

A current overview of diagnosis of IPF

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American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), THE EUROPEAN RESPIRATORY SOCIETY (ERS), THE JAPANESE RESPIRATORY SOCIETY (JRS), AND THE LATIN AMERICAN THORACIC ASSOCIATION (ALAT) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, NOVEMBER 2010, THE ERS EXECUTIVE COMMITTEE, SEPTEMBER 2010, THE JRS BOARD OF DIRECTORS, DECEMBER 2010, AND THE ALAT EXECUTIVE COMMITTEE, NOVEMBER 2010

THIS STATEMENT HAS BEEN FORMALLY ENDORSED BY THE SOCIETY OF THORACIC RADIOLOGY AND BY THE PULMONARY PATHOLOGY SOCIETY

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DOI: 10.1164/rccm.2009-040GL

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Definition and epidemiology

- A specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults
- It is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP)
- It requires the exclusion of other forms of interstitial pneumonia including other idiopathic interstitial pneumonias and ILD associated with environmental exposure, medications, or systemic disease

Clinical Presentation

- IPF should be considered in all adult patients with unexplained chronic exertional dyspnoea, and commonly presents with cough, bibasilar inspiratory crackles, and finger clubbing
- Its incidence increases with older age, typically presents in the 60s and 70s
- Patients with IPF aged less than 50 years are rare; such patients may subsequently manifest overt features of an underlying connective tissue disease that was subclinical at the time IPF was diagnosed
- More men have been reported with IPF than women
- Majority of patients have a history of cigarette smoking

Incidence and prevalence

- There are no large-scale studies of the incidence or prevalence of IPF on which to base formal estimates
- But it ranges between 6.8 to 16.3 per 100,000 persons
- Prevalence varies from 2 to 29 cases per 100,000 in the general population
- The wide range in these numbers is likely explained by the previous lack of uniform definition used in identifying cases of IPF, as well as by differences in study designs and populations

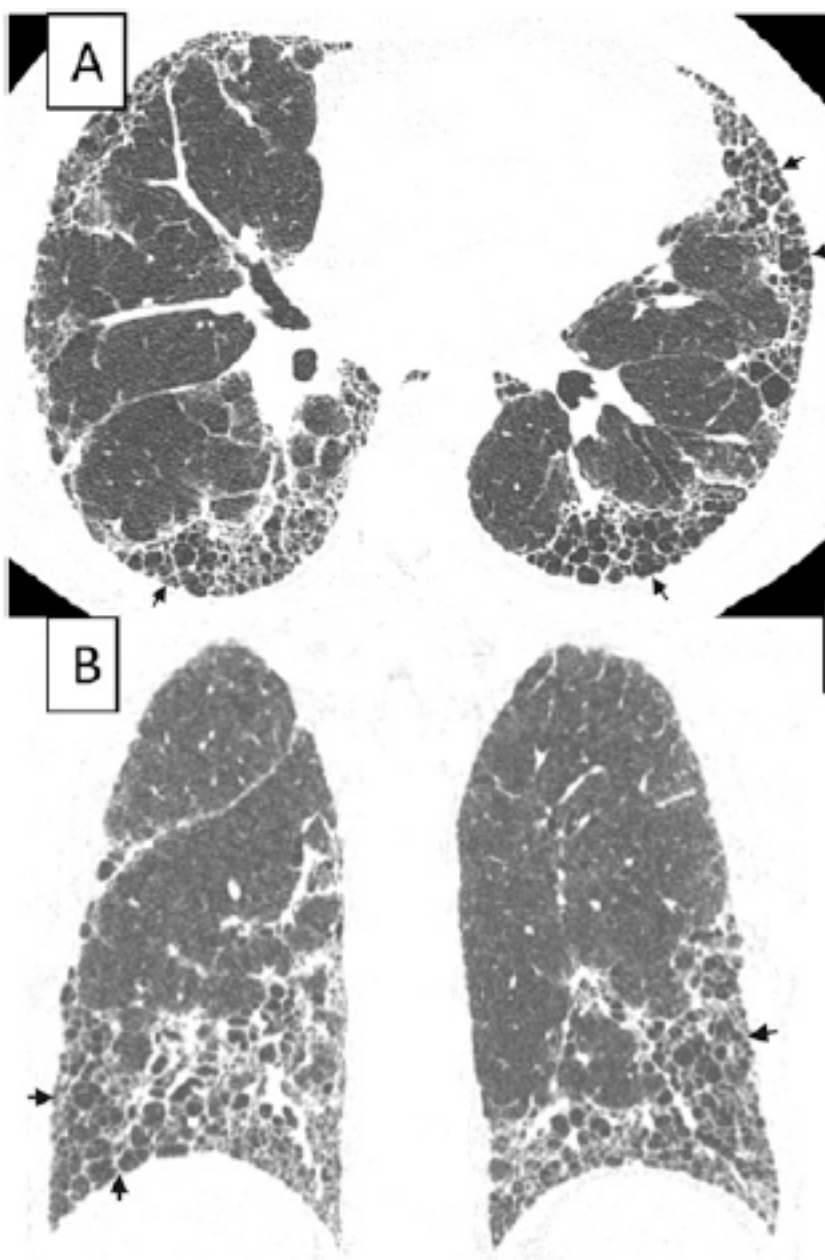
Diagnostic Criteria

- The diagnosis of IPF requires the following:
 1. Exclusion of other known causes of ILD (e.g. domestic and occupational environmental exposures, connective tissue disease and drug toxicity)
 2. The presence of a UIP pattern in HRCT in patients not subjected to surgical lung biopsy
 3. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy

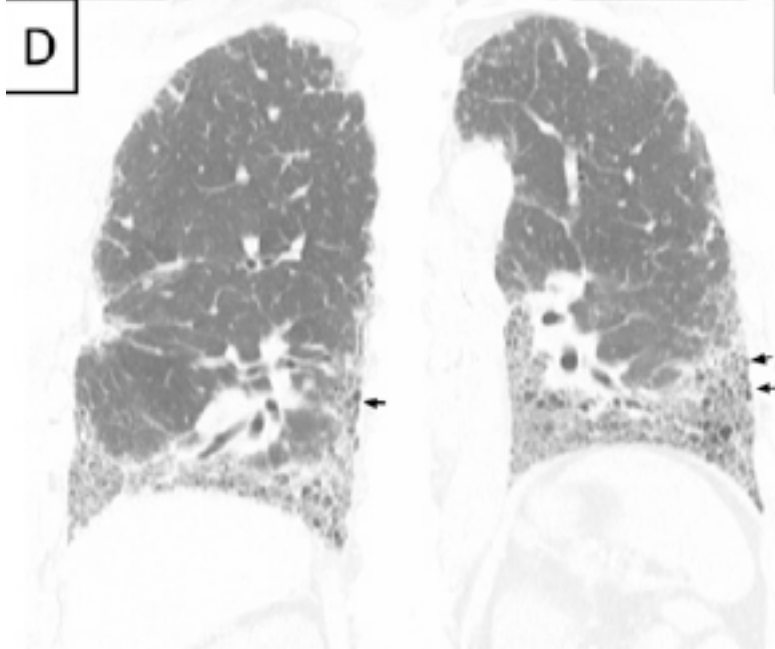
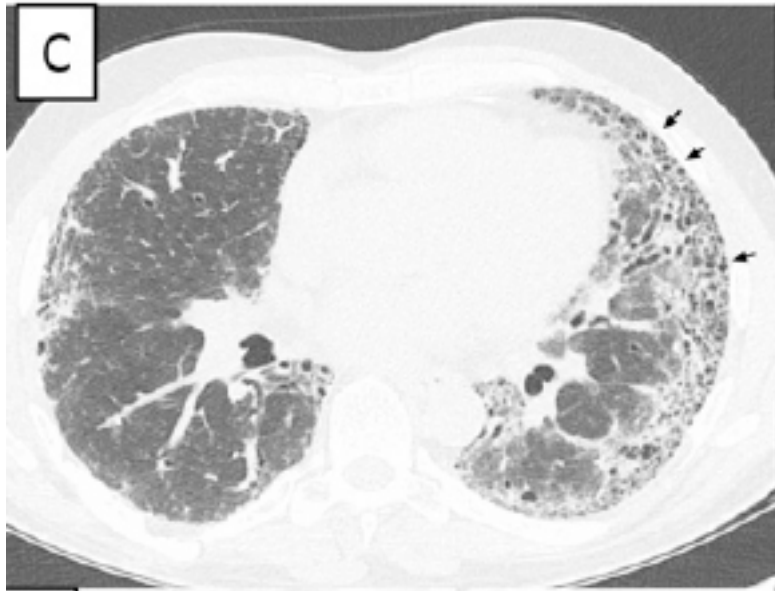
HRCT criteria for UIP pattern

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
<ul style="list-style-type: none">• Subpleural, basal predominance• Reticular abnormality• Honeycombing with or without traction bronchiectasis• Absence of features listed as inconsistent with UIP pattern (<i>see</i> third column)	<ul style="list-style-type: none">• Subpleural, basal predominance• Reticular abnormality• Absence of features listed as inconsistent with UIP pattern (<i>see</i> third column)	<ul style="list-style-type: none">• Upper or mid-lung predominance• Peribronchovascular predominance• Extensive ground glass abnormality (extent > reticular abnormality)• Profuse micronodules (bilateral, predominantly upper lobes)• Discrete cysts (multiple, bilateral, away from areas of honeycombing)• Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes)• Consolidation in bronchopulmonary segment(s)/lobe(s)

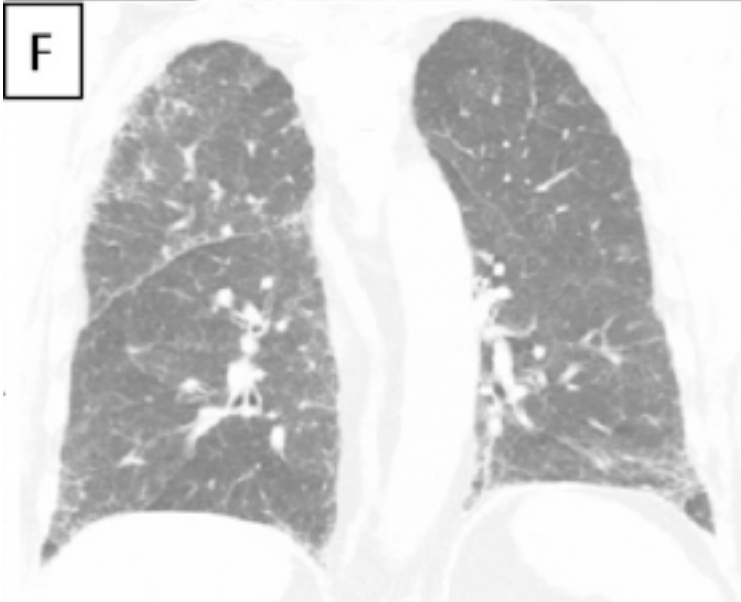
Definition of abbreviation: UIP = usual interstitial pneumonia.



A and B: UIP pattern with extensive honeycombing. Axial and coronal HRCT images show basal predominant, peripheral predominant reticular abnormality with multiple layers of honeycombing (arrows)



C and D: UIP pattern, with less severe honeycombing. Axial and coronal CT images show basal predominant, peripheral predominant reticular abnormality with subpleural honeycombing (arrows).



E and F: Possible UIP pattern: axial and coronal images show peripheral and basal predominant reticular abnormality with a moderate amount of ground glass abnormality, but without honeycombing.

UIP pattern: HRCT features

- UIP is characterised on HRCT by the presence of reticular opacities, often associated with traction bronchiectasis
- **Honeycombing is common, and is critical for making a definite diagnosis**
 - It is described as clustered cystic airspaces, typically of comparable diameters on the order of *3-10mm* but occasionally as large as *2.5cm*.
 - Usually subpleural and is characterised by well-defined walls
- GGO are common but usually less extensive than the reticulation
- UIP distribution is characteristically basal and peripheral, though often patchy
- The presence of coexistent pleural abnormalities (e.g pleural plaques, calcifications, significant pleural effusion) suggests an alternative aetiology for UIP pattern

HRCT features continued

- Micronodules, air trapping, non-honeycombing cysts, extensive GGO, consolidation, or a peribronchovascular-predominant distribution should lead to consideration of an alternative diagnosis
- Mild mediastinal LN enlargement (usually less than 1.5 cm in short axis) can be seen
- The CXR is often less useful than HRCT in evaluating patients with suspected IPF

Figure 61



Figure 61: Chest radiograph shows reticular pattern.

reticular pattern

Radiographs and CT scans.—On chest radiographs, a reticular pattern is a collection of innumerable small linear opacities that, by summation, produce an appearance resembling a net (synonym: *reticulation*) (Fig 61). This finding usually represents interstitial lung disease. The constituents of a reticular pattern are more clearly seen at thin-section CT, whether they are interlobular septal thickening, intralobular lines, or the cyst walls of honeycombing. (*Reticular pattern* and *honeycombing* should not be considered synonymous.

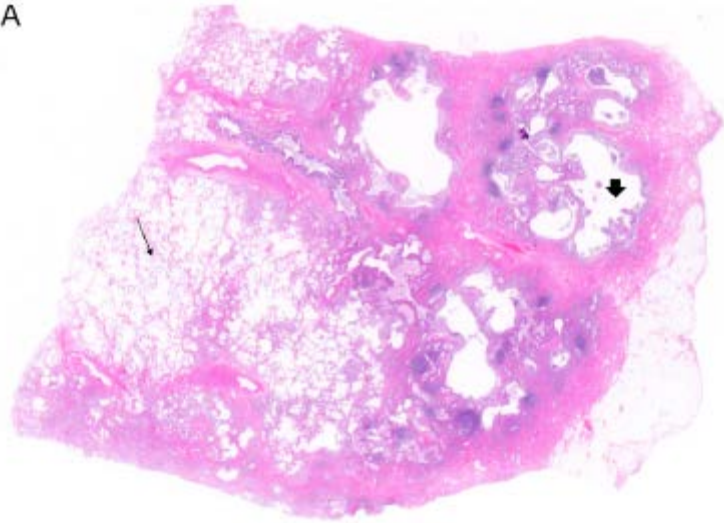
HRCT features continued

- Several studies have demonstrated that the positive predictive value of a HRCT diagnosis of UIP is 90 to 100%
- However, they are criticised for selection bias as they only included patients with biopsy-proven diagnoses
- Nonetheless, a UIP pattern on HRCT is highly accurate for the presence of UIP pattern on surgical lung biopsy
- If honeycombing is *absent*, but the imaging features otherwise meet criteria for UIP, it is then regarded as *possible UIP* – a surgical lung biopsy is necessary to make a definitive diagnosis
- In patients whose HRCT does not demonstrate a UIP pattern the surgical lung biopsy may still demonstrate UIP pattern on histopathology

UIP pattern Histopathology Features

- The histopathological hallmark and chief diagnostic criterion is
 - *A heterogeneous appearance at low magnification in which areas of fibrosis with scarring and honeycomb change alternate with areas of less affected or normal parenchyma*

A



B

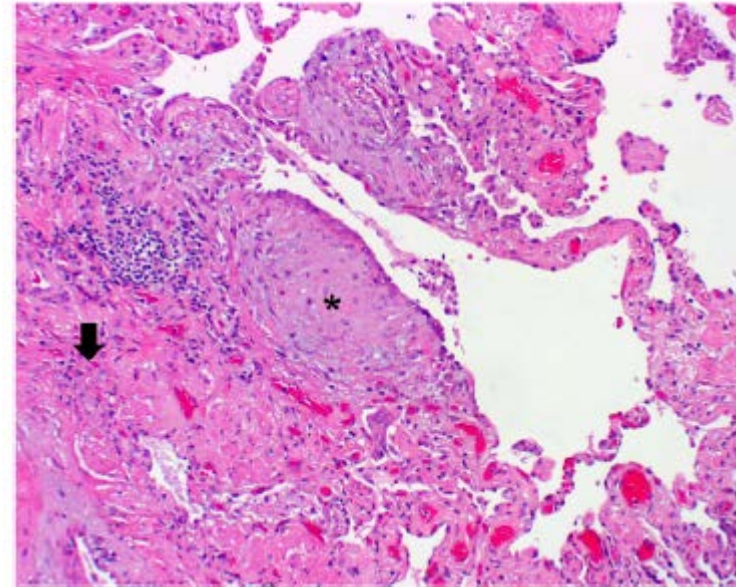


Figure 2. Surgical lung biopsy specimens demonstrating UIP pattern. (A) Scanning power microscopy showing a patchy process with honeycomb spaces (*thick arrow*), some preserved lung tissue regions (*thin arrow*), and fibrosis extending into the lung from the subpleural regions. (B) Adjacent to the regions of more chronic fibrosis (*thick arrow*) is a fibroblast focus (*asterisk*), recognized by its convex shape and composition of edematous fibroblastic tissue, suggestive of recent lung injury.

TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
<ul style="list-style-type: none"> • Evidence of marked fibrosis/ architectural distortion, \pm honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) 	<ul style="list-style-type: none"> • Evidence of marked fibrosis / architectural distortion, \pm honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) <p>OR</p> <ul style="list-style-type: none"> • Honeycomb changes only[‡] 	<ul style="list-style-type: none"> • Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (see UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) 	<ul style="list-style-type: none"> • Hyaline membranes* • Organizing pneumonia*[‡] • Granulomas[†] • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

TABLE 6. COMBINATION OF HIGH-RESOLUTION COMPUTED TOMOGRAPHY AND SURGICAL LUNG BIOPSY FOR THE DIAGNOSIS OF IPF (REQUIRES MULTIDISCIPLINARY DISCUSSION)

HRCT Pattern*	Surgical Lung Biopsy Pattern* (When Performed)	Diagnosis of IPF?†
UIP	<div> <div> UIP Probable UIP Possible UIP Nonclassifiable fibrosis[‡] </div> } </div>	YES
	Not UIP	No
Possible UIP	<div> <div> UIP Probable UIP </div> } </div>	YES
	<div> <div> Possible UIP Nonclassifiable fibrosis </div> } </div>	Probable [§]
	Not UIP	No
Inconsistent with UIP	UIP	Possible [§]
	<div> <div> Probable UIP Possible UIP Nonclassifiable fibrosis Not UIP </div> } </div>	No

COLDICE trial

Public title	The COLDICE Trial: Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease allianCE
Scientific title	In patients with interstitial lung disease requiring histopathologic evaluation for diagnosis, are the transbronchial lung cryobiopsy (TBLC) and the gold-standard video-assisted thoracoscopic surgical (VATS) lung biopsy, similar in their diagnostic yield?
Secondary ID [1]	Nil
Universal Trial Number (UTN)	U1111-1171-6880
Trial acronym	COLDICE
Linked study record	

Should serologic testing for connective tissues disease be used in the evaluation of suspected IPF?

- Connective tissue disease can present with a UIP pattern, and ILD has been described as the sole clinical manifestation of these conditions and can precede the overt manifestation of a specific connective tissue disease
- However, there are no reliable data on the role of screening serologies in patients with suspected IPF.
- **Recommendation:** serologic testing for connective tissue disease should be performed in the evaluation of IPF in the majority of patients
- It places a high value on distinguishing connective tissue disease from IPF
- These should be performed even in the absence of signs or symptoms of connective tissue disease, and should include RF, Anti-CCP, ANA titre and pattern
- The routine use of other serological tests such as anti-Jo-1, CK, SS-A, SS-B and scleroderma antibodies (Scl-70, PM-1) is of unclear benefit, but may be helpful in selected cases

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

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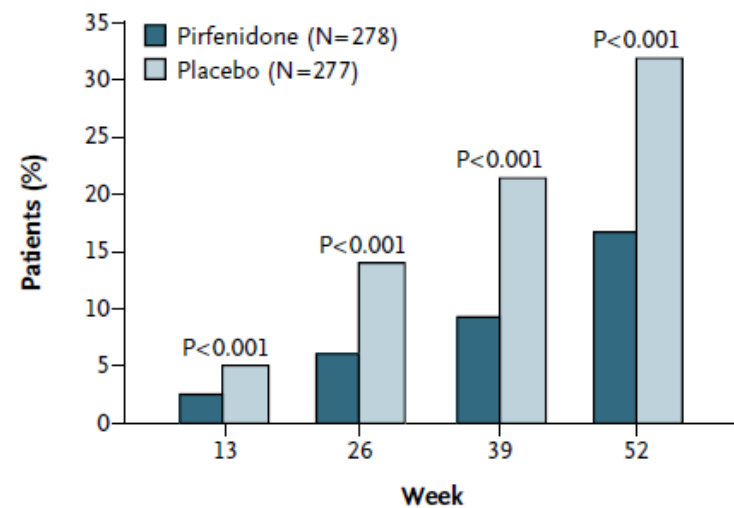
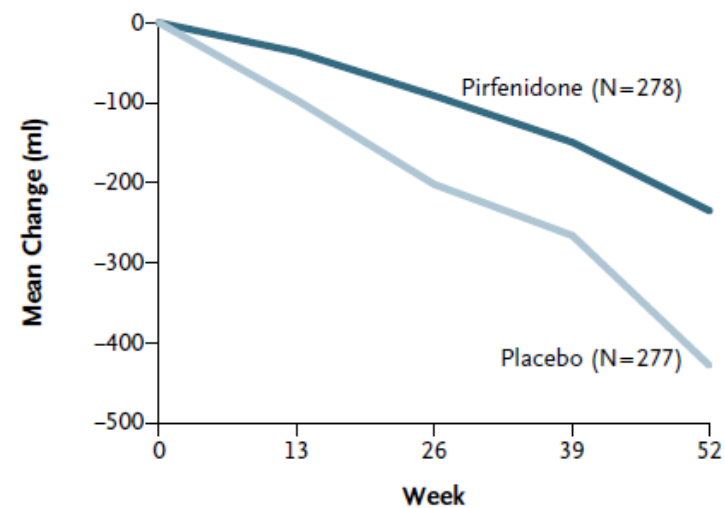
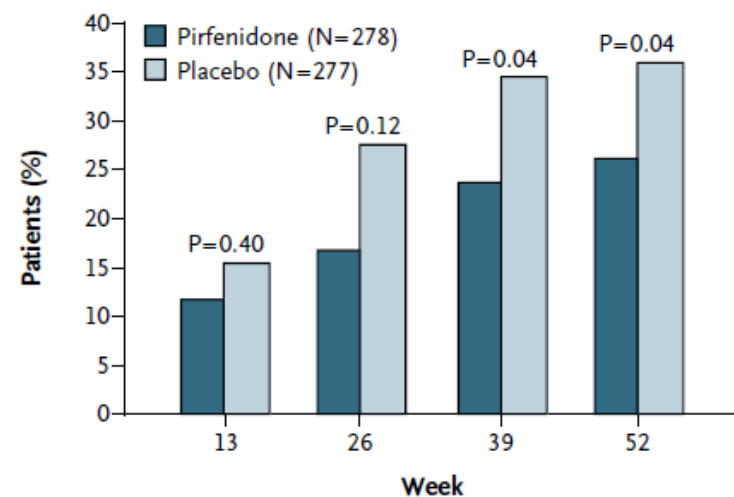
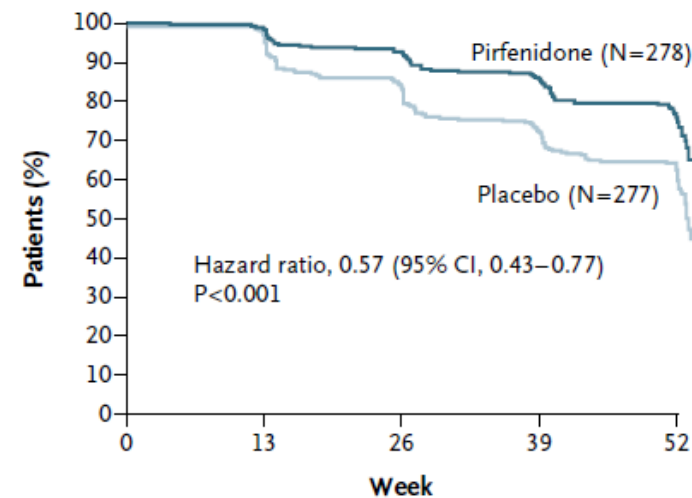
ABSTRACT

BACKGROUND

In two of three phase 3 trials, pirfenidone, an oral antifibrotic therapy, reduced disease progression, as measured by the decline in forced vital capacity (FVC) or vital capacity, in patients with idiopathic pulmonary fibrosis; in the third trial, this end point was not achieved. We sought to confirm the beneficial effect of pirfenidone on disease progression in such patients.

METHODS

In this phase 3 study, we randomly assigned 555 patients with idiopathic pulmonary fibrosis to receive either oral pirfenidone (2403 mg per day) or placebo for 52 weeks. The primary end point was the change in FVC or death at week 52. Secondary end points were the 6-minute walk distance, progression-free survival, dyspnea, and death from any cause or from idiopathic pulmonary fibrosis.

A Decreased FVC or Death**B Change in FVC****C Decreased Walk Distance or Death****D Progression-free Survival****No. at Risk**

Pirfenidone	276	269	243	219	144
Placebo	273	262	225	192	113

RESULTS

In the pirfenidone group, as compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC ($P<0.001$). Pirfenidone reduced the decline in the 6-minute walk distance ($P=0.04$) and improved progression-free survival ($P<0.001$). There was no significant between-group difference in dyspnea scores ($P=0.16$) or in rates of death from any cause ($P=0.10$) or from idiopathic pulmonary fibrosis ($P=0.23$). However, in a prespecified pooled analysis incorporating results from two previous phase 3 trials, the between-group difference favoring pirfenidone was significant for death from any cause ($P=0.01$) and from idiopathic pulmonary fibrosis ($P=0.006$). Gastrointestinal and skin-related adverse events were more common in the pirfenidone group than in the placebo group but rarely led to treatment discontinuation.

CONCLUSIONS

Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis. Treatment was associated with an acceptable side-effect profile and fewer deaths. (Funded by InterMune; ASCEND ClinicalTrials.gov number, NCT01366209.)

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Efficacy and Safety of Nintedanib in Idiopathic
Pulmonary Fibrosis

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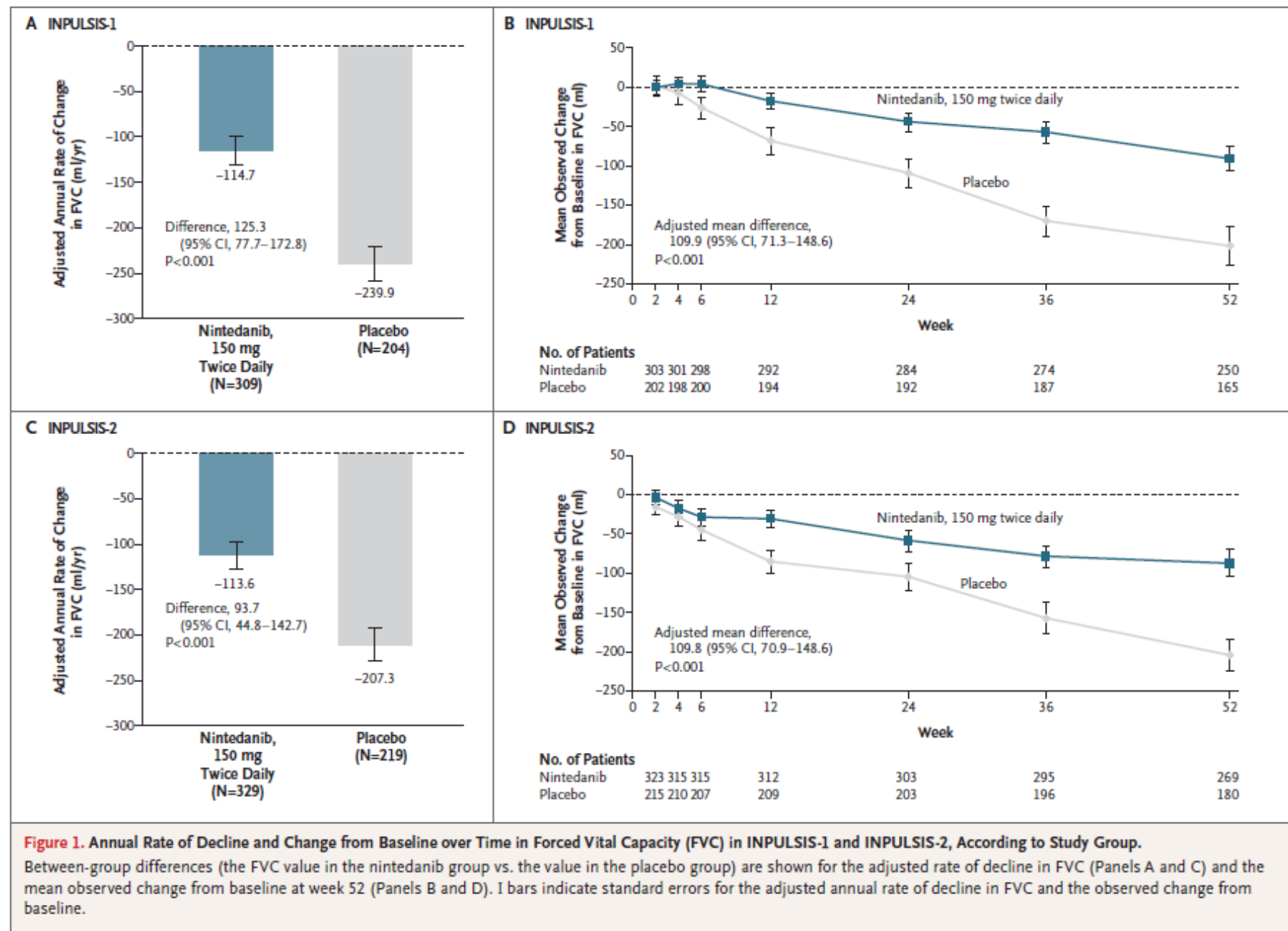
ABSTRACT

BACKGROUND

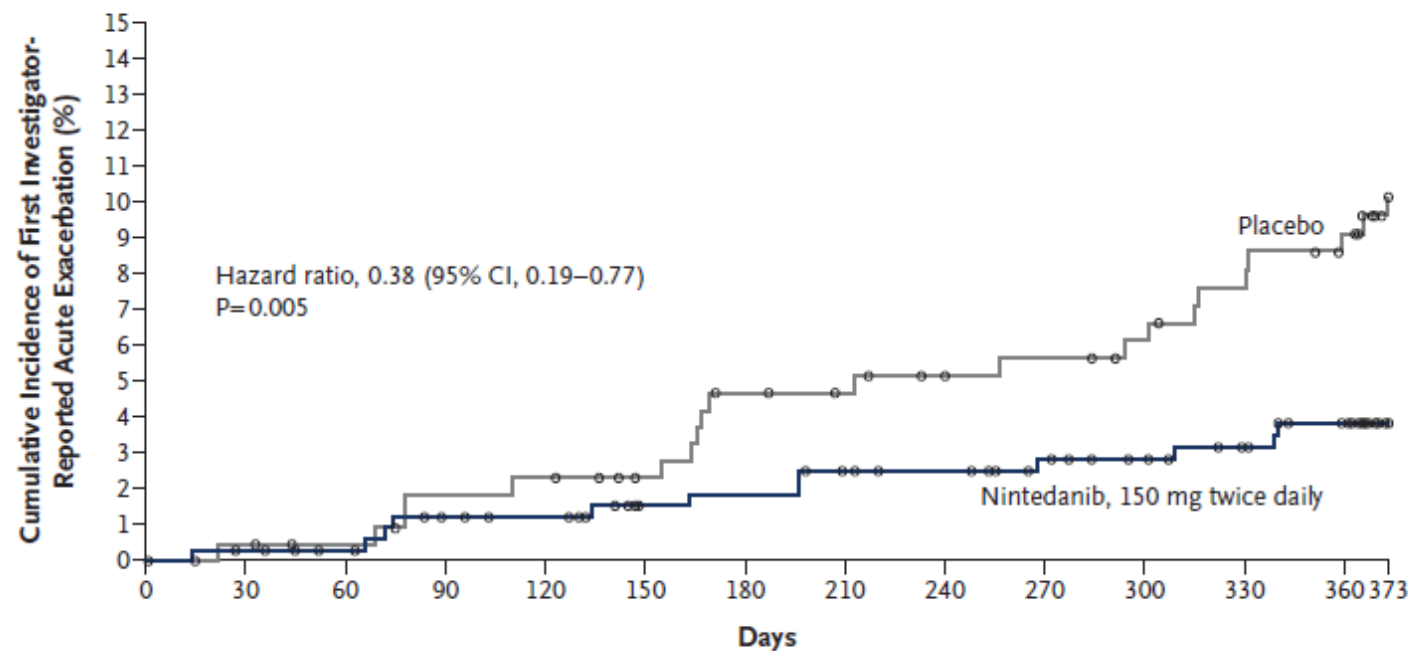
Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases. A phase 2 trial suggested that treatment with 150 mg of nintedanib twice daily reduced lung-function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.

METHODS

We conducted two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary end point was the annual rate of decline in forced vital capacity (FVC). Key secondary end points were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period.



B INPULSIS-2



No. of Patients

Nintedanib	329	326	323	317	315	307	306	302	300	295	291	286	279	259
Placebo	219	217	215	211	210	206	200	198	195	193	190	186	181	171

Figure 2. Time to First Investigator-Reported Acute Exacerbation in INPULSIS-1 and INPULSIS-2.

RESULTS

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was -114.7 ml with nintedanib versus -239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8 ; $P < 0.001$) in INPULSIS-1 and -113.6 ml with nintedanib versus -207.3 ml with placebo (difference, 93.7 ml; 95% CI, 44.8 to 142.7 ; $P < 0.001$) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with nintedanib, 1.15 ; 95% CI, 0.54 to 2.42 ; $P = 0.67$); in INPULSIS-2, there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38 ; 95% CI, 0.19 to 0.77 ; $P = 0.005$). The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively, in INPULSIS-1 and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2.

CONCLUSIONS

In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients. (Funded by Boehringer Ingelheim; INPULSIS-1 and INPULSIS-2 ClinicalTrials.gov numbers, NCT01335464 and NCT01335477.)

Anti-Fibrotics

- Limited generalisability of trials and patients' heterogeneity in the real world.
- Probably well tolerated
- Safety not main concern for Pirfenidone, or Nintedanib
- Anti-fibrotics appear to be improving survival in real life in Australia
 - Predicted improved life expectancy by 2.83 years when compared with best supportive care

Anti-Fibrotics

- No benefits associated with the drugs in terms of symptoms!

(Most freq sx in IPF are dyspnoea and cough, others include anxiety and depression – AIPF Registry – both not measured in trials)

- Limit progression and may improve survival
- New drugs needed.

Protease activated receptor-1 regulates macrophage-mediated cellular senescence: a risk for idiopathic pulmonary fibrosis

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ABSTRACT

Proton-pump inhibitors and IPF

- The prevalence of abnormal acid gastroesophageal reflux (GER) is higher in patients with IPF than in matched control subjects.
- Several studies demonstrated that more than one-third of patients with IPF have abnormal esophageal acid exposures.
- In addition, many of these studies indicate that the majority of patients with IPF have silent reflux with no symptoms of GER.

Proton-pump inhibitors and IPF

- “The recommendation for the treatment of asymptomatic gastroesophageal reflux in patients with IPF is **weak**; that is, asymptomatic gastroesophageal reflux should be treated in the majority of patients with IPF, but not treating asymptomatic gastroesophageal reflux may be a reasonable choice in a minority”

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DOI: 10.1164/rccm.2009-040GL
Internet address: www.atsjournals.org

Proton-pump inhibitors and IPF

- Retrospective, anecdotal data suggest a beneficial role of PPIs in IPF including stabilization of lung function, reduction in episodes of acute exacerbation, and enhanced longevity.
- Been reported that PPIs possess anti-inflammatory and anti-fibrotic activities by directly suppressing pro-inflammatory cytokines, pro-fibrotic proteins, and proliferation of lung fibroblasts.

Proton-pump inhibitors and IPF

The recent evidence-based guidelines for treatment of IPF approved conditional recommendation of PPIs for ***all*** patients with IPF regardless of their GER status.

Raghu G et al. Am J Respir Crit Care Med 2015;192:e3-e19.

Oxygen therapy and Pulmonary Rehab in IPF

- LTOT is generally well accepted
- The *recommendation* for long-term oxygen therapy in patients with IPF and clinically significant resting hypoxemia is *strong*

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011
DOI: 10.1164/rccm.2009-040GL
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- But... No RCT oxygen therapy for IPF

Oxygen therapy and Pulmonary Rehab in IPF

- No acute effect of oxygen on dyspnoea during exercise, however it may increase **exercise capacity** (Bell et al Euro Resp Rev 2017)
- Increased **exercise capacity** more than reduced dyspnoea (Khor et al Annals of ATS 2017)
- Increased **endurance time** with oxygen (Dowman et al Respirology 2017)

Oxygen therapy and Pulmonary Rehab in IPF

- However, embarrassment and stigma are negative effects of using ambulatory oxygen
- QOL is reduced in those on oxygen therapy – observation only (uncontrolled study)
 - ?reflects severity of disease, or effect of oxygen therapy.

Oxygen therapy and Pulmonary Rehab in IPF

Pulmonary Rehab - reduced breathlessness and improved QOL (J Alison et al Respirology 2017)

- Refer early important to achieve sustained benefits
- Non exercise component- education and support
- Important area, what to expect in the future - end of life planning, managing cough, managing medications and side effects