Clinical and hemodynamic effect of endothelin receptor antagonists in Eisenmenger Syndrome

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ABSTRACT

Introduction : **Endothelin receptor antagonists (ERAs) are widely accepted as a specific treatment for pulmonary arterial hypertension. Unfortunately, consensus and recommendations are lacking for the treatment of patients who suffer from pulmonary arterial hypertension and congenital heart disease, including Eisenmenger syndrome.**

Objective : **This meta-analysis aimed to compare the effect of ERA on patients with Eisenmenger syndrome.**

Methods : **Electronic search on PubMed (MEDLINE), EBSCO, EuropePMC, Clinicaltrials.gov, and Google Scholar was done. Studies involving the use of ERAs on Eisenmenger syndrome patients were included. There were 18 studies included. The primary outcome of interest was the 6-min walking test distance before and after exposure to ERA.**

Results : **There were 517 patients with Eisenmenger syndrome. The subjects had Eisenmenger syndrome secondary to congenital heart disorders, with WHO functional Class ranging from Class I–IV. The follow-up ranges from a mean of 4–60 months. Seventeen studies reported a statistically significant difference between pretreatment and the posttreatment result of 6-min walking test distance. Pooled mean difference comparing pre and posttreatment values yielded an increase of 55.24 m (42.15, 68.33) $P < 0.001$; moderate heterogeneity I^2 51% $P = 0.008$. Pooled mean pulmonary vascular resistance index difference comparing pre and posttreatment values yielded a decrease of 4.76 woods unit (−6.86, −2.66), $P < 0.001$ favoring posttreatment; low heterogeneity I^2 0%, $P = 0.82$. Pooled mean mean pulmonary arterial pressure difference comparing pre and posttreatment values yielded a decrease of 5.40 mmHg (−7.53, −3.28), $P < 0.001$ favoring posttreatment, low heterogeneity I^2 0%, $P = 0.65$.**

Conclusion : **Implementation of ERA in Eisenmenger improves 6-min walking distance and pulmonary vascular pressure indices. Earlier administration of ERA might be beneficial, further studies are needed to assess mortality benefit of this agent.**

Keywords : Adult, congenital heart disease, Eisenmenger syndrome, endothelin receptor antagonist

Access this article online

Quick Response Code:

Website: www.annalspc.com

DOI: 10.4103/apc.APC_196_19

How to cite this article: Yonas E, Pranata R, Yamin M, Nusarintowati N, Nauli SE, Abdulgani HB, *et al*. Clinical and hemodynamic effect of endothelin receptor antagonists in eisenmenger syndrome. Ann Pediatr Card 2020;13:309-19.

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Submitted: 29-Nov-2019 **Revised:** 17-Mar-2020 **Accepted:** 06-May-2020 **Published:** 24-Jul-2020

INTRODUCTION

Endothelin receptor antagonists (ERAs) are widely accepted as a specific treatment for pulmonary arterial hypertension. Unfortunately, consensus and recommendations are lacking for the treatment of patients that suffers from pulmonary arterial hypertension and congenital heart disease, including Eisenmenger syndromr as the possible consequence of uncorrected or suboptimal correction of congenital heart diseases. This lack of consensus arises from the limited data that is available on the efficacy of specific therapies for patients with pulmonary hypertension secondary to congenital heart disease (PH-CHD) and patients with Eisenmenger syndrome.

It is important to note that currently, there has been no established relation between PH-specific therapy and survival of patients with PH-CHD and Eisenmenger syndrome.

Several widely known trial such as the MAESTRO and BREATHE-5 trial have been conducted that studies specific subjects with Eisenmenger syndrome and the subsequent changes in hemodynamic and clinical profiles with the use of ERA agents, with the majority of studies using bosentan, with macitentan and sitaxentan to a lesser degree.[1,2]

This meta-analysis aims to pool results across studies that involve the use of ERAs on patients with Eisenmenger syndrome. The authors hoped that with the availability of these pooled results, a thorough analysis could be synthesized in this topic.

METHODS

We performed a comprehensive search on studies that assess the use of ERAs in Eisenmenger syndrome patients from inception up until January 2020. We searched (Endothelin receptor antagonist Eisenmenger syndrome) and its synonyms using PubMed, EuropePMC, EBSCOhost, Cochrane Central Database, ClinicalTrials.gov, and snowballing from potential articles cited by other studies. The records were then systematically evaluated using inclusion and exclusion criteria. Two researchers (E. Y and R. P) independently performed an initial search; discrepancies were resolved by discussion. (A preferred reporting items for systematic reviews and Meta-Analysis flowchart of the literature search strategy of studies).

Selection criteria

The inclusion criteria for the study are all studies that assess the use of ERAs on Eisenmenger syndrome patients. Cross-sectional and case–control studies were excluded as of those studies with insufficient data to assess the outcome of interest. The primary outcome measured was the 6 min walking test distance (6MWD). Secondary outcomes were Borg dyspnea index, resting oxygen saturation, liver function test results, and pulmonary vascular resistance index. We include all clinical researches/original articles and exclude case reports, review articles, and non-English language articles.

Data extraction

Data extraction and risk of bias assessment were done by two independent authors (E. Y and R. P) using standardized extraction form with includes authors, year of publication, study design, sample size, type of ablation, and length of follow-up.

Statistical analysis

Meta-analysis was performed using RevMan version 5.3 Software (Cochrane Collaboration). We used mean difference (MD) and its standard deviation (SD) as a pooled measure for the continuous data. Inconsistency index (I^2) test, which ranges from 0% to 100% was used to assess heterogeneity across studies. A value >50% or $P < 0.05$ indicates statistically significant heterogeneity. We used the generic inverse variance method (for HR and MD) with a fixed-effect model for meta-analysis and a random-effect model in case of significant heterogeneity. All P values were two-tailed with a statistical significance set at 0.05 or below.

RESULTS

The search result for studies that involve the use of ERA on Eisenmenger patients yielded a total of potential 298 articles. We removed 197 duplicates. We excluded 72 articles after screening the titles and abstracts. There were 29 potentially relevant articles. We screened the full articles and abstracts and after applying the inclusion and exclusion criteria, 11 studies were excluded because studies did not include outcome of interest (n = 7), studies being meta-analysis (n = 2), studies being systematic review (n = 1), studies comparing between ERA to another agent (n = 1). We included 18 studies for qualitative synthesis and 18 studies were available for meta-analysis. There were 517 patients with Eisenmenger who were administered ERA from these studies. All subjects suffered from Eisenmenger syndrome secondary to congenital heart diseases. The follow-up ranges from 4–60 months [Table 1 and Figure 1].

Six minutes walking test distance

Seventeen studies reported a statistically significant difference in walking distance between posttreatment and pretreatment with ERAs. Pooled MD comparing pre and posttreatment values yielded an increase of 55.24 m (42.15, 68.33) $P < 0.001$; moderate heterogeneity

Table 1: Result of the studies included in the qualitative synthesis

Author	Year	Study design	Sample size	ERA agent and dosing	Length of treatment (months)	6MWT pre- and post-treatment	WHO FC	Borg dyspnea index	SAT O2 (resting)	LFT Levels (pre- vs. post-ERA)	PVRI (pre vs. post)	MPAP (Pre vs. Post)	Follow up (months)
Abdelrahman *et al.*	2014	Prospective cohort	40	Bosentan 62.5 mg BID titrated to 125mg BID at 4th week	24 weeks	382.5 (312-430) versus 450 (390-510)	N/A	N/A	86±7 versus 88±7	AST 26 (20-32) versus 25.5 (21-30.2) ALT 18 (14.1-26.8) versus 20 (15-29.5)	N/A	80 (71-91) versus 78 (70-94)	6
Apostolopoulou *et al.*	2007	Prospective cohort	19	Bosentan 62.5 mg BID titrated to 125 mg BID at 4th week	4 months	417±25 versus 463±24	Pretreatment: 5 Px WHO FC II; 12 Px WHO FC III; 2 Px WHO FC IV Posttreatment WHO FC II: 13 WHO FC III: 6	2.8±0.2 versus 2.0±0.2	NA	NA	NA	NA	4 On treatment 29 In Total
Baptista *et al.*	2014	Prospective cohort	14	Bosentan 62.5 mg BID titrated to 125 mg BID at 4th week	6 months	371.9±90.3 versus 428.4±98.3	Pretreatment WHO FC II: 1 WHO FC III: 11 WHO FC IV: 2 Posttreatment WHO FC I: 1 WHO FC II: 8 WHO FC III: 5 WHO FC IV: 0	2.4±1.7 versus 3.3±2.3	82.0±6.9 versus 81.9±6.6	N/A	NA	NA	6
Crepaz *et al.*	2013	Prospective cohort	7	Bosentan 62.5 mg BID titrated to 125 mg BID at 4th week for 12 months	12 mo	199.6±69. 1versu s301.6±88.7 at 12 months	Pretreatment All subjects WHO FC III Post treatment: WHOFC II: 1 WHOFC III: 6	3.6±1.4 versus 2.1±1.2 at 12 months	81.7±6.6 versus 89.0±2.5 at 12 months	NA	NA	N/A	24
D Alto *et al.*	2007	Prospective Cohort	22	Bosentan 62.5mg BID titrated to 125mg BID at 4th week for 12 months	12 months	320±108 versus 394±73	3.1±0.7 versus 2.5±0.7	6.5±1.3 versus 5.3±1.8	81±9 versus 87±6	AST 24±9 versus 28±12 ALT 31±21 versus 31±19	22±12 versus 14±9 WU	73±18 versus 71±22	25 months
D Alto *et al.*	2012	Prospective Cohort	32	Bosentan 62.5mg BID titrated to 125mg BID at 4th week for 12 months±Sildenafil PO 20 mg QD	6 months	293±68 versus 360±51	2.9±0.3 versus 21.±0.4	4.4±2.3 versus 2.9±1.5	80±9 versus 82±8	AST 19±6 versus 18±7 ALT 28±9 versus 30±12	24±16 versus 19±9 WU	73±20 versus 71±17	6 months

Contd...

Table 1: Contd...

Author	Year	Study design	Sample size	ERA agent and dosing	Length of treatment (months)	6MWT pre- and post-treatment	WHO FC	Borg dyspnea index	SAT O2 (resting)	LFT Levels (pre- vs. post-ERA)	PVRI (pre vs. post)	MPAP (Pre vs. Post)	Follow up (months)
Diller *et al.*	2007	Prospective cohort	18	Bosentan 62.5mg BID titrated to 125mg BID at 4th week for 12 months	6 mo	284±144 versus 363±124	Pretreatment: WHO FC III: 18 Posttreatment	NA	81.1±4.9 versus 84.5±2.8	NA	NA	NA	29 months (median)
Gallie *et al.*	2006	RCT	37 subjects out of 54 total subjects. (17 subjects placebo)	Bosentan 62.5 mg BID titrated to 125 mg BID at 4th week for 12 months	4 mo	331.9±82.8 versus 375.2±8.1	Pretreatment: WHOFC III: 37 Posttreatment WHOFC II:13 WHO FCIII:13 WHOFC IV:1	NA	82.4±5.3 versus 80.2±8.9	NA	42.81±17.63 versus 38.85±0.0667 WU	77.8±15.2 versus 72.8±1.6	4 months
Gatzoulis *et al.*	2008	RCT	11 ERA NAÏVE subjects.	Bosentan 62.5 mg BID titrated to 125 mg BID at 4th week for 12 months	6 mo	354.9±95.6 versus 388.1±23.9	Pretreatmen WHOFC II: 2 WHOFC III: 9 Posttreatment WHOFC II: 7 WHOFC III: 4	NA	84.2±6.5 versus 85.0±1.3	NA	NA	NA	4 months
Gatzoulis *et al.*	2019	RCT	114	Macitentan 10 mg for 16 weeks	16 weeks	368.7±74.5 versus 387.1±101.8	Pretreatment WHOFC II: 69 WHOFC III: 45 Posttreatment WHOFC I:3 WHOFC II: 72 WHOFC III: 38 WHOFC IV: 1	NA	84.3±5.6 versus 85.4±5.8	NA	35.26±16.51 versus 30.14±12.64 WU	77.5±11.6 versus 71.1±13.6	4 mo
Kaya *et al.*	2012	Prospective Cohort	23	Bosentan 62.5 mg BID titrated to 125 mg BID at 4th week	24±9	286±129 sv 395±120	Pretreatment WHOFCIII: 20 WHOFC IV: 3 Posttreatment WHOFC II: 17 WHOFC III: 6	NA	84.6±6.5 sv 88.8±3.9	ALT 31±6 versus 34±7 AST 28±7 versus 30±8	NA	NA	24±9 months
Kermeen *et al.*	2010	Prospective Cohort	53	Bosentan (48 patients) 62.5 mg BID titrated to 125 mg BID Sitaxentan (5 patients) 100 mg/day	14.7±2.8 months	344 m±18 versus 417±25 (posttreatment value were taken from 17 cases $P<0.0005$)	Pretreatment WHOFC I: 0 WHOFC II: 3 WHOFC III: 39 WHOFC IV: 11 Posttreatment WHOFC I: 2 WHOFC II: 5 WHOFC III: 10 WHOFC IV: 0	N/A	85±1 versus 85±1.6 (posttreatment data were taken from 17 cases)	N/A	N/A	N/A	24 mo

Contd...

Table 1: Contd...

Author	Year	Study design	Sample size	ERA agent and dosing	Length of treatment (months)	6MWT pre- and post-treatment	WHO FC	Borg dyspnea index	SAT O2 (resting)	LFT Levels (pre- vs. post-ERA)	PVRI (pre vs. post)	MPAP (Pre vs. Post)	Follow up (months)
Kotlyar *et al.*	2006	Prospective Cohort	17 ERA Naïve	Bosentan 62.5 mg BID titrated to 125 mg BID at 4th week	15±10	318±129 versus 323±148 @ 6 months	Pretreatment WHOFC I: 0 WHOFC II: 3 WHOFC III: 12 WHO FC IV: 2 Posttreatment WHOFC I: 0 WHOFC II: 7 WHOFCIII: 6 WHOFC IV: 0 @ 6th month	5±2 versus 4±3 @ 6th month	82±9 versus 84±10 @ 6th month	ALT : 28±15 versus 22±11	NA	NA	15±10 Mo
Mehta *et al.*	2008	Prospective Cohort	24 (21 Bosentan±3 Sitaxentan)	Bosentan 62.5 mg BID titrated to 125mg BID at 4th week Sitaxentan 50 mg QD titrated to 100 mg QD at 4th week.	19±12 mo	226±159 versus 351±113	N/A	N/A	80±11 versus 87±9	ALT 25 (13-100) versus 28 (14-163) AST 27 (16-85) versus 26(15-104)	NA	59±16 versus 47±17	22 (3-48)
Schulze-Neick *et al.*	2005	Prospective Cohort	33	Bosentan 62.5 mg BID titrated to 125 mg BID at 4th week	25±6	362±105 versus 434±68	NA	5.2±2.1 versus 3.7±2.3	86±7 versus 88±7	AST 20.4±17.3 versus 30.6±20.7 ALT 21.1±14.6 versus 23.5±14.0	15.31±11.73 versus 12.58±3.43 WU	87.8±22 versus 84.5±25.1	25±6 mo
Serino *et al.*	2013	Retrospective	7	Bosentan 62.5 mg BID titrated to 125 mg BID at 4th week	24	261±64 versus 306±62 @12 months 298±60@24 months	NA	NA	NA	NA	NA	NA	24
Tacoy *et al.*	2014	Prospective Cohort	12	Bosentan 62.5 mg BID titrated to 125 mg BID at 4th week	60 months (5 years)	NA	NA	NA	NA	NA	NA	103.50±29.63 versus 113.87±28.56	60 months (5 years)
Zuckerman *et al.*	2011	Retrospective	17	Ambrisentan Initial dose 5 mg/day titrated to 10 mg/day	19 months	395±91 versus 402±70	N/A	N/A	89±5 versus 90±6	N/A	20.8±14.4 versus 14.6±4.2 WU (Data taken from 6 cases)	61.8±8.5 versus 55.7±4.6 (Mean taken from 6 cases)	2.5±0.5 years

NA: Not available, WHO: World health organization, AST: Aspartate transaminase, ALT: Alanine aminotransferase, WHOFC: World health organization functional class, ERA: Endothelin receptor antagonists, RCT: Randomized controlled trial, PVRI: Pulmonary vascular resistance index, MPAP: Mean pulmonary arterial pressure, 6MWT: Six minute walking test, BID: Twice A Day, LFT: Liver Function Test

I^2 51% $P = 0.008$. We performed sensitivity analysis and upon removal of study by Gatzoulis *et al.* 2019, Kermeen *et al.* 2010 and Zuckerman *et al.* 2011 heterogeneity decreased to I^2 0% $P = 0.46$. with a pooled result of 54.67 m (44.80, 64.55) $P < 0.001$ [Figure 2a and b].[1-17]

Borg dyspnea index

Seven studies reported a statistically significant difference in Borg dyspnea index between posttreatment and pretreatment with ERAs. Pooled MD comparing pre and posttreatment values yielded a decrease of 0.99 Borg dyspnea index [−1.43, −0.54], $P < 0.001$ favoring posttreatment; low-moderate heterogeneity I^2 42%, $P = 0.11$.[5,7,11-15]

We performed sensitivity analysis and upon removal of the study by Baptista *et al.* and D'alto *et al.* (2012). Heterogeneity decreased to I^2 0% $P = 0.51$ [Figure 3].

Resting oxygen saturation

Fifteen studies reported a statistically significant difference in resting oxygen saturation between posttreatment and pretreatment with ERAs. Pooled MD comparing pre and posttreatment values yielded an increase of 1.93% (0.75, 3.11), $P < 0.001$ favoring posttreatment; moderate heterogeneity I^2 57%, $P = 0.003$. Sensitivity analyses were performed and removal of the study by Crepaz *et al.* D'Alto *et al.* (2007) Gallie *et al.* and Kermeen *et al.* 2010 resulted in a pooled MD of 1.93% (1.02, 2.84) $P < 0.001$; I^2 0% $P = 0.53$ [Figure 4a and b].[1-7,9,10,12-17]

Pulmonary vascular resistance index

Six studies reported a statistically significant difference in pulmonary vascular resistance index between posttreatment and pretreatment with ERAs. Pooled MD comparing pre and posttreatment values yielded a decrease of 4.76 Woods unit (−6.86, −2.66), $P < 0.001$ favoring posttreatment; low heterogeneity I^2 0%, $P = 0.82$ [Figure 5].[1,7,9,14,15,17]

Mean pulmonary arterial pressure

Nine studies reported a statistically significant difference in mean pulmonary arterial pressure (MPAP) between posttreatment and pretreatment with ERAs. Pooled MD comparing pre- and post-treatment values yielded

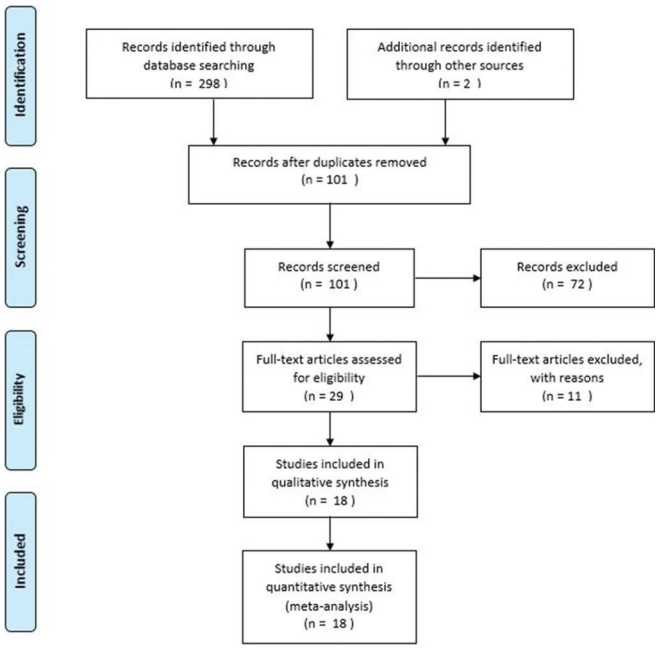

Figure 1: PRISMA diagram

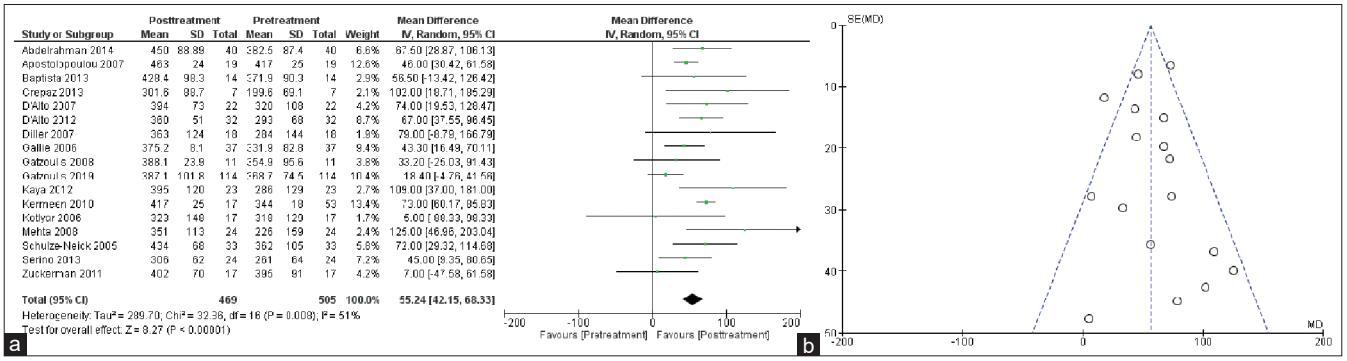

Figure 2: Meta analysis. (a) 6 min walking distance, pooled mean difference (meters) favoring posttreatment. (b) Funnel plot of analysis

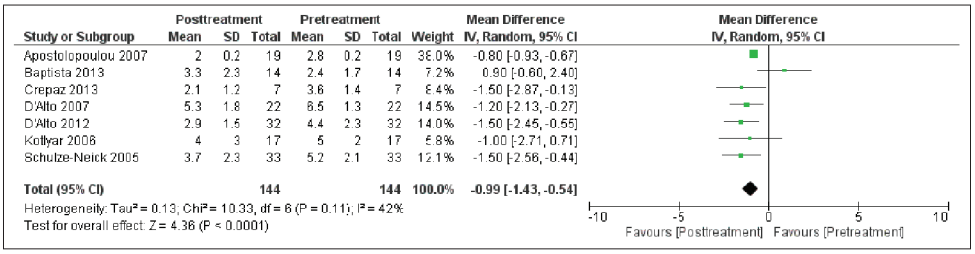

Figure 3: Borg dyspnea index, pooled mean difference favoring posttreatment

a decrease of 5.40 mmHg (–7.53, –3.28), $P < 0.001$ favoring posttreatment, low heterogeneity I^2 0%, $P = 0.65$ [Figure 6].[1,6,7,9,10,14,15,18]

Aspartate aminotransferase levels

We performed a meta-analysis comparing aspartate aminotransferase levels in patients who received ERAs before and after treatment with ERAs. The pooled MD yielded an increase of 0.69 U/L (–1.23, 2.61), $P = 0.48$, low-moderate heterogeneity I^2 29%, $P = 0.22$. However, these results were not statistically significant.[3,6,7,10,14,15]

Alanine aminotransferase levels

We performed a meta-analysis comparing alanine aminotransferase levels in patients who received ERAs before and after treatment with ERAs. The pooled MD yielded an increase of 1.81 U/L (–0.42, 4.05), $P = 0.11$, low heterogeneity I^2 0%, $P = 0.74$. However, these results were not statistically significant.[3,5-7,10,14,15]

Subgroup analysis

We performed subgroup analysis on 6MWD and pulmonary vascular resistance index (PVRI) based on follow-up length (short-term ≤ 6 months and long-term ± 24 months).

Six minutes walking distance, short-term follow-up

Seven Studies reported a statistically significant difference in walking distance between posttreatment and pretreatment with ERAs. Pooled MD comparing pre and posttreatment values yielded an increase of 44.96 m (31.31, 58.62) $P < 0.001$; low-moderate heterogeneity I^2 32% $P = 0.19$.[1,2,10-12,15,17]

Six minutes walking distance, long-term follow-up

Eight studies reported a statistically significant difference in walking distance between posttreatment and pretreatment with ERAs. Pooled MD comparing pre and posttreatment values yielded an increase of 72.96 m (54.57, 91.34) $P < 0.001$; low heterogeneity I^2 20% $P = 0.27$.[3,4,6,7,9,13,14,16]

Pulmonary vascular resistance index, short-term follow-up

Three studies reported a statistically significant difference in pulmonary vascular resistance index

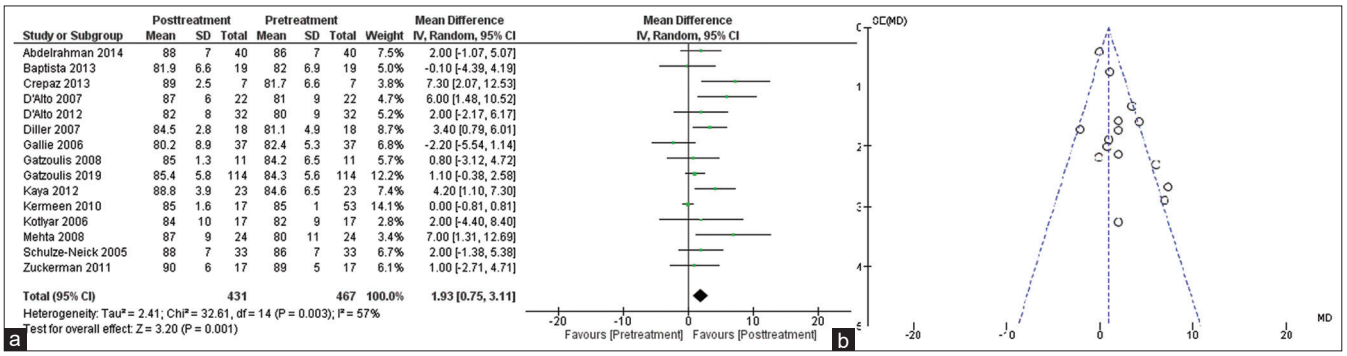

Figure 4: (a) Resting saturation of oxygen, pooled mean difference (%) favoring posttreatment. (b) Funnel plot of analysis

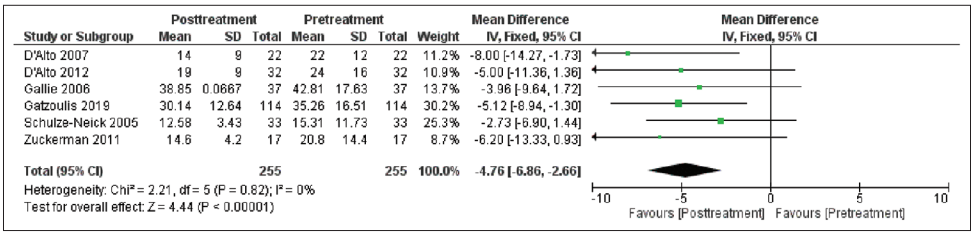

Figure 5: Pulmonary vascular resistance index, pooled mean difference (woods unit) favoring Posttreatment

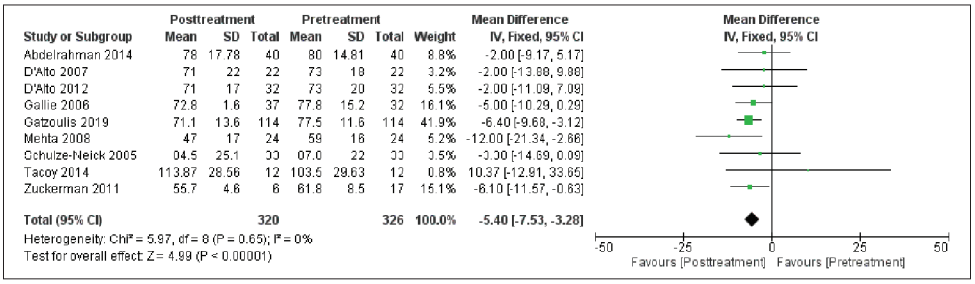

Figure 6: Mean pulmonary arterial pressure, pooled mean difference (mmHg) favoring posttreatment

between posttreatment and pretreatment with ERAs. Pooled MD comparing pre and posttreatment values yielded a decrease of 4.81 Woods unit (−7.64, −1.97), $P < 0.001$ favoring posttreatment; low heterogeneity I^2 0%, $P = 0.94$.[1,15,17]

Pulmonary vascular resistance index, long term follow up

Three studies reported a statistically significant difference in pulmonary vascular resistance index between posttreatment and pretreatment with ERAs. Pooled MD comparing pre and posttreatment values yielded a decrease of 4.70 Woods unit (−7.82, −1.58), $P = 0.003$ favoring posttreatment; low heterogeneity I^2 4%, $P = 0.35$.[7,9,14]

DISCUSSION

Our study showed that the use of ERAs significantly increases 6MWD of patients. In normal patients, a result of 400–700 m is achievable, this is contrasted with the pretreatment levels of patients in this meta-analysis, in which only 1 of 15 studies showed a pretreatment 6MWD higher than 400 m.[11,19]

We observed a MD of 55.24 m in between posttreatment and pretreatment results of 6MWD. This is in accordance with data from several studies that stated that in the light of available evidence, a minimally important difference in changes on 6MWD should be no less than 30 m.[20]

Due to the diversity of follow-up length of studies included in this meta-analysis, we performed a subgroup analysis on 6MWD and PVRI based on short term (≤6 months) and long-term (±24 months) to further observe the effect of ERA in eisenmenger patients and to avoid bias from synthesizing conclusion from such diverse length of follow up. The result of this subgroup analysis on 6MWD on both short and long term follow up shows that the use of ERA is associated with a longer posttreatment 6MWD (44.96 and 72.96 m MD, respectively). A similar result was also observed on a subgroup analysis of PVRI on short and long term follow-up showing that the use of ERA is associated with decreased posttreatment level of PVRI (4.81 vs. 4.70 woods unit MD, respectively).

Patients with Eisenmenger syndrome commonly suffer from dyspnea that hinders them from performing daily routines, a quantitative decrease of dyspnea can be observed by the decrease of mean Borg dyspnea index that can be observed in this meta-analysis, a cumulative decrease of Borg dyspnea index rating of 00.99 points can be observed on this meta-analysis. However, this kind of dyspnea scoring poses a risk of subjectivity due to these scores being rated by the patient on a subjective basis.

We did not observe a significant improvement in resting oxygen saturation even with treatment using ERAs, with only an increase of 1.93% in pooled results. However, we observed a significant decrease in pulmonary vascular resistance index of 4.76 woods unit in pooled results after treatment with ERA.

PVRI is thought to be the direct indices of pulmonary vascular resistance, and its decrease following treatment with ERA signifies the potential benefit of using this agent on Eisenmenger syndrome patients.

Furthermore, a cumulative decrease of mean Pulmonary artery pressure was also observed with an observed mean reduction of 5.40 mmHg after treatment with ERA.

Elevations in liver function test and subsequent hepatic injury are some major concerns in regards to treatment with ERA, in this meta-analysis, we did not find any significant alteration of liver function test in the studies that are included in this meta-analysis, a pooled result of changes in Aspartate transaminase and Alanine Transaminase showed only minimal alterations after treatment with ERA, however, this analysis were not statistically significant and further studies will need to be done.

Our initial meta-analysis on resting oxygen saturation showed a low-moderate heterogeneity of 57% with $P = 0.001$. Based on the approach suggested by Fletcher, this meta-analysis was comprised of studies that are mostly prospective cohort. This study only showed a low-moderate heterogeneity. The forest plot of this meta-analysis showed the consistent result of a trend of decrease in resting saturation of oxygen. The sensitivity analysis of this meta-analysis does not show a significant change in the exclusion of said studies.[21]

In this meta-analysis, we can observe improvement in the 4th month after the administration of ERA. This is due most studies performing first follow-up at the 4th month since the initial administration of ERA. Clinical improvement consists of improvement in 6-min walking distance and Borg dyspnea index while hemodynamic improvement consists of improvement in MPAP, pulmonary vascular resistance index and resting saturation of oxygen.

The observed improvement after treatment with ERAs on this meta-analysis showed that the use of ERAs in Eisenmenger syndrome patients is highly likely to be beneficial to patients.

The rationale and support for the use of Bosentan in Eisenmenger syndrome came from the BREATHE-5 study, in which 54 treatment naïve patients with WHO FC III was assigned to Bosentan or placebo. 6MWD significantly improved, PVR was reduced by a 5.9 woods unit., and MPAP was reduced by 5.5 mmHg.[17] However, the result two of major randomized control trials, namely MAESTRO and BREATHE-5, were conflicting in terms that in MAESTRO study which compared between macitentan

and placebo on patients >12 years old with congenital cardiac defects, 6MWD was not significantly improved in the macitentan versus placebo (18.3 m vs. 19.7 m in the placebo group). Unexpectedly, large improvement in 6MWD in the placebo group was observed. However, it is to be taken into consideration that the MAESTRO trial included a more heterogeneous study population than the BREATHE-5 Trial.[1,2] Currently, the statement of AHA/ACC on the 2018 AHA/ACC Guideline for the Management of Adults with Congenital Heart Disease stated that Bosentan is beneficial in symptomatic adults with Eisenmenger syndrome with ASD or VSD (recommendation Class I, level of Evidence A). In symptomatic adults with Eisenmenger syndrome, bosentan and PDE-5 inhibitors are reasonable in combination if symptomatic improvement does not occur with either medication alone (Recommendation Class IIa, Level of Evidence B-R [Moderate quality evidence from 1 or more RCTs/Meta-analyses of moderate quality RCTs]). Regarding Eisenmenger syndrome with ASD/VSD shunt, Bosentan is reasonable therapy to treat symptomatic adults with Eisenmenger syndrome with 1 of the following: Shunts other than ASD/VSD (PDA, aortopulmonary window) (Level of Evidence C-EO) or Complex congenital heart lesions (Level of Evidence B-NR).[22]

In comparison with the AHA/ACC guideline, the ESC guideline stated that the ERA bosentan should be initiated in WHO-FC III patients with Eisenmenger syndrome (Recommendation Class I, Level of Evidence B). Combination therapy may be considered in WHO-FC III patients with Eisenmenger Syndrome (Recommendation Class IIb, Level of Evidence C). Regarding other agents of pulmonary hypertension-specific therapy, ESC stated that Other ERAs, phosphodiesterase type-5 Inhibitors and prostanoids should be considered in WHO-FC III patients with Eisenmenger syndrome.(recommendation Class IIa, Level of Evidence C). The ESC guideline also highlights explicitly that currently there is only one randomized control trial including 54 patients that has a favorable effect on exercise capacity and hemodynamics of ERA treatment on Eisenmenger syndrome (BREATHE-5 Study).[23]

The results of this meta-analysis further solidify the latest recommendation of AHA/ACC and ESC regarding the use of ERA in Eisenmenger syndrome patients, that the use of these agents is beneficial. Despite the unavailability of data regarding the survival of patients on ERA, results of hemodynamic measurements showed significant improvement with the use of these agents. However, further studies will be needed to obtain data regarding mortality while on ERA treatment, and comparison of performance between ERA and other agents in Eisenmenger syndrome patients. Data regarding mortality benefit on ERA is crucial to determine whether earlier administration of ERA in Eisenmenger patients (WHO FC less than III) or even patients with early symptomatic pulmonary hypertension will be beneficial, as compared to ESC guideline in which ERA will only be considered in Eisenmenger patients with WHO FC III. Based on the hemodynamic improvements with the use of ERA, the authors of this meta-analysis postulated that earlier administration of ERA will be beneficial, however, further mortality data will be needed.

With the current guidelines mainly focusing on the BREATHE-5 Study which generated a favorable outcome in using ERA in Eisenmenger patients, the authors of this meta-analysis would like to bring a broader perspective using multiple other studies on the hemodynamic and clinical profile of patients who are exposed to ERA.

As per the recommendations from Cochrane collaborations, the authors of this manuscript utilizes the I2 method of projecting statistical heterogeneity on this meta-analysis. We performed a sensitivity analysis on results that are deemed to have significant heterogeneity. According to available literature, we classified heterogeneity to No observed heterogeneity, low, moderate, and high based on percentages (0, 25, 50, and 75% respectively).[24] We also performed sensitivity analysis based on the *P* value of heterogeneity quantification, and we performed a further sensitivity analysis on *P* value that exceeds $P = 0.1$ on heterogeneity quantification.[21] Due to the heterogeneity of methods of studies and data gathering, we are unable to include the World Health Organization functional class (WHO-FC) on our meta-analysis; however, we can observe that improvement occurs on patients that consume ERA on WHO FC II–IV. With patients being reclassified into milder functional classes at the end of studies.

The authors acknowledged that, based on the current data, we cannot establish a mortality benefit based on the use of ERA agents due to the lack of survival data. We observed improvement in clinical and hemodynamic parameters after treatment with ERA; however, these findings did not directly translate into mortality benefit of using ERA agents. In future, more randomized control trials and longer follow-up of these patients are needed to better understand the potential benefit, mortality benefit, and safety profile of ERAs in Eisenmenger syndrome. The limitation of this systematic review includes potential selection bias because not all of the studies included were randomized controlled trials. The majority of studies included in this meta-analysis only contain pre and posttreatment data of patients without control and no data regarding survival. Based on our analysis using funnel plots, we cannot exclude the possibility of publication bias on analysis regarding resting oxygen saturation. The study also included studies with varying lengths of follow-up and treatment using ERA. Ideally,

it is prudent to perform an analysis of studies with the longest follow-ups, however, due to the sparse nature of data regarding ERA in Eisenmenger patients, such an ideal approach was not applicable.

CONCLUSION

Administration of ERA on patients with Eisenmenger showed promising results in terms of 6-min walking distance, pulmonary vascular resistance index and MPAP. ERA also decreases the Borg dyspnea index in patients with Eisenmenger syndrome. Randomized Control trials should be done in the future to better compare the treatment effects of this agent. A longer follows-up period is needed to better understand mortality benefit and safety profile of this agent. We also suggest that future studies include all of the parameters studied in this meta-analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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