Idiopathic pulmonary fibrosis (IPF)

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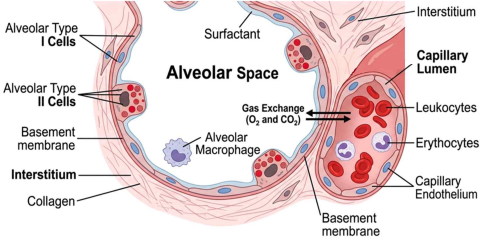
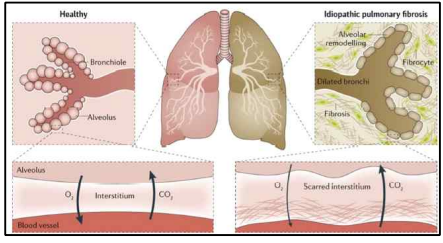
Definition of ILD

Alveolar-capillary interface



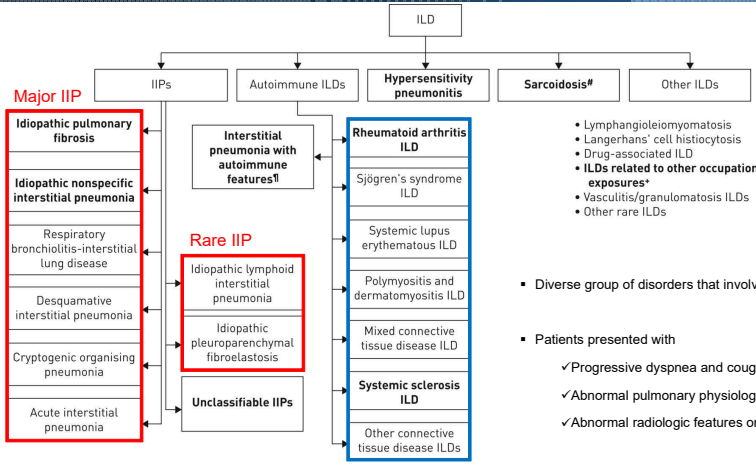
Interstitial lung disease (ILD)

- 간질을 주로 침범하는 비종양성, 비감염성 질환
- 간질 뿐 아니라 그 주위의 조직과 폐포 내에도 병변이 동반됨.
- 감염, 악성질환 등 다른 질환과의 감별이 중요!



Althobiani MA, et al. Front Med. 2024;11:1296890

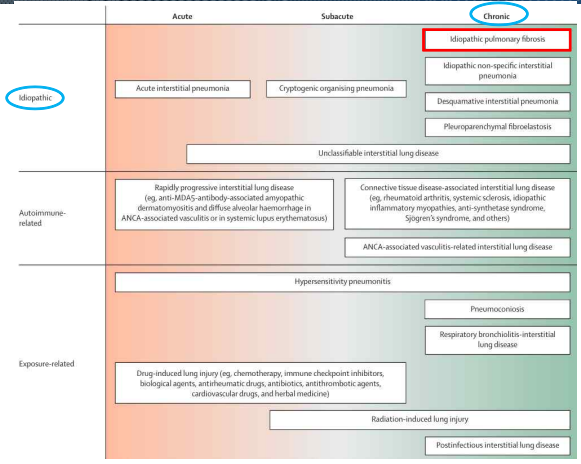
Classification of ILD



- Diverse group of disorders that involve the distal pulmonary parenchyma
- Patients presented with
  - ✓Progressive dyspnea and cough
  - ✓Abnormal pulmonary physiology
  - ✓Abnormal radiologic features on CXR and/or HRCT

Cottin V, et al. Eur Respir Rev 2018;27:180076

How to approach to ILD in real practice ?



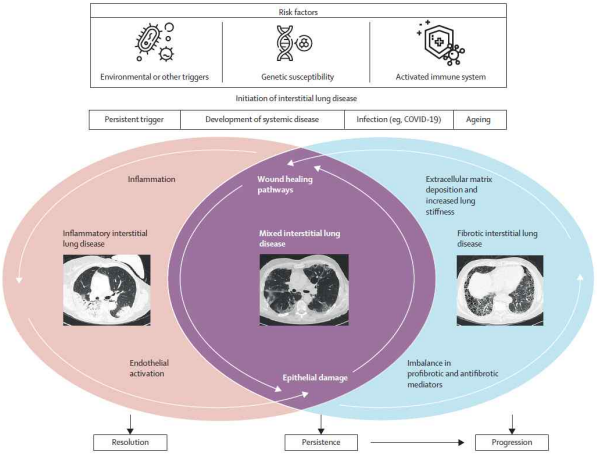
- **Onset of disease**
  - acute
  - subacute
  - chronic
- **Cause & Etiology**
  - idiopathic
  - autoimmune
  - exposure

Wijsenbeek M, et al. Lancet. 2022 Sep 3;400(10354):769-786.

Phenotype of ILD: Inflammation vs. Fibrosis

Inflammation

ex) Autoimmune disease

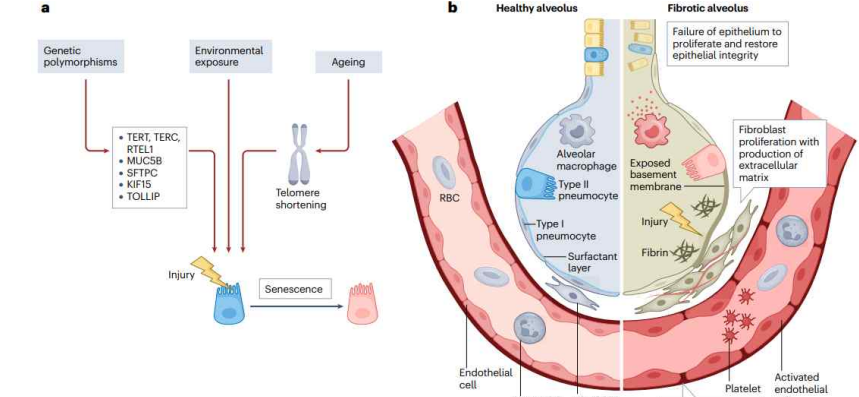


Fibrosis

ex) IPF

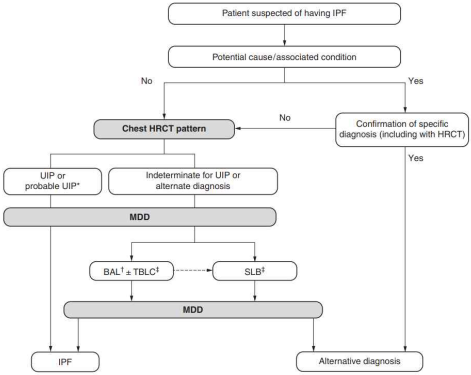
Wijsenbeek M, et al. Lancet. 2022 Sep 3;400(10354):769-786.

Key mechanisms of pulmonary fibrosis



Rieder F, et al. Nat Rev Drug Discov. 2025 Jul;24(7):543-569.

Diagnostic algorithm for IPF



IPF suspected*		Histopathology pattern†			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)‡	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)‡	Indeterminate§	Non-IPF dx
	Alternative diagnosis	IPF (Likely)‡	Indeterminate§	Non-IPF dx	Non-IPF dx

Raghu G, et al. Am J Respir Crit Care Med. 2022;205(9):e18-e47.

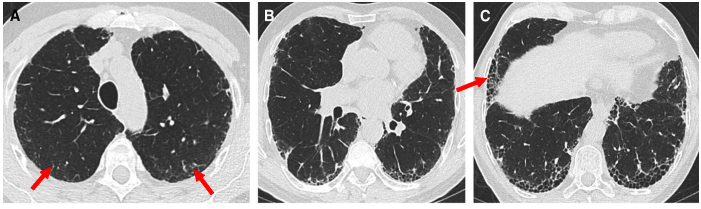
IPF : diagnostic approach

➢ **Idiopathic?**

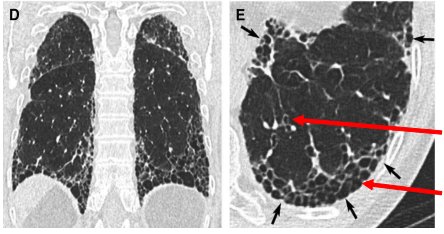
- Demographic factors : Old age, Sex, smoking history
- Family history
- Medical history & drug exposure
- Occupational exposure : asbestosis, silicosis, pneumoconiosis, infection
- Symptoms and suggestive of autoimmune disease : Sicca symptom, skin rash, hand, joint, muscular
- Systemic physical exam
- Laboratory tests : ANA, RF, anti-CCP, ANCA, etc

➢ **Chest CT and/or lung biopsy** : Usual Interstitial Pneumonia (UIP) pattern

UIP (Usual interstitial pneumonia) pattern



Reticular opacities



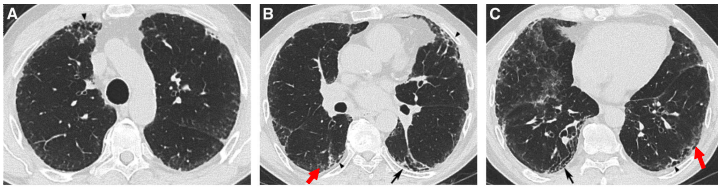
Traction bronchiectasis

Honeycombing

UIP
Subpleural and basal predominant; distribution is often heterogeneous*
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†

Raghu G, et al. Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68.

Probable UIP pattern



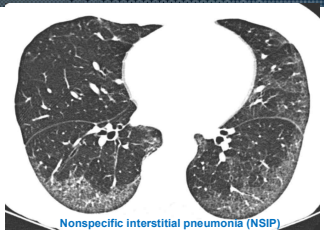
Reticular opacities

Traction bronchiectasis

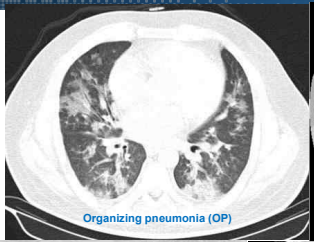
Probable UIP
Subpleural and basal predominant; distribution is often heterogeneous
Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis
May have mild GGO

Raghu G, et al. Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68.

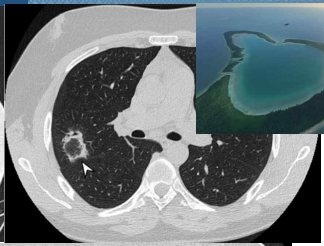
Radiologic features : alternative diagnosis

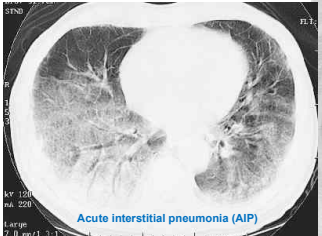


Nonspecific interstitial pneumonia (NSIP)

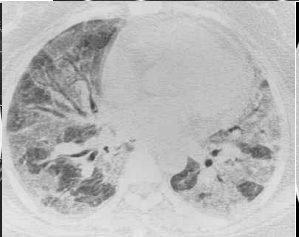


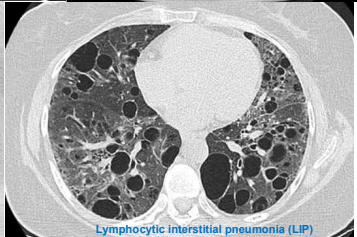
Organizing pneumonia (OP)





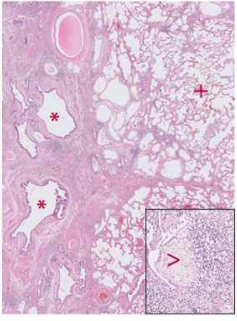
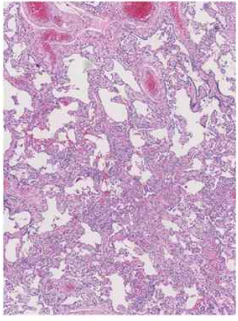
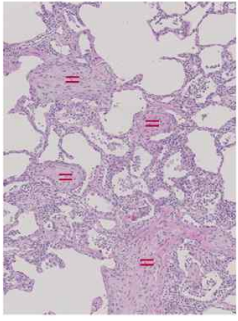
Acute interstitial pneumonia (AIP)





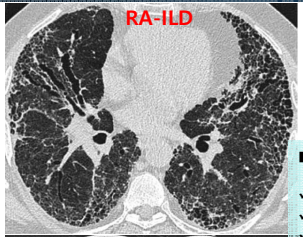
Lymphocytic interstitial pneumonia (LIP)

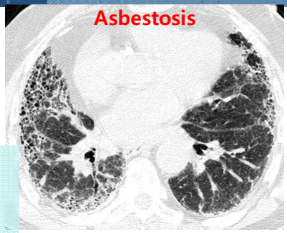
Pathologic UIP pattern

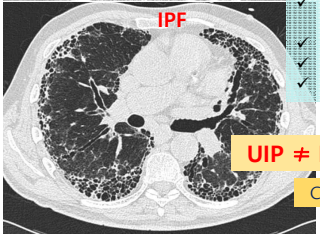
	Usual interstitial pneumonia	Non-specific interstitial pneumonia	Organising pneumonia
Typical pathology			
	Marked fibrosis, architectural distortion with or without honeycombing (*) in predominant subpleural or paraseptal distribution, presence of patchy involvement, and areas of preserved normal lung tissue (+). Presence of fibroblast foci (>) and absence of features suggesting an alternate diagnosis.	Diffuse alveolar wall thickening by uniform fibrosis (pale pink) with preservation of the alveolar architecture and mild interstitial inflammation (purple).	Patchy distribution, filling of the distal airways, and adjacent alveoli with fibromyxoid plugs (=) of granulation tissue with temporal uniformity. Relative preservation of the underlying pulmonary architecture. Mild to moderate interstitial inflammation can be present.

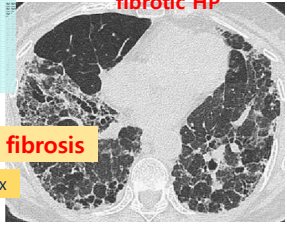
Wijsenbeek M, et al. Lancet . 2022 Sep 3;400(10354):769-786.

Differential diagnosis of UIP pattern







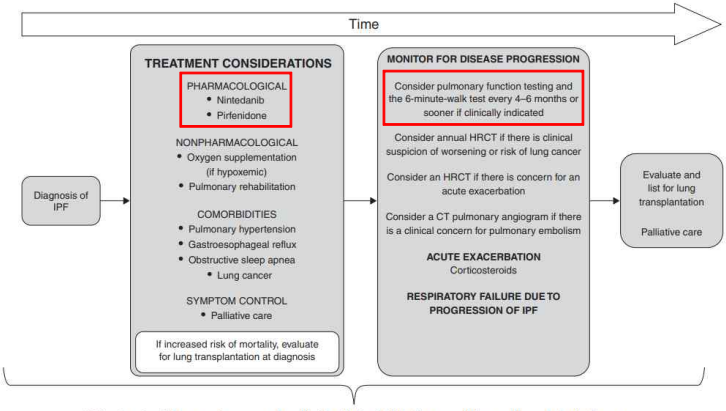


■ Differential diagnosis of UIP pattern
- ✓ CTD-ILD (esp. RA-ILD)
- ✓ Chronic HP
- ✓ Drug related pulmonary fibrosis (ex. Amiodarone)
- ✓ Asbestosis
- ✓ Progressive fibrosing ILD
- ✓ Familial IPF

UIP ≠ Idiopathic pulmonary fibrosis

Clinico-radiologic-pathologic Dx

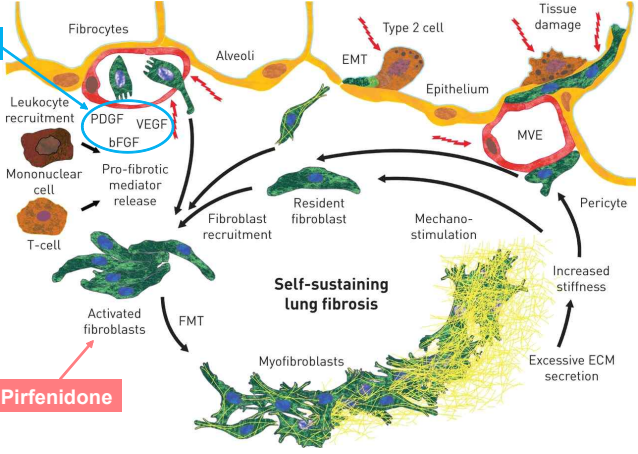
Current management of IPF



Raghu G et al. Am J Respir Crit Care Med. 2022 May 1;205(9):e18-e47.

Antifibrotic therapy in IPF

큐닌타 (일동제약)
닌테브로 (영진제약)
에피다닙 (코오롱제약)
오필드 (대웅제약)

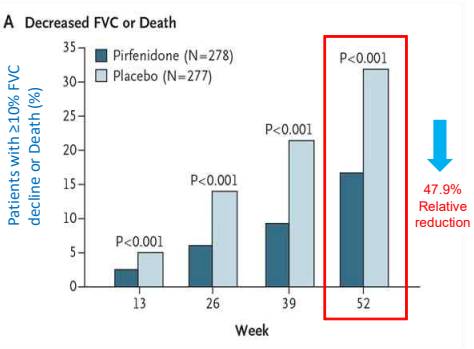


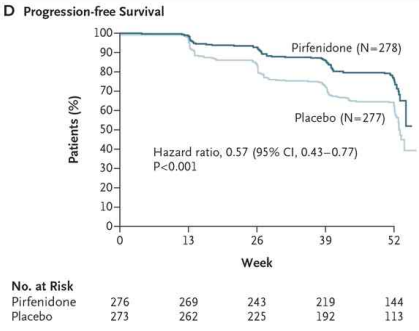
Wollin L et al. Eur Respir J 2019;54:1900161

Pirfenidone decreased disease progression in IPF

ASCEND trial

- Phase 3 RCT (N=555)
- Pirfenidone 2403mg/day or placebo for 52 weeks



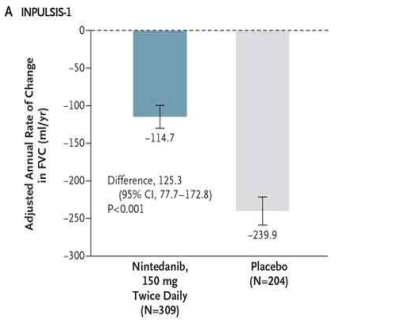


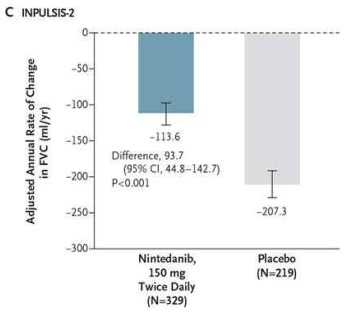
King TE Jr, et al. N Engl J Med. 2014;370(22):2083

Nintedanib decreased FVC decline in IPF

INPULSIS-I & II

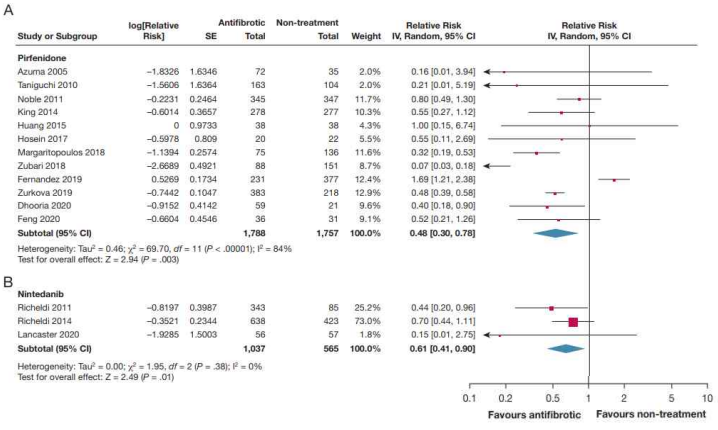
- Phase 3 RCT
- Nintedanib 150mg twice daily vs placebo, 52 week
- N=515 IPF in INPULSIS I & 551 IPF in INPULSIS II





Richeldi L, et al. N Engl J Med. 2014;370(22):2071-82

Antifibrotic therapy in mortality



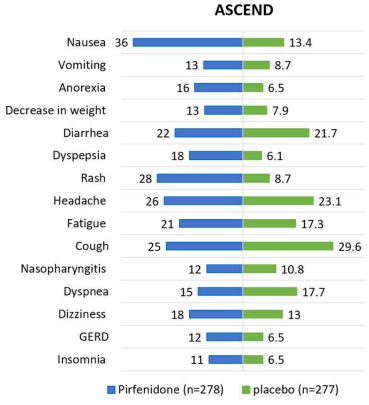
pirfenidone & nintedanib

→ risk of mortality ↓

Currently, median survival of IPF is no longer 2-3 years

Petnak T, et al. Chest. 2021;160(5):1751-1763.

Safety profile of Pirfenidone in IPF



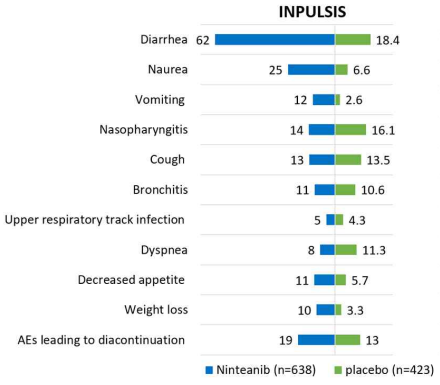
King TE Jr, et al. N Engl J Med 2014;370:2083-92.

PMS study in Korea

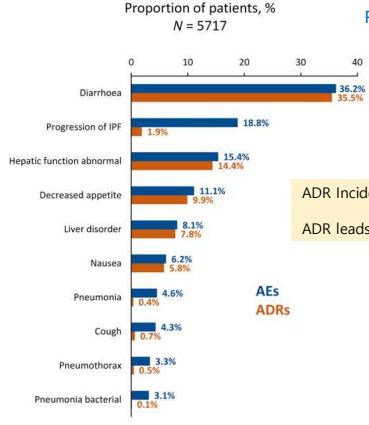
Reasons for discontinuation	Total	Advanced	Non-advanced	*p* value
Total patients, *n*	219	39	180	
Discontinued patients	119 (54.3)	29 (74.4)	90 (50.0)	0.006
Adverse event	50 (22.8)	8 (20.5)	42 (23.3)	0.704
Decreased appetite	10 (4.6)	1 (2.6)	9 (5.0)	1.000
Photosensitivity reaction	9 (4.1)	1 (2.6)	8 (4.4)	1.000
Rash	6 (2.7)	0 (0.0)	6 (3.3)	0.594
Cough	4 (1.8)	0 (0.0)	4 (2.2)	1.000
Dyspnea	4 (1.8)	1 (2.6)	3 (1.7)	0.546
Epigastric discomfort	4 (1.8)	1 (2.6)	3 (1.7)	0.546
Nausea	4 (1.8)	0 (0.0)	4 (2.2)	1.000
Pneumonia	4 (1.8)	0 (0.0)	4 (2.2)	1.000
Abdominal pain	2 (0.9)	0 (0.0)	2 (1.1)	1.000
Dizziness	2 (0.9)	0 (0.0)	2 (1.1)	1.000
Myocardial infarction	2 (0.9)	1 (2.6)	1 (0.6)	0.325
Pruritus	2 (0.9)	0 (0.0)	2 (1.1)	1.000
Pyrexia	2 (0.9)	1 (2.6)	1 (0.6)	0.325
Patient request[a]	35 (16.0)	10 (25.6)	25 (13.9)	0.069
Before October 2, 2015	28 (12.8)	8 (20.5)	20 (11.1)	0.118
After October 2, 2015	7 (3.2)	2 (5.1)	5 (2.8)	0.611
No revisit	20 (9.1)	5 (12.8)	15 (8.3)	0.365
Progression of IPF[b]	11 (5.0)	5 (12.8)	6 (3.3)	0.028
Insufficient efficacy	3 (1.4)	1 (2.6)	2 (1.1)	0.446

Chung MP, et al. Adv Ther. 2020 May;37(5):2303-2316.

Safety profile of Nintedanib in IPF



Corte T, et al. Respir Res 2015;16:116



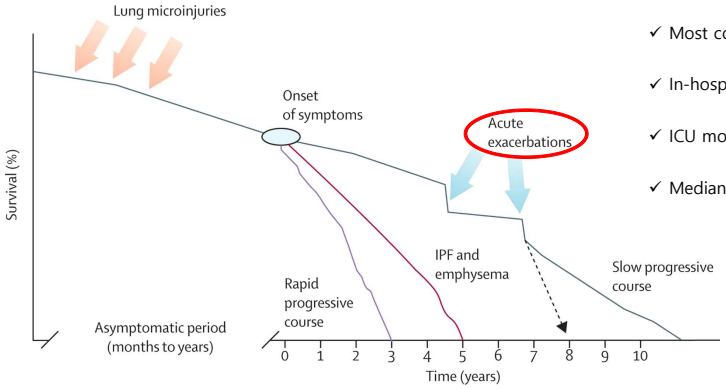
PMS study in Japan

ADR Incidence: 67.2%

ADR leads to discontinuation: 24.1%

Inoue Y, et al. Adv Ther (2025) 42:1075–1093

Acute exacerbation (AE) of IPF



- ✓ Most common cause of mortality in IPF (~46%)
- ✓ In-hospital mortality: 50%
- ✓ ICU mortality: 80-90%
- ✓ Median survival after AE : 3~4 months

King TE Jr, et al. Lancet. 2011;378(9807):1949-61
Collard HR, et al. Am. J. Respir. Crit. Care Med. 2016; 194: 265–75.
Kreuter M, et al. Eur Respir J. 2020;55(4):1901760

Incidence & risk factors of AE-IPF

Meta-analysis of cohort studies

1-year: ~9%

2-years: ~13%

3-years: ~19%

Wang Y, et al. Sci Rep. 2024;14(1):21080.

461 Korean patients with IPF

1- and 3-year incidence of 14.2% and 20.7%

Song JW, et al. Eur Respir J. 2011;37(2):356-63.

Clinical trials : lower AE than cohort studies

INPULSIS trial: nintedanib group 4.9%, placebo group 7.6%

Kreuter M, et al. Respir Res. 2019;20(1):71

- Disease severity
  - More advanced disease : low FVC / DLCO & shorter 6MWT distance
  - More dyspneic
  - Poor oxygenation: low PaO_2/FiO_2 ratio
  - Supplementary oxygen use
  - more GGO & fibrosis extent on chest CT
- Prior AE history
- Comorbidities
  - Pulmonary hypertension
  - High BMI
- Air pollution : O_3, NO_2, PM
- Viral infection

Collard HR, et al. Am. J. Respir. Crit. Care Med. 2016;194(3):265-75

Definition of AE-IPF

2007 IPF Clinical Trials Network (IPFnet)

Definition

An acute, clinically significant deterioration of unidentifiable cause in a patient with underlying IPF

Diagnostic Criteria

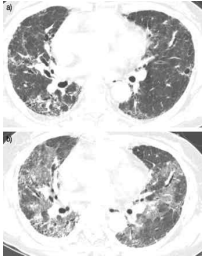
Previous or concurrent diagnosis of idiopathic pulmonary fibrosis*
Unexplained worsening or development of dyspnea within 30 days
High-resolution computed tomography with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern†
No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage‡
Exclusion of alternative causes, including the following:
- Left heart failure
- Pulmonary embolism
- Identifiable cause of acute lung injury§

2016 revised

Table 3. Proposed Revised Definition and Diagnostic Criteria for Acute Exacerbation of Idiopathic Pulmonary Fibrosis

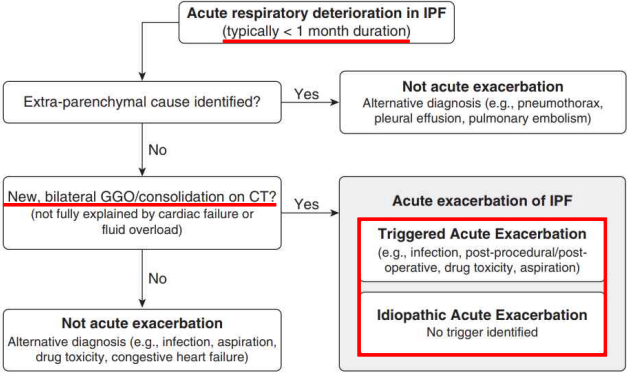
Revised definition
An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality

Revised diagnostic criteria
- Previous or concurrent diagnosis of IPF*
- Acute worsening or development of dyspnea typically <1 mo duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern†
- Deterioration not fully explained by cardiac failure or fluid overload



Collard HR, et al. Am J Respir Crit Care Med. 2007;176(7):636-43
Collard HR, et al. Am J Respir Crit Care Med. 2016;194(3):265-75.

Concept for evaluation of AE-IPF

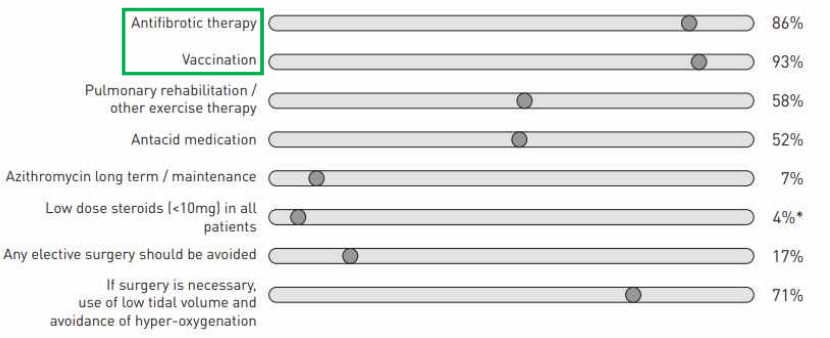


Collard HR, et al. Am J Respir Crit Care Med. 2016 Aug 1;194(3):265-75.

Preventive strategies of AE-IPF

International Expert Survey in 2017

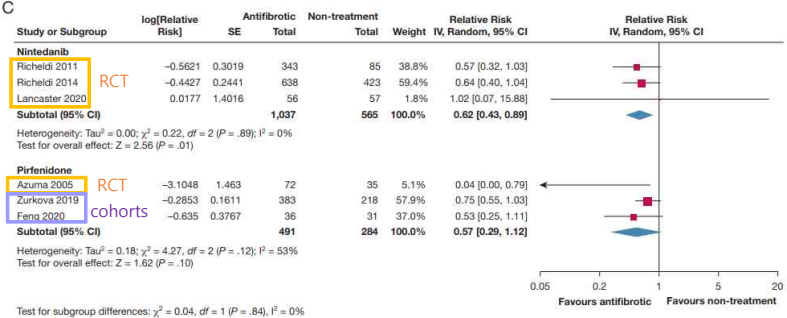
509 pulmonologists from 66 countries: Europe 42.6%, Asia 26.7%, North America 11.2%, South America 9.9% Australia 4.9%



Kreuter M, et al. Eur Respir J. 2020;55(4):1901760

Antifibrotic therapy in acute exacerbation

C



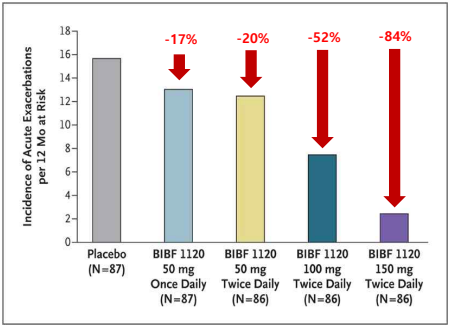
pirfenidone & nintedanib
→ risk of AE ↓

Petnak T, et al. Chest. 2021;160(5):1751-1763.

Nintedanib decreased the risk of AE-IPF

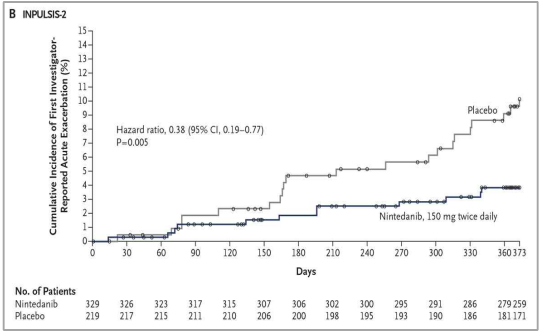
TOMORROW

- Phase 2 RCT
- Four different doses of Nintedanib (N=432)



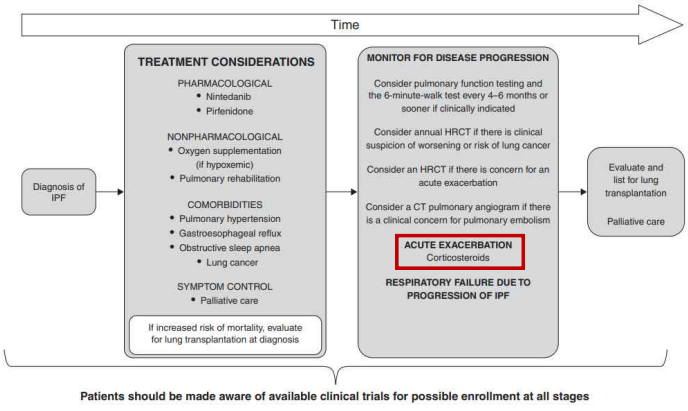
Richeldi L, et al. N Engl J Med. 2011;365(12):1079-87.

INPULSIS II



Richeldi L, et al. N Engl J Med. 2014;370(22):2071-82

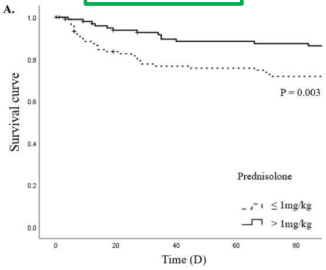
Current management of AE-IPF



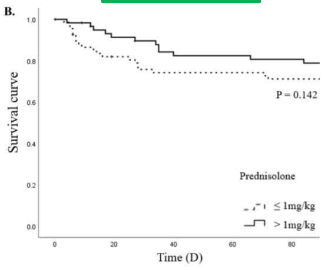
Raghu G et al. Am J Respir Crit Care Med. 2022 May 1;205(9):e18-e47.

Impact of corticosteroid in AE-ILD

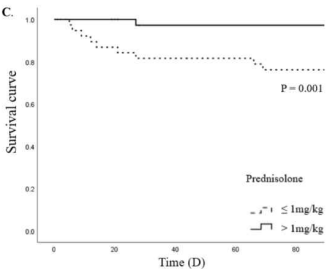
total patients (n=182)



IPF (n=117)



Non-IPF ILD (n=65)



- **Risk factors for 90-day mortality in AE-ILD**
  - ✓ Prednisolone>1 mg/kg : HR 0.221 (95% CI 0.102-0.480)
  - ✓ Initial P/F ratio : HR 0.995 (95% CI 0.992-0.999)
  - ✓ Need for MV care : HR 4.205 (95% CI 2.059-8.589)

Jang HJ, et al. Sci Rep. 2021 Mar 11;11(1):5762.

Impact of corticosteroid in AE-IPF

	Country (Year)	Sample size	Steroid regimen	Hospital mortality	Overall mortality
Farrand et al	USA (2018)	82	mPd pulse ≥500mg/day or Pd ≥ 0.5mg/kg for 2 days or more	HR: 1.31 (95% CI: 0.26-6.55) P = 0.74	HR: 6.17 (95% CI: 1.35-28.14) P = 0.019
Anan et al	Japan (2022)	153	mPd 1g/day for 3 days, then tapering - Early tapering : reduction >10% of the initial maintenance dose, within two weeks of admission	HR 0.37 (95% CI: 0.14-0.99)	
Cuerpo et al	Spain (2019)	50	Pd ≥ 55mg/day	Higher corticosteroid doses increased in-hospital mortality (OR 1.044; 95% CI: 1.006–1.085; p=0.024)	
Hyung et al	Korea (2023)	238	mPd pulse ≥250mg/day vs non-pulse 1mg/kg/day	Pulse group: 11/59 (18.6%) Non-pulse group: 65/179 (36.3%) P value: 0.018	3-month: HR 0.84 (95% CI 0.45–1.38) 12-month: HR 0.96 (95% CI 0.60–1.25)

Farrand E, et al. Respirology. 2020 Jun;25(6):629-635
Anan K, et al. Respir Res. 2022 Oct 26;23(1):291
Cuerpo S, et al. Chron Respir Dis. 2019 Jan-Dec;16:1479973119869334
Hyung K, et al. Respirology. 2024;29(3):235-242

Studies regarding CYC in AE-IPF

Study	Design	Size	Intervention	Clinical Outcome
Ambrosini et al. (2003)(37)	Single-center, retrospective study	5 patients	Steroids followed by CYC	Four patients died within one month, 1 patient lived at least 1.5 years.
Al-Hameed et al. (2004)(39)	Single-center, retrospective study	25 patients	Steroids or combination of steroids + CYC	All patients died in-hospital. One patient was discharged and returned after 30 days and died.
Parambil et al. (38)	Single-center, retrospective study	2 patients	Steroids followed by CYC	Both patients treated after biopsy. Both patients died in-hospital
Okamoto et al. (2006)(36)	Single-center, retrospective study	28 patients	Combination of steroids + CYC or Steroids + CyA	Twenty-four patients died within 4 months. Report did not specify whether the survivors received cyclophosphamide or cyclosporin. Survival rate at 1-month was 14% and 3-month was 14%.
Morawiec et al. (2011)(40)				-IPF; survival rate at at 3-month was 55%, 40%. Seven patients ival rate at 1-month nth was 100 %, and at was 71%.
Novelli et al. (2016)(35)	Single-center retrospective study	11 patients	Steroids + CYC	Survival rate at 3-month was 73%, at 6-month was 63%, at 12-month was 55%, at 18-month was 45% and at 2-year 27%.
Hozumi et al. (2019)(41)	Retrospective, multicenter study	102 patients	Steroid versus steroids plus CYC	No significant differences in 90-day survival rate between matched groups.
Aso et al. (2019)(42)	Retrospective, nationwide data base study	1847 patients	Steroids versus steroids + CYC	No significant differences between the two groups with respect to in-hospital mortality.

No robust evidence regarding benefit of CYC in AE-IPF

- EXAFIP, phase 3 RCT (N=119)
- CYC (600 mg/m^2) + high dose glucocorticoid (n=60) *vs.* Placebo + high dose glucocorticoid (n=59)

	Cyclophosphamide (n=60)	Placebo (n=59)	Difference (95% CI)	p value
Death at 3 months in the ITT population*	27/60 (45%)	18/59 (31%)	14·5 (-3·1 to 31·6)	0·10
Death at 3 months in the ITT population with available data	26/59 (44%)	18/59 (31%)	13·6 (-4·1 to 30·7)	0·13
Death at 3 months in the per-protocol population	17/42 (40%)	15/50 (30%)	10·5 (-9·6 to 30·1)	0·29

Data are n/N (%), unless otherwise specified. ITT=intention-to-treat. *The missing data for one patient have been replaced by death.

Table 2: **Primary outcomes**

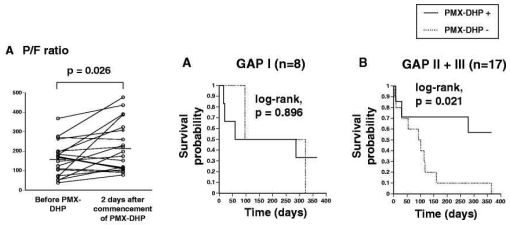
➔ Evidence against the use of cyclophosphamide in AE-IPF

Innabi A, et al. Sarcoidosis Vasc Diffuse Lung Dis. 2021;38(1):e2021002.

Naccache JM, et al. Lancet Respir Med. 2022 Jan;10(1):26-34.

Direct hemoperfusion with the polymyxin B-immobilised fibre column (PMX-DHP)

- Retrospective, single center study of AE-IPF patient (n=31): PMH-DHP (n=14), Japan
- All received steroid



➔ Treatment of AE-IPF with PMX-DHP
: tolerable
: improves short term oxygenation
: improves 12-month survival

Enomoto N, et al. BMC Pulm Med. 2015 Feb 22:15:15.

- Retrospective, cross-sectional study of AE-IPF patient (n=5616): PMX (n=199) vs high-dose mPd alone (n=5417), Japan
- All received steroid

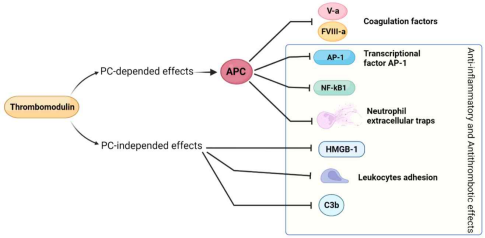
Logistic regression analyses of patients in the PMX and mPSL alone groups after the stabilised IPTW [a]

	Odds ratio	95% CI	*p* value
All patients			
In-hospital mortality	1.56	0.80–3.06	0.19
14-day mortality	1.16	0.58–2.31	0.67
28-day mortality	1.38	0.86–2.20	0.18

➔ Treatment of AE-IPF using MV
➔ : no effect on survival
➔ : no effect on length of hospital stay

N Awano et al. J Intensive Care. 2023 Oct 11:11(1):45

Thrombomodulin alfa for AE-IPF



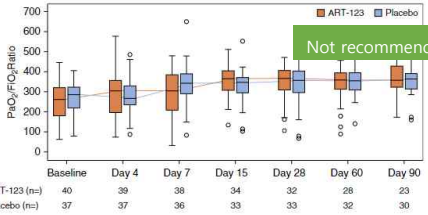
Background : several small, retrospective studies reported potential benefits

- Kataoka et al: 20 patients vs 20 control, HR 0.22 for 3mo mortality for treated group
- Isshiki et al: 16 patients vs 25 control, 3mo survival 69% vs 40%

Milone G, et al. J Clin Med. 2022;11(3):623
Kataoka K, et al. Chest. 2015;148(2):434-443
Isshiki T, et al. Respiration. 2015;89:201–207

- RCT, Japan from 2016 to 2018
- Basic Tx: High-dose corticosteroid (mPd 500-1000mg/d for 3 d), followed by Pd 0.5-1mg/kg/d for 4d
- Placebo (n=37) vs ART-123 (n=40) at a dose of 380 U/kg/d for 14 d

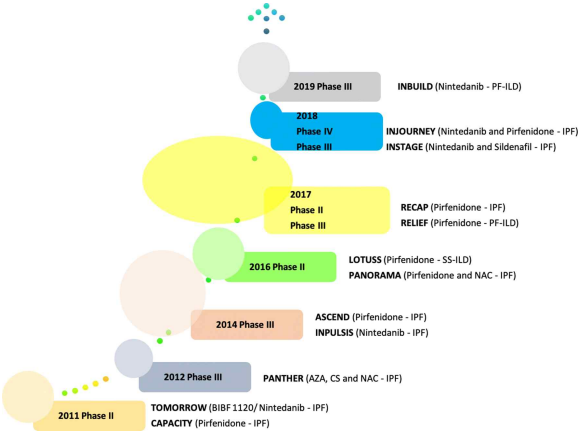
	Survival Proportion on Day 90	Estimate of Difference (95% CI*) (*Percentage Points*)	*P* Value†
ART-123	29/40 (72.5%)	−16.7 (−33.8 to 0.4)	0.0863
Placebo	33/37 (89.2%)		



Not recommended

Kondoh Y, et al. Am J Respir Crit Care Med. 2020;201(9):1110-1119.

Evolution of pharmacotherapy of IPF

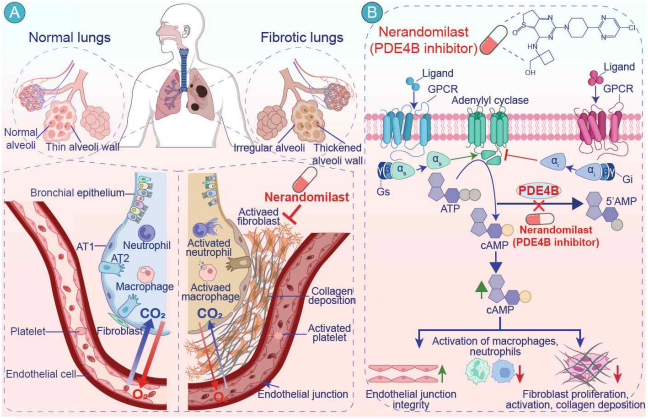


Nerandomilast

Inhaled Treprostinil

Gibson CD, et al. Lung. 2020 Aug;198(4):597-608.

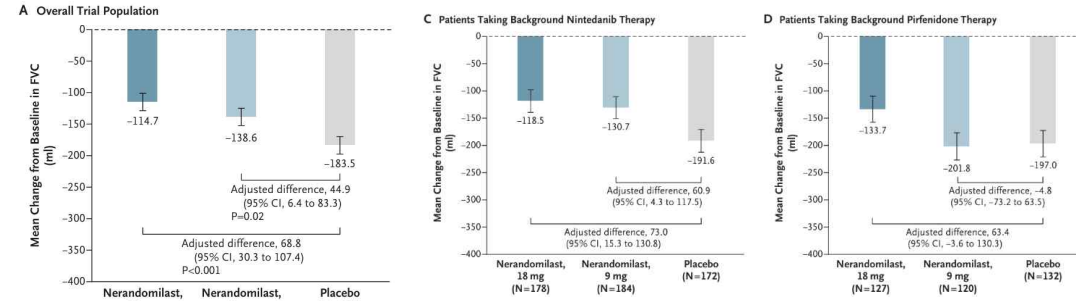
Nerandomilast: phosphodiesterase 4B inhibitor



Zhou A, et al. The Innovative Medicine 3(3): 100151, Aug 28, 2025

Nerandomilast in IPF

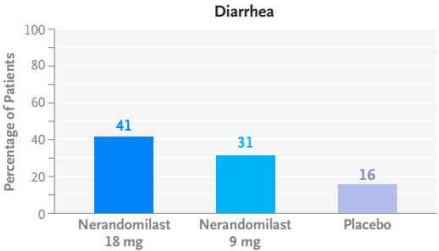
- Background treatment : Nintedanib (45.5%) Pirfenidone (32.3), no therapy (22.3%)
- FVC change in 52 weeks



Richeldi L, et al. N Engl J Med. Jun 12 2025;392(22):2193-2202

Adverse events

Diarrhea : the most frequent adverse event



Background therapy

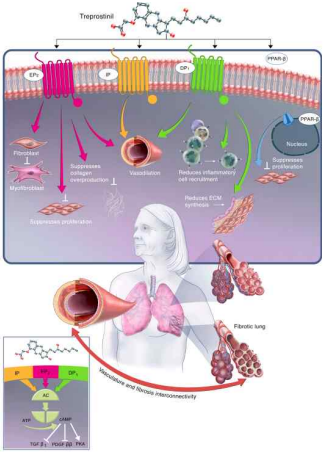
Nintedanib	110 / 178 (62)	91 / 184 (49)	46 / 173 (27)
Pirfenidone	29 / 127 (23)	16 / 120 (13)	10 / 133 (8)
None	23 / 87 (26)	15 / 88 (17)	7 / 87 (8)
Leading to discontinuation	6.1%	1.8%	0.5%

Adverse events led to permanent discontinuation

- 14.0% of the nerandomilast 18 mg group
- 11.7% of the nerandomilast 9 mg group
- 10.7% of the placebo group

Richeldi L, et al. N Engl J Med. Jun 12 2025;392(22):2193-2202

Inhaled Treprostinil



Mechanism of action

1. Activation of prostaglandin E type 2 (EP2), prostacyclin receptor (IP), prostaglandin D type 1 (DP1) receptor

→ *Vasodilation*

→ Inhibits fibroblast to myofibroblast differentiation

→ Suppresses *fibroblast proliferation*

→ Suppresses *collagen overproduction*

→ Reduces *inflammatory cell recruitment* & reduces *ECM synthesis*

2. Activation of the nuclear receptor, peroxisome proliferator-activated receptor b (PPAR-β)

→ Suppresses *fibroblast proliferation*

Kolb M, et al. Adv Ther. 2022 Sep;39(9):3881-3895.

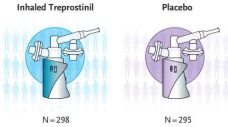
Inhaled Treprostinil for IPF

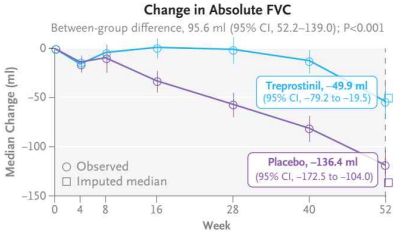
TETON trial

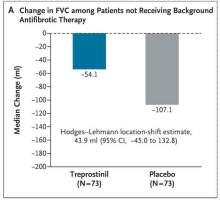
Phase 3, 593 IPF patients

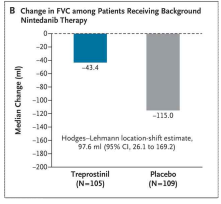
Inhaled Treprostinil vs placebo (12 breaths four times daily), over 52 weeks

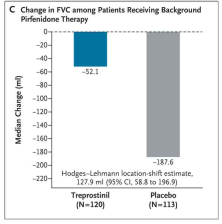
Background antifibrotic therapy allowed (75.4%; Nintedanib 36.1%, Pirfenidone 39.3%)





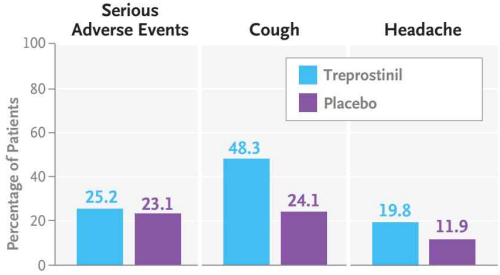






Nathan ST, et al. N Engl Med. 2026 Mar 11. Online ahead of print

Adverse events



Adverse events leading to discontinuation

- 50 / 298 (16.8%) in Treprostinil
- 37/295 (12.5%) in placebo

Nathan ST, et al. N Engl Med. 2026 Mar 11. Online ahead of print

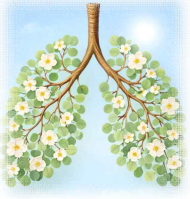
Summary

- **Diagnosis**
  - ✓ Thorough assessment: History, physical exam, and exposure history
  - ✓ HRCT: the cornerstone of diagnosis
  - ✓ MDD: Gold standard for accurate diagnosis

- **Anti-fibrotic therapy**
  - ✓ Slower disease progression
  - ✓ Better survival

- **Acute exacerbation (AE)**
  - ✓ High mortality and crucial to recognize and manage appropriately

- **Future perspectives**
  - ✓ Novel targets and new strategies



Thank you for your attention