Systematic review and cost-effectiveness of bosentan and sildenafil as therapeutic drugs for pediatric pulmonary arterial hypertension

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Abstract

Background:Pulmonary arterial hypertension (PAH) is a rare disease in children, with significant mortality. Because of the limited research on pediatric PAH, firstly systematic review of related drugs is conducted,and then economic evaluation of PAH drug treatment programs is conducted, which to provide a reference for the choice of more cost-effective treatment options. Methods: The search includes electronic databases such as Pubmed, ScienceDirect, Embase. Through inclusion and exclusion criteria, screen high-quality randomized controlled trials. We used TreeAge Pro 2011 software to construct the markov model, that to simulate the total medical cost and quality-adjusted life years (QALYs), and to calculate the incremental cost-effectiveness ratio (ICER). Sensitivity analysis of transfer probability, utility and cost was carried out. Results: Incorporate two studies that meet the criteria, one compared the therapeutic effects of bosentan and placebo on pediatric PAH, the other compared therapeutic effects of sildenafil and placebo on pediatric PAH, both articles were of good quality. Compared with the sildenafil group (3.38QALYs and $161120.14),the QALY of the bosentan treatment group (3.33QALYs and $257411.29) was reduced by 0.05,and the cost increased by $96291.15.The estimated improvement to quality of life and reduced costs result in an estimate of economic dominance for sildenafil over bosentan. This dominant result persisted probabilistic analyses. Conclusions: Based on this model,a more cost-effective treatment drug for PAH in children is sildenafil.

1Introduction

Pulmonary arterial hypertension (PAH) is a rare disease in children that is associated with significant morbidity and mortality.The disease is characterized by progressive pulmonary vascular functional and structural changes resulting in increased pulmonary vascular resistance and eventual right heart failure and death[1]. The annual incidence of pulmonary arterial hypertension in New Zealand averages 3.0 cases per million children, the most common cause is idiopathic pulmonary arterial hypertension (IPAH) and heart-related pulmonary arterial hypertension (PAH-CHD),with an incidence rate of 0.7 and 2.2 cases per million respectively[2]. If the targeted treatment is not performed,the prognosis of pulmonary arterial hypertension in children is extremely poor[3].In the NIH (National Institutes of Health) registry study, the average untreated survival of children diagnosed with idiopathic pulmonary arterial hypertension was 10 months, and the adulthood was 2.8 years[4]. In addition,the quality of life of children with pulmonary arterial hypertension is severely impaired, often resulting in social isolation due to restrictions on their ability to perform daily activities[5].Thus improving survival, stabilizing disease and improving quality of life are key objectives of any treatment strategy for PAH patients.

The pathogenesis of this disease is not fully understood, but includes vasoconstriction,inflammation,structural remodeling,in situ thrombosis,and vascular active media imbalance[6-8].

In order to improve the balance of these mediators,the current development of pulmonary arterial hypertension dilation and anti-proliferation therapy has been promoted[1].According to the evidence-based guidelines for children[9], PAH targeted therapy drugs mainly include endothelin receptor (ET-1) antagonist,5-type phosphodiesterase (PDE-5) inhibitor and prostacyclin analogue,with the recommended grade B. In recent years, randomized clinical trials of bosentan and sildenafil have been conducted, showing that both have good efficacy in paediatric pulmonary arterial hypertension and are first-line oral drugs for paediatric pulmonary arterial hypertension. Bosentan is an oral non-selective endothelin receptor antagonist with dual antagonism of ETA and ETB,which acts to dilate blood vessels,improve hemodynamics and enhance exercise capacity[10].Sildenafil is a drug that is orally active and selectively inhibits 5-type phosphodiesterase,producing vasodilation and antiproliferative effects through the nitric oxide cGMP pathway in the pulmonary vasculature[11].Calcium channel blockers are used as early-stage drugs,and the recommended grade is also grade B.Traditional treatments such as diuretics,digitalis, and anticoagulants are recommended at grade C, mainly for expert opinions or case studies.The current guidelines for the treatment of pediatric pulmonary arterial hypertension are based almost entirely on adult research experience and data,and some drugs have not been formally approved for use in children[12]. Due to the small number of data in pediatric clinical trials, this study will search for relevant drug therapy literature on pediatric PAH with a grade B of evidence,and conduct systematic reviews to obtain valid data.

Present,the price of drugs for treating pulmonary arterial hypertension is relatively expensive, if used in PAH patients'families, may cause a high economic burden.This study evaluated the economics of medication for PAH in children; provided a reference for patients to choose a more cost-effective treatment.

2 Materials and Methods

2.1 Search Strategy

Pubmed, Embase, ScienceDirect and other databases were searched by two independent reviewers, with the English index word “bosentan”, “ambrisentan”, “sildenafil”, “tadalafil”, “epoprostenol”, “iloprost”, “treprostinil”, “Calcium channel blocker”, “digoxin”, “diuretics”, “warfarin”, “pediatric pulmonary arterial hypertension”. The term of retrieval for all databases is from the establishment of the database to December 2019, and the combined search of MeSH subject words and free words is adopted. These drugs were selected according to the US 2015+AHA/ATS guidelines[9]. The inclusion criteria for the literature are: 1) pediatric pulmonary arterial hypertension patients,meeting the 2015+AHA/ATS guidelines:classification and diagnostic criteria for pulmonary hypertension in children; 2) all domestic and foreign published or to be published literature related to clinical studies on the treatment PAH of children with bosentan, ambrisentan, sildenafil, tadalafil, prostacyclin analogues (including iprostol, iloprost and triprost), calcium channel blockers, digoxin, diuretics and warfarin, only in English; 3) randomized controlled trials; 4) The outcome indicator must include at least one of the WHO functional grading change or the six-minute walk test data. In addition, all relevant references, trials, review articles, editorials, and conference summaries are retrieved. Exclusion criteria are: 1) summary of the review conference, letter, comment articles, etc; 2) non-randomized controlled trials; 3) animal experimental study; 4) research in addition to english; 5) republished studies.

2.2 Quality Assessment and Data Extraction

All quality assessments and data extractions are performed independently by two reviewers. If an inconsistent decision is encountered, the third party will participate in the discussion and arbitration[13]. The evaluation included the following:random sequence generation, allocation concealment, blinding for participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. In the assessment,each item is judged as a result, either "low risk" (+) or "unclear" (?) or "high risk" (-).The extracted data included the author, the year of publication, the number of research centers, the number of patients, the age of the patient, the clinical cause, the study follow-up time, and the study intervention/control measures.

2.3 Model Structure

Building a Markov model for the treatment of pediatric PAH using TreeAge Pro 2011 software.To evaluate the total cost of treatment and health outcomes of patients under two treatment regimens from a healthcare system research perspective.patients

are classified as grade I, II, III, and IV pulmonary arterial hypertension functional levels, as defined by the NYHA cardiac function classification revised by the World Health Organization (WHO)[14]. The patient was diagnosed as "II-III" PAH at the time of enrollment. For each subsequent 3-months cycle, patients may transition from II-III to I, from II-III to IV, or remain in their current state(Figure 1), the data to populate these health states were taken directly from the randomized trial data. The assumptions that exist in the model are:the transfer of patients from grade II-III to other states is one-way, and there will be not transfer between states. For example, patients who transition from the initial state to level I will not reversely move to level II-III, nor will shift to level IV or death. Since the treatment cycle is 3 months for most clinical trials, this selection is consistent with the clinical practice guidelines, which states that this period is the predictive period of long-term treatment response[15]. Finally runs 20 Cycles (five years in total). We estimate the impact of initial treatment for pulmonary arterial hypertension by quality-adjusted life years (QALYs) and costs, then use these values to calculate incremental cost-effectiveness ratios (ICERs) for cost-effective analysis.

2.4 Model parameters

2.4.1 Transition probability

The probability of death in children with PAH is alculated by using RStudio software to simulate the survival curve, based on key clinical trial data from two drugs and placebo[16, 17]. Its calculation formula is P=1-$\exp(-\lambda(t+1)^{\Upsilon}+\lambda t^{\Upsilon})$. The transition probability between states is calculated according to the ratio of the number of cases, in which the children are assigned from the initial state "II-III" level to the I, II, III and IV levels after three months of treatment.The transition probability between each health state is shown in Table 1.

2.4.2 Utility Values

We estimated the utility of children based on the severity of pulmonary arterial hypertension. The utility of each functional level was from a published study by Keogh and colleagues who used SF-36 to evaluate the efficacy of 177 Australian PAH patients[18]. In this study, the utility value of patients decreased as the increase of pulmonary arterial hypertension severity, as shown in Table 1. Patients who were eventually retained at grade II-III were assumed to have an effect value that was the average of the utility values of FCII and FCIII.

2.4.3 Cost Variables

The costs in the model include drug prices,ongoing treatment, adverse reactions, and costs associated with caring for the disease, as shown in Table 1. According to the US FDA drug label, the dose of bosentan is based on the weight of the child, weight: 4-8 kg, 16mg(b.i.d); 8-16kg, 32mg(b.i.d); 16-24kg, 48mg(b.i.d); 24-40kg, 64mg(b.i.d)[19]. In the included clinical trial literature FUTURE-2[16]of bosentan, the average weight of the children was 22.3±8.0kg, so the dose of bosentan in this study was set to 48mg/time(b.i.d). The dosage of sildenafil in PAH children in the US FDA drug label is not clear[20].According to the guidelines[9], weight<20kg, 10mg(t.i.d);>20kg, 20mg (t.i.d). A sildenafil randomized clinical trial conducted by Barst2012[18]et al, included in this study, showed that children with a weight of>20kg accounted for a larger proportion, and the final dose was set to 20mg(t.i.d) by referring to the average weight of children with bosentan. In order to calculate the cost of the drug,the specifications of bosentan tablets used were 125mg×60 tablets/box and sildenafil tablets were 20mg×90 tablets/box[20],The market price of bosentan tablets with a specification of 125mg/tablet and a specification of 62.5mg/piece is the same, out of economic consideration, choose 125mg/tablet of bosentan tablets for splitting, and take only one tablet per day. The cost of continuous treatment of the drug is related to the FC grade, according to a recent UK study, the cost of continuous treatment for patients with stage II-III and IV pulmonary arteria hypertension is described, including gene-

ral practitioner visits,specialist visits, nurse visits, hospitalizations, emergency room visits and therapeutic procedures (echocardiograph and blood work) and so on[22]. It is assumed that children at FC IV level during treatment need to receive long-term supportive care. As bosentan treatment can lead to elevated liver enzyme levels, which may lead to liver damage[16], so liver function examination should be conducted every three months during the treatment[23]. Children in sildenafil group did not have such adverse reactions,so there is no need to bear this cost.

2.5 Sensitivity analysis

This study assessed the impact of parameter uncertainty on cost-effective analysis by single factor sensitivity analysis and probability sensitivity analysis (PSA).We performed a single factor sensitivity analysis to test the uncertainty of each individual parameter (such as discount rate,transition probability,utility,cost,etc). The transition probability uses a range of 20% up and down the baseline value, the utility value uses the baseline value to float up and down by 10%, the various expenses is 25% above and below the fluctuation range, then the discount rate ranges from 0 to 8%. The effect of a single parameter on the model results is presented using a tornado graph. Probabilistic sensitivity analysis is based on the distribution assumptions of different model parameters,and estimates the total impact of uncertainty on the model, the results of the PSA are represented by a cost-effectiveness acceptance curve indicating the probability of cost-effectiveness for each treatment regimen under the different willingness to pay (WTP) for each QALY obtained.

The adopted thresholds in this study refer to WHO recommendations. If ICER<1 times per capita GDP, the increased cost is completely worth it. 1 times per capita GDP<ICER<3 times per capita GDP,the increased cost is acceptable; ICER>3 times per capita GDP, the increased cost is not worth[26]. In 2018, the U.S. per capita GDP was $6.2641, three times GDP per capita is $18.7923[27].

3 results

3.1 Literature search results

The detailed steps of literature screening are shown in Fig.2, Table 2 shows the basic features of the included literature. Based on systematic literature review, the only two relevant studies that met the inclusion criteria were a phase III clinical trial reported by Berger RM et al. for bosentan[16], and the study conducted by Berger RM et al. for sildenafil[17].

Two of the included literatures had low risk in the integrity of the outcome data and the results of the selective reporting study in the quality evaluation. One document did not clarify whether or not the allocation was hidden and did not indicate whether blinding was used. Neither of the two literatures can determine whether the outcome indicators will be affected by blinded deletions,the risks shown in these studies are unclear. The overall risk of bias of the included studies and the judgment of various bias risk items of the included studies are shown in Fig.3 and Fig.4.

3.2 Cost-effectiveness analysis

The total cost and QALYs of the two treatment regimens are shown in Table 3. For patients with FCII-III PAH who received oral medication, the incremental cost of the bosentan group was $96291.15, and the incremental benefit was -0.05QALYs, which is a disadvantage scheme. Through incremental cost-effectiveness analysis, it is more cost-effective to use sildenafil treatment regimens in children with pulmonary hypertension.

3.3 Sensitivity analysis

3.3.1 Single factor sensitivity analysis

Single-factor sensitivity analysis was used to verify the stability of the results. Fig.5 is a tornado diagram, which shows the results of single-factor sensitivity analysis of the drugs bosentan and sildenafil for the treatment of PAH in children, each ICER that obtains QALY is most sensitive to the utility value of the children at the FCII-III, followed by the probability of metastasis to FCI in the sildenafil-treated group and

the probability of metastasis to the FCI in the bosentan-treated group. With $187923 as the threshold, the influence range of the most sensitive factors on ICER is still less than the threshold,and the result is not reversed.

3.3.2 Probability sensitivity analysis

In order to consider the influence of the distribution hypothesis with different model parameters on the results, the results of probability sensitivity analysis are obtained by Monte Carlo simulation 1000 times. The incremental cost-effective scatter plot for the bosentan treatment group and the sildenafil treatment group is shown in Fig.6. Most of the scatter points fall above the threshold line,therefore,the bosentan group treatment regimen is not as robust as the cost-effective outcome of the sildenafil treatment regimen. Fig.7 shows the cost-effectiveness acceptable curve for the two treatment regimens, which is always a high acceptance rate for the sildenafil treatment regimen, regardless of the amount of the willingness to pay. When the willingness to pay was the threshold,the acceptable rate for sildenafil was 98.2% and the acceptable rate for bosentan was 1.8%. Therefore,treatment with sildenafil is a more acceptable option when using $187,923 as a willingness to pay for a QALY.

4 Discussion

The recommendations for the treatment of pediatric pulmonary arterial hypertension in this study were followed by a consensus guide issued by the American Heart Association and the Thoracic Society[9]. As more and more pediatric PAH treatment options are available,more and more information is available to influence potential clinical endpoints, including quality of life.When deciding which option to use to treat pediatric pulmonary arterial hypertension,more factors need to be considered, including efficacy, different costs, adverse effects, and potential burdens from different routes of administration. In this study, two targeted oral drugs sildenafil and bosentan were compared, and the Markov model was used to simulate pulmonary arterial hypertension of children. The results showed that sildenafil was more economical and effective. This is consistent with the results of the economic evaluation of drug therapy for PAH in adults[23,24], sildenafil is always the most cost-effective treatment option,and the possibility of bosentan will be cost-effective is minimal.

According to the recommended drug treatment in the US 2015+AHA/ATS guidelines[9], Patients using calcium channel blockers (CCB) need to respond positively to acute vasoddilation tests (AVT), but most children with severe PAH do not respond to AVT, so CCB should be used with caution in children [28]. Epoprostenol is a very potent prostacyclin analogue,but its management is inconvenient and requires a central venous catheter (CVC) and must be stored refrigerated[29], resulting in a decline in quality of life and a decrease in its desirability as an initial treatment. Iloprost and treprostinil avoid the use of central venous catheters and are relatively safe in treatment.However, current studies on prostacyclin analogues are mostly retrospective studies and cohort studies, there is a lack of high-quality randomized clinical trials, so it was excluded during the literature screening process. Ambesentan and tadalafil have been shown to be effective,but data from randomized pediatric clinical trials are lacking. According to the subjects and clinical endpoints of this study, there were only two articles that met the criteria and were of high quality. Judging from the results of the systematic review, another 6 studies are randomized controlled trials, although 4 of that reported changes in the WHO functional classification index,only Berger RM et al[16] and Berger RM et alreported outcomes in sufficient detail to allow for inclusion in the cost-effectiveness analysis. Although Maiya et al[30] and Antonio et al[31] reported changes in the FC function classification of each patient, they were not included in the analysis due to the small number of patients and the inconsistent follow-up time.

This study has some limitations. First, lack of more complete functional class conversion data information. According to the data of clinical randomized controlled trials, for children in the initial stage of FCII-III, only data on improvement, deterioration, and death are subsequently provided, and more complete metastasis data similar to adult patients are lacking.Second, the number of randomized clinical trials of PAH drug therapy in children was small, and both included studies were limited by the number of patients and limited study time, the efficacy of the two groups of drugs is uncertain for the results finally, which cannot accurately

reflect the actual effect of bosentan and sildenafil.Third,there are certain side effects of liver damage after the treatment with bosentan.In this study, only the cost of liver function tests was considered,the effects caused by it are not analyzed. In addition,pulmonary arterial hypertension is a rare disease for children, and the cost of drugs tends to be higher due to the lower number of patients. According to a social welfare framework—value-based pricing (VBP), the question is that whether a higher WTP threshold should be applied to orphan drugs to allow higher prices to increase the return on investment of orphan drugs[32]. However, there is no relevant research support yet,and whether it needs to be improved remains to be explored.In a cost-effectiveness analysis study of adult pulmonary arterial hypertension in Thailand[33], the WHO recommended three times per capita GDP as the threshold, so this study also adopted the WHO recommended threshold.

All classes of drugs to treat PAH deserve a more rigorous evaluation about their cost-effectiveness. For evidence of the potential economics of the drug, we hope that there will be more randomized clinical trials to assess the long-term benefits of various drugs for the treatment of pediatric pulmonary arterial hypertension.

5 Conclusion

Through systematic review,only two articles were included, indicating that there are limited clinical randomized trials on drug therapy for children with PAH. By studying the two articles included, the results show that sildenafil is superior to bosentan and is less costly than bosentan. It is a more cost-effective drug treatment for children with PAH. However,the data used in this analysis are limited, so the results cannot be considered sufficient evidence for the development of general guidelines.

However, this study can provide a certain theoretical basis for the medication of children with pulmonary arterial hypertension and provide a reference for choosing more economical and effective drugs.

Conflict of interest

The authors declare that they have no competing interests.

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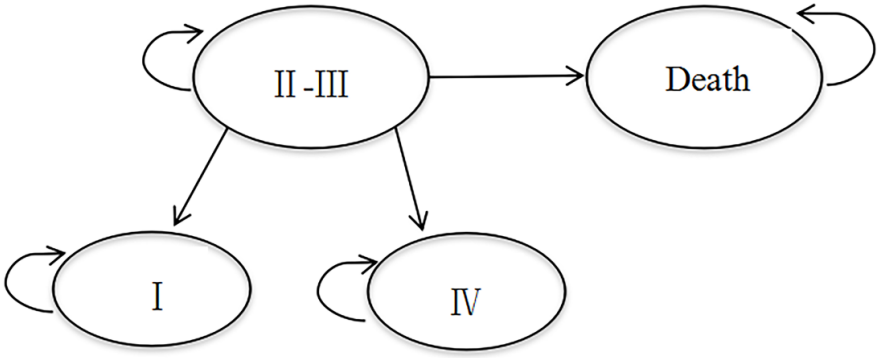

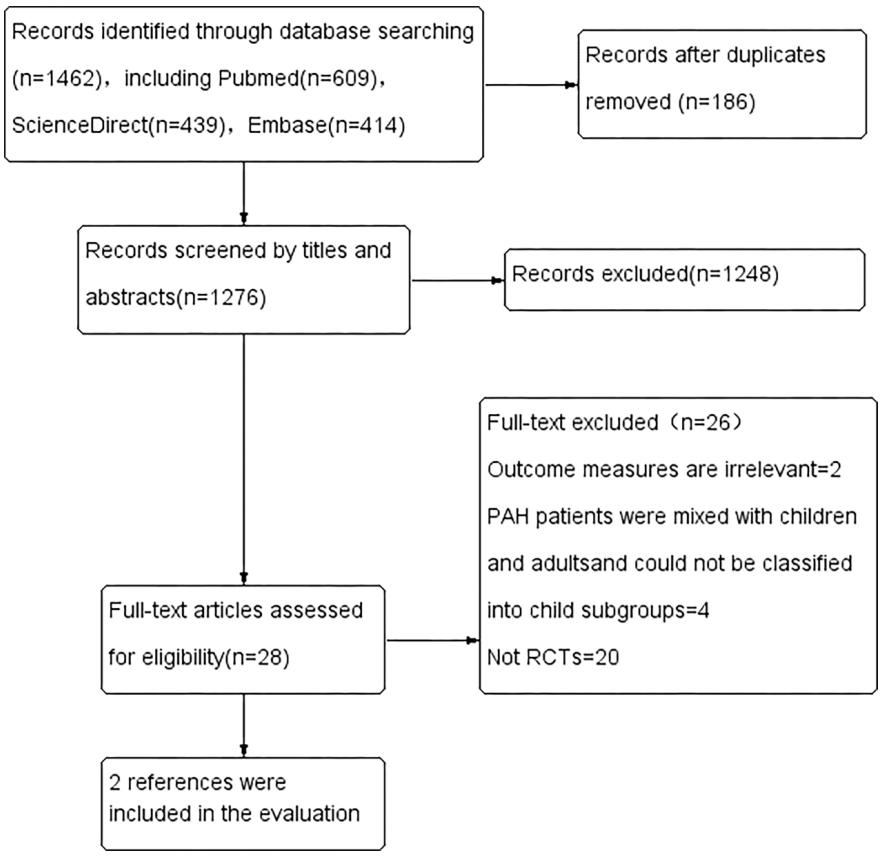

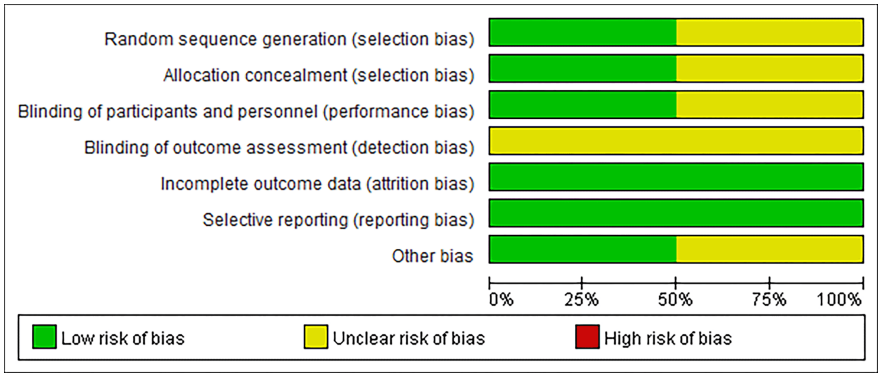

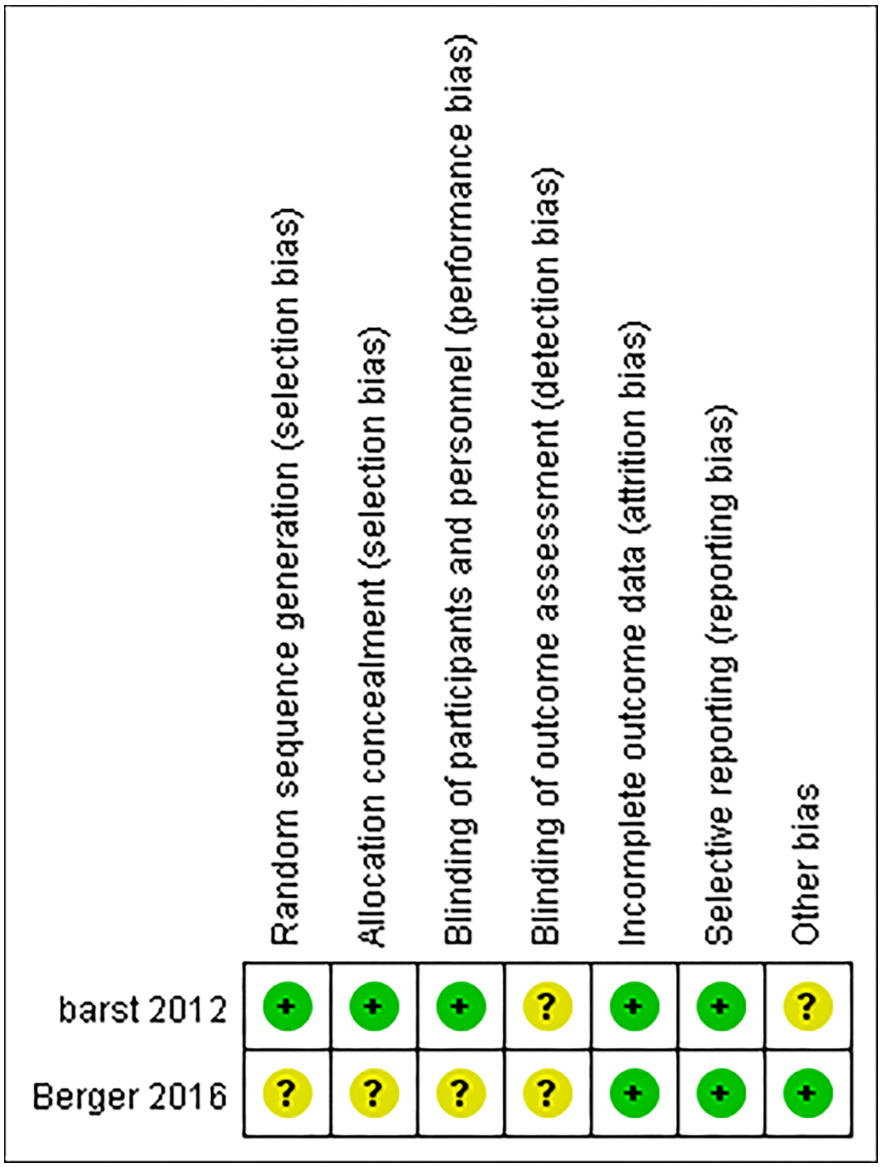

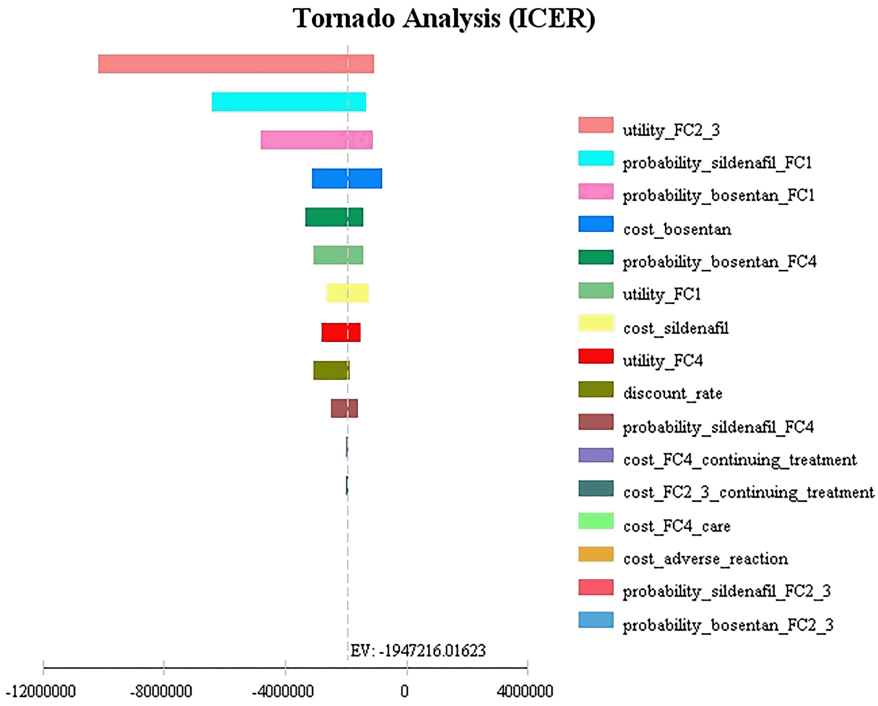

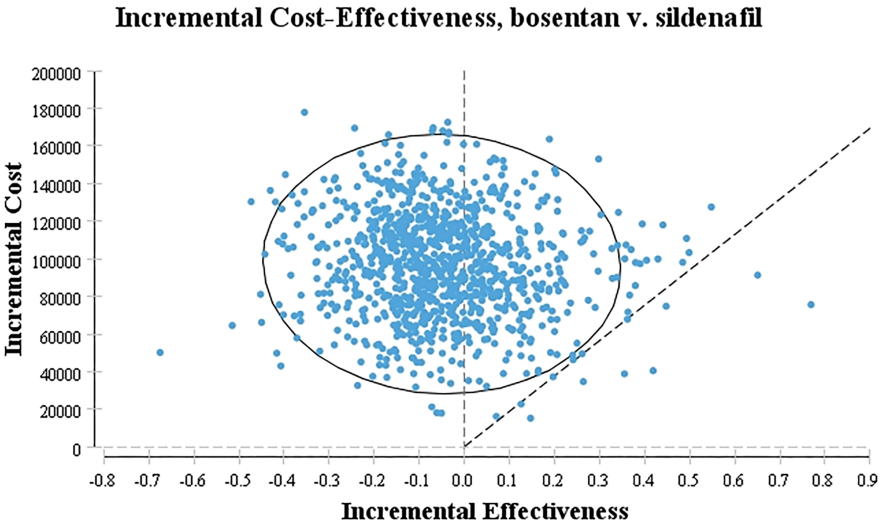

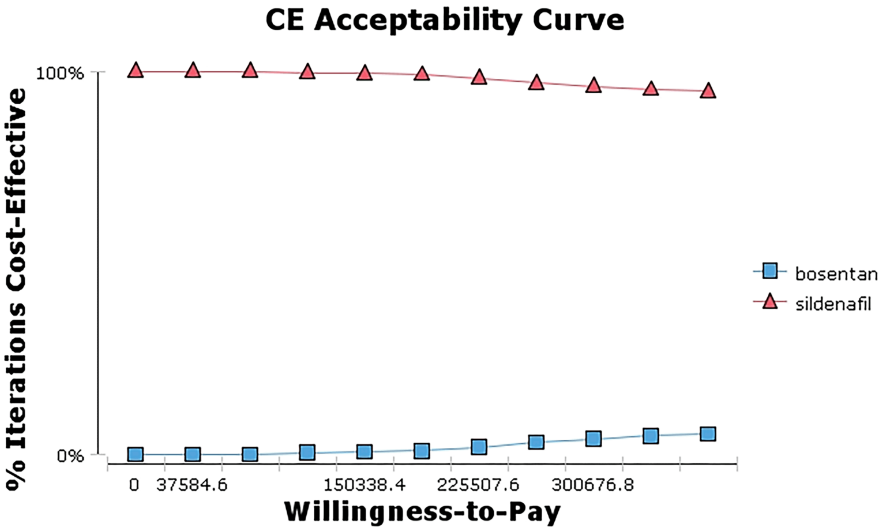

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