Μακροχρόνια παρακολούθηση ασθενών με IPF

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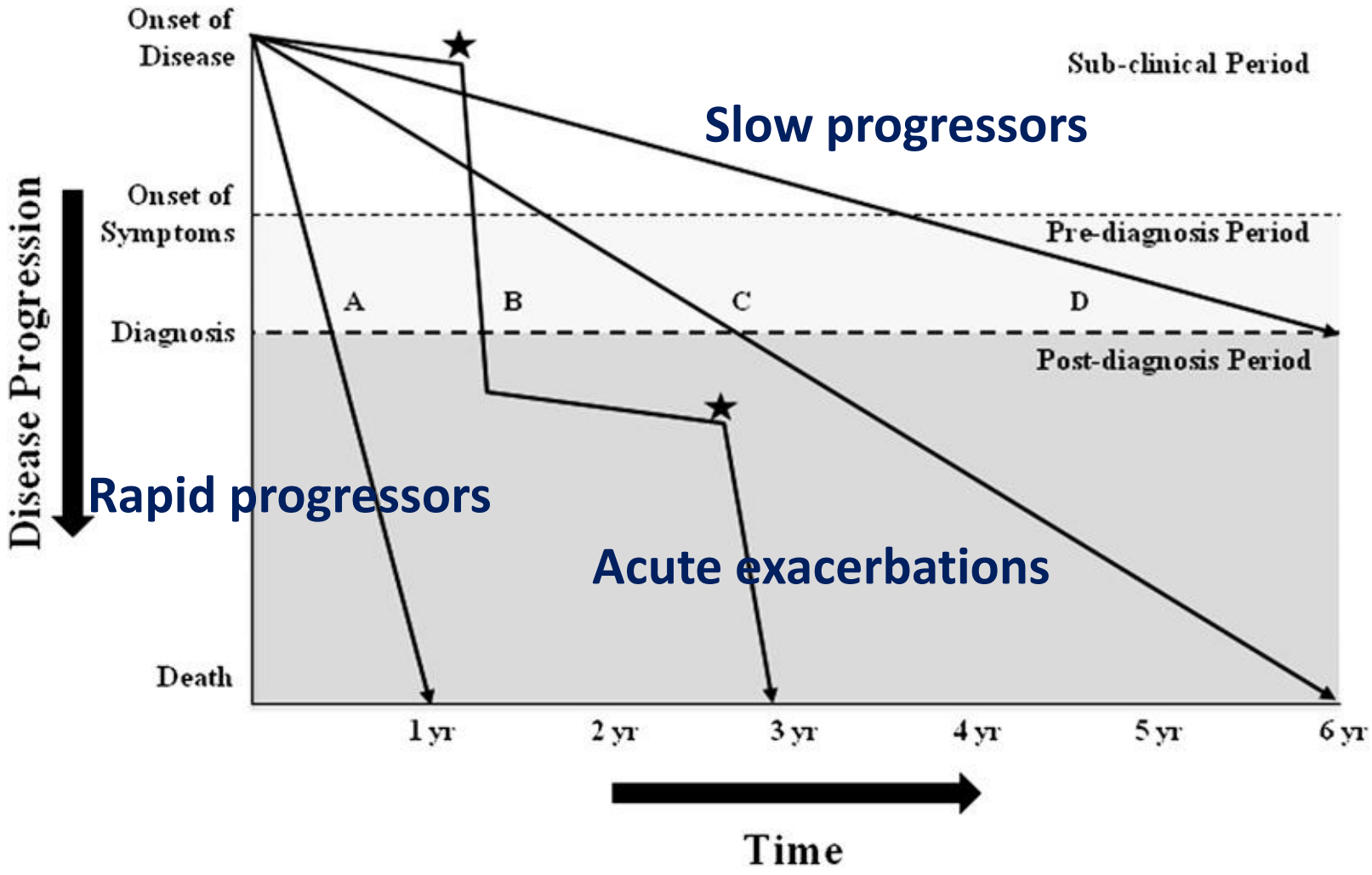
Δήλωση Συμφερόντων

Εταιρείες από τις οποίες έχω λάβει τιμητική αμοιβή τα τελευταία 2 έτη

- **AstraZeneca**
- **Boehringer Ingelheim**
- **Chiesi**
- **ELPEN**
- **Roche**
- **GSK**

Highly unpredictable and deadly clinical course



Ley et al. AJRCCM 2011;183:431-440

Εκτίμηση
Routine Follow-up

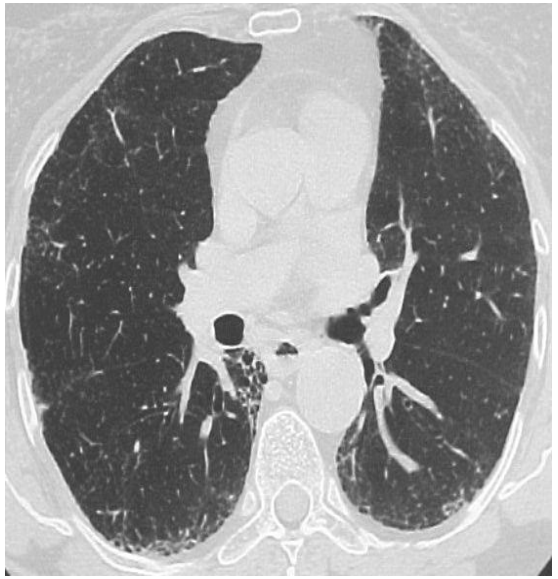
Early Disease	Advanced Disease
Every 3-6 months	Every 1-3 months

- ✓ Symptoms evaluation/drug s/e
- ✓ Hospitalizations
- ✓ FVC, DLCO
- ✓ 6MWT
- ✓ Pulse oximetry
- ✓ HRCT-echocardiography
- ✓ Comorbidities

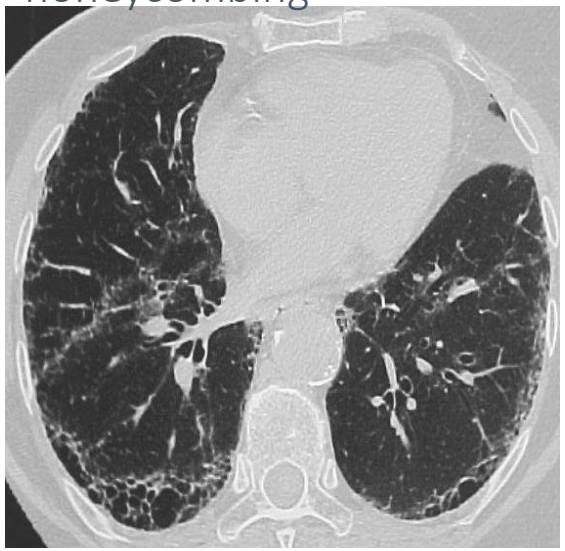
HRCT is not reliable to assess prognosis and treatment response

Poor k-agreement on extent of HCM/TBE

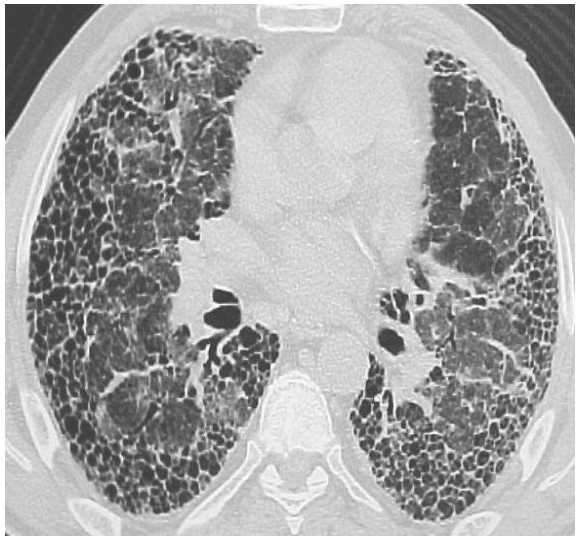
Early:
Reticular



Midcourse:
Subpleural
honeycombing

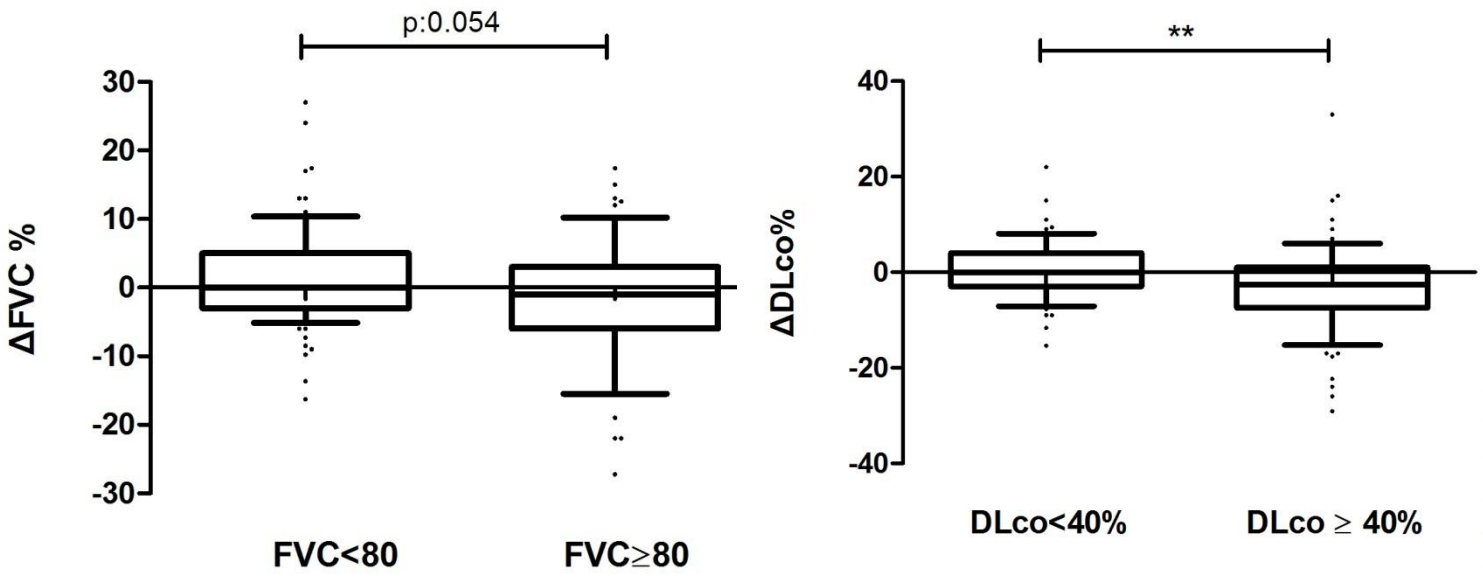


Diffuse honeycombing



PFTs are not reliable to assess prognosis and treatment response

Higher FVC% and DLco% decline at 6 months in patients with preserved pulmonary function



	No of pts
FVC<80	151
FVC≥80	91

PIRFENIDONE TRIALS

Forced vital capacity as a primary end point in idiopathic pulmonary fibrosis treatment trials: making a silk purse from a sow's ear

Athol U Wells

ficing accuracy. The current limitations* of FVC as the least flawed of the flawed primary end points used in IPF, are widely recognised. It is high time for them to be definitively addressed.

***Emphysema**

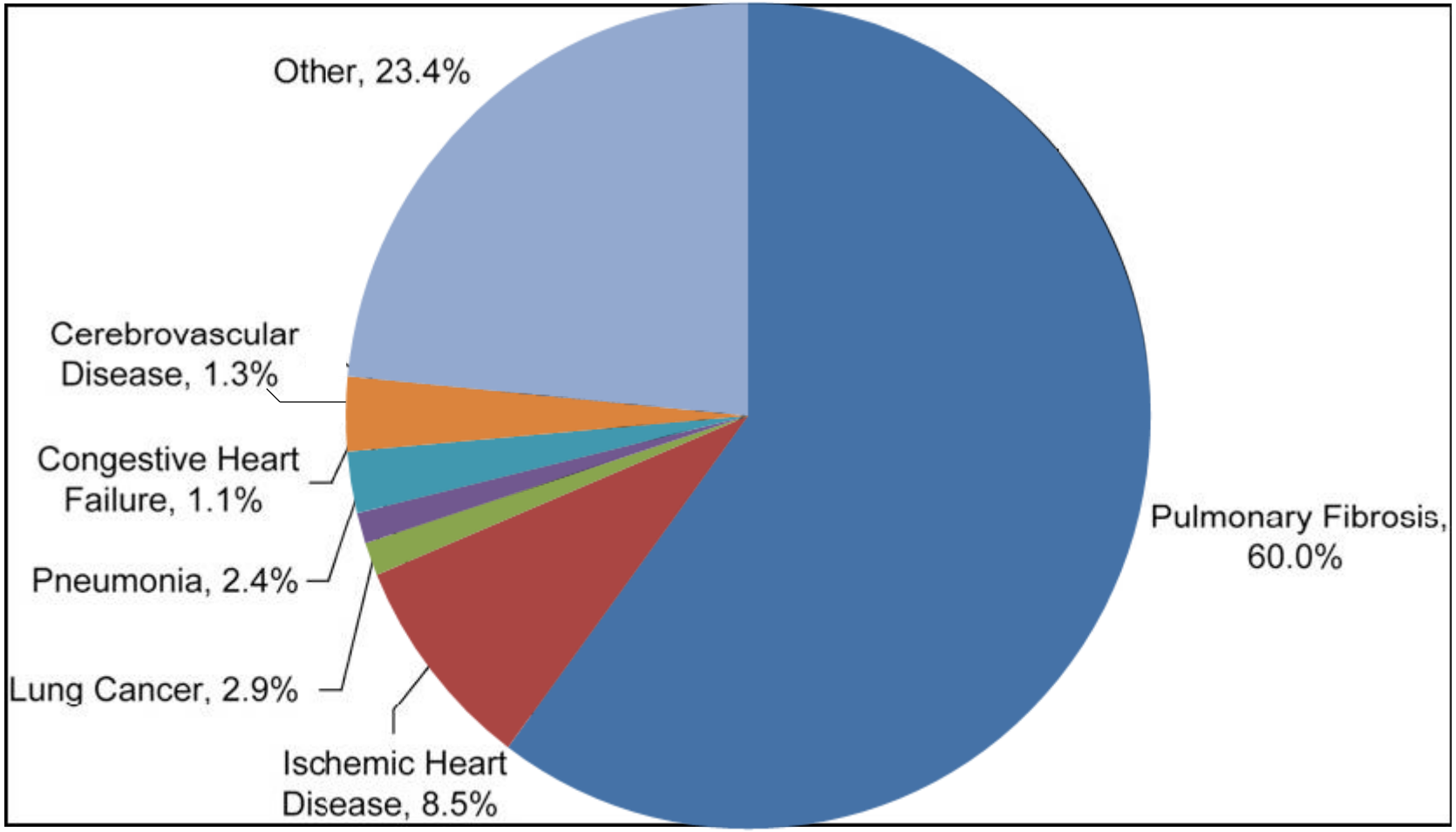
We need alternative approaches for accurate follow-up

Comorbidome

Repeated serology

Biomarkers

40% of patients with IPF die from non-IPF causes



Olson AL. *AJRCCM* 2007

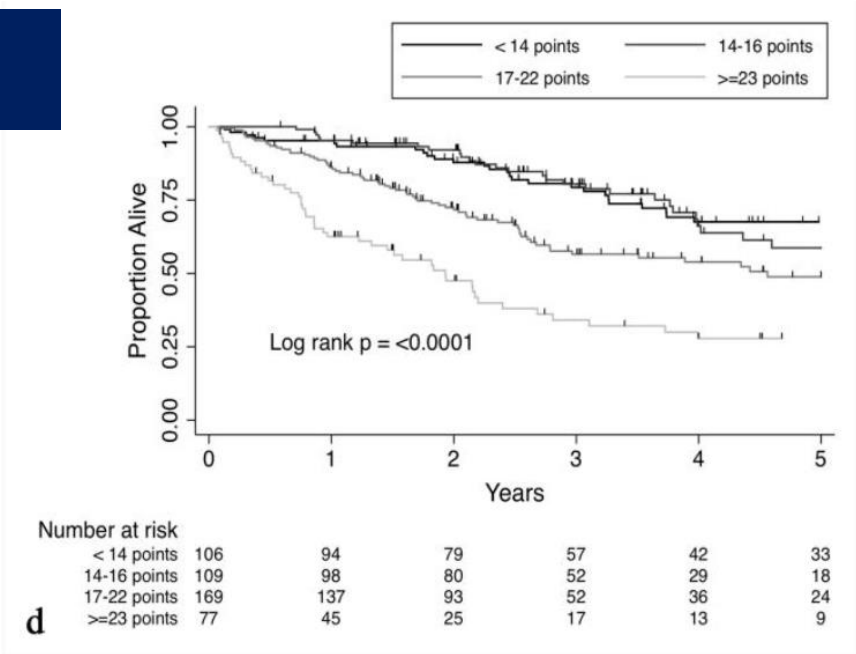
The added value of comorbidities in predicting survival in idiopathic pulmonary fibrosis: a multicenter observational study

ERJ Express. Published on December 21, 2018

Sebastiano Emanuele Torrisi, Brett Ley, Michael Kreuter, Marlies Wijsenbeek, Eric Vittinghoff, Harold R. Collard, Carlo Vancheri

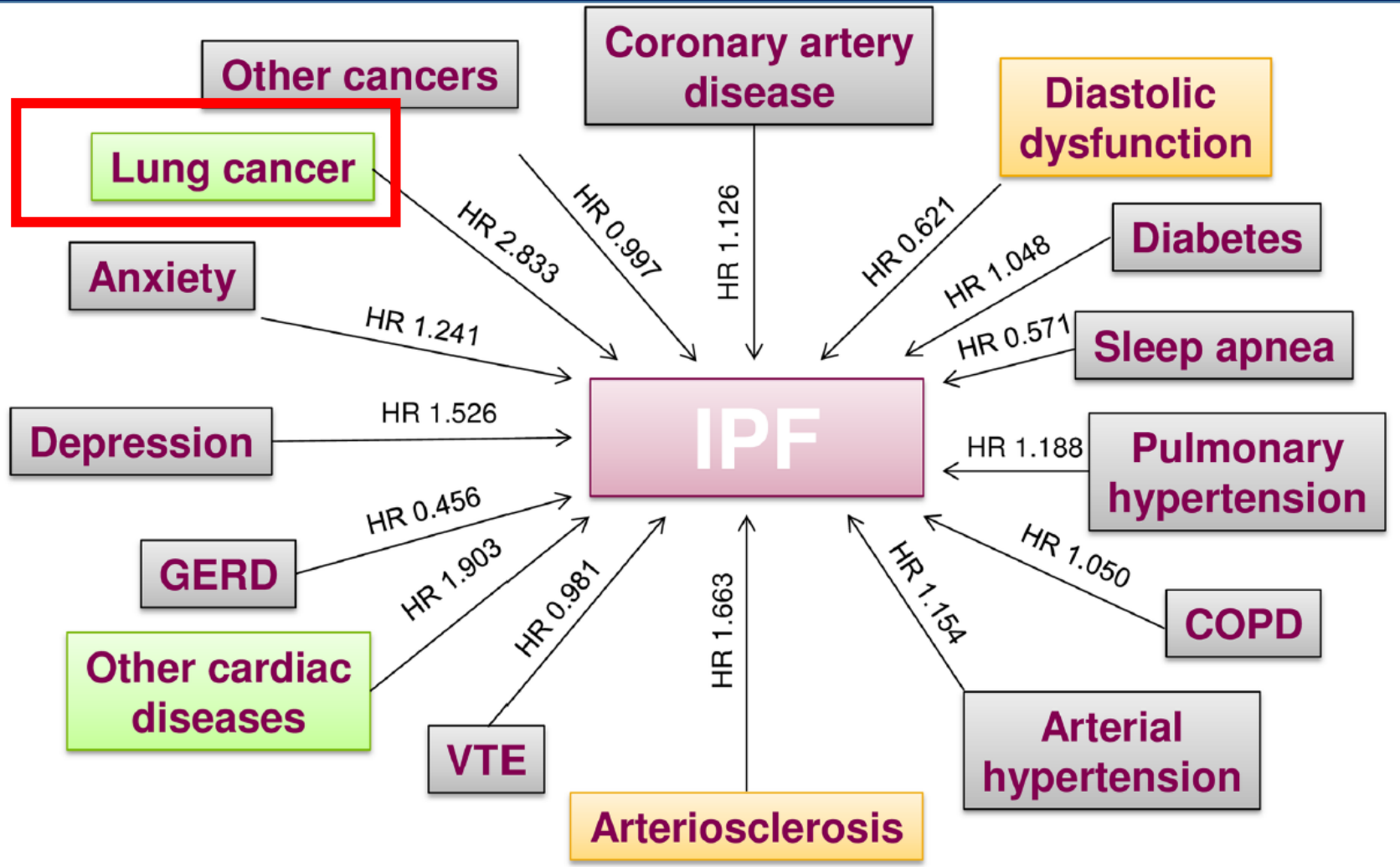
931 IPF patients

Diabetes mellitus	1	2
Systemic Hypertension	/	1
GERD	1 (Absence)	2 (Absence)
Pulmonary Hypertension	2	2
Major Depressive disorder	1	3
Lung Cancer	6	6
Valvular heart disease	5	6
Atrial Arrhythmias	6	6



Conclusions: The inclusion of comorbidities in TORVAN models significantly improved the discriminative performance in prediction of risk of death comparing to GAP.

Comorbidities Assessment



PLOS ONE | DOI:10.1371/journal.pone.0151425 March 29, 2016

i. Prevalence of lung cancer in IPF 2.7 -31.3 %

ii. Prevalence =50% during 10-yrs of follow-up

Pulmonary Pharmacology & Therapeutics

Volume 45, August 2017, Pages 1–10

Lung cancer in patients with idiopathic pulmonary fibrosis

Theodoros Karampitsakos[a], Vasilios Tzilas[a], Rodoula Tringidou[b], Paschalis Steiropoulos[c], Vasilis Aidinis[d], Spyros A. Papiris[e], Demosthenes Bouros[a], Argyris Tzouvelekis[a, d]

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[b] Pathology Department, Hospital for Diseases of the Chest,"Sotiria", Messogion Avenue 152, Athens 11527, Greece

[c] Department of Pneumonology, Democritus University of Thrace, Greece

[d] Division of Immunology, Biomedical Sciences Research Center "Alexander Fleming", Athens, Greece

[e] 2nd Pulmonary Medicine Department, Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Received 22 December 2016, Revised 28 February 2017, Accepted 31 March 2017, Available online 1 April 2017

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http://doi.org/10.1016/j.pupt.2017.03.016

Table 1: Studies reporting prevalence of lung cancer in patients with IPF

Study	Number of patients with IPF	Incidence of lung cancer	Year
Nagai	99	31 (31.3%)	1992
Park	281	63 (22.4%)	2001
Le Jeune	1064	29 (2.7%)	2007
Ozawa	103	21 (20.4%)	2009
Kreuter	265	42 (16%)	2014
Tomassetti	181	23(13%)	2015

iii. Squamous cell carcinoma (SCC)

Table 2: Studies reporting histologic predominance of lung cancer in patients with IPF

Study	Number of patients with IPF-lung cancer	SCC	ADC	Year
Nagai	31	45.2%	35.2%	1992
Park	63	35%	30%	2001
Kawasaki	53	46%	46%	2001
Ozawa	21	38%	29%	2009
Lee	70	40%	30%	2014
Kreuter	42	36%	31%	2014
Tomassetti	23	39%	35%	2015

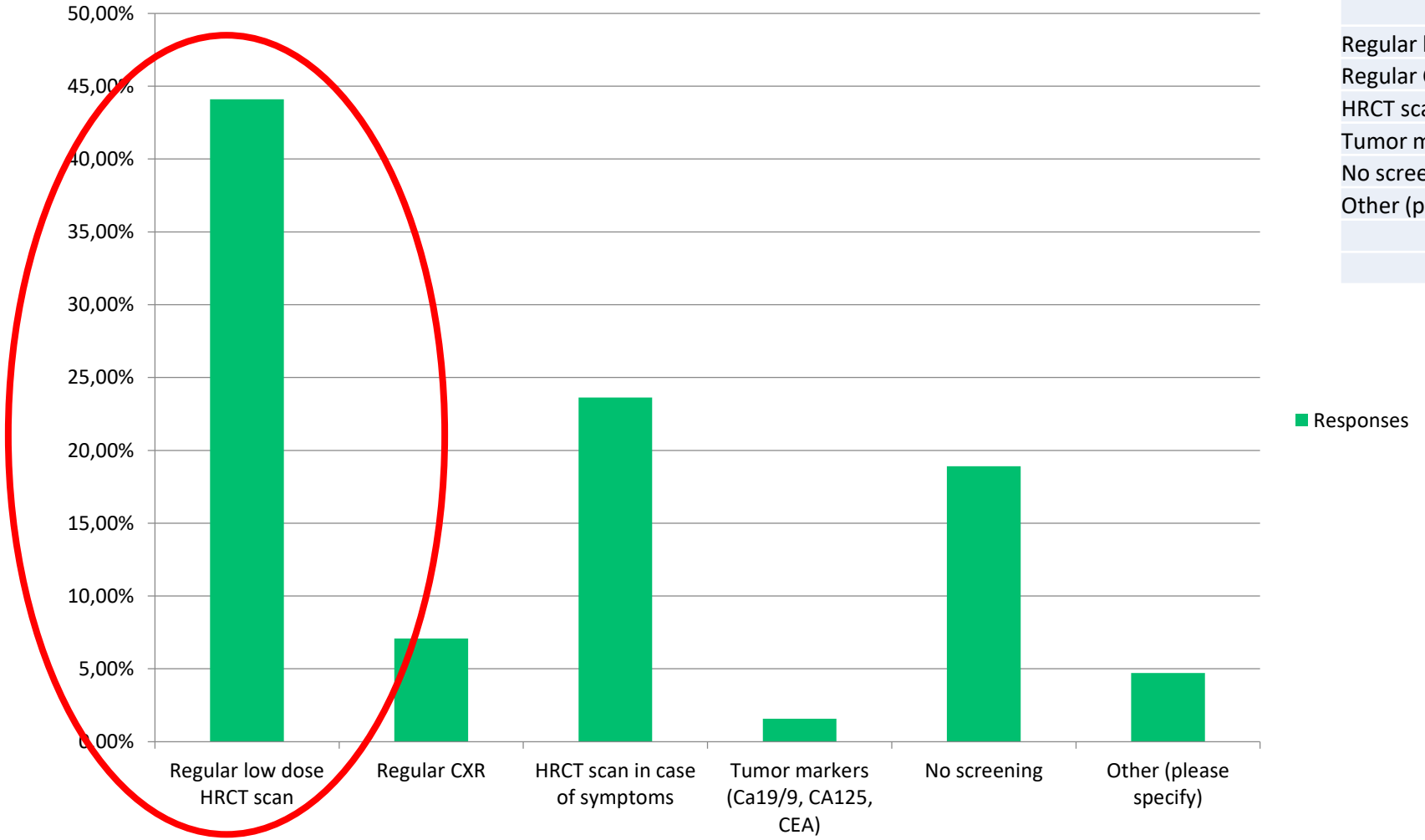
Abbreviations. IPF: Idiopathic pulmonary fibrosis, SCC: Squamous cell carcinoma, ADC: Adenocarcinoma

Otsuka MCO2016 Nagai TJEM 1992 Park ERJ 2001 Le Jeune Resp Med 2007 Ozawa Respirology 2009 Kreuter Sarc Vasc Dif Lung Dis 2014 Tomassetti Chest 2015

NO consensus statement

DIagnosis And Management Of lung canceR and FibrOSIS "DI-A-M-O-R-F-OSIS" survey

Q8: What diagnostic modality do you use to screen patients with IPF for lung cancer (more than one answers possible)?



Answer Choices	Responses	
Regular low dose HRCT scan	44.09%	56
Regular CXR	7.09%	9
HRCT scan in case of symptoms	23.62%	30
Tumor markers (Ca19/9, CA125, CEA)	1.58%	2
No screening	18.90%	24
Other (please specify)	4.72%	6
	Answered	127
	Skipped	3

Respondents=130

Clinical Guideline | Annals of Internal Medicine

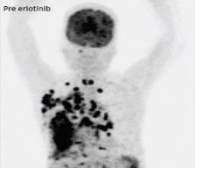
Screening for Lung Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Ann Intern Med. 2014;160:330-338.

Population	Asymptomatic adults aged 55 to 80 y who have a 30 pack-year smoking history and currently smoke or have quit smoking within the past 15 y
Recommendation	Screen annually for lung cancer with low-dose computed tomography. Discontinue screening when the patient has not smoked for 15 y. Grade: B

Risk Assessment	Age, total cumulative exposure to tobacco smoke, and years since quitting smoking are the most important risk factors for lung cancer. Other risk factors include specific occupational exposures, radon exposure, family history, and history of pulmonary fibrosis or chronic obstructive lung disease.



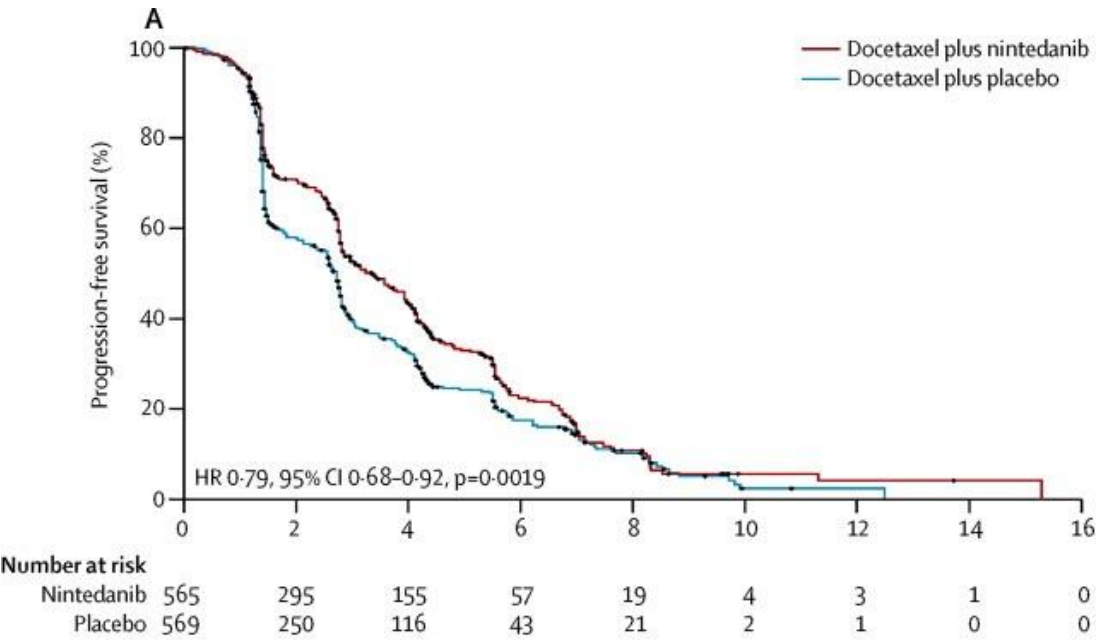
Nintedanib + docetaxel improves survival in ADC-IPF

Potential for AEx?

Articles

Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial

- Nintedanib 200 mg bid plus docetaxel
- Improved overall survival of advanced ADC



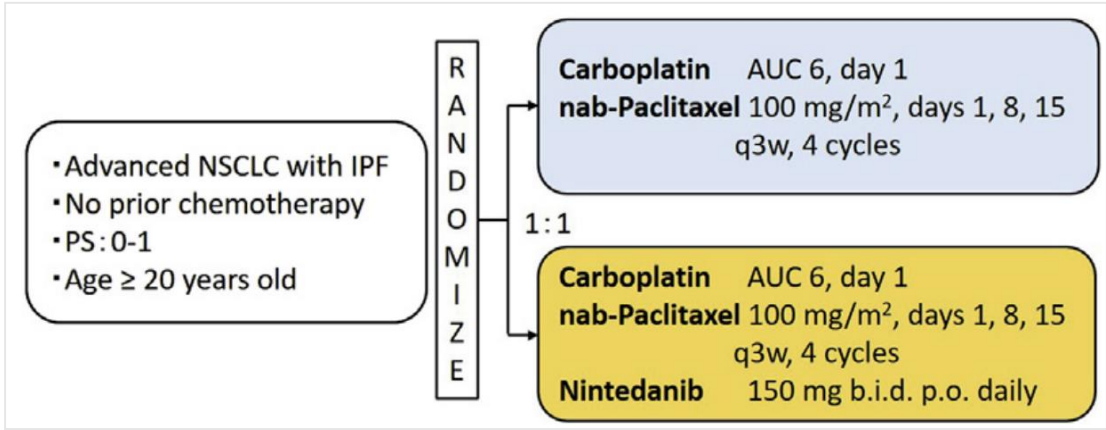
Reck M, Lancet Oncol 2014,15:143;

Current Trial Report

CrossMark

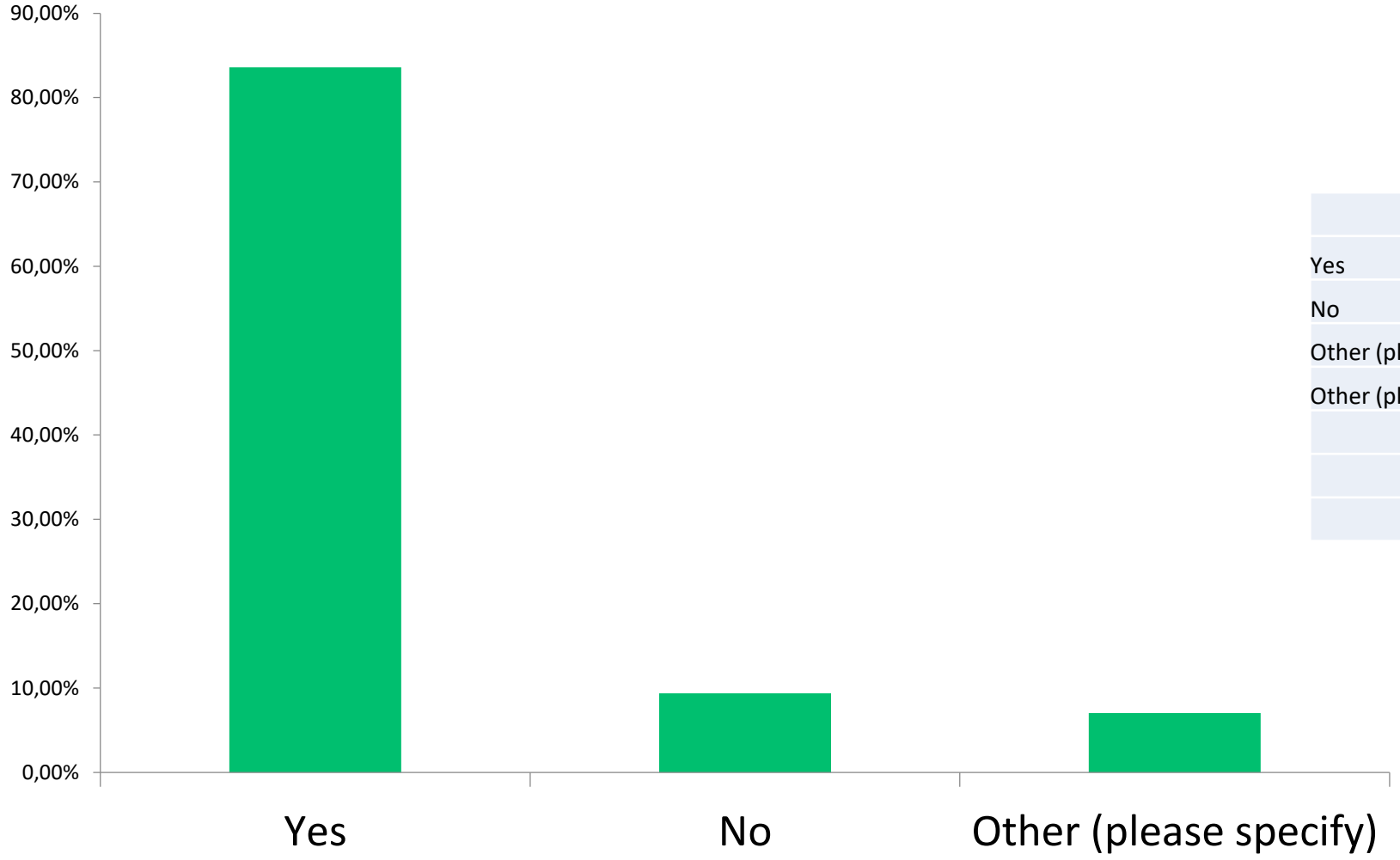
Treatment Rationale and Design for J-SONIC: A Randomized Study of Carboplatin Plus Nab-paclitaxel With or Without Nintedanib for Advanced Non–Small-cell Lung Cancer With Idiopathic Pulmonary Fibrosis

Kohei Otsubo,[1] Junji Kishimoto,[2] Hirotsugu Kenmotsu,[3] Yuji Minegishi,[4] Eiki Ichihara,[5] Akira Shiraki,[6] Terufumi Kato,[7] Shinji Atagi,[8] Hidehito Horinouchi,[9] Masahiko Ando,[10] Yasuhiro Kondoh,[11] Masahiko Kusumoto,[12] Kazuya Ichikado,[13] Nobuyuki Yamamoto,[14] Yoichi Nakanishi,[1] Isamu Okamoto[1]



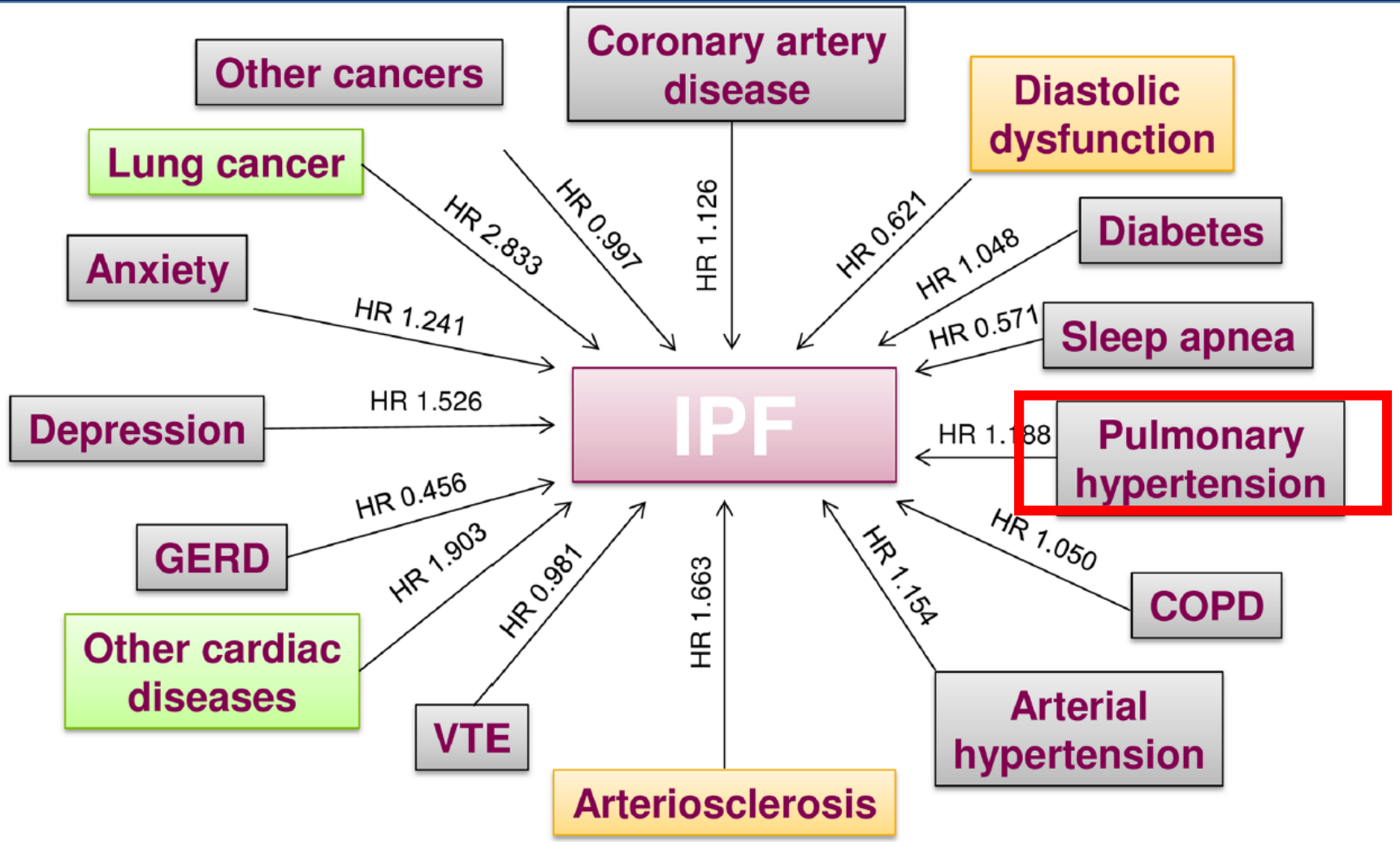
Otsubo K, Clin Lung Cancer 2017, 19:e5

Q16: Do you continue anti-fibrotic treatment (pirfenidone or nintedanib) when a patient is diagnosed with lung cancer (any stage)?



Answer Choices	Responses	
Yes	83.59%	107
No	9.38%	12
Other (please specify)	7.03%	9
Other (please specify)		6
	Answered	128
	Skipped	0

Comorbidities Assessment



PLOS ONE | DOI:10.1371/journal.pone.0151425 March 29, 2016

Author	Year	Patients	Diagnosis	Threshold	Prevalence (%)
Leuchte et al	2004	28	RHC	mPAP>35 mmHg	21.4
Nadrous et al potential for substantial selection bias	2005	88	Echo	sPAP>35 mmHg sPAP>50 mmHg	84 31
Lettieri et al Referred for transplantation	2006	79	RHC	mPAP>25 mmHg	31.6
Hamada et al Initial presentation-pro	2007	70	RHC	mPAP>25 mmHg	8.1
Zisman et al	2007	65	RHC	mPAP>25 mmHg	41.5
Patel et al Referred for transplantation	2007	41	RHC	mPAP>25 mmHg	20
Shorr et al* Lung transplant registry for the USA (1995 to 2004)	2007	2.525	RHC	mPAP>25 mmHg mPAP>40 mmHg	46.1 9.1
Nathan et al.	2008	118	RHC	mPAP>40 mmHg	40.7
Song et al	2009	131	Echo	mPAP>40 mmHg	25.2
Minai et al abstract	2009	148	RHC	mPAP>25 mmHg mPAP>40 mmHg	46 14
Kimura et al* Initial presentation-retro	2013	101	RHC	mPAP>25 mmHg	15
Raghu	2015	488	RHC	mPAP>25 mmHg	14

ERJ Express. Published on December 14, 2018 as doi: 10.1183/13993003.02148-2018

An overview of the 6th World Symposium on Pulmonary Hypertension

Nazzareno Galiè[1], Vallerie V. McLaughlin[2], Lewis J. Rubin[3] and Gerald Simonneau[4,5]

The task force has therefore proposed including a pulmonary vascular resistance (PVR) ⩾3 WU into the definition of pre-capillary PH associated with mPAP >20 mmHg, irrespective of aetiology. Future trials should assess the

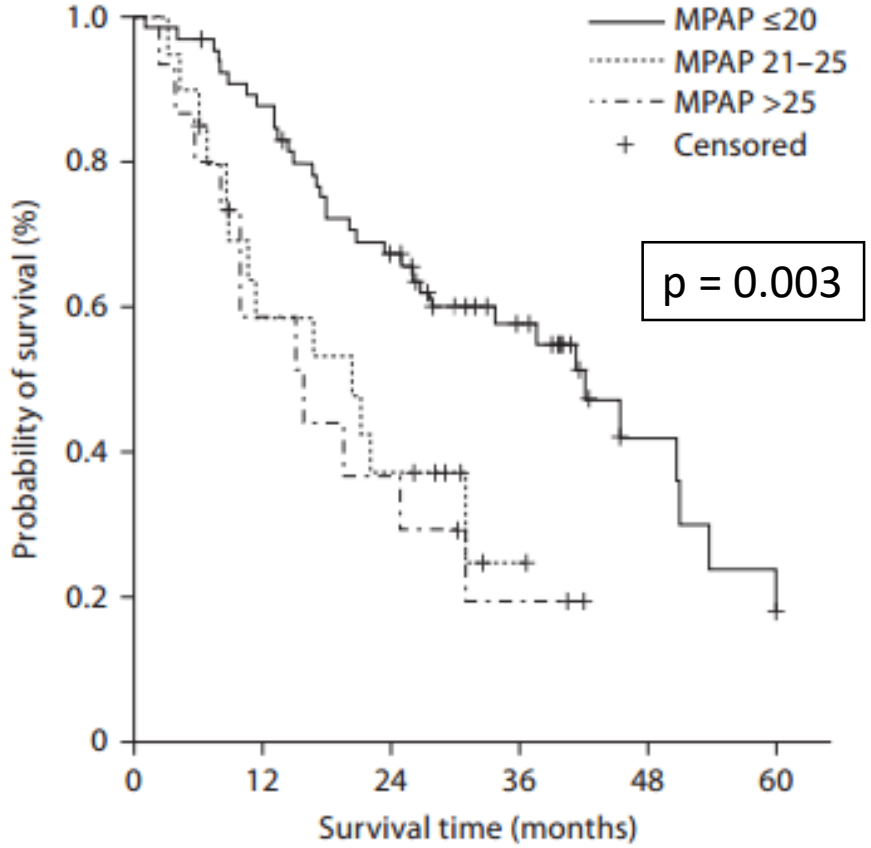
definition of PH [5]. Based on data from normal subjects, the normal mean pulmonary arterial pressure (mPAP) at rest is approximately 14.0±3.3 mmHg [6]. Two standard deviations above this mean value would indicate that a mPAP >20 mmHg is the threshold for abnormal pulmonary arterial pressure (above the

Negative prognostic factor irrespective of disease severity

Initial Presentation

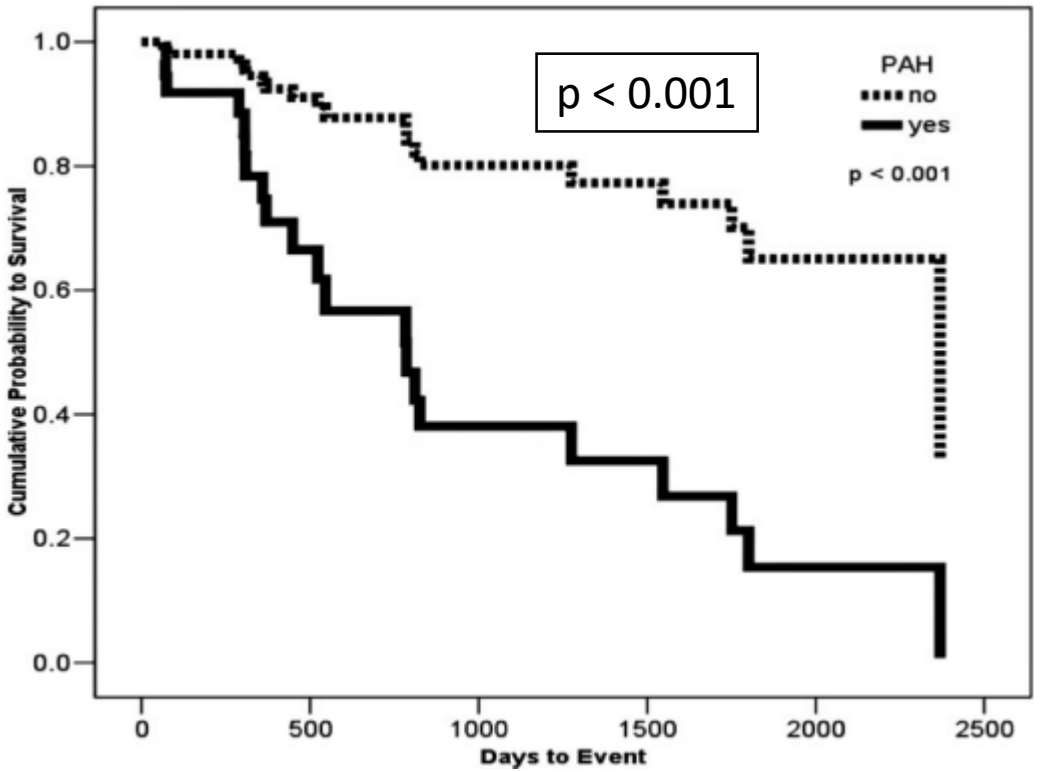
1 yr mortality w/o PH = 5%
1 yr mortality w PH = 35%

Advanced disease – Pre-lung Tx



Number at risk						
MPAP ≤20	66	57	41	22	7	4
MPAP 21–25	20	11	7	1	0	0
MPAP >25	15	8	5	2	0	0

Kimura M et al. Respiration 2013;85:456-63



Lettieri C, et al. Chest 2006; 126:746-752

Assessment of PH in IPF

- **RHC is the gold standard diagnostic modality – Select patients on U/S**
- **U/S operator dependent – not reliable especially in emphysema (>40%)**
- **Suspect PH when: "disproportionate" dyspnea+ LOW DLCO, 6MWD< 200m, dPA/DAA>1**

Pulmonary Pharmacology & Therapeutics 50 (2018) 38–46

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics 50 (2018) 38–46

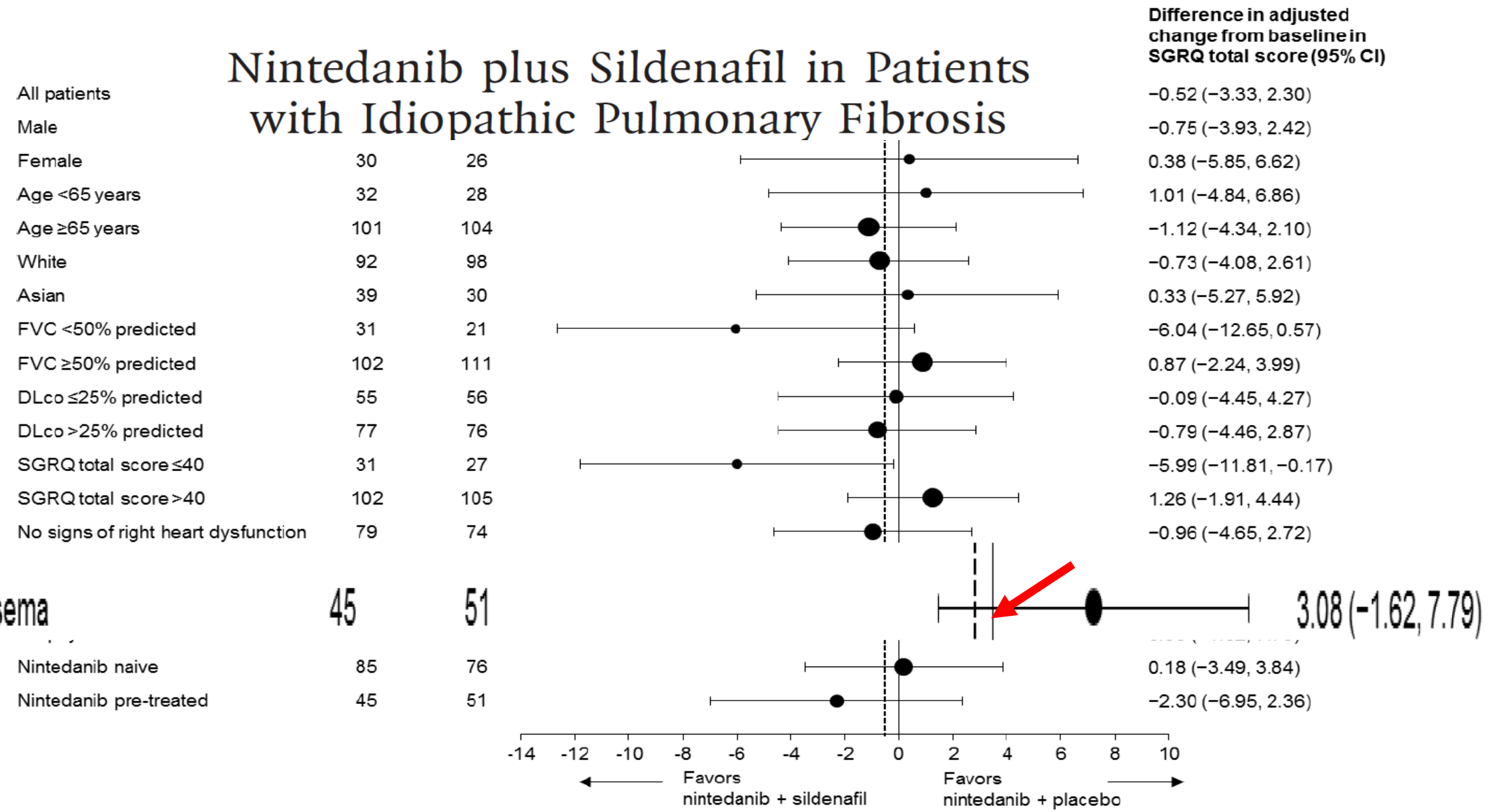
journal homepage: www.elsevier.com/locate/ypupt

Pulmonary hypertension in patients with interstitial lung disease

Theodoros Karampitsakos[a], Argyrios Tzouvelekis[b,c], Serafeim Chrysikos[a], Demosthenes Bouros[b], Iraklis Tsangaris[d], Wassim H. Fares[e,*]

This article was published on September 15, 2018, at NEJM.org.

Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis



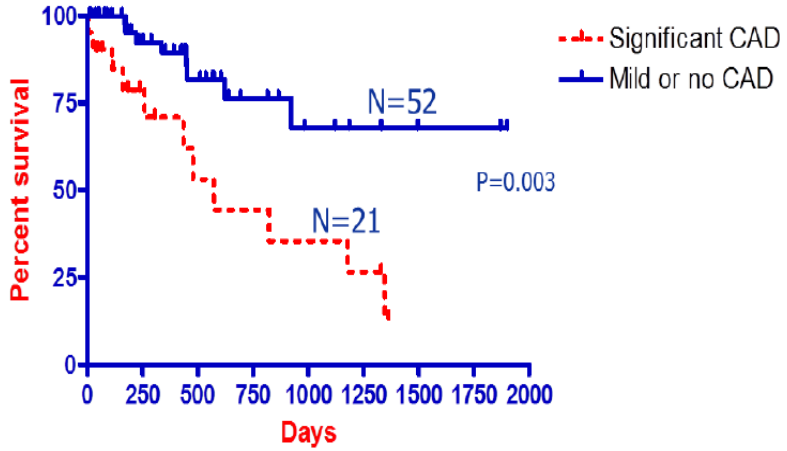
Cardiovascular disease in IPF

CAD is the most frequently reported CV comorbidity, also CHF, AH,ACS, VTE

Prevalence: 3-68%

Critical to assess especially if patient under nintedanib treatment

Symptomatic patients → Cardiac CT/MRI
Assessment of cardiac fibrosis-diastolic dysfunction



King CS. *Lancet Respir Med* 2016

A Clinical Perspective of Anti-Fibrotic Therapies for Cardiovascular Disease

Lu Fang[1], Andrew J. Murphy[1] and*

frontiers in Pharmacology

MINI REVIEW
published: 06 April 2017
doi: 10.3389/fphar.2017.00186

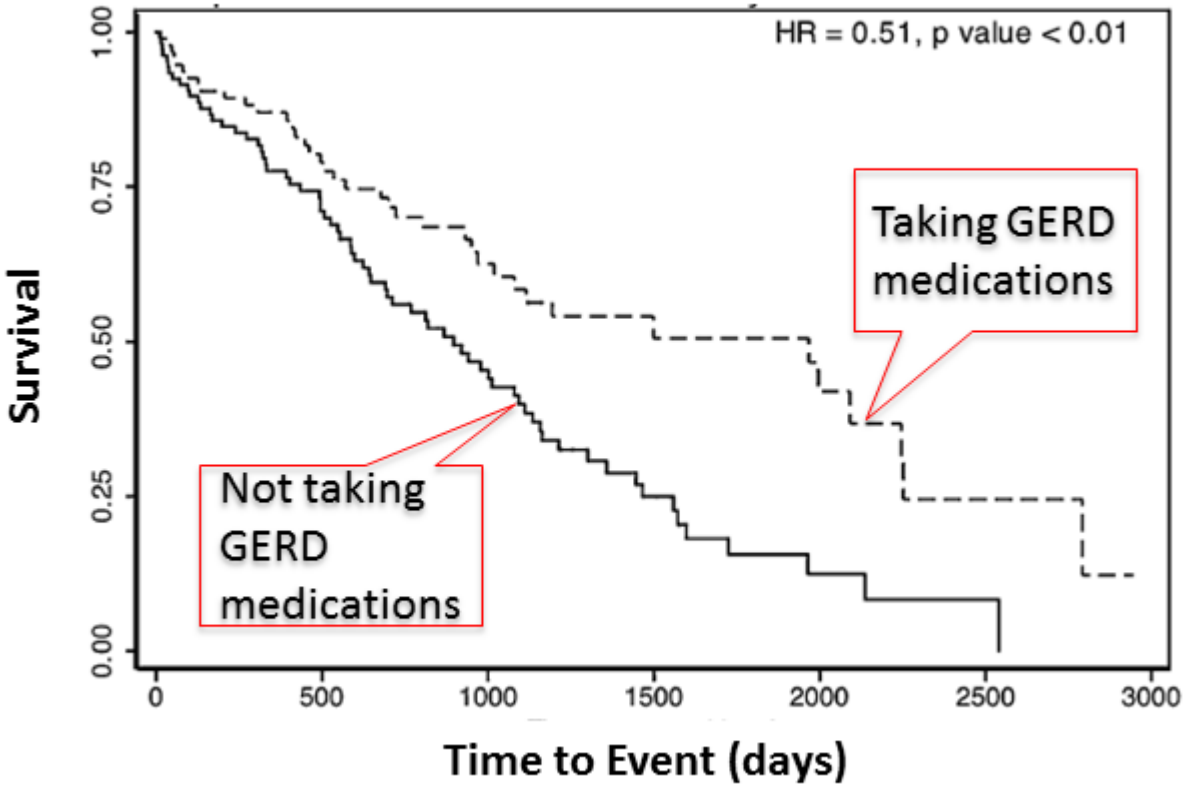
Gastroesophageal reflux disease in IPF

The most common comorbidity in IPF
Prevalence: ~90% IPF

Risk factor for IPF
Clinically silent in 35-55% of cases
Acid GERD >>>> alkaline GERD
Etiology unknown
GERD may play a role in AEIPF

Patients with asymmetric IPF are more likely to have GERD and AEIPF than patients with symmetric IPF.

Diagnosis
Barium swallow
Esophageal manometry
24h pH probe
Esophageal Impedance



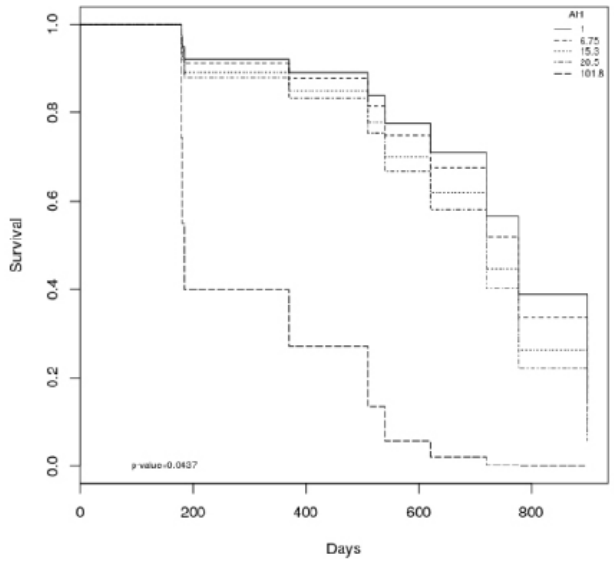
Raghu G. *Eur Respir J* 2006
Tcherakian C.*Thorax* 2011

Sleep breathing disorders in IPF

- ✓ **Screening for SBDs in all patients with IPF**

- ✓ **Treat SBDs**
  - Nocturnal O2 therapy if present only sleep hypoxemia
  - CPAP therapy if OSAS present according AASM guidelines

- ✓ Negative impact of AHI on survival



Kolilekas L. *J Clin Sleep Med* 2013

Serologic Tests Can Help Identify Other Conditions

Question 2: Should Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF Undergo Serological Testing to Exclude CTDs as Potential Causes of the ILD?

ATS/ERS/JRS/ALAT recommendation.

- For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF, we recommend serological testing to aid in the exclusion of CTDs as a potential cause of the ILD (*motherhood statement*).

Repeated Serologic Tests? How often?/yr?

- 10% of IPF patients may develop later a CTD-ILD
- 30% of IPF patients have positive ANA and/or RF w/o any autoimmune signs
- **Not clear whether all patients with IPF should have a repeated serologic evaluation on a regular basis**

An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features Eur Respir J 2015; 46: 976–987

Should patients with newly detected ILD undergo serum biomarker analysis for diagnosis?

Favoring measurement

>50% with high MMP7 levels will be distinguished from other ILDs

Favoring NO measurement

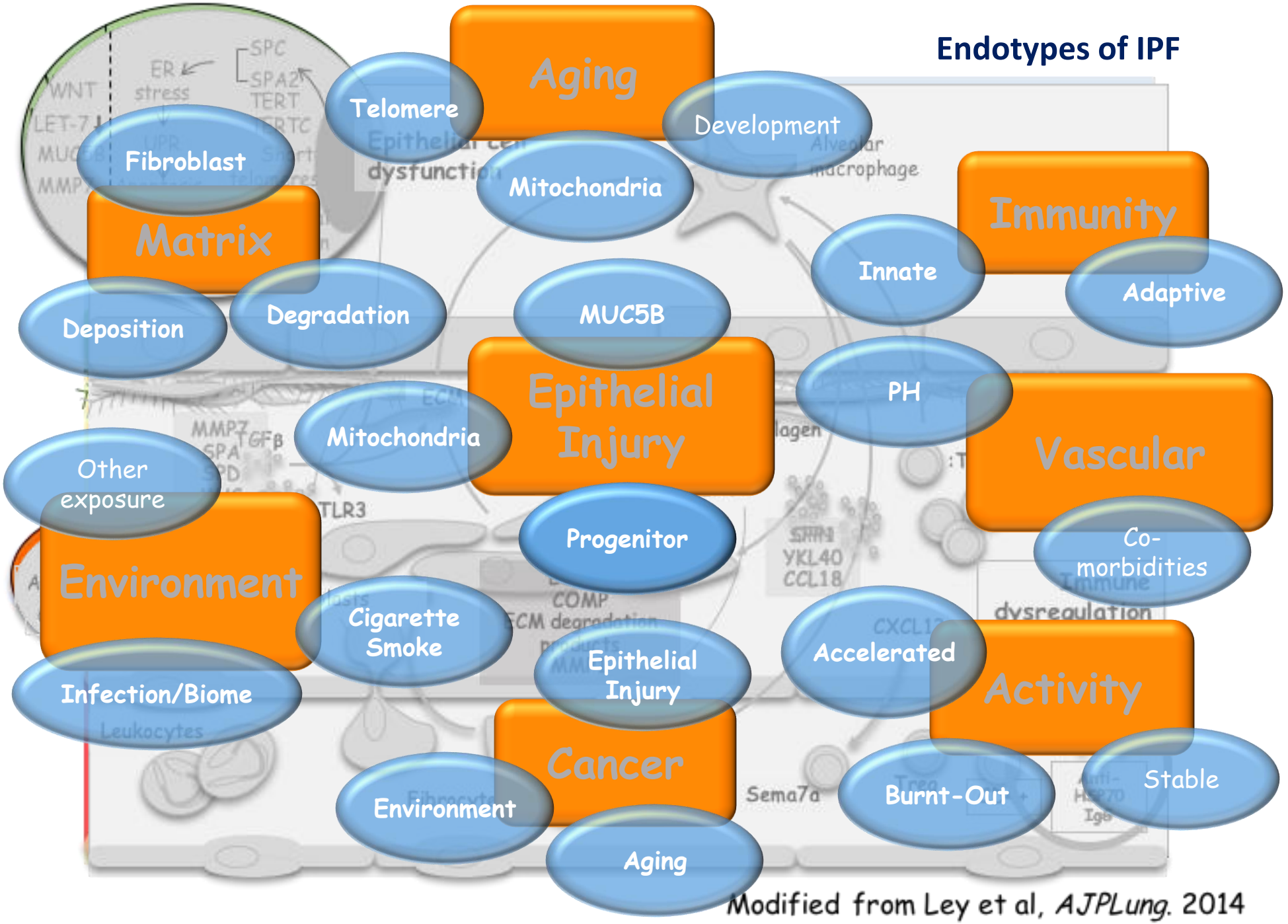
>1/3 of patients will have false positive results, delayed therapy, undesirable complications

- **We recommend NOT measuring serum MMP7, KL-6, CCL18 for IPF diagnosis – non specific**
- **Prognostic role??**

AMERICAN THORACIC SOCIETY DOCUMENTS
American Journal of Respiratory and Critical Care Medicine Volume 198 Number 5 | September 1 2018

Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Endotypes of IPF



Modified from Ley et al, *AJPLung*. 2014

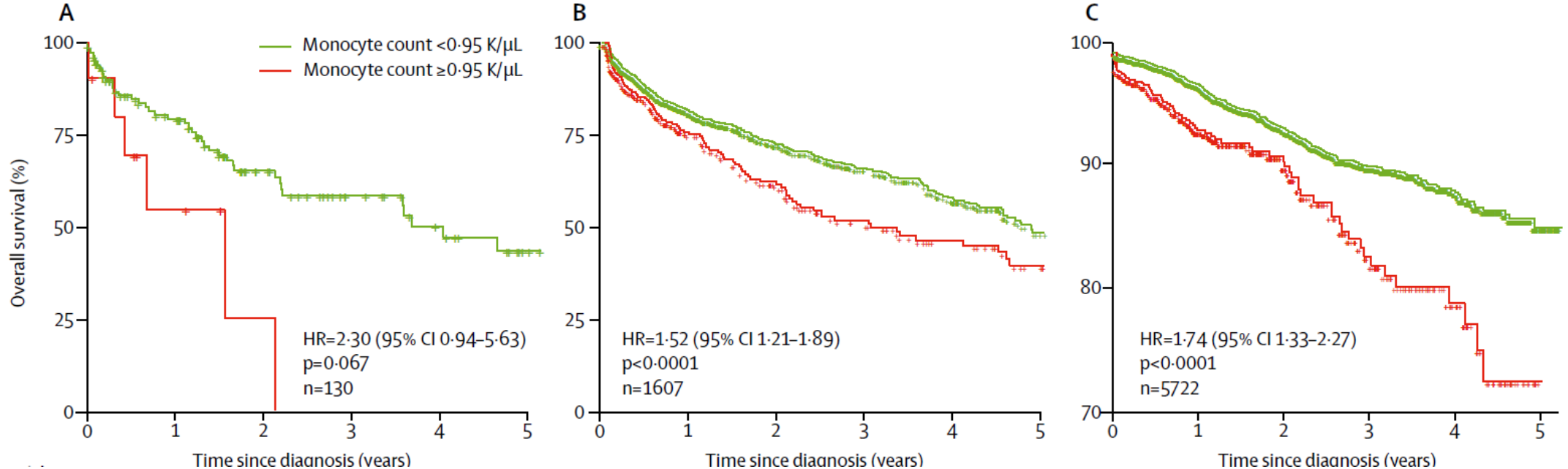
Increased monocyte count as a cellular biomarker for poor outcomes in fibrotic diseases: a retrospective, multicentre cohort study

Lancet Respir Med 2019
Published Online
March 29, 2019

Madeleine K D Scott, Katie Quinn, Qin Li, Robert Carroll, Hayley Warsinske, Francesco Vallania, Shirley Chen, Mary A Carns

Finally we have a clinician's friendly biomarker
3 agents were approved in asthma based on Eos count

7459 patients with idiopathic pulmonary fibrosis showed that patients with monocyte counts of 0·95 K/μL or greater were at increased risk of mortality



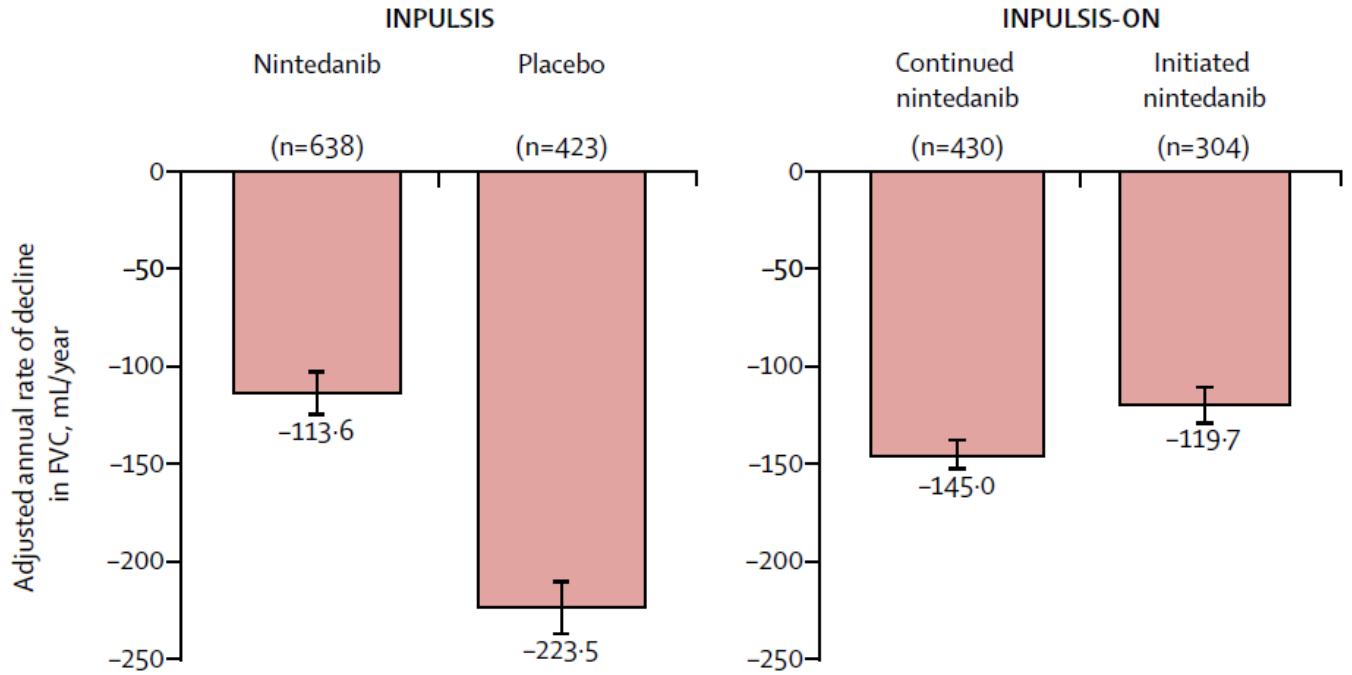
Do current anti-fibrotics have a longitudinal efficacy/safety profile?

Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON

Lancet Respir Med 2018

Published Online
September 14, 2018

- **734 patients (59% continued-41% initiated ND)**
- **No additional safety signals**
- **Acceptable cardiovascular profile**
- **Similar efficacy effects**
- **74% discontinutation**

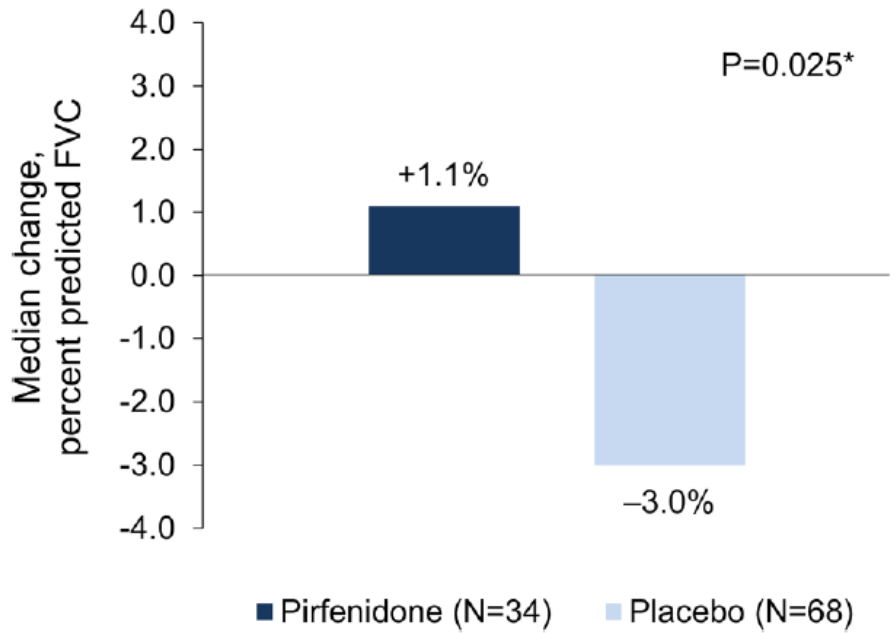


Do we stop anti-fibrotics if the patient progresses?

ORIGINAL ARTICLE Nathan SD, *et al*. *Thorax* 2016;

Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis

In patients who progressed during treatment, continued treatment with pirfenidone resulted in a lower risk of subsequent FVC decline or death.

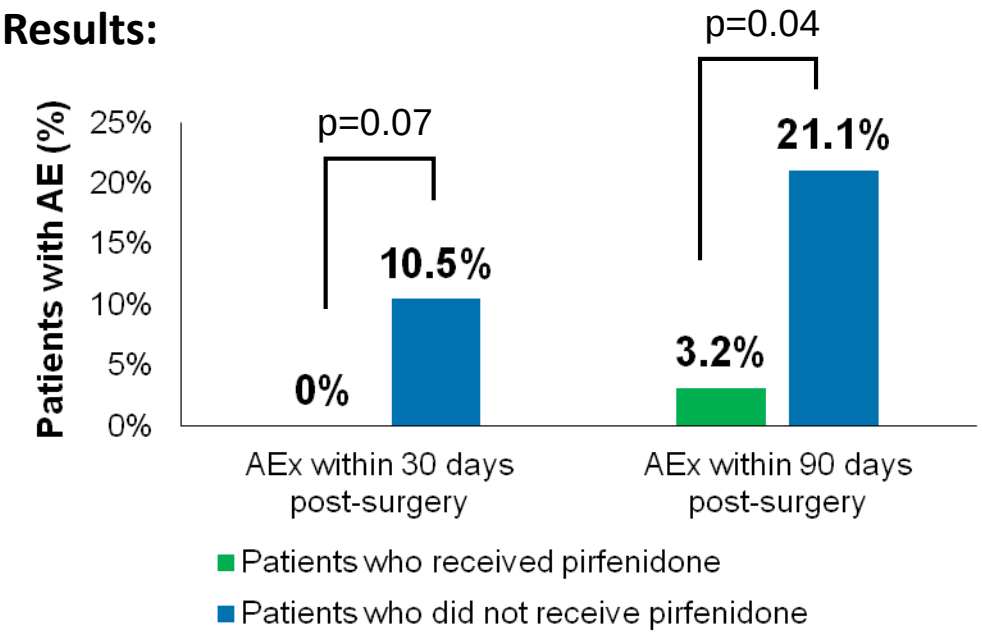


Do we stop anti-fibrotics before surgery of Lung Tx?

Pirfenidone reduces perioperative AEx in patients with NSCLC+IPF?

Effect of Perioperative Pirfenidone Treatment in Lung Cancer Patients With Idiopathic Pulmonary Fibrosis

- **Methods:**
  - A consecutive series of 50 lung cancer patients with IPF were retrospectively investigated
  - 31 patients received perioperative pirfenidone from 4 weeks before to 4 weeks after surgery; 19 patients did not receive pirfenidone
- **Results:**



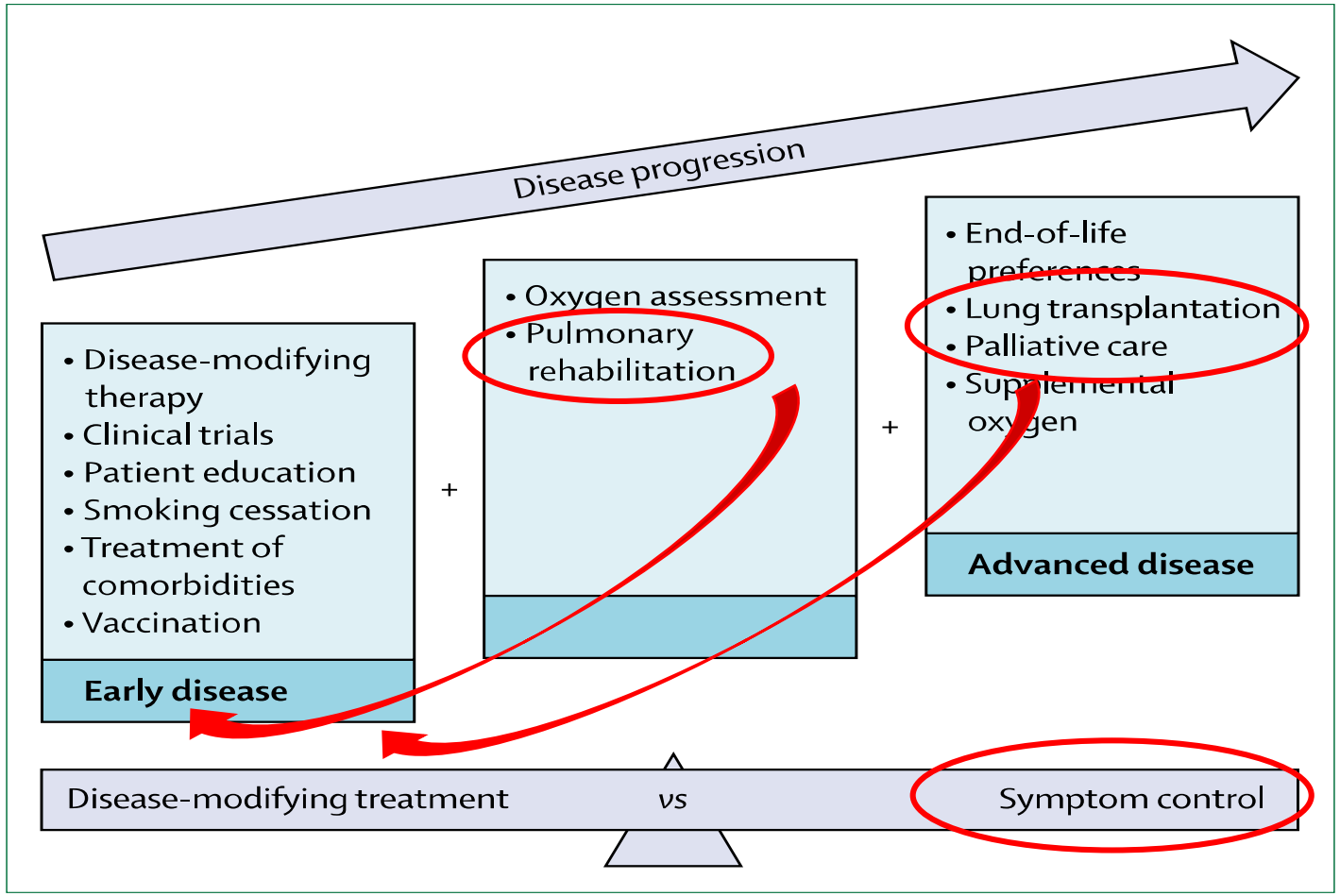
A phase II trial evaluating the efficacy and safety of perioperative pirfenidone for prevention of acute exacerbation of idiopathic pulmonary fibrosis in lung cancer patients undergoing pulmonary resection: West Japan Oncology Group 6711 L (PEOPLE Study)

- **Methods:**
  - 39 IPF patients who were candidates for lung cancer surgery received pirfenidone 1200 mg/day. Patients received pirfenidone for at least 2 weeks before surgery and for up to 30 days post-surgery
- **Results:**
  - Acute exacerbation within 30 days post surgery: **5.1%**
  - One patient died after an acute exacerbation of IPF; no other grade 3–5 adverse events were observed

Iwata T, Surg Today 2015, 45:1263; Iwata T, Ann Thorac Surg 2016, 102:1905; Iwata T, Respir Res 2016, 17:90

Patient at the center of treatment…..Improve QoL

Step-by-step approach for IPF management



Richeldi L, et al. Lancet, March 2018

Small studies confirm beneficial short-term effects of PR in IPF patients-Larger studies needed

Tonelli *et al. BMC Pulmonary Medicine* (2017) 17:130
DOI 10.1186/s12890-017-0476-5

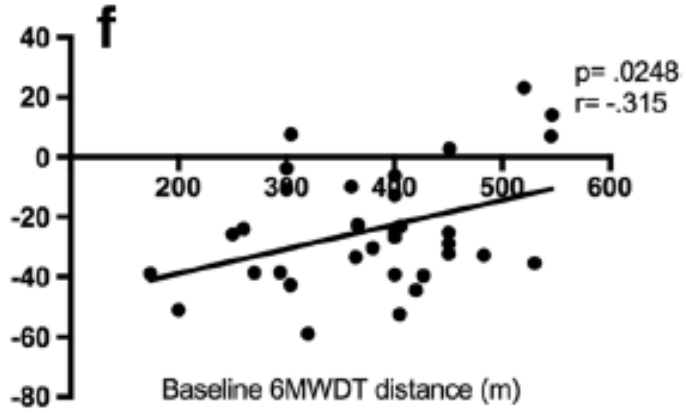
BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Effectiveness of pulmonary rehabilitation in patients with interstitial lung disease of different etiology: a multicenter prospective study

N=41

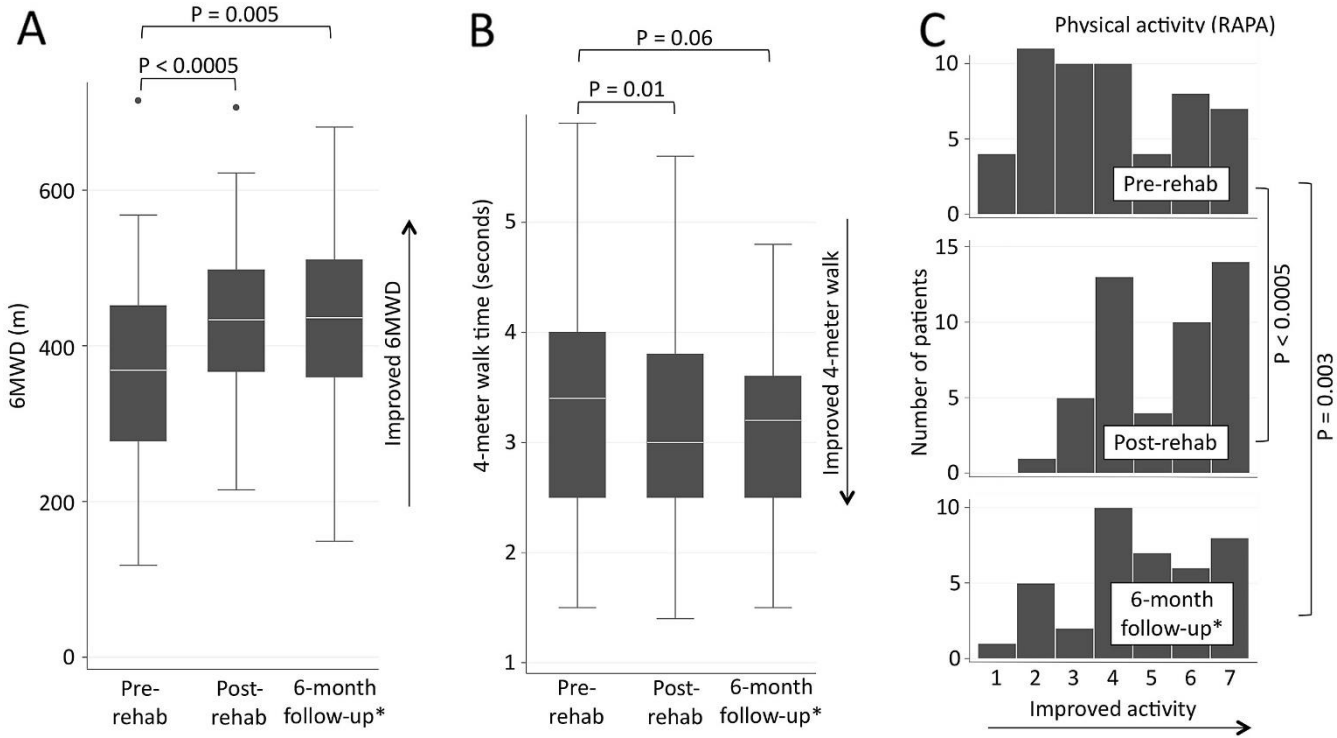
PR program lasted at least 24 sessions of rehabilitation training and was conducted 6 days a week, once daily the first week and twice daily thereafter. Each rehabilitation session lasted at least 3 h.



Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: A prospective cohort studv

Respiratory Medicine (2014) 108, 203–210

N=50



Palliative care in interstitial lung disease: living well

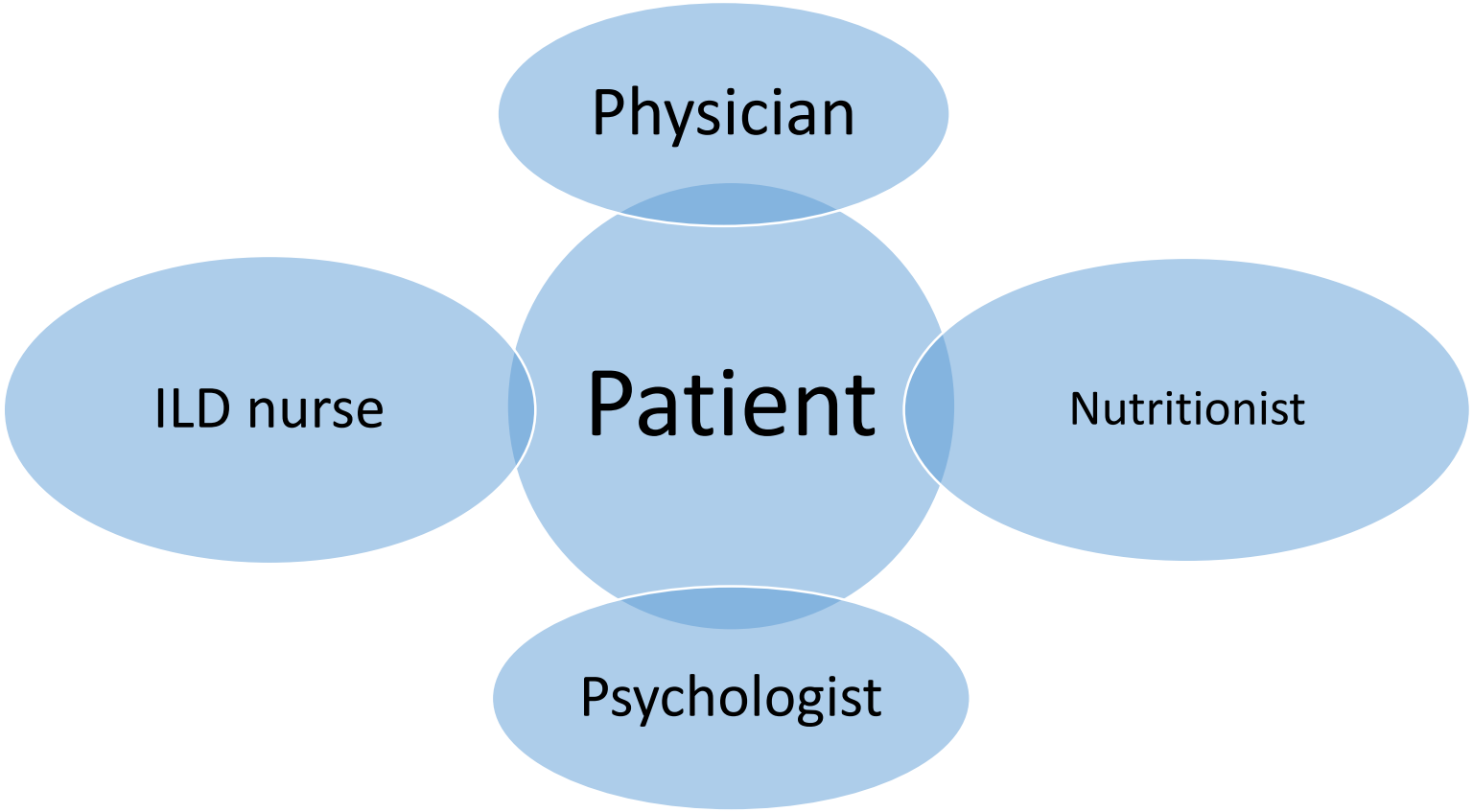
Michael Kreuter*, Elisabeth Bendstrup*, Anne-Marie Russell*, Sabrina Bajwah, Kathleen Lindell, Yochai Adir, Crystal E Brown, Greg Calligaro, Nicola Cassidy, Tamera J Corte, Klaus Geissler, Azza Adel Hassan, Kerri A Johannson, Ronaldo Kairalla, Martin Kolb, Yasuhiro Kondoh, Sylvia Quadrelli, Jeff Swigris, Zarir Udwadia, Athol Wells†, Marlies Wijsenbeek†

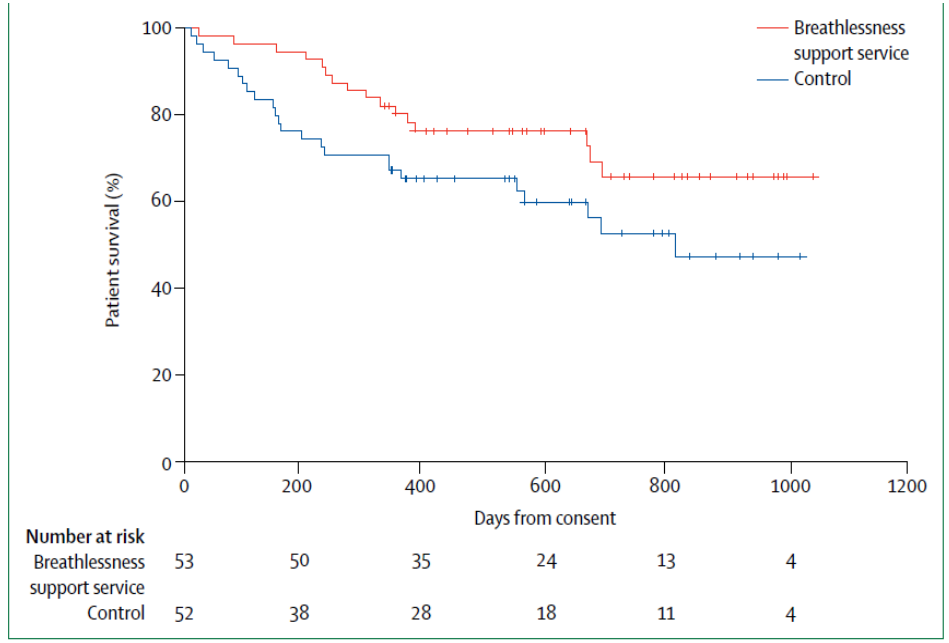
Progressive fibrotic interstitial lung diseases (ILDs) are characterised by major reductions in quality of life and survival and have similarities to certain malignancies. However, palliative care expertise is conspicuously inaccessible to many patients with ILD. Unmet patient and caregiver needs include effective pharmacological and psychosocial interventions to improve quality of life throughout the disease course, sensitive advanced care planning, a

Lancet Respir Med 2017
Published Online
October 12, 2017
http://dx.doi.org/10.1016/

Palliative care is NOT end-of-life care

Early palliative care improves survival





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, Ma… …n H Morice

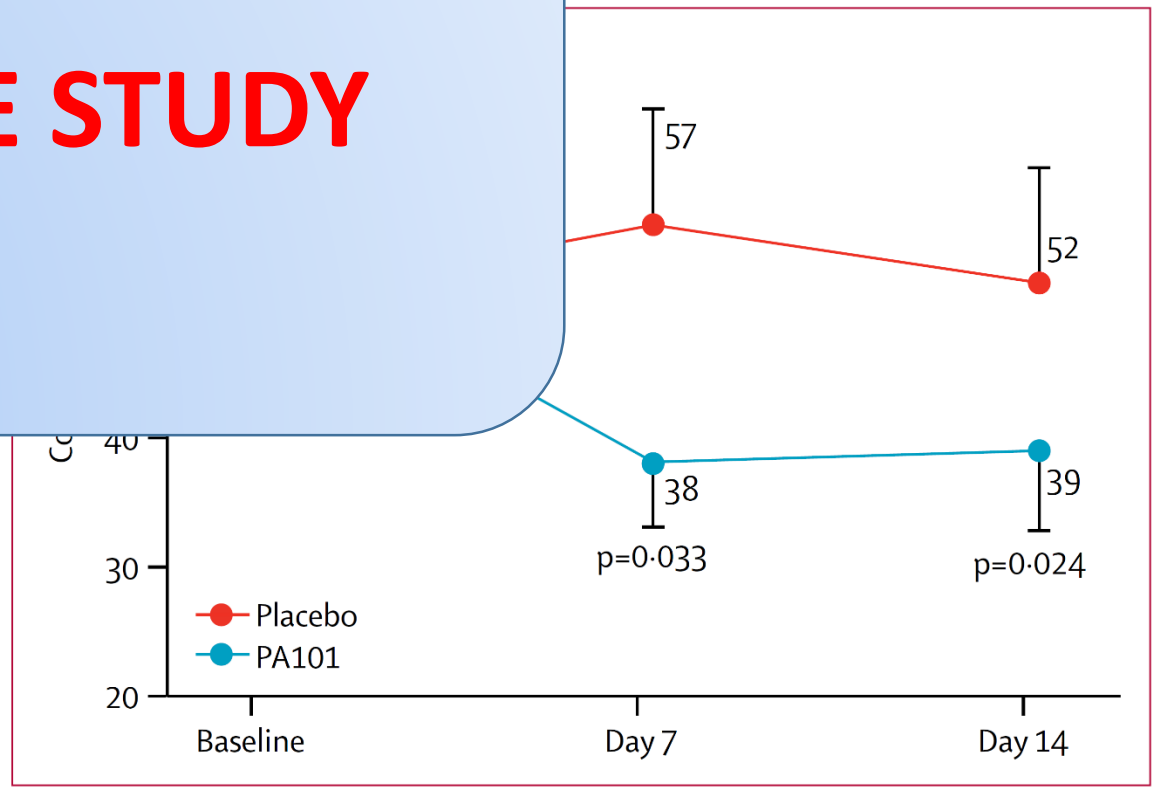
Lancet Respir Med 2017

Published Online
September 8, 2017

Inhaled Cromoglica… …uency in patients with IPF

POSITIVE STUDY

pleotropic effects.[9,10] Histo… has been attributed to inhib… and the consequential inh… immune activation.[9,11] Cromo… reduce C-fibre sensory nerve activity via an orphan G-protein coupled receptor, GPR35.[12] Furthermore,



Ευχαριστώ πολύ

Pulmonary Fibrosis: Thinking Outside the Box in Disease Management and Prognostication

Argyris Tzouvelekis[a, b] Evangelos Bouros[a] Demosthenes Bouros[a]

Respiration
DOI: 10.1159/000480093 Published online: August 26, 2017