Sildenafil for Asian Adult Patients with Pulmonary Arterial Hypertension: A Systematic Review and Meta-analysis

Qianling Shi
Lanzhou University First Affiliated Hospital
Zijun Wang
Lanzhou University School of Basic Medical Sciences
Nan Yang
Lanzhou University School of Basic Medical Sciences
Yanfang Ma
Lanzhou University School of Basic Medical Sciences
Yaolong Chen
Lanzhou University School of Basic Medical Sciences
Hua Yao (18119372718@163.com)
Guangdong Provincial People's Hospital

Research

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Abstract

Background: The prognosis of patients with untreated pulmonary arterial hypertension (PAH) has historically been poor. Previous studies have recommended that sildenafil was beneficial, but the dose varies greatly. We aimed to evaluate sildenafil effectiveness and safety in dose of 20mg/three times a day (TID) for Asian adult patients with PAH.

Methods: Electronic databases (MEDLINE, Embase, Web of Science, the Cochrane Library, CBM, CNKI and Wanfang Data) from their inception to May 2020 were searched. We included all randomized controlled trials and non-randomized studies of interventions that comparing sildenafil (20mg/TID) versus placebo or symptomatic treatment for PAH Asian adults.

Results: Eight studies totaling 364 participants were included. When compared to symptomatic treatment, sildenafil treated patients were more likely to walk 68.3 meters further in six-minute walk distance [mean difference (MD)=68.3 meters, 95% confidence interval (CI) 48.85 to 87.76, *P*<0.00001], to achieve an improvement in systemic arterial oxygen saturation (MD=2.48%, 95% CI 1.26 to 3.71, *P*<0.00001) and in score on the Borg scale of dyspnea (MD=-0.99 points, 95% CI -1.45 to -0.53, *P*<0.00001). The total number of patients with WHO class III and IV also showed downtrend. When compared to placebo, sildenafil was associated with a greater reduction in the mean pulmonary artery pressure (MD=-4.13 mmHg, 95% CI -6.52 to -1.74, *P*=0.0007) and level of brain natriuretic peptide (MD=-86.16 pg /mL, 95% CI -103.39 to -68.93, *P*<0.00001). The most adverse reactions were headache, flushing, dyspepsia, and diarrhea, which were relatively mild.

Conclusions: Sildenafil in dose of 20mg/TID is well tolerated in Asian adults with PAH, and associated with statistically significant improvements in exercise capacity, cardio-pulmonary function and haemodynamic indices. The long-term prognosis still needs to be evaluated and confirmed by further trials.

Systematic review registration: PROSPERO CRD42020190582

Background

Pulmonary hypertension (PH) is a group of complex conditions characterized by progressive increase in pulmonary artery pressure (PAP) with or without irreversible vascular remodeling, leading to right ventricular failure and premature death. Present estimates suggest a PH prevalence of about 1% of the global population, which increases up to 5–10% in individuals aged more than 65 years [1–2]. According to the clinical presentations, pathophysiological and haemodynamic characteristics, PH can be classified into five groups, of which, pulmonary arterial hypertension (PAH) is a group of diseases where PH occurs in the setting of increased pulmonary vascular resistance (PVR) [3–5]. The overall estimated rate of PAH was 10 to 52 per million of the population [6], and reported incidence and prevalence for developed world is 1.1 to 7.6 and 6.6 to 26.0 per million adults per year [7–9]. For patients without effective interventions, PAH can be hugely devastating and exert an adverse impact on all aspects of life. The prognosis was once very poor with a median survival of only 2.8 years [10–11]. Recent years have seen the introduction of targeted medications to enhance survival rate with an improvement in the one-year from 69–85% and five-year from 38–57% [12–14].

Sildenafil was first approved for the treatment of PAH since 2005 by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for oral administration at a dose of 20 mg/three times a day (TID). It specifically reduces the activity of cGMP degrading enzyme, thereby increasing the antiproliferative and vasodilating

effects of endogenous NO [4, 15]. Due to the reliable efficacy, good tolerability and affordability (the average cost in the United States for 1 year of treatment with sildenafil 20mg/TID [13, 000 dollars] compares favorably with bosentan [annual cost, 40, 000 dollars]), sildenafil has become the drug of choice for PAH patients with World Health Organization (WHO) II or III functional class. and was recommended in several guidelines [4,16–19]. Although a number of systematic reviews have confirmed its short-term clinical efficacy [15,20–21], the dose varies greatly and they did not focus on Asian population and other important outcomes. Especially for China, iloprost and bosentan were approved for the treatment of PAH, but few patients have been treated with these agents, because the cost of one-month supply of bosentan and iloprost [3,000 dollars] is much more than sildenafil 20mg/TID [300 dollars] per month, which was approved recently [22]. Therefore, the purpose of this study is to quantify effectiveness and safety of sildenafil (20mg/TID) for adult PAH patients in Asia in order to provide guidance for patient preference, clinician treatment choices and guidelines development.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) standards [23] and PRISMA extension for literature searches [24] (Additional file 1). Our protocol was registered in PROSPERO (registration number CRD42020190582).

Data sources and searches

Two researchers (S.Q.L.and W.Z.J.) independently searched the following databases up to 3 May 2020: MEDLINE (via PubMed), Embase, Web of Science, The Cochrane Library, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI) and Wanfang Data [25]. We also searched clinical trial registry platforms (US National Institutes of Health Trials Register and WHO Clinical Trials Registry Platform), Google Scholar, and reference lists of retrieved articles to identify studies that may have been missed.

The search strategy was also peer reviewed by an external specialist. We systematically searched by combining the MeSH and free words. The keywords and terms in the MEDLINE included “sildenafil”, “Pulmonary Arterial Hypertension”, “PAH” and their derivatives. The details of search strategies can be found in the Additional file 2.

Inclusion and exclusion criteria

Types of studies

We included all randomized controlled trials (RCTs) and non-randomized studies of interventions (NRSIs) that compared effectiveness and safety of sildenafil (20mg/TID) with placebo, or comparing the combination of sildenafil (20mg/TID) and symptomatic treatment with symptomatic treatment alone. Considering that PAH is a rare disease and there maybe few studies, we also included multi-center RCTs and NRSIs involving Asian adult PAH patients. In vitro studies, animal experiments and basic researches were excluded. Duplicates, articles written in languages other than English or Chinese, conference abstracts were also excluded.

Types of participants

We included any Asian adult patient with a diagnosis of PAH who required medical treatment for their condition. We defined PAH as a mean PAP equal to or more than 25 mmHg by right-heart catheterisation according to accepted criteria [3,17–18], and included the following categories: (1) idiopathic PAH; (2) PAH with vasoreactivity; (3) heritable PAH; (4) drugs and toxins related PAH; (5) PAH associated with connective tissue disease (CTD), HIV, portal

hypertension, congenital heart disease (CHD) and schistosomiasis; (6) pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis.

Types of outcome measures

The primary outcomes were six-minute walk distance (6MWD), dyspnoea score on any scale, level of brain natriuretic peptide (BNP), change in WHO functional class, mean PAP, systemic arterial oxygen saturation and adverse events. The secondary outcomes included but not limited to haemodynamic parameters (right atrium pressure [RAP], PVR, cardiac index [CI]), quality of life, time to clinical worsening, incidence of clinical worsening and mortality.

Study selection

After eliminating duplicates, two researchers (S.Q.L.and W.Z.J.) independently screened the titles, abstracts, and full-texts of potentially relevant articles, using pre-defined criteria. The specific bibliographic software EndNote X9 was used. Discrepancies were discussed, or solved with a third researcher (Y.N.). All reasons for excluding ineligible studies were recorded. The process of study selection was documented using a PRISMA flow diagram [23].

Data extraction

Two researchers (S.Q.L.and W.Z.J.) extracted data independently with a pre-determined data collection form. Disagreements were resolved by discussion. We extracted the following data: (1) methods: first author, study design, study setting, number of study centres and location; (2) participants: sample, age, gender, diagnostic criteria, important baseline data, inclusion and exclusion criteria; (3) intervention: dose, mode of administration and control measures; (4) outcomes: primary and secondary outcomes as specified, type of scale used, time points collected (for dichotomous data, the number of events and total participants in per group; for continuous data, means, standard deviations (SD), and the number of total participants in per group); (5) characteristics of trial design as outlined in the “risk of bias assessment in included studies” section; (6) other: funding and conflicts of interest for trial authors.

Risk of bias assessment

Four researchers (S.Q.L., W.Z.J., Y.N. and M.Y.F.) assessed the risk of bias for included studies independently in pairs. Discrepancies were resolved by discussion. For RCTs, we used the Cochrane Risk-of-Bias assessment tool [26], and graded each bias as low risk, unclear risk (insufficient information to form a judgement) or high risk. For NRSIs, we used Risk of Bias In non-randomized Studies-of Interventions (ROBINS-I) tool [27], and graded each bias as low, moderate, serious, critical and no information.

Data analysis

We performed Meta-analysis of outcomes for which the data were sufficiently compatible. For dichotomous data, we calculated odds ratio (OR) with 95% confidence intervals (CI); for continuous data, we calculated mean difference (MD) or standardized mean difference (SMD) with 95% CI, depending on whether the same scale is used to measure an outcome. Analyses were performed by Review Manager 5.3 software. We used a fixed-effects model, and the level of statistical significance was set at $P < 0.05$ with two-sided. If both data from baseline and endpoint scores were available for continuous data, we used change from baseline scores. Missing data were obtained by graphical software or other means [28–29].

We quantified statistical heterogeneity using the I^2 statistic, and considered that a 0% value indicated no heterogeneity, and higher values of 25%, 50%, and 75% represented increasing levels of low, moderate, and high, respectively. An I^2 less than 50% was considered as acceptable. If we detected high heterogeneity, we conducted

subgroup or sensitivity analysis, then random-effects model would be used [28, 30]. Where sufficient studies were present, we planned to assess publication bias by examining the symmetry of the funnel plot [28].

Results

Results of the search

We identified 9,806 references from the databases, and three records from additional searches. A total of 2,919 records were excluded as duplicates. After screening for titles and abstracts, we selected 94 studies for full-text review. Finally, a total of eight studies (five RCTs and three NRSIs) with 364 patients were included (see Fig. 1) [22,31–37].

Study and patient characteristics

Characteristics of included studies and patients are illustrated in Table 1. These studies were published between 2005 and 2015 and the sample size ranged from 21 to 139, of which, sildenafil was all administered orally with 20mg/TID. Most studies recruited participants with WHO functional class II and III. The etiologies of majority were idiopathic PAH, PAH associated with CTD and CHD. Included studies were conducted for 20 weeks on average.

Table 1
Baseline characteristics of included studies

Study ID	Study Type	Etiology (%)	Sample	Age(T/C)*	WHO functional class (%)				Follow up	Outcomes †
					I	II	III	IV		
Galiè 2005[31]	RCT	IPAH (61.87) CTD-PAH (30.94) CHD-PAH (7.19)	139	47 ± 14/49 ± 17	0.72	40.29	53.24	5.76	12W	□□□□□□□□□□ □□□□
Pepke-Zaba 2008[32]	RCT	NR	NR	NR	NR				12W	□□
Xu 2009[22]	NRSI	IPAH (66.67) CHD-PAH (20.00) CTD-PAH (13.33)	60	33.56 ± 14.12	0	43.33	53.34	3.33	16W	□□□□□□□□□□□□
Zhang 2011[33]	NRSI	CHD-PAH (100.00)	84	28 ± 9	0	52	39	8	12M	□□□□□□□□□□□□□□
Satoh 2011[34]	NRSI	IPAH (28.57) FPAH (23.81) APAH (47.62%)	21	47.1 ± 14.7	0	31.80	36.60	0	12W	□□□□□□□□□□□□
Wirostko 2012[35]	RCT	IPAH (61.87) CTD-PAH (30.94) CHD-PAH (7.19)	139	47 ± 14/49 ± 17	0.72	40.29	53.24	5.76	12W	□
Xu 2013[36]	RCT	NR	42	33.7 ± 14.3	NR				3M	□□□

Study ID	Study Type	Etiology (%)	Sample	Age(T/C)*	WHO functional class (%)				Follow up	Outcomes †
					I	II	III	IV		
Webb 2015[37]	RCT	IPAH (61.87) CTD-PAH (30.94) CHD-PAH (7.19)	139	47 ± 14/49 ± 17	0.72	40.29	53.24	5.76	12W	□

* Ages were reported as mean ± standard deviation.

† **Outcomes**: □Six-minute walk distance□Mean pulmonary artery pressure □WHO functional class□Level of brain natriuretic peptide□Dyspnoea score on Borg scale □Systemic arterial oxygen saturation □Adverse events □Mortality □Clinical worsening □Pulmonary vascular resistance □Cardiac index □ Right atrial pressure □ Quality of life □ Renal function □ Hospitalization □ Heart rate □ Pulmonary capillary wedge pressure □ Systemic vascular resistance index.

Abbreviation: RCT: Randomized Controlled Trial; NRSI: Non randomized Studies of Interventions; IPAH: Idiopathic Pulmonary Arterial Hypertension; CTD-PAH: Connective-Tissue Disease-Pulmonary Arterial Hypertension; CHD-PAH: Congenital Heart Disease- Pulmonary Arterial Hypertension; FPAH: Familial Pulmonary Arterial Hypertension; APAH: Associated with Pulmonary Arterial Hypertension; NR: Not Reported; W: Week; M: Month; T: Treatment; C: Control.

Risk of bias in included studies

For the five RCTs, we assessed random sequence generation, allocation concealment, blinding of participants and personnel and blinding of outcomes as low risk for only one study [35]. Galiè 2005[31], Pepke-Zaba 2008 [32], Xu 2013 [36] and Webb 2015[37] were at unclear risk, as they did not report the relevant methods. As for incomplete outcome data and selective reporting, all studies were assessed as low risk [31–32,35–37]. In the domain of other potential sources of bias, four studies [31–32, 35, 37] received funding from Pfizer and one contained error in data [36], so we rated all of them at high risk. For the three NRSIs, two [22, 33] were assessed as moderate risk and one [34] was serious risk. Details can be found in Additional file 3.

Clinical outcomes

6MWD

Five studies [22,31–34] (two RCTs and three NRSIs) evaluated 6MWD. Two studies [31–32] which reported only *P* values and 99% CI with significant improvement in 6MWD were excluded from the pooled analysis. In comparison with symptomatic treatment, sildenafil yielded greater improvement in 6MWD (MD = 68.3 meters, 95% CI 48.85 to 87.76). There was no heterogeneity between trials (I^2 = 0%, Fig. 2).

Dyspnoea score

Three studies [31,33–34] (one RCT and two NRSIs) evaluated dyspnoea score based on Borg scale. One study [31] only reported the change from baseline did not differ significantly from that in the placebo group with no other data available was excluded from the pooled analysis. When comparing to symptomatic treatment, sildenafil was associated with a significant decrease (reflecting improvement) in dyspnoea score (MD=-0.99 points, 95% CI -1.45 to -0.53). There was no heterogeneity between trials (I^2 = 0%, Fig. 3).

WHO functional class

Four studies [22,31,33–34] (one RCT and three NRSIs) evaluated WHO functional class. We described them in narrative form because most data were missing for Meta-analysis (Table 2). In general, when compared to placebo or symptomatic treatment, the total number of patients with WHO class III and IV in group of sildenafil showed an overall trend of decline (reflecting improvement).

Table 2

Improvement in WHO functional class

Study ID	Study Type	Placebo/Before	Sildenafil /After	P
Galiè 2005[31]	RCT	patients with an improvement of at least one functional class were 7 percent	patients with an improvement of at least one functional class were 28 percent	0.003
Xu 2009[22]	NRSI	I: 0 II: 26 III: 32 IV: 2	I: 6 II: 42 III: 12 IV: 0	NR*
Zhang 2011[33]	NRSI	I: 0 II: 44 III: 33 IV: 7	I: 7 II: 68 III: 8 IV: 1	< 0.001
Satoh 2011[34]	NRSI	I: 0 II: 7 III: 14 IV: 0	I: 1 II: 11 III: 9 IV: 0	NR
Abbreviation: RCT: Randomized Controlled Trial; NRSI: Non randomized Studies of Interventions; NR: Not Reported.				

Level of BNP

Three studies [22, 34, 36] (one RCT and two NRSIs) evaluated the level of BNP. One study [34] that only reported plasma BNP decreased from baseline was excluded from the pooled analysis. When compared to placebo or symptomatic treatment, sildenafil was associated with a decrease in level of BNP (MD=-86.16 pg /mL, 95% CI -103.39 to -68.93). There was not important heterogeneity between trials (I^2 = 14%, Fig. 4).

Mean PAP

Four studies [22, 31, 33, 36] (two RCTs and two NRSIs) evaluated the mean PAP. When compared to placebo, sildenafil was associated with a greater reduction in mean PAP (MD=-4.13 mmHg, 95% CI -6.52 to -1.74). There was considerable heterogeneity between trials (I^2 = 89%, Fig. 5). We conducted sensitivity analysis by excluding one study

[36] which involved surgery with low-quality. Results showed that sildenafil reduced mean PAP (MD=-2.70 mmHg, 95% CI -5.26 to -0.14). When compared to symptomatic treatment, sildenafil could reduce the mean PAP with no statistically significant difference found (MD=-4.90 mmHg, 95% CI -10.36 to 0.55, Fig. 6).

Systemic arterial oxygen saturation

Two NRSIs [22, 33] evaluated the systemic arterial oxygen saturation. When compared with symptomatic treatment, patients received sildenafil had higher level of systemic arterial oxygen saturation (MD = 2.48 %, 95% CI 1.26 to 3.71). There was no heterogeneity between trials (I^2 = 0%, Fig. 7).

Haemodynamic parameters other than mean PAP

Two studies [22, 31] (one RCT and one NRSI) evaluated PVR. When compared to placebo, sildenafil was associated with a greater reduction in PVR (MD=-171.00 dyn·sec·cm-5, 95% CI -311.49 to -30.51). When compared to symptomatic treatment, sildenafil could decrease PVR with no statistically significant difference (MD=-1.02 Wood Units, 95% CI -3.73 to 1.69).

Four studies [22,31,33–34] (one RCT and three NRSIs) evaluated RAP. When compared to symptomatic treatment, the results showed that sildenafil therapy decreased RAP (MD=-1.17 mm Hg, 95% CI -2.14 to -0.20). When compared to placebo, reduction in RAP was also observed with no statistically significant difference found (MD=-1.10 mm Hg, 95% CI -2.73 to 0.53).

Three studies [22, 31, 34] (one RCT and two NRSIs) evaluated CI. When compared to symptomatic treatment, the use of sildenafil improved the level of CI (MD = 0.35 L/(min·m^2), 95% CI 0.07 to 0.63). While no statistically significant difference was observed in the level of CI (MD = 0.23 L/(min·m^2), 95% CI -0.18 to 0.64) between sildenafil and placebo.

Adverse events

Five studies [22, 31, 33–34, 36] (two RCTs and three NRSIs) evaluated adverse events. One study that reported adverse events with no data available was excluded from the pooled analysis [36]. When compared to symptomatic treatment or placebo, there was no statistically significant difference in the risk of headache, flushing, dyspepsia, diarrhea, limb pain, skin rash (Fig. 8).

No statistically significant difference was also observed in blood pressure (systolic and diastolic) and ocular safety (including change in intraocular pressure and risk of deterioration in visual acuity). In general, sildenafil was mild and well tolerated in most patients.

Long-term prognosis

Four studies reported outcomes related to long-term prognosis. Three studies [22, 31, 33] (one RCT and two NRSIs) evaluated mortality (OR 1.01, 95% CI 0.06 to 16.55) and incidence of clinical worsening (OR 3.36, 95% CI 0.19 to 60.54), when compared sildenafil to symptomatic treatment and placebo, no statistically significant difference was found.

Galiè 2005 [31] evaluated quality of life. There was a statistically significant improvement in SF-36 domains of physical functioning, general health and vitality for sildenafil treated participants when compared to placebo.

Statistically significant improvements were also observed in terms for current health status and utility index in the EQ-5D questionnaires. Results from Webb 2015 [37] showed that sildenafil treatment improved kidney function when compared to placebo, but the difference was not statistically significant.

In addition, there was no significant difference in hospitalization, heart rate, pulmonary capillary wedge pressure and systemic vascular resistance index when compared to placebo or symptomatic treatment.

Publication bias

Due to insufficient studies for each outcome, we were unable to evaluate publication bias.

Discussion

Our systematic review identified a total of eight studies. When compared to placebo or symptomatic treatment, use of sildenafil (20mg/TID) had a clear statistical and clinical benefit for PAH patients of Asian adults in terms of 6MWD, mean PAP, systemic arterial oxygen saturation, dyspnoea score on Borg scale, level of BNP and PVR. Regarding to the safety, clinicians should be aware of headache, flushing, dyspepsia, and diarrhea, which were usually relatively mild.

According to existing guidelines [3,17–19], PAH patients should be clearly diagnosed as soon as possible and establish treatment strategies on the basis of risk stratification. During this process, making full use of targeted drugs accounts for great importance. As one of five classes of drugs now available for PAH, PDE5 inhibitors included sildenafil, tadalafil and vardenafil [4,12–13]. Among these, both FDA and EMA recommended sildenafil be orally administered at a dose of 20 mg/TID. Although increasing evidence suggested sildenafil therapy is beneficial [21–22,39–42], the dose varies greatly. A Cochrane systematic review published in 2019 indicated that sildenafil had better therapeutic effect with lower incidence of adverse events when compared to placebo [16]. However, sildenafil in the included PAH trials was prescribed in eight hourly divided doses, with dosages ranging from 20 to 100 mg/TID [16].

In this study, we focused on 20 mg/TID, and included participants who were mainly idiopathic PAH, as well as CTD and CHD related PAH. The results on 6MWD, mean PAP, dyspnoea score, level of BNP were similar to those identified in other systematic reviews [16, 21–22, 39–42]. As an important indicator for severity evaluation and prognosis [43], previous studies have shown that there was a significant improvement in WHO functional class favouring sildenafil when comparing to placebo [16]. Our systematic review however demonstrated that four studies assessed this but with too much data missing to combine in a Meta-analysis. On the other hand, we identified gaps in the existing literature that limited our conclusions. Included studies focused less on long-term outcomes, and did not pay attention to pharmacoeconomics. When comparing to placebo, PAH participants treated with sildenafil have been proven to 23% less likely to die [16], but results from our study indicated only three studies analysed mortality with a non-statistically significant difference found, and only one study assessed quality of life. Further trials are needed to evaluate the effectiveness of sildenafil in dose of 20 mg/TID on long-term outcomes.

In terms of safety, one of the most frequent concerns during the use of PDE5 is the risk of hypotension [15]. Although we found no statistically significant difference in systolic and diastolic blood pressure when compared to symptomatic treatment or placebo, nitrates should not be used in combination with sildenafil, especially be prudent in patients with low systemic blood pressure or presyncope [4, 15].

Considering sildenafil has been poorly studied for the treatment of adult PAH patients in Asia, we also included Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study [31–32, 35, 37], a Pfizer-sponsored randomized trial. But

for the final included studies, the total sample size is still so small and risk of bias for methodology is high, especially in the domains of randomization, allocation concealment and blindness. Therefore, we put forward some suggestions for the further research: (1) conducting high-quality studies at the recommended dose of 20mg/TID; (2) trials should measure outcomes which are clinically relevant (e.g., mortality, quality of life and clinical worsening) so that long term effects can be established; (3) attach importance to the real-world data and evaluation of pharmacoeconomics.

This study is to our knowledge the first systematic review to summarize the evidence of sildenafil effectiveness and safety for patients with PAH at the recommended dose of 20mg/TID, which is of great importance for clinicians and patients. We focus on the Asian adult and included Chinese literatures to find research gaps. We also focus on multiple outcome measures (both short-term and long-term). This study has also several limitations. First, missing data for some outcomes and small participant samples may undermined the real effect of treatment. Second, we excluded studies other than English and Chinese, as well as conference abstract that cannot be obtained the full-text, some degree of publication bias may exist. Third, we found one study [36] in which PAP was measured by echocardiography, although it was not right cardiac catheterization, we included it and synthesized data in the final Meta-analysis.

Conclusions

Despite data comparing sildenafil in dose of 20mg/TID whilst on Asian adult patients with PAH were limited by the small number of included trials, our study provides conclusive evidence that sildenafil (20mg/TID) is effective and safe. Statistically significant improvements in exercise capacity, cardio-pulmonary function and haemodynamics have been observed with mild to moderate adverse reactions and good tolerance. We suggest future trials should be large sample, high-methodological quality and pay more attention to the long-term prognosis.

Abbreviations

BNP: Brain natriuretic peptide; CHD: Congenital heart disease; CI: Cardiac index; 95% CI: 95% confidence intervals; CTD: Connective tissue disease; MD: Mean difference; NRSI: Non-randomized studies of interventions; OR: Odds ratio; PAH: Pulmonary arterial hypertension; PAP: Pulmonary artery pressure; PH: Pulmonary hypertension; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; PVR: Pulmonary vascular resistance; RAP: Right atrium pressure; RCT: Randomized controlled trials; ROBINS-I: Non-randomized Studies-of Interventions; 6MWD: Six-minute walk distance; TID: Three times a day; WHO: World Health Organization.

Declarations

Availability of data and materials:

All data generated or analysed during this study are included in this published article.

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Contributions:

Y.H. designed the paper. S.Q.L. selected the literature, extracted data, carried out the statistical analysis, produced the tables and figures, and wrote the first edition of the paper. W.Z.J selected the literature and extracted data. S.Q.L., W.Z.J., Y.N. and M.Y.F all evaluated the methodological quality of included trials. Y.L.C. and Y.H were consulted and helped to revise the manuscript. All authors contributed to the review and approval of the final manuscript.

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Figures

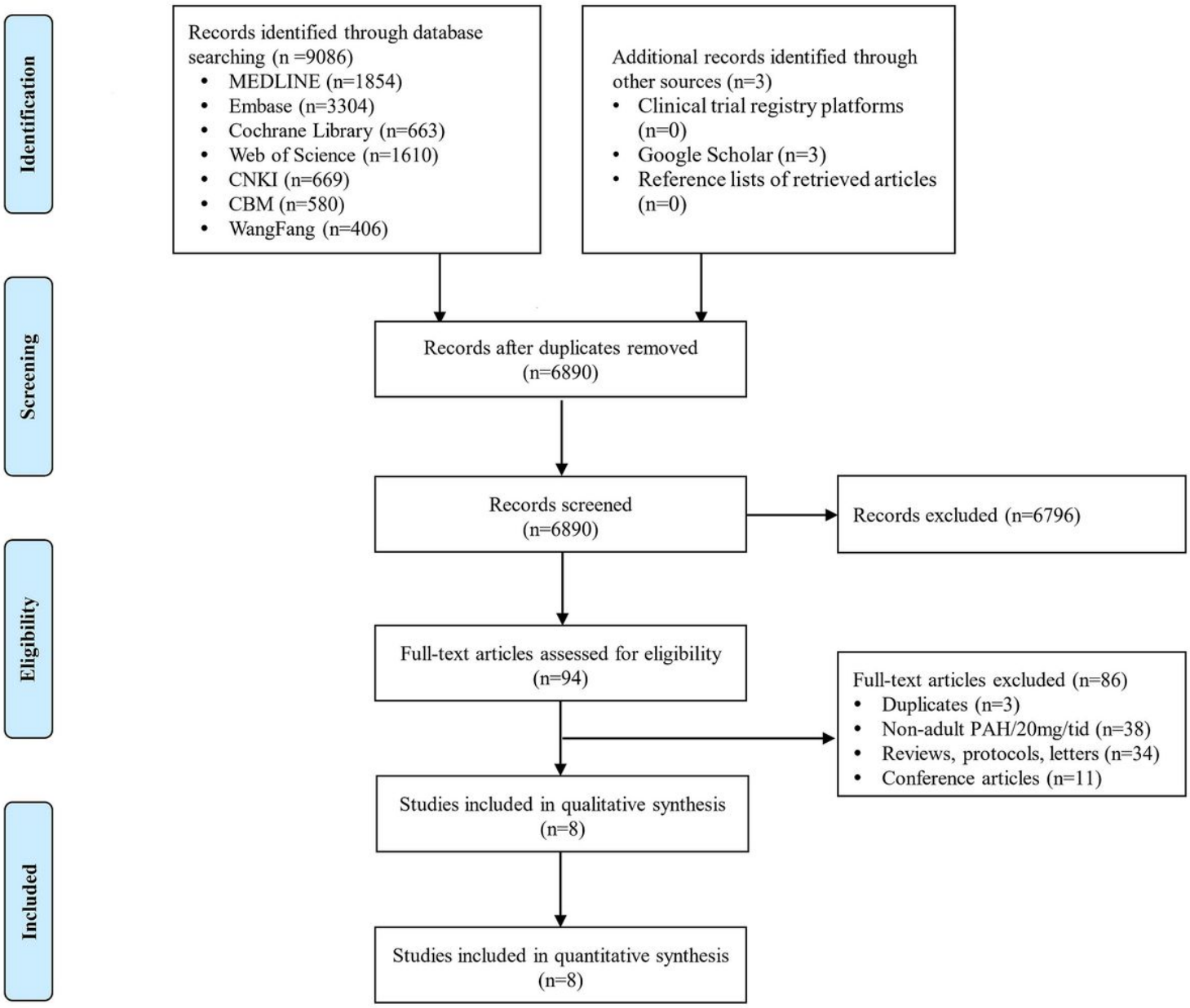

Figure 1

Flow diagram of the literature search

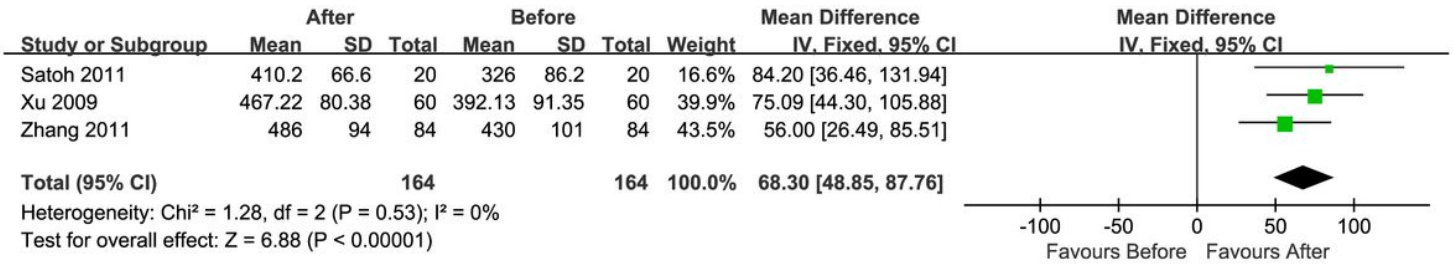

Figure 2

Forest plot of 6MWD comparing sildenafil with symptomatic treatment

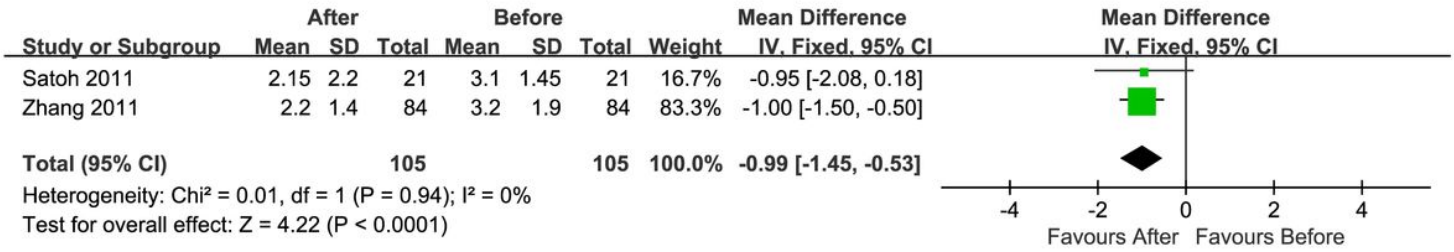

Figure 3

Forest plot of dyspnoea score comparing sildenafil with symptomatic treatment

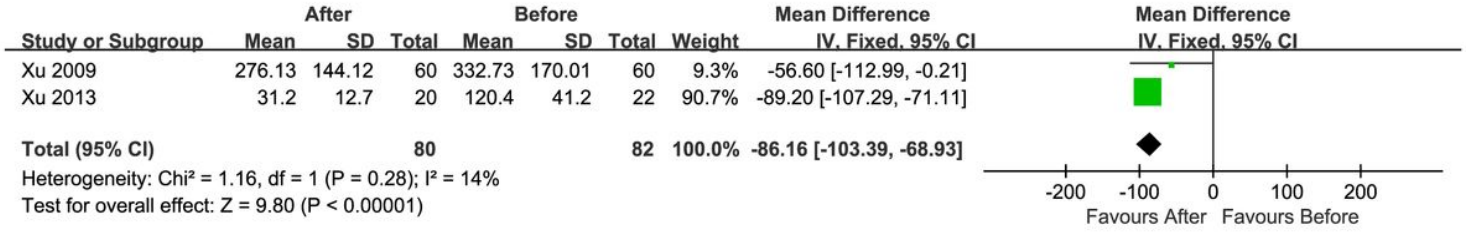

Figure 4

Forest plot of BNP comparing sildenafil with placebo or symptomatic treatment

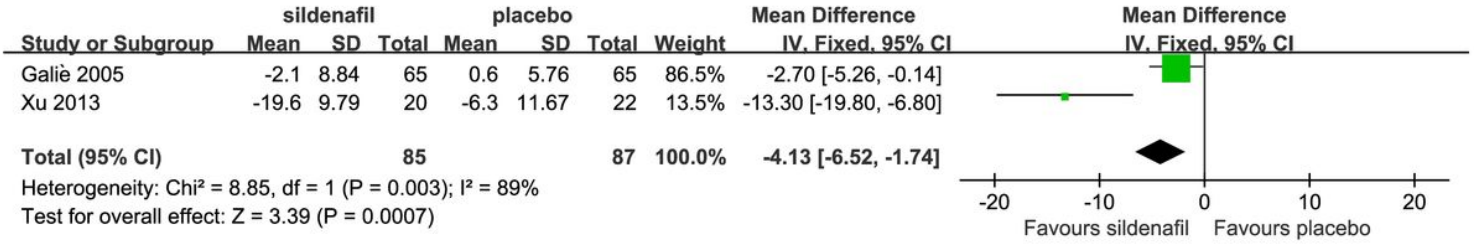

Figure 5

Forest plot of reduction in mean PAP comparing sildenafil with placebo

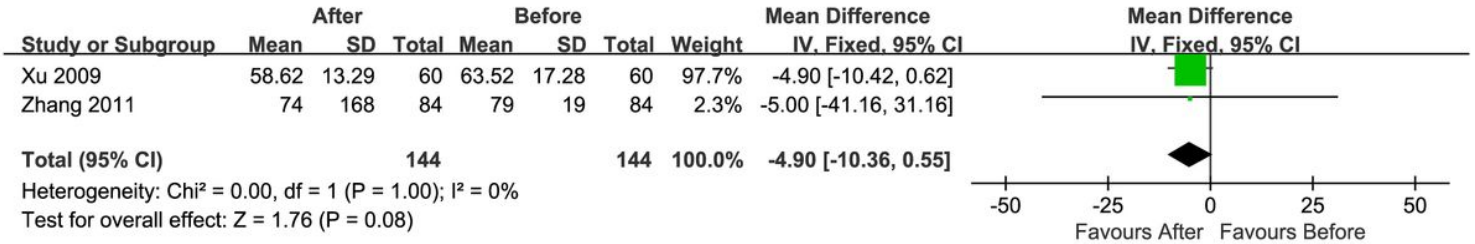

Figure 6

Forest plot of mean PAP comparing sildenafil with symptomatic treatment

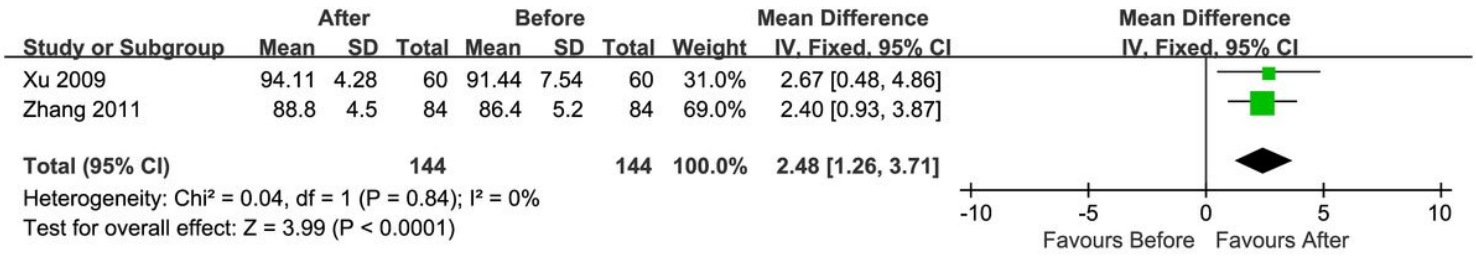

Figure 7

Forest plot of systemic arterial oxygen saturation comparing sildenafil with symptomatic treatment

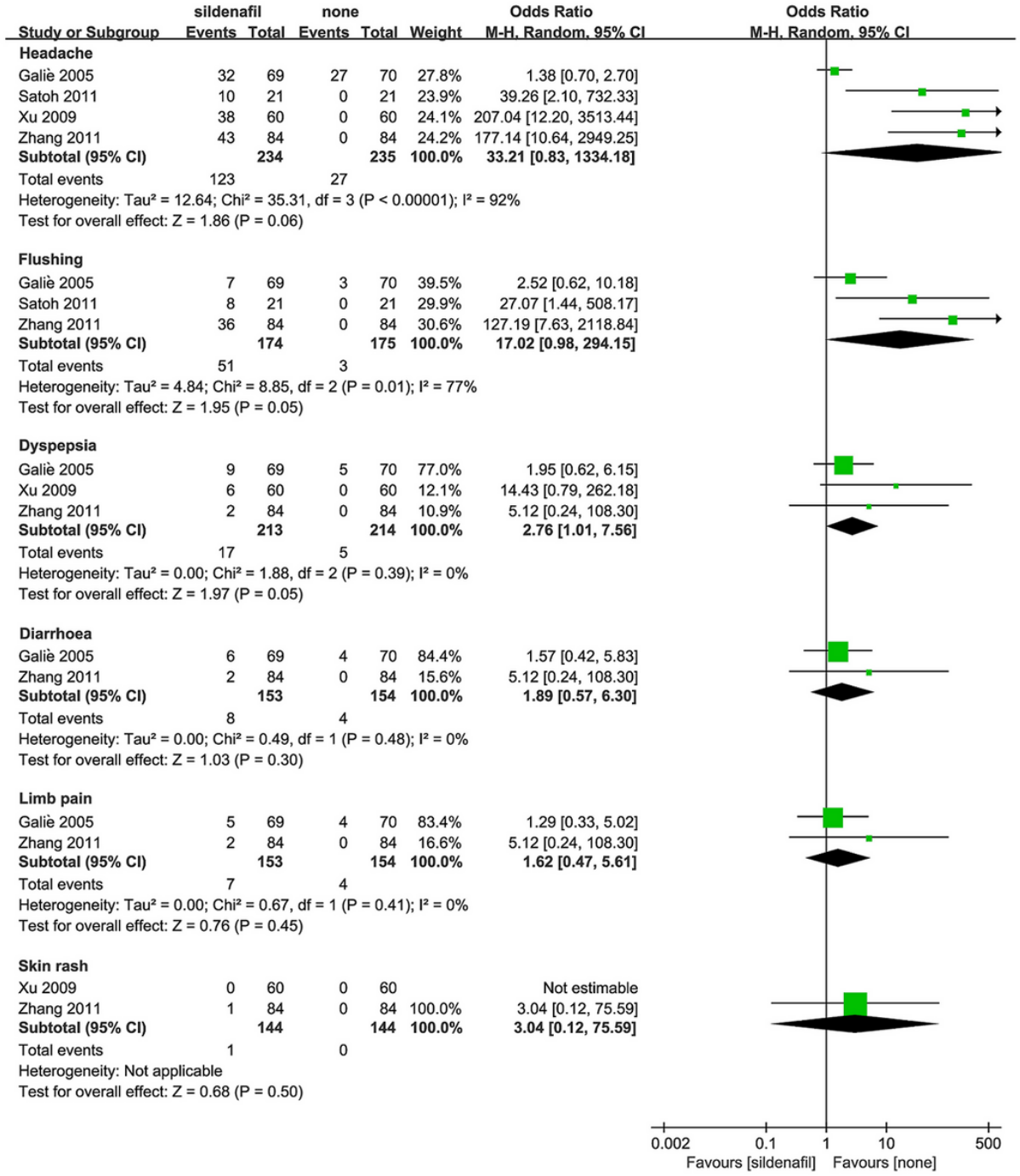

Figure 8

Forest plot of adverse events

Supplementary Files

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- Additionalfile2forSearchStrategies.docx
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