility for integrity of the work. W. J. C. helped design, conduct and analyze the meta-analysis. S. H. F. helped conduct the review and abstract data as a second reviewer with W. J. C. G. R., a leading clinician, helped interpret our results in the context of the best available evidence as well as recent guidelines. L. H., another clinician, helped us design the review. B. E. D., senior author, helped with design and analysis and also served as a senior statistical consultant.

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Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

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