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Phosphodiesterase 5 inhibitors for pulmonary hypertension (Review)

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TABLE OF CONTENTS

[Intervention Review]

Phosphodiesterase 5 inhibitors for pulmonary hypertension

Hayley Barnes[1], Zoe Brown[2], Andrew Burns[2], Trevor Williams[1]

[1]Department of Respiratory Medicine, The Alfred Hospital, Melbourne, Australia. [2]St Vincent's Hospital, Melbourne, Australia

Contact address: Hayley Barnes, Department of Respiratory Medicine, The Alfred Hospital, Commercial Rd, Melbourne, 3004, Australia. hayleynbarnes@gmail.com.

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ABSTRACT

Background

Pulmonary hypertension (PH) comprises a group of complex and heterogenous conditions, characterised by elevated pulmonary artery pressure, and which left untreated leads to right-heart failure and death. PH includes World Health Organisation (WHO) Group 1 pulmonary arterial hypertension (PAH); Group 2 consists of PH due to left-heart disease (PH-LHD); Group 3 comprises PH as a result of lung diseases or hypoxia, or both; Group 4 includes PH due to chronic thromboembolic occlusion of pulmonary vasculature (CTEPH), and Group 5 consists of cases of PH due to unclear and/or multifactorial mechanisms including haematological, systemic, or metabolic disorders. Phosphodiesterase type 5 (PDE5) inhibitors increase vasodilation and inhibit proliferation.

Objectives

To determine the efficacy of PDE5 inhibitors for pulmonary hypertension in adults and children.

Search methods

We performed searches of CENTRAL, MEDLINE, Embase, CINAHL, and Web of Science up to 26 September 2018. We handsearched review articles, clinical trial registries, and reference lists of retrieved articles.

Selection criteria

We included randomised controlled trials that compared any PDE5 inhibitor versus placebo, or any other PAH disease-specific therapies, for at least 12 weeks. We include separate analyses for each PH group.

Data collection and analysis

We imported studies identified by the search into a reference manager database. We retrieved the full-text versions of relevant studies, and two review authors independently extracted data. Primary outcomes were: change in WHO functional class, six-minute walk distance (6MWD), and mortality. Secondary outcomes were haemodynamic parameters, quality of life/health status, dyspnoea, clinical worsening (hospitalisation/intervention), and adverse events. When appropriate, we performed meta-analyses and subgroup analyses by severity of lung function, connective tissue disease diagnosis, and radiological pattern of fibrosis. We assessed the evidence using the GRADE approach and created 'Summary of findings' tables.

Main results

We included 36 studies with 2999 participants (with pulmonary hypertension from all causes) in the final review. Trials were conducted for 14 weeks on average, with some as long as 12 months. Two trials specifically included children.

Nineteen trials included group 1 PAH participants. PAH participants treated with PDE5 inhibitors were more likely to improve their WHO functional class (odds ratio (OR) 8.59, 95% confidence interval (CI) 3.95 to 18.72; 4 trials, 282 participants), to walk 48 metres further in

6MWD (95% CI 40 to 56; 8 trials, 880 participants), and were 22% less likely to die over a mean duration of 14 weeks (95% CI 0.07 to 0.68; 8 trials, 1119 participants) compared to placebo (high-certainty evidence). The number needed to treat to prevent one additional death was 32 participants. There was an increased risk of adverse events with PDE5 inhibitors, especially headache (OR 1.97, 95% CI 1.33 to 2.92; 5 trials, 848 participants), gastrointestinal upset (OR 1.63, 95% CI 1.07 to 2.48; 5 trials, 848 participants), flushing (OR 4.12, 95% CI 1.83 to 9.26; 3 trials, 748 participants), and muscle aches and joint pains (OR 2.52, 95% CI 1.59 to 3.99; 4 trials, 792 participants).

Data comparing PDE5 inhibitors to placebo whilst on other PAH-specific therapy were limited by the small number of included trials. Those PAH participants on PDE5 inhibitors plus combination therapy walked 19.66 metres further in six minutes (95% CI 9 to 30; 4 trials, 509 participants) compared to placebo (moderate-certainty evidence). There were limited trials comparing PDE5 inhibitors directly with other PAH-specific therapy (endothelin receptor antagonists (ERAs)). Those on PDE5 inhibitors walked 49 metres further than on ERAs (95% CI 4 to 95; 2 trials, 36 participants) (low-certainty evidence). There was no evidence of a difference in WHO functional class or mortality across both treatments.

Five trials compared PDE5 inhibitors to placebo in PH secondary to left-heart disease (PH-LHD). The quality of data were low due to imprecision and inconsistency across trials. In those with PH-LHD there were reduced odds of an improvement in WHO functional class using PDE5 inhibitors compared to placebo (OR 0.53, 95% CI 0.32 to 0.87; 3 trials, 285 participants), and those using PDE5 inhibitors walked 34 metres further compared to placebo (95% CI 23 to 46; 3 trials, 284 participants). There was no evidence of a difference in mortality. Five trials compared PDE5 inhibitors to placebo in PH secondary to lung disease/hypoxia, mostly in COPD. Data were of low quality due to imprecision of effect and inconsistency across trials. There was a small improvement of 27 metres in 6MWD using PDE5 inhibitors compared to placebo in those with PH due to lung disease. There was no evidence of worsening hypoxia using PDE5 inhibitors, although data were limited. Three studies compared PDE5 inhibitors to placebo or other PAH-specific therapy in chronic thromboembolic disease. There was no significant difference in any outcomes. Data quality was low due to imprecision of effect and heterogeneity across trials.

Authors' conclusions

PDE5 inhibitors appear to have clear beneficial effects in group 1 PAH. Sildenafil, tadalafil and vardenafil are all efficacious in this clinical setting, and clinicians should consider the side-effect profile for each individual when choosing which PDE5 inhibitor to prescribe.

While there appears to be some benefit for the use of PDE5 inhibitors in PH-left-heart disease, it is not clear based on the mostly small, short-term studies, which type of left-heart disease stands to benefit. These data suggest possible harm in valvular heart disease. There is no clear benefit for PDE5 inhibitors in pulmonary hypertension secondary to lung disease or chronic thromboembolic disease. Further research is required into the mechanisms of pulmonary hypertension secondary to left-heart disease, and cautious consideration of which subset of these patients may benefit from PDE5 inhibitors. Future trials in PH-LHD should be sufficiently powered, with long-term follow-up, and should include invasive haemodynamic data, WHO functional class, six-minute walk distance, and clinical worsening.

PLAIN LANGUAGE SUMMARY

PDE5 inhibitors for pulmonary hypertension

Review question:

We wanted to review whether a group of drugs called PDE5 inhibitors (which may work to open up the vessels in the lung) can help people with pulmonary hypertension (increased pressures in the blood vessels of the lungs). Cochrane researchers collected and analysed all relevant studies to answer this question, and found 36 studies.

Why the review is important:

Approximately three people in every 1000 have pulmonary hypertension, due to different causes. This can lead to reduced exercise capacity, reduced quality of life, increased hospitalisations, and early death. A group of drugs called PDE5 inhibitors may improve blood circulation in the right heart and lungs. We wanted to make sure that if these drugs are being used, there is evidence of benefit and little or no harm.

Main findings:

We included 36 studies with 2999 people. Trials were conducted for 14 weeks on average, with some as long as 12 months. Most trials involved adults, and two trials specifically included children.

Nineteen trials included those with group 1 pulmonary arterial hypertension (inherited, unknown, due to connective tissue diseases). People who were given PDE5 inhibitors were compared with those not given PDE5 inhibitors. This review shows that when given PDE5 inhibitors, on average people walked 48 meters further in six minutes (8 trials, 880 people). They also improved their functional class (reducing the physical limitations associated with PH), and were less likely to die (high-certainty evidence). They were also more likely to have side effects, including headache, flushing and muscle aches.

Five trials included people with pulmonary hypertension due to left-heart disease. This review shows that when given PDE5 inhibitors, these people were on average able to walk 34 metres further in six minutes (3 trials, 284 people; low-certainty evidence). However, there was

no difference in survival, compared to those who were not given PDE5 inhibitors. Five trials included people with pulmonary hypertension due to lung disease (mostly chronic obstructive pulmonary disease and some idiopathic pulmonary fibrosis). When given PDE5 inhibitors, they were able to walk 27 meters further in six minutes (low-certainty evidence), but with no difference in survival, compared to those who were not given PDE5 inhibitors. Three trials included people with pulmonary hypertension due to blood clots; there was no significant difference in outcomes for those who used PDE5 inhibitors compared to those who did not.

Limitations:

There was good-quality evidence for those with pulmonary arterial hypertension, giving us some confidence that the results are correct. The evidence for those with pulmonary hypertension due to heart disease was less certain. The quality of evidence in this group was low because there were few trials, small numbers of people taking part, and the trials were quite different from each other, making it difficult to draw firm conclusions.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Group 1 Pulmonary arterial hypertension - PDE5i compared to placebo

Group 1 Pulmonary arterial hypertension - PDE5i compared to placebo

Patient or population: people with pulmonary arterial hypertension
Setting: outpatients
Intervention: PDE5 inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PDE5i				
Improvement in WHO functional class	61 per 1000	358 per 1000 (204 to 549)	OR 8.59 (3.95 to 18.72)	282 (4 RCTs)	⊕⊕⊕⊕ HIGH	-
Six-minute walk distance	Ranges from 170 - 319 m[a]	MD 48 metres higher (40 higher to 56 higher)	-	880 (8 RCTs)	⊕⊕⊕⊖[b] MODERATE	6MWD in PAH MCID is 41 metres
Mortality	41 per 1000	9 per 1000 (3 to 28)	OR 0.22 (0.07 to 0.68)	1119 (8 RCTs)	⊕⊕⊕⊕ HIGH	-
Quality of life SF-36: (scores 1 to 100, higher scores indicate better QoL) EQ-5D questionnaire: (higher scores indicate worse QoL) CHFQ: (lower scores indicate worse QoL)	Galiè 2005a found a statistically significant improvement in all SF-36 domains for sildenafil-treated participants, and when compared to placebo in physical functioning ($P < 0.001$), general health ($P < 0.001$), and vitality ($P < 0.05$). There was also a statistically significant improvement in placebo-treated participants in the physical functioning domain. Galiè 2005a found statistically significant improvements for the EQ-5D current health status ($P < 0.01$) and utility index ($P < 0.01$). Sastry 2004 found a statistically significant difference for the CHFQ fatigue domain (sildenafil post-treatment score 22.33, SD 4.82 compared to placebo post-treatment score 20.67, SD 5.19; $P = 0.04$), and a non-statistically significant difference in the emotional function domain (sildenafil post-treatment score 37.33, SD 9.3, compared to placebo post-treatment score 34.71, SD 10.91; $P = 0.06$), favouring sildenafil compared with placebo.			163 (2 RCTs)	-	Data considered too heterogeneous to meta-analyse
PAP	-	MD 6.43 mmHg lower (8.13 lower to 4.74 lower)	-	453 (6 RCTs)	⊕⊕⊕⊖[b] MODERATE	The higher the mean PAP, the worse the PH

RAP	-	MD 1.35 mmHg lower (2.34 lower to 0.36 lower)	-	341 (3 RCTs)	⊕⊕⊕⊕ HIGH	The higher the RAP, the worse the PH
Cardiac index	-	MD 0.28L/min/m^2 higher (0.16 higher to 0.4 higher)	-	239 (4 RCTs)	⊕⊕⊕⊖[b] MODERATE	The lower the cardiac index, the worse the PH
PVR	-	MD 4.74 WU lower (6.13 lower to 3.35 lower)	-	266 (3 RCTs))	⊕⊕⊕⊕ HIGH	The higher the PVR. the worse the PH

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** Confidence interval; **EQ-5D**: EuroQoL 5D; **MCID:** minimal clinically important difference; **MD**: mean difference; **OR:** odds ratio; **PAP**: pulmonary arterial pressure; **PDE-5i:** phosphodiesterase-5 inhibitor; **PH**: pulmonary hypertension; **PVR**: pulmonary vascular resistance; **RAP**: right atrial pressure; **RCT**: randomised controlled trials; **SD**: standard deviation; **SF-36**: Medical Outcomes Study 36-item short form; **WU**: woods units; **WHO**: World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Post-treatment values for participants in the placebo group were presented in two studies only; the remaining included studies presented a mean difference only.
[b]Downgraded due to imprecision owing to significantly high heterogeneity, although the direction of effect is consistent.

Summary of findings 2. Group 1 Pulmonary arterial hypertension - PDE5i compared to placebo, on combination therapy

Group 1 Pulmonary arterial hypertension - PDE5i compared to placebo, on combination therapy

Patient or population: people with pulmonary arterial hypertension
Setting: outpatients
Intervention: PDE5 inhibitors plus other disease-modifying therapies
Comparison: placebo plus other disease-modifying therapies

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo, on	Risk with PDE5i				

	combination therapy					
Improvement in WHO functional class	263 per 1000	300 per 1000 (191 to 437)	OR 1.20 (0.66 to 2.17)	227 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	-
Six-minute walk distance	Ranges from 341 - 377 m[b]	MD 20 metres higher (9 higher to 30 higher)	-	509 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]	6MWD in PAH MCID is 41 metres
Mortality	32 per 1000	9 per 1000 (2 to 34)	OR 0.26 (0.07 to 1.06)	492 (3 RCTs)	⊕⊕⊕⊖ MODERATE[c]	-
Quality of life physical functioning on SF-36 (higher scores indicate better quality of life)	0.3 (4.7 higher to 4.1 higher)	7.8 (3.6 higher to 12.1 higher)	-	267 (1 RCT)	⊕⊕⊕⊖ MODERATE[d]	-
PAP	-	MD 4.58 mmHg lower (6.14 lower to 3.01 lower)	-	387 (2 RCTs)	⊕⊕⊕⊕ HIGH	The higher the PAP, the worse the pulmonary hypertension
Cardiac output	-	MD 0.87 L/min higher (0.53 higher to 1.21 higher)	-	310 (3 RCTs)	⊕⊕⊕⊕ HIGH	The lower the cardiac output, the worse the pulmonary hypertension
PVR	-	SMD 0.48 lower (0.72 lower to 0.25 lower)	-	303 (3 RCTs)	⊕⊕⊕⊕ HIGH	The higher the PVR, the worse the pulmonary hypertension

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** Confidence interval; **MCID:** minimal clinically important difference; **MD**: mean difference; **OR:** odds ratio; **PAP**: pulmonary arterial pressure; **PDE-5i:** phosphodiesterase-5 inhibitor; **PVR**: pulmonary vascular resistance; **RCT**: randomised controlled trials; **SMD**: standardised mean difference; **WHO**: World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded due to imprecision owing to small participant numbers and inconsistent direction of effect.
[b]Range of baseline values, as studies only presented mean difference values for analysis.
[c]Downgraded due to imprecision as the confidence interval crosses the line of no difference.
[d]Downgraded due to imprecision owing to small participant numbers in one trial.

Summary of findings 3. Group 1 Pulmonary arterial hypertension - PDE5i compared to ERA

Group 1 Pulmonary Arterial Hypertension - PDE5i compared to ERA

Patient or population: people with pulmonary arterial hypertension
Setting: outpatients
Intervention: PDE5 inhibitors
Comparison: endothelin receptor antagonists**(**ERA)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ERA	Risk with PDE5i				
Improvement in WHO functional class	339 per 1000	325 per 1000 (220 to 450)	OR 0.94 (0.55 to 1.60)	244 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	-
Six-minute walk distance	Ranges from 290 - 354 m[b]	MD 49 higher (4 higher to 95 higher)	-	36 (2 RCTs)	⊕⊕⊖⊖ LOW[c]	6MWD in PAH MCID is 41 metres
Mortality	14 per 1000	45 per 1000 (11 to 167)	OR 3.19 (0.74 to 13.64)	272 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	-
Quality of life Kansas City Cardiomyopathy Quality-of-Life questionnaire (higher scores indicate better quality of life)	-	MD 22 higher (9 higher to 35 higher)	-	25 (1 RCT)	⊕⊕⊖⊖ LOW[c]	-
PAP	-	MD 7.00 mmHg lower (4.82 lower to 18.82 higher)	-	11 (1 RCT)	⊕⊕⊖⊖ LOW[d]	The higher the mean PAP, the worse the PH
RAP	-	MD 2 mmHg higher (2.14 lower to 6.14 higher)	-	11 (1 RCT)	⊕⊕⊖⊖ LOW[d]	The higher the RAP, the worse the PH

Cardiac index	-	MD 0 L/min/m^2 higher (0.49 lower to 0.49 higher)	-	11 (1 RCT)	⊕⊕⊖⊖ LOW[d]	The lower the cardiac index, the worse the PH
PVR	-	MD 0 WU lower (1.93 lower to 1.93 higher)	-	11 (1 RCT)	⊕⊕⊖⊖ LOW[d]	The higher the PVR. the worse the PH

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** Confidence interval; **MCID:** minimal clinically important difference; **MD**: mean difference; **OR:** odds ratio; **PDE-5i:** phosphodiesterase-5 inhibitor; **RCT**: randomised controlled trials; **WHO**: World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded once due to imprecision.
[b]Range of baseline values, as studies only presented mean difference values for analysis.
[c]Downgraded twice due to imprecision and small participant numbers.
[d]Downgraded twice due to very small participant numbers and high risk of bias.

Summary of findings 4. Group 2 Pulmonary hypertension due to left-heart disease - PDE5i compared to placebo

Group 2 Pulmonary hypertension due to left-heart disease - PDE5i compared to placebo

Patient or population: people with pulmonary hypertension due to left-heart disease
Setting: outpatients
Intervention: PDE5 inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PDE5i				

Improvement in WHO functional class	403 per 1000	263 per 1000 (178 to 370)	OR 0.53 (0.32 to 0.87)	285 (3 RCTs)	⊕⊕⊕⊖ MODERATE[a]	-
Six-minute walk distance	No data reported	MD 34 metres higher (23 higher to 46 higher)	-	284 (3 RCTs)	⊕⊕⊕⊖ MODERATE[a]	-
Mortality	22 per 1000	27 per 1000 (6 to 114)	OR 1.27 (0.28 to 5.80)	286 (3 RCTs)	⊕⊕⊕⊖ MODERATE[b]	-
Quality of life	19.83 points higher (8.23 higher to 31.44 higher)	12.05 points higher (1.14 higher to 22.96 higher)	-	52 (1 RCT)	⊕⊕⊖⊖ LOW[c]	Kansas City Cardiomyopathy Questionnaire (higher scores reflect better health status)
Mean PAP	-	MD 10.17 mmHg lower (11.99 lower to 8.35 lower)	-	130 (3 RCTs)	⊕⊕⊕⊖ MODERATE[a]	The higher the mean PAP, the worse the pulmonary hypertension
Cardiac index	-	MD 0.07 L/min/m^2 higher (0.17 lower to 0.3 higher)	-	96 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	The lower the cardiac index, the worse the pulmonary hypertension

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** Confidence interval; **MCID:** minimal clinically important difference; **MD**: mean difference; **OR:** odds ratio; **PAP**: pulmonary arterial pressure; **PDE-5i:** phosphodiesterase-5 inhibitor; **RCT**: randomised controlled trials; **WHO**: World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded due to high heterogeneity and inconsistent direction of effect.
[b]Downgraded due to imprecision as the confidence interval crosses the line of no difference.
[c]Downgraded twice due to imprecision owing to few participant numbers in one trial.

Summary of findings 5. Group 3 Pulmonary hypertension due to lung disease - PDE5i compared to placebo

Group 3 Pulmonary hypertension due to lung disease - PDE5i compared to placebo

Patient or population: people with pulmonary hypertension due to lung disease
Setting: outpatients
Intervention: PDE5 inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PDE5i				
Improvement in WHO functional class	50 per 1000	700 per 1000 (201 to 956)	OR 44.33 (4.78 to 410.94)	40 (1 RCT)	⊕⊕⊖⊖ LOW[a]	-
Six-minute walk distance	Ranges from 237 - 297 metres	MD 27 metres higher (2 higher to 51 higher)	-	350 (5 studies)	⊕⊕⊕⊕ HIGH	-
Mortality	-	-	-	No studies	-	-
Quality of life	-	MD 0.19 higher (0.07 lower to 0.44 higher)	-	238 (2 RCTs)	⊕⊕⊕⊖ MODERATE[b]	SF-36 overall quality of life (higher scores indicate better quality of life)
Mean PAP	-	MD 0.14 mmHg lower (6.65 lower to 6.37 higher)	-	61 (2 RCTs)	⊕⊕⊕⊖ MODERATE[b]	The higher the mean PAP, the worse the pulmonary hypertension
Cardiac index	-	MD 0.3 L/min/m^2 higher (0.14 lower to 0.74 higher)	-	28 (1 RCT)	⊕⊕⊖⊖ LOW[a]	The lower the cardiac index, the worse the pulmonary hypertension
PVR	-	MD 1.31 WU lower (3.67 lower to 1.05 higher)	-	28 (1 RCT)	⊕⊕⊖⊖ LOW[a]	The higher the PVR, the worse the pulmonary hypertension
RAP	-	MD 0.36 mmHg higher (2.76 lower to 3.48 higher)	-	28 (1 RCT)	⊕⊕⊖⊖ LOW[a]	The higher the RAP, the worse the pulmonary hypertension

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MCID:** minimal clinically important difference; **MD**: mean difference; **OR:** odds ratio; **PAP**: pulmonary arterial pressure; **PDE-5i:** phosphodiesterase-5 inhibitor; **PVR**: pulmonary vascular resistance; **RAP**: right atrial pressure; **RCT**: randomised controlled trials; **WHO**: World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded twice due to imprecision owing to small participant numbers.
[b]Downgraded once due to imprecision.

Summary of findings 6. Group 4 Pulmonary hypertension due to CTEPH - PDE5i compared to placebo

Group 4 Pulmonary hypertension due to CTEPH - PDE5i compared to placebo

Patient or population: people with pulmonary hypertension due to CTEPH
Setting: outpatients
Intervention: PDE5 inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with comparison (placebo/sildenafil)	Risk with PDE5i				
Improvement in WHO functional class	0 per 1000	444 per 1000	OR 17.18 (0.78 to 380.84)	19 (1 RCT)	⊕⊕⊖⊖ LOW[a]	-
Six-minute walk distance - sildenafil compared to placebo	Baseline 331 metres	MD 18 metres higher (24 lower to 59 higher)	-	19 (1 RCT)	⊕⊕⊖⊖ LOW[a]	-
Six-minute walk distance - sildenafil compared to bosentan	Ranges from 422 - 455 metres	MD 20 metres higher (28 lower to 69 higher)	-	227 (2 RCTs)	⊕⊕⊕⊖ MODERATE[b]	-
Mortality - sildenafil versus placebo	No deaths reported		not estimable	20 (1 RCT)	⊕⊕⊖⊖ LOW[a]	-

Mortality - sildenafil versus bosentan	40 per 1000	54 per 1000 (9 to 261)	OR 1.36 (0.22 to 8.48)	106 (1 RCT)	⊕⊕⊝⊝ LOW[a]	-
Quality of life	-	MD 0.26 lower (1.17 lower to 0.64 higher)	-	34 (1 RCT)	⊕⊕⊝⊝ LOW[a]	CamPHOR scale; higher scores indicate worse quality of life
Mean PAP - sildenafil versus placebo	-	MD 6.2 mmHg lower (12.4 lower to 0 higher)	-	19 (1 RCT)	⊕⊕⊝⊝ LOW[a]	The higher the PAP, the worse the pulmonary hypertension
Mean PAP - sildenafil versus bosentan	-	MD 0.76 mmHg higher (3.96 lower to 5.48 higher)	-	227 (2 RCTs)	⊕⊕⊕⊝ MODERATE[b]	The higher the PAP, the worse the pulmonary hypertension
Cardiac index - sildenafil versus placebo	-	MD 0 L/min/m^2 higher (0.4 lower to 0.4 higher)	-	19 (1 RCT)	⊕⊕⊝⊝ LOW[a]	The lower the cardiac index, the worse the pulmonary hypertension
Cardiac index - sildenafil versus bosentan	-	MD 0.04 L/min/m^2 higher (0.22 lower to 0.31 higher)	-	227 (2 RCTs)	⊕⊕⊕⊝ MODERATE[b]	The lower the cardiac index, the worse the pulmonary hypertension
PVR - sildenafil versus placebo	-	MD 0.89 WU lower (1.85 lower to 0.06 higher)	-	19 (1 RCT)	⊕⊕⊝⊝ LOW[a]	The higher the PVR, the worse the pulmonary hypertension
PVR - sildenafil versus bosentan	-	MD 0.01 WU lower (0.27 lower to 0.25 higher)	-	227 (2 RCTs)	⊕⊕⊕⊝ MODERATE[b]	The higher the PVR, the worse the pulmonary hypertension

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CTEPH:** chronic thromboembolic pulmonary hypertension; **MD**: mean difference; **OR:** odds ratio; **PAP**: pulmonary arterial pressure; **PDE-5i:** phosphodiesterase-5 inhibitor; **PVR**: pulmonary vascular resistance; **RCT**: randomised controlled trials; **WHO**: World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded twice due to imprecision owing to small participant numbers in only one trial.
[b]Downgraded once due to imprecision.

Summary of findings 7. Mixed Pulmonary hypertension group 2 - 4 - PDE5i compared to placebo

Mixed pulmonary hypertension group 2 - 4 - PDE5i compared to placebo

Patient or population: people with pulmonary hypertension group 2 - 4
Setting: outpatients
Intervention: PDE5 inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PDE5i				
Improvement in WHO functional class	Study population		OR 11.31 (4.90 to 26.14)	146 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a,b]	-
	137 per 1000	642 per 1000 (438 to 806)				
Six-minute walk distance	No data provided	MD 51 metres higher (7 higher to 95 higher)	-	106 (1 RCT)	⊕⊕⊕⊖ MODERATE[a,b]	-
Mortality	-	-	no studies	-	-	-
Quality of life	-	-	no studies	-	-	-
PASP	-	MD 10 mmHg lower (11.92 lower to 8.08 lower)	-	146 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a,b]	The higher the PASP, the worse the pulmonary hypertension

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD**: mean difference; **OR:** odds ratio; **PASP**: pulmonary artery systolic pressure; **PDE-5i:** phosphodiesterase-5 inhibitor; **RCT**: randomised controlled trials; **WHO**: World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded due to imprecision owing to small participant numbers.
[b]The information is from studies at low or unclear risk of bias.

BACKGROUND

Description of the condition

Pulmonary hypertension (PH) (defined as a mean pulmonary artery pressure ≥ 25 mmHg at rest on right-heart catheterisation) comprises a complex group of conditions (see Table 1), characterised by increased right ventricular afterload, which ultimately leads to right-heart failure (McLaughlin 2009). The increased afterload may be due to passive transmission of high left-sided pressures (post-capillary pulmonary hypertension), obstruction of the pulmonary arterial bed (pre-capillary pulmonary hypertension) or a combination of both. Pulmonary arterial hypertension (PAH-WHO Group 1) is a group of diseases where pulmonary hypertension occurs in the setting of increased pulmonary vascular resistance. The more recent availability of medications and therapies targeting the pulmonary arterial bed has led to the prospect of an improvement in what had previously been a very poor prognosis. Although PAH is rare, PH secondary to left-heart disease and lung disease is much more common. The availability of drugs with efficacy in PAH has led to great interest in the use of these drugs in other forms of pulmonary hypertension.

In PAH, increased pulmonary vascular resistance is caused by vascular remodelling and thickening in the small- and medium-sized arterioles, fibrinoid necrosis, the formation of eccentric, concentric, or plexiform lesions, and the loss of vascular tone. This process of cellular hypertrophy and hyperplasia is mediated by intracellular calcium and protein kinase C, inflammatory cytokines, and altered energy metabolism. Remodelling and vasoconstriction lead to hypoxia, causing further vasoconstriction and further hypoxia (Guignabert 2013; Sim 2010).

Pulmonary hypertension is classified into five groups of multiple clinical conditions, grouped according to similar clinical presentations and pathophysiological and haemodynamic characteristics, with distinct treatment strategies for each group. Group 1 pulmonary arterial hypertension (PAH) includes idiopathic and heritable PAH and PAH due to pathology of the small pulmonary arterioles resulting from connective tissue disorders, drugs or toxins, portal pulmonary hypertension, and others (see Table 1). Pulmonary arterial hypertension is caused by increased pulmonary vascular resistance due to occlusive vasculopathy of the small pulmonary arteries and arterioles. Pulmonary arterial hypertension is a rare disease, with an estimated prevalence of 10 to 52 cases per million (Ling 2012; Peacock 2007). However, screening for pulmonary hypertension for all causes demonstrates a prevalence of 320 cases per 100,000 (Strange 2012).

Group 2 consists of pulmonary hypertension due to left-heart disease, caused by increased flow through the pulmonary vasculature, or increased pulmonary pressures (e.g. mitral valve disease, left ventricular disease, and constrictive myopathies). Group 3 comprises pulmonary hypertension as a result of lung diseases or hypoxia, or both, caused by a decrease in the area of the pulmonary vascular bed (e.g. interstitial lung disease), or conditions that induce hypoxic vasoconstriction. Group 4 refers to cases of pulmonary hypertension due to chronic thromboembolic occlusion of pulmonary vasculature, and Group 5 consists of cases of pulmonary hypertension due to unclear or multifactorial mechanisms or both, including haematological, systemic, or metabolic disorders (see Table 1) (McLaughlin 2009). The extent to which WHO Groups 2 to 5 have pulmonary arterial bed changes analogous to WHO Group 1 (and thus respond similarly to the medications) remains unclear. Furthermore, potential detrimental effects of selective arterial vasodilatation (pulmonary oedema in WHO Group 2 and hypoxia in WHO group 3) will probably present a quite different risk/benefit profile to the same medications used in PAH.

People with PAH often present with symptoms of dyspnoea, fatigue, syncope, and right-heart failure (Galiè 2016b). Right-heart catheterisation remains the gold standard of diagnosis to confirm pulmonary hypertension and to further investigate potential causes and treatment targets. Pulmonary arterial hypertension is defined as a mean pulmonary artery pressure equal to or greater than 25 mmHg; a pulmonary artery wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure less than or equal to 15 mmHg; and a pulmonary vascular resistance greater than three Wood units (Galiè 2016b). Elevation of the pulmonary artery wedge pressure suggests pulmonary hypertension secondary to left-heart disease. People with confirmed PAH should undergo acute vasodilator testing to assess for pulmonary vasoreactivity, as a small proportion may respond very favourably to long-term high-dose calcium channel blocker therapy (McLaughlin 2009).

Following history, examination, electrocardiogram, echocardiogram, and chest X-ray, other investigations for people with pulmonary hypertension should include pulmonary function tests and high-resolution computed tomography chest to assess for underlying lung disease, a ventilation/perfusion scan to assess for chronic thromboembolic pulmonary hypertension, thyroid function tests, autoimmune serology, HIV and hepatitis screening to assess for underlying aetiologies, and a six-minute walk test or exercise testing, biomarkers to monitor response to treatment and for prognostication (Galiè 2016b).

The natural history and prognosis of pulmonary hypertension varies amongst the WHO Groups. However the presence of pulmonary hypertension irrespective of WHO group generally reflects the presence of a progressive and often fatal condition. Known independent predictors of poor prognosis include advanced WHO functional class, poor performance in six-minute walk test, high right atrial pressure, significant right ventricular dysfunction, evidence of right ventricular failure, elevated pro-B-type natriuretic peptide (BNP), and low cardiac index (Thenappan 2007).

Description of the intervention

Recent years have seen the introduction of evolving therapies for PAH, with an improvement in the one-year survival rate to 84% from 68% in the 1980s (Archer 2009). The goals of therapy are to achieve a state associated with good quality of life and exercise tolerance with low mortality risk and to maintain right ventricular function, using supplemental oxygen and treatment of the underlying cause. The underlying pulmonary artery endothelial dysfunction in Group 1 PAH enables the use of PAH-specific targeted treatments promoting vasorelaxation and suppression of cellular proliferation within the pulmonary artery wall, including nitric oxide and phosphodiesterase type 5 inhibitors (PDE5i, prostanoids, endothelin receptor antagonists, and calcium channel blockers) (McLaughlin 2009).

How the intervention might work

Nitric oxide performs as a pulmonary vasodilator by activating soluble guanylate cyclase, stimulating the production of cyclic guanosine monophosphate (cGMP), which in turn activates myosin light chain phosphatase, which reduces phosphorylation of myosin to reduce pulmonary vascular tone. Increased intracellular cGMP also inhibits calcium entry, thereby reducing intracellular calcium leading to less hypertrophy and hyperplasia, as well as antiproliferative and pro-apoptotic effects that may reverse pulmonary artery remodelling. Nitric oxide also inhibits platelet recruitment, adhesion, and aggregation (Sim 2010).

However, nitric oxide administration is not without risk. High levels of inhaled nitric oxide may lead to oxidative stress and cause tissue damage, reperfusion injury, and a pulmonary inflammatory reaction. Inhaled nitric oxide is rapidly absorbed into the blood stream, where it is converted to methaemoglobin, leading to impaired rather than improved oxygen delivery (Sim 2010).

Phosphodiesterase type 5 (PDE5) specifically reduces cGMP-degrading enzyme activity, thereby increasing cGMP production. Phosphodiesterase type 5 inhibitors are not thought to induce the same levels of oxidation as inhaled nitric oxide (Ghofrani 2004d). Phosphodiesterase type 5 inhibitors that have been investigated for use in Group 1 PAH include sildenafil, tadalafil, and vardenafil. These agents have been shown in clinical trials to improve six-minute walk distance and haemodynamics (Archer 2009; Galiè 2016b; McLaughlin 2009).

The data are less clear in WHO Group 2 to 5 patients, in whom this class of drug may be potentially harmful. There are different pathobiological and pathophysiological factors at play, leading to the development of pulmonary hypertension in these people. The nature of the pulmonary arteriopathy may be quite different (e.g. hypoxic vasoconstriction and pulmonary vascular bed obstruction in Group 3; thrombotic obstruction in Group 4). The consequences of 'selective' pulmonary arterial vasodilation may also be detrimental (pulmonary oedema in WHO group 2 and hypoxia in Group 3). Thus, as with other selective pulmonary vasodilators, a reduction in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) by PDE5 inhibitors may not improve the overall well-being of patients, especially in the non-PAH Groups (2 to 5) (Guazzi 2012).

Phosphodiesterase type 5 inhibitors may theoretically improve function in Group 2 patients with left-heart disease. Previous studies in heart-failure patients have demonstrated that nitric oxide is responsible for regulation of vascular tone, and infusion of NG-monomethyl-L-arginine, an inhibitor of nitric oxide synthase, caused less vasoconstriction in heart-failure patients compared to those with a normal pulmonary vascular resistance (Cooper 1996). Trials using sildenafil in Group 2 pulmonary hypertension patients have shown some evidence of improvement in exercise capacity, ventilation efficiency, and quality of life (Lewis 2007). However, other studies have demonstrated unbalanced pulmonary dilatation as a consequence of nitric oxide and analogues may lead to increased preload due to a poorly compliant left ventricle, and therefore a significant increase in pulmonary artery wedge pressure, which may even precipitate acute pulmonary oedema (Bocchi 1994).

Furthermore, trials using other PAH-specific therapies including epoprostenol and endothelin receptor antagonists in people with Group 2 pulmonary hypertension demonstrated an increased risk of hospitalisations, disease progression, and hypoxaemia. People with left ventricular dysfunction may not be able to tolerate the increased flow across a newly-dilated pulmonary vascular bed (Guazzi 2012).

People with Group 3 chronic lung diseases may experience worsening ventilation perfusion mismatch and increased hypoxaemia. A study in people with pulmonary hypertension associated with chronic obstructive pulmonary disease demonstrated an improvement in pulmonary artery pressures, but at the cost of worsening arterial oxygenation (Blanco 2010).

Why it is important to do this review

Given recent advances in the understanding of the pathophysiological mechanisms and treatments for pulmonary hypertension with significant contributions in the area in the last decade, we planned to summarise the current evidence relating to the use of PDE5 inhibitors in pulmonary hypertension.

This review aimed to quantify any potential benefit for PDE5 inhibitors in people with PAH in terms of haemodynamic measurements and patient-centred outcomes, and to balance this against any potential treatment harms, in order to guide patient preference, clinician treatment choices, and guidelines for policymakers.

This review also examines the available evidence to determine whether there is any potential benefit or harm in using PDE5 inhibitors in people with Group 2 to 5 pulmonary hypertension.

This review builds on a previous review (Kanthapillai 2004), since which further concepts about pathophysiology have been developed, and a number of more recent randomised controlled trials using PDE5 inhibitors have been published.

OBJECTIVES

To determine the efficacy of PDE5 inhibitors for pulmonary hypertension in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We include single- or double-blinded randomised controlled trials (RCTs) in which PDE5 inhibitors are compared to placebo or to any other treatment. We defined 'randomised' as studies described by the author as 'randomised' anywhere in the study report. All trials defined as such, published or unpublished, in any language, were eligible for inclusion.

Types of participants

We include any individual with a diagnosis of pulmonary hypertension from any cause who required medical treatment for their condition. We define pulmonary hypertension according to accepted criteria (Galiè 2016b; McLaughlin 2009).

1. Comparison 1 specifically assesses the effects of PDE5 inhibitors compared to placebo on Group 1 PAH, confirmed as a

mean pulmonary artery pressure ≥ 25 mmHg by right-heart catheterisation.
2. Comparison 2 compares PDE5 inhibitors with placebo in PAH participants on combination therapy.
3. Comparison 3 compares PDE5 inhibitors to ERAs in PAH participants.
4. Comparison 4 includes group 2 pulmonary hypertension participants with a diagnosis of pulmonary hypertension and left-heart disease, as defined by the authors.
5. Comparison 5 includes group 3 pulmonary hypertension participants with a diagnosis of pulmonary hypertension and lung disease, as defined by the authors.
6. Comparison 6 includes group 4 pulmonary hypertension participants with a diagnosis of pulmonary hypertension and chronic thromboembolic disease (CTEPH), as defined by the authors.
7. Comparison 7 includes mixed group 2 to 5 pulmonary hypertension participants with a diagnosis of pulmonary hypertension as defined by the authors.

We planned to specify subgroups of adults (older than 18 years) and a paediatric population younger than 18 years.

Types of interventions

We include studies comparing any type of PDE5 inhibitors by any route of administration with placebo or any other treatment used for pulmonary hypertension. We include studies with co-interventions provided they are not part of the randomised treatment. We aimed to perform subgroup analyses depending on the co-interventions used. Where studies were too heterogenous for meta-analyses, we describe them in narrative form.

Types of outcome measures

Primary outcomes

1. Change in WHO functional class
2. Six-minute walk distance (6MWD)
3. Mortality

Secondary outcomes

1. Haemodynamic parameters, including change in mean pulmonary artery pressure, change in cardiac output, cardiac index
2. Exercise capacity other than six-minute walk distance
3. Quality of life/health status, by any validated scale
4. Dyspnoea score, including visual analogue scale or Borg scale
5. Hospitalisation/intervention
6. Adverse events

Reporting one or more of the outcomes listed here in the study was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We identified trials from searches of the following databases up to 26 September 2018:

1. The Cochrane Airways Group Register of Trials;
2. Cochrane Central Register of Controlled Trials (CENTRAL) through the Cochrane Register of Studies Online (crso.cochrane.org);
3. MEDLINE (Ovid) 1950 to 26 September 2018;
4. Embase (Ovid) 1974 to 26 September 2018;
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
6. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

We provide the database search strategies in Appendix 1. We searched all databases from their inception to the present, with no restriction on language of publication. We searched for handsearched conference abstracts and grey literature through the CENTRAL database.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We handsearched reference lists of included studies, relevant chapters, and review articles. We used Google to search for grey literature and conference abstracts. We translated any relevant article into English for potential inclusion. Where data were missing, we attempted to contact the trial investigators.

Data collection and analysis

Selection of studies

Two review authors (HB and ZB) independently screened all abstracts to determine if they met the inclusion criteria for the review. We sought full-text publications for those papers that possibly or definitely met the inclusion criteria. Two review authors independently reviewed all full-text articles to determine eligibility, recording reasons for ineligibility of those that did not. We resolved any disagreements through discussion, or by seeking consensus from a third review author (AB). We included a PRISMA study flow diagram in the full review to document the screening process, and included a Characteristics of included studies table (Moher 2009).

Data extraction and management

Two review authors (HB and ZB) independently extracted data from included studies, and where appropriate, pooled data in the Cochrane statistical software Review Manager 5 for further analysis (RevMan 2014). We used a data collection form that we piloted on one study for inclusion in the review, containing the following data.

1. Methods: study design, duration, study setting, date of study.
2. Participants: number, mean age and age range, gender, inclusion and exclusion criteria.
3. Intervention: type of PDE5 inhibitor, dose, mode of administration, control drug, co-interventions, and exclusions.
4. Outcomes: primary and secondary outcomes as specified, type of scale used, time points collected.
5. Risk of bias summary.
6. Other: funding for trial, any conflicts of interest for trial authors.

Assessment of risk of bias in included studies

Two review authors (HB and ZB) independently assessed the included studies for risks of bias using the Cochrane 'Risk of

bias' assessment tool (Higgins 2011). We assessed the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other potential sources of bias.

We judged each potential source of bias as low risk, unclear risk (insufficient information to form a judgement), or high risk, and provided justification with evidence from each trial in the 'Risk of bias' table. When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the previously published protocol, and justified any deviations from it in the Differences between protocol and review section of the review.

Measures of treatment effect

Where possible, we pooled and presented results from dichotomous data as odds ratios (ORs). Where possible, we presented results from continuous variables and calculated the mean difference (MD) or standardised mean difference (SMD) where scales are combined, with the 95% confidence interval (95% CI). Where we combined data from rating scales in a meta-analysis, we ensured that they were entered with a consistent direction of effect (e.g. lower scores always indicate improvement). If both change from baseline and endpoint scores were available for continuous data, we used change from baseline scores. Where outcomes were reported at multiple time points, we consistently extracted and included the latest reported time point, but also considered outcomes reported at other time points. We only combined data reported at different time points if this was clinically appropriate.

We described skewed data narratively (e.g. as medians and interquartile ranges for each group).

We used intention-to-treat or 'full analysis set' analyses where they were reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per-protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we used participants rather than events as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). Where rate ratios were reported in a study, we analysed them on that basis. We planned to only meta-analyse data from cluster-randomised controlled trials if the available data have been adjusted (or could be adjusted) to account for the clustering, however there were no cluster-randomised controlled trials identified for inclusion.

Dealing with missing data

We contacted investigators in order to verify key study characteristics including methods of randomisation, and obtained missing numerical outcome data where possible (e.g. when we identified a study as an abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we took this into consideration in the GRADE rating for affected outcomes. We planned to only meta-analyse data from cluster-RCTs if the available data had been adjusted (or could be adjusted), to account for the clustering.

Assessment of heterogeneity

For pooled analyses we quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials due to heterogeneity rather than to sampling error. We considered significant statistical heterogeneity to be present if the I^2 is greater than 50%. Where we identified significant heterogeneity, we attempted to explore possible causes using prespecified subgroup analyses.

Assessment of reporting biases

Where sufficient studies were present, we planned to create and examine a funnel plot to explore small-study and publication biases; however, there are currently insufficient studies.

Data synthesis

We used a fixed-effects model and performed a sensitivity analysis comparing the fixed- and random-effects model. Where possible we pooled dichotomous outcome variables using a Mantel-Haenszel OR with 95% CIs. For continuous outcomes, we analysed data as MDs or standardised mean difference (SMD) where scales are combined, with the 95% confidence interval (95% CI). We calculated the number needed to treat for an additional beneficial outcome (NNTB) from the pooled OR and assumed control risk using the formula described in Section 12.5 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

'Summary of findings' table

We created seven 'Summary of findings' tables that include WHO functional class status, quality of life, mortality, change in haemodynamics, and six-minute walk distance. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We used the methods and recommendations described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schüneman 2017), employing GRADEpro software (GRADEpro GDT). We justified all decisions to downgrade the quality of studies using footnotes, and made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses:

1. Paediatric population up to 18 years and an adult population aged 18 years or over.
2. Dosage of PDE5 inhibitor.
3. Mode of administration.

With the following outcomes in subgroup analyses:

1. WHO functional class.

2. Mortality.
3. Six-minute walk distance.
4. Haemodynamic criteria.

However, there were insufficient studies per comparison to perform meta-analyses for these subgroups, so we present narrative results (described in-text where applicable).

Sensitivity analysis

We planned to carry out the following sensitivity analyses:

- Exclusion of trials identified as being at high risk of selection bias (described in-text where applicable).
- Fixed-effect model compared with random-effects model (presented in table form).

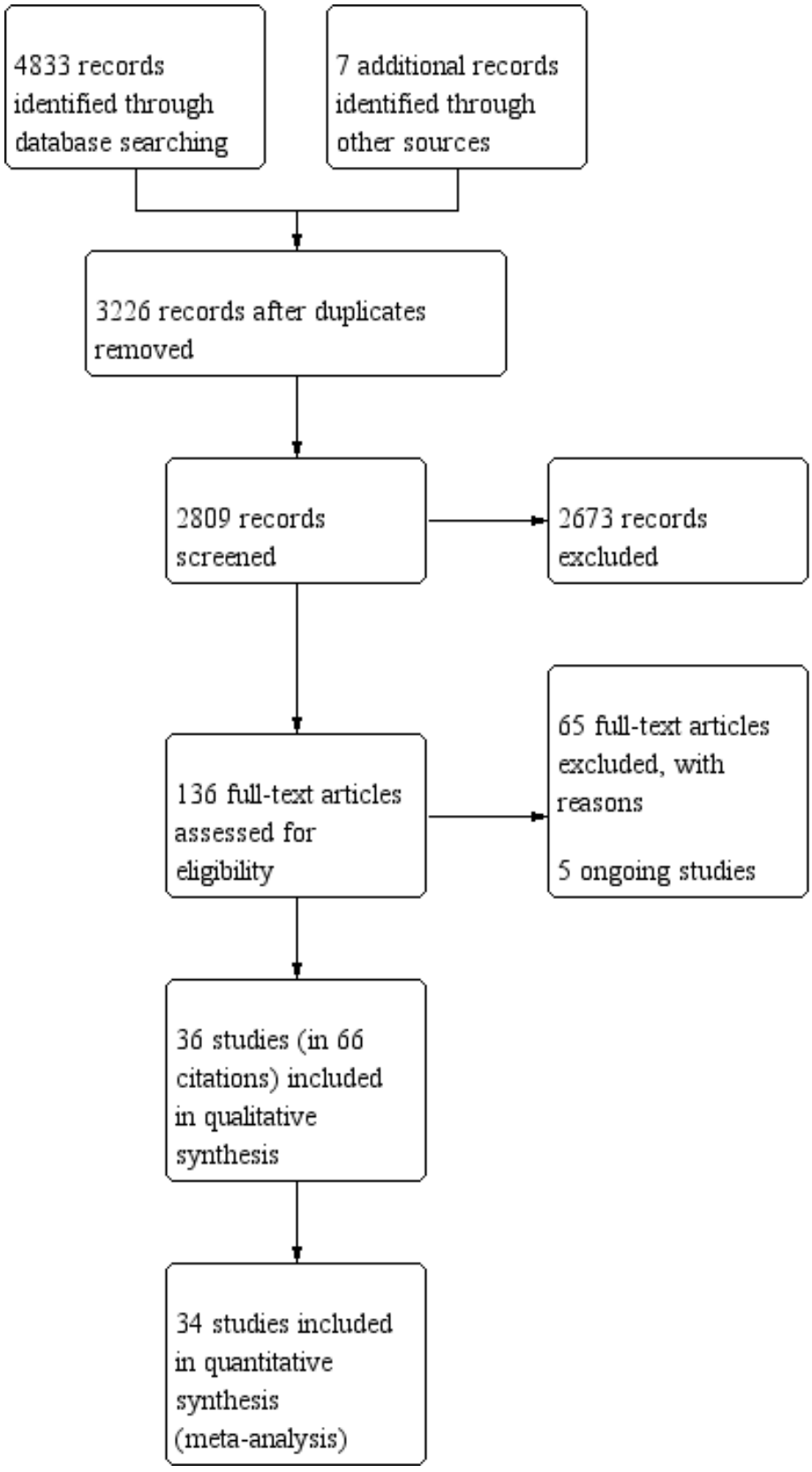
RESULTS

Description of studies

Results of the search

We identified 4840 citations in the initial search, and after screening abstracts, selected 136 studies for full-text review. We included 36 trials with 2999 participants in the final review, plus earlier published abstracts, further post hoc analyses and analyses of secondary outcomes (see Figure 1). We also found five ongoing studies (see Characteristics of ongoing studies).

Figure 1. Study flow diagram.



Included studies

Group 1: Pulmonary arterial hypertension

We included all but two of the 36 studies in the final meta-analysis; Jalalian 2015 included participants with pulmonary hypertension secondary to sickle cell disease, and Machado 2009 included participants with pulmonary hypertension secondary to beta-thalassemia, and was stopped early due to increased adverse events in the treatment arm. All studies were randomised; 30 were parallel-controlled and six were cross-over trials.

Nineteen trials included group 1 PAH participants (Albini 2017; Bharani 2003; Bharani 2007; Boonstra 2005; Galiè 2005a; Galiè 2009; Galiè 2015; Iversen 2009 (specifically Eisenmenger's syndrome); Jing 2011; Mazzanti 2013; Mukhopadhyay 2011; (Barst 2012; Palii 2014 - specifically children with PAH); Sastry 2004; Simonneau 2008; Singh 2006; Vizza 2017a; Wilkins 2005; Zhuang 2014). Most trials recruited participants with WHO functional class II and III (see Characteristics of included studies).

Eleven trials in PAH participants compared a PDE5 inhibitor to placebo: seven trials compared sildenafil to placebo (Barst 2012; Bharani 2003; Boonstra 2005; Galiè 2005a; Palii 2014; Sastry 2004; Singh 2006), three compared tadalafil to placebo (Bharani 2007; Galiè 2009; Mukhopadhyay 2011), and one compared vardenafil to placebo (Jing 2011).

Four studies compared PDE5 inhibitors to placebo, whilst on additional combination therapy (all as add-on therapy) (Iversen 2009; Simonneau 2008; Vizza 2017a; Zhuang 2014), and four studies (Albini 2017; Galiè 2015; Mazzanti 2013; Wilkins 2005) compared PDE5 inhibitors to endothelin receptor antagonists.

In the PAH trials, sildenafil was prescribed in eight hourly divided doses, with dosages ranging from 20 to 100 mg three times daily. Where multiple doses were compared, we used results from the highest dose where appropriate (e.g. haemodynamics), and aggregated doses where appropriate (e.g. mortality). Tadalafil was dosed 2.5 to 40 mg daily and vardenafil 5 mg twice daily. The duration of trials ranged from two weeks to 12 months, with a mean treatment duration of 14 weeks.

In PAH participants, the primary outcomes of six-minute walk distance (6MWD) was reported in 15 trials (Albini 2017; Bharani 2003; Bharani 2007; Boonstra 2005; Galiè 2005a; Galiè 2009; Iversen 2009; Jing 2011; Mukhopadhyay 2011; Palii 2014; Sastry 2004; Simonneau 2008; Singh 2006; Vizza 2017a; Zhuang 2014), WHO functional class improvement in seven of 19 trials (Bharani 2007; Galiè 2005a; Galiè 2015; Jing 2011; Mukhopadhyay 2011; Vizza 2017a; Zhuang 2014), and mortality in 13 of 19 trials (Barst 2012; Bharani 2003; Bharani 2007; Galiè 2005a; Galiè 2009; Galiè 2015; Jing 2011; Palii 2014; Sastry 2004; Simonneau 2008; Wilkins 2005; Vizza 2017a; Zhuang 2014). Haemodynamic data were reported in 12 of 19 trials (Albini 2017; Barst 2012; Bharani 2003; Bharani 2007; Galiè 2005a; Iversen 2009; Jing 2011; Mukhopadhyay 2011; Sastry 2004; Simonneau 2008; Singh 2006; Zhuang 2014), For quality of life, two trials used the SF-36 form (scores 1 to 100, higher scores indicate better quality of life) (Galiè 2005a; Simonneau 2008); minimum clinical improvement difference (MCID) for physical functioning domain for PAH = 13, vitality = 15 (Gilbert 2009). One used a heart failure questionnaire (Sastry 2004), where the higher the score the better the quality of life, and one (Wilkins 2005) used the Kansas City Cardiomyopathy Questionnaire, where higher scores indicated better quality of life. Six trials measured dyspnoea using the Borg dyspnoea scale (MCID for PAH = 1 (Khair 2016)) (Bharani 2003; Bharani 2007; Galiè 2005a; Jing 2011; Sastry 2004; Vizza 2017a). Eleven studies reported adverse events (Albini 2017; Galiè 2005a; Galiè 2009; Galiè 2015; Iversen 2009; Jing 2011; Mukhopadhyay 2011; Sastry 2004; Simonneau 2008; Vizza 2017a; Zhuang 2014).

Group 2: Pulmonary hypertension due to left-heart disease

Five trials included PH secondary to left-heart disease (Bermejo 2017 (valvular heart disease); Guazzi 2011a (HFpEF); Hoendermis 2015 (HFpEF); Lewis 2007 (systolic heart failure); Ovchinnov 2015 (diastolic heart failure)). Heart failure was reported as optimally treated according to accepted guidelines at the time of enrolment. All five trials used sildenafil 25 to 75 mg three times daily compared to placebo. Three trials had a 12-week duration, one trial was for six months (Bermejo 2017), and one trial (Guazzi 2011a) had a 12-month duration. In terms of primary outcomes, three of the five reported improvement in WHO functional class (Bermejo 2017; Hoendermis 2015; Lewis 2007), three of the five reported 6MWD (Bermejo 2017; Lewis 2007; Ovchinnov 2015), and three of the five reported mortality (Bermejo 2017; Hoendermis 2015; Lewis 2007). Haemodynamic data were assessed using right-heart catheterisation in three of the five trials (Guazzi 2011a; Hoendermis 2015; Lewis 2007), and pulmonary artery systolic pressure (PASP) using transthoracic ultrasound in one trial (Bermejo 2017). Quality of life was reported in one trial (Hoendermis 2015) using the Kansas City Cardiomyopathy Questionnaire (23 items, a higher score indicating better quality of life), and one trial (Guazzi 2011a) reported dyspnoea. Two trials reported adverse events, including exacerbation of heart failure (Bermejo 2017; Guazzi 2011a).

Group 3: Pulmonary hypertension due to lung disease

Five trials included PH secondary to lung disease, predominantly that of COPD (Blanco 2013; Goudie 2014; Rao 2011; Vitulo 2016), and one with IPF (Han 2013). The duration was 12 to 16 weeks (median 12 weeks). Four compared sildenafil to placebo (Blanco 2013; Han 2013; Rao 2011; Vitulo 2016) and one (Goudie 2014) compared tadalafil to placebo. The primary outcomes of improvement in WHO functional class were reported in only one trial (Rao 2011); 6MWD in all five trials, and no trials reported mortality. Only two trials (Rao 2011; Vitulo 2016) reported haemodynamic data. Blanco 2013 reported quality of life using SFGRQ (although this was reported using median and IQR) and SF-36. Goudie 2014 reported SF-36 and Minnesota Questionnaire. Vitulo 2016 reported SF-36 and BODE index. No trials reported dyspnoea. Three trials reported adverse events, although insufficient data were provided to produce a meta-analysis.

Group 4: Chronic thromboembolic pulmonary hypertension

Three trials included CTEPH participants (Galiè 2016a; Palazzini 2010; Suntharalingham 2008). All trials used sildenafil, with two (Palazzini 2010; Suntharalingham 2008) comparing to placebo, and Galiè 2016a comparing to bosentan. Trial duration was a mean of 3.5 months. Improvement in functional class was reported in one study, 6MWD in all three studies, mortality in all three studies, and haemodynamic data in all three studies. One study (Suntharalingham 2008) measured quality of life using the CAMPHOR scale (higher scores indicate worse quality of life), and also reported dyspnoea using the Borg scale. Only one study reported adverse events.

Mixed group 2 to 4 pulmonary hypertension

Two trials enrolled participants with PH across WHO Groups 2 and 3 (Dwivedi 2015; Salem 2013), including participants with secondary pulmonary hypertension due to COPD, heart failure, valvular heart disease, and cardiomyopathy. Sildenafil 20 to 50 mg three times daily was compared to placebo. Only improvement in functional class, 6MWD, and PASP were reported.

Group 5: Haematological disorders

Two trials included participants with PH secondary to haematological disorders (Machado 2009 (sickle cell disease); Jalalian 2015 (beta-thalassemia)). We analysed these trials descriptively and separately.

Excluded studies

We excluded 65 studies for the following reasons: ineligible participant population (6); ineligible intervention (13); ineligible study design (22); extension of a previous study (9); post-hoc analysis (15) (see Characteristics of excluded studies).

Risk of bias in included studies

We assessed the risks of bias in the included studies using the Cochrane 'Risk of bias' assessment tool (Higgins 2017), and included the domains of allocation, blinding, incomplete outcome data, selective reporting, and other potential sources of bias. Please see Figure 2 for a summary of the 'Risk of bias' findings.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

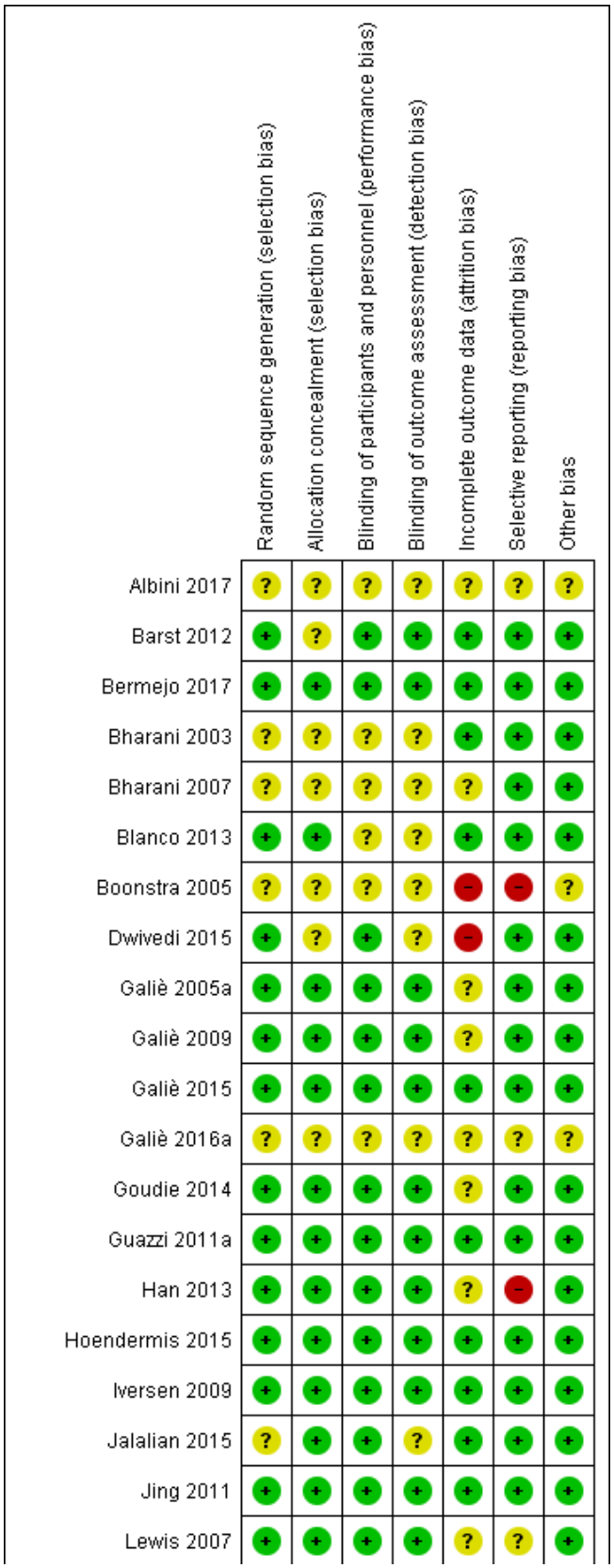
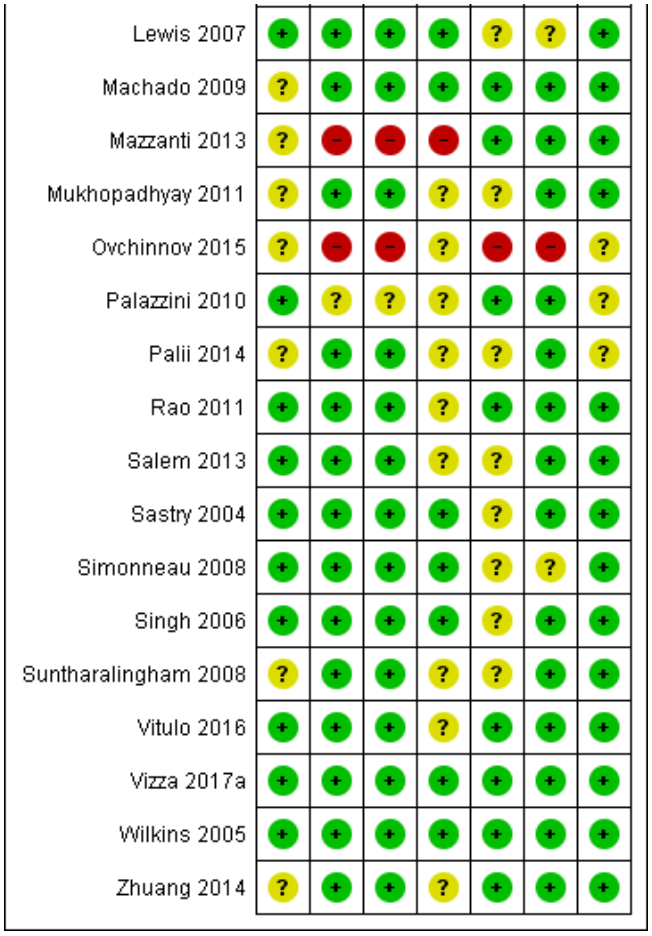


Figure 2. (Continued)



Allocation

We assessed random sequence generation as low risk for 23 studies. Albini 2017; Bharani 2003; Bharani 2007; Boonstra 2005; Galiè 2016a; Jalalian 2015; Machado 2009; Mazzanti 2013; Mukhopadhyay 2011; Ovchinnov 2015; Palii 2014; Suntharalingham 2008; Zhuang 2014 were at unclear risk, as they did not report methods of random sequence generation.

We assessed allocation concealment as low risk for 26 studies and unclear risk for Albini 2017; Barst 2012; Bharani 2003; Bharani 2007; Boonstra 2005; Dwivedi 2015; Galiè 2016a; Palazzini 2010, as allocation concealment was not reported. We assessed Mazzanti 2013 and Ovchinnov 2015 as high risk, as each study was reported as an open-label study.

Blinding

We assessed Bharani 2003; Bharani 2007; Blanco 2013; Boonstra 2005; Galiè 2016a; Palazzini 2010; Palii 2014; Rao 2011; Salem 2013; Suntharalingham 2008; Vitulo 2016 as being at unclear risk, as blinding of participants and personnel was not clearly reported. Ovchinnov 2015 and Mazzanti 2013 were assessed as being at high risk as the trials were reported as open-label studies, so it was likely that participants knew which intervention they were receiving.

We assessed Albini 2017; Bharani 2003; Bharani 2007; Blanco 2013; Boonstra 2005; Dwivedi 2015; Galiè 2016a; Jalalian 2015; Mukhopadhyay 2011; Ovchinnov 2015; Palazzini 2010; Palii 2014; Rao 2011; Salem 2013; Suntharalingham 2008; Vitulo 2016; Zhuang 2014 as being at unclear risk of detection bias, as methods for blinding of outcomes were not clearly reported. We assessed Mazzanti 2013 as being at high risk, as this trial was reported as open-label and there were no specified methods to keep outcomes blinded from assessors.

Incomplete outcome data

We assessed attrition bias as unclear risk in 15 studies: Albini 2017; Bharani 2007; Galiè 2005a; Galiè 2009; Galiè 2016a; Goudie 2014; Han 2013; Lewis 2007; Mukhopadhyay 2011; Palii 2014; Salem 2013; Sastry 2004; Simonneau 2008; Singh 2006; Suntharalingham 2008, given that only a proportion of participants who were enrolled completed the study, for reasons which were not given; however, this included both intervention and comparator arms in approximately equal proportions.

For Boonstra 2005 and Dwivedi 2015, about one-third of enrolled participants did not complete the study, for unknown reasons, so we assigned this a high risk of bias. For Ovchinnov 2015, the number of enrolled participants and the number of completers were not reported, so we rated this at high risk.

Selective reporting

We found reporting bias to be high risk in Boonstra 2005, as only one outcome was reported. Han 2013 was a substudy of the STEP-IPF trial, and it is not clear if this analysis was planned a priori so we assessed it as high risk. Ovchinnov 2015 only reported quantitative data from the intervention group and not from the comparator group, and no between-group effect sizes were reported, so we rated it at high risk. Simonneau 2008 reported that they only assessed secondary outcomes if the primary outcomes were significant, although it is unclear if this affected the overall reporting of the trial outcomes, as a number of secondary outcomes were reported; we assessed this as high risk of bias.

Other potential sources of bias

We assessed Albini 2017; Boonstra 2005; Galiè 2016a; Ovchinnov 2015; Palazzini 2010; and Palii 2014 as unclear risk of other bias, as these were abstracts from conference proceedings, and were not recorded in any clinical trials registry, with limited information about methods used and limited data presented to determine if other significant risk was present.

Effects of interventions

See: **Summary of findings for the main comparison** Group 1 Pulmonary arterial hypertension - PDE5i compared to placebo; **Summary of findings 2** Group 1 Pulmonary arterial hypertension - PDE5i compared to placebo, on combination therapy; **Summary of findings 3** Group 1 Pulmonary arterial hypertension - PDE5i compared to ERA; **Summary of findings 4** Group 2 Pulmonary hypertension due to left-heart disease - PDE5i compared to placebo; **Summary of findings 5** Group 3 Pulmonary hypertension due to lung disease - PDE5i compared to placebo; **Summary of findings 6** Group 4 Pulmonary hypertension due to CTEPH - PDE5i compared to placebo; **Summary of findings 7** Mixed Pulmonary hypertension group 2 - 4 - PDE5i compared to placebo

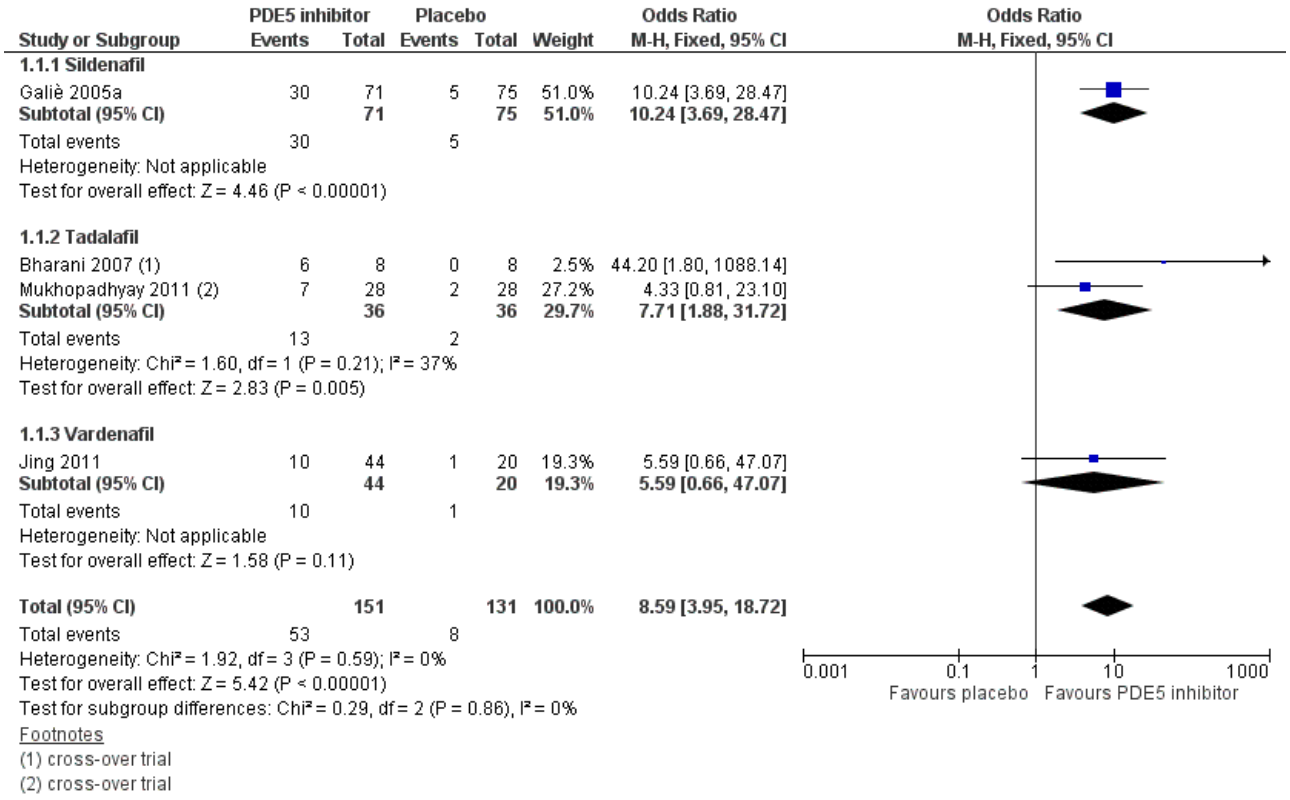
Group 1: Pulmonary arterial hypertension

PDE5 inhibitors compared to placebo

Change in WHO functional class

Four studies assessed change in WHO functional class (Comparison 1). There was a significant improvement in WHO functional class favouring PDE5 inhibitors when compared to placebo, (odds ratio (OR) 8.59, 95% CI 3.95 to 18.72; P < 0.001; 4 trials, 282 participants; I^2 = 0%; Analysis 1.1; see Figure 3).

Figure 3. Forest plot of comparison: 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, outcome: 1.1 Improvement in WHO functional class.



Six-minute walk distance

Eight studies assessed 6MWD. There was a significant improvement in 6MWD using PDE5 inhibitors compared to placebo (mean difference between PDE5i and placebo (MD) 48 metres, 95% CI 40 to 56; P <0.001; 8 trials, 880 participants; Analysis 1.2). The effect was clinically significant, with a mean difference of 48 metres (MCID in PAH is 41 metres (Gilbert 2009)). The effect on 6MWD was comparable between drugs (sildenafil MD 57 metres, 95% CI 44

to 69; P < 0.001; 4 trials, 339 participants; tadalafil MD 38 metres, 95% CI 28 to 49; P < 0.001; 3 trials, 477 participants; vardenafil MD 69 metres, 95% CI 41 to 97; P < 0.001; 1 trial, 64 participants). There was significant heterogeneity between trials (I^2 = 71; P = 0.03), which is not fully explained by the different drugs used in each trial (subgroup difference I^2 = 51%; P = 0.03).

Mortality

There was a significant effect on mortality using PDE5 inhibitors compared to placebo (OR 0.22, 95% CI 0.07 to 0.68, P = 0.009; 8 trials, 1119 participants; Analysis 1.3; see Figure 4). In the placebo group four people out of 100 died, compared to one (95% CI 0 to 3) out of 100 for the PDE5 inhibitor group; see Figure 5. The number needed to treat to prevent one additional death was 32 (95% CI 27 to 78).

Figure 4. Forest plot of comparison: 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, outcome: 1.3 Mortality.

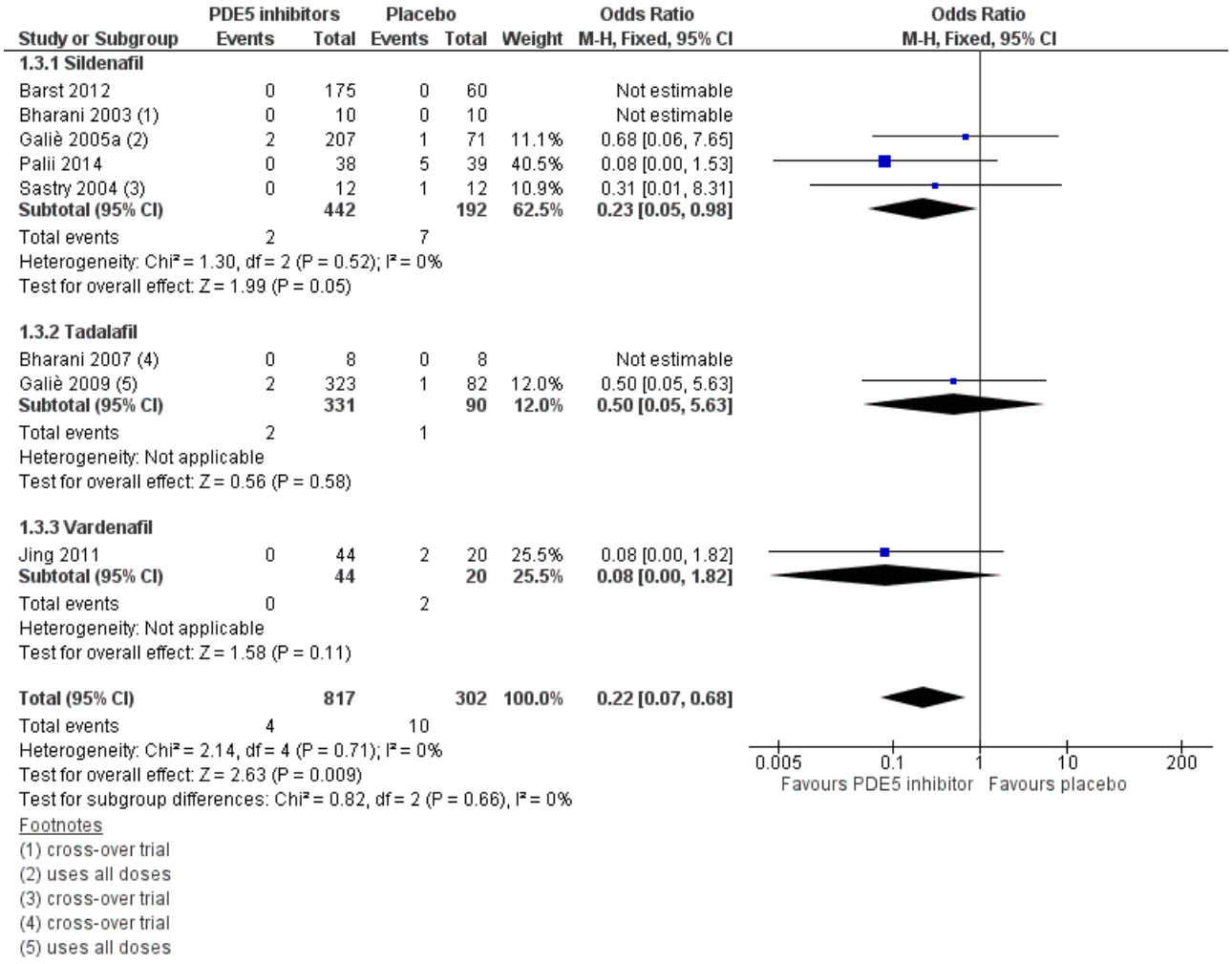


Figure 5. Cates Plot for mortality with PDE5 inhibitor treatment in Group 1 PAH

Haemodynamics

There was a significant reduction in the mean PAP (MD −6.43 mmHg, 95% CI −8.13 to −4.74; P < 0.001; 6 trials, 453 participants; Analysis 1.4), in the right arterial pressure (RAP) (MD −1.35 mmHg, 95% CI −2.34 to −0.36; P = 0.008; 3 trials, 341 participants; Analysis 1.5), in cardiac index (MD 0.28 L/min/m^2, 95% CI 0.16 to 0.40; P < 0.001; 4 trials, 239 participants; Analysis 1.6), in PVR (MD −4.74 WU, 95% CI −6.13 to −3.35; P < 0.0001; 3 trials, 266 participants; Analysis 1.7), and in PASP (MD −11.62 mmHg, 95% CI −25.18 to 1.94; P = 0.09; 2 trials, 48 participants; Analysis 1.8). There was significant heterogeneity between trials for mean PAP (I^2 = 76%; P = 0.01). However, the test for subgroup difference was not significant (P = 0.23; I^2 = 31%), suggesting that factors other than different drugs across trials may account for this heterogeneity. There was also significant heterogeneity for cardiac index (I^2 = 77%; P = 0.005). The test for subgroup difference (P = 0.03; I^2 = 82%) indicated that the difference between different drugs used may account for this heterogeneity.

Exercise capacity other than six-minute walk distance

Two studies assessed exercise capacity. Sastry 2004 examined time on treadmill (using the Naughton protocol) and found a statistically significant difference favouring sildenafil with post-treatment sildenafil 686.82 metres (SD 224.02) compared to placebo 475.05 metres (SD 168.02; P < 0.001). Singh 2006 assessed Mets achieved using a modified Bruce exercise protocol. There was a statistically significant difference favouring sildenafil post-treatment 687 seconds (SD 243.9 sec) compared to placebo 452.1 seconds (SD 165.6 sec) (P < 0.001).

Quality of life

Only two studies assessed quality of life, and data were considered too heterogenous to combine in a meta-analysis. Galiè 2005a assessed quality of life using two measures: the Medical Outcomes Study 36-item short form (SF-36), divided into physical functioning, general health, and vitality domains (scores 1 to 100, higher scores indicate better quality of life), and found a statistically significant improvement in all SF-36 domains for sildenafil-treated participants, and when compared to placebo in physical functioning (P < 0.001), general health (P < 0.001), and vitality (P < 0.05). There was also a statistically significant improvement in placebo-treated participants in the physical functioning domain. They also used the EuroQol 5D (EQ-5D) questionnaires at baseline and after 12 and 24 weeks of treatment (comprise five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; higher scores indicate worse quality of life). Statistically significant improvements were also observed for the EQ-5D current health status (P < 0.01) and utility index (P < 0.01).

Sastry 2004 assessed quality of life using a chronic heart failure questionnaire, includes the following domains: dyspnoea, fatigue,

and emotional function of daily living; lower scores indicate worse quality of life. There was a statistically significant difference in the fatigue domain (sildenafil post-treatment score 22.33, SD 4.82 compared to placebo post-treatment score 20.67, SD 5.19; P = 0.04), and a statistically non-significant difference in the emotional function domain (sildenafil post-treatment score 37.33, SD 9.3, compared to placebo post-treatment score 34.71, SD 10.91; P = 0.06), favouring sildenafil compared with placebo.

Dyspnoea

Five trials assessed dyspnoea: four (Bharani 2003; Bharani 2007; Galiè 2005a; Jing 2011) used the Borg scale and one (Sastry 2004) used a chronic heart failure questionnaire. When we combined the studies using Borg scale, there was a statistically significant improvement in dyspnoea (MD −0.72, 95% CI −0.99 to −0.44; P < 0.001; 4 studies, 239 participants; Analysis 1.9), but the effect size did not meet the minimum clinical improvement difference (MCID = 1, Khair 2016). There was significant heterogeneity across trials (I^2 = 64%; P = 0.04), but the test for subgroup differences (I^2 = 37%; P = 0.20) suggests that factors other than different drugs may account for differences across the trials.

Hospitalisation/intervention

Three trials (746 participants) reported clinical worsening requiring intervention, including hospitalisation and initiation or addition of new therapy. There was no statistically significant difference, although the effect estimate favoured PDE5 inhibitors compared to placebo (OR 0.58, 95% CI 0.27 to 1.23; P = 0.16; Analysis 1.10).

Adverse events

There were more adverse events in the PDE5 inhibitor participants compared to placebo (Analysis 1.11).

There was a statistically significant increase in headache (OR 1.97, 95% CI 1.33 to 2.92; P < 0.001; 5 studies, 848 participants), in gastrointestinal (GI) upset (OR 1.63, 95% CI 1.07 to 2.48; P = 0.02; 5 studies, 848 participants), in flushing (OR 4.12, 95% CI 1.83 to 9.26; P < 0.001; 3 studies, 748 participants), and in muscle aches and joint pains (OR 2.52, 95% CI 1.59 to 3.99; P < 0.001; 4 studies, 792 participants).

There was no statistically significant difference in epistaxis (OR 2.37, 95% CI 0.83 to 6.77; P = 0.11; 2 studies, 682 participants), in respiratory symptoms (OR 1.74, 95% CI 0.89 to 3.40; P = 0.10; 3 studies, 748 participants), or in visual disturbance (OR 2.04, 95% CI 0.58 to 7.14; P = 0.27; 3 studies, 748 participants).

Although different formulation of drugs were not compared head-to-head, when comparing the odds of developing an adverse event, tadalafil appeared to cause greater frequency of headaches (OR 2.86, 95% CI 1.51 to 5.42; P = 0.001) compared to sildenafil (OR 1.43, 95% CI 0.83 to 2.44; P = 0.20), greater GI upset (OR 1.93, 95% CI 1.07 to 3.50; P = 0.03) compared to sildenafil (OR 1.50, 95% CI 0.81 to 2.78; P = 0.19), and greater frequency of muscle and joint pains (OR 4.02, 95% CI 2.05 to 7.89; P < 0.001) compared to sildenafil (OR 1.48, 95% CI 0.93 to 2.99; P = 0.27).

Subgroup analyses

There were no individual patient data to compare outcomes for a paediatric population versus an adult population. Palii 2014 recruited only children with PAH due to congenital cardiac shunts and found benefit in improvement in functional class, mortality (5 of 39 died at 6 to 12 months in the placebo group compared to none of 38 in the sildenafil group), improved exercise tolerance, and improved haemodynamics. Barst 2012 recruited only children with pulmonary arterial hypertension, and found no significant difference in terms of exercise duration or cardiopulmonary haemodynamics.

Almost all trials included participants with WHO functional class II/III. Boonstra 2005 compared participants with WHO FC I/II and III/IV and found that the six-minute walk distance improved in both groups (49 metres improvement in WHO FC I/II (n = 27) and 54 metres improvement in WHO FC III/IV (n = 42)).

PDE5 inhibitors compared to placebo on additional therapy

Four trials compared PDE5 inhibitors to placebo, whilst on other therapy for pulmonary hypertension (Comparison 2). Iversen 2009 and Vizza 2017a compared sildenafil to placebo as add-on therapy to bosentan. Simonneau 2008 compared sildenafil to placebo as add-on therapy to intravenous epoprostenol. Zhuang 2014 compared tadalafil to placebo as add-on therapy to ambrisentan.

Change in WHO functional class

There was no significant difference in WHO functional class (OR 1.20, 95% CI 0.66 to 2.17; P = 0.55; 2 trials, 227 participants; Analysis 2.1).

Six-minute walk distance

There was a statistically significant difference in 6MWD using PDE5 inhibitors compared to placebo as add-on therapy (MD 20, 95% CI 9 to 30; P < 0.001; 4 trials, 509 participants; Analysis 2.2), but this did not meet the MCID threshold (41 metres; Gilbert 2009).

Mortality

There was no statistically significant difference in mortality using PDE5 inhibitors compared to placebo as add-on therapy (OR 0.26, 95% CI 0.07 to 1.06; P = 0.06; 3 trials, 492 participants; Analysis 2.3).

Haemodynamics

There was a statistically significant reduction in mean PAP (MD −4.58 mmHg, 95% CI −6.14 to −3.01; P < 0.001; 2 trials, 387 participants; Analysis 2.4), and in PVR (SMD −0.48, 95% CI −0.72 to −0.25; P > 0.001; 3 trials, 303 participants; Analysis 2.6) and a statistically significant increase in cardiac output (MD 0.87 L/min, 95% CI 0.53 to 1.21; P < 0.001; 3 trials, 310 participants; Analysis 2.5) using sildenafil compared to placebo as add-on therapy.

Exercise capacity other than six-minute walk distance

No studies reported additional exercise testing.

Quality of life

One trial (Simonneau 2008) assessed quality of life using SF-36. There was a significant improvement in the sildenafil group in terms of physical functioning (MD 0.3, 95% CI 4.7 to 4.1 for placebo versus MD 7.8, 95% CI 3.6 to 12.1 for sildenafil; P = 0.003), general health (MD 1.4, 95% CI 4.8 to 2.1 versus MD 6.6, 95% CI 3.3 to 9.9; P = 0.001), vitality (MD 0.8, 95% CI 3.3 to 4.9 versus MD 10.2, 95% CI 6.2 to 14.2; P = 0.001), social functioning (MD 2.5, 95% CI 7.8 to 2.9 versus MD 4.0, 95% CI 1.1 to 9.2; P = 0.05), and mental health (MD 3.7, 95% CI 7.0 to 0.5 versus MD 3.0, 95% CI 0.1 to 6.2; P = 0.001), but

not in physical role (MD 3.6, 95% CI 5.4 to 12.7 versus MD 10.7, 95% CI 2.0 to 19.4; P = 0.20), bodily pain (MD 0.6, 95% CI 4.3 to 5.5 versus MD 5.8, 95% CI 1.0 to 10.6; P = 0.09), or emotional role (MD 4.6, 95% CI 4.2 to 13.5 versus MD 1.8, 95% CI 6.8 to 10.3; P = 0.60).

Dyspnoea

No studies assessed the effect on dyspnoea.

Hospitalisation/intervention

Four studies assessed clinical worsening requiring hospitalisation or additional therapy. There was a statistically significant difference favouring PDE5 inhibitors compared to placebo as add-on therapy (OR 0.38, 95% CI 0.21 to 0.68; P = 0.001; 4 trials, 717 participants; Analysis 2.7).

Adverse events

There was a statistically significant increased risk of headache (OR 2.49, 95% CI 1.74 to 3.56; P < 0.001; 5 studies, 768 participants), GI upset (OR 1.95, 95% CI 1.30 to 2.93; P = 0.001; 4 studies, 726 participants), muscle and joint pain (OR 2.17, 95% CI 1.28 to 3.67; P = 0.004; 3 studies, 494 participants), and visual disturbance (OR 3.95, 95% CI 0.97 to 16.08; P = 0.06; 2 studies, 368 participants). There was no statistically significant difference in flushing (OR 1.11, 95% CI 0.63 to 1.96; P = 0.71; 2 studies, 368 participants) or epistaxis (OR 1.32, 95% CI 0.34 to 5.12; P = 0.69; 2 studies, 358 participants) Analysis 2.8.

PDE5 inhibitors compared to endothelin receptor antagonists (ERA)

Three trials compared PDE5 inhibitors head-to-head with an endothelin receptor antagonist (Comparison 3): Albini 2017 compared monotherapy (ambrisentan or tadalafil) with combination therapy; for the purpose of this meta-analysis ambrisentan was compared to tadalafil. Galiè 2015 compared ambrisentan monotherapy with tadalafil monotherapy with combination therapy; for this meta-analysis, ambrisentan 10 mg daily monotherapy was compared to tadalafil 40 mg daily monotherapy. Wilkins 2005 compared sildenafil (50 mg twice daily for 4 weeks, then 50 mg three times daily) with bosentan (62.5 mg twice daily for 4 weeks, then 125 mg twice daily).

Change in WHO functional class

There was no significant difference in WHO functional class (OR 0.94, 95% CI 0.55 to 1.60; P = 0.82; 1 trial, 244 participants; Analysis 3.1).

Six-minute walk distance

There was a statistically and clinically significant difference in 6MWD favouring sildenafil compared to bosentan (MD 49 metres, 95% CI 4 to 95; P = 0.03; 2 trials, 36 participants; Analysis 3.2). As Galiè 2015 reported 6MWD as median and IQR, it was not possible to include it in the meta-analysis (Higgins 2011). The median change from baseline distance in the tadalafil group was 23 metres (IQR −8 to 66) compared to the ambrisentan group 27 metres (IQR −14 to 63).

Mortality

There was no significant difference in mortality comparing PDE5 inhibitors to ERA (OR 3.19, 95% CI 0.74 to 13.64; P = 0.12; 2 trials, 272 participants; Analysis 3.3).

Haemodynamics

There was no significant difference in haemodynamics in one small study (32 participants), including mean PAP (MD 7.00, 95% CI −4.82 to 18.82; P = 0.25), RAP (MD 2.00, 95% CI −2.14 to 6.14; P = 0.34), cardiac index (MD 0.00, 95% CI −0.49 to 0.49; P = 1.00), and PVR (MD 0.00, 95% CI −1.93 to 1.93; P = 1.00). Wilkins 2005 assessed participants using cardiac magnetic resonance imaging (MRI) and found no significant difference in cardiac index (MD 0 L/min/m^2, 95% CI −0.2 to 0.2).

Exercise capacity other than six-minute walk distance

No studies reported additional exercise testing.

Quality of life

One study (Wilkins 2005) found a significant difference in quality of life favouring sildenafil compared to bosentan using the Kansas City Cardiomyopathy Quality-of-Life questionnaire (higher scores indicate better quality of life) (MD 22.00, 95% CI 9.00 to 35.00; P = 0.009).

Dyspnoea

No studies assessed dyspnoea.

Hospitalisation/intervention

There was a statistically significant incidence of clinical worsening in the ERA group compared to the PDE5 inhibitor group (OR 0.52, 95% CI 0.30 to 0.89; P = 0.02; 2 trials, 275 participants; Analysis 3.9).

Adverse events

Only one trial assessed adverse events (Analysis 3.10). There was no significant difference in headache (OR 1.10, 95% CI 0.65 to 1.87; P = 0.72), GI upset (OR 0.79, 95% CI 0.42 to 1.45; P = 0.44), flushing (OR 0.60, 95% CI 0.27 to 1.33; P = 0.21), muscle or joint pain (OR 1.34, 95% CI 0.60 to 3.00; P = 0.47), or respiratory symptoms (OR 0.80, 95% CI 0.47 to 1.35; P = 0.40).

Group 2: Pulmonary hypertension due to left-heart disease

Five trials assessed participants with pulmonary hypertension secondary to left-heart disease (Comparison 4). All trials compared sildenafil with placebo.

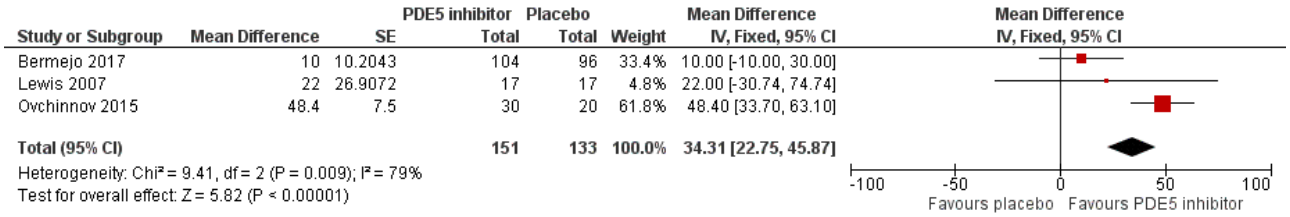
Change in WHO functional class

Significantly fewer people receiving sildenafil improved in WHO functional class compared to placebo (OR 0.53, 95% CI 0.32 to 0.87; P = 0.01; 3 trials, 285 participants; Analysis 4.1), although there was considerable heterogeneity between trials (I^2 = 67%, P = 0.05).

Six-minute walk distance

Three studies assessed the 6MWD. There was a significant difference favouring sildenafil (MD 34 metres, 95% CI 23 to 46; P < 0.001; 3 studies, 284 participants; Analysis 4.2; see Figure 6).

Figure 6. Forest plot of comparison: 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), outcome: 4.2 Six-minute walk distance.



Mortality

Three studies assessed mortality. There was no significant difference between sildenafil and placebo (OR 1.27, 95% CI 0.28 to 5.80; P = 0.76; 3 trials, 286 participants; Analysis 4.3).

Haemodynamics

There was a significant reduction in mean PAP (MD −10.17 mmHg, 95% CI −11.99 to −8.35; P < 0.001, although with significant heterogeneity (I^2 = 98%, P < 0.001); 3 trials, 130 participants; Analysis 4.4), transpulmonary pressure gradient (TPG) (MD −14.60 mmHg, 95% CI −15.63 to −13.57; P < 0.001; 1 trial, 44 participants; Analysis 4.6), and PASP (MD −27.60 mmHg, 95% CI −30.37 to −24.83; P < 0.001; 1 trial, 44 participants; Analysis 4.8) using sildenafil compared to placebo. There was no significant difference in cardiac index (MD 0.07 L/min/m^2, 95% CI −0.17 to 0.30; P = 0.59; 2 trials, 96 participants; Analysis 4.5) or RAP (MD −1.00 mmHg, 95% CI −3.77 to 1.77; P = 0.48; 1 trial, 34 participants; Analysis 4.7). Bermejo 2017 reported results in median and IQR so we could not combine the data in the meta-analysis, but there was no significant difference in haemodynamic parameters measured by Doppler echocardiography or magnetic resonance.

Exercise capacity other than six-minute walk distance

Two studies reported exercise capacity testing. Hoendermis 2015 reported no significant difference in VO_2 peak (treatment effect sildenafil MD 0.2 mL/kg/min^{-1} (95% CI -0.9 to 1.4) compared to placebo MD 0.70 mL/kg/min^{-1} (95% CI −0.3 to 1.6); P = 0.51). Lewis 2007 reported a statistically significant difference in VO_2 peak favouring sildenafil (post-treatment sildenafil MD 1.8 ± 0.7 mL/kg/min^{-1} compared to placebo MD 0.27 mL/kg/min^{-1}; P = 0.02).

Quality of life

One study (Hoendermis 2015) assessed quality of life using the Kansas City Cardiomyopathy Questionnaire (KCCQ: higher scores reflect better health status). The mean change in the KCCQ clinical summary score from baseline to 12 weeks was 12.05 points higher (95% CI 1.14 to 22.96) in the sildenafil group and 19.83 points higher (95% CI 8.23 to 31.44) in the placebo group, although the difference was not significant (P = 0.32).

Dyspnoea

One study (Guazzi 2011a) assessed dyspnoea using the 16-item Chronic Heart Failure Questionnaire (CHQ) (Guyatt 1989). There was a significant improvement in dyspnoea using sildenafil compared to placebo (MD 1.15, 95% CI 0.51 to 1.79; P < 0.001; 1 trial, 44 participants; Analysis 4.9).

Hospitalisation/intervention

There were mixed results in terms of clinical worsening requiring intervention including hospitalisation. Lewis 2007 (PH with systolic dysfunction) reported no significant difference in clinical worsening (OR 0.32, 95% CI 0.05 to 1.95; P = 0.22; 34 participants; Analysis 4.10), but Bermejo 2017 (valvular heart disease) reported an increased risk of hospitalisations, particularly relating to heart failure in those treated with sildenafil compared to placebo (OR 1.43; 95% CI 0.76 to 2.70; P = 0.05; 200 participants).

Adverse events

Three studies reported adverse events. In Lewis 2007 the incidence of headache occurred more commonly in those treated with sildenafil compared to placebo (1 trial; P < 0.05) but there was no significant difference in terms of arrhythmias, hypotension, diarrhoea, flushing, or myalgia, and no incidence of visual disturbance. Hoendermis 2015 reported that adverse events occurred in 22 participants (85%) who received sildenafil and 21 participants (81%) who received placebo (P = 1.00). Prevalence of known adverse effects of sildenafil, such as headache, dyspepsia, (orthostatic) hypotension, increased erection and respiratory tract infection, were reported to be higher in the sildenafil group, but event data were not supplied. Bermejo 2017 reported an increased risk of gastrointestinal events (OR 2.82, 95% CI 0.91 to 10.41; P = 0.06), and infections (OR 0.22, 95% 0.02 to 1.13; P = 0.05).

Group 3: Pulmonary hypertension due to lung disease

Five trials included participants with pulmonary hypertension secondary to lung disease or hypoxaemia; in four trials this was secondary to COPD, and in one trial secondary to IPF (Comparison 5) (Han 2013) . Four trials compared sildenafil to placebo, and one trial (Goudie 2014) compared tadalafil to placebo.

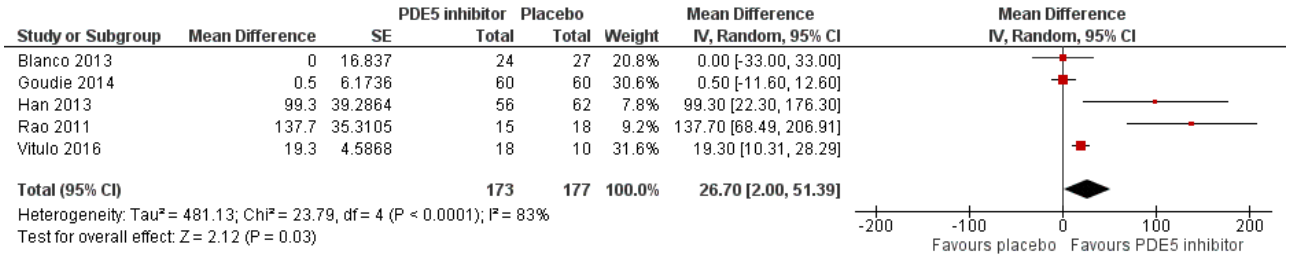
Change in WHO functional class

One trial assessed improvement in WHO functional class, and found a statically significant improvement using sildenafil compared with placebo (OR 44.33, 95% CI 4.78 to 410.93; P < 0.001; 40 participants; Analysis 5.1).

Six-minute walk distance

There was a significant improvement in the 6MWD with the use of sildenafil compared to placebo (MD 27 metres, 95% CI 2 to 51; P < 0.001; 5 trials, 350 participants; Analysis 5.2; see Figure 7).

Figure 7. Forest plot of comparison: 5 Group 3 Pulmonary Hypertension due to lung disease, outcome: 5.2 Six-minute walk distance.



Mortality

No studies assessed mortality.

Haemodynamics

There was no significant difference in terms of mean PAP (MD −0.14 mmHg, 95% CI −6.65 to 6.37; P = 0.97; 2 trials, 61 participants; Analysis 5.4), cardiac index (MD 0.30 L/min/m^2, 95% CI −0.14 to 0.74; P = 0.18; 1 trial, 28 participants; Analysis 5.5), RAP (MD 0.36 mmHg, 95% CI −2.76 to 3.48; P = 0.82; 1 trial, 28 participants; Analysis 5.7) and PVR (MD −1.31 mmHg, 95% CI −3.67 to 1.05; P = 0.28; 1 trial, 28 participants; Analysis 5.6).

Exercise capacity other than six-minute walk distance

Blanco 2013 reported exercise capacity after three months pulmonary rehabilitation and treatment with sildenafil or placebo. There was no difference in the placebo-corrected difference in the cycle endurance time: −7 seconds, 90% CI −540 to 244; P = 0.77, or maximal exercise tolerance 1 watt, 90% CI −2 to 5; P = 0.60.

Quality of life

Three studies assessed quality of life. Goudie 2014 used SF-36 (lower scores indicate worse quality of life), and Vitulo 2016 assessed the BODE index and the Minnesota Questionnaire. Han 2013 used the St George's Respiratory Questionnaire (SGRQ), the EuroQOL, and the SF-36. We pooled data for the SF-36 physical function, and demonstrated no significant difference in overall quality of life (MD 0.19, 95% CI −0.07 to 0.44; P = 0.15; 2 trials, 238 participants; Analysis 5.3). Blanco 2013 reported outcomes using mean and IQR, so results could not be pooled in the meta-analysis. There was no significant difference in SGRQ score (placebo-corrected difference median 1.3, IQR −3.5 to 6.9, P = 0.53), or SF-36 physical score (median −1.7, IQR −7.2 to 2.3, P = 0.38), or SF-36 mental score (median 1.6, IQR −3.7 to 8.5 P = 0.64).

Dyspnoea

No studies assessed dyspnoea.

Hospitalisation/intervention

No studies assessed clinical worsening.

Adverse events

Three trials reported adverse events, but none reported event data that could be pooled in a meta-analysis. Blanco 2013 reported that adverse events were similar across groups. Rao 2011 reported that headache was the most common side effect with sildenafil. Other adverse effects noted were epigastric pain or discomfort, headache, paraesthesias, and numbness. Vitulo 2016 reported that adverse events were observed in five participants in the sildenafil arm. The events were mild to moderate and included headache, diarrhoea, flushing, limb pain, dyspnoea, myalgia, and peripheral oedema. None interrupted the study treatment because of adverse events. No significant adverse effects were reported in the placebo arm. Two studies reported oxygenation parameters. Vitulo 2016 reported no difference in SpO_2 or PaO_2 in the sildenafil group from the start to the end of the study. Blanco 2013 reported no significant differences in arterial oxygen tension or saturation between the sildenafil and placebo groups.

Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)

Three trials included CTEPH participants (Galiè 2016a; Palazzini 2010; Suntharalingham 2008; Comparison 6). All trials used sildenafil, two (Palazzini 2010; Suntharalingham 2008) compared to placebo, and Galiè 2016a compared to bosentan.

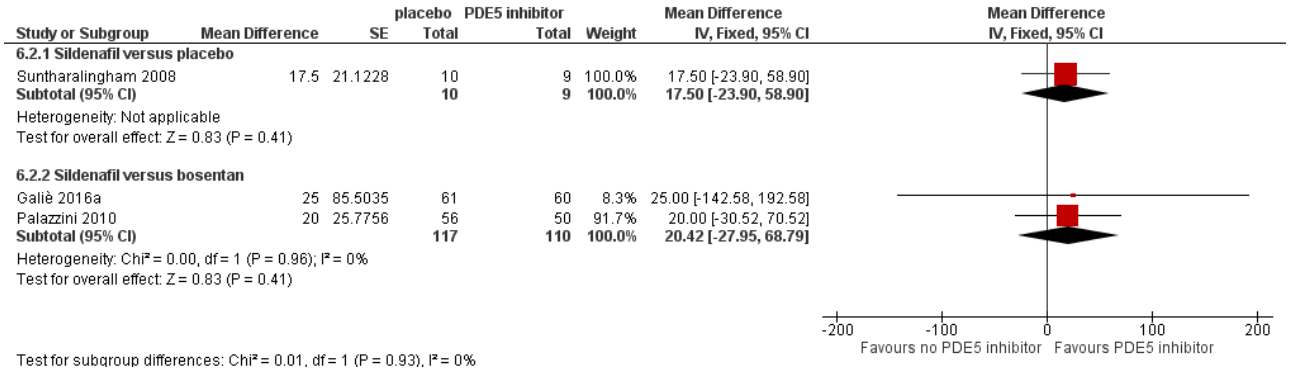
Change in WHO functional class

Only one trial examined improvement in WHO functional class in CTEPH participants, and found no significant difference in the use of PDE5 inhibitors compared to placebo (OR 17.18, 95% CI 0.78 to 380.84; P = 0.07; 1 trial, 19 participants; Analysis 6.1).

Six-minute walk distance

There was no significant difference in 6MWD using PDE5 inhibitors when compared to placebo (MD 18 metres, 95% CI −24 to 59; P = 0.41; 1 trial, 19 participants; Analysis 6.2; see Figure 8) or when compared to bosentan (MD 20 metres, 95% CI −28 to 69; P = 0.41; 2 trials, 227 participants).

Figure 8. Forest plot of comparison: 6 Group 4 Pulmonary Hypertension due to CTEPH, outcome: 6.2 Six-minute walk distance.



Mortality

There were no deaths in either arm in one trial comparing sildenafil with placebo (20 participants). There was no significant difference in mortality in one trial comparing PDE5 inhibitors to bosentan (OR 1.36, 95% CI 0.22 to 8.48; P = 0.74; 106 participants; Analysis 6.3).

Haemodynamics

There was no difference in haemodynamic parameters. There was no difference in mean PAP using PDE5 inhibitors when compared to placebo (MD −6.20 mmHg, 95% CI −12.40 to −0.00; P = 0.05; 1 trial, 19 participants; Analysis 6.4) or when compared to bosentan (MD 0.76 mmHg, 95% CI −3.96 to 5.48; P = 0.75; 2 trials, 227 participants). There was no difference in cardiac index using PDE5 inhibitors when compared to placebo (MD 0.00 L/min/m^2, 95% CI −0.40 to 0.40; P = 1.0; 1 trial, 19 participants; Analysis 6.5) or when compared to bosentan (MD 0.04 L/min/m^2, 95% CI −0.22 to 0.31; P = 0.76; 2 trials, 227 participants). There was no difference in PVR using PDE5 inhibitors when compared to placebo (MD −0.89, 95% CI −1.85 to 0.06; P = 0.07; 1 trial, 19 participants; Analysis 6.6) or when compared to bosentan (MD −0.01, 95% CI −0.27 to 0.25; P = 0.96; 2 trials, 227 participants). There was no difference in RAP using PDE5 inhibitors when compared to placebo (MD −0.90 mmHg, 95% CI −6.10 to 4.30; P = 0.73; 1 trial, 19 participants; Analysis 6.7) or when compared to bosentan (MD −1.00 mmHg, 95% CI −3.77 to 1.77; P = 0.48; 1 trial, 121 participants).

Exercise capacity other than six-minute walk distance

No studies reported exercise capacity testing.

Quality of life

Only one trial examined quality of life, using the CamHOR scale (higher scores indicate worse quality of life). There was no significant difference (MD −0.26, 95% CI −1.17 to 0.64; P = 0.57; 34 participants; Analysis 6.8).

Dyspnoea

No trials assessed dyspnoea.

Hospitaisation/intervention

No trials examined clinical worsening.

Adverse events

There were no significant differences in terms of headache (OR 2.57, 95% CI 0.19 to 34.47; P = 0.48; 19 participants; Analysis 6.9) or GI upset (OR 4.50, 95% CI 0.37 to 54.16; P = 0.24; 19 participants) between PDE5-inhibitors and placebo in one trial.

Mixed group 2 to 4 pulmonary hypertension

We combined two studies in this meta-analysis: Salem 2013, which included participants with secondary pulmonary hypertension due to valvular heart disease, chronic thromboembolic disease, COPD, IPF, and idiopathic dilated cardiomyopathy, and Dwivedi 2015, which included participants with symptomatic secondary PAH including idiopathic dilated cardiomyopathy, heart failure with preserved ejection fraction, COPD, and other lung parenchymal disease, and valvular heart disease (Comparison 7).

Change in WHO functional class

There was a significant improvement in WHO functional class favouring PDE5 inhibitors (OR 11.31, 95% CI 4.90 to 26.14; P < 0.001; 2 trials, 146 participants; Analysis 7.1).

Six-minute walk distance

There was a significant difference in 6MWD in one trial favouring PDE5 inhibitors (MD 51 metres, 95% CI 7 to 95; P=0.02; 106 participants; Analysis 7.2).

Mortality

No trials assessed mortality.

Haemodynamics

There was a significant improvement in PASP (MD −10.00 mmHg, 95% CI −11.92 to −8.08; P < 0.001; 2 trials, 146 participants; Analysis 7.3). No other haemodynamic parameters were measured.

Exercise capacity other than six-minute walk distance

No studies reported exercise capacity testing.

Quality of life

No trials assessed quality of life.

Dyspnoea

No trials assessed dyspnoea.

Hospitalisation/intervention

No trials assessed clinical worsening.

Adverse events

No trials reported adverse events.

Sensitivity analyses

We planned to use the fixed-effect model a priori to assess effect sizes. We present a comparison of fixed- versus random-effects in Table 2. Where effect sizes differed, this was explained by high heterogeneity between trials.

Group 5: Haematological disorders

Jalalian 2015 included 44 participants with beta-thalassaemia intermedia and pulmonary hypertension on transthoracic echocardiogram, and were treated for six weeks with tadalafil (40 mg daily) or placebo. The authors reported a significant improvement in the PASP (post-treatment tadalafil MD 34.26 mmHg; SE 1.15, compared to post-treatment placebo MD 44.57 mmHg; SE 0.56; P < 0.001). In the tadalafil group two participants dropped out due to severe headache and one due to severe oedema. Three other participants experienced a mild headache with initiation of tadalafil, which resolved after one week. No deaths occurred after six weeks of this trial.

Machado 2009 included those with pulmonary hypertension secondary to sickle cell disease and tested sildenafil versus placebo. The study was prematurely stopped due to a statistically significant increase in serious adverse events requiring hospitalisation in the sildenafil arm.

DISCUSSION

Summary of main results

This review demonstrates clear statistical and clinical benefit for the use of PDE5 inhibitors in group 1 PAH compared to placebo, in terms of mortality, improvement in WHO functional class, time to clinical worsening, haemodynamics, six-minute walk distance (6MWD), and quality of life including dyspnoea. Clinicians and patients should be aware of side effects, especially headache, flushing, GI upset, and muscle and joint pain.

Three formulations of PDE5 inhibitors were used: sildenafil, tadalafil and vardenafil. Although none of these were compared head-to-head, a beneficial direction of effect appeared across all three drugs. Although the magnitude of effect appeared greater in sildenafil compared with tadalafil or vardenafil, this could be due to more studies and participant numbers in the sildenafil arm. In terms of adverse events, there appeared to be a higher chance of headache, GI upset and muscle aches and pains in the tadalafil arm compared to the sildenafil arm.

We demonstrate mixed evidence for the use of PDE5 inhibitors for left-heart disease. The trials included were heterogenous in left-heart disease secondary to different mechanisms. Overall, there was a statistically and clinically significant improvement across all trials in terms of WHO functional class and 6MWD, and an improvement in haemodynamics, quality of life, and dyspnoea, but this did not confer a clear benefit for mortality. It is unclear if this is due to underpowered studies. In addition, there was some evidence of heart failure exacerbations in one study which included participants with valvular heart disease, but despite this being a known potential side effect of these drugs, few studies reported any adverse events.

There is no clear benefit from the use of PDE5 inhibitors in pulmonary hypertension secondary to lung disease, according to this meta-analysis. There was a statistically but not clinically significant difference in 6MWD, but no benefit for mortality, haemodynamics, quality of life, and clinical worsening. Most studies included COPD patients with pulmonary hypertension; only one included IPF patients. There are no data on PDE5 inhibitors in other lung disease patients.

There was no significant benefit for the use of PDE5 inhibitors in CTEPH, when compared to placebo or bosentan, for mortality, clinical worsening, 6MWD, and haemodynamics, but the numbers of participants were small.

There may be an improvement in cardiopulmonary haemodynamics with the use of PDE5 inhibitors in pulmonary hypertension due to beta-thalassaemia intermedia. There may be evidence of harm from the use of PDE5 inhibitors in people with pulmonary hypertension secondary to sickle cell disease.

Overall completeness and applicability of evidence

There are sufficient trials of high quality in the use of PDE5 inhibitors compared to placebo for group 1 PAH. Most trials had a low risk of bias, and the direction of effect was consistent across studies. PDE5 inhibitors are one of five classes of drugs now available for group 1 PAH. Current European Society of Cardiology (ESC) guidelines stratify patients according to levels of risk, which correlate with expected survival (Boucly 2017; Hoeper 2017; Kylhammar 2018). The guidelines suggest the use of monotherapy with either a PDE5 inhibitor or an endothelin receptor antagonist (ERA) for people at low risk, and the use of combination therapy or intravenous prostacyclin for those at high risk. Two studies compared the use of PDE5 inhibitors with ERAs, and found a possible benefit for ERA in terms of 6MWD and quality of life, and a non-statistically significant benefit for improvement in WHO functional class, and clinical worsening, favouring ERAs.

The use of step-up or upfront combination therapy in people at intermediate risk has been suggested by several recent studies, including SERAPHIN 2013 (where macitentan was added to a PDE5 inhibitor or non-parenteral prostacyclin, and demonstrated delay in clinical worsening), COMPASS-2 2014 (where bosentan was added to sildenafil, and demonstrated a small but statistically significant improvement in 6MWD (22 m), but no change in morbidity or mortality), PACES (Simonneau 2008) (where sildenafil was added to epoprostenol and demonstrated a delay in clinical worsening), and GRIPHON 2015 (where the addition of selexipag to monotherapy demonstrated a delay in clinical worsening). The AMBITION 2015 study (included in this review) examined upfront combination therapy and demonstrated a reduction in clinical failure, and an improvement in 6MWD.

Pulmonary hypertension secondary to left-heart disease (PH-LHD) is by far the most common cause of pulmonary hypertension, and the presence of PH-LHD leads to worse survival (Strange 2012). Studies including participants with PH-LHD were mixed; when we pooled the studies there was a benefit for exercise parameters and quality of life, but an increased risk of heart failure

exacerbations. Previous studies (Jiang 2014; Lindman 2012) have demonstrated acute haemodynamic benefit in these participants, but the long-term effect remains controversial. Bermejo 2017 suggested an initial benefit in 6MWD at three months (although not statistically significant), but this effect disappeared at six months, with no difference in effect between the two arms. In contrast, the other long-term study (Guazzi 2011a (12 months)) demonstrated a continued, persistent benefit in haemodynamics over time. This suggests that the controversy may lie in the heterogeneity of the cause of left-heart disease leading to pulmonary hypertension.

The evidence for pulmonary hypertension secondary to lung disease was limited to people with COPD. Although there was one small study (an a priori planned substudy of a larger trial) in people with IPF, it is difficult to extrapolate the evidence presented in this meta-analysis beyond the COPD population. Theoretically, worsening ventilation-perfusion mismatch induced by pulmonary vasodilators may lead to more pronounced dyspnoea and clinical worsening (Smith 2013), but included studies did not assess dyspnoea, and limited data were provided on clinical worsening. Further trials should include these outcomes.

Appropriate and accurate outcome assessment did not occur in all studies. In trials with PH-LHD, although most participants were initially diagnosed using right-heart catheterisation, outcome assessment was performed with noninvasive measures such as PASP on transthoracic echocardiogram (TTE). Previous studies (Farber 2011) have demonstrated that these noninvasive techniques do not always correlate with invasive haemodynamics, especially in those with left-heart disease. In addition, the presence of pulmonary hypertension in left-heart disease has been shown to reduce exercise tolerance and increase hospitalisations for heart failure (Vachiéry 2013). However, despite this, only three of five studies reported exercise tolerance, and only two of five reported heart failure exacerbations. Any further studies in PH-LHD should include 6MWD, invasive haemodynamic data, clinical worsening including heart failure exacerbations, and be adequately powered to detect a difference in these outcomes.

Quality of the evidence

For trials including group 1 PAH participants comparing PDE5 inhibitors to placebo, the quality of evidence was high across all outcomes except for six-minute walk distance, and cardiac index, which were downgraded to moderate due to high heterogeneity, although the effect was consistent across trials. For PAH trials comparing PDE5 inhibitors to placebo whilst on additional therapy and trials comparing PDE5 inhibitors to ERAs, the quality of the evidence was reduced due to smaller participant numbers. Follow-up was as long as 12 months, but the average follow-up was only 14 weeks. Open-label extension or real world registry data may be useful for longer-term effects.

Although there were five studies examining PH-LHD, the numbers in each study were small, and studies were significantly heterogeneous. Ovchinnov 2015 was a poor-quality study, where randomisation and allocation concealment were not reported, dropouts and cross-overs were not reported, and only quantitative data from the intervention arm was reported.

Potential biases in the review process

We conducted this review in accordance with established Cochrane standards. Two review authors independently screened search results and resolved discrepancies by discussion and consensus. We did not restrict the literature search by language. Publication bias is possible, whereby failure to identify unpublished negative trials could have led to an overestimation of effect.

Agreements and disagreements with other studies or reviews

Our findings are consistent with the current ESC/ERS guidelines (Galiè 2016b), which recommend the use of PDE5 inhibitors for monotherapy as level IA/B evidence for WHO functional class I - III patients, and as level IIb evidence for WHO functional class IV patients (as there is stronger evidence of effect for combination therapy and intravenous prostacyclins). Similarly, the current ESC/ERS guidelines do not recommend the use of PDE5 inhibitors for left-heart disease- or lung disease-related pulmonary hypertension. Where PDE5 inhibitors are used as part of combination therapy, caution should be used in adding these to riociguat, due to potentially unfavourable side effects and lack of additional clinical benefit (Galiè 2015b).

No trials have compared individual PDE5 inhibitors head-to-head, and given the overall class benefit it is unlikely that these studies will be conducted. Our data suggest that there may be a better treatment effect with sildenafil compared to tadalafil, but this may be influenced by the greater number of studies conducted using sildenafil compared to tadalafil. The choice of agent is likely to be nuanced and influenced by the individual patient profile with respect to side effects. The SITAR study (Frantz 2014) rotated participants from sildenafil to tadalafil, and found an initial increase in side effects including headache and gastrointestinal upset, but this improved over time.

Our data demonstrating no clear benefit for the use of PDE5 inhibitors in those with lung disease-associated pulmonary hypertension is consistent with the ESC guidelines (Galiè 2016b) and with other published data using PH-specific therapy in people with interstitial lung disease (ILD). Han 2013 (pulmonary hypertension associated with lung disease) was a prespecified substudy of the STEP-IPF trial (Zisman 2010), which included people with idiopathic pulmonary fibrosis (IPF), and found no benefit in terms of 6MWD, exacerbations or mortality.

Interestingly, there appeared to be no significant benefit for the use of PDE5 inhibitors in people with CTEPH. Current ESC/ERS guidelines (Galiè 2016b) recommend surgical pulmonary endarterectomy as first line treatment based on long term international registry data which demonstrates a mortality benefit (Delcroix 2016), and the use of riociguat medical therapy in those who are non-operable candidates (Ghofrani 2013). Therefore, these treatments could be considered in preference to PDE5 inhibitors.

AUTHORS' CONCLUSIONS

Implications for practice

- Data from this review suggest a benefit for the use of PDE5 inhibitors in group 1 PAH, for improvement in WHO functional class, reduction in clinical worsening, and improvement in

haemodynamics, six-minute walk distance, quality of life, and mortality.

- Sildenafil, tadalafil and vardenafil are all efficacious in this clinical setting.
- Clinicians may wish consider the side-effect profile for each drug when choosing which to prescribe to an individual patient.
- This review suggests that a PDE5 inhibitor may be better than an ERA for six-minute walk distance and quality of life, but that there appears to be no difference in WHO functional class or mortality. These conclusions are limited by the small number of trials.
- While there appears to be some benefit for the use of PDE5 inhibitors in PH-LHD, it is not clear based on the mostly small, short-term studies which type of left-heart disease stands to benefit. The use of PDE5 inhibitors does not appear to be beneficial in valvular heart disease.
- This review suggests there is no clear benefit for PDE5 inhibitors in pulmonary hypertension secondary to lung disease or CTEPH.
- There may be evidence of harm in the use of PDE5 inhibitors for pulmonary hypertension secondary to sickle cell disease.

Implications for research

- Further research is required into the mechanisms of pulmonary hypertension secondary to left-heart disease.
- Clinical trials in PH-LHD should be sufficiently powered, with long-term follow-up, and should include invasive haemodynamic data, WHO functional class, six-minute walk distance, and clinical worsening.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Albini 2017

Methods	Randomised controlled trial 3 - 6 months duration
Participants	Inclusion criteria: • PAH WHO FC II/III n = 11
Interventions	Tadalafil monotherapy (N=6) versus ambrisentan monotherapy (N=5)
Outcomes	6MWD, cardiopulmonary haemodynamics
Notes	Compared tadalafil monotherapy to ambrisentan monotherapy No funding source stated Trial conducted at the University of Bologna, Bologna, Italy (dates not stated)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States "randomised", although methods of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Not specified
Other bias	Unclear risk	Abstract from conference proceedings only, does not report a registration in a clinical trials database, limited information about methods used

Barst 2012

Methods	Randomised, double-blind, placebo-controlled trial 16 weeks duration

Barst 2012 *(Continued)*

Participants	Inclusion Criteria: • Children (aged 1 – 17 years) weighing 8 kg with iPAH, PAH associated with connective tissue disease or congenital heart disease (unrepaired or partially repaired shunts with oxygen saturation at rest 88%, D-transposition of the great arteries repaired at 30 days of life, or congenital lesions surgically repaired at 6 months) were eligible • PAH, defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest, pulmonary capillary wedge pressure ≤ 15 mmHg, and pulmonary vascular resistance index (PVRI) ≥ 3 Wood units, confirmed by right-heart catheterisation at baseline • Children with unrepaired shunts were enrolled only if their condition was considered inoperable because of their pulmonary vascular obstructive disease. Exclusion criteria: • Nitrates, cytochrome P450 3A4 inhibitors, prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and L-arginine were prohibited n = 234 WHO FC I/II
Interventions	Three sildenafil dose levels (low, medium, and high) (total N=174) were selected to achieve maximum plasma concentrations of 47, 140, and 373 ng/mL, respectively, at steady state after oral administration 3 times a day, versus placebo (N=60)
Outcomes	Primary: percent change in PVO_2 Secondary: change from baseline to week 16 in mPAP, PVRI, FC, cardiac index, right atrial pressure, physical and psychosocial scales of the Child Health Questionnaire–Parent Form 28 (for patients aged 5 years), and percent change from baseline in exercise duration Tertiary: Participant/parent and physician global assessments, changes in medications, and clinical worsening (defined as death, transplantation, hospitalisation due to PAH, or initiation of a prostacyclin analogue or bosentan for worsening PAH)
Notes	NCT00159913 This study was sponsored by Pfizer Inc. Editorial support was provided by Tiffany Brake, PhD, and Janet E. Matsuura, PhD, from Compete Healthcare Communications, Inc, and was funded by Pfizer Inc Trial conducted in 16 countries (32 centers) in North, South, and Central America; Asia; and Europe between August 2003 and June 2008.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The central computer-generated pseudo-random code used the method of random permuted blocks within stratum (block size 4). An automated interactive voice response system assigned randomisation numbers to eligible patients".
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Drug supply consisted of a list of package numbers and corresponding treatment types. A unique package number identified each package of medication. The interactive voice response system assigned patients with a package number from the list corresponding to the treatment assigned."

Barst 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs were accounted for
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	Other bias unlikely

Bermejo 2017

Methods	Randomised placebo parallel controlled trial 6 months duration
Participants	Pulmonary hypertension following repaired valvular heart disease (WHO Group 2) Inclusion criteria: • Age at the date of selection ≥ 18 years • Mean pulmonary pressure ≥ 30 mmHg, measured by a Swan-Ganz catheter placed in the pulmonary artery • Heart valve intervention: surgical or percutaneous replacement, repair or dilatation performed at least 1 year before inclusion • Stable clinical condition for at least 1 month, without hospital admissions for heart failure, and on appropriate and stable doses of conventional cardiovascular medications Exclusion criteria: • Requiring or likely to require the following medications: organic nitrates, alpha-blocker therapy, potent cytochrome P450 3A4 inhibitors (erythromycin, ketoconazole, cimetidine, HIV protease inhibitors such ritonavir and saquinavir). People who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months. • People with resting hypotension, with systolic blood pressure < 90 mmHg • People with retinitis pigmentosa • Anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease) or men who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma, or leukaemia) • Severe renal impairment with creatinine clearance < 30 ml/min • Significant hepatic dysfunction • Prosthesis or valvular dysfunction with haemodynamic repercussion. • Pregnant or breast-feeding women • People unlikely to co-operate in the study or with inability or unwillingness to give informed consent • Life expectancy < 2 years due to non-cardiac disease n = 200
Interventions	Sildenafil 40 mg 3 times a day (N=104) versus placebo (N=96)
Outcomes	Primary outcome: clinical composite score combining all-cause mortality, hospital admission for heart failure, WHO functional class, and the patient global assessment score

Bermejo 2017 *(Continued)*

	6MWD WHO functional class PASP Heart failure hospitalisations
Notes	Publicly funded The trial was conducted in 18 academic hospitals in Spain, enrolled from May 2009 to December 2015

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment allocation codes generated
Allocation concealment (selection bias)	Low risk	Quote: "The study drugs (i.e. sildenafil and placebo) were identical in appearance and were packaged in identical containers. The study drugs were prepared by an independent laboratory from commercially purchased sildenafil and specifically manufactured placebo powder".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators and participants were masked to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators and participants were masked to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Discontinuations and deviations were reported and equal among groups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported; a primary composite outcome was reported with separate reporting of outcomes
Other bias	Low risk	Other bias is unlikely

Bharani 2003

Methods	Randomised placebo-controlled cross-over trial 2 weeks duration
Participants	Inclusion criteria: • Adults (> 18 years) who were symptomatic, NYHA class > II • Doppler-estimated pulmonary systolic pressure ≥ 35 mmHg • normal LV function and no reversible cause for PH (WHO Group 1) WHO FC II/III/IV n = 10

Bharani 2003 *(Continued)*

Interventions	Sildenafil 25 mg 8-hourly or matching placebo for 2 weeks Washout at least 2 weeks before cross-over Participants were receiving conventional therapy including: warfarin, nifedipine, diuretics, digoxin
Outcomes	Improvement in NYHA class 6MWD Borg dyspnoea index (scale 0 - 10; the higher the score the worse the dyspnoea) PASP on TTE Side effects
Notes	Did not perform right-heart catheterisation to confirm PAH Funding source not stated The trial was conducted through a large referral centre in central India (dates not stated)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This study was carried out at a large referral centre of central India as a prospective, randomised, double-blind, crossover trial", but no further details are given Unclear method of randomisation/allocation/blinding of participants and personnel and measurement of outcomes
Allocation concealment (selection bias)	Unclear risk	Method of allocation is not clearly stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not clear if participants and personnel were blinded, although authors state "placebo" was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not clear if the measurements were performed by those blinded to the allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants who were randomised were accounted for
Selective reporting (reporting bias)	Low risk	Most outcomes stated in the Methods are reported
Other bias	Low risk	None detected

Bharani 2007

Methods	Randomised double-blind placebo-controlled cross-over trial 4 weeks duration

Bharani 2007 *(Continued)*

Participants	Inclusion criteria: • People with symptomatic PH, related to previous left to right shunts (PASP > 35 mmHg) with a 6MWD ≥ 50 m and no contraindications to tadalafil. (WHO Group 1) Exclusion criteria: • PAH due to disease other than congenital left to right shunt lesion • Chronic thromboembolic PAH • Neuromuscular diseases • Orthopaedic conditions • Unwilling participants • People using PDE5 inhibitors for other indications • Contra-indication to PDE5 • People on vasodilator therapy • People enrolled in other trials during study period • 6MWD < 50 m • People with comorbid conditions limiting life expectancy < 6 months. WHO FC II/III n = 11
Interventions	4 weeks of tadalafil 20 mg orally daily, or placebo orally daily 2-week drug-free interval Cross-over 4 weeks of tadalafil 20 mg orally daily or placebo orally daily Continued pre-trial medications including: frusemide, spironolactone, warfarin, iron, digoxin
Outcomes	Improvement in NYHA class 6MWD Borg dyspnoea index (scale 0 - 10; the higher the score the worse the dyspnoea) PASP on TTE Side effects
Notes	Did not perform right-heart catheterisation to confirm PAH Funding source not stated Trial was conducted at MY Hospital, Indore, India, with enrolment from September 2005 to February 2006.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients received tadalafil 20 mg once a day or visually matching placebo for 4 weeks each with a drug free interval of at least 2 weeks between the two therapies in a randomised, doubled blind, cross over design, " but specific methods are not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation is not clearly stated

Bharani 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not clear if participants and personnel were blinded, although authors state "placebo" was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not clear if the measurements were performed by those blinded to the allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only 8 of 11 participants completed the trial, for reasons which are unclear
Selective reporting (reporting bias)	Low risk	All outcomes stated in the study design were reported, although some incompletely, in the text
Other bias	Low risk	None detected

Blanco 2013

Methods	Randomised, double-blind, placebo-controlled trial 3 months duration
Participants	Inclusion criteria: • Adults, aged 40 to 80 years, with COPD according to the Global Initiative for COPD guidelines • Increased pulmonary artery pressure (PAP), defined as tricuspid regurgitation velocity > 2.7 m/s, which is equivalent to systolic PAP > 34 mmHg, calculated using Bernoulli's equation, assuming right atrial systolic pressure 5 mmHg; or in people who had previously had right-heart catheterisation (n = 14), pulmonary hypertension defined as mean PAP ≥ 25 mmHg. (WHO Group 3) • At randomisation were in a stable clinical condition free of exacerbation episodes for ≥ 4 weeks Exclusion criteria: • Other causes for pulmonary hypertension such as chronic thromboembolic pulmonary hypertension or left-heart disease • Previous history of ischaemic/mitral/aortic valve diseases • Ejection fraction, left atrium diameter, septum diameter, left ventricular mass index and posterior wall thickness between normal ranges • History of Ischaemic heart disease, treated with nitrates or unable to exercise on a cycloergometer • Not allowed to use sildenafil or other PDE5 inhibitors n = 63
Interventions	Sildenafil 20 mg orally 3 times daily and pulmonary rehabilitation programme, 3 times a week for 12 weeks, standardised across participating centres (N=29) Placebo, with pulmonary rehabilitation programme, 3 times a week for 12 weeks, standardised across participating centres (N=31)
Outcomes	Cycle endurance time 6MWD Quality of life including SGRQ and SF-36 Lung function tests

Blanco 2013 *(Continued)*

	PAP on TTE Borg dyspnoea score
Notes	Publicly funded Trial conducted in Spain (dates not stated)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients meeting eligibility criteria were randomly assigned in a 1:1 ratio … via a four-permuted-block design, with no stratification."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation was performed by a pharmacologist not involved directly in the study." Central randomisation by a third party, as above, should be effective allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The study was a 3-month, randomised, double-blind, placebo-controlled trial", "Asssessments before the study and at the end of the study were performed in the coordinating centre", but blinding is not made clear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not clear if the measurements were performed by those blinded to the allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	289 patients were screened. 63 underwent randomisation, 60 made up the modified ITT population whose data were used in the primary effectiveness analysis Missing outcome data balanced across the groups Intention-to-treat analysis was used
Selective reporting (reporting bias)	Low risk	Study protocol registered and adhered to, and reporting on planned outcomes appears complete
Other bias	Low risk	Other bias is unlikely

Boonstra 2005

Methods	Randomised double-blind, placebo-controlled trial 12 weeks duration
Participants	Inclusion criteria: • People with PAH, subdivided into WHO functional class I/II and III/IV people (WHO Group 1) WHO I/II and III/IV n = 136
Interventions	sildenafil (20, 40, or 80 mg) 3 times daily (N=200) compared to placebo (N=66)

Boonstra 2005 *(Continued)*

Outcomes	6MWD
Notes	Abstract only Funding source not stated Location of trial and dates of enrolment not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods for random sequence generation are not described within the abstract
Allocation concealment (selection bias)	Unclear risk	Methods for allocation concealment are not described within the abstract
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel is not described within the abstract
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment is not described within the abstract
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 200/278 participants are presented in the final outcome analysis. Reasons for attrition is not described within the abstract
Selective reporting (reporting bias)	High risk	Only 1 outcome is reported
Other bias	Unclear risk	Unlear if other risk is present - abstract only from conference proceedings, and limited data are presented

Dwivedi 2015

Methods	Randomised, parallel-group, placebo-controlled trial 6 weeks duration

Participants	Inclusion criteria:
	• People with symptomatic secondary PAH (WHO group 2 - 5):
	  • COPD n = 21 (19.8%)
	  • Valvular heart disease n = 53 (50%)
	  • Heart failure with preserved EF n = 16 (15%)
	  • Idiopathic DCMP n = 11 (10.2%)
	  • Other lung parenchymal diseases n = 5 (5%)
	Exclusion criteria:
	• Primary pulmonary hypertension
	• Hypotension

Dwivedi 2015 *(Continued)*

	• Allergy to sildenafil • Ischaemic heart disease • On other vasodilators (ex. nitrates) • Prior treatment with other anti-PAH drugs • Prior cardiac valve surgery • Severe valve stenosis Total n = 106
Interventions	Oral sildenafil 25 mg 3 times daily compared to placebo
Outcomes	6MWD Improvement in NYHA functional class LVEF PASP RV function NT-Pro BNP level safety and tolerability
Notes	Further information about the trial is taken from the Clinical Trials Registry - India: CTRI/2017/01/007686 (Registered on: 12/01/2017) Publicly funded Study was conducted at King George Medical University, India, enrolled from December 2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified block randomisation
Allocation concealment (selection bias)	Unclear risk	Authors report "centralised" though it is unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participant blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear whether assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 106/122 participants completed the study, for reasons which are unclear
Selective reporting (reporting bias)	Low risk	Specified outcomes are reported
Other bias	Low risk	Other bias unlikely

Galiè 2005a

Methods	Randomised, parallel, placebo-controlled trial 12-week study with an additional open-label extension study
Participants	Inclusion criteria: • People with pulmonary arterial hypertension (idiopathic, associated with connective-tissue disease, occurring after surgical repair of congenital systemic-to-pulmonary shunts at least 5 years previously) • Pulmonary arterial hypertension defined as mean PAP of 25 mmHg or more and a pulmonary-capillary wedge pressure (PCWP) of 15 mmHg or less at rest. (WHO Group 1) Exclusion criteria: • Treatment with IV epoprostenol oral bosentan, IV or inhaled iloprost or subcutaneous treprostinil and supplementation with L-arginine prohibited. • People with 6MWD of < 100 m or > 450 m excluded WHO FC II/III n = 277
Interventions	20 mg Sildenafil n = 69 40 mg Sildenafil n = 67 80 mg Sildenafil n = 71 compared to placebo n = 70 People assigned to 80 mg sildenafil 3 times daily received 40 mg of sildenafil 3 times daily for the first 7 days before the dose was escalated to 80 mg; people randomised to the other 3 treatment groups underwent dummy dose escalation after 7 days Study medication added to their currently prescribed conventional therapy
Outcomes	6MWD Haemodynamics Improvement in WHO functional class Borg dyspnoea score Mortality was reported, but the study was not powered to assess mortality Adverse events
Notes	Industry funded Trial was conducted in 53 centers in the United States, Mexico, South America, Europe, Asia, Australia, South Africa, and Israel between October 2002 and November 2003

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation with respect to baseline walking distance and cause of pulmonary hypertension A stratified central-randomisation scheme was used
Allocation concealment (selection bias)	Low risk	Placebo was used

Galiè 2005a *(Continued)*

		Participants randomly assigned to the other 3 treatment groups underwent dummy dose escalation after 7 days.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It is likely outcome assessment was blinded although it is not explicitly stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analyses were used Very few (only 2) exclusions and balanced attrition between groups: 1 not treated 277 treated 4 died 8 withdrew - 2 protocol violation, 2 withdrew consent, 4 side effects (reduced renal function, lower leg oedema, cardiac arrhythmias, headache) 265 completed 12 weeks 259 entered long-term study 222 completed 1 year of treatment with monotherapy with sildenafil
Selective reporting (reporting bias)	Low risk	All outcomes proposed in Methods were described in the report, non-significant outcomes reported
Other bias	Low risk	Other bias is unlikely

Galiè 2009

Methods	Randomised, double-blind, double-dummy, placebo-controlled, multicentre trial, followed by a blinded long-term extension study 16 weeks duration
Participants	Inclusion criteria: • Participants were at least 12 years of age • Symptomatic PAH that was idiopathic/heritable or related to anorexigen use, connective tissue disease, HIV infection, or congenital systemic-to-pulmonary shunts (i.e. an atrial septal defect with resting arterial oxygen saturation 88% on room air or at least 1-year post-surgical repair of a ventricular septal defect or patent ductus arteriosus, or both) (WHO Group 1) • The diagnosis of PAH included resting mean PAP ≥ 25 mmHg, pulmonary wedge pressure 15 mmHg, and pulmonary vascular resistance 3 Wood units Exclusion criteria: • Participants with a 6MWD > 150 m or < 450 m • Treatment with IV epoprostenol, IV or inhaled iloprost, or subcutaneous treprostinil WHO FC II/III n = 405
Interventions	Participants were randomised to groups receiving tadalafil 2.5 mg (N=82), 10 mg (N=80), 20 mg (N=82), 40 mg (n=79), or placebo (n=82) once daily

Galiè 2009 *(Continued)*

	The randomisation was stratified for baseline walking distance (> 325 m or < 325 m), type of PAH (idiopathic/heritable and anorexigen use versus other types), and bosentan use
Outcomes	6MWD Improvement in WHO functional class Clinical worsening Health-related quality of life Borg dyspnoea score Adverse events
Notes	Industry funded Trial was conducted in 84 centers in Canada, the United States, Europe, and Japan between August 2005 and August 2007

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permutated randomisation
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It is likely outcome assessment was blinded although it is not explicitly stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other bias is unlikely

Galiè 2015

Methods	Multicentre, double-blind, randomised, placebo-controlled trial 24 weeks duration
Participants	Inclusion criteria: • 18 to 75 years of age • weighed at least 40 kg

Galiè 2015 *(Continued)*

	• WHO functional class II or III symptoms of PAH • diagnosis of idiopathic PAH, hereditary PAH, or PAH that was associated with connective tissue disease, drugs or toxins, HIV (stable disease status), or repaired congenital heart defects (group 1 of the WHO classification of PH). • The diagnosis of PAH was established by ruling out other known causes, according to the criteria in current guidelines. (WHO Group 1) • For each participant, the mean PAP was required to be ≥ 25 mmHg. • Enrolled participants had either not received previous treatment with an approved therapy for PAH or had received treatment for < 14 days and had not received any approved therapy for PAH within 7 days before enrolment WHO FC II/III n = 500
Interventions	There were 3 groups: 253 were assigned to the combination-therapy group, 126 to the ambrisentan-monotherapy group, and 121 to the tadalafil-monotherapy group Ambrisentan monotherapy was compared to tadalafil monotherapy for the purpose of this meta-analysis
Outcomes	6MWD Haemodynamics including PAP, cardiac index, PVR, RAP Improvement in WHO functional class ProBNP Adverse events
Notes	Industry funded Trial was conducted at 120 centers in 14 countries between October 18, 2010 (first visit), and July 31, 2014 (last study visit)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not stated, but likely low risk
Allocation concealment (selection bias)	Low risk	Placebo was used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study design took into account that following each participant's final assessment visit, investigators would need to make decisions regarding future treatment, and future treatment decisions would be informed by knowing what treatment participants had been randomised to. Therefore, investigators would need to be unblinded at a participant's end-of-study visit so they could provide appropriate treatment for each participant upon study completion. To accommodate this, we included 2 database freezes. The first database freeze was planned after the last randomised participant had received ≥24 weeks of therapy and the 105th adjudicated first clinical failure event was projected to have occurred in the primary analysis set. At that time, all participants were notified to return for a final assessment visit or their Week 24 visit, whichever was later. The database was frozen for each participant's visit-based data through the final assessment visit. The primary analysis was per-

Galiè 2015 *(Continued)*

		formed on these data. Participants then returned to the clinic for their end-of-study visit, the investigator was unblinded and participants were treated per investigator discretion."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As described above
Incomplete outcome data (attrition bias) All outcomes	Low risk	610 participants were enrolled, but only 500 completed the final primary analysis; the reasons for withdrawals were documented in the supplementary index
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

Galiè 2016a

Methods	Randomised double-blind controlled trial Mean duration of follow-up 4.7 months
Participants	Inclusion criteria: • Consecutive naïve patients with operable and non-operable chronic thromboembolic pulmonary hypertension (WHO Group 4) n = 121
Interventions	Sildenafil (20 mg 3 times ar day) (N=61) versus bosentan (125 mg bid) (N=60)
Outcomes	6MWD RAP Mean PAP CI PVR Adverse events
Notes	Abstract only States the abstract is funded by "none" Location of trial and dates of enrolment not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported, although information given was limited as this was an abstract only. We contacted the authors but there was no reply at the time of publication

Galiè 2016a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was not clear if there were issues with attrition bias
Selective reporting (reporting bias)	Unclear risk	It is not clear if there was selective reporting bias
Other bias	Unclear risk	Unclear if other bias is present - abstract only from conference proceedings

Goudie 2014

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial 12 weeks duration
Participants	People with COPD confirmed on respiratory function tests, and associated pulmonary hypertension, confirmed on TTE (WHO Group 3) Inclusion criteria: • Men or women, aged between 35 and 85 years inclusive • Known diagnosis of COPD • A post-bronchodilator FEV1 < 80% predicted • Pulmonary acceleration time < 120 ms or right ventricular systolic pressure > 30 mmHg Exclusion criteria: • Pulmonary stenosis • Left-ventricular outflow obstruction confirmed by echocardiography • Left-ventricular systolic dysfunction (< 45%) • Taking nitrates, nicorandil, or doxazosin • Systolic blood pressure < 90 mmHg, recent stroke, unstable angina, past history of non-arteritic anterior ischaemic optic neuropathy Baseline characteristics: Mean FEV1 1.06 ± 0.41 L (41% pred.), mPAP 30 ± 7 mmHg (PAT derived), RVSP 42 ± 10 mmHg. n = 120
Interventions	Tadalafil 10 mg daily (N=60) compared to placebo (N=60)
Outcomes	Primary endpoint: 6MWD Secondary endpoints: SGRQ;

Goudie 2014 *(Continued)*

	SF-36 and Minnesota questionnaires (QOL); BNP DLCO and echo parameters. Inclusion: moderate-severe COPD and PH (RVSP > 30 mmHg or a pulmonary acceleration time (PAT) < 120 ms, or both)
Notes	Publicly funded Trial was conducted at three centres in Scotland, UK (Dundee, Perth, and Fife), between Sept 1, 2010, and Sept 1, 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomly assigned in a 1:1 ratio, via centralised randomisation with a computer-generated sequence and block sizes of four, to receive daily tadalafil 10 mg or matched placebo, orally"
Allocation concealment (selection bias)	Low risk	Quote: "The intervention and placebo packs were identical in presentation (capsules and bottle) and double blinding was maintained throughout"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients, study investigators, outcome assessors, and those administering drugs were masked to group allocation. Unmasking was done only after the end of the trial once all data had been collected and analysed"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, study investigators, outcome assessors, and those administering drugs were masked to group allocation. Unmasking was done only after the end of the trial once all data had been collected and analysed"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	120 patients were randomly assigned to receive tadalafil (n = 60) or placebo (n = 60), of whom 113 (94%) completed the study, reasons not given
Selective reporting (reporting bias)	Low risk	Unlikely selective reporting bias
Other bias	Low risk	Other risk unlikely

Guazzi 2011a

Methods	Randomised placebo-controlled trial 12 months duration
Participants	Inclusion criteria: • Participants with heart failure with preserved EF (heart failure signs and symptoms, diastolic dysfunction, EF 50%, and PASP 40 mmHg). (WHO Group 2) • PASP > 40 mmHg at a preliminary ultrasound estimation • Heart failure was independently adjudicated by 3 cardiologists on the basis of presence of 2 major criteria (nocturnal dyspnoea, distention of the jugular veins, moist rales over the lung bases, proto-diastolic sound) or the presence of 1 major criterion together with 3 minor criteria (liver enlargement, oedema in the feet or ankles not resolving after a night's rest, accentuation of P2, tricuspid systolic murmur, fatigue, signs of interstitial oedema at chest roentgenogram). • LVEF 50%, sinus rhythm, and no hospitalisation in the 6 months preceding recruitment

Guazzi 2011a *(Continued)*

	Exclusion criteria: • People receiving nitrates • history of pulmonary disease or in whom alternative causes of PH were likely • angina pectoris • acute coronary syndrome • atrial flutter/fibrillation with more than a trace of mitral or aortic regurgitation or stenosis • anaemia • pericardial disease • renal failure (creatinine 2 mg/dL) • cardiac amyloidosis, genetically-determined cardiomyopathy • systemic diseases precluding participation PH was confirmed on right-heart catheterisation n = 44
Interventions	Sildenafil (50 mg 3 times a day) (N=22) compared to placebo (N=22)
Outcomes	Haemodynamics, including: mean RAP, PASP, pulmonary artery diastolic pressure, mean PAP, mean wedge pulmonary pressure, transpulmonary gradient, pulmonary arteriolar resistance, pulmonary arterial elastance, RV end-diastolic pressure, RV mean systolic ejection rate, TAPSE, RV maximal short-axis dimension, cardiac index, systemic vascular resistance, systolic arterial pressure, diastolic arterial pressure Quality of life, including breathlessness, fatigue, emotional function Lung function tests including FEV1, FVC, and DLCO
Notes	Publicly funded Trial conducted at San Paolo Hospital in Milan, Italy, and at Virginia Commonwealth University, Richmond, USA, enrolled between January 15, 2006, and December 18, 2008

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned in a 1:1 ratio according to computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled, with nursing staff checking compliance unaware of the study aims or assignment to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not explicitly stated but assumed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were accounted for: Quote: "No participants in the sildenafil group was lost to follow-up; in the placebo group, 2 participants were withdrawn at months 7 and 9 because at repeated Holter monitoring they showed persistent atrial fibrillation".

Guazzi 2011a *(Continued)*

Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

Han 2013

Methods	Double-blind, placebo-controlled trial 12 weeks duration
Participants	Inclusion criteria: • Consensus criteria-defined IPF and CO diffusing capacity < 35% predicted • Evidence of right ventricular hypertrophy or right ventricular dysfunction. Exclusion criteria: • Resting oxygen saturation < 92% on 6 L of supplemental oxygen • Aortic stenosis • Idiopathic hypertrophic subaortic stenosis • Severe heart failure (left-sided VEF < 25%) (WHO Group 3) N = 119
Interventions	Oral sildenafil (20 mg 3 times a day) (N=56) compared with placebo (N=63)
Outcomes	6MWD SGRQ SF-36 EuroQol visual analogue scores
Notes	This was a substudy of the STEP-IPF study which examined all participants with IPF and compared sildenafil with placebo This substudy examined only those with pulmonary hypertension and IPF Industry-funded Trial conducted at 14 centres in the USA, dates of enrolment not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants meeting eligibility criteria were randomly assigned in a 1:1 ratio to receive sildenafil or matched placebo with the use of a permuted-block design, with stratification according to clinical centre
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias)	Low risk	Placebo-controlled

Han 2013 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All echocardiograms were performed prior to randomisation and scored independently and in a blinded fashion by two cardiologists with advanced expertise in echocardiography.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Sixty-one echocardiograms could not be transferred to the study centre, thus ineligible for inclusion".
Selective reporting (reporting bias)	High risk	This is a substudy
Other bias	Low risk	Other bias is unlikely

Hoendermis 2015

Methods	Single-centre, randomised double-blind, placebo-controlled trial 12 weeks duration
Participants	Inclusion criteria: • ≥ 18 years with symptomatic HFpEF (LVEF) ≥ 45% • NYHA functional class II – IV) • PH - diagnosed by mean PAP > 25 mmHg and mean PAWP > 15 mmHg, invasively measured by right-sided cardiac catheterisation. (WHO Group 2) Exclusion criteria: • Severe non-cardiac limitation to exercise • Significant left-sided valve disease • Other causes of pulmonary hypertension n = 52
Interventions	Sildenafil, titrated to 60 mg 3 times a day (N=26), or placebo (N=26)
Outcomes	The primary endpoint was change in mean PAP after 12 weeks Secondary endpoints were change in mean PAWP, cardiac output, and peak oxygen consumption (peak VO_2)
Notes	Publicly funded Trial conducted at University of Medical Center Groningen, Hanzeplein, The Netherlands, enrolled between October 2011 and September 2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomly assigned in a 1:1 ratio according to a computer-generated random sequence to 1 of the 2 treatment groups using a block size of 4

Hoendermis 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sildenafil and matching placebo were administered orally in tablets and were provided by Pfizer Global Pharmaceuticals, were identical in appearance and were supplied to the study site in identical-masked kits
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were recorded, and were even across the groups. Quote: "One participant in the sildenafil group withdrew due to heart failure, and four discontinued due to adverse events".
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were accounted for
Other bias	Low risk	Other bias is unlikely

Iversen 2009

Methods	Randomised, placebo-controlled, double-blinded, cross-over trial 3 months duration
Participants	Inclusion criteria: • People with Eisenmenger syndrome (WHO Group 1) WHO FC II/III n = 21
Interventions	Participants were randomised to sildenafil 25 mg 3 times a day. for 2 weeks followed by 50 mg 3 times a day for 10 weeks or matching placebo as add-on therapy to bosentan. After this period, evaluation identical to baseline examinations was performed again and a cross-over was performed so that participants receiving sildenafil were now treated with placebo and vice versa All participants were treated open-label with bosentan for the entire study period (9 months). During the first 2 weeks, the participants received bosentan 62.5 mg twice daily, and thereafter bosentan 125 mg twice daily for the rest of the trial
Outcomes	6MWT Oxygen saturations N-terminal pro-brain natriuretic peptide Improvement in NYHA classification Cardiac catheterisation Magnetic resonance imaging
Notes	Publicly funded Trial was conducted through Department of Cardiology at Copenhagen University Hospital Rigshospitalet in Copenhagen, Denmark between January 2006 and April 2007

Iversen 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by Copenhagen County Hospital Pharmacy
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not explicitly stated but assumed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were accounted for: Quote: "All the screened patients fulfilled the inclusion criteria and all were included in the study. No code breaks were done during the study. Two patients were excluded during the study (one due to side-effects of the medication and one due to death)".
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other bias is unlikely

Jalalian 2015

Methods	Randomised placebo-controlled trial 6 weeks duration
Participants	Inclusion criteria: • Participants with beta-thalassaemia intermedia • PH based on TTE Exclusion criteria: • Participants with hepatic or renal insufficiency • Treated with organic nitrates or alpha-blockers (WHO Group 5) n = 22
Interventions	Tadalafil (40 mg daily) (N=22) or placebo (N=22)
Outcomes	PASP TRV and parameters related to systolic function of the right ventricle including changes in TAPSE, pulsed Doppler peak velocity at the tricuspid annulus (S') were measured by TTE
Notes	Publicly funded

Jalalian 2015 *(Continued)*

Trial conducted at Babol, Northern Iran between December 2013 and April 2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the participants were randomly divided" but methods are not stated
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not clear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were accounted for, and were even across both groups. Quote: "Three participants in the tadalafil group and one participant in the placebo group withdrew due to side effects"
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other bias is unlikely

Jing 2011

Methods	Randomised, double-blind, placebo-controlled trial, 12 weeks duration, followed by an open-label trial, of another 12 weeks duration
Participants	Inclusion criteria: • Between 12 and 65 years of age • WHO functional classes II and III PAH despite the use of conventional therapies, including oral anticoagulants, digoxin, diuretics, or supplemental oxygen. (WHO Group 1) • A baseline 6MWD between 150 metres and 550 metres • a resting mean PAP ≥ 25 mmHg and PAWP ≤15 mmHg, and PVR > 4 Wood Units measured by right-heart catheterisation at enrolment Exclusion criteria: • No PAH-specific treatments (prostanoids, endothelin receptor antagonists, or phosphodiesterase type 5 inhibitors) were allowed for at least 3 months before enrolment • Acute responders to a vaso-reactivity test were excluded. WHO FC II/III n = 66
Interventions	Vardenafil (5 mg once daily for 4 weeks then 5 mg twice daily; n = 44) or placebo (n = 22)

Jing 2011 *(Continued)*

Outcomes	The primary efficacy endpoint was the 6MWD, assessed at the end of the 12-week randomised treatment period. Secondary measures of efficacy included cardiopulmonary haemodynamics (mean RAP, cardiac index, mean PAP, and PVR) measured by right-heart catheterisation; the Borg dyspnoea index; WHO functional class (at baseline and Week 12); and occurrence of clinical worsening events defined as death (all causes) or hospitalisation for PAH progression
Notes	Publicly funded Trial was conducted at nine centers in China and were enrolled in the trial between September 2008 and May 2009

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated using the DMS System, with a block size of 6. The 2:1 randomisation ratio (vardenafil: placebo) was the same for each centre
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not explicitly stated but assumed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were accounted for: 2 participants randomised to placebo were lost to follow-up without any follow-up data being recorded. 4 participants in the placebo group and 1 participant in the vardenafil group withdrew because of clinical worsening. Thus, 59 participants completed the randomised phase
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

Lewis 2007

Methods	Randomised, parallel-group, double-blinded, single-centre, placebo-controlled trial 12 weeks duration
Participants	Inclusion criteria: • adults who were 18 years of age • LVSD (LVEF > 0.4) • NYHA class II to IV chronic HF despite standard HF therapies • with secondary PH as defined by a mean PAP of 25 mmHg (WHO Group 2) • Participants who enrolled in a previous study of the short-term effects of 1-time administration of sildenafil on exercise capacity were eligible to enrol in this study

Lewis 2007 *(Continued)*

	Exclusion criteria: • Those with a noncardiac limitation to exercise • Provocable ischaemia • Haemodynamic instability • Ongoing nitrate therapy • Concentric LV hypertrophy • Critical aortic stenosis • Long-term use of medications that inhibit cytochrome P450 3A4 n = 34
Interventions	Sildenafil (25 to 75 mg orally 3 times daily) (N=17) or placebo (N=17)
Outcomes	6MWD Cardiopulmonary exercise test Haemodynamics using right-heart catheterisation, including RAP, PCWP, CI, stroke volume, PVR, SVR Quality of life questionnaire including the Minnesota Heart Failure Questionnaire (a 21-question self-administered instrument in which scores can range from 0 to 5 for each question and higher scores indicate a poorer quality of life) Clinical worsening Mortality Adverse events
Notes	Public and industry funded Trial conducted at multiple centres (location not stated) from May 2003 to March 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The Massachusetts General Hospital Pharmacy was responsible for the blinding and randomisation procedure
Allocation concealment (selection bias)	Low risk	The Massachusetts General Hospital Pharmacy was responsible for the blinding and randomisation procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators adjudicated all primary and secondary endpoints and reviewed data on safety before unblinding of the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is not clear whether there were any withdrawals; does not explicitly state that all recruited completed the trial
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes were reported

Lewis 2007 *(Continued)*

Other bias	Low risk	Other bias is unlikely

Machado 2009

Methods	Multicentre, placebo-controlled, double-blind trial 16 weeks duration
Participants	Inclusion criteria: • Adults and children (aged > 12 years) • with sickle cell disease (including, but not limited to SS, SC, SD, or S-beta zero thalassemia) • with doppler-defined PH (TRV ≥ 2.7 m/s) and 6MWD of 150 to 500 metres (WHO Group 5) • Randomised participants were stratified by TRV (2.7 to 2.9 m/s and ≥ 3.0 m/s), and those in upper strata underwent a right-heart catheterisation (RHC) Exclusion criteria: • Current pregnancy or lactation • Stroke within the last 6 weeks • Diagnosis of pulmonary embolism within the last 3 months • History of retinal detachment or retinal haemorrhage in the last 6 months • Non-arteritic anterior ischaemic optic neuropathy (NAION) in 1 or both eyes • History of sustained priapism requiring medical or surgical treatment, unless currently impotent or on transfusion programme within the last 2 years • Any unstable (chronic or acute) condition that in the opinion of the investigator will prevent completion of the study • People taking nitrate-based vasodilators, prostacyclin, or endothelin antagonists • LVEF < 40% or clinically significant ischaemic, valvular or constrictive heart disease • LVEF < 40% or SF < 22%, people in other research studies with investigational drugs (with the exception of hydroxyurea) unless the other trial has been approved by the walk-PHaSST Executive Committee for co-participation • Acute or chronic impairment (other than dyspnoea), limiting the ability to comply with study requirements (in particular with 6MWT), e.g. angina pectoris, intermittent claudication, symptomatic hip osteonecrosis, tonsillectomies for sleep apnoea within 3 months prior to randomisation • People taking potent CYP3A4 inhibitor therapy (e.g. itraconazole, ritonavir, ketoconazole) • People who are anticoagulated and have proliferative retinopathy (unless they have had ophthalmologist-recommended intervention (e.g. phototherapy) or have been cleared by the ophthalmologist to participate in the study) • People with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg n = 74, with a planned study size of 132
Interventions	Oral sildenafil 20 mg 3 times daily for 6 weeks,followed by 40 mg 3 times daily for 4 weeks, followed by 80 mg 3 times daily for 6 weeks, compared to placebo in a similarly uptitrated fashion
Outcomes	Primary outcome measures: Change in exercise capacity as assessed by 6MWD Secondary outcome measures: Change from baseline in PH at week 16 as assessed by tricuspid regurgitant jet velocity, Borg dyspnoea score, (severity is measured on a 10-point scale with 0 = nothing at all and 10 = maximum severity of breathlessness), BNP levels.
Notes	The study was prematurely stopped due to a statistically significant increase in serious adverse events in the sildenafil arm Published as an abstract only, but also registered on the clinical trial registry: NCT00492531

Machado 2009 *(Continued)*

	Publicly funded
	Trial conducted at 10 United States and United Kingdom Centers, dates not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised, but methods not clearly stated
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and reasons for trial termination clearly described
Selective reporting (reporting bias)	Low risk	Study was published despite early termination
Other bias	Low risk	Risk of other bias is unlikely. Although this is an abstract only, further methods were published on the clinical trials registry

Mazzanti 2013

Methods	Randomised, open-label trial Average duration of treatment: 4.1 ± 1.2 months
Participants	Inclusion criteria: • PAH (no further details given) (WHO Group 1) WHO FC not stated n = 205
Interventions	Bosentan (125 mg twice daily) (N=100) compared with sildenafil (20 mg 3 times a day) (N=105)
Outcomes	6MWD Haemodynamics using right-heart catheterisation Survival Adverse events
Notes	Abstract only

Mazzanti 2013 *(Continued)*

	Source of funding not stated Trial conducted at Department of Specialized, Diagnostic and Experimental Medicine, BOLOGNA, Italy, from November 2006 to January 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only - reports as randomised but no further details given
Allocation concealment (selection bias)	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were reported and similar across both groups: 20 participants (20%) in the bosentan group and 13 (12%) in the sildenafil group did not complete the short-term evaluation because of death, adverse events, protocol violations, lack of haemodynamic data or were lost to follow-up
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other bias is unlikely - within the abstract clear and detailed methods and outcomes are presented

Mukhopadhyay 2011

Methods	Randomised controlled cross-over trial 6 weeks duration per treatment arm with a wash-out of 2 weeks
Participants	Inclusion criteria: • People with Eisenmgers Syndrome (confirmed by cardiac catheterisation as mean PAP > 40 mmHg, PAWP < 15 mmHg, and PVR > 10 Wood units/m^2) • Age 18 years • Weight > 30 kg • WHO functional class II and III • Congenital heart defects (atrial septal defect > 2 cm, ventricular septal defect > 1 cm, and aortopulmonary communication > 0.4 cm) with echocardiographic evidence of right to left shunt • systemic pulse oximetry between 70% and 90% at rest in room air • Baseline 6MWD between 150 and 450 metres. (WHO Group 1) • Medical therapy and clinical condition of the participants had to be stable for 3 months prior to screening Exclusion criteria:

Mukhopadhyay 2011 *(Continued)*

	• Treatment with prostanoids, ERA, PDE5 inhibitors, or any other vasodilator within 1 month prior to screening • WHO class IV • In congestive heart failure or had PAWP > 15 mmHg, had LVEF < 40%, atrial fibrillation, PDA (for haemodynamic assessment difficulties) • Complex congenital heart defects • Restrictive lung disease (total lung capacity < 70% of predicted) • Obstructive lung disease (FEV1 < 70% of predicted with FEV1/FVC < 60%) • Previously diagnosed coronary artery disease requiring nitrate therapy • Abnormal biochemical profile • Hypersensitivity to PDE5 inhibitors WHO FC II/III n = 28
Interventions	Tadalafil 40 mg or matching placebo for 6 weeks, followed by cross-over to the other drug after a wash-out period of 2 weeks
Outcomes	The primary endpoint was improvement in exercise tolerance by 6MWD The secondary end points were the effect of the drug on SO2, EPBF, PVR, SVR, and WHO functional class
Notes	Drugs were supplied free of cost from industry. Other sources of funding were not stated Trial conducted at G.B. Pant Hospital, New Delhi, India (dates not given)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated as randomised, but methods are not specified
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not clear whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Any withdrawals and reasons were not stated. It is not clear whether all participants who were enrolled completed the study
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

Ovchinnov 2015

Methods	Randomised parallel-group placebo-controlled trial 12 weeks duration
Participants	Inclusion criteria: • Participants with HFpEF (diagnosed by the ESC algorithm, 2007) • Reactive pulmonary hypertension (systolic pulmonary artery pressure ≥ 35 mmHg at rest and Doppler-derived pulmonary vascular resistance > 3.0 units Wood) • On standard CHF therapy (WHO Group 2) n = 50
Interventions	Sildenafil (25 mg 3 times a day for 12 weeks followed by 50 mg 3e times a day for 12 weeks; n = 30) or to control group (no sildenafil, n = 20)
Outcomes	6MWD Cycle ergometer exercise duration Systolic pulmonary artery pressure RV function assessed by tricuspid annular systolic excursion Left-sided diastolic function (E/é ratio)
Notes	Quantitative outcomes were only reported for the sildenafil group; the trial reported "no improvement in control group was observed" so this trial was unable to be included in the meta-analysis We tried to contact all authors, but at the time of this review publication there has been no reply, or contact details were unavailable Funding source not stated Location and dates not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states participants were randomly assigned, but no methods were given
Allocation concealment (selection bias)	High risk	Compared sildenafil to "no sildenafil" - unclear if placebo was used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unclear if placebo was used or if participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of completers were not reported. Mortality or loss to follow-up were not reported. Methods using intention-to-treat or per-protocol analysis was not specified

Ovchinnov 2015 *(Continued)*

Selective reporting (reporting bias)	High risk	Quantitative outcome data were only reported for the sildenafil group, not placebo group, and no P values between groups were reported
Other bias	Unclear risk	Not clear if other bias is possible - abstract from conference proceedings with limited data presented

Palazzini 2010

Methods	Randomised, open-label trial Mean follow-up 3.8 ± 0.8 months
Participants	Inclusion criteria: • PAH secondary to non-operable chronic thromboembolic pulmonary hypertension, further details not specified (WHO Group 4) n = 128
Interventions	Bosentan versus sildenafil (doses not provided)
Outcomes	6MWD Haemodynamics using right-heart catheterisation including mean PAP, cardiac index, PVR Mortality
Notes	Abstract only Quote: "This abstract is funded by: none". Otherwise no other funding information is supplied Trial conducted at Orsola Malpighi Hospital, Bologna, Italy (dates not given)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified randomisation used
Allocation concealment (selection bias)	Unclear risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were reported: "6 withdrew from the bosentan group and 2 from sildenafil group due to side effects, 3 in bosentan and 1 in sildenafil group withdrew due to protocol violations, 2 did not undergo RHC, and 1 withdrew consent"

Palazzini 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Unclear risk	Unclear if other risk is present - abstract only from conference proceedings with limited data presented

Palii 2014

Methods	Monocentric, randomised placebo-controlled trial 12 months duration
Participants	Inclusion criteria: • Children with severe PAH secondary to congenital shunts (simple (14 patients), mixed (35), complex (28)). 77 PAH patients (35 – repaired shunts, 31 – palliative, 11 inoperable) (WHO Group 1) WHO FC III n = 77
Interventions	Sildenafil – dose of 1 to 2 mg/kg/day every 8 hours (N=38), compared to placebo (N=39)
Outcomes	NYHA functional class; 6MWT; O_2 saturation; echocardiography PAPm, myocardial performance index (MPI/Tei index), right-cardiac catheterisation – PVRI; questionnaire for adverse reactions
Notes	Abstract only Funding source not stated Trial conducted at Institute of Mother and Child, Chisinau, Moldova (dates not given)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States randomised, although information given was limited as this was an abstract only. We tried to contact authors but there was no reply at the time of publication
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals were not specified

Palii 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Unclear risk	Unclear if other risk is present - abstract only with limited data presented

Rao 2011

Methods	Randomised, double-blind placebo-controlled trial 12 weeks duration
Participants	Inclusion criteria: • Ambulatory participants • Severe or very severe COPD (according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification) • Past history of smoking of at least 20 pack years • PASP > 40 mmHg as measured by Doppler echocardiography Exclusion criteria: • An acute exacerbation of COPD in last month • History of bronchial asthma or > 12% increase in FEV1 with bronchodilator • History of primary cardiac disease or documented IHD • Use of nitrates or other vasodilator throughout the study period • Haemoglobin < 12 g/dL • Any severe concomitant disease • Evidence of PAH due to any other cause, such as pulmonary thromboembolism, HIV, scleroderma, congenital heart disease and de-compensated right or left heart failure. (WHO Group 3) n = 37
Interventions	Oral sildenafil 20 mg 3 times a day (N=17) compared to identical placebo (N=20)
Outcomes	Primary outcome: change in 6MWD. Improvement in PAP was taken as secondary outcome of the study
Notes	Industry provided the drugs. No other funding source stated Trial conducted at SMS Medical College and Hospital, Jaipur (Rajasthan), India (dates of recruitment not stated)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sildenafil and placebo were dispensed according to random allocation of computer-generated code
Allocation concealment (selection bias)	Low risk	Drug was dispensed by an unblinded co-ordinator, who dispensed the drug to blinded co-ordinator, who gave it to the participants
Blinding of participants and personnel (performance bias)	Low risk	Drug was dispensed by an unblinded co-ordinator, who dispensed the drug to blinded co-ordinator, who gave it to the participants

Rao 2011 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not explicitly stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were accounted for and similar across the 2 groups - where in each group 1 was lost to follow-up, 1e in the sildenafil group had an acute exacerbation, and 1 in the placebo group withdrew consent
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

Salem 2013

Methods	Randomised, placebo-controlled trial 6 weeks duration
Participants	Inclusion criteria: • Adults with symptomatic secondary PH with NYHA functional class • The underlying aetiologies of PH were: dilated cardiomyopathy, COPD, chronic thromboembolic disease, ILD, and valvular heart disease (mitral and aortic regurgitation) Exclusion criteria: • Primary pulmonary hypertension • Hypotension • Allergy to sildenafil • IHD (WHO Group 2 - 5) n = 40
Interventions	Oral sildenafil (N=20) or matched placebo (N=20) was given in a titrated dose, starting with 25 mg 3 times daily for 1 week, then the dose was doubled to 50 mg 3 times daily according to side effects and tolerability until 6-week period
Outcomes	Improvement in NYHA functional class PASP LVEF
Notes	Funding source not stated Location of trial and dates of recruitment not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using simple randomisation (1:1) to either sildenafil therapy in a titrating dose or placebo

Salem 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear if the outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was not explicitly stated if all randomised participants completed the trial; no withdrawals were reported
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

Sastry 2004

Methods	Randomised, double-blind, cross-over trial 6 weeks duration
Participants	Inclusion criteria: • 12 and 65 years of age • PAH • NYHA functional class II to III • An estimated mean PAP > 30 mmHg on Doppler echocardiography • Able to walk on a treadmill. (WHO Group 1) Exclusion criteria: • NYHA functional class IV • Significant right-to-left shunt • Valvular heart disease • Left ventricular systolic dysfunction • Systemic hypertension • Secondary pulmonary hypertension • Other severe co-morbid conditions WHO FC II/III n = 22
Interventions	Sildenafil compared to placebo Medication dosage was assigned on the basis of body weight, with participants weighing up to 25 kg receiving 25 mg 3 times daily, those weighing between 26 and 50 kg receiving 50 mg 3 times daily, and those weighing 51 kg receiving 100 mg 3 times daily

Sastry 2004 *(Continued)*

	Digoxin, diuretics, and oral anticoagulants were used at the clinician's discretion. No other vasodilators were allowed, and participants were specifically advised not to take nitrate preparations in any form
Outcomes	Time spent on treadmill PASP Cardiac index as measured on doppler echocardiography Adverse events Quality of life (a chronic heart failure questionnaire with 16 questions, including 5 to assess dyspnoea, 4 to assess fatigue, and 7 to assess emotional function of daily living. The answers to each question may be scored from 1 (denoting worst function) to 7 (denoting best function). The maximum possible score of 108 would denote the best QOL, whereas a minimum score of 16 would denote worst QOL)
Notes	PAH diagnosed on echo, did not use right-heart catheterisation Funding source not stated Trial was conducted at CARE Hospital, Hyderabad, India, between September 17, 2002, and December 13, 2002

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed on the basis of computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The participant, clinical investigator, echocardiographer, and the person supervising the exercise were blinded to the participant's treatment regimen
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals were reported and similar across groups: Quote: "One participant in the sildenafil first group opted out of the study one week after randomisation. This was not the result of any serious adverse effect of medication. Another participant in the placebo-first group died one week after randomisation".
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

Simonneau 2008

Methods	Multicentre, double-blind, placebo-controlled, parallel group trial

Simonneau 2008 *(Continued)*

	16 weeks duration
Participants	Inclusion criteria: • Adults least 18 years of age (16 years of age in the United States) • PAH (idiopathic, familial, associated with anorexigen use or connective tissue disease, or occurring after surgical repair of congenital systemic-to-pulmonary shunts done at least 5 years earlier). Participants had to have received long-term intravenous epoprostenol therapy for at least 3 months, with a stable dose for at least 4 weeks before randomisation. (WHO Group 1) Exclusion criteria: • People with a 6MWD < 100 metres or > 450 m or those whose 6MWD was affected by conditions other than PAH • Who had a change in epoprostenol dose within 4 weeks before receiving the randomly-assigned drug • Those receiving bosentan, nitrates, or nitric oxide donor drugs • With PAH secondary to causes other than those listed, people with cardiovascular disease • People with retinopathy • COPD • Severe impairment of hepatic function • Pregnant or lactating women WHO FC II/III n = 265
Interventions	Placebo (N=133) or sildenafil (N=134), 20 mg 3 times daily, titrated to 40 mg and 80 mg 3 times daily, as tolerated, at 4-week intervals
Outcomes	Change from baseline in exercise capacity measured by 6MWD (primary endpoint) Haemodynamic measurements, time to clinical worsening, and Borg dyspnoea score (secondary endpoints) Not clear whether right-heart catheterisation was used
Notes	Also called the PACES study Industry funded Trial conducted at 46 centers in 11 countries (United States, 26; Canada, 6; France, 3; Netherlands, 2; Spain, 2; United Kingdom, 2; Belgium, 1; Czech Republic, 1; Denmark, 1; Israel, 1; and Italy, 1), recruited from 3 July 2003 to 27 January 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used a central, computer-generated pseudo-random code (by using random, permuted blocks within strata) to assign patients to treatment groups across all centers. Eligible patients were randomly assigned to receive sildenafil or placebo in a 1:1 ratio. The randomisation was stratified by the baseline 6MWD (325 m or 325 m) and cause (idiopathic pulmonary arterial hypertension or pulmonary arterial hypertension due to other causes)".
Allocation concealment (selection bias)	Low risk	Placebo-controlled

Simonneau 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals were accounted for and similar across groups: Quote: "Only 1 participant in the study (in the placebo group) did not adhere to treatment. No unplanned crossovers occurred during the trial"
Selective reporting (reporting bias)	Unclear risk	Quote: "We analysed treatment effects for the secondary end points sequentially only if a statistically significant effect was seen for the primary outcome"
Other bias	Low risk	Other bias is unlikely

Singh 2006

Methods	Randomised, double-blind, placebo-controlled cross-over trial 6 weeks duration with a wash-out of 2 weeks
Participants	Inclusion criteria: • People with severe PAH, 10 each of IPAH and Eisenmenger syndrome. Exclusion criteria: • People with coronary artery disease • Significant hepatic and renal dysfunction • Those with contraindication to sildenafil therapy • Cases of PH as a result of other causes were excluded from the study (WHO Group 1) WHO FC II/III n = 20
Interventions	Oral sildenafil versus placebo Adult participants were given 25 mg sildenafil on the first day and repeated after 6 hours under observation. If there was no hypotension, they were given 100 mg 3 times a day. In children weighing < 30 kg, an initial dose of 3.125 mg of sildenafil was given and maintained at 25 mg 3 times daily. In older children weighing > 30 kg, initial dose of 6.25 mg was given and maintained at 50 mg 3 times a day. Participants were given second dose only if there was no significant fall in BP. Treatment was given for 6 weeks, which was followed by a 2-week washout before crossing over Routine medication, as prescribed by the treating physician, including digitalis, diuretics, and oral anticoagulants, was continued throughout the study Compliance was assessed by the pill-count method
Outcomes	The primary endpoint of efficacy was the improvement in distance covered in 6MWD. Secondary endpoints were reduction in PAP as measured by Doppler echocardiography after 6 weeks of treatment, improvement in clinical condition, NYHA class, and exercise duration and metabolic equivalents (Mets) achieved on modified Bruce exercise protocol

Singh 2006 *(Continued)*

Notes	Funding source not stated Location and dates of enrolment not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation, blinding, and drug/placebo administration were done by the Department of Pharmacology
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is not explicitly stated if there were any withdrawals
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

Suntharalingham 2008

Methods	Randomised, double-blind, placebo-controlled trial 12 weeks duration
Participants	Inclusion criteria: • Adults with distal CTEPH. (WHO Group 4) • Diagnosis of PH at right-heart catheterisation using standard diagnostic criteria. • CTEPH was confirmed by ventilation perfusion scanning, CT pulmonary angiography, and either catheter-directed pulmonary angiography or magnetic resonance pulmonary angiography. • All imaging had been reviewed by a panel of specialist physicians, radiologists, and surgeons to determine the distribution of disease. • People with de novo distal CTEPH and those with persistent PH 3 months post-PEA surgery were approached. • Post-PEA patients were re-imaged prior to enrolment both with CT pulmonary angiography and magnetic resonance pulmonary angiography to ensure no proximal disease remained. Exclusion criteria: • Received any PH-specific therapy or nitrate therapy in the 6 months prior to enrolment • 6MWD < 100 metres or > 450 metres

Suntharalingham 2008 *(Continued)*

	n = 19
Interventions	Sildenafil at 40 mg 3 times a day (N=9) or placebo (N=10) at 2 tablets 3 times per day in a 1:1 ratio At the end of the study, all participants were transferred to open-label sildenafil at 40 mg 3 times a day and offered repeat assessment at 12 months
Outcomes	Primary endpoint was change in 6MWD Secondary endpoints included changes in WHO class, cardiopulmonary haemodynamics, QOL scores, and NT-proBNP
Notes	Funding source not stated Trial conducted at the Pulmonary Vascular Diseases Unit, Papworth Hospital, Cambridgeshire, UK, enrolled between August 2004 and August 2007

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly stated if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals were accounted for: Quote: "An extensive urticarial rash developed in one subject in the sildenafil arm, who was thus withdrawn from the study"
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

Vitulo 2016

Methods	Randomised, placebo-controlled double-blind trial 16 weeks duration
Participants	Inclusion criteria: • Adults aged between 40 and 80 years • Diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease guidelines.

Vitulo 2016 *(Continued)*

	• People with COPD referred with symptoms suggestive of PH were screened with Doppler echocardiography: an estimated SPAP > 50 mmHg was the indication for the baseline RHC. Exclusion criteria: • Decompensated heart failure • A severe mental disorder preventing appropriate judgement concerning study participation • Known intolerance to or formal contraindication for the use of sildenafil. (WHO Group 3) • Other potential causes of PH, such as chronic thromboembolic pulmonary hypertension or left-sided heart disease, as was ischaemic or cardiac valve disease • Concomitant nitrate or PAH treatment • Those with liver/kidney dysfunction • Those who had experienced a recent bronchial exacerbation (within 4 weeks). n = 28
Interventions	20 mg sildenafil or placebo 3 times a day
Outcomes	Primary endpoint was the reduction in pulmonary vascular resistance Secondary endpoints included BODE index, 6MWT, and quality of life questionnaire
Notes	There is a correction to the original study report: in Table 4 the difference in change for 6MWT should read +19.3, not −19.3, as has been communicated by the authors Dario Vizza with thanks. Industry funded Trial conducted at 7 Italian centers with expertise in the management of PH and COPD, from March 2012 to March 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A pharmacologist not involved directly in the study used an electronic system to manage randomisation
Allocation concealment (selection bias)	Low risk	A pharmacologist not involved directly in the study used an electronic system to manage randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A pharmacologist not involved directly in the study used an electronic system to manage randomisation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were accounted for: Included in the intention-to-treat analysis were 3 participants who did not perform the end-of-study RHC for refusal or technical reasons
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

Vizza 2017a

Methods	Randomised, placebo-controlled double-blind trial 12 weeks duration
Participants	Inclusion criteria: • Adults (≥ 18 years) with PAH (mean PAP ≥ 25 mmHg; PAWP < 15 mmHg at rest) confirmed by right-heart catheterisation within the previous 3 years • Receiving treatment with bosentan (62.5 or 125 mg 3 times a day) at a stable dose for ≥ 3 months PAH was idiopathic, heritable, or associated with connective tissue disease, or surgical repair (≥ 5 years previously) of septal defect. (WHO Group 1) Exclusion criteria: • Acutely decompensated heart failure within 30 days before randomisation • LVEF < 45% or LV shortening fraction of < 0.2 within 3 months before randomisation • Congenital heart disease • History of MI, stroke, or atrial septostomy within 6 months before randomisation • Uncontrolled brady- or tachy-arrhythmias, placement of pacemakers/implantable defibrillators < 60 days before randomisation • History of verified pulmonary embolism • History of chronic/restrictive lung disease (e.g. COPD or scleroderma) with TLC < 60% and/or FEV1 ≤ 80% predicted within 30 days of randomisation • Change of dose/class of standard background PAH therapy (i.e. oxygen, calcium channel blockers, digoxin, diuretics) within 30 days • Current chronic PAH-specific therapy (e.g. prostacyclin, PDE5 inhibitors, ERAs other than bosentan) WHO FC II/III n = 103
Interventions	Sildenafil (20 mg 3 times daily) (N=53) or placebo (N=50)
Outcomes	6MWD WHO functional class Borg dyspnoea score Clinical worsening (death, lung transplantation, hospitalisation due to pulmonary hypertension, or clinical deterioration of PAH requiring additional therapy) Survival was assessed at week 64, including participants who had discontinued treatment
Notes	Industry funded Trial was conducted between September 2006 and August 2012 at 29 sites in 10 countries

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (via interactive voice response system incorporating a central randomisation and drug supply scheme)
Allocation concealment (selection bias)	Low risk	Participants and investigators were blinded to treatment

Vizza 2017a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and investigators were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 104 randomised participants, 103 were treated in the double-blind study and 91 continued in the extension
Selective reporting (reporting bias)	Low risk	Outcomes were all reported
Other bias	Low risk	Other bias is unlikely

Wilkins 2005

Methods	Randomised double-blind controlled trial 20 weeks duration
Participants	Inclusion criteria: • Adults with PAH that was either idiopathic or associated with connective tissue disease (scleroderma or systemic lupus erythematosus) • Were eligible for bosentan therapy were considered for the study (WHO Group 1) • The PAH diagnosis was based on cardiac catheter data (mean PAP at rest ≥ 25 mmHg) obtained within the preceding 12 months and the results of extensive screening for other causes according to current guidelines • All participants were symptomatic despite conventional therapy with diuretics, digoxin, and anticoagulants • 6MWD was required to be between 150 and 450 metres at entry Exclusion criteria: • Elevated baseline liver enzymes (3 times the upper limit of the normal range) • Previous bosentan or sildenafil treatment • Urgent need for prostanoid therapy on clinical grounds WHO FC III n = 26
Interventions	Sildenafil (50 mg twice daily for 4 weeks, then 50 mg 3 times daily) (N=14) or bosentan (62.5 mg twice daily for 4 weeks, then 125 mg twice daily) (N=12)
Outcomes	Changes in right ventricular mass (using cardiovascular magnetic resonance), 6MWD, cardiac function, BNP, and Borg dyspnoea index
Notes	Also called the SERAPH study Supported by public funding Trial conducted at Hammersmith Hospital, London, UK, during February 2002 to September 2003

Wilkins 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The medication was blinded in identical-looking gelatin capsules and randomised using a computer-generated random list by the Hammersmith Hospital pharmacy
Allocation concealment (selection bias)	Low risk	The medication was blinded in identical-looking gelatin capsules and randomised using a computer-generated random list by the Hammersmith Hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The measurements from images were made by an experienced operator who was unaware of each participant's clinical information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were accounted for: 1 participant died suddenly in the sildenafil arm
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk is unlikely

Zhuang 2014

Methods	Randomised placebo-controlled trial 16 weeks duration
Participants	Inclusion criteria: • Adults aged 18 to 70 years • Symptomatic PAH • Received ambrisentan for 4 months or more • All diagnoses were confirmed as either idiopathic/familial PAH or PAH-related to anorexigen use, connective tissue disease or repaired congenital heart disease. (WHO Group 1) • Resting mPAP ≥ 25 mmHg, pulmonary wedge pressure < 15 mmHg and PVR > 3 Wood units • 6MWD between 150 and 400 metres (6MWD stable for at least 1 month) • Stable World Health Organization (WHO) functional class (FC) for at least 1 month before stud Exclusion criteria: • Thromboembolic disease • Untreated obstructive sleep apnoea • Portal hypertension • Chronic liver disease • Renal insufficiency • Left-sided or unrepaired congenital heart disease

Zhuang 2014 *(Continued)*

	• Substantial obstructive (FEV1/FVC ratio of 50% predicted) or restrictive (total lung capacity of 60% predicted) lung disease • People taking prostanoids or other PDE inhibitors WHO FC II/III n = 124
Interventions	Tadalafil (40 mg a day) (N=60) or placebo to existing therapy with oral ambrisentan (10 mg a day) (n=64)
Outcomes	6MWD Improvement in WHO functional class Clinical worsening was defined as the occurrence of the following events: death, transplantation, arterial septostomy, hospitalisation due to worsening PAH, initiation of new therapy or worsening FC by week 16 Haemodynamic parameters were measured by right-heart catheterisation
Notes	Funding source not stated Trial was conducted at Shanghai Tenth People's Hospital of Tongji University, Shanghai, China, between September 2011 and March 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Type of randomisation is not clear The randomisation was stratified for baseline walking distance and type of PAH (idiopathic/familial and anorexigen use vs. other types)
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were accounted for: In the tadalafil group: 6 participants discontinued: 3 for toxicity, 1 for worsening PAH, 2 for non-compliance In the placebo group: 5 participants discontinued: 4 for worsening PAH; 1 for irrelevant accidental death
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	Low risk	Other risk of bias is unlikely

6MWD: six-minute walk distance; BNP: brain nutrietic peptide; BODE: Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity; CHF: congenital heart failure; CI: cardiac index; COPD: chronic obstructive pulmonary disease; CTEPH: chronic thromboembolic pulmonary hypertension; DCMP: dilated cardiomyopathy; DLCO: diffusing capacity for carbon monoxide; EF: ejection fraction; EPBF: effective pulmonary blood flow; ERA: endothelin receptor antagonist; FEV1: forced expiratory volume in one second; HFpEF: heart failure with preserved ejection fraction; HIV: human immunodeficiency virus; IV: intravenous; LV: left ventricle; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; m: metres; n: number; NT-Pro BNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PAP: pulmonary artery pressure; PASP: pulmonary artery systolic pressure; PAWP: pulmonary artery wedge pressure; PCWP: pulmonary capillary wedge pressure; PDA: patent ductus arteriosus; PDE5: phosphodiesterase 5; PEA: pulmonary endarterectomy; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; QOL: quality of life; RAP: right atrial pressure; RHC: right heart catheterisation; SF-36: short form 36; SGRQ: St George's Respiratory Questionnaire; SO_2: saturation of oxygen; SVR: systemic vascular resistance; TAPSE: tricuspid annular plane systolic excursion; TLC: total lung capacity; TTE: transthoracic echocardiogram; TRV: tricuspid regurgitation velocity; VO_2: volume of oxygen; WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aldashev 2005	Ineligible patient population
Alkhayat 2016	According to correspondence from the author, this study was not randomised
Arneson 2010	Post hoc analysis
Bachetti 2015	Ineligible intervention
Badesch 2005	Post hoc analysis
Badesch 2007	Post hoc analysis
Badesch 2011	Post hoc analysis
Barst 2011	Post hoc analysis
Bates 2011	Ineligible patient population
Benza 2011	Extension of a previous study
Benza 2018	Point of randomisation was macitentan, not PDE5 inhibitor
Botha 2009	Ineligible patient population
Butrous 2006	Not randomised
Cappelleri 2010a	Post hoc analysis
Cappelleri 2010b	Ineligible intervention and study design
Cappelleri 2010c	Ineligible intervention and study design
Chin 2012	Ineligible intervention
Corris 2005	Post hoc analysis
Dandekar 2012	Ineligible comparator
Farah 2013	Ineligible intervention

Study	Reason for exclusion
Farrero 2009	Not randomised
Feldman 2010	Post hoc analysis
Fernandes 2014	Ineligible study design
Fischler 2009	Too short treatment duration
Galiè 2005b	Ineligible study design
Galiè 2011a	Post hoc analysis
Galiè 2011b	Extension of a previous study
Galiè 2013	Extension of a previous study
Ghofrani 2002a	No comparator group, not randomised, acute term study
Ghofrani 2002b	Acute term study
Ghofrani 2002c	Acute term study
Ghofrani 2004a	Acute term study
Ghofrani 2004b	Acute term study (120 mins)
Ghofrani 2004c	Acute term study
Girgis 2009	Open-label extension of included study
Gotti 2014	Post hoc analysis
Guazzi 2007	Ineligible patient population
Guazzi 2011b	Ineligible patient population
Guazzi 2017	Review
Jackson 2010	Not randomised
Mclaughlin 2010	Ineligible intervention
McLaughlin 2014	Ineligible intervention
McLaughlin 2015	Ineligible intervention
Mychaskiw 2010a	Ineligible intervention
Mychaskiw 2010b	Ineligible intervention
Nazeem 2014	Ineligible intervention
Oudiz 2009a	Extension of a previous study
Oudiz 2009b	Extension of a previous study

Study	Reason for exclusion
Oudiz 2009c	Post hoc analysis
Oudiz 2009d	Post hoc analysis
Oudiz 2012	Extension of a previous study
Peacock 2005	Extension of a previous study
Roig 2014	Ineligible study design
Rubin 2005	Post hoc analysis
Rubin 2011	Post hoc analysis
Santos-Martinez 2015	Ineligible patient population
Shamma 2002	Not randomised
Sharma 2014	Ineligible intervention
Shrestha 2017	No placebo
Simonneau 2010	Extension of a previous study
Sitbon 2005	Post hoc analysis
Sun 2014	No placebo or other intervention
Vizza 2011	Ineligible comparator
Vizza 2017b	Ineligible comparator
Zeng 2012	Ineligible study design

Characteristics of ongoing studies *[ordered by study ID]*

Cooper 2013

Trial name or title	Sildenafil versus placebo in chronic heart failure (SilHF)
Methods	Double-blind, parallel, randomised controlled trial, 2:1
Participants	• Outpatients with chronic HF, NYHA class II - III on optimal treatment in sinus rhythm or atrial fibrillation • LVEF < 40% measured during the past 12 months • PAP > 40 mmHg using echocardiography
Interventions	Sildenafil 40 mg 3 times daily compared to placebo
Outcomes	6MWD Quality of life (QoL) evaluation by EuroQol5D Kansas City Questionaire

Cooper 2013 *(Continued)*

	NYHA function class All measured at 24 weeks
Starting date	March 2013
Contact information	Helse Stavanger HF
Notes	ClinicalTrials.gov Identifier: NCT01616381 Estimated study completion date: March 2018

Maron 2013

Trial name or title	Tadalafil for pulmonary hypertension due to chronic lung disease (TADA-PHILD)
Methods	Randomised, double-blind, parallel, placebo-controlled trial
Participants	• Gold Stage II COPD by pulmonary function testing (FEV1/FVC < 0.70) • Eligible participants must have PH documented on TTE within 6 months of baseline visit demonstrating an RV systolic pressure > 40 mmHg. To confirm the presence of PH, a right-heart catheterisation will be performed, with people randomised to treatment only if catheterisation shows a: mPAP ≥ 25 mmHg, PVR > 2.5 Wood units PAWP 18 mmHg or less at rest
Interventions	Tadalafil 40 mg daily versus placebo
Outcomes	• 6MWD • Maximum volume of oxygen extraction on exercise testing • Pulmonary vascular resistance (assessed on right-heart catheterisation) • Mean PAP (assessed by right-heart catheterisation) • TAPSE • Dyspnoea and health-related quality of life (HRQL) • N-type brain natriuretic peptide (BNP) concentration • Resting hypoxaemia • Exercise-induced hypoxaemia Outcomes measured at 12 months
Starting date	October 1, 2013
Contact information	VA Boston Healthcare System Jamaica Plain Campus, Jamaica Plain, MA
Notes	ClinicalTrials.gov Identifier: NCT01862536 Estimated study completion date: August 2019

NCT 02951429

Trial name or title	Efficacy, safety, and tolerability study of pirfenidone in combination with sildenafil in participants with advanced idiopathic pulmonary fibrosis (IPF) and risk of Group 3 pulmonary hypertension
Methods	Phase IIb, randomised parallel-group controlled trial

NCT 02951429 *(Continued)*

Participants	Participants with advanced IPF and risk of Group 3 pulmonary hypertension (PH)
Interventions	Pirfenidone plus sildenafil versus pirfenidone plus placebo
Outcomes	• Percentage of participants with disease progression, as determined by relevant decline in 6MWD of at least ≥ 15 percent from baseline, respiratory-related non-elective hospitalisation, or death from any cause • Progression-free survival • 6MWD • Time to all-cause non-elective hospitalisation • Time to death from any cause • Time to respiratory-related death • Percentage of participants with lung transplantation • Peak tricuspid regurgitation velocity • PAP • FVC • FEV1 • FEV1/FVC ratio • CO diffusing capacity/pulmonary diffusing capacity (DCLO) • Change from baseline to weeks 6, 12, 26, 39, and 52 in SpO_2 at rest and during the 6MWD • Perceived exertion, as assessed by BORG rating of perceived exertion scale • Percentage of participants by WHO functional class • Change from baseline to weeks 12, 26, 39, and 52 in dyspnoea, as assessed by the University of California San Diego shortness of breath questionnaire (UCDS SOBQ) • Change from baseline to weeks 12, 26, 39, and 52 in health-related quality of life (hrqol), as assessed by the SGRQ • Change from baseline to weeks 12, 26, and 52 in NT-proBNP level at baseline, weeks 12, 26, and 52 • Adverse events and serious adverse events Measured at 52 weeks
Starting date	Currently recruiting
Contact information	global-roche-genentech-trials@gene.com
Notes	ClinicalTrials.gov Identifier: NCT02951429 Currently recruiting

NCT 03185364

Trial name or title	The safety and efficiency of sildenafil in the treatment of severe post-capillary pulmonary hypertension caused by COPD
Methods	Randomised, double-blind, parallel, placebo-controlled trial
Participants	Aged 40 to 85 years with COPD and PH (mean PAP ≥ 35 mmHg, PAWP ≤ 15 mmHg)
Interventions	Sildenafil 20 mg t3 times daily
Outcomes	• PAP • PVR

NCT 03185364 *(Continued)*

	Measured at 12 weeks
Starting date	June 14, 2017
Contact information	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology Wuhan, Hubei, China, 430030
Notes	ClinicalTrials.gov Identifier: NCT03185364 Currently recruiting

REPLACE 2017

Trial name or title	REPLACE: A prospective, randomized trial of riociguat replacing phosphodiesterase 5 inhibitor therapy in patients with pulmonary arterial hypertension who are not at treatment goal
Methods	Prospective, randomised, multicentre, double-arm, 24-week, controlled, open-label study
Participants	People with PAH not at treatment goal (WHO FC III, 6MWD 165 – 440 metres) despite receiving stable doses of PDE5i with or without ERA
Interventions	Participants will be randomised to continue PDE5i therapy or switch to riociguat (up to 2.5 mg 3 times daily)
Outcomes	The composite primary efficacy endpoint is satisfactory clinical response at Week 24, defined as fulfilment of at least 2 out of 3 efficacy parameters (≥ 10% or ≥ 30 metres increase from baseline in 6MWD, WHO FC I/II or ≥ 30% reduction from baseline in NT-proBNP) in the absence of clinical worsening (independent central adjudication). Secondary outcomes include change from baseline in 6MWD and WHO FC (blinded assessment), NT-proBNP and clinical worsening. Exploratory endpoints include quality of life (Living with Pulmonary Hypertension), REVEAL risk score and MRI parameters of right-heart function. Safety will be assessed by adverse events and all-cause mortality
Starting date	8 September 2016
Contact information	Bayer Clinical Trials Contact (+) 1-888-8422937 clinical-trials-contact@bayer.com
Notes	Recruiting ClinicalTrials.gov Identifier: NCT02891850

6MWD: six minute walk distance; COPD: chronic obstructive pulmonary disease; DLCO: diffusing capacity for carbon monoxide; ERA: endothelin receptor antagonist; FEV1: forced expiratory volume in one second; FVC: functional vital capacity; HF: heart failure; IPF: idiopathic pulmonary fibrosis; LVEF: left ventricular ejection fraction; NCT: National Clinical Trials portal; NT-Pro BNP@ N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PDE5: phosphodiesterase 5; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; QOL: quality of life; RV: right ventricle; SGRQ: St George's Respiratory Questionnaire; TAPSE: tricuspid annular plane systolic excursion; TTE: transthoracic echocardiogram; UCDS SOBQ - The University of California, San Diego shortness of breath questionnaire; WHO: World Health Organization

DATA AND ANALYSES

Comparison 1. Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Improvement in WHO functional class	4	282	Odds Ratio (M-H, Fixed, 95% CI)	8.59 [3.95, 18.72]
1.1 Sildenafil	1	146	Odds Ratio (M-H, Fixed, 95% CI)	10.24 [3.69, 28.47]
1.2 Tadalafil	2	72	Odds Ratio (M-H, Fixed, 95% CI)	7.71 [1.88, 31.72]
1.3 Vardenafil	1	64	Odds Ratio (M-H, Fixed, 95% CI)	5.59 [0.66, 47.07]
2 Six-minute walk distance	8	880	Mean Difference (Fixed, 95% CI)	48.17 [40.30, 56.04]
2.1 Sildenafil	4	339	Mean Difference (Fixed, 95% CI)	56.91 [44.40, 69.41]
2.2 Tadalafil	3	477	Mean Difference (Fixed, 95% CI)	38.46 [27.60, 49.31]
2.3 Vardenafil	1	64	Mean Difference (Fixed, 95% CI)	69.0 [41.00, 97.00]
3 Mortality	8	1119	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.07, 0.68]
3.1 Sildenafil	5	634	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.05, 0.98]
3.2 Tadalafil	2	421	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.63]
3.3 Vardenafil	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.82]
4 PAP	6	453	Mean Difference (Fixed, 95% CI)	-6.43 [-8.13, -4.74]
4.1 Sildenafil	4	333	Mean Difference (Fixed, 95% CI)	-7.34 [-9.35, -5.33]
4.2 Tadalafil	1	56	Mean Difference (Fixed, 95% CI)	-3.67 [-7.55, 0.21]
4.3 Vardenafil	1	64	Mean Difference (Fixed, 95% CI)	-5.3 [-10.60, -0.00]
5 RAP	3	341	Mean Difference (Fixed, 95% CI)	-1.35 [-2.34, -0.36]
5.1 Sildenafil	2	277	Mean Difference (Fixed, 95% CI)	-1.20 [-2.30, -0.11]
5.2 Vardenafil	1	64	Mean Difference (Fixed, 95% CI)	-2.0 [-4.30, 0.30]
6 CI	4	239	Mean Difference (Fixed, 95% CI)	0.28 [0.16, 0.40]
6.1 Sildenafil	2	152	Mean Difference (Fixed, 95% CI)	0.47 [0.28, 0.66]
6.2 Tadalafil	1	28	Mean Difference (Fixed, 95% CI)	0.02 [-0.18, 0.22]
6.3 Vardenafil	1	59	Mean Difference (Fixed, 95% CI)	0.4 [0.10, 0.70]
7 PVR	3	266	Mean Difference (Fixed, 95% CI)	-4.74 [-6.13, -3.35]
7.1 Sildenafil	1	146	Mean Difference (Fixed, 95% CI)	-3.87 [-5.67, -2.08]
7.2 Tadalafil	1	56	Mean Difference (Fixed, 95% CI)	-7.32 [-10.42, -4.22]

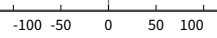
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3 Vardenafil	1	64	Mean Difference (Fixed, 95% CI)	-4.7 [-7.80, -1.60]
8 PASP	2	48	Mean Difference (Fixed, 95% CI)	-11.62 [-25.18, 1.94]
8.1 Sildenafil	1	24	Mean Difference (Fixed, 95% CI)	-7.0 [-23.64, 9.64]
8.2 Tadalafil	1	24	Mean Difference (Fixed, 95% CI)	-20.75 [-44.14, 2.64]
9 Dyspnoea	4	239	Mean Difference (Fixed, 95% CI)	-0.72 [-0.99, -0.44]
9.1 Sildenafil	2	155	Mean Difference (Fixed, 95% CI)	-0.57 [-0.90, -0.24]
9.2 Tadalafil	1	20	Mean Difference (Fixed, 95% CI)	-0.64 [-1.65, 0.37]
9.3 Vardenafil	1	64	Mean Difference (Fixed, 95% CI)	-1.15 [-1.70, -0.60]
10 Clinical worsening requiring intervention	3	746	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.27, 1.23]
10.1 Sildenafil	1	277	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.17, 1.25]
10.2 Tadalafil	1	405	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.27, 5.95]
10.3 Vardenafil	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.02, 2.46]
11 Adverse events	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Headache	5	848	Odds Ratio (M-H, Fixed, 95% CI)	1.97 [1.33, 2.92]
11.2 GI upset	5	848	Odds Ratio (M-H, Fixed, 95% CI)	1.63 [1.07, 2.48]
11.3 Flushing	3	748	Odds Ratio (M-H, Fixed, 95% CI)	4.12 [1.83, 9.26]
11.4 Muscle and joint pain	4	792	Odds Ratio (M-H, Fixed, 95% CI)	2.52 [1.59, 3.99]
11.5 Epistaxis	2	682	Odds Ratio (M-H, Fixed, 95% CI)	2.37 [0.83, 6.77]
11.6 Respiratory symptoms	3	748	Odds Ratio (M-H, Fixed, 95% CI)	1.74 [0.89, 3.40]
11.7 Visual disturbance	3	748	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [0.58, 7.14]

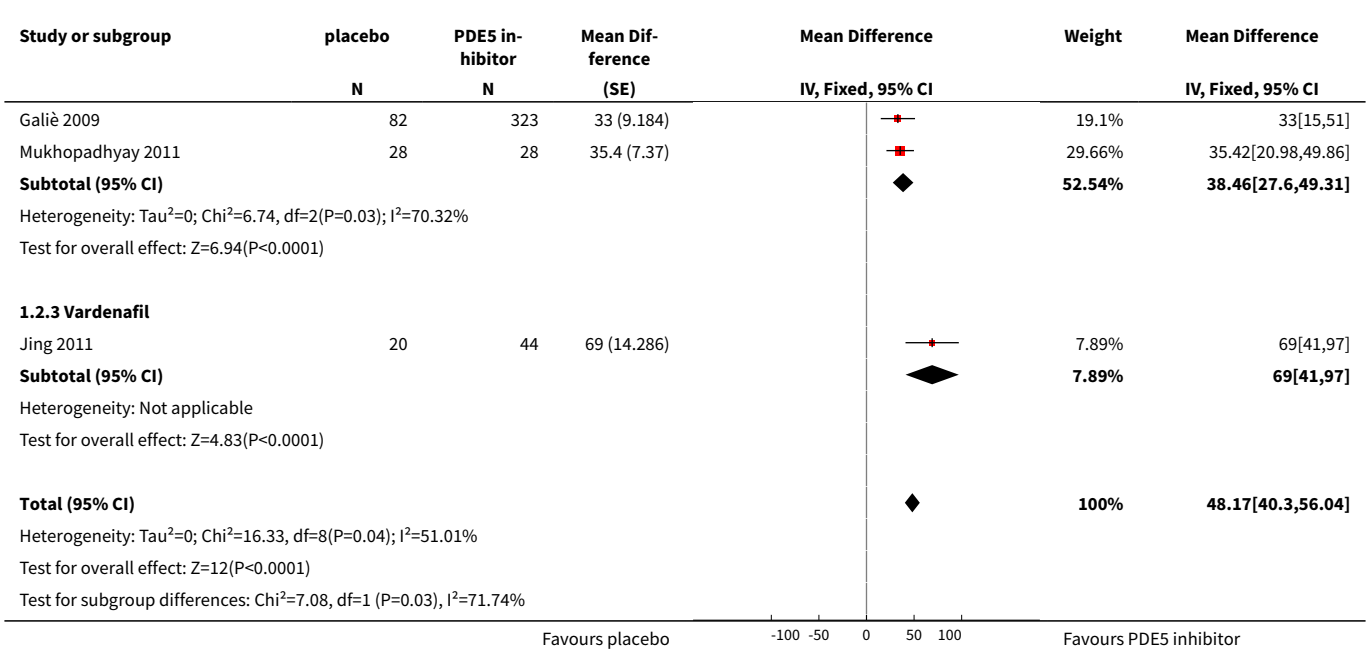
Analysis 1.1. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 1 Improvement in WHO functional class.

Study or subgroup	PDE5 inhibitor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Sildenafil					
Galiè 2005a	30/71	5/75		50.97%	10.24[3.69,28.47]
Subtotal (95% CI)	**71**	**75**		**50.97%**	**10.24[3.69,28.47]**
Total events: 30 (PDE5 inhibitor), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.46(P<0.0001)					
1.1.2 Tadalafil					
Bharani 2007	6/8	0/8		2.52%	44.2[1.8,1088.14]
Mukhopadhyay 2011	7/28	2/28		27.23%	4.33[0.81,23.1]
Subtotal (95% CI)	**36**	**36**		**29.75%**	**7.71[1.88,31.72]**
Total events: 13 (PDE5 inhibitor), 2 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.6, df=1(P=0.21); I^2=37.38%					
Test for overall effect: Z=2.83(P=0)					
1.1.3 Vardenafil					
Jing 2011	10/44	1/20		19.28%	5.59[0.66,47.07]
Subtotal (95% CI)	**44**	**20**		**19.28%**	**5.59[0.66,47.07]**
Total events: 10 (PDE5 inhibitor), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.58(P=0.11)					
Total (95% CI)	**151**	**131**		**100%**	**8.59[3.95,18.72]**
Total events: 53 (PDE5 inhibitor), 8 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.92, df=3(P=0.59); I^2=0%					
Test for overall effect: Z=5.42(P<0.0001)					
Test for subgroup differences: Chi^2=0.29, df=1 (P=0.86), I^2=0%					

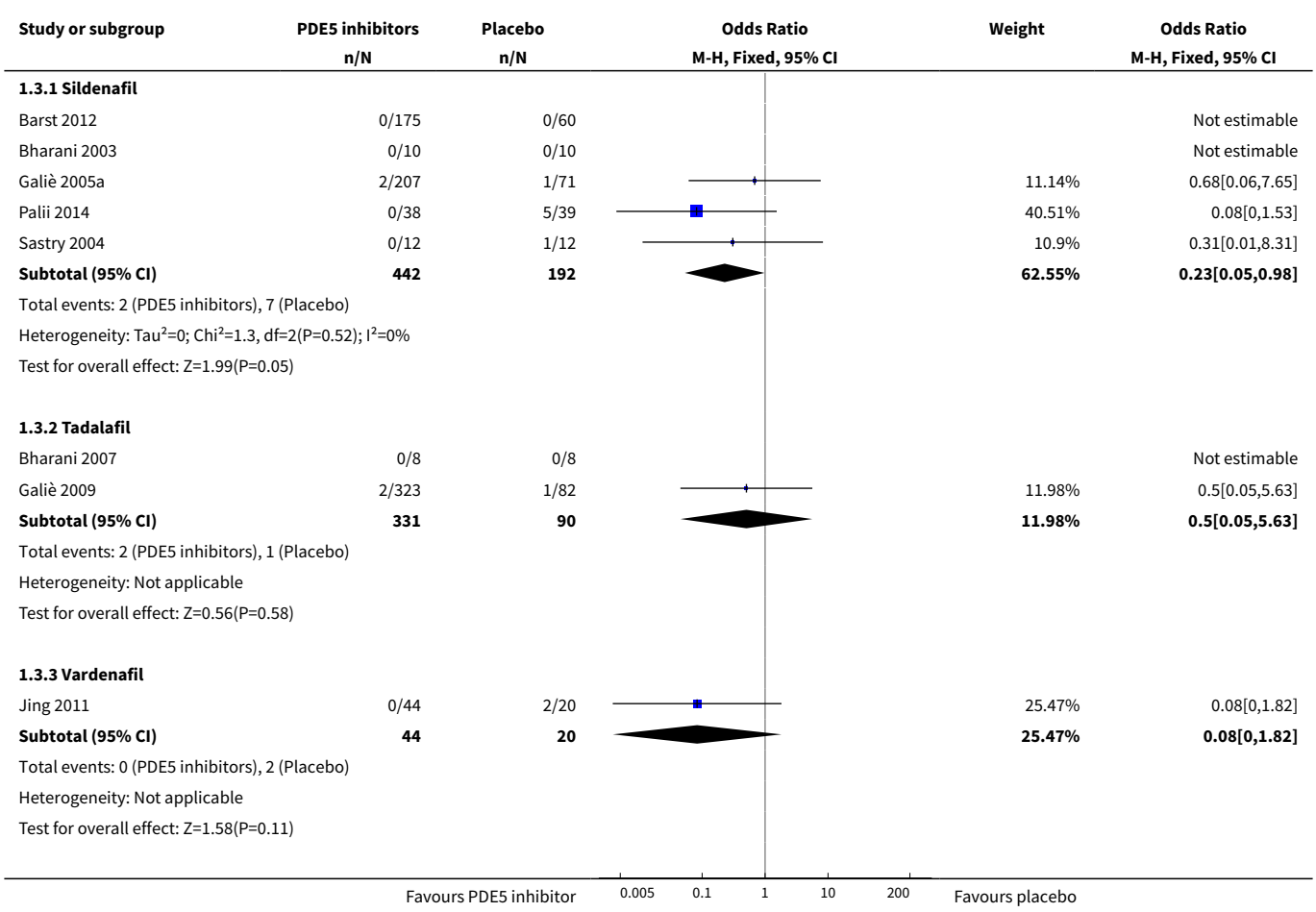
Analysis 1.2. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 2 Six-minute walk distance.

Study or subgroup	placebo N	PDE5 inhibitor N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Sildenafil						
Bharani 2003	9	9	98 (36.85)		1.19%	98[25.78,170.22]
Boonstra 2005	31	27	54.4 (16.939)		5.61%	54.4[21.2,87.6]
Boonstra 2005	35	42	49.3 (11.888)		11.4%	49.3[26,72.6]
Galiè 2005a	75	71	50 (13.776)		8.49%	50[23,77]
Singh 2006	20	20	65.5 (11.185)		12.88%	65.5[43.58,87.42]
Subtotal (95% CI)					**39.57%**	**56.91[44.4,69.41]**
Heterogeneity: Tau^2=0; Chi^2=2.52, df=4(P=0.64); I^2=0%						
Test for overall effect: Z=8.92(P<0.0001)						
1.2.2 Tadalafil						
Bharani 2007	8	8	90 (20.667)		3.77%	89.98[49.47,130.49]

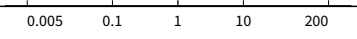




Analysis 1.3. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 3 Mortality.

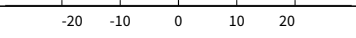


Study or subgroup	PDE5 inhibitors n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total (95% CI)	**817**	**302**		**100%**	**0.22[0.07,0.68]**
Total events: 4 (PDE5 inhibitors), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.14, df=4(P=0.71); I^2=0%					
Test for overall effect: Z=2.63(P=0.01)					
Test for subgroup differences: Chi^2=0.82, df=1 (P=0.66), I^2=0%					



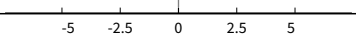
Analysis 1.4. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 4 PAP.

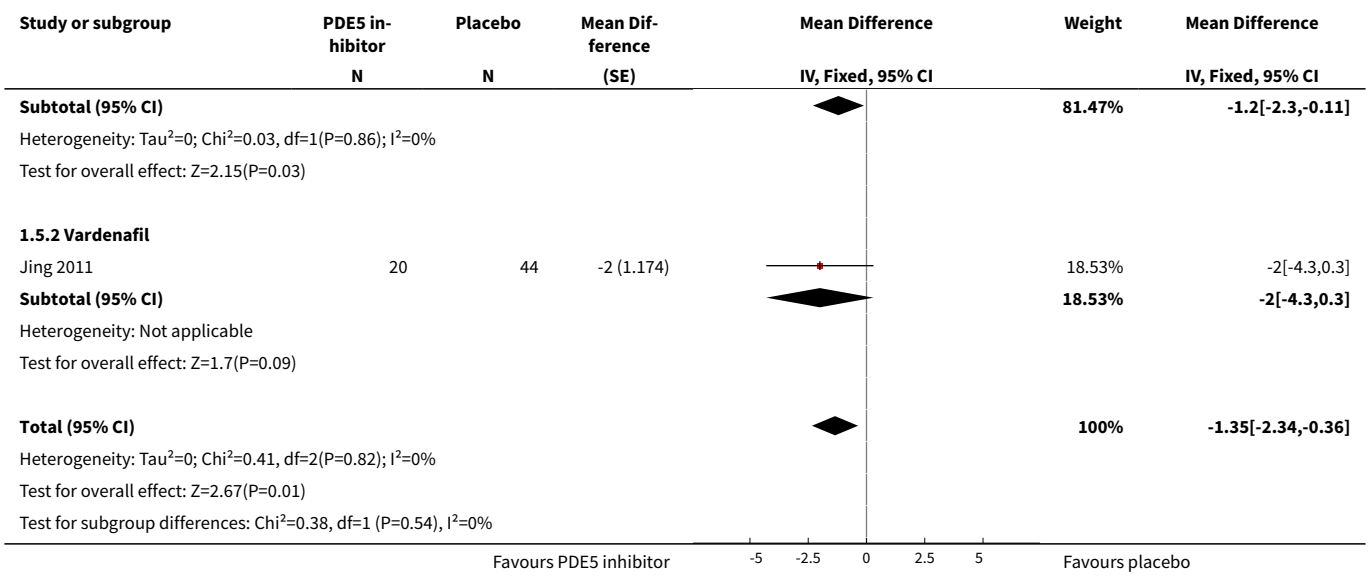
Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 Sildenafil						
Barst 2012	71	60	-7.3 (2.6)		11.04%	-7.3[-12.4,-2.2]
Bharani 2003	8	8	-20 (4.61)		3.51%	-20[-29.04,-10.96]
Galiè 2005a	75	71	-5.3 (1.222)		49.96%	-5.3[-7.7,-2.9]
Singh 2006	20	20	-16.6 (3.45)		6.27%	-16.6[-23.36,-9.84]
Subtotal (95% CI)					**70.77%**	**-7.34[-9.35,-5.33]**
Heterogeneity: Tau^2=0; Chi^2=17.53, df=3(P=0); I^2=82.89%						
Test for overall effect: Z=7.15(P<0.0001)						
1.4.2 Tadalafil						
Mukhopadhyay 2011	28	28	-3.7 (1.98)		19.03%	-3.67[-7.55,0.21]
Subtotal (95% CI)					**19.03%**	**-3.67[-7.55,0.21]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.85(P=0.06)						
1.4.3 Vardenafil						
Jing 2011	20	44	-5.3 (2.704)		10.2%	-5.3[-10.6,-0]
Subtotal (95% CI)					**10.2%**	**-5.3[-10.6,-0]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.96(P=0.05)						
Total (95% CI)					**100%**	**-6.43[-8.13,-4.74]**
Heterogeneity: Tau^2=0; Chi^2=20.44, df=5(P=0); I^2=75.54%						
Test for overall effect: Z=7.45(P<0.0001)						
Test for subgroup differences: Chi^2=2.91, df=1 (P=0.23), I^2=31.18%						



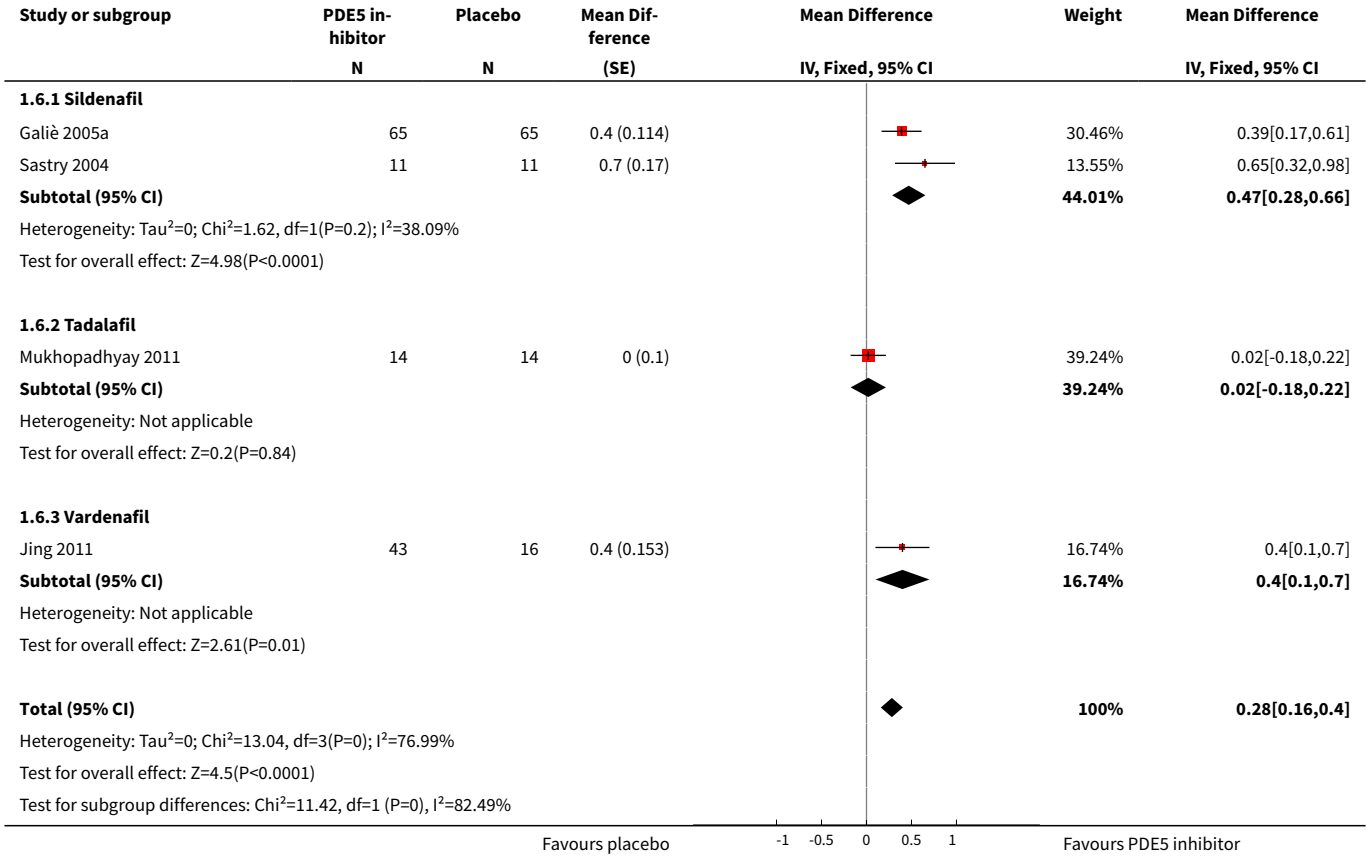
Analysis 1.5. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 5 RAP.

Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Sildenafil						
Barst 2012	71	60	-1.1 (0.8)		39.87%	-1.1[-2.67,0.47]
Galiè 2005a	75	71	-1.3 (0.783)		41.61%	-1.3[-2.83,0.23]



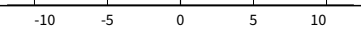


Analysis 1.6. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 6 CI.



Analysis 1.7. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 7 PVR.

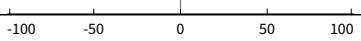
Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 Sildenafil						
Galiè 2005a	75	71	-3.9 (0.918)		59.73%	-3.87[-5.67,-2.08]
Subtotal (95% CI)					**59.73%**	**-3.87[-5.67,-2.08]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%						
Test for overall effect: Z=4.22(P<0.0001)						
1.7.2 Tadalafil						
Mukhopadhyay 2011	28	28	-7.3 (1.58)		20.16%	-7.32[-10.42,-4.22]
Subtotal (95% CI)					**20.16%**	**-7.32[-10.42,-4.22]**
Heterogeneity: Not applicable						
Test for overall effect: Z=4.63(P<0.0001)						
1.7.3 Vardenafil						
Jing 2011	20	44	-4.7 (1.582)		20.11%	-4.7[-7.8,-1.6]
Subtotal (95% CI)					**20.11%**	**-4.7[-7.8,-1.6]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.97(P=0)						
Total (95% CI)					**100%**	**-4.74[-6.13,-3.35]**
Heterogeneity: Tau²=0; Chi²=3.56, df=2(P=0.17); I²=43.75%						
Test for overall effect: Z=6.68(P<0.0001)						
Test for subgroup differences: Chi²=3.56, df=1 (P=0.17), I²=43.75%						



Favours PDE5 inhibitor — Favours placebo

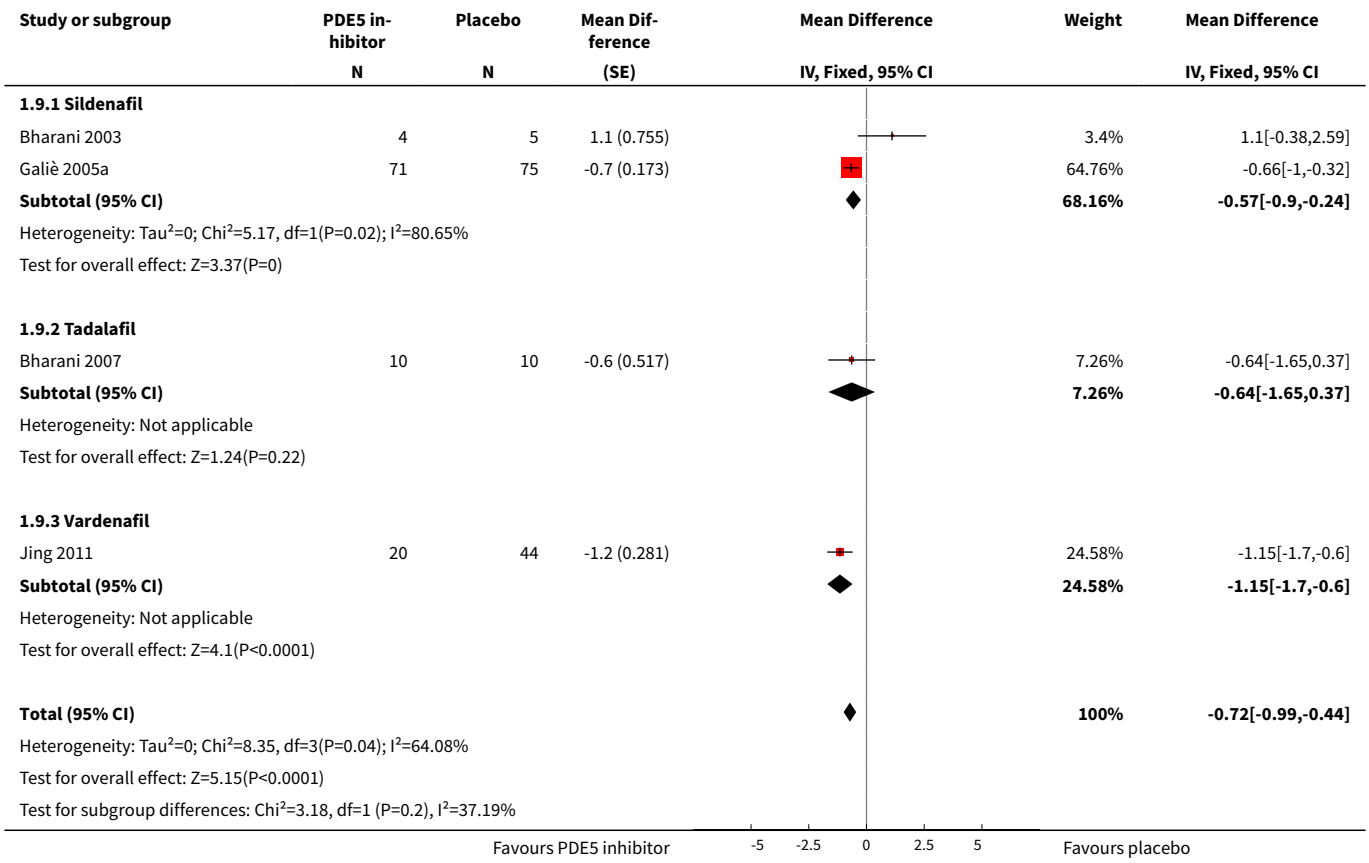
Analysis 1.8. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 8 PASP.

Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.8.1 Sildenafil						
Sastry 2004	12	12	-7 (8.49)		66.4%	-7[-23.64,9.64]
Subtotal (95% CI)					**66.4%**	**-7[-23.64,9.64]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.82(P=0.41)						
1.8.2 Tadalafil						
Bharani 2007	12	12	-20.7 (11.935)		33.6%	-20.75[-44.14,2.64]
Subtotal (95% CI)					**33.6%**	**-20.75[-44.14,2.64]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.74(P=0.08)						
Total (95% CI)					**100%**	**-11.62[-25.18,1.94]**
Heterogeneity: Tau²=0; Chi²=0.88, df=1(P=0.35); I²=0%						
Test for overall effect: Z=1.68(P=0.09)						
Test for subgroup differences: Chi²=0.88, df=1 (P=0.35), I²=0%						

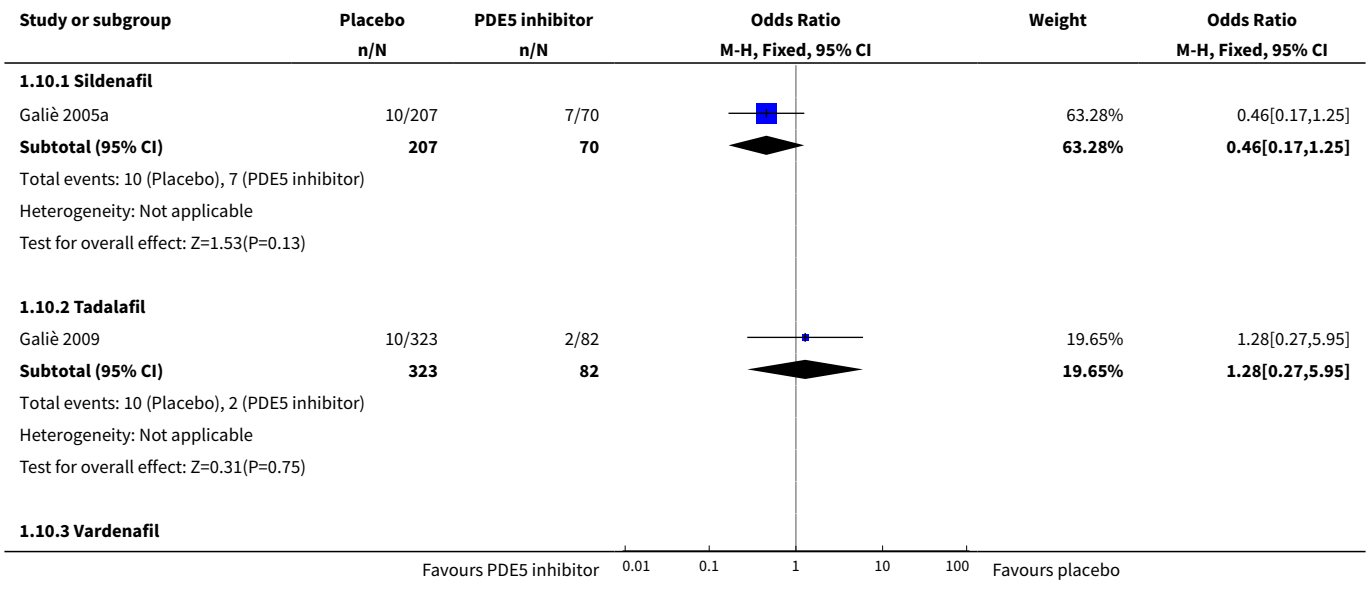


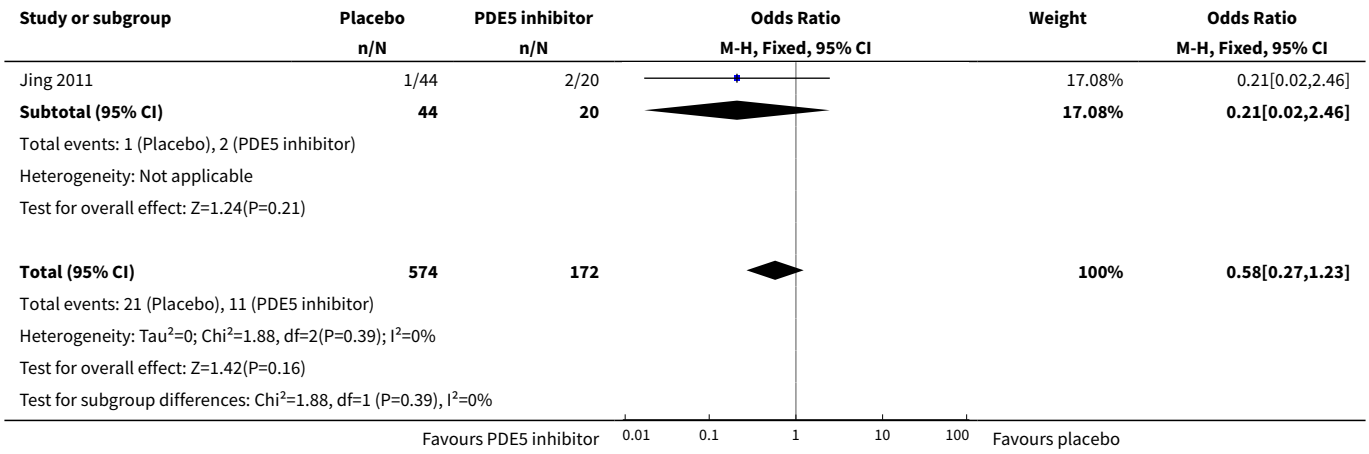
Favours PDE5 inhibitor — Favours placebo

Analysis 1.9. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 9 Dyspnoea.

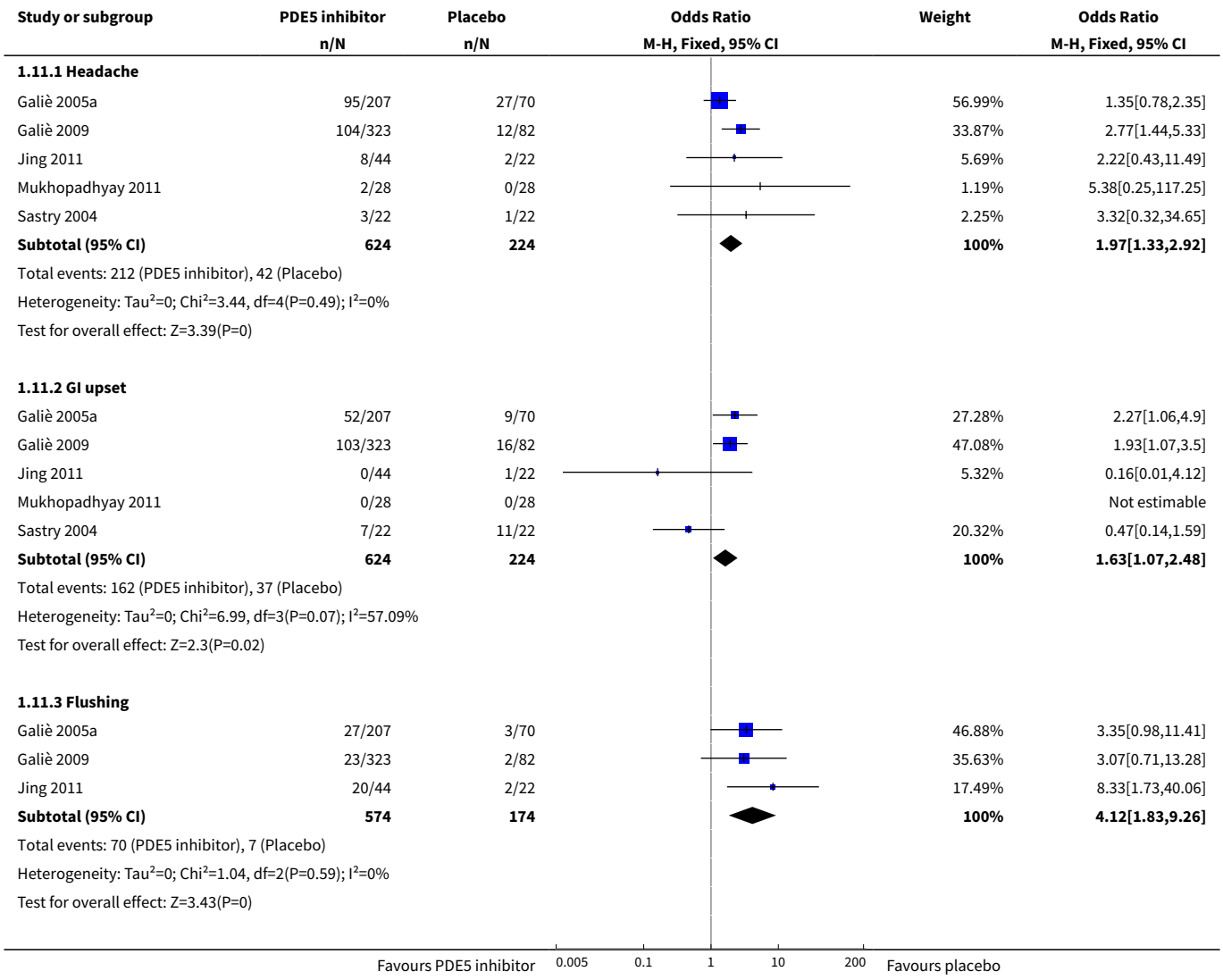


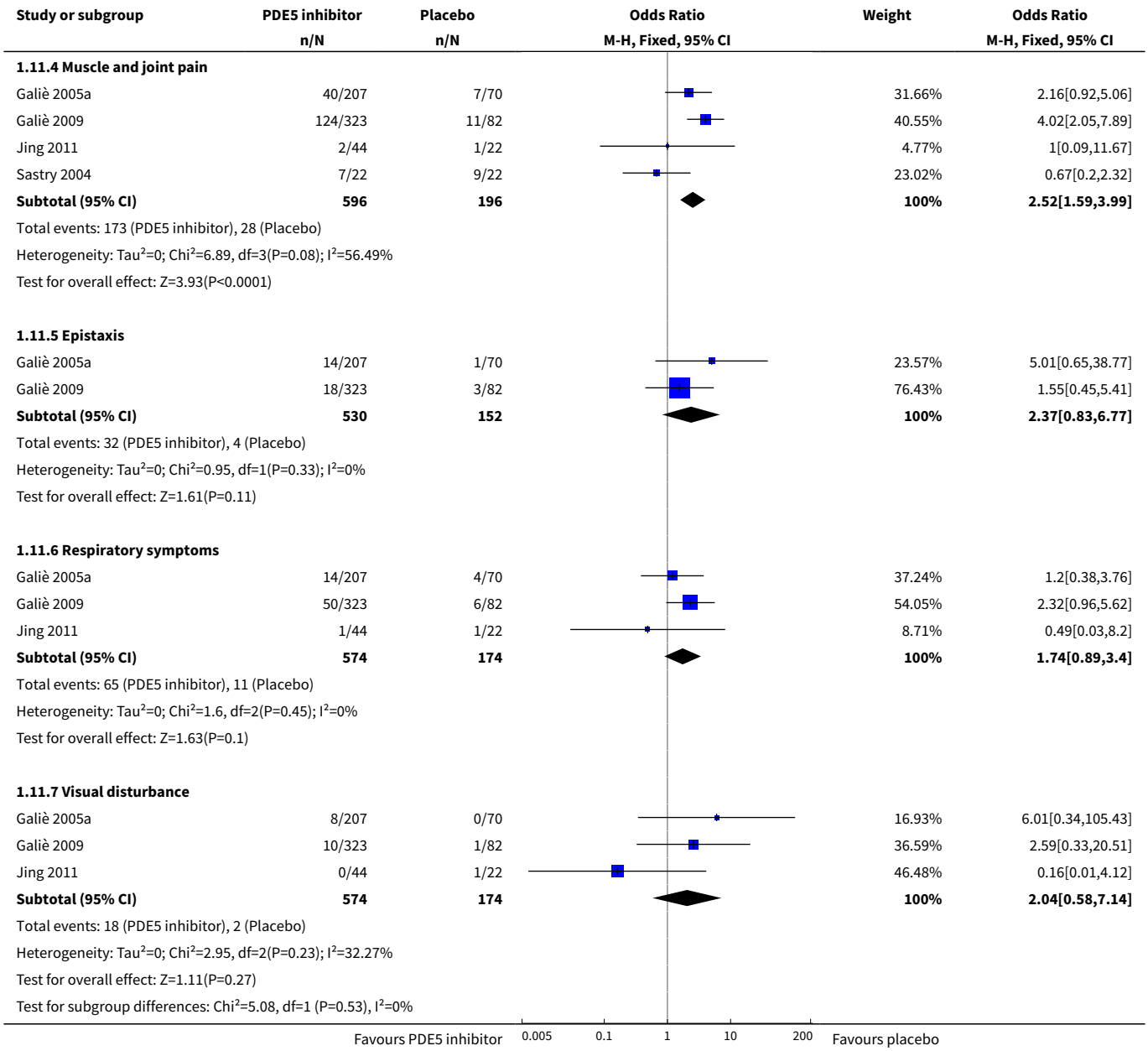
Analysis 1.10. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 10 Clinical worsening requiring intervention.





Analysis 1.11. Comparison 1 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, Outcome 11 Adverse events.





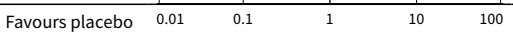
Comparison 2. Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, on combination therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in WHO functional Class	2	227	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.66, 2.17]
2 Six-minute walk distance	4	509	Mean Difference (Fixed, 95% CI)	19.66 [9.22, 30.10]
3 Mortality	3	492	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.07, 1.06]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
4 PAP	2	387	Mean Difference (Fixed, 95% CI)	-4.58 [-6.14, -3.01]
5 Cardiac Output	3	310	Mean Difference (Fixed, 95% CI)	0.87 [0.53, 1.21]
6 PVR	3	303	Std. Mean Difference (Fixed, 95% CI)	-0.48 [-0.72, -0.25]
7 Clinical worsening	4	717	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.21, 0.68]
8 Adverse events	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Headache	5	768	Odds Ratio (M-H, Fixed, 95% CI)	2.49 [1.74, 3.56]
8.2 GI upset	4	726	Odds Ratio (M-H, Fixed, 95% CI)	1.95 [1.30, 2.93]
8.3 Flushing	2	368	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.63, 1.96]
8.4 Muscle and joint pain	3	494	Odds Ratio (M-H, Fixed, 95% CI)	2.17 [1.28, 3.67]
8.5 Epistaxis	2	358	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.34, 5.12]
8.6 Visual disturbance	2	368	Odds Ratio (M-H, Fixed, 95% CI)	3.95 [0.97, 16.08]

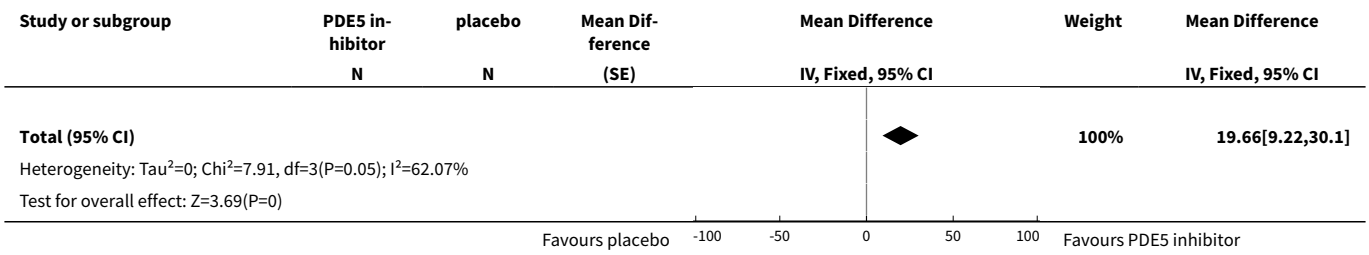
Analysis 2.1. Comparison 2 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, on combination therapy, Outcome 1 Improvement in WHO functional Class.

Study or subgroup	PDE5 inhibitor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Vizza 2017a	7/53	10/50		44.89%	0.61[0.21,1.75]
Zhuang 2014	26/60	20/64		55.11%	1.68[0.81,3.51]
Total (95% CI)	**113**	**114**		**100%**	**1.2[0.66,2.17]**
Total events: 33 (PDE5 inhibitor), 30 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.4, df=1(P=0.12); I^2=58.38%					
Test for overall effect: Z=0.6(P=0.55)					

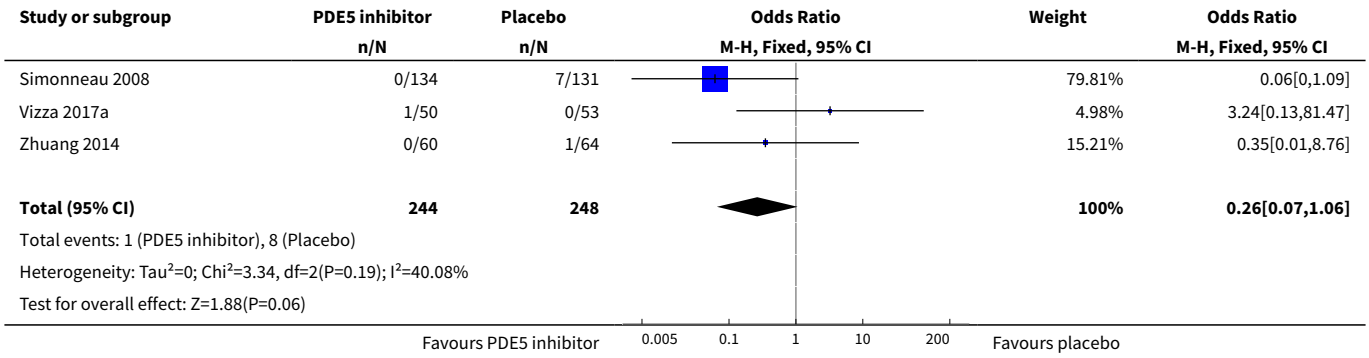


Analysis 2.2. Comparison 2 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, on combination therapy, Outcome 2 Six-minute walk distance.

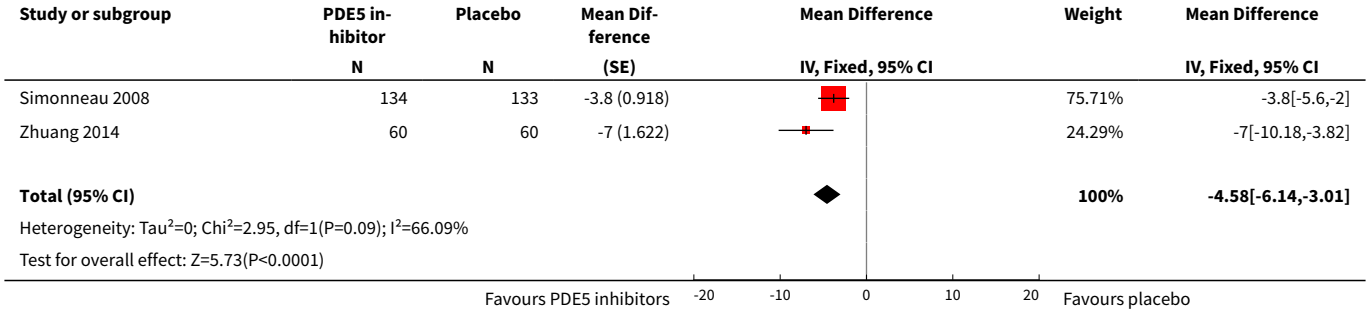
Study or subgroup	PDE5 in-hibitor N	placebo N	Mean Dif-ference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Iversen 2009	10	9	13.1 (19.557)		7.42%	13.1[-25.23,51.43]
Simonneau 2008	134	133	28.8 (7.602)		49.1%	28.8[13.9,43.7]
Vizza 2017a	53	50	-2.4 (9.898)		28.96%	-2.4[-21.8,17]
Zhuang 2014	60	60	36.1 (13.977)		14.52%	36.1[8.71,63.49]



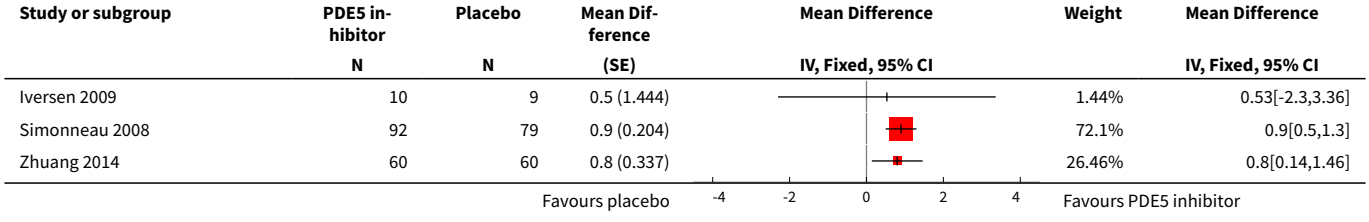
Analysis 2.3. Comparison 2 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, on combination therapy, Outcome 3 Mortality.

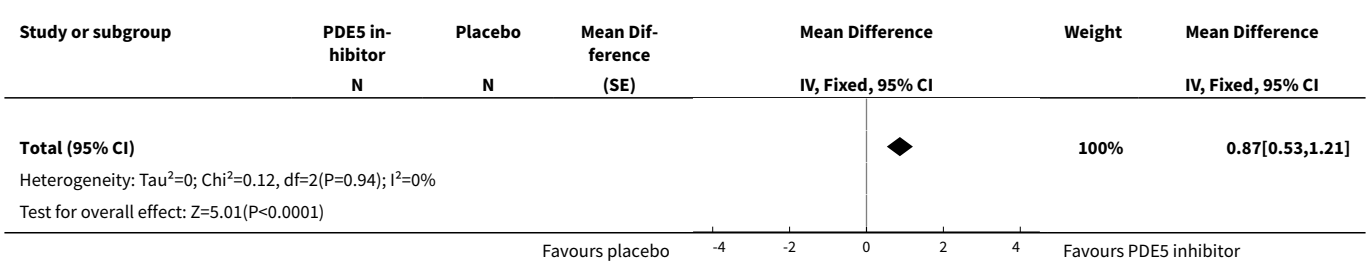


Analysis 2.4. Comparison 2 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, on combination therapy, Outcome 4 PAP.

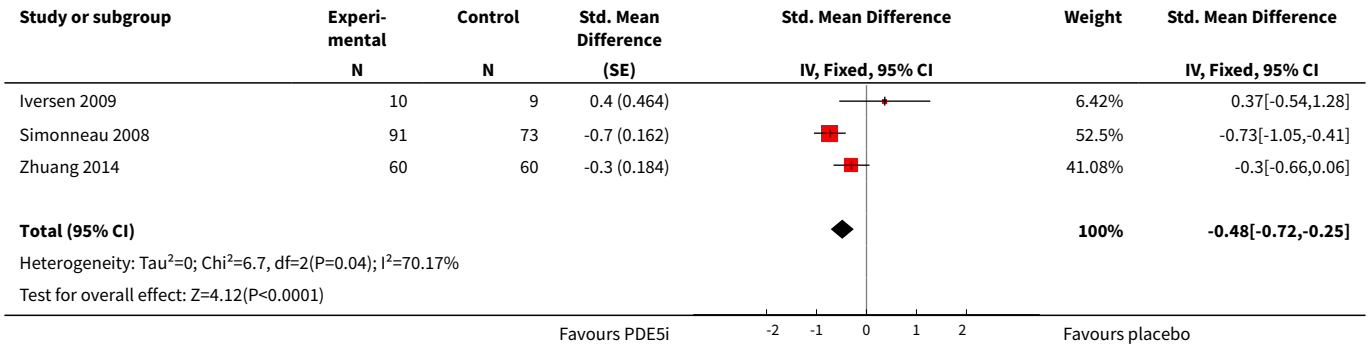


Analysis 2.5. Comparison 2 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, on combination therapy, Outcome 5 Cardiac Output.

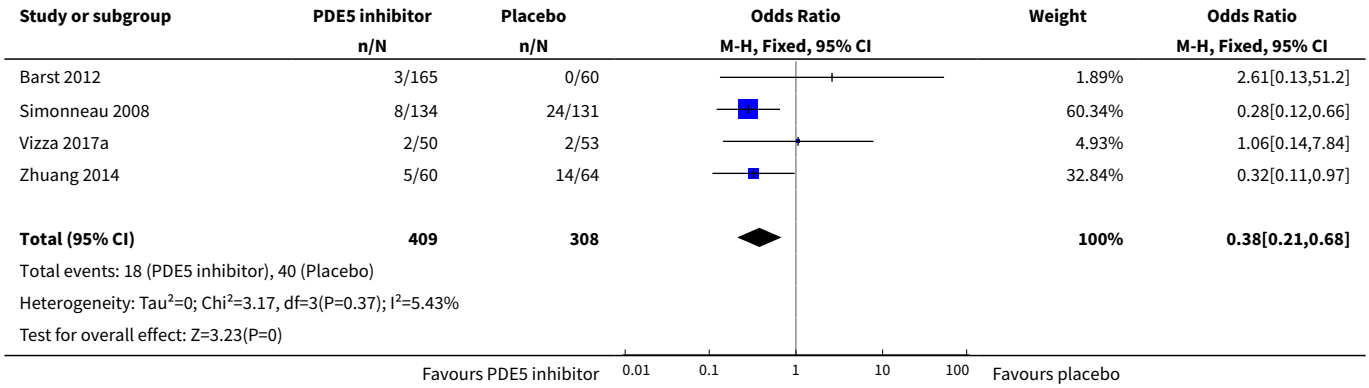




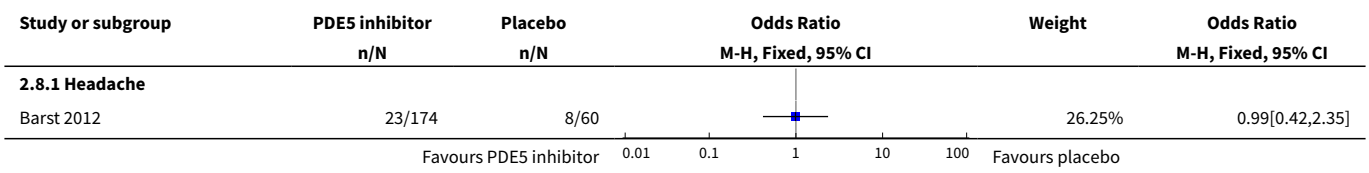
Analysis 2.6. Comparison 2 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, on combination therapy, Outcome 6 PVR.

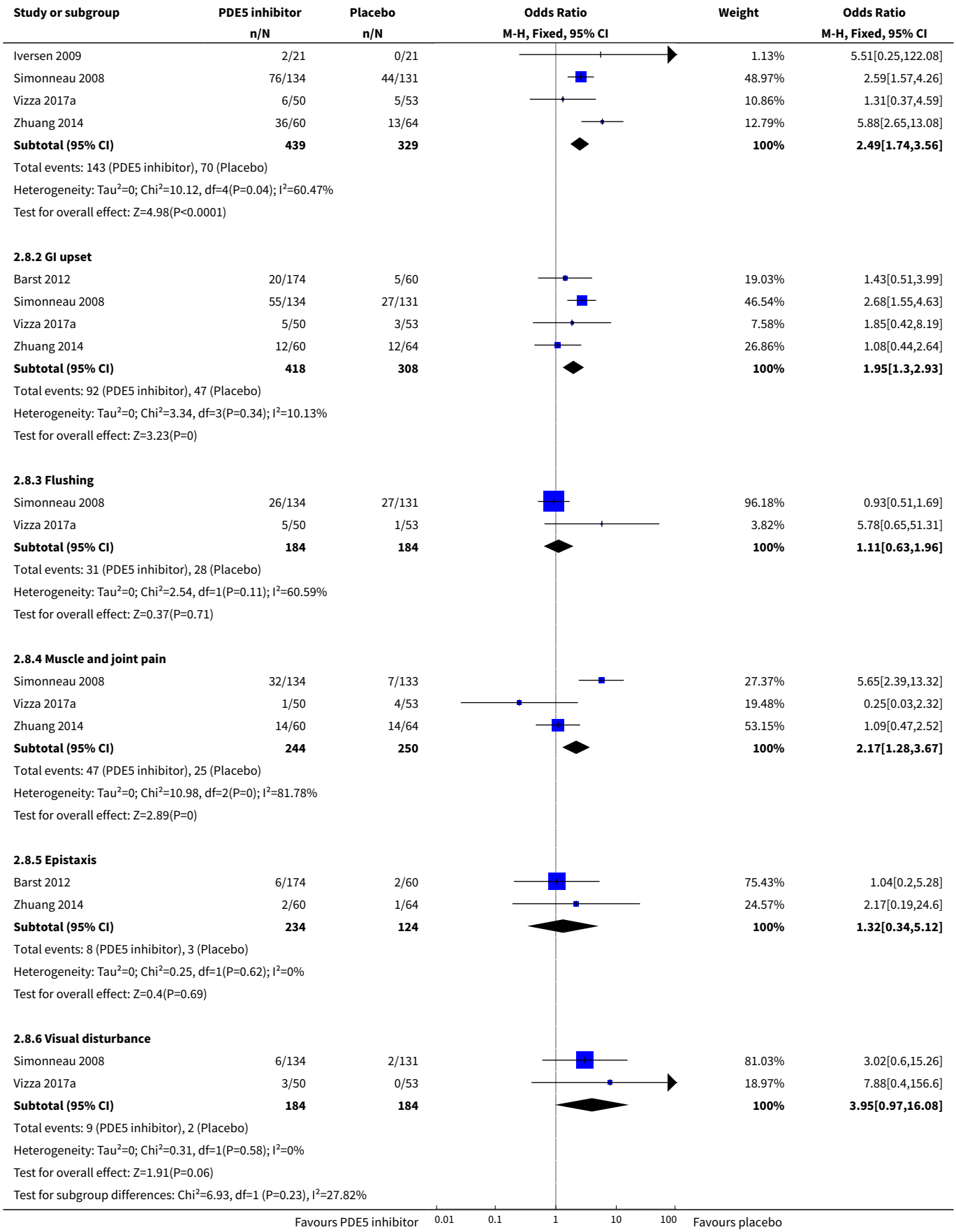


Analysis 2.7. Comparison 2 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, on combination therapy, Outcome 7 Clinical worsening.



Analysis 2.8. Comparison 2 Group 1 Pulmonary Arterial Hypertension - PDE5i versus placebo, on combination therapy, Outcome 8 Adverse events.



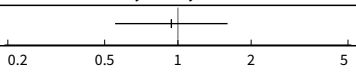


Comparison 3. Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA

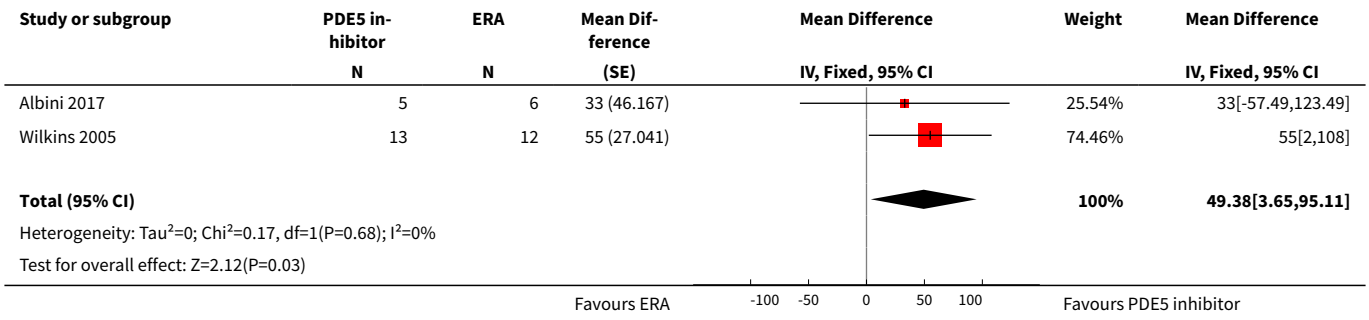
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in WHO functional class	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Six-minute walk distance	2	36	Mean Difference (Fixed, 95% CI)	49.38 [3.65, 95.11]
3 Mortality	2	272	Odds Ratio (M-H, Fixed, 95% CI)	3.19 [0.74, 13.64]
4 PAP	1		Mean Difference (Fixed, 95% CI)	7.00 [-4.82, 18.82]
5 RAP	1		Mean Difference (Fixed, 95% CI)	2.0 [-2.14, 6.14]
6 CI	1		Mean Difference (Fixed, 95% CI)	0.0 [-0.49, 0.49]
7 PVR	1		Mean Difference (Fixed, 95% CI)	0.0 [-1.93, 1.93]
8 Quality of life	1		Mean Difference (Fixed, 95% CI)	Subtotals only
9 Clinical worsening requiring hospitalisation	2	275	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.30, 0.89]
10 Adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 Headache	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 GI upset	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Flushing	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.4 Muscle or joint pain	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.5 Respiratory symptoms	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA, Outcome 1 Improvement in WHO functional class.

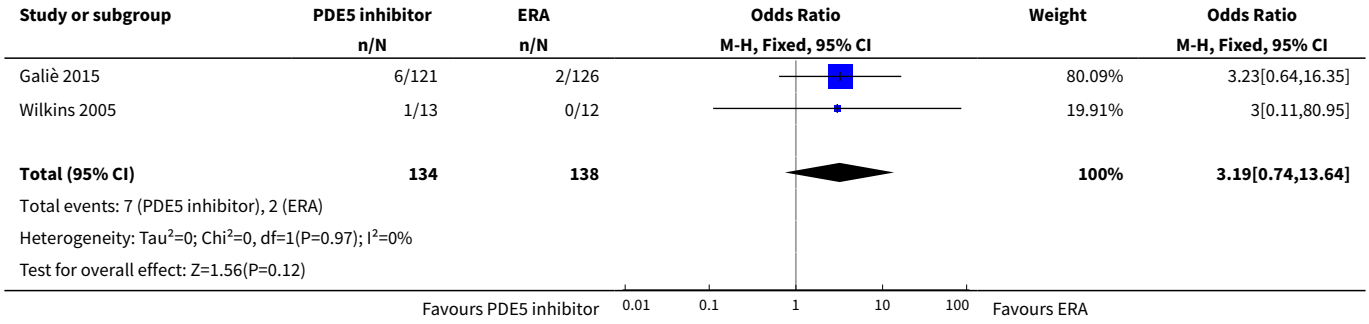
Study or subgroup	PDE5 inhibitor n/N	ERA n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Galiè 2015	39/120	42/124		0%	0.94[0.55,1.6]



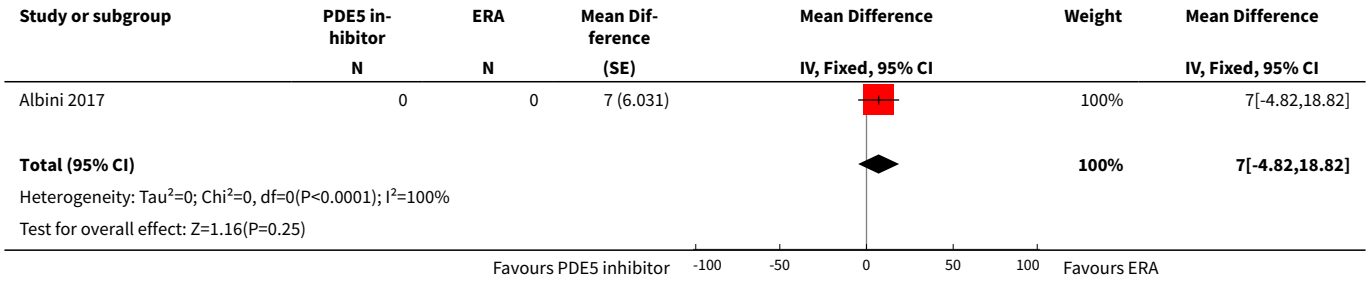
Analysis 3.2. Comparison 3 Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA, Outcome 2 Six-minute walk distance.



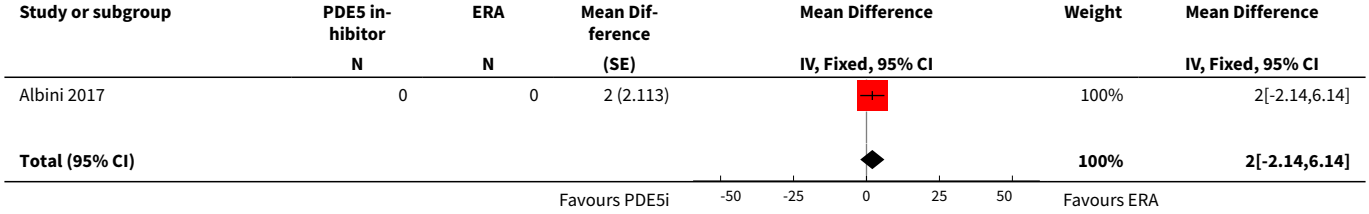
Analysis 3.3. Comparison 3 Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA, Outcome 3 Mortality.

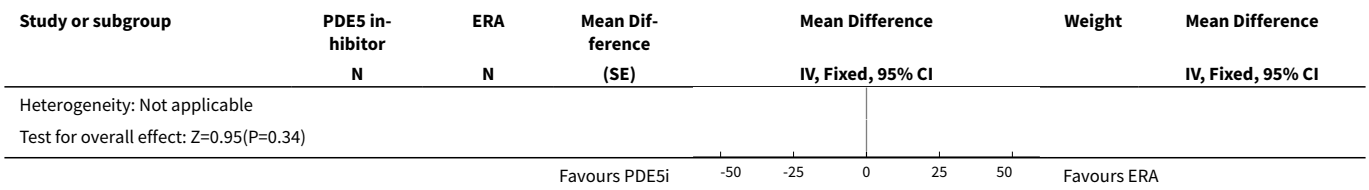


Analysis 3.4. Comparison 3 Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA, Outcome 4 PAP.

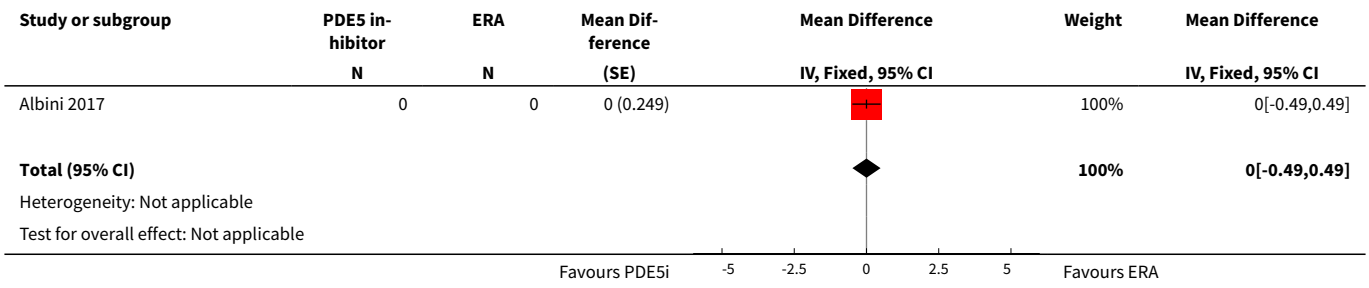


Analysis 3.5. Comparison 3 Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA, Outcome 5 RAP.

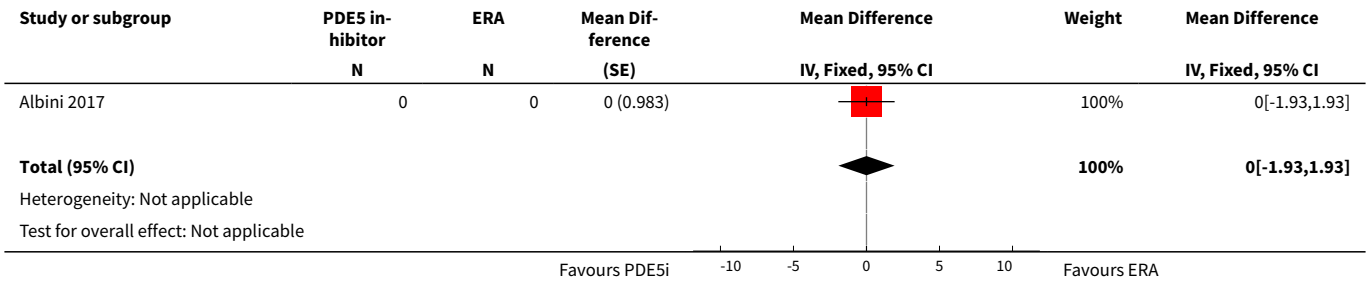




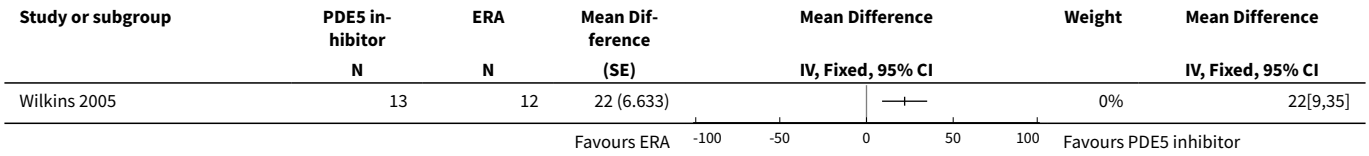
Analysis 3.6. Comparison 3 Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA, Outcome 6 CI.



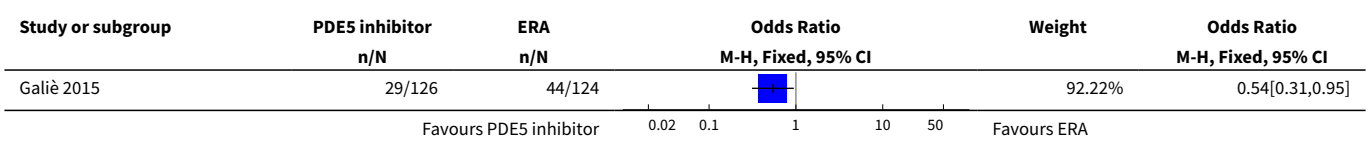
Analysis 3.7. Comparison 3 Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA, Outcome 7 PVR.

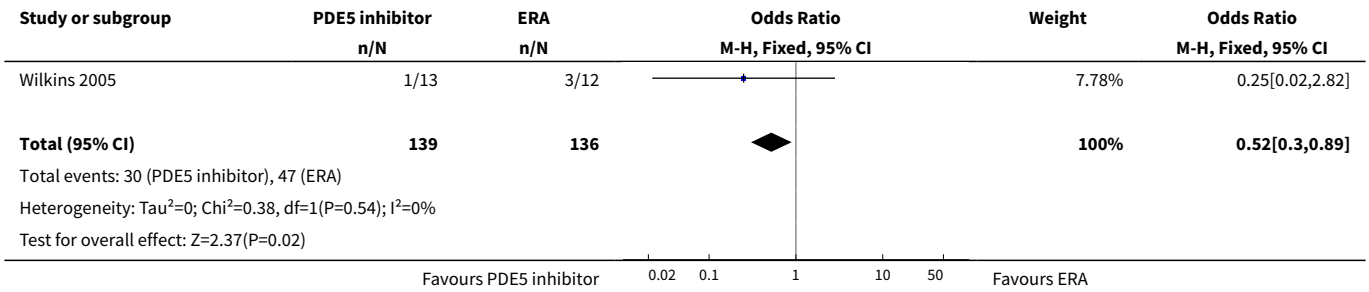


Analysis 3.8. Comparison 3 Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA, Outcome 8 Quality of life.

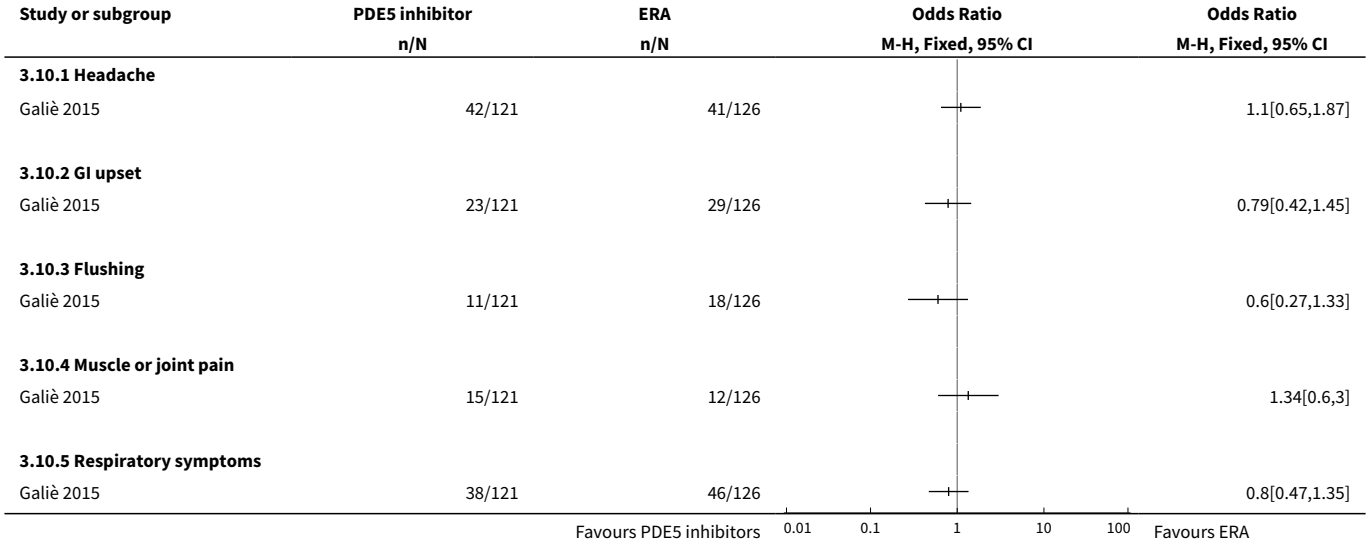


Analysis 3.9. Comparison 3 Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA, Outcome 9 Clinical worsening requiring hospitalisation.





Analysis 3.10. Comparison 3 Group 1 Pulmonary Arterial Hypertension - PDE5i versus ERA, Outcome 10 Adverse events.



Comparison 4. Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in WHO functional class	3	285	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.32, 0.87]
2 Six-minute walk distance	3	284	Mean Difference (Fixed, 95% CI)	34.31 [22.75, 45.87]
3 Mortality	3	286	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.28, 5.80]
4 mean PAP	3	130	Mean Difference (Fixed, 95% CI)	-10.17 [-11.99, -8.35]
5 Cardiac Index	2	96	Mean Difference (Fixed, 95% CI)	0.07 [-0.17, 0.30]
6 TPG	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7 RAP	1		Mean Difference (Fixed, 95% CI)	Totals not selected

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
8 PASP	1		Mean Difference (Fixed, 95% CI)	Totals not selected
9 Dyspnoea	1		Mean Difference (Fixed, 95% CI)	Totals not selected
10 Clinical worsening	2	234	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.22, 3.46]

Analysis 4.1. Comparison 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), Outcome 1 Improvement in WHO functional class.

Study or subgroup	PDE5 inhibitor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bermejo 2017	28/104	46/96		83.59%	0.4[0.22,0.72]
Hoendermis 2015	2/25	5/26		10.78%	0.37[0.06,2.09]
Lewis 2007	9/17	5/17		5.63%	2.7[0.66,11.09]
Total (95% CI)	**146**	**139**		**100%**	**0.53[0.32,0.87]**
Total events: 39 (PDE5 inhibitor), 56 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.14, df=2(P=0.05); I^2=67.43%					
Test for overall effect: Z=2.49(P=0.01)					

Favours placebo — Favours PDE5 inhibitor

Analysis 4.2. Comparison 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), Outcome 2 Six-minute walk distance.

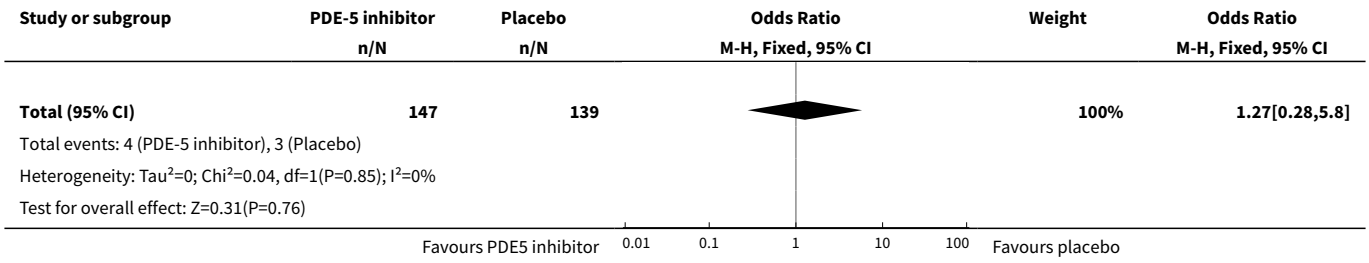
Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Bermejo 2017	104	96	10 (10.204)		33.39%	10[-10,30]
Lewis 2007	17	17	22 (26.907)		4.8%	22[-30.74,74.74]
Ovchinnov 2015	30	20	48.4 (7.5)		61.81%	48.4[33.7,63.1]
Total (95% CI)					**100%**	**34.31[22.75,45.87]**
Heterogeneity: Tau^2=0; Chi^2=9.41, df=2(P=0.01); I^2=78.76%						
Test for overall effect: Z=5.82(P<0.0001)						

Favours placebo — Favours PDE5 inhibitor

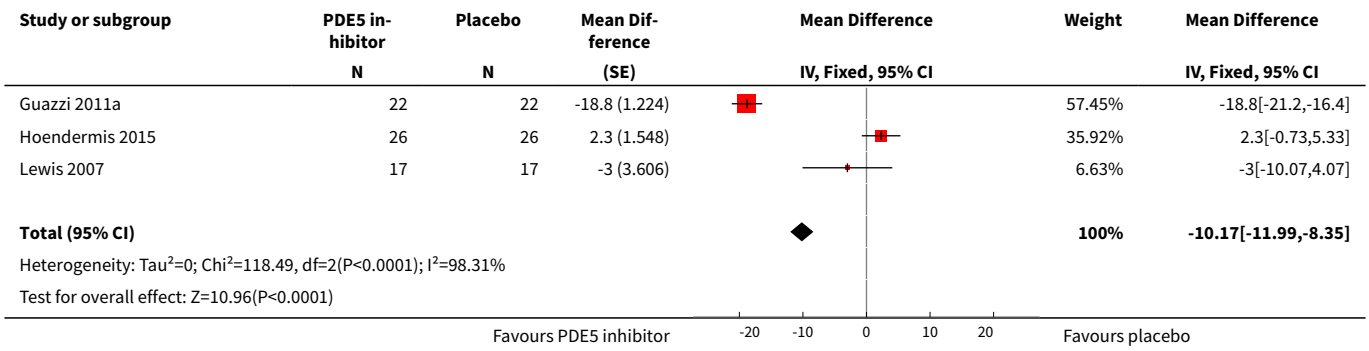
Analysis 4.3. Comparison 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), Outcome 3 Mortality.

Study or subgroup	PDE-5 inhibitor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bermejo 2017	3/104	2/96		67.75%	1.4[0.23,8.54]
Hoendermis 2015	1/26	1/26		32.25%	1[0.06,16.89]
Lewis 2007	0/17	0/17			Not estimable

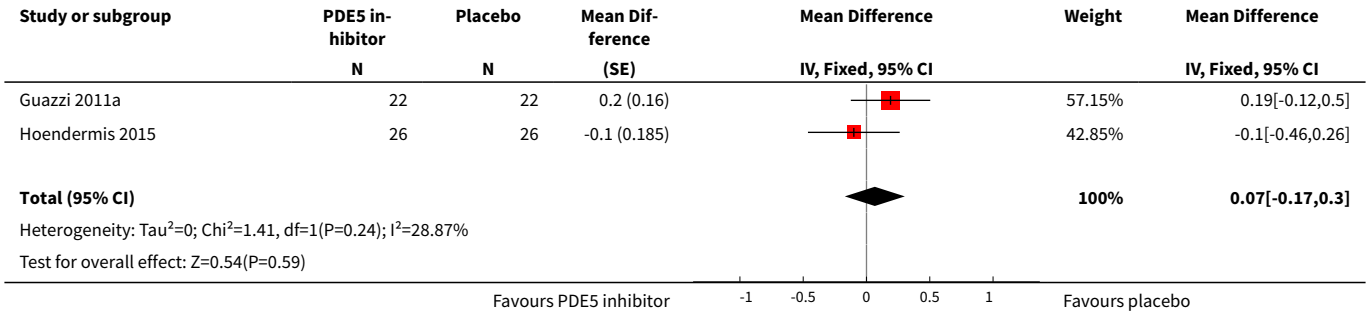
Favours PDE5 inhibitor — Favours placebo



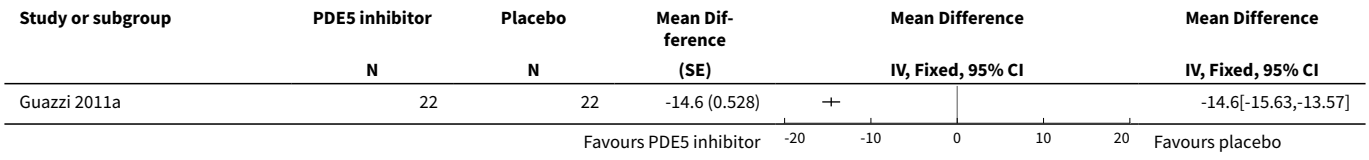
Analysis 4.4. Comparison 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), Outcome 4 mean PAP.



Analysis 4.5. Comparison 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), Outcome 5 Cardiac Index.

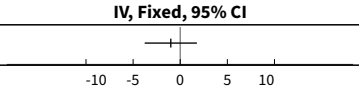


Analysis 4.6. Comparison 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), Outcome 6 TPG.



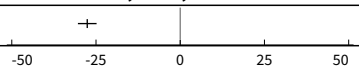
Analysis 4.7. Comparison 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), Outcome 7 RAP.

Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Lewis 2007	17	17	-1 (1.414)		-1[-3.77,1.77]



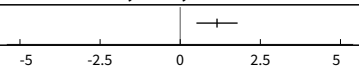
Analysis 4.8. Comparison 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), Outcome 8 PASP.

Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Guazzi 2011a	22	22	-27.6 (1.413)		-27.6[-30.37,-24.83]



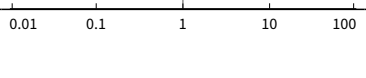
Analysis 4.9. Comparison 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), Outcome 9 Dyspnoea.

Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Guazzi 2011a	22	22	1.1 (0.328)		1.15[0.51,1.79]



Analysis 4.10. Comparison 4 Group 2 Pulmonary hypertension due to left heart disease (sildenafil v placebo), Outcome 10 Clinical worsening.

Study or subgroup	PDE5 inhibitor n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Bermejo 2017	31/104	22/96		66.62%	1.43[0.76,2.7]
Lewis 2007	2/17	5/17		33.38%	0.32[0.05,1.95]
Total (95% CI)	**121**	**113**		**100%**	**0.87[0.22,3.46]**
Total events: 33 (PDE5 inhibitor), 27 (Placebo)					
Heterogeneity: Tau²=0.64; Chi²=2.35, df=1(P=0.13); I²=57.4%					
Test for overall effect: Z=0.2(P=0.84)					

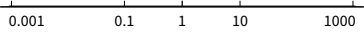


Comparison 5. Group 3 Pulmonary Hypertension due to lung disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in WHO functional class	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Six-minute walk distance	5	350	Mean Difference (Random, 95% CI)	26.70 [2.00, 51.39]
3 QOL	2	238	Mean Difference (Random, 95% CI)	0.19 [-0.07, 0.44]
4 mean PAP	2	61	Mean Difference (Fixed, 95% CI)	-0.14 [-6.65, 6.37]
5 Cardiac Index	1		Mean Difference (Fixed, 95% CI)	Totals not selected
6 PVR	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7 RAP	1		Mean Difference (Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Group 3 Pulmonary Hypertension due to lung disease, Outcome 1 Improvement in WHO functional class.

Study or subgroup	PDE5 inhibitor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Rao 2011	14/20	1/20		44.33[4.78,410.94]



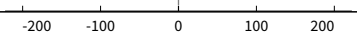
Favours placebo — Favours PDE5 inhibitor

Analysis 5.2. Comparison 5 Group 3 Pulmonary Hypertension due to lung disease, Outcome 2 Six-minute walk distance.

Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Blanco 2013	24	27	0 (16.837)		20.77%	0[-33,33]
Goudie 2014	60	60	0.5 (6.174)		30.58%	0.5[-11.6,12.6]
Han 2013	56	62	99.3 (39.286)		7.84%	99.3[22.3,176.3]
Rao 2011	15	18	137.7 (35.311)		9.19%	137.7[68.49,206.91]
Vitulo 2016	18	10	19.3 (4.587)		31.62%	19.3[10.31,28.29]
Total (95% CI)					**100%**	**26.7[2,51.39]**

Heterogeneity: Tau²=481.13; Chi²=23.79, df=4(P<0.0001); I²=83.19%

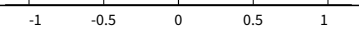
Test for overall effect: Z=2.12(P=0.03)



Favours placebo — Favours PDE5 inhibitor

Analysis 5.3. Comparison 5 Group 3 Pulmonary Hypertension due to lung disease, Outcome 3 QOL.

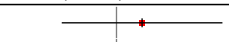
Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Goudie 2014	60	60	0.3 (0.183)		50.3%	0.27[-0.09,0.63]
Han 2013	56	62	0.1 (0.185)		49.7%	0.1[-0.26,0.46]
Total (95% CI)					**100%**	**0.19[-0.07,0.44]**
Heterogeneity: Tau²=0; Chi²=0.42, df=1(P=0.52); I²=0%						
Test for overall effect: Z=1.42(P=0.15)						



Favours placebo — Favours PDE5 inhibitor

Analysis 5.4. Comparison 5 Group 3 Pulmonary Hypertension due to lung disease, Outcome 4 mean PAP.

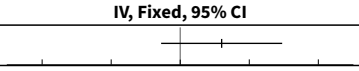
Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Rao 2011	15	18	5 (8.006)		17.21%	5[-10.69,20.69]
Vitulo 2016	18	10	-1.2 (3.65)		82.79%	-1.21[-8.36,5.94]
Total (95% CI)					**100%**	**-0.14[-6.65,6.37]**
Heterogeneity: Tau²=0; Chi²=0.5, df=1(P=0.48); I²=0%						
Test for overall effect: Z=0.04(P=0.97)						



Favours PDE5 inhibitor — Favours placebo

Analysis 5.5. Comparison 5 Group 3 Pulmonary Hypertension due to lung disease, Outcome 5 Cardiac Index.

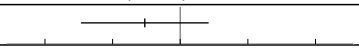
Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Vitulo 2016	18	10	0.3 (0.224)		0.3[-0.14,0.74]



Favours PDE5 inhibitor — Favours placebo

Analysis 5.6. Comparison 5 Group 3 Pulmonary Hypertension due to lung disease, Outcome 6 PVR.

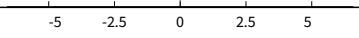
Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Vitulo 2016	18	10	-1.3 (1.204)		-1.31[-3.67,1.05]



Favours PDE5 inhibitor — Favours placebo

Analysis 5.7. Comparison 5 Group 3 Pulmonary Hypertension due to lung disease, Outcome 7 RAP.

Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Vitulo 2016	18	10	0.4 (1.593)		0.36[-2.76,3.48]



Favours PDE5 inhibitor — Favours placebo

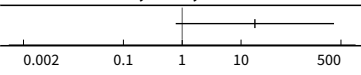
Comparison 6. Group 4 Pulmonary Hypertension due to CTEPH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in WHO functional class	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Six-minute walk distance	3		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 Sildenafil versus placebo	1	19	Mean Difference (Fixed, 95% CI)	17.5 [-23.90, 58.90]
2.2 Sildenafil versus bosentan	2	227	Mean Difference (Fixed, 95% CI)	20.42 [-27.95, 68.79]
3 Mortality	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Sildenafil versus placebo	1	20	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Sildenafil versus bosentan	1	106	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.22, 8.48]
4 mean PAP	3		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 Sildenafil versus placebo	1	19	Mean Difference (Fixed, 95% CI)	-6.2 [-12.40, -0.00]
4.2 Sildenafil versus bosentan	2	227	Mean Difference (Fixed, 95% CI)	0.76 [-3.96, 5.48]
5 Cardiac Index	3		Mean Difference (Fixed, 95% CI)	Subtotals only
5.1 Sildenafil versus placebo	1	19	Mean Difference (Fixed, 95% CI)	0.0 [-0.40, 0.40]
5.2 Sildenafil versus bosentan	2	227	Mean Difference (Fixed, 95% CI)	0.04 [-0.22, 0.31]
6 PVR	3		Mean Difference (Fixed, 95% CI)	Subtotals only
6.1 Sildenafil versus placebo	1	19	Mean Difference (Fixed, 95% CI)	-0.89 [-1.85, 0.06]
6.2 Sildenafil versus bosentan	2	227	Mean Difference (Fixed, 95% CI)	-0.01 [-0.27, 0.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 RAP	2		Mean Difference (Fixed, 95% CI)	Subtotals only
7.1 Sildenafil versus placebo	1	19	Mean Difference (Fixed, 95% CI)	-0.9 [-6.10, 4.30]
7.2 Sildenafil versus bosentan	1	121	Mean Difference (Fixed, 95% CI)	-1.0 [-3.77, 1.77]
8 QOL	1		Mean Difference (Fixed, 95% CI)	Totals not selected
9 Adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Headache	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 GI upset	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

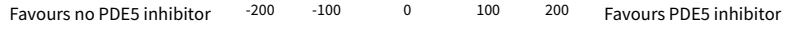
Analysis 6.1. Comparison 6 Group 4 Pulmonary Hypertension due to CTEPH, Outcome 1 Improvement in WHO functional class.

Study or subgroup	PDE5 inhibitor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Suntharalingham 2008	4/9	0/10		17.18[0.78,380.84]



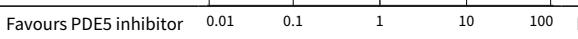
Analysis 6.2. Comparison 6 Group 4 Pulmonary Hypertension due to CTEPH, Outcome 2 Six-minute walk distance.

Study or subgroup	placebo N	PDE5 inhibitor N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
6.2.1 Sildenafil versus placebo						
Suntharalingham 2008	10	9	17.5 (21.123)		100%	17.5[-23.9,58.9]
Subtotal (95% CI)					**100%**	**17.5[-23.9,58.9]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.83(P=0.41)						
6.2.2 Sildenafil versus bosentan						
Galiè 2016a	61	60	25 (85.504)		8.33%	25[-142.58,192.58]
Palazzini 2010	56	50	20 (25.776)		91.67%	20[-30.52,70.52]
Subtotal (95% CI)					**100%**	**20.42[-27.95,68.79]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.96); I²=0%						
Test for overall effect: Z=0.83(P=0.41)						
Test for subgroup differences: Chi²=0.01, df=1 (P=0.93), I²=0%						



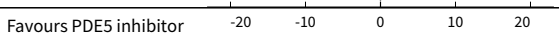
Analysis 6.3. Comparison 6 Group 4 Pulmonary Hypertension due to CTEPH, Outcome 3 Mortality.

Study or subgroup	PDE5 inhibitor n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
6.3.1 Sildenafil versus placebo					
Suntharalingham 2008	0/10	0/10			Not estimable
Subtotal (95% CI)	**10**	**10**			**Not estimable**
Total events: 0 (PDE5 inhibitor), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.3.2 Sildenafil versus bosentan					
Palazzini 2010	3/56	2/50		100%	1.36[0.22,8.48]
Subtotal (95% CI)	**56**	**50**		**100%**	**1.36[0.22,8.48]**
Total events: 3 (PDE5 inhibitor), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.33(P=0.74)					
Test for subgroup differences: Not applicable					



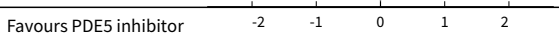
Analysis 6.4. Comparison 6 Group 4 Pulmonary Hypertension due to CTEPH, Outcome 4 mean PAP.

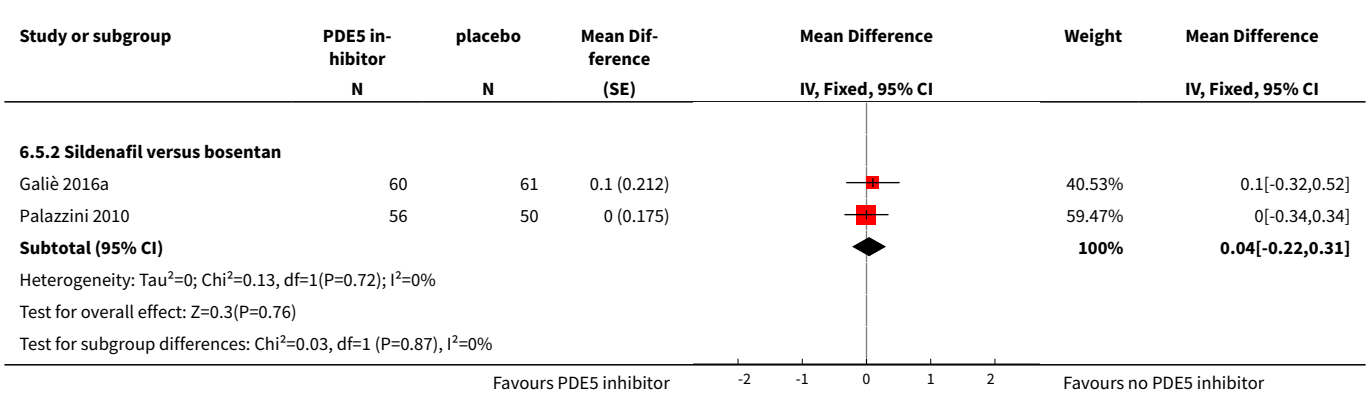
Study or subgroup	PDE5 inhibitor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
6.4.1 Sildenafil versus placebo						
Suntharalingham 2008	9	10	-6.2 (3.163)		100%	-6.2[-12.4,-0]
Subtotal (95% CI)					**100%**	**-6.2[-12.4,-0]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.96(P=0.05)						
6.4.2 Sildenafil versus bosentan						
Galiè 2016a	60	61	2 (3.904)		38.04%	2[-5.65,9.65]
Palazzini 2010	56	50	0 (3.059)		61.96%	0[-6,6]
Subtotal (95% CI)					**100%**	**0.76[-3.96,5.48]**
Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%						
Test for overall effect: Z=0.32(P=0.75)						
Test for subgroup differences: Chi²=3.07, df=1 (P=0.08), I²=67.38%						



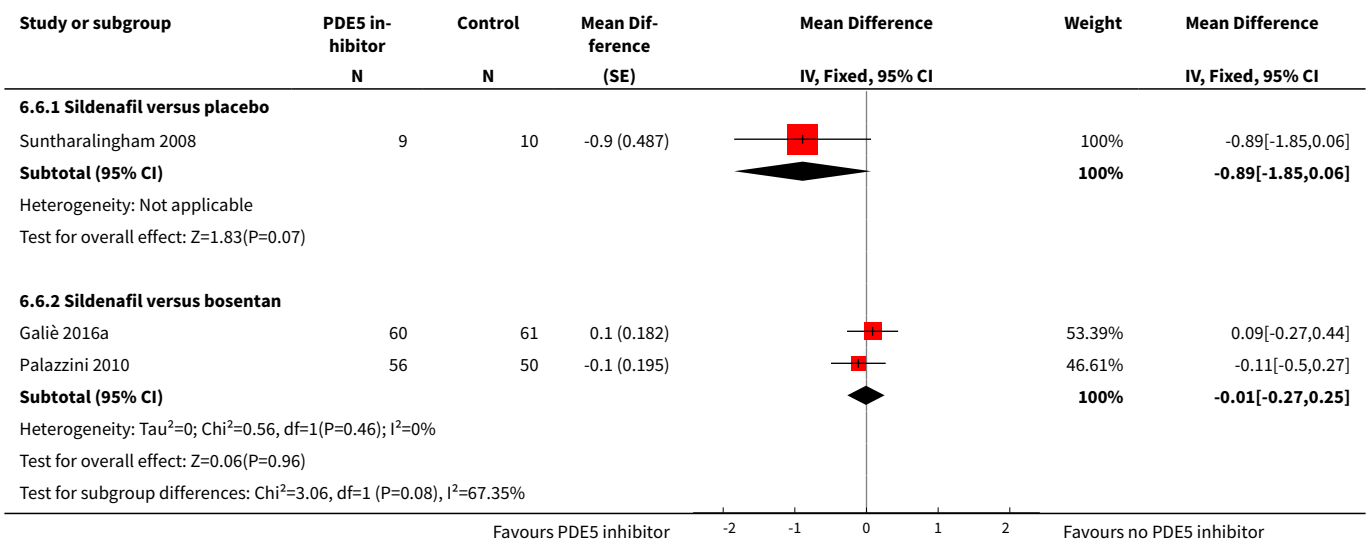
Analysis 6.5. Comparison 6 Group 4 Pulmonary Hypertension due to CTEPH, Outcome 5 Cardiac Index.

Study or subgroup	PDE5 inhibitor N	placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
6.5.1 Sildenafil versus placebo						
Suntharalingham 2008	9	10	0 (0.204)		100%	0[-0.4,0.4]
Subtotal (95% CI)					**100%**	**0[-0.4,0.4]**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

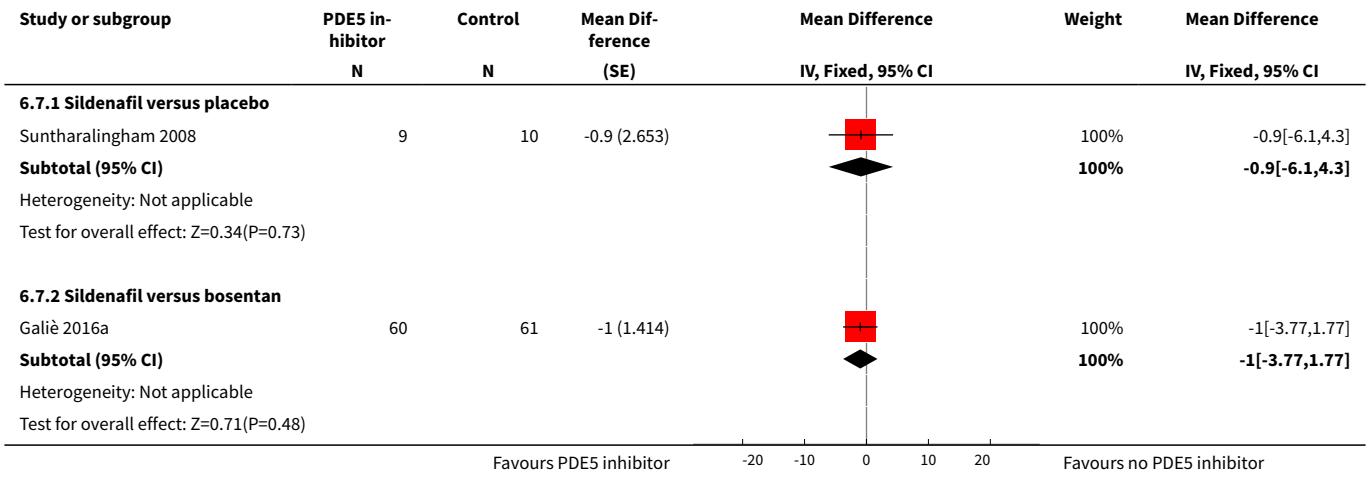


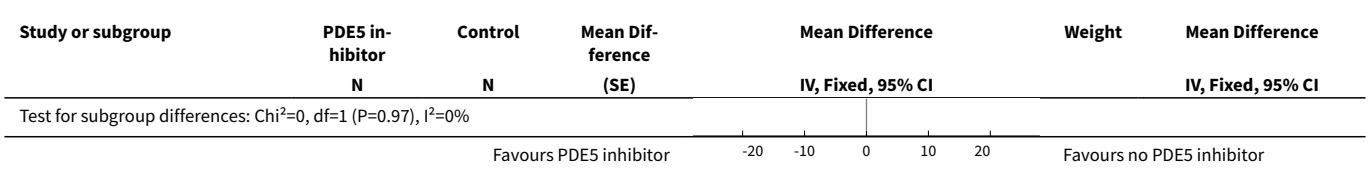


Analysis 6.6. Comparison 6 Group 4 Pulmonary Hypertension due to CTEPH, Outcome 6 PVR.

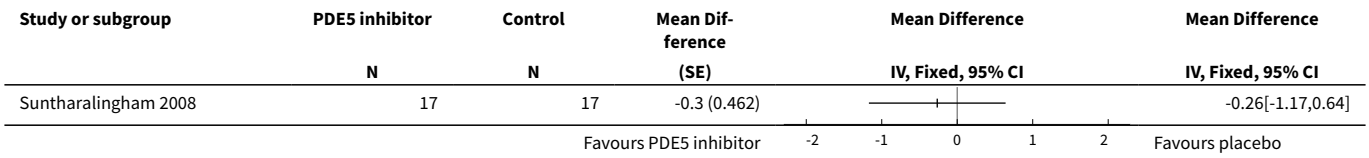


Analysis 6.7. Comparison 6 Group 4 Pulmonary Hypertension due to CTEPH, Outcome 7 RAP.

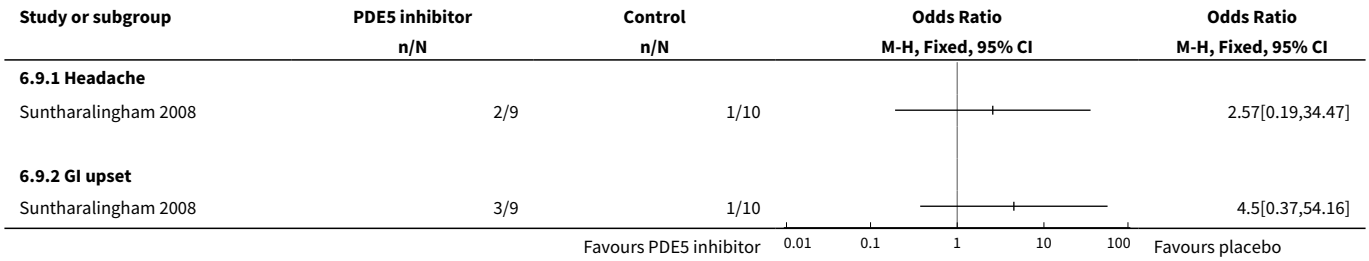




Analysis 6.8. Comparison 6 Group 4 Pulmonary Hypertension due to CTEPH, Outcome 8 QOL.



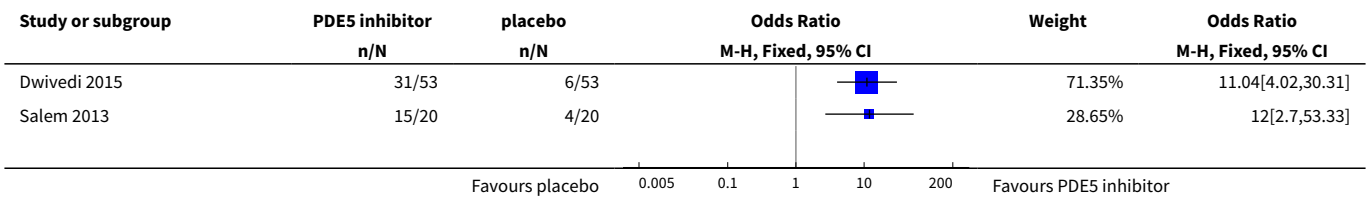
Analysis 6.9. Comparison 6 Group 4 Pulmonary Hypertension due to CTEPH, Outcome 9 Adverse events.

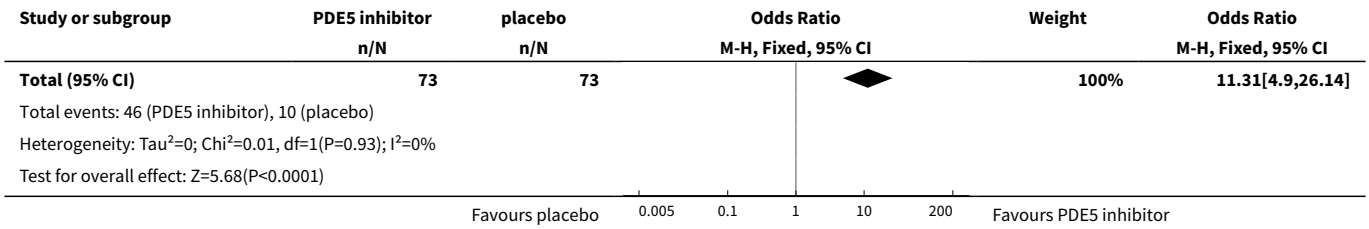


Comparison 7. Mixed Pulmonary Hypertension group 2-4

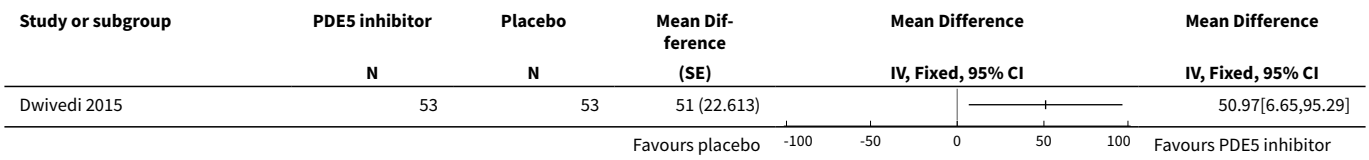
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in WHO functional class	2	146	Odds Ratio (M-H, Fixed, 95% CI)	11.31 [4.90, 26.14]
2 6MWD	1		Mean Difference (Fixed, 95% CI)	Totals not selected
3 PASP	2	146	Mean Difference (Fixed, 95% CI)	-10.0 [-11.92, -8.08]

Analysis 7.1. Comparison 7 Mixed Pulmonary Hypertension group 2-4, Outcome 1 Improvement in WHO functional class.

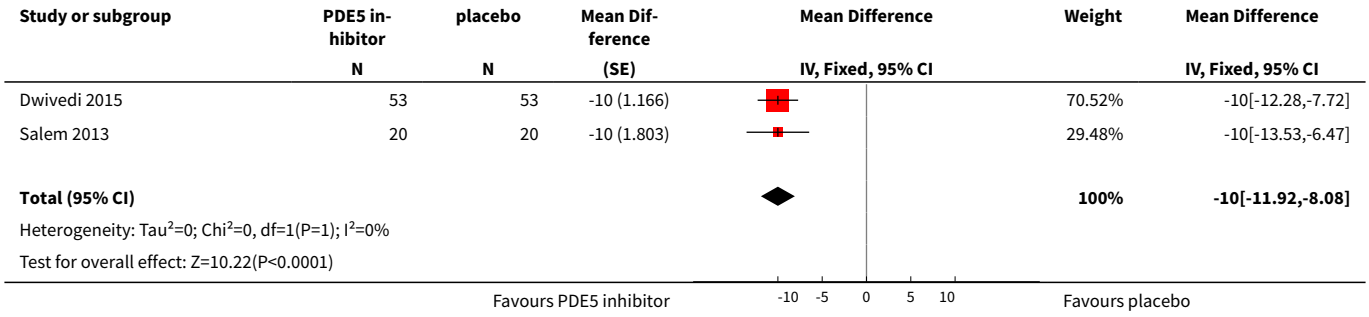




Analysis 7.2. Comparison 7 Mixed Pulmonary Hypertension group 2-4, Outcome 2 6MWD.



Analysis 7.3. Comparison 7 Mixed Pulmonary Hypertension group 2-4, Outcome 3 PASP.



ADDITIONAL TABLES

Table 1. World Health Organisation/World Symposium classification of pulmonary hypertension

WHO group	Classification
Group 1	Pulmonary arterial hypertension • idiopathic PAH • PAH with vasoreactivity • heritable PAH • drugs and toxins • associated with: * connective tissue disease; * HIV; * portal hypertension; * congenital heart disease; * schistosomiasis. Pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis

Table 1. World Health Organisation/World Symposium classification of pulmonary hypertension *(Continued)*

	Persistent pulmonary hypertension of the newborn
Group 2	Pumonary hypertension due to left heart disease • due to left heart failure with preserved ejection fraction • due to left heart failure with reduced ejection fraction Valvular heart disease Congenital post-capillary obstructive lesions
Group 3	Pulmonary hypertension due to chronic lung disease or chronic hypoxaemia, or both • obstructive lung disease • restrictive lung disease • other lung diseases with a mixed obstructive/restrictive pattern • sleep disordered breathing • alveolar hypoventilation disorders • chronic exposures to high altitudes • developmental lung diseases
Group 4	Pulmonary hypertension due to pulmonary artery obstruction • chronic thromboembolic pulmonary hypertension • other pulmonary artery obstructions
Group 5	Pulmonary hypertension with unclear mechanisms • haematologic disorders (chronic haemolytic anaemia, myeloproliferative disorders, splenectomy) • systemic disorders (sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis) • metabolic disorders (glycogen storage disease, Gaucher disease, thyroid disorders) • others (pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension)

PAH: pulmonary arterial hypertension

Table 2. Sensitivity analysis: fixed-effect versus random-effects

Meta-analysis	Number of studies	Effect measure	Fixed-effect size and CI	Random-effect size and CI
Group 1 Pulmonary arterial hypertension - PDE5i versus placebo				
Improvement in WHO functional class	4	OR	8.59 (3.95 to 18.72)	8.53 (3.90 to 18.67)
Six-minute walk distance	8	MD	48.17 (40.30 to 56.04)	52.98 (40.74 to 65.23)[1]
Mortality	7	OR	0.22 (0.07 to 0.68)	0.28 (0.08 to 0.95)
PAP	5	MD	−6.33 (−8.12 to −4.53)	−8.94 (−13.73 to −4.15)
RAP	2	MD	−1.52 (−2.79 to −0.24)	−1.52 (−2.79 to −0.24)

Table 2. Sensitivity analysis: fixed-effect versus random-effects *(Continued)*

Cardiac index	4	MD	0.28 (0.16 to 0.40)	0.35 (0.08 to 0.61)[a]
PVR	3	MD	−4.74 (−6.13 to −3.35)	−5.02 (−7.02 to −3.02)
PASP	2	MD	−11.62 (−25.18 to 1.94)	−11.62 (−25.18 to 1.94)
Dypnoea	4	MD	−0.72 (−0.99 to −0.44)	−0.61 (−1.19 to −0.02)
Clinical worsening requiring intervention	3	OR	0.58 (0.27 to 1.23)	0.55 (0.25 to 1.23)
Group 1 Pulmonary arterial hypertension - PDE5i versus placebo to on combination therapy				
Improvement in WHO functional Class	2	OR	1.20 (0.66 to 2.17)	1.09 (0.41 to 2.92)
Six-minute walk distance	4	MD	19.66 (9.22 to 30.10)	18.94 (0.23 to 37.65)
Mortality	3	OR	0.26 (0.07 to 1.06)	0.38 (0.04 to 3.81)
PAP	2	MD	−4.58 (−6.14 to −3.01)	−5.12 (−8.21 to −2.03)
Cardiac output	2	MD	0.87 (0.53 to 1.21)	0.87 (0.53 to 1.21)
PVR	3	SMD	−0.48 (−0.72 to −0.25)	−0.36 (−0.84 to 0.12)[a]
Clinical worsening	3	OR	0.34 (0.18 to 0.63)	0.34 (0.18 to 0.63)
Group 1 Pulmonary arterial hypertension - PDE5i versus ERA				
Improvement in WHO functional Class	1	OR	0.94 (0.55 to 1.60)	0.94 (0.55 to 1.60)
Six-minute walk distance	2	MD	49.38 (3.65 to 95.11)	49.38 (3.65 to 95.11)
Mortality	2	OR	3.19 (0.74 to 13.64)	3.19 (0.74 to 13.64)
Quality of life	1	MD	22.00 (9.00 to 35.00)	22.00 (9.00 to 35.00)
PAP	1	MD	7.00 (−4.82 to 18.82)	7.00 (−4.82 to 18.82)
RAP	1	MD	2.00 (−2.14 to 6.14)	2.00 (−2.14 to 6.14)
Cardiac index	1	MD	0.00 (−0.49 to 0.49)	0.00 (−0.49 to 0.49)
PVR	1	MD	0.00 (−1.93 to 1.93)	0.00 (−1.93 to 1.93)
Clinical worsening	2	OR	0.52 (0.30 to 0.89)	0.52 (0.30 to 0.89)
Group 2 Pulmonary hypertension due to left-heart disease				
Improvement in WHO functional Class	3	OR	0.53 (0.32 to 0.87)	0.70 (0.20 to 2.37)

Table 2. Sensitivity analysis: fixed-effect versus random-effects *(Continued)*

Six-minute walk distance	3	MD	34.31 (22.75 to 45.87)	28.44 (-1.82 to 58.69)[a]
Mortality	3	OR	0.01 (−0.03 to 0.04)	0.01 (−0.03 to 0.04)
Mean PAP	3	MD	−10.17 (−11.99 to −8.35)	−6.58 (−22.28 to 9.12)[a]
Cardiac index	2	MD	0.07 (−0.17 to 0.30)	0.06 (−0.22 to 0.34)
TPG	1	MD	−14.60 (−15.63 to −13.57)	−14.60 (−15.63 to −13.57)
RAP	1	MD	−1.00 (−3.77 to 1.77)	−1.00 (−3.77 to 1.77)
PASP	1	MD	−27.60 (−30.37 to −24.83)	−27.60 (−30.37 to −24.83)
Dypnoea	1	MD	1.15 (0.51 to 1.79)	1.15 (0.51 to 1.79)
Clinical worsening requiring intervention	2	OR	1.19 (0.66 to 2.14)	0.87 (0.22 to 3.46)
Group 3 Pulmonary hypertension due to lung disease				
Improvement in WHO functional Class	1	OR	44.33 (4.78 to 410.93)	44.33 (4.78 to 410.93)
Six-minute walk distance	5	MD	14.04 (7.05 to 21.02)	26.70 (2.00 to 51.39)[1]
Mean PAP	2	MD	−0.14 (−6.65 to 6.37)	−0.14 (−6.65 to 6.37)
Cardiac index	1	MD	0.30 (−0.14 to 0.74)	0.30 (−0.14 to 0.74)
PVR	1	MD	−1.31 (−3.67 to 1.05)	−1.31 (−3.67 to 1.05)
RAP	1	MD	0.36 (−2.76 to 3.48)	0.36 (−2.76 to 3.48)
Quality of life	3	MD	0.19 (−0.07 to 0.44)	0.19 (−0.07 to 0.44)
Group 4 Pulmonary hypertension due to CTEPH				
Improvement in WHO functional Class	1	OR	17.18 (0.78 to 380.85)	17.18 (0.78 to 380.85)
Six-minute walk distance	3	MD	18.73 (−12.72 to 50.19)	18.73 (−12.72 to 50.19)
Mortality	2	OR	0.01 (−0.06 to 0.08)	0.01 (−0.06 to 0.08)
Mean PAP	2	MD	−1.79 (−5.55 to 1.96)	−1.67 (−6.48 to 3.15)
Cardiac index	3	MD	0.03 (−0.19 to 0.25)	0.03 (−0.19 to 0.25)
PVR	3	MD	−0.07 (−0.32 to 0.18)	−0.12 (−0.50 to 0.25)
RAP	2	MD	−0.98 (−3.42 to 1.47)	−0.98 (−3.42 to 1.47)

Table 2. Sensitivity analysis: fixed-effect versus random-effects *(Continued)*

Quality of life	1	MD	−0.26 (−1.17 to 0.64)	−0.26 (−1.17 to 0.64)
Mixed pulmonary hypertension group 2 to 4				
Improvement in WHO functional Class	2	OR	11.33 (4.91 to 26.15)	11.33 (4.91 to 26.15)
Six-minute walk distance	1	MD	50.97 (44.88 to 57.06)	50.97 (44.88 to 57.06)
PASP	2	MD	−10.00 (−11.92 to −8.08)	−10.00 (−11.92 to −8.08)

[a]statistically high heterogeneity
CI - confidence interval; CTEPH - chronic thromboembolic pulmonary hypertension; OR - odds ratio; MD - mean difference; PAP - pulmonary artery pressure; PASP - pulmonary artery systemic pressure; PDE5i - phosphodiesterase-5 inhibitor; PVR - pulmonary vascular resistance; RAP - right atrial pressure; SMD - standardised mean difference; TPG - transpulmonary gradient; WHO - World Health Organization

APPENDICES

Appendix 1. Database search strategies

CENTRAL & Cochrane Airways Register of Trials search strategy

#1 MESH DESCRIPTOR Hypertension, Pulmonary EXPLODE ALL TREES
#2 MESH DESCRIPTOR Pulmonary Heart Disease
#3 (pulmonary NEAR2 hypertensi*):TI,AB,KY
#4 #1 OR #2 OR #3
#5 MESH DESCRIPTOR Phosphodiesterase 5 Inhibitors EXPLODE ALL TREES
#6 (PDE5 or PDE5):TI,AB,KY
#7 ("Phosphodiesterase 5" or Phosphodiesterase-5):TI,AB,KY
#8 (sildenafil or Viagra):TI,AB,KY
#9 (tadalafil or Cialis):TI,AB,KY
#10 (vardenafil or Levitra or Staxyn):TI,AB,KY
#11 (avanafil or Stendra):TI,AB,KY
#12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13 #4 AND #12

MEDLINE (Ovid) search strategy

1. exp Hypertension, Pulmonary/
2. Pulmonary Heart Disease/
3. (pulmonary adj2 hypertensi$).tw.
4. 1 or 2 or 3
5. exp Phosphodiesterase 5 Inhibitors/
6. (PDE5 or PDE-5).tw.
7. ("Phosphodiesterase 5" or Phosphodiesterase-5).tw.
8. (sildenafil or viagra).tw.
9. (tadalafil or Cialis).tw.
10. (vardenafil or Levitra or Staxyn).tw.
11. (avanafil or Stendra).tw.
12. or/5-11
13. 4 and 12
14. (controlled clinical trial or randomised controlled trial).pt.
15. (randomised or randomised).ab,ti.
16. placebo.ab,ti.
17. dt.fs.
18. randomly.ab,ti.
19. trial.ab,ti.

20. groups.ab,ti.
21. or/14-20
22. Animals/
23. Humans/
24. 22 not (22 and 23)
25. 21 not 24
26. 13 and 25

Embase (Ovid) search strategy

1. exp pulmonary hypertension/
2. (pulmonary adj2 hypertensi$).tw.
3. 1 or 2
4. exp phosphodiesterase V inhibitor/
5. (PDE5 or PDE-5).tw.
6. ("Phosphodiesterase 5" or Phosphodiesterase-5).tw.
7. (sildenafil or viagra).tw.
8. (tadalafil or Cialis).tw.
9. (vardenafil or Levitra or Staxyn).tw.
10. (avanafil or Stendra).tw.
11. or/4-10
12. 3 and 11
13. Randomized Controlled Trial/
14. randomization/
15. controlled clinical trial/
16. Double Blind Procedure/
17. Single Blind Procedure/
18. Crossover Procedure/
19. (clinica$ adj3 trial$).tw.
20. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw.
21. exp Placebo/
22. placebo$.ti,ab.
23. random$.ti,ab.
24. ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw.
25. (crossover$ or cross-over$).ti,ab.
26. or/13-25
27. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
28. human/ or normal human/ or human cell/
29. 27 and 28
30. 27 not 29
31. 26 not 30
32. 12 and 31

WHAT'S NEW

Date	Event	Description
28 February 2019	Amended	Two minor amendments made to the "Agreements and disagreements with other studies or review" section of the discussion. Thank you to the Spanish translation team for highlighting these errors. 1. First paragraph: minor typographical error corrected 2. Final paragraph: Galiè 2016a reference corrected to Galiè 2016b and paragraph restructured to improve clarity

CONTRIBUTIONS OF AUTHORS

HB and ZB screened all abstracts, with TW providing third-party consensus.

HB and ZB extracted the data.
HB drafted the review, and ZB and AB and TW provided comments and changes.

DECLARATIONS OF INTEREST

HB: H Barnes received a travel scholarship that was determined by an independent abstract committee, funded by GSK. GSK had no involvement in the determination of recipients. The Cochrane funding arbiter was consulted and agreed it did not represent a conflict of interest as GSK had no role in the allocation of the travel scholarship.

ZB: none known

AB: none known

TW: Actelion Australia Scientific Advisory Board and Research/Education unrestricted grant; GSK Australia Scientific Advisory Board; Bayer Australia Scientific Advisory Board

SOURCES OF SUPPORT

Internal sources

- The authors declare that no such funding was received for this systematic review, Other.

External sources

- The authors declare that no such funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we intended to assess changes in New York Heart Association (NYHA) functional class, but the nomenclature for people with PAH is now WHO functional class. It should be noted, however, that the NHYA and WHO classification system both classify patients in the same way.

INDEX TERMS

Medical Subject Headings (MeSH)

Endothelin Receptor Antagonists [therapeutic use]; Hypertension, Pulmonary [*drug therapy] [etiology] [mortality]; Numbers Needed To Treat; Phosphodiesterase 5 Inhibitors [adverse effects] [*therapeutic use]; Placebos [therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Walk Test

MeSH check words

Adult; Child; Humans