Early Treatment in IPF; Anti-Fibrotic Therapy: pro

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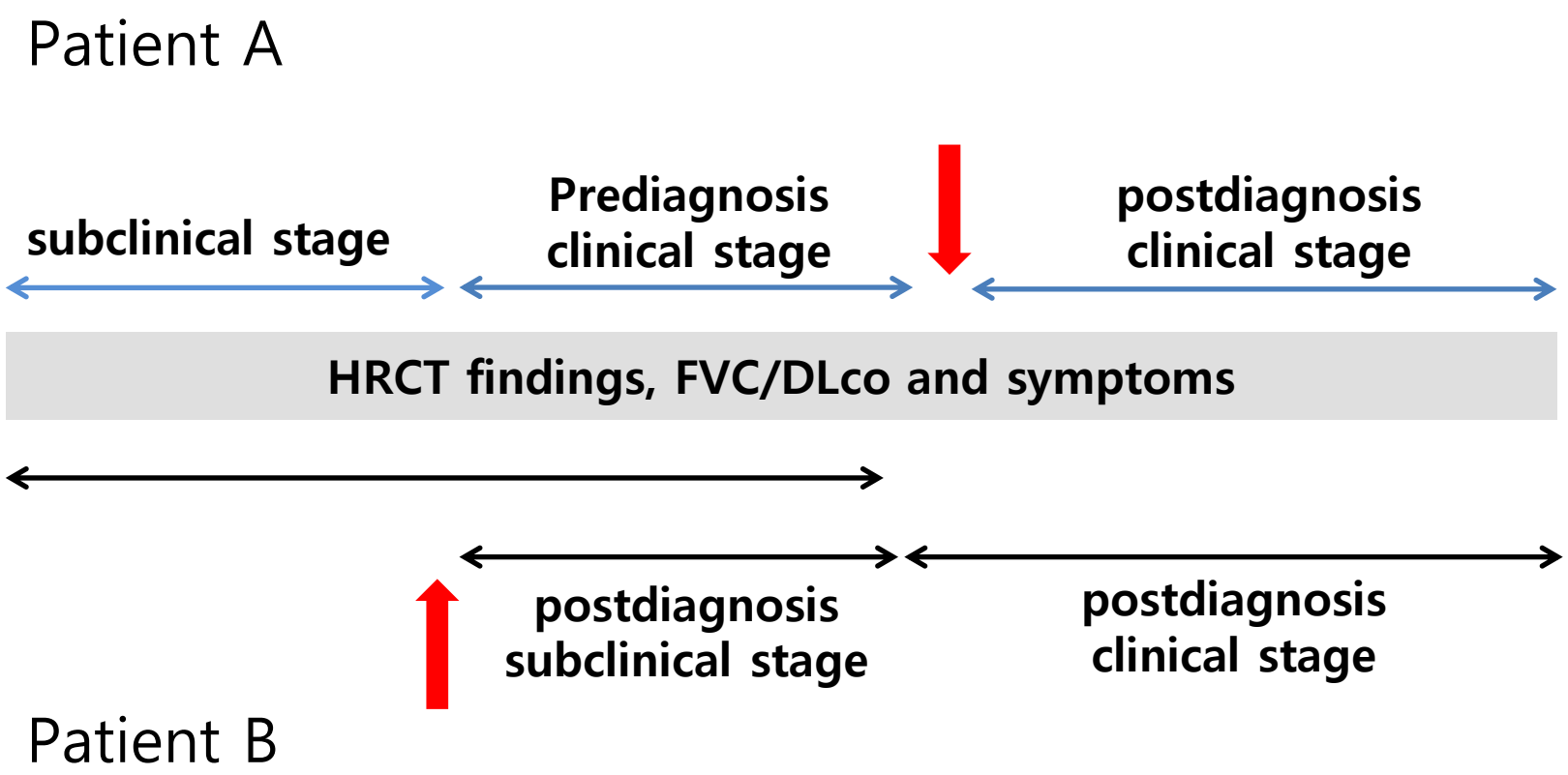
Early treatment in IPF

- What is the meaning of early treatment
  - According to the Disease severity ?
  - Timing of treatment after diagnosis ?

Clinical situation in real field

- Will you treat following patient with antifibrotic agent ?
  - Asymptomatic old patient with subtle radiologic changes (detected on routine exam) and minimally decreased lung function
  - Asymptomatic IPF patient with normal lung function (FVC >100 % pred.)
  - Asymptomatic IPF patient with near-normal lung function (FVC 75 % pred. and DLco 70% pred.)

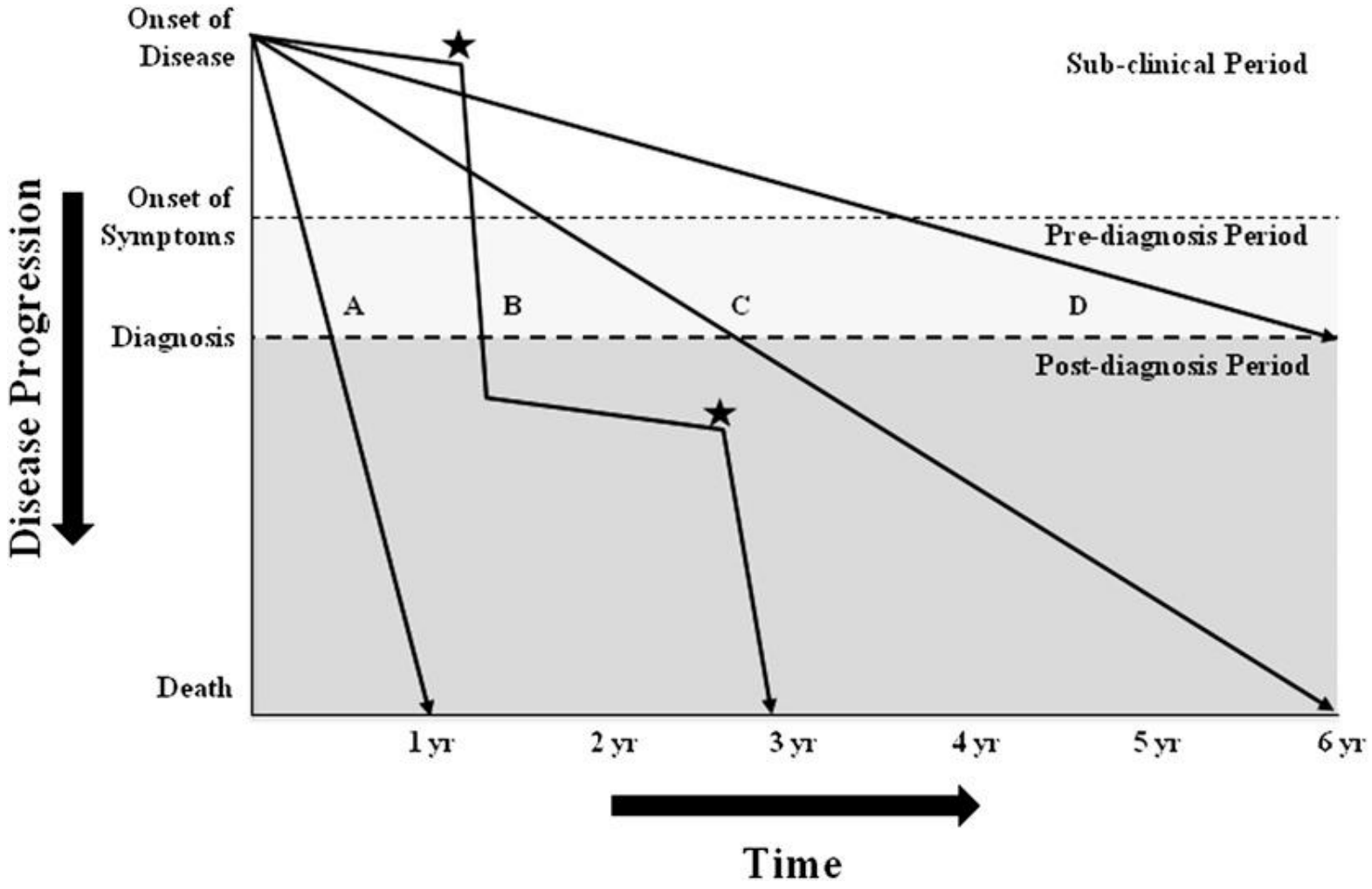
Clinical situation in real field



Factors that be considered for treatment

- as a clinician
  - Natural clinical course of IPF
  - Age and expected survival
  - Disease severity (Initial and overtime)
  - Benefit and adverse effect of treatment
  - Comorbidity

The variable clinical course of IPF



Prediction of survival in IPF

- How can we predict the prognosis of patients with IPF ?
  - Accumulated data on predictors of survival in many studies
  - Clinical prediction models

Individual predictors of survival in IPF

Clinical Predictors	Radiographic Predictors	Physiologic Predictors	Pathologic Predictors	Biomarker Predictors
Demographic	HRCT	Pulmonary function tests	Histopathology	Blood
Age	UIP pattern	FVC	UIP pattern	BNP
Sex	Extent of fibrosis	TLC	Fibroblastic foci	Albumin
Ethnicity		D_{LCO}		KL-6M
Smoking status		CPI		MP-7
Symptom-based		Change in FVC		CCL-18
Dyspnea scores		Change in D_{LCO}		SP-A & -D
				Circulating fibrocytes
Physical examination		Exercise tests		BAL
Clubbing		6MWT		SP-A & -D
BMI		Desaturation		MMP-3, -7, -8, -9
Comorbidities		Distance		CCL-2, -17, -22
Emphysema		Heart rate recovery		Neutrophilia
Pulmonary hypertension		Others		
		15-step test		
		4-min step test		

Am J Respir Crit Care Med Vol 183. pp 431–440, 2011

More consistent predictors of survival

- Age
- Gender
- Physiologic parameters
  - Baseline or changes in FVC, DLco
- Exercise tests (ex. 6MWT)

A Multidimensional Index and Staging System for Idiopathic Pulmonary Fibrosis.

- **Patients with IPF**
  - Predicting prognosis is a challenge for clinicians

- **Objective;**
  - To develop a multidimensional prognostic staging system for IPF by using commonly measured clinical and physiologic variables.

Ann Intern Med. 2012;156:684-691

The GAP index and staging system

	Predictor	Points
G	Gender	
	Female	0
	Male	1
A	Age, y	
	≤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	I	II	III
Points	0–3	4–5	6–8
Mortality			
1-y	5.6	16.2	39.2
2-y	10.9	29.9	62.1
3-y	16.3	42.1	76.8

GAP index performance

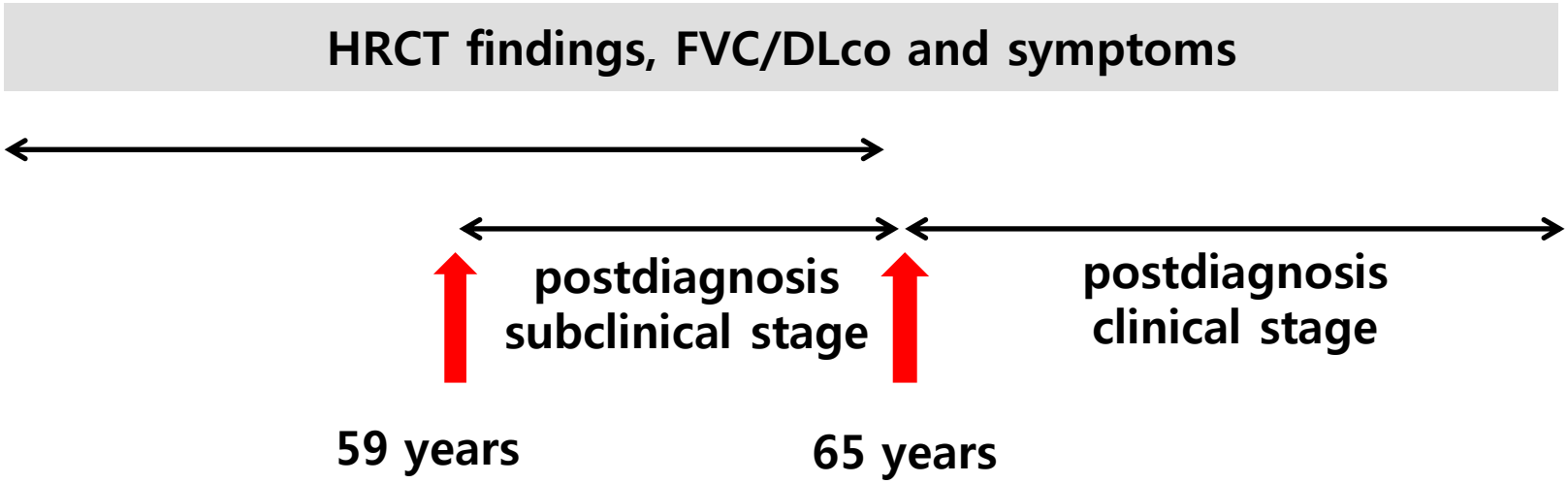
Table 3. Model Performance in the GAP Index (Point-Score Model)

Variable	Derivation Cohort		Validation Cohort*		Combined Cohort*	
	Predicted	Observed	Predicted	Observed	Predicted	Observed
C-index (95% CI)	69.3 (62.2–73.1)		68.7 (64.9–72.7)		69.7 (66.5–72.6)	
1-y mortality, %						
Stage I	5.2	1.5	5.4	6.5	5.6	4.8
Stage II	16.9	17.7	16.2	16.7	16.2	17.2
Stage III	41.7	44.5	41.1	37.3	39.2	40.5
2-y mortality, %						
Stage I	10.2	5.4	10.6	12.9	10.9	10.5
Stage II	30.9	33.3	29.8	32.6	29.9	33.0
Stage III	65.2	63.7	64.1	68.2	62.1	67.1
3-y mortality, %						
Stage I	15.4	12.5	15.9	24.6	16.3	21.0
Stage II	43.4	47.4	42.0	47.8	42.1	47.7
Stage III	79.7	70.2	78.4	75.5	76.8	74.2

GAP = gender, age, and 2 lung physiology variables (FVC and DLCO).
* Predicted estimates use shrinkage factor based on cross-validation in the derivation cohort (see Methods section for more information).

Age, in real field

Patient B



The GAP index and staging system

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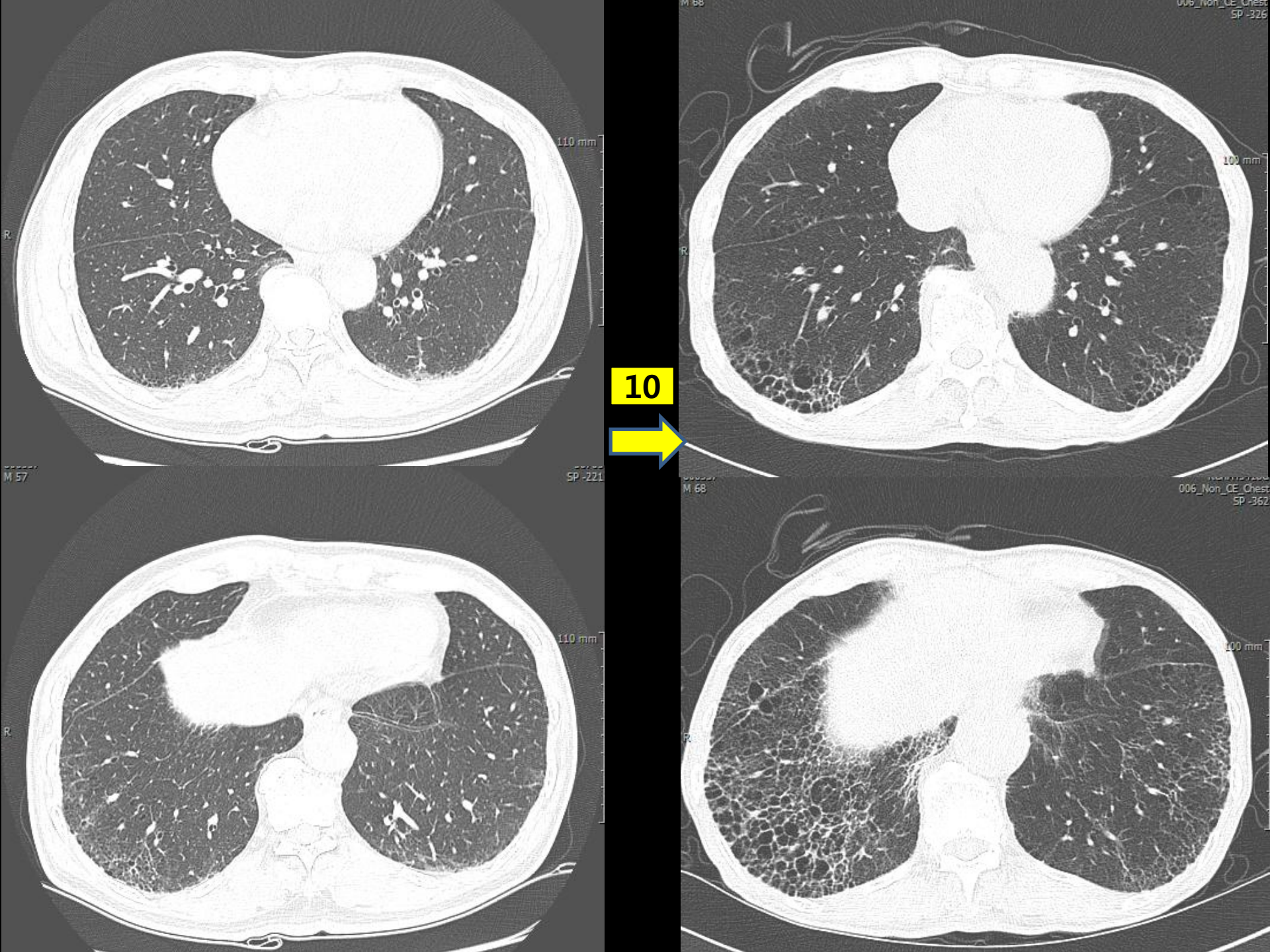
110 mm
M 57
SP -221
10
M 68
006_Non_CE_Chest
SP -326
100 mm
110 mm
M 68
006_Non_CE_Chest
SP -362
100 mm

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2011 VOL. 364 NO. 10

Lung Volumes and Emphysema in Smokers with Interstitial Lung Abnormalities

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Table 1. Baseline Characteristics of the Study Participants.*

Variable	Participants without ILA	P Value	Participants with Indeterminate HRCT Scans	P Value	Participants with ILA	P Value
Total — no. (%)	1361 (56)		861 (36)		194 (8)	
Demographic characteristics						
Median age — yr	60 (52–67)	<0.001	63 (55–70)	0.12	64 (56–72)	<0.001
Female sex — no. (%)	648 (48)	0.54	422 (49)	0.47	101 (52)	0.25
Black race — no. (%)	328 (24)	0.19	229 (27)	0.53	56 (29)	0.15
Median body-mass index	27 (24–31)	<0.001	29 (25–33)	0.25	28 (25–33)	0.006
Median pack-yr of smoking	40 (29–54)	0.08	41 (28–60)	0.15	44 (31–63)	0.01
Current smoker — no. (%)	609 (45)	0.10	354 (41)	0.02	97 (50)	0.19
Variable	**Participants without ILA**	**P Value**	**Participants with Indeterminate HRCT Scans**	**P Value**	**Participants with ILA**	**P Value**
Median FEV_1 — % of predicted‡	80 (52–97)	0.02	77 (55–92)	0.03	82 (67–93)	0.15
Median FVC — % of predicted‡	88 (75–100)	0.08	87 (74–99)	0.30	88 (77–98)	0.80
Median FEV_1:FVC %‡	70 (51–79)	0.04	68 (53–76)	0.01	71 (61–77)	0.32
Spirometric restriction — no. (%)§	414 (30)	0.82	266 (31)	0.004	81 (42)	0.002
Chest CT findings						
Median % emphysema¶						
–950 HU	4.1 (1.3–12.4)	<0.001	3.3 (0.9–9.7)	<0.001	2.2 (0.7–6.0)	<0.001
–910 HU	30 (15–47)	<0.001	23 (10–41)	<0.001	14 (7–29)	<0.001
Total lung capacity‖						
Median volume at full inspiration — liters	5.70 (4.80–6.78)	<0.001	5.21 (4.38–6.27)	0.08	5.02 (4.15–5.96)	<0.001
Median % of predicted value	107 (92–120)	<0.001	100 (84–112)	0.04	95 (81–109)	<0.001
<80% of predicted value — no. (%)	134 (10)	<0.001	169 (20)	0.77	40 (21)	<0.001
Median lung volume at relaxed exhalation — liters	3.13 (2.51–3.98)	0.06	3.04 (2.48–3.84)	<0.001	2.67 (2.23–3.44)	<0.001

Summary

- Interstitial lung abnormalities were associated with reduced TLC (-0.444 L; 95% CI, -0.596-0.292; P<0.001)

Even, Subtle radiologic abnormality is associated with physiologic derangement in PFT

Clinical significance of physiologic derangement ?

Original Investigation

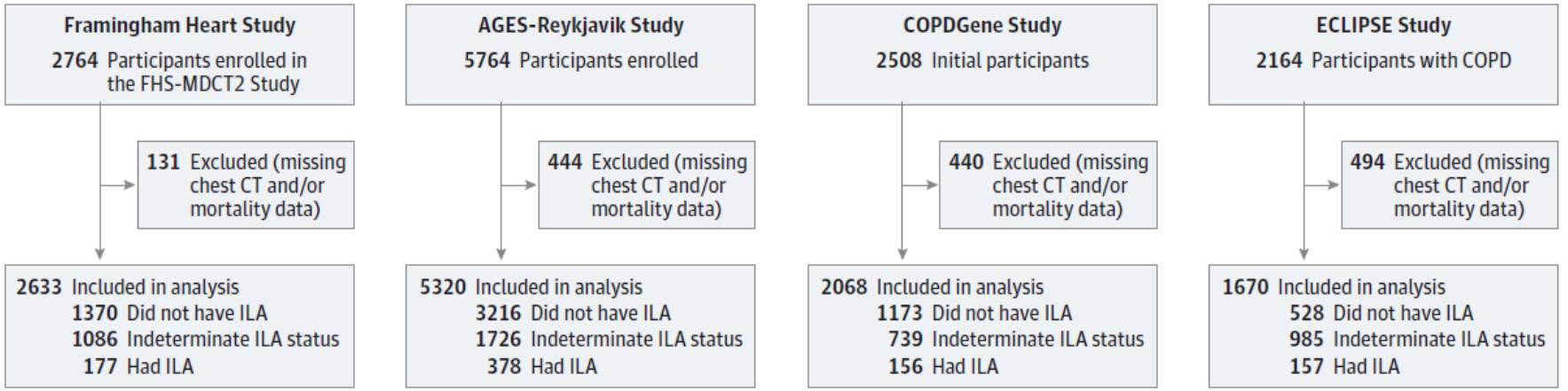
Association Between Interstitial Lung Abnormalities and All-Cause Mortality

Rachel K. Putman, MD; Hiroto Hatabu, MD, PhD; Tetsuro Araki, MD, PhD; Gunnar Gudmundsson, MD, PhD; Wei Gao, MS; Mizuki Nishino, MD; Yuka Okajima, MD; Josée Dupuis, PhD; Jeanne C. Latourelle, DSc; Michael H. Cho, MD, MPH; Souheil El-Chemaly, MD, MPH; Harvey O. Coxson, PhD; Bartolome R. Celli, MD; Isis E. Fernandez, MD; Oscar E. Zazueta, MD; James C. Ross, PhD; Rola Harmouche, PhD; Raúl San José Estépar, PhD; Alejandro A. Diaz, MD; Sigurdur Sigurdsson, BSc, MSc; Elías F. Gudmundsson, MSc; Gudny Eiríksdottír, MSc; Thor Aspelund, MSc, PhD; Matthew J. Budoff, MD; Gregory L. Kinney, PhD; John E. Hokanson, MPH, PhD; Michelle C. Williams, MD; John T. Murchison, MD; William MacNee, MD; Udo Hoffmann, MD, MPH; Christopher J. O'Donnell, MD, MPH; Lenore J. Launer, PhD; Tamara B. Harrris, MD, MS; Vilmundur Gudnason, MD, PhD; Edwin K. Silverman, MD, PhD; George T. O'Connor, MD; George R. Washko, MD; Ivan O. Rosas, MD; Gary M. Hunninghake, MD, MPH; for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) and COPDGene Investigators

JAMA. 2016;315(7):672-681. doi:10.1001/jama.2016.0518

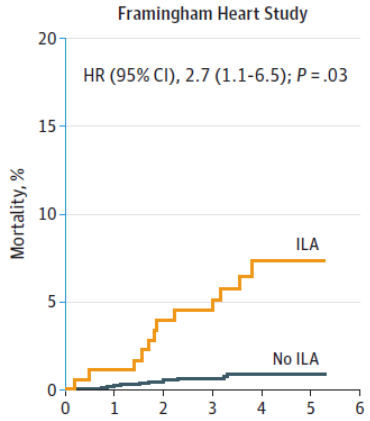
4 separate research cohorts

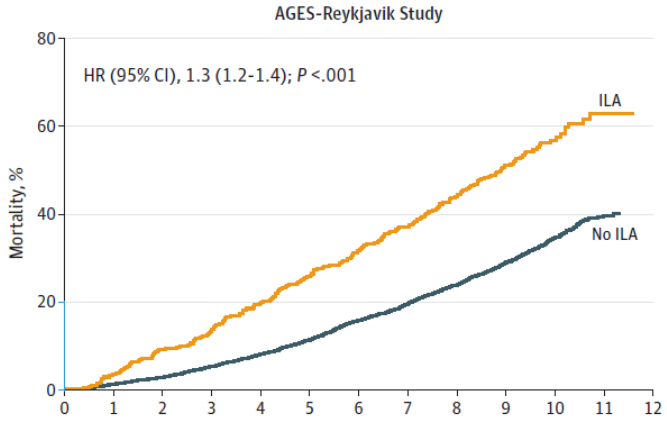
Figure 2. Participant Flow for the FHS, AGES-Reykjavik, COPDGene, and ECLIPSE Studies



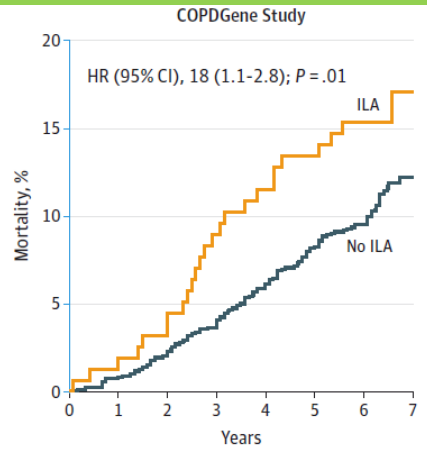
AGES indicates the Age Gene/Environment Susceptibility; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FHS-MDCT2, Framingham Heart Study Multidetector Computed Tomography 2; *ICD*, *International Classification of Diseases*; ILA, interstitial lung abnormalities.

Mortality Rates by ILA Status



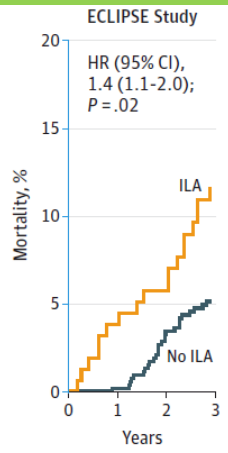


ILA were associated with a greater risk of all-cause mortality



No. at risk

ILA	156	153	149	142	138	135	131
No ILA	1173	1163	1146	1125	1104	1079	1062



No. at risk

ILA	156	151	145
No ILA	528	525	505

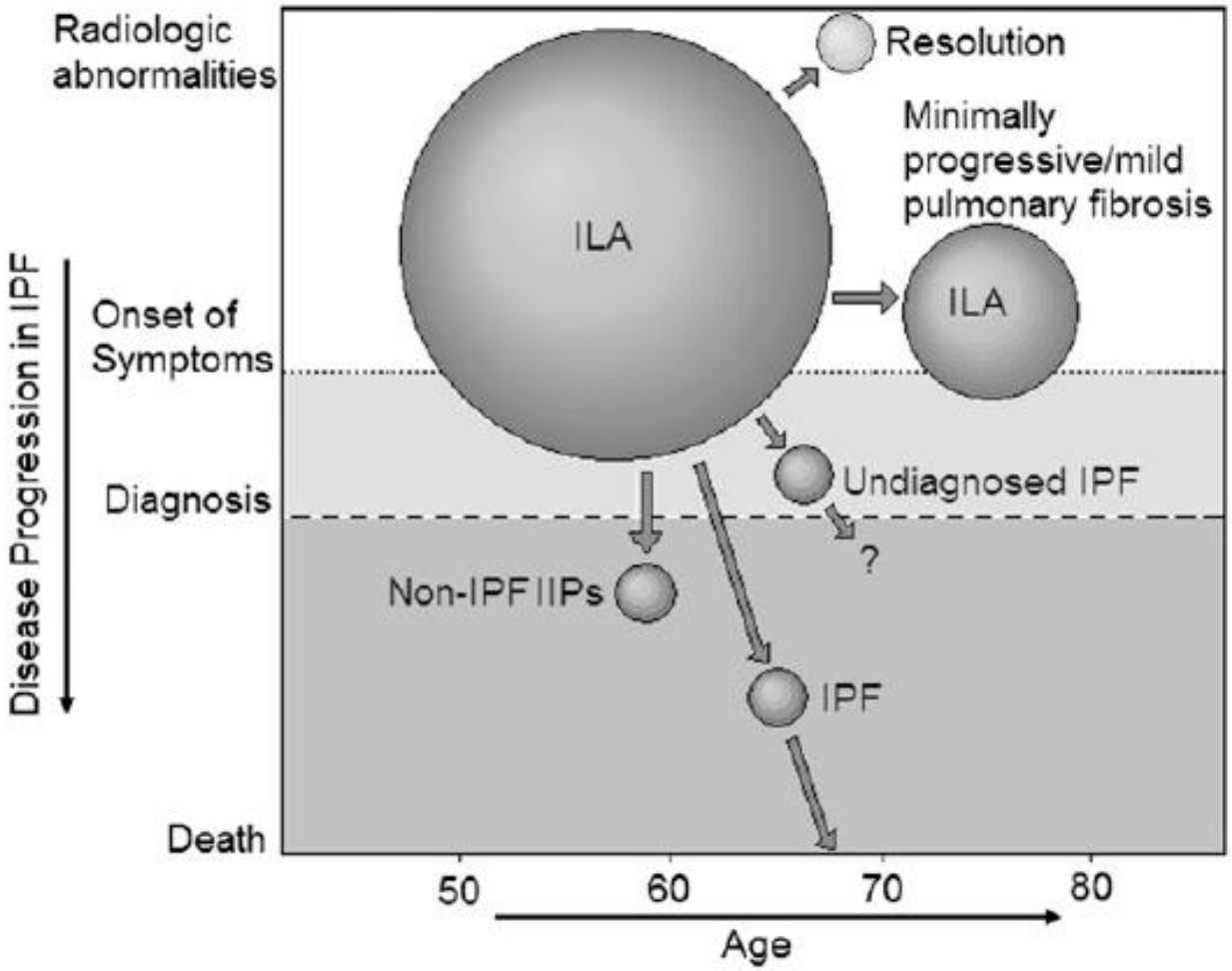
Mortality, Interstitial Lung Abnormalities, and Cause of Death for the AGES-Reykjavik Study

	No. (%)[a]			
	ILA	Indeterminate	No ILA	Overall
No. of participants	378	1726	3216	5320
Deaths				
Total	115 (100)	382 (100)	468 (100)	965
Cardiovascular[b]	48 (42)	161 (42)	204 (44)	413
Cancer[c]	29 (25)	111 (29)	151 (32)	291
Respiratory[d]	15 (13)	22 (6)	20 (4)	57
Pulmonary fibrosis	7	1	0	8
Other	8	21	20	49
Other[e]	23 (20)	88 (23)	93 (20)	204

Table 1: Comparisons of the Features Noted in Subjects with Interstitial Lung Abnormalities to Those in Patients with Idiopathic Pulmonary Fibrosis

Variable	Percent or Median/Means Where Appropriate and Noted						
	Research Subjects with ILA						
	MESA*	Nagano, Japan†	COPDGene‡	MILD§	FHS‖	NLST¶	Patients with IPF**
Prevalence of ILA, %	2	3	8	4	7	10	0.01–0.04
Radiologic features, %							
Reticular markings	4–9	62	85	21	97	24	All
Ground glass	61–93	15	97	90	100	78	Occasional
Centrilobular nodules	—	—	28	28	20		Rare
Cysts	—	—	51	—	47	27	Rare
Traction bronchiectasis	—	—	30	21	50		Common
Honeycombing	2–13	9	9	7	3	10	Common
High-attenuation areas in >10% of the lung	100% (by definition)	—	—	—	—		Unknown (but likely elevated)
Demographic parameters							
Age, yr	—	62	64	60	70	62	66
Sex, female, %	—	26	50	14	52	28	41–49
History of smoking, current or former, %	—	70	100	100	62	100	60–72
Respiratory symptoms, %							
Chronic cough, yes	—	13	41	—	12	—	73–86
Chronic shortness of breath, yes	—	15	60	—	18	—	Present in most patients
Physical examination findings							
Fine crackles, %	—	26	—	—	—	—	Present in most patients
Pulmonary physiologic testing							
FVC % predicted	—	113–116	88	101	101	—	68–89
Total lung capacity % predicted	—	—	95	—	79	—	46–78
Diffusion capacity of carbon monoxide, % predicted	—		—	—	86	—	46–61
6-min walk distance, m	—	555–573	403	—	—	—	373–392
Radiologic progression, %, follow-up time							
Improvement	—	16, 4 yr	—	0, 3 yr	—	33, 2 yr	The median survival of IPF
Unchanged		40, 4 yr		75, 3 yr		47, 2 yr	patients is 3 yr
Overall progression	—	46, 4 yr	—	25, 3 yr	—	20, 2 yr	
Progression to UIP pattern	—	5, 4 yr	—	8, 3 yr	—	—	—

Am J Respir Crit Care Med Vol 189, Iss 7, pp 770–778, Apr 1, 2014



A schematic demonstrating the potential outcomes of subjects with interstitial lung abnormalities (ILA)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

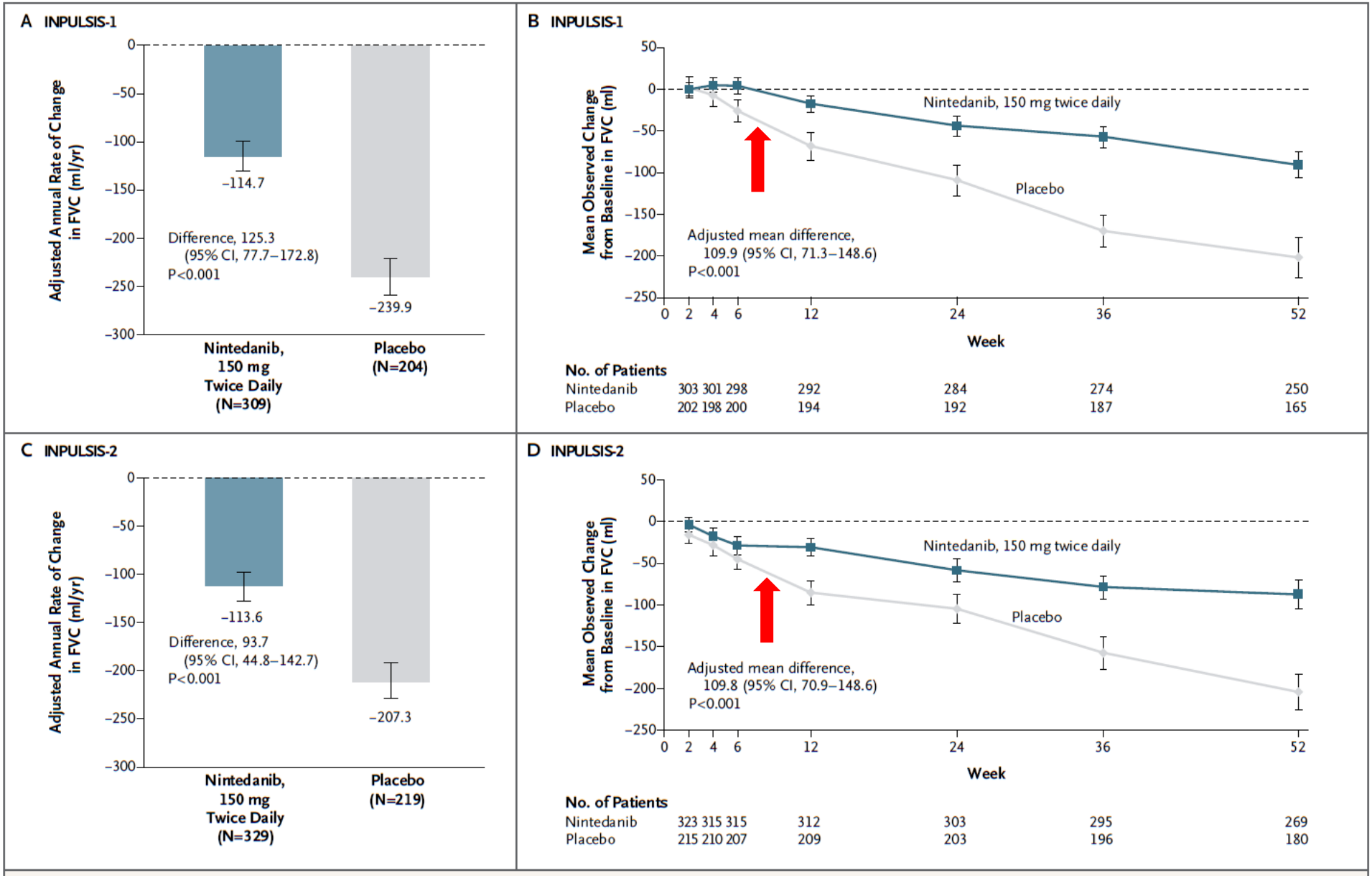
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

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*

Table 1. Baseline Characteristics of Patients in INPULSIS-1 and INPULSIS-2.*

Characteristic	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
Male sex — no. (%)	251 (81.2)	163 (79.9)	256 (77.8)	171 (78.1)
Age — yr	66.9±8.4	66.9±8.2	66.4±7.9	67.1±7.5
Weight — kg	82.0±16.8	81.2±16.3	76.6±15.9	76.3±16.5
Body-mass index†	28.6±4.5	28.1±4.6	27.6±4.6	27.2±4.5
Smoking status — no. (%)				
Never smoked	71 (23.0)	51 (25.0)	103 (31.3)	71 (32.4)
Former smoker	217 (70.2)	144 (70.6)	218 (66.3)	139 (63.5)
Current smoker	21 (6.8)	9 (4.4)	8 (2.4)	9 (4.1)
Time since diagnosis of idiopathic pulmonary fibrosis — yr	1.7±1.4	1.6±1.4	1.6±1.3	1.6±1.3
Specimen from surgical lung biopsy available — no. (%)	60 (19.4)	33 (16.2)	84 (25.5)	52 (23.7)
Systemic corticosteroid therapy — no. (%)‡	68 (22.0)	43 (21.1)	68 (20.7)	46 (21.0)
FVC				
Mean — ml	2757±735	2845±820	2673±776	2619±787
Median — ml	2700	2721	2615	2591
Percentage of predicted value	79.5±17.0	80.5±17.3	80.0±18.1	78.1±19.0
FEV_1:FVC (%)	81.5±5.4	80.8±6.1	81.8±6.3	82.4±5.7
D_{LCO}				
mmol/min/kPa	4.0±1.2	4.0±1.1	3.8±1.2	3.7±1.3
Percentage of predicted value§	47.8±12.3	47.5±11.7	47.0±14.5	46.4±14.8
Spo_2 — %	95.9±2.0	95.9±1.9	95.8±2.6	95.7±2.1
Total SGRQ score¶	39.6±17.6	39.8±18.5	39.5±20.5	39.4±18.7

Annual Rate of Decline and Change of 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*

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pirfenidone (N=278)	Placebo (N=277)
Age — yr	68.4±6.7	67.8±7.3
Male sex — no. (%)	222 (79.9)	213 (76.9)
U.S. enrollment — no. (%)	187 (67.3)	184 (66.4)
Former smoker — no. (%)	184 (66.2)	169 (61.0)
Lung physiological features		
FVC — % of predicted value	67.8±11.2	68.6±10.9
FEV_1:FVC	0.84±0.03	0.84±0.04
Carbon monoxide diffusing capacity — % of predicted value	43.7±10.5	44.2±12.5
Dyspnea score†	34.0±21.9	36.6±21.7
Distance on 6-min walk test — m	415.0±98.5	420.7±98.1
Use of supplemental oxygen — no. (%)	78 (28.1)	76 (27.4)
Time since diagnosis — yr	1.7±1.1	1.7±1.1
Diagnostic finding on high-resolution computed tomography — no. (%)		
Definite pattern of usual interstitial pneumonia	266 (95.7)	262 (94.6)
Possible pattern of usual interstitial pneumonia‡	12 (4.3)	15 (5.4)
Surgical lung biopsy — no. (%)	86 (30.9)	79 (28.5)

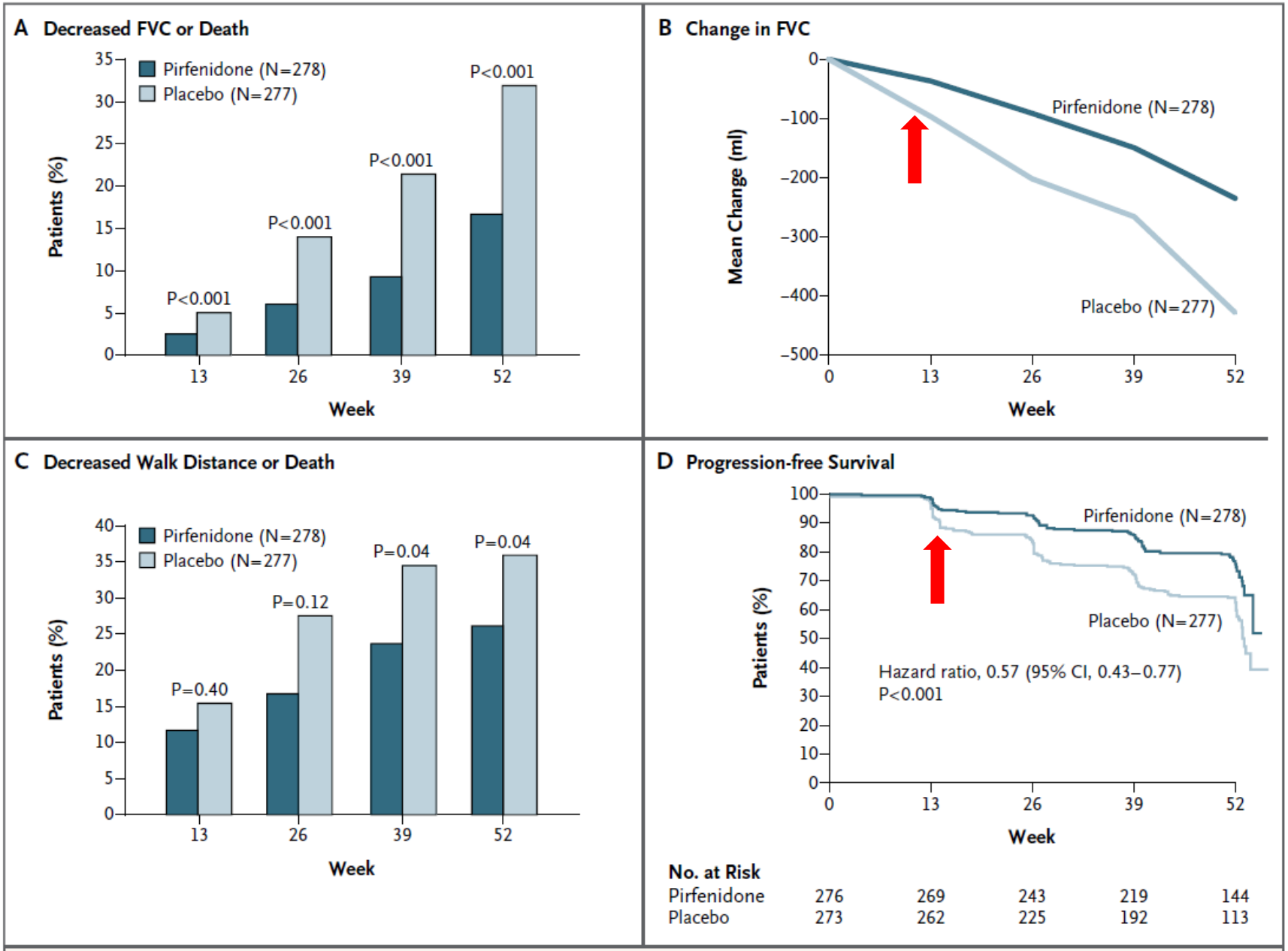


Figure 2. Primary and Key Secondary Efficacy Outcomes during the 52-Week Study Period.

Summary of Recent studies

- Disease progression (on FVC decline)
  - Pirfenidone (+)/ nintedanib (+)
- Mortality
  - Pirfenidone (+)/ nintedanib (-)
- Dyspnea or quality of life
  - Pirfenidone (-)/ nintedanib (-)

Summary, Annual decline in FVC

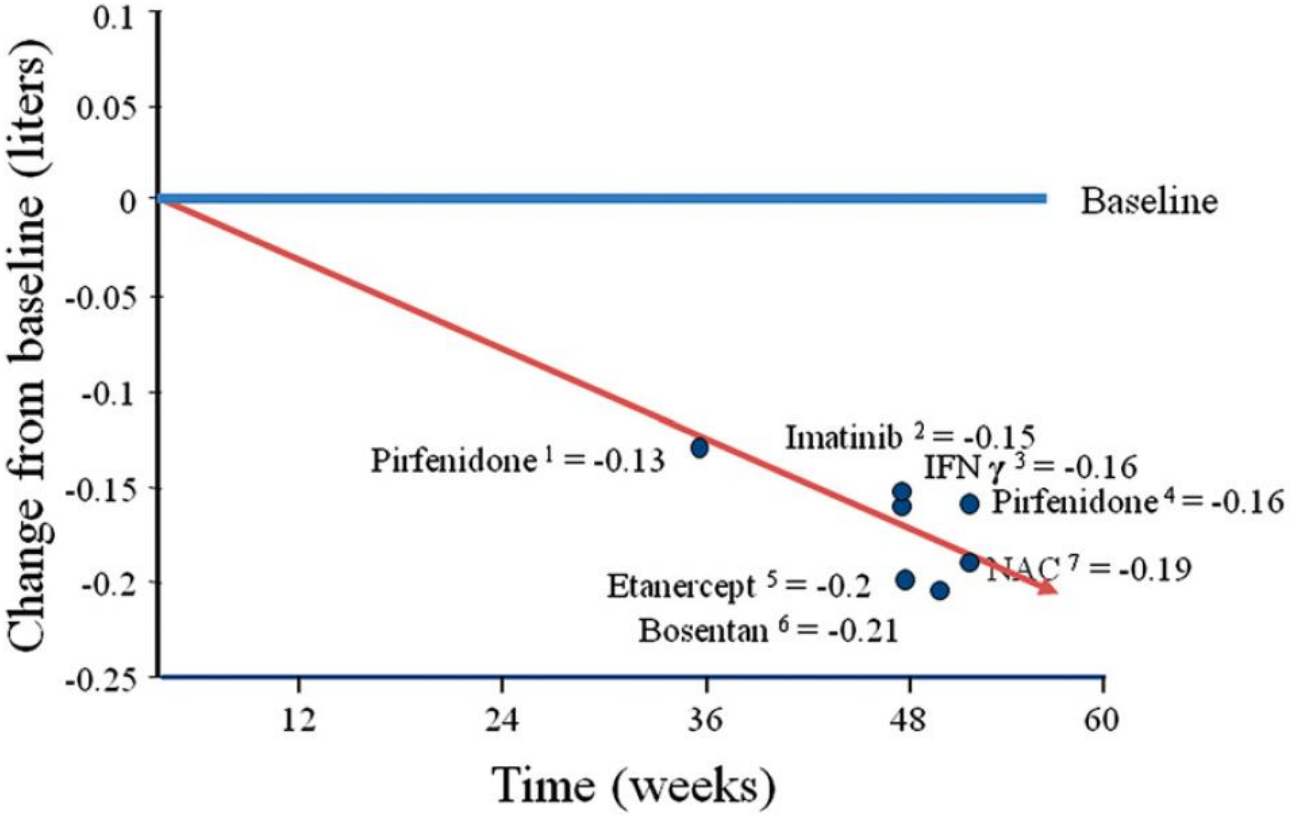
	Acetylcystein	Pirfenidone	Nintedanib	Placebo
FVC (%)	72.2 ±15.9	67.8±11.2	79.5±17.0 80.0±18.1	
DLco (%)	44.7± 10.8	43.7± 10.5	47.8± 12.3 47.0± 14.5	
FVC change (mL)	- 180	-122	-95.1 -95.3	-190 -262 -205

Physiologic predictors

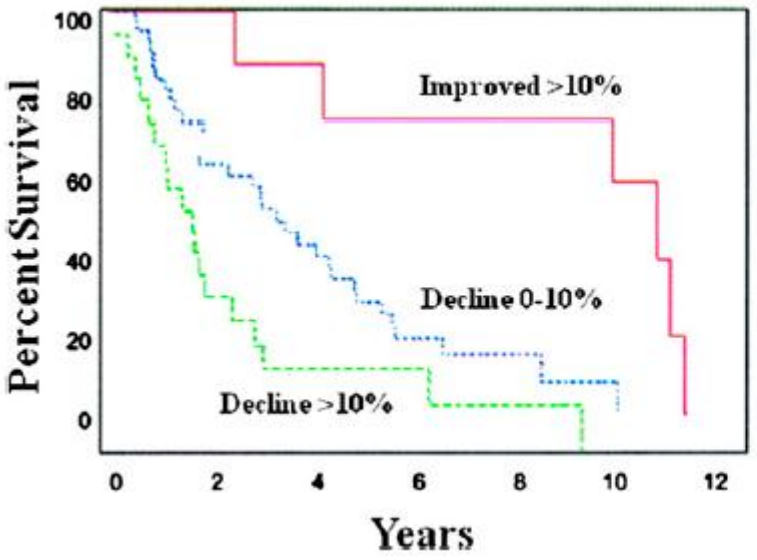
Baseline or changes in FVC

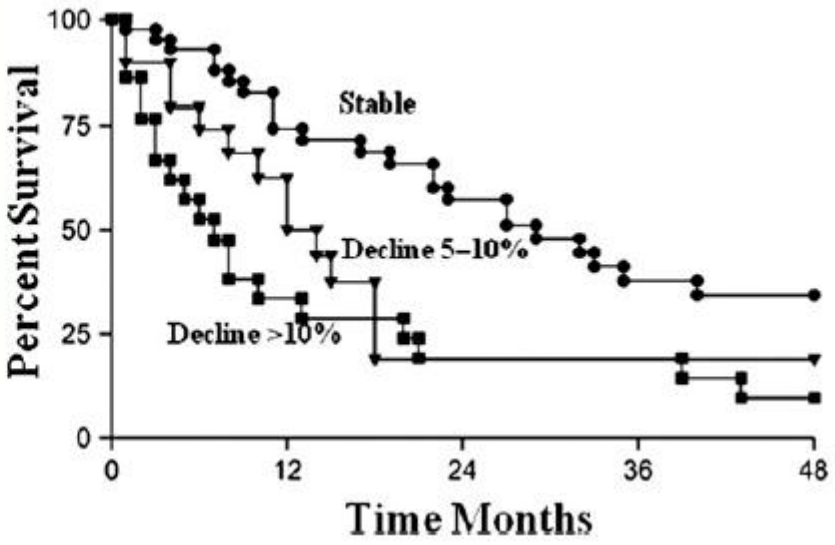
Diffusion capacity

Decline in FVC in IPF without treatment ; approximately 150 to 200 ml/yr



Survival in relation to the magnitude of serial change in FVC at 6 months in patients with IPF (two separate studies)





Am J Respir Crit Care Med Vol 183. pp 431–440, 2011

CHEST

Original Research

DIFFUSE LUNG DISEASE

Predicting Pulmonary Fibrosis Disease Course From Past Trends in Pulmonary Function

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Background: **The clinical course of idiopathic pulmonary fibrosis (IPF) is characterized by progressive decline in lung function and eventual mortality. We sought to determine if future declines in pulmonary function, mortality, or both can be predicted from prior trends in pulmonary function tests (PFTs).**

Methods: **Data from 1981 to 2008 on 4,431 PFTs and mortality were analyzed from 734 subjects with IPF. The Kaplan-Meier method was used for mortality analyses. Mixed models were used to describe longitudinal pulmonary function dynamics, since PFTs were observed at varying time points from baseline.**

Results: **During the first year of follow-up, 135 subjects (73%) had stable FVC while 50 subjects (37%) showed a decline in FVC. During months 12 to 24 (1-2 years after diagnosis), a stable FVC occurred with the same frequency among both subjects whose FVC had declined during year 1 and whose FVC had remained stable (84.0% and 80.7%, respectively; $P = .59$). Among subjects alive at the end of year 1, those with a stable FVC were more likely to be alive at the end of year 2 than those whose FVC declined (hazard ratio [HR], 0.91 [95% CI, 0.87-0.94] and HR, 0.71 [95% CI, 0.62-0.78], respectively).**

Conclusions: **PFT decline predicts early mortality, but not future declines in physiology, regardless of time since diagnosis.**

CHEST 2014; 145(3):579–585

Abbreviations: DLCO = diffusion capacity of the lung for carbon monoxide; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function test

Table 3—*Subsequent Change in FVC Over the Next Year, Based on the Previous Year's Change*

PFT in Prior Year	PFT in Next Year			*P* Value
	No.	FVC Stable	FVC Declined[a]	
Baseline to year 1				.60
FVC stable	135	109 (80.7)	26 (19.3)	
FVC declined	50	42 (84.0)	8 (16.0)	
Year 1 to 2				.11
FVC stable	85	63 (74.1)	22 (25.9)	
FVC declined	12	6 (50.0)	6 (50.0)	
Year 2 to 3				.89
FVC stable	48	33 (68.8)	15 (31.3)	
FVC declined	12	8 (66.7)	4 (33.3)	

Table 4—*Subsequent Change in DLCO Over the Next Year, Based on the Previous Year's Change*

PFT in Prior Year	PFT in Next Year: No.	DLCO Stable	DLCO Declined[a]	*P* Value
Baseline to year 1				.76
DLCO stable	87	53 (60.9)	34 (39.1)	
DLCO declined	36	23 (63.9)	13 (36.1)	
Year 1 to 2				.74
DLCO stable	44	23 (52.3)	21 (47.7)	
DLCO declined	23	13 (56.5)	10 (43.5)	
Year 2 to 3				.94
DLCO stable	28	19 (67.9)	9 (32.1)	
DLCO declined	12	8 (66.7)	4 (33.3)	

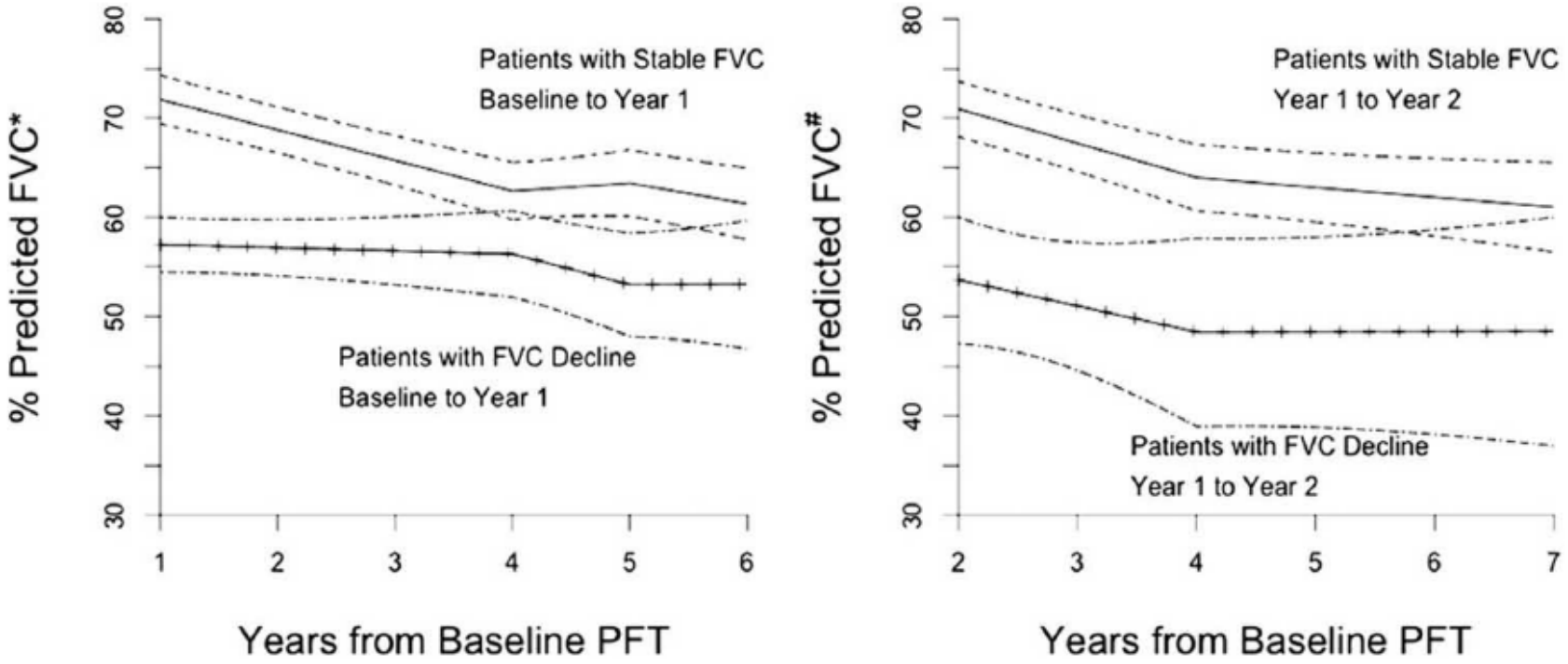


FIGURE 1. Mixed models analysis of the trend in FVC (solid lines: mean FVC, dashed lines: 95% CI) for patients with a stable FVC the year prior (solid line) vs those who declined the year prior (tick marks). *$P < .0001$ for the difference in intercept between stable and declined; $P < .0001$ for the difference in trajectory. #$P < .0001$ for the difference in intercept between stable and declined for the difference in trajectory 0.78. PFT = pulmonary function test.

Table 5—*Change in PFT the Previous Year and Subsequent 1-y Survival by Kaplan-Meier Method*

PFT Status	FVC, 1-y Survival (95% CI)	DLCO, 1-y Survival (95% CI)
Baseline to year 1		
PFT stable	0.91 (0.87-0.94)	0.90 (0.84-0.93)
PFT declined[a]	0.71 (0.62-0.78)	0.72 (0.63-0.79)
P value	< .0001	< .0001
Year 1 to 2		
PFT stable	0.89 (0.82-0.93)	0.88 (0.79-0.93)
PFT declined	0.77 (0.58-0.88)	0.78 (0.64-0.87)
P value	.0528	.1161
Year 2 to 3		
PFT stable	0.96 (0.88-0.99)	0.96 (0.83-0.99)
PFT declined	0.75 (0.54-0.87)	0.75 (0.57-0.87)
P value	.0009[b]	.0102[b]

Messages from this study

- The change in pulmonary function in the prior year does not predict the change in pulmonary function in the subsequent year

- Mortality and decline in pulmonary function occur with greatest frequency **the first year** after presentation

Inclusion criteria for INPULSIS and ASCEND trials

Inclusion criteria	ASCEND (nintedanib)	INPULSIS (pirfenidone)
Duration of clinical symptoms	Clinical symptoms consistent with IPF >12 months	No information
Duration of diagnosis	6-48 months	<5 years
Age	40-80 yrs	>40 years
FVC	50-90% predicted	>50%
FEV1/FVC ratio	Postbronchodilator FEV1/FVC <0.8	FEV1/FVC <0.7
Bronchodilator response	Change in pre and postbronchodilator response <10%	No information
DLCO	DLCO: 30-90% predicted	DLCO: 30-79%
Natural history	No improvement in preceding year	No information
6 MWT distance	>150 m	No information

IPF/CPFE 여부	Non-CPFE	CPFE	p
	(N=103)	(N=36)	
Sex			0
- Female	56 (54.4%)	5 (13.9%)	
- Male	47 (45.6%)	31 (86.1%)	
Age	69.8 ± 11.0	72.2 ± 9.4	0.25
Smoking			0
- Non-smoker	59 (58.4%)	5 (14.3%)	
- Smoker	42 (41.6%)	30 (85.7%)	
Pack-years	12.3 ± 18.3	37.5 ± 24.0	0
proBNP	613.5 ± 2543.2	455.0 ± 1267.0	0.745
FVC	13.9 ± 110.9	2.9 ± 0.7	0.349
FVC pred(%)	**75.7 ± 18.0**	**85.9 ± 16.7**	0.007
FEV1	13.8 ± 112.6	2.2 ± 0.5	0.337
FEV1 pred(%)	92.0 ± 26.2	98.7 ± 19.7	0.202
FEV1/FVC(%)	84.3 ± 7.1	80.1 ± 9.5	0.033
DLco(%)	**65.7 ± 31.2**	**69.4 ± 16.4**	0.419

Data from Bucheon St. Mary's Hospital

Limitation of two studies

- The patients with IPF for >4 or 5 years
  - Excluded from both clinical trials
  - No data in patients with longstanding IPF
- little information about the use of these drugs in patients with more severe disease (FVC <50% pred.)

- There is no information about *not-early treatment* for IPF
- There are more evidences for early treatment

More direct evidence for early treatment in IPF ?

But, I still need more some to justify my early treatment for IPF patient

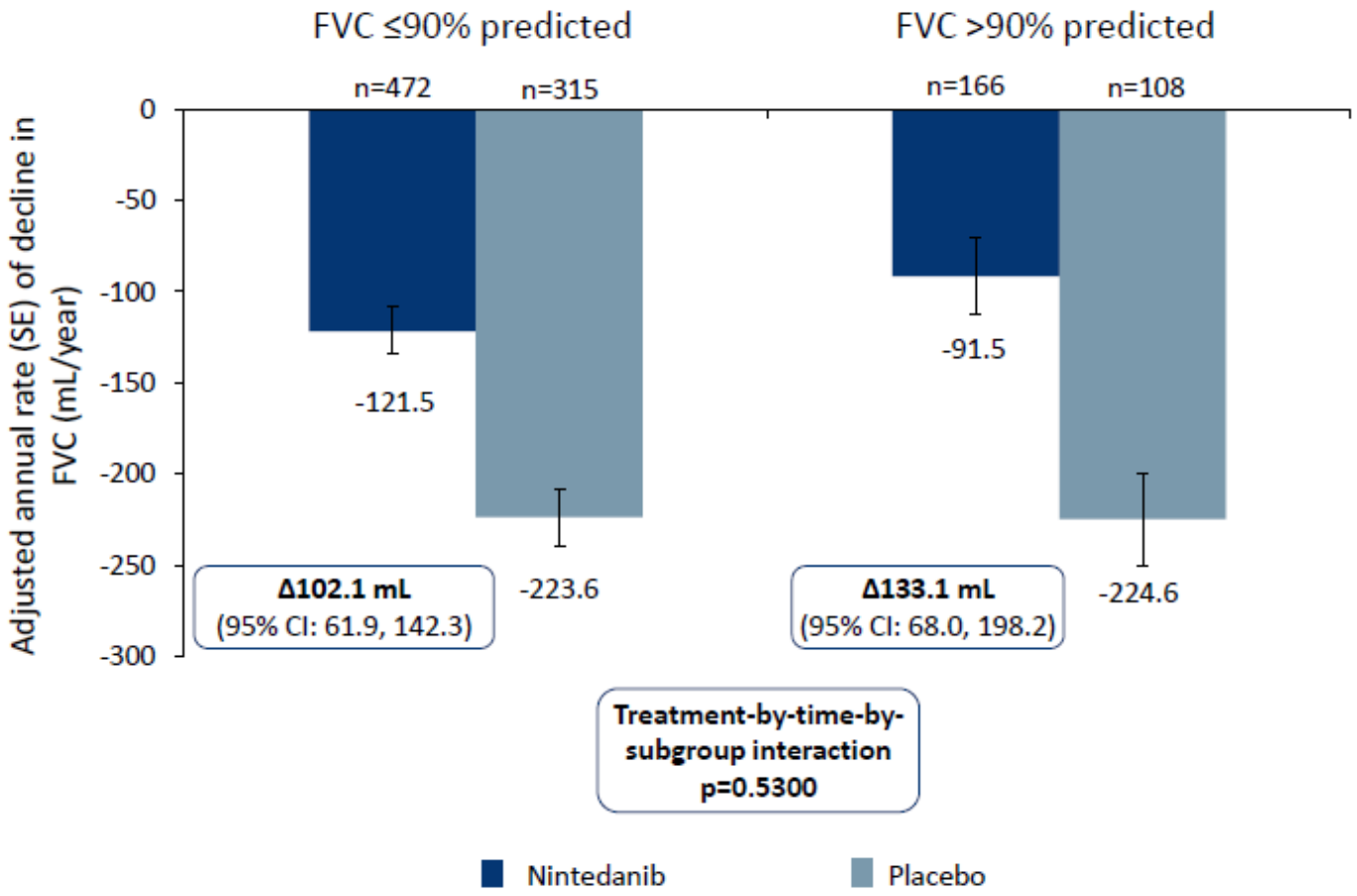
Post-hoc subgroup analyses of patients with baseline FVC ≤90% versus >90% of pred.

Baseline characteristics

	FVC ≤90% predicted		FVC >90% predicted	
	Nintedanib (n=472)	Placebo (n=315)	Nintedanib (n=166)	Placebo (n=108)
Age, years, mean (SD)	66.1 (8.1)	66.8 (8.0)	68.2 (8.0)	67.5 (7.6)
Male, n (%)	386 (81.8)	259 (82.2)	121 (72.9)	75 (69.4)
Race, n (%)				
White	273 (57.8)	187 (59.4)	87 (52.4)	61 (56.5)
Asian	140 (29.7)	91 (28.9)	54 (32.5)	37 (34.3)
Former or current smoker, n (%)	343 (72.7)	226 (71.7)	121 (72.9)	75 (69.4)
FVC, mL, mean (SD)	2505 (610)	2491 (598)	3306 (821)	3420 (945)
FVC, % predicted, mean (SD)	71.5 (10.7)	70.8 (10.6)	103.1 (11.0)	103.9 (12.4)
FEV_1/FVC ratio, %, mean (SD)	82.5 (5.5)	82.7 (5.8)	79.2 (6.0)	78.7 (5.6)
DL_{CO}, % predicted, mean (SD)	45.5 (13.1)	45.1 (13.2)	52.8 (13.3)	52.3 (12.6)
SGRQ total score, mean (SD)*	42.0 (18.7)	42.4 (18.7)	32.2 (18.5)	31.3 (15.2)

pooled data from the two INPULSIS®trials, unpublished

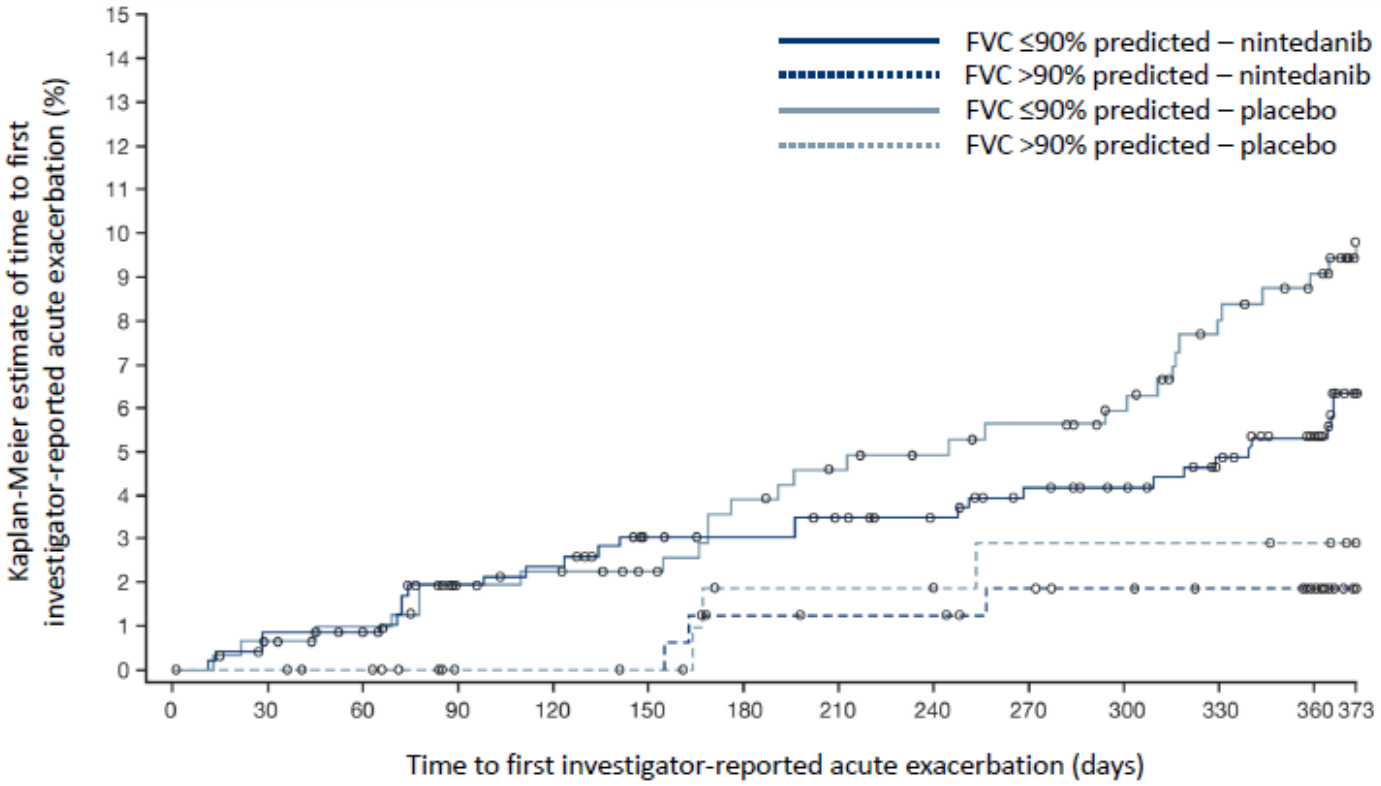
Annual rate of decline in FVC



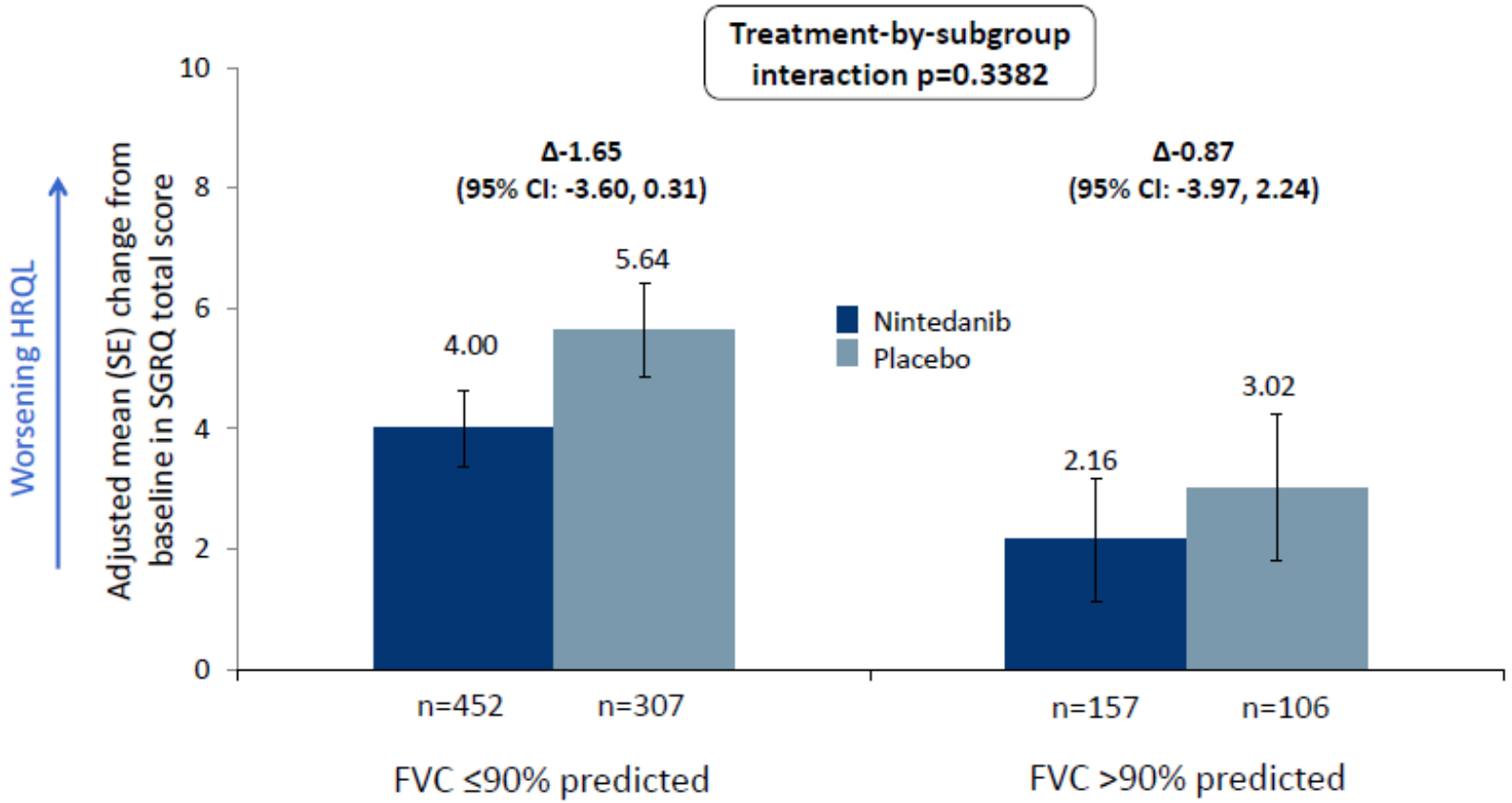
Proportion of patients with an acute exacerbation and hazard ratio for time to first event

	FVC ≤90% predicted		FVC >90% predicted	
	Nintedanib (n=472)	Placebo (n=315)	Nintedanib (n=166)	Placebo (n=108)
Patients with ≥1 acute exacerbation, n (%)	28 (5.9)	29 (9.2)	3 (1.8)	3 (2.8)
HR (95% CI)	0.66 (0.39, 1.11)		0.46 (0.09, 2.48)	
Treatment by subgroup interaction	0.9560			

Time to first acute exacerbation



Change from baseline in SGRQ total score at week 52



Safety and tolerability

Patients, n (%)	FVC ≤90% predicted		FVC >90% predicted	
	Nintedanib (n=472)	Placebo (n=315)	Nintedanib (n=166)	Placebo (n=108)
≥1 adverse event(s)	453 (96.0)	278 (88.3)	156 (94.0)	100 (92.6)
≥1 severe adverse event(s)	137 (29.0)	81 (25.7)	37 (22.3)	18 (16.7)
≥1 adverse event(s) leading to treatment discontinuation	87 (18.4)	46 (14.6)	36 (21.7)	8 (7.4)
≥1 serious adverse event(s)	156 (33.1)	99 (31.4)	38 (22.9)	28 (25.9)
Fatal adverse event(s)	33 (7.0)	29 (9.2)	4 (2.4)	2 (1.9)

Messages from this subgroup analyses

- The annual rate of decline in FVC in the placebo groups was similar in patients with marginally impaired lung function and in patients with more advanced lung function impairment

- Nintedanib slowed the decline in lung function independent of degree of lung function impairment

- The effect of nintedanib on time to first acute exacerbation and change in SGRQ total score was consistent between the subgroups

Summary I

- At present, we don't have the definition of early treatment and any direct evidence for early treatment in IPF
- Even interstitial lung abnormalities were associated with clinical outcome (mortality)
- Age, important predictor for prognosis
  - Early treatment a patient with younger age may be more beneficial

Summary II

- We don't have powerful tools to predict the clinical course of individual patient with IPF
  - It means the Risk of "wait and see"

- Recent two landmark trials suggested data of early treatment rather than delayed treatment
  - Study population: so called mild to moderate subgroup and not-longstanding IPF patients

- Indirect evidence for early treatment
  - From subgroup analyses

My conclusions

Considering
the poor prognosis of IPF
and lack of alternative therapies,

It makes sense to introduce therapy

as early as possible