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Endothelin receptor antagonists for the treatment of diabetic and nondiabetic chronic kidney disease

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Purpose of review
To summarize new clinical findings of endothelin receptor antagonists (ERA) in various etiologies of kidney disease targeted in clinical trials.

Recent findings
Endothelin-1 is a multifunctional peptide with potential relevance to glomerular and tubulointerstitial kidney diseases. The phase 3 SONAR trial demonstrated a significant reduction in clinically relevant kidney outcomes for patients with diabetic kidney disease (DKD) after long-term treatment with the ERA, atrasentan, in addition to blockade of the renin-angiotensin-aldosterone system. Promising preclinical disease models and small clinical trials in non-DKD resulted in the initiation of phase 3 trials investigating the effects of long-term treatment with ERA in patients with immunoglobulin A (IgA) nephropathy and focal segmental glomeruloscelerosis (FSGS). The mechanisms by which ERA protects the kidneys have been extensively studied with evidence for the protection of tubule cells, podocytes, mesangial cells, the endothelial glycocalyx, and a reduction in glomerular perfusion pressure. The occurrence of fluid retention during ERA treatment, particularly in susceptible populations, necessitates strategies to support safe and effective treatment.

Summary
Treatment with ERA induces long-term kidney protection in DKD. Phase 3 trials are underway to investigate ERA effects in patients with IgA nephropathy and FSGS.

Keywords
albuminuria, chronic kidney disease, endothelin receptor antagonist, nephropathy

INTRODUCTION

Since the identification of endothelin-1 (ET-1) in 1988 as a potent vasoactive peptide, three isoforms of endothelin have been described: ET-1, ET-2, and ET-3. These three ET-1 isoforms act on two G-protein coupled receptors: ET_A and ET_B. Increased ET-1 expression in the kidney contributes to chronic kidney disease (CKD) pathogenesis [1]. Multiple injurious factors commonly associated with the progression of kidney diseases such as type 2 diabetes, hypertension, and obesity promote renal ET-1 production which, via the ET_A receptor, stimulates pathologic processes in the kidney such as cell proliferation, hypertrophy, inflammation, and extracellular matrix accumulation [1]. ET_B activation seems to have a more protective role through vasodilatory and antifibrotic effects. Selective ET_A antagonists have been developed which have been shown to be protective in experimental models of kidney disease, including diabetic kidney disease (DKD), various glomerulonephritides, and models of reduced kidney mass [2]. This review summarizes new findings on the effects of ET receptor antagonists (ERA) in various etiologies of kidney diseases that are currently targeted or considered for targeting in clinical trials.

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KEY POINTS

- Endothelin receptor antagonists induce long-term kidney protective effects in patients with diabetes and CKD.
- Additional research is required to reduce the safety risk due to fluid retention and heart failure and improve the understanding of the protective mechanism of ERA.
- Phase 3 trials are ongoing to investigate to long-term effects of ERA on kidney protection in non-DKD.

GENERAL PATHOBIOLOGY OF ENDOTHELIN AND THE KIDNEY

Almost all kidney cells synthesize ET-1 and the ET receptor is abundantly expressed in the kidney [3]. The ET system regulates several key physiologic functions in the kidney including total and regional blood flow, fluid and electrolyte excretion, and glomerular filtration rate (GFR). The ET system is also relevant to glomerular and tubulointerstitial pathophysiology [3]. Within the glomerulus, ET-1 is produced by and acts upon glomerular endothelial cells (GEC), mesangial cells, and podocytes, hence the potential for complex autocrine and paracrine regulation exists [4]. In rats, infusion of ET-1 induced a prolonged state of glomerular large-pore hyperpermeability. ET_A, but not ET_B, blockade reversed the state of glomerular hyperpermeability [5]. Thus, glomerular leakage of plasma proteins could be due, at least in part, to increased local ET-1 activity. In addition, ET-1 hyperactivity can damage the glycocalyx. The glycocalyx is a mesh-like layer on the luminal surface of the glomerular capillary endothelium, primarily composed of glycoproteins such as heparan sulfate glycosaminoglycans. Heparanase degrades heparan sulfate glycosaminoglycans and is upregulated in renal epithelial cells in diabetic nephropathy [6]. ET_A antagonism increased the endothelial glycocalyx, decreased glomerular heparanase, and reduced proteinuria in diabetic mice [7]. Podocyte-derived heparanase increased endothelial cell albumin permeability, whereas podocyte-specific knockout of ET_A and ET_B prevented diabetes-induced increases in glomerular heparanase, restored the glycocalyx, and reduced proteinuria [8]. Podocytes form another essential component of the glomerular barrier function and podocyte damage is often associated with the progression of CKD. In podocytes, ET_A activation induces actin cytoskeleton disruption, slit diaphragm dysfunction, basement membrane alterations, apoptosis, and inflammation [4]. Endothelin receptor antagonism with darusentan reversed these processes and improved podocyte function in an animal model of age-dependent glomerulosclerosis [9]. Thus, ET-1 is involved in intra- and inter-cellular regulation of all components of the glomerular filtration barrier.

Within the tubulointerstitial system, the presence of ET-1 in the collecting duct (CD) has been implicated in kidney injury. The CD produces far more ET-1 than other kidney cell types. CD ET-1 inhibits Na^+ transport and prevents salt-induced blood pressure elevations [3]. CD-specific knockout of Dot1, a histone methyltransferase that represses *EDN1* gene expression (ET-1 is synthesized from the *EDN1* gene), exacerbated kidney fibrosis associated with DKD, aging, or ureteral obstruction in mice; this was prevented by coincident CD ET-1 knockout [10].

Inflammation is an important mechanism in the development of CKD; genes overexpressed in CKD kidneys are specifically associated with molecular processes involved in inflammatory and immune networks [11]. Renal ET-1 induces inflammatory processes via ET_A [12]; however, recent studies found that inflammatory cell ET_B may also contribute to renal injury since deletion of myeloid cell ET_B mitigated angiotensin-II induced renal injury and macrophage-mediated inflammation [13].

The central role of the ET system in the pathogenesis of experimental CKD suggests that blockade of the ERA, in particular with interventions that selectively target ET_A, may translate into beneficial effects in various causes of CKD. We first review clinical studies in patients with DKD, which is characterized by glomerular damage and tubulo-interstitial inflammation, and subsequently discuss the use of ERA in non-DKD.

EFFECTS OF ERA IN DIABETIC KIDNEY DISEASE

Several clinical studies have described increased ET-1 activity in patients with diabetes and CKD. A study on the renal expression of ET-1 and ET_A found that patients with diabetes and CKD had increased immunostaining for ET-1 and ET_A in renal endothelial cells [14]. In patients with type 2 diabetes mellitus, plasma ET-1 concentration was positively correlated with urinary albumin excretion even when albuminuria levels were relatively low [15]. Moreover, increased plasma ET-1 concentration has been associated with a reduction in measured GFR ($< 60\,mL/min/1.73m^2$) [16]. These observational studies suggest a role for ET-1 in the progression of CKD in patients with diabetes.

Ensuring clinical trials have investigated the effect of ERA on albuminuria and CKD progression in patients with diabetes. Here, treatment with ERA

was always in addition to angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB), as blockade of the renin-angiotensin system (RAS) is the mainstay of DKD treatment.

Treatment with the ERA avosentan significantly decreased the median urinary albumin creatinine ratio relative to baseline in a group of 286 patients with DKD [17]. Posthoc analysis showed a dose-dependent increase in the incidence of fluid retention up to 32.1% in the 50 mg/day group versus 3.5% in the placebo group [17]. The authors concluded that the optimal risk-benefit ratio for albuminuria lowering versus fluid retention was 10 mg. However, despite these recommendations, the dosages used in the subsequent phase 3 ASCEND trial in patients with type 2 diabetes and CKD were 25 and 50 mg/day. The ASCEND trial was terminated prematurely because of excess heart failure in the avosentan group after a median follow-up of 4 months. At the time the trial was terminated, significantly reduced albuminuria and fewer doubling of serum creatinine or end-stage kidney disease endpoints occurred in the avosentan group compared to the placebo group (Fig. 1) [18]. In retrospect, the dosage of avosentan was too high in the ASCEND trial [19].

The high rates of fluid retention and congestive heart failure in the ASCEND trial may be attributed to the high avosentan doses, relatively poor patient selection (eliminating those at higher risk for heart failure), and/or the relative low selectivity of avosentan for the ET_A compared to the ET_B receptor. Two phase II clinical trials with the more selective ET_A antagonist, atrasentan, demonstrated significant reductions in albuminuria after 8–12 weeks of treatment in patients with type 2 diabetes and CKD; at the 0.75 mg dose, there were minimal fluid retention and no heart failure events [20,21]. These findings led to a large confirmatory trial to assess the long-term renal protection and safety of atrasentan in patients with type 2 diabetes and CKD. The SONAR trial employed an active 6-weeks run-in period to select patients with a favorable response to atrasentan (defined as an albuminuria reduction of at least 30%) without known side effects (fluid retention or increases in serum creatinine) [22▪▪].

The trial sponsor decided to terminate SONAR early because of an unexpected low rate for the primary composite outcome (doubling of serum creatinine or onset of end-stage kidney disease). Despite this, atrasentan (0.75 mg/day), compared to placebo, significantly reduced the risk of the primary composite renal outcome by 35% (hazard ratio [HR] 0·65 [95% CI 0·49–0·88]) after a median follow-up of 2.2 years. However, despite precautionary measures to avoid significant fluid retention, including diuretic treatment recommendation and exclusion of patients with signs of excessive fluid retention during the active run-in period, there was a higher proportion of fluid retention related adverse events (36.6% versus 32.3%) and a numerically higher incidence of hospitalized heart failure (3.5% versus 2.6%) with atrasentan compared to placebo, respectively. Thus, additional strategies, as described below, to manage fluid retention in patients with diabetes and CKD during ERA treatment should be explored. In this respect, it is of interest to note that bio-active adrenomedullin, which is a biomarker reflecting interstitial fluid overload, may be a promising new biomarker to identify at an earlier stage and monitor patients at risk for fluid overload, edema, and heart failure during ERA treatment [23].

Studies examining the mechanisms by which ERA protect the kidney support a role for beneficial kidney hemodynamic effects. A cross-over study in 10 patients with type 1 diabetes examined the

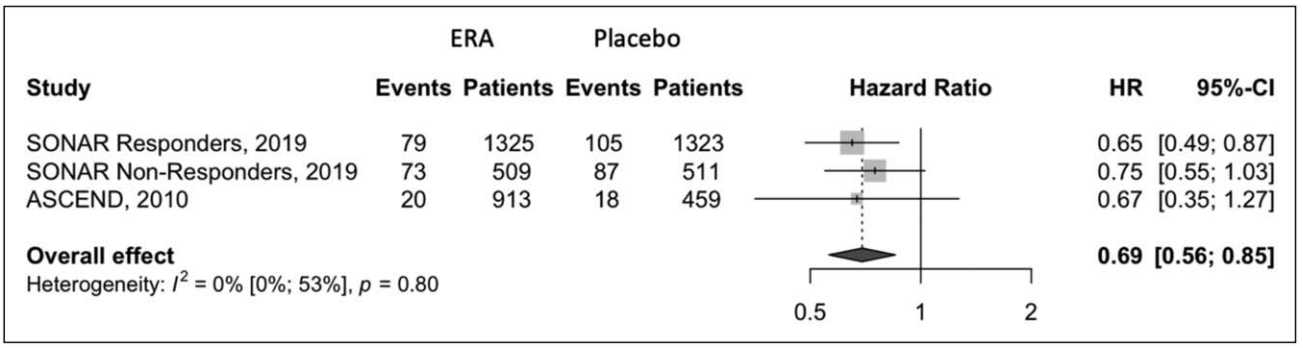

FIGURE 1. Endothelin receptor antagonists reduce the risk of major kidney outcomes in patients with diabetic kidney disease. The figure shows a meta-analysis of two clinical trials establishing the long-term efficacy of endothelin receptor antagonists in patients with diabetic kidney disease. The efficacy of atrasentan in the SONAR trial is presented for the 'responders' and 'nonresponder' separately [18,53▪]. The outcomes shown in the forest plot are the primary composite outcome of doubling of serum creatinine or end-stage renal disease in the SONAR trial and doubling of serum creatinine in the ASCEND trial.

systemic and renal hemodynamic response to 6 weeks treatment with atrasentan (5 mg/day) in the absence of ACE inhibitors or ARBs [24]. Compared to placebo, mean arterial pressure (MAP) and albuminuria decreased significantly, and measured GFR (inulin clearance) tended to decrease with atrasentan. Atrasentan did not detectably alter effective renal plasma flow or renal blood flow (RBF), suggesting a reduction in filtration fraction and renovascular resistance (RVR) (Fig. 2). The small sample size of this study did not allow for definitive conclusions and the findings have to be confirmed in other dedicated kidney hemodynamic studies. The tendency towards a reduction in filtration fraction and RVR suggest dilation of the efferent glomerular arterioles similar to the renal hemodynamic effects observed with ARB. Whether these hemodynamic effects can be generalized to patients with type 2 diabetes and whether they persist when added to an ACE inhibitor or ARB requires additional study.

EFFECTS OF ENDOTHELIN RECEPTOR ANTAGONIST IN NONDIABETIC KIDNEY DISEASE

The use of ERA in kidney disease extends beyond diabetes as the ET system is activated in virtually all causes of experimental and human CKD in which it has been investigated [1]. Accordingly, various clinical trials in patients with CKD without type 2 diabetes are currently ongoing.

Endothelin receptor antagonist in immunoglobulin a nephropathy

Immunoglobulin A (IgA) nephropathy is the most common primary glomerulonephritis in the world. Although the development of IgA nephropathy likely involves multiple steps, the primary renal defect entails mesangial deposition of aberrantly glycosylated IgA1 immune complexes. The immune deposits induce proliferation of mesangial cells, local release of cytokines, and loss of podocytes [25]. The most important risk factor for progressive renal function loss in IgA nephropathy is sustained albuminuria. For IgA nephropathy patients at risk for progressive kidney injury, ACEi and ARB are the first line of treatment. There is no clear consensus for second-line therapy, however, one possibility is ET system blockade since ET-1 likely contributes to the pathogenesis of IgA nephropathy. Inhibition of ET_A improves renal histology and decreases proteinuria in ddY mice, a model of IgA nephropathy [26]. ET-1 is elevated in IgA nephropathy monocytes and kidneys [14,27–29], and neutrophils from IgA nephropathy patients, compared to controls,

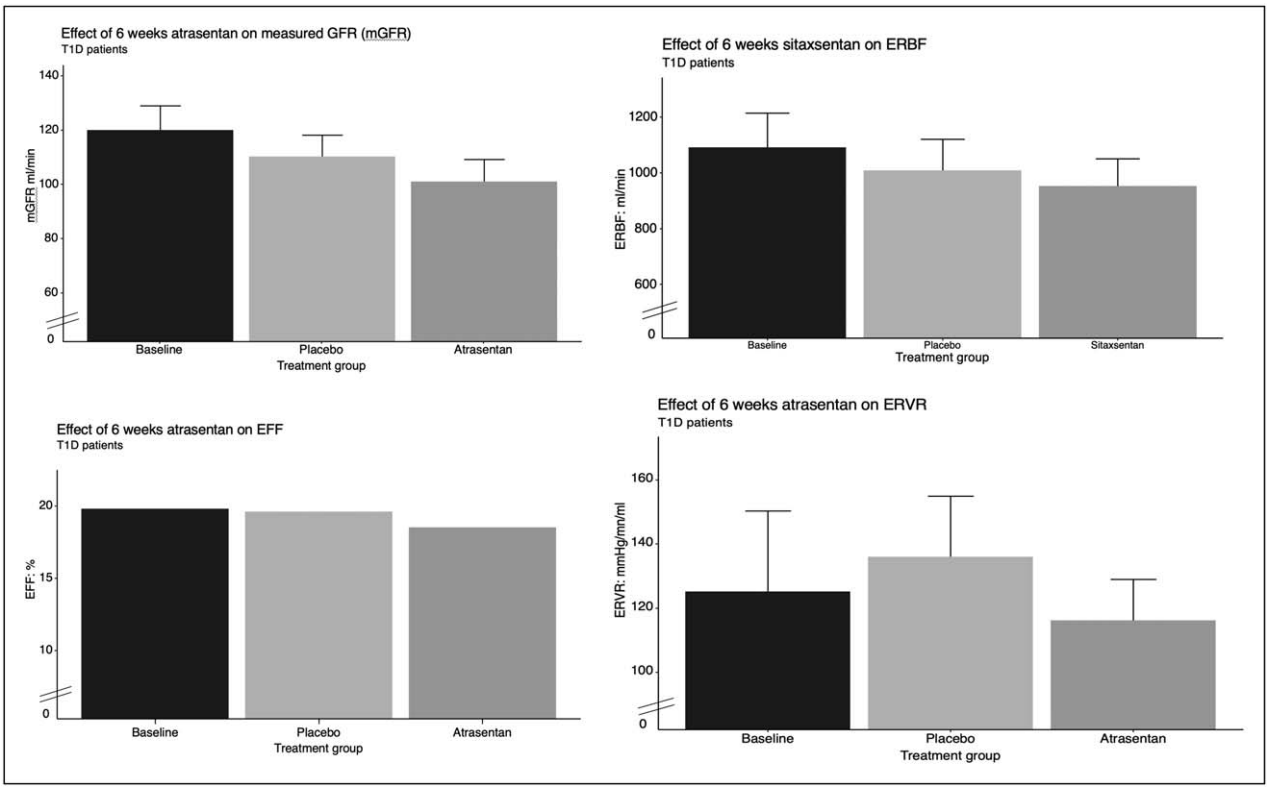

FIGURE 2. Effect of atrasentan on kidney hemodynamics in patients with type 1 diabetes. ERPF, effective renal plasma flow; ERBF, effective renal blood flow; ERVR, effective renal vascular resistance; GFR, glomerular filtration rate. Honing *et al.* [24].

hyper-stimulate mesangial cell ET-1 production [30]. Further, renal ET-1 levels measured in biopsies from patients with IgA nephropathy directly correlates with albuminuria and 1-year progression [14,28,29].

Additional evidence for targeting the ET system in IgA nephropathy comes from small randomized controlled clinical trials in nondiabetic CKD. The selective ET_A antagonist sitaxsentan reduced 24-h proteinuria by approximately 30% in 27 patients with CKD without diabetes already on optimal RAS inhibition; 52% of the subjects had biopsy proven IgA nephropathy [31]. There was considerable variability in the response to sitaxsentan: 9 patients had $>$ 40% reduction in proteinuria and 2 patients showed no change. The change in proteinuria was strongly related to the baseline urinary protein excretion irrespective of baseline GFR [31]. The same study included a substudy that investigated the renal hemodynamic effects of 6 weeks sitaxsentan in 13 patients. Sitaxsentan significantly reduced proteinuria, MAP, measured GFR and effective filtration fraction (EFF); Figs. 3 and 4 [31]. No significant change was observed in the effective RBF. The observed drop in EFF (−4%) could be due to a reduction in the efferent arterial tone in response to ET_A receptor antagonism although no significant change in effective RVR was observed. Another placebo-controlled cross-over trial reported the short-term systemic and kidney hemodynamic effects of BQ-123 (a selective ET_A antagonist), BQ-788 (a selective ET_B antagonist), or a combination of BQ-123/BQ-788. The study enrolled 8 patients with CKD (4 had IgA nephropathy) and 8 healthy controls [32]. In patients with CKD, but not in healthy controls, BQ-123 decreased MAP by 12.9 mmHg (SD 1.7). BQ-123 reduced RVR (−243 mmHg/min/L^{-1} (SD 91)) and FF (−4.2% (SD 2.9)). In contrast, BQ-788 reduced ERBF and increased ERVR, which was associated with a decrease in GFR and increase in EFF. These findings suggest a reduced glomerular efferent arteriolar tone in response to selective ET_A antagonists similar to that observed in patients with type 1 diabetes.

Two clinical trials are investigating the effects of ERA in patients with IgA nephropathy on the primary endpoint of change in proteinuria and a confirmatory endpoint of change in eGFR. These endpoints are based on accumulating evidence demonstrating that change in proteinuria is a

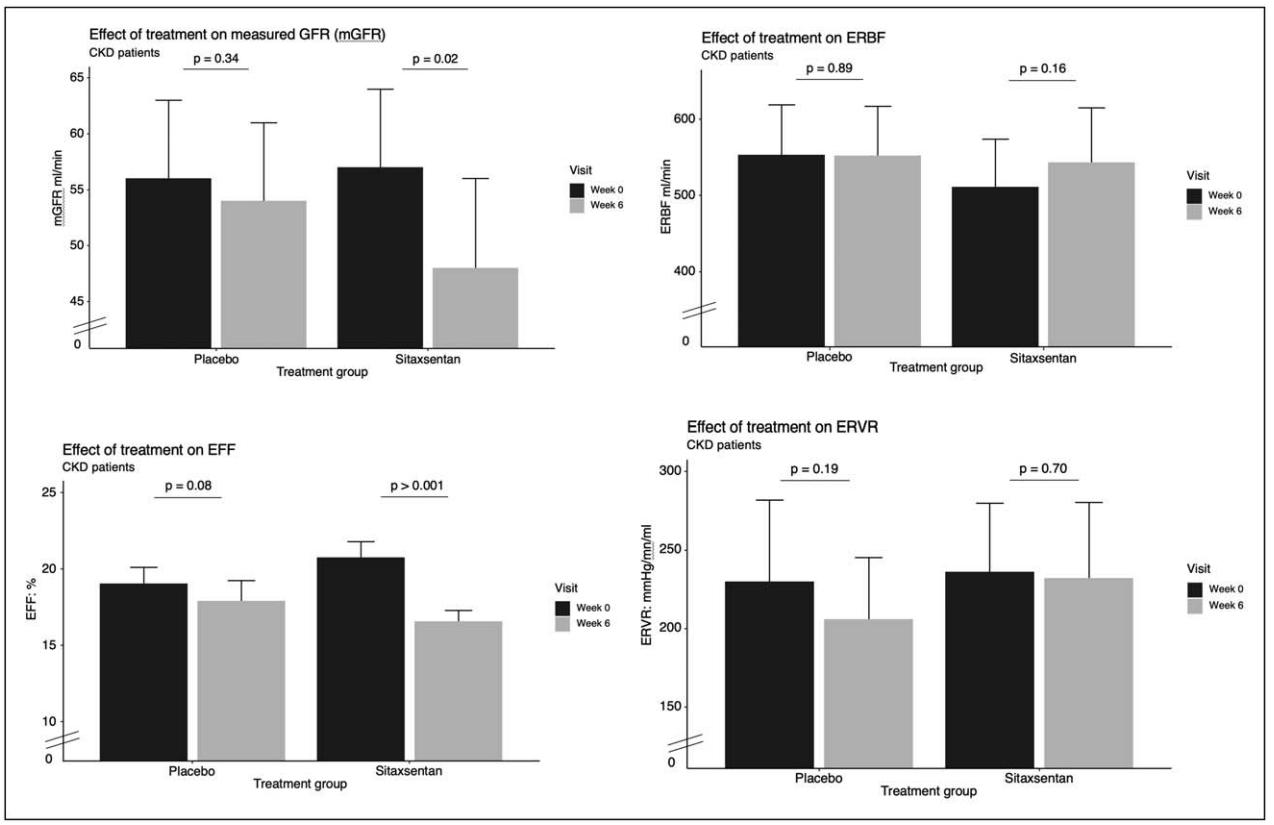

FIGURE 3. Effect of sitaxsentan on kidney hemodynamics in patients with chronic kidney disease. ERPF, effective renal plasma flow; ERBF, effective renal blood flow; ERVR, effective renal vascular resistance; GFR, glomerular filtration rate. From Dhaun *et al.* [31].

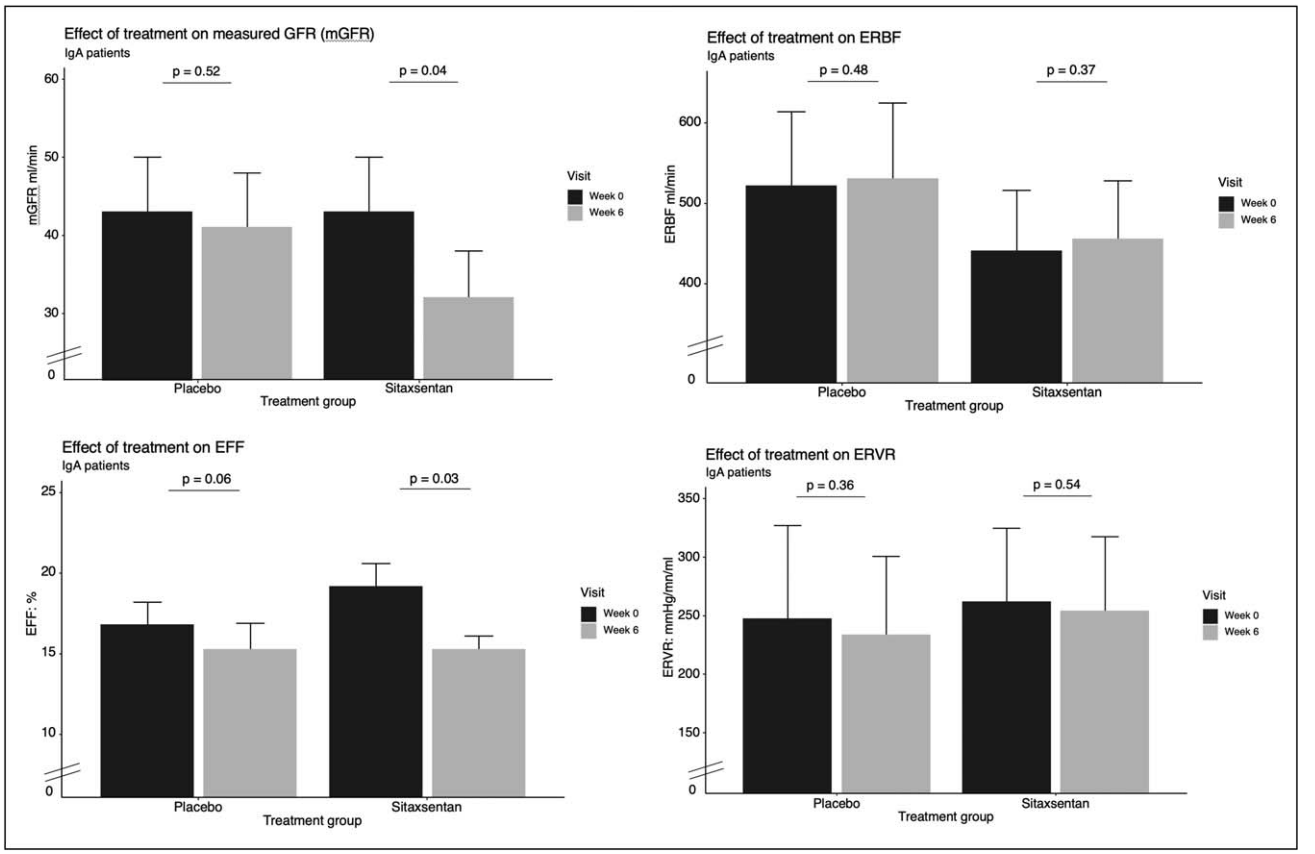

FIGURE 4. Effect of sitaxsentan on kidney hemodynamics in patients with IgA nephropathy. ERPF, effective renal plasma flow; ERBF, effective renal blood flow; ERVR, effective renal vascular resistance; GFR, glomerular filtration rate. From Dhaun *et al.* [31].

valid surrogate for CKD progression in patients with IgA nephropathy [33]. The phase 3 PROTECT (NCT03762850] trial examines the nephroprotective effect of sparsentan, a dual acting ARB and ERA, compared to irbesartan (ARB) in 380 patients with biopsy-proven IgA nephropathy who have proteinuria of at least 1.0 gram/day and eGFR greater than 30 ml/min/1.73 m^2 (Table 1). The primary endpoint of the trial is urinary protein to creatinine ratio based on a 24-h urine sample. The secondary endpoint is the rate of change in eGFR over a 58- and 110-week period following the acute effect of sparsentan on eGFR at week 6. Other endpoints are the rate of change in eGFR over 104 weeks following the acute effect on eGFR. Another phase 3 clinical trial, the ALIGN trial (NCT04573478) will enroll biopsy-proven IgA nephropathy patients with a urinary protein:creatinine ratio of at least 1.0 gm/gm and eGFR greater than 30 ml/min/1.73m^2 (Table 1) [34]. The ALIGN trial is designed to assess the effect of atrasentan 0.75 mg/day on the primary endpoint of change in urinary protein:creatinine ratio at week 24. The confirmatory endpoint in the ALIGN trial is the change in eGFR from baseline to 4 weeks post cessation of randomized treatment [35].

Endothelin receptor antagonist in focal segmental glomerulosclerosis

Experimental and clinical data suggest ET-1 is involved in focal segmental glomerulosclerosis (FSGS) as well. Renal ET-1 production is increased in FSGS [36]. Podocytes are key targets in FSGS [37] and are involved in ET-1-mediated autocrine and paracrine glomerular cell injury. Podocyte-derived ET-1, via ET_A, enhances glomerular injury in FSGS [38]. In adriamycin nephropathy, a model of FSGS, ET_A blockade prevented GEC glycocalyx reduction and proteinuria [39]. Further, ET_A blockade ameliorated glomerulosclerosis and proteinuria in aging-associated FSGS; this effect may be due to, at least in part, preventing upregulation of p21, a cell-cycle inhibitor, in podocytes [9]. In humans participating in the phase II DUET study, 8 weeks of treatment with sparsentan induced significant reductions in proteinuria compared to irbesartan [40]. The phase 3 DUPLEX (NCT03493685) study will investigate the long-term nephroprotective potential of sparsentan as compared to an ARB in patients with primary and genetic FSGS [41]. The sponsor of the trial recently announced that the trial achieved its prespecified interim FSGS partial remission of proteinuria

Table 1. Ongoing phase 3 clinical trials on the effect of endothelin receptor antagonists in patients with nondiabetic kidney disease

Trial Name	Patient population	Study drug	Mechanism of action	Endpoint(s)	Follow-up duration	Sample size
PROTECT (NCT03762850)	Biopsy proven IgA nephropathy: eGFR>30 mL/min Proteinuria ≥ 1 g/day creatinine	Sparsentan 400mg/day	Dual acting ETA and Angiotensin Receptor Blocker	Change in UPCR from baseline to week 36. The rate of change in eGFR over a 58- and 110-week period.	114 weeks.	380 subjects
ALIGN (NCT04573478)	Biopsy proven IgA nephropathy eGFR>30 mL/min UPCR ≥ 1 g/g.	Atrasentan 0.75mg/day	Endothelin A antagonist	Change in UPCR to week 24 Change in eGFR from baseline to 4 weeks postdrug cessation (week 136)	136 weeks	320 subjects
DUPLEX (NCT03493685)	Biopsy-proven focal segmental glomerulosclerosis (FSGS): Urine protein/creatinine (UP/C) ≥1.5 g/g eGFR ≥30 mL/min	Sparsentan 800mg/day (target dose)	Dual acting ETA and Angiotensin Receptor Blocker	Proportion of patients achieving a UP/C ≤1.5 g/g and a >40% reduction from baseline in UP/C at Week 36 Slope of eGFR from Week 6 to Week 108	108 weeks.	300 subjects

The PROTECT and DUPLEX clinical trials compare treatment with sparsentan (a dual ETA and Angiotensin Receptor Blocker) to an active control (Irbesartan). The ALIGN clinical trial compares atrasentan (an ETA antagonist) to placebo as adjunct to maximally tolerated and stable dose of a RAS (renin-angiotensin system) inhibitor. GFR, glomerular filtration rate.
ETA, endothelin type A; UPCR, urine protein creatinine ratio.

endpoint after 36 weeks of treatment [42]. The long-term effects of sparsentan on the rate of eGFR decline in patients with FSGS will become available in 2022. See Table 1 for an overview of the phase 3 clinical trials on the treatment of IgA Nephropathy and FSGS with ERA.

Endothelin receptor antagonist in other etiologies of chronic kidney disease

ET-1 is also implicated in the pathophysiology of Alport syndrome (AS). Patients with AS have a genetically impaired ability to synthesize collagen type IV, a key component of the glomerular basement membrane. Glomerular ET-1 was markedly elevated in Alport mice and ET_A blockade improved renal structure and function [43]. ET-1, via ET_A, induced drebrin (an actin-associated protein) filopodial microspikes in cultured mesangial cells [43]. Interestingly, ET_A inhibition reduced stria vascularis capillary basement membrane thickening in an Alport model [44,45], suggesting that ET_A antagonism may improve both renal function and hearing in AS.

Sickle cell disease (SCD) is being increasingly recognized as a cause of CKD [46]. Renal ET-1 is increased in patients with SCD; ET_A antagonism, either alone or in combination with hydroxyurea, ameliorates renal disease progression in a mouse model of SCD [47,48]. The ET system may also contribute to other aspects of SCD; an *EDN1* gene polymorphism is associated with vaso-occlusive crisis risk in patients with SCD [49]. ET_A inhibition or knockdown in dorsal root sensory neurons alleviated pain hypersensitivities in SCD mice [50].

A phase 2, open-label, basket study (AFFINITY, NCT04573920) will evaluate the efficacy and safety of atrasentan in patients with proteinuric glomerular disease due to different underlying causes who are at risk of progressive loss of renal function. Four cohorts will consist of patients with IgA nephropathy, FSGS, AS, or DKD. Approximately 80 patients will receive 0.75 mg atrasentan for a duration of 1 year [51].

COMBINATION THERAPY WITH SODIUM GLUCOSE COTRANSPORTER-2 AND ENDOTHELIN RECEPTOR ANTAGONIST TREATMENT

Despite use of low doses of ERA with high selectivity for the ET_A receptor, their fluid retaining effects and associated risks of edema and heart failure remain present. Diuretic treatment in combination with ERA may mitigate fluid retention as previously shown. Sodium glucose cotransporter-2 (SGLT2) inhibitors were originally developed as glucose-

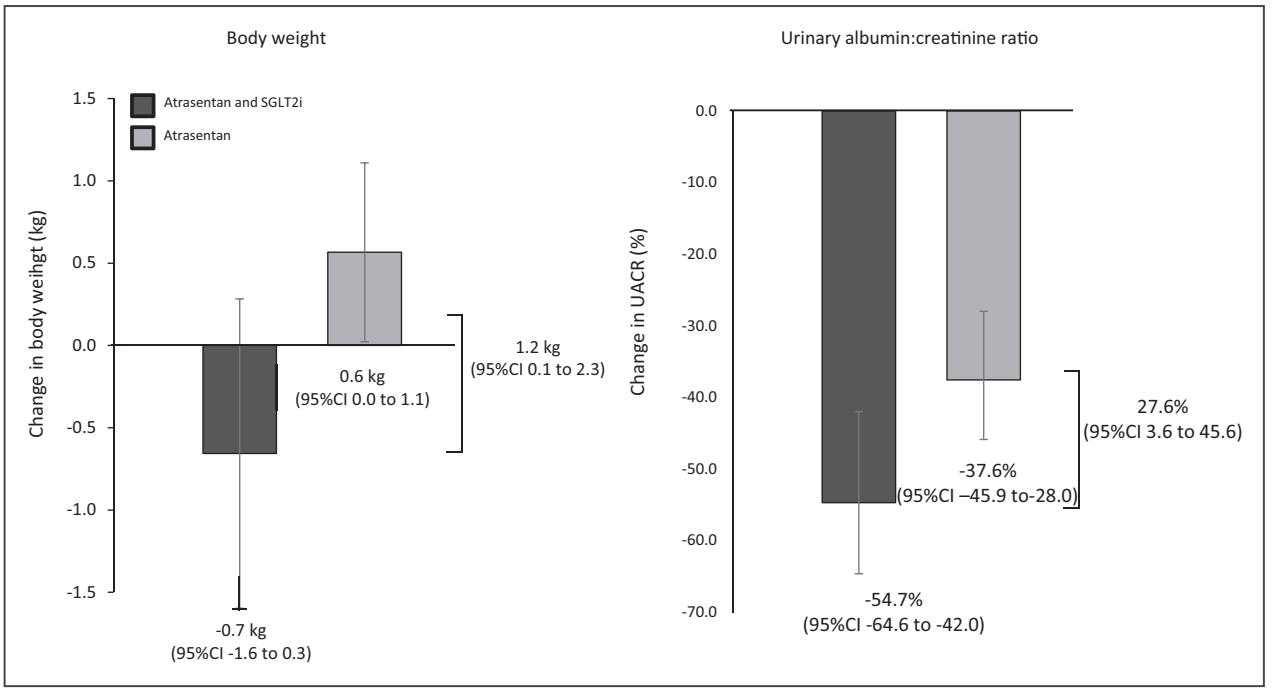

FIGURE 5. Effect of the ERA atrasentan versus combination treatment of atrasentan and SGLT2 inhibition on body weight and urinary albumin:creatinine ratio (UACR). The increase in body weight was abrogated with combination treatment whereas combination treatment was associated with a larger reduction in UACR compared to atrasentan alone. Data published in Ref [53▪] and used with permission. ERA, endothelin receptor antagonists; UACR, urinary albumin creatinine ratio.

lowering drugs and have been shown to exert diuretic effects. In addition, SGLT2 inhibitors reduce albuminuria and reduce the risks of kidney failure, heart failure, and mortality in patients with CKD with and without type 2 diabetes [52]. Because SGLT2 inhibitors exert diuretic effects, whereas ERA heighten the risk of sodium and fluid retention, the diuretic properties of an SGLT2i could attenuate the fluid retaining effects of an ERA, whereas the antialbuminuric effects may be complimentary owing to the different mechanisms of action of the two drug classes. Interestingly, a recent posthoc analysis of the SONAR trial reported that combination treatment with SGLT2 and atrasentan indeed enhanced albuminuria reduction, whereas the fluid retaining effects of atrasentan were mitigated when atrasentan was co-administered with an SGLT2 inhibitor (Fig. 5) [53▪]. As this analysis concerned a retrospective analysis of small number of patients, prospective clinical trials are needed. The ongoing phase 2 ZENITH trial (NCT04724837) will examine whether fluid retention with the ERA zibotentan can be mitigated by the SGLT2 inhibitor dapagliflozin in patients with type 2 diabetes and CKD.

CONCLUSIONS

Long-term treatment with ERA reduces clinically relevant kidney outcomes in patients with type 2 diabetes and CKD. Current phase 3 trials are investigating the effect of ERA in IgA nephropathy and FSGS. The increased risk of fluid retention and heart failure due to ERA in patients with type 2 diabetes and CKD requires new strategies. Patient selection is a key factor; the risk of edema and heart failure with ERA is likely lower in patients with CKD without diabetes who have a lower cardiovascular risk profile. The ongoing PROTECT, DUPLEX, and ALIGN trials will provide more insight in this clinically relevant issue. Since SGLT2 inhibitors exert diuretic effects, the combination of SGLT2i and ERA could be a promising strategy in particular for patients at risk of edema such as patients with type 2 diabetes and CKD.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

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