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ORIGINAL ARTICLE

Pilot Study of Endothelin Receptor Blockade in Heart Failure with Diastolic Dysfunction and Pulmonary Hypertension (BADDHY-Trial)

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Background In this multi-centre, randomised, placebo-controlled pilot trial, we investigated the clinical and haemodynamic effects of the endothelin-receptor blocker Bosentan in patients with heart failure, preserved ejection fraction and pulmonary hypertension (PH-HFpEF).

Materials and Methods Eligible patients received either 12 weeks of Bosentan therapy, or a placebo drug. Patients were thereafter followed for a further period of 12 weeks without the study medication. At three points during the study (study Commencement, Week 12 and Week 24), a six-minute walk test (6MWT), echocardiographic and laboratory assessments were performed, as well as a quality of life survey. Right heart catheterisation (RHC) was undertaken at commencement only. The study was aborted early, after an interim analysis favoured the placebo.

Results Six-minute walk distance (6MWD) did not change in the Bosentan group (309.7 ± 96.3m (Commencement), 317.0 ± 126.1m (Week 12), 307.0 ± 84.4m (Week 24); p = 0.86), but almost reached statistical significance in the placebo group from 328.8 ± 79.6m, to 361.6 ± 98.2m and 384.0 ± 74.9m (Week 24); p = 0.075. In the placebo group, estimated systolic pulmonary artery pressure (measured via echocardiography) significantly decreased (from 62.3 ± 16.7 mmHg [Commencement], 45.3 ± 13.9 mmHg [Week 12], to 44.6 ± 14.5 mmHg [Week 24]; p = 0.014) as did right atrial pressure (13.1 ± 5.3 [Commencement], 10.0 ± 3.8 [Week 12], to 9.4 ± 3.2 [Week 24]; p = 0.046).

Conclusion Despite this study's limited sample size and premature cessation, it nevertheless suggests that endothelin receptor blockade in patients with PH-HFpEF may have no beneficial effects and could even be detrimental in comparison to a placebo.

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Keywords Heart failure preserved ejection fraction • Pulmonary hypertension • Endothelin receptor blockade • 6 minute walk test

Introduction

One to two per cent of adults in developed countries suffer from heart failure, yet nearly half of these patients are diagnosed with heart failure with preserved ejection fraction (HFpEF), defined as a left ventricular ejection fraction (LVEF) $\geq$ 50%. [1] Pulmonary hypertension (PH) is very common in HFpEF patients, with a reported occurrence of 70 to 83%. [2–4] HFpEF seems to be the most common cause of PH in the elderly.[5] Pulmonary hypertension with left heart disease [2] is considered to be a result of chronic elevation in left ventricular filling pressure.[6,7] A subset of patients may develop combined post-capillary and pre-capillary PH with a diastolic pressure gradient (DPG) $\geq$ 7 mmHg and/or a pulmonary vascular resistance (PVR) > 3 Wood Units (WU) [2] as a consequence of additional pulmonary arterial vasoconstriction and remodelling.[4,8] Pulmonary hypertension in heart failure is associated with a poorer prognosis. [2–4,9] One recently published study reported improvements in mean pulmonary artery pressure (PAPm), right ventricle function and quality of life (QOL) with the phosphodiesterase 5 inhibitor sildenafil,[3] suggesting PH as a therapeutic target in patients with PH-HFpEF. In the RELAX-trial, sildenafil had no beneficial effects with respect to peak VO2 and 6MWT. However in this study, PH was not pre-specified nor was sildenafil targeted to this condition.[10] Several other small studies invasively measuring PH may confirm the ineffectiveness of sildenafil in PH-HFpEF.[11,12]

The endothelin-1 system plays an important role in cardiac remodelling, and regulating vascular tone in both the pulmonary and peripheral systems. [13–15] Bosentan, a non-selective endothelin receptor antagonist (ERA), is widely used in pulmonary arterial hypertension.[2] Although they showed improvements in exercise capacity and haemodynamics in a small cohort of patients with Eisenmenger syndrome,[16] ERAs failed to show beneficial effects in other studies concerning systolic heart failure.[17–21] The endothelin A receptor blocker sitaxsentan recently demonstrated an increased exercise tolerance in HFpEF patients, but this study does not concern PH and haemodynamic measures of pulmonary circulation.[22]

To summarise, until now no single medication has demonstrated beneficial effects in controlled trials dealing with PH-HFpEF.[2] We hypothesised that Bosentan 125 mg twice daily as used in several studies [16,19,23] may improve 6MWT, echocardiographic measures and/or QOL.

Materials and Methods

This study was performed between 2009 and 2011 as a randomised, placebo-controlled, multi-centre trial in four hospitals in Austria. Because of safety concerns, the study was designed as pilot study with only a small sample size. The primary objective was to observe a statistically significant difference in 6MWD between placebo and Bosentan at Week 12. Secondary objectives were to observe a difference in 6MWD at Week 24, as well as to measure changes in NTpBNP, NYHA functional classes, echocardiographically assessed haemodynamic parameters of the right ventricle, and subjective QOL measures at Week 12 and 24. The study protocol was approved by the ethics board of the Innsbruck Medical University and the local ethics boards of all participating hospitals, as well as the AGES-Pharm Med, a governmental institution for interventional trial. The BADDHY-trial was registered at the European Medicines Agency (EMEA, EudraCT number: 2008-005514-40) and at clinicaltrials.gov (NCT00820352). All patients gave written informed consent and the study was performed in accordance with the Declaration of Helsinki.

Study Population and Screening

In order to be included in this trial, patients were required to be aged between 18 to 75 years and to suffer from PH-HFpEF and right ventricular dysfunction, without worsening for at least four weeks before randomisation. Participants were recruited in specialised heart failure units. In all patients, a 6MWT was performed if PH-HFpEF was suspected, as well as echocardiography. Those patients who were only able to walk between 150 and 450 m in six minutes were then indicated for RHC.

PH-HFpEF was defined as a PAPm > 25 mmHg at rest and a pulmonary artery wedge pressure (PAWP) of > 15 mmHg according to the ESC guidelines on PH at the time of study. [24] Right ventricular dysfunction and diastolic heart failure were defined according specific ESC-guidelines.[25,26]

Exclusion criteria were age under 18 and over 75 years, no written informed consent, pregnancy and lactation, not guideline-conform heart failure therapy an LVEF of < 50%, moderate to severe aortic and mitral valve disease, coronary heart disease or peripheral artery disease limiting physical activity, PH patients with an aetiology other than group 2 PH, more than three-fold elevated liver enzymes, haemoglobin values < 10 g/dl, known allergy or hypersensitivity against the study medication, and medication with Rifampicin, Glibenclamid, Cyclosporin-A, Tacrolimus or Sirolimus.

Study Phases

This study was performed in three phases. The first contained screening and RHC. During the second (interventional) phase, eligible patients received study medication for 12 weeks followed by an assessment of 6MWT, echocardiography,

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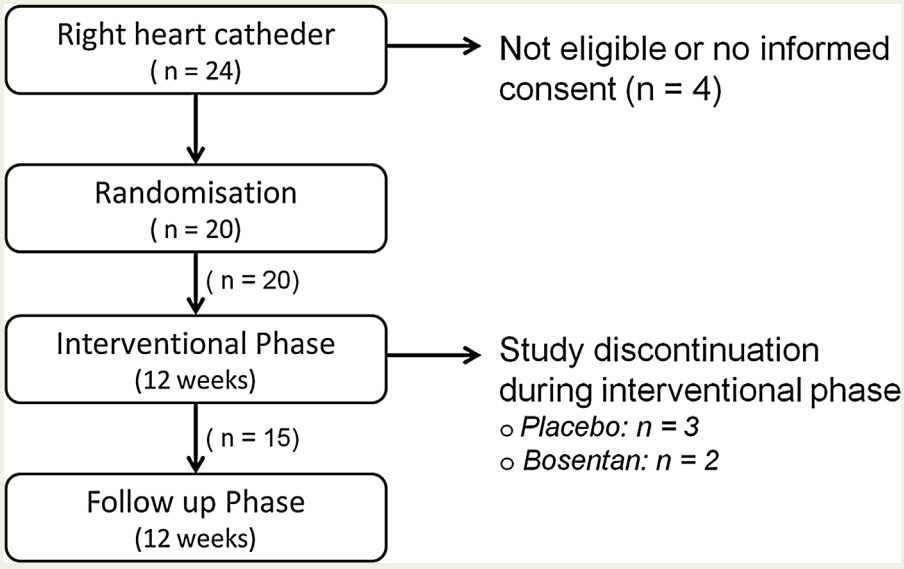

Figure 1 Flow diagram. Overview of study population and study phases.

QOL-Assessment and laboratory investigations. The third was a non-interventional follow-up phase (without study medication) for another 12 weeks. At Week 24 the same investigations as in Week 12 were performed (Figure 1). No patient entered a physical rehabilitation program.

Study Medication

Bosentan 65 mg b.i.d. was given for four weeks, followed by 125 mg b.i.d. for eight weeks. Pharma-spheres pellets (Allphamed Pharbil Arzneimittel GmbH) were used as placebo. To ensure blinding, placebo and Bosentan were capsulated and randomised by block randomisation with the assistance of a drug company (Mono Chem-Pharm, Wien, Austria). Compliance and adherence to the study medication was checked at each visit by pill count. Dosage of co-medications was at the discretion of physicians to limit symptoms and establish heart rate, blood-pressure and weight control.

Six Minute Walk Test

The 6MWT was performed according to the 2002 guidelines of the American Thoracic Society [27] at screening, Week 12 and Week 24.

Laboratory Measurements

Complete blood count, liver enzymes, creatinine, calculated glomerular filtration rate, electrolytes and C-reactive protein (CRP) were measured at the local hospitals at Screening, Week 2, 4, 6, 8, 12, 16 and 24. N-terminal pro brain-type natriuretic peptide (NTpBNP) was measured at Commencement, Week 12 and Week 24.

Echocardiography

Echocardiographic measurements followed a standardised protocol and were performed at screening, Week 12 and Week 24, or after suspected worsening of heart failure. Ejection fraction was measured by the biplane Simpson method. Ventricular and atrial diameters were quantified in the apical four-chamber view. Diastolic dysfunction and right ventricle dysfunction were assessed according to pre-defined parameters specified in the inclusion criteria. Pulmonary hypertension was calculated via the transtricuspid pressure gradient plus the estimated right-atrial pressure (RAP) deducted from vena cava size and respiratory variations.[25]

Right Heart Catheterisation

Right heart catheterisation was performed according to local protocols. Systolic (PAPs), diastolic and mean pulmonary artery pressure, PAWP, PVR as well as peripheral vascular resistance index and central venous pressure were measured. Right heart catheterisation was performed at commencement of this pilot trial to avoid further potential risks associated with RHC.

Quality of Life Assessment and Safety

Quality of Life was measured by Minnesota Living with Heart Failure Questionnaire (MLHFQ, University of Minnesota) and Short Form 36 (SF-36) 4 weeks form (license by Testzentrale.de). Both assessments were performed at Commencement, Week 12 and Week 24.

Worsening of heart failure was defined as clinical symptoms and signs of congestion with new onset of dyspnoea, leg oedema, pulmonary congestion and the need for diuretic therapy adjustment.

Interim Analysis

The study was planned to include 40 patients (20 in each group). However, since patient recruitment and inclusion

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was limited due to safety concerns about ERA in heart failure, an unplanned interim analysis was performed after 20 patients had been included. The results of this analysis – which favoured the placebo and therefore restricted funding – ultimately drove the decision to prematurely abort the study.

Statistics

The primary objective of this pilot study was to show a statistically significant difference in the 6MWT at Week 12 between treatment groups. Secondary objectives were to observe a difference in the 6MWT at Week 24, in the echocardiographically assessed systolic pulmonary artery pressures (PASP) and estimated right-atrial pressures, as well as QOL assessments at Weeks 12 and 24 respectively.

The study was planned to include a sample size of 40 patients, which would prospectively require a mean difference of 35 m in 6MWT between the treatment groups in order to be statistically significant (with 80% power).

In the actual smaller sample size (due to early termination) using 80% power, a difference of approximately 100 m would be needed to demonstrate statistically significance (depending on the observed standard deviations).

Continuous data are presented as mean values with standard deviation, if not otherwise indicated. Normality distribution of variables was tested with Shapiro Wilks tests and was fulfilled in all variables except CRP and NTpBNP. Baseline characteristics between Bosentan and placebo were compared with either Student's t-test for normal distributed continuous variables, Mann-Whitney-U test for non-normal distributed continuous variables or Fisher's exact test for categorical variables. Analysis of variance for repeated measurement was performed to compare outcome variables such as 6MWT between the treatment groups and placebo over the three study phases.

A Spearman-Rho correlation analysis was performed to determine the relationship between systolic pulmonary arterial pressures obtained via echocardiography and those derived from pulmonary artery catheterisation. P-values <0.05 were considered to indicate statistical significance. The SPSS software package (SPSS 13.0; SPSS Inc; Chicago, IL) was used for all statistical analyses.

Results

Twenty-four eligible patients underwent RHC. Twenty of them were included in the BADDHY-Trial – of these, nine received Bosentan. Baseline characteristics of the two groups were well balanced, except for LVEF and co-medication with beta blockers and thiazide diuretics (Table 1).

Four patients exited the study early due to side effects, which included: headache (placebo *n = 1*, Bosentan *n = 1*), unspecific complaints (placebo *n = 1*) and a three-fold rise of liver function enzymes (Bosentan *n = 1*). One patient of the placebo group withdrew informed consent at Week 2 (Figure 1).

Six Minute Walk Test

Six minute walk test results for patients in the Bosentan group at study Commencement, Week 12 and Week 24 were 309.7 ± 96.3 m, 317.0 ± 126.1 m and 307.0 ± 84.4 m. In the placebo group, distances almost significantly increased from 328.8 ± 79.6 m, to 361.6 ± 98.2 m, to 384.0 ± 74.9 m (Week 0, Week 12, Week 24; p = 0.08). At Week 24, the placebo group had a better, though not significant, 6MWT in comparison to the Bosentan group (384.0 ± 74.9 vs 307.0 ± 84.4 m; p = 0.084; Figure 2).

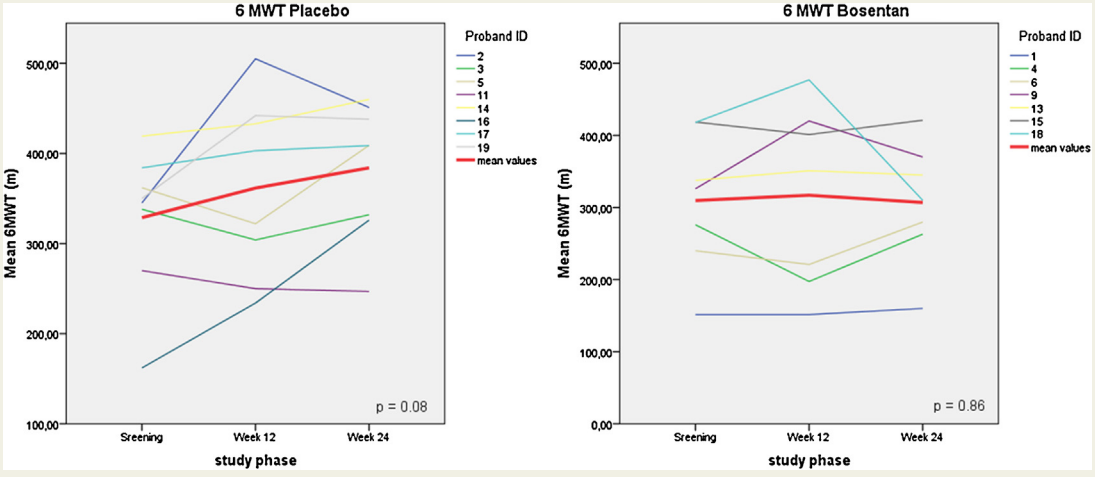

Figure 2 Line diagram of mean 6 minute walk distance. Six minute walk distance improved in the placebo group from study entrance to Week 24 (p = 0.08). P values for trend were calculated over the whole study periods. Each line represents a single patient. The thick lines represent mean values.

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Table 1 Baseline characteristics.

	Unit	Bosentan	Placebo	p-value
n		9	11	
Female Sex	N, (%)	4, (44)	5, (45.5)	
Age	Years (SD)	68.1 (9.7)	67.4 (10.0)	p = 0.87
BMI	kg/m2 (SD)	29. (8.2)	29.5 (4.5)	p = 0.87
eGFR*	ml/min (SD)	72.4 (36.7)	73.6 (30.8)	p = 0.94
Furosemid	% of patients	66.7	90.9	p = 0.36
	mean dose mg (SD)	32.2 (29.4)	45.9 (32.3)	
Thiazide diuretics	% of patients	55.6	36.4	p = 0.03
	mean dose mg	20.8 (22.5)	4.5 (6.3)	
ACE Inhibitor	% of patients	44.4	45.5	P = 0.45
	% of maximum dose	19.4	34	
AT II Blocker	% of patients	33.3	45.5	P = 0.67
	% of maximum dose	19.4	20.5	
ß-Blocker	% of patients	33.3	90.9	P = 0.01
	% of maximum dose	13.9	59.1	
Weight	kg (SD)	81.2 (26.8)	81.9 (17.3)	p = 0.94
6MWT baseline	M (SD)	309.0 (86.7)	302.3 (86.7)	p = 0.87
Haemodynamics				
Heart Rate	bpm (SD)	76.6 (15.5)	75.3 (12.8)	p = 0.87
RRsyst	mmHg (SD)	137.0 (16.9)	116.2 (39.1)	p = 0.15
RRdiast	mmHg (SD)	78.2 (6.3)	74.9 (11.4)	p = 0.45
PAPm	mmHg (SD)	35.9 (11.4)	41.0 (10.1)	p = 0.30
PAWP	mmHg (SD)	21.0 (4.5)	21.2 (3.7)	p = 0.92
TPG	mmHg (SD)	14.9 (9.0)	19.8 (8.5)	p = 0.22
PVR	WU (SD)	3.7 (2.5)	4.6 (1.2)	P = 0.48
Echocardiography				
LVEF	% (SD)	55.9 (5.0)	65.1 (6.5)	P = 0.003
RVEDD	mm (SD)	44.8 (6.7)	41.0 (7.4)	p = 0.25
TAPSE	mm (SD)	19.1 (13.4)	14.9 (4.6)	p = 0.34
PASP	mmHg (SD)	61.0 (17.3)	66.2 (17.0)	p = 0.51
Laboratory				
NTpBNP	pg/ml (SD)	2651,91 (3356,40)	2353,45 (965,03)	p = 0.78
Quality of Life				
MLHFQ	points reached (SD)	52.3 (24.6)	61.0 (17.5)	p = 0.38
SF-36, physical sum scale	points reached (SD)	30.3 (7.7)	33.4 (4.6)	p = 0.29
SF-36, mental sum scale	points reached (SD)	38.7 (14.2)	29.5 (10.2)	p = 0.12

* for estimation of the creatinin clearance the Cockroft-Gault formula was used; (SD): standard deviation; eGFR: estimated glomerular filtration rate. BMI: body mass index; MRA: mineralocorticoid receptor antagonists; 6MWT: six minute walk test; PAPm: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; TPG: transpulmonary gradient; LVEF: left ventricular ejection fraction; RVEDD: right ventricular end diastolic diameter; RRsyst: systolic blood pressure; RRdiast: diastolic blood pressure; TAPSE: tricuspid annular plane systolic excursion; PASP: echocardiographic estimated systolic pulmonary artery pressure; NTpBNP: n-terminal pro brain type natriuretic peptide; MLHFQ: Minnesota Living with Heart Failure Questionnaire; SF-36: short form 36

Echocardiography

At study commencement, PASP strongly correlated with PAPs assessed by RHC (r = 0.8; p = 0.009). Within the placebo group there was a significant decrease of PASP; from 62.3 ± 16.7 mmHg to 45.3 ± 13.9 mmHg at Week 12 and to 44.6 ± 14.5 at Week 24 (p = 0.01; Figure 3).

Additionally estimated right-atrial pressures in the placebo group significantly decreased from 13.1 ± 5.3 mmHg to 9.4 ± 3.2 mmHg after 24 weeks (p = 0.046). There were no differences or changes for right ventricular end-diastolic diameter, and TAPSE between and within the study groups (Table 2).

Quality of Life Assessment, Safety and Clinical Parameters and Safety

There was no difference in body weight and QOL either determined by the MLHFQ, or by the SF-36 between or within the two groups throughout all study phases

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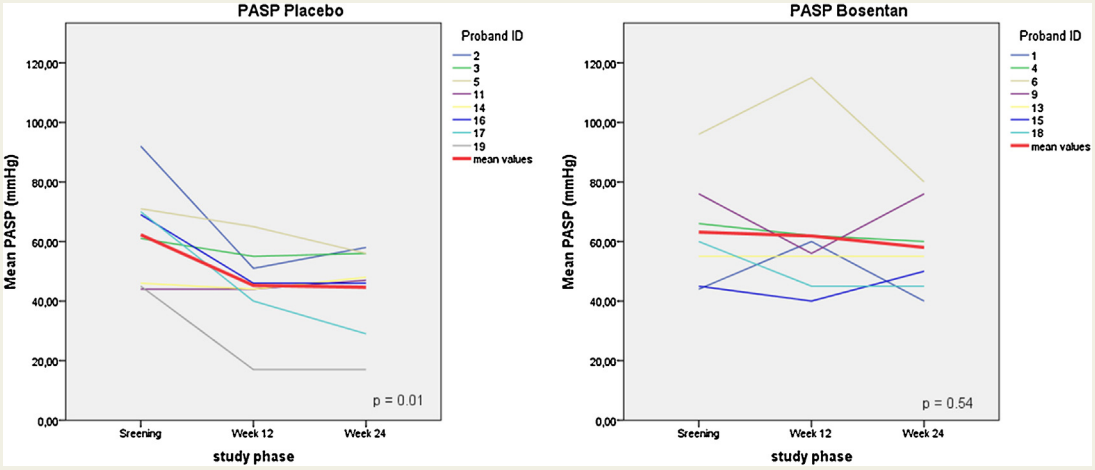

Figure 3 Line diagram of echocardiographic estimated systolic pulmonary arterial pressure. PASP decreased highly significant in the placebo group over the course of the study (p = 0.01). P values for trend were calculated over the whole study periods. Each line represents a single patient. The thick lines represent mean values.

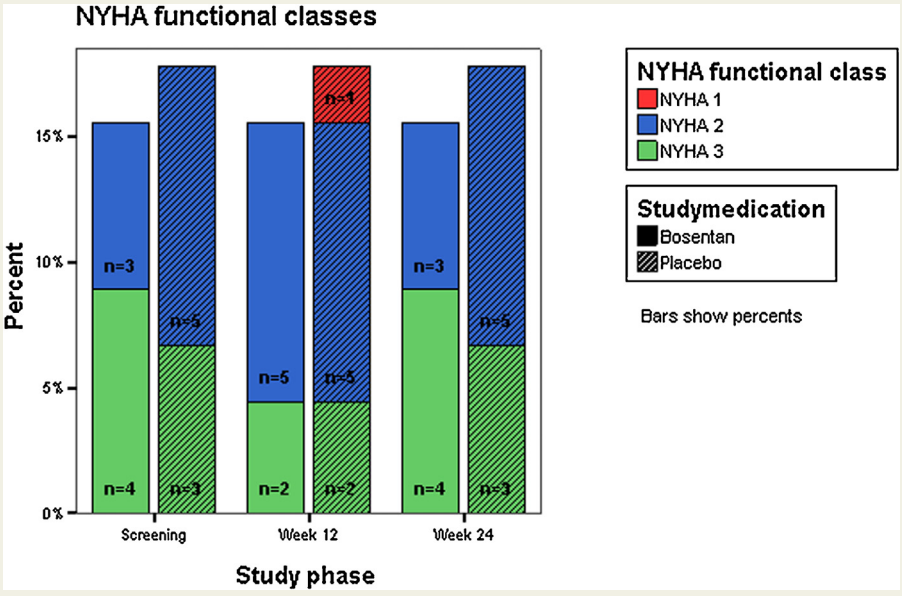

Figure 4 Distribution of NYHA functional classes over study periods.

(Table 2). There were no acute heart failure episodes during the intervention phase, whereas in the follow-up phase four patients developed symptoms of congestive heart failure: Bosentan $n = 3$, placebo $n = 1$ [dyspnoea ($n = 4$), peripheral oedema ($n = 3$) and pleural effusions ($n = 1$)]. All of them were admitted to hospital and received intravenous diuretic therapy. For the dynamic of NYHA functional classes and co-medication see Figure 4 and Table 1 and 2 respectively.

Discussion

This is the first study investigating the effects of Bosentan in PH-HFpEF. Overall PH was moderate (PAPm 38.7 ± 10.7 mmHg; Table 1) but the assumed left atrial pressure was substantial according to a mean PAWP of 21.1 mmHg ± 3.9 mmHg at study commencement.

Right ventricle dysfunction was inferred when RVEDD, TAPSE and RAP were beyond normal range. Right-atrial

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Table 2 Overview of outcomes at week 0, week 12 and week 24.

Parameter		Week 0	Week 12	Week 24	P value for trend
6MWT	Bosentan (n = 7)	309.7 ± 96.3	317.0 ± 126.1	307.0 ± 84.4*	p = 0.86
(m)	Placebo (n = 8)	328.8 ± 79.6	361.6 ± 98.2	384.0 ± 74.9*	p = 0.08
Weight	Bosentan (n = 7)	81.3 ± 30.8	82.7 ± 33.7	82.9 ± 33.4	p = 0.86
(kg)	Placebo (n = 8)	77.2 ± 16.6	77.9 ± 19.0	79.1 ± 18.9	p = 0.26
Heart rate	Bosentan (n = 7)	89.6 ± 12.8	88.9 ± 12.4	83.7 ± 20.6	p = 0.03
(bpm)	Placebo (n = 8)	82.0 ± 13.8	85.4 ± 15.1	90.8 ± 14.6	p = 0.33
RRsyst	Placebo (n = 8)	125. 0 ± 21.3	123.1 ± 15.6	123.1 ± 12.5	p = 0.66
(mmHg)	Bosentan (n = 7)	136.7 ± 19.5	130.4 ± 23.1	134.1 ± 21.4	p = 0.85
RRdiast	Placebo (n = 8)	73.6 ± 13.3	75.1 ± 12.4	74.4 ± 11.2	p = 0.91
(mmHg)	Bosentan (n = 7)	78.7 ± 6.9	74.4 ± 14.0	76.0 ± 9.6	p = 0.72
PASP	Bosentan (n = 7)	63.1 ± 18.4	61.9 ± 24.7	58.0 ± 15.2†	p = 0.54
(mmHg)	Placebo (n = 8)	62.3 ± 16.7	45.3 ± 13.9	44.6 ± 14.5†	p = 0.01
Est. RApress	Bosentan (n = 7)	11.4 ± 5.6	12.1 ± 3.9	10.7 ± 5.3	p = 0.88
(mmHg)	Placebo (n = 8)	13.1 ± 5.3	10.0 ± 3.8	9.4 ± 3.2	p = 0.046
RVEDD	Bosentan (n = 7)	45.6 ± 7.4	41.6 ± 7.0	43.3 ± 5.3	p = 0.39
(mm)	Placebo (n = 8)	39.5 ± 7.4	40.1 ± 9.1	38.8 ± 7.0	p = 0.73
TAPSE	Bosentan (n = 7)	18.0 ± 15.2	19.9 ± 5.1	18.1 ± 5.9	p = 0.72
(mm)	Placebo (n = 8)	13.5 ± 4.6	15.7 ± 4.5	15.1 ± 3.2	p = 0.22
LAD§ (long axis; mm)	Bosentan (n = 7)	62.8 ± 18.5	59.0 ± 10.3	54.1 ± 10.6	p = 0.50
	Placebo (n = 8)	58.5 ± 7.7	62.08 ± 7.7	57.1 ± 14.5	p = 0.60
PSC‖	Bosentan (n = 7)	30.0 ± 9.1	35.4 ± 9.6	33.0 ± 11.5	p = 0.39
	Placebo (n = 8)	34.4 ± 4.5	38.4 ± 9.3	37.1 ± 8.4	p = 0.13
MSC#	Bosentan (n = 7)	41.4 ± 14.5	42.6 ± 19.4	39.6 ± 16.9	p = 0.81
	Placebo (n = 8)	32.1 ± 7.3	40.7 ± 13.0	36.1 ± 16.1	p = 0.19
MLHFQ	Bosentan (n = 7)	47.3 ± 24.8	37.7 ± 23.2	49.2 ± 21.4	p = 0.45
	Placebo (n = 8)	59.4 ± 19.1	41.3 ± 24.0	41.3 ± 16.4	p = 0.21
NTpBNP (pg/ml)	Bosentan (n = 7)	2613.6 ± 3567.4	1517.3 ± 1859.4	3022.6 ± 3601.0	p = 0.44
		2239.0 ± 1058.2	2046.4 ± 1230.9	2228.8 ± 1490.0	
	Placebo (n = 8)				p = 0.81
Loop diuretics (mg)	Bosentan (n = 7)	31.4 ± 33.8	89.3 ± 183.1	89.3 ± 183.1	p = 0.38
	Placebo (n = 8)	38.8 ± 22.3	42.5 ± 23.1	55.0 ± 47.8	p = 0.35
Thiazide diuretics (mg)	Bosentan (n = 7)	26.8 ± 22.2**	29.6 ± 24.9##	27.1 ± 22.4##	p = 0.36
	Placebo (n = 8)	4.7 ± 6.5**	4.7 ± 6.5##	4.7 ± 6.5##	n.a.

*: p-value for between groups p = 0.084; †: p-value for between groups p = 0.10; ‡: p-value for between groups p = 0.09; § LAD: left atrial diameter; ‖ PSC: physical sum scale SF-36; # MSC: mental sum scale SF-36; **: p-value for between groups p = 0.018; ##: p-value for between groups p = 0.017; n.a.: not applicable

pressure is reported to be one of the most important measures of right ventricle dysfunction with regard to clinical outcome. [28]

In accordance with the 2009 guidelines on PH, 65% of our patients (Bosentan $n = 5$, placebo $n = 8$) had a transpulmonary gradient (TPG) of more than 12 mmHg.[24] Nowadays, the 2015 ESC guidelines on PH define combined post-capillary and pre-capillary PH by a PAPm > 25 and a DPG of ≥ 7 mmHg.[2] Only 25% of our cohort (Bosentan $n = 3$, placebo $n = 2$) would comply with this definition.

Our study could not demonstrate a benefit of Bosentan in any of our measurements when compared to placebo. Throughout the study, up until and including the non-interventional phase, the 6MWT was consistently better in the placebo group. This improvement was accompanied by a significant decrease of PASP and RAP. In our opinion, this observation is probably due to a relevant decrease of left ventricle filling pressures resulting from co-medication. Endothelin receptor antagonists are known to lead to oedema and congestion in patients with heart failure [19,21,29] and hence may offset the positive effects of co-medication seen in the placebo group. In fact, the overall diuretic load was even higher in the Bosentan group due to thiazides. However we could not find significant differences in body weight or blood pressure between both groups. This finding may simply be one of chance, due to under-powered statistics (Table 2). Filling pressures may increase dramatically in HFpEF patients during exercise,[4] so even small differences in

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overloading the left ventricle – not recognised by body weight measures – may worsen or limit improvement of 6MWT in patients treated with Bosentan. Therefore, our study design of an interventional and non-interventional follow-up period of the entire group, and subsequent impressive increase of 6MWT, suggests that Bosentan may even actively worsen outcome.

Our study is in line with several other studies dealing with HFpEF and PH, all of which have been unable to demonstrate favourable clinical effects of Bosentan [10,11,30]. In the recently published DILATE-1 study, Riociguat was tested in PH-HFpEF patients with a comparable sample size as in our study. It also could not demonstrate beneficial effects on PAPm, TPG or PVR. The authors were able to demonstrate an increased stroke volume and decreased systolic blood pressure, as well as right ventricular end-diastolic area, in patients administered Riociguat.[30] However, these effects seem to be primarily deducted from lowering PVR than direct effects on the pulmonary vasculature. Unfortunately they do not explain the clinical effects of Riociguat on exercise capacity.

Our study had several limitations. First, the small sample size was the main limitation in interpreting the results, even though follow-up measures correcting for multiple testing served to strengthen the statistical power of the results. For safety purposes we undertook an interim analysis after 20 patients had been included and 15 patients had completed the 24-week trial. The results of this analysis informed the decision to abort the trial. Furthermore, the surprisingly strong and long-lasting placebo effect may even suggest a harmful effect of Bosentan. This finding, however, may not apply to patients with combined pre- and postcapillary PH according to the newer definition.

Secondly, the 6MWT is controversially discussed as a potent outcome parameter in PH, but it is used in most studies as a primary endpoint. In this study, the dual assessment of 6MWT improvement, in combination with the dynamics of echocardiographic parameters, gives rise to a meaningful interpretation of this test in patients with PH-HFpEF.

Thirdly, the placebo group was treated more frequently and more intensely with beta blockers. Beta blockers do have a relatively lesser impact on blood-pressure in elderly patients,[31] but may influence chronotropic competence. [32] In our study we did not find differences in heart rates between both groups when directly measured after 6MWT (Table 2). Lastly we did not repeat RHC due to the associated risk/benefit ratio in the case of a pilot study.

Conclusions

Dual endothelin receptor blockade is probably of no benefit in patients with PH-HFpEF and may even have detrimental effects. Further studies should be undertaken with clearly defined combined pre-capillary and post-capillary PH.

Author Contribution

The study was proposed and designed by first and senior authors. All authors listed (Koller B, Steringer-Mascherbauer R, Ebner CH, Weber Th, Ammer M, Eichinger J, Pretsch I, Herold M, Schwaiger J, Ulmer H, Grander W) contributed substantially to data collection, analysis and interpretation as well as writing and revising the manuscript.

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Conflict of Interest Disclosure

None of the authors (Koller B, Steringer-Mascherbauer R, Ebner CH, Weber Th, Ammer M, Eichinger J, Pretsch I, Herold M, Schwaiger J, Ulmer H, Grander W) has a conflict of interest.

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