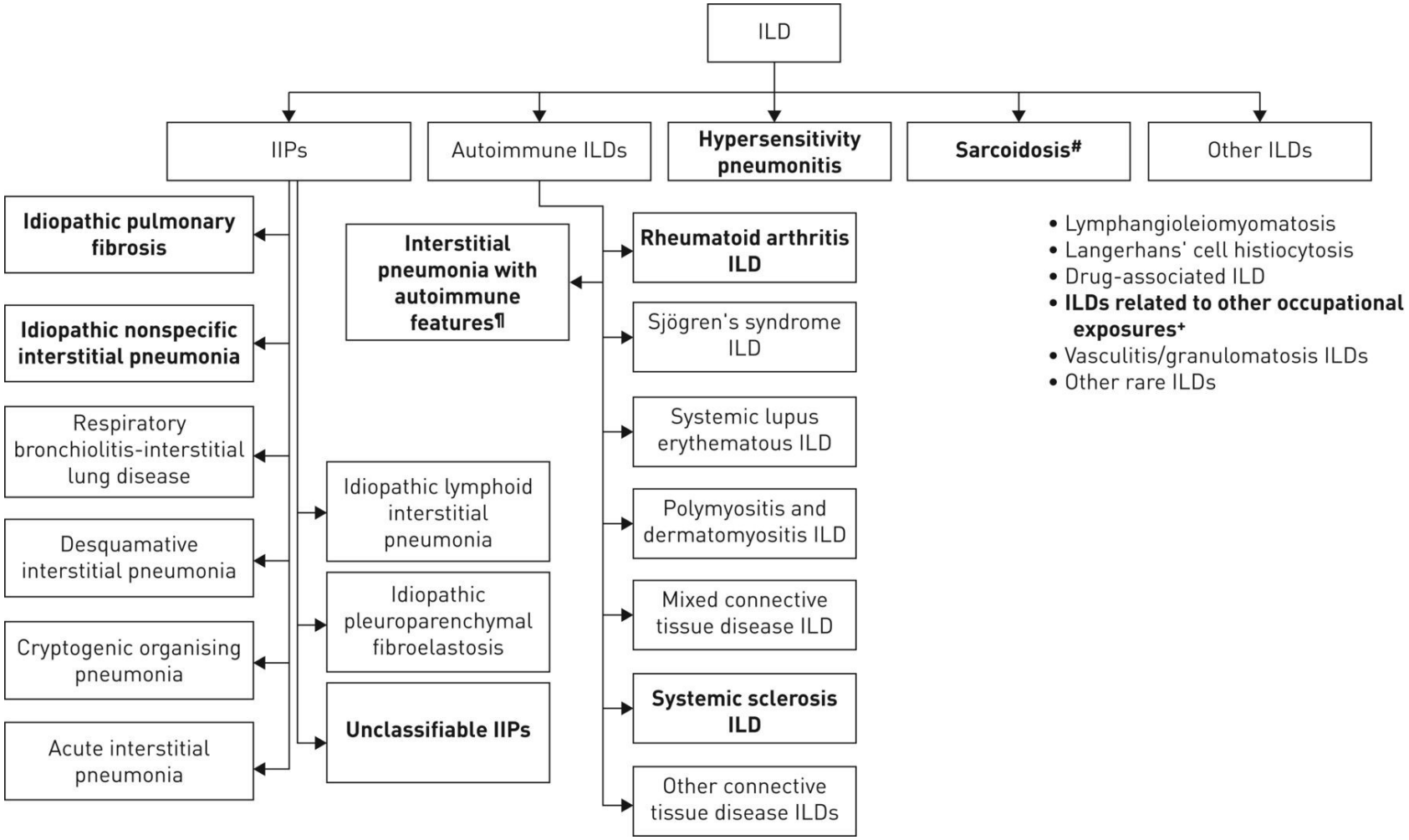
İdiyopatik Pulmoner Fibrozis

Dr Dildar Duman

SBÜ Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi EAH

İAH Sınıflama



JAMA | Review

Interstitial Lung Disease
A Review

Toby M. Maher, MD, MSc, PhD

JAMA. doi:10.1001/jama.2024.3669
Published online April 22, 2024.

OBSERVATIONS The most common forms of ILD are idiopathic pulmonary fibrosis (IPF), whic accounts for approximately one-third of all cases of ILD, hypersensitivity pneumonitis, accounting for 15% of ILD cases, and connective tissue disease (CTD), accounting for 25% of ILD cases. ILD typically presents with dyspnea on exertion. Approximately 30% of patients with ILD report cough. Thoracic computed tomography is approximately 91% sensitive and 71% specific for diagnosing subtypes of ILDs such as IPF. Physiologic assessment provides important prognostic information. A 5% decline in forced vital capacity (FVC) over 12 months is associated with an approximately 2-fold increase in mortality compared with no change in FVC. Antifibrotic therapy with nintedanib or pirfenidone slows annual FVC decline by approximately 44% to 57% in individuals with IPF, scleroderma associated ILD, and in those with progressive pulmonary fibrosis of any cause. For connectiv tissue disease–associated ILD, immunomodulatory therapy, such as tocilizumab, rituximab, and mycophenolate mofetil, may slow decline or even improve FVC at 12-month follow-up.

Pictorial Review of Fibrotic Interstitial Lung Disease on High-Resolution CT Scan and Updated Classification

[165#4 CHEST APRIL 2024]

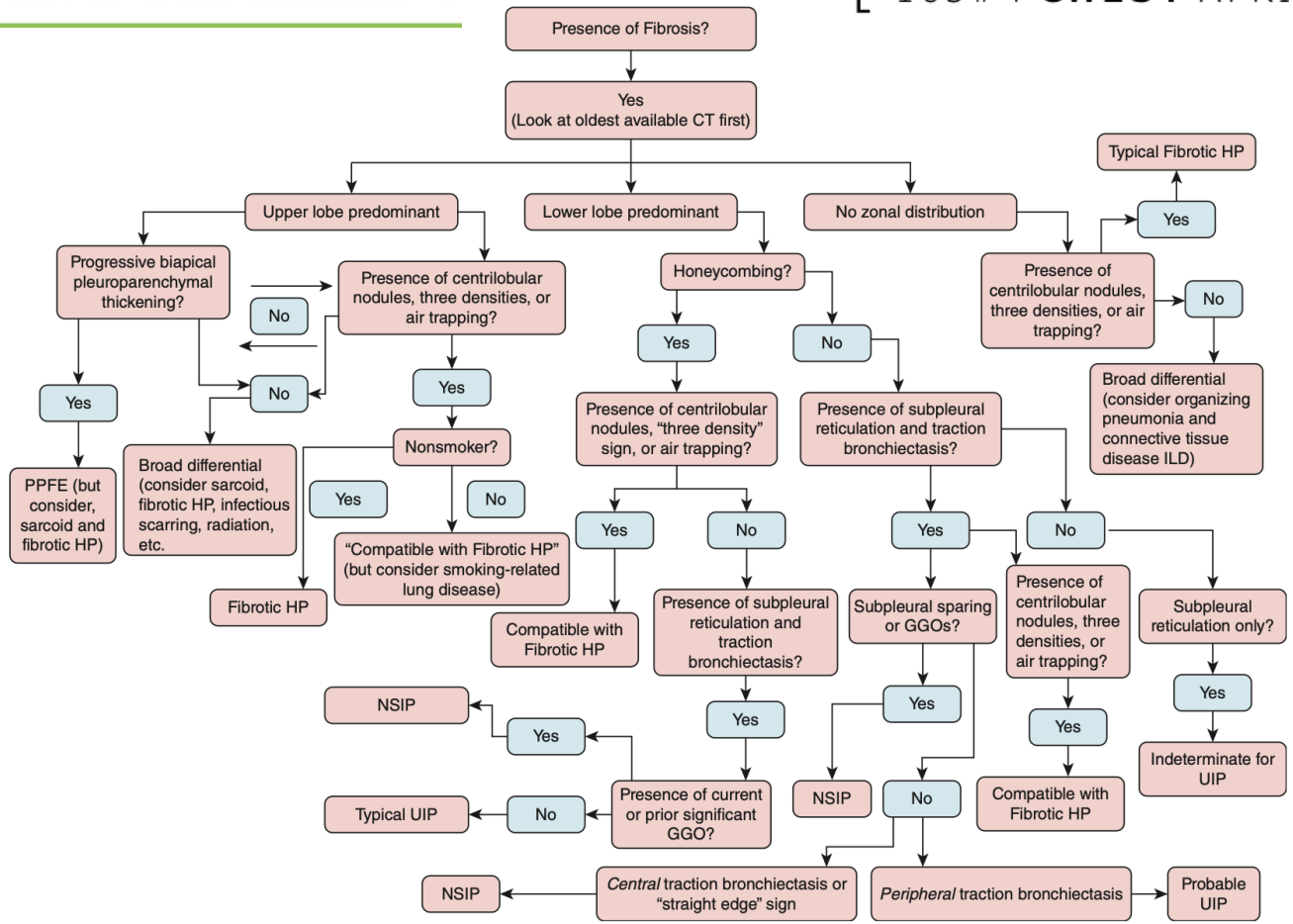
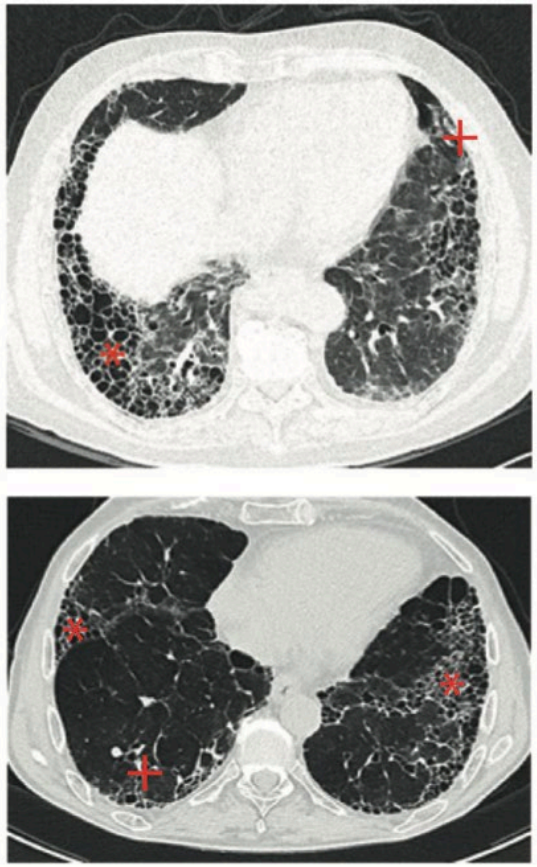


Figure 14 – *Decision-making algorithm for fibrotic lung disease: for patients with symptoms or being screened for ILD (not used for patients with incidental interstitial lung abnormality). GGO = ground glass opacity; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; NSIP = nonspecific interstitial pneumonia; PPFE = pleuroparenchymal fibroelastosis; UIP = usual interstitial pneumonia.*

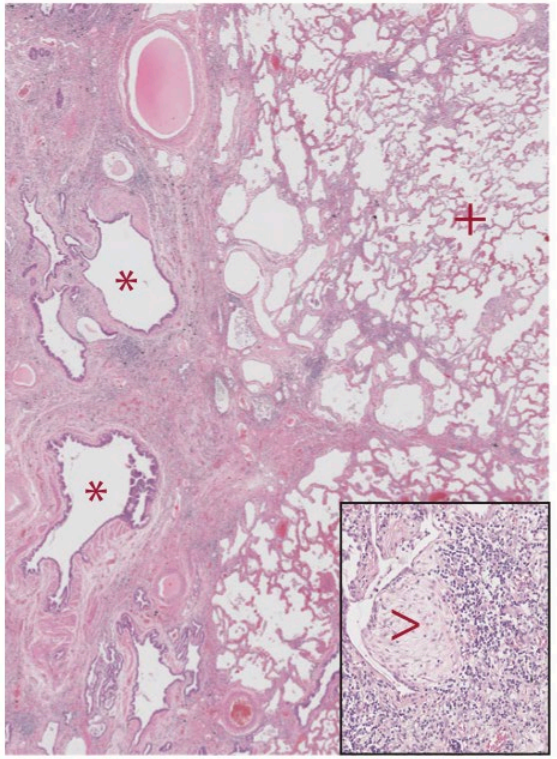
Usual interstitial pneumonia

Typical image



Honeycombing (*) with or without peripheral traction bronchiectasis (+), in a subpleural and basal predominant, often heterogeneous, distribution.

Typical pathology



Marked fibrosis, architectural distortion with or without honeycombing (*) in predominant subpleural or paraseptal distribution, presence of patchy involvement, and areas of preserved normal lung tissue (+). Presence of fibroblast foci (>) and absence of features suggesting an alternate diagnosis.

Usual interstitial pneumonia: a clinically significant pattern, but not the final word

Table 1. Unanswered questions in ILD diagnosis and sources of confusion and controversy.

Is UIP a diagnosis or merely a pattern?
Is pathology the gold standard for a diagnosis of UIP?
Does a diagnosis of UIP imply a diagnosis of IPF?
How does one "prove" the etiology of a given case of UIP?
What should be done when radiologic and pathologic findings are discordant?
Should biopsy interpretation be influenced by clinical and imaging findings?
What histologic features reliably distinguish etiologies of fibrotic ILD?
What is the threshold for number or extent of granulomas/interstitial inflammation/airway-centered changes/etc. to issue an alternate non-UIP diagnosis?
Can UIP be diagnosed at an earlier stage, and if so, what terminology should be used?
Does UIP indicate a specific pathobiology, or simply a common disease endpoint (cf. hepatic cirrhosis)?
When does organizing pneumonia or acute lung injury argue against UIP, or suggest acute exacerbation of UIP of IPF?
How should the broader histologic context influence interpretation of an individual histologic feature?

Modern Pathology (2022) 35:589 – 593

Time for a change: is idiopathic pulmonary fibrosis still idiopathic and only fibrotic?

	Disorders in classification
Group 1: pulmonary fibrosis driven by epithelial cell dysfunction	IPF
Group 2: pulmonary fibrosis driven by inflammatory cell dysfunction	RA-ILD, scleroderma, MCTD, Sjögren's syndrome, hypersensitivity pneumonitis, sarcoidosis, NSIP
Group 3: occupational or drug induced pulmonary fibrosis	Asbestosis, silicosis, medications
Group 4: pulmonary fibrosis due to smoking	RBILD, DIP, LCH

RA-ILD=rheumatoid-arthritis-associated interstitial lung disease. IPF=idiopathic pulmonary fibrosis. MCTD=mixed connective-tissue disease. NSIP=non-specific interstitial pneumonitis. RBILD=respiratory bronchiolitis with interstitial lung disease. DIP=desquamative interstitial pneumonia. LCH=Langerhan's cell histiocytosis.

Table 1: **Proposed groups for subtypes of pulmonary fibrosis**

Panel: Advantages and disadvantages of diagnostic unification of UIP

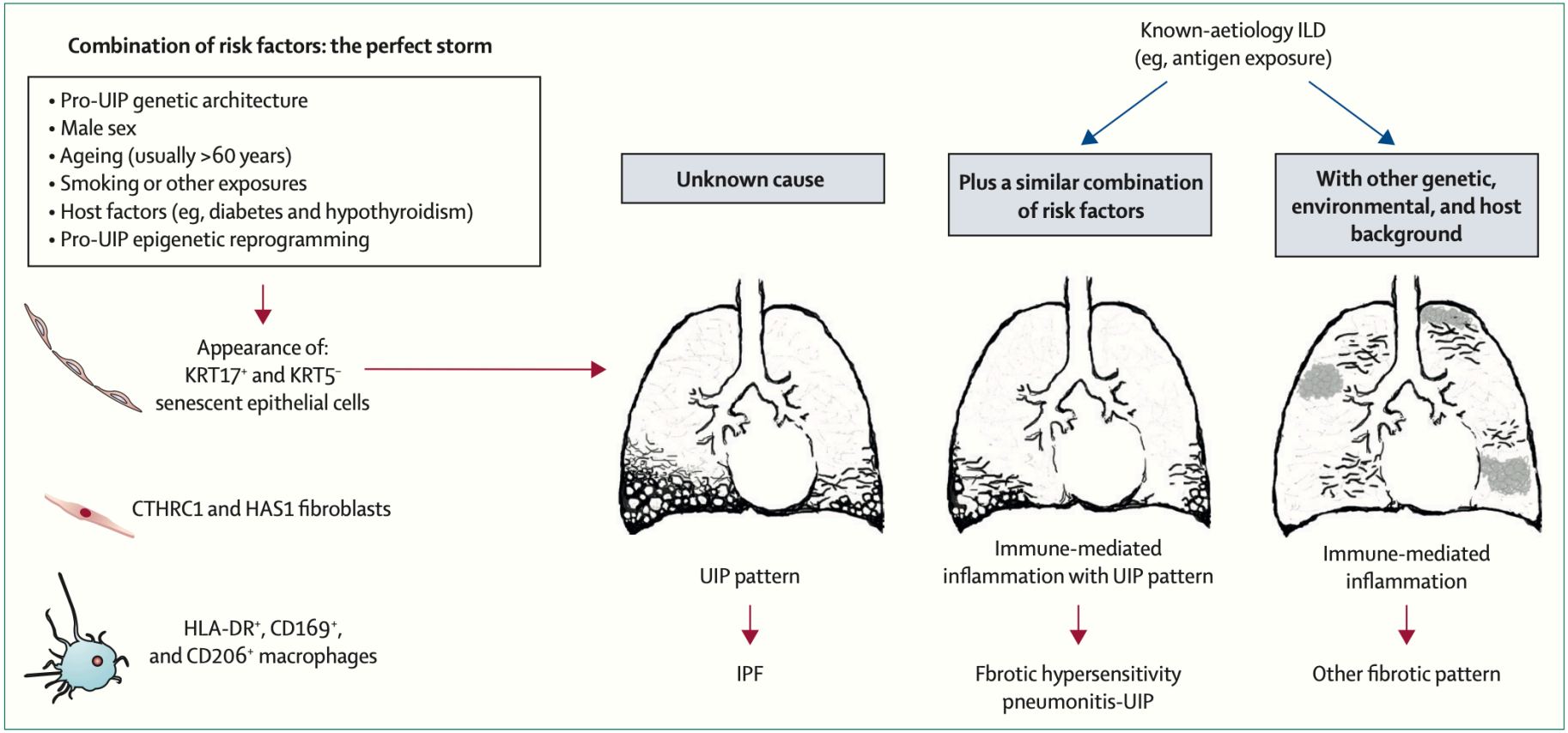
Advantages

- Similarities in mortality and lung function decline in idiopathic pulmonary fibrosis (IPF) and secondary usual interstitial pneumonia (UIP)
- Outcomes in individual secondary UIPs much worse than outcomes associated with secondary non-UIP histological and CT patterns
- Acute exacerbations with poor outcomes associated with both primary and secondary UIP
- Diagnostic simplification when UIP identified at biopsy or by genomic classifier
- Pathogenetic pathways shared between primary and secondary UIP, with some key pathways specific to UIP
- Treatment effects of anti-fibrotic therapy very similar in progressive secondary UIP (the expected course) and in (probable or definite) IPF treatment trials
- Unification of UIP as a single diagnostic entity would facilitate urgently needed anti-fibrotic trials for secondary UIP and trials of novel agents
- Clear precedence in the amalgamation of primary and secondary acute exacerbation of IPF in the revised definition of acute exacerbation of IPF

Personal View

Usual interstitial pneumonia as a stand-alone diagnostic entity: the case for a paradigm shift?

Moisés Selman, Annie Pardo, Athol U Wells



Time for a change: is idiopathic pulmonary fibrosis still idiopathic and only fibrotic?

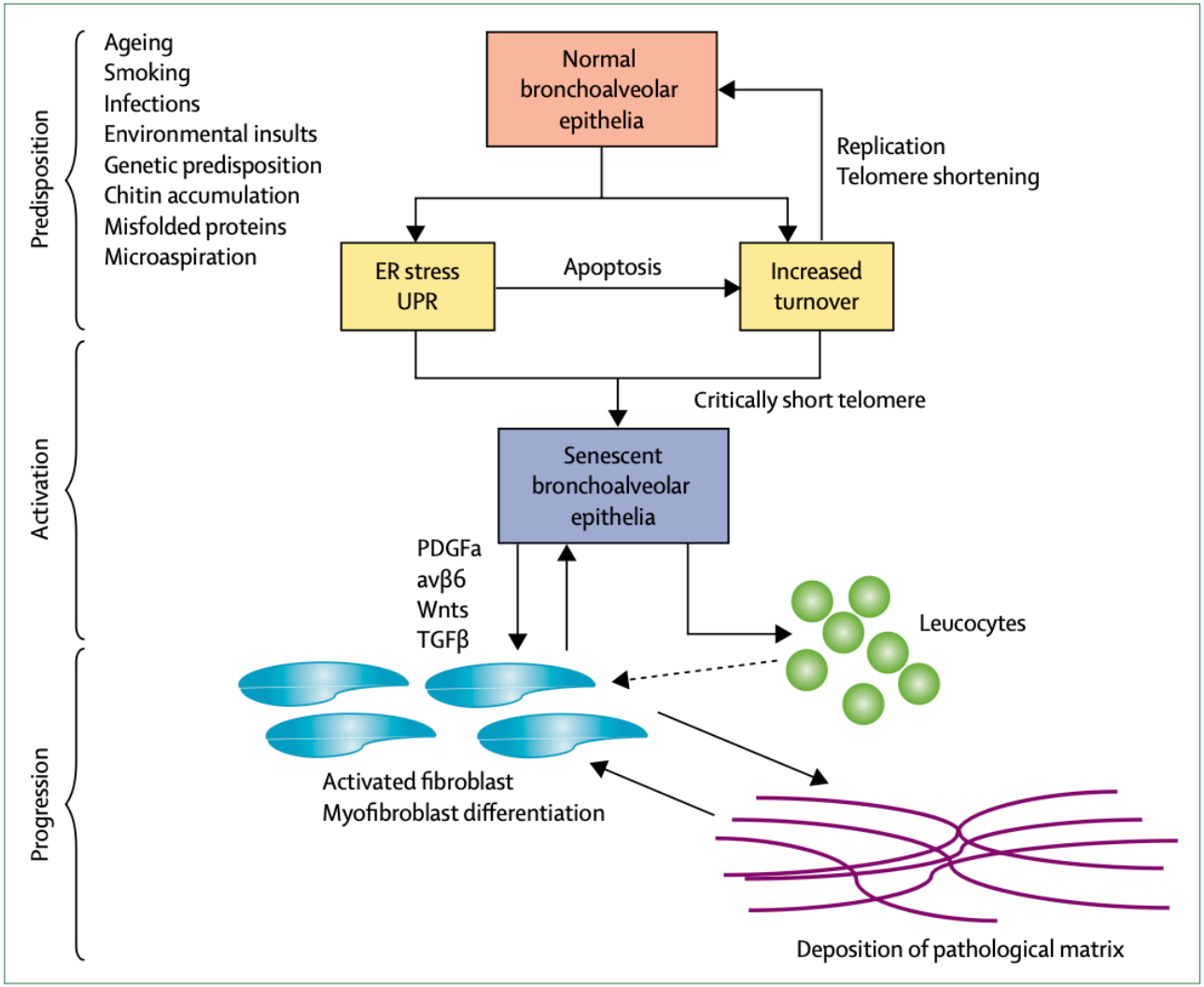


Figure: **Three-stage description of the pathogenesis of idiopathic pulmonary fibrosis**

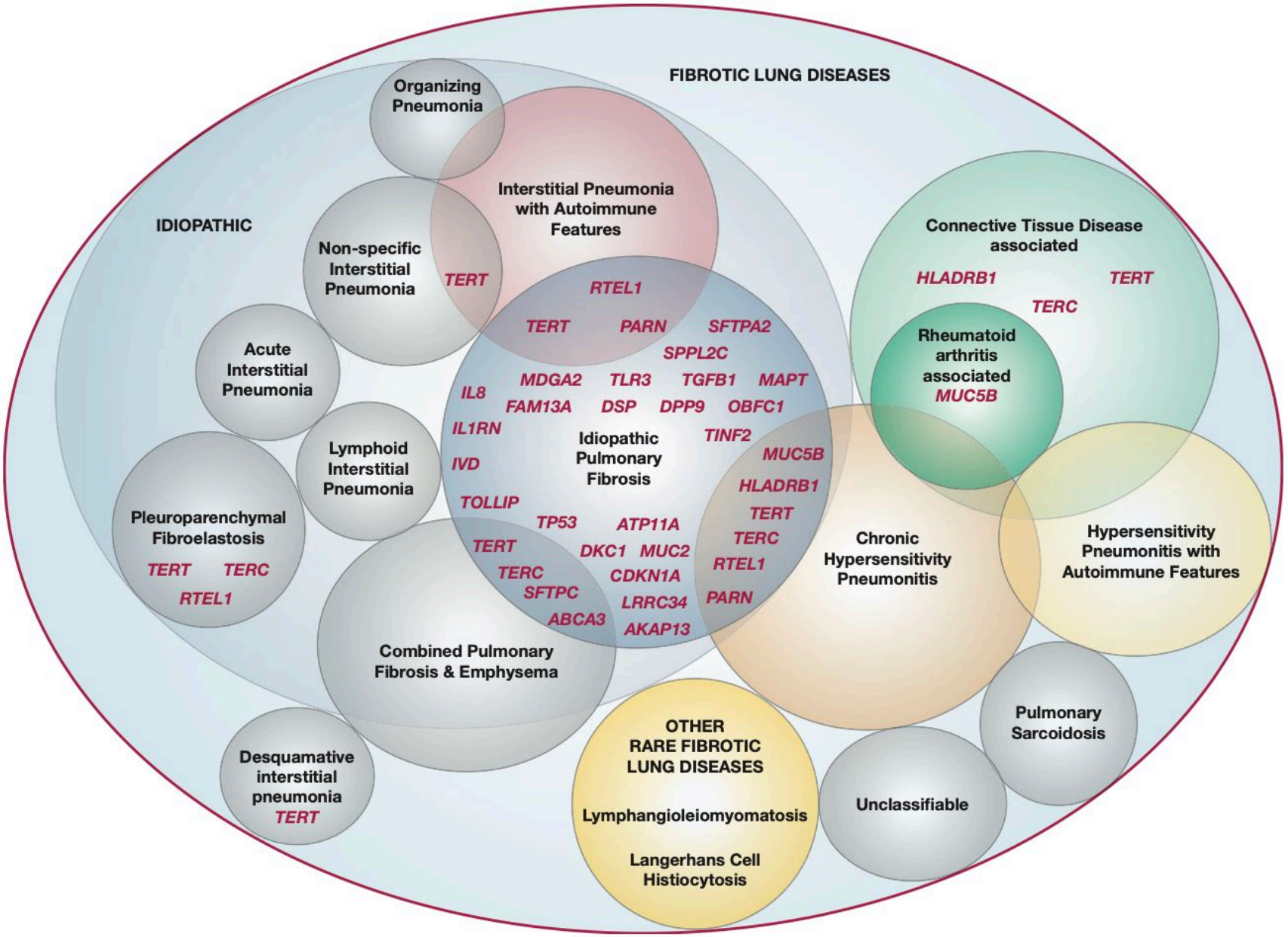
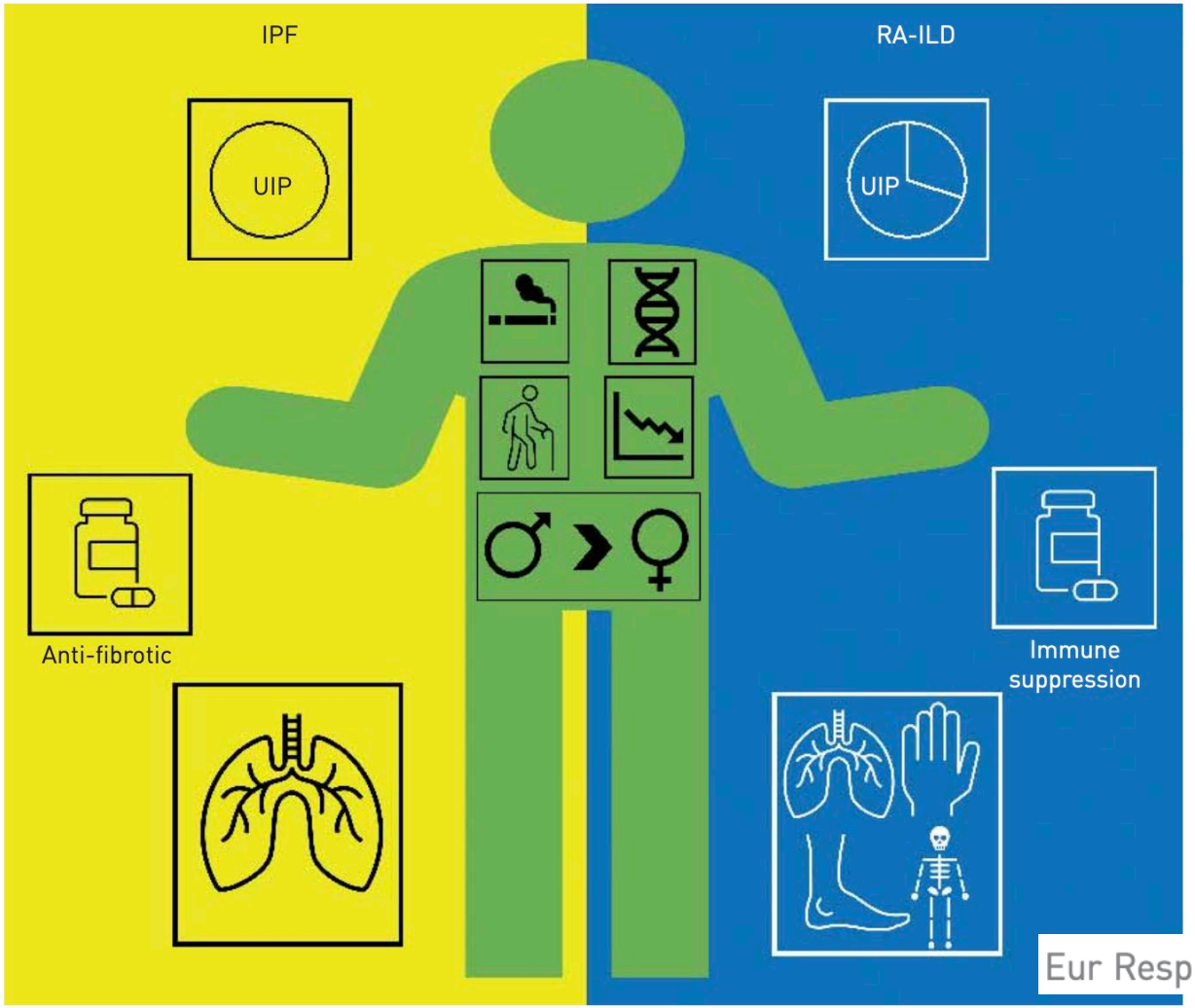


Figure 4 – *Heterogeneity in classification of fibrotic interstitial lung disease depicting overlap in gene variants (red) and clinical phenotypes (black).*

İPF risk faktörleri

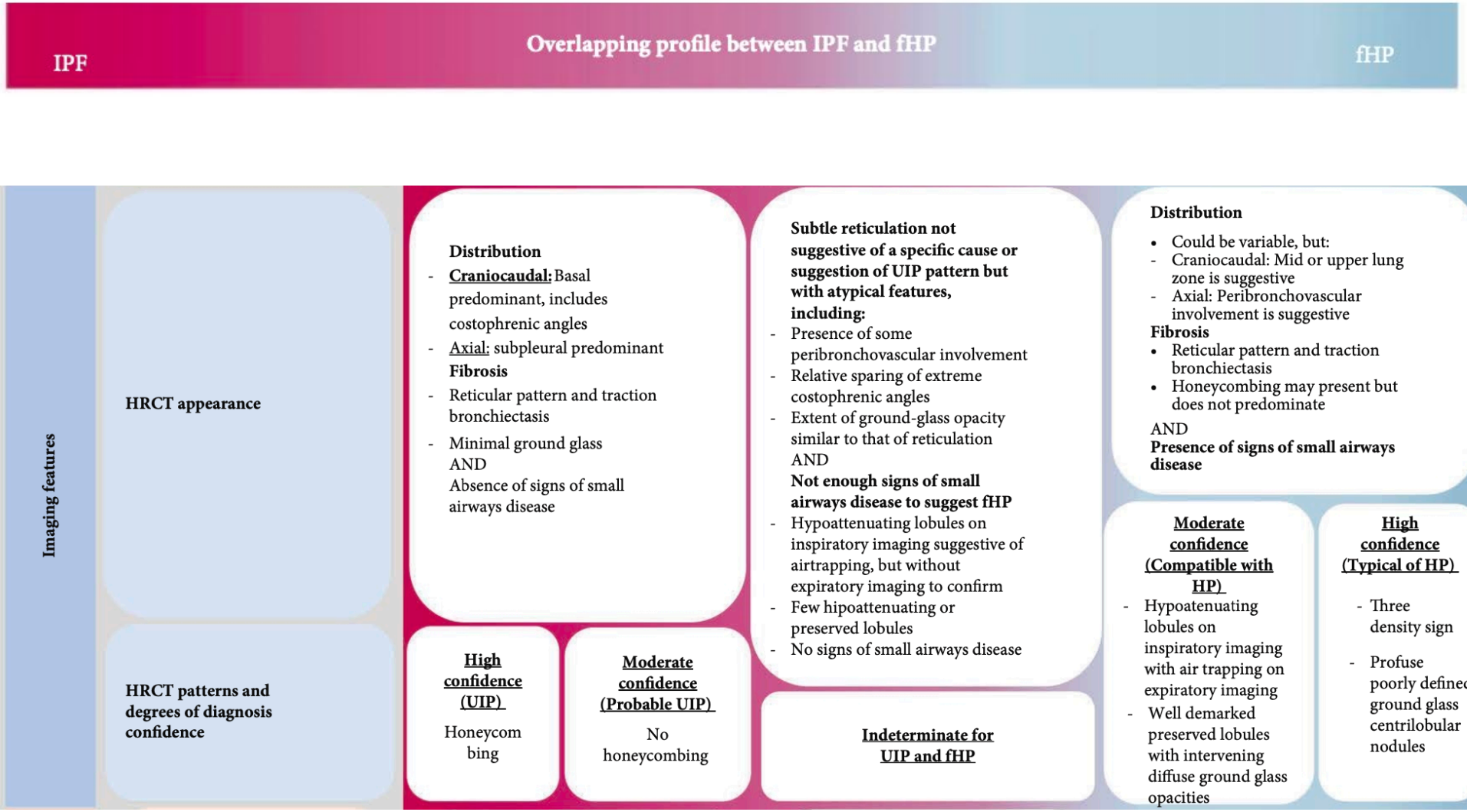
Genetik yatkınlık
Telomer kısalığı
MUC5B'ye bağlı mukosilyer klirens azalması
Sürfaktan protein değişiklikleri
TOLLIP mutasyonu
Yaşlanma
Gastroözofagial reflü; mikroaspirasyon
Epigenetik Değişiklikler
DNA metilasyonu, RNA disregülasyonu
Epitel hücre hasarı, yara iyileşe bozukluğu
Kök hücre disfonksiyonu ve tükenmesi
Fibroblast ve miyofibroblastlarda değişiklikler
Büyüme faktörleri
TGF-ß1, TNF-α MCP-1, VEGF, PDGF, IL-1, IL-6, vb.
Ekstraselüler matriks depolanması
Matriks sertleşmesi ve skar dokusu gelişimi
Çevresel maruziyet
Sigara
Metal tozu, odun talaşı, tarım, hayvancılık,
Tekstil tozu, kum-taş-silika,

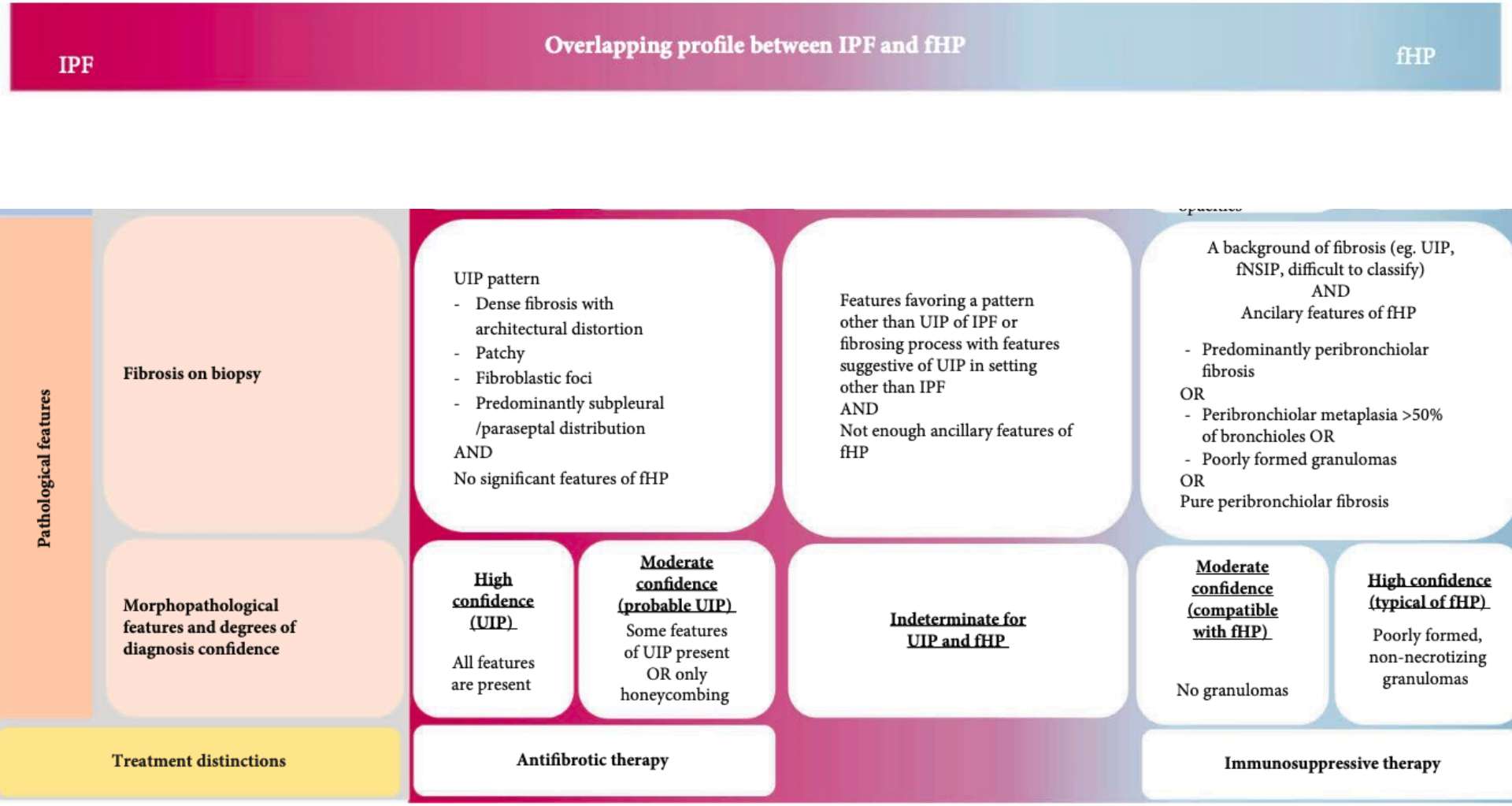
Two sides of the same coin? A review of the similarities and differences between idiopathic pulmonary fibrosis and rheumatoid arthritis-associated interstitial lung disease



Eur Respir J 2021; 57: 2002533

		IPF	Overlapping profile between IPF and fHP	fHP
Clinical features	**Demographic data and smoking history**	Male predominance Older age (>60 y) Smoker or former smoker		No known sex predominance Any age Smoker, former smoker, or nonsmoker
	Family history and genetics		Family history of fibrosis and/or predisposing genetic factors (MUC5B, short telomere etc)	
	Symptoms		Dyspnea and cough Insidious onset Absence of symptoms to suggest systemic disease	
	Exposure history	No identified antigen	No identifiable or indeterminate antigen	Identified antigen May stabilize or improve with antigen avoidance
	Physical examination		Inspiratory crackles Clubbing (may be more common in IPF)	Mid-inspiratory squeaks
	Functional findings		Restrictive ventilator defect Obstructive or mixed pattern (eg. Smoker in IPF, fHP)	
	Laboratory findings		Negative or only weakly positive autoimmune serologic findings, BAL neutrophilia and absence of lymphocytosis	BAL lymphocytosis
	Disease behavior		Typically progressive over months to years	May be stable and/or slowly progressive over years


IPF
Overlapping profile between IPF and fHP
fHP
Imaging features
HRCT appearance
HRCT patterns and degrees of diagnosis confidence
Distribution
- Craniocaudal: Basal predominant, includes costophrenic angles
- Axial: subpleural predominant
Fibrosis
- Reticular pattern and traction bronchiectasis
- Minimal ground glass
AND
Absence of signs of small airways disease
High confidence (UIP)
Honeycombing
Moderate confidence (Probable UIP)
No honeycombing
Subtle reticulation not suggestive of a specific cause or suggestion of UIP pattern but with atypical features, including:
- Presence of some peribronchovascular involvement
- Relative sparing of extreme costophrenic angles
- Extent of ground-glass opacity similar to that of reticulation
AND
Not enough signs of small airways disease to suggest fHP
- Hypoattenuating lobules on inspiratory imaging suggestive of airtrapping, but without expiratory imaging to confirm
- Few hipoattenuating or preserved lobules
- No signs of small airways disease
Indeterminate for UIP and fHP
Distribution
- Could be variable, but:
- Craniocaudal: Mid or upper lung zone is suggestive
- Axial: Peribronchovascular involvement is suggestive
Fibrosis
- Reticular pattern and traction bronchiectasis
- Honeycombing may present but does not predominate
AND
Presence of signs of small airways disease
Moderate confidence (Compatible with HP)
- Hypoatenuating lobules on inspiratory imaging with air trapping on expiratory imaging
- Well demarked preserved lobules with intervening diffuse ground glass opacities
High confidence (Typical of HP)
- Three density sign
- Profuse poorly defined ground glass centrilobular nodules


IPF
Overlapping profile between IPF and fHP
fHP
Pathological features
Fibrosis on biopsy
Morphopathological features and degrees of diagnosis confidence
Treatment distinctions
UIP pattern
- Dense fibrosis with architectural distortion
- Patchy
- Fibroblastic foci
- Predominantly subpleural /paraseptal distribution
AND
No significant features of fHP
High confidence (UIP)
All features are present
Moderate confidence (probable UIP)
Some features of UIP present OR only honeycombing
Antifibrotic therapy
Features favoring a pattern other than UIP of IPF or fibrosing process with features suggestive of UIP in setting other than IPF
AND
Not enough ancillary features of fHP
Indeterminate for UIP and fHP
A background of fibrosis (eg. UIP, fNSIP, difficult to classify)
AND
Ancilary features of fHP
- Predominantly peribronchiolar fibrosis
OR
- Peribronchiolar metaplasia >50% of bronchioles OR
- Poorly formed granulomas
OR
Pure peribronchiolar fibrosis
Moderate confidence (compatible with fHP)
No granulomas
High confidence (typical of fHP)
Poorly formed, non-necrotizing granulomas
Immunosuppressive therapy

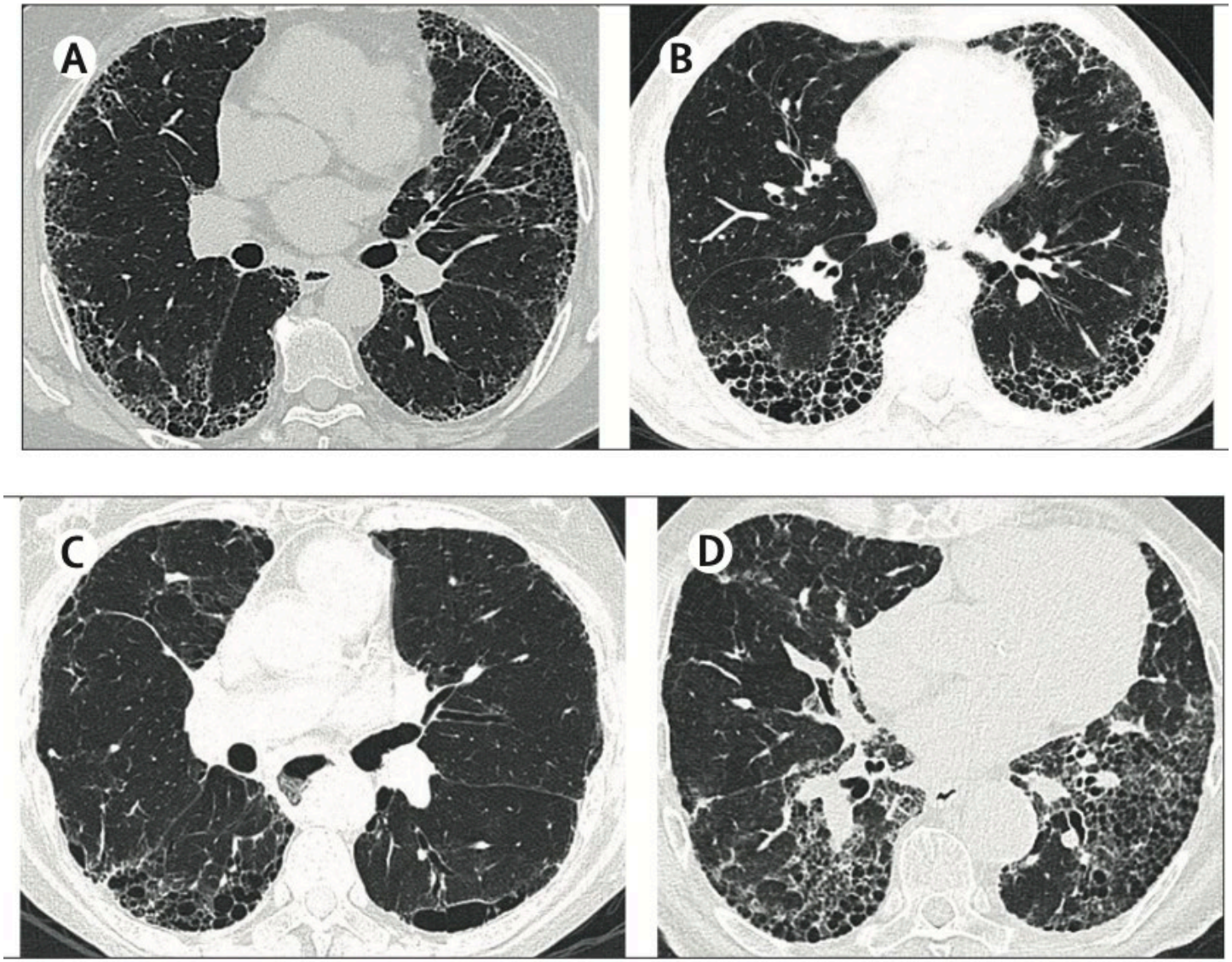


Figure 1: **High-resolution CT images of different interstitial lung diseases**
Images show features of usual interstitial pneumonia, subpleural and basal predominant reticulation, traction bronchiectasis, and honeycombing. (A) Idiopathic pulmonary fibrosis; (B) ILD associated with rheumatoid arthritis; (C) ILD-associated with systemic sclerosis; and (D) fibrotic hypersensitivity pneumonitis. ILD=interstitial lung disease.

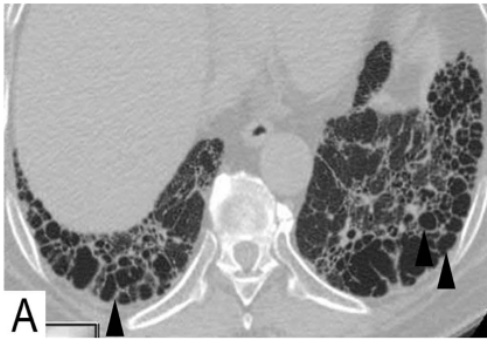
Usual interstitial pneumonia-*pattern* fibrosis in surgical lung biopsies. Clinical, radiological and histopathological clues to aetiology

Smith M, *et al*. *J Clin Pathol* 2013;**66**:896–903. doi:10.1136/jclinpath-2013-201442

Table 1 UIP in IPF

Clinical features	Radiological features	Histopathological features
▶ Age greater than 60 years ▶ More frequent in men ▶ Smoking history common ▶ Dyspnoea longer then 3 months ▶ Dry, non-productive cough ▶ Restrictive pattern of respiratory impairment common ▶ Inhalational exposures uncommon ▶ Digital clubbing, common in advanced disease ▶ Oxygen desaturation with exercise common	▶ Subpleural and basal predominance ▶ Progressive gradient toward bases ▶ Reticular abnormalities ▶ Traction bronchiectasis ▶ Subpleural honeycomb cysts (necessary for confident radiological diagnosis) ▶ Minimal ground-glass opacities: common in areas of reticulation, but never extensive	▶ Spatial heterogeneity ▶ Temporal heterogeneity ▶ Fibroblastic foci common ▶ Peripheral lobular distribution commonly present ▶ Microscopic honeycomb remodelling ▶ Smooth muscle in fibrosis

IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.



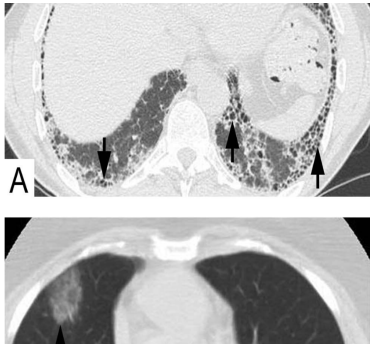


Table 2 UIP in rheumatic disease

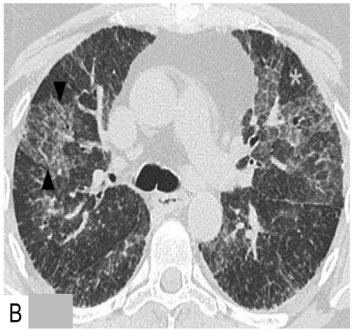
Clinical features	Radiological features	Histopathological features
▶ Age less than 60 years common ▶ Men more frequently affected than women (despite RD prevalence in women) ▶ Systemic manifestations common (but not always) ▶ Laboratory evidence of collagen vascular disease common (not always) ▶ Sometimes only non-specific serum markers (erythrocyte sedimentation rate, C-reactive protein)	▶ Reticular opacities with lobular distortion ▶ Honeycomb cysts uncommon and fewer than UIP in IPF ▶ Traction bronchioloectasis ▶ Airway-associated abnormalities ▶ Pleural effusion, sometimes	▶ Fibrosis more haphazard and more airway-centred ▶ Nodular inflammatory (lymphoid) infiltration, often with germinal centres ▶ NSIP-like alveolar septal fibrosis common ▶ Follicular bronchiolitis common ▶ Bronchiolar remodelling common (peribronchiolar metaplasia) ▶ Pleural inflammation and fibrosis common ▶ Occasional fibroblast foci (always fewer than UIP in IPF)

IPF, idiopathic pulmonary fibrosis; RD, rheumatic diseases; UIP, usual interstitial pneumonia.

Table 3 UIP in CHrHP

Clinical features	Radiological features	Histopathological features
▶ Middle age to older individuals ▶ Slowly progressive dyspnoea ▶ Cough frequent, often productive ▶ Exposure history, frequent, with focused questioning or home visit ▶ Positive precipitin antibodies, inconsistent	▶ Reticular pattern with traction bronchiectasis ▶ Ground-glass opacities, common ▶ Mid and upper lung zones commonly affected in a bronchovascular distribution with resulting micronodules ▶ Non-basilar distribution common ▶ Mosaic attenuation ▶ Irregular bronchovascular bundles ▶ Subpleural honeycomb cysts, not always basilar	▶ Patchy fibrosis along the bronchovascular bundle with rare fibroblast foci ▶ Individual interstitial giant cells, some with cholesterol clefts. ▶ Honeycomb cysts (lower and upper lobes) ▶ Extensive peribronchiolar metaplasia. ▶ Bridging fibrosis across lobules

CHrHP, chronic hypersensitivity pneumonitis; UIP, usual interstitial pneumonia.



Usual interstitial pneumonia-*pattern* fibrosis in surgical lung biopsies. Clinical, radiological and histopathological clues to aetiology

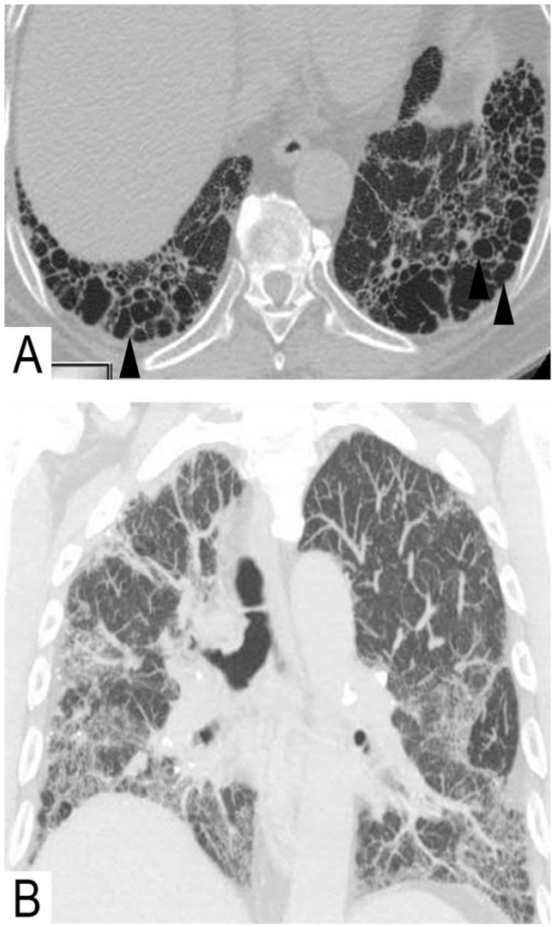


Figure 2 Radiological characteristics of usual interstitial pneumonia in idiopathic pulmonary fibrosis. Sagittal CT sections (A) show characteristic heterogeneous fibrosis and honeycombing in lung bases (arrow heads). Coronal maximum intensity projection (B) shows the typical apico-basilar gradient of fibrosis.

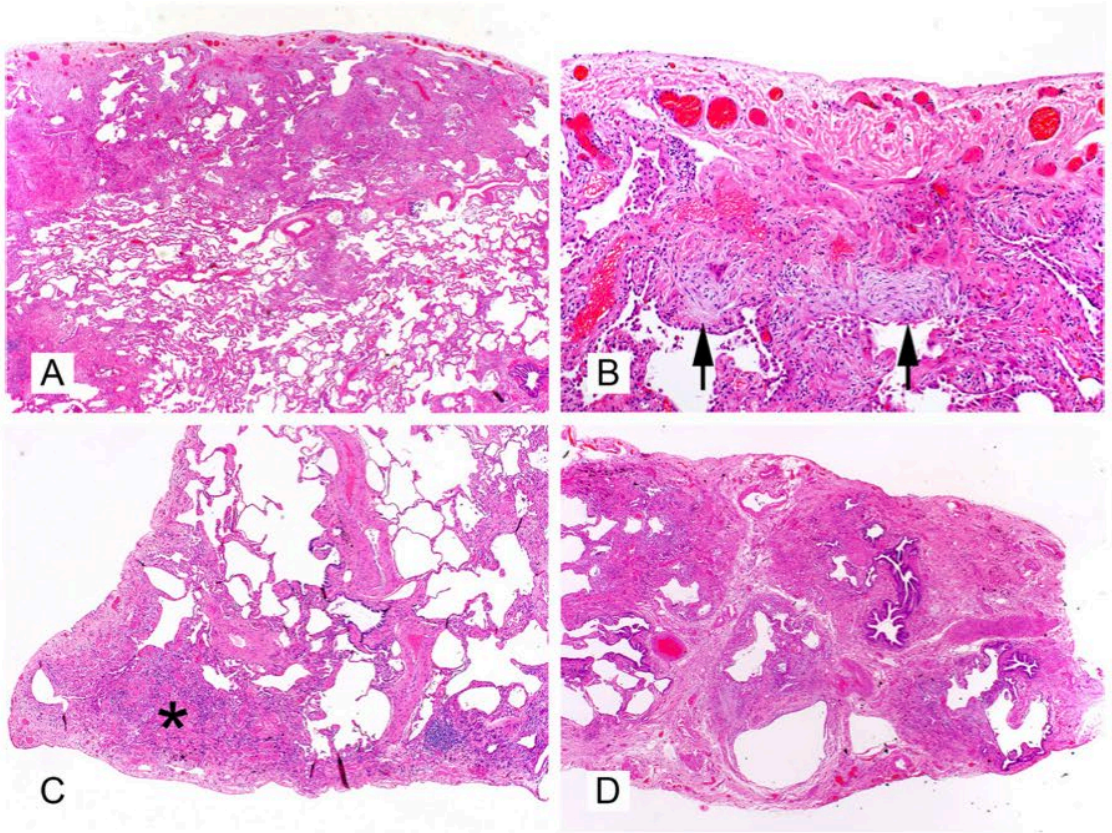
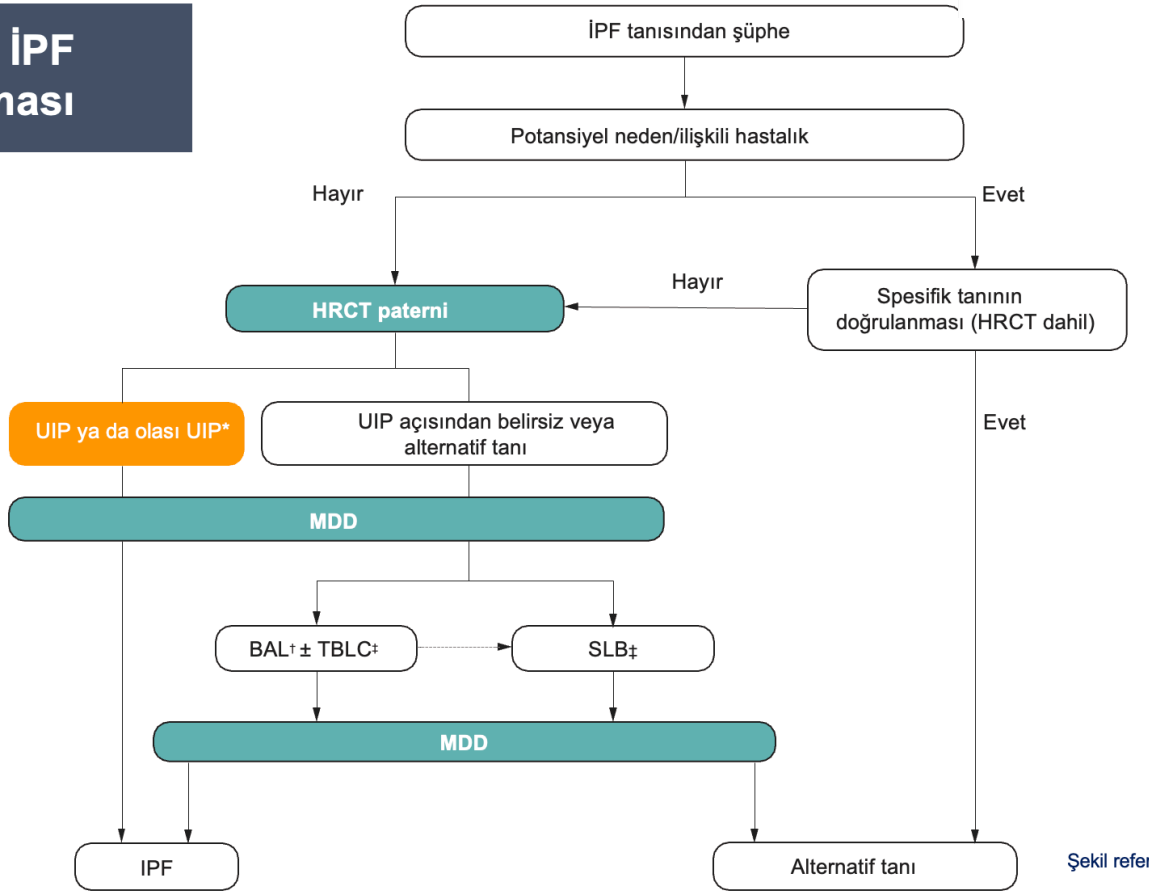


Figure 3 Characteristics of advanced fibrosis in usual interstitial pneumonia of idiopathic pulmonary fibrosis include a subpleural distribution of fibrosis (A, 20×, H&E), relative frequency of fibroblast foci (arrows) and relative absence of any significant inflammatory cell infiltrate (B, 400×, H&E), smooth muscle proliferation in the subpleural scars (asterisk) (C, 40×, H&E), and the frequent occurrence of microscopic honeycomb remodelling (D, 20×, H&E).

Smith M, *et al*. *J Clin Pathol* 2013;**66**:896–903. doi:10.1136/jclinpath-2013-201442

Güncel 2022 İPF Tanı Algoritması



Şekil referanstan uyarlanmıştır

AMERICAN THORACIC SOCIETY DOCUMENTS

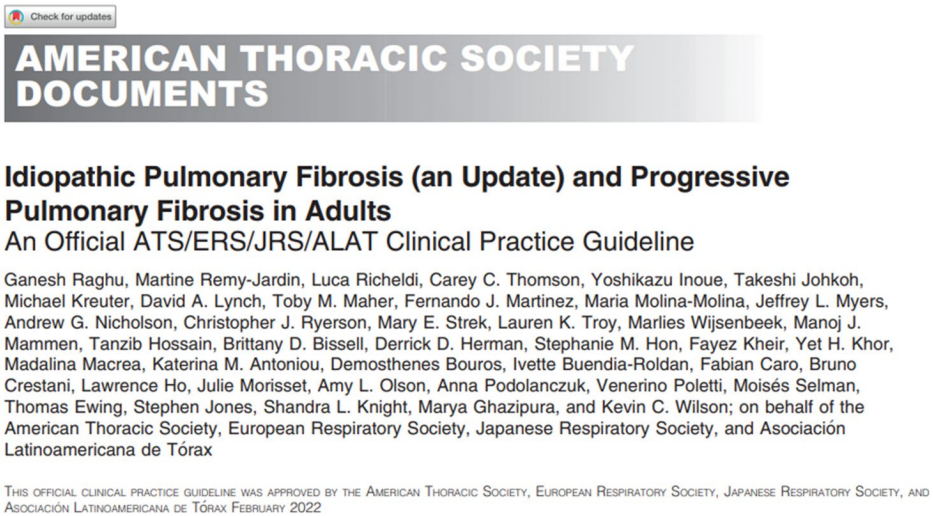
Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This official clinical practice guideline was approved by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax February 2022

Raghu, Ganesh, et al. "Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline." American Journal of Respiratory and Critical Care Medicine 205.9 (2022): e18-e47.

İPF Rehberdeki Değişiklikler



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Radyolojik olarak olası UIP paterni bulunan hastalara, biyopsi yapılmadan multidisipliner tartışma yoluyla İPF tanısı konulması önerildi

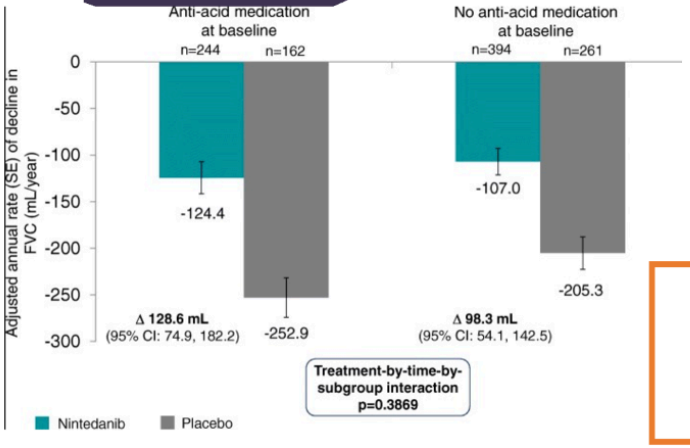
Transbronşiyal akciğer **kriyobiyopsinin**, İPF'nin histopatolojik tanısında cerrahi akciğer biyopsisine alternatif olarak kullanılması **koşullu olarak önerildi**

Anti-asit ilaçların İPF'de akciğerin tedavisine yönelik **kullanımı aleyhinde öneri getirildi**

Raghu, Ganesh, et al. "Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline." American Journal of Respiratory and Critical Care Medicine 205.9 (2022): e18-e47.

IPF- GER

Antiasit tedavi İPF seyrini iyileştirmez



Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis

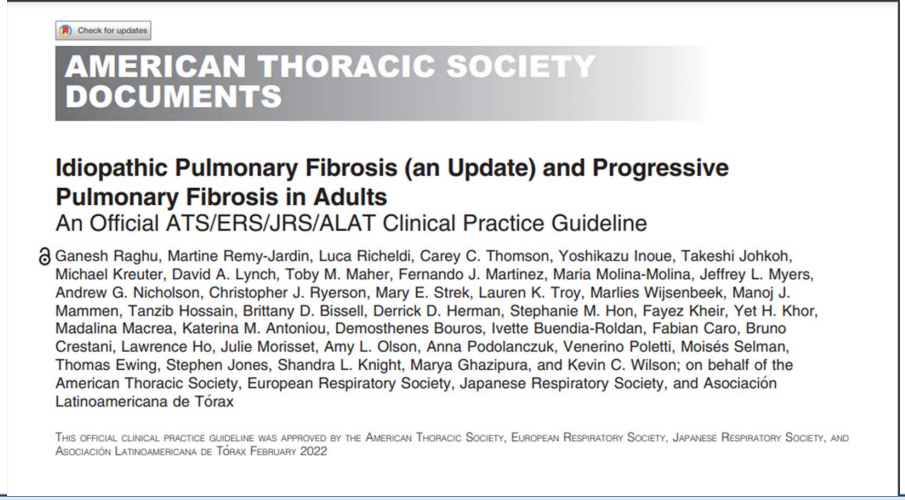
Meta-Analysis > Lancet Respir Med. 2016 May;4(5):381-9.

Interpretation: Antacid therapy did not improve outcomes in patients with IPF and might potentially be associated with an increased risk of infection in those with advanced disease.

Anti-acid therapy in idiopathic pulmonary fibrosis: insights from the INPULSIS® trials

Clinical Trial > Respir Res. 2018 Sep 3;19(1):167.

Conclusions: In post-hoc analyses of data from the INPULSIS® trials, anti-acid medication use at baseline was not associated with a more favorable course of disease, and did not impact the treatment effect of nintedanib, in patients with IPF.



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Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This official clinical practice guideline was approved by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax February 2022

Zaman

İPF Tanısı

TEDAVİDE DİKKATE ALINMASI GEREKENLER

İlaç
- Nintedanib
- Pirfenidon

İlaç dışı
- Oksijen desteği (hasta hipoksemikse)
- Pulmoner rehabilitasyon

Komorbiditeler
- Pulmoner hipertansiyon
- Gastroözofageal reflü
- Obstrüktif uyku apnesi
- Akciğer kanseri

Semptom kontrolü
- Palyatif bakım

Hastada mortalite riski yüksekse, tanı anında akciğer nakli açısından değerlendirilir

PROGRESYON TAKİBİ

4-6 ayda bir veya klinik olarak endike olduğunda daha kısa aralıklarla **solunum fonksiyon testi ve 6 dakika yürüme testi düşünülür**

Klinik kötüleşme şüphesi veya akciğer kanseri riski varlığında yılda bir HRCT çekilmesi düşünülür

Akut alevlenme endişesi varlığında HRCT çekilmesi düşünülür

Pulmoner emboli açısından klinik endişe varsa, pulmoner BT anjiyografi düşünülür

AKUT ALEVLENMELER
Kortikosteroidler

İPF PROGRESYONUNA BAĞLI SOLUNUM YETMEZLİĞİ
Solunum yetmezliği olan hastaların büyük bölümünde mekanik ventilasyon önerilmemektedir

Akciğer nakli açısından değerlendirilir ve listeye alınır

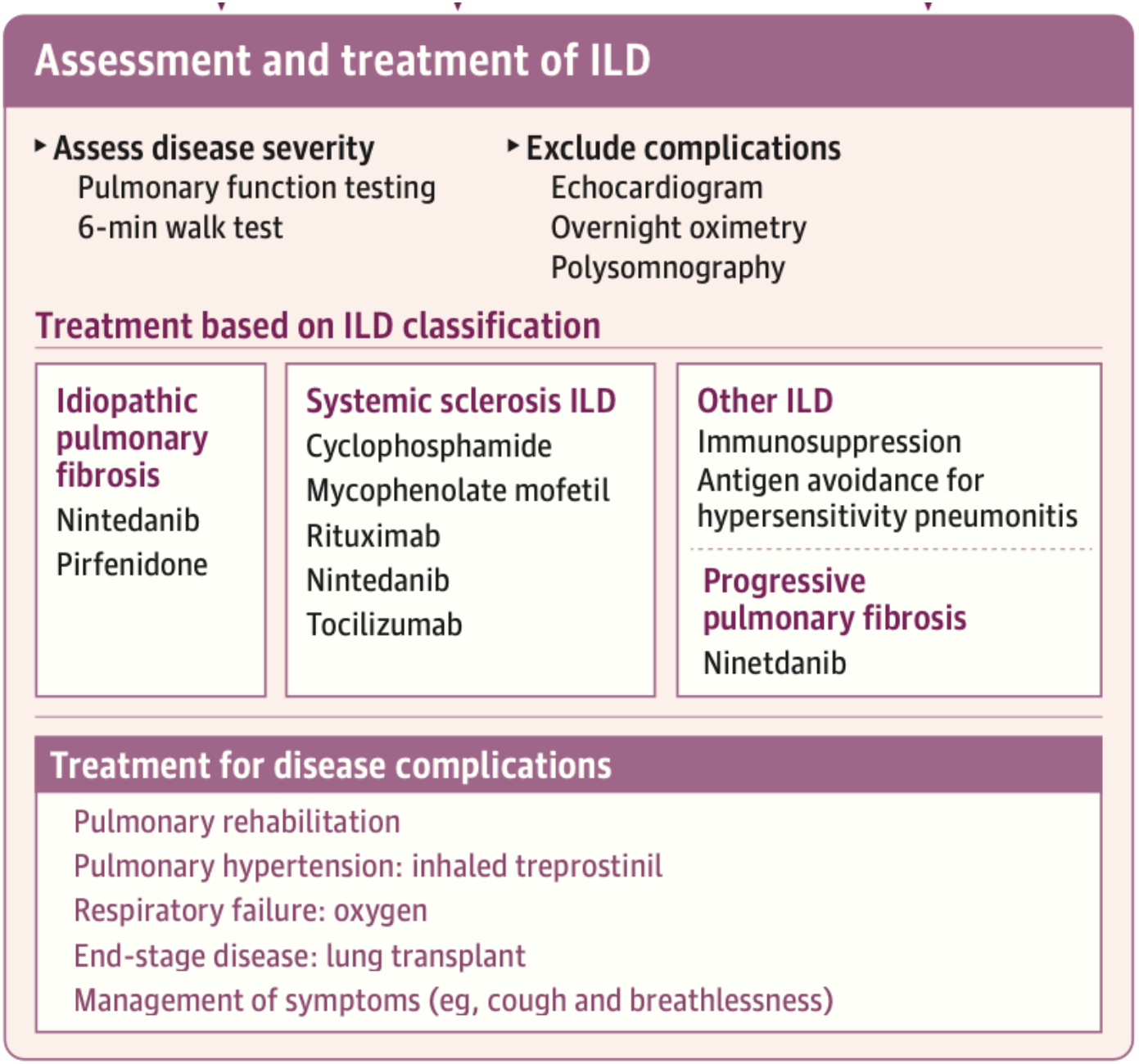
Palyatif bakım

JAMA | Review

Interstitial Lung Disease
A Review

Toby M. Maher, MD, MSc, PhD

JAMA. doi:10.1001/jama.2024.3669
Published online April 22, 2024.



- İlaç seçimi neye göre yapılmalıdır?
- Etkinlikleri nasıldır?
- Semptomlarda iyileşme sağlar mı?
- Mortaliteyi azaltır mı?
- Komorbiditeler üzerine etkisi var mıdır?
- Yan etkilerin yönetimi nasıl olmalıdır ?

Marijic et al. Respir Res (2021) 22:268
https://doi.org/10.1186/s12931-021-01857-y

Respiratory Research

RESEARCH Open Access

Pirfenidone vs. nintedanib in patients with idiopathic pulmonary fibrosis: a retrospective cohort study

Pavo Marijic[1,2,3*], Larissa Schwarzkopf[1,2,4,5], Lars Schwettmann[1,6], Thomas Ruhnke[7], Franziska Trudzinski[8] and Michael Kreuter[8]

Abstract

Background: Two antifibrotic drugs, pirfenidone and nintedanib, are licensed for the treatment of patients with idiopathic pulmonary fibrosis (IPF). However, there is neither evidence from prospective data nor a guideline recommendation, which drug should be preferred over the other. This study aimed to compare pirfenidone and nintedanib-treated patients regarding all-cause mortality, all-cause and respiratory-related hospitalizations, and overall as well as respiratory-related health care costs borne by the Statutory Health Insurance (SHI).

Methods: A retrospective cohort study with SHI data was performed, including IPF patients treated either with pirfenidone or nintedanib. Stabilized inverse probability of treatment weighting (IPTW) based on propensity scores was applied to adjust for observed covariates. Weighted Cox models were estimated to analyze mortality and hospitalization. Weighted cost differences with bootstrapped 95% confidence intervals (CI) were applied for cost analysis.

Results: We compared 840 patients treated with pirfenidone and 713 patients treated with nintedanib. Both groups were similar regarding two-year all-cause mortality (HR: 0.90 95% CI: 0.76; 1.07), one-year all cause (HR: 1.09, 95% CI: 0.95; 1.25) and respiratory-related hospitalization (HR: 0.89, 95% CI: 0.72; 1.08). No significant differences were observed regarding total (€− 807, 95% CI: €− 2977; €1220) and respiratory-related (€− 1282, 95% CI: €− 3423; €534) costs.

Conclusion: Our analyses suggest that the patient-related outcomes mortality, hospitalization, and costs do not differ between the two currently available antifibrotic drugs pirfenidone and nintedanib. Hence, the decision on treatment with pirfenidone versus treatment with nintedanib ought to be made case-by-case taking clinical characteristics, comorbidities, comedications, individual risk of side effects, and patients' preferences into account.

Keywords: Idiopathic pulmonary fibrosis, Mortality, Hospitalization, Health care costs, Administrative data, Drugs, Statutory health insurance

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2019, VOL. 13, NO. 7, 601–614
https://doi.org/10.1080/17476348.2019.1627204

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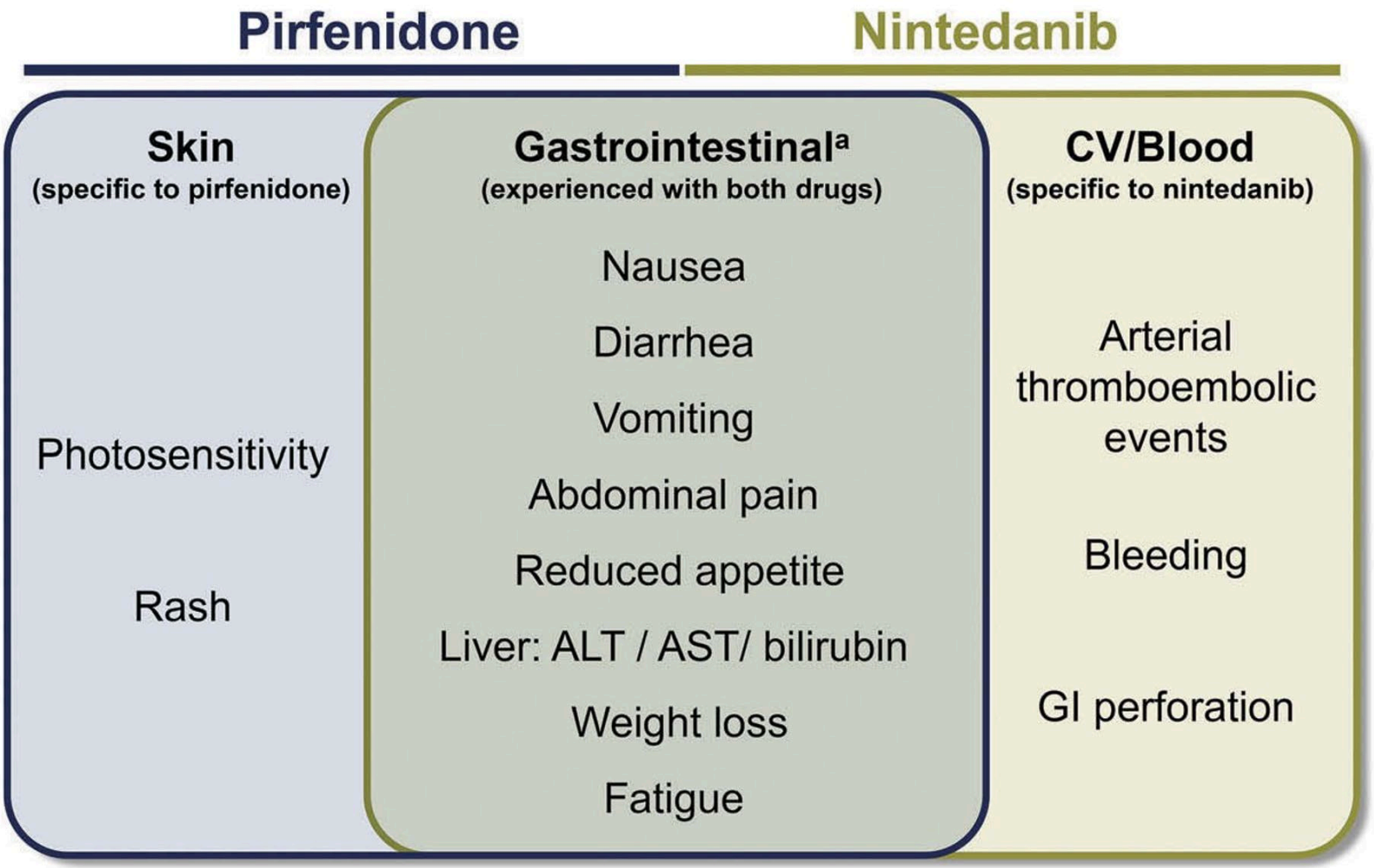
REVIEW

A comprehensive and practical approach to the management of idiopathic pulmonary fibrosis

Onofre Moran-Mendoza[a], Rebecca Colman[b], Meena Kalluri[c], Czerysh Cabalteja[d] and Ingrid Harle[e]



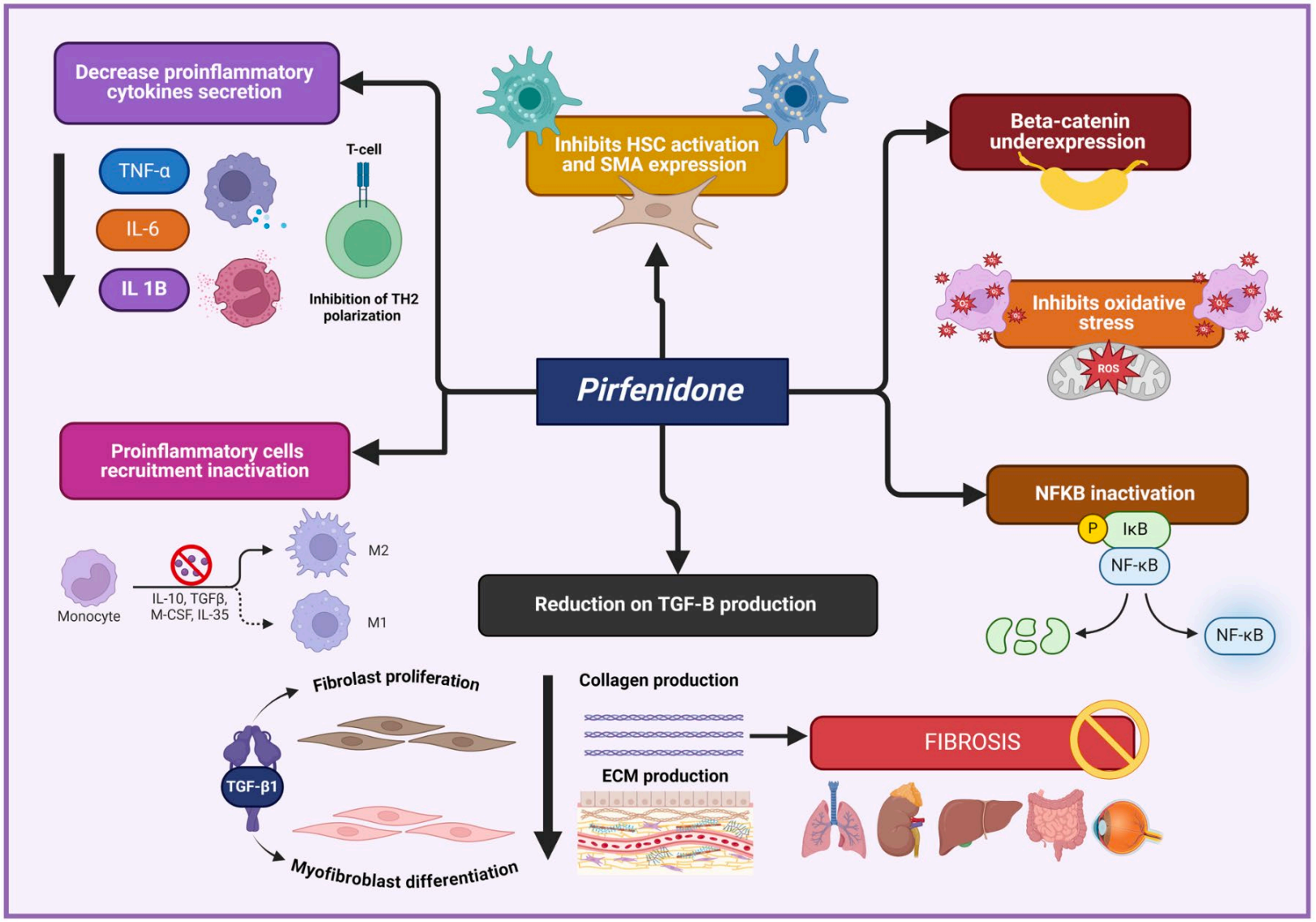
Impact of novel antifibrotic therapy on patient outcomes in idiopathic pulmonary fibrosis: patient selection and perspectives

Table 1 Comparison of antifibrotic agents approved for the treatment of IPF

	Nintedanib	Pirfenidone
Efficacy	• Slower rate of decline in forced vital capacity over 1 year when compared with placebo • Reduction in acute exacerbations • Lower all-cause mortality at 1 year	• Slower rate of decline in forced vital capacity over 1 year when compared with placebo • Improved progression-free survival • Reduction in respiratory-related hospitalizations • Lower all-cause mortality at 1 year
Potential side effects	• Diarrhea • Weight loss • Elevated liver enzymes	• Nausea • Photosensitivity • Elevated liver enzymes
Dosing	• One capsule taken twice per day	• Three capsules taken three times per day
Contraindications	• No absolute contraindications • Not recommended in Child Pugh Class B or C hepatic impairment • Caution in patients with high cardiovascular risk or high risk for bleeding	• No absolute contraindications
Impact on quality of life	• Slower rate of decline in respiratory-specific quality of life as measured by St. George's Respiratory Questionnaire	• May slow the progression of worsening dyspnea

Abbreviation: IPF, idiopathic pulmonary fibrosis.

Pirfenidon etki mekanizması



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

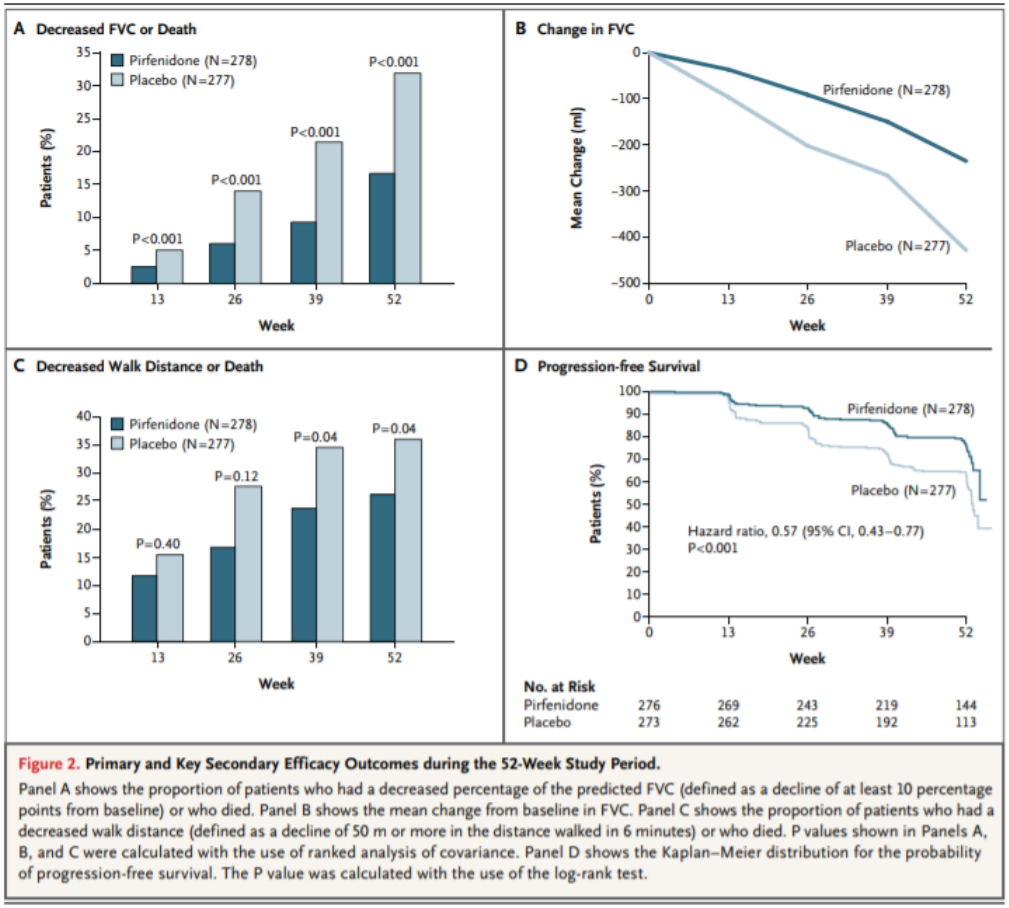


Figure 2. Primary and Key Secondary Efficacy Outcomes during the 52-Week Study Period.

Panel A shows the proportion of patients who had a decreased percentage of the predicted FVC (defined as a decline of at least 10 percentage points from baseline) or who died. Panel B shows the mean change from baseline in FVC. Panel C shows the proportion of patients who had a decreased walk distance (defined as a decline of 50 m or more in the distance walked in 6 minutes) or who died. P values shown in Panels A, B, and C were calculated with the use of ranked analysis of covariance. Panel D shows the Kaplan–Meier distribution for the probability of progression-free survival. The P value was calculated with the use of the log-rank test.

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.

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.)

Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials

Paul W Noble, Carlo Albera, Williamson Z Bradford, Ulrich Costabel, Marilyn K Glassberg, David Kardatzke, Talmadge E King Jr, Lisa Lancaster, Steven A Sahn, Javier Szwarcberg, Dominique Valeyre, Roland M du Bois, for the CAPACITY Study Group

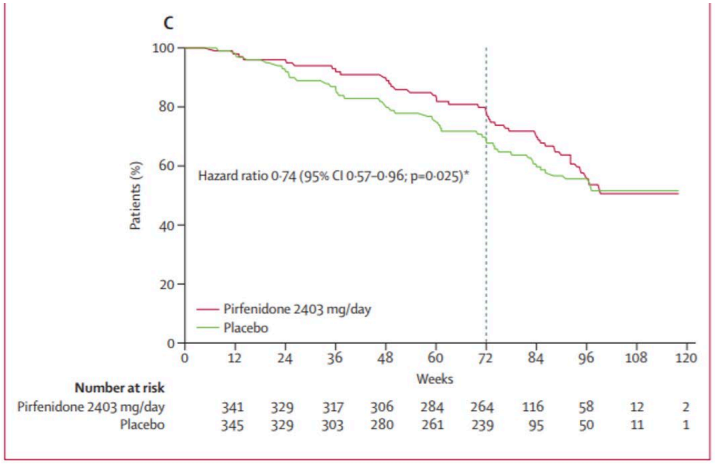


***Figure 3*: Kaplan-Meier distribution of progression-free survival time in study 004 (A), Study 006 (B), and the pooled population (C)**
*Pirfenidone 2403 mg/day versus placebo.

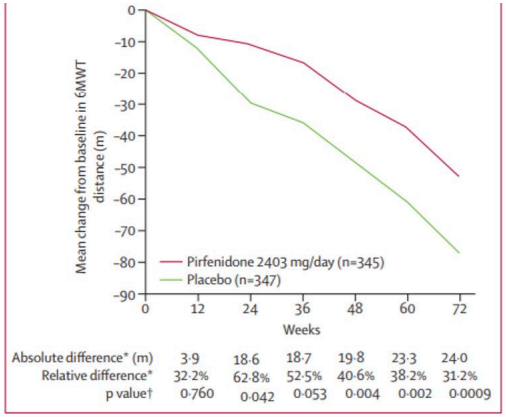
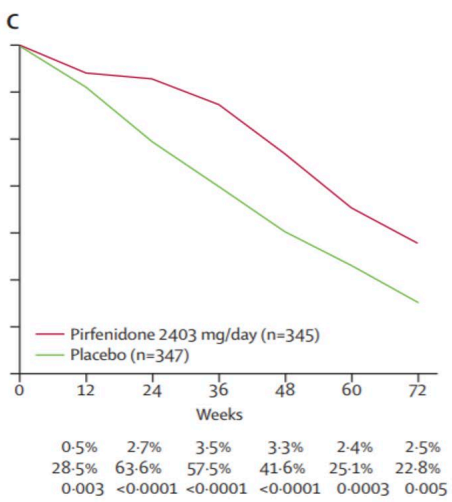
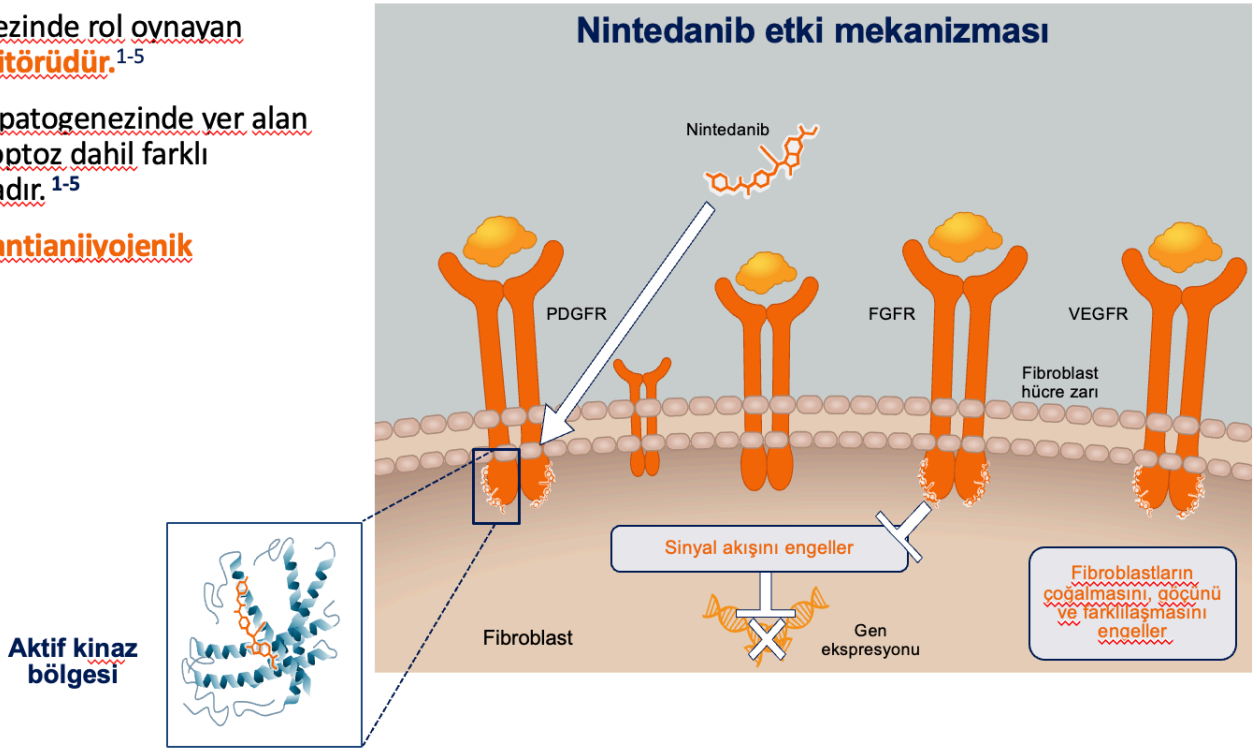


***Figure 4*: Mean change from baseline in 6-min walk test distance in the pooled patient population (studies 004 and 006)**
6MWT=6-min walk test. *Pirfenidone 2403 mg/day versus placebo. †Rank ANCOVA (pirfenidone 2403 mg/day *vs* placebo).



Nintedanib, antifibrotik ve antienflamatuvar etkileri olan, birden fazla reseptörü hedef alan bir tirozin kinaz inhibitörüdür. [1-5]

- Nintedanib, pulmoner fibrozisin patogenezinde rol oynayan tirozin kinazların **güçlü bir hücre içi inhibitörüdür.**[1-5]
- Bu tirozin kinazların, pulmoner fibrozisin patogenezinde yer alan hücre proliferasyonu, farklılaşması ve apoptoz dahil farklı yolaklarda kilit rol oynadığına inanılmaktadır. [1-5]
- Nintedanib **ayrıca anti-enflamatuvar ve antianjiyojenik** aktiviteye sahiptir.[3]



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

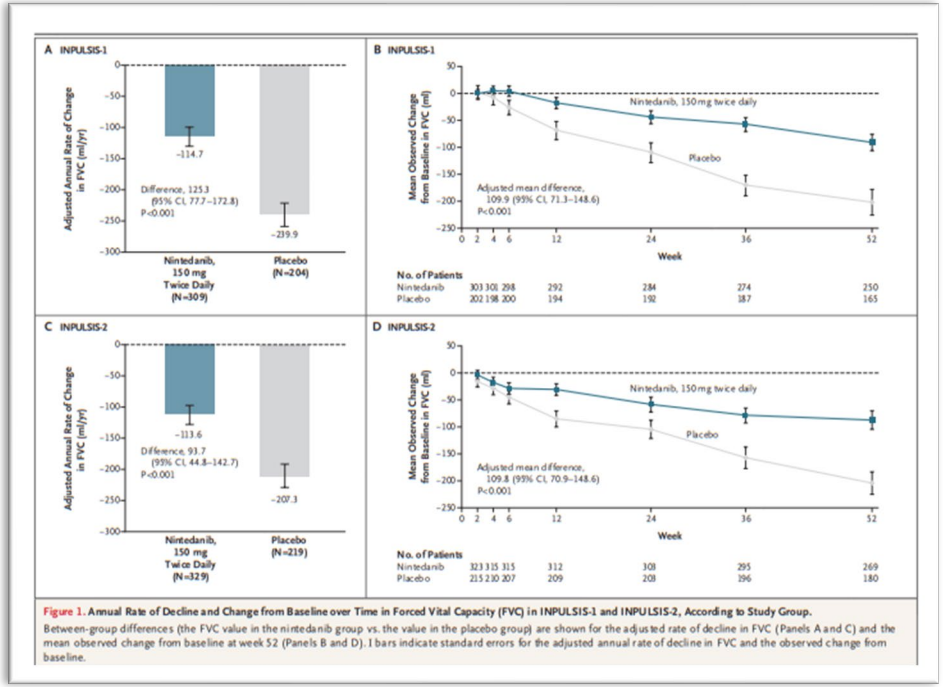


Figure 1. Annual Rate of Decline and Change from Baseline over Time in Forced Vital Capacity (FVC) in INPULSIS-1 and INPULSIS-2, According to Study Group.
Between-group differences (the FVC value in the nintedanib group vs. the value in the placebo group) are shown for the adjusted rate of decline in FVC (Panels A and C) and the mean observed change from baseline at week 52 (Panels B and D). I bars indicate standard errors for the adjusted annual rate of decline in FVC and the observed change from baseline.

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.

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.)

CHEST

Comparison of Pirfenidone and Nintedanib

Post Hoc Analysis of the CleanUP-IPF Study

BACKGROUND: Antifibrotics are effective in slowing FVC decline in idiopathic pulmonary fibrosis (IPF). However, whether antifibrotic type is differentially associated with FVC decline remains inconclusive.

RESEARCH QUESTION: Are there significant differences in 12-month FVC decline between pirfenidone and nintedanib?

RESULTS: Out of the 513 participants with IPF randomized in the CleanUP-IPF trial, 407 reported using pirfenidone (n = 264, 65%) or nintedanib (n = 143, 35%). The pirfenidone group had more participants with a history of coronary artery disease than the nintedanib group (34.1% vs 20.3%, respectively). Patients treated with nintedanib had a higher 12-month visit FVC than patients treated with pirfenidone (mean difference, 106 mL; 95% CI, 34-178). This difference was attenuated at the 24-month study visit. There were no significant differences in overall survival and nonelective respiratory hospitalization between the pirfenidone- and nintedanib-treated groups.

INTERPRETATION: Patients with IPF who used nintedanib had a slower 12-month FVC decline than pirfenidone in a post hoc analysis of a clinical trial. CHEST 2024; 165(5):1163-1173

TABLE 2] Differences in FVC Between Nintedanib and Pirfenidone

Visit	Mean FVC (95% CI), mL		Mean Difference (95% CI)	*P* Value
	Nintedanib	Pirfenidone		
Overall cohort				
Baseline	2,808 (2,800-2,819)	2,806 (2,798-2,814)	3 (−11 to 16)	.70
12 mo	2,745 (2,687-2,804)	2,640 (2,598-2,681)	106 (34 to 178)	.004
24 mo	2,471 (2,341-2,601)	2,539 (2,451-2,627)	−68 (−225 to 89)	.39

Take-home Points

Study Question: Are there differences in lung function trajectories by antifibrotic type in patients with idiopathic pulmonary fibrosis?

Results: Patients with idiopathic pulmonary fibrosis who reported to be using nintedanib had a slower 12-month decline in FVC than patients who used pirfenidone. There were no significant differences in survival and hospitalization.

Interpretation: Compared with patients who used pirfenidone, patients who used nintedanib had a slower decline in FVC over a period of 12 months.

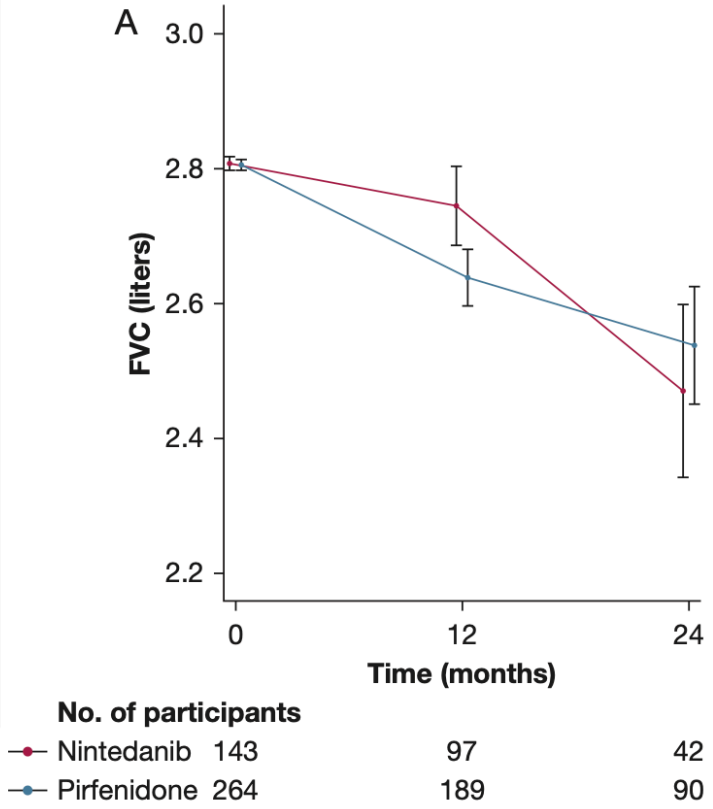
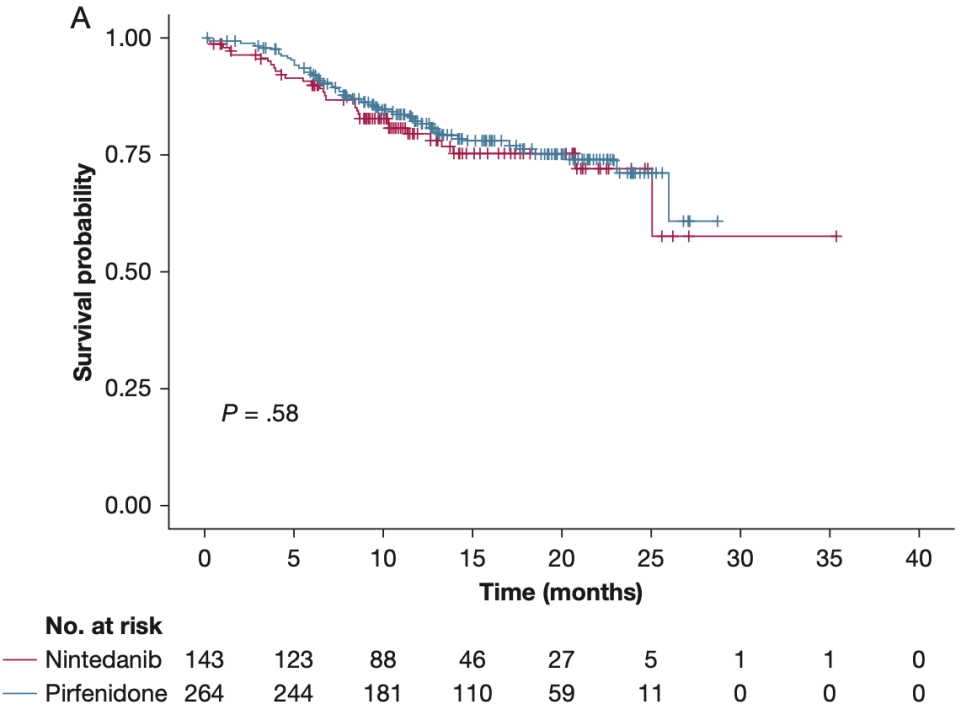
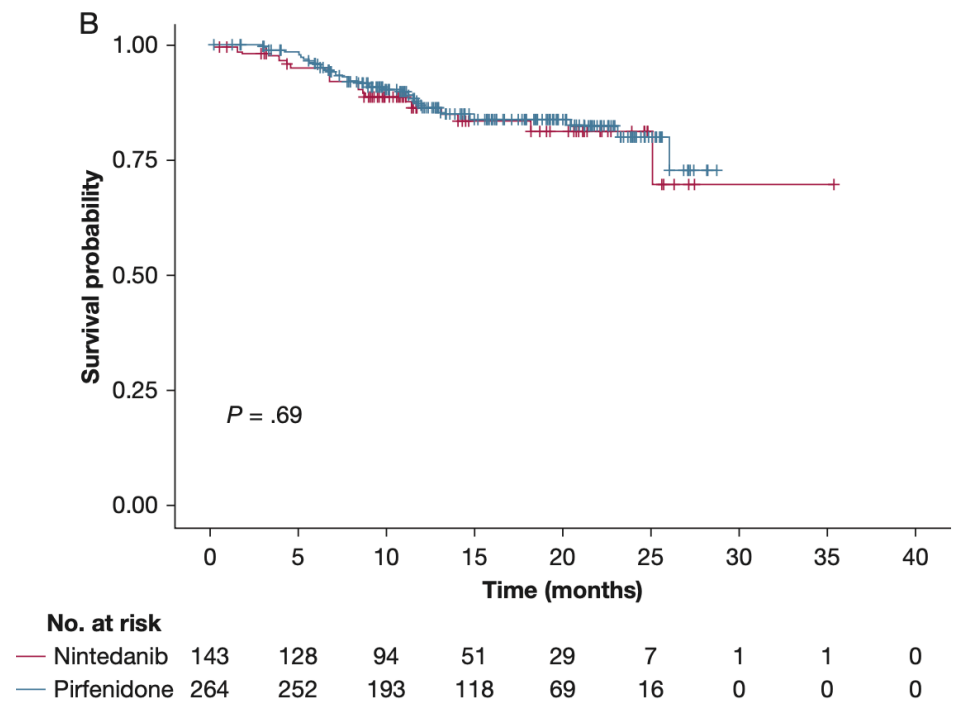


Figure 3 – *A, Time to composite outcome of death or nonelective respiratory hospitalization and (B) death by pirfenidone- and nintedanib-treated groups with log-rank*



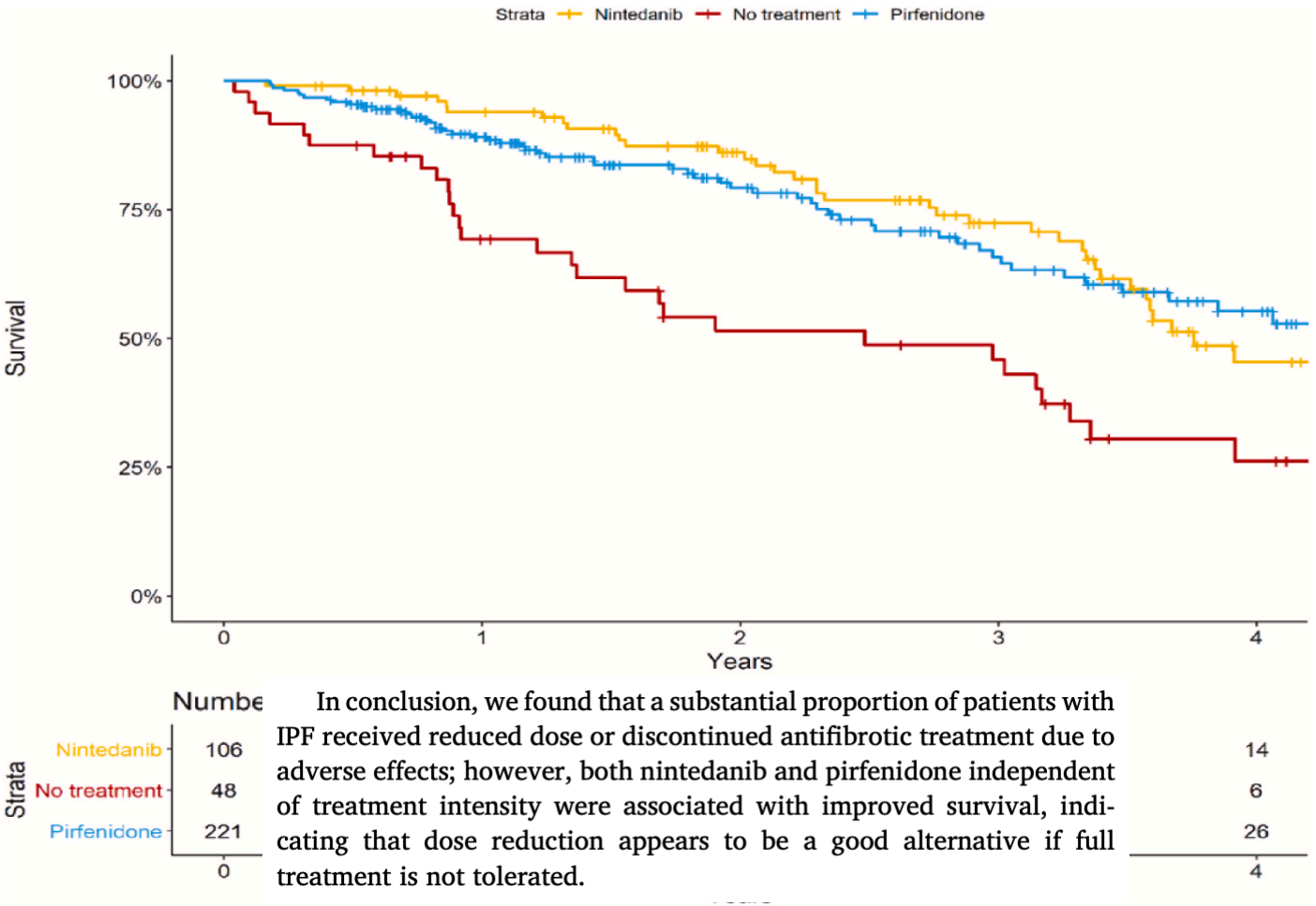


İPF'de mortalite nedenleri

1. Solunum yetmezliği (%60)
2. Kardiyovasküler hastalık (%8.5)
3. Akciğer kanseri (%2.9)

Impact of reduction in antifibrotic treatment on mortality in idiopathic pulmonary fibrosis

Respiratory Medicine 204 (2022) 107015



In conclusion, we found that a substantial proportion of patients with IPF received reduced dose or discontinued antifibrotic treatment due to adverse effects; however, both nintedanib and pirfenidone independent of treatment intensity were associated with improved survival, indicating that dose reduction appears to be a good alternative if full treatment is not tolerated.

Fig. 1. Overall survival of patients receiving nintedanib, pirfenidone or no treatment.

Ortalama survi nintedanib grubunda 8.5 yıl iken, plasebo grubunda 3.3 yıldır

BMJ Open Respiratory Research

Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials

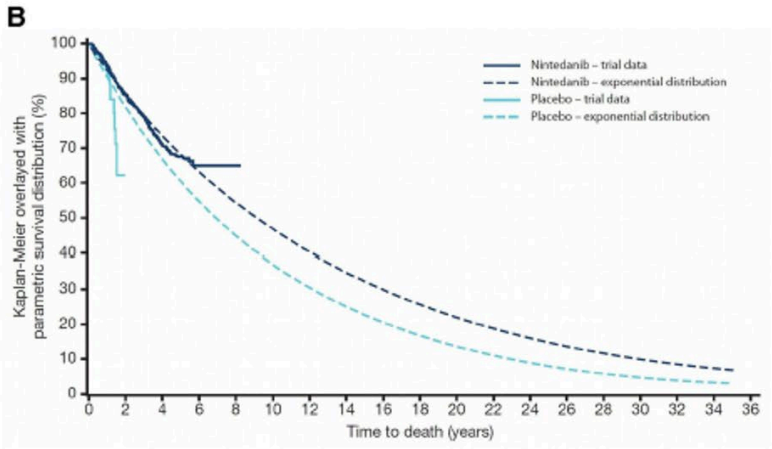


Figure 2 Estimated time to death using (A) the Weibull distribution and (B) exponential distribution.

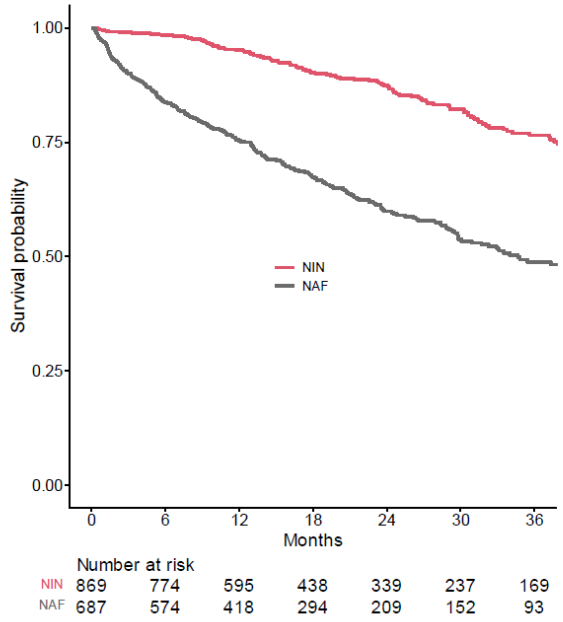
nintedanib.

Modelling and extrapolation of survival data from the clinical trials included in this pooled analysis suggest that nintedanib extends life expectancy in patients with IPF. Median survival based on the better fitting statistical model (Weibull) was extended by approximately 5 years in patients treated with nintedanib compared with placebo. Clearly such extrapolations have limitations and should be interpreted with caution, but these data add to the growing body of evidence suggesting that antifibrotic therapies are associated with improved survival in patients with IPF.[6 12 23–26]

Strengths of these analyses include the use of a large and well-characterised cohort of patients participating in prospectively designed clinical trials and a maximum treatment duration of over 7 years. Limitations include

Gerçek yaşamda, Nintedanib tedavisi alanlarda tedavi almayan hastalara kıyasla medyan sağkalımda yaklaşık 3 yıllık artış saptanmıştır

Figure 1. Overall survival of NIN and NAF patients



Toplam 1560 İPF hastasının araştırıldığı, Türkiye'nin de aralarında bulunduğu 11 ülkeden gelen 2022 *EMPIRE* gerçek yaşam verilerine göre;

	Nintedanib	Plasebo
Medyan sağkalım	**66.1 ay**	**34.7 ay**

NIN: Nintedanib NAF: No antifibrotic treatment Koziar Vašáková M, Šterclová M, Moğulkoç N, Lewandowska K, Müller V, Kramer M, et al. Long-term effect of nintedanib treatment of idiopathic pulmonary fibrosis in 11 countries of Europe and Asia . Poster presentation at the ERS International Congress 2022, 4–6/9/2022, Barcelona.

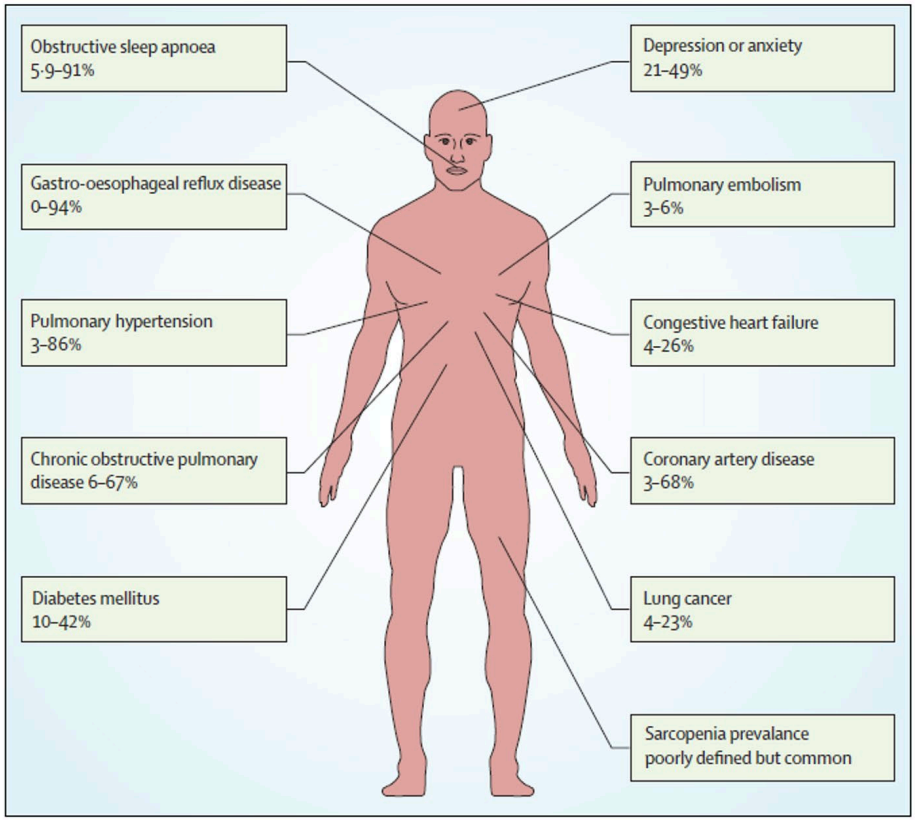
TABLE 4 Comparison of Survival in Patients Receiving Pirfenidone and BSC Using the Weibull Distribution

	Survival (Years)		
	Pirfenidone	**BSC**	**Difference**
Median	7.25	4.67	2.58
Mean (95% CI)	8.72 (7.65-10.15)	6.24 (5.38-7.18)	2.47 (1.26-4.17)

BSC = best supportive care; CI = confidence interval.

J Manag Care Spec Pharm. 2017;23(3-b):S17-S24.

İPF- Komorbiditeler



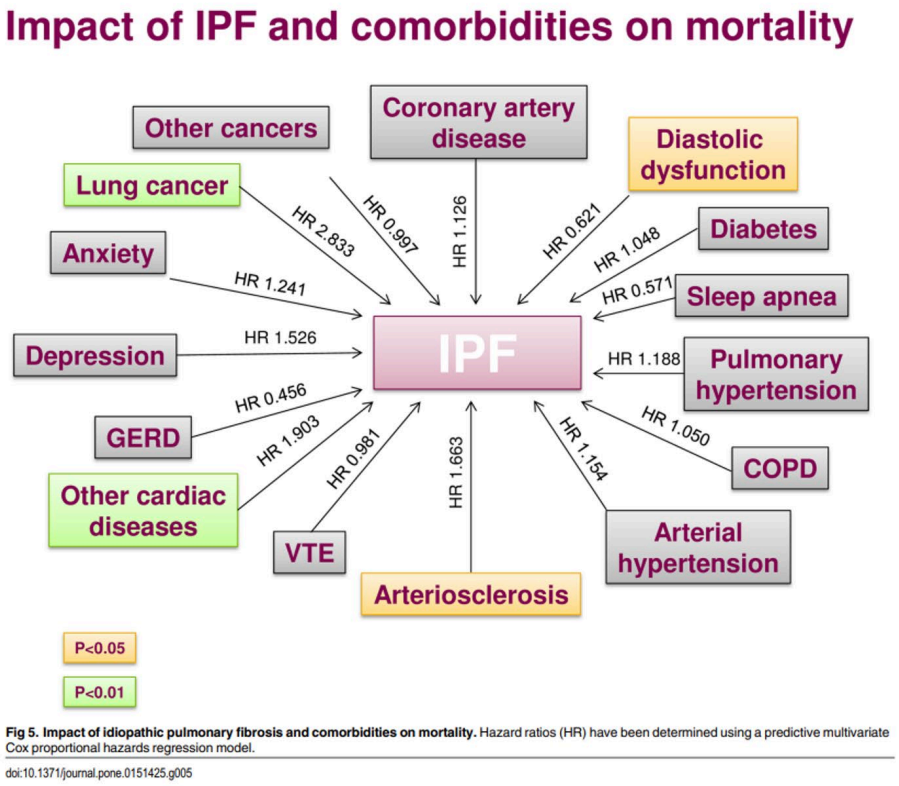
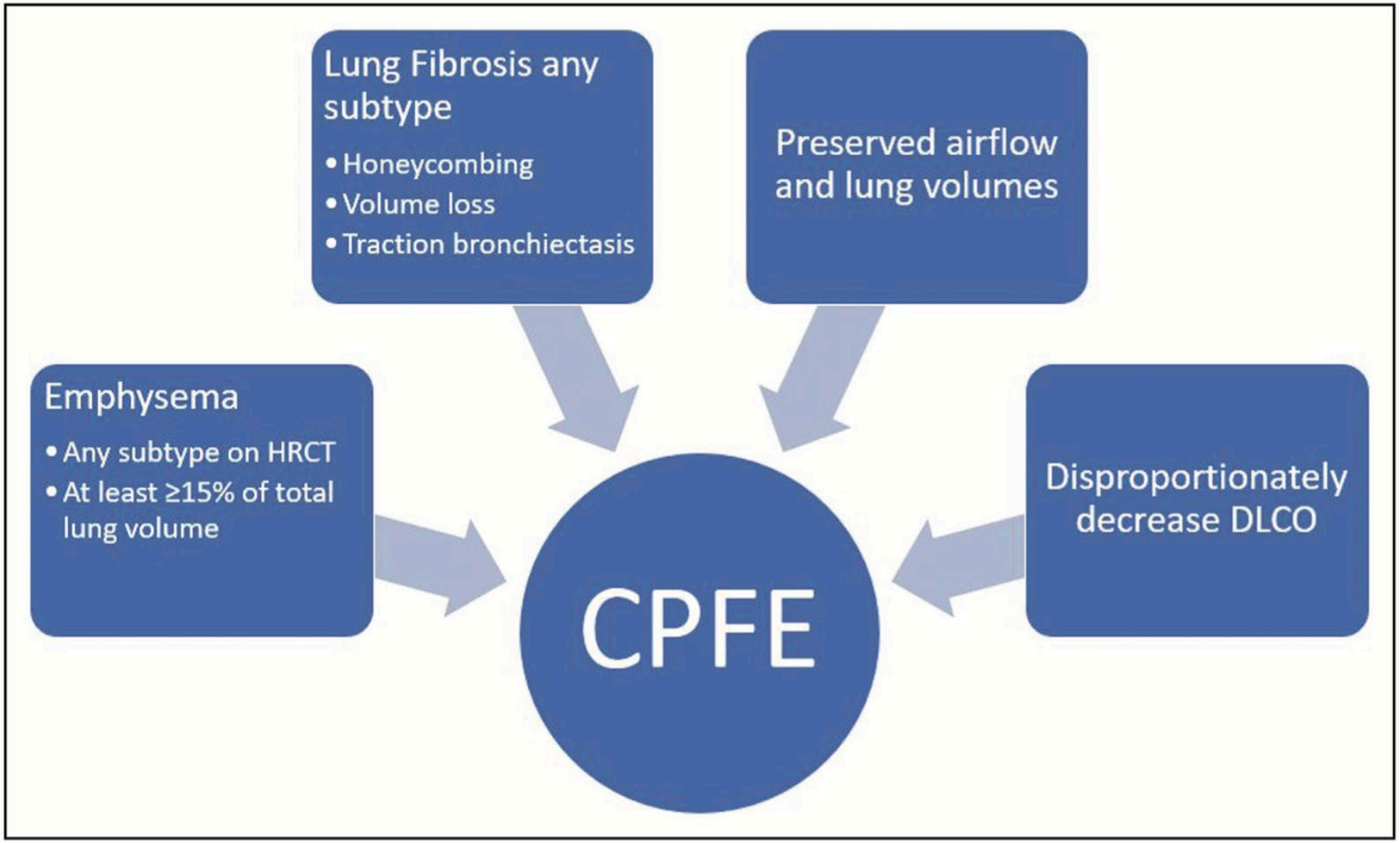


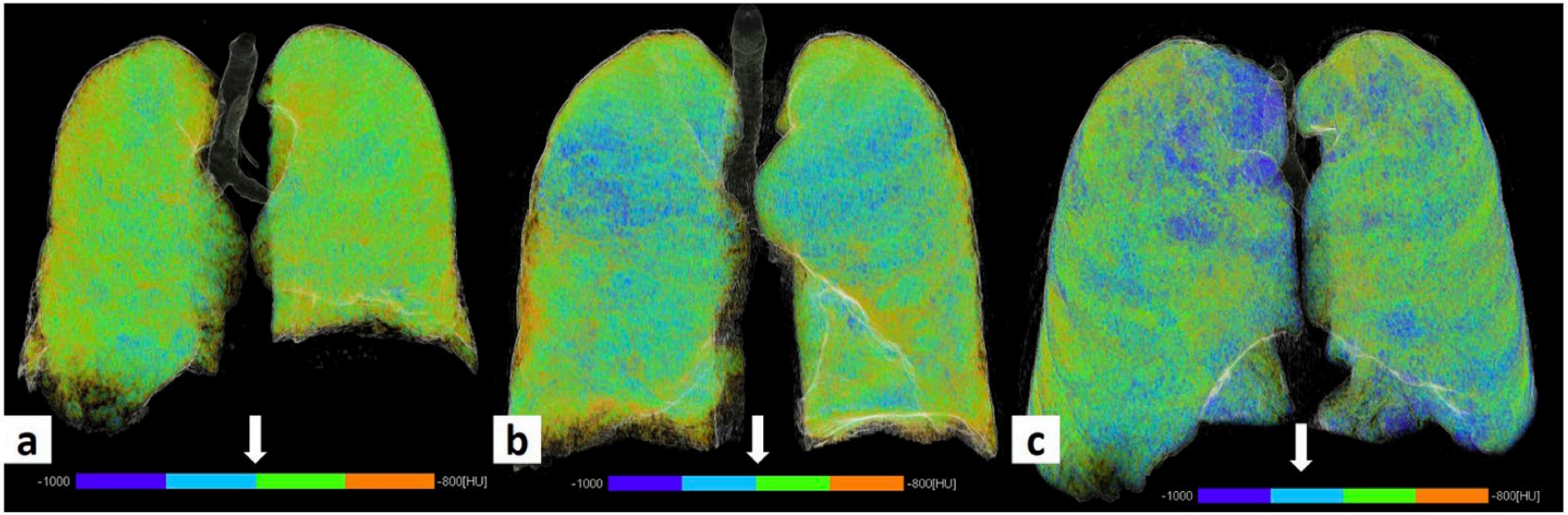
Fig 5. Impact of idiopathic pulmonary fibrosis and comorbidities on mortality. Hazard ratios (HR) have been determined using a predictive multivariate Cox proportional hazards regression model.

doi:10.1371/journal.pone.0151425.g005


Lung Fibrosis any subtype
• Honeycombing
• Volume loss
• Traction bronchiectasis
Preserved airflow and lung volumes
Emphysema
• Any subtype on HRCT
• At least ≥15% of total lung volume
Disproportionately decrease DLCO
CPFE

Kombine Pulmoner Fibrozis Amfizem (KPFA)

Akciğer volümleri korunur



A-idiopathic pulmonary fibrosis,
B-combined pulmonary fibrosis and emphysema
C-emphysema only

blue color : low density, that is, emphysema, and orange :high density, that is, reticular density-fibrosis.

KPFA Tedavi

Table 13. Key Points of Current Practice Management in Patients with Combined Pulmonary Fibrosis and Emphysema

General measures	Smoking cessation
	Pulmonary rehabilitation
	Vaccination against influenza, *Pneumococcus*, and COVID-19
	Supplemental oxygen therapy as per recommendations (286, 290)
	Consider lung transplantation
Pulmonary fibrosis	Lack of evidence specific to CPFE
	Individual management and decisions about pharmacologic treatment (e.g., antifibrotic medication, immunosuppressants) should be discussed by a multidisciplinary team based on type of fILD, relative predominance of fibrosis versus emphysema, and disease progression
	Consider antifibrotic medications at first presentation of patients with IPF with CPFE, and in other forms of pulmonary fibrosis with CPFE, progressing despite management
Pulmonary emphysema	Lack of evidence specific to CPFE
	Consider inhaled bronchodilators and inhaled corticosteroids as per indications in COPD
Complications and comorbidities	Lack of evidence related to treatment of PH specific to CPFE
	Management of comorbidities, especially cardiovascular disease and lung cancer

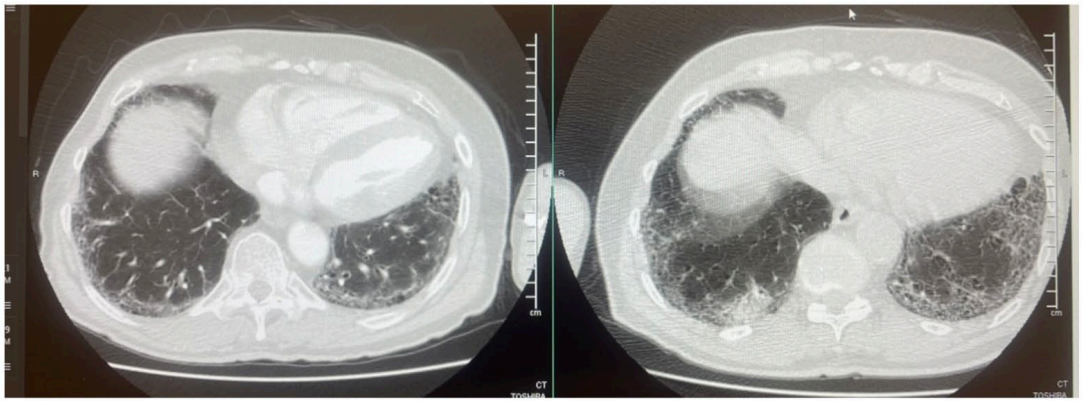
American Journal of Respiratory and Critical Care Medicine Volume 206 Number 4 | August 15 2022

İPF ➡ Akciğer kanseri

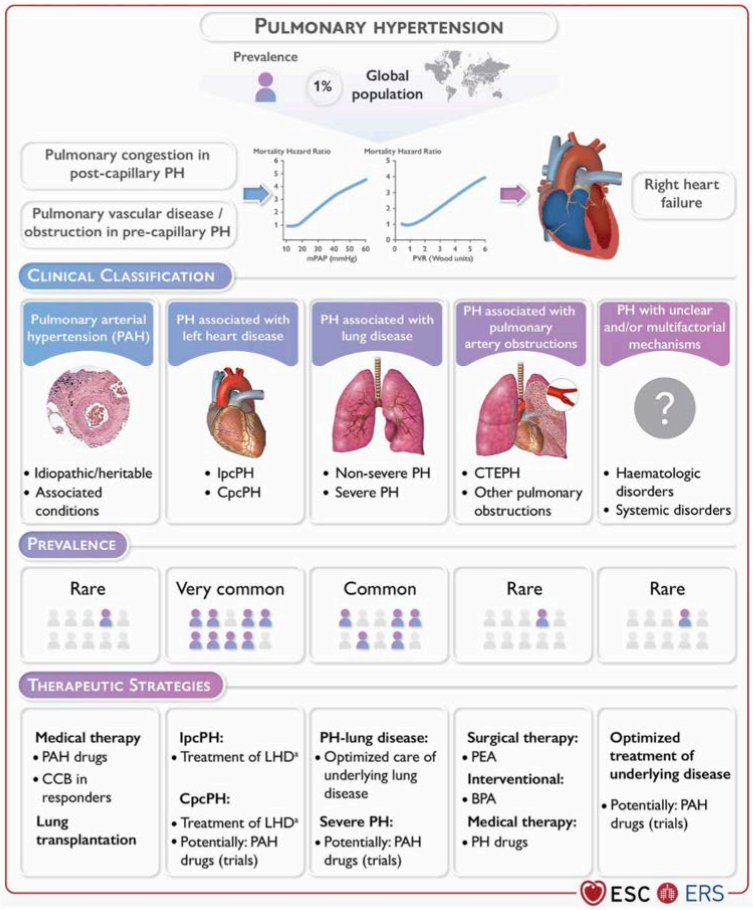
- İPF'li yüksek riskli hastalarda, özellikle KPFA li ve/veya yoğun sigara içme öyküsü olanlarda, düşük doz BT ile yıllık akciğer kanseri taraması düşünülebilir.
- İPF'de klinik kötüleşme gösteren veya yeni atipik semptomlar gelişen hastalarda BT düşünülmelidir.
- Pirfenidon ve nintedanib'in antiproliferatif etkileri ve antitümör aktivitesi, mevcut kemoterapötik rejimlerle sinerjistik bir etkiye sahip olabilir.

En sık SCC !!

Fibrotik alanda

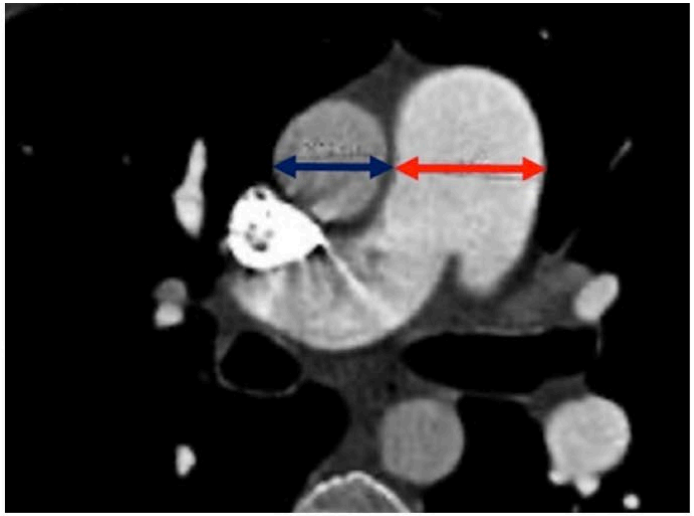


İPF ➡ Pulmoner hipertansiyon



PA/aorta diameter > 1:1

PA>29 mm : PA ectasia



Treatment for disease complications

- Pulmonary rehabilitation
- Pulmonary hypertension: inhaled treprostinil
- Respiratory failure: oxygen
- End-stage disease: lung transplant
- Management of symptoms (eg, cough and breathlessness)

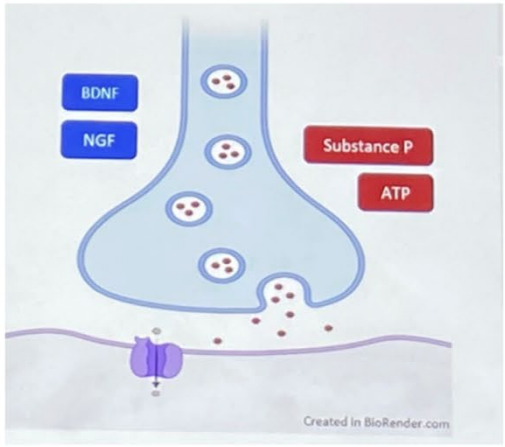
Öksürük Patofizyolojisi

HAVAYOLU İNFLAMASYONU
- Mast hücresi (balgam eozinofilisi)
- Artmış substance P (BAL)
- Artmış ATP (BAL)

ARTMIŞ MUKUS
- n=68 olan küçük ölçekli bir çalışmada MUC5B polimorfizmi öksürük ile ilişkili
- Daha yeni PROFILE çalışmasında (n=632) ilişki gösterilmemiş

MEKANİK GERİLME
- Göğüs duvarına vurulması öksürüğe sebep olur
- Gerilmenin yol açtığı TGF-β1 salınımı

NÖRONAL DEĞİŞİKLİKLER
- Artmış sensitivite (kapsaisin cevabı)
- Nörotropik faktörler (NGF, BDNF, GFL)



REFLÜ
- Hiatus hernisi sok
- Asid ve non-asid reflü
- Öksürü reflü episodlarının 1/3'ünden azı ile senkronize olur
- Kohort çalışmalarda tanımlamak zor

KOMORBİDİTELER
- Astım, amfizem / KOAH, OUA
- ACEi kullanımı

The Burden and Impact of Cough in Patients with Idiopathic Pulmonary Fibrosis: An Analysis of the Prospective Observational PROFILE Study

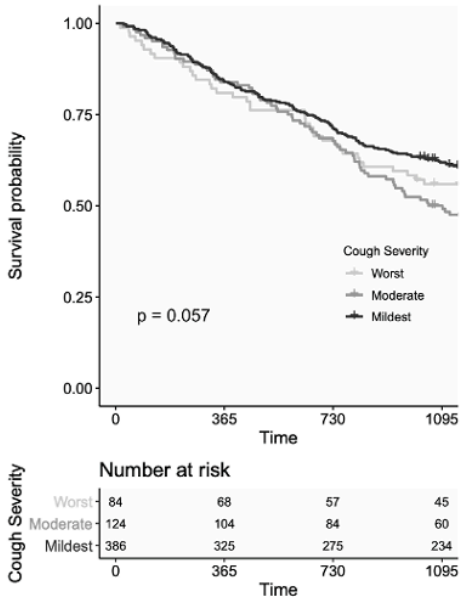


Figure 1. There is no association between Leicester Cough Questionnaire (LCQ) score at baseline and survival in idiopathic pulmonary fibrosis. Kaplan-Meier survival curves according to baseline LCQ score split by disease severity (LCQ scores were ⩽10 for the "worst" group, >10 to ⩽14 for the "moderate" group, and >14 for the "mildest" group). There was no significant difference in survival demonstrated between groups.

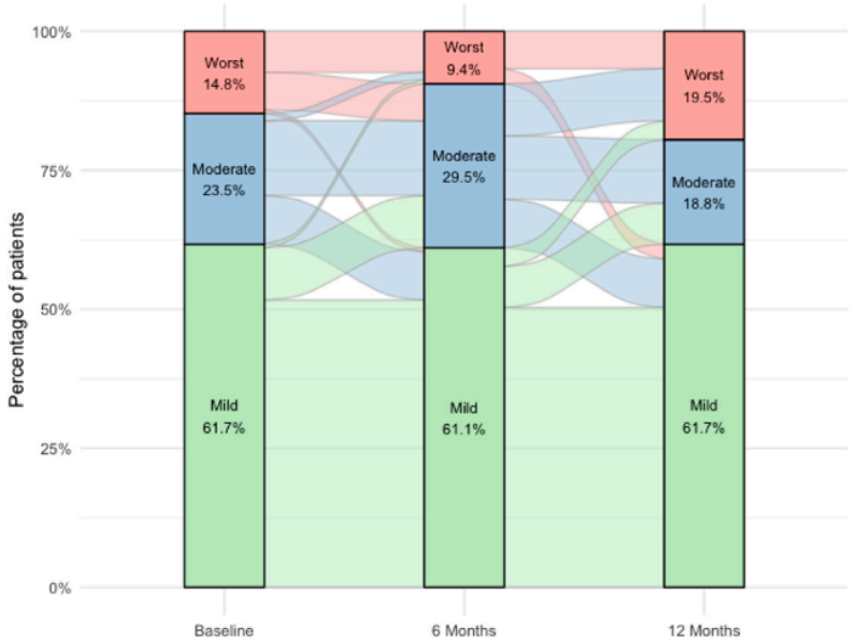


Figure 3. Stability of Leicester Cough Questionnaire (LCQ) scores over time. When split into groups on the basis of disease severity (LCQ scores were ⩽10 for the "worst" group, >10 to ⩽14 for the "moderate" group, and >14 for the "mildest" group), there is little movement between groups at baseline and at the 6- and 12-month time points.

İPF_ Öksürük Çalışmaları

Review article

Etiology and treatment of cough in idiopathic pulmonary fibrosis

Respiratory Medicine 123 (2017) 98–104

Summary of cough trials in IPF.

Study	Treatment	Study Design	Summary
[39]	• Prednisolone • 40–60 mg/day • 4 weeks	• Cohort study • 6 patients with IPF cough	• Reduced cough symptoms by VAS* • Reduced cough sensitivity to inhaled capsaicin and substance P
[67]	• Pirfenidone • 1200 mg/d (low does) • 52 weeks	• Post-hoc analysis of randomized, double-blind, placebo-controlled trial • 267 IPF patients (55 in low dose group)	• Prevented increase in cough symptoms on F, H-J questionnaire* in subgroup of patients with %VC* */ = 70% and SpO2 during 6MET* <90%
[78]	• Interferon-α • 150 IU TID • 12 Months	• Cohort study • 20 patients IPF • (6 with IPF cough)	• Reduced cough severity in 5/6 patients with cough by LCQ*
[13]	• Thalidomide • 50–100 mg/d • 12 weeks	• Randomized, double-blind, placebo-controlled crossover trial • 24 patients with IPF cough	• Reduced cough severity by VAS • Improved respiratory quality of life by CQLQ* and SGRQ*
[10]	• Lansoprazole Omeprazole • 30–40 mg BID • 8 weeks	or • Cohort study • 18 patients with GERD and IPF cough by 24 h esophageal impedance and cough count monitoring	• No decrease in cough frequency despite effective suppression of acid reflux • Increase in non-acid reflux events

* VAS = visual analogue scale; F, H-J = Fletcher, Hugh-Jones Classification scale; VC = Vital Capacity Questionnaire; CQLQ = Cough Quality of Life Questionnaire; SGRQ = St. George's Respiratory Questionı

Tackling the Neuropathic Cough of Idiopathic Pulmonary Fibrosis (IPF): More Needs to be Done

Lung (2022) 200:673–675

When it comes to antitussives for IPF cough, neuromodulators such as gabapentin are recommended on the basis of their short-term efficacy in RCC [9], but this has not been evaluated in cough of IPF. There is recommendation for speech pathology therapy that has been shown to be beneficial in RCC [13, 14] but its efficacy in IPF cough remains unclear, particularly in the absence of any evidence for the presence of laryngeal hypersensitivity in IPF. Finally, morphine has been recommended for symptom control of chronic cough when other treatments have failed, based on evidence of its efficacy in RCC [15], but as yet no evidence for chronic cough of IPF although there is an ongoing trial for IPF cough [16].

Nintedanib ile öksürük %52'den %21'e gerilemiştir

Respiration

Clinical Investigations

Respiration
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Nintedanib in IPF: Post hoc Analysis of the Italian FIBRONET Observational Study

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Christian Amici[g] Giovanna Crespi[h] Benedetta Campolo[h] Carlo Vancheri[i]
on behalf of the FIBRONET study group

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Keywords
Idiopathic pulmonary fibrosis · Nintedanib · Antifibrotic treatment · Observational study · Lung function

Abstract
Background: The FIBRONET study was an observational study of patients with idiopathic pulmonary fibrosis (IPF) in Italy. ***Objectives:*** In this post hoc descriptive analysis, we describe changes in lung function, anxiety/depression, coughing, exacerbations, and adverse events (AEs) in patients receiving nintedanib treatment. ***Methods:*** Patients with IPF from 20 centers in Italy, aged ≥40 years who received nintedanib for ≥7 months, were followed up for 12 months from study enrollment, attending clinic visits every 3 months. Outcomes included change in forced vital capacity (FVC)% predicted from baseline to 12 months, anxiety/depression measured by the Hospital Anxiety and Depression Scale (HADS), and the proportion of patients with cough, AEs, and exacerbations. ***Results:*** In total, 52 patients received nintedanib (mean duration of 11.6 months). Ten patients had dose reductions from 150 mg to 100 mg twice daily, due to AEs. FVC% predicted was unchanged in the overall nintedanib population (78.7% at baseline; 79.8% at 12 months) and those with a reduced dose (77.7% at baseline; 81.0% at 12 months). HADS score was low at baseline and throughout the study. The proportion of patients with cough decreased from 50.0% to 21.2% over 12 months. Two patients experienced exacerbations, 2 patients discontinued treatment, and 27 (51.9%) reported AEs. The most common AE was diarrhea (34.6%). ***Conclusions:*** In patients with IPF who received nintedanib in the FIBRONET study, FVC% predicted was stable over 12 months, and the proportion of patients with cough decreased. The safety profile was consistent with the known safety profile for nintedanib in IPF.

Benedetta Campolo was an employee of Boehringer Ingelheim (Italy) at the time of this study.
Trial registration: This study was registered at clinicaltrials.gov; https://clinicaltrials.gov/ct2/show/NCT02803580.

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Pirfenidon öksürüğü %34 azaltmıştır

Effect of pirfenidone on cough in patients with idiopathic pulmonary fibrosis

Eur Respir J 2017; 50: 1701157

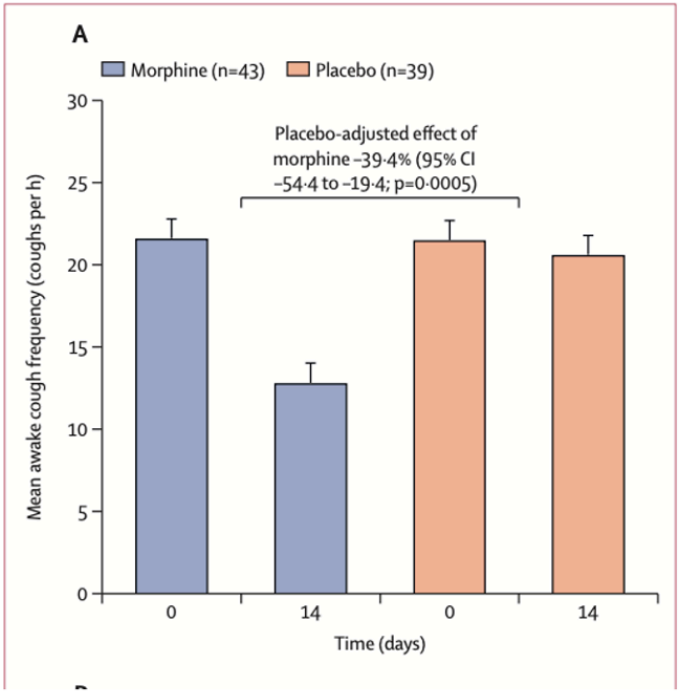
This international, multicentre, prospective, observational study at four sites (The Netherlands, Italy, France and UK) recruited patients between 2013 and 2016. Treatment-naïve IPF patients aged 40–85 years with a forced vital capacity (FVC) ⩾50% and corrected transfer factor of the lung for carbon monoxide (T_{LCOc}) ⩾30%, in whom pirfenidone therapy was about to be initiated according to regular practice, who had daily IPF-related cough for ⩾8 weeks with a cough score of ⩾40 mm on a 0–100 mm visual analogue scale (VAS), were eligible for the present study.

After 12 weeks of pirfenidone treatment, objective 24-h cough decreased by 34% (95% CI −48% to −15%) (table 1). An improvement in 24-h cough was observed in 20 out of 27 patients (74%). Sensitivity analysis showed similar results (data available on request). Subjective cough measures showed consistent improvements (table 1). No significant changes in disease-specific QoL and anxiety were found. Even at the earlier time point of 4 weeks, a smaller, but significant effect on cough counts was observed, with a 14% reduction in 24-h cough frequency (95% CI −22% to −6%; p=0.002). At this time point, improvements in cough were observed in 24 out of 35 patients (69%).

Öksürük- Morfin

Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial

Zhe Wu, Lisa G Spencer, Winston Banya, John Westoby, Veronica A Tudor, Pilar Rivera-Ortega, Nazia Chaudhuri, Ira Jakupovic, Brijesh Patel, Muhunthan Thillai, Alex West, Marlies Wijsenbeek, Toby M Maher, Jacky A Smith, Philip L Molyneaux



Summary

Background Idiopathic pulmonary fibrosis is a progressive fibrotic lung disease, with most patients reporting cough. Currently, there are no proven treatments. We examined the use of low dose controlled-release morphine compared with placebo as an antitussive therapy in individuals with idiopathic pulmonary fibrosis.

Methods The PACIFY COUGH study is a phase 2, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial done in three specialist centres in the UK. Eligible patients aged 40–90 years had a diagnosis of idiopathic pulmonary fibrosis within 5 years, self-reported cough (lasting >8 weeks), and a cough visual analogue scale (VAS) score of 30 mm or higher. Patients were randomly assigned (1:1) to placebo twice daily or controlled-release morphine 5 mg orally twice daily for 14 days followed by crossover after a 7-day washout period. Patients were randomised sequentially to a sequence group defining the order in which morphine and placebo were to be given, according to a computer-generated schedule. Patients, investigators, study nurses, and pharmacy personnel were masked to treatment allocation. The primary endpoint was percentage change in objective awake cough frequency (coughs per h) from baseline as assessed by objective digital cough monitoring at day 14 of treatment in the intention-to-treat population, which included all randomised participants. Safety data were summarised for all patients who took at least one study drug and did not withdraw consent. This study was registered at ClinicalTrials.gov, NCT04429516, and has been completed.

Findings Between Dec 17, 2020, and March 21, 2023, 47 participants were assessed for eligibility and 44 were enrolled and randomly allocated to treatment. Mean age was 71 (SD 7·4) years, and 31 (70%) of 44 participants were male and 13 (30%) were female. Lung function was moderately impaired; mean forced vital capacity (FVC) was 2·7 L (SD 0·76), mean predicted FVC was 82% (17·3), and mean predicted diffusion capacity of carbon monoxide was 48% (10·9). Of the 44 patients who were randomised, 43 completed morphine treatment and 41 completed placebo treatment. In the intention-to-treat analysis, morphine reduced objective awake cough frequency by 39·4% (95% CI −54·4 to −19·4; p=0·0005) compared with placebo. Mean daytime cough frequency reduced from 21·6 (SE 1·2) coughs per h at baseline to 12·8 (1·2) coughs per h with morphine, whereas cough rates did not change with placebo (21·5 [SE 1·2] coughs per h to 20·6 [1·2] coughs per h). Overall treatment adherence was 98% in the morphine group and 98% in the placebo group. Adverse events were observed in 17 (40%) of 43 participants in the morphine group and six (14%) of 42 patients in the placebo group. The main side-effects of morphine were nausea (six [14%] of 43 participants) and constipation (nine [21%] of 43). One serious adverse event (death) occurred in the placebo group.

Interpretation In patients with cough related to idiopathic pulmonary fibrosis, low dose controlled-release morphine significantly reduced objective cough counts over 14 days compared with placebo. Morphine shows promise as an effective treatment to palliate cough in patients with idiopathic pulmonary fibrosis, and longer term studies should be the focus of future research.

Öksürük- Morfin

Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial

www.thelancet.com/respiratory **Vol 12 April 2024**

Zhe Wu, Lisa G Spencer, Winston Banya, John Westoby, Veronica A Tudor, Pilar Rivera-Ortega, Nazia Chaudhuri, Ira Jakupovic, Brijesh Patel, Muhunthan Thillai, Alex West, Marlies Wijsenbeek, Toby M Maher, Jacky A Smith, Philip L Molyneaux

	Morphine (n=43)	Placebo (n=42)
Any adverse event	17 (40%)	6 (14%)
Serious adverse events	0	1 (2%)
Gastrointestinal disorders		
Nausea	6 (14%)	3 (7%)
Vomiting	2 (5%)	1 (2%)
Constipation	9 (21%)	0
Nervous system disorders		
Hypersomnia	4 (9%)	2 (5%)
General disorders		
Lethargy	2 (5%)	0
Respiratory disorders		
Lung infection	1 (2%)	1 (2%)

Data are n (%). The single serious adverse event with placebo treatment resulted in death.

***Table 3*: Adverse events**

	Morphine			Placebo			Difference at 14 days	
	Baseline	Day 14	Change	Baseline	Day 14	Change	Placebo-adjusted effect of morphine (95% CI)*	p value
Awake cough frequency (coughs per h; ITT)	21·6 (1·2); n=43	12·8 (1·2); n=43	−40·8% (−54·2 to −23·6); p<0·0001	21·5 (1·2); n=39	20·6 (1·2); n=39	−4·3% (−21·8 to 17·0); p=0·66	−39·4% (−54·4 to −19·4)	0·0005
Awake cough frequency (coughs per h; per protocol)	24·2 (1·2); n=37	13·8 (1·2); n=37	−43·1% (−57·0 to −24·7); p<0·0001	23·6 (1·2); n=37	22·4 (1·2); n=37	−5·2% (−23·2 to 13·6); p =0·62	−40·3% (−55·9 to −18·9)	0·0009
Cough VAS†	61·5 (2·4); n=43	45·5 (3·7); n=43	−16·1 (−22·3 to −9·9); p<0·0001	57·7 (2·8); n=41	57·3 (2·7); n=41	−0·4 (−5·8 to 4·9); p=0·88	−14·6 (−22·8 to −6·5)	0·0004
LCQ‡	13·2 (0·5); n=43	15·0 (0·6); n=43	1·8 (0·9 to 2·8); p=0·0002	13·0 (0·5); n=41	13·6 (0·5); n=41	0·6 (−0·2 to 1·3); p=0·15	1·3 (0·4 to 2·3)	0·0047
Dyspnoea-12§	13·0 (1·2); n=43	12·9 (1·3); n=43	−0·1 (−1·9 to 1·6) p = 0·87	13·5 (1·4); n=41	14·3 (1·4); n=41	0·9 (−0·5 to 2·2); p=0·22	−1·2 (−3·1 to 0·8)	0·24
HADS anxiety¶	5·1 (0·5); n=43	5·2 (0·6); n=43	0·1 (−0·1 to 0·2); p=0·30	4·9 (0·6); n=40	5·0 (0·6); n=40	0·0 (−0·1 to 0·0); p=0·43	−0·2 (−0·9 to 0·6)	0·64
HADS depression¶	5·3 (0·6); n=43	5·3 (0·6); n=43	0·0 (0·0 to 0·0); p=0·68	5·5 (0·7); n=40	5·4 (0·7); n=40	−0·1 (−0·2 to 0·1); p=0·23	−0·2 (−1·0 to 0·6)	0·57
KBILD‖	58·2 (3·1); n=43	57·9 (3·1); n=43	−0·2 (−0·6 to 0·2); p=0·31	55·7 (3·3); n=40	55·9 (3·4); n=40	0·2 (−0·5 to 0·9); p=0·61	2·7 (−2·6 to 8·1)	0·32
L-IPF impacts**	60·9 (3·8); n=42	55·8 (3·8); n=42	−5·2 (−9·9 to −0·4); p=0·033	61·8 (4·0); n=40	60·1 (3·8); n=40	−1·7 (−5·5 to 2·1) p=0·38	−4·5 (−8·3 to −0·7)	0·019
L-IPF symptoms (total)**	40·9 (2·9); n=41	35·7 (3·1); n=41	−5·2 (−8·9 to −1·4); p=0·0078	40·9 (3·3); n=40	41·4 (3·4); n=40	0·5 (−2·5 to 3·4); p=0·75	−6·7 (−11·2 to −2·3)	0·0031
Dyspnoea domain	31·9 (3·7)	28·8 (3·6)	−3·1 (−7·9 to 1·8); p=0·22	32·1 (3·9)	31·9 (4·0)	−0·1 (−2·6 to 2·5); p=0·95	−1·5 (−6·2 to 3·2)	0·53
Cough domain	50·3 (3·7)	39·5 (3·8)	−10·8 (−16·9 to −4·8); p=0·0004)	50·1 (3·6)	49·6 (3·8)	−0·5 (−6·2 to 5·1); p=0·85	−11·9 (−18·7 to −5·1)	0·0006
Energy domain	44·2 (3·3)	44·8 (3·6)	0·6 (−4·3 to 5·6); p=0·81	44·5 (3·9)	47·9 (3·9)	3·4 (−1·3 to 8·2); p=0·16	−3·3 (−8·3 to 1·6)	0·19

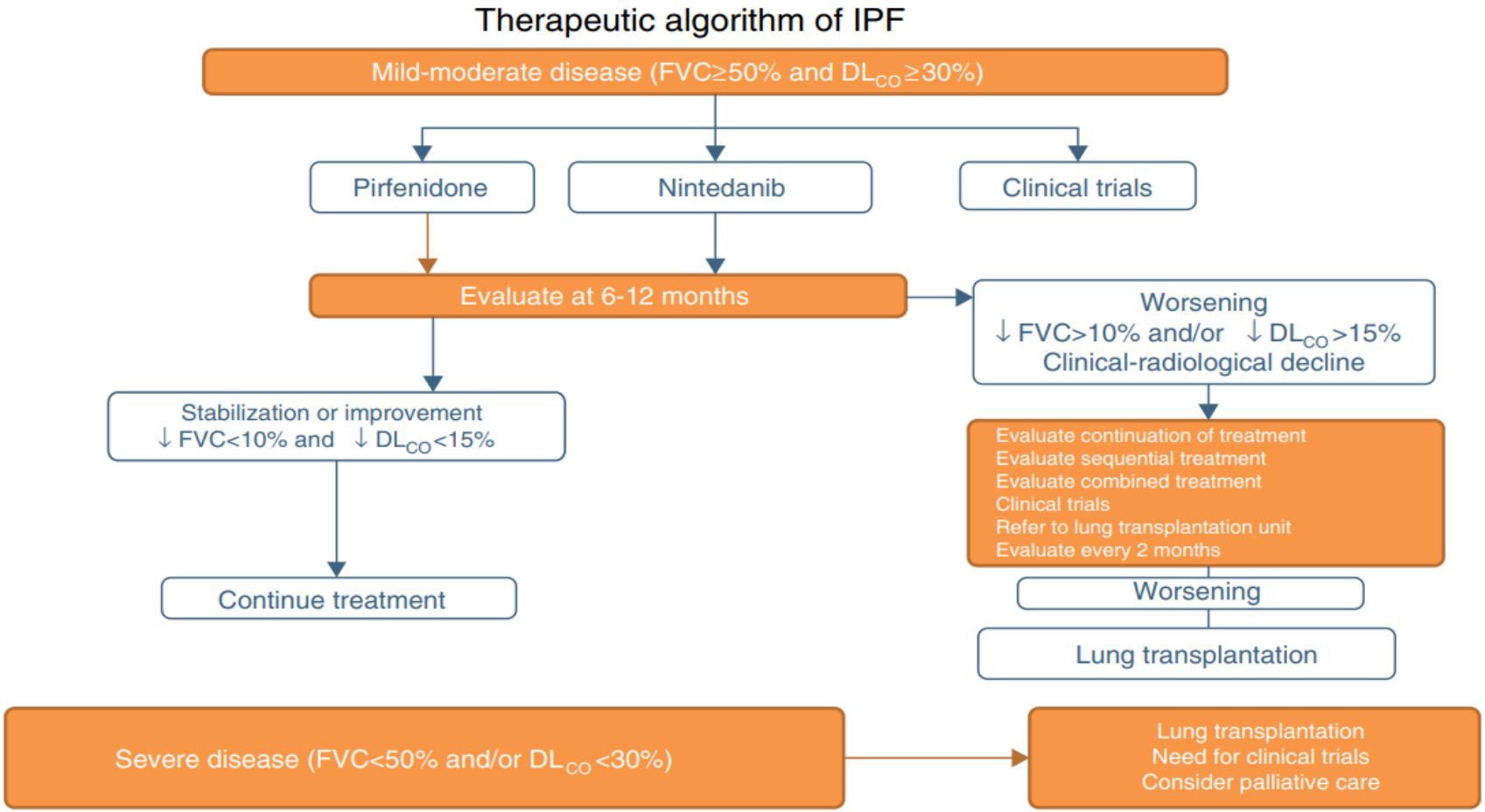


Fig. 1. IPF pharmacological treatment algorithm. FVC: forced vital capacity; DL_{CO}: carbon monoxide diffusing capacity.

RESEARCH Open Access

A comprehensive comparison of the safety and efficacy of drugs in the treatment of idiopathic pulmonary fibrosis: a network meta-analysis based on randomized controlled trials

Table 4 SUCRA ranking of the incidence of SAEs

Treatment	SUCRA	PrBest	MeanRank
Warfarin	89.4	44.9	2.4
Ambrisentan	81.6	10.3	3.4
Pamrevlumab	80.1	30.5	3.6
N-acetylcysteine	66.1	5.3	5.4
Simtuzumab	54.1	0.1	7
Pirfenidone	48.5	0	7.7
Placebo	48	0	7.8
Imatinib	44	1.6	8.3
Nintedanib	42.7	0	8.5
Sildenafil	38.7	1.2	9
Macitentan	37.6	0.7	9.1
PRM151	34	4.4	9.6
Bosentan	29	0	10.2
GLPG1690	6.1	1	13.2

Higher values of SUCRA indicate higher incidence of SAEs

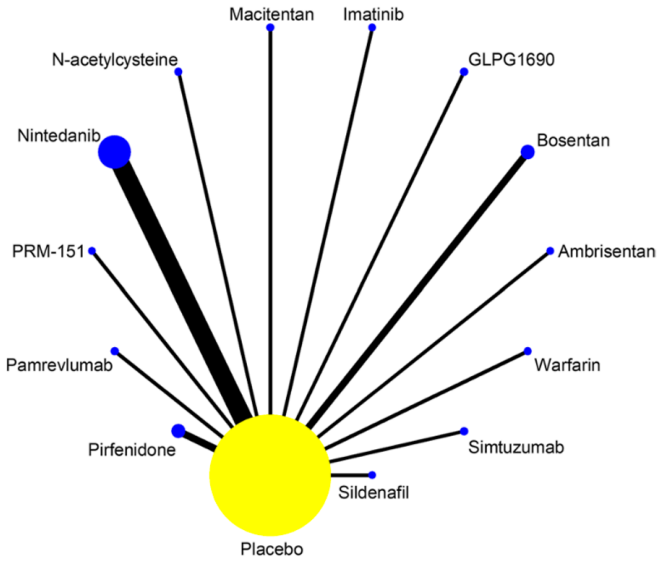


Fig. 4 Network evidence map of SAEs. A total of 19 studies reported SAEs in the treatment of IPF with 13 drugs: 1 of Ambrisentan, 2 of Bosentan, 1 of GLPG1690, 1 of Imatinib, 1 of Macitentan, 1 of N-acetylcysteine, 5 of Nintedanib, 1 of Pamrevlumab, 2 of Pirfenidone, 1 of PRM-151, 1 of Sildenafil, 1 of Simtuzumab, 1 of Warfarin

A comprehensive comparison of the safety and efficacy of drugs in the treatment of idiopathic pulmonary fibrosis: a network meta-analysis based on randomized controlled trials

Table 6 SUCRA ranking of all-cause mortality

Treatment	SUCRA	PrBest	MeanRank
Warfarin	96.6	75.7	1.4
Ambrisentan	82.9	9.4	2.9
N-acetylcysteine	75	11.9	3.8
Bosentan	60.9	0.1	5.3
Macitentan	54.1	2	6
Placebo	51.3	0	6.4
Simtuzumab	48.2	0	6.7
Imatinib	36.4	0.2	8
Pirfenidone	25.6	0	9.2
Nintedanib	24.2	0	9.3
Sildenafil	23.7	0.6	9.4
Pamrevlumab	21.2	0.2	9.7

Higher values of SUCRA indicate higher all-cause mortality

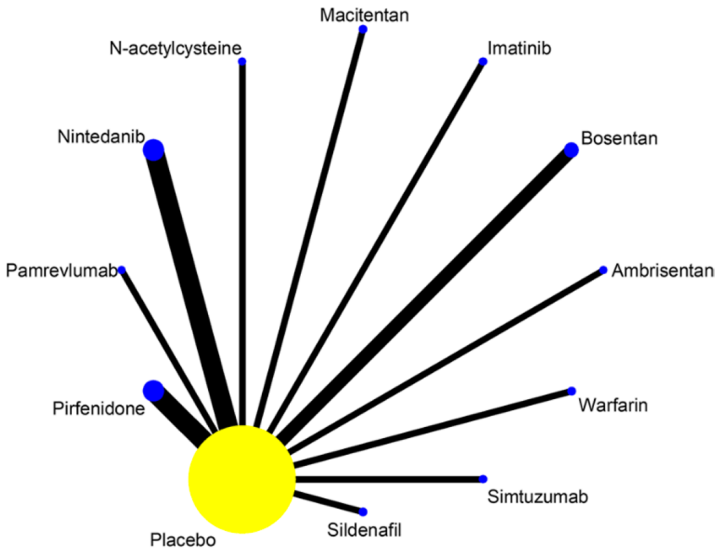


Fig. 5 Network evidence map of all-cause mortality. A total of 16 studies reported the all-cause mortality of IPF treated with 11 drugs: 1 of Ambrisentan, 2 of Bosentan,1 of Imatinib, 1 of Macitentan, 1 of N-acetylcysteine, 3 of Nintedanib, 1 of Pamrevlumab, 3 of Pirfenidone, 1 of Sildenafil, 1 of Simtuzumab, 1 of Warfarin

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Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with idiopathic pulmonary fibrosis (FIBRONEER-IPF)

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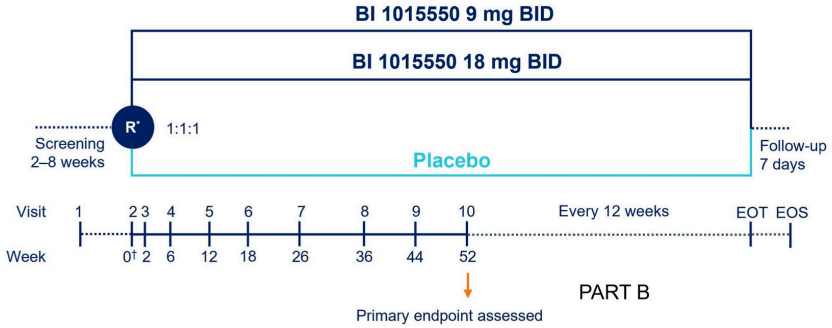

CONCLUSIONS

FIBRONEER-IPF is the first phase III trial of a preferential PDE4B inhibitor in patients with IPF. The results of this trial will increase our understanding of the safety and efficacy of BI 1015550 as a monotherapy or in combination with current antifibrotic standard of care in a larger and broader population of patients with IPF. These data will help to address an unmet need for new treatments for patients with IPF and potentially provide evidence for combination treatment in IPF.

NONFARMAKOLOJİK TEDAVİ

- Sigaranın bırakılması
- USOT
- HFO VE NIV
- Pulmoner rehabilitasyon
- Transplantasyon
- Aşılama

İZLEM

Hastalar her 12 ayda bir yeniden değerlendirilmelidir.

FVC'de ≥%10 düşme olmadığı her raporda belirtilmelidir.

FVC değerinde ≥%10 düşme olması ilaca yanıtsızlık olarak kabul edilir ve tedavi sonlandırılır.

İlaçlardan birine yanıtsızlık veya intolerans gelişmişse ilaçlar arasında geçiş yapılabilir.

Teşekürler

Dr Dildar Duman

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