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Effect of Co-trimoxazole (Trimethoprim-Sulfamethoxazole) vs Placebo on Death, Lung Transplant, or Hospital Admission in Patients With Moderate and Severe Idiopathic Pulmonary Fibrosis The EME-TIPAC Randomized Clinical Trial

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IMPORTANCE Idiopathic pulmonary fibrosis (IPF) has a poor prognosis and limited treatment options. Patients with IPF have altered lung microbiota, with bacterial burden within the lungs associated with mortality; previous studies have suggested benefit with co-trimoxazole (trimethoprim-sulfamethoxazole).

OBJECTIVE To determine the efficacy of co-trimoxazole in patients with moderate and severe IPF.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, placebo-controlled, parallel randomized trial of 342 patients with IPF, breathlessness (Medical Research Council dyspnea scale score >1), and impaired lung function (forced vital capacity ≤75% predicted) conducted in 39 UK specialist interstitial lung disease centers between April 2015 (first patient visit) and April 2019 (last patient follow-up).

INTERVENTIONS Study participants were randomized to receive 960 mg of oral co-trimoxazole twice daily (n = 170) or matched placebo (n = 172) for between 12 and 42 months. All patients received 5 mg of folic acid orally once daily.

MAIN OUTCOMES AND MEASURES The primary outcome was time to death (all causes), lung transplant, or first nonelective hospital admission. There were 15 secondary outcomes, including the individual components of the primary end point respiratory-related events, lung function (forced vital capacity and gas transfer), and patient-reported outcomes (Medical Research Council dyspnea scale, 5-level EuroQol 5-dimension questionnaire, cough severity, Leicester Cough Questionnaire, and King's Brief Interstitial Lung Disease questionnaire scores).

RESULTS Among 342 individuals who were randomized (mean age, 71.3 years; 46 [13%] women), 283 (83%) completed the trial. The median (interquartile range) duration of follow-up was 1.02 (0.35-1.73) years. Events per person-year of follow-up among participants randomized to the co-trimoxazole and placebo groups were 0.45 (84/186) and 0.38 (80/209), respectively, with a hazard ratio of 1.2 ([95% CI, 0.9-1.6]; P = .32). There were no statistically significant differences in other event outcomes, lung function, or patient-reported outcomes. Patients in the co-trimoxazole group had 696 adverse events (nausea [n = 89], diarrhea [n = 52], vomiting [n = 28], and rash [n = 31]) and patients in the placebo group had 640 adverse events (nausea [n = 67], diarrhea [n = 84], vomiting [n = 20]).

CONCLUSIONS AND RELEVANCE Among patients with moderate or severe IPF, treatment with oral co-trimoxazole did not reduce a composite outcome of time to death, transplant, or nonelective hospitalization compared with placebo.

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Group Information: EME-TIPAC team members appear at the end of the article.

Corresponding Author: Andrew M. Wilson, MD, University of East Anglia, James Watson Road, Norwich Research Park, Bob Champion Research and Education Building, Floor 2, Norwich, Norfolk NR4 7TJ, United Kingdom (a.m.wilson @uea.ac.uk). diopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease with a median survival of 5.7 years,¹ increasing incidence,² and limited treatment options. Respiratory tract infection is common in patients with IPF³ and bronchial washings contain pathogenic bacteria, as identified by quantitative culture^{4,5} or non-culturedependent techniques.⁶ Bronchoalveolar lavage studies from 2 separate groups have shown that a high bacterial load was associated with reduced lung function and death,^{7,8} and a lung microbiota enriched with *Streptococcus* species and *Staphylococcus* species was associated with reduced progression-free survival⁹ in IPF. Moreover, innate immune responses may be abnormal in IPF, potentially increasing susceptibility to infection.^{10,11}

Co-trimoxazole (trimethoprim-sulfamethoxazole), a broad-spectrum antibiotic, was reported to improve clinical outcomes in IPF in 2 small randomized clinical trials,^{12,13} and was found to be cost-effective.¹⁴ An exploratory analysis suggested an improvement in health-related quality of life and oxygen requirements and, in those adhering to the study protocol, a reduction in mortality over a 12-month period; however, evidence of a survival benefit was not conclusive.¹³

The aim of the current study was to determine the clinical efficacy of co-trimoxazole in patients with moderate or severe IPF (defined as forced vital capacity [FVC] ≤75% predicted) in terms of the time to death (all-cause), lung transplant, or first nonelective hospital admission. Secondary aims were to assess the effects on respiratory-related outcomes, patientreported outcomes (in terms of health-related quality of life, cough, and breathlessness), and lung function.

Methods

This was a phase 3 double-blind, placebo-controlled, parallel, randomized, multicenter study of oral co-trimoxazole added to standard care. The protocol has been published,¹⁵ and the final protocol, amendments, and statistical analysis plan are available in Supplement 1 and Supplement 2. The study was conducted according to good clinical practice, and the study protocol received ethical approval (14/LO/1800).

Patients were treated from randomization until withdrawal, death, first nonelective admission (for any reason), lung transplant, or the end of the study follow-up, with a minimum duration of 12 months and maximum of 42 months. The study was conducted in 43 specialist interstitial lung disease centers, or in sites affiliated with them, from all regions in the UK.

All participants provided written informed consent. Participants were randomized between April 2015 and April 2018, and follow-up was completed in April 2019. In May 2016, modifications removed an exclusion of participants given diagnoses more than 2 years before randomization and increased the permitted FVC predicted value from 70% to 75% to improve recruitment. An optional bronchoscopy substudy was discontinued in June 2017.

Patients were recruited to the study if they had IPF diagnosed according to contemporaneous international guide**Key Points**

Question What is the clinical efficacy of co-trimoxazole (trimethoprim-sulfamethoxazole) in idiopathic pulmonary fibrosis (IPF) in terms of time to death (all causes), lung transplant, or first nonelective hospital admission?

Findings In this randomized clinical trial, which included 343 patients with moderate or severe IPF, the incidence of the composite outcome among those treated with oral co-trimoxazole, 960 mg twice daily, vs those treated with placebo was 0.45 vs 0.38 per person-year after a median follow-up of 1.02 years; the hazard ratio was not statistically significant.

Meaning Co-trimoxazole compared with placebo did not improve a composite clinical outcome among patients with moderate or severe IPF.

lines¹⁶ and had a modified Medical Research Council (MRC) dyspnea scale score greater than 1. They could receive licensed medication for IPF at a stable regimen. Patients were excluded if they had FVC greater than 75% predicted, a significant coexisting respiratory or other comorbidity, or a respiratory tract infection during the preceding 4 weeks or were receiving immunosuppression.

Patients were randomized on a 1:1 basis to receive 960 mg of oral co-trimoxazole (2 480-mg tablets) or 2 matched placebo tablets twice daily. The treatment allocation was generated via a computer code, using minimization for site, current use of antifibrotic therapy, and involvement in bron-choscopy substudy, under the supervision of the study statistician. All patients received 5 mg of folic acid orally once daily to prevent impaired hematopoiesis. Treatments were given in addition to standard care as defined by National Institute for Health and Clinical Excellence guidelines (https://www.nice.org.uk/CG163).

A reduction of treatment dose to 2 tablets (ie, 960 mg of co-trimoxazole or 2 placebo tablets daily) plus 5 mg of folic acid 3 times per week was permitted if a participant developed gastrointestinal adverse effects, rash, grade 1 hyperkalemia, or any other adverse event requiring dose reduction in the view of the principal investigator.

Outcomes

The primary outcome was the time to death (all causes), lung transplant, or first nonelective hospital admission for any reason. These data were obtained at each site until the date of withdrawal or the end of the study by screening hospital records and capturing details of out-of-hospital death from primary care records, if required. The primary outcome was censored at the date of withdrawal if patients withdrew consent to be followed up. Secondary outcomes included the individual components of the primary outcome. Respiratory-related events, determined by an independent committee, were analyzed separately. Spirometry¹⁷ and gas transfer (an assessment of carbon monoxide uptake by the lung that reflects the ability of the lungs to exchange gas into the bloodstream)¹⁸ were captured at baseline and at 6 and 12 months. The MRC dyspnea scale,¹⁹ 5-level Euroqol

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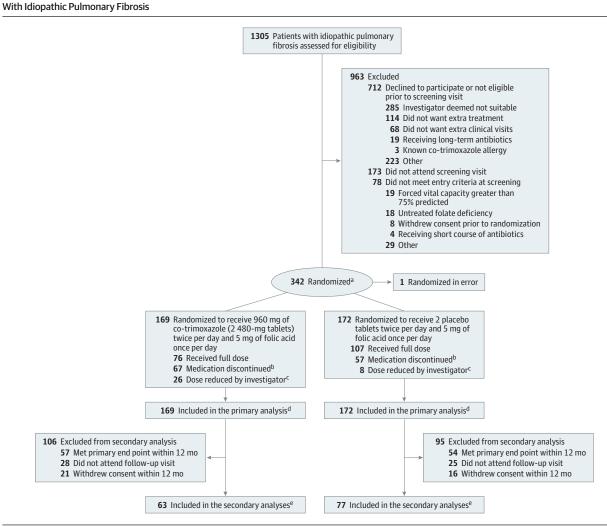


Figure 1. Flow of Participants in a Study of the Effect of Co-trimoxazole vs Placebo on Death, Lung Transplant, or Hospital Admission in Patients With Idiopathic Pulmonary Fibrosis

^a In a 1:1 ratio, with minimization for site and baseline fibrotic therapy.

- ^b Five patients in the co-trimoxazole group and 8 in the control group previously had their dose reduced by the investigator.
- ^c A reduction of the dose to 2 tablets (ie, 960 mg co-trimoxazole or 2 placebo tablets daily) plus 5 mg of folic acid 3 times weekly was permitted if a participant developed gastrointestinal adverse effects or rash, grade 1

5-dimension (EQ-5D-5L) questionnaire,²⁰ cough severity score (visual analog scale ranging from 0 ["I have not been bothered by my cough at all"] to 100 ["My cough has been the worst it can be"]), Leicester Cough Questionnaire (LCQ),²¹ and King's Brief Interstitial Lung Disease (K-BILD) questionnaire²² were given at baseline and 3 and 6 months, then every 6 months throughout the study, including a final assessment at the end of the study. Sputum was obtained, when clinically relevant, and sent for local microbiological culture and antibiotic susceptibility testing. Blood was taken for complete blood cell count, urea and electrolytes, and liver function at baseline; 6 weeks; and 3, 6, 9, and 12 months, then every 6 months for the duration of the study. Adverse events were captured at each visit and assessed for severity. Blood biomarker analysis is not reported here.

Statistical Analysis

withdrawal

The trial was designed to have 80% power (2-sided significance level of 5%) to show a change in hospitalization-free survival from a median value of 28.8 months in the placebo group to 51.1 months in the co-trimoxazole group (hazard ratio [HR], 0.56) over this study period assuming that 330 patients were randomized and 20% withdrew from the study. This was based on a sensitivity analysis of patients from a previous study¹³ with reduced lung function (FVC <70% predicted) using an intention-to-treat analysis.

hyperkalemia (potassium >5.0 mmol/L), or any other adverse event requiring

group withdrew during the study, and their data are included until the point of

^d A total of 32 individuals from the co-trimoxazole and 26 from the placebo

dose reduction in the view of the principal investigator.

^e The secondary outcome data illustrate that of lung function.

The primary outcome and secondary event measurements were analyzed using a Cox proportional hazards model adjusted for licensed IPF medication use as a fixed effect and site a random effect. If the model did not converge then site was included as a strata in the analysis and a sandwich-based Table 1. Baseline Characteristics of Participants in a Study of the Effect of Co-trimoxazole vs Placebo on Death, Lung Transplant, or Hospital Admission in Patients With Idiopathic Pulmonary Fibrosis

Sex, No. (%) Men 138 (81.7) 157 (91.3) Women 31 (18.3) 15 (8.7) Age, mean (SD), y 71.9 (7.8) 70.7 (7.1) Smoking status, No. (%)	Characteristic	Co-trimoxazole (n = 169ª)	Placebo (n = 172ª)
Women 31 (18.3) 15 (8.7) Age, mean (SD), y 71.9 (7.8) 70.7 (7.1) Smoking status, No. (%)	Sex, No. (%)		
Age, mean (SD), y 71.9 (7.8) 70.7 (7.1) Smoking status, No. (%) Never 59 (34.9) 56 (32.6) Ex-smoker 109 (64.5) 114 (66.3) Current 1 (0.6) 2 (1.2) Comorbidities, No. (%) ^b Gastroesophageal reflux disease 69 (40.8) 62 (36.1) Ischemic heart disease or angina 38 (22.5) 44 (25.6) Anxiety or depression 17 (10) 23 (13.4) Pulmonary hypertension 13 (7.7) 10 (5.8) Osteoporosis 11 (6.5) 11 (6.4) Chronic obstructive pulmonary disease 6 (3.6) 6 (3.5) Branchiectasis 2 (1.2) 7 (4.1) Mainteaance treatments, No. (%) Proton pump inhibitor 87 (51.5) 78 (45.3) Pirfenidone 71 (42.0) 66 (38.4) Nintedanib 56 (33.1) 61 (35.5) Prednisolone 12 (7.1) 10 (5.8) N-acetylcysteine 8 (4.7) 7 (4.1) Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^c Absolute value FVC, L 2.2 (0.6) 2	Men	138 (81.7)	157 (91.3)
Smoking status, No. (%) Never 59 (34.9) 56 (32.6) Ex-smoker 109 (64.5) 114 (66.3) Current 1 (0.6) 2 (1.2) Gastroesophageal reflux disease 69 (40.8) 62 (36.1) Ischemic heart disease or angina 38 (22.5) 44 (25.6) Diabetes 40 (23.7) 25 (14.5) Anxiety or depression 17 (10) 23 (13.4) Pulmonary hypertension 13 (7.7) 10 (5.8) Osteoporosis 11 (6.5) 11 (6.4) Chronic obstructive pulmonary disease 6 (3.6) 6 (3.5) Bronchiectasis 2 (1.2) 7 (4.1) Maintenance treatments, No. (%) Proton pump inhibitor 87 (51.5) 78 (45.3) Pirfenidone 71 (42.0) 66 (38.4) Nintedanib N-acetylcysteine 8 (4.7) 7 (4.1) Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^e Jen (1.1) In = 1711 Absolute value FVC, L 2.2 (0.6) 2.3 (0.5) FEV ₁ , L 1.9 (0.5) <td< td=""><td>Women</td><td>31 (18.3)</td><td>15 (8.7)</td></td<>	Women	31 (18.3)	15 (8.7)
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Anxiety or depression 17 (10) 23 (13.4) Pulmonary hypertension 13 (7.7) 10 (5.8) Osteoporosis 11 (6.5) 11 (6.4) Chronic obstructive pulmonary disease 6 (3.6) 6 (3.5) Bronchiectasis 2 (1.2) 7 (4.1) Maintenance treatments, No. (%) Proton pump inhibitor 87 (51.5) 78 (45.3) Pirfenidone 71 (42.0) 66 (38.4) Nintedanib 56 (33.1) 61 (35.5) Prednisolone 12 (7.1) 10 (5.8) N-acetylcysteine 8 (4.7) 7 (4.1) Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^c Absolute value FFV ₁ , L 1.9 (0.5) 1.9 (0.4) [n = 171] FEV ₁ , L 0.8 (0.1) 0.8 (0.1) [n = 127] Predicted value, % FVC 56.2 (8.9) 55.2 (10.0) FEV ₁ 1.9 (0.5) [n = 127] DLCO, mmoL/min/kPa 3.6 (1.8) [n = 123] (2.00-3.00) [n = 171] DLCO 43.3 (20.2) (4.5 (18.0) [n = 171] DLCO <	Ischemic heart disease or angina	38 (22.5)	44 (25.6)
Pulmonary hypertension 13 (7.7) 10 (5.8) Osteoporosis 11 (6.5) 11 (6.4) Chronic obstructive pulmonary disease 6 (3.6) 6 (3.5) Bronchiectasis 2 (1.2) 7 (4.1) Maintenance treatments, No. (%) P Proton pump inhibitor 87 (51.5) 78 (45.3) Pirfenidone 71 (42.0) 66 (38.4) Nintedanib 56 (33.1) 61 (35.5) Prednisolone 12 (7.1) 10 (5.8) N-acetylcysteine 8 (4.7) 7 (4.1) Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^c Absolute value FEV1, L 1.9 (0.5) 1.9 (0.4) [n = 171] FEV1, L 1.9 (0.5) 1.9 (0.4) [n = 171] 1.9 (1.5) 1.9 (1.4) Predicted value, % Sc (1.8) 3.7 (1.5) [n = 123] 1.1 (2.0) FEV1, L 0.8 (0.1) [n = 171] DLCO, mmoL/min/kPa 3.6 (1.8) [n = 171] 3.7 (1.5) [n = 171] DLCO, mmoL/min/kPa 3.6 (1.8) [n = 171] 2.2 (1.0.0) [n = 171] FEV1 61.	Diabetes	40 (23.7)	25 (14.5)
	Anxiety or depression	17 (10)	23 (13.4)
$\begin{tabular}{ c c c c c } \hline Chronic obstructive pulmonary disease 6 (3.6) 6 (3.5) \\ \hline Bronchiectasis 2 (1.2) 7 (4.1) \\\hline \end{tabular} \end{tabuar} \end{tabular} \end{tabuar} \end{tabular} $	Pulmonary hypertension	13 (7.7)	10 (5.8)
Bronchiectasis 2 (1.2) 7 (4.1) Maintenance treatments, No. (%) Proton pump inhibitor 87 (51.5) 78 (45.3) Pirfenidone 71 (42.0) 66 (38.4) Nintedanib 56 (33.1) 61 (35.5) Prednisolone 12 (7.1) 10 (5.8) N-acetylcysteine 8 (4.7) 7 (4.1) Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^C Absolute value FVC, L 2.2 (0.6) 2.3 (0.5) FEV1, L 1.9 (0.5) 1.9 (0.4) [n = 171] [n = 171] DLC0, mmoL/min/kPa 3.6 (1.8) 3.7 (1.5) [n = 123] [n = 127] Predicted value, % FVC 56.2 (8.9) 55.2 (10.0) FEV1 61.5 (9.3) 60.0 (10.6) [n = 171] [n = 127] DLCO 43.3 (20.2) 44.5 (18.0) [n = 123] [n = 127] Outcome measures, mean (SD) Condemic (10R) ^d 2.00 (2.00-3.00) [n = 167] 2.00 (2.00-3.00) [n = 171] EQ-5D-5L utility score ^e 0.67 (0.20) 0.69 (0.22) [n = 168] 2.00 (2.00-3.00) [n = 167] 1.10 (n = 168]	Osteoporosis	11 (6.5)	11 (6.4)
Maintenance treatments, No. (%) Proton pump inhibitor 87 (51.5) 78 (45.3) Pirfenidone 71 (42.0) 66 (38.4) Nintedanib 56 (33.1) 61 (35.5) Prednisolone 12 (7.1) 10 (5.8) N-acetylcysteine 8 (4.7) 7 (4.1) Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^c Absolute value FVC, L 2.2 (0.6) 2.3 (0.5) FEV ₁ , L 1.9 (0.5) 1.9 (0.4) (n = 171] 1.9 (0.5) 1.9 (0.4) (n = 171] DLCO, mmoL/min/kPa 3.6 (1.8) (3.7 (1.5) (n = 172]) 1.7 (1.5) (n = 172] 1.7 (1.5) (n = 172] Predicted value, % FVC 56.2 (8.9) 55.2 (10.0) FEV ₁ 61.5 (9.3) 60.0 (10.6) (n = 171] DLCO 43.3 (20.2) (n = 127] 44.5 (18.0) (n = 127] Outcome measures, mean (SD) Subscience 2.00 (2.00-3.00) (n = 127] Detection (1QR) ^d 39.5 (27.5) (n = 168] 40.9 (26.6) (n = 171] Eq5D-5L utility score ^e 0.67 (0.20) (n = 0.69 (0.22) (n = 168] (n = 171] Cough severity score ^f	Chronic obstructive pulmonary disease	6 (3.6)	6 (3.5)
Proton pump inhibitor 87 (51.5) 78 (45.3) Pirfenidone 71 (42.0) 66 (38.4) Nintedanib 56 (33.1) 61 (35.5) Prednisolone 12 (7.1) 10 (5.8) N-acetylcysteine 8 (4.7) 7 (4.1) Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^c Absolute value 2.2 (0.6) 2.3 (0.5) FVC, L 2.2 (0.6) 2.3 (0.5) 1.9 (0.4) (n = 171] FEV ₁ , L 1.9 (0.5) 1.9 (0.4) (n = 171] FEV ₁ /FVC ratio 0.8 (0.1) 0.8 (0.1) (n = 171] DLCO, mmoL/min/kPa 3.6 (1.8) (3.7 (1.5) (n = 123) FVC 56.2 (8.9) 55.2 (10.0) FEV ₁ 61.5 (9.3) 60.0 (10.6) (n = 171] DLCO 43.3 (20.2) (n = 123) 44.5 (18.0) (n = 171] DLCO 43.3 (20.2) (n = 167] (2.00 - 3.00) (n = 171] DLCO 43.3 (20.2) (n = 167] (2.00 - 3.00) (n = 171] Eq-5D-5L utility score ^a 0.67 (0.20) (0.69 (0.22) (n = 168] (n = 171] EQ-5D-5L utility score ^a 0.67 (0.20) (0.69 (0.22) (n = 168	Bronchiectasis	2 (1.2)	7 (4.1)
$\begin{tabular}{ c c c c c } \hline Pirfenidone & 71 (42.0) & 66 (38.4) \\ \hline Nintedanib & 56 (33.1) & 61 (35.5) \\ \hline Prednisolone & 12 (7.1) & 10 (5.8) \\ \hline N-acetylcysteine & 8 (4.7) & 7 (4.1) \\ \hline Other antioxidant & 3 (1.8) & 5 (2.9) \\ \hline Lung function, mean (SD)^C & & & & \\ \hline Absolute value & & & & \\ \hline FVC, L & 2.2 (0.6) & 2.3 (0.5) \\ \hline FEV_1, L & 1.9 (0.5) & 1.9 (0.4) \\ [n = 171] \\ \hline FEV_1/FVC ratio & 0.8 (0.1) & 0.8 (0.1) \\ [n = 171] \\ \hline DLCO, mmoL/min/kPa & 3.6 (1.8) \\ [n = 123] & [n = 127] \\ \hline Predicted value, \% & & & \\ \hline FVC & 56.2 (8.9) & 55.2 (10.0) \\ \hline FEV_1 & 61.5 (9.3) & 60.0 (10.6) \\ [n = 171] \\ \hline DLCO & 43.3 (20.2) \\ FEV_1 & 61.5 (9.3) & 60.0 (10.6) \\ [n = 171] \\ \hline DLCO & 43.3 (20.2) \\ median (IQR)^d & & & \\ \hline Medical Research Council dyspnea score, \\ median (IQR)^d & & & \\ \hline Medical Research Council dyspnea score, \\ median (IQR)^d & & & \\ \hline Cough severity score^f & 39.5 (27.5) \\ elicester Cough Questionnaire scores^9 \\ \hline Leicester Cough Questionnaire scores^9 \\ \hline Total & & & 16.1 (3.6) \\ [n = 161] & & & 15.8 (3.7) \\ [n = 164] \\ \hline Physical & & & 5.2 (1.1) \\ Fyclological & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end{tabular}$	Maintenance treatments, No. (%)		
Nintedanib 56 (33.1) 61 (35.5) Prednisolone 12 (7.1) 10 (5.8) N-acetylcysteine 8 (4.7) 7 (4.1) Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^c Absolute value FVC, L 2.2 (0.6) 2.3 (0.5) FEV ₁ , L 1.9 (0.5) 1.9 (0.4) [n = 171] [n = 171] DLCO, mmoL/min/kPa 3.6 (1.8) 3.7 (1.5) [n = 123] [n = 127] Predicted value, % FVC 56.2 (8.9) 55.2 (10.0) FEV ₁ 61.5 (9.3) 60.0 (10.6) [n = 171] [n = 171] DLCO 43.3 (20.2) [n = 123] [n = 127] Outcome measures, mean (SD) [n = 167] [n = 171] DLCO 43.3 (20.2) [n = 163] 2.00 [n = 171] EQ-5D-5L utility score ^e 0.67 (0.20) [n = 168] 0.69 (0.22) [n = 171] EQ-5D-5L utility score ^e 0.67 (0.20) [n = 168] 0.69 (0.22) [n = 168] Leicester Cough Questionnaire scores ⁹ 16.1 (3.6) [n = 161] 15.8 (3.7) [n = 168] Leicester Cough Questionnaire scores ⁹ 16.1 (3.6) [n = 161] 16.61	Proton pump inhibitor	87 (51.5)	78 (45.3)
Instrum If (cris) If (cris) Prednisolone 12 (7.1) 10 (5.8) N-acetylcysteine 8 (4.7) 7 (4.1) Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^c Absolute value FVC, L 2.2 (0.6) 2.3 (0.5) FEV ₁ , L 1.9 (0.5) 1.9 (0.4) [n = 171] Decomposition (n = 171] DLCO, mmoL/min/kPa 3.6 (1.8) [n = 123] 3.7 (1.5) [n = 127] Predicted value, % FVC 56.2 (8.9) 55.2 (10.0) FEV ₁ 61.5 (9.3) [n = 127] 60.0 (10.6) [n = 171] DLCO 43.3 (20.2) [n = 123] [n = 127] Predicted value, % FVC 56.2 (8.9) 55.2 (10.0) [n = 123] [n = 127] Outcome measures, mean (SD) Medical Research Council dyspnea score, median (IQR) ^d 3.0 (2.0-3.0) [n = 127] Outcome measures, mean (SD) So (2.0-3.0) [n = 167] [n = 171] EQ-5D-5L utility score ^e 0.67 (0.20) [n = 168] [n = 171] Equation (IQR) ^d 3.9.5 (27.5) [n = 168] [n = 171] Cough severity score ^f 39.5 (27.5) [n = 168] Leicester Cough Questionnaire scores ⁹ Total [n = 161] [n = 164] [n = 164] [n = 164] Physical 5.2 (1.1) [n	Pirfenidone	71 (42.0)	66 (38.4)
N-acetylcysteine 8 (4.7) 7 (4.1) Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^c Absolute value FVC, L 2.2 (0.6) 2.3 (0.5) FEV ₁ , L 1.9 (0.5) 1.9 (0.4) [n = 171] [n = 171] FEV ₁ , L 0.8 (0.1) 0.8 (0.1) [n = 171] 0.8 (0.1) [n = 171] DLCO, mmoL/min/kPa 3.6 (1.8) [n = 123] 3.7 (1.5) [n = 127] [n = 127] Predicted value, % FVC 56.2 (8.9) 55.2 (10.0) FEV ₁ 61.5 (9.3) 60.0 (10.6) [n = 171] [n = 171] DLCO 43.3 (20.2) (n = 123] 44.5 (18.0) [n = 127] [n = 127] Outcome measures, mean (SD) Medical Research Council dyspnea score, median (IQR) ^d 3.0 (2.0-3.0) [n = 167] 2.00 (2.00-3.00) [n = 171] EQ-5D-5L utility score ^e 0.67 (0.20) [n = 168] 0.69 (0.22) [n = 171] Cough severity score ^f 39.5 (27.5) [n = 168] 40.9 (26.6) [n = 171] Leicester Cough Questionnaire scores ^g 16.1 (3.6) [n = 161] 15.8 (3.7) [n = 168] Leicester Cough Questionnaire scores ^g 16.1 (3.6) [n = 161] 15.8 (3.7) [n = 165]<	Nintedanib	56 (33.1)	61 (35.5)
Other antioxidant 3 (1.8) 5 (2.9) Lung function, mean (SD) ^c Absolute value FVC, L 2.2 (0.6) 2.3 (0.5) FEV ₁ , L 1.9 (0.5) 1.9 (0.4) [n = 171] FEV ₁ /FVC ratio 0.8 (0.1) 0.8 (0.1) [n = 171] DLCO, mmoL/min/kPa 3.6 (1.8) [n = 123] 3.7 (1.5) [n = 127] Predicted value, % FVC 56.2 (8.9) 55.2 (10.0) FEV ₁ 61.5 (9.3) 60.0 (10.6) [n = 171] [n = 171] DLCO 43.3 (20.2) [n = 123] 24.5 (18.0) [n = 127] [n = 171] Outcome measures, mean (SD) Medical Research Council dyspnea score, median (IQR) ^d 3.0 (2.0-3.0) [n = 167] 2.00 (2.00-3.00) [n = 171] EQ-5D-5L utility score ^e 0.67 (0.20) [n = 168] 0.69 (0.22) [n = 168] Leicester Cough Questionnaire scores ^g 3.5 (2.7.5) [n = 167] 40.9 (26.6) [n = 168] Leicester Cough Questionnaire scores ^g 16.1 (3.6) [n = 161] 15.8 (3.7) [n = 164] Physical 5.2 (1.1) [n = 161] 5.1 (1.0) [n = 165] Psychological 5.4 (1.4) 5.3 (1.5)	Prednisolone	12 (7.1)	10 (5.8)
Lung function, mean (SD) ^c Absolute value FVC, L 2.2 (0.6) 2.3 (0.5) FEV ₁ , L 1.9 (0.5) 1.9 (0.4) [n = 171] FEV ₁ /FVC ratio 0.8 (0.1) 0.8 (0.1) [n = 171] DLCO, mmoL/min/kPa 3.6 (1.8) [n = 123] 3.7 (1.5) [n = 127] Predicted value, % FVC 56.2 (8.9) 55.2 (10.0) FEV ₁ 61.5 (9.3) 60.0 (10.6) [n = 171] [n = 171] DLCO 43.3 (20.2) [n = 123] 2.44.5 (18.0) [n = 127] [n = 127] Outcome measures, mean (SD) Medical Research Council dyspnea score, median (IQR) ^d 3.0 (2.0-3.0) [n = 167] 2.00 (2.00-3.00) [n = 171] EQ-5D-5L utility score ^e 0.67 (0.20) [n = 168] 0.69 (0.22) [n = 171] Cough severity score ^f 39.5 (27.5) (n = 168] 40.9 (26.6) [n = 171] Leicester Cough Questionnaire scores ^g 16.1 (3.6) [n = 161] 15.8 (3.7) [n = 164] Physical 5.2 (1.1) [n = 161] 5.1 (1.0) [n = 164] Physical 5.2 (1.1) [n = 165] 5.1 (1.0) [n = 165]	N-acetylcysteine	8 (4.7)	7 (4.1)
Absolute value FVC, L 2.2 (0.6) 2.3 (0.5) FEV ₁ , L 1.9 (0.5) 1.9 (0.4) [n = 171] FEV ₁ /FVC ratio 0.8 (0.1) 0.8 (0.1) [n = 171] DLCO, mmoL/min/kPa 3.6 (1.8) [n = 123] 3.7 (1.5) [n = 127] Predicted value, % 56.2 (8.9) 55.2 (10.0) FVC 56.2 (8.9) 55.2 (10.0) FEV ₁ 61.5 (9.3) 60.0 (10.6) [n = 171] DLCO 43.3 (20.2) [n = 123] 44.5 (18.0) [n = 127] Outcome measures, mean (SD) Medical Research Council dyspnea score, median (IQR) ^d 3.0 (2.0-3.0) [n = 167] 2.00 (2.00-3.00) [n = 171] EQ-5D-5L utility score ^e 0.67 (0.20) [n = 168] 0.69 (0.22) [n = 167] 16.1 (3.6) [n = 171] Cough severity score ^f 39.5 (27.5) [n = 167] 40.9 (26.6) [n = 167] [n = 171] Leicester Cough Questionnaire scores ^g 16.1 (3.6) [n = 161] [n = 164] Physical 5.2 (1.1) [n = 161] 5.1 (1.0) [n = 165] Psychological 5.4 (1.4) 5.3 (1.5)	Other antioxidant	3 (1.8)	5 (2.9)
$\begin{tabular}{ c c c c } \hline FVC, L & 2.2 (0.6) & 2.3 (0.5) \\ \hline FEV_1, L & 1.9 (0.5) & 1.9 (0.4) \\ [n = 171] \\ \hline FEV_1/FVC ratio & 0.8 (0.1) & 0.8 (0.1) \\ [n = 171] \\ \hline DLCO, mmoL/min/kPa & 3.6 (1.8) & 3.7 (1.5) \\ [n = 123] & [n = 127] \\ \hline Predicted value, % \\ \hline FVC & 56.2 (8.9) & 55.2 (10.0) \\ \hline FEV_1 & 61.5 (9.3) & 60.0 (10.6) \\ [n = 171] \\ \hline DLCO & 43.3 (20.2) & 44.5 (18.0) \\ [n = 123] & [n = 127] \\ \hline Outcome measures, mean (SD) \\ \hline Medical Research Council dyspnea score, median (IQR)^d & 3.0 (2.0-3.0) \\ median (IQR)^d & 3.0 (2.0-3.0) & 2.00 \\ [n = 167] & (2.00-3.00) \\ [n = 171] \\ \hline EQ-5D-5L utility score^e & 0.67 (0.20) & 0.69 (0.22) \\ [n = 168] & [n = 171] \\ \hline Cough severity score^f & 39.5 (27.5) & 40.9 (26.6) \\ [n = 167] & [n = 168] \\ \hline Leicester Cough Questionnaire scores^g \\ \hline Total & 16.1 (3.6) & 15.8 (3.7) \\ [n = 161] & [n = 164] \\ \hline Physical & 5.2 (1.1) & 5.1 (1.0) \\ [n = 161] & [n = 165] \\ \hline Psychological & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.4) & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.4) & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.4) & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.4) & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.4) & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.5) & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.5) & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.5) & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.5) & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.5) & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end tabular (1.5) &$	Lung function, mean (SD) ^c		
$\begin{tabular}{ c c c c c } \hline FEV_1, L & 1.9 (0.5) & 1.9 (0.4) \\ [n = 171] \\ \hline FEV_1/FVC ratio & 0.8 (0.1) & 0.8 (0.1) \\ [n = 171] \\ \hline DLCO, mmoL/min/kPa & 3.6 (1.8) & 3.7 (1.5) \\ [n = 123] & [n = 127] \\ \hline Predicted value, % & & & & & & & & & & & & & & & & & & $	Absolute value		
$\begin{tabular}{ c c c c } \hline & & & & & & & & & & & & & & & & & & $	FVC, L	2.2 (0.6)	2.3 (0.5)
$\begin{tabular}{ c c c c } \hline & & & & & & & & & & & & & & & & & & $	FEV ₁ , L	1.9 (0.5)	
$\begin{tabular}{ c c c c c } \hline [n = 123] & [n = 127] \\ \hline [n = 123] & [n = 127] \\ \hline \end{tabular} \$	FEV ₁ /FVC ratio	0.8 (0.1)	[n = 171]
$\begin{tabular}{ c c c c } \hline FVC & 56.2 (8.9) & 55.2 (10.0) \\ \hline FEV_1 & 61.5 (9.3) & 60.0 (10.6) \\ \hline [n = 171] \\ \hline DLCO & 43.3 (20.2) \\ [n = 123] & 44.5 (18.0) \\ [n = 127] \\ \hline \end{tabular} t$	DLCO, mmoL/min/kPa		
$\begin{tabular}{ c c c c c c c } \hline FEV_1 & & & & & & & & & & & & & & & & & & &$			
$\begin{tabular}{ c c c c c } \hline & & & & & & & & & & & & & & & & & & $		56.2 (8.9)	55.2 (10.0)
$\begin{tabular}{ c c c c c } \hline [n = 123] & [n = 127] \\ \hline \mbox{Outcome measures, mean (SD)} \\ \hline \end{tabular} \e$	FEV ₁	61.5 (9.3)	
$\begin{tabular}{ c c c c c } \hline Medical Research Council dyspnea score, \\ median (IQR)^d & 1.0 & 2.00 & (2.00-3.00) & [n = 167] & (2.00-3.00) & [n = 171] & (2.00-3.00) & [n = 167] & [n = 168] & (2.00-3.00) & [n = 171] & (2.00-3.00) & [n = 167] & [n = 168] & (2.00-3.00) & [n = 167] & [n = 168] & (2.00-3.00) & [n = 167] & [n = 168] & (2.00-3.00) & (2.00-3.00) & [n = 161] & [n = 164] & (2.00-3.00) & [n = 161] & [n = 164] & [n = 164] & [n = 165] & [n = 165]$			
$\begin{tabular}{ c c c c c } \hline median (IQR)^d & [n = 167] & (2.00-3.00) \\ [n = 171] \\ \hline EQ-5D-5L utility score^e & 0.67 (0.20) & 0.69 (0.22) \\ [n = 168] & [n = 171] \\ \hline Cough severity score^f & 39.5 (27.5) & 40.9 (26.6) \\ [n = 167] & [n = 168] \\ \hline Leicester Cough Questionnaire scores^g \\ \hline Total & 16.1 (3.6) & 15.8 (3.7) \\ [n = 161] & [n = 164] \\ \hline Physical & 5.2 (1.1) & 5.1 (1.0) \\ [n = 161] & [n = 165] \\ \hline Psychological & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end{tabular}$			
$\begin{tabular}{ c c c c c c } \hline EQ-5D-5L utility score^e & 0.67 (0.20) & 0.69 (0.22) \\ [n = 168] & [n = 171] \\ \hline Cough severity score^f & 39.5 (27.5) & 40.9 (26.6) \\ [n = 167] & [n = 168] \\ \hline Leicester Cough Questionnaire scores^g \\ \hline Total & 16.1 (3.6) & 15.8 (3.7) \\ [n = 161] & [n = 164] \\ \hline Physical & 5.2 (1.1) & 5.1 (1.0) \\ [n = 161] & [n = 165] \\ \hline Psychological & 5.4 (1.4) & 5.3 (1.5) \\ \hline \end{tabular}$	Medical Research Council dyspnea score, median (IQR) ^d		(2.00-3.00)
[n = 167] [n = 168] Leicester Cough Questionnaire scores ⁹ Total 16.1 (3.6) 15.8 (3.7) Physical 5.2 (1.1) [n = 164] [n = 164] Physical 5.2 (1.1) 5.1 (1.0) [n = 165] Psychological 5.4 (1.4) 5.3 (1.5)	EQ-5D-5L utility score ^e		0.69 (0.22)
Total 16.1 (3.6) [n = 161] 15.8 (3.7) [n = 164] Physical 5.2 (1.1) [n = 161] 5.1 (1.0) [n = 161] Psychological 5.4 (1.4) 5.3 (1.5)	Cough severity score ^f	39.5 (27.5)	40.9 (26.6)
[n = 161] [n = 164] Physical 5.2 (1.1) 5.1 (1.0) [n = 161] [n = 165] Psychological 5.4 (1.4) 5.3 (1.5)	Leicester Cough Questionnaire scores ⁹		
[n = 161] [n = 165] Psychological 5.4 (1.4) 5.3 (1.5)	Total		
	Physical		
	Psychological		
Social 5.4 (1.4) 5.4 (1.4) [n = 167] [n = 168]	Social		

(continued)

Table 1. Baseline Characteristics of Participants in a Study of the Effect of Co-trimoxazole vs Placebo on Death, Lung Transplant, or Hospital Admission in Patients With Idiopathic Pulmonary Fibrosis (continued)

Ch	naracteristic	Co-trimoxazole (n = 169ª)	Placebo (n = 172ª)
King's Brief Interstitial Lung Disease questionnaire scores ^h		(n = 168)	(n = 171)
	Total	53.7 (9.7)	53.6 (10.6)
	Breathlessness	37.7 (15.3)	38.9 (14.3)
	Chest	62.9 (20.8)	62.6 (20.7)
	Psychological	55.2 (14.9)	54.9 (17.1)

Abbreviations: DLCO, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; IQR, interquartile range.

^a These data exclude the individual who was excluded after randomization.

^b Comorbidities were as detailed in the medical records.

^c The lung function test values were obtained at screening.

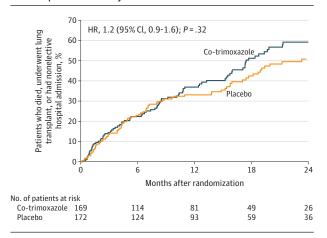
- ^d Medical Research Council dyspnea score is a 5-point scale ranging from 1 to 5 (higher values represent increasing breathlessness); a value of 3 represents walking slower than contemporaries or having to stop when walking at own pace.
- ^e The 5-level Euroqol 5-dimension questionnaire (EQ-5D-5L) utility score ranges from -0.59 to 1 (higher score indicates better health utility); a value of 0.75 indicates that the quality of life-adjusted years has been reduced by a slight amount. Utilities are calculated by mapping to standard health state valuations.
- ^f The cough severity score is a cough severity visual analog scale ranging from 0 to 100 (higher scores represent greater cough severity); a value of 40 indicates that coughing is two-fifths of the maximum perceived cough severity.
- ^g The Leicester Cough Questionnaire is a cough-related quality of life score that ranges from 3 to 21 (domain scores range from 1-7; higher values represent better quality of life); a value of 15 suggests a cough that has affected life activities a small amount of the time over the past 2 weeks. It is calculated as the sum of the individual domains.

^h The King's Brief Interstitial Lung Disease questionnaire total and domain scores range from 0 to 100 (higher values indicate better health status); a value of 50 indicates that idiopathic pulmonary fibrosis has affected life activities some of the time over the past 2 weeks. It is calculated using the logit-scoring method.

robust cluster variance was used. The proportionality assumption was assessed using the global test with Schoenfeld residual. This had a test statistic of 1.58 and a P value of .45, thus providing no evidence that the assumption was violated. The results are presented as the Kaplan-Meier estimate with median time to outcome. The EQ-5D-5L was converted to utilities by mapping to standard health state valuations²³ and the K-BILD was calculated using the logit-scoring method.²⁴ The MRC dyspnea score was analyzed using a Mann-Whitney test at 12 months; other questionnaires and lung function measurements were analyzed using linear mixed models to compare the mean values at 12 months between the treatment and placebo groups, adjusted for licensed IPF medication use as a fixed effect and site as a random effect. A repeated-measures model was fitted for each outcome at all time points with a fixed term for licensed IPF medication, randomization group, and time, and random effects were included for site and the person identification number. For this analysis, the significance of the between-group difference at each time point was adjusted using a Bonferroni correction.

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Figure 2. Primary End Point in a Study of the Effect of Co-trimoxazole vs Placebo on Death, Lung Transplant, or Hospital Admission in Patients With Idiopathic Pulmonary Fibrosis



Kaplan-Meier estimates for time to event for the primary end point (death [all causes], lung transplant, or first nonelective hospital admission), analyzed according to the group to which participants were randomized. There was no significant difference between the co-trimoxazole and placebo groups. Median (interquartile range) follow-up was 12.0 (4.4-21.0) months.

All analyses were 2-sided at the 5% level of significance and were undertaken as prespecified, including all participants analyzed in the group to which they were randomized. Additionally, prespecified per-protocol (≥80% adherence to study medication) and modified per-protocol (those who adhered to the high-dose regimen) analyses were done.

The missing end points at 12 months were imputed using the iterative chained equations approach.²⁵ The outcomes at 12 months and baseline were included in the equations, along with randomization group, body mass index, and sex. Because the rate of missing data was high, a total of 45 imputations were created and the results model estimates combined using Rubin equations. The analysis was conducted using Stata/MP, version 16. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. The model assumptions were assessed visually by plotting the residuals, which were all approximately normally distributed.

The adverse event analysis was based on all patients who received at least 1 dose of the study drug or placebo. Data were analyzed for event rates and percentage of patients with at least 1 adverse event and were coded according to the Medical Dictionary for Regulatory Activities. Safety blood measures were compared at 12 months.

Results

A total of 1305 participants were screened at 43 sites; 349 met the inclusion criteria and 342 were randomized from 39 sites (Figure 1). One participant randomized to the intervention (co-trimoxazole) group was randomized in error and their data were not analyzed. Fifty-eight individuals (17%) withdrew from the study during follow-up without meeting an end point: 32 (19%) from the co-trimoxazole group (21 [12%] in the first 12 months) and 26 (15%) from the placebo group (16 [9%] in the first 12 months); their data are included until the point of with-drawal. A total follow-up of 395 person-years was assessed. The mean (SD) patient age was 71.3 (7.5) years, with a mean FVC of 2.25 (0.56) L or 55.7% (9.4%) predicted. Baseline characteristics and other factors were balanced between the 2 treatment groups, aside from sex and the presence of diabetes (Table 1).

The mean (SD) percentage of adherence in the co-trimoxazole group was 81.4% (22.8%), compared with 85.5% (21.7%) in the control (placebo) group. The number of participants who met the 80% treatment threshold was 120 of 167 (71.9%) in the co-trimoxazole group compared with 124 of 172 (72.1%) in the placebo group. Dose reduction occurred in 31 of 167 patients (19%) in the co-trimoxazole group and 16 of 172 (9%) in the placebo group (eTable 1 in Supplement 3).

Primary Outcome

A total of 164 primary outcome events occurred (**Figure 2**). The incidence of events was 0.45 (84/186) per person-year in the co-trimoxazole group and 0.38 (80/209) per person-year in the placebo group (HR, 1.2 [95% CI, 0.9-1.6] for the unadjusted and adjusted analyses). The median (interquartile range) survival was 1.45 (1.28-1.78) years in the co-trimoxazole group and 1.94 (1.48-2.84) years in the placebo group. The site could not be included in this model due to model instability; a robust variance method gave an HR of 1.2 ([95% CI, 0.8-1.6]; P = .37), and an HR of 1.2 ([95% CI, 0.9-1.7]; P = .24) with stratification. There were no statistically significant differences between the groups for the perprotocol or modified per-protocol analyses for event out-comes (eTable 2 in Supplement 3).

Secondary Outcomes

The individual components of the primary outcome are shown in Figure 2 and eTable 2 in **Supplement 3**. There was no statistically significant difference in all-cause mortality (HR, 1.5 [95% CI, 0.8-2.8]; P = .17), respiratory-related death (HR, 1.4 [95% CI, 0.7-2.6]; P = .34), all-cause hospitalization (HR, 1.1 [95% CI, 0.7-1.5]; P = .75), or respiratory-related hospitalization (HR, 1.0 [95% CI, 0.7-1.6]; P = .83) between the 2 groups. There were no statistically significant differences between the 2 groups for the per-protocol or modified per-protocol analyses for event outcomes (eTable 2 in Supplement 3).

There was no statistically significant differences between the groups for the lung function or patient-reported outcomes (**Table 2**). In the per-protocol analysis there were no statistically significant differences between the co-trimoxazole or placebo groups for the lung function measurements or the patient-reported outcomes, other than for the chest domain of the K-BILD (adjusted and unadjusted analysis) and physiological and social domains of the LCQ (unadjusted analysis), which favored co-trimoxazole (eTable 3 in Supplement 3). The modified per-protocol analysis is shown in eTable 4 in Supplement 3.

	Mean (SD) ^a		Adjusted for site and baseline antifibrotic therapy		Adjusted for site, baseline antifibrotic therapy and baseline value	
Outcome	Co-trimoxazole	Placebo	Mean difference (95% CI)	P value	Mean difference (95% CI)	P value
Lung function						
Absolute value						
FVC, L	2.26 (0.53) [n = 63]	2.23 (0.51) [n = 77]	-0.02 (-0.19 to 0.15)	.81	-0.01 (-0.09 to 0.07)	.80
FEV ₁ , L	1.86 (0.43) [n = 63]	1.86 (0.42) [n = 77]	0 (-0.14 to 0.14)	>.99	-0.02 (-0.08 to 0.05)	.62
DLCO, mmoL/min/kPa	3.49 (1.75) [n = 50]	3.71 (1.50) [n = 60]	0.19 (-0.39 to 0.77	.51	0.3 (-0.26 to 0.85)	.30
Predicted value, %						
FVC	54.0 (8.9) [n = 63]	53.6 (9.1) [n = 77]	-0.5 (-3.56 to 2.47)	.72	-0.6 (-2.6 to 1.5)	.59
FEV ₁	57.8 (9.7) [n = 63]	58.2 (10.4) [n = 77]	0.2 (-3.2 to 3.6	.93	-0.7 (-2.8 to 1.5)	.55
DLCO	40.2 (17.7) [n = 50]	43.2 (16.3) [n = 60]	2.5 (-3.7 to 8.7)	.43	3.9 (-2.4 to 10.3)	.22
Medical Research Council dyspnea score, median (IQR) ^b	3.0 (2.0-4.0) [n = 72]	3.0 (2.0-4.0) [n = 86]		.94		.29
EQ-5D-5L utility score ^c	0.41 (0.36) [n = 103]	0.45 (0.35) [n = 118]	0.04 (-0.05 to 0.13)	.37	0.03 (-0.06 to 0.11)	.55
Cough severity score ^d	44.7 (27.0) [n = 72]	49.7 (26.7) [n = 84]	5.1 (-3.4 to 13.6)	.24	2.2 (-5.4 to 9.9)	.57
Leicester Cough Question	nnaire scores ^e					
Total	15.4 (4.09) [n = 69]	14.6 (4.0) [n = 71]	-0.8 (-2.1 to 0.6)	.27	-0.6 (-1.6 to 0.4)	.22
Physical	4.9 (1.2) [n = 69]	4.7 (1.2) [n = 72]	-0.2 (-0.6 to 0.2)	.36	-0.1 (-0.4 to 0.2)	.43
Psychological	5.2 (1.4) [n = 69]	4.9 (1.5) [n = 75]	-0.3 (-0.8 to 0.2)	.25	-0.3 (-0.6 to 0.1)	.17
Social	5.3 (1.5) [n = 69]	5.0 (1.5) [n = 75]	-0.3 (-0.8 to 0.2)	.28	-0.2 (-0.6 to 0.1)	.20
King's Brief Interstitial Lu	ung Disease questionnaire	scores ^f				
Total	50.3 (12.3) [n = 71]	50.7 (11.20) [n = 85]	0.4 (-3.3 to 4.1)	.83	0.1 (-2.8 to 3.0)	.93
Breathlessness	34.4 (17.4) [n = 72]	35.0 (14.55) [n = 86]	0.9 (-4.1 to 5.9)	.73	-0.5 (-4.4 to 3.3)	.79
Chest	59.9 (20.3) [n = 72]	56.8 (22.82) [n = 86]	-3.4 (-10.2 to 3.4)	.33	-2.0 (-7.8 to 3.8)	.50
Psychological	49.7 (17.9) [n = 71]	51.9 (16.9) [n = 85]	2.0 (-3.5 to 7.5)	.48	1.5 (-3.0 to 5.9)	.53

Table 2. Secondary Outcomes at 12 Months in a Study of the Effect of Co-trimoxazole vs Placebo on Patients With Idiopathic Pulmonary Fibrosis

Abbreviations: DLCO, diffusing capacity for carbon monoxide; FEV_1 , forced expiratory volume in the first second of expiration; FVC, forced vital capacity; IQR, interquartile range.

^a Data were incomplete for some patients because they did not complete the questionnaires or attend lung function assessments.

- ^b Medical Research Council dyspnea score is a 5-point scale ranging from 1 to 5 (higher values represent increasing breathlessness); a value of 3 represents walking slower than contemporaries or having to stop when walking at own pace.
- ^c eThe 5-level Euroqol 5-dimension questionnaire (EQ-5D-5L) utility score ranges from -0.59 to 1 (higher scores indicate better health utility); a value of 0.75 indicates that the quality of life-adjusted years has been reduced by a slight amount. Utilities are calculated by mapping to standard health state valuations.

^d The cough severity score is a cough severity visual analog scale ranging from 0 to 100 (higher score represents greater cough severity); a value of 40 indicates that coughing is two-fifths of the maximum perceived cough severity.

^e The Leicester Cough Questionnaire is a cough-related quality of life score that ranges from 3 to 21 (domain scores range from 1-7; higher values represent better quality of life); a value of 15 suggests a cough that has affected life activities a small amount of the time over the past 2 weeks. It is calculated as the sum of the individual domains.

^f The King's Brief Interstitial Lung Disease questionnaire total and domain scores range from 0 to 100 (higher values represent better health status); a value of 50 indicates that idiopathic pulmonary fibrosis has affected life activities some of the time over the past 2 weeks. It is calculated using the logit-scoring method.

When reviewing the data at all time points, there was a statistically significant (P = .02) difference in cough severity score (15.0 [95% CI, 1.2-28.8]) at 18 months in favor of the cotrimoxazole group and, overall, the differential between the groups was statistically significant (P = .04) with a mean difference of 5.7 (95% CI, 0.1-11.2) (eTable 5 in Supplement 3). There were no statistically significant differences for the LCQ and K-BILD total or subdomain scores, MRC score, or lung function measurements between the groups, and no overall treatment effect.

Adverse Events

There were 696 adverse events (20 serious adverse events) in the co-trimoxazole group and 640 (17 serious adverse events) in the placebo group (**Table 3**). There were more reports of nausea in the co-trimoxazole group compared with the placebo group (89/157 vs 67/163), whereas diarrhea was reported more frequently in the placebo group (52/157 vs 84/163). There were more episodes of hyperkalemia (24/157 vs 14/163), vomiting (28/157 vs 20/163), and rash (31/157 vs 20/163) in the cotrimoxazole group than the placebo group (Table 3; eTable 6 in Supplement 3). There was no difference in the 12-month safety blood analysis between the groups (eTable 7 in Supplement 3) aside from creatinine, which was statistically significantly higher in the co-trimoxazole group.

Seventeen sputum samples and 1 nasal swab were obtained in total for all patient visits. Three of these grew possible relevant microbiological agents on culture: *Staphylococcus aureus* (n = 1), *Haemophilus influenzae* (n = 1), and "yeasts" (n = 1).

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Table 3. Adverse Events in a Study of the Effect of Co-trimoxazole vs Placebo on Death, Lung Transplant, or Hospital Admission in Patients With Idiopathic Pulmonary Fibrosis

	No. of events		
Adverse event ^a	Co-trimoxazole	Placebo	
Blood and lymphatic system disorders	3	3	
Cardiac disorders	6	4	
Ear and labyrinth disorders	3	0	
Eye disorders	5	6	
Gastrointestinal disorders	216	224	
Nausea	89	67	
Diarrhea	52	84	
Vomiting	28	20	
Constipation	11	5	
General disorders and administration site conditions	36	20	
Fatigue	15	11	
Chest pain	8	6	
Edema peripheral	5	0	
Immune system disorders	1	1	
Infections and infestations	110	127	
Lower respiratory tract infection	63	66	
Injury, poisoning, and procedural complications	7	10	
Investigations ^b	44	22	
Weight decrease	24	16	
Metabolism and nutrition disorders	57	27	
Decreased appetite	26	9	
Hyperkalemia ^c	24	14	
Musculoskeletal and connective tissue disorders	21	20	
Neoplasm/s benign, malignant, and unspecified (including cysts and polyps)	3	1	
Nervous system disorders	41	32	
Headache	22	14	
Psychiatric disorders	5	2	
Kidney and urinary disorders	14	7	
Reproductive system and breast disorders	0	2	
Respiratory, thoracic, and mediastinal disorders	77	95	
Cough	27	33	
Dyspnea	31	34	
Skin and subcutaneous tissue disorders	46	30	
Rash	31	20	
Surgical and medical procedures	1	2	
Vascular disorders	0	5	
Total adverse events	696	640	
≥1 adverse event, No. (%)	146 (86)	142 (83)	
≥2 adverse events, No. (%)	119 (70)	121 (70)	

^a Adverse events were captured at each study visit and coded using Medical Dictionary for Regulatory Activities terms.

^b Investigations include abnormal laboratory results and weight change.

^c Hyperkalemia was defined as a potassium greater than 5.0 mmol/L.

Discussion

In this double-blind, randomized, placebo-controlled trial, there was no significant reduction in the incidence of the composite outcome of death, lung transplant, or nonelective hospitalization with co-trimoxazole in patients with moderate or severe IPF.

In contrast to the previous smaller study that compared co-trimoxazole with placebo in patients with IPF,¹³ there was no reduction in mortality with co-trimoxazole. In this previous study, nearly 60% of patients were taking prednisolone (mostly at a high dose) and 30% were taking azathioprine, whereas in the current trial, those receiving immunosuppression other than low-dose corticosteroids (6% of individuals) were excluded. It is therefore plausible that, in the previous study,¹³ co-trimoxazole prevented infection-related adverse outcomes that were contingent on immunosuppression, which is known to result in poor outcomes in IPF.²⁶ Furthermore, antifibrotic therapy (pirfenidone and nintedanib) was not available at the time of the previous study,13 whereas 75% of patients in the current study were receiving this treatment. Pirfenidone, for example, has been estimated to improve IPF life expectancy by 2.47 years.²⁷ Overall, the changes between the 2 studies resulted in a doubling of the hospital-free survival (mean of 23.3 months vs 12.8 months). In addition, inclusion in the current study was restricted to people with moderate to severe IPF, as defined by FVC less than or equal to 75% predicted, whereas no such restriction pertained in the previous study. However, it is unlikely that co-trimoxazole would have been more effective in a less severe population with better lung function (FVC >75% predicted), because there was no subgroup effect of baseline disease severity in the previous study¹³ and neither bacterial burden²⁸ nor response to antifibrotic therapy^{29,30} is known to be related to FVC in IPF.

The benefit of co-trimoxazole in terms of the cough severity score, LCQ, and the chest symptom domain of the K-BILD questionnaire (which captures chest tightness, air hunger, and wheeze) only met clinically relevant thresholds at 18 months, but support the previously identified clinical benefit of co-trimoxazole13 in respect to the "symptom" domain of the St George's Respiratory Questionnaire³¹ (which captures cough, sputum, breathlessness, and wheeze). However, given the null primary outcome results and large number of secondary outcomes, the findings for cough should be considered only hypothesis-generating.

The results of this study do not disprove the hypothesis that the "lung microbiome" influences disease progression and outcomes in IPF.^{7,9,28} A potential antibacterial benefit of cotrimoxazole may have been lost owing to widespread bacterial resistance, despite in-therapy selection of resistance being rare for co-trimoxazole³² and acquired resistance, while not uncommon, is unlikely to have been so universal as to overwhelm a positive effect. Furthermore, the possibility of an unrecognized IPF-associated co-trimoxazole-resistant pathogen cannot be entirely dismissed, although there is no evidence to support such a hypothesis; an ongoing randomized openlabel trial of co-trimoxazole or doxycycline vs standard care may provide further insight.³³ However, a study of explanted lungs yielded very few bacterial 16S rRNA gene reads in the IPF interstitium compared with the airways of patients with IPF and healthy control patients. It is therefore possible that airway and lung tissue compartments are separate in IPF with different microbiota.³⁴

This was an adequately powered, multicenter, academic clinical trial using a clinically relevant outcome with high follow-up rates and long timescales. A total of 342 individuals were recruited and evaluated from 39 geographically diverse sites of varying sizes for up to 3 years. The primary end point included unplanned hospital admission, which is financially and socially costly with a high frequency of death, and all-cause mortality, which is the most clinically meaningful primary end point.³⁵ The study was aligned to clinical care, minimizing the research burden for patients. The event rate (164 events) was higher than anticipated (99 events), so the study likely had adequate power to detect a meaningful difference in the primary end point.

Limitations

This study has several limitations. First, there was a lack of evaluation of the lung microbiome or quantitation of the influence that co-trimoxazole had on its composition and ecology, including antimicrobial resistance. However, given the lack of efficacy, it is questionable whether any such analysis would have been clinically meaningful. Second, it is not possible to determine whether co-trimoxazole reduced infectionrelated events, because the numbers of respiratory tract infections were not captured; rather, "respiratory-related" events were assessed, encompassing all events related to the respiratory system. Assessing whether respiratory infection is present during acute exacerbations or other clinical settings is challenging.³⁶ Third, a protocol exclusion was allergy to cotrimoxazole and, although few people were reported to have this allergy, this exclusion criteria and the FVC criteria may have limited the generalizability of the study. Fourth, the entry criteria were modified by removing the exclusion of participants given diagnoses more than 2 years before randomization as well as increasing the permitted FVC predicted value from 70% to 75%. Fifth, the statistical analysis plan did not include adjustment for gastroesophageal reflux disease or proton pump inhibitor usage; however, the occurrences of these were similar in both groups, and an exploratory post hoc analysis adjusting for these variables did not change the conclusion of the study.

Conclusions

Among patients with moderate or severe IPF, treatment with oral co-trimoxazole did not reduce a composite outcome of time to death, lung transplant, or nonelective hospitalization compared with placebo.

ARTICLE INFORMATION

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REFERENCES

1. Guenther A, Krauss E, Tello S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. *Respir Res*. 2018;19(1):141. doi:10.1186/ s12931-018-0845-5

2. Navaratnam V, Fleming KM, West J, et al. The rising incidence of idiopathic pulmonary fibrosis in the UK. *Thorax.* 2011;66(6):462-467. doi:10.1136/thx.2010.148031

3. Atkins CP, Loke YK, Wilson AM. Outcomes in idiopathic pulmonary fibrosis: a meta-analysis from placebo controlled trials. *Respir Med*. 2014;108(2): 376-387. doi:10.1016/j.rmed.2013.11.007

4. Richter AG, Stockley RA, Harper L, Thickett DR. Pulmonary infection in Wegener granulomatosis and idiopathic pulmonary fibrosis. *Thorax*. 2009; 64(8):692-697. doi:10.1136/thx.2008.110445

5. Vidal S, de la Horra C, Martín J, et al. Pneumocystis jirovecii colonisation in patients with interstitial lung disease. *Clin Microbiol Infect*. 2006;12(3):231-235. doi:10.1111/j.1469-0691.2005. 01337.x **6**. Garzoni C, Brugger SD, Qi W, et al. Microbial communities in the respiratory tract of patients with interstitial lung disease. *Thorax*. 2013;68(12): 1150-1156. doi:10.1136/thoraxjnl-2012-202917

7. Molyneaux PL, Cox MJ, Willis-Owen SA, et al. The role of bacteria in the pathogenesis and progression of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2014;190(8):906-913. doi:10. 1164/rccm.201403-05410C

8. Hilty M, Burke C, Pedro H, et al. Disordered microbial communities in asthmatic airways. *PLoS One*. 2010;5(1):e8578. doi:10.1371/journal.pone. 0008578

9. Han MK, Zhou Y, Murray S, et al; COMET Investigators. Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study. *Lancet Respir Med*. 2014l;2(7):548-556. doi:10.1016/S2213-2600(14) 70069-4

10. Savici D, Campbell PA, King TE Jr. Bronchoalveolar macrophages from patients with idiopathic pulmonary fibrosis are unable to kill facultative intracellular bacteria. *Am Rev Respir Dis.* 1989;139(1):22-27. doi:10.1164/ajrccm/139.1.22

11. Samara KD, Antoniou KM, Karagiannis K, et al. Expression profiles of Toll-like receptors in non-small cell lung cancer and idiopathic pulmonary fibrosis. *Int J Oncol.* 2012;40(5):1397-1404. doi:10. 3892/ijo.2012.1374

12. Varney VA, Parnell HM, Salisbury DT, Ratnatheepan S, Tayar RB. A double blind randomised placebo controlled pilot study of oral co-trimoxazole in advanced fibrotic lung disease. *Pulm Pharmacol Ther*. 2008;21(1):178-187. doi:10. 1016/j.pupt.2007.02.001

13. Shulgina L, Cahn AP, Chilvers ER, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. *Thorax.* 2013;68(2):155-162. doi:10.1136/thoraxjnl-2012-202403

14. Wilson EC, Shulgina L, Cahn AP, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: an economic evaluation alongside a randomised controlled trial. *Pharmacoeconomics*. 2014;32(1):87-99. doi:10.1007/s40273-013-0112-z

15. Hammond M, Clark AB, Cahn AP, et al. The efficacy and mechanism evaluation of treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole (EME-TIPAC): study protocol for a randomised controlled trial. *Trials*. 2018;19(1):89. doi:10.1186/s13063-018-2453-6

16. Raghu G, Collard HR, Egan JJ, et al; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 2011;183 (6):788-824. doi:10.1164/rccm.2009-040GL

17. Miller MR, Hankinson J, Brusasco V, et al; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338. doi:10.1183/ 09031936.05.00034805

18. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26(4):720-735. doi:10.1183/09031936.05. 00034905

19. Manali ED, Lyberopoulos P, Triantafillidou C, et al. MRC chronic Dyspnea Scale: relationships

with cardiopulmonary exercise testing and 6-minute walk test in idiopathic pulmonary fibrosis patients: a prospective study. *BMC Pulm Med*. 2010; 10:32. doi:10.1186/1471-2466-10-32

20. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011;20(10):1727-1736. doi:10.1007/s11136-011-9903-x

21. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax.* 2003;58(4):339-343. doi:10.1136/thorax.58.4.339

22. Patel AS, Siegert RJ, Brignall K, et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. *Thorax*. 2012;67(9):804-810. doi:10. 1136/thoraxjnl-2012-201581

23. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15(5):708-715. doi:10.1016/j.jval.2012.02.008

24. Sinha A, Patel AS, Siegert RJ, et al. The King's Brief Interstitial Lung Disease (KBILD) questionnaire: an updated minimal clinically important difference. *BMJ Open Respir Res.* 2019;6 (1):e000363. doi:10.1136/bmjresp-2018-000363

25. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med.* 2011;30(4):377-399. doi:10.1002/sim.4067

26. Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ; Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med*. 2012;366(21):1968-1977. doi:10.1056/ NEJMoa1113354

27. Fisher M, Nathan SD, Hill C, et al. Predicting life expectancy for pirfenidone in idiopathic pulmonary fibrosis. *J Manag Care Spec Pharm*. 2017;23(3-b Suppl):S17-S24. doi:10.18553/jmcp.2017.23.3-b.s17

28. Invernizzi R, Barnett J, Rawal B, et al. Bacterial burden in the lower airways predicts disease progression in idiopathic pulmonary fibrosis and is independent of radiological disease extent. *Eur Respir J*. 2020;55(4):1901519. doi:10.1183/ 13993003.01519-2019

29. Nathan SD, Costabel U, Albera C, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment. *Respir Med.* 2019;153:44-51. doi:10. 1016/j.rmed.2019.04.016

30. Noble PW, Albera C, Bradford WZ, et al; CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011;377(9779):1760-1769. doi:10.1016/S0140-6736(11)60405-4

31. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *Am Rev Respir Dis*. 1992; 145(6):1321-1327. doi:10.1164/ajrccm/145.6.1321 **32.** Lacey RW, Lord VL, Gunasekera HK, Leiberman PJ, Luxton DE. Comparison of trimethoprim alone with trimethoprim sulphamethoxazole in the treatment of respiratory and urinary infections with particular reference to selection of trimethoprim resistance. *Lancet.* 1980;1(8181):1270-1273. doi:10. 1016/S0140-6736(80)91732-8

33. Anstrom KJ, Noth I, Flaherty KR, et al; CleanUP-IPF Study Team. Design and rationale of a multi-center, pragmatic, open-label randomized trial of antimicrobial therapy: the study of clinical efficacy of antimicrobial therapy strategy using pragmatic design in idiopathic pulmonary fibrosis (CleanUP-IPF) clinical trial. *Respir Res.* 2020;21(1): 68. doi:10.1186/s12931-020-1326-1

34. Jenkins G. A big beautiful wall against infection. *Thorax*. 2018;73(5):485. doi:10.1136/thoraxjnl-2017-211220

35. Wells AU, Behr J, Costabel U, Cottin V, Poletti V, Richeldi L; European IPF Consensus Group. Hot of the breath: mortality as a primary end-point in IPF treatment trials: the best is the enemy of the good. *Thorax*. 2012;67(11):938-940. doi:10.1136/thoraxjnl-2012-202580

36. Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis: an international working group report. *Am J Respir Crit Care Med*. 2016;194(3):265-275. doi:10.1164/rccm. 201604-0801CI