Con il patrocinio di

Associazione Italiana Pneumologi Ospedalieri

Ospedale San Giuseppe
MultiMedica S.p.A.

PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

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Come gestire le comorbidità e il follow-up

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Comorbidities in IPF

Elderly population, median age 66 years at diagnosis

→ multimorbidity is common

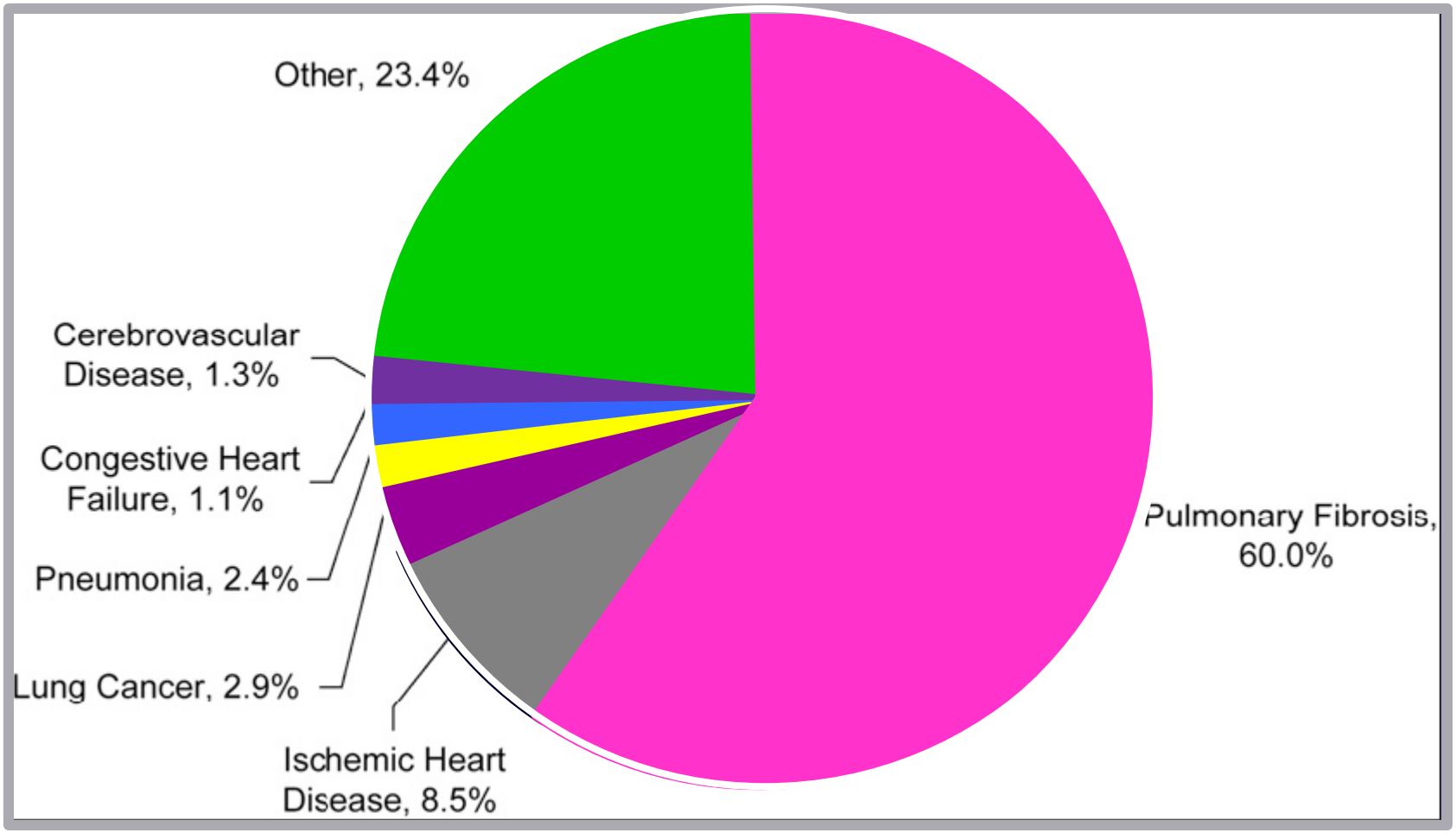
Treatment options for IPF are limited

The impact of comorbidites and their treatment may influence the clinical course of the disease

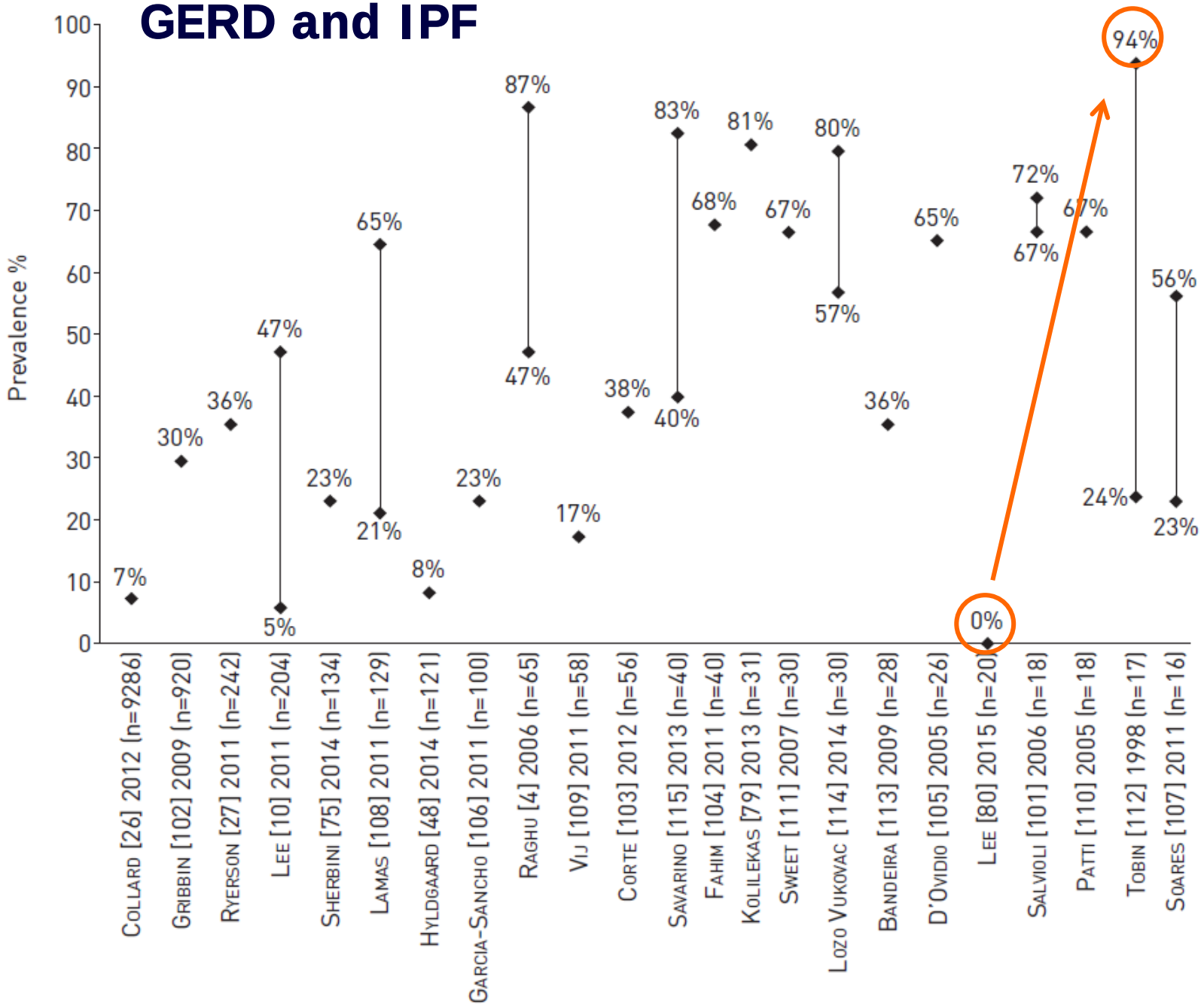
The knowledge about **which comorbidities are most prevalent** in IPF patients and **how comorbidities modify** the disease course is important for providing best care and ultimately improving clinical outcomes in this patient population.

Mortality from Pulmonary Fibrosis Increased in the United States from 1992 to 2003

Olson et al. Am J Respir Crit Care Med 2007; 176:277



GERD and IPF



Raghu G. et al. Eur Respir Rev 2015; 46: 1113

GERD and IPF

GERD is a common co-morbidity in patients with IPF

Patients with IPF and GERD are at higher risk for hospitalizations from any cause and from respiratory illness, perhaps resulting, at least in part, from the contribution of uncontrolled reflux and microaspiration to pulmonary fibrosis.

Some case reports suggest that controlling reflux might stabilize IPF

Current guidelines give a conditional recommendation for the use of antiacid therapy in patients with IPF due to limited data

Patients with IPF randomized to placebo in CAPACITY and ASCEND studies were analyzed for treatment with AAT (H2 blockers and/or PPI) at trial baseline

No differences were observed between groups in disease progression or mortality

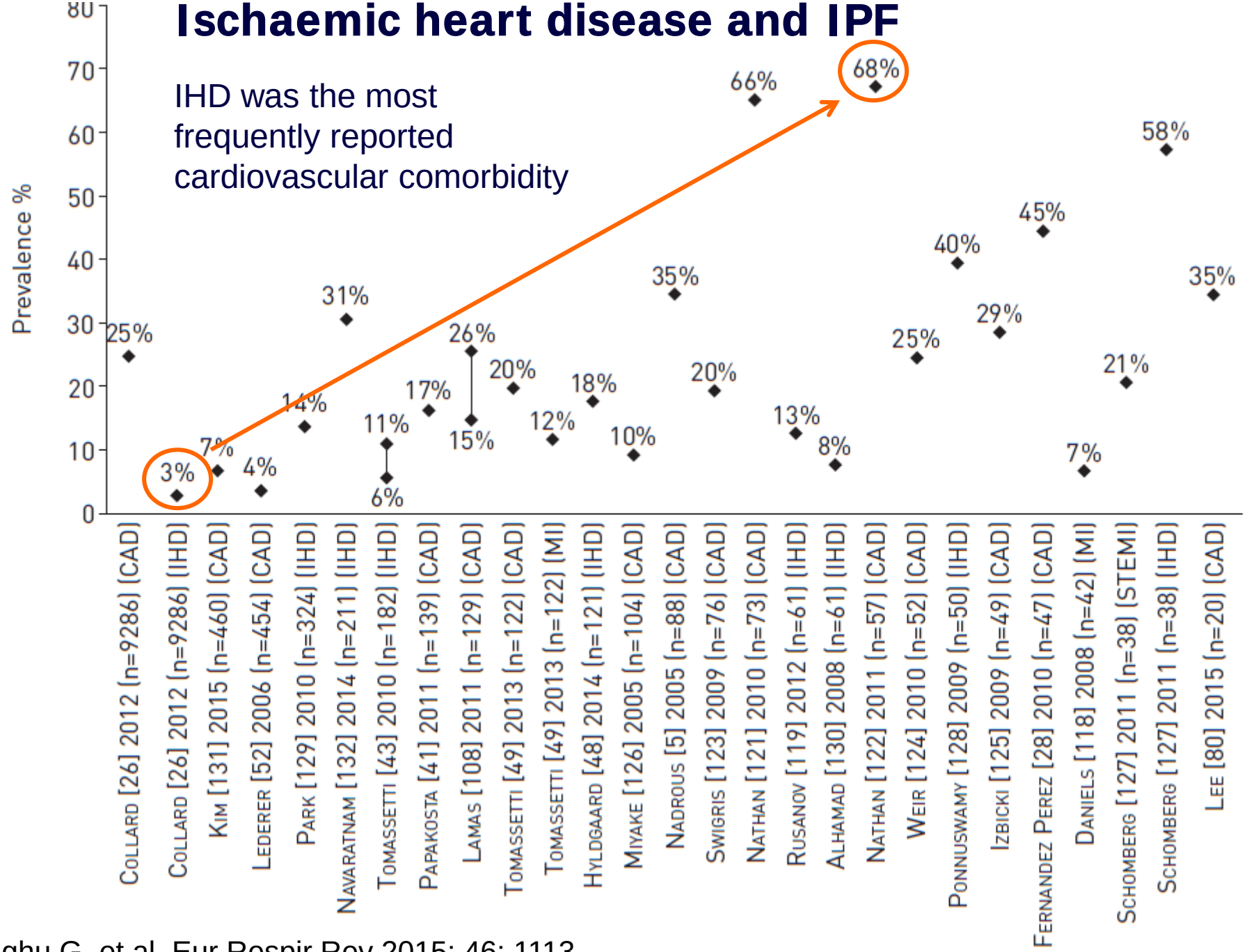
For patients with FVC < 70% predicted, infections were significantly higher with AAT use than no AAT use

Long-term double-blind randomized studies are needed to further explore the potential benefit (and possible harms) of AAT in patients with different stages of IPF, especially those with advanced disease

Kreuter M et al. Lancet Respir Med 2016

Ischaemic heart disease and IPF

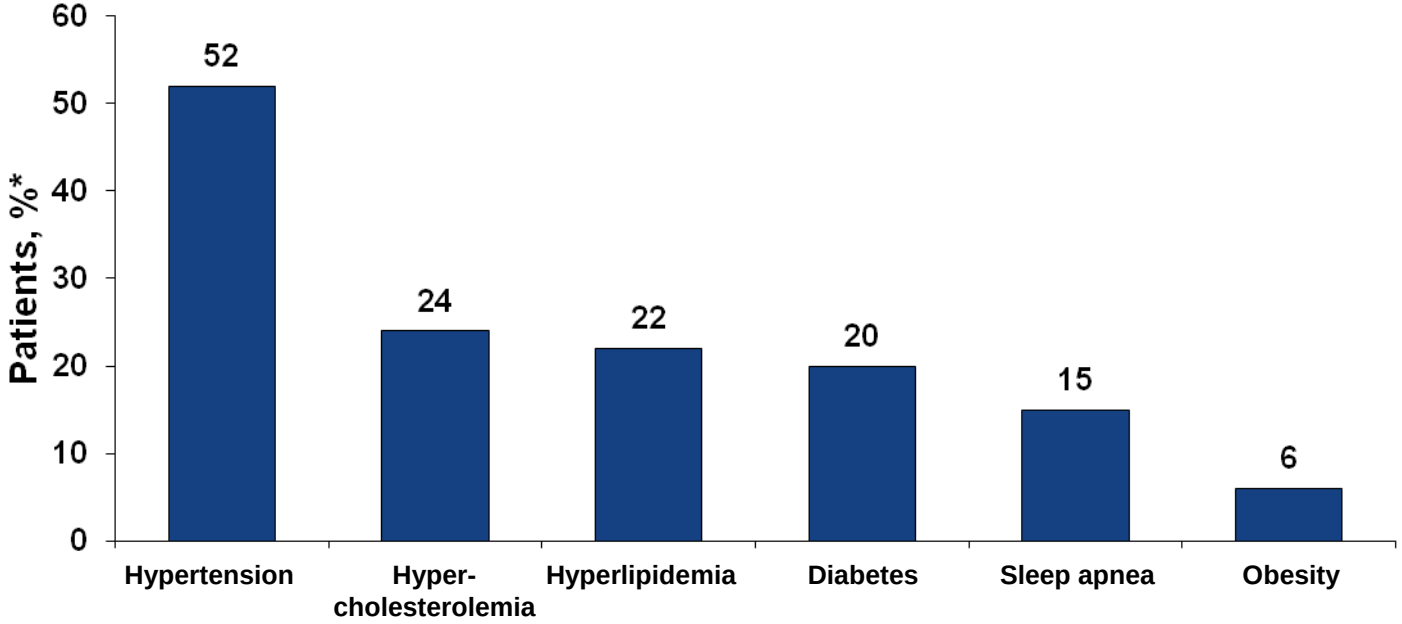
IHD was the most frequently reported cardiovascular comorbidity



Raghu G. et al. Eur Respir Rev 2015; 46: 1113

CV risk factors in pirfenidone phase III studies

In addition to age (median, 68 years), sex (male, 74.4%) and smoking history (65.6% previous/current smokers), the most common CV risk factors at baseline in patients with IPF from the pirfenidone Phase III trials were hypertension (52%), hypercholesterolemia (24%) and hyperlipidemia (22%)

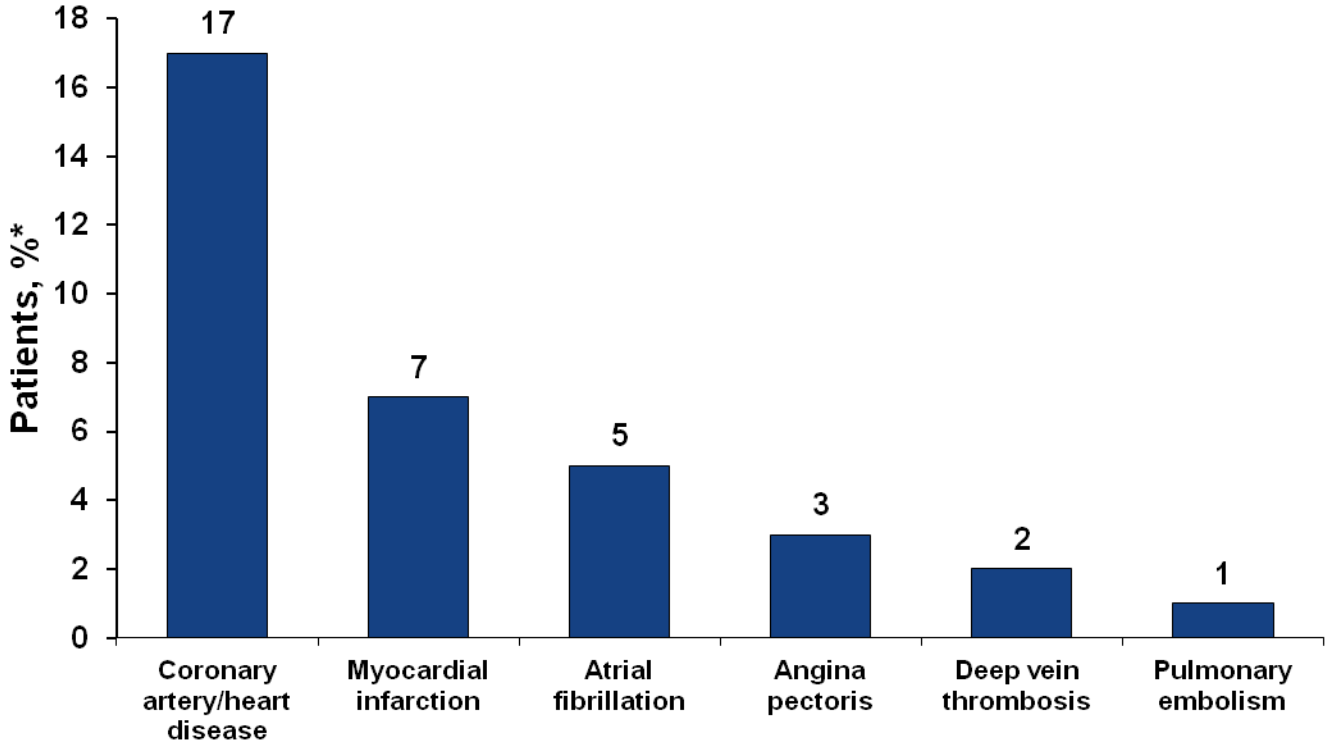


* N = 1334.

Glassberg et al. ATS 2016 P397

CV comorbidities in pirfenidone phase III studies

Cardiac disorders as a system organ class were reported in 36% of patients at baseline. The most commonly reported conditions were coronary artery/heart disease (17%), myocardial infarction (7%) and atrial fibrillation (5%)

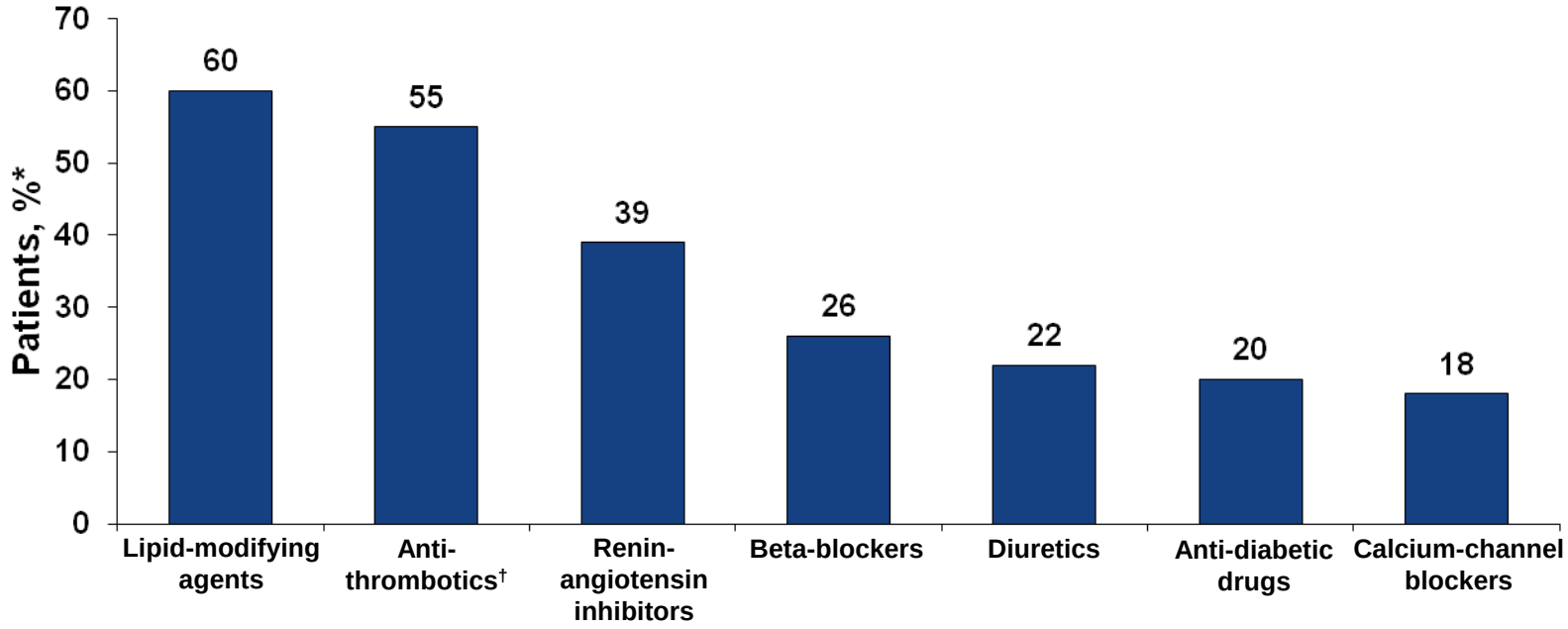


* N = 1334.

Glassberg et al. ATS 2016 P397

CV comorbidities and concomitant medication profile

During the treatment period of the pirfenidone Phase III trials, any use of concomitant CV medications by patients included lipid-modifying agents (60%), anti-thrombotics (55%) and renin-angiotensin inhibitors (39%)



* N = 1334.

† Includes both anti-platelets (e.g., acetylsalicylic acid) and anti-coagulants.

Glassberg et al. ATS 2016 P397

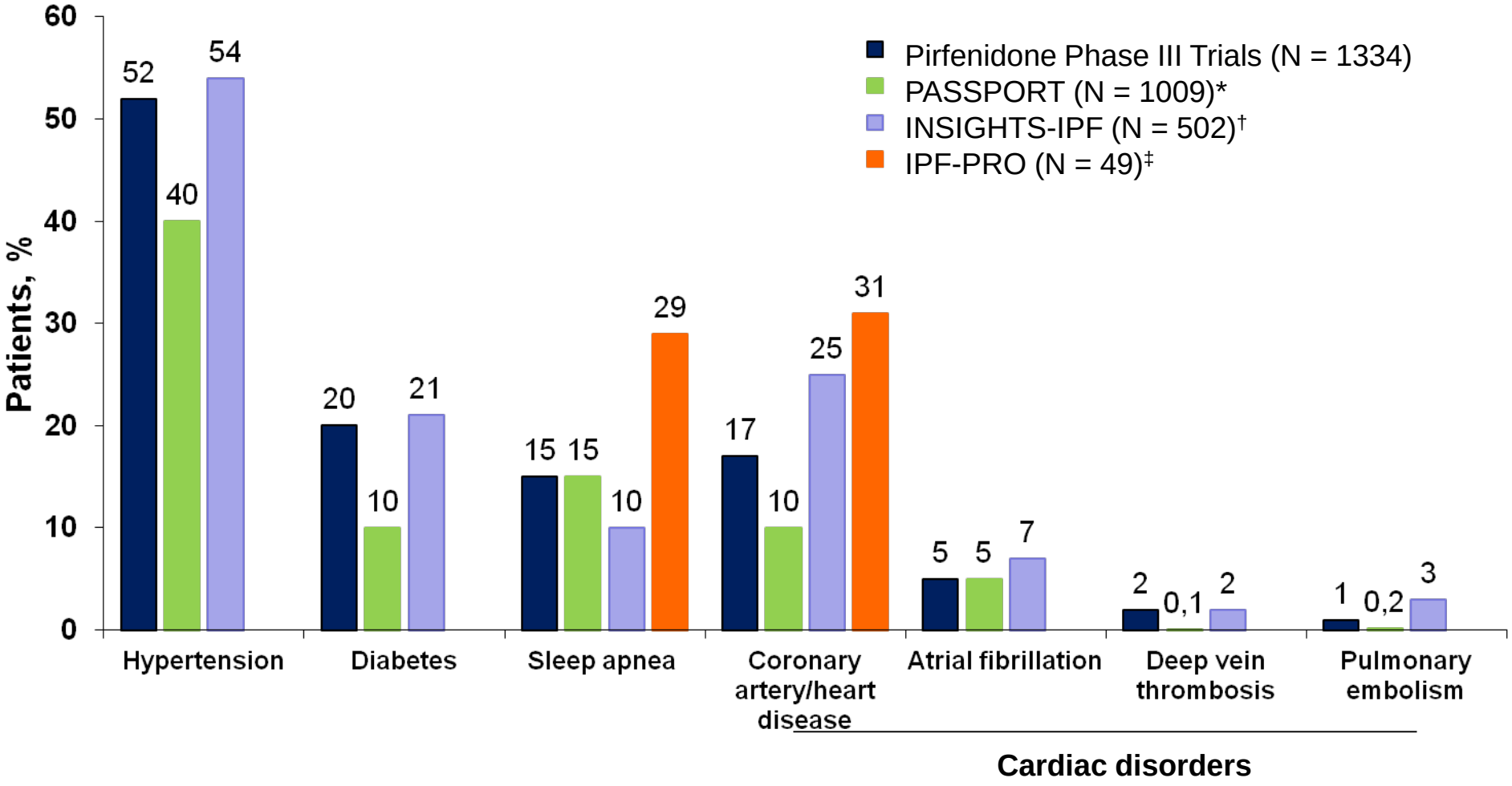
CV comorbidities and concomitant medication profile

During the treatment period of the pirfenidone Phase III trials, the most common concomitant CV medications used by patients included statins (50.7%), acetylsalicylic acid (47.5%), lisinopril (9.8%) and warfarin (6.5%)

Medication, n (%)*	N = 1334
Lipid-modifying agents	806 (60.4)
Statins	**676 (50.7)**
Fish oil	204 (15.3)
Nicotinic acid	57 (4.3)
Anti-thrombotic agents	730 (54.7)
Anti-platelet agents	656 (49.2)
Acetylsalicyclic acid	**634 (47.5)**
Clopidogrel	94 (7.0)
Cilostazol	6 (0.4)
Anti-coagulation agents	173 (13.0)
Warfarin	**87 (6.5)**
Enoxaparin	54 (4.0)
Heparin	50 (3.7)
Renin-angiotensin inhibitors	517 (38.8)
Lisinopril	**131 (9.8)**
Losartan	87 (6.5)
Valsartan	86 (6.4)

Glassberg et al. ATS 2016 P397

Comparison of CV comorbidity profiles with real-world registries



* Interim analysis (data up to July 2015). Cottin V, et al. Eur Respir J. 2015;46 (suppl 59):OA4500.
† Interim analysis (data up to October 2014). Behr J, et al. Eur Respir J. 2015;46:186–196. O'Brien EC, et al. BMJ Open Resp Res. 2016;3:e000108.
‡ For IPF-PRO, only numbers for sleep apnea and coronary artery/heart disease have been reported. Durheim M, et al. Chest. 2015;148(4_MeetingAbstracts):362A.

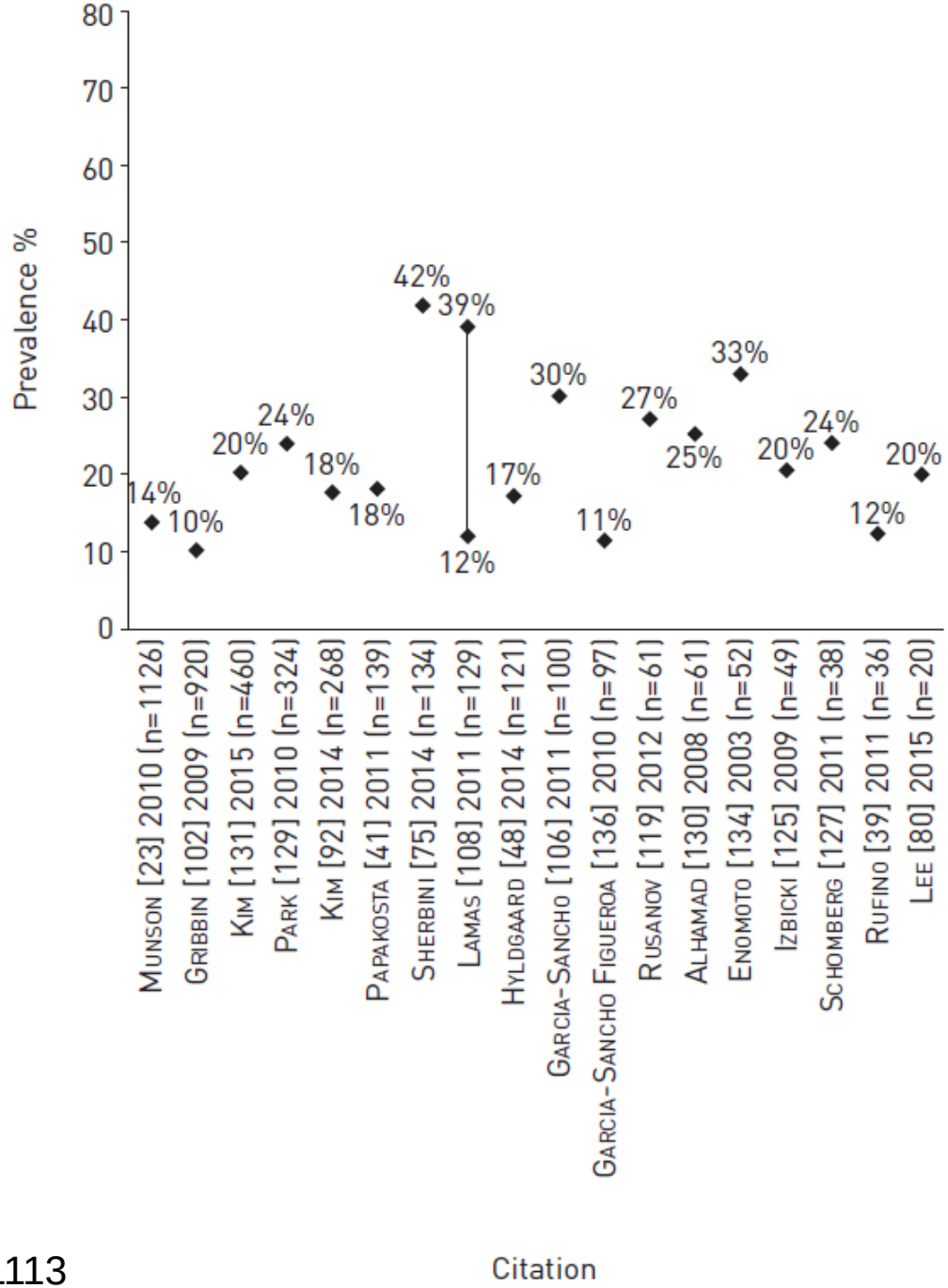
Glassberg et al. ATS 2016 P397

Conclusion and implications

- CV risk factors, comorbidities and use of related concomitant CV medications were prevalent in patients with IPF enrolled in the pirfenidone Phase III trials and are consistent with findings in real-world observational registries
- Awareness of CV risk factors, comorbidities and use of concomitant medications is an important consideration in the management and treatment of patients with IPF

Diabetes and IPF

Systemic steroids had been a major treatment regimen for the treatment of IPF and might have contributed to the high prevalence of diabetes mellitus in this population



Raghu G. et al. Eur Respir Rev 2015; 46: 1113

Other comorbidities

Venous thromboembolism

Patients with IPF are at increased risk for venous thromboembolism due to decreased mobility causing venous stasis, as well as possible involvement of the coagulation cascade in IPF pathogenesis

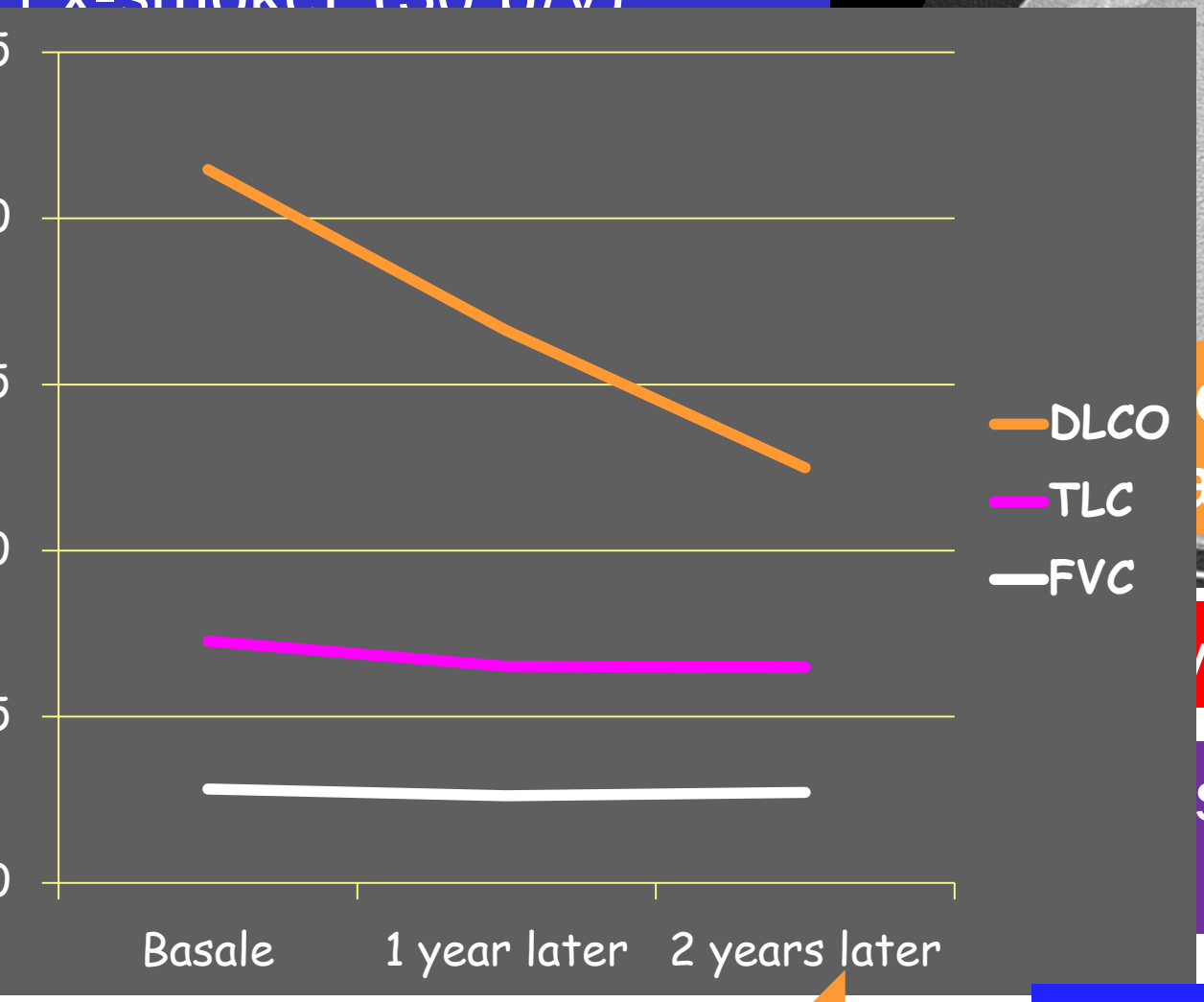
Depression and anxiety

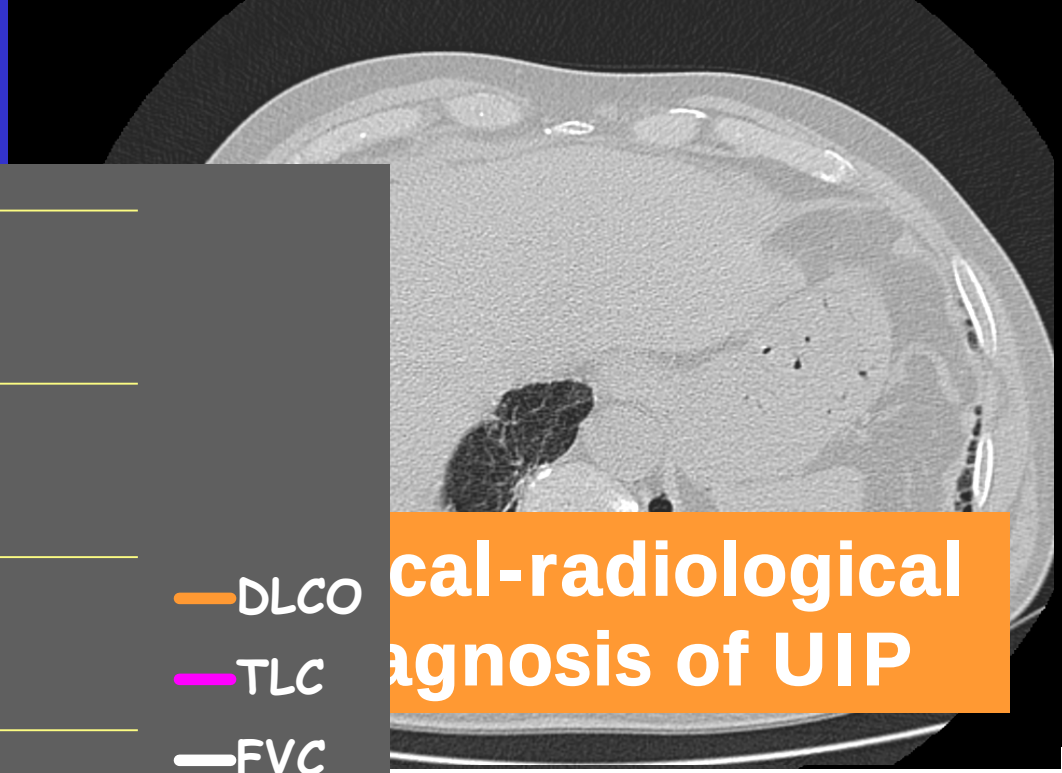
Clinically significant symptoms of depression and anxiety are present in up to 50% and 30% of IPF patients, respectively

Comorbidity	Selected screening and diagnostic considerations	Selected management considerations
Pulmonary comorbidities		
Venous thromboembolism	• Consider contrast CT in patients with acute respiratory worsening • Isolated sub-segmental filling defects are of uncertain significance in severe fibrosis	• Similar approach to management and prophylaxis compared to non-IPF patients • No role for anticoagulation in IPF patients that lack a conventional indication
Extra-pulmonary comorbidities		
Depression and anxiety	• Depression is more common in patients with dyspnea and severe fibrosis • Screen all patients for symptoms of depression and anxiety	• Consider cognitive behavioral therapy, antidepressants, and antianxiety treatments in patients with significant and persistent symptoms • Possible benefit of pulmonary rehabilitation

Modified from: Fulton BG et al. 2015

Man, 57 yrs,
Ex-smoker (30 p/y)





cal-radiological
agnosis of UIP

with pirfenidone

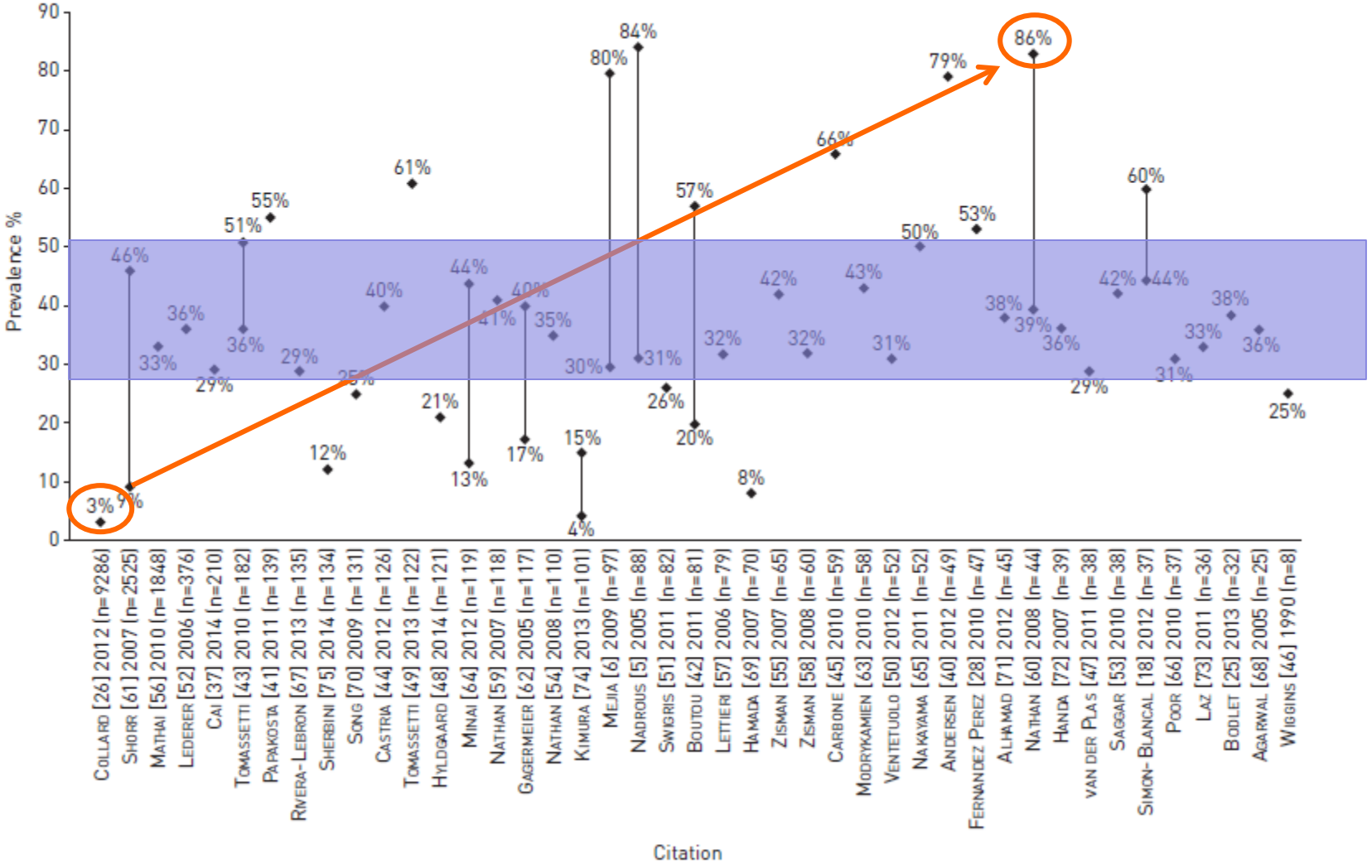
ssive respiratory
failure

Severe PH in IPF

RHC
mPAP 37 mmHg

Raghu G. et al. Eur Respir Rev 2015; 46: 1113

PH in IPF



A total of 43 studies included data on the prevalence of PH in patients with IPF using various definitions based on RHC or echocardiography

CLASSIFICATION
4th World Symposium 2008

1. Pulmonary Arterial Hypertension

- ❑ **Idiopathic PAH**

Disorders of the respiratory system and hypoxemia

- Chronic obstructive pulmonary disease
- **Interstitial lung disease**
- Sleep disorders
- Alveolar hypoventilation
- Chronic exposure to high altitude
- Others...

1'. Pulmonary veno occlusive disease (PVO) and/ or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension due to left heart disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

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

- COPD
- Interstitial lung disease
- Others pulmonary diseases
- Sleep-disordered breathing
- Chronic exposure to high altitude
- Developmental abnormalities

4. Chronic thromboembolic polmonary hypertension (CTEPH)

5. PH with unclear or multifactorial mechanisms

1: Hematologic disorders, myeloproliferative disorders, splenectomy
2: Systemic disorders: vasculitis, sarcoidosis, PLCH, LAM, neurofibromatosis
3: Metabolic disorders: GD, thyroid disorders, glycogen storage disease
4: Others: tumoral obstruction , fibrosing mediastinitis, dyalisis

PH in IPF

Definition of PH: resting mean pulmonary artery pressure > 25 mmHg, as measured by RHC

The differences in prevalence of PH in IPF reflect:

- varying patient populations
- varying underlying disease severity
- differing diagnostic modalities

PH in IPF

Patients assessed at the time of transplantation evaluation: PH prevalence of 36%

At the time of transplantation, 85% of the same patient cohort had PH

Conclusions

PH is progressive and the prevalence and severity of PH is temporally related to the progression of IPF

Nathan SD et al. Respiration 2008; 76: 288-94

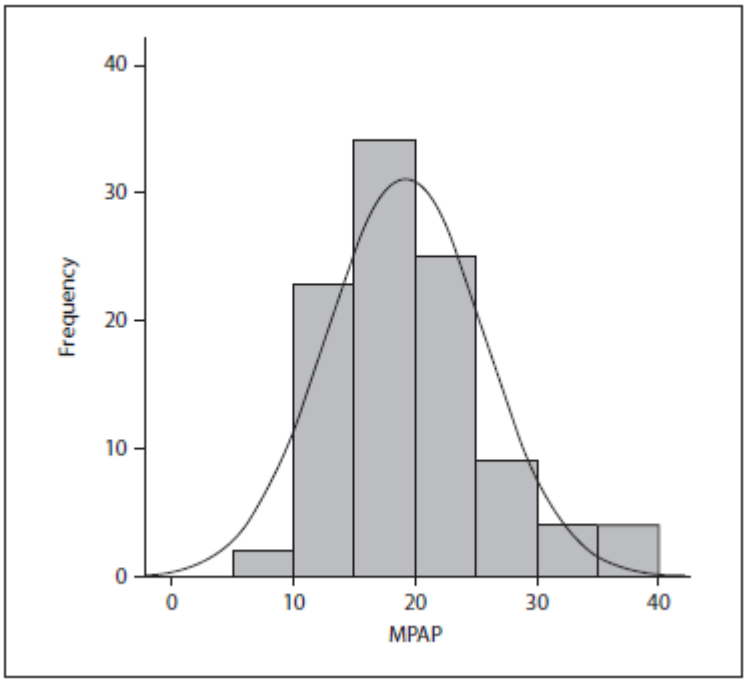
PH in IPF

88 patients with IPF	PAPs 0-34 mmHg (n=14)	PAPs 35-49 mmHg (n=47)	PAPs>50 mmHg (n=27)
Median survival	4.8y	4.1y	0.7y
1 year survival	100%	79%	44%
3 year survival	64%	61%	32%

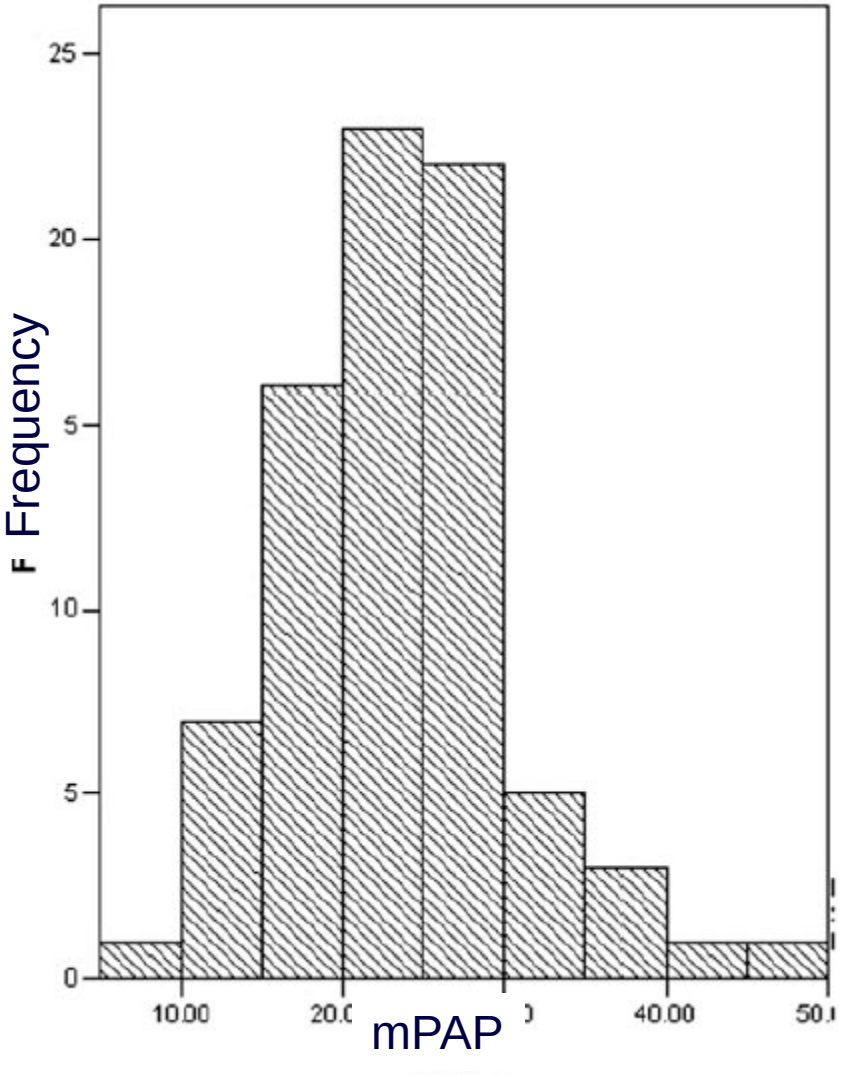
Pts with PAPs > 50 mmHg have bad survival than the others (p=0.009)

Nadrous et al Chest 2005: 128;616-7

- As opposed to PAH, the PH in IPF tends to be mild in most patients.



Kimura M et al. Respiration 2012



Lettieri CJ et al. Chest 2006;129: 746-752

Shorr AF et al. Eur Respir J 2007;30:715-721

Out-of-proportion pulmonary hypertension

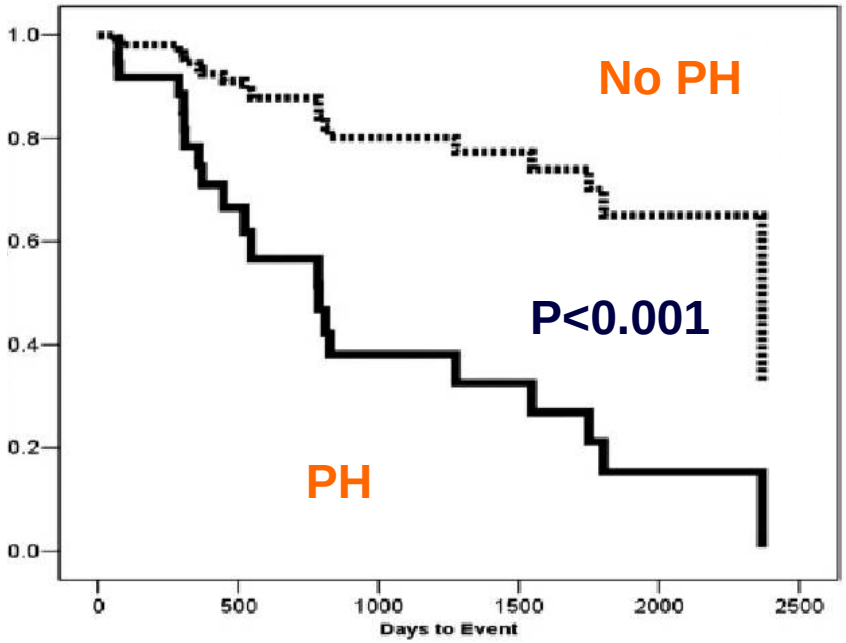
A paradigm for rare diseases

Out-of-proportion PH is defined as an unjustified degree of PH that occurs in patients suffering from different types of parenchymal lung diseases (ie COPD, IPF)

A possible goal for therapies?

Harari S. Chest, 2012*;* 142:1087-1088

PH in IPF



Variables	PAP m≤ 25 mmHg (n= 10)	PAPm > 25 mmHg (n= 24)	p value
PAPm, mmHg	18.2 ± 3.6	29.8 ± 5.1	NA
6MWT distance, m	365.9 ± 81.8	143.5 ± 65.5	< 0.001
SpO2 nadir on 6MWT, %	88.0 ± 3.5	80.1 ± 3.7	< 0.001
Mortality rate, %	37.5	70.0	0.003

Lettieri CJ et al. Chest 2006, 129:746-52

RHC and 6MWD in IPF

Variables	MAP ≤ 25 mmHg (n= 17)	MAP > 25 mmHg (n= 13)	MAP > 35 mmHg (n= 4)	P value
MPAP, mmHg	19.4 ± 3.6	32.4 ± 6	40,5 ± 2,6	NA
6MWT distance, m	222.0 ± 118.5	222.3 ± 118.5	203.7 ± 128.3	>0.1
FVC, %	51.6 ± 13.8*	63.8 ± 16*	56.0 ± 6.7	<0.05
FEV1, %	58.3 ± 16.3	65.8 ± 18.8	55.2 ± 3.7	>0.05
DLCO, %	31.4 ± 9.6	24.2 ± 13.0	29.0 ± 7.4	>0.05
CI, l/min/m2	3.4 ± 0.55*	2.9 ± 0.7*	2.8 ± 0.6	<0.05
PVR, wood units	3.5 ± 1.1*	6.9 ± 1.4*	10.3 ± 2.0	<0.05

Harari S. et al. Sarcoidosis 2015

Our data suggest that meters walked during 6MWT are not statistically different in IPF patients with or without PH

6MWD should not be used as surrogate end point in clinical study in IPF-PH pts

Harari S. et al. Sarcoidosis 2015

PH in IPF and mortality

The presence of PH in IPF is associated with higher mortality and its development contributes to the deterioration of IPF patients

Assessment of PH in IPF

Patients with IPF should be evaluated for PH when:

- The symptoms are more severe than one would expect from lung function data (dyspnea and fatigue are symptoms of IPF as well as PH)
- When signs of right heart failure develop
- If clinical deterioration is not matched by a decline in pulmonary function
- Profound hypoxemia, and a low DLCO are indicators of PH

Diagnosis of PH in IPF

Doppler echocardiography remains the most useful non-invasive, screening tool for assessing the presence of PH in patients with IPF, but both false-positive and false-negative results are not uncommon

Given the limitations of echocardiography, RHC remains the standard for the diagnosis of PH

Therapy of PH in IPF

- There is no sufficient evidence that the drugs currently used for PAH are safe and effective in patients with PH associated with chronic lung disease

STEP-IPF

- This study was intended to examine the effects of sildenafil in a population with advanced IPF, defined as a DLCO of less than 35% of the predicted value, not a population with IPF and documented PH.

- PH is common, although not universally present, in patients with advanced IPF.

- The lack of RHC before and after the study intervention precluded the ability to determine whether the potential benefits of sildenafil in patients with advanced IPF (e.g., decreased dyspnea, improved quality of life, and improved gas transfer) were driven by the subgroup with elevated PAP

N Engl J Med 2010;363:620-8

ARTEMIS STUDIES
Study design

AMBRISENTAN-IPF (mPAP <25 mmHg)

Ambrisentan (n= 400) 10 mg/d

PBO (n= 200)

Primary endpoint
Change in % predicted FVC and DLCO at 12 months

AMBRISENTAN-PH (mPAP> 25 mmHg)

Ambrisentan (n= 400) 10 mg/d

PBO (n=200)

Primary endpoint
Change in 6MWT at 12 months

Ambrisentan PH-IPF trial was interrupted prematurely because of a lack of superior activity of the experimental arm

Treatment of idiopathic pulmonary fibrosis with ambrisentan
A parallel, randomized trial

Raghu G. et al. Ann Inter Med 2013;158: 641 - 649

Objective: To determine whether ambrisentan, an ETA receptor– selective antagonist, reduces the rate of IPF progression

Design: Randomized, double-blind, placebo-controlled, event driven trial (ClinicalTrials.gov: NCT00768300)

Participants: Patients with IPF aged 40 to 80 years with minimal or no honeycombing on HRCT

Intervention: Ambrisentan, 10 mg/d, or placebo

Measurements: Time to disease progression, defined as death, respiratory hospitalization, or a categorical decrease in lung function.

Conclusion: Ambrisentan was not effective in treating IPF and may be associated with an increased risk for disease progression and respiratory hospitalizations

Efficacy and safety of riociguat in patients with symptomatic pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) (RISE-IIP)

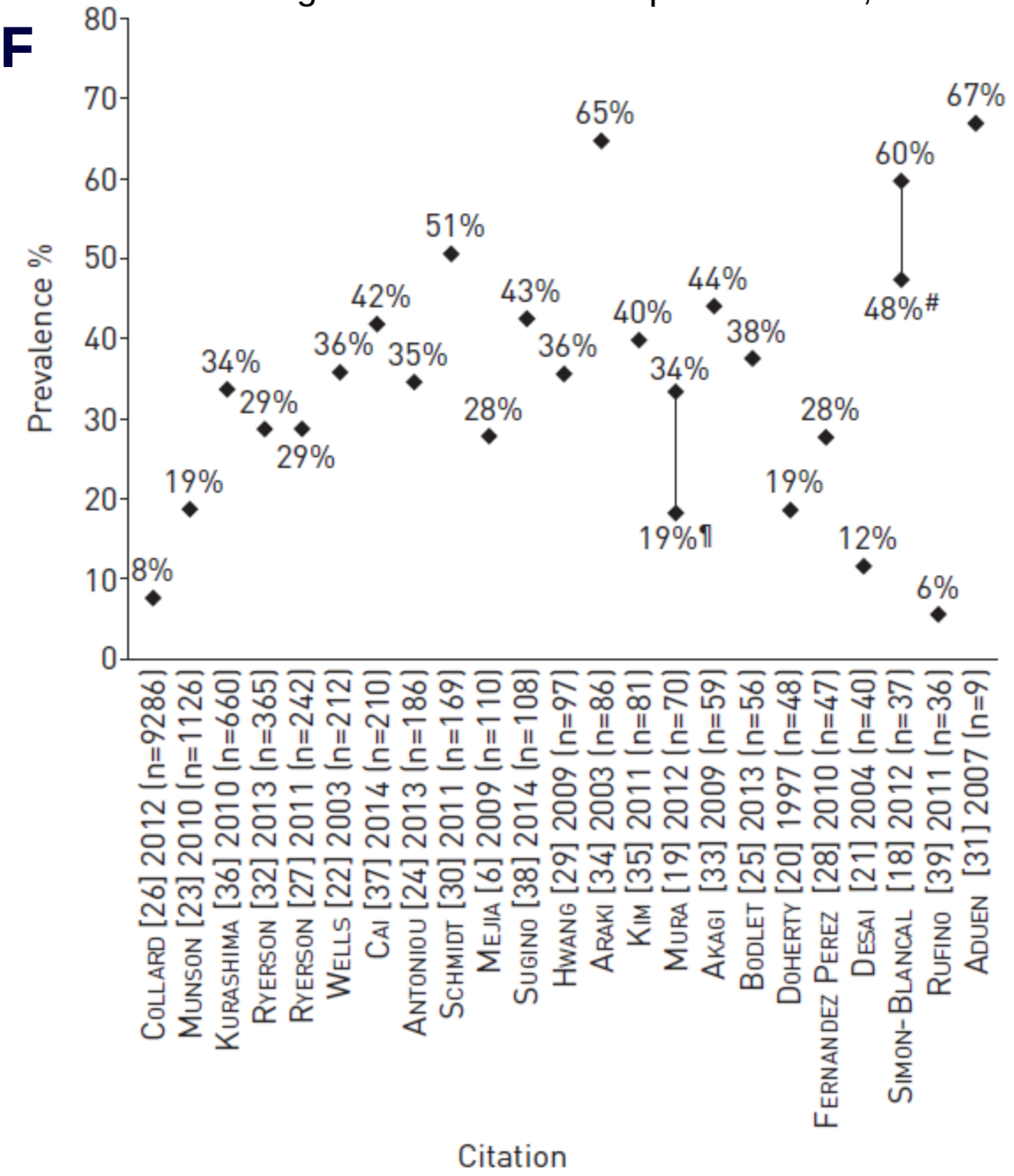
Phase 2 clinical study is terminated on 2016

The DMC recommended the study's immediate termination after observing that patients receiving riociguat were at a possibly increased risk of death and other serious adverse events as compared to patients receiving placebo

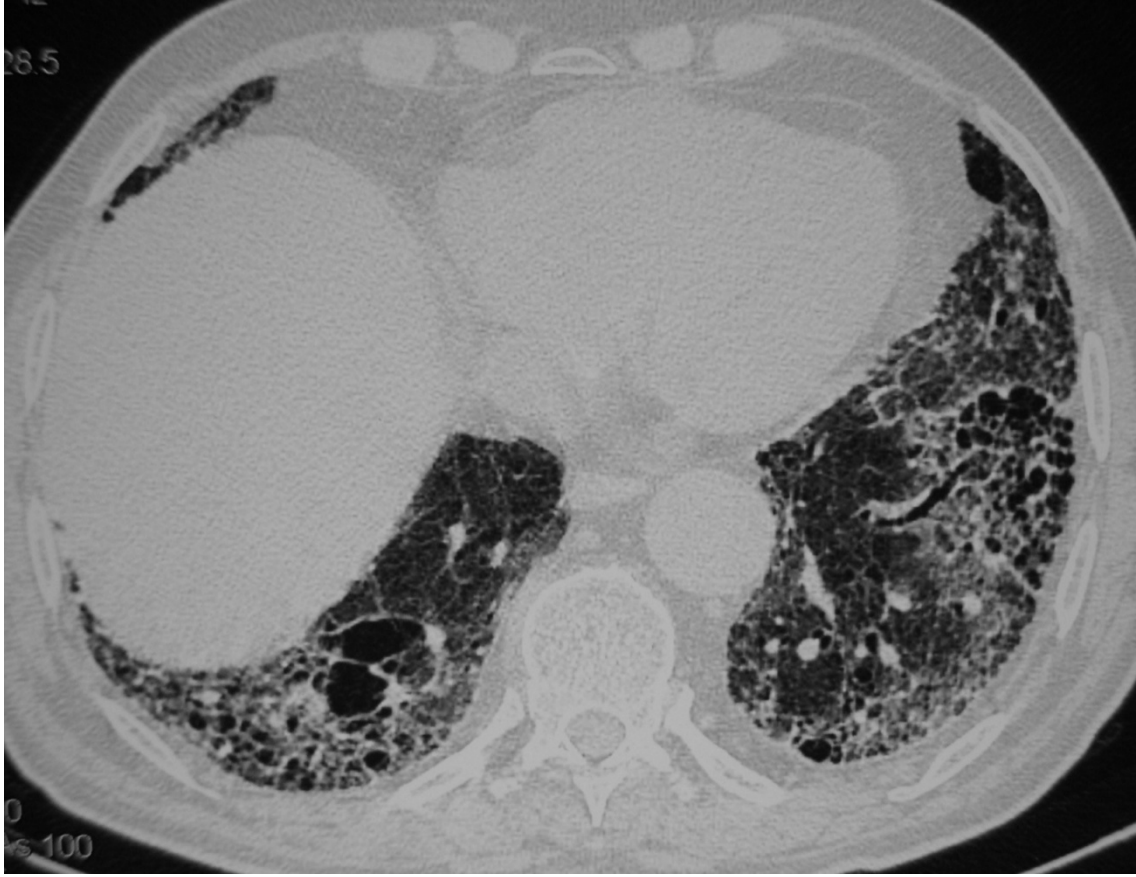
Emphysema and IPF

- Males
- Smokers
- Severe PH
- Worse survival than IPF

Raghu G. et al. Eur Respir Rev 2015; 46: 1113

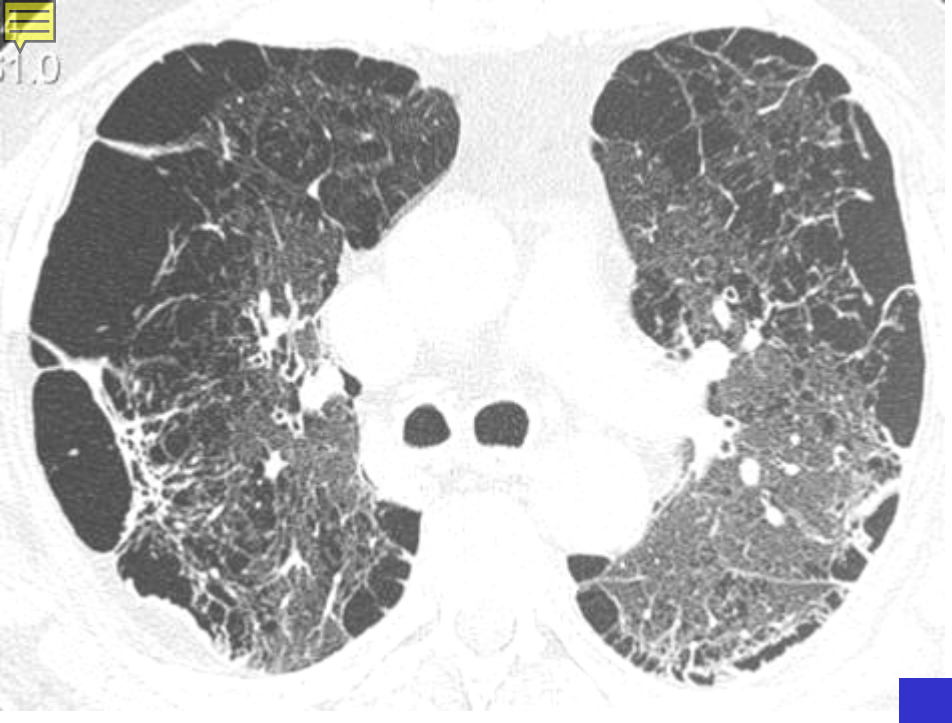


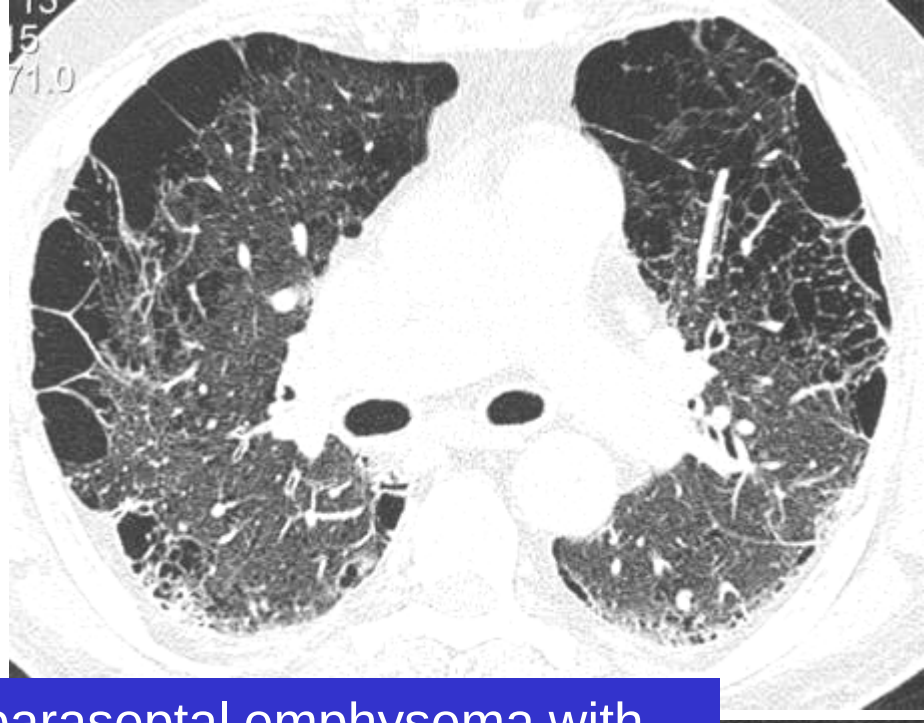
Combined pulmonary fibrosis emphysema (CPFE)



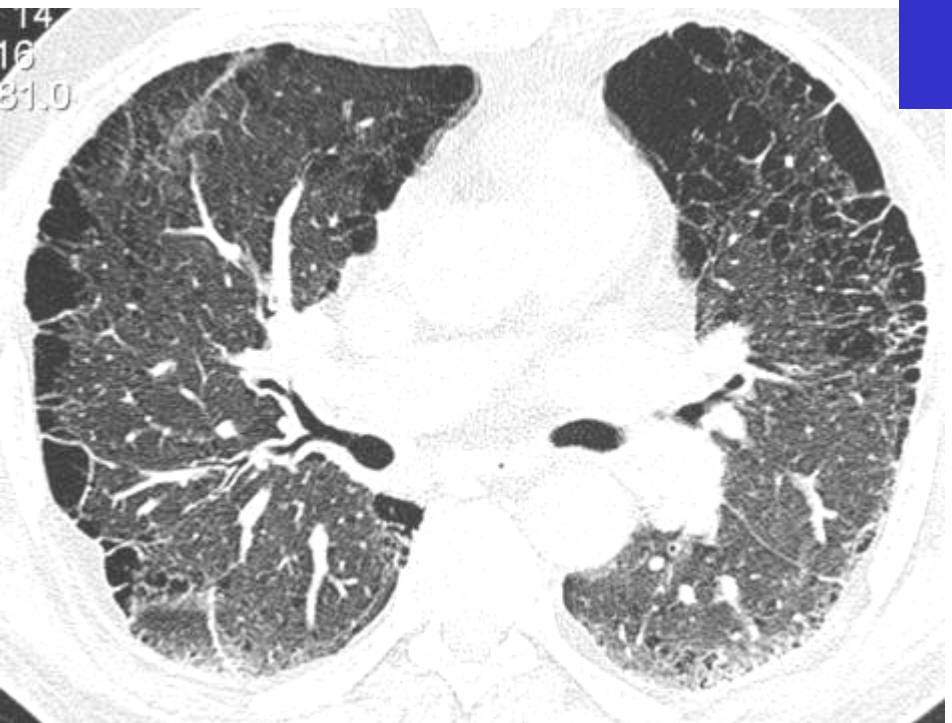
Definition: Presence on HRCT of the chest of both :

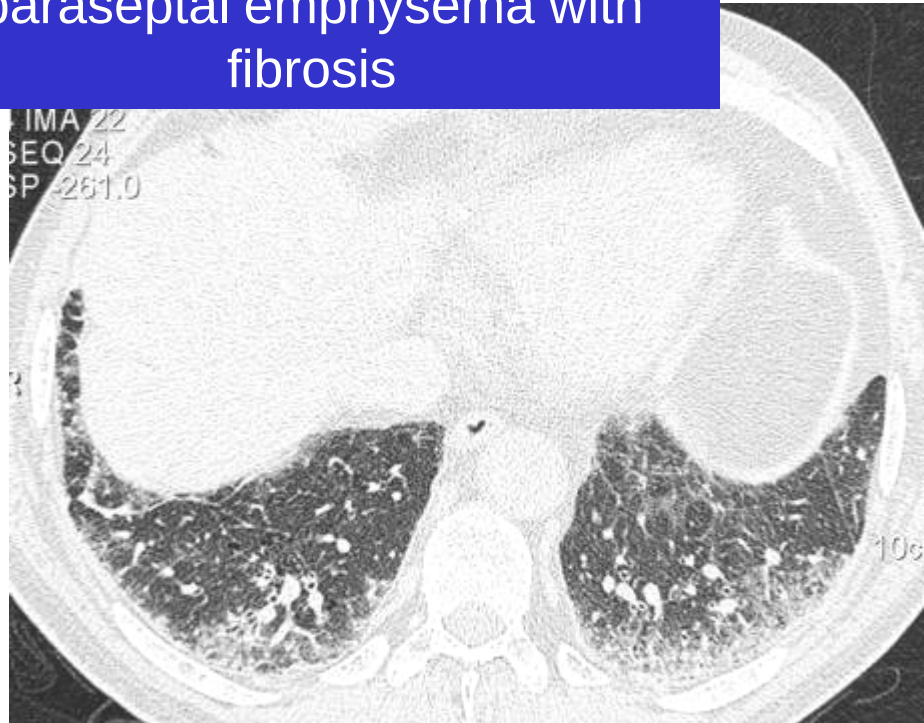
- emphysema of the upper lobes (areas of abnormally low attenuation with a very thin wall [< 1 cm] or no wall),
- opacities suggestive of fibrosis of the lung bases (reticular opacities, basal and sub-pleural predominance, traction bronchiectasis, possibly honeycombing, with no or little ground glass opacities or consolidation).

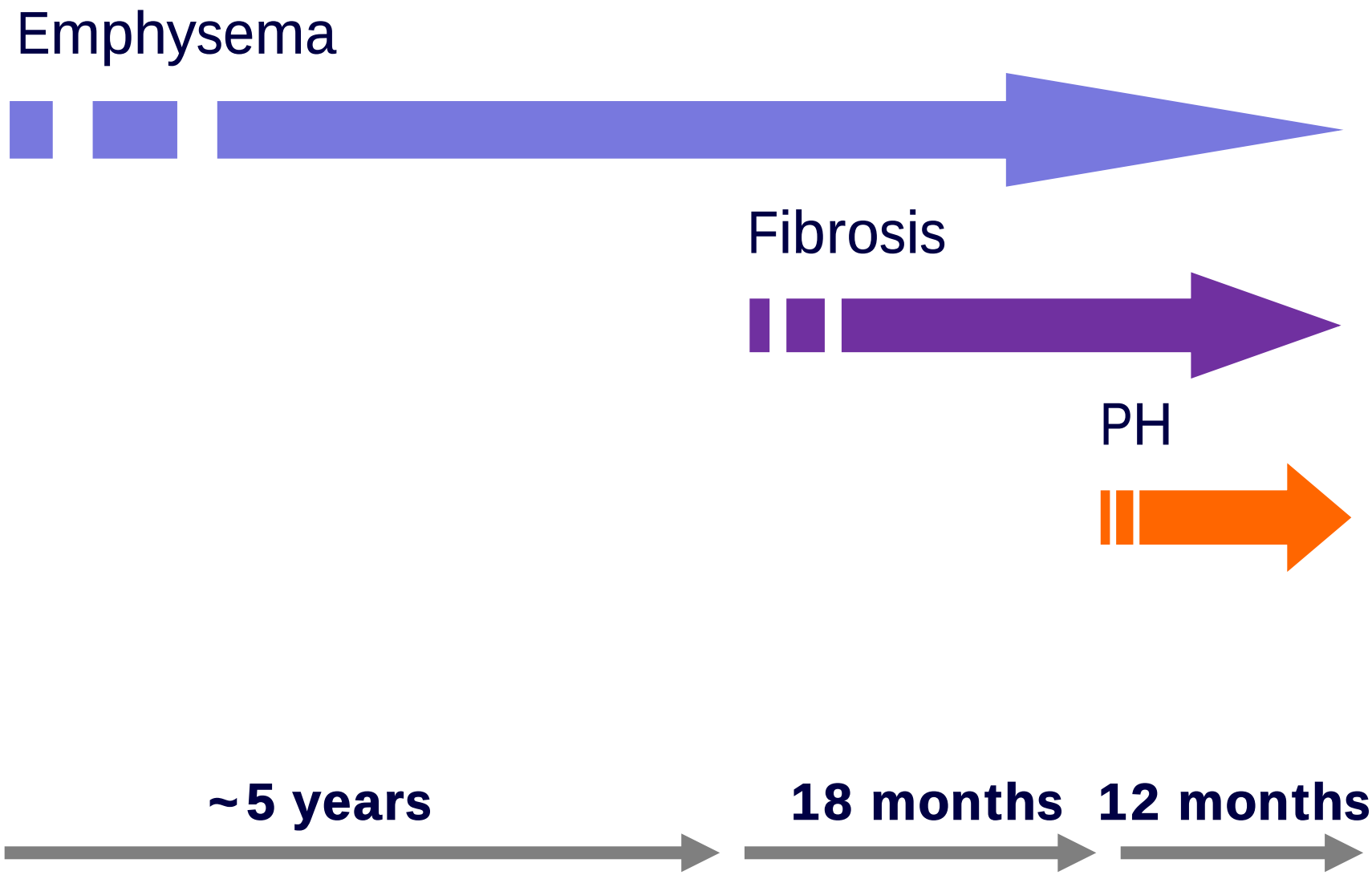




paraseptal emphysema with fibrosis






Emphysema
Fibrosis
PH
~5 years
18 months
12 months

The Syndrome of Combined Pulmonary Fibrosis and Emphysema

V. Cottin and JF Cordier Chest 2009; 136: 1-2

- Modalities of follow-up (preserved lung volumes, risk of developing pulmonary hypertension, lung cancer)
- Diagnostic criteria for IPF are not applicable
- Patients with CPFE should be excluded from IPF clinical trials (or stratified)

- CPFE is a distinct *syndrome* with characteristic presentation (including very low diffusion capacity)
- It may be overlooked because of subnormal spirometry; gas exchanges are severely altered
- Prognosis is related to frequent PH, with poor prognosis; lung cancer may be frequent

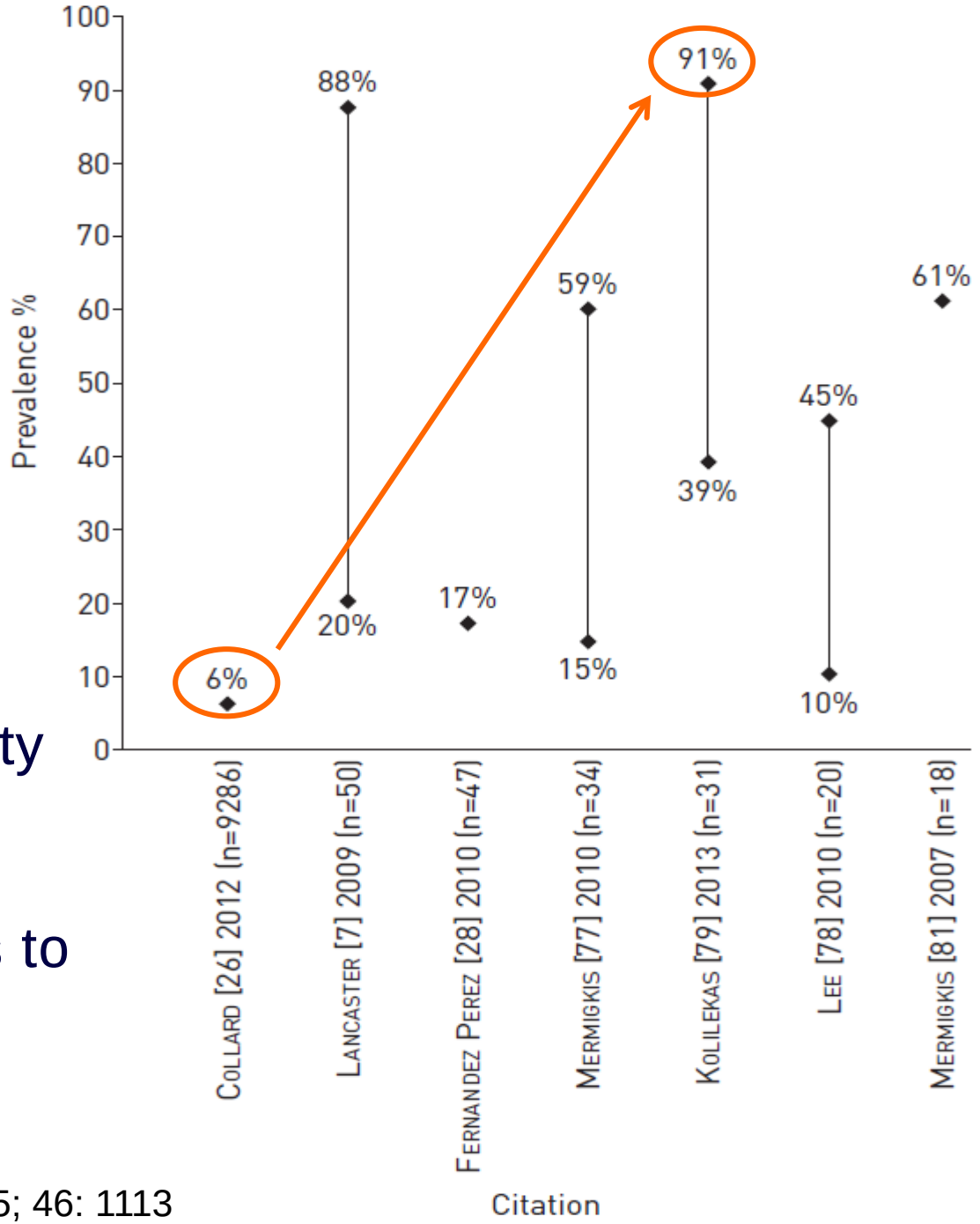
Comorbidity	Selected screening and diagnostic considerations	Selected management considerations
Pulmonary comorbidities		
Emphysema (CPFE)	▪ Most common in male former smokers ▪ Characterized by disproportionately reduced DLCO with relatively preserved flow rates and lung volumes ▪ Frequently associated with pulmonary hypertension and lung cancer	• Similar management approach to isolated COPD • Unclear role of bronchodilators in patients without flow limitation • Unclear role of inhaled corticosteroids • Typically treat acute exacerbation with systemic corticosteroids and antibiotics • Rapidly taper systemic corticosteroids after an acute exacerbation

Modified from: Fulton BG et al. 2015

Sleep apnea and IPF

OSA was observed only in moderately to severely obese IPF patients

There is an association between nocturnal hypoxaemia and mortality with the hypothesis that intermittent oxygen desaturation contributes to PH and associated mortality

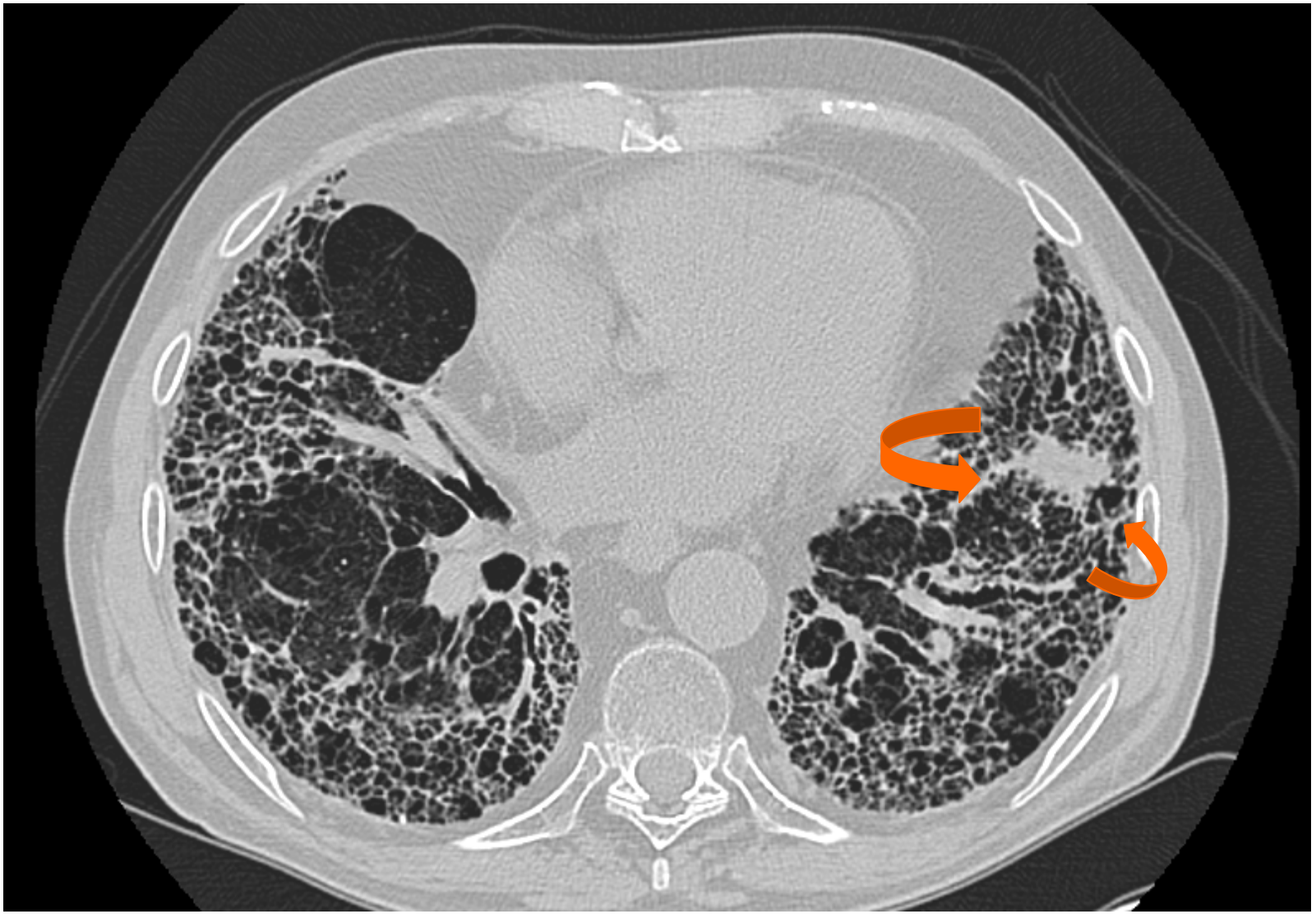


Raghu G. et al. Eur Respir Rev 2015; 46: 1113

Comorbidity	Selected screening and diagnostic considerations	Selected management considerations
Pulmonary comorbidities		
Sleed-disordered breathng	• Consider screening for OSA with overnight oximetry or polysomnography in all IPF patients	• Similar management approach compared to non-IPF patients • CPAP may improve quality of life and sleep quality in patients that do not endorse sleepiness

Modified from: Fulton BG et al. 2015

Lung cancer and IPF



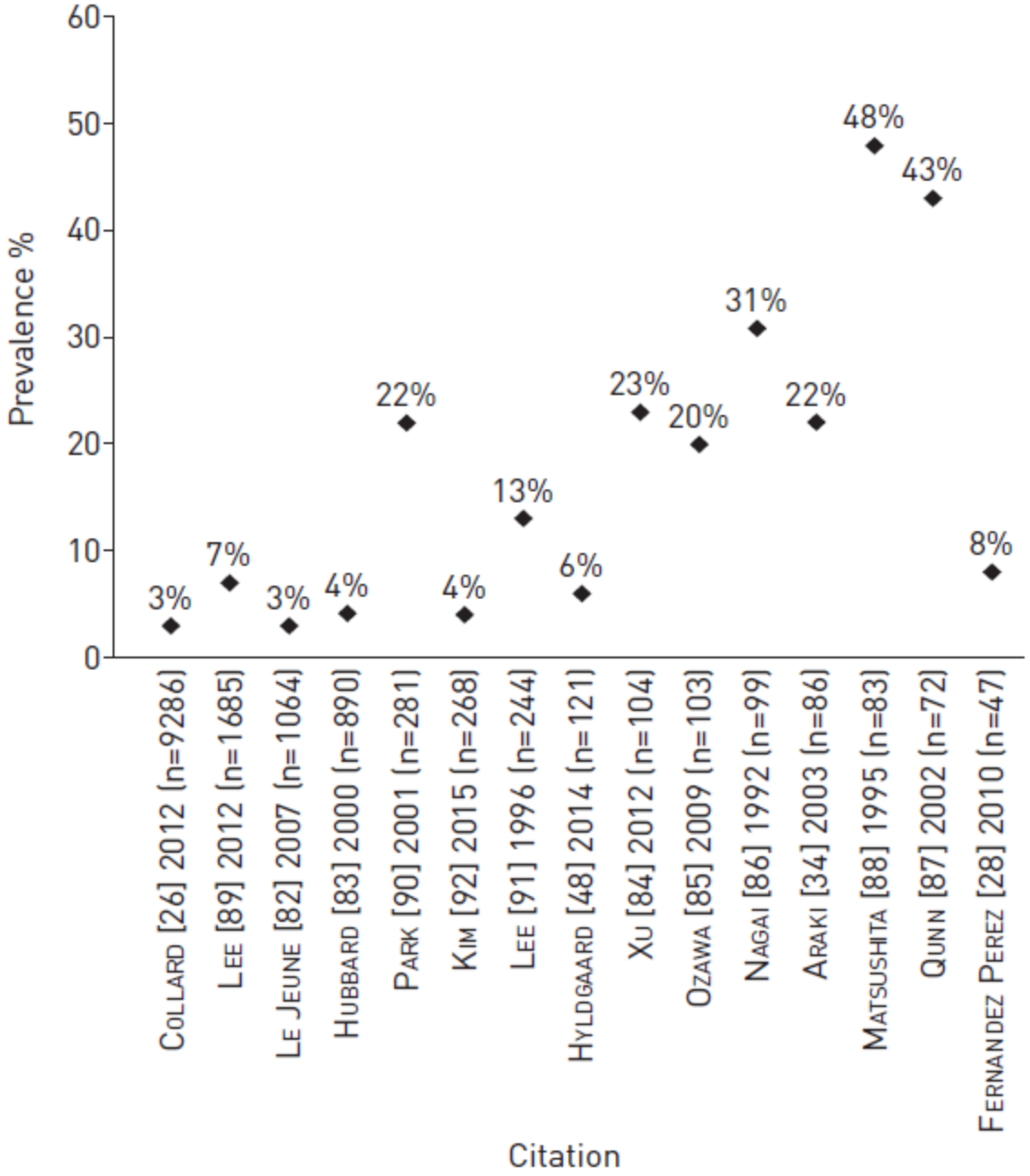
Raghu G. et al. Eur Respir Rev 2015; 46: 1113

Lung cancer and IPF

The mortality in IPF patients with lung cancer is confounded by:

- different follow-up times across studies,
- different severity of cancer and IPF,
- differences in cancer treatments, and other patient characteristics

The papers that reported mortality and survival among IPF patients with lung cancer were limited by small sample sizes.



Comorbidity	Selected screening and diagnostic considerations	Selected management considerations
Pulmonary comorbidities		
Lung cancer	• Frequently presents with nonspecific symptoms or as an incidental finding on chest imaging • Low-dose CT scan screening for lung cancer may have less benefit in IPF (compared to mortality benefit observed in the National Lung Screening Trial)	• Increased mortality and acute exacerbation of IPF following surgical resection, chemotherapy, or radiation • Decrease risk of postoperative acute exacerbation of IPF by reducing intravenous fluid replacement, avoiding high ventilatory pressures, and minimizing hyperoxia • Consider palliative therapies

Modified from: Fulton BG et al. 2015

Monitoring for disease progression

- Every 3 to 6 months (GAP index stratification):
  - PFTs
  - 6MWT (distance/nadir saturation)
  - O_2 requirement
  - Comorbidities
  - Consider dyspnea questionnaire (UCSD)

- HRCT
  - Annually or when suspicion for clinical worsening

Conclusions

Comorbidities may be associated with IPF as a result of shared risk factors such as smoking, the process of aging, or other pathogenetic mechanisms

Respiratory comorbidities, including COPD, PH and OSA, are common, although estimates varied widely

Non-respiratory comorbidities such as GER, systemic arterial hypertension, IHD and diabetes are also highly prevalent in this population of elderly patients

Mortality is highest among patients with concomitant COPD (23–77%) and lung cancer (38–81%); PH and IHD are also associated with an increased risk of death

Conclusions

Comorbidities in IPF should in general be treated the same way as in non-IPF patients, though anticoagulants have been associated with detrimental effects

Prompt detection of comorbid conditions and appropriate treatment of these comorbidities may contribute to enhanced survival of patients with IPF

The standard of care in general for patients with IPF has improved and may have accounted for the apparent change in the natural course of IPF