ILD Collaborative

Project ECHO

More Than Meds: Nonpharmacologic Treatments for ILD

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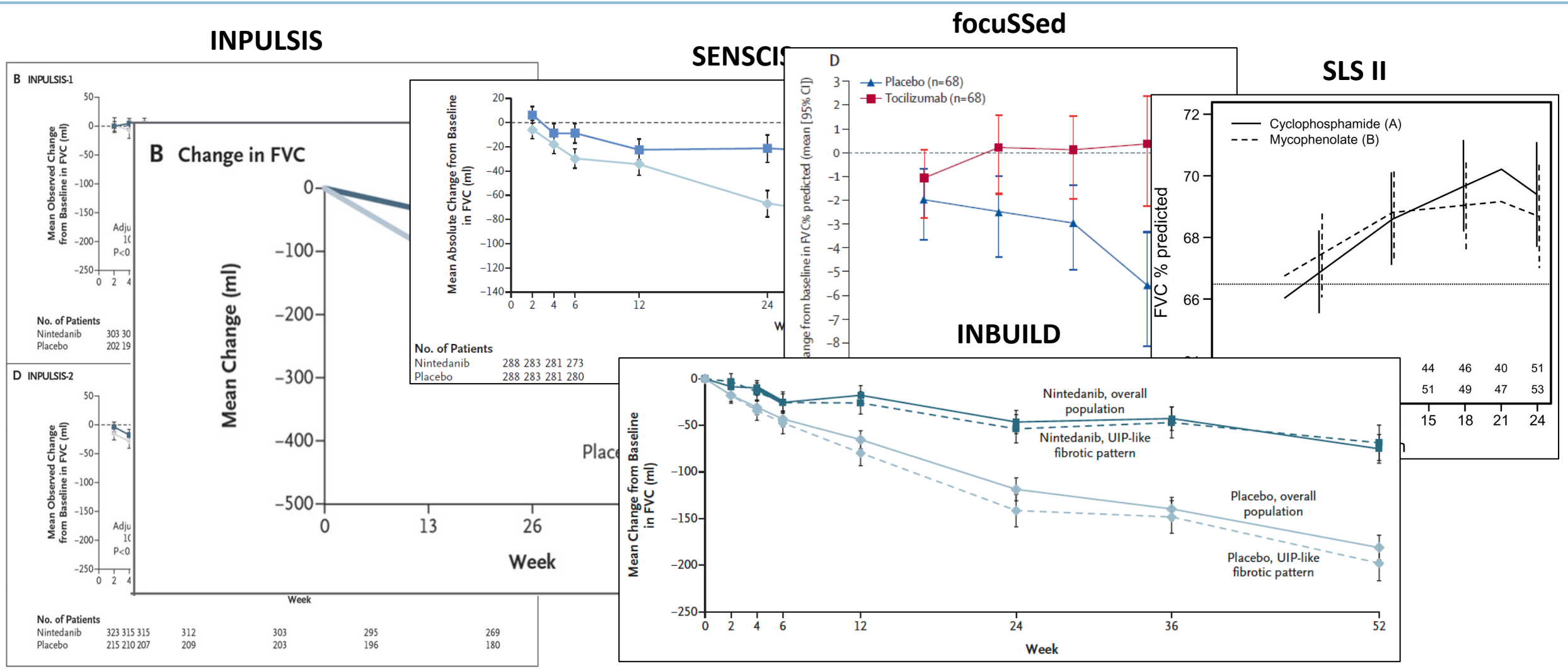
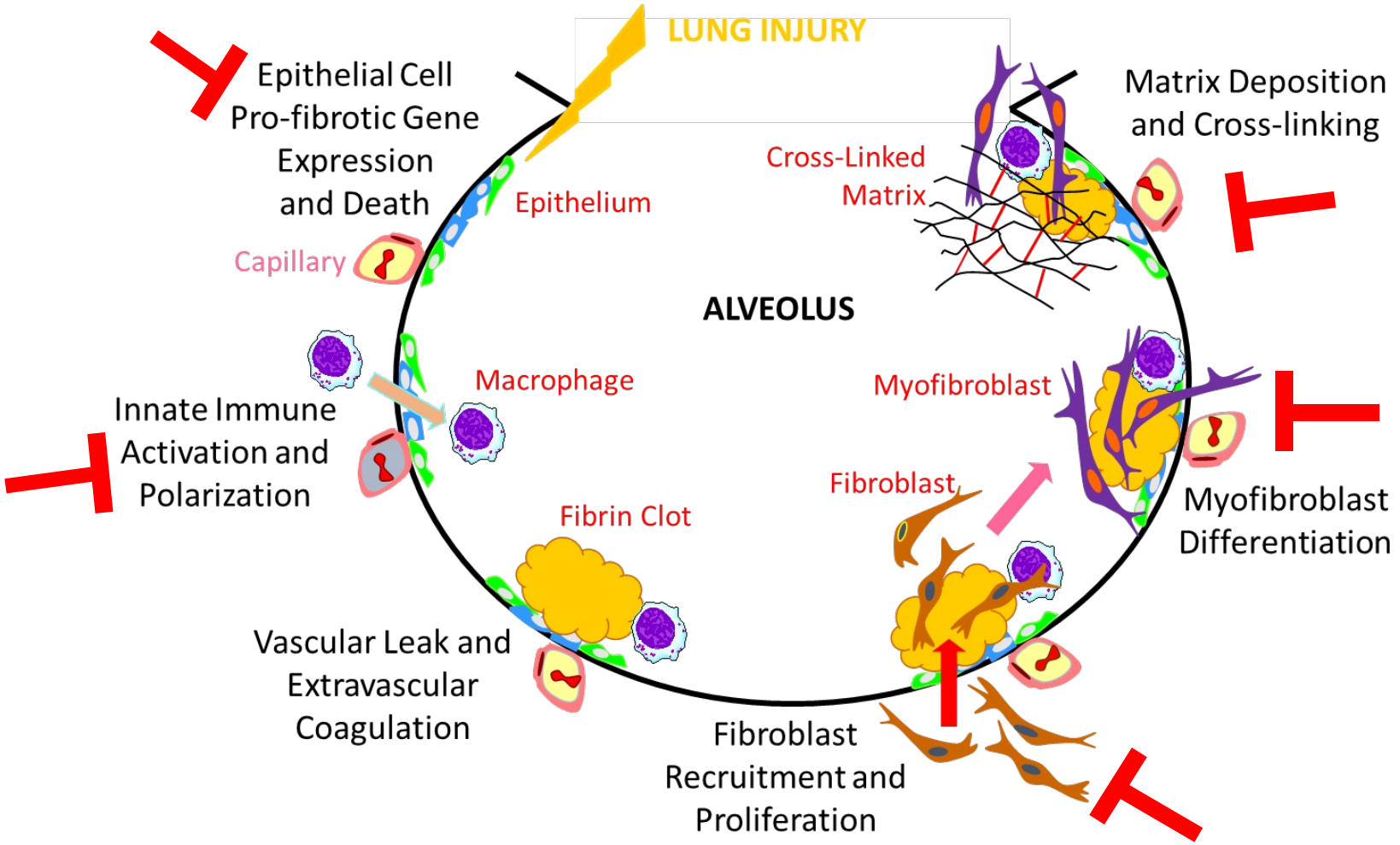
MGH Interstitial Lung Disease Program

May 1, 2024

Pharmacologic Treatment for ILD



Additional ILD therapies on the horizon?



Beyond FVC and survival – morbidity in ILD

- Dyspnea
- Exercise limitation / Fatigue
- Cough
- Anxiety and mood disturbances
- Quality of Life (QOL)

Treatment of IPF and other ILDs has to focus on limiting morbidity and improving QOL as much as it does on prolonging survival!

- Pulmonary rehab
- Supplemental O2
- Cough management

IPF Treatment Guidelines

Pharmacologic Therapy	Recommendation		
	For (√) /Against (X)	Strength	Evidence quality
Anticoagulation (warfarin)	X	Strong	Low
Azathioprine + prednisone + N-acetylcysteine	X	Strong	Low
Imatinib	X	Strong	Moderate
Selective endothelin receptor antagonists	X	Strong	Low
Dual endothelin receptor antagonists	X	Conditional	Moderate
Antipulmonary hypertension therapy	X	Conditional	Very low
N-acetylcysteine monotherapy	X	Conditional	Low
Phosphodiesterase-5 inhibitor (sildenafil)	X	Conditional	Moderate
Anti-reflux therapy	X	Conditional	Very low
Pulmonary rehabilitation	√	Conditional	Low
Supplemental oxygen	√	Strong	Very low
Lung transplantation	√	Strong	Low
Nintedanib	√	Conditional	Moderate
Pirfenidone	√	Conditional	Moderate

Raghu G et al. *Am J Respir Crit Care Med*. 2011;183:788-824.
Raghu G et al. *Am J Respir Crit Care Med.* 2015;192:e3-e19.
Raghu G et al. *Am J Respir Crit Care Med.* 2022;192:e18-e47.

Pulmonary rehab improves functional capacity and reduces symptoms in ILD

Retrospective analysis 402 patients with ILD (50% IPF)

- 80% on O2, mean FVC 54%

	Admission	Discharge	Change	p-value
Lung function parameters#				
P_{O_2} mmHg	61±1	63±1	2±1	0.012
P_{CO_2} mmHg	39±0	40±0	1±0	0.002
VC % pred	54±1	55±1	1±0	0.002
TLC % pred	65±1	65±1	0±0	0.322
FEV_1 % pred	55±1	56±1	1±0	<0.001
6MWT and dyspnoea rating¶				
6MWD m	308±6	354±6	46±3	<0.001
Dyspnoea-free walk distance m	291±7	343±7	52±4	<0.001
VAS (before exertion)	3.2±0.1	3.3±0.1	0.1±0.1	0.572
VAS (after exertion)	6.5±0.1	6.3±0.1	-0.2±0.1	0.176
Health status (SF-36)+				
Physical functioning	24±1	29±1	5±1	<0.001
Bodily pain	60±2	66±2	7±2	<0.001
Physical role functioning	12±2	17±2	5±2	0.009
General health perceptions	29±1	33±1	4±1	<0.001
Vitality	32±1	45±1	13±1	<0.001
Social role functioning	52±2	63±2	11±2	<0.001
Emotional role functioning	49±3	56±3	7±3	0.029
General mental health	58±1	67±1	9±1	<0.001
Physical summary score	31±1	37±1	6±1	<0.001
Mental summary score	47±1	57±1	10±1	<0.001

Huppmann et al. *ERJ.* 2013.

Pulmonary rehab improves functional capacity and reduces symptoms in ILD

Prospective study of 41 patients with ILD (63% IPF)

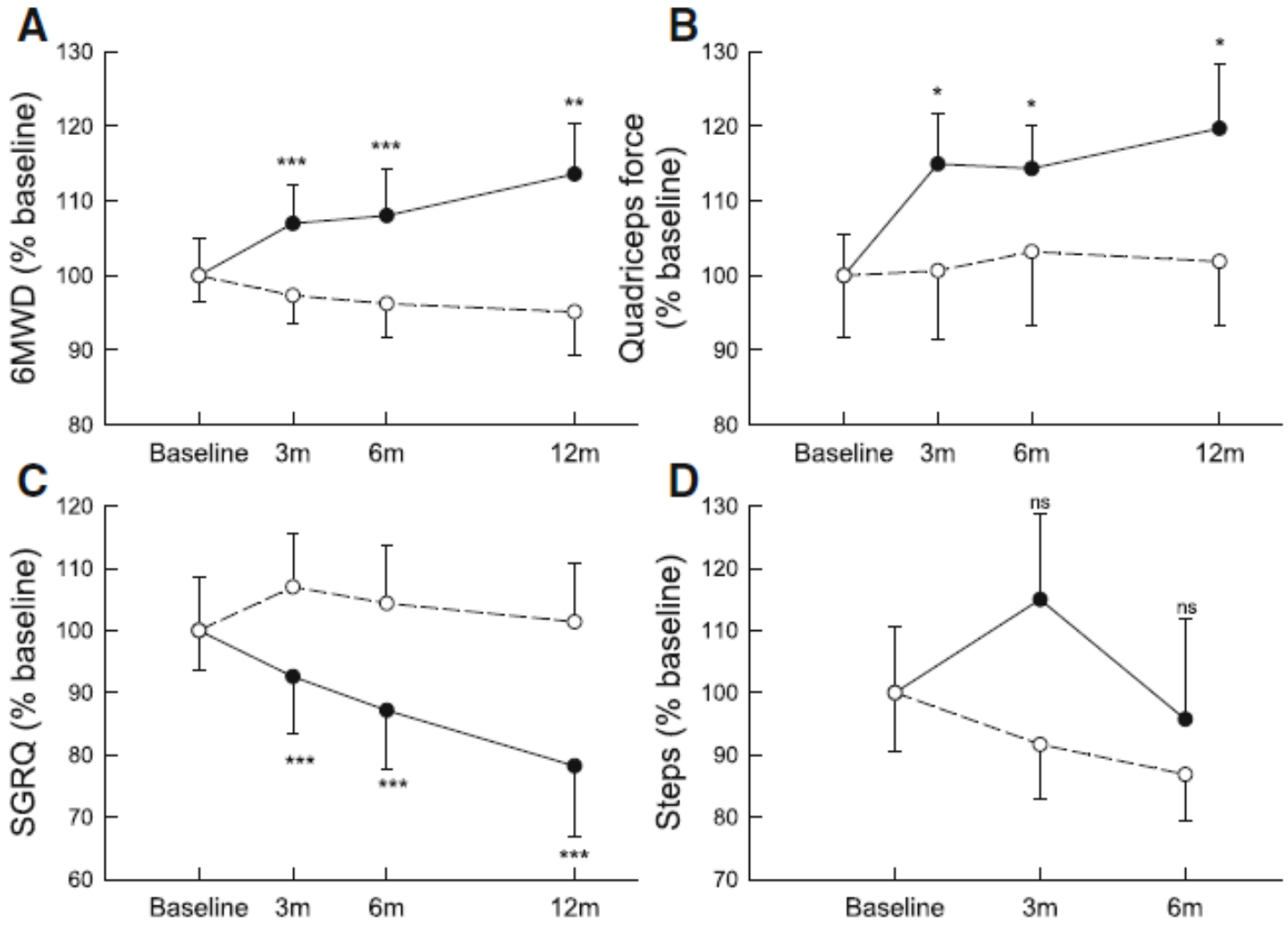
- Moderate disease (FVC 74.5%, DLCO 45.5%)
- Standardized PR course (24 sessions)

Table 2 Outcome measures with absolute and relative change following PR

Outcomes	n	Before PR	Post PR	Absolute change	Relative change (%)	*p*
MRC	40	2.8 ± 0.8	1.7 ± 1.1	- 1.1 ± 0.8	−40.8 ± 35	<.001
SGRQ (Total)	39	50.6 ± 13.9	38.5 ± 13.7	- 12.1 ± 11.1	−23.3 ± 19	<.001
SGRQ (Activity)	39	67.6 ± 14	589 ± 19.6	- 8.8 ± 17.6	−12.5 ± 24.7	0.009
SGRQ (Impact)	39	43.7 ± 19.1	29.9 ± 15.9	- 13.7 ± 14.6	−29.9 ± 41.5	<.001
SGRQ (Symptoms)	39	40.4 ± 20.9	26.7 ± 20.8	- 17 ± 19.8	−36 ± 22.1	<.001
6MWDT (m)	39	376.8 ± 94.6	430.9 ± 96.4	54.1 ± 55.4	16.7 ± 37.8	<.001
Dyspnea 6MWTD (Borg Scale)	39	5.2 ± 2.3	3.8 ± 2.2	−1.4 ± 2.1	−23.4 ± 40.1	.015
Leg fatigue 6MWTD (Borg Scale)	39	3.5 ± 2.7	2 ± 2.2	−1.6 ± 1.5	−48.1 ± 71.5	.006
Cycle dyspnea[a] (Borg scale)	40	6.1 ± 2	4.2 ± 2.7	- 1.8 ± 1.9	−33 ± 35.1	<.001
Cycle leg fatigue[a] (Borg scale)	40	5.9 ± 2.1	3.7 ± 2.7	- 2.2 ± 2	−39.5 ± 106	<.001
Cycle endurance time (min)	40	7.7 ± 3.8	12.5 ± 8.4	4.8 ± 6.9	66 ± 108.1	<.001
Cycle endurance power (watt)	40	57.5 ± 23.7	88.2 ± 57.1	31 ± 53.5	63.4 ± 33.9	.003

Tonelli et al. *BMC Pulm Med.* 2017.

Beneficial Effects of Pulmonary Rehab in ILD Persist at 12 Months



Perez-Bogerd S et al. *Resp Res.* 2018.

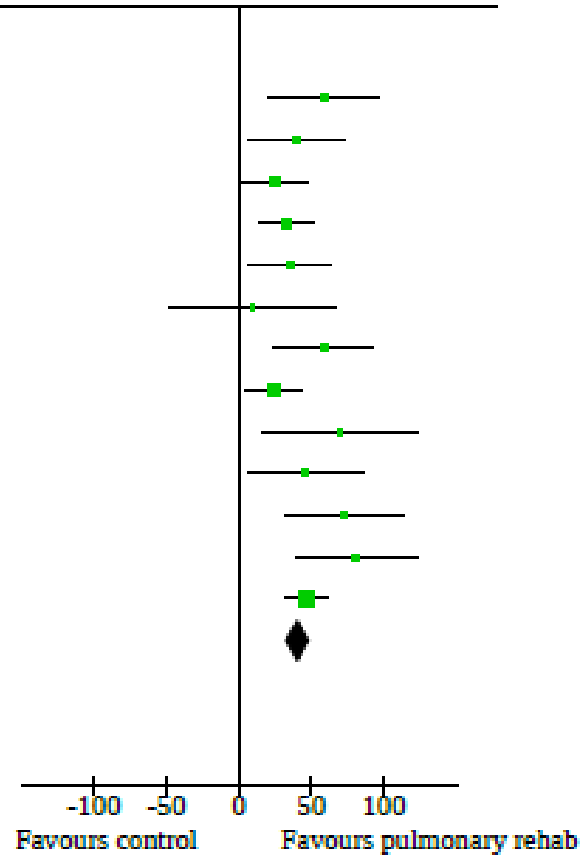
Pulmonary Rehab Improves 6MWD in ILD

Study or Subgroup	Pulmonary rehabilitation Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 All participants								
Dale 2014	71	25.7	7	13	34.4	4	3.6%	58.00 [19.28 , 96.72]
De Las Heras 2019	4.3	24	11	-35.2	47.4	10	5.1%	39.50 [6.88 , 72.12]
Dowman 2017	23	68	74	-2	69.2	68	10.6%	25.00 [2.40 , 47.60]
He 2016	58.7	26.2	15	25.5	25.8	15	15.7%	33.20 [14.59 , 51.81]
Holland 2008	31.2	48.6	30	-3.7	59.8	27	6.7%	34.90 [6.42 , 63.38]
Jackson 2014	-6.2	86.91	11	-15.3	42.89	10	1.6%	9.10 [-48.73 , 66.93]
Jarosch 2020	54.68	85.88	34	-3.83	38.02	17	4.7%	58.51 [24.45 , 92.57]
Ku 2017	27	30.8	20	3.2	29.1	20	15.7%	23.80 [5.23 , 42.37]
Naz 2018	47	33.5	9	-22.6	75.4	9	1.9%	69.60 [15.70 , 123.50]
Nishiyama 2008	42	50.8	13	-4	57.7	15	3.4%	46.00 [5.81 , 86.19]
Perez Bogerd 2018	49	80.4	30	-23	80.4	30	3.3%	72.00 [31.31 , 112.69]
Vainshelboim 2014	70.4	77	15	-10.6	35.4	17	3.0%	81.00 [38.56 , 123.44]
Xiao 2019	53.42	31.9	40	6.97	32.9	34	24.7%	46.45 [31.62 , 61.28]
Subtotal (95% CI)			**309**			**276**	**100.0%**	**40.07 [32.70 , 47.44]**

Heterogeneity: Chi² = 16.25, df = 12 (P = 0.18); I² = 26%

Test for overall effect: Z = 10.66 (P < 0.00001)

Test for subgroup differences: Chi² = 5.42, df = 3 (P = 0.14), I² = 44.7%



Dowman L et al. *Cochrane Reviews* 2021.

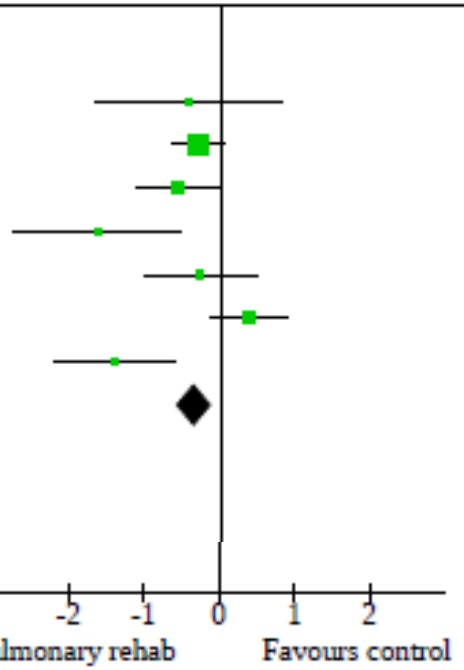
Pulmonary Rehab Improves Dyspnea in ILD

Study or Subgroup	Pulmonary rehabilitation Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.7.1 All participants								
Dale 2014	-0.29	0.49	7	0	0.82	4	3.0%	-0.43 [-1.68 , 0.82]
Dowman 2017	-0.2	0.9	74	0.07	0.9	68	42.7%	-0.30 [-0.63 , 0.03]
Holland 2008	-0.57	1.36	30	0.11	0.91	27	16.6%	-0.57 [-1.10 , -0.04]
Naz 2018	-1	0.7	9	0.2	0.7	9	3.8%	-1.63 [-2.74 , -0.53]
Nishiyama 2008	0	1.3	13	0.4	1.5	15	8.4%	-0.28 [-1.02 , 0.47]
Perez Bogerd 2018	0.1	0.8	30	-0.2	0.8	30	17.9%	0.37 [-0.14 , 0.88]
Vainshelboim 2014	-0.73	0.8	15	0.35	0.7	17	7.6%	-1.41 [-2.19 , -0.62]
Subtotal (95% CI)			**178**			**170**	**100.0%**	**-0.36 [-0.58 , -0.14]**

Heterogeneity: $Chi^2 = 20.59$, $df = 6$ ($P = 0.002$); $I^2 = 71\%$

Test for overall effect: $Z = 3.27$ ($P = 0.001$)

Test for subgroup differences: $Chi^2 = 0.38$, $df = 3$ ($P = 0.94$), $I^2 = 0\%$



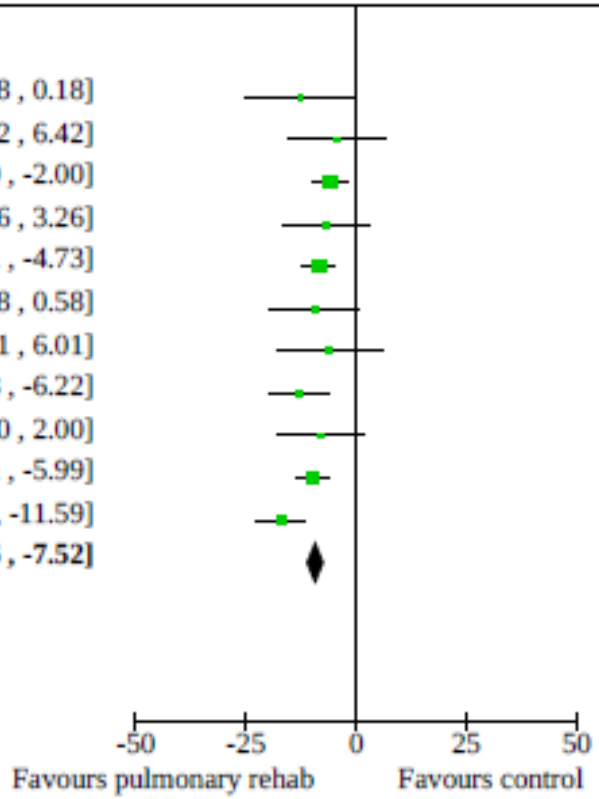
Dowman L et al. *Cochrane Reviews* 2021.

Pulmonary Rehab Improves QOL in ILD

Study or Subgroup	Pulmonary rehabilitation Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.12.1 All participants								
Dale 2014	-6.2	14.3	7	6.4	7.3	4	1.9%	-12.60 [-25.38 , 0.18]
De Las Heras 2019	-7	14	11	-2.5	11.5	10	2.6%	-4.50 [-15.42 , 6.42]
Dowman 2017	-4.8	11.8	74	1.1	11.9	68	20.6%	-5.90 [-9.80 , -2.00]
Gaunaurd 2014	-4.1	14.7	11	2.7	8.2	10	3.1%	-6.80 [-16.86 , 3.26]
Ku 2017	-8.89	3.6	20	-0.47	7.6	20	23.1%	-8.42 [-12.11 , -4.73]
Naz 2018	-15.4	13.2	9	-5.9	8	9	3.1%	-9.50 [-19.58 , 0.58]
Nishiyama 2008	-2.9	14.13	13	3.1	18.25	15	2.2%	-6.00 [-18.01 , 6.01]
Perez Bogerd 2018	-7	13.4	30	6	13.4	30	6.8%	-13.00 [-19.78 , -6.22]
Shen 2016	-9.2	13.5	16	-1.4	14.3	15	3.3%	-7.80 [-17.60 , 2.00]
Vainshelboim 2014	-6.9	6.5	15	2.8	3.6	17	22.9%	-9.70 [-13.41 , -5.99]
Xiao 2019	-18.13	12.6	40	-1.02	11.6	34	10.3%	-17.11 [-22.63 , -11.59]
Subtotal (95% CI)			**246**			**232**	**100.0%**	**-9.29 [-11.06 , -7.52]**

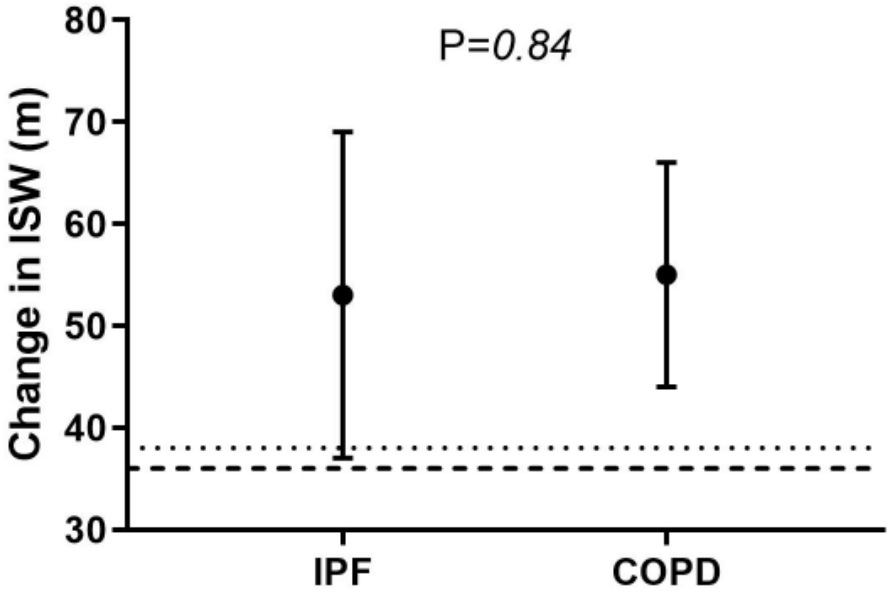
Heterogeneity: $Chi^2 = 13.64$, df = 10 (P = 0.19); $I^2 = 27\%$

Test for overall effect: Z = 10.27 (P < 0.00001)



Dowman L et al. *Cochrane Reviews* 2021.

PR has Similar Benefits in IPF and COPD



Variables	Within group response to PR				Between group difference in response to PR	
	IPF (n=113)		COPD (n=103)		Between group difference	p
	Mean (95 % CI)	p*	Mean (95 % CI)	p*	Mean (95 % CI)	p
Δ ISW (metres)	53 (37 to 69)	<0.001	55 (44 to 66)	<0.001	2 (-18 to 22)	0.84
Δ MRC	-0.7 (-0.8 to -0.5)	<0.001	-0.7 (-0.9 to -0.6)	<0.001	0.0 (-0.2 to 0.3)	0.36
Δ CRQ Dyspnoea	4.0 (2.9 to 5.1)	<0.001	5.0 (3.7 to 6.2)	<0.001	1.0 (-0.7 to 2.6)	0.25
Δ CRQ Fatigue	1.9 (1.0 to 2.8)	<0.001	2.2 (1.3 to 3.1)	<0.001	0.3 (-0.9 to 1.5)	0.62
Δ CRQ Emotional Function	2.3 (1.0 to 3.5)	<0.01	3.3 (2.0 to 4.7)	<0.001	1.1 (-0.7 to 2.9)	0.24
Δ CRQ Mastery	1.4 (0.6 to 2.2)	<0.001	2.2 (1.3 to 3.1)	<0.001	0.8 (-0.4 to 1.94	0.19
Δ CRQ Total	9.6 (6.5 to 12.6)	<0.001	12.7 (9.2 to 16.2)	<0.001	3.2 (-1.4 to 7.7)	0.18

Hypoxemia and Supplemental O2 in ILD

59 y.o. F
- FVC 96%
- DLCO 62%

	Effort #1	Effort #2
Exercise state	Rest	6min walk
Suppl O2 Flow (L/ min)	0	0
Exercise distance (m)		449
SpO2 site	Finger	Finger
SpO2 (%)	97	97
Heart rate (freq/ min)	89	118

55 y.o. M
- FVC 45%
- DLCO 32%

	Effort #1	Effort #2	Effort #3	Effort #4	Effort #5
Exercise state	Rest	Hall walk	Hall walk	Hall walk	Hall walk
Suppl O2 Flow (L/ min)	0	0	2	4	5
Exercise distance (m)		502	120	120	120
SpO2 site	Finger	Finger	Finger	Finger	Finger
SpO2 (%)	96	73	84	88	90
Heart rate (freq/ min)	90	132	112	119	119

69 y.o. M
- FVC 71%
- DLCO 41%

	Effort #1	Effort #2	Effort #3
Exercise state	Rest	Hall walk	Hall walk
Suppl O2 Flow (L/ min)	0	0	3
Exercise distance (m)			600
SpO2 site	Finger	Finger	Finger
SpO2 (%)	97	87	91
Heart rate (freq/ min)	74	110	112

Would he benefit from O2?

Does he need O2?

How much O2?

Supplemental O2 in ILD

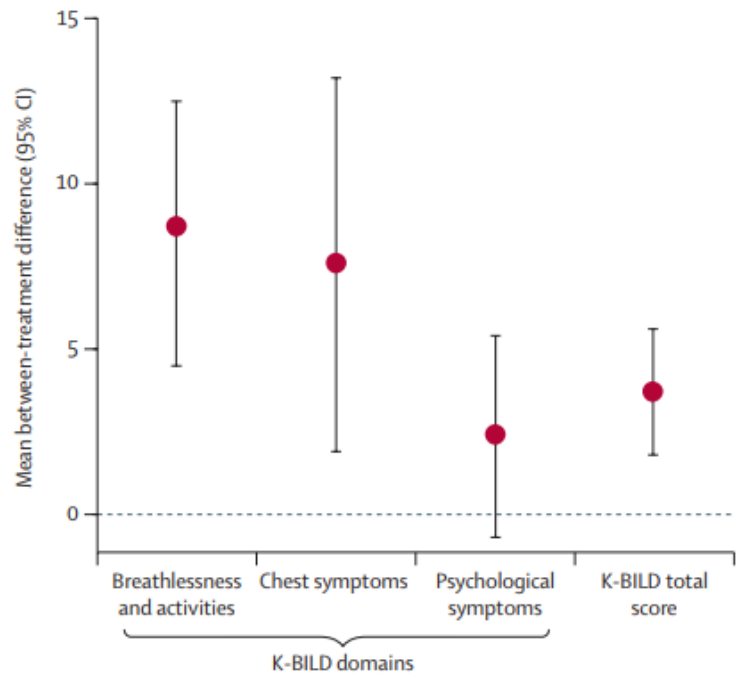
- 2011 International Consensus Guidelines on IPF:
  - Strong recommendation (*weak evidence*) for LTOT in IPF patients with resting hypoxemia (SpO2 <89%; based on data from COPD)
  - *No recommendation* for or against LTOT for isolated exertional hypoxemia

- LOTT Study: supplemental O2 for COPD with exertional hypoxemia or mild resting hypoxemia (NEJM 2016)
  - No difference in long term outcomes, symptoms, or exercise capacity!

- Bell et al. *Eur Resp Rev.* 2017:
  - Meta-analysis of 12 studies of O2 supplementation in ILD (n = 4185 total)
  - LTOT (>12h/day) and "short-term" (e.g. exertional) O2 administration
  - No clear effects on dyspnea during exercise, variable effects on exercise capacity (6MWD, cycle endurance time)

Supplemental O2 in ILD

AmbOx Study: 84 patients with fibrotic ILD and isolated exertional hypoxemia



Outcome	Oxygen	Placebo Air	Difference	*P* value
SpO2 at end of test	90.6 (5.7)	84.7 (4.7)	5.9 (4.8 to 7.0)	<0.0001
Minimum SpO2	88.9 (4.3)	82.9 (4.4)	5.9 (4.8 to 7.1)	<0.0001
Distance walked, m	373.2 (89.9)	354.7 (97.8)	18.5 (10.9 to 26.1)	0.001
Heart rate at end of test	99.9 (14.3)	102 (18.3)	−2.2 (−4.9 to 0.6)	0.12
Maximum heart rate	104.4 (13.8)	108.9 (15)	−4.5 (−6.2 to −2.8)	0.01
SpO2 recovery time, s	117 (101)	217.7 (124)	−101 (−129 to −73)	<0.0001
Heart rate recovery time	163.7 (138.7)	191.9 (145.3)	−28.2 (−67.9 to 11.5)	0.06
Borg dyspnea score	2.1 (0.7 to 3.4)	3.0 (2.0 to 5.1)	−1.6 (−2.1 to −1.1)	<0.0001
Borg fatigue score	0.0 (0.0 to 1.4)	0.1 (0.0 to 2.6)	−0.4 (−1.1 to −0.2)	<0.0001
Borg dyspnea score recovery time, s	112 (72 to 164)	171 (114 to 229)	−49 (−99 to −1)	0.0008
Borg fatigue score recovery time, s	0 (0 to 82)	0 (0 to 174)	−14 (−64 to −0.5)	<0.0001

Data in table are expressed as mean (standard deviation) for first 7 rows and as median (interquartile range) for Borg score data;
K-BILD= King's Brief Interstitial Lung Disease questionnaire. Visca D et al. *Lancet Respir Med.* 2018;6:759-770.

Barriers to O2 use in ILD

Physiologically, the ideal scenario is SpO2 ≥ 90% at all times

- This is not realistic!

Physical/Mechanical Barriers	Psychological/Social Barriers
Equipment weight and size	Dependency
Tank duration/battery life	Emotionally constrained
Flow rate	Appearance of weakness, illness, vulnerability
Continuous vs. pulsed flow	Stigma (self-inflicted problem?)
Severity of hypoxemia	
Physically constrained	

Pragmatic Approach to O2 in ILD

Scenario	Treatment Approach
Resting SpO2 <89%	- Strong recommendation for O2
Mild exertional hypoxemia (SpO2min 86-88%)	- Self-monitoring SpO2 - Trial of O2 based on symptoms - PR-guided O2
Mod-severe exertional hypoxemia (SpO2min ≤85%)	- Recommend O2 with self-monitoring

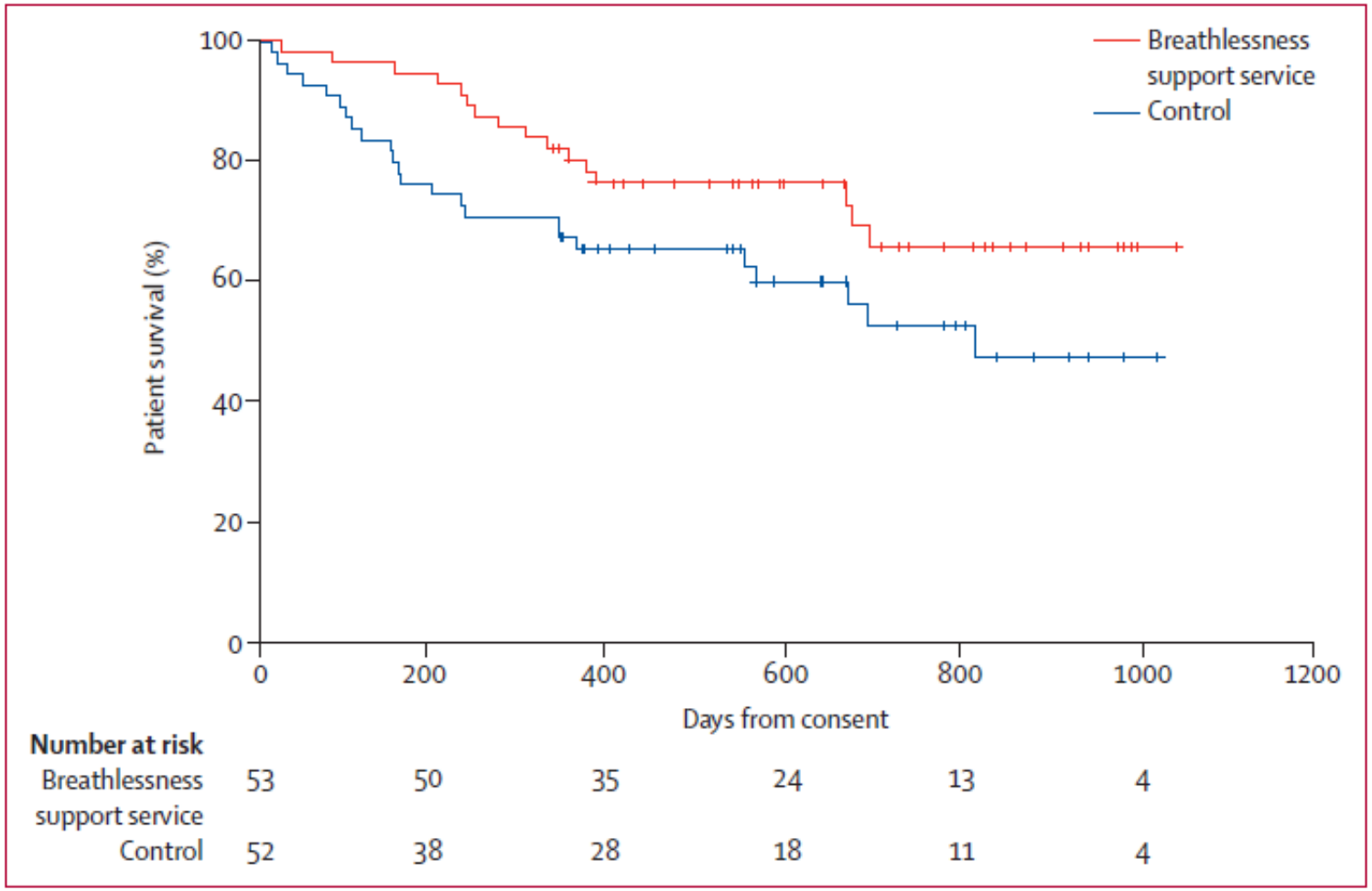
2020 ATS Guidelines on home O2

- *Strong* recommendation for O2 Rx for severe resting hypoxemia (very low quality evidence)
- *Conditional* recommendation for O2 Rx for severe exertional hypoxemia (low quality evidence)

- Spot-check self-monitoring SpO2 is very helpful!
  - Rest vs. usual activities (room-to-room, stairs, etc.) vs. formal exercise

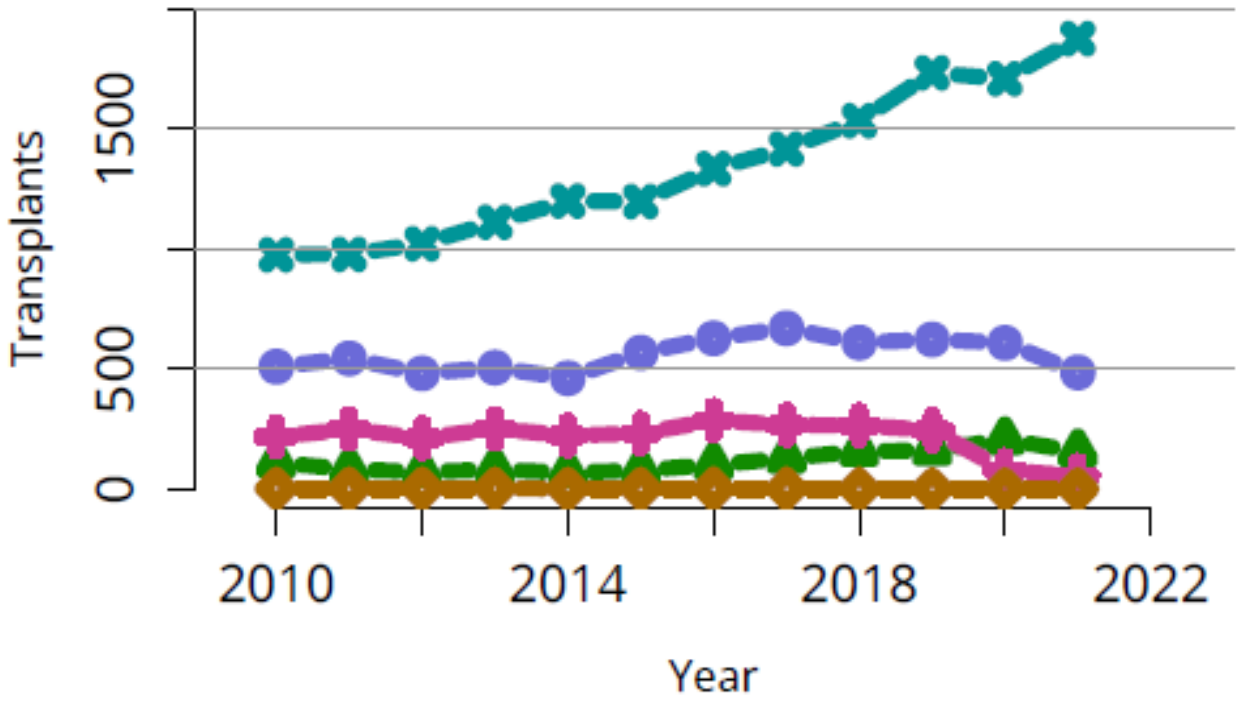
- Goal SpO2 has to be individualized and based on many factors
  - Symptoms, SpO2min and recovery time
  - Feasibility: maximum flow rate vs. tank size/battery life
  - May be a moving target as disease changes over time
  - Some is better than none!

Palliative Care for ILD



Higginson et al. *Lancet Resp*. 2014

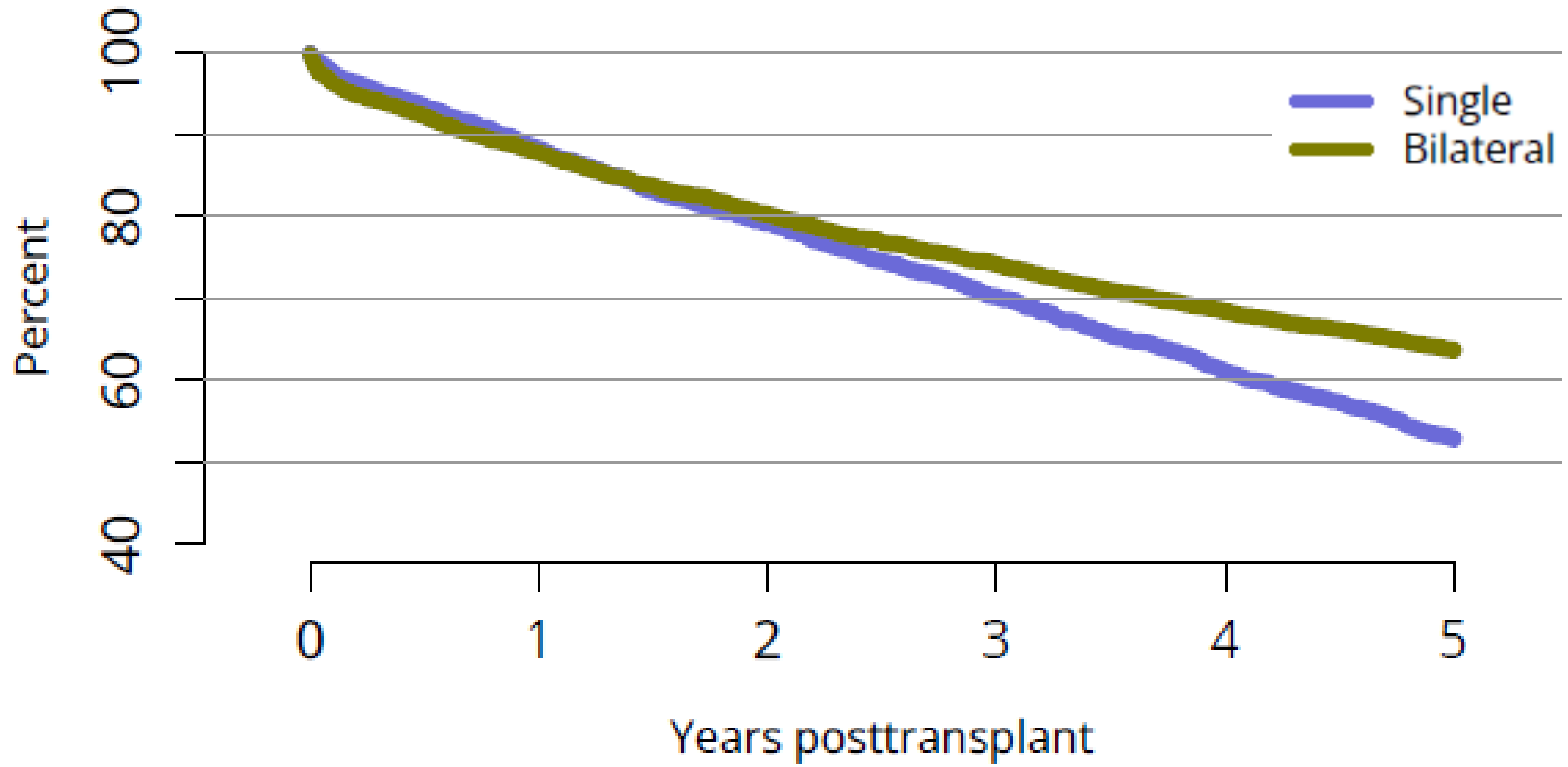
ILD is the Leading Indication for Lung Transplant in the U.S.



Most common indication is restrictive lung disease (ILD)

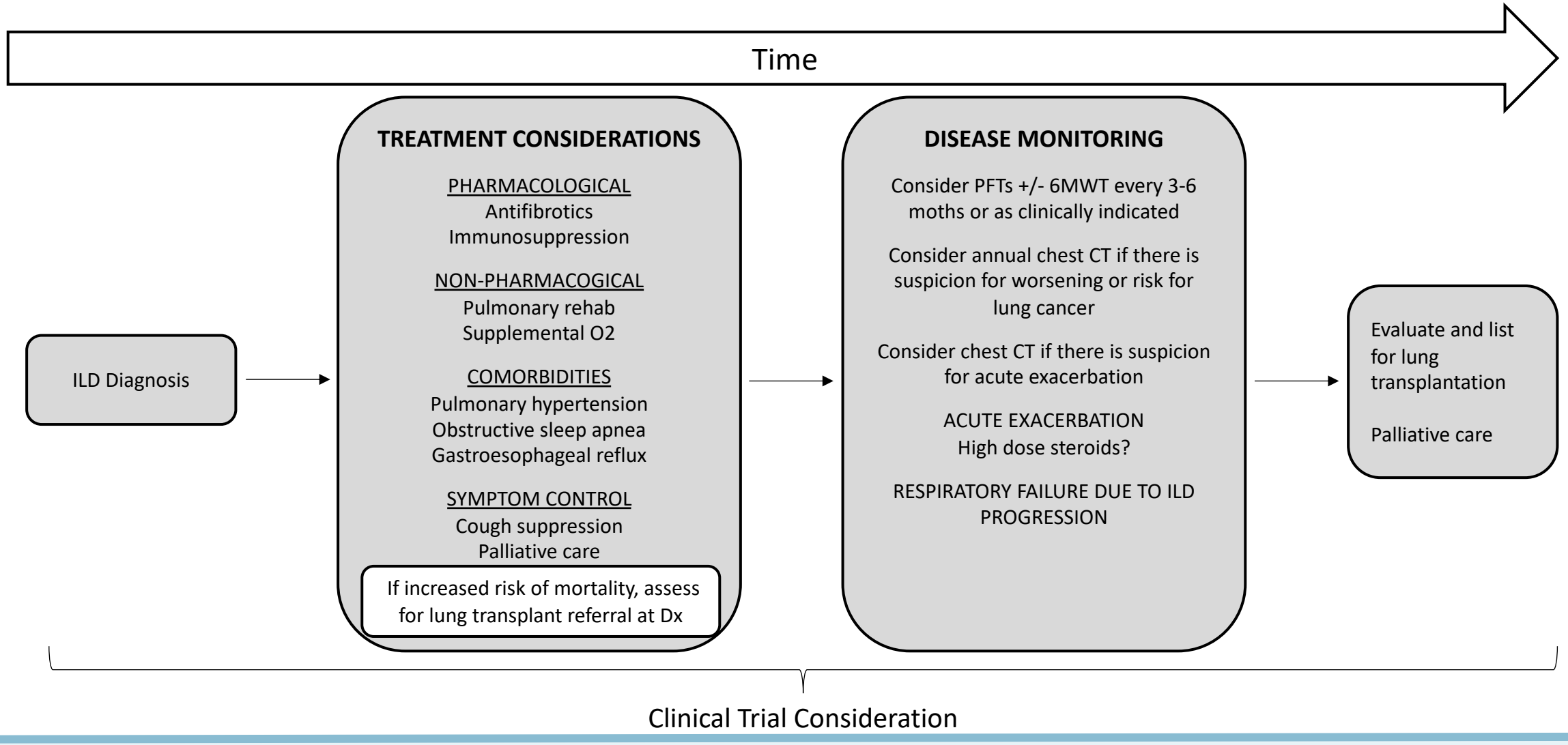
- ~70% in 2021

Survival after Lung Transplantation



OPTN=Organ Procurement and Transplantation Network; SRTR=Scientific Registry of Transplant Recipients.

Summary/Overview of ILD Management



Modified from: Raghu G et al. *Am J Respir Crit Care Med.* 2022;192:e18-e47.