IPF의 이해 및 치료

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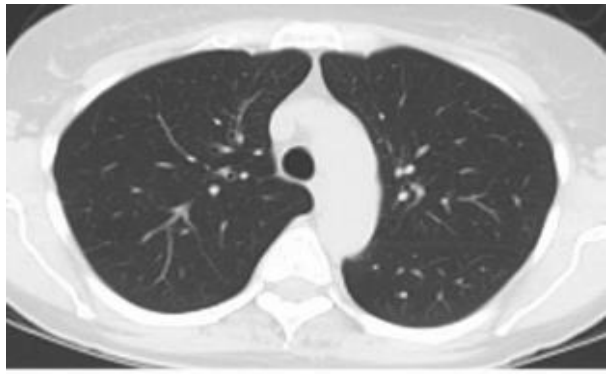
Contents

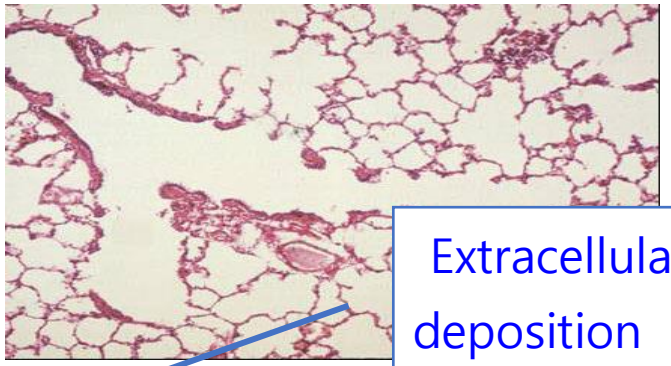
- IPF pathogenesis, epidemiology
- Current medication_ practical issues
- New drug candidates

Idiopathic pulmonary fibrosis (IPF)

지속적으로 진행되는 섬유화를 특징으로 하는 원인 미상의 간질성 폐질환 (interstitial pneumonitis)

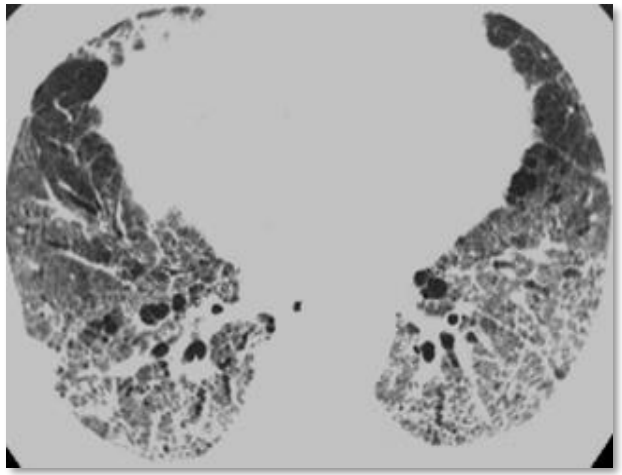
Healthy subject

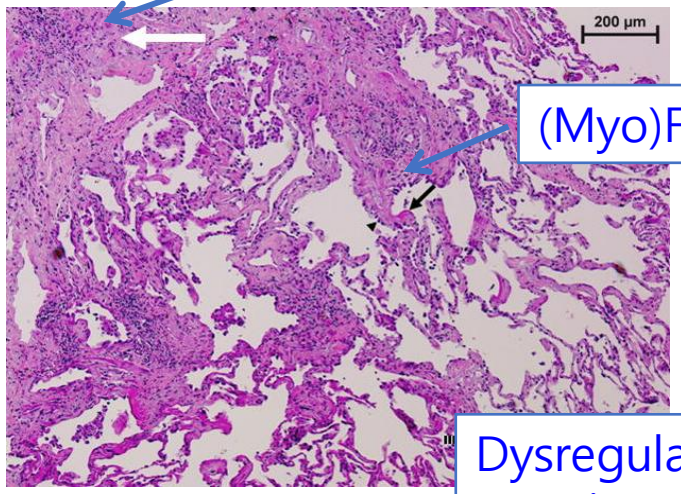




Extracellular matrix collagen deposition

IPF

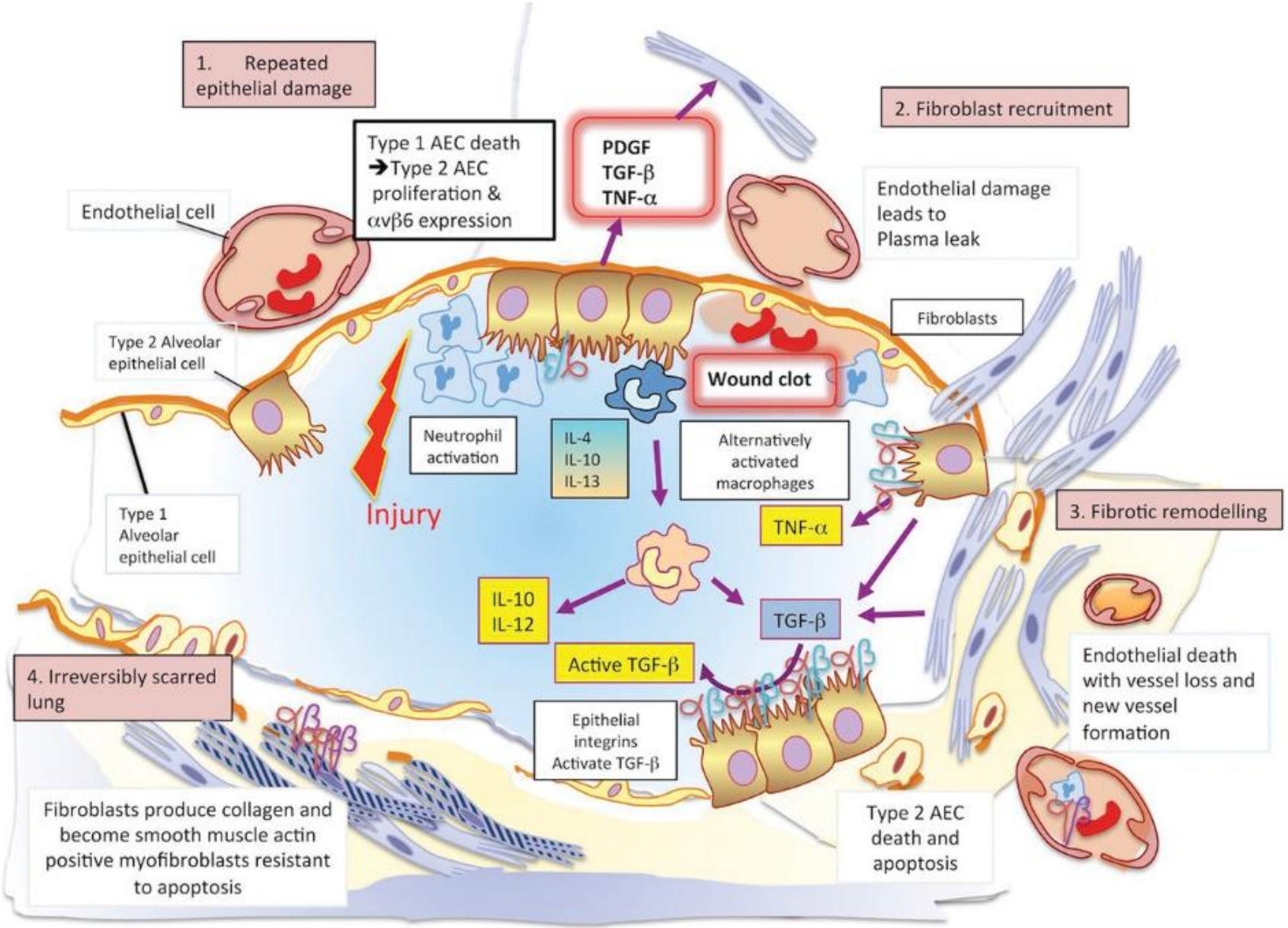




(Myo)Fibroblast proliferation

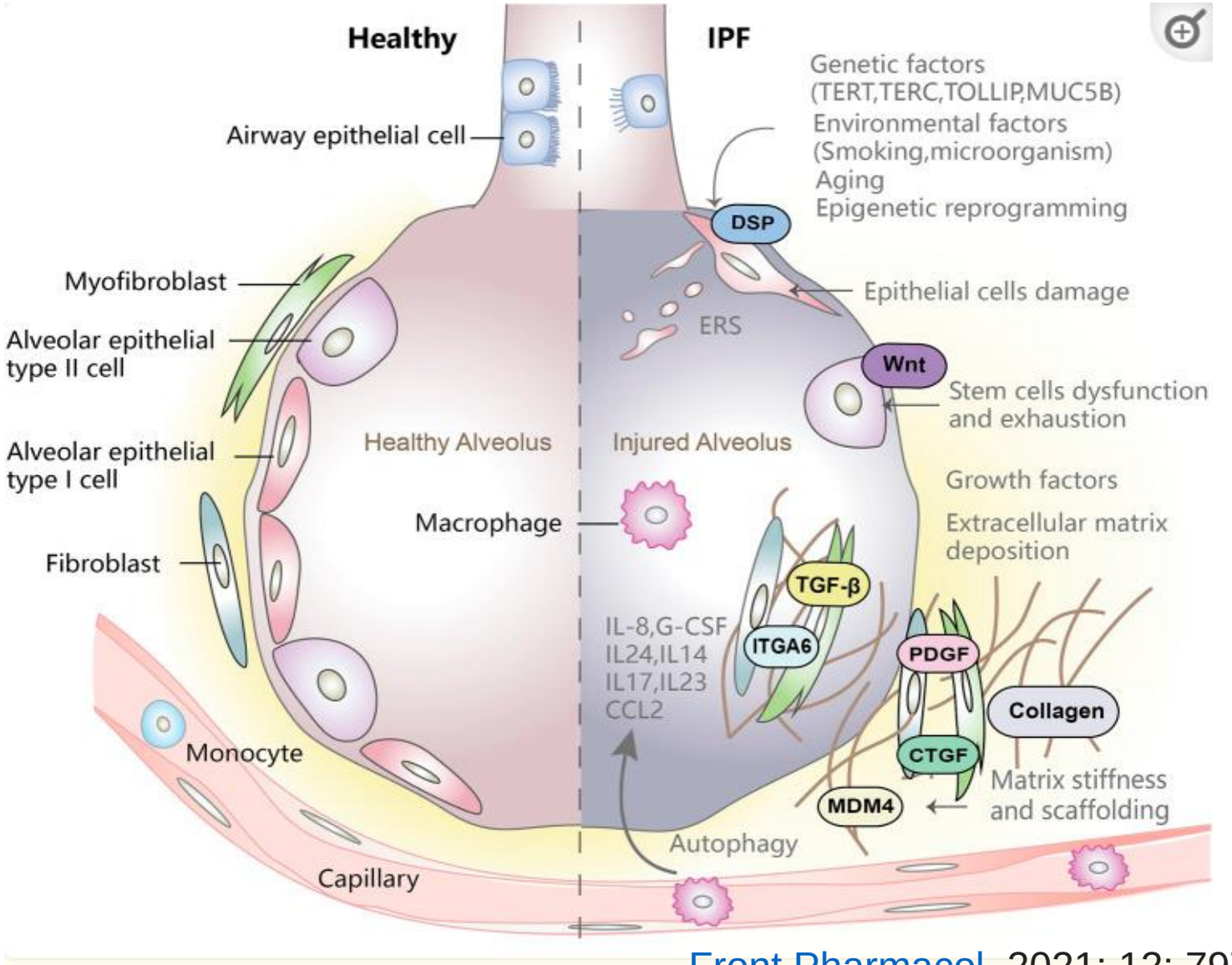
Dysregulated alveolar epithelial cell repair

IPF: 현재까지의 병인


1. Repeated epithelial damage
Type 1 AEC death
➔Type 2 AEC proliferation &
αvβ6 expression
PDGF
TGF-β
TNF-α
2. Fibroblast recruitment
Endothelial cell
Endothelial damage leads to Plasma leak
Type 2 Alveolar epithelial cell
Fibroblasts
Wound clot
Neutrophil activation
IL-4
IL-10
IL-13
Alternatively activated macrophages
Injury
Type 1 Alveolar epithelial cell
TNF-α
3. Fibrotic remodelling
IL-10
IL-12
TGF-β
Active TGF-β
4. Irreversibly scarred lung
Epithelial integrins Activate TGF-β
Endothelial death with vessel loss and new vessel formation
Fibroblasts produce collagen and become smooth muscle actin positive myofibroblasts resistant to apoptosis
Type 2 AEC death and apoptosis

Repetitive Alveolar epithelial cell injury

- Genetic factors
- Environmental factors
- Aging (senescence)
- Epigenetic reprogramming



Front Pharmacol. 2021; 12: 797292.

IPF- Genetic factors

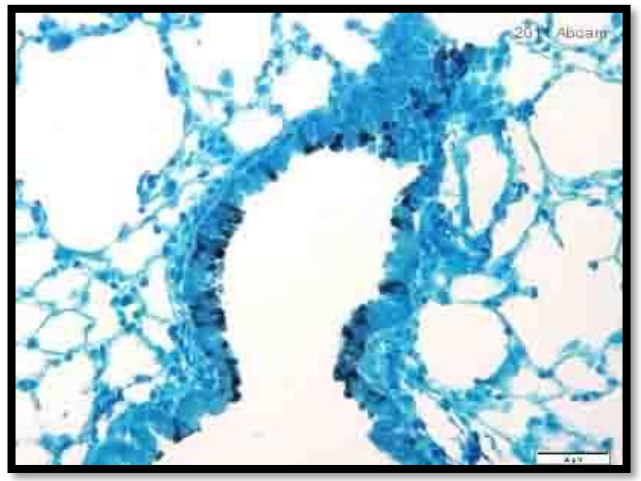
Mutation

- **surfactant protein c** (SFTPC), A2(SFTPA2) : abnormal surfactant folding
  → increased ER stress → apoptosis 증가
- **telomerase** : shortening of telomere length correlates with worse survival in IPF

Polymorphism

- **MUC5B promotor** : gain of function,
  30-40% of western IPF

overexpressed distal bronchiolar epithelium.
: excess mucin production and
impaired mucociliary clearance
activation of UPR



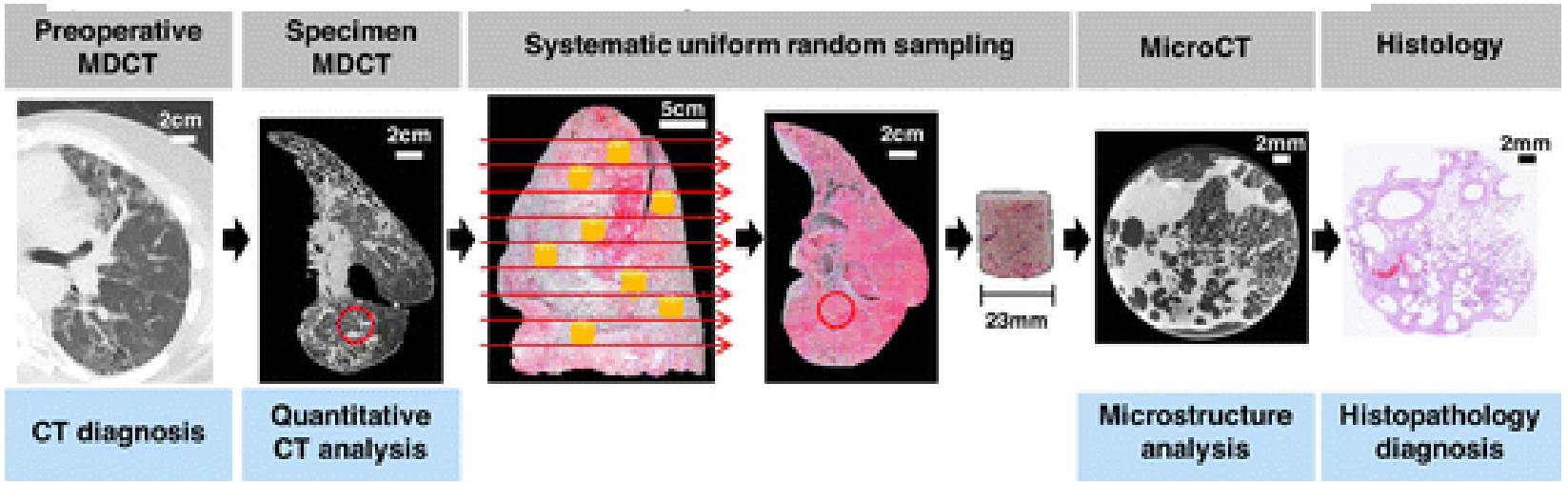
Small airway reduction and fibrosis is an early pathology in IPF

- loss of terminal bronchioles, thickening of small airway walls in the region of no microscopic fibrosis

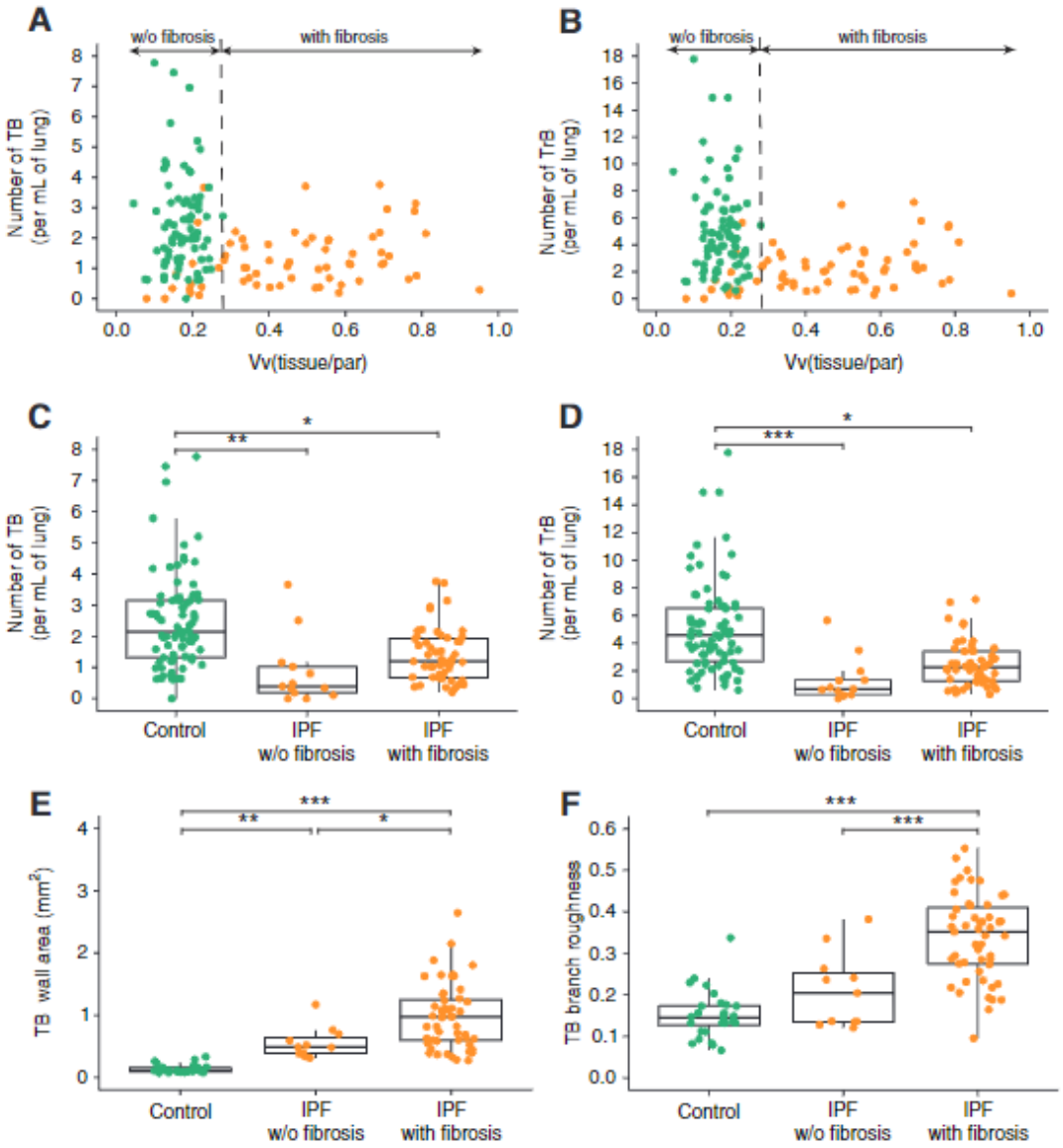
ORIGINAL ARTICLE

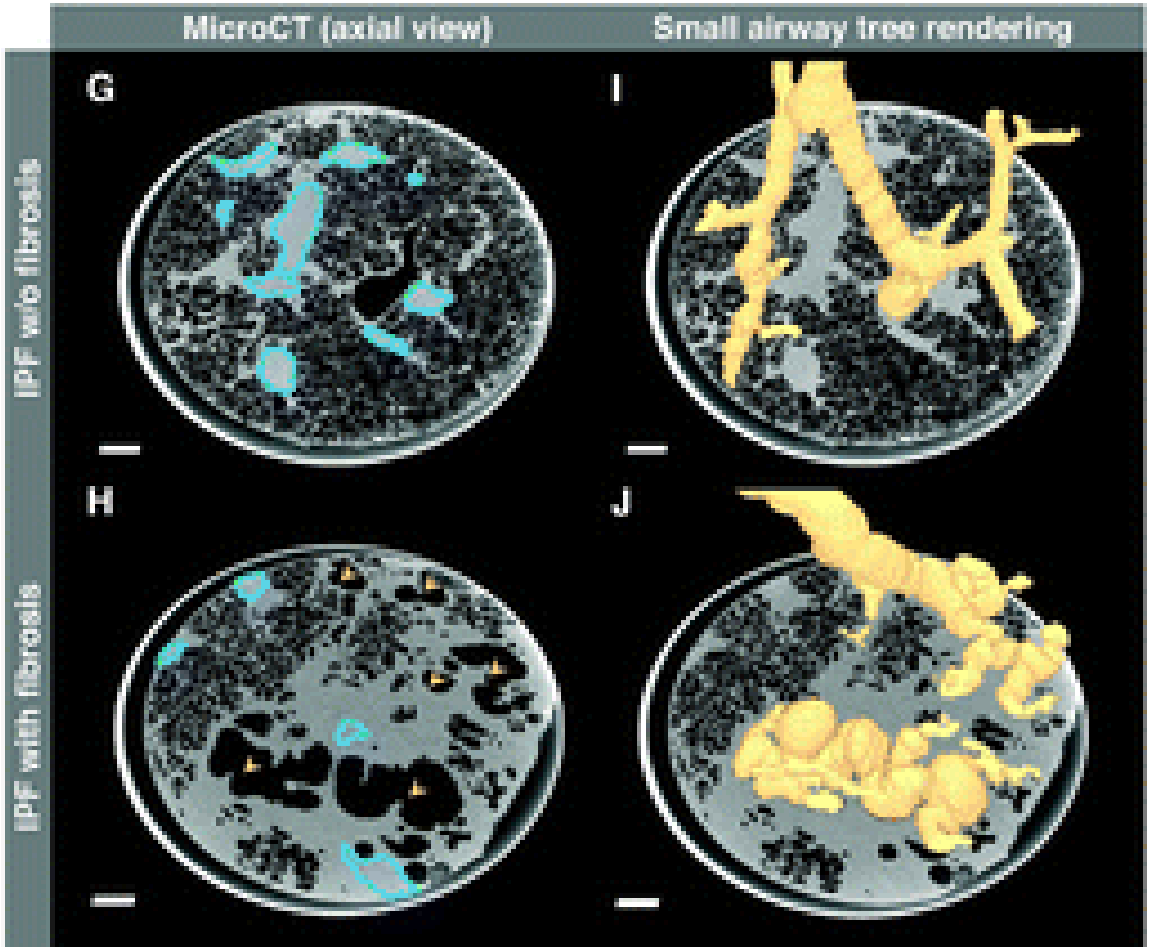
Small Airway Reduction and Fibrosis Is an Early Pathologic Feature of Idiopathic Pulmonary Fibrosis

Kohei Ikezoe[1], Tillie-Louise Hackett[1], Samuel Peterson[2], Dante Prins[1], Cameron J. Hague[3], Darra Murphy[3], Stacey LeDoux[1], Fanny Chu[1], Feng Xu[1], Joel D. Cooper[4], Naoya Tanabe[5], Christopher J. Ryerson[1], Peter D. Paré[1], Harvey O. Coxson[1], Thomas V. Colby[6], James C. Hogg[1], and Dragoş M. Vasilescu[1]



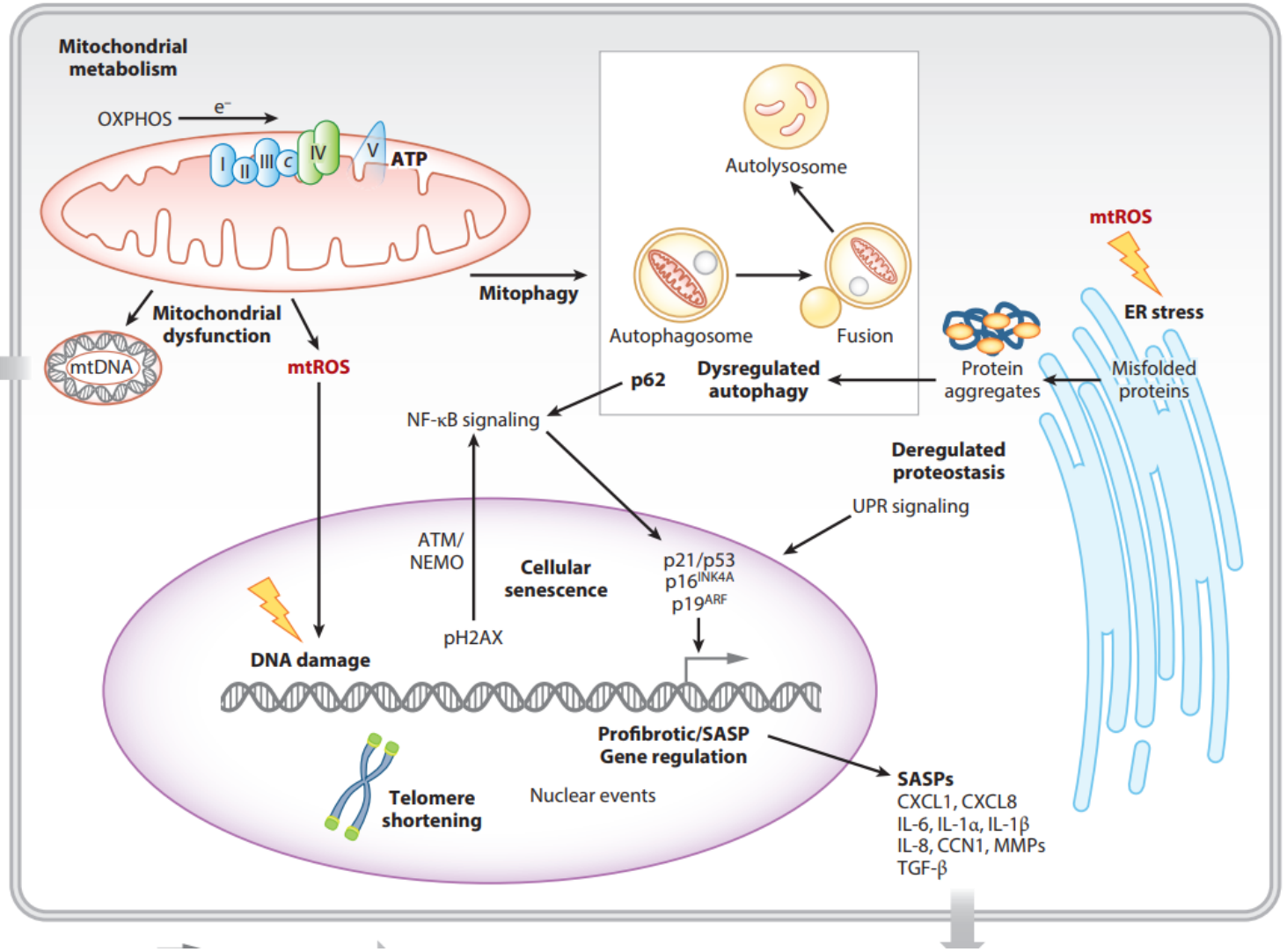
AJRCCM 204, 1048–1059, 2021





- MUC5B promotor variant (gain of function)
  : overexpression of MUC5B in bronchioloalveolar junction
    reduced mucocillary clearance

Senescence : accelerated aging



- Telomere mutations, shortening
- Reducing mitochondrial biogenesis
- Metabolic change
- Protein misfolding : SPC, MUC5B

Annu. Rev. Pathol. Mech. Dis. 2022. 17:515–46

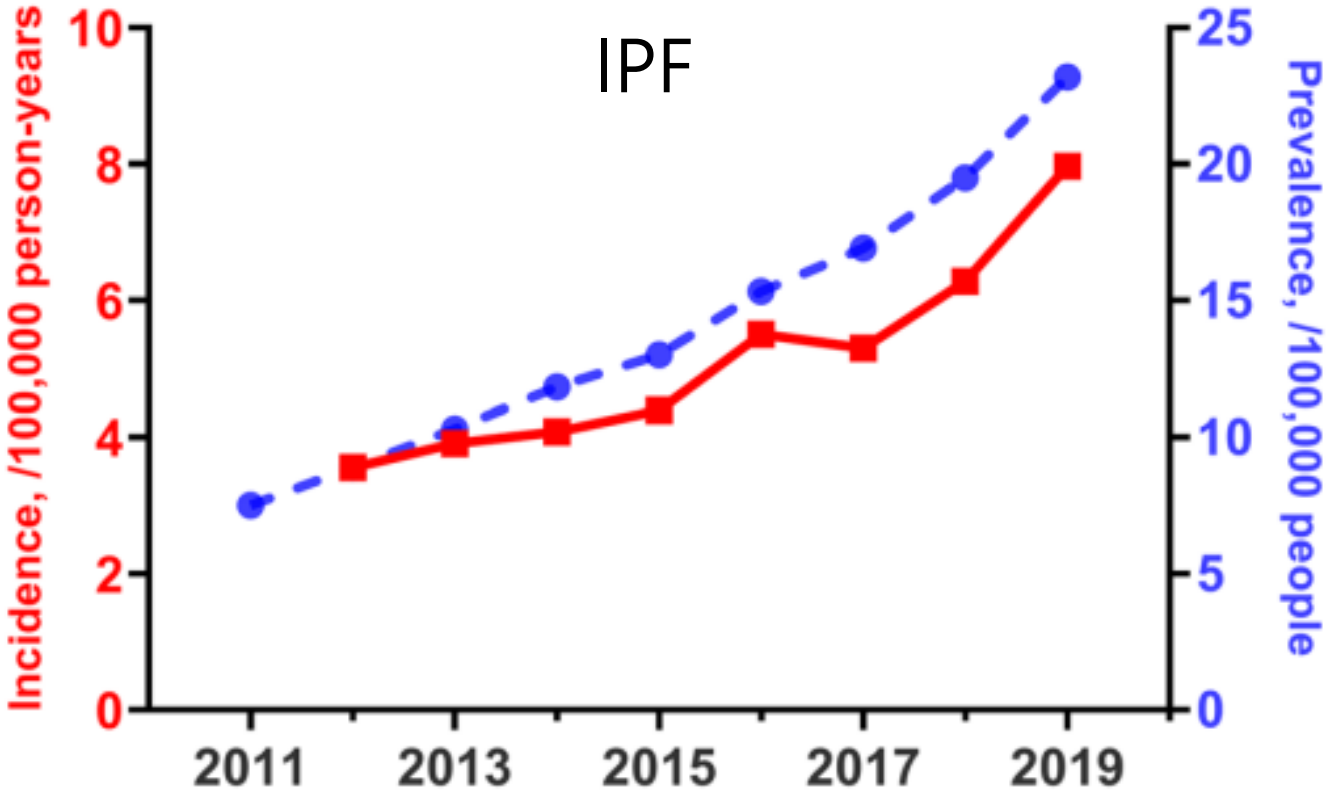
Korea; highest incidence and prevalence of IPF estimates

Country	Study	Publication year	Mean unadjusted incidence (per 10,000)	Adjusted incidence (per 10,000)	95% CI adjusted incidence (per 10,000)
Asia–Pacific					
South Korea	Han et al. [51]	2013	0.19	1.30	(0.62, 2.74)
	Kim et al. [41]	2017	1.31		
	Lee et al. [44]	2016	1.29		
	Combined		1.28		
Taiwan	Lai et al. [43]	2012	0.31	0.35	(0.17, 0.72)
Europe					
Finland	Kaunisto et al. [40]	2015	0.13	0.10	(0.04, 0.22)
France	Duchemann et al. [35]	2017	0.28	0.31	(0.07, 1.29)
Greece	Karakatsani et al. [52]	2009	0.09	0.09	(0.04, 0.18)
Italy	Agabiti et al. [33]	2014	0.93	0.49	(0.27, 0.91)
	Harari et al. [37]	2016	0.26		
	Combined		0.48		
United Kingdom	Strongman et al. [13]	2018	0.12	0.14	(0.06, 0.32)
North America					
Canada	Hopkins et al. [38]	2016	0.90	0.93	(0.54, 1.60)
	Tarride et al. [12]	2018	2.17		
	Combined		1.11		
United States	Fernández Pérez et al. [11]	2010	0.88	0.75	(0.28, 2.00)
	Raghu et al. [47]	2014	2.42		
	Raghu et al. [46]	2016	0.26		
	Combined		0.64		

Country	Study	Publication year	Mean unadjusted prevalence (per 10,000)	Adjusted prevalence (per 10,000)	95% CI Adjusted prevalence (per 10,000)	Rare disease threshold (per 10,000)	Rare disease threshold met?
Asia–Pacific							
Japan	Kondoh et al. [42]	2016	0.59	0.89	(0.51, 1.55)	< 50,000 cases[a] [25]	NA
	Natsuizaka et al. [45]	2014	1.00				
	Combined		0.79				
South Korea	Kim et al. [41]	2017	3.52	4.51	(2.99, 6.79)	< 20,000 cases[a] [26]	NA
	Lee et al. [44]	2016	3.89				
	Combined		3.70				
Taiwan	Lai et al. [43]	2012	0.49	0.57	(0.34, 0.94)	1 [27]	Yes
Europe							
Denmark	Hyldgaard et al. [39]	2014	1.01	1.17	(0.56, 2.44)	1–2 [28]	Yes (upper CI out of bounds)
Finland	Kaunisto et al. [40]	2015	0.86	0.65	(0.36, 1.18)	5 [29]	Yes
France	Duchemann et al. [35]	2017	0.82	0.94	(0.44, 1.99)	5 [29]	Yes
Greece	Karakatsani et al. [52]	2009	0.34	0.33	(0.21, 0.53)	5 [29]	Yes
Italy	Agabiti et al. [33]	2014	2.56	2.37	(1.38, 4.09)	5 [29]	Yes
	Harari et al. [37]	2016	2.12				
	Combined		2.46				
Poland	Szafrański [50]	2012	2.56	2.51	(1.55, 4.05)	5 [29]	Yes
United Kingdom	Strongman et al. [13]	2018	1.16	0.78	(0.38, 1.63)	5 [29]	Yes
North America							
Canada	Hopkins et al. [38]	2016	2.00	2.98	(1.7, 5.19)	5 [30]	Yes (upper CI out of bounds)
	Tarride et al. [12]	2018	7.27				
	Combined		2.98				
United States	Fernández Pérez et al. [11]	2010	2.81	2.4	(1.33, 4.34)	< 200,000[a] [31]	Yes
	Raghu et al. [47]	2014	11.1				
	Raghu et al. [46]	2016	0.67				
	Combined		1.37				

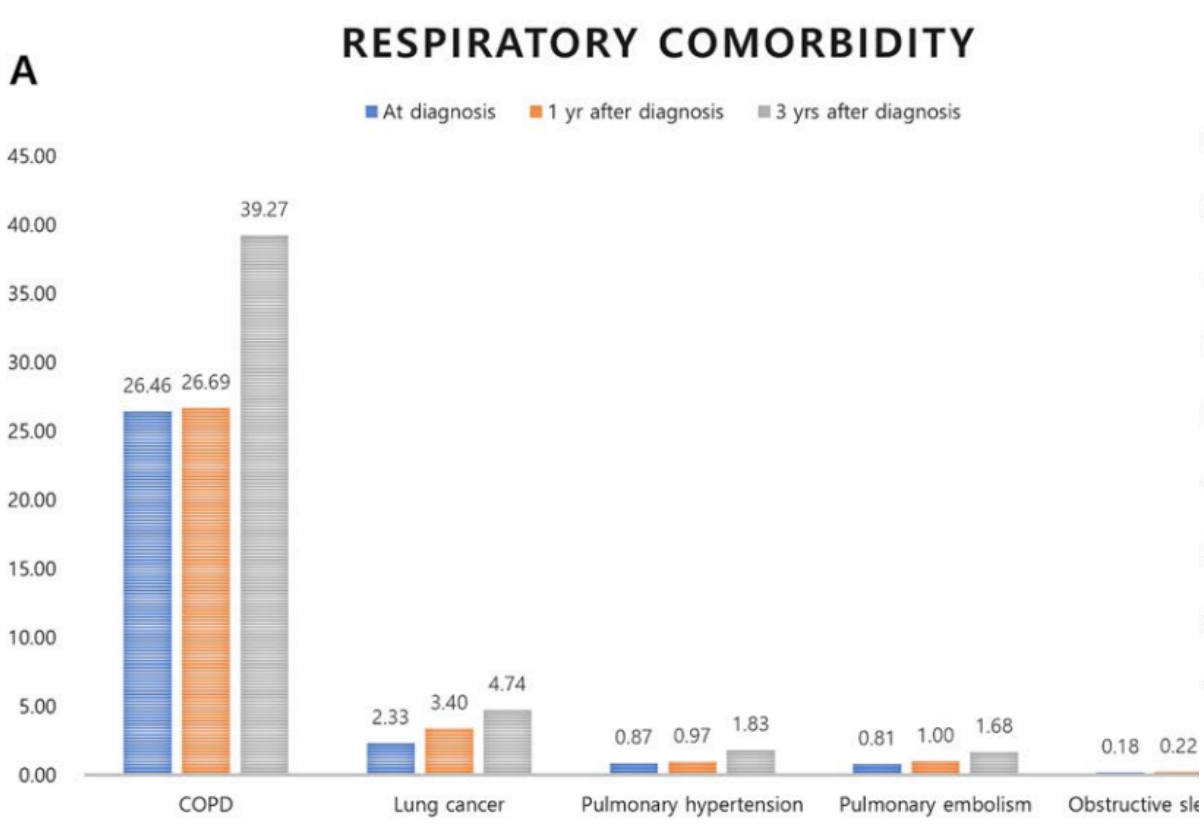
Maher et al. Respir Res (2021) 22:197

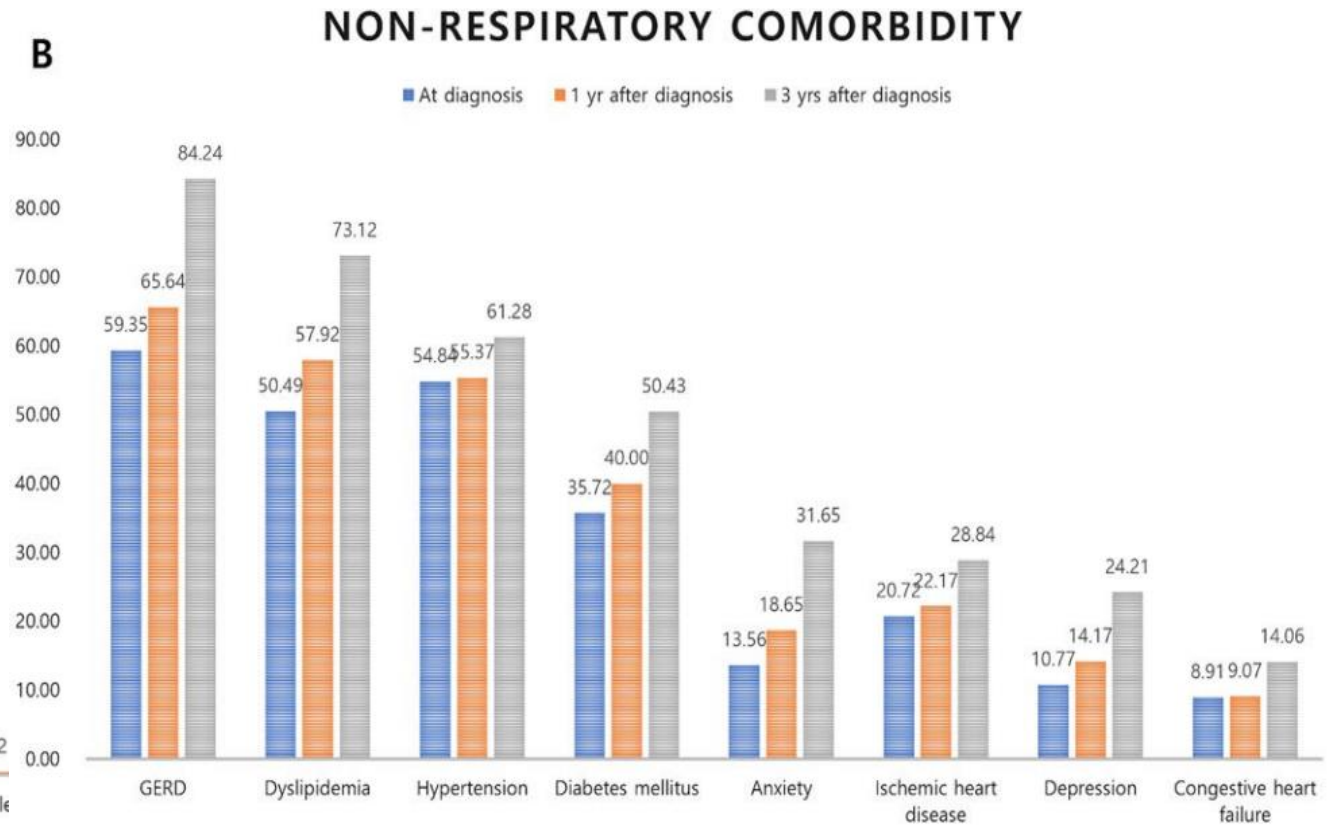
Annual incidences and prevalence in Korea ; nation wide cohort study



Lee et al. BMC Pulmonary Medicine (2023) 23:54

Prevalence of co-morbidities of IPF in korea





COPD > Lung cancer > Pul. HTN

GERD > dyslipidemia > HTN > DM

Lee et al. BMC Pulmonary Medicine (2023) 23:54

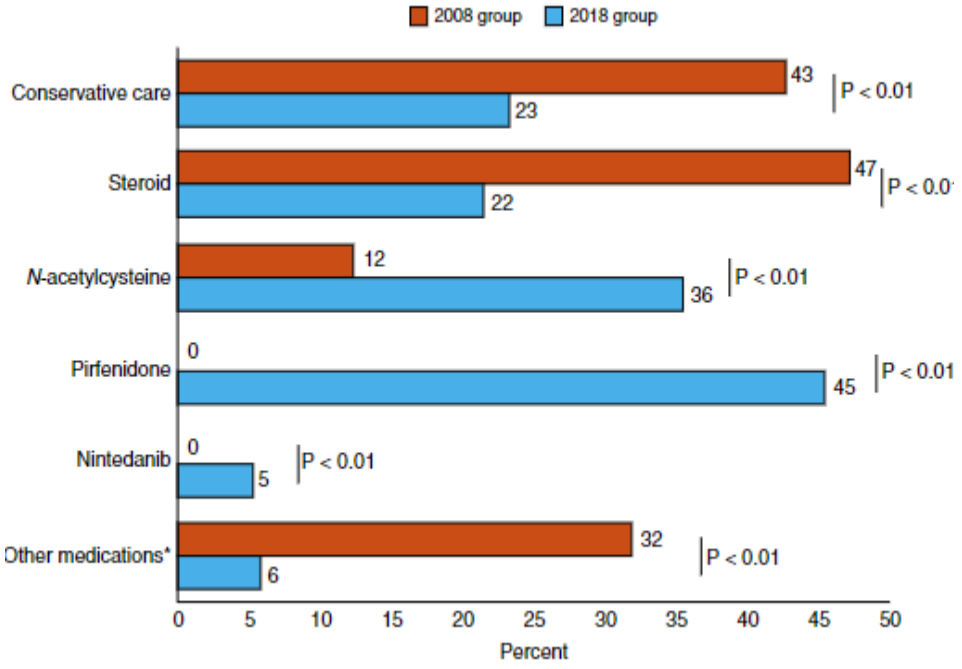
Longitudinal Changes in Clinical Features, Management, and Outcomes of Idiopathic Pulmonary Fibrosis

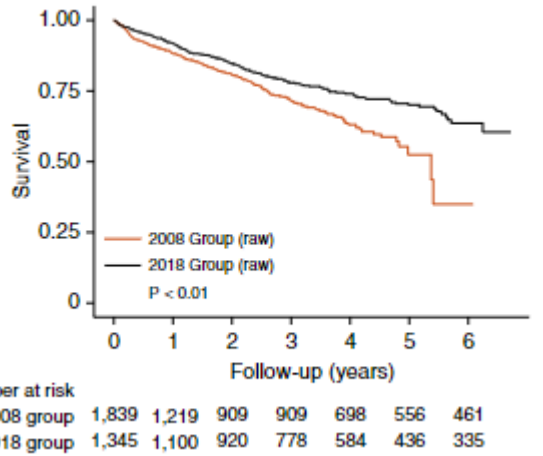
A Nationwide Cohort Study

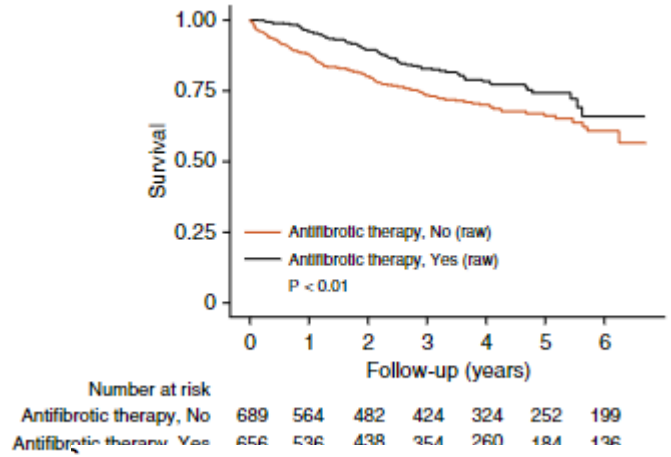
Korea IPF Cohort (KICO) Registry- 32 university hospital

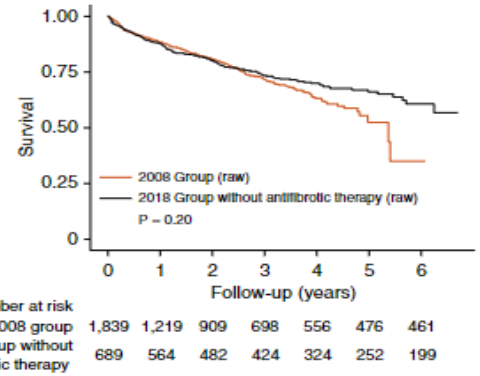
- **2008 group : 2000-2008. diagnosed IPF**
- **2018 group : 2010- 2018**

Variables	2008 Group (*n* = 1,839)	2018 Group (*n* = 1,345)
Age, yr	68 ± 9	68 ± 8
Sex, male	1,349 (73)	1,029 (76)
Smoking status*		
Never	574 (35)	378 (28)
Ex-smoker	623 (38)	776 (58)
Current smoker	460 (28)	178 (13)
Smoking, pack-years	38 ± 21	33 ± 21
Family history of interstitial lung disease	21 (2)	61 (5)
Comorbidities		
Hypertension	412 (22)	465 (35)
Diabetes	358 (20)	335 (25)
Tuberculosis	223 (12)	174 (13)
Cardiovascular disease	117 (6)	52 (4)
Hepatitis	35 (2)	49 (4)
Cancer	186 (10)	86 (6)
Diagnosed by surgical biopsy	535 (29)	268 (20)
Antinuclear antibody test performed	826 (45)	936 (70)
Rheumatoid factor test performed	828 (45)	1,005 (75)
Ground-glass opacity on HRCT imaging	868 (47)	798 (59)
Honeycombing on HRCT imaging	1,486 (81)	932 (70)
Dyspnea at time of diagnosis	1,255 (68)	697 (52)
Cough at time of diagnosis	1,145 (62)	733 (55)
Mean Pa_{O_2}, mm Hg	82 ± 26	96 ± 44
Mean Pa_{CO_2}, mm Hg	38 ± 8	36 ± 15
Initial GAP score†	3.2 ± 1.4	3.3 ± 1.4
Initial mean FVC, % predicted	77 ± 20	74 ± 18
Initial mean D_{LCO}, % predicted	64 ± 24	63 ± 22
Received lung transplantation	2 (0.1)	30 (2)
Follow-up months	18 ± 16	30 ± 21
Death during follow-up	352 (19)	257 (19)









Ann Am Thorac Soc 18, 780–787, 2021

Clinical feature and outcome of IPF : Analysis of the Korea IPF Cohort (KICO) Registry

- Tuberc Respir Dis 2022;85:185-194

- 2139 IPF (From 2008)
- Mortality (from 2016)

6-minute walk test (mean±SD) (n=1,088)	
Walk distance (m)	399±182
Minimum saturation (%)	90.3±14.1
Arterial blood gas (mean±SD) (n=950)	
PaO_2 (mm Hg)	92.4±42.7
$PaCO_2$ (mm Hg)	36.1±12.4
Pulmonary function test (mean±SD)	
FVC (L)	2.77±1.57
FVC, % predicted	74.6±17.5
FEV_1 (L)	2.49±8.01
FEV_1, % predicted	85.2±19.1
DLco (mL/mm Hg/min)	11.92±5.58
DLco, % predicted	63.6±22.0
CT patterns	
UIP pattern	972 (45.4)
Probable UIP pattern	907 (42.4)
Inconsistent with UIP pattern	124 (5.8)
CT findings	
Honeycombing	1,434 (67.0)
GGO	1,256 (58.7)
Emphysema	699 (32.7)
GAP stage	
Stage I	1,026 (56.9)
Stage II	589 (32.7)
Stage III	187 (10.4)

Table 6. Cox regression analyses of risk factors for mortality

	Univariate analysis			Multivariate analysis		
	HR	CI	p-value	HR	CI	p-value
Age	1.038	1.014–1.063	0.002	1.046	1.007–1.086	0.021
Sex	1.210	0.766–1.911	0.414	-	-	-
Smoking			0.489			
Nonsmoker	1					
Ex-smoker	0.517	0.210–1.271		-	-	-
Never smoker	0.634	0.313–1.288		-	-	-
Six-minute walking test						
Walking distance	0.997	0.995–0.998	<0.001	0.999	0.996–1.002	0.435
Minimum saturation	0.945	0.919–0.972	<0.001	0.949	0.949–0.908	0.993
Pulmonary function test						
FVC	0.969	0.957–0.981	<0.001	0.999	0.977–1.022	0.956
DLco	0.965	0.954–0.975	<0.001	0.996	0.978–1.014	0.685
Initial CT pattern			0.168			
Inconsistent with UIP	1	-	-			
Probable UIP	2.393	0.746–7.675	0.142	-	-	-
UIP	2.861	0.894–9.161	0.077	-	-	-
Honeycombing	1.459	0.961–2.217	0.076	-	-	-
Initial GAP index	1.551	1.377–1.747	<0.001	1.099	0.819–1.473	0.530
Antifibrotics	2.037	1.329–3.120	0.001	0.497	0.262–0.944	0.033
Acute exacerbation	5.392	3.698–7.859	<0.001	3.703	2.165–6.332	<0.001
Clinical trial participation	0.723	0.293–1.789	0.483	-	-	-
Exposure						
Chemicals	1.285	0.715–2.310	0.402	-	-	-
Wood dust	2.099	1.089–4.048	0.027	2.449	1.094–5.484	0.029
Metal dust	3.772	0.929–15.316	0.063	-	-	-
Fabric dust	0.845	0.267–2.675	0.775	-	-	-
Stone dust	2.037	1.242–3.339	0.005	2.269	1.225–4.204	0.009
Family history of ILD	0.587	0.186–1.852	0.364	-	-	-

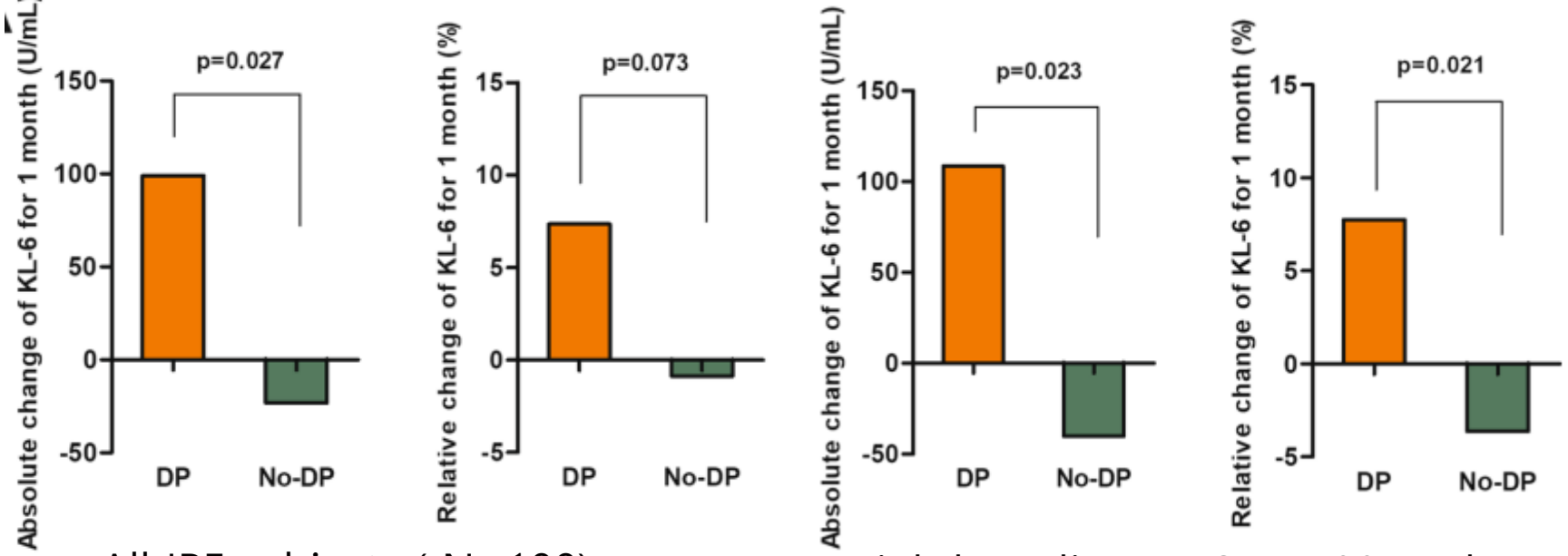
Prognostic and predictive factors

- KL-6

Blood KL-6 levels predict treatment response to antifibrotic therapy in patients with idiopathic pulmonary fibrosis

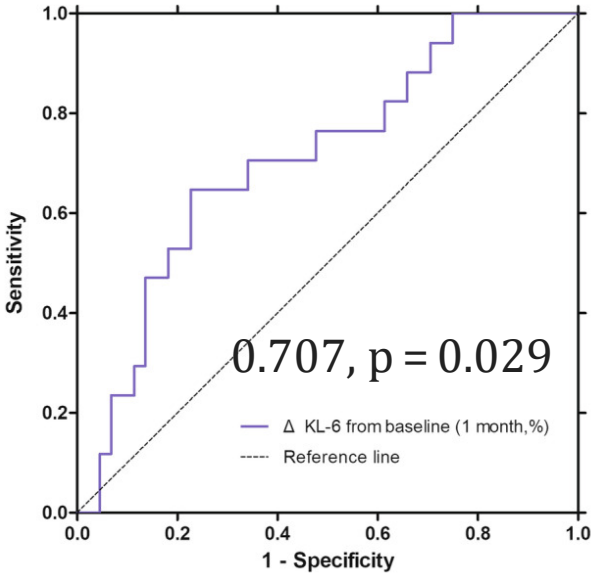
Respir Res. 2022; 23: 334.

- DP : decline in FVC > 10% or DLCO > 15% after 6 month PFD



All IPF subjects (N=188)

High base line KL-6 (> 500U/ml)

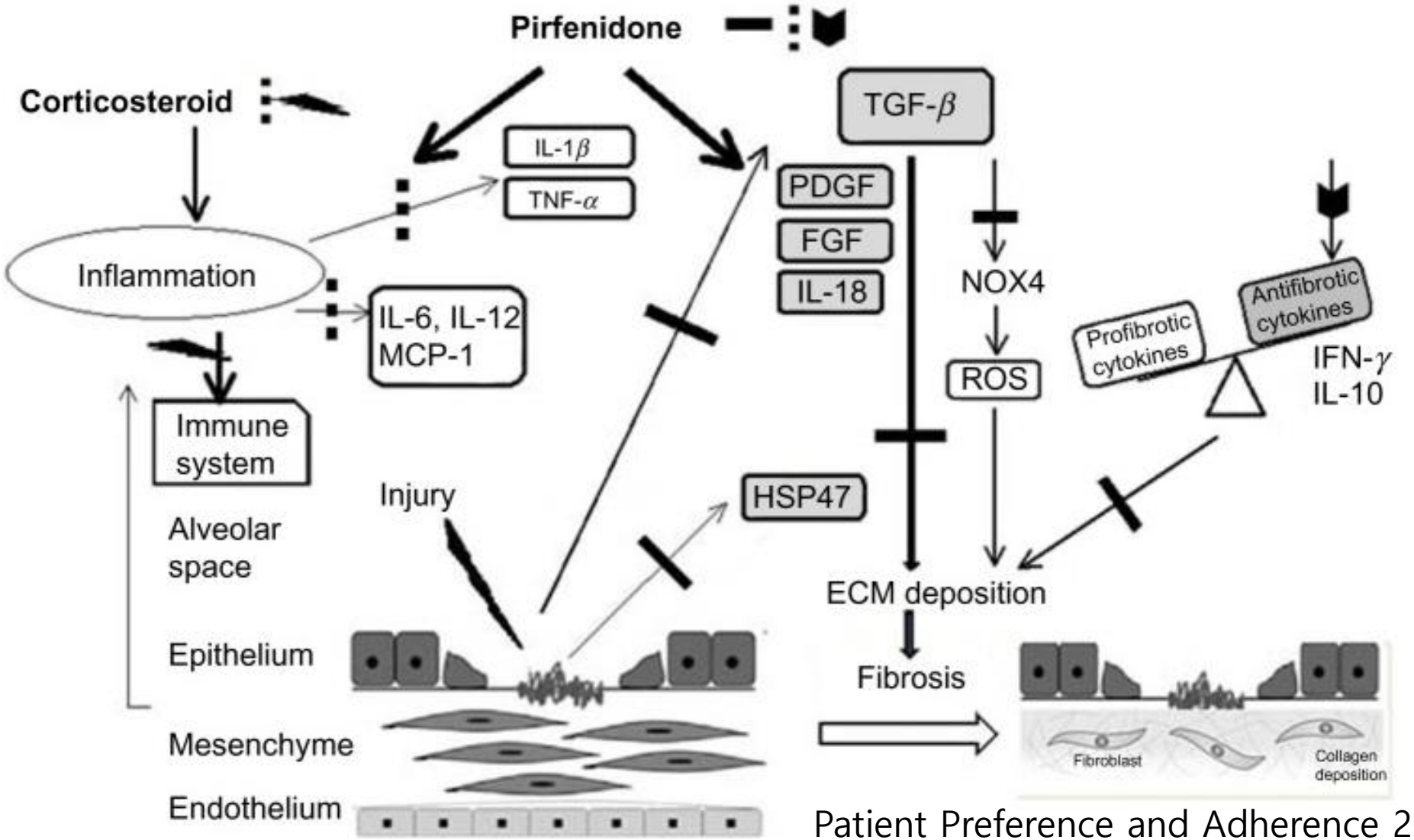


Effective(FDA approved) Drug in IPF

Variable	Nintedanib	Pirfenidone
Mechanism of action	Tyrosine kinase inhibition	Inhibition of TGF-β production and downstream signaling, collagen synthesis, and fibroblast proliferation (selected list)
Efficacy	Slows FVC decline by 50%	Slows FVC decline by 50%
FDA-approved dose	150 mg by mouth twice daily	801 mg by mouth thrice daily
Common side effects	Diarrhea	Anorexia, nausea, photosensitivity
Enzyme metabolism	Ester cleavage (major), CYP 3A4 (minor)	CYP 1A2 (major), other CYP enzymes (minor)
Cautions	Risks of both bleeding and arterial thrombosis; risk of gastrointestinal perforation (rare); anticoagulant and prothrombotic drugs should be avoided	CYP 1A2 inhibitors (e.g., fluvoxamine and ciprofloxacin) can raise pirfenidone levels; CYP 1A2 inducers (e.g., omeprazole and smoking) can lower pirfenidone levels
Need for liver-function monitoring	Yes†	Yes‡
Clinical strategies to minimize side effects	Use of antidiarrheal agents, temporary dose reduction to 100 mg twice daily	Slow dose increase over 14-day period, medication to be taken with food, use of antacids, use of antiemetic agents, sun avoidance

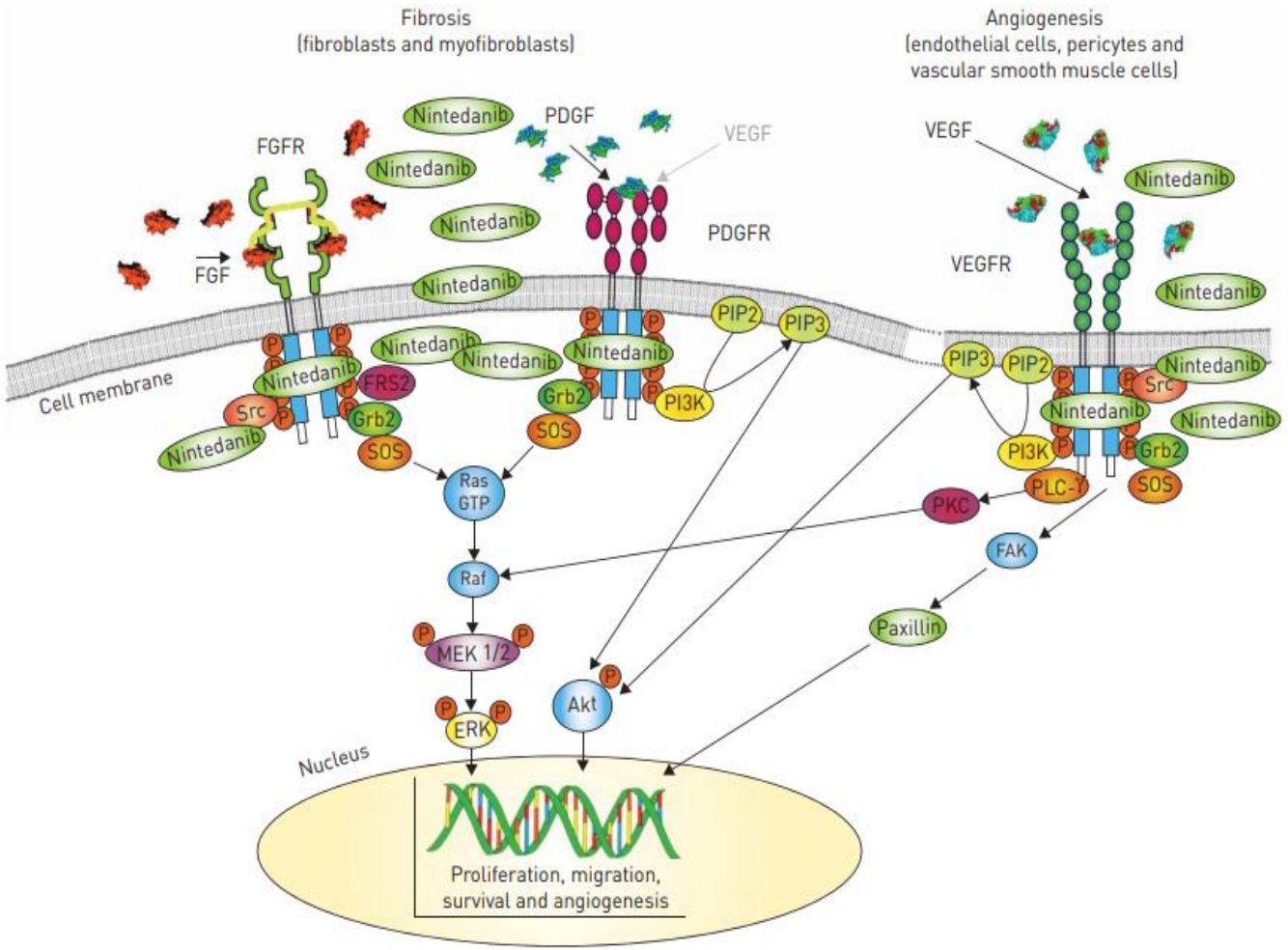
N Engl J Med 2018;378:1811-23

Pirfenidone : Potential mechanisms for the suppression of fibrogenesis



Patient Preference and Adherence 2014:8 361–370

Nintedanib : Mode of action in lung fibrosis



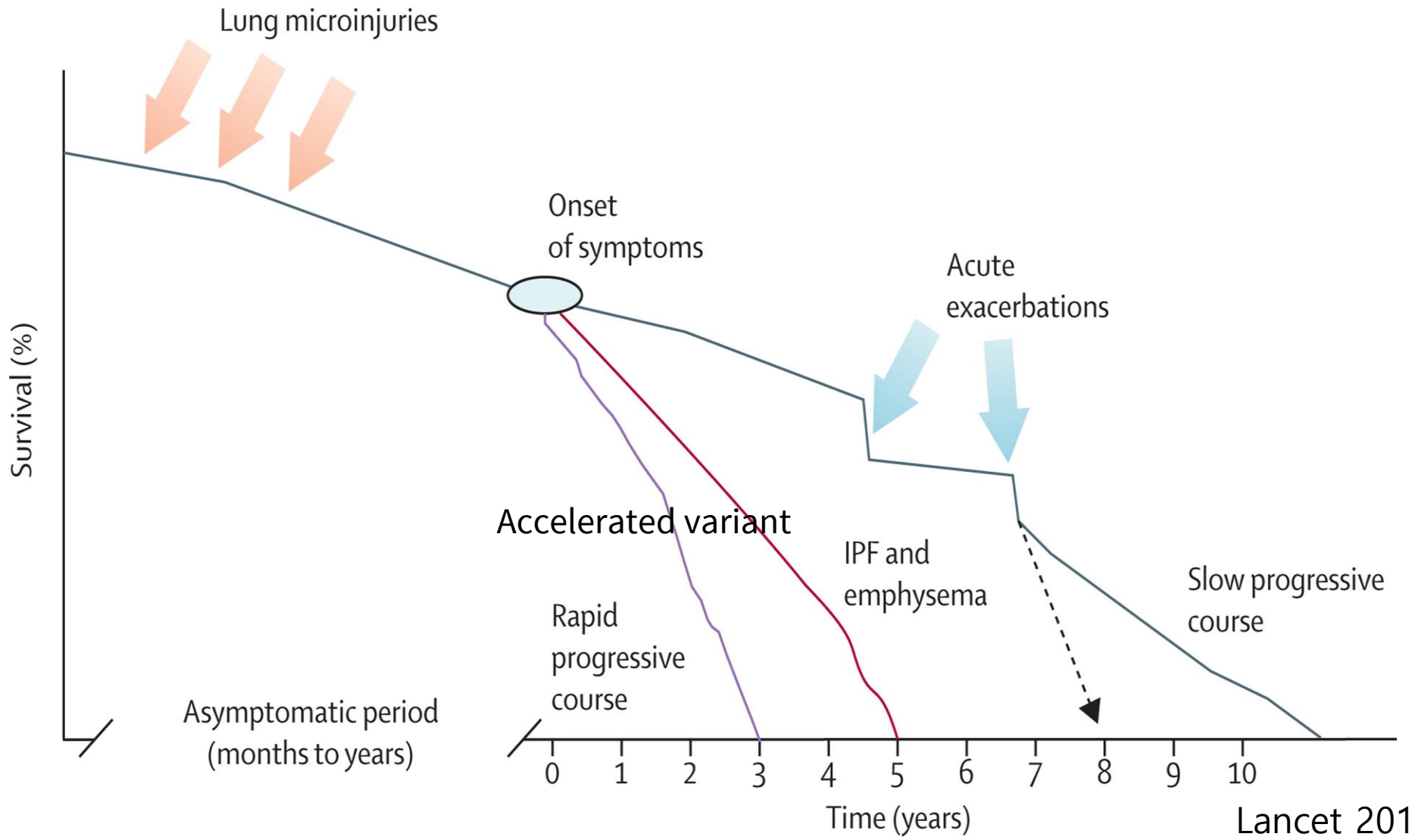
- Triple tyrosine kinase inhibitor
  ; FGFR , PDGFR, VEGFR

: blocking fibroblast into myofibroblast and migration

: anti-inflammatory activity
: anti- angiogenesis

Eur Respir J 2015; 45: 1434–1445

Clinical phenotypes of IPF ; heterogenous

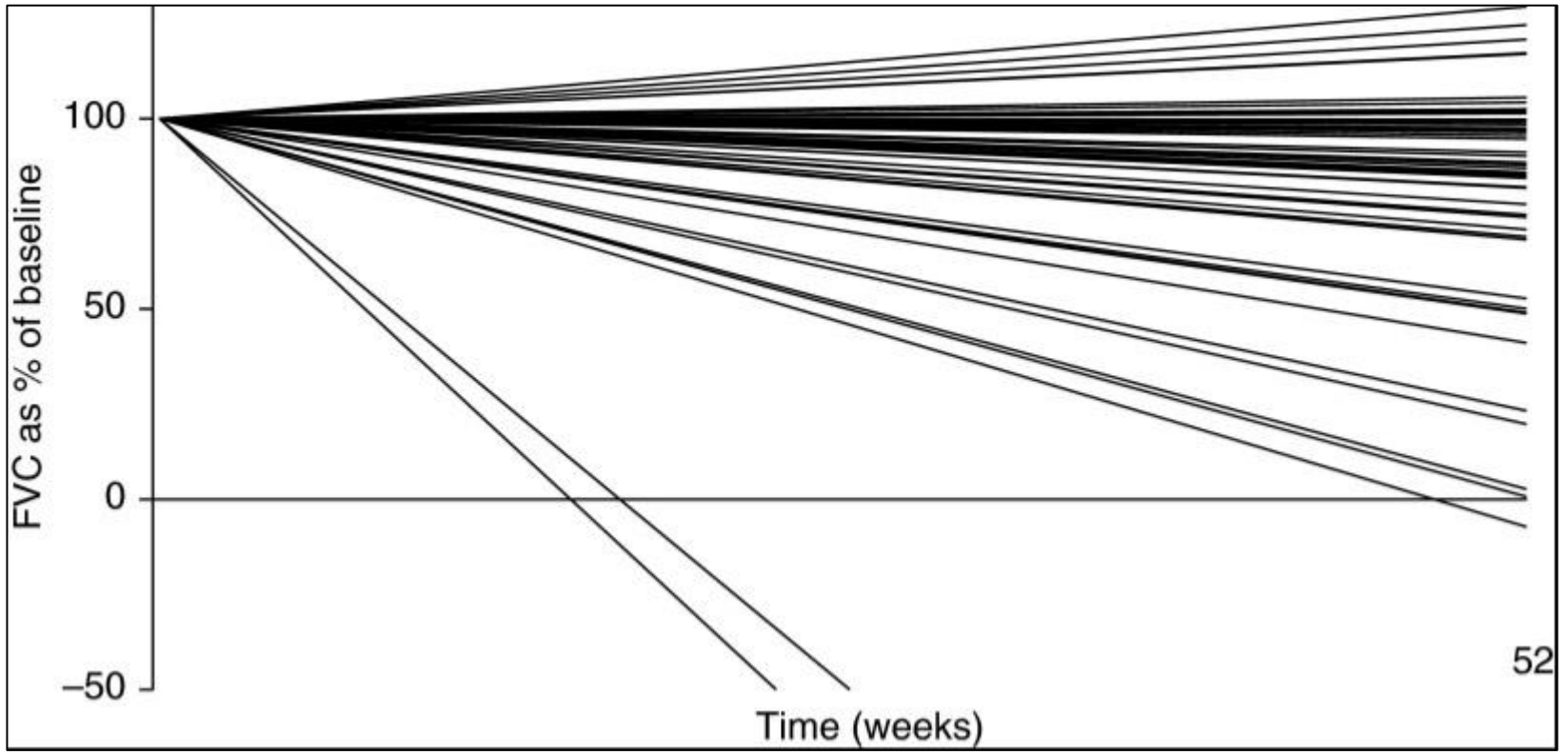


Lancet 2011; 378: 1949–61

Clinical course

- single-center study based on daily hand-held spirometry

- 50 subjects of IPF



- Only 8 % of IPF subjects show stable FVC after 1 year

- 18 death during study period

AJRCCM 2016; 15 194:989

When to start treatment with antifibrotic drugs

Four reasons for early treatment

1) poor prognosis

- median survival 3-5 yrs, worse than most of cancers

2) unpredictable behavior

- speed of progress is variable ; slow, rapid, exacerbation

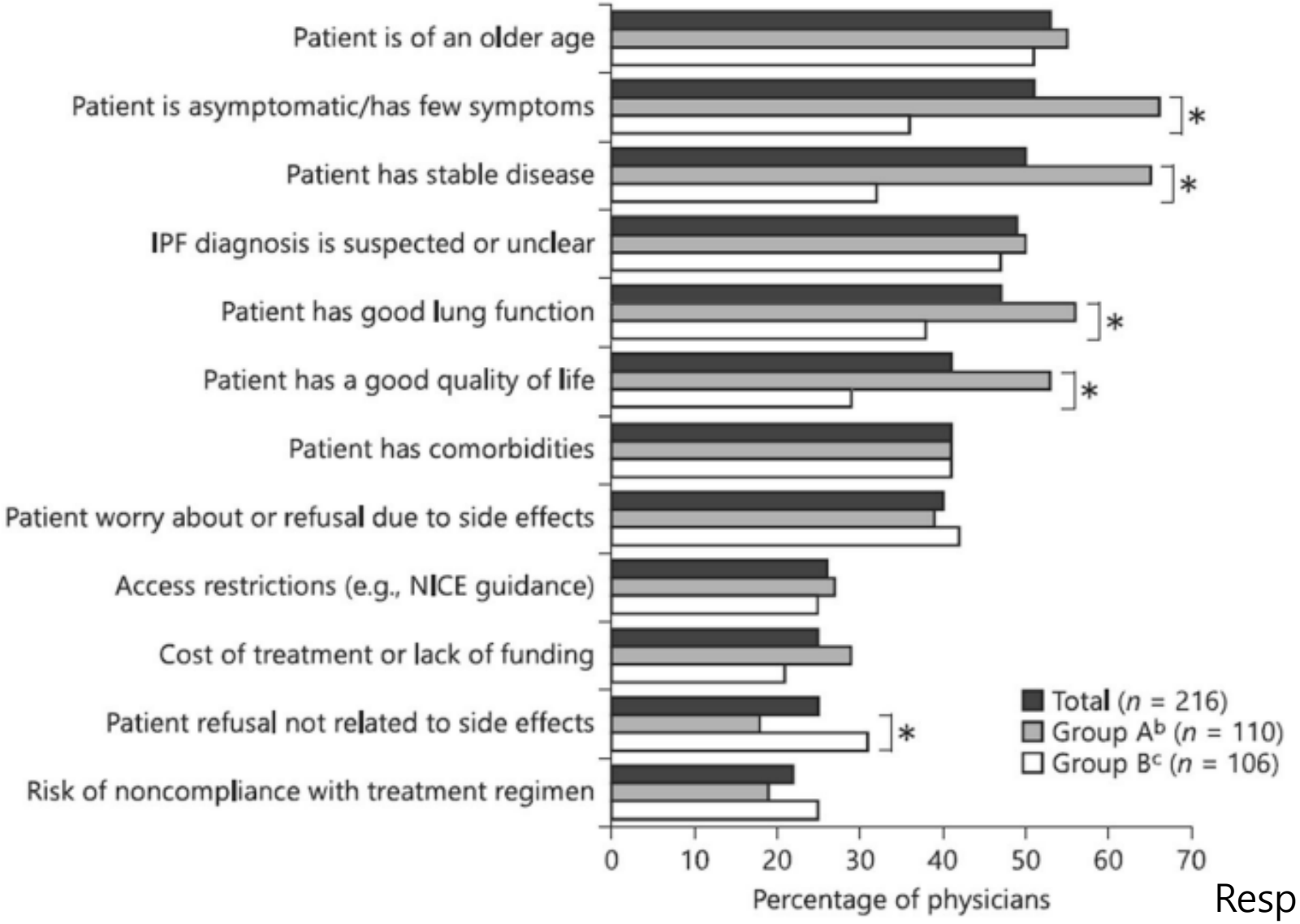
3) FVC tends to decline

- mean annual FVC decline in placebo > 200ml

4) Changes in FVC is associated with increased mortality

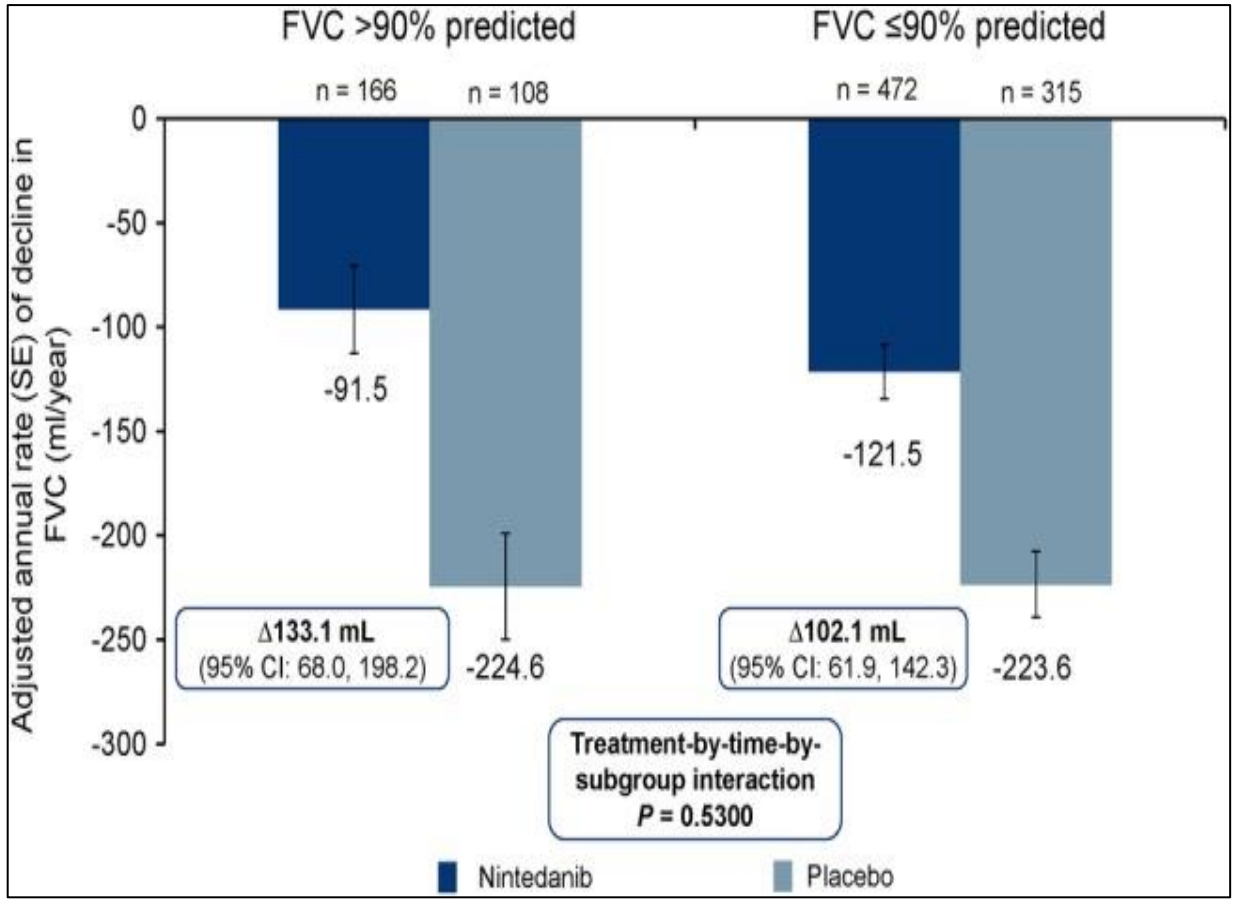
- 10% decline in FVC within either 6 or 12 months is associated with a significant increase in mortality

Reasons given by pulmonologists for not treating with "mild" IPF in an international survey

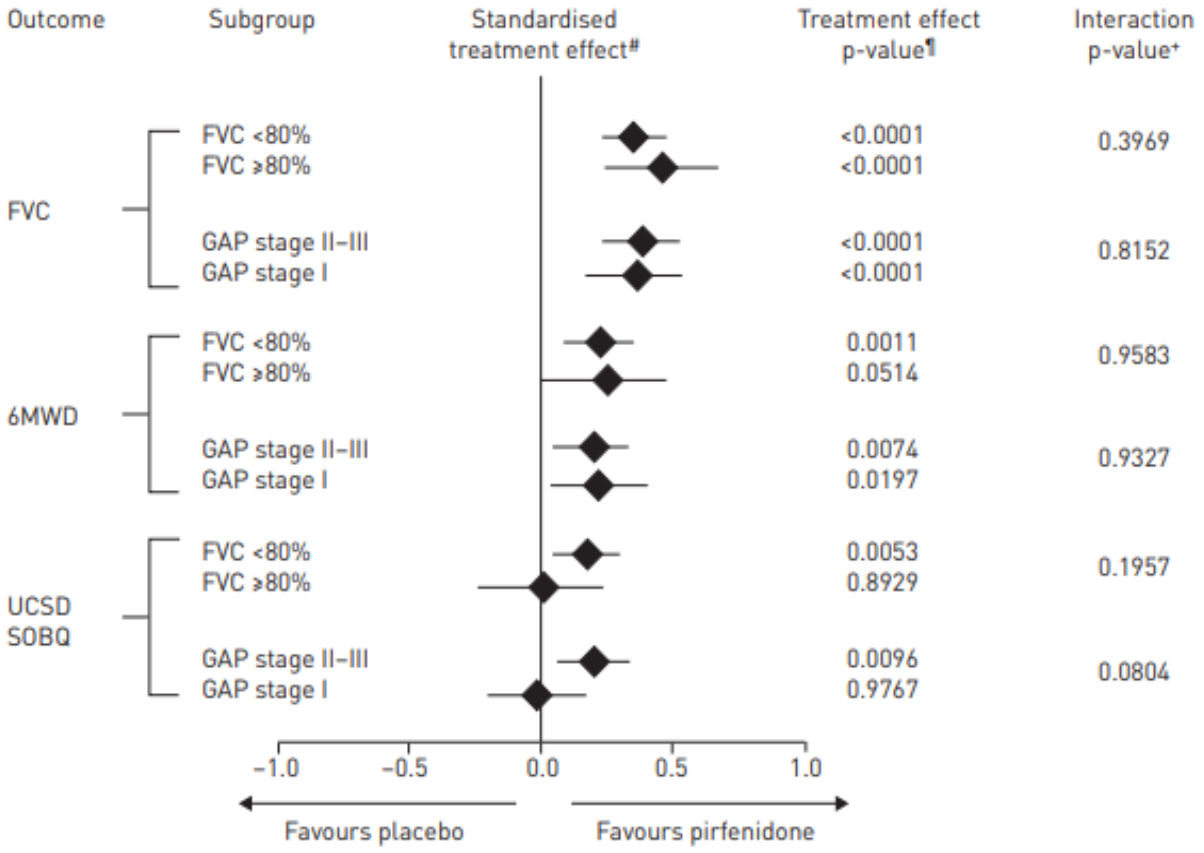


Respiration. 2019;96:514–24.

Early treatment is effective in early IPF



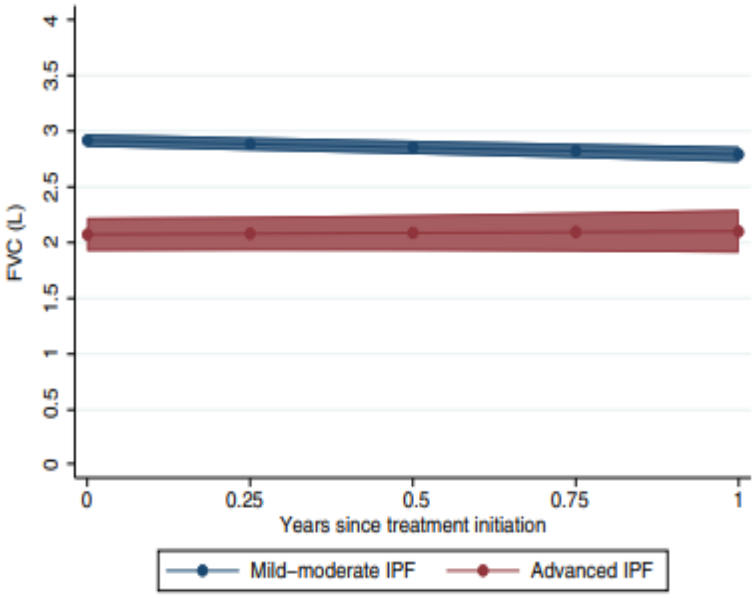
Thorax. 2017; 72(4): 340–346.

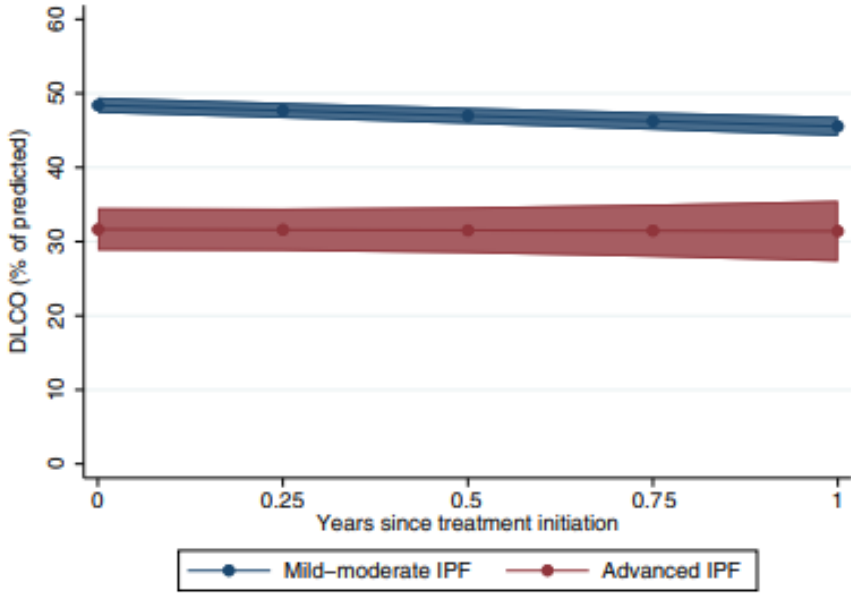


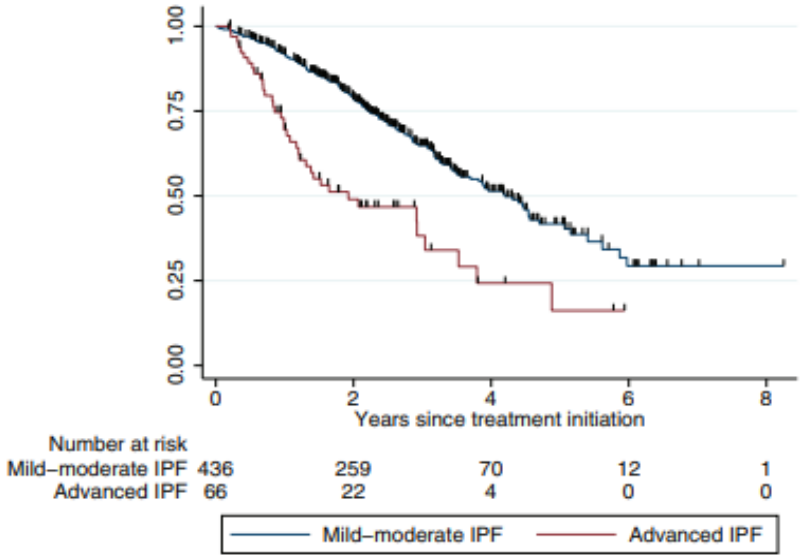
Eur Respir J 2016; 48: 843–851 |

Efficacy in anti-fibrotics in advanced IPF

- Advanced IPF : FVC < 50% and/or DLCO <30%
- 502 IPF subjects with Tx. PFD or nintedanib (13% had advanced IPF)
- FVC, DLCO, mortality : mild- moderate vs advanced IPF







Respirology. 2021;26:982–988.

Adv Ther. 2020; 37(5): 2303–2316.

When to stop therapy

- Unbearable side effects
- Lack of efficacy - non-adequate response to therapy
  : absolute decline of > 10% in FVC

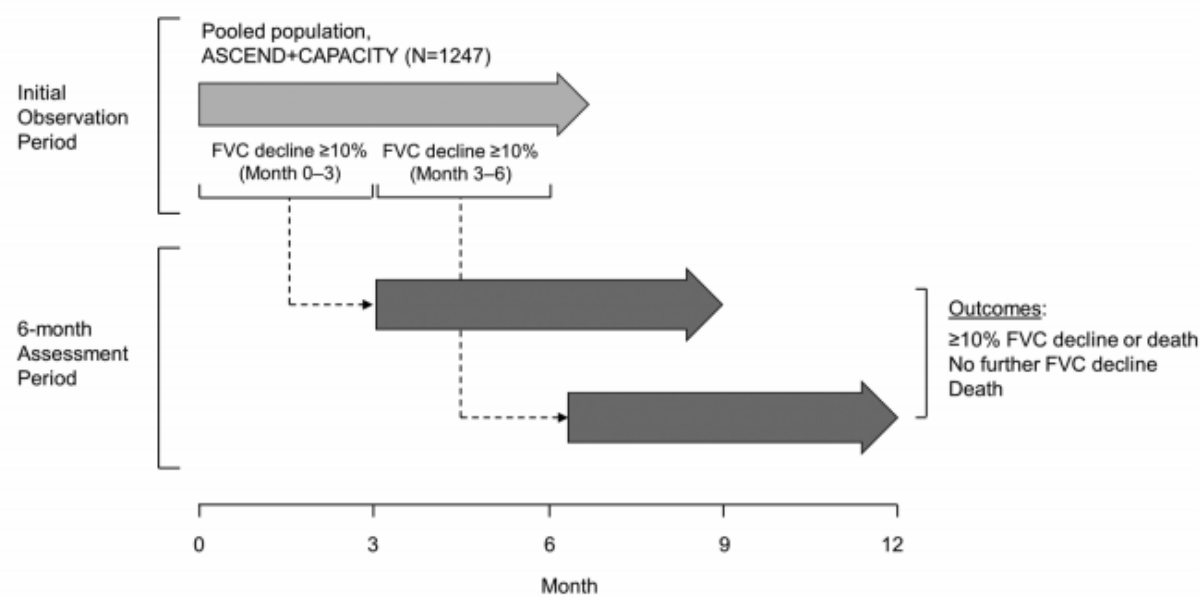
ORIGINAL ARTICLE

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

Steven D Nathan,[1] Carlo Albera,[2] Williamson Z Bradford,[3] Ulrich Costabel,[4] Roland M du Bois,[5] Elizabeth A Fagan,[3] Robert S Fishman,[3] Ian Glaspole,[6] Marilyn K Glassberg,[7] Kenneth F Glasscock,[3] Talmadge E King Jr,[8] Lisa Lancaster,[9] David J Lederer,[10] Zhengning Lin,[3] Carlos A Pereira,[11] Jeffrey J Swigris,[12] Dominique Valeyre,[13] Paul W Noble,[14] Athol U Wells[15]

Nathan SD, et al. Thorax 2016;71:429–435

Continued treatment with PFD reduced risk second >10 % FVC decline or death



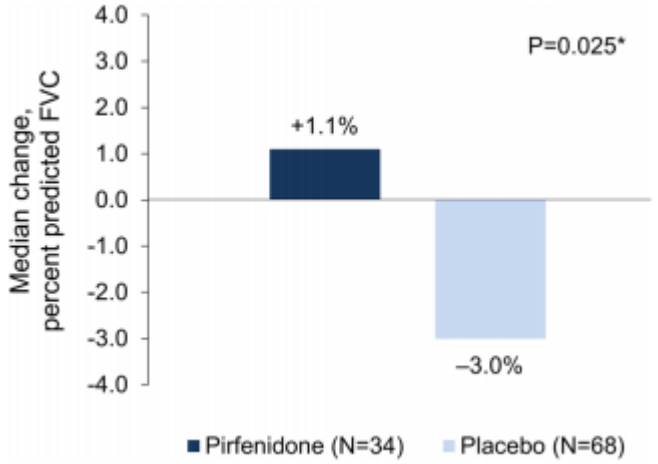


Table 2 Outcomes after 6 months of continued treatment following an initial decline in per cent predicted FVC ≥10%*

	Pirfenidone (N=34)	Placebo (N=68)	Relative difference (%)	p Value†
≥10% decline in FVC or death	2 (5.9%)	19 (27.9%)	−78.9	0.009
No further decline in FVC‡	20 (58.8%)	26 (38.2%)	53.8	0.059
Death	1 (2.9%)	14 (20.6%)	−85.7	0.018

*Initial decline in per cent predicted FVC ≥10% occurring during the first 3 months or 6 months of study treatment.
†Fisher's exact test.
‡Either no decline or increase in FVC.

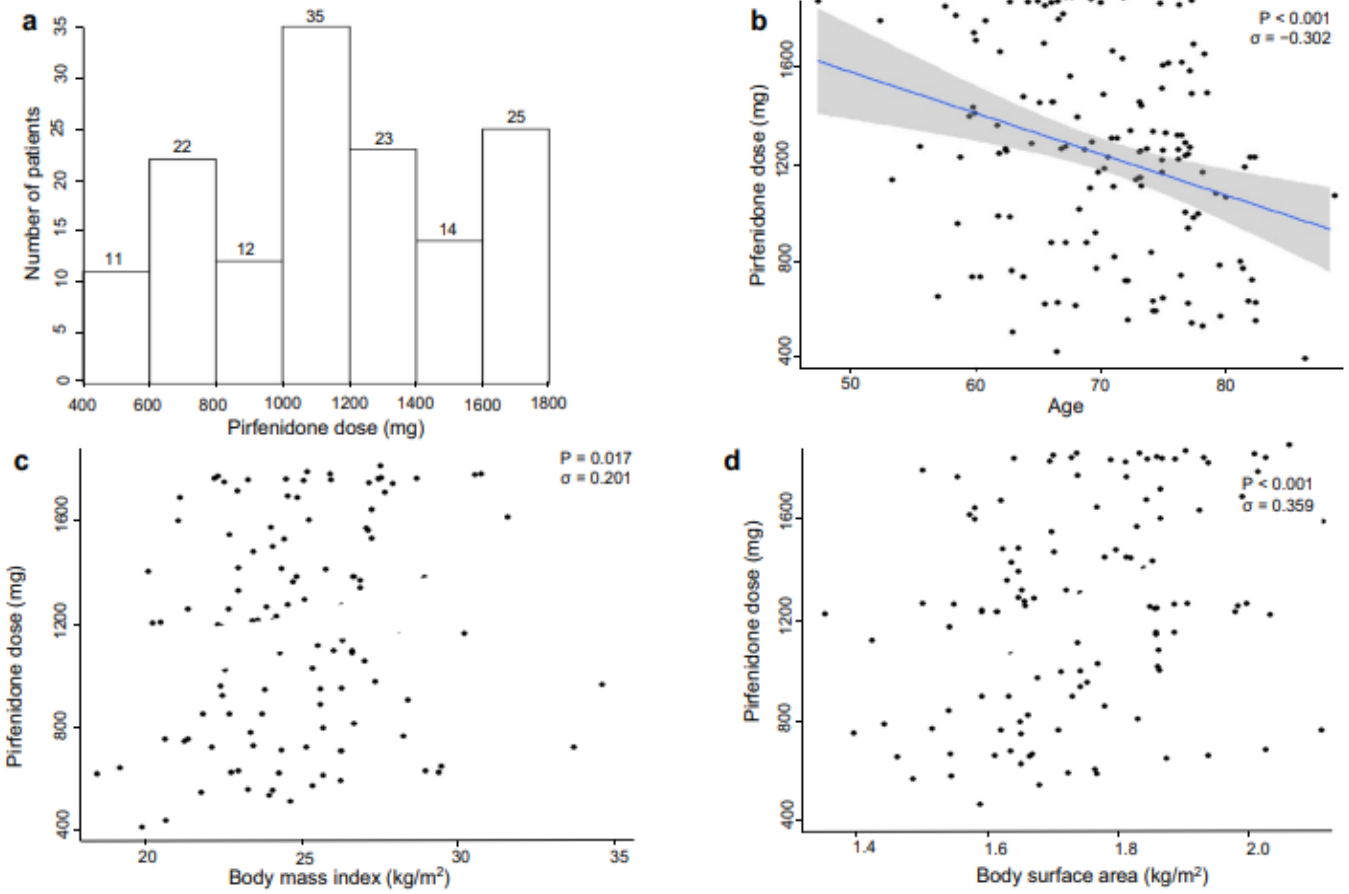
Table 3 Outcomes after 6 months of continued treatment following hospitalisation*

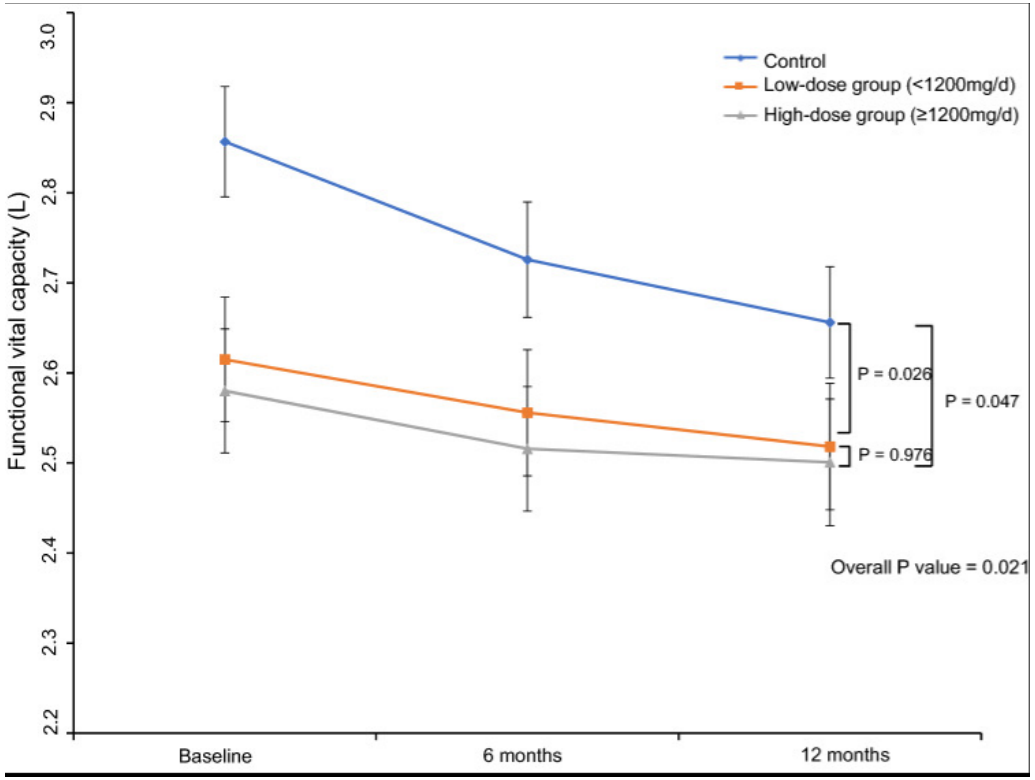
	Pirfenidone (N=44)	Placebo (N=49)	Relative difference (%)	p Value†
≥10% decline in FVC or death	4 (9.1%)	16 (32.7%)	−72.2	0.010
No further decline in FVC‡	15 (34.1%)	12 (24.5%)	39.2	0.364
Death	2 (4.5%)	14 (28.6%)	−84.3	0.002

*All-cause hospitalisation between baseline and month 6; treatment outcomes assessed during the 6-month interval beginning with the first study visit following the date of hospitalisation.
†Fisher's exact test.
‡Either no decline or increase in FVC.

Nathan SD, et al. Thorax 2016;71:429–435

Efficacy of low dose PFD ;real world experience



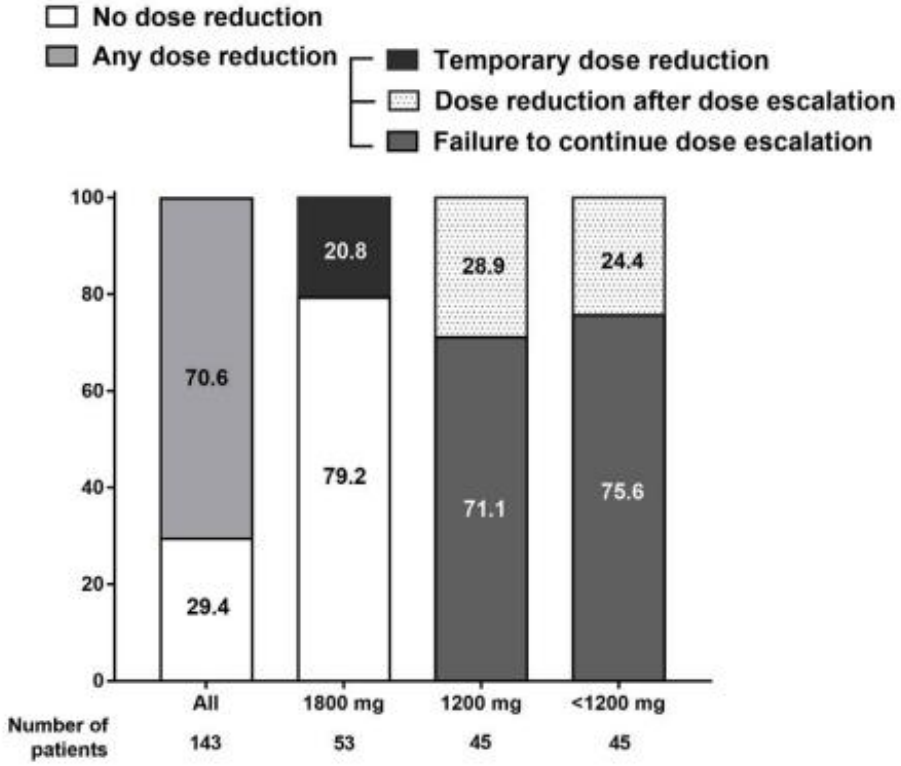


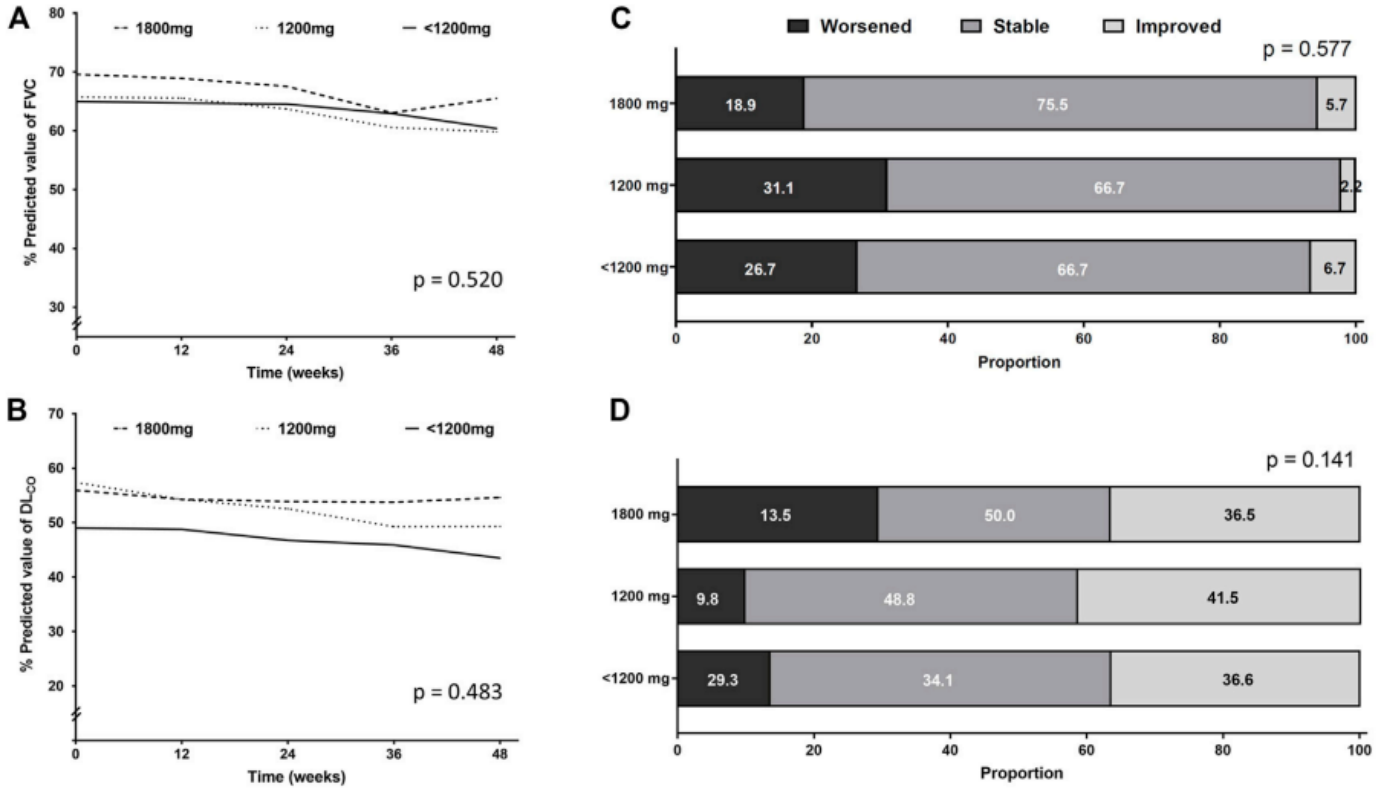
In total, 234 IPF, with 92 patients not treated with pirfenidone (control group) and 142 patients treated with pirfenidone

Sci Rep. 2020; 10: 21218.

Dose modification during pirfenidone treatment for IPF

- Multicenter prospective postmarketing study of PFD, KOREA
- Classified most frequently administered dose during 48wks , 1800, 1200, < 1200mg
- 143 IPF subjects





Frontiers in pharmacology .2022.1025947

Lung surgery in IPF patients

- Lung surgery significantly increased risk of acute exacerbation , > 20%
- Perioperative use of pirfenidone decreased

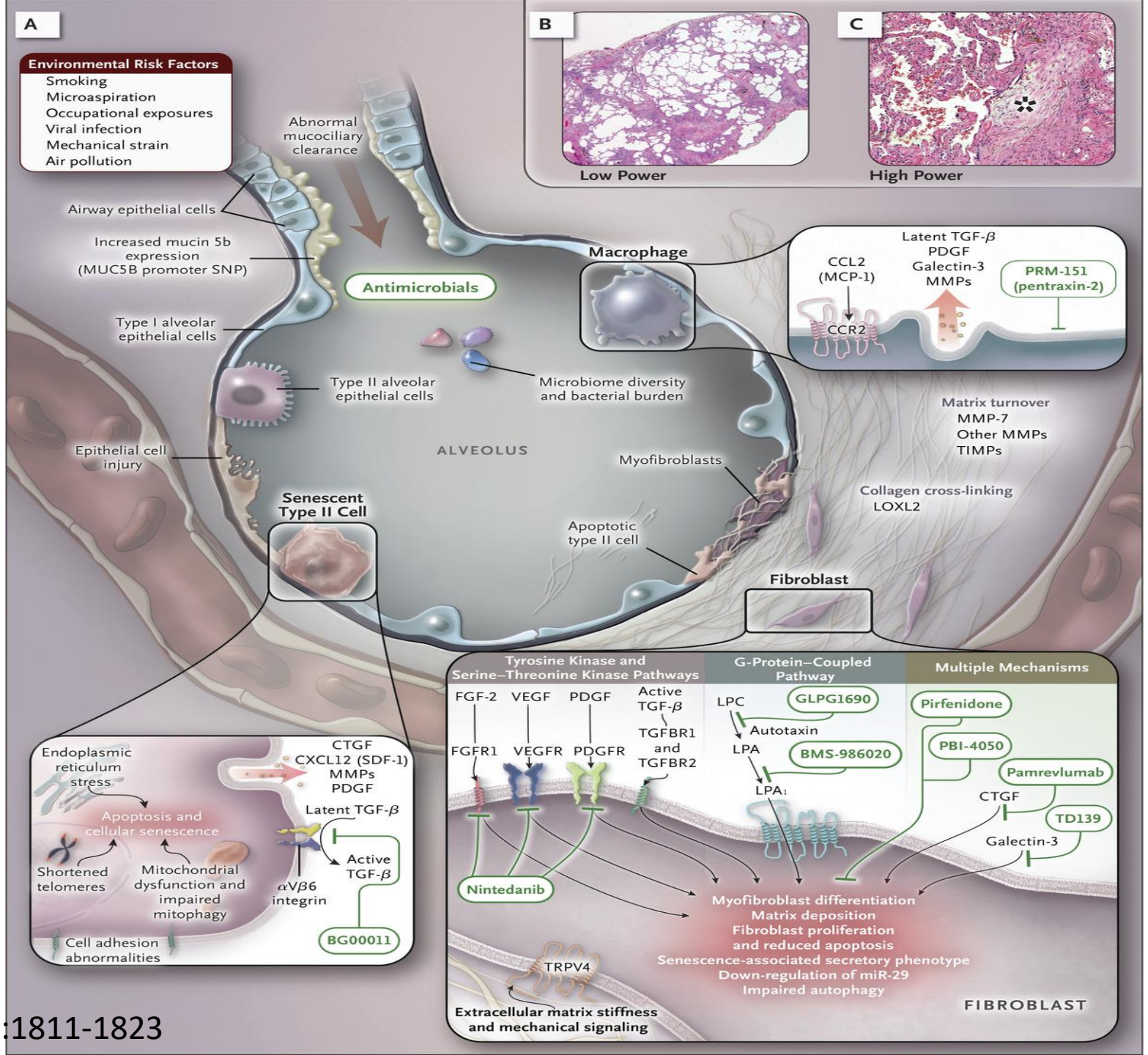
  IPF acute exacerbation in lung cancer patients undergoing pulmonary resection

  - 2wks 1200mg/day before operation
  - 38 out of 39 patients

Respir Res 2016; **17**:90

Challenges in the development of new treatment

- Incomplete knowledge of mechanism of disease
- Lack of optimal experimental models
- Diagnostic pitfalls
- Limitation of RCTs – Disease heterogeneity



N Engl J Med 2018; 378:1811-1823

Ongoing clinical trials about some investigational compounds for IPF.

Targets	Drugs	Clinical trial information
LPC-ATX-LPA	BMS-986278 (LPA1R antagonist)	Phase 2 (recruiting, NCT04308681)
PTX-2/SAP	PRM-151(Intravenous recombinant human pentraxin-2)	Phase 3 (recruiting, NCT04594707, NCT04552899)
CTGF/CNN2	FG-3019/Pamrevlumab (CTGF mAb)	Phase 3 (recruiting, NCT04419558, NCT03955146)
Galectin 3	TD139 (small-molecule antagonist of Galectin-3)	Phase 2 (recruiting, NCT03832946)
Oxidative stress	Niacin (nicotinic acid)	Phase 2 (recruiting, NCT0386592)
	Setanaxib/GKT137831(NOS1/4 inhibitor)	Phase 2 (recruiting, NCT03865927)
JNK	Jaktinib Dihydrochloride Monohydrate (JNK1/2 inhibitor)	Phase 2 (recruiting, NCT04312594)
	CC-90001 (JNK1/2 inhibitor)	Phase 2 (active, not recruiting, NCT03142191)
Src	Saracatinib (Src kinase inhibitor)	Phase 1/2 (recruiting, NCT04598919)
Hedgehog pathways	taladegib/ENV-101(Smo receptor inhibitor)	Phase 2 (not yet recruiting, NCT04968574)
Leukotrienes	MN-001/Tipelukast (leukotriene receptor antagonist)	Phase 2(Active, not recruiting, NCT02503657)
LOXL2	EGCG (irreversible inhibitor of both LOXL2 and TGF-β receptors 1 and 2 kinase)	Early Phase 1 (recruiting, NCT03928847)
IRE1	ORIN1001(IRE1 inhibitor)	Phase 1 (recruiting, NCT04643769)
PDE4b	BI 1015550(PDE4b inhibitor)	Phase 2 (active, not recruiting, NCT04419506)
NDMA	NP-120/Ifenprodil (N-methyl-d-aspartate (NDMA) receptor glutamate receptor antagonist)	Phase 2 (recruiting, NCT04318704)
B cell	Ianalumab/VAY736(B-cell activating factor receptor mAb)	Phase 2 (active, not recruiting, NCT03287414)
	Rituximab (CD20 chimeric mAb)	Phase 2 (active, not recruiting, NCT01969409); Phase 2 (recruiting, NCT03584802); Phase 2 (recruiting, NCT03286556); Phase2 (recruiting, NCT03500731)
Traditional medicine	Jin-shui Huan-xian granule	Not Applicable (recruiting, NCT04187690)
	Fuzheng Huayu tablet	Phase 2 (recruiting, NCT04279197)

Summary

- IPF is progressive irreversible fibrotic lung disease
- Aberrant reparative response to repetitive alveolar epithelial injury in a genetically susceptible ageing individual
- The incidence and prevalence of IPF are increasing dramatically with age
- Early treatment with anti-fibrotics, such as pirfenidone and nintedanib, is beneficial in slowing lung function decline, reducing exacerbations, and improving progression-free survival.
- Due to an incomplete response to the current drug, novel drug candidates targeting fibrosis were needed.

Thanks for your attentions