

Safety and tolerability evaluation of oral bosentan in adult congenital heart disease associated pulmonary arterial hypertension: a systematic review and meta-analysis

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Abstract. – OBJECTIVES: In this study, we performed a systematic review and meta-analysis of oral bosentan in adult congenital heart disease associated pulmonary arterial hypertension (CHD-PAH) to evaluate its safety and tolerability.

MATERIALS AND METHODS: Online electronic database including PubMed, EMBASE and Springer were searched from October 2006 to October 2013 to collect the clinical studies or cohort trials on CHD-PAH with bosentan treatment. Weight Mean Difference (WMD) and Standard Mean Difference (SMD) were used to evaluate the treatment safety and tolerability. Review Manager (RevMan) version 5.0 was performed for the data analysis.

RESULTS: Totally 8 studies including 215 patients with CHD-PAH were enrolled in this research. With a period of 3-6 months oral bosentan treatment in patients, there were no significant differences in the scores of resting oxygen saturation (Resting SpO₂), post-6-MWT SpO₂ after 6-minutes' walktest (6-MWT) and Borg dyspnea index score (BDIs) compared with the baseline; the walking distance on 6-MWT increased significantly. With a period of one year or more oral bosentan treatment, the scores of resting SpO₂ and post-6-MWT SpO₂ increased significantly; there was no significant difference in BDIs and walking distance on 6-MWT.

CONCLUSIONS: The short-term treatment with oral bosentan could increase walking distance on 6-MWT, and long-term treatment could increase the Resting SpO₂ in CHD-PAH patients. Oral bosentan in CHD-PAH patients was safe and well tolerated.

Key Words:

Oral bosentan, Adult congenital heart disease, Pulmonary arterial hypertension, Weight mean difference, Borg dyspnea index score.

Introduction

Pulmonary arterial hypertension (PAH) associated with congenital heart disease is the result of a large systemic-to-pulmonary shunt, and can lead to right ventricular failure and early death¹. Actually, congenital heart defects (CHD) is one of risk factors for PAH, and the international community has proposed the management of pulmonary hypertension². Treatment options of congenital heart disease-related pulmonary hypertension are very limited for a long time, and the effective programs are constraints to avoid and cure complications until the introduction of endothelin receptor antagonists³. Bosentan, one kind of oral endothelin receptor antagonist, is concerned greatly nowadays. It significantly improved the exercise capacity, functional class and haemodynamics of patients with connective tissue disease associated pulmonary hypertension^{4,5}. Bosentan has an effect like endothelin-receptor antagonist for blocking endothelin A and endothelin B receptor. The 6-minutes' walk test (6-MWT), a measure of exercise capacity in patients, was administered a minimum of 2 hours after the pulmonary function test by a certified technician using a protocol similar to that of Scurba et al⁶. It is reported that bosentan can significantly improve the result of 6-MWT for pulmonary hypertension patients^{4,7}, meanwhile, patients showed a very satisfactory clinical response to bosentan⁸⁻¹⁰. However, its safety and tolerability on CHD-PAH remains controversial, especially after the long-term treatment. Some studies suggest that the positive benefit of sustainable and stable is still remained after the long-term treatment^{11,12}. To the contrary, some studies suggest that the positive benefits will de-

crease after long-term treatment^{13,14}. Thus, it is necessary to evaluate the safety and tolerability of oral bosentan treatment in CHD-PAH.

In this study, we performed a systematic review and meta-analysis of oral bosentan in adult congenital heart disease associated pulmonary arterial hypertension to evaluate its safety and tolerability.

Materials and Methods

Search Strategy

Two independent reviewers were conducted in online databases (Pubmed, Embase and Springer Database) and paper version (manual search) from October 2006 to October 2013. The terms of Bosentan, “pulmonary arterial hypertension”, “Pulmonary hypertension” and “congenital heart disease” were used.

Study Selection Criteria

The inclusion criteria for this study were as follows: (1) Study design for clinical experiment; (2) patients of congenital heart disease associated with pulmonary hypertension; (3) Age of adult ≥ 18 years old; (4) The treatment program is the oral bosentan; and (5) Study outcomes are oxygen saturation, Borg dyspnea index score and 6-MWT walking distance. The exclusion criteria for this study were non-English references and non-original article including overview, letters, comments and etc.

Data Extraction

Eligible studies were independently scored by Two reviewers according to the Cochrane Collaborations tool for assessing risk of bias for RCTs and Newcastle-Ottawa scale¹⁵ for NRCS. Extracted data included first author, publication year, study design, regional of experiment, sample size, age and gender of patients and dose of oral bosentan. Disagreements were resolved by discussion between the two reviewers, or with a third reviewer.

Statistical Analysis

The statistical analysis was performed by Review Manager (RevMan) 5.0 software, which was provided by Cochrane Collaboration. Weight Mean Difference (WMD) and Standard Mean Difference (SMD) were used to

evaluate the safety and tolerability of bosentan. Moreover, resting oxygen saturation (resting SpO₂) and post-6-MWT SpO₂ were set as the index for safety evaluation. Borg dyspnea index scores (BDIs) was set as the index for the tolerance evaluation.

Statistical heterogeneity was assessed with Cochran's Q via a chi-square test and quantified with the I² test¹⁶, $p < 0.05$ and $I^2 > 50\%$ suggesting significant heterogeneity, then random effects model was used. $I^2 \leq 50\%$ and $p \geq 0.05$ considering low heterogeneity, and then fixed effects model was adopted.

Results

Literature Search and Selection

A total of 680 studies were retrieved in the Emabse, PubMed and Springer database (Figure 1). There were only 21 articles left when removed the duplicated studies and the studies not suitable for the present research. We, then, excluded 13 studies (including 1 review, 1 non-English article, 1 treatment without bosentan and 10 articles for children) after reading the full text. There was no suitable study for our research with manual search. Finally 8 studies were included in the present meta-analysis (see Table I).

The 6 studies including 215 congenital heart diseases associated with congenital heart disease patients; there were two short-term treatment (≤ 6 months) studies^{17,18} and six long-term treatment (≥ 12 months) studies^{11,13,19-22}. In these studies, the oral dose of bosentan for the patients was 2 times a day (62.5 mg for each time). If there was no adverse reaction, then the dose was increased to 125 mg each time. The detail treatment effect evaluated by resting SpO₂, 6-MWT post-6-MWT SpO₂ and BDIs were listed in Table II.

Safety and Tolerability Evaluation

After short-term treatment of oral bosentan, the scores of resting SpO₂ and post-6-MWT SpO₂ were increased (Figures 2 and 3), but not significant (resting SpO₂: WMD = 0.74, 95% CI = -2.47-3.95; post-6-MWT SpO₂: WMD = 0.14, 95% CI = -6.89-7.17). To the contrary, there was a significant difference in the scores of resting SpO₂ and post-6-MWT SpO₂ after the long-term treatment (resting SpO₂ WMD = 2.69, 95% CI = 0.69-4.68; post-6-MWT SpO₂:

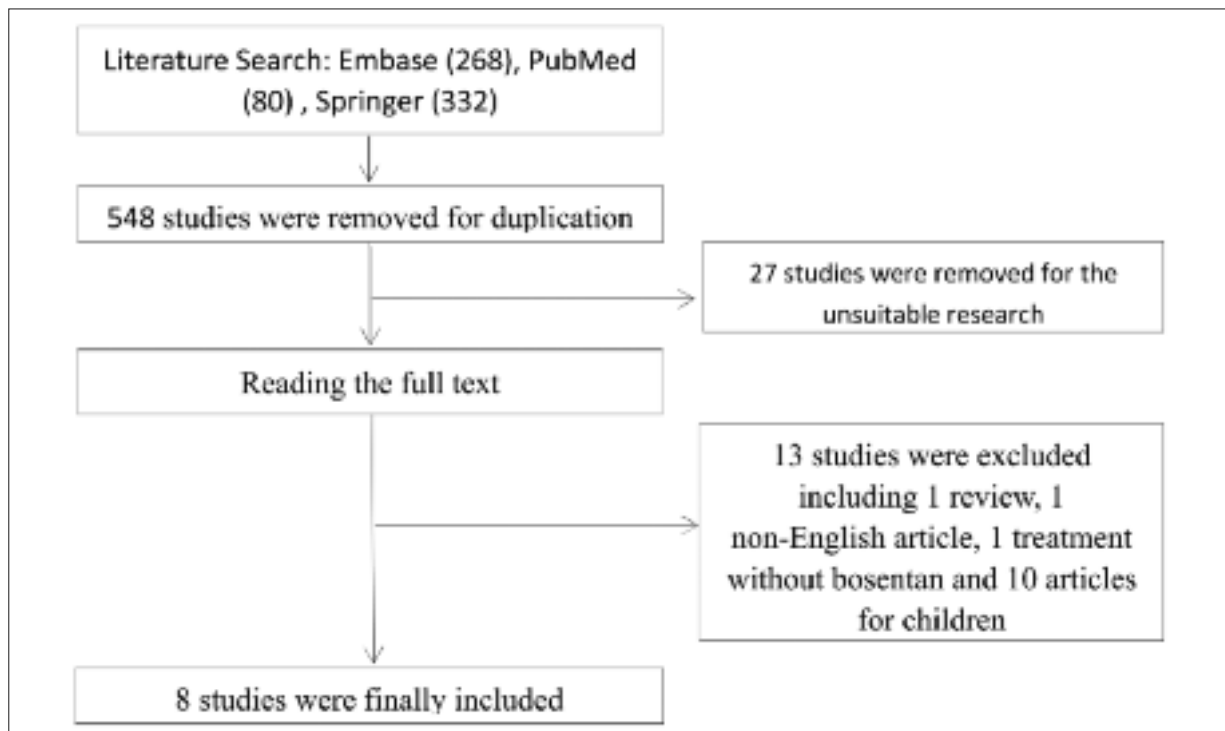


Figure 1. Flow diagram of the literature search.

WMD = 4.31, 95% CI = 0.39-8.23). Since the huge differences in the mean of 6-MWT, SMD was used as the evaluation index. After short-term treatment (Figure 4), bosentan significantly improved the exercise capacity of patients (SMD = 0.68, 95% CI: 0.24-1.13). However, the effect of long-term treatment (Figure 4) was not satisfactory (SMD = 0.35 95% CI: -0.23-0.94). The scores of BDIs was decreased either

in the short-term treatment or in the long-term treatment, the difference was not significant (Figure 5).

Discussion

Bosentan, one kind of oral endothelin receptor antagonist, is concerned greatly nowadays.

Table I. Basic information of the included articles in this study.

Author/date	Area	Sample size	Age	Sex*	Treatment duration	Study type
Ibrahim 2006	Canada	10	31.9 ± 10.7	3M/7F	NA	Multicenter pilot study
D'Alto 2007	Italy	22	38 ± 10	8M/14F	12 months	Open label, single arm, prospective pilot study
Vis 2013	Netherlands	34	46 ± 14	11M/23F	6 months	Prospectively pilot study
Apostolopoulou 2007	Greece	19	22 ± 3	10M/9F	2 years	Open-label non-controlled extension study
Duffels 2009	Netherlands	18	48 ± 25	5M/13F	12 months	Retrospectively pilot study
Baptista 2013	Portugal	14	37.1 ± 11.7	7M/7F	6 months	Prospectively pilot study
Diller 2007	UK	18	41 ± 9	4M/14F	29 months	Prospectively pilot study
D'Alto 2013	Italy	56	39 ± 14	25M/31F	14 ± 3 months	Open-label, single-arm, prospective pilot study

*M is short for Male and F is short for Female.

Table II. Therapeutic effects evaluation of bosentan.

Author	Resting SpO ₂ (%)			Post-6-MWT SpO ₂ (%)			6-MWT (m)			Borg dyspnea index score		
	Baseline	Short-term treatment	Long-term treatment	Baseline	Short-term treatment	Long-term treatment	Baseline	Short-term treatment	Long-term treatment	Baseline	Short-term treatment	Long-term treatment
Ibrahim	81.9 ± 6.1	83.0 ± 4.6	83.6 ± 4.7	68.7 ± 15.1	70.1 ± 10.9	68.6 ± 12.8	304.1 ± 78.5	332.1 ± 74.7	338.1 ± 74.1	5.2 ± 2.2	3.7 ± 2.5	3.4 ± 1.8
D'Alto	81 ± 9	—	87 ± 6	63 ± 17	—	71 ± 14	320 ± 108	—	394 ± 73	6.5 ± 1.3	—	5.3 ± 1.8
Vis	—	—	—	—	—	—	417 ± 108	458 ± 104	—	—	—	—
Apostolopoulou	—	—	—	—	—	—	417 ± 25	463 ± 24	402 ± 19	2.8 ± 0.2	2.0 ± 0.2	3.0 ± 0.
Duffels	90 ± 8	86 ± 9	—	—	—	—	414 ± 133	444 ± 112	376 ± 152	—	—	—
Baptista	82.0 ± 6.9	81.9 ± 6.6	—	73.4 ± 13.2	72.8 ± 10.6	—	371.9 ± 90.3	428.4 ± 98.3	439.5 ± 97.5	2.4 ± 1.7	—	3.3 ± 2.3
Diller	81.1 ± 4.9	84.7 ± 2.6	84.2 ± 4.8	—	—	—	248 ± 144	363 ± 124	408 ± 114	—	—	—
D'Alto	84 ± 9	—	85 ± 8	69 ± 13	—	73 ± 12	—	—	—	5.0 ± 2.1	—	4.3 ± 1.9

"—": There was no related statistics in this study.

However, its safety and tolerability on CHD-PAH remains controversial, especially after the long-term treatment. In this study, we performed a systematic review and meta-analysis of oral bosentan in adult CHD-PAH to evaluate its safety and tolerability. Totally 8 studies including 215 patients with CHD-PAH were enrolled in this research. With a period of 3-6 months treatment in patients, there were no significant differences in the scores of resting SpO₂, post-6-MWT SpO₂ after 6-MWT and BDIs compared with the baseline; the walking distance on 6-MWT increased significantly. With a period of one year or more treatment, the scores of resting SpO₂ and post-6-MWT SpO₂ increased significantly; there was no significant difference in BDIs and walking distance on 6-MWT. The result indicated that oral bosentan in CHD-PAH patients was safe and well tolerated.

Apostolopoulou et al¹³ indicated that a long-term oral bosentan treatment in patients with CHD-PAH is safe, but the objective exercise values appear to slowly return to baseline. Meanwhile, bosentan associated with other drugs such as sildenafil can also resulting in a significant improvement in clinical status, effort SpO₂, exercise tolerance and haemodynamics²³. In our study, the result showed that a long-term treatment could increase the scores of Resting SpO₂ significantly; it was consistent with previous studies: the long-term treatment is safe for the CHD-PAH patients. In the research of human immunodeficiency virus-associated pulmonary arterial hypertension, the distance walked in 6 minutes of patients after 16 weeks of treatment with bosentan improved significantly²⁴. Badesch et al²⁵ also point out that the distance walked in 6 minutes improved after a 12 weeks of treatment, and they support the potential clinical value of endothelin receptor antagonists in the treatment of patients with PAH. In our study, the short-term treatment could also increase the distance of 6-MWT. We believed that oral bosentan has good clinical manifestation in either short-term treatment or long-term treatment for CHD-PAH patients. It was also proved in our study that oral bosentan in CHD-PAH patients was safe and well tolerated.

The result of heterogeneity test on four index combined effect size showed that there were significant heterogeneity in the combined effect size except for post-6-MWT SpO₂ and

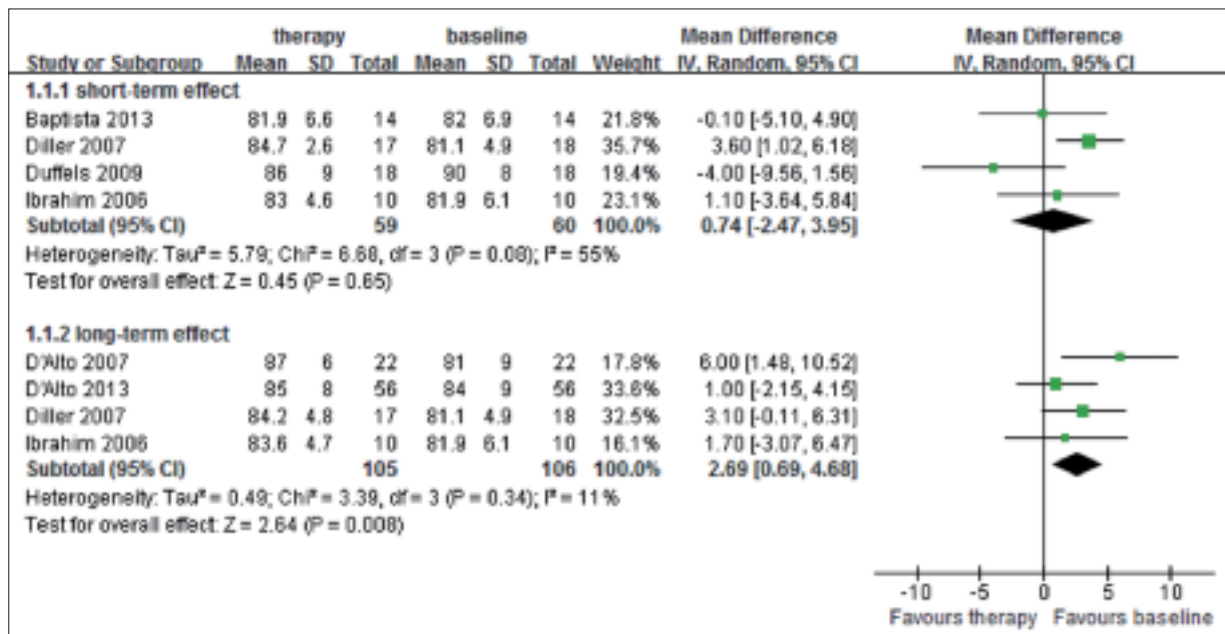


Figure 2. Forest plot of studies that compared the scores of Resting SpO₂ with short and long-term treatment of oral Bosentan.

resting SpO₂ after the long-term treatment. This might be because of the different design, the sample size, research object and other factors of these studies. The limitation of this study was as follows: (1) the existence of heterogeneity; (2) small sample size, and (3) research limitation on some unpublished literature. It was necessary to carry out large-scale multi-

center randomized controlled trial to verify the stability of our results.

Conclusions

In conclusion, the meta-analysis in the present study indicated that oral bosentan in CHD-

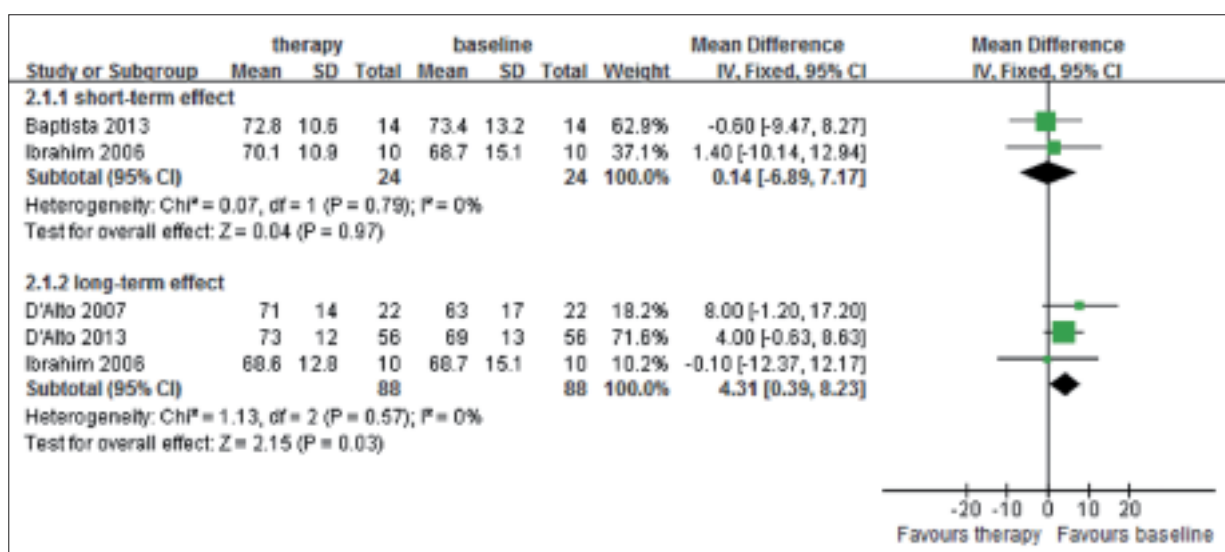


Figure 3. Forest plot of studies that compared the scores of post-6-MWT SpO₂ with short and long-term treatment of oral Bosentan.

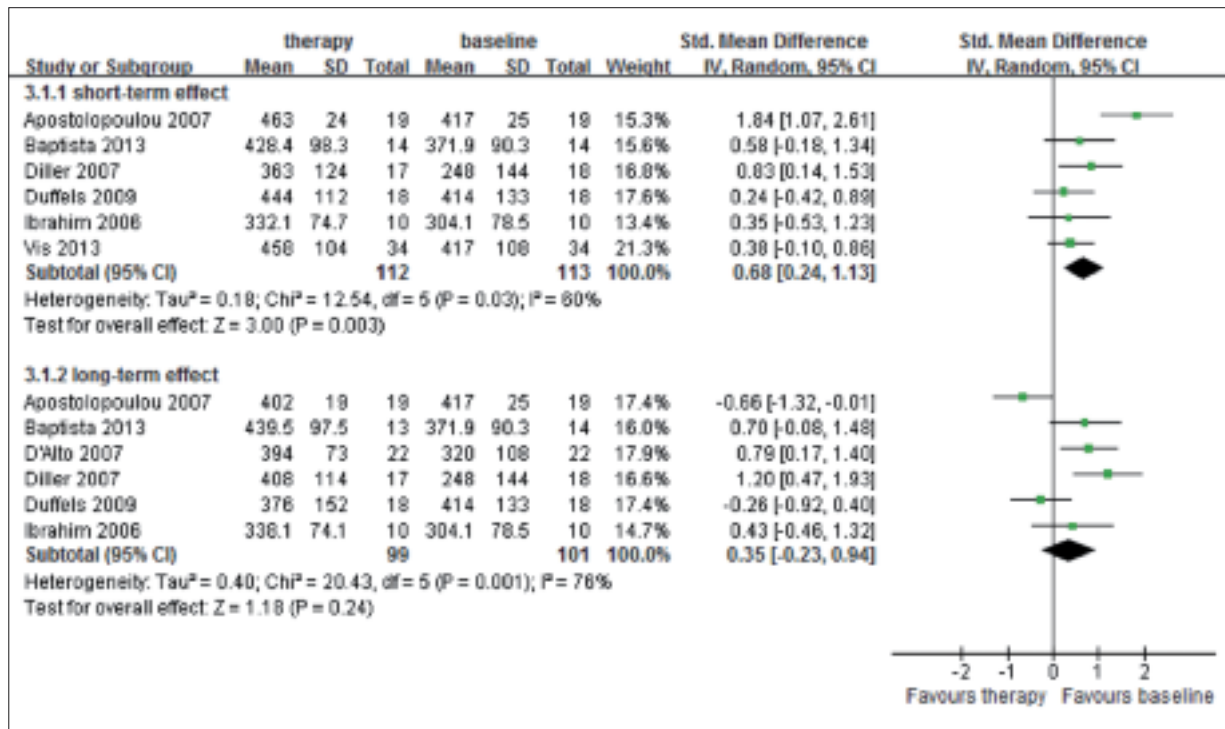


Figure 4. Forest plot of studies that compared the scores of 6-MWT with short and long-term treatment of oral Bosentan.

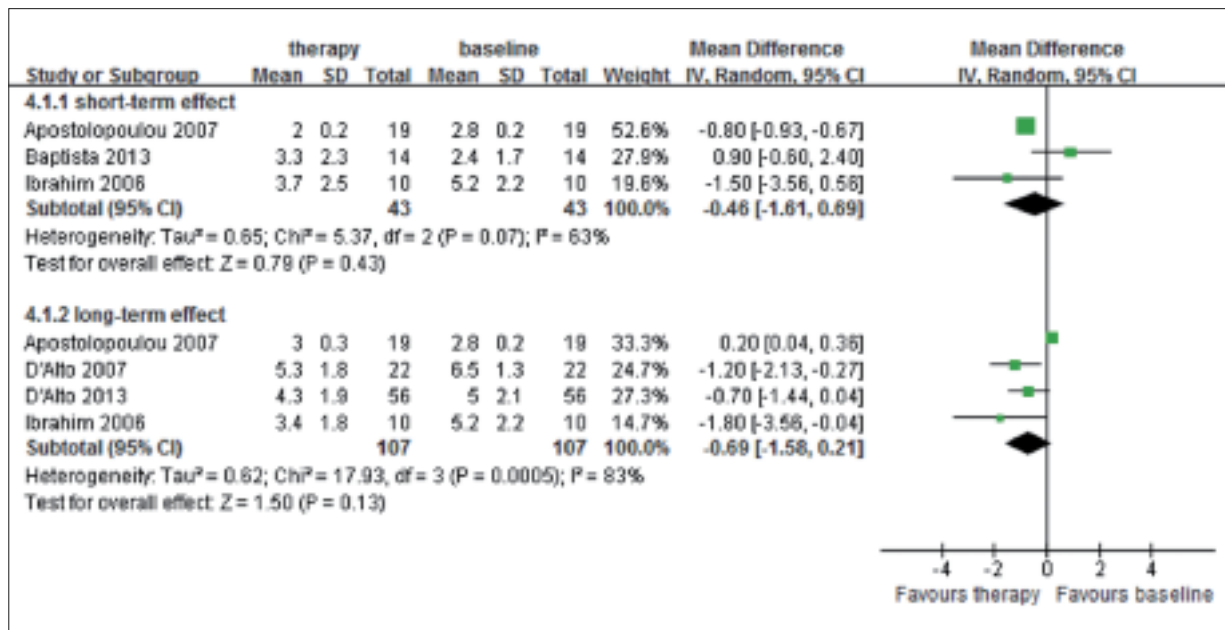


Figure 5. Forest plot of studies that compared the scores of BDIs with short and long-term treatment of oral Bosentan.

PAH patients was safe and well tolerated. So, bosentan was suggested to use in the absence of potent drugs for CHD-PAH.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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