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REVIEW ARTICLE

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Endothelin receptor antagonists in kidney protection for diabetic kidney disease and beyond?

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Abstract

The burden of chronic kidney disease is increasing worldwide, largely due to the increasing global prevalence of diabetes mellitus and hypertension. While renin angiotensin system inhibitors and sodium-glucose cotransporter two inhibitors are the management cornerstone for reducing kidney and cardiovascular complications in patients with diabetic and non-diabetic kidney disease (DKD), they are partially effective and further treatments are needed to prevent the progression to kidney failure. Endothelin receptor antagonism represent a potential additional therapeutic option due to its beneficial effect on pathophysiological processes involved in progressive kidney disease including proteinuria, which are independently associated with progression of kidney disease. This review discusses the biological mechanisms of endothelin receptor antagonists (ERA) in kidney protection, the efficacy and safety of ERA in randomised controlled trials reporting on kidney outcomes, and its potential future use in both diabetic and non-DKDs.

KEYWORDS
chronic kidney disease, endothelin, fluid retention, kidney failure, proteinuria

Summary at a Glance

This review will provide an detailed review of the biological mechanisms of endothelin receptor antagonists (ERA) in kidney protection, the efficacy and safety of ERA in randomised controlled trials reporting on kidney outcomes, and its potential therapeutic role especially in non-diabetic chronic kidney diseases.

1 | INTRODUCTION

Chronic kidney disease (CKD) is an increasing global public health problem, with an estimated prevalence in the adult population of 10%–15%, accounting for 850 million cases and 1.2 million deaths annually.[1,2] The prevalence of CKD has increased by 32% over the past 10 years and driven largely by diabetic kidney disease (DKD) and hypertension.[3] Agents that inhibit the renin-angiotensin-aldosterone system (RAAS) are the accepted standard-of-care for CKD. Despite maximum RAAS inhibition, progression of CKD still occurred in 30%–45% of participants randomised to RAAS inhibition in large clinical trials of both DKD and non-diabetic CKD.[4–6] Recent evidence of kidney and cardiac protection from sodium glucose co-transporter 2 (SGLT2) inhibitors in people with CKD due to type 2 diabetes mellitus (T2DM)

and non-diabetic CKD has prompted the Food and Drug Administration (FDA) to approve the use of SGLT2 inhibitors in people with CKD with an estimated glomerular filtration rate (eGFR) ≥25 ml/min/1.73 m^2 for dapagliflozin in DKD and non-diabetic CKD and ≥30 ml/min/1.73 m^2 for canagliflozin in DKD.[7–9] However, the residual risk of kidney endpoints (doubling of serum creatinine, 50% decline in eGFR, kidney failure requiring dialysis/transplantation or death) remains high at 9%–11% after approximately 2 years despite combined SGLT2 inhibitor and maximum tolerated dose of RAAS blockade in DKD and non-diabetic CKD.[7,8] More recently, the non-steroidal mineralocorticoid receptor antagonist finerenone has also received regulatory approval after demonstrating kidney and cardiac protection in DKD.[10] Its use in non-diabetic CKD is currently being investigated (NCT05047263).

The Study of Diabetic Nephropathy with Atrasentan Renal outcomes (SONAR) trial demonstrated the addition of endothelin receptor antagonists (ERA) to RAAS inhibition further reduced proteinuria and kidney endpoints in 3668 people with DKD.[11] However, the early termination of the study (due to slower than expected accrued kidney endpoints) and concerns over potential adverse events in an earlier trial,[12] have resulted in ERAs currently not being FDA-approved for use in DKD, despite evidence of long-term kidney protection in selected patients with DKD and low risk of heart failure.[11] The Kidney Disease Improving Global Outcomes 2020 Guideline for Diabetes Management in CKD makes no specific recommendations on the use of ERAs.[13] There are several large-scale randomised controlled trials (RCT) currently underway to address the safety and efficacy of ERA in non-diabetic CKD. This review aims to examine the biologic effects of ERAs on kidney disease, to review the evidence of the efficacy and safety of ERAs with a focus on kidney endpoints through pooling data from RCTs, and to discuss their potential future use in the treatment of both DKD and non-diabetic CKD.

2 | THE PHYSIOLOGY OF ENDOTHELIN-1 IN THE PATHOPHYSIOLOGY OF KIDNEY AND HEART DISEASE

Endothelin-1 (ET-1), the most biologically relevant isoform of endothelin, is a potent vasoconstrictor produced by endothelial cells, vascular smooth muscle cells, epicardial cells and in the kidney by glomerular epithelial cells, mesangial cells and medullary collecting duct cells.[14] ET-1 acts in an autocrine or paracrine manner on two types of endothelin receptors, ET_A localised on the afferent and efferent arterioles of the glomerulus, podocyte, mesangial cells, vasa recta and arcuate arteries, and ET_B mainly in the collecting system.[14] In general, ET_A receptor activation causes afferent and efferent arteriolar vasoconstriction, cell proliferation, and matrix accumulation, whilst ET_B receptor activation causes efferent arteriolar vasodilation, and has antiproliferative and antifibrotic effects.[15]

Both mediators and consequences of almost any form of CKD increase endogenous kidney production of ET-1, which further contributes to the progression of CKD mostly via ET_A receptor-mediated effects on the kidney microenvironment (Figure 1).[15,16] Accordingly, plasma ET-1 levels has been found to correlate with worsening kidney function and albuminuria in DKD, and increased ET-1 staining in kidney biopsy from individuals with Immunoglobulin A nephropathy (IgAN) with proteinuria.[17]

Activation of ET-1 via the ET_A receptor leads to renovasoconstriction and production of angiotensin II, which in turn stimulates more ET-1 production in the kidney.[18,19] This positive feedback loop worsens hypertension and endothelial injury which is further exacerbated by ET-1 production by podocytes causing ET_A receptor-mediated mitochondrial oxidative stress in glomerular endothelial cells and loss of the endothelial glycocalyx.[20] Direct activation of ET_A receptor on podocytes cause F-actin cytoskeletal disruption and loss of the slit diaphragm protein nephrin, predisposing podocytes to detachment. Both mechanisms result in proteinuria irrespective of the aetiology of CKD.[21–23] In addition, ET_A receptor activation causes mesangial matrix accumulation, and monocyte chemoattract protein-1-induced inflammatory glomerular infiltrate, and promotes sclerosis in models of diabetes, glomerulonephritis and hypertension.[24–27]

ET-1 is also implicated in cardiovascular disease through its effect on hypertension, endothelial dysfunction, inflammation, and atherosclerosis. ET-1 mediates endothelial dysfunction through multiple molecular mechanisms including inhibition of endothelial nitric oxide synthase-induced vasodilation and oxidative stress through stimulation of NADPH oxidase.[28] ET-1 expression levels also correlates with the extent of atherosclerosis and chronic inflammation in patients with atherosclerosis.[29,30]

It is important to understand the diuresis and natriuretic effect of ET-1 as it is responsible for the fluid retention side effect commonly associated with ERAs. ET-1-induced natriuresis is mediated primarily through the ET_B receptor, which inhibits the collecting duct epithelial sodium channel via nitric oxide pathways (Figure 2).[32] While this suggests selective ET_A receptor inhibition should reduce the risk of fluid retention compared with non-selective ET_A/ET_B receptor inhibition, pre-clinical data suggests selective ET_A receptor inhibition may still induce fluid retention through ET_B receptor overstimulation, which causes vascular permeability, vasodilation-mediated upregulation of aldosterone and vasopressin-mediated water reabsorption.[33] Therefore, it is critical to review the current available clinical evidence on fluid retention in both trials of non-selective ET_A/ET_B and selective ET_A receptor inhibitors.

3 | THE POTENTIAL MECHANISMS OF KIDNEY PROTECTION FROM ENDOTHELIN RECEPTOR ANTAGONISM IN MODELS OF CHRONIC KIDNEY DISEASE

3.1 | The effect of ERAs on vasculature and endothelium

Animal data suggest selective ET_A receptor inhibition causes afferent and efferent arteriolar vasodilation,[34] overall reducing glomerular

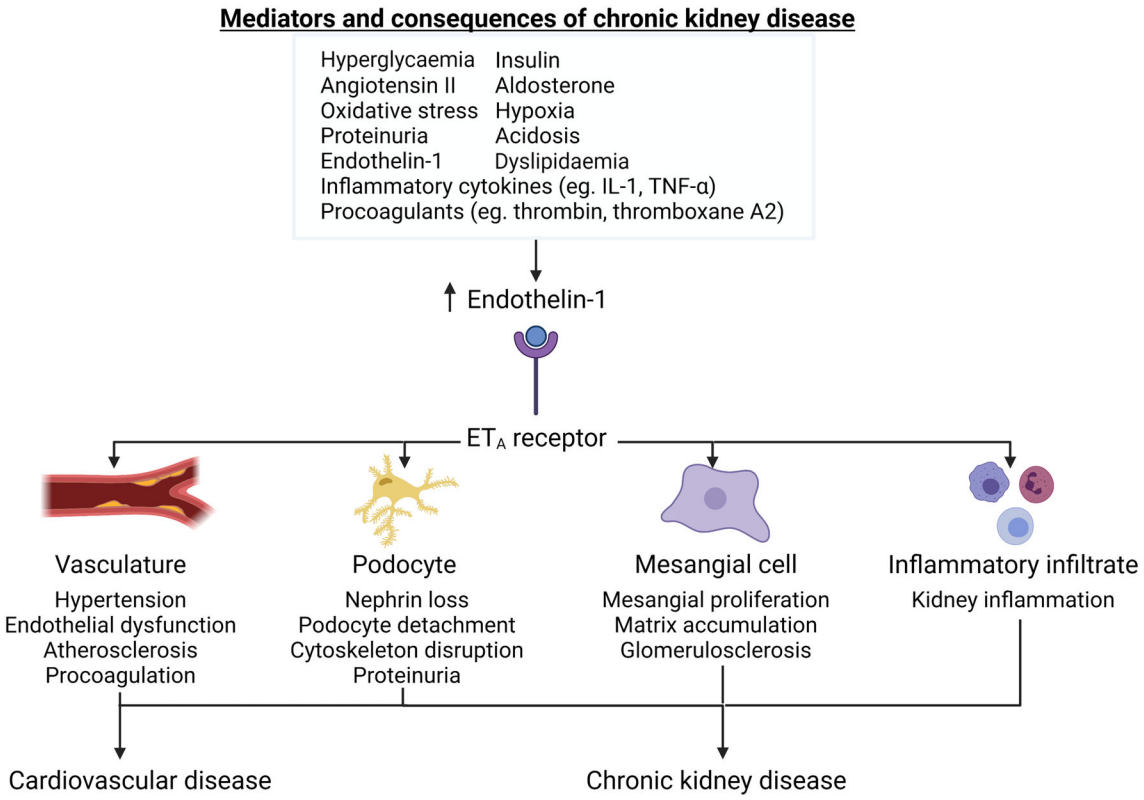

FIGURE 1 The role of endothelin-1 (ET-1) in the pathophysiology of chronic kidney disease. ET-1 is highly expressed in many organs including kidney cells such as podocytes, mesangial cells, endothelial and inflammatory cells. ET-1 can be triggered by common mediators of chronic kidney disease as well as its complications. Chronic stimulation of ET-1 leads to unchecked proinflammatory and pro-fibrotic milieu that promotes progressive CKD. ET_A receptor, endothelin A receptor; IL-1, interleukin-1; TNF-α, tumour-necrosis factor-α.

hypertension and albuminuria. This is mediated by the differential effects of endothelin receptors on glomerular haemodynamics whereby the ET_A receptor causes vasoconstriction of the both the afferent and efferent arteriole while the ET_B receptor causes vasoconstriction of the afferent arteriole and vasodilation of the efferent arteriole.[35] Therefore, selective ET_A receptor inhibition preferentially causes efferent arteriolar vasodilation and reduces glomerular filtration pressure. Accordingly, selective ET_A receptor inhibition in patients with CKD reduced effective filtration fraction and reduced proteinuria by 46%.[36] Human and animal data have also demonstrated selective ET_A receptor inhibition can ameliorate the effect of ET-1 associated epicardial vasoconstriction, accelerated aortic atherosclerosis, and peripheral arterial stiffness.[37–39] However, effects of ERAs on kidney endothelium have not been specifically studied.

3.2 | The effect of ERAs on podocytes

Restoration of podocyte morphology by selective ET_A receptor inhibition has been demonstrated in animal models of hypertension, diabetes and age-dependent glomerulosclerosis.[40–42] Selective ET_A receptor inhibition prevented the loss of nephrin and synaptopodin caused by ET-1, and reduced proteinuria.[21–23] Both selective ET_A receptor inhibition and non-selective ET_A/ET_B receptor inhibition reduced glomerular expression of fibronectin and collagen IV, which are implicated in glomerulosclerosis and fibrosis.[43,44]

3.3 | The effect of ERAs on mesangial cells

Non-selective ET_A/ET_B receptor inhibition have been demonstrated to reduce mesangial cell proliferation and mesangial matrix expansion in animal models of mesangial proliferative glomerulonephritis and DKD, respectively.[45,46] Angiotensin II-induced fibronectin synthesis and mesangial cell proliferation has also been attenuated using selective ET_A receptor inhibition.[47]

4 | THE PHARMACOLOGY OF ENDOTHELIN RECEPTOR ANTAGONISTS

Table 1 lists the selective ET_A receptor ERAs and non-selective ET_A/ET_B receptor ERAs currently available for clinical use.[48–68] Both classes of ERAs vary in their half-life and time of onset though data on their oral bioavailability are limited. Most are metabolised by cytochrome P450 (CYP) 3A4 and/or 2C9 apart from the aprocitentan (non-selective ERA) which undergoes CYP-independent metabolism. Overall, apart from their selectivity for the endothelin receptor, the

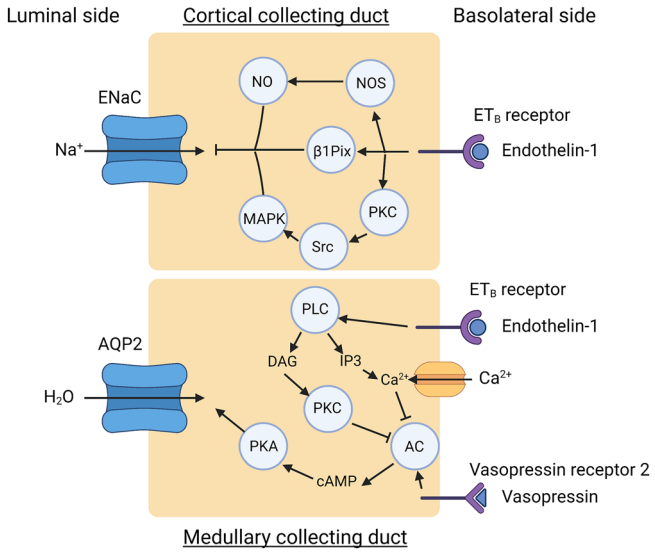

FIGURE 2 Regulation of sodium and water homeostasis by the actions of ET-1 on the collecting ducts. ET-1-mediated ET_B receptor activation causes natriuresis by inhibiting sodium reabsorption at the cortical collecting duct and inhibiting water reabsorption at the medullary collecting duct. Cortical collecting duct (upper figure): ET-1-mediated ET_B receptor activation leads to: (1) inhibition of epithelial sodium channel (ENaC) functioning activity (nitric oxide and MAPK dependent pathways), (2) promote ENaC endocytosis. Medullary collecting duct (lower figure): ET-1-mediated ET_B receptor activation leads to: (1) inhibition of vasopressin activity, and (2) inhibition of aquaporin-2 (AQP2)-mediated water reabsorption. Therefore, non-selective ERAs (especially inhibition of ET_B antagonism) can lead to sodium retention and water resorption.[31] Created with Biorender.com. AC, adenylyl cyclase; β1Pix, beta 1 Pix; DAG, diacylglycerol; ENaC, epithelial sodium channel; IP3, inositol trisphosphate; MAPK, mitogen-activated protein kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C.

two classes of ERAs do not significantly differ in terms of their pharmacokinetics or their safety profile. Pre-clinical data also suggests that kidney protection from ERAs is mostly mediated through ET_A receptor inhibition and accordingly, most RCTs reporting the effect of ERAs on kidney endpoints evaluated ET_A receptor inhibitors (Table 2).[11,12,69,70]

5 | CURRENT RCTS OF ENDOTHELIN RECEPTOR ANTAGONISTS REPORTING ON KIDNEY OUTCOMES

We reviewed all RCTs with a study duration of at least 12 weeks reporting on the effect of ERAs on kidney endpoints such as doubling of serum creatinine or kidney failure, or surrogate endpoints such as changes in kidney function or albuminuria. We included four trials of DKD, two trials of cardiovascular disease and one trial of resistant hypertension comparing ERAs with placebo.[11,12,69–73] A total of 7606 participants were included (73% with DKD). The median age was 61.8 years, and median duration of follow-up 16 weeks (interquartile range 38). (Table 2). The Reducing Residual Albuminuria in Subjects With Diabetes and Nephropathy With *Atrasentan* (RADAR) trial was a multicentre, double-blind RCT assessing the effect of the selective ET_A receptor inhibitor atrasentan on albuminuria over 12 weeks in 211 participants with CKD due to T2DM, an eGFR between 30–75 ml/min/1.73 m^2 and urine albumin-to-creatinine ratio (UACR) of 300–3500 mg/g despite RAAS blockade.[69] The Avosentan on Time to Doubling of Serum Creatinine, End Stage Renal Disease or Death in Patients With Type 2 Diabetes Mellitus and Diabetic Nephropathy (ASCEND) trial evaluated the selective ET_A receptor inhibitor avosentan on a composite outcome of doubling of serum creatinine, kidney failure or death in 1402 participants with CKD due to T2DM, a serum creatinine of 106–265 μmol/l and UACR ≥309 mg/g despite RAAS blockade.[12] In the SONAR trial, following a 6-week enrichment period where all 5117 participants with CKD due to T2DM, an eGFR between 25–75 ml/min/1.73 m^2, UACR 300–5000 mg/g despite RAAS blockade received atrasentan, 2648 responders (defined as ≥30% reduction in UACR, no significant fluid retention and rise in serum creatinine of ≤44 μmol/l and ≤20% from baseline) and 1020 non-responders were randomised to atrasentan or placebo.[11] The Endothelin Antagonist with Bosentan and Lowering of Events (ENABLE) trial evaluated the non-selective ET_A/ET_B receptor inhibitor bosentan in 1613 diabetic or non-diabetic participants with New York Heart Association class III and IV heart failure with reduced ejection fraction.[70] Reriani et al.[71] evaluated the effect of atrasentan or placebo on coronary artery blood flow in 47 participants with coronary artery disease over 6 months. Weber et al.[72] investigated the effect of the selective ET_A receptor inhibitor darusentan on blood pressure in 379 participants with resistant hypertension over 14 weeks. Finally, Wenzel et al.[73] reported the effect of avosentan on albuminuria over 12 weeks in 286 participants with diabetic nephropathy, preserved kidney function and macroalbuminuria despite RAAS blockade.

6 | EVIDENCE OF KIDNEY PROTECTION BY ENDOTHELIN RECEPTOR ANTAGONISTS

6.1 | Effect of ERAs on albuminuria

Selective ERAs using atrasentan or avosentan in the RADAR, ASCEND, SONAR, Weber et al. and Wenzel et al. studies significantly reduced albuminuria by 34%–58% compared with placebo over a period of 12 weeks to 2.2 years (Figure 3).[11,12,69,72,73]

6.2 | Effect of ERA on kidney function (eGFR or creatinine clearance)

In RADAR, Weber et al. and Wenzel et al., selective ERAs (atrasentan, darusentan, and avosentan) showed no overall acute effect on eGFR or creatinine clearance over 12 to 14 weeks compared with placebo.[69,72,73] In ASCEND, eGFR declined significantly faster with avosentan 50 mg daily compared with placebo over 6 months (−4.1 vs. −2.5 ml/min/1.73 m^2) though there was no difference between

TABLE 1 Pharmacology and clinical indications/contraindications for endothelin receptor antagonists

Drug	Route	Dose	Approved indication (potential indications based on clinical studies)	Contra-indications	Half-life (hours)	Bio-availability	Metabolism	Excretion	Adverse effects
Selective ET_A antagonists									
Ambrisentan	Oral	5–10 mg daily	PAH	Moderate/severe hepatic impairment, pregnancy, IPF	13.6–16.5	NR	CYP3A4, CYP3A5, CYP2C19	Biliary	Fluid retention (22%), anaemia (7%), liver injury (3%)
Atrasentan	Oral	0.75–1.25 mg daily	(DKD, metastatic prostate cancer [NS])	NR	24	NR	CYP3A4	NR	Fluid retention (37%), anaemia (19%)
Avosentan	Oral	5–50 mg daily	(DKD)	NR	7.5–15	72–81	NR	Biliary	Fluid retention (17%), heart failure (5%), anaemia (12%)
Darusentan	Oral	50–300 mg daily	(Resistant hypertension)	NR	16–18	NR	NR	Biliary	Fluid retention (27%), anaemia (NR)
Sitaxentan	Oral	25–100 mg daily	(PAH)	NR	8.4	70–100	CYP2C9, CYP3A4	Urine (50%–60%)	Fluid retention (9%), liver injury (2%), headache (15%–26%)
Zibotentan	Oral	5–15 mg daily	(Metastatic prostate cancer [NS])	NR	5–23	NR	CYP3A4	Urine (35%–77%)	Fluid retention (14%–17%), headache (33%–100%)
Nonselective ET_A/ET_B antagonists									
Bosentan	Oral	62.5–250 mg twice daily	PAH (ILD [NS], COPD [NS], chronic heart failure [NS])	Moderate/severe hepatic impairment, pregnancy	5.6	41%	CYP2C9, CYP3A4	Biliary	Liver injury (11%), fluid retention (10%), anaemia (6%), drug interactions (bosentan induces CYP2C9 and CYP3A4)
Macitentan	Oral	10 mg daily	PAH	Moderate/severe hepatic impairment, pregnancy	16 (48 for active metabolite)	NR	CYP3A4, CYP2C8, CYP2C9, CYP2C19	Urine	Fluid retention (22%), anaemia (13%), liver injury (3%)
Aprocitentan	Oral	5–50 mg daily	(Hypertension)	NR	47.4–53.2	NR	Not dependent on CYP	Urine and faeces	Hypertension (3%), headache (4%), fluid retention (2%)
Tezosentan	IV	1–50 mg/h	(PAH [NS], acute heart failure [NS])	NR	6 min (initial), 3 h (terminal)	Not applicable	NR	NR	Headache (32%), hypotension (23%)
Dual ET_A/AT_1 antagonist									
Sparsentan	Oral	200–800 mg daily	(FSGS, IgAN)	NR	NR	NR	NR	NR	Headache (19%), hypotension (12%), fluid retention (12%)

Abbreviations: AT1, angiotensin II type 1 receptor; CYP, cytochrome P450 enzymes; DKD, diabetic kidney disease; ET_A, endothelin receptor A; ET_B, endothelin receptor B; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; IPF, idiopathic pulmonary fibrosis; IV, intravenous; NR, not reported; NS, results from trials showed no significant benefit from endothelin receptor antagonism; liver injury defined as liver aminotransferases ≥3 times the upper limit of normal; PAH, pulmonary arterial hypertension.

TABLE 2 Characteristics of the included trials and the effect of endothelin receptor antagonists on kidney function or patient-level kidney endpoints

Study/Author	N	Study population	Intervention/Control	Age (year)	Baseline eGFR (ml/min per 1.73 m^2)/serum creatinine (μmol/l)	Diabetes (%)	Follow-up (weeks)	Primary outcome	Relative difference in kidney endpoints (RR) [95% CI]	Mean difference in kidney function at the end of study [95% CI]
RADAR trial De Zeeuw et al.[69]	211	T2DM with UACR 300–3500 mg/g	Atrasentan 0.75–1.25 mg daily (selective ET_A)/ Placebo	64.6	49.3/NR	100	12	Change in UACR	NR	−0.50 [−5.23–4.23][a]
ASCEND trial Mann et al.[12]	1402	T2DM with UACR ≥309 mg/g	Avosentan 25–50 mg daily (selective ET_A)/ Placebo	61.0	33.1/186	100	16	Kidney composite outcome[b]	0.63 [0.42–0.94][b]	−0.51 [−2.36–1.34][a]
SONAR trial Heerspink et al.[11]	3668	T2DM with UACR 300–500 mg/g	Atrasentan 0.75 mg daily (selective ET_A)/ Placebo	64.8	43.8/150	100	114.4	Kidney composite outcome[c]	0.79 [0.65–0.97][c]	+0.65 [0.28–1.02][a]
ENABLE trial Packer et al.[70]	1613	Heart failure with reduced ejection fraction	Bosentan 62.5–125 mg BD (nonselective ET_A/ ET_B)/Placebo	67.2	NR/115	33.3	78	Heart failure composite outcome[d]	0.78 [0.56–1.09][e]	NR
Reriani et al.[71]	47	Coronary non-obstructive disease but endothelial dysfunction on angiogram	Atrasentan 10 mg daily (selective ET_A)/ Placebo	48.8	NR/89	11.1	24	Coronary artery blood flow and diameter	NR	+2.00 [−5.05–9.05][f]
Weber et al.[72]	379	Resistant hypertension	Darusentan 50–300 mg daily (selective ET_A)/ Placebo	61.8	78.9/NR	40.4	14	Blood pressure	NR	−5.05 [−11.78–1.68][a]
Wenzel et al.[73]	286	Type 1 or 2 diabetes with UAER 0.2–5.6 mg/min	Avosentan 5–50 mg daily (selective ET_A)/ Placebo	52.2	NR/103	100	12	Mean UAER	NR	+0.85 [−8.28–9.98][f]

Note: All participants in RADAR, ASCEND, SONAR, ENABLE, and Wenzel et al were treated with an angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (unless intolerant or contraindicated).

Abbreviations: BD, twice daily dosing; CI, confidence interval; eGFR, estimated glomerular filtration rate; ET_A, endothelin receptor A; ET_B, endothelin receptor B; RR, relative risk; T2DM, type 2 diabetes mellitus; UACR, urine albumin/creatinine ratio; UAER, urine albumin excretion rate.

[a]eGFR (ml/min/1.73 m^2).

[b]Doubling of serum creatinine, end-stage kidney disease or death.

[c]Doubling of serum creatinine, end-stage kidney disease or death from kidney failure.

[d]Death or hospitalization from heart failure.

[e]Kidney failure not further defined.

[f]Creatinine clearance (ml/min).

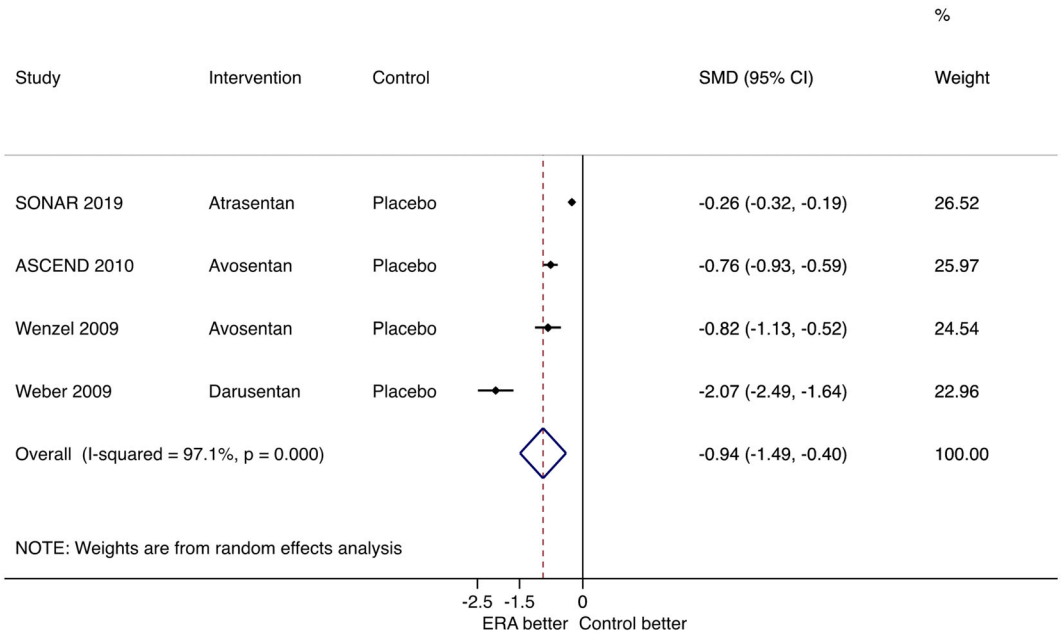

FIGURE 3 Forest plot of the treatment effect of selective ET_A receptor inhibitors on albuminuria compared with placebo. ERA, endothelin receptor antagonist; SMD, standardized mean difference; CI, confidence interval. The RADAR trial could not be included in the meta-analysis as standard deviation of change in albuminuria was not reported.

avosentan 25 mg daily and placebo.[12] In comparison, Reriani et al.[71] reported no difference in creatinine clearance between atrasentan 10 mg daily and placebo over 6 months.

By contrast, SONAR demonstrated a long-term benefit in significantly slowing the rate of eGFR decline compared with placebo over 2.2 years (−2.4 vs. −3.1 ml/min/1.73 m^2 per year).[11] Patient populations were similar in both RADAR and SONAR in terms of age, severity of albuminuria, blood pressure, and glycaemic control though the baseline eGFR was lower in SONAR compared with RADAR (43.8 vs. 49.3 ml/min/1.73 m^2). By contrast, participants in ASCEND had a lower baseline eGFR (33.1 ml/min/1.73 m^2) and higher albuminuria (median 1425–1531 mg/g compared with 671–878 mg/g), while participants in studies by Reriani et al., Weber et al., and Wenzel et al. had higher baseline kidney function (eGFR 76–81 ml/min/1.73 m^2 and creatinine clearance 58–84 ml/min).

6.3 | Effect of ERAs on blood pressure

In RADAR, atrasentan significantly reduced both 24-h ambulatory systolic blood pressure (−4.5 to −5.4 mmHg from baseline) and diastolic blood pressure (−4.2 to −4.6 mmHg from baseline) in a dose-dependent manner over 12 weeks.[69] In SONAR, atrasentan demonstrated a smaller but significant long-term reduction in systolic blood pressure compared with placebo (mean between-group difference −1.6 mmHg).[11] In ASCEND, avosentan also reduced systolic blood pressure (−4.3 to −6.1 mmHg) and diastolic blood pressure (−3.6 to −4.4 mmHg), though the effect was not dose-dependent.[12] The antihypertensive effects of darusentan appear to be greater, reducing 24-h ambulatory systolic blood pressure (−17 to −18 mmHg from baseline) and diastolic blood pressure (−10 to −11 mmHg from baseline) over 14 weeks, though these differences may reflect higher baseline blood pressure and lack of CKD in the study population of the study by Weber et al.[72] In ENABLE, bosentan reduced the systolic and diastolic blood pressure by 1–2 mmHg compared with placebo over 78 weeks.[70]

6.4 | Effect of ERAs on kidney endpoints (defined as a composite of doubling of creatinine or 50% decline in eGFR, kidney failure requiring dialysis or transplantation, or death due to kidney disease)

There is a consistent beneficial effect of ERAs on kidney composite endpoints in RCTs. Kidney endpoints were adjudicated in SONAR, ASCEND, and ENABLE trials. SONAR was the only study powered to assess the effect of ERAs on patient-level kidney endpoints. Despite the lower-than-expected clinical event rate, SONAR demonstrated a 35% reduced risk of a composite of doubling of serum creatinine or end-stage kidney disease with atrasentan compared with placebo over 2.2 years, which did not differ from the responder (hazards ratio [HR] 0.65, 95% confidence interval [CI] 0.49–0.88) and non-responder group (HR 0.75, 95% CI 0.55–1.03).[11] In ENABLE, kidney failure captured in serious adverse event reporting occurred in 7% of the bosentan group and 9% of the placebo group.[70] Overall, ERAs show a consistent reduction of the composite of the doubling of serum creatinine or kidney failure by 24% (Figure 4) with similar treatment effects across the three studies. However, the quality of this evidence is

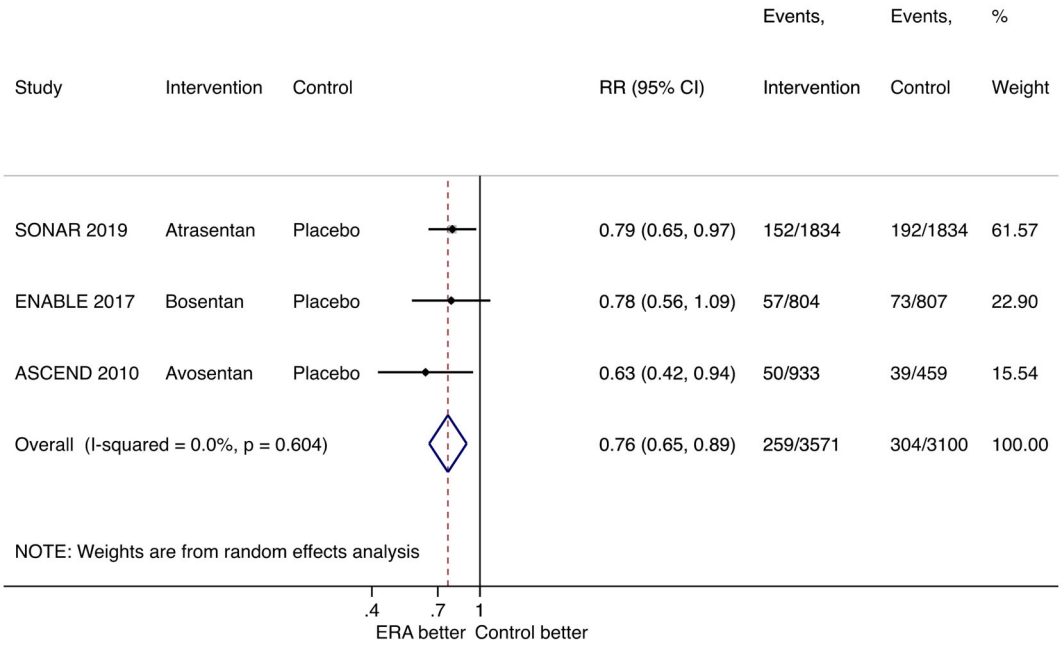

FIGURE 4 wForest plot of the treatment effect of selective ET_A receptor inhibitors or non-selective ET_A/ET_B receptor inhibitors on patient-level kidney endpoints compared with placebo. ERA, endothelin receptor antagonist; RR, relative risk; CI, confidence interval. Patient-level kidney endpoints defined as the composite of the doubling of serum creatinine, end-stage kidney disease, or kidney failure reported in as a serious adverse event.

limited by the paucity of studies and heterogeneity in the reported outcomes.

7 | ARE ENDOTHELIN RECEPTOR ANTAGONISTS SAFE?

The ASCEND trial was terminated prematurely due to an excess of cardiovascular events with avosentan, mostly driven by increased heart failure in 4%–6% of participants, with an associated study drop-out of 20% in the avosentan group.[12] Despite the enrichment period, exclusion of participants with heart failure and liberal use of diuretics in the SONAR trial, atrasentan compared with placebo was still associated with an increased risk of fluid retention (38% vs. 33%), anaemia (18% vs. 11%) and a trend towards increased heart failure which did not reach statistical significance (6% vs. 4%). The mechanism of anaemia is unclear but is thought to be haemodilution secondary to fluid retention.[74] In the atrasentan group, 10% of responders and 14% of non-responders discontinued due to side-effects though this did not differ compared with the placebo group.[11] Similarly, new or worsening peripheral oedema was reported in 42% of patients on high-dose atrasentan in RADAR though this was not different compared with placebo.[69]

Interestingly, ENABLE included only participants with NYHA class III or IV heart failure with reduced ejection fraction and found no difference between bosentan or placebo for hospitalisation for heart failure (38% vs. 39%) though there was an increased risk of peripheral oedema (10% vs. 8%) and anaemia (10% vs. 5%).[70] Neither SONAR or ENABLE found any difference between ERAs and placebo for the composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, hospitalization for heart failure, or death from any cause.

It is difficult to compare the relative safety of selective ERAs (atrasentan, darusentan, and avosentan) and non-selective ERAs (bosentan) in CKD due to differences in the study populations of ENABLE compared to other trials reporting the effect of selective ERAs on kidney endpoints (Table 2). Regarding the relative specificity of selective ET_A receptor inhibitors, avosentan was associated with a higher risk of hospitalisation for heart failure in ASCEND compared to atrasentan (a more selective ET_A receptor inhibitor than avosentan) in SONAR (HR 2.76, 95% CI 1.68-4.54 versus HR 1.33, 95% CI 0.85-2.07).[11,81] The difference in heart failure risk can be likely attributed to the different ETA selectivity of the two agents (avosentan being less selective than atrasentan), the high dose of avosentan used in the ASCEND trial compared to the much lower dose of atrasentan, and the precautionary measures included in the design of the SONAR trial including the careful patient selection. The lesson from the ASCEND and SONAR trials is that the risk of fluid retention and heart failure can be substantially mitigated, although additional research is required to identify patients most likely to benefit while minimising harm.

8 | ENDOTHELIN RECEPTOR ANTAGONISTS FOR THE TREATMENT OF NON-DIABETIC CHRONIC KIDNEY DISEASE?

A dual ET_A and AT1 receptor antagonist, sparsentan has been evaluated in the phase 2b study in patients with Primary Focal Segmental Glomerulosclerosis (FSGS), the DUET trial, which demonstrated a significantly higher likelihood of achieving the FSGS partial remission

endpoint (FPRE) (defined as urine protein-to-creatinine ratio [UP/C] ≤1.5 g/g and a >40% reduction in proteinuria from baseline) with sparsentan compared with irbesartan over 8 weeks (28% vs. 9%).[75] This is currently being further evaluated in the phase 3 DUPLEX study (NCT03493685) which will assess the effect of sparsentan compared with irbesartan on the eGFR slope at week 108 in participants with primary FSGS. A press release recently reported the DUPLEX study has met its protocol-specified interim analysis showing a statistically significant higher FPRE of sparsentan compared with the active control at 36 weeks (42% vs. 26%, $p = .0094$).[76] In a parallel ongoing phase 3 trial, the PROTECT study (NCT03762850) will examine the safety and efficacy of 400 mg of sparsentan, compared with 300 mg of irbesartan, in 404 adults with biopsy proven IgA nephropathy with persistent proteinuria despite 3 months of RAAS inhibition. A protocol specified interim analysis of 280 PROTECT participants demonstrated a threefold reduction of proteinuria from baseline after 36 weeks of treatment, compared with irbesartan ($p < .0001$).[77] Both studies reported sparsentan has been generally well-tolerated and consistent with the observed safety profile to date. Both DUPLEX and PROTECT trials have completed recruitment and are ongoing, with the final study outcomes anticipated in 2023. The FDA has accepted and granted for accelerated approval of sparsentan for the treatment of IgA Nephropathy.[78]

Another phase 3 study Atrasentan in Patients With IgA Nephropathy (ALIGN) (NCT04573478) is underway evaluating the effect of atrasentan compared with placebo in individuals who are receiving maximally tolerated RAAS inhibition on change in UP/C and eGFR in participants with IgA nephropathy with persistent proteinuria of ≥1 g/day. The expanded indications of ERAs have been examined in another phase 2, open-label, basket study using Atrasentan in Patients With Proteinuric Glomerular Diseases (AFFINITY) (NCT04573920). There are four cohort of patients in each group ($n = 20$ in each group), namely (1) IgA nephropathy with UP/C ratio between 0.5 and 1.0 g/g, (2) FSGS, (3) Alport syndrome, and (4) DKD on top of background care of a RAAS inhibitor and SGLT2 inhibitor. A protocol prespecified interim analysis of the IgAN cohort of the AFFINITY trial reported the baseline characteristic of this cohort at the European Renal Association meeting, 2022. Following a 12 and 24-week of treatment with atrasentan, there was a mean 24-h urine protein reduction from baseline of 50% and 59%, respectively with no significant weight gain or acute change in eGFR.[79] Finally, aprocitentan, an orally active, daily dosing, non-selective ERA has an ongoing phase 3 randomized clinical trial (PRECISION) evaluating its efficacy and safety in patients with treatment resistant hypertension receiving multiple antihypertensives (NCT03541174). A press release recently reported the PRECISION study achieved its primary endpoint measure of systolic blood pressure reduction at 4 weeks in both the aprocitentan 12.5 mg ($p < .005$) and 25 mg ($p < .005$) groups compared with placebo, and was well-tolerated.[80]

9 | DISCUSSION

Activation of endothelin system through its ET_A and ET_B receptors have been associated with pathogenesis and progression of CKD, irrespective of its primary aetiology. ERAs, especially selective ETA antagonism, are orally available, promising therapeutic agents that have been examined in both diabetic and non-diabetic CKD. Pooled analysis in this review from published RCTs of ERAs reporting on kidney outcomes have shown a consistent reduction in composite kidney endpoints (doubling of creatinine or 50% decline in eGFR, kidney failure requiring dialysis or transplantation, or death due to kidney disease), with consistent effects on albuminuria reduction. Several ongoing large scale clinical trials will determine the long-term efficacy and safety of ERAs in FSGS and IgA nephropathy.

Despite these kidney protective effects, the future clinical use of ERAs will depend on its safety, in particular the risk of fluid retention and heart failure. The SONAR trial demonstrated that careful identification of patients using an enrichment design can minimize but not completely abrogate the risk of fluid retention. Although the incidence of cardiac failure was not statistically significant, it was numerically higher in the atrasentan group compared with placebo (5.5% vs. 3.9%).

Current strategies to prevent fluid retention include judicious use of diuretics, which lowered body weight in participants receiving avosentan in the ASCEND trial,[81] and careful selection of patients at low risk of heart failure. In the SONAR trial, participants at a relatively low risk of heart failure were selected,[11] and subsequent ERA trials have focused on non-diabetic CKD populations such as FSGS and IgA nephropathy who tend to be younger, less comorbid and therefore have a lower risk of heart failure.[76–78] Another strategy would be the addition of a SGLT2 inhibitor, which is known to have mild diuretic effects. Post hoc analyses from SONAR suggest that participants who received combined atrasentan and SGLT2 inhibitor had a lower weight gain and greater percentage of albuminuria reduction as compared with atrasentan alone during the 6-week enrichment period suggesting a potential role of this combination therapy.[82] We eagerly await the results of the Zibotentan and Dapagliflozin for the Treatment of CKD (ZENITH-CKD) phase 2 trial (NCT04724837) evaluating the efficacy and safety of combined ERA and SGLT2 inhibitor therapy for the treatment of non-diabetic CKD.

On the other hand, sparsentan (PROTECT and DUPLEX trial) and atrasentan (AFFINITY) are reportedly well-tolerated in patients with FSGS and IgA nephropathy. Unlike the diabetic population, individuals with IgAN and FSGS are likely to be younger with lower cardiovascular risk. Despite that, more granular data on fluid retention and weight gain is anticipated once these studies are completed and published in the near future. In a hypertension study of participants with normal or near-normal kidney function, the incidence of peripheral oedema appears to be lower with the non-selective ET_A/ET_B antagonist aprocitentan (1.2%).[63,83] Therefore, close monitoring and judicious use of diuretics may be useful in selected populations treated with ERAs.[32] There may be potential synergistic effects of combining ERAs with potassium-sparing diuretics especially in non-selective ET_A/ET_B antagonists since potassium-sparing diuretics such as amiloride inhibit the epithelial sodium channel in collecting tubules, which is responsible for fluid retention activated by ET_B antagonism. However, this requires further robust testing in an adequately powered RCT.

We should acknowledge the limitations of the data on kidney protection, which we interpret with caution since most trials are short-term with a median duration of 16 weeks. Although the effect on albuminuria is consistent across all trials, the effects on eGFR is not consistent across all seven trials. Only the SONAR and ENABLE trials provide long-term data on kidney endpoints, and the data on kidney failure in the ENABLE trial is obtained from serious adverse event reporting. The DUPLEX, PROTECT, and ALIGN trials will provide crucial long-term data on proteinuria reduction and eGFR decline to better determine the kidney protective effects of ERAs.

Overall, it is an exciting period for discovery of novel therapeutic strategies in delaying progressive CKD. There are strong clinical data demonstrating the anti-albuminuric effect and promising long-term kidney protective effects of ERAs, especially selective ERAs, when added onto standard-of-care, which make it an attractive treatment for both diabetic and non-diabetic CKD.

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CONFLICT OF INTEREST

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REFERENCES

1. Ortiz A, Cozzolino M, Duivenvoorden R, et al. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. *Nephrol Dial Transplant*. 2021;36(1):87-94.
2. Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2020;395(10225):709-733.
3. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the global burden of disease study 2015. *Lancet*. 2016;388(10053):1459-1544.
4. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):851-860.
5. Brenner BM, Cooper ME, De Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861-869.
6. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288(19):2421-2431.
7. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306.
8. Heerspink HJ, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446.
9. de Boer IH, Caramori ML, Chan JC, et al. Executive summary of the 2020 KDIGO diabetes management in CKD guideline: evidence-based advances in monitoring and treatment. *Kidney Int*. 2020;94:839.
10. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;383:2219-2229.
11. Heerspink HJ, Parving H-H, Andress DL, 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*. 2019;393(10184):1937-1947.
12. Mann JF, Green D, Jamerson K, et al. Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol*. 2010;21(3):527-535.
13. KDOQI. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis*. 2007;49(2 Suppl 2):S12-S154.
14. Dhaun N, Goddard J, Webb D. The endothelin system and its antagonism in chronic kidney disease. *J Am Soc Nephrol*. 2006;17(4):943-955.
15. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int*. 2014;86(5):896-904.
16. Barton M, Sorokin A. Endothelin and the glomerulus in chronic kidney disease. *Semin Nephrol*. 2015;35(2):156-167.
17. Zanatta CM, Gerchman F, Burttet L, et al. Endothelin-1 levels and albuminuria in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2008;80(2):299-304.
18. Kawaguchi H, Sawa H, Yasuda H. Endothelin stimulates angiotensin I to angiotensin II conversion in cultured pulmonary artery endothelial cells. *J Mol Cell Cardiol*. 1990;22(8):839-842.
19. Barton M, Shaw S, d'Uscio LV, et al. Angiotensin II increases vascular and renal endothelin-1 and functional endothelin converting enzyme activity in vivo: role of ETA receptors for endothelin regulation. *Biochem Biophys Res Commun*. 1997;238(3):861-865.
20. Ebefors K, Wiener RJ, Yu L, et al. Endothelin receptor-a mediates degradation of the glomerular endothelial surface layer via pathologic crosstalk between activated podocytes and glomerular endothelial cells. *Kidney Int*. 2019;96(4):957-970.
21. Collino F, Bussolati B, Gerbaudo E, et al. Preeclamptic sera induce nephrin shedding from podocytes through endothelin-1 release by endothelial glomerular cells. *Am J Physiol Renal Physiol*. 2008;294(5):F1185-F1194.
22. Morigi M, Buelli S, Angioletti S, et al. In response to protein load podocytes reorganize cytoskeleton and modulate endothelin-1 gene: implication for permselective dysfunction of chronic nephropathies. *Am J Pathol*. 2005;166(5):1309-1320.
23. Morigi M, Buelli S, Zanchi C, et al. Shigatoxin-induced endothelin-1 expression in cultured podocytes autocrinally mediates Actin remodeling. *Am J Pathol*. 2006;169(6):1965-1975.
24. Kuo HT, Kuo MC, Chen HC, Shin SJ. Effects of specific endothelin-1 receptor antagonists on proliferation and fibronectin production of glomerular mesangial cells stimulated with angiotensin II. *Kaohsiung J Med Sci*. 2006;22(8):371-376.
25. Ishizawa K, Yoshizumi M, Tsuchiya K, et al. Dual effects of endothelin-1 (1-31): induction of mesangial cell migration and facilitation of monocyte recruitment through monocyte chemoattractant protein-1 production by mesangial cells. *Hypertens Res*. 2004;27(6):433-440.
26. Mishra R, Wang Y, Simonson MS. Cell cycle signaling by endothelin-1 requires Src nonreceptor protein tyrosine kinase. *Mol Pharmacol*. 2005;67(6):2049-2056.
27. Lenoir O, Milon M, Virsolvy A, et al. Direct action of endothelin-1 on podocytes promotes diabetic glomerulosclerosis. *J Am Soc Nephrol*. 2014;25(5):1050-1062.
28. Böhm F, Pernow J. The importance of endothelin-1 for vascular dysfunction in cardiovascular disease. *Cardiovasc Res*. 2007;76(1):8-18.

29. Ihling C, Szombathy T, Bohrmann B, Brockhaus M, Schaefer HE, Loeffler BM. Coexpression of endothelin-converting enzyme-1 and endothelin-1 in different stages of human atherosclerosis. *Circulation*. 2001;104(8):864-869.
30. Lerman A, Edwards BS, Hallett JW, Heublein DM, Sandberg SM, Burnett JC Jr. Circulating and tissue endothelin immunoreactivity in advanced atherosclerosis. *N Engl J Med*. 1991;325(14):997-1001.
31. Kohan DE. Role of collecting duct endothelin in control of renal function and blood pressure. *Am J Physiol Regul Integr Comp Physiol*. 2013;305(7):R659-R668.
32. Schneider MP, Boesen EI, Pollock DM. Contrasting actions of endothelin ETA and ETB receptors in cardiovascular disease. *Annu Rev Pharmacol Toxicol*. 2007;47:731-759.
33. Vercauteren M, Trensz F, Pasquali A, et al. Endothelin ETA receptor blockade, by activating ETB receptors, increases vascular permeability and induces exaggerated fluid retention. *J Pharmacol Exp Ther*. 2017;361(2):322-333.
34. Inscho EW, Imig JD, Cook AK, Pollock DM. ETA and ETB receptors differentially modulate afferent and efferent arteriolar responses to endothelin. *Br J Pharmacol*. 2005;146(7):1019-1026.
35. Dhaun N, Pollock DM, Goddard J, et al. Selective and mixed endothelin receptor antagonism in cardiovascular disease. *Trends Pharmacol Sci*. 2007;28(11):573-579.
36. Goddard J, Johnston NR, Hand MF, et al. Endothelin-a receptor antagonism reduces blood pressure and increases renal blood flow in hypertensive patients with chronic renal failure: a comparison of selective and combined endothelin receptor blockade. *Circulation*. 2004;109(9):1186-1193.
37. Barton M, Haudenschild CC, d'Uscio LV, et al. Endothelin ETA receptor blockade restores NO-mediated endothelial function and inhibits atherosclerosis in apolipoprotein E-deficient mice. *Proc Natl Acad Sci U S A*. 1998;95(24):14367-14372.
38. Halcox JP, Nour KR, Zalos G, et al. Coronary vasodilation and improvement in endothelial dysfunction with endothelin ETA receptor blockade. *Circ Res*. 2001;89(11):969-976.
39. McEniery CM, Qasem A, Schmitt M, et al. Endothelin-1 regulates arterial pulse wave velocity in vivo. *J Am Coll Cardiol*. 2003;42(11):1975-1981.
40. Opočenský M, Kramer HJ, Bäcker A, et al. Late-onset endothelin-a receptor blockade reduces podocyte injury in homozygous ren-2 rats despite severe hypertension. *Hypertension*. 2006;48(5):965-971.
41. Gagliardini E, Corna D, Zoja C, et al. Unlike each drug alone, lisinopril if combined with avosentan promotes regression of renal lesions in experimental diabetes. *Am J Physiol Renal Physiol*. 2009;297(5):F1448-F1456.
42. Ortmann J, Amann K, Brandes RP, et al. Role of podocytes for reversal of glomerulosclerosis and proteinuria in the aging kidney after endothelin inhibition. *Hypertension*. 2004;44(6):974-981.
43. Hocher B, Schwarz A, Reinbacher D, et al. Effects of endothelin receptor antagonists on the progression of diabetic nephropathy. *Nephron*. 2001;87(2):161-169.
44. Nerlich A, Schleicher E. Immunohistochemical localization of extracellular matrix components in human diabetic glomerular lesions. *Am J Pathol*. 1991;139(4):889-899.
45. Chen S, Evans T, Deng D, Cukiernik M, Chakrabarti S. Hyperhexosemia induced functional and structural changes in the kidneys: role of endothelins. *Nephron*. 2002;90(1):86-94.
46. Gómez-Garre D, Largo R, Liu XH, et al. An orally active ETA/-ETB receptor antagonist ameliorates proteinuria and glomerular lesions in rats with proliferative nephritis. *Kidney Int*. 1996;50(3):962-972.
47. Gómez-Garre D, Ruiz-Ortega M, Ortego M, et al. Effects and interactions of endothelin-1 and angiotensin II on matrix protein expression and synthesis and mesangial cell growth. *Hypertension*. 1996;27(4):885-892.
48. MIMS. Ambrisentan. 2019. In: MIMS Online [Internet]. http://www.mimsonline.com
49. MIMS. Bosentan. 2019. In: MIMS Online [Internet]. http://www.mimsonline.com
50. MIMS. Macitentan. 2020. In: MIMS Online [Internet]. http://www.mimsonline.com
51. Carducci MA, Nelson JB, Kathy Bowling M, et al. Atrasentan, an endothelin-receptor antagonist for refractory adenocarcinomas: safety and pharmacokinetics. *J Clin Oncol*. 2002;20(8):2171-2180.
52. Dieterle W, Hengelage T. Absolute bioavailability and pharmacokinetics of avosentan in man. *Int J Clin Pharmacol Ther*. 2009;47(9):587-594.
53. Epstein BJ. Efficacy and safety of darusentan: a novel endothelin receptor antagonist. *Ann Pharmacother*. 2008;42(7–8):1060-1069.
54. Stavros F, Kramer WG, Wilkins MR. The effects of sitaxentan on sildenafil pharmacokinetics and pharmacodynamics in healthy subjects. *Br J Clin Pharmacol*. 2010;69(1):23-26.
55. Scott LJ. Sitaxentan. *Drugs*. 2007;67(5):761-770.
56. Tomkinson H, Kemp J, Oliver S, Swaisland H, Taboada M, Morris T. Pharmacokinetics and tolerability of zibotentan (ZD4054) in subjects with hepatic or renal impairment: two open-label comparative studies. *BMC Clin Pharmacol*. 2011;11(1):3.
57. Ranson M, Wilson R, O'Sullivan J, et al. Pharmacokinetic and tolerability profile of once-daily zibotentan (ZD4054) in Japanese and Caucasian patients with hormone-resistant prostate cancer. *Int J Clin Pharmacol Ther*. 2010;48(11):708-717.
58. Stolz D, Rasch H, Linka A, et al. A randomised, controlled trial of bosentan in severe COPD. *Eur Respir J*. 2008;32(3):619-628.
59. Seibold JR, Denton C, Furst D, et al. Randomized, prospective, placebo-controlled trial of bosentan in interstitial lung disease secondary to systemic sclerosis. *Arthritis Rheum*. 2010;62(7):2101-2108.
60. King TE Jr, Brown KK, Raghu G, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2011;184(1):92-99.
61. Sidharta PN, Melchior M, Kankam MK, Dingemanse J. Single-and multiple-dose tolerability, safety, pharmacokinetics, and pharmacodynamics of the dual endothelin receptor antagonist aprocitentan in healthy adult and elderly subjects. *Drug des Devel Ther*. 2019;13:949-964.
62. Sidharta PN, Ulč I, Dingemanse J. Single-dose pharmacokinetics and tolerability of Aprocitentan, a dual endothelin receptor antagonist, in subjects with severe renal function impairment. *Clin Drug Investig*. 2019;39(11):1117-1123.
63. Verweij P, Danaietash P, Flamion B, Ménard J, Bellet M. Randomized dose-response study of the new dual endothelin receptor antagonist Aprocitentan in hypertension. *Hypertension*. 2020;75(4):956-965.
64. Dingemanse J, Clozel M, Van Giersbergen PL. Pharmacokinetics and pharmacodynamics of tezosentan, an intravenous dual endothelin receptor antagonist, following chronic infusion in healthy subjects. *Br J Clin Pharmacol*. 2002;53(4):355-362.
65. Dingemanse J, Clozel M, van Giersbergen PL. Entry-into-humans study with tezosentan, an intravenous dual endothelin receptor antagonist. *J Cardiovasc Pharmacol*. 2002;39(6):795-802.
66. McMurray JJ, Teerlink JR, Cotter G, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA*. 2007;298(17):2009-2019.
67. Denault AY, Pearl RG, Michler RE, et al. Tezosentan and right ventricular failure in patients with pulmonary hypertension undergoing cardiac surgery: the TACTICS trial. *J Cardiothorac Vasc Anesth*. 2013;27(6):1212-1217.
68. O'Connor CM, Gattis WA, Adams KF, et al. Tezosentan in patients with acuteheart failure and acute coronary syndromes: results of the randomized intravenous tezosentan study (ritz-4). *J Am Coll Cardiol*. 2003;41(9):1452-1457.

69. De Zeeuw D, Coll B, Andress D, et al. The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. *J Am Soc Nephrol*. 2014;25(5):1083-1093.
70. Packer M, McMurray JJ, Krum H, et al. Long-term effect of endothelin receptor antagonism with bosentan on the morbidity and mortality of patients with severe chronic heart failure: primary results of the ENABLE trials. *J Am Coll Cardiol*. 2017;5(5):317-326.
71. Reriani M, Raichlin E, Prasad A, et al. Long-term administration of endothelin receptor antagonist improves coronary endothelial function in patients with early atherosclerosis. *Circulation*. 2010;122(10):958-966.
72. Weber MA, Black H, Bakris G, et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;374(9699):1423-1431.
73. Wenzel RR, Littke T, Kuranoff S, et al. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol*. 2009;20(3):655-664.
74. Gabbay E, Fraser J, McNeil K. Review of bosentan in the management of pulmonary arterial hypertension. *Vasc Health Risk Manag*. 2007;3(6):887-900.
75. Trachtman H, Nelson P, Adler S, et al. DUET: a phase 2 study evaluating the efficacy and safety of sparsentan in patients with FSGS. *J Am Soc Nephrol*. 2018;29(11):2745-2754.
76. Komers R, Diva U, Inrig JK, Loewen A, Trachtman H, Rote WE. Study Design of the Phase 3 Sparsentan vs irbesartan (DUPLEX) study in patients with focal segmental glomerulosclerosis (FSGS). *Kidney Int Rep*. 2020;5:494-502.
77. Travere Therapeutics Announces Positive Topline Interim Results from the Ongoing Phase 3 PROTECT Study of Sparsentan in IgA Nephropathy [press release]. 2021.
78. Travere Therapeutics Announces FDA Acceptance and Priority Review of New Drug Application for Sparsentan for the Treatment of IgA Nephropathy [press release]. 2022.
79. Kim S-G, Vo N, Lee S-H, et al. FC052: Atrasentan for the treatment of IGA nephropathy: interim results from the affinity study. *Nephrol Dial Transplant*. 2022;37(Supplement_3): gfac107.004. https://doi.org/10.1093/ndt/gfac107.004
80. Positive Phase 3 study with aprocitentan demonstrates significant antihypertensive efficacy in patients with resistant hypertension [press release]. 2022.
81. Hoekman J, Lambers Heerspink HJ, Viberti G, Green D, Mann JFE, de Zeeuw D. Predictors of congestive heart failure after treatment with an endothelin receptor antagonist. *Clin J Am Soc Nephrol*. 2014;9(3):490-498.
82. Heerspink HJL, Kohan DE, de Zeeuw D. New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction. *Kidney Int*. 2021;99(2):346-349.
83. Gueneau de Mussy P, Sidharta PN, Wuerzner G, et al. Effects of the dual endothelin receptor antagonist Aprocitentan on body weight and fluid homeostasis in healthy subjects on a high sodium diet. *Clin Pharmacol Ther*. 2021;109(3):746-753.

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