

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

An Update of the 2011 Clinical Practice Guideline

Evidence to Decision Frameworks

Ganesh Raghu, Bram Rochweg, Yuan Zhang, Carlos A. Cuello Garcia, Arata Azuma, Juergen Behr, Jan L. Brozek, Harold R. Collard, William Cunningham*, Sakae Homma, Takeshi Johkoh, Fernando J. Martinez, Jeffrey Myers, Shandra L. Protzko, Luca Richeldi, David Rind, Moises Selman, Arthur Theodore, Athol U. Wells, Henk Hoogsteden and Holger J Schünemann

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Evidence to Decision Frameworks

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EtD: Should imatinib be used in patients with idiopathic pulmonary fibrosis (IPF)?

	Criteria	Judgements	Research evidence	Additional considerations																									
Problem	Is there a problem priority?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	<p><i>IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults. An aberrant proliferation of fibrous tissue and tissue remodeling due to the abnormal function and signaling of alveolar epithelial cells and interstitial fibroblasts (secondary to an activation of cell-signaling pathways through tyrosine kinases, e.g., platelet-derived growth factor [PDGF] among others) has been associated with the pathogenesis of the disease. Tyrosine Kinase Inhibitors (TKI) such as imatinib, represents a new set of anti-proliferative agents with activity against platelet-derived growth factor receptors.</i></p>	The prevalence, disruptive clinical presentation, ominous outcomes such as mortality and decrease in quality of life, afflicting patients and families are worrisome enough to consider this a priority																									
Benefits & harms of the options	What is the overall certainty of this evidence?	<input type="radio"/> No included studies <input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High	<p>The relative importance or values of the main outcomes of interest:</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Mortality</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Disease progression</td> <td>CRITICAL</td> <td>⊕⊕⊕○ MODERATE</td> </tr> <tr> <td>Adverse events</td> <td>CRITICAL</td> <td>⊕⊕⊕⊕ HIGH</td> </tr> <tr> <td>Serious Adverse Outcome</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> </tbody> </table> <p>Summary of findings: no imatinib</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Without</th> <th>With imatinib</th> <th>Difference (95%)</th> <th>Relative effect</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Outcome	Relative importance	Certainty of the evidence (GRADE)	Mortality	CRITICAL	⊕⊕○○ LOW	Disease progression	CRITICAL	⊕⊕⊕○ MODERATE	Adverse events	CRITICAL	⊕⊕⊕⊕ HIGH	Serious Adverse Outcome	CRITICAL	⊕⊕○○ LOW	Outcome	Without	With imatinib	Difference (95%)	Relative effect						
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Outcome	Without	With imatinib	Difference (95%)	Relative effect																									
	Is there important uncertainty about how much people value the main outcomes?	<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably																											

	Criteria	Judgements	Research evidence					Additional considerations
		y no important uncertainty of variability <input type="radio"/> No important uncertainty of variability <input type="radio"/> No known undesirable	e	imatinib		CI)	(RR) (95% CI)	
		<input type="radio"/> No important uncertainty of variability <input type="radio"/> No known undesirable	Mortality	167 per 1000	135 per 1000 (58 to 320)	32 fewer per 1000 (from 108 fewer to 153 more)	RR 0.81 (0.35 to 1.92)	
	Are the desirable anticipated effects large? <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		Disease progression	The mean disease progression in the control group was 0	The mean disease progression in the intervention group was 0.01 lower (0.13 lower to 0.11 higher)	MD 0.01 lower (0.13 lower to 0.11 higher)	-	
	Are the undesirable anticipated effects small? <input type="radio"/> No <input checked="" type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		Adverse events	617 per 1000	950 per 1000 (771 to	333 more per 1000 (from 154 more to 555	RR 1.54 (1.25 to 1.9)	

	Criteria	Judgements	Research evidence					Additional considerations
	Are the desirable effects large relative to undesirable effects?	<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies			1172)	more)		
			Serious Adverse Outcome	300 per 1000	288 per 1000 (165 to 504)	12 fewer per 1000 (from 135 fewer to 204 more)	RR 0.96 (0.55 to 1.68)	
Resource use	Are the resources required small?	<input type="radio"/> No <input checked="" type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Median price of imatinib is 26.00 USD per 100 mg					
	Is the incremental cost small relative to the net benefits?	<input type="radio"/> No <input checked="" type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies						
Equity	What would be the impact on health inequities?	<input type="radio"/> Increased <input type="radio"/> Probably increased <input checked="" type="radio"/> Uncertain <input type="radio"/> Probably						

	Criteria	Judgements	Research evidence	Additional considerations
		y reduced <input type="radio"/> Reduced <input type="radio"/> Varies		
Acceptability	Is the option acceptable to key stakeholders?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		
Feasibility	Is the option feasible to implement?	<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		

Recommendation

Should imatinib vs. no imatinib be used in patients with idiopathic pulmonary fibrosis?

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings
	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Type of	We recommend against	We suggest not	We suggest offering this	We recommend	

recommendation	offering this option	offering this option	option	offering this option
	●	○	○	○
Recommendation	We recommend that clinicians not use imatinib in patients with IPF (strong recommendation, moderate confidence in estimates of effect).			
Justification	Imatinib is a relatively expensive drug with no current evidence suggesting benefit in IPF patients to prevent disease progression or mortality. In the context of no demonstrated clinical benefit, this recommendation puts a high value on adverse events and the cost of treatment. There was consensus amongst the committee in this recommendation.			
Subgroup considerations	none			
Implementation considerations	none			
Monitoring and evaluation	none			
Research possibilities				

EtD: Should anticoagulants be used in patients with idiopathic pulmonary fibrosis (IPF)?

	Criteria	Judgements	Research evidence	Additional considerations																		
Problem	Is there a problem priority?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	<p><i>IPF is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, with a histologic appearance of usual interstitial pneumonia and occurring primarily in older adults. Protrombotic stimulus and thrombosis in the pulmonary vasculature have been associated with the pathophysiological events that lead to morbidity and mortality in patients with IPF. Anticoagulant medications (warfarin, unfractionated or low-molecular-weight heparin) are proposed therapies with some observed benefits in mortality.</i></p>																			
Benefits & harms of the options	What is the overall certainty of this evidence?	<input type="radio"/> No included studies <input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High	<p>The relative importance or values of the main outcomes of interest:</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Mortality</td> <td>CRITICAL</td> <td>⊕⊕⊕⊖ MODERATE</td> </tr> <tr> <td>Disease progression</td> <td>CRITICAL</td> <td>⊕⊕⊕⊖ MODERATE</td> </tr> <tr> <td>Disease progression</td> <td>CRITICAL</td> <td>⊕⊕⊕⊖ MODERATE</td> </tr> <tr> <td>Adverse events</td> <td>CRITICAL</td> <td>⊕⊕⊕⊖ MODERATE</td> </tr> <tr> <td>Serious adverse events</td> <td>CRITICAL</td> <td>⊕⊕⊕⊖ MODERATE</td> </tr> </tbody> </table> <p>Summary of findings: no anticoagulants</p>	Outcome	Relative importance	Certainty of the evidence (GRADE)	Mortality	CRITICAL	⊕⊕⊕⊖ MODERATE	Disease progression	CRITICAL	⊕⊕⊕⊖ MODERATE	Disease progression	CRITICAL	⊕⊕⊕⊖ MODERATE	Adverse events	CRITICAL	⊕⊕⊕⊖ MODERATE	Serious adverse events	CRITICAL	⊕⊕⊕⊖ MODERATE	
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Serious adverse events	CRITICAL	⊕⊕⊕⊖ MODERATE																				
Is there important uncertainty about how much people value the main outcomes?	<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty																					

	Criteria	Judgements	Research evidence					Additional considerations
		y of variability <input checked="" type="radio"/> No important uncertainty of variability <input type="radio"/> No known undesirable	Outcome	Without anticoagulants	With anticoagulants	Difference (95% CI)	Relative effect (RR) (95% CI)	
			Mortality	41 per 1000	194 per 1000 (58 to 648)	153 more per 1000 (from 17 more to 607 more)	RR 4.73 (1.42 to 15.77)	
	Are the desirable anticipated effects large?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Disease progression	The mean disease progression in the control group was 0	The mean disease progression in the intervention group was 0.04 lower (0.12 lower to 0.04 higher)	MD 0.04 lower (0.12 lower to 0.04 higher)	-	
	Are the undesirable anticipated effects small?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Disease progression	877 per 1000	947 per 1000 (850 to 1043)	70 more per 1000 (from 26 fewer to 167 more)	RR 1.08 (0.97 to 1.19)	
			Adverse events	836 per 1000	902 per 1000 (794 to 1028)	67 more per 1000 (from 42 fewer to 192 more)	RR 1.08 (0.95 to 1.23)	
			Serious adverse events	164 per 1000	291 per 1000 (155 to 547)	127 more per 1000 (from 10 fewer to 383 more)	RR 1.77 (0.94 to 3.33)	
	Are the desirable effects large relative to undesirable effects?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes						

	Criteria	Judgements	Research evidence	Additional considerations
		<input type="radio"/> Varies		
Resource use	Are the resources required small?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		Oral warfarin was not considered to be an expensive medication
	Is the incremental cost small relative to the net benefits?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		There is no net benefit. Cost becomes irrelevant.
Equity	What would be the impact on health inequities?	<input type="radio"/> Increased <input type="radio"/> Probably increased <input type="radio"/> Uncertain <input type="radio"/> Probably reduced <input type="radio"/> Reduced <input type="radio"/> Varies		Panel cannot see any impact on health equity
Acceptability	Is the option acceptable	<input type="radio"/> No <input type="radio"/> Probabl		

	Criteria	Judgements	Research evidence	Additional considerations
	to key stakeholders?	<input type="radio"/> No <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		
Feasibility	Is the option feasible to implement?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		

Recommendation

Should anticoagulants vs. no anticoagulants be used for patients with Idiopathic Pulmonary Fibrosis (IPF)?

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings
	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option	
	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Recommendation	We recommend that clinicians do not use routine anticoagulation in patients with IPF (strong, moderate).
Justification	The evidence is available only for use of warfarin.
Subgroup considerations	Those with indications for anticoagulation for other reasons: e.g. Afib or DVT.
Implementation considerations	
Monitoring and evaluation	
Research possibilities	Anticoagulants other than warfarin and antiplatelet agents.

EtD: Should Prednisone, Azathioprine, N-acetylcysteine be used in patients with idiopathic pulmonary fibrosis (IPF)?

	Criteria	Judgements	Research evidence	Additional considerations																		
Problem	Is there a problem priority?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		High mortality and morbidity associated with IPF with a small number of proven treatment options.																		
Benefits & harms of the options	What is the overall certainty of this evidence ?	<input type="radio"/> No included studies <input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High	<p>The relative importance or values of the main outcomes of interest:</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Mortality</td> <td>CRITICAL</td> <td>⊕○○○ VERY LOW</td> </tr> <tr> <td>Adverse Event</td> <td>CRITICAL</td> <td>⊕○○○ VERY LOW</td> </tr> <tr> <td>Disease Progression</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Disease Progression</td> <td>CRITICAL</td> <td>⊕○○○ VERY LOW</td> </tr> <tr> <td>Quality of Life</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> </tbody> </table> <p>Summary of findings: NAC/Imuran/Prednisone compared to placebo for IPF</p>	Outcome	Relative importance	Certainty of the evidence (GRADE)	Mortality	CRITICAL	⊕○○○ VERY LOW	Adverse Event	CRITICAL	⊕○○○ VERY LOW	Disease Progression	CRITICAL	⊕⊕○○ LOW	Disease Progression	CRITICAL	⊕○○○ VERY LOW	Quality of Life	CRITICAL	⊕⊕○○ LOW	The overall quality of evidence is low.
	Outcome	Relative importance		Certainty of the evidence (GRADE)																		
Mortality	CRITICAL	⊕○○○ VERY LOW																				
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	Criteria	Judgements	Research evidence	Additional considerations
	Are the desirable effects large relative to undesirable effects?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		
Resource use	Are the resources required small?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies		Depending on setting.
	Is the incremental cost small relative to the net benefits?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		No benefit (and maybe harm) was observed.
Equity	What would be	<input type="radio"/>	Dependent on setting.	

	Criteria	Judgements	Research evidence	Additional considerations
	the impact on health inequities?	Increased <input type="radio"/> Probably increased <input type="radio"/> Uncertain <input type="radio"/> Probably reduced <input type="radio"/> Reduced <input checked="" type="radio"/> Varies		
Acceptability	Is the option acceptable to key stakeholders?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		
Feasibility	Is the option feasible to implement?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	Already approved for use in most countries.	

Recommendation

Should NAC/Imuran/Prednisone vs. placebo be used for IPF?

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings
	●	○	○	○	○
Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option	
	●	○	○	○	
Recommendation	We recommend against use of triple therapy in patients with IPF.				
Justification	<p>This is a recommendation based on “PANTHER” Trial, comparing the triple therapy with placebo. We cannot make recommendation or generalize the recommendation to other interstitial lung disease other than study population from PANTHER trial—only applied to IPF patients!</p> <p>Some guideline panels feel uncomfortable to generalize the recommendation to subgroups. (see subgroup consideration)</p>				
Subgroup considerations	<p>No significant subgroups.</p> <p>For those who are currently on treatment, there is no evidence of “continuing/discontinuing” the treatment. It is related to individual preference although if we are recommending against hard to rationalize that those on treatment should remain on treatment.</p> <p>If patients currently on triple therapy and appear to benefit from the treatment, they should reapproach the initial diagnosis of IPF (maybe it is another interstitial lung disease)</p>				

EtD: Should selective ER-As be used in patients with idiopathic pulmonary fibrosis (IPF)?

	Criteria	Judgements	Research evidence	Additional considerations									
Problem	Is there a problem priority?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="checkbox"/> Yes <input type="radio"/> Varies	<p>IPF is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults and with a median survival of 2 to 3 years. Endothelin-1 is one of many profibrotic cytokines and growth factors believed to be involved in the pathogenesis of IPF.</p>	<p>Based on this pathophysiological connection, several endothelin receptor antagonists (e.g., Bosentan, Ambrisentan, and Macitentan) have been evaluated in randomized trials to assess its efficacy and safety. Selective ET-A receptor antagonists (selective ERA-A) include sitaxentan, ambrisentan, atrasentan, BQ-123, zibotentan. They are known to affect endothelin A receptors. On this group we only find one randomized trial evaluating ambrisentan versus placebo.</p>									
Benefits & harms of the options	What is the overall certainty of this evidence?	<input type="radio"/> No included studies <input type="radio"/> Very low <input checked="" type="checkbox"/> Low <input type="radio"/> Moderate <input type="radio"/> High	<p>The relative importance or values of the main outcomes of interest:</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Mortality</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Mortality and/or</td> <td>CRITICAL</td> <td>⊕⊕⊕○</td> </tr> </tbody> </table>	Outcome	Relative importance	Certainty of the evidence (GRADE)	Mortality	CRITICAL	⊕⊕○○ LOW	Mortality and/or	CRITICAL	⊕⊕⊕○	
	Outcome	Relative importance		Certainty of the evidence (GRADE)									
Mortality	CRITICAL	⊕⊕○○ LOW											
Mortality and/or	CRITICAL	⊕⊕⊕○											
Is there important uncertainty	<input type="radio"/> Important <input type="radio"/> Uncertain												

<p>about how much people value the main outcomes?</p>	<p>y or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty of variability <input checked="" type="checkbox"/> No important uncertainty of variability <input type="radio"/> No known undesirable</p>	disease progression		MODERATE		
		Disease progression	CRITICAL	⊕⊕○○ LOW		
		Adverse events	CRITICAL	⊕⊕○○ LOW		
		Serious adverse events	CRITICAL	⊕⊕○○ LOW		
<p>Summary of findings: no ambrisentan</p>						
<p>Are the desirable anticipated effects large?</p>	<p><input type="radio"/> No <input checked="" type="checkbox"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies</p>	Outcome	Without ambrisentan	With ambrisentan	Difference (95% CI)	Relative effect (RR) (95% CI)
		Mortality	37 per 1000	79 per 1000 (33 to 188)	42 more per 1000 (from 4 fewer to 151 more)	RR 2.15 (0.9 to 5.11)
		Mortality and/or disease progression	209 per 1000	353 per 1000 (252 to 492)	144 more per 1000 (from 44 more to 284 more)	RR 1.69 (1.21 to 2.36)
		Disease progression	The mean disease progression in the control group was 0	The mean disease progression in the intervention group was 3.2 lower (7.39 lower to 0.99 higher)	MD 3.2 lower (7.39 lower to 0.99 higher)	-
<p>Are the undesirable anticipated effects small?</p>	<p><input type="radio"/> No <input checked="" type="checkbox"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies</p>					
		<p>Are the desirable effects large relative to undesirable</p>	<p><input checked="" type="checkbox"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain</p>			

	effects?	<input type="radio"/> Probably <input type="radio"/> Yes <input type="radio"/> Varies	<table border="1"> <tr> <td>Adverse events</td> <td>834 per 1000</td> <td>843 per 1000 (776 to 918)</td> <td>8 more per 1000 (from 58 fewer to 83 more)</td> <td>RR 1.01 (0.93 to 1.1)</td> </tr> <tr> <td>Serious adverse events</td> <td>153 per 1000</td> <td>222 per 1000 (147 to 336)</td> <td>69 more per 1000 (from 6 fewer to 183 more)</td> <td>RR 1.45 (0.96 to 2.19)</td> </tr> </table>	Adverse events	834 per 1000	843 per 1000 (776 to 918)	8 more per 1000 (from 58 fewer to 83 more)	RR 1.01 (0.93 to 1.1)	Serious adverse events	153 per 1000	222 per 1000 (147 to 336)	69 more per 1000 (from 6 fewer to 183 more)	RR 1.45 (0.96 to 2.19)	
Adverse events	834 per 1000	843 per 1000 (776 to 918)	8 more per 1000 (from 58 fewer to 83 more)	RR 1.01 (0.93 to 1.1)										
Serious adverse events	153 per 1000	222 per 1000 (147 to 336)	69 more per 1000 (from 6 fewer to 183 more)	RR 1.45 (0.96 to 2.19)										
Resource use	Are the resources required small?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Ambrisentan is the most expensive of the three currently endothelin receptor antagonists evaluated in randomized trials, with an approximate cost of 1,636 GBP per month or 3940 USD per month.											
	Is the incremental cost small relative to the net benefits?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies												
Equity	What would be the impact on health inequities?	<input type="radio"/> Increased <input type="radio"/> Probably increased <input checked="" type="radio"/> Uncertain <input type="radio"/> Probably reduced <input type="radio"/> Reduced <input type="radio"/> Varies		Not considered										
Acceptability	Is the option	<input type="radio"/> No <input checked="" type="radio"/> Probably		There is uncertainty due										

ty	acceptable to key stakeholders?	no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		to a probable increase in risks and high costs.
Feasibility	Is the option feasible to implement?	<input type="radio"/> No <input checked="" type="checkbox"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		Given the high costs and possible harms the option is not considered feasible.

Recommendation

Should ambrisentan vs. no ambrisentan be used in patients with idiopathic pulmonary fibrosis?

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequences is <i>closely balanced or uncertain</i>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings
	<input checked="" type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option	
	<input checked="" type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Recommendation	We recommend that clinicians do not use Ambrisentan in patients with idiopathic pulmonary fibrosis (strong recommendation, low certainty of the evidence)				

Justification	Based in only one study that was stopped early for lack of benefit and an increased likelihood of mortality in the intervention group, plus a high price of the medication that would generate an increased use of resources.
Subgroup considerations	No subgroups were considered
Implementation considerations	None considered
Monitoring and evaluation	Not applicable
Research possibilities	None considered

EtD: Should Pirfenidone be used in patients with idiopathic pulmonary fibrosis (IPF)?

	Criteria	Judgements	Research evidence	Additional considerations																		
Problem	Is there a problem priority?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		There is a high mortality and morbidity associated with IPF with a small number of proven treatment options.																		
Benefits & harms of the options	What is the overall certainty of this evidence?	<input type="radio"/> No included studies <input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High	The relative importance or values of the main outcomes of interest: <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Mortality</td> <td>CRITICAL</td> <td>⊕⊕⊕○ MODERATE</td> </tr> <tr> <td>Acute exacerbation</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Oxygen saturation (higher numbers are better)</td> <td>IMPORTANT</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Disease progression</td> <td>CRITICAL</td> <td>⊕⊕⊕⊕ HIGH</td> </tr> <tr> <td>Photosensitivity</td> <td>IMPORTANT</td> <td>⊕⊕⊕⊕ HIGH</td> </tr> </tbody> </table>	Outcome	Relative importance	Certainty of the evidence (GRADE)	Mortality	CRITICAL	⊕⊕⊕○ MODERATE	Acute exacerbation	CRITICAL	⊕⊕○○ LOW	Oxygen saturation (higher numbers are better)	IMPORTANT	⊕⊕○○ LOW	Disease progression	CRITICAL	⊕⊕⊕⊕ HIGH	Photosensitivity	IMPORTANT	⊕⊕⊕⊕ HIGH	FVC data from King Jr study not pooled due to reporting differences however magnitude of effect similar to other studies that were pooled. Quality of Life was not collected. Would this have changed recommendation? Unlikely. Photosensitivity - less of a problem if taking proper precautions.
	Outcome	Relative importance		Certainty of the evidence (GRADE)																		
Mortality	CRITICAL	⊕⊕⊕○ MODERATE																				
Acute exacerbation	CRITICAL	⊕⊕○○ LOW																				
Oxygen saturation (higher numbers are better)	IMPORTANT	⊕⊕○○ LOW																				
Disease progression	CRITICAL	⊕⊕⊕⊕ HIGH																				
Photosensitivity	IMPORTANT	⊕⊕⊕⊕ HIGH																				
Is there important uncertainty about how much people value the main outcomes?	<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty																					

	Criteria	Judgements	Research evidence				Additional considerations
		y of variability <input checked="" type="radio"/> No important uncertainty of variability <input type="radio"/> No known undesirable	Anorexia	IMPORTANT	⊕⊕⊕⊕ HIGH		
			Fatigue	IMPORTANT	⊕⊕⊕○ MODERATE		
			Summary of findings: Pirfenidone compared to placebo for patients with IPF				
	Are the desirable anticipated effects large?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Outcome	Without Pirfenidone	With Pirfenidone	Difference (95% CI)	Relative effect (RR) (95% CI)
			Mortality	77 per 1000	54 per 1000 (36 to 79)	23 fewer per 1000 (from 2 more to 41 fewer)	RR 0.70 (0.47 to 1.02)
			Acute exacerbation	29 per 1000	20 per 1000 (6 to 70)	9 fewer per 1000 (from 23 fewer to 41 more)	RR 0.69 (0.20 to 2.42)
	Are the undesirable anticipated effects small?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Oxygen saturation (higher numbers are better)	The mean oxygen saturation (higher numbers are better) in the control group was 0	The mean oxygen saturation (higher numbers are better) in the intervention group was 0.53 higher (1.01 lower to 2.06 higher)	MD 0.53 higher (1.01 lower to 2.06 higher)	-
	Are the desirable effects large relative to undesirable	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/>		The mean oxygen saturation (higher numbers are better)	The mean oxygen saturation (higher numbers are better)		

	Criteria	Judgements	Research evidence				Additional considerations
	e effects?	Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		better) in the control group was 0	better) in the intervention group was 0.53 higher (1.01 lower to 2.06 higher)	higher)	
			Disease progression	The mean disease progression in the control group was 0	The mean disease progression in the intervention group was 0.23 standard deviations higher (0.06 higher to 0.41 higher)	SMD 0.23 higher (0.06 higher to 0.41 higher)	-
				The mean disease progression in the control group was 0	The mean disease progression in the intervention group was 0.23 standard deviations higher (0.06 higher to 0.41 higher)	SMD 0.23 higher (0.06 higher to 0.41 higher)	
			Photosensitivity	61 per 1000	325 per 1000 (90 to 1000)	264 more per 1000 (from 28 more to 1119 more)	RR 5.30 (1.46 to 19.24)
			Anorexia	47 per 1000	139 per 1000 (97 to 201)	92 more per 1000 (from 50 more to 154)	RR 2.96 (2.06 to 4.27)

	Criteria	Judgements	Research evidence	Additional considerations										
			<table border="1"> <tr> <td></td> <td></td> <td></td> <td>more)</td> <td></td> </tr> <tr> <td>Fatigue</td> <td>182 per 1000</td> <td>259 per 1000 (182 to 368)</td> <td>76 more per 1000 (from 0 fewer to 186 more)</td> <td>RR 1.42 (1.00 to 2.02)</td> </tr> </table>				more)		Fatigue	182 per 1000	259 per 1000 (182 to 368)	76 more per 1000 (from 0 fewer to 186 more)	RR 1.42 (1.00 to 2.02)	
			more)											
Fatigue	182 per 1000	259 per 1000 (182 to 368)	76 more per 1000 (from 0 fewer to 186 more)	RR 1.42 (1.00 to 2.02)										
Resource use	Are the resources required small? <ul style="list-style-type: none"> <input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies 		Pirfenidone is expensive. Estimated yearly cost around \$40,000/patient. In Europe around 40k euros.											
	Is the incremental cost small relative to the net benefits? <ul style="list-style-type: none"> <input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies 			Balancing the costs versus the net benefit, the costs still are not small.										
Equity	What would be the impact on health inequities? <ul style="list-style-type: none"> <input type="radio"/> Increased <input checked="" type="radio"/> Probably increased <input type="radio"/> Uncertain <input type="radio"/> 			Likely treatment would only be affordable to those in developed world.										

	Criteria	Judgements	Research evidence	Additional considerations
		Probably reduced <input type="radio"/> Reduced <input type="radio"/> Varies		
Acceptability	Is the option acceptable to key stakeholders?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		There is uncertainty about acceptability owing to large resources required.
Feasibility	Is the option feasible to implement?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		Pirfenidone is approved in most countries and already being used for other indications.

Recommendation

Should Pirfenidone vs. placebo be used for patients with IPF?

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably outweigh</i> desirable consequences in	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i>	Desirable consequences <i>probably outweigh</i> undesirable consequences in	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings
--------------------------------	--	---	--	---	--

		most settings		most settings	
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option	
	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	
Recommendation	We suggest pirfenidone in patients with IPF (conditional, moderate). 1 panel member was insistent on a strong recommendation in favour and wanted this documented.				
Justification	One panel member thought it should be a strong recommendations for using the treatment. Th rationale was that the cost required is similar to costs in e.g. oncology.				
Subgroup considerations	Inclusion criteria for most of the trials were relatively narrow (excluded patients with emphysema and severe PFTs) so less certainty regarding patients with severe disease but no real reason to think they would respond differently. Also patients with major comorbidities were excluded.				
Implementation considerations	There is some uncertainty when the treatment should be started and when should be stopped. There is uncertainty how long does the tx effect endure. In most studies follow-up was 1y. Shared (between clinician and patient) and informed decision making about adverse effects needs to be done as with any intervention.				
Monitoring and evaluation	Drug interactions may be relevant.				
Research possibilities	How long does the tx effect endure? How long should patients be treated for?				

EtD: Should nintedanib be used in patients with idiopathic pulmonary fibrosis (IPF)?

	Criteria	Judgements	Research evidence	Additional considerations																		
Problem	Is there a problem priority?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	<p><i>IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults. An aberrant proliferation of fibrous tissue and tissue remodeling due to the abnormal function and signaling of alveolar epithelial cells and interstitial fibroblasts (secondary to an activation of cell-signaling pathways through tyrosine kinases, e.g., platelet-derived growth factor [PDGF] among others) has been associated with the pathogenesis of the disease. Tyrosine Kinase Inhibitors (TKI) such as nintedanib, represents a new set of anti-proliferative agents with activity against platelet-derived growth factor receptors</i></p>	<p><i>The prevalence, disruptive clinical presentation, ominous outcomes such as mortality and decrease in quality of life, afflicting patients and families are worrisome enough to consider this a priority</i></p>																		
Benefits & harms of the options	What is the overall certainty of this evidence?	<input type="radio"/> No included studies <input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High	<p>The relative importance or values of the main outcomes of interest:</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>mortality</td> <td>CRITICAL</td> <td>⊕⊕⊕○ MODERATE</td> </tr> <tr> <td>Disease progression</td> <td>CRITICAL</td> <td>⊕⊕⊕○ MODERATE</td> </tr> <tr> <td>Disease progression</td> <td>CRITICAL</td> <td>⊕⊕⊕○ MODERATE</td> </tr> <tr> <td>Adverse events</td> <td>CRITICAL</td> <td>⊕⊕⊕⊕ HIGH</td> </tr> <tr> <td>Serious Adverse Outcome</td> <td>CRITICAL</td> <td>⊕⊕⊕○ MODERATE</td> </tr> </tbody> </table>	Outcome	Relative importance	Certainty of the evidence (GRADE)	mortality	CRITICAL	⊕⊕⊕○ MODERATE	Disease progression	CRITICAL	⊕⊕⊕○ MODERATE	Disease progression	CRITICAL	⊕⊕⊕○ MODERATE	Adverse events	CRITICAL	⊕⊕⊕⊕ HIGH	Serious Adverse Outcome	CRITICAL	⊕⊕⊕○ MODERATE	
	Outcome	Relative importance	Certainty of the evidence (GRADE)																			
mortality	CRITICAL	⊕⊕⊕○ MODERATE																				
Disease progression	CRITICAL	⊕⊕⊕○ MODERATE																				
Disease progression	CRITICAL	⊕⊕⊕○ MODERATE																				
Adverse events	CRITICAL	⊕⊕⊕⊕ HIGH																				
Serious Adverse Outcome	CRITICAL	⊕⊕⊕○ MODERATE																				
	Is there important uncertainty about how much people value the main outcomes?	<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty																				

	Criteria	Judgements	Research evidence					Additional considerations
		ty of variability <input checked="" type="radio"/> No important uncertainty of variability <input type="radio"/> No known undesirable	Summary of findings					
Are the desirable anticipated effects large?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		Outcome	Without nintedanib	With nintedanib	Difference (95% CI)	Relative effect (RR) (95% CI)	
Are the undesirable anticipated effects small?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		mortality	83 per 1000	58 per 1000 (39 to 85)	25 fewer per 1000 (from 2 more to 44 fewer)	RR 0.7 (0.47 to 1.03)	
Are the desirable effects large relative to undesirable effects?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes		Disease progression	The mean disease progression in the control group was 0	The mean disease progression in the intervention group was 0.11 higher (0.08 higher to 0.14 higher)	MD 0.11 higher (0.08 higher to 0.14 higher)	-	
			Disease progression	601 per 1000	691 per 1000 (637 to 751)	90 more per 1000 (from 36 more to 150 more)	RR 1.15 (1.06 to 1.25)	
			Adverse events	898 per 1000	951 per 1000 (916 to 978)	54 more per 1000 (from 18 more to 81 more)	RR 1.06 (1.02 to 1.09)	
			Serious Adverse Outcome	301 per 1000	295 per 1000 (250 to 349)	6 fewer per 1000 (from 48 more to 51 fewer)	RR 0.98 (0.83 to 1.16)	

	Criteria	Judgements	Research evidence	Additional considerations
		<input type="radio"/> Varies		
Resource use	Are the resources required small?	<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	The cost of nintedanib is not known yet	
	Is the incremental cost small relative to the net benefits?	<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		
Equity	What would be the impact on health inequities?	<input type="radio"/> Increased <input type="radio"/> Probably increased <input checked="" type="radio"/> Uncertain <input type="radio"/> Probably reduced <input type="radio"/> Reduced <input type="radio"/> Varies		
Acceptability	Is the option acceptable to key	<input type="radio"/> No <input type="radio"/> Probably no		Depends on the cost of therapy

	Criteria	Judgements	Research evidence	Additional considerations
	stakeholders?	<input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		
Feasibility	Is the option feasible to implement?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		

Recommendation

Should nintedanib vs. no nintedanib be used in patients with idiopathic pulmonary fibrosis?

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option	
	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	
Recommendation	We suggest clinicians use nintedanib in patients with idiopathic pulmonary fibrosis (conditional recommendation, moderate certainty of evidence)				

Justification	<p>When the cost of nintedanib is known and if it is low then this might be a strong recommendation to use nintedanib.</p> <p>1 panel member thought it should be a strong recommendation.</p>
Subgroup considerations	<p>Trials included patients with probable IPF. Uncertainty whether the effects would be same for more severe patients</p>
Implementation considerations	<p>Despite the increased risk of adverse events, when considering implementing the medication it should state the adverse events (such as diarrhea) can be managed accordingly without further complications</p>
Monitoring and evaluation	
Research possibilities	<p>Whether side effects are similar in patients with different sub-groups and/or ethnic backgrounds.</p>

EtD: Should anti-GERD medications be used in patients with idiopathic pulmonary fibrosis (IPF)?

	Criteria	Judgements	Research evidence	Additional considerations												
Problem	Is there a problem priority?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	<p>The incidence and prevalence of IPF is highly linked to advanced age with an estimated incidence and prevalence of 71 and 271 per 100,000 per year for males and 67 and 266 per 100,000 per year for females aged 75 yrs or greater versus an overall incidence and prevalence of 16.3 and 42.7 per 100,000 per year using broad diagnostic criteria.</p> <p>The natural history of IPF has been described as a progressive decline in subjective and objective pulmonary function until eventual death from respiratory failure or complicating comorbidity.</p>	<p>Abnormal acid gastroesophageal reflux (GER) is highly prevalent in patients with IPF, and up to one half of patients are asymptomatic. One study showed that Sixteen of 17 IPF patients with IPF had abnormal distal and/or proximal esophageal acid exposure.</p> <p>Abnormal GER is a risk factor for aspiration, which is a known cause of pneumonitis, and may contribute to chronic airways inflammation and fibrosis.</p> <p>Although the vast majority of patients with IPF had abnormal acid GER, only 47% exhibited symptoms of GER.</p>												
Benefits & harms of the options	What is the overall certainty of this evidence?	<input type="radio"/> No included studies <input checked="" type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High	<p>The relative importance or values of the main outcomes of interest:</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Mortality</td> <td>CRITICAL</td> <td>⊕○○○ VERY LOW</td> </tr> <tr> <td>All cause mortality</td> <td>CRITICAL</td> <td>⊕○○○ VERY LOW</td> </tr> <tr> <td>Acute Exacerbation</td> <td>CRITICAL</td> <td>⊕○○○ VERY LOW</td> </tr> </tbody> </table>	Outcome	Relative importance	Certainty of the evidence (GRADE)	Mortality	CRITICAL	⊕○○○ VERY LOW	All cause mortality	CRITICAL	⊕○○○ VERY LOW	Acute Exacerbation	CRITICAL	⊕○○○ VERY LOW	<p>The panel acknowledged this is a weak recommendation based on large uncertain in evidence (very low quality of evidence).</p>
	Outcome	Relative importance		Certainty of the evidence (GRADE)												
Mortality	CRITICAL	⊕○○○ VERY LOW														
All cause mortality	CRITICAL	⊕○○○ VERY LOW														
Acute Exacerbation	CRITICAL	⊕○○○ VERY LOW														
Is there important uncertainty about how much people value the	<input type="radio"/> Important uncertainty or variability															

	Criteria	Judgements	Research evidence				Additional considerations
	main outcomes?	<input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input checked="" type="radio"/> No important uncertainty or variability <input type="radio"/> No known undesirable	All Cause Hospitalization	CRITICAL	⊕○○○ VERY LOW		
			Disease progression	CRITICAL	⊕○○○ VERY LOW		
			Function	CRITICAL	⊕○○○ VERY LOW		
			abnormal acid GER	IMPORTANT	⊕○○○ VERY LOW		
			Summary of findings: Should patients with IPF be treated with anti-acid medication?				
			Outcome	Without anti-acid medication	With anti-acid medication	Difference (95% CI)	Relative effect (RR) (95% CI)
	Are the desirable anticipated effects large?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	Mortality	-	-	not estimable	HR 0.47 (0.24 to 0.93)
			All-cause mortality	0 per 1000	0 per 1000 (0 to 0)	11% vs 18%	not estimable
			Acute Exacerbation	0 per 1000	0 per 1000 (0 to 0)	0 vs 12%	not estimable
	Are the undesirable anticipated effects small?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	All Cause Hospitalization	0 per 1000	0 per 1000 (0 to 0)	17% vs 30	not estimable
			Disease progression	The mean disease progression in the control group was 0	The mean disease progression in the intervention group was 0.07 higher (0	MD 0.07 higher (0 higher to 0.14 higher)	-

	Criteria	Judgements	Research evidence					Additional considerations
	Are the desirable effects large relative to undesirable effects?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies			higher to 0.14 higher)			
			Function	The mean function in the control group was 0	The mean function in the intervention group was 35.73 higher (52.08 lower to 123.54 higher)	MD 35.73 higher (52.08 lower to 123.54 higher)	-	
			abnormal acid GER	870 per 1000	635 per 1000 (443 to 904)	235 fewer per 1000 (from 35 more to 426 fewer)	RR 0.73 (0.51 to 1.04)	
Resource use	Are the resources required small?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	The cost of medical management of gastroesophageal reflux is low. In one clinical trial based cost-utility analysis, the total cost of proton pump inhibitors in the first year was \$4,237.					
	Is the incremental cost small relative to the net benefits?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably	No cost-effectiveness study was conducted to compare the cost-effectiveness of anti-acid medication treatment in IPF patients. But the cost is generally small.					

	Criteria	Judgements	Research evidence	Additional considerations
		yes <input type="radio"/> Yes <input type="radio"/> Varies		
Equity	What would be the impact on health inequities?	<input type="radio"/> Increased <input type="radio"/> Probably increased <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably reduced <input type="radio"/> Reduced <input type="radio"/> Varies	This treatment may help relieve the symptoms of IPF patients, reduce risk factors of further progression and probably reduce the health inequity.	
Acceptability	Is the option acceptable to key stakeholders?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	The physicians and patients may be in favor of the treatment.	
Feasibility	Is the option feasible to implement?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	This anti-acid medication is feasible due to low cost and easy administration.	

Recommendation

Should anti-acid treatment vs. no anti-acid be used for idiopathic pulmonary fibrosis patients for GERD?

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings
	○	○	○	●	○
Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option	
	○	○	●	○	
Recommendation	We suggest that clinicians use regular anti-acid treatment for patients with IPF (conditional recommendation, very low confidence in estimates of effect).				
Justification	<p>This recommendation places a higher value on possible improved lung function and survival and the low cost of therapy and a lower value on the potential increased risk of pneumonia with anti-acid therapy. The panel acknowledged this is a weak recommendation based on large uncertain in evidence (very low quality of evidence). Although the individual studies might be well conducted, the nature of observational studies suggested that the indication of anti-acid treatment was based on the individual physician's decision, which may induce risk of bias.</p> <p>The evidence was on anti-acid treatment, but mainly on PPI; a very small proportion of included patients were on H2RAs.</p> <p>This recommendation applies to all IPF patients as it is based on IPF being the treatment indication, rather than abnormal GER.</p>				
Subgroup considerations	It is unclear if the benefit of anti-acid therapy in IPF would be different in symptomatic versus asymptomatic patients.				
Implementation considerations	It is important to note that this recommendation applies to all IPF patients as it is based on IPF being the treatment indication, rather than abnormal GER.				
Monitoring and evaluation					
Research possibilities	Further studies, including randomized controlled trial to compare anti-acid treatment vs no anti-acid treatment for IPF patients, the drug interaction of PPI with other IPF medical treatment, safety issue of PPI treatment for IPF patients, as well as the role of GERD and microaspiration in the pathogenesis of IPF are needed.				

EtD: Should phosphodiesterase inhibitors be used in patients with idiopathic pulmonary fibrosis (IPF)?

	Criteria	Judgements	Research evidence	Additional considerations																					
Problem	Is there a problem priority?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		High mortality and morbidity associated with IPF with a small number of proven treatment options.																					
Benefits & harms of the options	What is the overall certainty of this evidence?	<input type="radio"/> No included studies <input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High	<p>The relative importance or values of the main outcomes of interest:</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Mortality</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Exacerbations</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Borg Dyspnea Score Change (higher numbers are worse)</td> <td>IMPORTANT</td> <td>⊕⊕⊕○ MODERATE</td> </tr> <tr> <td>SOBQ Dyspnea Score Change (higher numbers are worse)</td> <td>IMPORTANT</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Quality of Life (SGRQ) (higher numbers are worse)</td> <td>CRITICAL</td> <td>⊕⊕⊕○ MODERATE</td> </tr> <tr> <td>Disease progression</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> </tbody> </table>	Outcome	Relative importance	Certainty of the evidence (GRADE)	Mortality	CRITICAL	⊕⊕○○ LOW	Exacerbations	CRITICAL	⊕⊕○○ LOW	Borg Dyspnea Score Change (higher numbers are worse)	IMPORTANT	⊕⊕⊕○ MODERATE	SOBQ Dyspnea Score Change (higher numbers are worse)	IMPORTANT	⊕⊕○○ LOW	Quality of Life (SGRQ) (higher numbers are worse)	CRITICAL	⊕⊕⊕○ MODERATE	Disease progression	CRITICAL	⊕⊕○○ LOW	
	Outcome	Relative importance		Certainty of the evidence (GRADE)																					
Mortality	CRITICAL	⊕⊕○○ LOW																							
Exacerbations	CRITICAL	⊕⊕○○ LOW																							
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Disease progression	CRITICAL	⊕⊕○○ LOW																							
Is there important uncertainty about how much people value the main outcomes?	<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty of																								

	Criteria	Judgements	Research evidence			Additional considerations	
		variability <input checked="" type="radio"/> No important uncertainty of variability <input type="radio"/> No known undesirable	Disease Progression	CRITICAL	⊕⊕○○ LOW		
			Summary of findings: Phosphodiesterase Inhibitors compared to placebo for IPF patients				
	Are the desirable anticipated effects large?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Outcome	Without Phosphodiesterase Inhibitors	With Phosphodiesterase Inhibitors	Difference (95% CI)	Relative effect (RR) (95% CI)
			Mortality	38 per 1000	19 per 1000 (4 to 103)	18 fewer per 1000 (from 34 fewer to 65 more)	RR 0.51 (0.10 to 2.72)
			Exacerbations	33 per 1000	11 per 1000 (1 to 106)	22 fewer per 1000 (from 32 fewer to 73 more)	RR 0.34 (0.04 to 3.22)
	Are the undesirable anticipated effects small?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Borg Dyspnea Score Change (higher numbers are worse)	The mean borg Dyspnea Score Change (higher numbers are worse) in the control group was 0	The mean borg Dyspnea Score Change (higher numbers are worse) in the intervention group was 0.18 lower (0.61 lower to 0.25 higher)	MD 0.18 lower (0.61 lower to 0.25 higher)	-
	Are the desirable effects large relative to undesirable effects?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain	SOBQ Dyspnea Score Change (higher numbers are worse)	The mean SOBQ Dyspnea Score Change (higher numbers are worse) in the control group was 0	The mean SOBQ Dyspnea Score Change (higher numbers are worse) in the intervention group was 6.59 lower (0 higher	MD 6.59 lower (0 higher to 0 higher)	-

	Criteria	Judgements	Research evidence					Additional considerations
		<input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies			to 0 higher)			
			Quality of Life (SGRQ) (higher numbers are worse)	The mean quality of Life (SGRQ) (higher numbers are worse) in the control group was 0	The mean quality of Life (SGRQ) (higher numbers are worse) in the intervention group was 4.09 lower (7.31 lower to 0.87 lower)	MD 4.09 lower (7.31 lower to 0.87 lower)	-	
			Disease progression	The mean disease progression in the control group was 0	The mean disease progression in the intervention group was 0.07 higher (0.2 lower to 0.34 higher)	MD 0.07 higher (0.2 lower to 0.34 higher)	-	
			Disease Progression	The mean disease Progression in the control group was 0	The mean disease Progression in the intervention group was 0.01 lower (0.33 lower to 0.31 higher)	MD 0.01 lower (0.33 lower to 0.31 higher)	-	
Resource use	Are the resources required small?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Not sure costs regarding sildenafil. Likely around \$5000/year. In Netherlands estimate is 5k euro per month.					Cost may be substantial if patients pay out of pocket or in less well resourced settings.
	Is the incremental cost	<input checked="" type="radio"/> No						There was no evidence of net

	Criteria	Judgements	Research evidence	Additional considerations
	small relative to the net benefits?	<input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		benefits.
Equity	What would be the impact on health inequities?	<input checked="" type="radio"/> Increased <input type="radio"/> Probably increased <input type="radio"/> Uncertain <input type="radio"/> Probably reduced <input type="radio"/> Reduced <input type="radio"/> Varies		Patients often need to pay for it themselves (not covered in many jurisdictions).
Acceptability	Is the option acceptable to key stakeholders?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		
Feasibility	Is the option feasible to	<input type="radio"/> No <input type="radio"/>		Sildenafil is a widely approved drug which

	Criteria	Judgements	Research evidence	Additional considerations
	implement?	Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		is used for many other indications.

Recommendation

Should Phosphodiesterase Inhibitors vs. placebo be used for IPF patients?

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings
	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option	
	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Recommendation	We suggest that clinicians do not use sildenafil in pts with IPF.				
Justification	2 abstentions, 2 in favor, 5 against - was weak recommendation either way but couldn't decide on direction so went to vote. Given signal in right direction in a few outcomes (Mortality, exacerbations, QOL, DLCO) even if not significant all were trending - some concern that we are now recommending against a drug which may work however given the cost and no significant improvement the majority of panel were ok with this.				
Subgroup considerations	This does not apply to using sildenafil for other indications eg. Pulmonary HTN or RV dysfunction.				

	<p>(consider here the STEP IPF subgroup study Han et al)</p> <p>Decided to not offer a separate recommendation for pHTN subgroup however subgroup considerations here are significant.</p>
Implementation considerations	
Monitoring and evaluation	
Research possibilities	<p>More research in patients with PH and evidence of RV dysfunction may be justified. There is some evidence suggesting a benefit in this subgroup.</p> <p>More QoL studies needed.</p>

EtD: Should NAC monotherapy be used in patients with idiopathic pulmonary fibrosis (IPF)?

	Criteria	Judgements	Research evidence	Additional considerations																		
Problem	Is there a problem priority?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	<p>The incidence of IPF was estimated at 10.7 cases per 100,000 per year for men and 7.4 cases per 100,000 per year for women in a population-based study from the county of Bernalillo, New Mexico. A study from the United Kingdom reported an overall incidence rate of only 4.6 per 100,000 person-years, but estimated that the incidence of IPF increased by 11% annually between 1991 and 2003. A third study from the United States estimated the incidence of IPF to be between 6.8 and 16.3 per 100,000 persons using a large database of healthcare claims in a health plan. Prevalence estimates for IPF have varied from 2 to 29 cases per 100,000 in the general population.</p> <p>The natural history of IPF has been described as a progressive decline in subjective and objective pulmonary function until eventual death from respiratory failure or complicating comorbidity.</p>																			
Benefits & harms of the options	What is the overall certainty of this evidence?	<input type="radio"/> No included studies <input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High	<p>The relative importance or values of the main outcomes of interest:</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Mortality</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Adverse Effects</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Quality of Life (higher scores indicate better)</td> <td>CRITICAL</td> <td>⊕⊕⊕○ MODERATE</td> </tr> <tr> <td>Disease progression</td> <td>CRITICAL</td> <td>⊕⊕⊕⊕ HIGH</td> </tr> <tr> <td>Function</td> <td>CRITICAL</td> <td>⊕○○○ VERY LOW</td> </tr> </tbody> </table> <p>Summary of findings: Acetylcysteine monotherapy compared to other treatments for Idiopathic Pulmonary Fibrosis</p>	Outcome	Relative importance	Certainty of the evidence (GRADE)	Mortality	CRITICAL	⊕⊕○○ LOW	Adverse Effects	CRITICAL	⊕⊕○○ LOW	Quality of Life (higher scores indicate better)	CRITICAL	⊕⊕⊕○ MODERATE	Disease progression	CRITICAL	⊕⊕⊕⊕ HIGH	Function	CRITICAL	⊕○○○ VERY LOW	<p>Quality of evidence is lower for the inhaled route of administration.</p> <p>Desirable effects were decided to be not large, so the relative effects of desirable to undesirable effects was not large.</p>
	Outcome	Relative importance		Certainty of the evidence (GRADE)																		
Mortality	CRITICAL	⊕⊕○○ LOW																				
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		higher)							
Resource use	Are the resources required small?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	The cost of N-Acetylcysteine is generally low.						
	Is the incremental cost small relative to the net benefits?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	No cost-effectiveness study was conducted.						
Equity	What would be the impact on health inequities?	<input type="radio"/> Increased <input type="radio"/> Probably increased <input checked="" type="radio"/> Uncertain <input type="radio"/> Probably	It may help provide the IPF patients the healthcare.						

	Criteria	Judgements	Research evidence	Additional considerations
		reduced <input type="radio"/> Reduced <input type="radio"/> Varies		
Acceptability	Is the option acceptable to key stakeholders?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		
Feasibility	Is the option feasible to implement?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies		

Recommendation

Should Acetylcysteine monotherapy vs. other treatments be used for Idiopathic Pulmonary Fibrosis?

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in	Undesirable consequences <i>probably outweigh</i> desirable	The balance between desirable and undesirable consequences <i>is closely balanced</i>	Desirable consequences <i>probably outweigh</i> undesirable	Desirable consequences <i>clearly outweigh</i> undesirable consequences in
--------------------------------	--	---	---	---	--

	most settings	consequences in most settings	<i>or uncertain</i>	consequences in most settings	most settings
	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option	
	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Recommendation	We suggest that clinicians not use N-acetylcysteine monotherapy in patients with IPF (conditional recommendation, low confidence in estimates of effect).				
Justification	This recommendation places a higher value on the potential risks, inconvenience and cost of therapy and a low value on possible improvement of outcomes with unclear patient importance. The benefit of using acetylcysteine monotherapy in IPF patients is uncertain while there might also be small harms related to the treatment.				
Subgroup considerations	Evidence was from patients with mild to moderately reduced patients and there is uncertainty on to what extent it applies to those with severe impairment of pulmonary function.				
Implementation considerations	We have not found evidence for difference between inhaled vs. oral way of administration. In the minority of patients who decide to use it the way of administration may depend on patient preferences. No suggestion for discontinuation as we found no evidence of net harm.				
Monitoring and evaluation					
Research possibilities	The panel perceived a paucity of studies of biomarkers of oxidative stress and studies of inhaled NAC in patients with IPF . Future trials should identify if there are subgroup of patients with a higher burden of oxidative stress more likely to benefit from therapy than others. Studies assessing different delivery of N-acetylcysteine, inhaled vs oral N-acetylcysteine in patients with IPF could be considered.				

EtD: Should dual endothelin receptor antagonists be used in patients with idiopathic pulmonary fibrosis (IPF)?

	Criteria	Judgements	Research evidence	Additional considerations																												
Problem	Is there a problem priority?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	IPF is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults and with a median survival of 2 to 3 years. Endothelin-1 is one of many profibrotic cytokines and growth factors believed to be involved in the pathogenesis of IPF. Based on this pathophysiologic connection several endothelin receptor antagonists (e.g., Bosentan, Ambrisentan, and Macitentan) have been evaluated in randomized trials to assess its efficacy and safety.																													
Benefits & harms of the options	What is the overall certainty of this evidence?	<input type="radio"/> No included studies <input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High	<p>The relative importance or values of the main outcomes of interest:</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Relative importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Mortality</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Mortality and disease progression</td> <td>CRITICAL</td> <td>⊕⊕○○ LOW</td> </tr> <tr> <td>Disease progression</td> <td>CRITICAL</td> <td>⊕⊕⊕○ MODERATE</td> </tr> <tr> <td>Adverse events</td> <td>CRITICAL</td> <td>⊕⊕⊕⊕ HIGH</td> </tr> <tr> <td>Serious Adverse Events</td> <td>CRITICAL</td> <td>⊕⊕⊕○ MODERATE</td> </tr> </tbody> </table> <p>Summary of findings: no endothelin receptor antagonists</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Without endothelin receptor antagonists</th> <th>With endothelin receptor antagonists</th> <th>Difference (95% CI)</th> <th>Relative effect (RR) (95% CI)</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Outcome	Relative importance	Certainty of the evidence (GRADE)	Mortality	CRITICAL	⊕⊕○○ LOW	Mortality and disease progression	CRITICAL	⊕⊕○○ LOW	Disease progression	CRITICAL	⊕⊕⊕○ MODERATE	Adverse events	CRITICAL	⊕⊕⊕⊕ HIGH	Serious Adverse Events	CRITICAL	⊕⊕⊕○ MODERATE	Outcome	Without endothelin receptor antagonists	With endothelin receptor antagonists	Difference (95% CI)	Relative effect (RR) (95% CI)						
	Outcome	Relative importance		Certainty of the evidence (GRADE)																												
Mortality	CRITICAL	⊕⊕○○ LOW																														
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Outcome	Without endothelin receptor antagonists	With endothelin receptor antagonists	Difference (95% CI)	Relative effect (RR) (95% CI)																												
Is there important uncertainty about how much people value the main outcomes?	<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input checked="" type="radio"/> No important uncertainty of																															

	Criteria	Judgements	Research evidence					Additional considerations
		variability <input type="radio"/> No known undesirable	Mortality	34 per 1000	39 per 1000 (19 to 77)	4 more per 1000 (from 15 fewer to 43 more)	RR 1.13 (0.57 to 2.27)	
	Are the desirable anticipated effects large?	<input type="radio"/> No <input checked="" type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Mortality and disease progression	402 per 1000	341 per 1000 (285 to 402)	60 fewer per 1000 (from 0 fewer to 116 fewer)	RR 0.85 (0.71 to 1)	
	Are the undesirable anticipated effects small?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies	Disease progression	The mean disease progression in the control group was 0	The mean disease progression in the intervention group was 0.02 higher (0.09 lower to 0.13 higher)	MD 0.02 higher (0.09 lower to 0.13 higher)	-	
			Adverse events	740 per 1000	755 per 1000 (710 to 792)	15 more per 1000 (from 30 fewer to 52 more)	RR 1.02 (0.96 to 1.07)	
	Are the desirable effects large relative to undesirable effects?	<input type="radio"/> No <input checked="" type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Serious Adverse Events	349 per 1000	311 per 1000 (259 to 377)	38 fewer per 1000 (from 28 more to 91 fewer)	RR 0.89 (0.74 to 1.08)	
Resource use	Are the resources required small?	<input checked="" type="radio"/> No <input type="radio"/> Probably no	In the UK, the cost (in GBP) per month is: Bosentan– £1,636.00 Macitentan– £2,331.00 In the US, the cost (USD) per month is:					

	Criteria	Judgements	Research evidence	Additional considerations
		<input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies	Bosentan– \$2,970.00 Macitentan– \$8,208.00	
	Is the incremental cost small relative to the net benefits?	<input checked="" type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		
Equity	What would be the impact on health inequities?	<input type="radio"/> Increased <input type="radio"/> Probably increased <input type="radio"/> Uncertain <input type="radio"/> Probably reduced <input type="radio"/> Reduced <input type="radio"/> Varies		not considered. Opportunity cost may be large.
Acceptability	Is the option acceptable to key stakeholders?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies		There is uncertainty about acceptability related to the cost.

	Criteria	Judgements	Research evidence	Additional considerations
Feasibility	Is the option feasible to implement?	<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Uncertain <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies		Depends on cost and jurisdiction.

Recommendation

Should endothelin receptor antagonists vs. no endothelin receptor antagonists be used for patients with Idiopathic Pulmonary Fibrosis?

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings
	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option	
	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Recommendation	We suggest that clinicians do not use dual Endothelin Receptor Antagonists-A (dual ERA-A) in patients with idiopathic pulmonary fibrosis (Conditional recommendation, low certainty of the evidence)				
Justification	Resources required are large compared to uncertain benefit.				
Subgroup considerations	-				
Implementation considerations	-				

Monitoring and evaluation	-
Research possibilities	Research could still be feasible in patients with IPF and pulmonary hypertension