호흡기내과의사를 위한 Respiratory Review of 2013

Interstitial Lung Diseases

가톨릭대학교 의과대학
호흡기 내과 김용현

A Multidimensional Index and Staging System for Idiopathic Pulmonary Fibrosis.

Ann Intern Med. 2012;156:684-691

- **Patients with IPF**
  - widely variable clinical courses and survival
  - 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.

Methods

- **Study patients (2001 – 2010)**
  - The derivation cohort: 228 patients in UCSF Lung Disease Program's longitudinal cohort
  - The validation cohort: 330 patients, the Mayo Clinic at Rochester (n=208) and the Morgagni-Pierantoni Hospital (n=122)

- **The primary outcome;**
  - Mortality (Lung transplantation was treated as a competing risk)

Methods

- **Retrospectively screened 4 potential predictors of mortality by using competing- risks regression modeling**
  - Predictor Variables (Candidates): Age, sex, body mass index, smoking status, use of long-term oxygen therapy, FVC, FEV1, total lung capacity, and DLCO

- **Developed an individual risk calculator (the GAP calculator) and a simple point-score model/staging system (the GAP index and staging system) on the basis of 4 predictors.**

- **Retrospectively validated both these systems**

Results

- 4 variables in the final model;
  - **gender(G), age (A), and 2 physiology variables (P) (FVC and DLCO)**

- GAP calculator (a model using continuous predictors) and GAP index (a simple point-scoring system) performed similarly in derivation (c-index of 70.8 and 69.3, respectively) and validation (c-index of 69.1 and 68.7, respectively)

- The GAP models performed similarly in pooled follow-up visits (c-index ≥71.9).

- 3 stages (stages I, II, and III) were identified based on the GAP index with 1-year mortality of 6%, 16%, and 39%, respectively.

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).

Calculating mortality risks by using the GAP calculator (1)

Step 1: Calculate S

S = [0.337 (GENDER) – 0.015 (FVC – 68.464) + 0.092 (AGE1 – 67.676) – 0.052 (AGE2) + 2.237 (DLCO1) + 0.024 (DLCO2)] x 0.909

Where:

1) GENDER =
   a. 0.293 if the patient is male
   b. –0.707 if the patient is female
2) FVC = forced vital capacity, *% predicted*
3) AGE1 = patient's age, *y*
4) AGE2 = refer to the table below. Enter the value of AGE2 that corresponds to the patient's age.

AGE	AGE2	AGE	AGE2	AGE	AGE2	AGE	AGE2
≤50	0	60	0.236	70	6.345	80	22.043
51	0	61	0.408	71	7.625	81	23.739
52	0	62	0.648	72	9.009	82	25.435
53	0	63	0.968	73	10.481	83	27.130
54	0	64	1.378	74	12.027	84	28.826
55	0	65	1.890	75	13.632	85	30.522
56	0.002	66	2.516	76	15.280	86	32.217
57	0.015	67	3.266	77	16.959	87	33.913
58	0.051	68	4.153	78	18.652	88	35.609
59	0.121	69	5.183	79	20.348	89	37.304

5) $D_{LCO}1$ =
   a. 0.921 if the patient could not do the D_{LCO} test
   b. –0.079 if the patient could do the D_{LCO} test

6) $D_{LCO}2$ =
   a. –50.549 if the patient could not do the D_{LCO} test
   b. (49.451 – the patient's D_{LCO}) if the patient could do the test

<u>4 variables in the final model</u>; gender(G), age (A), and 2 physiology variables (P) (FVC and DLCO)

Calculating mortality risks by using the GAP calculator (2)

Step 2: Calculate risk using S:
1-y risk = 100 x [1 – exp(–exp (S) x 0.225)]
2-y risk = 100 x [1 – exp(–exp (S) x 0.486)]
3-y risk = 100 x [1 – exp(–exp (S) x 0.768)]

Example: 60-year-old man with an FVC of 65% predicted and a D_{LCO} of 40% predicted

Step 1: Calculate S

S = [0.337 (0.293) – 0.015 (65 – 68.464) + 0.092 (60 – 67.676) – 0.052 (0.236) + 2.237 (0.921) + 0.024 (49.451 – 40)] x 0.909 = –0.471

Step 2: Calculate risk using S

1-y risk = 100 x [1 – exp(–exp (–0.471) x 0.225)] = 13.1%

2-y risk = 100 x [1 – exp(–exp (–0.471) x 0.486)] = 26.3%

3-y risk = 100 x [1 – exp(–exp (–0.471) x 0.768)] = 38.1%

GAP calculator (a model using continuous predictors) performance

Table 2. Model Performance in the GAP Calculator (Continuous Model)

Variable	Derivation Cohort		Validation Cohort*		Combined Cohort	
	Predicted	Observed	Predicted	Observed	Predicted	Observed
C-index (95% CI)	70.8 (63.7–75.0)		69.1 (64.3–73.5)		69.5 (65.6–72.7)	
1-y mortality, %						
Stage I	5.3	2.9	5.8	6.6	6.1	4.9
Stage IIa	12.6	14.2	12.5	8.0	12.3	9.7
Stage IIb	17.7	14.7	18.1	21.6	18.0	17.1
Stage IIc	25.2	21.3	24.8	17.7	24.8	24.3
Stage III	42.3	48.2	43.3	42.1	40.3	46.1
2-y mortality, %						
Stage I	10.3	6.3	11.3	13.8	12.7	11.3
Stage IIa	23.7	28.5	23.6	21.3	24.7	21.3
Stage IIb	32.4	29.4	33.0	34.4	34.9	33.2
Stage IIc	44.1	43.3	43.6	39.4	45.9	44.5
Stage III	65.7	65.8	66.9	70.5	66.4	71.8
3-y mortality, %						
Stage I	15.4	12.5	16.9	22.7	19.2	19.8
Stage IIa	34.3	43.5	34.2	34.3	36.0	34.1
Stage IIb	45.6	42.5	46.3	56.4	49.2	51.8
Stage IIc	59.5	57.1	58.9	53.7	62.1	59.0
Stage III	80.2	75.8	81.2	77.0	81.5	76.6

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).

Useful in both clinical (guide the timing of lung transplantation) and research fields

Table 4. **Proposed Utility of the Staging System**

Stage	Clinical Utility	Research Utility
Stage I	Low risk for mortality at 1 y (5.6%) Close monitoring (every 6 mo) for evidence of disease progression may be appropriate May not require immediate listing for lung transplantation Aggressive management of symptoms and comorbid conditions	May not be ideal for mortality-driven clinical trials because of infrequent events at 1 and 2 y May be better for symptom– and quality-of-life–driven clinical trials
Stage II	Moderate risk for mortality at 1 y (16.2%) Close monitoring (every 3–6 mo) for evidence of disease progression Consider listing for lung transplantation based on patient preferences, evidence of disease progression, and individual risk assessment by using the GAP calculator	May be ideal for mortality-driven clinical trials because of the moderate number of events at 1 and 2 y
Stage III	High risk for mortality at 1 y (39.2%) List immediately for lung transplantation if appropriate Palliative care referral if not a transplant candidate	May not be ideal for mortality-driven clinical trials, given advanced and possibly irreversible disease Would be appropriate for trials focused on pretransplantation and palliative care

Conclusion and Discussion

- **GAP models predict mortality;**
  - 3 stages (stages I, II, and III) were identified with 1-year mortality of 6%, 16%, and 39%, respectively
  - Useful in both clinical (guide the timing of lung transplantation) and research fields
  - But do not directly predict other outcomes (ex. acute deterioration or physiologic progression)

- **The need for expanded models based on more complex baseline variables (ex. radiologic features, biomarkers and change in FVC or DLCO)**

Clinical features and outcomes in combined pulmonary fibrosis and emphysema in IPF

Chest 2013 doi:10.1378/chest.12-2403 (on line first)

- **The syndrome of combined pulmonary fibrosis and emphysema (CPFE);**
  - Defined by the presence of emphysema and parenchymal fibrosis in the same patient
  - Proposed as a phenotype of pulmonary fibrosis
- **Distinct clinical features (CPFE);**
  - A heavy smoking history, more severe dyspnea on exertion, relatively preserved lung volumes associated with disproportionate impairment of gas exchange, more severe pulmonary arterial hypertension and frequent lung cancer
  - Prognosis – inconsistent results
- **Objectives;**
  - For determine the prevalence, clinical features, and prognosis of CPFE in IPF

Methods

- **Patients**
  - IPF based on multi-disciplinary review according to established 2011 criteria
  - from two ongoing IPF cohorts (UCSF and Mayo Clinic Rochester, 2000-2010)

- **Two radiologists scored emphysema and fibrosis severity on HRCT**
  - CPFE was defined as ≥10% emphysema

Prevalence of CPFE in IPF;

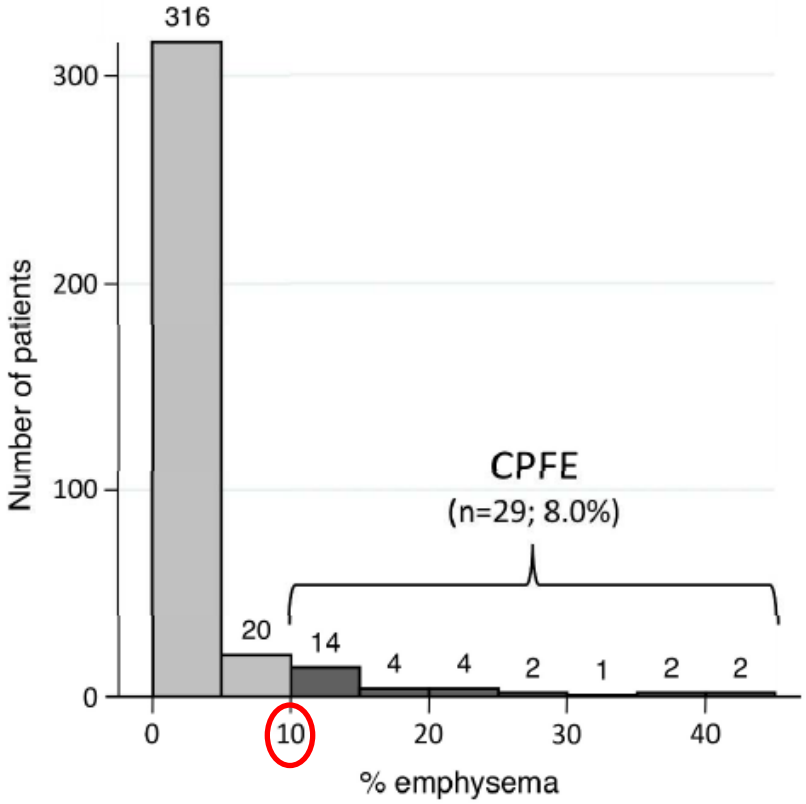


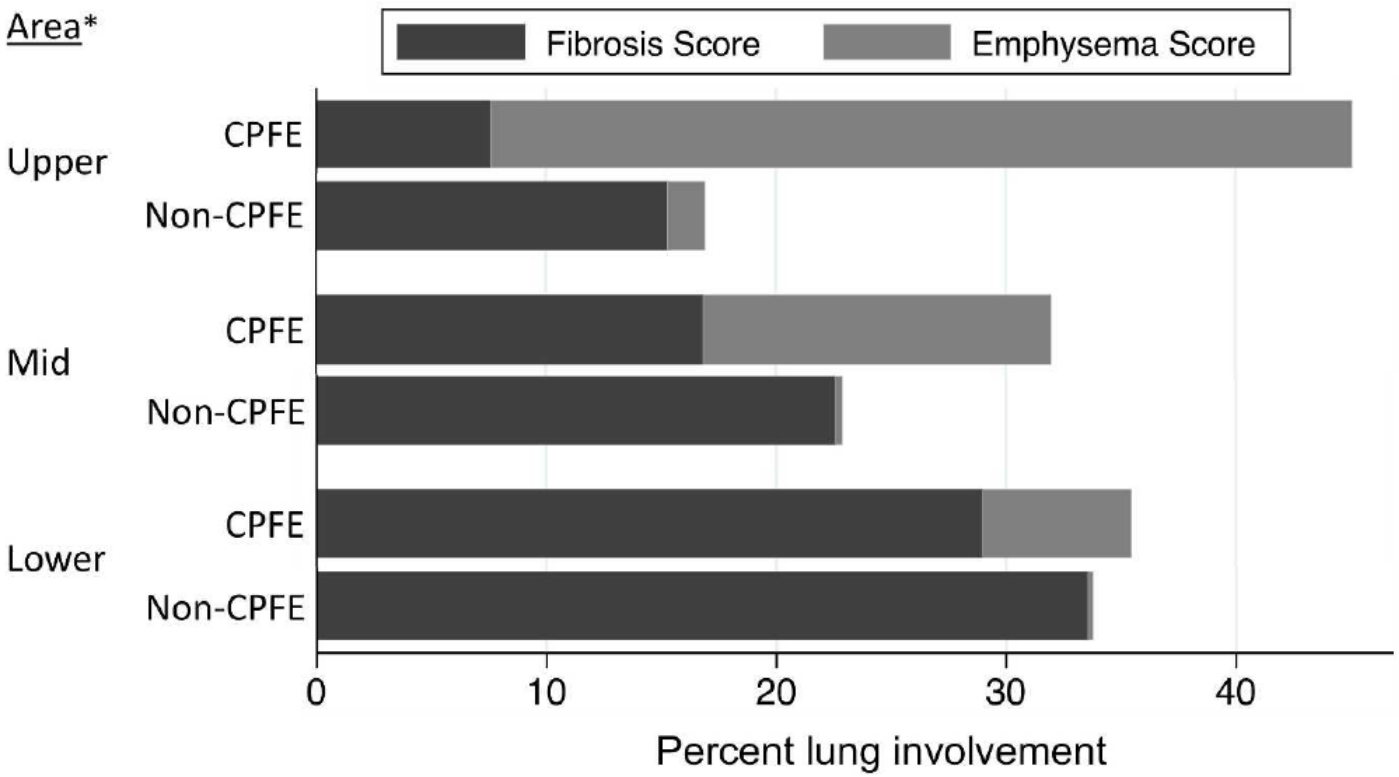
Figure 1. Distribution of emphysema score.

Scores were averaged for the two radiologists.

More extensive smoking history, greater oxygen requirements, higher pulmonary artery pressure, less restrictive physiology, and lower diffusing capacity

Variable	Non-CPFE (n = 336)	CPFE (n = 29)	P value
Age, years at baseline	69.0 (8.6)	69.9 (8.7)	0.59
Male sex	71%	69%	0.83
Body mass index, kg/m^2 *	28.1 (4.8)	28.0 (5.4)	0.91
Smoking history			
Current or former smoker	71%	100%	0.007
Pack-years*	16.1 (23.5)	46.4 (15.3)	< 0.001
Measures of disease severity			
Dyspnea score*	9.3 (5.6)	10.7 (6.3)	0.33
Long-term oxygen therapy	25%	55%	0.001
Pulmonary arterial pressure			
Echo SPAP, mmHg*	39.6 (12.7)	56.6 (20.3)	0.008
Pulmonary function			
FVC, % predicted	65.0 (16.9)	79.8 (15.7)	< 0.001
FEV_1, % predicted	71.4 (17.5)	80.3 (16.8)	0.01
FEV_1/FVC ratio*	0.83 (0.07)	0.74 (0.06)	< 0.001
TLC, % predicted	66.0 (12.9)	78.9 (14.4)	< 0.001
RV, % predicted*	66.2 (22.8)	73.8 (29.7)	0.24
DLCO, % predicted	44.4 (14.7)	37.1 (14.0)	0.02
HRCT fibrosis score	22.6 (11.4)	16.8 (10.3)	0.003

Patients with CPFE had less HRCT fibrosis



* Scores were averaged for the corresponding areas in the right and left lungs.

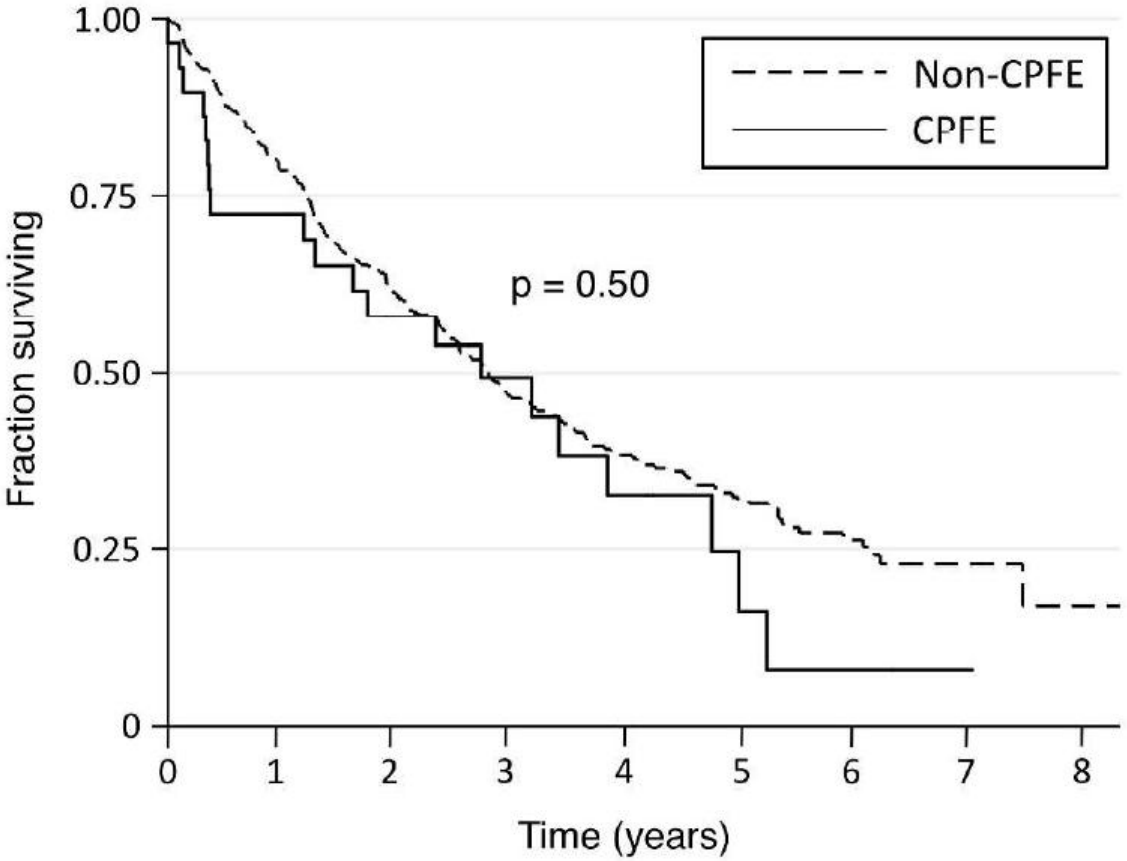
Figure 2. Mean extent of fibrosis and emphysema in upper, mid, and lower lung zone

Scores were averaged for the corresponding areas in the right and left lungs.

On adjustment for fibrosis score

Variable	Adjusted mean difference (CPFE – non-CPFE)	P value
Measures of disease severity		
Dyspnea score*	2.0 (-0.7 to 4.8)	0.15
Long-term oxygen therapy†	7.7 (3.2 to 18.6)	< 0.001
Pulmonary arterial pressure		
Echo SPAP, mmHg*	16.5 (5.0 to 28.0)	0.006
Pulmonary function		
FVC, % predicted	11.1 (5.0 to 17.2)	< 0.001
FEV_1, % predicted	5.5 (-1.03 to 11.9)	0.10
FEV_1/FVC ratio*	-0.08 (-0.12 to -0.04)	< 0.001
TLC, % predicted	10.3 (5.4 to 15.3)	< 0.001
RV, % predicted*	7.4 (-5.4 to 20.2)	0.26
DLCO, % predicted	-10.1 (-15.5 to -4.6)	< 0.001
Outcomes		
Death‡	1.14 (0.61 to 2.13)	0.69
12-month progression†	1.50 (0.38 to 5.95)	0.57

No significant difference in mortality comparing CPFE to non-CPFE IPF patients (hazard ratio 1.14, 95% CI 0.61-2.13)



Treated more as having COPD –
however, only 53% of CPFE patients used inhaled therapy

Table 3. Diagnosis and management of emphysema at presentation.

Variable	Non-CPFE (n = 175)	CPFE (n = 17)	P value
Diagnosis			
Physician-reported diagnosis of COPD/emphysema	17 (10%)	14 (82%)	< 0.001
Self-reported diagnosis of COPD/emphysema	41 (24%)	13 (76%)	< 0.001
Management			
Inhaled bronchodilator	52 (30%)	9 (53%)	0.0496
Short-acting β-agonist	31 (18%)	8 (47%)	0.004
Short-acting anticholinergic	13 (7%)	5 (29%)	0.003
Long-acting β-agonist	27 (15%)	3 (18%)	0.81
Long-acting anticholinergic	13 (7%)	4 (24%)	0.03
Inhaled corticosteroid	29 (17%)	4 (24%)	0.47
Not on inhaled bronchodilator or corticosteroid	120 (69%)	8 (47%)	0.07

Conclusion and Discussion

- **The first IPF-specific Study**;
  - Prespecified cut-off 10% emphysema in this study : need a validation of CPFE definition

    (cf. >25% emphysema in PANTHER-IPF)
  - CPFE is a phenotype of IPF or a phenotype of emphysema?

- **Therapies for COPD are effective in patients with CPFE? and How?**

Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy

Eur Respir J 2012; 40: 641–648

- **Rituximab;**
  - A chimeric (human/mouse) monoclonal antibody with a high affinity for the CD20 expressed on pre-B and B-lymphocytes -> **rapid depletion of B cells**
  - Effective in non-Hodgkin's lymphoma, rheumatoid arthritis (RA), ANCA-associated vasculitis, pulmonary alveolar proteinosis and immune thrombocytopenic purpura
- A few case series have suggest rituximab may also be effective in ILD occurring in the context of immunological over-activity

Methods

- **Review of medical records (observational study) : 8 patients**

- **Severe, progressive connective tissue disease-interstitial lung disease (CTD-ILD) patients**
  - A median DLCO 25% (range 16–32%) and FVC 45% (range 37–59%), and an anticipated survival of less than 6–12 months
  - Rituximab 1,000 mg on day 0 and day 14

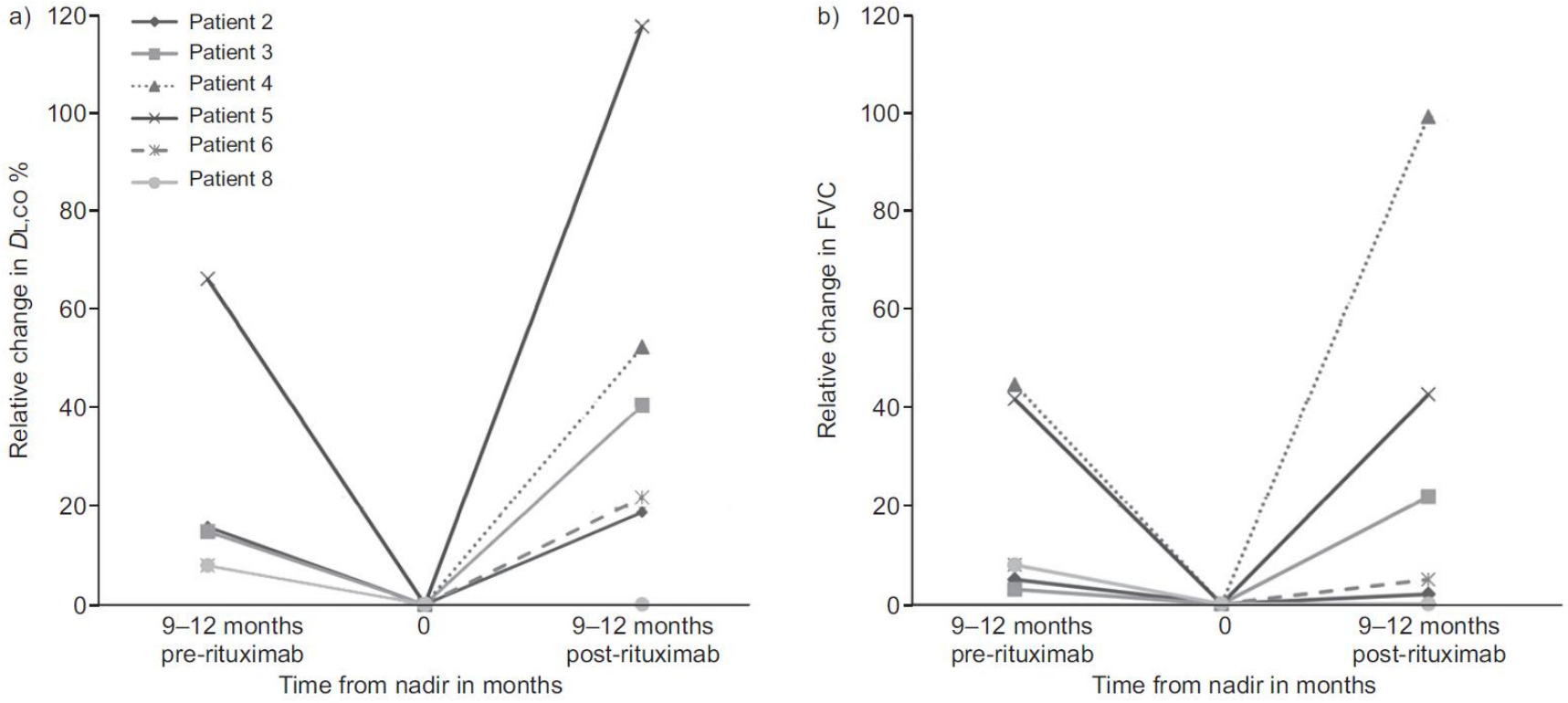
- **Evaluate the categorical variables of change** (combined with FVC, DLCO, and clinical status);
  - Change was assessed 9–12 months before and after rituximab

Severe, progressive CTD-ILD patients
All patients had failed to respond to conventional immunosuppressive therapy

TABLE 1 Baseline characteristics of patients treated with rituximab, including immunosuppressive therapy in the previous 12 months

Patient	Age/sex	HRCT pattern	Year of ILD diagnosis	Serum auto-antibody/CTD features	Pre-rituximab immunosuppression
Polymyositis/dermatomyositis					
1	45/M	Organising pneumonia/DAD	2009	ENA, anti-Ro positive DM on muscle biopsy	*i.v.* methylprednisolone
2	60/M	Fibrotic NSIP*	2003	Anti-Jo 1, myositis	MMF, prednisolone, cyclosporine *i.v.* cyclophosphamide
3	60/F	Fibrotic NSIP	2000	Anti-Jo 1, myositis rheumatoid factor	MMF, prednisolone *i.v.* cyclophosphamide
4	29/F	Fibrotic NSIP	2009	Anti-Jo 1, myositis anti-Ro	MMF, prednisolone *i.v.* cyclophosphamide
5	51/M	Fibrotic NSIP	2005	Anti-Jo 1, myositis	MMF, prednisolone *i.v.* cyclophosphamide
Undifferentiated CTD					
6	49/M	Fibrotic NSIP	2006	ANA +++ (speckled) Raynaud's, GORD	*i.v.* cyclophosphamide prednisolone, MMF
7	37/F	Organising pneumonia/DAD	2009	Rheumatoid factor anti-CCP, anti-Ro	*i.v.* methylprednisolone
Systemic sclerosis					
8	63/M	Fibrotic NSIP	1999	ATA	MMF, prednisolone

A median improvement in DLCO of 22% (range 0–119%; p=0.04) and FVC of 18% (range 0–100%; p=0.03)



2 patients - successful extubation (initially mechanically ventilated patients)

TABLE 2 Change in pulmonary function tests and symptoms for individual patients 9–12 months pre- and post-rituximab treatment

Patient no.	Pulmonary function tests				Symptoms post-rituximab	Categorical response to rituximab
	Pre-	Nadir	Post-	% change post rituximab		
Polymyositis/dermatomyositis						
1				n/a	Improved	Improved
FVC	83%	Ventilated	99%			
$D_{L,CO}$	54%		50%			
2					Improved	Improved
FVC	57%	54%	55%	+2%		
$D_{L,CO}$	32%	27%	33%	+19%		
3					Improved	Improved
FVC	61%	59%	72%	+22%		
$D_{L,CO}$	26%	22%	31%	+41%		
4					Improved	Improved
FVC	n/a	40%	80%	+100%		
$D_{L,CO}$	73%	30%	46%	+53%		
5					Improved	Improved
FVC	85%	49%	70%	+43%		
$D_{L,CO}$	48%	16%	35%	+119%		
Undifferentiated CTD						
6					Improved	Improved
FVC	56%	40%	42%	+5%		
$D_{L,CO}$	40%	32%	39%	+22%		
7					Improved	Improved
FVC	n/a	ventilated	44%	n/a		
$D_{L,CO}$	n/a		23%			
Systemic sclerosis						
8					Improved	Stable
FVC	39%	37%	37%	0%		
$D_{L,CO}$	24%	22%	22%	0%		

Conclusion and Discussion

- More severe lung function group in this study compared to other previous reports

- **Rituximab is an effective rescue therapy in some patients with severe CTD-ILD**

- This study can be criticized as observational – but, may be the only feasible option in rare and/or clinically heterogeneous ILDs

- Increased risk of infection following rituximab?
  - In a recent meta-analysis of 745 patients with RA, the rate of serious infections was not significantly different between rituximab and placebo-treated patients (2.3% versus 1.5%)

Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis (PANTHER-IPF)

N Engl J Med 2012;366:1968-77

- **A combination of prednisone, azathioprine, and N-acetylcysteine (NAC);**
  - Widely used as a treatment for idiopathic pulmonary fibrosis, conventional approach
  - On the basis of 2000 consensus-based guideline/2011 Evidence-based guidelines “weak no”
- **The safety and efficacy of this three-drug regimen is unknown**

Methods

- **Randomized, double-blind, placebo-controlled trial**
- **Study patient;**
  - Mild to-moderate IPF patients by 2011 diagnostic criteria;
  - Defined as a FVC of ≥50% and a DLCO of ≥30% of the predicted value
- **Study design;**
  - Three groups —combination therapy, NAC alone, or placebo — in a 1:1:1 ratio
    - Prednisone 0.5mg/kg -> 0.15mg/kg during a period of 25 weeks.
    - Azathioprine dose (maximum, 150 mg per day)
    - NAC 600 mg orally three times/day

A planned interim analysis; patients in the combination-therapy group had an increased rate of death

Table 2. Safety End Points.*

End Point	Combination Therapy (N=77)	Placebo (N=78)	Hazard Ratio	P Value
Death — no. (%)				
From any cause	8 (10)	1 (1)		0.01
From respiratory causes	7 (9)	1 (1)		0.02
Hospitalization for any cause — no. (%)	23 (30)	7 (9)		<0.001
Acute exacerbation — no. (%)	5 (6)	0		0.03
Serious adverse event — no. (%)	24 (31)	8 (10)		0.001
Based on Kaplan–Meier estimate at 60 wk — % (95% CI)				
Death from any cause	19.8 (9.9–37.2)	2.0 (0.3–13.6)	9.26 (1.16–74.1)	0.01
Death from any cause or hospitalization	43.6 (30.7–59.0)	16.9 (8.7–31.5)	3.74 (1.68–8.34)	<0.001
Death from any cause or ≥10% decline in FVC	36.3 (23.7–53.0)	32.4 (19.7–50.3)	1.46 (0.70–3.05)	0.30

Kaplan–Meier Curves for the Time until Death, Disease Progression, or Hospitalization

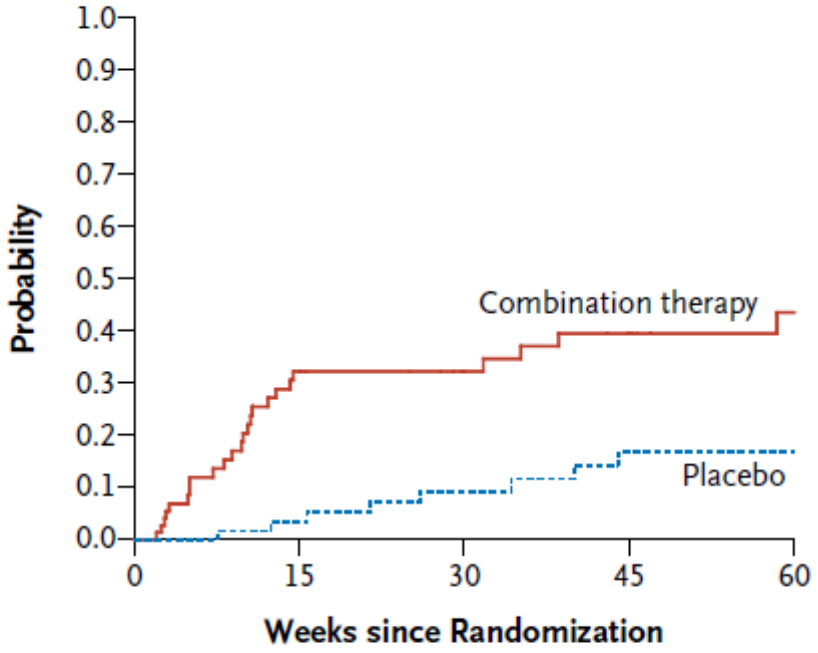
A Time to

No. at Ri
Combinat
Placebo

B Time to Death

No. at Risk
Combination the
Placebo

C Time to Death or Hospitalization



No. at Risk

Combination therapy	77	40	29	23	10
Placebo	78	55	42	26	16

Adverse Events

Adverse Event	Combination Therapy (N=77)	Placebo (N=78)	P Value
	no. of patients (%)		
Serious adverse event			
Any	24 (31)	8 (10)	0.001
Respiratory system	12 (16)	4 (5)	0.03
Infectious	5 (6)	1 (1)	0.12
Gastrointestinal system	1 (1)	3 (4)	0.62
Cardiac	3 (4)	0	0.12
General disorder*	3 (4)	0	0.12
Neoplasm	2 (3)	0	0.25
Metabolism	1 (1)	0	0.50
Musculoskeletal system	0	1 (1)	1.00
Nervous system	1 (1)	0	0.50
Reproductive system	1 (1)	0	0.50
Adverse event†			
Any	68 (88)	61 (78)	0.09
General disorder	34 (44)	21 (27)	0.03
Skin	13 (17)	4 (5)	0.02
Renal and urinary system	10 (13)	1 (1)	0.005

Conclusion and Discussion

- **Combination therapy;**
  - The primary outcome;
    - No significant difference in the change in FVC between the combination-therapy group and the placebo group (–0.24 liters vs. –0.23 liters, P = 0.85)
  - The adjudicated cause of death was related to respiratory events in 8 of the 9 patients
  - High rate of adverse events
  - 2011 Evidence-based guidelines “weak no -> **strong No** (evidence of not to use)

A Placebo-Controlled Randomized Trial of Warfarin in Idiopathic Pulmonary Fibrosis (ACE-IPF trial)

Am J Respir Crit Care Med 2012;186:88–95

- **A previous clinical trial (chest 2005)**

  survival benefit of anticoagulation (87 vs. 58%) in 56 patients with IPF who required hospitalization

- **Objectives**

  Treatment with warfarin would reduce rates of mortality, hospitalization, and declines in FVC for planned treatment period of 48 weeks?

Methods

- **A double-blind, randomized, placebo-controlled trial, performed at 22 U.S clinical centers**

- **Patients – progressive IPF patients (2011 diagnostic criteria)**
  - Definition of progressive IPF
    - worsening of dyspnea
    - physiologic deterioration defined as an absolute decline of either ≥10% FVC or ≥15% DLCO , a reduction ≥5% in arterial oxygen saturation or
    - progression of radiographic findings

Methods

- **Target INR 2.0 -3.0**

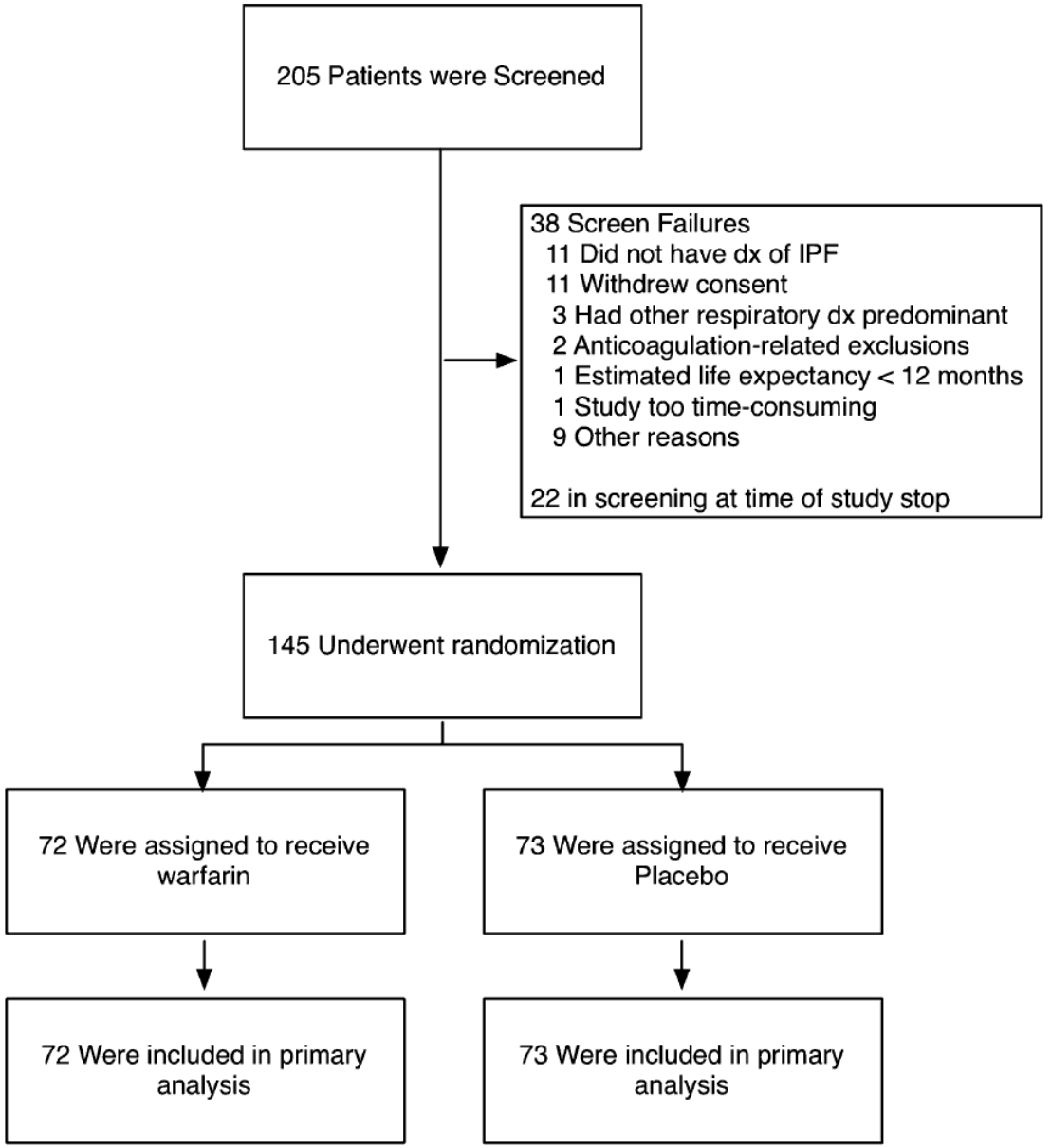
- **Primary outcome**

  The composite outcome of time to death, hospitalization (non-bleeding, non-elective), or a 10% or greater absolute decline in FVC

- **Secondary outcome**

  Rates of mortality, hospitalization, respiratory-related hospitalization, acute exacerbation, bleeding, cardiovascular events, and changes over time in FVC, 6-minute walk test distance, DLCO, plasma fibrin D-dimer levels, and quality of life (QOL) assessments

The patients Enrollment

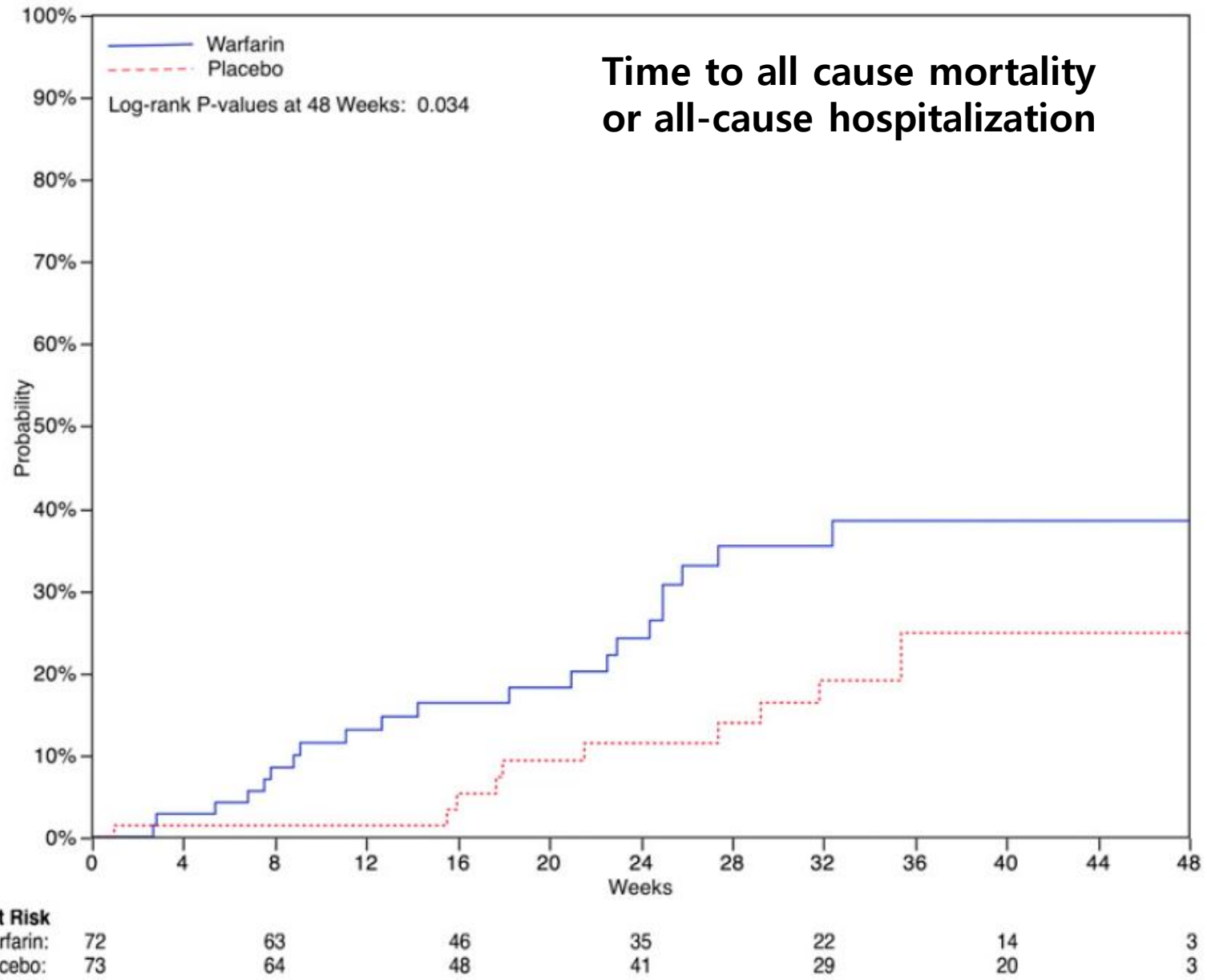


The warfarin group;
Associated with greater all-cause mortality
(14 vs. 3; P= 0.005 / adjusted hazard ratio, 4.85)

No significant treatment effects observed in the physiologic secondary endpoints (FVC, 6-minute walk distance, DLCO) or in the QOL indicators

	Warfarin (*N* = 72)*	Placebo (*N* = 73)*	Log-Rank *P* Value	Adjusted Hazard Ratio†
Primary endpoint	23/72 42.1% (29.6%, 57.3%)	17/73 39.0% (25.8%, 55.9%)	0.271	1.32 (0.70, 2.47)
All-cause mortality	14/72 28.1% (16.8%, 44.8%)	3/73 6.2% (2.0%, 18.1%)	0.005	4.85 (1.38, 16.99)
Combined all-cause mortality or nonelective, nonbleeding hospitalizations	21/72 38.4% (26.4%, 53.6%)	10/73 23.7% (13.4%, 40.1%)	0.020	2.12 (1.00, 4.52)
Combined all-cause mortality or ≥10% FVC drop	18/72 37.0% (24.0%, 54.2%)	12/73 25.1% (14.9%, 40.2%)	0.280	1.44 (0.69, 2.99)

A B C



Time to all cause mortality or all-cause hospitalization

# at Risk							
Warfarin:	72	63	46	35	22	14	3
Placebo:	73	64	48	41	29	20	3

Causes of death;
11/14 were respiratory-related in the warfarin group versus 3/3 in the placebo group. No deaths were attributed to bleeding

Cause of Death	Acute Exacerbation Occurred	D_{LCO} % Predicted	FVC % Predicted	Age (*yr*)
Warfarin				
Respiratory: pulmonary hypertension	No	28	75	72
Respiratory: IPF	No	14	37	78
Respiratory: IPF	No	18	33	72
Cardiovascular: myocardial infarction	No	43	61	67
Cardiovascular: sudden cardiovascular death	No	36	53	68
Respiratory: IPF	No	27	43	68
Respiratory: IPF	No	18	37	63
Respiratory: respiratory failure	No	44	86	71
Cardiovascular: sudden cardiovascular death	No	25	48	76
Respiratory: respiratory failure	No	8	39	77
Respiratory: IPF	Yes	17	44	65
Respiratory: IPF	Yes	21	58	81
Respiratory: IPF	Yes	17	37	66
Respiratory: pneumonia	Yes	36	53	69
Summary	4	25.1 ± 11.06	50.3 ± 15.51	70.9 ± 5.37
Placebo				
Respiratory: IPF	No	18	53	73
Respiratory: IPF	No	12	39	72
Respiratory: respiratory failure	Yes	16	34	69
Summary	1	15.3 ± 3.06	42.0 ± 9.85	71.3 ± 2.08

Conclusion and Discussion

- The mechanism of excess mortality in warfarin group – unknown but anyway contributed to a worsening of the underlying respiratory status

- All deaths in both treatment arms occurring among subjects with lower DLCO (less than 45%).

- **Warfarin should not be used for the treatment of progressive IPF**

Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomized controlled trial

Thorax 2013;68:155–162

- **Infections;**
  - Possible role of progression and acute decline of lung function in IPF

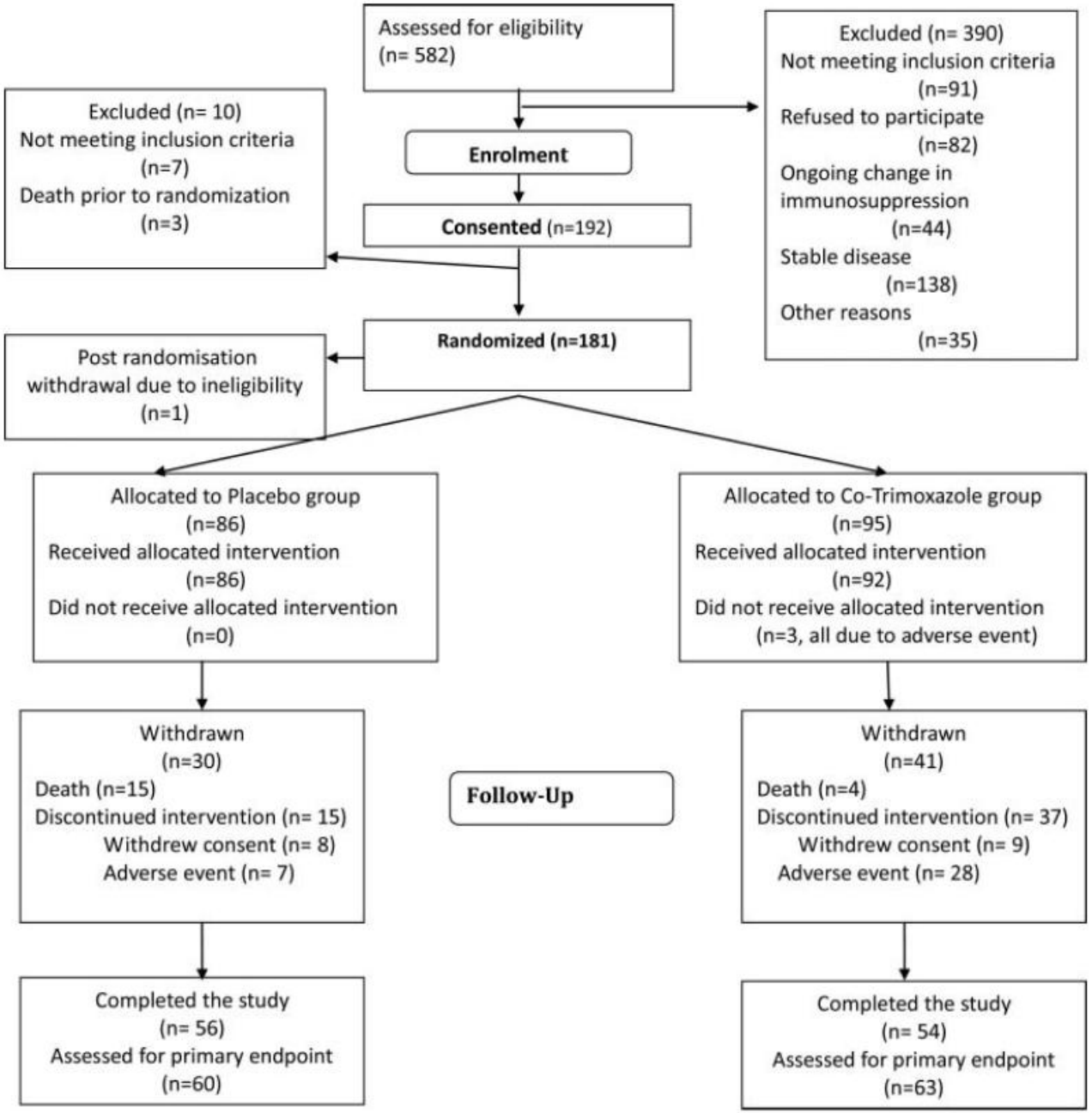
- **Co-trimoxazole;**
  - Some evidence of an immunomodulatory effect leading to a reduction in the rate of relapse in patients with granulomatosis with polyarteritis and to beneficial effects in rheumatoid arthritis.

- **Beneficial effect in IPF patients in a previous small study**

Methods

- **Patient;**
  - 181 patients with fibrotic idiopathic interstitial pneumonia (89% definite/probable IPF and fibrotic NSIP)
- **Study design;**
  - Randomized to receive co-trimoxazole 960 mg twice daily or placebo for 12 months in addition to usual care
- **Primary endpoint:**
  - forced vital capacity (FVC)
- **Secondary endpoints:**
  - diffusing capacity of carbon monoxide (DLCO), EuroQol (EQ5D)-based utility, 6-minute walk test (6MWT) and Medical Research Council (MRC) dyspnoea score
- **Tertiary endpoints:**
  - All-cause mortality and adverse events

Patients


Assessed for eligibility
(n= 582)
Excluded (n= 390)
Not meeting inclusion criteria
(n=91)
Refused to participate
(n=82)
Ongoing change in
immunosuppression
(n=44)
Stable disease
(n=138)
Other reasons
(n=35)
Excluded (n= 10)
Not meeting inclusion criteria
(n=7)
Death prior to randomization
(n=3)
Enrolment
Consented (n=192)
Randomized (n=181)
Post randomisation
withdrawal due to ineligibility
(n=1)
Allocated to Placebo group
(n=86)
Received allocated intervention
(n=86)
Did not receive allocated intervention
(n=0)
Allocated to Co-Trimoxazole group
(n=95)
Received allocated intervention
(n=92)
Did not receive allocated intervention
(n=3, all due to adverse event)
Withdrawn
(n=30)
Death (n=15)
Discontinued intervention (n= 15)
Withdrew consent (n= 8)
Adverse event (n= 7)
Follow-Up
Withdrawn
(n=41)
Death (n=4)
Discontinued intervention (n= 37)
Withdrew consent (n= 9)
Adverse event (n= 28)
Completed the study
(n= 56)
Assessed for primary endpoint
(n=60)
Completed the study
(n= 54)
Assessed for primary endpoint
(n=63)

Baseline characteristics for all individuals

Characteristic	Placebo (n=86) Mean/number (SD/%)	Co-trimoxazole (n=95) Mean/number (SD/%)
Women	21 (24.4%)	29 (30.5%)
Age (years)	70.65 (8.56)	72.38 (8.45)
Body mass index (kg/m^2)	28.61 (5.54)	28.86 (8.03)
Smoking history		
Current	1 (1.2%)	1 (1.1%)
Ex-smoker	65 (75.6%)	71 (74.7%)
Never	20 (23.3%)	23 (24.2%)
Clinical diagnosis		
UIP	81 (94.2%)	89 (93.7%)
NSIP	5 (5.8%)	6 (6.3%)
Biopsy		
Open lung	5/15 (5.8%)	3/14 (3.2%)
Video-assisted thoracic surgery	10/15 (11.6%)	11/14 (11.6%)
Pathological/radiological diagnosis		
Definite IPF (UIP histopathology, honeycombing on HRCT or in report on destroyed HRCT)	38	37
Probable IPF (Fell probability score ≥0.6)	41	46
Probable IPF (all features consistent with UIP except honeycombing on HRCT or in report on destroyed HRCT)	40	46
Time from diagnosis to randomisation (months)*	31.1 (56.8)	25.5 (37.1)
Diagnosis within 12 months	21 (24.4%)	25 (26.3%)
Co-existing emphysema	9 (10.5%)	6 (6.3%)

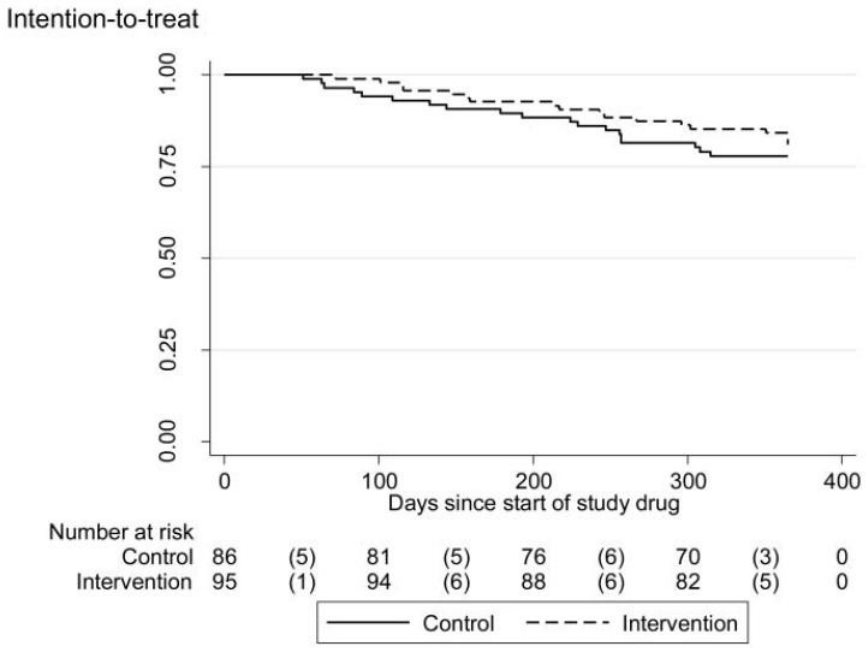
Characteristic	Placebo (n=86) Mean/number (SD/%)	Co-trimoxazole (n=95) Mean/number (SD/%)
MRC dyspnoea score		
2	17 (19.8%)	12 (12.6%)
3	28 (32.6%)	42 (44.2%)
4	31 (36.1%)	31 (32.6%)
5	10 (11.6%)	10 (10.5%)
FVC (l)	2.4 (0.8)	2.3 (0.9)
FVC percent predicted (%)	71.5 (21.0)	70.0 (21.5)
TLC (l)	4.2 (1.6)	3.8 (1.1)
TLC percent predicted (%)	66.3 (22.5)	61.8 (15.8)
D_{LCO} (mmol/min/kPa)	3.5 (1.9)	3.2 (1.6)
D_{LCO} percent predicted (%)	39.1 (12.8)	36.0 (10.0)
6 MW distance (m)	331.2 (117.6)	285.6 (96.1)
6 MW desaturation ≥4%	32/43 (74.4%)	31/38 (81.6%)
SGRQ total (units)	59.3 (17.5)	55.7 (17.9)
Treatment		
Prednisolone	52 (60·5%)	54 (56.8%)
<10 mg/day	11 (12.8%)	17 (17.9%)
10–20 mg/day	39 (45.3%)	36 (37.9%)
>20 mg/day	2 (2.3%)	1 (1%)
Azathioprine	26 (30.2%)	28 (29.5%)
Mycophenolate mofetil	3 (3.5%)	4 (4.2%)
Carbocysteine	2 (2.3%)	2 (2.1%)
Mecysteine	0 (0.0%)	1 (1.1%)
N-acetylcysteine	20 (23.3%)	25 (26.3%)
Oxygen	10 (11.6%)	12 (12.6%)
FVC% ≤60	26 (30.2%)	34 (35.8%)

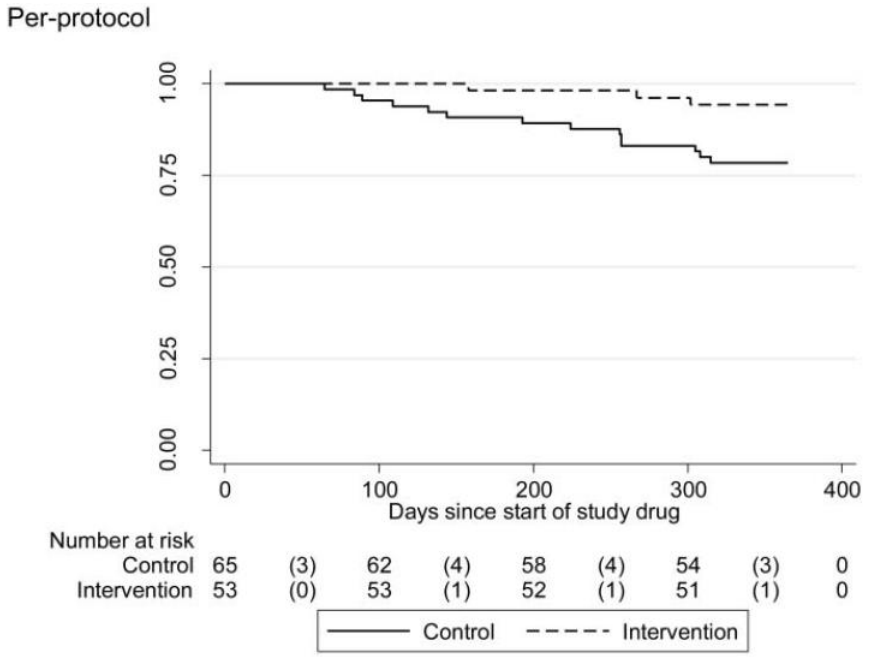
Results

- **Intention-to-treat population Analysis**
  - No effect on FVC, DLCO, 6MWT or MRC dyspnea score

- **Per-protocol population Analysis**
  - A significant improvement in health-related quality of life (EQ5D-based utility and SGRQ) and a reduction in the percentage of patients requiring an increase in oxygen therapy (OR 0.05 (95% CI 0.00 - 0.61))

A significant reduction in all-cause mortality : co-trimoxazole 3/53, placebo 14/65, HR 0.21 (95% CI 0.06 to 0.78, p=0.02)





Reduced respiratory tract infections

Table 3 Number of adverse events by category and safety group

Group	Subgroup	Placebo Number of individuals with ≥1 (%)	Co-trimoxazole Number of individuals with ≥1 (%)	p Value
Blood disorder		3 (3.5)	6 (6.5)	0.356
Cardiac disorder		9 (10.5)	3 (3.3)	0.055
Dental condition		1 (1.2)	2 (2.2)	1
Ear disorder		1 (1.2)	0 (0.0)	0.483
Eye disorder		3 (3.5)	5 (5.4)	0.722
General disorders		14 (16.3)	17 (18.5)	0.699
Gastrointestinal		21 (24.4)	41 (44.6)	0.005
	Nausea	6 (7.0)	17 (18.5)	0.022
Immune system disorder		1 (1.2)	0 (0.0)	0.483
Infection		59 (68.6)	38 (41.3)	<0.001
	Pneumonia	8 (9.3)	0 (0.0)	0.002
	LRTI	38 (44.2)	27 (29.4)	0.04
	URTI	14 (16.3)	6 (6.5)	0.039

Conclusion and Discussion

- **Co-trimoxazole;**

  No effect on lung functions but resulted in improved quality of life and a reduction in mortality in patients adhering to treatment.

  Might be effective in real life patients

- **The mechanism might be by reduction of respiratory infection;**

  Patients on immunosuppressive treatment at entry were more likely to die if they were in the control group (immunosuppression 12/35, no immunosuppression 2/30, p=0.015)

- **High rate of adverse events;**

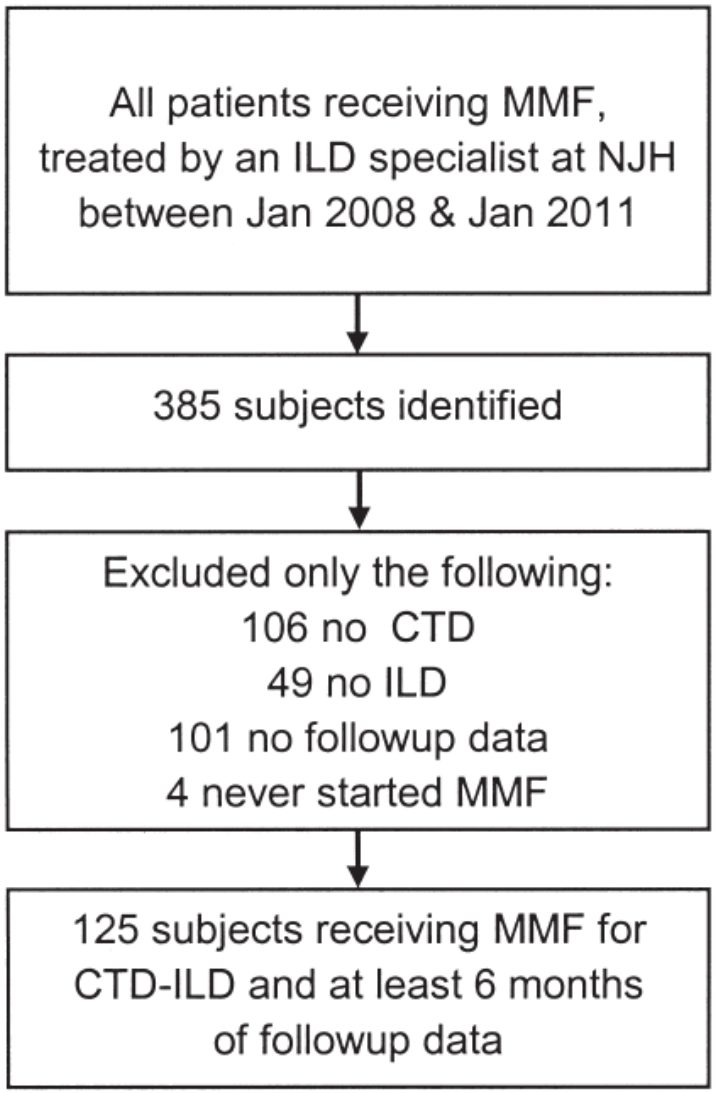
  30% (28/92) in the co-trimoxazole group and 8% (7/86) in the placebo group withdrew due to an adverse event (Nausea & skin rash) -> dose reduction ?

Mycophenolate Mofetil Improves Lung Function in Connective Tissue Disease-associated Interstitial Lung Disease

(J Rheumatol First Release March 1 2013; doi:10.3899/jrheum.121043)

- **Mycophenolate mofetil (MMF)**
  - an immunosuppressant agent that inhibits proliferative responses of T and B lymphocytes
  - for prevention of organ rejection following allogeneic transplants or used for induction and maintenance therapy of lupus nephritis

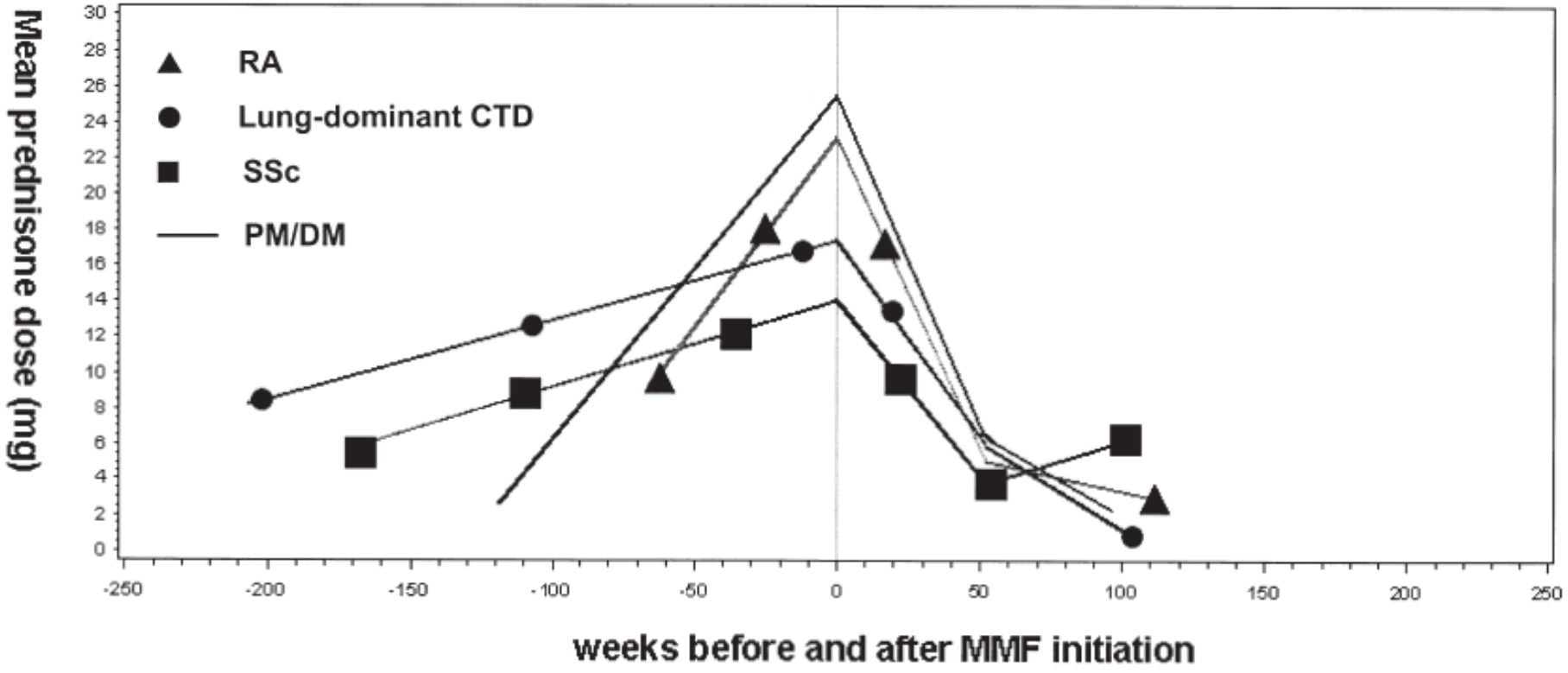
The patients



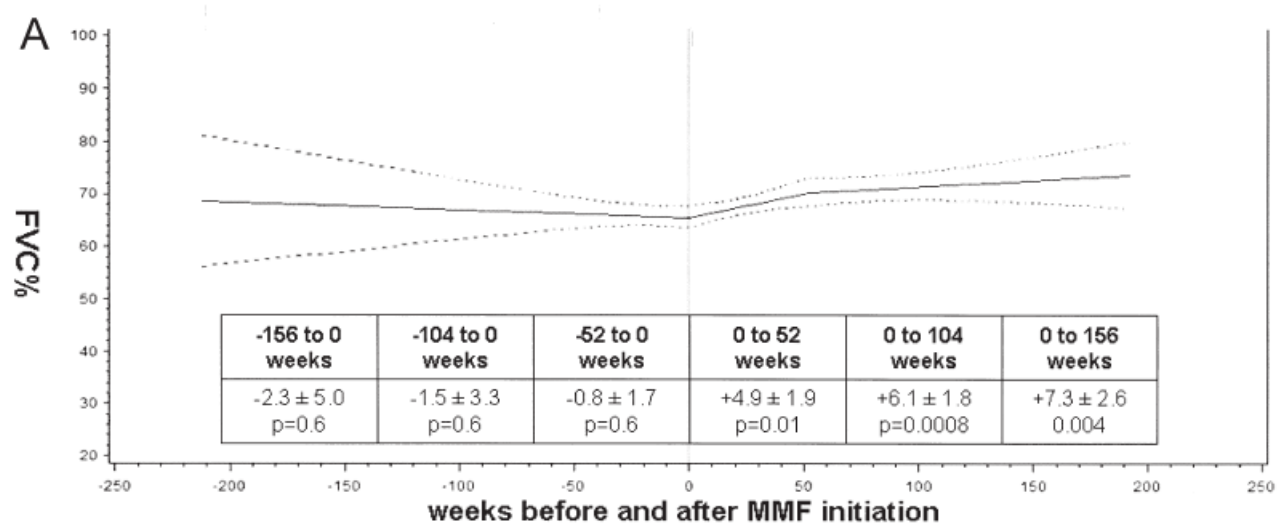
125 subjects treated with MMF for a median 897 days

Connective tissue disease, n	
Systemic sclerosis	44
Polymyositis/dermatomyositis	32
Lung-dominant connective tissue disease	19
Rheumatoid arthritis	18
Sjögren disease	5
Systemic lupus erythematosus	4
Mixed connective tissue disease	3
Mode of ILD diagnosis	
Clinical/HRCT, n (%)	74 (59)
Surgical lung biopsy, n (%)	51 (41)
Pathological pattern, n	
fNSIP	17
fNSIP + OP	10
UIP	14
UIP + OP	1
OP	8
DIP	1
Pulmonary physiology	
FVC%	66.7 ± 16.0
DLCO%	47.4 ± 16.4

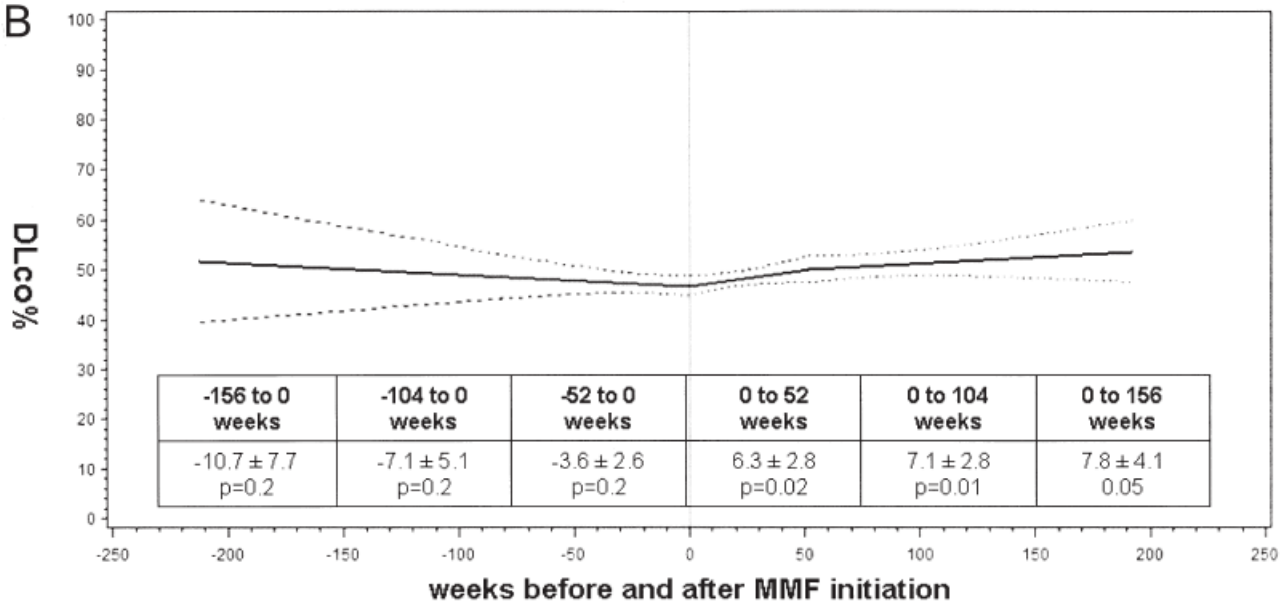
Corticosteroid sparing effect



Treatment with MMF was associated with either stable or improved pulmonary physiology over a median 2.5 years of follow up

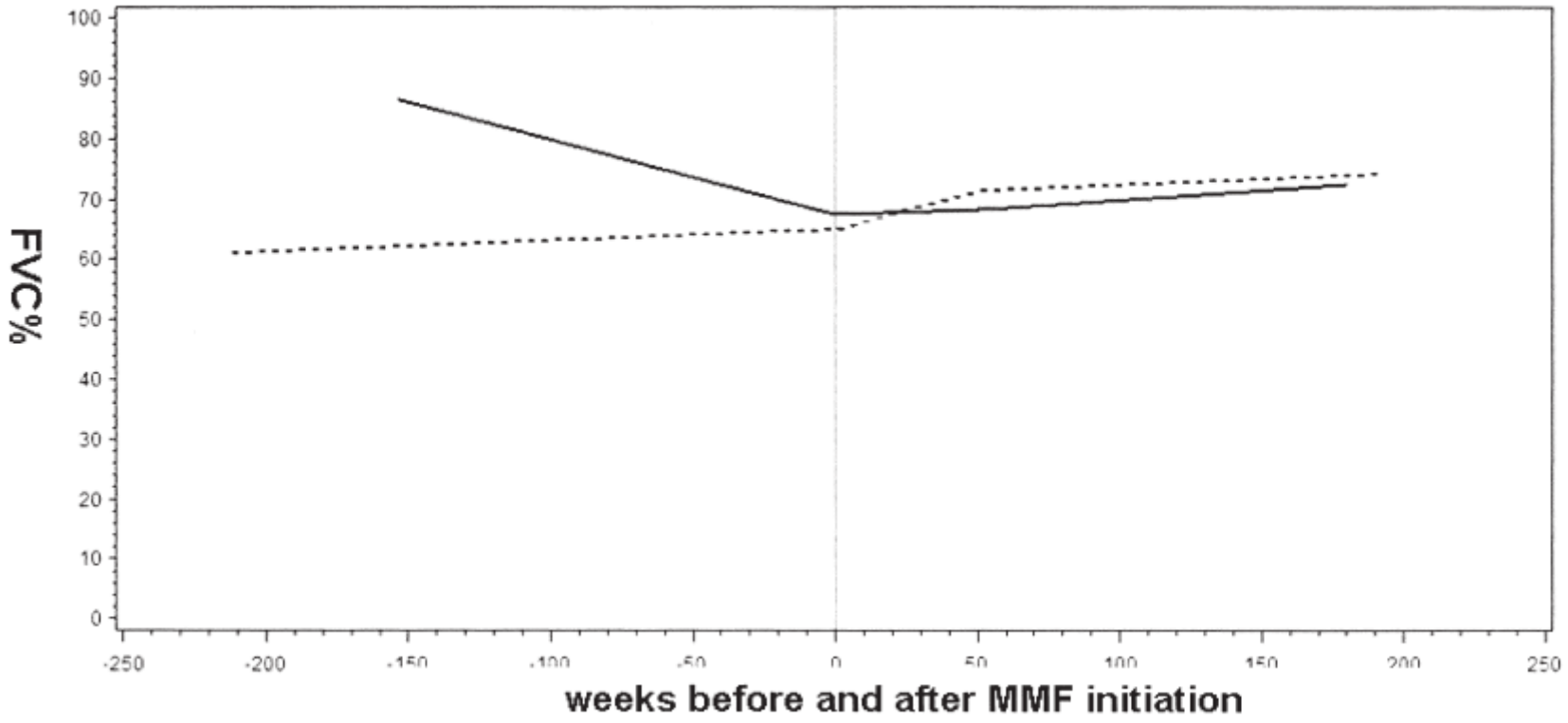


-156 to 0 weeks	-104 to 0 weeks	-52 to 0 weeks	0 to 52 weeks	0 to 104 weeks	0 to 156 weeks
-2.3 ± 5.0 p=0.6	-1.5 ± 3.3 p=0.6	-0.8 ± 1.7 p=0.6	+4.9 ± 1.9 p=0.01	+6.1 ± 1.8 p=0.0008	+7.3 ± 2.6 0.004



-156 to 0 weeks	-104 to 0 weeks	-52 to 0 weeks	0 to 52 weeks	0 to 104 weeks	0 to 156 weeks
-10.7 ± 7.7 p=0.2	-7.1 ± 5.1 p=0.2	-3.6 ± 2.6 p=0.2	6.3 ± 2.8 p=0.02	7.1 ± 2.8 p=0.01	7.8 ± 4.1 0.05

Mixed-effects model estimates for predicted FVC% in subjects with CTD-UIP or non-UIP



Conclusion and Discussion

- **The largest cohort of CTD-ILD in which the safety and effectiveness of MMF have been evaluated**
- **MMF was well tolerated and efficacious and allowed for corticosteroid tapering in a cohort of patients that had substantial exposure (41% of the sample) to cyclophophamide or azathioprine**
- **There are no published data to guide clinical decision making regarding how long to continue immunomodulatory therapy in patients with CTD-ILD**