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*Research Article*

# A Comprehensive Review on the Role of Renin Angiotensin Aldosterone System Blockade in Chronic Kidney Disease

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## Abstract

Chronic kidney disease (CKD) is a growing global health burden associated with substantial morbidity, mortality, and progression to end-stage renal disease (ESRD). Activation of the renin angiotensin aldosterone system (RAAS) plays a central role in the pathogenesis and progression of CKD by promoting intraglomerular hypertension, proteinuria, inflammation, oxidative stress, and renal fibrosis. These mechanisms provide a strong rationale for RAAS inhibition as a cornerstone of renoprotective therapy.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been extensively studied in both diabetic and non-diabetic CKD. Beyond effective blood pressure control, these agents reduce proteinuria, preserve glomerular structure, and slow the decline in glomerular filtration rate. Landmark clinical trials have demonstrated that reductions in albuminuria strongly correlate with improved renal outcomes, establishing proteinuria as both a marker and mediator of CKD progression. Consequently, current clinical guidelines recommend ACEIs or ARBs as first-line therapy in patients with proteinuria CKD.

Dual RAAS blockade with combined ACEI and ARB therapy has been proposed to achieve more complete RAAS suppression and greater proteinuria reduction. However, large randomized trials have failed to demonstrate additional benefit in hard renal outcomes and have consistently reported increased risks of hyperkalemia, hypotension, and acute kidney injury. As a result, routine dual RAAS blockade is not recommended in clinical practice.

This review summarizes the pathophysiological role of RAAS in CKD, the pharmacological mechanisms and clinical benefits of ACEIs and ARBs, and evidence from major clinical trials. It also highlights safety considerations, current guideline recommendations, and the evolving role of RAAS blockade within a broader therapeutic landscape aimed at slowing CKD progression and improving patient outcomes.

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## 1. INTRODUCTION

Chronic kidney disease (CKD) represents a major and growing global public health challenge, contributing substantially to morbidity, mortality, and healthcare burden worldwide. It is a progressive disorder characterized by persistent abnormalities in kidney structure or function lasting for more than three months, with significant implications for patient health and survival. The global prevalence of CKD continues to rise at an alarming rate, largely driven by the increasing incidence of diabetes mellitus, hypertension, obesity, and the expanding elderly population. Despite remarkable advances in renal replacement therapies over recent decades, outcomes for patients with end-stage renal disease (ESRD) have shown only modest improvement, underscoring the urgent need for effective strategies to prevent or delay disease progression.

Diabetes mellitus remains the leading cause of ESRD, accounting for nearly half of all cases worldwide, followed by hypertension, glomerulonephritis, and other less common etiologies. Regardless of the underlying cause, CKD progression follows a relatively uniform pathological trajectory characterized by early renal inflammation, glomerular injury, tubulointerstitial fibrosis, tubular atrophy, and eventual glomerulosclerosis. These structural changes lead to a gradual decline in glomerular filtration rate (GFR) and the accumulation of metabolic waste products, ultimately resulting in irreversible renal failure.

The renin angiotensin aldosterone system (RAAS) plays a central role in the pathophysiology of CKD progression. Traditionally recognized as a systemic endocrine system responsible for blood pressure regulation and fluid electrolyte balance, RAAS is now understood to exert significant local effects within renal tissue. Intrarenal RAAS activation operates independently of the systemic circulation and contributes to sustained angiotensin II production within the kidney. Angiotensin II promotes efferent arteriolar vasoconstriction, increases intraglomerular pressure, enhances sodium retention, and stimulates inflammatory and pro-fibrotic pathways, thereby accelerating renal injury and structural damage [1].

Clinical and experimental studies have demonstrated that strict blood pressure control is a critical determinant in slowing CKD progression. Beyond their antihypertensive effects, pharmacologic agents that inhibit the RAAS namely angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have been extensively investigated for their potential renoprotective properties. These agents have been shown to reduce proteinuria, mitigate intraglomerular hypertension, and attenuate inflammatory and fibrotic processes within the kidney. Consequently, current clinical guidelines recommend ACEIs or ARBs as first-line therapy in patients with diabetic kidney disease and in those with non-diabetic CKD accompanied by albuminuria.

However, the extent to which RAAS inhibition confers renal protection independent of blood pressure reduction remains a subject of ongoing debate. While numerous trials support their beneficial role in preserving renal function, particularly in proteinuria CKD, evidence is limited and inconclusive in patients with non-diabetic, non-albuminuria kidney disease. Furthermore, intensified RAAS blockade through the combined use of ACEIs and ARBs has been explored as a means to achieve more complete suppression of angiotensin II activity. Although early studies suggested potential benefits in reducing proteinuria, subsequent trials raised concerns regarding safety, including increased risks of hyperkalemia, hypotension, and acute kidney injury. As a result, dual RAAS blockade is not routinely recommended in current clinical practice [2, 3].

Given the pivotal role of RAAS in CKD progression and the widespread use of ACEIs and ARBs in clinical nephrology, a comprehensive understanding of their therapeutic benefits, limitations, and safety profiles is essential.

This review aims to critically examine the role of ACEIs and ARBs in the management of CKD, focusing on their mechanistic basis, clinical evidence for renoprotection, and guideline-based recommendations, while highlighting existing controversies and areas requiring further investigation [4, 5].

### 1.1 Pathophysiology of Chronic Kidney Disease

Chronic kidney disease is characterized by a progressive and irreversible decline in renal structure and function resulting from sustained hemodynamic, inflammatory, and fibrotic injury. Although the initiating insult varies among etiologies such as diabetes mellitus, hypertension, and glomerulonephritis, the downstream mechanisms leading to nephron loss are largely shared. Central to these mechanisms is persistent activation of the renin angiotensin aldosterone system (RAAS), which plays a fundamental role in mediating both functional and structural renal damage.

### 1.2 RAAS Activation in CKD

The RAAS is a complex hormonal cascade essential for the regulation of blood pressure, sodium homeostasis, and intravascular volume. Systemically, renin is released from the juxtaglomerular apparatus in response to reduced renal perfusion, sympathetic nervous system activation, or decreased sodium delivery to the macula densa. Renin catalyses the conversion of angiotensinogen to angiotensin I, which is subsequently cleaved by angiotensin-converting enzyme (ACE) to form angiotensin II (Ang II), the principal effector molecule of the system.

Beyond its systemic role, extensive evidence now supports the existence of a local or tissue RAAS that operates independently within various organs, particularly the kidney. Components of RAAS, including renin, ACE, angiotensinogen, and angiotensin receptors, are synthesized locally within renal tissue. In CKD, intrarenal RAAS remains persistently activated even when circulating RAAS activity is suppressed by pharmacologic intervention or volume expansion. This sustained local Ang II production creates a maladaptive environment that perpetuates renal injury and accelerates disease progression.

### 1.3 Hemodynamic Effects of Angiotensin II

One of the earliest and most critical mechanisms by which Ang II contributes to CKD progression is its effect on renal

hemodynamics. Ang II preferentially constricts efferent arterioles more than afferent arterioles, leading to increased intraglomerular capillary pressure. While this response initially helps maintain glomerular filtration rate (GFR) in the setting of reduced renal perfusion, chronic elevation of intraglomerular pressure results in mechanical stress on the glomerular basement membrane and podocytes. Over time, this promotes glomerular hypertrophy, capillary wall damage, and increased permeability to plasma proteins, manifesting clinically as proteinuria.

Proteinuria itself is not merely a marker of kidney damage but acts as a pathogenic factor. Filtered proteins are reabsorbed by proximal tubular cells, triggering inflammatory and fibrotic signalling pathways that further exacerbate tubulointerstitial injury.

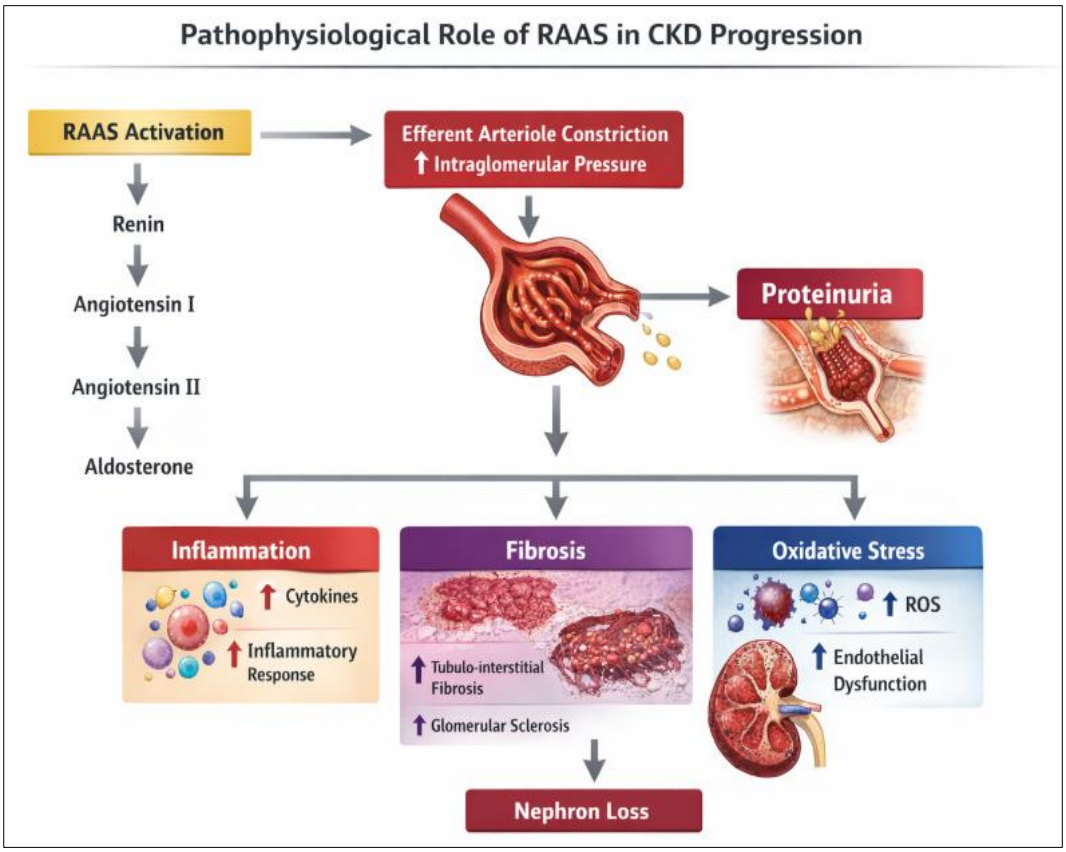


**Fig 1:** Pathophysiological role of RAAS in CKD Progression

### 1.4 Pro-Inflammatory and Pro-Fibrotic Actions

Angiotensin II exerts potent non-hemodynamic effects that are central to CKD pathogenesis. It stimulates the production of pro-inflammatory cytokines, chemokines, and adhesion molecules, leading to the recruitment of inflammatory cells such as macrophages and T lymphocytes into renal tissue. Among these mediators, transforming growth factor-β (TGF-β) plays a pivotal role in renal fibrosis. Ang II induces TGF-β expression, which in turn promotes fibroblast activation, epithelial-to-mesenchymal transition, and excessive deposition of extracellular matrix proteins, including collagen and fibronectin.

This fibrotic response results in progressive glomerulosclerosis and tubulointerstitial fibrosis, hallmark features of advanced CKD. Fibrosis disrupts normal nephron architecture, compromises peritubular capillary blood flow, and leads to hypoxia, further perpetuating renal injury.

### 1.5 Oxidative Stress and Endothelial Dysfunction

Angiotensin II also contributes to oxidative stress through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, resulting in increased generation of reactive oxygen species (ROS). Excess ROS impair nitric oxide bioavailability, leading to endothelial dysfunction and vasoconstriction. Endothelial injury further compromises renal microcirculation and exacerbates ischemic damage to renal parenchyma.

Oxidative stress additionally amplifies inflammatory and fibrotic signalling pathways, creating a self-perpetuating cycle of injury that accelerates nephron loss.

### 1.6 Mesangial Cell Proliferation and Matrix Expansion

Within the glomerulus, Ang II stimulates mesangial cell proliferation and promotes the synthesis of extracellular matrix components. Mesangial expansion reduces the surface area

available for filtration and contributes to capillary obliteration. This structural remodelling impairs glomerular function and plays a key role in the progression toward glomerulosclerosis.

### 1.7 Consequences for CKD Progression

The combined hemodynamic, inflammatory, oxidative, and fibrotic effects of persistent RAAS activation ultimately result in progressive nephron loss. As functional nephron mass declines, compensatory hyperfiltration in remaining nephrons further increases intraglomerular pressure, perpetuating a vicious cycle of injury. Clinically, this manifests as worsening proteinuria, declining GFR, and progression toward ESRD.

Given its central role in CKD pathophysiology, RAAS represents a critical therapeutic target. Interventions aimed at inhibiting Ang II production or blocking its receptor-mediated effects have been shown to attenuate proteinuria, reduce intraglomerular hypertension, and slow structural damage, forming the foundation for RAAS blockade in CKD management.

**Table 1:** Role of RAAS in CKD Progression

| RAAS Component | Pathophysiological Effect in CKD |
|---|---|
| Angiotensin II | Efferent arteriolar vasoconstriction → ↑ intraglomerular pressure |
| Aldosterone | Sodium retention, volume expansion, fibrosis |
| TGF-β stimulation | Glomerulosclerosis and tubulointerstitial fibrosis |
| Oxidative stress | Endothelial dysfunction and inflammation |
| Cytokine activation | Progression of renal scarring |

### 2.1 Clinical Manifestations of Chronic Kidney Disease

The signs and symptoms of chronic kidney disease (CKD) typically develop insidiously and often remain clinically silent during the early stages. This delayed presentation is largely attributable to the kidney's' substantial functional reserve, which allows maintenance of homeostasis despite progressive nephron loss. As renal function declines over time, the kidney's' ability to excrete metabolic waste products, regulate fluid balance, and maintain electrolyte and acid base homeostasis becomes increasingly impaired, leading to a broad spectrum of systemic manifestations.

Gastrointestinal symptoms are common in advanced CKD and include nausea, vomiting, and loss of appetite, primarily due to the accumulation of uremic toxins. These symptoms may contribute to malnutrition and weight loss, further worsening patient outcomes. Fatigue and generalized weakness are frequently reported and result from anaemia, metabolic acidosis, and toxin accumulation.

Neurological and cognitive manifestations may occur as kidney function deteriorates. Patients may experience sleep disturbances, decreased mental sharpness, impaired concentration, and in severe cases, features of uremic encephalopathy. Muscle cramps, particularly at night, are commonly associated with electrolyte imbalances such as hypocalcaemia and hyperphosphatemia.

Alterations in urinary output are another hallmark of CKD progression. Patients may report polyuria or nocturia in early stages due to impaired urinary concentrating ability, followed by oliguria in advanced disease as nephron loss becomes severe. Dermatologic manifestations, including dry and pruritic skin, arise from uraemia, secondary hyperparathyroidism, and reduced sweat gland activity.

Fluid and electrolyte dysregulation contributes significantly to cardiovascular and respiratory symptoms. Peripheral edema, particularly swelling of the feet and ankles, results from sodium and water retention as well as hypoalbuminemia. Hypertension, often difficult to control, is both a cause and consequence of CKD and is closely linked to volume expansion and activation of the renin angiotensin aldosterone system. In more advanced stages, shortness of breath may develop due to pulmonary edema caused by fluid overload.

Serous cavity effusions may occur in severe CKD. Chest pain can result from uremic pericarditis or fluid accumulation in the pericardial sac, representing a serious complication that requires urgent medical attention.

Overall, the clinical manifestations of CKD reflect the progressive loss of renal excretory, endocrine, and regulatory functions. Recognition of these symptoms is essential for timely diagnosis, appropriate intervention, and prevention of life-threatening complications associated with advanced kidney disease.

## 3. Proteinuria

### 3.1 Causes of Proteinuria

Proteinuria refers to the abnormal presence of protein in the urine and is a key indicator of kidney dysfunction. Under normal physiological conditions, the glomerular filtration barrier comprising fenestrated endothelium, the glomerular basement membrane, and podocytes prevents significant loss of plasma proteins into the urine. Proteinuria develops when this finely regulated barrier is disrupted or when tubular reabsorption mechanisms are impaired.

Glomerular damage is the most common cause of persistent proteinuria. Injury to the glomeruli compromises selective permeability, allowing proteins, particularly albumin, to pass into the urinary space. Such damage frequently results from chronic conditions including diabetes mellitus, systemic hypertension, cardiovascular disease, and primary or secondary glomerular disorders. In these conditions, sustained intraglomerular hypertension and inflammatory processes lead to structural alterations in the filtration barrier.

Systemic diseases may also contribute to proteinuria by affecting renal hemodynamics or tubular function. Disorders such as autoimmune diseases, infections, and metabolic abnormalities can impair the kidney's ability to reabsorb

filtered proteins in the proximal tubules, resulting in increased urinary protein excretion.

In addition, non-pathological or transient causes of proteinuria are well recognized. Functional proteinuria may occur during febrile illness, strenuous physical exercise, emotional stress, or prolonged upright posture (orthostatic proteinuria). These forms are typically benign, reversible, and not associated with underlying structural kidney disease [4, 5].

### 3.2 Symptoms of Proteinuria

Proteinuria is often asymptomatic in its early stages and may only be detected through routine laboratory testing. As protein loss increases or as kidney disease progresses, clinical manifestations may become evident.

Common symptoms include foamy or frothy urine, resulting from the presence of excess protein. Edema is a hallmark feature, particularly swelling of the face, hands, feet, ankles, and abdomen, due to hypoalbuminemia and altered oncotic pressure. Patients may also experience increased urinary frequency, especially at night (nocturia).

Systemic symptoms associated with significant proteinuria and underlying kidney dysfunction include fatigue, loss of appetite, nausea, vomiting, and muscle cramps, particularly at night. In advanced cases, shortness of breath may develop as a consequence of fluid overload or anaemia. These symptoms often reflect both renal impairment and associated metabolic disturbances [5, 6].

### 3.3 Proteinuria as a Marker and Mediator of CKD Progression

Proteinuria, particularly albuminuria, is not only a sensitive marker of kidney damage but also an independent mediator of CKD progression and a strong predictor of cardiovascular morbidity and mortality. The degree of proteinuria correlates closely with the severity of glomerular injury and the rate of decline in renal function.

Damage to the glomerular filtration barrier permits excessive leakage of plasma proteins into the tubular lumen. Filtered proteins are taken up by proximal tubular epithelial cells, triggering the activation of pro-inflammatory and pro-fibrotic signalling pathways. This process leads to the release of cytokines, chemokines, and growth factors that promote interstitial inflammation, fibroblast activation, and extracellular matrix accumulation.

Persistent tubular injury and interstitial fibrosis result in progressive nephron loss and deterioration of glomerular filtration rate (GFR). Importantly, proteinuria contributes to a vicious cycle in which ongoing protein leakage exacerbates renal injury, thereby accelerating CKD progression.

Clinical trials have consistently demonstrated that reductions in proteinuria are strongly associated with slower decline in GFR and improved renal outcomes, independent of blood pressure control. Consequently, proteinuria is widely used as both a prognostic marker and a therapeutic target in CKD management. Therapeutic strategies aimed at reducing proteinuria, particularly through inhibition of the renin angiotensin aldosterone system, form a cornerstone of evidence-based CKD treatment.

### 3.4 Proteinuria in CKD: Pathophysiological Link to RAAS

Proteinuria is a central feature of chronic kidney disease (CKD) and serves not only as a marker of glomerular injury but also as a key mediator of disease progression. Increasing evidence indicates that activation of the renin angiotensin aldosterone system (RAAS), particularly within the kidney, plays a pivotal role in the development and perpetuation of proteinuria. Consequently, pharmacological blockade of RAAS using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) has become a cornerstone in the management of proteinuria CKD.

**RAAS-Mediated Mechanisms of Proteinuria:** Angiotensin II (Ang II), the principal effector hormone of RAAS, contributes to proteinuria through both hemodynamic and non-hemodynamic mechanisms. Hemodynamically, Ang II preferentially constricts the efferent arteriole, leading to elevated intraglomerular capillary pressure. Although this initially preserves glomerular filtration rate (GFR), sustained intraglomerular hypertension causes mechanical stress on the glomerular filtration barrier, resulting in podocyte injury, disruption of the glomerular basement membrane, and increased permeability to plasma proteins, particularly albumin.

Beyond its hemodynamic effects, Ang II exerts direct cellular actions that exacerbate protein leakage. It stimulates mesangial cell proliferation and promotes extracellular matrix accumulation, leading to mesangial expansion and glomerulosclerosis. Ang II also induces oxidative stress and endothelial dysfunction, further compromising the integrity of the filtration barrier. In addition, Ang II activates pro-inflammatory and pro-fibrotic signalling pathways, including upregulation of transforming growth factor-β (TGF-β), which accelerates structural damage within the glomerulus and tubulointerstitial.

### 3.5 Proteinuria as a Driver of Progressive Renal Injury

Proteinuria is not merely a passive consequence of glomerular injury but actively contributes to CKD progression. Excessive filtration of proteins into the tubular lumen leads to increased uptake by proximal tubular epithelial cells. This triggers inflammatory responses characterized by the release of cytokines, chemokines, and growth factors, promoting macrophage infiltration, tubular apoptosis, and interstitial fibrosis. These processes result in progressive nephron loss and decline in renal function.

RAAS activation amplifies this injury cascade by sustaining intrarenal Ang II levels, thereby reinforcing proteinuria-induced inflammation and fibrosis. Thus, proteinuria represents a critical link between RAAS dysregulation and irreversible kidney damage [7-9].

**3.6 Therapeutic Impact of ACEIs and ARBs on Proteinuria**

ACEIs and ARBs exert potent antiproteinuric effects that extend beyond their systemic blood pressure lowering properties. By inhibiting Ang II formation or blocking its interaction with angiotensin II type 1 (AT1) receptors, these agents reduce efferent arteriolar constriction, thereby lowering intraglomerular pressure and decreasing mechanical stress on the glomerular filtration barrier. This hemodynamic effect leads to a significant reduction in protein leakage across the glomerulus.

In addition to improving intraglomerular hemodynamics, ACEIs and ARBs attenuate Ang II mediated inflammatory and fibrotic signalling. Suppression of TGF-β expression, reduction in oxidative stress, and inhibition of mesangial cell proliferation contribute to stabilization of glomerular structure and preservation of nephron function. These non-hemodynamic effects are particularly important in slowing CKD progression.

Clinical trials have consistently demonstrated that reductions in proteinuria achieved with ACEI or ARB therapy strongly correlate with slower decline in GFR and improved renal outcomes, especially in patients with diabetic kidney disease and non-diabetic CKD with albuminuria. Notably, the magnitude of proteinuria reduction has been shown to be an independent predictor of long-term renal protection.

**3.7 Clinical Implications and Guideline Recommendations**

Given the strong association between proteinuria, RAAS activation, and CKD progression, current clinical guidelines recommend ACEIs or ARBs as first-line therapy for patients with CKD and albuminuria, irrespective of diabetes status. These agents are particularly indicated in patients with moderate to severe proteinuria, where their renoprotective benefits are most pronounced.

Although intensified RAAS blockade using combined ACEI and ARB therapy was initially proposed to achieve greater reductions in proteinuria, large clinical trials have raised safety concerns, including increased risk of hyperkalemia, hypotension, and acute kidney injury. Consequently, dual RAAS blockade is not routinely recommended, and therapy should be individualized with careful monitoring.

**4. Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Chronic Kidney Disease**

The renin angiotensin aldosterone system (RAAS) plays a central role in the regulation of blood pressure, intraglomerular hemodynamics, sodium balance, and renal structural integrity. Pharmacological interruption of RAAS using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) forms the cornerstone of therapy for hypertension, heart failure, and chronic kidney disease (CKD), particularly in patients with proteinuria.

Both ACEIs and ARBs exert their therapeutic benefits by attenuating the deleterious effects of angiotensin II, including vasoconstriction, sodium retention, inflammation, oxidative stress, and fibrosis. Importantly, their renoprotective effects extend beyond systemic blood pressure reduction.

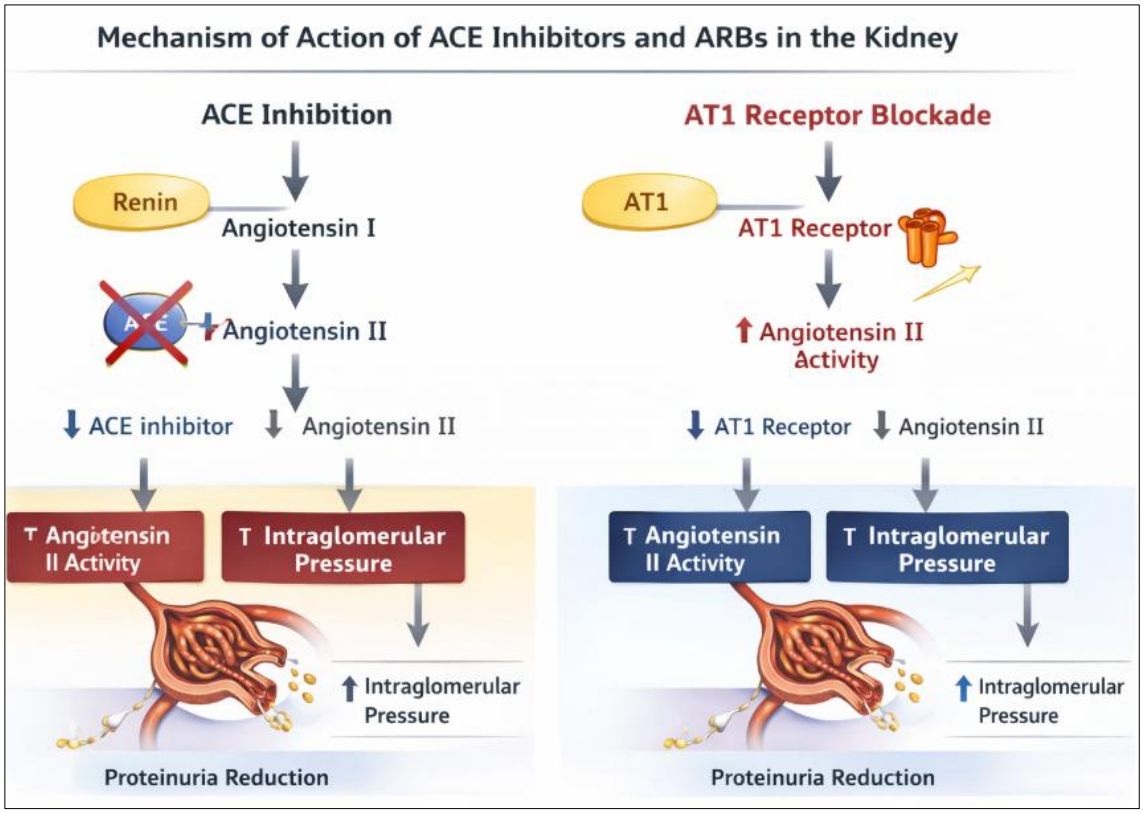


**Fig 2:** MOA of ACEIs and ARBs

### 4.1 Angiotensin-Converting Enzyme Inhibitors

#### 4.1.1 Mechanism of Action

ACE inhibitors block the conversion of angiotensin I to angiotensin II, resulting in reduced angiotensin II mediated vasoconstriction and aldosterone secretion. In addition, ACEIs inhibit the degradation of bradykinin, a potent vasodilator, which contributes to improved endothelial function and enhanced renal blood flow.

By preferentially dilating the efferent arteriole, ACEIs reduce intraglomerular pressure, thereby decreasing mechanical stress on the glomerular filtration barrier. This mechanism is particularly beneficial in proteinuria CKD.

#### 4.1.2 Renoprotective Effects

Beyond their antihypertensive properties, ACEIs demonstrate multiple non-hemodynamic renoprotective effects. These include restoration of glomerular size and charge selectivity, reduction of proteinuria independent of blood pressure lowering, and suppression of pro-inflammatory and pro-fibrotic cytokines such as transforming growth factor β (TGF-β). Through these mechanisms, ACEIs slow the progression of glomerulosclerosis and tubulointerstitial fibrosis.

#### 4.1.3 Common ACE Inhibitors

Commonly prescribed ACE inhibitors include captopril, enalapril (and enalaprilat), lisinopril, ramipril, benazepril, fosinopril, perindopril, quinapril, trandolapril, and moexipril.

### 4.2 Angiotensin Receptor Blockers

#### 4.2.1 Mechanism of Action

Angiotensin receptor blockers selectively inhibit the angiotensin II type 1 (AT1) receptor, thereby preventing angiotensin II from exerting its harmful effects on vasoconstriction, aldosterone release, inflammation, oxidative stress, and fibrosis. Unlike ACEIs, ARBs do not interfere with bradykinin metabolism and are therefore associated with a lower incidence of adverse effects such as cough and angioedema.

#### 4.2.2 Renal and Cardiovascular Benefits

ARBs effectively reduce intraglomerular pressure through efferent arteriolar dilation and significantly lower proteinuria. They also demonstrate anti-inflammatory and antifibrotic effects within the kidney, contributing to preservation of nephron function. In addition, ARBs reduce cardiovascular morbidity and mortality, including the risk of myocardial infarction and stroke, which is particularly relevant in CKD patients who are at high cardiovascular risk.

#### 4.2.3 Common ARBs

Frequently used ARBs include losartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan, and azilsartan [10, 11].

### 4.3 Role of ACEIs and ARBs in Hypertension Associated with CKD

Hypertension is both a cause and a consequence of CKD and is a major modifiable risk factor for disease progression. Activation of RAAS contributes to volume expansion, increased systemic vascular resistance, and intraglomerular hypertension. Multiple clinical trials have demonstrated that strict blood pressure control significantly slows the progression of CKD.

ACEIs and ARBs are particularly advantageous in CKD because they lower systemic blood pressure while simultaneously reducing intraglomerular pressure. This dual action distinguishes them from other antihypertensive classes and explains their superior renoprotective effects in proteinuria CKD.

**Table 2:** Mechanisms of Renoprotection by ACE Inhibitors and ARBs

| Mechanism | ACE Inhibitors | ARBs |
|---|---|---|
| Angiotensin II suppression | ✓ (via ACE inhibition) | ✓ (via AT1 receptor blockade) |
| Efferent arteriolar dilation | ✓ | ✓ |
| Reduction in intraglomerular pressure | ✓ | ✓ |
| Proteinuria reduction | ✓ | ✓ |
| Bradykinin preservation | ✓ | ✗ |
| Anti-fibrotic effects | ✓ | ✓ |
| Anti-inflammatory effects | ✓ | ✓ |

### 4.4 Antihypertensive Efficacy of ACEIs and ARBs

Meta-analyses of randomized, double-blind, placebo-controlled trials involving thiazide diuretics, beta-blockers, ACEIs, ARBs, and calcium channel blockers have demonstrated that all major antihypertensive classes produce comparable reductions in blood pressure at standard doses. Average reductions of approximately 9 mmHg systolic and 5 mmHg diastolic have been observed.

Long-term studies indicate that ACEIs and ARBs provide similar blood pressure lowering efficacy. Combination therapy with ACEIs and ARBs produces only modest additional reductions in blood pressure, generally in the range of 3-5 mmHg, with minimal benefit in patients with chronic renal failure and increased risk of adverse events. As a result, routine dual RAAS blockade is not recommended.

**Table 3:** Adverse Effects and Monitoring of ACEIs and ARBs

| Adverse Effect | Clinical Significance | Monitoring |
|---|---|---|
| Rise in serum creatinine | Acceptable up to 30% increase | Baseline and 2–4 weeks |
| Hyperkalemia | Potentially life-threatening | Serum potassium |
| Hypotension | Especially in volume depletion | Blood pressure |
| Cough | ACEI-specific | Clinical assessment |

**4.5 Safety and Adverse Effects**

The most clinically significant adverse effects of ACEIs and ARBs include hyperkalemia and increases in serum creatinine. A mild rise in serum creatinine is expected due to reduced intraglomerular pressure; however, an increase exceeding 30% within four weeks of therapy initiation warrants discontinuation of the drug and evaluation for renal artery stenosis, volume depletion, or other underlying pathology.

**5.1 Emerging Therapies for Proteinuria Reduction**

In addition to RAAS blockade, newer pharmacologic agents have demonstrated antiproteinuric effects. Sodium glucose cotransporter-2 (SGLT2) inhibitors significantly reduce proteinuria and slow CKD progression in both diabetic and non-diabetic patients. Mineralocorticoid receptor antagonists further lower proteinuria in diabetic kidney disease, although the risk of hyperkalemia limits their use. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have also shown promise in reducing albuminuria and preserving renal function in patients with type 2 diabetes mellitus.

**6.1 Renoprotective Benefits of RAAS Blockade beyond Blood Pressure Reduction**

While blood pressure (BP) reduction is a key determinant of slowing chronic kidney disease (CKD) progression, substantial evidence indicates that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) provide renoprotective effects that extend beyond their antihypertensive action. These benefits arise from their ability to modulate intrarenal hemodynamics and suppress inflammatory and fibrotic pathways mediated by the renin angiotensin aldosterone system (RAAS).

**7.1 Limitations of ACE Inhibition and the Concept of Angiotensin II Escape**

Despite the effectiveness of ACEIs in suppressing RAAS activity, complete inhibition of angiotensin II (Ang II) generation is not achieved in many patients. A phenomenon termed “Ang II escape” has been described, wherein Ang II levels return to or exceed baseline values during chronic ACEI therapy. This occurs due to the activation of alternative, non-ACE enzymatic pathways such as chymase, cathepsin G, and tissue plasminogen activator that contribute to Ang II synthesis, particularly in the setting of established organ damage.

Furthermore, ACE inhibition has a limited effect on local (intrarenal) Ang II production, which is increasingly recognized as a major driver of progressive renal injury. Persistent intrarenal Ang II activity sustains efferent arteriolar vasoconstriction, glomerular hypertension, inflammation, and fibrosis, thereby diminishing the full renoprotective potential of ACEIs.

**8.1 ARBs and Selective AT1 Receptor Blockade**

In contrast to ACEIs, ARBs directly and selectively block the angiotensin II type 1 (AT1) receptor, preventing Ang II from exerting its deleterious hemodynamic and cellular effects regardless of the pathway by which Ang II is generated. As a result, Ang II escape does not limit ARB efficacy, and AT1 receptor blockade provides more complete inhibition of Ang II mediated vasoconstriction, sodium retention, oxidative stress, and fibrotic signalling at both systemic and local tissue levels.

However, AT1 receptor blockade leads to a compensatory neurohumoral feedback response characterized by increased circulating and intrarenal Ang II levels. This excess Ang II may bind to unblocked angiotensin receptors, including AT2, AT3, and AT4. While AT3 and AT4 receptor functions remain poorly understood, activation of the AT2 receptor has been associated with vasodilation and antiproliferative effects in some experimental models. Conversely, AT2 stimulation has also been linked to potentially unfavourable outcomes, including apoptosis, pro-inflammatory signalling, and chemokine induction, raising concerns about the long-term implications of unopposed AT2 activation.

**8.2 Rationale and Limitations of Combination Therapy**

Based on these mechanistic considerations, combined ACEI and ARB therapy was initially proposed as a strategy to achieve more complete RAAS blockade. This approach theoretically addresses Ang II escape, enhances suppression of intrarenal RAAS, and allows beneficial AT2 receptor stimulation while limiting AT1-mediated injury. Early studies demonstrated greater reductions in proteinuria with combination therapy compared with monotherapy.

However, large clinical trials subsequently revealed that these potential benefits were offset by increased risks of adverse events, including hyperkalemia, hypotension, and acute kidney injury. Consequently, despite strong mechanistic rationale, routine dual RAAS blockade is not recommended in clinical practice.

**9.1 Reno-protective Effects Independent of Blood Pressure Lowering**

Extensive experimental and clinical evidence supports the concept that ACEIs and ARBs confer renoprotection beyond their capacity to lower BP. These BP-independent benefits are particularly evident in patients with proteinuria CKD and include:

1. Reduction in proteinuria independent of systemic BP changes, reflecting decreased intraglomerular pressure and stabilization of the glomerular filtration barrier
2. Preservation of endothelial function, improving renal microvascular integrity
3. Attenuation of oxidative stress and inflammatory mediators, limiting tubulointerstitial injury
4. Suppression of profibrotic pathways, particularly those mediated by transforming growth factor-β
5. Slowing of glomerular filtration rate (GFR) decline, delaying progression to end-stage renal disease

Notably, the magnitude of proteinuria reduction achieved with ACEI or ARB therapy has been shown to be a strong predictor of long-term renal outcomes, independent of BP control [15, 16].

**9.2 Clinical Implications**

The renoprotective efficacy of ACEIs and ARBs reflects their dual capacity to control systemic hypertension and directly modulate intrarenal pathophysiological processes. While limitations such as Ang II escape and compensatory receptor activation exist, RAAS blockade remains a cornerstone of CKD management. Current therapeutic strategies favor optimized monotherapy with careful monitoring, complemented by emerging agents such as SGLT2 inhibitors, rather than aggressive dual RAAS inhibition.

**10.1 Evidence from Major Clinical Trials Supporting Renoprotection with ACEIs and ARBs**

Large randomized controlled trials, including RENAAL, IDNT, IRMA-2, REIN, and AASK, have provided robust evidence that blockade of the renin angiotensin aldosterone system (RAAS) using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) significantly reduces the risk of doubling of serum creatinine (DSC), progression to end-stage renal disease (ESRD), and rate of decline in renal function, particularly in patients with diabetic nephropathy and those with significant albuminuria. These benefits have been consistently observed to extend beyond blood pressure (BP) lowering alone.

**10.2 Experimental and Clinical Evidence of Endothelial and Anti-Inflammatory Effects**

Experimental studies in animal models have demonstrated that ACEIs and ARBs improve and restore endothelial function and reduce atherosclerotic burden. Becker *et al*. showed that ramipril preserved acetylcholine-mediated vasodilation in rabbits fed a highly atherogenic diet compared with controls. Similarly, Clozel and colleagues demonstrated that captopril reduced atherosclerotic lesion formation in normotensive, hyperlipidaemic rabbits more effectively than β-blockers or calcium channel blockers. In non-human primates, olmesartan significantly decreased atherosclerotic plaque formation.

Human studies corroborate these findings. In the Val-MARC trial, valsartan reduced high-sensitivity C-reactive protein (hsCRP) independently of BP reduction when compared with valsartan combined with hydrochlorothiazide. Olmesartan has been shown to reduce markers of vascular microinflammation, including hsCRP, tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). Additional studies demonstrated reductions in intrarenal vascular resistance, improved renal perfusion, and decreased levels of oxidative stress markers such as plasma 8-isoprostane. Renke *et al*. reported that combined high-dose telmisartan and cilazapril did not further reduce proteinuria but significantly lowered urinary 15-F2t-isoprostane, suggesting an additive antioxidant effect.

**10.3 Effects on Proteinuria**

Proteinuria reduction is a key mechanism by which ACEIs and ARBs exert renoprotection. A meta-analysis by Kunz *et al*. encompassing 49 randomized trials and over 6,000 patients demonstrated that ARBs significantly reduce proteinuria across a broad spectrum of patients, regardless of baseline proteinuria, diabetic status, or comparator therapy. The antiproteinuric effects of ARBs were comparable to those of ACEIs and superior to calcium channel blockers, while combination therapy produced greater proteinuria reduction though with limited safety data.

Several landmark trials reinforce these findings. In the MARVAL study, valsartan reduced urinary albumin excretion more effectively than amlodipine despite equivalent BP reduction, including in normotensive patients with type 2 diabetes mellitus. The LIFE sub study demonstrated greater albuminuria reduction with losartan compared with atenolol. In MICRO-HOPE, ramipril significantly lowered the albumin-to-creatinine ratio versus placebo. The BENEDICT trial showed that trandolapril reduced the incidence of microalbuminuria, whereas verapamil had no independent effect. In IRMA-2, irbesartan significantly reduced progression to overt nephropathy and increased regression to normal albuminuria in a dose-dependent manner, independently of BP [17].

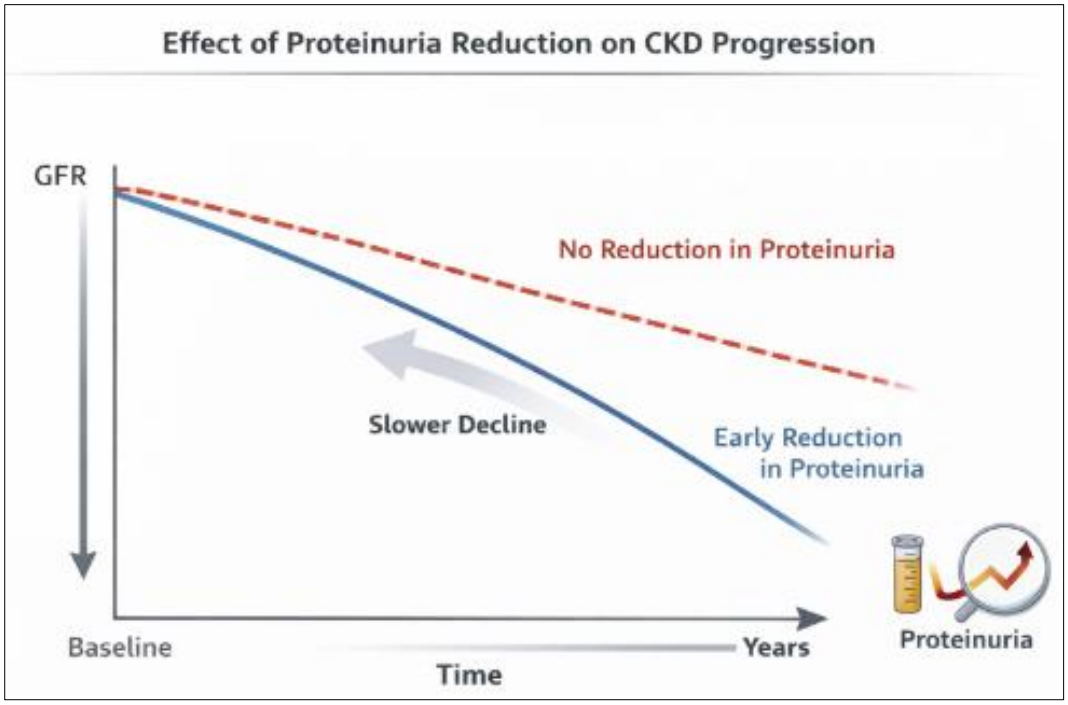


**Fig 3:** Effects on Proteinuria Reduction

**10.4 Preservation of Renal Function and Long-Term Outcomes**

Multiple studies indicate that early changes in proteinuria predict long-term renal outcomes. In RENAAL, reductions in albuminuria at six months were directly proportional to the degree of renal protection, and residual albuminuria on therapy was a strong predictor of ESRD. In IDNT, each halving of proteinuria during the first year reduced the risk of kidney failure by more than 50%, with irbesartan providing greater protection than amlodipine for the same BP change. Similarly, in AASK, early proteinuria reduction predicted slower GFR decline even in patients with baseline urinary protein <300 mg/day.

**11 ACEIs and ARBs in Diabetic and Non-Diabetic CKD**

**11.1 Diabetic Nephropathy**

In both type 1 and type 2 diabetes, ACEIs and ARBs are established first-line therapies for patients with microalbuminuria or overt nephropathy. Trials such as the Captopril Trial, IRMA-2, IDNT, and RENAAL consistently demonstrated delayed progression to ESRD and preservation of renal function, effects largely independent of BP control. Meta-analyses confirm significant reductions in DSC and ESRD, although effects on all-cause mortality remain inconclusive.

**11.2 Non-Diabetic CKD**

In non-diabetic proteinuria CKD, ACEIs and ARBs slow disease progression more effectively than other antihypertensive agents, particularly in patients with higher baseline proteinuria. Trials such as AIPRI, REIN, and AASK demonstrated significant reductions in GFR decline, DSC, and ESRD with ACEI therapy compared to placebo or other antihypertensive classes at equivalent BP levels. In contrast, evidence supporting their superiority in non-proteinuria CKD is limited, with benefits comparable to other antihypertensive agents.

**11.3 Conflicting Evidence and Ongoing Controversies**

Despite strong trial data in high-risk proteinuria populations, some large general-population studies and meta-analyses have failed to demonstrate additional renoprotective benefits beyond BP lowering. Trials such as ALLHAT and TRANSCEND, which included patients with low baseline renal risk and limited proteinuria data, did not show significant renal benefit. Meta-analyses by Casas *et al*. questioned whether ACEIs and ARBs provide added renoprotection in diabetes beyond BP reduction alone.

These discrepancies may be explained by the low incidence of renal endpoints in low-risk populations and the prolonged time required for ESRD to develop. Observational studies, including analyses by Suissa *et al*., have also raised concerns regarding rising ESRD incidence despite increased ACEI/ARB use, although confounding by indication remains likely. Importantly, major trials demonstrating renoprotection did not show parallel reductions in cardiovascular or all-cause mortality, an unexpected finding given the high cardiovascular risk in CKD populations [18].

**11.4 Dual Blockade of the RAAS with ACE Inhibitors and ARBs: What's New**

Dual blockade of the renin angiotensin aldosterone system (RAAS) using an angiotensin-converting enzyme inhibitor

(ACEI) in combination with an angiotensin receptor blocker (ARB) was proposed to overcome incomplete RAAS suppression, commonly referred to as "angiotensin II escape," observed during ACEI monotherapy. By targeting RAAS at two distinct points, this strategy theoretically offers more complete inhibition of angiotensin II mediated hemodynamic and non-hemodynamic renal injury. Early studies demonstrated that combination therapy achieved greater reductions in blood pressure and proteinuria compared with monotherapy, supporting its potential renoprotective role.

The CALM (Candesartan and Lisinopril in Microalbuminuria) study was among the first to show that combined ACEI ARB therapy produced a greater reduction in systolic blood pressure and an additional 50% decrease in albuminuria compared with either agent alone, albeit with slightly higher serum creatinine and potassium levels. However, the subsequent CALM II trial, which employed high-dose lisinopril monotherapy, found no significant differences in blood pressure or urinary albumin excretion compared with combination therapy, suggesting that maximal RAAS inhibition may be achievable with optimized monotherapy. Several meta-analyses, including those by Doulton and MacKinnon, confirmed that dual RAAS blockade consistently reduced proteinuria by approximately 30 40% more than monotherapy in both diabetic and non-diabetic CKD, but this benefit was accompanied by a modest yet significant increase in hyperkalemia and no meaningful improvement in glomerular filtration rate (GFR).

Further analyses reinforced these findings. A 2008 pooled analysis reported additional reductions in proteinuria with combination therapy but noted higher treatment discontinuation rates. In patients with primary glomerulonephritis, dual therapy resulted in greater proteinuria reduction and blood pressure lowering without significant effects on GFR, but with increased potassium levels. The IMPROVE trial failed to demonstrate additional albuminuria reduction with combination therapy despite slightly greater blood pressure lowering, although subgroup analyses suggested a non-significant trend toward benefit in patients with overt nephropathy. In contrast, the VALERIA trial showed that combination therapy reduced microalbuminuria more effectively than maximal-dose monotherapy, without differences in blood pressure, but with a higher incidence of hypotension.

The ONTARGET trial provided the most influential and cautionary data regarding dual RAAS blockade. Although combination therapy resulted in slightly greater reductions in blood pressure and albuminuria, it did not improve primary cardiovascular or renal outcomes and was associated with significantly higher rates of hypotension, hyperkalemia, and acute kidney injury. Importantly, renal sub-analyses demonstrated no benefit even among patients with higher renal risk, while outcomes tended to be worse in low-risk populations. Although ONTARGET was not specifically powered for renal endpoints and included patients with high cardiovascular but relatively low renal risk, its findings substantially shifted clinical practice away from routine combination therapy.

Ongoing and terminated trials, including VA NEPHRON-D, VALID, SDBRAS, and HALT-PKD, have further highlighted safety concerns, particularly in patients with diabetic nephropathy or advanced CKD. VA NEPHRON-D, in particular, was terminated early due to excess adverse renal events, reinforcing the unfavourable risk benefit profile of dual blockade.

From a safety perspective, ACEIs and ARB especially when combined are associated with hyperkalemia, rises in serum creatinine, and hypotension. A creatinine increase of up to 30% after initiation is generally acceptable and reflects reduced intraglomerular pressure; however, larger increases necessitate dose adjustment or discontinuation. Close monitoring of renal function and serum potassium is essential, particularly in elderly patients, those with advanced CKD, or during states of reduced renal perfusion such as dehydration or major surgery.

Current clinical guidelines recommend ACEIs or ARBs as first-line therapy in patients with diabetic CKD and albuminuria, as well as non-diabetic proteinuria CKD. In non-proteinuria CKD, these agents may be used but do not confer clear superiority over other antihypertensive classes. Routine combination ACEI ARB therapy is not recommended due to lack of proven benefit on hard renal outcomes and increased safety risks. Until further evidence emerges from carefully selected high-risk populations, dual RAAS blockade should be avoided in general practice and, if considered, used with extreme caution and rigorous monitoring [19-21].

**Table 4:** Key Clinical Trials and Evidence on Dual RAAS Blockade (ACEI + ARB)

| Trial (Year) | Population | Intervention | Comparator | Key Renal Outcomes | BP-Independent Renoprotection |
|---|---|---|---|---|---|
| Captopril Trial | Type 1 DM with nephropathy | Captopril (ACEI) | Placebo | ↓ Doubling of sr creatinine, ↓ progression to ESRD | Yes |
| RENAAL | Type 2 DM with nephropathy | Losartan (ARB) | Placebo + conventional therapy | ↓ Risk of ESRD, ↓ doubling of sr creatinine, ↓ proteinuria | Yes |
| IDNT | Type 2 DM with nephropathy | Irbesartan (ARB) | Amlodipine or placebo | ↓ ESRD, ↓ doubling of sr creatinine; | Yes |
| IRMA-2 | Type 2 DM with microalbuminuria | Irbesartan (300 mg) | Placebo | ↓ Progression to overt nephropathy; ↑ normoalbuminuria | Yes |
| MICRO-HOPE | DM with CV risk | Ramipril (ACEI) | Placebo | ↓ Albumin/creatinine ratio; ↓ nephropathy progression | Partly |
| BENEDICT | Type 2 DM, normoalbuminuric | Trandolapril (ACEI) | Conventional therapy or verapamil | ↓ Incidence of microalbuminuria | Yes |

| | | | | | |
|---|---|---|---|---|---|
| MARVAL | Type 2 DM with microalbuminuria | Valsartan (ARB) | Amlodipine | Greater ↓ UAER despite similar BP reduction | Yes |
| LIFE (Sub study) | Hypertensive patients | Losartan (ARB) | Atenolol | Greater ↓ albuminuria | Yes |
| AIPRI | CKD (diabetic & non-diabetic) | Benazepril (ACEI) | Placebo | ↓ Doubling of creatinine, ↓ ESRD; greatest benefit with proteinuria >1 g/day | Yes |
| REIN | Non-diabetic proteinuria CKD | Ramipril (ACEI) | Placebo + standard therapy | ↓ GFR decline; ↓ ESRD and DSC | Yes |
| REIN-2 | Non-diabetic CKD | Ramipril + felodipine | Ramipril alone | No additional renal benefit with further BP lowering | |
| AASK | Hypertensive nephrosclerosis (African Americans) | Ramipril (ACEI) | Metoprolol or amlodipine | Slower GFR decline, especially with proteinuria | Yes |
| VAL-MARC | Hypertension | Valsartan | Valsartan + HCTZ | ↓ hsCRP independent of BP lowering | Yes |
| ALLHAT | Hypertension, low renal risk | ACEI / CCB / Diuretic | Comparative arms | No clear renal benefit without proteinuria | No |
| TRANSCEND | CV disease or diabetes, low renal risk | Telmisartan (ARB) | Placebo | No significant renal outcome benefit | No |

## 12. CONCLUSION

Chronic kidney disease is a major global health problem with high morbidity and mortality. Activation of the renin angiotensin aldosterone system plays a key role in CKD progression by promoting intraglomerular hypertension, proteinuria, inflammation, and fibrosis. Targeting this pathway remains central to strategies aimed at slowing renal function decline.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers provide proven renoprotective benefits, particularly in diabetic and non-diabetic proteinuria CKD. Their effects extend beyond blood pressure reduction to include lowering proteinuria, preserving glomerular structure, and attenuating inflammatory and fibrotic processes. Clinical trials consistently demonstrate that reductions in albuminuria are closely associated with improved long-term renal outcomes.

Although dual RAAS blockade with ACEI ARB combination therapy results in greater proteinuria reduction, large trials have shown no additional benefit in hard renal endpoints and a higher risk of adverse events such as hyperkalemia, hypotension, and acute kidney injury. Therefore, routine combination therapy is not recommended.

In conclusion, ACEIs and ARBs remain first-line therapy in proteinuria CKD, while their use in non-proteinuria disease should be guided by blood pressure control. Careful patient selection and monitoring are essential to maximize benefit and minimize harm, and emerging therapies may further enhance renoprotection when used alongside RAAS inhibition.

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