

# Bosentan Effects on Hemodynamics and Clinical Outcome in Heart Failure Patients with Pulmonary Hypertension Awaiting Cardiac Transplantation\*

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## Abstract

**Background** In heart failure (HF) patients, pulmonary hypertension (PH) is associated with a poor prognosis. We assessed whether low dose treatment with the dual endothelin-1 receptor antagonist bosentan is associated with improved hemodynamics and clinical outcome in these patients.

**Methods** We performed a retrospective data analysis in 82 end-stage heart failure patients on the waiting list for cardiac transplantation since January 2006. All patients had pulmonary arterial pressure >35 mmHg, pulmonary vascular resistance >240 dyn × s × cm<sup>-5</sup>, and/or a transpulmonary gradient (TPG) >15 mmHg. Fifty-four patients received a median dose of 125 mg bid bosentan (BOS group), and 28 patients received standard medical treatment (CON group). Data were assessed until June 2009.

**Results** Hemodynamic parameters improved significantly in the BOS group but remained unchanged in the CON group. The percentage of patients who fell below the thresholds of PAP, PVR, and TPG for cardiac transplantation increased significantly by 20.3%, 34.5%, and 20.8%, respectively ( $p = 0.007–0.013$ ) in the BOS group, but did not change significantly in the CON group. One-year survival on the waiting list was approximately 20% higher in the BOS group than in the CON group ( $p = 0.020$ ). Bosentan treatment remained an independent predictor of reduced mortality risk on the waiting list after propensity score adjustment (relative risk = 0.107; 95% CI: 0.013–0.869;  $p = 0.036$ ).

**Conclusion** Treatment with the endothelin-1 antagonist bosentan is associated with improvements in hemodynamics and clinical outcome in end-stage heart failure patients with PH. If these results can be confirmed by randomized controlled trials, bosentan may represent a treatment option in these patients.

## Keywords

- ▶ end-stage heart failure
- ▶ bosentan
- ▶ pulmonary hypertension
- ▶ cardiac transplantation
- ▶ mortality
- ▶ survival
- ▶ endothelin-1

## Introduction

Pulmonary hypertension (PH) is a pathophysiological condition defined as an increase in mean pulmonary arterial

pressure (PAP)  $\leq 25$  mmHg at rest.<sup>1</sup> PH due to left heart failure is associated with increased pulmonary vascular resistance (PVR) and elevated transpulmonary pressure gradient (TPG).<sup>2</sup> In addition, it carries a poor prognosis. Mortality rates of 57% in patients with moderate PH compared with 17% in patients without PH have been reported after 28 months of follow-up.<sup>3</sup> Survival rates are lower in patients with

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pulmonary hypertension and poor right ventricular (RV) function compared to patients with elevated PAP but preserved RV function.<sup>4</sup>

In end-stage heart failure patients, preoperatively existing PH is associated with a high risk of right heart failure and mortality after cardiac transplantation.<sup>5,6,7</sup> According to the International Society for Heart and Lung Transplantation and the German Standing Committee on Organ Transplantation, cardiac transplantation is contraindicated as long as values of PAP, PVR, and/or TPG are above 40 mmHg, 240 dyn  $\times$  s  $\times$  cm<sup>-5</sup> and 15, respectively.<sup>5,8</sup> At present, no specific therapy for PH due to left heart disease is available.<sup>1</sup>

The endothelin A and B receptor antagonist bosentan has been shown to improve pulmonary and systemic hemodynamics in patients with heart failure.<sup>7,9,10</sup> The plasma concentration of endothelin-1 (ET-1) is elevated in chronic heart failure patients and is inversely related to left ventricular ejection fraction (EF) and cardiac index (CI).<sup>9,11</sup> ET-1 seems to be a key mediator in the pathogenesis of PH in chronic heart failure.<sup>9,11,12</sup>

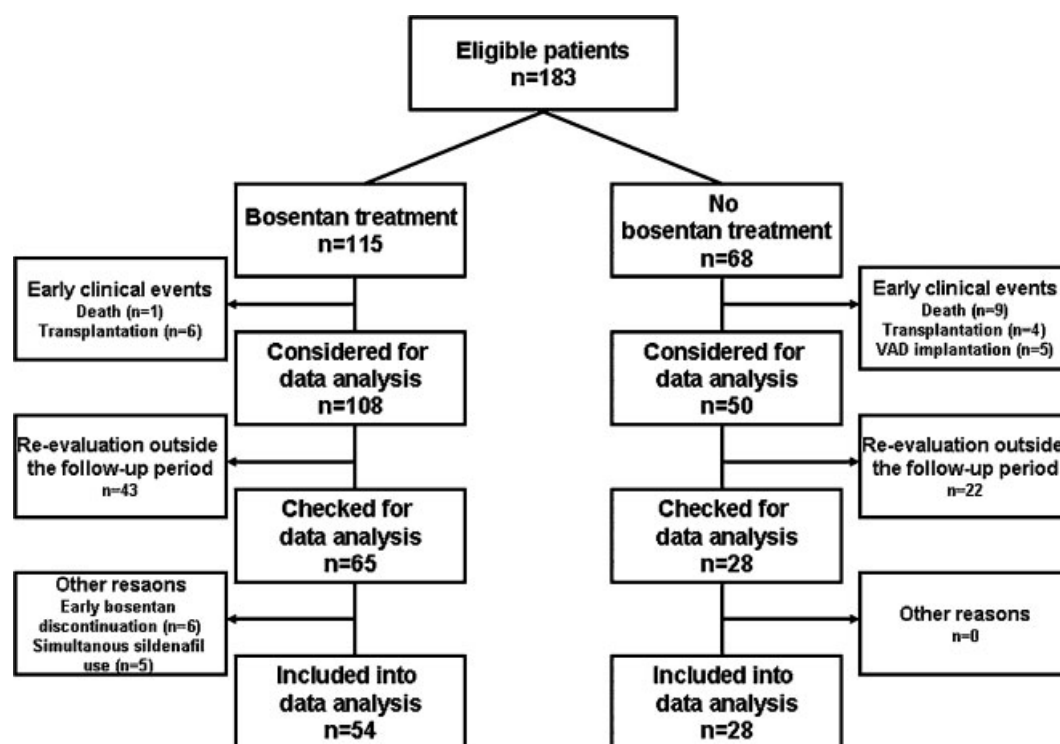
The REACH-1 (Research on Endothelin Antagonism in Chronic Heart Failure) trial has used bosentan doses of 500 mg daily in patients with advanced heart failure. The duration of the trial was planned for 24 weeks. Unfortunately, however, the REACH-1 trial has been terminated prematurely due to concerns about elevations in hepatic transaminases.<sup>13</sup> Nevertheless, this study also demonstrated a significantly greater clinical improvement in patients who received bosentan therapy for 6 months compared to controls. We therefore administered bosentan in several of our patients with end-stage heart failure and PH as an off-label use during

recent years. But we used a considerably lower daily bosentan dose than that used in the REACH-1 trial. We provide the results of a retrospective data analysis based on our medical records. We performed this analysis to assess whether low dose bosentan treatment is associated with improved pulmonary hemodynamics and clinical outcome in cardiac transplant candidates with PH.

## Materials and Methods

### Patients and study design

Since January 2006, 183 patients with end-stage heart failure and longstanding PH were eligible for cardiac transplantation at our institution (**► Fig. 1**). All patients fulfilled the functional, echocardiographic, and hemodynamic indications for cardiac transplantation provided by the German Standing Committee on Organ Transplantation.<sup>8</sup> However, all patients also had values of PAP >35 mmHg, PVR >240 dyn  $\times$  s  $\times$  cm<sup>-5</sup>, and/or TPG >15 mmHg despite optimal treatment with angiotensin-converting enzyme-inhibitors,  $\beta$ -blockers, anticoagulants, digitalis derivatives or/and diuretics,<sup>1</sup> whereas PAP and PVR decreased with the administration of intravenous phosphodiesterase III inhibitor. As mentioned before, elevated PAP, PVR, and/or TPG values are considered a contraindication for cardiac transplantation.<sup>8</sup> To achieve transplantability, we decided to treat the aforementioned group of patients with oral bosentan as off-label use. Generally, all 183 patients with PH and end-stage heart failure were eligible for the off-label use of oral bosentan. However, initial bosentan administration was done under intensive care unit monitoring, including Swan-Ganz catheter measurement. Since



**Figure 1** Study flow chart.

intensive care unit capacity was limited, only 115 patients received bosentan. Sixty-eight other patients did not receive bosentan. The decision for bosentan administration was made by the head of the transplant unit, based on inclusion criteria and according to bed capacity. All patients gave their written informed consent to receive bosentan. The majority of patients started with an oral bosentan dose of 62.5 mg bid ( $n = 3$  with 32.5 mg bid,  $n = 8$  with 125 mg bid) and were up-titrated to 125 mg bid. We performed a retrospective data analysis of clinical outcome parameters in patients who received bosentan or did not receive bosentan. For data analysis, we checked only those patients who had at least three echocardiographic and hemodynamic measurements within a time interval of 15 months. Patients with simultaneous sildenafil or iloprost treatment were excluded from data analysis. We finally included only those patients who received bosentan treatment or did not receive bosentan treatment during the entire follow-up period. Thus, we could retrospectively analyze the data of 54 patients receiving bosentan (BOS group) and of 28 patients not receiving bosentan (CON group). The latter group served as the control group. Patients were maintained on 125 mg bid bosentan until the end of the study, cardiac transplantation, or death. The CON group received standard conventional medication. In both groups, echocardiographic parameters and hemodynamics were assessed at baseline, e.g., before bosentan treatment ( $t_0$ ), after 4 months ( $t_1$ ; range 2–6 months), and after 12 months ( $t_2$ ; range 9–15 months). All measurements were performed as routine examinations at regular time intervals. Hemodynamics were measured using a Swan-Ganz pulmonary artery thermodilution catheter through the right internal jugular vein. Cardiac output (CO) was determined in triplicate and calculated by the Stewart-Hamilton indicator dilution formula.<sup>14</sup> Cardiac index (CI) was calculated by CO, taking current body surface into account. Central venous pressure (CVP), RV pressure, PAP, and PCWP were measured directly by right heart catheterization. Systemic vascular resistance (SVR), PVR and TPG were calculated according to standard formulas:

$$\begin{aligned} \text{SVR} &= [(\text{PAP} - \text{PCWP}) \times 80] / \text{CI} \\ \text{PVR} &= [(\text{PAP} - \text{PCWP}) \times 80] / \text{CO} \\ \text{TPG} &= \text{PAP} - \text{PCWP} \end{aligned}$$

Transthoracic echocardiography was performed to assess left ventricular end-diastolic and end-systolic diameter, right ventricular shortening, and left ventricular ejection fraction (Agilent Sonos 5500 device, Hewlett Packard, Andover, MA, USA). Since bosentan shows liver toxicity,<sup>15</sup> biochemical safety parameters were also measured. In addition, we assessed clinical symptoms such as nocturia and dyspnea by questionnaire and peripheral edema by physical examination. We also registered clinical outcome parameters such as ventricular assist device (VAD) implantation, cardiac transplantation, and death in both groups up until June 2009.

### Statistical analysis

We report categorical variables using the percentage of observations and express continuous variables as mean val-

ues and standard deviation or median and interquartile range as appropriate. We tested normal distribution of the data using the Kolmogorov-Smirnov test. Normal distribution was considered present if  $p$  values were above 0.05. For comparative analyses between groups, we used Fisher's exact test, McNemar test, unpaired  $t$ -test, and Mann-Whitney test as appropriate. We used ANOVA and the Friedman test for evaluations of time-dependent effects. A  $p$  value  $<0.05$  (two-tailed test) was considered significant.

We generated Kaplan-Meier estimates to investigate the association between bosentan and survival probability during follow-up as a function of time after study inclusion. Log-rank test was used to test for differences in survival rates between groups. We then examined the associations between bosentan and mortality risk using Cox proportional hazard analysis. Since treatment assignment was not based on random allocation and the bosentan and control group were therefore not expected to be completely comparable with regard to important covariates, we also analyzed whether propensity score adjustments were necessary. We used 38 baseline demographic, anthropometric, clinical, and biochemical variables for each patient, using logistic regression. The propensity score ranged from a low of 0.13 to a high of 0.63. The discriminate power of the propensity score was quantified by measurement of the receiver operating characteristics area and was found to be 0.651 only (95% confidence interval: 0.465–0.836;  $p = 0.110$ ), indicating that the two study groups were comparable with respect to baseline and clinical characteristics. We used the statistical software package SPSS, version 18 (SPSS, Inc., Chicago, IL, USA) to perform the analysis.

### Results

Baseline characteristics of the study groups are given in ►Table 1. Patients did not differ with regard to age, sex, and anthropometric data. Moreover, the prevalence of smokers and concomitant diagnoses such as diabetes, hypertension, elevated cholesterol levels, hyperuricemia, and dyspnea was similar between groups. Likewise, concomitant medications did not differ between groups. The majority of patients in each study group were in NYHA functional class III. The BOS group was, however, significantly younger than the CON group and suffered less often from diagnoses other than dilated cardiomyopathy or ischemic heart disease. More patients in the BOS group had pacemaker implants than in the CON group. In addition, some hemodynamic parameters such as right ventricular pressure, PAP, and PCWP were significantly higher in the BOS group than in the CON group at baseline (►Table 2). In the BOS group, the cut-off values for cardiac transplantation of PAP ( $>40$  mmHg), PVR ( $>240$  dyn  $\times$  s  $\times$  cm<sup>-5</sup>), and TPG ( $>15$ ) were exceeded in 75.9%, 67.9%, and 47.2% of patients, respectively. The corresponding values for the CON group were 57.1%, 75.0%, and 25.0%, respectively.

In the BOS group, the median daily bosentan dose was 125 mg (interquartile range: 125–125 mg; mean  $\pm$  SD: 139  $\pm$  50 mg/d) at the beginning and 250 mg (interquartile range: 250–250 mg; mean  $\pm$  SD: 216  $\pm$  77 mg/d) at the end of the

**Table 1** Baseline characteristics of the bosentan and control group.

Parameter	Bosentan group (n = 54)	Control group (n = 28)	p value
Age (years)	54 ± 11.0	59.2 ± 9.3	0.015
Height (cm)	176 ± 9	174 ± 9	0.269
Weight (kg)	82.0 ± 16.2	80.4 ± 14.0	0.665
Body mass index (kg/m <sup>2</sup> )	26.4 ± 4.2	25.8 ± 5.9	0.587
Gender (% males)	87.0	86.2	>0.999
Heart rate (per min)	77.4 ± 13.4	75.2 ± 11.0	0.472
Mean blood pressure (mmHg)	78.4 ± 12.1	80.2 ± 12.8	0.528
NYHA functional class ≥ III (%)	79.63	86.21	0.380
<b>Diagnosis</b>			
Dilated cardiomyopathy (%)	46.3	34.5	0.351
Coronary heart disease (%)	44.4	27.6	0.240
Others <sup>a</sup> (%)	9.3	37.9	0.008
<b>Concomitant diagnoses</b>			
Diabetes mellitus (%)	35.2	28.6	0.625
Hypercholesterolemia (%)	9.3	14.3	0.483
Hyperuricemia (%)	9.3	14.3	0.483
Chronic kidney disease (%)	11.1	28.6	0.064
Hypertension (%)	33.3	21.4	0.314
Nicotine abuse (%)	13.0	21.4	0.351
<b>Pacemaker and defibrillator</b>			
Only pacemaker implantation (%)	57.4	32.1	<0.001
Only defibrillator implantation (%)	0	0	>0.999
Implantation of both (%)	7.4	7.1	>0.999
<b>Medications</b>			
ACE inhibitors/AT blockers (%)	72.2	82.1	0.420
β-blockers (%)	79.6	71.4	0.420
Diuretics (%)	88.9	78.6	0.320
Digitalis derivatives (%)	42.6	25.0	0.150
Oral anticoagulants (%)	66.7	46.4	0.098
Aspirin (%)	39.3	24.0	0.201

<sup>a</sup>Amyloidosis, cor pulmonale, hypertrophic cardiomyopathy, condition after coronary artery bypass grafting

follow-up period. Down titration of bosentan was necessary in 6 patients due to marked decreases in PAP and PVR. In 2 of these 6 patients, a parallel increase in aspartate aminotransferase and alanine aminotransferase occurred, whereas in 1 of the 6 patients only alanine aminotransferase increased.

In the CON group, hemodynamic and echocardiographic parameters did not change significantly during follow-up (► **Table 2**). In the BOS group, echocardiographic parameters also remained unchanged. However, mean blood pressure and all measured hemodynamic parameters showed significant improvements in the BOS group during follow-up. The three determinants of PVR (i.e., PAP, PCWP, and CO) improved significantly from  $t_0$  to  $t_2$  by 18.0%, 15.7%, and 23.5%, respectively. Consequently, mean PVR decreased significantly from a mean of  $382 \text{ dyn} \times \text{s} \times \text{cm}^{-5}$  to  $256 \text{ dyn} \times \text{s} \times \text{cm}^{-5}$ . In

the BOS group, the percentage of patients with values below the cut-offs increased from  $t_0$  to  $t_2$  for PAP from 24.1% to 44.4% ( $p = 0.007$ ), for PVR from 32.1% to 56.6% ( $p = 0.013$ ), and for TPG from 52.8% to 73.6% ( $p = 0.007$ ). SVR values declined by 17.0%. None of the patients in the BOS group developed hypotension (mean arterial pressure <50 mmHg).

In the CON group, the percentages increased nonsignificantly from 42.9% to 53.6% for PAP ( $p = 0.581$ ), from 25.0% to 39.3% for PVR ( $p = 0.388$ ), and remained constant for TPG (75.0% vs. 71.4%,  $p > 0.999$ ). SVR values tended to decline to a similar extent compared with the BOS group. NYHA functional class did not change significantly during follow-up, neither in the BOS group nor in the CON group (data not shown).

Biochemical safety parameters are presented in ► **Table 3**. In the BOS group, mean concentrations of liver enzymes such

**Table 2** Hemodynamic and echocardiographic parameters of the bosentan (BOS) and control (CON) group at baseline and during follow-up.

	t <sub>0</sub>	t <sub>1</sub>	t <sub>2</sub>	p value
	BOS group (n = 54)	BOS group (n = 54)	BOS group (n = 54)	
	CON group (n = 28)	CON group (n = 28)	CON group (n = 28)	
Mean arterial pressure (mmHg)				
▶BOS group	78.6 ± 12.1	77.7 ± 9.7	74.9 ± 9.0	0.007
▶CON group	80.2 ± 12.8	79.7 ± 12.7	73.4 ± 17.9	0.217
<b>Hemodynamics</b>				
Central venous pressure (mmHg)				
▶BOS group	13.5 ± 4.8	12.3 ± 5.7	11.2 ± 5.9	0.023
▶CON group	13.1 ± 5.2	13.3 ± 6.1	14.3 ± 4.7	0.611
Mean right ventricular pressure (mmHg)				
▶BOS group	31.5 ± 8.6*	28.4 ± 9.5	25.8 ± 9.2	0.002
▶CON group	27.5 ± 6.9	27.6 ± 8.7	29.0 ± 8.9	0.944
Mean pulmonary arterial pressure (mmHg)				
▶BOS group	45.2 ± 8.7*	42.2 ± 11.3	38.4 ± 12.5	0.001
▶CON group	39.6 ± 6.7	38.1 ± 8.5	37.4 ± 8.5	0.537
Pulmonary capillary wedge pressure (mmHg)				
▶BOS group	30.6 ± 6.7*	29.0 ± 8.5	26.9 ± 9.3	0.049
▶CON group	26.6 ± 6.9	23.9 ± 9.2	25.6 ± 8.1	0.446
Cardiac output (l/min)				
▶BOS group	3.4 ± 0.8	3.9 ± 1.2	4.1 ± 1.0	0.001
▶CON group	3.4 ± 0.9	3.6 ± 1.0	3.6 ± 1.0	0.154
Cardiac index (l/minm <sup>2</sup> )				
▶BOS group	1.7 ± 0.5	2.0 ± 0.5	2.1 ± 0.4	0.003
▶CON group	1.6 ± 0.5	1.9 ± 0.7	1.9 ± 0.4	0.559
Systemic vascular resistance (dyn × s × cm <sup>-5</sup> )				
▶BOS group	1600 ± 508	1410 ± 528	1236 ± 456	0.001
▶CON group	1717 ± 544	1644 ± 672	1432 ± 584	0.095
Pulmonary vascular resistance (dyn × s × cm <sup>-5</sup> )				
▶BOS group	382 ± 208	301 ± 191	231 ± 127	0.001
▶CON group	336 ± 133	348 ± 193	293 ± 164	0.230
Transpulmonary pressure gradient (mmHg)				
▶BOS group	14.7 ± 6.9	13.4 ± 6.7	11.2 ± 5.9	0.001
▶CON group	13.0 ± 6.1	14.2 ± 7.6	11.9 ± 4.6	0.209
<b>Echocardiography</b>				
Left ventricular end-diastolic diameter (mm)				
▶BOS group	68.4 ± 11.5	69.1 ± 11.3	66.2 ± 12.8	0.179
▶CON group	68.4 ± 12.3	68.2 ± 12.9	65.5 ± 14.1	0.334
Left ventricular end-systolic diameter (mm)				
▶BOS group	60.6 ± 12.4	60.3 ± 13.4	57.8 ± 15.4	0.385
▶CON group	59.6 ± 13.3	60.3 ± 14.5	57.5 ± 15.2	0.405
Right ventricular fractional shortening (%)				
▶BOS group	11.8 ± 6.9	12.0 ± 5.6	12.7 ± 7.4	0.987

**Table 2** (Continued)

	t <sub>0</sub>	t <sub>1</sub>	t <sub>2</sub>	p value
	BOS group (n = 54)	BOS group (n = 54)	BOS group (n = 54)	
	CON group (n = 28)	CON group (n = 28)	CON group (n = 28)	
▶ CON group	12.8 ± 6.1	13.5 ± 8.0	13.1 ± 7.6	0.626
Left ventricular ejection fraction (%)				
▶ BOS group	28.9 ± 13.2	29.4 ± 11.8	29.6 ± 13.4	0.466
▶ CON group	29.8 ± 12.8	31.1 ± 14.0	28.9 ± 10.4	0.067

t<sub>0</sub>: baseline; t<sub>1</sub>: 4 months after inclusion; t<sub>2</sub>: 12 months after inclusion; \*, \*\*: p < 0.05 and p < 0.01 vs. controls at the same time point

as aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase remained constant. In the BOS group, there was a decrease in hematocrit values, which also tended to occur in the CON group. Sodium concentrations improved significantly in the BOS group from t<sub>0</sub> to t<sub>2</sub>.

In the BOS group, 35 patients (64.8%) were not hospitalized, whereas 15 patients (27.8%), one patient (1.9%), and three patients (5.6%) were hospitalized once, twice, and three times, respectively, during follow-up. The corresponding values for the CON group were 20 (71.4%), 8 (28.6%), zero, and zero, respectively. In the BOS and CON group, the percentage of patients with nocturia (22.2% vs. 28.6%, respectively), peripheral edema (20.4% vs. 14.4%, respectively), and dyspnea (18.5% vs. 7.1%, respectively) did not differ significantly (p = 0.205–0.592).

During follow-up, ten patients in the BOS group (18.5%) and one patient in the CON group (3.6%) were transplanted (p = 0.088). All transplanted patients were alive at the end of the follow-up period. One patient in the BOS group and 11 patients in the CON group died during follow-up. Causes of death were acute lung edema in the BOS group, and multiple organ failure (6 ×), low output syndrome (2 ×), intracranial bleeding (1 ×), intestinal ischemia (1 ×), and pancytopenia (1 ×) in the CON group. ▶ **Fig. 2** illustrates the Kaplan-Meier survival curves on the waiting list after t<sub>2</sub> according to study group. One-year survival on the waiting list was 93.3% in the BOS group and 70.7% in the CON group (p = 0.020). The corresponding values for freedom from cardiac related deaths was 93.3% and 100%, respectively (p = 0.407).

In the univariate Cox regression analysis, bosentan treatment was significantly related to reduced risk of mortality on the waiting list (RR = 0.109; 95%CI: 0.013–0.881; p = 0.038). Bosentan treatment remained an independent predictor of reduced mortality risk on the waiting list after propensity score adjustment (RR = 0.107; 95%CI: 0.013–0.869; p = 0.036).

## Discussion

Our data demonstrate that patients with end-stage heart failure and PH not receiving bosentan have a poor prognosis.

Results support earlier findings of high mortality rates in heart failure patients with PH.<sup>7</sup> However, this study could also demonstrate significantly higher survival rates of end-stage heart failure patients with PH who were treated with bosentan compared to patients who were not treated with bosentan while awaiting cardiac transplantation. Moreover, compared with the patients not treated with bosentan a higher percentage of bosentan-treated patients tended to be transplanted during follow-up.

Although the REACH-1 trial was stopped prematurely due to liver toxicity, this earlier study already demonstrated a significantly greater clinical improvement in patients with advanced heart failure who received bosentan therapy for 6 months.<sup>13</sup> Thus, our data support the assumption that bosentan may be a new treatment option for end-stage heart failure patients. Compared to the REACH-1 trial, our retrospective data analysis is based on a longer duration of follow-up and a sicker patient population. In addition, our analysis includes invasive hemodynamic assessment, and defined hemodynamic criteria including TPG for enrolment.

The development of new and more effective pharmacological treatment strategies for PH in patients with end-stage heart failure is urgently needed. In this context, bosentan seems to be a promising candidate. In our analysis, bosentan treatment was associated with an improvement in various hemodynamic parameters. For example, PVR decreased by 33% in the BOS group, whereas it declined only nonsignificantly by 12.8% in the CON group (▶ **Table 2**). Our results are in line with the fact that bosentan treatment is also able to reduce PVR in patients with pulmonary arterial hypertension.<sup>16,17</sup> In addition, our data analysis demonstrates an improvement in RV pressure, which is an important prognostic value for survival in patients with chronic heart failure.<sup>4</sup> The improvement in RV pressure and the partial revision in PH may therefore be an important explanation for the fact that one year after t<sub>2</sub> the survival rate on the waiting list was 22% higher (93% vs. 71%) in the BOS group than in the CON group. Note that patients with end-stage heart failure are at an increased risk for cardiac decompensation. This can lead to systemic immunosuppression and thus to an increased risk of developing multiple organ failure.

**Table 3** Biochemical parameters of the bosentan and control group at baseline and during follow-up.

	t <sub>0</sub>	t <sub>1</sub>	t <sub>2</sub>	p value
	BOS group (n = 54)	BOS group (n = 54)	BOS group (n = 54)	
	CON group (n = 28)	CON group (n = 28)	CON group (n = 28)	
<b>Liver function</b>				
Aspartate aminotransferase (U/l)				
▶BOS group	38.7 ± 37.0	28.22 ± 8.76	28.2 ± 8.8	0.319
▶CON group	28.0 ± 9.1	29.2 ± 10.4	31.4 ± 12.5	0.471
Alanine aminotransferase (U/l)				
▶BOS group	54.4 ± 12.4	25.9 ± 14.0	26.4 ± 15.1	0.093
▶CON group	33.4 ± 18.2	28.3 ± 14.6	26.7 ± 36.9	0.042
gamma-glutamyltransferase (U/l)				
▶BOS group	114 ± 88	103 ± 88	112 ± 99	0.048
▶CON group	150 ± 137	144 ± 124	190 ± 182	0.303
Total bilirubin (mg/dL)				
▶BOS group	1.30 ± 0.86	0.92 ± 0.53	0.88 ± 0.52	0.163
▶CON group	0.97 ± 0.48	1.02 ± 0.66	1.15 ± 0.89	0.608
<b>Kidney function</b>				
Creatinine (mg/dL)				
▶BOS group	1.39 ± 0.4	1.45 ± 0.51	1.67 ± 0.80	0.080
▶CON group	1.39 ± 0.4	1.43 ± 0.44	1.51 ± 0.48	0.519
Blood urea nitrogen (mg/dL)				
▶BOS group	68.2 ± 36.4	75 ± 47	85.0 ± 56.9	0.093
▶CON group	76.2 ± 43.6	82 ± 54	84.6 ± 50.0	0.639
<b>Hematology</b>				
Leukocytes (10 <sup>9</sup> /l)				
▶BOS group	8.97 ± 12.5	9.15 ± 12.4	8.92 ± 12.7	0.722
▶CON group	8.41 ± 3.16	8.44 ± 2.86	8.20 ± 2.29	0.857
Red blood cells (10 <sup>12</sup> /l)				
▶BOS group	4.33 ± 0.63	4.23 ± 0.66	4.17 ± 4.12	0.106
▶CON group	4.63 ± 1.9	4.24 ± 0.64	4.12 ± 0.83	0.435
Hemoglobin (mg/dL)				
▶BOS group	12.5 ± 1.9	12.6 ± 2.1	12.5 ± 3.13	0.215
▶CON group	14.1 ± 5.7	13.0 ± 2.53	12.7 ± 4.1	0.025
Hematocrit (%)				
▶BOS group	38.1 ± 5.2	37.2 ± 6.1	36.4 ± 5.18	0.005
▶CON group	40.4 ± 11.8	38.3 ± 7.6	37.8 ± 12.7	0.063
Platelets (10 <sup>9</sup> /l)				
▶BOS group	197 ± 61	212 ± 72	212 ± 78	0.145
▶CON group	198 ± 81	204 ± 84	217 ± 107	0.476
<b>Electrolytes</b>				
Sodium (mmol/l)				
▶BOS group	137 ± 4	136 ± 4	138 ± 4	0.008
▶CON group	137 ± 6	136 ± 5	137 ± 5	0.513
Potassium (mmol/l)				

**Table 3** (Continued)

	t <sub>0</sub>	t <sub>1</sub>	t <sub>2</sub>	p value
	BOS group (n = 54)	BOS group (n = 54)	BOS group (n = 54)	
	CON group (n = 28)	CON group (n = 28)	CON group (n = 28)	
►BOS group	4.25 ± 0.50	4.08 ± 0.54	4.08 ± 0.54	0.611
►CON group	4.05 ± 0.76	4.09 ± 0.80	4.00 ± 0.51	0.889

t<sub>0</sub>: baseline; t<sub>1</sub>: 4 months after inclusion; t<sub>2</sub>: 12 months after inclusion

In our analysis, bosentan treatment was associated with a more pronounced reduction in PVR than in SVR. Similar results have been observed in patients with chronic heart failure and high circulating ET-1 concentrations who received short-term intravenous bosentan.<sup>10</sup> Likewise, our data of unchanged echocardiographic measurements in the BOS group confirm an earlier multicenter randomized controlled trial (RCT) of bosentan in heart failure patients with severe systolic dysfunction and PH.<sup>18</sup> In that earlier RCT, echocardiographic measurements were not influenced by bosentan treatment.

Since bosentan is an ET-1 receptor antagonist, our data support the assumption that ET-1 plays an important role in the etiology of PH in heart failure patients. This assumption is in line with the fact that the plasma concentrations of ET-1 are increased in patients with heart failure and correlate with the prognosis.<sup>9,11</sup> In animal models of heart failure, ET-1 antagonists are also able to improve hemodynamics and survival.<sup>19</sup>

In addition to the improvement in the survival of patients on the waiting list, bosentan seems to offer an important additional benefit. Due to the significant decrease in hemodynamic parameters, a relatively high number of patients in the BOS group compared to the CON group could be transplanted during follow-up (18.5% vs. 3.6%). Since all patients had end-stage heart failure, cardiac transplantation was the

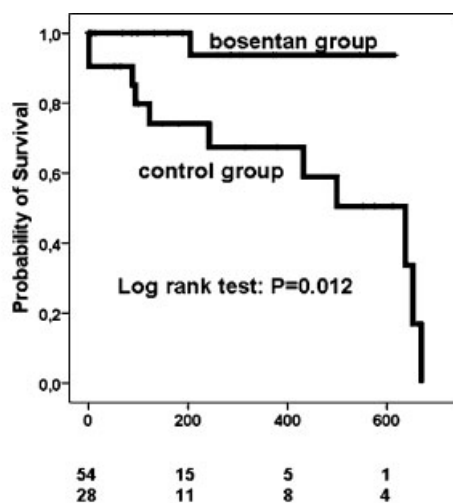
last option for these patients. None of the transplanted patients had died by the end of the follow-up period, supporting the assumption that survival after cardiac transplantation seems to be similar in patients without pre-existing PH and in patients where preoperatively existing PH is reversible.<sup>7</sup>

Elevated liver aminotransferase levels seemed to be characteristic for bosentan treatment.<sup>9,16</sup> In the present data analysis, however, the BOS group in its entirety showed no pathological elevations in serum alanine aminotransferase or aspartate aminotransferase concentrations from t<sub>0</sub> to t<sub>2</sub>. This is probably due to the fact that we prescribed only 250 mg bosentan daily, whereas others have used daily doses of 500 mg.<sup>4</sup> In previous investigations, peripheral edema occurred more frequently in patients treated with bosentan.<sup>9</sup> In our retrospective analysis, clinical complications such as edema and dyspnea as well as the percentage of patients who reported nocturia were not adversely affected by bosentan treatment. In addition, the hospitalization rate was similar between the BOS and CON groups.

In contrast to earlier results,<sup>16</sup> the BOS group showed no improvement in NYHA functional class. However, it should be noted that NYHA functional class is a subjective parameter. Hemodynamic parameters are much more reliable for the assessment of cardiac function. Initial CI measurements demonstrate that our patients suffered from advanced heart failure, leaving only a limited possibility of improvement in NYHA functional class.

It must be stated that our data analysis has several limitations due to its retrospective nature. It lacks randomization, blinding, and a clear study protocol. In addition, this retrospective data analysis is short of defined dose up- and down-titration, follow-up visits, and adverse event reporting. Although we have performed propensity score adjustments to assess mortality rates, this can not compensate for nonrandomization. Finally, the study is a single center report without an independent core lab, adjudicated event committee, data monitoring and safety committee. Since earlier randomized controlled trials with bosentan focused on patients with pulmonary arterial hypertension,<sup>16,17</sup> a randomized controlled multicenter study with survival on the waiting list as the primary endpoint and cardiac transplantation as a secondary endpoint is urgently needed.

In conclusion, our data demonstrate that bosentan treatment is associated with improvements in hemodynamics and clinical outcome in end-stage heart failure patients with PH. If



**Figure 2** Probability of survival on the waiting list after t<sub>2</sub> in the bosentan group and the control group.



these results are confirmed by randomized controlled trials bosentan may represent a treatment option.

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