Clinical Experience With Endothelin Antagonists

David J. Webb and Fiona E. Strachan

Endothelin-1, discovered in 1988, is a 21–amino-acid peptide and currently the most potent vasoconstrictor and pressor substance known. Generated by vascular endothelial cells in response to a variety of chemical and mechanical signals, endothelin-1 is known to potentiate the actions of other vasoconstrictor substances and act as a comitogen in addition to directly causing vasoconstriction. There is evidence that endothelin-1 may contribute to the pathophysiology of conditions associated with sustained vasoconstriction, such as hypertension and heart failure, vasospastic conditions, such as subarachnoid hemorrhage, and atherogenesis.


KEY WORDS: Bosentan, endothelin-1, endothelin receptor antagonist.
human cardiovascular physiology and pathophysiology, and to the process of early drug development and identification of suitable therapeutic targets.

THE ENDOTHELIN SYSTEM

Endothelin-1 (Figure 1) was originally identified in the culture medium of porcine aortic endothelial cells. It is now recognized to be a member of a family comprising three isoforms: endothelin-1, endothelin-2, and endothelin-3. Each isoform contains 21 amino acids, two intrachain disulfide bonds constraining overall structure, and a conserved C-terminal sequence necessary for biological activity. This structure is unique among the mammalian peptides, but is shared by the sarafotoxins—snake venom peptides from the Israeli burrowing asp, Actractaspis engaddensis—one of which, sarafotoxin S6c, has proved particularly valuable as a pharmacologic tool. While there is evidence that endothelin-2 may possibly function as a mediator in the kidney and that endothelin-3 may act as a mediator in the gut and nervous system, endothelin-1 is the major isoform generated in blood vessels and appears to be of greatest significance in cardiovascular regulation. Hence, endothelin-1 is the major focus of this review.

Within the human genome, the endothelins are each represented by a separate gene encoding a specific precursor for the mature isoform. Currently, regulation of endothelin synthesis is thought to be primarily at the level of gene transcription, with de novo production and release occurring in response to endothelial cell stimulation. Factors acting at this level to stimulate endothelin-1 synthesis (Figure 1) include vasoactive hormones, inflammatory mediators, and physicochemical factors, such as altered vascular shear stress and hypoxia. In contrast, other factors—including nitric oxide, nitric oxide donor drugs, natriuretic peptides, and the dilator prostanoids—serve to inhibit endothelin-1 generation by promoting production of cyclic GMP or cyclic AMP. In the 5′ gene-flanking sequence, there are binding sites for activating protein 1 (API) and nuclear factor 1 through which angiotensin II and transforming growth factor-β, respectively, act to induce endothelin-1 expression. There are also binding sites for acute phase reactants, which may mediate the effects of acute physiologic stress. In the 3′ region there is a sequence-regulating selective destabilization of preproendothelin-1 mRNA, possibly accounting for its short half-life. These sites serve as potential mechanisms for regulating production of endothelin at the level of transcription and translation. Although endothelin-1 can be identified within endothelial cells, it remains unclear whether intracellularly stored peptide represents an important pool available for rapid release.

The product of human endothelin-1 gene transcription is preproendothelin-1, a peptide of 212 amino acid residues (Figure 1). After removal of a short secretory sequence, proendothelin-1 undergoes cleavage by a dibasic pair-specific endoprotease to generate the 38–amino-acid peptide “big endothelin-1.” Subsequent conversion to the mature, biologically active peptide, endothelin-1, occurs through the action of endothelin converting enzyme (ECE). The gene encoding endothelin-1 can be detected in a wide variety of tissues, including the endothelial and smooth muscle cells of blood vessels, heart, lung, brain, kidney, pancreas, and spleen. Big endothelin-1, endothelin-1, and endothelin-3 are normally present in plasma at picomolar concentrations that are probably insufficient to exert a direct influence on vascular tone. Indeed, endothelin-1 is generally thought to be a paracrine and autocrine mediator rather than an endocrine hormone, and its secretion by endothelial cells is largely abluminal, ie, toward the adjacent vascular smooth muscle. Also, the half-life of endothelin-1 in blood is short (<5 min), with clearance predominantly via receptor binding and metabolism in the lungs and kidneys.
The endothelins act on two receptor subtypes, ET\textsubscript{A} and ET\textsubscript{B}, which have been characterized on the basis of their pharmacology (Table 1). Endothelin-1 has a similar binding affinity for ET\textsubscript{A} and ET\textsubscript{B} receptors—in the nanomolar range—but has a much higher binding affinity for the ET\textsubscript{A} receptor than has endothelin-3. In contrast, endothelin-1 and endothelin-3 have equal affinity for the ET\textsubscript{B} receptor. The understanding of the function of endothelin receptors has been aided by the use of specific pharmacologic agonists and antagonists. Currently, there are unfortunately no selective agonists at the ET\textsubscript{A} receptor. However, endothelin-3, sarafotoxin S6c, and BQ-3020 are selective agonists at the ET\textsubscript{B} receptor. BQ-123 and BQ-788 are selective antagonists at the ET\textsubscript{A} and ET\textsubscript{B} receptors, respectively; nonselective antagonists include bosentan and TAK-044. ET\textsubscript{A} receptor mRNA can be detected in many tissues, with the highest expression in aorta, heart, and kidney. The ET\textsubscript{A} receptor predominates on vascular smooth muscle cells and is responsible for causing vasoconstriction in both large and small blood vessels.\textsuperscript{7} It is also the major receptor subtype in the heart.\textsuperscript{8} ET\textsubscript{A} mRNA cannot be detected in the liver or endothelial cells.\textsuperscript{9} The ET\textsubscript{B} receptor can be detected in endothelial and vascular smooth muscle cells and is predominantly found in brain, lung, kidney, and aorta.\textsuperscript{10} The ET\textsubscript{B} receptor on endothelial cells modulates vasoconstriction in response to endothelin-1 through the production of vasodilator substances including prostacyclin and nitric oxide. It is now widely recognized that the ET\textsubscript{B} receptors on vascular smooth muscle cells can mediate vasoconstriction, particularly in small resistance vessels and veins. There has been a recent tendency to subclassify the ET\textsubscript{B} receptor on the basis of responses to selective agonists and antagonists,\textsuperscript{11} but this currently cannot be justified on a molecular basis.

The ET\textsubscript{A} and ET\textsubscript{B} receptors are classic heptahelical G-protein–coupled receptors activating phospholipase C to cause hydrolysis of phosphatidylinositol and generation of cytosolic inositol trisphosphate and membrane-bound diacylglycerol.\textsuperscript{12} Inositol trisphosphate causes an early rapid rise in \([Ca^{2+}]_i\), through its release from intracellular stores. A more sustained rise of intracellular calcium occurs through the opening of membrane \(Ca^{2+}\) channels. Diacylglycerol activates protein kinase C, increasing the sensitivity of the contractile apparatus to \(Ca^{2+}\), which activates nuclear signaling mechanisms—with possible effects on long-term regulation of cellular function—and causes a rise in the intracellular pH through an effect on the sodium-hydrogen ion exchange membrane pump. Endothelin-1 may also interact with the ATP-sensitive potassium channel, thus contributing to the rise in \([Ca^{2+}]_i\). In addition, it may activate phospholipase A\textsubscript{2}, increasing production of arachidonic acid and hence of prostacyclin (PGI\textsubscript{2}) and thromboxane A\textsubscript{2}. Endothelin-1 binds tightly to its receptors and the endothelin-receptor complex is rapidly internalized. Slow dissociation from these receptors may contribute to its prolonged effects on vascular tone.

### CARDIOVASCULAR PHARMACOLOGY

Bolus administration of endothelin-1 is known to cause a marked pressor effect lasting for more than 60 min in both animals\textsuperscript{1} and humans,\textsuperscript{13,14} mediated predominantly through an increase in peripheral vascular resistance. The pressor effect tends to reduce cardiac output,\textsuperscript{15} probably through a baroreceptor-mediated decrease in heart rate, although an increase in afterload may contribute. Coronary vasoconstriction occurs with endothelin-1 administration to healthy subjects.\textsuperscript{14} It is also recognized that bolus administration of endothelin-1 in animals causes initial transient hypotension associated with systemic vasodilatation, through stimulation of the endothelial ET\textsubscript{B} receptor, before the development of a long-lasting pressor response. However, such studies require high doses of endothelin-1, and because endothelin-1 preferentially causes vasoconstriction in the renal, cardiac, and cerebral circulations, such studies should clearly be avoided in humans.

One way to directly address the potential vasoconstrictor and dilator effects of the endothelins in vivo in

### TABLE 1. ENDOTHELIN RECEPTORS

<table>
<thead>
<tr>
<th>Agonist potency</th>
<th>ET\textsubscript{A}</th>
<th>ET\textsubscript{B}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>Aorta</td>
<td>Coronary artery, small arteries, veins</td>
</tr>
<tr>
<td>Action</td>
<td>Constriction</td>
<td>Constriction</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Antagonists</td>
<td>BQ-123</td>
<td>Nonselective Bosentan</td>
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<pre><code>                                        | TAK-044         |
</code></pre>
humans is to study vascular responses in the forearm to brachial artery infusion of locally active doses of endothelins. Avoiding confounding effects on organs such as the brain, kidney, and heart, as well as potential influences on neurohumoral reflexes, allows vascular responses to be attributed to a direct effect of the drug, providing a powerful, reproducible, and safe method of directly assessing vascular responses in vivo. Importantly, the responses obtained are also broadly predictive of those seen in the systemic and coronary circulation.

Continuous infusion of endothelin-1 into the brachial artery causes a slowly developing dose-dependent reduction in forearm blood flow, with vasoconstriction sustained for more than 2 h after the infusion is halted. When given via the brachial artery, low doses of the ET<sub>B</sub>-selective agonists endothelin-3, sarafotoxin S6c, and BQ-3020 also produce vasoconstriction in human resistance vessels in vivo, consistent with vascular ET<sub>B</sub> receptors’ mediating at least part of the functional response to endothelin-1 in these vessels. Endothelin-1 and endothelin-3, as well as sarafotoxin S6c (unpublished observations), can produce initial transient forearm vasodilatation. This vasodilatation is greater and more prolonged in response to endothelin-3 and sarafotoxin S6c than in response to endothelin-1, consistent with involvement of the endothelial ET<sub>B</sub> receptor. However, vasodilatation in response to the endothelins occurs only at high doses in bolus administration, suggesting that this is not a physiologic response. In human resistance vessels, transient vasodilatation is mediated predominantly by stimulated release of nitric oxide (unpublished observations).

Endothelin-1, sarafotoxin S6c, and BQ-3020 cause constriction of human dorsal hand veins in vivo, suggesting that both vascular ET<sub>A</sub> and ET<sub>B</sub> receptors can contribute to vasoconstriction due to endothelin-1 in humans. Venoconstriction in vivo is blocked by the K<sub>ATP</sub> channel opener cromakalim and the Ca<sup>2+</sup> channel antagonist nicardipine, suggesting that endothelin-1 responses in human veins depend at least in part on Ca<sup>2+</sup> entry through dihydropyridine-sensitive Ca<sup>2+</sup> channels. However, the greater efficacy of K<sub>ATP</sub> channel-opening agents is consistent with other vasoconstritor mechanisms in addition to the opening of voltage-operated Ca<sup>2+</sup> channels.

**CARDIOVASCULAR PHYSIOLOGY**

Studies with endothelin antagonists are likely to be considerably more informative than agonist-based studies in helping us understand the physiologic role of the endothelin system in the cardiovascular system. The first such drug to become available for human studies was the ECE inhibitor phosphoramidon. Phosphoramidon (30 nmol/min) given into the forearm circulation abolished the 40% vasoconstriction caused by big endothelin-1 (50 pmol/min) and, given alone, resulted in a slowly progressive vasodilatation. This effect could not be accounted for by the action of phosphoramidon as an inhibitor of neutral endopeptidase (NEP), because potent and selective inhibitors of NEP cause slowly progressive forearm vasoconstriction. These observations were consistent with a role for endothelin-1 in maintenance of basal vascular tone.

Confirmation that endogenous endothelin-1 generation contributes to the maintenance of basal tone in forearm resistance vessels of healthy human subjects came from studies with the cyclic pentapeptide ET<sub>A</sub> receptor-selective antagonist BQ-123 and the cyclic hexapeptide combined ET<sub>AB</sub> antagonist TAK-044 given via the brachial artery. Both agents caused a progressive vasodilatation of the forearm vessels. The substantial effect of BQ-123 suggests that vasoconstriction due to endothelin-1 is mediated mainly through the ET<sub>A</sub> receptor on vascular smooth muscle, as it also appears to be in the human skin microcirculation. Subsequent studies have confirmed forearm vasodilatation to BQ-123 and shown that it can be achieved with lower doses and when given for a shorter period. The L-arginine/nitric oxide system, the sympathetic nervous system, and the endothelin system are currently the only mediator systems known to maintain basal vascular tone. It now remains to be shown how the endothelin system is regulated; such regulation probably occurs at a local level.

The fact that BQ-123 has a greater effect than a substantial local dose of TAK-044 is consistent with the ET<sub>B</sub> receptor having a role mainly as a dilator. Further and more direct support for this view comes from recent arterial experiments with an ET<sub>B</sub>-selective inhibitor BQ-788. This agent causes progressive forearm vasoconstriction in healthy subjects, and coadministration of BQ-788 attenuates the vasodilatation due to the ET<sub>A</sub>-selective inhibitor BQ-123, consistent with a predominantly vasodilator role for ET<sub>B</sub> receptors. Studies using the nitric oxide “clamp,” in which endogenous nitric oxide synthesis is inhibited with brachial artery infusion of L-N<sup>G</sup>-monomethyl-arginine and basal tone is restored by brachial artery coinfusion of the nitric oxide donor sodium nitroprusside, have also been revealing. In the presence of the “clamp,” the vasodilatation caused by BQ-123 is substantially attenuated, suggesting that an important component of the dilator response to BQ-123 is mediated by nitric oxide, probably through unopposed stimulation of endothelial ET<sub>B</sub> receptors. Interestingly, many of the endothelin receptor antagonists seem to cause a “nitrate-like” headache, at least after acute administration in healthy volunteers. This may be a useful
marker of the pharmacodynamic activity of endothelin antagonists, based on enhanced vascular nitric oxide release.

Responses of the forearm resistance vessels to drugs infused into the brachial artery are usually predictive of the responses in the major resistance beds that serve to regulate blood pressure.29 Hence, predictions were made that systemic endothelin receptor antagonism would generate hypotension. These predictions were confirmed recently in healthy subjects24 with the peptide drug TAK-044, which functionally inhibits both ET_A- and ET_B-mediated responses.23,30 TAK-044 was given to healthy subjects at a range of doses from 10 to 1000 mg systemically and was generally well tolerated.24 A 15-min intravenous infusion of TAK-044 of 1000 mg reduced systolic blood pressure by ~4%, diastolic blood pressure by ~18%, and systemic vascular resistance by ~26% over a 24-h period (Figure 2), suggesting that a major part of the effect of TAK-044 is mediated in the resistance vessels. At this dose, but not consistently at lower doses, the major hemodynamic effect on systemic vascular resistance was accompanied by a compensatory increase in cardiac output and heart rate. The substantial and long-lasting effect of TAK-044 on systemic vascular resistance is even more remarkable considering the short half-life of this peptide in the circulation and fully confirms that endogenous endothelin generation is critical for cardiovascular homeostasis and control of blood pressure. Systemically administered TAK-044 also abolished the vasoconstriction due to endothelin-1 infused via the brachial artery for up to 3 h,24 but inhibited responses only partially at 8 and 12 h.31 Such studies can confirm the efficacy of endothelin receptor antagonists and determine the duration of their action. This appears to be especially important for this class of drug, in which standard pharmacokinetic parameters do not always successfully predict pharmacodynamic activity.

CARDIOVASCULAR PATHOPHYSIOLOGY

It is becoming clear that endothelin-1 plays a role in the pathophysiology of a range of cardiovascular diseases.4,32 These include ischemic heart disease and atherosclerosis, as well as conditions associated either with sustained vasoconstriction, including hypertension and chronic heart failure, or with intermittent vasoconstriction, including subarachnoid hemorrhage and acute renal failure. There are many mechanisms whereby endothelin-1 may be involved in cardiovascular disease: enhanced production in congestive heart failure, enhanced receptor number/affinity with cyclosporin treatment, reduced peptide clearance in chronic renal failure, and unopposed action with endothelial dysfunction affecting the l-arginine/nitric oxide system, which may be a factor in a number of cardiovascular diseases, including atherosclerosis.33,34 Given the beneficial effects of nitric oxide—vasodilation, inhibition of platelet aggregation, and inhibition of vascular growth—and the potentially adverse effects of endothelin-1—vasoconstriction and promotion of vascular growth—it may be important that conditions associated with reduced nitric oxide production are further compounded by increased production of endothelin-1. Indeed, it is clear that these systems do not function independently. Endothelin-1 generation is enhanced by a range of other constrictor and growth-promoting substances and is inhibited by

**FIGURE 2.** Graph showing time course of the effects of the highest dose of TAK-044 (1000 mg) on mean arterial pressure (MAP), heart rate (HR), stroke index (SI), cardiac index (CI), and total peripheral resistance index (TPRI). TAK-044 significantly decreased mean arterial pressure (P < .001) and total peripheral resistance (P < .001) and increased heart rate (P < .001), stroke index (P = .34), and cardiac index (P < .001); these effects reached their maximum at 4 h and were sustained for at least 12 h. Data shown represent placebo-corrected changes from predose (change from predose [active]-mean change from predose [placebo]). (bpm indicates beats per minute; AU indicates arbitrary units.) Reproduced from Haynes WG, et al,24 with kind permission of the American Heart Association.
dilators, including nitric oxide (Figure 1). Conversely, endothelin-1 promotes the production of nitric oxide but may also account for some of the vasoconstriction that accompanies its inhibition by L-N^6^-monomethyl-arginine and clinically for the development of tolerance to exogenous nitrate administration. These interactions are complex and require further investigation.

As well as having direct effects on vascular tone, endothelin-1 may enhance vascular tone indirectly by augmenting vasoconstriction due to other agents, such as angiotensin II, norepinephrine, and serotonin, by enhancing central and peripheral sympathetic function, and by activating the renin-angiotensin system. Endothelin-1 is also a mitogen, enhancing cell division and proliferation, gene expression, and protein synthesis, and ultimately promoting hypertrophy of vascular smooth muscle, as well as of cardiac myocytes and fibroblasts. Thus, endothelin-1 may serve to amplify vasoconstriction through the development of vascular hypertrophy.

As a result of its complex vascular effects, endothelin-1 clearly has a role in the pathophysiology of cardiovascular disease and has emerged as a novel therapeutic target in this area. This review will focus on clinical studies implicating the endothelin system in hypertension and chronic heart failure.

HYPERTENSION

The studies in healthy subjects showing that local administration of BQ-123 reduces forearm vascular resistance and that systemic administration of TAK-044 reduces systemic vascular resistance and blood pressure would be consistent with blood pressure lowering with endothelin receptor antagonists in hypertensive patients. Indeed, a randomized, double-blind, placebo-controlled, parallel-group study comparing four doses of the combined ET_{AB} receptor antagonist bosentan with the angiotensin converting enzyme inhibitor enalapril shows that bosentan was well tolerated and effective in lowering blood pressure in hypertensive patients (Data on file, Roche Laboratories).

Clearly there are already a number of well-tolerated and cost-effective drugs that can be used to treat hypertension. Nevertheless, the potential additional benefits of endothelin antagonists on atherogenesis, cardiac and vascular hypertrophy, and progression of renal impairment may make this an attractive option to pursue. Indeed, it can be argued that this may be an important market to develop, given its large size, by analogy with the ACE inhibitors. These drugs were developed on the basis of their benefit to a relatively narrow range of high-renin hypertensive patients. We now know, however, that ACE inhibitors are also useful in low-renin hypertension, chronic heart failure, and diabetic renal disease. Without initial investment, such benefits for endothelin antagonists may never be realized.

CHRONIC HEART FAILURE

Chronic heart failure (CHF) is a common and disabling condition causing substantial morbidity and mortality. It is associated with stimulation of compensatory neurohumoral reflexes, including effects on the renin-angiotensin and sympathetic nervous systems that not only maintain perfusion pressure but also increase peripheral vascular resistance, renal sodium reabsorption, and cardiac workload. This leads to a "vicious circle" of declining cardiac function and provides a rationale for the current mainstay of treatment, which is vasodilator therapy with ACE inhibitors. Although current treatment regimens are undoubtedly successful, CHF still carries substantial morbidity and mortality, and there is a need for new approaches.

Neurohumoral activation and tissue hypoxia should increase endothelin-1 production. Also, the actions of endothelin-1—vasoconstriction, cardiac and vascular hypertrophy, enhanced activity of the renin-angiotensin and sympathetic nervous systems, renal vasoconstriction, and sodium retention—are all consistent with the circulatory abnormalities found in CHF. Indeed, plasma endothelin concentrations are elevated in CHF, mainly through an increase in plasma big endothelin-1, consistent with increased synthesis of endothelin-1. Plasma immunoreactive endothelin levels correlate with the degree of hemodynamic and functional impairment in CHF, associated with a worse prognosis, irrespective of the cause of the cardiac failure, and predict mortality or the need for cardiac transplantation. Currently, measurement of plasma big endothelin-1 concentration is the best available predictor of outcome in CHF. Interestingly, raised plasma endothelin concentrations also appear to be an extremely powerful predictor of 1 year mortality after acute myocardial infarction.

In the first clinical trial of an endothelin antagonist in CHF, in patients withdrawn from ACE inhibitor treatment, acute intravenous administration of the combined ET_{AB} antagonist bosentan increased cardiac output and reduced systemic and pulmonary vascular resistance without inducing reflex tachycardia or increasing plasma concentrations of angiotensin II or norepinephrine (Figure 3). These beneficial hemodynamic effects are similar to those associated with ACE inhibitors, raising the question of whether endothelin antagonists would still be of benefit during full ACE inhibition. Importantly, in patients maintained on ACE inhibitors, local brachial artery administration of the ECE inhibitor phosphoramidon and the ET_{A} receptor antagonist BQ-123 both caused substantial va-
sodilatation of the forearm resistance vessels, supporting an additional role for endothelin receptor antagonists in the treatment of CHF.\textsuperscript{48} Interestingly, the selective ET\textsubscript{B} antagonist BQ-788 caused vasoconstriction, suggesting that even in CHF patients the dilator ET\textsubscript{B} response predominates. However, despite some evidence that the vasoconstriction in CHF is mainly ETA receptor mediated, it should be recognized that adverse effects on renal sodium handling may be ET\textsubscript{B} receptor mediated. This should be a focus of future research in CHF.

From a more recent randomized, double-blind, placebo-controlled study of 14 days’ treatment with bosentan in CHF patients maintained on ACE inhibitor therapy, it appears that bosentan is well tolerated, that its beneficial hemodynamic effects do occur in the presence of ACE inhibitors, and that these benefits can be sustained on chronic oral treatment (Data on file, Roche Laboratories). In these patients, it also seemed that symptoms were broadly improved by bosentan. Large phase III clinical trials of morbidity and mortality are now underway with bosentan in CHF, and it is likely that the role of endothelin antagonists in CHF will be resolved within the next few years.

**SUMMARY**

Endothelin-1 is an endothelium-derived vasoconstrictor and mitogenic agent that acts as a local paracrine and autocrine mediator and is the most potent and sustained vasoconstrictor and pressor substance yet
identified. On the basis of studies in healthy men, endothelin-1 is now known to play an important physiologic role in maintaining peripheral vascular tone and blood pressure. Endothelin-1 also has actions that might influence the function of the heart, kidney, and nervous system. However, endothelin-1’s physiologic importance in these organs remains to be determined.

Abnormalities of the endothelin system are now recognized to occur in a range of diseases associated with vasoconstriction, vasospasm, and vascular hypertrophy, and it appears that endothelin-1 may be causal, or at least contributory, in some of these pathophysiologic processes. The use of endothelin receptor antagonists in experimental models of cardiovascular disease and in human clinical pharmacology studies has indicated a number of conditions, including hypertension, heart failure, acute renal failure, subarachnoid hemorrhage, and pulmonary hypertension, in which further clinical studies would be worthwhile. A number of peptide and orally active nonpeptide endothelin receptor antagonists are now under clinical investigation, and further studies are now required in specific diseases to determine whether selective ET \textsubscript{A} or combined ET \textsubscript{AB} receptor antagonists would be more effective.

The discovery of endothelin-1 and the design of endothelin antagonists have been among the most promising developments in cardiovascular medicine since the launch of ACE inhibitors and calcium antagonists. Major clinical trials are now needed to confirm the predicted benefits for endothelin antagonists in patients with cardiovascular disease.

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