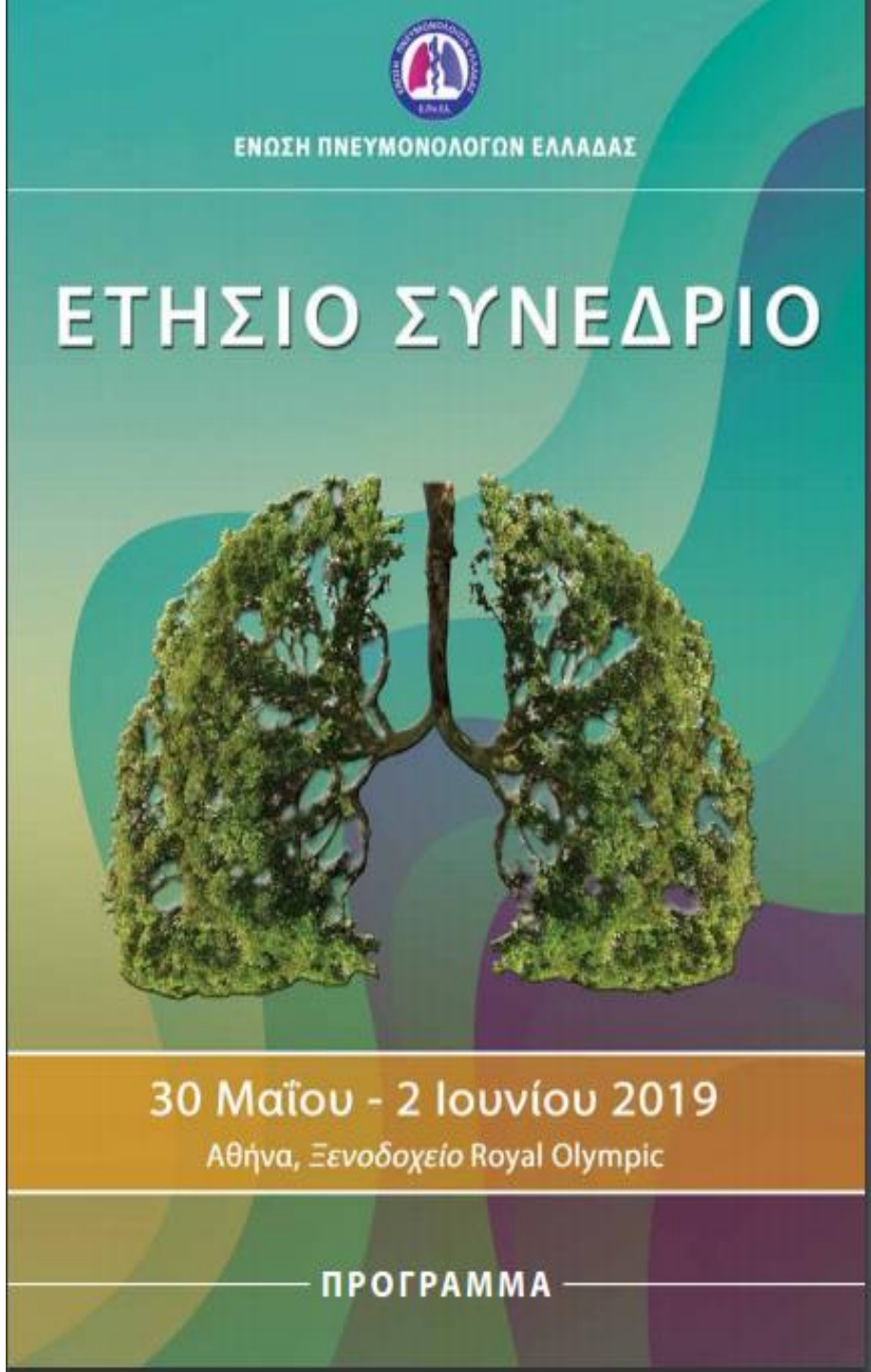
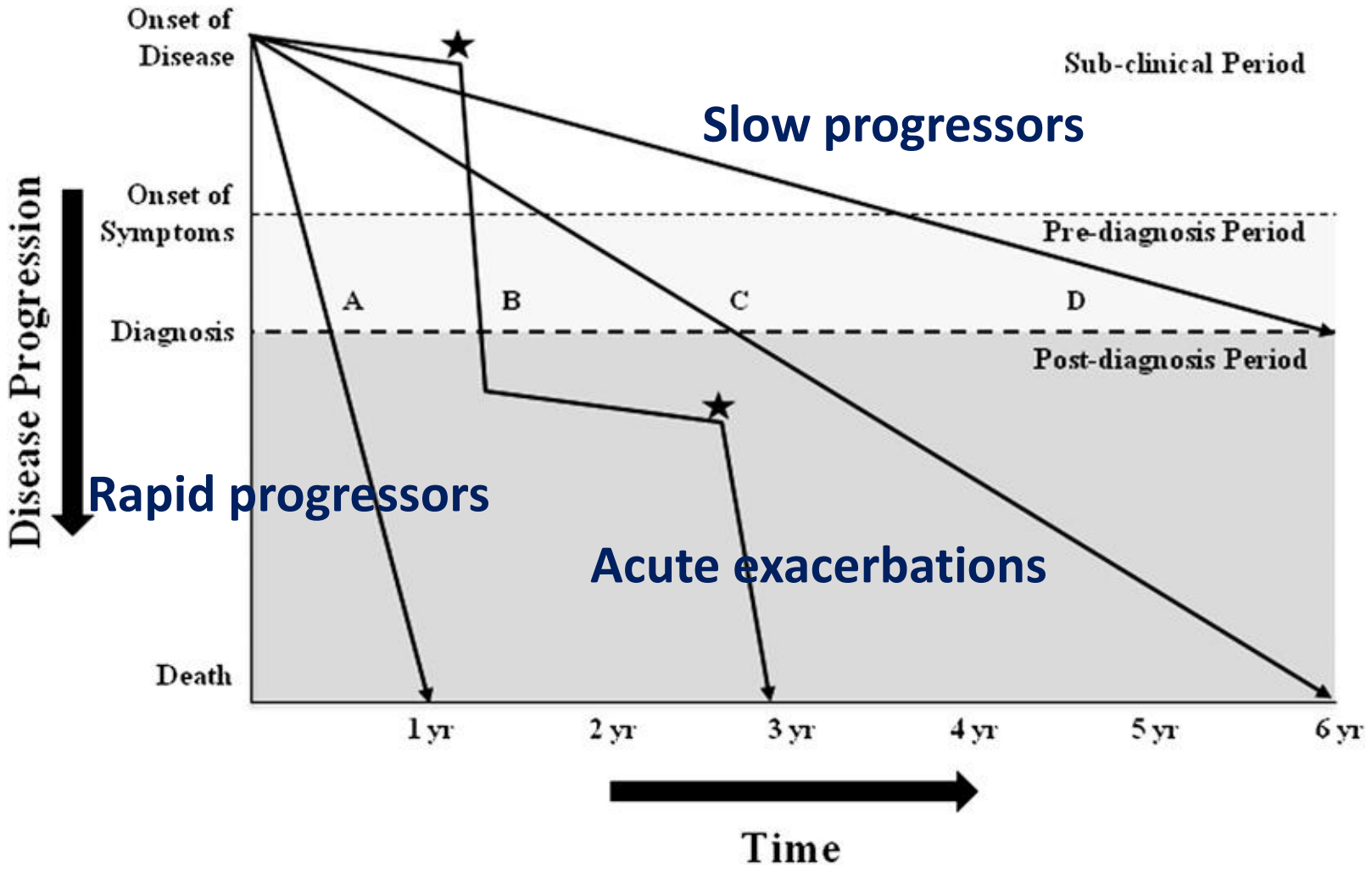
Ιδιοπαθής Πνευμονική Ίνωση & Συννοσηρότητες

Θεόδωρος Καραμπιτσάκος
5η Πνευμονολογική Κλινική, ΓΝΝΘΑ «ΣΩΤΗΡΙΑ»

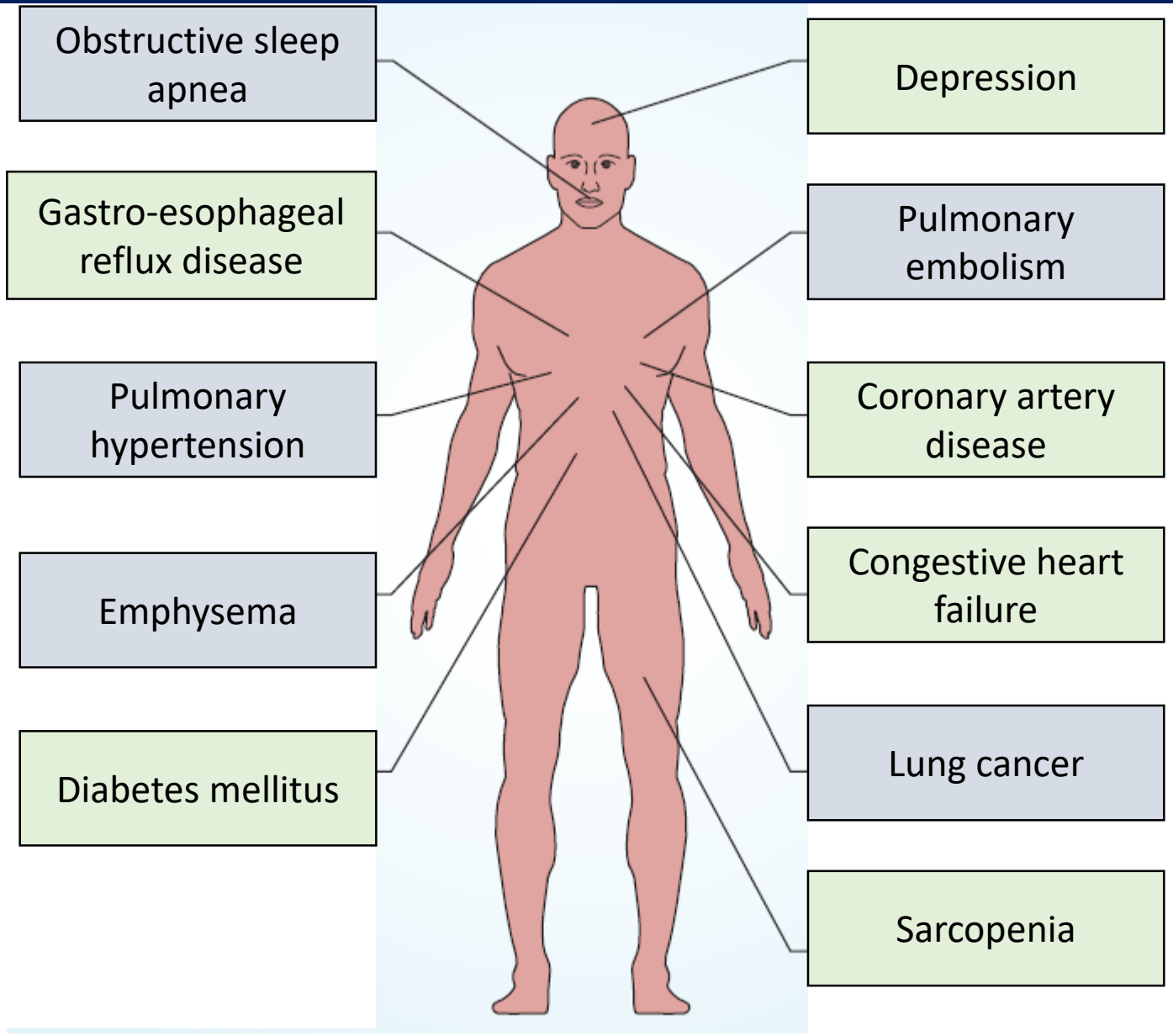


IPF - Highly unpredictable clinical course



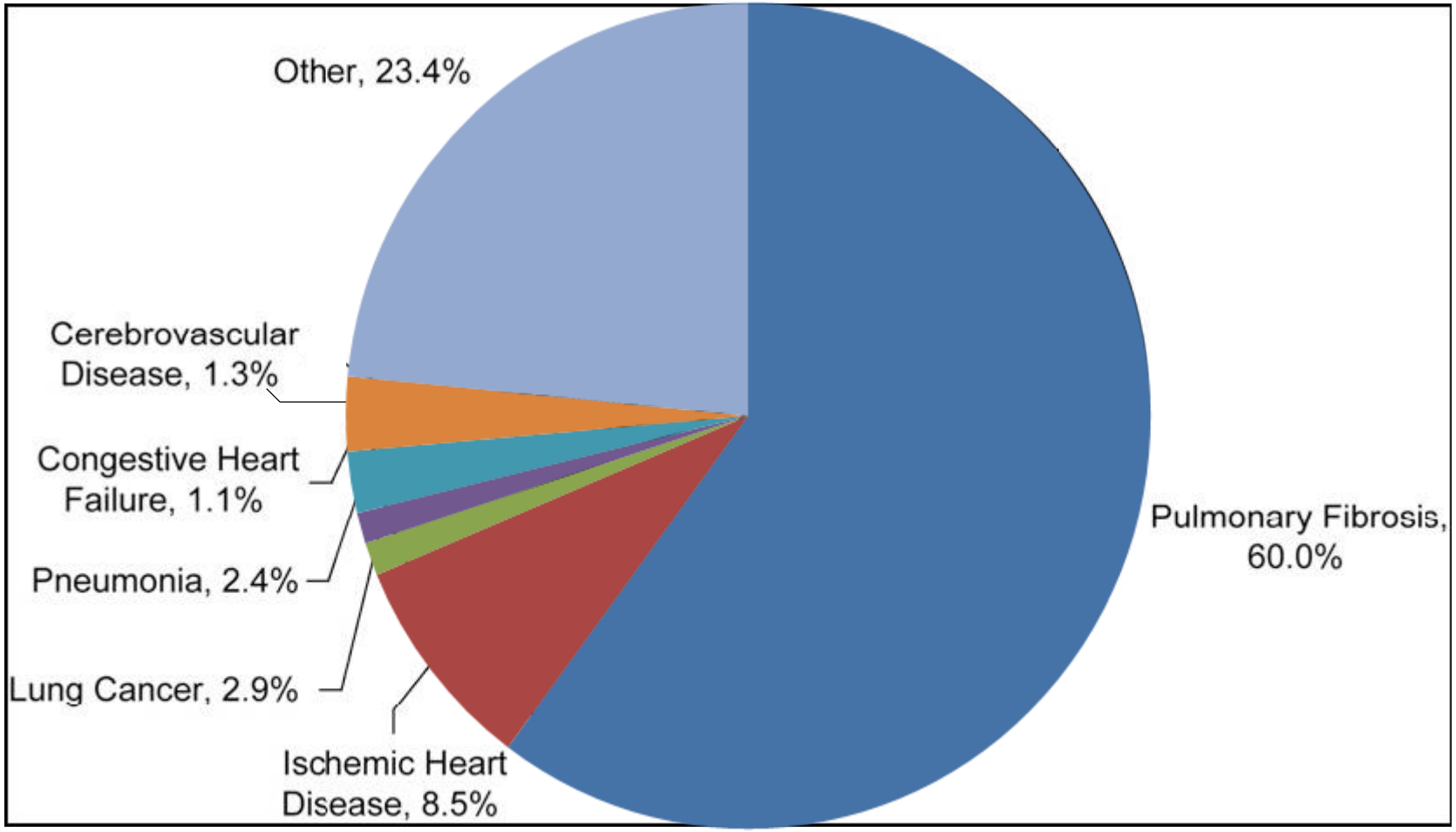
Ley et al. AJRCCM 2011;183:431-440

Comorbidities in IPF



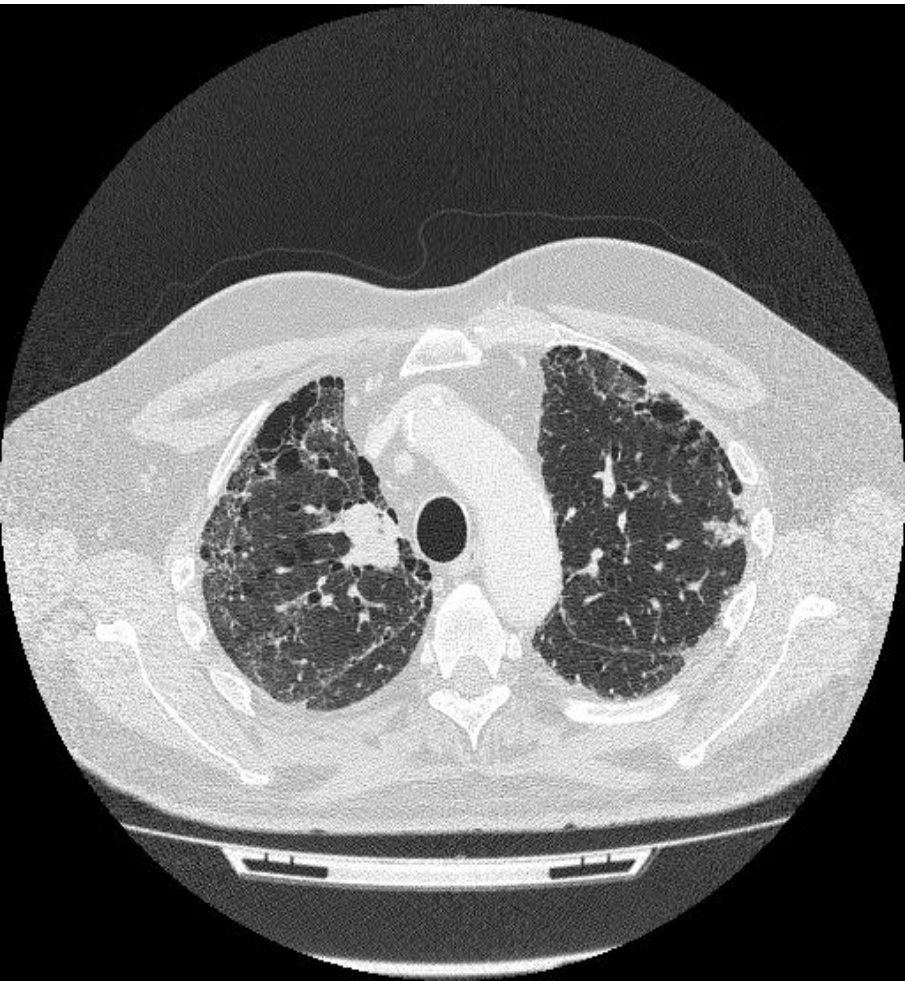
King CS. *Lancet Respir Med* 2016

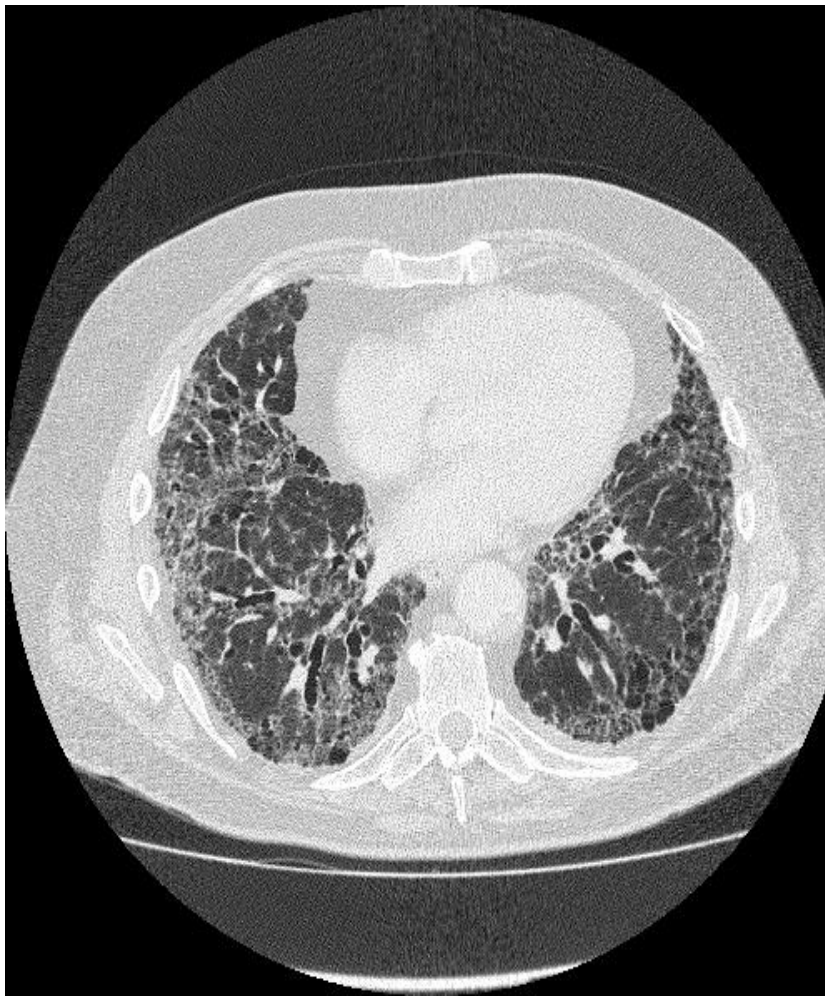
Mortality in IPF



Olson AL. *AJRCCM* 2007

Lung cancer in IPF





IPF RISK FACTOR FOR LUNG CANCER

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]

[a] First Academic Department of Pneumonology, Hospital for Diseases of the Chest, "Sotiria", Medical School, National and Kapodistrian University of Athens, Athens, Greece

[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

Επιδημιολογία καρκίνου πνεύμονα σε IPF 2.7 -31.3 %

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

Πλακώδες καρκίνωμα ο πιο συχνός ιστολογικός τύπος σε IPF (35-46%)

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

EPIDEMIOLOGY

PLOS ONE

RESEARCH ARTICLE

Lung cancer in idiopathic pulmonary fibrosis: A systematic review and meta-analysis

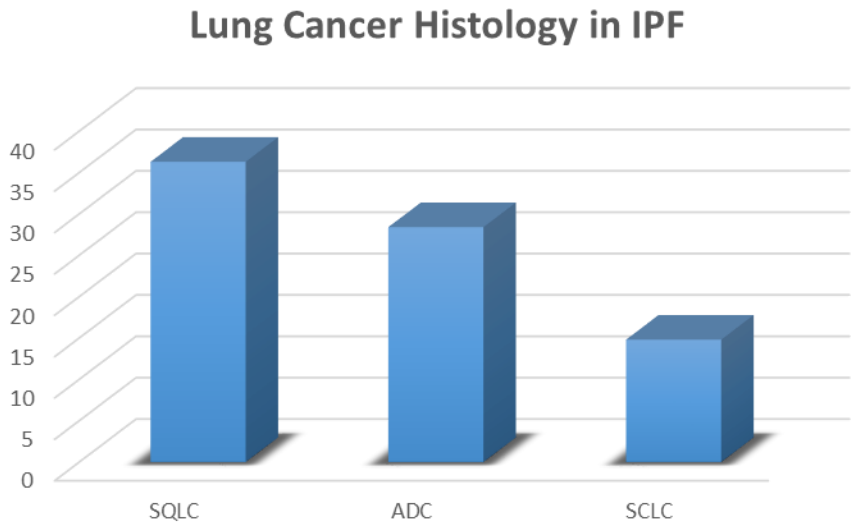
AliReza JafariNezhad[1☯], Mohammad Hossein YektaKooshali[1,2☯*]

PLOS ONE | https://doi.org/10.1371/journal.pone.0202360 August 16, 2018

- **35 (0.18% studies included)**
- **Prevalence of LC in IPF: 13.54% - x9 in men**
- **38% SQCC, 31% ADC, 20% SmCC, 5%LCC, 4% Adeno-squamous**
- **31% stage III, 13% stage II**
- **84% peripheral area, 16% central – RLL most common**

GREEK COHORT

CHARACTERISTICS	BASELINE DATA (N,%)
Total patients with IPF	**835**
Patients with IPF and lung cancer	**88/835 (10.5%)**
Males/ Females	82/6
Age (mean ± SD), years	71.8 ± 7.1
FVC %pred (mean ± SD)	73.5 ± 18.9
DLco %pred (mean ± SD)	45.3 ± 15.6
Both lung and other type of cancer	6/88 (7%)
Non-small cell lung cancer	68/88 (77.3 %)
Squamous cell carcinoma	32/88 (36.3 %)
Adenocarcinoma	25/88 (28.4 %)
Small cell lung cancer	13/88 (14.8 %)
Lung cancer post IPF diagnosis	60/88 (68%)
Median latency time (months) + SD	15.9 + 35.5
Lung cancer and IPF synchronously	26/88 (29.3%)
Lung cancer prior IPF diagnosis	2/88 (2.2%)
Median survival (months)	27.4 months (95% CI: 20.6 to 36.8).



ERS Madrid 2019

PATHOGENETIC COMMONALITIES

SCARCINOMA

Is there a direct relationship between fibrotic areas and cancer development?

Vancheri *BMC Medicine* (2015) 13:220
DOI 10.1186/s12916-015-0478-1

BMC Medicine

Idiopathic pulmonary fibrosis: diagnosis, management and new therapies

OPINION Open Access

CrossMark

Idiopathic pulmonary fibrosis and cancer: do they really look similar?

Carlo Vancheri

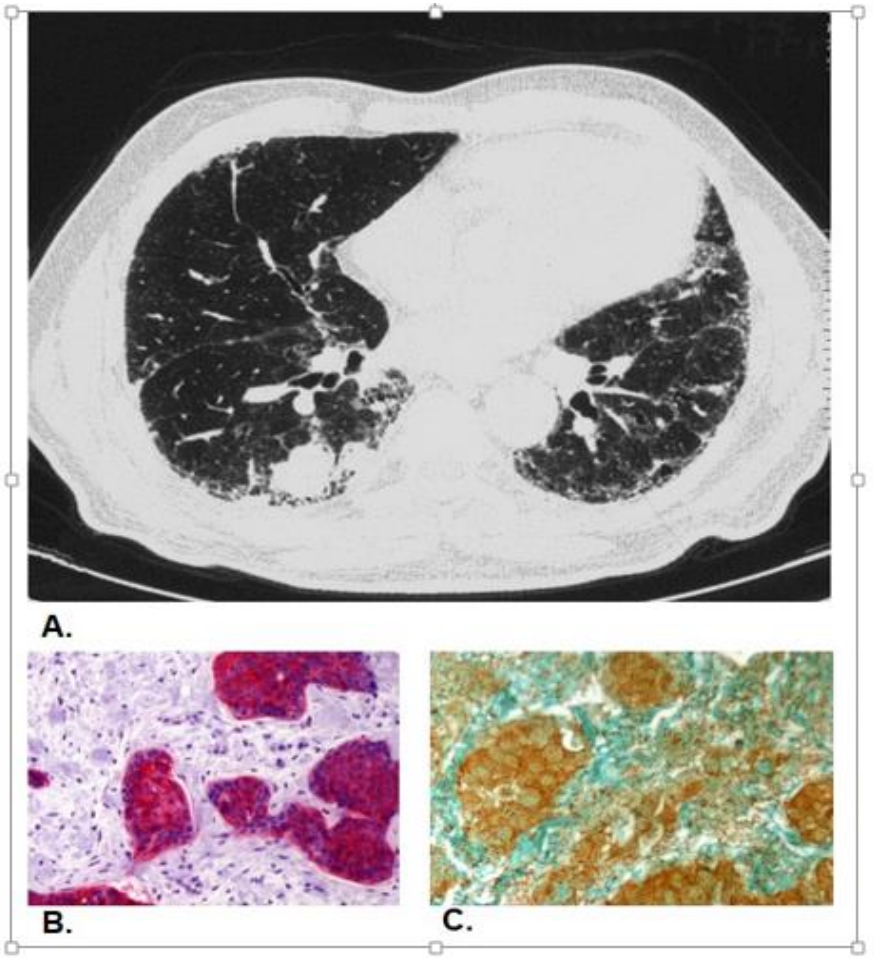


Figure 1: A) High Resolution Computed Tomography of a 78-years-old male with IPF and squamous cell carcinoma. B) CK-18 positive cancer cells in a fibrotic lung stroma. C) Masson stain positive for fibrosis in lung stroma surrounding solid nests of cancer cells.

This phenomenon has been coined out as

'' scarcinoma''

CLINICAL DATA

Patients v
IPF for th

i.Increas

ii.Increas

iii.Relaps

iv. Comp
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pneumo

Negative

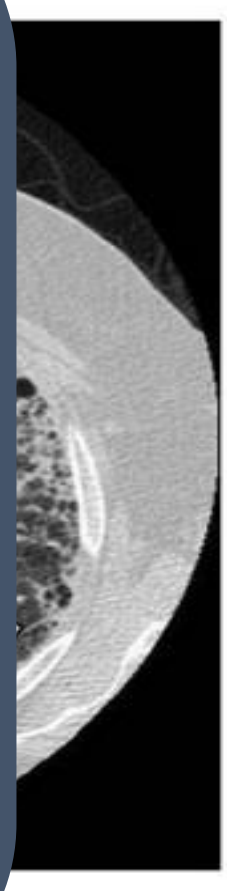
i.Increas

ii.Decrea

iii.Male ge
definite UIP pa

How do we approach a patient with IPF and a nodule?

How do we approach a patient with IPF and lung cancer?



Sato J Thorac Cardiovasc Surg2015 Fujimoto Ann Thorac Surg 2003

Lancet Respir Med 2017
Published Online
December 11, 2017

Patients with IPF and lung cancer: diagnosis and management

*Argyris Tzouvelekis, Paolo Spagnolo, Francesco Bonella, Carlo Vancheri, Vasilios Tzilas, Bruno Crestani, Michael Kreuter, Demosthenes Bouros

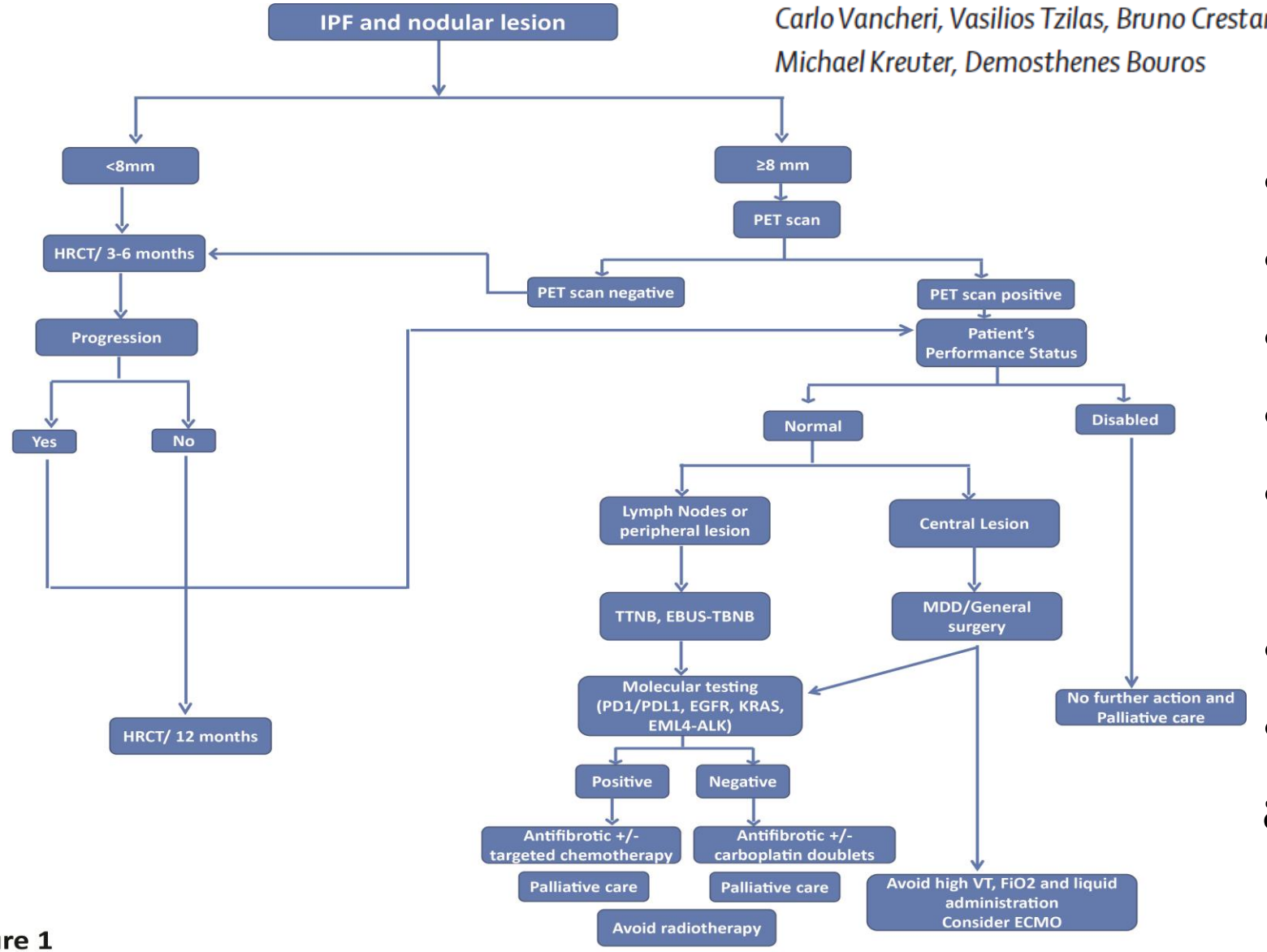


Figure 1

- LDCT/PET scan
- PFS
- Location of the lesion
- Avoid irradiation
- Beware of surgical interventions
- Platin doublets/1st line
- Don't discontinue antifibrotics

FUTURE PERSPECTIVES

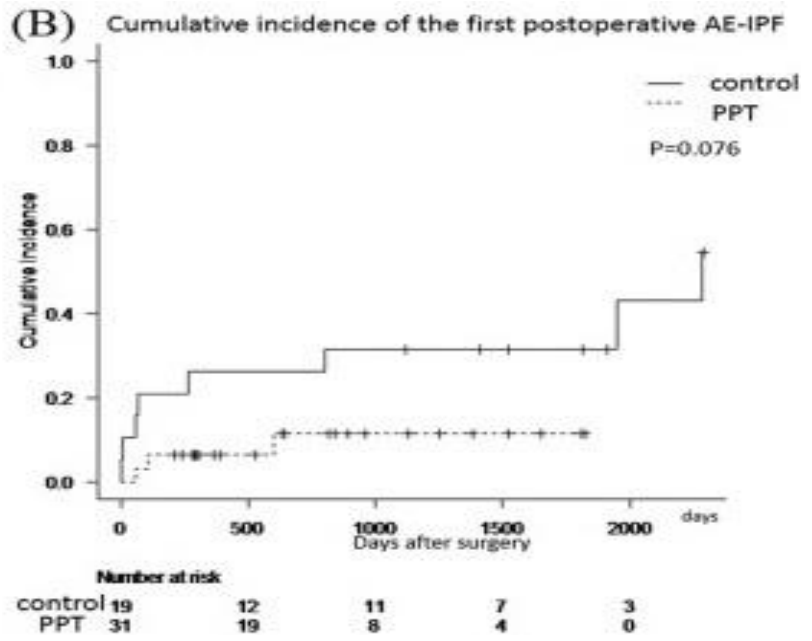
The approval of nintedanib and pirfenidone alters the scenario:

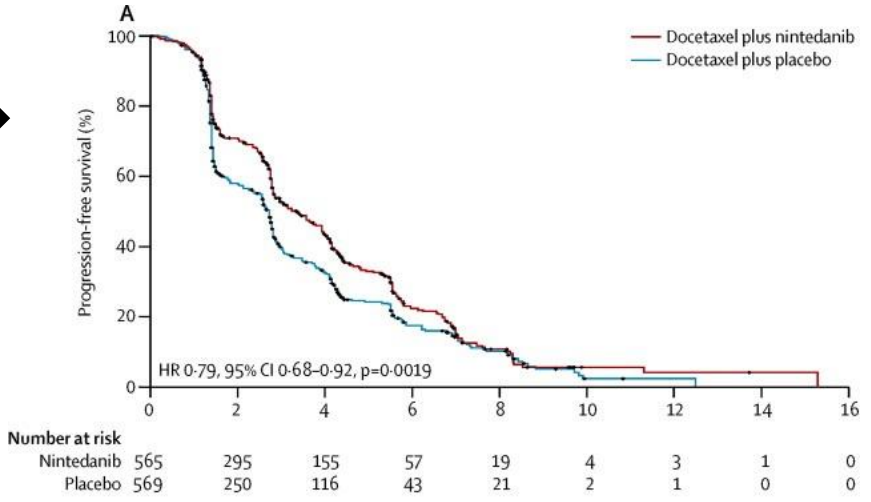
i. Pirfenidone **decreases** the incidence of lung cancer (**2.9% vs 20.3%**)

ii. **Prophylactic effect** of preoperative treatment with pirfenidone for postoperative acute exacerbations (**3.2% vs 21.1%** within 90 postoperative days)

iii. Nintedanib **improves** the outcome for docetaxel-based second-line therapy especially for patients with **adenocarcinoma**

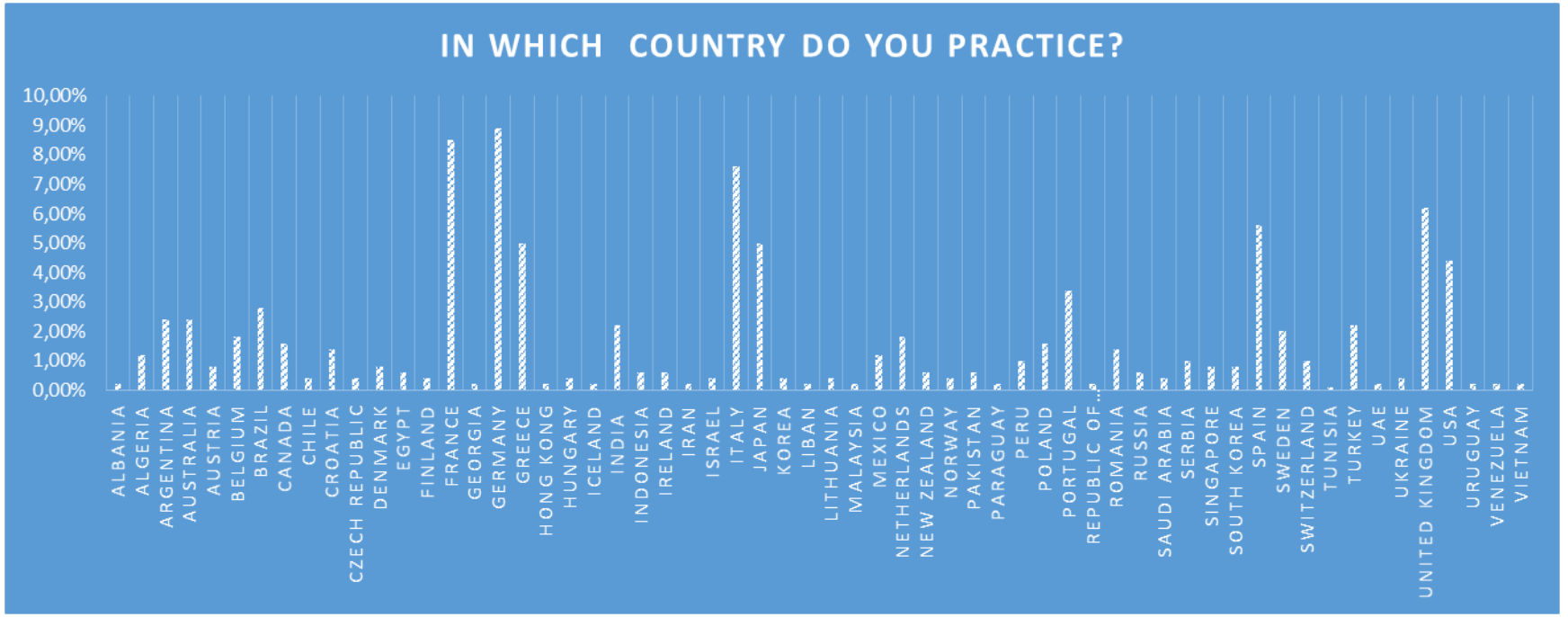
iv. Drug **repositioning** like nintedanib (pan-class I **PI3K/mTOR** inhibitor ?)





Yazaki Chest 2016 *Iwata Ann Thorac Surg 2016* *Reck Lancet Oncol 2014* *Mercer Thorax 2016*

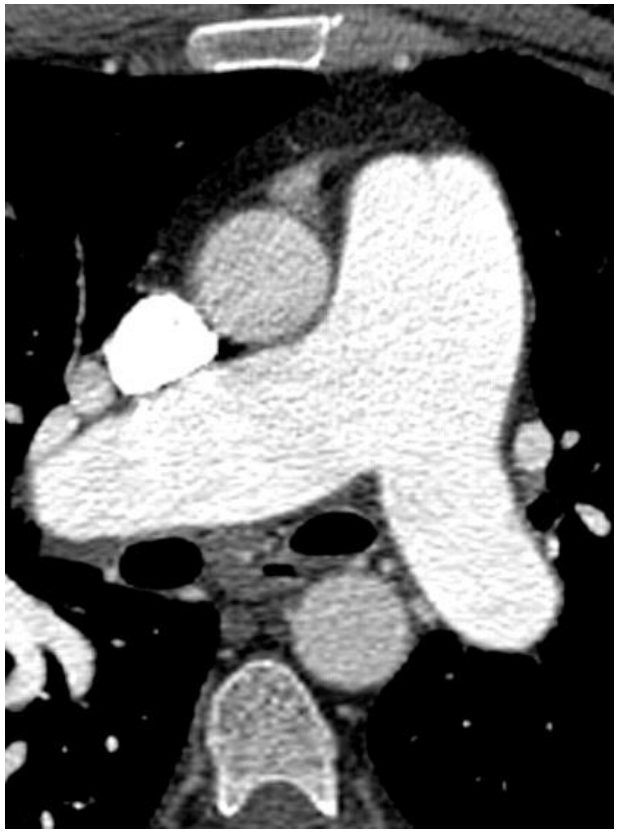
DIagnosis And Management Of lung canceR and FibrOSIS
“DI-A-M-O-R-F-OSIS” survey
494 answers from clinicians worldwide so far

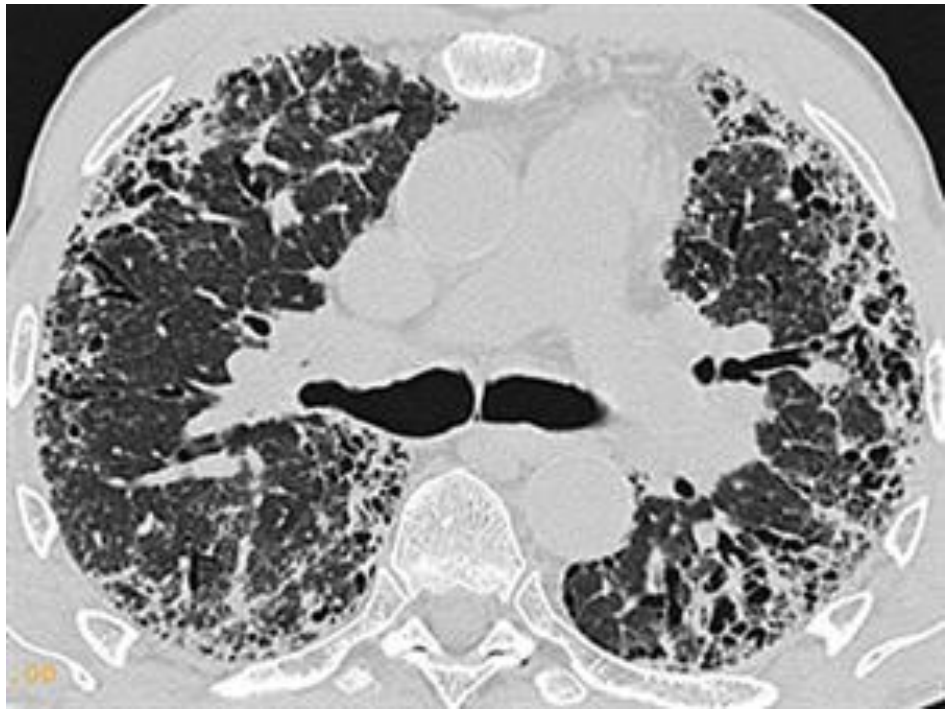


TAKE HOME MESSAGE

i. IPF is an independent risk factor for lung cancer (10-15% prevalence)
ii. Pathogenetic similarities - scarcinoma
iii. Need for a consensus for the management of patients with IPF-LC
iv. Pirfenidone and nintedanib alter the scenario? PD-1 inhibitors?
v. Early diagnosis is the key – Role of Liquid biopsies- EBUS/TBNB – low dose CT

Πνευμονική Υπέρταση και IPF





Classification of PH-Nice 2013

1. Pulmonary arterial hypertension

1.1 Idiopathic PAH

3. Pulmonary hypertension due to lung diseases and/or hypoxia

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emia,

stiocytosis,

e, Gaucher

tinitis,

chronic renal failure, segmental PH

tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease

3.2 Interstitial lung disease

3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4 Sleep-disordered breathing

3.5 Alveolar hypoventilation disorders

3.6 Chronic exposure to high altitude

3.7 Developmental lung diseases

Simonneau G et al. J Am Coll Cardiol 2013;62:D34-41

Pathogenetic Mechanisms

- Uncorrected hypoxaemia
- Aberrant angiogenesis
- Endothelial dysfunction
- Profibrogenic/vasoactive mediators (TNFα, PDGF, FGF)

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

EDITORIAL
WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

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

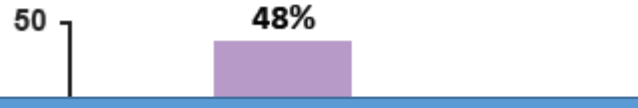
Is PH prevalent in IPF patients?

indicate that a mPAP >20 mmHg is the threshold for abnormal pulmonary arterial pressure (above the

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	2006	79	RHC	mPAP>25 mmHg	21.6
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

1. Disease stage
2. Diagnostic modality
3. mPAP threshold

Diagnostic accuracy of Echo

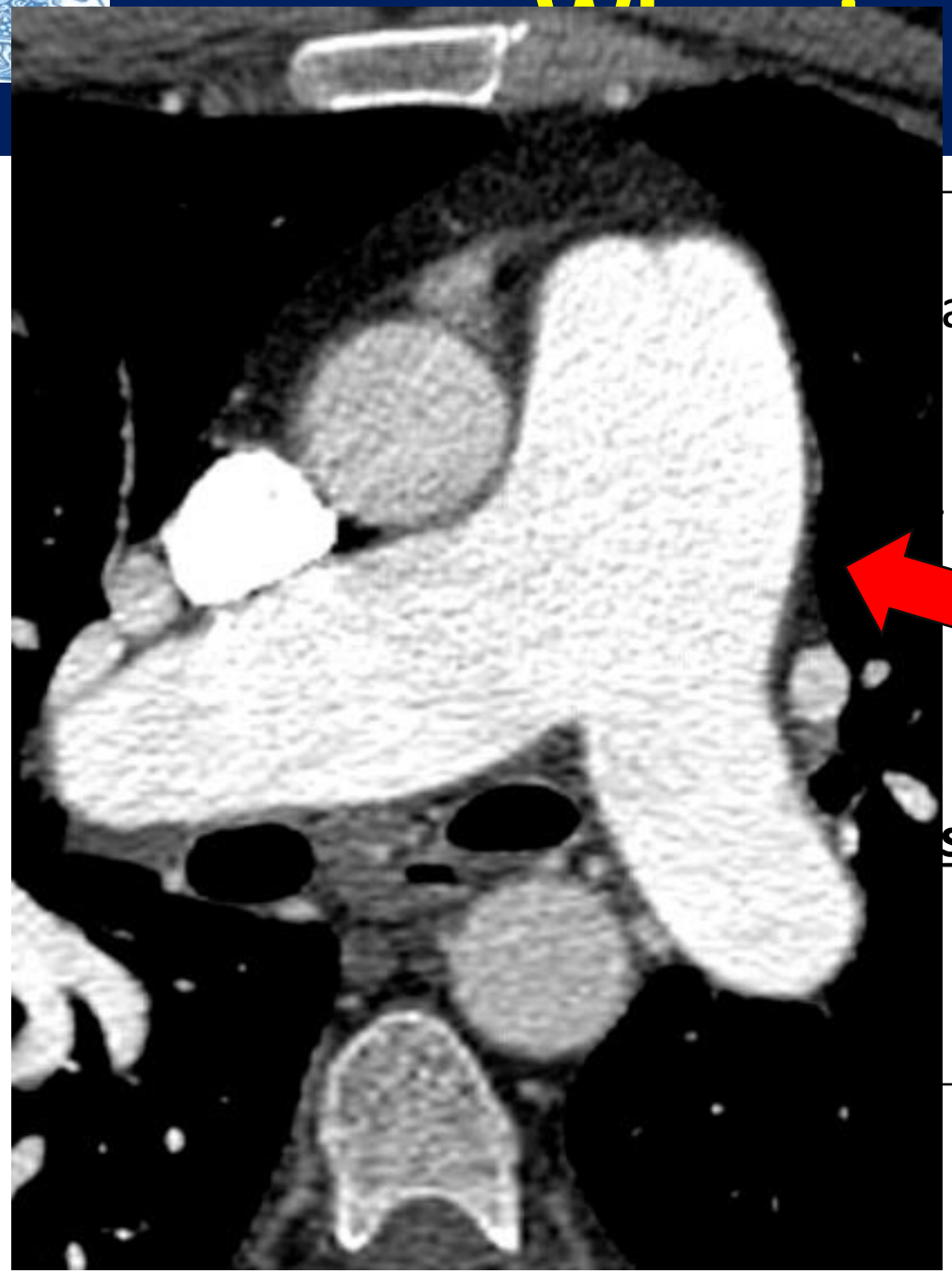


35% of IPF pts have emphysema!!
Poor acoustic window - Hyperinflation

✓ $RVSP_{ECHO}$ vs $PASP_{RHC}$

Nathan SD, et al. Respir Med. 2008;102:1305-1310
Arcasoy SM, et al. Am J Respir Crit Care Med. 2003;167:735-40

suspect PH in IPF



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- **6 Minute Walk Test**

✓Distance <200m

✓SpO2<88%

✓Pulse rate recovery <13 beats/min

- **HRCT**

✓Ratio of PA/AA>1

- **Echocardiography**

✓Elevated RVSP

✓RV/PA dilation

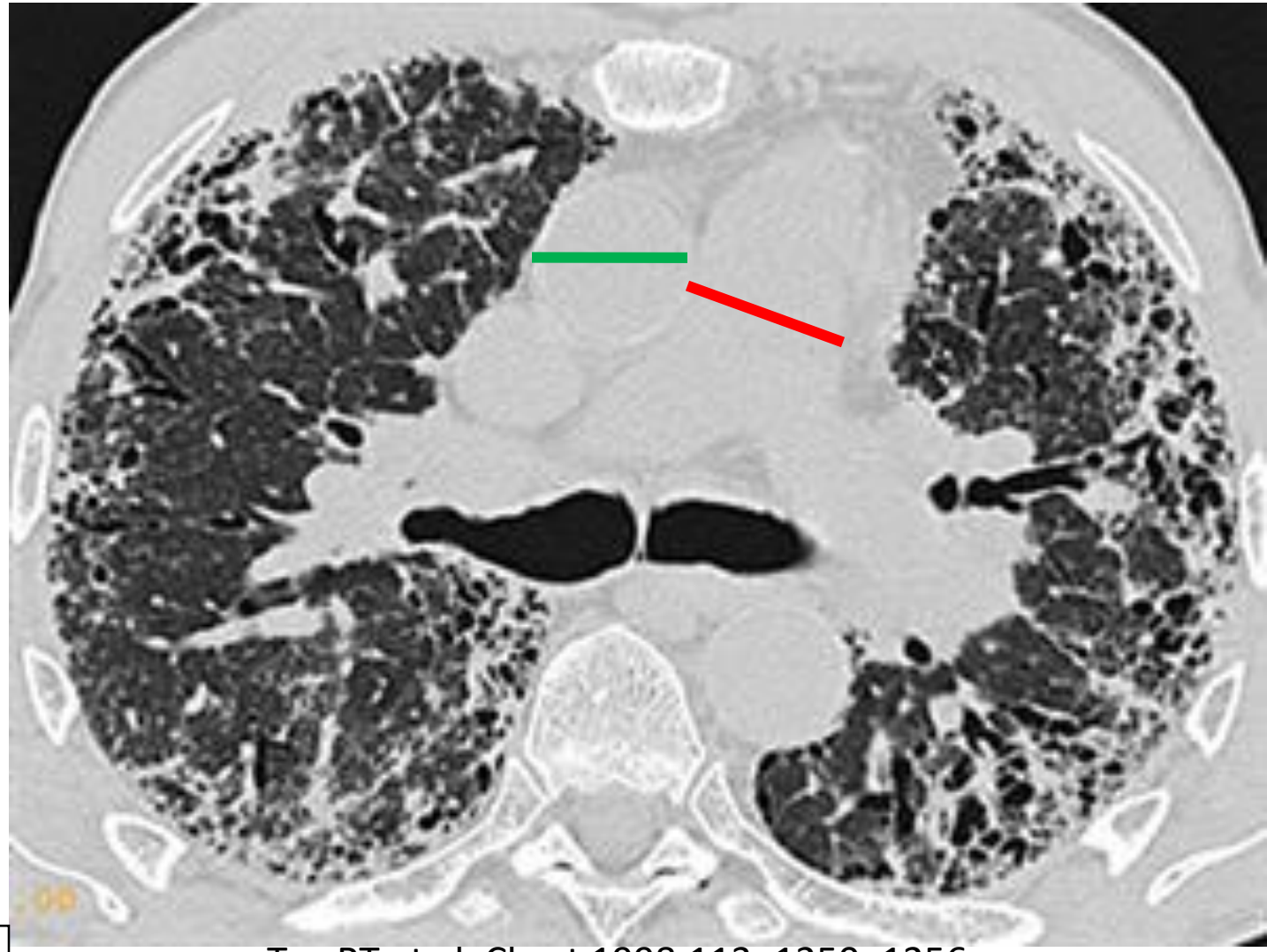
✓RV dysfunction

CT yield for PH diagnosis

- Pulmonary artery diameter ≥29 mm:

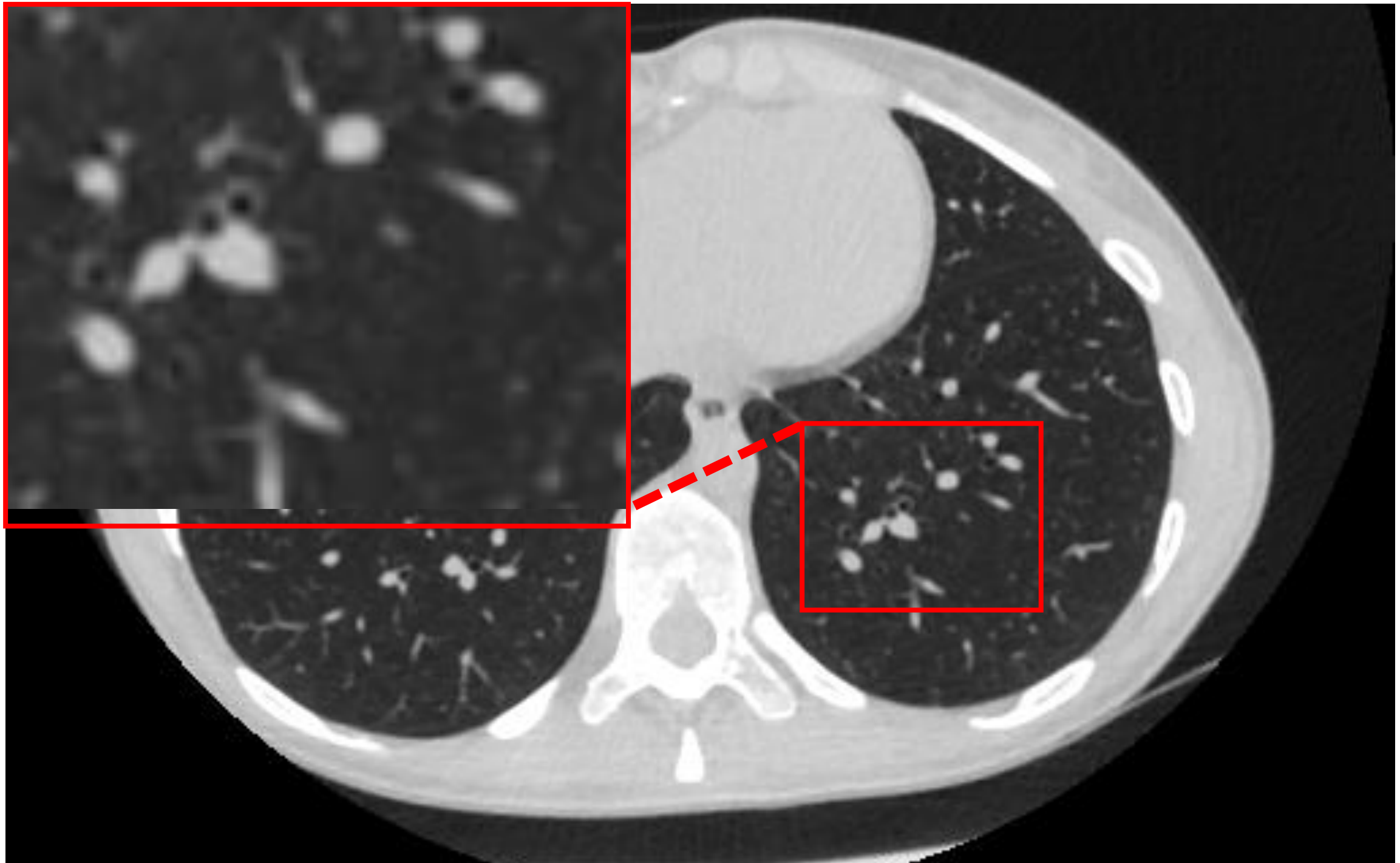
✓Positive predictive value: 97%

- In patients with pulmonary fibrosis, the PA dilates in the absence of PH.
- **dPA/dAA>1 is a more reliable indicator of PH**



Do not forget peripheral branches

Tan RT et al. Chest 1998;113: 1250–1256
Devaraj A. Radiology 2008;249:1042–1049



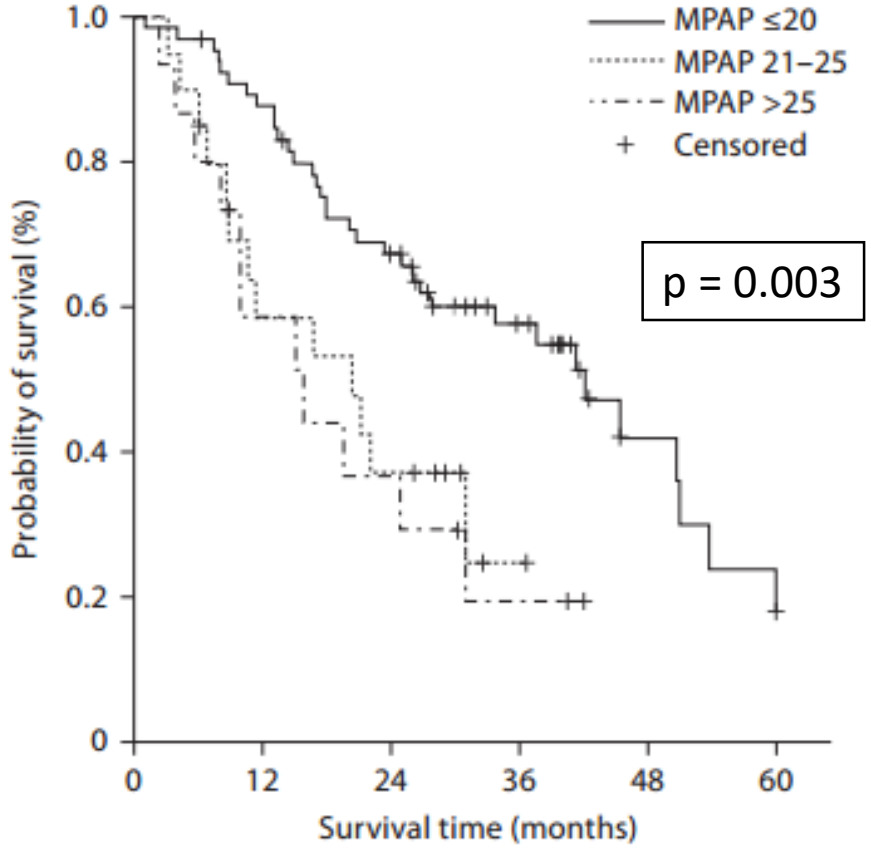
Does PH affect IPF survival?

Negative prognostic factor irrespective of disease severity

Initial Presentation

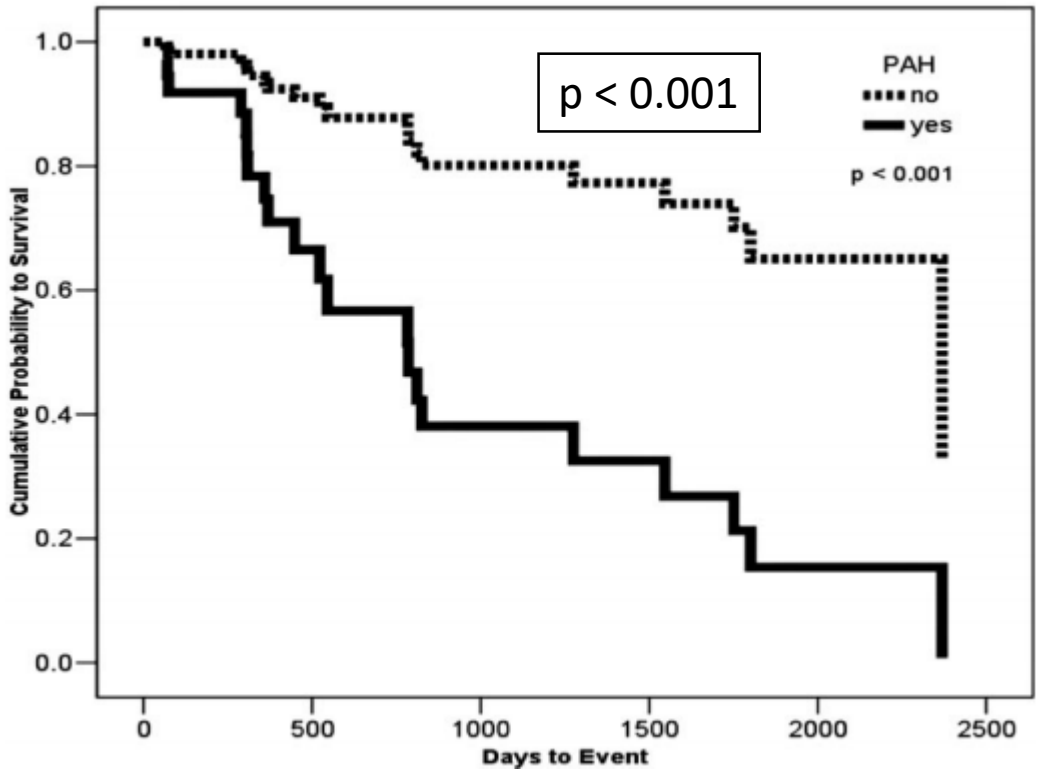
1 yr mortality w/o PH = 5%
1 yr mortality w PH = 35%

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

Therapeutic approaches

Target the PH or IPF? or both?

A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis

N Engl J Med 2010;363:620-8.

- **180 patients with advanced IPF – 1 year sildenafil (60 mgr) vs placebo**
- **No effect in primary end-point (6-MWD) – Negative study!!!!!!**
- **Positive secondary end-points (QoL, Dyspnea, DLCO)**

The NEW ENGLAND JOURNAL of MEDICINE

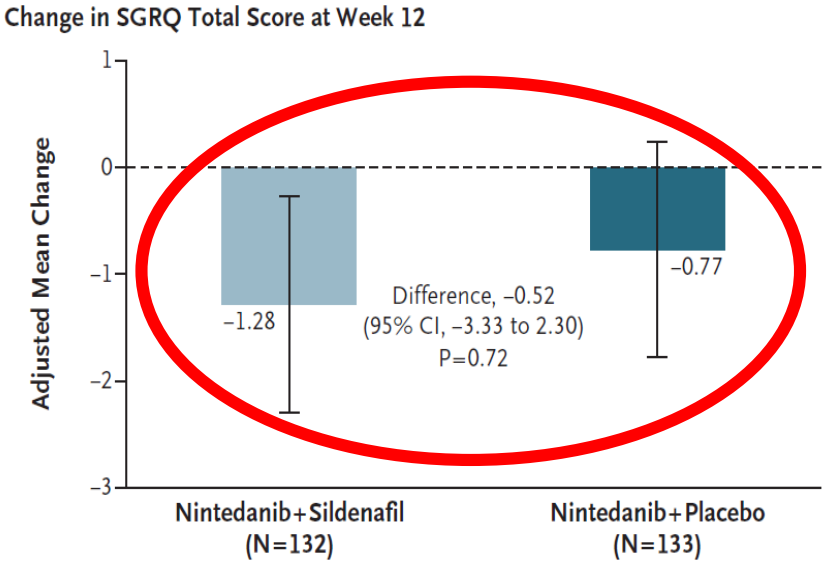
ORIGINAL ARTICLE

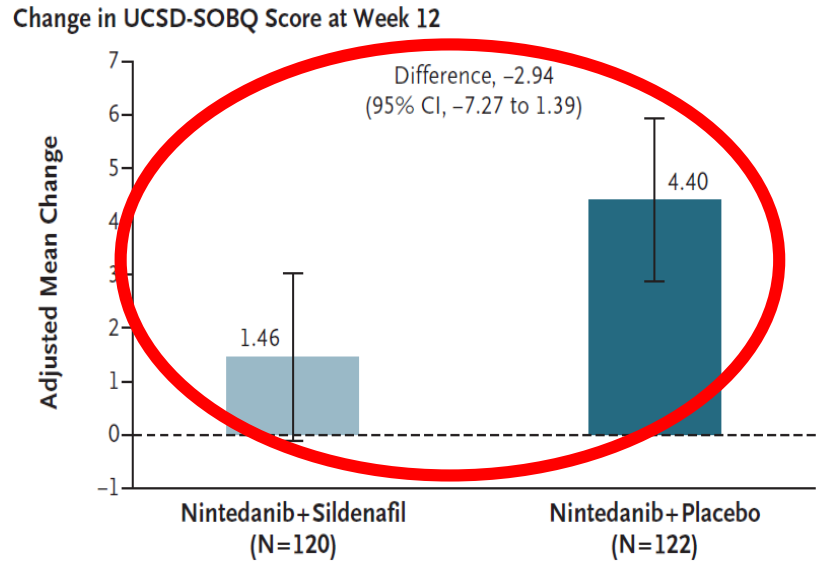
This article was published on September 15, 2018, at NEJM.org.

Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis

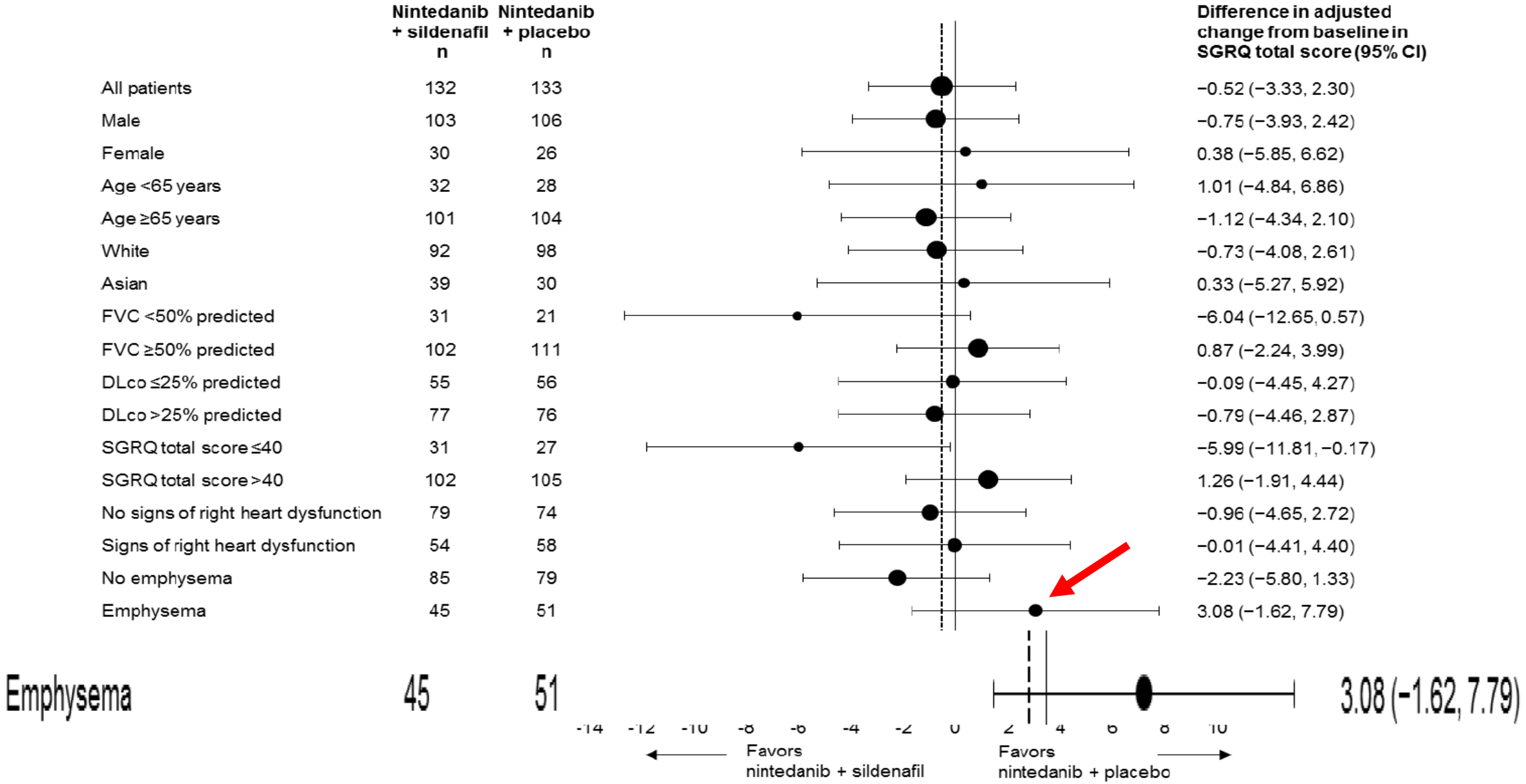
- **406 patients – 274 randomized (32% screening failure)**
- **Nintedanib 150 mg (bid) + Sildenafil 20 mg (tid)/placebo (1:1)**
- **No difference in SGRQ (primary end-point)**
- **No difference in UCSD dyspnea score (primary end-point)**
- **Negative study….**

BUT……





Subgroup Analysis

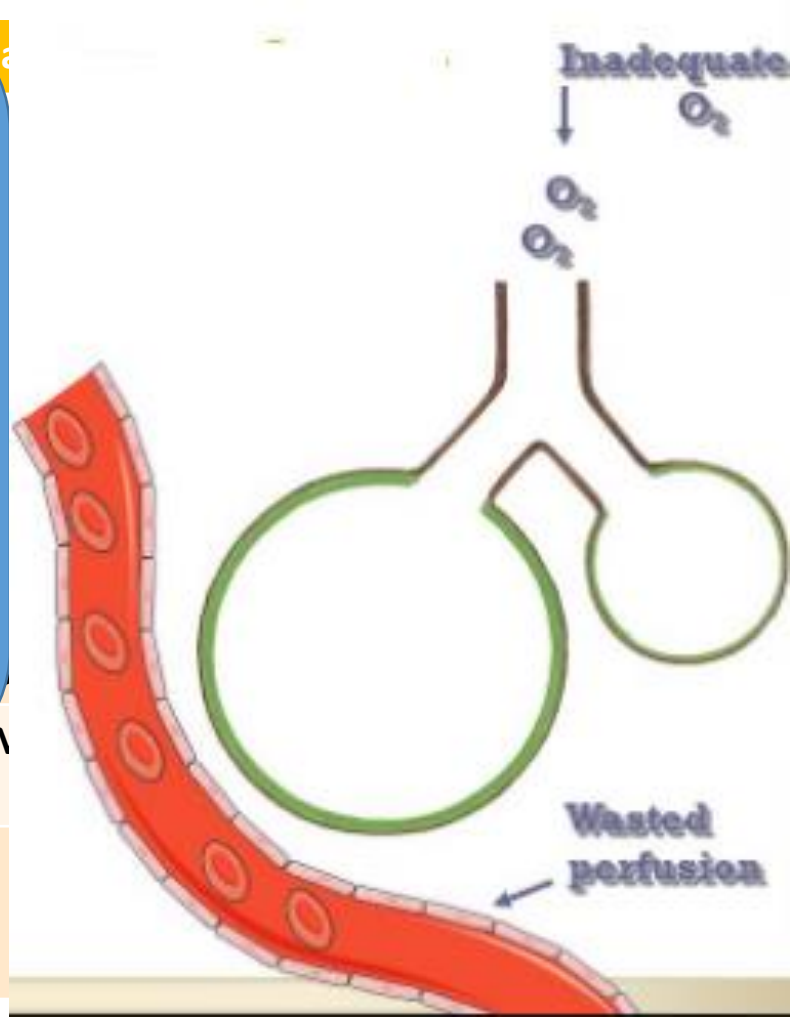


Major Clinical trials in Patients with IPF-PH

Do not dilate remodeled vessels!!

Worsens V/Q mismatch w/o CO improvement

				weeks	
Riociguat	**RISE-IIP**	**2017**	**Major IIPs**	**26 weeks**	



What lies in the future?

FEATURED ARTICLES

Long-term safety and efficacy of imatinib in pulmonary arterial hypertension

- **Extension trial – 204 weeks -144 patients**
- **93% drop outs!!!**
- **6 hematomas – 17 deaths!!!**

CONCLUSIONS: Severe adverse events, significant side effects, and a high discontinuation rate limit the utility of imatinib in the treatment of PAH. These risks outweigh any possible improvements in hemodynamics and walk distance seen in those patients able to remain on drug. The off-label use of this compound in PAH is discouraged.

J Heart Lung Transplant 2015;34:1366–1375

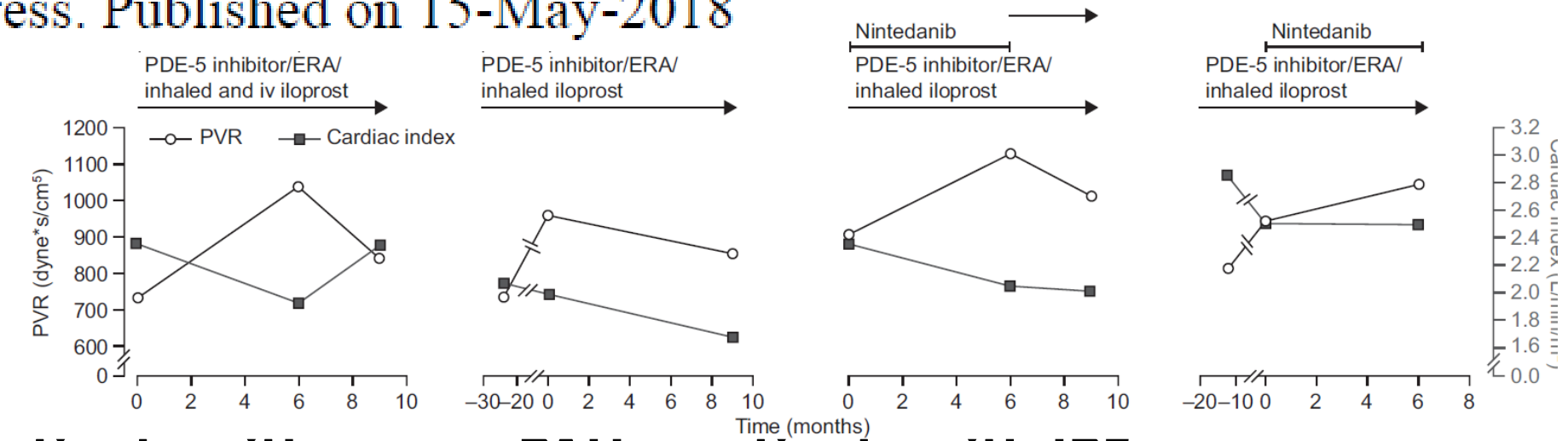
Chronic Treatment Of Nintedanib Ameliorates The Development Of Pulmonary Hypertension In Rat Model

T. Takeo[1], T. Nagaoka[1], Y. Suzuki[1], T. Yoshida[1], E. Kuwasaki[1], S. Kuriyama[1], Y. Morio[1], K. Takahashi[1]

Conclusion: Nintedanib ameliorated pulmonary hemodynamics via inhibition of smooth muscle cell proliferation in PAH rat model, and might be a novel treatment for PAH. **ATS abstract 2016**

Nintedanib in Severe Pulmonary Arterial Hypertension

AJRCCM Articles in Press. Published on 15-May-2018



- **Animal model – 4 patients with severe PAH – patients with IPF**
- **Detrimental effects in all cases (experimental – human) !!! – No effect of PH in IPF patients receiving Nintedanib**

Pulmonary Pharmacology & Therapeutics 50 (2018) 38–46

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

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,*]

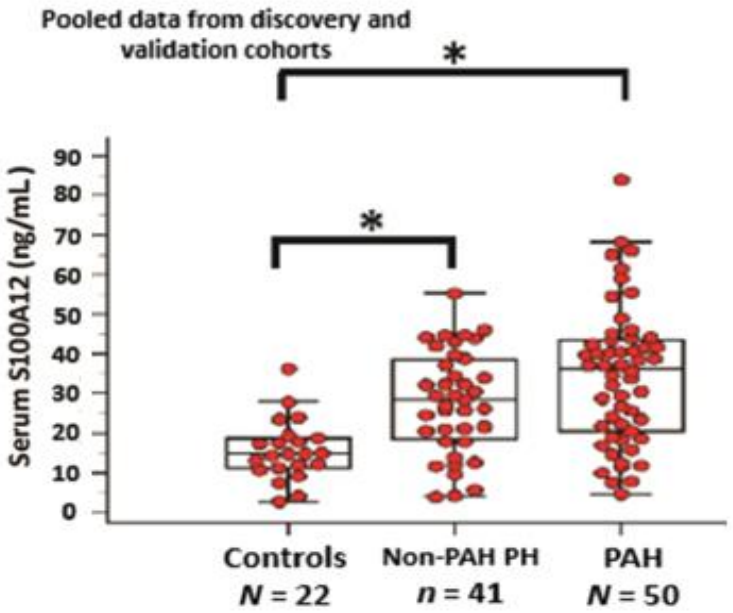
Pulmonary Pharmacology & Therapeutics 50 (2018) 38–46

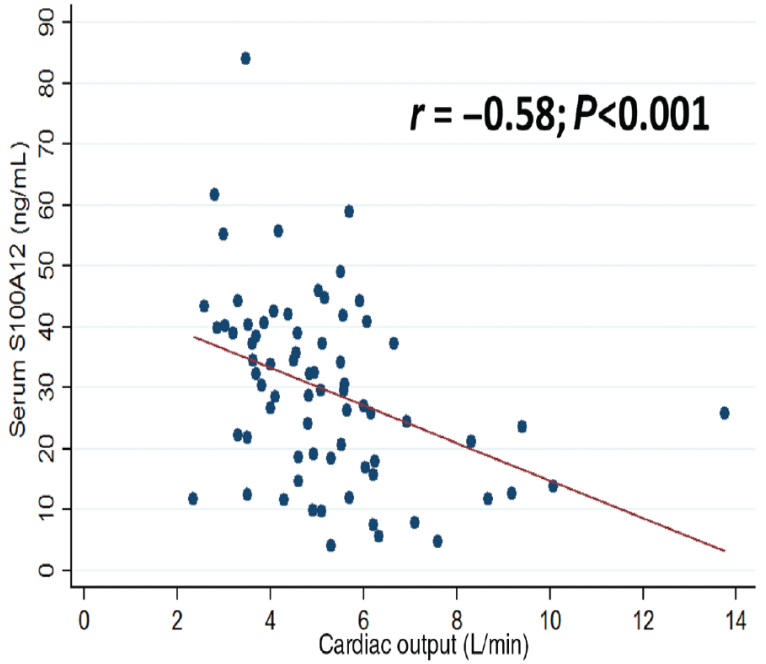
- **Do not dilate remodeled vessels, do not worsen V/Q mismatch**
- **Inhibiting pulmonary fibrosis and concomitantly targeting vascular remodeling and increasing vasodilation in well (but not in poorly) ventilated areas**
- **An open question is the optimal management of patients with severe PH not necessarily explained by the severity of underlying fibrosis**

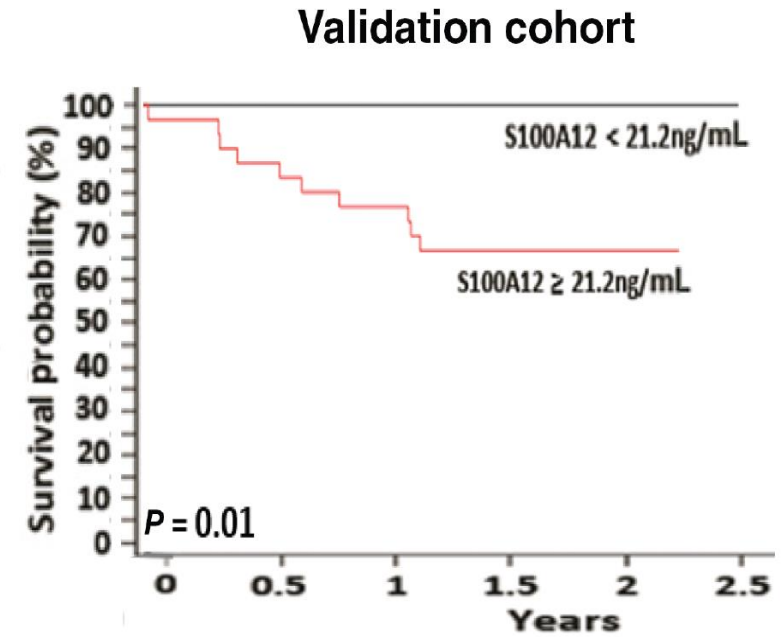
Need for biomarkers

S100A12 as a marker of worse cardiac output and mortality in pulmonary hypertension

ARGYRIOS TZOUVELEKIS,[1] JOSE D. HERAZO-MAYA,[1] CHANGWAN RYU,[1] JEN-HWA CHU,[1] YINGZE ZHANG,[2] KEVIN F. GIBSON,[2] PERCY K. ADONTENG-BOATENG,[1] QIN LI,[1] HONGYI PAN,[1] BENJAMIN CHERRY,[1] FERHAAN AHMAD,[3] HUBERT J. FORD,[4] ERICA L. HERZOG,[1] NAFTALI KAMINSKI[1] AND WASSIM H. FARES[1]







Take home messages

- **RHC is the gold standard diagnostic modality – Select patients on U/S**
- **Negative prognosticator**
- **Suspect PH when: “disproportionate” dyspnea+ LOW DLCO, 6MWD< 200m, dPA/dAA>1**
- **No approved vasoactive therapy– DO NO HARM!!!!! – BEST SUPPORTIVE CARE, LTOT to maintain arterial oxygen saturation> 90%, diuretics, referral for lung transplantation, enroll in clinical trials**
- **Need for biomarkers, BNP limited used, only prognostic role**
- **Identify and exclude patients with worse V/Q mismatches**

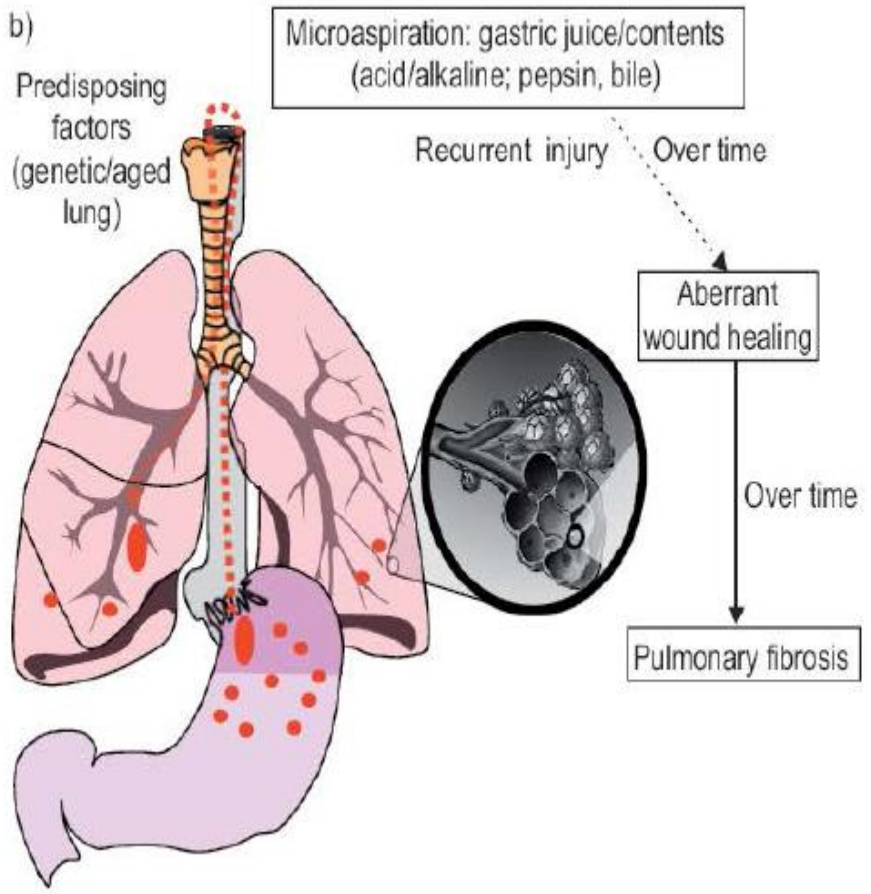
Gastro esophageal reflux disease (GERD)

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

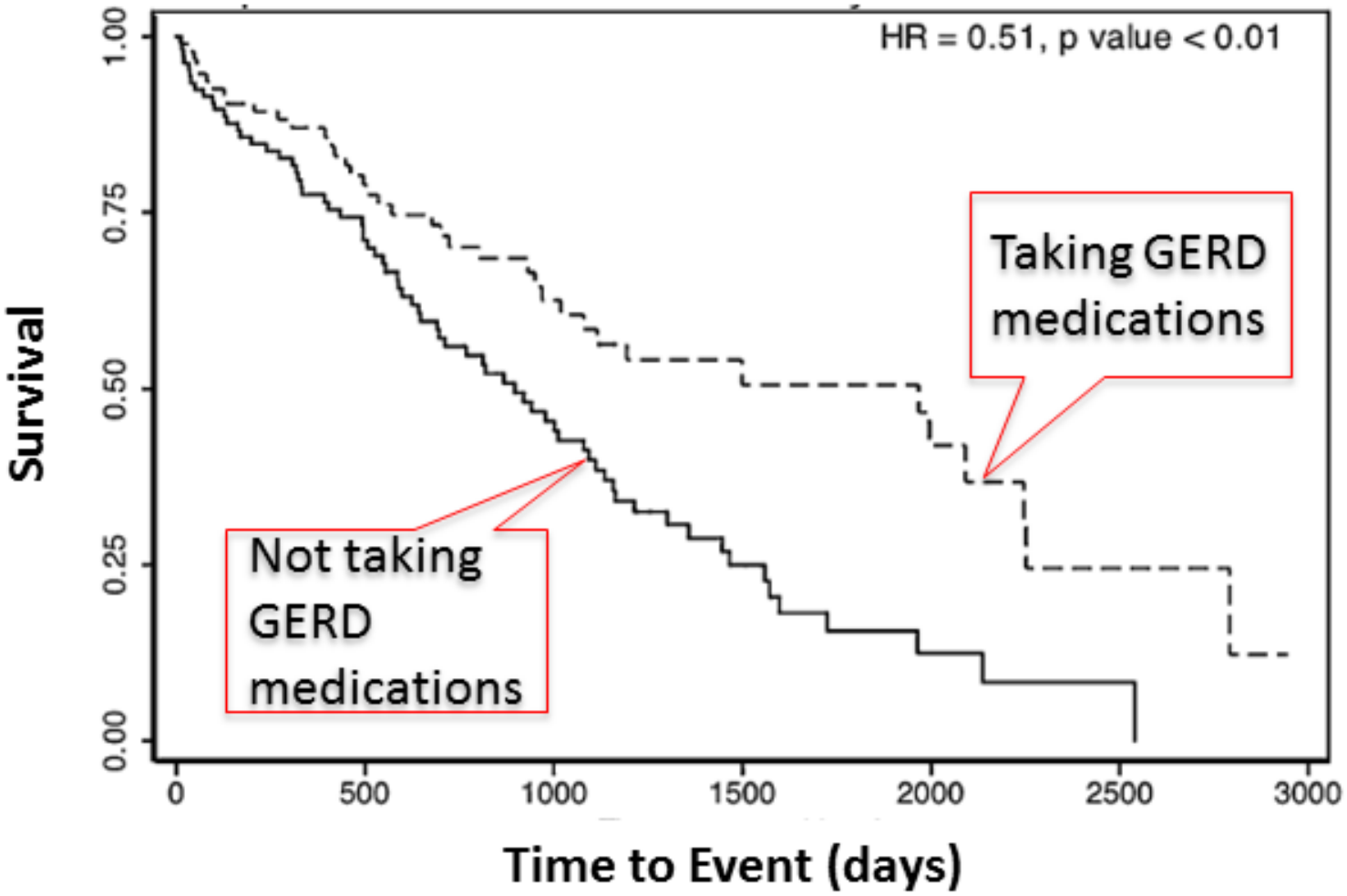
Patients with asymmetric IPF are more likely to have GERD and AEIPF than patients with symmetric IPF.

Diagnosis
Barium swallow
Esophageal manometry
24h pH probe
Esophageal Impedance



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

GERD TREATMENT AND SURVIVAL



Lee JS. *AJRCCM* 2011

Laparoscopic anti-reflux surgery
WRAP IPF TRIAL

	Surgery (n=29)	No surgery (n=29)	p value
Clinical events*			
Acute exacerbation	1 (3%)	4 (16%)	0·19
Respiratory hospitalisation	2 (7%)	6 (21%)	0·25
Non-elective hospitalisation	5 (17%)	8 (28%)	0·35
Lung transplantation	0	1 (3%)	>0·99
Disease progression†			
Death	1 (3%)	4 (18%)	0·13
10% FVC decline or death	2 (9%)	7 (29%)	0·038
10% FVC decline, acute exacerbation, or death	2 (9%)	7 (28%)	0·048
Respiratory hospitalisation or death	2 (9%)	5 (19%)	0·16
Non-elective hospitalisation or death	5 (17%)	7 (26%)	0·50
10% FVC decline, 5 point UCSD Shortness of Breath Questionnaire increase, respiratory hospitalisation, or death	15 (57%)	15 (56%)	0·74
Change in symptoms and physical function‡			
Visual analogue scale for cough severity	4·74 (−3·14 to 12·63)	7·15 (−2·01 to 16·31)	0·69
UCSD Shortness of Breath Questionnaire	−0·71 (−5·62 to 4·21)	−0·69 (−6·24 to 4·86)	>0·99
St George's Respiratory Questionnaire	1·04 (−3·66 to 5·74)	−3·18 (−8·35 to 1·99)	0·23
6-min walk distance, m	16·54 (−4·80 to 37·88)	9·13 (−14·77 to 33·02)	0·65

Data are n (%), n (Kaplan–Meier estimates), or slope estimate (95% CI). FVC=forced vital capacity. UCSD=University of California San Diego. *We used the χ^2 and Fisher's exact tests to calculate p values. †Rates are Kaplan–Meier estimates at 48 weeks. We used the log-rank test at 48 weeks to calculate p values. ‡Slope parameter estimates with 95% CIs from a mixed effects model with adjustment for baseline use of nintedanib or pirfenidone therapy.

Table 2: **Secondary endpoints**

GERD TREATMENT

ATS/ERS/JRS/ALAT Clinical Practice Guideline 2015

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

- **The Pilot Trial Of Omeprazole in Idiopathic Pulmonary Fibrosis (IPF) (PPIPF**; **NCT02085018)** -> ongoing

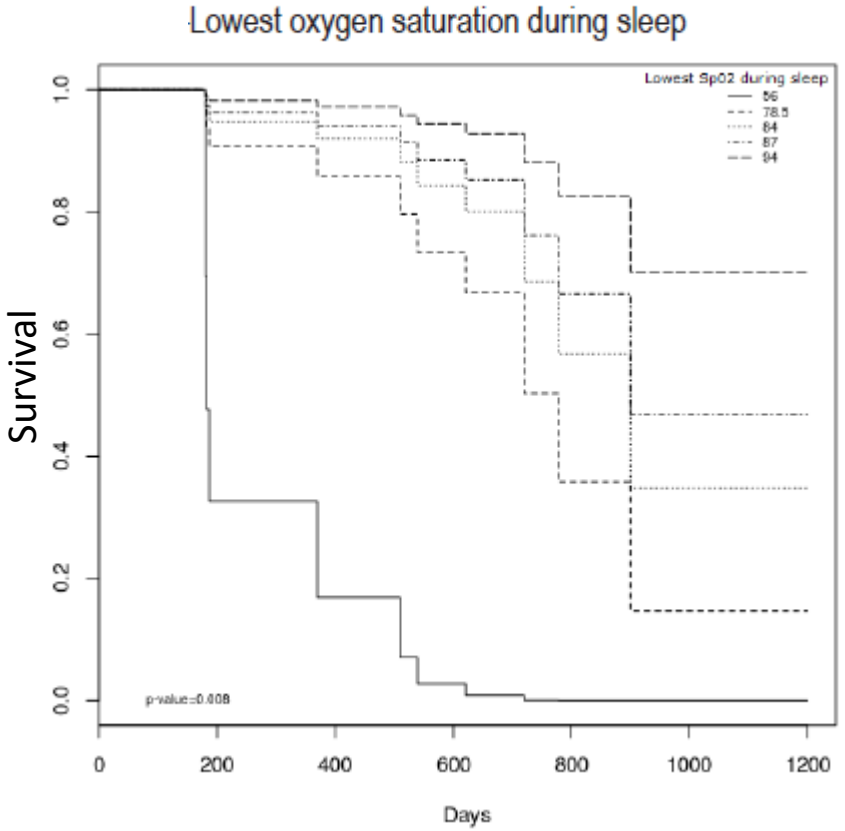
- **WRAP-IPF trial** -> safe, well tollerated, failed primary endpoint (FVC decline)

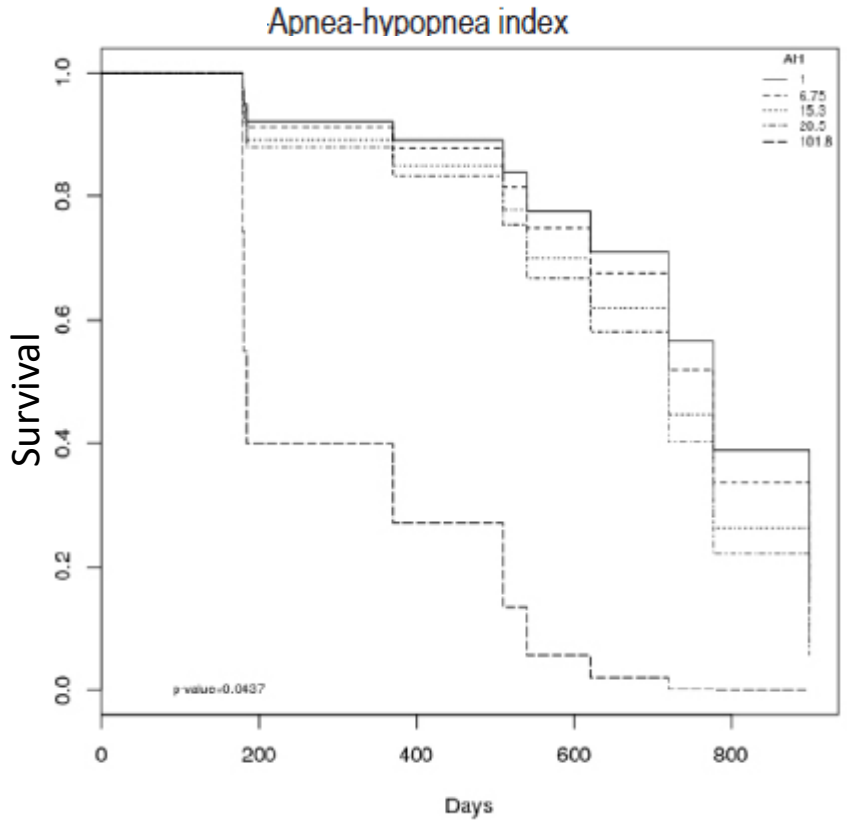
More RCTs are warranted

Raghu G. *AJRCCM* 2015
Raghu G. *Lancet Respir Med* 2018

Obstructive sleep apnea (OSA) in IPF

Study	Type	Dx IPF	Nº patients	Method	BMI	DLCO % pred	AHI >5
Aydogdu et al 2006	Prospective	ATS /ERS 2002	18	PSGN	-	65	12 **(65%)**
Mermigkis et al 2007	Retrospective	ATS /ERS 2002	18	PSGN	33.2	49.9	11 **(61%)**
Lancaster et al 2009	Prospective	ATS/ERS 2002	50	PSGN	32	45.4	44 **(88%)**
Mermigkis et al 2010	Prospective	ATS /ERS 2002	34	PSGN	27.3	53.6	20 **(59%)**
Kolilekas et al 2013	Prospective	ATS/ERS 2010	31	PSGN	28.6	43.7	28 **(89%)**
Pihtili et al 2013	Prospective	ATS/ERS 2002	14	PSGN	26.4	56.7	14 **(82%)**
Lee et al 2015	Retrospective	ATS/ERS 2002	20	PSGN	28.5	51.1%	9 **(45%)**
Gill et al 2017	Prospective	ATS/ERS 2002	45	PSGN	28.5	42.7	40 **(89%)**
Bosi et al 2017	Prospective	ATS/ERS 2010	35	PSGN	22.7	45.6	25 **(75%)**





Negative impact of nocturnal desaturation and AHI on survival in IPF patients

Kolilekas L. *J Clin Sleep Med* 2013

Obstructive sleep apnea (OSA) in IPF

32 patients diagnosed with both IPF and OSA

CPAP compliant vs non-compliant

At 5 years, survival 90% vs 40%

CPAP use may improve survival and quality of life

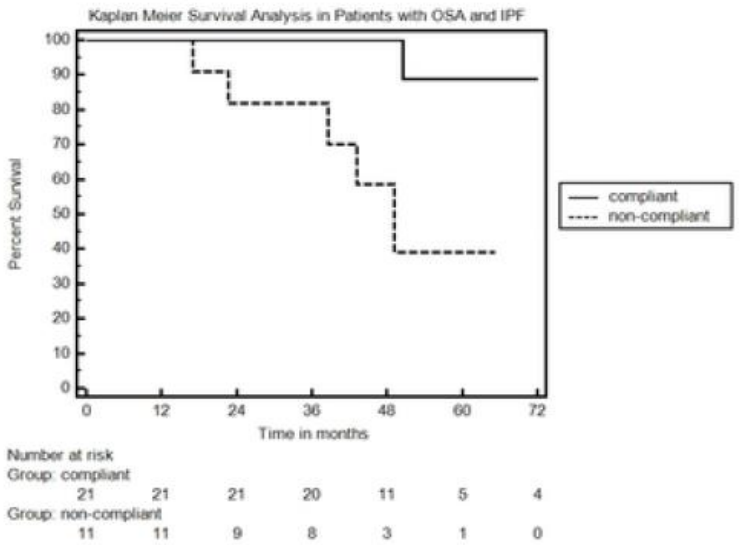


Table 2 Values of instruments used to assess quality of life and sleep at CPAP initiation and at the 1-year time point in the good and poor CPAP compliance group

	Good CPAP compliance group (n=37)			Poor CPAP compliance group (n=18)		
	CPAP initiation	After 1 year with CPAP	p	CPAP initiation	After 1 year with CPAP	p
ESS	9.2±5.6	5.8±3.8	0.04	7.1±3.2	6.2±5.5	0.45
BDI	12.1±5.1	7.7±4.2	0.01	11.8±5.8	12.2±4.2	0.81
PSQI	10.9±4.5	5.8±4.1	0.002	10.6±4.3	7.6±4.8	0.05
FOSQ	13.2±3.3	17.1±1.7	0.0002	13.5±3.2	12.7±3.6	0.22
FSS	40.9±11.1	27.9±8.6	0.0007	51.5±10.1	41.4±15.8	0.02
SF-36 physical component	60.8±12.4	76.4±11.6	0.008	53.7±18.3	63.8±18.1	0.08
Physical functioning (PF)	62.1±22.4	75.9±11.7	0.02	51.1±29.3	47.7±21.7	0.69
Role physical (RP)	65.2±28.3	80.7±18.6	0.03	50.2±27.3	52.8±21.6	0.63
Bodily pain (BP)	64.4±27	79.7±18.6	0.04	52.4±31.3	69.2±27.8	0.04
General health (GH)	53.5±16.2	68.1±13.4	0.009	48.5±19.2	53.9±17.2	0.09
SF-36 mental health component	65.3±17.1	79.5±10.3	0.007	61.2±20.4	66.5±16.4	0.36
Vitality (VT)	61.5±15.7	72.1±13.7	0.04	52.5±19.4	63.1±16.3	0.04
Social functioning (SF)	77.2±16.8	90.6±11.6	0.01	74.4±21.6	76.1±17.8	0.78
Role emotional (RE)	63.6±23.9	80.7±13.5	0.02	56.5±29.1	66.8±22.9	0.29
Mental health (MH)	59.2±22.7	74.7±14.7	0.03	60.3±20.1	61.6±18.7	0.97

Giddings OK. Am J Respir Crit Care Med 185; 2012

Mermigkis C. Sleep Breath 2015

Sleep breathing disorders in IPF

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

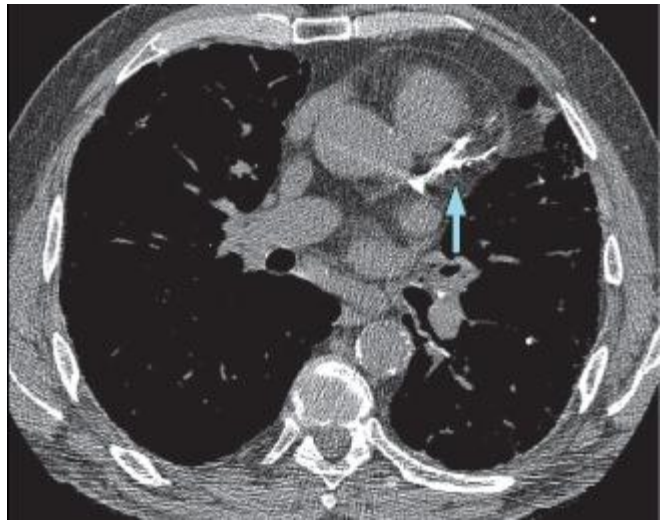
✓ **Treat SBDs**

- Nocturnal O2 therapy if present only sleep hypoxemia
- CPAP therapy if OSAS present according AASM guidelines

Cardiovascular disease in IPF

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

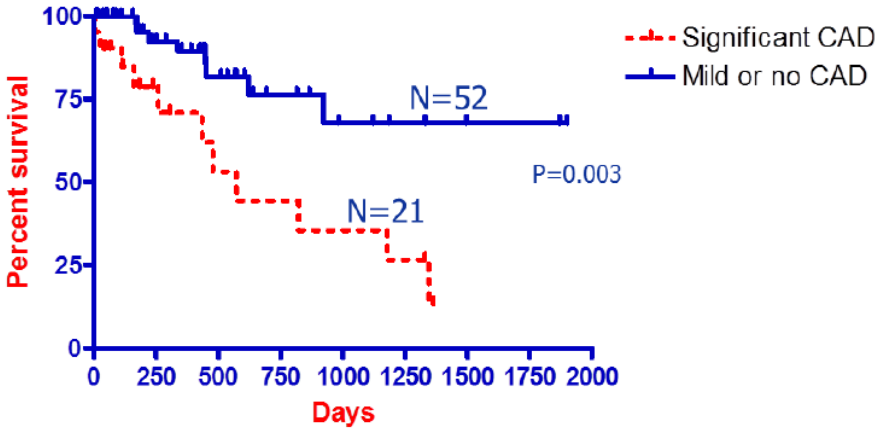
Prevalence: 3-68%



Sensitivity and specificity >80%

Symptomatic patients → Cardiac CT/MRI

Treatment CAD according 2012 AHA guidelines

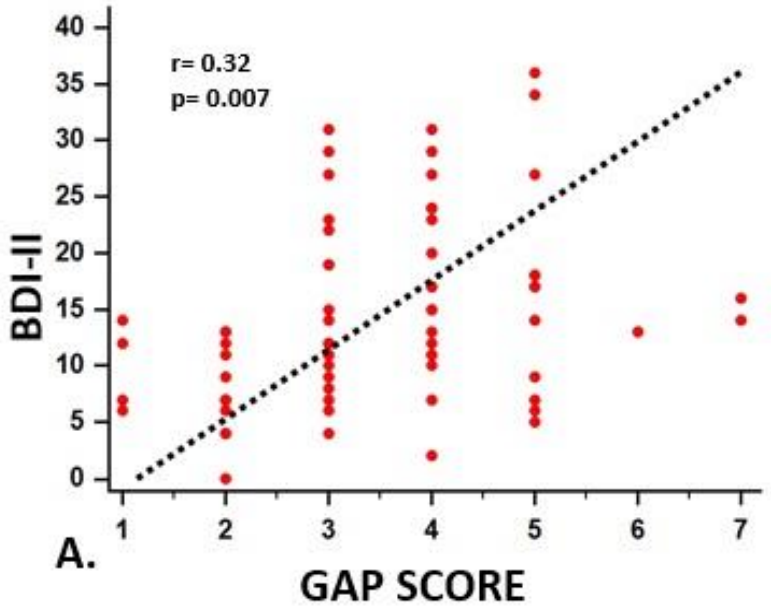


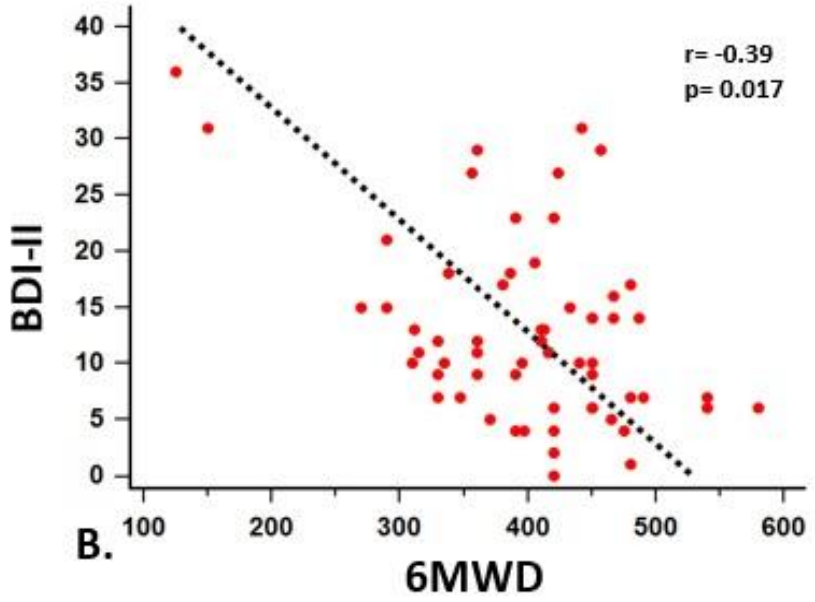
Nathan SD. *Respir Med* 2010

King CS. *Lancet Respir Med* 2016

Depression in IPF

- **Prevalence of depression in IPF between 24.3 and 49.2%**





- **<u>Antidepressants such as fluvoxamine interact with antifibrotics</u>**

Greek cohort unpublished data

nature medicine

Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function

Guoying Yu[1,10], Argyris Tzouvelekis[1,2,10], Rong Wang[1], Jose D Herazo-Maya[1], Gabriel H Ibarra[1], Anup Srivastava[1], Joao Pedro Werneck de Castro[3,4], Giuseppe DeIuliis[1], Farida Ahangari[1], Tony Woolard[1], Nachelle Aurelien[1], Rafael Arrojo e Drigo[5], Ye Gan[1], Morven Graham[6], Xinran Liu[6], Robert J Homer[7,8], Thomas S Scanlan[9], Praveen Mannam[1], Patty J Lee[1], Erica L Herzog[1], Antonio C Bianco[3] & Naftali Kaminski[1]

[10]These authors contributed equally to this work.

Respiration

Editorial Comment

Respiration
DOI: 10.1159/000490917

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Metformin in Idiopathic Pulmonary Fibrosis "Seeking the Holy-Grail through Drug-Repositioning"

Argyrios Tzouvelekis[a, b] Vasilios Tzilas[a] Maria Dassiou[a] Demosthenes Bouros[a]

nature medicine

LETTERS

https://doi.org/10.1038/s41591-018-0087-6

NATURE MEDICINE | VOL 24 | AUGUST 2018 | 1121–1127 |

Metformin reverses established lung fibrosis in a bleomycin model

A bibliometric review of drug repurposing

Drug Discovery Today • Volume 00, Number 00 • December 2018

Nancy C. Baker[1,2], Sean Ekins[3], Antony J. Williams[4] and Alexander Tropsha[1,5]

relationships. We find that >60% of the ~35 000 drugs or drug candidates identified in our study have been tried in more than one disease, including 189 drugs that have been tried in >300 diseases each.

Take Home messages

Treatment for all endotypes

Monitor - treatment of comorbidities

Quality of Life – Perceptive Outcomes