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DEAD LETTER OFFICE

Long-Term Effect of Endothelin Receptor Antagonism With Bosentan on the Morbidity and Mortality of Patients With Severe Chronic Heart Failure

Primary Results of the ENABLE Trials

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ABSTRACT

OBJECTIVES The objective of this clinical trial was to evaluate the long-term effect of endothelin receptor antagonism with bosentan on the morbidity and mortality of patients with severe chronic heart failure.

BACKGROUND Endothelin may play a role in heart failure, but short-term clinical trials with endothelin receptor antagonists have reported disappointing results. Long-term trials are lacking.

METHODS In 2 identical double-blind trials, we randomly assigned 1,613 patients with New York Heart Association functional class IIIb to IV heart failure and an ejection fraction <35% to receive placebo or bosentan (target dose 125 mg twice daily) for a median of 1.5 years. The primary outcome for each trial was clinical status at 9 months (assessed by the hierarchical clinical composite); the primary outcome across the 2 trials was death from any cause or hospitalization for heart failure.

RESULTS Bosentan did not influence clinical status at 9 months in either trial ($p = 0.928$ and $p = 0.263$). In addition, 321 patients in the placebo group and 312 patients in the bosentan group died or were hospitalized for heart failure (hazard ratio [HR]: 1.01; 95% confidence interval [CI]: 0.86 to 1.18; $p = 0.90$). The bosentan group experienced fluid retention within the first 2 to 4 weeks, as evidenced by increased peripheral edema, weight gain, decreases in hemoglobin, and an increased risk of hospitalization for heart failure, despite intensification of background diuretics. During follow-up, 173 patients died in the placebo group and 160 patients died in the bosentan group (HR: 0.94; 95% CI: 0.75 to 1.16). About 10% of the bosentan group showed meaningful increases in hepatic transaminases, but none had acute or chronic liver failure.

CONCLUSIONS Bosentan did not improve the clinical course or natural history of patients with severe chronic heart failure and but caused early and important fluid retention. (J Am Coll Cardiol HF 2017;5:317–26) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval(s)

ET_A = endothelin type A

HR = hazard ratio(s)

Endothelin-1 is a potent vasoconstrictor that may exert adverse biological and pathophysiological effects in heart failure (1–4). The peptide leads to vasoconstriction, causes salt and water retention, enhances the actions of detrimental neurohormonal systems, and promotes myocardial hypertrophy and remodeling (2–12). Antagonism of endothelin receptors retards the development and progression of heart failure in experimental models of the disease; in these studies, long-term endothelin receptor blockade reduced the magnitude of left ventricular dilatation, attenuated the progressive impairment of systolic function, and prolonged survival (1–4,12–14).

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Despite favorable effects reported in the laboratory, endothelin antagonism has not produced clinical benefits in patients with chronic heart failure. Short-term treatment with these drugs has led to immediate hemodynamic improvement (15,16), but studies of intermediate duration with truncated follow-up have reported minimal benefits and an increased risk of deleterious effects (17–20). The most worrisome adverse event seen to date in clinical trials of endothelin antagonists has been early fluid retention and worsening of heart failure (17–19,21), which has been attributed to initiation of treatment with high doses of these drugs, a phenomenon reminiscent of experience with beta-blockers (17,22). In the case of beta-blockers, the consequences of early worsening were minimized and the likelihood of clinical improvement was enhanced when therapy was initiated at low doses, doses were increased gradually, and fluid retention was prevented by aggressive adjustment of diuretics (22,23). Such strategies were not consistently followed in earlier trials with endothelin antagonists, which may explain why early worsening of heart failure was short-lived and followed by clinical improvement in 1 trial (17), but persisted and became more marked with prolonged follow-up in another study (18).

The ENABLE (Endothelin Antagonist with Bosentan and Lowering of Events) trials were carried out to determine whether low doses of the dual endothelin receptor antagonist, bosentan, when used together with early aggressive diuresis, might avoid the risk of early deterioration and have a favorable effect on the natural history of patients with chronic heart failure.

METHODS

The ENABLE trial program was carried out as 2 identical studies of similar size, 1 in Europe and Australia (ENABLE-1) and 1 in North America (ENABLE-2). The trials were conducted from June 1999 through January 2002.

STUDY OVERSIGHT. The steering committee, in conjunction with the sponsor, developed and amended the protocol, oversaw the recruitment of patients and the analysis of data, and provided an independent interpretation of the results. An independent data monitoring committee reviewed the safety of the patients and the results of interim analyses. A blinded clinical events committee classified all hospitalizations >24 h in duration and all permanent discontinuations of treatment. Data were analyzed according to a predefined statistical analysis plan, and an independent statistician verified and replicated the analyses. The first author, who had unrestricted access to the data, prepared the drafts of the manuscript, which were then reviewed and edited by all authors. The authors collectively submitted the manuscript for publication and assume responsibility for the accuracy and completeness of the analyses.

STUDY PATIENTS. Patients were eligible if they had symptoms of heart failure at rest or on minimal exertion (New York Heart Association functional class IIIb or IV) for at least 2 months due to an ischemic or nonischemic cardiomyopathy. In addition, patients were required to have a left ventricular ejection fraction <35%, to have received treatment with diuretics and an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker (unless intolerant or contraindicated), and either to have been hospitalized for heart failure within 12 months or to have been unable to walk >375 m during a 6-min corridor walk test. Treatment with a beta-blocker was encouraged; if prescribed, the dose was kept

London, United Kingdom. This study was funded by Actelion. Dr. DeMets provides consulting services to and receives honoraria for serving on data monitoring committees for industry-sponsored clinical trials. Dr. Roux is an employee of Actelion. Dr. Swedberg provides consulting services to Amgen, AstraZeneca, Novartis, and Servier. Each author had a consulting and/or research and/or employment relationship with the sponsor at the time that the trials were ongoing. Except for S. Roux (an employee of Actelion), none of these relationships have been active for at least the past 5 years. Drs. Krum and Kiowski are deceased.

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constant for the prior month. The use of digoxin, amiodarone, spironolactone, nitrates, and hydralazine was allowed at the discretion of the investigator. For 72 h before randomization, no intravenous drugs for heart failure were given and doses of oral cardiovascular medications were kept constant.

Patients were excluded if they had the following: 1) active myocarditis, constrictive pericarditis, hypertrophic cardiomyopathy, or congenital heart disease; 2) hemodynamically important primary valvular heart disease, unless corrected by a properly functional prosthetic valve; 3) myocardial infarction, unstable angina, cardiac revascularization procedure, stroke, or transient ischemic attack within 1 month; 4) history of resuscitated sudden death, sustained ventricular tachycardia, or ventricular fibrillation within 12 months unless occurring within 24 h of an acute myocardial infarction or treated with an implantable cardiac defibrillator; 5) prior cardiac transplant, surgical remodeling procedure, left ventricular assist device, or cardiomyoplasty or expectation of any of these procedures in the next 12 months; 6) third-degree atrioventricular block or symptomatic bradyarrhythmias, unless treated with a permanent pacemaker; 7) scheduled outpatient treatment with an intravenously administered vasodilator drug or positive inotropic agent; 8) heart rate <50 or >130 beats/min; 9) systolic blood pressure <85 mm Hg; and 10) treatment within 4 weeks with drugs known to have adverse effects on heart failure (encainide, flecainide, disopyramide, propafenone or moricizine, pinacidil, minoxidil, or oral positive inotropic drug other than digoxin). In addition, patients were not to participate if they had the following: 1) primary pulmonary disease of sufficient severity to have been the primary reason for dyspnea; 2) serum creatinine >3.0 mg/dl; 3) hepatic transaminases >3× the upper limit of normal; 4) hemoglobin concentration, hematocrit, or leukocyte count of more than 30% outside the normal range; 5) current use of drugs known to be excreted by the bile salt export pump (glibenclamide [glyburide], cyclosporine A, troglitazone); 6) any investigational drug use within 1 month or prior use of bosentan; and 7) any condition that would interfere with the study conduct or any illness other than heart failure than might limit life expectancy within 3 years.

The protocol was approved by the institutional review boards of all 151 participating institutions; written informed consent was obtained from all patients.

STUDY DESIGN. Following the initial evaluation, patients were randomly assigned (double-blind, 1:1 allocation) to receive either oral bosentan or matching placebo, in addition to their usual medications. The initial dose was 62.5 mg or placebo twice daily, which was increased after 4 weeks to 125 mg twice daily. These hemodynamically active doses were one-fourth of those targeted in an earlier placebo-controlled trial with bosentan in heart failure (17). In addition, patients were observed for signs and symptoms of fluid retention during the first 2 months of treatment, which (if seen) was aggressively treated with diuretics.

Clinical status and laboratory variables were evaluated during each week for the first month and every 2 to 3 months thereafter until the end of the study. Patients were followed continuously for the occurrence of death or worsening heart failure, regardless of whether they continued to take the study medications. During the entire duration of follow-up, if adverse effects occurred, the dose of the study medication could be reduced or discontinued, but investigators were encouraged to reinstitute treatment at a later time. If the patient's condition warranted, physicians could use any clinically-indicated interventions, but patients were not permitted to receive open-label bosentan.

STUDY ENDPOINTS. The primary endpoint for each of the ENABLE trials (ENABLE-1 and ENABLE-2) was the change in clinical status, assessed by the hierarchical clinical composite (24), after 9 months of therapy (a 2-sided alpha of 0.04 was assigned to this endpoint in each trial). For this assessment, each patient was classified as improved, unchanged, or worse. Patients were considered to be worse if, during the 9-month period following randomization, they had died; had been hospitalized for or with worsening heart failure (for ≥24 h and requiring intensification of therapy); or had permanently discontinued the study drug because of or accompanied by worsening of heart failure. Patients were considered improved if, after 9 months, their New York Heart Association functional class had improved substantially (from class IV to class IIIa or II or from class IIIb to class II) or had moderate or marked improvement in the patient global assessment and had not experienced an event that would qualify them as worse. Patients were considered as unchanged if they were classified as neither improved nor worse.

To evaluate the effect of bosentan on the risk of a major clinical event, the occurrence of such events in both studies was prospectively combined and assigned a 2-sided alpha of 0.01. The primary endpoint for the combined trials was the risk of all-cause mortality or hospitalization for heart failure. To qualify as a component of the primary endpoint, a hospitalization was required to be >24 h in duration

TABLE 1 Baseline Demographic and Clinical Characteristics

	Placebo (n = 807)	Bosentan (n = 804)
Age, yrs	66.9 ± 11.0	67.5 ± 11.0
Men/women	602/205	595/209
Race, black	47 (5.8)	53 (6.6)
Left ventricular ejection fraction	25.2 ± 6.3	24.8 ± 6.5
Etiology of heart failure, ischemic	575 (70.9)	542 (67.4)
Hospitalization for heart failure within 12 months	333 (41.3)	324 (40.7)
NYHA functional class IIIb/IV	734/73	730/74
History of coronary artery surgery	256 (31.7)	293 (36.4)
History of diabetes	265 (32.8)	271 (33.7)
Use of loop diuretics	769 (95.3)	767 (95.4)
Use of ACE inhibitor or angiotensin receptor blocker	773 (95.8)	772 (96.0)
Use of beta-blocker	404 (50.1)	417 (51.9)
Use of digitalis glycosides	460 (57.0)	468 (58.2)
Use of spironolactone	199 (24.7)	222 (27.6)
Use of nitrates	387 (44.2)	358 (44.5)
Use of hydralazine	17 (2.1)	16 (2.0)
Use of aspirin	410 (50.8)	391 (48.6)
Use of implantable cardioverter-defibrillator	45 (5.6)	66 (8.2)
Systolic blood pressure, mm Hg	119.8 ± 17.5	121.2 ± 18.5
Heart rate, beats/min	74.1 ± 11.6	74.3 ± 11.8
Serum creatinine, mg/dl	1.3 ± 0.4	1.3 ± 0.4

Values are mean ± SD, N/n, or n (%).
ACE = angiotensin-converting enzyme; NYHA = New York Heart Association.

and be triggered or accompanied by worsening heart failure at the time of admission that was treated with an intravenous medication. The major secondary endpoint for the combined trials was all-cause mortality.

STATISTICAL ANALYSIS. The sample size for the study was estimated separately for the 2 coprimary endpoints. For the hierarchical clinical composite, for both ENABLE-1 and ENABLE-2, it was anticipated that bosentan would increase the likelihood of improvement by 50% and decrease the likelihood of worsening by 33%, assuming that the proportion of patients who improved or worsened in the placebo group was 20% and 30%, respectively. Based on an alpha of 0.04 (2-tailed, 90% power), the estimated sample size was 686 patients in each of the ENABLE trials (total of 1,372 patients). For the combined risk of all-cause mortality and hospitalization for heart failure for both trials combined, it was anticipated that bosentan would reduce the 1-year risk from 40% to 30%, with an alpha of 0.0094 (2-tailed, 0.01 adjusted for interim analyses, 90% power). Based on these assumptions, the trial required 589 primary endpoint events in the 2 treatment groups, which necessitated the enrollment of 1,236 patients. To test both primary hypotheses, the recruitment goal for the trial was set at 1,400 patients, who were to be followed until 600 patients had died for any reason or been hospitalized for heart failure and until the last patient had been followed for 9 months. A data and safety monitoring board periodically reviewed the unblinded results at 3 interim analyses and was empowered to recommend early termination of the program if it observed a treatment effect that exceeded the pre-specified boundaries.

Differences between treatment groups in the distribution of hierarchical categorical responses (primary endpoint) were tested for significance with the use of the Mann-Whitney *U* test. Cumulative survival curves were constructed by Kaplan-Meier survivorship methods, and differences between the curves were tested for significance by the log-rank statistic. Cox proportional hazards regression models were used to estimate bosentan-placebo hazard ratios (HRs) and their 95% confidence intervals (CIs), without covariate adjustment; to maintain consistency of the displays of morbidity and mortality, 99% CI were not used for the coprimary endpoint of all-cause death or heart failure hospitalization. All survival analyses included all randomized patients, and all events were assigned to the patient's randomized treatment group (according to the intention-to-treat principle). No nominal p values are reported.

RESULTS

A total of 1,613 patients were randomized into the trial: 808 to the placebo group and 805 to the bosentan group. Two patients (1 in each treatment group) withdrew consent prior to receiving the study medication and were excluded from all analyses. The 2 treatment groups were similar with respect to baseline characteristics (Table 1).

Most patients were successfully titrated to and maintained on target doses of placebo or bosentan. During follow-up, 19.3% patients in the placebo group and 24.8% patients in the bosentan group permanently discontinued treatment with the study medication; differences between the 2 groups were primarily related to differences in the frequency of reports of cardiac failure (4.6% vs. 2.2%, bosentan and placebo, respectively) and elevated liver transaminases (2.4% vs. 0.1%, bosentan and placebo, respectively). The median and maximum durations of follow-up were 1.5 and 2.4 years, respectively.

EFFECT OF BOSENTAN ON HIERARCHICAL CLINICAL COMPOSITE. There was no difference in the distribution of changes in clinical status (the primary endpoint) between patients in the placebo and bosentan groups, either in the European/Australian

TABLE 2 Hierarchical Clinical Composite at 9 Months

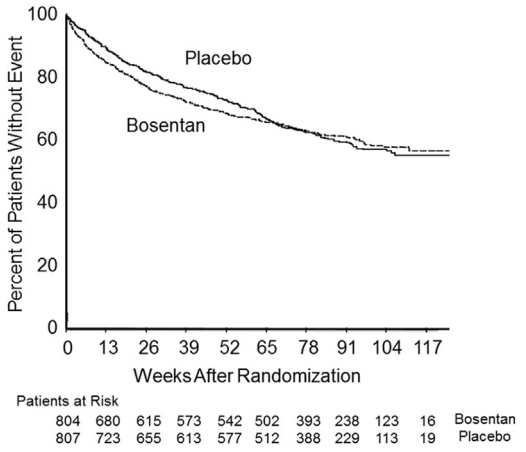
	ENABLE-1		ENABLE-2	
	Placebo (n = 409)	Bosentan (n = 405)	Placebo (n = 398)	Bosentan (n = 399)
Improved	79 (19.3)	97 (24.0)	93 (23.4)	98 (24.6)
Unchanged	231 (56.5)	194 (47.9)	203 (51.0)	172 (43.1)
Worse	99 (24.2)	114 (28.1)	102 (25.6)	129 (32.3)
p value	0.928		0.263	

Values are n (%).
ENABLE = Endothelin Antagonist with Bosentan and Lowering of Events trial.

trial (p = 0.928) or the North American trial (p = 0.263) (Table 2).

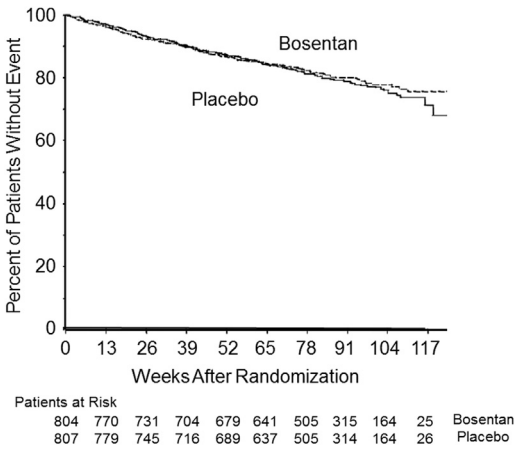
EFFECT OF BOSENTAN ON MORBIDITY AND MORTALITY. By intention-to-treat, there were 321 patients who died or were hospitalized for heart failure in the placebo group and 312 such patients in the bosentan group (HR: 1.01; 95% CI: 0.86 to 1.18; p = 0.90) (Figure 1). Time-to-first event plots for death or hospitalization for heart failure revealed an early increase in risk in patients randomized to bosentan, which emerged largely during the first 4 weeks following randomization (Figure 1). This risk was entirely related to an early increase in the risk of hospitalizations for heart failure, because an increase in risk early in treatment was not seen in the time-to-event plot for mortality (Figure 2). During follow-up, 173 patients died in the placebo group and 160 patients died in the bosentan group (HR: 0.94; 95% CI: 0.76 to 1.16). The 2 major modes of death (according to the investigator) were pump failure in 128 patients and sudden death in 98 patients, with no difference between the treatment groups. Pre-specified subgroup analyses did not identify any baseline characteristic that exerted an influence on the magnitude or direction of the difference between the 2 treatment groups on either primary endpoint (Figure 3).

FIGURE 1 Freedom From All-Cause Mortality or Hospitalization for Heart Failure (Coprimary Endpoint)



Kaplan-Meier plots of freedom from the primary endpoint of all-cause mortality or hospitalization for heart failure.

FIGURE 2 Freedom From All-Cause Mortality

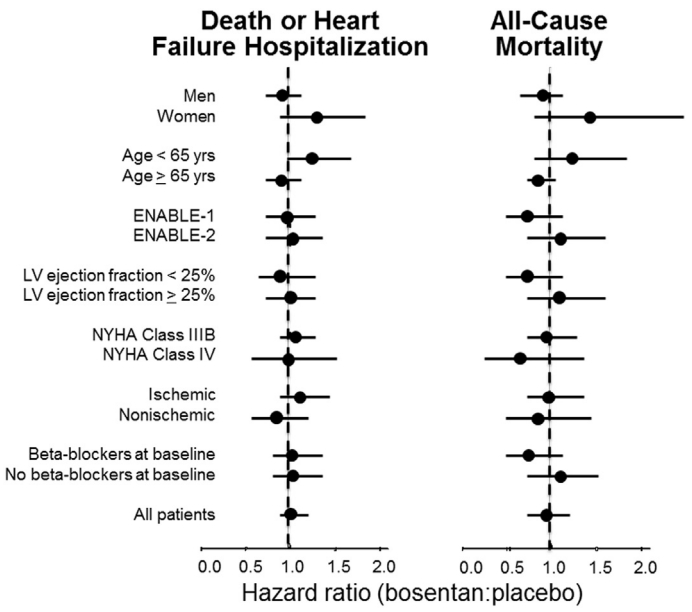


Kaplan-Meier plots of freedom from all-cause mortality.

ADVERSE EVENTS AND CHANGES IN PHYSIOLOGICAL AND LABORATORY VARIABLES. Adverse events occurring in ≥5% of patients in the bosentan group are summarized in Table 3. When compared with the placebo group, patients in the bosentan group were more likely to report peripheral edema, anemia, or decreased hemoglobin, headache, and abnormal liver function tests, but they were less likely to report renal impairment or renal failure. The increased risk of edema in the bosentan group was apparent within 2 weeks of the start of the study (when patients were receiving low starting doses of the study medications) and persisted throughout the duration of follow-up (Online Figure 1). In contrast, a decrease in the risk of renal impairment or renal failure in the bosentan group emerged after 3 to 6 months (Online Figure 2).

When compared with placebo, systolic and diastolic blood pressures were 1 to 2 mm Hg lower in the bosentan group (Online Figure 3) with no differences in heart rate. Body weight increased in the bosentan group when compared with the placebo group (difference of ≈ 0.5 kg between the groups) (Figure 4).

FIGURE 3 HR of Effect of Bosentan on Death or Heart Failure Hospitalization or on All-Cause Mortality in Subgroups



Hazard ratio (HR) and 95% confidence intervals for effect of bosentan in subgroups defined by various baseline characteristics. **(Left)** The effect on the primary endpoint of all-cause mortality or hospitalization for heart failure is shown. **(Right)** The effect on all-cause mortality is shown. HR <1.00 indicates an effect that favors bosentan; HR >1.00 indicates an effect that favors placebo. ENABLE = Endothelin Antagonist with Bosentan and Lowering of Events trial; LV = left ventricular; NYHA = New York Heart Association.

TABLE 3 Adverse Events With a Frequency ≥5% in Bosentan Group

	Placebo (n = 807)	Bosentan (n = 804)
Heart failure	317 (39.3)	304 (37.8)
Dyspnea	200 (24.8)	203 (25.2)
Dizziness	146 (18.1)	142 (17.7)
Chest pain	133 (16.5)	139 (17.3)
Fatigue	124 (15.4)	105 (13.1)
Hypotension	88 (10.9)	88 (10.9)
Peripheral edema	66 (8.2)	83 (10.3)
Anemia	42 (5.2)	81 (10.1)
Cough	93 (11.5)	79 (9.8)
Headache	53 (6.6)	71 (8.8)
Nausea	83 (10.3)	66 (8.2)
Upper respiratory infection	43 (5.3)	62 (7.7)
Abnormal hepatic function	27 (3.3)	60 (7.5)
Renal failure	73 (9.0)	57 (7.1)
Diarrhea	69 (8.6)	54 (6.7)
Angina pectoris	49 (6.1)	54 (6.7)
Pneumonia	62 (7.7)	52 (6.5)
Urinary tract infection	41 (5.1)	51 (6.3)
Weakness	63 (7.8)	50 (6.2)
Renal impairment	70 (8.7)	49 (6.1)
Arthralgia	40 (5.0)	49 (6.1)
Atrial fibrillation	47 (5.8)	46 (5.7)
Nasopharyngitis	43 (5.3)	46 (5.7)
Bronchitis	42 (5.2)	45 (5.6)
Back pain	43 (5.3)	43 (5.3)
Decreased hemoglobin	17 (2.1)	43 (5.3)
Pulmonary edema	33 (4.1)	42 (5.2)
Myocardial infarction	42 (5.2)	41 (5.1)

Values are n (%).

The increase in body weight was apparent within 2 to 4 weeks of the start of therapy and was maintained for the duration of follow-up.

Patients in the bosentan group had decreases in hemoglobin concentrations (difference of ≈0.6 g/l between the groups) (**Figure 4**), as well as in erythrocyte count and hematocrit, which were apparent at 2 weeks and persisted throughout the trial. In contrast, increases in serum creatinine were less marked in the bosentan group (Online Figure 4).

During the trial, 9.7% of the patients in the bosentan group and 3.4% of the patients in the placebo group experienced an increase in serum levels of hepatic transaminases to a level >3× the upper limit of normal. This increase in risk was apparent when the analysis was confined to patients with an increase of >5× or >8× the upper limit of normal. These elevations were observed during the first 6 months of therapy (Online Figure 5) and dissipated despite continued treatment or following discontinuation of the study medication. No patient developed acute or chronic liver disease.

DISCUSSION

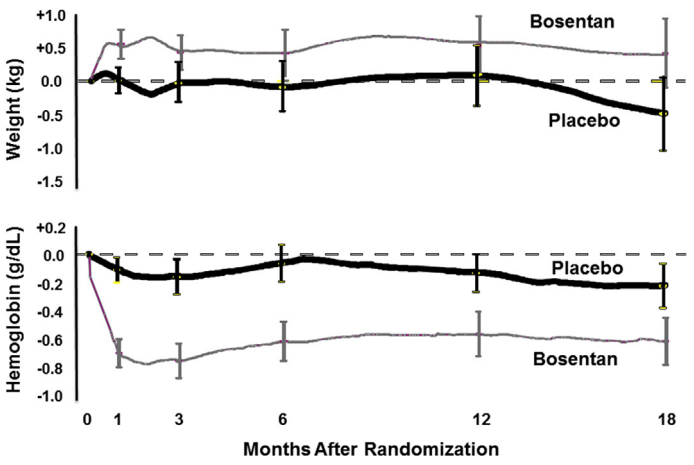
In the current trial, dual receptor endothelin antagonism with bosentan did not have a favorable effect on the natural history of heart failure, as assessed by the risk of death or the combined risk of death or hospitalization for heart failure. Instead, the administration of bosentan was accompanied by an early risk of worsening heart failure leading to hospitalization, a risk that was similar to that reported in earlier trials (17,18,21). This risk was seen even though the trial initiated treatment with low doses of the drug and investigators made a concerted effort to detect and treat fluid retention during the 8 weeks following initiation of treatment. Such strategies had been successful in managing early worsening of heart failure during the initiation of treatment with beta-blockers (22).

These results fail to confirm the possibility raised in an earlier trial (REACH-1 [Research on Endothelin Antagonism in Chronic Heart failure] trial) that the

response to treatment with bosentan might be biphasic, with early worsening followed by a period of clinical benefit. In the REACH-1 trial (17), short-term administration of the drug was associated with an increased risk of worsening heart failure, which was most marked in patients who received high doses during the first weeks of treatment. Continuation of therapy with the drug, however, was accompanied by dissipation of this early risk, followed by the appearance of favorable clinical effects after 6 months; the longer the duration of follow-up, the more likely were bosentan-treated patients to demonstrate improvement and the less likely were they to experience clinical deterioration. However, the finding of delayed benefit was based on a post hoc analysis of a small number of events observed in a subgroup of patients—characteristics that increase the likelihood of the play of chance. No biphasic response was seen in a dose-ranging trial with the more endothelin type A (ET_A) receptor-selective antagonist enrasentan (18), which noted an excess early risk of worsening heart failure, which persisted for the duration of follow-up (**Figure 5**).

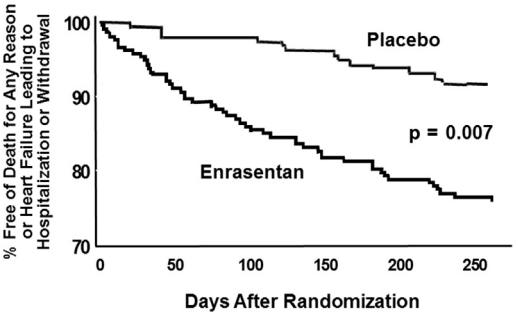
The mechanisms leading to early worsening heart failure in patients treated with endothelin antagonists (17,19,25) have not been fully elucidated. Receptor antagonism may interfere with the positive inotropic and negative lusitropic effects of endothelin (26) or may have adverse effects on neurohormonal activation or cardiac remodeling (27). In addition, endothelin receptor antagonists dilate the pulmonary arterioles (28), and thus, may interfere with the restraint that pulmonary vasoconstriction normally exerts on blood flow into the lungs and the transudation of fluid into alveoli when pulmonary venous pressures are increased (29,30). In the current trial and earlier studies (17,19,21), however, early worsening heart failure was related to fluid retention. Within days following initiation of treatment, patients in the bosentan group experienced an increase in body weight, a decrease in hemoglobin, and the appearance of peripheral edema. This fluid retention is related to antagonism of endothelin receptors in the renal tubules, which normally act to mediate sodium excretion (31–34); such receptors may be particularly dysregulated in heart failure (35). When the ENABLE trials were designed, early fluid accumulation in the bosentan group was anticipated (17), and investigators were specifically instructed to intensify diuretics to minimize sodium retention. However, such a strategy did not prevent early worsening heart failure in the current study.

FIGURE 4 Changes in Body Weight and Hemoglobin in the Placebo and Bosentan Groups During Double-Blind Therapy



Changes in body weight **(upper)** and hemoglobin **(lower)** in the placebo and bosentan treatment groups (depicted in **dark black lines** and **light gray lines,** respectively) at various time points during the first 18 months following randomization.

FIGURE 5 Effect of Enrasentan on All-Cause Mortality or Heart Failure Leading to Hospitalization or Permanent Withdrawal in the ENCOR Trial



Kaplan-Meier plots of freedom from all-cause mortality or heart failure leading to hospitalization or withdrawal of treatment in the ENCOR (Enrasentan Cooperative Randomized) trial. In this study, 419 patients with New York Heart Association functional class II to III heart failure being treated with diuretics and angiotensin-converting enzyme inhibitors (often with digoxin and beta-blockers) were randomized (double-blind) to placebo, to high dose angiotensin-converting enzyme inhibition or to 1 of 4 doses of enrasentan (30 to 90 mg daily). The study duration was 9 months (3 months uptitration followed by 6 months at target doses). The primary endpoint was a hierarchical clinical composite (24). Because there was no dose-response relationship in the enrasentan groups, these 4 groups are combined in the analysis. Enrasentan-treated patients worsened, withdrew more frequently because of adverse events (21.2% vs. 8.3% for the enrasentan and placebo groups, respectively), and had a greater mortality (51).

Patients in the bosentan group were less likely to experience renal insufficiency or failure than were patients in the placebo group. This difference was also reflected in a lower serum creatinine in the bosentan group for the duration of follow-up. A benefit on renal function was seen even though patients in the bosentan group had lower blood pressures and were more likely to have their diuretic therapy intensified to counteract the occurrence of fluid retention. Dual endothelin receptor antagonism has been shown to enhance renal plasma flow in experimental models of heart failure (36,37).

A reversible elevation in serum levels of hepatic transaminases was observed in about 10% of the patients in our study. Bosentan is primarily metabolized in the liver and excreted into the bile using the bile salt export pump (38). Administration of drugs that use this export pump may retard the secretion of and thereby cause the intrahepatic accumulation of bile acids, which may exert toxic effects on hepatocytes, particularly when they are given together with other drugs that inhibit the pump (39,40). Such a mechanism would be expected to be ameliorated by reducing the dose of bosentan and by the avoidance of the coadministration of drugs that might competitively use the export pump. However, despite the utilization of such strategies in the current trial, long-term use of bosentan was still associated with a nearly 3-fold increase in the frequency of transaminase elevations. These elevations, however, were not associated with the development of acute or chronic liver disease.

Do our findings refute the hypothesis formulated in experimental studies that endothelin plays a role in the evolution and progression of heart failure? Endothelin antagonism may represent an example of drug benefits reported in experimental heart failure, which could not be confirmed in the clinic (41). Alternatively, endothelin may be important in heart failure under conditions different than those studied in the current trial. Some have proposed that effective and safe endothelin antagonism requires agents that act selectively on the ET_A receptor (5,42–44). However, trials with relatively selective ET_A receptor antagonists in patients with heart failure have yielded disappointing results (19,20), and selective agents do not mitigate the risk of fluid retention (32). Others may suggest that the dose of bosentan used in our trials was too high (although it was far lower than those used in earlier studies) (45,46); yet, ultra-low doses of bosentan (e.g., 8 mg) produce few hemodynamic benefits but are still associated with fluid retention (45). Still others might postulate that the risk of fluid retention would be minimized if endothelial antagonists were administered to patients with less severe heart failure, but there is currently little evidence that such patients show meaningful long-term benefits (20,27).

We conclude that endothelin antagonism does not play a role in the current treatment of chronic heart failure. However, this pharmacological action is of established value in the treatment of patients who have pulmonary hypertension due to a primary pulmonary vascular disorder in the absence of left heart failure (pulmonary arterial hypertension). Such patients show improved exercise tolerance and symptoms and a reduced risk of disease progression (47–49). Given these benefits, physicians should distinguish pulmonary arterial hypertension from pulmonary hypertension associated with chronic heart failure before prescribing endothelin receptor antagonists for long-term use (45,50).

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KEY WORDS bosentan, clinical trial, endothelin, heart failure, placebo

APPENDIX For a list of the ENABLE committees and investigators as well as supplemental figures, please see the online version of this article.