Table of contents:

S1. Embase Search Strategy

An experienced medical librarian helped develop a search strategy from Medline (896), Embase (2191), Cochrane (1591) and clinicaltrials.gov (189). We present below the Embase strategy which can be translated into the relevant search engines. We utilized the following RCT filter: https://guides.library.ualberta.ca/c.php?g=342568&p=5096194.

Database: Embase 1974 to 2021 December 23 2021
Search Strategy:
---
1 exp pulmonary hypertension/ (100716)
2 (pulmonary adj2 hypertens*).mp. (106672)
3 1 or 2 (112061)
4 (Sotatercept or ACE-011).tw,kw. (207)
5 (Bosentan or Tracleer or Stayveer).tw,kw. (4381)
6 (Ambrisentan or Letairis or Volibris or Pulmonext).tw,kw. (1027)
7 (Macitentan or Opsumit).tw,kw. (794)
8 (Sitaxentan/sitaxsentan or TBC-11251 or Thelin).tw,kw. (367)
9 Beraprost.tw,kw. (724)
10 (Treprostinil or Remodulin or Orenitram or Tyvaso).tw,kw. (1539)
11 prostacyclin/ or (Epoprostenol or Flolan).tw,kw. (26632)
12 phosphodiesterase V inhibitor/ or (Tadalafil or Cialis or Cidala or Adcirca or Sildenafil or Viagra or Revatio or Vardenafil or Levitra or Staxyn or Vivanza).tw,kw. (23909)
13 (Iloprost or Ventavis or Ilomedine).tw,kw. (4042)
14 (Riociguat or Adempas).tw,kw. (890)
15 (Selexipag or Uptravi).tw,kw. (418)
16 matinib.mp. or Imatinib Mesylate/ (44952)
17 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (100947)
18 Randomized Controlled Trials as Topic/ or randomized controlled trial/ or randomization/ or Double Blind Procedure.mp. (945677)

19 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or method* or procedure*)).ti,ab,kw. (354287)
20 (((clinical or control*) adj2 trial*) or random*).tw,kw. (2173955)
21 18 or 19 or 20 (2485917)
22 3 and 17 and 21 (2923)
23 animal/ or animal experiment/ (4273317)
24 juvenile/ or exp adolescent/ or exp child/ or exp postnatal development/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre term or preterm* or premature birth or NICU or preschool* or pre school* or kindergarten* or elementary school* or nursery school* or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or prepubesc* or pre pubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. (5061386)
25 23 or 24 (9058842)
26 22 not 25 (2229)
27 limit 26 to em=202126-202152 (126)
****

1.

Page 2

Catheter-based therapies in acute and chronic pulmonary embolism.
Michaud E., Pan M., Aggarwal V.
Current opinion in cardiology. 36(6) (pp 704-710), 2021. Date of Publication: 01 Nov 2021.
AN: 636118418
PURPOSE OF REVIEW: The aim of this study is to summarize currently available catheter-based therapies in acute and chronic pulmonary embolic disease. RECENT FINDINGS: Catheter-based therapies to treat acute pulmonary embolism and its sequelae such as chronic thromboembolic pulmonary hypertension (CTEPH) are emerging as the next frontier within interventional

cardiology. However, the true benefit of these catheter-based therapies in intermediate-risk and high-risk pulmonary embolism and CTEPH remains unclear. The current evidence supporting such interventions comes primarily from small single-arm studies in acute pulmonary embolism and case series in CTEPH. SUMMARY: Appropriately powered randomized controlled trials with meaningful clinical outcomes as endpoints are needed to elucidate the true benefit of catheter-based therapies in pulmonary embolism compared with other treatment modalities such as anticoagulation and systemic thrombolysis in acute pulmonary embolism and riociguat and pulmonary endarterectomy in CTEPH.

PMID
34508032 [http://www.ncbi.nlm.nih.gov/pubmed/?term=34508032]
Institution
(Michaud, Pan) Department of Internal Medicine (Aggarwal) Division of Cardiology (Frankel Cardiovascular Center), Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, United States
Publisher
NLM (Medline)

S2. Modified cochrane risk of bias tool 2.0 (Rob 2.0)

We used a modified version of the cochrane RoB 2.0 to simplify the overall guidance and provide more detailed guidance on rating the risk of bias for domains with more judgment based characteristics (i.e. missing data).

Bias from the randomization process	
Issues to consider: Random sequence generation Allocation concealment	
Definitely low risk of bias	Trials that assign participants to alternative interventions using a randomly generated sequence and maintain allocation concealment. Examples of methods for developing a randomly generated allocation sequence include a random number generator, random number table, coin tossing, shuffling cards or envelopes, and throwing dice. If a trial is described as 'randomized' without any additional details related to how the allocation sequence was developed, we will assume that the allocation sequence was appropriately developed. Examples of methods for maintaining allocation concealment include using central allocation via a computer or phone system, pharmacy-controlled allocation, opaque sealed envelopes, and sequentially numbered drug containers. *Note that an explicit description of random sequence generation is not necessary for a rating of definitely low risk of bias.*

Probably low risk of bias	Trials in which healthcare providers were blind to the intervention but which provide no information on allocation concealment and in which there are no major baseline imbalances. *Note that an explicit description of random sequence generation is not necessary for a rating of probably low risk of bias.*
Probably high risk of bias	Trials in which healthcare providers were not blind to the intervention and which provide no information on allocation concealment. Trials in which there are substantial baseline differences between trial arms that suggest a problem with the randomization process but there are no other limitations related to randomization.
Definitely high risk of bias	Trials in which allocation is by judgment of the clinician, by preference of the participant, by availability of the intervention, based on the results of a laboratory test, or other non-random rules (e.g., birthdate, etc.). Trials in which investigators enrolling participants could possibly foresee the arm to which each subsequent patient would be randomized, such as allocation using an open allocation schedule (e.g. a list of random numbers), assignment envelopes used without appropriate safeguards (e.g. use of unsealed, non-opaque or not sequentially numbered envelopes), alternation between arms, case record number, or any other explicitly unconcealed procedure, rate as high risk.
Bias due to deviations from the intended intervention	
Issues to consider: Blinding of healthcare providers/clinicians and participants Imbalances in co interventions for behaviors	

Definitely low risk of bias	Therapy trials in which healthcare providers are blind to the intervention administered and in which there are no significant differences in administered co-interventions. Therapy trials that are described as double or triple blind.
Probably low risk of bias	
Probably high risk of bias	Therapy trials in which healthcare providers are not blind to the intervention administered. Therapy trials in which healthcare providers are blind to the intervention administered but there are significant differences in administered co-interventions that suggest that blinding may have been compromised. Therapy trials in which healthcare providers are described as being blind to the intervention but allocation concealment was inadequate.
Definitely high risk of bias	Therapy trials in which healthcare providers are not blind to the intervention and in which there are significant differences in administered co-interventions.
Bias due to missing data	
Issues to consider: Missing outcome measures Loss to follow-up	
Definitely low risk of bias	Trials in which missing outcome data (including outcome data that has been imputed) < 10%.

	For in-patient trials, we will assume low risk of bias due to missing data unless otherwise specified.
Probably low risk of bias	Trials in which missing outcome data (including outcome data that has been imputed) is between 10% to 15% and missing outcome data is unlikely to be related to the true outcome and there is no imbalance in numbers of or reasons for missing data across intervention groups.
Probably high risk of bias	Trials in which missing outcome data (including outcome data that has been imputed) is between 10% to 15% and missing outcome data is likely to be related to the true outcome or there are imbalances in numbers of or reasons for missing data across intervention groups.
Definitely high risk of bias	Trials in which missing outcome data (including outcome data that has been imputed) > 15%.
Bias due to measurement of the outcome	
Issues to consider: Blinding of outcome adjudicators Objectivity of outcome *Note that the judgments may differ across outcomes.*	
Definitely low risk of bias	Trials in which patients are blind to the intervention and in which outcomes are patient-reported. Trials in which outcomes are measured by a third-party (investigator or clinician) and in which the third-party is blind to the intervention. Trials in which the outcomes are objective. Trials that are described as double or triple blind.
Probably low risk of bias	

Probably high risk of bias	
Definitely high risk of bias	Trials in which patients are not blind and in which outcomes are patient-reported (e.g., time to symptom resolution). Trials in which outcome adjudicators are not blind and the outcomes are not objective (e.g., adverse effects leading to discontinuation, transfusion-related acute lung injury, transfusion-associated circulatory overload, allergic reactions, infection with suspected/symptomatic COVID-19, venous thromboembolism, time to symptom resolution including fever, time to clinical improvement if the criteria for clinical improvement are not objective).
Bias in selection of the reported results	
Issues to consider: Selective reporting of timepoints Selective reporting of outcome measures *Note that we are only interested in selective reporting for the outcomes for which we are extracting data.* *Note that the judgments may differ across outcomes.*	
Definitely low risk of bias	Results for outcomes that were analyzed and reported according to a pre-specified statistical analysis plan or protocol (including the timepoint for the measurement of the outcome).
Probably low risk of bias	Results for outcomes that were analyzed and reported but that were not prespecified in a statistical analysis plan or protocol but the timepoint at which results are reported is consistent with the timepoint for other outcomes in the trial report or there is little reason to believe the outcome was selectively reported.

	Please note that outcomes that were not prespecified in a protocol or statistical analysis plan and that are reported in the trial preprint or publication should be rated at probably low risk of bias unless there are other important reasons to suspect that results for those outcomes were selectively reported (e.g., results are presented at timepoints that don't match the timepoints reported for other outcomes).
Probably high risk of bias	Results for outcomes that were analyzed and reported but that were not prespecified in a statistical analysis plan or protocol but the timepoint at which results are reported is not consistent with the timepoint for other outcomes in the trial report or there are other reasons to believe that the outcome is selectively reported.
Definitely high risk of bias	Results for outcomes that were analyzed and reported for which there are inconsistencies with the statistical analysis plan or protocol. These inconsistencies may include outcome measures of interest or the timepoints for the measurement of outcomes.

S3. Treatment node categories

We grouped drug treatments into similar nodes on the basis of 1) similar mechanism of action and 2) consistent effect estimates overall. For drug treatments that were studied intravenously, inhaled or given as tablets orally, we separated into separate nodes. Combination treatments directly studied in randomized trials were included as distinct nodes. Novel or investigational drugs were treated separately regardless of mechanism or effect size. The following table describes how nodes were grouped.

Drug treatment	Node
Ambrisentan	ERA
Bosentan	ERA
Macitentan	ERA
Sitaxsentan	ERA
Ambrisentan+Tadalafil	ERA+PDE5i
Sildenafil	PDE5i
Tadalafil	PDE5i
Vardenafil	PDE5i
Ralinepag	Prostacyclin receptor agonist
Selexipag	Prostacyclin receptor agonist
Treprostinil	Prostanoid(Inh)

Iloprost	Prostanoid(Inh)
Iloprost+Bosentan	Prostanoid(Inh)+ERA
Iloprost	Prostanoid(IV)
Epoprostenol	Prostanoid(IV)
Treprostinil	Prostanoid(IV)
Treprostinil	Prostanoid(PO)
Beraprost	Prostanoid(PO)
Riociguat	Riociguat
Imatinib	Imatinib
Selonsertib	Selonsertib
Sotatercept	Sotatercept

S4. Methods terminology for GRADE and network meta-analysis

Network meta-analysis - a type of meta-analysis that compares more than two treatments against one another using direct and indirect estimates to produce a network estimate. Normally, the network estimates are presented in the results, unless the certainty of the direct estimates are higher..

Frequentist network meta-analysis - this is one of the two methods of analysis for network meta-analysis. The other is a Bayesian network meta-analysis. They differ in the usual way that Bayesian and frequentist statistics differ, mainly that Bayesian methods use probabilities in the analysis whereas frequentists do not. The consequence of this is that Bayesian methods usually produce wider confidence intervals than frequentist estimates, as a result of assumed greater network wide heterogeneity. Both are valid methods of performing network analysis.

Node splitting - network estimates that have indirect and direct evidence, these estimates are split into three components. The network estimate, indirect estimate and direct estimate are inspected for consistency. Consistency is assessed mainly by inspection of the point estimate and the confidence intervals (i.e., whether they overlap).

Heterogeneity estimators - are methods for calculating heterogeneity (differences between studies) in meta-analysis. Restricted Maximum Likelihood (REML) estimator is one such example. Simulation studies show that this method produces better error rates.

Meta-regression - is similar to simple regression, where the outcome of interest is predicted on the basis of one or more explanatory variables.

ICEMAN tool - is a validated instrument designed to evaluate the credibility of a subgroup.

GRADE - GRADE is the most widely adopted tool for grading the quality of evidence and for making recommendations with over 100 organizations worldwide officially endorsing GRADE. The GRADE framework requires judgements to be made by the researchers and may not be reproducible [1-3].

Domains for evaluating evidence for network meta-analysis [4-9].

Risk of bias - using a validated tool, researchers can assess the risk of bias of studies included in an estimate. They rate the certainty down once for studies at risk of bias.

We rated studies using a modification of the risk of bias tool 2.0, which was used in two previous peer reviewed meta-analyses. For each estimate, we looked at the proportion of studies that were at risk of bias. We rated down for risk of bias once if removal of the risk of bias studies from the analysis significantly changed the results. We rated down for risk of bias also if all the studies were at risk of bias. We did not rate down more than once.

Imprecision - using minimally important differences, we rated down the certainty of evidence by once, twice or three times, depending on how uncertain the result is.

Using a minimally contextualized framework, we rated down once for imprecision if the confidence intervals included the MID. If the confidence interval included the MID in both directions we rated down twice. We did not rate down three times for any estimate. .

Indirectness - This is assessed whether the population and intervention of interest are congruent with the research question. If it is not, researchers may rate down the certainty of evidence.

We assessed this by evaluating each trial and making judgements on the included trials, interventions (dose, route, duration) and how each outcome was measured.

Publication bias - In estimates with 10 more studies, publication bias can be assessed. If there is publication bias, investigators may rate down. We assessed publication bias by inspecting funnel plots and Egger's statistical test.

Inconsistency - The individual study estimates may be inconsistent with each other. If this is detected, we may further rate down the certainty of evidence.

We assessed for inconsistency by reviewing forest plots for each estimate. Both the width and overlap of confidence intervals were measured. I^2 statistics were also assessed. If inconsistency was detected, we rated down if removal of that study changed the results.

Incoherence - coherence refers to consistency between direct and indirect estimates

We planned to rate down for incoherence when the indirect and direct estimates were different enough such that there was no overlap in confidence intervals. We did not detect incoherence in our networks and therefore never rated down for this.

Intransitivity - Intransitivity is the dissimilarity of important factors that may affect the outcome being investigated (i.e., effect modifiers) across comparisons.

We looked at multiple possible effect modifiers across the network to determine whether there was intransitivity.

Related methodological clarifications

<u>Point estimates and statistical significance</u>

A common interpretation confusion is around statistical significance. GRADE does not include statistical significance in the rating of the certainty of the evidence. To illustrate why, take for example, a point estimate of drug X versus placebo may indicate a reduction in

mortality by 1% and be statistically significant but the certainty of the estimate may be very low, based on the methods described above. Despite the result being statistically significant, you may not trust the result and limit its implications for practice. Furthermore, statistical significance does not translate into clinical significance. Therefore, the GRADE approach does not place emphasis on statistical significance. Rather, the focus is on the certainty around the point estimate using the validated methods described above. Further issues with interpretation of p-values and the importance of interpreting the effect size has been previously discussed [10-13].

Minimally contextualized approach

A minimally contextualized approach minimizes value judgments regarding the magnitude of intervention effects. It involves a multi-step process, including choosing a reference intervention (i.e placebo) and a decision threshold. A decision threshold can be determined by pre-existing analysis of minimally important differences or by researcher judgment (i.e. a 2% reduction in mortality or a 5% reduction in serious adverse events). The decision threshold is important in determining imprecision, as interventions with 95% credibility interval that cross the decision threshold may be labeled imprecise [4].

Simple language summary

The GRADE approach uses a standardized method for reporting the certainty of evidence in simple language [14]. The use of language will also depend on whether the researchers chose a partially or fully contextual approach. For our paper, we chose a partially contextualized approach. The simple language summary used in our paper is as follows:

High certainty evidence = Drug X reduces mortality
Moderate certainty evidence = Drug X probably reduces mortality
Low certainty evidence = Drug X may reduce mortality
Very low certainty evidence = The evidence of drug X on mortality is very uncertain

Summary of findings (Table 2)

We present the results of our NMA in table 2, which summarizes the network estimates of each treatment node versus placebo. Direct estimates were occasionally presented if the certainty of the evidence was higher. All head-to-head comparisons are presented in the supplementary files, but one can determine the relative effectiveness of one drug versus another by looking at how each drug compares against placebo. This is possible because the network estimates essentially standardize the results against placebo. This is the accepted method for presenting the summary of findings for NMA, which is elegantly demonstrated in the largest living network meta-analysis in the world [15].

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S5. Table of trial characteristics

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
Vizza 2017	United States, Australia, Czechia, France, Germany, Greece, Israel, Italy, Taiwan, UK	NCT00323297	104	56.07	75.7	352.34	NR	NR	35	NR	0	34	65	1
Torres 2019	United States, Australia, Poland, Romania, Bulgaria, Serbia, Spain, Hungary and Czech Republic	NCT02279160	61	49.4	77	378	52.5	10	NR	NR	0	56	43	2

SERAPHIN	Argentina, Australia, Austria, Belarus, Belgium, Bulgaria, Canada, Chile, China, Colombia, Croatia, France, Germany, Hong Kong, Hungary, India, Israel, Italy, Malaysia, Mexico, Netherlands, NRrway, Peru, Poland, Romania, Russian Federation, Serbia, Singapore, Slovakia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States	NCT00660179	742	45.6	76.5	360	55	1.8	30.5	1.4	0.1	52.4	45.6	1.9

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
FREEDOMC2	United States, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Portugal, Spain, Sweden, UK	NCT00887978	310	51	78	333.05	65	Idiopathic or heritable combined	31.3	1.9	0	25.8	72.6	0
FREEDOMC	United States, Australia, Austria, Belgium, Canada, France, Germany, Ireland, Israel, Italy, Netherlands, Poland, Spain, and UK	NCT00325442	350	50	82.3	345.7	66.2	NR	26.3	1.1	0.8	20.6	76	2.6
Sastry, 2004	India	NR	22	NR	54.5	NR	NR	NR	NR	NR	0	81.8	18.2	0
Rubin 1990	United States	NR	23	36.2	69.6	226.6	NR	NR	NR	NR	0	8.7	65.2	26.1

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
Han 2017	China	NCT01712997	27	36.5	66.7	324.3	85.7	NR	NR	NR	NR	NR	71.4	28.6
White 2019	United States, Argentina, Australia, Austria, Brazil, Canada, Chile, China, Denmark, France, Germany, Greece, India, Israel, Italy, Korea, Mexico, Netherlands, Poland, Singapore, Sweden, Taiwan, UK	NCT01560624	690	45.2	78.8	395.7	NR	NR	25.8	1.3	3.2	62.8	33.9	0.1
BREATHE-1	Europe, North America, Israel, Australia	NR	213	48.2	78.7	334.5	70.7	NR	29.3	NR	0	0	91.3	8.7

GRIPHON	USA, Argentina, Australia, Austria, Belgium, Belarus, Canada, Chile, Colombia, Czechia, China, Denmark, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Malaysia, Korea, Mexico, Netherlands, Peru, Poland, Romania, Russia, Serbia, Slovakia, Singapore, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, UK	NCT01106014	1156	48.1	79.8	353.2	56.1	2.2	28.9	0.9	0.8	45.8	52.5	1

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
Simonneau, 2012	Austria, Belgium, France, Germany, Hungary, Italy, Poland, UK	NCT00993408	43	54.6	81.4	385.5	72.1	4.6	13.9	NR	0	39.2	60.4	0
Simmoneau 2009	United States, Belgium, Canada, Czechia, Denmark, France, Israel, Italy, Netherlands, Spain, and UK	NCT00159861	267	47.7	79.8	345.26	79.4	NR	20.6	NR	1.1	25.5	65.5	6

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
AMBITION	United States, Australia, Austria, Belgium, Canada, France, Germany, Greece, Italy, Japan, Netherlands, Spain, Sweden, UK	NCT01178073	500	54.3	77.6	352.61	53	2.8	37.4	1.8	0	31	69	0
Jing 2011	China	NR	66	31.1	82.8	392.8	60.9	0	29.7	0	0	46.9	53.1	0
COMBI	Germany	NCT00120380	40	52.2	77.5	305.98	NR	NR	NR	NR	0	0	100	0
Hiremath 2010	India	NR	45	32	61	250.4	95	95	5	0	0	0	95	5
Galie 2002	Italy, Poland, Germany, France	NR	130	45.4	61.5	372.5	48.5	NR	10	7	NR	49	51	NR
Galie 2005	Italy, Germany, Poland, USA, UK, France, Mexico, South Africa, Israel	NR	278	48.7	75.5	343.7	63.2	NR	30	NR	0.36	38.6	57.8	3.2

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
Galie 2009	Canada, USA, Japan, Italy, Germany, France, UK	NCT00125918	406	53.8	78.4	343.6	61	NR	23.5	NR	0.99	32	65.2	1.7
COMPASS2	United States, Brazil, Czech, Denmark, Germany, Greece, Portugal, Saudi, Slovakia, Spain, Sweden, UK	NCT00303459	334	53.9	75.7	360.3	63.8	1.5	26.3	NR	0	41.9	57.5	0.6
Jing 2013	United States, Austria, Belgium, Canada, China, France, India, Israel, Italy, Mexico, Netherlands, Poland, Puerto Rico	NCT00325403	349	41.2	75.1	329.9	NR	NR	19.2	1.1	0	35.8	60.7	0

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
ARIES1	United States, Mexico, South America, Australia, and Europe	NCT00091598	202	50	83.6	341	62.7	0	30.8	3.5	2.5	32.3	58.2	7
ARIES2	Europe, Israel, and South America	NCT00091598	192	51	74	348.3	65.1	0	32.3	2.1	1.6	44.8	51.5	2.1
Dwivedi 2018	India	NCT03053739	34	NR	NR	NR	NR	NR	100	NR	NR	NR	NR	NR
Barst 1996	United States	NR	81	40	72.8	294.3	100	NR	NR	NR	NR	NR	74.1	25.9

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
SUPER	United States, Australia, Belgium, Brazil, Czechia, Denmark, France, Germany, Hong Kong, Hungary, Israel, Italy, Korea, Malaysia, Mexico, Netherlands, Poland, Singapore, South Africa, Spain, Sweden and UK	NCT00159887	84	53	83.3	342	0	0	100	0	0	38.1	60.7	1.2
Barst 2003	United States	NR	116	42	85.3	438.8	74.1	NR	10.5	NR	NR	52.6	47.4	NR
Barst 2006	Canada, United States, Belgium, Italy	NR	247	54	78	337	59	NR	30	NR	NR	37	59	4
Badesch 2000	USA, Canada	NR	111	55.13	86.5	255.89	0	0	100	0	0	4.5	78.3	17.1

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
Badesch 2002	United States, France	NR	32	50.55	87.9	358.28	84.4	0	15.6	0	NR	NR	NR	NR

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
REPLACE	Austria, Belgium, Brazil, Canada, the Czech Republic, Denmark, France, Germany, Greece, Italy, Japan, Republic of Korea, Mexico, The Netherlands, Poland, Portugal, Spain, Switzerland, Taiwan, Turkey, the United Kingdom, and the United States of America.	NCT02891850	226	49.2	78.5	370.46875	63.4	3.6	19.2	0	0	0	100	0

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
PULSAR	USA, UK, Australia, Brazil, France, Germany, Israel, Spain	NCT03496207	106	48.3	87	397.5	58	16	17	0	0	53	47	0

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
PATENT1	USA, Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Czech republic, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Japan, Korea, Mexico, Netherlands, Poland, Portugal, Russia, Singapore, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, UK	NCT00810693	445	51	79	363	61	9	25	NR	3	42	53	1

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
Ghofrani 2010	Germany, the United Kingdom, Austria, United States	NCT00477269	59	44.3	67.8	380.3	80	3.4	10	NR	0	32	63	5
IMPRESS	USA, Austria, Belgium, Canada, France, Germany, Italy, Japan, Korea, Netherlands, Spain, Sweden, Switzerland, UK,	NCT00902174	202	48.5	80.7	360.4	75.5	0	24.5	NR	0.5	25.2	67.3	6.4
TRIUMPH-I	United States, Austria, Belgium, France, Germany, Ireland, Israel, Italy, Spain, UK	NCT00147199	235	53.5	81.3	348.6	55.7	Idiopathic or heritable combined	32.8	0	0	0	97.9	2.1

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
PHIRST-1	Italy, United States, Germany, Canada, UK, Belgium, France, Japan, Spain, Ireland	NR	406	51.1	81	351	57	NR	26	NR	0.9	34	64	1
ARROW	United States, Canada, France, Germany, Italy, Netherlands, Spain, UK	NCT02234141	150	50	79	437	NR	NR	19.3		0	60	40	0
Olschewski 2002	Germany, United Kingdom, Belgium, France, Italy, Spain, Poland, Sweden, Switzerland	NR	203	52	67.5	323.46	NR	50.2	17.2	NR	0	0	58.6	41.4
Channick 2001	United States, France	NR	32	50.6	87.5	358.3	84.4	0	15.6	0	0	0	100	0

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
Sandoval 2012	Mexico, Argentina, Brazil, Spain, and Poland	NR	98	41.3	83.7	345.27	68.4	NR	15.3	NR	0	61.2	37.8	1
EARLY	United States, Australia, Austria, Belgium, Canada, China, Czech Republic, France, Germany, Italy, Netherlands, Spain, Switzerland, United Kingdom	NCT00091715	185	44.7	69.7	434.5	60.6	0	17.8	3.8	0	100	0	0
Zhuang 2014	China	SH2010-1065 - Shanghai Municipal Public Health Bureau	124	51.4	79	349.3	62.9	Idiopathic or heritable combined	22.6	0	0	57.3	38.7	4
Wilkins, 2005	United Kingdom	NR	26	42.88	80.77	296.74	88.46	NR		NR	0	0	100	0
Singh, 2006	India	NR	20	25	75	262	50	NA	NA	NA				

											NYHA/WHO (%) FC			
StudyID	**Country**	**TRN**	**N**	**Age**	**Female %**	**6-MWD (m)**	**Idiopathic**	**Heritable**	**Connective tissue**	**HIV**	**I**	**II**	**III**	**IV**
Simonneau, 2002	Canada, Mexico, United States, Australia, Austria, Belgium, France, Germany, Israel, Italy, Poland, Spain, UK	NR	470	44.5	81.45	326.5	57.57	NA	19.19	NA				
BREATHE-2	USA, France, Italy, Netherlands	NR	33	45.7	69.7	NR	81.8	NR	14.9	NR	0	0	75.6	24.3
STRIDE-1	USA, Canada	NR	178	46	79	398	53	24	NR	NR	0	33	66	1
STEP	USA	NR	67	50	79	335	55	0	0	0	0	1.5	94	4.5
Oudiz 2004	USA,Canada,UK,Israel,Australia,Belgium,	NR	90	50.7	90.8	288.7	0	0	100	0	0	9.7	74.8	15.5
EDITA	Germany	NCT02290613	38	21.1	43.16	459.16	0	0	100	0	0	84.2	15.8	0
Rubenfire 2006	USA	NR	22	45.46	86.37	432	72.45	0	13.6	0	4.7	54.54	41	0

Legend:
NR = not reported
TRN = trial registration number
N = number randomized
6MWD = 6 minute walk test distance
FC = functional class

S6. Individual trial characteristics, definitions and background therapy

StudyID	**Galie 2015 (AMBITION)**
Trial arms	Ambrisentan + Tadalafil vs. Tadalafil vs Ambrisentan
Background therapy	None
Clinical worsening definition	Defined as the first occurrence of a composite of death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response.
StudyID	**Vizza 2017**
Trial arms	Sildenafil vs. Placebo
Background therapy	Bosentan
Clinical worsening definition	Defined as death, lung transplantation, hospitalization due to pulmonary hypertension, or clinical deterioration of PAH requiring additional therapy.
StudyID	**Torres 2019**
Trial arms	Ralinepag vs. Placebo

Background therapy	Mono (35%) or dual (65%) combination PAH-specific background therapy (ERA, PDE5i)
Clinical worsening definition	Based on the predefined criteria of death occurring ≤14 days after study drug discontinuation, hospitalisation for heart–lung or lung transplantation or atrial septostomy, addition or change in dose of PAH-specific medications, or the combined occurrence of ≥20% decrease in 6MWD from baseline with worsening in WHO/NYHA functional class and worsening of signs of right heart failure that did not respond to optimised oral diuretic therapy.
StudyID	**Pulido 2013 (SERAPHIN)**
Trial arms	Macitentan vs. Placebo
Background therapy	63.7% Yes (Inhaled or oral prostanoid or PDE5i) 36.3% No
Clinical worsening definition	Defined by the occurrence of all three of the following: a decrease in the 6-minute walk distance of at least 15% from baseline, confirmed by a second 6-minute walk test performed on a different day within 2 weeks; worsening of symptoms of pulmonary arterial hypertension; and the need for additional treatment for pulmonary arterial hypertension.
StudyID	**Tapson 2013 (FREEDOM-C2)**
Trial arms	Treprostinil (Oral) vs. Placebo
Background therapy	Patients were required to have received ERA or PDE-5I therapy for ≥ 90 days with a stable dose for ≥ 30 days before baseline and throughout the duration of the study

Clinical worsening definition	Defined as death, transplantation, or atrial septostomy; hospitalization as a result of right-side heart failure; a decrease in 6MWD of ≥ 20% from baseline (or too ill to walk) and the addition of an inhaled prostacyclin analog, ERA, or PDE-5I; or initiation of parenteral prostacyclin therapy for the treatment of PAH.
StudyID	**Tapson 2012 (FREEDOM-C)**
Trial arms	Treprostinil (Oral) vs. Placebo
Background therapy	Patients were required to have received ERA or PDE-5I therapy for ≥ 90 days with a stable dose for ≥ 30 days before baseline and throughout the duration of the study.
Clinical worsening definition	Defined as death, transplantation, or atrial septostomy; hospitalization as a result of right-side heart failure; a decrease in 6MWD of ≥ 20% from baseline (or too ill to walk) and the addition of an inhaled prostacyclin analog, ERA, or PDE-5I; or initiation of parenteral prostacyclin therapy for the treatment of PAH.
StudyID	**White 2019**
Trial arms	Treprostinil (Oral) vs. Placebo
Background therapy	All patients received either monotherapy with ERA, PDE5i or combination therapy.
Clinical worsening definition	Defined as death, transplantation, or atrial septostomy; hospitalization as a result of right-side heart failure; a decrease in 6MWD of ≥ 20% from baseline (or too ill to walk) and the addition of an inhaled prostacyclin analog, ERA, or PDE-5I; or initiation of parenteral prostacyclin therapy for the treatment of PAH
StudyID	**Simmoneau 2009**

Trial arms	Sildenafil vs. Placebo
Background therapy	Patients had to have received long-term intravenous epoprostenol therapy for at least 3 months, with a stable dose for at least 4 weeks before randomization
Clinical worsening definition	Defined as death, lung transplantation, hospitalization due to pulmonary arterial hypertension, initiation of bosentan therapy, or change in epoprostenol dose of >10% due to clinical deterioration.
StudyID	**Hiremath 2010**
Trial arms	Treprostinil (IV) vs. Placebo
Background therapy	Mix of diuretics, digoxin, anti-coagulants, antibiotics, and vasodilators.
Clinical worsening definition	Defined as death, lung transplant, hospitalization, unblinding for rescue or too-ill-to-walk.
StudyID	**McLaughlin 2015 (COMPASS-2)**
Trial arms	Bosentan vs. Placebo
Background therapy	Sildenafil
Clinical worsening definition	Defined as the time to the first morbidity/mortality event, defined as time to death from any cause, hospitalisation for worsening PAH or start of intravenous prostanoid therapy, atrial septostomy, lung transplant, or worsening PAH.

StudyID	**Jing 2013**
Trial arms	Treprostinil (PO) vs. Placebo
Background therapy	None
Clinical worsening definition	Defined as one of the following: Cardiovascular death, transplantation, atrial septostomy, or clinical deterioration. Clinical deterioration was defined as the initiation of new, approved PAH-specific therapy (ERA, PDE-5I, or prostacyclin) plus either hospitalization for decompensated PAH or a ≥20% decrease in 6MWD from baseline combined with worsening WHO functional class.
StudyID	**Badesch 2002**
Trial arms	Bosentan vs. Placebo
Background therapy	None
Clinical worsening definition	Defined as right ventricular heart failure or aggravated pulmonary hypertension.
StudyID	**Hoeper 2021 (REPLACE)**
Trial arms	Riociguat vs. Tadalafil or sildenafil
Background therapy	None; all patients started with either tadalafil or sildenafil, if patients were treated with other PH medications in a recent period, they were excluded.

Clinical worsening definition	Defined as death from any cause, hospitalisation for worsening PAH (non-elective hospitalisation due to PAH or initiation of parenteral prostanoid therapy), or disease progression (decrease in 6MWD ≥15% on two separate days plus either worsening WHO functional class, need for new PAH-targeted medication, or decompensated right-sided heart failure).
StudyID	**Humbert 2021 (PULSAR)**
Trial arms	Sotatercept vs. Placebo
Background therapy	Patients were receiving stable background therapy for pulmonary arterial hypertension for at least 90 days before enrollment and continued to receive the treatment. Either monotherapy, double therapy, or triple therapy with combinations of endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, or prostacyclin-receptor agonists.
Clinical worsening definition	Defined as death, worsening-related listing for lung and/or heart transplant, need to initiate rescue therapy with an approved PAH SOC therapy, need for atrial septostomy, PAH-specific hospitalization, functional deterioration as defined by both of the below events occurring together at any time, even if they began at different times, as compared to their screening values: worsening WHO functional class and decrease of >=15% in 6MWD at any time point as compared with screening. This must be confirmed by a second 6MWD conducted between 4 hours and 1 week after the first.
StudyID	**Ghofrani 2013 (PATENT-1)**
Trial arms	Riociguat vs. Placebo
Background	50% Yes (87.4% ERA; 12.6% Prostanoids)

therapy	50% No
Clinical worsening definition	Defined as the first occurrence of the following: death, heart/lung transplantation, atrial septostomy, hospitalization, start of new specific PAH therapy or modification, persistent decrease of >15% from baseline or >30% compared with the last study related to 6-MWT or worsening PAD, persistent worsening of WHO functional class.
StudyID	**Ghofrani 2010**
Trial arms	Imatinib vs. Placebo
Background therapy	Treatment with at least one PAH-specific drug (i.e. prostacyclin analogs, ERAs, PDE5 inhibitors) who had not adequately improved were enrolled (56% of patients were receiving two drugs and 24% were receiving three drugs at baseline).
Clinical worsening definition	Defined as worsening of death, worsening of PAH, worsening of general condition, respiratory infection, or RVH failure.
StudyID	**Hoeper 2013 (IMPRESS)**
Trial arms	Imatinib vs. Placebo
Background therapy	ERA+PDE5I, ERA+Prostanoid, Prostanoid+PDE5I, ERA+PDE5I+Prostanoid
Clinical worsening definition	Defined as the first occurrence of any of the following: death; overnight hospitalization for worsening of PAH (blind adjudication); worsening of World Health Organization functional class by at least 1 level; or ≥15% decrease from baseline in 6MWD (confirmed in 2 six-minute walk tests at 2 consecutive visits).

StudyID	**Channick 2001**
Trial arms	Bosentan vs. Placebo
Background therapy	None
Clinical worsening definition	Decompensated right heart failure or aggravated PAH.
StudyID	**Galie 2008 (EARLY)**
Trial arms	Bosentan vs. Placebo
Background therapy	None
Clinical worsening definition	Defined as death of any cause (during the treatment period or as the outcome of a treatment-emergent adverse event that led to permanent discontinuation of study treatment), hospitalisation due to pulmonary arterial hypertension complications, or symptomatic progression of pulmonary arterial hypertension.
StudyID	**Galie 2008 (ARIES 1 and 2)**
Trial arms	Ambrisentan (Variable dosing) vs. Placebo
Background therapy	None

Clinical worsening definition	Defined as the time from randomization to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal because of the addition of other PAH medications, or early escape criteria.
StudyID	**Rubin 1990**
Trial arms	Epoprostenol vs. Conventional
Background therapy	None
Clinical worsening definition	N/A
StudyID	**Badesch 2007 (SUPER)**
Trial arms	Sildenafil (Variable dosing) vs. Placebo
Background therapy	Anticoagulants, digoxin, calcium channel blockers, diuretics, and/or supplemental oxygen.
Clinical worsening definition	N/A
StudyID	**Badesch 2000**
Trial arms	Epoprostenol vs. Conventional

Background therapy	Conventional therapy
Clinical worsening definition	N/A
StudyID	**Sandoval 2012**
Trial arms	Sitaxsentan vs. Placebo
Background therapy	Conventional treatment (including calcium-channel blockers, digitalis, diuretics, anticoagulants, and/or oxygen).
Clinical worsening definition	Defined as hospitalization for worsening PAH, death, need for heart-lung or lung transplant, atrial septostomy, or addition of any new type of chronic treatment for PAH (including a calcium-channel blocker, digitalis, prostacyclin or prostacyclin analog, alternative ETRA, PDE5i, or oxygen), or a combination of deterioration in WHO functional class and ≥15% decrease in 6MWD from baseline.
StudyID	**Rosenkranz 2021 (ARROW)**
Trial arms	Selonsertib vs. Placebo
Background therapy	15.3% of patients enrolled in ARROW were pretreated with bosentan (for comparison: ambrisentan 45.3%, macitentan 22.7%). Otherwise, background treatment included 1-3 approved PAH medications.
Clinical worsening	Defined by all-cause death or hospitalisation for worsening PAH or disease progression (>15% decrease from baseline in 6-min walk distance and WHO functional class III or IV

definition	symptoms at two consecutive visits after baseline ≥14 days apart); echocardiographic variables of right ventricular function (ie, tricuspid annular plane systolic excursion, right ventricular myocardial strain, tricuspid annular systolic velocity, right ventricular Tei index, and right ventricular fractional area change); and health-related quality of life, as measured by the Short Form 36 (SF-36) Health Survey and the emPHasis10 questionnaire.
StudyID	**Hoeper 2006 (COMBI)**
Trial arms	Iloprost+Bosentan vs. Bosentan
Background therapy	None
Clinical worsening definition	Defined as the occurrence of death, hospital admission for right-heart failure, deterioration in functional class or a decrease in 6MWD by 20% from baseline or 150 m.
StudyID	**Jing 2011**
Trial arms	Vardenafil vs. Placebo
Background therapy	Digoxin, warfarin, diuretics, or supplemental oxygen
Clinical worsening definition	Defined as death (all causes) or hospitalization for PAH progression.
StudyID	**McLaughlin 2010 (TRIUMPH I)**

Trial arms	Treprostinil vs. Placebo
Background therapy	Bosentan or Sildenafil
Clinical worsening definition	Defined as death, transplantation, hospital stay due to worsening PAH, or initiation of additional approved PAH-specific therapy, Borg Dyspnea Score, NYHA functional class, trough 6 MWD at week 12 (obtained at least 4 h after study drug administration), peak 6MWD at Week 6, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms
StudyID	**Zhuang 2014**
Trial arms	Ambrisentan+Tadalafil vs. Ambrisentan
Background therapy	None
Clinical worsening definition	Defined as the occurrence of the following events: death, transplantation, atrial septostomy, hospitalization due to worsening PAH, initiation of new therapy or worsening FC by week 16.
StudyID	**Barst 1996**
Trial arms	Epoprostenol vs. Conventional therapy
Background therapy	None
Clinical	N/A

worsening definition	
StudyID	**Barst 2003**
Trial arms	Beraprost vs. Placebo
Background therapy	None
Clinical worsening definition	Defined as either the occurrence of death, transplantation, initiation of chronic intravenous epoprostenol rescue therapy, or hospitalization for PAH, p = 0.01), but no significant improvement in Borg dyspnea score (p = 0.42).
StudyID	**Barst 2006**
Trial arms	ERA (Sitasaxentan or. Bosentan) vs. Placebo
Background therapy	None
Clinical worsening definition	Defined as the number of days between the first dose date and the first date when clinical worsening occurred.
StudyID	**Barst 2011 (PHIRST-1)**
Trial arms	Tadalafil vs. Placebo
Background	Bosentan

therapy	
Clinical worsening definition	Defined as the time from randomization to first occurrence of any of the following: death; transplantation; atrial septostomy; hospitalization due to worsening PAH; initiation of new PAH therapy (prostacyclin analog, endothelin-receptor antagonist, PDE-5 inhibitor); or worsening FC.
StudyID	**Dwivedi 2018**
Trial arms	Sildenafil+Bosentan vs Sildenafil
Background therapy	None
Clinical worsening definition	
StudyID	**Galie 2002**
Trial arms	Beraprost vs. Placebo
Background therapy	None
Clinical worsening definition	N/A
StudyID	**Galie 2005**

Trial arms	Sildenafil vs. Placebo
Background therapy	N/A
Clinical worsening definition	Defined as death, transplantation, hospitalization for pulmonary arterial hypertension, or initiation of additional therapies for pulmonary arterial hypertension, such as intravenous epoprostenol or oral bosentan
StudyID	**Galie 2009**
Trial arms	Tadalafil vs. Placebo
Background therapy	53% Bosentan
Clinical worsening definition	Defined as death; lung or heart-lung transplantation; atrial septostomy; hospitalization due to worsening PAH; initiation of new PAH-approved therapy; worsening WHO functional class
StudyID	**Han 2017**
Trial arms	Bosentan+Iloprost vs. Bosentan vs. Iloprost
Background therapy	None
Clinical worsening definition	N/A

StudyID	**Rubin 2002 (BREATHE-1)**
Trial arms	Bosentan vs. Placebo
Background therapy	None
Clinical worsening definition	Defined as the combined end point of death, lung transplantation, hospitalization for pulmonary hypertension, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy.
StudyID	**Simmoneau 2012**
Trial arms	Selexipag vs. Placebo
Background therapy	ERA and/or PDE5i
Clinical worsening definition	Defined as death, transplantation, hospitalisation due to worsening PAH, or aggravation of PAH symptoms, i.e. a ≥10% deterioration in 6-min walk distance or the need for additional PAH-specific therapies
StudyID	**Sitbon 2015 (GRIPHON)**
Trial arms	Selexipag vs. Placebo
Background therapy	ERA, PDE5I, both (79.6%) or none (20.4%)
Clinical	Defined as a result in hospitalization, initiation of parenteral prostanoid therapy or

worsening definition	long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy as judged by the physician.
StudyID	**Langleben 2004 (STRIDE-1)**
Trial arms	Sitaxsentan vs. Placebo
Background therapy	None
Clinical worsening definition	N/A
StudyID	**McLaughlin 2006 (STEP)**
Trial arms	Iloprost vs. Placebo
Background therapy	Concurrent anticoagulants, vasodilators, diuretics, cardiac glycosides, or supplemental oxygen were allowed; phosphodiesterase inhibitors or other prostanoids were not.
Clinical worsening definition	Defined as the occurrence of PAH-related death, hospitalization or early study discontinuation due to worsening PAH, initiation of new PAH-specific therapy, lung transplantation, or atrial septostomy.
StudyID	**Oudiz 2004**
Trial arms	Treprostinil vs. Placebo
Background	None

therapy	
Clinical worsening definition	N/A
StudyID	**Pan 2019 (EDITA)**
Trial arms	Ambrisentan vs. Placebo
Background therapy	None
Clinical worsening definition	Defined as occurrence of death, lung transplantation, atrial septostomy, and study withdrawal because of addition of other PAH medication or “early escape” criteria (the occurrence of two of the following: > 20% decrease of a 6-min walking distance (6MWD), increase in the World Health Organization functional class (WHO-FC), worsening right ventricular function, hepatic or renal failure, systolic blood pressure < 85 mmHg).
StudyID	**Rubenfire 2007**
Trial arms	Treprostinil vs. Placebo
Background therapy	None
Clinical worsening definition	Defined by the investigator and objective criteria (Unclear).

StudyID	**Simmoneau 2001**
Trial arms	Treprostinil vs. Placebo
Background therapy	None
Clinical worsening definition	Not defined
StudyID	**Sastry 2004**
Trial arms	Sildenafil vs. Placebo
Background therapy	None
Clinical worsening definition	N/A

S7. Network estimates for each combination of head-to-head comparisons with associated GRADE ratings.

S7.1. Clinical worsening

Clinical worsening	**Comparison**	**Network estimate**			**Network estimate**			
		Relative estimate			**Risk Difference**			
Treatment 1	Treatment 2	Point estimate	CI Lower limit	CI upper limit	Point estimate	CI Lower limit	CI upper limit	GRADE rating
ERA	Imatinib	0.45	0.25	0.81	-84.1225	-114.7125	-29.0605	Low
ERA	Placebo	0.53	0.41	0.68	-75.67	-94.99	-51.52	High
ERA	PRA	0.94	0.54	1.64	-3.48	-26.68	37.12	High
ERA	Prostanoid(Inh)	0.83	0.4	1.71	-14.501	-51.18	60.563	Very low
ERA	Prostanoid(PO)	0.7	0.44	1.1	-28.98	-54.096	9.66	Moderate
ERA	Selonsertib	0.74	0.24	2.29	-30.16	-88.16	149.64	Low
ERA+PDE5i	ERA	0.48	0.3	0.76	-37.674	-50.715	-17.388	Moderate

ERA+PDE5i	Imatinib	0.21	0.1	0.44	-120.8305	-137.655	-85.652	Moderate
ERA+PDE5i	PDE5i	0.53	0.32	0.88	-36.3216	-52.5504	-9.2736	Moderate
ERA+PDE5i	Placebo	0.25	0.15	0.42	-120.75	-136.85	-93.38	High
ERA+PDE5i	PRA	0.45	0.22	0.9	-31.9	-45.24	-5.8	High
ERA+PDE5i	Prostanoid(Inh)	0.4	0.17	0.92	-51.18	-70.799	-6.824	Moderate
ERA+PDE5i	Prostanoid(Inh)+ERA	0.83	0.21	3.27	-8.211	-38.157	109.641	Low
ERA+PDE5i	Prostanoid(IV)	0.54	0.25	1.17	-28.1428	-45.885	10.4006	High
ERA+PDE5i	Prostanoid(PO)	0.33	0.18	0.62	-64.722	-79.212	-36.708	Moderate
ERA+PDE5i	Selonsertib	0.35	0.1	1.18	-75.4	-104.4	20.88	Moderate
ERA+PDE5i	Sotatercept	1.17	0.1	13.76	6.0214	-31.878	451.9592	Low
Imatinib	Placebo	1.19	0.69	2.04	29.0605	-47.4145	167.44	Low
PDE5i	ERA	0.89	0.61	1.3	-7.9695	-28.2555	21.735	High
PDE5i	Imatinib	0.4	0.21	0.76	-91.77	-120.8305	-36.708	Low

PDE5i	Placebo	0.47	0.33	0.68	-85.33	-107.87	-51.52	High
PDE5i	PRA	0.84	0.46	1.54	-9.28	-31.32	31.32	High
PDE5i	Prostanoid(Inh)	0.74	0.34	1.62	-22.178	-56.298	52.886	Low
PDE5i	Prostanoid(IV)	1.01	0.51	2.03	0.6118	-29.9782	63.0154	Moderate
PDE5i	Prostanoid(PO)	0.62	0.37	1.04	-36.708	-60.858	3.864	Moderate
PDE5i	Selonsertib	0.66	0.21	2.1	-39.44	-91.64	127.6	Low
PRA	Imatinib	0.47	0.23	0.98	-81.0635	-117.7715	-3.059	Low
PRA	Placebo	0.56	0.34	0.92	-70.84	-106.26	-12.88	Moderate
PRA	Prostanoid(Inh)	0.88	0.37	2.08	-10.236	-53.739	92.124	Low
PRA	Prostanoid(PO)	0.74	0.4	1.37	-25.116	-57.96	35.742	Moderate
PRA	Selonsertib	0.78	0.23	2.61	-25.52	-89.32	186.76	Low
Prostanoid(Inh)	Imatinib	0.54	0.22	1.31	-70.357	-119.301	47.4145	Low
Prostanoid(Inh)	Placebo	0.64	0.32	1.3	-57.96	-109.48	48.3	Moderate

Prostanoid(Inh)	Prostanoid(PO)	0.84	0.38	1.87	-15.456	-59.892	84.042	Low
Prostanoid(Inh)	Selonsertib	0.89	0.24	3.3	-12.76	-88.16	266.8	Low
Prostanoid(Inh)+ERA	ERA	0.57	0.16	2.08	-31.1535	-60.858	78.246	Very low
Prostanoid(Inh)+ERA	Imatinib	0.26	0.06	1.05	-113.183	-143.773	7.6475	Low
Prostanoid(Inh)+ERA	PDE5i	0.64	0.17	2.45	-27.8208	-64.1424	112.056	Very low
Prostanoid(Inh)+ERA	Placebo	0.3	0.08	1.13	-112.7	-148.12	20.93	Low
Prostanoid(Inh)+ERA	PRA	0.54	0.13	2.19	-26.68	-50.46	69.02	Low
Prostanoid(Inh)+ERA	Prostanoid(Inh)	0.48	0.11	1.98	-44.356	-75.917	83.594	Low
Prostanoid(Inh)+ERA	Prostanoid(IV)	0.65	0.15	2.74	-21.413	-52.003	106.4532	Very low
Prostanoid(Inh)+ERA	Prostanoid(PO)	0.4	0.1	1.56	-57.96	-86.94	54.096	Very low
Prostanoid(Inh)+ERA	Selonsertib	0.42	0.08	2.34	-67.28	-106.72	155.44	Very low
Prostanoid(IV)	ERA	0.88	0.46	1.68	-8.694	-39.123	49.266	High
Prostanoid(IV)	Imatinib	0.39	0.18	0.88	-93.2995	-125.419	-18.354	Low

Prostanoid(IV)	Placebo	0.47	0.26	0.85	-85.33	-119.14	-24.15	Moderate
Prostanoid(IV)	PRA	0.83	0.38	1.79	-9.86	-35.96	45.82	High
Prostanoid(IV)	Prostanoid(Inh)	0.73	0.29	1.84	-23.031	-60.563	71.652	Low
Prostanoid(IV)	Prostanoid(PO)	0.61	0.3	1.24	-37.674	-67.62	23.184	Moderate
Prostanoid(IV)	Selonsertib	0.65	0.19	2.27	-40.6	-93.96	147.32	Low
Prostanoid(PO)	Imatinib	0.64	0.33	1.23	-55.062	-102.4765	35.1785	Low
Prostanoid(PO)	Placebo	0.76	0.52	1.11	-38.64	-77.28	17.71	Moderate
Riociguat	ERA	0.31	0.11	0.91	-49.9905	-64.4805	-6.5205	Moderate
Riociguat	ERA+PDE5i	0.65	0.21	2.06	-8.995	-20.303	27.242	High
Riociguat	Imatinib	0.14	0.04	0.45	-131.537	-146.832	-84.1225	Moderate
Riociguat	PDE5i	0.35	0.12	1.03	-50.232	-68.0064	2.3184	Low
Riociguat	Placebo	0.17	0.06	0.47	-133.63	-151.34	-85.33	High
Riociguat	PRA	0.29	0.09	0.93	-41.18	-52.78	-4.06	Moderate

Riociguat	Prostanoid(Inh)	0.26	0.07	0.91	-63.122	-79.329	-7.677	Moderate
Riociguat	Prostanoid(Inh)+ERA	0.54	0.1	2.9	-22.218	-43.47	91.77	Low
Riociguat	Prostanoid(IV)	0.35	0.11	1.18	-39.767	-54.4502	11.0124	Moderate
Riociguat	Prostanoid(PO)	0.22	0.07	0.66	-75.348	-89.838	-32.844	Moderate
Riociguat	Selonsertib	0.23	0.05	1.05	-89.32	-110.2	5.8	Moderate
Riociguat	Sotatercept	0.77	0.06	10.64	-8.1466	-33.2948	341.4488	Moderate
Selonsertib	Imatinib	0.61	0.18	2.07	-59.6505	-125.419	163.6565	Very low
Selonsertib	Placebo	0.72	0.24	2.17	-45.08	-122.36	188.37	Low
Selonsertib	Prostanoid(PO)	0.95	0.3	3.04	-4.83	-67.62	197.064	Low
Sotatercept	ERA	0.41	0.04	4.62	-42.7455	-69.552	262.269	Low
Sotatercept	Imatinib	0.18	0.02	2.16	-125.419	-149.891	177.422	Very low
Sotatercept	PDE5i	0.46	0.04	5.24	-41.7312	-74.1888	327.6672	Low
Sotatercept	Placebo	0.22	0.02	2.42	-125.58	-157.78	228.62	Low

Sotatercept	PRA	0.38	0.03	4.51	-35.96	-56.26	203.58	Low
Sotatercept	Prostanoid(Inh)	0.34	0.03	4.18	-56.298	-82.741	271.254	Low
Sotatercept	Prostanoid(Inh)+ERA	0.71	0.05	11.07	-14.007	-45.885	486.381	Low
Sotatercept	Prostanoid(IV)	0.46	0.04	5.56	-33.0372	-58.7328	278.9808	Low
Sotatercept	Prostanoid(PO)	0.28	0.02	3.27	-69.552	-94.668	219.282	Low
Sotatercept	Selonsertib	0.3	0.02	4.27	-81.2	-113.68	379.32	Low

S7.2. Mortality

Mortality	**Comparison**	**Network estimate**			**Network estimate**			
		Relative risk			**Risk difference**			
Treatment 1	Treatment 2	Point estimate	CI Lower limit	CI upper limit	Point estimate	CI Lower limit	CI upper limit	GRADE rating
ERA	Imatinib	0.8	0.3	2.13	-8.38	-29.33	47.347	Very low
ERA	Placebo	0.81	0.64	1.03	-7.885	-14.94	1.245	Moderate
ERA	PRA	0.86	0.61	1.21	-9.464	-26.364	14.196	Very low
ERA	Prostanoid(Inh)+ERA	0.91	0.02	43.56	-3.3615	-36.603	1589.616	Very low
ERA	Prostanoid(IV)+ERA	0.62	0.03	12.72	-7.885	-20.1275	243.19	Very low
ERA	Prostanoid(PO)	0.94	0.59	1.49	-2.166	-14.801	17.689	Very low
ERA	Selonsertib	0.83	0.09	7.81	-6.9139	-37.0097	276.9627	Very low

ERA	Sotatercept	0.62	0.03	14.97	-14.022	-35.793	515.493	Very low
ERA+PDE5i	ERA	0.76	0.28	2.09	-4.464	-13.392	20.274	Low
ERA+PDE5i	Imatinib	0.61	0.15	2.45	-16.341	-35.615	60.755	Very low
ERA+PDE5i	PDE5i	0.84	0.34	2.06	-2.656	-10.956	17.596	Low
ERA+PDE5i	Placebo	0.62	0.23	1.7	-15.77	-31.955	29.05	Very low
ERA+PDE5i	PRA	0.66	0.23	1.85	-22.984	-52.052	57.46	Very low
ERA+PDE5i	Prostanoid(Inh)+ERA	0.69	0.01	37.84	-11.5785	-36.9765	1375.974	Very low
ERA+PDE5i	Prostanoid(IV)+ERA	0.48	0.02	11.35	-10.79	-20.335	214.7625	Very low
ERA+PDE5i	Prostanoid(PO)	0.72	0.24	2.11	-10.108	-27.436	40.071	Very low
ERA+PDE5i	Selonsertib	0.63	0.05	7.31	-15.0479	-38.6365	256.6277	Very low
ERA+PDE5i	Sotatercept	0.47	0.02	13.24	-19.557	-36.162	451.656	Very low
Imatinib	Placebo	1.01	0.39	2.6	0.415	-25.315	66.4	Low
Imatinib	PRA	1.07	0.4	2.83	4.732	-40.56	123.708	Very low

PDE5i	ERA	0.91	0.42	1.97	-1.674	-10.788	18.042	Low
PDE5i	Imatinib	0.73	0.22	2.46	-11.313	-32.682	61.174	Very low
PDE5i	Placebo	0.74	0.34	1.58	-10.79	-27.39	24.07	Low
PDE5i	PRA	0.78	0.35	1.73	-14.872	-43.94	49.348	Low
PDE5i	Prostanoid(Inh)+ERA	0.82	0.02	42.67	-6.723	-36.603	1556.3745	Very low
PDE5i	Prostanoid(IV)+ERA	0.57	0.03	12.58	-8.9225	-20.1275	240.285	Very low
PDE5i	Prostanoid(PO)	0.85	0.36	2	-5.415	-23.104	36.1	Low
PDE5i	Selonsertib	0.75	0.07	7.93	-10.1675	-37.8231	281.8431	Very low
PDE5i	Sotatercept	0.56	0.02	14.73	-16.236	-36.162	506.637	Very low
PRA	Placebo	0.95	0.74	1.21	-2.075	-10.79	8.715	Moderate
Prostanoid(Inh)	ERA	0.39	0.08	1.87	-11.346	-17.112	16.182	Low
Prostanoid(Inh)	ERA+PDE5i	0.51	0.08	3.24	-4.263	-8.004	19.488	Low
Prostanoid(Inh)	Imatinib	0.31	0.05	1.93	-28.911	-39.805	38.967	Very low

Prostanoid(Inh)	PDE5i	0.43	0.08	2.42	-9.462	-15.272	23.572	Low
Prostanoid(Inh)	Placebo	0.32	0.07	1.49	-28.22	-38.595	20.335	Low
Prostanoid(Inh)	PRA	0.33	0.07	1.61	-45.292	-62.868	41.236	Low
Prostanoid(Inh)	Prostanoid(Inh)+ERA	0.35	0.01	23.02	-24.2775	-36.9765	822.447	Very low
Prostanoid(Inh)	Prostanoid(IV)	0.57	0.11	2.99	-9.288	-19.224	42.984	Low
Prostanoid(Inh)	Prostanoid(IV)+ERA	0.24	0.01	7.15	-15.77	-20.5425	127.6125	Very low
Prostanoid(Inh)	Prostanoid(PO)	0.36	0.07	1.81	-23.104	-33.573	29.241	Low
Prostanoid(Inh)	Selonsertib	0.32	0.02	4.88	-27.6556	-39.8566	157.7996	Very low
Prostanoid(Inh)	Sotatercept	0.24	0.01	8.26	-28.044	-36.531	267.894	Very low
Prostanoid(Inh)+ERA	Imatinib	0.89	0.02	48.08	-4.609	-41.062	1972.652	Very low
Prostanoid(Inh)+ERA	Placebo	0.9	0.02	43.32	-4.15	-40.67	1756.28	Very low
Prostanoid(Inh)+ERA	PRA	0.95	0.02	46.11	-3.38	-66.248	3049.436	Very low
Prostanoid(Inh)+ERA	Prostanoid(IV)+ERA	0.69	0.01	93.08	-6.4325	-20.5425	1910.66	Very low

Prostanoid(Inh)+ERA	Prostanoid(PO)	1.04	0.02	51.08	1.444	-35.378	1807.888	Very low
Prostanoid(Inh)+ERA	Selonsertib	0.91	0.01	80.07	-3.6603	-40.2633	3215.7769	Very low
Prostanoid(Inh)+ERA	Sotatercept	0.68	0	102.77	-11.808	-36.9	3755.313	Very low
Prostanoid(IV)	ERA	0.69	0.36	1.3	-5.766	-11.904	5.58	Moderate
Prostanoid(IV)	ERA+PDE5i	0.9	0.28	2.88	-0.87	-6.264	16.356	Low
Prostanoid(IV)	Imatinib	0.55	0.18	1.68	-18.855	-34.358	28.492	Very low
Prostanoid(IV)	PDE5i	0.76	0.29	1.98	-3.984	-11.786	16.268	Low
Prostanoid(IV)	Placebo	0.56	0.31	1	-18.26	-28.635	0	Moderate
Prostanoid(IV)	PRA	0.59	0.31	1.12	-27.716	-46.644	8.112	Moderate
Prostanoid(IV)	Prostanoid(Inh)+ERA	0.62	0.01	31.5	-14.193	-36.9765	1139.175	Very low
Prostanoid(IV)	Prostanoid(IV)+ERA	0.43	0.02	8.16	-11.8275	-20.335	148.57	Very low
Prostanoid(IV)	Prostanoid(PO)	0.64	0.32	1.31	-12.996	-24.548	11.191	Low
Prostanoid(IV)	Selonsertib	0.57	0.06	5.71	-17.4881	-38.2298	191.5557	Very low

Prostanoid(IV)	Sotatercept	0.43	0.02	10.75	-21.033	-36.162	359.775	Very low
Prostanoid(IV)+ERA	Imatinib	1.29	0.06	30.08	12.151	-39.386	1218.452	Very low
Prostanoid(IV)+ERA	Placebo	1.3	0.06	26.26	12.45	-39.01	1048.29	Very low
Prostanoid(IV)+ERA	PRA	1.37	0.07	28.01	25.012	-62.868	1825.876	Very low
Prostanoid(PO)	Imatinib	0.86	0.31	2.38	-5.866	-28.911	57.822	Very low
Prostanoid(PO)	Placebo	0.86	0.59	1.28	-5.81	-17.015	11.62	Low
Prostanoid(PO)	PRA	0.91	0.58	1.45	-6.084	-28.392	30.42	Low
Prostanoid(PO)	Prostanoid(IV)+ERA	0.66	0.03	13.76	-7.055	-20.1275	264.77	Very low
Prostanoid(PO)	Selonsertib	0.88	0.09	8.49	-4.8804	-37.0097	304.6183	Very low
Prostanoid(PO)	Sotatercept	0.66	0.03	16.18	-12.546	-35.793	560.142	Very low
Riociguat	ERA	0.36	0.09	1.52	-11.904	-16.926	9.672	Moderate
Riociguat	ERA+PDE5i	0.48	0.09	2.56	-4.524	-7.917	13.572	Low
Riociguat	Imatinib	0.29	0.05	1.6	-29.749	-39.805	25.14	Very low

Riociguat	PDE5i	0.4	0.09	1.83	-9.96	-15.106	13.778	Very low
Riociguat	Placebo	0.3	0.07	1.21	-29.05	-38.595	8.715	Moderate
Riociguat	PRA	0.31	0.07	1.31	-46.644	-62.868	20.956	Low
Riociguat	Prostanoid(Inh)	0.94	0.12	7.65	-0.768	-11.264	85.12	Low
Riociguat	Prostanoid(Inh)+ERA	0.33	0.01	20.49	-25.0245	-36.9765	727.9515	Very low
Riociguat	Prostanoid(IV)	0.53	0.12	2.45	-10.152	-19.008	31.32	Low
Riociguat	Prostanoid(IV)+ERA	0.23	0.01	6.29	-15.9775	-20.5425	109.7675	Very low
Riociguat	Prostanoid(PO)	0.34	0.08	1.48	-23.826	-33.212	17.328	Low
Riociguat	Selonsertib	0.3	0.02	4.22	-28.469	-39.8566	130.9574	Very low
Riociguat	Sotatercept	0.23	0.01	7.29	-28.413	-36.531	232.101	Very low
Selonsertib	Imatinib	0.97	0.09	10.99	-1.257	-38.129	418.581	Very low
Selonsertib	Placebo	0.98	0.11	9.16	-0.83	-36.935	338.64	Very low
Selonsertib	PRA	1.04	0.11	9.8	2.704	-60.164	594.88	Very low

Selonsertib	Prostanoid(IV)+ERA	0.76	0.02	31.91	-4.98	-20.335	641.3825	Very low
Selonsertib	Sotatercept	0.75	0.02	36.36	-9.225	-36.162	1304.784	Very low
Sotatercept	Imatinib	1.3	0.05	35.58	12.57	-39.805	1448.902	Very low
Sotatercept	Placebo	1.31	0.05	31.28	12.865	-39.425	1256.62	Very low
Sotatercept	PRA	1.38	0.06	33.35	25.688	-63.544	2186.86	Very low
Sotatercept	Prostanoid(IV)+ERA	1.01	0.01	79.6	0.2075	-20.5425	1630.95	Very low

S7.3. Hospitalization

Hospitalizations	**Comparison**	**Network estimate**			**Network estimate**			
		Relative risk			**Risk difference**			
Treatment 1	Treatment 2	Point estimate	CI Lower limit	CI upper limit	Point estimate	CI Lower limit	CI upper limit	GRADE rating
ERA	ERA+PDE5I	1.2556	0.828	1.9038	11.16972	-7.5164	39.49606	High
ERA	Imatinib	0.5229	0.2326	1.1756	-50	-79.932384	18.290496	Low
ERA	PDE5I	1.117	0.7656	1.6297	5.20884	-10.435488	28.034244	High
ERA	Placebo	0.6506	0.4882	0.8671	-29.3496	-42.9912	-11.1636	Moderate
ERA	PRA	0.7911	0.4846	1.2915	-13.51583	-33.34638	18.86005	High
ERA	Prostanoid(inh)	1.104	0.3166	3.85	3.84064	-28.42944	118.56	Moderate
ERA	Prostanoid(PO)	0.6786	0.4014	1.1473	-25.917696	-48.271104	11.878272	High

ERA	Riociguat	8.1419	1.7468	37.95	59.55196	5.83312	309.94	Moderate
ERA	Selonsertib	0.6624	0.0678	6.4714	-27.791232	-76.738704	450.405648	Low
ERA+PDE5I	Imatinib	0.4165	0.1703	1.0187	-60.77736	-86.421552	1.947792	Moderate
ERA+PDE5I	PDE5I	0.8896	0.5826	1.3583	-4.915008	-18.582648	15.951516	High
ERA+PDE5I	Placebo	0.5182	0.3221	0.8338	-40.4712	-56.9436	-13.9608	Moderate
ERA+PDE5I	PRA	0.6301	0.3391	1.1709	-23.93253	-42.76023	11.05723	High
ERA+PDE5I	Prostanoid(inh)	0.8793	0.2383	3.2439	-5.408012	-31.68672	93.34624	Moderate
ERA+PDE5I	Prostanoid(PO)	0.5405	0.2828	1.033	-37.05408	-57.835008	2.66112	Moderate
ERA+PDE5I	Riociguat	6.4846	1.3529	31.0823	45.63064	2.52436	252.25132	Low
ERA+PDE5I	Selonsertib	0.5275	0.0523	5.3182	-38.8962	-78.014664	355.474224	Low
Imatinib	PDE5I	2.136	0.905	5.0411	50.57472	-4.2294	179.909772	Low
Imatinib	Placebo	1.2442	0.5834	2.6537	20.5128	-34.9944	138.9108	Very low
Imatinib	PRA	1.5129	0.6432	3.5582	33.18463	-23.08496	165.51554	Low

Imatinib	Prostanoid(inh)	2.1111	0.504	8.8427	45.292876	-20.6336	326.25632	Low
Imatinib	Prostanoid(PO)	1.2977	0.5405	3.1155	24.006528	-37.05408	170.59392	Low
Imatinib	Riociguat	15.5696	2.8232	85.8647	121.94464	14.87488	712.42348	Low
Imatinib	Selonsertib	1.2666	0.1167	13.7498	21.946512	-72.713256	1049.563536	Very low
PDE5I	Placebo	0.5825	0.3887	0.8729	-35.07	-51.3492	-10.6764	Moderate
PDE5I	PRA	0.7083	0.4018	1.2485	-18.87299	-38.70354	16.07795	High
PDE5I	Prostanoid(inh)	0.9884	0.2745	3.5592	-0.917456	-30.1808	106.46272	Moderate
PDE5I	Prostanoid(PO)	0.6075	0.3343	1.1042	-31.6512	-53.682048	8.402688	Moderate
PDE5I	Riociguat	7.2893	1.5831	33.5622	52.39012	4.45804	273.08248	Low
PDE5I	Selonsertib	0.593	0.0596	5.8974	-33.50424	-77.413728	403.153968	Low
PRA	Placebo	0.82	0.55	1.22	-15.12	-37.8	18.48	Moderate
PRA	Prostanoid(inh)	1.3954	0.3884	5.0134	15.834664	-25.44256	166.95744	Moderate
PRA	Prostanoid(PO)	0.8577	0.4743	1.5512	-11.475072	-42.392448	44.448768	High

PRA	Riociguat	10.2913	2.1178	50.0105	77.60692	8.94952	411.2482	Moderate
PRA	Selonsertib	0.8372	0.0843	8.3155	-13.401696	-75.380424	602.21196	Low
Prostanoid(inh)	Placebo	0.59	0.17	1.98	-34.44	-69.72	82.32	Low
Prostanoid(inh)	Prostanoid(PO)	0.6147	0.1687	2.2392	-31.070592	-67.036032	99.929088	Low
Prostanoid(inh)	Riociguat	7.375	1.0447	52.0639	53.11	-0.06452	428.49676	Moderate
Prostanoid(inh)	Selonsertib	0.6	0.046	7.8177	-32.928	-78.53328	561.233064	Low
Prostanoid(PO)	Placebo	0.95	0.62	1.5	-4.2	-31.92	42	Low
Prostanoid(PO)	Riociguat	11.9981	2.4414	58.9629	91.94404	11.66776	486.44836	Moderate
Prostanoid(PO)	Selonsertib	0.9761	0.0975	9.7699	-1.967448	-74.2938	721.938168	Low
Riociguat	Placebo	0.08	0.017	0.37	-77.28	-82.572	-52.92	High
Riociguat	Selonsertib	0.0814	0.0053	1.2477	-75.619152	-81.883704	20.390664	Moderate
Selonsertib	Placebo	0.98	0.1	9.4	-1.68	-75.6	705.6	Low

S7.4. 6-MWD

6-MWD	Comparison	Network estimate			
		Mean difference			
Treatment 1	Treatment 2	Point estimate	CI Lower limit	CI upper limit	GRADE rating
ERA	ERA+PDE5i	-18.85	-41.16	3.46	Moderate
ERA	PDE5i	-10.07	-28.11	7.97	High
ERA	Placebo	31	17.93	44.06	Moderate
ERA	Prostanoid(Inh)+ERA)	-83.99	-118.91	-49.06	Low
ERA	Prostanoid(IV)	-24.12	-49.88	1.64	Moderate
ERA	Riociguat	-18.49	-52.48	15.49	Moderate
ERA+PDE5i	Placebo	49.85	25.93	73.76	Moderate
ERA+PDE5i	Prostanoid(Inh+ERA)	-65.14	-106.29	-23.98	Very low

ERA+PDE5i	Prostanoid(IV)	-5.27	-37.9	27.36	Very low
ERA+PDE5i	Prostanoid(IV)+ERA	-11.27	-75.37	52.83	Very low
Imatinib	ERA	-1.2	-36.96	34.55	Very low
Imatinib	ERA+PDE5i	-20.05	-61.03	20.93	Low
Imatinib	PDE5i	-11.27	-48.23	25.69	Low
Imatinib	Placebo	29.79	-3.49	63.07	Low
Imatinib	Prostanoid(Inh+ERA)	-85.19	-134.32	-36.06	Low
Imatinib	Prostanoid(IV)	-25.32	-65.33	14.69	Low
Imatinib	Prostanoid(IV)+ERA	-31.32	-99.47	36.83	Very low
Imatinib	Riociguat	-19.7	-66	26.6	Low
PDE5i	ERA+PDE5i	-8.78	-32.41	14.85	Moderate
PDE5i	Placebo	41.07	24.99	57.14	Low
PDE5i	Prostanoid(Inh+ERA)	-73.92	-112.47	-35.36	Low

PDE5i	Prostanoid(IV)	-14.05	-41.46	13.36	Moderate
PDE5i	Prostanoid(IV)+ERA	-20.05	-81.66	41.55	Very low
PDE5i	Riociguat	-8.43	-40.63	23.78	Moderate
PRA	ERA	-13.99	-45.93	17.95	Low
PRA	ERA+PDE5i	-32.84	-70.54	4.86	Low
PRA	Imatinib	-12.79	-57.03	31.45	Low
PRA	PDE5i	-24.06	-57.34	9.22	Low
PRA	Placebo	17	-12.14	46.15	Low
PRA	Prostanoid(Ihn)	-6.58	-43.51	30.36	Low
PRA	Prostanoid(Inh+ERA)	-97.98	-144.41	-51.55	Low
PRA	Prostanoid(IV)	-38.11	-74.75	-1.47	Low
PRA	Prostanoid(IV)+ERA	-44.11	-110.34	22.11	Very low
PRA	Prostanoid(PO)	-2.6	-37.39	32.18	Low

PRA	Riociguat	-32.49	-75.91	10.94	Low
PRA	Sotatercept	-7.8	-62.31	46.71	Very low
Prostanoid(Ihn)	ERA	-7.42	-31.82	16.99	High
Prostanoid(Ihn)	ERA+PDE5i	-26.27	-58.24	5.7	Low
Prostanoid(Ihn)	Imatinib	-6.21	-46.49	34.07	Very low
Prostanoid(Ihn)	PDE5i	-17.49	-44.8	9.82	Moderate
Prostanoid(Ihn)	Placebo	23.58	0.89	46.27	Moderate
Prostanoid(Ihn)	Prostanoid(Inh)+ERA)	-91.4	-129.05	-53.75	Low
Prostanoid(Ihn)	Prostanoid(IV)	-31.54	-63.29	0.21	Moderate
Prostanoid(Ihn)	Prostanoid(IV)+ERA	-37.54	-101.19	26.12	Very low
Prostanoid(Ihn)	Riociguat	-25.91	-65.12	13.3	Moderate
Prostanoid(Ihn)	Sotatercept	-1.22	-52.57	50.13	Low
Prostanoid(Inh+ERA)	Placebo	114.98	78.84	151.13	Low

Prostanoid(IV)	Placebo	55.12	33	77.32	Low
Prostanoid(IV)	Prostanoid(Inh+ERA)	-59.87	-102.29	-17.45	Very low
Prostanoid(IV)+ERA	Placebo	61.12	1.65	120.59	Very low
Prostanoid(IV)+ERA	Prostanoid(Inh+ERA)	-53.87	-123.46	15.73	Very low
Prostanoid(IV)+ERA	Prostanoid(IV)	6	-49.17	61.17	Very low
Prostanoid(PO)	ERA	-11.39	-34.44	11.66	Moderate
Prostanoid(PO)	ERA+PDE5i	-30.24	-60.78	0.3	Low
Prostanoid(PO)	Imatinib	-10.19	-48.51	28.13	Low
Prostanoid(PO)	PDE5i	-21.46	-46.34	3.42	Moderate
Prostanoid(PO)	Placebo	19.61	0.62	38.6	Moderate
Prostanoid(PO)	Prostanoid(Ihn)	-3.97	-33.56	25.62	Moderate
Prostanoid(PO)	Prostanoid(Inh+ERA)	-95.38	-136.21	-54.55	Low
Prostanoid(PO)	Prostanoid(IV)	-35.51	-64.73	-6.29	Moderate

Prostanoid(PO)	Prostanoid(IV)+ERA	-41.51	-103.94	20.92	Very low
Prostanoid(PO)	Riociguat	-29.88	-67.26	7.49	Moderate
Prostanoid(PO)	Sotatercept	-5.19	-55.02	44.63	Low
Riociguat	ERA+PDE5i	-0.36	-38.73	38.02	Very low
Riociguat	Placebo	49.49	17.3	81.68	Moderate
Riociguat	Prostanoid(Inh+ERA)	-65.49	-113.49	-17.5	Very low
Riociguat	Prostanoid(IV)	-5.63	-44.73	33.48	Low
Riociguat	Prostanoid(IV)+ERA	-11.63	-79.25	56	Very low
Selonsertib	ERA	-18.4	-66.52	29.73	Low
Selonsertib	ERA+PDE5i	-37.25	-89.38	14.88	Low
Selonsertib	Imatinib	-17.19	-74.23	39.84	Very low
Selonsertib	PDE5i	-28.47	-77.5	20.56	Moderate
Selonsertib	Placebo	12.6	-33.72	58.92	Low

Selonsertib	PRA	-4.4	-59.13	50.32	Very low
Selonsertib	Prostanoid(Ihn)	-10.98	-62.56	40.6	Low
Selonsertib	Prostanoid(Inh+ERA)	-102.38	-161.14	-43.63	Low
Selonsertib	Prostanoid(IV)	-42.52	-93.89	8.85	Moderate
Selonsertib	Prostanoid(IV)+ERA	-48.52	-123.9	26.86	Very low
Selonsertib	Prostanoid(PO)	-7.01	-57.07	43.06	Low
Selonsertib	Riociguat	-36.89	-93.3	19.52	Moderate
Selonsertib	Sotatercept	-12.2	-77.53	53.13	Low
Sotatercept	ERA	-6.2	-54.08	41.69	Low
Sotatercept	ERA+PDE5i	-25.05	-76.95	26.85	Low
Sotatercept	Imatinib	-4.99	-61.82	51.83	Very low
Sotatercept	PDE5i	-16.27	-65.05	32.52	Moderate
Sotatercept	Placebo	24.8	-21.26	70.86	Moderate

Sotatercept	Prostanoid(Inh+ERA)	-90.18	-148.74	-31.63	Very low
Sotatercept	Prostanoid(IV)	-30.32	-81.45	20.82	Moderate
Sotatercept	Prostanoid(IV)+ERA	-36.32	-111.54	38.91	Very low
Sotatercept	Riociguat	-24.69	-80.89	31.51	Moderate

S7.5. Functional class

Functional class	**Comparison**	**Network estimate**			**Network estimate**			
		Relative risk			**Risk difference**			
Treatment 1	Treatment 2	Point estimate	CI Lower limit	CI upper limit	Point estimate	CI Lower limit	CI upper limit	GRADE rating
ERA	ERA+PDE5I	0.9956	0.6546	1.5143	-0.4862	-38.1667	56.83015	Moderate
ERA	ERA+Prostanoid(IV)	0.194	0.0473	0.7962	-638.352	-754.5384	-161.4096	Very low
ERA	Imatinib	1.2432	0.0237	65.3118	30.0352	-120.57305	7942.5073	Very low
ERA	PDE5I	1.1526	0.7588	1.7506	29.757	-47.034	146.367	Low
ERA	Placebo	1.1831	0.9029	1.5503	23.803	-12.623	71.539	Moderate
ERA	PRA	0.7885	0.3987	1.5595	-41.2425	-117.2535	109.1025	Very low
ERA	Prostanoid(Inh)	0.6092	0.2523	1.4711	-98.55976	-188.56994	118.81142	Low
ERA	Prostanoid(IV)	0.2293	0.0782	0.6724	-508.97028	-608.75672	-216.34704	Very low

ERA	Prostanoid(PO)	0.8647	0.5326	1.4039	-22.7304	-78.5232	67.8552	High
ERA	Riociguat	0.9742	0.5398	1.7583	-4.8633	-86.7477	142.93955	Moderate
ERA	Selonsertib	0.2177	0.0274	1.7328	-552.3038	-686.6556	517.3568	Low
ERA	Sotatercept	0.6437	0.1957	2.118	-85.22696	-192.38856	267.4256	Low
ERA+PDE5I	ERA+Prostanoid(IV)	0.1949	0.0452	0.8391	-637.6392	-756.2016	-127.4328	Very low
ERA+PDE5I	Imatinib	1.2486	0.0234	66.7499	30.7021	-120.6101	8120.11265	Very low
ERA+PDE5I	PDE5I	1.1576	0.7211	1.8584	30.732	-54.3855	167.388	Low
ERA+PDE5I	Placebo	1.1883	0.7503	1.8818	24.479	-32.461	114.634	Low
ERA+PDE5I	PRA	0.7919	0.3642	1.722	-40.5795	-123.981	140.79	Very low
ERA+PDE5I	Prostanoid(Inh)	0.6118	0.235	1.593	-97.90404	-192.933	149.5546	Very low
ERA+PDE5I	Prostanoid(IV)	0.2303	0.0738	0.7189	-508.30988	-611.66248	-185.63844	Very low
ERA+PDE5I	Prostanoid(PO)	0.8685	0.4715	1.5998	-22.092	-88.788	100.7664	Moderate
ERA+PDE5I	Riociguat	0.9785	0.5044	1.898	-4.05275	-93.4206	169.273	Low

ERA+PDE5I	Selonsertib	0.2187	0.0266	1.7989	-551.5978	-687.2204	564.0234	Very low
ERA+PDE5I	Sotatercept	0.6466	0.1857	2.2514	-84.53328	-194.78056	299.33488	Very low
ERA+Prostanoid(IV)	Imatinib	6.4079	0.0972	422.3058	667.87565	-111.4958	52031.2663	Very low
ERA+Prostanoid(IV)	PDE5I	5.941	1.399	25.2281	963.495	77.805	4724.4795	Very low
ERA+Prostanoid(IV)	Placebo	6.0983	1.5253	24.3813	662.779	68.289	3039.569	Low
ERA+Prostanoid(IV)	PRA	4.0643	0.8883	18.5955	597.5385	-21.7815	3431.1225	Very low
ERA+Prostanoid(IV)	Prostanoid(Inh)	3.14	0.6213	15.8687	539.708	-95.50814	3749.88614	Very low
ERA+Prostanoid(IV)	Prostanoid(IV)	1.1818	0.4737	2.9486	120.06072	-347.56852	1286.85544	Very low
ERA+Prostanoid(IV)	Prostanoid(PO)	4.4572	1.0529	18.8689	580.8096	8.8872	3001.9752	Low
ERA+Prostanoid(IV)	Riociguat	5.0217	1.1268	22.3802	758.09045	23.9018	4030.1677	Low
ERA+Prostanoid(IV)	Selonsertib	1.1223	0.094	13.3998	86.3438	-639.636	8754.2588	Very low
ERA+Prostanoid(IV)	Sotatercept	3.3182	0.5446	20.2174	554.51344	-108.93168	4596.80208	Very low
Imatinib	PDE5I	0.9271	0.0174	49.312	-14.2155	-191.607	9420.84	Very low

Imatinib	Placebo	0.9517	0.0183	49.5395	-6.279	-127.621	6310.135	Very low
Imatinib	PRA	0.6343	0.0116	34.684	-71.3115	-192.738	6568.38	Very low
Imatinib	Prostanoid(Inh)	0.49	0.0086	27.8577	-128.622	-250.03108	6773.51194	Very low
Imatinib	Prostanoid(IV)	0.1844	0.0031	10.987	-538.62224	-658.35276	6595.4148	Very low
Imatinib	Prostanoid(PO)	0.6956	0.0131	36.9547	-51.1392	-165.7992	6040.3896	Very low
Imatinib	Riociguat	0.7837	0.0145	42.4319	-40.77255	-185.76675	7809.91315	Very low
Imatinib	Selonsertib	0.1751	0.002	15.0767	-582.3794	-704.588	9938.1502	Very low
Imatinib	Sotatercept	0.5178	0.0084	31.844	-115.34224	-237.19072	7377.8848	Very low
PDE5I	Placebo	1.0265	0.6791	1.5517	3.445	-41.717	71.721	Moderate
PDE5I	PRA	0.6841	0.3231	1.4485	-61.6005	-131.9955	87.4575	Low
PDE5I	Prostanoid(Inh)	0.5285	0.2074	1.3469	-118.9123	-199.89372	87.48818	Moderate
PDE5I	Prostanoid(IV)	0.1989	0.0649	0.6099	-529.04644	-617.54004	-257.62204	Very low
PDE5I	Prostanoid(PO)	0.7503	0.4215	1.3355	-41.9496	-97.188	56.364	High

PDE5I	Riociguat	0.8453	0.489	1.4611	-29.16095	-96.3235	86.91735	Moderate
PDE5I	Selonsertib	0.1889	0.0232	1.539	-572.6366	-689.6208	380.534	Low
PDE5I	Sotatercept	0.5585	0.1631	1.9132	-105.6068	-200.18648	218.43744	Low
PRA	Placebo	1.5	0.8	2.8	65	-26	234	Low
PRA	Prostanoid(Inh)	0.7726	0.2712	2.2013	-57.35028	-183.80336	302.96786	Very low
PRA	Prostanoid(IV)	0.2908	0.0863	0.9802	-468.35568	-603.40748	-13.07592	Low
PRA	Prostanoid(PO)	1.0967	0.5211	2.3082	16.2456	-80.4552	219.7776	Low
PRA	Riociguat	1.2356	0.5337	2.8608	44.4106	-87.89755	350.7608	Low
PRA	Selonsertib	0.2761	0.0322	2.37	-511.0734	-683.2668	967.22	Very low
PRA	Sotatercept	0.8164	0.2185	3.0503	-43.91712	-186.9348	490.43176	Very low
Prostanoid(Inh)	Placebo	1.94	0.84	4.49	122.2	-20.8	453.7	Moderate
Prostanoid(Inh)	Prostanoid(IV)	0.3764	0.0988	1.4338	-411.82544	-595.15248	286.48152	Very low

Prostanoid(Inh)	Prostanoid(PO)	1.4195	0.5597	3.6	70.476	-73.9704	436.8	Moderate
Prostanoid(Inh)	Riociguat	1.5992	0.5833	4.3844	112.9492	-78.54795	637.9594	Low
Prostanoid(Inh)	Selonsertib	0.3574	0.0388	3.2947	-453.6756	-678.6072	1620.0582	Low
Prostanoid(Inh)	Sotatercept	1.0567	0.2525	4.4229	13.56264	-178.802	818.75768	Low
Prostanoid(IV)	Placebo	5.16	1.82	14.62	540.8	106.6	1770.6	Moderate
Prostanoid(IV)	Prostanoid(PO)	3.7715	1.235	11.5175	465.612	39.48	1766.94	Low
Prostanoid(IV)	Riociguat	4.2491	1.3029	13.8574	612.45535	57.09665	2423.6199	Low
Prostanoid(IV)	Selonsertib	0.9496	0.0947	9.5211	-35.5824	-639.1418	6015.8966	Very low
Prostanoid(IV)	Sotatercept	2.8077	0.5907	13.3451	432.40184	-97.90456	2952.94792	Very low
Prostanoid(PO)	Placebo	1.37	0.91	2.04	48.1	-11.7	135.2	Moderate
Prostanoid(PO)	Riociguat	1.1266	0.5657	2.2437	23.8641	-81.86555	234.43745	Low
Prostanoid(PO)	Selonsertib	0.2518	0.031	2.0469	-528.2292	-684.114	739.1114	Low

Prostanoid(PO)	Sotatercept	0.7445	0.2181	2.5409	-61.1156	-187.03048	368.58328	Low
Riociguat	Placebo	1.21	0.69	2.12	27.3	-40.3	145.6	Moderate
Riociguat	Selonsertib	0.2235	0.0265	1.8829	-548.209	-687.291	623.3274	Very low
Riociguat	Sotatercept	0.6608	0.1823	2.3948	-81.13664	-195.59384	333.63616	Very low
Selonsertib	Placebo	5.43	0.69	42.5	575.9	-40.3	5395	Very low
Selonsertib	Sotatercept	2.9567	0.2789	31.348	468.04264	-172.48712	7259.2416	Low
Sotatercept	Placebo	1.84	0.57	5.86	109.2	-55.9	631.8	Moderate

S7.6. Cardiac output

Cardiac output	**Comparison**	**Network estimate**			
		Mean difference			
Treatment 1	Treatment 2	Point estimate	CI Lower limit	CI upper limit	GRADE rating
ERA	Placebo	0.8458	0.1463	1.5452	Moderate
ERA	Riociguat	-0.1642	-1.138	0.8096	Moderate
ERA	Sotatercept	1.0458	0	2.0915	Moderate
ERA	ERA+PDE5I	-0.8	-1.7153	0.1153	Low
ERA	ERA+Prostanoid(IV)	-0.6472	-1.3254	0.0309	Low
ERA	Prostanoid(Inh)	0.3473	-0.2627	0.9573	Low
ERA	Prostanoid(IV)	0.8458	-0.3632	2.0547	Low
ERA	Imatinib	0.1126	-0.8487	1.0739	Very low

ERA	PDE5I	0.2276	-0.646	1.1012	Very low
ERA+PDE5I	Placebo	1.6458	0.5	2.7978	Moderate
ERA+PDE5I	Imatinib	0.9126	-0.4148	2.24	Low
ERA+PDE5I	PDE5I	1.0276	-0.2377	2.2929	Low
ERA+PDE5I	Prostanoid(Inh)	1.1473	0.0473	2.2473	Low
ERA+PDE5I	Prostanoid(IV)	1.6458	0.1294	3.1622	Low
ERA+PDE5I	Sotatercept	1.8458	0.456	3.2355	Low
ERA+PDE5I	ERA+Prostanoid(IV)	0.1528	-0.9864	1.292	Very low
ERA+PDE5I	Riociguat	0.6358	-0.7007	1.9722	Very low
ERA+Prostanoid(IV)	Placebo	1.493	0.6937	2.2924	Moderate
ERA+Prostanoid(IV)	Imatinib	0.7599	-0.2764	1.7961	Low
ERA+Prostanoid(IV)	PDE5I	0.8748	-0.0806	1.8303	Low
ERA+Prostanoid(IV)	Prostanoid(Inh)	0.9945	0.3131	1.676	Low

ERA+Prostanoid(IV)	Prostanoid(IV)	1.493	0.2237	2.7624	Low
ERA+Prostanoid(IV)	Sotatercept	1.693	0.578	2.8081	Low
ERA+Prostanoid(IV)	Riociguat	0.483	-0.5648	1.5309	Very low
Imatinib	Placebo	0.7332	0.0737	1.3926	Low
Imatinib	Prostanoid(IV)	0.7332	-0.4531	1.9194	Low
Imatinib	Sotatercept	0.9332	-0.0863	1.9526	Low
Imatinib	PDE5I	0.115	-0.727	0.9569	Very low
Imatinib	Prostanoid(Inh)	0.2347	-0.5828	1.0522	Very low
Imatinib	Riociguat	-0.2768	-1.2223	0.6686	Very low
PDE5I	Placebo	0.6182	0.0948	1.1416	Low
PDE5I	Prostanoid(IV)	0.6182	-0.4982	1.7346	Low
PDE5I	Riociguat	-0.3918	-1.248	0.4644	Low
PDE5I	Sotatercept	0.8182	-0.119	1.7554	Low

PDE5I	Prostanoid(Inh)	0.1197	-0.5926	0.832	Very low
Prostanoid(Inh)	Placebo	0.5	0.0154	0.9816	Low
Prostanoid(Inh)	Riociguat	-0.5115	-1.3436	0.3206	Low
Prostanoid(Inh)	Sotatercept	0.6985	-0.2168	1.6138	Low
Prostanoid(Inh)	Prostanoid(IV)	0.4985	-0.5996	1.5965	Very low
Prostanoid(IV)	Riociguat	-1.01	-2.2064	0.1864	Low
Prostanoid(IV)	Placebo	0	-0.9861	0.9861	Very low
Prostanoid(IV)	Sotatercept	0.2	-1.0557	1.4557	Very low
Riociguat	Placebo	1.01	0.3325	1.6875	Moderate
Riociguat	Sotatercept	1.21	0.1788	2.2412	Moderate
Sotatercept	Placebo	-0.2	-0.9774	0.5774	Low

S7.7. Cardiac index

Cardiac index	**Comparison**	**Network estimate**			
		Relative estimate			
Treatment 1	Treatment 2	Point estimate	CI Lower limit	CI upper limit	GRADE rating
ERA	ERA+Prostanoid(Inh)	-0.48	-0.9183	-0.0417	Moderate
ERA	ERA+Prostanoid(IV)	-0.0103	-0.6793	0.6588	Low
ERA	PDE5I	0.1066	-0.1732	0.3863	Moderate
ERA	Placebo	0.5463	0.3418	0.7507	Moderate
ERA	PRA	0.1173	-0.2894	0.524	Moderate
ERA	Prostanoid(Inh)	0.16	-0.2728	0.5928	Low
ERA	Prostanoid(IV)	0.1897	-0.1229	0.5024	Moderate
ERA	Prostanoid(PO)	0.4205	0.0057	0.8354	Moderate

ERA	Selonsertib	0.5473	0.0326	1.0619	Moderate
ERA	Sotatercept	0.6463	0.131	1.1615	Moderate
ERA+Prostanoid(Inh)	ERA+Prostanoid(IV)	0.4697	-0.3301	1.2696	Low
ERA+Prostanoid(Inh)	PDE5I	0.5866	0.0666	1.1066	Moderate
ERA+Prostanoid(Inh)	Placebo	1.0263	0.5426	1.5099	High
ERA+Prostanoid(Inh)	PRA	0.5973	-0.0007	1.1953	Moderate
ERA+Prostanoid(Inh)	Prostanoid(Inh)	0.64	0.2013	1.0787	Low
ERA+Prostanoid(Inh)	Prostanoid(IV)	0.6697	0.1314	1.2081	Moderate
ERA+Prostanoid(Inh)	Prostanoid(PO)	0.9005	0.297	1.504	High
ERA+Prostanoid(Inh)	Selonsertib	1.0273	0.3513	1.7032	High
ERA+Prostanoid(Inh)	Sotatercept	1.1263	0.4498	1.8027	High
ERA+Prostanoid(IV)	PDE5I	0.1169	-0.5681	0.8018	Low
ERA+Prostanoid(IV)	Placebo	0.5565	-0.0805	1.1936	Moderate

ERA+Prostanoid(IV)	PRA	0.1276	-0.6001	0.8552	Low
ERA+Prostanoid(IV)	Prostanoid(Inh)	0.1703	-0.6266	0.9671	Very low
ERA+Prostanoid(IV)	Prostanoid(IV)	0.2	-0.3915	0.7915	Low
ERA+Prostanoid(IV)	Prostanoid(PO)	0.4308	-0.3014	1.163	Low
ERA+Prostanoid(IV)	Selonsertib	0.5575	-0.2355	1.3505	Moderate
ERA+Prostanoid(IV)	Sotatercept	0.6565	-0.1369	1.45	Moderate
PDE5I	Placebo	0.4397	0.188	0.6914	Moderate
PDE5I	PRA	0.0107	-0.4217	0.4431	Low
PDE5I	Prostanoid(Inh)	0.0534	-0.4619	0.5687	Very low
PDE5I	Prostanoid(IV)	0.0831	-0.2622	0.4285	Moderate
PDE5I	Prostanoid(PO)	0.3139	-0.1261	0.754	Moderate
PDE5I	Selonsertib	0.4407	-0.0945	0.9758	Moderate
PDE5I	Sotatercept	0.5397	0.0039	1.0754	Moderate

PRA	Placebo	0.429	0.0774	0.7806	Moderate
PRA	Prostanoid(Inh)	0.0427	-0.5512	0.6366	Very low
PRA	Prostanoid(IV)	0.0724	-0.3513	0.4962	Low
PRA	Prostanoid(PO)	0.3032	-0.2007	0.8072	Moderate
PRA	Selonsertib	0.43	-0.1588	1.0187	Moderate
PRA	Sotatercept	0.529	-0.0604	1.1183	Moderate
Prostanoid(Inh)	Placebo	0.3863	-0.0924	0.8649	Very low
Prostanoid(Inh)	Prostanoid(IV)	0.0297	-0.5042	0.5636	Very low
Prostanoid(Inh)	Prostanoid(PO)	0.2605	-0.339	0.86	Very low
Prostanoid(Inh)	Selonsertib	0.3873	-0.2851	1.0597	Low
Prostanoid(Inh)	Sotatercept	0.4863	-0.1866	1.1592	Low
Prostanoid(IV)	Placebo	0.3565	0.12	0.593	Low
Prostanoid(IV)	Prostanoid(PO)	0.2308	-0.2008	0.6624	Moderate

Prostanoid(IV)	Selonsertib	0.3575	-0.1706	0.8857	Moderate
Prostanoid(IV)	Sotatercept	0.4565	-0.0722	0.9853	Moderate
Prostanoid(PO)	Placebo	0.1257	-0.2352	0.4867	Moderate
Prostanoid(PO)	Selonsertib	0.1267	-0.4677	0.7212	Low
Prostanoid(PO)	Sotatercept	0.2257	-0.3692	0.8207	Low
Selonsertib	Placebo	-0.001	-0.4733	0.4713	Low
Selonsertib	Sotatercept	0.099	-0.5694	0.7674	Low
Sotatercept	Placebo	-0.1	-0.573	0.373	Low

S7.8. Serious adverse events

Serious adverse events	**Comparison**	**Network estimate**			**Network estimate**			
		Relative risk			**Risk difference**			
Treatment 1	Treatment 2	Point estimate	CI Lower limit	CI upper limit	Point estimate	CI Lower limit	CI upper limit	GRADE rating
ERA	Placebo	0.6977	0.5658	0.8603	-68.0175	-97.695	-31.4325	High
ERA	Selonsertib	0.3174	0.1328	0.7584	-337.887	-429.264	-119.592	High
ERA	ERA+PDE5I	1.0836	0.6541	1.7953	12.0384	-49.8096	114.5232	Moderate
ERA	PRA	0.92	0.57	1.4834	-11.52	-61.92	69.6096	Moderate
ERA	Prostanoid(PO)	0.7413	0.4878	1.1263	-54.71505	-108.3303	26.71245	Moderate
ERA	Riociguat	1.7207	0.9122	3.2455	82.700325	-10.07505	257.671125	Moderate
ERA	Imatinib	0.4544	0.263	0.7852	-89.8876	-121.42075	-35.2809	Moderate
ERA	ERA+Prostanoid(IV)	1.2675	0.2173	7.3944	33.103125	-96.859125	791.307	Low

ERA	Prostanoid(IV)	0.8642	0.5264	1.4188	-25.35386	-88.42112	78.18996	Low
ERA	Sotatercept	0.4034	0.1097	1.4829	-232.674	-347.217	188.331	Low
ERA	PDE5I	1.0461	0.7214	1.5168	4.252725	-25.70085	47.6748	Moderate
ERA	Prostanoid(Inh)	0.6649	0.3913	1.1298	-76.4028	-138.7836	29.5944	Low
ERA	ERA+Prostanoid(Inh)	0.992	0.0358	27.4875	-1.26	-151.8615	4171.78125	Very low
ERA+PDE5I	Placebo	0.6439	0.3827	1.0831	-80.1225	-138.8925	18.6975	Moderate
ERA+PDE5I	Selonsertib	0.2929	0.1085	0.7904	-350.0145	-441.2925	-103.752	High
ERA+PDE5I	Imatinib	0.4193	0.2031	0.8659	-95.670325	-131.289275	-22.025925	Moderate
ERA+PDE5I	PRA	0.8541	0.44	1.6694	-21.0096	-80.64	96.3936	Moderate
ERA+PDE5I	Riociguat	1.5878	0.7407	3.404	67.45005	-29.754675	275.859	Moderate
ERA+PDE5I	ERA+Prostanoid(IV)	1.1696	0.1882	7.2682	20.988	-100.46025	775.68975	Low
ERA+PDE5I	Prostanoid(Inh)	0.6136	0.3008	1.2516	-88.0992	-159.4176	57.3648	Low
ERA+PDE5I	Prostanoid(IV)	0.7975	0.4011	1.5857	-37.80675	-111.81463	109.35019	Low

ERA+PDE5I	Prostanoid(PO)	0.684	0.3629	1.2892	-66.834	-134.74665	61.1658	Low
ERA+PDE5I	Sotatercept	0.3722	0.0931	1.4888	-244.842	-353.691	190.632	Low
ERA+PDE5I	PDE5I	0.9653	0.5851	1.5927	-38.274525	-38.274525	54.676575	Low
ERA+PDE5I	ERA+Prostanoid(Inh)	0.9154	0.0319	26.2972	-13.3245	-152.47575	3984.309	Very low
ERA+Prostanoid(Inh)	Placebo	0.7034	0.0254	19.4921	-66.735	-219.285	4160.7225	Very low
ERA+Prostanoid(Inh)	Prostanoid(Inh)	0.6703	0.0242	18.5694	-75.1716	-222.4824	4005.8232	Very low
ERA+Prostanoid(Inh)	ERA+Prostanoid(IV)	1.2777	0.0299	54.6146	34.365375	-120.049875	6634.80675	Very low
ERA+Prostanoid(Inh)	Imatinib	0.4581	0.0159	13.1891	-89.278025	-162.130475	2002.059675	Very low
ERA+Prostanoid(Inh)	PDE5I	1.0546	0.0374	29.7127	-88.79985	-88.79985	2648.746575	Very low
ERA+Prostanoid(Inh)	PRA	0.933	0.0328	26.5582	-9.648	-139.2768	3680.3808	Very low
ERA+Prostanoid(Inh)	Prostanoid(IV)	0.8712	0.0305	24.8842	-24.04696	-181.00565	4459.18014	Very low
ERA+Prostanoid(Inh)	Prostanoid(PO)	0.7473	0.0264	21.1198	-53.44605	-205.9164	4255.3377	Very low
ERA+Prostanoid(Inh)	Riociguat	1.7346	0.0593	50.7658	84.29535	-107.945325	5710.62555	Very low

ERA+Prostanoid(Inh)	Selonsertib	0.3199	0.0104	9.857	-336.6495	-489.852	4384.215	Very low
ERA+Prostanoid(Inh)	Sotatercept	0.4066	0.0115	14.3234	-231.426	-385.515	5196.126	Very low
ERA+Prostanoid(IV)	Placebo	0.5505	0.0955	3.1716	-101.1375	-203.5125	488.61	Low
ERA+Prostanoid(IV)	Prostanoid(IV)	0.6818	0.1255	3.7046	-59.40794	-163.26915	504.94882	Low
ERA+Prostanoid(IV)	Imatinib	0.3585	0.0579	2.2185	-105.687125	-155.210975	200.138625	Low
ERA+Prostanoid(IV)	PRA	0.7302	0.1205	4.4241	-38.8512	-126.648	493.0704	Low
ERA+Prostanoid(IV)	Prostanoid(Inh)	0.5246	0.0852	3.2314	-108.3912	-208.5744	508.7592	Low
ERA+Prostanoid(IV)	Prostanoid(PO)	0.5848	0.0978	3.4967	-87.8148	-190.8153	528.05205	Low
ERA+Prostanoid(IV)	Riociguat	1.3575	0.2125	8.6729	41.023125	-90.365625	880.465275	Low
ERA+Prostanoid(IV)	Selonsertib	0.2504	0.0358	1.7506	-371.052	-477.279	371.547	Low
ERA+Prostanoid(IV)	Sotatercept	0.3182	0.0363	2.793	-265.902	-375.843	699.27	Low
ERA+Prostanoid(IV)	PDE5I	0.8253	0.1382	4.929	-79.50105	-79.50105	362.45025	Very low
Imatinib	Placebo	1.5354	0.9265	2.5445	120.465	-16.5375	347.5125	High

Imatinib	Riociguat	3.7865	1.7146	8.3622	319.750875	82.00035	844.81245	High
Imatinib	PRA	2.0368	1.0542	3.9352	149.2992	7.8048	422.6688	Moderate
Imatinib	Prostanoid(IV)	1.9017	0.9672	3.7391	168.34739	-6.12376	511.38997	Moderate
Imatinib	Prostanoid(PO)	1.6312	0.8762	3.037	133.4988	-26.1837	430.8255	Moderate
Imatinib	Prostanoid(Inh)	1.4632	0.7246	2.9545	105.6096	-62.7912	445.626	Low
Imatinib	Selonsertib	0.6984	0.2608	1.8702	-149.292	-365.904	430.749	Low
Imatinib	Sotatercept	0.8877	0.2232	3.5306	-43.797	-302.952	986.934	Low
Imatinib	PDE5I	2.302	1.2405	4.2719	22.186125	22.186125	301.832775	Low
PDE5I	Placebo	0.667	0.467	0.9527	-74.925	-119.925	-10.6425	Low
PDE5I	Selonsertib	0.3034	0.1212	0.7595	-344.817	-435.006	-119.0475	moderate
PDE5I	Riociguat	1.6449	0.8786	3.0793	74.002275	-13.93065	238.599675	Low
PDE5I	Prostanoid(Inh)	0.6356	0.3473	1.1632	-83.0832	-148.8156	37.2096	Low
PDE5I	PRA	0.8848	0.509	1.538	-16.5888	-70.704	77.472	Very low

PDE5I	Prostanoid(IV)	0.8261	0.4655	1.4661	-32.46713	-99.79115	87.02087	Very low
PDE5I	Prostanoid(PO)	0.7086	0.4263	1.1779	-61.6311	-121.33755	37.62585	Very low
PDE5I	Sotatercept	0.3856	0.1016	1.463	-239.616	-350.376	180.57	Very low
PRA	Placebo	0.75	0.49	1.15	-56.25	-114.75	33.75	Moderate
PRA	Selonsertib	0.3429	0.1332	0.8825	-325.2645	-429.066	-58.1625	High
PRA	Riociguat	1.8591	0.8849	3.9059	98.581725	-13.207725	333.452025	Moderate
PRA	Prostanoid(Inh)	0.7184	0.3765	1.3706	-64.2048	-142.158	84.4968	Low
PRA	Prostanoid(IV)	0.9337	0.5039	1.7303	-12.37821	-92.62187	136.34701	Low
PRA	Prostanoid(PO)	0.8009	0.4591	1.3973	-42.10965	-114.40035	84.02895	Low
PRA	Sotatercept	0.4358	0.1127	1.6856	-220.038	-346.047	267.384	Low
Prostanoid(Inh)	Placebo	1.05	0.64	1.71	11.25	-81	159.75	Low
Prostanoid(Inh)	Riociguat	2.5878	1.1843	5.6547	182.20005	21.148425	534.126825	Moderate
Prostanoid(Inh)	Selonsertib	0.4773	0.1798	1.2674	-258.7365	-405.999	132.363	Moderate

Prostanoid(Inh)	Prostanoid(IV)	1.2997	0.6692	2.5242	55.95399	-61.76036	284.56814	Low
Prostanoid(Inh)	Prostanoid(PO)	1.1148	0.6069	2.0479	24.2802	-83.14065	221.63085	Low
Prostanoid(Inh)	Sotatercept	0.6067	0.1534	2.3986	-153.387	-330.174	545.454	Low
Prostanoid(IV)	Placebo	0.81	0.51	1.26	-42.75	-110.25	58.5	Low
Prostanoid(IV)	Riociguat	1.9911	0.9331	4.2487	113.728725	-7.676775	372.788325	Moderate
Prostanoid(IV)	Selonsertib	0.3672	0.141	0.9568	-313.236	-425.205	-21.384	Moderate
Prostanoid(IV)	Prostanoid(PO)	0.8577	0.4816	1.5275	-30.09645	-109.6416	111.56625	Low
Prostanoid(IV)	Sotatercept	0.4668	0.1197	1.8208	-207.948	-343.317	320.112	Low
Prostanoid(PO)	Placebo	0.94	0.65	1.35	-13.5	-78.75	78.75	Low
Prostanoid(PO)	Riociguat	2.3213	1.1416	4.7201	151.619175	16.2486	426.881475	Moderate
Prostanoid(PO)	Selonsertib	0.4281	0.1706	1.0742	-283.0905	-410.553	36.729	Moderate
Prostanoid(PO)	Sotatercept	0.5442	0.1432	2.0678	-177.762	-334.152	416.442	Low
Riociguat	Placebo	0.4	0.22	0.75	-135	-175.5	-56.25	Low

Riociguat	Selonsertib	0.1844	0.065	0.5233	-403.722	-462.825	-235.9665	Moderate
Riociguat	Sotatercept	0.2344	0.0565	0.9723	-298.584	-367.965	-10.803	Moderate
Selonsertib	Placebo	2.2	0.94	5.1	270	-13.5	922.5	Moderate
Selonsertib	Sotatercept	1.271	0.273	5.918	105.69	-283.53	1918.02	Low
Sotatercept	Placebo	1.73	0.49	6.25	164.25	-114.75	1181.25	Low

S8. Risk of bias judgements by trial and outcome

Study	Outcomes	Bias from the randomization process	Bias due to deviations from the intended intervention	Bias due to missing data	Bias due to measurement of the outcome	Bias in selection of the reported results
AMBITION	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
AMBITION	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
AMBITION	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
AMBITION	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
AMBITION	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
AMBITION	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARIES1	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARIES1	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARIES1	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARIES1	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARIES2	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARIES2	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARIES2	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARIES2	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARROW	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARROW	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARROW	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk

ARROW	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARROW	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
ARROW	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Badesch 2000	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Badesch 2000	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Badesch 2002	6MWD	definitely low risk	probably low risk	definitely low risk	definitely low risk	definitely low risk
Badesch 2002	CI	definitely low risk	probably low risk	definitely low risk	definitely low risk	definitely low risk
Badesch 2002	CW	definitely low risk	probably low risk	definitely low risk	definitely low risk	definitely low risk
Badesch 2002	Functional class	definitely low risk	probably low risk	definitely low risk	definitely low risk	definitely low risk
Badesch 2002	Mortality	definitely low risk	probably low risk	definitely low risk	definitely low risk	definitely low risk
Barst 1996	6MWD	probably high risk of bias	probably high risk	definitely low risk	definitely low risk	definitely low risk
Barst 1996	CI	probably high risk of bias	probably high risk	definitely low risk	definitely low risk	definitely low risk
Barst 1996	Mortality	probably high risk of bias	probably high risk	definitely low risk	definitely low risk	definitely low risk
Barst 2003	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Barst 2003	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Barst 2003	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Barst 2003	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Barst 2003	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Barst 2006	6MWD	definitely low risk	definitely low risk	probably low risk	definitely low risk	definitely low risk
Barst 2006	CW	definitely low risk	definitely low risk	probably low risk	definitely low risk	definitely low risk
Barst 2006	Hospitalisations	definitely low risk	definitely low risk	probably low risk	definitely low risk	definitely low risk
Barst 2006	Mortality	definitely low risk	definitely low risk	probably low risk	definitely low risk	definitely low risk
BREATHE-1	6MWD	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
BREATHE-1	CW	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
BREATHE-1	Functional class	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk

BREATHE-1	Hospitalisations	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
BREATHE-1	Mortality	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
BREATHE-2	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
BREATHE-2	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
BREATHE-2	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
BREATHE-2	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
BREATHE-2	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
BREATHE-2	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
BREATHE-2	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Channick 2001	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Channick 2001	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Channick 2001	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Channick 2001	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Channick 2001	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
COMBI	6MWD	definitely low risk	probably high risk	definitely low risk	definitely high risk	definitely low risk
COMBI	CW	definitely low risk	probably high risk	definitely low risk	definitely high risk	definitely low risk
COMBI	Mortality	definitely low risk	probably high risk	definitely low risk	definitely high risk	definitely low risk
COMPASS2	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
COMPASS2	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
COMPASS2	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
COMPASS2	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
COMPASS2	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
COMPASS2	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Dwivedi 2018	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EARLY	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk

EARLY	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EARLY	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EARLY	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EARLY	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EARLY	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EDITA	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EDITA	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EDITA	CO	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EDITA	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EDITA	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
EDITA	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
FREEDOMC	6MWD	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
FREEDOMC	CW	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
FREEDOMC	Functional class	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
FREEDOMC	Hospitalisations	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
FREEDOMC	Mortality	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
FREEDOMC	SAE	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
FREEDOMC2	6MWD	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
FREEDOMC2	CW	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
FREEDOMC2	Hospitalisations	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
FREEDOMC2	Mortality	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
FREEDOMC2	SAE	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Galie 2002	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Galie 2002	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Galie 2002	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk

Galie 2002	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Galie 2005	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Galie 2005	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Galie 2005	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Galie 2005	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Galie 2005	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Galie 2009	6MWD	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
Galie 2009	CW	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
Galie 2009	Functional class	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
Galie 2009	Hospitalisations	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
Galie 2009	Mortality	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
Galie 2009	SAE	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
Ghofrani 2010	6MWD	probably low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
Ghofrani 2010	CO	probably low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
Ghofrani 2010	Mortality	probably low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
Ghofrani 2010	SAE	probably low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
GHofrani 2010	CW	probably low risk	definitely low risk	definitely low risk	probably low risk	probably low risk
GRIPHON	6MWD	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
GRIPHON	Functional class	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
GRIPHON	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
GRIPHON	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
GRIPHON	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
GRIPHON	PAH mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
GRIPHON	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Han 2017	SAE	probably high risk of bias	probably high risk	definitely low risk	definitely high risk	definitely low risk

Han 2017	6MWD	probably high risk of bias	probably high risk	definitely low risk	definitely low risk	definitely low risk
Han 2017	CI	probably high risk of bias	probably high risk	definitely low risk	definitely low risk	definitely low risk
Han 2017	CO	probably high risk of bias	probably high risk	definitely low risk	definitely low risk	definitely low risk
Han 2017	CW	probably high risk of bias	probably high risk	definitely low risk	definitely low risk	definitely low risk
Hiremath 2010	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Hiremath 2010	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Hiremath 2010	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Hiremath 2010	PAH mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Hiremath 2010	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
IMPRESS	6MWD	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
IMPRESS	CO	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
IMPRESS	Functional class	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
IMPRESS	Hospitalisations	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
IMPRESS	Mortality	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
IMPRESS	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
IMPRESS	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Jing 2011	CI	definitely low risk	definitely low risk	Probably high risk	definitely low risk	probably low risk
Jing 2011	Hospitalisations	definitely low risk	definitely low risk	Probably high risk	definitely low risk	probably low risk
Jing 2011	Mortality	definitely low risk	definitely low risk	Probably high risk	definitely low risk	probably low risk
Jing 2011	6MWD	definitely low risk	definitely low risk	probably low risk	definitely low risk	probably low risk
Jing 2011	CW	definitely low risk	definitely low risk	probably low risk	definitely low risk	probably low risk
Jing 2011	Functional class	definitely low risk	definitely low risk	probably low risk	definitely low risk	probably low risk
Jing 2013	6MWD	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk

Jing 2013	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Jing 2013	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Jing 2013	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Jing 2013	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Olschewski 2002	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Olschewski 2002	CO	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Olschewski 2002	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Olschewski 2002	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Olschewski 2002	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Olschewski 2002	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Oudiz 2004	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Oudiz 2004	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Oudiz 2004	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Oudiz 2004	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PATENT1	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PATENT1	CO	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PATENT1	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PATENT1	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PATENT1	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PATENT1	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PATENT1	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PHIRST-1	CW	probably high risk of bias	probably high risk	Probably high risk	definitely high risk	definitely low risk
PHIRST-1	Mortality	probably high risk of bias	probably high risk	Probably high risk	definitely high risk	definitely low risk

PHIRST-1	6MWD	probably high risk of bias	probably high risk	Probably high risk	definitely low risk	definitely low risk
PHIRST-1	Functional class	probably high risk of bias	probably high risk	Probably high risk	definitely low risk	definitely low risk
PULSAR	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PULSAR	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PULSAR	CO	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PULSAR	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PULSAR	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
PULSAR	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
REPLACE	6MWD	definitely high risk	probably high risk	definitely low risk	definitely low risk	definitely low risk
REPLACE	CW	definitely high risk	probably high risk	definitely low risk	definitely low risk	definitely low risk
REPLACE	Functional class	definitely high risk	probably high risk	definitely low risk	definitely low risk	definitely low risk
REPLACE	Hospitalisations	definitely high risk	probably high risk	definitely low risk	definitely low risk	definitely low risk
REPLACE	SAE	definitely high risk	probably high risk	definitely low risk	definitely low risk	definitely low risk
Rubenfire 2006	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Rubenfire 2006	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Rubin 1990	6MWD	definitely low risk	definitely high risk	definitely high risk	probably low risk	probably low risk
Rubin 1990	CO	definitely low risk	definitely high risk	definitely high risk	probably low risk	probably low risk
Rubin 1990	functional class	definitely low risk	definitely high risk	definitely high risk	probably low risk	probably low risk
Rubin 1990	Mortality	definitely low risk	definitely high risk	definitely high risk	probably low risk	probably low risk
Sandoval 2012	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Sandoval 2012	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Sandoval 2012	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Sandoval 2012	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Sandoval 2012	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk

Sastry, 2004	CI	definitely low risk	definitely low risk	probably low risk	definitely low risk	definitely low risk
Sastry, 2004	CO	definitely low risk	definitely low risk	probably low risk	definitely low risk	definitely low risk
Sastry, 2004	Functional class	definitely low risk	definitely low risk	probably low risk	definitely low risk	definitely low risk
Sastry, 2004	Mortality	definitely low risk	definitely low risk	probably low risk	definitely low risk	definitely low risk
SERAPHIN	CI	definitely low risk	definitely low risk	definitely high risk	definitely low risk	definitely low risk
SERAPHIN	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
SERAPHIN	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
SERAPHIN	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
SERAPHIN	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
SERAPHIN	PAH mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
SERAPHIN	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Simmoneau 2009	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Simmoneau 2009	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Simmoneau 2009	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Simmoneau 2009	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Simmoneau 2009	6MWD	definitely low risk	definitely low risk	Probably high risk	definitely low risk	definitely low risk
Simmoneau 2009	CO	definitely low risk	definitely low risk	Probably high risk	definitely low risk	definitely low risk
Simmoneau 2012	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Simmoneau 2021	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Simonneau, 2002	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Simonneau, 2002	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Simonneau, 2002	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk

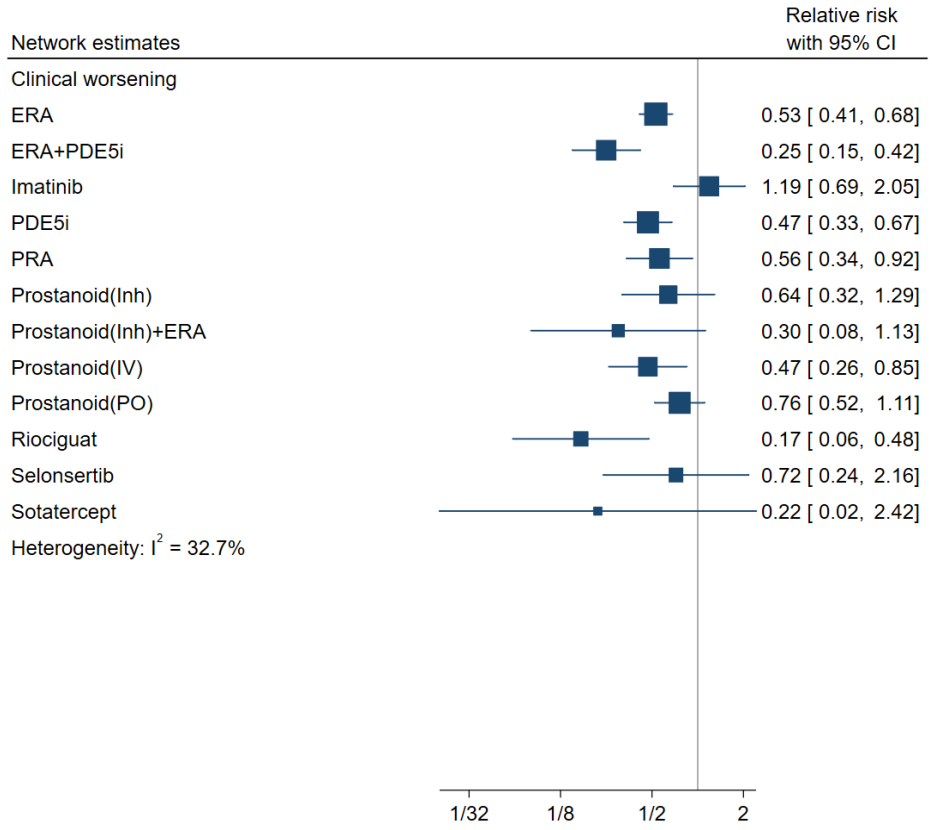
Simonneau, 2002	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Simonneau, 2002	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Simonneau, 2012	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Simonneau, 2012	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Simonneau, 2012	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Simonneau, 2012	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Singh, 2006	6MWD	probably low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Singh, 2006	SAE	probably low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
STEP	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STEP	CO	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STEP	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STEP	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STEP	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STEP	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STRIDE-1	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STRIDE-1	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STRIDE-1	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STRIDE-1	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STRIDE-1	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
STRIDE-1	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
SUPER-1	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
SUPER-1	CO	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
SUPER-1	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk

SUPER-1	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TORRES 2019	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TORRES 2019	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TORRES 2019	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TORRES 2019	functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TORRES 2019	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TORRES 2019	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TORRES 2019	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TRIUMPH-I	6MWD	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TRIUMPH-I	CW	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TRIUMPH-I	Hospitalisations	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TRIUMPH-I	Mortality	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
TRIUMPH-I	SAE	probably low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Vizza 2017	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Vizza 2017	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Vizza 2017	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Vizza 2017	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Vizza 2017	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Vizza 2017	PAH mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Vizza 2017	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
White 2019	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
White 2019	CW	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
White 2019	Functional class	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
White 2019	Hospitalisations	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
White 2019	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk

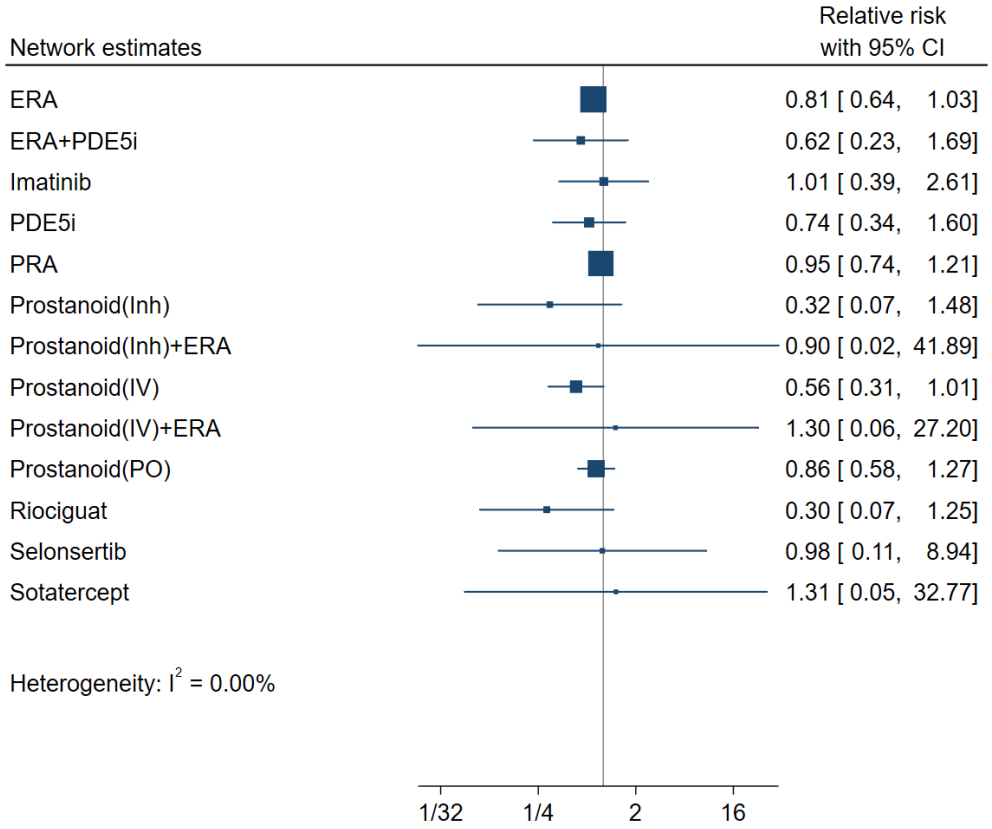
White 2019	SAE	definitely low risk	definitely low risk	definitely low risk	definitely low risk	definitely low risk
Wilkins 2005	6MWD	definitely low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Wilkins 2005	CI	definitely low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Wilkins 2005	Mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Wilkins 2005	PAH mortality	definitely low risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Zhuang 2014	6MWD	definitely high risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Zhuang 2014	CO	definitely high risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Zhuang 2014	CW	definitely high risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Zhuang 2014	Functional class	definitely high risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Zhuang 2014	Hospitalisations	definitely high risk	definitely low risk	definitely low risk	definitely low risk	probably low risk
Zhuang 2014	Mortality	definitely high risk	definitely low risk	definitely low risk	definitely low risk	probably low risk

S9. Network forest plots

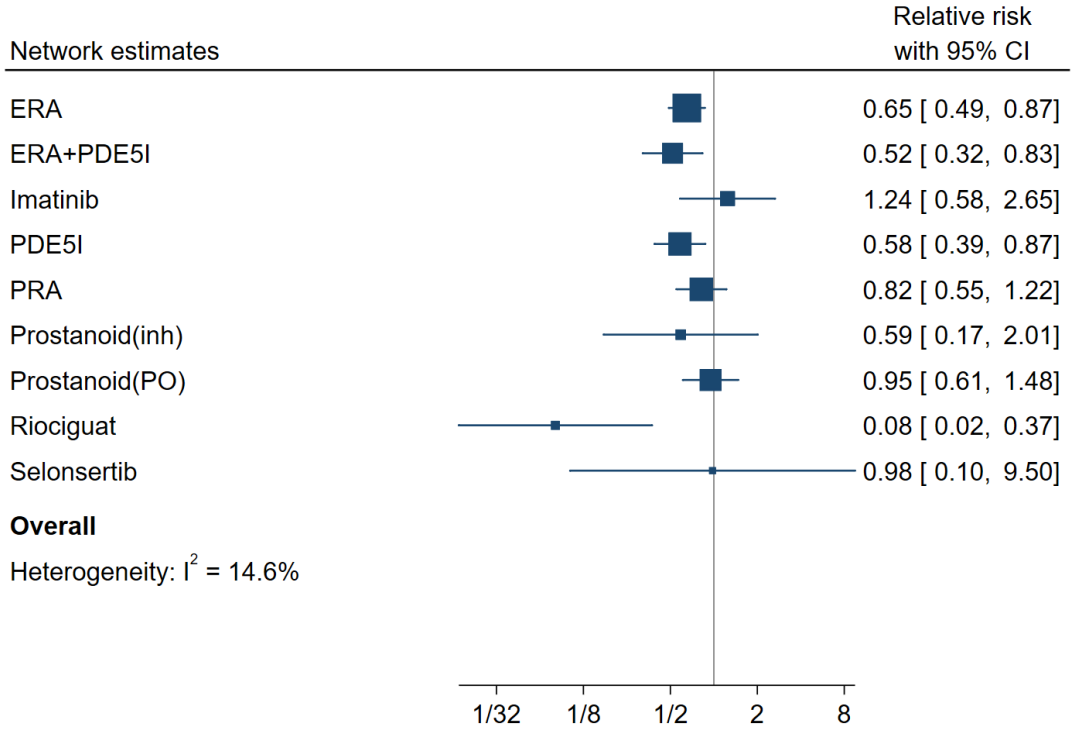
Clinical worsening



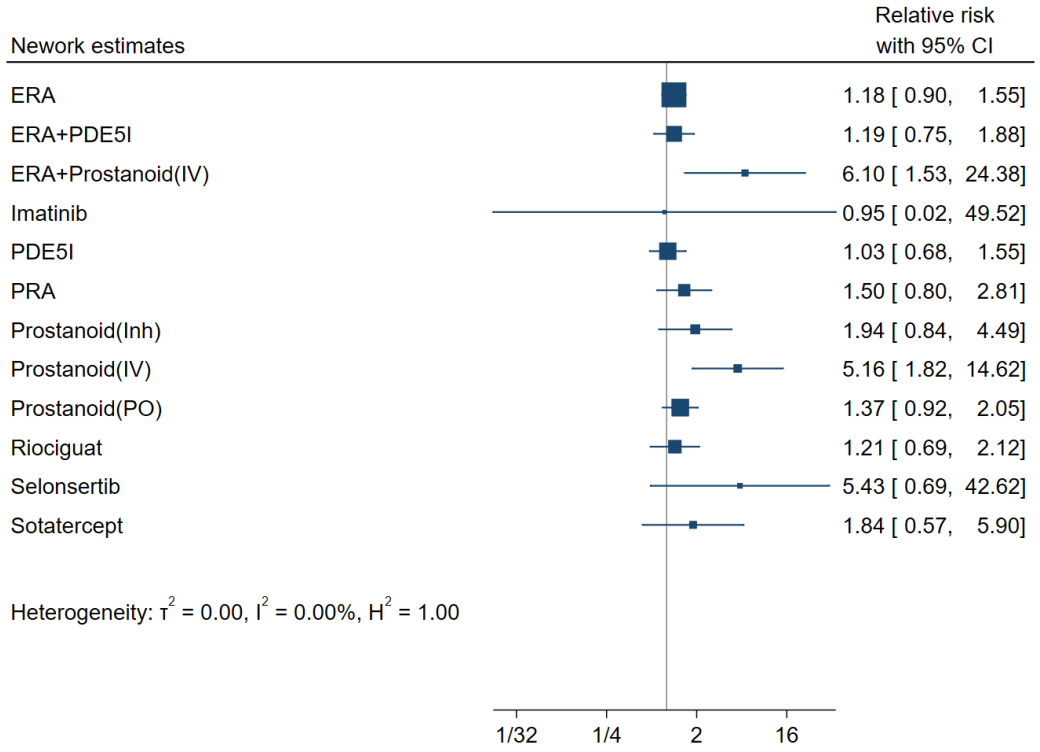
Mortality


Network estimates
Relative risk with 95% CI
ERA 0.81 [0.64, 1.03]
ERA+PDE5i 0.62 [0.23, 1.69]
Imatinib 1.01 [0.39, 2.61]
PDE5i 0.74 [0.34, 1.60]
PRA 0.95 [0.74, 1.21]
Prostanoid(Inh) 0.32 [0.07, 1.48]
Prostanoid(Inh)+ERA 0.90 [0.02, 41.89]
Prostanoid(IV) 0.56 [0.31, 1.01]
Prostanoid(IV)+ERA 1.30 [0.06, 27.20]
Prostanoid(PO) 0.86 [0.58, 1.27]
Riociguat 0.30 [0.07, 1.25]
Selonsertib 0.98 [0.11, 8.94]
Sotatercept 1.31 [0.05, 32.77]
Heterogeneity: I^2 = 0.00%
1/32
1/4
2
16

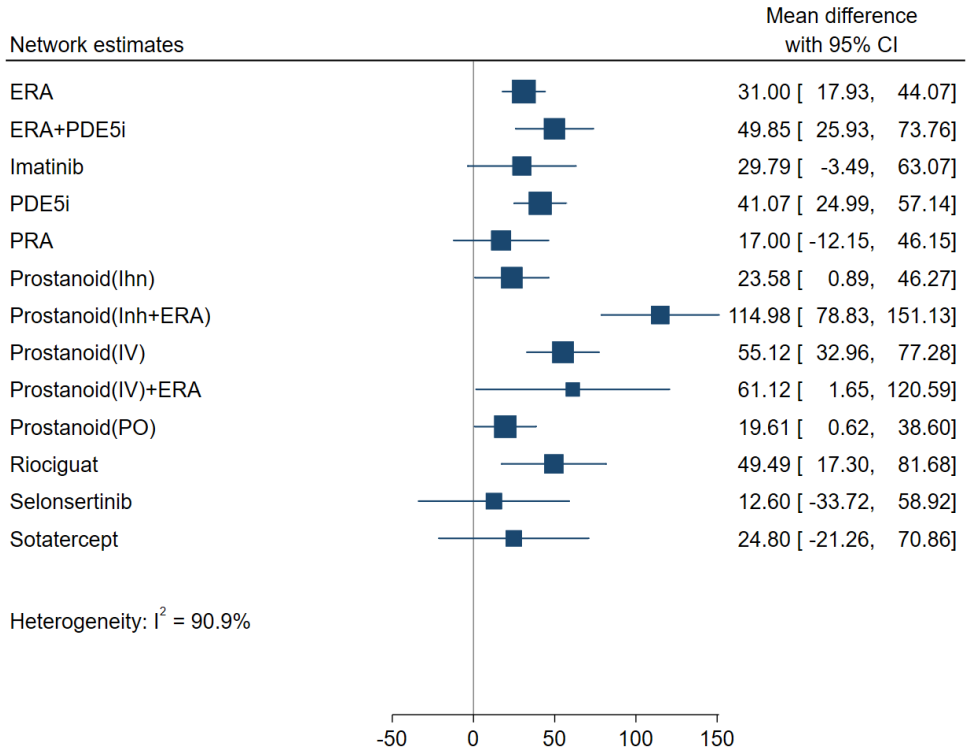
Hospitalizations



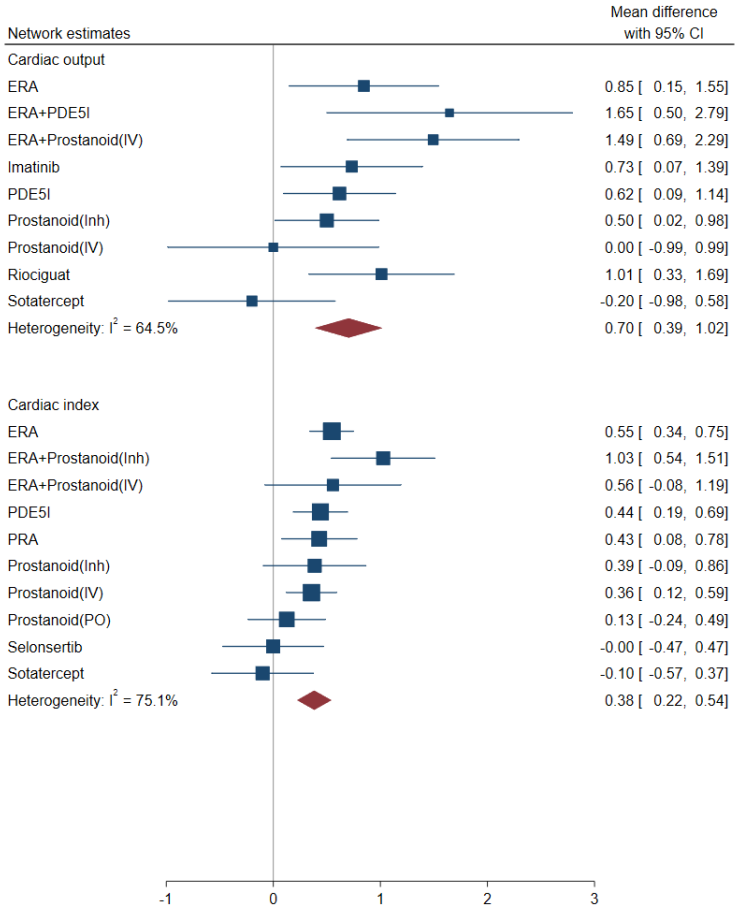
Functional class



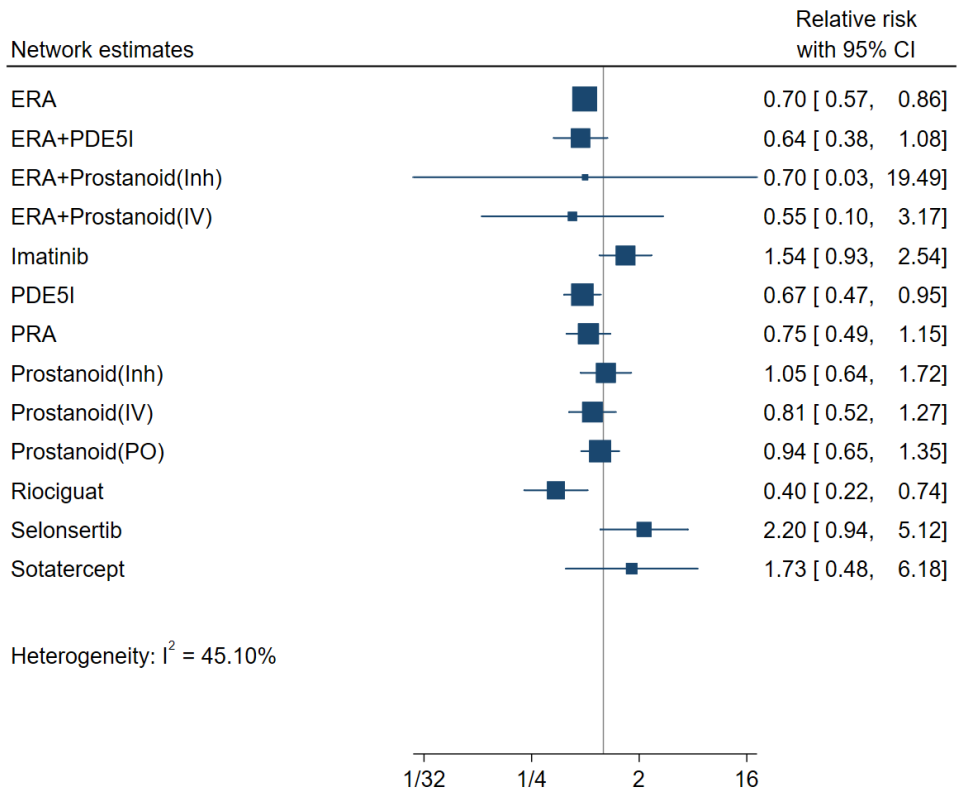
6-MWD


Network estimates
Mean difference with 95% CI
ERA 31.00 [17.93, 44.07]
ERA+PDE5i 49.85 [25.93, 73.76]
Imatinib 29.79 [-3.49, 63.07]
PDE5i 41.07 [24.99, 57.14]
PRA 17.00 [-12.15, 46.15]
Prostanoid(Ihn) 23.58 [0.89, 46.27]
Prostanoid(Inh+ERA) 114.98 [78.83, 151.13]
Prostanoid(IV) 55.12 [32.96, 77.28]
Prostanoid(IV)+ERA 61.12 [1.65, 120.59]
Prostanoid(PO) 19.61 [0.62, 38.60]
Riociguat 49.49 [17.30, 81.68]
Selonsertinib 12.60 [-33.72, 58.92]
Sotatercept 24.80 [-21.26, 70.86]
Heterogeneity: I^2 = 90.9%
-50
0
50
100
150

CO and CI


Network estimates
Mean difference with 95% CI
Cardiac output
ERA 0.85 [0.15, 1.55]
ERA+PDE5I 1.65 [0.50, 2.79]
ERA+Prostanoid(IV) 1.49 [0.69, 2.29]
Imatinib 0.73 [0.07, 1.39]
PDE5I 0.62 [0.09, 1.14]
Prostanoid(Inh) 0.50 [0.02, 0.98]
Prostanoid(IV) 0.00 [-0.99, 0.99]
Riociguat 1.01 [0.33, 1.69]
Sotatercept -0.20 [-0.98, 0.58]
Heterogeneity: I^2 = 64.5% 0.70 [0.39, 1.02]
Cardiac index
ERA 0.55 [0.34, 0.75]
ERA+Prostanoid(Inh) 1.03 [0.54, 1.51]
ERA+Prostanoid(IV) 0.56 [-0.08, 1.19]
PDE5I 0.44 [0.19, 0.69]
PRA 0.43 [0.08, 0.78]
Prostanoid(Inh) 0.39 [-0.09, 0.86]
Prostanoid(IV) 0.36 [0.12, 0.59]
Prostanoid(PO) 0.13 [-0.24, 0.49]
Selonsertib -0.00 [-0.47, 0.47]
Sotatercept -0.10 [-0.57, 0.37]
Heterogeneity: I^2 = 75.1% 0.38 [0.22, 0.54]
-1
0
1
2
3

SAE


Network estimates
Relative risk with 95% CI
ERA 0.70 [0.57, 0.86]
ERA+PDE5I 0.64 [0.38, 1.08]
ERA+Prostanoid(Inh) 0.70 [0.03, 19.49]
ERA+Prostanoid(IV) 0.55 [0.10, 3.17]
Imatinib 1.54 [0.93, 2.54]
PDE5I 0.67 [0.47, 0.95]
PRA 0.75 [0.49, 1.15]
Prostanoid(Inh) 1.05 [0.64, 1.72]
Prostanoid(IV) 0.81 [0.52, 1.27]
Prostanoid(PO) 0.94 [0.65, 1.35]
Riociguat 0.40 [0.22, 0.74]
Selonsertib 2.20 [0.94, 5.12]
Sotatercept 1.73 [0.48, 6.18]
Heterogeneity: I^2 = 45.10%
1/32
1/4
2
16