Systematic Review and Meta-Analysis

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The efficiency of endothelin receptor antagonist bosentan for pulmonary arterial hypertension associated with congenital heart disease

A systematic review and meta-analysis

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Abstract

Background: Oral bosentan has been widely applied in pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD). A systemic review and meta-analysis was conducted for a therapeutic evaluation of oral bosentan in both adult and pediatric patients with PAH-CHD. The acute responses and a long-term effect were respectively assessed in a comparison with baseline characteristics, and the improvement of exercise tolerance was analyzed.

Methods: PubMed, Medline, Embase, and Cochrane Central Register of clinical controlled trails or observational studies have been searched for a recording of bosentan effects on the PAH-CHD participants. For mortality and rate of adverse events (AEs), it was described in detail. Randomized-effects model or fixed-effects model was used to calculate different effective values with a sensitivity analysis.

Results: Seventeen studies were pooled in this review, and 3 studies enrolled the pediatric patients. Among all studies, 456 patients were diagnosed with PAH-CHD, and 91.7% were treated with oral bosentan. With a term less than 6 months of bosentan therapy, there existed a significant improvement in 6-minute walk distance (6MWD) and the World Health Organization functional class (WHO-FC), but no such differences in Borg dyspnea index scores (BDIs) and the resting oxygen saturation (SpO_2). Although with a prolonged treatment, not only 6MWD and FC, but also the resting SpO_2 and heart rate were changed for a better exercise capability. Additionally, compared with the basic cardiopulmonary hemodynamics, it showed a statistically significant difference in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance index (PVRi). Although a limitation of pooled studies with comparative outcomes of different terms, outcomes presented a lower WHO-FC which contributes to a success in a prolonged treatment.

Conclusions: Bosentan in PAH-CHD is well established and still requires clinical trials for an identification of its efficiency on CHD patients for an optimized period lessening a serious complication and the common AEs.

Abbreviations: AE = adverse event, CHD = congenital heart disease, CI = confidence interval, ERA = endothelin receptor antagonist, ES = Eisenmenger syndrome, ET = endothelin, FC = functional class, mPAP = mean pulmonary artery pressure, 6MWD = 6-minute walk distance, PAH = pulmonary arterial hypertension, PCWP = pulmonary capillary wedge pressure, PVRi = pulmonary vascular resistance index, RCT = randomized controlled trail, SMD = standardized mean differences.

Keywords: bosentan, congenital heart disease, exercise capacity, hemodynamic parameters, pulmonary arterial hypertension

Editor: Yan Li.

H-YK and Y-HW contributed equally to this work.

Authorship: H-YK and Y-HW: study design, literature search, systematic review and data collection, statistical analysis, interpretation of results, and preparation of the manuscript; Q-JY, JT, and CW: a contribution to critical review of the manuscript; T-WL: principal investigator, study design, statistical analysis, and an assessment of all results; H-YK, Y-HW, Q-JY, JT, CW, and T-WL: The typographical and grammatical errors were checked and corrected; and T-WL confirmed all contributing authors gave permission to be named.

Funding/support: This study was supported by National Nature Science Foundation of China (No.81570218).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:10(e0075)

Received: 22 November 2017 / Received in final form: 5 February 2018 / Accepted: 6 February 2018

http://dx.doi.org/10.1097/MD.0000000000010075

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease with negative prognosis leading to right heart failure and premature death.[1] It is defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg in peace, also with a decreasing pulmonary capillary wedge pressure (PCWP) and increased pulmonary vascular resistance index (PVRi) via right heart catheterization.[2]

PAH is a common complication of congenital heart disease (CHD), especially with systemic-to-pulmonary shunts in children owing to an increasing pulmonary blood flow.[3] In that condition, it possibly causes obstructive lesions and persistently increasing PVRi. A timely corrective surgery is a critical prevention from a progressive pulmonary vascular changes and PAH in childhood. However, with the advances of pediatric interventions and cardiac surgery, a growth population with complex CHD in adulthood that may develop progressive vascular remodeling, causing an irreversible condition of Eisenmenger syndrome (ES). The prevalence of PAH in ES conditions probably is about 1% to 6%.[4,5] PAH associated with CHD (PAH-CHD) could be classified into 4 groups in clinical: group A, ES; group B, PAH associated with left to right shunts; group C, PAH with small defects (VSD < 1 cm and ASD < 2 cm assessed by echocardiogram); and group D, PAH after corrective cardiac surgery.[4]

In the pathophysiological progress, an elevated plasma level of endothelin (ET)-1, a vasoactive peptide that commonly considered as an important role driving fibrosis, vascular hypertrophy, proliferation, and vasoconstriction. Two identified receptor sub-type, including ET-A and ET-B, have influence on vascular smooth muscle.[6] Endothelin receptor antagonists (ERAs) mainly covers 4 medical agents in specific PAH therapy. Bosentan is a dual ET-A/ET-B ERA which is widely in clinical. In previous summary, it was identified as safe and well tolerated in PAH adults and children with or without a combination management.[7,8] A qualitative systematic review about bosentan in adults with PAH-CHD has indicated a significant improvement in exercise capacity (6-minute walk distance [6MWD] and clinical functional class [FC]) and hemodynamic parameters in 2014.[9] Although it was supported a short-term improvement of ERA in both adults and children with left-to-right shunts while a decline effect at a long-term follow-up. There still are with a lack of systemic analysis about efficiency in both a short-term and a long duration for patients with PAH-CHD. Consequently, we performed a meta-analysis and systemic review of patients with PAH-CHD to have a further idea of the structural and functional effects of bosentan.

2. Methods

This systematic review and meta-analysis was conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA)[10] and the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.[11] Since this study was a review of previous published studies, ethical approval or patient consent was not a requirement. The literature search, eligibility evaluation and data extraction were carried out by 2 reviewers (HY-K and YH-W) independently. And the language was not limited to English. The ethical approval was waived for a review and analysis of pooled studies published.

2.1. Literature search and selection criteria

PubMed, Medline, the Cochrane Library, and EMBASE were searched for records. The search strategy is shown in Table 1. The last search was conducted on September 29, 2017. The cited references of retrieved articles and previous reviews were manually checked to identify any additional eligible trails. And the investigators screened the study inclusion for twice. Studies meeting the following criteria were considered as the eligible: Population: patients were diagnosed with PAH-CHD and monitored not mixed with other causes (including age of <18 years or adults or both); Intervention: a monotherapy of bosentan; Study design: randomized controlled trails (RCTs) or clinical controlled trails or observational studies; Outcome: primary outcomes were comprised of mortality, exercise capacity (6MWD), World Health Organization (WHO) modification of FC, heart rate (HR), Borg dyspnea index scores (BDIs), and the resting oxygen saturation (SpO_2); the secondary outcomes mainly include cardiopulmonary hemodynamic parameters, mostly like mPAP, PVRi, and PCWP, etc., the morbidity of adverse events (AEs); and Study exclusion: the study without important outcomes, an evaluation of medicine on PAH with other cardiopulmonary lesions, and a combined therapy with other specific medicines, such as prostanoids and phosphodiesterase inhibitor and a study with a medical transition were all removed. Discrepancies of included studies between 2 authors (H-YK and Y-HW) were resolved by a discussion with the correspondence author (T-WL).

2.2. Data extraction

All relevant data were independently documented by 2 of the authors (H-YK and Y-HW) from each enrolled trail by using a unified data form. The items of extracted data included study characteristics (first author, publication year, and sample size of participants), pharmacotherapy intervention (active drug), and outcomes (primary outcomes and secondary outcomes). The oral term was defined as a short-term when less than 6 months, and a long period effect when more than it. Any discrepancies were resolved by consensus. And we contacted the authors to obtain original information through e-mail when necessary. For those abstracts, we have reviewed and excluded for not meeting the criteria. This study did not enroll the unpublished studies.

2.3. Quality assessment

RCTs were assessed using the Cochrane Risk-of-Bias tool.[12] And we adopted the Newcastle-Ottawa Scale for assessing the quality of Case–Control studies and Cohort studies (www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

2.4. Statistical analysis

To evaluate the effects of PAH-specific medicine in PAH-CHD, we computed 95% confidence intervals (CIs) of standardized

Table 1

Search strategy.

Search terms	
1.	Endothelin receptor antagonist or bosentan
2.	Pulmonary arterial hypertension or PAH
3.	Congenital heart disease or CHD
4.	1, 2, and 3

CHD = congenital heart disease, PAH = pulmonary arterial hypertension.

mean differences (SMD) for the continuous outcome data. Heterogeneity across pooled studies was tested using Cochrane Q via a Chi^2 test, quantifying with the I^2 statistic, $P < .05$ and $I^2 > 50\%$ indicates a significant heterogeneity between studies, and then a sensitivity analysis was used to explore the sources of heterogeneity.[13] After unavailability of homogenization, a random effect model of analysis was employed. Otherwise, a fixed effect model of analysis was applied to calculate pooled SMD and 95% CIs. Begg test was carried out to investigate publication bias of enrolled studies.[14] All the statistical analyses were analyzed with Stata 14.1 software (StataCorp, TX), and a P value was stated statistically significant when less than .05.

3. Results

3.1. Study identification and selection

The selection process was portrayed in Fig. 1. A total of 853 records were identified by the search strategy. About 110 articles were excluded for duplication. After reviewing the title and abstract, 701 articles were excluded for guidelines, reviews, case reports, animal trails, and ineligible participants (or pharmacotherapy). Finally, the remaining 42 full-text articles were assessed for the eligibility. Five articles were removed for a combined specific drug. Additional 11 articles were excluded for depicting those patients not only with CHD (including 9 articles with other etiology of PAH or 7 articles with CHD and 21-trisomy). The remaining 4 articles were excluded for a lack of important outcomes. Eventually, 17 trails[15–31] were enrolled in the meta-analysis. And 418/456 participants were treated with oral bosentan for a diagnosis of PAH secondary to CHD.

3.2. Study characteristics

The main characteristics of these included studies are demonstrated in Table 2. The included studies were published between 2005 and 2016, which was comprised of 15 cohort studies (10 prospective studies and 5 retrospective studies) 1 RCT and 1 clinical controlled trail. Among these 17 trails, 2 were conducted in China, 2 in US, 2 in Netherlands, 2 in UK, 2 in Germany, 2 in Italy, 1 in Greece, 1 in France, 1 in Portugal, 1 in India, and 1 in Iran. Three trails just identified the safety and efficiency of bosentan in pediatric patients with CHD.[25–27] In these 3 studies, the dose of bosentan was afforded according to body weight. And the patients involved in the remaining studies were treated with bosentan in a dosage of 62.5 mg twice daily in the first 4 weeks, after which, increasing this to 125 mg twice daily, as tolerated. Nine studies have mentioned patients suffered from ES, and the percentage of ES was about 49.6%. And about 34 patients were diagnosed with postoperative associated with PAH. All basic characteristics in enrolled articles are shown in Table 2. Additionally, the baseline, short-term, and long-term characteristics of all pooled studies were described in Table 3.

3.3. Quality assessment

The quality of the studies is assessed respectively by the Cochorane Risk-of-Bias Tool in Table 4 and Newcastle-Ottawa Scale in Tables 5 and 6. Almost all articles were evaluated as a high quality, except for 1 study of 5 stars.[26]

3.4. All efficiency of bosentan pharmacotherapy in PAH-CHD

Patients had no treatment regimen changes. Data for the efficiency of all PAH-specific management were extracted from all enrolled studies. In bosentan treatment group, a total of 14 patients was reported with a death endpoint. Although AEs occurred in 43 subjects mentioned in 13 articles, with a greater proportion of edema (25.6%), liver dysfunction (18.6%), headache (14.0%), palpitations (11.6%), chest pain (6.9%), flushing (6.9%), and other AEs (11.6%), which included a throat pain and hypoglycemia each episode. In pediatric management, Gillbert has reported a case with an elevating liver enzymes to about 3-fold the upper limit of normal.[27]

3.5. Short-term outcomes

After receiving a short-term oral bosentan, patients presented exercise capacity mainly in 6MWD (N = 8, in a study including

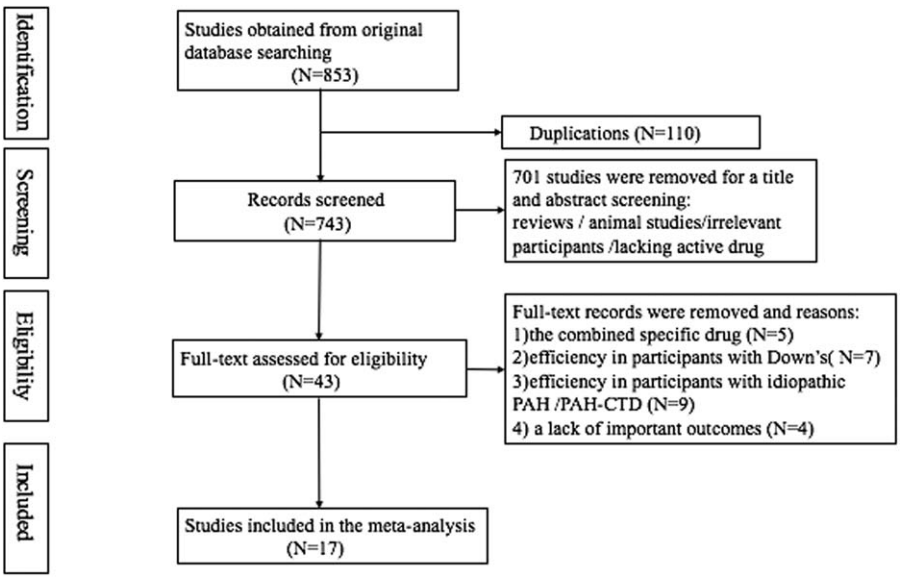

Figure 1. Selection flowchart of literature screening for the meta-analysis.

Table 2

Basic characteristics of included studies.

First author, year	D	Country	Age	Period*	Dose of ERAs, mg	Par†	Type‡	Additional specific-PAH therapy (yes/no)§	Active drug	Groups (N)	Primary outcome
Galie 2006[15]	RCT	Italy	37.2 (12.0) y 44.2 (8.5) y	16W	62.5 mg (Bid, 4W)+ 125 mg (Bid,12W)	54	ES (100%)	No	Bosentan	Bosentan (37) Placebo (17)	6MWD
Riel 2016[16]	CCT	Netherlands	47.0 (14.0) y 41.0 (14.0) y	12M	62.5 mg (Bid 4W)+125 mg (Bid, −)	74	ES (71%) Po-PAH (5%)‡	No	Bosentan/PDEi-5	Bosentan (45) Sildenafil (29)	6MWD
Ibrahim 2006[17]	Pro	UK	31.9 (10.7) y	16W	62.5 mg (Bid 4W)+125 mg (Bid, −)	10	NA	No	Bosentan	Bosentan (10)	6MWD
Apostolopoulou 2007[18]	Pro	Greece	22.0 (3.0) y	16 W/2Y	62.5 mg (Bid 4W)+125 mg (Bid, −)‖	19	ES (73.7%) Po-PAH (10.5%)	No	Bosentan	Bosentan (19)	6MWD
Schulze-Neick 2005[19]	Pro	Germany	43.0 (14.0) y	2.1 (0.5) Y	62.5 mg (Bid 4W)+125 mg (Bid, −)	33	ES (69.7%) Po-PAH (27.3%)	No	Bosentan	Bosentan (33)	6MWD
D'Alto 2013[20]	Pro	Italy	39.0 (14.0) y	14.0 (0.3) M	62.5 mg (Bid 4W)+ 125 mg (Bid, −)	56	NA	No	Bosentan	Bosentan (56)	6MWD
Vis 2011[21]	Pro	Netherlands	46.0 (14.0) y	3.5 (1.2) Y	NA	34	ES (79%)	No	Bosentan	Bosentan (34)	6MWD
Baptista 2013[22]	Pro	Portugal	37.1 (11.7) y	6M	62.5 mg (Bid 4W)+ 125 mg (Bid, −)	14	ES (NA)	No	Bosentan	Bosentan (14)	6MWD
Diller 2007[23]	Pro	UK	41.0 (9.0) y	24M	62.5 mg (Bid 4W)+ 125 mg (Bid, −)	18	ES (83, 3%) Po-PAH (16.7%)	NA	Bosentan	Bosentan (18)	6MWD
Ye 2014[24]	Pro	China	23.8 (17.6) y	2M/6M	Accordingly¶	24	ES (16.7%) PO-PAH (16.7%)	NA	Bosentan	Bosentan (24)	6MWD
Ajami 2014[25]	Pro	Iran	5.45 (4.5) y	3H	2 mg/kg orally	20	NA	Inhaled O2	Bosentan	Bosentan (20)	Hemodynamics
Xu 2009[26]	Pro	China	2M-15.0 y	3.0M	Accordingly# (after surgery)	18	Left-to-right shunts-PAH (100%)	NA	Bosentan	Bosentan (18)	6MWD
Gilbert 2005[27]	Ret	Germany	3.8 (2.0) y	8.6 (5.0) M	1.5 mg/kg/d (Qd-Tid,4W) +3 mg/kg/d (Qd-Tid, −)	7	PO-PAH (42.9%)	NA	Bosentan	Bosentan (7)	FC
Sitbon 2006[28]	Ret	France	35.0 (15.0) y	3M/15.2 (9.7) M	62.5 mg (Bid 4W)+125 mg (Bid, −)	27	PO-PAH (14.8%) ES (NA)	No	Bosentan	Bosentan (27)	6MWD
Benza 2006[29]	Ret	US	50.0 (13.0) y	3M/6M/12M	62.5 mg (Bid 4W)+ 125 mg (Bid, −)	24	Left to right shunts-PAH	Yes	Bosentan	Bosentan (24)	6MWD
Mehta 2008[30]	Ret	US	44.0 (12.0) y	19.0 (12.0)M	62.5 mg (Bid,4W)+125 mg (Bid, −) (B) 50 mg (4W)+100 mg (−)(S)	24	ES-PAH (100%)	NA	Bosentan (21) Sitaxsentan (3)	Bosentan (21)	6MWD
Durongpisitkul 2008[31]	Ret	India	51.1 (10.1) y	3M/6M	NA	11	ES-PAH (54.5%) PO-PAH (45.5%)	NA	Bosentan	Bosentan (11)	6MWD

CCT = clinical controlled trail, D = design, ES = Eisenmenger syndrome, 6MWD = 6-minute walk distance, ERA = endothelin receptor antagonist, NA = not available, Po-PAH = postoperative pulmonary arterial hypertension, Pro = prospective, open-labeled study, RCT = randomized controlled trail, Ret = retrospective study.

* H = hour, W = week, M = month, y = year.

† Par = participant.

‡ Type of PAH-CHD: ES-PAH (%); Po-PAH (%).

§ Traditional therapy includes vasodilators, cardiac glycosides, diuretics, and anticoagulants.

‖ The dose of treatment in groups over 40 kg (and if 20–40 kg, 31.25 kg Bid 4W + 62.5 mg Bid, −).

¶ 10 to 15 kg: 7.1825 mg Bid, 4W + 15.625 mg Bid, −; 15 to 20 kg: 15.625 mg Bid, 4W + 31.25 Bid, −; 20 to 40 kg: 15.625 to 31.25 mg Bid, 4W + 31.25 to 62.5 mg Bid, −; 40 to 60 kg: 31.25 to 62.5 mg Bid, 4W + 62.5 to 125 mg Bid, −.

< 15 kg 15.625 mg/d Qd; 10 to 20 kg 31.25 mg/d Qd; 21 to 40 kg 62.5 mg/d Qd; > 40 125 mg/d Qd.

Table 3

Baseline, short-term, and long-term characteristics of pooled bosentan studies.

Study	Drug	mPAP B/S/L	PVRi (Wood U‘m^2) B/S/L	PCWP B/S/L	6MWD B/S/L	SpO_2 (RESTing) B/S/L	WHO/FC B/S/L	HR B/S/L	BDIs B/S/L	Death	AE
Galie	Bos	77.8 (15.2) 72.8 (NA) –	42.8 (17.6) 38.9 (NA) –	–	331.9 (82.8) 288.5 (NA) –	82.4 (5.3) 80.2 (8.9) –	–	76.3 (16.7) 74.3 (NA) –	–	NA	22
Riel	Bos	–	–	–	395 (137) – 402 (NA)	–	–	–	–	7	NA
Ibrahim	Bos	–	–	–	304.1 (78.5) 332.1 (74.7) 338.1 (74.1)	81.9 (6.1) 83.0 (4.6) 83.6 (4.7)	3.0 (0) 2.5 (0.5) 2.3 (0.46)	–	5.2 (2.2) 3.7 (2.5) 3.4 (1.8)	0	3
Apostolopoulou	Bos	–	–	–	417 (25) 463 (24) 402 (19)	–	2.84 (0.59) 2.32 (0.46) 2.32 (0.46)	– – –	2.8 (0.2) 2.0 (0.2) 3.0 (0.0)	NA	4
Schulze-Neick	Bos	87.8 (22.0) – 84.5 (25.1)	15.3 (11.7) – 12.6 (3.4)	9.1 (5.1) – 7.8 (3.8)	362 (105) – 434 (68)	86 (7) – 88 (7)	3.10 (0.5) – 2.4 (0.5)	84 (15) – 82 (13)	–	0	1
D'Alto	Bos	74 (18) – 73 (21)	26 (15) – 20 (10)	11 (3) – 12 (3)	343 (86) – 389 (80)	84 (9) – 85 (8)	2.9 (0.5) – 2.5 (0.5)	91 (14) – 84 (11)	5.0 (2.1) – 4.3 (1.9)	0	2
Vis	Bos	84 (23) – 81 (NA)	–	–	417 (108) – 458 (104)	–	–	78 (11) – 77.9 (NA)	–	NA	3
Baptista	Bos	–	–	–	379.1 (90.3) – 428.4 (98.3)	82.0 (6.9) – 81.9 (6.6)	3.07 (0.46) – 2.29 (0.59)	88 (12) – 90 (14)	2.4 (1.7) – 3.3 (2.3)	2	1
Diller	Bos	–	–	–	284 (144) 363 (124) 408 (104)	81.1 (4.9) 84.7 (2.6) 84.2 (4.8)	–	–	–	1	0
Ye	Bos	–	–	–	317 (134.1) 488.1 (98.8) 491.3 (114.2)	–	2.9 (0.5) 2.0 (0.5) 1.7 (0.5)	–		1	3
Ajami	Bos	70 (16.3) 58 (20)	9.92 (2.97) 5.90 (2.69)	14.3 (3.99) 9.45 (3.28) –	–	83.9 (4.7) 86.2 (5.9) –	–	–	–	NA	NA
Xu	Bos	74 (15) 46 (22)	–	–	424 (31) 497 (56) –	–	3.44 (0.68) 2.17 (0.37)	–	–	1	NA
Gilbert	Bos	–	–	–	–	–	2.6 (0.6)* – 1.6 (0.6)	–	–	2	1
Sitbon	Bos	63 (16) – 60 (12)	21.6 (13.2) – 15.5 (8.7)	5.6 (3.9) – 5.7 (3.9)	298 (92) 255 (82) 364 (92)	89 (8) 88 (6) 88 (7)	3.11 (0.31) 2.74 (0.52) 2.63 (0.55)	–	2.8 (1.9) 2.2 (1.3) 2.4 (1.9)	0	0
Benza	Bos	60 (18) 56 (18) 52 (17)	8.0 (4.8) 6.7 (4.0) 6.5 (4.6)	15 (5) 12 (4) 14 (6)	299 (85) – 330 (95)	–	2.87 (0.44) 2.58 (0.49) 2.13 (0.67)	–	–	0	3
Mehta	Bos/Sit	59 (16)† – 47 (17)	–	15 (7) – 15 (4)	226 (159) – 351 (113)	80 (11) – 87 (9)	3.33 (0.47) – 1.96 (0.61)	–	–	0	NA
Durongpisitkul‡	Bos	–	–	–	151 (69) 287 ((56) 293 (61)	83 (12.7) 88.6 (11.2) 91.8 (5.6)	–	–		0	0

AE = adverse event, B = baseline, BDIs = Borg dyspnea index scores, Bos = bosentan, CI = cardiac index, CO = cardiac output, FC = functional class, HR = heart rate, L = long-term, mPAP = mean pulmonary arterial pressure, 6MWD = 6-minute walk distance, NA = not available, PCWP = pulmonary capillary wedge pressure, PVRi = pulmonary vascular resistance index, S = short-term, SpO_2 = oxygen saturation.

* Ross score was applied in 2 infants.

† The mean PAP were identified and recorded in 17/21 patients received bosentan treatment.

‡ Durogpisitkul: (in 5 patients with PAH postintervention) 6WMD: B: 274 (69), S: 314 (24), L: 312 (38); the resting SpO_2: B: 96.8 (1.3), S: 97.2 (1.3), L:98.2 (0.8).

Table 4

Risk-of-bias assessment of included randomized controlled trails[*].

Study (first author)	Adequate sequence generation?	Allocation concealment?	Blinding of participants	Blinding of assessment	Incomplete outcomes data addressed?	Selective reporting?	Free of other bias?	Overall risk of bias
Galie et al	Yes	Yes	Yes	Yes	Unclear	No	Yes	High

[*] Risk of bias was assessed with use of the Cochrane risk-of-bias tool.

Table 5

Assessment the quality of case–control studies[*].

	Selection					Exposure			
Study (first author)	Definition adequate?	Representativeness of cases	Selection of controls	Definition of controls	Comparability[†]	Ascertainment of exposure	Same method of ascertainment	Nonresponse rate	Score
Riel	☆	☆	☆	☆	☆☆	☆	☆	–	8

[*] The assessment was based on the Newcastle-Ottawa Scale. The full mark of total score is defined as 9; a score of >7 indicates a low risk of bias.
[†] Comparability of cases and controls on the bias of design or analysis.

different groups data with PAH-CHD). In this meta-analysis, heterogeneity test revealed heterogeneity chi-squared = 39.50, $P < .01$, $I^2 = 82.3\%$, indicating a significant heterogeneity. The sensitivity analysis was employed and it was uncovered a significant after excluding the pooled study by Sitbon et al.[28] A random effect model of analysis was used in Fig. S1 http://links.lww.com/MD/C158, showing an increase level of 6MWD ($I^2 = 53.3\%$, SMD = 1.201; 95%CI = 0.696–1.705; $P < .01$). As other important indicators of exercise capacity, WHO-FC was identified a significant change ($I^2 = 39.1\%$, SMD = 1.332; 95% CI = 0.931–1.734; $P < .01$) and scores of BDIs in 3 studies were assessed with an unsatisfactory improvement ($I^2 = 0\%$, SMD = 0.534; 95%CI = −0.173–1.242; $P = .139$) The resting SpO_2 was not been elevated in a short-term with a significant statistical difference ($I^2 = 44.7\%$, SMD = −0.139; 95%CI = −0.418–0.140; $P = .328$). HR was not regularly recorded in a short-term monitoring. The cardiopulmonary hemodynamics, covering mPAP, PVRi, and PCWP, were the secondary outcomes. The data were mentioned in studies showing a great heterogeneity in each hemodynamic parameters, including mPAP (4 studies): $I^2 = 71.6\%$; PVRi (3 studies): $I^2 = 83.3\%$; and PCWP (2 studies): $I^2 = 84.3\%$. After a discussion, meta-analysis could not be employed in these parameters.

3.6. Long-term outcomes

After a pharmacotherapy of oral bosentan more than 6 months, the exercise capacity was evaluated. In 6MWD assessment during a long-term, heterogeneity test revealed $I^2 = 59.7\%$, and a sensitivity analysis was applied presenting an abnormal deviation of study conducted by Apostolopoulou et al.[18] from others in Fig. L1 http://links.lww.com/MD/C158. The deviated study was excluded, and a fixed-effect model was applied in Fig. L2 http://links.lww.com/MD/C158 ($I^2 = 21.5\%$, SMD = 0.697; 95%CI =

Table 6

Assessment the quality of cohort studies[*].

	Selection					Outcome			
Study (first author)	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure to implants	Demonstration that outcome[†]	Comparability[‡]	Assessment	Enough follow-up	Adequacy of follow up of cohorts[§]	Score
Ibrahim	☆	–	☆	☆	☆☆	☆	–	☆	7
Apostolopoulou	☆	–	☆	☆	☆☆	☆	☆	☆	8
Schulze-Neick	☆	–	☆	☆	☆☆	☆	☆	☆	8
D'Alto	☆	–	☆	☆	☆☆	☆	☆	☆	8
Vis	☆	–	☆	☆	☆☆	☆	☆	☆	8
Baptisa	☆	–	☆	☆	☆☆	☆	–	☆	7
Diller	☆	–	☆	☆	☆☆	☆	☆	☆	8
Ye	☆	–	☆	☆	☆☆	☆	–	☆	7
Ajami	☆		☆	☆	☆☆	☆	–	☆	7
Xu	–	–	☆	☆	☆	☆	–	☆	5
Gilbert	☆	–	☆	☆	☆☆	☆	–	☆	7
Sitbon	☆	–	☆	☆	☆☆	☆	☆	☆	8
Benza	☆	–	☆	☆	☆☆	☆	☆	☆	8
Mehta	☆	–	☆	☆	☆☆	☆	☆	☆	8
Durongpisitkul	☆	–	☆	☆	☆☆	☆	–	☆	7

[*] The assessment was based on the Newcastle-Ottawa Scale. The full mark of total score is defined as 9; a score of >7 indicates a low risk of bias
[†] A demonstration about the outcomes of interest was not present initially.
[‡] Comparability: study controls the most important factor in a monotherapy of bosentan; additional important factor is a collection of data in a cohort group with PAH-CHD.
[§] Subjects lost to follow-up: small number lost: <5%.

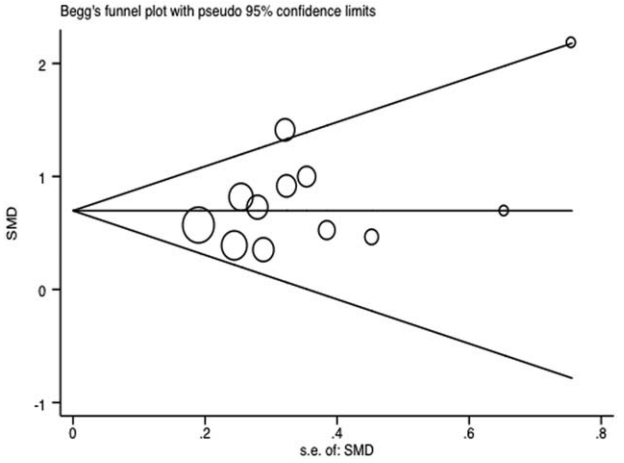

Figure 2. The publication bias of long-term efficiency of bosentan treatment with Begg funnel plot.

0.552–0.872; $P < .001$). The WHO-FC assessment in a long-term follow-up. After excluded the study researched by D'Alto et al[20] and Mehta et al,[30] it was calculated a heterogeneity chi-squared = 9.85, $P = .131$, $I^2 = 39.1\%$. A fixed-effects model was employed (SMD = −1.394, 95%CI = −1.652 to −1.137; $P < .001$), revealing a statistically significant difference in a decrease of FC evaluation which suggested a great improvement in exercise tolerance. The resting SpO_2 and HR were also as the symbols of exercise capacity, which was evaluated a lasting efficiency respectively in 8 studies[17,19–23,29,31–32] and 4 studies[19–22] of statistical significance. (SpO_2: $I^2 = 15.9\%$, SMD = 0.268, 95%CI = 0.065–0.472, $P = .01$; HR: $I^2 = 44.2\%$, SMD = −0.323, 95%CI = −0.599 to −0.047, $P = .022$). The BDIs were monitored comparing with baseline data in 5 pooled studies, indicating an unobvious decline to baseline condition,[17,18,21,23,29] ($I^2 = 45.1\%$, SMD = −0.257, 95%CI = −.528–0.014, $P = .063$). For a further hemodynamic changes rather than an acute response, bosentan could significantly lower the parameter in mPAP ($I^2 = 0\%$, SMD = −0.236, 95%CI = −.458 to −0.014, $P = .037$), in PVRi ($I^2 = 0\%$, SMD = −0.423, 95%CI = −0.663 to −0.184, $P = .001$), but with little change in PCWP ($I^2 = 14.4\%$, SMD = 0.038, 95%CI = −0.184–0.259, $P = .739$).

3.7. Comparative outcomes

A comparative analysis was conducted between short-term and long-term treatment for a quantitative review. Between a short-term and a long-term period, 6MWD was compared in 6 pooled trails with a great heterogeneity ($I^2 = 89.1\%$).[17,18,23,24,29,32] After a sensitivity analysis, the study by Apostolopoulou et al[18] was excluded, and it indicated an increase 6MWD not significantly compared with short-term outcomes ($I^2 = 0\%$, SMD = 0.140, 95% CI = −0.210–0.490, $P = .434$). Although it was identified with a significant decrease in WHO-FC ($I^2 = 0\%$, SMD = −0.401, 95%CI = −0.677 to −0.125, $P = .004$). The resting SpO_2 in a long-term period was showed a higher level than that in a short-term period without statistical difference ($I^2 = 0\%$, SMD = 0.079, 95%CI = −0.264–0.422, $P = .651$). Meanwhile, after a prolonged treatment of oral bosentan in 3 studies, the scores of BDIs were decreased, but the difference was not significant ($P = .822$).

3.8. Pediatric PAH-CHD therapy

In the 3 studies just enrolled the pediatric patients, including 1 in Iran,[25] 1 in China,[26] and 1 in Germany.[27] Totally, the subjects counted 45. Three individuals were recorded the death endpoint and 1 AE scenario was detected in a study, presenting an increasing liver enzymes.[27] Two studies depicted mPAP presenting a lower pressure in a short-term treatment.[25,26] In study conducted by Xu et al.,[26] there was existed an improvement in exercise capacity, identifying by 6MWD increasing by 17.2% (from 424 ± 31 m increased to 497 ± 56 m). FC was also expressed as a lowering level compared with the initial time point not only in a pilot with a short-term therapy from 3.44 (0.68) to 2.17 (0.37), but also in another study with a long-term treatment from 2.6 (0.6) to 1.6 (0.6).

3.9. Publication bias

For the meta-analysis in a long-term efficiency of bosentan treatment acting on 6MWD, there is existed no evidence of significant publication bias by the inspection of the Begg funnel plot in Fig. 2.

4. Discussion

In PAH patients associated with CHD could suffer from an increasing mortality and morbidity of severe conditions.[3,32] In postoperative PAH patients, it commonly formed an abnormal vascular resistance before surgery, after which, an acute response caused by vascular lesions and cardiopulmonary bypass. Although a sharply increasing blood flow in the systemic circulation could lead to acute left heart failure, presenting as a fatal scenario as pulmonary hypertensive crisis. PAH with left-to right shunts progressively causes the pulmonary vascular changes, to some extent, leading to the irreversible remodeling. Furthermore, the pulmonary vascular resistance persistently increased, and once the pulmonary vascular resistance exceeded the systemic circulation resistance, ES occurs which was totally freedom from a treatment of surgical management. For PAH patients with CHD, ERAs have been proved efficient in both monotherapy and combination therapy. Bosentan, a nonselective, dual ET-A/ET-B ERA, has been approved by FDA in 2001, and Current European Society of Cardiology guidelines have been recommended that bosentan therapy is initiated in PAH-CHD patients, even ES patients.[33]

In our study, we proved that a dual ERA, bosentan is a safe and efficient medicine for PAH-CHD patients in both adults and children, not only for ES, but also for PAH patients with closured systemic-to-pulmonary shunts. Previously, Kara et al proved benefits in mPAP and right heart function in ES patients during a lasting treatment.[34] Although, a qualitative systematic review has suggested an important functional benefit of bosentan therapy, while a limited evaluation in hemodynamics.[10] The drawbacks and AEs were considerable, especially a hepatotoxicity with elevated transaminase level most frequently in previous studies.[35] Currently, 17 trails were pooled in this review. Most studies enrolled adult subjects. The mean mortality was about 4.5% in 13 studies and AEs were counted as 13.7%. But AEs were showed just a greater proportion in peripheral edema than higher liver enzymes and other complications. These events were commonly reported a relief after a pause or decreasing dosage of bosentan. A mortality of all pooled studies indicated no significance. The traditional medicines (eg, oral anticoagulation, calcium channel blockers, and diuretics), but other ERAs, PDE-5

inhibitors, and prostacyclin analogues, were combined with bosentan in patients preoperative or postoperative both in adult and pediatric PAH-CHD patients.

Van Loon et al[36] found that bosentan therapy was shown to produce only short-term improvement in WHO-FC and 6MWD in both children and adults with PAH-CHD. Guo et al[37] have reviewed 8 trails and discussed bosentan was an efficient and tolerated treatment for CHD-PAH patients. However, it was just showed an increasing exercise capacity in a period of 3 to 6 months but a significant difference with a long-term, also leaving out the vascular parameters, safety, and AEs. A 2-year observational study also reported an improvement in 6MWD with ERA monotherapy proving a lasting effect on patients.[34] But there was still a lack of comparative analysis.

We conducted this meta-analysis constructing from a short-term period (<6 m) and a long-term period (≥6 m). And the idiopathic PAH (iPAH) and PAH associated with connective tissue diseases were all freedom from this review. On the other hand, those PAH-CHD subjects with Down syndrome were not enrolled. Data were on important surveillance indicators of exercise tolerance in a short-term therapy which indicated a significant difference in 6MWD and WHO-FC, but there were no obvious changes in the resting SpO_2. A considerable heterogeneity of cardiopulmonary hemodynamics detected by right catheterization was among each pooled studies. Hence, the changes in vascular hemodynamic parameters remained limited statistical significance. With a period of long-term, the evidence supported that ERA could further be safe and well tolerated compared with baseline. Outcomes demonstrated a clinical functional benefit of bosentan therapy, such as 6MWD, WHO-FC, and HR. Additionally, bosentan also improved the hypoxemia condition with or without ES patients. However, the scores of BDIs were still not decreased neither in a short-term therapy nor in a long-term therapy. In hemodynamic parameters, mPAP and PVRi were lowered a lot by bosentan treatment when a long-term therapy in patients with PAH-CHD. Hence, it is considered a possible importance of a prolonged therapy, which was contrary to some previous studies.[19,36]

Although clinically functional benefits were found either a short-term or a long-term outcomes compared with baseline characteristics. The necessity of a prolonged therapy with a dual ERA still is to be certified for a prevention from the AEs. For those studies with a prolonged treatment of monotherapy, the comparative outcomes were suggested a meaningful decline in WHO-FC. To the contrary, the results indicated a prolonged therapy of oral bosentan possibly could not an increase walking distance of 6MWD and the resting SpO_2, and a decrease the scores of BDIs significantly, which possibly was ascribed to a limitation of small sample capacity. Hence, we held a point of view that a prolonged treatment in PAH-CHD possibly a necessity, not only improving the clinical manifestations but also declining vascular resistance, and controlling the remodeling in pulmonary vessels as proved previously.[38]

It seemly exists a smaller proportion of ES group in pediatric patients, and the studies also supported an empirical clinical value of ERAs in children. But it lacked a qualitative proof for it. It is commonly known that a limited treatment strategy in adult PAH-CHD, especially ES conditions. Some PAH patients occurred after CHD occlusion.[4,39] In addition, the participants with trisomy-21 were excluded in this study, and the efficiency of ERAs contributing to in these individuals were neglected. For the greater numbers of patients with PAH-CHD surviving into adulthood inoperably, especially with complex CHD, specific-PAH therapy can improve the functional status and exercise tolerance which was recommended by ESC guidelines.[40] Our study has some limitations which are as follows: The effects were evaluated together, without the subgroup analysis in different CHD group; A small sample of trials with controlled group; and Risk of death and AEs could not calculated and compared between ERA treatment group and a blank group. Else, the optimal identification of clinical manifestations and cardiopulmonary hemodynamic parameters between the short period effect and long period effect remains to be explored in future trails.

5. Conclusions

Current evidence indicates that bosentan is a safe and effective specific-PAH therapy for PAH-CHD patients. Although this review was conducted without a differentiated analysis in CHD classification. We can conclude that this dual ERA is an effective treatment both in a short-term and a long-term, which suggesting an irreplaceable strategy in PAH with systemic-to-pulmonary shunts.

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