*ERJ Express*. Published on November 1, 2006 as doi: 10.1183/09031936.00081706

# Addition of Sildenafil to Bosentan Monotherapy in Pulmonary Arterial Hypertension

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Short Title: Sildenafil after Bosentan Failure in PAH

**Abstract**

Combination therapy has been recommended for the treatment of pulmonary arterial hypertension (PAH). However, there is scant information on combination therapy after failure of monotherapy, particularly in patients with scleroderma-associated PAH (PAH-SSD).

Among 82 consecutive patients with PAH who received initial bosentan monotherapy, 13 idiopathic PAH (IPAH) and 12 PAH-SSD patients requiring additional therapy with sildenafil were studied. Sildenafil was added for clinical deterioration based upon symptoms, New York Heart Association (NYHA) classification, or six minute walk distance (6MWD). Clinical data and hemodynamics were collected at baseline. Assessments were made at 1-3 month intervals.

At baseline, there were no differences in demographics, NYHA, hemodynamics, or 6MWD between the two groups. After initiation of bosentan, both groups experienced clinical improvement, but ultimately deteriorated (median time to monotherapy failure, 792 vs. 458 days, IPAH and PAH-SSD respectively, log-rank $P$=0.06). After addition of sildenafil, more IPAH patients tended to improve in NYHA class (5/13 vs. 2/12) and walked farther (mean difference in 6MWD, 47±77m vs. -7±40m, $P$=0.04) compared to PAH-SSD patients.

Addition of sildenafil after bosentan monotherapy failure improved NYHA and 6MWD in IPAH patients, but failed to improve either parameter in PAH-SSD patients. Additional studies are needed to assess the tolerability and efficacy of this combination in patients with PAH-SSD.

**Key Words**

bosentan

combination therapy

pulmonary hypertension

scleroderma

sildenafil

## Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature that leads to right heart failure and death.[1] Pulmonary endothelial dysfunction characterized by impaired production of vasodilators and over-expression of vasoconstrictors has been implicated in the pathogenesis of the disease[2] [3] and therefore, several novel therapies have been developed that target the prostacyclin (epoprostenol, treprostinil, and iloprost), nitric oxide (sildenafil), or endothelin (bosentan) pathways.

Although the optimal long-term management for patients with PAH has yet to be defined, combination therapy with agents that target different pathways in the putative pathogenesis of the disease has been proposed in treatment algorithms.[4-6] The combination of two oral agents, such as bosentan and sildenafil, is particularly attractive given the ease of administration, differing mechanisms of action, and tolerability. Several uncontrolled studies of the combination of these two agents in PAH have been reported,[7] [8]however, there are few data on the effect of combination therapy in patients with PAH associated with the scleroderma-spectrum of diseases (PAH-SSD). Since patients with PAH-SSD tend to have a poorer response to available therapies compared to the idiopathic PAH (IPAH) population, [9-13] combination therapy targeting multiple pathways may offer another option for these patients.

We reviewed our experience with the addition of sildenafil to bosentan therapy in patients with both IPAH and PAH-SSD who had clinically deteriorated on bosentan monotherapy. We hypothesized that the response to combination therapy might differ between these two groups of patients based upon previously described phenotypic characteristics and differential responses to therapy.[14]

## Methods

The Institutional Review Board reviewed and approved the conduct of this study. The Johns Hopkins Pulmonary Hypertension Program maintains a registry of all patients evaluated at our center. We identified 82 consecutive patients in the registry with a diagnosis of IPAH, anorexigen-associated PAH, or PAH-SSD who received bosentan as initial therapy between January 2002 and January 2006. For this study,

anorexigen–associated PAH patients were grouped with IPAH patients as there is no evidence that clinical or pathologic differences exist between these two groups.[15 16]

The diagnosis of PAH was confirmed by right heart catheterization revealing a mean pulmonary artery pressure (mPAP) greater than 25 mmHg, pulmonary capillary wedge pressure (PCWP) less than 15 mmHg, and pulmonary vascular resistance (PVR) greater than 3 Wood units. Other causes of pulmonary hypertension, such as significant chronic obstructive or interstitial disease, portal hypertension, severe obstructive sleep apnea, chronic thromboembolic disease or patients with scleroderma with significant interstitial lung disease were excluded. [12 17] Interstitial lung disease was defined based upon a combination of pulmonary function tests and chest radiography as previously described.[12] The diagnosis of scleroderma was based upon the American College of Rheumatology criteria.[18]

Bosentan therapy was prescribed at recommended doses according to the package insert (Tracleer ®; Actelion Pharmaceuticals; Switzerland). The patients were monitored clinically for treatment efficacy as determined by symptoms, New York Heart Association functional classification (NYHA FC), distance achieved on six minute walk testing (6MWD), and repeat hemodynamic assessment if clinically indicated. If patients deteriorated in any of these parameters, they were offered additional therapy with sildenafil. Bosentan monotherapy failure was defined as follows: worsening of symptoms of dyspnea or fatigue, decline in NYHA FC by at least one class, or decline in 6MWD by greater than 30m. Thirty meters was chosen as a minimal clinically important difference for the 6MWD in PAH as an estimated average treatment effect size found in recent clinical trials of novel therapies.[11 19-21] Twenty five patients who fulfilled these criteria were offered addition of sildenafil to bosentan or addition of intravenous or subcutaneous prostacyclin analogues; all 25 patients chose a trial of sildenafil over prostacyclin analogues. .Prior to July 2005, sildenafil was started at a dose of 25 mg three times a day (TID). Over the course of two to three weeks, the dose was increased to a goal of 50 mg TID as tolerated. If no clinical improvement was noted at this dose, sildenafil was further increased to a maximum of 100 mg TID as tolerated. After

sildenafil received regulatory approval for use in PAH in July 2005, patients who were started on sildenafil therapy received 20 mg three times a day, according to the package insert (Revatio ®; Pfizer; New York, New York). Patients who had received higher doses prior to regulatory approval of sildenafil remained on the higher doses for the duration of this study.

## Statistical Analysis

The baseline NYHA FC and 6MWD obtained prior to initiation of bosentan therapy were compared to values obtained after 3 months of combination therapy with bosentan and sildenafil. Effects of therapy were compared between values obtained at baseline and after 3 months of bosentan monotherapy (Period 1), at bosentan monotherapy failure (Period 2), and after 3 months on combination therapy (Period 3). Continuous variables were compared using the student's t-test or the Wilcoxon rank-sum test where appropriate. Categorical variables were compared using the Chi-squared statistic. Time to bosentan failure was compared using Kaplan-Meier analysis. Data were reported as mean values with standard deviation (SD) or standard error (SE) as noted. A 2-tailed p-value with a significance level of 0.05 was used to detect statistically significant differences between groups. All analyses were performed using STATA statistical software (version 9.0, College Station, Texas).

## Results

### *Patient Demographics*

Between January 2002 and January 2006, 82 PAH patients were identified who had received initial therapy with bosentan. Twenty five patients, including 13 with IPAH and 12 with PAH-SSD, received additional therapy with sildenafil for clinical deterioration. At baseline, patients with IPAH tended to be older, but there were no significant differences in demographic characteristics, NYHA FC, hemodynamic parameters, 6MWD, or medication use between the groups. (Table 1)

Table 2 shows the baseline characteristics of the patients who remained on bosentan monotherapy. When compared to the IPAH patients who received combination therapy, the IPAH patients who remained

on monotherapy were significantly younger (51±14 vs. 60±8 years, *P*=0.04). Conversely, PAH-SSD patients in the monotherapy group were significantly older than the PAH-SSD combination group (65±11 vs. 52±13, *P*=0.003). There were no differences in other demographic or clinical characteristics between groups, but IPAH patients in the combination group had significantly higher baseline mean right atrial pressure (RAP) compared to the bosentan only group (14±5 vs. 9±6 mmHg, *P*=0.02).

Although there were no significant differences in the durations of the follow-up periods between groups in Period 1 (110±31 days IPAH vs. 95±26 days PAH-SSD) or Period 3 (115±22 days IPAH vs. 110±27 days PAH-SSD), there was a trend towards a significant difference in time to bosentan failure (Period 2) by time-to-event analysis (proportion remaining on therapy at 1-,2-, and 3-years: 77%, 62%, and 8% versus 58%, 33%, and 0%, IPAH vs. PAH-SSD respectively, log-rank *P*=0.06).

***Change in Functional Class***

NYHA FC at baseline, after Period 1, Period 2, and Period 3 is shown in Figure 1. At baseline, there were no significant differences in the functional class between the two groups. After initiation of bosentan, 9/13 IPAH and 5/12 PAH-SSD patients improved at least one FC. At bosentan failure, 7 IPAH (6 of whom had initially improved on bosentan) and 6 PAH-SSD (5 of whom had initially improved on bosentan) patients deteriorated by at least one FC. Five of thirteen patients improved at least one FC after addition of sildenafil to bosentan in the IPAH group, whereas 2/12 patients improved in the PAH-SSD group (*P*=0.22). One subject deteriorated by one FC in the PAH-SSD group; none deteriorated in the IPAH group.

***Change in Six Minute Walk Distance***

The 6MWD at baseline, Period1, Period 2, and Period 3 is shown in Figure 2. There were no significant differences between the 6MWD in the IPAH and PAH-SSD patients at baseline (262±139m vs. 319±76m, *P*=0.31, IPAH vs. PAH-SSD), Period 1 (337±166m vs. 345±105m, *P*=0.90), or Period 2 (294±104m vs. 233±163m, *P*=0.28). There was a trend towards a difference in distance achieved between the IPAH and PAH-SSD groups after the addition of sildenafil to bosentan (340±141m vs. 224±159m,

*P*=0.06), corresponding to a mean difference of 47±77m in IPAH patients and -7±40m in PAH-SSD (*P*=0.04 for difference in mean change in 6MWD between groups). Within groups, 6MWD significantly improved in the IPAH group at Period 1 (262±139m vs. 337±166m, *P*=0.04), then declined by Period 2 (294±104m). However, this change in 6MWD was not significant (Period 1 vs. Period 2, *P*=0.18). After three months of combination therapy, the mean 6MWD increased significantly (294±104m vs. 340±141m, *P*=0.05). In the PAH-SSD group, there was no significant improvement in 6MWD after initiation of bosentan. However, there was a significant decline in 6MWD at Period 2 (345±105m vs.233±163m, *P*=0.01). No change in 6MWD was observed after the addition of sildenafil to bosentan monotherapy. Overall, patients in the IPAH group improved significantly from diagnosis to combination therapy with bosentan and sildenafil (262±139m vs. 340±141m, *P*=0.04). The PAH-SSD group experienced a significant decline in 6MWD from diagnosis to combination therapy (319±76m vs. 224±159m, *P*=0.04).

***Sildenafil Dosage and Side Effects***

The average daily dose of sildenafil was significantly different between groups (IPAH 98±65 mg/day vs. 168±82 mg/day, *P*=0.02). Two IPAH patients and one PAH-SSD patient started therapy after July 2005 (time of regulatory approval of sildenafil for PAH treatment) and thus received 20 mg TID (60 mg/day) total dose. Several patients discontinued sildenafil for side effects; one in the IPAH group after 4 months of 25 mg sildenafil TID (severe dyspepsia) and three in the PAH-SSD group. One patient had intractable headaches and discontinued sildenafil 25 mg TID after 3 months and two patients had liver function test (LFT) abnormalities that appeared after the addition of sildenafil to bosentan. Neither patient had prior LFT abnormalities on bosentan monotherapy. One of these patients discontinued sildenafil 75 mg TID after 5 months with subsequent resolution of the abnormalities; the other (sildenafil 50 mg TID) reduced the dose of bosentan to 62.5 mg twice daily, which normalized the LFTs.

Several patients required additional therapy for clinical deterioration after more than 3 months of combination therapy. Five of the 12 PAH-SSD patients required additional therapy with either inhaled

iloprost (n=4) or intravenous epoprostenol (n=1) (mean time to additional therapy, 123±52 days) whereas only one of the IPAH patients required additional therapy (continuous intravenous treprostinil after 118 days of combination therapy) for clinical worsening ($P$=0.05). Another patient in the PAH-SSD group required continuous intravenous dopamine for renal insufficiency and refractory right heart failure after more than 100 days on combination therapy. Four patients with PAH-SSD died during the study period from progressive right heart failure; one patient with IPAH died from gastrointestinal hemorrhage unrelated to pulmonary hypertension therapy.

## Discussion

This study suggests that the response to combination therapy with bosentan and sildenafil, after clinical failure of bosentan monotherapy, may vary between patients with IPAH and PAH-SSD. We found that while patients with IPAH experienced improvement in functional class and distance achieved on 6MWT, patients with PAH-SSD did not. Two PAH-SSD patients developed LFT abnormalities after the addition of sildenafil; neither patient had previous liver function abnormalities on bosentan monotherapy. Further, more PAH-SSD patients required additional therapy with a prostanoid. Additionally, four patients in the PAH-SSD group died during the study period compared with only one patient in the IPAH group.

Improvement in IPAH patients on combination therapy after failure of bosentan monotherapy is consistent with a recent report by Hoeper and colleagues on 9 patients with IPAH.[7] In this study, using a predefined treatment algorithm, IPAH patients who had failed bosentan monotherapy received additional oral therapy with sildenafil and experienced a significant improvement in both 6MWD and peak oxygen uptake. Other studies and case reports of combination therapy have also shown improvements in functional class, functional capacity, and/or hemodynamics in IPAH patients.[22-24] The BREATHE-2 trial, a randomized, double-blind, placebo-controlled study of the effects of the combination of bosentan and intravenous epoprostenol therapy, included patients with IPAH (n=27) and PAH-related to connective tissue disease (PAH-SSD n=5, PAH-SLE n=1).[25] This study failed to find a significant difference between

groups in PVR (the primary outcome), dyspnea rating, functional class, or exercise tolerance. Interestingly, the authors suggest that inclusion of a larger proportion of patients with PAH-SSD in the treatment group (18% vs. 9%) may have accounted for the failure to achieve the primary outcome, citing the poorer response to bosentan[11] and epoprostenol[26] in this group noted in prior studies.

There are limited studies of combination therapy in PAH-SSD patients. In a follow up study, Hoeper et al reported their experience with combination therapy in a cohort of 123 PAH patients.[8] Over a two year period, over 40% of patients required combination therapy with bosentan and sildenafil. More than 20% of the cohort required further addition of a prostanoid. Although 15 patients in the cohort were classified as having PAH related to connective tissue disease, whether this subset has PAH-SSD or another connective tissue disease and what proportion of this group required combination therapy is unclear.

Previous clinical investigations have also indicated differential response to therapy between IPAH and PAH-SSD patients. Continuous intravenous therapy with epoprostenol has been shown to reduce mortality in IPAH patients, but has no or only minimal long term benefit in PAH-SSD.[13 26] While approximately 7% of patients with IPAH have demonstrated a long-term response to oral calcium channel blocker therapy,[10] only about 1% of PAH-SSD patients will have a sustained benefit from this class of drugs.[27] This differential response to therapy has persisted with newer agents. Bosentan has been shown to improve functional class and exercise capacity while delaying clinical worsening in short-term studies of IPAH patients. [11 28] However, bosentan therapy only prevented decline in exercise capacity in the PAH-SSD group. Our own experience with long-term bosentan treatment in PAH-SSD compared to IPAH patients also suggests that PAH-SSD patients do not have sustained clinical response and have worse survival.[14 29 29] PAH-SSD patients in this study failed bosentan monotherapy earlier than IPAH patients (median time to failure 458 days vs 792 days, PAH-SSD and IPAH respectively). A recent study has suggested an improved survival in patients with bosentan monotherapy compared to historical controls treated with prostanoids.[30] However, nearly half of the patients in the historical cohort had clinically

evident pulmonary fibrosis, compared to less than one-third of the bosentan cohort which may account for the improved survival in the bosentan cohort. Further, time to initiation of treatment was significantly longer in the historical controls compared to the bosentan cohort which may have biased the survival analysis. Sildenafil has recently been shown to improve functional class, exercise capacity, and hemodynamics in patients with PAH including PAH associated with connective tissue disease.[9] However, PAH-SSD patients comprised a minority of the PAH associated with connective tissue disease cohort, with the majority of patients having systemic lupus erythematosus or "other" connective tissue disease. There are currently no studies reporting the long-term efficacy of sildenafil in PAH-SSD patients.

Several reasons for a diminished response to combination therapy in PAH-SSD may be contributing to this differential response to therapy compared to IPAH. First, it is possible that since the PAH-SSD patients deteriorated more on bosentan monotherapy than IPAH patients, the PAH-SSD group was less likely to respond to additional therapy, regardless of the medication chosen. Second, a drug-drug interaction between sildenafil and bosentan via the CYP3A4 enzyme can cause a significant reduction (up to 66%) in the plasma concentration of sildenafil.[31] The plasma concentration of sildenafil may be further reduced in patients with scleroderma due to gastrointestinal disease that may interfere with absorption, including esophageal dysmotility,[32] gastroparesis,[33] small bowel malabsorption,[34] and pancreatic insufficiency.[35] Thus, it is possible that despite the overall higher daily doses of sildenafil in this group, therapeutic levels were not achieved in the plasma. Significant clinical improvement in the IPAH group despite these potential drug-drug interactions with combination therapy may support this hypothesis.

Alternatively, cardiac involvement may account for some of the differences in response to therapy. Previous studies have shown that left ventricular diastolic dysfunction occurs frequently in the scleroderma population and may increase the risk of death. [36 37] We have recently shown that the prevalence of diastolic dysfunction as detected by echocardiography was significantly higher in the PAH-SSD group compared to the IPAH group.[14] Myocardial fibrosis may also contribute to cardiac dysfunction, including right

ventricular diastolic dysfunction and conduction abnormalities.[38] Large vessel pulmonary vascular disease related to scleroderma may increase the effective load on the right ventricle through increased impedance and wave reflection. Although this increased pulsatile load on the right ventricle is present in other forms of pulmonary hypertension,[39] it is possible that the pulmonary vascular stiffness in PAH-SSD results in greater impedance than in IPAH. This could potentially explain the poorer response to therapies that target the pulmonary microvasculature. Further, the increased impedance may lead to more rapid RV failure in PAH-SSD despite similar pulmonary artery pressure and pulmonary vascular resistance in IPAH patients. Other factors that could contribute to divergent responses to therapy include underlying coronary vascular disease, which is common in scleroderma but rarely reported in IPAH, [40] and associated sub-clinical interstitial lung disease.[41]

Although generally well-tolerated, the combination of bosentan and sildenafil may have potential toxicity. Two PAH-SSD patients who did not develop liver function abnormalities on bosentan monotherapy subsequently demonstrated elevation in transaminases after initiation of combination therapy, suggesting a possible drug-drug interaction. Prior studies in healthy volunteers have shown pharmacokinetic interactions between bosentan and sildenafil resulting in elevated plasma levels of bosentan in the presence of sildenafil along with reduction of the plasma levels of sildenafil.[42] Since the LFT abnormalities resolved with either reduction of the bosentan dose or cessation of sildenafil, it is possible that co-administration of sildenafil resulted in high plasma concentrations of bosentan that ultimately may have caused the hepatotoxicity. Additional pharmacokinetic studies are needed to define the mutual pharmacokinetic interactions between these medications.

There are several limitations to our study. This is a retrospective study and as such, is susceptible to many potential biases. Inherent selection bias related to the retrospective design is further augmented by the inclusion of only patients who failed initial monotherapy with bosentan. However, when compared to the PAH group who remained on bosentan monotherapy, many demographic, clinical characteristics, and

hemodynamic parameters were similar. IPAH patients who failed bosentan monotherapy were older and had significantly higher right atrial pressure than the IPAH patients who remained on monotherapy, suggesting that these older patients with more advanced disease at baseline may not respond as well to monotherapy and ultimately require more aggressive therapy. PAH-SSD patients who failed bosentan therapy were significantly younger than those PAH-SSD patients who did not receive bosentan and sildenafil. Escalation of therapy in younger patients with PAH-SSD suggests that these patients may have a more aggressive disease than their older counterparts. The definition of bosentan monotherapy failure used in this study has not been validated. However, the decision to escalate therapy in clinical practice is often based upon decline in symptoms, functional class, or functional capacity rather than serial invasive hemodynamic assessments. Further, although the minimal clinically important difference of 30 meters for the 6MWD has not been validated, a recent study by Gilbert et al.[43] found a similar value for the minimal clinically important difference in a population of PAH patients in the SUPER study.[9]

In summary, in this small cohort of patients who had failed initial monotherapy with bosentan, IPAH patients experienced significant improvements in functional class and exercise capacity with the addition of sildenafil, whereas PAH-SSD patients did not. Additional studies are required to define the basis for the inferior response in PAH-SSD patients and to identify an optimal therapeutic strategy.

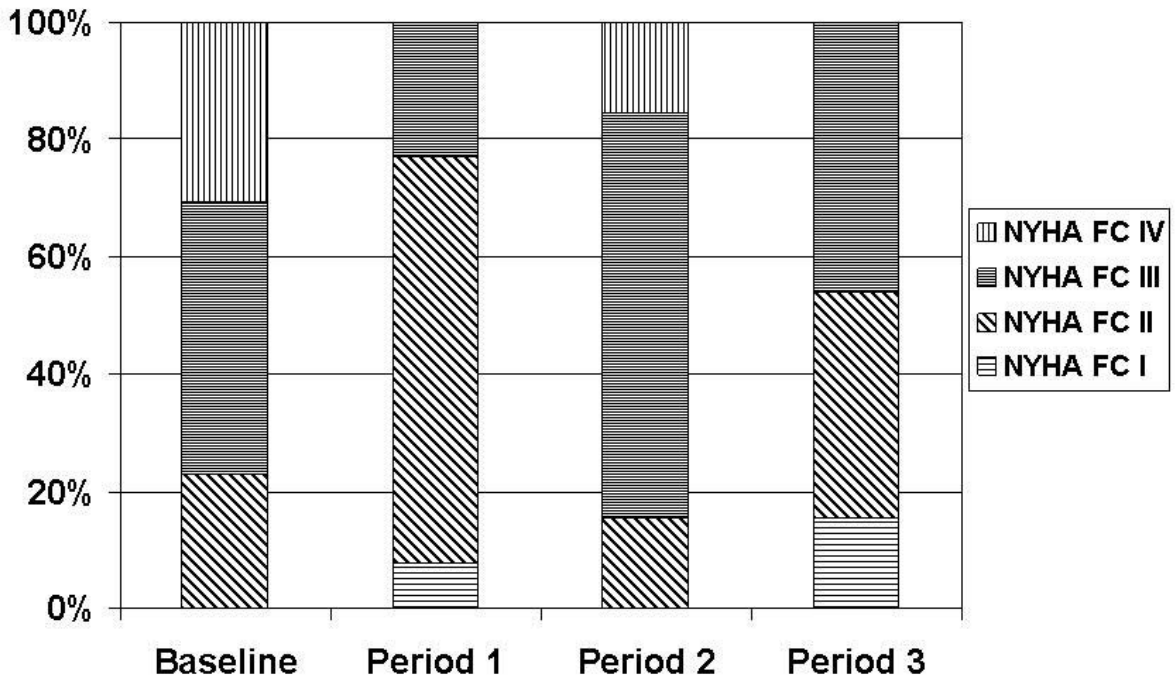
ACKNOWLEDGMENT: The authors would like to thank Meredith C. McCormack, MD MHS for her review of this manuscript.

## Legends

**Figure 1.**

New York Heart Association Functional Class (NYHA FC) at baseline, after 3 months of bosentan monotherapy (Period 1), at bosentan monotherapy failure (Period 2), and after three months of combination therapy with bosentan and sildenafil (Period 3) for IPAH patients (**Panel A**) and PAH-SSD patients (**Panel B**).

## Figure 1(A): NYHA by Treatment Period in IPAH



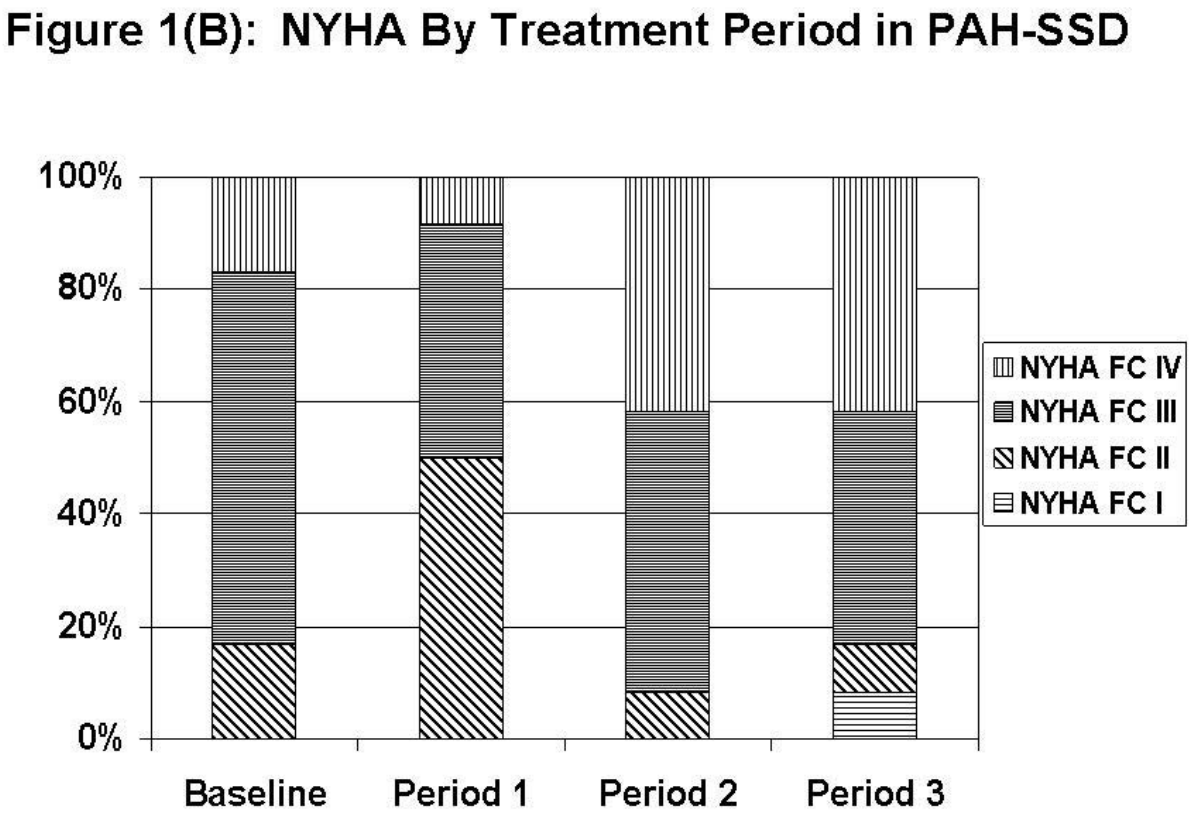



**Figure 2.**

Mean six minute walk distance (6MWD) at baseline, after 3 months of bosentan monotherapy (Period 1), at bosentan monotherapy failure (Period 2), and after three months of combination therapy with bosentan and sildenafil (Period 3) for IPAH patients (solid line) and PAH-SSD patients (dashed lines). Closed triangles and open circles: mean 6MWD; Error bars: standard error for mean 6MWD.

**Figure 2. 6MWD by Treatment Period**

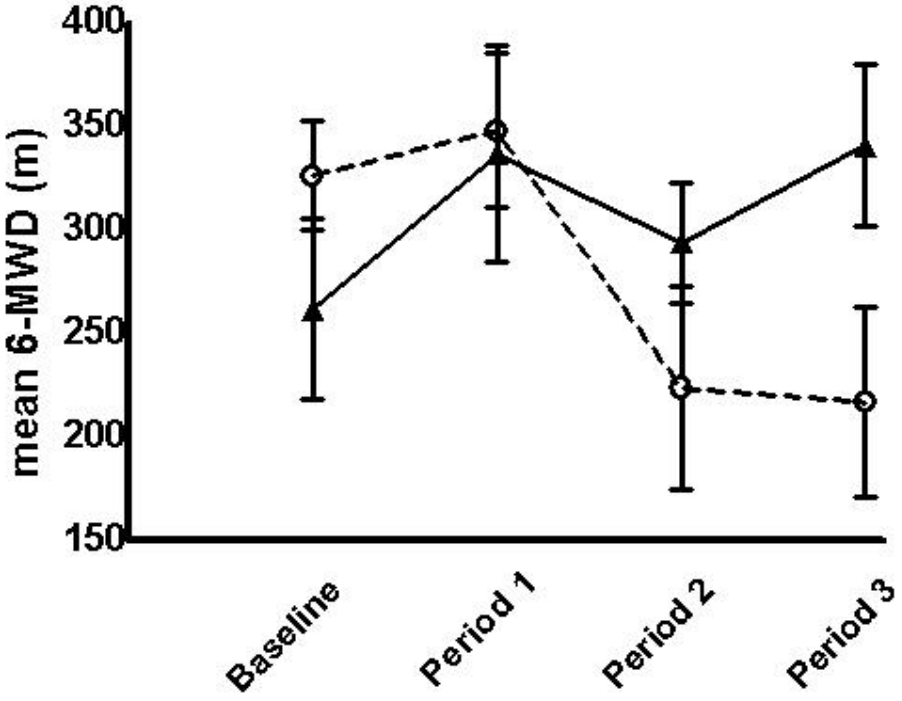


**Table 1: Baseline Characteristics of Patients**

| | IPAH (n=13) | PAH-SSD (n=12) | p-value |
|---|---|---|---|
| Age (yrs) | 60±8 | 52±13 | 0.06 |
| Race (no. white,%)) | 10 (77%) | 8 (75%) | NS |
| Gender (no. women,%) | 12 (92%) | 12 (100%) | NS |
| NYHA at diagnosis (I/II vs. III/IV) | 3/10 | 2/10 | NS |
| 6MWD (meters) | 270±147 | 318±76 | NS |
| RAP (mmHg) | 14±5 | 12±6 | NS |
| mPAP (mmHg) | 57±12 | 53±10 | NS |
| CI ($L/min/m^2$) | 2.3±1.0 | 2.1±0.4 | NS |
| PVR (Woods unit) | 13±5 | 11±4 | NS |
| PCWP (mmHg) | 12±3 | 12±3 | NS |
| Warfarin Use (n,%) | 9 (69%) | 6 (50%) | NS |
| Calcium Channel Blocker Use (n,%) | 1 (8%) | 3 (25%) | NS |
| Digoxin Use (n,%) | 2 (15%) | 1 (8%) | NS |

All values are expressed as mean ± SD, except where specified

**Table 2: Characteristics of Patients Remaining on Bosentan Monotherapy**

| | IPAH (n=29) | PAH-SSD (n=28) | p-value |
|---|---|---|---|
| Age (yrs) | 51±14 | 65±11 | 0.001 |
| Race (no. white,%) | 23 (79) | 22 (79) | NS |
| Gender (no. women,%) | 23 (79) | 25 (89) | NS |
| NYHA at diagnosis (I/II vs. III/IV) | 8/21 | 11/28 | NS |
| 6MWD (meters) | 361±183 | 275±51 | NS |
| RAP (mmHg) | 9±6 | 12±5 | NS |
| mPAP (mmHg) | 53±12 | 46±12 | NS |
| CI (L/min/$m^2$) | 2.2±0.5 | 2.2±0.6 | NS |
| PVR (Woods unit) | 11±5 | 14±4 | NS |
| PCWP (mmHg) | 11±4 | 12±3 | NS |
| Warfarin Use (n,%) | 22 (76) | 17 (62) | NS |
| Calcium Channel Blocker Use (n,%) | 3 (10) | 9 (32) | 0.04 |
| Digoxin Use (n,%) | 3 (10) | 2 (7) | NS |

All values are expressed as mean ± SD, except where specified

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