Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-253z Nintedanib

Stand: Februar 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Nintedanib zur Behandlung der idiopathischen Lungenfibrose (IPF)	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht "II. Zugelassene Arzneimittel im Anwendungsgebiet"*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Langzeit-Sauerstofftherapie • Lungentransplantation • Pulmonale Rehabilitation • Physikalische Therapie (i.S. der Heilmittel-RL)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• (Nintedanib (nAWG) *(Beschluss vom 03. September 2015))* • Pirfenidon *(Beschluss vom 15. März 2012)*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Nintedanib L01XE31 Ofev®	Nintedanib wird angewendet bei Erwachsenen zur Behandlung der idiopathischen Lungenfibrose (IPF). (Stand FI: Oktober 2018)
Methylprednisolon H02AB04 Methylprednisolon Jenapharm®	Bronchial- und Lungenkrankheiten […] – Interstitielle Lungenerkrankungen, wie akute Alveolitis, Lungenfibrose, zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte) (Stand FI: April 2018)
Prednisolon H02AB06 generisch	Pneumonologie: […] – interstitielle Lungenerkrankungen wie akute Alveolitis (DS: b), Lungenfibrose (DS: b), Bronchiolitis obliterans organisierende Pneumonie (BOOP) (DS: b ausschleichend), ggf. in Kombination mit Immunsuppressiva, chronische eosinophile Pneumonie (DS: b ausschleichend), zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte) (DS: b) […] (Stand FI: September 2017)
Prednison H02AB07 generisch	Pneumonologie: […] – interstitielle Lungenerkrankungen wie akute Alveolitis (DS: b), Lungenfibrose (DS: b), Bronchiolitis obliterans organisierende Pneumonie (BOOP) (DS: b ausschleichend), ggf. in Kombination mit Immunsuppressiva, chronische eosinophile Pneumonie (DS: b ausschleichend), zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte) (DS: b) […] (Stand FI: September 2017)
Pirfenidon L04AX05	Esbriet wird angewendet bei Erwachsenen zur Behandlung von leichter bis mittelschwerer idiopathischer pulmonaler Fibrose (IPF). (Stand FI: April 2018)

Esbriet®	

Quellen: AMIS-Datenbank, Fachinformationen (Stand: Februar 2019)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-253z (Nintedanib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	30. Januar 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
6MWD	6-Minute Walking Distance
FVC	Forced vital capacity
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ILD	Interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IPF	Idiopathic pulmonary fibrosis
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PFS	Progression Free Survival
PR	Pulmonary rehabilitation
RR	Relatives Risiko
SGRQ-I	IPF specific St. George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization
WMD	Weighted mean difference

1 Indikation

Erwachsenen zur Behandlung der idiopathischen Lungenfibrose (IPF)

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *idiopathische Lungenfibrose* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 10.12.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 251 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 17 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2012 [9].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. März 2012 – Pirfenidon

Anwendungsgebiet

Esbriet® wird angewendet bei Erwachsenen zur Behandlung von leichter bis mittelschwerer idiopathischer pulmonaler Fibrose (IPF).

Für Arzneimittel zur Behandlung eines seltenen Leidens (Orphan Drugs), die nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 zugelassen sind, gilt gemäß § 35a SGB V Abs. 1 Satz 10 Halbs. 1 SGB V der medizinische Zusatznutzen durch die Zulassung als belegt. Nachweise zum medizinischen Nutzen und zum medizinischen Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie müssen nicht vorgelegt werden (§ 35a SGB V Abs. 1 Satz 10 Halbs. 2 SGB V).

Ausmaß des Zusatznutzens

Aus Tragenden Gründen: ein Zusatznutzen liegt vor, ist aber nicht quantifizierbar, weil die wissenschaftliche Datenlage dies zum derzeitigen Zeitpunkt nicht zulässt.

G-BA, 2015 [8].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 3. September 2015 – Nintedanib

Anwendungsgebiet

Nintedanib (Ofev®) wird angewendet bei Erwachsenen zur Behandlung der idiopathischen Lungenfibrose (IPF).

Nintedanib ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 10 gilt der medizinische Zusatznutzen durch die Zulassung als belegt.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Geringer Zusatznutzen

3.2 Cochrane Reviews

Dowman L et al., 2014 [6].

Pulmonary rehabilitation for interstitial lung disease

Fragestellung

- To determine whether pulmonary rehabilitation in patients with ILD has beneficial effects on exercise capacity, symptoms, quality of life and survival compared with no pulmonary rehabilitation in patients with ILD.
- To assess the safety of pulmonary rehabilitation in patients with ILD.

Methodik

Population:

- People with ILD of any origin, diagnosed according to investigator definitions, were included. No exclusions were based on age, gender or physiological status

Intervention:

- any type of prescribed exercise training, supervised or unsupervised, provided with or without education

Komparator:

- no intervention or another intervention

Endpunkte:

- Primary endpoint: Functional or maximal exercise capacity, measured during formal exercise tests (maximal oxygen uptake (VO2 max), peak oxygen uptake (VO2 peak), maximal ventilation (Ve max), maximum heart rate (HR max)) or field exercise tests (increase in distance walked)
- Dyspnoea: All measures of dyspnoea used were considered.
- Quality of life: All quality of life instruments used were considered.
- Adverse effects: Adverse cardiovascular events during exercise training were recorded, as were fractures, skeletal muscle injuries and deaths.
- Survival

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 6), MEDLINE (Ovid), EMBASE (Ovid), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO) and the Physiotherapy Evidence Database (PEDro). All databases were searched from the period of their inception to June 2014

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

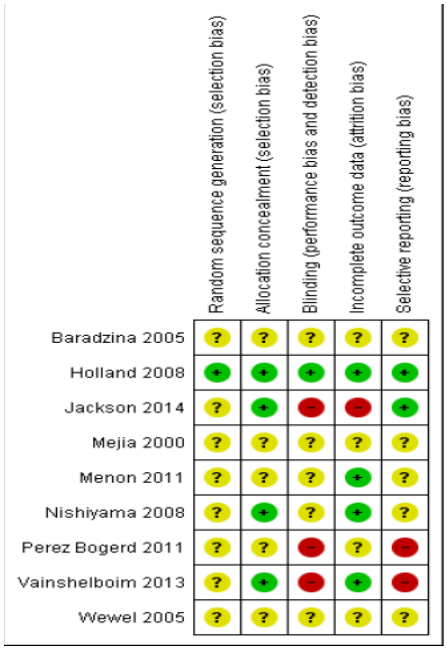
Anzahl eingeschlossener Studien:

- Nine studies; all were parallel randomised controlled trials. Three studies included only participants with IPF (Jackson 2014; Nishiyama 2008; Vainshelboim 2013)
- Six studies had been published in abstract form only (Baradzina 2005; Mejia 2000; Menon 2011; Perez Bogerd 2011; Vainshelboim 2013; Wewel 2005). Sample sizes ranged from 21 to 99 participants.

Charakteristika der Population:

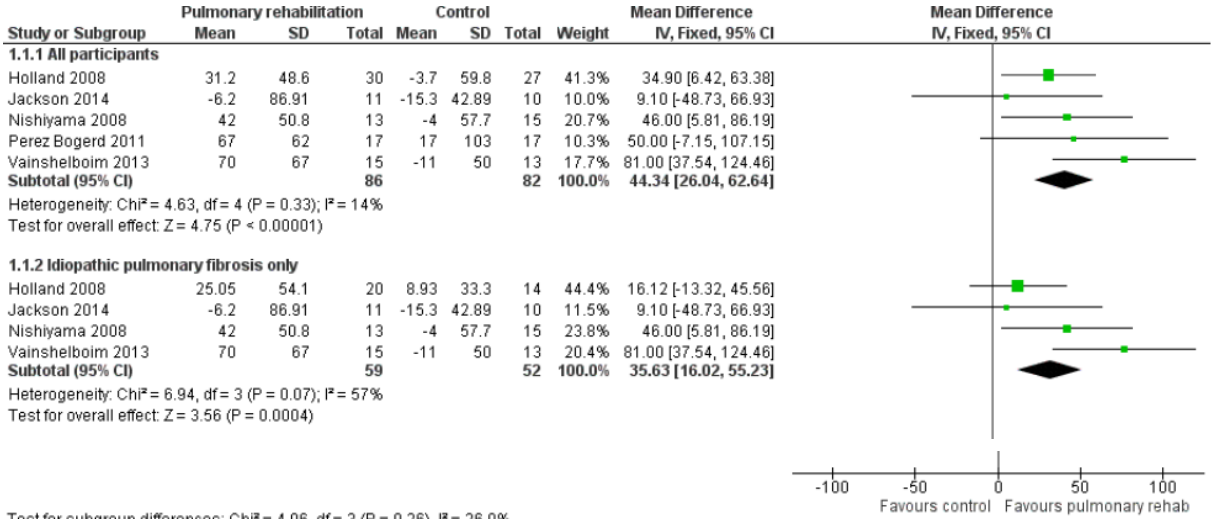
- Most studies included participants with a variety of ILDs (Holland 2008; Mejia 2000; Menon 2011; Perez Bogerd 2011; Wewel 2005), one of which was stratified for IPF (Holland 2008). Three studies included only participants with IPF (Jackson 2014; Nishiyama 2008; Vainshelboim 2013)
- All studies compared pulmonary rehabilitation versus no pulmonary rehabilitation or a sham training control group. Eight studies examined pulmonary rehabilitation programmes conducted in the outpatient setting (Baradzina 2005; Holland 2008; Jackson 2014; Mejia 2000; Menon 2011; Nishiyama 2008; Perez Bogerd 2011; Vainshelboim 2013), whilst one study evaluated a home-based pulmonary rehabilitation programme (Wewel 2005).
- The length of pulmonary rehabilitation programmes varied from five to 12 weeks for outpatient rehabilitation and six months for home-based rehabilitation.

Qualität der Studien:



Studienergebnisse:

Change in 6-minute walk test immediately following pulmonary rehabilitation



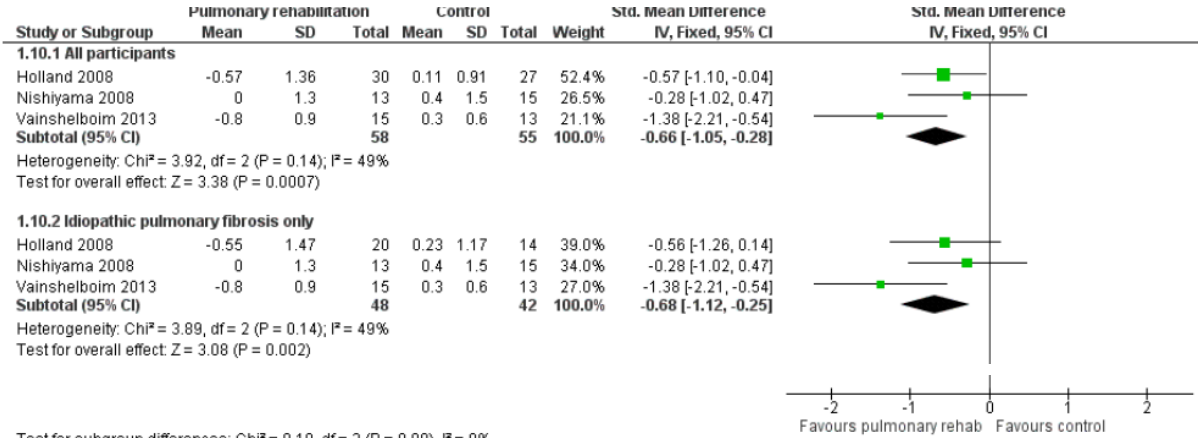
Study or Subgroup	Pulmonary rehabilitation Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 All participants								
Holland 2008	31.2	48.6	30	-3.7	59.8	27	41.3%	34.90 [6.42, 63.38]
Jackson 2014	-6.2	86.91	11	-15.3	42.89	10	10.0%	9.10 [-48.73, 66.93]
Nishiyama 2008	42	50.8	13	-4	57.7	15	20.7%	46.00 [5.81, 86.19]
Perez Bogerd 2011	67	62	17	17	103	17	10.3%	50.00 [-7.15, 107.15]
Vainshelboim 2013	70	67	15	-11	50	13	17.7%	81.00 [37.54, 124.46]
Subtotal (95% CI)			**86**			**82**	**100.0%**	**44.34 [26.04, 62.64]**
Heterogeneity: Chi² = 4.63, df = 4 (P = 0.33); I² = 14%								
Test for overall effect: Z = 4.75 (P < 0.00001)								
1.1.2 Idiopathic pulmonary fibrosis only								
Holland 2008	25.05	54.1	20	8.93	33.3	14	44.4%	16.12 [-13.32, 45.56]
Jackson 2014	-6.2	86.91	11	-15.3	42.89	10	11.5%	9.10 [-48.73, 66.93]
Nishiyama 2008	42	50.8	13	-4	57.7	15	23.8%	46.00 [5.81, 86.19]
Vainshelboim 2013	70	67	15	-11	50	13	20.4%	81.00 [37.54, 124.46]
Subtotal (95% CI)			**59**			**52**	**100.0%**	**35.63 [16.02, 55.23]**
Heterogeneity: Chi² = 6.94, df = 3 (P = 0.07); I² = 57%								
Test for overall effect: Z = 3.56 (P = 0.0004)								

Mean Difference IV, Fixed, 95% CI

-100 -50 0 50 100

Favours control Favours pulmonary rehab

Dyspnoea immediately following pulmonary rehabilitation



Study or Subgroup	Pulmonary rehabilitation Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.10.1 All participants								
Holland 2008	-0.57	1.36	30	0.11	0.91	27	52.4%	-0.57 [-1.10, -0.04]
Nishiyama 2008	0	1.3	13	0.4	1.5	15	26.5%	-0.28 [-1.02, 0.47]
Vainshelboim 2013	-0.8	0.9	15	0.3	0.6	13	21.1%	-1.38 [-2.21, -0.54]
Subtotal (95% CI)			**58**			**55**	**100.0%**	**-0.66 [-1.05, -0.28]**
Heterogeneity: Chi² = 3.92, df = 2 (P = 0.14); I² = 49%								
Test for overall effect: Z = 3.38 (P = 0.0007)								
1.10.2 Idiopathic pulmonary fibrosis only								
Holland 2008	-0.55	1.47	20	0.23	1.17	14	39.0%	-0.56 [-1.26, 0.14]
Nishiyama 2008	0	1.3	13	0.4	1.5	15	34.0%	-0.28 [-1.02, 0.47]
Vainshelboim 2013	-0.8	0.9	15	0.3	0.6	13	27.0%	-1.38 [-2.21, -0.54]
Subtotal (95% CI)			**48**			**42**	**100.0%**	**-0.68 [-1.12, -0.25]**
Heterogeneity: Chi² = 3.89, df = 2 (P = 0.14); I² = 49%								
Test for overall effect: Z = 3.08 (P = 0.002)								

Std. Mean Difference IV, Fixed, 95% CI

-2 -1 0 1 2

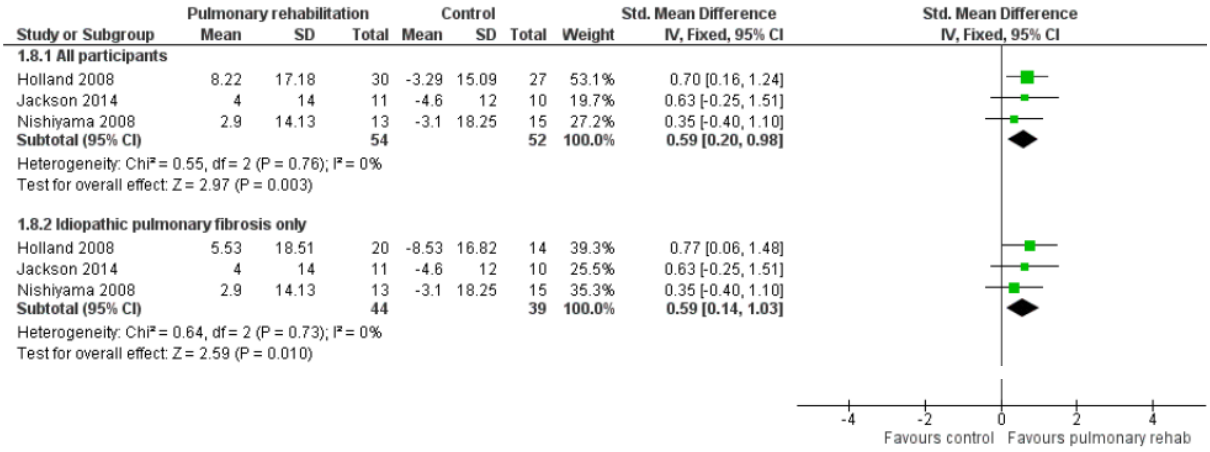
Favours pulmonary rehab Favours control

Quality of life immediately following pulmonary rehabilitation

Health-related quality of life was measured in eight studies, with significant differences between groups reported immediately following pulmonary rehabilitation in three studies (Holland 2008; Nishiyama 2008; Vainshelboim 2013).

Two studies utilized the Chronic Respiratory Disease Questionnaire (Holland 2008), one used the St George's Respiratory Questionnaire (Nishiyama 2008) and the other used the St George's Respiratory Questionnaire (idiopathic pulmonary fibrosis version) (Jackson 2014).

Figure 6. Forest plot of comparison: 1 Pulmonary rehabilitation versus no pulmonary rehabilitati outcome: 1.8 Change in quality of life immediately following pulmonary rehabilitation.



Survival

Six-month survival was reported in one study including 57 participants (Holland 2008) in which two deaths were reported in each group

Adverse events

Information regarding adverse events was available fromtwo studies (Holland 2008; Nishiyama 2008), neither of which reported adverse events during the study period. One study reported the death of one pulmonary rehabilitation participant during the intervention period; however this was believed to be unrelated to the intervention received, and the data were not included in the analysis (Jackson 2014).

Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short-term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax 2008;63:549-5

Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka A, Ogawa T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology 2008;13:394-9.

Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, et al. Pulmonary rehabilitation in idiopathic pulmonary fibrosis. American Thoracic Society 100th International Conference; May 21-26; Orlando. 2004:D96 Poster 110.

Kramer M, Vainshelboim B, Oliveira J, Yohoshua L, Wais I, Rusanov V, et al. Pulmonary rehabilitation improves exercise capacity and function in patients with idiopathic pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine 2013;187(Meeting Abstracts):A1832.

Vainshelboim B, Oliveira L, Yohoshua L, Weis I, Fox B, Kramer M. The effect of pulmonary rehabilitation on exercise tolerance, pulmonary function, dyspnea and quality of life in patients with idiopathic pulmonary fibrosis. European Respiratory Society 23rd Annual Congress; Sep 7-11; Barcelona. 2013; Vol. 187, issue Meeting Abstracts:A1832.

Anmerkung/Fazit der Autoren

This review indicates that pulmonary rehabilitation seems to be safe for people with ILD and results in significantly improved functional exercise capacity, maximum exercise capacity, dyspnoea and health-related quality of life immediately following pulmonary rehabilitation. It is appropriate to include people with ILD in a standard pulmonary rehabilitation programme. To date, little evidence has suggested a long-term benefit of pulmonary rehabilitation in ILD.

3.3 Systematische Reviews

Gomes-Neto M et al., 2018 [10].

Impact of pulmonary rehabilitation on exercise tolerance and quality of life in patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis

Fragestellung

The purpose of this study was to determine the effects of pulmonary rehabilitation on exercise tolerance and quality of life in patients with idiopathic pulmonary fibrosis

Methodik

Population:

- patients with idiopathic pulmonary fibrosis

Intervention:

- PR was defined as a comprehensive, multidisciplinary program composed of a combination of exercise training, education, and behavior modification techniques

Komparator:

- Others

Endpunkte:

- Exercise tolerance and quality of life

Recherche/Suchzeitraum:

- MEDLINE, Cochrane Library, Embase, Scielo, PEDro, and CINAHL (from the earliest date available to June 2016)

Qualitätsbewertung der Studien:

- PEDro scale is a useful tool for assessing the methodological quality of physiotherapy and rehabilitation RCTs. 14. The score range is 0 to 10

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 articles

Charakteristika der Population:

- The number of participants in the included studies ranged from 21 20 , 22 to 32. 19 , 21 The mean age of the participants ranged from 66 to 68 years. All of the studies included patients of both genders, but there was an overall predominance of male participants.
- The parameters used in the application of PR were reported in most studies. In all, 10 to 12 weeks of PR programs were performed. Furthermore, sessions were performed 2 times per week. The PR program included aerobic, resistance, and fl exibility exercise modes in all studies.

Qualität der Studien:

Table 1
Study Quality According to the PEDro Scale[a]

		1[b]	2	3	4	5	6	7	8	9	10	11	Total
1	Nishiyama et al (2008) [23]	✓	✓	✓	✓				✓		✓	✓	6
2	Gaunaurd et al (2014)[22]		✓								✓	✓	3
3	Jackson et al (2014)[20]		✓		✓							✓	3
4	Vainshelboim et al (2014)[21]	✓	✓	✓	✓				✓	✓	✓	✓	7
5	Vainshelboim et al (2015)[19]	✓	✓	✓	✓				✓		✓	✓	6

[a]PEDro Scale: 1, eligibility criteria and source of participants; 2, random allocation; 3, concealed allocation; 4, baseline comparability; 5, blinded participants; 6, blinded therapists; 7, blind assessors; 8, adequate follow-up; 9, intention-to-treat analysis; 10, between-group comparisons; 11, point estimates and variability.
[b]Item 1 does not contribute to the total score.

Studienergebnisse:

Exercise tolerance

- significant improvement in exercise tolerance of 44 m (95% CI, 5.3-82.8; n = 113, 4 studies) for 6-minute walk distance (6MWD) for patients in the PR group compared with the control group

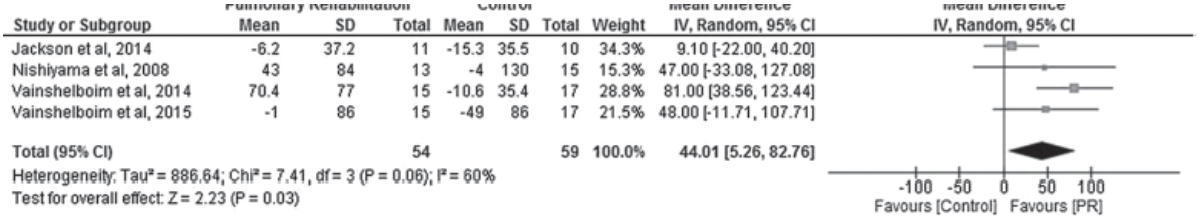


Figure 2. Pulmonary rehabilitation versus control: exercise tolerance. Review Manager (RevMan, version 5.3, The Cochrane Collaboration, 2013).
Abbreviation: PR, pulmonary rehabilitation.

Quality of life with St George's Respiratory Questionnaire although Gaunaurd et al

- A total of 113 patients were included in these 4 studies.
- In the study by Vainshelboim et al, 21 quality of life showed a between-group difference in 2 dimensions (Symptoms and Impact) and in total score, whereas Gaunaurd et al 22 showed a between-group difference in the Symptoms dimension in favor of PR.
- Meta- analyses showed significant improvement in Symptoms score, Impact score, and total score for participants in the PR group compared with the control group (Figure 3).
- A nonsignificant difference in activity score was found for participants in the PR group compared with the control group.

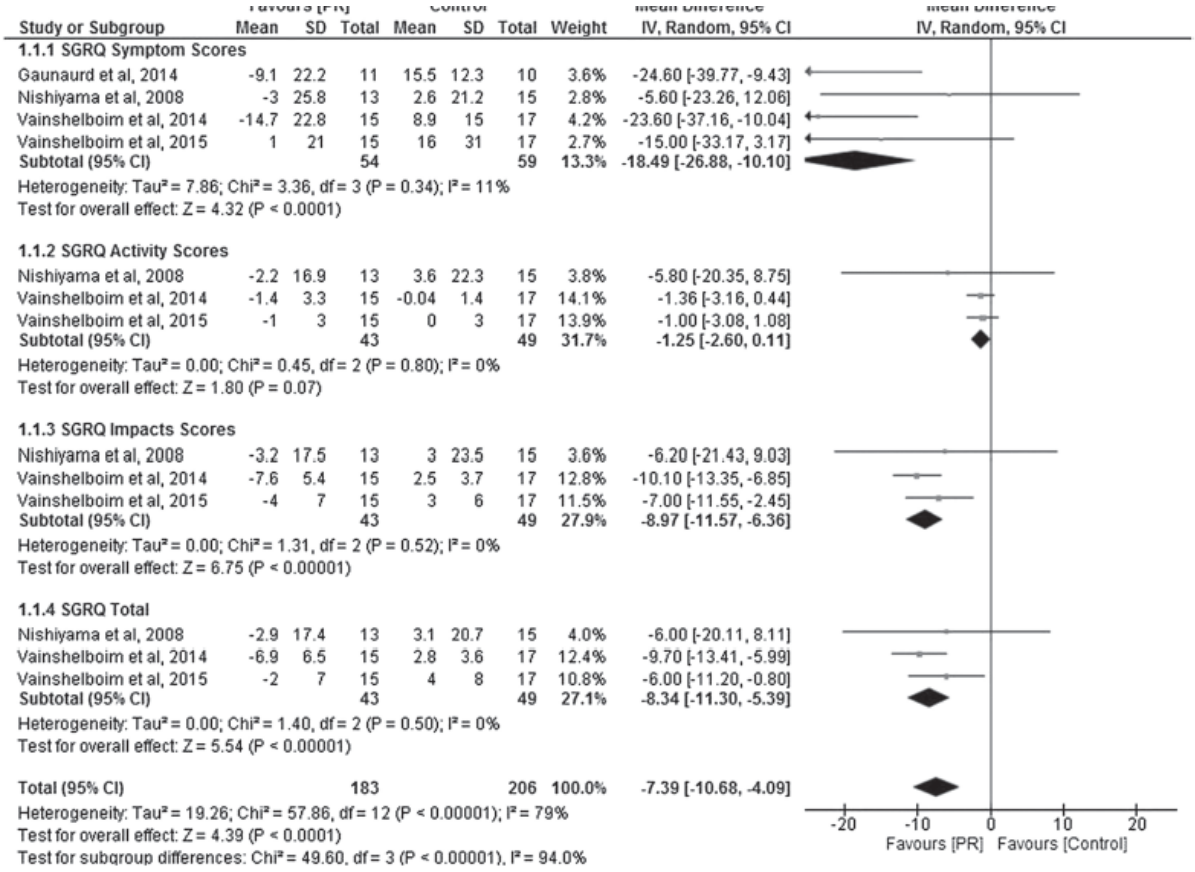


Figure 3. Pulmonary rehabilitation versus control: quality of life. Review Manager (RevMan, version 5.3, The Cochrane Collaboration, 2013). Abbreviations: PR, pulmonary rehabilitation; SGRQ, St George's Respiratory Questionnaire.

19. Vainshelboim B , Oliveira J , Fox BD , Soreck Y , Fruchter O , Kramer MR . Long-term effects of a 12-w eek exercise training program on clinical outcomes in idiopathic pulmonary fi brosis . Lung . 2015 ; 193 : 345-354 .
20. Jackson RM , Gomez-Marin OW , Ramos CF , et al. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. Lung . 2014 ; 192 : 367-376 .
21. Vainshelboim B , Oliveira J , Yehoshua L , et al. Exercise training-based pulmonary rehabilitation program is clinically benefi cial for idiopathic pulmonary fi brosis . Respiration . 2014 ;88(5) :378-388 .
22. Gaunaurd IA , Gómez-Marín OW , Ramos CF , et al. Physical activity and quality of life improvements of patients w ith idiopathic pulmonary fi brosis completing a pulmonary rehabilitation program . Respir Care . 2014 ; 59 : 1872-1879 .
23. Nishiyama O , Kondoh Y , Kimura T , et al. Effects of pulmonary rehabilitation in patients w ith idiopathic pulmonary fi brosis . Respirology 2008 ; 13 : 394-399 .

Anmerkung/Fazit der Autoren

This systematic review with meta-analysis showed that PR is effective in increasing exercise tolerance and quality of life in patients with idiopathic pulmonary fibrosis

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Cheng L et al., 2018 [5].

Short- and long-term effects of pulmonary rehabilitation for idiopathic pulmonary fibrosis: a systematic review and meta-analysis

Fragestellung

We performed this systematic review and meta-analysis to investigate the short- and long-term effects of pulmonary rehabilitation in patients with IPF.

Methodik

Population:

- Patients with IPF

Intervention:

- Exercise based pulmonary rehabilitation

Komparator:

- No pulmonary rehabilitation

Endpunkte:

- Exercise capacity and health-related quality of life

Recherche/Suchzeitraum:

- MEDLINE (through PubMed), Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception to 15 March 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Heterogenität

I^2 values of less than 25%, 25%–50% or more than 50% indicated low, moderate or high heterogeneity, respectively.[12] A random-effects model was used in the presence of significant heterogeneity

Ergebnisse

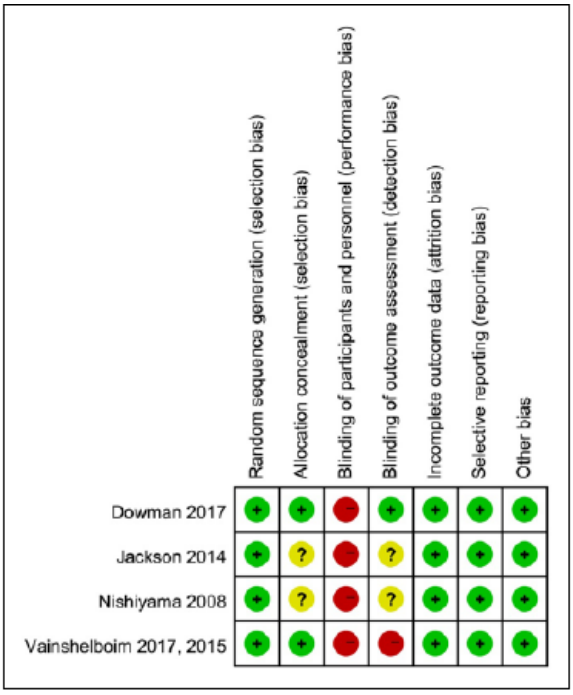
Anzahl eingeschlossener Studien:

- 4 RCTs (n=142)

Charakteristika der Population:

- The short-term effects of pulmonary rehabilitation were described by all RCTs,2,8,15,16 while the long-term effects were described by two RCTs only.2,14 The pulmonary rehabilitation programs included outpatient exercise training, home exercise, supplemental oxygen, education and medical care and varied in duration between 9 and 12 weeks.

Qualität der Studien:



All of the four studies were randomized and had similar group characteristics at baseline. Two studies did not report on their methods of allocation concealment or[15,16] blinding of outcome assessment[15,16] (while outcome assessment was un-blinded in one study).[8,14] None of the studies blinded their participants because of the nature of the intervention.

Studienergebnisse:

Short-term outcomes

- aggregate analyses of four studies showed that pulmonary rehabilitation significantly enhanced 6-minute walk distance (6-MWD) (4 RCTs, WMD = 38.38, 95% CI = 4.64– 72.12, I2 = 60.7%; P < 0.05);
- health-related quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ)8,16 or IPF-specific SGRQ (SGRQ-I).2 The SGRQ/ SGRQ-I total scores were reduced significantly in the pulmonary rehabilitation group, compared to control group (3 RCTs, WMD = –8.40, 95% CI = –11.44 to −5.36, I2 = 0%; P < 0.00001);

Long-term follow up

- no significant difference between both groups in terms of 6-MWD (2 RCTs, WMD = 17.02, 95% CI = –26.87 to 60.81, I2 = 36.3%; P = 0.43).
- no significant differences were seen in the SGRQ/SGRQ-I total scores (2 RCTS, WMD = –3.45, 95% CI =–8.55 to 1.64, I2 = 38.3%; P = 0.088)

8. Vainshelboim B, Kramer MR, Fox BD, et al. Supervised exercise training improves exercise cardiovascular function in idiopathic pulmonary fibrosis. Eur J Phys Rehabil Med 2017; 53(2): 209–218.
9. Dowman LM, McDonald CF, Hill CJ, et al. The evidence of benefits of exercise training in interstitial lung disease: randomised controlled trial. Thorax 2017; 72(7): 610–619.
14. Vainshelboim B, Oliveira J, Fox BD, et al. Long-term effects of a 12-week exercise training program on clinical outcomes in idiopathic pulmonary fibrosis. Lung 2015; 193(3): 345–354.
15. Gaunaurd IA, Gomez-Marin OW, Ramos CF, et al. Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. Respir Care 2014; 59(12): 1872–1879.
16. Nishiyama O, Kondoh Y, Kimura T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology 2008; 13(3): 394–399.

Anmerkung/Fazit der Autoren

Our study indicated that pulmonary rehabilitation significantly improved exercise capacity and health-related quality of life in patients with IPF at the end of the intervention (short term). However, it showed no significant impact on these parameters on the long term. The long-term improvement in exercise capacity,

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Aravena C et al., 2015 [2,3].

Pirfenidone for Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta- Analysis

Fragestellung

The aim of this study is to assess the efficacy and security of pirfenidone on several clinical (including mortality, acute exacerbations and worsening of IPF) and physiological outcomes in IPF.

Methodik

Population:

- idiopathic pulmonary fibrosis

Intervention:

- Pirfenidone

Komparator:

- Placebo

Endpunkte:

- 1) Change in all cause- mortality 2) Change in IPF related mortality 3) Progression-free Survival (PFS) 4) Decrease in predicted Forced Vital Capacity (FVC) 5) Worsening of Idiopathic pulmonary fibrosis 6) Acute exacerbation 7) Change in Six-Minute Walk Test (6MWT) Distance 8) Adverse Effect (all included adverse events, skin related adverse events and change in aminotransferases

Recherche/Suchzeitraum:

- Lilacs, Clinical Trials Registry Platform (ICTRP), clinicaltrials.gov and the Cochrane Controlled Trials Register up to October 30th of 2014

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Heterogenität

- For results showing significant heterogeneity (I2>50%), A random- effects meta-analysis was performed

Ergebnisse

Anzahl eingeschlossener Studien:

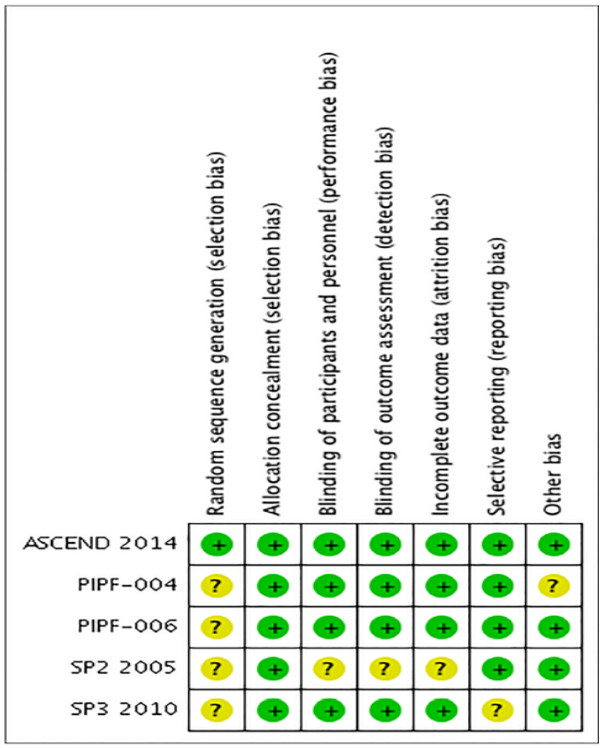
- 5 RCTs

Charakteristika der Population:

Table 1. Characteristics of included studies in this systematic review.

Trial	Year	N° subjects (intervention/ placebo)	Type of studies	Intervention	Comparison	Primary outcome	GRADE
CAPACITY (PIPF 004)	2011	174/174	Parallel	Pirfenidone 1197 mg/day or pirfenidone 2403 mg/day	Placebo pills	Change from baseline to week 72 in predicted FVC	MODERATE
CAPACITY (PIPF 006)	2011	171/173	Parallel	Pirfenidone 2403 mg/day	Placebo pills	Change from baseline to week 72 in predicted FVC	MODERATE
SP2	2005	72/35	Parallel	Pirfenidone 200 mg TID for 2 days, 400 mg TID for 2 days and 600 mg TID for 3 days	Placebo pills	Change in the lowest spo2 during 6 mwt	LOW
SP3	2010	163/104	Parallel	Pirfenidone in stepwise doses; 1800 mg/day in high dose and 1200 mg/day in low dose	Placebo pills	Change from baseline to week 52 in predicted FVC	LOW
ASCEND	2014	278/277	Parallel	Pirfenidone 2403 mg/day	Placebo pills	Change from baseline to week 52 in predicted FVC	MODERATE

Qualität der Studien:



Studienergebnisse

Table 2. Summary of finding form Pirfenidone for idiopathic pulmonary fibrosis. 1: Non primary outcome from RCTs, 2: High heterogeneity; 6MWT: Six minutes walk test; RCT: Randomized controlled trial; RR: Risk ratio; CI: confidence interval

Outcomes	Anticipate absolute effects (Study population) (95% CI)		Relative Effect	NO of participants	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Pirfenidone			
All cause-mortality	67 per 1000	36 per 1000 (22 to 59)	RR 0.53 (0.32 to 0.88)	1247 (3 RCTs)	⊕⊕⊕◯MODERATE1
Progression free-survival	442 per 1000	372 per 1000 (332 to 416)	RR 0.82 (0.73 to 0.92)	1514 (4 RCTs)	⊕⊕⊕◯MODERATE1
Acute exacerbation	26 per 1000	15 per 1000 (5 to 47)	RR 0.59 (0.19 to 1.84)	374 (2 RCTs)	⊕⊕◯◯LOW1,2
Worsening of IPF	168 per 1000	107 per 1000 (84 to 139)	RR 0.64 (0.50 to 0.83)	1621 (5 RCTs)	⊕⊕⊕◯MODERATE1
Change on 6MWT	417 per 1000	308 per 1000 (267 to 358)	RR 0.74 (0.64 to 0.86)	1236 (3 RCTs)	⊕⊕⊕⊕HIGH
Change on aminotransferases	30 per 1000	68 per 1000 (40 to 115)	RR 2.26 (1.33 to 3.83)	1621 (5 RCTs)	⊕⊕⊕◯MODERATE1

Mortality

- Three RCTs (1247 patients) were identified that reported the effect of pirfenidone and mortality (ASCEND 2014; PIPF004 2011 and PIPF006 2011)[11,15,22,23].
- The meta-analysis includes 623 patients in intervention group and 624 in placebo group. Pirfenidone compared to placebo decreased all cause-mortality (RR: 0.53 IC 0.32–0.88, I2:0%) and IPF related mortality (RR: 0.32, IC 0.14–0.75; I2: 0%) at week 52.
- We rated the quality of evidence as moderate, because this outcome was not of primary interest in the different studies (indirectness).

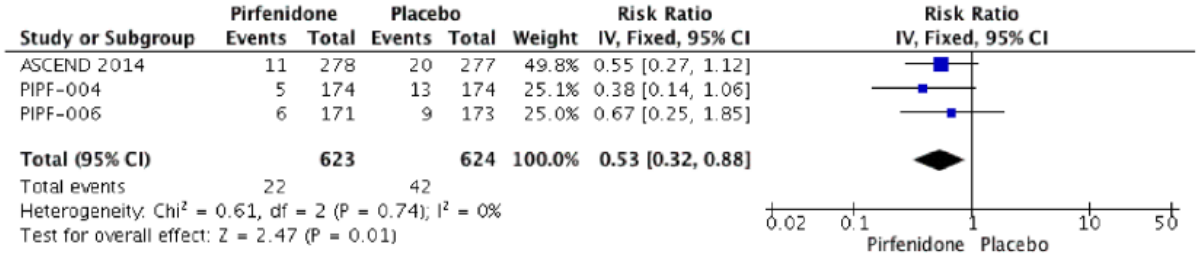


Fig 3. Comparison 1. All cause-mortality at week 52.

doi:10.1371/journal.pone.0136160.g003

Predicted Forced Vital Capacity (FVC)

- Five RCTs (PIPF004, PIPF006, ASCEND, SP3 and SP2) were identified that reported the effect of pirfenidone and FVC or vital capacity (VC). In three RCTs (ASCEND, SP3 and SP2) change of percentage of predicted forced vital capacity >10% were reported.
- The meta-analysis includes 623 patients in intervention group and 624 in placebo group. Pirfenidone decrease the risk of change >10% of FVC with a Risk ratio of 0.63 (IC 0.47–0.85%, I2: 53%) compared to placebo.
- We rated the quality of evidence as Moderate due imprecision.

Adverse events

- Five RCTs (PIPF004, PIPF006, ASCEND, SP3 and SP2) were identified that reported the effect of pirfenidone and adverse events. Pooled data from all studies were evaluated at

the end of each trial. The meta-analysis includes 859 patients in intervention group and 763 in placebo group.

- Pirfenidone is not associated with severe adverse events RR: 1.02 (IC 0.93–1.11, I2: 2%) compared to placebo. But other adverse events such as photosensitivity (RR: 4.92; IC 2.10–11.53, I2: 57%) or change on aminotransferases (RR: 2.26; IC 1.33–3.83, I2: 23%) were more frequent than placebo.
- We rated the quality of evidence as Moderate, because of imprecision between results.

11. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, et al. (2011) Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 377: 1760–1769. doi: 10.1016/S0140-6736(11)60405-4 PMID: 21571362
15. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, et al. (2014) A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 370: 2083–2092. doi: 10.1056/ NEJMoa1402582 PMID: 24836312
22. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, et al. (2005) Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 171: 1040–1047. PMID: 15665326
23. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, et al. (2010) Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 35: 821–829. doi: 10.1183/09031936.00005209 PMID: 19996196

Anmerkung/Fazit der Autoren

Finally, given the results of this Systematic Review on a poor prognosis disease without previously proven treatment, the associated lower risk and benefits in physiological and clinically relevant outcomes, and considering a future RCT with a mortality primary endpoint is not feasible because the necessary population size, duration and cost. [32] The use of this drug should be highly considered. However, according to our data, this drug does not decrease the risk of acute exacerbation, but more evidence from future RCT is need to improve this outcome.

Ren H et al., 2017 [16].

Efficacy and adverse events of pirfenidone in treating idiopathic pulmonary fibrosis

Fragestellung

To analyze the efficacy and adverse events (AEs) of pirfenidone in idiopathic pulmonary fibrosis (IPF) trials.

Methodik

Population:

- Patients with IPF and aged 40-80 years, with diagnostic criteria conforming to the current guideline1-2

Intervention:

- the dose of pirfenidone ≥1800 mg daily.

Komparator:

- others

Endpunkte:

- lowest oxygen saturation in the 6-min exercise test; the change from baseline to week 52 in the percentage of predicted forced vital capacity (FVC), vital capacity, and diffusing capacity for carbon monoxide (DLCO)%; progression-free survival (PFS), AEs (nausea, rash, photosensitivity reaction), and mortality (from any cause, related to IPF)

Recherche/Suchzeitraum:

- MEDLINE, Cochrane Library, and ClinicalTrials.gov were searched for studies published before June 2016 (gemäß Abstrakt) bzw. September 2015 (gemäß Volltext)

  Anmerkung: Widersprüchliche Angaben im Abstrakt und Volltext

Qualitätsbewertung der Studien:

- Cochrane review handbook and Jadad, which assigned a maximum of 2 points for concealment.13 Under this system, a maximum score of 7 could be assigned. Studies with a score of ≥4 were considered to be high quality studies.

Heterogenität

chi-squared test revealing $p<0.1$[14] or an I-squared value measuring > 50%.[15] When the heterogeneity was not significant, a fixed-effects model was used to pool the results

Ergebnisse

Anzahl eingeschlossener Studien:

- five RCTs5,8-10,14 enrolled a total of 1568 participants (804 in the pirfenidone group and 764 in the placebo group)

Charakteristika der Population:

Table 1 - Characteristics of included randomized controlled trials.

Study	Location	Phase	Drug (mg/day)	N	Male	Age (year)	MJS
Azuma et al[5]	Japan	II	1800 placebo	73	62	64.0 ± 7.1	7
				36	33	64.3 ± 7.6	
Noble et al[8] (CAPACITY 004)	Multinational	III	2403 placebo	174	118	65.7 ± 8.2	7
				174	128	66.3 ± 7.5	
Noble et al[8] (CAPACITY 006)	Multinational	III	2403 placebo	171	123	66.8± 7.9	7
				173	124	67.0± 7.8	
Taniguchi et al[10] (SP3)	Japan	III	1800 placebo	108	85	65.4 ± 6.2	7
				104	81	64.7 ± 7.3	
King et al[16] (ASCEND)	Multinational	III	2403 placebo	278	222	68.4 ± 6.7	7
				277	213	67.8± 7.3	

Data are mean ± standard error of the mean, N - Number of pairwise comparisons; MJS - modified Jadad score.

Studienergebnisse:

Change in lung function

- Change in FVC% ≥10% predicted In the SP3 study, a significantly smaller decline in FVC (0.09 L versus 0.16 L, p<0.0416) was seen in the high-dose pirfenidone treatment arm compared with placebo but the change in FVC% >10% predicted was not reported.6
- The CAPACITY 1 and 2 phase III multinational randomized doubleblind placebo trials were performed concurrently.8 […] A significant reduction in decline in FVC was found in the

CAPACITY 1 study between high-dose pirfenidone and placebo arm (8% versus 12.4%, p=0.001). Primary endpoint was not met in the CAPACITY 2 study.

- Three trials (CAPACITY 1 and 2 and ASCEND) reported the change in FVC% ≥10% predicted. The forest plot showed that the change in FVC was statistically significantly different between the 2 groups favoring pirfenidone over placebo (RR: 0.62; 95% CI: 0.51-0.76, p<0.01)

Progression-free survival

- 4 studies6,8,16 (Taniguchi 2010; CAPACITY1; CAPACITY 2; ASCEND, 2014) were included in the meta-analysis of PFS. The meta-analysis of the HR of PFS was performed using the fixed-effects model (P for heterogeneity = 0.994, I-squared = 0.00%) and revealed a significant reduction in the risk of progression in patients treated with placebo (HR: 0.93, 95% CI: 0.15–5.68; P = 0.99)

Mortality.

- Four studies5,6,8,16 (CAPACITY 2011(1 and 2); ASCEND, 2014; Taniguchi 2010; Azuma 2005) reported the mortality from any cause. Pooled analysis showed a reduced mortality with pirfenidone, which was statistically not significant (OR: 0.63; 95% CI: 0.36–1.09; p=0.22)

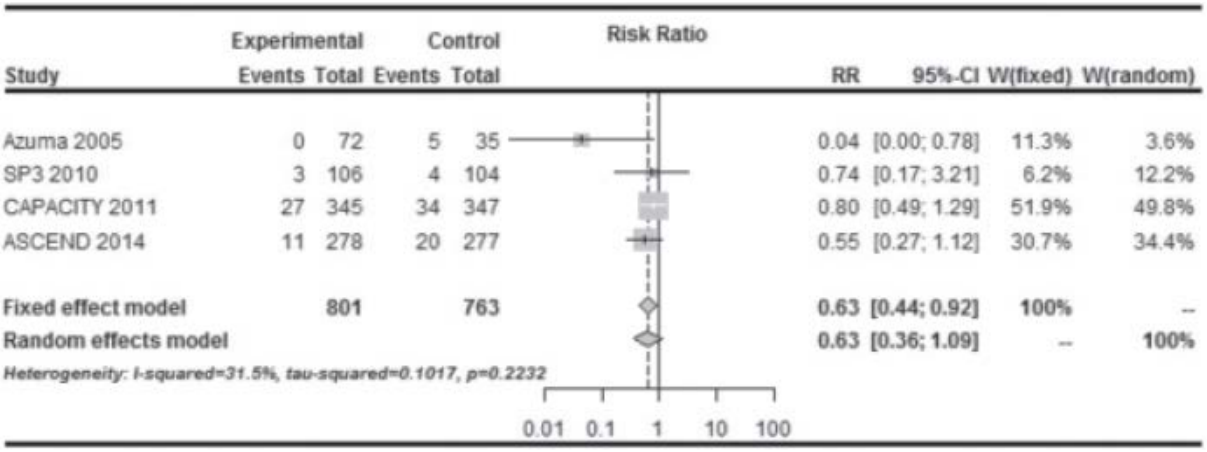


Figure 4 - Forest plot showing comparison of the effect of pirfenidone versus placebo on mortality from any cause and mortality related to Idiopathic pulmonary fibrosis

Anmerkung: Im Volltext wird für den gleichen Zahlenwert als Effektschätzer OR und im Forrest Plot RR für den Endpunkt Mortalität angegeben. Gemeint ist vermutlich das Relative Risiko. Gemäß Volltext wurde IPF-abhängige Mortalität nicht ermittelt.

Adverse events.

- Almost all patients in the 5 studies5,6,8,16 (Azuma,2005; Taniguchi 2010; ASCEND, 2014;CAPACITY 1 and 2) reported at least one treatment-emergent AE.
- Two trials (Azuma, 2005; ASCEND, 2014) reported AEs. The present metaanalysis showed that the difference between the 2 groups was statistically significant (Figure 5).
- Two trials5,16 (Azuma, 2005; ASCEND, 2014) reported the incidence of nausea in the pirfenidone and the placebo arm, pooled analysis showed that the difference between the 2 groups was statistically significant (OR: 3.73; 95% CI: 2.48-5.62; p=0.75).

- Three trials (Azuma, 2005; SP3, 2010; CAPACITY 2011) reported that a significant number of patients receiving pirfenidone manifested a photosensitivity reaction. Pooled analysis showed that the difference between 2 groups was statistically significant (OR: 5.29; 95% CI: 1.45-19.30; p=0.004).
- Four trials (SP3, 2010; CAPACITY 1 and 2 2011; ASCEND, 2014) reported the incidence of rash. Pooled analysis showed that the difference between the 2 groups was statistically significant (OR: 2.95; 95% CI: 2.28-3.83; p=0.86).

Anmerkung/Fazit der Autoren

In conclusion, pirfenidone significantly reduced the progression of IPF, as measured by changes in FVC and PFS. The pirfenidone group was associated with a significantly higher rate of AEs (nausea, rash, photosensitivity reaction) compared with placebo, but the treatment was generally safe and the side-effect profile was acceptable. Hence, pirfenidone represents a suitable treatment option for patients with IPF.

Rogliani P et al., 2016 [17].

Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: a systematic review and meta-analysis

Fragestellung

we have carried out a treatment comparison by systematic reviewand synthesis of the available clinical variables to evaluate the effectiveness and safety of pirfenidone, nintedanib and NAC for IPF treatment vs. placebo, with unbiased analyses that incorporated exclusively the data from high quality RCTs lasting at least 6 months.

Methodik

Population:

- patients suffering from IPF diagnosed by high-resolution computed tomography (HRCT) or biopsy

Intervention:

- oral administration of pirfenidone

Komparator:

- others (placebo)

Endpunkte:

- FVC, FVC >10% or 10% decline in percent predicted, occurrences of IPF exacerbations, safety as serious adverse events (SAE), overall deaths by any causes and by specific respiratory causes, and change from baseline in 6MWD

Recherche/Suchzeitraum:

- PubMed and Google Scholar in order to provide for relevant studies published up to February 29, 2016

Qualitätsbewertung der Studien:

- The Jadad score

Heterogenitätsmaß

- Moderate to high levels of heterogeneity were considered for I2>50% [26]. Meta-analysis: The analysis was performed via a binary random-effects model

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 studies (Pirfenidone)

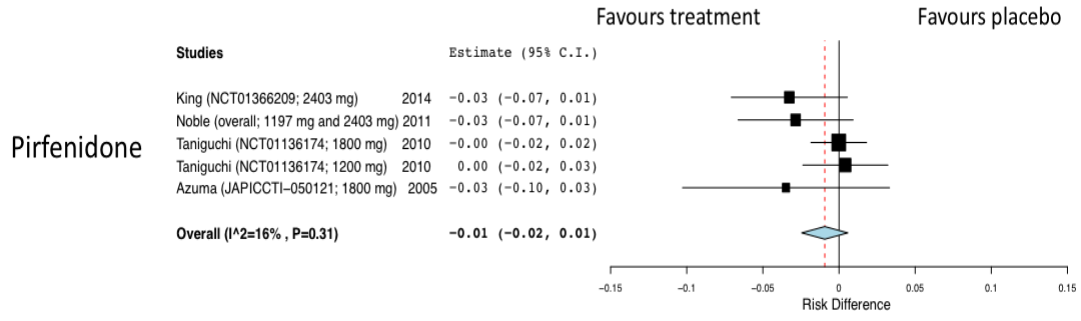
Charakteristika der Population:

Patient demographics, baseline and study characteristics.

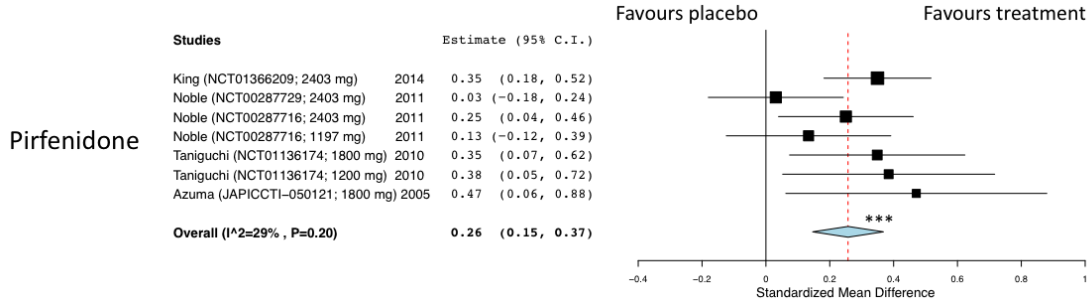
Study and year	ClinicalTrials.gov Identifier	Study characteristics	Duration of study (weeks)	Number of analyzed patients	Drugs (doses)	Administration regimen	Patients characteristics	Age (years)	Male (%)	Current smokers (%)	Time since diagnosis (yr)	FVC or VC (% or L)	6MWD (metres)	DL_{CO} (% or mmol/min/kPa)	Jadad score
Azuma et al., 2005 [34]	NA	A multicentre, double-blind, placebo-controlled, randomized clinical trial	39	107	Pirfenidone (1800 mg/die; 200 mg)	3 tablets t.i.d. (oral)	PaO2≥70 mmHg at rest; SpO2 of 90% or less during exertion while breathing air	64.0	86.0	10.0	<1yr 28.0%	81.6%	NA	57.6%	4
Taniguchi et al., 2010 [42]	NA	A multicentre, double-blind, placebo-controlled, randomized clinical trial	52	267	Pirfenidone (1800 mg/die; 200 mg); (1200 mg/die; 200 mg)	3 tablets t.i.d.(oral); 2 tablets t.i.d. (oral)	Oxygen desaturation of ≥5% difference between resting SpO2 and the lowest SpO2 during a 6MET; the lowest SpO2 during the 6MET of ≥85% while breathing air	64.7	82.1	9.2	<1yr 35.6%	2.4 L	NA	52.9%	4
Noble et al., 2011 (CAPACITY 04) [37]	NCT00287716	A multicentre, double-blind, placebo-controlled, randomized clinical trial	72	435	Pirfenidone (2403 mg/die; 267 mg); (1197 mg/die; 133 mg)	3 tablets t.i.d.(oral); 3 tablets t.i.d. (oral)	FVC of 50% until 90%; Dlco of 35% until 90%; 6MWD of at least 150 m	66.9	71.5	4.2	<1yr 49.4%	75.5%	4	46.8%	4
Noble et al., 2011 (CAPACITY 06) [37]	NCT00287729	A multicentre, double-blind, placebo-controlled, randomized clinical trial	72	344	Pirfenidone (2403 mg/die; 267 mg)	3 tablets t.i.d.(oral)	FVC of 50% until 90%; Dlco of 35% until 90%; 6MWD of at least 150 m	66.8	72.0	0.0	<1yr 58.0%	74.9%	378.0	47.8%	4
King et al., 2014 (ASCEND) [44]	NCT01366209	A multicentre, double-blind, placebo-controlled, randomized clinical trial	52	555	Pirfenidone (2403 mg/die; 267 mg)	3 tablets t.i.d. (oral)	FVC of 50% until 90%; Dlco of 30% until 90%; FEV1/FVC of 0.80 or more; 6MWD of 150 m or more	68.4	79.9	NA	1.7	67.8%	415.0	43.7%	4

Studienergebnisse:

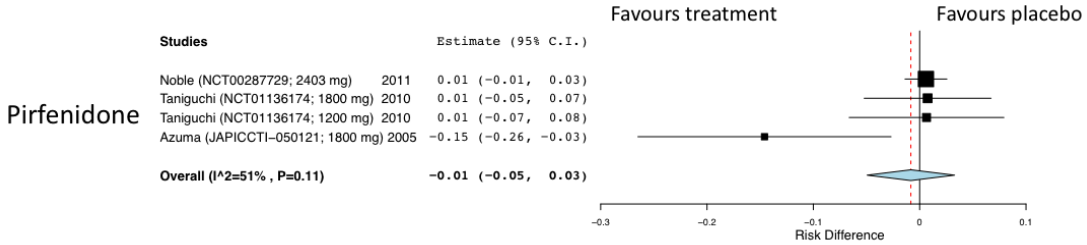
- Forest plot meta-analysis of the impact of pirfenidone on the overall risk difference of **death**, vs. placebo



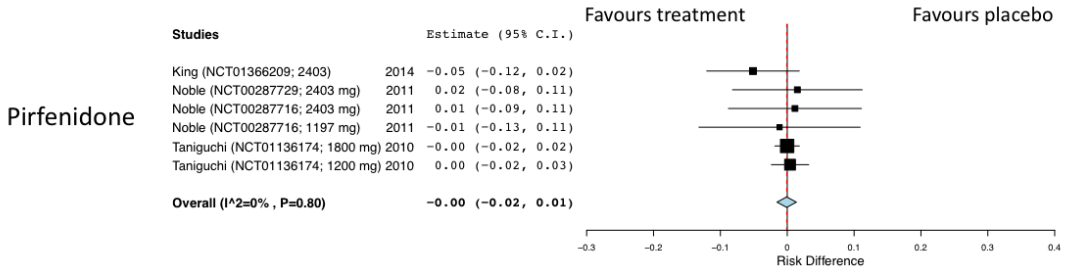
- Forest plot meta-analysis of the impact of pirfenidone on the standardized mean difference of change from baseline in **FVC (%predicted)** vs. placebo



- Forest plot meta-analysis of the impact of pirfenidone on the risk difference of **acute exacerbations**, vs. placebo



- Forest plot meta-analysis of the impact of pirfenidone on the risk difference of **serious adverse events**, vs. placebo



[34] A. Azuma, T. Nukiwa, E. Tsuboi, M. Suga, S. Abe, K**. Nakata, et al., Double-blind,** placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis, Am. J. Respir. Crit. Care Med. 171 (2005) 1040e1047.
[37] P.W. Noble, C. Albera, W.Z. Bradford, U. Costabel, M.K. Glassberg, D. Kardatzke, et al., Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials, Lancet 377 (2011) 1760e1769.
[42] H. Taniguchi, M. Ebina, Y. Kondoh, T. Ogura, A. Azuma, M. Suga, et al., Pirfenidone in idiopathic pulmonary fibrosis, Eur. Respir. J. 35 (2010) 821e829.
[44] T.E. King Jr., W.Z. Bradford, S. Castro-Bernardini, E.A. Fagan, I. Glaspole, M.K. Glassberg, et al., A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis, N. Engl. J. Med. 370 (2014) 2083e2092.

Anmerkung/Fazit der Autoren

The results of this meta-analysis confirm that both pirfenidone and nintedanib reduce the progression of IPF with a similar safety profile, although nintedanib appears to be more effective in reducing the risk of exacerbations and mortality rate. Of course these findings needs to be confirmed by comparative head-to-head RCTs in which adequate outcomes and clinically meaningful endpoints will be identified.

Kommentare zum Review

Es wurden weitere Reviews, bei denen auch Netzwerk-Metaanalysen durchgeführt wurden, identifiziert. In diesen Reviews war der Fokus der Vergleich von u.a Pirfenidon mit nicht-zugelassenen AM. Die Ergebnisse der direkten Vergleiche wurden sowohl in den unten aufgeführten als auch in diesem Review abgebildet, weshalb auf eine erneute Darstellung hier verzichtet wird. Es handelt sich um folgende Reviews:

Canestaro WJ et al. 2016, [4].

Drug Treatment of Idiopathic Pulmonary Fibrosis: Systematic Review and Network Meta-Analysis

Fleetwood, K et al. 2017, [7].

Systematic Review and Network Meta-analysis of Idiopathic Pulmonary Fibrosis Treatments

Loveman E et al. 2015, [11].

Comparing new treatments for idiopathic pulmonary fibrosis – a network meta-analysis

3.4 Leitlinien

Raghu G et al., 2015 [1,15].

Official ATS/ERS/JRS/ALAT Clinical Practice Guidelines: Treatment of Idiopathic Pulmonary Fibrosis

Update from 2011

Leitlinienorganisation/Fragestellung

The purpose of this guideline is to analyze evidence reported since publication of the prior guideline in 2011 and to update the treatment recommendations accordingly.

Methodik

Grundlage der Leitlinie

This guideline was developed by a multidisciplinary committee that consisted of pulmonologists with recognized IPF expertise, general pulmonologists, a pulmonologist methodologist, an allergist-methodologist, a general internist, a chest radiologist, a pulmonary pathologist, an information scientist, and a patient with IPF, who was recommended for participation by the Coalition for Pulmonary Fibrosis and was not known to any of the committee members.

The committee worked with the Methods Group (MG), which comprised five health research methodologists

All of the eight pulmonologists with recognized IPF expertise were considered to either have major financial or intellectual conflicts based on disclosures or participation in IPF clinical trials/studies. although they were permitted to participate in the discussions of the evidence with the rest of the committee, they were instructed to abstain from discussions related to the evidence to decision framework (described later), formulating and grading recommendations, and voting on recommendations if necessary

Recommendations and their strength were decided by consensus, and only one recommendation required voting because of inability to achieve consensus

Recherche/Suchzeitraum:

- The Ovid platform was used to search MEDLINE, EMBASE, Cochrane Registry of Controlled Trials, Health Technology Assessment, and the Database of Abstracts of Reviews of Affects for May 2010 through May 2014. An update was performed in June 2014.

LoE

Cochrane risk of bias tool

GoR

GRADE

Implications for:	Strong Recommendation	Conditional Recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Empfehlungen

Table 2. Comparison of Recommendations in the 2015 and 2011 Idiopathic Pulmonary Fibrosis Guidelines

Agent	2015 Guideline	2011 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Strong recommendation against use*	Conditional recommendation against use‡
Combination prednisone + azathioprine + *N*-acetylcysteine	Strong recommendation against use†	Conditional recommendation against use†
Selective endothelin receptor antagonist (ambrisentan)	Strong recommendation against use†	Not addressed
Imatinib, a tyrosine kinase inhibitor with one target	Strong recommendation against use*	Not addressed
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Conditional recommendation for use*	Not addressed
Pirfenidone	Conditional recommendation for use*	Conditional recommendation against use†
Dual endothelin receptor antagonists (macitentan, bosentan)	Conditional recommendation against use†	Strong recommendation against use*
Phosphodiesterase-5 inhibitor (Sildenafil)	Conditional recommendation against use*	Not addressed
Unchanged recommendations		
Antiacid therapy	Conditional recommendation for use‡	Conditional recommendation for use‡
N-acetylcysteine monotherapy	Conditional recommendation against use†	Conditional recommendation against use†
Antipulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Reassessment of the previous recommendation was deferred	Conditional recommendation against use‡
Lung transplantation: single vs. bilateral lung transplantation	Formulation of a recommendation for single vs. bilateral lung transplantation was deferred	Not addressed

*⊕⊕⊕⊖, moderate confidence in effect estimates.
†⊕⊕⊖⊖, low confidence in effect estimates.
‡⊕⊖⊖⊖, very low confidence in effect estimates.

Question 6: Should Patients with IPF Be Treated with Pirfenidone?

We suggest that clinicians use pirfenidone in patients with IPF (conditional recommendation, moderate confidence in estimates of effect).

New evidence that has become available since the prior edition of this guideline has led to a conditional recommendation in favor of treatment.

This recommendation puts a high value on the potential benefit of pirfenidone on patient-important outcomes such as disease progression as measured by rate of FVC decline and mortality and a lower value on potentially significant adverse effects and the cost of treatment. Quality-of-life data were sporadically reported across pirfenidone trials. The adverse effects of pirfenidone treatment fall on a spectrum, and some patients may not be willing to tolerate certain adverse effects even in the setting of treatment benefit, as assessed by measurement of FVC. Shared decisionmaking should be used, and patients starting this treatment must be educated on all potential adverse effects.

Given the different inclusion criteria for the pirfenidone trials, these results cannot necessarily be generalized to patients with IPF with more severe impairment in PFTs or for patients with other significant comorbidities. The evidence does not allow suggestions about the optimal duration of therapy, and it is unknown how long the treatment effect endures with ongoing drug therapy.

The 2011 guideline document reported on two relatively small RCTs that compared pirfenidone with placebo in Japanese patients with IPF who had mild to moderate impairment in PFTs (35, 36). One of these trials (35) was stopped early for potential benefit, as acute exacerbation, a secondary outcome, was found to occur more frequently in the placebo group. The second trial (36) had significant methodological concerns, including a highly selected enrolment and alteration of the primary endpoint midstudy.

The CAPACITY trial reported on two independent study protocols: study 004 included 435 patients randomized to one of three treatment groups (high-dose pirfenidone [2,403 mg/d], low-dose pirfenidone [1,197 mg/d], and placebo), whereas study 006 had 344 patients randomized to only two treatment groups (high-dose pirfenidone [2,403 mg/d] and placebo).We chose to focus on the results of the high-dose pirfenidone group versus those of the placebo group across both studies.

The ASCEND trial (A Randomized, Double-Blind, Placebo Controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis) randomized 555 patients with IPF to either high-dose pirfenidone (2,403 mg/d) or placebo (38). As opposed to the CAPACITY trials, the ASCEND trial had stricter patient selection criteria, such as a FEV1/FVC ratio below 0.8. Of 1,562 screened patients, 1,007 were excluded because of these predefined exclusion criteria.Pooled results fromthese trials (35–38) suggested improved mortality with pirfenidone (RR, 0.70; 95% CI, 0.47–1.02; moderate confidence). Pirfenidone reduced the rate of FVC decline (standardized mean difference, 0.23; 95% CI, 0.06–0.41; high confidence). This pooled estimate did not include the positive results from one study (38) because of heterogeneity in reporting, which made pooling including this trial impossible. Pooled analysis showed increased rates of photosensitivity (high confidence), fatigue (moderate confidence), stomach discomfort (moderate confidence), and anorexia (high confidence) in patients treated with pirfenidone.

Question: Should patients with IPF be treated with pirfenidone?

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pirfenidone	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 72 weeks)												
5	Randomized trials	Not serious	Not serious	Not serious	Serious [1]	None	41/804 (5.1%)	59/763 (7.7%)	**RR 0.7** (0.47 to 1.02)	23 fewer per 1000 (from 7 more to 41 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Acute exacerbation (follow up: 72 weeks; assessed with worsening PFTs or hospitalization)												
4	Randomized trials	Serious [2]	Not serious	Not serious	Serious [3]	None	10/526 (1.9%)	14/486 (2.9%)	**RR 0.69** (0.2 to 2.42)	9 fewer per 1000 (from 23 fewer to 41 more)	⊕⊕◯◯ LOW	CRITICAL
Disease progression (follow up: 72 weeks; assessed with: change in FVC in liters (higher numbers are better))												
1	Randomized trials	Not serious [4]	Not serious	Not serious	Not serious	None	521	185		MD **0.23 higher** (0.06 higher to 0.41 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Photosensitivity (follow up: 72 weeks)												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	130/526 (24.7%)	30/489 (6.1%)	**RR 5.3** (1.46 to 19.24)	264 more per 1000 (from 28 more to 1119 more) [1]	⊕⊕⊕⊕ HIGH	IMPORTANT
Anorexia												
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	122/804 (15.2%)	36/766 (4.7%)	**RR 2.96** (2.06 to 4.27)	92 more per 1000 (from 50 more to 154 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Fatigue												
4	Randomized trials	Not serious	Not serious	Serious [7]	Not serious	None	178/695 (25.6%)	120/659 (18.2%)	**RR 1.42** (1 to 2.02)	76 more per 1000 (from 0 fewer to 186 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Stomach discomfort												
4	Randomized trials	Not serious	Not serious	Serious [7]	Not serious	None	54/526 (10.3%)	10/489 (2.0%)	**RR 4.2** (2.17 to 8.11)	65 more per 1000 (from 24 more to 145 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

1. Confidence interval does not exclude an appreciable benefit or no efect. Relatively wide confidence intervals. Even if at upper limit of CI, one would not tolerate cost/side effects of drug.
2. One trial stopped early (Azuma et al.) because of perceived benefit in regards to exacerbations. This trial was not included in the other outcomes and therefore only acute exacerbation was downgraded for risk of bias.
3. Only 24 events; confidence interval dies not exclude an appreciable benefit or an apreciable harm.
4. Data were imputed in studies 004 and 006.

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NICE, 2013 [12].

Diagnosis and management of suspected idiopathic pulmonary fibrosis

+

NICE, 2018 [13].

Pirfenidone for treating idiopathic pulmonary fibrosis: Technology appraisal guidance [TA504]

+

NICE, 2017 [14].

Surveillance report 2017 – Idiopathic pulmonary fibrosis in adults: diagnosis and management (2013) NICE guideline CG163

Leitlinienorganisation/Fragestellung

What are the benefits of pulmonary rehabilitation programmes for patients with confirmed IPF?

Which drug should be initiated first, for how long, and what combination in the treatment of IPF?

What is the clinical and cost effectiveness of pharmacological interventions to manage patients with suspected or confirmed IPF?

What is the optimal timing to consider a patient with IPF for lung transplantation referral?

Methodik

Grundlage der Leitlinie

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate.

Recherche/Suchzeitraum:

- MEDLINE, Embase, Cochrane Library, CINAHL, PsychInfo. All searches were updated on the 1st November 2012.

LoE/GoE

- GRADE

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Surveillance report 2017 – Idiopathic pulmonary fibrosis in adults: diagnosis and management (2013) NICE guideline CG163

We identified evidence that supports current recommendations on:

management – pulmonary rehabilitation

management – disease-modifying pharmacological interventions.

We also found new evidence that was not thought to have an impact on current recommendations, including:

management – best supportive care.

We will not update the guideline on idiopathic pulmonary fibrosis (IPF) at this time.

Empfehlungen

Pulmonary rehabilitation

14. Assess people with idiopathic pulmonary fibrosis for pulmonary rehabilitation at the time of diagnosis. Assessment may include a 6-minute walk test (distance walked and oxygen saturation measured by pulse oximetry) and a quality-of-life assessment.

15. Repeat the assessment for pulmonary rehabilitation for people with idiopathic pulmonary fibrosis at 6-month or 12-month intervals.

16. If appropriate after each assessment, offer pulmonary rehabilitation including exercise and educational components tailored to the needs of people with idiopathic pulmonary fibrosis in general.

Evidence was retrieved from 13 studies (this included 1 Cochrane review was which provided data on 2 RCTs, 9 observational studies and 1 abstract). Quality of life outcomes ranged from moderate to very low quality due to small sample size, lack of blinding and no allocation concealment.

The quality and study type of evidence received showed conflicting effects in domain scores for SF36 and SGRQ at certain time points (immediately after training and after long term follow-up of 6 months). Differences in baseline characteristics between patient groups in the trials may explain the conflicting results seen at certain points, as differences in lung function would not have been accounted for. The GDG acknowledged that difference in 'change' scores from baseline showed an overall improvement in health related quality of life domain scores.

Best supportive care

Offer best supportive care to people with idiopathic pulmonary fibrosis from the point of diagnosis. Best supportive care should be tailored to disease severity, rate of progression, and the person's preference, and should include if appropriate: ☐ information and support ☐ symptom relief ☐ manageme ineffective or causing harm ☐ end of life care.

This recommendation was partially based on GDG consensus due to the lack of evidence regarding the key components and timing of a best supportive care package for people with IPF. Overall, nine studies were identified for best supportive care which ranged from very low to moderate quality and which covered oxygen management, palliation of cough and breathlessness. The GDG considered that there was uncertainty in the interpretation of the results from these studies due to the risk of bias.

19. If the person is breathless on exertion consider assessment for:

- the causes of breathlessness and degree of hypoxia and
- ambulatory oxygen therapy and long-term oxygen therapy and/or
- pulmonary rehabilitation.

20. If the person is breathless at rest consider:

- assessment for the causes of breathlessness and degree of hypoxia and
- assessment for additional ambulatory oxygen therapy and long-term oxygen therapy and
- the person's psychosocial needs and offering referral to relevant services such as palliative care services and
- pharmacological symptom relief with benzodiazepines and/or opioids.

Two systematic reviews and one RCT were identified for oxygen management. The quality of evidence ranged from moderate to very low quality. The studies showed that oxygen is more effective than air at improving perceived levels of dyspnoea, arterial oxygen saturation, and improved 12 month mortality rates compared with no oxygen therapy. They also showed that oxygen increased 24 month mortality rates, but showed no difference in mortality at three years compared to no oxygen therapy. However, there was uncertainty in the effect.

One study was identified for the palliation of breathlessness. Data was taken from the phase II arm of a pharmacovigilance study, which was investigating the use of morphine for the palliation of breathlessness. Again due to the lack of a direct comparison, the data could not be meta-analysed. The evidence showed that morphine was effective at reducing the perceived levels of breathlessness. However, there was uncertainty in the effect and the study was of very low quality.

11 Pharmacological interventions

There is no conclusive evidence to support the use of any drugs to increase the survival of people with idiopathic pulmonary fibrosis.

28. Do not use any of the drugs below, either alone or in combination, to modify disease progression in idiopathic pulmonary fibrosis:

- ambrisentan
- azathioprine
- bosentan
- co-trimoxazole
- mycophenolate mofetil
- prednisolone
- sildenafil
- warfarin

29. Advise the person that oral N-acetylcysteineg is used for managing idiopathic pulmonary fibrosis, but its benefits are uncertain.

30. If people with idiopathic pulmonary fibrosis are already using prednisolone or azathioprine, discuss the potential risks and benefits of discontinuing, continuing or altering therapy.

31. Manage any comorbidities according to best practice

We searched for randomised control trials and systematic reviews comparing the effectiveness of the pharmacological treatments with placebo or other pharmacological treatments in patients with confirmed IPF.

No studies answered the question 'Which drug should be initiated first, for how long, and in what combination in the treatment of IPF?', but fourteen included studies were used to address the clinical effectiveness of these drugs. In all studies it was unclear what line of therapy patients were undergoing.

No evidence was retrieved for either azathioprine or corticosteroids used as monotherapy in IPF. Both drugs have known adverse effects and after considerable deliberation the GDG considered that both azathioprine and prednisolone were not to be recommended in combination or alone on the basis of their adverse events profile and current concern with their safety when used in triple therapy form. The GDG acknowledged that corticosteroids may have unproven beneficial effects on patient symptoms e.g. cough and high doses may have unproven benefits in people experiencing acute exacerbations of IPF. However the GDG decided that corticosteroids should not be used to modify disease progression in IPF.

Quality of evidence

Evidence quality was downgraded across some of the studies for indirect population as in some instances the populations were exclusively Japanese, high drop- out rate, unclear allocation concealment and unclear blinding.

The Panther trial showed higher mortality, exacerbations and adverse events in the triple therapy group. Most clinical experience lies with a regimen comprising triple therapy of prednisolone, azathioprine and N-acetylcysteine. The quality of evidence was very low due to attrition bias and unclear blinding method, as well as very imprecise outcomes. The GDG considered that both azathioprine and prednisolone were not to be recommended on the basis of their adverse events profile and current concern with their safety when used as in triple therapy form.

The GDG noted that N-acetylcysteine was included in the triple therapy trial, but considered that the evidence for its single use showed some improvement in outcomes and was overall relatively safe when compared to other pharmacological options. The studies measured the effects of inhaled and oral N-acetylcysteine on indirect populations (Japanese populations) and most of the outcomes were of very low quality. The GDG noted that even though this drug is not licensed, the fact that it is relatively safe, and that given that it is frequently prescribed for people with IPF and bought over the counter at low doses, built the case for the GDG to advise patients that it is used in managing IPF, but when non-other exists, but that its benefits remain uncertain.

Lung transplantation

- Refer people with idiopathic pulmonary fibrosis for lung transplantation assessment if they wish to explore lung transplantation and if there are no absolute contraindications. Ask the transplant centre for an initial response within 4 weeks.

This recommendation was based on GDG consensus as no directly relevant studies on the optimal timing to refer a patient with IPF for lung transplantation were retrieved.

Early assessment and referral for lung transplantation could increase the probability of survival; improve symptoms, and quality of life (physical and mental components) post transplantation. It was recognised that a patient's prognosis, the unknown rate of disease progression, risk of acute exacerbation and length of waiting times due to donor organ availability, were all factors to acknowledge when considering whether a patient would benefit from lung transplantation. That the status of a patient with IPF initially deemed suitable for lung transplantation, may change and some patients accepted for transplantation may deteriorate to the point of no longer being actively listed.

As well as considering a patient's prognosis and clinical suitability for lung transplantation, the GDG acknowledged that a patient's social, financial and mental well-being (support from family and carers, and psychosocial support) would have a considerable impact on their eligibility for an invasive procedure. The GDG agreed that a patient should also be assessed on their social and mental capacity for lung transplantation. Complications associated with transplantation may include cellular or humeral rejection, infection, and primary organ dysfunction and airway complications.

Pirfenidone for the treatment of idiopathic pulmonary fibrosis (NICE technology appraisal guidance 282)

Pirfenidone is recommended as an option for treating idiopathic pulmonary fibrosis in adults only if:

- the person has a forced vital capacity (FVC) between 50% and 80% predicted
- treatment is stopped if there is evidence of disease progression (an absolute decline of 10% or more in predicted FVC within any 12-month period).

Clinical effectiveness

The committee was aware that the results of SP3 and the CAPACITY trials were considered during NICE's previous technology appraisal of pirfenidone. It recognized that the new data presented by the company came from ASCEND, RECAP (an open label extension follow-up study of the CAPACITY trials) and observational data for best supportive care (the 'INOVA' registry).

The committee noted that the inclusion criteria of the trials differed with respect to percent predicted FVC: the CAPACITY trials recruited patients with an FVC above 50% predicted and without an upper limit. ASCEND recruited patients with an FVC between 50% and 90% predicted, and the SP3 trial did not specify the range, but reported an average baseline FVC of 77% predicted. The committee understood that most of the data presented by the company (92% of patients in ASCEND and the CAPACITY trials) came from patients with an FVC up to 90% predicted. The committee concluded that the trial evidence was most generalisable to people with an FVC of up to 90% predicted.

4.7 The committee discussed whether the populations in the pirfenidone trials reflected people with idiopathic pulmonary fibrosis in current NHS practice. It understood that only 25% of patients across ASCEND and the CAPACITY trials had an FVC above 80% predicted, compared with 36% to 41% in UK practice (as a proportion of people with an FVC above 50% predicted; estimates are based on data from the British Thoracic Society idiopathic pulmonary fibrosis registry and comments from the company at the committee meeting). The committee concluded that people with an FVC above 80% predicted were underrepresented in the clinical trials.

4.8 The committee discussed the clinical effectiveness of pirfenidone. It was aware that in NICE's previous technology appraisal for pirfenidone the committee concluded that 'pirfenidone seemed to have a modest but measurable effect on slowing the decline in lung function'. [...] It agreed that pirfenidone reduced disease progression compared with placebo. It also agreed that there was evidence that it may reduce mortality. appraisal. The committee concluded that pirfenidone is effective in people with an FVC between 50% and 90% predicted.

The committee observed that none of the studies were designed to determine the effectiveness of pirfenidone in people with FVC above 80% predicted, or to compare this group with those with an FVC between 50% and 80% predicted. The committee acknowledged the practical difficulties in designing studies to detect differences in outcomes between subgroups. The committee agreed to accept that pirfenidone has the same relative effectiveness in people with an FVC above 80% predicted and in people with an FVC of 80% predicted or less.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2018) am 30.11.2018

#	Suchfrage
1	MeSH descriptor: [Idiopathic Pulmonary Fibrosis] explode all trees
2	MeSH descriptor: [Idiopathic Interstitial Pneumonias] this term only
3	(idiopathic next (lung or pulmon*) next fibros*):ti,ab,kw
4	IPF:ti,ab,kw
5	(fibrosing alveolitis):ti,ab,kw
6	((idiopathic or usual) next interstitial next pneumon*):ti,ab,kw
7	UIP:ti,ab,kw
8	#1 or #2 or #3 or #4 or #5 or #6 or #7
9	#8 with Cochrane Library publication date from Nov 2013 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 30.11.2018

#	Suchfrage
1	idiopathic pulmonary fibrosis[MeSH Terms]
2	idiopathic interstitial pneumonias[MeSH:noexp]
3	((idiopathic[Title/Abstract]) AND (pulmon*[Title/Abstract] OR lung[Title/Abstract])) AND fibros*[Title/Abstract]
4	IPF[Title/Abstract]
5	fibrosing alveolitis[Title/Abstract]
6	(idiopathic[Title/Abstract] OR usual[Title/Abstract]) AND interstitial[Title/Abstract] AND pneumon*[Title/Abstract]
7	UIP[Title/Abstract]
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
10	(#9) AND ("2013/11/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT "The Cochrane database of systematic reviews"[Journal]
12	(#11) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 30.11.2018

#	Suchfrage
1	idiopathic pulmonary fibrosis[MeSH Terms]
2	idiopathic interstitial pneumonias[MeSH:noexp]
3	lung diseases, interstitial[MeSH:noexp]
4	((idiopathic[Title/Abstract]) AND (pulmon*[Title/Abstract] OR lung[Title/Abstract])) AND fibros*[Title/Abstract]
5	IPF[Title/Abstract]
6	fibrosing alveolitis[Title/Abstract]
7	(idiopathic[Title/Abstract] OR usual[Title/Abstract]) AND interstitial[Title/Abstract] AND pneumon*[Title/Abstract]
8	UIP[Title/Abstract]
9	"Interstitial lung disease"[Title/Abstract] OR ILD[Title/Abstract] OR "diffuse parenchymal lung disease"[Title/Abstract] OR DPLD[Title/Abstract]
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	(#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
12	(#11) AND ("2013/11/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT retracted publication[ptyp]

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