

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis: Executive Summary An Update of the 2011 Clinical Practice Guideline

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This guideline is dedicated to the memory of Mr. William Cunningham (June 7, 1935–October 23, 2014)

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS, MAY 2015, THE EUROPEAN RESPIRATORY SOCIETY (ERS), APRIL 2015, THE JAPANESE RESPIRATORY SOCIETY (JRS), APRIL 2015, AND THE LATIN AMERICAN THORACIC ASSOCIATION (ALAT), APRIL 2015

Background: This document updates the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guideline on idiopathic pulmonary fibrosis treatment.

Methods: Systematic reviews and, when appropriate, meta-analyses were performed to summarize all available evidence pertinent to our questions. The evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach and then discussed by a multidisciplinary panel. Predetermined conflict-of-interest management strategies were

applied, and recommendations were formulated, written, and graded exclusively by the nonconflicted panelists.

Results: After considering the confidence in effect estimates, the importance of outcomes studied, desirable and undesirable consequences of treatment, cost, feasibility, acceptability of the intervention, and implications to health equity, recommendations were made for or against specific treatment interventions.

Conclusions: The panel formulated and provided the rationale for recommendations in favor of or against treatment interventions for idiopathic pulmonary fibrosis.

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Editor's Note

*Mr. William Cunningham's active participation in the development of this guideline and his invaluable input were greatly appreciated and respected by the entire committee. Mr. Cunningham, having suffered from idiopathic pulmonary fibrosis for many years, was confronted directly with the issues related to managing the condition. The authors strongly believe that his objective, balanced, and in-depth participation as a patient strengthens the guideline's significance and applicability.

This Executive Summary is part of the full official ATS/ERS/JRS/ALAT document, which readers may access online at <http://www.atsjournals.org/doi/abs/10.1164/rccm.201506-1063ST>. Only the Executive Summary is appearing in the print edition of the *Journal*. The article of record, and the one that should be cited, is: An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis: an update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med* 2015;192:e3–e19. Available at <http://www.atsjournals.org/doi/abs/10.1164/rccm.201506-1063ST>

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Overview

The purpose of this guideline is to analyze evidence reported since publication of the prior guideline in 2011 and to update the treatment recommendations accordingly. The guideline should empower clinicians to interpret these recommendations in the context of individual patient values and preferences and to make appropriate clinical decisions about treatment of patients with idiopathic pulmonary fibrosis (IPF). For each recommendation, both the summary of evidence discussed by the nonconflicted members of the committee and the related remarks for each specific treatment question, including the values and preferences, should be considered before applying these recommendations to specific clinical situations or policy decisions.

Clinicians, patients, third-party payers, and other stakeholders should never view these recommendations as absolute. No guideline or recommendations can take into account all of the often compelling unique individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from this guideline by rote or in a blanket fashion. The implications of the strength of the

recommendation for various stakeholders are described in Table 1.

This guideline does not provide recommendations for one treatment regimen over another. With the exception of the recommendation against using prednisone with azathioprine and N-acetylcysteine, the guideline does not provide suggestions for or against combination regimens or sequential therapies. Therefore, the strong or conditional rating for each recommendation must be weighed individually (i.e., two recommendations with the same strong or conditional rating should not by default be considered equivalent recommendations), factoring in all components used to determine the grade of the recommendation, including the confidence in effect estimates, outcomes studies, desirable and undesirable consequences of treatment, cost of treatment, implications of treatment on health equity, and feasibility of treatment. The methods used by guideline panels to appraise the evidence are different than those used by regulatory agencies when they review applications seeking market approval for the use of pharmacologic agents for treatment of IPF.

The following recommendations are new or revised from the 2011 guideline, as shown in Table 2:

Table 1. Interpretation of Strong and Conditional Recommendations for Stakeholders (Patients, Clinicians, and Health Care Policy Makers)

Implications for:	Strong Recommendation	Conditional Recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

1. The recommendation against the use of the following agents for the treatment of IPF is strong:

- a. Anticoagulation (warfarin) (⊕⊕⊕⊖, low confidence in effect estimates).
- b. Imatinib, a selective tyrosine kinase inhibitor against platelet-derived growth factor (PDGF) receptors (⊕⊕⊕⊖, moderate confidence in effect estimates).
- c. Combination prednisone, azathioprine, and N-acetylcysteine (⊕⊕⊕⊖, low confidence in effect estimates).
- d. Selective endothelin receptor antagonist (ambrisentan) (⊕⊕⊕⊖, low confidence in effect estimates).

2. The recommendation for the use of the following agents for the treatment of IPF is conditional:

- a. Nintedanib, a tyrosine kinase inhibitor that targets multiple tyrosine kinases, including vascular endothelial growth factor, fibroblast growth factor, and PDGF receptors (⊕⊕⊕⊖, moderate confidence in effect estimates).
- b. Pirfenidone (⊕⊕⊕⊖, moderate confidence in effect estimates).

3. The recommendation against the use of the following agents for the treatment of IPF is conditional:

- a. Phosphodiesterase-5 inhibitor (sildenafil) (⊕⊕⊕⊖, moderate confidence in effect estimates).
- b. Dual endothelin receptor antagonists (macitentan, bosentan) (⊕⊕⊕⊖, low confidence in effect estimates).

The following recommendations are unchanged from the 2011 guideline (Table 2):

- 1. Updated evidence syntheses related to N-acetylcysteine monotherapy and antacid therapy were presented to the panel, and both recommendations were left unchanged from the 2011 guideline (a conditional recommendation against N-acetylcysteine monotherapy based on low confidence in effect estimate and a conditional recommendation for antacid therapy based on very low confidence in effect estimate).
- 2. An updated evidence synthesis related to the treatment of pulmonary hypertension associated with IPF was also presented to the panel, but decisions regarding modifying the recommendation from the 2011 guideline were deferred until the next update.

Table 2. Comparison of Recommendations in the 2015 and 2011 Idiopathic Pulmonary Fibrosis Guidelines

Agent	2015 Guideline	2011 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Strong recommendation against use*	Conditional recommendation against use [‡]
Combination prednisone + azathioprine + N-acetylcysteine	Strong recommendation against use [†]	Conditional recommendation against use [‡]
Selective endothelin receptor antagonist (ambrisentan)	Strong recommendation against use [†]	Not addressed
Imatinib, a tyrosine kinase inhibitor with one target	Strong recommendation against use*	Not addressed
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Conditional recommendation for use*	Not addressed
Pirfenidone	Conditional recommendation for use*	Conditional recommendation against use [‡]
Dual endothelin receptor antagonists (macitentan, bosentan)	Conditional recommendation against use [†]	Strong recommendation against use*
Phosphodiesterase-5 inhibitor (Sildenafil)	Conditional recommendation against use*	Not addressed
Unchanged recommendations		
Antacid therapy	Conditional recommendation for use [‡]	Conditional recommendation for use [‡]
N-acetylcysteine monotherapy	Conditional recommendation against use [†]	Conditional recommendation against use [‡]
Anti-pulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Reassessment of the previous recommendation was deferred	Conditional recommendation against use [‡]
Lung transplantation: single vs. bilateral lung transplantation	Formulation of a recommendation for single vs. bilateral lung transplantation was deferred	Not addressed

*⊕⊕⊕⊕, moderate confidence in effect estimates.

†⊕⊕⊕⊖, low confidence in effect estimates.

‡⊕⊕⊖⊖, very low confidence in effect estimates.

3. Recommendations for multiple other interventions that were addressed in the 2011 guideline (e.g., treatment of acute exacerbation of IPF with corticosteroids, oxygen supplementation, mechanical ventilation, pulmonary rehabilitation, and lung transplantation in general) were not prioritized for an update in this guideline

An evidence synthesis was also performed for a new question about single versus bilateral lung transplantation, but decisions regarding a recommendation were deferred until the next version of the guideline to gather additional information that was felt necessary before formulating a recommendation. Questions regarding newer treatments (e.g., antibiotics) were not addressed and were deferred until the next version of the guideline because of resource constraints.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause occurring in adults. Radiologic and/or histopathologic patterns are consistent

with usual interstitial pneumonia (1). The first guideline on the management of IPF was published in 2000 and was based on the consensus opinion of a group of international experts (2). The next guideline was published in 2011 and was a rigorous, evidence-based, joint effort by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) (3). Since then, important new evidence for the treatment of IPF has been published. This guideline updates several recommendations for treatment from the previous guideline and provides new recommendations on topics not considered in the previous guideline.

Methods

The guideline development panel consisted of a chair (G.R.) and two co-chairs (H.J.S. and H.H.) and 15 panelists. All participants disclosed their conflicts of interest during panel composition. Evidence syntheses were presented to the panel at a face-to-face meeting and two subsequent teleconferences. The presentations were followed by a discussion of the evidence and

then the formulation and grading of recommendations using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. Among the co-chairs and panelists, nine individuals (J.L.B., W.C., H.H., S.H., T.J., J.M., D.R., A.T., and H.J.S.) were judged by ATS to have no relevant conflicts of interest and were allowed to participate without restrictions; however, eight individuals (A.A., J.B., H.R.C., F.J.M., G.R., L.R., M.S., and A.U.W.) were judged to have conflicts of interest and were allowed to participate in discussions about the evidence, but were not permitted to discuss, formulate, grade, or vote on the recommendations. The medical librarian (S.L.P.) similarly did not participate in the development of recommendations. Adherence to the rules was strictly enforced during the meeting, teleconferences, and manuscript preparation.

Recommendations for Specific Treatment Questions

Please see online supplement, which includes supporting evidence profiles for each recommendation.

Question 1: Should Patients with IPF Be Treated with Anticoagulation?

Background. Studies have suggested a procoagulant state may be involved in promoting fibrosis via cell-surface receptor-mediated pathways (4, 5) providing biological plausibility for a mechanistic link between thrombosis and lung fibrosis (6, 7). It is less clear what role systemic anticoagulants may have in preventing this effect in patients with IPF.

Summary of the evidence. The 2011 guideline included one study, an open randomized trial that compared oral warfarin plus prednisolone against prednisolone alone in 56 patients with IPF (8). Treatment with warfarin led to a reduction in the secondary outcome of IPF acute exacerbation-associated mortality. This trial was associated with significant methodological concerns, specifically the lack of a clear description of how randomization or concealment of allocation was undertaken, the lack of a description of how patient drop-out was managed, and a failure to exclude pulmonary embolus as a potential cause for clinical deterioration. For these reasons, in addition to the absence of a placebo control, it was considered to have a high risk of bias and was excluded from pooled analysis in this treatment update.

One randomized controlled trial (RCT) published since the 2011 guideline randomized 145 patients with IPF to oral warfarin (target international normalized ratio, 2.0–3.0) versus placebo control (9). This study was stopped early after a mean follow-up of 28 weeks because of a lack of benefit from warfarin and a signal for potential harm with treatment. Despite a relatively low number of events, a significant increase in mortality was seen with warfarin at interim analysis (relative risk [RR], 4.73; 95% confidence interval [CI], 1.42–15.77; low confidence), although this was not associated with bleeding complications. No significant difference was seen between groups in terms of FVC change (low confidence) or percentage of patients with a greater than 10% decrease in FVC during the study period (low confidence). There was also a trend toward more serious adverse events in patients receiving warfarin (RR, 1.77; 95% CI, 0.94–3.33; low confidence).

Recommendation. We recommend that clinicians not use warfarin anticoagulation in patients with IPF who do not have a known alternative indication for its use (strong recommendation against, low confidence in estimates of effect).

Justification and implementation considerations. This recommendation places a high value on potential adverse outcomes such as death. The committee members felt that the increased risk for mortality required a strong recommendation against using oral warfarin as a treatment for IPF in patients with IPF. However, this recommendation applies only to oral warfarin with a target international normalized ratio of 2.0–3.0 and does not include the use of other anticoagulants for other indications. Patients who have an alternate and/or known indication for anticoagulation, such as venous thromboembolic disease or atrial fibrillation, should follow treatment guidelines for these conditions independent of their underlying IPF. Given that there were no net benefits of oral warfarin cost was considered irrelevant.

Question 2: Should Patients with IPF Be Treated with Imatinib, a Tyrosine Kinase Inhibitor?

Background. Imatinib is a potent inhibitor of lung fibroblast-myofibroblast differentiation and proliferation, as well as an inhibitor of extracellular matrix production through inhibition of PDGF and transforming growth factor- β signaling. For the recommendation on nintedanib, a less selective tyrosine kinase inhibitor, see Question 5. No recommendation was offered for either of these medications in the 2011 guideline document.

Summary of the evidence. Imatinib for patients with IPF has been evaluated in one placebo-controlled RCT, which randomized 119 patients and included a median follow-up of 96 weeks (10). No difference in mortality was seen between the intervention and control groups (RR, 0.81; 95% CI, 0.35–1.92; low confidence). Disease progression, the study's primary outcome, which was defined as a more than 10% decline in FVC or death at 96 weeks, also showed no benefit for imatinib therapy (hazard ratio [HR], 1.05; 95% CI, 0.56–1.96; moderate confidence). There was

a statistically significant increased risk of adverse events in the imatinib group compared with control (RR, 1.54; 95% CI, 1.25–1.90; high confidence); however, most of the undesirable effects were not considered bothersome enough to discontinue the medication. There was no significant difference in the number of serious adverse events between groups (low confidence).

Recommendation. We recommend that clinicians not use imatinib in patients with IPF (strong recommendation, moderate confidence in estimates of effect).

Justification and implementation considerations. Imatinib is a relatively expensive drug with no current evidence suggesting benefit in IPF patients to prevent disease progression or mortality. In the context of no demonstrated clinical benefit, this recommendation puts a high value on adverse events and the cost of treatment.

Question 3: Should Patients with IPF Be Treated with Combination Prednisone, Azathioprine, and N-Acetylcysteine?

Background. Previously, immune suppression was considered important in the treatment of IPF (2). It was thought that a two-drug regimen including glucocorticoids in addition to either azathioprine or cyclophosphamide may be superior to glucocorticoids alone (2). Given some early studies in favor of N-acetylcysteine (11), clinicians and researchers have examined the potential benefit of this three-drug regimen for IPF.

Summary of the evidence. The 2011 guideline included one RCT that compared N-acetylcysteine versus placebo in patients receiving prednisone and azathioprine (12). In this study, 12-month declines in vital capacity and diffusing capacity of the lung for carbon monoxide (DL_{CO}) were significantly less with the addition of N-acetylcysteine, although no significant effect on mortality, dyspnea scores, or quality of life was observed. Given the limitations of this study, specifically the lack of a true placebo group for all active therapies, a more recent RCT has been reported that randomized patients to combination therapy versus placebo for all active agents (13). This multicenter study was stopped early after a signal for harm was seen in patients receiving combination

therapy compared with placebo, with an increase in mortality (HR, 9.26; 95% CI, 1.16–74.1; very low confidence) and hospitalization ($P < 0.001$). No significant difference between groups was seen in FVC change (moderate confidence), DL_{CO} change (low confidence), or quality-of-life indices (low confidence).

Recommendation. We recommend that clinicians not use the combination therapy of *N*-acetylcysteine, azathioprine, and prednisone in patients with IPF (strong recommendation, low confidence in estimates of effect).

Justification and implementation considerations. This recommendation is primarily based on the results of a single trial that was stopped early for harm (13). Although trials stopped early prompt concerns about the true underlying effect (14), a clear negative effect was seen for multiple patient-important outcomes after enrolling 50% of targeted patients to this study. This recommendation places a high value on these potential adverse effects of the intervention. The committee felt that this recommendation only applies to patients with IPF treated with the dose of agents used in the trial and may not necessarily be generalizable to other forms of interstitial lung disease or other doses of treatment medications. There was no consensus on how to deal with patients with IPF who have been receiving a combination therapy long-term with good tolerance, as studies did not address stopping this treatment. In such circumstances, the committee recommended that an informed discussion is necessary and should take place between the individual patient and practitioner discussing the potential harms of treatment in combination with considerations for the patient's values and preferences. Despite challenges in judging benefit in individual patients, with those who seemed to have responded to combination therapy, it is prudent to readdress the accuracy of the diagnosis of IPF and reconsider other disease processes that may be more responsive to this treatment.

Question 4: Should Patients with IPF Be Treated with Ambrisentan, a Selective ER-A Endothelin Receptor Antagonist?

Background. Clinically significant endothelin receptors fall into one of a few

categories, including endothelin type A (ET-A) receptors, which induce vasoconstriction and are usually found on vascular smooth muscle cells, and the endothelin type B1 (ET-B1) receptors, located in the endothelial cells, which are known to stimulate the release of nitric oxide (NO) and prostacyclin to produce a vasodilating effect (15). ET-A receptors have also been shown to propagate epithelial-to-mesenchymal transition through intermediary cytokines, leading to a profibrotic state (16). ET-B2 receptors antagonize ET-B1 receptors and vasoconstrict through an unknown mechanism (15). Clinically available endothelin receptor antagonists (ERAs) include selective ET-A antagonists (e.g., ambrisentan) and dual antagonists that affect both ET-A and ET-B receptors (e.g., bosentan and macitentan). Increased ET-A and ET-B receptor levels have been found in IPF-affected fibrotic lung (17), and as such, both selective and dual antagonists have been investigated for potential benefit in treating patients with IPF. Given the differential mechanism of action, this guideline update looked at these two subtypes separately and decided to offer independent recommendations. No recommendation was made in the 2011 guideline for selective ERAs (see dual ERAs, recommendation 8 below).

Summary of the evidence. Ambrisentan is the only selective ERA with RCT evidence, with a single study that randomized 492 patients with IPF in a 2:1 ratio to either drug or placebo (18). This study also stratified randomization based on the presence or absence of pulmonary hypertension (PH) by right heart catheterization at baseline. Importantly, this study was stopped early for lack of benefit and a high likelihood of harm seen with intervention.

The HR for mortality with ambrisentan after a median follow-up of 52 weeks was 2.08 (95% CI, 0.75–5.76; low confidence). Ambrisentan increased disease progression, assessed as worsening DL_{CO} or FVC, independent of the presence or absence of PH (HR, 1.74; 95% CI, 1.14–2.66; moderate confidence). There was no significant difference between groups in terms of FVC, DL_{CO} , 6-minute-walk distance, or quality-of-life indices when assessed at week 48. There was no difference in adverse events (moderate confidence) or serious adverse events (low confidence) between patients receiving ambrisentan and those receiving placebo.

Recommendation. We recommend that clinicians not use ambrisentan, a selective ER-A endothelin receptor antagonist, in patients with IPF, regardless of the presence or absence of PH (strong recommendation against, low confidence in estimates of effect).

Justification and implementation considerations. Because ambrisentan is indicated for treatment of PH in patients other than those with IPF, the committee recommends against the use of ambrisentan in patients with IPF manifesting PH. It is reasonable for patients with IPF who are taking ambrisentan to discontinue treatment, given the lack of benefit and potential for harm. The committee did not suggest subgroup considerations or future research opportunities.

Question 5: Should Patients with IPF Be Treated with Nintedanib, a Tyrosine Kinase Inhibitor?

Background. Nintedanib (previously known as molecule BIBF 1120) is an intracellular inhibitor of several tyrosine kinases that targets multiple growth factor receptors, including vascular endothelial growth factor, fibroblast growth factor, and PDGF.

Summary of the evidence. Nintedanib treatment in patients with IPF was evaluated in three RCTs published in two separate reports (19, 20). The first was a phase 2 safety and efficacy trial that studied four different doses of nintedanib (50 mg once daily, 50 mg twice daily, 100 mg twice daily, and 150 mg twice daily) versus placebo (19). No significant difference between groups was seen in terms of mortality. The percentage of patients with more than 10% FVC decline during the 12 month follow-up period was lower with the highest dose of nintedanib ($P = 0.004$) but was not significantly different at the other doses when compared with placebo. Patients treated with any dose of nintedanib did have fewer IPF acute exacerbations compared with controls (HR, 0.16; 95% CI, 0.04–0.70). There were more adverse events and serious adverse events in the patients receiving nintedanib; however, neither of these was statistically significant.

INPULSIS-1 (Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients) and INPULSIS-2 (Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients II) were replicate phase 3 RCTs that

enrolled a total of 1,066 patients in a 3:2 ratio to receive 150 mg of nintedanib twice daily versus placebo (20). Follow-up for both of these studies was 52 weeks. Considering these trials as one, there was no significant benefit of nintedanib on mortality (RR, 0.70; 95% CI, 0.44–1.11) or acute exacerbation of IPF (HR, 0.64; 95% CI, 0.39–1.05). However, fewer patients treated with nintedanib had a more than 10% absolute decline in FVC during the study period (RR, 1.16; 95% CI, 1.06–1.27). Also, the adjusted annual rate of change in FVC was –114.7 ml with nintedanib therapy versus –239.9 ml with placebo (difference, 125.2 ml; 95% CI, 77.7–172.8). Significantly more patients treated with nintedanib reported an adverse event (RR, 1.07; 95% CI, 1.03–1.11); however, there was no significant increase in serious adverse events. Patients treated with nintedanib did report significantly more diarrhea and nausea compared with those receiving placebo.

Pooled analysis of these three trials (19, 20) showed an RR of 0.70 (95% CI, 0.47–1.03; moderate confidence) for mortality and a HR of 0.47 (95% CI, 0.17–1.29; low confidence) for acute exacerbations. A benefit was seen with nintedanib for the outcome number of patients with more than 10% absolute decline in FVC (RR, 1.15; 95% CI, 1.06–1.25; moderate confidence). Significantly more patients treated with nintedanib reported adverse events (high confidence), but not serious adverse events (high confidence).

Recommendation. We suggest that clinicians use nintedanib in patients with IPF (conditional recommendation, moderate confidence in estimates of effect).

Justification and implementation considerations. This recommendation puts a high value on the potential benefit of nintedanib on patient-important outcomes such as disease progression as measured by rate of FVC decline and mortality and a lower value on potentially significant adverse effects and the expected cost of treatment. As opposed to more selective tyrosine kinase inhibitors, nintedanib appears to have some benefit in terms of patient-important outcomes in patients with IPF, although no significant effect on overall mortality was seen. The concerns based on current costs may limit feasibility and use. These considerations are important, were discussed by the committee as part of the

recommendation, and must be factored into any decision for treatment. Adverse effects were commonly reported with nintedanib therapy, specifically diarrhea, and patients must be informed of this when deciding on treatment. As noted earlier, there was no increase in serious adverse events with nintedanib, and relatively few patients discontinued the study drug secondary to adverse effects. Of note, one committee member felt that the recommendation should be strong in favor; all other members agreed with a conditional recommendation. As with other interventions, the available evidence focuses on patients with IPF with mild to moderate impairment in pulmonary function tests (PFTs). It is unknown whether the therapeutic benefits would differ in patients with a more severe impairment in pulmonary function testing or those with other comorbidities. Some of the patients enrolled in the clinical trials included patients with a high-resolution computed tomography image pattern that was suggestive of the usual interstitial pneumonia (UIP) pattern (and was designated as “probable UIP” pattern), rather than those with definite UIP pattern (i.e., without confirmation of UIP on surgical lung biopsy in patients whose high-resolution computed tomography scan had not demonstrated a pattern consistent with definite UIP [3]). The evidence does not allow suggestions about the optimal duration of therapy, and it is unknown how long the treatment effect endures with ongoing drug therapy.

Question 6: Should Patients with IPF Be Treated with Pirfenidone?

Background. Pirfenidone is an oral antifibrotic drug with pleiotropic effects. It has been shown to regulate important profibrotic and proinflammatory cytokine cascades *in vitro* (21) while reducing fibroblast proliferation and collagen synthesis in animal models of lung fibrosis (22–24).

Summary of the evidence. The 2011 guideline document reported on two relatively small RCTs that compared pirfenidone with placebo in Japanese patients with IPF who had mild to moderate impairment in PFTs (25, 26). One of these trials (25) was stopped early for potential benefit, as acute exacerbation, a secondary outcome, was found to occur more frequently in the placebo group. Similarly, and despite an incomplete data set,

a benefit with pirfenidone was seen when evaluating the frequency of oxygen desaturation during 6-minute-walk test and the decline in vital capacity (VC) over time. The second trial (26) had significant methodological concerns, including a highly selected enrolment and alteration of the primary endpoint midstudy. Understanding this, it also demonstrated a benefit to pirfenidone treatment in terms of a reduction in the rate of decline in VC (–90 ml vs. –160 ml; $P=0.04$) and improved progression-free survival ($P=0.03$). The CAPACITY trial (27), the combined results of two large-scale RCTs (Safety and Efficacy of Pirfenidone in Patients With Idiopathic Pulmonary Fibrosis, and Three-Arm Study of the Safety and Efficacy of Pirfenidone in Patients With Idiopathic Pulmonary Fibrosis) considering pirfenidone for IPF, had not been published. However, preliminary results were available, and were considered in the last iteration of the guideline.

The CAPACITY trial reported on two independent study protocols: study 004 included 435 patients randomized to one of three treatment groups (high-dose pirfenidone [2,403 mg/d], low-dose pirfenidone [1,197 mg/d], and placebo), whereas study 006 had 344 patients randomized to only two treatment groups (high-dose pirfenidone [2,403 mg/d] and placebo). The results of the low-dose pirfenidone group were intermediate to the higher dose, and to avoid heterogeneity of intervention, we chose to focus on the results of the high-dose pirfenidone group versus those of the placebo group across both studies. In study 004, pirfenidone showed a reduction in decline of FVC during the 72-week treatment period. Study 006 did not show a benefit in the same outcome during the same period. Importantly, patients from both studies who were assigned to receive high-dose pirfenidone reported increased rates of nausea, dyspepsia, vomiting, anorexia, photosensitivity, and rash compared with placebo. The ASCEND trial (A Randomized, Double-Blind, Placebo Controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis) randomized 555 patients with IPF to either high-dose pirfenidone (2,403 mg/d) or placebo (28). As opposed to the CAPACITY trials, the ASCEND trial had stricter patient selection criteria, such as a FEV₁/FVC ratio below 0.8. Of 1,562 screened patients, 1,007 were excluded

because of these predefined exclusion criteria. Pirfenidone significantly reduced the proportion of patients who had a more than 10% decline in their FVC during the 52-week follow-up period. Pirfenidone treatment increased 6-minute-walk distance and progression-free survival when compared with placebo. Mortality or dyspnea scores did not differ. Consistent with previous studies, patients randomized to pirfenidone reported more treatment-related adverse effects.

Pooled results from these trials (25–28) suggested improved mortality with pirfenidone (RR, 0.70; 95% CI, 0.47–1.02; moderate confidence). Pirfenidone reduced the rate of FVC decline (standardized mean difference, 0.23; 95% CI, 0.06–0.41; high confidence). This pooled estimate did not include the positive results from one study (28) because of heterogeneity in reporting, which made pooling including this trial impossible. Pooled analysis showed increased rates of photosensitivity (high confidence), fatigue (moderate confidence), stomach discomfort (moderate confidence), and anorexia (high confidence) in patients treated with pirfenidone.

Recommendation. We suggest that clinicians use pirfenidone in patients with IPF (conditional recommendation, moderate confidence in estimates of effect).

Justification and implementation considerations. New evidence that has become available since the prior edition of this guideline has led to a conditional recommendation in favor of treatment. Only one committee member felt that the recommendation should be strong in favor; all other nonconflicted members agreed with a conditional recommendation. This recommendation puts a high value on the potential benefit of pirfenidone on patient-important outcomes such as disease progression as measured by rate of FVC decline and mortality and a lower value on potentially significant adverse effects and the cost of treatment. Quality-of-life data were sporadically reported across pirfenidone trials. The adverse effects of pirfenidone treatment fall on a spectrum, and some patients may not be willing to tolerate certain adverse effects even in the setting of treatment benefit, as assessed by measurement of FVC. Shared decision-making should be used, and patients starting this treatment must be educated on all potential adverse effects. In addition,

pirfenidone is currently a very costly intervention, and this must be factored into the decision-making process, especially when patients directly carry the financial burden of treatment. Given the different inclusion criteria for the pirfenidone trials, these results cannot necessarily be generalized to patients with IPF with more severe impairment in PFTs or for patients with other significant comorbidities. The evidence does not allow suggestions about the optimal duration of therapy, and it is unknown how long the treatment effect endures with ongoing drug therapy.

Question 7: Should Patients with IPF Be Treated with Sildenafil, a Phosphodiesterase-5 Inhibitor?

Background. Sildenafil, an oral phosphodiesterase-5 inhibitor, has been studied in two RCTs that enrolled patients with IPF (29, 30). This evidence was included in the 2011 guideline; however, one of the studies (30) only became available after the guideline committee had met, and therefore no formal recommendation on phosphodiesterase inhibitor use in patients with IPF was provided.

Summary of the evidence. STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) was a phase 3 study that randomized 180 patients with advanced IPF ($DL_{CO} < 35\%$ predicted) to either sildenafil (20 mg three times daily) or placebo for 12 weeks, with a subsequent 12-week open-label phase during which all patients received active drug (30). There was no significant benefit of sildenafil on the primary outcome, which was the proportion of patients who showed more than 20% improvement in their 6-minute-walk distance after the initial 12-week period (10.1% vs. 6.6%; $P = 0.39$). There were small benefits seen with sildenafil on the secondary outcomes, with improved shortness of breath, improved quality of life, improved DL_{CO} , and improved arterial oxygen saturation, all at the end of the 12-week randomized period. There was no difference in serious adverse events between the groups receiving sildenafil versus those receiving placebo. A predefined subgroup analysis was performed in the 119 patients with available echocardiograms to see whether there was a differential effect of sildenafil on patients with IPF with documented right ventricular hypertrophy or right ventricular systolic dysfunction

(RVSD) (31). In patients with echocardiogram-documented RVSD, sildenafil treatment was found to result in a significant improvement in the primary outcome of 6-minute-walk distance (mean distance, 99.3 m; 95% CI, 22.3–176.2 m). Similar results to patients without RV dysfunction were seen in the other secondary outcomes.

The second, smaller study randomized 29 patients with mild or moderate disease (average DL_{CO} , 42% predicted) to receive either sildenafil (20 mg three times daily) or placebo for a 6-month treatment period (29). Patients with known PH or RV dysfunction were excluded. In this small study, no significant benefit of sildenafil treatment was seen on 6-minute-walk test distance, Borg dyspnea scores, FVC, DL_{CO} , or arterial oxygen saturation. More adverse events occurred in the sildenafil group; however, these were not serious.

Pooled analysis of these two trials (29, 30) showed no significant benefit of sildenafil treatment on mortality (RR, 0.51; 95% CI, 0.1–2.72; low confidence) or acute exacerbation (RR, 0.34; 95% CI, 0.04–3.22; low confidence). There was a significant improvement in quality of life with sildenafil when assessed by the St. George Respiratory Questionnaire (moderate confidence). Similar to the individual trials, no significant benefit with treatment was seen on the other outcomes of FVC (moderate confidence), DL_{CO} (low confidence), Borg dyspnea score (moderate confidence), oxygen saturation (low confidence), or 6-minute-walk distance (low confidence).

Recommendation. We suggest that clinicians not use sildenafil, a phosphodiesterase-5 inhibitor, for treatment of IPF (conditional recommendation against, moderate confidence in estimates of effect).

Justification and implementation considerations. Although there was a slight improvement in quality of life with sildenafil, given the lack of benefit in any other outcomes, including mortality, acute exacerbations, or dyspnea scores, there was felt to be net harm. In addition to potential drug-related adverse effects, the cost of sildenafil treatment was considered a potential barrier for patients who would have to pay out of pocket for sildenafil. This recommendation puts a higher value on the mortality, acute exacerbation, and dyspnea (which did not improve) adverse events

and the cost of treatment, and a relatively lower value on quality of life. This recommendation required a vote by the committee: two panel members voted for a conditional recommendation in favor, five voted for a conditional recommendation against treatment, and two abstained. This recommendation does not apply to patients receiving phosphodiesterase inhibitors for other indications such as PH or other RV dysfunction. Given that echocardiogram is not the gold standard for diagnosing RV dysfunction or PH, and that only subgroup evidence was available, the committee made no specific subgroup recommendation in patients with IPF with documented PH.

Question #8: Should Patients with IPF Be Treated with Bosentan or Macitentan, Dual Endothelin Receptor Antagonists (ER-A and ER-B)?

Background. One small study looking at the effect of a dual ERA (bosentan) was available at the time of the 2011 guideline, and given the lack of benefits, a strong recommendation against therapy was made.

Summary of the evidence. Two RCTs examined the effect of bosentan versus placebo (32, 33), whereas a single RCT tested macitentan versus placebo (34). BUILD-1 (Bosentan Use in Interstitial Lung Disease) randomized 158 patients to either bosentan or placebo and followed patients for 12 months (33). No significant benefit was seen in mortality (RR, 1.14; 95% CI, 0.24–5.54), although the data suggested an improvement in the composite outcome of mortality and disease progression (RR, 0.62; 95% CI, 0.37–1.05), as measured by worsening PFTs or clinical status. There was no statistically significant increase in adverse events or serious adverse events with bosentan therapy. The follow-up study, BUILD-3, attempted to clarify this potential beneficial effect of bosentan by including a larger sample ($n = 616$) and by being more specific, including only patients with biopsy-proven usual interstitial pneumonia, a pathologic diagnosis consistent with IPF (32). Despite these modifications in study design, bosentan did not show a conclusive effect on mortality (RR, 1.25; 95% CI, 0.53–2.96) or disease progression (RR, 0.86; 95% CI, 0.71–1.05). Differences were also not seen in FVC, health-related quality of life (assessed by 36-Item Short Form Health Survey),

dyspnea scores, reported adverse events, or serious adverse events in the bosentan group.

Macitentan, a novel dual-receptor ERA, was compared with placebo in a phase 2 study of 178 patients with lung biopsy-proven IPF (34). Similar to bosentan, no significant difference was seen in patients treated with macitentan versus those receiving placebo for the outcomes mortality (RR, 0.74; 95% CI, 0.13–4.33), mortality or disease progression (RR 1.02; 95% CI, 0.63–1.66), or change in FVC (mean difference, 0.00; 95% CI, –0.16 to 0.16). No difference in rates of reported adverse or serious adverse events was seen.

Given the relatively similar mechanism of action between these two dual ERAs and the homogenous results, these three studies were pooled for analysis (32–34). No overall effect on mortality was seen using dual ERAs for patients with IPF (RR, 1.13; 95% CI, 0.57–2.27; low confidence). The composite outcome of death or disease progression appeared improved, with the upper confidence interval just crossing unity (RR, 0.85; 95% CI, 0.71–1.00; low confidence). No important difference between groups was seen in FVC change (moderate confidence) or in the rates of adverse events (high confidence) or serious adverse events (high confidence).

Recommendation. We suggest that clinicians not use bosentan or macitentan, both dual ER-A and ER-B endothelin receptor antagonists, for the treatment of IPF (conditional recommendation against, low confidence in estimates of effect).

Justification and implementation considerations. This recommendation places a relatively higher value on the reported patient-important outcomes and the high cost of this medication and a relatively lower value on possible reduction of the risk of mortality or disease progression. Given the inconsistency of a composite outcome (mortality or disease progression) across trials and the imprecision in the estimate of the effect, the committee recommended against this therapy. The increased cost of dual-receptor ERAs was also considered, especially in the context of unclear desirable effects. It is important to mention that only studies examining bosentan or macitentan were considered, and that other dual ERAs may be beneficial in patients with IPF. The committee felt that patients with PH secondary to IPF might benefit from dual

ERAs more than patients without; however, the evidence did not allow a specific subgroup recommendation. A recently published study, not considered by the committee, showed no benefit of bosentan therapy on pulmonary hemodynamics in patients with IPF with right heart catheter-diagnosed PH (35).

Additional Deliberations

Evidence syntheses were performed for four additional questions: whether or not to use *N*-acetylcysteine monotherapy, whether or not to use antacid therapy in patients without symptoms of gastroesophageal reflux, whether or not to treat IPF-associated PH, and whether to undergo single or bilateral lung transplantation. For the questions about *N*-acetylcysteine monotherapy and antacid therapy, the decision was made that no changes to the previous recommendations in the 2011 guideline were warranted (both conditional recommendations, against treatment with *N*-acetylcysteine monotherapy and for treatment with antacid therapy) (1). For the question about treatment of IPF-associated PH, decisions regarding modifying the previous recommendation in the 2011 guideline were deferred until the next update. Finally, for the new question about single versus bilateral lung transplantation, decisions regarding a recommendation were deferred until the next version of the guideline. Full rationale and evidence summary for these questions can be found in the full online version of the manuscript (see online supplement).

Conclusions

Significant advances have been recently made in the clinical management of IPF. As a result, this updated guideline includes several new and revised recommendations (Table 2). All of the recommendations in favor of treatment are conditional. Clinicians treating patients with IPF should individualize decisions with their patients, as indicated by the conditional grade, and they should be cautious in comparing the relative net benefit of one intervention with that of another. Recommendations of similar strength should not be interpreted as achieving the same net benefit or harm. Each recommendation's strength is net result of multiple factors, and therefore, there may be

different reasons two recommendations are rated with the same strength (e.g., one recommendation may be conditional because it is based on very low confidence in effect estimates, whereas another recommendation may be conditional because of resource considerations).

Significant variations in inclusion criteria, the confidence in effect estimates, and cost are important factors that need to be considered by the clinician.

The potential of combined, sequential, or adjunctive treatment regimens with agents (other than prednisone plus azathioprine

plus *N*-acetylcysteine) included in this guideline have not been studied, and therefore, recommendations regarding this have not been made. Also, the duration of benefit seen with these newer agents is not clear. Such topics are appropriate for future research (*see* online full-length version). ■

Editor's Note (Kevin Wilson, M.D.): An important aspect of this guideline was the intense effort to balance the need to minimize bias with the need for expertise to inform decisions. According to international standards for guideline development, the strategy was to compose a panel in which the majority of co-chairs and members had no conflicts of interest. The nonconflicted members were able to participate without restrictions, whereas the conflicted members were allowed to discuss the evidence, but were prohibited from discussing the recommendations, formulating and grading the recommendations, and voting on the recommendations. Having observed the deliberations, I can attest that adherence to this strategy was strict, without a single violation. A common question that was subsequently posed by the peer reviewers, however, is whether or not the recommendations would have differed if the conflicted experts had been allowed unrestricted participation. I had the privilege of corresponding with the conflicted experts at the conclusion of the project, and therefore, I can answer this question. In general, the conflicted experts would have made the same recommendations as this guideline, with one exception: there were varying opinions regarding the antacid recommendation. Many of the conflicted experts would have made no recommendation, citing a lack of randomized trials and concern that the antacid recommendation would be perceived as equivalent to other conditional recommendations based on better evidence.

This Clinical Practice Guideline was prepared by the ATS/ERS/JRS/ALAT Committee on Treatment of IPF.

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Mr. Cunningham actively participated in every one of the guideline meetings without reservation, and whenever he spoke to offer input, other members listened with great care. His comments were always objective, balanced, to the point, insightful, and respectful of other patients and the community of healthcare providers caring for patients with IPF. The entire committee held him in the highest regard. His most meaningful input surrounded his own experiences with IPF from the perspective of someone living with this disease and having encountered problems and

frustrations directly. His ability to endure the very long hours of teleconference-webinars and of intense discussions over 2 consecutive days, including late evenings, is proof of his commitment. His diligent review of the evidence and documents circulated and his comments were commendable and simply incredible. His understanding of the evidence was astounding and was reflected in his remarks.

He was very aware of the evolving knowledge and updates concerning the management of IPF and the clinical and political landscape including patient advocacy groups, decisions of regulatory agencies, and available medications and their relevant adverse effects. This commitment was very evident up until the end, as his last communication to the group was just a few days before he sadly passed away. Mr. Cunningham's ability to be objective with facts and figures studies in the midst of his own illness and what he was experiencing is one of a kind.

In essence, Mr. Cunningham was a true gentleman, scholar, and intellect, and a remarkably wise man whose input was greatly respected and appreciated by this committee and strengthened the significance of this document. The IPF community at large is truly fortunate to have had his invaluable input.

His voice was heard, loud and clear, and will be ringing in the authors' ears and minds. The authors offer their most sincere respects to his family. May his soul rest in peace.

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