IPF의 최신 치료 약제

가천대 길병원 호흡기내과 정성환

Definition of IPF

- **chronic, progressive fibrosing interstitial pneumonia**
- **unknown cause**
- **occurring primarily in older adults**
- **limited to the lungs**
- **associated with the histopathologic and/or radiologic pattern of UIP.**

ATS . Idiopathic pulmonary fibrosis:guidelines. AJRCCM 2011

Main Pathogenic mechanism of IPF

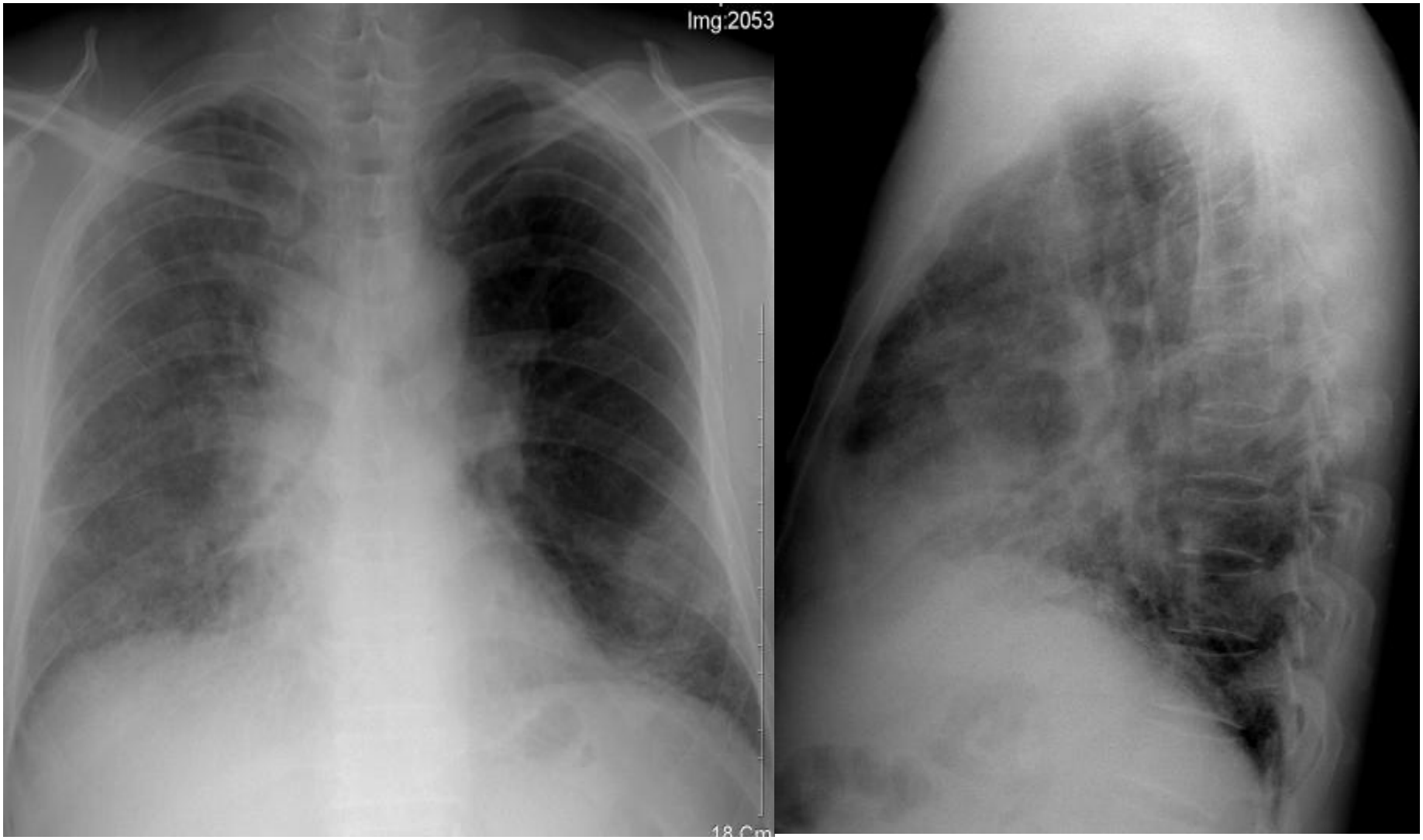
- **Alveolar epithelial cell injury and apoptosis**
- **Abnormal Fibroblast increase and proliferation, myofibroblast formation**
- **Inflammatory response: neutrophils, other inflammatory cells**

Pathogenic mechanism of IPF

The other factors for pathogenesis of IPF

- **Cytokine and chemokine imbalance; TGF, INF-g, CTGF**
- **Genetic factors; TNF-alpha gene,ACE polymorphism, Nrf2**
- **Microaspiration of gastric acid**
- **Othres: AGEs**
- **Environmental and occupational ; Dust, Metal particles**
  metabolic diseases ; DM

Virus; HHV8, EBV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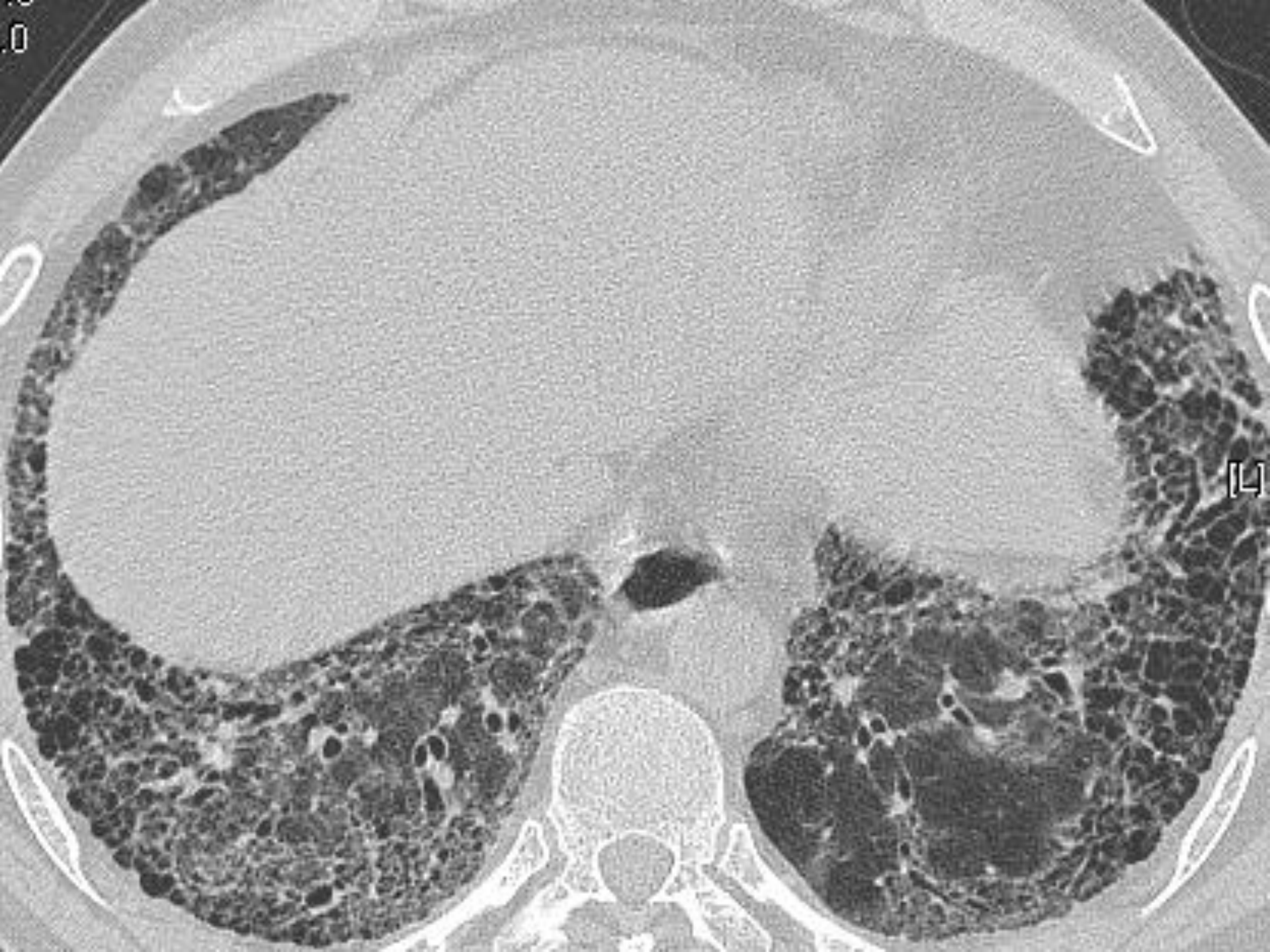
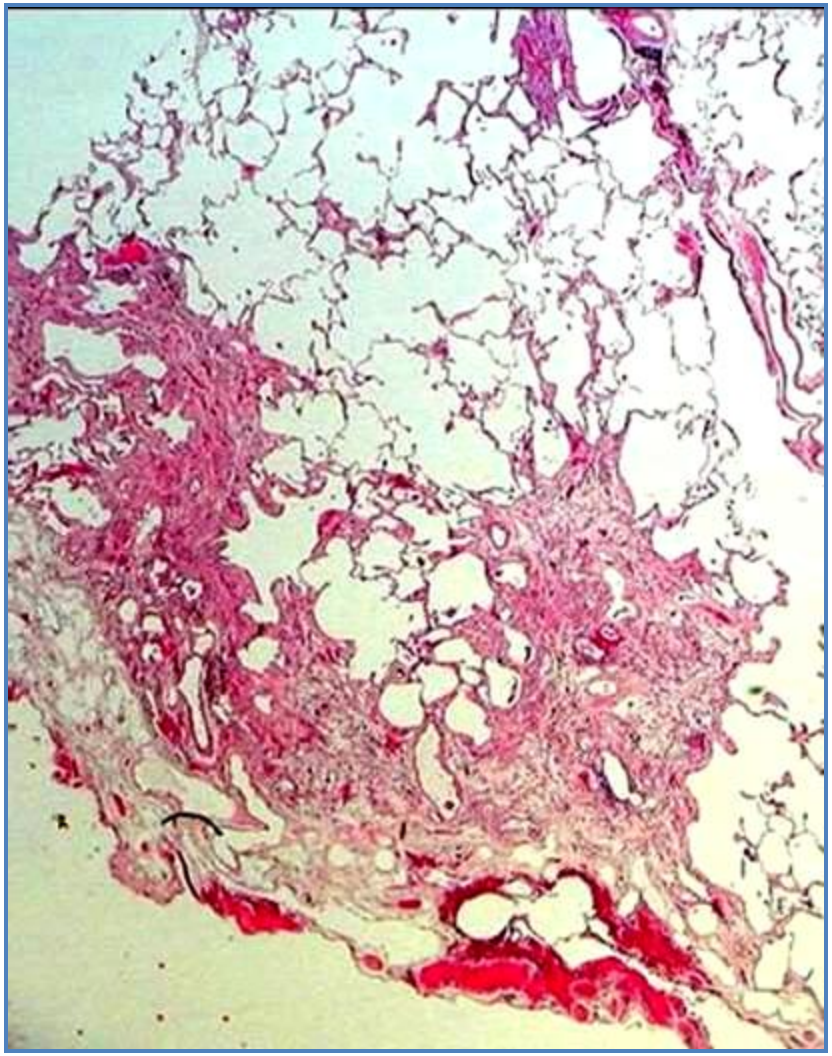
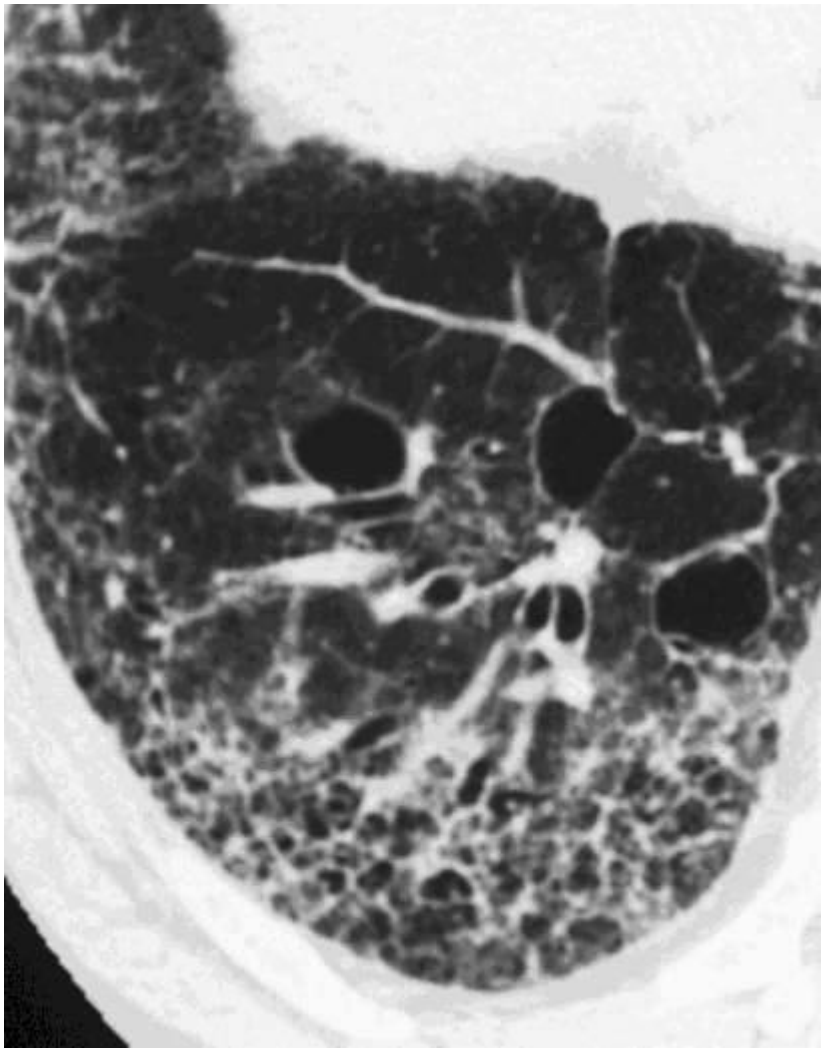


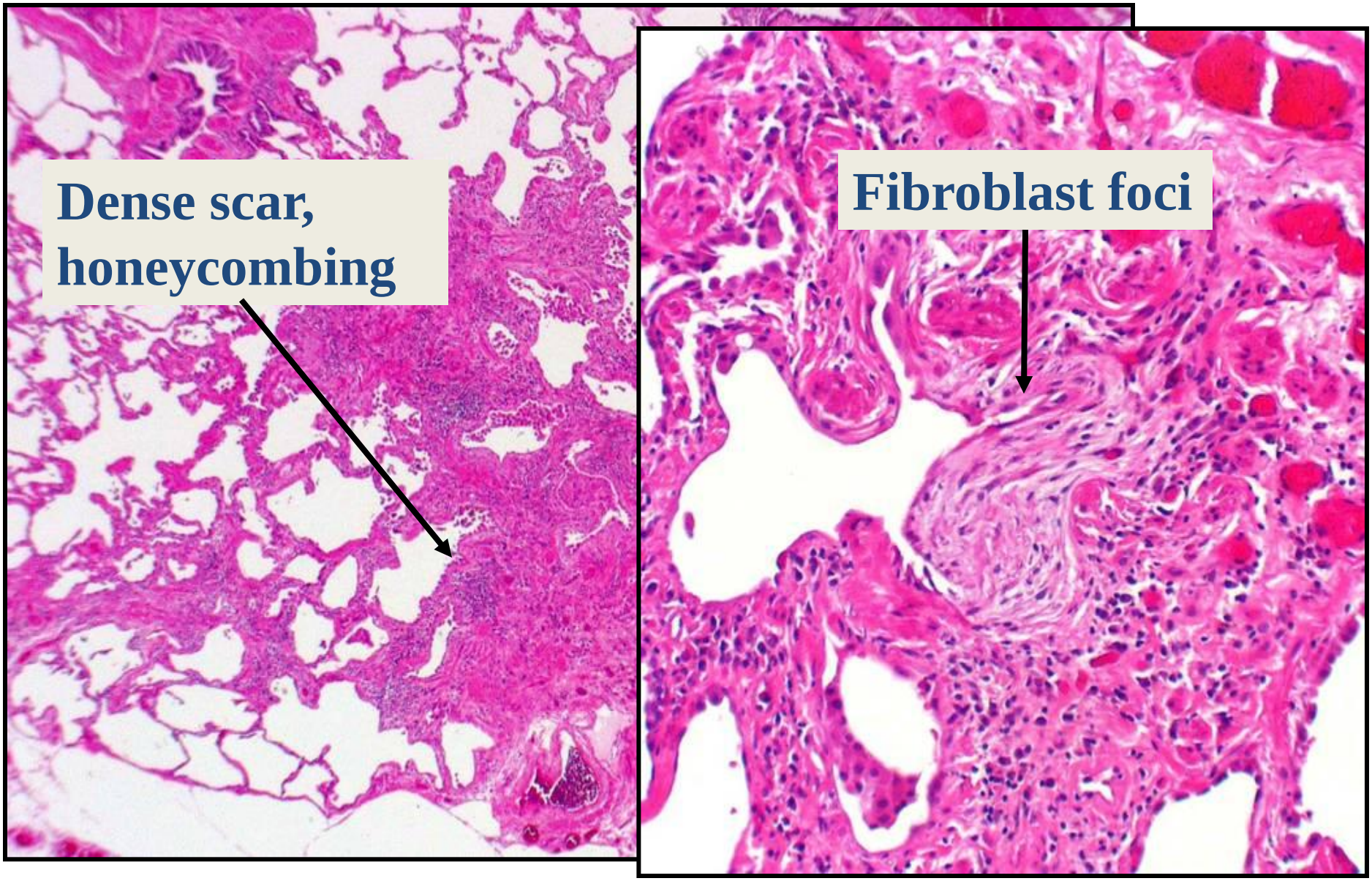
IPF(UIP)





- *Courtesy of Alessandra Cancellieri, Bologna, I*

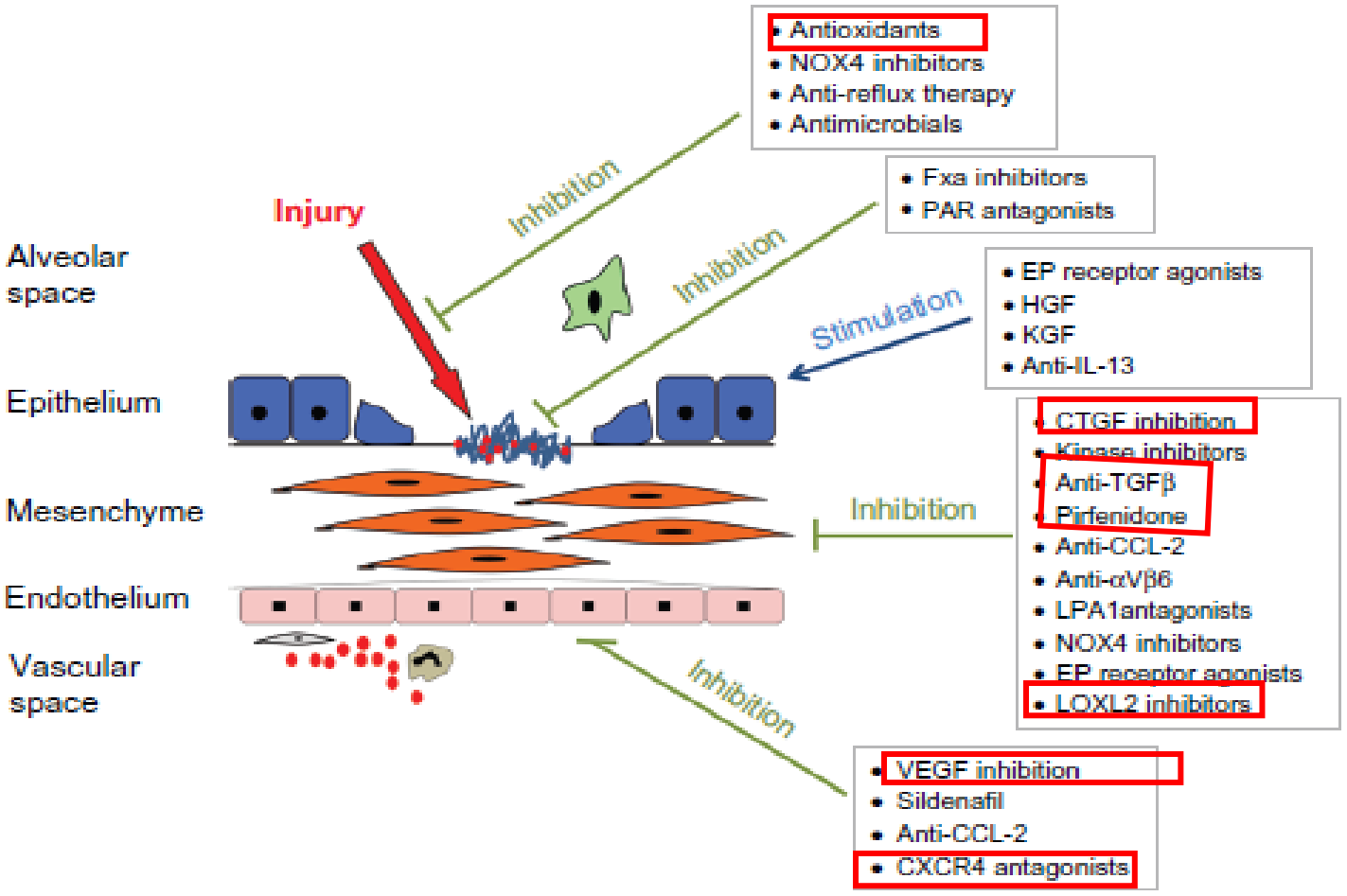
UIP: The most important pattern



IPF의 최 신 치 료 약 제

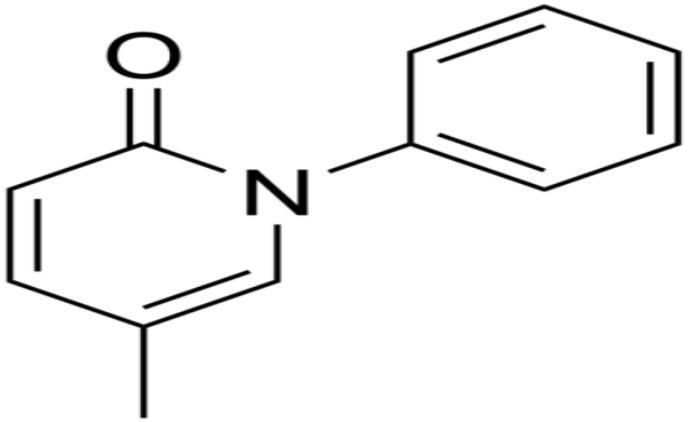
1. Pirfenidone
2. N acetyl cystein(NAC)
3. PDGF-R blocker(Nintedanib;BIBF1120)
4. IL-13 inhibitor(QAX576), IL-4 inhibitor, CCL2 inhibitor(CNTO888)
5. LOXL2(Lysyl oxidase like 2)inhibitor
6. Stem cell
7. Others;) NRF2 activator, TGF-beta inhibitor(GC1008), CTGF inhibitor (FG-3019

Current understanding of the pathogenesis of idiopathic pulmonary fibrosis (IPF)



* Huzaifa I Adamali et al. Drug Des Devel Ther. 2012

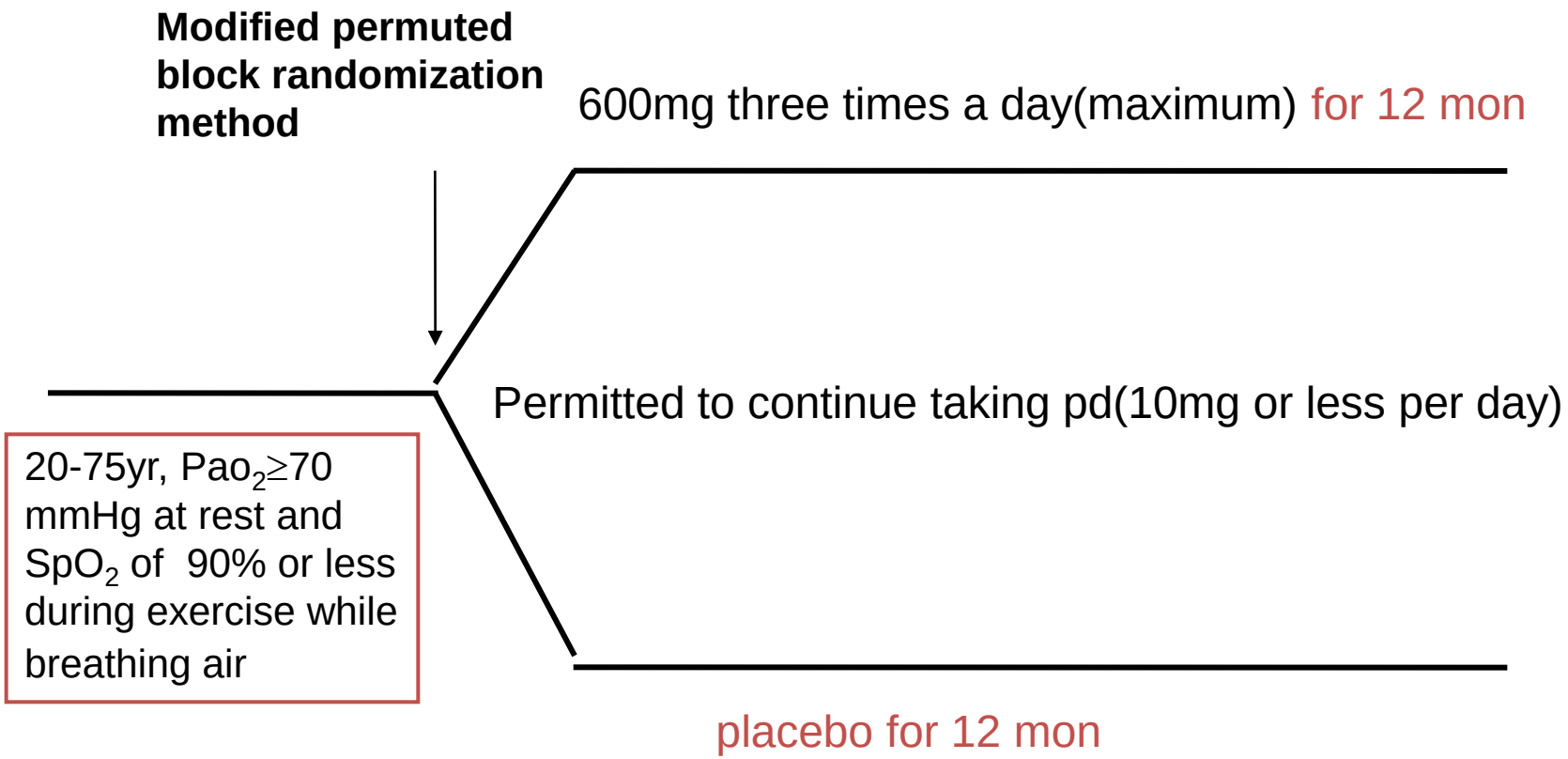
Pirfenidone



1. Oral pyridine
2. anti-inflammatory and antioxidant agent
3. inhibits transforming growth factor- beta , collagen

Double-blind, placebo-controlled Trial of Pirfenidone in patients with Idiopathic Pulmonary Fibrosis

Azuma A, 2005;171:1040-1047 AJRCCM



Between November 2000 and January 2001, 107 patients at 25 sites in Japan.

Primary end point ;

change in the lowest Spo_2 during a 6-minute steady- state exercise test(6MET) walk on treadmill at a constant speed improved ; greater than 4% increase in the lowest Spo deteriorated ; a 4% decreased or less

Adjusted the treadmill speed ; 40-80m/min on the base of the patient's comfort to be able to perform the 6MET while the lowest Spo_2 reached 90% or below.

Pirfenidone

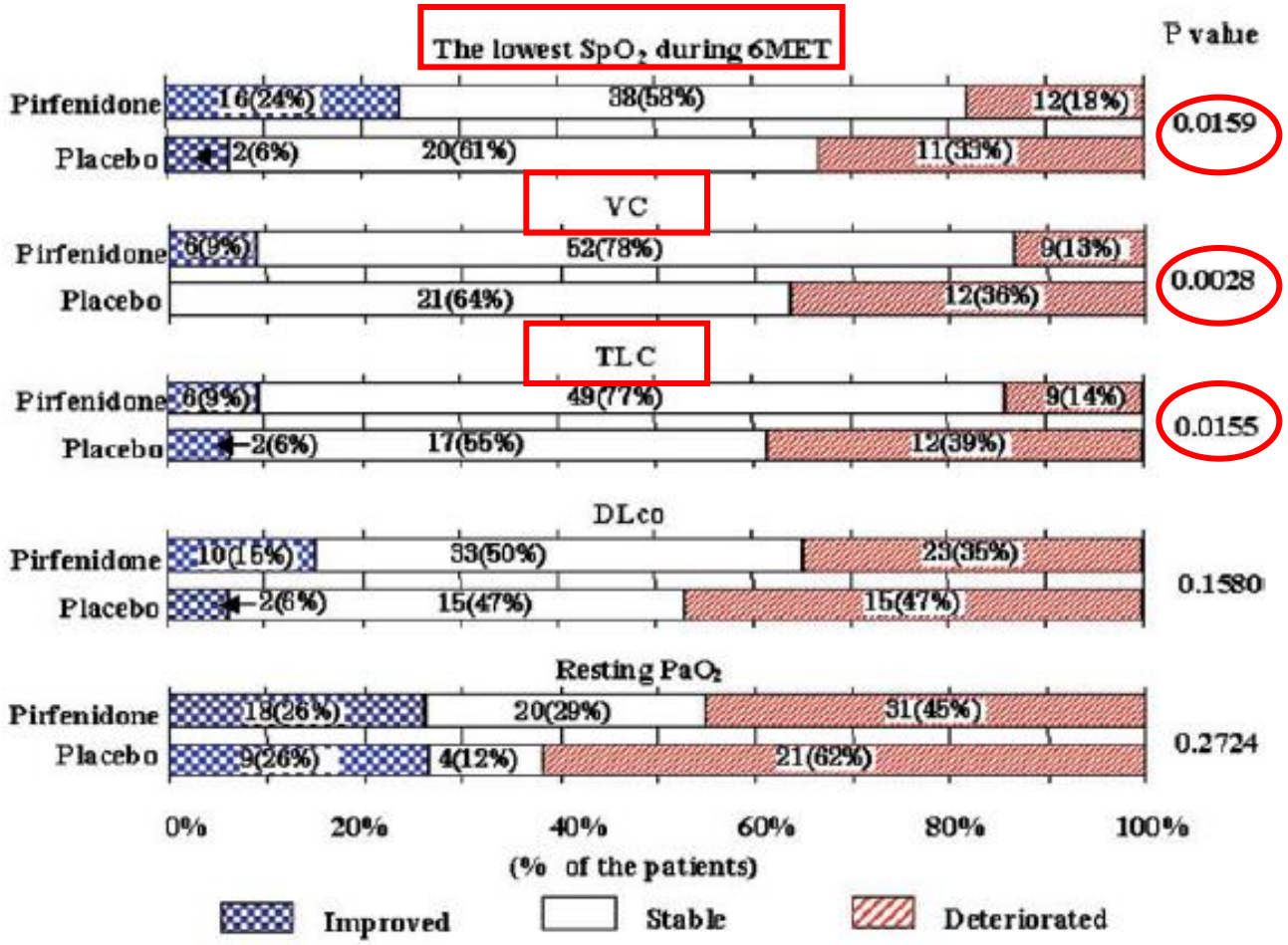
200mg three times a day for the first 2days
400mg three times a day for the 2 following days
600mg three times a day(maximum) for the last 3days

Comparison of change from baseline lowest Spo2 value during the 6MET and pulmonary functions

Comparison of Change from Baseline Lowest Sp_{O_2} Value during the 6MET and Pulmonary Functions

Analysis Group		6 Months			9 Months		
		Pirfenidone Mean ± SD	Placebo Mean ± SD	p Value[§]	Pirfenidone Mean ± SD	Placebo Mean ± SD	p Value[§]
All patients: full analysis set (FAS*)	Δ the lowest Sp_{O_2}, %	0.6364 ± 3.5502	−0.5484 ± 3.7933	0.1489	0.4697 ± 3.8838	−0.9355 ± 3.3559	0.0722
Patients completed 6MET[†]	Δ the lowest Sp_{O_2}, %	0.5600 ± 3.7643	−1.9091 ± 3.2500	0.0069	0.4600 ± 3.9857	−1.5909 ± 3.4039	0.0305
All patients: full analysis set (FAS*)	Δ VC, L	−0.01 ± 0.21	−0.08 ± 0.19	0.0995	−0.03 ± 0.22	−0.13 ± 0.19	0.0366
	Δ TLC, L	−0.02 ± 0.34	0.00 ± 0.35	0.7550	−0.05 ± 0.39	−0.09 ± 0.45	0.6154
	Δ $D_{L_{CO}}$, ml/min/mm Hg	−0.50 ± 2.07	−0.83 ± 2.16	0.4894	−0.57 ± 2.15	−1.19 ± 2.30	0.2120
	Δ Resting Pa_{O_2}, mm Hg	−2.09 ± 9.71	−3.19 ± 10.97	0.6171	−2.48 ± 10.30	−3.66 ± 10.43	0.5981

Categorized analysis of the lowest Spo_2 during the 6 MET and pulmonary functions in all patients at 9 months



Pirfenidone: Treatment for IPF

Double-Blind, Placebo Controlled Clinical Trial in Japan*

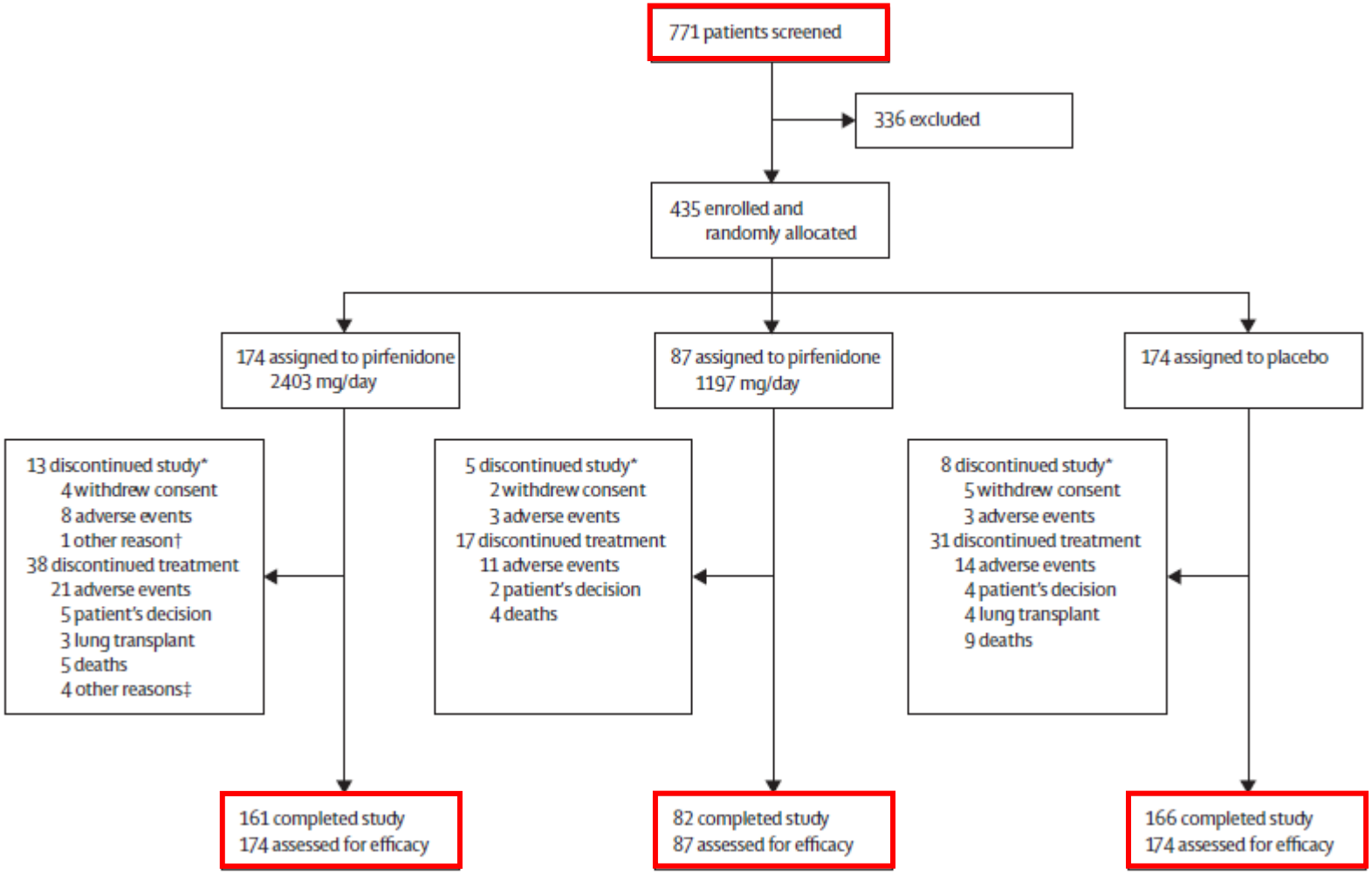
Results

Primary Endpoint;

- **Lowest SpO_2 during 6MET higher in the subset of pirfenidone group of patients completing the 6 minute walk at 6 months (p=0.0069), 9 months (p=0.0305)**
  - **a positive trend(p =0.07) was seen in all the patients in the pirfenidone group(full analysis set)**

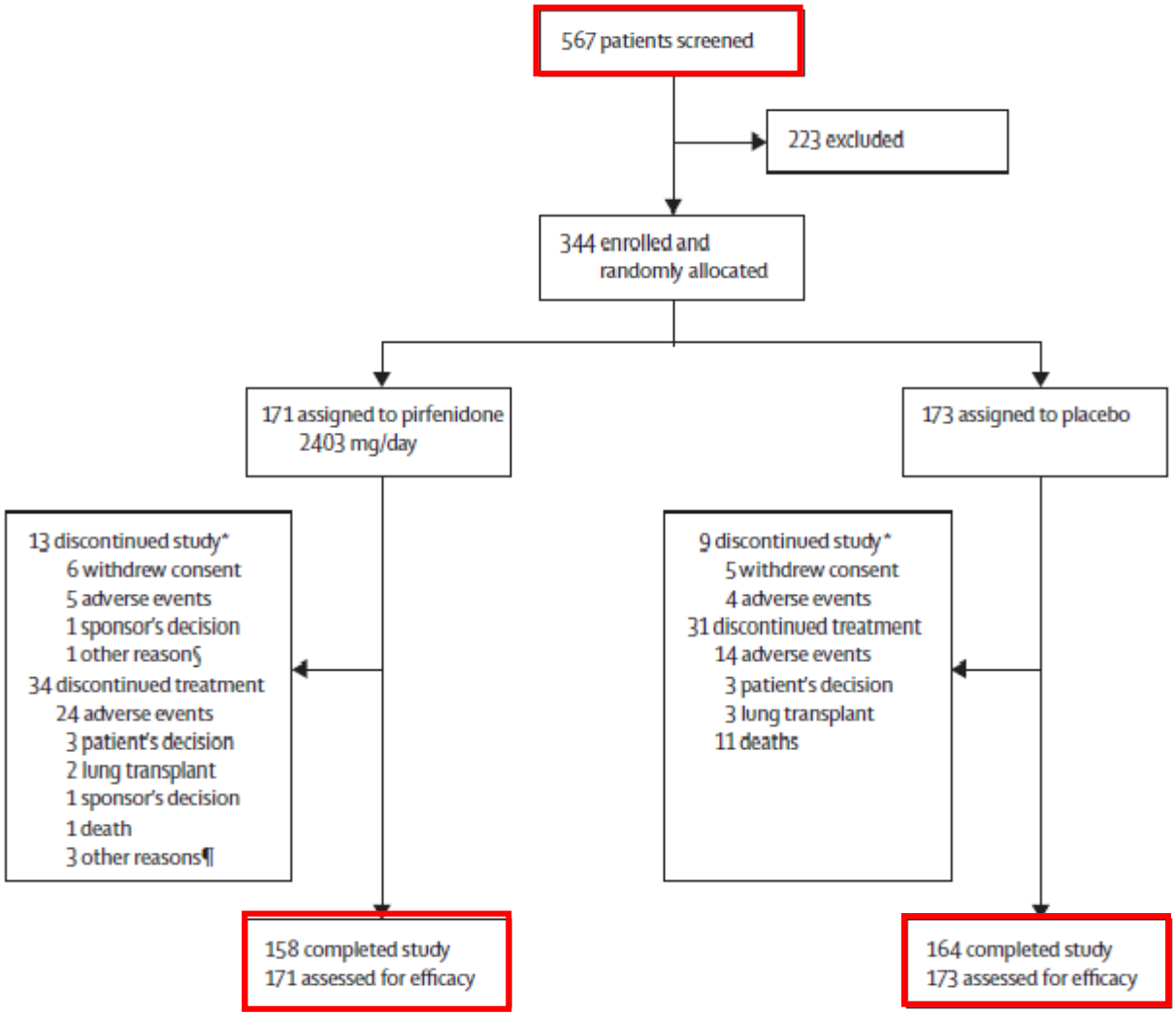
Azuma et al. AJRCCM (2005)

CAPACITY Trial profile Study 004



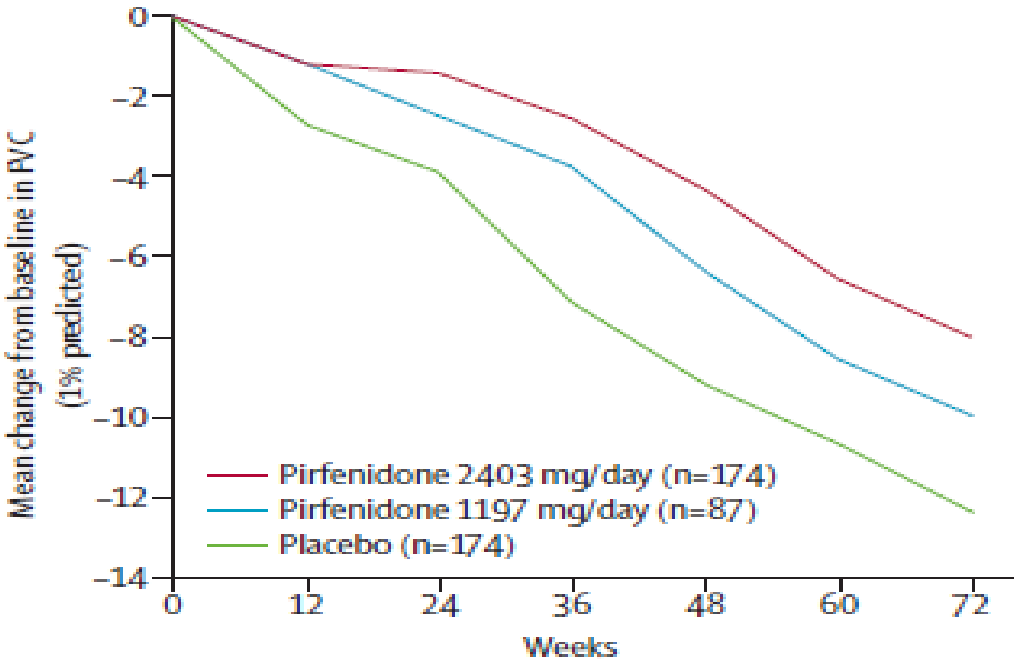
* Paul W Noble et al Lancet. 2011

CAPACITY Trial profile Study 006



* Paul W Noble et al Lancet. 2011

Mean change from baseline in percentage predicted FVC in study 004

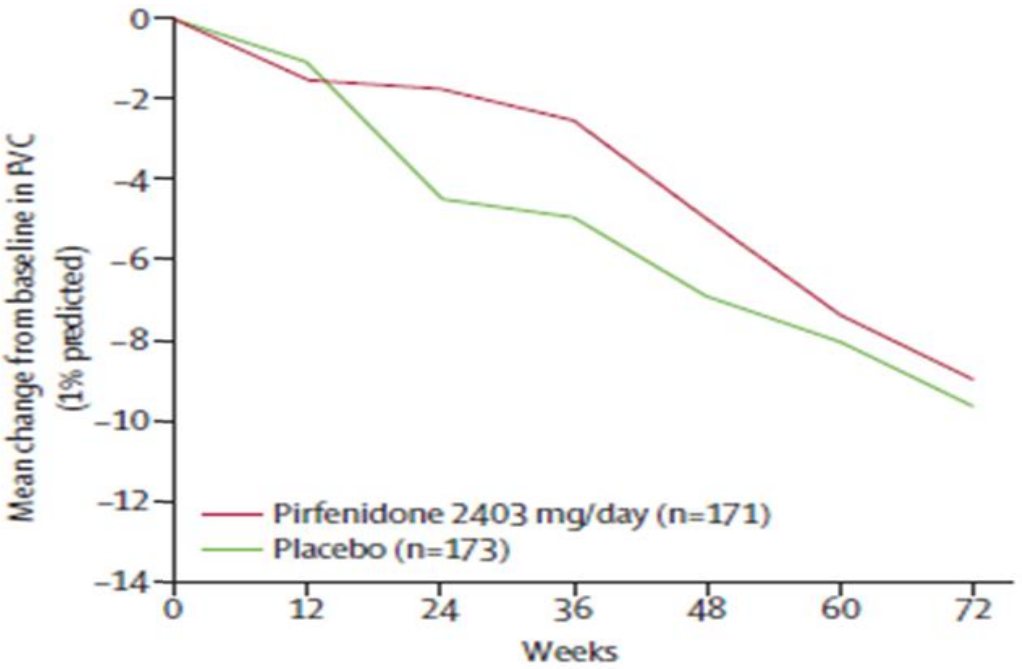


Absolute difference*	1·4%	2·5%	4·6%	4·8%	4·1%	4·4%
Relative difference*	53·5%	65·2%	63·7%	52·3%	38·3%	35·3%
p value†	0·061	0·014	0·0001	0·0009	0·0002	0·001

FVC=forced vital capacity. *Pirfenidone 2403 mg/day versus placebo. †Rank ANCOVA (pirfenidone 2403 mg/day vs placebo). 95% CIs were only calculated for absolute diff erences for the week 72 timepoint in study 004 (0 · 7 to 9 · 1) and study 006 (–3 · 5 to 4 · 7).

* Paul W Noble et al Lancet. 2011

Mean change from baseline in percentage predicted FVC in study 006

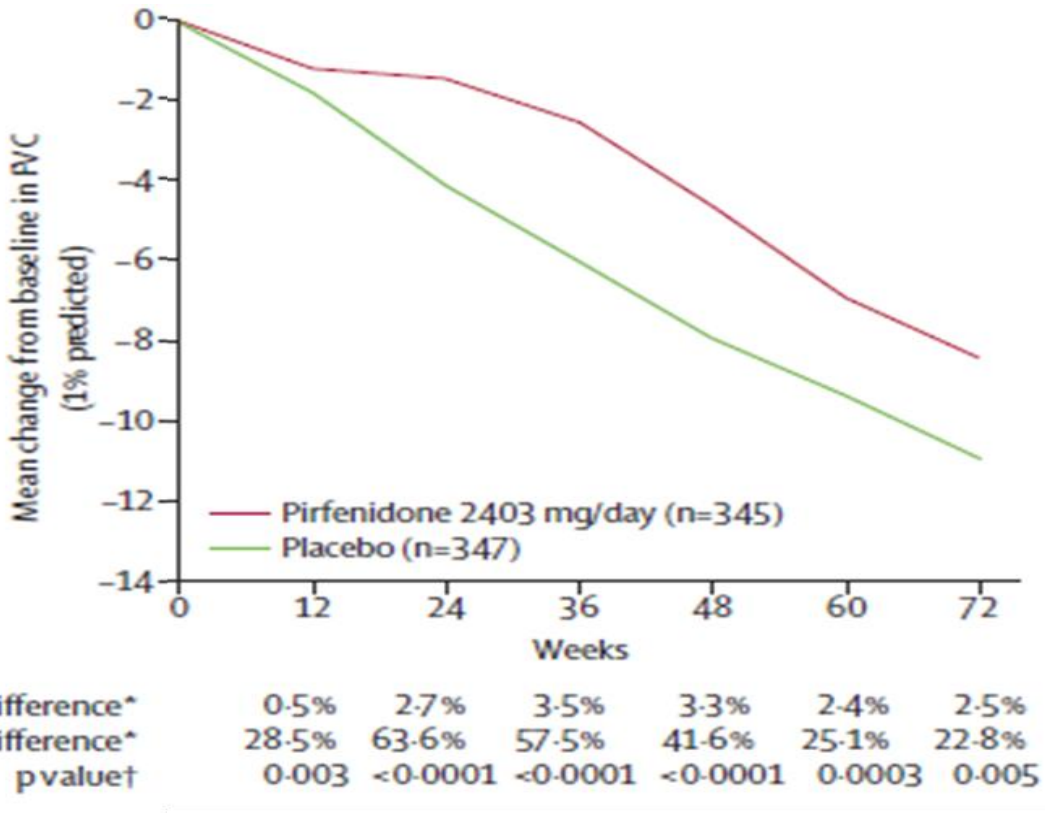


Absolute difference*	−0·4%	2·8%	2·4%	1·9%	0·6%	0·6%
Relative difference*	−31·5%	62·1%	48·2%	27·3%	7·6%	6·5%
p value†	0·021	0·0001	0·011	0·005	0·172	0·501

FVC=forced vital capacity. *Pirfenidone 2403 mg/day versus placebo. †Rank ANCOVA (pirfenidone 2403 mg/day vs placebo). 95% CIs were only calculated for absolute diff erences for the week 72 timepoint in study 004 (0・7 to 9・1) and study 006 (–3・5 to 4・7).

* Paul W Noble et al Lancet. 2011

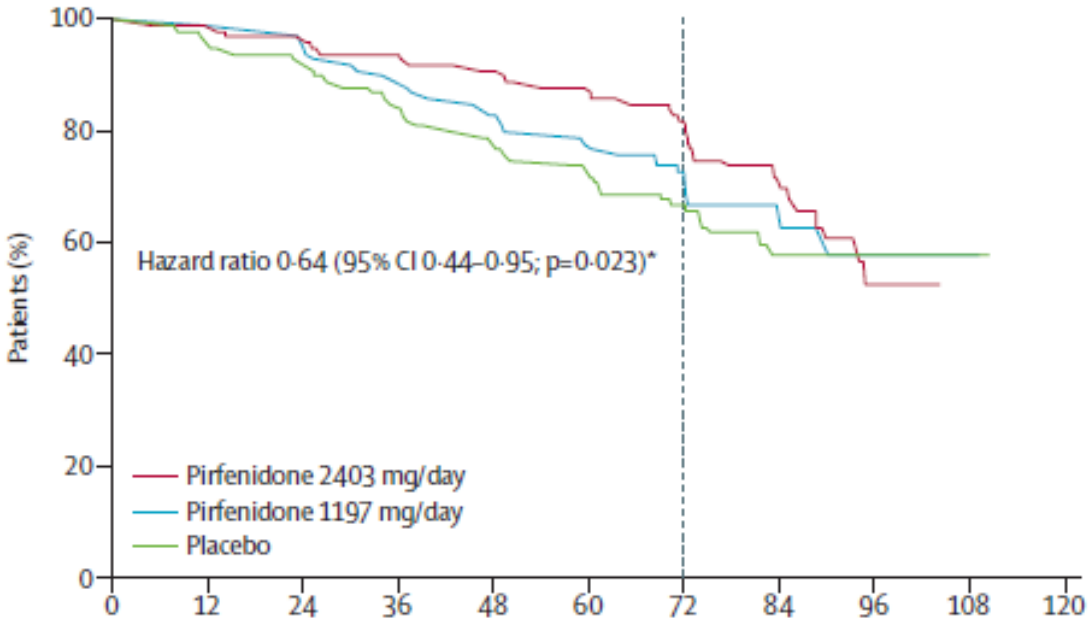
Mean change from baseline in percentage predicted FVC in the pooled population



FVC=forced vital capacity. *Pirfenidone 2403 mg/day versus placebo. †Rank ANCOVA (pirfenidone 2403 mg/day vs placebo). 95% CIs were only calculated for absolute diff erences for the week 72 timepoint in study 004 (0・7 to 9・1) and study 006 (–3・5 to 4・7).

* Paul W Noble et al Lancet. 2011

Kaplan-Meier distribution of progression-free survival time in study 004

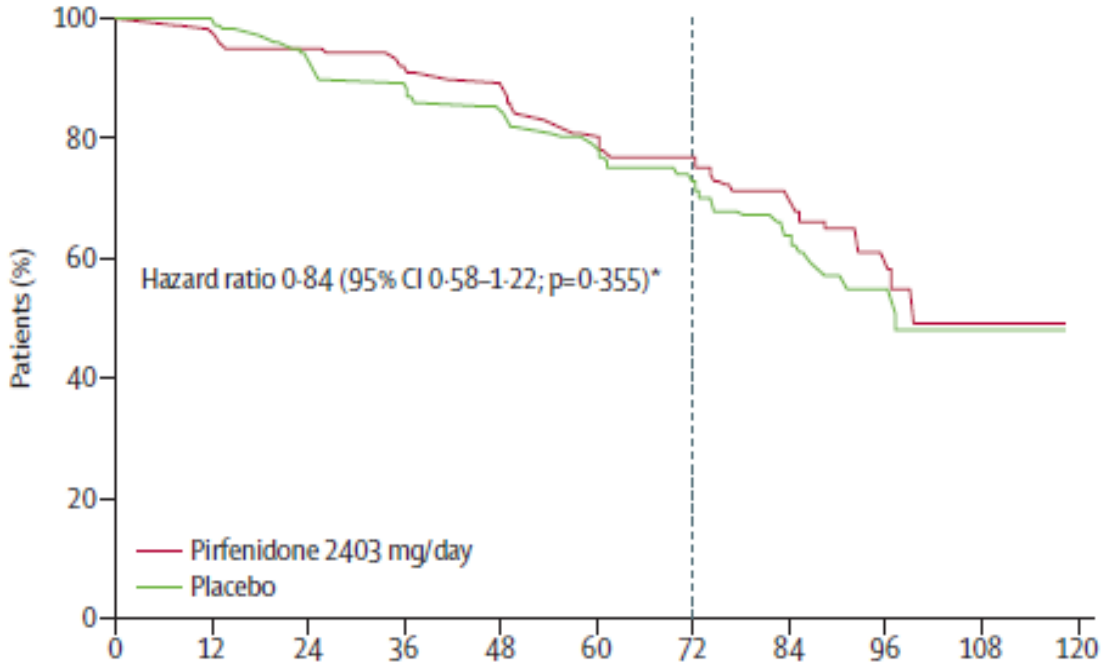


Number at risk									
Pirfenidone 2403 mg/day	171	167	160	157	148	138	55	23	5
Pirfenidone 1197 mg/day	87	86	79	74	68	64	27	11	5
Placebo	173	162	150	136	126	116	44	21	4

*Pirfenidone 2403 mg/day versus placebo.

* Paul W Noble et al Lancet. 2011

Kaplan-Meier distribution of progression-free survival time in study 006

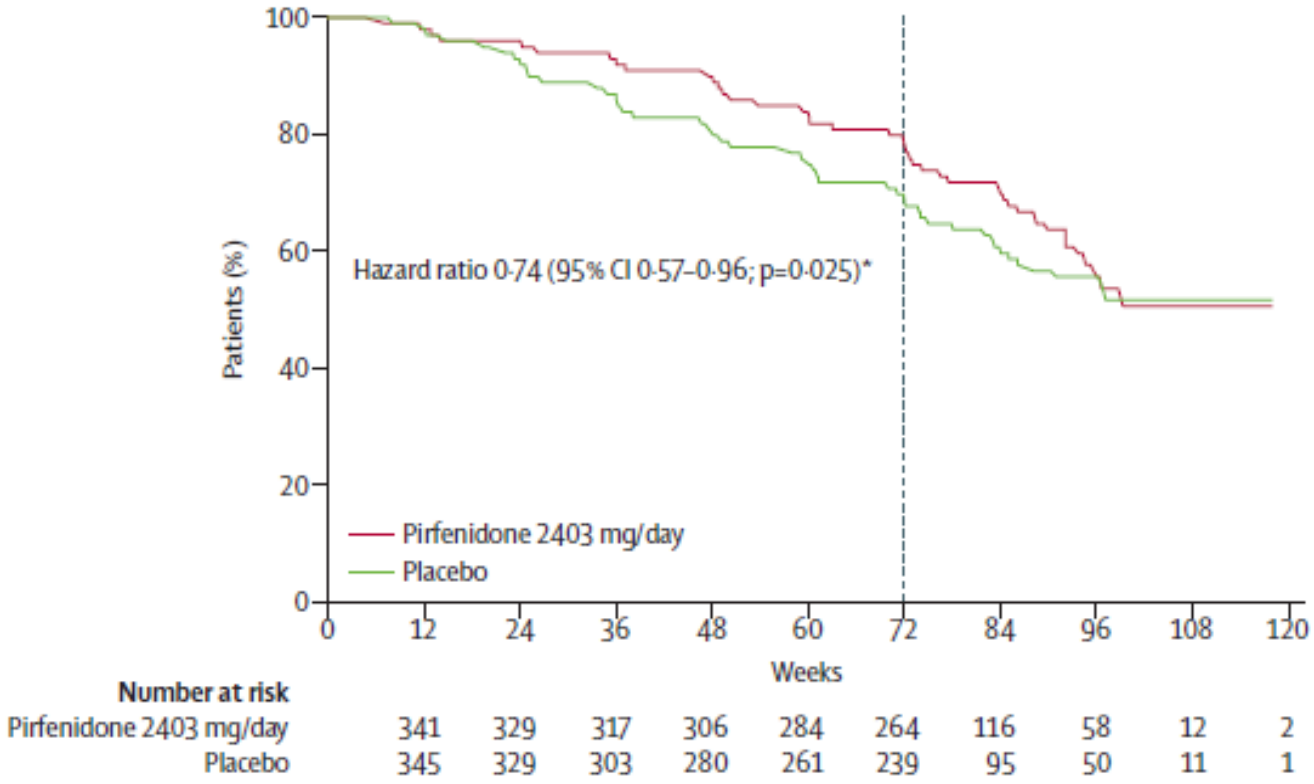


Number at risk										
Pirfenidone 2403 mg/day	170	162	157	149	136	126	61	35	7	2
Placebo	172	167	153	144	135	123	51	29	7	1

*Pirfenidone 2403 mg/day versus placebo.

* Paul W Noble et al Lancet. 2011

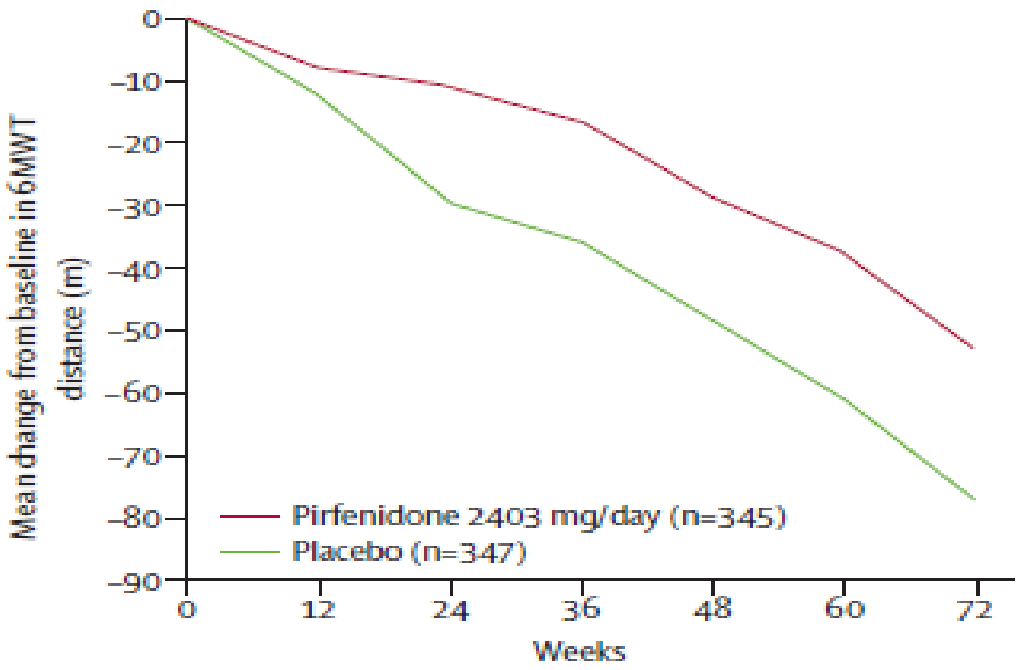
Kaplan-Meier distribution of progression-free survival time in the pooled population



*Pirfenidone 2403 mg/day versus placebo.

* Paul W Noble et al Lancet. 2011

Mean change from baseline in 6-min walk test distance in the pooled patient population (studies 004 and 006)



Absolute difference* (m)	3·9	18·6	18·7	19·8	23·3	24·0
Relative difference*	32·2%	62·8%	52·5%	40·6%	38·2%	31·2%
p value†	0·760	0·042	0·053	0·004	0·002	0·0009

6MWT=6-min walk test. *Pirfenidone 2403 mg/day versus placebo. †Rank ANCOVA (pirfenidone 2403 mg/day vs placebo).

* Paul W Noble et al Lancet. 2011

Treatment-emergent adverse events*

	Pirfenidone 2403 mg/day (n=345)	Placebo (n=347)
Nausea	125 (36%)	60 (17%)
Rash	111 (32%)	40 (12%)
Dyspepsia	66 (19%)	26 (7%)
Dizziness	63 (18%)	35 (10%)
Vomiting	47 (14%)	15 (4%)
Photosensitivity reaction	42 (12%)	6 (2%)
Anorexia	37 (11%)	13 (4%)
Arthralgia	36 (10%)	24 (7%)
Insomnia	34 (10%)	23 (7%)
Abdominal distension	33 (10%)	20 (6%)
Decreased appetite	30 (9%)	10 (3%)
Stomach discomfort	29 (8%)	6 (2%)
Weight reduction	28 (8%)	12 (3%)
Abdominal pain	26 (8%)	12 (3%)
Asthenia	24 (7%)	13 (4%)
Pharyngolaryngeal pain	24 (7%)	16 (5%)
Pruritus	22 (6%)	14 (4%)
Hot flush	18 (5%)	4 (1%)

Data are number of patients (%). *Occurring in 5% or more of patients given pirfenidone 2403 mg/day in study 004 and study 006, and with an incidence 1·5 times greater than that in patients given placebo.

* Paul W Noble et al Lancet. 2011

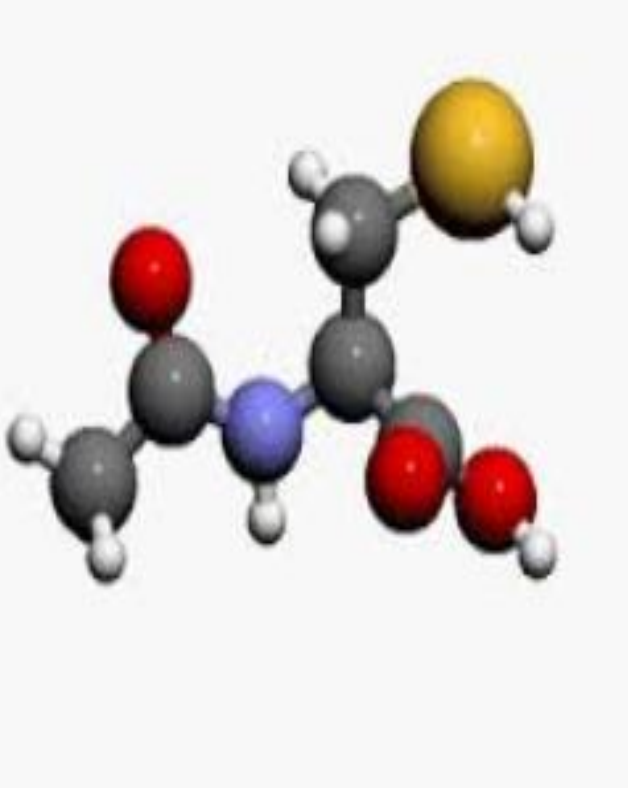
Mortality data from the CAPACITY study.

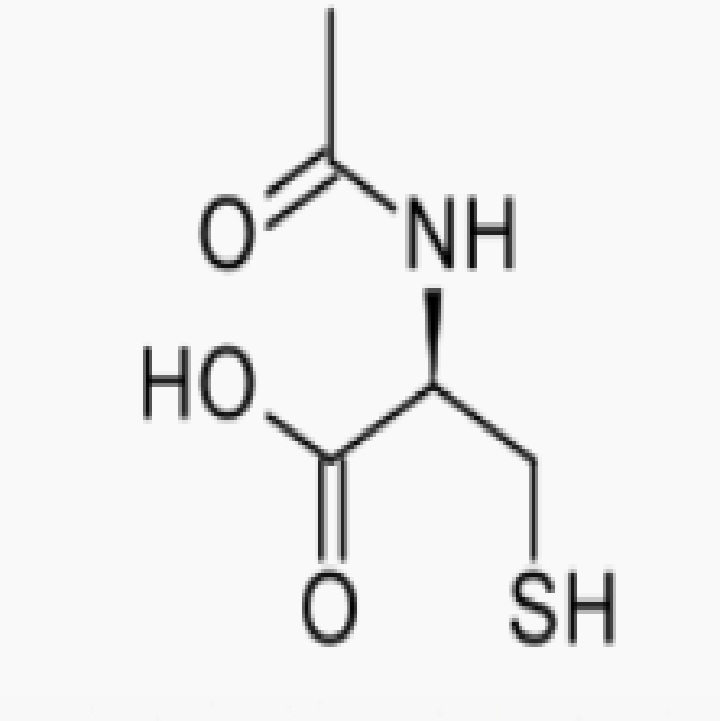
	Pifenidone[#] 2403 mg·day^{-1}	Placebo[¶]	Hazard ratio (95% CI)[+]	p-value[§]
Overall				
All-cause mortality	27 (8)	34 (10)	0.77 (0.47–1.28)	0.315
IPF-related mortality[/]	18 (5)	28 (8)	0.62 (0.35–1.13)	0.117
On-treatment[##]				
All-cause mortality	19 (6)	29 (8)	0.65 (0.36–1.16)	0.141
IPF-related mortality[/]	12 (3)	25 (7)	0.48 (0.24–0.95)	0.030

Summary of evidenced-based treatments for idiopathic pulmonary fibrosis.

	ATS/ERS/JRS/ALAT guidelines [2]	New evidence 2012
Anticoagulation	Weak No	Strong No (ACE) [8, 9]
NAC monotherapy	Weak No	Weak No [2, 11]
Prednisone/ azathioprine/NAC	Weak No	Strong No (PANTHER) [9, 13]
Pirfenidone	Weak No	Weak Yes [22] (German guidelines [9])

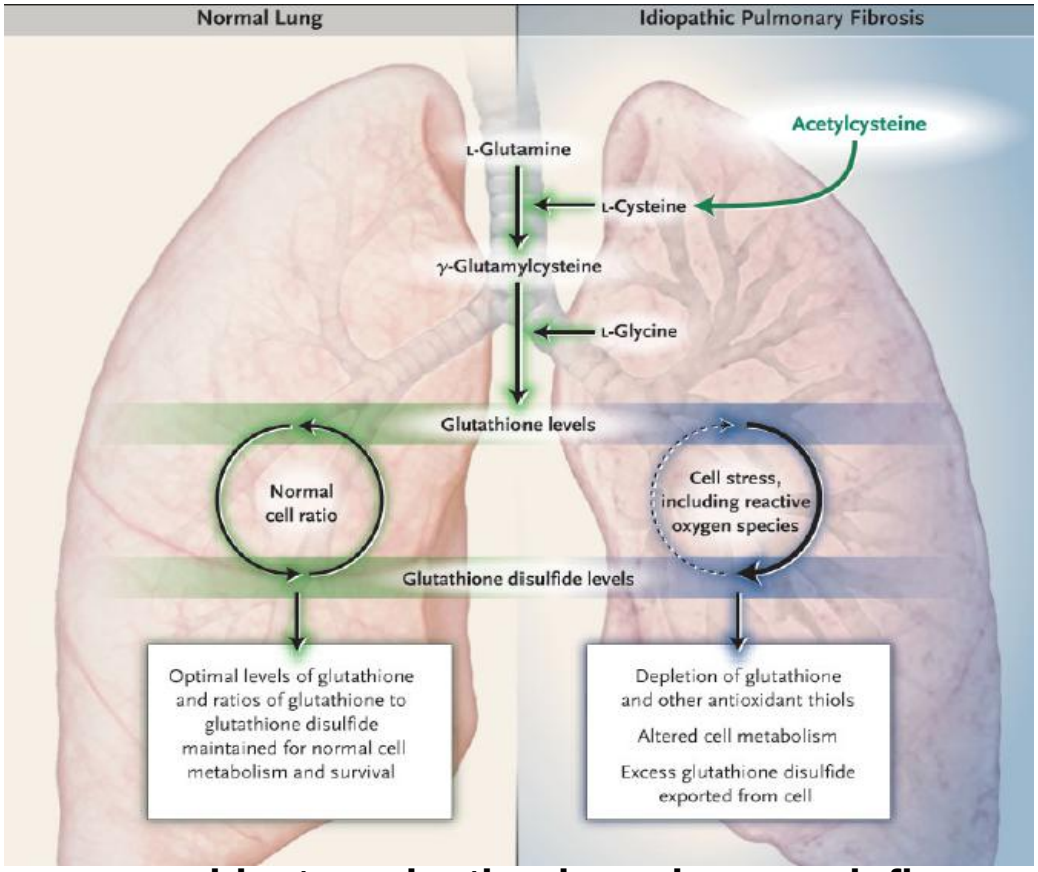
N-Acetylcysteine





N-Acetylcysteine effect in IPF Lung

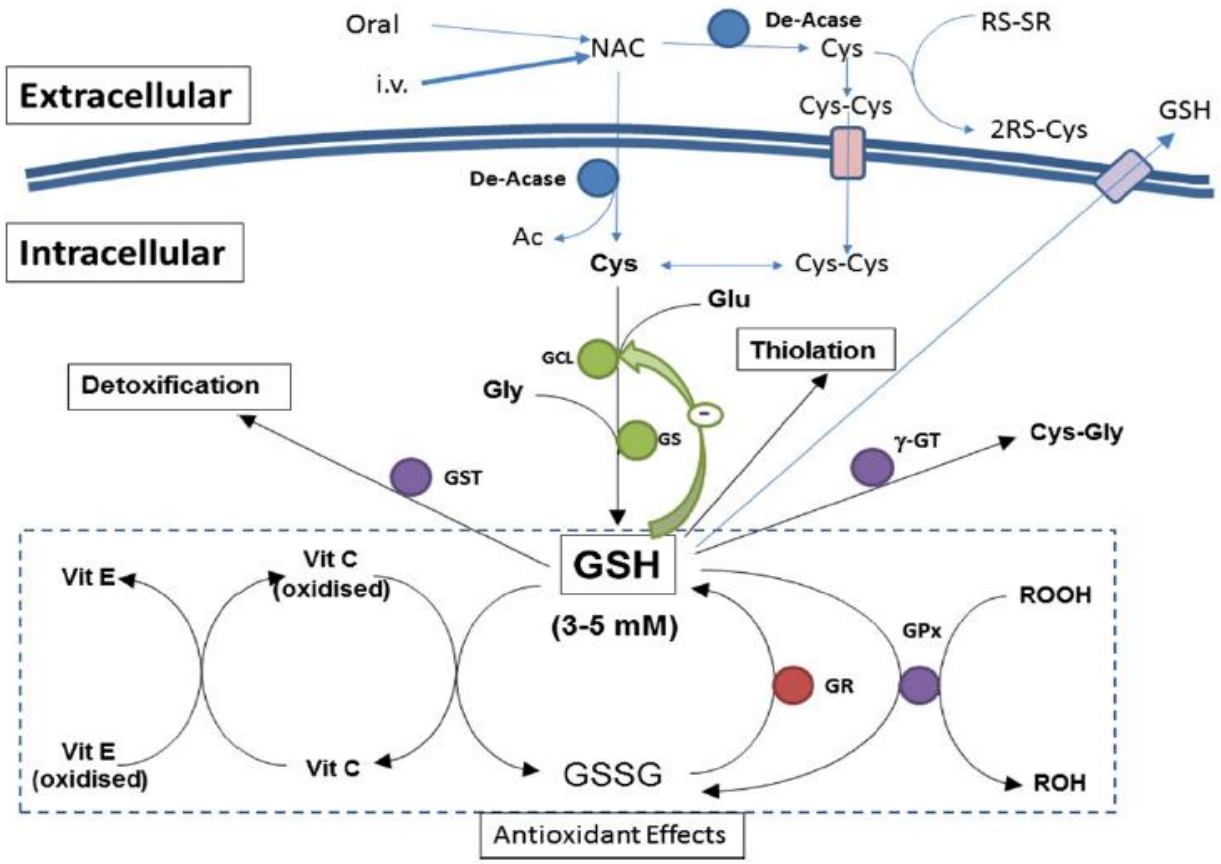
Synthesis of Glutathione



Increased spontaneous oxidant production by pulmonary inflammatory cells, suggesting that oxidation may also be implicated in the epithelial cell injury seen in IPF.

Cantin AM et al. J Clin Invest 1987

Impact of NAC on synthesis and utilisation pathways for GSH



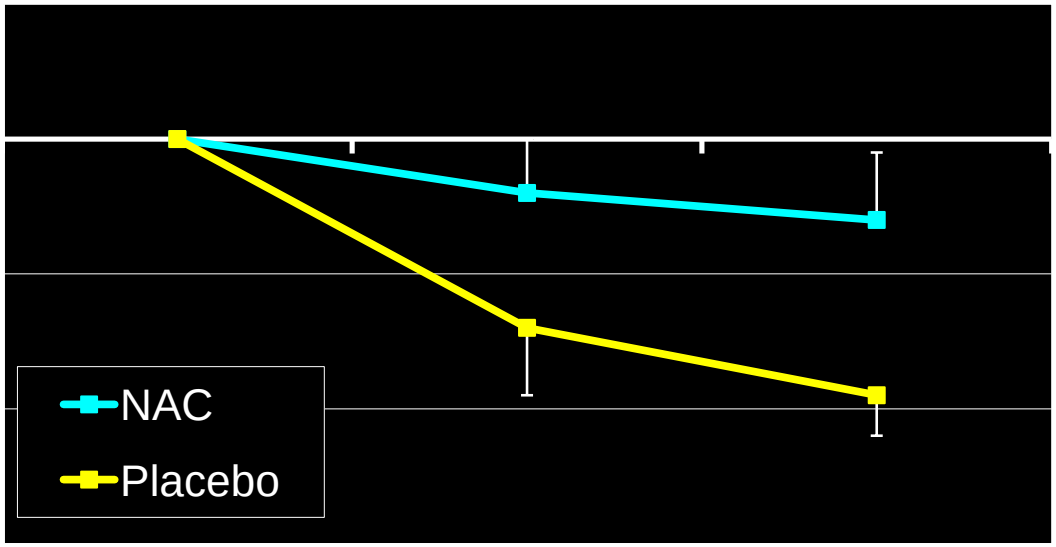
High Dose N-acetylcysteine in Idiopathic Pulmonary Fibrosis: the IFIGENIA-Trial*

- **Multinational, double-blind, randomized, placebo-controlled, parallel-group trial**
- **Prednisone + Azathioprine + NAC vs. Prednisone + Azathioprine**

* Maurits Demedts et al NEJM 2005

High Dose N-acetylcysteine in Idiopathic Pulmonary Fibrosis: the IFIGENIA-Trial*

Primary endpoint : VC (L)



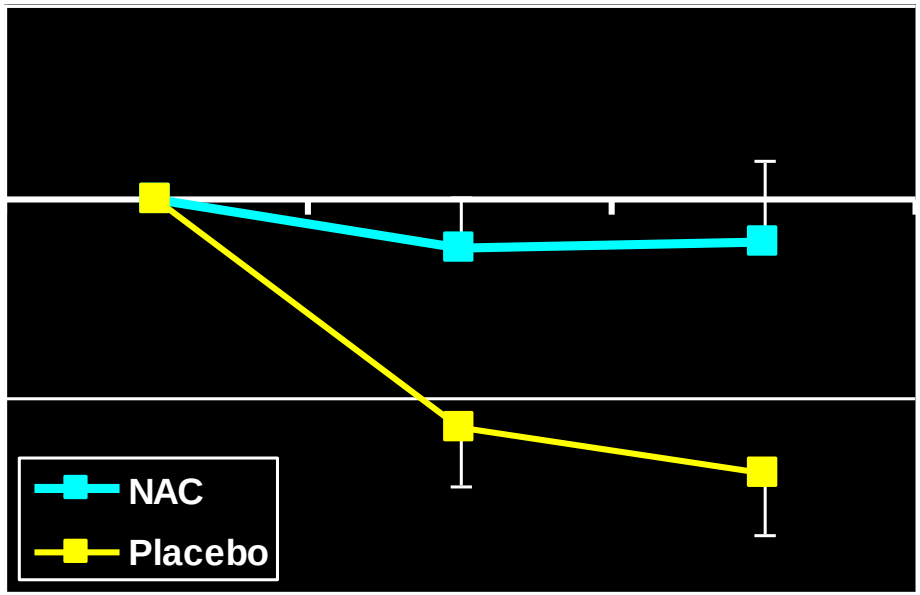
P = 0.02

NAC (n=)	**80**	**63**	**55**
Placebo (n=)	**75**	**60**	**51**

* Maurits Demedts et al NEJM 2005

High Dose N-acetylcysteine in Idiopathic Pulmonary Fibrosis: the IFIGENIA-Trial*

Primary endpoint : DLCO (mmol/min/kPa)



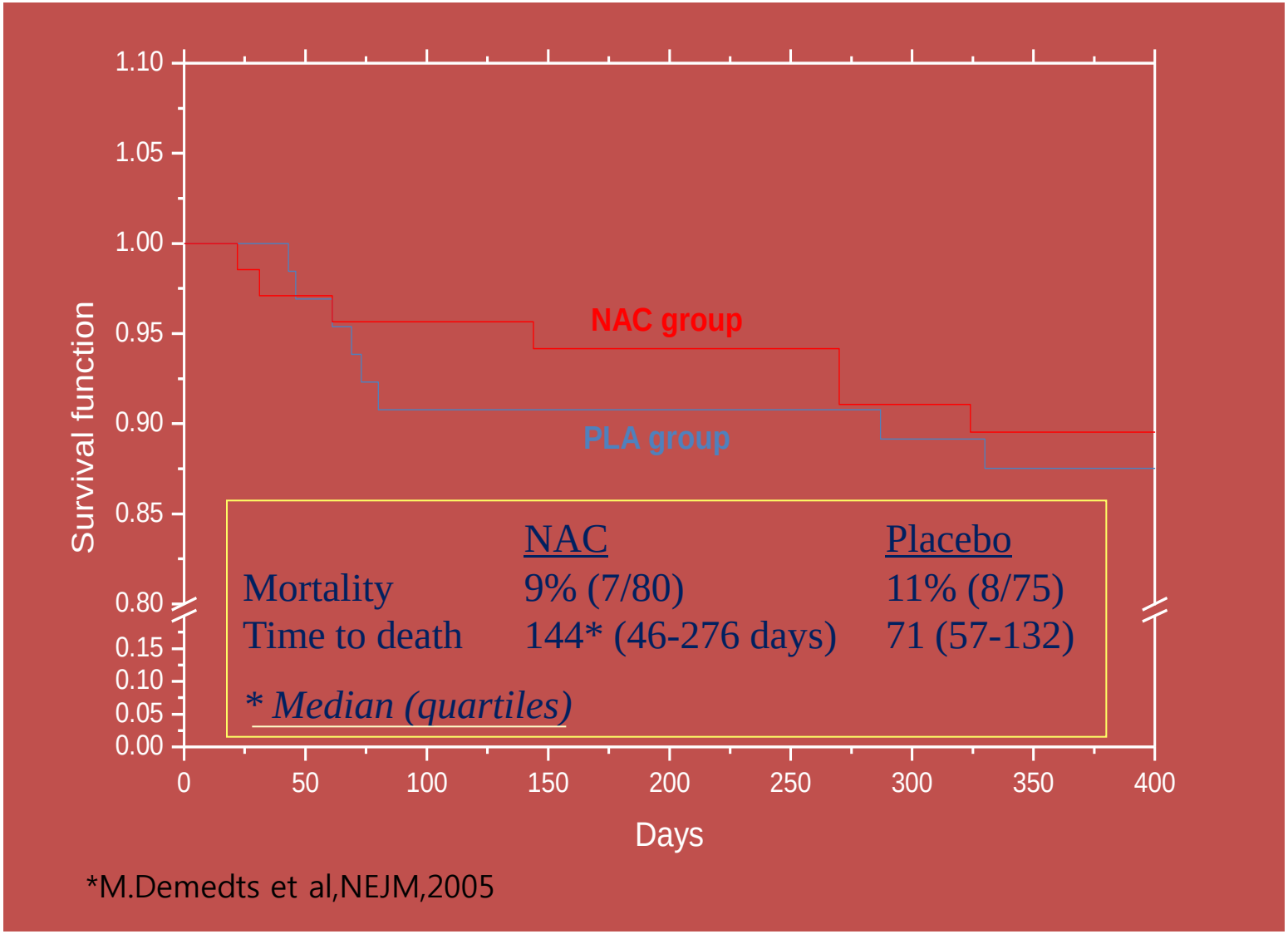
P= 0.003

NAC (n=)	79	58	48
Placebo (n=)	74	59	47

* Maurits Demedts et al NEJM 2005

Idiopathic Pulmonary Fibrosis: Results of the European Trial (IFIGENIA STUDY)*
Prednisone plus Azathioprine +/- N-Acetyl Cysteine (NAC)

Survival within one year



*M.Demedts et al,NEJM,2005

Adverse Events (AE) Occurring in at least 5% of Patients

	NAC			Placebo			
	AE	Patient		AE	Patient		
	n	n	%	n	n	%	
Total number of patients		80	100		75	100	
Total AE	322	72	90	303	67	89	
Blood alkaline phos increased	6	6	8	1	1	1	
Blood lactate dehydrogenase inc.	6	6	8	2	2	3	
Back pain	6	6	8	6	5	7	
Respiratory failure	5	5	6	1	1	1	
Bone marrow toxicity	3	3	4	10	10	13	P=0.03
Edema	3	3	4	5	5	7	
Headache	4	3	4	6	6	8	
Asthenia	3	3	4	5	5	7	
Influenza like illness	3	3	4	5	5	7	
Muscle cramp	1	1	1	4	4	5	
Tremor				4	4	5	

* Demedts et al *NEJM* 2005; 353: 229-42

High Dose N-acetylcysteine in Idiopathic Pulmonary Fibrosis: the IFIGENIA-Trial*

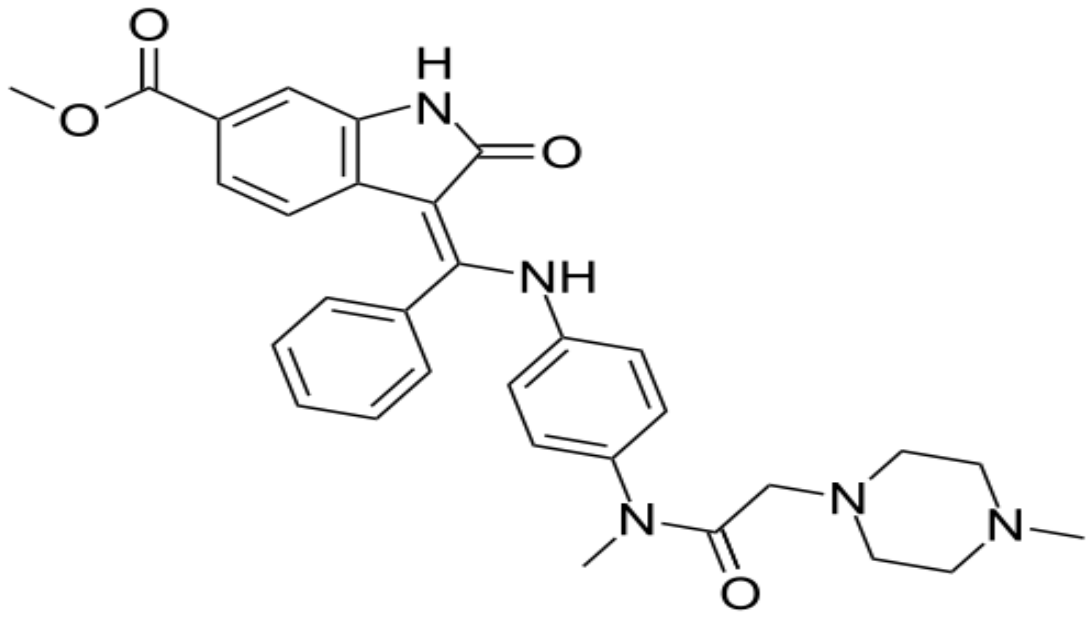
Conclusions

- **Therapy with NAC 600 mg TID added to prednisone and azathioprine, preserves VC and DLCO in IPF better than prednisone and azathioprine**

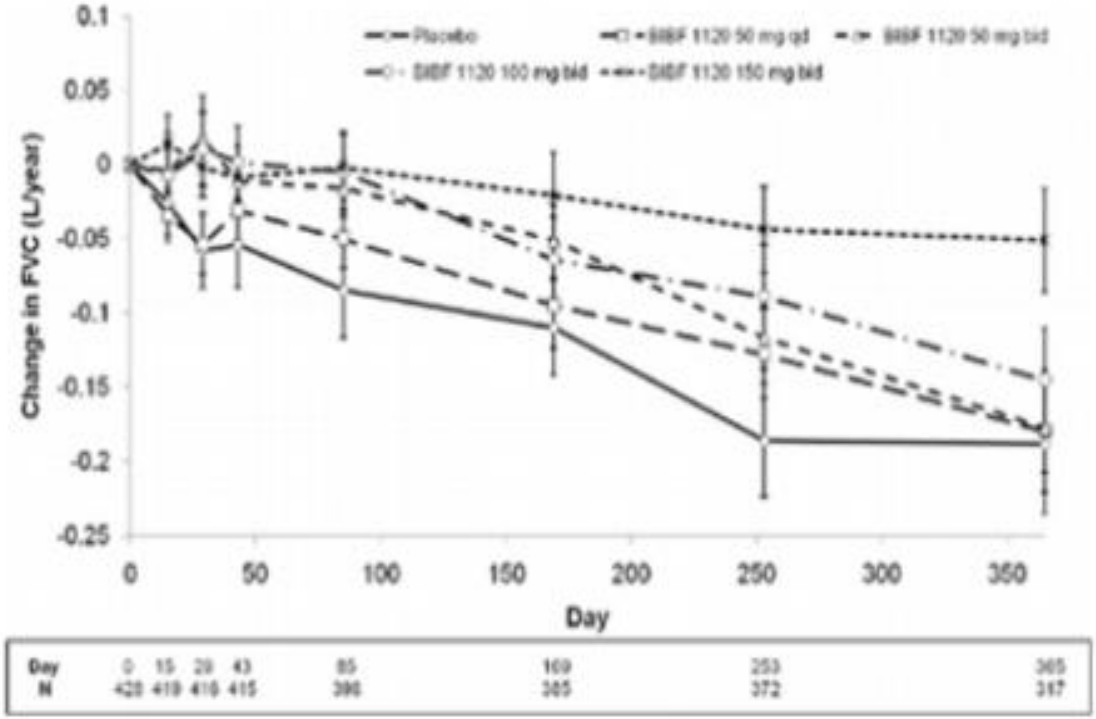
* Demedts et al NEJM,2005

Nintedanib(BIBF 1120)

- **BIBF1120 (Vargatef, Nintedanib) | VEGFR/PDGFR/FGFR inhibitor**



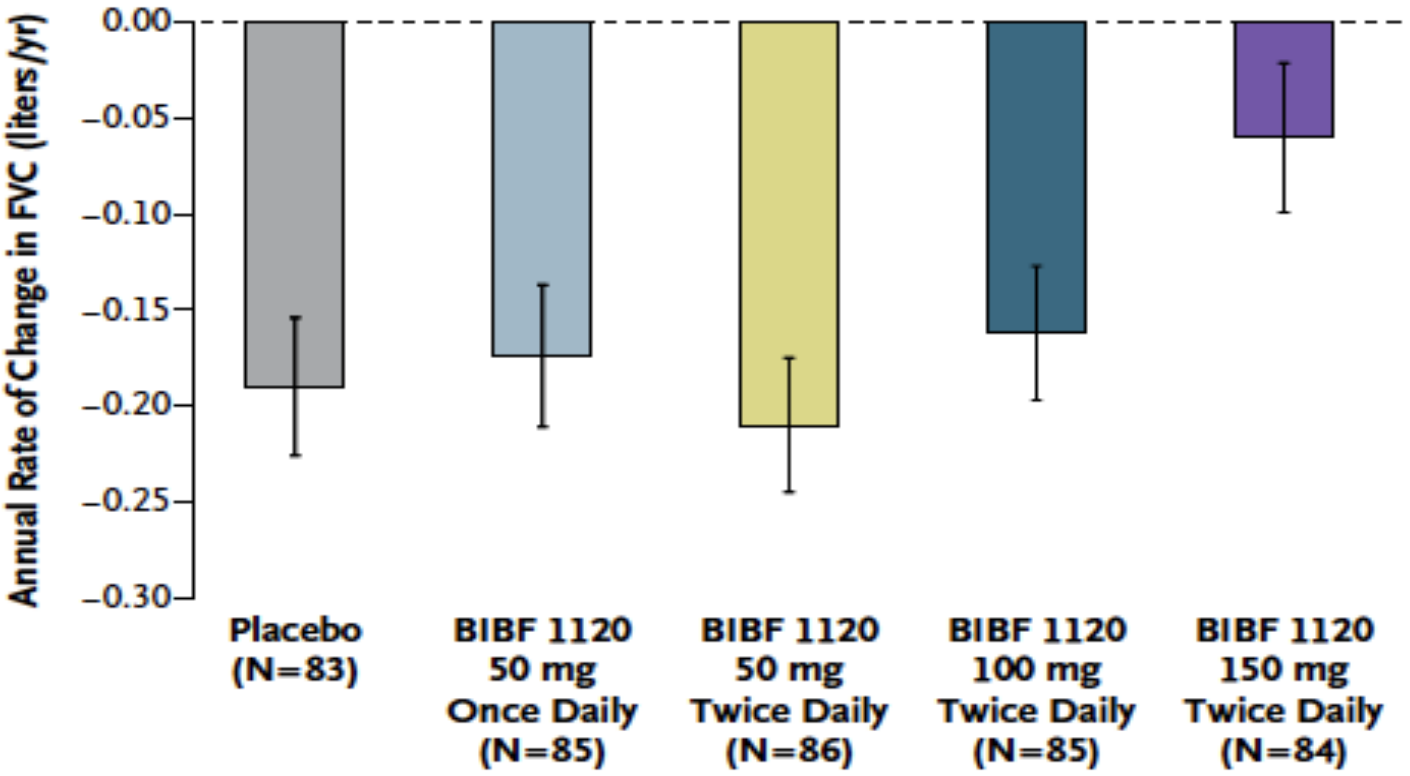
Nintedanib(BIBF 1120)



Treatment of IPF with BIBF 1120 reduced decline in lung function and incidence of acute exacerbations in a dose-dependent way.

* Ulrich Costabel et al ERJ 2011

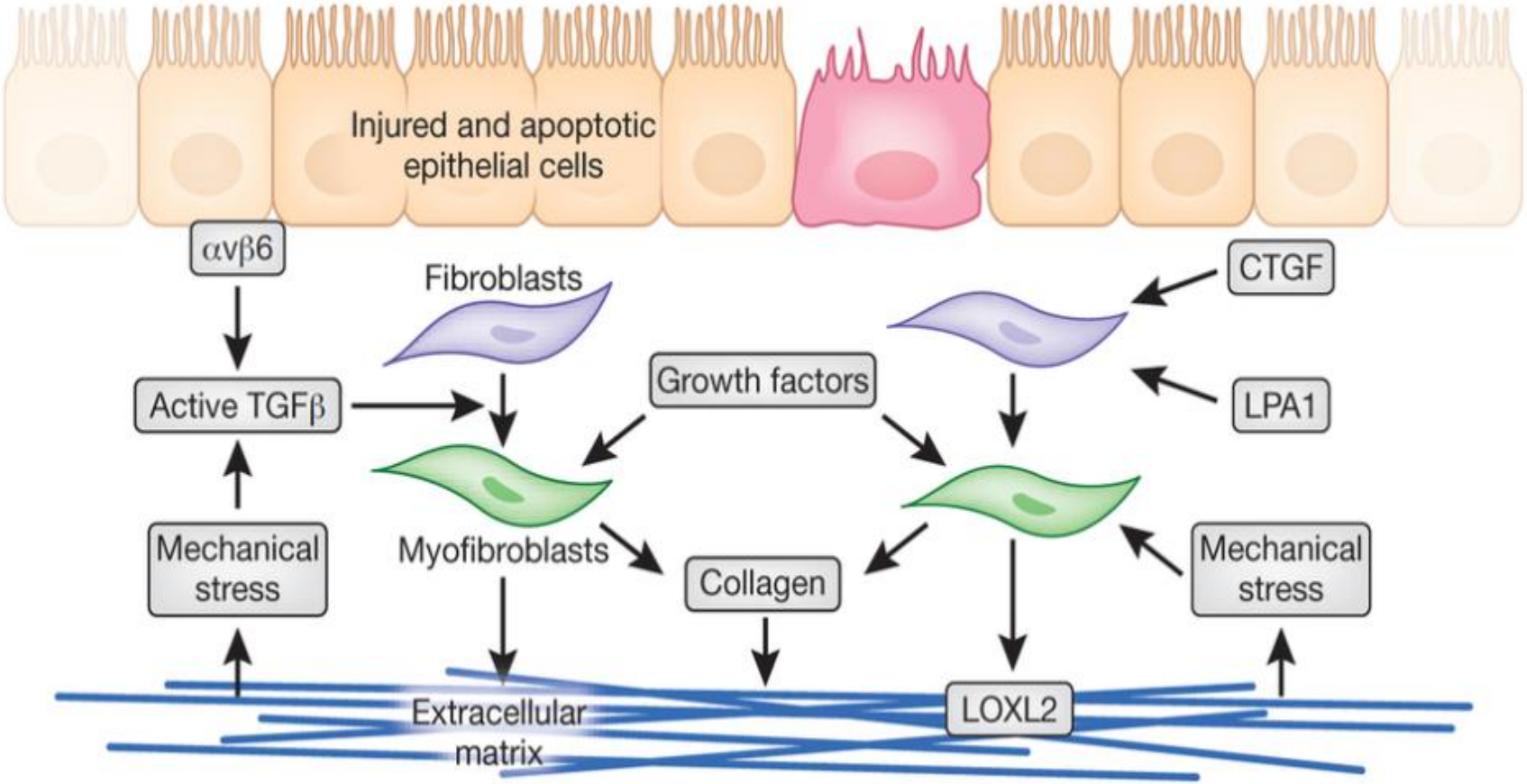
Nintedanib(BIBF 1120)



Lysyl Oxidase Like-2 (LOXL-2)

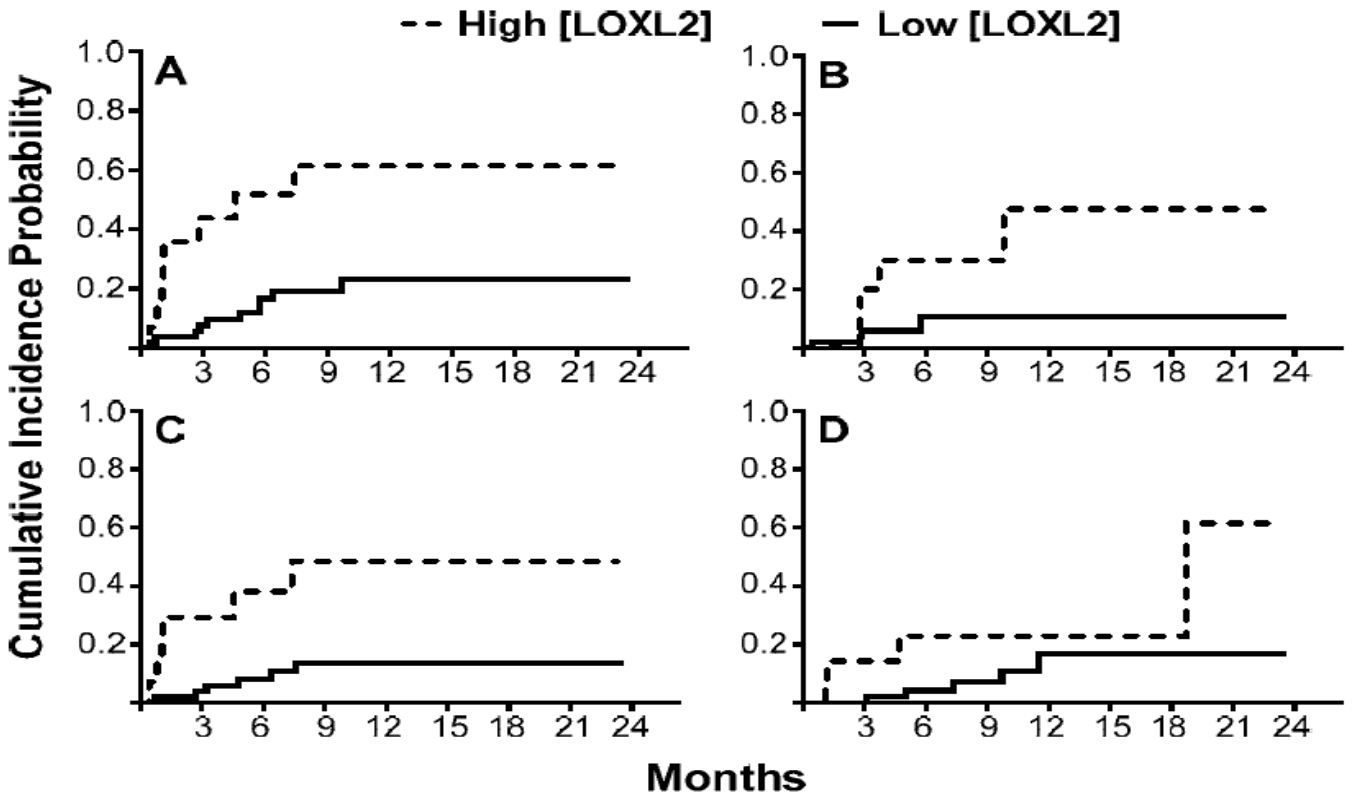
- Clinical study Phase 2 진행 중

LOXL-2 inhibitor anti-fibrotic action



* Nature Biotechnology. 2013, 31, 781–783.

Lysyl Oxidase Like-2 (LOXL-2) Levels and IPF Disease



Cumulative incidence curves comparing low (≤800 pg/mL) and high (>800 pg/ml) sLOXL2 levels for **disease progression (A)** and its com ponents (**lung function decline [B], respiratory hospitalizations [C]** and **death [D]**) in ARTEMIS-IPF.

* Jason W. Chien et al ERJ 2013

Stem cell;

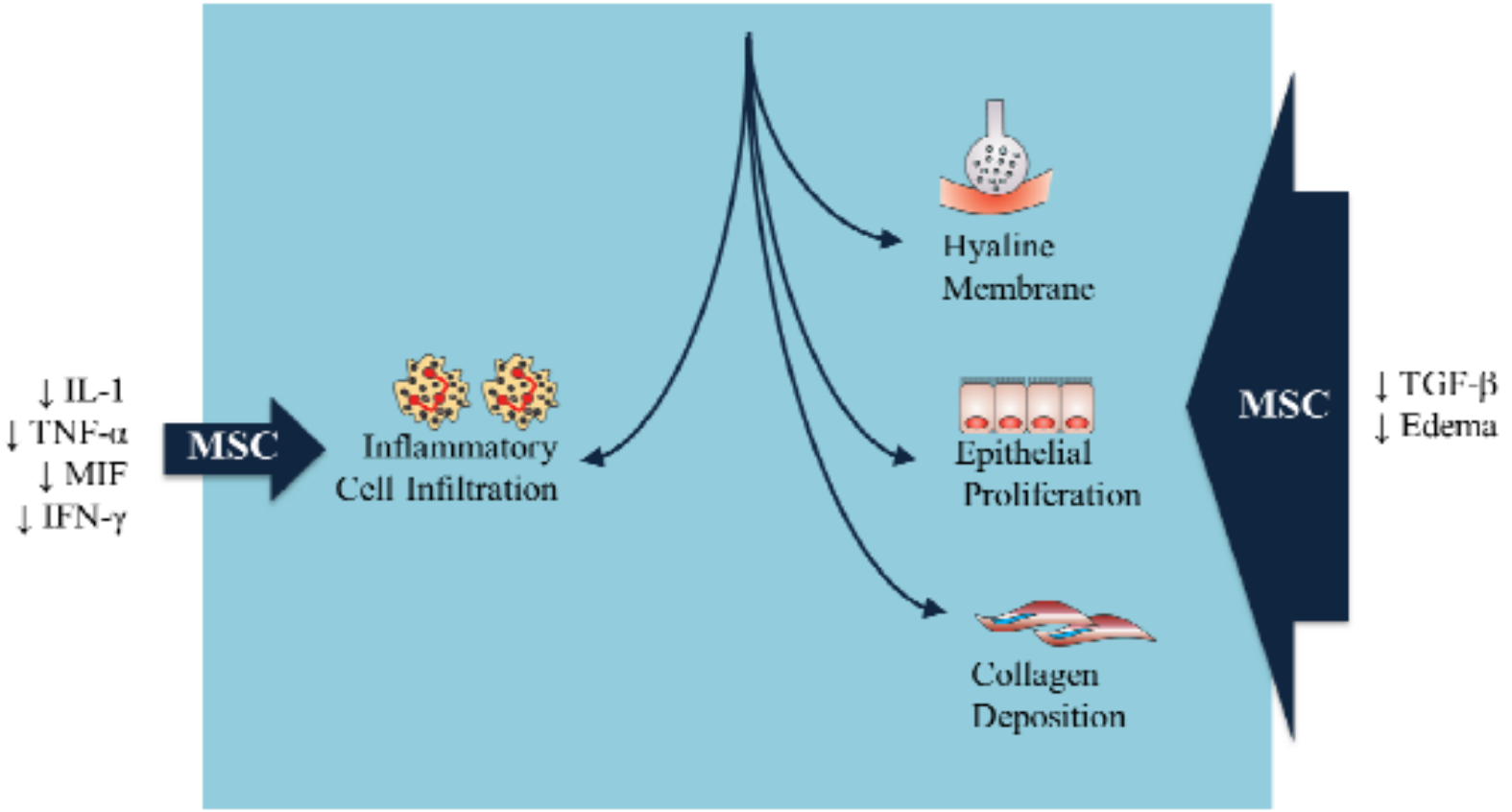
Clinical trials of mesenchymal stem cells in IPF.

Disease	Location	Patients	Cell Type	Dose	Frequency	Delivery	Follow-up	Status	ClinicalTrials.gov
IPF	USA	25	BM-MSC	2×10^7	Single dose	Intravenous	60 weeks	Recruiting	NCT02013700
	Spain	18	BM-MSC	Escalating doses	*	Endobronchial	12 months	Recruiting	NCT01919827
	Australia	8	Placental MSC	$1\text{-}2 \times 10^6$/kg	Single dose	Intravenous	6 months	Not recruiting	NCT01385644

IPF: idiopathic pulmonary fibrosis; BM-MSC: bone marrow-derived mesenchymal stem cells; Placental MSC: placental-derived mesenchymal stem cells. * Data not available.

* Mariana A. Antunes et al J Cell Biochem. 2014

Potential mechanisms of action of MSCs in



IL: interleukin; TNF-α: tumor necrosis factor-α; MIF: macrophage migr atory inhibitor factor; IFN-γ: interferon gamma; TGF-β: transforming growth factor-β.

* Mariana A. Antunes et al J Cell Biochem. 2014

Other target in IPF treatment;AGE-RAGE

In pulmonary fibrosis: AGEs, and RAGE

Loss of RAGE promote fibrosis in lung

In animal models of pulmonary fibrosis, RAGE protein levels were reduced following treatment with bleomycin.

RAGE-deficient (RAGE -/-) mice develop fibrosis-like alterations in lungs.

RAGE protein levels in IPF lung homogenates and BALF were reduced.

RAGE and AGEs have profibrotic potential

RAGE-/- mice were resistant to bleomycin induced lung injury.

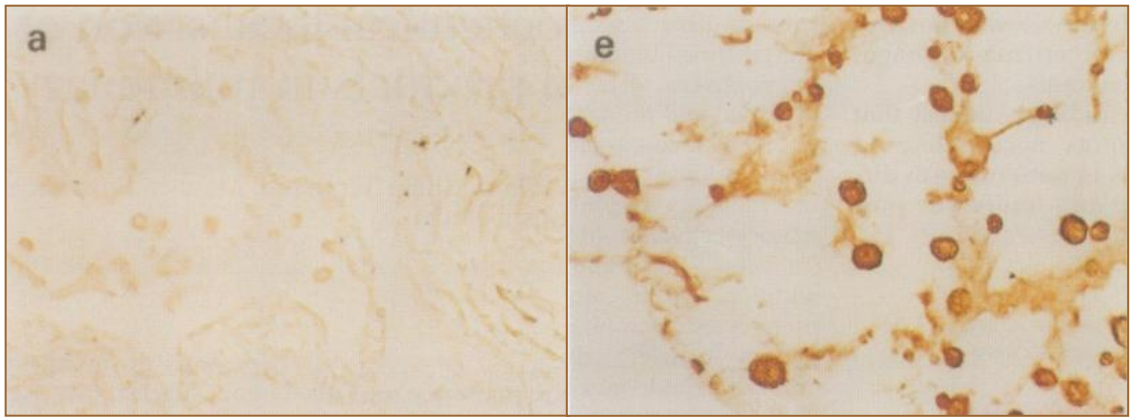
HMGB1 increased in mice treated with bleomycin.

Overexpression of RAGE and AGEs in IPF lungs was observed.

AGEs levels in rat lungs were increased following bleomycin instillation.

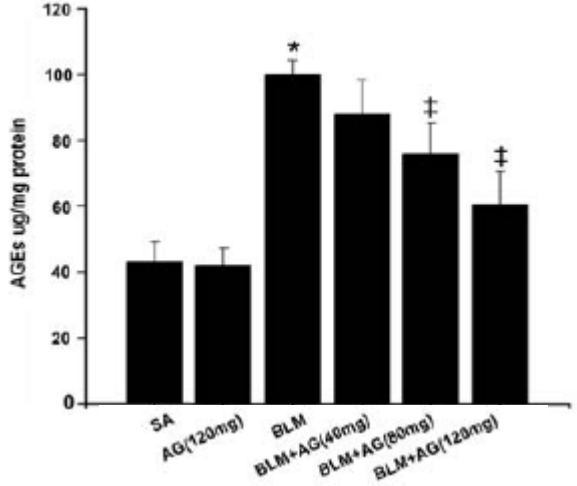
Background: AGEs have fibrotic potential

6D12 (reacts with all AGEs) IHC.



a) Normal lung b) IPF lung

Matsuse et al. J Clin Pathol 1998

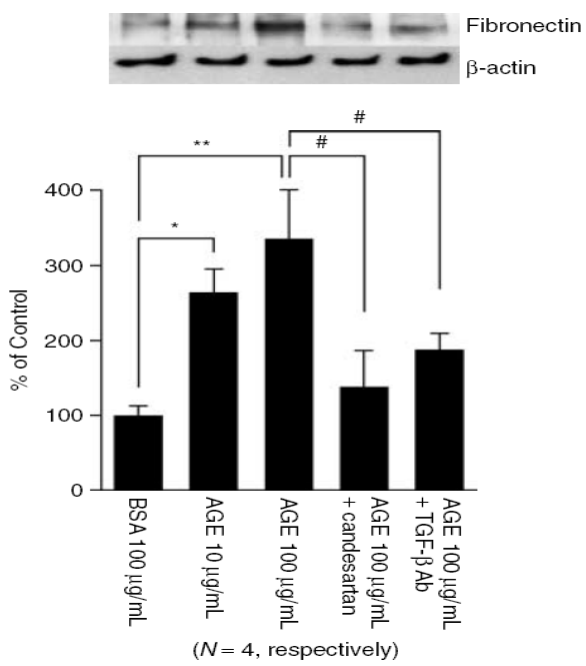


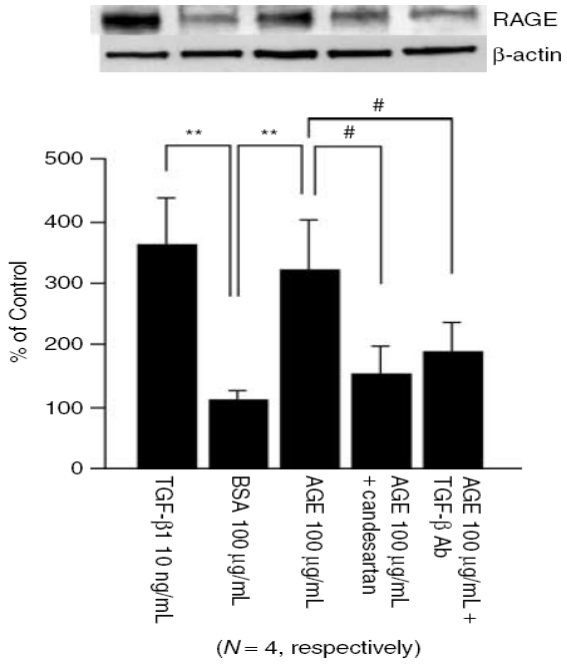
Compared with the SA group, AGEs level in lung tissues (ELISA) was markedly increased in the BLM group ($p<0.01$).

Chen et al. Respir Res 2009

Back ground:AGE and fibrosis

AGE-RAGE–mediated ROS induces mesangial cell hypertrophy and fibronectin synthesis





Effects of advanced glycation end products(AGEs) on fibronectin synthesis in mesangial cells

Effects of advanced glycation end products (AGEs) on receptor for AGE (RAGE) expression in mesangial cells

Fukami et al. Kideny International,2004

Published data - Int J Clin Exp Pathol 2014;7(1):221-228)

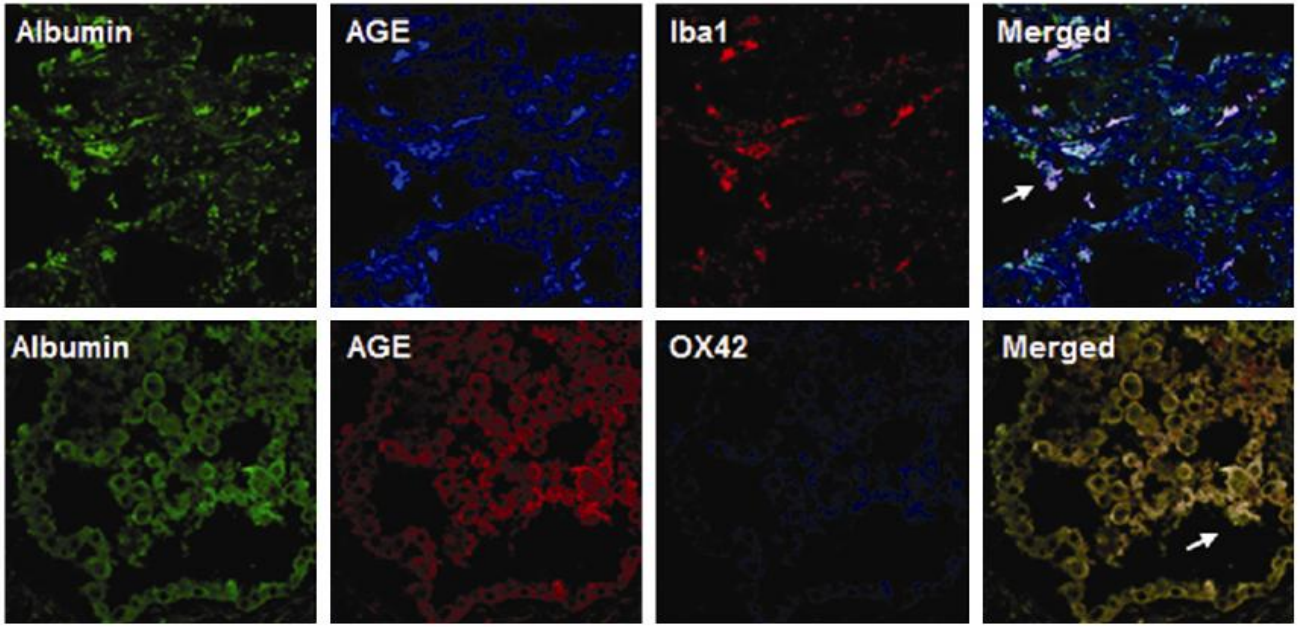


Figure 2. Localization of advanced glycation end-product (AGE) expression in lung tissues from patients with iopathic pulmonary fibrosis (IPF). Immunofluorescent staining for macrophage-specific Iba1 and OX42 shown as a merge with AGE-modified albumin in lung tissue from patients with IPF.

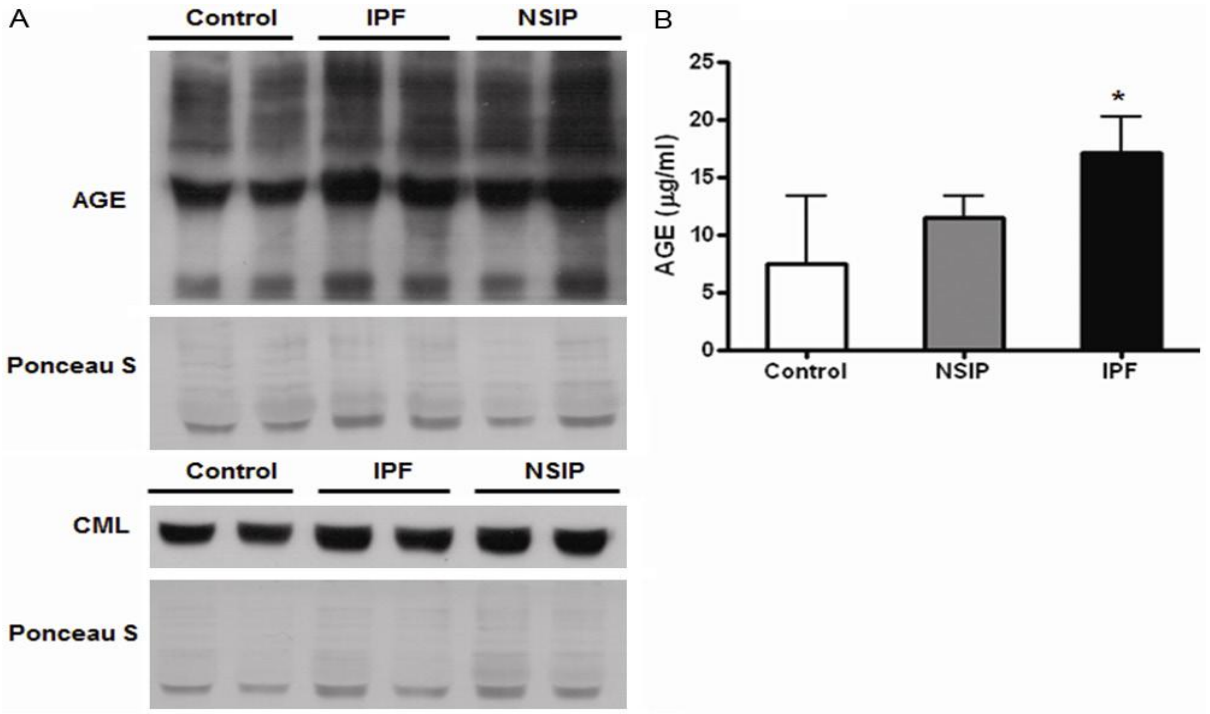


Figure 3. Circulating advanced glycation end-products (AGEs) in plasma from patients with idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonia (NSIP). Western blotting for AGEs and N-ε-carboxymethylated lysine (CML) (a), Enzyme-linked immunosorbent assay (ELISA) for AGEs (b). Western blot shows increased expression of circulating AGEs (AGEs and CML) in patients with IPF and NSIP, compared to that in the control. ELISA results show significantly higher levels of circulating AGEs in patients with IPF, compared to the NSIP and control. *P < 0.05 compared to the control.

Conclusion

- **AGEs –RAGE over-expression may be associated with pathogenesis of idiopathic pulmonary pneumonia.**

- Circulating HMGB1s are needed to further evaluation whether another confounding factors affect levels of circulating AGEs such as **diabetes, atherosclerosis.** Furthermore, it is needed to correlation between lung tissue AGEs levels and circulating AGEs levels.