DIABETIC NEPHROPATHY

SONAR propels endothelin A receptor antagonists to success

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The SONAR trial reports that treatment with the selective endothelin A receptor antagonist atrasentan reduced the risk of renal events in patients with diabetes and chronic kidney disease. This study was designed to select patients who were likely to benefit from the therapy and minimize the risk of adverse effects.

Refers to Heerspink, H. J. L. et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet* **393**, 1937–1947 (2019).

The development of drugs for the treatment of renal disease has been slow to evolve, but considerable new hope exists for patients with diabetic nephropathy[1,2]. The SONAR trial reports that treatment with atrasentan (0.75 mg daily), a selective endothelin A (ETA) receptor antagonist, significantly reduced the risk of renal events in patients with type 2 diabetes mellitus and chronic kidney disease (CKD)[1]. This randomized, double-blind placebo-controlled trial was conducted at 689 sites in 41 countries and enrolled over 5,000 participants. The primary end point (a composite of doubling of serum creatinine levels, end-stage renal disease, kidney transplantation or death as a result of kidney failure) was reached by 6% of patients in the atrasentan group and 7.9% of those in the placebo group at a median follow up of 2.2 years (HR 0.65, 95% CI 0.49–0.88, $P = 0.0047$).

An ETA receptor antagonist, ambrisentan, and the dual ETA and ETB receptor antagonists, bosentan and macitentan, have been approved by the US Food and Drug Administration for the treatment of pulmonary hypertension, but additional targets for this class of drugs have been difficult to establish despite considerable promise in animal models and early clinical trials. Over the past 15 years, many laboratories, including our own, have provided compelling rationale that selective ETA receptor antagonists could reduce or slow the progression of renal injury and disease.

Endothelin-1 (ET-1) was first described as a potent vasoactive factor that produces complex and opposing actions within the vasculature. Owing to the autocrine and paracrine nature of this system, understanding the biology has been extremely complex and slow to develop. ET-1 acts through two receptor pathways, ETA and ETB. Within the kidney, ETA receptor activation mediates sodium retention, fibrosis and inflammation, whereas ETB receptor activation facilitates sodium excretion via activation of the nitric oxide synthase 1β–nitric oxide (NO) pathway in the collecting duct and subsequent inhibition of epithelial sodium channel activity as well as protection against the actions of ETA receptor activation on fibrosis and inflammation (FIG. 1). In endothelial cells, ETB receptor activation facilitates the production of nitric oxide synthase 3–NO, promoting vasodilation and anti-inflammatory actions. Knowledge of the complex interactions of the ET-1 system within numerous cells and the actions of ETA and ETB receptors assisted in the design of the SONAR trial.

> “ETA receptor antagonists hold … promise for slowing the progression of a wide range of renal diseases”

Many of the early trials in patients with cardiovascular and renal disease were conducted using dual ETA and ETB receptor antagonists, such as bosentan, that produce variable effects depending on the dose of drug and heterogeneity of the target population. Most of the selective ETA receptor antagonists are more potent than bosentan and thus have an increased potential for benefit, but also an increased risk of adverse effects when given at similar doses. For example, ETA receptor antagonists may produce fluid retention when given at doses higher than the effective range. Such fluid retention does not occur with bosentan, which is an order of magnitude less potent than ETA receptor antagonists and also blocks ETB receptor actions. Fluid retention can be life threatening in at-risk patients, such as those with congestive heart failure[3]. An early phase II study of atrasentan indicated that when the drug was given at low effective doses, the frequency of fluid retention was similar to that seen in the placebo group[4]. In the SONAR trial, the incidence of fluid retention was higher in the atrasentan group (36.6%) than in the placebo group (32.3%), but this increased incidence was not associated with a significantly increased incidence of adverse events that led to patients discontinuing the trial[1].

The beauty of the SONAR trial was the use of an approach that selected for those individuals who were most likely to benefit. The clinical trial design included a run-in period to select patients who responded to atrasentan (that is, those who showed a ≥30% reduction in urinary albumin:creatinine ratio (UACR) after 6 weeks of treatment and did not develop fluid retention)[1]. All participants were also required to be treated with a stable, maximally tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for 4 weeks before entry into the trial, which was used to ensure effective standard of care. Thus, atrasentan treatment was effective when combined with maximal blockade of the renin–angiotensin system at an individual level. Incorporating this personalized approach into the clinical trial design facilitated a successful outcome for atrasentan in slowing the progression of diabetic nephropathy.

Several ETA receptor antagonists have previously shown great promise in patients with resistant hypertension and prostate cancer in various phase II trials, but the phase III trials were designed without regard to the participants' potential for benefit and/or risk for fluid retention. In addition, previous phase III trials of ETA receptor antagonists did not

meet their primary end points and the results were not sufficient to move towards marketing the drugs even though they may have been effective in a subpopulation or met some important secondary end points. In-depth analysis of these phase III trials as well as further analysis of the SONAR trial data may provide additional rationale for proceeding with trials of ETA receptor antagonists that incorporate a more personalized approach in patients with resistant hypertension[5] or prostate cancer[6] as well as for additional renal targets such as hypertension-induced kidney disease or sickle cell nephropathy[7].

The SONAR trial and the CREDENCE trial of sodium–glucose transporter 2 inhibitors, both reported in April 2019, are the first successful trials of kidney-targeted therapeutics specifically in patients with diabetes in over 10 years[1,2]. ETA receptor antagonists hold substantial promise for slowing the progression of a wide range of renal diseases as their beneficial effects are not limited to patients at risk of hyperglycaemia. Preclinical and small clinical studies show that ETA receptor antagonists are effective in models of non-diabetic CKD including focal segmental glomerulosclerosis, hypertension-induced kidney disease and sickle cell nephropathy[8]. Furthermore, ETA receptor antagonists might be favourable agents for alleviating chronic pain and reducing opioid tolerance. A proof-of-concept study showed that specific knockout of ETA receptors in the dorsal root ganglia normalized heat and cold-induced pain thresholds in a mouse model of sickle cell disease with pain hypersensitivity[9]. Thus, the potential for ETA receptor antagonists has not yet been fully realized.

There is much excitement about atrasentan as a potential new kidney disease therapeutic, but this excitement is dampened by the question of whether AbbVie will develop this potentially life-saving drug given the manner in which the SONAR trial was abruptly ended. The tremendous potential of atrasentan cannot be overstated; thus, further in-depth analysis of data from the SONAR trial will be necessary to go forward. The future of ETA receptor antagonists is somewhat uncertain given that the patents of most of these compounds will soon expire or have already expired. Several pharmaceutical companies are now looking at alternative compounds with longer patent lives. Newer agents with combined mechanisms of action such as sparsentan, a dual ETA receptor and type 1 angiotensin II receptor antagonist, are promising candidates for blunting diabetic and non-diabetic renal disease progression as well as for cardiovascular disease targets[10].

The SONAR trial demonstrates that clinical trial design must be based on fundamental scientific knowledge of the therapeutic target and incorporate effective dosing of potent antagonists. Identifying those patients who would benefit from atrasentan therapy and those who were at risk of adverse effects propelled SONAR to success.

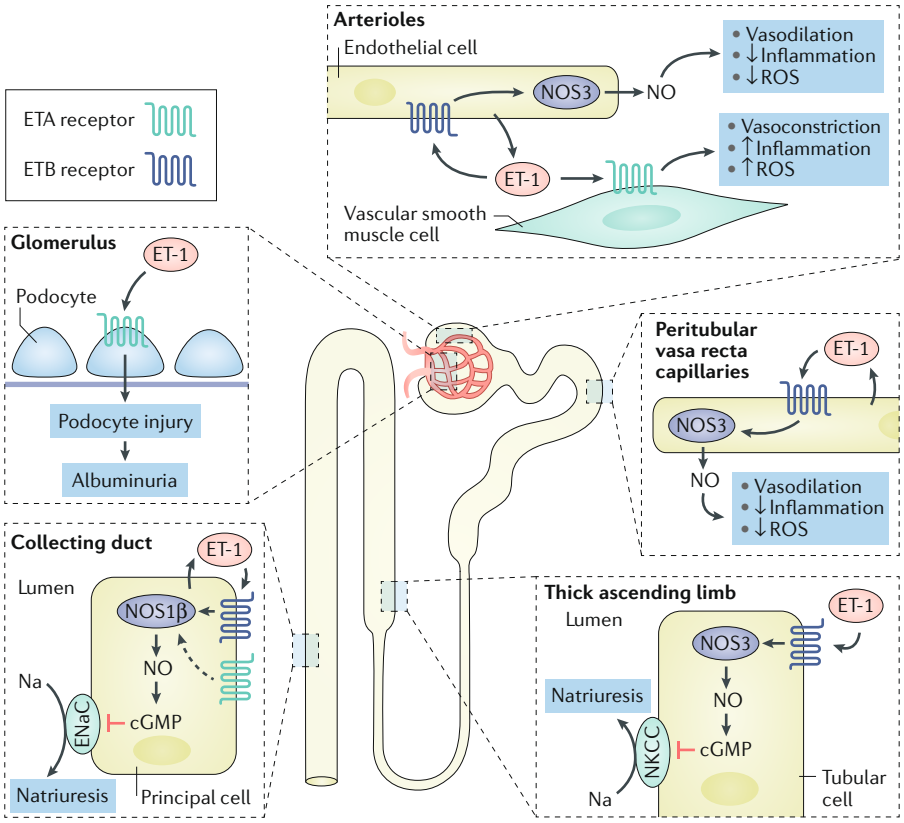

Fig. 1 | **Summary of the major known actions of the ET-1 system in the kidney.** The autocrine and paracrine nature of the endothelin-1 (ET-1) system enables a variety of functions. The endothelin A (ETA) receptor and ETB receptor pathways are generally in opposition, but this is not the case under all conditions. The actions of the ET-1 system are further complicated by differential changes in ETA receptor and ETB receptor expression in a variety of cardiovascular and kidney diseases. cGMP, cyclic guanosine monophosphate; ENaC, epithelial sodium channel; NKCC, Na-K-Cl cotransporter; NO, nitric oxide; NOS1β, nitric oxide synthase 1β; NOS3, nitric oxide synthase 3; ROS, reactive oxygen species.

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Competing interests
The authors declare no competing interests.