Systematic Review and Meta-Analysis

Medicine®

OPEN

What is the position of pulmonary arterial hypertension-specific drug therapy in patients with Eisenmenger syndrome

A systematic review and meta-analysis

Qiang Li, BM[a,b,c,d], Hong-Yu Kuang, BM[a,b,c,d], Yu-Hao Wu, BM[e], Tie-Wei Lu, MD[a,b,c,d], Qi-Jian Yi, MD[a,b,c,d,*]

Abstract

Background: It is commonly reported a limitation of therapeutic strategy in Eisenmenger syndrome (ES) historically. This qualitative systematic review is conducted to evaluate the safety and efficacy of pulmonary arterial hypertension-specific drug therapy (PAH-SDT) for ES patients for a clinical therapeutic strategy based on evidence.

Methods: PubMed, EMBASE, and the Cochrane Library databases have been systematically reviewed up to January 2019. Two reviewers independently conducted a literature search, quality evaluation, and data extraction. The occurrence of death, deterioration, and adverse events (AEs) has respectively been described as a count or percentage. Meta-analysis was conducted by Stata 15.1, and weighted mean differences (WMD) with 95% confidence intervals (CI) were recorded for continuous data. Randomized-effect model or fixed-effect model was applied according to the heterogeneity test.

Results: Fifteen citations recruiting 456 patients associated with ES were eventually pooled, which involved 4 RCTs, 6 prospective studies, and 5 retrospective studies. Within the first year, it indicated PAH-SDT significantly ameliorated exercise capacity in 6-minute walk distance (6MWD) (I^2 = 60.5%; WMD: 53.86 m, 95% CI [36.59, 71.13], $P < .001$), functional class (FC) (WMD = –0.71, 95% CI [–0.98, –0.44], $P < .001$) and Borg dyspnea index (WMD = –1.28, 95% CI [–1.86, –0.70], $P < .001$), in addition to hemodynamics, especially mean pulmonary arterial pressure by 5.70 mmHg (WMD = –5.70 mmHg, 95% CI [–8.19, –3.22], $P < .001$) and pulmonary vascular resistance by 4.20 wood U (WMD: –4.20, 95% CI [–7.32, –1.09], $P = .008$), but unsatisfactory effects in oxygen saturation at exercise ($P = .747$). In a prolonged medication, bosentan, a dual ERA, has been proved acting an important role in improving exercise tolerance of patients with ES (6MWD: I^2 = 47.5%; WMD: 88.68 m, 95% CI [54.05, 123.3], $P < .001$; FC: I^2 = 0.0%; WMD = –0.65, 95% CI [–1.10, –0.19], $P = .006$). While a nonsignificant change of 6MWD was noted in a long-term therapy of ambrisentan ($P = .385$). There existed rare evidence about the efficacy and safety of macitentan, phosphodiesterase-5 inhibitors (PDE5i), and prostanoids in a prolonged medication. Most AEs were recorded as mild to moderate with PAH-SDT, but about 4.3% individuals treated with endothelin receptor antagonists (ERAs) suffered from serious ones, and 3.9% suffered from death.

Conclusions: This systematic review and meta-analysis proved PAH-SDT as a safe and effective role in ES in an early stage. However, in a long-term treatment, bosentan has been supported for a lasting effect on exercise tolerance. A further multicenter research with a large sample about pharmacotherapy of ES is necessary.

Abbreviations: 6MWD = 6-minute walk distance, AEs = adverse events, ASD = arterial septal defects, AVC = atrioventricular canal, BDI = Borg dyspnea index, CHD = congenital heart disease, CI = confidence intervals, DS = Down's syndrome, ERAs = endothelin receptor antagonists, ES = Eisenmenger syndrome, FC = functional class, HR = heart rate, mPAP = mean pulmonary arterial hypertension, PAH = pulmonary arterial hypertension, PAH-SDT = PAH-specific drug therapy, PDA = patent ductus arteriosus, PDE5i = phosphodiesterase-5 inhibitors, PVR = pulmonary vascular resistance, RCT = randomized controlled trails, SpO_2 = oxygen saturations, VSD = ventricular septal defects, WMD = weighted mean differences.

Keywords: Eisenmenger syndrome, pulmonary arterial hypertension-specific drug therapy, pulmonary arterial hypertension, systematic review and meta-analysis

Editor: Robert Chen.

QL and H-YK have contributed equally to this work.

Q-JY who takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

No funding has been mentioned in this manuscript.

The authors have stated that there exist no conflicts of interest in this study.

[a] Department of Cardiology, [b] Ministry of Education Key Laboratory of Child Development and Disorders, [c] China International Science and Technology Cooperation Base of Child Development and Critical Disorders, [d] Chongqing Key Laboratory of Pediatrics, [e] Department of Cardiothoracic Surgery, Children's Hospital of Chongqing Medical University, Chongqing, China.

[*] Correspondence: Qi-Jian Yi, Department of Cardiology, Children's Hospital of Chongqing Medical University, Chongqing, 400014, China (e-mail: 625523648@qq.com).

Medicine (2019) 98:20(e15632)

Received: 22 October 2018 / Received in final form: 5 March 2019 / Accepted: 18 April 2019

http://dx.doi.org/10.1097/MD.0000000000015632

1. Introduction

Eisenmenger syndrome (ES) is the most advanced form of pulmonary arterial hypertension (PAH) that is defined as congenital heart disease (CHD) associated with an initial great systemic-to-pulmonary shunt, inducing an elevated vascular resistance with a reverse direction.[1] As reported in western countries, the prevalence of PAH-CHD is 1.6 to 12.5 cases per million adults, commonly resulted from atrial septal defects (ASD), ventricular septal defects (VSD), patent ductus arteriosus (PDA), and more in complex lesions.[2] And 25% to 50% of this population affected by ES, with a progressive deterioration over time.[3] And patients with Down syndrome (DS) are considered as an important subgroup in ES population who suffered from a risk of a worse exercise capacity and cardiopulmonary functions.[4] ES is characterized as an elevated vascular resistance persistently, leading to progressive cyanosis, an impaired exercise capacity proportional to the degree of hypoxemia, and a reduced life expectancy.[5] When untreated, adult populations with ES might exhibit a better survival and prognosis than idiopathic PAH, even presenting an 50% to 80% survival rate at 10 to 20 years. However, a numerous of life-threatening complications in ES conditions, such as cerebrovascular accidents, hemoptysis, and syncope, which indicated a poor quality of life.[6]

Historically, the options for patients with ES are limited with a principle to avoid any factors affecting the physiology. The conditional drugs, including digoxin, diuretics, antiarrhythmic agents, and anticoagulants, were aimed to improve clinical symptoms temporarily, with a disappointing prognosis. And when severely incapacitated, lung transplantation or heart–lung transplantation was to be selected.[7] Hence, the therapeutic strategy of these patients carries a greater importance. The 3 major classes of agents targeting the correction pathways of abnormalities in endothelial dysfunction were involved in the pathogenesis of PAH, which have been approved for a significant improvement as followed: endothelin receptor antagonists (ERAs); phosphodiesterase-5 inhibitors (PDE5i); and prostacyclin derivatives (prostanoids).[8] Nevertheless, the therapeutic strategy of patients with ES is mainly based on clinical experience rather than being evidence based. Therefore, we conducted this systematic review and meta-analysis to address the efficacy and safety of pulmonary arterial hypertension-specific drug therapy (PAH-SDT) for patients with ES.

2. Methods

This systematic review and meta-analysis is based on the recommendations on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[9] Two independent reviewers (QL and HYK) have conducted the literature search, eligibility assessment, data extraction, and meta-analysis. All the enrolled citations were limited in English. As this study was a review of studies published, the ethical approval was waved.

2.1. Literature search and selection

Databases including PubMed, EMBASE, the Cochrane Library databases of Systematic Reviews were searched up to January 2019. We have applied the search strategy "pulmonary arterial hypertension" paired with "Eisenmenger syndrome," and in combination with "endothelin receptor antagonists," "phosphodiesterase-5 inhibitors," or "prostanoids." In addition, manual retrieval of the cited references and related reviews was conducted for any potentially eligible literatures. The studies having been screened for twice, any discrepancies were resolved by a discussion with the corresponding author (QJY) for a consensus. We should contact the authors to get the original data through e-mail when it is necessary.

Each citation was pooled when meeting the criteria as follows: study design: a cohort report treated with PAH-SDT from a randomized controlled trial (RCT), case-control study, and observational study (prospective or retrospective). Participants: ES population with or without Trisomy 21 (DS), and none had received previous PST or a switched pharmacotherapy during treatment. Interventions: PAH-SDT, such as ERAs (bosentan, ambrisentan, macitentan), PDE5i (sildenafil, tadalafil), or prostanoids (epoprostenol, treprostinil, iloprost, beraprost). Outcomes: the enrolled citations should display the assessment of at least one of the following outcome: primary outcomes (rate of deterioration, 6MWD, FC) or any secondary outcomes, such as oxygen saturation (SpO_2), Borg dyspnea index (BDI), heart rate (HR), mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), meanwhile AEs were recorded.

The studies were excluded as: the duplicated studies, case reports (<5 cases), review, meta-analysis, animal experiments; the study with previous medications or a combined therapy of PAH-specific agents; the population of researches recruited other types of PAH; lacking important outcomes. Any discrepancies about the inclusion and exclusion of each study were determined by a discussion with Q-JY.

2.2. Study quality evaluation and data extraction

After a retrieval, the quality of the literatures has been assessed by 2 independent reviews (QL and HYK). We adopted the Newcastle-Ottawa Scale for evaluating the methodological quality (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). And quality assessment including 3 main domains, involving selection domain: representativeness of exposed cohort; selection of non-exposed cohort; ascertainment of exposure to implants; demonstration that outcome, comparability domain, and outcome domain: assessment, enough period of follow-up, adequacy of follow-up of cohorts. A study could be awarded a maximum of 1 star for each numbered item within the Selection and Outcome domain. And for comparability, a maximum of 2 stars can be given. The full mark of total score is defined as 9, and a score no <7 indicates a high quality.[10] The relevant data were documented by the 2 review authors from each study using a standard data form, of which the items included study characteristics (first author, publication year, study design, subjects), the proportion of ES etiologies, including ASD, VSD, PDA, atrioventricular canal (AVC), and other complex CHD (TOF, single ventricular, TGA) or compound CHD, medical intervention, primary endpoint, and rate of loss. A short-term period has been defined as no more than 1 year (12 months) in this systematic review.

2.3. Statistical analysis

The selected studies were researched and analyzed by the statistical software Stata 15.1 (StataCorp, TX). To evaluate the safety of medications, the occurrence of clinical deterioration and rate of AEs scenario have been displayed as a percentage, and WMD with 95% CI for continuous data. Heterogeneity was

tested using Cochrane Q test, quantifying with the I^2 statistic. When $P < .05$ or $I^2 > 50\%$, it indicated a significant heterogeneity between studies, and then a sensitivity analysis or subgroup analysis was used to explore the sources. After unavailability of homogenization, a random effect model of analysis was employed. Otherwise, a fixed effect model of analysis was applied. Begg test was carried out to investigate publication bias of enrolled studies. In this research, it is stated that $P < .05$ as statistically significant.

3. Results

3.1. Eligible studies and characteristics

The selection process has been portrayed in Fig. 1. A sum up of 170 citations were identified from the primary database search, finally 15 of which meet the inclusion criteria those were pooled in this qualitative systematic review, including 4 RCTs, 6 prospective cohort studies, and 5 retrospective studies.[11–25] It enrolled 456 patients with ES treated with PAH-SDT, which was recorded caused by different types of CHD, accordingly indicating 16.4% with ASD, 45.9% with VSD, 7.7% with PDA, 2.3% with AVC, 23.0% ES individuals were suffered from a complex CHD or compound CHD, and about 5% with unclear types. The specific-therapy of ES in this systematic review and meta-analysis contained 9 studies with ERAs, 3 studies with PDE-5i, and 3 studies with prostanoids, and these patients had no treatment regimen changes. Additionally, the incidence of dual ES and DS were revealed in patients accounting for 11.8%. The characteristics of enrolled studies were shown in Table 1.

3.2. Comparative outcomes

3.2.1. Efficacy in different terms. After a pharmacotherapy of PAH-SDT, the change of exercise capacity and cardiopulmonary hemodynamics from baseline were evaluated in this research. Within the first year, a meta-analysis of 6MWD was firstly conducted, and heterogeneity test revealed a significant one with a chi-squared = 83.1% ($P_h < .001$) in 12 studies covering 6 ERAs, 3 PDE5i, and 3 prostanoids. A sensitivity analysis was employed indicating a deviation from the research conducted by Bharani et al.[21] After the deviated study excluded, a randomized-effect model has been used ($I^2 = 60.5\%$), demonstrating that PAH-SDT could significantly improve 6MWD by 53.86 m ($I^2 = 60.5\%$; 95% CI [36.59, 71.13], $P < .001$), which was shown in Fig. 2. Additionally, FC was also ameliorated in an early targeted therapy with a statistical significance at the early period ($I^2 = 85.5\%$; WMD = –0.71, 95% CI [–0.98, –0.44], $P < .001$), and a subgroup analysis further proved it. As to the exercise parameters, BDI was demonstrated an obvious decrease with statistical significance in 3 studies[14,20,21] ($I^2 = 0.0\%$, WMD = –1.28, 95% CI [–1.86, –0.70], $P < .001$). Meanwhile, PAH-SDT was identified significantly elevate rest SpO_2 ($I^2 = 67.6\%$, WMD = 2.09%, 95% CI [0.66%, 3.51%], $P = .004$) as well as a decreased HR ($I^2 = 0.0\%$, WMD = –1.89, 95% CI [–3.67, –0.12], $P = .036$), but an unsatisfactory improvement in SpO_2 at the end of 6MWD ($P = .747$). For hemodynamics in patients with ES, PAH-SDT monotherapy could greatly lower mPAP ($I^2 = 0.0\%$; WMD: –5.70 mmHg, 95% CI [–8.19, –3.22], $P < .001$) and PVR ($I^2 = 67.3\%$; WMD: –4.20 wood U, 95% CI [–7.32, –1.09], $P = .008$).

In this systematic review, there existed rare evidence about the efficacy and safety of PDE5i and prostanoids in a prolonged

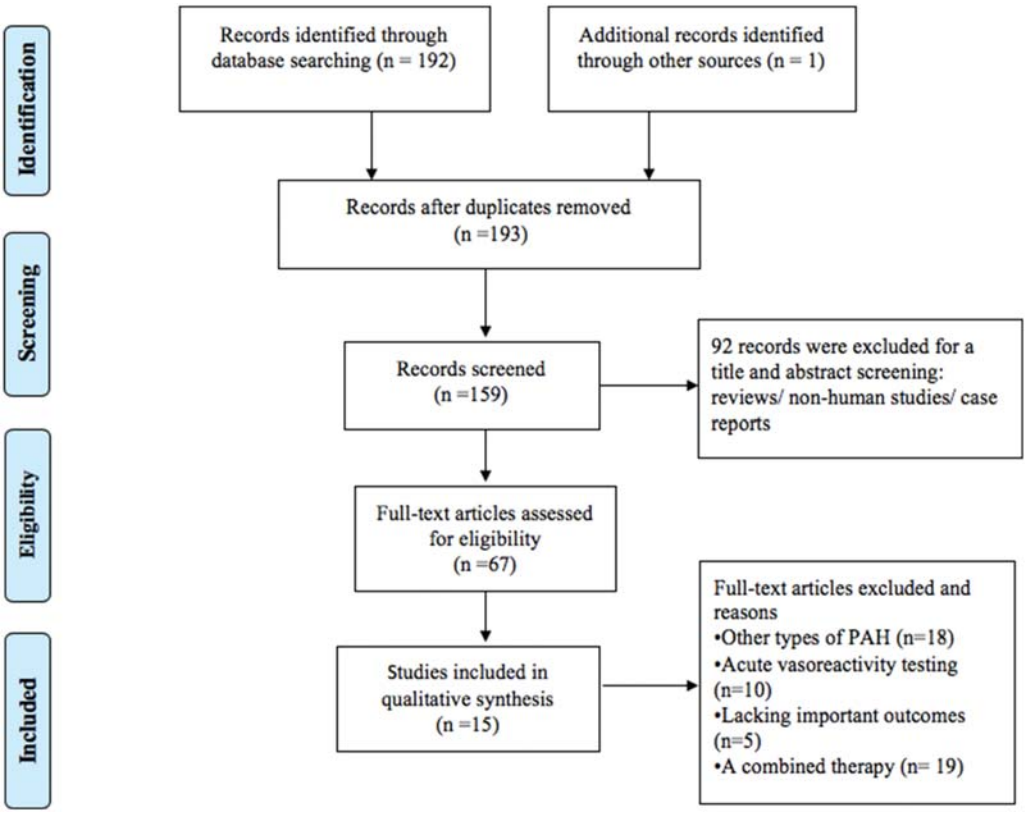

Figure 1. Selection flowchart of literature screening for this meta-analysis.

Table 1

Basic characteristics of pooled studies.

First author	Year	D	P	Age, y	ES etiologies					Down's		Period*		Deteri*,‡	
					ASD	VSD	PDA	AVC	Com	Yes (n)/No	Active drug	(m)	Primary end-point	(death)	Serious AEs
ERAs															
Mehta[11]	2008	Ret	24	44.0(12.0)	5	6	1	3	9	No	Bosentan (87.5%)	19	6MWD	NA	0
Crepaz[12]	2013	Ret	7	29.6(11.2)	0	7	0	0	0	Yes (7)	Bosentan	24	6MWD	0(0)	0
Serino[13]	2013	Ret	7	31.7(–)	0	5	0	2	0	Yes(7)	Bosentan	24	6MWD	1(0)	0
D'Alto[14]	2007	Pro	22	38.0(10.0)	1	12	0	5	4	No	Bosentan	12	6MWD	0(0)	0
Kermeen[15]	2010	Pro	53	34.0(12.0)	2	20	1	0	24	Yes(17)	Bosentan(90.6%)	24	6MWD	13(7)	1
Kaya[16]	2012	Pro	23	31.0(12.0)	6	15	2	0	0	No	Bosentan	24	6MWD	0(0)	0
Galie[17]	2006	RCT	37	37.2(12.0)	8	24	0	0	5	No	Bosentan	4	6MWD	1(0)	5
Gatzoulis[18]	2019	RCT	114	33(12,82)	NA	NA	NA	NA	55	Yes(20)	Macitentan	4	6MWD	8(2)	7
Zuckerman[19]	2011	Ret	17	32.2(11.9)	9	7	0	0	1	Yes(3)	Ambrisentan	30	6MWD	3(3)	0
PDE5i															
Zhang[20]	2014	Pro	84	28.0(9.0)	25	34	23	0	2	No	Sildenafil	12	6MWD	10(0)	0
Bharani[21]	2007	RCT†	8	28.0(9.4)	NA	NA	NA	NA	NA	No	Tadalafil	1	6 MWD	0(0)	0
Mukhopadhyay[22]	2011	RCT†	28	29.3(11.7)	14	13	0	0	1	No	Tadalafil	1.5	6 MWD	0(0)	0
Prostanoids															
Chon[23]	2016	Pro	11	44.2(12.2)	1	6	3	0	1	No	Iloprost	12	6MWD	0(0)	0
Cha[24]	2013	Pro	13	45.0(11.0)	4	8	4	0	2	No	Iloprost	6	6MWD	0(0)	0
Fernandes[25]	2003	Ret	8	36.3(14.9)	3	2	1	0	1	NA	Epoprostenol	3	6MWD	NA	NA

* Period: the period of therapy.

† Therapies in a randomized, double blind, cross over design.

‡ Deteri = deterioration (death, a deteriorated functional class, hospitalization, significant decline of SpO_2, lung or heart–lung transplantation); 6MWD = 6-minute walk distance, ASD = atrial septal defect, AVC = atrioventricular canal, Com = Complex congenital heart disease, D = design, ERAs = endothelin receptor antagonists, ES = Eisenmenger syndrome, NA = not available, P = participants, PDA = patent ductus arteriosus, PDE5i = phosphodiesterase type 5 inhibitor, Pro = prospective study, RCT = randomized controlled trials, Ret = retrospective study, VSD = ventricular septal defect.

medication. A meta-analysis indicted ERAs could contribute to an enhanced 6MWD by 75.24 m (I^2 = 48.2%; WMD: 79.24 m, [47.81, 110.7], $P < .001$). For hemodynamics, only one study indicated a decrease of mPAP from 59 ± 16 to 47 ± 17 mmHg with bosentan about 19 months.[11]

3.2.2. ERAs. Currently, a total of 9 studies researched the efficacy of ERAs,[11–19] including bosentan (n = 7),[11–17] macitentan (n = 1),[18] and ambrisentan (n = 1).[19] In hemodynamics, monotherapy of ERAs was associated with a significant increase, especially in mPAP (I^2 = 0.0%; WMD: –6.38 mmHg, 95% CI [–9.39, –3.38], $P < .001$). Clinically, meta-analysis and subgroup analysis were conducted to evaluate the clinical efficacy of ERAs monotherapy on ES, respectively, in 6MWD (Fig. 3), FC, and exercise parameters.

Bosentan, a dual ERA, could greatly increase distance by 66.16 m (I^2 = 0.0%; WMD: 66.16 m, 95% CI [59.7, 72.6], $P < .001$) in a short term and by 88.68 m (I^2 = 47.5%, 95% CI [54.05, 123.3], $P < .001$) in a prolonged medication. It also demonstrated that bosentan acted as an important role in decreasing the grade of FC by 0.67 (I^2 = 0.0%; WMD: –0.67, 95% CI [–0.21, 0.05], $P < .001$), and a lasting effect after 12 months (I^2 = 0.0%; WMD = –0.65, 95% CI [–1.10, –0.19], $P = .006$). Within the first year, bosentan was associated with unsatisfactory change in exercise parameters (HR: I^2 = 68.4%; WMD = 0.55, 95% CI [–11.68, 12.79], $P = .93$; SpO_2: I^2 = 55.3%; WMD = 2.05%, 95% CI [–0.91, 5.02], $P = .18$), but a significant improvement of SpO_2 by 4.06% ($P = .015$). Macitentan was reported in a 16-week RCT, which has been indicated an unsatisfactory increase from baseline (WMD: 18.4 m, $P = .119$), associated with a minor functional benefit in FC (WMD: –0.08, $P = .241$). Ambrisentan has been noted a nonsignificant change of 6MWD in both a short-term ($P = .280$) and long-term therapy ($P = .385$).

Two trials determined the symptomatic benefits and cardiac function of dual ERAs in Eisenmenger and Down syndrome. Crepaz et al[12] assessed the effect of bosentan monotherapy for an assessment and the mean 6MWD increased from 199.6 ± 69.1 m at baseline versus 303.7 ± 99.9 m ($P = .016$), in addition to a significant change of mean SpO_2 at the end of 6MWD, while without an obvious decrease of BDI (from 3.6 ± 1.4 to 2.4 ± 1.1), approving a possible improvement of clinical exercise capacity. In the Serino et al study,[13] it more identified that trisomy 21 influenced the response little to a dual ERA bosentan therapy in ES patients.

3.2.3. PDE5i. The therapeutic effects of PDE5i monotherapy were described in 3 studies.[20–22] A meta-analysis in 6MWD was not applied for an unacceptable heterogeneity ($I^2 > 85\%$). There proved a mean increased distance was 80.76 m following an administration in a short-term therapy. In addition, an obvious improvement of FC (I^2 = 0.0%; WMD = –0.31, 95% CI [–0.42, –0.20], $P < .001$) and BDI (I^2 = 67.8%; WMD = –1.44, 95% CI [–2.52, –0.36], $P = .009$) were analyzed, proving a significant improvement in exercise functions. Zhang et al[20] and Mukhopadhyay et al[22] reported data on hemodynamics, which indicated a nonsignificant decrease in mPAP (I^2 = 0.0%; WMD = –4.04 mmHg, 95% CI [–8.58, 0.51], $P = .082$), but a great change in PVR (I^2 = 0.0%; WMD = –6.10 wood U, 95% CI [–9.14, –3.95, $P < .001$).

3.2.4. Prostanoids. In 3 trials concentrated on the prostanoids for ES patients.[23–25] Indicators of exercise capacity were evaluated by a meta-analysis and subgroup analysis, certifying a significant improvement in 6MWD (Ilo: I^2 = 0.0%; WMD: 85.14 m, 95% CI [46.13, 124.15], $P < .001$; Epo: WMD: 203.6 m, 95% CI [47.27, 359.93], $P = .011$), and a functional benefit in

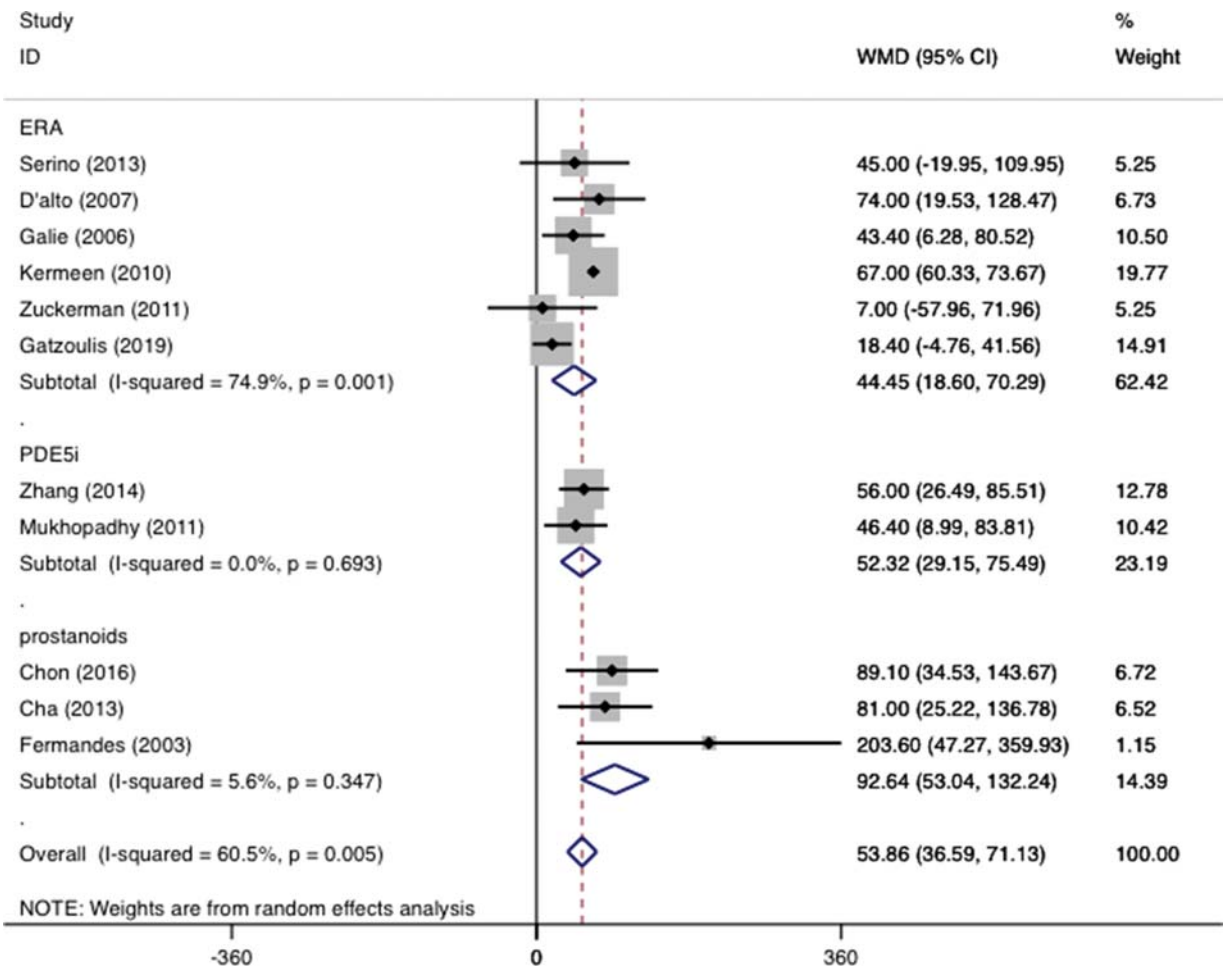

Figure 2. Meta-analysis of 6WMD in patients with ES treated with PAH-SDT in a short term. ES = Eisenmenger syndrome, PAH-SDT = PAH-specific drug therapy, WMD = weighted mean differences.

FC was shown by 1.41 in iloprost ($I^2 = 0.0\%$; 95% CI [–1.39, –0.89], $P < .001$), and 1.62 in epoprostenol (95% CI [–2.24, –1.00], $P < .001$). For vascular changes, Cha et al[24] found an inhaled iloprost could lead to an improvement in mPAP about 17.9, and in PVR about 10.9%. Meanwhile, epoprostenol has been recorded to decrease PVR of ES about 34.8%, from 41.4 ± 18.2 wood U to 27.0 ± 13.2 wood U.

3.3. Safety

Most PAH-specific drugs were proved generally well tolerated and no serious adverse events occurred eventually. The rate of clinical deterioration was calculated as 7.9% overall, indicating 8.7% in ERAs therapy and 8.3% in PDE-5i therapy. In ERAs monotherapy, the mortality of ES was about 3.9%, while rare death events in PDE5i and prostanoids. Totally, 44.1% ES patients were found AEs scenarios overall specific therapy. Having individuals received ERAs, AEs were recorded commonly as liver dysfunction (20.7%), peripheral edema (17.8%), and headache (14.8%), in addition to serious AEs in 4.3%. While the PDE-5i could contribute to a headache in 36.6% patients, flushing in 29.3%, and nasal congestion in 7.3%. No adverse drug reactions were noted in a short-term inhaled iloprost management.

3.4. Quality assessment

The quality of each study is evaluated according to newcastle-ottawa scale shown in Table 2. It indicated the pooled studies were of high quality except for 1 study.[13]

3.5. Publication bias

There existed no significant proof of publication bias by the inspection of PAH-SDT acting on 6MWD at an early endpoint reported ($P = .631$). And the funnel plot of Begg test was shown in Fig. 4.

4. Discussion

When associated with CHD, PAH could be a devastating condition suffered from a persistent exposure of the pulmonary vasculature to this increased blood flow causes some obstructive lesions in pulmonary arteriopathy.[26] And this irreversible remodeling could lead to an extreme risk factor of operation, even a poor postoperative outcome after a repair of CHD. Once the pulmonary vascular resistance exceeded systemic circulation resistance, will result in the shunt reversal, and ES condition occurred.[27] In this scenario, patients could experience the apparent functional impairment in the advanced stages primarily,

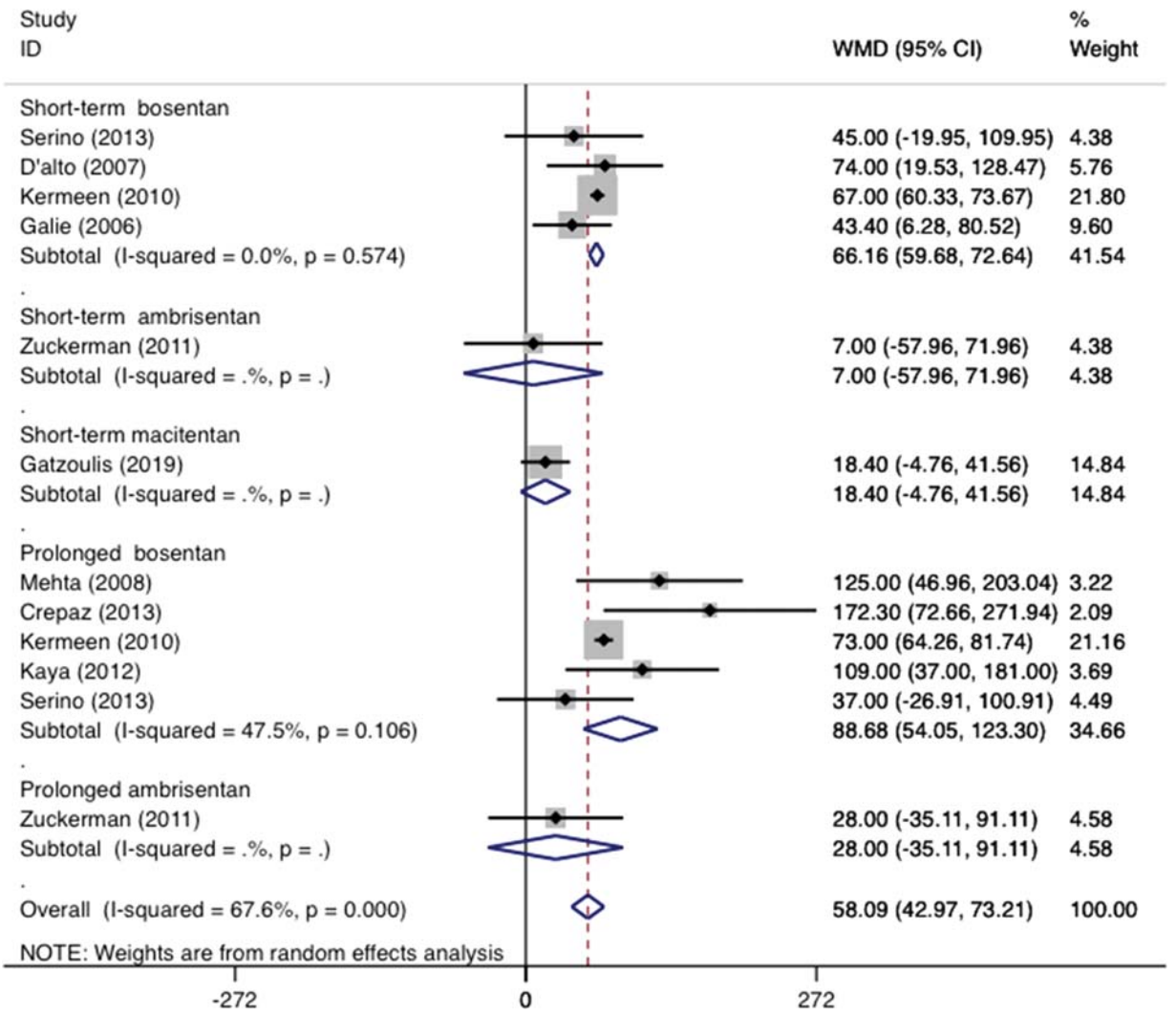

Figure 3. Meta-analysis of 6MWD in patients with ES treated with ERAs. 6MWD = 6-minute walk distance, ERAs = endothelin receptor antagonists, ES = Eisenmenger syndrome.

with the signs and symptoms, such as central cyanosis, dyspnea, fatigue, and syncope, etc. Even, right heart failure is a potential complication.[28] The limited exercise tolerance and exertional dyspnea could remain persistent for years, which identify a risk for hospitalization, severe cardiovascular events, or death point. Inai[29] concluded that pulmonary vasodilators are probably available to interfere with the ongoing disease process to improve functional capacity and delay the decision for transplantation with no conclusive evidence. Although retrospective studies suggested ES patients with PAH-SDT benefitted from a longer lifespan, improved hemodynamics lasting period for operation, no recommendations for patients with ES have existed.[30,31]

The present review enrolled researches reporting different novel pulmonary vasodilators against 3 pathophysiological pathways in ES, involving ERAs (60.0%), PDE-5i (20.0%), and prostanoids (20.0%). However, sitaxsentan, a selective ERA, has been removed from the market for a deadly dysfunction of liver in 2010. We have found that almost 45.9% patients with Eisenmenger syndrome in this study were caused by VSD, and 16.4% with ASD, 7.7% with PDA, 2.3% with AVC. And 23% ES individuals were ascribed to a complex or compound CHD, which were basically accordance to the findings recorded by Kidd et al[32] and Vongpatanasin et al[33] before. Almost all specific drugs were well tolerated with a low risk of death and clinical deterioration in a short-term treatment. Almost all drawbacks and AEs of PDE5i and prostanoids were mild to moderate in intensity. While, 13 serious AE scenarios were observed in ERAs therapy, of which a greater proportion with a dysfunction of hepatic, in addition to vasovagal syncope, angina pectoris, and sinus tachycardia.

In a short-term treatment of PAH-SDT monotherapy to patients with ES (≤12 months), 6MWD, as an important surveillance of exercise tolerance, was significantly improved (WMD: 53.86 m, 95% CI [36.59, 71.13], $P < .001$), in addition that it could contribute to some clinical functional benefits lowering FC grade ($P < .001$) and BDIs ($P < .001$), clinically with a higher rest SpO_2 ($P = .004$) and a lower HR ($P = .036$). Meanwhile improved cardiopulmonary parameters, especially mPAP and PVR, demonstrated that the specific vasodilators could greatly relieve the progress in vascular remodeling, with a WMD of –5.70 mmHg for mPAP ($P < .001$) and –4.20 wood U for PVR ($P = .008$). However, a short-term medication probably

Table 2

Assessment the quality of cohort studies in ES patients[*].

Study	Selection				Comparability[†]	Outcome			Score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure to implants	Demonstration that outcome		Assessment	Enough follow-up[‡]	Adequacy of follow-up of cohorts[§]	
Mehta[11]	Δ	–	Δ	Δ	Δ	Δ	Δ	Δ	7
Crepaz[12]	Δ	–	Δ	Δ	Δ	Δ	Δ	Δ	7
Serino[13]	Δ	–	Δ	Δ	Δ	Δ	Δ	–	6
D'Alto[14]	Δ	–	Δ	Δ	ΔΔ	Δ	Δ	Δ	8
Kermeen[15]	Δ	–	Δ	Δ	Δ	Δ	Δ	Δ	7
Kaya[16]	Δ	–	Δ	Δ	Δ	Δ	Δ	Δ	7
Galie[17]	Δ	Δ	Δ	Δ	ΔΔ	Δ	Δ	Δ	9
Gatzoulis[18]	Δ	Δ	Δ	Δ	ΔΔ	Δ	Δ	Δ	9
Zuckerman[19]	Δ	–	Δ	Δ	Δ	Δ	Δ	Δ	7
Zhang[20]	Δ	–	Δ	Δ	Δ	Δ	Δ	Δ	7
Bharani [21]	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	8
Mukhopadhyay[22]	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	8
Chon[23]	Δ	–	Δ	Δ	Δ	Δ	Δ	Δ	7
Cha[24]	Δ	–	Δ	Δ	Δ	Δ	Δ	Δ	7
Fernandes[25]	Δ	–	Δ	Δ	Δ	Δ	Δ	–	6

[*] The full mark is defined as 9, and no <7 is considered as a high quality.

[†] Comparability of cases on the basis of the design or analysis in this study: study controls for patients associated with Eisenmenger syndrome; study controls for no combined PAH-STD added to initial therapeutic strategy and right catheterization for hemodynamics.

[‡] An adequate follow period when a primary endpoint was obtained.

[§] Incomplete follow up-all subjects <5%.

could not mediate SpO_2 at exercise ($P=.747$), which hinted a potential danger of cyanosis and severe cardiovascular events as exercise moments. However, there existed limited evidence about the efficacy and safety of PAH-SDT in a prolonged medication, which indicated ERAs could improve exercise tolerance.

Our review analyzed the subgroup of PAH-specific drugs in different pathways. Firstly, ERAs could contribute to an improve exercise capacity and vascular remodeling of patients with ES within the first year. Subgroup analysis indicated bosentan, a dual ERA, could significantly improve 6MWD (WMD: 66.16 m, 95% CI [59.7, 72.6], $P<.001$) and FC (WMD: –0.67, 95% CI [–0.21, 0.05], $P<.001$) in a short term, moreover, enhanced functional benefits of which were proved in a prolonged treatment. It was associated with an increase of 6MWD by 88.68 m ($I^2=47.5\%$, 95% CI [54.05, 123.3], $P<.001$) and a decrease of FC by 0.65 (95% CI [–1.10, –0.19], $P=.006$). Although unsatisfactory outcomes were observed in HR and SpO_2 with bosentan in a short term, a significant improvement of SpO_2 was associated with a lasting therapy, identifying a maintained treatment of bosentan for ES might be effective. Hence, bosentan in ES patients is confirmed as a safe, well tolerated and effective therapy with or without DS, which is probably accord with the outcomes approved by Hascoet in 2017.[34] Nevertheless, macitentan and ambrisentan could contribute to a non-significant amelioration in exercise capacity and cardiopulmonary hemodynamics compared with those at baseline. For safety, ERAs could result in some AE conditions, mostly as mild to moderate, such as an increase of hepatic transaminase levels, headache, and peripheral edema. Still, there existed 4.3% individuals treated with ERAs suffered from serious AEs, showing a potential risk of deadly liver dysfunction, arrhythmia, heart failure etc.,[15,17,18] and 3.9% suffered from death.

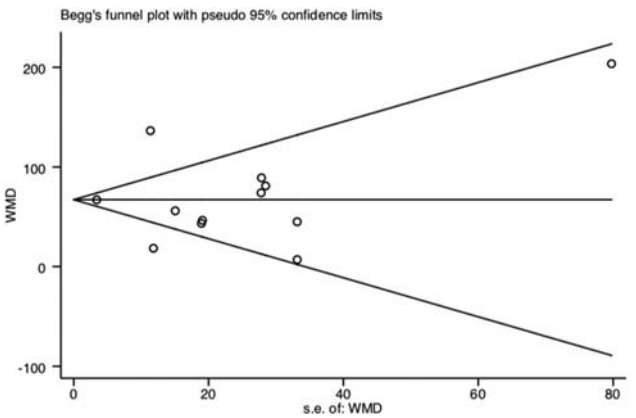

Figure 4. Begg funnel plot of 6WMD at an early stage of PAH-SDT acting on ES. ES = Eisenmenger syndrome, PAH-SDT = PAH-specific drug therapy, WMD = weighted mean differences

In the first year, PDE5i could improve 6WMD (WMD: 80.76 m, 95% CI: [19.46, 142.05], $P=.01$), FC (WMD: –0.31, 95% CI [–0.42, –0.20], $P<.001$), and PVR (WMD: –6.10 wood U, 95% CI [–9.14, –3.95, $P<.001$). And some AEs, like headache, edema, flushing, and nasal congestion, were commonly recorded with a PDE-5i management (sildenafil and tadalafil). No deaths and severe adverse events occurred. Data on prostanoids in patients with ES are limited to small sample size studies and case reports previously, and the long-term effects of prostanoids remain unknown. It is previously proved continuous prostacyclin analogs contribute to some maintained effects in a long-term therapy on PAH-CHD, including Eisenmenger syndrome.[35] Limsuwan et al[36] has presented a report on children with serious PH-CHD with beraprost treatment for 6 months, showing a reduced level of the pulmonary-to-systemic vascular resistance ratio, without a significant change of pulmonary vascular remodeling. We meta-analyzed 6MWD and FC as the measure

of exercise tolerance, showing that inhaled iloprost for 6 to 12 months was associated with an improvement in 6MWD by 85.14 m ($P < .001$), and in FC by 1.41 ($P < .001$). For vascular changes, Cha et al[24] found an inhaled iloprost could lead to an improvement in mPAP about 17.9% and PVR about 10.9%. Also, epoprostenol has been demonstrated to greatly improve exercise capacity and cardiopulmonary hemodynamics for ES with limited functional capacity (FC III or IV).

Some limitations still existed in this review: some investigators did not perform an invasive evaluation such as right cardiac catheterization during follow-up visits; most of the pooled trials had a relatively small sample size, and we only concentrated on the cohorts of ES patients interfered with active drugs which neglected a comparative effect from placebo or control group; the enrolled studies were limited to describe the safety and efficacy of medications, and no combined outcomes were concentrated on. The duration of studies ranged from 1 month to 24 months, lacking lasting clinical worsening, deterioration, AEs, exercise capacity, quality of life and reversal of pulmonary changes at 5 years or 10 years. There lacked evidence concentrating on the efficacy and safety of PDE5i and prostanoids for ES in a long-term.

5. Conclusions

In a conclusion, PAH-SDT can induce an early relief in clinical status and cardiopulmonary hemodynamics of ES patients. However, there probably still existed a limited exercise ability with PAH-SDT in a short term, hinting an acute cardiovascular event at exercise. Among the specific agents in this review, bosentan, an active dual ERA, is a commonest application as safe and effective in ES with or without DS. Still, a minority of death or serious AEs could occur ascribed to it during a short-term. It also indicated that PDE-5i and inhaled iloprost could temporarily ameliorate exercise tolerance, functional grade, in addition to favorable short-term outcomes in hemodynamic parameters, with mild to moderate AEs. Even lung transplantation with repair of the cardiac defect or combined heart–lung transplantation are options for Eisenmenger syndrome patients with a poor prognosis, an early PAH-SDT could delay the process of PAH, expanding the operative indications for ES, and a maintained efficacy is obtained with a prolonged therapy at least over 12 months. Furthermore, a combined therapy should be considered for a better safety and efficiency, without severe active drug responses.

Author contributions

Author contributions were as follows: Qiang Li and Hong-Yu Kuang: study design, literature search, systematic review and data collection, statistical analysis, interpretation of results, and preparation of the manuscript; Yu-Hao Wu and Tie-Wei Lu: a contribution to critical review of the manuscript; Qi-Jian Yi: principal investigator, study design, statistical analysis, and an assessment of all results. The typographical and grammatical errors were checked and corrected by authors above. The corresponding author confirmed all contributing authors gave permission to be named.

Conceptualization: Qiang Li, Hong-Yu Kuang, Qi-Jian Yi.
Data curation: Qiang Li, Hong-Yu Kuang, Yu-Hao Wu.
Formal analysis: Qiang Li, Hong-Yu Kuang, Tie-Wei Lu.
Methodology: Qiang Li, Hong-Yu Kuang, Yu-Hao Wu, Qi-Jian Yi.
Software: Qiang Li, Hong-Yu Kuang, Yu-Hao Wu, Qi-Jian Yi.
Supervision: Tie-Wei Lu, Qi-Jian Yi.
Writing – original draft: Qiang Li, Hong-Yu Kuang.
Writing – review & editing: Tie-Wei Lu, Qi-Jian Yi.

References

[1] Galie N, Vongpatanasin W, Brickner ME, et al. The Eisenmenger syndrome in adults. Ann Intern Med 1998;128:745–55.
[2] Galie N, Manes A, Palazzini M, et al. Management of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. Drugs 2008;68:1049–66.
[3] Chen I, Dai ZK. Insight into pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD): classification and pharmacological management from a pediatric cardiological point of view. Zhonghua Minguo Xin Zang Xue Hui Za Zhi 2015;31:507–15.
[4] Vande Bruaene A, Delcroix M, Pasquet A, et al. The Belgian Eisenmenger syndrome registry: implications for treatment strategies? Acta Cardiol 2009;64:447–53.
[5] Daliento L, Somerville J, Presbitero P, et al. Eisenmenger syndrome. Factors relating to deterioration and death. Eur Heart J 1998;19:1845–55.
[6] Beghetti M, Galiè N. Eisenmenger syndrome. J Am Coll Cardiol 2009;53:733–40.
[7] Elshafay A, Truong DH, Aboelnas MM, et al. The effect of endothelin receptor antagonists in patients with eisenmenger syndrome: a systematic review. Am J Cardiovasc Drugs 2018;18:93–102.
[8] Budts W. Eisenmenger syndrome: medical prevention and management strategies. Expert Opin Pharmacother 2005;6:2047–60.
[9] Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;21:b2700.
[10] Mcpheeters ML. Newcastle-Ottawa Quality Assessment Scale; 2012.
[11] Mehta PK, Simpson L, Lee EK, et al. Endothelin receptor antagonists improve exercise tolerance and oxygen saturations in patients with Eisenmenger syndrome and congenital heart defects. Tex Heart Inst J 2008;35:256–61.
[12] Crepaz R, Romeo C, Montanaro D, et al. Long-term results of treatment with bosentan in adult Eisenmenger's syndrome patients with Down's syndrome related to congenital heart disease. BMC Cardiovasc Disord 2013;13:74.
[13] Serino G, Guazzi M, Micheletti A, et al. Effect of bosentan on exercise capacity and clinical worsening in patients with dual Down and Eisenmenger syndrome. Clin Med Insights Cardiol 2013;7:29–34.
[14] D'Alto M, Vizza CD, Romeo E, et al. Long-term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and hemodynamic effect. Heart 2007;93:621–5.
[15] Kermeen FD, Franks C, O'Brien K, et al. Endothelin receptor antagonists are an effective long-term treatment option in pulmonary arterial hypertension associated with congenital heart disease with or without trisomy-21. Heart Lung Circ 2010;19:595–600.
[16] Kaya MG, Lam YY, Erer B, et al. Long-term effect of bosentan therapy on cardiac function and symptomatic benefits in adult patients with Eisenmenger syndrome. J Card Fail 2012;18:379–82.
[17] Galiã N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 2006;114:48–54.
[18] Gatzoulis MA, Landzberg M, Beghetti M, et al. Evaluation of macitentan in patients with Eisenmenger syndrome: results from the randomized, controlled MAESTRO study. Circulation 2019;139:51–63.
[19] Zuckerman WA, Leaderer D, Rowan CA, et al. Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. Am J Cardiol 2011;107:1381–5.
[20] Zhang ZN, Jiang X, Zhang R, et al. Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicentre study. Heart 2011;97:1876–81.
[21] Bharani A, Patel A, Saraf J, et al. Efficacy and safety of PDE-5 inhibitor tadalafil in pulmonary arterial hypertension. Indian Heart J 2007;59:323–8.
[22] Mukhopadhyay S, Nathani S, Yusuf J, et al. Clinical efficacy of phosphodiesterase-5 inhibitor tadalafil in Eisenmenger syndrome-randomized, placebo-controlled, double. Congenit Heart Dis 2011;6:424–31.

[23] Chon MK, Cho KI, Cha KS, et al. Effects of long-term iloprost treatment on right ventricular function in patients with Eisenmenger syndrome. J Cardiol 2017;69:e1–6.
[24] Cha KS, Cho KI, Seo JS, et al. Effects of inhaled iloprost on exercise capacity, quality of life, and cardiac function in patients with pulmonary arterial hypertension secondary to congenital heart disease (the Eisenmenger syndrome) (from the EIGER Study). Am J Cardiol 2013;112:1834–9.
[25] Fernandes SM, Newburger JW, Lang P, et al. Usefulness of epoprostenol therapy in the severely ill adolescent/adult with Eisenmenger physiology. Am J Cardiol 2003;91:632–5.
[26] Zuckerman WA, Krishnan U, Rosenzweig EB. Pulmonary arterial hypertension associated with congenital heart disease. Curr Pediatrics Rep 2012;21:328–37.
[27] Agarwal A, Aggarwal S, Harris IS. Pathophysiology and pharmacotherapy of adult congenital heart disease. Pathophysiology and Pharmacotherapy of Cardiovascular Disease 2015; Springer International Publishing, 1269–91.
[28] Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. Circulation 2007;115:1039–50.
[29] Inai K. Can pulmonary vasodilator therapy expand the operative indications for congenital heart disease? Int Heart J 2015;56(suppl): S12–6.
[30] Adriaenssens T, Delcroix M, Van Deyk K, et al. Advanced therapy may delay the need for transplantation in patients with the Eisenmenger syndrome. Eur Heart J 2006;27:1472–7.
[31] Hascoët S, Baruteau AE, Humbert M, et al. Long-term outcomes of pulmonary arterial hypertension under specific drug therapy in Eisenmenger syndrome. J Heart Lung Transplant 2017;36:386–98.
[32] Kidd L, Driscoll DJ, Gersony WM, et al. Second natural history study of congenital heart defects. Results of treatment of patients with ventricular septal defects. Circulation 1993;87(suppl):I38–51.
[33] Vongpatanasin W, Brickner ME, Hillis LD, et al. The Eisenmenger syndrome in adults. Ann Intern Med 1998;128:745–55.
[34] Hascoet S, Fournier E, Jais X, et al. Outcome of adults with eisenmenger syndrome treated with drugs specific to pulmonary arterial hypertension: a french multicentre study. Arch Cardiovasc Dis 2017;110:303–16.
[35] Thomas IC, Glassnerkolmin C, Gombergmaitland M. Long-term effects of continuous prostacyclin therapy in adults with pulmonary hypertension associated with congenital heart disease. Int J Cardiol 2013; 168:4117–21.
[36] Limsuwan A, Pienvichit P, Khowsathit P. Beraprost therapy in children with pulmonary hypertension secondary to congenital heart disease. Pediatric Cardiol 2005;26:787–91.