15 June 2020 Webinar on NEW Normal in IPF

Medical Management of IPF in Present Times

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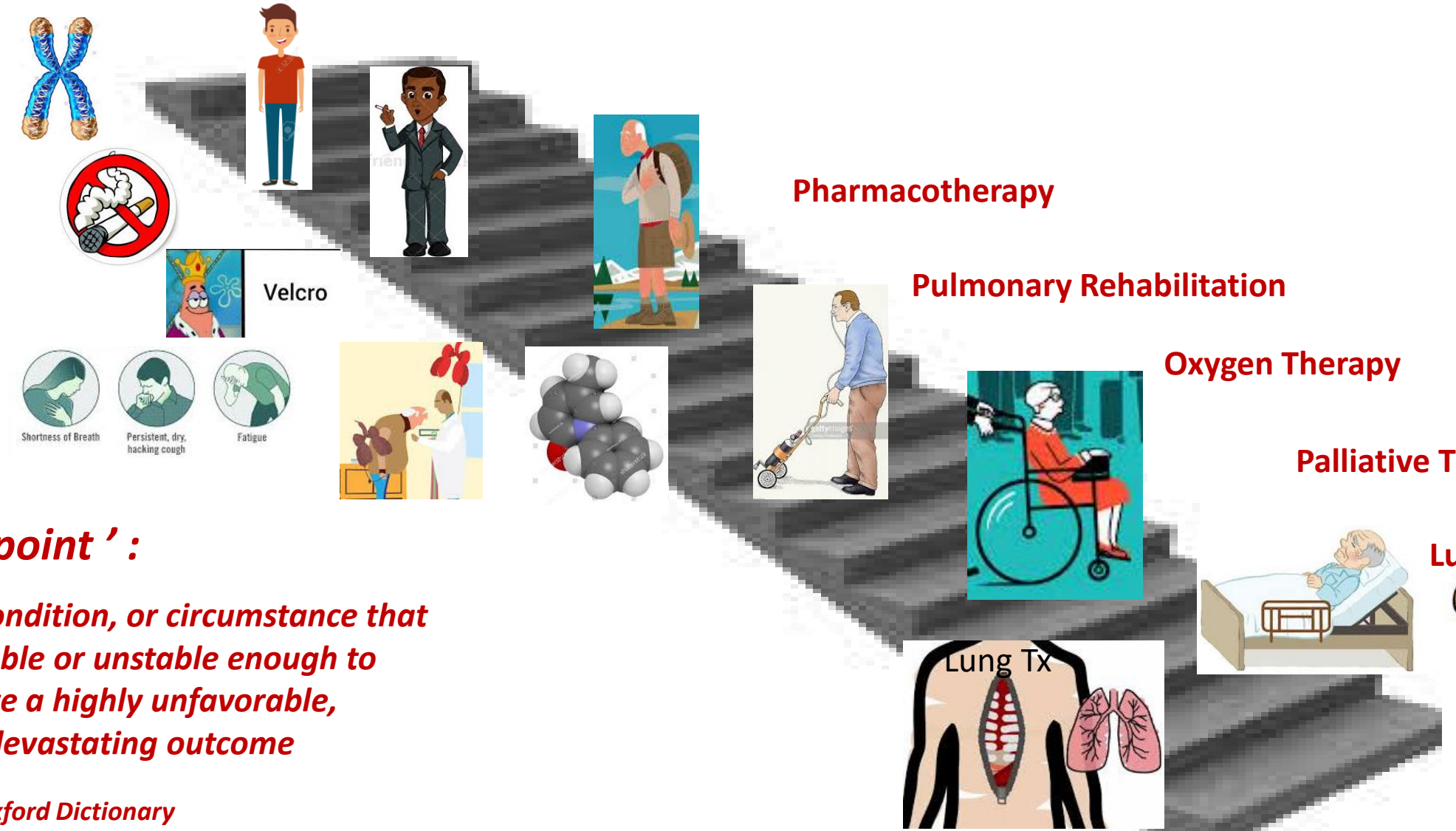
Various Touch Points in IPF … In Present Times



‘ touchpoint ’ :

A time, condition, or circumstance that is vulnerable or unstable enough to precipitate a highly unfavorable, possibly devastating outcome

– English Oxford Dictionary

Issues in Medical Management of IPF During COVID Times :

Pharmacotherapy & Non-Pharmacological Therapies

Q 1 What do you think is *Not Achievable* by use of Antifibrotics in IPF ?

A. Improvement in symptoms
B. Better survival
C. Less decline in lung functions
D. Lesser exacerbations
E. More transplant free survival

Issues with Pharmacotherapy in Present Times : Antifibrotics

- Safety & Efficacy of Antifibrotics
- Monitoring with lung functions may be sub optimal
- Targeting optimal dose of antifibrotic drugs to achieve best clinical response is the aim
- Drug related adverse events needs to be minimized
- Long term maintenance and adherence to antifibrotics to be ascertained
- Choosing an antifibrotic drug in new cases

Q 2 What do you think is main *Plus Point* of Nintedanib over Pirfenidone in IPF ?

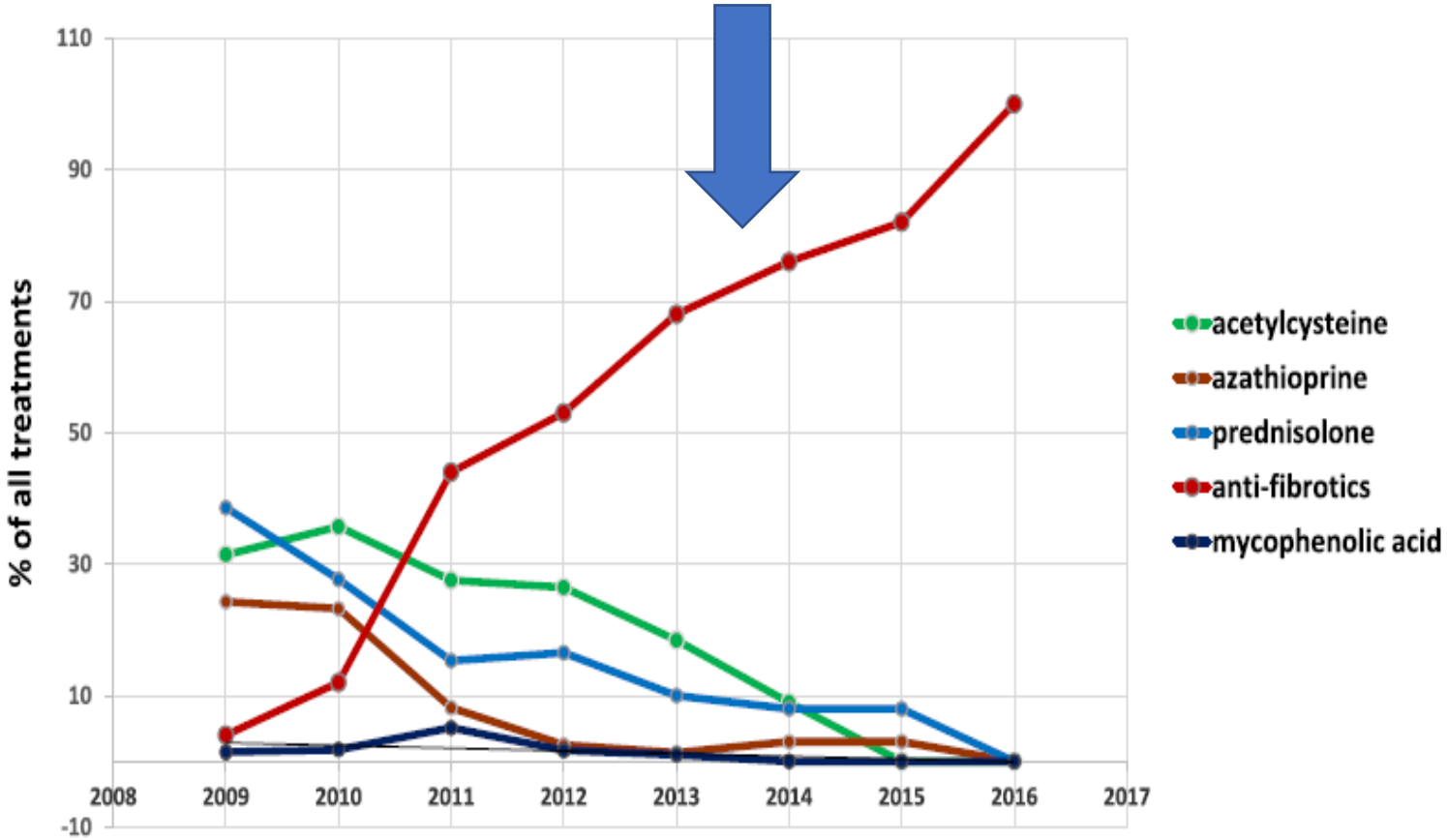
A. Better drug tolerability
B. Better survival
C. Better in cardiac comorbidities
D. More effective in Severe disease

Pharmacotherapy : Antifibrotics

N= 525 IPF

83% on Pirfenidone

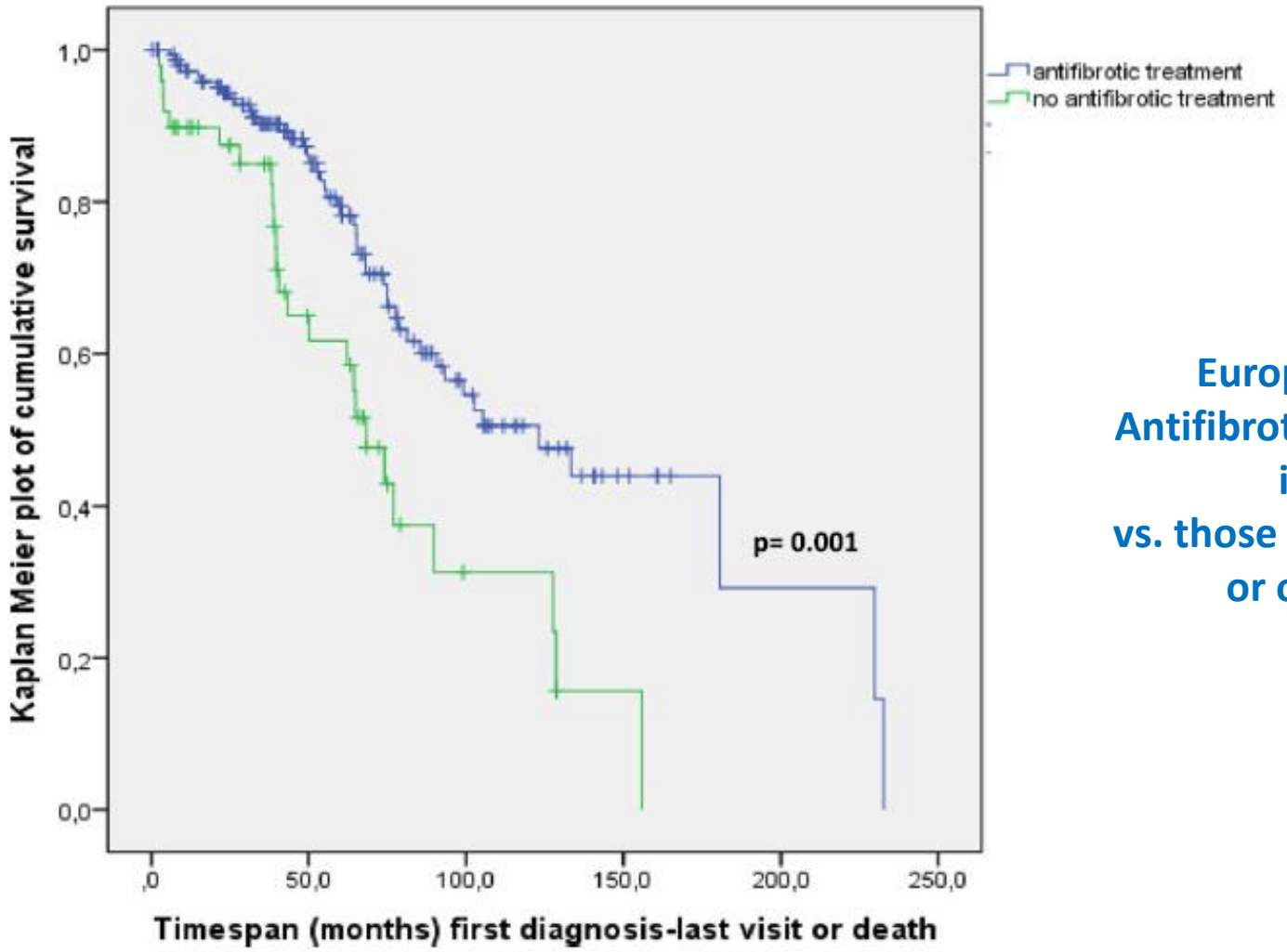
European IPF Network: Over time antifibrotics have replaced other therapies



Respiratory Research 2018; 19:141

Antifibrotics Improve Survival too …

N= 525 IPF



European IPF Network:
Antifibrotics* improved survival
in IPF patients
vs. those receiving prednisolone
or other treatments

*83% on pirfenidone

Respiratory Research 2018; 19:141

Which Anti-fibrotic to Choose in IPF…

Nintedanib	2016 - 2019	Pirfenidone
2/2 phase III trials positive		2/3 phase III trials positive
Efficacious in broad range of IPF patients	• Safety	Efficacious in patients with strict inclusion criteria
Reduces the risk of acute exacerbations	• Efficacy	Does not decrease the risk of acute exacerbations
One capsule twice a day	• Cost	4 tablets 3 times a day
Lower GI side effects		Upper GI side effects
Avoid in unstable CAD /AC		Avoid if eGFR < 30ml

Real World Experience with Antifibrotics in IPF

Patients with total drug exposure as high as 9.9 years still appeared to tolerate pirfenidone therapy

Pirfenidone

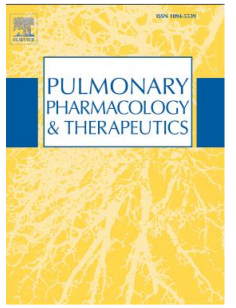
frontiers in Medicine 2018

Longitudinal "Real-World" Outcomes of Pirfenidone in Idiopathic Pulmonary Fibrosis in Greece

Argyrios Tzouvelekis[1,2†‡], Theodoros Karampitsakos[3†], Paschalis Ntolios[4], Vasilios Tzilas[1],*

- Acceptable long-term safety and efficacy
- @> 3 years of treatment.
- AE led to discontinuation in 22.5%
- Skin-related adverse events (25%)
- Liver toxicity in 5%
- FVC improved in 20%, stable in 65% @ 2 years
- Mortality at 3 years 32.5%

Nintedanib



Safety and efficacy of nintedanib in idiopathic pulmonary fibrosis: A real-life observational study

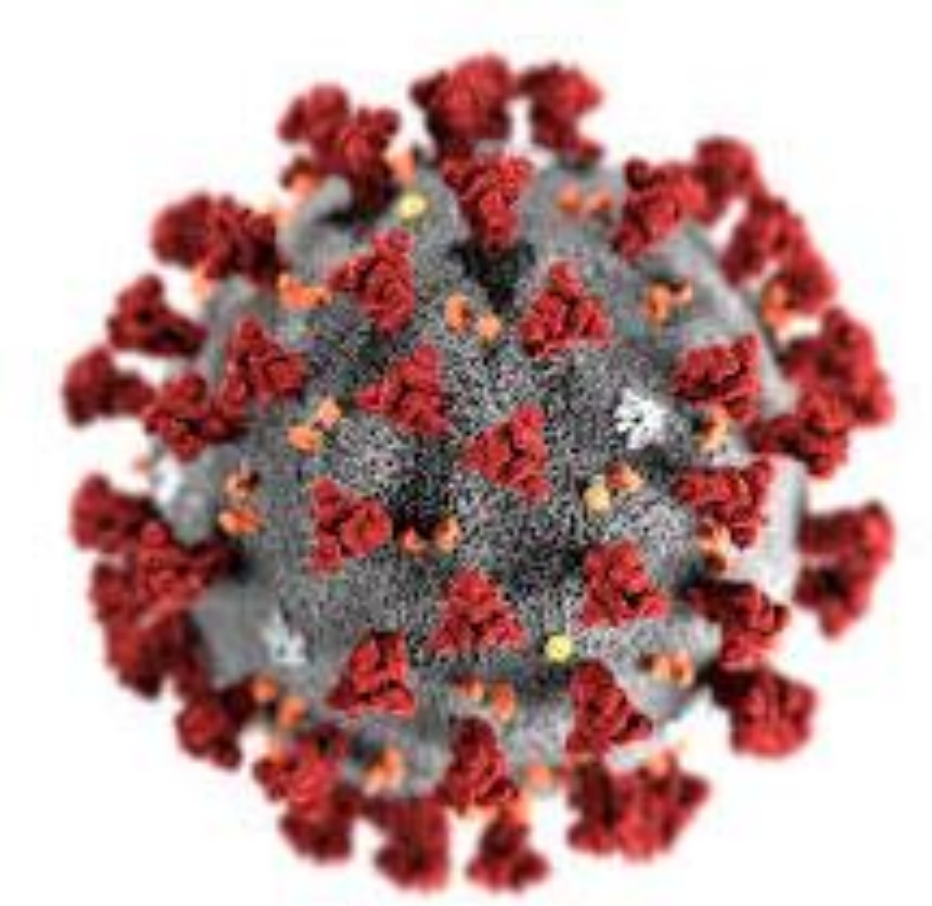
Argyrios Tzouvelekis, Theodoros Karampitsakos, Maria Kontou, Andreas Granitsas,

- Safety and efficacy @ 1 year 21% discontinued due to severe AE
- 18% mortality
- 20% had pre-existing CAD
- 2 % had MI
- Efficacy irrespective of IPF severity : mild to severe (FVC >80% < 50%

Jury's Still Out

Pulmonary Pharmacology and Therapeutics 2018

IPF in 2020 is Different !



ATS INTERNATIONAL CONFERENCE

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Session A23 - ILD PROGNOSIS AND BIOMARKERS I

725 - Outcomes in Patients Receiving Nintedanib or Pirfenidone for Idiopathic Pulmonary Fibrosis

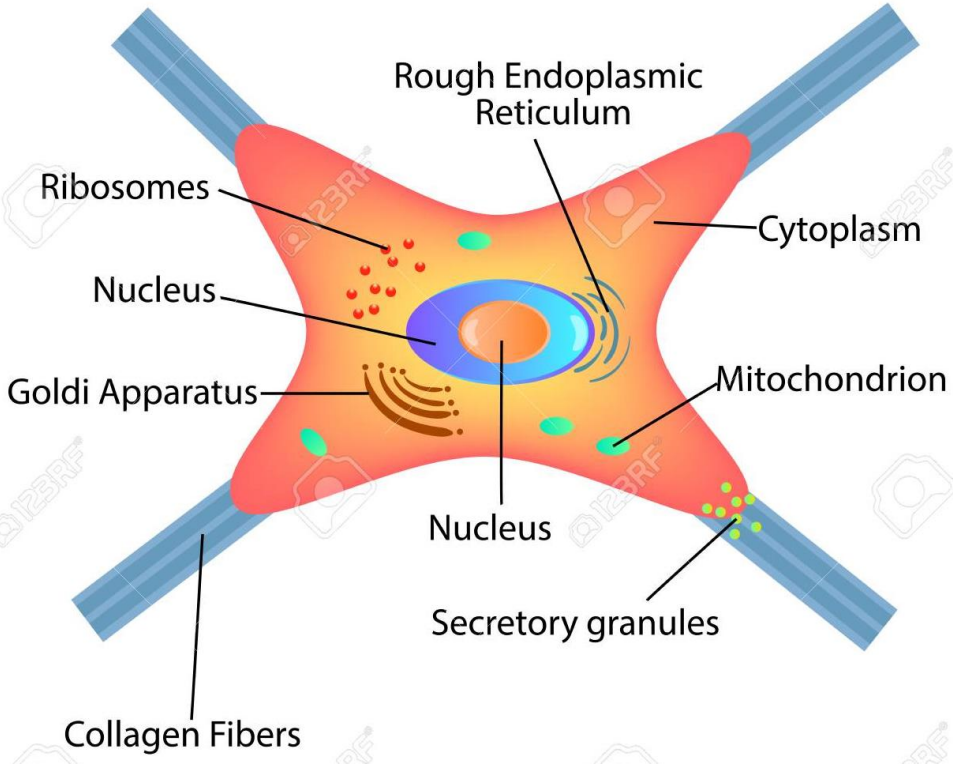
January 1, 0001, 12:00 AM - 12:00 AM

V. Cottin[1], P. Spagnolo[2], P. Bonniaud[3], M. Nolin[4], F. Dalon[4], K. Kirchgässler[5], J. Chia[6], T. V. Kamath[6], E. Van Ganse[7], M. Belhassen[4];

- The cumulative all-cause mortality @ 3 years:
  - 50.23% (95% CI=[48.34%-52.09%]) in untreated
  - 25.5% (95% CI=[19.6%-31.7%]) in Pirfenidone
  - 31.1% (95% CI=[21.2%-41.6%] in Nintedanib

IPF : Pirfenidone

- IPF is the result of '*fibroblast dysfunction'* rather than dysregulated inflammation
- Anti-inflammatory therapy does not improve disease outcome (PANTHER Trial)
- Pirfenidone inhibits TGF-β stimulated collagen synthesis

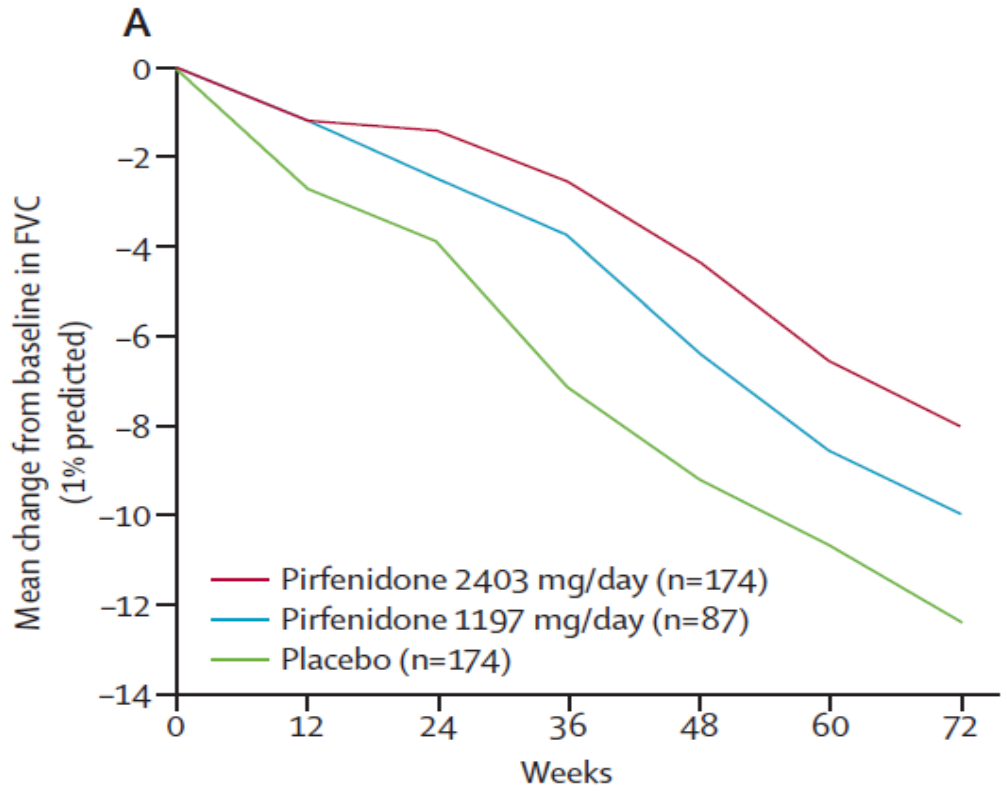


1.ID Drugs 2004; 7: 166-172
2.Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD003134
3.A 389, ERS 2010, Barcelona
4.Am J Respir Crit Care Med 1999; 159: 1061-69

- Slows the decline in lung function
- 30% improvement in progression-free survival

Slower Decline in FVC :

High-dose (2403 mg/d) vs Low Dose (1197mg/d) Pirfenidone



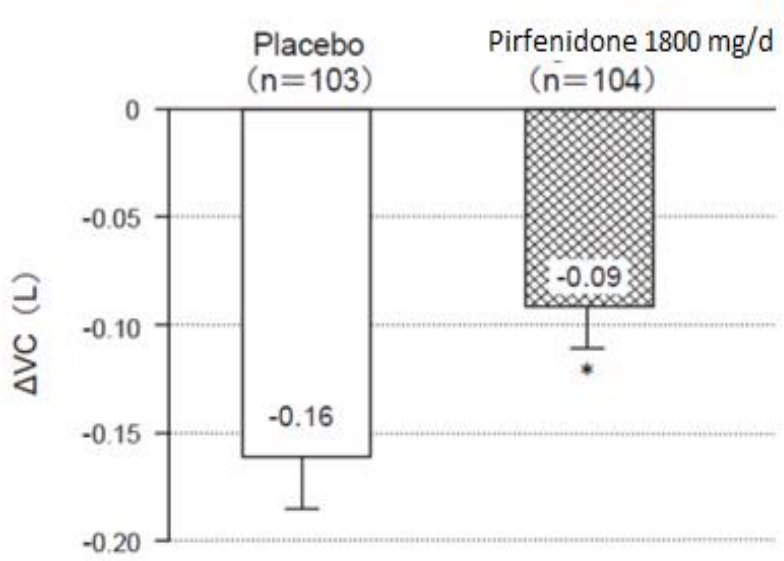
Absolute difference*	1·4%	2·5%	4·6%	4·8%	4·1%	4·4%
Relative difference*	53·5%	65·2%	63·7%	52·3%	38·3%	35·3%
p value†	0·061	0·014	0·0001	0·0009	0·0002	0·001

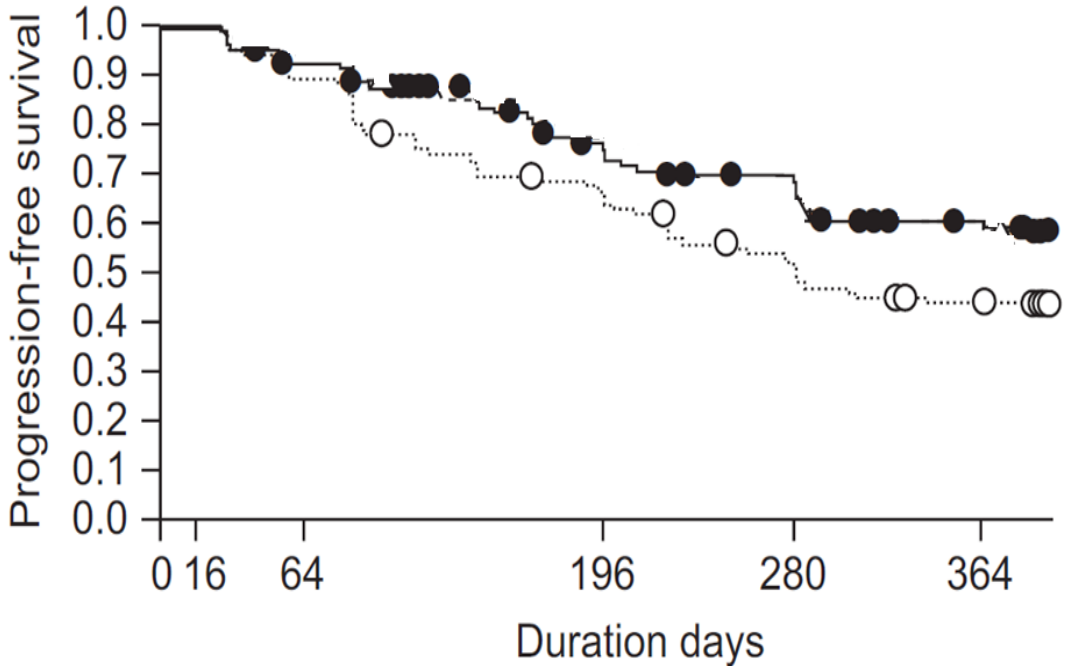
Preclinical and clinical studies on pirfenidone have indicated that pirfenidone acts in a dose-dependent manner; hence IPF patients should be maintained on high dose (ie 1800-2400mg/d) pirfenidone

BMJ Open Resp Res 2018;5: e000323. doi:10.1136/ bmjresp-2018-000323

CAPACITY trials; Lancet 2011; 377: 1760–69

Better Progression-free Survival with high-dose Pirfenidone





Multicenter, double-blind, placebo-controlled, randomized phase III clinical trial

N= 275; Total Study Duration : 52 weeks

Solid circle: Pirfenidone (1800mg/d)

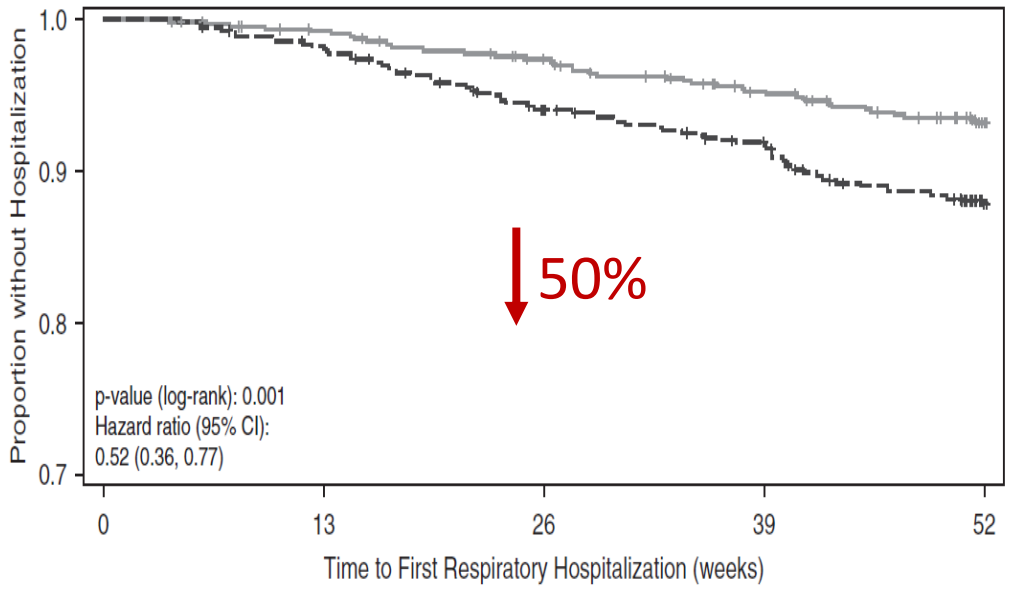
Blank circle: Placebo

Eur Respir J 2010; 35: 821–829

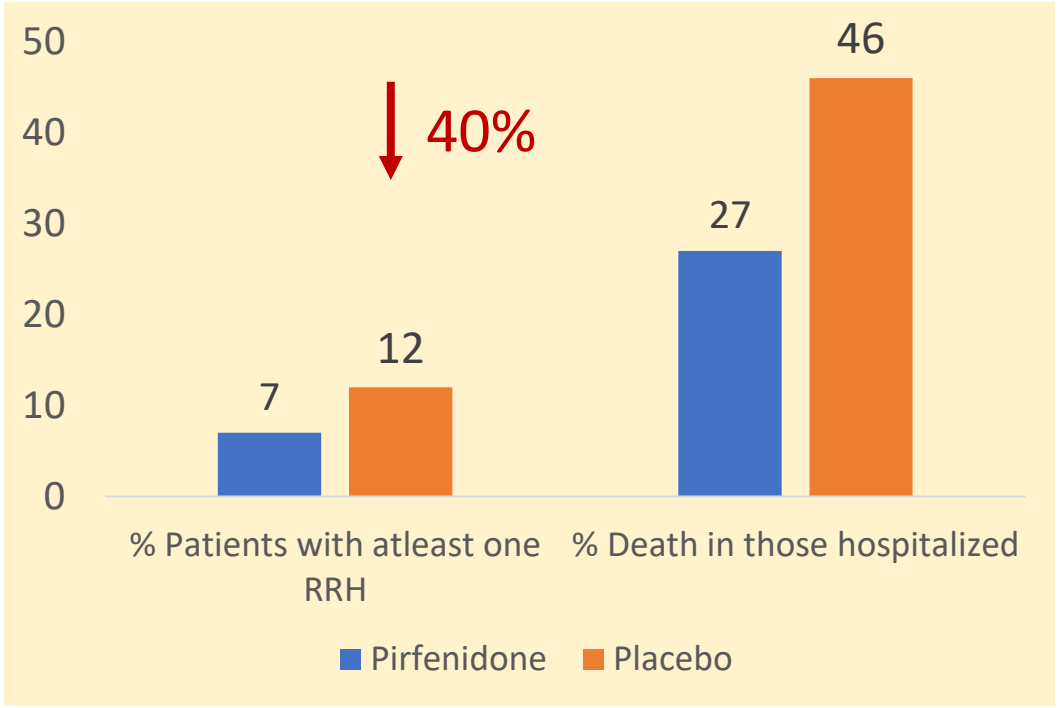
High dose Pirfenidone Reduces the Risk of Respiratory Related Hospitalization (RRH)

77% of hospitalizations in IPF patients are due to RRH[1]

Significant risk reduction in RRH by 48%[2]



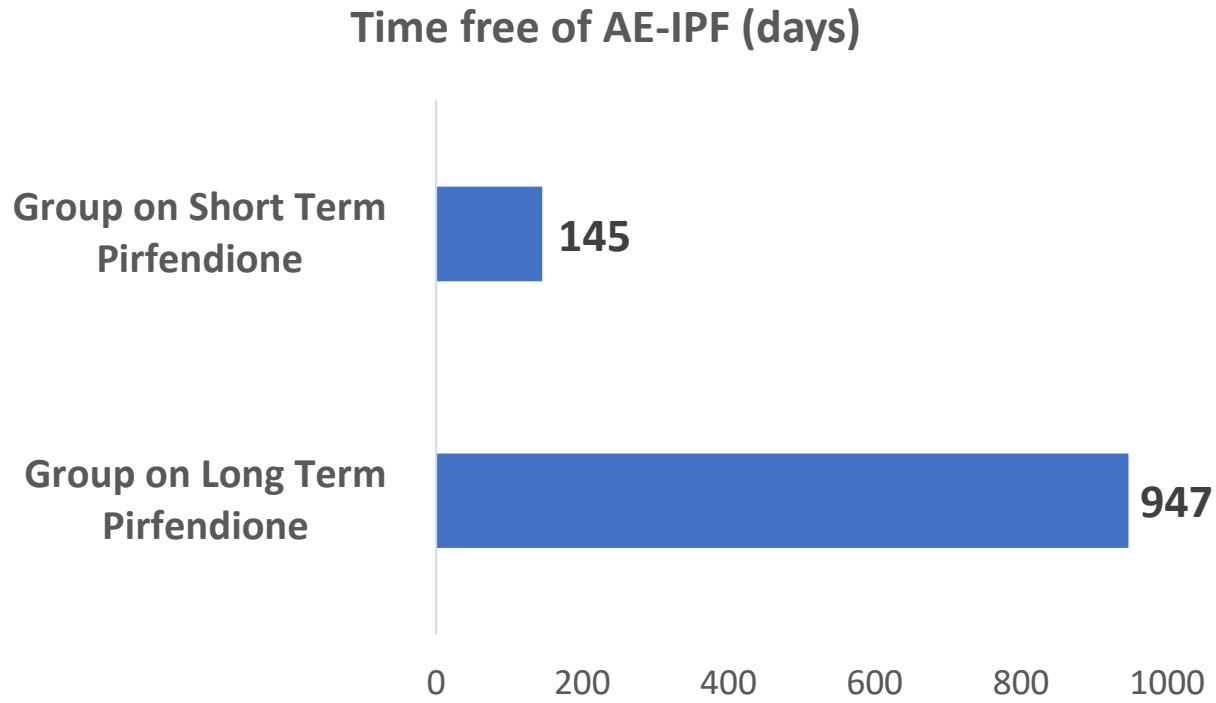
Fewer deaths in those with RRH[2]

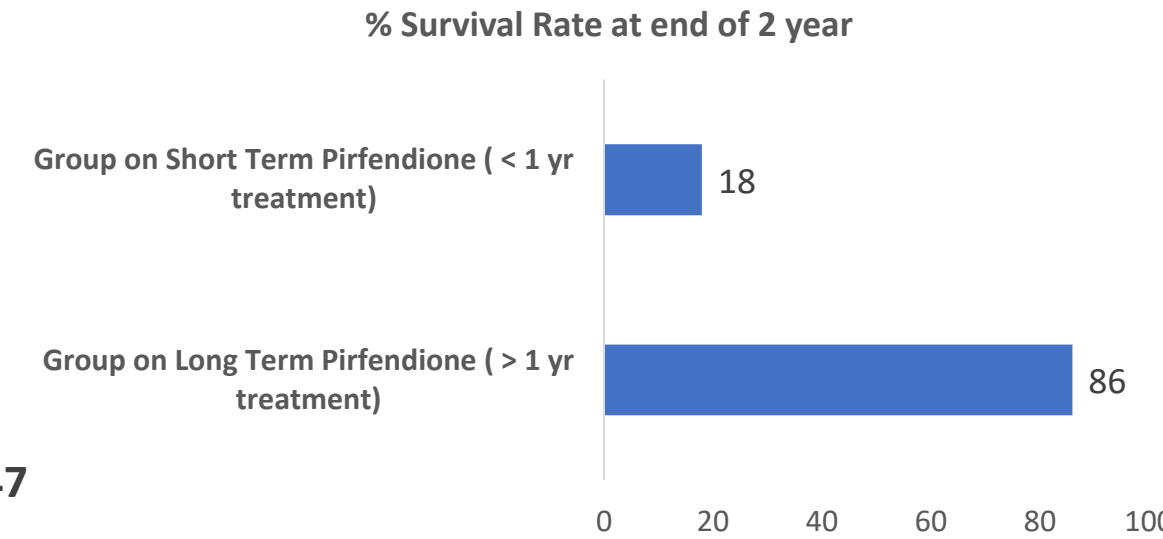


N= 1274 IPF patients *(623 pirfenidone 2403 mg vs 624 placebo)*
Duration of Study: 52 weeks

1. Chest 2015; 147(1): 173 - 179
2. Am J Respir Crit Care Med 196 (6): 756–761

Long term Pirfenidone : 2.5 years free of the 1st Acute Exacerbation and Improved Survival Rate





46 patients with IPF who received PFD
- Group Long term : PFD for over 1 year (n=30)
- Group Short term : PFD for less than 1 year (n =16)

Median age : 70.5 years
Median baseline % predicted forced vital capacity (%FVC): 70.0%

Intern Med 2018; 57: 2813-2818

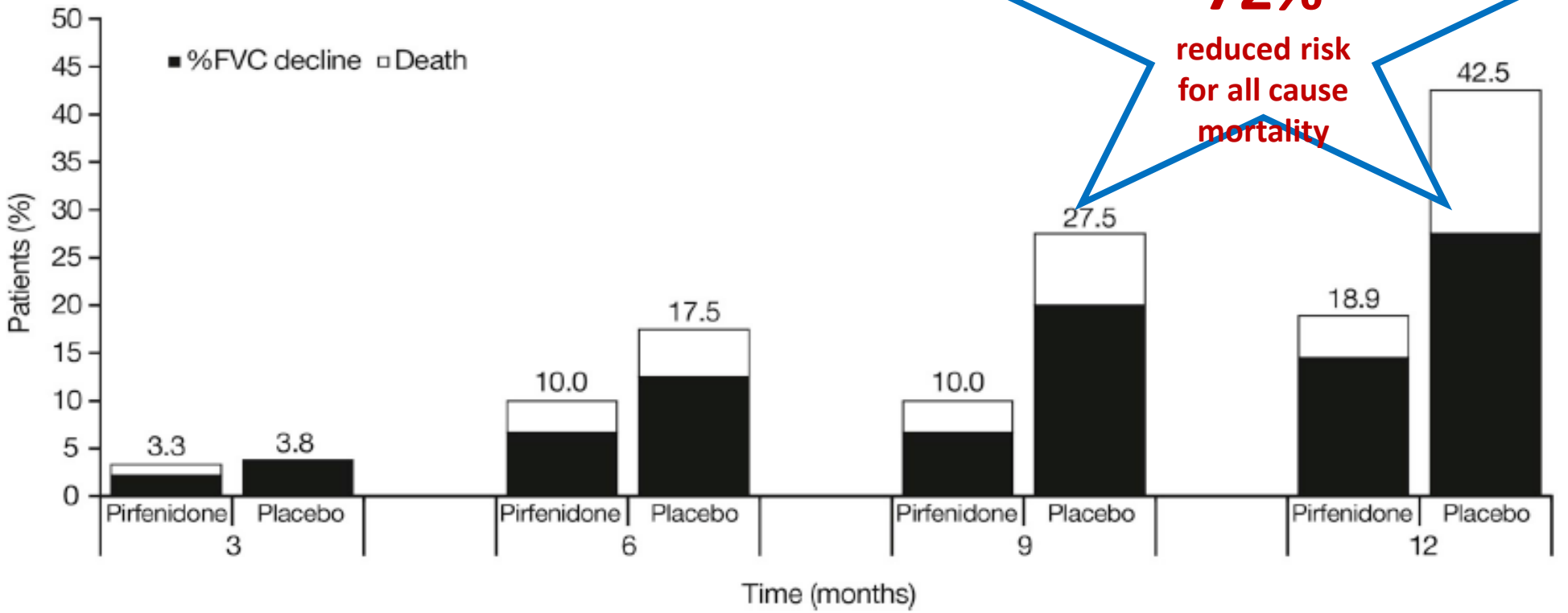
Pirfenidone in Severe IPF : It Still Works !

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment



72%

reduced risk for all cause mortality

Fewer patients with advanced disease receiving pirfenidone reported ≥10% decline in FVC or death compared to placebo

Respiratory Medicine 153 (2019) 44–51

Pirfenidone : Symptomatic Relief in Cough in IPF

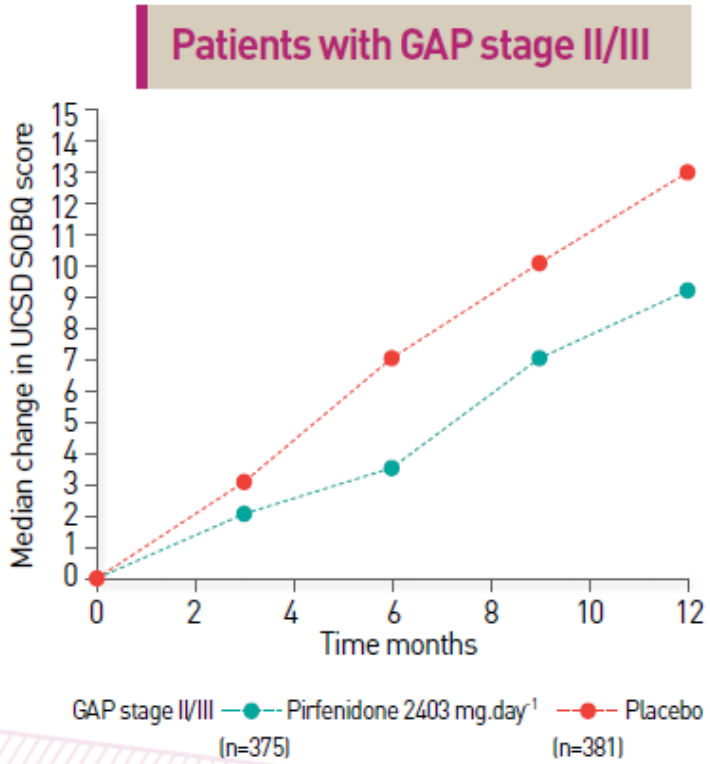
After 12 weeks of pirfenidone treatment, objective 24-h cough decreased by 34%

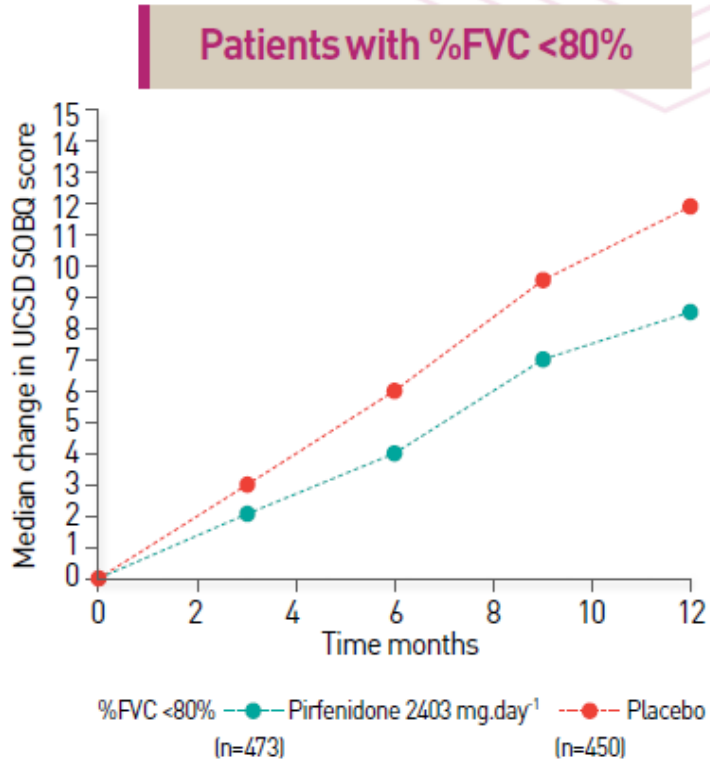
	Baseline	At 12 weeks	Change# (95% CI)	p-value#
Subjects n	43	31		
24-h cough	520 (91 to 3394)	392 (75 to 1746)	−34% (−48 to −15%)	0.002
Coughs per hour	23 (4 to 141)	17 (3 to 73)	−35% (−49 to −17%)	<0.001
Daytime	28 (5 to 171)	20 (4 to 121)	−33% (−47 to −14%)	0.003
Night-time	7.2 (0.7 to 101)	3.3 (0 to 54)	−34% (−54 to −5%)	0.029

43 treatment-naïve IPF patients aged 40–85 years, who had daily IPF-related cough for ≥8 weeks with a cough score of ≥40 mm on a 0–100 mm visual analogue scale (VAS). FVC ≥50% and TLCOc) ≥30%

Eur Respir J 2017; 50: 1701157

High Dose Pirfenidone: Significantly reduces the worsening of patient-reported breathlessness *



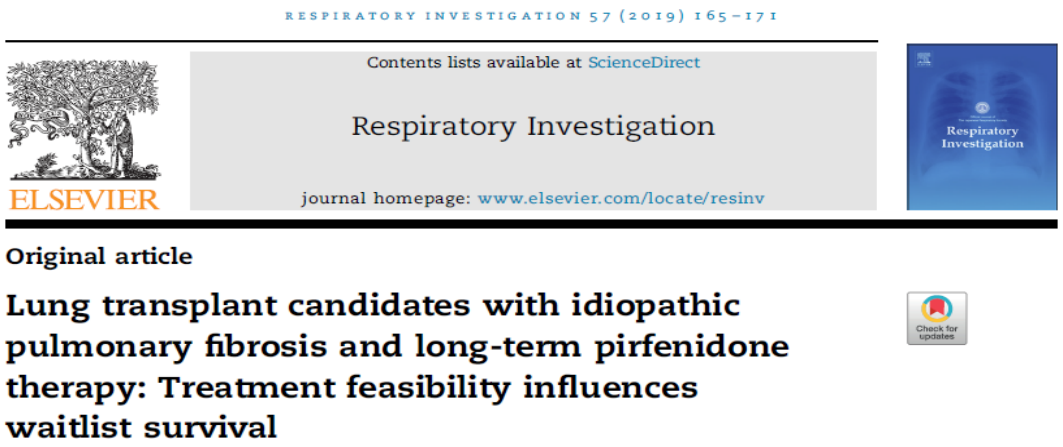


IPF of various severities

* measured by change in the UCSD SOBQ score (University of California, San Diego Shortness of Breath Questionnaire) from the baseline to month 12

Eur Respir J 2019; 54: 1900399

Pirfenidone : Transplant Free Survival



RESPIRATORY INVESTIGATION 57 (2019) 165–171

Contents lists available at ScienceDirect

Respiratory Investigation

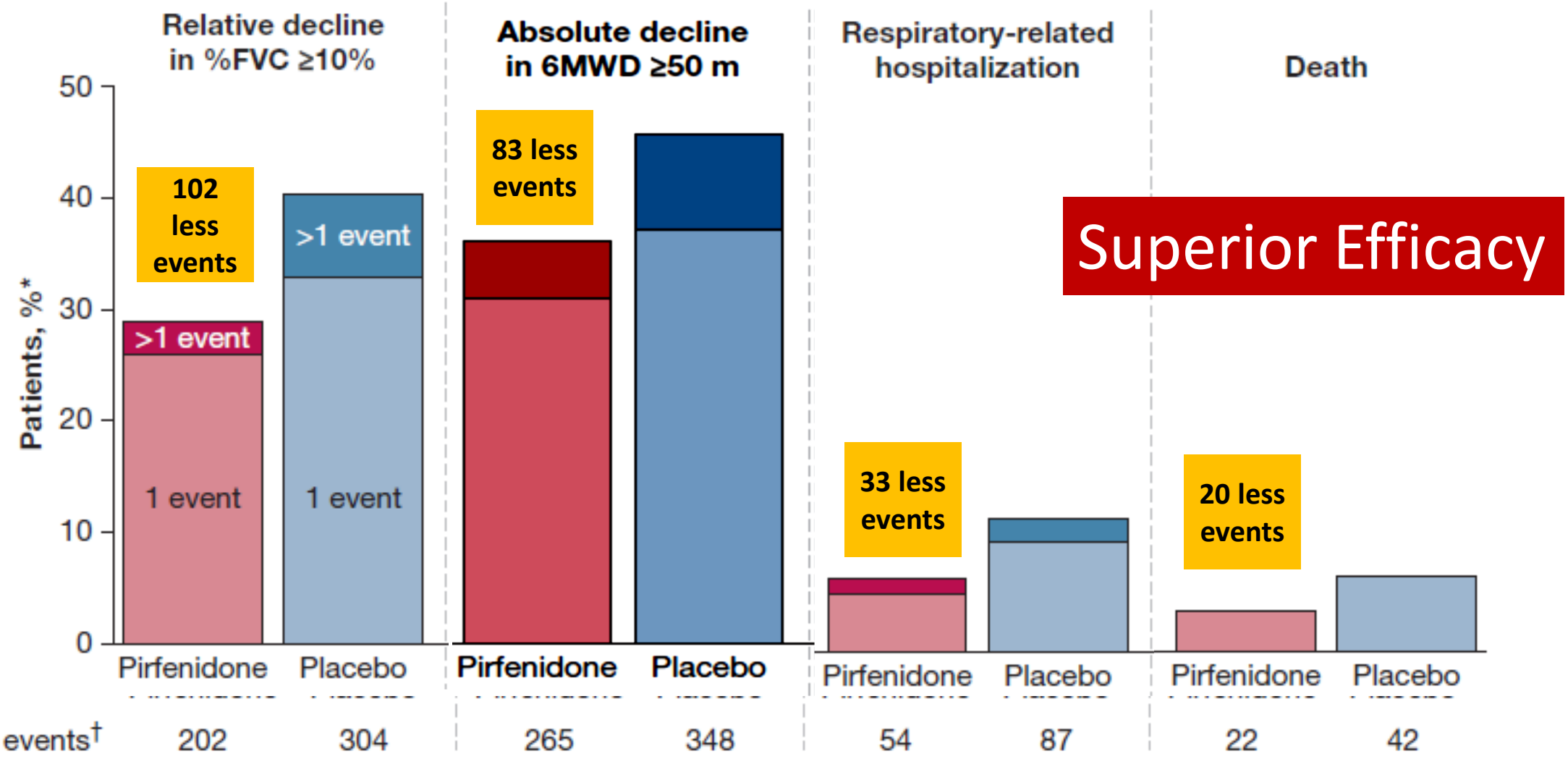
journal homepage: www.elsevier.com/locate/resinv

Original article

Lung transplant candidates with idiopathic pulmonary fibrosis and long-term pirfenidone therapy: Treatment feasibility influences waitlist survival

- 24% patients received Pirfenidone as pre transplant therapy for 45.2 months.
- **During the treatment period, the pirfenidone group achieved a significant reduction in the decline rate of the forced vital capacity (-6.2%vs.-0.3%,p =0.04) and a lower lung allocation score (31 vs.41,p=0.013) compared with the non- Pirfenidone group.**
- The pirfenidone group exhibited 100% waitlist survival three years after registration that was comparable to other indications, and 66% of the patients were still alive at the time of organ availability.

High Dose Pirfenidone (2403mg/d) Lowers the Risk of Disease Progression



Superior Efficacy

CHEST 2019; 155(4):712-719

Pirfenidone : Low discontinuation in Phase III & Real-World Studies

	RECAP[1] N= 603	CAPACITY[1] N= 345	PASSPORT (REAL WORLD STUDY)[2] N= 1009
Nausea	30.0	36.2	20.6
Discontinuation	1.3	1.4	4.1
Diarrhea	22	28.7	9.5
Discontinuation	0.5	0	2.5
Photosensitivity	8.8	12.2	5.8
Discontinuation	0.3	0.9	1.5
Rash	13.3	32.2	12.2
Discontinuation	1.2	1.4	3.2

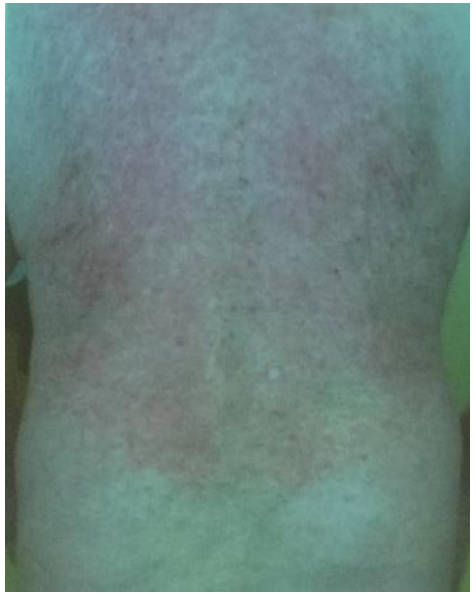
S/E due to pirfenidone was rarely associated with discontinuation

Data presented as %
Dose in all 3 studies: 2403mg/d
Passport study duration: 2 years

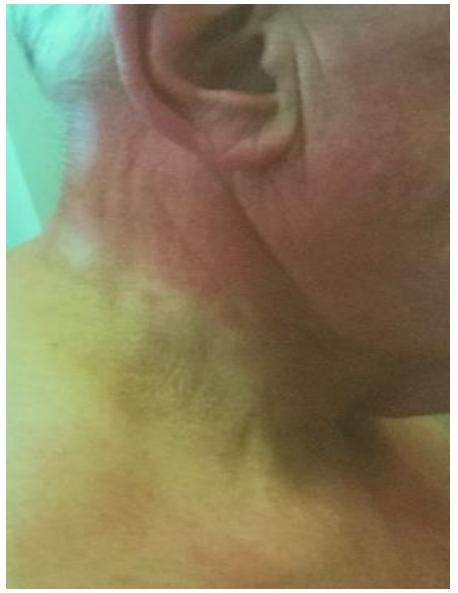
1.Eur Respir Rev 2015;24:58-64; 2.ERJ Open Res 2018; 4: 00084-2018

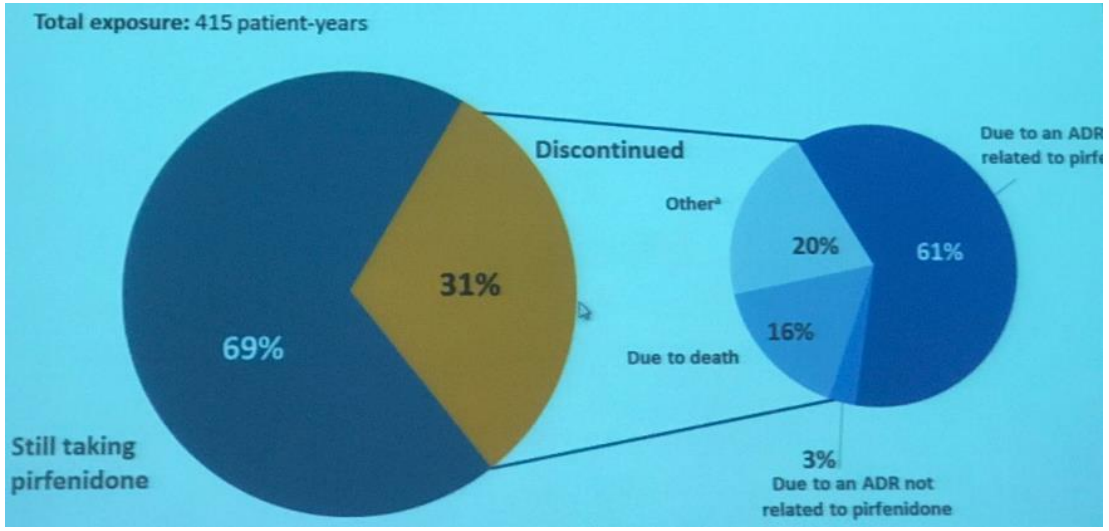
Managing Side Effects of Pirfenidone

- 67, Male Physician, IPF
- Pirfenidone 2400 mg /day (ramped - 2 months)
- Developed rash
- Stopped for 4 weeks and now being ramped to same dose (3 months)



Rash





Drug discontinuation due to adverse drug reactions was lower in patients who had a dose adjustment compared with those who did not (20% vs 33%)

PASSPORT Study Cottin et al Chest 2015

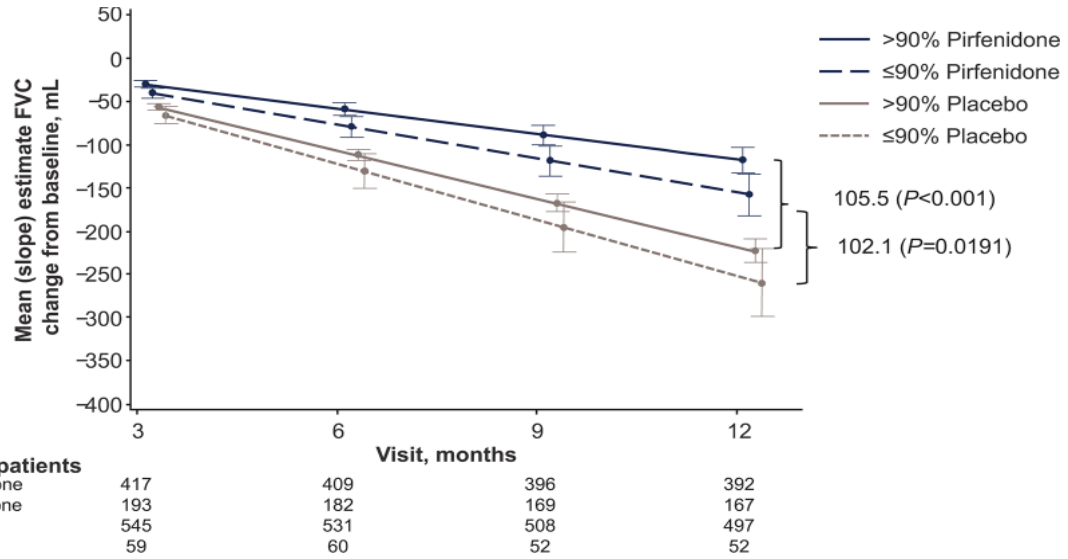
Dose modification in First 6 months Doesn't Effect Outcomes of Pirfenidone in IPF ?

BMJ Open Respiratory Research

July 2018

Dose modification and dose intensity during treatment with pirfenidone: analysis of pooled data from three multinational phase III trials

Steven D Nathan,[1] Lisa H Lancaster,[2] Carlo Albera,[3] Marilyn K Glassberg,[4]



Number of patients				
>90% Pirfenidone	417	409	396	392
≤90% Pirfenidone	193	182	169	167
>90% Placebo	545	531	508	497
≤90% Placebo	59	60	52	52

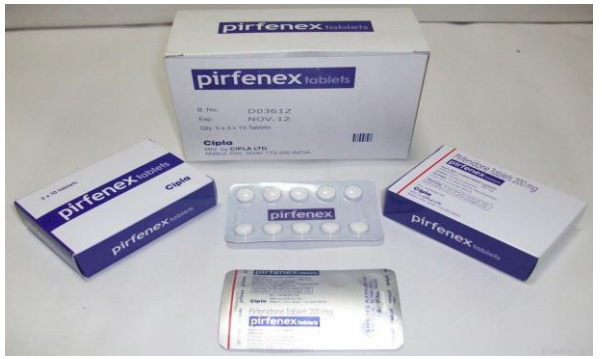
- Dose interruptions, required to manage Treatment Emergent AEs, mostly occurred during the first 6 months of treatment
- Despite dose reductions and interruptions, most patients with IPF maintained relatively high dose intensity on pirfenidone, without compromising its treatment effect

BMJ Open Resp Res 2018;**5**:e000323.

Pirfenidone – Pill Burden in India & World

Country	Approval Year	Drug name	Strengths approved	Approved Target Daily Dose
Japan	2008	Pirespa	200mg	1800 mg
India	2010	Pirfenex	200mg **400mg** **600 mg** **801 mg**	1800 mg to 2400 mg
EU (Italy, Germany, France, UK)	2011	Esbriet	267mg, 534mg, 801mg	2400 mg
USA	2014	Esbriet	267mg, 534mg, 801mg	2400 mg
Canada	2017	PrESBRIT	267mg, 801mg	2400 mg

No Longer an issue



Costs : Better with Pirfenidone Worldwide

CHEST Annual Meeting 2019

HEALTHCARE RESOURCE USE AND COSTS IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS IN THE US MEDICARE POPULATION

SHEILA REDDY PHD, RPH* EUNICE CHANG MICHAEL BRODER SOHUM GOKHALE AND MITRA CORRAL

CLINICAL IMPLICATIONS: Patients receiving Pirfenidone vs Nintedanib may have overall lower all-cause inpatient costs and fewer respiratory-related hospital days.

Q 3 Which antifibrotic would be *Safe & Better* during COVID times ?

A. Pirfenidone
B. Nintedanib
C. None

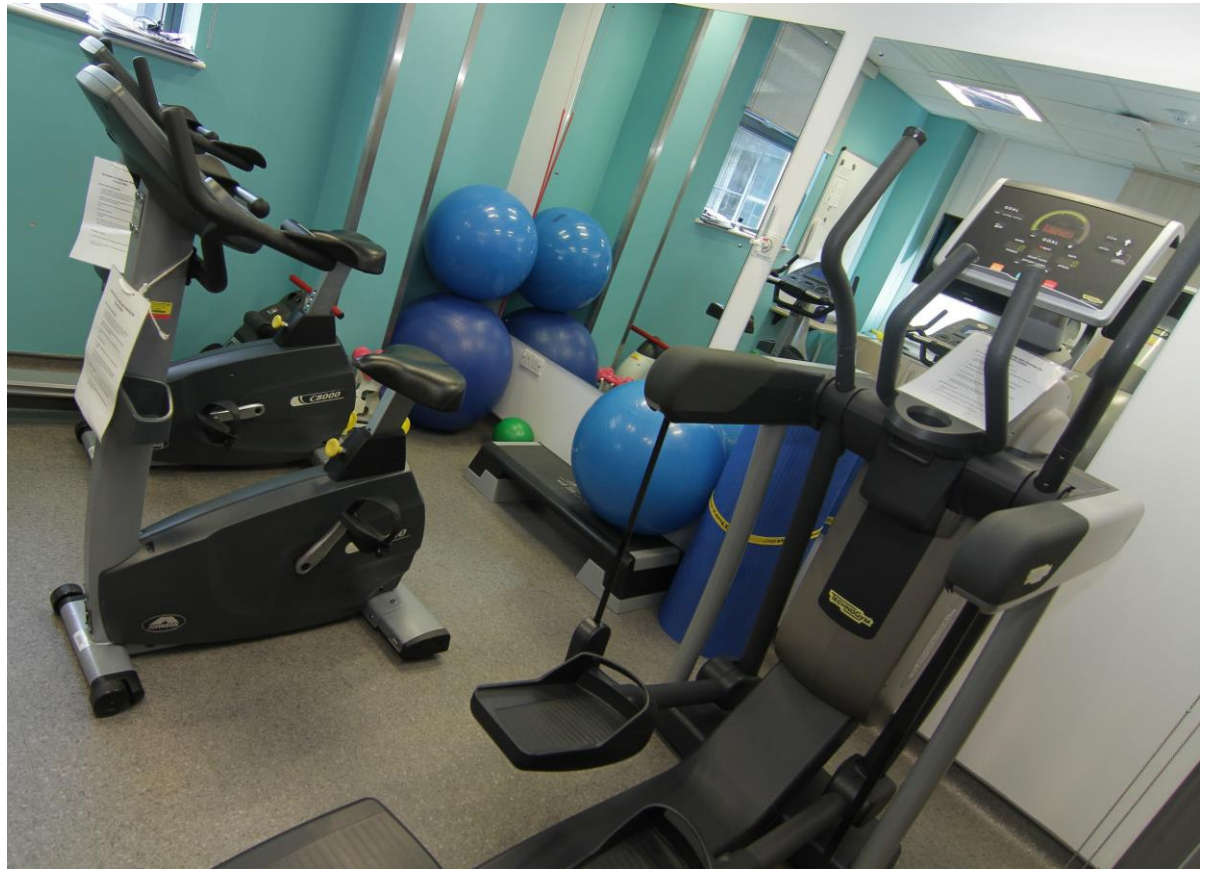
To Summarize …

- Pirfenidone bettered Nintedanib in mortality risk and respiratory-related hospitalizations among treated patients with IPF over a 12-month assessment.

Vincent Cottin ATS 2020

Issues with Non-Pharmacological Treatment in IPF

The current exercise training data in IPF provide *'sufficient evidence of clinical benefit'* for consideration to be given to recommending exercise-based pulmonary rehabilitation as standard of care for IPF

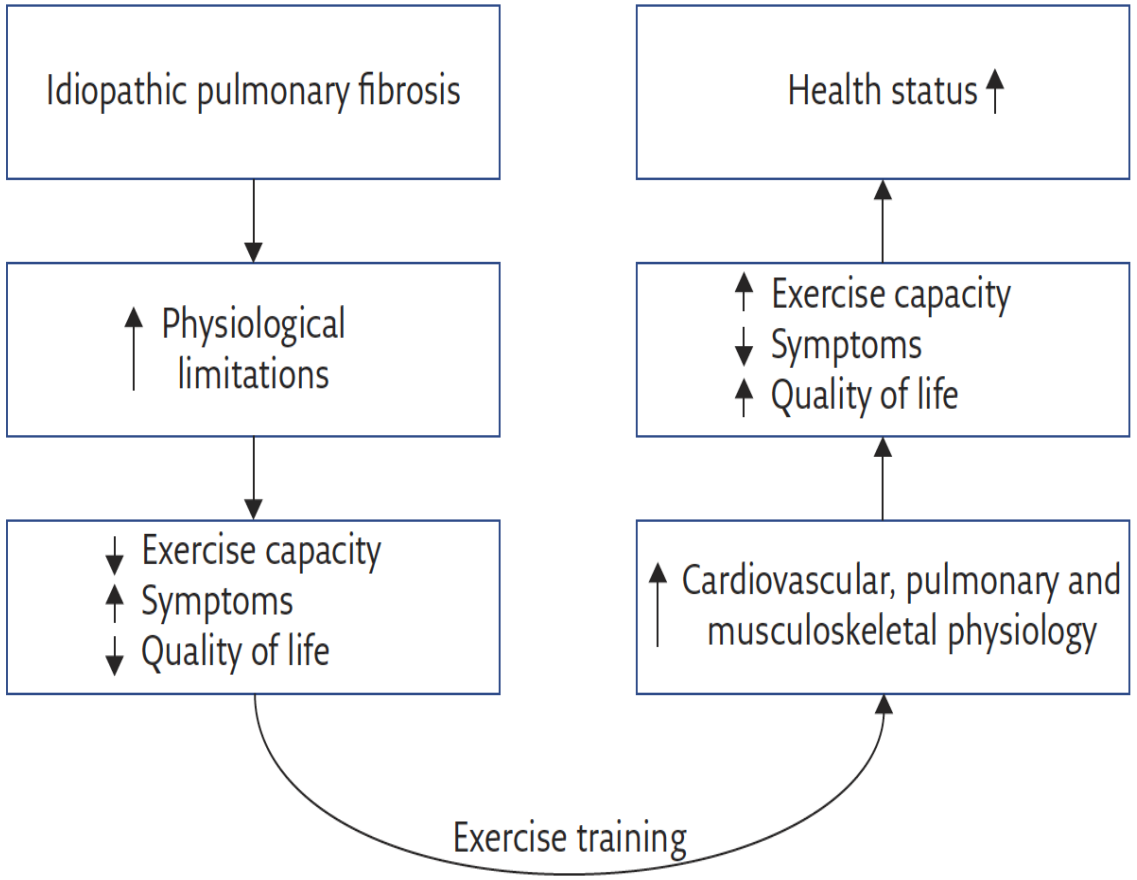


Breathe 2016; 12: 130–138.

Home Based PR Programs

	Supervised programmes	Home-based, unsupervised programmes
Reference(s)	[27, 29, 35, 37–41]	[34]
IPF subjects n	430	17
Mean Δ6MWD m	50	40

Δ6MWD: improvement in pre- to post-intervention 6MWD.



Issues with Non-Pharmacological Treatment in IPF

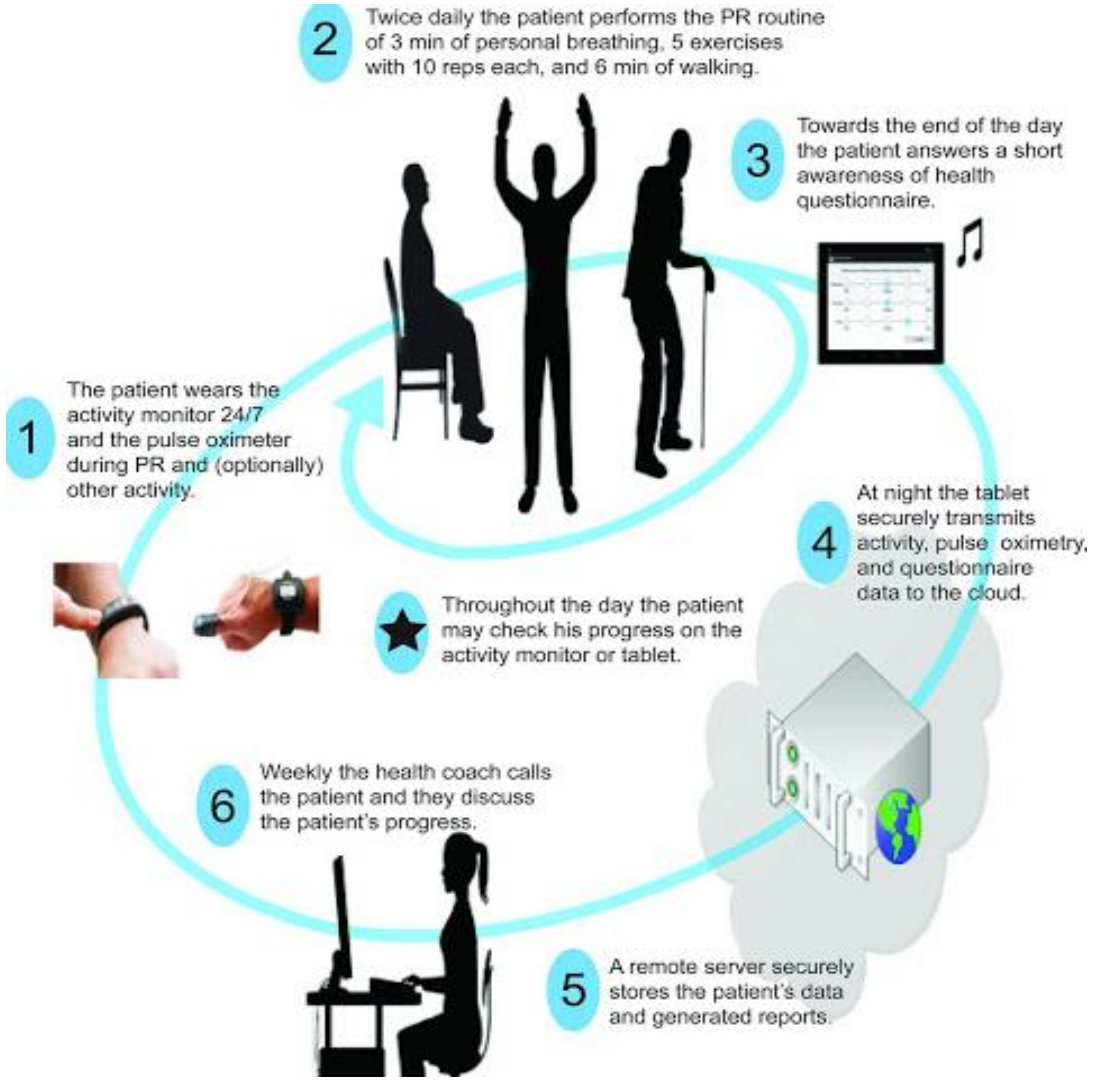
What to Do When Pulmonary Rehabilitation (PR) Is Unavailable

Pulmonary Rehabilitation (PR), a program of supervised exercise, education and support, can help people with lung disease live a better quality of life. This fact sheet offers some ways to continue your pulmonary rehabilitation at home when you are not able to get to your program.

Home Exercises & Tele-Rehabilitation

Tele Rehabilitation Services :

'An Opportunity Amidst Despair'



Conclusions: IPF management in Present Times

- Choose antifibrotics Early and Appropriately:
  - Efficacy : Survival, RRH, Time to 1st exacerbation, Symptomatic improvement
  - Safety : Adverse events, discontinuations, availability, cost, serious side effects
  - Tolerability : Long-term, less monitoring
  - Drug- Drug / Drug- COVID 19 interactions: Thrombosis & AC
- Avoid drugs of ? Role in IPF; steroids and immunosupressives
- Virtual Consultations and Pulmonary Rehabilitation

"For it happens…that in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, it becomes easy to detect but difficult to cure."

-N. Machiavelli, *The Prince*