10.5152/turkjnephrol.2022.2231300

Review

Turkish Journal of Nephrology

Overview of Nonspecific and Innovative Therapies with the Potential to Reduce Chronic Kidney Disease Progression

Nereida Spahia, Merita Rroji, Alma Idrizi, Myftar Barbullushi

Department of Nephrology, University Hospital, Tirana, Albania

ABSTRACT

Management of chronic kidney disease has always been challenged by the need for therapies or interventions that prolong time to dialysis. Given the high global incidence and prevalence of chronic kidney disease, the need for cost-effective and patient-centered interventions, aiming to postpone dialysis initiation, becomes crucial. Longevity increase and prolongation of dialysis-free interval would mean improvement in quality of life for millions of people and their families worldwide. It also decreases pressure on the health system. In the last years, the efforts of the scientific community on this matter have been rewarded by the excellent results of sodium-glucose 2-co-transport inhibitors and selective aldosterone blockers on chronic kidney disease progression, and these innovations merit to be considered milestones in nephrology.

Several non-specific therapies for chronic kidney disease, such as antifibrotic/anti-inflammatory, and anti-diabetic therapies targeting cellular metabolism and beyond, have an effect on the progression of chronic kidney disease. This review discusses in a comprehensive way these therapies on the view of the potential for decrease of chronic kidney disease progression.

Keywords: Anemia, cell metabolism, CKD progression, fibrosis, Inflammation

Corresponding author: Merita Rroji ✉ Nereida Spahia edaspahia01@gmail.com & meritarroji@yaho.com

Received: February 18, 2022

Accepted: April 10, 2022

Publication Date: October 5, 2022

Cite this article as: Spahia N, Rroji M, Idrizi A, Barbullushi M. Overview of nonspecific and innovative therapies with the potential to reduce chronic kidney disease progression. *Turk J Nephrol.* 2022;31(4):269-278.

INTRODUCTION

Management of CKD involves therapies/interventions aiming to prolong dialysis-free interval. This would improve the quality of life of CKD patients and their families. It will also decrease the health system costs. Actually, there have been much progress in this field with the novel proven effective therapies and with other potential therapies, effects of which are under investigation.

CLINICAL AND RESEARCH CONSEQUENCES

Despite the progress it is needed to enhance our insight into early CKD mechanisms, aiming to enable early intervention for delaying CKD progression or even reversing it. The recent research has identified potential therapeutic targets such as inflammation, fibrosis, cellular metabolism, vascular changes, and some innovative therapies are already undergoing clinical trials. This review focuses on therapies with the potential to reduce CKD progression.

THERAPIES FOR METABOLIC ACIDOSIS

Sodium Bicarbonate

Metabolic acidosis, which mainly results from reducing the excretion of hydrogen ions, is characteristic of chronic kidney disease (CKD), especially when glomerular filtration rate (GFR) falls <25 mL/min/1.73 m^2.

Table 1. Summary of Research of Nonspecific and Innovative Therapies with the Potential to Reduce CKD Progression

Type of Therapy	Drug	Direct Effect	Beneficial Effect	Studies	Results
Anti-metabolic acidosis	Sodium bicarbonate Veverimer	Increase in serum bicarbonate level Oral HCL binder	Decreases kidney ammonia genesis and its consequences (i.e., glomerular and tubulointerstitial damage) Decreases the precipitation of calcium phosphate in kidney	Meta-analysis; Susantitaphong et al (2012) *VALOR-CKD study	Improvement in GFR and RR of dialysis initiation only after long-term administration Study completion expected on December 2024
Xantine oxidase inhibitors	Allopurinol purine XOR inhibitor Febuxostat non-purine noncompetitive XOR inhibitor	Decrease of uric acid levels	Improves endothelial dysfunction Inhibits ROS formation	RCT; Goicoechea et al (2010) PERL study; Doria et al (2020) CKD-FIX study RCT; Badve et al (2020) Meta-analysis; Lin et al (2019)	Slow in CKD progression after a mean time of 23.4 ± 7.8 months. No CKD progression benefit of allopurinol in type 1 early-to-moderate DKD No change in eGFR in allopurinol group versus placebo. Febuxostat has a reno-protective effect in CKD patients.
HIF stabilizers	Roxadustat	Direct protective effect against hypoxia	Optimizes adaptive cell responses to hypoxia.	FibroGen, Inc. Nov. 8, 2019 (pooled analyses of data from six global pivotal Phase 3 trials)	The 1-year decline in eGFR in roxadustat group was significantly lower compared to placebo, with a difference of 1.62 mL/min/1.73 m^2.
DPP-4 inhibitors	Gliptins	Antihyperglycemic	Antihypertensive, anti-inflammatory, antifibrotic, immunomodulatory, anti-apoptotic (independent of action on incretins)	Meta-analysis ; Von Eynatten et al (2012) CARMELINA study; Perkovic et al (2020)	Linagliptin was associated with a 16% reduction in composite kidney endpoints (including loss > 50% of mGFR compared to baseline) in type 2 diabetes patients During 2.2 years of follow-up, there was no difference between linagliptin vs. placebo, for risk of composite kidney endpoints (including decrease in mGFR ≥ 40%) across all mGFR categories
Anti-inflammatory/ antifibrotic	Pentoxifylline Pirfenidone Bardoxolone	Anti-proteinuric Block of transforming growth factor-β (TGF-β) Disable the (KEAP1/Nrf2) signal transduction pathway	Anti-inflammatory, immuno-regulatory GFR restoration linked to antifibrotic effects on Dynamic increase of the glomerular filtration surface and chronic antifibrotic effect	Meta-analysis ; Tian et al (2015) RCT; de Morales et al (2019) RCT; Sharma et al (2011) RCT; *TOP-CKD study BEAM trial; Pergola et al (2011) BEACON trial phase 3 RCT; de Zeeuw et al (2013) CARDINAL trial phase 2,3 RCT; Chertow et al (2021) TSUBAKU study phase 2 RCT; Nangaku et al (2020) *MERLIN study phase 2	Pentoxifylline use is associated with improved kidney function. Long-term treatment with pentoxifylline may reduce the rate of CKD progression improvement of GFR after 1 year and decreased progression toward ESKD in the pirfenidone-treated group compared to placebo in DKD Study completion date December 2024 Bardoxolone use for 52 weeks resulted in an almost double-digit increase in GFR on patients with CKD stage > 3 and DM type 2 Discontinued for high rate of CHF (high base-line levels of natriuretic peptide type-B and previous hospitalizations for CHF were risk factors found in post hoc analysis) Bardoxolone reduced by 50% the risk of progress toward ESKD in Alport patients The mean change of mGFR was significantly different between bardoxolone and placebo groups (6.64 mL/min/1.73 m^2) in DKD patients Effect of bardoxolone in patients with rapid progression of CKD. Results expected

(*Continued*)

Table 1. Summary of Research of Nonspecific and Innovative Therapies with the Potential to Reduce CKD Progression (*Continued*)

Type of Therapy	Drug	Direct Effect	Beneficial Effect	Studies	Results
Endothelin A selective receptor antagonists	Atrasentan	Selectively antagonizes ETA receptor activation	Maintenance of endothelial integrity through modification of endothelin system hyperactivity	SONAR RCT; Heerspink et al (2019) *ALIGN study phase 3	Atrasentan significantly reduced the risk of kidney events (creatinine doubling, mGFR <15 mL/min/1.73 m^2, chronic HD, kidney transplant, death from kidney failure) in type 2 DKD Results expected on late 2025 (Atrasentan efficacy in IgA nephropathy on risk for progressive loss of kidney function)
Others	AST-120 (Kremezin)	High absorption capacity for uremic toxins and organic acids	Use is associated with reduced ROS levels, decreased indoxyl sulfate and p-cresyl sulfate levels, and improved the profile of CVr biomarkers	EPIC-1 & EPIC-2 RCT; Schulman et al (2012) Schulman et al (2016) (EPIC-1 and EPIC-2 post hoc analysis of the subgroup of patients in the United States)	No benefit on CKD progression with AST-120 use vs. placebo AST-120 was associated with a positive effect on the progression of CKD
Inhibitors of MCP-1 synthesis Anti-inflammatory	Bindarit **CCX140-B	Inhibition of the CCR2 receptor	Anti-inflammatory effect, modulates the activation of the NF-KB pathway and its associated effects	RCT; Ruggenenti et al (2010) *Stage 2 RCT; NCT01440257	Bindarit in diabetic patients significantly decreased macroalbuminuria compared to placebo Results awaited
Cell therapy	Mesenchymal autogenous stem cells	Stem cells may have regenerative abilities		Meta-analysis Papazova et al (2015)	Cell therapy reduced the development and progression of CKD

*Study not yet completed; ** Experimental drug.
GFR, glomerular filtration rate; RR, risk reduction; HCL, hydrochloric acid; RCT, randomized controlled trials; DKD, early-to-moderate diabetic kidney disease; HIF, hypoxia-inducible factor prolyl-hydroxylase; KEAP1/Nrf2, the Kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; CCR2 receptor, C-C chemokine receptor 2; CHF, congestive heart failure; ESKD, end-stage kidney disease; CKD, chronic kidney disease; RCT, randomized controlled trial.

Observational studies in subjects with low serum bicarbonate levels show a considerable risk for progression of CKD,[1] potentially through probiotic effects associated with stimulation of kidney regulatory/compensatory mechanisms, such as increased ammonium production, endothelin-A receptor activation, and prolonged activation of the renin-angiotensin system (RAS).[2] Besides, an increased risk of mortality has been identified.[3] Chronic metabolic acidosis is associated with complications such as disturbed albumin synthesis, thyroid dysfunction, insulin resistance, exacerbation of CKD mineral-bone disorders, and muscle atrophy.[4] A systematic review, which included 6 randomized controlled trials (RCTs), demonstrated a positive effect in predialysis subjects where sodium bicarbonate was administered orally compared with placebo.[5] Although no benefit was found from short-term administration of sodium bicarbonate, results of long-term administration studies showed a substantial benefit with decreased serum creatinine (–0.07 mg/dL, 95% CI –0.09 to –0.05; $P < .001$), improvement in GFR (3.2 mL/min/1.73 m^2, 95% CI 1.6-4.7; $P < .001$), and reduction in the incidence of dialysis initiation (risk ratio 0.21, 95% CI 0.08-0.54; $P = .001$; $I^2 = 0$). In addition, the long-term safety profile of the treatment was very good.[6] Sodium bicarbonate is currently considered a safe, inexpensive, and effective therapy for reducing CKD progression.

Veverimer

Veverimer is currently being tested in a phase 3b study named VALOR-CKD. Veverimer was developed as a polymer, hydrochloric acid (HCL) binder, the first of its kind, to treat metabolic acidosis in CKD. The drug is administered orally, is indigestible, nonabsorbable, and acts through the binding of H+ and Cl- ions, resulting in a net reduction of HCl and its elimination from the gastrointestinal tract, with the final effect of increasing the level of bicarbonate in the blood. Veverimer has high binding capacity and selectivity for H+ and Cl-. VALOR-CKD is a randomized, placebo-controlled trial undertaken in 2018 to evaluate the efficacy and safety profile of TRC101 (Veverimer) in reducing CKD progression

MAIN POINTS

- The need to develop novel therapeutics for CKD retardation is an all-time challenge in nephrology.
- In addition to RAS blockade, SGLT2 inhibitors and selective aldosterone blockers have demonstrated a very positive effect on CKD progression.
- Sodium bicarbonate is currently considered a safe, inexpensive, and effective therapy for reducing CKD progression.
- The recent research has identified potential therapeutic targets such as inflammation, fibrosis, cellular metabolism, vascular changes, and some innovative therapies are already undergoing clinical trials.
- An approach combining hemodynamic, metabolic, and inflammatory targets might provide benefits above and further single drug treatments in CKD patients.

in subjects with metabolic acidosis. The subjects included have a measured estimated GFR (eGFR) 20-40 mL/min/1.73 m^2 and serum bicarbonate 12-20 mEq/L. Kidney events to be evaluated include reducing eGFR $\geq$ 40%, end-stage kidney disease (ESKD), and kidney death. The study is planned to be completed in December 2024, and its results will further shed light on the effect of correcting metabolic acidosis on the progression rate of CKD.

XANTHINE OXIDASE INHIBITORS

Hyperuricemia is an independent risk factor for CKD, hypertension (HTA), cardiovascular (CV) disease, and mortality in the general population. In this population, reducing serum uric acid level with allopurinol in observational studies has significantly improved HTA, mortality, and GFR.[7] Hyperuricemia is very frequent in CKD and increases in parallel with decreased GFR. Uricemia increase has to do mainly (but not only) with decreased uric acid excretion; metabolic syndrome, insulin resistance, obesity, and diet are strongly associated with uric acid levels.

Observational studies in patients with CKD have proven that high serum uric acid levels are associated with CV mortality and all-cause mortality.[8] It remains unclear whether hyperuricemia in CKD is a mediator of CV or is a confounding factor in CV morbidity and mortality. The epidemiology of CKD is such that CKD influences many biochemical markers and potentially vice versa; these biomarkers affect CKD progress. Observational studies have also identified that hyperuricemia may also contribute to CKD progression.[9] In patients with GFR <60 mL/min/1.73 m^2, administration of 100 mg/day of allopurinol for 2 years was associated with relative preservation of residual kidney function, reduction of CV events, and reduction of hospitalizations compared to placebo.[10] It is worth commenting that recent studies with allopurinol have not proven any positive effect in reducing CKD progression[11,12] in diabetic and nondiabetic patients. While allopurinol has been used since the 1960s, a newer xanthine oxidase inhibitor is febuxostat, which received Food and Drug Administration (FDA) approval in 2009. Febuxostat is metabolized primarily in the liver and, unlike allopurinol (which is excreted by the kidneys), requires dose adjustment only in advanced stages of CKD (GFR <30 mL/min/1.73 m^2). A formula that predicts the effective dose (to achieve the desired uricemia level) of febuxostat in patients with CKD has been proposed by Aoun et al.[13] The following formula uses serum uric acid levels at baseline (Baseline UA); Diuretic use: Yes = 1, No = 0; serum uric acid reduction ratio (UARR) and estimated GFR (eGFR):

$$\text{Dose} = [5.624/\text{baseline UA} + (0.165 \times \text{diuretic use}) + (0.019 \times \text{UARR}) + (0.025 \times \text{eGFR}) + 0.944]^3$$

In several studies, febuxostat was found to have more efficacy and had a better safety profile than allopurinol.[14] In a cohort, retrospective study, with a small number of patients with CKD (73 patients), febuxostat was found to have a more positive effect than allopurinol in maintaining residual kidney function and reducing hyperuricemia. In a systematic review of literature and meta-analysis in 2019, which included RCTs to evaluate the efficacy and safety of febuxostat versus control in patients with CKD, it was found that febuxostat has a renoprotective effect in patients with CKD. The number of studies included in the meta-analysis was 11, and the total number of patients was 1317. However, the authors concluded that more extensive studies would further clarify the role of febuxostat in CKD progression.[15] Regarding the safety profile of febuxostat, concerns raised in pre-marketing studies about the potential for increased CV events prompted the implementation of 2 studies recommended by the FDA, and the European Medicines Agency (EMA) called, respectively, CARES (Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities) and FAST (Febuxostat Versus Allopurinol Streamlined Trial). In the CARES study, it was found that febuxostat was not inferior to allopurinol in terms of major CV adverse events but was associated with higher mortality (of all causes) (HR 1.22; 95% CI, 1.01-1.47) and higher CV mortality (hazard ratio (HR) 1.34; 95% CI, 1.03-1.73).[16] In contrary to the above findings in the FAST study, febuxostat was not found inferior to allopurinol in composite CV events (hospitalization for nonfatal myocardial infarction, acute coronary syndrome with positive biomarkers, nonfatal vascular-cerebral event, and fatal stroke) [HR 0.85; 95% CI, 0.70-1.03]. Also, mortality from all causes had no differences between the 2 treatment groups.[17] In a recently published cohort study of approximately 110 000 patients treated with febuxostat (27 881 patients) or allopurinol (83 643 patients), initiation of febuxostat therapy was not associated with a higher CV risk or with higher mortality (CV or all causes) compared with allopurinol in patients > 65 years of age, with or without the pre-existing CV disease.[18] The latest guidelines of KDIGO (2012) are ambivalent regarding the benefits of therapy with agents that reduce uricemia in CKD and do not specifically recommend the use or the nonuse of this strategy.[19]

ERYTHROPOIESIS STIMULATING AGENTS, HYPOXIA-INDUCIBLE FACTOR STABILIZERS, AND IRON SUPPLEMENTS

Erythropoiesis Stimulating Agents

Iron deficiency and anemia are evident in about 60% of patients with CKD. Severe anemia in CKD is associated with increased CV events and hospitalization, decreased survival, and increased progression toward ESKD.[20]

Erythropoiesis stimulating agents (ESAs) have enabled the correction of anemia in these patients. However, it has been observed that, in contrast to the correction of severe anemia (Hb <9 g/dL), the correction of mild or moderate anemia is not associated with the improvement of CV events.[21] Furthermore, rapid correction, use of high doses of erythropoietin, and correction to conventionally "normal" Hb levels have been found (contrary to expectations) associated with increased risk for

CV events and mortality, as well as without any measurable benefit, proportional to the rate of increase in hemoglobin.[22] Regarding renoprotection, the use of EASs does not seem to be associated with benefit in patients with advanced CKD, while early use, in the early stages of CKD, may provide advantages in reducing CKD progression. Thus, in terms of the effect of ESAs on residual kidney function in predialysis patients, early studies showed that use of ESAs delayed the progression of CKD. A meta-analysis[23] was conducted in 2014 about the reno-protective effect of EAS. Although, it did not reveal any benefit in the final results, including mortality, dialysis initiation, and kidney death, in terms of doubling serum creatinine level it identified a reduction in relative risk to 0.53 (95% CI, 0.31-0.89), suggesting that early intervention with ESAs may have a reno-protective effect.[21] It is confirmed that early intervention with ESAs, maintaining Hb levels above 12 g/dL, resulted in a positive effect on reducing progression to ESKD. Despite those results, the most recent meta-analysis did not confirm any positive effect of ESA on the progression of CKD regardless of its stage.[24] Considering the level of Hb in advanced CKD (eGFR 8-20 mL/min/1.73 m^2), in nondiabetic subjects, a multicenter RCT, finalized in 2020, found no change in kidney survival between the high Hb group (11.2 ± 1.1 g/dL) and the low Hb group (10.0 ± 0.9 g/dL).[25] Based on the results, the authors concluded that targeting high hemoglobin values had no advantage in the progression of CKD in nondiabetic patients with advanced CKD.

Hypoxia-Inducible Factor Stabilizers

The newest agents in the treatment of anemia in CKD are HIF (prolyl-hydroxylase) inhibitors, which have the potential, at least theoretically, to serve as reno-protective agents by optimizing adaptive cell responses to hypoxia. Chronic kidney disease is characterized by a decrease in oxygen pressure on kidney cells, and chronic kidney hypoxia is the last common link (regardless of CKD etiology) of progression to ESKD. However, the results of the experimental studies are somewhat contradictory. Thus, in the 5/6 nephrectomy model (a widely used CKD model), HIF activation showed reno-protective effects, while in some experiments in rats, HIF activation was associated with the progression of kidney fibrosis.[26] In 2019, it was made public (by the manufacturing company) that in the joint analysis of 3 global phases, 3 studies on the effect of roxadustat in patients with eGFR $\geq$ 15 mL/min/1.73m^2 at baseline, the 12-month decline in eGFR in the group with roxadustat was lower versus placebo, with a difference of 1.62 mL/min/1.73 m^2. Hypoxia inducible factor stabilizers can prevent CKD progression through a direct protective effect against hypoxia. However, this remains to be proven in the future. In June 2021, EMA authorized the use of roxadustat to treat anemia in patients with CKD, while authorization from the FDA is awaited.

Iron Supplements

Iron deficiency in CKD may be functional, inflammation-associated, or attributed to poor diet, iron malabsorption, or occult blood loss. In ischemic CKD on subjects with congestive heart failure, known as cardiorenal syndrome, iron supplementation in patients with its deficiency is associated with improved kidney function.[27] Several studies have shown that iron administration in patients with chronic heart failure positively affected cardiac events and myocardial function.[28] Intravenous (iv) iron administration, compared to oral administration, is more efficient in terms of deficit correction, ESA demand reduction, and has a good safety profile. One study of interest is REVOKE, which questioned whether iv iron supplements accelerated the decline in GFR compared with oral supplements. This study compared ferrous sulfate 325 mg 3 times/day for 8 weeks, with iv iron sucrose 200 mg every 2 weeks (total 1 g). The likelihood of a 50% reduction in eGFR after 2 years was low, and the results of this study were non-conclusive. However, long-term use of iv iron (although not associated with a more pronounced decrease in eGFR) in patients with moderate to advanced iron deficiency anemia was associated with a higher risk of infections and CV complications. Oral iron supplementation was the preferred route of administration in patients with stage 3 and 4 CKD and iron deficiency anemia. The results of a 1-year analysis in the FIND-CKD study support the conclusion that the correction of iron deficiency anemia with iv ferric carboxymaltose is safe in patients with CKD, not on dialysis treatment.[29]

The latest KDIGO conference (June 2021) emphasized that low serum ferritin is a valuable marker for diagnosing absolute iron deficiency. Nevertheless, normal or high ferritin levels ($\geq$100 µg/L) do not rule out iron deficiency, which may be linked to other causes such as infection or inflammation. Understanding the clinical effect of iron deficiency and its correction, independent of anemia, is recommended by this conference as an area of primary interest for research. Although data on iron deficiency anemia in CKD are limited, they may have clinical value in some circumstances.[30]

ANTI-LIPID THERAPIES

Statins are indicated in patients with CKD to reduce CV events based on RCT. Regarding the CKD progression, the SHARP (Study of Heart and Kidney Protection) trial did not demonstrate any significant effect of statins. Also, in a systematic review of 38 prospective randomized controlled studies on CKD patients, no clear benefit of statin use was observed in reducing CKD progression or delaying the time of hemodialysis. Meanwhile, it was confirmed a 20% reduction in mortality and major CV events.[31]

The use of statins or statin+ezetimibe is recommended by KDIGO guidelines in all patients > 50 years of age with CKD. In patients 18-49 years old, the use of statins is recommended in case of comorbidity such as coronary artery disease, DM type 2, ischemic vascular accident, 10-year risk (estimated) for fatal coronary events, or non-fatal myocardial infarction > 10%.[32]

NEW ORAL HYPOGLYCEMIC AGENTS

Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl Peptidase (DPP)-4 inhibitors are new oral hypoglycemic agents known as gliptins, which have attracted attention in the treatment of diabetic nephropathy (DN). Dipeptidyl peptidase-4 is a universal enzyme that acts on incretins (mainly glucagon-like peptide-1 and gastric inhibitory peptide), which are intestinal hormones responsible for glucose homeostasis after ingestion. Dipeptidyl peptidase-4 degrades these incretins immediately, while DPP-4 inhibitors increase their levels, stimulating insulin secretion by pancreatic beta cells. In addition to antihyperglycemic effects, gliptins possess antihypertensive, anti-inflammatory, antifibrotic, immunomodulatory, anti-apoptotic effects independent of the action on incretins. In several studies, linagliptin, which has predominantly hepatic elimination and does not require dose adjustment in CKD, has demonstrated a positive effect on kidney outcomes. In a meta-analysis, which included 13 RCTs, with a total number of 5466 patients, linagliptin was associated with a 16% reduction in composite kidney endpoints (defined as micro/macroalbuminuria, loss >50% of eGFR compared to baseline, acute kidney failure, death). It is important to remark that the studies included in the meta-analysis were not explicitly designed to study kidney endpoints.[33] Linagliptin is the first and only DPP-4 inhibitor evaluated in a randomized controlled clinical trial designed to assess kidney endpoints, named CARMELINA (Cardiovascular and Kidney Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus). A secondary analysis of this study with 6979 subjects followed up for 2.2 years showed that across all eGFR categories, in the study subjects, there was no difference between linagliptin versus placebo in terms of risk for composite kidney endpoints (defined as kidney death, ESKD, sustained decrease in eGFR ≥40% compared to baseline). There was no difference in side effects, while a significant reduction in proteinuria was observed in the linagliptin group.[34]

ANTI-INFLAMMATORY AND ANTIFIBROTIC THERAPIES

Pentoxifylline

Chronic kidney disease is considered a chronic inflammatory condition. Indeed, circulating markers of inflammation are more pronounced in CKD compared to the normal population. Pentoxifylline has been shown to have anti-inflammatory and immuno-regulatory effects, attributed to CKD's potential inflammatory modifying effect. A systematic review of the literature and meta-analysis showed that pentoxifylline used in combination with RAS inhibitors exhibits a pronounced antiproteinuric effect, is associated with improved kidney function, and the safety profile is favorable.[35] A RCT in 91 patients, followed for an additional 7 years after the completion of a 12-month study, investigated the effect of pentoxifylline on CV mortality and kidney endpoints (defined as the initiation of dialysis treatment and/or serum creatinine doubling and/or decrease > 50% of eGFR compared to baseline). This study found a 55% reduction in CV mortality and a 35% reduction in kidney endpoints in the pentoxifylline group (400 mg 2 times/day), compared to the control group (HR 0.65 (0.45–0.94), P = .022). The authors concluded that long-term treatment with pentoxifylline might reduce the rate of CKD progression.[36] However, the data are insufficient to recommend the massive use of pentoxifylline to reduce the rate of progression of CKD. Meanwhile, the results of a randomized, double-blind, phase 2 study with a placebo-treated control group (NCT01487109) are awaited. This study evaluates the efficacy and safety profile of an active metabolite of pentoxifylline (CTP-499) in nephropathy from DM type 2 in patients receiving RAS inhibitor therapy.

Pirfenidone

Pirfenidone is an antifibrotic that acts by blocking transforming growth factor-β (TGF-β), which in animal studies has shown promising effects on GFR restoration. A clinical study in patients with segmental focal glomerulosclerosis demonstrated the preservation of GFR by pirfenidone. However, this study was conducted on a limited number of subjects, had no placebo control group, and somewhat criticized the GFR calculation methodology. A few years later, a randomized, placebo-controlled, double-blind study was also performed on a small number of patients with DN.[37] This study demonstrated improvement of GFR after 1 year and decreased progression toward ESKD in the pirfenidone-treated group compared to placebo. An ongoing study is TOP CKD (Trial of Pirfenidone in CKD), scheduled to be undertaken in 2 centers, double-blind, placebo-controlled phase 2b. This study will determine the effects of pirfenidone on kidney fibrosis in 1 group evaluated by magnetic resonance imaging (diffusion-weighted kidney MRI). While in the other group, the effects of pirfenidone on changes in urinary biomarkers are known to reflect the severity of fibrosis on biopsy and are comprehended as predictors of progressive loss of kidney function. Meanwhile, the results of another study, randomized, placebo-controlled, using 2 regimens with different doses of pirfenidone, in young patients with CKD stage 1-4, with different etiologies (NCT00001959) have been completed, and results are expected.

Endothelin Receptor Antagonists

Endothelin-1 is a vasoactive substance secreted by endothelial cells. It affects vascular tone and regulates cell proliferation by activating subtype A (ETA) and subtype B (ETB) receptors. Activation of ETA receptors in vascular smooth muscle induces potent vasoconstriction. Activation of ETB receptors causes vasodilation by releasing nitric oxide and prostaglandins. Activation of ETB receptors also reduces blood pressure by directly inhibiting sodium and water reabsorption in the kidneys (promotes natriuresis and diuresis). In CKD, endothelin-1 is almost always increased, and this increase can have a pathological effect by promoting vasoconstriction, proteinuria, inflammation, cell damage, and eventually fibrosis, effects mediated by stimulation of ETA receptors.

Since endothelin system disorder is essential in the pathogenesis of some CV diseases, ETA/ETB receptor antagonists, thanks to their ability to maintain endothelial integrity, can be considered disease-modifying agents in conditions where the endothelin system is hyperactive. The Avosentan on Time to Doubling of Serum Creatinine, End Stage Kidney Disease or Death in Patients With Type 2 Diabetes Mellitus and Diabetic Nephropathy [ASCEND) study tested the effect of avosentan, an ETA receptor antagonist, on the progression of CKD and mortality in patients with DM under RAS blockade. Avosentan caused an additional reduction (above that of RAS blockade) in proteinuria, but the study ended prematurely due to serious side effects (including increased risk for congestive heart failure).[38] These effects were hypothesized to be related to relatively high doses of avosentan, which may have selectively antagonized ETB receptors resulting in vasoconstriction and retention of sodium and water. Potential, lower doses could have more selectively antagonized ETA receptors. Fluid retention as a side effect of avosentan was predicted in another study, confirming the antiproteinuric effect of avosentan supplementation (over the effect of RAS blockade). Another highly selective ETA antagonist, called atrasentan, during short-term low-dose treatment was found to affect proteinuria positively and was not associated with significant sodium and water retention in patients with type 2 DM. Investigators of the Study Of Diabetic Nephropathy With Atrasentan (SONAR), a multinational, randomized, controlled, double-blind study, reported the long-term effects of atrasentan treatment on major kidney events. The study included 2648 type 2 diabetic patients, with eGFR 25-75 mL/min per 1.73 m^2, albumin/creatinine ratio in urine 300-5000 mg/g, treated with RAS blockade, and subjected to a treatment period of atrasentan saturation before randomization. The average follow-up time was 2.2 years, and the study ended prematurely due to the slow rhythm of recruitment. Atrasentan significantly decreased the risk of kidney events (HR 0.65 [95% CI 0.49–0.88]; $P = .0047$), defined as creatinine doubling, eGFR <15 mL/min per 1.73 m^2, chronic HD, kidney transplant, death from kidney failure; the risk of side effects was no different from placebo. These data support the potential role of selective endothelin receptor antagonists in maintaining kidney function in patients with type 2 DM and at high risk for ESKD.[39] A post doc analysis of the SONAR study was performed, driven by recognizing and evaluating different and potentially complementary mechanisms of action of sodium-glucose 2-co-transport inhibitors (SGLT2) and endothelin receptor antagonists. Thus atrasentan-induced fluid retention could potentially be neutralized by the diuretic effects of SGLT2 inhibitors. This analysis showed that after 6 weeks, the combination (SGLT2 + ETA inhibitor) compared to ETA (atrasentan) reduced body weight and further reduced proteinuria in patients with type DM type 2 and CKD. These data may prompt future studies on CKD progression and the efficacy and long-term safety of combined treatment. Another study is Atrasentan in patients with IgA nephropathy (ALIGN), a phase 3, double-blind, placebo-controlled study whose results will be public in late 2025. This study compares the efficacy and safety of atrasentan versus placebo in patients with nephropathy on the risk of progressive loss of kidney function.

Bardoxolone

Two basic mechanisms by which bardoxolone increases GFR are the dynamic increase of the glomerular filtration surface and the chronic antifibrotic effect. It promotes the resorption of inflammation by restoring mitochondrial function, reducing oxidative stress, and inhibiting pro-inflammatory signals. Bardoxolone works by disabling the major regulator of redox homeostasis called "the Kelch-like ECH-associated protein1/nuclear factor erythroid 2-related factor 2 (KEAP1/Nrf2) signal transduction pathway." Bardoxolone releases Nrf2 from KEAP1, allowing it to inhibit Nuclear factor kappa B (NF-κB) and activate the transcription of some anti-inflammatory and antioxidant genes. In preclinical models, bardoxolone increased GFR, attributed to the increased glomerular surface through inhibition of inflammation on the glomeruli.[40] The enthusiasm that followed the Bardoxolone methyl treatment: Kidney function in CKD/Type 2 diabetes (BEAM) trial in 2011, where Bardoxolone, for 52 weeks, resulted in an almost double-digit increase in GFR on patients with CKD stage >3 and DM type 2, led to the undertaking of the BEACON trial.[41] Bardoxolone Methyl Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes was a phase 3, randomized, double-blind, placebo-controlled study designed to determine whether bardoxolone would reduce progression to ESKD and CV events. The pace of recruitment was much higher than expected, which reflected enthusiasm within the nephrology community. The study was discontinued due to the increase in hospitalizations for congestive heart failure (CHF) in the bardoxolone group, and the enthusiasm somewhat faded. Post hoc analysis of side effects on the BEACON trial showed that hospitalization for CHF occurred within the first month of treatment and was associated with sodium and water retention. This analysis suggested that the cause may be modulation of endothelin activity (inhibition of so-called "endothelin signaling pathways," some of which have cardiac protective effects). Another Bardoxolone Methyl Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes (BEACON) analysis found that high baseline levels of natriuretic peptide type-B and previous hospitalizations for CHF were risk factors for the adverse effect of bardoxolone (leading to discontinuation of the BEACON trial).[42] The evaluations of the above studies, the lack of specific therapy for Alport syndrome, and the fact that CKD progression in Alport syndrome is characterized by glomerular, tubular, and interstitial inflammatory changes may have served as arguments in favor of testing the bardoxolone effect in patients with CKD from Alport Syndrome. Thus began the A Phase 2/3 trial of the efficacy and safety of Bardoxolone Methyl in patients with Alport Syndrome-CARDINAL (CARDINAL) trial, an international, multicenter, 2, 3 phase study that would evaluate methyl bardoxolone's safety, tolerability, and efficacy in patients with Alport syndrome. The study was designed to determine whether bardoxolone would slow the rate of CKD progression evaluated by the decrease in GFR. CARDINAL is one

of the largest RCTs on patients with Alport syndrome.[43] After 48 weeks of treatment, in subjects treated with bardoxolone, a statistically significant GFR increase of 4.72 mL/min/1.73 m^2 was observed compared to the baseline level, while on subjects under placebo, an average GFR decrease of -4.78 mL/min/1.73 m^2 was observed. This improvement of GFR reduced by 50% the risk of progress toward ESKD. Another RCT is The Phase 2 Study of Bardoxolone Methyl in Patients with Chronic Kidney Disease and Type 2 Diabetes (TSUBAKI), which was undertaken to evaluate the effects of bardoxolone on GFR in patients with CKD and DM type 2. The study aimed to determine whether in patients without the risk mentioned above (high natriuretic peptide and CHF hospitalizations history), fluid overload risk during bardoxolone use was low, and changes in GFR reflected a real improvement in kidney function. The results of phase 2 of the TSUBAKI study were published in 2020. The mean change of eGFR (95% CI) from baseline was respectively 5.95 (2.29 to 9.60) and -0.69 (-3.83 to 2.45) mL/min/1.73 m^2, in patients randomized to bardoxolone and placebo, with a significant difference between groups of 6.64 mL/min/1.73 m^2 (P = .008). The author concluded that bardoxolone significantly increased eGFR, and the investigation continues to assess whether this clinical benefit is not associated with major side effects on certain patients (without risk factors) with CKD.[44] Bardoxolone is also being tested in several studies such as MERLIN (NCT04702997, a phase 2 study in patients with rapid progression CKD).

OTHER THERAPIES

AST-120 (Kremezin)

AST-120 (Kremezin), administered per os, is a spherical activated carbon on the surface to maximize the absorbent surface. Absorption capacity is high for small molecules, including uremic toxins. Also, the absorption capacity of AST-120 for organic acids is higher than medicinal carbon. AST-120 reduces serum and urinary levels of indoxyl sulfate (a uremic toxin that stimulates the progression of glomerular sclerosis) by absorbing indole in the intestine and eliminating it in the feces. Clinical studies with a restricted number of patients AST-120 have found positive results in reducing CKD progression. The drug has been approved for this indication in Japan since the early 1990s. However, RCTs of EPIC-1 and EPIC-2 (Evaluating Prevention of Progression in Chronic Kidney Disease), undertaken in Europe and the United States (13 countries in total), did not demonstrate any benefit in the progression of CKD compared to placebo in a cohort of 2035 patients.[45] Indeed, a post hoc analysis of the subgroup of patients in the United States (AST-120, N = 290; placebo, N = 293) highlighted that AST-120 was associated with a positive effect in reducing CKD progression in these patients. This finding was interpreted as potentially related to compliance, diet, etiology of CKD, and the difference in the natural course of CKD progression in different populations. AST-120 reduced Reactive oxigen species (ROS) levels, decreased indoxyl sulfate and p-cresyl sulfate levels, and improved the profile of CV biomarkers.[46] AST-120 has been shown to prevent the development of left ventricular concentric hypertrophy in CKD.[47] In another study, abdominal aortic calcifications were less pronounced in patients with predialysis CKD receiving AST-120. Interestingly, in the post hoc analysis of the Kremezin study against kidney disease progression in Korea study (in Korean patients with CKD), it was found that long-term use of AST-120 on CKD patients was associated with potential kidney protective effect (especially in diabetic patients) and CV benefits.

Inhibition of Monocyte Chemoattractant Protein-1 Synthesis

Monocyte chemoattractant protein-1 (MCP-1) is a potent cytokine involved in kidney inflammation, whose urinary levels correlate with the degree of proteinuria on DN and the reduction of proteinuria after RAS inhibition. Inhibition of MCP-1 synthesis can be achieved by inhibiting the CCR2 receptor (C-C chemokine receptor 2). The results of a completed stage 2, randomized, placebo-controlled, double-blind study (NCT01440257) on patients with DN that used an experimental CCR2 antagonist (CCX140-B) are currently awaited. A drug that directly inhibits the synthesis of MCP-1 and has an anti-inflammatory effect, which modulates the activation of the NF-kB pathway and its associated effects, is Bindarit. Bindarit significantly reduced proteinuria in diabetic patients with macroalbuminuria compared to placebo in a randomized study. This effect was not seen in patients with microalbuminuria.[48]

Cell Therapy

Cell therapy could potentially be an innovative therapeutic strategy to slow the progression of CKD. Administration of mesenchymal autogenous stem cells has been used in early studies in kidney transplantation. Preclinical studies suggest that stem cells may have regenerative abilities. Their administration was safe on a phase 1 study on patients who had undergone cardiac surgery and were at high risk for acute kidney failure.[49] A systematic review of the literature and meta-analysis of 71 preclinical studies revealed that cell therapy reduced the development and progression of CKD. The time of initiation of therapy (related to clinical signs), dose, and cell origin were not found to be significantly associated with efficacy.[50] Statistically significant improvements were observed in proteinuria and urea levels.

CONCLUSION

Drug combination strategies could potentially not only prevent CKD progression but even reverse CKD An approach combining hemodynamic, metabolic and inflammatory targets might provide benefits above and further single drug treatments.

FUTURE DIRECTIONS

The need to develop novel therapeutics for CKD retardation is an all-time challenge in nephrology. Therefore, a holistic approach should target the various processes and biological contexts related to CKD progression. To date, therapeutic interventions

after tubulointerstitial fibrosis has already been installed are insufficient, raising the need to enhance our insight into early CKD mechanisms, aiming to enable early intervention for delaying CKD progression or even reversing it. In addition to RAS blockade, SGLT2 inhibitors and selective aldosterone blockers have demonstrated a very positive effect on CKD progression. The recent research has identified potential therapeutic targets such as inflammation, fibrosis, cellular metabolism, vascular changes, and some innovative therapies are already undergoing clinical trials. Once a particular drug exhibits clinical benefit by delaying the progression of functional decline, it will be critical to determine whether drug combination strategies could potentially not only prevent CKD progression but also even reverse CKD. In this regard, an approach combining hemodynamic, metabolic, and inflammatory targets might provide benefits above and further single drug treatments.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.S.; Design N.S., M.R.; Supervision-A.I.; Materials – N.S., M.R.; Data Collection and/or Processing – N.S., M.R.; Analysis and/or Interpretation – N.S., M.R.; Literature Review – N.S., M.R.; Writing – N.S., M.R.; Critical Review – M.B.

Declaration of Interests: The authors declare no conflict of interest.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Shah SN, Abramowitz M, Hostetter TH, Melamed ML. Serum bicarbonate levels and the progression of kidney disease: a cohort study. *Am J Kidney Dis*. 2009;54(2):270-277. [CrossRef]
2. Ng HY, Chen HC, Tsai YC, Yang YK, Lee CT. Activation of intrarenal renin-angiotensin system during metabolic acidosis. *Am J Nephrol*. 2011;34(1):55-63. [CrossRef]
3. Menon V, Tighiouart H, Vaughn NS, et al. Serum bicarbonate and long-term outcomes in CKD. *Am J Kidney Dis*. 2010;56(5):907-914. [CrossRef]
4. Kraut JA, Kurtz I. Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. *Am J Kidney Dis*. 2005;45(6):978-993. [CrossRef]
5. Susantitaphong P, Sewaralthahab K, Balk EM, Jaber BL, Madias NE. Short- and long-term effects of alkali therapy in chronic kidney disease: a systematic review. *Am J Nephrol*. 2012;35(6):540-547. [CrossRef]
6. Hultin S, Johnson DW, Badve SV. Recent evidence on the effect of treatment of metabolic acid on the progression of kidney disease. *Curr Opin Nephrol Hypertens*. 2021;30(5):467-473. [CrossRef]
7. Kanbay M, Huddam B, Azak A, et al. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. *Clin J Am Soc Nephrol*. 2011;6(8):1887-1894. [CrossRef]
8. Suliman ME, Johnson RJ, García-López E, et al. J-shaped mortality relationship for uric acid in CKD. *Am J Kidney Dis*. 2006;48(5):761-771. [CrossRef]
9. Levy GD, Rashid N, Niu F, Cheetham TC. Effect of urate-lowering therapies on renal disease progression in patients with hyperuricemia. *J Rheumatol*. 2014;41(5):955-962. [CrossRef]
10. Goicoechea M, de Vinuesa SG, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol*. 2010;5(8):1388-1393. [CrossRef]
11. Doria A, Galecki AT, Spino C, et al. Serum urate lowering with allopurinol and kidney function in Type 1 diabetes. *N Engl J Med*. 2020;382(26):2493-2503. [CrossRef]
12. Badve SV, Pascoe EM, Tiku A, et al. Effects of allopurinol on the progression of chronic kidney disease. *N Engl J Med*. 2020;382(26):2504-2513. [CrossRef]
13. Aoun M, Salloum R, Dfouni A, Sleilaty G, Chelala D. A formula predicting the effective dose of febuxostat in chronic kidney disease patients with asymptomatic hyperuricemia based on a retrospective study and a validation cohort. *Clin Nephrol*. 2020;94(2):61-69. [CrossRef]
14. Li S, Yang H, Guo Y, et al. Comparative efficacy and safety of urate-lowering therapy for the treatment of hyperuricemia: a systematic review and network meta-analysis. *Sci Rep*. 2016;6:33082. [CrossRef]
15. Lin TC, Hung LY, Chen YC, et al. Effects of febuxostat on renal function in patients with chronic kidney disease: a systematic review and meta-analysis. *Med (Baltim)*. 2019;98(29):e16311. [CrossRef]
16. White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med*. 2018;378(13):1200-1210. [CrossRef]
17. Mackenzie IS, Ford I, Nuki G, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. *Lancet*. 2020;396(10264):1745-1757. [CrossRef]
18. Pawar A, Desai RJ, Liu J, Kim E, Kim SC. Updated assessment of cardiovascular risk in older patients with gout initiating febuxostat versus allopurinol. *J Am Heart Assoc*. 2021;10(7):e020045. [CrossRef]
19. KDIGO CKD Work Group. KDIGO 2012 clinical practice guidelines for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1-150.
20. Thorp ML, Johnson ES, Yang X, Petrik AF, Platt R, Smith DH. Effect of anaemia on mortality, cardiovascular hospitalizations and end-stage renal disease among patients with chronic kidney disease. *Nephrology (Carlton)*. 2009;14(2):240-246. [CrossRef]
21. Covic A, Nistor I, Donciu MD, Dumea R, Bolignano D, Goldsmith D. Erythropoiesis-stimulating agents (ESA) for preventing the progression of chronic kidney disease: a meta-analysis of 19 studies. *Am J Nephrol*. 2014;40(3):263-279. [CrossRef]
22. Koulouridis I, Alfayez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis- stimulating agents and adverse outcomes in CKD: a metaregression analysis. *Am J Kidney Dis*. 2013;61(1):44-56. [CrossRef]
23. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. *Kidney Int*. 2004;66(2):753-760. [CrossRef]
24. Elliott S, Tomita D, Endre Z. Erythropoiesis stimulating agents and reno-protection: a meta-analysis. *BMC Nephrol*. 2017;18(1):14. [CrossRef]
25. Hayashi T, Maruyama S, Nangaku M, et al. Darbepoetin alfa in patients with advanced CKD without diabetes: randomized, controlled trial. *Clin J Am Soc Nephrol*. 2020;15(5):608-615. [CrossRef]

26. Yu X, Fang Y, Liu H, et al. The balance of beneficial and deleterious effects of hypoxia-inducible factor activation by prolyl hydroxylase inhibitor in rat remnant kidney depends on the timing of administration. *Nephrol Dial Transplant*. 2012;27(8):3110-3119. [CrossRef]
27. Ponikowski P, Filippatos G, Colet JC, et al. The impact of intravenous ferric carboxymaltose on renal function: an analysis of the FAIR-HF study. *Eur J Heart Fail*. 2015;17(3):329-339. [CrossRef]
28. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. *Eur Heart J*. 2015;36(11):657-668. [CrossRef]
29. Roger SD, Gaillard CA, Bock AH, et al. Safety of intravenous ferric carboxymaltose versus oral iron in patients with nondialysis-dep endent CKD: an analysis of the 1-year FIND-CKD trial. *Nephrol Dial Transplant*. 2017;32(9):1530-1539. [CrossRef]
30. Babitt JL, Eisenga MF, Haase VH, et al. Controversies in optimal anemia management: conclusions from a Kidney Disease: improving Global Outcomes (KDIGO) Conference. *Kidney Int*. 2021;99(6):1280-1295. [CrossRef]
31. Palmer SC, Navaneethan SD, Craig JC, et al. HMG CoA Reductase Inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2014;5:CD007784. [CrossRef]
32. Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int*. 2014;85(6):1303-1309. [CrossRef]
33. Von Eynatten M, Emser A, Cooper M, Rosenstoch J, Wanner Ch, Worle H. Renal safety and outcomes with linagliptin: meta-analysis of individual data for 5466 patients with type 2 diabetes. *J Am Soc Nephrol*. 2012;23(suppl 1):218A.
34. Perkovic V, Toto R, Cooper ME, et al. Effects of linagliptin on cardiovascular and kidney outcomes in people with normal and reduced kidney function: secondary analysis of the Carmelina randomized trial. *Diabetes Care*. 2020;43(8):1803-1812. [CrossRef]
35. Shan D, Wu HM, Yuan QY, Li J, Zhou RL, Liu GJ. Pentoxifylline for diabetic kidney disease. *Cochrane Database Syst Rev*. 2012;2(2):CD006800. [CrossRef]
36. de Morales AM, Goicoechea M, Verde E, et al. Pentoxifylline, progression of chronic kidney disease (CKD) and cardiovascular mortality: long-term follow-up of a randomized clinical trial. *J Nephrol*. 2019;32(4):581-587. [CrossRef]
37. Sharma K, Ix JH, Mathew AV, et al. Pirfenidone for diabetic nephropathy. *J Am Soc Nephrol*. 2011;22(6):1144-1151. [CrossRef]
38. Mann JF, Green D, Jamerson K, et al. Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol*. 2010;21(3):527-535. [CrossRef]
39. Heerspink HJL, Parving HH, 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. [CrossRef] [published correction appears in *Lancet*. 2019;11:393(10184):1936].
40. Ding Y, Stidham RD, Bumeister R, et al. The synthetic triterpenoid, RTA 405, increases the glomerular filtration rate and reduces angiotensin II-induced contraction of glomerular mesangial cells. *Kidney Int*. 2013;83(5):845-854. [CrossRef]
41. de Zeeuw D, Akizawa T, Audhya P, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med*. 2013;369(26):2492-2503. [CrossRef]
42. Chin MP, Wrolstad D, Bakris GL, et al. Risk factors for heart failure in patients with type 2 diabetes mellitus and stage 4 chronic kidney disease treated with Bardoxolone methyl. *J Card Fail*. 2014;20(12):953-958. [CrossRef]
43. Chertow GM, Appel GB, Andreoli S, et al. Study design and baseline characteristics of the CARDINAL trial: a Phase 3 study of Bardoxolone methyl in patients with Alport syndrome. *Am J Nephrol*. 2021;52(3):180-189. [CrossRef]
44. Nangaku M, Kanda H, Takama H, Ichikawa T, Hase H, Akizawa T. Randomized clinical trial on the effect of Bardoxolone methyl on GFR in diabetic kidney disease patients (TSUBAKI study). *Kidney Int Rep*. 2020;5(6):879-890. [CrossRef]
45. Schulman G, Berl T, Beck G, Remuzzi G, Ritz E. Results from two randomized placebo controlled double blind clinical trials of AST-120 in adults with CKD. *J Am Soc Nephrol*. 2012;23(suppl 1):7B.
46. Lee CT, Hsu CY, Tain YL, et al. Effects of AST-120 on blood concentrations of protein-bound uremic toxins and biomarkers of cardiovascular risk in chronic dialysis patients. *Blood Purif*. 2014;37(1):76-83. [CrossRef]
47. Nakai K, Fujii H, Kono K, Goto S, Fukagawa M, Nishi S. Effects of AST-120 on left ventricular mass in predialysis patients. *Am J Nephrol*. 2011;33(3):218-223. [CrossRef]
48. Ruggenenti P. Effects of MCP-1 inhibition by Bindarit therapy in type 2 diabetes subjects with micro- or macro-albuminuria. *J Am Soc Nephrol*. 2010;21(suppl 1):44A.
49. Tögel FE, Westenfelder C. Kidney protection and regeneration following acute injury: progress through stem cell therapy. *Am J Kidney Dis*. 2012;60(6):1012-1022. [CrossRef]
50. Papazova DA, Oosterhuis NR, Gremmels H, van Koppen A, Joles JA, Verhaar MC. Cell-based therapies for experimental chronic kidney disease: a systematic review and meta-analysis. *Dis Model Mech*. 2015;8(3):281-293. [CrossRef]