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Comparison of the dual receptor endothelin antagonist enrasentan with enalapril in asymptomatic left ventricular systolic dysfunction: A cardiovascular magnetic resonance study

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Abstract

Objective: Endothelin (ET) is an important vasoconstrictor and growth factor, levels of which are increased in proportion to heart failure (HF) severity and predict adverse outcomes. It is unclear whether ET mediates HF progression. We compared the effect of the dual $ET_{A/B}$ receptor antagonist enrasentan with enalapril on left ventricular (LV) remodeling.

Methods: A multicenter, randomized, double-blind, parallel group study was performed in 72 asymptomatic patients with left ventricular dysfunction. Patients received enrasentan (60-90mg/day) or enalapril (10-20mg/day). The primary endpoint was the change in LV end-diastolic volume index (EDVI) after 6 months treatment.

Results: LVEDVI increased on enrasentan but decreased with enalapril (+3.9 ±1.8 vs -3.4 ± 1.4mL/m^2; p=0.001). Enrasentan increased resting cardiac index compared with enalapril (+0.11 ±0.07 vs -0.10 ±0.07 L/m^2; p = 0.04), and also LV mass index (+0.67 ±1.6 vs -3.6 ±1.6g/m^2, p = 0.04). Other variables were comparable between groups. Enalapril lowered brain natriuretic peptide more than enrasentan (–19.3 ±9.4 vs –5.8 ±6.9pg/mL; p=0.005). Norepinephrine (p=0.02) increased more with enrasentan than enalapril. Enrasentan was associated with more serious adverse events compared to enalapril (16.7% patients vs 2.8 %; p=0.02), but there was no difference in the rate of progression of HF.

Conclusion: In asymptomatic patients with LV dysfunction, LVEDVI increased over 6 months on enrasentan compared to enalapril, with adverse neurohormonal effects. This suggests that enrasentan at a dose of 60-90 mg/day over 6 months causes adverse ventricular remodeling despite an increase in the resting cardiac index.

Introduction

Heart failure (HF) is characterized by progressive deterioration in cardiac function and symptoms resulting in a high morbidity and mortality. Individuals with asymptomatic left ventricular systolic dysfunction (ALVD) are at high risk of HF and death even when only mild impairment of EF is present. Neurohormone activation, linked to adverse ventricular remodeling, may be an important pathway for progression. The importance of the renin-angiotensin-aldosterone and sympathetic nervous systems is well documented, but more recently the endothelins have also been linked with disease progression.

Endothelin–1 (ET) is a 21 amino acid vasoactive peptide that is released predominantly from vascular endothelium,[1] and synthesized by a variety of cell types including vascular smooth muscle, cardiomyocytes and cardiac fibroblasts.[2] It is the predominant isoform of the endothelin peptide family and mediates both autocrine and paracrine actions via 2 G-protein coupled receptor subtypes (ET_A and ET_B). ET stimulates potent vasoconstriction and cell proliferation through activation of ET_A receptors on vascular smooth muscle cells, whereas ET_B receptors are primarily involved in the mediation of vasodilation through effects on the clearance of ET, inhibition of endothelial apoptosis, release of nitric oxide and prostacyclin, and inhibition of endothelin converting enzyme-1 expression.[3] Local activation of the endothelin system has been documented in hypertension, atherosclerosis and HF. ET augments sympathetic activity, enhances the activity of the renin-angiotensin-aldosterone system with modulation of sodium reabsorption,[4] mediates cardiac hypertrophy through upregulation of GATA4 DNA,[5] and induces myocyte injury.

In animal models of chronic HF, ET receptor antagonists have mostly shown significant promise with improved survival, reduction of preload and afterload and decreased left ventricular (LV) hypertrophy, dilatation and cardiac fibrosis.[6] The combined $ET_{A/B}$ receptor antagonist, bosentan, has been evaluated in patients with HF, including those on angiotensin converting enzyme (ACE) inhibitor therapy, showing hemodynamic improvements with reduced peripheral and pulmonary vascular resistance and increased cardiac output.[3] A direct relationship was observed between ET levels and bosentan effect in the patients. Enrasentan is an orally active mixed $ET_{A/B}$ receptor antagonist with a 100-fold greater affinity for ET_A receptor. It is effective in animal models of cardiovascular disease including hypertension and HF. Enrasentan treated rats with cardiac hypertrophy and dysfunction induced by banding, had a higher stroke volume and cardiac index, improved survival, and a reduction in LV mass index, aldosterone and proANP levels.[7] This study is the first to have compared an ET antagonsist, enrasentan directly with an ACE inhibitor, enalapril in *asymptomatic patients with LV dysfunction.* The aim was to determine if therapy with an ET receptor antagonist may play an early role in slowing the progression of heart-failure.

Methods

Study Design

We performed a phase II, multicenter, double-blind, parallel group study, in which asymptomatic patients with LV systolic dysfunction (NYHA I) were randomized to receive enrasentan or enalapril once daily. Although long term ACE inhibitors have been shown to be beneficial, these patients have a low morbidity and mortality over the short-term, and it was considered a direct comparison over 6 months using 2 active agents and intensive monitoring would not compromise patient safety. Consecutive patients meeting the inclusion criteria were recruited from Cardiology Out-Patient clinics – the majority of patients (70%) were being

followed up for documented previous myocardial infarction. The remainder of patients were being followed up for hyperlipidaemia (12%), atypical chest-pain (8%), mild valve disease (10%) . Enrasentan was initiated at 30mg and enalapril at 2.5mg, both once daily. Dosage was up-titrated over 6-10 weeks to reach a maximum tolerated level with minimum doses of 60 mg enrasentan or 10 mg enalapril, and maximal doses of 90 mg of enrasentan or 20 mg of enalapril. Patients remained in the maintenance phase for 6 months at this dose level and then continued into a follow-up period of up to 10 days.

LV dysfunction was defined as an ejection fraction (EF) during screening of ≤40% measured by two-dimensional echocardiography. Studies were performed by experienced operators using fundamental frequency with the subject in the left lateral recumbent position in breath-hold expiration. Subsequently all echo studies were analyzed in a central core-lab.

Exclusion criteria included acute coronary syndromes within 6 weeks, clinically significant valvular disease, hypertrophic cardiomyopathy, uncontrollable or symptomatic arrhythmias, systolic blood pressure <85mmHg or >160mmHg, second or third degree heart block, significant comorbidity, or any contraindications to CMR. Patients were not allowed to enter the study if they had received HF treatment in the preceding 6 weeks, or there was concomitant use for other reasons of ACE inhibitors or angiotensin receptor blockers. Patients on short acting calcium channel blockers, or beta blockers were admissible only if they had been on a stable dose without adjustment for greater than 3 months. Treatment with diuretics was not permitted prior to entry into the study, but these could be prescribed during the study if required to control developing symptoms of heart failure. Doses of other concomitant medications could be altered if necessary, at the discretion of the Investigator, throughout the study. The study protocol was approved by the institutional Ethics Review Committee at each study site, and all patients provided written informed consent prior to entry into the study. Patients were recruited from 3 centers in the United Kingdom. A single computer-generated randomization code was used for all sites and was coordinated by an independent randomization centre. All study medication was blinded to both the investigator and patient. Enrasentan was provided by SmithKline Beecham. Matching capsules containing enalapril were manufactured by Merck.

Study objectives

The primary study objective was to compare the effects of enrasentan and enalapril on LV end diastolic volume index (LVEDVI). The secondary objectives were to compare the drug effects on other remodeling and cardiac function measurements, circulating neurohormones, the safety of enrasentan, progression of heart failure, and patient symptoms.

CMR

CMR cardiac volume and function scans were performed at baseline and at 6 months using standard techniques.[8] The CMR scans were read in a core-laboratory at Royal Brompton Hospital and analyzed using dedicated software (CMRtools © Imperial College).

Laboratory Analyses

Blood was obtained at baseline and after completion of the study at 6 months, or at early withdrawal, for brain natriuretic peptide (BNP) and norepinephrine (NE), levels. Plasma samples for neurohormonal levels were obtained at all visits with 10-mL EDTA syringes used for sampling. Plasma was separated and stored at -80°C until assays were performed. Frozen plasma samples were forwarded to a central laboratory for processing. BNP was measured with an immunoradiometric assay (Shionogi, Osaka, Japan). The intra- and interassay coefficients of variation were 3.9 and 4.8%, respectively, with a lower detection limit of 1

pg/ml (0.6 pM). Endothelin levels were assessed once only during the screening phase. Endothelin levels were measured by enzyme immunoassay and Norepinephrine levels by HPLC. Clinical laboratory safety tests were taken in the screening phase, during the up-titration period and at 1, 3 and 6 months of the maintenance phase or at early withdrawal.

Progression of Heart Failure
This was defined by any of the following: requirement for addition of diuretic therapy, worsening of NYHA class, hospitalization for HF, or death.

Clinical HF Self-Assessment
This was determined at 1, 3 and 6 months during the maintenance phase of the study or at early withdrawal. The patient was asked to answer "How do you feel today as compared to how you felt before taking this medication?" Global clinical status was rated by the patient on a 7-category scale (markedly improved, moderately improved, mild improvement, no change, slightly worse, moderately worse, or markedly worse) as used in previous heart-failure trials.[9]

Statistical methods
The study was powered at 90% with a significance level of p=0.05 to detect a difference of 2.5mL/m^2 in LVEDVI between enrasentan and enalapril. All remodeling data was tested by analysis of variance and values are shown as mean ±1 SD, except where stated. The correlations between the plasma levels of neurohormones and remodeling variables were assessed using Spearman's rank correlation. The progression of HF and the clinical patient self-assessments were analyzed using Fisher's exact test. All safety data was analyzed using the intention-to-treat population, which was defined as all patients who received at least one dose of randomized medication and had post-baseline assessments performed. Comparisons were made at study endpoint, defined as the last available on-therapy record of randomized patients.

All patients were evaluated for clinical safety and tolerability including determination of all adverse experiences and abnormal vital signs regardless of their relationship to the study medication. Laboratory values and ECG changes were reported as an adverse event if clinically significantly abnormal in the investigator's opinion. Non-compliant patients were included in the analysis. All tests were two-sided, and a p value of ≤ 0.05 was considered significant.

Results

Baseline characteristics and analysis populations
Of 96 patients enrolled into the study, 72 patients were randomized (36 enalapril, 36 enrasentan) and entered the titration phase, 67 patients (93.1%) entered the maintenance phase and 63 patients (87.5%) completed the study. Baseline characteristics of the patients are shown in table 1. Treatment groups were comparable at baseline except for body height and weight parameters, right ventricular volumes, resting cardiac index and BNP. Sixty-four patients (95.5%) entered the maintenance phase of the study on the maximal dosage level of enrasentan or enalapril. Of the 63 patients completing the full protocol, thirty-two patients were randomized to enrasentan and 31 were randomized to enalapril. After randomization, 4 patients (11.1%) withdrew from the enrasentan group and 5 patients (13.9%) from the enalapril group.

Primary outcome measure
Treatment with enrasentan resulted in an increase in LVEDVI of +3.9 ±1.8 mL/m^2 (p=0.04) compared with a reduction of –3.4 ±1.4 mL/m^2 in the enalapril group (p=0.01), and the between groups difference was significant (p=0.001, figure 1).

Secondary outcome functional measures
There was no significant difference in the change from baseline between the 2 treatment groups in the LV end systolic volume index (ESVI) or EF (table 2), but LV mass index was significantly different between groups, with a reduction on enalapril but no change with enrasentan. There was a significant difference between the groups in the change in resting cardiac index (0.11 ±0.07 vs -0.10 ±0.07L/m^2; p=0.04, figure 2). The stroke volume increased from baseline with enrasentan (75.1 ±15.5mL to 82.9 ±19.4mL, p=0.002), with a trend towards reduction with enalapril (71.7 ±16.9 to 68.9 ±20.2mL; p=0.09).

There were no significant differences between groups over the treatment period in systolic blood pressure (enrasentan -4.1 ±14.4 mmHg vs enalapril -9.3 ±19.2mmHg, p=0.20) or in diastolic blood pressure (enrasentan -5.2 ±8.4 mmHg vs enalapril -5.4 ±10.8 mmHg, p=0.93). There was no difference in the heart rate response to treatment (enrasentan 0.83 ±10.8 vs -3.4 ± 9.9 bpm, p=0.29).

A trend to reduction in hemoglobin on enrasentan was not significant while hemoglobin did not change on enalapril. The change in the enalapril group from baseline to end of study was -0.9 ±8.0 g/dl (p=0.26), while the change in the enrasentan group was -2.0 ±10.6 g/dl (p=0.12). The differences between the groups were not significant.

Neurohormone Measurements
Baseline BNP levels were elevated in both groups but with a significantly higher level in the enalapril group (72.7 ±19 vs 53.2 ±8.2 pg/ml; p=0.03). Both treatments reduced BNP levels although this reduction was greater in the enalapril group (-19.3 ± 9.4 vs -5.8 ±6.9 pg/ml; p=0.005). NE (p=0.02) increased more with enrasentan than enalapril (figure 3). There was no correlation between plasma endothelin levels at baseline and the cardiac remodeling parameters of LV EDVI, ESVI and EF.

Progression of Heart Failure
By the predefined criteria, in the enrasentan group 8 (22%) patients had a deterioration in their condition, compared with 10 (28%) patients in the enalapril treatment group (p=0.6). Twenty eight (78%) patients in the enrasentan treatment group reported no change in their condition compared with 26 (72%) in the enalapril treatment group (p=0.6). No patient in the enalapril group required hospitalization for cardiovascular related reasons compared with 8% in the enrasentan group (p=0.08). The requirement for addition of diuretic therapy was seen in 8% of patients in the enrasentan group compared with 6% in the enalapril group (p=0.7).

Patient Heart Failure Self-Assessment
For the single criterion of patient self reported symptoms, by study end 38% of patients in the enalapril group reported feeling better (mild-markedly improved) compared with 28% in the enrasentan group (p=0.4), and 9.4% in the enrasentan group felt slightly worse than at baseline compared with 3.1% in the enalapril group (p =0.3).

Adverse events

Overall, 5 patients (14%) in the enrasentan group had a laboratory value of potential clinical concern compared to 6 (17%) in the enalapril group (p=0.7). No patients were withdrawn from the study due to abnormal laboratory values. Twenty patients had at least one vital sign which met the criteria for potential clinical concern, 8 (22%) in the enrasentan group and 12 (33%) in the enalapril group (p=0.3). Thirty-four (94%) patients in the enrasentan group reported at least one adverse event during the study period compared to 31 (86%) in the enalapril group (p=0.2, table 3).

There were 2 deaths during the study. One patient had received enalapril 20mg and died of an acute coronary syndrome 19 days after the last dose whilst the other patient received enrasentan 90mg and died of endocarditis 34 days after the first dose and 10 days after premature cessation of study medication; both cases were considered unlikely to be related to study medication. Seven patients had serious non-fatal adverse events after randomization. In the up-titration phase 3 patients in the enrasentan group reported endocarditis, pneumonia or thrombophlebitis; 1 patient in the enalapril group reported angina (p=0.3). In the maintenance phase, 4 patients, all in the enrasentan group, experienced serious adverse events (chest-pain, deep venous thrombosis (DVT), sinusitis and dyspepsia) and none in the enalapril group (p=0.02). The same patient with thrombophlebitis in the uptitration phase experienced DVT in the maintenance phase. Thus, in total, 6 (16.7%) patients in the enrasentan group experienced serious adverse events that were deemed by the study investigators to be potentially attributable to study medication compared to 1 (2.8%) in the enalapril group (p=0.02).

Adverse events resulted in 6 patients withdrawing prematurely from the study, 3 in each treatment group (p=0.7). This included the two serious fatal events above, and one patient with a serious non-fatal adverse event (DVT). Three patients were withdrawn with non-serious events considered to have a probable/suspected relationship to study medication. These included dizziness and cardiac failure in 1 patient receiving enrasentan 30mg and cough in 2 patients receiving enalapril 20mg (p=0.6).

Discussion

This study is the first head-to-head comparison of monotherapy with an endothelin antagonist to monotherapy with an ACE inhibitor in aymptomatic patients with LV dysfunction. Previous studies have examined the effects of endothelin antagonists compared to placebo on a background of ACE inhibitor and diuretic therapy and usually in more advanced cases of heart-failure. The key finding was the relative inability of monotherapy with enrasentan to prevent an increase in LVEDVI over 6 months compared to monotherapy with enalapril. The reduction in BNP on enrasentan was also less than that observed on enalapril, and changes in other neurohormones were likewise more favorable with enalapril. Although the study was not devised to investigate clinical outcomes, in general these tended to favor enalapril. Overall, these data suggest that enrasentan is less able than enalapril to retard adverse ventricular remodelling in asymptomatic patients with LV dysfunction.

The precise role of ET in the pathophysiology of chronic HF is still to be defined, but it is already clear, from this study and others, that the relationship is much more complex than initially expected. Although increased plasma concentrations of ET appear associated with more severe cardiac dysfunction, higher vascular resistance, worse symptoms and a poorer outcome, our study and others suggest that it is far from clear that interfering with activation

by endothelin receptor blockade is beneficial. The adverse remodelling seen with enrasentan is in accord with the adverse mortality reported in the ENCOR study and suggests that the LV EDV in the current study, which was relatively small, was an appropriate surrogate for outcome in the larger ENCOR study.[13]**Error! Bookmark not defined.** However, the mechanism for the adverse remodelling in the LV EDV in patients on enrasentan is not clear. A number of possible factors might contribute to the adverse remodelling. One possibility is the effect on blood-pressure as enalapril is known to lower blood pressure in heart failure. In the current study however, there were no significant differences between the enrasentan and enalapril groups in blood pressure at baseline and there were no significant differences between groups over the treatment period. Another possibility is that enrasentan caused a fall in hemoglobin concentration as has been observed in other studies of endothelin antagonists,[10] but in this study, there was no clinically significant change in hemoglobin concentration. There is some evidence that ET_A receptor blockade may reduce myocardial contractility in patients with less severe ventricular dysfunction, when the direct effects of endothelin on the myocardium may not be offset by the benefits of peripheral vasodilatation.[11] However, cardiac index increased on enrasentan compared to enalapril, which appeared to be due to an increase in stroke volume as the heart rate did not change. This could reflect greater vasodilatation with the endothelin antagonist. Alternatively, a more speculative mechanism might be an increase in pulmonary shunting with the endothelin antagonist. There is some evidence for this in a study of Tezosentan in acute heart failure, where the endothelin antagonist caused a drop in arterial oxygen saturation.[12] If such an effect occurred with enrasentan, then it might explain the increase in cardiac output seen, combined with the increase in LV EDV and an adverse outcome. The minor effects in blood pressure and haemoglobin could contribute to this, although a larger study would be required to establish this. Another possibility is the receptor selectivity of the drug. Enrasentan is more selective for the ET_A receptor but at the doses used in this study will also have blocked ET_B receptors on vascular smooth muscle and the endothelium.[13] Blockade of endothelial ET_B receptors results in a rise in plasma endothelin, which could have adverse consequences in the absence of adequate blockade of ET_A receptors.[14] The dosage of enrasentan used in this study was based on a combination of animal studies, human safety and efficacy data and matched the dose used in the ENCOR trial.[13] It is possible that a different dose or a more selective ET_A receptor antagonist would have less adverse effects, although recent reports suggest that this is not the case.[15] However, an alternative explanation is that none of the endothelin antagonists used so far is selective enough and doses of relatively selective agents may have been used at such a high dose that selectivity was lost.[3] Finally it is possible that ET-1 is a protective factor against myocardial cell apoptosis in HF and ET antagonists may confound this process.[16] The observed changes in LV volumetric measurements correlate with the changes in LV mass and therefore suggest that true remodeling effects are being assessed rather than the impact of active drug-induced load-related effects.

Other endothelin antagonist trials in HF

The chronic effects of ET antagonists have been evaluated in patients with symptomatic HF. The Enrasentan Cooperative Randomised Evaluation (ENCOR) trial randomized 419 HF patients (NYHA class II-III) and an EF of <35% on standard therapy to two doses of enrasentan, placebo or high dose enalapril.[13] After nine months of treatment there was no improvement in the composite endpoint (improvement in either NYHA functional class or global patient assessment or both). In the enrasentan group there was a worsening of clinical status compared to placebo with an increased rate of hospitalization and withdrawals from study medication due to adverse effects including deterioration of HF. There was a trend

towards progressive LV dysfunction with LV dilatation and increased total mortality with enrasentan. No differences between enrasentan doses were noted. Subsequently, in REACH-1 (Randomised Endothelin Antagonism in Chronic Heart Failure with Bosentan) trial, ENABLE 1 and 2 (Endothelin Antagonist Bosentan for Lowering Events)[17] and the EARTH study (Endothelin A Receptor Antagonist Trial in Heart Failure trial),[15] the results of treatment with ET antagonists have also been disappointing in symptomatic heart failure and have not mirrored the highly promising effects in animal disease models. Notably, however, all of these studies have assessed symptomatic patients predominantly in NYHA Class II-III with more advanced heart-failure. An unaddressed question from these earlier trials was whether we had reached the ceiling with neurohumoral blockade in chronic heart failure? Is it possible that ET antagonists could have been successful drugs in heart failure, if they had been introduced before ACE inhibitors, betablockers and spironolactone? Does the early introduction of an ET antagonist help to halt some of the progression in heart-failure in those patients with the mild form of the disease? In animal models, following chronic angiotensin infusion, both AT blockade and ET_A blockade appear to exert comparable protective effects.[18] Accordingly, it might be that ET blockade is less efficacious on the background of ACE- or AT -inhibition. To test this hypothesis a direct comparison with ACE-inhibitors is required as was done with betablockers in the CARMEN study.[19] The present study is unique in comparing ACE inhibitors versus an ET-antagonist in an asymptomatic population with a mild form of heart-failure to address some of these questions.

Limitations

There was no placebo group and therefore the size of benefit achieved with enalapril is unknown. It is possible that both enrasentan and enalapril would have shown beneficial effects on remodeling compared with placebo, despite our data showing that enrasentan is less effective than enalapril. Data from a radionuclide substudy of the SOLVD trial suggest that over 6 months, LVEDVI should increase by about $3mL/m^2$, which is similar to the change observed on enrasentan in our study, although mean baseline LVEDVI ($129mL/m^2$) was much higher in SOLVD.[20] The patients in the current study had systolic dysfunction with impaired EF as determined by echo criteria. Post-randomization, EF was determined again at baseline by CMR and was in the lower range of normal. This discrepancy is partly methodological, a recent study indicating that CMR may give higher EF values than by echo.[21] The echo EF was chosen for screening rather than the CMR measurement to reflect routine clinical practice. Echo has also formed the basis for inclusion in previous large-scale multi-centre heart-failure trials.[22] There was a disparity in BNP levels at baseline and changes that may affect the differences for this parameter between the 2 drug regimens. An exclusion criterion for the study was use of ACE-inhibtor or AII- receptor antagonsist therapy in the 6 weeks prior to enrolment. Potentially however, if patients had discontinued such therapy in the 3-6 months prior to the study, some decompensation may have occurred producing adverse remodelling. No difference was noted, however, in such withdrawal between the two groups. Serial endothelin levels were not measured reflecting the poor correlation between overall endothelin levels and response to treatment. In addition, there is at present little evidence to indicate that reduction in endothelin-1 is a useful marker of therapy success.

Conclusion

In this unique study of the comparative effects of the mixed $ET_{A/B}$ receptor endothelin antagonist, enrasentan, with an ACE inhibitor, enalapril in asymptomatic patients with LV dysfunction, the results suggest that enrasentan does not appear to have favorable effects on ventricular remodelling and is not an effective substitute for an ACE inhibitor.

Sponsors

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Table legends

Table 1a. Baseline demographic characteristics of the randomized patients
Table 1b. Baseline cardiovascular conditions and medications of the randomized patients
Table 1c. Baseline hemodynamic and neurohormone parameters of the randomized patients
Table 2. Change from baseline in cardiac remodelling parameters after 6 months treatment. (mean changes ±SEM).
Table 3. Adverse events occurring in greater than 10% of patients in either group during the uptitration and maintenance phases

Figure legends

Figure 1
Comparison of change in LVEDVI after 6 months treatment

Figure 2
Comparison of change in cardiac index after 6 months treatment

Figure 3
Comparison of change in neurohormone levels after 6 months treatment (BNP- brain natriuretic peptide; NE –norepinephrine)

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Table 1a

Characteristic	Enrasentan (n=36)	Enalapril (n=36)	p value
Male gender	35 (97%)	31 (86%)	0.07
Caucasian	33 (92%)	34 (94%)	0.6
Age (years)			
≤65	22	19	0.5
65-74	13	16	0.5
≥75	1	1	0.8
Mean ± SEM	61.4 ±1.5	62.6 ±1.4	0.6
Range	35-76	41-77	
Weight (kg)			
Mean ± SEM	83.3 ±2.8	75.9 ±2.2	0.01
Range	59-121	53-102	
Height (cm)			
Mean ± SEM	173 ±1.4	169 ±1.3	0.008
Range	151-187	150-185	

Table 1b

Baseline conditions	Enrasentan (n=36)	Enalapril (n=36)	p value
Angina Pectoris	12 (33%)	14 (39%)	0.6
Hypertension	6 (17%)	4 (11%)	0.5
Diabetes (non-insulin dependent)	2 (5.6%)	4 (11%)	0.4
Diabetes (insulin dependent)	0	1 (2.8%)	0.3
Prior myocardial infarction	24 (67%)	25 (69%)	0.8
CABG	25 (69%)	22 (61%)	0.45
Hyperlipidemia	14 (39%)	13 (36%)	0.8
Conduction disorder	5 (14%)	7 (19%)	0.5
Peripheral vascular disease	3 (8.3%)	3 (8.3%)	0.7
AV Block	1 (2.8%)	4 (11%)	0.2
Concurrent Medications -			
Aspirin	32 (89%)	33 (92%)	0.7
Beta-blockers	9 (25%)	11 (31%)	0.6
Statin	5 (14%)	7 (19%)	0.5

Table 1c

Baseline characteristics, mean ±SEM	Enrasentan (n=36)	Enalapril (n=36)	P value
Body Surface Area (m^2)	1.92 ±0.04	1.81 ±0.04	0.02
Sitting systolic BP (mmHg)	132.6 ±2.9	135.9 ±2.6	0.3
Sitting diastolic BP (mmHg)	79.0 ±1.5	80.0 ±1.5	0.5
Sitting heart rate (bpm)	67.5 ±1.7	67.4 ±2.4	0.9
LV End Diastolic Volume Index (mL/m^2)	65.2 ±3.0	63.5 ±3.5	0.23
LV End Systolic Volume Index (mL/m^2)	29.1 ±2.5	24.9 ±2.6	0.1
LV Ejection Fraction	61% ±2.0	63% ±2.0	0.37
RV End Systolic Volume Index (mL/m^2)	26.1 ±1.1	21.8 ±1.1	0.005
RV End Diastolic Volume Index (mL/m^2)	69.7 ±1.7	64.4 ±2.0	0.004
LV Mass Index (g/m^2)	97.6 ±2.4	94.2 ±3.4	0.17
RV Mass Index (g/m^2)	25.9 ±0.8	24.7 ±0.7	0.15
LV Sphericity Index	0.63 ±0.01	0.63 ±0.02	0.95
Cardiac Index at rest ($L/min/m^2$)	2.37 ±0.1	2.14 ±0.1	0.03
Brain Natriuretic Peptide (pg/mL)	53.2 ±8.23	72.7 ±18.7	0.03
Norepinephrine (nmol/L)	2.13 ±0.14	2.26 ±0.17	0.4
Plasma Endothelin (fmol/mL)	1.64 ±0.46	1.14 ±0.31	0.3

Table 2

Change from baseline Mean ±SEM	Enrasentan n=31	Enalapril n=32	p value
LV EDVI mL/m^2	+3.9 ±1.8	-3.4 ±1.4	0.001
LV ESVI mL/m^2	-0.06 ±1.1	-2.0 ±0.93	0.2
LV EF %	+1.8 ±0.8	+1.5 ±1.0	0.8
Cardiac Index at rest L/m^2	+0.11 ±0.070	-0.096 ±0.069	0.04
LV mass index g/m^2	+0.67 ±1.6	-3.8 ±1.6	0.04

Table 3

Adverse event	Frequency of adverse event	
	Enrasentan	Enalapril
Up-titration		
Fatigue	5 (13.9%)	5 (13.9%)
Flushing	4 (11.1%)	0
Maintenance		
Respiratory	5 (13.9%)	4 (11.1%)
Viral infection	1 (2.8%)	5 (13.9%)
Back pain	4 (11.1%)	0

Figure 1

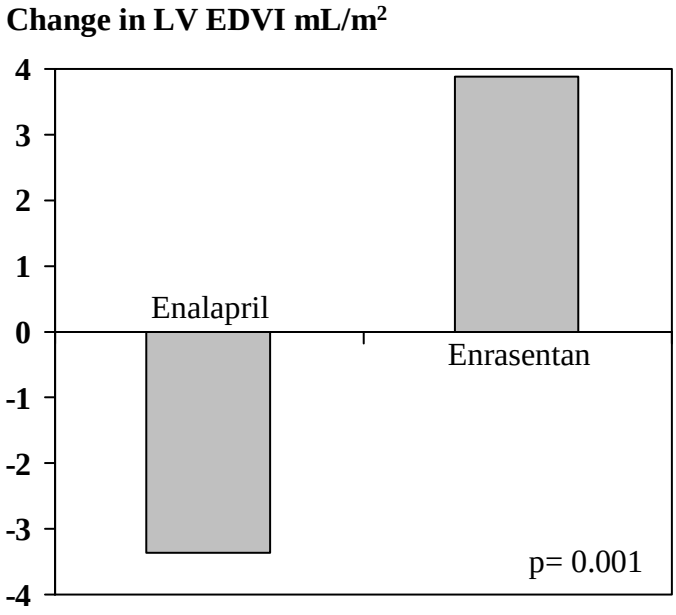

Figure 2

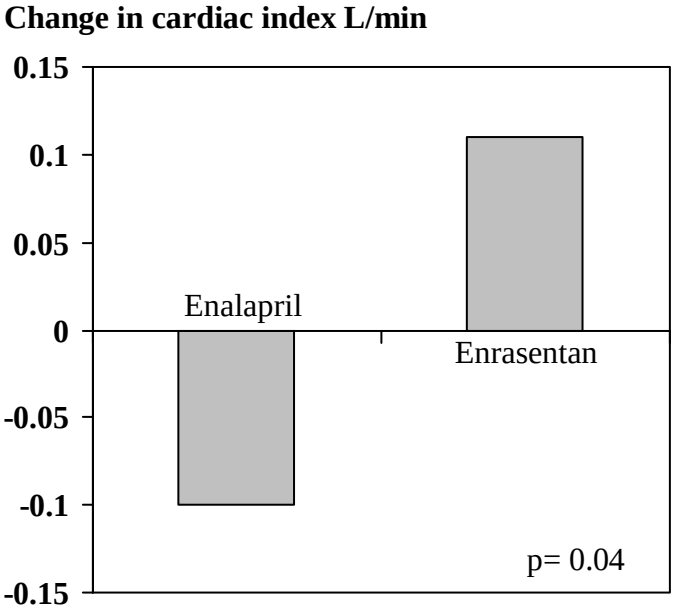

Figure 3