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Clinical trials of endothelin antagonists in heart failure: publication is good for the public health

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The failure of endothelin antagonists to show benefit in heart failure cannot be understood until all the clinical trials are fully published

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Endothelin-1 (ET-1) activates endothelin A (ET_A) and B (ET_B) receptors on vascular smooth muscle cells, resulting in profound vasoconstriction and cellular proliferation.^{1–3} By contrast, endothelial cell ET_B receptors release nitric oxide and prostacyclin, which are antimitotic and mediate vasodilatation.⁴ The relative expression of vascular smooth muscle ET_B to endothelial ET_B receptors varies in different vascular beds and with cardiovascular disease.⁵ Endothelial cell ET_B receptors are also responsible for clearance of ET-1 from the circulation, and thus raised plasma ET-1 concentrations act as an index of ET_B blockade.^{6,7} Renal ET_B receptors may contribute to natriuresis.⁴ Drugs have been developed that are active against ET_A receptors (ET_A selective antagonists) or against both ET_A and ET_B receptors (mixed antagonists).

ROLE OF ET-1 IN CHRONIC HEART FAILURE

Like several other neurohumoral systems, the endothelin system is activated in chronic heart failure (CHF). In experimental heart failure, treatment with either mixed or ET_A-selective antagonists considerably ameliorated left ventricular dysfunction, prevented ventricular remodeling and prolonged survival after coronary artery ligation.⁸ Plasma ET-1 concentrations in patients with CHF correlate with both morbidity and mortality, prompting investigators to pursue the therapeutic potential of endothelin blockade in CHF,⁸ and short-term haemodynamic studies were promising. Two weeks of oral treatment with the mixed endothelin antagonist, bosentan, reduced pulmonary vascular resistance by around 40% and systemic vascular resistance by 30%, without affecting heart rate.⁹ Similarly favourable results were found using the ET_A selective antagonist darusentan, in the Haemodynamic and Neurohumoral Effects of Selective Endothelin A Receptor Blockade in Chronic Heart Failure (HEAT) Study.¹⁰

In light of these, and other, encouraging results, clinical trials were undertaken. In the Research on Endothelin Antagonists in Chronic Heart Failure Study,¹¹ the long-term effects of the mixed endothelin antagonist bosentan (n = 244) versus placebo (n = 126) in patients with New York Heart Association (NYHA) class IIIB/IV CHF were

assessed. This trial was halted prematurely because of increased incidence of raised liver transaminase levels. Nevertheless, patients who had been receiving treatment over a 6-month period showed a trend towards a reduced risk of CHF-related mortality and morbidity. The possibility that long-term bosentan treatment, at a lower dose, would improve the clinical course of patients with CHF was evaluated in two companion large-scale clinical trials, Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure 1 and 2, which were conducted in the US and Europe, respectively. Patients with NYHA class IIIB/IV CHF were given bosentan (n = 805) or placebo (n = 808) in addition to standard treatment. However, the study failed to show that bosentan reduced either morbidity or mortality.¹² Treatment of patients (class II/III CHF) with another mixed antagonist enrasentan (n = 212) or placebo (n = 157) failed to show benefit in a composite end point including NYHA class, hospitalisation rate and global assessment; it rather showed a trend in favour of placebo (Enrasentan Cooperative Randomized Evaluation Study).¹³ None of the clinical trials described above have been fully published. The data required to understand the effects of treatment with endothelin antagonists in CHF are not in the public domain and cannot be subjected to independent peer review. Hence, there has been no opportunity to look across the trials to learn potentially important lessons from them, including whether there may be ways in which patients with CHF might benefit from endothelin antagonists.

ENDOTHELIN ANTAGONISTS: NO EFFECT ON END SYSTOLIC VOLUME

In the Endothelin A Receptor Antagonist Trial in Heart Failure (EARTH) Study, patients with NYHA class II-IV CHF, already receiving standard treatment, were randomised to treatment either with darusentan (n = 532) or with placebo (n = 110) over 24 weeks.¹⁴ The primary end point was the change in left ventricular end systolic volume over the 24 weeks of the study measured by magnetic resonance imaging, rather than long-term mortality, a more conventional end point in CHF trials. The effect of darusentan on left ventricular end systolic volume was no different from that of placebo. Furthermore, during the 6-month-long

Abbreviations: CHF, chronic heart failure; EARTH, Endothelin A Receptor Antagonist Trial in Heart Failure; HEAT, Haemodynamic and Neurohumoral Effects of Selective Endothelin A Receptor Blockade in Chronic Heart Failure; NYHA, New York Heart Association

See end of article for authors' affiliations

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study, no difference was seen in terms of mortality or the progression of CHF. Perhaps importantly, as had previously been shown in the HEAT Study,¹⁰ plasma levels of endothelin-1 increased dose dependently in all groups receiving darusentan ($p = 0.0028$), suggesting that the doses were not ET_A selective.

WHY DID THE CLINICAL TRIALS YIELD NEGATIVE RESULTS?

The promise of clinical benefit from endothelin antagonists in CHF, on the basis of the results of initial preclinical and human haemodynamic studies, has clearly not been fulfilled by the results of large clinical trials, for which there are several possible explanations.

1. Although with some drugs, such as angiotensin-converting enzyme (ACE) inhibitors, short-term haemodynamic studies showing acute improvement can translate into reduced morbidity and mortality in longer-term clinical trials,¹⁵ this is not a reliable surrogate for all therapeutic agents in CHF.¹⁶
2. Despite early studies using endothelin antagonists showing improvements in haemodynamic variables, and indeed in mortality in animal models of CHF post-myocardial infarction,^{17,18} most likely owing to an effect on cardiac remodelling, a recent meta-analysis of the many preclinical studies indicates that endothelin antagonists have no net beneficial effect on mortality.¹⁹ Indeed, early administration of endothelin antagonists after experimental myocardial infarction may increase mortality, most likely due to a remodelling-related increase in cardiac dimensions.^{20,21}
3. Endothelin blockade might have been successful if it had been introduced before the incremental introduction of ACE inhibitors, β -blockers and spironolactone, which are now established as "standard" CHF treatment. Once several neurohumoral systems are blocked, there may be little room for additional benefit, especially if the beneficial actions of endothelin antagonists overlap with those of pre-existing drugs.
4. There may only be specific subgroups, within the total population of patients with CHF, in whom endothelin blockade is beneficial. These may not have been recognised from the clinical trials so far. Endothelin antagonists are known to reduce pulmonary artery pressures in both patients with primary pulmonary hypertension and secondary pulmonary hypertension, due to left ventricular dysfunction.²² Thus, it is possible that patients with CHF with raised pulmonary arterial pressures might benefit from treatment with endothelin antagonists.
5. In contrast with the CHF clinical trials associated with either ACE inhibitors or angiotensin receptor antagonists,²³ treatment with darusentan in both the HEAT¹⁰ and the EARTH¹⁴ studies did not reduce norepinephrine plasma concentrations, thus suggesting that endothelin antagonism, unlike blockade of the renin-angiotensin system, does not have an inhibitory effect on the sympathetic nervous system in CHF.
6. Given the darusentan data, the benefits of endothelin blockade in CHF may derive from ET_A, but not ET_B blockade, which causes deleterious effects including increased plasma ET-1 levels.²⁴ In patients with chronic renal failure and hypertension, the ET_A antagonist, BQ-123, reduced renal vascular resistance and induced natriuresis, effects not seen with mixed ET_{A/B} blockade.²⁵ Hence, in patients with CHF, selective ET_A antagonism might be more likely than mixed ET_{A/B} blockade to avoid fluid retention. In the coronary microcirculation of

patients with ischaemic heart disease, endothelial dysfunction, a known independent risk factor for the development of cardiovascular disease,²⁶ was improved after ET_A,²⁷ but not with combined ET_{A/B} blockade.²⁸

All endothelin antagonists currently under clinical development show greater affinity towards the ET_A than towards ET_B receptor (table 1), but are generally classified as ET_A receptor antagonists if they show more than 100-fold selectivity for the ET_A over the ET_B receptor.²⁹ However, selectivity is dependent on dose, and higher doses of these agents can result in ET_B receptor blockade,³⁰ causing increased ET-1 plasma levels. By contrast, when truly ET_A selective ($>2000\times$) antagonists are used, no significant increase in plasma ET-1 is seen.^{7,24,31,32}

Such data are not dependent on standardised assays, and are given only to allow broad comparison between different antagonists.

The first three clinical trials of endothelin antagonists in CHF (Research on Endothelin Antagonists in Chronic Heart Failure, Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure, Enrasentan Cooperative Randomized Evaluation) have not been published, hence their detailed results, including the effect of drug treatment on plasma ET-1 levels, are not known. However, treatment with darusentan, the most ET_A selective of the agents so far studied in CHF trials, dose dependently increased plasma ET-1 levels in the HEAT¹⁰ and EARTH studies.¹⁴ Thus, probably none of the endothelin antagonists studied so far, at the doses used in the clinical trials, have tested the outcomes with an ET_A-selective approach in CHF.

ENDOTHELIN ANTAGONISTS IN CHF: THE NEXT STEPS

Although the International Committee of Medical Journal Editors will now consider publishing only trials that have been centrally registered before the first patient was recruited,⁴¹ this does not apply retrospectively. Of the clinical trials of endothelin antagonists in CHF, only the EARTH Study has been published. Although we acknowledge that there is little commercial pressure to publish negative studies (and there may be little new to uncover), until the data from these trials are made publicly available, full independent analysis and interpretation of the results, from which patients might serve to benefit, will not be possible. We, like others,⁴² would argue that it is an ethical imperative that trial coordinators should honour their responsibility to the patients that they recruit for clinical studies not only by registering their trials but also by publishing their results.⁴³

Although the EARTH Study investigated the effect of darusentan, an agent with modest selectivity for the ET_A receptor in CHF, at the doses used in this trial, it seems to have

Table 1 Drug codes, names and selectivity for the ET_A receptor for a range of endothelin antagonists used in preclinical and clinical studies

Drug code	Drug name	ET _A selectivity	Ref
J-104132	NA	X 5	Nishikibe <i>et al</i> ^{B3}
RO-470203	Bosentan	X 20	Clozel <i>et al</i> ^{B4}
RO-610612	Tezosentan	X 30	Clozel <i>et al</i> ^{B5}
SB-217242	Enrasentan	X 110	Ohlstein <i>et al</i> ^{B6}
LU-135252	Darusentan	X 130	Munter <i>et al</i> ^{B7}
A-627; A-127722	Atrasentan	X 1860	Opgenorth <i>et al</i> ^{B8}
BQ-123	NA	X 2500	Ishikawa <i>et al</i> ^{B9}
TBC-11251	Sitaxsentan	X 6500	Wu <i>et al</i> ^{B0}
ZD-4054	NA	$>X$ 10000	Morris <i>et al</i> ^{B2}

NA, not available.

had considerable activity at the ET_B receptor. Truly, ET_A-selective endothelin antagonism, therefore, remains untested in these patients, although reduced interest from the pharmaceutical industry in this area means that such trials are unlikely to be undertaken in the near future. Acute treatment of patients with CHF with sitaxsentan, a selective ET_A blocker, seemed to have a preferential effect on the pulmonary circulation, without affecting systemic haemodynamics,⁴⁴ suggesting that this approach might be particularly worthwhile for patients with pulmonary hypertension. Even if the consensus emerges that endothelin antagonists do not confer benefit in CHF, they are now licensed for the treatment of pulmonary arterial hypertension and are being developed for other clinical applications in chronic renal disease, systemic sclerosis, oncology and the management of pain. If the pharmaceutical industry acted in a more open and transparent fashion, allowing full peer review of past trial outcomes, then valuable lessons might be better applied to successful developments in these new areas. For all of these reasons, we would argue that publication is good for the public health.

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