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Dual Renin-Angiotensin-Aldosterone System Blockade for Diabetic Kidney Disease

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Abstract

Blockade of the renin-angiotensin-aldosterone system (RAAS) prevents the development and progression of diabetic kidney disease (DKD). It is controversial whether the simultaneous use of two RAAS inhibitors (ie, dual RAAS blockade) further improves renal outcomes. This review examines the scientific rationale and current clinical evidence addressing the use of dual RAAS blockade to prevent and treat DKD. It is concluded that dual RAAS blockade should not be routinely applied to patients with low or moderate risk of progressive kidney disease (normoalbuminuria or microalbuminuria with preserved glomerular filtration rate). For patients with high risk of progressive kidney disease (substantial albuminuria or impaired glomerular filtration rate), clinicians should carefully weigh the potential risks and benefits of dual RAAS blockade on an individual basis until ongoing clinical trials provide further insight.

Keywords

Diabetes; Kidney; Diabetic kidney disease; Chronic kidney disease; Renin; Angiotensin II; Aldosterone; Angiotensin-converting enzyme inhibitors; Angiotensin II receptor blockers; Albuminuria; Microalbuminuria; Glomerular filtration rate

Introduction

Blockade of the renin-angiotensin-aldosterone system (RAAS) is a proven cornerstone of therapy for the prevention and treatment of diabetic kidney disease (DKD). An elegant body of scientific accomplishment from basic science through clinical trials has solidified the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and other RAAS inhibitors in patients with diabetes. The simultaneous use of two RAAS inhibitors (ie, dual RAAS blockade) is supported by strong biologic rationale, and such therapy has been recommended by experts and frequently used in clinical practice. However, data evaluating long-term clinical effects of dual RAAS blockade are limited, and recent clinical trial results question the implementation of this strategy on a wide scale. Therefore, the purpose of this review is to critically evaluate the role of dual RAAS

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blockade in the clinical care of patients with diabetes, in the context of its scientific evolution and the most recent available clinical evidence. We focus on the effects of dual RAAS blockade on DKD, acknowledging that effects on other organs (heart, vasculature, and eye) may also be important.

Rationale for RAAS Blockade

The RAAS is currently the primary therapeutic target for the prevention and treatment of DKD (Fig. 1). Angiotensinogen produced in the liver is converted to angiotensin I by renin, which is produced in the juxtaglomerular apparatus of the kidney. Angiotensin I is converted to angiotensin II by ACE. Angiotensin II promotes the release of aldosterone from the adrenal glands.

High-quality animal experimental and human studies clearly demonstrate that RAAS overactivity plays a central role in the pathogenesis of DKD (Fig. 1). Specifically, angiotensin II and aldosterone are each directly implicated in the pathogenesis of DKD. Angiotensin II promotes elevations in blood pressure by direct vasoconstriction and by increasing sodium reabsorption in the proximal tubule. Angiotensin II also raises intraglomerular pressure through efferent arteriolar vasoconstriction and directly stimulates tubulointerstitial fibrosis through transforming growth factor- β and other mediators. Aldosterone promotes renal sodium retention and elevated blood pressure by increasing sodium reabsorption in the cortical collecting duct and also directly stimulates tubulointerstitial fibrosis. In addition, recent evidence suggests a pathogenic role for renin itself. Renin binding to the prorenin receptor can lead to mitogen-activated protein kinase signaling, even in the presence of an ARB.

The RAAS can now be blocked by a number of therapeutic interventions, including direct renin inhibitors, ACE inhibitors, ARBs, aldosterone antagonists (spironolactone and eplerenone), and prorenin receptor antagonists (only available experimentally) (Fig. 1). These agents reduce glomerulosclerosis, tubulointerstitial fibrosis, albuminuria, and loss of glomerular filtration rate (GFR) in animal experimental models and/or human randomized clinical trials.

Proven Clinical Benefits of Single RAAS Blockade

The prevention and treatment of DKD with ACE inhibitors or ARBs is a major therapeutic success. Landmark clinical trials have demonstrated that these interventions prevent development or progression of albuminuria, loss of GFR, development of end-stage renal disease (ESRD), and death among persons with diabetes (Table 1). Among persons with normal urine albumin excretion (<30 mg/24 h) and preserved GFR, RAAS blockade has been demonstrated to prevent the development of albuminuria in the presence of hypertension, although not without hypertension [1,2]. Among persons with microalbuminuria (30–300 mg/24 h), RAAS blockade has been demonstrated to reduce progression to macroalbuminuria (≥ 300 mg/24 h) [3,4]. In persons with established DKD (macroalbuminuria and/or impaired GFR), RAAS blockade has been demonstrated to reduce risk of GFR loss, ESRD, and death [5–7].

Impact of Disease Severity on the Benefits of Single RAAS Blockade

Clinical trials have demonstrated that the benefits of single RAAS blockade depend on the baseline risk of progressive kidney disease. In the Collaborative Study Group trial, captopril strongly reduced the relative and absolute risks of doubling of serum creatinine among participants with baseline serum creatinine 1.5–2.5 mg/dL (participants with higher serum creatinine concentrations were excluded from this trial), whereas no significant benefit was

observed among participants with baseline serum creatinine less than 1.5 mg/dL [5]. In the RENAAL trial, benefits of losartan with regard to prevention of doubling of creatinine, ESRD, and death were substantially greater among participants with higher level of baseline urine albumin/creatinine ratio (ACR) [8].

In these trials and numerous other epidemiologic studies and clinical trials, it has been well documented that higher baseline levels of serum creatinine and albuminuria are strong predictors of adverse renal outcomes. It is thus somewhat intuitive that these baseline predictors of renal risk modify the effects of therapeutic interventions, including RAAS inhibitors. Persons with more severe kidney disease at baseline are most likely to have severe underlying pathophysiologic abnormalities amenable to alteration (ie, RAAS overactivity), and these persons are at the highest risk for disease progression. Because clinical effects of single RAAS blockade are strongly determined by the severity of baseline kidney disease, it is to be expected that the clinical effects of dual RAAS blockade will also be strongly determined by the severity of baseline kidney disease.

Rationale for Dual RAAS Blockade

Given the demonstrated clinical success of single RAAS blockade, there are three main pathophysiologic rationales for dual RAAS blockade.

First, any single RAAS inhibitor blocks its step of the RAAS cascade incompletely, given the redundancy of this important system. Thus, RAAS blockade at serial levels may result in greater downregulation of the RAAS as a whole, possibly at lower doses of individual RAAS inhibitors with resulting diminished adverse effects.

Second, many patients treated with ACE inhibitors or ARBs experience aldosterone escape. Clinical trials with both ACE inhibitors and ARBs have shown that aldosterone levels increase toward baseline within 6–12 months in 30%–40% of patients [9•]. Several mechanisms appear to contribute. As both ACE inhibitors and ARBs interfere with the negative feedback regulation of renin secretion, both drugs are associated with significantly elevated renin and angiotensin I levels. Even with ACE inhibitor use, increased levels of angiotensin I can be converted to angiotensin II by non-ACE proteases (eg, chymase), leading to generation of aldosterone. With ARB use, angiotensin II levels are elevated in addition to renin and angiotensin I, which can lead to 1) angiotensin II competing with the ARB for the angiotensin II type 1 receptor, and 2) angiotensin II binding to angiotensin II type 2 receptors on the adrenal glands, leading to secretion of aldosterone [10]. Finally, both ACE inhibitors and ARBs cause an increase in plasma potassium, an independent stimulus for aldosterone secretion.

Third, many patients treated with ACE inhibitors or ARBs for elevated urine albumin excretion continue to have residual albuminuria despite single RAAS blockade. Albuminuria is an established, strong risk factor for kidney disease progression, cardiovascular disease, and death [11–14]. In RENAAL, greater baseline albuminuria, greater albuminuria 6 months after treatment, and lesser reduction in albuminuria from baseline to 6 months were each strongly associated with the primary composite end point of doubling of serum creatinine, ESRD, or death [8]. These observations have contributed to the theory that reducing albuminuria will lead to reduced risk of long-term clinical outcomes, such as ESRD and death. If this theory is correct, adding a second RAAS inhibitor to reduce residual albuminuria present after single RAAS blockade should improve long-term outcomes in DKD. At issue is whether albuminuria is causally related to progressive kidney and cardiovascular disease or is simply a marker of intrinsic risk that cannot be modified with therapy. Although the success of RAAS inhibition in both lowering albuminuria and preventing long-term renal and cardiovascular outcomes supports a causal role for

albuminuria, the observation that other interventions (NSAIDs, cyclosporine, avosentan) reduce albuminuria but do not improve clinical outcomes raises reasonable doubt [15,16•]. This uncertainty is reflected by the US Food and Drug Administration's reluctance to accept albuminuria reduction as an end point for approving new therapies and leaves the optimal clinical response to residual albuminuria unclear [17].

There is randomized clinical trial evidence to support using residual albuminuria as an indication for increasing the overall level of therapeutic RAAS blockade. The ROAD (Renoprotection of Optimal Antiproteinuric Doses) study demonstrated that use of residual albuminuria is one reasonable method to help determine the most appropriate dose of RAAS blockade [18••]. This study tested the strategy of single RAAS inhibitor treatment at fixed dose versus the strategy of single RAAS inhibitor treatment at a dose titrated to urine albumin excretion and other clinical parameters among patients with proteinuric, non-DKD (mean urine protein excretion, 1.8 g/d; estimated GFR, 31 mL/min/1.73 m²). After a run-in phase excluded participants with adverse effects to benazepril (an ACE inhibitor)—including elevated serum creatinine, hyperkalemia, and cough—a total of 360 participants were assigned to one of four treatment arms: 1) fixed-dose benazepril, 10 mg/d, 2) titrated-dose benazepril, 10–40 mg/d, 3) fixed-dose losartan (an ARB), 50 mg/d, or 4) titrated-dose losartan, 50–200 mg/d. Participants were seen frequently during follow-up. In the titrated-dose groups, optimal dose of RAAS inhibitor was determined using a complex but clinically relevant strategy. Dose was automatically titrated up every month, with titrations back down when urine protein excretion failed to fall by greater than 10%, serum creatinine increased by $\geq 30\%$, serum creatinine exceeded 6 mEq/L, or systolic blood pressure fell below 120 mm Hg. Once established, fixed or optimal doses were continued for a median total follow-up of 3.7 years. The combined end point of doubling of serum creatinine, dialysis, or death occurred with equal frequency in each fixed-dose group. In comparison, this end point was significantly reduced in the groups assigned to a titrated dose: hazard ratio 0.49 for titrated-versus fixed-dose benazepril ($P=0.03$), hazard ratio 0.47 for titrated- versus fixed-dose losartan ($P=0.02$). Although the ROAD study does not exclude the possibility that other dose titration methods prevent kidney disease progression, including the simple method of pushing RAAS blockade dose to the maximum level tolerated by serum potassium and creatinine levels, it does suggest that RAAS blockade dose is important and that level of residual proteinuria may be useful in determining this dose.

Effects of Dual RAAS Blockade on Albuminuria

Most studies of dual RAAS blockade have focused on short-term reduction of albuminuria. As discussed above, albuminuria is well established as a strong marker of risk of DKD progression, and may have a pathogenic role in the progression of DKD. Thus, although demonstration of albuminuria reduction by new therapeutic interventions does not prove long-term clinical effectiveness, it may identify interventions that are most likely to provide long-term health benefits.

ACE inhibitor plus ARB is the best studied combination of RAAS inhibitors. Effects of this combination regimen on albuminuria were recently evaluated in a meta-analysis of placebo-controlled randomized clinical trials [19•]. Analyzing seven clinical trials of ACE inhibitor plus ARB versus placebo plus ARB, the addition of an ACE inhibitor reduced albuminuria by 24% (95% CI, 15%, 32% reduction) over 1–4 months follow-up. Analyzing seven clinical trials of ARB plus ACE inhibitor versus placebo plus ACE inhibitor, the addition of an ARB reduced albuminuria by 22% (95% CI, 16%, 28% reduction) over 1–4 months follow-up. Responses for individual patients and trials are necessarily heterogeneous, but these data clearly demonstrate that the combination of an ACE inhibitor and ARB reduces albuminuria compared with an ACE inhibitor or ARB alone.

“Supramaximal doses” of ARBs (ie, doses of ARBs beyond those known to provide marginal blood pressure reduction) have also been demonstrated to reduce albuminuria in randomized clinical trials [20–22]. One such study tested effects of three doses of candesartan on urine protein excretion among 269 patients with baseline proteinuria ≥ 1 g/d, 54% of whom had diabetes [22]. Compared with a standard antihypertensive dose of 16 mg/d, doses of 64 and 128 mg/d (each above the accepted maximal antihypertensive dose) reduced urine protein excretion by 16% and 30% after 30 weeks, respectively.

The aldosterone antagonists spironolactone and eplerenone have been tested in addition to ACE inhibitors and/or ARBs for the reduction of albuminuria. Effects were recently summarized in a systematic review [23•]. Fourteen studies evaluated spironolactone, whereas one study evaluated eplerenone. These aldosterone antagonists were added to an ACE inhibitor in the majority of studies, although some studies added aldosterone antagonists to an ARB or to an ACE inhibitor and an ARB (triple RAAS blockade). Compared with placebo or no additional intervention, most studies reported that addition of an aldosterone antagonist reduced albuminuria by 30%–40% (range, 15%–54%).

Recently, in a three-arm randomized clinical trial, spironolactone was compared with losartan (an ARB) and placebo as add-on therapy to high-dose ACE inhibitor [24•]. Included were 81 participants with diabetes (mostly type 2), hypertension, and urine ACR ≥ 300 mg/g who were already treated with lisinopril, 80 mg/d. Compared with placebo, the addition of spironolactone, 25 mg/d, to lisinopril reduced albuminuria by 34% at 48 weeks ($P=0.007$), whereas the addition of losartan, 100 mg/d, to lisinopril reduced albuminuria by 17% ($P=0.2$). A direct statistical comparison of spironolactone versus losartan was not reported.

The direct renin inhibitor aliskiren has emerged as the newest RAAS inhibitor available for clinical use. Aliskiren does not reduce the production or secretion of renin from the juxtaglomerular apparatus, but directly blocks the activity of secreted renin. Effects of aliskiren on albuminuria in the setting of DKD were studied in the AVOID study [25•]. Included were 599 participants with type 2 diabetes and urine ACR greater than 300 mg/g (or >200 mg/g while using a RAAS inhibitor). All participants were treated with losartan. Compared with participants assigned to add-on placebo, participants assigned to add-on aliskiren experienced a 20% reduction in albuminuria ($P<0.001$).

One of the conundrums of DKD is that prorenin but not renin levels are elevated. Therefore, recent attention has shifted to the prorenin receptor [26]. Elevated prorenin levels have been associated with incipient nephropathy, and prorenin receptors have been demonstrated in glomeruli, macula densa, and distal tubules [27–29]. Blockade of the prorenin receptor in experimental models of DKD was shown to provide more substantial reduction in proteinuria and glomerulosclerosis when used in addition to ACE inhibition [30].

Vitamin D interventions potentially block renin transcription and release by juxtaglomerular cells in animal experimental models [31]. Thus, vitamin D interventions may represent a novel method of blocking the RAAS, which could be used in combination with a traditional RAAS inhibitor to achieve a nontraditional dual RAAS blockade. In the streptozotocin model of DKD, the addition of paricalcitol (an activated vitamin D analogue) to losartan (an ARB) completely abrogated the development of albuminuria [32]. In humans, lower serum 25-hydroxyvitamin D concentrations are associated with increased risk of prevalent albuminuria and incident ESRD [33–35]. Moreover, a recent randomized clinical trial of paricalcitol among persons with type 2 diabetes and albuminuria (urine ACR 100–1000 mg/g) reported reduction in albuminuria of up to 15%, comparing high-dose paricalcitol to placebo [36].

Long-Term Renal Effects of Dual RAAS Blockade

Previously, clinical use of an ACE inhibitor in combination with an ARB was supported by many experts based on results of the COOPERATE trial, a single-center study from Japan [37]. Per report, 263 participants with proteinuric, non-DKD were randomly assigned to treatment with trandolapril (an ACE inhibitor), losartan (an ARB), or the combination of trandolapril plus losartan; combination therapy reduced the incidence of the composite end point of doubling of serum creatinine or death by 62% versus trandolapril alone and by 60% versus losartan alone (each $P=0.02$). After inconsistencies in the reported methods and results of COOPERATE were noted [38], the sponsoring institution of COOPERATE conducted a full review of this study. This investigation revealed a number of contradictions to published study methods and results, including lack of ethics committee approval, improper participant consent, no documented involvement of a statistician, and lack of investigator blinding to treatment allocation. In addition, the investigative committee was unable to prove data authenticity via chart review. As a result, COOPERATE has now been retracted from the literature, and should no longer be used to guide clinical practice [39].

Currently, the only other published randomized clinical trial assessing the long-term renal impact of dual versus single RAAS blockade is the ONTARGET trial. The primary objective of ONTARGET was to test whether combination therapy with lisinopril (an ACE inhibitor) and telmisartan (an ARB) was superior to single RAAS blockade for the prevention cardiovascular disease [40•]. Eligibility criteria included known clinical vascular disease or diabetes with evidence of end-organ damage. A total of 25,620 participants were randomly assigned in a 1:1:1 ratio to treatment with lisinopril plus telmisartan, lisinopril alone, or telmisartan alone. A total of 9612 participants had diabetes (38%). At a median follow-up of 56 months, there was no difference in the primary composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

Renal outcomes were also assessed in ONTARGET [41•]. The primary renal outcomes were defined as a composite of dialysis, doubling of serum creatinine, and death. The occurrence of this outcome was similar for the lisinopril alone and telmisartan alone groups, but was significantly increased for combination therapy (hazard ratio 1.09, $P=0.037$). Death constituted the majority of events for the primary renal outcome. A secondary renal outcome of dialysis or doubling of serum creatinine was similar with lisinopril or telmisartan, but again more frequent with combination therapy (hazard ratio 1.24, $P=0.038$). Doubling of serum creatinine constituted the majority of events for the secondary renal outcome. However, an analysis of change in serum creatinine over time demonstrated that differences by treatment group were not due solely to the expected initial rise attributable to diminished renal perfusion. Specifically, the combination therapy group continued to have higher serum creatinine concentration throughout the duration of the study, without evidence of slower progression even after the 6-week study visit. These unfavorable effects on serum creatinine were observed despite favorable effects of combination treatment on urine albumin excretion. In addition, a statistically significant increase in the incidence of dialysis for acute kidney injury was observed in the combination treatment group, although absolute numbers of acute kidney injury events were small.

Renal results of ONTARGET have been the subject of vigorous scientific debate. Perhaps most importantly, by virtue of its primary focus on cardiovascular disease outcomes, ONTARGET enrolled a population that on average was at low risk for progressive kidney disease. For the full ONTARGET population, geometric mean urine ACR was only 7 mg/g, and mean estimated GFR was 74 mL/min/1.73 m². At baseline, prevalence of urine ACR ≥ 30 mg/g was 13%, prevalence of urine ACR ≥ 300 mg/g was 4%, prevalence of estimated

GFR less than 60 mL/min/1.73 m² was 24%, and prevalence of estimated GFR less than 30 mL/min/1.73 m² was 1%. In this population, it would be expected that incidence rates of cardiovascular disease and death would exceed those of clinically meaningful kidney disease progression [42].

To assess effects of ONTARGET combination treatment on persons at moderate-high risk of kidney disease progression, a number of subgroup analyses were performed [41••]. Combination treatment did not reduce the incidence of the primary renal outcome among participants with diabetes ($n=6900$). Among subgroups with microalbuminuria or macroalbuminuria ($n=2648$) and overt diabetic nephropathy (diabetes and baseline urine ACR ≥ 300 mg/g, $n=474$), relative risk for the combination treatment group was slightly less than 1 (mild favorable effect), but results were not statistically significant.

Overall, results of the ONTARGET trial strongly suggest that combination treatment with an ACE inhibitor and ARB do not reduce renal, cardiovascular, and mortality outcomes among patients with low-moderate risk of progressive kidney disease, and that combination treatment may lead to harm in this population. Subgroup analyses must be viewed with caution, and do not provide definitive evidence for or against combination treatment for patients with diabetes and high risk for progressive kidney disease.

Hyperkalemia

Dual RAAS blockade is not without adverse effects. In particular, dual RAAS blockade is known to cause more hyperkalemia than a single RAAS antagonist alone. In ONTARGET, a serum potassium greater than 5.5 mmol/L was observed in 3.3% in the ramipril group, 3.4% in the telmisartan group, and 5.6% in the combination group ($P<0.001$ vs ramipril) [40••]. In the much smaller IMPROVE trial, the incidence of hyperkalemia was not different between combination therapy (2.9%) and ramipril (3%) [43]. In the RALES study, spironolactone, 25 mg/d, added to an ACE inhibitor and loop diuretic increased median serum potassium concentration by 0.3 mEq/L compared with placebo, although only 14 cases of serious hyperkalemia were reported (compared with 10 for placebo) [44].

Compared with the clinical trial setting, risk of hyperkalemia with dual RAAS blockade may be greater in practice, in which “eligibility criteria” may be less strict, patients have not already been screened as part of a run-in phase, and follow-up may be less frequent. This concern was demonstrated using analysis of temporal trends following publication of the RALES trial [45]. In the general Canadian population, prescription rate of spironolactone for patients recently hospitalized for heart failure rose dramatically after online publication of RALES in 1999. Parallel temporal trends were observed for rates of hospital admission for hyperkalemia and in-hospital death associated with hyperkalemia.

Ongoing Clinical Trials

There are two large, well-powered, ongoing randomized clinical trials that will test effects of dual RAAS blockade in diabetes populations at high risk for progressive kidney disease.

The US Veterans Affairs NEPHRON-D is an ongoing randomized clinical trial designed to assess the effect of combination losartan (an ARB) and lisinopril (an ACE inhibitor), compared with losartan alone, on the progression of kidney disease [46]. The study aims to enroll 1850 US veterans with type 2 diabetes and overt proteinuria, defined as urine ACR greater than 300 mg/g. The primary outcome is time to a composite end point of reduction in estimated GFR, ESRD, and death. Follow-up is planned for up to 5 years.

The primary objective of the ALTITUDE is to determine whether aliskiren (a direct renin inhibitor) reduces progression of kidney disease, cardiovascular disease, and death when added to conventional treatment, including an ACE inhibitor or ARB [47]. The study aims to enroll 8600 participants with type 2 diabetes and macroalbuminuria (urine ACR ≥ 200 mg/g) or impaired GFR (estimated GFR < 60 mL/min/1.73 m²). The primary outcome is time to first occurrence of the composite end point of cardiovascular death, resuscitated death, myocardial infarction, ESRD, or doubling of baseline serum creatinine concentration. Planned follow-up time is 48 months.

Conclusions

Single RAAS blockade is a proven intervention for the prevention and treatment of DKD. Reasonable theories suggest that dual RAAS blockade may offer incremental benefit. These theories are supported by short-term clinical trials demonstrating that various combinations of RAAS inhibitors reduce albuminuria, compared with single RAAS inhibition. However, the only valid long-term trial of dual RAAS blockade (ONTARGET) demonstrated no benefit, and possible harm, with regard to clinical renal outcomes. These results strongly suggest that dual RAAS blockade should not be routinely applied to patients with low or moderate risk for progressive kidney disease (normoalbuminuria or microalbuminuria with normal estimated GFR). Whether dual RAAS blockade prevents progression of kidney disease among patients at high risk (macroalbuminuria or impaired GFR) remains an open question. For such patients, until ongoing clinical trials report results of dual RAAS blockade in this population, clinicians should carefully weigh the potential benefits of dual RAAS blockade against potential adverse effects including hyperkalemia on an individual basis.

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Clinical Study Acronyms

ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints
AVOID	Aliskiren in the Evaluation of Proteinuria in Diabetes
COOPERATE	Combination Treatment of Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor in Nondiabetic Renal Disease
IMPROVE	Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events
NEPHRON-D	Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy
ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial
RALES	Randomized Aldactone Evaluation Study
RENAAL	Reduction in Endpoints in Non-Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan
ROAD	Renoprotection of Optimal Antiproteinuric Doses

Fig. 1. Components of the renin-angiotensin-aldosterone system (RAAS), pathophysiologic actions of the RAAS, and pharmacologic agents clinically available to block the RAAS. Angiotensin (AT) II raises intraglomerular pressure through efferent arteriolar vasoconstriction, increases sodium reabsorption in the proximal tubule, and directly stimulates tubulointerstitial fibrosis. Aldosterone promotes distal renal sodium retention and stimulates tubulointerstitial fibrosis. ACEI—angiotensin-converting enzyme inhibitor; ARB—angiotensin receptor blocker; DRI—direct renin inhibitor

Selected landmark placebo-controlled clinical trials of single RAAS inhibition for the prevention and treatment of DKD

Table 1

Study	Study population		Intervention		Average duration of follow-up, y	Primary end point	Effect of intervention (95% CI)
	Diabetes type	N	Baseline urine albumin excretion	Baseline SCr			
Collaborative Study Group [5]	Type 1	409	≥500 mg/d	≤2.5 mg/dL	3	Doubling of SCr	↓ 48% (16%, 69%)
IDNT [6]	Type 2 ^a	1715	≥900 mg/d	1.0–3.0 mg/dL ^b	2.6	Doubling of SCr, ESRD, or death	↓ 20% (3%, 34%)
RENAAL [7]	Type 2	1513	≥300 mg/d	1.3–3.0 mg/dL ^c	3.4	Doubling of SCr, ESRD, or death	↓ 16% (2%, 28%)
IRMA 2 [3]	Type 2 ^a	590	20–200 µg/min	≤1.1 mg/dL ^d	2	AER≥200 µg/min	300 mg ↓ 70% (39%, 86%), 150 mg ↓ 39% (18%, ↓66%)
BENEDICT [1]	Type 2 ^a	1204	<20 µg/min	≤1.5 mg/dL	3.6	AER≥20 µg/min	↓ 53% (17%, 74%)

AER albumin excretion rate; BENEDICT Bergamo Nephrologic Diabetic Complication Trial; DKD diabetic kidney disease; ESRD end-stage renal disease; IDNT Irbesartan Diabetic Nephropathy Trial; IRMA 2 Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria; RAAS renin-angiotensin-aldosterone system; RENAAL Reduction in Non-Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan; SCr serum creatinine concentration; tid three times a day

^a Hypertension also required for eligibility

^b 1.2–3.0 mg/dL for men

^c 1.5–3.0 for men weighing more than 60 kg

^d ≤1.5 mg/dL for men