# Endothelin Receptor Antagonists for Kidney Protection

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Endothelin Receptor Antagonists for Kidney Protection: Lessons from the SONAR Trial

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The endothelin system has been widely implicated in chronic kidney disease (CKD). Binding of ET-1, the effector peptide of the endothelin system, to the endothelin-A receptor (ET-A) causes endothelial glycocalyx damage, glomerulosclerosis, podocyte injury and activates pro-inflammatory and pro-fibrotic pathways. Clinical studies demonstrated that ET-A receptor antagonists (ERA) reduce albuminuria in patients with CKD suggesting long term clinical benefit. However, ERAs may also cause sodium retention and edema, mediated via ET-B receptors, which may increase the risk of heart failure in high-risk patients. These studies also demonstrated that the degree of albuminuria reduction and sodium retention in response to ERAs vary between and within patients suggesting it is possible to identify patients with maximal potential benefit (albuminuria reduction) and minimal risk of known adverse events (sodium retention).

Based on strong anti-albuminuric effects of the ERA atrasentan in a phase 2 study, the SONAR trial was designed to assess the long-term benefit of atrasentan on the risk of kidney failure. The trial design included a six weeks open label treatment period before patients were randomized, termed enrichment period. The enrichment period was included to select patients with a large reduction (≥30%) in urinary albumin:creatinine ratio (UACR) without signs of sodium retention. The trial recruited 2648 of such responder patients. This cohort constituted the primary population to study the long-term efficacy and safety of atrasentan. However, since it was unknown if atrasentan could also benefit the non-selected patients, 1020 "non-responders", defined as patients with no signs of sodium retention and UACR reduction <30% during enrichment, were randomized in a separate stratum.

During the conduct of the SONAR trial it became apparent that the rate for the primary outcome (doubling of serum creatinine, end-stage kidney disease or death due to kidney failure) was much lower than originally anticipated. This meant that it would take much longer to complete the trial. The sponsor of the trial therefore decided to stop the trial after a median follow-up of 2.2 years. When the close-out visits were completed, the results showed that atrasentan significantly decreased the risk of the primary outcome compared to placebo by 35% (hazard ratio 0.65 [95%CI 0.49, 0.88]; p=0.005).

Since the SONAR trial demonstrated for the first time the long-term efficacy of an ERA for the treatment of CKD and because the trial used a design novel to diabetic kidney disease several pre-specified and post-hoc analyses have been conducted to inform future trial designs in nephrology and understand the role of ERAs in kidney disease.

The early termination of the trial and the low number of endpoints have raised questions about the credibility of the trial results. Indeed, 184 of the 425 pre-defined primary outcomes had occurred at completion of the trial and one could thus question whether the trial results are robust enough to draw reliable conclusions. To determine robustness of a trial result the fragility index has been proposed. It determines the number of events that has to be added to the intervention group to reverse the p-value from ≤0.05 to >0.05. Such a calculation was made for the SONAR trial by Walsh and suggested that only 1 event had to be added to the atrasentan group to slip the observed p-value of 0.005 (not 0.05!) to >0.05. This would indicate that it is difficult to draw firm conclusions of the trial. However, before we dismiss the SONAR results, it is important to consider some aspects of the fragility index in more detail. The fragility index is based on reported trial results and is not using the individual patient data. It compares the number of events in the intervention and control group but does not take into account the time to the event of interest. It is therefore inappropriate to use the index in trials where the outcome depends on survival time, such as the time to kidney failure. We have re-calculated the fragility index using individual patient data and the pre-specified Cox proportional hazards model from SONAR taking into account the time to event. These analyses...
demonstrated that only when 11 events were added to the atrasentan group the results of the trial became non-significant with a P-value >0.05. This fragility index is thus much larger than the previously reported index of 1. Although there is no consensus about a clinically relevant fragility index threshold, a fragility index of 11 is also higher than the median fragility index of 399 high impact clinical trials which has been reported to be 8. This indicates that the results of SONAR are robust and unlikely a chance finding.

A key design aspect of the SONAR trial was the enrichment period and enrollment of patients with and without a 30% reduction in albuminuria. Although the trial was not powered to detect a treatment effect in non-responders, the observed hazard ratio of 0.75 [95%CI 0.55,1.03] in this group suggests that the benefit of atrasentan would be independent of the degree of albuminuria lowering during the six weeks enrichment period. This finding was unexpected and led to further analyses. These analyses demonstrated that within the atrasentan group, larger reductions in albuminuria were statistically significantly associated with a lower risk of kidney outcomes. However, in patients who were assigned to placebo treatment, the early reduction in albuminuria during the enrichment period was also associated with a lower risk of the kidney outcome. This was no expected since we had expected that the reduction in albuminuria during 6-weeks atrasentan treatment would not predict kidney outcomes during the subsequent years when patients were treated with placebo. Nevertheless, because of this effect, the effect of atrasentan compared to placebo on kidney outcomes was similar in responder and non-responders. The important question to answer is why the albuminuria change during enrichment predicted kidney outcomes in the placebo group? It appears that the albuminuria levels after transitioning from atrasentan to placebo at the randomization visit did not return to pre-enrichment values. As a result, the difference in albuminuria between atrasentan and placebo after randomization was similar in responders and non-responders. We don’t know why albuminuria did not return to baseline after randomization but legacy effects, variability in albuminuria measurements and introduction of concomitant medications, as well as improved adherence to standard of care treatment may have contributed. Importantly, these results do not dismiss albuminuria as a valid surrogate since during double blind treatment in both responders and non-responders the UACR levels and risk of kidney outcomes were lower in the atrasentan compared to placebo group (figure 1). However, they underscore careful consideration of trial design when using UACR as a response enrichment criterion in future trials.

Because previous trials demonstrated increased risk of edema and heart failure with ERA treatment, the enrichment period in SONAR also provided an opportunity to assess tolerability to atrasentan and exclude patients with signs of sodium retention in order to enhance the benefit-risk profile. During enrichment 574 patients were excluded due to signs of sodium retention (body weight increase ≥3 kg or a BNP increase ≥300 pg/mL). Although comparisons between trials should be done with caution, the annual heart failure hospitalization rate with atrasentan in SONAR was markedly lower than the observed rate in a previous trial with the ERA avosentan (1.9% vs 18%). This suggests that the enrichment period along with other mitigation strategies including the use of diuretics and exclusion of patients with prior heart failure seemed to work.

How does the future look like for ERAs? Various trials with ERAs are ongoing. These trials use different strategies to mitigate risk of sodium retention and optimize the benefit-risk profile. A couple of trials enroll patients at relatively low risk of heart failure such as patients with CKD without diabetes. The efficacy and safety of atrasentan (ALIGN and AFFINITY) and sparsentan (PROTECT and DUPLEX) are investigated in patients with IgA or FSGS nephropathy. It is noteworthy that in the PROTECT and DUPLEX trials sparsentan significantly reduced albuminuria and was well tolerated.
compared to control treatment supporting potential long-term beneficial effects in these populations. Another strategy used to mitigate the risk of heart failure is to combine an ERA with a sodium glucose co-transporter 2 inhibitor (SGLT2). SGLT2 inhibitors have natriuretic/diuretic effects which may abrogate sodium retention and reduce the risk of heart failure in a similar way as thiazide or loop-diuretics. The ZENITH trial tests this hypothesis and randomizes patients with CKD, with and without type 2 diabetes, to zibotentan in combination with the SGLT2 inhibitor dapagliflozin. Results of this trial are expected in 2023.

The SONAR trial has proven the efficacy of ET-1 blockade to reduce the risk of kidney failure in patients with type 2 diabetes and CKD. Endothelin receptor antagonist are a welcome addition to the pharmacological armamentarium to further reduce the risk of kidney outcomes in patients already treated with RAAS and/or SGLT2-inhibitors. The degree of albuminuria lowering seems to be a valid surrogate to target ERAs, although long-term efficacy and safety data are needed from well designed trials based on the lessons from SONAR.
Disclosures

D. de Zeeuw served on advisory boards and/or speaker for Bayer, Boehringer Ingelheim, Fresenius, Mitsubishi-Tanabe, Traver Pharmaceuticals; steering committees and/or speaker for AbbVie and Janssen; and Data Safety and Monitoring Committees for Bayer. Honoraria paid to institution and consultant/speaker. D. de Zeeuw reports consultancy agreements with Abbvie, Bayer, Boehringer Ingelheim, Fresenius, Janssen, Mitsubishi Tanabe, and Traver Pharmaceuticals and honoraria from Bayer, Boehringer Ingelheim, Fresenius, Janssen, Mitsubishi Tanabe, and Traver Pharmaceuticals.

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Author Contributions
Dick de Zeeuw: Writing – review & editing
Hiddo J.L. Heerspink: Writing – original draft
Figure 1: Trial level analysis for the association between effects of atrasentan compared to placebo on albuminuria and effects of atrasentan compared to placebo on the clinical endpoint for UACR responders and non-responders using a previously published meta-analysis of clinical trials among participants who had baseline UACR of more than 30 mg/g. The data from UACR responders and non-responder fall are within the 95% Bayesian confidence and prediction bands indicating that the data from the SONAR trial support albuminuria as a potential surrogate for clinical kidney outcomes.

The vertical axis indicate the estimated treatment effect on a clinical endpoint (hazard ratio [HR]) and the horizontal axis are the estimated treatment effects on the change in UACR (geometric mean ratio [GMR] of log-transformed ACR). The clinical endpoint was defined as a composite of end-stage kidney disease, doubling of serum creatinine. The different colored circles indicate intervention types; each circle is a separate clinical trial/intervention with the size of each circle proportional to the number of events. The regression line through the studies and the Bayesian confidence and prediction bands are shown. The filled green circle represents the SONAR responder stratum and the filled blue circle the SONAR non-responder stratum. The size of the filled circles are not proportional to the size of the study relative to the other studies. Difference in UACR between atrasentan and placebo in UACR responders 33.6% (95%CI 29.1, 38.2); Difference in UACR between atrasentan and placebo in UACR non-responders 27.4% (95%CI 19.7, 34.3). (Figure adapted from reference: Heerspink HJL et.al. Lancet Diabetes & Endocrinology 2019 Feb;7(2):128-139)
References: