Cough in IPF Studies – Why does it count

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Vitalograph®

Disclosures

Steven Nathan has the following financial relationships:

- Consultant: Boerhinger-Ingelheim, United Therapeutics, Merck, Astra-Zeneca, Avalyn Pharma, Roivant, PureTech, Daewoong, Ferrer, Insmed, Gossamer, Trevi, Fibrogen
- DSMB/Adjudication committees: Horizon, Astra-Zeneca
- Speakers Bureau; Boehringer-Ingelheim, United Therapeutics
- Research funding: Boerhinger-Ingelheim, Tvardi, United Therapeutics

Objectives

- Overview of IPF and other ILDs
- Significance/clinical relevance of cough in IPF
- Cough assessment in clinical practice
- Cough as an endpoint in IPF drug trials
- Challenges in assessing cough in clinical trials

ILD: A Pragmatic Pneumonic

Category	Diseases	Sub-categories/examples
Idiopathic	Idiopathic Interstitial Pneumonias (IIPs)	IPF NSIP Unclassifiable
	Sarcoidosis Amyloidosis Lymphangiolyomyomatosis PLCH, Eosinophilic pneumonia. Neurofibromatosis, DAH	COP RB-ILD DIP AIP LIP PPFE CPFE
Immunologic	Connective Tissue Disorders	
Inhalational	Inorganic	Asbestosis, Silicosis
	Organic: Chronic hypersensitivity pneumonitis	Bird fanciers disease, Farmer's lung
Iatrogenic	Antiarrhythmics, Antimicrobials, Chemotherapy agents, Biologics Radiation	
Infectious	Viral	CMV, influenza
	Fungal	Pneumocystis carinii
Chronic CHF		
Neoplastic	Lymphangitic carcinomatosis Bronchoalveolar carcinoma	

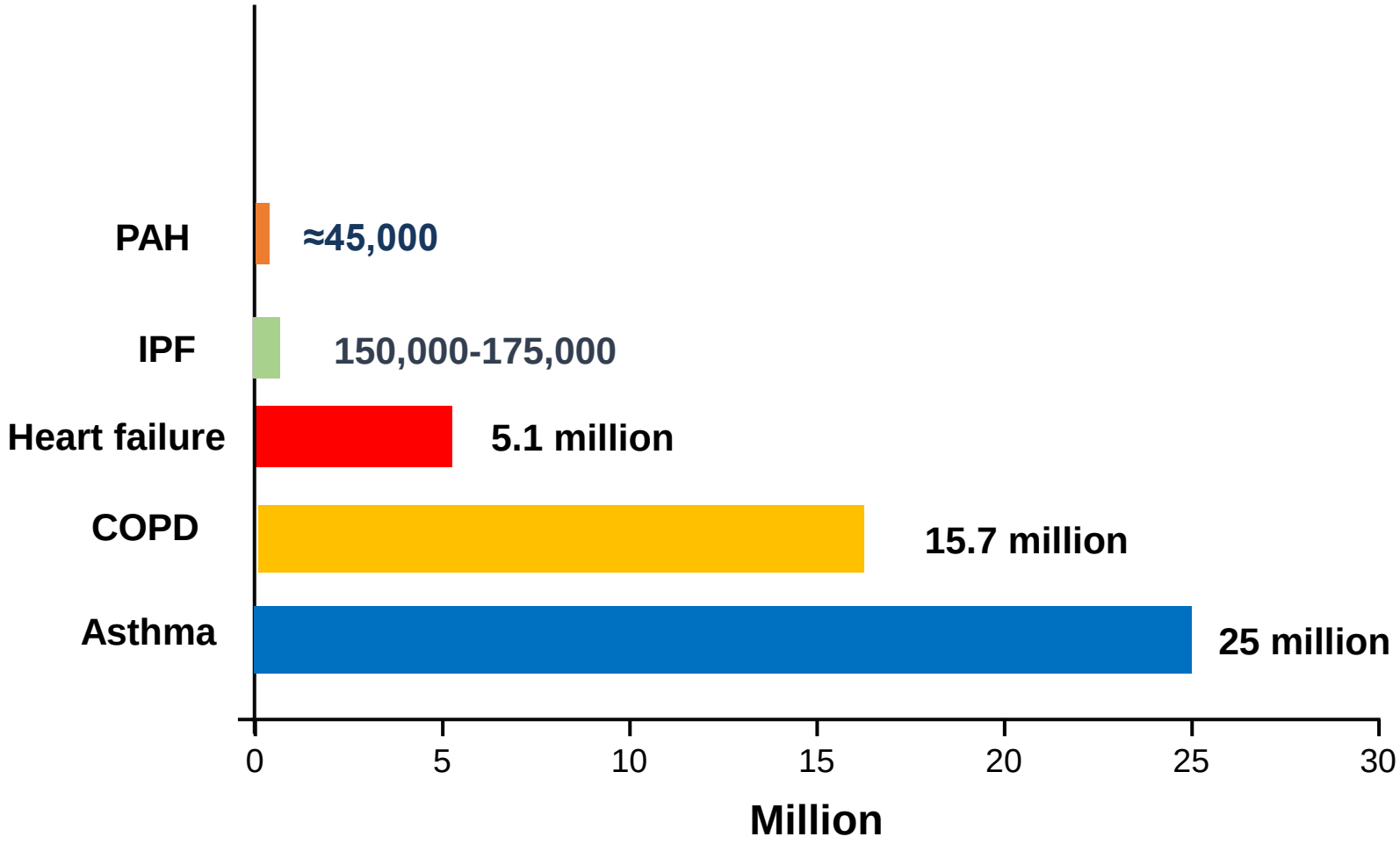
Adapted from Guide to Clinical Management of IPF. Nathan, Brown and King. Springer 2016.

Current Definition of IPF

- Specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause
- Occurring primarily in older adults
- Limited to the lungs

ATS/ERS/JRS/ALAT consensus statement *Am J Respir Crit Care Med.* 2011;183:788-824

Disease Prevalence, United States



Raghu G, et al. *Resp Crit Care Med*. 2006;174:810-816; Go AS, et al. *Circulation*. 2013;127:e6-e245; Wheaton AG, et al. *MMWR Morb Mortal Wkly Rep*. 2015;64:289-295.

Common Risk Factors for IPF

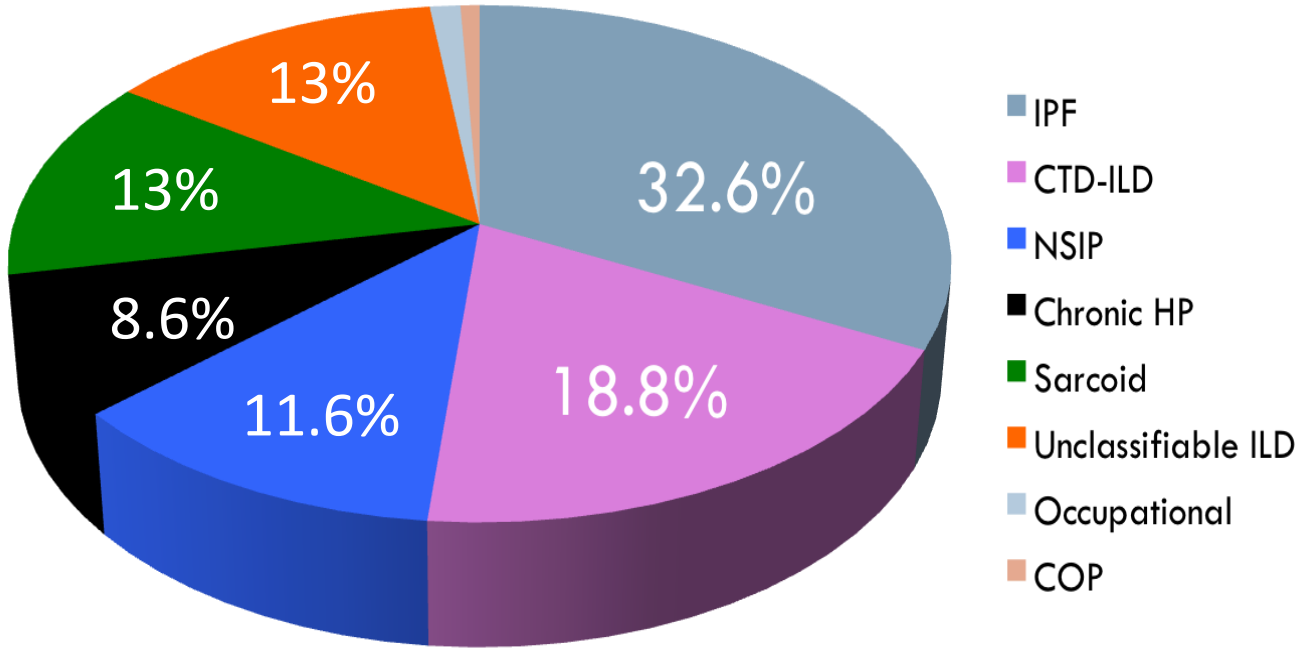
- Age
- Male gender
- Cigarette smoking
- Gastroesophageal reflux
- Occupational exposure to metal dust or wood dust
- Genetic predisposition

Raghu G, et al. *Am J Respir Crit Care Med*. 2011;183(6):788–824..

How Do IPF Patients Present?

- Shortness of breath (dyspnea)
- Dry cough
- Fatigue
- Exercise desaturation
- “Velcro” rales at lung bases
- Clubbing of fingers and/or toes may be present
- Incidentally
  - ILD on routine CXR or CT chest
  - ILD at bases of abdominal CT
  - Fluoroscopy at time of cardiac catheterization
  - Family history

Inova Fairfax: Distribution of Specific ILDs



Global Variability: Prevalence of ILD

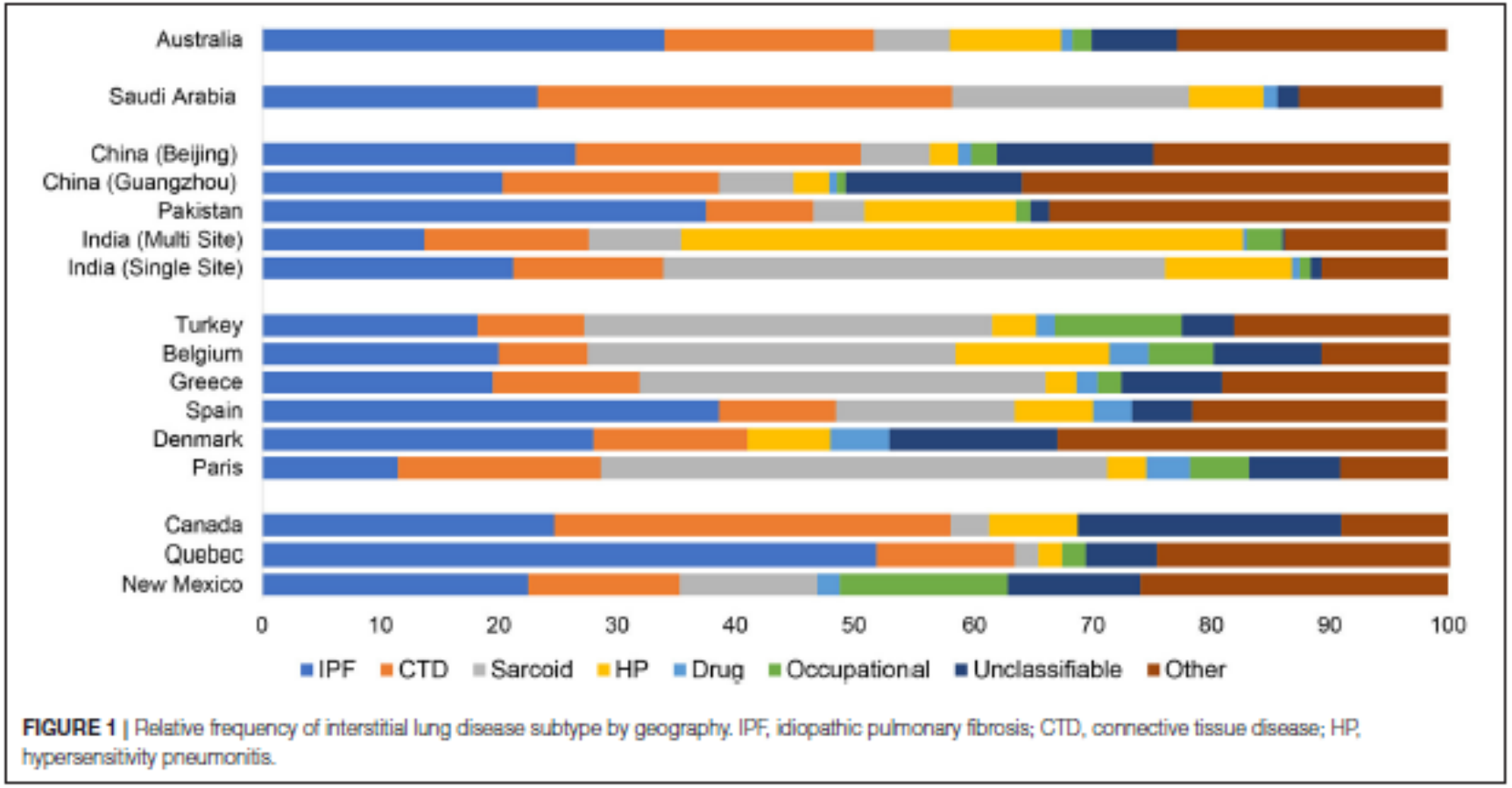
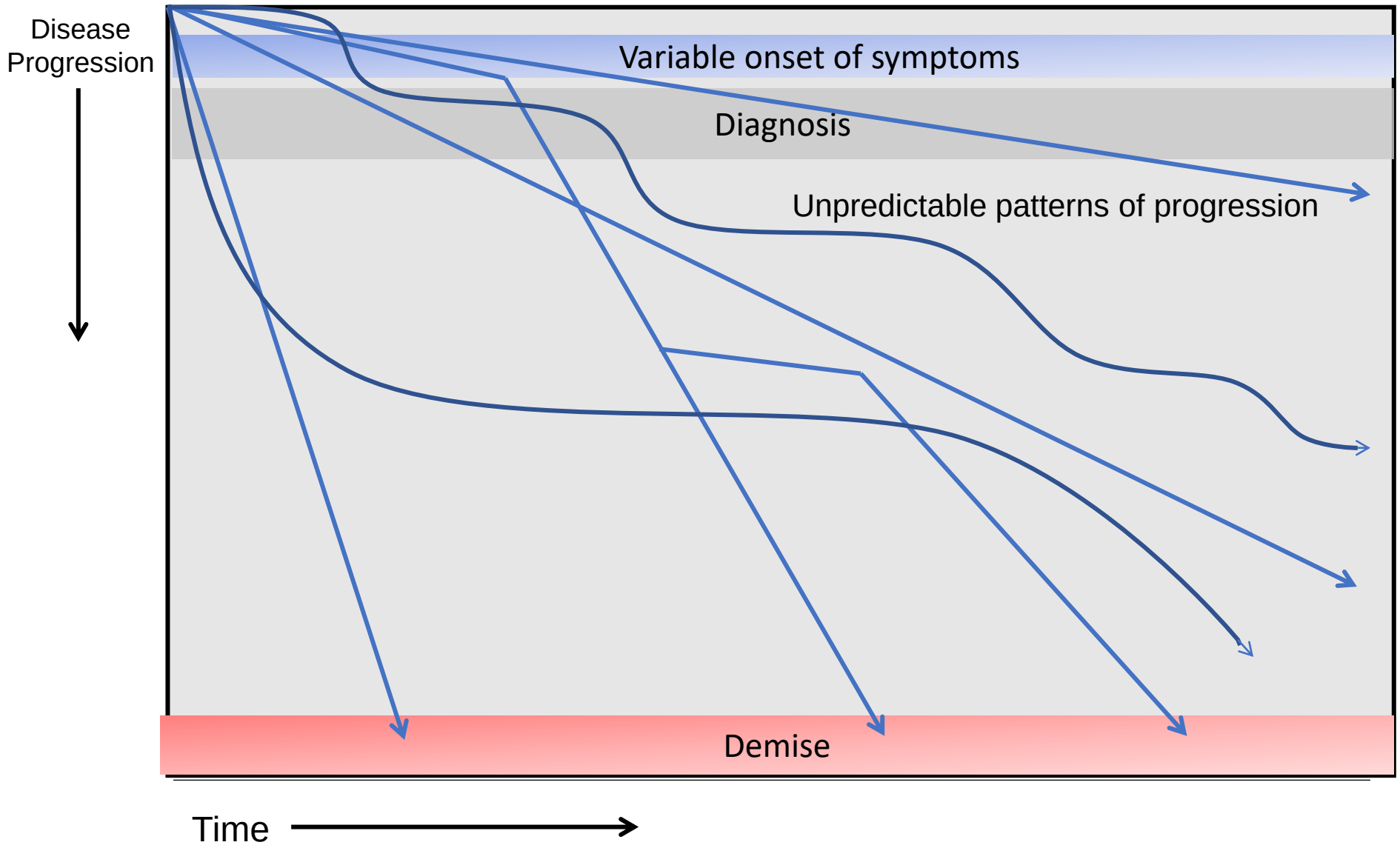


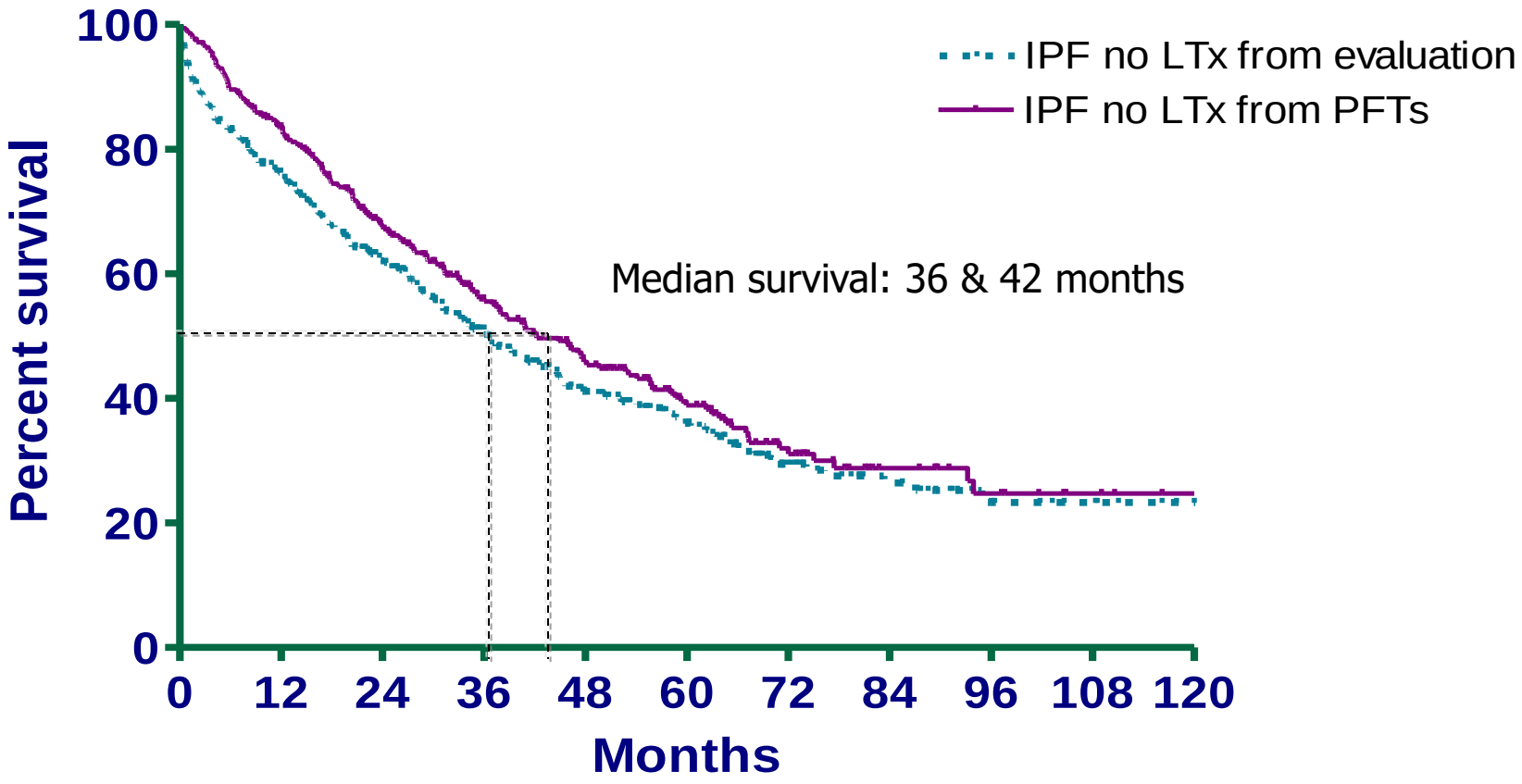
FIGURE 1 | Relative frequency of interstitial lung disease subtype by geography. IPF, idiopathic pulmonary fibrosis; CTD, connective tissue disease; HP, hypersensitivity pneumonitis.

Disease progression in IPF



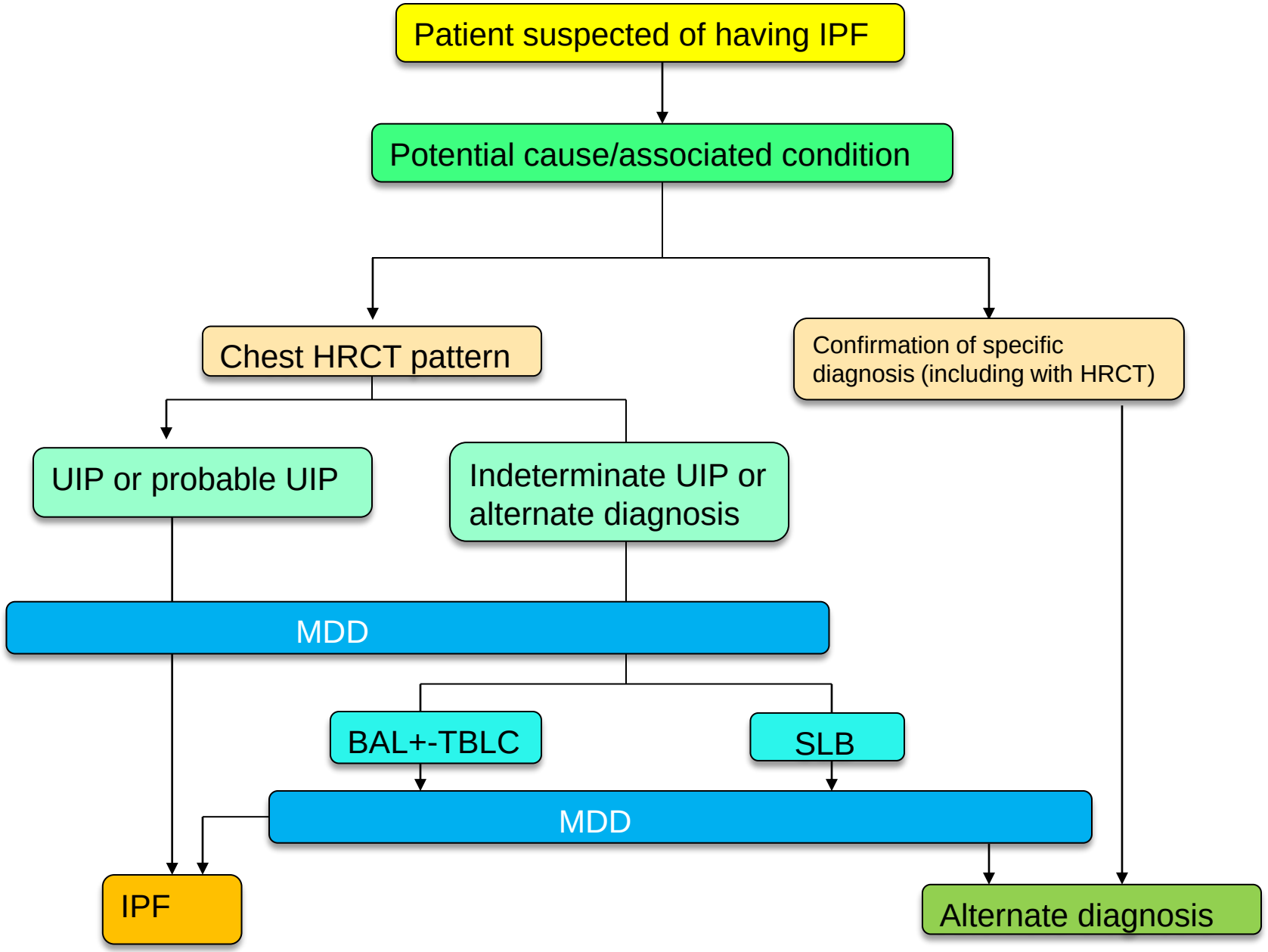
IPF: Survival in the pre-antifibrotic era

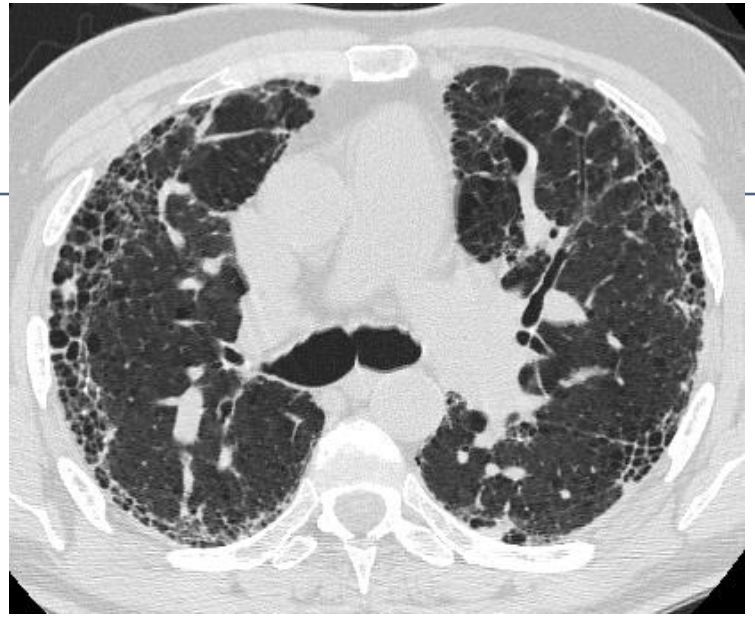
2000-2009 (N=521)

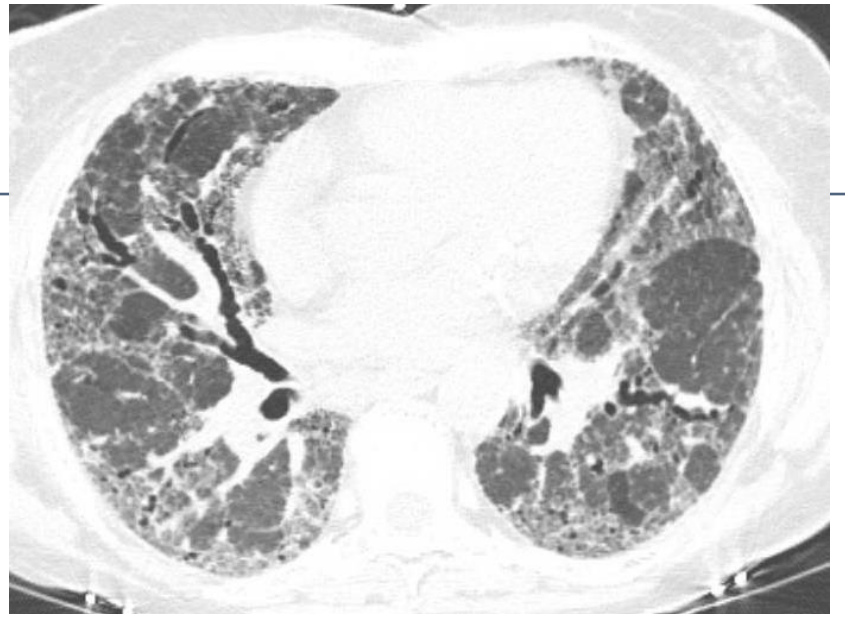


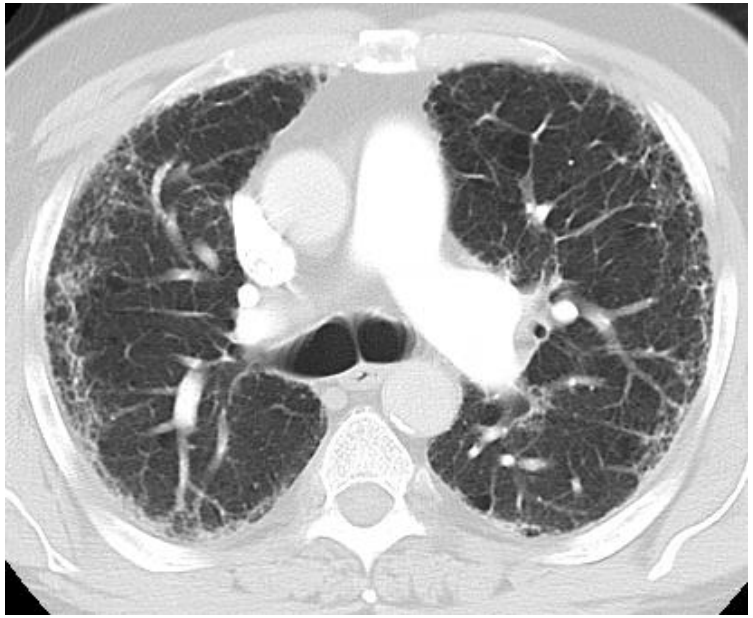
Chest 2011;140:221-229

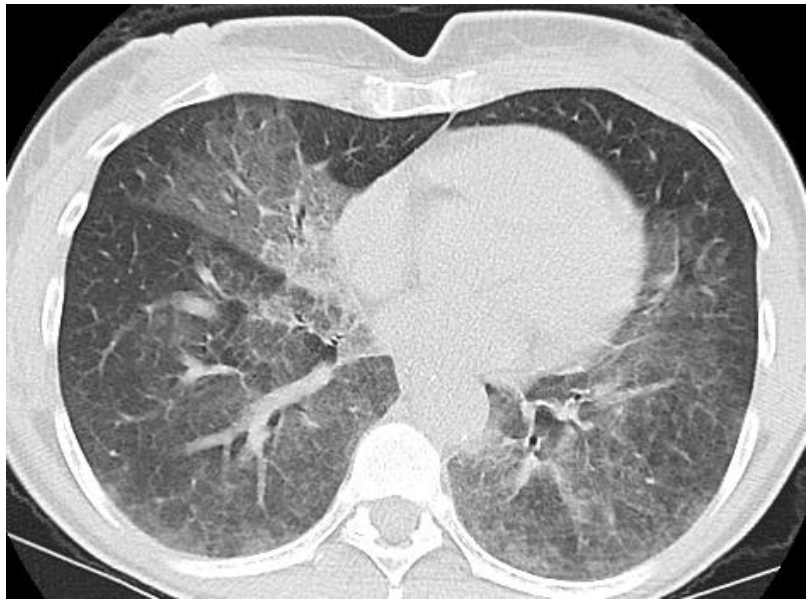
2022 Diagnosis of IPF: An Official ATS/ERS/JRS/ALAT Practice Guideline











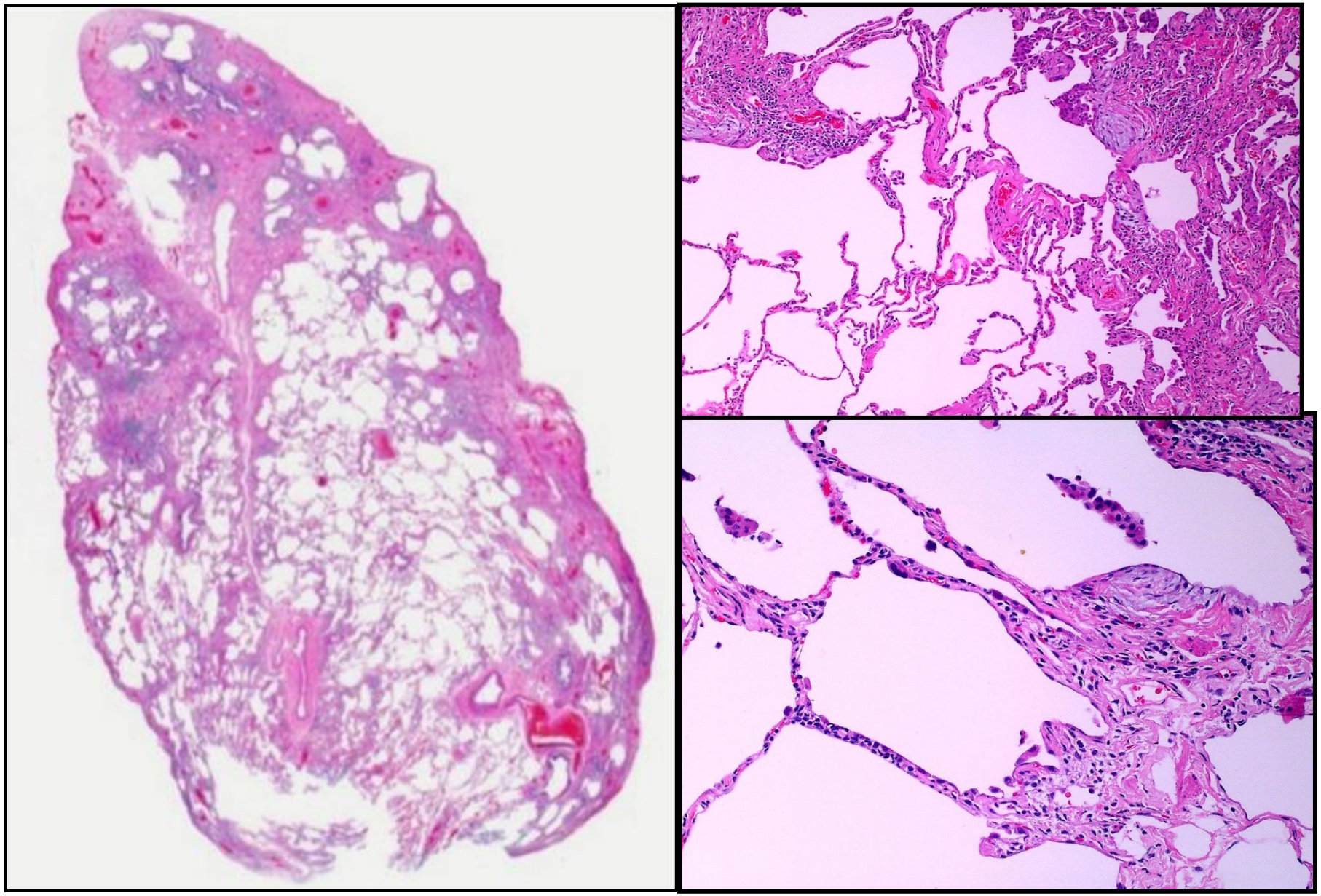
Do ILD docs agree with each other?

N= 50
Each row of the two columns represents the same sequence of the individual cases

2B-2018 guidelines

Ther Adv Respir Dis. 2020 Jan-Dec;14:1753466620968496. doi: 10.1177/1753466620968496

PATHOLOGY of UIP



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

IPF suspected*		Histopathology pattern†			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)‡	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)‡	Indeterminate§	Non-IPF dx
	Alternative diagnosis	IPF (Likely)‡	Indeterminate§	Non-IPF dx	Non-IPF dx

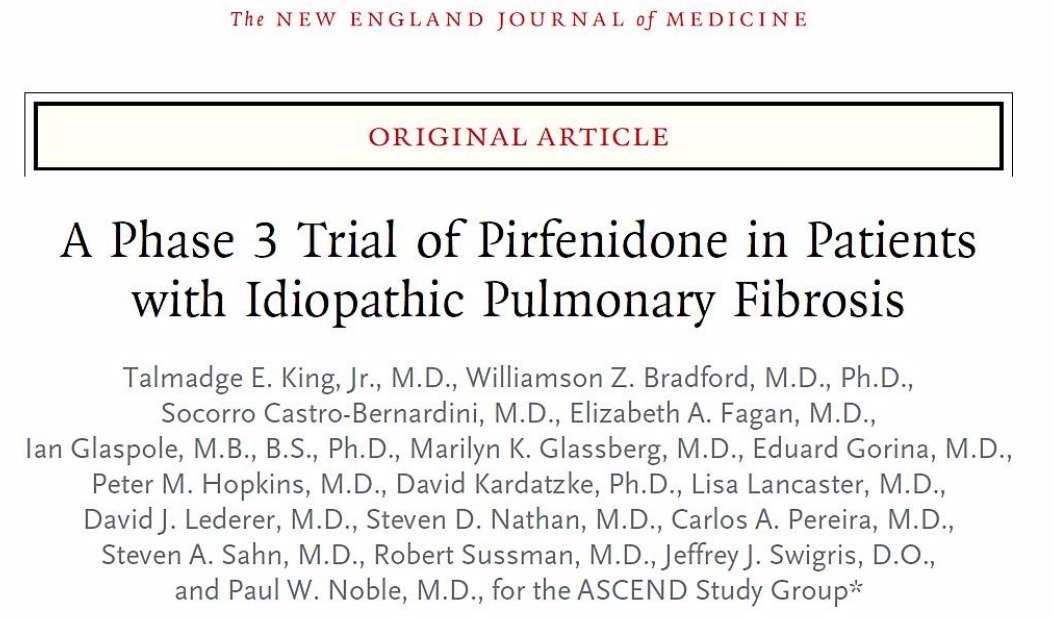
Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

Clinical likelihood + HRCT

Clinical likelihood	HRCT pattern: UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
High (70% or more)	**Definite diagnosis of IPF** (biopsy not indicated)	**Definite diagnosis of IPF** (biopsy not indicated)	**Low-confidence provisional diagnosis of IPF** (biopsy is likely to inform diagnosis)	**Probability of IPF comparable to that of other ILD diagnosis** (biopsy, if performed, is highly likely to inform diagnosis)
Intermediate for IPF (30-70%)	**High-confidence provisional diagnosis of IPF** (biopsy generally not indicated)	**Low-confidence provisional diagnosis of IPF** (biopsy is likely to inform diagnosis)	**Probability of IPF comparable to that of other ILD diagnosis** (biopsy, if performed, is highly likely to inform diagnosis)	**Probability of ILD other than IPF greater than IPF** (biopsy, if performed, is highly likely to inform diagnosis)
Low (30% or less)	**Low-confidence provisional diagnosis of IPF** (further evaluation needed to make a diagnosis)	**Probability of IPF comparable to that of other ILD diagnosis** (biopsy, if performed, is highly likely to inform diagnosis)	**Probability of ILD other than IPF greater than IPF** (biopsy, if performed, is highly likely to inform diagnosis)	**Probability of ILD other than IPF greater than IPF** (biopsy, if performed, is highly likely to inform diagnosis)

Am J Respir Crit Care Med. 2022 Mar 30. doi: 10.1164/rccm.202111-2607PP.

Treatment



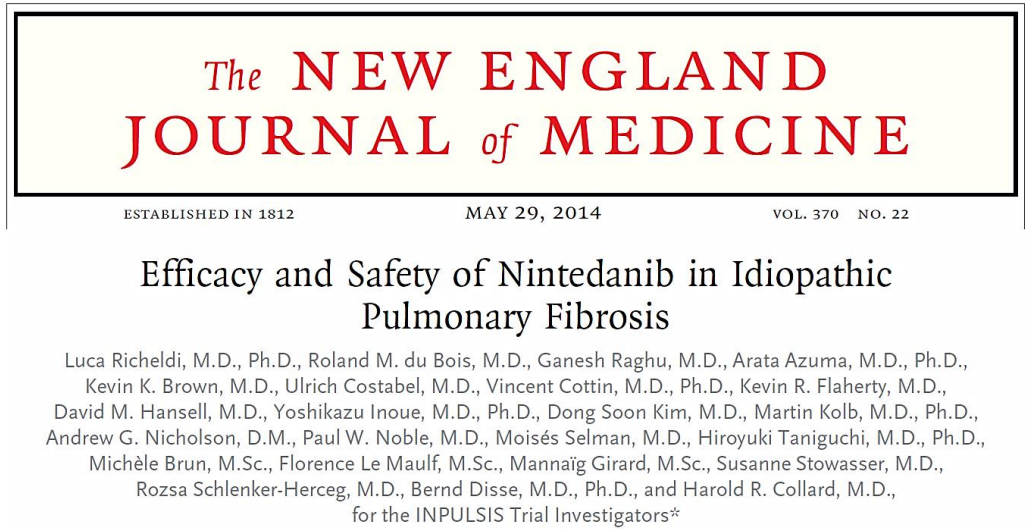
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

King TE Jr., et al. *N Engl J Med*. 2014;370:2083-2092.



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

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

Richeldi L, et al. *N Engl J Med.* 2014;370:2071-2082.

ΔFVC with the approved antifibrotics

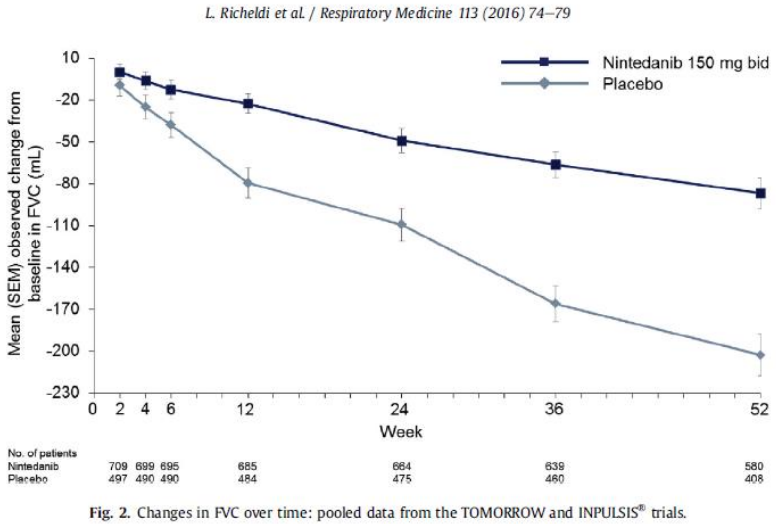
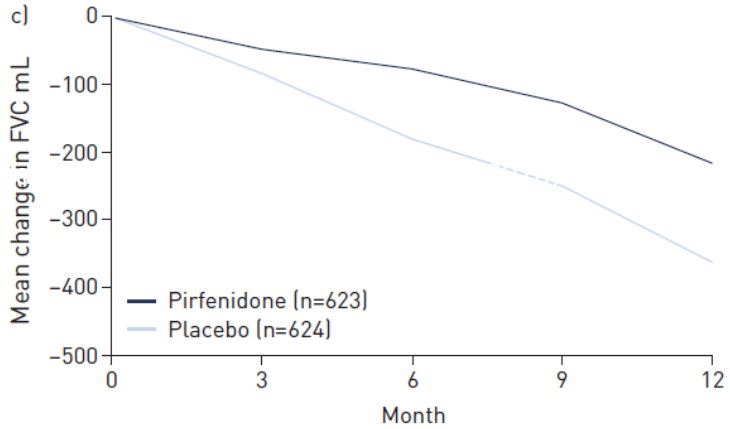


Fig. 2. Changes in FVC over time: pooled data from the TOMORROW and INPULSIS® trials.

Richeldi et al. Respiratory Medicine 113 (2016) 74e79

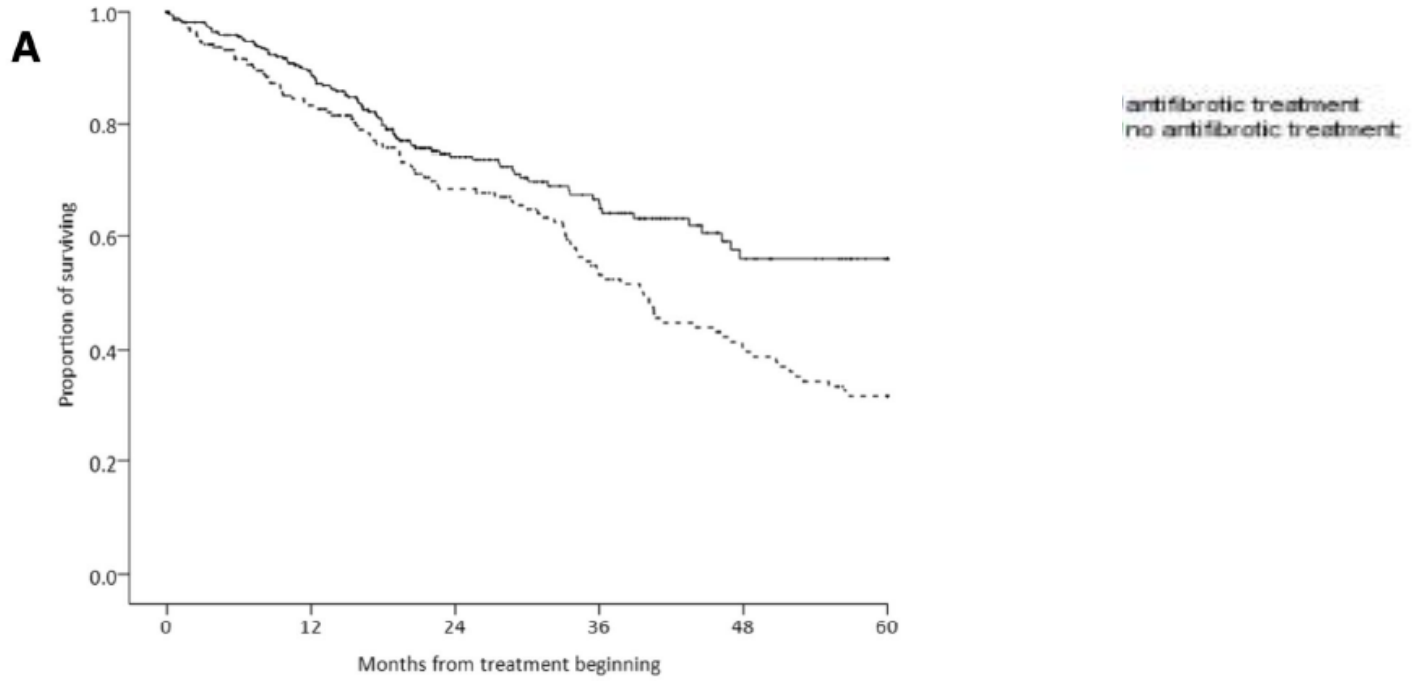
1231 patients (nintedanib n=723, placebo n=508)
FVC loss = -112 cc versus 223 cc/year



Absolute difference mL	36	104	123	148
Relative difference %	43.5	57.3	49.1	40.7
Rank ANCOVA p-value	<0.001	<0.001	<0.001	<0.001

1247 patients (pirfenidonen=623, placebo n=624)
FVC loss = -216cc versus 363cc/year

Registries: Survival On & Off Antifibrotic Rx



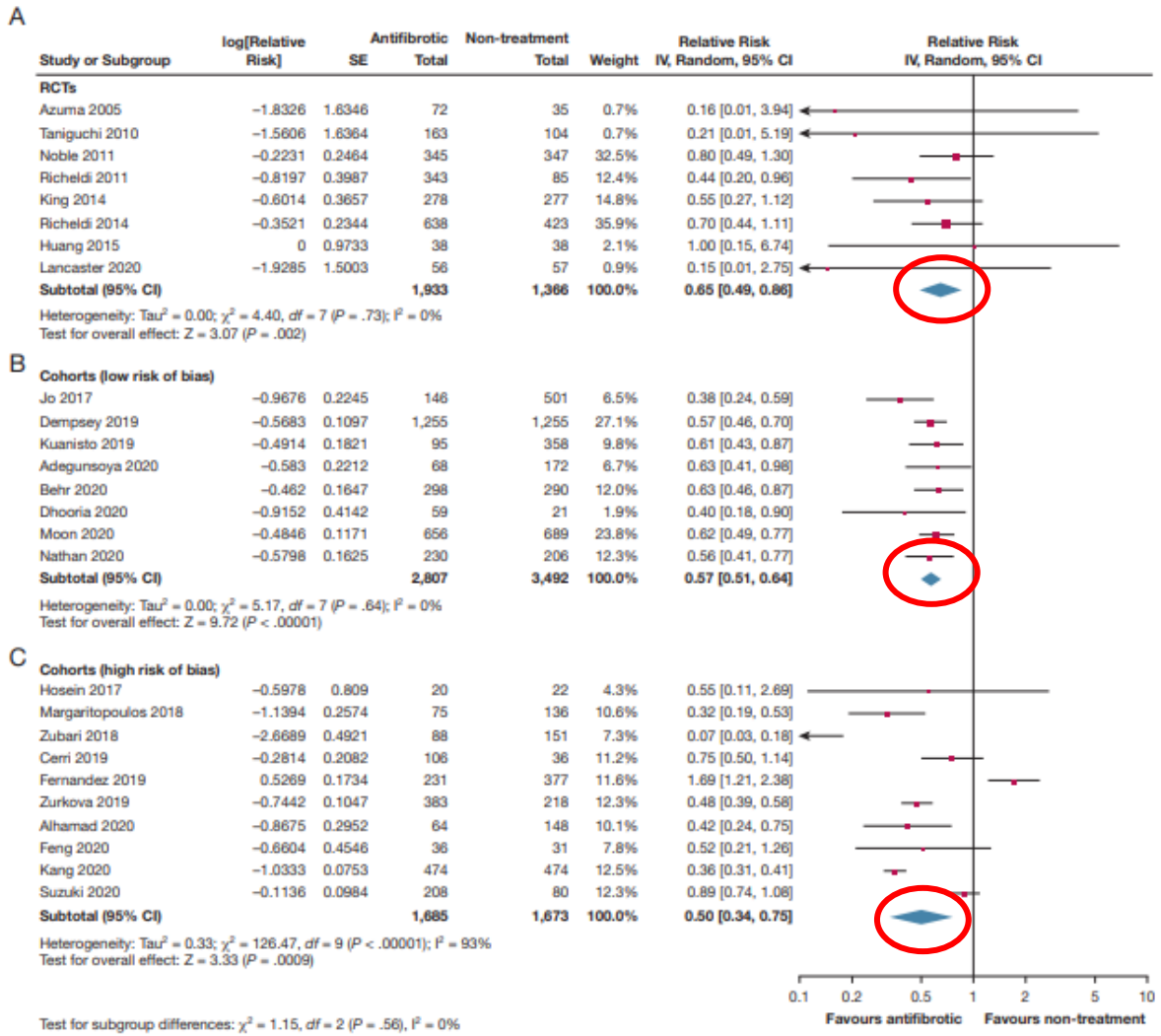
	12-moOS (95% CI)	24-mo OS (95% CI)	60-mo OS (95% CI)	P (LogRank)
Pirfenidone	0.888 (0.855; 0.922)	0.742 (0.690; 0.793)	0.559 (0.474; 0.644)	**0.002**
No-antifibrotic treatment	0.833 (0.780; 0.886)	0.684 (0.613; 0.754)	0.315 (0.234; 0.396)	

Jo et al. *Eur Respir J* 2017;49:1601592

Guenther et al. Respiratory Research 2018;19:141

Zurkova et al. Respiratory Research (2019) 20:16

Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis A Systematic Review and Meta-Analysis



CHEST 2021; 160(5):1751-1763

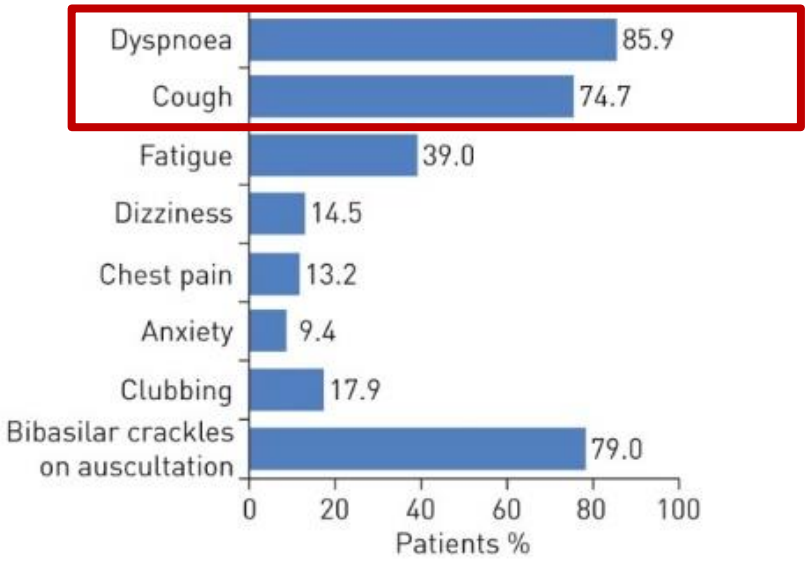
Dyspnea and cough are the most common presenting symptoms in IPF

Table 2 Initial presentation

	Respondents (*N* = 600)
Initial symptoms, n (%)	
Shortness of breath	463 (77.2)
Cough	318 (53.0)
Fatigue/weakness	228 (38.0)
Chest discomfort	104 (17.3)
Unexplained weight loss	40 (6.7)
Loss of appetite	33 (5.5)
Pneumonia	13 (2.2)
Other	58 (9.7)

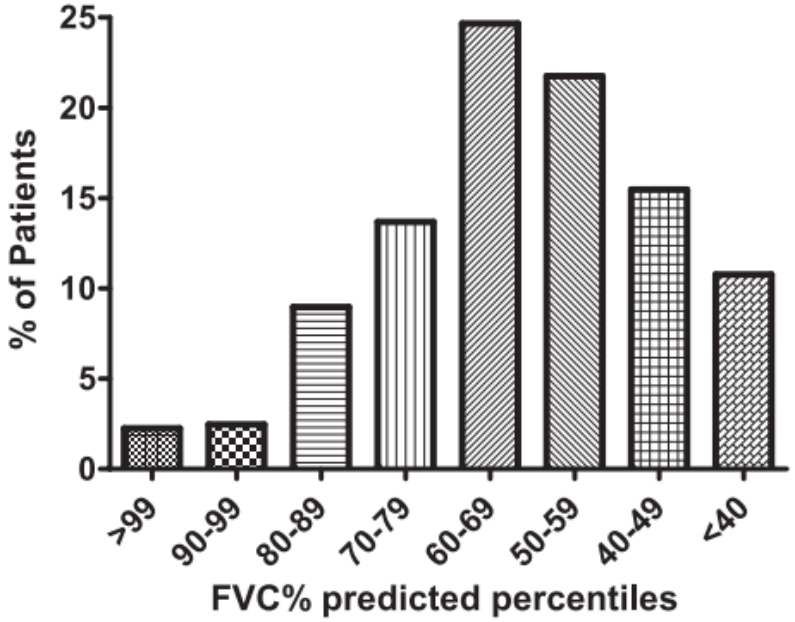
Cosgrove et al., BMC Pulmonary Medicine 2018

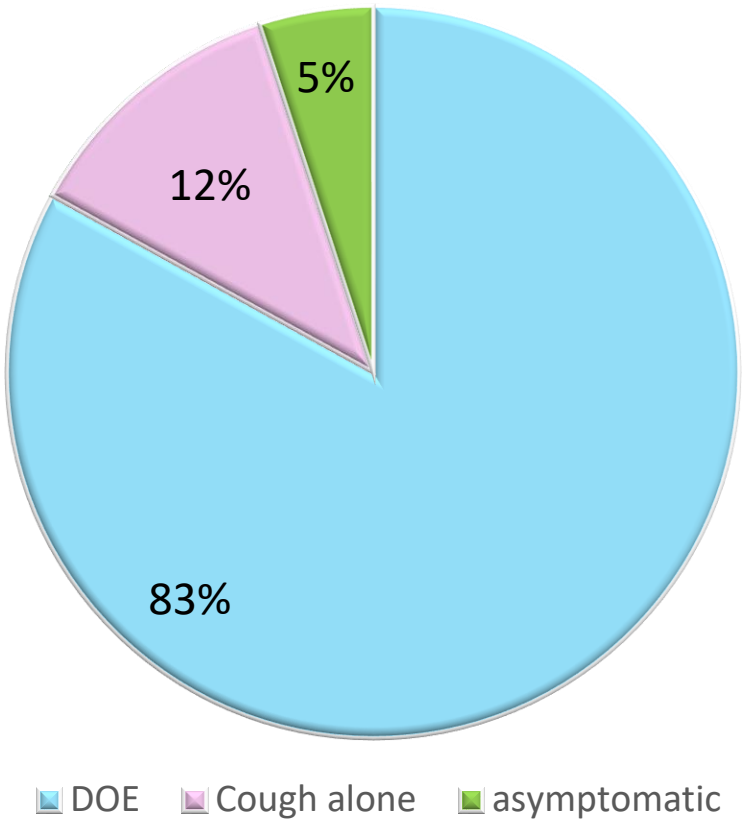
Symptoms at baseline Insight IPF registry



Behr et al., Eur Respir J 2015:46:186-96

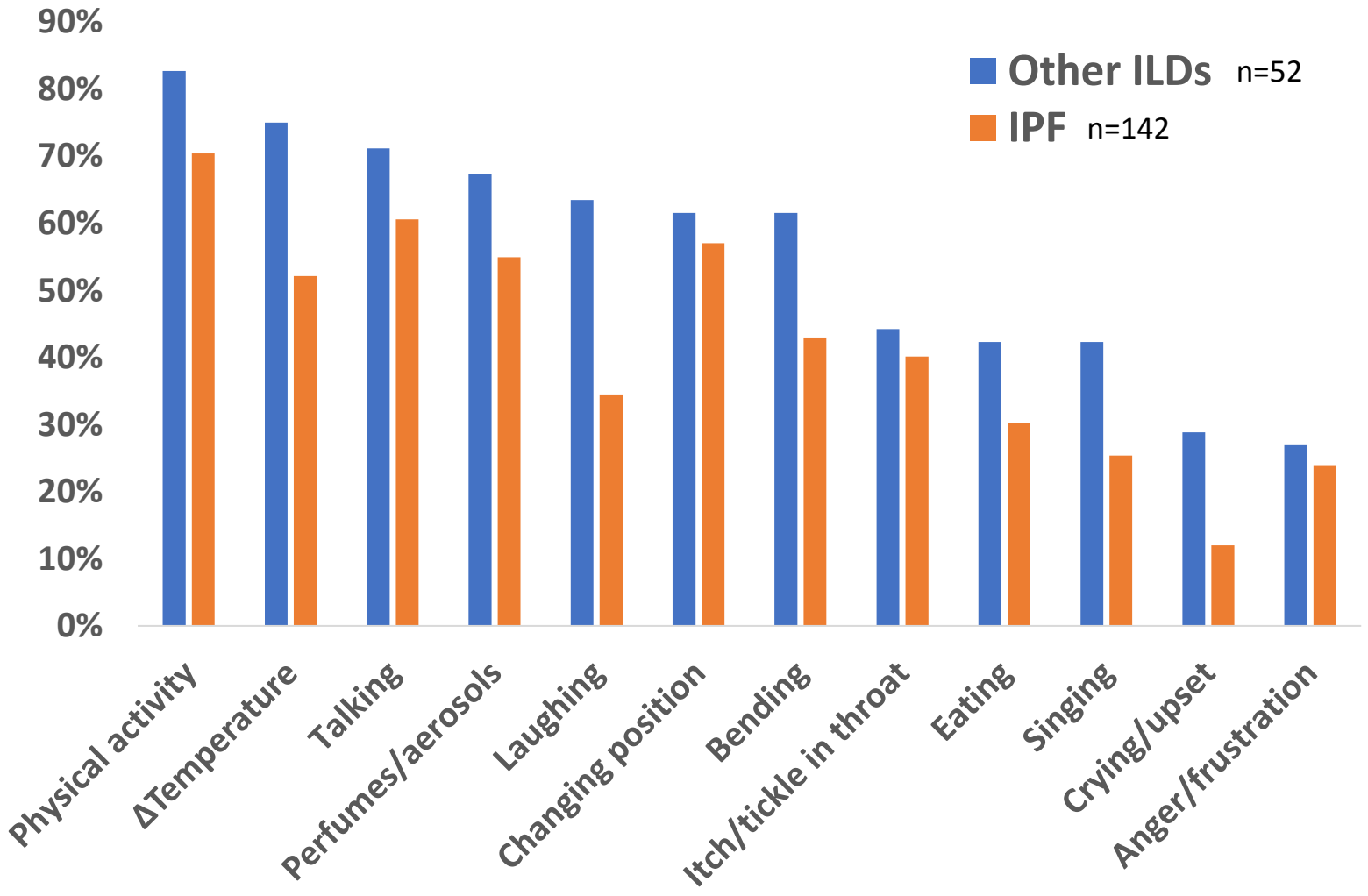
IPF symptoms at presentation (n=521)





CHEST 2011; 140(1):221–229

Cough Triggers in ILD: hypersensitivity profile



Slide courtesy of Marlies Wijsenbeek.

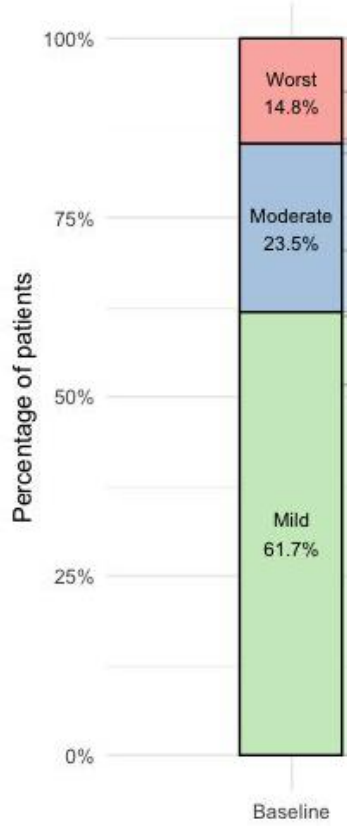
B Hirons *et al*, ERS Congress 2022, ERJ; Vol 60. Suppl 66

The voice of the patient: Public meeting Sep 26th, 2014

- Coughing was mentioned by **over three-fourths** of patients as being one of their most significant symptoms.
- “Coughing fits”- prolonged periods of dry, hacking coughs.
- “Debilitating” and “violent” → coughing fits
- “Unable to catch his breath”.
- Inability to control coughing episodes of shortness of breath, hypoxia, or exhaustion.

https://www.fda.gov/files/about%20fda/published/The-Voice-of-the-Patient--Idiopathic-Pulmonary-Fibrosis.pdf

Cough specific quality of life in IPF (PROFILE) (N=632)



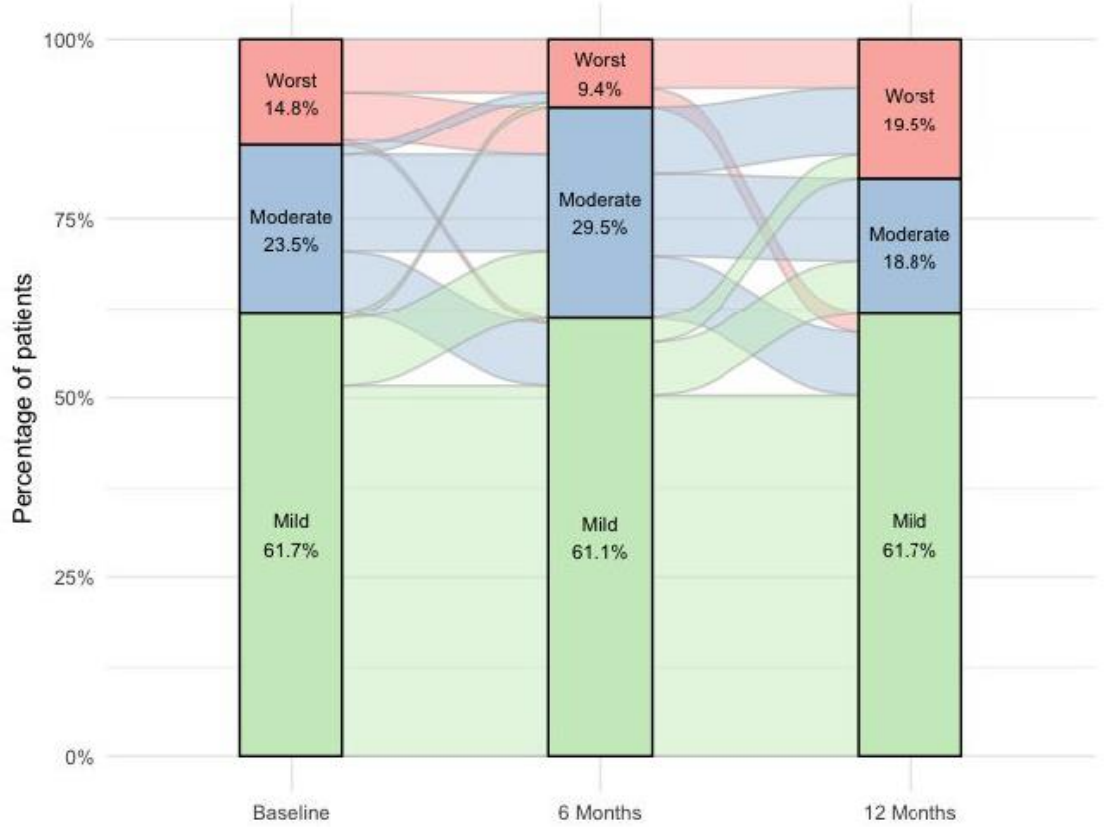
Weak correlation of cough burden with lung function:

-FVC (R^2=0.14, P<0.001)

-Dlco (R^2=0.2, P<0.001)

Saunders P et al. Annals of ATS 2023 online ahead of print

The Burden and Impact of Cough in Patients with IPF: Analysis of the Prospective Observational PROFILE Study

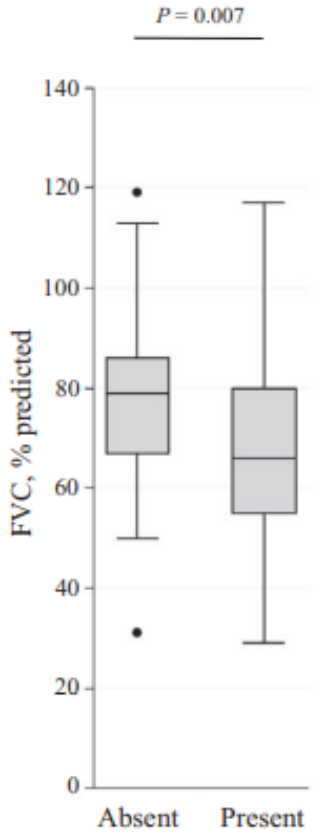


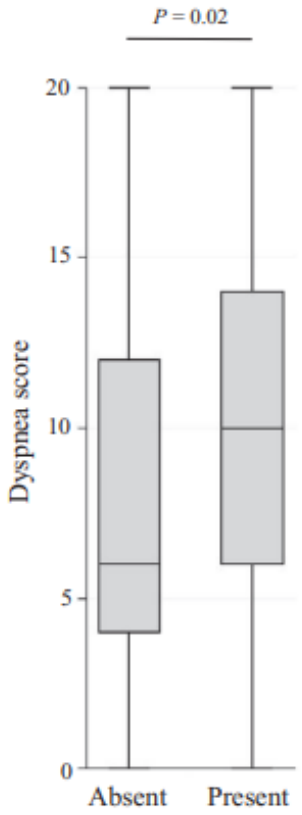
N=216

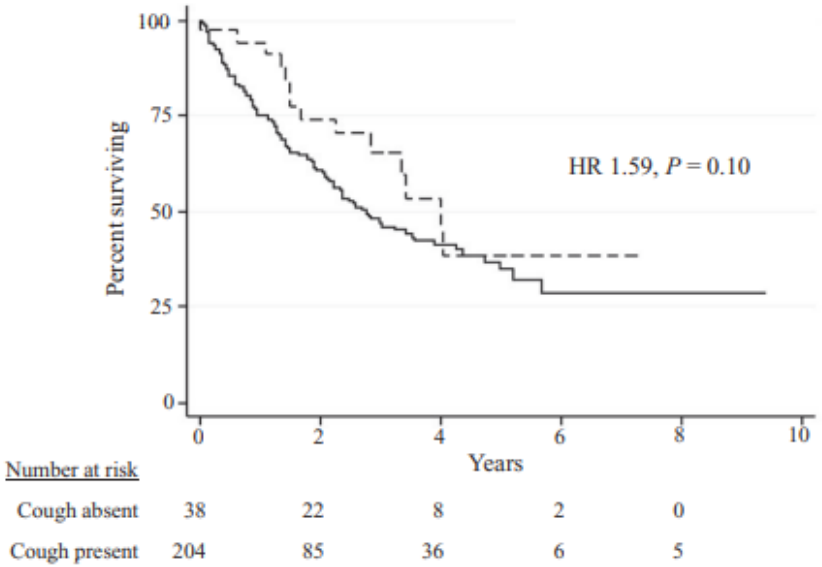
Cough specific quality of life remained largely unchanged

Published online May 9,2023. https://doi.org/10.1513/AnnalsATS.202302-174OC

Cough associated with disease severity





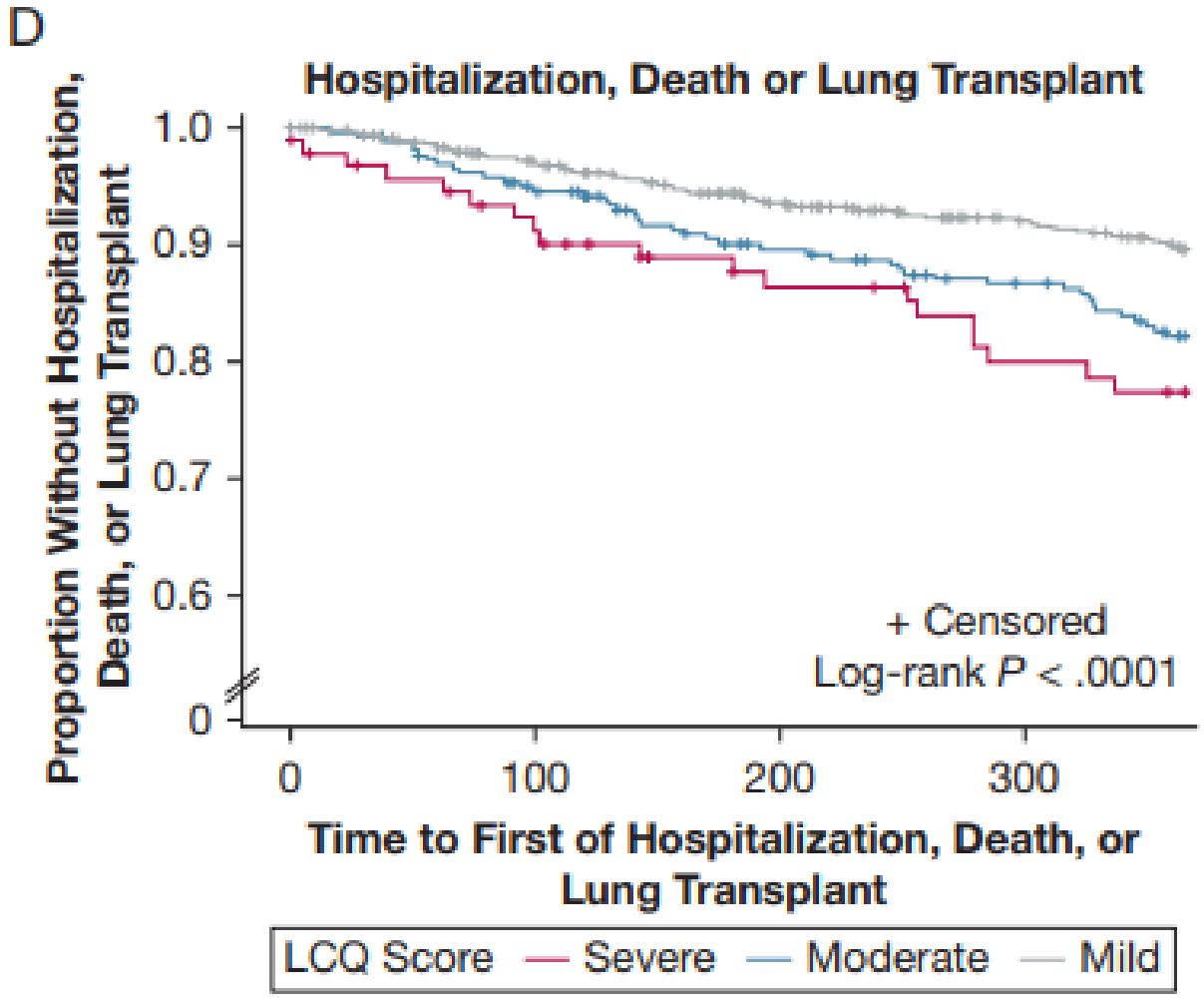


Number at risk					
Cough absent	38	22	8	2	0
Cough present	204	85	36	6	5

Ryerson et al. Respirology (2011) 16, 969–975

Kaplan-Meier estimates for respiratory hospitalization, death, and lung transplant by LCQ score severity

Patients stratified into groups based on Leicester Cough Questionnaire score: mild disease (≥14), moderate disease (10 to < 14), and severe disease (< 10).



CHEST 2022; 162(3):603-613

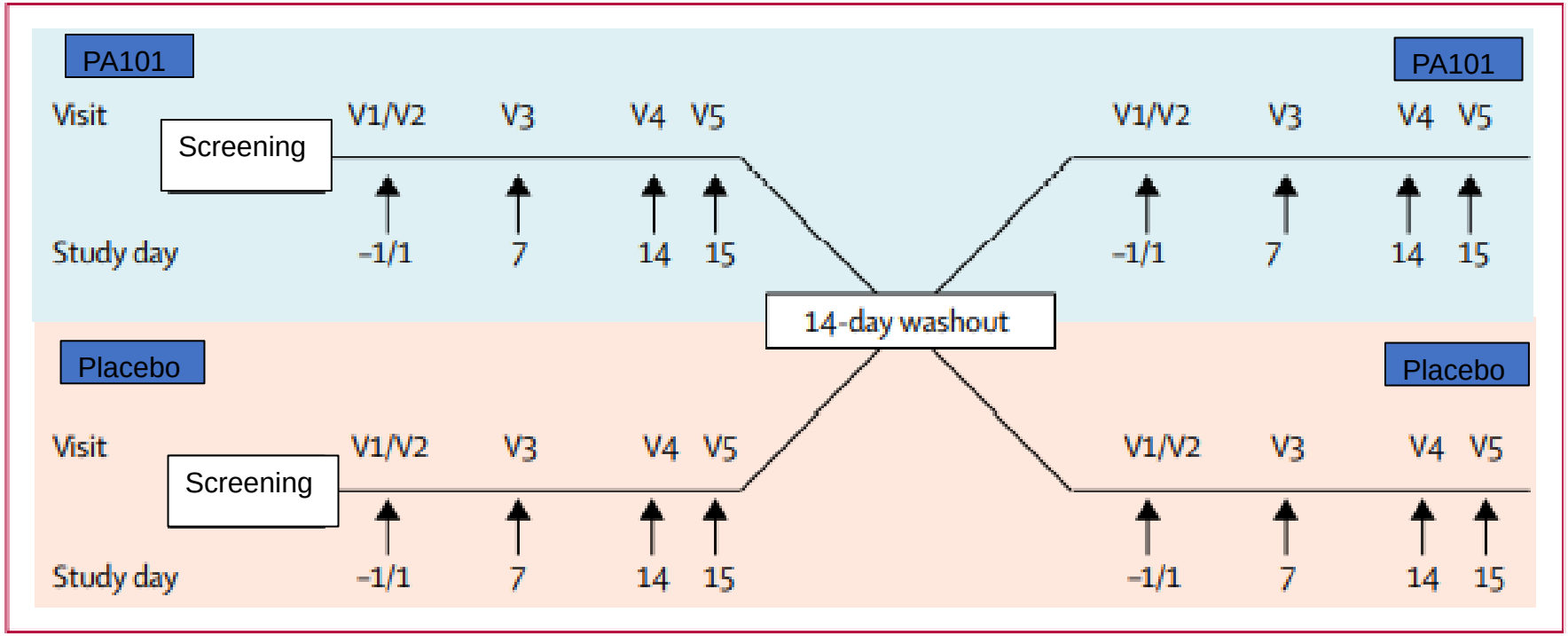
Cough Studies in IPF: completed

Author/yr/study name	Agent	Administration	Entry	Study Type	Duration	N	Primary	Outcome
AIM (2012)	Thalidomide	50-100mg qHS	Chronic cough ≥8 weeks FVC 40-90%	double-blind, crossover trial	12 weeks per period	24	Cough Quality of Life Questionnaire	CQLQ scores improved (mean difference, -11.4 (P 0.001).
Van Mannen, ERJ research letter (2017)	Pirfenidone	-	cough for ⩾8 weeks a VAS ⩾40 mm	Prospective, observational	12 weeks	43	Leicester Cough Monitor	objective 24-h cough ↓by 34% 20/27 improved
Birring (LRM 2017)	Inhaled sodium cromoglycate /PA101	Inhaled 3x/day	≥15 coughs/hour Cough severity>40mm VAS	Double-blind crossover	2 weeks	24	Leicester cough monitor	Decreased cough frequency 31%
Thorax (2019)	Omeprazole (25 pts were on PPI prior)	20 mg bid	-	Single Center Double blind RCT	3 months	23/22 (280 screened)	objective cough frequency/24 hrs	39% reduction in cough frequency
Maher (ERS 2022)	Nalbuphine	Oral bid	Chronic cough ≥8 weeks	randomised, double-blind, crossover trial	22 days	26	Digital cough monitor	52% placebo-adjusted change in cough
Afferent (Merck)	Gefapixant	Oral bid		randomised, double-blind, crossover trial	14 days	51	Change From Baseline in Awake Objective Cough Frequency	Negative
SCENIC study	RVT-1601, 3 doses three times daily or placebo	10/40/80 mg	VAS>40 mm, 24-hour average cough >10 coughs/hour	randomized, double-blind, placebo-controlled, parallel-design	12 weeks	108/66 complete	Δfrom baseline in log transformed 24- hr cough count	Stopped-COVID

A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial

Surinder S Birring, Marlies S Wijsenbeek, Sanjay Agrawal, Jan W K van den Berg, Helen Stone, Toby M Maher, Ahmet Tutuncu, Alyn H Morice

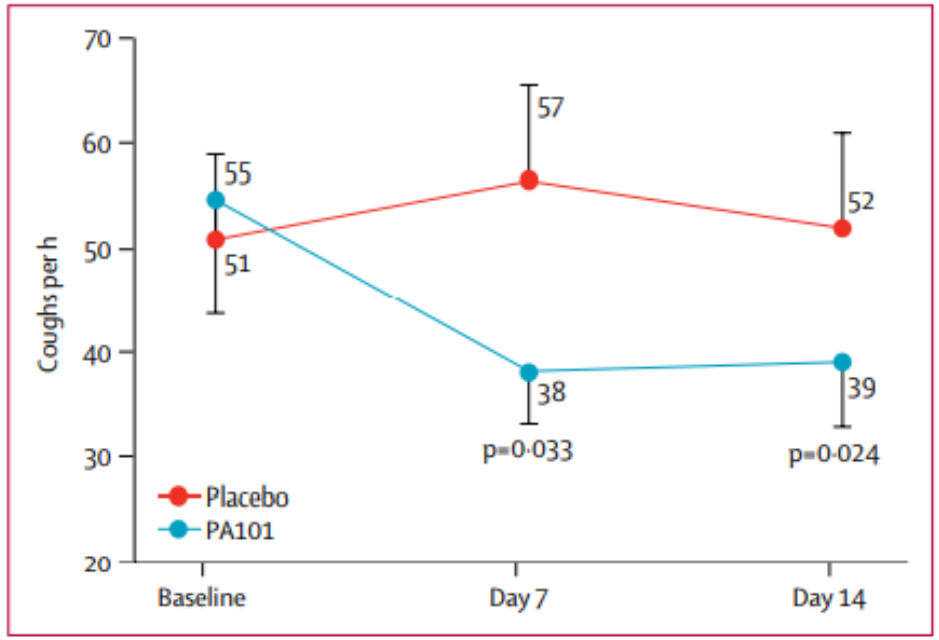
40 mm on a visual analogue scale (VAS), mean daytime objective frequency of 15 coughs or more per h as measured with the Leicester Cough Monitor



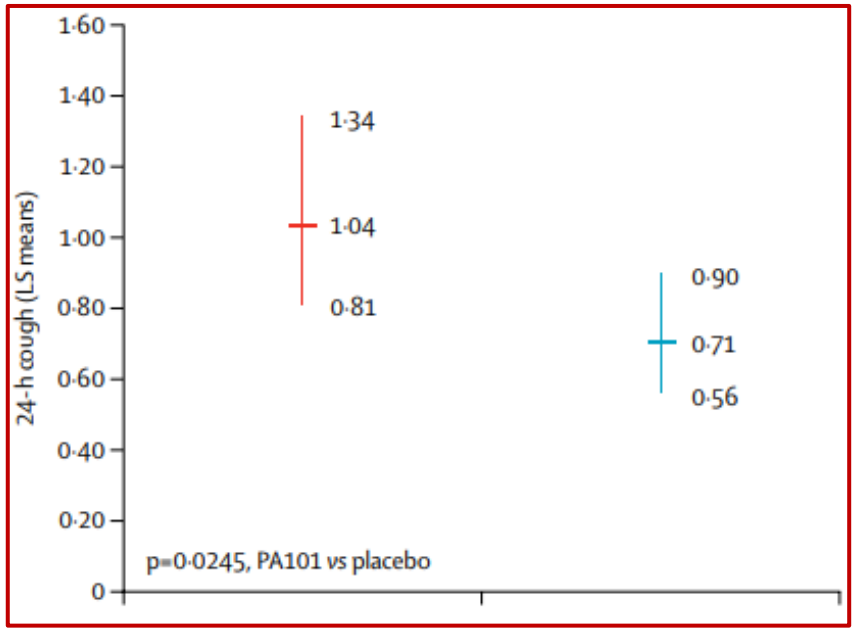
Lancet Respir Med 2017
Published Online September 8, 2017
http://dx.doi.org/10.1016/ S2213-2600(17)30310-7

RESULTS

Change in objective daytime cough frequency



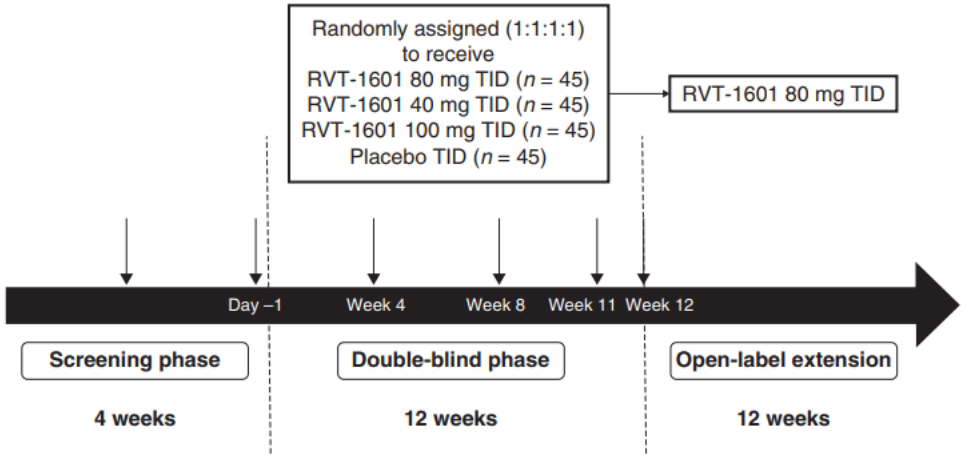
Change in 24 hour cough frequency

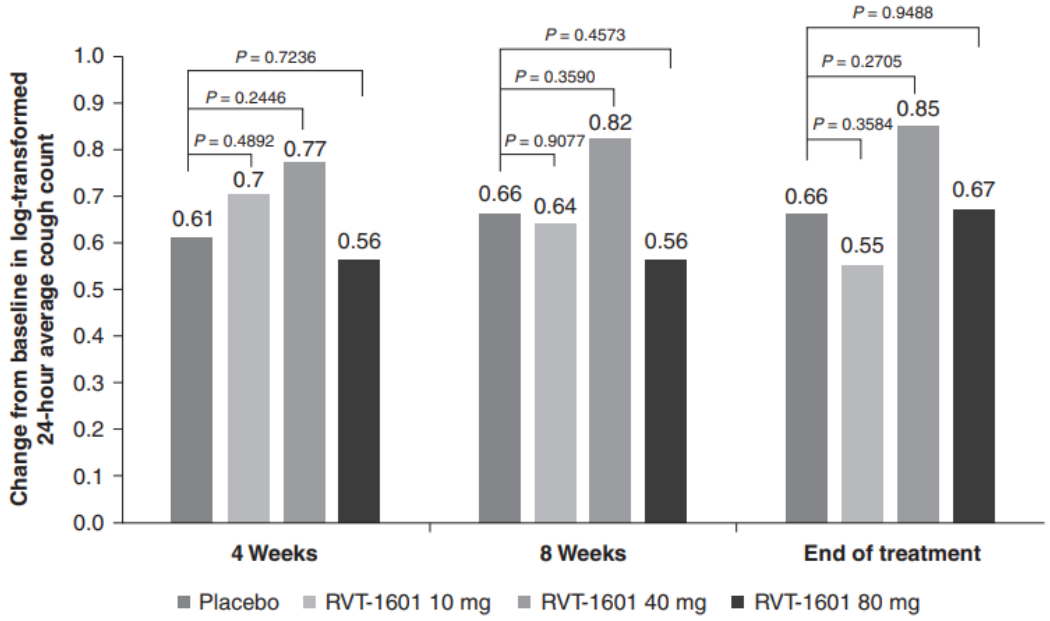


Lancet Respir Med 2017
Published Online September 8, 2017
http://dx.doi.org/10.1016/ S2213-2600(17)30310-7

Phase 2B Study of Inhaled RVT-1601 for Chronic Cough in Idiopathic Pulmonary Fibrosis

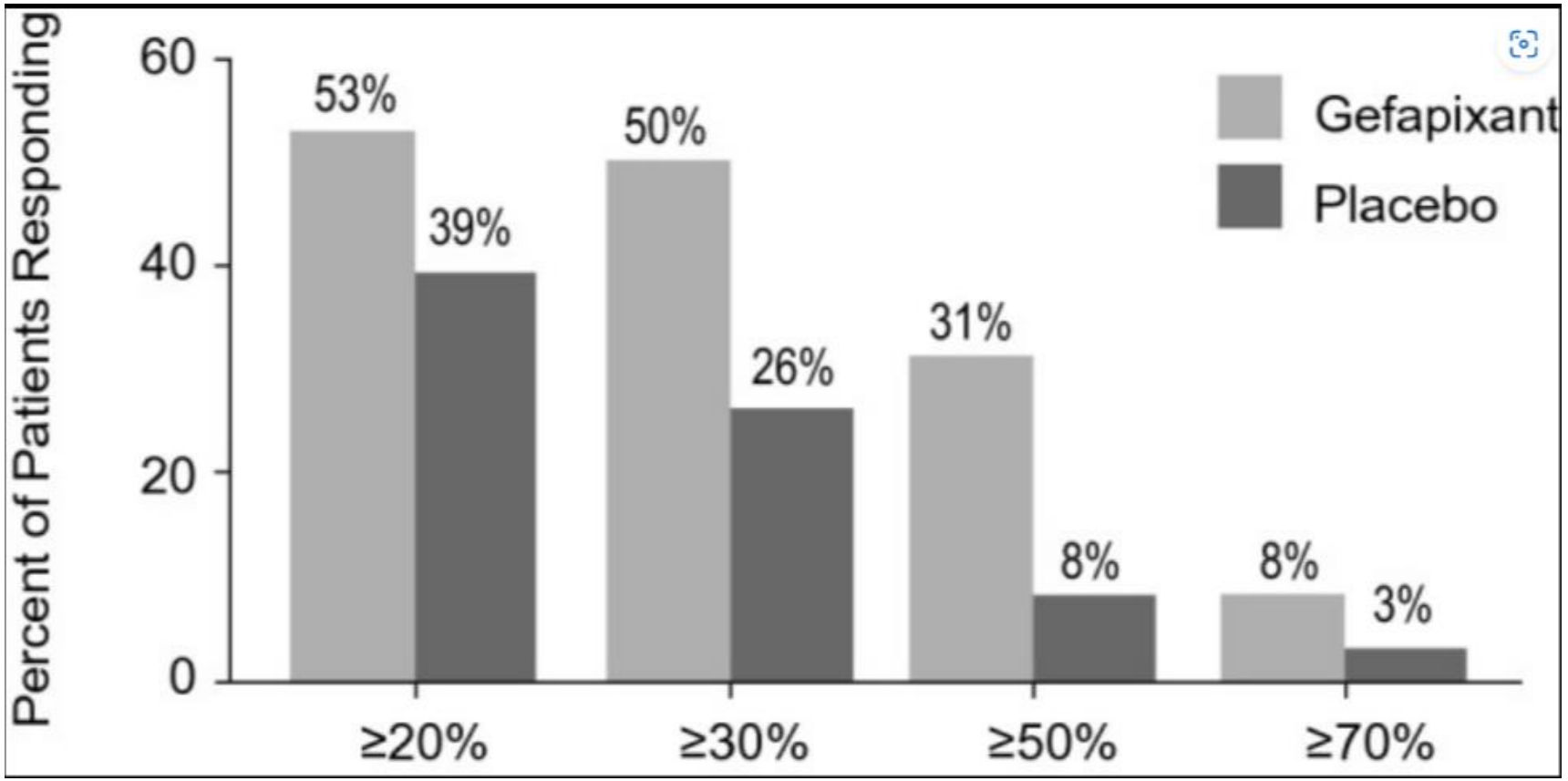
A Multicenter, Randomized, Placebo-controlled Study (SCENIC Trial)





Am J Respir Crit Care Med Vol 205, Iss 9, pp 1084–1092, May 1, 2022

Treatment of Persistent Cough in IPF with Gefapixant, a P2X3 Antagonist, in a Randomized, Placebo-Controlled Clinical Trial

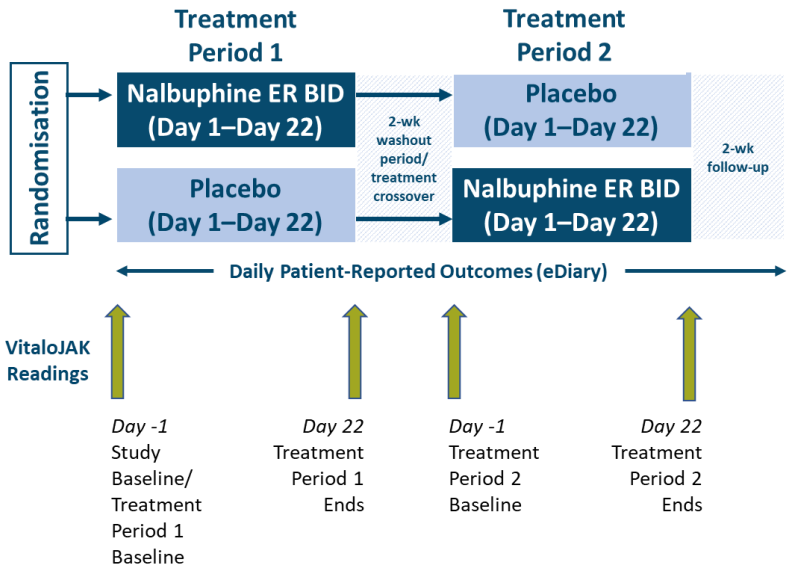


Pulm Ther 2021 Dec;7(2):471-486

NALBUPHINE PHASE 2 STUDY

METHODS

- A randomised, double-blind, placebo-controlled, crossover trial with two 22-day treatment periods separated by a 2-week washout period
- Nalbuphine ER 27 mg once daily titrated up to 162 mg twice daily at day 16
- Subjects: Definite/probable IPF and chronic cough for >8 weeks



PRIMARY ENDPOINT

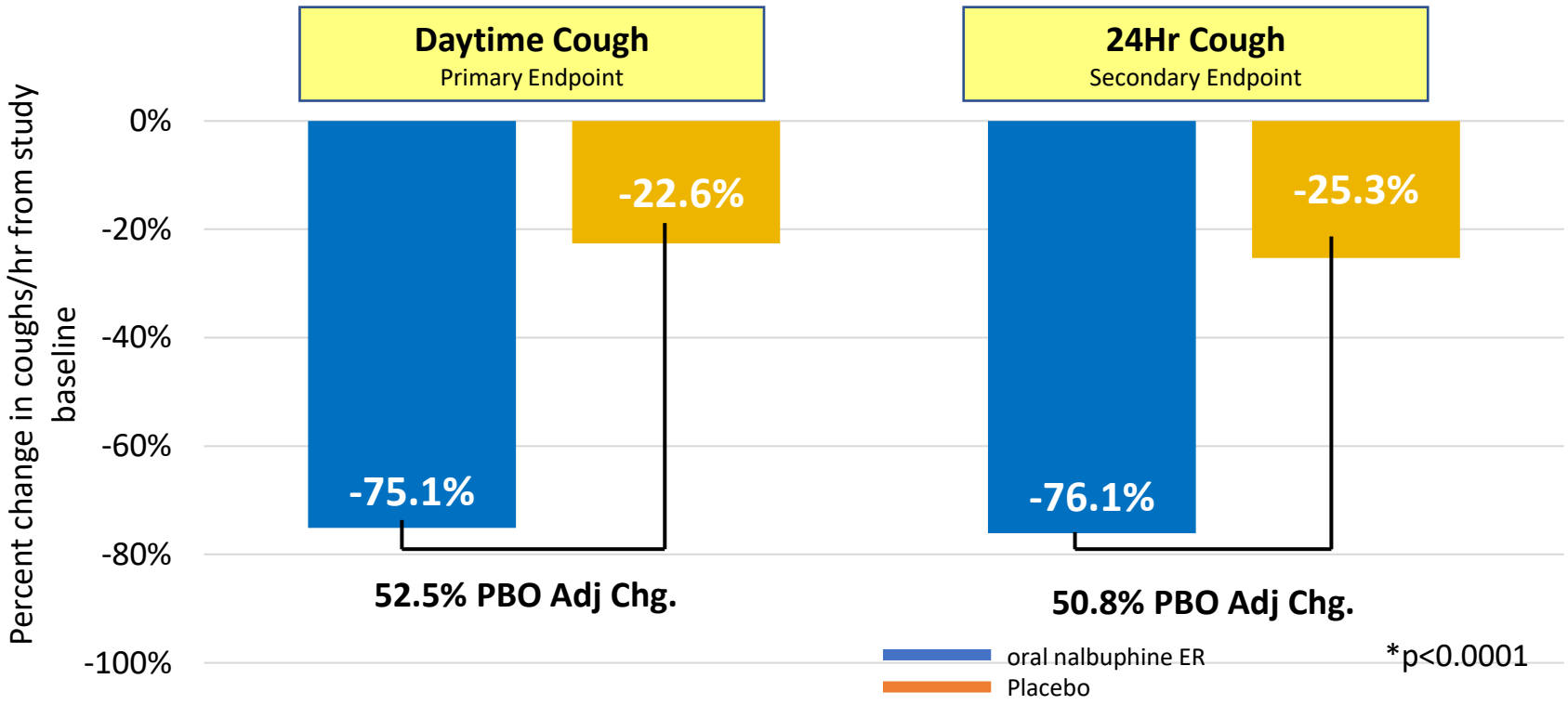
- Change in daytime cough frequency from baseline as measured by a digital cough monitor (**VitaloJAK®**) between the nalbuphine ER and placebo treatments

SECONDARY ENDPOINTS

- Cough severity
- Fatigue
- Dyspnea

Maher, TM et al. *NEJM Evidence* 2023 Doi: 10.1056/EVIDoa2300083

Reduction of Cough Frequency And Placebo-Adjusted Change Were Consistent Between Daytime and 24Hr Cough Frequency (n=38)



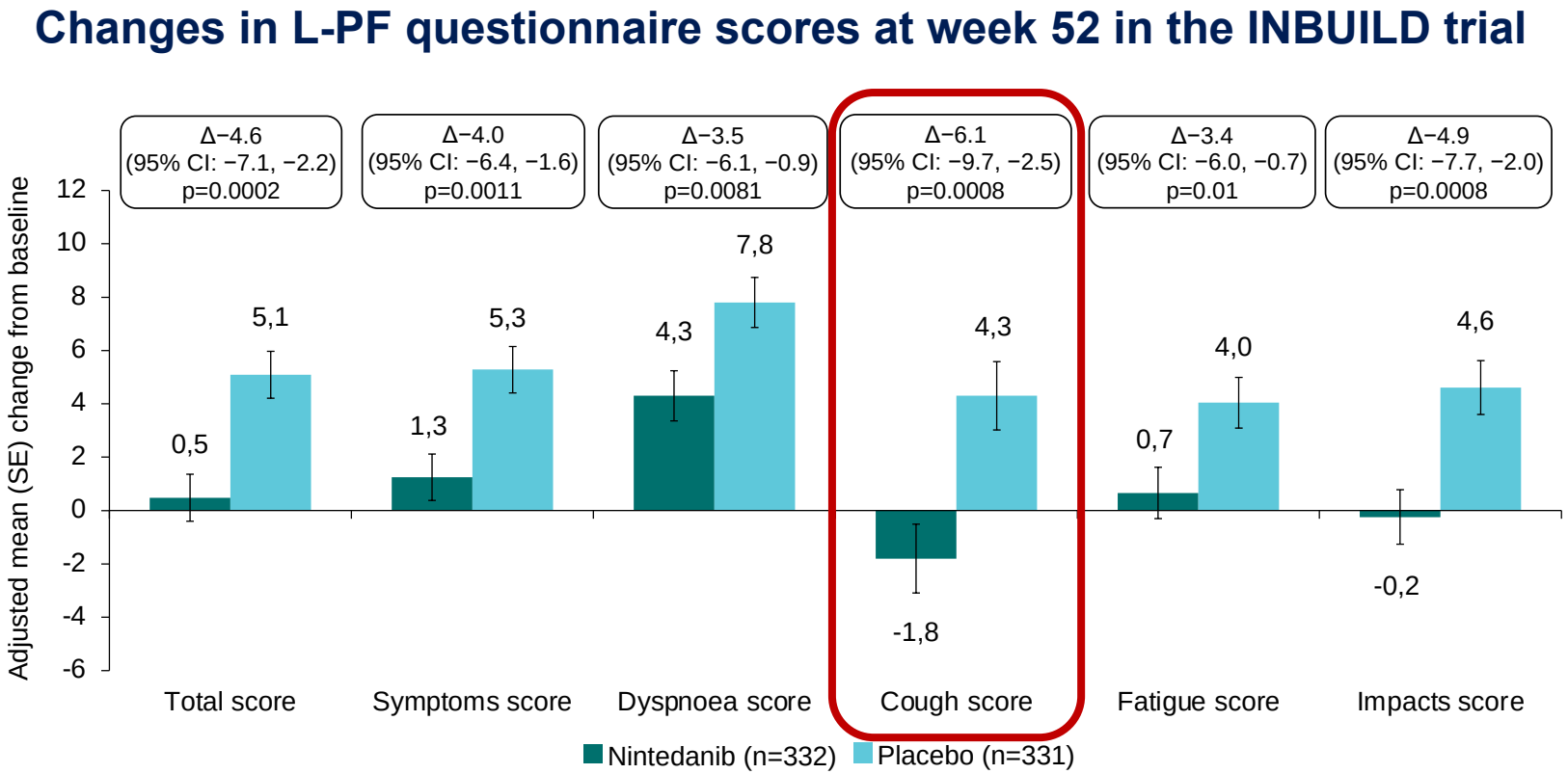
Maher, TM et al. *NEJM Evidence* 2023 Doi: 10.1056/EVIDoa2300083

Effects of Pirfenidone on cough over 12 weeks

	Baseline	12 weeks	Change	P-value
Subjects	43	31		
24-h cough	520	392	-34%	0.002
Coughs/hr	23	17	-35%	<0.001
-day	28	20	-33%	0.003
-night	7.2	3.3	-34%	0.029
LCQ	12	15	2	<0.001
VAS cough	67	47	-19%	<0.0001
VAS urge to cough	68	49	-18%	<0.0001

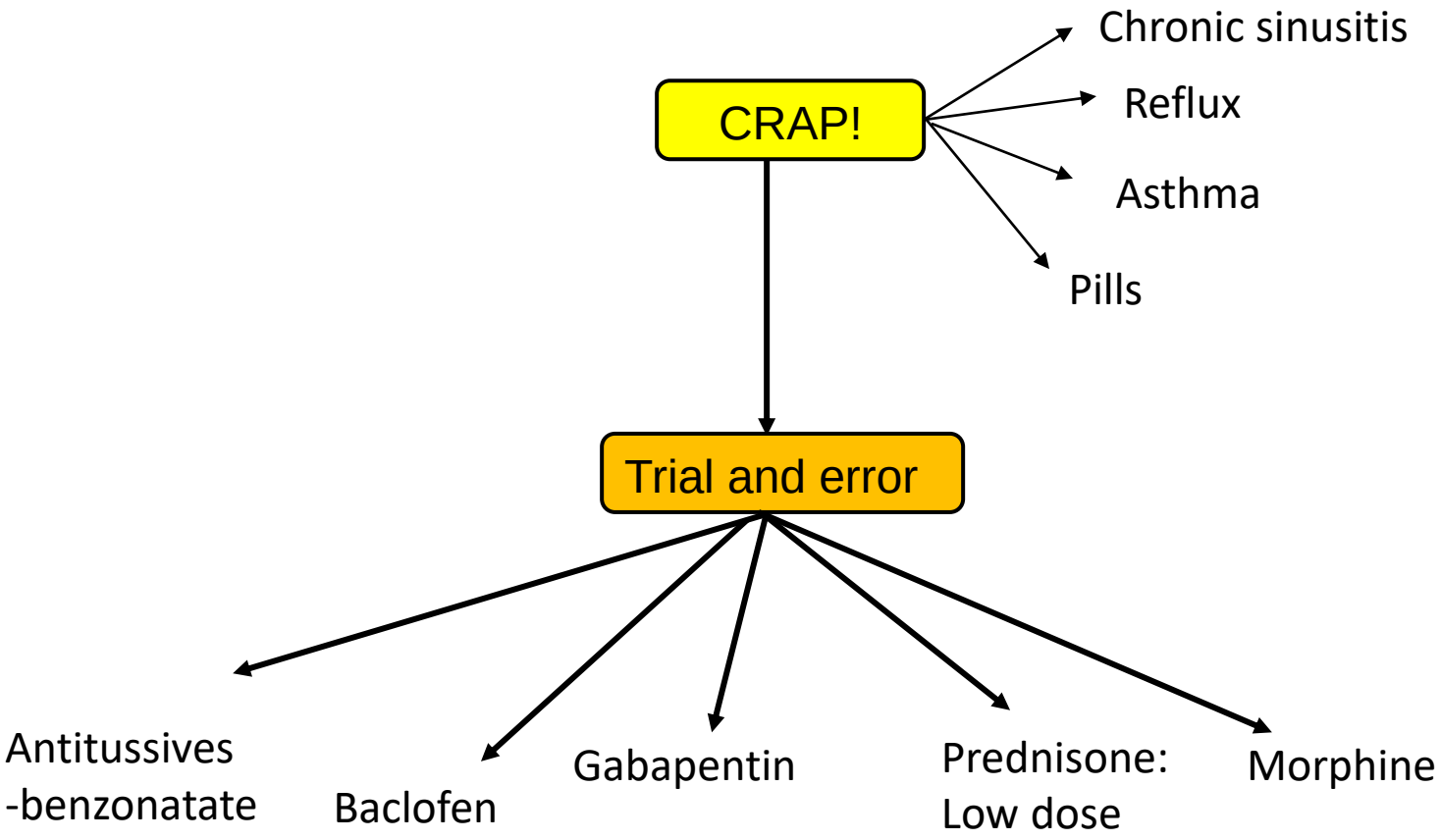
van Manen et al. Eur Respir J 2017; 50: 1701157

Nintedanib and cough



Slide courtesy of Marlies Wijsenbeek.
Manuscript submitted

Management of cough in IPF



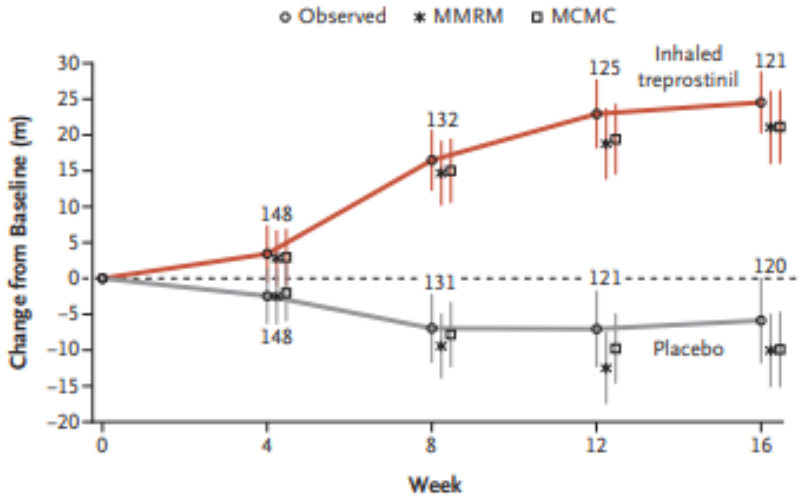
COUGH IN IPF CLINICAL TRIALS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Waxman et al. N Engl J Med 2021; 384:325-334 DOI: 10.1056/NEJMoa2008470



COUGH: 15-84%

Cough-specific agents

Endpoint in trials of antifibrotic therapy

Trials of inhaled antifibrotic therapy

Start point

Table 3. Summary of Adverse Events.

Variable	Inhaled Treprostinil (N=163)	Placebo (N=163)	P Value*
Total no. of adverse events	890	793	
Patients with ≥1 adverse event — no. (%)	152 (93.3)	149 (91.4)	0.68
Total no. of serious adverse events†	53	89	
Patients with ≥1 serious adverse event — no. (%)	38 (23.3)	42 (25.8)	0.70
Total no. of adverse events leading to withdrawal of treprostinil or placebo	47	38	
Most frequently occurring adverse events — no. of patients (%)‡			
Cough	71 (43.6)	54 (33.1)	0.07
Headache	45 (27.6)	32 (19.6)	0.12
Dyspnea	41 (25.2)	51 (31.3)	0.27
Dizziness	30 (18.4)	23 (14.1)	0.37
Nausea	25 (15.3)	26 (16.0)	>0.99
Fatigue	23 (14.1)	23 (14.1)	>0.99
Diarrhea	22 (13.5)	19 (11.7)	0.74
Throat irritation	20 (12.3)	6 (3.7)	0.007
Oropharyngeal pain	18 (11.0)	4 (2.5)	0.003
NT-proBNP increased	9 (5.5)	25 (15.3)	0.006

Design of a cough study in IPF: Inclusionary/Exclusionary

- How much cough- what threshold?
- Severity range:
  - ? FVC

    ?DLCo

    ?oxygen use
- R/o other causes as an inclusionary criteria
  - FEV1/FVC%<60-70
- What meds not to allow initiated during the study
  - ACE/ARDS
  - Sinus meds
  - GERD meds
  - Stable antifibrotic therapy
  - smoking

Recruitment: How much cough to get in?

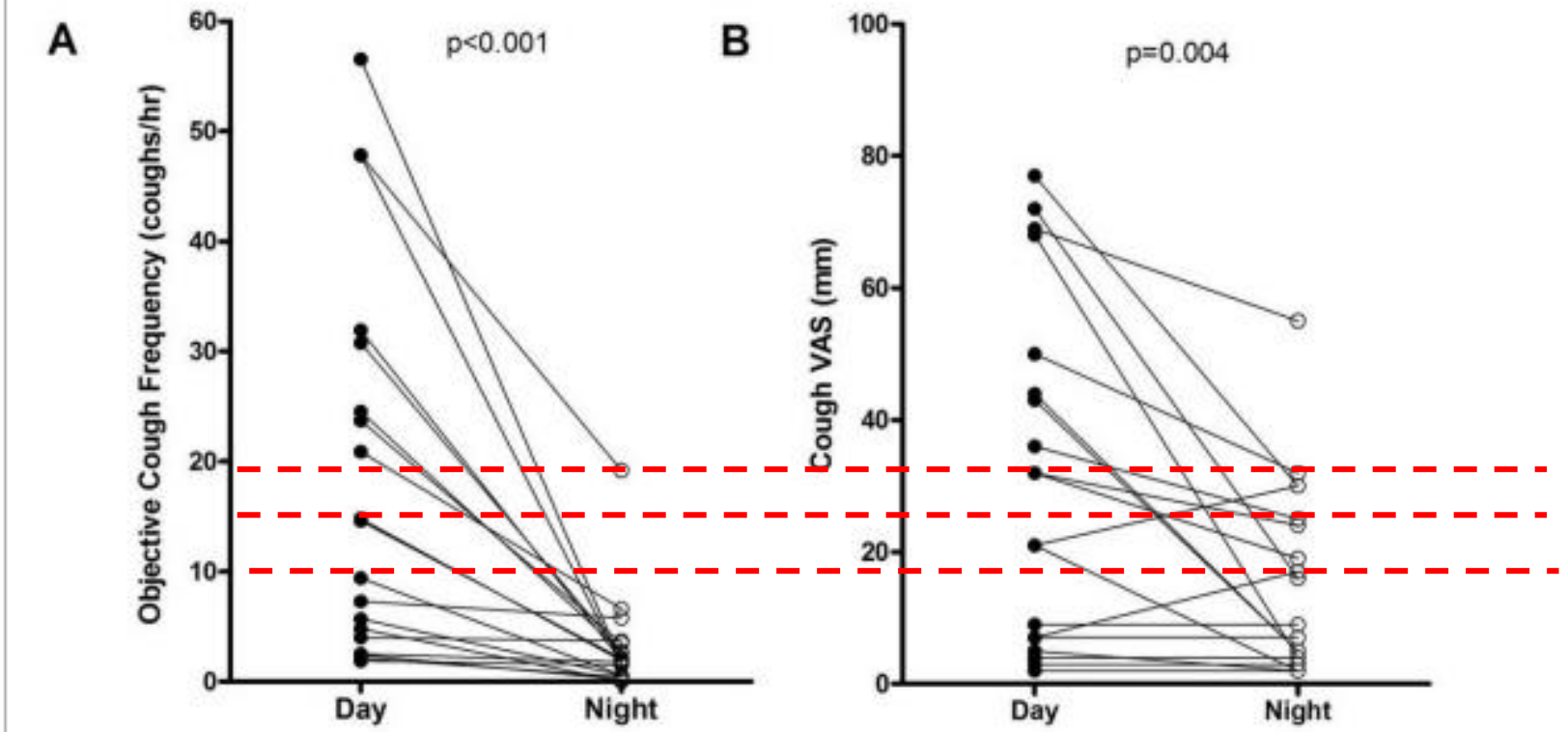
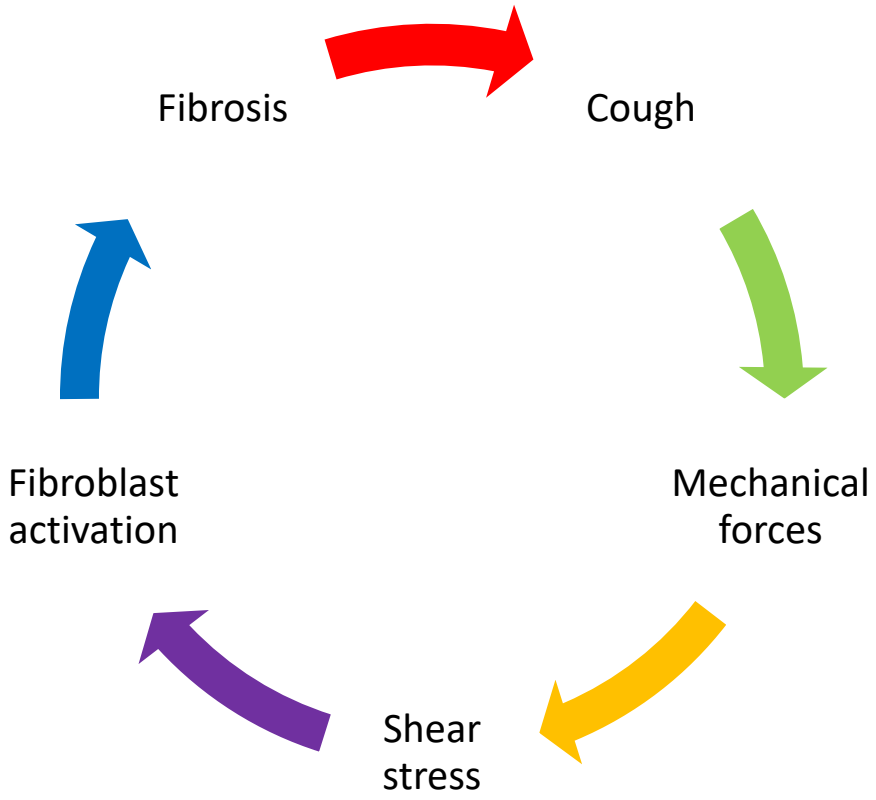


Figure 1 Objective cough frequency (A) and cough VAS scores (B) for day and night in patients with IPF.

Key *et al. Cough* 2010, **6**:4
http://www.coughjournal.com/content/6/1/4

Design of a cough study in IPF:

- Primary endpoint: Cough
- Secondary endpoints:
  - FVC: Disease modification?



Ryerson CJ, Abbritti M, Ley B, et al. Cough predicts prognosis in idiopathic pulmonary fibrosis. Respirology 2011; 16: 969–975.

Composing a composite with cough

FVC change

Hospitalization | 6MWT | Cough

Death

IPF Clinical trial endpoint ..applying the “win” ratio

CONCLUSION

- Cough is a huge problem in IPF
- Better management strategies sorely needed
- Cough studies in IPF encouraged
- A secondary endpoint for all future antifibrotic trials
- Cough PROs/cough monitoring in IPF trials
- Start point for trials of inhaled therapies