Endothelin receptor antagonist therapy in congenital heart disease with shunt-associated pulmonary arterial hypertension: A qualitative systematic review


BACKGROUND: Congenital heart disease (CHD) with systemic-to-pulmonary shunting is associated with pulmonary arterial hypertension (PAH). There are similar clinical and pathophysiological features between CHD with shunt-associated PAH and idiopathic PAH. Endothelin-receptor antagonists (ERAs) are oral medications that improve pulmonary hemodynamics, symptoms and functional capacity in many PAH patients. However, the role of ERAs in CHD with shunt-associated PAH is unclear.

METHODS: MEDLINE, EMBASE and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases were searched for articles published from 1966 through September 2006, as well as bibliographies of all retrieved papers. All published English-language studies of adult CHD patients with shunt-associated PAH treated with ERAs were reviewed for clinical, functional and hemodynamic outcomes.

RESULTS: Ten studies of 174 adult CHD subjects with shunt-associated PAH were identified. Other than one placebo-controlled, randomized clinical trial, all studies were open-label, uncontrolled observational trials. Subjects were treated with the ERA bosentan for a mean (± SD) of 9±7 months. Nine studies reported improved World Health Organization (WHO) modification of the New York Heart Association functional class, with 95 of 164 subjects (58%) improving by at least one functional class. The 6 min walk distance improved in all eight studies in which it was assessed. Bosentan was generally well tolerated; 2.3% of subjects withdrew because of elevated liver enzymes. Two patients with WHO functional class IV PAH died during bosentan therapy.

CONCLUSION: Treatment of CHD patients with shunt-associated PAH with the ERA bosentan is associated with an improvement in functional class and objectively measured exercise capacity. The consistency of the uncontrolled data and the positive results of a single randomized clinical trial suggest a role for ERA therapy in CHD patients with shunt-associated PAH. Caution is suggested when considering bosentan therapy for CHD patients with WHO functional class IV PAH.

Key Words: Congenital heart disease; Eisenmenger syndrome; Endothelin receptor antagonists; Pulmonary artery hypertension; Systematic review

Can J Cardiol Vol 25 No 3 March 2009 e63-e68.

Maladie cardiaque congénitale avec hypertension artérielle pulmonaire associée à un shunt, traitée par antagoniste des récepteurs de l’endothéline : Analyse qualitative systématique

HISTORIQUE : La maladie cardiaque congénitale (MCC) associée à un shunt entre la circulation systémique et pulmonaire s’accompagne d’hypertension artérielle pulmonaire (HTAP). Au plan des caractéristiques cliniques et pathophysiologiques, il y a des similitudes entre la MCC avec HTAP associée à un shunt et l’HTAP idiopathique. Les antagonistes des récepteurs de l’endothéline (ARE) administrés par voie orale améliorent l’hémodynamique, les symptômes et la capacité fonctionnelle pulmonaire chez de nombreux patients atteints d’HTAP. Toutefois, le rôle des ARE dans la MCC avec HTAP associée à un shunt reste à déterminer.

METHODES : Les auteurs ont interrogé les bases de données MEDLINE, EMBASE et CINAHL (pour Cumulative Index of Nursing and Allied Health Literature) afin d’y recenser les articles publiés de 1996 à septembre 2006 et ils ont consulté les listes bibliographiques de tous les articles retenus. Toutes les études publiées en langue anglaise sur des patients adultes atteints de MCC avec HTAP associée à un shunt et traités par ARE ont été passées en revue et les résultats cliniques, fonctionnels et hémodynamiques ont été colligés.

RÉSULTATS : Dix études regroupant 174 sujets adultes souffrant de MCC avec HTAP associée à un shunt ont ainsi été regroupées. À l’exception d’une étude clinique randomisée et contrôlée par placebo, toutes les autres se sont déroulées selon un protocole d’observation ouvert non contrôlé. Les sujets ont été traités au moyen de l’ARE bosentan pendant une moyenne (± E.T.) de 9 ± 7 mois. Neuf études ont fait état d’une amélioration (critères de l’OMS) de la classe fonctionnelle NYHA, 95 sujets sur 164 (58 %) ayant vu leur état s’améliorer d’au moins une classe fonctionnelle. La distance parcourue en six minutes s’est améliorée dans les huit études au cours desquelles elle a été évaluée. Le bosentan a en général été bien toléré, 2,3 % des sujets ont abandonné en raison d’une élévation de leurs enzymes hépatiques. Deux patients atteints d’HTAP de classe fonctionnelle IV selon les critères de l’OMS sont décédés durant leur traitement par bosentan.

CONCLUSIONS : Le traitement des patients atteints de MCC avec HTAP associée à un shunt au moyen de l’ARE bosentan donne lieu à une amélioration de la classe fonctionnelle et de la tolérance à l’effort mesurée objective. La constante des données non contrôlées et les résultats positifs d’une seule étude randomisée donnent à penser que le traitement par ARE serait utile chez les patients souffrant de MCC avec HTAP associée à un shunt. La prudence s’impose lorsqu’on envisage d’administrer le bosentan à des patients atteints de MCC qui présentent une HTAP de classe fonctionnelle IV selon les critères de l’OMS.

©2009 Pulsus Group Inc. All rights reserved
Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries characterized by increased pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), which leads to disabling dyspnea and fatigue, right ventricular failure and often, premature death (1-3). Many novel, effective medications are now available and indicated for the treatment of PAH, including parenteral prostaglandin analogues, oral phosphodiesterase-5 (PDE5) inhibitors and endothelin receptor antagonists (ERAs). Treatment with these agents improves symptoms, functional capacity, quality of life and, often, survival in many patients with PAH, including patients with idiopathic PAH (IPAH) and PAH associated with connective tissue disease (CTD-PAH) (3-5).

Congenital heart disease (CHD) is the most common form of major congenital malformations and occurs in five to eight cases per 1000 births (6,7). Some CHD malformations produce chronic intracardiac left-to-right shunting, exposing the pulmonary vasculature to high pressure and flow, resulting in PAH. PAH associated with congenital systemic to pulmonary shunts occurs frequently in CHD patients (CHD with shunt-associated PAH), including approximately 50% of patients with ventricular septal defects (VSDs) and 10% of patients with atrial septal defects (ASDs) (6,7). Increased PVR may lead to Eisenmenger's physiology, characterized by reversed right-to-left intracardiac shunting of blood and significant hypoxemia (8). Although CHD patients with shunt-associated PAH may have prolonged survival (for decades), their quality of life is often poor because of the multiple systemic complications of their disease, including (but not exclusive to) the disabling symptoms of PAH. PAH treatment options have been poorly studied in CHD patients with shunt-associated PAH because of the more gradual clinical and physiological decline, longer life expectancy and concern regarding potential adverse effects such as worsening oxygenation. As such, heart and lung transplantation has long been the only treatment option in severely limited CHD patients with shunt-associated PAH (9,10).

Despite differences in the pathogenesis of IPAH and CHD with shunt-associated PAH, there are also similar clinical, pathological and pathophysiological features (4,11). For example, both IPAH and CHD with shunt-associated PAH are associated with elevated plasma levels of endothelin (ET)-1, a potent endogenous vasoconstrictor that also promotes vascular cell proliferation and pulmonary vascular remodeling (12-14). ET-1 levels correlate with PAH disease severity and prognosis (15). ET-1 acts by binding to two identified receptors – ET-A and ET-B (16). Both receptors are found on vascular smooth muscle and mediate vasoconstriction, vascular hypertrophy, inflammation and fibrosis. ET-B receptors are also found on endothelial cells and mediate ET-1 clearance as well as the release of the endogenous vasodilators nitric oxide and prostacyclin (17).

ERAs are a pharmacological class of oral agents indicated for the treatment of PAH that currently includes three agents – bosentan (a nonselective or dual ET-A/ET-B ERA) and two ET-A-selective ERAs (sitaxsentan and ambrisentan). In randomized controlled trials (RCTs), all three ERAs have improved pulmonary hemodynamics, exercise capacity, World Health Organization (WHO) modification of the New York Heart Association (NYHA) functional class in patients with IPAH and CTD-PAH, and may even improve long-term clinical outcomes (18-22). However, the role of ERAs in the treatment of CHD with shunt-associated PAH has not been systematically studied, nor has it been widely accepted. Thus, we performed a qualitative systematic review of the literature describing the current state of knowledge regarding the efficacy and safety of ERAs in the treatment of adult CHD patients with shunt-associated PAH.

METHODS

Two groups of authors independently searched the MEDLINE database for English-language articles published between 1966 and September 2006 using the following search terms: pulmonary hypertension AND (congenital heart disease OR Eisenmenger) AND (endothelin receptor antagonist OR bosentan OR sitaxsentan OR ambrisentan). The

RESULTS

Study design, subjects and ERA treatment

The screening and selection process of the relevant studies is summarized in Figure 1. Of the 74 studies identified through a systematic review of the literature, 10 were selected for full review (23-32) (Table 1). One recent study was a blinded, placebo-controlled RCT of bosentan in CHD patients with shunt-associated PAH (28). All of the other studies were open-label, uncontrolled observational trials of bosentan in CHD patients with shunt-associated PAH, including two reports of single cases (27,30). Six of the studies were prospective (24-26,28,29,32), and four were retrospective (23,27,30,31). Six of the studies reported obtaining informed consent from subjects (24-26,28,29,31) and six reported independent ethics review board approval (23,25,26,28,29,32).

A total of 174 CHD subjects with shunt-associated PAH were treated with an ERA; 120 (69%) of them were female. There were many types of CHD (Table 1), including 107 (61%) subjects with Eisenmenger syndrome, and the RCT of bosentan in CHD patients with shunt-associated PAH included only subjects with Eisenmenger's syndrome (28). Eight studies only included adults. In the other two studies, children accounted for nine of 21 subjects (26) and three of 27 subjects (31). In all 10 studies, ERA therapy consisted of oral bosentan for a minimum period of 12 weeks, with a weighted mean exposure of 9.2 months (range 12 weeks to 2.1±0.5 years). Eight of the studies (23,24,27-32) administered bosentan according to the standard dosing
regimen indicated for the treatment of IPAH subjects, initiating therapy at 62.5 mg orally twice daily for four weeks, and then titrating up to 125 mg twice daily (18,19). One study initiated therapy at 31.25 mg twice daily and then titrated up at four-week intervals sequentially to 62.5 mg and 125 mg twice daily (25), and another used a weight-based dosing regimen because of the inclusion of children (26). In two studies, subjects received concomitant PAH-specific therapy, consisting of parenteral prostacyclin therapy in eight of 24 subjects in one study (32), and oral prostacyclin therapy in three subjects and subcutaneous prostacyclin therapy in one of 27 subjects in the other (31).

Functional efficacy of ERA therapy in CHD patients with shunt-associated PAH

Only statistically significant results are reported here. All studies assessed the clinical benefit of ERA therapy in CHD patients with shunt-associated PAH, as well as the safety and tolerability. Efficacy was assessed in all studies by objective exercise testing and/or by quantifying functional capacity as per the WHO/NYHA functional class (33) (Table 2). Nine of the studies, including the single RCT of bosentan in CHD patients with shunt-associated PAH, reported significant improvements in WHO/NYHA functional class with bosentan treatment, with 95 of 164 (58%) subjects improving by at least one functional class.

Eight studies assessed 6 min walk distance (6MWD) at baseline and following ERA treatment. Bosentan treatment of CHD subjects with shunt-associated PAH was associated with a significant improvement in 6MWD in all eight studies (Table 2), ranging from a mean improvement of 28.0±24.5 m in 10 subjects after 16 weeks of treatment (29) to a 136 m improvement in one patient after nine months of bosentan therapy (27). In the single RCT, bosentan treatment resulted in a mean placebo-corrected improvement in 6MWD of 53.1 m (P<0.008) in 37 subjects after 16 weeks, which was sustained in the 26 subjects assessed 24 weeks later (28). A long-term benefit of bosentan treatment in CHD with shunt-associated PAH was also suggested in one open-label, uncontrolled study of 33 subjects followed for a mean period of 2.1±2.5 years (24). The Borg dyspnea index (BDI), a subjective measure of perceived dyspnea, decreased (improved) for a mean period of 2.1±0.5 years (24,26,28). Only statistically significant results are reported here. All studies assessed resting arterial oxygen saturation at baseline and at the end of the study (24,25,27,29,32). Three of five studies reported significant improvements in echocardiographic parameters following treatment with bosentan, including decreased right ventricular-right atrial pressure gradient (27) and/or right ventricular systolic pressure (24), improved pulmonary blood flow (PBF) and PBF index (25), and improved systolic tissue Doppler velocity (25). In contrast, two of the five studies reported no significant changes in echocardiographic parameters following bosentan treatment in CHD subjects with shunt-associated PAH (29,32).

Pulmonary hemodynamic efficacy of ERA therapy in CHD patients with shunt-associated PAH

There was considerable heterogeneity in the assessment and reporting of hemodynamic parameters. In five of ten studies, subjects underwent echocardiography at baseline and at the end of the study (24,25,27,29,32). Three of five studies reported significant improvements in echocardiographic parameters following treatment with bosentan, including decreased right ventricular-right atrial pressure gradient (27) and/or right ventricular systolic pressure (24), improved pulmonary blood flow (PBF) and PBF index (25), and improved systolic tissue Doppler velocity (25). In contrast, two of the five studies reported no significant changes in echocardiographic parameters following bosentan treatment in CHD subjects with shunt-associated PAH (29,32).

Five studies performed right heart catheterization (RHC) at baseline and study end (24,26,28,31,32). Only one study performed follow-up RHC in all subjects (28), whereas the other studies reported RHC in 14 of 33 subjects (24), 18 of 21 subjects (26), 21 of 24 subjects (32) and 11 of 27 subjects (31). The single RCT of bosentan in CHD patients with shunt-associated PAH and Eisenmenger's syndrome assessed PVR index as the primary efficacy end point, and demonstrated a significant reduction following 16 weeks of bosentan treatment, in association with reduced mean PAP (28) (Table 2). This hemodynamic benefit is consistent with the findings in other uncontrolled studies of bosentan, including reduced PVR and PVR index, systolic PAP, mean PAP and right atrial pressure, and improved PBF index (26,31,32). In one study (24), no significant changes in pulmonary hemodynamics were found following treatment with bosentan.

Tolerability of ERA therapy in CHD patients with shunt-associated PAH

ERA therapy was generally well tolerated by CHD subjects with shunt-associated PAH in all studies. Two sudden deaths occurred in one study (26), following five months and nine months of bosentan therapy. Both subjects were WHO functional class IV at baseline and had improved to WHO functional class III before death. Postmortem examination in the first patient was not obtained, but the death was witnessed and was preceded by complaints of palpitations. Postmortem examination of the second patient revealed generalized myocardial ischemia as the cause of death, which the authors stated as possibly due to arrhythmia. None of the other studies reported any episodes of sudden cardiac death, and there are no other reports in the literature of ERAs being associated with sudden cardiac death.

All studies assessed resting arterial oxygen saturation at baseline and following bosentan therapy, and four studies also assessed oxygen saturation following exercise (26,29,31,32). Arterial oxygen saturation did not decline significantly following bosentan therapy in any study; in fact, four studies reported improvement in resting (23,25,30) or end-exercise oxygen saturation (26).

In two of the 10 studies of bosentan treatment in CHD patients with shunt-associated PAH, four subjects (2.3% of all subjects) had elevated hepatic transaminase levels, requiring withdrawal of bosentan after two to nine months of therapy (28,32). Transaminase levels returned to normal in all subjects after stopping bosentan. Neither study indicated whether ERA therapy was reinstituted. Other reported adverse effects of bosentan included transient leg edema (n=74) (25,28), and dizziness or syncope (n=5; 2.9%) (25,26,28). These side effects were generally mild and well tolerated; none of the subjects required withdrawal from the studies, although one subject required a dose reduction from 125 mg to 62.5 mg twice daily because of dizziness (25).

DISCUSSION

In the present qualitative systematic review of the literature, we identified and reviewed 10 studies that assessed the efficacy and tolerability of the treatment of ERAs in adult CHD patients with shunt-associated PAH.
PAH. All studies used bosentan, a nonselective, dual ET-A/ET-B ERA, and reported significant clinical benefit during treatment over a minimum of 12 weeks and as long as two years. Clinical benefits included improved exercise capacity, as assessed by improvements in 6MWD in eight of the 10 studies, and improved WHO/NYHA functional class in all nine studies in which it was assessed. Bosentan treatment was generally well tolerated in all studies, with no evidence of worsening arterial oxygen saturation at rest or during exercise. Bosentan treatment was associated with the expected adverse effects of hepatotoxicity, edema, dizziness and flushing in a small number of subjects, which required withdrawal of bosentan in less than 5% of subjects. Notably, two subjects with WHO functional class IV died while taking bosentan, presumably from cardiac arrhythmia. The potential clinical benefits and generally good tolerability of bosentan treatment in CHD patients with shunt-associated PAH, as suggested by the majority of uncontrolled, open-label trials, was recently confirmed by a multicentre, placebo-controlled RCT, although the trial only included patients with Eisenmenger's syndrome (28).

PAH is a serious, progressive and often fatal disease. There are currently a number of PAH-specific medical therapies available for patients with IPAH and CTD-PAH or HIV infection. These include oral anticoagulation and calcium channel blockers, parenteral prostanol analogues (ep, epoprostenol, treprostinil), and more recently, oral ERAs (eg, bosentan) and PDE5 inhibitors (eg, sildenafil). A progressive and severe form of PAH can affect patients with CHD. While CHD patients with shunt-associated PAH often survive 20 to 30 years after being diagnosed with PAH, they suffer a poor quality of life due to disabling symptoms and limited functional capacity (6,7,10). Current therapeutic options for CHD patients with shunt-associated PAH are limited because there are no systematic trials of PAH-specific therapies in these patients. Uncontrolled, long-term administration of intravenous epoprostenol has favourable effects on hemodynamics and exercise capacity in CHD patients with shunt-associated PAH, although the studies performed have only included a small number of subjects (34,35). However, this treatment approach is complex, impractical for many patients and can be associated with life-threatening side effects. Heart-lung transplantation is an option in patients with advanced CHD with shunt-associated PAH, although the drawbacks are considerable (9,36), including the scarcity of organs, numerous complications and significant mortality.

The recent WHO and Venice revisions of PAH classification recognize the increasing evidence of significant parallels in pathological, pathophysiologial and clinical features between different types of PAH, including IPAH and CHD with shunt-associated PAH (4,11). As a result, PAH therapies initially only tested in IPAH are increasingly being assessed and clinically used to treat patients with other types of PAH. However, the novel PAH therapies have generally not been widely used in CHD patients with shunt-associated PAH because of concerns about potential toxicity, such as worsening oxygenation due to systemic hemodynamic effects. Moreover, there are few clinical trials to support the clinical and hemodynamic benefit of novel PAH therapies in CHD patients with shunt-associated PAH.

The results of the present systematic review suggest a clinically important functional benefit of ERA therapy in CHD patients with shunt-associated PAH. There was also evidence of pulmonary hemodynamic benefit, as assessed by either invasive hemodynamics or echocardiography. However, there was considerable heterogeneity among the hemodynamic parameters reported in each study, and there was limited statistical significance of many of the hemodynamic results. Perhaps most importantly, the clinical significance of hemodynamic parameters in evaluating treatment efficacy in CHD patients with shunt-associated PAH remains uncertain because they correlate poorly with clinical state, functional class, exercise capacity and prognosis (37).

Bosentan was generally well tolerated by CHD patients with shunt-associated PAH. Hepatotoxicity with elevated transaminase levels, the most frequent significant adverse effect of bosentan, was no more likely in CHD patients with shunt-associated PAH than previously reported in IPAH and CTD-PAH patients (18,19). Two sudden deaths, possibly caused by arrhythmia, were reported in one study (26). Although it is unclear whether sudden death was related to bosentan, and given a lack of any other literature reports of sudden death with bosentan, this is an issue that requires further study. However, these reports highlight the importance of carefully considering the risks and benefits of bosentan therapy in WHO functional
class IV CHD patients with shunt-associated PAH. Bosentan did not cause a worsening of hypoxemia in CHD patients with shunt-associated PAH at rest or following exercise, and the primary end point of the single RCT of bosentan in CHD with shunt-associated PAH was a safety end point that demonstrated no reduction in arterial oxygen saturation following treatment with bosentan (28). Four studies reported a small but significant improvement in arterial oxygen saturation following treatment with bosentan (23,25,26,30). The theoretical concern that bosentan causes worsening hypoxemia in CHD with shunt-associated PAH patients by causing a greater reduction in systemic vascular resistance compared with PVR, thereby worsening the right to left shunt, was not observed in any of the studies reviewed.

Our review has several limitations. First, we recognize a likely publication bias in favour of positive studies, such that the clinical benefit of ERA therapy in CHD patients with shunt-associated PAH may be exaggerated. As well, the effects of ERA therapy have been assessed in relatively few CHD patients with shunt-associated PAH. Clinical studies in CHD are difficult, due in part to the broad clinical spectrum of CHD patients who differ according to the type, size and surgical treatment status (corrected or noncorrected) of their CHD defect, as well as the severity and direction of intracardiac shunt (6). Moreover, assessing clinical benefit in CHD patients with shunt-associated PAH is often difficult given the longer natural history of these patients, even with Eisenmenger's physiology (the most severe form of CHD with shunt-associated PAH) and better survival than patients with PAH or CTD-PAH (38,39). Thus, the favourable results from previous trials of ERAs for PAH and CTD-PAH (18,19) do not necessarily apply to CHD patients with shunt-associated PAH. It is noteworthy that recent trials of novel oral PAH therapies, such as sitaxsentan, a novel ET-A-selective ERA, and the PDE5 inhibitor, sildenafil, have included CHD patients with shunt-associated PAH (20,22). However, in these studies, the specific benefit of therapy in CHD patients with shunt-associated PAH was not analyzed or reported. As such, these studies were excluded from the present review. We recognize this as another limitation, because our review only includes studies of bosentan in CHD patients with shunt-associated PAH. Whether sitaxsentan or other novel ERAs are more or less efficacious than bosentan for treating CHD with shunt-associated PAH has not been studied. We also recognize that CHD patients with shunt-associated PAH and Eisenmenger's syndrome may differ physiologically from CHD patients with shunt-associated PAH who do not have Eisenmenger's syndrome may differ physiologically from CHD patients with shunt-associated PAH who do not have Eisenmenger's physiology, and that oral ERA therapy may have different effects in these two patient populations. However, due to the nature of result reporting in the studies included in the present review, we were unable to adequately assess for any difference in the effects of bosentan in CHD patients with shunt-associated PAH with and without Eisenmenger's physiology. Whether any clinically relevant difference of oral ERA therapy exists between these two patient populations is an area requiring further study. Finally, we appreciate the marked heterogeneity in the patient population (one study included children) and clinical end points in the studies reviewed. Indeed, it was exactly because of this heterogeneity that a meta-analysis was inappropriate, but a qualitative systematic review could still be clinically useful.

**CONCLUSION**

The present qualitative systematic review of the literature indicates that treatment of CHD with shunt-associated PAH using the ERA bosentan is associated with significant clinical benefit, as reflected by improvements in clinical functional class and objectively measured hemodynamic function. **TABLE 2**

<table>
<thead>
<tr>
<th>Study</th>
<th>WHO/NYHA functional class, mean ± SD</th>
<th>6MWD, m, mean ± SD</th>
<th>Hemodynamic parameters, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
<td>Change</td>
</tr>
<tr>
<td>Christensen et al (23)</td>
<td>–</td>
<td>–</td>
<td>6 of 9 improved</td>
</tr>
<tr>
<td>Schmude-Neick et al (24)</td>
<td>3.1±0.5</td>
<td>2.4±0.5</td>
<td>27 of 33 improved</td>
</tr>
<tr>
<td>Apostolopoulos et al (26)</td>
<td>–</td>
<td>–</td>
<td>13 of 21 improved</td>
</tr>
<tr>
<td>Galie et al (28)</td>
<td>3</td>
<td>2</td>
<td>16 of 24 improved</td>
</tr>
<tr>
<td>Ibrahim et al (29)</td>
<td>–</td>
<td>–</td>
<td>5 of 11 improved</td>
</tr>
<tr>
<td>Kourouklis et al (30)</td>
<td>3.1</td>
<td>–</td>
<td>13 of 27 improved</td>
</tr>
</tbody>
</table>

*Versus placebo. 6MWD 6 min walk distance; mPAP Mean pulmonary artery pressure (mmHg); mRAP Mean right atrial pressure (mmHg); mSAP Mean systemic arterial pressure (mmHg); NYHA New York Heart Association; PBF Pulmonary blood flow (L/min); PBF/SBF Systemic blood flow (L/min); sPAP Systolic pulmonary artery pressure (mmHg); WHO World Health Organization*
exercise capacity. Improvements in pulmonary hemodynamics have also been reported in some studies, but these data are limited. Bosentan treatment was generally well tolerated, and was associated with recognized adverse effects of hepatotoxicity, edema, dizziness and flushing in a small number of patients, requiring withdrawal of bosentan in less than 5% of patients. Two deaths in WHO functional class IV patients, possibly due to arrhythmia, suggest a note of caution when considering bosentan therapy in such patients. Based on the degree of clinical benefit, the similarities between CHD with shunt-associated PAH and other types of PAH, including IPAH, and the lack of effective alternative therapies in this patient population, we suggest that ERA therapy be considered in functionally limited CHD patients with shunt-associated PAH.

COMPETING INTERESTS: NF and BD have no competing interests. SM has received consulting and speaking fees from Actelion Pharmaceuticals Ltd, Enzyme Pharmaceuticals, GlaxoSmithKline and Pfizer, and clinical investigator fees from Actelion Pharmaceuticals Ltd, Enzyme Pharmaceuticals and Pfizer, which are pharmaceutical companies that own and market drugs for PAH. GJS has received consulting and speaking fees from Actelion Pharmaceuticals Ltd.

CONTRIBUTORS: All authors contributed substantially to the literature review, abstracting of data, data analysis, as well as writing and revision of the article. All authors approved the final version for publication.

REFERENCES