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 utitlized (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.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present (Run on June 23, 2015, 3542 results. Rerun on March 2, 2016, 3653 Results)

#	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

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)
7. (tripl* near/1 blind*) or (tripl* near/1 mask*):ti,ab,kw (Word variations have been searched)
8. (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

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 treatments[1-12]. Eleven RCTs were excluded because they studied exclusively patients with Eisenmenger's syndrome[13-19], congenital heart disease[20], sickle cell disease[21] or included only children[22] or pregnant females[23] 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.

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

(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 (I^2: 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 PAH-related 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 (I^2: 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 (I^2: 0-64%). For the continuous outcome of 6MWD, most active agents were associated with significant improvements in 6MWD over placebo (I^2: 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

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) 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 ≥20% from the previous visit or ≥30% from the baseline visit, together with the initiation of a subcutaneous or inhaled prostanoid or use of open-label Bosentan.
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 ≥10% from baseline in two 6MWD done 2 weeks or more apart; or ≥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 ≥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].
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 (BREATHE-I)	All-cause death + lung transplantation + hospitalization for pulmonary hypertension + lack of clinical improvement or worsening leading to discontinuation + need for epoprostenol therapy + atrial septostomy
Channick, 2001	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 ≥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 ≥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 ≥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 6MWD 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 published before 2000 (B)		*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.

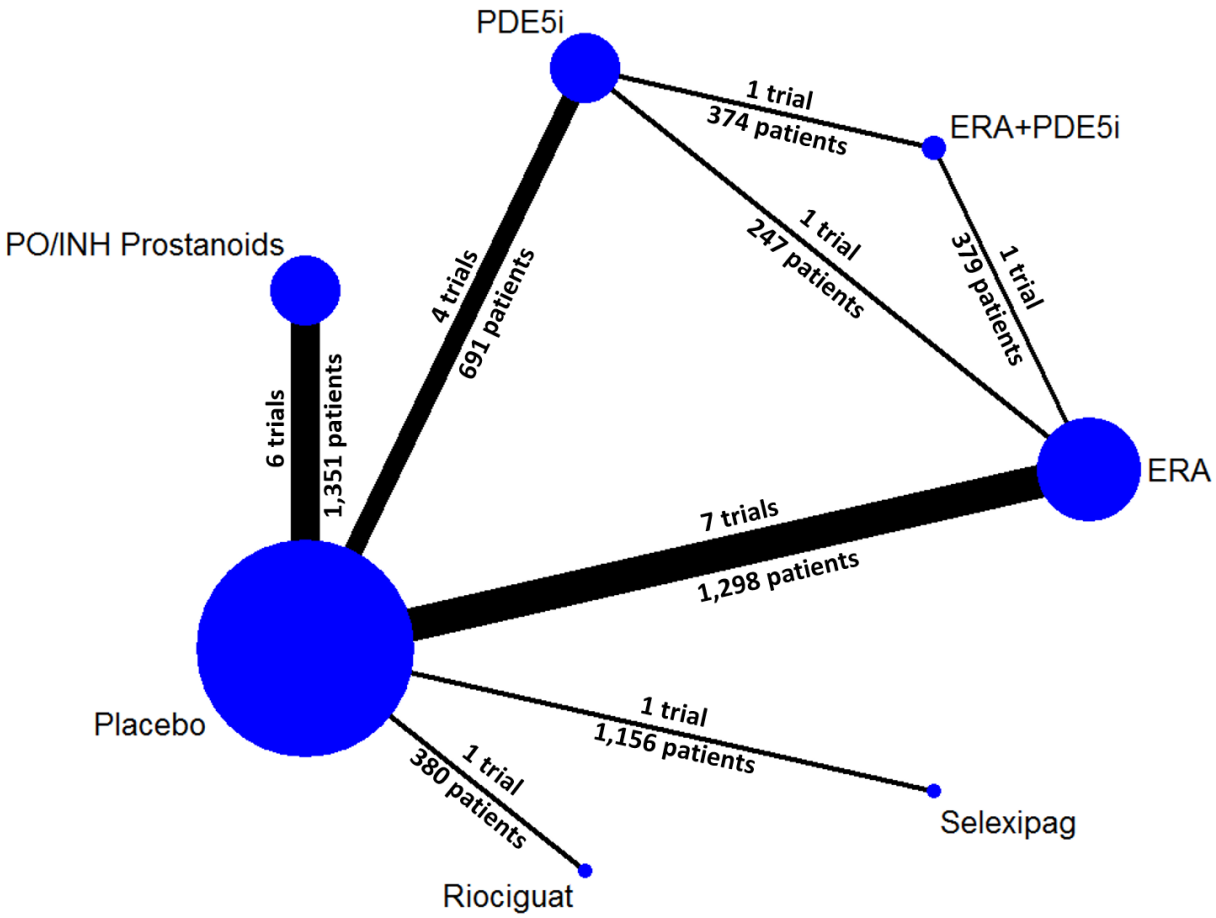
e-Table 6. GRADE quality of evidence derived From Direct and Indirect Estimates and Network Meta-Analysis Informing on Comparative Efficacy of Pharmacological Strategies.

Pharmacological Intervention	Direct- Functional Class	Direct- clinical worsening	Network- Functional Class	Network – Clinical worsening
Compared with Placebo				
ERA	Moderate (indirectness)	Moderate (indirectness)	Moderate	Moderate
PDE5i	Low (indirectness, imprecision)	Moderate (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 with ERA				
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)

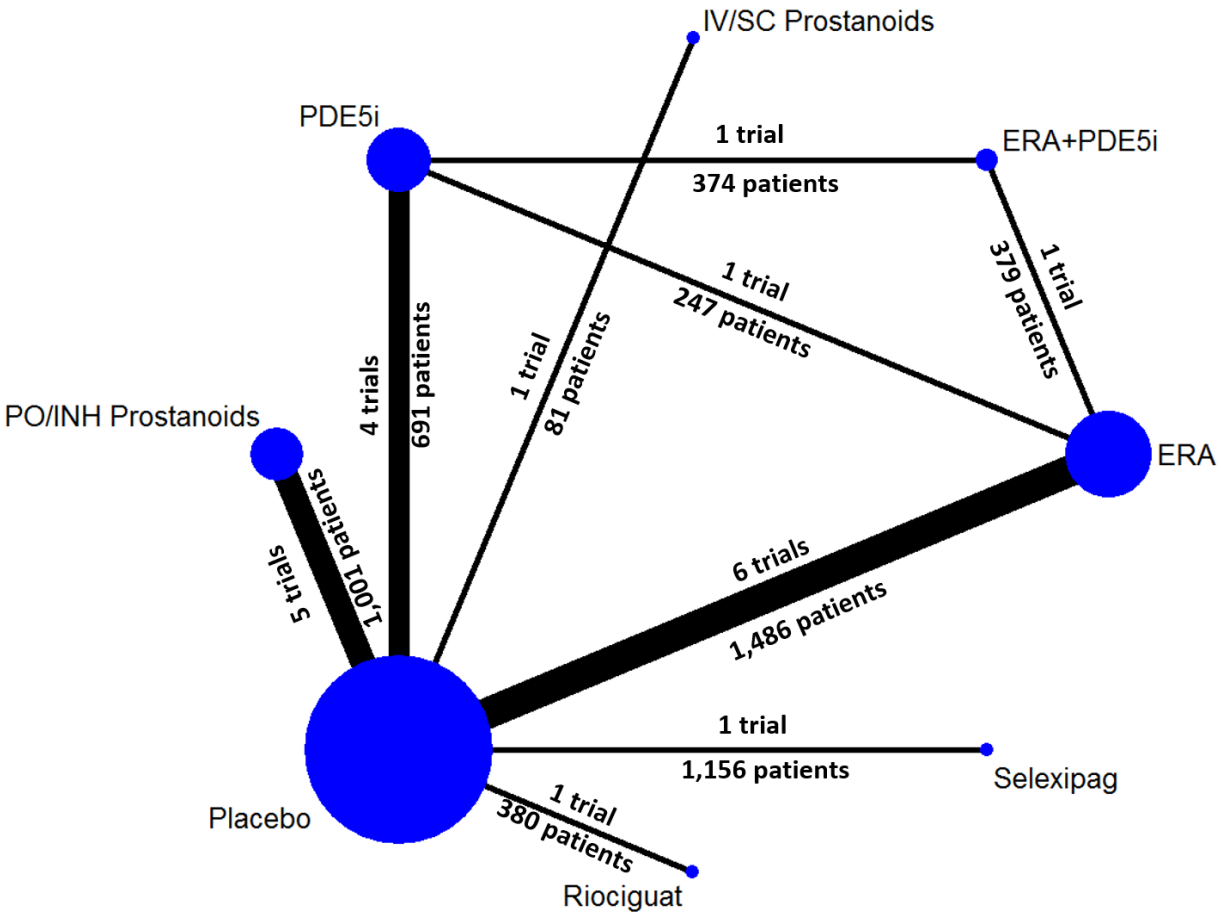
Compared with PDE5i				
PO/ INH Prostacyclins	-	-	Low	Low (favors PDE5i)
IV/ SC Prostacyclins	-	-	Low	-
Riociguat	-	-	Low (favors PDE5i)	Very low (favoring Rioci, very serious imprecision)
ERA+ PDE5i	Moderate (imprecision)	High	Low (very serious imprecision)	Moderate (imprecision)
Selexipag	-	-	Very 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 with 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.

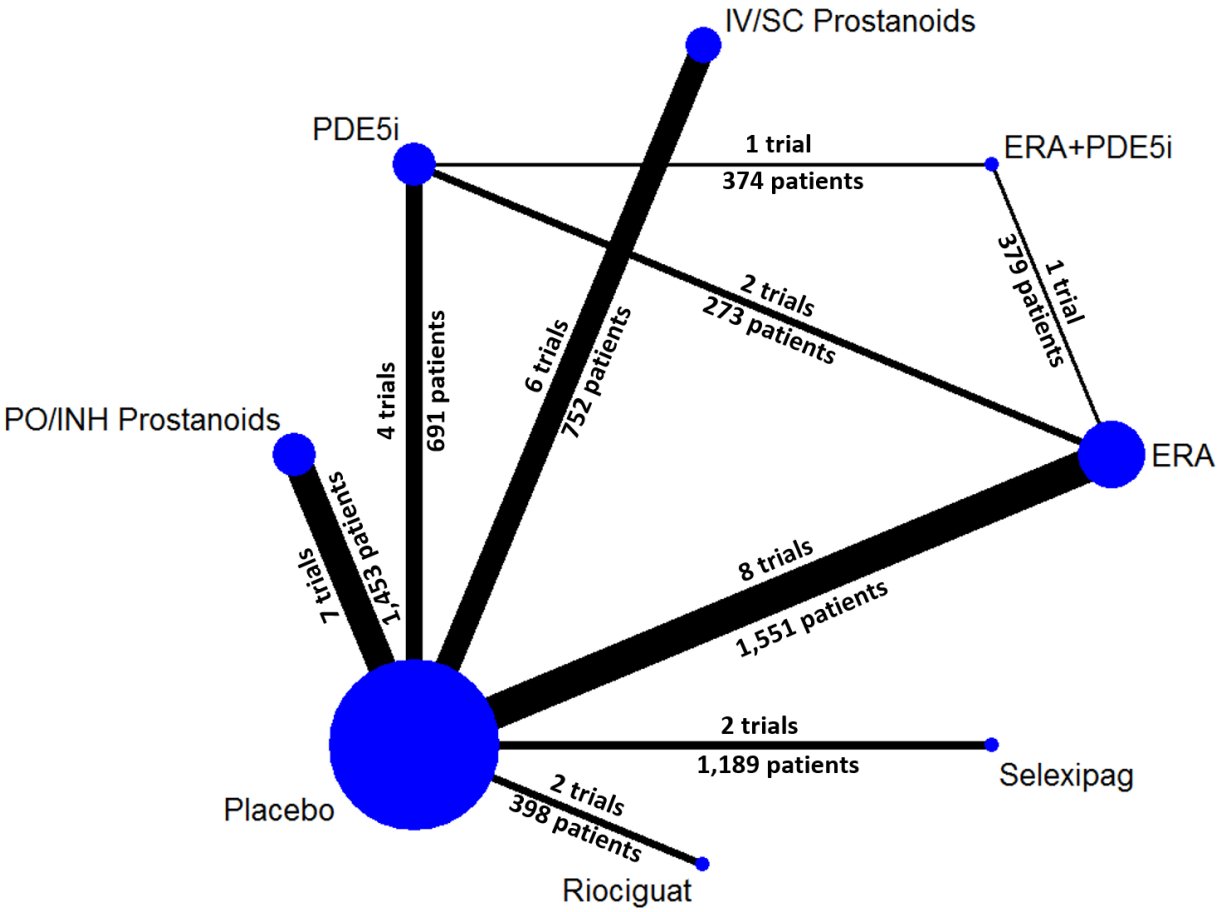
A: Clinical worsening



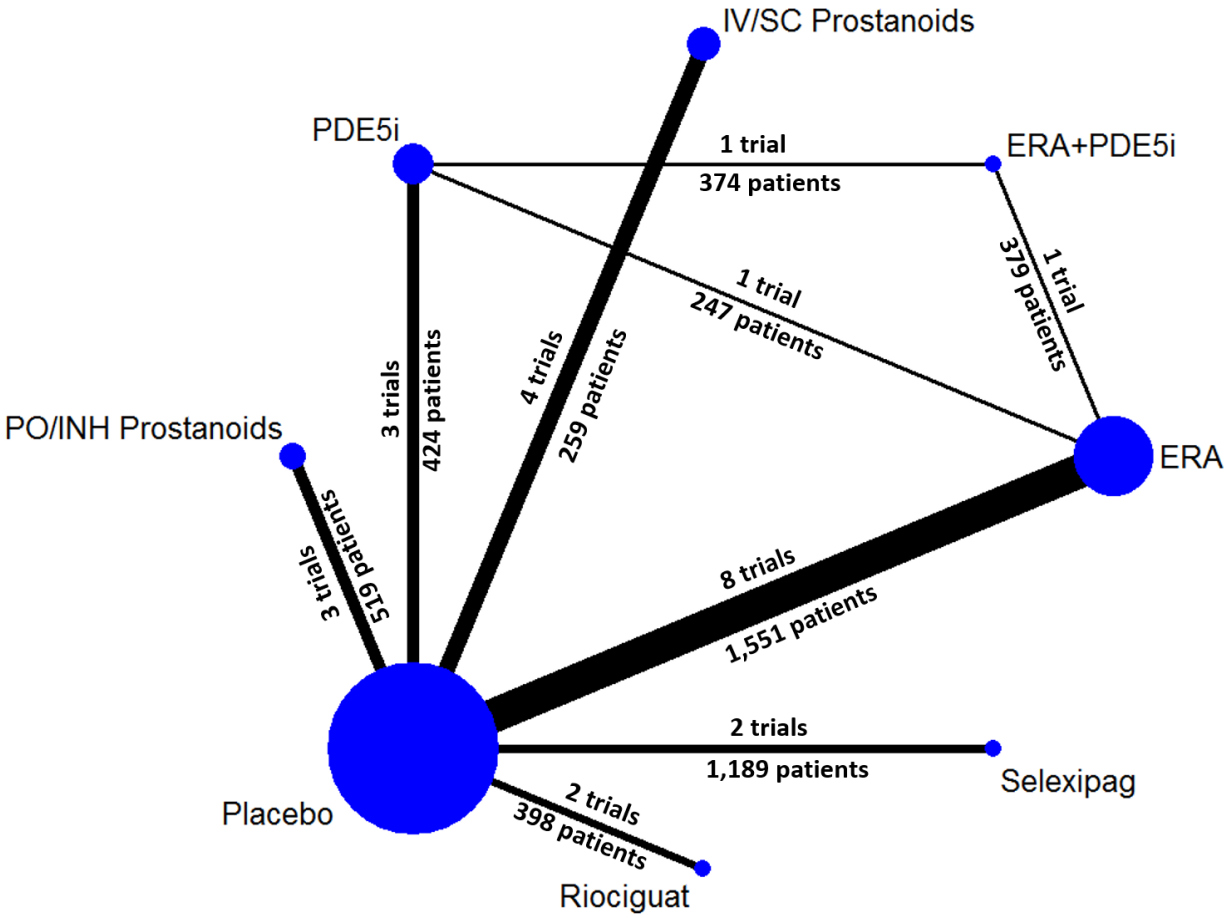
B: PAH – related hospitalization



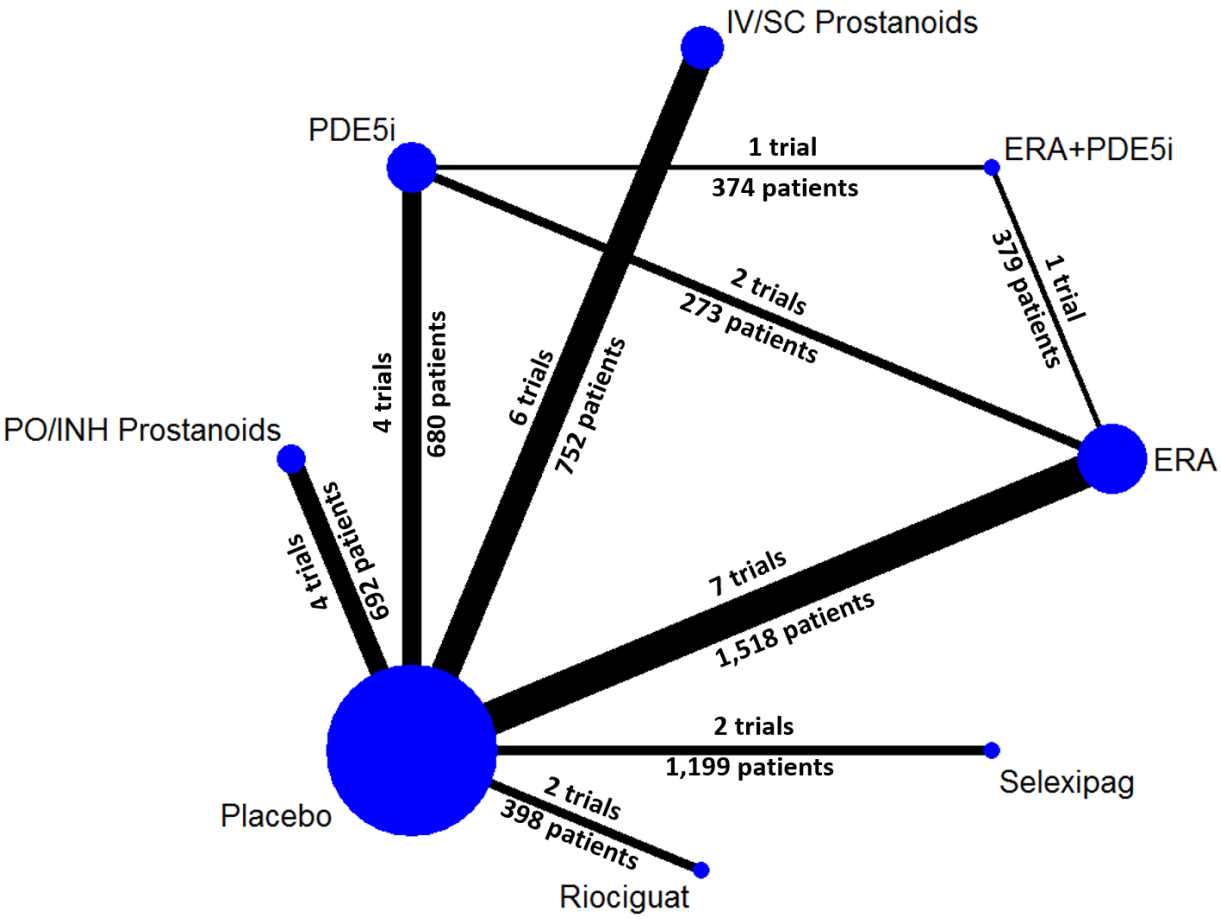
C: Mortality



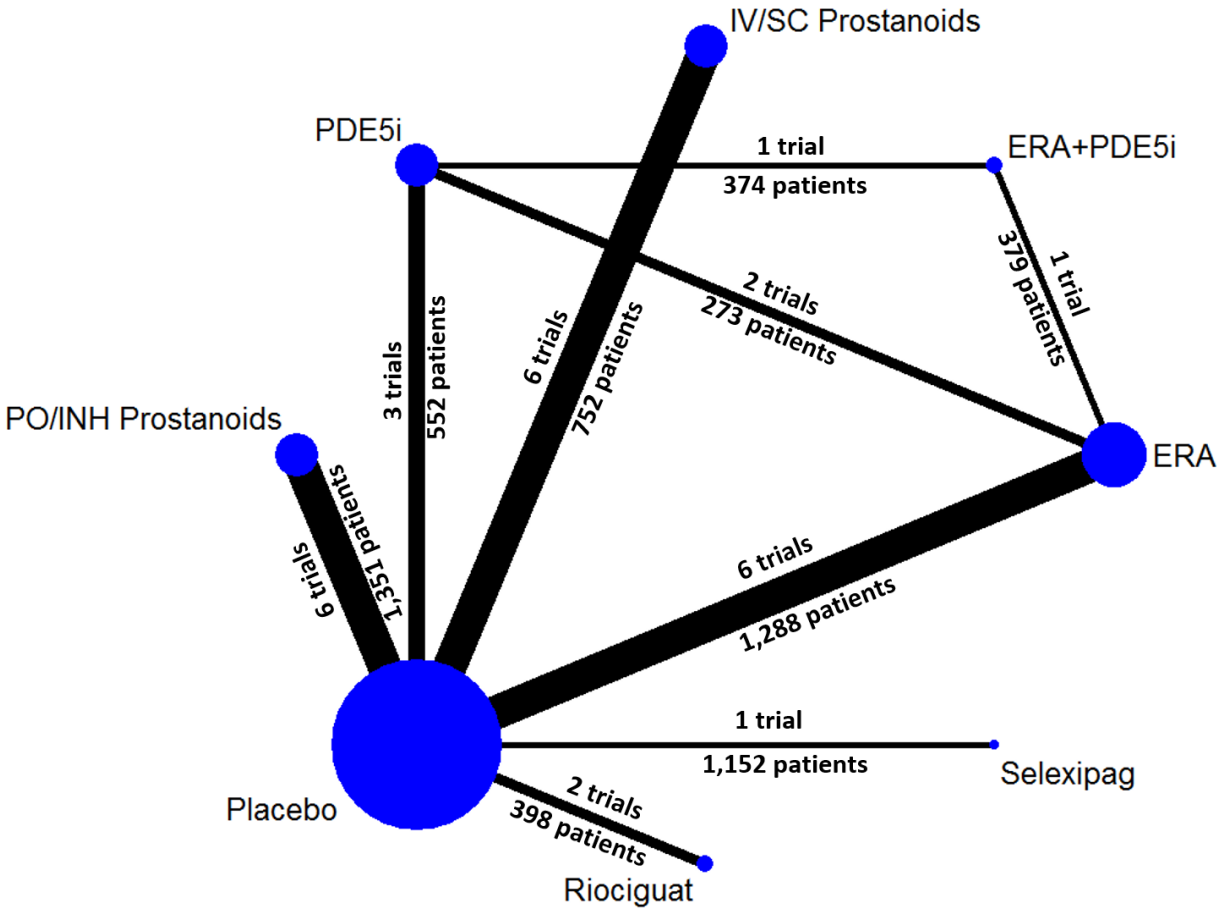
D: Functional class



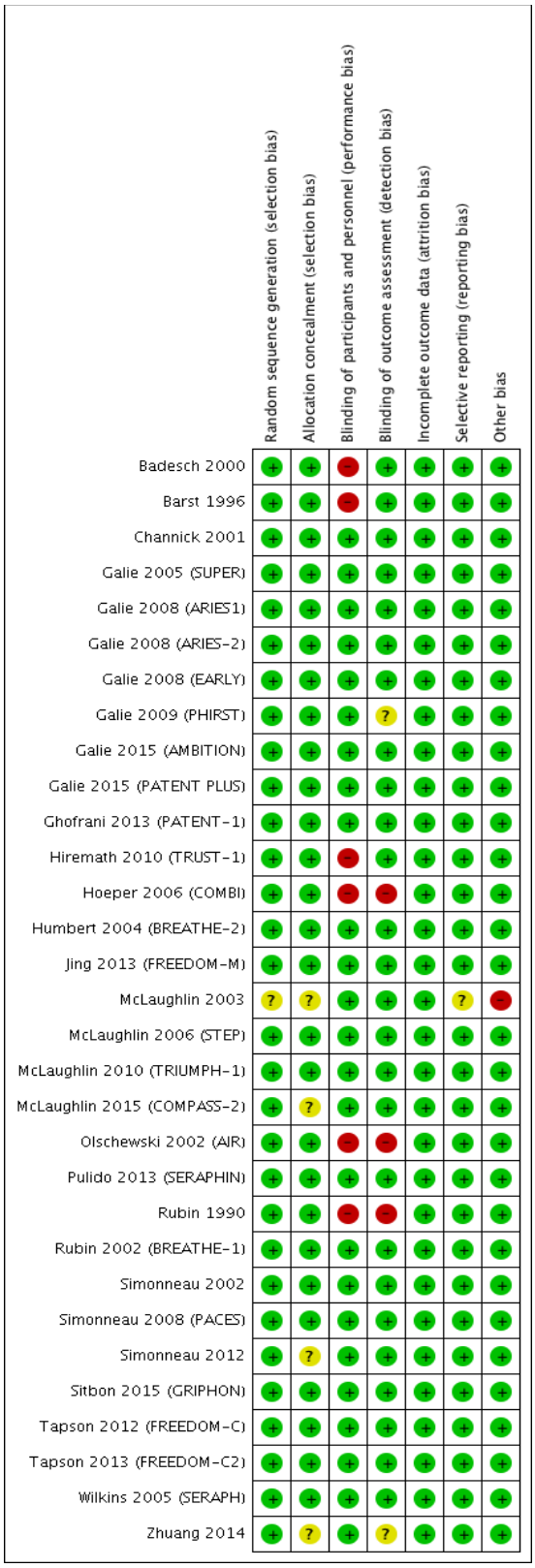
E: 6-minute walk distance



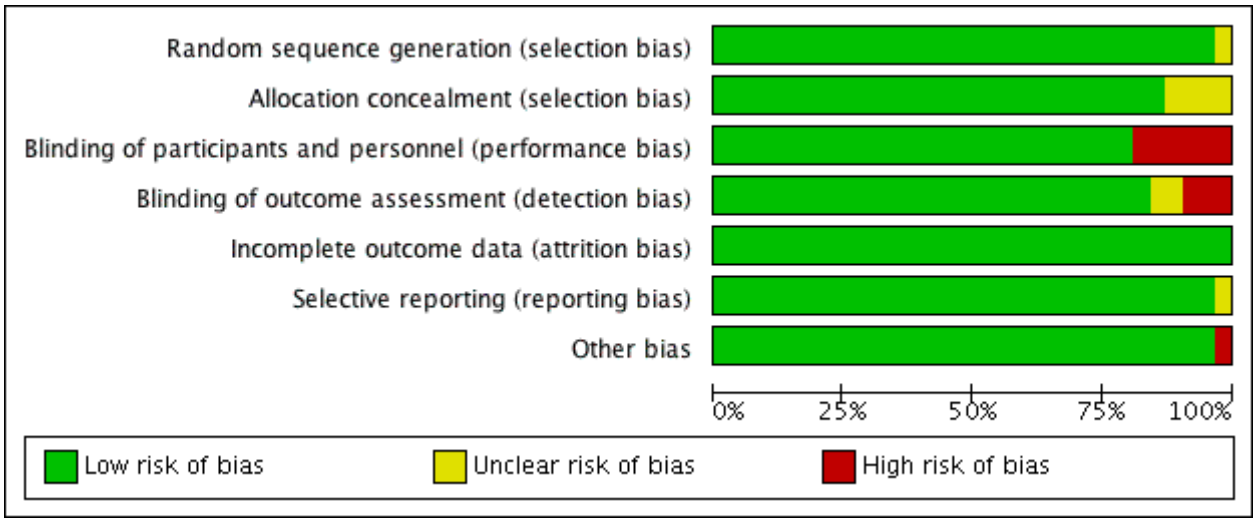
F: Adverse events leading to discontinuation



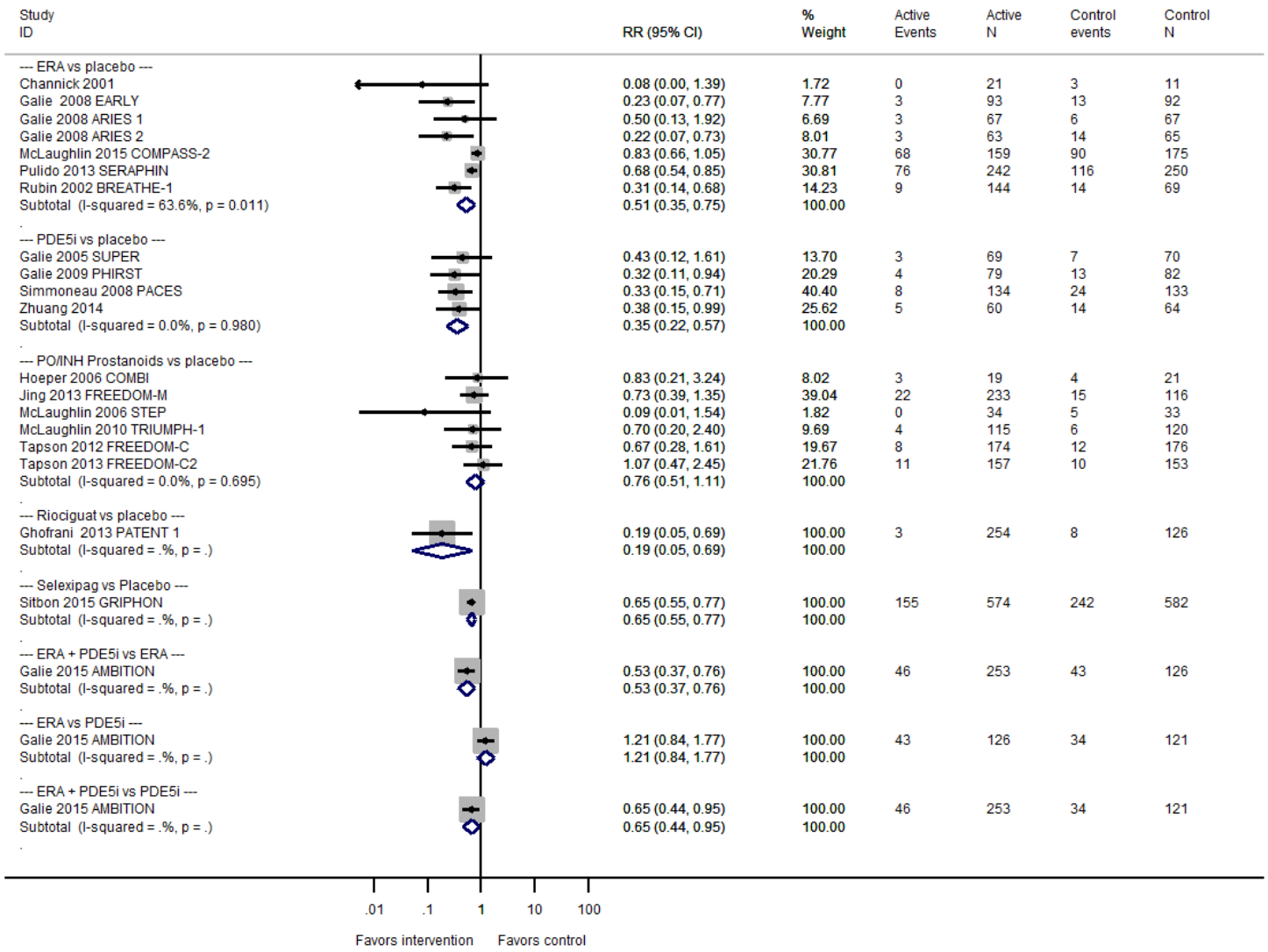
e-Figure 2A. Risk of bias summary for all studies



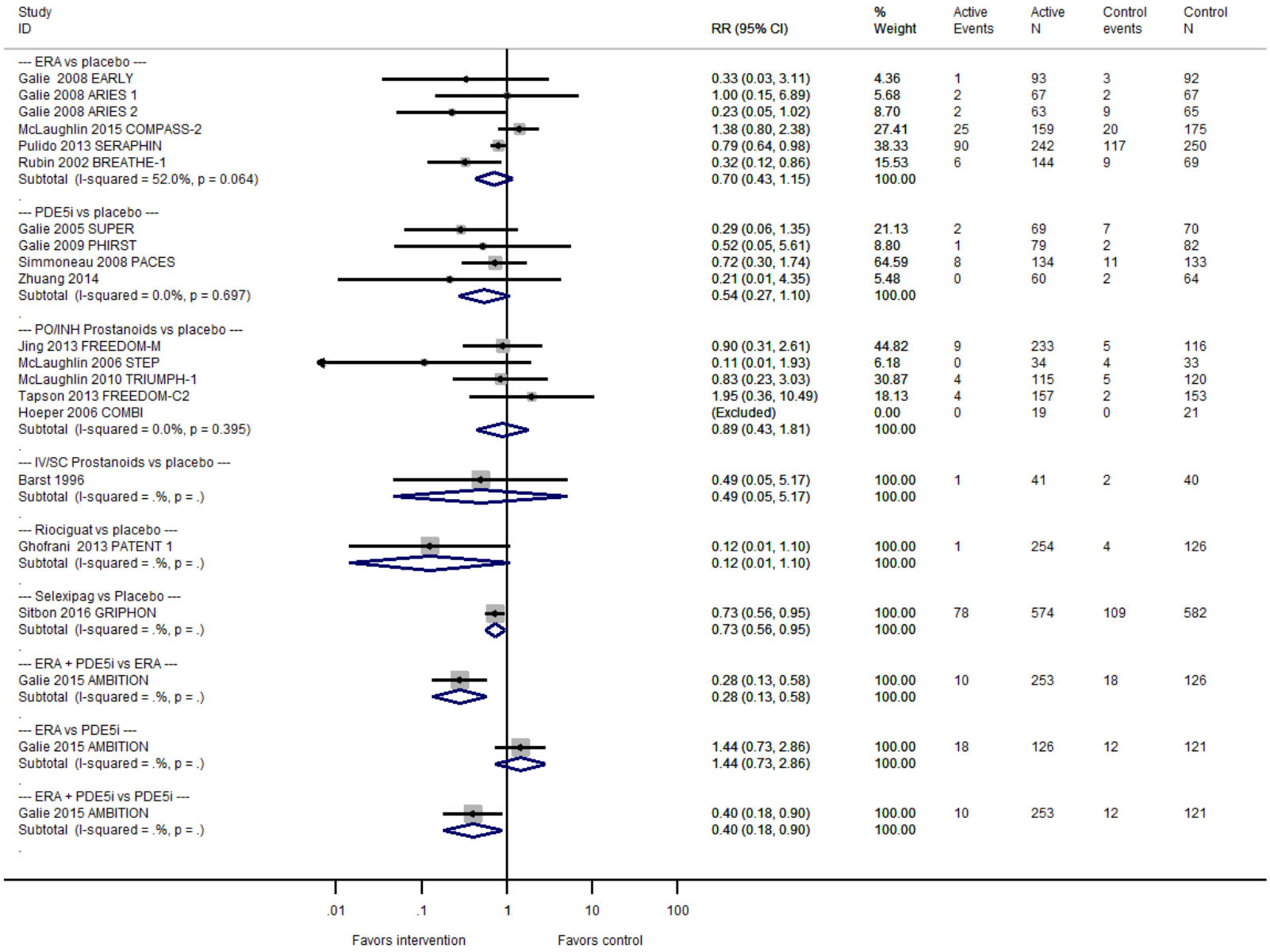
e-Figure 2B. Risk of bias - overall



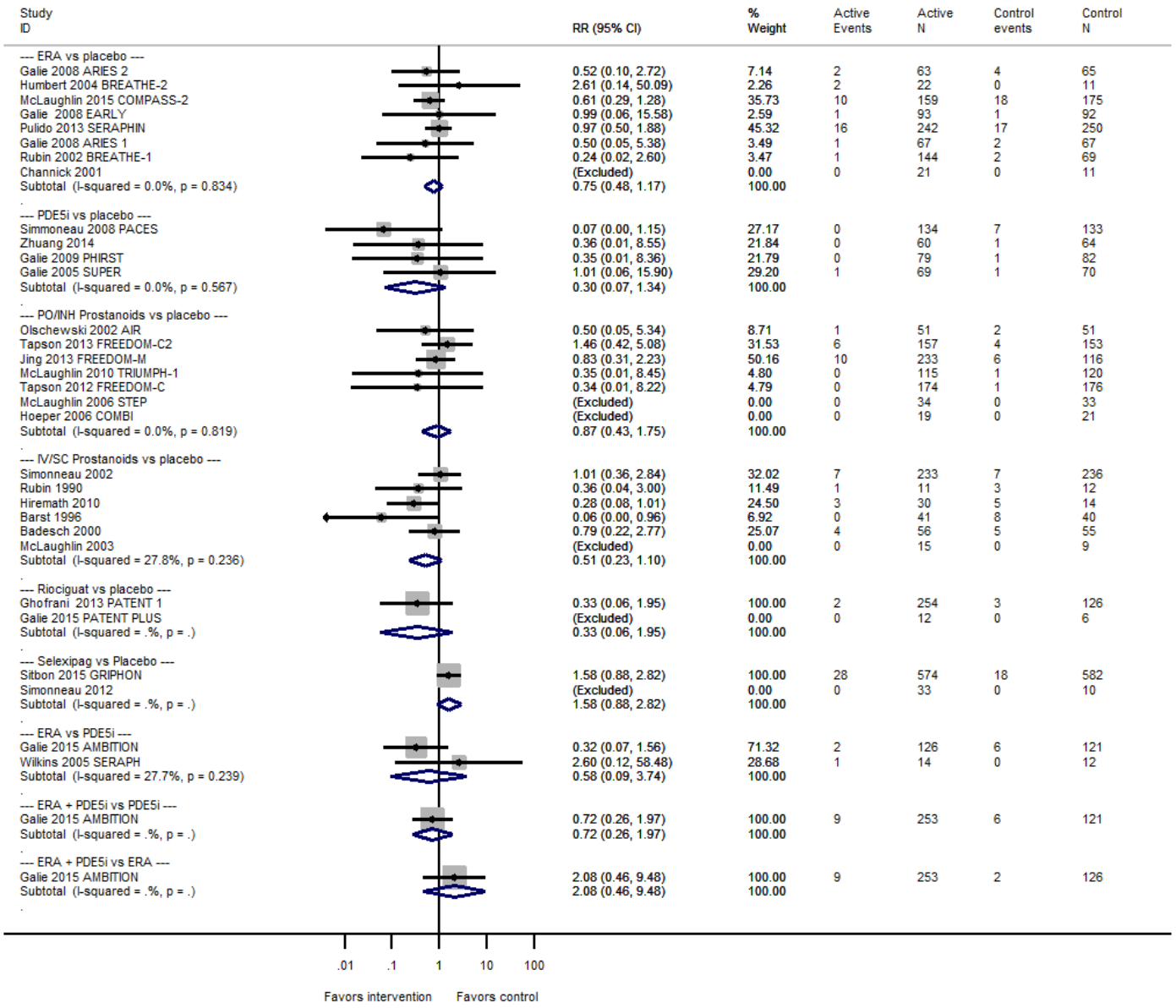
e-Figure 3. Results of Direct Meta-Analysis for Clinical Worsening



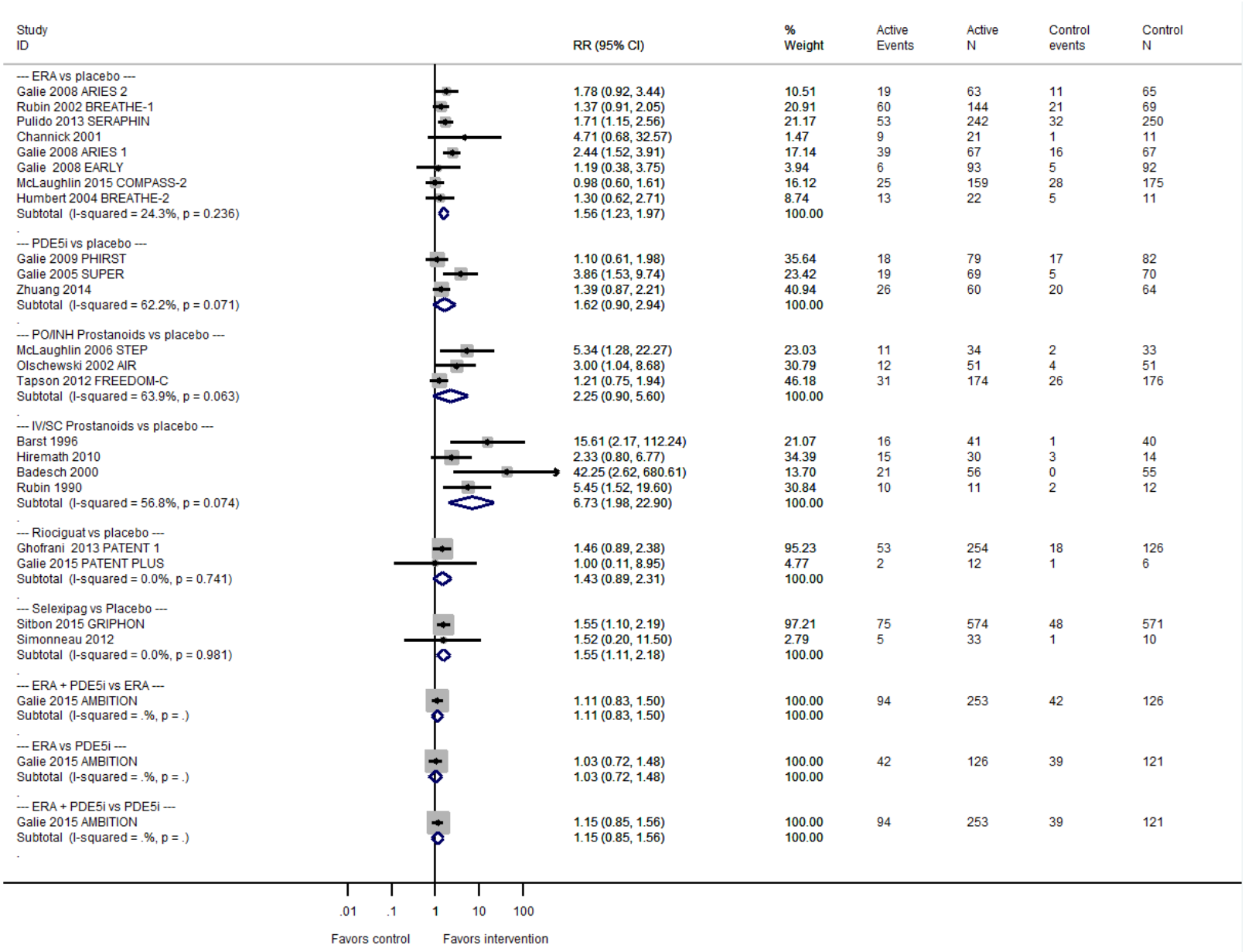
e- Figure 4. Results of Direct Meta-Analysis for PAH-related hospitalization



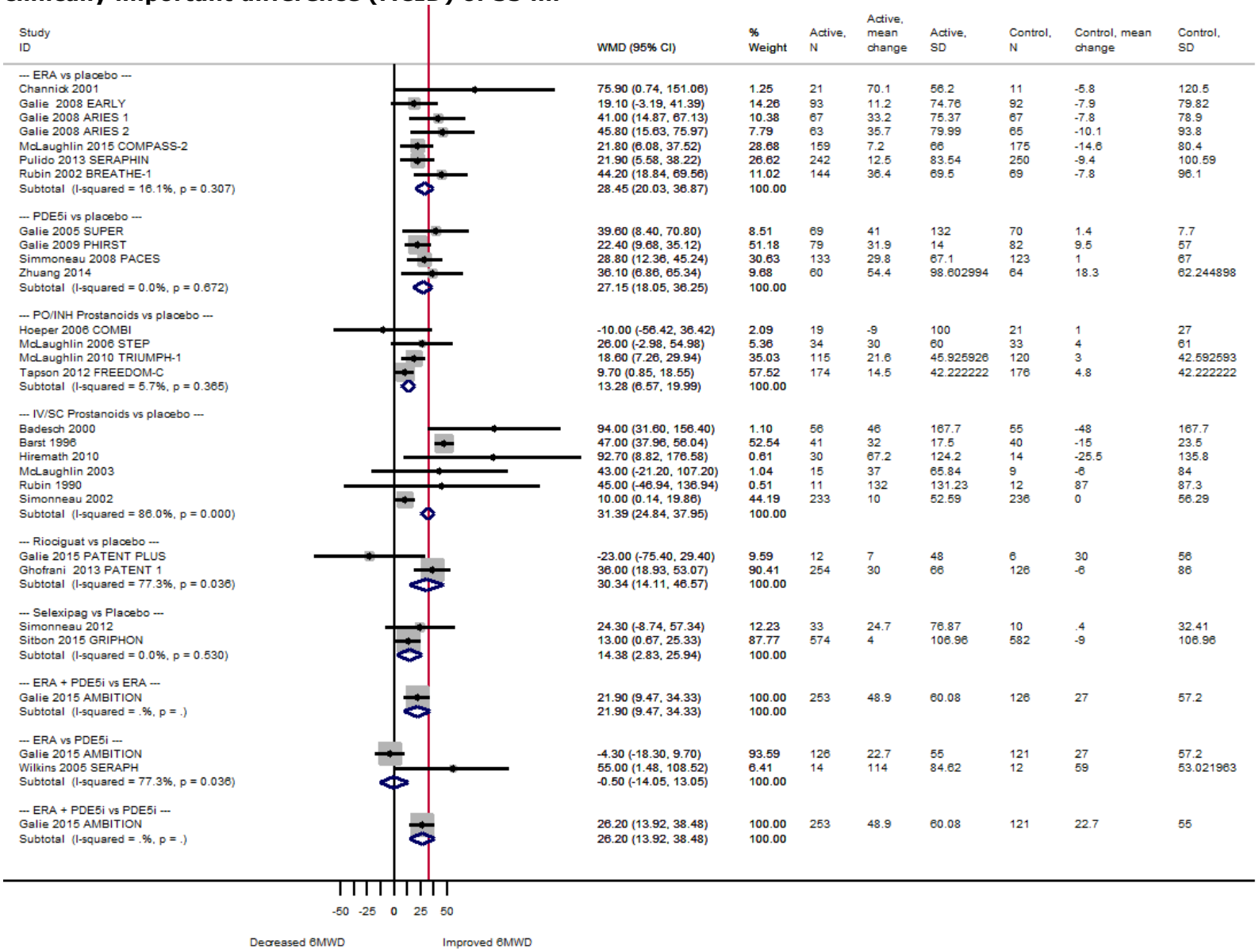
e- Figure 5. Results of Direct Meta-Analysis for All Cause Mortality



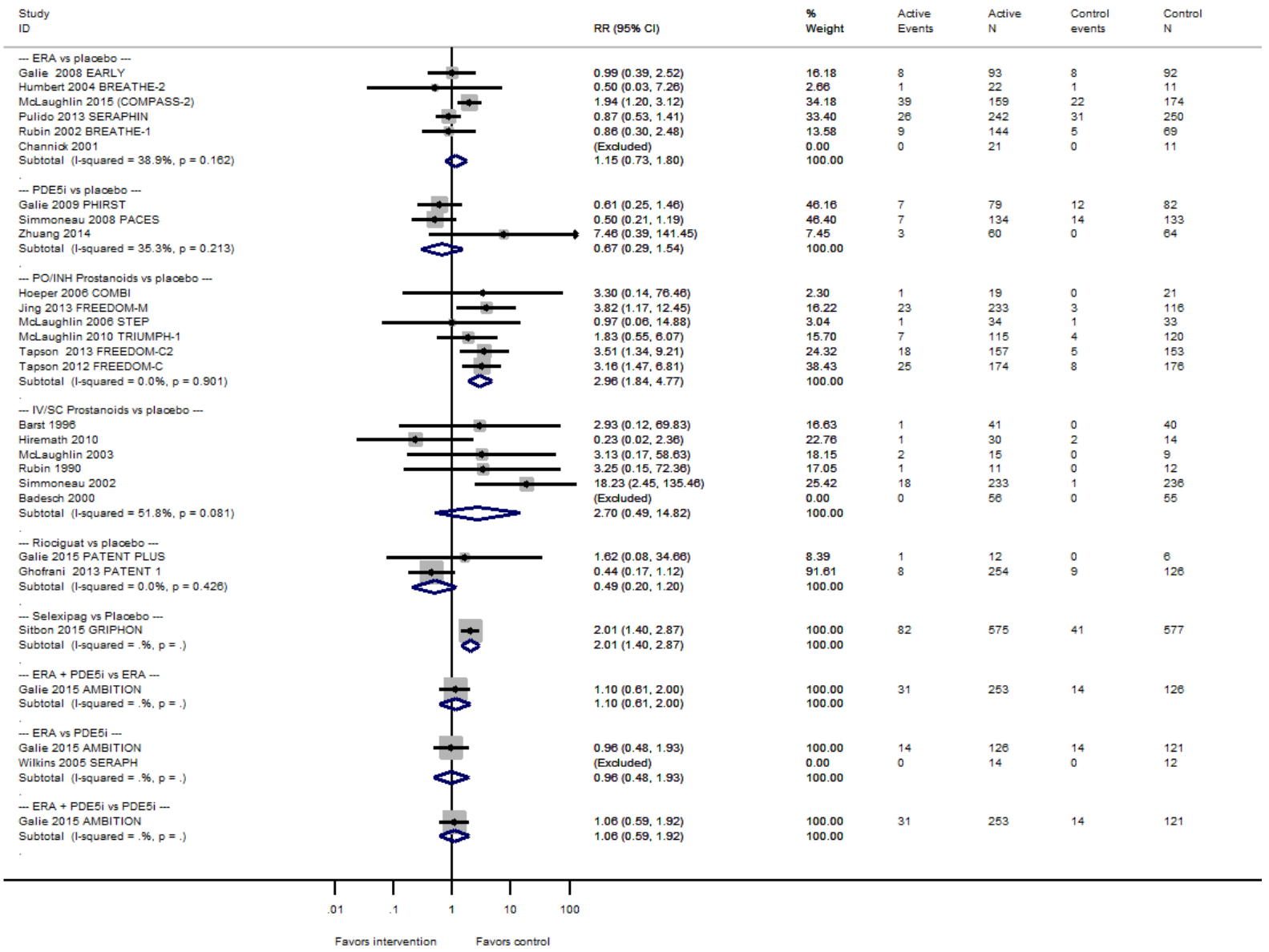
e-Figure 6. Results of Direct Meta-Analysis for Improvement in Functional Class



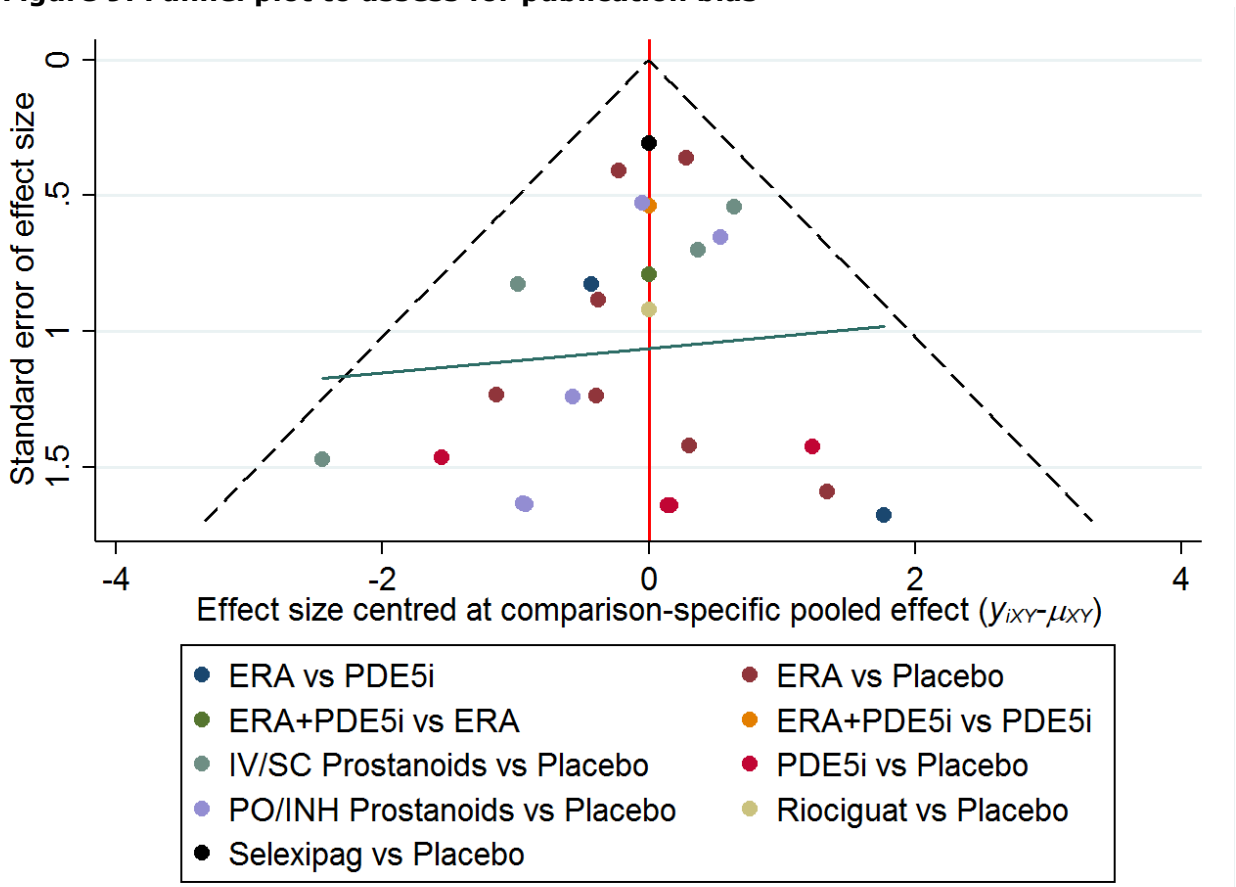
e-Figure 7. Results of Direct Meta-Analysis for Improvement in 6MWD. The red line represents the minimal clinically important difference (MCID) of 33 m.



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



e-Figure 9. Funnel plot to assess for publication bias



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.

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