Endothelin A Receptor Antagonism and Angiotensin-Converting Enzyme Inhibition Are Synergistic via an Endothelin B Receptor–Mediated and Nitric Oxide–Dependent Mechanism

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Abstract. Animal studies suggest that endothelin A (ETA) receptor antagonism and angiotensin-converting enzyme (ACE) inhibition may be synergistic. This interaction and the role of ETB receptors and endothelial mediators were investigated in terms of systemic and renal effects in humans in two studies. In one study, six subjects received placebo, the ETA receptor antagonist BQ-123 alone, and BQ-123 in combination with the ETB receptor antagonist BQ-788 after pretreatment with the ACE inhibitor enalapril (E) or placebo. In the other, six subjects who were pretreated with E received placebo, BQ-123, and BQ-123 with concomitant inhibition of nitric oxide (NO) synthase or cyclo-oxygenase (COX). Both were randomized, double-blind, crossover studies. Mean arterial pressure was reduced by BQ-123, an effect that was doubled versus placebo. BQ-123 increased effective renal blood flow (BQ-123, −0.1 ± 2.4%; BQ-123+E, 10.9 ± 4.2%; P < 0.01 versus BQ-123), reduced effective renal vascular resistance (BQ-123, −1.2 ± 3.1%; BQ-123+E, −12.8 ± 3.0%; P < 0.01 versus placebo and versus BQ-123), and increased urinary sodium excretion markedly (BQ-123, 2.6 ± 12.8%; BQ-123+E, 25.2 ± 12.6%; P < 0.05 versus BQ-123, P < 0.01 versus placebo and versus E) only during ACE inhibition. These effects were abolished by both ETB receptor blockade and NO synthase inhibition, whereas COX inhibition had no effect. In conclusion, the combination of ETA receptor antagonism and ACE inhibition is synergistic via an ETB receptor–mediated, NO-dependent, COX-independent mechanism. The reduction of BP and renal vascular resistance and associated substantial natriuresis make this a potentially attractive therapeutic combination in renal disease.

Endothelin-1 (ET-1) is a vasoactive peptide that is produced by the vascular endothelium (1) and acts through two receptors to regulate vascular tone. Vascular smooth muscle ETA and ETB receptors (2,3) mediate vasoconstriction, whereas endothelial ETB receptors mediate vasodilation through generation of nitric oxide (NO) and prostanooids (3). Angiotensin II (Ang II) is another powerful vasoconstrictor involved in the regulation of vascular tone, and there is considerable evidence for an interaction between the endothelin and renin-angiotensin systems (4). Ang II increases ET-1 transcription and secretion in vitro in a variety of cell types, including endothelial and vascular smooth muscle cells (5,6), and ET receptor antagonists attenuate the acute hemodynamic effects of Ang II in rats in vivo (7,8). However, this is by no means a uniform finding (9) and has not been replicated in dogs (10) or humans (11). Data in animals suggest that concomitant ET blockade and angiotensin-converting enzyme (ACE) inhibition produce changes greater than those seen with blockade of either system alone (12–15). In addition, clinical studies that demonstrated major hemodynamic effects of ET receptor antagonists have generally been performed in patients who were already receiving ACE inhibitors (16,17).

ACE inhibition, by promoting the effects of bradykinin (18), and ET-1 acting on endothelial ETB receptors (19) both enhance endothelium-dependent vasodilation. Vascular studies in humans suggest that the vasodilator effects of ETA receptor antagonism are dependent on the unblocked ETB receptor and NO generation (20). The aim of this study, therefore, was to explore the possible systemic and renal interaction between ET receptor antagonism and ACE inhibition and the mechanisms by which such an interaction might occur. We hypothesized that previous ACE inhibition would augment the systemic and renal hemodynamic response to ETA receptor antagonism and that this interaction would be dependent on NO production and mediated, at least in part, through the ETB receptor.
Materials and Methods

A total of eight healthy men (six in each protocol) were recruited to the studies, which were performed in the University of Edinburgh’s Clinical Research Centre with the approval of the local research ethics committee and the written informed consent of each participant. The investigations conformed to the principles outlined in the Declaration of Helsinki.

For 3 d before each study, participants adhered to a standard diet that contained 150 mmol of sodium. All participants abstained from over-the-counter medication for 2 wk, alcohol, nicotine, and caffeine-containing products for 24 h and had a light breakfast before attending on each study day. All studies were carried out in a quiet, temperature-controlled room, at 22 to 24°C, with the participant recumbent throughout, except when voiding urine.

Drugs

BQ-123 (Clinalfa AG, Laufelfingen, Switzerland), a selective ETA receptor antagonist (21), was infused at 100 and 1000 nmol/min for 15 min at each dose. These doses were selected from a previous study as having a threshold and maximum hemodynamic effect in healthy control subjects (22). The higher dose produces a peak plasma concentration of BQ-123 (22) 7-fold higher than the \( K_i \) for ETA receptor inhibition and 20-fold lower than the \( K_i \) for ETB receptor inhibition (21), confirming ETA selectivity, and did not increase plasma ET-1, an index of ETB receptor blockade (23). BQ-788 (Clinalfa AG), a selective ETB receptor antagonist (24), was infused at 30 and 300 nmol/min for 15 min, doses shown to be hemodynamically active in a previous systemic dose-ranging study (25). Drugs were dissolved in physiologic saline (0.9%; Baxter Healthcare Ltd, Thetford, UK) and infused intravenously at a constant rate of 1 ml/min via an 18 standard wire gauge (SWG) cannula sited in the right antecubital fossa. Saline was administered as placebo.

Enalapril (Dexcel Pharma Ltd, Daventry, UK) was the chosen ACE inhibitor and was administered orally for 5 d before each visit at a dose of 20 mg twice daily, taking the final dose at 8:30 a.m. on each study day. This dose was chosen from data suggesting that it would achieve significant inhibition of serum ACE activity (26,27), with steady-state plasma concentrations reached by 3 to 4 d (28). With this dosing regimen, the maximal effect of enalapril occurs 2 to 3 h after administration and persists for 5 to 7 h (27,29). By administering a final dose 2.5 h before baseline measurements, therefore, we aimed to achieve maximal ACE inhibition throughout each study visit.

The nonselective cyclo-oxygenase (COX) inhibitor indomethacin was administered as a single 100-ng oral dose at 8:30 a.m. on the relevant study day to reach peak plasma concentrations by the time of baseline measurements. The dose is known to inhibit prostaglandin production over the course of the study, as evidenced by decreased urinary excretion rates of prostaglandins (30), \( \text{N}^2 \)-monomethyl-L-arginine (L-NMMA; Clinalfa AG, Laufelfingen, Switzerland) was administered at a dose of 3 mg/kg over 5 min as an NO synthase inhibitor, with each dose of BQ-123, during the relevant study day. This dose is sufficient to cause a small transient increase in BP (by ~7 to 10%) and decrease renal blood flow (by ~10%) (31). Thereafter, BP returns to baseline by 30 min and renal blood flow by 60 min, with a plasma half-life of 75 min (31).

Para-aminohippurate sodium (PAH; Clinalfa AG) and inuret (Fre- senius Pharma, Austria) were dissolved in dextrose 5% (Baxter Healthcare) and administered as a bolus loading dose of 0.4 g of PAH and 3.5 g of inuret in 100 ml of dextrose over 15 min and a maintenance infusion of 6.6 g/L PAH and 10 g/L inuret at a rate of 2 ml/min via an 18 SWG cannula in the left antecubital fossa. All drugs were prepared from sterile stock solutions on the day of the study.

Assays

At prespecified time points, venous blood was collected into tubes that contained EDTA (Sarstedt, Newton, CA) for the measurement of PAH, inulin, and hematocrit (Hct) and into plain tubes (Sarstedt) for the measurement of plasma sodium. Twenty-milliliter aliquots of urine from each voiding were collected into plain tubes for the measurement of urinary PAH, inulin, and sodium.

Hct was measured on whole blood using a Coulter counter. All other blood samples were centrifuged immediately at 1000 × g at 4°C for 20 min, and plasma and urine were stored in plain tubes at −80°C. Inulin concentrations were determined by spectrophotometry after hydrolysis to fructose, and PAH and BQ-123 (22) were determined by HPLC. BQ-788 assay was not sufficiently sensitive for its detection in plasma. Urinary and plasma sodium concentrations were determined using standard flame photometry. Subaliquots of plasma were used to measure serum ACE activity by generation of Ang II from Ang I (32).

Study Design

Both studies were double blind and placebo controlled. Visits were separated by at least 1 wk. The first study was designed to examine the interaction between ET receptor antagonism and ACE inhibition, and the second was designed to examine the effect of NO synthase inhibition and inhibition of prostaglandin synthesis on this interaction.

Study 1. Participants attended a total of six visits. On two sets of three visits, they received placebo, BQ-123, or the combination of BQ-123 and BQ-788 in a randomized order. With one set, they received pretreatment with enalapril and the other placebo.

Study 2. Participants attended a total of four visits. On each visit, they received pretreatment with enalapril. During the study day, they then received placebo, BQ-123, BQ-123 + indomethacin, or BQ-123 + L-NMMA in a randomized order.

Study Protocol

On each study day, 18-SWG cannulae were sited in an antecubital vein in each arm. At 8:30 a.m., diuresis was induced by the administration of 500 ml of 5% dextrose over 30 min through the cannula in the left arm. The loading dose of PAH and inuret was administered through the same cannula from 8:45 a.m. Thereafter, maintenance infusions of PAH and inuret, and 5% dextrose at 260 ml/h, continued throughout the study. BP, cardiac output, and heart rate were recorded using well-validated noninvasive automated techniques every 15 min (33,34), and urine was collected every 30 min by spontaneous voiding. After a 2-h equilibration period, baseline measurements were made over two 30-min urine collection periods. The lower dose of ET receptor antagonist was then administered at 12:00 p.m. through the right antecubital cannula, followed by three 30-min collection periods. At 1:30 p.m., the higher dose of antagonist was administered followed by five additional 30-min collection periods.

At the midpoint of each urine collection period, blood was sampled from the right antecubital cannula for the measurement of PAH, inulin, sodium, and Hct. BQ-123 was measured before and at 15, 45, and 90 min after the start of each dose of antagonist and at the end of the study, and serum ACE activity was determined at 8:30 a.m. and at 2:30 p.m. (60 min after the start of the higher dose of antagonist).

Statistical Analyses

Data were stored and analyzed using a Microsoft Excel data analysis package (Excel 5.0, Microsoft, Wokingham, UK). Demographic
Data are expressed as mean ± SEM. BP at each time point was calculated as the mean of two recordings and represented as mean arterial pressure (MAP; = diastolic BP + 1/3 pulse pressure). Bioimpedance data at each time point were calculated as the mean of four recordings, each the average of 15 consecutive heart beats. Data were corrected using body surface area to give cardiac index for direct comparison of participants. Systemic vascular resistance index (SVRI) was calculated by dividing MAP by cardiac index and expressed in dyne.s m⁻²/cm⁵. GFR and effective renal plasma flow (ERPF) were calculated from inulin and PAH clearances, respectively (35). Effective renal blood flow (ERBF) was calculated by dividing ERPF by (1 – Hct); effective renal vascular resistance (ERVR) was calculated by dividing MAP by ERBF. Effective filtration fraction (EFF) was calculated as GFR divided by ERPF × 100%. Urinary sodium excretion rate was calculated as urinary sodium × urinary flow rate; and fractional excretion of sodium (FeNa) was calculated as urinary sodium × plasma inulin, divided by plasma sodium × urine inulin.

Study baseline data were calculated as the mean of the two time points immediately preceding the administration of the first study drug. Hemodynamic results are expressed as maximum placebo-corrected change from baseline (mean ± SEM). Statistical analysis was performed on untransformed data, and responses were examined by repeated measures ANOVA. In addition, area under the curve was calculated as a summary statistic of each time curve, and responses were compared by paired t test. Statistical significance was taken at the 5% level. Power calculations from previous studies (22,36) suggested that, with n = 6 participants, the studies had 80% power to achieve statistical significance for systemic hemodynamic indices. In study 1, the response to BQ-123 and BQ-123/788 in the presence or absence of enalapril was preidentified as the comparison of interest. In study 2, comparison of BQ-123+enalapril with the other three drug combinations individually was preidentified as the comparison of interest.

Results

Six participants were recruited to study 1, and seven were recruited to study 2. Participants completed all phases of study 1 without adverse event. During study 2, one participant experienced an increase in MAP of 50 mmHg after indomethacin administration and before receiving BQ-123 and was withdrawn from the study. Baseline characteristics for the eight participants who completed the studies (four of whom were common to both studies) are shown in Table 1.

### Table 1. Participant demographic data

| Age (yr) | 47 ± 5 (23–64) |
| MK (kg/m²) | 25 ± 2 (18–31) |
| Mean arterial pressure (mmHg) | 88.5 ± 2.7 (71.4–99.4) |
| Creatinine (mg/dl) | 1.01 ± 0.08 (0.70–1.35) |
| Creatinine clearance (ml/min) | 96 ± 7 (70–132) |
| 24-h urinary sodium excretion (mEq/24 h) | 118 ± 15 (64–185) |
| Cholesterol (mg/dl) | 201 ± 12 (151–236) |

*Values are given as mean ± SEM with the range of values given in parentheses.

Study 1: Interaction between ET Receptor Antagonism and ACE Inhibition

**Systemic and Renal Hemodynamics.** Administration of placebo, either alone or after pretreatment with enalapril, did not alter systemic hemodynamics. MAP was reduced after both BQ-123 by 4.2 ± 1.6 mmHg (ANOVA P < 0.05 versus placebo) and BQ-123/788 by 4.4 ± 2.0 mmHg (Figure 1A). After pretreatment with enalapril, the BP reduction after BQ-123 was almost doubled, with MAP falling by 8.3 ± 3.0 mmHg (P < 0.01 versus BQ-123 alone). However, this synergy was not seen when BQ-788 was co-administered with BQ-123, when MAP was reduced by 4.3 ± 3.3 mmHg. SVRI followed a similar pattern (Figure 1B).

Placebo, enalapril alone, BQ-123, and BQ-123/788 all were neutral in respect of ERBF, ERVR, EFF, and GFR. After pretreatment with enalapril, BQ-123 increased ERBF by 146 ± 41 ml/min (P < 0.01 versus placebo and versus BQ-123 alone), reduced ERVR by 32 ± 15 mmHg/min per L (P < 0.01 versus placebo and versus BQ-123 alone), and reduced EFF by 3.4 ± 2.5% (P < 0.05 versus placebo, P < 0.01 versus BQ-123 alone; Figure 2). By contrast, after pretreatment with enalapril, BQ-123/788 reduced ERBF by 224 ± 31 ml/min (P < 0.01 versus placebo and versus BQ-123/788 alone) and increased ERVR by 26 ± 6 mmHg/min per L (P < 0.05 versus BQ-123/788 alone).

**Sodium Excretion.** No significant natriuresis was observed after placebo, enalapril alone, and either BQ-123 or BQ-123/788 alone. However, after pretreatment with enalapril, BQ-123 produced a striking increase in urinary sodium excretion with a maximum excretion rate of 58 ± 27 μmol/min (P < 0.01 versus placebo and BQ-123 alone). FeNa followed a similar pattern. As with renal hemodynamics, this increase was not observed with BQ-123/788 (Figure 3).

**Serum ACE Activity.** Compared with placebo, pretreatment with enalapril reduced serum ACE activity by 75% at baseline (36.4 ± 4.3 versus 9.1 ± 2.3 U; P < 0.01) and by 79% at 150 min (26.5 ± 2.1 versus 5.4 ± 1.7 U; P < 0.01). ET receptor antagonist administration did not alter ACE activity.

**Plasma BQ-123.** BQ-123 was detectable in plasma at 15 min after the start of the low-dose and at 15 and 45 min after the start of the high-dose infusion. Peak BQ-123 concentrations tended to be higher after pretreatment with enalapril, although the difference was not statistically significant (BQ-123, 1.26 ± 0.18 pg/ml; BQ-123/788, 1.32 ± 0.23; BQ-123 + enalapril, 2.06 ± 0.65; BQ-123/788 + enalapril, 2.32 ± 0.53).

Study 2: Effect of NO Synthase Inhibition and Inhibition of Prostaglandin Synthesis on Combined ETA Receptor Antagonism and ACE Inhibition

**Systemic and Renal Hemodynamics.** MAP was reduced by 6.0 ± 1.7 mmHg after BQ-123 in the presence of enalapril. This effect was augmented by indomethacin, with MAP falling by 11.0 ± 2.3 mmHg at the end of the study (P < 0.01 versus BQ-123; Figure 4) and abolished by L-NMMA (P < 0.01...
versus BQ-123). Again, SVRI followed a similar pattern (Figure 4). Indomethacin did not affect the renovascular changes induced by BQ-123 + enalapril, but L-NMMA abolished the effects of BQ-123 + enalapril on both ERBF and ERVR ($P < 0.01$) (Figure 4).

**Sodium Excretion.** The natriuresis produced by the combination of BQ-123 and enalapril was attenuated by indomethacin ($P < 0.01$ versus BQ-123 + enalapril) and abolished by L-NMMA ($P < 0.01$ versus BQ-123 + enalapril) (Figure 4).

**Discussion**

In these studies, we demonstrated a synergy between the effects of ACE inhibition and ETA receptor antagonism in humans, affecting both systemic and renal hemodynamics, as well as renal tubular function. This synergy is abolished by either ETB receptor blockade or NO synthase inhibition but not COX inhibition. We conclude that ETA receptor antagonism and ACE inhibition act synergistically through an ETB receptor–mediated, NO-dependent, and COX-independent mechanism.

The ET and renin-angiotensin systems are known to interact (4), and an *in vivo* synergistic effect between ETA receptor antagonism and ACE inhibition has been demonstrated in animals (12) and between ET receptor antagonism and angiotensin AT1 receptor antagonism in humans (37). We have shown, in healthy men who were subjected to systemic ACE inhibition with a clinically relevant dose of enalapril, that the effects of ETA receptor blockade on systemic hemodynamics are enhanced. With respect to BP, ACE inhibition almost doubled the hypotensive effect of ETA receptor blockade. In addition, in contrast to the absence of an effect of ETA receptor antagonism alone on the renal circulation, the combination with ACE inhibition increased renal perfusion, in association with a fall in EFF. Thus, by inference, this combination causes preferential effenter renal arteriolar vasodilation that should be associated with a fall in glomerular capillary pressure. Such changes in glomerular hemodynamics have the potential to be renoprotective in a manner analogous to the effect of ACE inhibition alone. In addition, this combination produced a striking natriuresis that was still developing to the end of the study, 4 h after initial administration of BQ-123. At its maximum, this natriuresis measured 10 mmol/h, a clinically important degree of sodium loss.

Our results also demonstrate that although maximal hemodynamic changes occurred after the higher dose of BQ-123, potentially useful systemic and renal hemodynamic changes were achieved after a lower dose of BQ-123 in the presence of ACE inhibition. As adverse effects in clinical trials with ET receptor antagonists seem to be largely dose related (38), this

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**Figure 1.** (A) Effects of endothelin (ET) receptor antagonism and angiotensin-converting enzyme (ACE) inhibition on mean arterial pressure. (Left) Mean of percentage change from baseline ± SEM; □, placebo; ■, placebo + enalapril; ○, BQ-123; ◊, BQ-123 + enalapril; ○, BQ-123/788; ●, BQ-123/788 + enalapril; ▼, administration of study drug. (Right) Mean area under curve of percentage change from baseline ± SEM; □, placebo; ■, placebo + enalapril; ■, BQ-123; ○, BQ-123 + enalapril; ●, BQ-123/788; ▼, BQ-123/788 + enalapril. *$P < 0.05$ versus placebo, **$P < 0.05$ versus placebo + enalapril, §$P < 0.05$ versus BQ-123. (B) Effects of ET receptor antagonism and ACE inhibition systemic vascular resistance index. Legend as for A.
Figure 2. (A) Effects of ET receptor antagonism and ACE inhibition on effective renal blood flow. Legend as for Figure 1A. (B) Effects of ET receptor antagonism and ACE inhibition on effective renal vascular resistance. Legend as for Figure 1A. (C) Effects of ET receptor antagonism and ACE inhibition on effective filtration fraction. Legend as for Figure 1A.
Combination might allow the use of a lower and better tolerated dose of ETA receptor antagonist without compromising efficacy.

Montanari et al. (37) demonstrated that ETA receptor antagonism can produce renal hemodynamic changes under conditions of angiotensin AT1 receptor blockade and that this action is inhibited by NO synthase inhibition. We demonstrated a similar synergy between ETA receptor antagonism and ACE inhibition, again dependent on NO, but extended this work by showing that this synergistic effect is abolished, for all indices studied, when the ETB receptor is blocked, suggesting that the ETB receptor is crucial to the mechanism of this interaction. As both L-NMMA and BQ-788 are vasoconstrictors, it is possible that their ability to abolish the vasodilator effect of enalapril and BQ-123 is nonspecific. However, indo- methacin has also been shown to produce renal vasoconstriction in healthy subjects (39) but had no effect on the renal vasodilation seen in this study after enalapril and BQ-123. Similarly, previous studies in healthy volunteers have demonstrated that although this dose of BQ-788 alone produces systemic and renal vasoconstriction, it does not abolish the vasodilator effects of BQ-123 (36), suggesting that the effect seen here is specific to the interaction between ACE inhibition and ETA receptor antagonism. In an experimental rat model of interstitial renal fibrosis, enalapril treatment was shown to increase ETB mRNA expression (40), providing a possible mechanism for this ET-1/ACE interaction. It is possible that ETA receptor antagonism then results in displacement of endogenous ET-1 from the ETA receptor onto the unblocked, upregulated ETB receptor.

Figure 3. Effects of ET receptor antagonism and ACE inhibition on fractional urinary excretion of sodium. Legend as for Figure 1A.
These studies were performed in subjects in a salt-replete state (mean 24-h urine excretion, 119 ± 6 mmol). A recent study suggested that ET-1 plays a role in angiotensin-dependent hypertension in humans (41), particularly with respect to BP and proteinuria. Salt depletion, with enhancement of renin-angiotensin activity, therefore might further enhance the synergy seen between ETA receptor antagonism and ACE inhibition.
It is interesting that in the presence of ACE inhibition in our study, combined ETA/B receptor antagonism tended to increase renal vascular tone and reduce blood flow, underlining the importance of ETB-mediated vasodilation. This finding has important implications for the therapeutic use of ET receptor antagonists, suggesting that, in conjunction with ACE inhibitors, ETA receptor antagonists may be superior to nonselective ETA/B receptor antagonists with respect to some important hemodynamic effects. Indeed, we previously demonstrated in patients who had chronic renal failure and were already being treated with ACE inhibitors that ETA but not combined ETA/B receptor antagonism increases renal blood flow (36). The current demonstration of an ETB receptor–dependent, synergistic interaction between ETA receptor antagonism and ACE inhibition suggests that these differences observed in renal patients may, at least in part, be due to concomitant chronic treatment with ACE inhibitors.

Although prostacyclin is the major COX product of macrovascular endothelium in vitro, COX activity can produce both vasconstrictor and vasodilator achedonic acid derivatives. Prostaglandins stimulate renin release (42). Thus, indomethacin may produce both vasodilation, by inhibition of renin-mediated Ang II generation and COX-1-mediated thromboxane A2 synthesis, and vasoconstriction, by blocking synthesis of vasoconstrictor prostanooids. Studies in animals also suggest that vasconstrictor COX products, such as thromboxane A2 and prostaglandin H2, might be implicated in ET-1–induced vasoconstriction, particularly in disease models (43–47). The greater fall in BP when indomethacin was co-administered with enalapril and BQ-123 may represent blockade of the action of these constrictor COX products. There is evidence from studies in animals that vasodilator prostaglandins may additionally be involved in the actions of ET-1 in the renal circulation, particularly the renal medulla (45,48). We could not demonstrate, however, any inhibitory effect of indomethacin on either the systemic or the renal hemodynamic effects of the combination of ACE inhibition and ETA receptor antagonism. With respect to renal blood flow, however, clearance studies only measure total renal blood flow. It is possible, therefore, that opposite changes are occurring in the renal cortex and medulla.

With respect to natriuresis, knockout and antagonist studies in animals have implicated ETB receptors, linked to NO production, in ET-1–mediated sodium excretion (49). COX inhibition, however, augments big ET-1–mediated natriuresis, suggesting an antinatriuretic role for prostaglandins (50). Our studies demonstrate, in the presence of ACE inhibition, an ETB-dependent natriuresis that is mediated by both NO and, to a lesser extent, prostanooids.

In summary, in this mechanistic study, we demonstrated that ACE inhibition increases the systemic hemodynamic effects of ETA receptor antagonism, at both low and high dose, and unmasks a renal hemodynamic and tubular effect. This synergy is mediated mainly by NO and requires an unblocked ETB receptor. These findings would preferentially support the further investigation of selective ETA receptor antagonism, over combined ETA/B receptor antagonism, as a useful adjunct to ACE inhibition in the management of the systemic and renal vascular consequences of diseases characterized by vasoconstriction. This may be particularly important in circumstances in which sodium loss would also be beneficial, such as hypertension and chronic renal failure. This interaction should now be explored in longer term studies in patients with such conditions.

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