J Bras Pneumol. 2020;46(2):e20190423
https://dx.doi.org/10.36416/1806-3756/e20190423

Brazilian guidelines for the pharmacological treatment of idiopathic pulmonary fibrosis. Official document of the Brazilian Thoracic Association based on the GRADE methodology

José Baddini-Martinez[1,2], Juliana Ferreira[3], Suzana Tanni[4], Luis Renato Alves[1], Benedito Francisco Cabral Junior[5], Carlos Roberto Ribeiro Carvalho[3], Talita Jacon Cezare[4], Claudia Henrique da Costa[6], Marcelo Basso Gazzana[7], Sérgio Jezler[8], Ronaldo Adib Kairalla[3], Leticia Kawano-Dourado[9], Mariana Silva Lima[10], Eliane Mancuzo[11], Maria Auxiliadora Carmo Moreira[12], Marcelo Palmeira Rodrigues[13], Silvia Carla Sousa Rodrigues[14], Adalberto Sperb Rubin[15], Rogério Lopes Rufino[6], Leila John Marques Steidle[16], Karin Storrer[17], Bruno Guedes Baldi[3]

Chart S1. Declaration of conflicts of interest of the authors of the guidelines.[a]

Name	Commercial interest(s) with which the author has some connection
Adalberto Sperb Rubin	AstraZeneca, Boehringer Ingelheim, Celgene, Chiesi, Eurofarma, GSK, Novartis, Roche
Benedito Francisco Cabral Júnior	AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis
Bruno Guedes Baldi	Boehringer Ingelheim, Celgene
Carlos Roberto Ribeiro Carvalho	None
Claudia Henrique da Costa	Actelion, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Roche
Eliane Mancuzo	Boehringer Ingelheim, Pfizer, Roche
José Baddini-Martinez	Boehringer Ingelheim, Roche
Juliana Ferreira	None
Karin Storrer	Boehringer Ingelheim, Roche
Leila John Marques	Bayer, Boehringer Ingelheim, Roche
Leticia Kawano-Dourado	Boehringer Ingelheim, Bristol-Myers-Squibb, Roche
Luis Renato Alves	Boehringer Ingelheim, Chiesi, Roche
Marcelo Basso Gazzana	Actelion, Bayer, Boehringer Ingelheim, Jansen
Marcelo Palmeira Rodrigues	Boehringer Ingelheim, Roche
Maria Auxiliadora Carmo Moreira	Boehringer Ingelheim, Roche
Mariana Silva Lima	Boehringer Ingelheim, Roche
Rogério Lopes Rufino Alves	Actelion, Bayer, Boehringer Ingelheim, Roche
Ronaldo Adib Kairalla	Boehringer Ingelheim, Roche
Sérgio Jezler	Boehringer Ingelheim, Roche
Silvia Carla Sousa Rodrigues	ALPHARAD, Boehringer Ingelheim, Roche
Suzana Tanni	AstraZeneca
Talita Jacon Cezare	Roche

[a]Regarding the 24 months preceding the writing of the document. interested parties can request additional information by contacting the Secretariat of the *Jornal Brasileiro de Pneumologia*.

Chart S2. Primary and secondary criteria used in the search for articles in the PubMed and EMBASE databases.

Primary criteria		Secondary criteria
Pulmonary fibrosis, idiopathic OR idiopathic pulmonary fibrosis OR pulmonary fibrosis	AND	- Nintedanib - Pirfenidone - Sildenafil OR PDF-5 inhibitors OR phosphodiesterase type 5 inhibitors OR phosphodiesterase inhibiting drugs - Bosentan OR macitentan OR ambrisentan OR endothelin receptor antagonists - Treatment of gastroesophageal reflux OR gastroesophageal reflux therapy OR acid suppression therapy OR anti-acid OR proton pump inhibitor - N-acetylcysteine OR acetylcysteine - Corticosteroid OR corticosteroids OR glucocorticoids OR glucocorticoid OR prednisone OR methylprednisolone

Chart S3. Committee member vote counts on the recommendations for each question of the guidelines.

Question	Voting members (n)	Result
1. Should we recommend the use of nintedanib for patients with IPF?	19	Unanimous for a recommendation
2. Should we recommend the use of pirfenidone for patients with IPF?	19	Unanimous for a recommendation
3. Should we recommend the use of phosphodiesterase-5 inhibitors for patients with IPF?	19	17 for a suggestion 2 for a recommendation
4. Should we recommend the use of endothelin-receptor antagonists for patients with IPF?	19	Unanimous for a recommendation
5. Should we recommend pharmacological treatment of gastroesophageal reflux for patients with IPF?	19	Unanimous for a recommendation
6. Should we recommend the use of N-acetylcysteine for patients with IPF?	19	Unanimous for a recommendation
7. Should we recommend the use of corticosteroids for patients with IPF?	19	Unanimous for a recommendation

IPF: idiopathic pulmonary fibrosis.

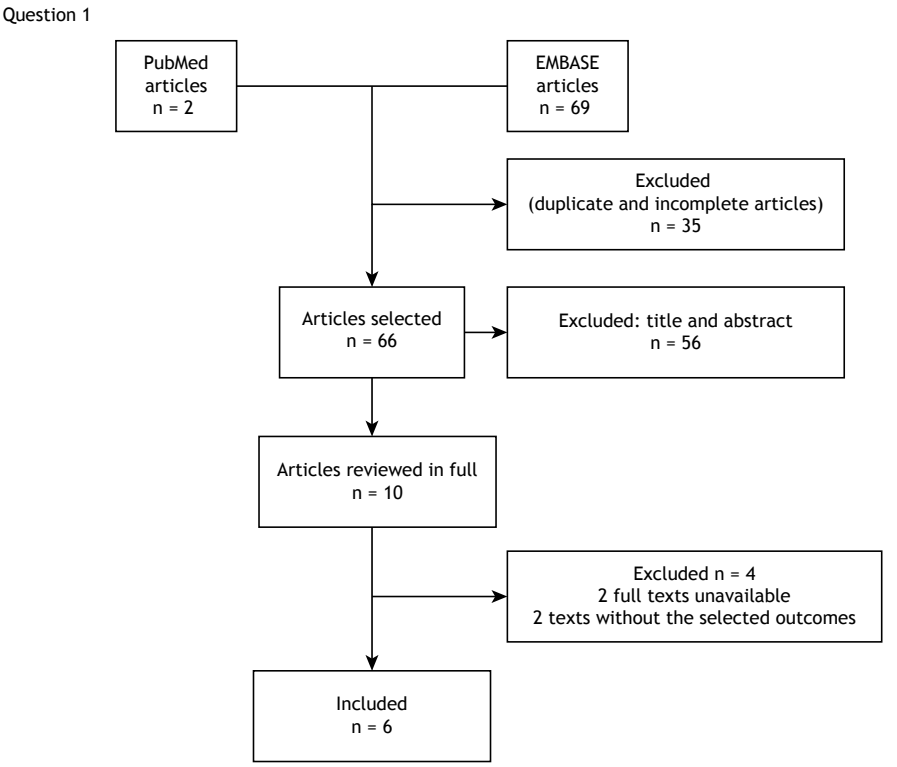

Figure S1. Summary of the article selection process, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol, for question 1 (regarding the use of nintedanib).

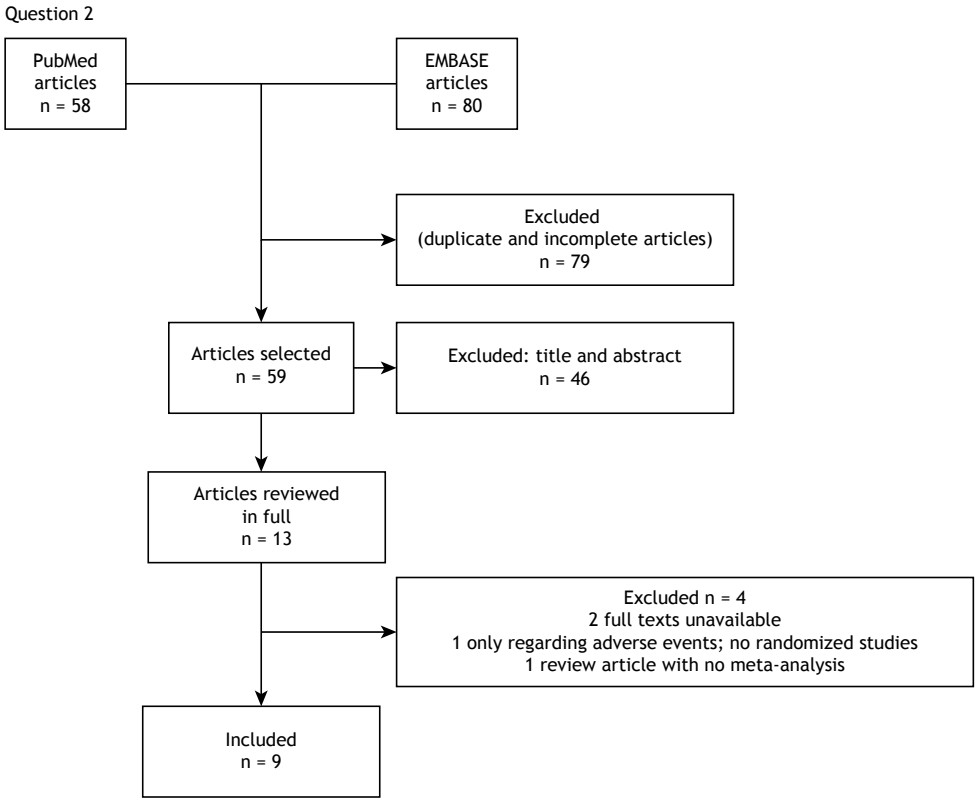

Figure S2. Summary of the article selection process, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol, for question 2 (regarding the use of pirfenidone).

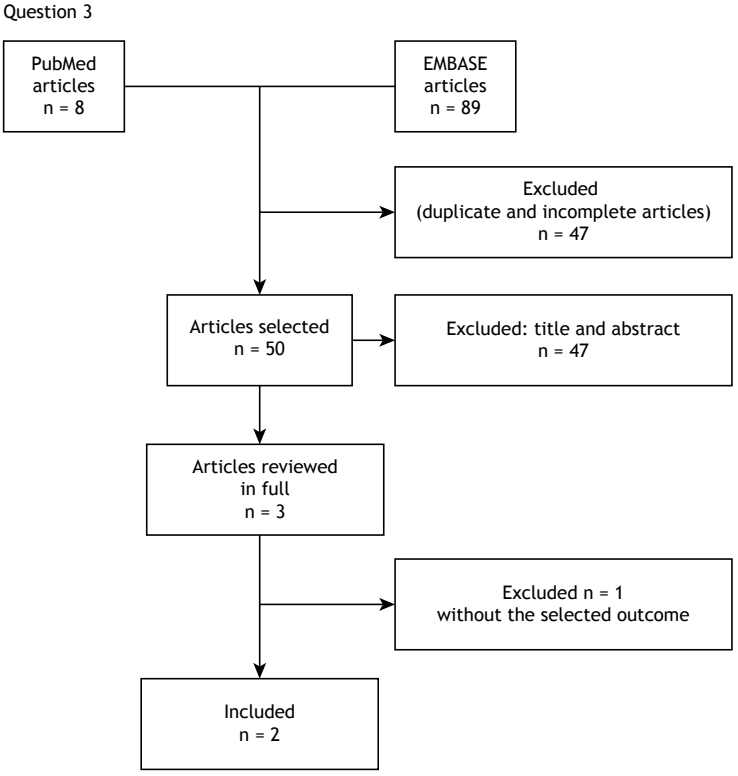

Figure S3. Summary of the article selection process, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol, for question 3 (regarding the use of phosphodiesterase-5 inhibitors).

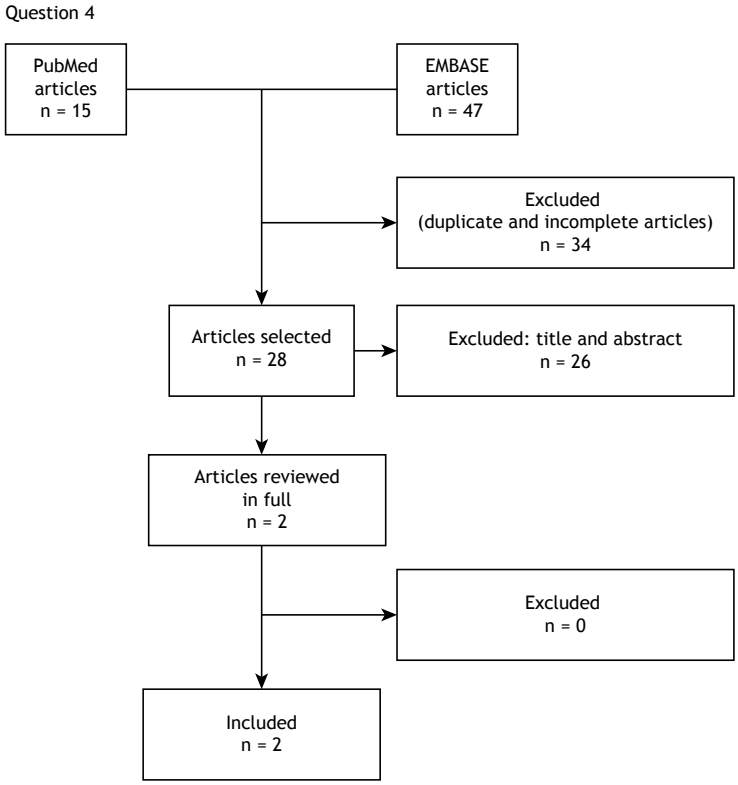

Figure S4. Summary of the article selection process, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol, for question 4 (regarding the use of endothelin-receptor antagonists).

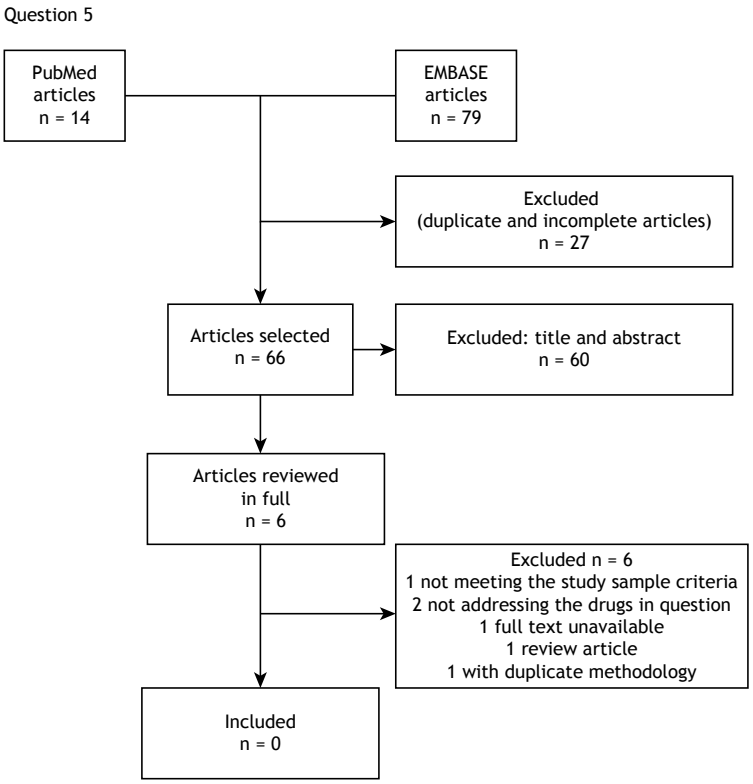

Figure S5. Summary of the article selection process, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol, for question 5 (regarding the routine pharmacological treatment of gastroesophageal reflux).

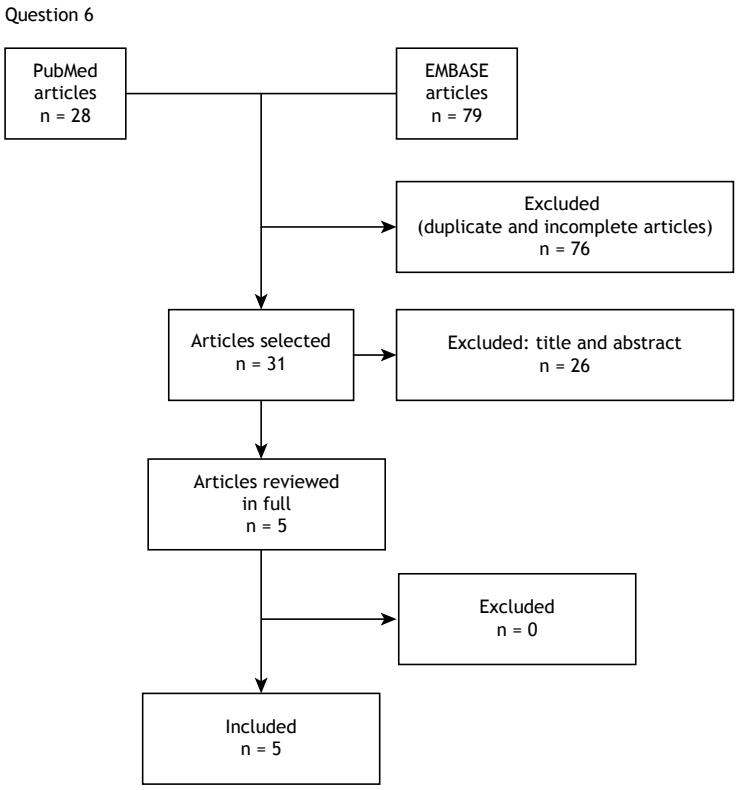

Figure S6. Summary of the article selection process, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol, for question 6 (regarding the use of N-acetylcysteine).

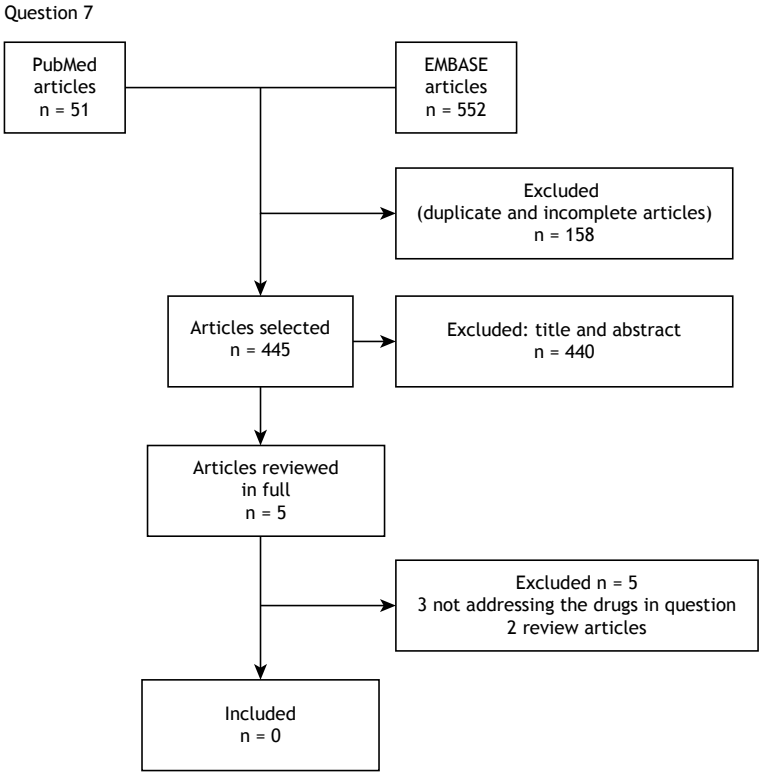

Figure S7. Summary of the article selection process, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol, for question 7 (regarding the use of corticosteroids).

Table S1. Summary of the quality of the evidence of the articles selected for question 1 (regarding the use of nintedanib).

Certainty assessment							Patient, n/N		Effect size		Certainty	Importance
Article, n	Study design	Bias risk	Inconsistence	Indirect evidence	Imprecision	Other remarks	Nintedanib	Placebo	Relative OR (95% CI)	Absolute (95% CI)		
Mortality (follow-up period: 12 months)												
3[1-6]	RCTs	not serious	not serious	not serious	serious[a]	none	26/723 (3.6%)	29/508 (5.7%)	0.70 (0.45-1.09)	−16/1.000 (−31 to 5)	⊕⊕⊕◯ MODERATE	CRITICAL
Exacerbations (follow-up period: 12 months)												
3[1-6]	RCTs	not serious	not serious	not serious	serious[a]	none	33/723 (4.6%)	45/508 (8.9%)	0.50 (0.31-0.79)	−42/1.000 (−59 to −17)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events (follow-up period: 12 months)												
2[1-6]	RCTs	not serious	not serious	not serious	serious[a]	none	284/981 (29.0%)	153/508 (30.1%)	0.96 (0.55-1.56)	−9/1,000 (−110 to 101)	⊕⊕⊕◯ MODERATE	NOT IMPORTANT
Decline in FVC (follow-up period: 12 months)												
3[1-6]	RCTs	not serious	not serious	not serious	not serious	none	211/723 (29.2%)	204/508 (40.2%)	0.61 (0.48-0.78)	−111/1,000 (−158 to −58)	⊕⊕⊕⊕ HIGH	CRITICAL

RCTs: randomized clinical trials.

EXPLANATIONS

[a]The number of events did not reach the estimated optimal information size.

REFERENCES

1. Canestaro WJ, Forrester SH, Raghu G, Ho L, Devine BE. Drug Treatment of Idiopathic Pulmonary Fibrosis: Systematic Review and Network Meta-Analysis. Chest. 2016;149(3):756-766. https://doi.org/10.1016/j.chest.2015.11.013
2. Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Med. 2016;14:18. https://doi.org/10.1186/s12916-016-0558-x
3. Rogliani P, Calzetta L, Cavalli F, Matera MG, Cazzola M. Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Pulm Pharmacol Ther. 2016;40:95-103. https://doi.org/10.1016/j.pupt.2016.07.009
4. Fleetwood K, McCool R, Glanville J, Edwards SC, Gsteiger S, Daigl M, et al. Systematic Review and Network Meta-analysis of Idiopathic Pulmonary Fibrosis Treatments. J Manag Care Spec Pharm. 2017;23(3-b Suppl):S5-S16. https://doi.org/10.18553/jmcp.2017.23.3-b.s5
5. Jeldres A, Labarca G. Is nintedanib effective for idiopathic pulmonary fibrosis? Medwave. 2017;17(Suppl2):e6918. https://doi.org/10.5867/medwave.2017.6918
6. Loveman E, Copley VR, Scott DA, Colquitt JL, Clegg AJ, O'Reilly KM. Comparing new treatments for idiopathic pulmonary fibrosis--a network meta-analysis. BMC Pulm Med. 2015;15:37. https://doi.org/10.1186/s12890-015-0034-y

Table S2. Summary of the quality of the evidence of the articles selected for question 2 (regarding the use of pirfenidone).

Certainty assessment							Patient, n/N		Effect size		Certainty	Importance
Article, n	Study design	Bias risk	Inconsistence	Indirect evidence	Imprecision	Other remarks	Pirfenidone	Placebo	Relative RR (95% CI)	Absolute (95% CI)		
Mortality (follow-up period: 12 months)												
3[1-9]	RCTs	not serious	not serious	not serious	serious[a]	none	22/623 (3.5%)	42/624 (6.7%)	0.53 (0.32-0.88)	−32/1,000 (−46 to −8)	⊕⊕⊕◯ MODERATE	CRITICAL
Exacerbations (follow-up period: 12 months)												
2[1-9]	RCTs	not serious	serious[b]	not serious	serious[a]	none	6/235 (2.6%)	9/139 (6.5%)	0.59 (0.19-1.84)	−27/1,000 (−52 to 54)	⊕⊕◯◯ LOW	CRITICAL
Decline in FVC (follow-up period: 12 months)												
3[1-9]	RCTs	not serious	not serious	not serious	serious[a]	none	76/623 (12.2%)	112/624 (17.9%)	0.64 (0.50-0.83)	−65/1,000 (−90 to −31)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events (follow-up period: 12 months)												
2[1-9]	RCTs	not serious	not serious	serious[c]	serious[a]	none	165/623 (26.5%)	165/624 (26.4%)	1.0 (0.6-1.7)	0/1,000 (−106 to 185)	⊕⊕◯◯ LOW	NOT IMPORTANT

RR: risk ratio; and RCTs: randomized clinical trials.

EXPLANATIONS

[a]The number of events did not reach the estimated optimal information size.
[b]High heterogeneity.
[c]Different outcomes.

REFERENCES

1. Aravena C, Labarca G, Venegas C, Arenas A, Rada G. Pirfenidone for Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis PLoS One. 2015;10(8):e0136160. https://doi.org/10.1371/journal.pone.0136160
2. Aravena C, Labarca G, Venegas C, Arenas A, Rada G. Correction: Pirfenidone for Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(10):e0140288 https://doi.org/10.1371/journal.pone.0140288
3. Ren H, Wang K, Yang H, Gao L. Efficacy and adverse events of pirfenidone in treating idiopathic pulmonary fibrosis. Saudi Med J. 2017;38(9):889-894. https://doi.org/10.15537/smj.2017.9.19349
4. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760-1769. https://doi.org/10.1016/S0140-6736(11)60405-4
5. Spagnolo P, Del Giovane C, Luppi F, Cerri S, Balduzzi S, Walters EH, et al. Non-steroid agents for idiopathic pulmonary fibrosis. Cochrane Database Syst Rev. 2010;(9):CD003134. https://doi.org/10.1002/14651858.CD003134.pub2
6. Nathan SD, Albera C, Bradford WZ, Costabel U, Glaspole I, Glassberg MK, et al. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis [published correction appears in Lancet Respir Med. 2017 Jan;5(1):e7]. Lancet Respir Med. 2017;5(1):33-41. https://doi.org/10.1016/S2213-2600(16)30326-5
7. Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Med. 2016;14:18. https://doi.org/10.1186/s12916-016-0558-x
8. Canestaro WJ, Forrester SH, Raghu G, Ho L, Devine BE. Drug Treatment of Idiopathic Pulmonary Fibrosis: Systematic Review and Network Meta-Analysis. Chest. 2016;149(3):756-766. https://doi.org/10.1016/j.chest.2015.11.013
9. Loveman E, Copley VR, Scott DA, Colquitt JL, Clegg AJ, O'Reilly KM. Comparing new treatments for idiopathic pulmonary fibrosis--a network meta-analysis. BMC Pulm Med. 2015;15:37. https://doi.org/10.1186/s12890-015-0034-y

Table S3. Summary of the quality of the evidence of the articles selected for question 3 (regarding the use of phosphodiesterase-5 inhibitors).

Certainty assessment							Patient, n/N		Effect size		Certainty	Importance
Article, n	Study design	Bias risk	Inconsistence	Indirect evidence	Imprecision	Other remarks	Phosphodiesterase-5 inhibitors	Placebo	Relative OR (95% CI)	Absolute (95% CI)		
Mortality (follow-up period: 6 months)												
1[1,2]	RCTs	not serious	not serious	not serious	serious[a]	none	3/103 (2,9%)	9/106 (8,5%)	0.29 (0.05-1.26)	−59/1,000 (−80 to 20)	⊕⊕⊕◯ MODERATE	CRITICAL
Reduction in dyspnea (follow-up period: 12 weeks)												
2[1,2]	RCTs	serious[b]	not serious	very serious[c]	serious[a]	none	-/103	-/106	not estimable	0/1,000 (−0 to 1)[d]	⊕◯◯◯ VERY LOW	IMPORTANT
Improved quality of life (follow-up period: 12 weeks)												
1[1,2]	RCTs	serious[b]	not serious	very serious[c]	serious[a]	none	-/89	-/91	not estimable	−3/1,000 (−5 to −1)[d]	⊕◯◯◯ VERY LOW	IMPORTANT

RCTs: randomized clinical trials.

EXPLANATIONS

[a]The number of events did not reach the estimated optimal information size.
[b]Quasi-randomized studies, high bias risk.
[c]Different study populations.
[d]Estimates obtained from a systematic review

REFERENCES

1. Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Med. 2016;14:18. https://doi.org/10.1186/s12916-016-0558-x
2. Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel AS, et al. Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature. Thorax. 2013;68(9):867-879. https://doi.org/10.1136/thoraxjnl-2012-202040

Table S4. Summary of the quality of the evidence of the articles selected for question 4 (regarding the use of endothelin-receptor antagonists).

Article, n	Certainty assessment						Patient, n/N		Effect size		Certainty	Importance
	Study design	Bias risk	Inconsistence	Indirect evidence	Imprecision	Other remarks	Endothelin-receptor antagonists	Placebo	Relative OR (95% CI)	Absolute (95% CI)		
Ambrisentan - Mortality (follow-up period: 12 months)												
1[1,2]	RCTs	serious[a]	not serious	not serious	serious[a]	none	26/329 (7.9%)	6/163 (3.7%)	**2.33** (0.99-6.25)	**45/1,000** (−0 to 156)	⨁⨁◯◯ LOW	CRITICAL
Bosentan - Mortality (follow-up period: 12 months)												
2[1,2]	RCTs	not serious	not serious	not serious	serious[b]	none	20/481 (4.2%)	10/293 (3.4%)	**1.02** (0.52-2.08)	**1/1,000** (−16 to 34)	⨁⨁⨁◯ MODERATE	CRITICAL
Macitentan - Mortality (follow-up period: 12 months)												
1[1,2]	RCTs	not serious	not serious	not serious	serious[b]	none	8/119 (6.7%)	4/59 (6.8%)	**1.18** (0.35-5.00)	**11/1,000** (−43 to 199)	⨁⨁⨁◯ MODERATE	CRITICAL
Ambrisentan – Adverse effects (follow-up period: 12 months)												
1[1,2]	RCTs	serious[a]	not serious	not serious	serious[b]	none	73/329 (22.2%)	25/163 (15.3%)	**1.60** (0.73-3.52)	**71/1,000** (−37 to 236)	⨁⨁◯◯ LOW	NOT IMPORTANT
Bosentan - Adverse effects (follow-up period: 12 months)												
2[1,2]	RCTs	not serious	not serious	not serious	serious[b]	none	22/781 (2.8%)	29/293 (9.9%)	**0.84** (0.48-1.44)	**−14/1,000** (−49 to 38)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Macitentan - Adverse effects (follow-up period: 12 months)												
1[1,2]	RCTs	not serious	not serious	not serious	serious[b]	none	37/119 (31.1%)	20/59 (33.9%)	**0.87** (0.35-2.17)	**−30/1,000** (−187 to 188)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT

RCTs: randomized clinical trials.

EXPLANATIONS

[a]The number of events in the intervention group was greater than that in the placebo group; the study had to be interrupted.
[b]The number of events did not reach the estimated optimal information size.

REFERENCES

1. Canestaro WJ, Forrester SH, Raghu G, Ho L, Devine BE. Drug Treatment of Idiopathic Pulmonary Fibrosis: Systematic Review and Network Meta-Analysis. Chest. 2016;149(3):756-766. https://doi.org/10.1016/j.chest.2015.11.013
2. Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Med. 2016;14:18. https://doi.org/10.1186/s12916-016-0558-x

Table S5. Summary of the quality of the evidence of the articles selected for question 5 (regarding the routine pharmacological treatment of gastroesophageal reflux).

Certainty assessment							Patient, n/N		Effect size		Certainty	Importance
Article, n	Study design	Bias risk	Inconsistence	Indirect evidence	Imprecision	Other remarks	Pharmacological treatment of gastroesophageal reflux	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up period: 12 months)												
	observational study								not estimable		-	CRITICAL
Hospitalization (follow-up period: 12 months)												
	observational study								not estimable		-	CRITICAL
Decline in FVC (follow-up period: 12 months)												
	observational study								not estimable		-	CRITICAL
Exacerbations ((follow-up period: 30 weeks)												
	observational study								not estimable		-	CRITICAL

Table S6. Summary of the quality of the evidence of the articles selected for question 6 (regarding the use of N-acetylcysteine).

Certainty assessment							Patient, n/N		Effect size		Certainty	Importance
Article, n	Study design	Bias risk	Inconsistence	Indirect evidence	Imprecision	Other remarks	N-acetylcysteine	Placebo	Relative OR (95% CI)	Absolute (95% CI)		
Mortality (follow-up period: 12 months)												
4[1-5]	RCTs	not serious	not serious	not serious	serious[a]	none	15/284 (5.3%)	16/282 (5.7%)	0.84 (0.20-4.50)	−9/1,000 (−45 to 156)	⊕⊕⊕◯ MODERATE	CRITICAL
Decline in FVC (follow-up period: 12 months)												
1[1-5]	RCTs	serious[b]	serious[c]	not serious	not serious	none			not estimable		⊕⊕◯◯ LOW	CRITICAL

RCTs: randomized clinical trials.

EXPLANATIONS

[a]The number of events did not reach the estimated optimal information size.
[b]Study with a relevant bias risk.
[c]Heterogeneity.

REFERENCES

1. Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Med. 2016;14:18. https://doi.org/10.1186/s12916-016-0558-x
2. Sun T, Liu J, Zhao de W. Efficacy of N-Acetylcysteine in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Medicine (Baltimore). 2016;95(19):e3629. https://doi.org/10.1097/MD.0000000000003629
3. Kandhare AD, Mukherjee A, Ghosh P, Bodhankar SL. Efficacy of antioxidant in idiopathic pulmonary fibrosis: A systematic review and meta-analysis. EXCLI J. 2016;15:636–651. https://doi.org/10.17179/excli2016-619
4. Canestaro WJ, Forrester SH, Raghu G, Ho L, Devine BE. Drug Treatment of Idiopathic Pulmonary Fibrosis: Systematic Review and Network Meta-Analysis. Chest. 2016;149(3):756-766. https://doi.org/10.1016/j.chest.2015.11.013
5. Loveman E, Copley VR, Scott DA, Colquitt JL, Clegg AJ, O'Reilly KM. Comparing new treatments for idiopathic pulmonary fibrosis--a network meta-analysis. BMC Pulm Med. 2015;15:37. https://doi.org/10.1186/s12890-015-0034-y

Table S7. Summary of the quality of the evidence of the articles selected for question 7 (regarding the use of corticosteroids).

Certainty assessment							Patient, n/N		Effect size		Certainty	Importance
Article, n	Study design	Bias risk	Inconsistence	Indirect evidence	Imprecision	Other remarks	Corticosteroids	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
									not estimable		-	CRITICAL
Decline in FVC												
									not estimable		-	CRITICAL