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The role of endothelin receptor antagonists in kidney disease

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ABSTRACT

Kidney diseases are among the most prevalent conditions worldwide, impacting over 850 million individuals. They are categorized into acute kidney injury and chronic kidney disease. Current preclinical and clinical trials have demonstrated that endothelin (ET) is linked to the onset and progression of kidney disease. In kidney diseases, pathological conditions such as hyperglycemia, acidosis, insulin resistance, and elevated angiotensin II levels lead to an increase in ET. This elevation activates endothelin receptor type A, resulting in harmful effects like proteinuria and a reduced glomerular filtration rate (GFR). Therefore, to slow the progression of kidney disease, endothelin receptor antagonists (ERAs) have been proposed as promising new therapies. Numerous studies have demonstrated the efficacy of ERAs in significantly reducing proteinuria and improving GFR, thereby slowing the progression of kidney diseases. This review discusses the mechanisms of action of ERAs in treating kidney disease, their efficacy and safety in preclinical and clinical studies, and explores future prospects for ERAs.

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Introduction

Acute kidney injury (AKI) is a clinical syndrome characterized by a rapid decline in renal function over a short period, primarily caused by decreased renal blood flow (RBF) among various etiologies. AKI is associated with increased incidence, mortality, and the risk of developing chronic kidney disease (CKD) [1]. CKD refers to conditions characterized by abnormal kidney structure or function persisting for at least three months. Common causes of CKD include diabetic nephropathy (DN), hypertensive nephropathy (HTN), IgA nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), Alport syndrome, and autosomal dominant polycystic kidney disease (ADPKD) [2–4]. The global prevalence of CKD is estimated at 13.4%, and it can progress to end-stage kidney disease (ESKD), which requires renal replacement therapy or may result in death [5]. This highlights the need to identify and research therapeutic targets for kidney disease. In recent years, endothelin receptor antagonists (ERAs) have shown promising results in clinical trials for treating kidney disease. Endothelin (ET) is a peptide composed of 21 amino acids and acts as a potent vasoconstrictor [6]. It synthesizes three isoforms—ET-1, ET-2, and ET-3—based on their amino acid sequences [7]. ET exerts its effects through G protein-coupled receptor subtypes ETA and ETB. ETs are produced by vascular endothelial cells and act on vascular smooth muscle cells. Endothelin receptor type A (ETAR) and endothelin receptor type B (ETBR) are expressed throughout the renal vasculature, with ETAR predominantly located in vascular smooth muscle and ETBR in endothelial cells [8,9]. Additionally, both receptors are expressed in the renal tubules, primarily as ETBR [10]. In the kidney, ETAR activation by ET-1 promotes vasoconstriction, cell proliferation, inflammation, and stromal accumulation. In contrast, ETBR activation leads to vasodilation, as well as antiproliferative and antifibrotic effects [11]. Therefore, ETAR is considered a promising therapeutic target for selective blockade in kidney disease.

This review examines the mechanisms of action of ERAs in kidney disease, as well as their efficacy and safety in preclinical and clinical studies, to offer insights for future research.

Physiology and pathophysiology of endothelin

ET plays a crucial role in regulating blood flow, glomerular filtration rate (GFR), and water-electrolyte balance in the kidneys. Among its isoforms, ET-1 is the most potent vasoconstrictor and may hold greater clinical significance compared to ET-2 and ET-3 [12]. Under physiological conditions, ET-1 binds to ETAR, mediating vasoconstriction in both afferent arterioles (AA) and efferent arterioles (EA), with a more

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pronounced effect on AA. This results in decreased RBF and increased renal vascular resistance, ultimately reducing GFR. In contrast, activation of ETBR stimulates vascular endothelial cells to release nitric oxide (NO) and prostaglandins, inducing vasodilation. This leads to increased renal medullary perfusion and decreased sodium reabsorption, exerting an overall diuretic effect and facilitating sodium excretion, thereby contributing to lower blood pressure [13–15]. In pathological conditions associated with renal disease progression, such as hyperglycemia, acidosis, elevated insulin levels, angiotensin II (Ang II), reactive oxygen species, and pro-inflammatory cytokines, ET-1 concentrations are elevated [16]. The binding of ET-1 to ETAR in these settings results in sustained vasoconstriction, which may be linked to hyperfiltration or podocyte damage, thereby reducing GFR and causing proteinuria [17]. Elevated ET-1 levels also promote inflammation and fibrosis. Studies have demonstrated that renal overexpression of ET-1 in mice induces glomerulosclerosis and interstitial fibrosis [18]. Additionally, increased ET-1 may stimulate the production of Ang II, creating a positive feedback loop that further elevates ET-1 levels and exacerbates kidney damage [19] (Figure 1).

Endothelin receptor antagonists

Tables 1 and 2 list the effects and adverse reactions of ETA and non-ETA receptor antagonists in kidney disease, respectively. ERAs are a class of drugs that selectively block ETA and ETB to varying degrees [20]. For ERAs to be considered selective for a specific receptor, they must exhibit more than a 100-fold selectivity for either ETA or ETB. Otherwise, antagonists with less than a 100-fold selectivity are classified as nonselective or mixed antagonists [21].

Darusentan (LU 135252) is an acrylic acid derivative [22] with a relative selectivity ratio of 170:1 (ETA:ETB) [23]. Clinical studies have used darusentan to lower blood pressure in patients with refractory hypertension. However, it is also associated with fluid retention events [24], which may explain the limited clinical research on this drug in kidney diseases. Sitaxsentan, a sulfonamide analogue [25], exhibits an *in vitro* ETA:ETB selectivity of >6500:1 [26]. Dhaun et al. [27] found that sitaxsentan can reduce proteinuria, blood pressure, and arterial stiffness in CKD patients, thereby modifying risk factors for cardiovascular disease in CKD. Ambrisentan is a propionic acid derivative with high selectivity for ETA. An ongoing clinical trial (NCT06072326) aims to investigate whether combining ambrisentan with sotagliflozin (an SGLT1/2 inhibitor) enhances renal protection and reduces fluid retention and ketone effects in type 1 diabetes patients, thereby providing new insights into ERA treatment strategies [28]. Avosentan is a selective ETA antagonist, exhibiting ~500-fold selectivity for ETA over ETB [29]. Mann et al. [30] reported that avosentan combined with renin-angiotensin system blockers significantly reduces proteinuria in patients with DN. However, due to increased adverse reactions such as fluid overload, congestive heart failure, and mortality, the study was terminated prematurely. Atrasentan, a carboxylic acid derivative [31], demonstrates a selectivity ratio of 1200:1 for ETA over ETB [32]. It not only reduces the risk of renal events and lowers urinary albumin-to-creatinine ratio (UACR) but also alleviates pain in patients with diabetes and CKD [33,34]. Finally, zibotentan, an oxadiazole-based agent [35], is the most ETA-selective ERA [34,36]. Stern et al. [37] investigated the effect of zibotentan in CKD secondary to systemic sclerosis (SSc) and showed that it can improve eGFR. Based on this, a recent clinical trial demonstrated that zibotentan in

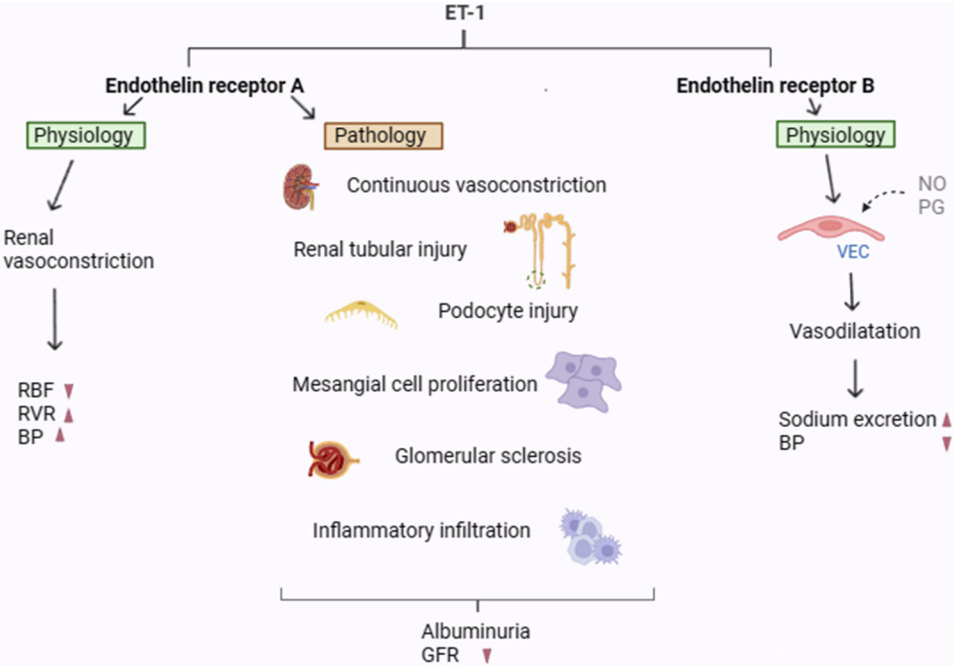

Figure 1. Physiological and pathological processes of kidney induced by endothelin. Created by BioRender.com.

Table 1. ETA receptor antagonists in kidney disease.

Drugs	Disease	Main outcomes	Adverse effects
Sitaxsentan	AKI, FSGS, AS	Reduce blood pressure, proteinuri, inflammation, and fibrosis of the kidneys	Liver injury
Atrasentan	DN, HTN, IgAN, AS	Reduce proteinuria, weaken mesangial cell activation, improve glomerular damage and renal fibrosis	Edema, anemia, put on weight
Avosentan	HTN, DN	Reduce proteinuria, prevent glomerular fibrosis and tubulointerstitial damage	Fluid overload, congestive heart failure, anemia, headache
Ambrisentan	FSGS	Reduce proteinuria and improve podocyte number and volume	NR
Darusentan	PKD	Increase renal tubular cell proliferation	Fluid retention

Table 2. Non-ETA receptor antagonists in kidney disease.

Drugs	Disease	Main outcomes	Adverse effects
BQ-788	DN	Reduce RBF and cortical perfusion	NR
Bosentan	HTN, PKD	Reduce proteinuria, improve renal fibrinoid necrosis	NR
Sparsentan	IgAN, FSGS, AS	Reduce ACR and improve the function of endothelial cells and podocytes	Hypotension, edema, hyperkalemia

combination with dapagliflozin reduced proteinuria in patients with CKD with acceptable tolerability and safety, making it a viable option to improve disease progression in patients already receiving currently recommended treatments [38] (Table 1).

Since the harmful effects of ET-1 in the kidney are primarily mediated by ETA, while the beneficial effects are mediated by ETB [39], ETB-selective antagonists are not suitable therapeutic options for kidney disease. BQ-788 is a highly selective ETB antagonist, showing 1000-fold specificity for ETB in human cell lines [40]. Preclinical studies indicate that BQ-788 causes renal vasoconstriction, reducing RBF and cortical perfusion in mice [41]. Furthermore, BQ-788 has been shown to reduce GFR in patients with CKD [42].

Bosentan, a non-peptide pyrimidine derivative, is a competitive antagonist of both ETA and ETB, with a slightly higher affinity for ETA (ETA:ETB ratio of 20:1) [32]. In patients with type 2 diabetes mellitus (T2DN), bosentan failed to reduce urine albumin levels compared to placebo [43]. Clinical trials examining bosentan in SSc-related renal crisis were suspended, likely because preliminary data showed no significant benefits compared to historical controls [44]. Thus, the clinical use of bosentan in kidney disease remains in the exploratory phase.

Sparsentan (BMS-346567) is a dual endothelin receptor/angiotensin II type 1 receptor antagonist (DEARA) with ~1000-fold greater affinity for ETA [45]. In patients with IgAN and FSGS, sparsentan significantly reduces proteinuria while maintaining a favorable safety profile [46,47]. Consequently, sparsentan has been approved in the United States as a specific treatment for IgAN [46], highlighting the therapeutic potential of ERAs in kidney disease.

In summary, clinical trials show that some ERAs lack proven efficacy in improving renal function, while others show benefits limited to specific kidney diseases. Additionally, some ERAs lack clinical trials for kidney diseases, underscoring the need for further preclinical studies to clarify their effects and explore new therapeutic options.

Acute kidney injury and endothelin receptor antagonists

AKI is a significant global health issue [48], frequently caused by ischemia-reperfusion injury (IRI) [49]. IRI leads to microcirculatory dysfunction, inflammatory cell infiltration, and subsequent damage to glomeruli and renal tubules. Cardiopulmonary bypass (CPB) can induce AKI through multiple mechanisms, including aortic cross-clamping and subsequent IRI [50]. In an adult pig model of CPB, sitaxsentan reverses endothelial dysfunction, local hypoxia, inflammation, and tubular damage [51]. However, in mouse models of IRI, sitaxsentan neither reduces ET-1 expression nor prevents the progression of AKI to CKD, but it may facilitate kidney repair by promoting noncanonical monocyte migration [52]. Czopek et al. [53] reported that the duration of sitaxsentan blockade is critical to its efficacy. Treatments shorter than seven days offer no long-term protection, while blockade for seven days to four weeks fails to prevent AKI progression to CKD. Only continuous sitaxsentan blockade for at least four weeks effectively prevents AKI progression. Sitaxsentan reduces B cells, Cluster of Differentiation 4 positive (CD4+), and Cluster of Differentiation 8 positive (CD8+) T cells, decreases pro-inflammatory cytokine levels, and increases anti-inflammatory cytokines. It also enhances ET-1 clearance by increasing lymphocyte antigen 6 complex, locus C (Ly6C) low monocytes. Furthermore, sitaxsentan prevents long-term microvascular rarefaction, preserves cortical perfusion, and maintains vasoconstrictor/vasodilator balance in the cortex and medulla. These effects are partially mediated by reducing oxidative stress through the prevention of endothelial NO synthase uncoupling, thereby improving renal hemodynamics.

Patel et al. [54] demonstrated that sitaxsentan increases creatinine clearance in adult pigs undergoing CPB [51]. In contrast, Boesen et al. [55] reported that ABT-627, an ETA receptor antagonist, failed to reduce plasma creatinine concentrations in a mouse model of IRI. These discrepancies may be attributed to differences in animal models and methods used to induce IRI. Additionally, evidence suggests that ETA activation may not significantly contribute to the initial loss of renal function. Czopek et al. [53] further examined the

therapeutic time window for ETA blockade in an IRI mouse model. Their findings indicated that early initiation of sitaxsentan after AKI and continuous treatment for at least four weeks are required to prevent AKI progression to CKD. Sitaxsentan also reduces kidney inflammation and fibrosis in IRI and lowers blood pressure but does not mitigate the initial hypertensive response. Another study using a unilateral IRI mouse model showed that sitaxsentan completely prevents hypertension and fibrosis development [56]. While one study suggests that AKI patients have an increased risk of developing hypertension (>140/90 mmHg) [57], the antihypertensive effects of sitaxsentan observed in animal studies may help mitigate this risk.

Chronic kidney disease and endothelin receptor antagonists

CKD progression includes glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis [58]. In conditions like diabetes, obesity, hypertension, IgAN, FSGS, and other nephropathy-related risk factors, renal ET-1 production is increased [59–62]. Due to species and experimental model differences, research on the vasoconstrictive effects of ET-1 in afferent and EA has shown inconsistent results [63]. ET-1 preferentially contracts EA *via* ETA receptors. ETA receptor antagonists can significantly reduce blood pressure in CKD patients, along with renal vasodilation, suggesting that these antagonists primarily affect EA. Furthermore, in CKD patients treated with renin-angiotensin system (RAS) inhibitors, ETAR inhibitors further reduce albuminuria [64,65]. These findings suggest that simultaneous inhibition of ETAR and RAS receptors in EA may further dilate them. Excessive activation of ETAR in podocytes disrupts the actin cytoskeleton, impairs the slit membrane, causes renal tubule detachment, triggers cell apoptosis, depletes podocytes, and leads to fibrosis [66]. Endothelial cells are a major source of ET-1 in normal human kidneys [67], and their interaction with podocytes plays a key role in glomerular injury. ET-1 induces the release of heparinase from podocytes, degrading the endothelial glycocalyx, which contributes to proteinuria and renal failure. Removing ET receptors from podocytes effectively prevents this process [68]. Endothelial dysfunction promotes podocyte apoptosis *via* mitochondrial oxidative stress, which can be prevented by inhibiting ETA receptors [69]. ETA receptor antagonists may also enhance endothelial-dependent vasodilation and vascular motility, further protecting renal function. ET-1 induces mesangial cell (MC) contraction, proliferation, and matrix accumulation *via* ETA receptors [70], potentially contributing to positive feedback mechanisms that sustain glomerular injury [66]. The generation of ET-1 in renal tubules and activation of ETAR in both tubules and interstitial cells may significantly contribute to the pathological progression of CKD. In nephrotic syndrome models, ET-1 generation correlates closely with proteinuria [71]. In membranous nephropathy models with significant proteinuria, tubular-derived ET-1 may exacerbate proteinuria by promoting tubulointerstitial fibrosis [72]. These findings suggest that proteinuria and tubular-derived ET-1 may cause kidney damage through a positive feedback loop. Notably, ERA can improve glomerular basement membrane (GBM) structure and has beneficial effects on tubular sclerosis and proteinuria [73]. Therefore, ERA may play a crucial role in slowing CKD progression and improving kidney function (Figure 2).

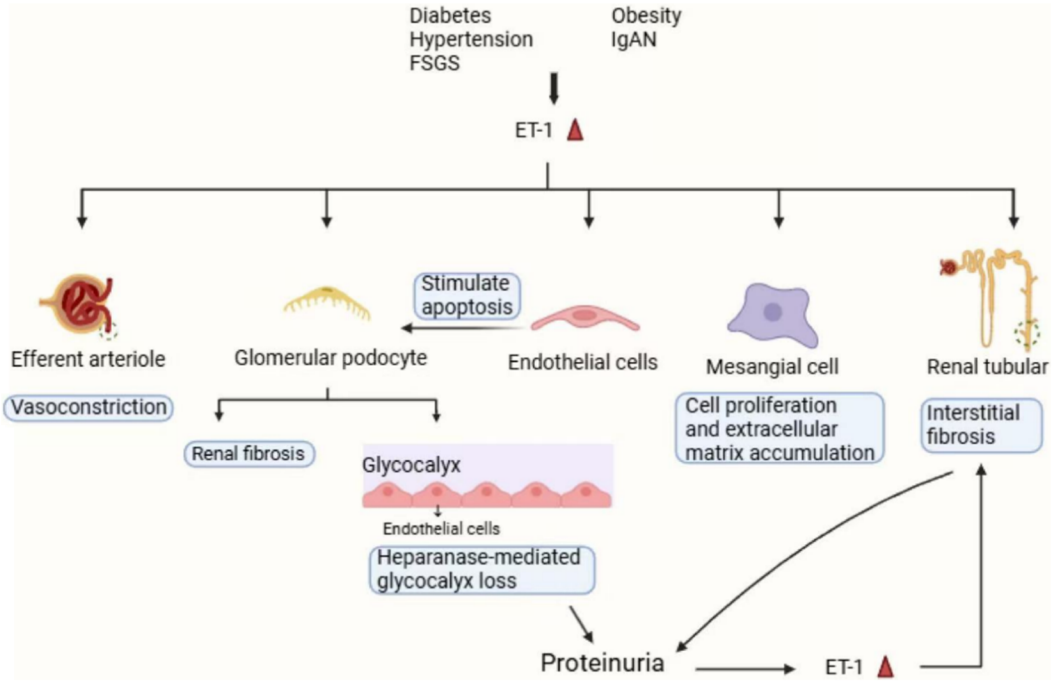

Figure 2. Mechanism of endothelin-1 action in chronic kidney disease in pathological state. Created by BioRender.com.

Diabetic nephropathy

DN affects nearly one-third of individuals with diabetes and is a leading global cause of ESKD [74]. The pathogenesis of DN is complex and not fully understood, with hyperglycemia being a key driving factor [75]. Podocyte loss and proteinuria are key characteristics of DN [76]. Hyperglycemia increases ET-1 expression, which binds to the ETAR, leading to vasoconstriction, inflammation, and fibrosis. Endothelin A receptor antagonists not only block ETAR signaling but also protect the kidneys through other mechanisms. Klotho, a transmembrane protein highly expressed in the proximal tubule lumen, is closely linked to renal function, particularly in tubulointerstitial lesions. Plasma-soluble Klotho and renal Klotho levels are significantly lower in diabetic patients compared to non-diabetic individuals [77,78]. In a streptozotocin-induced DN mouse model, atrasentan improved Klotho expression under high-glucose conditions by increasing Klotho levels in renal tubular epithelial cells. Atrasentan may promote Klotho recovery and exert renal protective effects by downregulating miR-199b-5p activation [79]. Mice treated with high glucose exhibited higher apoptosis rates and lower autophagic activity compared to those treated with normal glucose. Atrasentan alleviates kidney damage by downregulating miR-21 and promoting autophagy [80]. The endothelial glycocalyx, a carbohydrate layer covering endothelial cells, is degraded enzymatically, increasing proteinuria flux. Diabetes is closely linked to endothelial dysfunction and a reduction in glycosaminoglycan size [81,82]. In diabetic apoE-deficient mice, atrasentan reduces heparanase expression *via* an anti-inflammatory effect, restores endothelial glycocalyx integrity, and decreases albumin filtration [83]. In a DN mouse model, downregulation of thrombomodulin expression leads to glomerular apoptosis, tubular sclerosis, and increased proteinuria. Atrasentan may reduce glomerular macrophage infiltration by upregulating endothelial thrombomodulin, decreasing heparinase-activating enzyme (cathepsin L) expression, and inhibiting glycocalyx degradation mediated by heparinase [84]. These mechanisms highlight atrasentan's potential in treating DN, particularly in reducing glycocalyx degradation and protecting renal function. Streptozotocin-treated Dahl salt-sensitive (STZ-SS) rats and T2DN mice, models of type 1 and type 2 diabetic nephropathy, respectively, show a significant increase in ET-1 levels in the kidney. Spires et al. found that atrasentan reduces glomerular injury and renal fibrosis in both models. However, it effectively lowers arterial pressure and proteinuria only in STZ-SS rats, potentially due to the diabetes type or nephropathy severity [85]. In the BTBR ob/ob mouse model, combination therapy with ACE inhibitors and ET-1 receptor antagonists enhances podocyte recovery, reduces proteinuria, and alleviates interstitial and glomerular injury compared to ET-1 receptor antagonists alone. In the unilateral nephrectomy male db/db mouse model of this study, treatment with sodiumglucose cotrans- porter 2 (SGLT2) inhibitors and/or ETA receptor antagonists showed no significant improvement in proteinuria, GFR, or renal inflammation/fibrosis [76]. However, dual treatment improved renal tubular sclerosis and podocyte damage in mice. This phenomenon may be due to the mild kidney damage in the model and the lack of RAS inhibitor treatment [86]. Vergara et al. [87] confirmed that only dual or triple treatment with empagliflozin and ramipril (including ET-1 receptor antagonist) effectively reduces glomerular hyperfiltration in diabetes, emphasizing the importance of including RAS inhibitors in the treatment.

Hypertensive nephropathy

Hypertension is a leading cause of ESKD and CKD [88]. HTN is characterized by renal vasculitis, hyaline degeneration, and tubulointerstitial fibrosis of the glomerular plexus [89]. The mechanism of renal damage in hypertension partly results from the interaction between renin-angiotensin-aldosterone system (RAAS) and ET. Hypertension causes endothelial damage, leading to sparse blood vessels in the renal medullary capillaries, which ultimately results in tissue hypoxia and kidney damage. Ang II stimulates reactive oxygen species (ROS) production by inducing vascular nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and renal ET-1 expression, leading to vasoconstriction, inflammation, and fibrosis, which exacerbates renal injury [60]. In TG (mRen 2) 27 rat kidney sections, ET-1 drives epithelial-mesenchymal transition (EMT) in proximal renal tubular cells. Iwano et al. found that up to 36% of mesenchymal stromal cells originated from tubular cells through EMT, suggesting that ET-1 may contribute to renal tubular interstitial fibrosis [89]. In deoxycorticosterone acetate (DOCA) salt hypertensive rats, renal ET-1 levels significantly increased, accompanied by proteinuria. Renal dysfunction is likely due to an imbalance in ET-1 and NO production. Reduced NO production in the kidneys activates NF-κB, which increases ET-1 production, leading to renal dysfunction. ABT-627 nearly completely inhibits renal dysfunction and tissue damage caused by DOCA salt and inhibitor NG-nitro-L-arginine (NOARG) (which reduces NO production), suggesting that ABT-627 acts through the NF-κB/ET-1/ETA pathway [90]. The role of ERAs has been studied in combination with RAS blockade. In a hypertensive rat model, combining avosentan with the angiotensin receptor blocker (ARB) valsartan significantly improved glomerular and tubulointerstitial inflammation and fibrosis compared to atorvastatin monotherapy. This effect may result from the combined action of ET and RAAS in HTN. However, high-dose avosentan causes fluid retention, suggesting that side effects may be dose-dependent. Therefore, dose control should be strengthened to minimize adverse reactions [91].

IgA nephropathy

IgAN is the most common primary glomerular disease worldwide [92], caused by glycosylation abnormalities in the hinge region (Gd-IgA1), and is characterized by mesangial proliferative glomerulonephritis with IgA deposition in the mesangium [93]. Renal biopsies of IgAN patients show activation of the ET pathway and increased expression

of ET-1 mRNA, along with elevated ET-1 and ETAR in both the glomerular and tubulointerstitial regions [94]. Additionally, multiple inflammation and extracellular matrix-related genes are upregulated in the MCs of IgAN patients. Atrasentan prevents excessive proliferation of cultured human MCs and inhibits the upregulation of genes involved in proliferation, inflammation, and fibrosis [95,96]. Activation of the renal ET pathway was observed in the ddY mouse IgAN model, and treatment with an ETAR antagonist significantly improved proteinuria, glomerular overgrowth, and mesangial dilation in this model [61]. Similarly, in the anti-Thy1.1 rat model, atrasentan affects the transcription of pro-inflammatory and pro-fibrotic genes, reduces renal tubular interstitial injury damage scores, and modulates the expression of repair genes in proximal renal tubular epithelial cells, ultimately improving proteinuria and renal dysfunction [97,98]. In the IgAN model, the expression changes of pathogenic genes induced by repair failure of proximal renal tubular epithelial cells were minimally affected by the RAS inhibitor enalapril but were reversed by atorvastatin [99]. These findings highlight the importance of ET-1 signaling in regulating pathological gene expression. In gddY mice, sparsentan has more significant advantages in podocyte protection and glycocalyx recovery compared to losartan. In another study, 8 weeks of treatment with the dual ERA/AngII type 1 receptor antagonist sparsentan not only reduced MC proliferation but also prevented immune complex-induced changes in renal gene transcription and network activity, significantly reducing proteinuria and tubular sclerosis [100,101].

Focal segmental glomerulosclerosis

FSGS is characterized by primary podocyte injury [102], and renal failure is associated with substantial clinical and economic burdens, highlighting the need for new therapies for FSGS [103]. In experimental FSGS, ETAR-dependent signaling in glomerular endothelial cells induces mitochondrial stress and dysfunction. This is initially characterized by the loss of glomerular endothelial cell fenestrations and glomerular glycocalyx (GLX), followed by podocyte damage and compromised glomerular filtration barrier integrity [69,104]. In FSGS patients, ETAR expression is upregulated in glomerular endothelial cells and is associated with podocyte injury and increased glomerular oxidative stress [105]. Both *in vivo* and *in vitro* oxidative stress can induce podocyte apoptosis [106]. Gyarmati et al. [107] found that sparsentan inhibited podocyte apoptosis by attenuating mitochondrial stress in podocytes, potentially reducing oxidative stress in glomeruli. Furthermore, sparsentan promotes the restoration of the glomerular endothelial surface layer, which may be one of its mechanisms for treating FSGS. In the ADR model of FSGS, sparsentan attenuates the urine protein/creatinine ratio (UPCR) and podocyte loss, maintains GBM width and protects the GLX [108]. Li et al. [109] found that the levels of Ang II and ET-1 positively correlated with the levels of IL-15. Sparsentan ameliorates podocyte injury by inhibiting the formation and activation of $CD8^+$ TRM cells mediated by IL-15 signaling activated by Ang II and ET-1.

Doxorubicin and puromycin are the most commonly used podocyte toxins for inducing FSGS [110]. Buelli et al. [111] studied sitaxsentan in doxorubicin-induced mouse models of FSGS and found that these mice exhibited elevated renal ET-1 levels. Sitaxsentan treatment attenuated cellular damage and inflammation in these mice. However, the therapeutic effect was not specifically reflected in renal function. To address this gap, Jiro Kino et al. [112] demonstrated that ambrisentan has an anti-proteinuric effect in puromycin nephropathy rats, possibly by inhibiting CD80 expression on podocytes. Indeed, selective ERAs have a definite nephroprotective effect. In this regard, sparsentan improves the function of glomerular endothelial cells and podocytes in the FSGS mouse model. Additionally, sparsentan exhibits a stronger nephroprotective effect when combined with ARBs, which are used to reduce proteinuria in CKD. This therapeutic approach is currently being evaluated in a randomized controlled trial (RCT). A study using multiphoton microscopy imaging in confetti mice with FSGS induced by transient receptor potential ion channel protein 6 (TRPC6) overexpression demonstrated better protection of kidney function in mice treated with sparsentan compared to those treated with losartan or untreated [113].

Autosomal dominant polycystic kidney disease

ADPKD is an inherited disorder characterized by renal cyst growth, early-onset HTN, and late-stage renal insufficiency. RBF has been proposed as a marker to assess disease severity in ADPKD [114]. V2 receptor antagonists effectively delay the progression of cystic disease in several rodent models. ETBR blockade enhances vasopressin action in the collecting ducts and promotes sodium reabsorption, leading to worsening of the renal cystic phenotype. ETAR blockade reversed the severe changes observed after ETBR blockade alone, suggesting that ETBR blockade may redirect ET-1 to unopposed ETARs. This redirection may accelerate disease progression through vasopressin-independent pathways, inducing fibrosis, inflammation, apoptosis, and vasoconstriction [115]. ETAR blockade induces a decrease in RBF in ADPKD rats, which in turn stimulates enhanced hypoxia-inducible factors (HIF) expression in renal tubular cells. HIF may further stimulate the proliferation of renal tubular cells in ADPKD rats. Furthermore, additional ETAR blockade may direct ET-1 toward ETBRs, further enhancing tubular cell proliferation. This results in a significant increase in renal weight, number of renal cysts, and cyst surface area. In contrast, ETBR blockade has no effect on tubular cell proliferation [116].

Holcher et al. [117] investigated the effect of bosentan in normal rats and polycystic kidney rats, demonstrating that bosentan reduced RBF and GFR in polycystic kidney (Han:SPRD) rats. Similar results were obtained in a study by Hocher et al. who compared the effects of LU 135252 (ETAR antagonist) and LU 224332 (combined ETAR/ETBR antagonist) in polycystic kidney rats [115]. Renal fibrosis worsened and

GFR decreased following treatment with LU 135252 and LU 224332. Regarding RBF, only the LU 135252 group experienced a significant decline. Additionally, ADPKD rats treated with LU 135252 exhibited a significant increase in renal weight, number of kidney cysts, and cyst surface area. This illustrates that additional blockade of ETBRs by combined ETAR/ETBR antagonists mitigates the adverse effects of ETAR blockade alone in polycystic kidney rats, compared to ETAR antagonists alone. In this context, Chang et al. [116] tested the effects of ABT-627 (ETAR antagonist), A-192621 (ETBR antagonist), and their combination in a mouse model of polycystic kidney disease. The ETBR group exhibited the most severe fibrosis and the worst end-renal function. Additionally, a more severe cystic phenotype was observed in the ETBR group, manifested by increased kidney size, kidney weight fraction, and cystic area. However, unlike the ETAR group, tubular cell proliferation in the ETBR group remained unchanged, whereas the ETAR group showed a significant increase in renal tubular cell proliferation. This suggests that changes in tubular cell proliferation are not directly related to the progression of cystic disease. Similar to the study by Hocher et al. [117], the changes associated with ETAR blockade alone or ETBR blockade were normalized by combined ETAR and ETBR blockade, suggesting that ET is a major regulator of cystic lesion progression in human ADPKD.

Alport syndrome

Alport syndrome (AS) is a type IV collagen disorder characterized by glomerular disease associated with hearing loss and thickening of the GBM and the SCBM of the inner ear [118]. ET-1 is upregulated in the endothelium of Alport glomeruli and binds to ETAR on MCs, leading to cell division control protein 42 (CDC42) activation and mesangial filopodia formation. Mesangial filopodia progressively invade the subendothelial space of the GBM, depositing mesangial matrix proteins such as laminin 211. Sitaxsentan prevents interstitial fibrosis by reducing the invasion of mesangial filopodia and suppressing the expression of pro-fibrotic genes. Laminin α2 activates focal adhesion kinase (FAK), which subsequently induces genes encoding pro-inflammatory cytokines and metalloproteinases. Sitaxsentan normalizes the expression of glomerular metalloproteinases and pro-inflammatory cytokines, mitigating GBM damage [119,120]. Furthermore, sparsentan ameliorates glomerulosclerosis by reducing podocyte loss and prevents extracellular matrix accumulation in the SCBM of the inner ear, thereby reducing susceptibility to hearing loss [121,122].

Preclinical studies using animal models of AS were conducted to explore the therapeutic effects of ERAs. Dufek et al. [120] administered sitaxsentan to mice model of Alport syndrome and demonstrated that it improved interstitial fibrosis and glomerulosclerosis in the kidneys, significantly delaying the onset and progression of proteinuria and reducing serum blood urea nitrogen (BUN) levels. However, the lifespan of Alport mice treated with sitaxsentan was reduced by 20%, potentially reflecting its toxicity. Similar results were observed in a study comparing the effects of losartan and sparsentan on Col4a3 KO mice. Sparsentan delayed the decline in GFR, proteinuria, and renal pathology in this mice model of AS. Unlike sitaxsentan, sparsentan significantly prolonged lifespan and mitigated the progression of hearing loss [121]. This indicates that sparsentan has a broader clinical application potential than sitaxsentan.

ERA is used in clinical trials for kidney disease

Clinical trials investigating ERAs for kidney disease are summarized in Table 3. Atrasentan and avosentan demonstrate nephroprotective effects in patients with DN. The ASCEND trial assessed the impact of avosentan on the progression of DN. Short-term results showed that avosentan reduced the UACR in DN patients without significantly affecting blood pressure when added to standard ACEI/ARB therapy. However, the trial was terminated early after a median follow-up of four months due to a higher incidence of cardiovascular adverse events (AEs), including fluid overload and congestive heart failure, in the avosentan group [30]. Two smaller RCTs demonstrated that atrasentan significantly reduced the UACR and AEs such as fluid retention were manageable. These findings suggest that atrasentan is an effective option for managing residual proteinuria [123,124]. The large Phase 3 SONAR trial evaluated the efficacy of atrasentan (0.75 mg/day) in addressing AEs related to ETAR-mediated fluid retention observed in the ASCEND trial. The trial employed an enrichment response design with a four-week run-in period to optimize the dosage of RAS inhibitors. Participants who achieved at least a 30% reduction in UACR without substantial fluid retention (responders) proceeded to a six-week double-blind treatment phase [33]. The SONAR trial reported a 35% reduction in the risk of doubling serum creatinine or progressing to ESKD with atrasentan after a median follow-up of 2.2 years [128]. Safety analysis indicated that the incidence of AEs in the atrasentan group was similar to that in the placebo group, although fluid retention and anemia were more common in the atrasentan group [127,129]. Although the SONAR trial demonstrated that atrasentan significantly reduced the HR for major renal outcomes, it was prematurely terminated due to slow participant recruitment at the median follow-up [130].

The clinical benefits of atrasentan in DN patients, demonstrated by the SONAR trial, supported its design in the IgA Nephropathy Global Evaluation (ALIGN) trial. The ALIGN trial studied the change in the 24-h urinary protein/creatinine ratio from baseline to week 36 in IgAN patients with an eGFR of at least 30 mL/min/1.73 m^2, daily urinary protein excretion of at least 1 g, and stable doses of ACE inhibitors or ARBs at the maximum tolerable dose for at least 12 weeks. The trial also included patients receiving SGLT2 inhibitors, which have demonstrated renal protective effects in IgAN patients in previous studies. After 36 weeks of treatment, the atrasentan group showed a 36.1 percentage point decrease in the urinary protein/creatinine ratio compared to placebo (95% CI, −44.6 to −26.4; $p < 0.001$). Surprisingly, atrasentan's effect in

Table 3. Summary of endothelin receptor antagonism for renal disease.

Source	Clinicaltrials.gov registration no.	Study type/phase	Disease	Sample size	Patient's condition	Intervention	Duration	Study status	Conclusions/outcomes
Mann et al. [30]	NCT00120328	Phase III	Diabetic nephropathy	1392	21–80 years. Creatinine 1.2–3 mg/dL. UACR ≥ 309 mg/g.	Avosentan *vs.* Placebo (receiving RAS inhibitor)	4 months	Terminated	Short-term results showed avosentan significantly reduced albuminuria, and the trial was terminated after 4 months due to higher cardiovascular adverse events.
Kohan et al. [123]	NCT00920764	Phase IIa	Diabetic nephropathy	89	≥18 years. GFR > 20 mL/min/1.73 m^2. UACR 100–3000 mg/g.	Atrasentan *vs.* Placebo (receiving RAS inhibitor)	8 weeks	Completed	Atrasentan significantly reduces residual albuminuria.
Zeeuw et al. [124]	NCT01356849	Phase IIb	Diabetic nephropathy	211	>18 years. GFR 30–75 mL/min/1.73 m^2. UACR 300–5000 mg/g.	Atrasentan *vs.* Placebo (receiving RAS inhibitor)	12 weeks	Completed	Atrasentan reduces albuminuria and improves blood pressure and lipid profile.
Heerspink et al. [33]	NCT01858532	Phase III	Diabetic nephropathy	2648	18–85 years. GFR 25–75 mL/min/1.73 m^2. UACR 300–5000 mg/g.	Atrasentan *vs.* Placebo (receiving RAS inhibitor)	2.2 years	Terminated	Atrasentan significantly reduces hazard ratio for primary renal outcome but is terminated early due to slow participant recruitment.
Rovin et al. [47]	NCT03762850	Phase III	IgA nephropathy	404	>18 years. Proteinuria ≥ 1 g/d. eGFR ≥30 mL/min/1.73 m^2.	Sparsentan *vs.* Irbesartan (receiving RAS inhibitor)	110 weeks	Completed	Sparsentan reduces proteinuria and has long-term renal protective potential.
Trachtman et al. [125]	NCT01613118	Phase II	Focal segmental glomerulosclerosis	109	8–75 years. eGFR > 30 mL/min/1.73 m^2. Urinary protein-to-creatinine ratio (UP/C) ≥ 1.0 g/g.	Sparsentan *vs.* Irbesartan (receiving RAS inhibitor)	8 weeks	Completed	Sparsentan significantly reduces proteinuria.
Rheault et al. [126]	NCT03493685	Phase III	Focal segmental glomerulosclerosis	371	8–75 years. eGFR > 30 mL/min/1.73 m^2. Urinary protein-to-creatinine ratio (UP/C) ≥ 1.5 g/g.	Sparsentan *vs.* Irbesartan (washout from RAS inhibitor)	108 weeks	Completed	Sparsentan reduces proteinuria and has long-term renal protective potential.
Stern et al. [37]	NCT02047708	Phase II	Renal scleroderma	16	>18 years. Systemic sclerosis. CKD stages 2 to 3a.	Zibotentan *vs.* Placebo	52 weeks	Completed	Zibotentan improves eGFR and has long-term renal protective potential.
Heerspink et al. [38]	NCT04724837	Phase IIb	Chronic kidney disease	495	>18 years. UACR ≥ 150 and ≤5000 mg/g. eGFR ≥ 20 mL/min/1.73 m^2.	Dapagliflozin and Zibotentan *vs.* Placebo	12 weeks	Completed	The combination therapy of zibotentan and dapagliflozin can significantly reduce proteinuria and the incidence of fluid retention.

reducing proteinuria in the SGLT2 inhibitor subgroup was similar to that in the main group. However, due to the small sample size, the results should be interpreted with caution. Atrasentan did not cause serious cardiovascular side effects in the trial, though fluid retention and anemia were observed as side effects [131]. Postmortem analysis of the SONAR trial found that combining SGLT2 inhibitors with atrasentan may reduce fluid retention. Further observation is needed to determine if the SGLT2 inhibitor subgroup reduces fluid retention incidence [132]. Anemia may be due to blood dilution. The AFFINITY study investigated the safety and efficacy of atrasentan in treating IgAN. In a cohort of IgAN patients receiving a maximally tolerated and stable dose of RASi, a 24-week interim analysis showed that atrasentan reduced the UPCR by an average of 54.7% in 19 patients. Additionally, 79% of patients experienced a UPCR reduction of more than 40%, and the safety profile was overall well tolerated. These findings demonstrate that atrasentan can sustainably and clinically reduce proteinuria in patients with IgAN. The absence of fluid retention-related AEs during treatment suggests that atrasentan is well tolerated, confirming its therapeutic potential [133]. In contrast, the PROTECT trial evaluated the efficacy of sparsentan compared to irbesartan in patients with IgAN. At week 36, sparsentan significantly reduced proteinuria compared to irbesartan (49.8 *vs.* 15.1%) [134]. At week 110, sparsentan maintained a 40% relative reduction in proteinuria [47], indicating its significant therapeutic effect on reducing proteinuria and its long-term nephroprotective potential in IgAN. No significant difference was observed between the sparsentan and irbesartan groups in the incidence of AEs or in the change in body weight from baseline (a marker of fluid retention) throughout the trial. This indicates that sparsentan is well tolerated. In the valsartan and irbesartan groups, 9 and 13% of patients, respectively, reached the composite renal failure endpoint (RR 0.7, 95% CI: 0.4–1.2) [47]. Although the RR was not statistically significant, this may suggest a positive trend for sparsentan in reducing the risk of composite renal failure endpoints from a clinical perspective. In summary, the FDA has granted accelerated approval to sparsentan for treating proteinuria in adults with primary IgAN at risk of rapid disease progression, typically with a UPCR of ≥1.5 g/g, based on these clinical benefits [135].

Patients with FSGS have an urgent need for new therapies, and sparsentan is being developed as a treatment for FSGS. In the DUET study, sparsentan demonstrated significant anti-proteinuria efficacy and good tolerability [125]. The DUET trial then entered the Open Label Extension (OLE) phase [136], where results indicated a sustained decline in proteinuria over time, suggesting that long-term sparsentan administration could preserve renal function in FSGS patients [137]. Based on the positive outcomes of the DUET study, Komers et al. [138] conducted the DUPLEX trial, the largest Phase 3 RCT in FSGS to date. At the 36-week interim analysis, 42% of patients in the sparsentan group achieved partial remission of proteinuria compared to 26% in the irbesartan group, defined as UPCR ≤ 1.5 g/g with a reduction of >40% from baseline. Consistent with the OLE phase results [137], the reduction in proteinuria persisted throughout the 108-week trial, and sparsentan remained well-tolerated, further confirming its long-term renal protective effect in FSGS patients. However, at 108 weeks, there was no significant difference in the improvement of the eGFR slope, the primary efficacy endpoint, between the two groups. Possible reasons include the heterogeneity of the trial population, such as different etiologies (hereditary or immune-mediated) and varying disease severities (extent of interstitial fibrosis or tubular atrophy). Additionally, as data obtained after the initiation or intensification of immunosuppressive therapy were excluded due to eGFR decline in the sparsentan group, differing effects of immunosuppressive therapy may explain the lack of improvement in the eGFR slope [126]. Improvements in proteinuria and the eGFR slope are strongly associated with preserving renal function [139]. Therefore, establishing a quantitative relationship between proteinuria and eGFR changes or related efficacy endpoints is crucial for developing FSGS therapies.

The ZENITH-CKD study is the first to evaluate the efficacy and safety of combining zibotentan with SGLT2 inhibitor in CKD patients. The trial was randomized and stratified to reflect the real-world incidence of diabetic and non-diabetic CKD [140]. At 12 weeks, zibotentan 1.5 mg plus dapagliflozin 10 mg and zibotentan 0.25 mg plus dapagliflozin 10 mg reduced UACR by 33.7 and 27.0%, respectively, compared to dapagliflozin 10 mg plus placebo. These findings suggest that combining zibotentan with dapagliflozin significantly reduces proteinuria and has clinical relevance. Safety analysis revealed that fluid retention occurred in 8% of placebo patients, compared to 18% in the high-dose and 9% in the low-dose zibotentan groups [38]. While 1.5 mg zibotentan was more effective at reducing albuminuria than 0.25 mg, it was associated with higher fluid retention. Thus, 0.25 mg zibotentan may provide a better risk-benefit balance and is considered optimal for future studies. This trial offers critical data supporting a Phase III (NCT06087835) study on the long-term efficacy and safety of zibotentan and dapagliflozin for renal outcomes.

Zibotentan has also shown promise in the Phase II study for CKD secondary to SSc, which consists of three sub-studies: ZEBRA 1, ZEBRA 2 A, and ZEBRA 2B. The results of ZEBRA 1 indicated that zibotentan had no effect on serum sVCAM-1 (a potential marker of AKI), suggesting that serum sVCAM-1 is not a useful marker for SSc-CKD. Zibotentan was found to improve eGFR at 26 weeks, with more pronounced effects at 52 weeks, suggesting that zibotentan can enhance renal function and may have long-term nephroprotective potential to support disease remission. ZEBRA 2 A found no significant difference in the incidence of AEs between the placebo and zibotentan groups, indicating good tolerability of zibotentan. ZEBRA 2B proposed a viable dosing regimen for patients undergoing HD, which can be further investigated in future trials to enhance treatment quality for HD patients [37].

Conclusion

In this review, we summarize the mechanisms of action of various ERAs in preclinical trials for different kidney diseases, as well as the safety and efficacy of clinical trials. Recent large RCTs have confirmed the protective effects of adding ERAs to RAS inhibitors on renal function, although AEs such as fluid retention still occur. Post-hoc analysis of the SONAR study found that the combination therapy of ERAs and SGLT2 inhibitor effectively reduced the occurrence of AEs, such as fluid retention [132], which was further confirmed by the ZENITH-CKD study [140]. Based on this, there are currently several ongoing clinical trials investigating the safety and efficacy of 'triple therapy' (ERAs, SGLT2 inhibitor, and RAS inhibitors) in kidney disease. This provides new insights for the future application of ERAs in the treatment of kidney diseases.

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