

**Additional file 1 Search Strategies****MEDLINE**

- #1 "Hypertension, Pulmonary"[Mesh]
- #2 "Pulmonary Arterial Hypertension, Hereditary Hemorrhagic Telangiectasia-Related" [Supplementary Concept]
- #3 "pulmonary arterial hypertension" [Title/Abstract]
- #4 "pulmonary hypertension" [Title/Abstract]
- #5 "lung hypertension" [Title/Abstract]
- #6 "PAH" [Title/Abstract]
- #7 "PVOD" [Title/Abstract]
- #8 "PCH" [Title/Abstract]
- #9 #1-#8/ OR
- #10 "Sildenafil Citrate" [Mesh]
- #11 "Phosphodiesterase 5 Inhibitors"[Mesh]
- #12 "sildenafil" [Title/Abstract]
- #13 "Revatio" [Title/Abstract]
- #14 "Homosildenafil" [Title/Abstract]
- #15 "Hydroxyhomosildenafil" [Title/Abstract]
- #16 "phosphodiesterase inhibitor\*" [Title/Abstract]
- #17 "PDE 5" [Title/Abstract]
- #18 "Phosphodiesterase 5" [Title/Abstract]
- #19 #10-#18/ OR
- #20 #9 AND #19
- #21 "Animals"[Mesh]
- #22 "Humans"[Mesh]
- #23 #21 NOT # 22
- #24 #20 NOT # 23
- #25 Filters: Humans

**Embase**

- #1 'pulmonary hypertension'/exp
- #2 'pulmonary arterial hypertension':ab,ti
- #3 'pulmonary hypertension':ab,ti
- #4 'lung hypertension':ab,ti
- #5 'PAH':ab,ti
- #6 'PVOD':ab,ti
- #7 'PCH':ab,ti
- #8 #1-#7 / OR
- #9 'sildenafil'/exp
- #10 'phosphodiesterase V inhibitor'/exp
- #11 'sildenafil':ab,ti
- #12 'Revatio':ab,ti
- #13 'Homosildenafil':ab,ti
- #14 'Hydroxyhomosildenafil ':ab,ti
- #15 'phosphodiesterase inhibitor\* ':ab,ti
- #16 'PDE 5':ab,ti
- #17 'Phosphodiesterase 5':ab,ti
- #18 #9-#17 / OR
- #19 #8 AND #18

- #20 'animal'/exp
- #21 'human'/exp
- #22 #20 NOT # 21
- #23 #19 NOT # 22
- #24 [medline]/lim in #23
- #25 #23 NOT #24

### Web of science

- #1 TITLE: “pulmonary arterial hypertension”
- #2 TITLE: “pulmonary hypertension”
- #3 TOPIC: “lung hypertension”
- #4 TITLE: “PAH”
- #5 TOPIC: “PVOD”
- #6 TOPIC: “PCH”
- #7 #1-#6 /OR
- #8 TOPIC: (“sildenafil”)
- #9 TOPIC: (“phosphodiesterase inhibitor\*”)
- #10 TOPIC: (“Revatio”)
- #11 TOPIC: (“Homosildenafil”)
- #12 TOPIC: (“Hydroxyhomosildenafil”)
- #13 TOPIC: (“PDE 5”)
- #14 TOPIC: (“Phosphodiesterase 5”)
- #15 #8-#14 / OR
- #16 #7 AND #15

### The Cochrane Library

- #1 MeSH descriptor: [Hypertension, Pulmonary] explode all trees
- #2 “pulmonary arterial hypertension”:ti,ab,kw
- #3 “pulmonary hypertension”:ti,ab,kw
- #4 “lung hypertension”:ti,ab,kw
- #5 “PAH”:ti,ab,kw
- #6 “PVOD”:ti,ab,kw
- #7 “PCH”:ti,ab,kw
- #8 #1-#7/ OR
- #9 MeSH descriptor: [Sildenafil Citrate] explode all trees
- #10 MeSH descriptor: [phosphodiesterase 5 inhibitors] explode all trees
- #11 “sildenafil”: ti, ab, kw
- #12 “phosphodiesterase inhibitor\*”: ti, ab, kw
- #13 “Revatio”: ti, ab, kw
- #14 “Homosildenafil”: ti, ab, kw
- #15 “Hydroxyhomosildenafil”: ti, ab, kw
- #16 “PDE 5”: ti, ab, kw
- #17 “Phosphodiesterase 5”: ti, ab, kw
- #18 #9-#17 / OR
- #19 #8 AND #18

### CNKI

- #1 主题 : (“ 肺动脉高压 ”)
- #2 主题 : (“ 肺高压 ”)

- #3 #1-#2/ OR
- #4 主题 : (“ 西地那非 ”)
- #5 主题 : (“ 万艾可 ”)
- #6 主题 : (“ 昔多芬 ”)
- #7 #4-#6/ OR
- #8 #3 AND #7
- #9 限定医药卫生

### CBM

- #1 “ 高血压，肺性 ” [ 不加权 : 扩展 ]
- #2 “ 肺动脉高压 ” [ 常用字段 : 智能 ]
- #3 “ 肺高压 ” [ 常用字段 : 智能 ]
- #4 #1-#3/ OR
- #5 “ 枸橼酸西地那非 ” [ 不加权 : 扩展 ]
- #6 “ 西地那非 ” [ 常用字段 : 智能 ]
- #7 “ 万艾可 ” [ 常用字段 : 智能 ]
- #8 “ 昔多芬 ” [ 常用字段 : 智能 ]
- #9 #5-#8 / OR
- #10 #4 AND #9

### Wanfang

- #1 主题 : (“ 肺动脉高压 ”)
- #2 主题 : (“ 肺高压 ”)
- #3 #1-#2/ OR
- #4 主题 : (“ 西地那非 ”)
- #5 主题 : (“ 万艾可 ”)
- #6 主题 : (“ 昔多芬 ”)
- #7 #4-#6/ OR
- #8 #3 AND #7
- #9 限定医药、卫生
- #10 限定万方来源

**Table S1** Risk of bias assessment—the risk of bias of included RCTs

| Study ID        | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective outcome reporting | Other potential sources of bias |
|-----------------|----------------------------|------------------------|--|--------------------------------|-------------------------|-----------------------------|---------------------------------|
| Galiè 2005      | Unclear                    | Unclear                | Unclear                                | Unclear                        | Low risk                | Low risk                    | High risk                       |
| Wirotko 2012    | Low risk                   | Low risk               | Low risk                               | Low risk                       | Low risk                | Low risk                    | High risk                       |
| Pepke-Zaba 2008 | Unclear                    | Unclear                | Unclear                                | Unclear                        | Low risk                | Low risk                    | High risk                       |
| Webb 2015       | Unclear                    | Unclear                | Unclear                                | Unclear                        | Low risk                | Low risk                    | High risk                       |
| Xu 2013         | Unclear                    | Unclear                | Unclear                                | Unclear                        | Low risk                | Low risk                    | High risk                       |

RCT, randomized controlled trial.

**Table S2** Risk of bias assessment—the risk of bias of included NRSIs

| Study ID      | Confounding   | Selection of participants into the study | Classification of the intervention | Deviations from intended interventions | Missing Data | Measurements of outcomes | Selections of the reported result | Overall risk  |
|---------------|---------------|--|------------------------------------|--|--------------|--------------------------|-----------------------------------|---------------|
| Xu 2009       | Moderate risk | Low risk                                 | Low risk                           | Low risk                               | Low risk     | Low risk                 | Low risk                          | Moderate risk |
| Zhang 2011    | Moderate risk | Low risk                                 | Low risk                           | Low risk                               | Low risk     | Low risk                 | Low risk                          | Moderate risk |
| Sato 2011     | Moderate risk | Low risk                                 | Low risk                           | Moderate risk                          | Serious risk | Low risk                 | Low risk                          | Serious risk  |
| Guo 2014      | Moderate risk | Low risk                                 | Low risk                           | Low risk                               | Low risk     | Low risk                 | Moderate risk                     | Moderate risk |
| Hidayati 2020 | Moderate risk | Low risk                                 | Moderate risk                      | Moderate risk                          | Low risk     | Low risk                 | Low risk                          | Moderate risk |

NRSI, Non-Randomized Studies of Interventions.

**Table S3** GRADE evidence profile—summary of Sildenafil for Asian adults with pulmonary arterial hypertension

| No. of studies   | Certainty assessment |                      |              |                      |                  |                           |                        |                       | Sample | I <sup>2</sup> | Effect value (95% CI)            | Overall certainty of evidence |
|--|----------------------|----------------------|--------------|----------------------|------------------|---------------------------|------------------------|-----------------------|--------|----------------|----------------------------------|-------------------------------|
|  | Risk of bias         | Inconsistency        | Indirectness | Imprecision          | Publication bias | Large magnitude of effect | Dose response gradient | Plausible confounding |        |                |                                  |                               |
| Six-minute walking distance (m)                                      |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| NRSI (4)   | Serious <sup>a</sup> | Not serious          | Not serious  | Serious <sup>c</sup> | None             | Yes <sup>d</sup>          | None                   | None                  | 262    | 39%            | WMD =57.68 (41.55 to 73.81)      | ⊕⊕○○ (low)                    |
| Dyspnoea score (points)  |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| NRSI (2)   | Serious <sup>a</sup> | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 105    | 0%             | WMD =-0.99 (-1.45 to -0.53)      | ⊕○○○ (very low)               |
| Level of brain natriuretic peptide (pg /mL)                          |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1), NRSI (1)  | Serious <sup>a</sup> | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 102    | 14%            | WMD =-86.16 (-103.39 to -68.93)  | ⊕○○○ (very low)               |
| Reduction in the mean pulmonary artery pressure (mmHg)               |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (2)  | Serious <sup>a</sup> | Serious <sup>b</sup> | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 172    | 89%            | WMD =-4.13 (-6.52 to -1.74)      | ⊕○○○ (very low)               |
| Mean pulmonary artery pressure (mmHg)                                |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| NRSI (2)   | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 144    | 0%             | WMD =-4.90 (-10.36 to 0.55)      | ⊕⊕○○ (low)                    |
| Systemic arterial oxygen saturation (%)                              |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| NRSI (2)   | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 144    | 0%             | WMD =2.48 (1.26 to 3.71)         | ⊕⊕○○ (low)                    |
| Reduction in pulmonary vascular resistance (dyn·s·cm <sup>-5</sup> ) |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1)  | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | Yes <sup>d</sup>          | None                   | None                  | 130    | NA             | WMD =-171.00 (-311.49 to -30.51) | ⊕⊕⊕○ (moderate)               |
| Pulmonary vascular resistance (Wood Units)                           |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| NRSI (1)   | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 60     | NA             | WMD =-1.02 (-3.73 to 1.69)       | ⊕⊕○○ (low)                    |
| Reduction in the right atrium pressure (mmHg)                        |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1)  | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 130    | NA             | WMD =-1.10 (-2.73 to 0.53)       | ⊕⊕⊕○ (moderate)               |
| Right atrium pressure (mmHg)   |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| NRSI (3)   | Serious <sup>a</sup> | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 164    | 15%            | WMD =-1.17 (-2.14 to -0.20)      | ⊕○○○ (very low)               |
| Reduction in the cardiac index (min·m <sup>2</sup> )                 |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1)  | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 130    | NA             | WMD =0.23 (-0.18 to 0.64)        | ⊕⊕⊕○ (moderate)               |
| Cardiac index (min·m <sup>2</sup> )                                  |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| NRSI (2)   | Serious <sup>a</sup> | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 80     | 0%             | WMD =0.35 (0.07 to 0.63)         | ⊕○○○ (very low)               |
| Adverse event-headache (%)   |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1), NRSI (3)  | Serious <sup>a</sup> | Serious <sup>b</sup> | Not serious  | Serious <sup>c</sup> | None             | Yes <sup>e</sup>          | None                   | None                  | 304    | 92%            | OR =33.21 (0.83 to 1,334.18)     | ⊕⊕○○ (low)                    |
| Adverse event-flushing (%)   |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1), NRSI (2)  | Serious <sup>a</sup> | Serious <sup>b</sup> | Not serious  | Serious <sup>c</sup> | None             | Yes <sup>e</sup>          | None                   | None                  | 244    | 77%            | OR =17.02 (0.98 to 294.15)       | ⊕⊕○○ (low)                    |
| Adverse event-dyspepsia (%)  |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1), NRSI (2)  | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | Yes <sup>d</sup>          | None                   | None                  | 283    | 0%             | OR =2.76 (1.01 to 7.56)          | ⊕⊕⊕○ (moderate)               |
| Adverse event-diarrhoea (%)  |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1), NRSI (1)  | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 223    | 0%             | OR =1.89 (0.57 to 6.30)          | ⊕⊕○○ (low)                    |
| Adverse event-limb pain (%)  |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1), NRSI (1)  | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 223    | 0%             | OR =1.62 (0.47 to 5.61)          | ⊕⊕○○ (low)                    |
| Adverse event-skin rash (%)  |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| NRSI (2)   | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | Yes <sup>d</sup>          | None                   | None                  | 144    | 0%             | OR =3.04 (0.12 to 75.59)         | ⊕⊕○○ (low)                    |
| Mortality (%)  |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1), NRSI (2)  | Not serious          | Not serious          | Not serious  | Serious <sup>c</sup> | None             | None                      | None                   | None                  | 283    | 0%             | OR =1.01 (0.06 to 16.55)         | ⊕⊕○○ (low)                    |
| Incidence of clinical worsening (%)                                  |                      |                      |              |                      |                  |                           |                        |                       |        |                |                                  |                               |
| RCT (1), NRSI (2)  | Not serious          | Serious <sup>b</sup> | Not serious  | Serious <sup>c</sup> | None             | Yes <sup>d</sup>          | None                   | None                  | 283    | 77%            | OR =3.36 (0.19 to 60.54)         | ⊕⊕○○ (low)                    |

a, downgrade one level: the risk of bias is high due to the limitations of study design; b, downgrade one level: heterogeneity of data synthesis results, I<sup>2</sup>>50%; c, downgrade one or two levels: sample size is less than optimal information sample (OIS) or the confidence interval is too wide; d, upgrade one level: large magnitude of effect with OR >2 or WMD reached the clinical significance; e, upgrade two levels: large magnitude of effect with OR >5. RCT, randomized controlled trial; NRSI, non-randomized studies of interventions; OR, odds ratio; WMD, weighted mean difference; CI, confidence interval; NA, not applicable.