



# A Retrospective Evaluation of Pulmonary Vasodilator Monotherapy and Sequential Combination Therapy in Thai Patients with Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

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## Abstract

**Objective:** This retrospective study evaluated the outcomes of Thai patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) treated with initial monotherapy and subsequent sequential combination therapy upon clinical worsening.

**Methods:** Patients aged 1–65 years with a diagnosis of PAH-CHD who received initial monotherapy at Siriraj Hospital, Bangkok, Thailand, from January 01, 2013 to December 31, 2014 were included in this retrospective analysis. Clinical worsening was assessed using the 6-minute walking distance (6MWD) test.

**Results:** A total of 88 patients who met study inclusion criteria had received initial monotherapy with either bosentan (n=6), sildenafil (n=47) or beraprost (n=35). Forty-four (50%) of these patients experienced a predefined clinical worsening event within 12 months of commencing treatment. Patients who received initial bosentan monotherapy were significantly less likely to experience clinical worsening compared with sildenafil and beraprost recipients at 12 months (16.7% vs. 38.3% and 71.4%, respectively;  $p=0.039$ ), and 24 months (16.7% vs 61.7% and 77.1%, respectively;  $p=0.007$ ). Thirty-three patients who failed initial monotherapy were subsequently prescribed sequential combination therapy. The 6MWD (mean  $\pm$  standard error) increased significantly after commencement of sequential combination therapy from 208.9  $\pm$  67.2 m before the addition of the second drug to 285.5  $\pm$  92.1 m at 1 month ( $p=0.09$ ) and 326.3  $\pm$  62.7 m at 3 months ( $p=0.001$ ).

**Conclusion:** This retrospective analysis showed that PAH-CHD patients who received initial bosentan monotherapy were significantly less likely to experience clinical worsening over 24 months than those who received sildenafil or beraprost. Sequential combination therapy initiated upon clinical worsening significantly improved 6MWD at 3 months. The findings support the use of sequential combination therapy in patients with PAH-CHD who fail initial monotherapy.

## Keywords

Combination therapy; Pulmonary hypertension; Congenital heart disease; Thailand

## Introduction

Pulmonary arterial hypertension (PAH), a progressive condition characterized by elevated pulmonary arterial pressure, can present at any age from infancy to adulthood. PAH associated with congenital heart disease (PAH-CHD) is one of the most common forms of the disease in Thailand. Without appropriate management, patients with PAH have a poor prognosis with respect to quality of life and survival. The REVEAL registry study showed 5-year survival rates of 64% for idiopathic PAH and of 74% for PAH-CHD [1,2].

There is wide variability in terms of how patients with PAH-CHD present, and individualized patient assessments and treatment approaches are required. Right heart catheterization is the essential diagnostic procedure for PAH-CHD for evaluation of baseline hemodynamic data, including pulmonary arterial pressure and pulmonary vascular resistance (PVR) [3]. Many patients with PAH-CHD are not suitable candidates for surgery to repair their defects, and therefore require long-term PAH-specific drug therapy to manage their condition.

In Thailand, six different compounds used to treat PAH are currently available – the endothelin receptor antagonists (ERA) bosentan and ambrisentan, the phosphodiesterase type-5 inhibitors sildenafil and tadalafil, and the prostanoids beraprost and iloprost. Of these, only sildenafil is approved as monotherapy for PAH in Thailand. PAH-specific monotherapies have been shown to significantly improve clinical symptoms, exercise capacity, and survival of patients with PAH [4-6], including those with PAH-CHD [7-9]. However, one in five patients who are treated with monotherapy experience symptomatic deterioration over time and require escalation of treatment, either an increased dose or addition of a second drug, after a median of approximately 2.5 years [10,11]. Addition of a second PAH-specific drug, as part of a risk-based approach in which combination therapy is recommended for those who fail to achieve or maintain a low 1-year mortality risk on monotherapy, is recommended by the most recent European Society of Cardiology European Respiratory Society (ESC/ERS) guidelines [12] and the Thai management guidelines [13].

While the value of combination therapy in PAH has already been extensively studied [14,15], only a few studies have evaluated the outcomes of sequential combination therapy specifically in PAH-CHD. These studies show that addition of a second PAH-targeting drug in PAH-CHD patients who experience clinical worsening on initial monotherapy limits further deterioration and improves exercise capacity [10,16,17].

The purpose of this current retrospective study is to add to current literature by evaluating the outcomes of Thai patients with PAH-CHD treated with initial monotherapy and subsequent sequential combination therapy upon clinical worsening.

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Received: March 14, 2016 Accepted: June 06, 2016 Published: June 13, 2016

## Material and Methods

### Study design and patient selection

This retrospective study included patients aged 1–65 years with a diagnosis of PAH-CHD, who were followed-up at Siriraj Hospital, Bangkok, Thailand, from January 01, 2013 to December 31, 2014, for whom echocardiographic and catheterization data were available as part of their medical records. The study protocol was approved by the Siriraj Hospital Institutional Review Board and Ethics Committee 373/2557 (EC4).

Patients were categorized according to the ESC/ERS guidelines clinical classification of PAH-CHD [12]: (1) Eisenmenger syndrome; (2) PAH associated with prevalent systemic-to-pulmonary shunts; (3) PAH with small/coincidental defects; and (4) PAH after defect correction. Patients in category 2 (those with PAH associated with prevalent systemic-to-pulmonary shunts) were further classified into non-correctable PAH, in which PVR may be as high as 6 Wood units and patients may benefit from PAH-specific therapy during the follow-up period, and PAH that is correctable by surgery or intravenous percutaneous procedure, in which defects are moderate to large, PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, and cyanosis at rest is not a feature. Patients with correctable PAH were excluded from this analysis.

Only patients who received PAH-specific monotherapy at study initiation were included in this analysis. Patients who received initial (upfront) combination therapy were excluded. Patients were also excluded if they had comorbidities that could affect hospitalization, worsening of functional class, or right heart failure such as severe left-sided valvular regurgitation.

### Outcome measures

Similar to the SERAPHIN trial [6], the composite primary endpoint was time to clinical worsening (TTCW) defined as the time from baseline to death from any cause, or to lung transplantation, atrial septostomy or worsening of PAH, which was defined as a decrease in 6-minute walking distance (6MWD) of at least 15% from baseline, confirmed by tests performed on two different days, and worsening of New York Heart Association (NYHA) functional class.

Patients on initial PAH monotherapy were initiated on sequential combination therapy at the physician's discretion if they had a primary endpoint event.

Data on monitoring of clinical symptoms including NYHA functional class, 6MWD, and symptoms of right heart failure were obtained. Data were analyzed at baseline (start of data collection period) and at visits 1, 2, 3, and 4, which approximately corresponded to months 3, 6, 12, and 24.

### Statistical analysis

Only observed data were included in the analyses and imputations for missing data were not made. Chi-square analysis was performed to compare the demographic data of patients who continued to receive monotherapy and those who subsequently received sequential combination therapy (upon a clinical worsening event). A two-tailed p-value of <0.05 was used to indicate a statistically significant difference between these two patient groups.

Kaplan–Meier survival curve analyses were used to determine survival from TTCW over time, and the Friedman test was performed to compare 6MWD values at each time period.

Statistical analyses were performed with SPSS 19.0 for Windows (SPSS-Inc., Chicago, IL, USA).

## Results

Of 104 patients with PAH-CHD who were followed-up at our center between January 01, 2013 and December 31, 2014, 88 patients met the inclusion criteria and initiated PAH pulmonary vasodilator monotherapy, in accordance with both Thai and ESC/ERS guidelines for the management of PAH [12,13]. A total of 16 patients were excluded for various reasons including severe comorbidity (stroke, cholecystitis, esophageal varices, or cirrhosis), pregnancy, adverse events associated with oral pulmonary vasodilator therapy, acute renal failure, breast cancer, lost to follow-up, and being on combination therapy (four patients) at the time of study initiation. Treatment regimens of patients included in this retrospective study are illustrated in Figure 1. The oral pulmonary vasodilators bosentan, beraprost, and sildenafil were prescribed as initial monotherapies in 6, 35, and 47 patients, respectively.

The majority of patients had Eisenmenger syndrome (n=39; 44%) with NYHA class either II (n=44; 50%) or III (n=41; 47%) (Table 1). Baseline characteristics and demographic data were comparable between all patients who initiated monotherapy (all combined [n=88]), those who continued to receive only monotherapy (n=55), and those subsequently received sequential combination therapy (n=33).

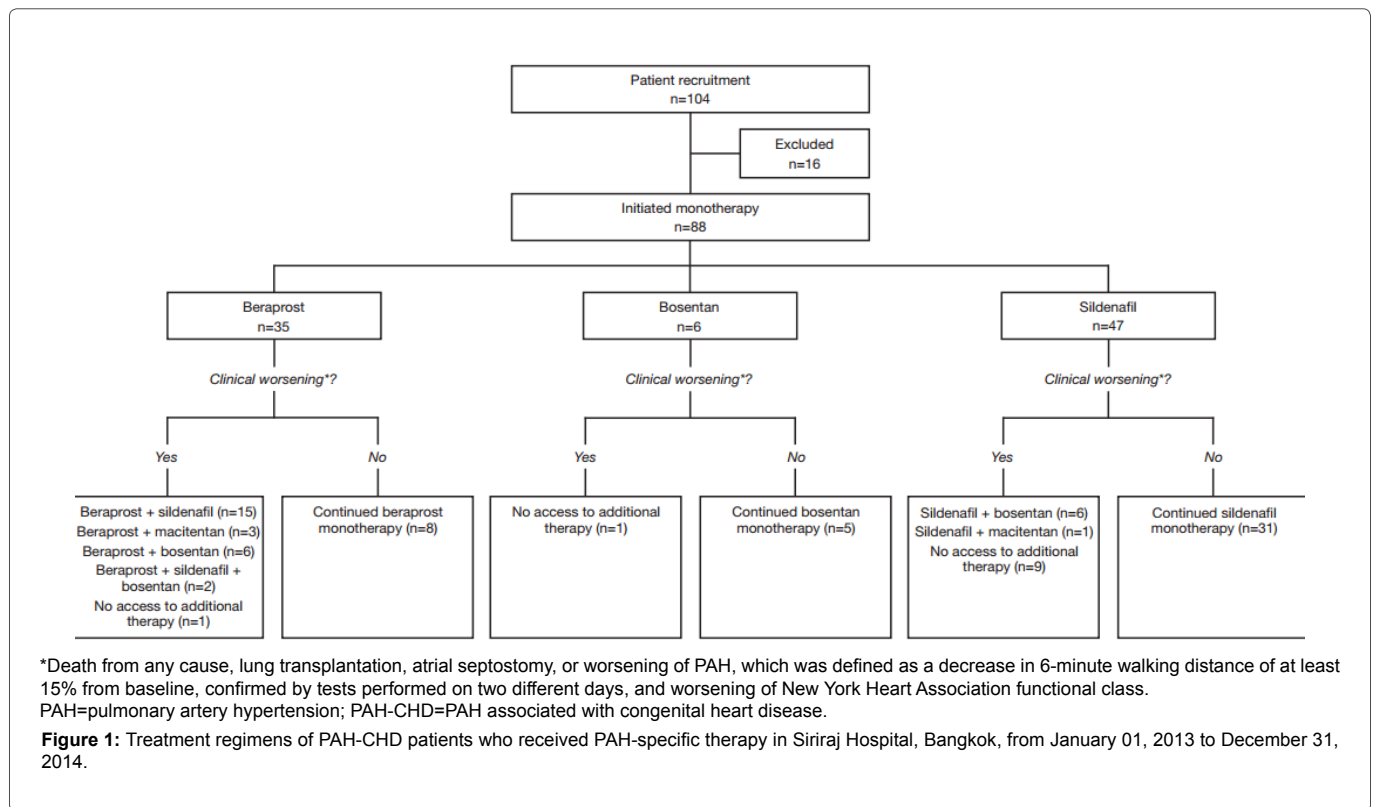
### Time to clinical worsening on initial monotherapy

Forty-four (50%) of the 88 patients who initiated monotherapy experienced a primary endpoint event within 12 months of commencing treatment; all 44 patients experienced worsening of PAH and no patients had lung transplantation, atrial septostomy, or died. A Kaplan–Meier analysis was conducted to compare survival from enrollment to clinical worsening in patients receiving initial monotherapy with each of the three different agents – bosentan, sildenafil, and beraprost (Figure 2). As shown, patients who initially received bosentan were significantly less likely to have experienced clinical worsening at 12 months compared with those who initially received sildenafil or beraprost (16.7% vs. 38.3% and 71.4%, respectively; p=0.039) and 24 months (16.7% vs 61.7% and 77.1%, respectively; p=0.007). It appeared that patients receiving initial beraprost monotherapy had slightly shorter TTCW than patients given sildenafil.

### Sequential combination therapy

Of the 44 patients who failed initial monotherapy, 33 subsequently received sequential combination therapy (Figure 1). The other 11 patients did not have access to additional pulmonary vasodilator drug therapy and therefore continued to receive monotherapy. Among the 35 patients who experienced a primary endpoint event on initial beraprost monotherapy, the majority went on to receive add-on sildenafil. Among the 47 patients who experienced a primary endpoint event on initial sildenafil monotherapy, six went on to receive add-on bosentan and one patient received add-on macitentan.

Sequential combination therapy was associated with marked improvements in NYHA functional class over time. Among the 33 patients who had access to a second pulmonary vasodilator and received combination therapy, the number with PAH functional class III/IV decreased from 22 (66.67%) at 0–1 months pre-combination therapy to 17 (51.52%) at 6 months. Meanwhile, the corresponding



**Table 1:** Baseline patient demographic data.

	All patients (N=88)	Patients who continued to receive MT (n=55)	Patients who received sequential CT (n=33)	p-value
Gender (n)				
• Male	17	13	4	
• Female	71	42	29	
Age (years)	31 ± 13	32 ± 13	29 ± 12	0.99
PAH-CHD classification (n)				
• Eisenmenger syndrome	39	25	14	
• PAH associated with prevalent systemic-to-pulmonary shunts	26	20	6	
• PAH with small/coincidental defects	8	2	6	
• PAH after defect correction	15	8	7	
NYHA functional class (n)				
• I	0	0	0	
• II	44	33	11	
• III	41	21	20	
• IV	3	1	2	
Oxygen saturation (SpO <sub>2</sub> , %)	91 ± 8	92 ± 7	89 ± 9	0.34
6MWD (m)	286 ± 72	309 ± 59	260 ± 78	0.25
Mean RAP (mmHg)	8.89 ± 4.37	9.53 ± 4.40	8.18 ± 4.36	0.17
Mean PAP (mmHg)	66.07 ± 18.30	66.36 ± 18.29	65.75 ± 18.79	0.39
PVRi (Wood units.m <sup>2</sup> )	15.24 ± 12.26	12.93 ± 12.85	17.89 ± 11.19	0.38

Mean ± standard deviation values are provided.

6MWD=6-minute walking distance; CHD=congenital heart disease; CT=combination therapy; MT=monotherapy; NYHA=New York Heart Association; PAP=pulmonary arterial pressure; PVRi=peripheral vascular resistance index; RAP=right atrial pressure; RHF=right heart failure.

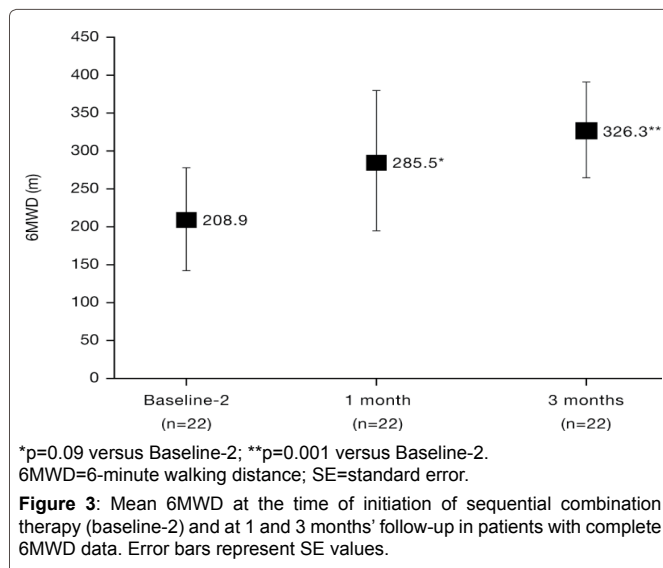
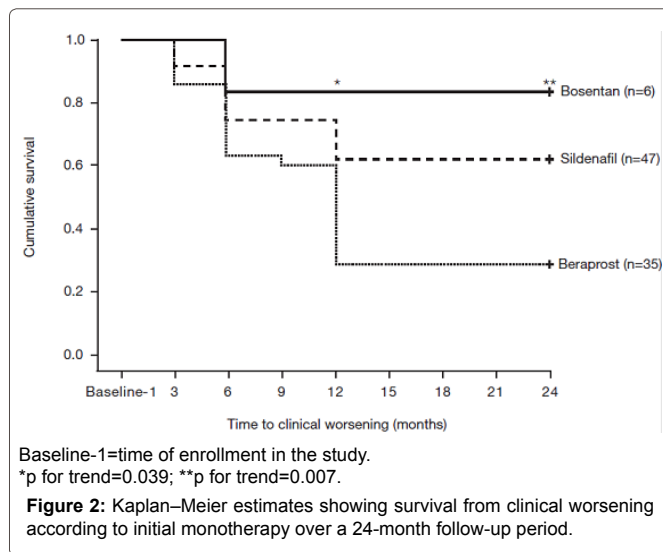
number with PAH functional class I/II rose from 11 (33.33%) to 16 (48.48%).

In the 2-year data collection period, a total of 22 patients had complete data available from 6MWD testing up to 3 months following the initiation of sequential combination therapy. As shown in Figure 3, significant improvements were seen when comparing 6MWD (mean ± standard error) at time of initial monotherapy failure (208.9

± 67.2 m) to those observed at 1 month (285.5 ± 92.1 m, p=0.009) and 3 months after initiating combination therapy (326.3 ± 62.7 m; p=0.001).

## Discussion

Our retrospective study evaluated outcomes in PAH-CHD patients who received initial PAH-specific monotherapy at our center.



The decision to initiate sequential combination therapy was based on patients experiencing clinical worsening, an established outcome measure for evaluating the effectiveness of PAH therapies that has been used in several recent studies [6,18,19]. Our evaluation yielded two key findings. Firstly, we found that patients receiving initial bosentan monotherapy were significantly less likely to experience clinical worsening compared with sildenafil and beraprost recipients at 12 months and 24 months. Secondly, we found that half of all patients experience clinical worsening within the first 12 months of initial monotherapy and that addition of a second PAH therapy upon clinical worsening significantly improved 6MWD to above pre-deterioration levels.

Our findings are broadly consistent with two previous studies that have shown that sequential combination therapy initiated upon failure of initial monotherapy improved 6MWD [10,16]. In contrast, a recent similar retrospective analysis in the UK reported no improvement in 6MWD with add-on combination therapy, although it arrested deterioration in exercise capacity upon failure of initial sildenafil or bosentan monotherapy [17]. This UK study included only PAH-CHD

patients with World Health Organization (WHO) functional class III; in contrast, half of all patients included in our study had less severe functional impairment (NYHA functional class II).

While sildenafil was the most commonly prescribed first-line medication for PAH in our center, many patients received beraprost because of the lower acquisition costs at the time [13]. Findings from a cost-utility analysis conducted in 2013 [20] led to recommendations by the Thai guidelines, released midway through 2013, for the use of sildenafil as first-line therapy in adult patients with PAH WHO functional class II-III, and sequential or combination therapy with sildenafil plus an ERA (bosentan) or a prostanoid (iloprost or beraprost) in those with more advanced stage PAH (WHO/NYHA functional class IV) [13]; clinical practice changed accordingly to reflect the updated recommendations.

A previous study in patients with Eisenmenger syndrome showed that upfront combination therapy with bosentan and sildenafil was not superior to bosentan monotherapy with regard to changes in 6MWD [21]. As such, in our center, we used clinical worsening to guide the decision to escalate treatment, as opposed to prescribing combination therapy from the outset. While a goal-oriented treatment approach based on predictors of improved survival has been shown to be an important strategy for managing patients with PAH [22,23], evidence for this strategy in PAH-CHD patients is limited. In addition, a recent analysis of the German National Register for CHD found similar survival benefits between monotherapy and sequential combination therapy regimens, suggesting that therapy escalation may be associated with clinical stabilization and preservation of the benefits of PAH-specific therapies on long-term survival [11]. Thus, TTCW as an endpoint can provide better understanding of patient outcomes and may lead to rational use of sequential add-on PAH-specific therapy, particularly in resource-constrained settings where access to certain PAH therapies is limited.

The main limitations of this study were its retrospective design and the small number of patients included, which likely limited the statistical power of the analyses.

## Conclusion

In conclusion, this retrospective study showed that in PAH-CHD patients, initial bosentan monotherapy prolonged TTCW more than sildenafil and beraprost. Further, sequential combination therapy, initiated upon clinical worsening on initial monotherapy, significantly improved 6MWD. Our findings add to the current literature to provide physicians with real-world evidence when considering management strategies to improve the prognosis of PAH-CHD patients.

## Acknowledgments

The authors would like to thank the patients who participated in this study.

Editorial support was provided by AMICULUM (Singapore) Pte Ltd, funded by Actelion Pharmaceuticals Singapore Pte Ltd.

## Authors' contributions

All authors contributed to the conception and design of this study, and participated in collection and analysis of the data. All authors were involved in drafting the manuscript and have read and approved the final manuscript to be published.

## Competing interests

The authors declare that they have no conflict of interest. K. Durongpisitkul was a coinvestigator in the SERAPHIN study. He is also the chair-person of the Thai Pulmonary Hypertension Guideline Committee (Heart Association of Thailand) 2013.



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