Endothelin Receptor Blockers in Cardiovascular Disease

Stuart Rich, MD; Vallerie V. McLaughlin, MD

Abstract—The endothelin (ET) system is comprised of 4 active ETs, with ET-1 being the predominant isoform in the cardiovascular system. Because of the potent vasoconstricting and mitogenic effects of ET-1 and its involvement in various cardiovascular diseases, blockade of the ET receptor has received considerable attention. ET receptor antagonism has been demonstrated to be beneficial in patients with pulmonary hypertension. The nonselective ET receptor antagonist bosentan improves exercise capacity and increases time to clinical worsening in patients with pulmonary arterial hypertension. The selective ET A receptor antagonist sitaxsentan also improves hemodynamics and exercise capacity in patients with pulmonary arterial hypertension. Results with ET receptor antagonists in congestive heart failure have been disappointing. Although some studies have suggested benefit, larger studies have been neutral. The use of ET receptor antagonists for other conditions has not been fully explored. Future studies with the use of ET receptor antagonists as part of a multidrug regimen are also needed. (Circulation. 2003;108:2184-2190.)

Key Words: endothelin ▪ heart failure ▪ pulmonary arterial hypertension

The endothelin (ET) system, like other vascular regulatory systems, consists of a parent peptide that undergoes enzymatic activation and exerts its biologic effects by modulating specific receptors. Of the 4 active ETs (ET 1 through 4), ET-1 is the predominant isoform in the cardiovascular system, which is generated through the cleavage of prepro ET-1 to big ET-1 and then to ET-1 by the action of ET-converting enzymes. ET-1 is found in endothelial cells and is released toward the vascular smooth muscle consistent with a paracrine role, but it is also produced by smooth muscle cells and cardiomyocytes. ET-1 has vasoconstrictive and mitogenic effects, stimulates the production of growth factors such as vascular endothelial growth factor and basic fibroblast growth factor, and potentiates the effects of transforming growth factor-β and platelet-derived growth factor. Chronic ET-1 stimulation can result in myocardial fibrosis and hypertrophy and vascular fibrosis with extracellular matrix proliferation. In the lung, ET-1 is abundantly expressed in the pulmonary vasculature and appears to play an important role in the regulation of pulmonary vascular tone. ET-1 is also produced in leukocytes where it influences the production of a wide range of cytokines in the inflammatory response. ET is regulated in an autocrine fashion by physiochemical factors such as blood flow, pulsatile stretch, shear stress, and pH. Acute hypoxia leads to selective stimulation of the ET-1 gene and ET synthesis in the pulmonary vasculature. ET-1 biosynthesis is also stimulated by low-density lipoprotein cholesterol and glucose, and thrombin. Endogenous inhibitors of ET-1 synthesis include nitric oxide, prostacyclin, atrial natriuretic peptides, and estrogens.

ET-1 exerts its major vascular effects through activation of 2 distinct G protein coupled ET A and ET B receptors. ET A receptors are found in the medial smooth muscle layers of the blood vessels, and atrial and ventricular myocardium. When stimulated, the ET A receptors induce vasoconstriction and cellular proliferation by increasing intracellular calcium. ET B receptors are localized on endothelial cells and, to some extent, smooth muscle cells and macrophages. The activation of ET B receptors stimulates the release of nitric oxide and prostacyclin and prevents apoptosis. Normally, there is a balance between production and clearance, which is mediated by the ET B receptor such that circulating ET is at a low level. In normal states, it appears that stimulation of the ET A receptor on the smooth muscle cell causes vasoconstriction and mitogenic effects that are opposed by stimulation of the ET B receptor on the endothelial cell (see Figure 1). Thus, in the absence of disease, the influence of ET-1 on the circulation will be manifest by the regulatory state of the ET A and ET B receptors. In pathological states, however, there could be upregulation of the ET B receptors located on smooth muscle cells that function similar to the ET A receptor, which amplify the vasoconstrictive and mitogenic effects of ET-1.

There could also be underexpression of the ET A receptor on the endothelial cell.

ET Receptor Blockade for Cardiovascular Disease

Antagonists have been developed that can selectively block ET A or ET B receptors, or both. It remains unclear whether selective ET A or nonselective ET antagonists will confer the most therapeutic benefit. There is experimental evidence that
The interaction between ET-1 on endothelial and smooth muscle cells, and the ETA and ETB receptors is shown. The potential role of ET-1 in the regulation of vascular tone becomes apparent. In normal states, the endothelial cell responds to stimulation from cytokines, growth factors, wall stress, and hypoxia by increasing ET-1 production. The net effect will reflect the expression of the ETA receptor on the vascular smooth muscle cell producing constriction, proliferation, and migration, and the ETB receptor on the endothelial cell, which produces vasodilation and growth inhibition indirectly through stimulation of nitric oxide and prostacyclin production. In pathological states, upregulation of the ETA receptor on the vascular smooth muscle cell (and possible downregulation of the ETB receptor on the endothelial cell) will result in a predominate effect of ET producing vasoconstriction, smooth muscle cell proliferation, and migration. ECE indicates ET-converting enzyme; NO, nitric oxide; NOS, nitric oxide synthase; PGI2, prostacyclin; CAMP, cyclic AMP; and cGMP, cyclic GMP.

Both ETA and ETB receptors modulate ET-1 responses in small muscular pulmonary arteries of humans, and that combining blockade of both receptor subtypes can block ET-1-induced pulmonary vasoconstriction. Nevertheless, ETA selective antagonists have been effective in improving cardiovascular function and structure in numerous experimental animal studies, suggesting therapeutic efficacy with ETA receptor blockade alone. It has been demonstrated that ETB receptor blockade alone impairs pulmonary clearance of ET-1 and reduces nitric oxide-mediated vasodilation. No clear clinical use for selective ETB antagonists has yet been defined.

**Pulmonary Hypertension**

ET-1 has been implicated as a growth factor that is expressed in pulmonary arterial hypertension (PAH). There is increasing evidence that pulmonary vascular smooth muscle cells as well as endothelial cells synthesize and release ET-1, particularly when stimulated by cytokines. ET-1 is also produced in the lung in response to increased pressure. Gaia et al described an increase expression of ET-1 mRNA in pulmonary vascular endothelial cells of patients with pulmonary hypertension. A significant correlation between serum levels of ET and pulmonary vascular resistance, right atrial pressure, and oxygen saturation in patients with pulmonary hypertension has been reported. In thromboembolic pulmonary hypertension, it was shown that there is upregulation of the ETB receptor in the pulmonary artery.

Bosentan is the most widely tested ET receptor antagonist in pulmonary arterial hypertension. Its first reported use was in 7 female patients, 5 with primary pulmonary hypertension and 2 with pulmonary hypertension associated with scleroderma in an open-label dose-ranging study. Bosentan infused intravenously in 50-, 150-, and 300-mg doses at 2-hour intervals produced a dose-dependent fall in pulmonary artery pressure and pulmonary vascular resistance and a slight increase in cardiac index. The trial, however, was prematurely terminated when 2 of the 7 patients died within 36 hours of entering the second part of the study.

Channick et al reported the results of a 12-week randomized, placebo-controlled, double-blind trial in 32 patients with primary pulmonary hypertension and PAH associated with scleroderma (Table 1). The primary end point of the trial, 6-minute walk, improved in the patients receiving bosentan by 70 m, whereas there was no change seen in those randomized to placebo. Treatment with bosentan also improved cardiopulmonary hemodynamics and functional class. Over the 12-week period, there was also a mean improvement in cardiac index of 0.5 L · min⁻¹/(mol/L)², whereas there was a decrement of 0.5 L · min⁻¹/(mol/L)² in the placebo group. There was no significant effect on in pulmonary artery pressure. This pilot study led to the large multicenter, randomized trial referred to as BREATHE-1 (Bosentan Randomized Trial of Endothelin Antagonist Therapy). Rubin and colleagues reported the results of 213 patients with PAH randomized to receive placebo or bosentan titrated to a target dose of either 125 mg twice per day or 250 mg twice per day for 16 weeks. After 16 weeks of treatment, the 6-minute walk distance improved by 36 m in the bosentan group, whereas there was a deterioration of 8 m in the placebo group. A secondary end point of the trial was the composite end point of time to clinical worsening, which included death, lung

**TABLE 1.** Endothelin Receptor Blockers for Pulmonary Hypertension—Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Comments</th>
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<tbody>
<tr>
<td>351</td>
<td>Bosentan 62.5 mg twice per day for 4 weeks, then 125 mg twice per day for 8 weeks (n=21) vs placebo (n=11)</td>
<td>6 MW increased 70 m PVR reduced 2.8 units</td>
<td>2 patients had increased LFTs</td>
</tr>
<tr>
<td>BREATHE-1</td>
<td>Bosentan 62.5 mg twice per day for 4 weeks then 125 mg twice per day for 12 weeks (n=74) or 250 mg twice per day for 12 weeks (n=70) vs placebo (n=69)</td>
<td>6 MW increased 44 m</td>
<td>No hemodynamic data</td>
</tr>
<tr>
<td>BREATHE-2</td>
<td>Bosentan 125 mg twice per day for 16 weeks (n=20) vs placebo (n=10) in patients starting epoprostenol</td>
<td>No effect on exercise or hemodynamics</td>
<td>2 deaths, 1 worsening in bosentan group</td>
</tr>
<tr>
<td>STRIDE-1</td>
<td>Sitaxsentan 100 mg (n=60) or 300 mg (n=60) vs placebo (n=60) for 12 weeks</td>
<td>Improvement in peak VO₂ and 6 MW in 300-mg group</td>
<td>Increased LFTs in 21% patients at 300-mg dose</td>
</tr>
</tbody>
</table>

6 MW indicates 6-minute walk test; PVR, pulmonary vascular resistance; and LFTs, liver function tests.
transplantation, hospitalization for pulmonary hypertension, lack of improvement or worsening leading to discontinuation, or need for epoprostenol rescue therapy. At the end of the study, there was less clinical worsening in the bosentan group versus the placebo group with the effect more pronounced in the 250-mg twice-per-day dose than the 125-mg twice-per-day dose.

Despite the improvements, 59% of the patients receiving 125 mg Bosentan and 65% of the patients receiving 250 mg bosentan remained either functional class III or IV at the end of the trial. There was also less effectiveness in the subgroup of patients with PAH related to connective tissue diseases. Among the patients with primary pulmonary hypertension, there was a 46-m improvement in 6-minute walk in the bosentan group compared with a 5-m decline in the placebo group. In contrast, in the patients with pulmonary arterial hypertension associated with connective tissue diseases, there was an improvement of 3 m in the bosentan group compared with a decline of 40 m in the placebo group. There was also a dose-dependent increase in hepatic transaminases noted with significant elevations in 14% of patients randomized to the 250-mg dose of bosentan. In November 2001, the US Food and Drug Administration approved bosentan at a dose of 125 mg twice per day to improve exercise tolerance and extend the time to clinical worsening in patients with pulmonary arterial hypertension of World Health Organization class III and IV severity.

BREATHE-2 was a randomized, double-blind clinical trial to evaluate whether the combination of bosentan and intravenous epoprostenol was better than epoprostenol alone in patients who were functional class III requiring initiation of epoprostenol therapy. Thirty patients were randomized in a 2 to 1 fashion to receive epoprostenol with bosentan or epoprostenol alone over a 16-week period. The dose of epoprostenol was kept similar in both groups. The trial failed to show any significant difference between the groups with respect to hemodynamics or 6-minute walk distance between therapies. However, 2 of the patients randomized to the combination therapy died, and a third patient had worsening pulmonary hypertension requiring them to drop out. Although it remains possible that the combination therapy might be of benefit in certain patients, the possibility of a negative drug interaction is real and the use of these agents together needs to be monitored very carefully.33

The selective ETα receptor antagonist sitaxsentan has also been studied in pulmonary hypertension. In an open-label study, Barst et al34 reported the effects on hemodynamics and 6-minute walk test distance in 6 children and 14 adults who were given sitaxsentan at doses of 100 to 500 mg twice per day for 12 weeks. Exercise distance walked in 6 minutes improved significantly, from 466±132 m at baseline to 507±153 m at week 12. Right heart catheterization at the end of the trial showed a 17% reduction in mean pulmonary artery pressure and a 22% increase in cardiac index. Serious liver function abnormalities occurred in 2 of the 20 patients in this study (including 1 death related to fulminant hepatic failure). The STRIDE-I trial (Sitaxsentan To Relieve Impaired Exercise in pulmonary arterial hypertension) evaluated the safety and efficacy of 100 or 300 mg sitaxsentan daily versus placebo over 12 weeks, a placebo-controlled, randomized trial in 178 patients. This trial used a primary end point of change in percent of predicted peak Vo2 with cardiopulmonary exercise testing. There was a statistically significant improvement in this end point for the 300-mg sitaxsentan dose group but not for the 100-mg dose group. Six-minute walk distance, however, did improve significantly in both the 100-mg and 300-mg groups, as well as hemodynamics. Reversible liver enzyme abnormalities were noted in 5% of the patients at the 100-mg sitaxsentan dose and 21% of the patients at the 300-mg sitaxsentan dose.35

Congestive Heart Failure
Circulating ET-1 levels have been correlated with the severity of hemodynamics and with symptoms in patients with congestive heart failure.36,37 Tissue ET levels are increased in the failing human heart. Studies have also shown that big ET is an independent predictor of survival.38 It is likely that there is an interplay between the ET system and neurohormonal system because the activation of 1 appears to increase levels of the other. ET-1 appears to exert differential effects on the normal and failing myocardium. Patients with reduced left ventricular function have increased contractility in response to ETα receptor blockade, whereas patients with normal left ventricular function manifest a reduction in contractility. ETα receptors are upregulated in heart failure, whereas the ETβ receptor appears to be downregulated.39,40

Both intravenous and oral ET receptor antagonists have been studied for acute and chronic heart failure (Table 2). The nonselective ET receptor antagonist tezosentan was studied in the RITZ Trials (Randomized Intravenous TeZosentan), which consisted of 4 phase III studies of tezosentan, run in parallel, in patients with acute heart failure requiring hospitalization. The objective of RITZ-1 was to examine the effect of tezosentan on symptoms of dyspnea and time to death or worsening heart failure.41 The trial included 669 patients with decompensated heart failure requiring hospitalization for parenteral therapy. Three hundred thirty-eight patients were randomized to standard therapy for acute heart failure plus placebo, whereas 331 received standard therapy plus 25 mg tezosentan per hour intravenously for 1 hour followed by uptitration to 50 mg per hour intravenously for 24 to 72 hours. There was no improvement in the primary end point (patient assessment of dyspnea at 24 hours) or secondary end points of time to death or worsening symptoms of heart failure in the first 24 hours. Notably, the 50-mg-per-hour dose of tezosentan was associated with an excess of hypotension, dizziness, and renal failure, suggesting that the dose might have been excessive. In contrast, RITZ-2 demonstrated beneficial hemodynamic effects of tezosentan in an acute heart failure population.42 In RITZ-2, 285 patients experiencing acute heart failure who required hospitalization, intravenous treatment, and continuous hemodynamic monitoring were randomized to receive either placebo or 1 of 2 doses of tezosentan (50 and 100 mg/hour). All participants had a cardiac index of less than 2.5 L · min−1 · m−2 and pulmonary capillary wedge pressure of greater than 15 mm Hg. The mean ejection fraction in this study population was 23%. The primary end point was improvement of
cardiac index at 6 hours, and the net treatment effect in the groups receiving tezosentan was a benefit of 0.37 to 0.38 L \cdot min^{-1} \cdot mol/L^{-2}. There was also a substantial reduction in pulmonary capillary wedge pressures.

In the RITZ-4 trial, the effect of tezosentan in patients with acute decompensated heart failure associated with acute coronary syndromes was evaluated.43 In this multicenter, acute decompensated heart failure associated with acute pulmonary capillary wedge pressures.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Comments</th>
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<tbody>
<tr>
<td>RITZ-1</td>
<td>Tezosentan 25 mg/hour IV for 72 hours vs placebo (n=669)</td>
<td>No difference in all end points</td>
<td>Tezosentan associated with excess of hypotension and renal failure</td>
</tr>
<tr>
<td>RITZ-2</td>
<td>Tezosentan 50 mg or 100 mg/hour IV vs placebo (n=219)</td>
<td>Both doses produced similar increase in cardiac index and fall in PCWP</td>
<td>No serious AEs</td>
</tr>
<tr>
<td>RITZ-4</td>
<td>Tezosentan 25–40 mg/hour for 24–48 hours vs placebo (n=193)</td>
<td>No difference in all end points</td>
<td>Patients with recent AMI</td>
</tr>
<tr>
<td>RITZ-5</td>
<td>Tezosentan 50–100 mg/hour IV for 24 hours (n=84)</td>
<td>No improvements in end points</td>
<td>Higher dose had worse effects</td>
</tr>
<tr>
<td>REACH-1</td>
<td>Bosentan 250 mg twice per day vs placebo (n=370)</td>
<td>No improvements in end points</td>
<td>Terminated early as a result of excessive increase in LFTs</td>
</tr>
<tr>
<td>ENABLE I/II</td>
<td>Bosentan 125 mg twice per day vs placebo (n=1613) for 9 months</td>
<td>No improvements in end points</td>
<td>Worsening CHF early in bosentan group</td>
</tr>
<tr>
<td>HEAT</td>
<td>Darusentan 3 doses vs placebo (n=157) for 3 weeks</td>
<td>Improvement in cardiac index</td>
<td>Increased adverse events at higher doses</td>
</tr>
</tbody>
</table>

TABLE 2. Endothelin Receptor Blockers for Congestive Heart Failure—Randomized Clinical Trials

AEs indicates adverse events; PCWP, pulmonary capillary wedge pressure; AMI, acute myocardial infarction; LFTs, liver function tests; and CHF, congestive heart failure.

nated following the recommendation of the Data Safety Monitoring Board as a result of a concern over the incidence of asymptomatic elevations in liver enzymes, which was 15.6% in the bosentan group. There was no significant difference in clinical status between the 2 groups at the time of study termination (Actelion Pharmaceuticals, personal communication, March 2003).

The ENABLE trials (Endothelin Antagonist Bosentan for Lowering Cardiac Events) consisted of 2 pivotal phase III trials conducted in parallel in Europe and Australia (ENABLE I) and the United States and Canada, (ENABLE II).45 Patients with NYHA class IIIB and IV congestive heart failure and a left ventricular ejection fraction of less than 35% were eligible. Patients had to be stable on background therapy, including a diuretic and ACE inhibitor. Patients were randomized to receive either bosentan to a target dose of 125 mg twice per day or placebo. The primary end point was clinical status at the end of the 9-month period of treatment in addition to all-cause mortality and congestive heart failure–related hospitalizations. A total of 1613 patients were enrolled in a 1:1 fashion. There was no difference detected between the 2 treatment groups in either of the primary end points. Notably, there was an early worsening of congestive heart failure leading to a greater rate of hospitalization in the bosentan group during the first 4 to 8 weeks. This was demonstrated with a larger percentage of patients with a weight gain of at least 2 kg, increased edema, and lower hemoglobin concentration. Importantly, the weight gain was observed as early as 2 weeks after treatment of initiation at the dose of 62.5 mg twice per day. There was no difference in mortality at any point during the clinical trial. During the course of the trial, 9.5% of patients on bosentan had elevation of transaminases greater than 3 times the upper limit of normal (Actelion Pharmaceuticals, personal communication, March 2003).

The selective ET₄ receptor antagonist darusentan was studied in the HEAT trial (Heart Failure ET[4] Receptor Blockade Trial). One hundred fifty-seven patients with class III heart failure were randomized to placebo or 1 of 3 doses
of darusentan. This study evaluated hemodynamic changes over 3 weeks. Only cardiac index significantly improved, but higher doses were associated with a trend toward more adverse events.46

Essential Hypertension
Although plasma levels of ET are not consistently elevated in patients with systemic hypertension, there is often an exaggerated vasodilator response to ET receptor blockade in these patients.47 This could speak to a change in the sensitivity of the vasculature to endogenous ET-1 as being altered as part of the disease. There are data suggesting that certain polymorphisms of the genes coding for ET-1 and ET receptors could be associated with chronic elevations in blood pressure.48 In experimental animals with induced hypertension, ET\textsubscript{A} receptor blockade prevents vascular hypertrophy and attenuates left ventricular hypertrophy.49 Hypertension develops in ET\textsubscript{B} knockout mice and blood pressure rises after ET\textsubscript{B} blockade in people.50,51

In patients with essential hypertension, the nonselective ET receptor antagonist TAK-044 caused greater forearm vasodilatation compared with normotensive controls, and the nonselective antagonist bosentan resulted in greater forearm vasodilatation than the selective ET\textsubscript{A} receptor blocker BQ-123.52,53 A 4-week treatment trial with bosentan at a fairly high dose of 1000 mg twice per day produced a fall in ambulatory diastolic blood pressure of approximately 10 mm Hg, an effect similar to treatment with 20 mg enalapril.54 Large clinical trials of ET receptor antagonists have not been conducted for hypertension.

Coronary Artery Disease
Because of the effects of ET in promoting vasoconstriction, smooth muscle cell proliferation, neutrophil adhesion, and platelet aggregation, it likely contributes to coronary artery disease. ET-1 is markedly increased in the aortas of rabbits fed high-cholesterol diets.55 Oxidized low-density lipoprotein cholesterol induces the production of ET-1 in human macrophages and increases ET release from endothelial cells.56 Tissue ET levels have been shown to correlate with the severity of angina in patients with coronary artery disease and increase in patients with unstable angina.57,58 ET-1 plasma levels have also been found to be elevated in patients with acute myocardial infarction and correlate with 1-year prognosis.59

No clinical trials have yet been conducted to evaluate the effect of ET receptor blockade on the development of chronic atherosclerotic vascular disease. Data to date come from 2 acute studies only. Intravenous administration of bosentan to patients with angiographic stable coronary artery disease produced an increase in coronary diameter in those vessels with minimal angiographic changes.60 The selective ET\textsubscript{A} receptor blocker BQ-123 given to patients with stable angina was shown to prevent distal coronary vasoconstriction after percutaneous transluminal coronary angioplasty.61

Conclusions
ET appears to have a diverse role as a modulator of vascular tone and growth, and a mediator in many cardiovascular diseases. To date, no disease entity, however, has been attributed solely to an abnormality in ET alone. Consequently, it would be unrealistic to expect the use of ET receptor antagonists to result completely in disease reversal.

ET receptor antagonists, however, have been studied in clinical trials involving a wide spectrum of cardiovascular diseases. Overall, their effects have been very modest. The only proven efficacy has been in patients with PAH in which short-term ET receptor blockade results in an improvement in exercise capacity. The long-term effectiveness of ET blockade for patients with PAH, either alone or in combination with other therapies, remains to be determined. Because the only other class of drugs approved for pulmonary hypertension, the prostacyclins, require parenteral administration, it is reasonable to initiate therapy with bosentan in stable patients with mild to moderate symptoms. Frequent assessments of efficacy, using exercise tests and/or cardiac catheterization, are advisable. Patients who fail to improve should then be considered for a prostacyclin.

Because of the high incidence of liver toxicity, patients receiving bosentan need liver function tests monitored monthly. An increase in transaminases to above 3 times the upper level of normal would require reducing or discontinuing therapy. In addition, the use of bosentan is contraindicated in patients receiving cyclosporine A and Glucophage. Bosentan also reduces circulating levels of the statin drugs.

To date, there has been no proven clinical efficacy for using ET receptor blockers in patients with congestive heart failure or essential hypertension. It is largely untested in patients with chronic atherosclerosis.

Whether selective ET\textsubscript{A} receptor blockade is superior to nonselective blockade remains unclear. Arguments in favor of 1 or the other type of receptor antagonists have been made. It does, however, appear that most, if not all, of the ET receptor blockers predispose to hepatic toxicity as manifest by an increase in transaminases. These are generally reversible on discontinuation of therapy. Given the redundant pathways that control vascular tone and growth, it could be that ET receptor blockade will ultimately be used as part of a combined regimen. Future clinical studies to explore this potential are warranted.

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References


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