Comorbidities in IPF: still things to learn

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Conflict of interests disclosures

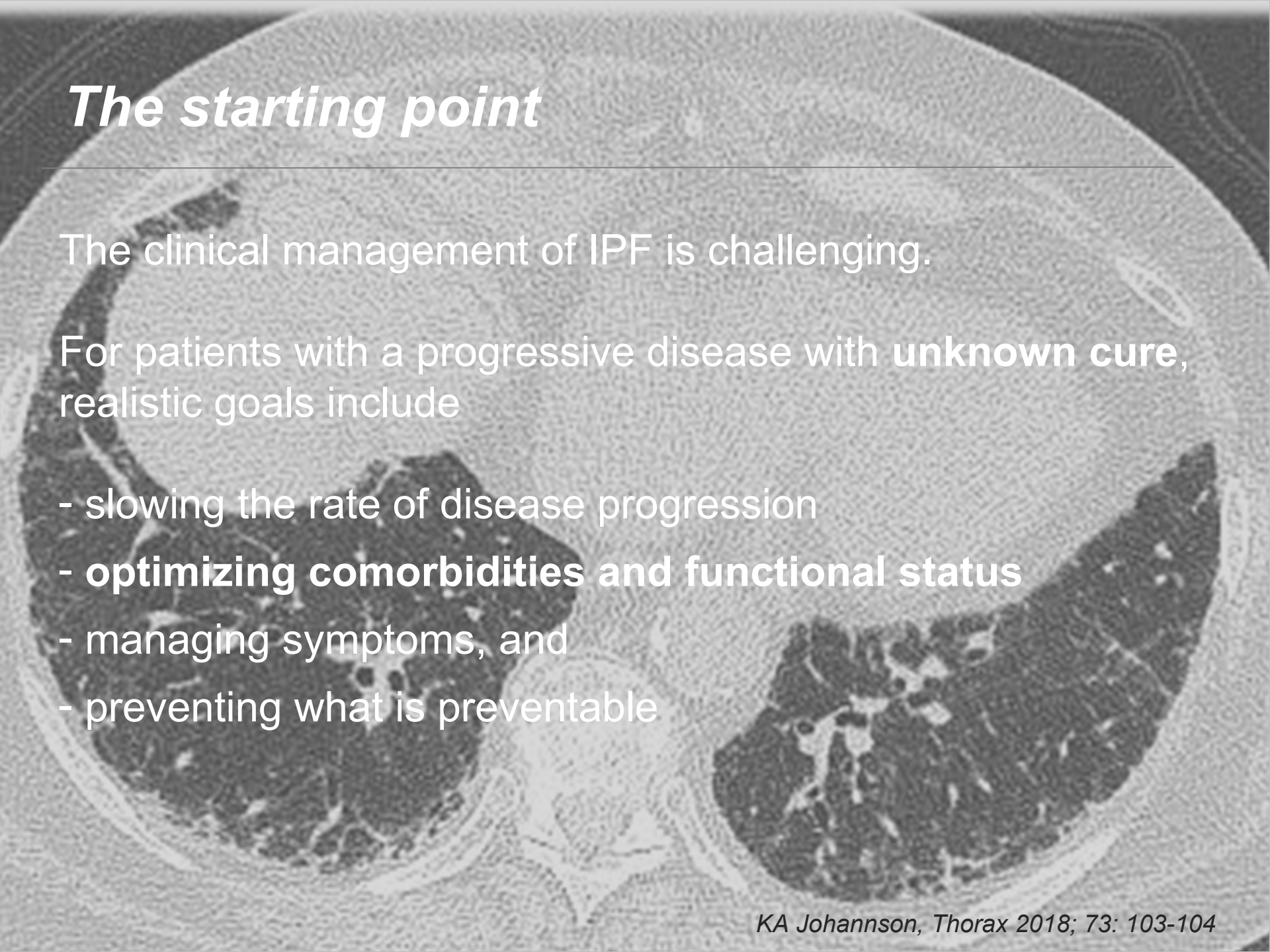
Boehringer Ingelheim

The starting point

The clinical management of IPF is challenging.

For patients with a progressive disease with **unknown cure**, realistic goals include

- slowing the rate of disease progression
- **optimizing comorbidities and functional status**
- managing symptoms, and
- preventing what is preventable



KA Johannson, Thorax 2018; 73: 103-104

- Prospective multicenter clinical trials provide many valuable information about the natural history of IPF
- The inclusion/exclusion criteria of these studies are restrictive relating to disease severity
- Patients with unstable or deteriorating cardiac or pulmonary disease or **severe comorbidities** are excluded

Real-world evidence

- *Real-world evidence suggests that **comorbid conditions are prevalent** in patients with IPF in clinical practice*

- *In a real-world study about 272 patients with IPF at a tertiary care centre found that 12% had no comorbidities, 58% had 1-3 comorbidities and 30% had 4-7 comorbidities*

Kreuter M et al. PlosOne 2016; 11(3):e0151425. doi: 10.1371/journal.pone.0151425

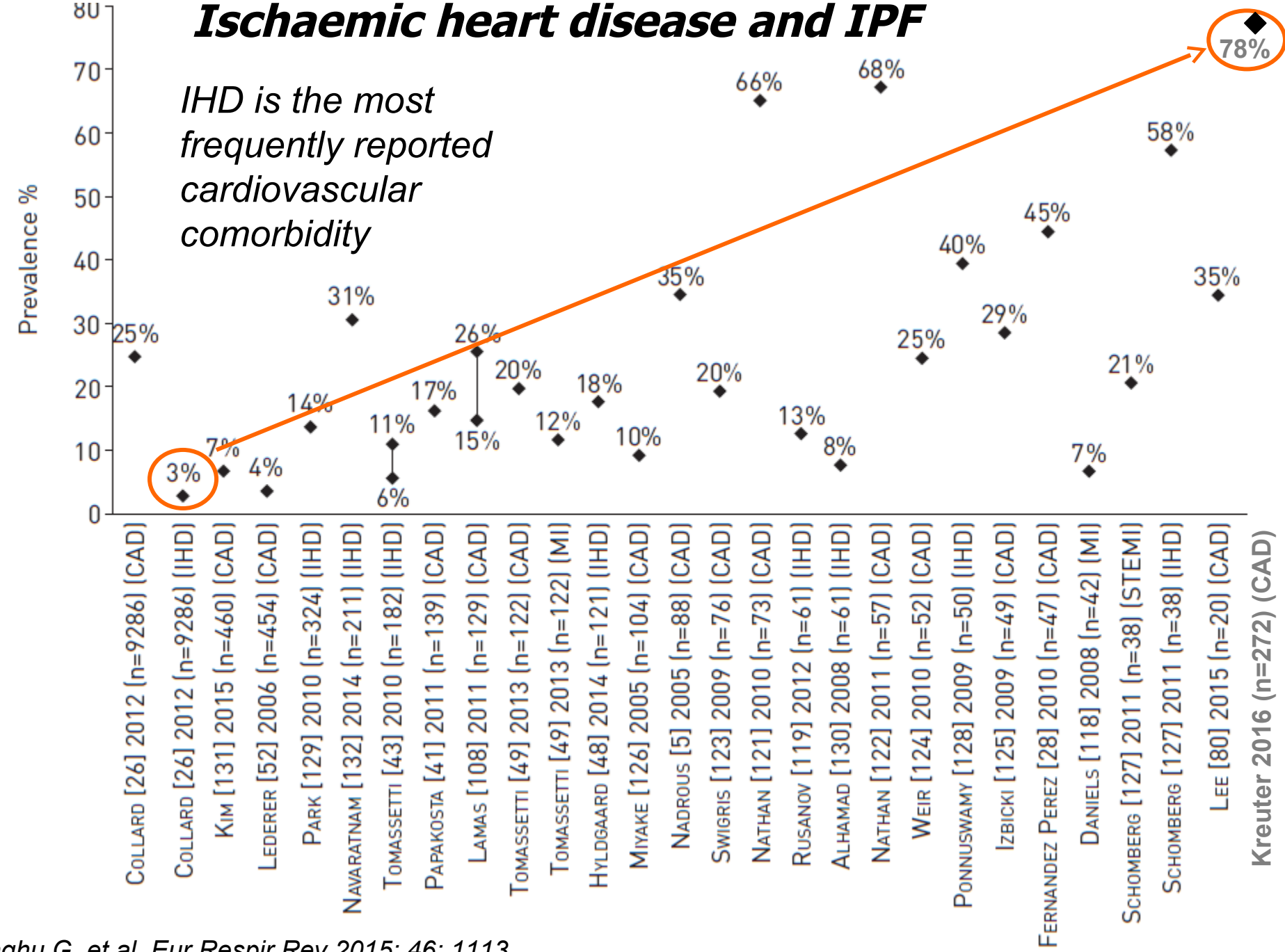
- ***Identification and treatment of comorbidities may help to improve patients' health-related quality of live and survival***

What's the prevalence of comorbidites in IPF?

*The reported **prevalence of comorbidities is variable;** this depends on the type of studies in which the data was analyzed and how comorbidities were studied and defined*

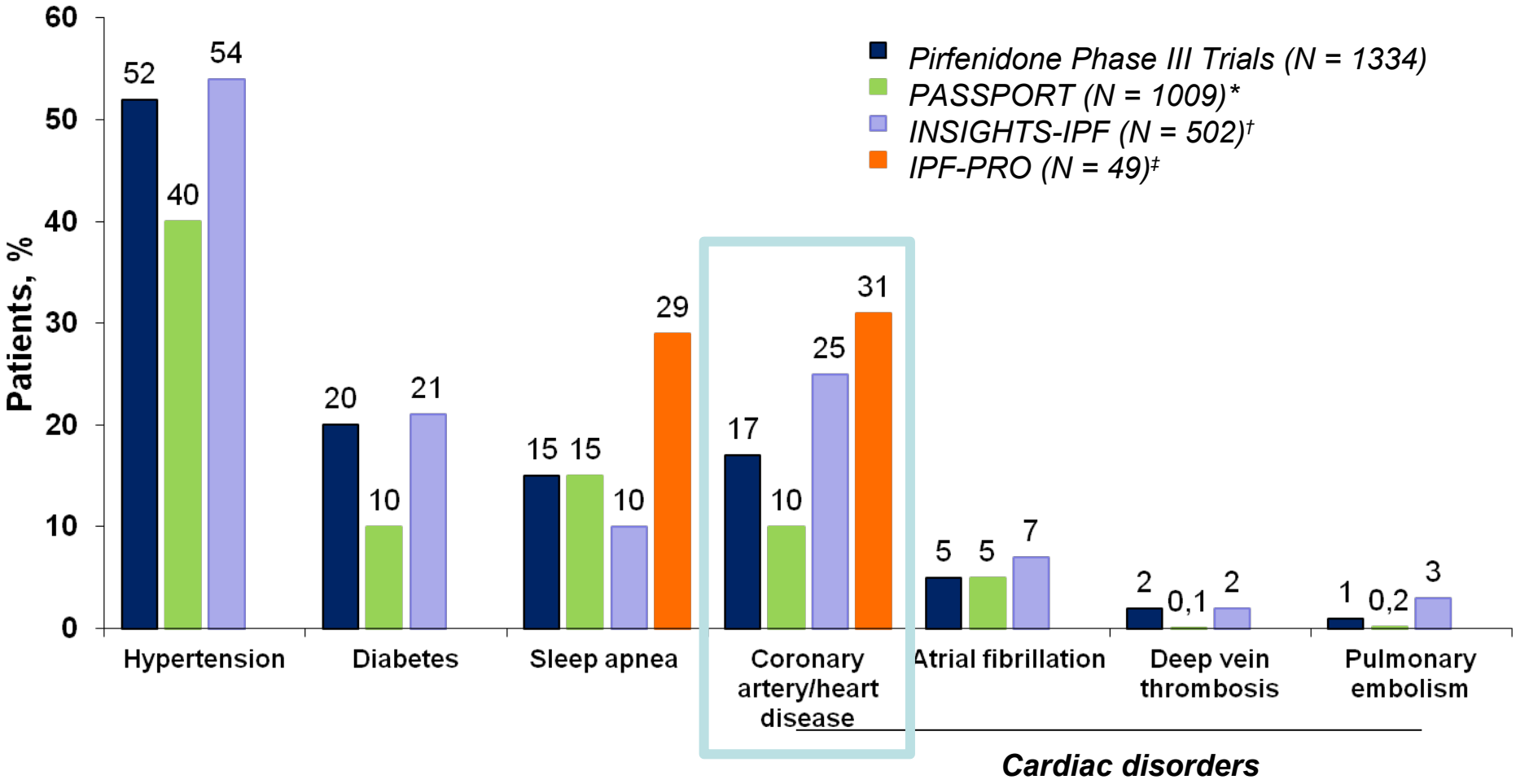
Ischaemic heart disease and IPF

IHD is the most frequently reported cardiovascular comorbidity



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

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):363A.

Glassberg et al. ATS 2016 P397

- Some comorbidities are conseguences of the IPF itself (i.e. pulmonary hypertension*)*

- Others can be explained by common risk factors (i.e. smoke for lung cancer and COPD)

- Several comorbidities, especially gastroesophageal reflux disease, are discussed as a potential cause of IPF

- Their presence may also be associated with a higher risk of acute exacerbations and mortality

What's the role of comorbidities on survival and hospitalizations in IPF?

Methods

- This is a retrospective observational study using administrative databases of Lombardy region
- **Incident IPF cases** from 2005 to 2010 are identified based on hospitalizations and outpatient visits
- Healthcare accesses and vital status are traced up to December 31st 2010
- Demographic and clinical characteristics at onset are evaluated
- The effect of sex, age and Charlson Comorbidity Index (CCI) on survival and time to first hospitalization are assessed through Cox proportional hazard models

Caminati A et al. Intern Emerg Med. 2021; 7:1793-1802.

Characteristics of the study population

	Female	Male	Total
N (%)	841 (40.18)	1,252 (59.82)	2,093
Age at onset			
mean ± sd	70.69 ± 13.55	69.71 ± 12.60	69.98 ± 12.99
Chronic comorbidity			
Myocardial Infarction*	39 (4.64)	185 (14.78)	224 (10.70)
Congestive Heart Failure*	153 (18.19)	269 (21.49)	422 (20.16)
Peripheral Vascular Disease*	29 (3.45)	134 (10.70)	163 (7.79)
Dementia	16 (1.90)	18 (1.44)	34 (1.62)
Chronic Pulmonary Disease*	283 (33.65)	520 (41.53)	803 (38.37)
Peptic Ulcer Disease*	7 (0.83)	30 (2.40)	37 (1.77)
Renal Disease*	48 (5.71)	120 (9.58)	168 (8.03)
AIDS/HIV*	0 (0.00)	3 (0.24)	3 (0.14)
Diabetes*	111 (13.20)	214 (17.09)	325 (15.53)
Cerebrovascular Diseases*	97 (11.53)	190 (15.18)	287 (13.71)
Liver Diseases	60 (7.13)	116 (9.27)	176 (8.41)
Tumour*	95 (11.30)	175 (13.98)	270 (12.90)
Charlson Comorbidity Index			
0*	303 (36.03)	319 (25.48)	622 (29.72)
1-2	353 (41.97)	548 (43.77)	901 (43.05)
≥ 3*	185 (22.00)	385 (30.75)	570 (27.23)

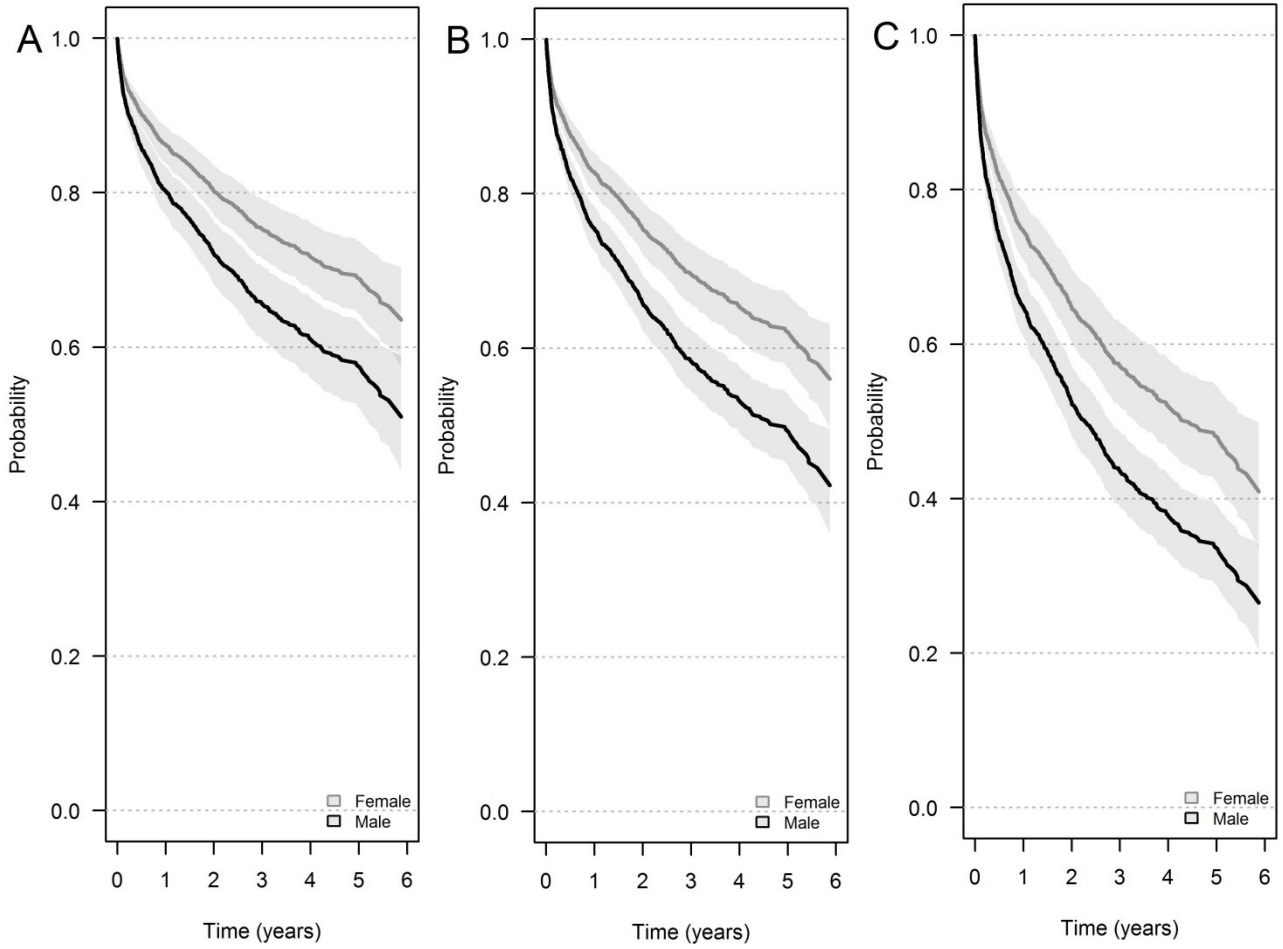
**p-value<0.05, Female vs. Male*

Outcomes of interest during the follow-up

	Female	Male	Total
N	841	1,252	2,093
Deaths, n (%)*	271 (32.22)	553 (44.17)	824 (39.37)
Drop-out, n (%)	6 (0.71)	12 (0.96)	18 (0.86)
Patients hospitalized, n (%)			
For any cause*	510 (60.64)	828 (66.13)	1,338 (63.93)
For causes related to IPF	221 (26.28)	375 (29.95)	596 (28.48)
Patients hospitalized in acute wards, n (%)			
For any cause*	449 (53.39)	759 (60.62)	1,208 (57.72)
For causes related to IPF*	161 (19.14)	311 (24.84)	472 (22.55)
Survival time (years), mean ± s.e.*	4.07 ± 0.09	3.39 ± 0.08	3.66 ± 0.06
Time to a 1st admission in hospital (years), mean ± s.e.			
For any cause*	1.94 ± 0.09	1.53 ± 0.07	1.71 ± 0.06
For causes related to IPF*	4.12 ± 0.10	3.84 ± 0.09	3.96 ± 0.07
Time to a 1st admission in acute hospital ward (years), mean ± s.e.			
For any cause*	2.46 ± 0.10	1.92 ± 0.07	2.14 ± 0.06
For causes related to IPF*	4.65 ± 0.09	4.19 ± 0.09	4.38 ± 0.06

** p value <0.05 female vs male*

Survival probability during follow-up



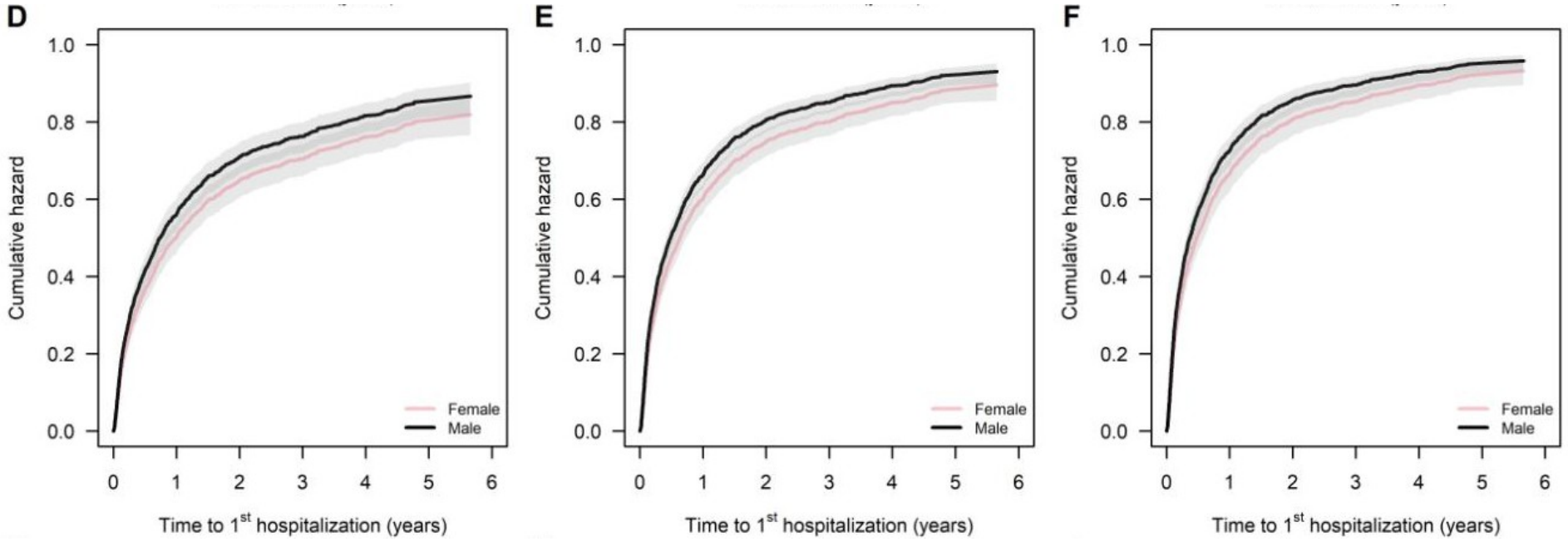
Panel A: *survival functions estimated by sex, for 70-year old patient (mean age at IPF onset) and no chronic comorbidities (CCI equal to 0).*

Panel B*: survival functions estimated by sex, for 70-year old patient (mean age at IPF onset) and CCI equal to 1 or 2.*

Panel C: *survival functions estimated by sex, for 70-year old patient (mean age at IPF onset) and CCI more than 2.*

Caminati A et al. Intern Emerg Med. 2021; 7:1793-1802.

Probability of a first hospital admission for any cause during follow-up



Panel D-F. *Probability of first hospitalization estimated by sex, for 70-year old patient (mean age at IPF onset) and no chronic comorbidities (CCI equal to 0) (**panel D**), CCI equal to 1 or 2 (**panel E**) and CCI more than 2 (**panel F**).*

Caminati A et al. Intern Emerg Med. 2021; 7:1793-1802.

Our data source provided one of the largest samples of unselected patients ever considered with a long period of follow up

Our study, based on real-life data, confirmed that the risks of death and hospitalization are high in IPF patients

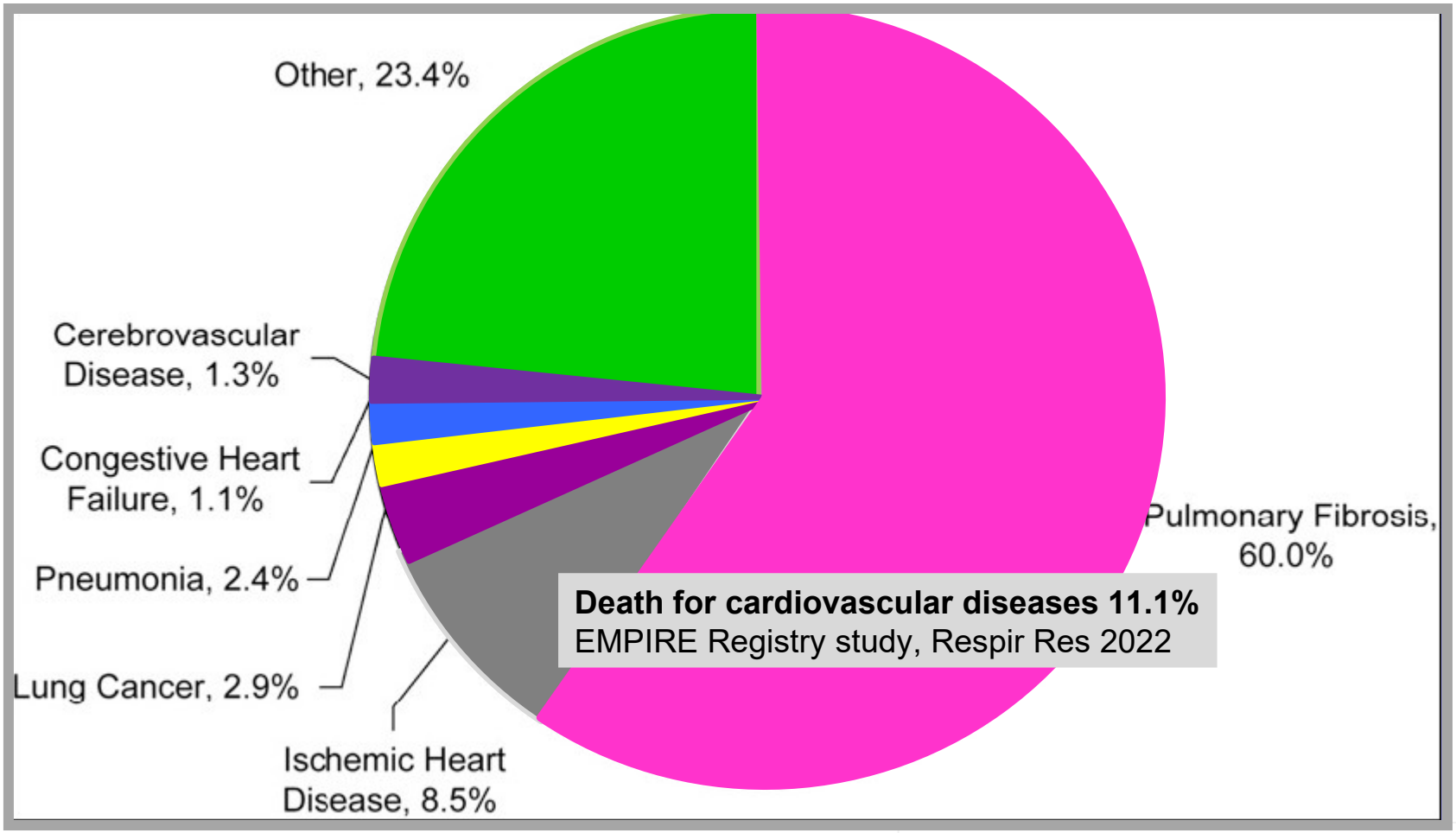
Age, sex, and comorbidities play a role in the clinical course of the disease

The number of comorbidities influenced prognosis

Caminati A et al. Intern Emerg Med. 2021; 7:1793-1802.

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



Cardiovascular disease *is the second most common cause of death in IPF patients, being responsible for up to*

10% of deaths

It's important to research a cardiovascular marker that could independently predict the risk of cardiovascular accidents in IPF patients

Among surrogate markers of cardiovascular risk, ***arterial elastance*** *is a plausible candidate. It represents the net arterial load exerted on the left ventricle, reflecting systemic arterial pressure and wall distensibility, and describing the rigidity of the arterial wall*

Arterial elastance may be significantly increased in patients with mild-to-moderate IPF

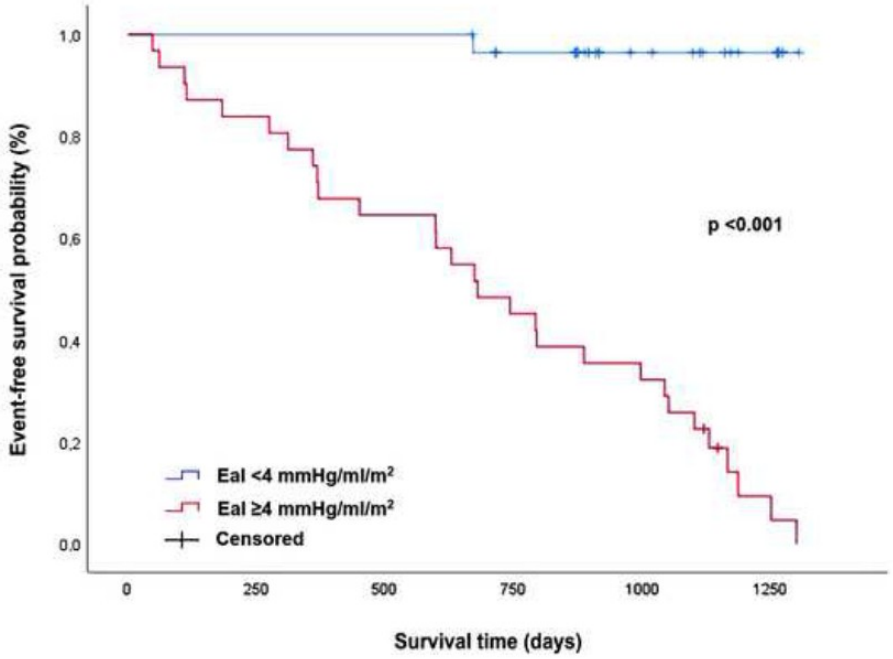
It can be used as noninvasive tool for the diagnostic and prognostic risk stratification of stable patients with mild-to-moderate IPF

An arterial elastance index ≥4 mmHg/ml/m2 at basal evaluation could help the clinician to identify IPF patients with faster disease progression and/or increased probability of adverse pulmonary and/or cardiovascular events over a medium-term follow-up

Sonaglioni A. et al. Int J Cardiovasc Imaging ; 2022: doi: 10.1007/s10554-022-02541-y

CLINICAL PARAMETERS			
	IPF pts (n = 60)	**Controls (n = 60)**	**p value**
Demographics and anthropometrics			
Age (yrs)	73.8 ± 6.6	72.1 ± 9.0	0.24
Males (%)	45 (75.0)	40 (66.6)	0.42
BSA (m^2)	1.90 ± 0.2	1.87 ± 0.1	0.30
MHI	2.40 ± 0.36	2.33 ± 0.45	0.34
Yrs from diagnosis of IPF	3.4 ± 2.9	/	
Cardiovascular risk factors			
Smokers (%)	45 (75.0)	40 (66.6)	0.42
Smoking exposure pack-years	27 ± 8.3	25 ± 7.6	0.17
Hypertension (%)	26 (43.3)	30 (50.0)	0.58
Type 2 diabetes mellitus (%)	12 (20.0)	14 (23.3)	0.82
Dyslipidemia (%)	20 (33.3)	22 (36.6)	0.85

HEMODYNAMIC INDICES AND VAC PARAMETERS			
	IPF pts (n = 60)	**Controls (n = 60)**	**p value**
HR (bpm)	76.8 ± 12.3	69.0 ± 8.3	**<0.001**
ESP (mmHg)	122.9 ± 16.0	120.1 ± 12.7	0.29
SVi (ml/m^2)	32.1 ± 7.8	35.6 ± 8.3	**0.01**
COi ($ml/min/m^2$)	2.4 ± 0.6	2.5 ± 0.6	0.36
LVESVi (ml/m^2)	21.4 ± 2.9	20.9 ± 3.3	0.38
EaI ($mmHg/ml/m^2$)	4.1 ± 1.3	3.5 ± 1.0	**0.01**
EesI ($mmHg/ml/m^2$)	5.8 ± 1.2	5.9 ± 1.2	0.89
VAC	0.7 ± 0.2	0.6 ± 0.2	**0.01**



Sonaglioni A. et al. Int J Cardiovasc Imaging ; 2022: doi: 10.1007/s10554-022-02541-y

Coronary artery calcium (CAC) is a highly specific feature of coronary atherosclerosis

In recent years, chest CT has become the most important noninvasive tool to detect CAC

Calcium scoring, mainly the Agatston score, has been used to predict future risk of cardiovascular events

We investigated the possible association between the CAC score at IPF diagnosis and adverse cardiovascular events and all-cause mortality in a mid-term follow-up

Multidisciplinary diagnosis of IPF

(patients were retrospectively included from June 2014 to February 2019)

Demographic data, smoking history, comorbidities and PFT were recorded

Exclusion criteria were evaluated

Evaluation of HRCT at diagnosis time
Visual score and CAC score were calculated

Evaluation of HRCT during follow-up
(almost 2 years)

Visual score and CAC score were calculated

Mortality for all cause and hospitalization for cardiovascular events were reported

Study Population, n	79
Age, mean ± SD	74.4 ± 7.6
Male sex, n (%)	57 (72.15)
Smoking history, n (%)	67 (86)
Tobacco consumption (pack-years), mean ± SD	26.5 ± 17.8
Systemic hypertension, n (%)	38 (48)
Diabetes mellitus, n (%)	18 (22.8)
Dyslipidemia, n (%)	29 (36.7)
Anti-fibrotic treatment, n (%) **Nintedanib** **Pirfenidone**	 38 (48) 41 (52)
Radiological aspects, n (%) **UIP definite** **UIP probable** **Undeterminate**	 50 (63.3) 18 (22.8) 11 (13.9)

Our findings suggest that IPF patients with ***a higher CAC score at diagnosis time have a marked increase in the risk of adverse cardiovascular events and mortality for all-cause*** *over a mid-term follow-up time.*

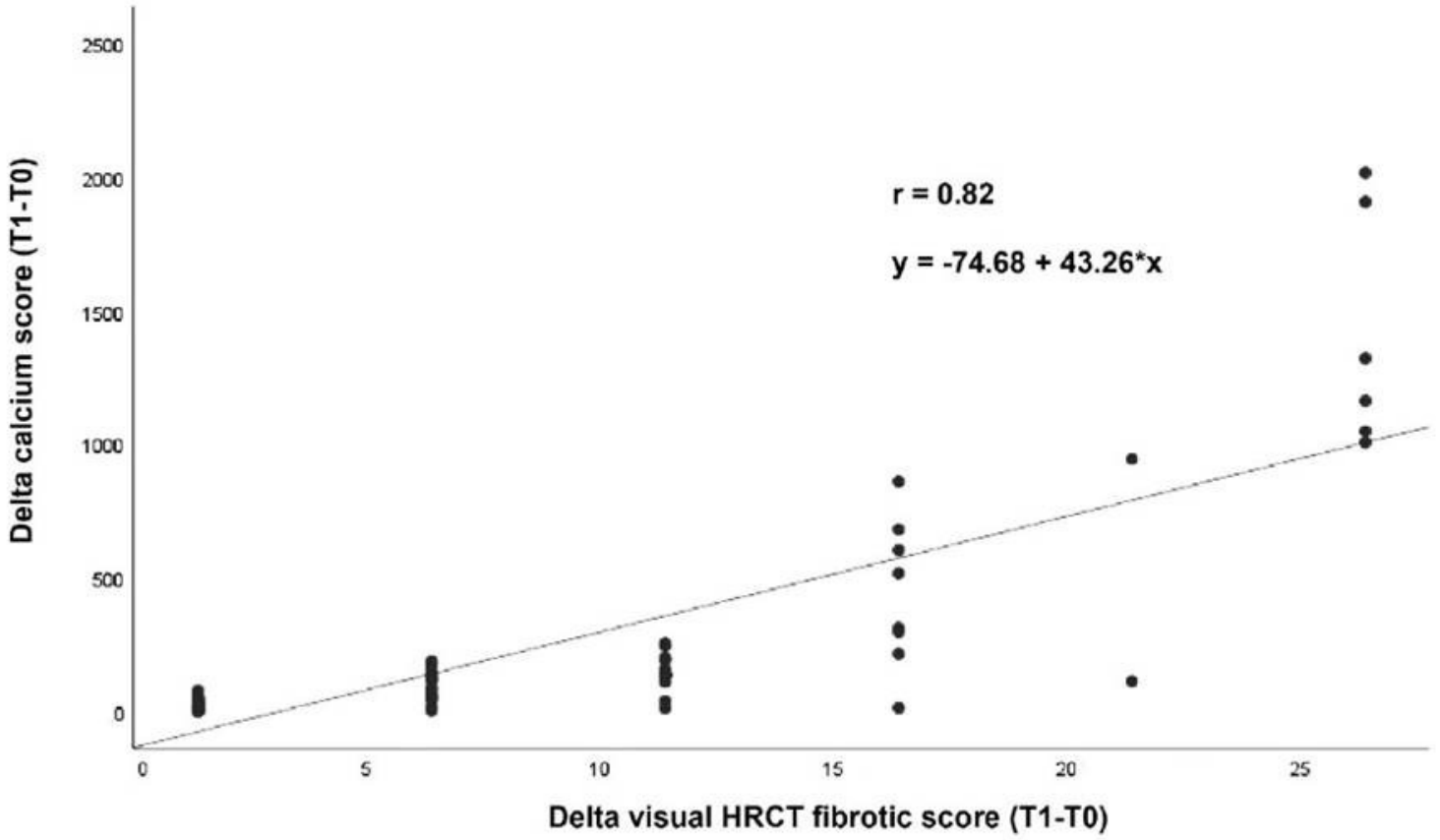
A higher CAC score ***is also associated with a higher functional and radiological progression of IPF itself****.*

This observation should be considered during the routine care of these patients.

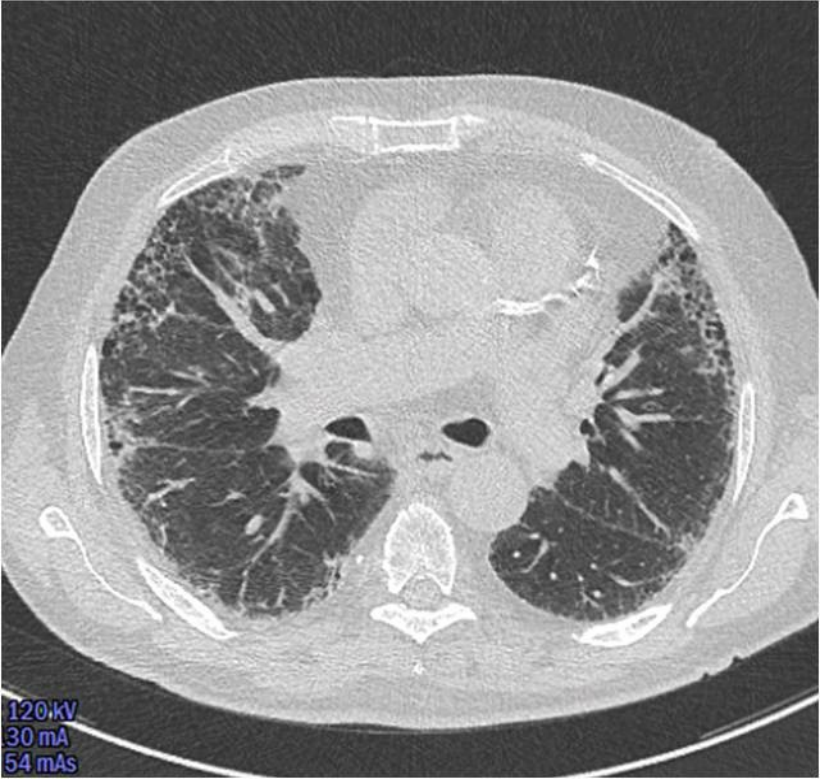
Radiologists should always describe the presence and extension of CAC in their reports and pulmonologists should consider CAC score as a significant prognostic factor.

Caminati A. et al. Minerva Med, 2022

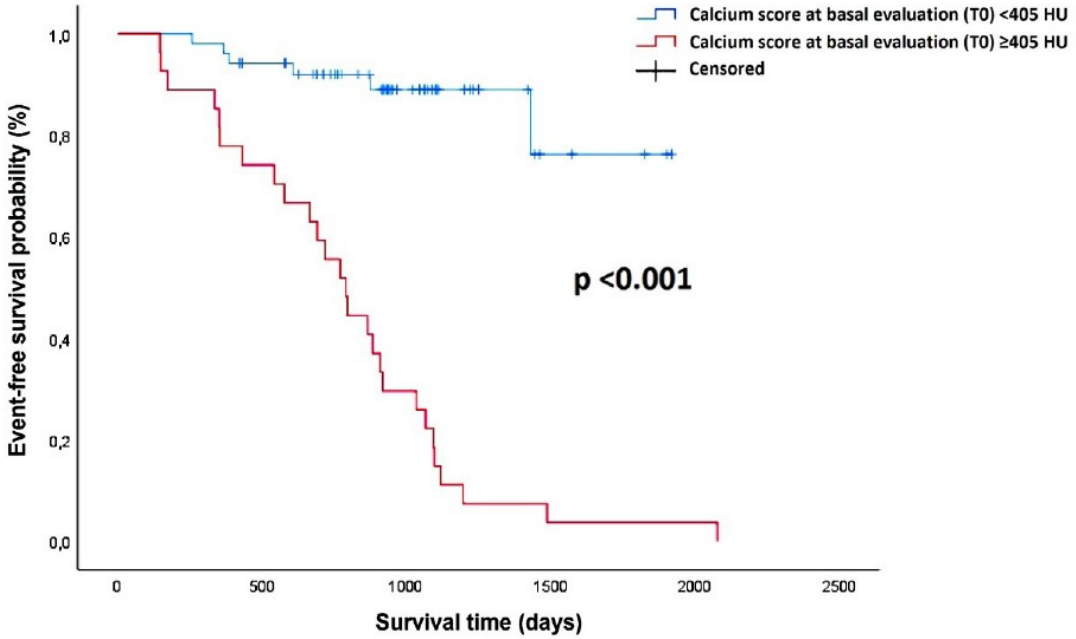
This correlation suggests a possible association between CAC score and radiological and functional IPF progression. The concomitant worsening of the atherosclerotic pathology and the pulmonary disease suggests that the two issues are strictly correlated, or at least have some risk factors in common



Caminati A. et al. Minerva Med, 2022



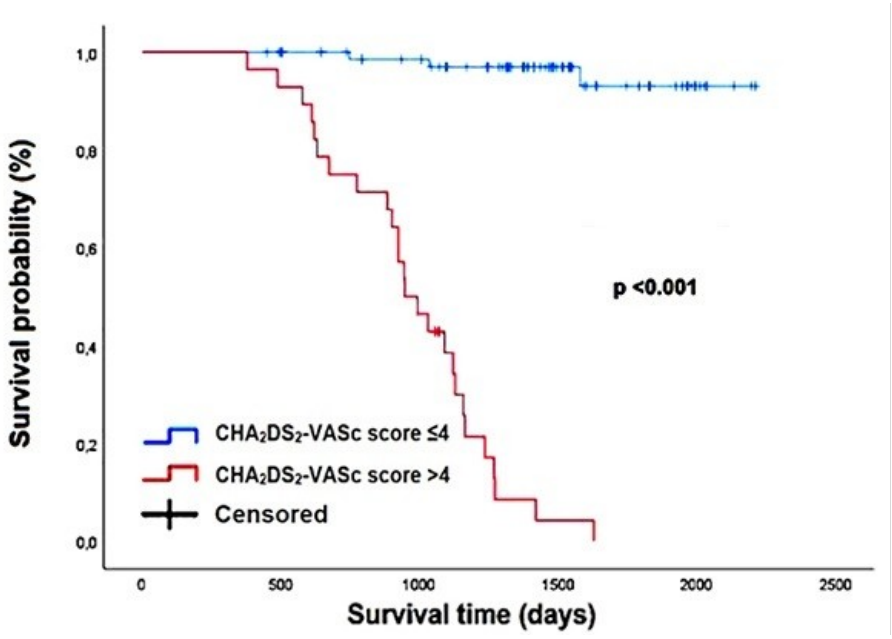
HRCT scan with parenchymal window in a patient with definite UIP pattern and coronary calcification of left anterior descending artery (LAD). CAC score is 410.



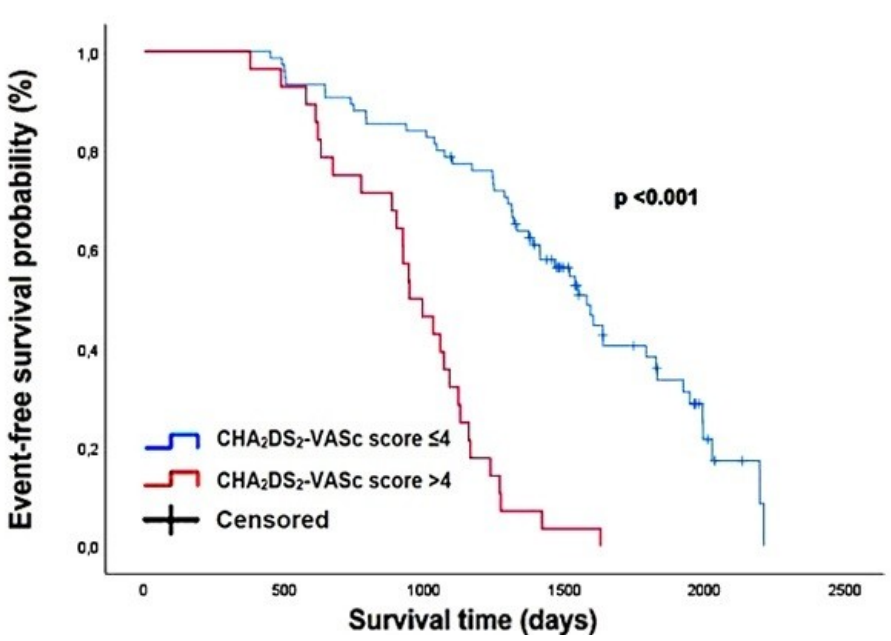
Caminati A. et al. Minerva Med, 2022

CHA_2DS_2-VASc score: Congestive heart failure or left ventricular dysfunction (1 point), Hypertension (1 point), Age ≥75 years (2 points), Diabetes (1 point), Stroke/TIA (2 points), Vascular disease (1 point), Age 65–74 years (1 point), and Sex category (female; 1 point)

Survival probability in IPF patients

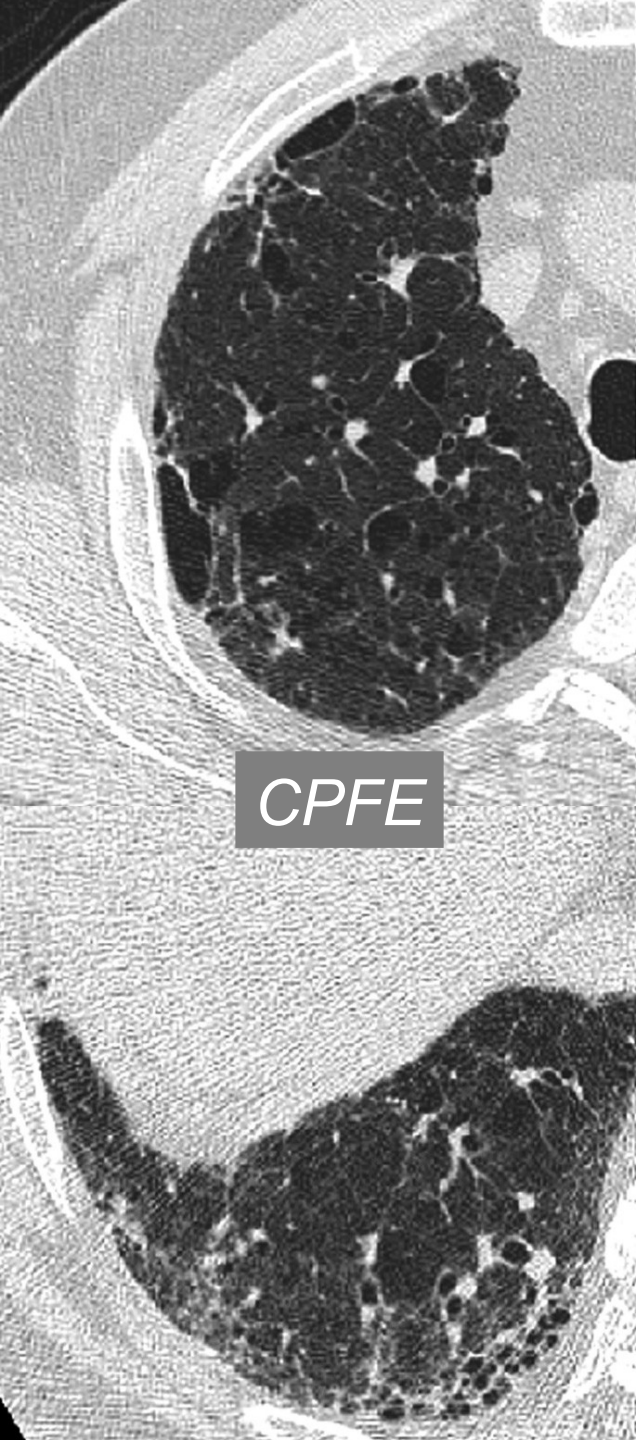


Event-free survival in IPF patients



Sonaglioni A. et al. Intern Emerg Med, in press

We focalized on cardiovascular diseases but many others comorbidities influence the prognosis in IPF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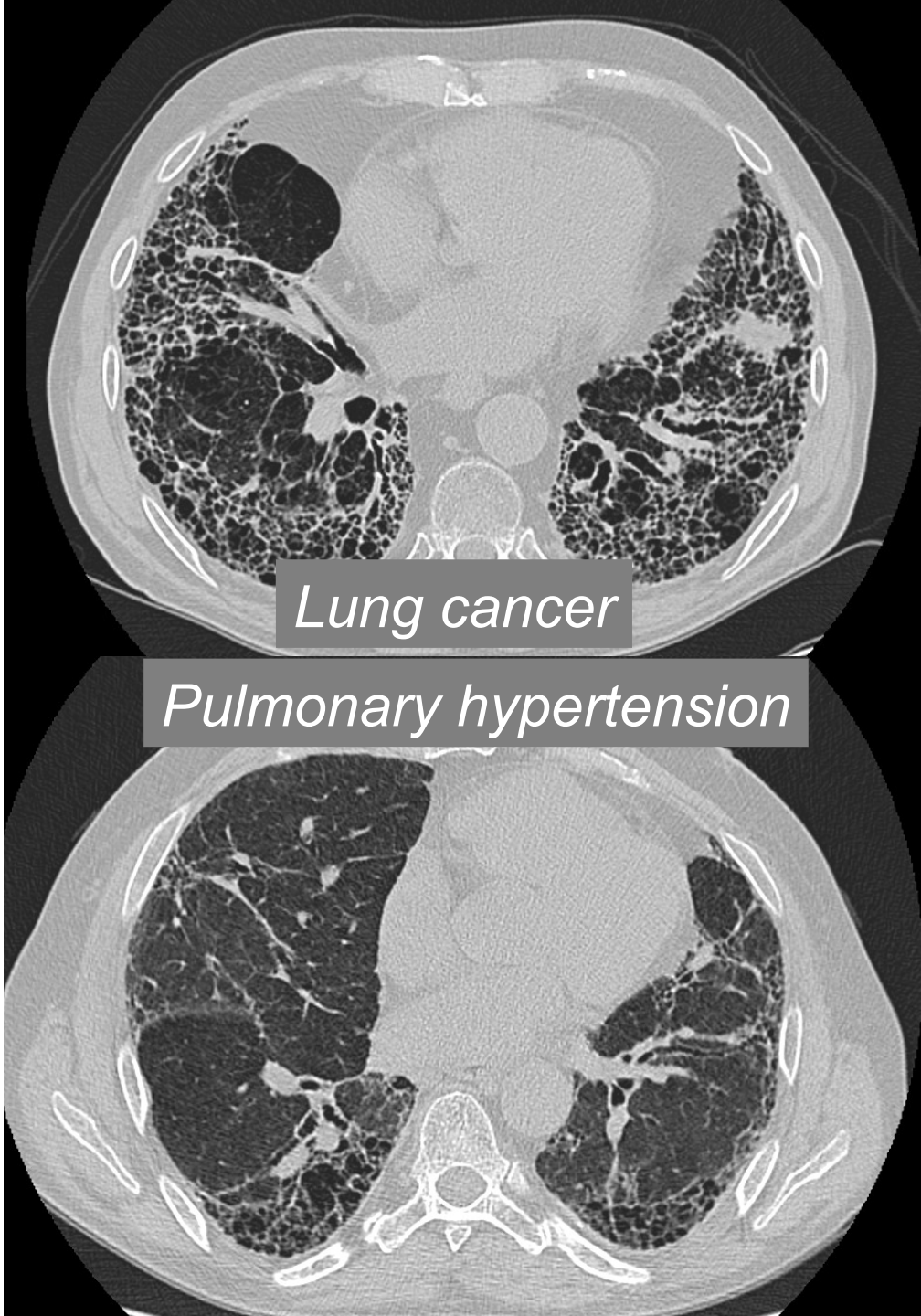
Lung cancer
Pulmonary hypertension

We focalized on cardiovascular diseases but many others comorbidities influence the prognosis in IPF

Is now the time for new international IPF guidelines to consider management and treatment of comorbidities how it was done for pulmonary hypertension?

Conclusions

- *Comorbidities are common in IPF patients and several may impact on survival*
- *The real prevalence of comorbidities varies in different studies and is difficult to define but* ***the number of comorbidities modify prognosis***
- *Arterial elastance and CAC score at IPF diagnosis may be used for prognostic risk stratification not only for adverse cardiovascular events but also for all-cause mortality*
- *It is unclear whether the increased prevalence of cardiovascular comorbidity in IPF patients is a result of the common risk factors or whether IPF in itself is an independent risk factor*

Conclusions

- *We have to adopt a global approach to IPF patients and consider all possible managing options, including the proactive identification and treatment of comorbidities*

- *We should go toward the concept of personalized medicine also in IPF patients*


Thank you