KU KONKUK UNIVERSITY

Early Treatment IPF; Anti-Fibrotic Therapy "Con"

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결핵 및 호흡기 학회 춘계학술대회
건국대학교 병원 호흡기내과 김희정

건국대학교병원 KONKUK UNIVERSITY MEDICAL CENTER

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- New Anti-fibrotic agents
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Introduction

- Idiopathic pulmonary fibrosis
  - **Chronic, progressive lung disease** of unknown cause characterized by the histopathological pattern of UIP

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis

Maurits Demedts, M.D., Juergen Behr, M.D., Roland Buhl, M.D., Ulrich Costabel, M.D., P.N., Richard Dekhuijzen, M.D., Henk M. Jansen, M.D., William MacNee, M.D., Michiel Thomeer, M.D., Benoit Wallaert, M.D., François Laurent, M.D., Andrew G. Nicholson, M.D., Eric K. Verbeken, M.D., Johny Verschakelen, M.D., Christopher D.R. Flower, M.D., Frédérique Capron, M.D., Stefano Petruzzelli, M.D., Paul De Vuyst, M.D., Jules M.M. van den Bosch, M.D., Eulogio Rodriguez-Becerra, M.D., Giuseppina Corvasce, Ph.D., Ida Lankhorst, M.D., Marco Sardina, M.D., and Mauro Montanari, Ph.D., for the IFIGENIA Study Group*

Preserved VC and DLco

Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

Risks of death and hospitalization ↑

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

No significant benefit (FVC)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

Reduced disease progression

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

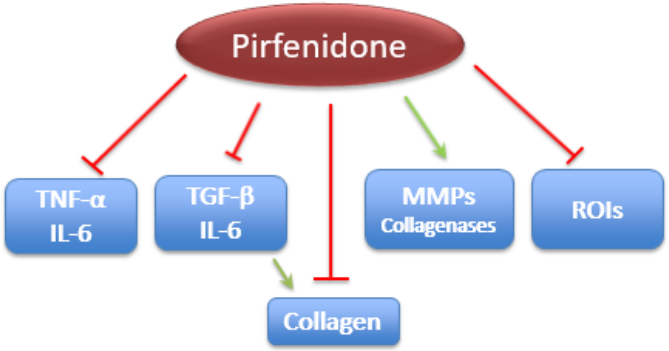
Reduced the decline in FVC

Comparison of recommendations

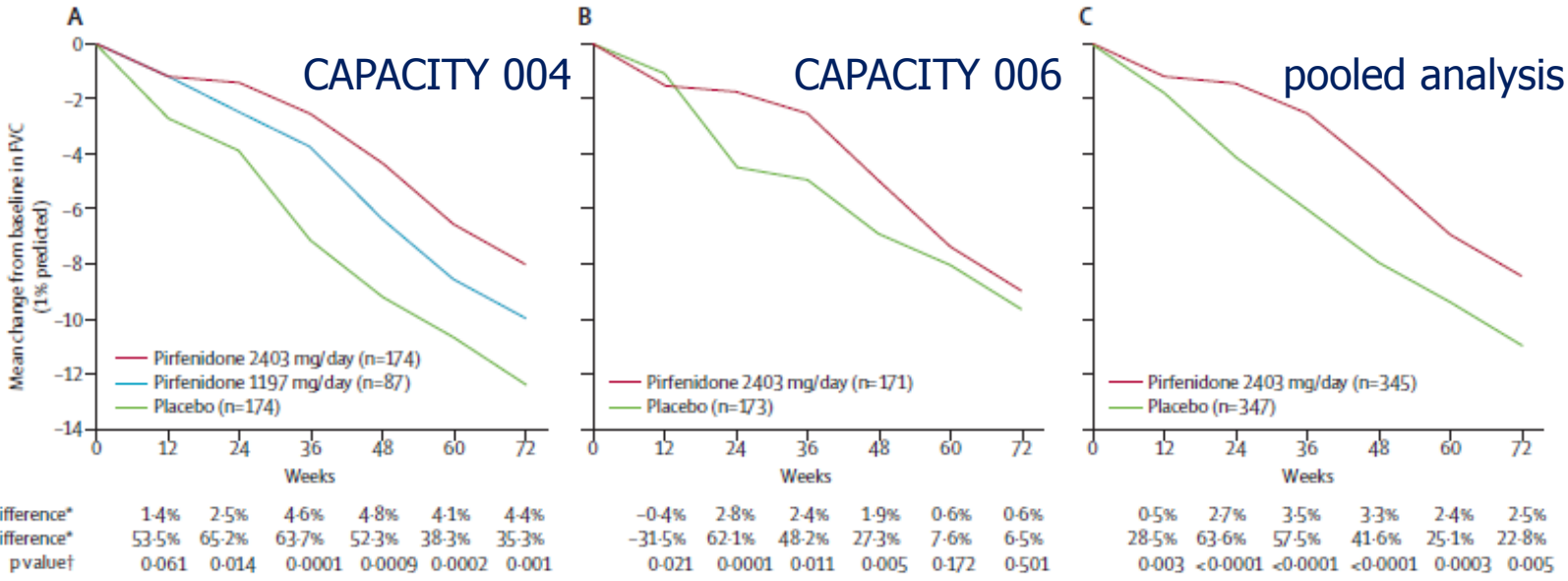
Agent	2015 Guideline	2011 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Strong recommendation against use*	Conditional recommendation against use‡
Combination prednisone + azathioprine + *N*-acetylcysteine	Strong recommendation against use†	Conditional recommendation against use†
Selective endothelin receptor antagonist (ambrisentan)	Strong recommendation against use†	Not addressed
Imatinib, a tyrosine kinase inhibitor with one target	Strong recommendation against use*	Not addressed
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Conditional recommendation for use*	Not addressed
Pirfenidone	Conditional recommendation for use*	Conditional recommendation against use†
Dual endothelin receptor antagonists (macitentan, bosentan)	Conditional recommendation against use†	Strong recommendation against use*
Phosphodiesterase-5 inhibitor (Sildenafil)	Conditional recommendation against use*	Not addressed
Unchanged recommendations		
Antiacid therapy	Conditional recommendation for use‡	Conditional recommendation for use‡
N-acetylcysteine monotherapy	Conditional recommendation against use†	Conditional recommendation against use†
Antipulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Reassessment of the previous recommendation was deferred	Conditional recommendation against use‡
Lung transplantation: single vs. bilateral lung transplantation	Formulation of a recommendation for single vs. bilateral lung transplantation was deferred	Not addressed

Raghu *et al*. *Am J Respir Crit Care Med* 2015; 192: e3-19.

Pirfenidone - CAPACITY

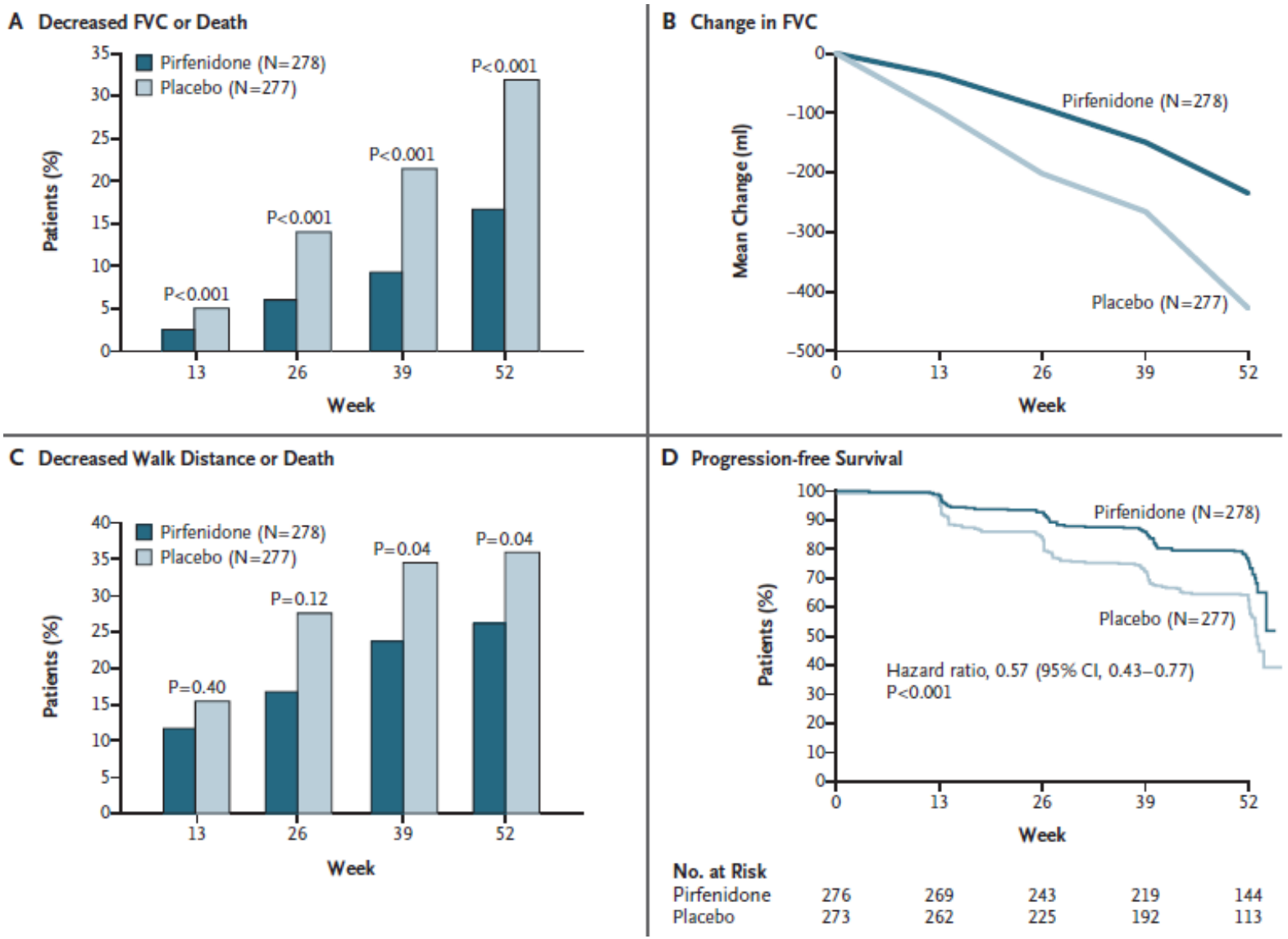


- Mechanisms of action
  - Anti-inflammatory, antifibrotic, and antioxidant properties, with antagonism of activities mediated by TGF β1 & TNF α
- Mean change from baseline in % predicted FVC



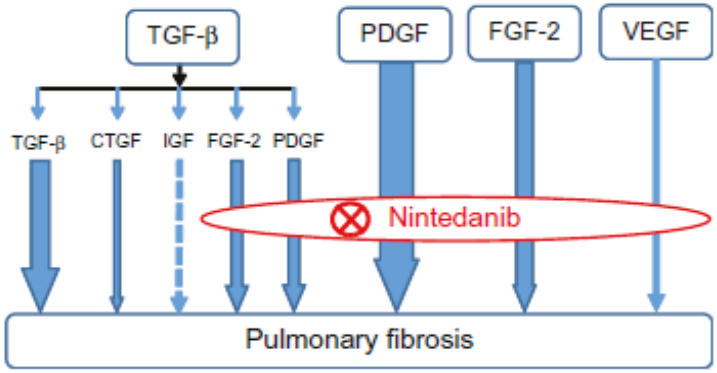
Noble *et al*. *Lancet* 2011; 377: 1760–69.

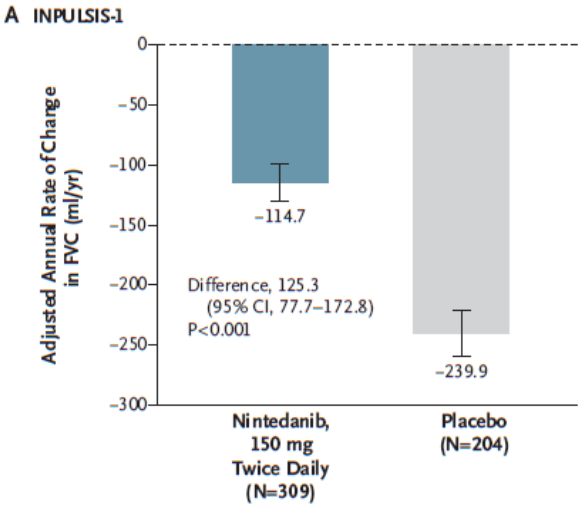
Pirfenidone - ASCEND

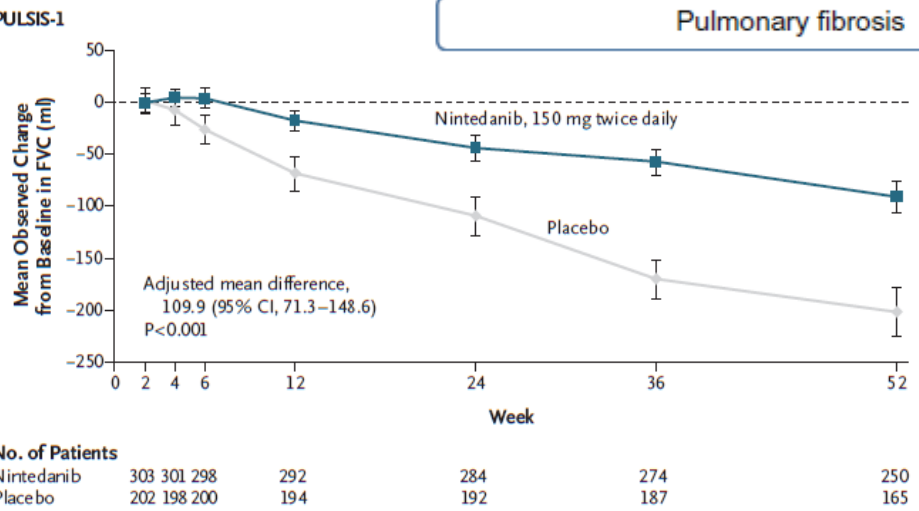


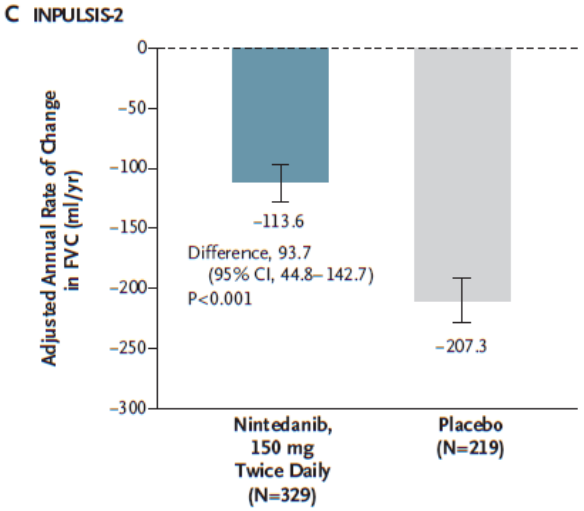
King *et al*. *N Engl J Med* 2014;370:2083-92.

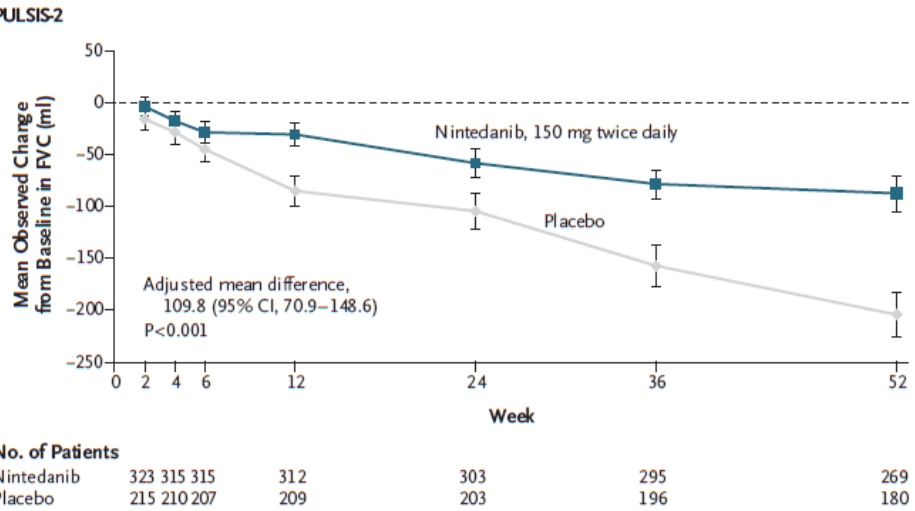
Nintedanib-INPULSIS











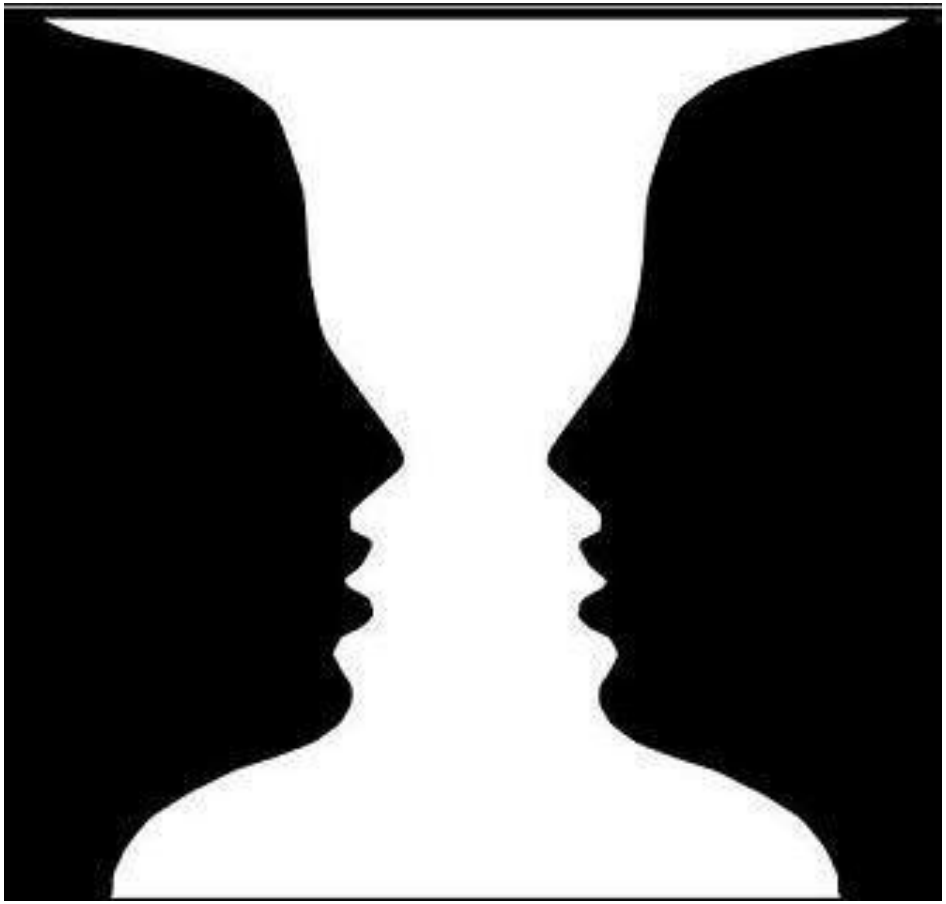
Richeldi *et al*. *N Engl J Med* 2014;370:2071-82.

Annual rate of decline in FVC

Trial	Active drug	Placebo	Difference in mL (relative difference %)
Annual rate of decline in FVC (as assessed by linear slope analysis)			
ASCEND	-164	-280	116 (41.5%)
INPULSIS-1	-114.7	-239.9	125.3 (52%)
INPULSIS-2	-113.6	-207.3	93.7 (45%)
Absolute mean change from baselines over time			
ASCEND	-235	-428	193 (45.1%)
INPULSIS-1	-95.1	-205.0	109.9 (53.6%)
INPULSIS-2	-95.3	-205.0	109.8 (53.6%)

Spagnolo *et al*. *Drug Discov Today.* 2015;20:514-24.

Limitations of clinical trials



Limitations of clinical trials

	Study 004				Study 006				Pooled data			
	Pirfenidone 2403 mg/day (n=174)	Placebo (n=174)	Absolute difference (95% CI)	p value*	Pirfenidone 2403 mg/day (n=171)	Placebo (n=173)	Absolute difference (95% CI)	p value*	Pirfenidone 2403 mg/day (n=345)	Placebo (n=347)	Absolute difference (95% CI)	p value*
Categorical change in FVC ≥10%	35 (20%)	60 (35%)	14·4 (7·4 to 21·3)	0·001†	39 (23%)	46 (27%)	3·8 (−2·7 to 10·2)	0·440†	74 (21%)	106 (31%)	9·1 (4·3 to 13·9)	0·003†
Progression-free survival time‡	..	..	0·64 (0·44 to 0·95)	0·023§	..	..	0·84 (0·58 to 1·22)	0·355§	..	..	0·74 (0·57 to 0·96)	0·025§
Mean change in 6MWT distance (m)	−60·4	−76·8	16·4 (−10·9 to 43·7)	0·171	−45·1	−76·9	31·8 (3·2 to 60·4)	0·0009	−52·8	−76·8	24·0 (4·3 to 43·7)	0·0009
Mean change in DLco (% predicted)	−7·9	−9·9	2·0 (−0·4 to 4·4)	0·145	−9·8	−9·2	−0·5 (−3·2 to 2·2)	0·996	−8·8	−9·6	0·7 (−1·1 to 2·5)	0·301
Mean change in dyspnoea score¶	12·1	15·2	−3·1 (−8·5 to 2·3)	0·509	11·9	13·9	−2·0 (−7·6 to 3·6)	0·604	12·0	14·5	−2·5 (−6·4 to 1·4)	0·405
Mean change in worst SpO_2 during 6MWT (%)	−1·5	−2·3	0·8 (−0·2 to 1·8)	0·087	−1·9	−1·3	−0·5 (−1·7 to 0·7)	0·893	−1·7	−1·8	0·1 (−0·7 to 0·9)	0·261
Time to worsening in idiopathic pulmonary fibrosis	..	..	0·84 (0·50 to 1·42)‡	0·515§	..	..	0·73 (0·43 to 1·24)‡	0·248§	..	..	0·78 (0·54 to 1·14)‡	0·201§
Categorical change in HRCT-diagnosed fibrosis‖	NA	NA	NA	NA	NA	NA	NA	0·894	NA	NA	NA	NA

FVC=forced vital capacity. 6MWT=6-minute walk test. DLco=haemoglobin-corrected carbon monoxide diffusing capacity. SpO_2=peripheral oxygen saturation. HRCT=high-resolution CT. NA=not applicable. *Rank ANCOVA (pirfenidone 2403 mg/day *vs* placebo), unless otherwise indicated. †Cochran-Mantel-Haenszel row mean score test (pirfenidone 2403 mg/day *vs* placebo) based on five categories (severe decline, ≥20%; moderate decline, <20% but ≥10%; mild decline; <10% but ≥0; mild improvement, >0 but <10%; and moderate improvement, ≥10%). ‡Hazard ratio (95% CI) based on the Cox proportional hazard model with geographic region (USA *vs* non-USA) as a stratum. §Log-rank test (pirfenidone 2403 mg/day *vs* placebo). ¶Based on the University of California San Diego Shortness of Breath Questionnaire: total score ranges from 0 to 120, with larger scores indicating greater shortness of breath. ‖Cochran-Mantel-Haenszel row mean score test (pirfenidone 2403 mg/day *vs* placebo) based on five categories (much better, better, same, worse, or much worse); assessed in study 006 only.

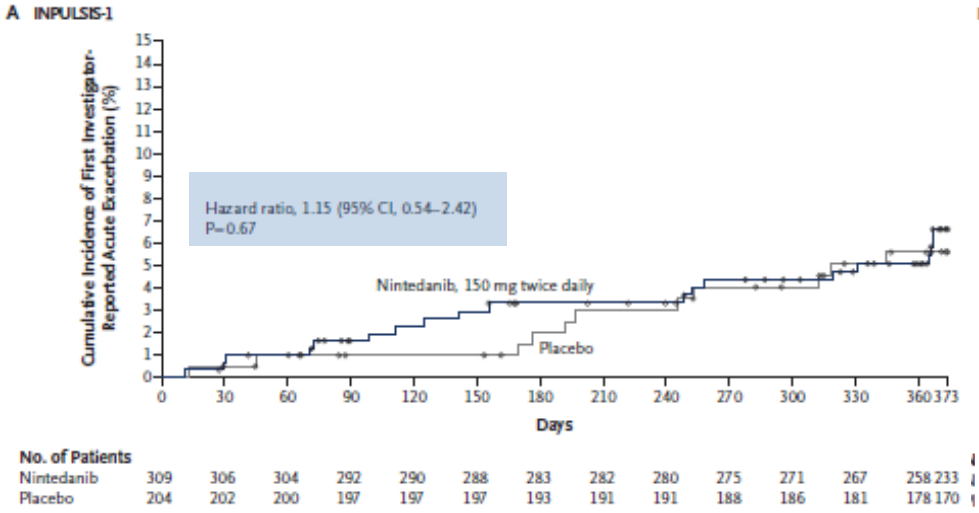
***Table 2:* Secondary efficacy endpoints at week 72**

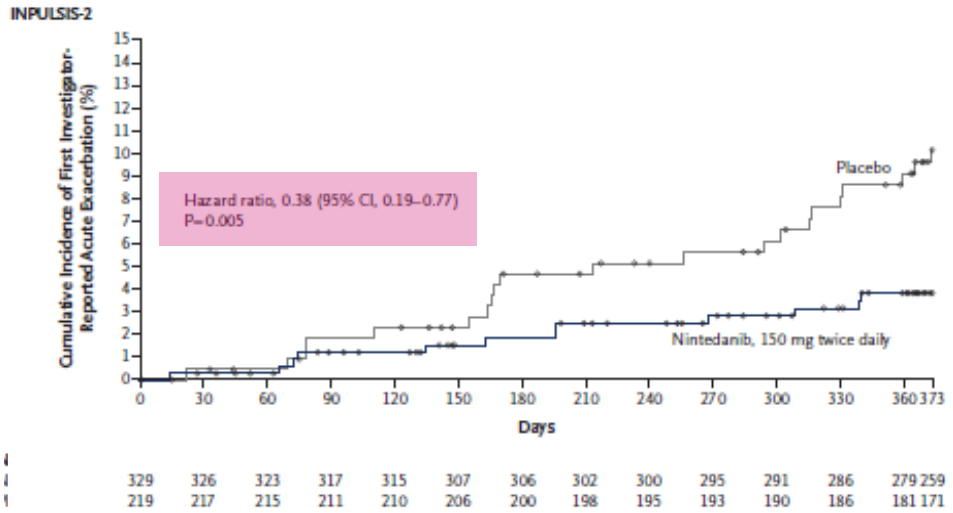
Noble *et al*. *Lancet* 2011; 377: 1760–69.

Limitations of clinical trials

Table 2. Secondary Lung-Function End Points at Week 52.

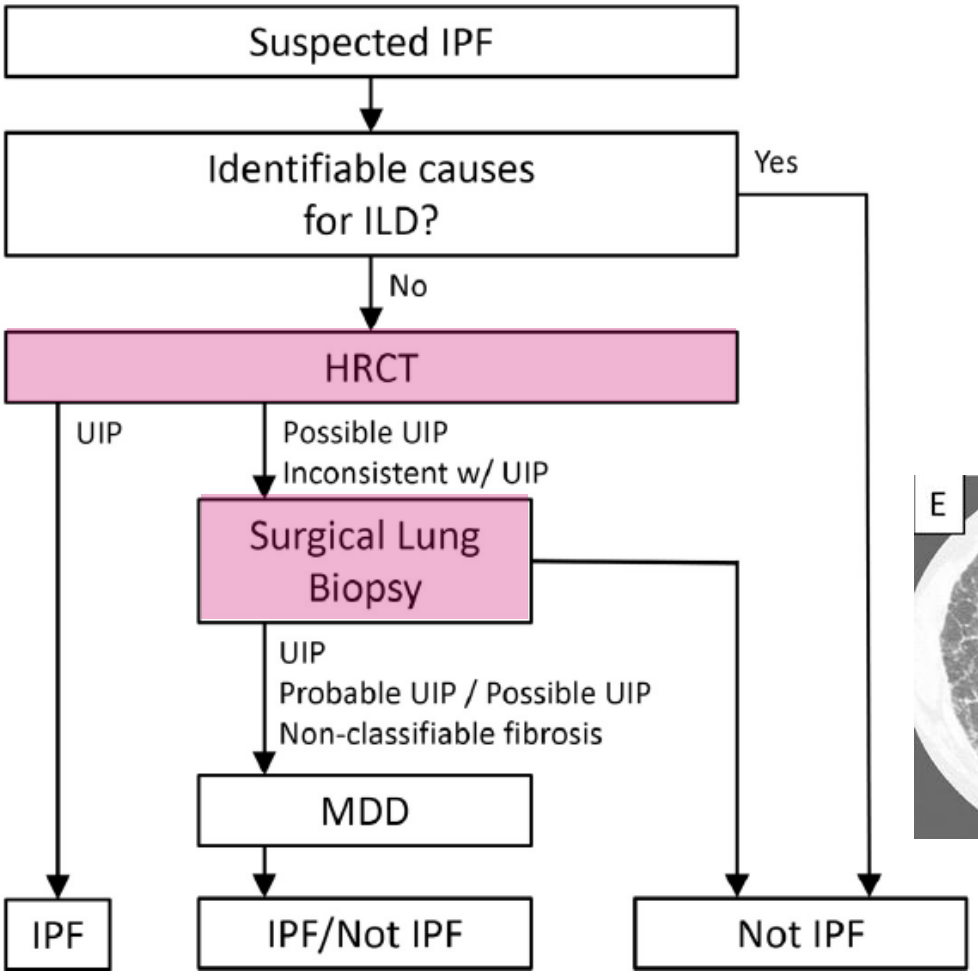
End Point	INPULSIS-1				INPULSIS-2			
	Nintedanib (N=307)	Placebo (N=204)	Difference, Nintedanib vs. Placebo (95% CI)	P Value	Nintedanib (N=327)	Placebo (N=217)	Difference, Nintedanib vs. Placebo (95% CI)	P Value
Adjusted absolute mean change from baseline in FVC — ml	−95.1	−205.0	109.9 (71.3 to 148.6)	<0.001	−95.3	−205.0	109.8 (70.9 to 148.6)	<0.001
Adjusted absolute mean change from baseline in FVC — % of predicted value	−2.8	−6.0	3.2 (2.1 to 4.3)	<0.001	−3.1	−6.2	3.1 (1.9 to 4.3)	<0.001
FVC response at wk 52 — no. (%)*								
FVC decline ≤5 percentage points	163 (52.8)	78 (38.2)	1.85 (1.28 to 2.66)	0.001	175 (53.2)	86 (39.3)	1.79 (1.26 to 2.55)	0.001
FVC decline ≤10 percentage points	218 (70.6)	116 (56.9)	1.91 (1.32 to 2.79)	<0.001	229 (69.6)	140 (63.9)	1.29 (0.89 to 1.86)	0.18

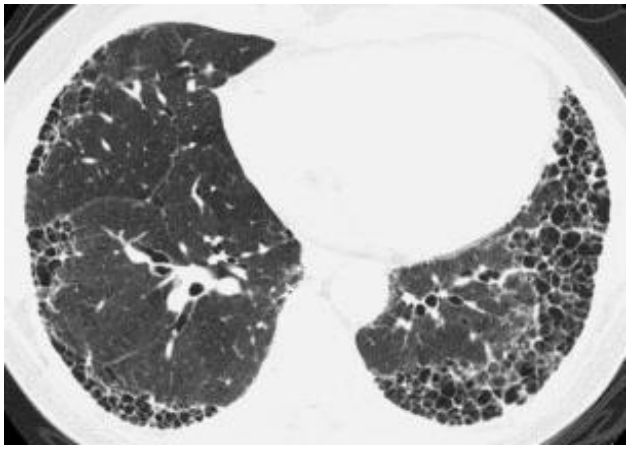




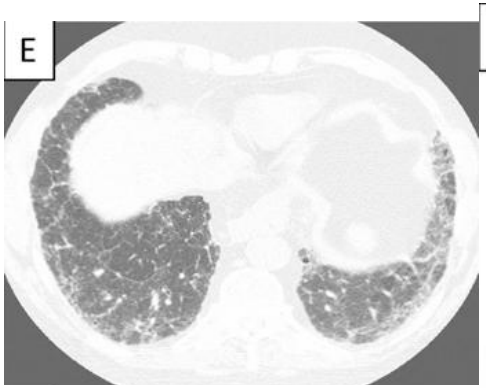
Richeldi *et al*. *N Engl J Med* 2014;370:2071-82.

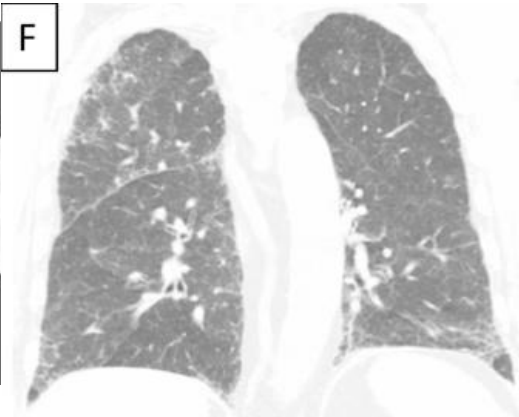
Diagnostic algorithm





UIP pattern





Possible UIP pattern

Raghu *et al*. *Am J Respir Crit Care Med* 2011;183:788-824.

Key problems in diagnostic approach

- HRCT misdiagnosis
  - Atypical HRCT findings : GGO/ pleural effusion, nodules
  - Interobserver variation
- Surgical lung biopsy
  - Clinical contraindications (comorbidities, severity, old age,)
  - Criteria which can select patients who can undergo a SLB with an acceptably low risk
- Bronchoalveolar lavage
  - Increase the index of suspicion for alternative disorders
- Lack of integration of clinical data in the designation of the diagnostic likelihood of IPF

Cohort study in Denmark

Table 2 IPF diagnosis by 2001 criteria.

Major criteria	Total $n = 121$	Biopsy $n = 52$	No biopsy $n = 69$
Exposures excluded	121 (100%)	52 (100%)	69 (100%)
Abnormal PFT	121 (100%)	52 (100%)	69 (100%)
HRCT reticulation	121 (100%)	52 (100%)	69 (100%)
BAL or TBB with no features to support other diagnosis	BAL 93 (77%) BAL + TBB 13 (11%)	BAL 45 (87%) BAL + TBB 7 (13%)	47 (68%) 6 (9%)
Minor criteria	**Total $n = 121$**	**Biopsy $n = 52$**	**No biopsy $n = 69$**
Age >50	118 (97%)	49/52 (94%) Age <50: biopsy 3/3	69/69 (100%)
Gradual onset of symptoms	121 (100%)	52/52 (100%)	69/69 (100%)
Symptoms >3 months	121 (100%)	52/52 (100%)	69/69 (100%)
Crackles	97 (80%)	41/52 (79%)	56/69 (81%)

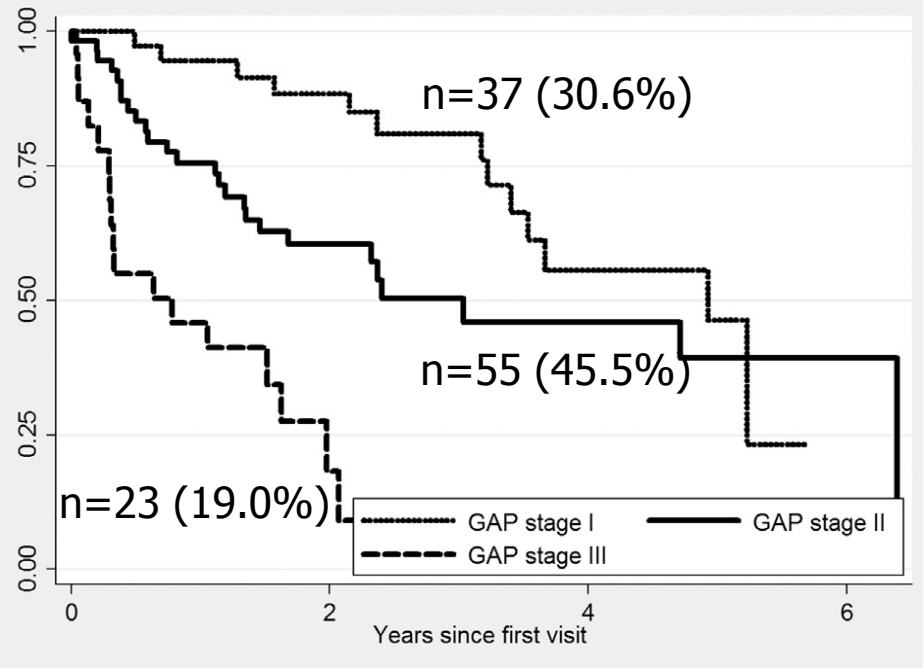
HRCT	Histopathology				
	Definite UIP	Probable UIP	Possible UIP	Non-classifiable fibrosis	No biopsy
UIP 60	IPF 8	IPF 5	IPF 1	IPF 0	IPF 46
Possible UIP 61	IPF 30	IPF 7	Probable IPF 1	Probable IPF 0	23
Not UIP	Possible IPF 0	Not IPF 0	Not IPF 0	Not IPF 0	Not IPF 0

Hyldgaard *et al*. *Respir Med.* 2014;108:793-9.

Severity - GAP index

	Predictor	Points
G : Gender	Female	0
	Male	1
	Male	1
A : Age (years)	≤60	0
	61-65	1
	> 65	2
P : Physiology		
FVC, % predicted	> 75	0
	50-75	1
	< 50	2
DLCO, % predicted	> 55	0
	36-55	1
	≤ 35	2
	Cannot perform	3
	Total possible points	8

Stage Points	I 0-3	II 4-5	III 6-8
Mortality			
1-year	5.6	16.2	39.2
2-year	10.9	29.9	62.1
3-year	16.3	42.1	76.8



Tomassetti *et al. Curr Opin Pulm Med* 2015, 21:463–9.
Hyldgaard *et al. Respir Med.* 2014;108:793-9.

Uncertainties regarding FVC

- Forced vital capacity (FVC)
  - Measure of lung function
  - Strong
    - Logical to monitor for a change in a lung function parameter (progressive decline in a restrictive pattern)
  - Weak
    - Threshold for a clinically meaningful decline in FVC is uncertain
    - Not been validated as a surrogate for likelihood of death or other clinically meaningful efficacy variables
- Effect on mortality would be the most unequivocal and clinically important measure of efficacy

Comorbidities in Danish cohort

Table 4 Comorbidity present at first hospital visit for IPF and its association to survival (adjusted for age, gender and FVC).

	n	HR (95% CI)	*p*
Cardiovascular disease	24	0.66 (0.32; 1.37)	0.27
Diabetes	11	2.5 (1.04; 5.9)	0.041
Pulmonary hypertension	12	2.2 (0.94; 5.2)	0.068
Gastro-oesophageal reflux	10	1.6 (0.60; 4.4)	0.34
GER medication	61	1.0 (0.58; 1.8)	0.95
Anticoagulant treatment (Non-PH indication)	13	3.3 (1.5; 7.2)	0.002

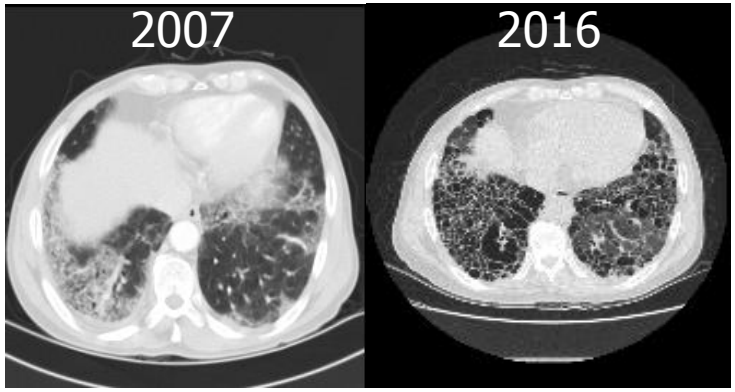
Table 5 Comorbidity diagnosed during IPF follow-up and its association to survival (adjusted for age, gender and FVC).

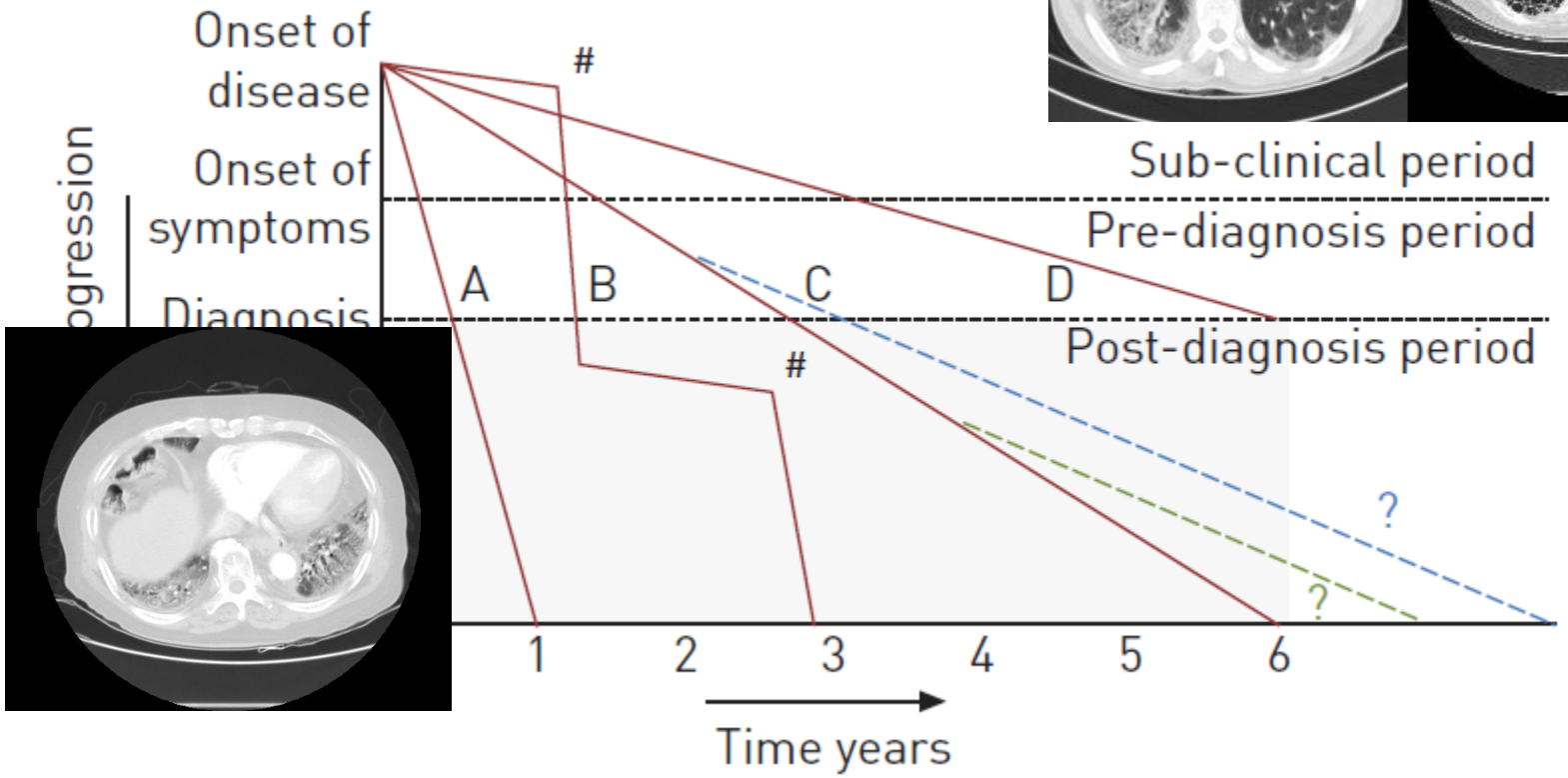
	n	Mean follow-up time to comorbid diagnosis Days (range)	HR (95% CI)	*p*
Cardiovascular disease	9	516 (118; 986)	4.7 (2.0; 11.1)	<0.001
Diabetes	10	597 (78; 1464)	1.1 (0.33; 3,8)	0.85
Pulmonary hypertension	14	620 (192; 1213)	2.2 (0.82; 6.0)	0.12

Hyldgaard *et al. Respir Med.* 2014;108:647-53.

Applications in Real world

When to start



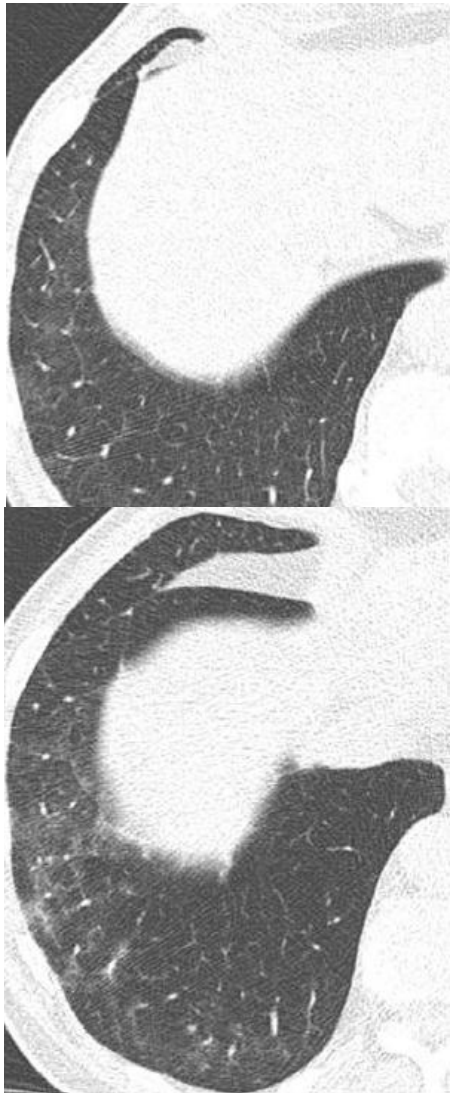


Cottin *et al*. *Eur Respir Rev* 2014; 23: 106-10.

Interstitial lung abnormalities in LDCT

Changes in CT Findings at 2-year Follow-up in 79 Participants with ILA

Parameter	No.	Findings at 2-year Follow-up: Improved	Same	Progression
Overall extent of abnormality*		26 (32.9)	37 (46.8)	16 (20.3)
Nonfibrotic ILA	47	23 (48.9)	19 (40.2)	5 (10.9)
Fibrotic ILA	19	0	12 (63.2)	7 (36.8)
Mixed nonfibrotic and fibrotic ILA	13	3 (23.1)	6 (46.2)	4 (30.7)
Individual CT findings				
Nonfibrotic ILA				
GGO	32	13 (40.6)	9 (28.1)	10 (31.3)
Mosaic attenuation	40	0	37 (92.5)	3 (7.5)
Consolidation	9	2 (22.3)	7 (66.7)	0
Mixed nonfibrotic and fibrotic ILA				
GGO	5	3 (60)	0	2 (40)
Mosaic attenuation	4	0	4 (100)	0
Consolidation	1	0	1 (100)	0
GGO with reticular abnormality	7	0	4 (57.1)	3 (42.9)
Pure reticular abnormality	2	0	2 (100)	0
Honeycombing	5	0	5 (100)	0
Fibrotic ILA				
GGO with reticular abnormality	12	0	5 (41.7)	7 (58.3)
Pure reticular abnormality	9	0	5 (55.6)	4 (44.4)
Honeycombing	9	0	5 (55.6)	4 (44.4)



Jin *et al*. *Radiology.* 2013;268:563-71.

Which drug to use

Table 1 Summary of inclusion and exclusion criteria for INPULSIS and ASCEND trials

Inclusion/exclusion criteria	ASCEND	INPULSIS
Inclusion		
Duration of clinical symptoms	Clinical symptoms consistent with IPF >12 months	No information
Duration of IPF diagnosis	6–48 months	<5 years
Age	40–80 yrs	>40 years
Clinical diagnosis	Diagnosis of IPF following centralised histopathology and radiology review	Diagnosis of IPF following centralised histopathology and radiology review
Radiological features	Fulfil criteria for IPF according to ATS/ERS guidelines.	A. Definite honeycomb lung destruction with basal and
FVC	50–90% predicted	>50%
FEV_1/FVC ratio	Postbronchodilator FEV_1/FVC <0.8	Postbronchodilator FEV_1/FVC <0.7
Bronchodilator response	Change in pre and postbronchodilator response <10%	No information
DL_{CO}	DL_{CO}—30–90% predicted	DL_{CO}—30–79%
Natural history	No improvement in preceding year	No information
6MWT distance	>150 m	No information
Exclusion		
Natural history	Significant clinical worsening between screening and day 1	No information
Smoking	Cigarette smoking within 3 months of study	No information
Exposures	Significant environmental exposures	No information
Infection	Active infection	No information
Comorbidities	Significant comorbidities	Significant comorbidities
Transplant	Expected transplant within 1 year	Expected transplant within 1 year
Excluded medications	Mycophenolate mofetil, tacrolimus, montelukast, sildenafil, tetrathiomolybdate, TNF-α inhibitors, N-acetylcysteine (NAC), imatinib mesylate, interferon gamma-1b (IFN γ 1b) and tyrosine kinase Inhibitors. angiotensin converting enzyme (ACE) inhibitors, colchicine, corticosteroids, heparin, warfarin, and HMG-CoA reductase inhibitors.	NAC or prednisone >15 mg/day or equivalent within 2 weeks of screening, or pirfenidone, azathioprine, cyclophosphamide, cyclosporine A or any investigational drug within 8 weeks of screening.

King et al. *N Engl J Med* 2014;370:2083-92.
Richeldi *et al*. *N Engl J Med* 2014;370:2071-82.

Agents in current clinical trials

Agent	Target	Purported mechanism of action	ClinicalTrials.gov study ID
Tralokinumab	IL-13	Decreases expression of TGF-β and macrophage CCL2	NCT01629667
Lebrikizumab	IL-13	(As above)	NCT01872689
FG-3019	CTGF	Decreases CTGF-mediated profibrotic actions on fibroblasts	NCT01890265
Simtuzumab	LOXL2	Decreases ECM cross-linking	NCT01769196
STX-100	Integrin αvβ6	Decreases activation of latent TGF-β	NCT01371305
BMS-986020	LPA1 receptor	Decreases vascular leak and fibroblast recruitment	NCT01766817
Rituximab	CD20	Decreases contribution of antibody-mediated autoimmunity	NCT01969409
Carbon monoxide	Inflammation	Anti-inflammatory, may also suppress fibroblast proliferation	NCT01214187
Azithromycin	Bacteria, inflammation	Antimicrobial, immunomodulatory	NCT02173145
Cotrimoxazole	*Pneumocystis jiroveci*, bacteria	Antimicrobial	NCT01777737

CCL2 chemokine (C–C motif) ligand 2, *CTGF* connective tissue growth factor, *ECM* extracellular matrix, *IL-13* interleukin-13, *LOXL2* lysyl oxidase-like 2, *LPA* lysophosphatidic acid, *TGF-β* transforming growth factor-β

Rangarajan *et al*. *Drugs* 2016;76: 291-300.

When to discontinue

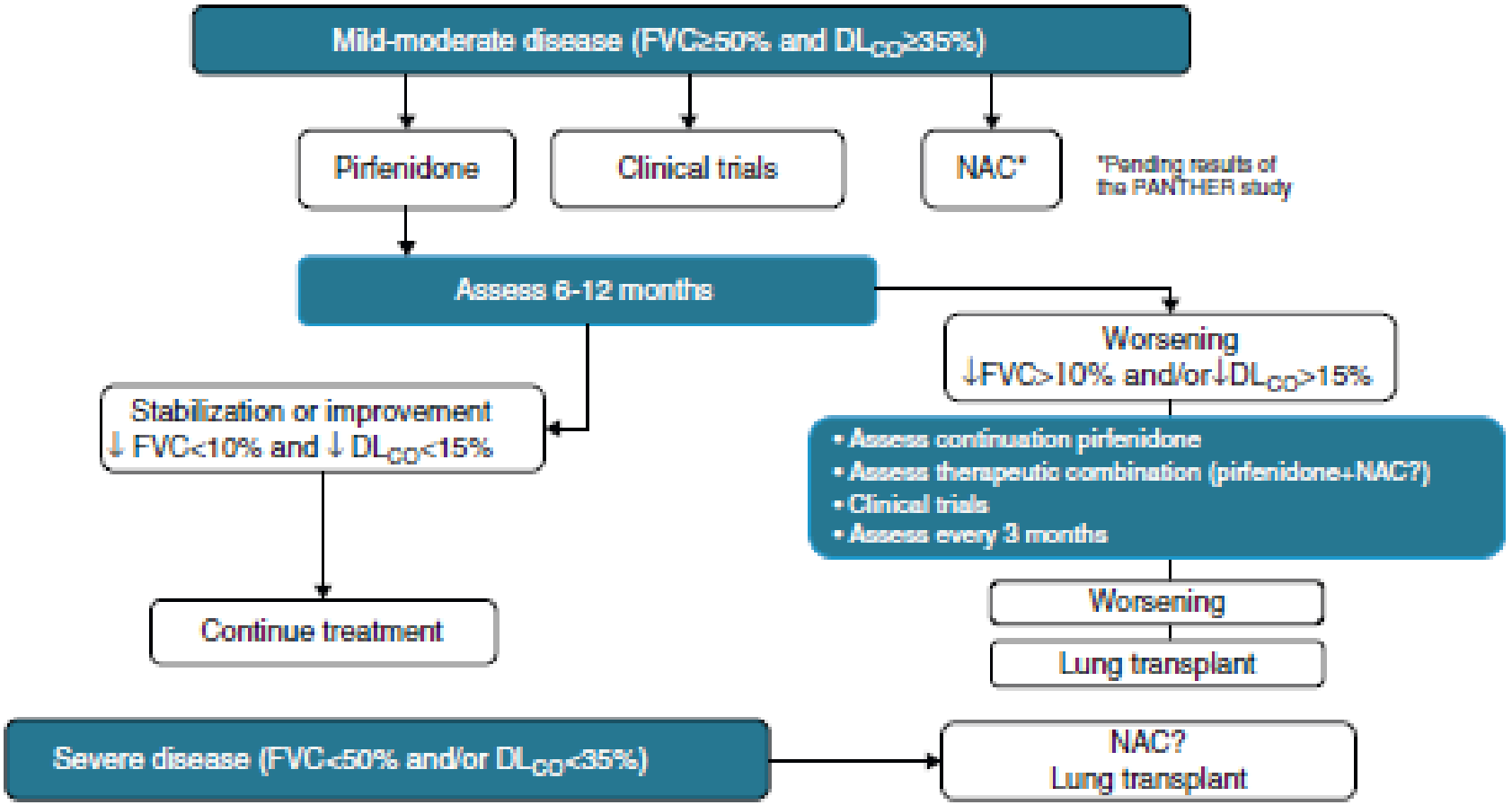


Fig. 6. Pharmacological treatment of idiopathic pulmonary fibrosis.

Xaubet *et al. Arch Bronconeumol.* 2013;49(8):343–53.

Long term treatment after progression

Table 1 Categorical shift analysis of absolute change in per cent predicted FVC during two consecutive 6-month intervals in the pooled placebo population

Patients, n (%)*		Month 6 to month 12					
		FVC stable or improved	FVC decline >0 to <10%	FVC decline ≥10%	Death	Missing†	Total, n
Baseline to month 6	FVC stable or improved	32 (19.8)	102 (63.0)	19 (11.7)	2 (1.2)	7 (4.3)	162
	FVC decline >0 to <10%	117 (31.7)	213 (57.7)	17 (4.6)	6 (1.6)	16 (4.3)	369
	FVC decline ≥10%	16 (27.1)	17 (28.8)	7 (11.9)	13 (22.0)	6 (10.2)	59
	Death	0	0	0	19 (100)	0	19
	Missing†	0	0	0	1 (6.7)	14 (93.3)	15
Total, n		165	332	43	41	43	624

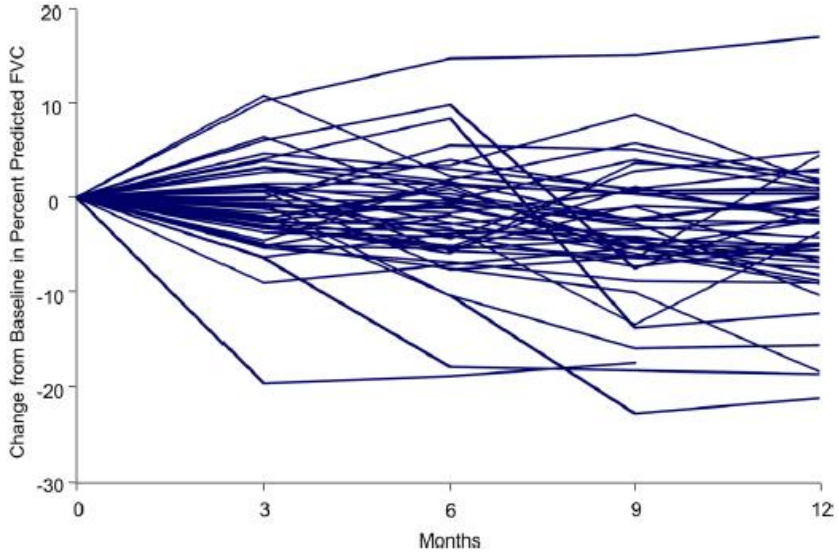


Table 2 Outcomes after 6 months of continued treatment following an initial decline in per cent predicted FVC ≥10%*

	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

Nathan *et al*. *Thorax*. 2016.

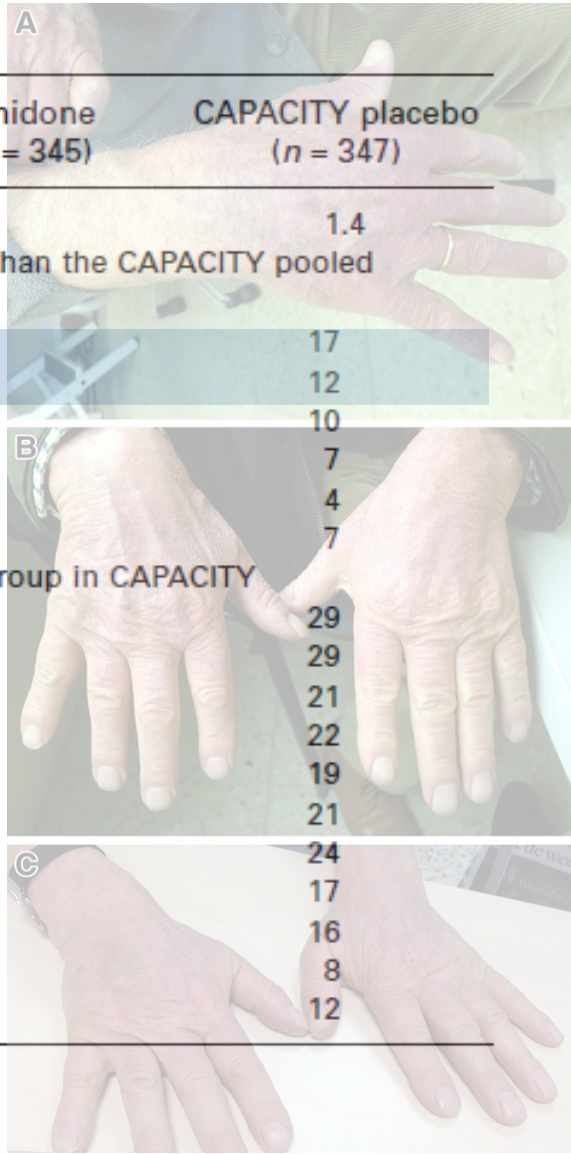
Adverse events - pirfenidone

Patients (%)	Integrated population (n = 789)	CAPACITY pirfenidone 2403 mg/day (n = 345)	CAPACITY placebo (n = 347)
Median duration of exposure, years	2.6	1.4	1.4
TEAEs with a greater frequency in the CAPACITY pooled pirfenidone 2403 mg/day group than the CAPACITY pooled placebo group‡			
Nausea	40	36	17
Rash	26	32	12
Dizziness	23	18	10
Dyspepsia	21	19	7
Vomiting	18	14	4
Insomnia	17	10	7

group in CAPACITY

Table 2 Skin-related adverse events in the CAPACITY studies

	Rash		Photosensitivity reaction	
	Pirfenidone 2,403 mg/day (N = 345)	Placebo (N = 347)	Pirfenidone 2,403 mg/day (N = 345)	Placebo (N = 347)
Grade 3 or 4 TEAEs, n (%)	2 (0.6)	0 (0.0)	3 (0.9)	1 (0.3)
TE SAEs, n (%)	1 (0.3)[a]	0 (0.0)	1 (0.3)	0 (0.0)
Deaths (n)	0	0	0	0
Hospitalization, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation, n (%)	5 (1.4)	0 (0.0)	3 (0.9)	1 (0.3)
Dose modification, n (%)	42 (12.2)	5 (1.5)	19 (5.5)	1 (0.3)
Events (n)	159	52	60	8
Median duration (days)	38	31	88	60
Resolved, n (%)	132 (83)	46 (88)	47 (78)	6 (75)



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Valeyre *et al*. *Respirology.* 2014;19:740-7.
Costabel *et al. Adv Ther* 2014; 31: 375-91.

Long term clinical experience

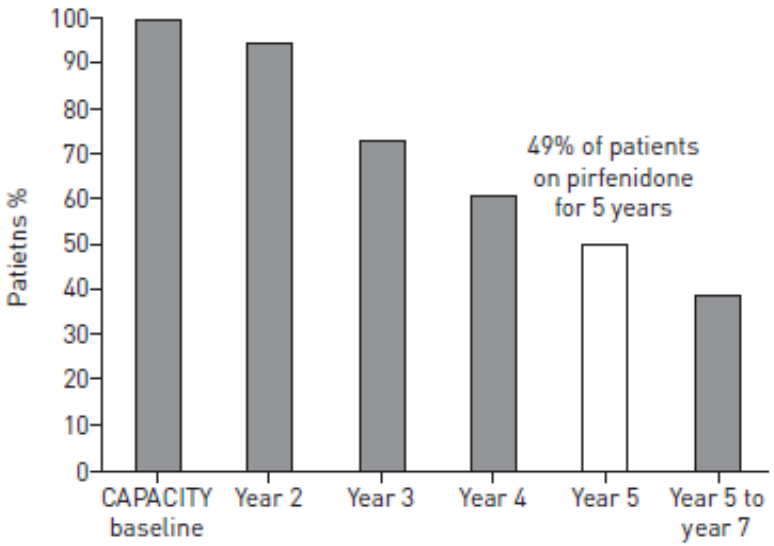

FIGURE 1 RECAP study: duration of study follow-up for 345 patients randomised to pirfenidone in the CAPACITY (Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research on Efficacy and Safety Outcomes) study.

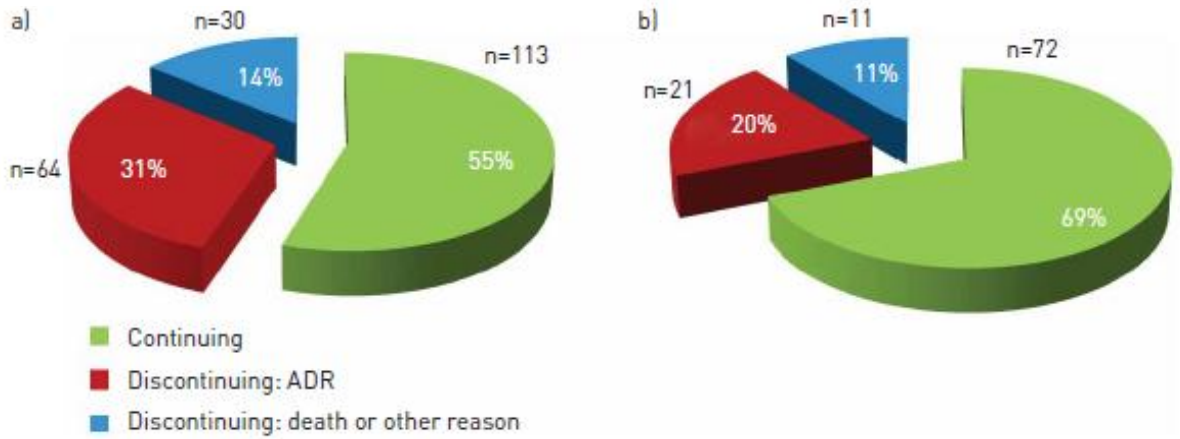

FIGURE 2 Impact of dose adjustment in case of adverse drug reaction (ADR; includes dose interruption and/or reduction). a) No dose adjustment and b) dose adjustment. Dose adjustment appeared to be associated with more patients continuing treatment and fewer discontinuing due to ADR. Data from [12].

Cottin *et al*. *Eur Respir Rev* 2015; 24: 58–64.

Real world experience with pirfenidone

First author [ref.]	Country	Patients	Patient characteristics	Efficacy outcome	Adverse events		Treatment discontinuation due to adverse events %
					GI	Skin	
Wijsenbeek [13]	Netherlands	52	Age: 63.4±7.7 years Baseline FVC (% pred): 68.3±18.4	Stable lung function in 17 out of 20 patients treated for >6 months (three out of 20 declined). In 11 out of 19 patients cough score decreased (unchanged: n=7; increased: n=1)	NA	NA	19
Ravaglia [14]	Italy	81[#]	Age: 69 (41–81) years Baseline FVC (% pred): 70.8	Stable or significantly improved lung function in 40 (59%) out of 68 patients	NA	NA	16
Nieto Barbero [15]	Spain	86	Age: NA Baseline FVC (% pred): 70±19	Stable FVC and D_{LCO} in those who had pulmonary function testing (n=20)	35 (41)	11 (13)[+]	14
Bonella [16]	Germany	45	Age: 69±7 years Baseline FVC (% pred): 61±15	Stable lung function in 28 (70%) out of 40 patients; subjective improvement in cough in 12 (33%) out of 36 patients	17 (38)	10 (22)	13
Okuda [17]	Japan	76	Age: 70.5±8.3 years Baseline FVC (% pred): 65.3±16.1	Reduction in FVC and D_{LCO} decline	18 (24)[§]	19 (25)[f]	18
Arai [18]	Japan	41	Age: 70 (65.5–75.5) years Baseline FVC (% pred): 66.7 (54.8–77.8)[¶]	Significant reduction in vital capacity decline in patients with severity grades I–II (Japanese Respiratory Society criteria)	24 (59)[##]	5 (12)[+]	15
Oltmanns [19]	Germany	63	Age: 68±7 years Baseline FVC (% pred): 70±19	Stable lung function in 62% of patients	NA	NA	13
Chaudhuri [20]	UK	40	Age: 65.8 (48–80) years Baseline FVC (% pred): 77.3 (46–146)	Reduction in FVC and D_{LCO} decline at 9 months	87	10[+]	15

Cottin *et al*. *Eur Respir Rev* 2015; 24: 58–64.

Adverse events - Nintedanib

Event	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
	number of patients (percent)			
Any adverse event	298 (96.4)	181 (88.7)	311 (94.5)	198 (90.4)
Any adverse event, excluding progression of idiopathic pulmonary fibrosis*	296 (95.8)	179 (87.7)	311 (94.5)	197 (90.0)
Most frequent adverse events†				
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of idiopathic pulmonary fibrosis*	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)
Upper respiratory tract infection	28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)
Dyspnea	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)
Decreased appetite	26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)
Vomiting	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)
Weight loss	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)
General disorders and conditions involving site of study-drug administration‖	8 (2.6)	3 (1.5)	2 (0.6)	1 (0.5)

Richeldi *et al*. *N Engl J Med* 2014;370:2071-82.

Treatment goal

- IPF : progressive scarring with destruction of the normal alveolar architecture of the lung

Return to normal lung tissue

Impossible !!

Slowing the rate of deterioration
Extending survival time
Slow disease progression
Delay respiratory failure

Expectations

Cost-effectiveness

Table 4 Summary of base case results

Treatment	Total costs (£)	Total QALYs	ICER vs. BSC (£/QALY)	ICER vs. next best option (£/QALY)
BSC	3,084	2.98	-	-
Azathioprine & prednisolone	4,313	2.66	Dominated	Dominated
NAC triple therapy	5,021	3.03	41,811	Extended Dominance
Inhaled NAC	5,029	3.37	5,037	5,037
Sildenafil	12,008	3.11	68,116	Dominated
Pirfenidone	70,118	3.34	190,146	Dominated
Nintedanib	139,613	4.01	132,658	209,246

NB: Nintedanib uses an assumed cost.

Loveman *et al*. *BMC Pharmacol Toxicol. 2014; 15*:63.

Older patients

- May not respond in the same manner to treatment
- Presence and severity of **comorbidities** must also be balanced against any treatment benefits
- Cardiac, renal and liver failure may increase **complications** of therapy (could be contraindications)
- **Compliance** is a major issue in management
- Treatment should only be commenced in subjects who would attend consistent follow up

In Korea

- Predicted forced vital capacity(FVC): ≥50%
- Predicted carbon monoxide diffusing capacity(DLco): ≥ 35%
- 6분 보행검사 ≥ 150m 이상
- 단, 폐쇄성기도질환, 교원성질환, 다른 원인으로 설명되는 간질성폐질환 및 폐이식 대기등록 환자는 투여대상에서 제외
- 위험분담제 적용

2014.8. - 식약처 심사중

건강보험심사평가원

Early diagnosis and treatment

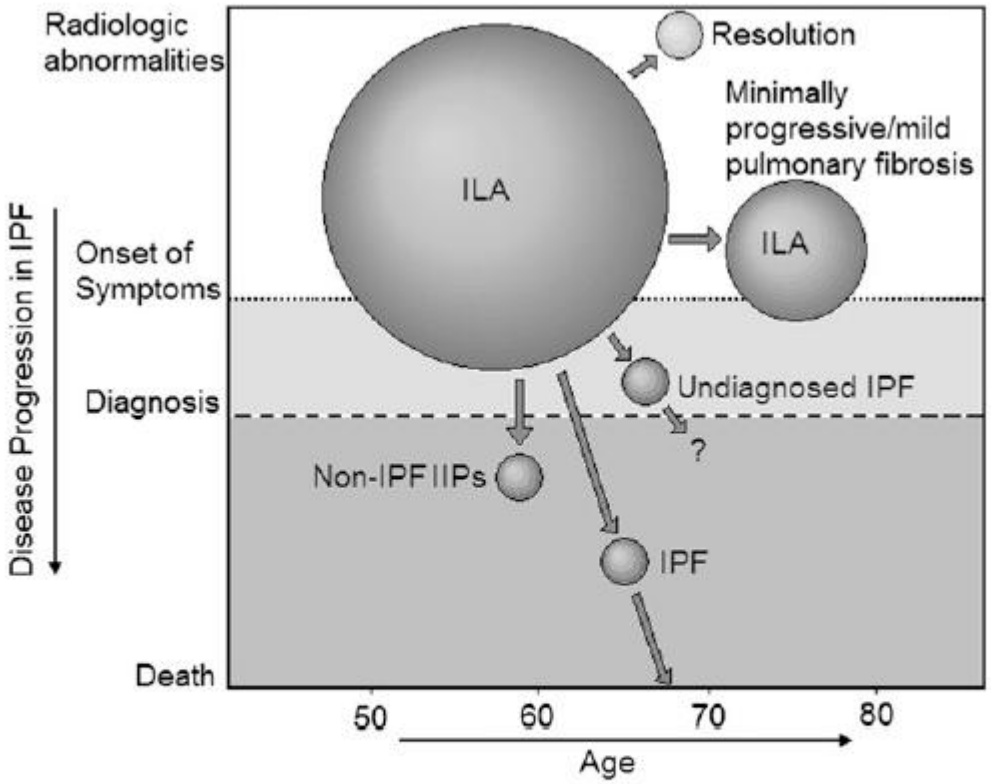

Figure 2. A schematic demonstrating the potential outcomes of subjects with interstitial lung abnormalities (ILA). Circle sizes in those with ILA and IPF reflect the minimum relative differences in prevalence we have noted between these two conditions. IIP = idiopathic interstitial pneumonia; ILA = interstitial lung abnormalities; IPF = idiopathic pulmonary fibrosis. Adapted by permission from Reference 14.

Putman *et al*. *Am J Respir Crit Care Med* 2014;189: 770-8.

Summary

- Early diagnosis
  - Uncertain diagnosis/ Invasive procedure
- Treatment
  - Patient : comorbidities, severity, old age
  - Medication : regimen, timing of start, duration, S/E
  - Efficacy : lung function, mortality
- Personalized treatment