e-Appendix 1.

Supplementary Methods

Search Strategy

A health sciences librarian ran extensive literature searches in MEDLINE via Ovid, Cochrane Central Register of Controlled Trials via Wiley (CENTRAL), EMBASE via Wiley, Web of Science, CINAHL via EBSCO, and ClinicalTrials.gov during June – July 2015. No filters for date or language were used, however the Randomized Controlled Trials (From Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/methodology/filters.html#random) was applied to the Ovid MEDLINE search and modified for all other databases with the exception of EMBASE. For EMBASE, a filter described in the Cochrane Handbook for Systematic Reviews of Interventions was utilized (Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org). Duplicates and pre-1990 studies were removed using EndNote. Full search strategies are included in the appendix.

#	Searches	Results	Search Type
1	exp Hypertension, Pulmonary/	27061	Advanced
2	(pulmonary adj3 hypertension).tw.	32741	Advanced
3	PAH.tw.	15270	Advanced
4	or/1-3	50829	Advanced
5	Randomized Controlled Trials as Topic/	98368	Advanced
6	randomized controlled trial/	397829	Advanced
7	Random Allocation/	83781	Advanced
8	Double Blind Method/	130918	Advanced
9	Single Blind Method/	20630	Advanced
10	clinical trial/	495717	Advanced
11	clinical trial, phase i.pt.	15315	Advanced
12	clinical trial, phase ii.pt.	24644	Advanced
13	clinical trial, phase iii.pt.	10149	Advanced
14	clinical trial, phase iv.pt.	1034	Advanced
15	controlled clinical trial.pt.	89715	Advanced
16	randomized controlled trial.pt.	397829	Advanced

to Present (Run on June 23, 2015, 3542 results. Rerun on March 2, 2016, 3653 Results)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946

17	multicenter study.pt.	188398	Advanced
18	clinical trial.pt.	495717	Advanced
19	exp Clinical Trials as topic/	290521	Advanced
20	or/5-19	1084627	Advanced
21	(clinical adj trial\$).tw.	238487	Advanced
22	((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.	136764	Advanced
23	PLACEBOS/	33038	Advanced
24	placebo\$.tw.	168958	Advanced
25	randomly allocated.tw.	18726	Advanced
26	(allocated adj2 random\$).tw.	21411	Advanced
27	(randomised controlled trial* or randomized controlled trial*).tw.	94148	Advanced
28	or/21-27	520039	Advanced
29	20 or 28	1274362	Advanced
30	case report.tw.	220376	Advanced
31	letter/	883670	Advanced
32	historical article/	317457	Advanced
33	or/30-32	1409280	Advanced
34	29 not 33	1242943	Advanced
35	4 and 34	3542	Advanced
36	("19155250" or "23755974" or "22691882" or "24371842" or "25173912").ui.	5	Advanced
37	36 not 35	1	Advanced

CINAHL (Run on June 23, 2015, 613 results. Rerun on March 2, 2016, 660 results.)

- 1. (MH "Hypertension, Pulmonary+")
- 2. pulmonary N3 hypertension
- 3. PAH
- 4. S1 OR S2 OR S3
- 5. (MH "Clinical Trials+")
- 6. PT Clinical trial
- 7. clinic* n1 trial*
- 8. (tripl* n1 blind*) or (tripl* n1 mask*)
- 9. (doubl* n1 blind*) or (doubl* n1 mask*)
- 10. (singl* n1 blind*) or (singl* n1 mask*)
- 11. randomi* control* trial*
- 12. MH "Random Assignment"
- 13. random* allocat*
- 14. placebo*
- 15. (MH "Placebos")
- 16. (MH "Quantitative Studies")
- 17. allocat* random*

18. S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 S17 19. S4 AND S18

CDSR, DARE, and CENTRAL via Wiley (run on June 23, 2015, 122 results. Rerun on March 3, 2016, 117 results.[NOTE: CDSR (0 results) and DARE (133) were only run on March 3, 2016.)

- 1. MeSH descriptor: [Hypertension, Pulmonary] explode all trees
- 2. pulmonary near/3 hypertension:ti,ab,kw (Word variations have been searched)
- 3. PAH:ti,ab,kw (Word variations have been searched)
- 4. #1 or #2 or #3
- 5. MeSH descriptor: [Clinical Trial] explode all trees
- 6. clinic* near/1 trial*:ti,ab,kw (Word variations have been searched)
- (tripl* near/1 blind*) or (tripl* near/1 mask*):ti,ab,kw (Word variations have been searched)
- (doubl* near/1 blind*) or (doubl* near/1 mask*):ti,ab,kw (Word variations have been searched)
- 9. (singl* near/1 blind*) or (singl* near/1 mask*):ti,ab,kw (Word variations have been searched)
- 10. randomi* control* trial*:ti,ab,kw (Word variations have been searched)
- 11. MeSH descriptor: [Random Allocation] explode all trees
- 12. MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees
- 13. MeSH descriptor: [Double-Blind Method] explode all trees
- 14. MeSH descriptor: [Single-Blind Method] explode all trees
- 15. MeSH descriptor: [Clinical Trials as Topic] explode all trees
- 16. MeSH descriptor: [Placebos] explode all trees
- 17. randomly allocated:ti,ab,kw (Word variations have been searched)
- 18. placebo*:ti,ab,kw (Word variations have been searched)
- 19. allocated near/2 random*:ti,ab,kw (Word variations have been searched)
- 20. randomised controlled trial* or randomized controlled trial*:ti,ab,kw (Word variations have been searched)
- 21. #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
- 22.#5 AND #21

Web of Science (All terms run as topic. Run on June 23, 2015, 2561 results. Rerun on March 3, 2016, 2754 results.)

- 1. pulmonary Near/3 hypertension
- 2. PAH
- 3. #1 OR #2
- 4. clinical Near/3 trial*
- 5. ((singl* or doubl* or treb* or tripl*) Near/3 (blind* or mask*))
- 6. Placebo*
- 7. "randomly allocated"
- 8. allocated Near/2 random*
- 9. "randomised controlled trial*" or "randomized controlled trial*"
- 10. #4 OR #5 OR #6 OR #7 OR #8 OR #9
- 11.#3 AND #10

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Embase (Run on July 21, 2015, 6481 results. Rerun on March 3, 2016, 8494 results.)

- 1. 'pulmonary hypertension'/exp
- 2. pulmonary NEAR/3 hypertension
- 3. PAH
- 4. #1 OR #2 OR #3
- 5. 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti
- 6. #4 AND #5

Clinicaltrials.gov (run on July 21, 2015, 390, [306 after removing duplicates]. Rerun on March 3, 2016, 425 results [332 after removing duplicates].)

"Pulmonary arterial hypertension" AND random (145 studies. Rerun on March 3, 2016, 156 studies.)

"Pulmonary hypertension" AND random (245 studies. Rerun on March 3, 2016, 269 studies.)

Study exclusion criteria

We excluded (a) observational studies, (b) trials with a cross-over design since the adequate washout period for medications is not well-defined for PAH therapies, (c) non-FDA approved or investigational therapies including sitaxsentan, beraprost, imatinib and vardenafil, (d) conventional therapy not specific to PAH - calcium channel blockers, anticoagulants, diuretics and other heart failure therapy, (e) other WHO groups of pulmonary hypertension, where data for group 1 pulmonary hypertension was not separately reported, (f) trials studying exclusively patients with sickle cell disease, congenital heart disease or Eisenmenger's syndrome, and (g) trials that did not report any of our selected efficacy outcomes.

Excluded RCTs with reasons for exclusion

Twelve RCTs were excluded because they studied non-FDA approved treatments¹⁻¹². Eleven RCTs were excluded because they studied exclusively patients with Eisenmenger's syndrome¹³⁻¹⁹, congenital heart disease²⁰, sickle cell disease²¹ or included only children²² or pregnant females²³ in the study. Two RCTs including patients with pulmonary hypertension other than Group I were excluded because they did not report separately data for Group I PAH patients.^{24,25} Three other RCTs were excluded for lack of appropriate comparator group (two different doses of the same medication were studied in the two arms of the study).²⁶⁻²⁸ The details are presented in supplementary Table 1.

Data Abstraction Protocol

Data was abstracted for the following characteristics:

 (a) study characteristics – primary author, year of publication, geographic location of the study, single versus multi center, duration of follow-up, total number of patients in intervention and comparator group

- (b) patient characteristics age, sex
- (c) disease characteristics etiology of PAH, baseline 6MWD, baseline NYHA/ WHO functional class
- (d) treatment characteristics –intervention and comparator treatment, percentage of patients on concomitant background therapy, type of background therapy
- (e) outcome assessment mortality, change in 6MWD from baseline, proportion of subjects with improvement in NYHA/ WHO functional class, proportion of subjects hospitalized for any reason
- (f) adverse effects proportion of patients with serious adverse events requiring medication discontinuation.

Outcome assessment

A hierarchical approach was used for timing of outcome assessment. A 16 (±4) week follow-up period was used as the preferential time-point for outcome assessment in our study; when outcomes were reported at multiple periods of follow up, the time-point closest to 16 weeks was selected for all outcomes. Intention-to-treat analysis was performed for all outcomes, that is, all randomized patients were included in the analysis. In our primary analysis, we used study reported event rates for categorical outcomes and the last-observation carried forward (LOCF) data for the continuous 6MWD. For Phase III trials reporting data for multiple doses of the same medication, we used the FDA approved dose. For Phase-II trials reporting the same, we used the following approach in order of preference depending on availability 1) pooled data for all patients with multiple doses combined, 2) data for the most commonly used dose across all trials of that agent or 3) data for the FDA approved dose.

Statistical analysis

Direct meta-analysis was performed for all treatment comparisons using a DerSimonian-Laird random effects approach, which incorporates within- and between-study heterogeneity to estimate pooled relative risk (RR) and 95% confidence intervals (CI) for each comparison. For the continuous outcome (6MWD), pooled weighted mean difference and its 95% CI was estimated. We performed network meta-analyses for all available interventions using a multivariate random-effects meta-regression developed by Ian White ²⁹. For this analysis, we used a "consistency" approach which assumes that study design does not affect estimates. In this approach, it is assumed that the estimate for a comparison between two agents, A and B, does not differ by trial design (A-B or one with a third agent, C, A-B-C). To examine the applicability of this approach, we repeated these analysis using the design-by-treatment approach suggested by Higgins et al, which includes study design as an additional covariate in the model ("inconsistency" model),³⁰ and a Wald test for inconsistency was performed.

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We calculated a point estimate from the network along with a 95% confidence intervals from the frequency distribution of the estimate. This approach is similar to a Bayesian model with non-informative priors (when no assumptions are made about treatment effect of these drugs from data external to the trials included in this systematic review). The details of the procedure have been reportedly previously.³¹

Ranking of agents

We ranked drugs in order of their efficacy and tolerability using the surface under the cumulative ranking (SUCRA).³² We estimated the highest cumulative rank for improving efficacy outcomes, and for being most safe for the adverse event outcome, by comparing each against an imaginary agent that is always the highest ranked, with a SUCRA of 1 and another agent that is always lowest ranked with SUCRA of 0. However, this information is provided only as an additional piece evidence for the readership and given the uncertainty in ranking estimates,³³ we do not use SUCRA estimates in deriving any of our study conclusions.

Sensitivity analyses

We performed sensitivity analyses to assess the robustness of our findings. First, to allow for sufficient follow up period, we included trials which with a follow up of at least 12 weeks. Second, to limit the impact of temporal variation in trial design, we repeated the analysis limiting to trials published after the year 2000. Finally, we repeated our analysis for trials where the less than 20% of included participants were receiving background therapy with another agent at the beginning of the trial. Results of these analyses are presented in e-Table 5.

Quality of Evidence

We followed the GRADE framework to rate the quality of evidence of estimates derived from network meta-analysis for efficacy outcomes – clinical worsening and improvement in functional class.¹⁶ In this approach,

(A) Results from the meta-analysis of randomized clinical trials starts at the highest quality of evidence (of the four levels – high-, moderate-, low- and very low-quality evidence) and is subsequently rated down for any of the five criteria: (i) within-study risk of bias (methodological quality), (ii) indirectness of evidence (includes consideration for head-to-head trials, representativeness of study populations, nature of interventions/outcomes) (iii) heterogeneity between direct and indirect estimates, (iv) imprecision of effect estimates (width of confidence intervals, particularly if includes the null) and (v) risk of publication bias. The risk of a particular bias is rated as 'severe' or 'very severe', and evidence rating is subsequently downgraded by 1 (severe) or 2 (very-severe) categories accordingly.

(B) The rating of indirect estimates starts at the lowest rating of the two pairwise estimates that contribute as first-order loops (comparison involving a single additional intervention, such as placebo) to the indirect estimate, but can be rated down further for imprecision or intransitivity

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(dissimilarity between studies in terms of clinical or methodological characteristics). If direct and indirect estimates were similar (i.e. coherent), then the higher of their rating can be assigned to the network meta-analysis estimates. The interpretation of GRADE categories is described in e-Table 3.

SUPPLEMENTAL RESULTS

Efficacy outcomes: Clinical worsening, hospitalization and mortality

Direct meta-analysis

The primary outcome, clinical worsening was available in 20 RCTs with 22 direct comparisons (e-Figure 3). Compared to placebo, ERA (RR 0.51, 95% CI 0.35, 0.75), PDE5i (RR 0.35, 95% CI 0.22, 0.57), riociguat (RR 0.19, 95% CI 0.05, 0.69) and selexipag (RR 0.65, 95% CI 0.55, 0.77) were associated with reduction in clinical worsening (I²: 0-64%). However, data for both riociguat and selexipag were available from only one RCT each. The combination of ERA+PDE5i was associated with reduced clinical worsening compared to both ERA (RR 0.53, 95% CI 0.37, 0.76) and PDE5i (RR 0.65, 95% CI 0.44, 0.95) in the single study for these comparisons. For the outcome of PAHrelated hospitalization (e-Figure 4), compared to placebo, selexipag was associated with reduced hospitalizations (RR 0.73, 95% CI 0.56, 0.95). The combination of ERA+PDE5i was associated with lower hospitalization compared to ERA (RR 0.28, 95% CI 0.13, 0.58) and to PDE5i (RR 0.40, 95% CI 0.18, 0.90), but ERA or PDE5i were not significant in placebo comparisons. All-cause mortality was reported by all included studies. For this outcome, the pooled RR for all direct placebo comparisons was lower than 1 for most comparisons; however, none of these reached statistical significance (I²: 0-28%, e-Figure 5).

Efficacy outcomes: Functional status

Direct meta-analysis

Improvement in NYHA/WHO functional class was reported in 23 RCTs with 25 comparisons (e-Figure 6). Compared to placebo, ERA (RR 1.56, 95% CI 1.23, 1.97), IV/SC prostanoids (RR 6.73, 95% CI 1.98, 22.90) and selexipag (RR 1.55, 95% CI 1.11, 2.18) were efficacious in improving the functional status by at least one NYHA/WHO class (I²: 0-64%). For the continuous outcome of 6MWD, most active agents were associated with significant improvements in 6MWD over placebo (I²: 0-86%) with varying magnitudes of weighted mean difference [WMD] – 28.5m with ERA, 27.2m with PDE5i, 13.3m for PO/INH prostanoids, 31.4m with IV/SC prostanoids, 30.3m with riociguat and 14.4m with selexipag (e-Figure 7).

Adverse events leading to discontinuation

Direct meta-analysis

The rates of adverse-event related medication discontinuation were examined as a marker for tolerability, with lower discontinuation rates suggesting higher tolerability. 26 RCTs reported data *Online supplements are not copyedited prior to posting and the author(s) take full responsibility for the accuracy of all data.*



on this outcome. Compared to placebo, PO/INH prostanoids (6 RCTs; RR 2.96, 95% CI 1.84, 4.77, $I^2 = 0\%$) and selexipag (1 RCT, RR 2.01, 95 % CI: 1.40, 2.87) were more likely to be discontinued. None of the other agents differed significantly in available comparisons against each other or placebo (e-Figure 8).



e-Table 1. Randomized controlled trials excluded from the meta-analysis with reasons for exclusion.

Author, Year (Study name)	Reason for Exclusion
Sun, 2014 ²³	Patients: Pregnant females only
Chin, 2014 (EPITOME-1) ²⁶	Intervention: Two different doses of epoprostenol compared in
	the two arms of the RCT
Cha, 2013 (EIGER) ¹³	Patients: Exclusively patients with Eisenmenger syndrome
Fukumoto, 2013 ¹	Intervention: Non FDA approved drug (AT-877ER)
Hoeper, 2013 ³⁴	Intervention: Non FDA approved therapy (Imatinib)
Van de Bruaene A, 2013 ²⁰	Patients: Congenital heart disease with late ASD closure
Badesch, 2012 (ARIES 3) ²⁴	Patients: Included other classes of PH with data not separately reported for PAH
Barst, 2012 ²²	Patients: Children (all subjects less than 17 years of age)
Kaya, 2012 ¹⁴	Patients: Exclusively patients with Eisenmenger syndrome
Sandoval, 2012 ³	Intervention: Non FDA approved drug (Sitaxsentan)
Zeng, 2012 ⁴	Intervention: Non FDA approved drug (Atorvastatin)
5,	Patients: Included other classes of PH with data not separately reported for PAH
Kawut, 2011 (ASA-STAT) ⁵	Intervention: Non FDA approved therapies (Aspirin and Statin)
Mukhopadhyay, 2011 ¹⁵	Patients: Exclusively patients with Eisenmenger syndrome
Barst, 2010 (ASSET) ²¹	Patients: Exclusively patients with sickle cell disease
Ghofrani, 2010 ⁶	Intervention: Non FDA approved drug (Imatinib)
Iversen, 2010 ¹⁶	Patients: Exclusively patients with Eisenmenger syndrome
Wilkins, 2010 ¹²	Intervention: Non FDA approved drug (Simvastatin)
Bharani, 2007 ¹⁷	Patients: Exclusively patients with Eisenmenger syndrome
Chau, 2007 ¹⁸	Patients: Exclusively patients with Eisenmenger syndrome
Rubenfire, 2007 ²⁸	Intervention: Studied transition from Epoprostenol to treprsotinil
Wang, 2007 ⁷	Intervention: Non pharmacologic treatment studied (endothelial progenitor cell transplant)
Singh, 2006 ³⁵	Design: Cross-over
Channick, 2006 ²⁷	Intervention: Two different doses of the same drug compared in the two arms of the RCT (Inhaled treprostinil)
Galie, 2006 (BREATHE-5) ¹⁹	Patients: Exclusively patients with Eisenmenger syndrome
Barst, 2006 (STRIDE-2) ⁸	Intervention: Non FDA approved drug (Sitaxsentan)
Sastry, 2004 ³⁶	Design: Cross-over
Barst, 2004 (STRIDE-1) ⁹	Intervention: Non FDA approved drug (Sitaxsentan)
Barst, 2003 ¹⁰	Intervention: Non FDA approved therapy (Beraprost)
Galie, 2002 ¹¹	Intervention: Non FDA approved therapy (Beraprost)
Ghofrani, 2002 ²⁵	Patients: Included other classes of PH with data not separately reported for PAH

e-Table 2. Definition of Clinical Worsening

Study author, year (Study name)	Definition of Clinical Worsening
Galie, 2015 (AMBITION)	All-cause death + hospitalization for worsening PAH + disease progression (decrease of ≥15% from baseline 6MWD combined with WHO FC III or IV symptoms at two consecutive visits separated by at least 14 days) or unsatisfactory long term clinical response (any decrease from baseline in 6MWD at two consecutive clinic visits after baseline separated by at least 14 days, and WHO FC III symptoms assessed at two clinic visits separated by at least 6 months).
McLaughlin, 2014 (COMPASS-2)	All-cause death + hospitalization for worsening PAH + start of intravenous prostanoid therapy + atrial septostomy + lung transplantation + worsening PAH defined as – 1) moderate or marked worsening of PAH symptoms on the PGSA together with the initiation of a subcutaneous or inhaled prostanoid or use of open-label bosentan or 2) no change or mild worsening of PAH symptoms accompanied by a decrease in 6MWD by \geq 20% from the previous visit or \geq 30% from the baseline visit, together with the initiation of a subcutaneous or a subcutaneous or inhaled prostanoid or use of open-label bosentanid or use o
Galie, 2008 (EARLY)	All-cause death (during the treatment period or as the outcome of a treatment-emergent adverse event that led to permanent discontinuation of study treatment) + hospitalization due to PAH complications + symptomatic progression of PAH (presence of one of the following: appearance or worsening of right heart failure; decrease of $\geq 10\%$ from baseline in two 6MWD done 2 weeks or more apart; or $\geq 5\%$ decrease from baseline in two 6MWD done 2 weeks or more apart associated with a 2-point or greater increase in Borg dyspnea index).
Galie, 2008 (ARIES 1)	All-cause death + lung transplantation + hospitalization for PAH + atrial septostomy + study withdrawal because of the addition of other PAH medications, or early escape criteria [presence of 2 of the following criteria: (1) a decrease of \geq 20% in the 6MWD, (2) an increase of \geq 1 WHO FC, (3) worsening right ventricular failure (as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites, or peripheral edema), (4) rapidly progressing hepatic or renal failure, and (5) refractory systolic hypotension (systolic blood pressure \leq 85 mm Hg].
Galie, 2008 (ARIES 2)	All-cause death + lung transplantation + hospitalization for PAH + atrial septostomy + study withdrawal because of the addition of other PAH medications, or early escape criteria [presence of 2 of the following criteria: (1) a decrease of ≥20% in the 6MWD, (2) an increase of ≥1 WHO FC, (3) worsening right ventricular failure (as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites, or peripheral edema), (4) rapidly progressing hepatic or renal failure, and (5) refractory systolic hypotension (systolic blood pressure ≤ 85 mm Hg].
Rubin, 2002	All-cause death + lung transplantation + hospitalization for pulmonary hypertension + lack of
(BREATHE-I) Channick, 2001	clinical improvement or worsening leading to discontinuation + need for epoprostenol therapy + atrial septostomy Right ventricular failure or aggravated PAH
Pulido, 2013 (SERAPHIN)	All-cause death upto the end of treatment period + lung transplantation + atrial septostomy + worsening of pulmonary arterial hypertension (occurrence of all three of the following: a decrease in 6MWD of ≥15% from baseline, confirmed by a second 6-minute walk test performed on a different day within 2 weeks; worsening of symptoms of PAH; and the need for additional treatment of PAH) + initiation of treatment with intravenous or subcutaneous prostanoids.

Zhuang, 2014	All-cause death + transplantation + arterial septostomy + hospitalization due to worsening PAH + initiation of new therapy or worsening FC by week 16.
Galie, 2009 (PHIRST)	All-cause death + lung or heart-lung transplantation + atrial septostomy + hospitalization due to worsening PAH + initiation of new PAH approved therapy + worsening WHO FC.
Simmoneau, 2008 (PACES)	All-cause death + lung transplantation + hospitalization due to PAH + initiation of bosentan therapy + change in epoprostenol dose of $\geq 10\%$ due to clinical deterioration.
Galie, 2005 (SUPER)	All-cause death + transplantation + hospitalization for PAH + initiation of additional therapies for PAH such as intravenous epoprostenol or oral bosentan.
Jing, 2013 (FREEDOM-M)	Cardiovascular death + transplantation + atrial septostomy + clinical deterioration [initiation of new, approved PAH-specific therapy (ERA, PDE5i, or prostacyclin) + either hospitalization for decompensated PAH or a \geq 20% decrease in 6MWD from baseline combined with worsening WHO FC].
Tapson, 2013 (FREEDOM-C2)	All-cause death + transplantation + atrial septostomy + hospitalization as a result of right side heart failure + initiation of parenteral prostacyclin therapy + decrease in 6MWD of \geq 20% from baseline (or too ill to walk) and the addition of an inhaled prostacyclin analog, ERA or PDE5i.
Tapson, 2012 (FREEDOM-C)	All-cause death + transplantation + atrial septostomy + clinical deterioration defined as hospitalization related to PAH, 20% decrease in 6MWD from baseline and a decrease in World Health Organization [WHO] FC + initiation of a new PAH therapy
McLaughlin, 2010 (TRIUMPH-1)	Death + transplantation + hospital stay due to worsening PAH + initiation of additional approved PAH-specific therapy
McLaughlin, 2006 (STEP)	Death due to PAH + hospitalization + early study discontinuation due to worsening PAH + initiation of new, chronic PAH-specific therapy + lung transplantation + atrial septostomy
Hoeper, 2006 (COMBI)	All-cause death + hospital admission for right heart failure + deterioration in FC or decrease in 6 MWD by 20% from baseline or <150 m
Ghofrani, 2013 (PATENT 1)	All-cause death + heart or lung transplantation + atrial septostomy + hospitalization due to persistent worsening of PAH + start of new specific PAH treatment (ERAs, prostanoids, or PDE5i) or modification of a preexisting prostanoid treatment (i.e., increase in number of daily iloprost inhalations from six to nine, or increase of iloprost dosage from 2.5 to 5.0 µg per inhalation, or start of an intravenous prostanoid) due to worsening pulmonary arterial hypertension + persistent decrease of >15% from baseline or >30% compared with the last study related measurement in 6MWDdue to worsening PAH + persistent worsening of World Health Organization (WHO) FC due to deterioration of PAH.
Sitbon, 2016 (GRIPHON)	All- cause death + PAH-related hospitalization + need for transplantation + need for septostomy + initiation of parenteral prostanoids therapy or long-term oxygen therapy + disease progression defined as decrease from baseline of at least 15% in the 6MWD(confirmed by means of a second test on a different day) accompanied by a worsening in WHO FC (for the patients with WHO FC II or III at baseline) or the need for additional treatment of PAH (for the patients with WHO FC III or IV at baseline).

e-Table 3. GRADE categories of quality of evidence

GRADE quality of evidence	Interpretation
High quality	Further research is VERY UNLIKELY to change our confidence in the estimate of effect
Moderate quality	Further research is LIKELY to have an impact on our confidence in the estimate of effect and MAY change the estimate
Low quality	Further research is VERY LIKELY to have an impact on our confidence in estimate of effect and is LIKELY to change the estimate
Very low quality	Any estimate of effect is very uncertain

e-Table 4. SUCRA rankings for all outcomes for the primary analysis

Pharmacologic intervention	Clinical Worsening	Hospitalization	Mortality	Improvement in functional class	6MWD	Adverse events leading to discontinuation
Placebo	0.03	0.15	0.28	0.04	0.02	0.61
ERA	0.46	0.39	0.59	0.48	0.69	0.57
PDE5 inhibitor	0.68	0.57	0.56	0.45	0.53	0.80
PO/ INH Prostanoids	0.24	0.26	0.40	0.59	0.26	0.09
IV/ SC Prostanoids	-	0.51	0.73	0.99	0.74	0.16
Riociguat	0.89	0.87	0.80	0.39	0.48	0.92
ERA + PDE5 inhibitor	0.86	0.86	0.58	0.60	0.97	0.62
Selexipag	0.34	0.39	0.07	0.47	0.32	0.24

SUCRA rankings for the primary analysis for all outcomes. The larger number represent the better agent for both efficacy and safety outcomes. ERA = endothelin receptor antagonist, PDE5 inhibitor = Phosphodiesterase inhibitor, PO/INH = Per oral/ Inhaled, IV/SC = Intravenous/ Subcutaneous, 6MWD = 6 – minute walk distance.

e-Table 5. Results of sensitivity analysis

Pharmacological intervention	Timing of outcome assessment (A)		Excluding trials 2000	*Excluding trials with >20% subjects on background therapy	
	Clinical Worsening RR (95% CI)	Improvement in functional class RR (95% CI)	Clinical Worsening RR (95% CI)	Improvement in functional class RR (95% CI)	Improvement in functional class RR (95% CI)
ERA	0.53 (0.36,0.78)	1.56 (1.21,2.01)	0.53 (0.36,0.78)	1.56 (1.23,1.99)	2.03 (1.32,3.10)
PDE5i	0.39 (0.24,0.62)	1.53 (1.06,2.21)	0.39 (0.24,0.62)	1.52 (1.07,2.16)	2.37 (1.17,4.79)
PO/INH Prostanoids	0.75 (0.47,1.19)	1.77 (0.99,3.19)	0.75 (0.47,1.19)	1.74 (0.99,3.05)	3.00 (0.89,10.09)
IV/SC Prostanoids	-	4.91 (1.88,12.80)	-	2.33 (0.75,7.30)	5.20 (2.28,11.86)
Riociguat	0.19 (0.05,0.76)	1.42 (0.74,2.69)	0.19 (0.05,0.76)	1.42 (0.77,2.62)	_
ERA + PDE5i	0.27 (0.14,0.52)	1.75 (1.04,2.96)	0.27 (0.14,0.52)	1.75 (1.07,2.85)	2.48 (1.18,5.23)
Selexipag	0.65 (0.38,1.12)	1.55 (0.89,2.69)	0.65 (0.38,1.12)	1.55 (0.93,2.60)	-

Sensitivity analysis based on timing of outcome assessment including only trials that reported outcomes at 12+/-4 weeks (A), excluding older trials published before 2000 (B), excluding trials where percentage of patients on PAH specific background therapy was >20% (C). The estimate for each intervention is represented against placebo and is derived from network meta-analysis combining both direct and indirect comparisons. Numbers in parentheses indicate 95% Confidence Intervals. ERA = Endothelin Receptor Antagonist, PDE5i = Phosphodiesterase 5 inhibitor, 6MWD = 6-minute walk distance, RR = Relative Risk, *The number of trials in this subgroup was too few to perfrom network meta-analysis for the outcome of clinical worsening.

e-Table 6. GRADE quality of evidence derived From Direct and Indirect Estimates and Network Meta-Analysis Informing on Comparative Efficacy of Pharmacological Strategies.

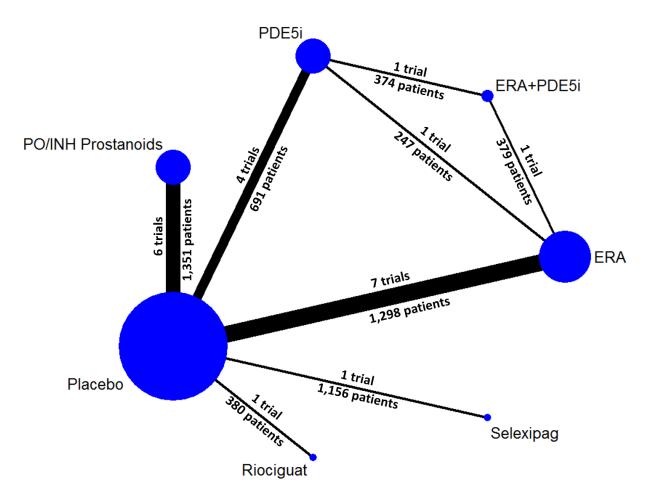
Pharmacological	Direct- Functional	Direct- clinical	Network-	Network – Clinical
Intervention	Class	worsening	Functional Class	worsening
	Compared wit		1	
ERA	Moderate (indirectness)	Moderate (indirectness)	Moderate	Moderate
	Low (indirectness,	Moderate		
PDE5i	imprecision)	(indirectness)	Low	Moderate
PO/ INH Prostacyclins	Low (indirectness, imprecision)	Low (indirectness, imprecision)	Low	Low
IV/ SC Prostacyclins	Moderate (risk of bias)	-	Moderate	-
Riociguat	Low (indirectness, imprecision)	Moderate (indirectness)	Low	Moderate
ERA+ PDE5i	-	-	Moderate	Moderate
Selexipag	Moderate (indirectness)	Moderate (indirectness)	Moderate	Moderate
	Compared v		•	
PDE5i	Low (very serious imprecision)	Moderate (imprecision)	Low	Low (rating down for imprecision)
PO/ INH Prostacyclins	-	_	Low	Low
IV/ SC Prostacyclins	-	-	Moderate	-
Riociguat	-	-	Low (favor ERA)	Very low (favoring riociguat, rated down twice for very serious imprecision)
ERA+ PDE5i	Moderate (imprecision)	High	Low (imprecision)	High (favoring combo)
Selexipag	-	-	Low (imprecision)	Very low (favoring ERA; very serious imprecision)

	Compared w	ith PDE5i		
PO/ INH Prostacyclins	-	-	Low	Low (favors PDE5i)
IV/ SC Prostacyclins	-	-	Low	-
Riociguat	-	-	Low (favors PDE5i)	Very low (favoring Rioci, very serious imprecision)
ERA+ PDE5i	Moderate (imprecision)	High	Low (very serious imprecision)	Moderate (imprecision)
Selexipag	-	-	Very low (very serious imprecision)	Low (favors PDE5i; imprecision)
	Compared with PO/	INH Prostacyclins		
IV/ SC Prostacyclins	-	-	Low	-
Riociguat	-	-	Low	Low
ERA+ PDE5i	-	-	-	-
Selexipag	-	-	Very low (very serious imprecision)	Very low (favors PCAs; very serious imprecision)
	Compared with IV/	SC Prostacyclins		
Riociguat	-	-	Low (favors PC)	-
ERA+ PDE5i	-	-	-	-
Selexipag	-	-	Moderate (favors PC)	-
	Compared wit	h Riociguat		
ERA+ PDE5i	-	-	-	-
Selexipag	-	-	Very low (very serious imprecision)	Low (favors Riociguat, imprecision)
	Compared with	ERA + PDE5i		
Selexipag	-	_	-	-

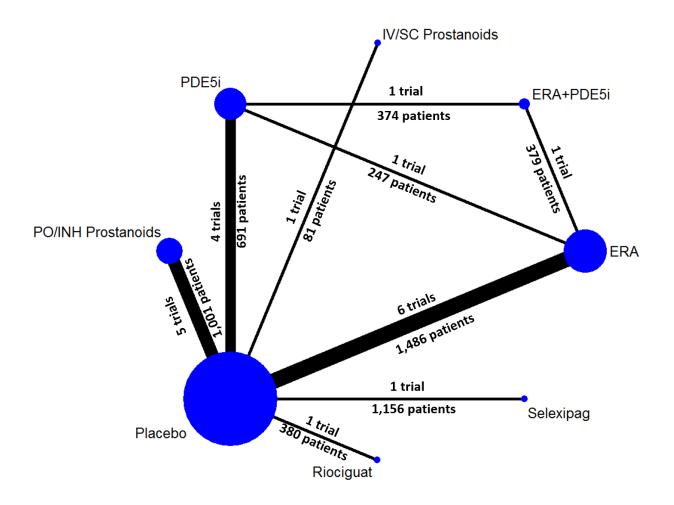


e-Figure 1(A-F): Network diagrams for all study outcomes.

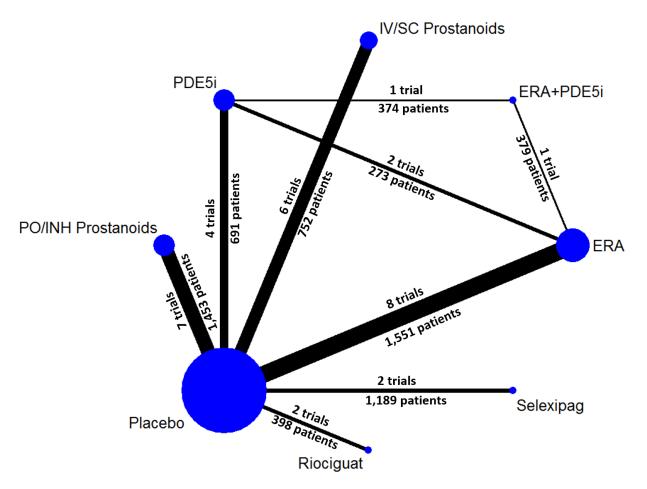
A: Clinical worsening



B: PAH – related hospitalization

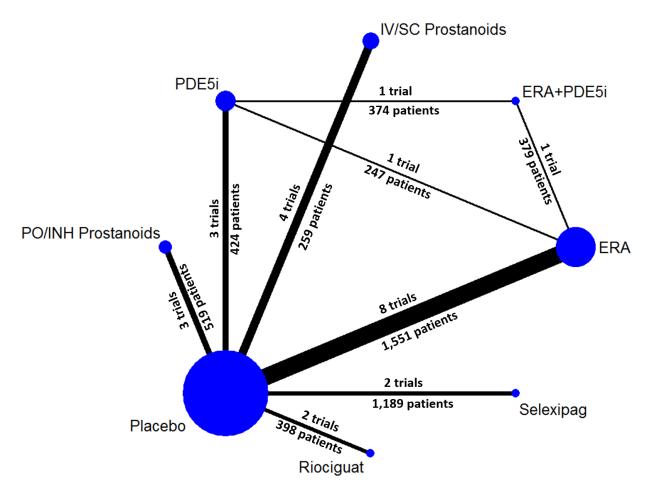


C: Mortality

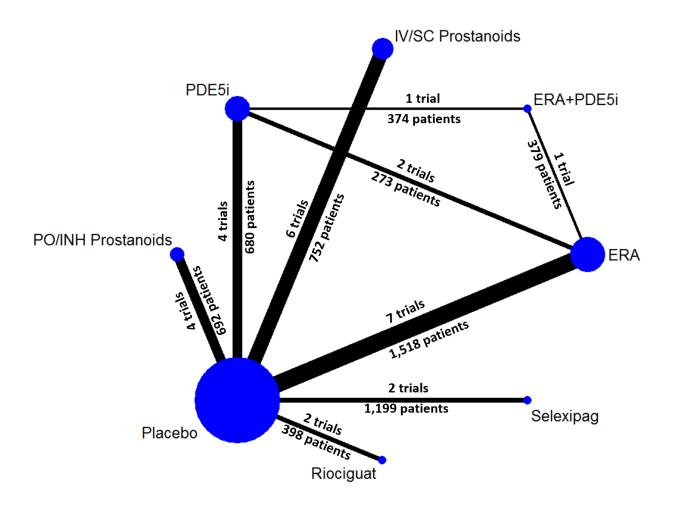




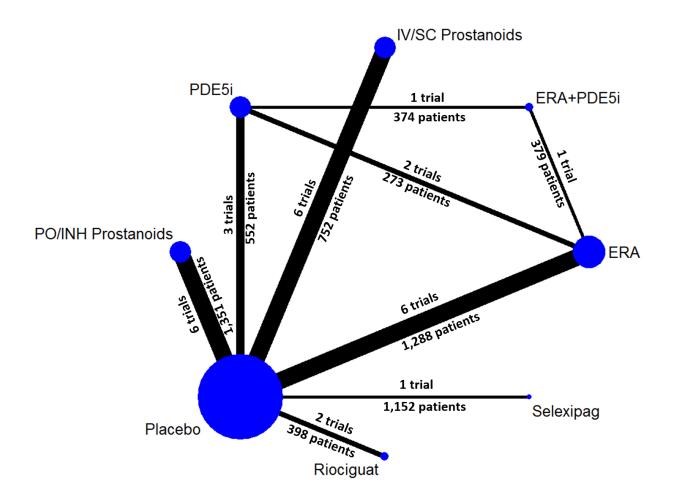
D: Functional class



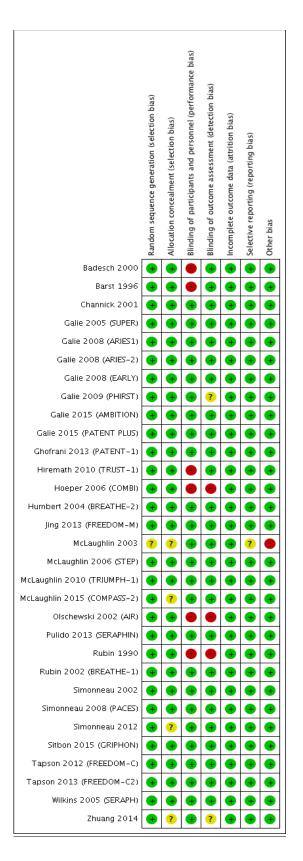
E: 6-minute walk distance



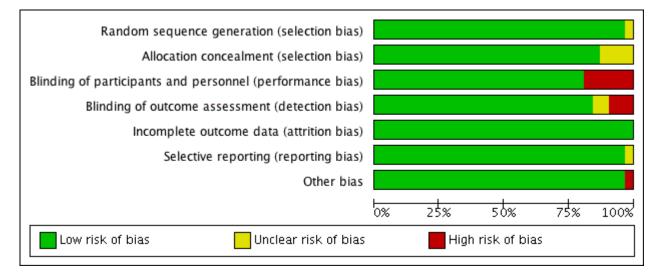
F: Adverse events leading to discontinuation



e-Figure 2A. Risk of bias summary for all studies



e-Figure 2B. Risk of bias - overall



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e-Figure 3. Results of Direct Meta-Analysis for Clinical Worsening

Study ID		RR (95% CI)	% Weight	Active Events	Active N	Control events	Control N
ERA vs placebo Channick 2001 Galie 2008 EARLY Galie 2008 ARIES 1 Galie 2008 ARIES 2 McLaughlin 2015 COMPASS-2		0.08 (0.00, 1.39) 0.23 (0.07, 0.77) 0.50 (0.13, 1.92) 0.22 (0.07, 0.73) 0.83 (0.66, 1.05)	1.72 7.77 6.69 8.01 30.77	0 3 3 3 68	21 93 67 63 159	3 13 6 14 90	11 92 67 65 175
Pulido 2013 SERAPHIN Rubin 2002 BREATHE-1 Subtotal (I-squared = 63.6%, p = 0.011)	*	0.68 (0.54, 0.85) 0.31 (0.14, 0.68) 0.51 (0.35, 0.75)	30.81 14.23 100.00	76 9	242 144	116 14	250 69
PDE5i vs placebo Galie 2005 SUPER Galie 2009 PHIRST Simmoneau 2008 PACES Zhuang 2014 Subtotal (I-squared = 0.0%, p = 0.980)	*	0.43 (0.12, 1.61) 0.32 (0.11, 0.94) 0.33 (0.15, 0.71) 0.38 (0.15, 0.99) 0.35 (0.22, 0.57)	13.70 20.29 40.40 25.62 100.00	3 4 8 5	69 79 134 60	7 13 24 14	70 82 133 64
PO/INH Prostanoids vs placebo Hoeper 2006 COMBI Jing 2013 FREEDOM-M McLaughlin 2006 STEP McLaughlin 2010 TRIUMPH-1 Tapson 2012 FREEDOM-C Tapson 2013 FREEDOM-C2 Subtotal (I-squared = 0.0%, p = 0.695)		0.83 (0.21, 3.24) 0.73 (0.39, 1.35) 0.09 (0.01, 1.54) 0.70 (0.20, 2.40) 0.67 (0.28, 1.61) 1.07 (0.47, 2.45) 0.76 (0.51, 1.11)	8.02 39.04 1.82 9.69 19.67 21.76 100.00	3 22 0 4 8 11	19 233 34 115 174 157	4 15 5 6 12 10	21 116 33 120 176 153
Riociguat vs placebo Shofrani 2013 PATENT 1 subtotal (I-squared = .%, p = .)	⇒	0.19 (0.05, 0.69) 0.19 (0.05, 0.69)	100.00 100.00	3	254	8	126
- Selexipag vs Placebo itbon 2015 GRIPHON ubtotal (I-squared = .%, p = .)	¢	0.65 (0.55, 0.77) 0.65 (0.55, 0.77)	100.00 100.00	155	574	242	582
- ERA + PDE5i vs ERA alie 2015 AMBITION ubtotal (I-squared = .%, p = .)	*	0.53 (0.37, 0.76) 0.53 (0.37, 0.76)	100.00 100.00	46	253	43	126
ERA vs PDE5i salie 2015 AMBITION subtotal (I-squared = .%, p = .)	t t	1.21 (0.84, 1.77) 1.21 (0.84, 1.77)	100.00 100.00	43	126	34	121
ERA + PDE5i vs PDE5i Salie 2015 AMBITION Subtotal (I-squared = .%, p = .)	ŧ	0.65 (0.44, 0.95) 0.65 (0.44, 0.95)	100.00 100.00	46	253	34	121
	.01 .1 1 10	I 100					
	Favors intervention Favors co	ntrol					

e- Figure 4. Results of Direct Meta-Analysis for PAH-related hospitalization

Galie 2008 ARIES 1 1.00 (0 Galie 2008 ARIES 2 0.23 (0 McLaughlin 2015 COMPASS-2 1.38 (0 Pulido 2013 SERAPHIN 0.79 (0 Rubin 2002 BREATHE-1 0.32 (0 Subtotal (I-squared = 52.0%, p = 0.064) 0.70 (0	0.03, 3.11) 4.36 0.15, 6.89) 5.68 0.05, 1.02) 8.70 0.80, 2.38) 27, 4' 0.64, 0.98) 38.33 0.12, 0.86) 15.53 0.43, 1.15) 100.6 0.06, 1.35) 21.13 0.05, 5.61) 8.80 0.30, 1.74) 64.53 0.01, 4.35) 5.48 0.27, 1.10) 100.6 0.31, 2.61) 44.82 0.01, 1.93) 6.18 0.23, 3.03) 30.81	3 90 3 6 00 3 2 1 9 8 0 00	93 67 63 159 242 144 69 79 134 60 233	3 2 9 20 117 9 7 2 11 2	92 67 175 250 69 70 82 133 64
Galie 2005 SUPER 0.29 (0 Galie 2009 PHIRST 0.52 (0 Simmoneau 2008 PACES 0.72 (0 Zhuang 2014 0.21 (0 Subtotal (I-squared = 0.0%, p = 0.697) 0.54 (0	0.05, 5.61) 8.80 0.30, 1.74) 64.51 0.01, 4.35) 5.48 0.27, 1.10) 100.0 0.31, 2.61) 44.83 0.01, 1.93) 6.18 0.23, 3.03) 30.83	1 9 8 0 00	79 134 60 233	2 11 2	82 133
Jing 2013 FREEDOM-M 0.90 (0 McLaughlin 2006 STEP 0.11 (0 McLaughlin 2010 TRIUMPH-1 0.83 (0 Tapson 2013 FREEDOM-C2 1.95 (0 Hoeper 2006 COMBI (Exclude) Subtotal (I-squared = 0.0%, p = 0.395) 0.89 (0	0.01, 1.93) 6.18 0.23, 3.03) 30.8				
Barst 1996 0.49 (0	0.36, 10.49) 18.13 ded) 0.00 0.43, 1.81) 100.0	3 4 0	34 115 157 19	5 4 5 2 0	116 33 120 153 21
Subtotal (I-squared = .%, p = .)	0.05, 5.17) 100.0 0.05, 5.17) 100.0		41	2	40
	0.01, 1.10) 100.0 0.01, 1.10) 100.0		254	4	126
	0.56, 0.95) 100. 0.56, 0.95) 100.		574	109	582
	0.13, 0.58) 100.0 0.13, 0.58) 100.0		253	18	126
	0.73, 2.86) 100.0 0.73, 2.86) 100.0		126	12	121
	0.18, 0.90) 100.0 0.18, 0.90) 100.0		253	12	121

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e- Figure 5. Results of Direct Meta-Analysis for All Cause Mortality

ıdy	RR (95% CI)	% Weight	Active Events	Active N	Control events	Control N
ERA vs placebo lie 2008 ARES 2 mbert 2004 BREATHE-2	0.52 (0.10, 2.72) 2.61 (0.14, 50.09)	7.14 2.26	2	63 22	4 0	65 11
Laughlin 2015 COMPASS-2	0.61 (0.29, 1.28) 0.99 (0.06, 15.58)	35.73 2.59	10 1	159 93	18 1	175 92
lido 2013 SERAPHIN	0.97 (0.50, 1.88) 0.50 (0.05, 5.38)	45.32 3.49	16 1	242 67	17 2	250 67
bin 2002 BREATHE-1	0.24 (0.02, 2.60) (Excluded)	3.47	1 0	144 21	2	69 11
btotal (I-squared = 0.0%, p = 0.834)	0.75 (0.48, 1.17)	100.00	U	21	U	
PDE5i vs placebo nmoneau 2008 PACES	0.07 (0.00, 1.15)	27.17	0	134	7	133
uang 2014	0.36 (0.01, 8.55)	21.84	ŏ	60	1	64
lie 2009 PHIRST	0.35 (0.01, 8.36)	21.79	0	79	1	82
lie 2005 SUPER btotal (I-squared = 0.0%, p = 0.567)	1.01 (0.06, 15.90) 0.30 (0.07, 1.34)	29.20 100.00	1	69	1	70
PO/INH Prostanoids vs placebo						
schewski 2002 AIR pson 2013 FREEDOM-C2	0.50 (0.05, 5.34) 1.46 (0.42, 5.08)	8.71 31.53	1 6	51 157	2 4	51 153
g 2013 FREEDOM-M	0.83 (0.31, 2.23)	50.16	10	233	6	116
Laughlin 2010 TRIUMPH-1	0.35 (0.01, 8.45)	4.80	0	115	1	120
pson 2012 FREEDOM-C	0.34 (0.01, 8.22)	4.79	0	174	1	176
cLaughlin 2006 STEP	(Excluded)	0.00	0	34 19	0	33 21
eper 2006 COMBI btotal (I-squared = 0.0%, p = 0.819)	(Excluded) 0.87 (0.43, 1.75)	0.00 100.00	0	19	v	21
IV/SC Prostanoids vs placebo			-		-	
nonneau 2002	1.01 (0.36, 2.84) 0.36 (0.04, 3.00)	32.02 11.49	7	233 11	7 3	236 12
emath 2010	0.28 (0.08, 1.01)	24.50	3	30	5	14
rst 1996	0.06 (0.00, 0.96)	6.92	0	41	8	40
desch 2000	0.79 (0.22, 2.77)	25.07	4	56	5	55
:Laughlin 2003 btotal (I-squared = 27.8%, p = 0.236)	(Excluded) 0.51 (0.23, 1.10)	0.00 100.00	0	15	0	9
Riociguat vs placebo	0.00 (0.00 4.05)	400.00		054		400
Initiation of the second secon	0.33 (0.06, 1.95) (Excluded)	100.00 0.00	2	254 12	3 0	126 6
btotal (I-squared = .%, p = .)	0.33 (0.06, 1.95)	100.00	U	12	U	0
Selexipag vs Placebo	4 59 /0 99 0 90	100.00	28	574	49	690
bon 2015 GRIPHON	1.58 (0.88, 2.82) (Excluded)	100.00 0.00	28 0	574 33	18 0	582 10
bitotal (I-squared = .%, p = .)	1.58 (0.88, 2.82)	100.00	v	55	Ū	10
ERA vs PDE5i lie 2015 AMBITION	0.32 (0.07, 1.56)	71.32	2	126	6	121
Ikins 2005 SERAPH	- 2.60 (0.12, 58.48)	28.68	1	14	0	12
biotal (I-squared = 27.7%, p = 0.239)	0.58 (0.09, 3.74)	100.00			-	
ERA + PDE5i vs PDE5i lie 2015 AMBITION	0.72 (0.26, 1.97)	100.00	9	253	6	121
btotal (I-squared = .%, p = .)	0.72 (0.26, 1.97)	100.00	3	200		121
ERA + PDESi vs ERA	2.08 (0.46, 9.48)	100.00	9	253	2	126
bitotal (I-squared = .%, p = .)	2.08 (0.46, 9.48) 2.08 (0.46, 9.48)	100.00	э	253	2	120

Favors intervention Favors control

e-Figure 6. Results of Direct Meta-Analysis for Improvement in Functional Class

Study D	RR (95% CI)	% Weight	Active Events	Active N	Control events	Control N
ERA vs placebo						
Galie 2008 ARIES 2	1.78 (0.92, 3.44)	10.51	19	63	11	65
Rubin 2002 BREATHE-1	1.37 (0.91, 2.05)	20.91	60	144	21	69
Pulido 2013 SERAPHIN	1.71 (1.15, 2.56)	21.17	53	242	32	250
Channick 2001	4.71 (0.68, 32.57)	1.47	9	21	1	11
Galie 2008 ARIES 1	2.44 (1.52, 3.91)	17.14	39	67	16	67
Galie 2008 EARLY	1.19 (0.38, 3.75)	3.94	6	93	5	92
McLaughlin 2015 COMPASS-2	0.98 (0.60, 1.61)	16.12	25	159	28	175
Humbert 2004 BREATHE-2	1.30 (0.62, 2.71)	8.74	13	22	5	11
Subtotal (I-squared = 24.3%, p = 0.236)	• 1.50 (0.02, 2.77) • 1.56 (1.23, 1.97)	100.00	15	22	5	
PDE5i vs placebo						
Galie 2009 PHIRST	1.10 (0.61, 1.98)	35.64	18	79	17	82
Galie 2005 SUPER	3.86 (1.53, 9.74)	23.42	19	69	5	70
Zhuang 2014	1.39 (0.87, 2.21)	40.94	26	60	20	64
Subtotal (I-squared = 62.2%, p = 0.071)	1.62 (0.90, 2.94)	100.00				
PO/INH Prostanoids vs placebo						
AcLaughlin 2006 STEP	5.34 (1.28, 22.27)	23.03	11	34	2	33
Dischewski 2002 AIR	3.00 (1.04, 8.68)	30.79	12	51	4	51
Tapson 2012 FREEDOM-C	► 1.21 (0.75, 1.94)	46.18	31	174	26	176
Subtotal (I-squared = 63.9%, p = 0.063)	2.25 (0.90, 5.60)	100.00				
IV/SC Prostanoids vs placebo						
Barst 1996	15.61 (2.17, 112.24)	21.07	16	41	1	40
Hiremath 2010	2.33 (0.80, 6.77)	34.39	15	30	3	14
Badesch 2000	42.25 (2.62, 680.61)	13.70	21	56	õ	55
Rubin 1990	5.45 (1.52, 19.60)	30.84	10	11	2	12
Subtotal (I-squared = 56.8%, p = 0.074)	6.73 (1.98, 22.90)	100.00	10		2	12
Riociguat vs placebo						
Ghofrani 2013 PATENT 1	← 1.46 (0.89, 2.38)	95.23	53	254	18	126
Galie 2015 PATENT PLUS	1.40 (0.89, 2.38)	4.77	2	12	10	6
			2	12	1	0
Subtotal (I-squared = 0.0%, p = 0.741)	1 .43 (0.89, 2.31)	100.00				
Selexipag vs Placebo		07.04				
Sitbon 2015 GRIPHON	 1.55 (1.10, 2.19) 	97.21	75	574	48	571
Simonneau 2012	1.52 (0.20, 11.50)	2.79	5	33	1	10
Subtotal (I-squared = 0.0%, p = 0.981)	• 1.55 (1.11, 2.18)	100.00				
ERA + PDE5i vs ERA	_					
Galie 2015 AMBITION	1.11 (0.83, 1.50)	100.00	94	253	42	126
Subtotal (I-squared = .%, p = .)	1.11 (0.83, 1.50)	100.00				
ERA vs PDE5i	_					
Galie 2015 AMBITION	1.03 (0.72, 1.48)	100.00	42	126	39	121
Subtotal (I-squared = .%, p = .)	1.03 (0.72, 1.48)	100.00				
ERA + PDE5i vs PDE5i	_					
Galie 2015 AMBITION	1.15 (0.85, 1.56)	100.00	94	253	39	121
	1.15 (0.85, 1.56)	100.00				
.01 .1 1	1 I 10 100					

Favors control Favors intervention

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e-Figure 7. Results of Direct Meta-Analysis for Improvement in 6MWD. The red line represents the minimal clinically important difference (MCID) of 33 m.

tudy)	WMD (95% CI)	% Weight	Active, N	mean change	Active, SD	Control, N	Control, mean change	Control, SD
ERA vs placebo								
hannick 2001	75.90 (0.74, 151.06)	1.25	21	70.1	56.2	11	-5.8	120.5
alie 2008 EARLY	19.10 (-3.19, 41.39)	14.26	93	11.2	74.76	92	-7.9	79.82
alie 2008 ARIES 1	41.00 (14.87, 67.13)	10.38	67	33.2	75.37	67	-7.8	78.9
alie 2008 ARIES 2	45.80 (15.63, 75.97)	7.79	63	35.7	79.99	65	-10.1	93.8
IdLaughlin 2015 COMPASS-2	21.80 (6.08, 37.52)	28.68	159	7.2	66	175	-14.6	80.4
ulido 2013 SERAPHIN	21.90 (5.58, 38.22)	26.62	242	12.5	83.54	250	-9.4	100.59
ubin 2002 BREATHE-1	44.20 (18.84, 69.56)	11.02	144	36.4	69.5	69	-7.8	96.1
ubtotal (I-squared = 18.1%, p = 0.307)	28.45 (20.03, 36.87)	100.00						
- PDE5i vs placebo								
alie 2005 SUPER	39.60 (8.40, 70.80)	8.51	69	41	132	70	1.4	7.7
alie 2009 PHIRST	22.40 (9.68, 35.12)	51.18	79	31.9	14	82	9.5	57
immoneau 2008 PACES	28.80 (12.36, 45.24)	30.63	133	29.8	67.1	123	1	67
huang 2014	36.10 (6.86, 65.34)	9.68	60	54.4	98.602994	64	18.3	62.244898
ubtotal (I-squared = 0.0%, p = 0.872)	27.15 (18.05, 36.25)	100.00						
- PO/INH Prostanoids vs placebo								
oeper 2006 COMBI	-10.00 (-56.42, 36.42)	2.09	19	-9	100	21	1	27
IcLaughlin 2006 STEP	26.00 (-2.98, 54.98)	5.36	34	30	60	33	4	61
IdLaughlin 2010 TRIUMPH-1	18.60 (7.26, 29.94)	35.03	115	21.6	45.925926	120	3	42.592593
Idlaughlin 2000 TRIUMPH-1 apson 2012 FREEDOM-C ubtotal (I-squared = 5.7%, p = 0.385)	9.70 (0.85, 18.55)	57.52	174	14.5	42.222222	176	4.8	42.222222
ubtotal (I-squared = 5.7%, p = 0.365)	13.28 (6.57, 19.99)	100.00						
IV/SC Prostanoids vs placebo								
adesch 2000	94.00 (31.60, 156.40)	1.10	56	46	167.7	55	-48	167.7
arst 1996	47.00 (37.96, 56.04)	52.54	41	32	17.5	40	-15	23.5
iremath 2010	92.70 (8.82, 176.58)	0.61	30	67.2	124.2	14	-25.5	135.8
IcLaughlin 2003	43.00 (-21.20, 107.20)	1.04	15	37	65.84	9	-6	84
ubin 1990	45.00 (-46.94, 136.94)	0.51	11	132	131.23	12	87	87.3
imonneau 2002	10.00 (0.14, 19.86)	44.19	233	10	52.59	236	0	56.29
ubtotal (I-squared = 86.0%, p = 0.000)	31.39 (24.84, 37.95)	100.00						
- Riociguat vs placebo								
alie 2015 PATENT PLUS	-23.00 (-75.40, 29.40)	9.59	12	7	48	6	30	56
hofrani 2013 PATENT 1	 36.00 (18.93, 53.07) 	90.41	254	30	66	126	-6	86
ubtotal (I-squared = 77.3%, p = 0.038)	30.34 (14.11, 46.57)	100.00						
- Selexipag vs Placebo								
imonneau 2012	24.30 (-8.74, 57.34)	12.23	33	24.7	76.87	10	.4	32.41
itbon 2015 GRIPHON ubtotal (I-squared = 0.0%, p = 0.530)	13.00 (0.67, 25.33)	87.77	574	4	106.96	582	-9	106.96
ubtotal (I-squared = 0.0%, p = 0.530)	14.38 (2.83, 25.94)	100.00						
- ERA + PDE5i vs ERA								
alie 2015 AMBITION ubtotal (I-squared = .%, p = .)	21.90 (9.47, 34.33)	100.00	253	48.9	60.08	126	27	57.2
ubtotal (I-squared = .%, p = .)	21.90 (9.47, 34.33)	100.00						
- ERA vs PDE5i								
alie 2015 AMBITION	-4.30 (-18.30, 9.70)	93.59	126	22.7	55	121	27	57.2
/ilkins 2005 SERAPH	55.00 (1.48, 108.52)	6.41	14	114	84.62	12	59	53.021963
ubtotal (I-squared = 77.3%, p = 0.038)	-0.50 (-14.05, 13.05)	100.00						
ERA + PDE5i vs PDE5i								
alie 2015 AMBITION	26.20 (13.92, 38.48)	100.00	253	48.9	60.08	121	22.7	55
alie 2015 AMBITION ubtotal (I-squared = .%, p = .)	26.20 (13.92, 38.48)	100.00						
	- · · · •							

-50 -25 0 25 50

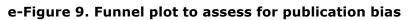
Decreased 6MWD Improved 6MWD

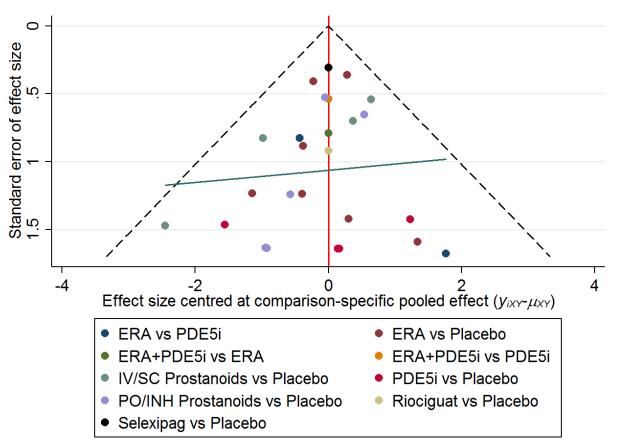
e-Figure 8. Results of Direct Meta-Analysis for adverse events leading to drug discontinuation

Puido 2013 SERAPHINE I 0.87 (0.53, 1.41) 33.40 20 2.22 31 2.52 Channik 2001 Statustal Insurance 38.39%, p = 0.162) 0.80 (0.32, 2.48) 13.58 9 14.4 56 Channik 2001 Statustal Insurance 38.39%, p = 0.162) 0.80 (0.32, 2.48) 13.58 9 14.4 56 Simonosau 2008 PACES 0.60 (0.25, 1.40) 0.00 0 2.1 0 11 Subtosli Insurance 31 0.61 (0.25, 1.40) 40.16 7 7.9 12 2.82 Simonosau 2008 PACES 7.46 (0.32, 1.44) 0.40 (0.25, 1.44) 0.40 (0.25, 1.44) 0.41 (0.25, 1.44) 0	Study ID		RR (95% CI)	% Weight	Active Events	Active N	Control events	Control N
Jale 2016 (DARLY 0.99 (39, 2.2) 10.18 8 93 8 92 1 McLaughing 2014 (COMPASC) 1.94 (120, 3.12) 34.18 33 199 2.2 17 McLaughing 2014 (COMPASC) 1.94 (120, 3.12) 34.18 33 199 2.2 17 McLaughing 2014 (COMPASC) 1.94 (120, 3.12) 34.18 30 199 2.2 17 Daming 2014 (200, 34.02) 0.07 (0.33, 140) 10.00 0.00 21 0 0 Daming 2014 (200, 34.02) 0.07 (0.33, 140) 100.00 0 21 0 0 - FOEH vs placed - Sant 2004 PHRCE Subtled (Isquared = 30.38, p = 0.213) -	ERA vs placebo							
Humber 2004 BREATHE-2 0.50 (0.3, 7.26) 2.66 1 22 1 11 Hundbarghin 2015 (CMPARS-2) 0.87 (0.53, 1.41) 33.44 20 24.2 31 22.6 Hundbarghin 2015 (CMPARS-2) 0.87 (0.53, 1.41) 33.44 20 24.2 31 22.6 1 1.6 (0.73, 1.20) 34.16 39 159 22 17 Hundbarghin 2015 (CMPARS-2) 0.87 (0.53, 1.41) 33.44 20 24.2 31 22.6 Hundbarghin 2015 (FMEALS-2) 0.87 (0.25, 1.40) 100.00 0 21 0 11 Baladoo Finite 3.33 (0.14 77.44) 7.46 7 12 23 11 19 0 22.3 31 11 Magaghin 2015 TRUMPH-1 3.33 (0.14 77.440) 2.32 1 15			0.99 (0.39, 2.52)	16 18	8	93	8	92
Mdaughin 2019 (COMPASS_2) 194 (120, 3.12) 34.18 39 199 22 17. Mula 2013 EREATHEL 0.86 (0.30, 2.48) 13.84 9 144 8 09 Databasi 0.75 (0.53, 1.41) 33.40 2.84 13.84 9 144 8 09 Databasi 0.75 (0.53, 1.41) 33.40 2.75 1.9 1.14 8 09 Databasi 0.00 0.21 0.00 0 1 1.15 0.73, 1.80) 100.00 11 Databasis 0.56 (0.21, 1.49) 46.40 7 7.9 12 82.2 2.3 3 11 Subtasis 1.9 0.56 (0.21, 1.49) 4.6.40 7 1.9 0.60 0.67 (0.23, 1.41) 1.4 1.3 1.4 1.3 1.5 1.4 1.3 1.4 1.3 1.4 1.3 1.4 1.3 1.4 1.3 1.4 1.3 1.4 1.3 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>								
Puido 2013 SERAPHINI M 0.07 (0.53, 1.41) 33.40 20 2.22 31 2.52 Delin 2020 SERAPHIE 1 0.80 (0.32, 2.48) 13.58 9 14.4 6 66 Channel 2001 SeraPhie 1 0.80 (0.32, 2.48) 13.58 9 14.4 6 66 Channel 2005 PACES 0.80 (0.23, 1.40) 0.00 0 2.1 0 11 Subtosl (1.4yuared = 3.5 Mp, p = 0.213) 0.61 (0.25, 1.40) 40.18 7 7.45 3 60 0 64 Subtosl (1.4yuared = 3.5 Mp, p = 0.213) 0.67 (0.23, 1.54) 0.000 0 2.30 1 15 0 2.1 14 0.33 0.14 14 13 13 14 14 13 14 14 13 14 14 13 14 14 14 14 13 13 13 14 14 13 14 14 13 14 14 13 13 13 13 14 14 14 14 13 13 13 14 14 14 14 14 14 <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>174</td></t<>								174
Dubin 2002 BTEATHE:1 0.80 (b 30, 2.46) 13.88 9 144 5 68 Definition 0.80 (b 30, 2.46) 1.80 (b 10, 2.46) 0.00 0 0.01 0 11 PDEDI to placebo - - 0.61 (b 25, 1.40) 46.16 7 79 1.2 2.8 PDEDI to placebo - 0.61 (b 25, 1.40) 46.40 7 134 1.4 3.2 PDIMI Potabodis va placebo - 0.61 (b 25, 1.40) 1.00 (b 0.00 -								
Channel 2001 (Excudeed) 0.00 0 21 0 11 Integration of the please								
Subtrail (hypuned = 38 9%, p = 0.102) 1.15 (0.72, 1.80) 100.00 PDEI vp plasbo Simmonsau 208 PACES 0.01 (0.25, 1.46) 46.16 7 79 12 52 Simmonsau 208 PACES 0.01 (0.25, 1.46) 46.16 7 79 12 52 Simmonsau 208 PACES 0.01 (0.25, 1.46) 46.16 7 79 12 52 Simmonsau 208 PACES 0.07 (0.23, 1.54) 100.00 - - - POINT Protonois vs ploxbo -								
→ DDESi vs plaxabo Gale 2009 PHIRST 0.61 (0.25, 1.46) 40.16 7 79 12 62 Simmoneau 2008 PACES 0.61 (0.25, 1.46) 40.16 7 79 12 62 Simmoneau 2008 PACES 7.46 (0.38, 14.46) 7.45 3 60 0 64 Distribution (insyname* = 55.3%, p = 0.213)					0	21	0	11
Jaile 2008 PHIRST 0.61 (0.25, 1.46) 40.16 7 79 12 62 Strimonesu 2008 PACES 0.50 (0.21, 1.19) 46.40 7 134 14 132 Chang 2014 0.746 (0.33, 14.44) 7.45 3 60 0 64 Decomposition 2008 COMBI 0.746 (0.33, 14.44) 7.46 (0.33, 14.44) 7.45 3 60 0 64 Decomposition 2008 COMBI 0.76 (0.28, 1.54) 100.00 1 19 0 21 Decomposition 2008 STEP 0.57 (0.60, 1.488) 3.04 1 14 13 3 Data 2008 COMBI 3.20 (0.14, 70.46) 2.30 1 19 0 21 Distribution 2008 STEP 0.57 (0.06, 1.488) 3.04 1 3.16 1 1 3 17 Distribution 2008 STEP 3.10 (1.47, 7.246) 3.26 17.4 8 17 15 17 18 10.00 0 1 17 13 17 17 100.00 17 17 10 17 13 17 17 10 17 14	Subtotal (I-squared = 38.9%, p = 0.162)	•	1.15 (0.73, 1.80)	100.00				
Simonosis 2008 PACES Zhuang 2014 Zhuang 2014 Subball (Isquared - 93.83, p. e 0.213) 	PDE5i vs placebo							
Zhuang 2014 Zhuang 2014 Zhuang 2014 Chornel 25.3%, p = 0.213) 	Galie 2009 PHIRST		0.61 (0.25, 1.46)	46.16	7	79	12	82
Zhuang 2014 Zhuang 2014 Zhuang 2014 Chornel 25.3%, p = 0.213) 	Simmoneau 2008 PACES		0.50 (0.21, 1.19)	46.40	7	134	14	133
Subbial (laquared = 35.3%, p = 0.213) 0.67 (0.25, 1.54) 100.00				7.45				
Hoeper 2000 COMBI 3.30 (014, 76, 464) 2.30 1 19 0 211 Jing 2013 FREEDOM-M 3.82 (1.17, 12.46) 16.22 2.32 233 3 111 Malaughin 2008 STEP 3.82 (1.17, 12.46) 16.22 2.32 233 3 111 Malaughin 2015 TRUMPH-1 3.82 (1.17, 12.46) 16.22 2.32 233 3 111 Tapson 2013 FREEDOM-C2 3.61 (1.47, 6.81) 38.43 2.5 174 8 175 5 165 Subtotal (Lsquared = 0.0%, p = 0.901) 2.99 (1.8.4, 4.77) 100.00 1 40 0.22 (0.0.2, 2.36) 12.65 14 0.40 0.02 16.63 1 41 0 40 Subtotal (Lsquared = 51.8%, p = 0.081) 18.23 (2.46, 138.46) 2.842 18 12 6 6 Subtotal (Lsquared = 51.8%, p = 0.081) 1.82 (0.08, 34.86) 8.39 1 12 0 6 Subtotal (Lsquared = 51.8%, p = 0.081) 1.62 (0.08, 34.86) 8.39 1 12 0				100.00	-		-	
Hoeper 2000 COMBI 3.30 (014, 76, 464) 2.30 1 19 0 211 Jing 2013 FREEDOM-M 3.82 (1.17, 12.46) 16.22 2.32 233 3 111 Malaughin 2008 STEP 3.82 (1.17, 12.46) 16.22 2.32 233 3 111 Malaughin 2015 TRUMPH-1 3.82 (1.17, 12.46) 16.22 2.32 233 3 111 Tapson 2013 FREEDOM-C2 3.61 (1.47, 6.81) 38.43 2.5 174 8 175 5 165 Subtotal (Lsquared = 0.0%, p = 0.901) 2.99 (1.8.4, 4.77) 100.00 1 40 0.22 (0.0.2, 2.36) 12.65 14 0.40 0.02 16.63 1 41 0 40 Subtotal (Lsquared = 51.8%, p = 0.081) 18.23 (2.46, 138.46) 2.842 18 12 6 6 Subtotal (Lsquared = 51.8%, p = 0.081) 1.82 (0.08, 34.86) 8.39 1 12 0 6 Subtotal (Lsquared = 51.8%, p = 0.081) 1.62 (0.08, 34.86) 8.39 1 12 0								
Jing 2013 FREEDOM-M McLaughin 2006 STEP 3.82 (1.7, 12, 45) 16, 22 2.3 3 111 McLaughin 2006 STEP 3.82 (1.7, 12, 48) 3.44 1 34 1 33 McLaughin 2010 TRIUMPH-1 1.83 (0.55, 6.07) 16, 70 7 115 4 122 Tapson 2013 FREEDOM-C2 1.83 (0.48, 921) 24.32 18 167 5 16 Tapson 2013 FREEDOM-C3 3.16 (1.47, 0.81) 38.43 25 174 8 177 UNSC Protanoids to placebo 2.93 (0.12, 69.83) 16.63 1 41 0 40 McLaughin 2003 2.93 (0.12, 69.83) 16.63 1 41 0 40 McLaughin 2003 2.93 (0.12, 69.83) 16.63 1 41 0 40 Simoneau 2002 2.82 (0.16, 72.36) 17.52 1 10 12 5 Subtal (J-squared = 51.8%, p = 0.081) 2.70 (0.49, 14.82) 100.00 1 2.73 (0.49, 14.82) 100.00 1 2.73 (0.49, 14.82) 100.00 1 1.82 (2.45, 138.40) 8.39 1 1.2 0 6		i	2 20 (0 14 78 48)	2 20	1	19	0	21
McLaughin 2006 STEP 0.97 (00, 14.88) 3.04 1 34 1 33 McLaughin 2010 FRUMPH-1 1.83 (0.56, 0.07) 15.70 7 115 4 12 Tapon 2012 FREEDOM-C2 3.51 (1.34, 9.21) 24.32 18 157 5 167 Subtal (1-squared = 0.0%, p = 0.501) 2.90 (1.8, 4.77) 100.00 1 4 0 40 McLaughin 2010 2.93 (0.12, 69.83) 16, 63 1 41 0 40 McLaughin 2003 2.35 (1.1, 68.1) 3.84, 135 2 15 2 14 McLaughin 2003 2.39 (0.12, 69.83) 16, 63 1 41 0 40 McLaughin 2003 2.31 (0.17, 78, 88.3) 18, 15 2 15 23 1 23 Subtal (1-squared = 51.8%, p = 0.081) 2.70 (0.43, 14.82) 0.00 0 55 50 55 50 12 23 1 23 12 0 6 6 55 55 1 57 41 57 57 41 57 57 41 57 57 57<								
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Tapon 2015 FREEDON-C2 3.5 (1 (3.4, 9.21) 24.32 18 167 5 15 Tapon 2015 FREEDON-C2 3.5 (1 (3.4, 9.21) 24.32 18 167 5 15 Subtotal (L-quared = 0.0%, p = 0.901) 2.90 (18.4, 4.77) 100.00 7 8 17/		Ť						
Tapban 2012 FREEDONC 38.43 25 174 8 177 Subtotal (I-squared = 0.096, p = 0.901) 2.96 (1.8.4, 4.77) 100.00 100.00 100.00 Divisor 1996 2.93 (0.12, 68.83) 16.63 1 41 0 40 Malaughin 2003 2.93 (0.12, 68.83) 18.15 2 15 0 9 Simmoneau 2002 3.13 (0.17, 58.63) 18.15 2 16 0 9 Simmoneau 2002 3.23 (0.15, 72.30) 17.05 1 10 12 9 Simmoneau 2002 3.23 (0.17, 75.63) 18.15 2 16 0 9 12 233 1 223 1 223 1 223 1 10 12 10 12 10 12 10 12 10 12 10 10 12 10 10 12 0 6 0 55 11 11 12 0 6 0 55 16 10 10 12 0 6 0 15 2 10 10 10								120
Subtotal (I-squared = 0.0%, p = 0.901) 	Tapson 2013 FREEDOM-C2		3.51 (1.34, 9.21)	24.32	18	157	5	153
Subtotal (I-squared = 0.0%, p = 0.901) 	Tapson 2012 FREEDOM-C		3.16 (1.47, 6.81)	38.43	25	174	8	176
Barst 1996 Hirmants 2010 Hirmants 2010 Rubin 1990 Shimonesu 2002 Badesol 2000 Understand Particle State Stat				100.00				
Barst 1996 Hirmants 2010 Hirmants 2010 Rubin 1990 Shimonesu 2002 Badesol 2000 Understand Particle State Stat	IV/SC Prostanoids vs placebo							
Hiremath 2010 0.23 (0.02, 2.39) 22.76 1 30 2 14 MdLaughlin 2003 3.13 (0.17, 58.63) 18.15 2 15 0 9 Simmonesu 2002 Badesch 2000 18.23 (2.6, 13, 5.46) 2.6.42 18 233 1 233 Subtal (!squared = 51.8%, p = 0.081) - <			2 93 (0 12 69 83)	16.63	1	41	0	40
McLauphin 2003 McLauphin 2003 Rubin 1990 31.13 (0.17, 58, 63) 32.5 (0.15, 72.38) 32.5 (0.15, 72.38) 32.5 (0.15, 72.38) 17.05 1 11 0 12 33.25 (0.15, 72.38) 17.05 1 11 0 12 33.25 (0.15, 72.38) 17.05 1 11 0 12 33.25 (0.15, 72.38) 17.05 1 11 0 0.12 33.25 (0.15, 72.38) 17.05 1 11 0 0.12 33.25 (0.15, 72.38) 18.15 2 15 0 9 3.25 (0.15, 72.38) 17.05 1 11 0 0 12 33.25 (0.15, 72.38) 10.000 0 56 0 55 0.00 0 56 0 65 0.00 0 56 0.00 0 57 1.00 0.00 12 0.00 0 12 0.00 0 14 126 14 122 0.96 (0.48, 1.93) 100.00 14 126								
Rubin 1990 3.25 (0.15, 72.36) 17.05 1 11 0 12 Simmoneau 2002 18.23 (2.45, 135.46) 25.42 18 233 1 233 Subtotal (Isquared = 51.8%, p = 0.081) <								
Simmoneau 2002 Badesoh 2000 U								
Badesch 2000 (Excluded) 0.00 0 56 0 55 Subtotal (I-squared = 51.8%, p = 0.081) 2.70 (0.49, 14.82) 100.00 0 56 0 55								
Subtotal (I-squared = 51.8%, p = 0.081) 2.70 (0.49, 14.82) 100.00	Simmoneau 2002		18.23 (2.45, 135.46)	25.42	18	233	1	236
	Badesch 2000	_	(Excluded)	0.00	0	56	0	55
Galie 2015 PATENT PLUS 1.62 (0.08, 34.66) 8.39 1 12 0 6 Ghofrani 2013 PATENT 1 0.44 (0.17, 1.12) 91.61 8 254 9 126 0.49 (0.20, 1.20) 100.00 100.00 127 128 <t< td=""><td>Subtotal (I-squared = 51.8%, p = 0.081)</td><td></td><td>2.70 (0.49, 14.82)</td><td>100.00</td><td></td><td></td><td></td><td></td></t<>	Subtotal (I-squared = 51.8%, p = 0.081)		2.70 (0.49, 14.82)	100.00				
Galie 2015 PATENT PLUS 1.62 (0.08, 34.66) 8.39 1 12 0 6 Ghofrani 2013 PATENT 1 0.44 (0.17, 1.12) 91.61 8 254 9 126 0.49 (0.20, 1.20) 100.00 100.00 127 128 <t< td=""><td> Riociquat vs placebo</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	Riociquat vs placebo							
Ghofrani 2013 PATENT 1 0.44 (0.17, 1.12) 91.61 8 254 9 124 Subtotal (I-squared = 0.0%, p = 0.426) 0.49 (0.20, 1.20) 100.00<			1 62 (0 08 34 66)	8.39	1	12	0	6
Subtotal (I-squared = 0.0%, p = 0.428) 								126
					•	204	5	120
Sitbon 2015 GRIPHON 2.01 (1.40, 2.87) 100.00 82 575 41 575 Subtotal (I-squared = .%, p = .) 2.01 (1.40, 2.87) 100.00 31 253 14 126 ····································	Subtotal (I-squared = 0.0%, p = 0.420)	4	0.49 (0.20, 1.20)	100.00				
Subtotal (I-squared = .%, p = .) . ERA + PDE5i vs ERA Galie 2015 AMBITION 								
					82	5/5	41	577
Galie 2015 AMBITION 1.10 (0.61, 2.00) 100.00 31 253 14 120 Subtotal (l-squared = .%, p = .) 1.10 (0.61, 2.00) 100.00	Subtotal (I-squared = .%, p = .)	♥	2.01 (1.40, 2.87)	100.00				
Subtotal (I-squared = .%, p = .) 		<u> </u>						
					31	253	14	126
Galie 2015 AMBITION 0.96 (0.48, 1.93) 100.00 14 126 14 12' Wilkins 2005 SERAPH (Excluded) 0.00 0 14 0 12' Subtotal (I-squared = .%, p = .) 0.96 (0.48, 1.93) 100.00 14 0 12' Galie 2015 AMBITION 1.06 (0.59, 1.92) 100.00 31 253 14 12'	Subtotal (I-squared = .%, p = .)		1.10 (0.61, 2.00)	100.00				
Wilkins 2005 SERAPH (Excluded) 0.00 0 14 0 12 Subtotal (I-squared = .%, p = .) 0.96 (0.48, 1.93) 100.00 100.00 14 0 12	ERA vs PDE5i							
Wilkins 2005 SERAPH (Excluded) 0.00 0 14 0 12 Subtotal (I-squared = .%, p = .) 0.96 (0.48, 1.93) 100.00 100.00 14 0 12	Galie 2015 AMBITION		0.96 (0.48, 1.93)	100.00	14	126	14	121
Subtotal (I-squared = .%, p = .) 0.96 (0.48, 1.93) 100.00 				0.00				
Galie 2015 AMBITION 1.06 (0.59, 1.92) 100.00 31 253 14 12		\diamond			-		-	
Galie 2015 AMBITION 1.06 (0.59, 1.92) 100.00 31 253 14 12	ERA + PDE5i vs PDE5i							
			1.08 (0.59, 1.92)	100.00	31	252	14	101
					31	205	14	121
Subiotai (i-squared = .76, p = .) 1.06 (0.59, 1.92) 100.00	Subtotal (I-squared = .%, p = .)	Υ .	1.06 (0.59, 1.92)	100.00				

Favors intervention Favors control

Section 2 CHEST[®] Online Supplement





Funnel plot of trials of pulmonary arterial hypertension (mortality outcome since all trial reported this outcome). There is no evidence for funnel plot asymmetry, however, number of pairwise treatments for each comparison is small.

References:

- 1. Fukumoto Y, Yamada N, Matsubara H, et al. Double-blind, placebo-controlled clinical trial with a rho-kinase inhibitor in pulmonary arterial hypertension. *Circ J.* 2013;77(10):2619-2625.
- 2. Hoeper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. *Circulation*. 2013;127(10):1128-1138.
- 3. Sandoval J, Torbicki A, Souza R, et al. Safety and efficacy of sitaxsentan 50 and 100 mg in patients with pulmonary arterial hypertension. *Pulm Pharmacol Ther.* 2012;25(1):33-39.
- 4. Zeng WJ, Xiong CM, Zhao L, et al. Atorvastatin in pulmonary arterial hypertension (APATH) study. *Eur Respir J.* 2012;40(1):67-74.
- 5. Kawut SM, Bagiella E, Lederer DJ, et al. Randomized clinical trial of aspirin and simvastatin for pulmonary arterial hypertension: ASA-STAT. *Circulation.* 2011;123(25):2985-2993.
- 6. Ghofrani HA, Morrell NW, Hoeper MM, et al. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. *Am J Respir Crit Care Med.* 2010;182(9):1171-1177.
- 7. Wang XX, Zhang FR, Shang YP, et al. Transplantation of autologous endothelial progenitor cells may be beneficial in patients with idiopathic pulmonary arterial hypertension: a pilot randomized controlled trial. *J Am Coll Cardiol.* 2007;49(14):1566-1571.
- 8. Barst RJ, Langleben D, Badesch D, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol.* 2006;47(10):2049-2056.
- 9. Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2004;169(4):441-447.
- 10. Barst RJ, McGoon M, McLaughlin V, et al. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol.* 2003;41(12):2119-2125.
- 11. Galie N, Humbert M, Vachiery JL, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol.* 2002;39(9):1496-1502.
- 12. Wilkins MR, Ali O, Bradlow W, et al. Simvastatin as a treatment for pulmonary hypertension trial. *Am J Respir Crit Care Med.* 2010;181(10):1106-1113.
- 13. Cha KS, Cho KI, Seo JS, et al. Effects of inhaled iloprost on exercise capacity, quality of life, and cardiac function in patients with pulmonary arterial hypertension secondary to congenital heart disease (the Eisenmenger syndrome) (from the EIGER Study). *Am J Cardiol.* 2013;112(11):1834-1839.
- 14. Kaya MG, Lam YY, Erer B, et al. Long-term effect of bosentan therapy on cardiac function and symptomatic benefits in adult patients with Eisenmenger syndrome. *J Card Fail.* 2012;18(5):379-384.
- 15. Mukhopadhyay S, Nathani S, Yusuf J, Shrimal D, Tyagi S. Clinical efficacy of phosphodiesterase-5 inhibitor tadalafil in Eisenmenger syndrome--a randomized, placebo-controlled, double-blind crossover study. *Congenit Heart Dis.* 2011;6(5):424-431.
- 16. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Sondergaard L. Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. *Eur Heart J.* 2010;31(9):1124-1131.
- 17. Bharani A, Patel A, Saraf J, Jain A, Mehrotra S, Lunia B. Efficacy and safety of PDE-5 inhibitor tadalafil in pulmonary arterial hypertension. *Indian Heart J.* 2007;59(4):323-328.
- Chau EM, Fan KY, Chow WH. Effects of chronic sildenafil in patients with Eisenmenger syndrome versus idiopathic pulmonary arterial hypertension. *Int J Cardiol.* 2007;120(3):301-305.
- 19. Galie N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation*. 2006;114(1):48-54.

- 20. Van De Bruaene A, Jansen K, De Meester P, et al. Bosentan for mild pulmonary vascular disease in ASD patients (the BOMPA trial): a double-blind, randomized controlled, pilot trial. *Int J Cardiol.* 2013;168(5):5081-5082.
- 21. Barst RJ, Mubarak KK, Machado RF, et al. Exercise capacity and haemodynamics in patients with sickle cell disease with pulmonary hypertension treated with bosentan: results of the ASSET studies. *Br J Haematol.* 2010;149(3):426-435.
- 22. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, doseranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. *Circulation.* 2012;125(2):324-334.
- 23. Sun X, Wang K, Wang W, Li B. [Clinical study on sildenafil in treatment of pregnant women with pulmonary arterial hypertension]. *Zhonghua Fu Chan Ke Za Zhi.* 2014;49(6):414-418.
- 24. Badesch DB, Feldman J, Keogh A, et al. ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. *Cardiovasc Ther.* 2012;30(2):93-99.
- 25. Ghofrani HA, Wiedemann R, Rose F, et al. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med.* 2002;136(7):515-522.
- 26. Chin KM, Badesch DB, Robbins IM, et al. Two formulations of epoprostenol sodium in the treatment of pulmonary arterial hypertension: EPITOME-1 (epoprostenol for injection in pulmonary arterial hypertension), a phase IV, open-label, randomized study. *Am Heart J.* 2014;167(2):218-225 e211.
- 27. Channick RN, Olschewski H, Seeger W, Staub T, Voswinckel R, Rubin LJ. Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. *J Am Coll Cardiol.* 2006;48(7):1433-1437.
- 28. Rubenfire M, McLaughlin VV, Allen RP, et al. Transition from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension: a controlled trial. *Chest.* 2007;132(3):757-763.
- 29. White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Research Synthesis Methods.* 2012;3(2):111-125.
- 30. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods.* 2012;3(2):98-110.
- 31. White IR, Barrett JK, Jackson D, Higgins J. Consistency and inconsistency in network metaanalysis: model estimation using multivariate meta-regression. *Research Synthesis Methods.* 2012;3(2):111-125.
- 32. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol.* 2011;64(2):163-171.
- 33. Trinquart L, Attiche N, Bafeta A, Porcher R, Ravaud P. Uncertainty in Treatment Rankings: Reanalysis of Network Meta-analyses of Randomized Trials. *Ann Intern Med.* 2016;164(10):666-673.
- 34. Hoeper MM, McLaughlin VV, Dalaan AM, Satoh T, Galie N. Treatment of pulmonary hypertension. *Lancet Respir Med.* 2016.
- 35. Singh TP, Rohit M, Grover A, Malhotra S, Vijayvergiya R. A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. *Am Heart J.* 2006;151(4):851 e851-855.
- 36. Sastry BK, Narasimhan C, Reddy NK, Raju BS. Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. *J Am Coll Cardiol.* 2004;43(7):1149-1153.