AMERICAN THORACIC SOCIETY DOCUMENTS

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis
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).

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.

Contents

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, it is important to consider both the summary of evidence reviewed and discussed by the nonconflicted members of the committee and remarks for each specific treatment question, including the values and preferences, 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 dictates. 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:

1. **The recommendation *against* the use of the following agents for the treatment of IPF is strong:**
   a. Anticoagulation (warfarin) ($\oplus\oplus\ominus\ominus$, low confidence in effect estimates).
   b. Imatinib, a selective tyrosine kinase inhibitor against platelet-derived growth factor (PDGF) receptors ($\oplus\oplus\oplus\ominus$, moderate confidence in effect estimates).
   c. Combination prednisone, azathioprine, and N-acetylcysteine ($\oplus\oplus\ominus\ominus$, low confidence in effect estimates).
   d. Selective endothelin receptor antagonist (ambrisentan) ($\oplus\oplus\ominus\ominus$, 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 ($\oplus\oplus\oplus\ominus$, moderate confidence in effect estimates).

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.

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		
Antiacid therapy	Conditional recommendation for use‡	Conditional recommendation for use‡
N-acetylcysteine monotherapy	Conditional recommendation against use†	Conditional recommendation against use†
Antipulmonary 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.

    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 antiacid 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 antiacid 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.
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

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). Although the first guideline on management of IPF, published in 2000, was based on the consensus of a group of international experts in the field (2), the 2011 guideline represented a rigorous joint effort by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT). It reviewed all available evidence, clarified the definition of IPF, provided precise diagnostic criteria, described the natural course of the disease, and provided evidence-based recommendations for treatment (3). The 2011 guideline also stated that updates would be provided based on pertinent new evidence. Although the 2011 guideline provided clear recommendations for several specific treatment regimens, new, important evidence for the treatment of IPF has become available since 2011.

This document updates the treatment guideline with the reappraisal of previously assessed treatment options and new recommendations for novel agents. Evidence surrounding the clinical management of IPF is rapidly evolving, and

it is intended that future iterations of the 2011 guideline dealing with questions related to diagnosis, genetics, and other new questions will be made available promptly. The ultimate goal for this guideline is for it to be a "living document," allowing new evidence to be incorporated as available, with periodic updates to guide clinical management based on the best available evidence in a timely manner.

Methods

Committee Composition
This guideline was developed by a multidisciplinary committee that consisted of pulmonologists with recognized IPF expertise (n = 8; G.R., F.J.M., H.R.C., A.U.W., J.B., L.R., A.A., and M.S.), general pulmonologists (n = 3; A.T., S.H., and H.H.), a pulmonologist-methodologist (n = 1; H.J.S.), an allergist-methodologist (n = 1; J.L.B.), a general internist (n = 1; D.R.), a chest radiologist (n = 1; T.J.), a pulmonary pathologist (n = 1; J.M.), an information scientist (n = 1; S.L.P.), and a patient with IPF (n = 1; W.C.), who was recommended for participation by the Coalition for Pulmonary Fibrosis and was not known to any of the committee members. The committee was chaired by G.R. and co-chaired by H.J.S. and H.H. Committee members represented the ATS, ERS, JRS, and ALAT.

The committee worked with the Methods Group (MG), which comprised five health research methodologists (B.R., C.A.C.G., Y.Z., J.L.B., and H.J.S.) from the MacGRADE Centre at McMaster University who had expertise in evidence synthesis and the guideline development process. Four of these methodologists are also clinicians (B.R., J.L.B., C.A.C.G., and H.J.S.). The MG conducted systematic reviews and prepared the systematic evidence summaries following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, as described here (4, 5).

Confidentiality Agreement and Conflict-of-Interest Management
Committee members signed a confidentiality agreement and disclosed all potential conflicts of interest according to the ATS and ERS policies. Two of the co-chairs (G.R. and H.J.S.) reviewed all potential conflicts of interest of committee members with the staff of the ATS conflict-of-interest and documents units.

All of the eight pulmonologists with recognized IPF expertise (G.R., F.J.M., H.R.C., A.U.W., J.B., L.R., A.A., and M.S.) were considered to either have major financial or intellectual conflicts based on disclosures or participation in IPF clinical trials/studies (6); although they were permitted to participate in the discussions of the evidence with the rest of the committee, they were instructed to abstain from discussions related to the evidence to decision framework (described later), formulating and grading recommendations, and voting on recommendations if necessary. This approach was applied to all questions, not just those in which they had a perceived conflict of interest. Conflicted members were allowed to stay in the same room while discussions among nonconflicted members took place to provide expert input; however, they could do so only when specifically requested by nonconflicted members. Adherence to the rules was strict, with one of the co-chairs (H.J.S.) responsible for monitoring the discussions for adherence to these rules.

The remaining nine nonconflicted committee members (A.T., S.H., H.H., H.J.S., J.L.B., D.R., T.J., J.M., and W.C.) were allowed unrestricted participation. Two of the voting members were members of the MG; they are clinicians with extensive expertise in the guideline development process (H.J.S. and J.L.B.). The rest of the MG and the librarian also participated in discussions, but were nonvoting participants.

Meetings
Face-to-face planning meetings were held during the 2013 ATS International Conference in Philadelphia, Pennsylvania, at which the committee discussed the scope and objectives of the project, and during the 2014 ATS International Conference in San Diego, California, to go over the proceedings of the upcoming face-to-face meeting in June 2014 in Hamilton, Ontario, Canada (described here). Members who could not attend the actual face-to-face meetings participated in person live by teleconference. Additional planning meetings were held regularly over telephone between G.R., H.J.S., and the MG. Conference calls and email correspondence were used to discuss specific issues requiring input from others.

The entire guideline committee met at the McMaster Health Forum in Hamilton, Ontario, Canada, on June 9–10, 2014, at which the evidence summaries were presented and discussed, and the recommendations were formulated. Three members participated through teleconference and webinar (H.H., M.S., and W.C.). The methodologists took notes of all matters and points discussed and documented all the recommendations and proceedings.

Two follow-up teleconference webinars were held on June 23 and July 15, 2014, to complete the guideline development for two of the 12 treatment questions (questions on single versus bilateral lung transplantation and treatment of IPF-associated pulmonary hypertension [PH]). Three members (A.A., S.H., and T.J.) were not able to participate live during the first teleconference-webinar, and five members (A.A., S.H., T.J., M.S., and H.H.) were not able to join the second teleconference-webinar, but all provided feedback and discussion via emails. All meetings were attended by staff from the ATS documents unit.

McMaster University provided meeting facilities and logistical support, and the sponsoring societies provided the financial support for expenses resulting from the meeting and conference calls. The views and interests of the ATS, ERS, JRS, and ALAT, as well as of any commercial entity that provided external funding for professional societies, had no influence on the topics discussed and recommendations made.

Formulating Clinical Questions
The committee used the treatment section of the 2011 guideline document (3) as a starting point. Twelve specific questions pertinent and relevant to current clinical practice were addressed to update the recommendations pertinent to treatment of IPF. Most of these questions were previously addressed, and formal recommendations had been provided in the 2011 document. Questions pertinent to the management of patients with IPF with pulmonary rehabilitation, oxygen supplementation, antibiotics, palliative care, mechanical ventilation, and specific questions that had received a "strong against" or "strong for" in the 2011

guideline were not readdressed in this update unless the literature search revealed new and pertinent evidence.

The committee selected outcomes of interest for each question, using the 2011 document as a guide in addition to following the approach suggested by the GRADE working group (5, 7). All outcomes were identified *a priori*, and the committee explicitly rated their relative importance (from the perspective of a patient with IPF) from not important to critical (7). Ranking outcomes by their relative importance helps focus attention on those that are most relevant to patients and helps resolve or clarify potential disagreements in decision making. Examples of critical outcomes include mortality or disease progression. Disease progression, defined in the 2011 document as increasing respiratory symptoms, worsening pulmonary function test (PFT) results, progressive fibrosis on high-resolution computed tomography scan, acute respiratory decline, or death, can be measured using multiple outcome measures (3). Changes over time in FVC or diffusing capacity of the lung for carbon monoxide ($D_{L_{CO}}$) were considered indirect measures of disease progression for the purpose of this guideline. Rankings of all outcomes were agreed on through consensus of the committee.

Literature Search

In collaboration with the MG, an information scientist (S.L.P.) designed a search strategy using medical subject heading keywords and text words (*see* online supplement) limited to human studies or nonindexed citations and articles in English or in any language with English abstracts. The Ovid platform was used to search MEDLINE, EMBASE, Cochrane Registry of Controlled Trials, Health Technology Assessment, and the Database of Abstracts of Reviews of Affects for May 2010 through May 2014. An update was performed in June 2014, immediately before the meeting at McMaster University. Reviewers contacted experts and reviewed previous meta-analyses for additional articles. The search retrieved 9,663 citations, minus duplicates. On the basis of predefined eligibility criteria, 54 citations were included for full text review, of which 34 were excluded with reasons and 20 were included in the evidence update (*see* online supplement).

Evidence Review and Development of Clinical Recommendations

Evidence summaries for each question were prepared by the McMaster methodology team, following the GRADE approach (4), using the GRADEpro Guideline Development Tool online software (8). All committee members reviewed the summaries of evidence, and corrections were made when appropriate. We based the evidence on the 2011 evidence summaries that had been produced for that document. These summaries were updated, if necessary, with additional recent randomized controlled trials (RCTs). Committee members were also queried for any additional studies not identified by the search. If adequate outcome data were not available from RCTs, observational studies were also used to support recommendations.

Two reviewers from the MG screened titles and abstracts to identify articles for full review and evaluated the full text of articles deemed potentially relevant by either reviewer. Disagreement was resolved by consensus among the MG group. Data abstraction occurred in duplicate, using predesigned data abstraction forms that had been piloted before being used. In addition to clinical data, individual study risk of bias was assessed independently by both reviewers, using the Cochrane Risk of Bias tool (9) for RCTs and the Ottawa-Newcastle tool (10) for observational studies.

Results from identified studies with the same treatment agent were pooled, and meta-analyses, using the Cochrane Collaboration Review Manager, version 5.2 (11), were reviewed. Pooling and meta-analyses of study data were independently performed by the MG specifically for this guideline document. All data fulfilling the *a priori* inclusion criteria were included, and pooled analysis presented in this document may at times differ from other published meta-analyses, depending on inclusion or exclusion criteria. Subsequently, the overall certainty in effect estimates (also known as confidence in effect estimate) for each outcome of interest was assessed following the GRADE approach (12), based on the following criteria: risk of bias, precision, consistency, directness of the evidence, risk for publication bias, presence of dose-effect relationship, magnitude of effect, and

assessment of the effect of plausible residual confounding or bias. The confidence in effect estimates for each outcome was categorized into one of four levels: high, moderate, low, or very low.

The committee developed recommendations based on the GRADE evidence profiles for each recommendation. We employed the GRADE evidence to decision frameworks in the guideline development tool to help organize discussion around each recommendation and ensure each of the following factors was considered in recommendation development: the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the values and preferences associated with the decision, the implications for resource use and health equity, the acceptability of intervention to stakeholders, and the feasibility of implementation (*see* online supplement). Recommendations and their strength were decided by consensus, and only one recommendation required voting because of inability to achieve consensus. The committee agreed on the final wording of recommendations and remarks with further qualifications for each recommendation (e.g., subgroup considerations, justification, implementation considerations).

The recommendations were either "strong" or "conditional," according to the GRADE approach (13). Conditional recommendations are synonymous with weak recommendations. The 2011 guideline had used the nomenclature "weak," but to improve clarity (which conditions are relevant to implement the recommendation) and facilitate translation of guidelines to other languages, GRADE uses the term "conditional" as an alternative. Factors influencing the strength of the recommendation include the strength of evidence, the outcomes studies and associated importance to patients, the desirable and undesirable consequences of treatment, the cost of treatment, the implications of treatment on health equity, the feasibility of treatment, the acceptability of treatment to important stakeholders, and potential treatment monitoring and implementation issues.

As suggested by GRADE, we used the phrasing "we recommend" for strong recommendations and "we suggest" for conditional recommendations. Table 1

provides suggested interpretation of these recommendations by intended stakeholders, including patients, clinicians, and health policy makers. For two questions, the panel decided to not offer a recommendation because it was realized that additional evidence, mostly indirect and resource- or cost-related, should be considered to fully inform the panel, and we documented this as "no recommendation."

There are two important aspects of the recommendations to consider. First, recommendations of similar strength should not be interpreted as equivalent recommendations. Each recommendation's strength is net result of considering the multiple factors described earlier, and therefore there may be different reasons that 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 the cost is so high that it is unclear that the potential benefits outweigh those costs for every patient). Second, the methodology used in making recommendations for or against the use of therapies in guidelines considers additional factors than those used by regulatory agencies (whose purpose is to review data submitted to them and subsequently consider approval of new treatments for use in patients).

Manuscript Preparation

The writing committee (B.R., G.R., C.A.C.G., Y.Z., and H.J.S.) drafted the guideline document. The manuscript was then reviewed by the entire committee. Feedback was provided primarily by electronic communication and, to a lesser extent, during a face-to-face meeting at the ERS Congress on September 7, 2014, that included some of the committee members (G.R., H.H., B.R., H.R.C., F.J.M., L.R., J.B., A.U.W., and A.A.).

The entire committee (both conflicted and nonconflicted members) had the opportunity to correct factual errors, clarify the presentation of background information or evidence summaries, and suggest changes to the rationale sections if they improperly captured the discussion from the face-to-face meetings. However, only the nonconflicted voting members were permitted to comment on the

recommendations. The conflicted chair and conflicted committee members were not permitted to comment on the recommendations and restricted their feedback to the presentation of the evidence and the identification of errors. The wording of recommendations (including strength and direction) was not altered once they were finalized by the nonconflicted members during the face-to-face meeting and teleconferences. One of the nonconflicted co-chairs (H.J.S.) confirmed that the written version of the guideline reflected the recommendations made by the nonconflicted members. The same process was followed for each version of the document. The final approved version was submitted to each cosponsoring professional society for peer review.

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 (14, 15), providing biological plausibility for a mechanistic link between thrombosis and lung fibrosis (16, 17). 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 (18). 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 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 (19). 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.

Future research opportunities. Committee members considered that new trials using oral warfarin in patients with

IPF are unlikely to be helpful, and therefore would be difficult to develop and fund.

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 (20). 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 patients with IPF 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 (21), 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 (22). In this study, 12-month declines in vital capacity and $D_{L_{CO}}$ 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 (23). 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), $D_{L_{CO}}$ 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 (23). Although trials stopped early prompt concerns about the true underlying effect (24), 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 (25). ET-A receptors have also been shown to propagate epithelial-to-mesenchymal transition through intermediary cytokines, leading to a profibrotic state (26). ET-B2 receptors antagonize ET-B1 receptors and vasoconstrict through an unknown mechanism (25). 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 (27), 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 ERA, recommendation 9 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 (28). This study also stratified randomization based on the presence or absence of 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 $D_{L_{CO}}$ 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, $D_{L_{CO}}$, 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 (29, 30). The first was a phase 2 safety and efficacy trial that studied four different doses of nintedanib (50 mg daily, 100 mg daily, 150 mg daily, and 150 mg twice daily) versus placebo (29). 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 (30). 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 (29, 30) 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 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.

Future research opportunities. Future nintedanib trials should focus on patients with IPF with impairment in PFTs more severe than mild to moderate. More information on proper duration of treatment is also needed.

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* (31) while reducing fibroblast proliferation and collagen synthesis in animal models of lung fibrosis (32–34).

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 (35, 36). One of these trials (35) 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 (36) 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 (37), 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 (38). As opposed to the CAPACITY trials, the ASCEND trial had stricter patient selection criteria, such as a FEV_1/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 (35–38) 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

(38) 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.

Future research opportunities. Future research should focus on duration of treatment and the effect of pirfenidone in patients with IPF with more impairment in

PFTs and in patients with coexisting airflow obstruction less than the FEV_1/FVC of 0.8 or those with comorbid emphysema.

Question 7: Should Patients with IPF Be Treated with Antiacid Medication?

Background. Abnormal gastroesophageal reflux (GER), including clinically silent acid (or at least untreated acid), has been observed in up to 90% of patients with IPF (39). GER is a risk factor for aspiration and microaspiration, which could subsequently cause pneumonitis, a mechanism that has been postulated to cause or worsen IPF. Antiacid treatments, used on a regular basis, such as proton pump inhibitors (PPIs) or histamine-2 blocker receptor antagonists (H2RAs), may decrease this risk for microaspiration-associated lung injury or damage (40, 41).

Summary of the evidence. Observational studies have attempted to look at the role of regular PPI and H2RA use in decreasing the progression of disease in patients with IPF (40, 42–44). One retrospective analysis of longitudinal cohorts suggested a survival benefit for patients receiving antiacid medication (HR, 0.47; 95% CI, 0.24–0.93; adjusted analysis), of whom 86 used PPIs and 12 used H2RAs (42, 43). Another aggregate analysis examined all the patients who were randomized to the placebo groups from three RCTs of different pharmacologic therapies on patients with IPF (40). One hundred twenty-four patients receiving a PPI or H2 blocker at baseline (91% PPI, 9% H2RA) were compared with 118 patients not receiving antiacid treatment and not receiving other study medications. This analysis showed a significantly smaller decrease in FVC during the study period for those receiving antiacid treatment at baseline (mean difference, 0.07 L; 95% CI, 0–0.14; $P = 0.05$) There were no episodes of adjudicated acute exacerbations in patients treated with antiacid treatment compared with placebo. However, this study showed no differences in all-cause mortality or all-cause hospitalization.

Recommendation. **We suggest that clinicians use regular antiacid treatment for patients with IPF (conditional recommendation, very low confidence in estimates of effect).**

Justification and implementation considerations. This recommendation

places a higher value on possible improved lung function and survival and the low cost of therapy and a lower value on the potential increased risk for pneumonia with antiacid therapy. Although the individual studies appear to have been well conducted, the nature of observational studies suggests that the indication for antiacid treatment was based on the individual physician's decision, which may introduce bias. In addition, it is unclear how well investigators controlled for co-interventions, although the effects of such treatments are also unknown. The evidence presented mostly focused on PPIs, as a very small proportion of included patients were receiving H2RAs; other antiacid treatments may need to be considered differently. It is important to note that this recommendation applies to all patients with IPF, as it is based on IPF being the treatment indication, rather than abnormal GER. It is unclear whether the benefit of antiacid therapy in IPF would be different in symptomatic versus asymptomatic patients. However, it is recognized that patients with clinically abnormal GER/GER disease (GERD) should receive best available treatment according to appropriate guidelines for GERD. The safety of PPI therapy was also considered in this recommendation. Despite some studies showing association, a recent meta-analysis of observational studies showed PPIs did not increase the risk for hospitalization for community-acquired pneumonia in the general population (45). The potential drug interaction of PPIs with other IPF medications and the long-term effect of treatment in patients with IPF are unknown.

Future research opportunities. Further RCTs are needed to compare antiacid treatment versus placebo in patients with IPF. Also, further research should focus on the drug interaction of PPIs with other IPF medical treatment, the long-term safety of PPI treatment for patients with IPF with or without symptoms of GER/GERD, the role of therapy in nonacid reflux, and the role of abnormal GER and microaspiration in the pathogenesis, progression, and/or exacerbation of IPF. Further studies are warranted to determine safety and efficacy

of decreasing risks for GER and microaspiration by surgical interventions in patients with IPF.

Question 8: 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 (46, 47). This evidence was included in the 2011 guideline; however, one of the studies (47) 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 ($D_{LCO} < 35\%$ 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 (47). 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 D_{LCO}, 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) (48). 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 $D_{L_{CO}}$, 42% predicted) to receive either sildenafil (20 mg three times daily) or placebo for a 6-month treatment period (46). 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, $D_{L_{CO}}$, or arterial oxygen saturation. More adverse events occurred in the sildenafil group; however, these were not serious.

Pooled analysis of these two trials (46, 47) 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), $D_{L_{CO}}$ (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.

Future research opportunities. Randomized trials focusing on phosphodiesterase inhibitor treatment of patients with IPF with RV-catheter documented PH are needed, as it is possible benefit could be seen in this subgroup of patients. In addition, further studies are needed to address this potential benefit on quality of life seen with sildenafil treatment.

Question 9: 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 (49, 50), whereas a single RCT tested macitentan versus placebo (51). BUILD-1 (Bosentan Use in Interstitial Lung Disease) randomized 158 patients to either bosentan or placebo and followed patients for 12 months (50). 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 (49). 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 (51). 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 (49–51). 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 (52).

Future research opportunities. Further studies, including assessment of treatment response of patient-important outcomes such as mortality and quality of life, are needed to determine the efficacy of dual ERAs in patients with IPF with PH.

Question 10: Should Patients with IPF Be Treated with *N*-Acetylcysteine Monotherapy?

Background. The only RCT that was included in the 2011 guideline document randomized 30 patients to receive either aerosolized *N*-acetylcysteine or bromhexine hydrochloride for 12 months and documented significant improvement in the extent of ground glass on computed tomography and reduction in KL-6 levels (21). No differences in physiologic measurements or walk distance were found.

Summary of the evidence. Two new RCTs have been performed examining *N*-acetylcysteine monotherapy and have been included in this update. A multicenter, prospective RCT done in Japan randomly assigned 76 patients to receive 352.4 mg inhaled *N*-acetylcysteine twice daily versus control during a period of 48 weeks (53). No significant difference was seen in the primary outcome of change in FVC between groups. The other RCT enrolled 264 patients who were subsequently randomized to receive 600 mg oral *N*-acetylcysteine three times a day or placebo (54). The original intent of this study was to compare three intervention groups, including one group of a combination therapy that consisted of oral prednisone, azathioprine, and *N*-acetylcysteine (23). Because of safety concerns encountered after interim analysis, the combination therapy group was dropped midstudy, and randomization continued with the two-group study design, including only *N*-acetylcysteine monotherapy and placebo groups. Results of this two-group analysis (including both pre- and poststudy design change) showed no significant difference in the FVC change with *N*-acetylcysteine monotherapy. Also, there were no significant differences seen in the rates of death or acute exacerbation.

After pooling the results of these three RCTs (21, 53, 54), no significant benefit on mortality was seen using *N*-acetylcysteine monotherapy for patients with IPF (RR, 1.97; 95% CI, 0.50–7.71; low confidence). There were no significant differences in FVC change (high confidence), quality of life (moderate confidence), or adverse outcomes (low confidence). Two studies (21, 54) reported on 6-minute-walk test distance, and a significant improvement was seen using *N*-acetylcysteine monotherapy (mean difference, 44.33 m; 95% CI, 2.92–85.75; very low confidence).

Recommendation. **We suggest that clinicians not use *N*-acetylcysteine monotherapy in patients with IPF (conditional recommendation, low confidence in estimates of effect).**

Justification and implementation considerations. This recommendation places a higher value on the potential risks, inconvenience, and cost of therapy and a low value on possible improvement of outcomes with unclear patient importance. This recommendation generated considerable debate among committee members. The available evidence focused on patients with IPF with mild to moderate impairment in PFTs, and as for other recommendations, it was acknowledged that generalization to patients with more severe impairment of PFTs should be done with caution. The committee did not find sufficient evidence for differences in outcomes between inhaled versus oral administration of *N*-acetylcysteine, and therefore the recommendation applies to both interventions. No evidence of significant harm was found, and therefore, no suggestion related to discontinuation in patients already receiving *N*-acetylcysteine monotherapy was made, although if there is no benefit from starting therapy, it is unlikely that there is benefit from continuing.

Future research opportunities. It is unclear whether a subset of patients with IPF with a higher burden of oxidative stress may benefit from *N*-acetylcysteine monotherapy. Future trials should identify whether there is a subgroup of patients more likely to benefit from therapy than others. It is possible that one route of administration may be more beneficial than another, and studies assessing different delivery of *N*-acetylcysteine in patients with IPF could be considered.

Question 11: Should Patients with IPF Be Treated with Bilateral Lung Transplantation versus Single-Lung Transplantation?

Background. Given the progressive and incurable nature of IPF, lung transplantation is commonly considered for patients with moderate to severe disease. It is unclear whether bilateral lung transplantation is superior to single-lung transplantation in patients with underlying IPF. Lacking RCT evidence to guide this recommendation, we considered observational studies that assessed the survival of patients with IPF, accepting bilateral lung transplantation versus single-lung transplantation (55–61).

Summary of the evidence. Pooled survival analysis of three observational studies showed no difference between patients who received single versus bilateral lung transplantation (HR, 0.47; 95% CI, 0.19–1.17) (56–58). Four additional studies were not included in the pooled analysis, as they did not report hazard ratios; however, consistent with the other studies, patients accepting bilateral lung transplantation showed no significant difference in terms of survival from those accepting single-lung transplantation (55, 59–61). A subsequent meta-analysis was published after the guideline committee had met, and therefore was not considered, although results presented in this review were consistent with previous studies and would not have changed the overall conclusion (62).

Recommendation. **The committee did not make a recommendation regarding single versus bilateral lung transplantation in patients with IPF.**

Justification. The committee acknowledged that additional evidence should be evaluated to guide this clinical decision. The shortage of organs is a universal problem, and the decision to give bilateral lung transplantation to a single patient rather than give single-lung transplantation to two patients, including the effect on health inequity, must be considered.

Future research opportunities. RCTs are needed to properly address this question. Also, future guidelines regarding this question need to be addressed by committees that include members with expertise in lung transplantation to better address this clinical question.

Question 12: Should PH Be Treated in Patients with IPF?

Background. Comorbid PH is commonly seen in patients with IPF and contributes to a worsened clinical prognosis (63, 64).

Summary of the evidence. The 2011 guideline considered the very limited available evidence at the time (65–69) in suggesting against treatment of PH in patients with IPF. The studies included in this initial guideline document were limited by focusing on short-term hemodynamics rather than long-term patient important outcomes (65–67, 69), not randomizing patients to treatment or control (65, 67, 68), not including an adequate placebo (66, 68, 69), analyzing data retrospectively (68), or a combination of these methodologic concerns.

Subsequent RCTs, already described in this document, which examined the treatment of patients with IPF with ambrisentan (28) and sildenafil (47), included *a priori* subgroup analysis for patients with comorbid PH. Ambrisentan treatment, stratified in the ARTEMIS-IPF (Randomized, Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in IPF) trial based on PH status, as assessed by right-sided heart catheterization, showed no significant subgroup effect in patients with documented mean pulmonary artery pressures higher than 25 mm Hg. Given the similar results, namely, an increase in disease progression and respiratory hospitalization in patients treated with ambrisentan, the strong recommendation against treatment above also applies to this subgroup of patients.

Within the STEP-IPF trial, investigators examined the effect of sildenafil treatment on the subgroup of patients with echocardiogram-documented right ventricular hypertrophy or RVSD (48). As described earlier, in patients with RVSD, but not right ventricular hypertrophy, sildenafil was found to have a significant improvement on the primary outcome of 6-minute-walk distance. Given that no other outcomes were significantly different, the lack of gold standard in diagnosing PH, and the exploratory nature of the analysis, no subgroup recommendation for phosphodiesterase inhibitor treatment in patients with IPF with documented PH was made.

Finally, a small, open-label, noncontrolled, pulmonary hemodynamic study has shown an acceptable safety profile for riociguat, a soluble guanylate cyclase stimulator, when used in patients with PH and associated interstitial lung disease of any cause (70). Further investigation, including large phase 3 and 4 trials specifically examining the effect of this medication in patients with documented IPF, will be needed before serious consideration of widespread use.

Recommendation. **The committee did not make a recommendation regarding treatment of PH in patients with IPF.**

Justification. The committee acknowledged that further evidence is needed and should be evaluated to guide this clinical decision.

Future research opportunities. Novel PH agents are increasingly becoming available, and future research should focus on their effect on PH in patients with underlying IPF. Future clinical trials in patients with IPF manifesting PH should consider studies with agents indicated for treatment of PH, especially the ones that have demonstrated an acceptable safety profile in patients with IPF (e.g., dual ERAs, phosphodiesterase-5 inhibitor), but not the ones with documented harmful effects (e.g., selective ERA, ambrisentan). Clinical trials should consider treatment with vasoactive medications stratified or subgroup analysis focusing on patients with known PH to assess for differential effect.

Conclusions

Significant advances have been made in the clinical management of IPF since the 2011 evidence-based guideline. New evidence for treatment recommendations that had received conditional (i.e., weak) recommendations by the committee developing the 2011 guideline have been reviewed carefully, and updated recommendations have been provided. Although there are no pharmacologic interventions that received strong recommendations for treatment, conditional recommendations have been made for treatment with novel agents such as pirfenidone and nintedanib, as well as antiacid treatment for patients with IPF.

Clinicians confronted with treating patients with IPF should individualize decisions with their patients, as suggested by the conditional recommendations, and they should be cautious in comparing the relative net benefit of one intervention with another. Significant variations in inclusion criteria, based on physiologic and anatomic variables between studies included in these evidence summaries, as well as variability in the level of confidence of the overall certainty in effect estimates available, are important factors that need to be considered by the clinician when confronted with treating a patient with IPF.

The potential of combined, sequential, or adjunctive treatment regimens with agents included in this guideline document have not been studied to date, and therefore recommendations have not been made. Future head-to-head RCTs of treatment interventions are necessary to address these important questions. Also, the duration of benefit seen with these newer agents is not clear. Further research is required to better inform optimal duration of therapy. It is hoped that the results of such anticipated research and ongoing research will clarify this soon.

Some treatment options with potential clinical benefit (e.g., clotrimazole) in IPF were not addressed in this update. This and other treatment interventions such as treatment for acute exacerbation, pulmonary rehabilitation, oxygen supplementation, mechanical ventilation, palliative care, and so on, as well other pertinent new evidence that may become available, will be addressed in another update focused on treatment in the near future by the committee.

Future Directions

There is an absolute need for further and long-term studies to determine the safety and efficacy of treatment options for IPF in patients with all spectrums of functional impairment. This is especially true for treatment with drugs that received conditional recommendations, including pirfenidone and nintedanib. Although it is clear that treatment with warfarin for IPF in patients without other indications is not beneficial, studies using other anticoagulants such as the new oral agents may be worthwhile. Triple therapy with prednisone, azathioprine, and *N*-acetylcysteine is harmful, although it is unknown which specific component or combination and what doses of the individual components cause harm. The feasibility of conducting another trial examining triple therapy is questionable,

especially in the context of the known adverse effects associated with prednisone and azathioprine and the encouraging results with the newer antifibrotic agents. Treatment with different formulation of *N*-acetylcysteine or other antioxidants, stratified on the basis of the burden of oxidant stress, are worthwhile considerations.

Although there is no benefit of endothelin receptor antagonists for the treatment of IPF in patients without PH, the safety profile of dual ERAs in patients with IPF and their known therapeutic benefits for treatment of PH, especially macitentan, are worthwhile considerations and should dictate future studies looking at their role in patients with IPF with documented PH. Pursuing treatment with ambrisentan, a selective ERA, is not appropriate, given the documented decline in respiratory status seen in the context of a large clinical trial. Future clinical studies must address the potential treatment with other agents of PH in patients with IPF.

Although the strong association of abnormal acid GER with IPF and the very high prevalence of abnormal acid GER in patients with IPF is well known, it is less clear whether the abnormal acid GER is the cause or the effect of IPF. Further studies are warranted to determine the safety and efficacy of antiacid treatment, the adherence of conservative measures to prevent or

decrease the risks of insults to the lung by microaspiration, and the role for surgical correction to eliminate or decrease GER.

Treatment studies looking at combination interventions and multiple targets implicated in the pathogenesis of IPF are needed. In this regard, the promising results that have been seen (and reported in this guideline document) using novel individual agents may lead to a cumulative benefit, or even a synergistic effect, when given in combination. Indeed, drug–drug interactions, pharmacokinetics, and safety profiles will need to be delineated before embarking on such clinical trials. Future clinical trials should include all consecutive patients with IPF and stratify the extent of disease by functional impairment and/or anatomic extent.

Importantly, the vast majority of patients with IPF are older than 60 years and are considered elderly, and they manifest an increasing number of comorbidities that warrant prompt detection and treatment strategies. This includes conditions such as PH, emphysema, airflow obstruction, GERD, sleep apnea, coronary artery diseases, and obesity.

Palliative care for symptoms, such as shortness of breath, cough, and fatigue, as well as comfort care for the terminally ill, is essential for patients with IPF at the end of life. Future studies need to address these as

endpoints in assessing response to new treatment strategies.

Lung transplantation is indicated for a subgroup of patients with IPF who meet criteria; however, it is unclear whether single or bilateral lung transplantation is preferential for long-term outcomes. Because several confounding and seemingly arbitrary factors determine the clinical decision of single versus bilateral lung transplantation at most centers, future multicenter studies are needed to determine the most appropriate use of donor lungs to maximize available organs in an efficacious manner.

Finally, approaches to personalized medicine such as treatment stratified by anatomic, clinical, or physiologic biomarkers found in the peripheral circulation or in the lung (tissue or bronchoalveolar lavage), and studies with pharmacogenomics and pharmacoeconomics, are worthy of future investigation. This will allow physicians treating patients with IPF to better understand the role of increasingly complex and costly treatment interventions aimed at improving the outcomes of those with this disease. Most important, with continued high-level and collaborative clinical and basic science research, dedicated efforts, and adequate resources and funds, the hopes of aborting disease progression and ultimately curing this disease will be met. ∎

Editor's (Kevin Wilson, M.D.) Note: 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 antiacid recommendation. Many of the conflicted experts would have made no recommendation, citing a lack of randomized trials and concern that the antiacid 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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*The ATS, ERS, JRS, and ALAT, including the IPF guideline committee, are deeply indebted to Mr. William Cunningham for his active participation and the invaluable input he provided in support of this document. Sadly, he passed away October 23, 2014.

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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[1]Authors for whom dollar ranges are not noted typically disclosed through the ICMJE form, which does not require dollar amounts.

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