Journal Syifa Sciences and Clinical Research (JSSCR)
Volume 7 Number 3, 2025
Journal Homepage: http://ejurnal.ung.ac.id/index.php/jsscr, E-ISSN: 2656-9612 P-ISSN:2656-8187
DOI : https://doi.org/10.37311/jsscr.v7i3.34331

Clinical Outcomes of Antihypertensive Therapy in Chronic Kidney Disease: A Literature Review

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ABSTRACT

Chronic kidney disease (CKD) carries high cardiovascular risk, and optimal antihypertensive therapy is central to slowing progression. This review synthesized randomized controlled trials from the past 10 years in adults with CKD identified via PubMed, focusing on estimated glomerular filtration rate (eGFR) decline, albumin/protein excretion, and cardiovascular outcomes; study selection followed PRISMA. Renin–angiotensin system inhibitors (RASi) consistently lowered blood pressure, reduced albumin/protein excretion, and attenuated eGFR decline versus comparators. In a crossover trial, azilsartan produced greater reductions in urine protein-to-creatinine ratio and faster blood-pressure control than candesartan. Among calcium channel blockers, benidipine (T/L-type) decreased urinary albumin excretion and improved vascular surrogates versus amlodipine (L-type), suggesting class-specific renal effects. Nifedipine GITS combined with candesartan improved blood-pressure control in high-risk subgroups. Adding spironolactone can further reduce albuminuria but increases hyperkalemia risk; co-administration of patiromer enables RASi/MRA intensification under biochemical monitoring. Overall, RASi remain first-line—particularly in albuminuric CKD—while selected combinations with a dihydropyridine calcium channel blocker or a mineralocorticoid receptor antagonist (with a potassium binder when needed) may augment renoprotection. Treatment should be individualized to CKD stage, comorbidities, and laboratory follow-up.

Keywords:
Antihypertensive therapy; Chronic kidney disease; Renin–angiotensin system; Calcium channel blockers; Proteinuria

Received:	*Accepted:*	*Online:*
2025-07-09	*2025-10-09*	*2025-10-14*

1. Introduction

Chronic Kidney Disease (CKD) is a progressive disease characterised by changes in the structure and function of the kidneys for various causes. It is generally defined as a persistent decrease in *Estimated Glomerular Filtration Rate (*eGFR) (60 mL/min/1.73 m²) or markers of kidney injury, such as proteinuria, haematuria, or abnormalities detected through biopsy or imaging over a period of three months [1],[2]. According to the 2021 *Global Burden of Disease (*GBD) systematic analysis, in 2017 there were approximately 697.5 million cases of CKD across all stages worldwide, with an estimated prevalence of

9.1%. Since 1990, CKD prevalence has risen by 29.3%, accompanied by a 41.5% increase in CKD-related mortality, and it is closely associated with an increased risk of mortality, particularly from cardiovascular events such as heart failure and myocardial infarction [1].

Several risk factors contribute to the progression and burden of CKD. Hypertension remains one of the most important contributors, exacerbating both renal impairment and cardiovascular complications. In addition, diabetes, obesity, and metabolic syndrome are strongly associated with increased CKD incidence, particularly among ageing populations. These comorbidities further complicate disease management and amplify the overall global health burden [3].

Although optimal blood pressure control is recognised as a cornerstone strategy to slow renal function decline and reduce cardiovascular complications in CKD, the choice of antihypertensive regimen remains debated. The blood pressure target for CKD patients is <130/80 mmHg. The first-line antihypertensive therapy used in CKD patients is *Renin Angiotensin System* (RAS) inhibitors, which can also reduce albuminuria [4] . A meta-analysis study states that although RAS inhibitors have increased side effects such as hyperkalaemia, hypotension, and cough in non-dialysis CKD patients, they still provide benefits. ACE inhibitors are superior to ARBs and other antihypertensive drugs in preventing renal, cardiovascular, and mortality deterioration in stage 3-5 CKD patients [4] .

The addition of CCB and diuretic drugs can be used to achieve the patient's blood pressure target [5]. Studies indicate that ACE inhibitor/ARB+CCB combination therapy does not have significant benefits in reducing the risk of stage 5 CKD and cardiovascular mortality, compared to ACE inhibitor/ARB monotherapy [6]. T/L type CCB drugs such as benidipine show better renal and vascular protection potential than L type drugs such as amlodipine [7], while CCB and ARB combinations such as nifedipine-candesartan have been proven to be effective and well tolerated in high-risk patients [8],[9],[10] . However, selecting the optimal combination remains a challenge, especially in patients with low GFR or severe albuminuria.

Given these uncertainties, there is a need to comprehensively evaluate and compare the efficacy and safety of different antihypertensive regimens in patients with CKD. Therefore, this review aims to summarise and critically appraise available evidence regarding antihypertensive therapy in CKD, with a focus on treatment effectiveness, safety profiles, and clinical outcomes.

2. Methods

Study design

This is a narrative review of randomized controlled trials (RCTs) in adults with chronic kidney disease (CKD). Study identification and selection are summarized in a PRISMA-style flow diagram (**Figure 1**). No quantitative meta-analysis was planned; findings were synthesized narratively due to anticipated heterogeneity.

Data source and search strategy

We searched PubMed from 1 January 2015 through 9 October 2025 (English, humans, adults). The reproducible query was: (("Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR ACE inhibitor* OR "Angiotensin Receptor Antagonists"[Mesh] OR

ARB* OR "Calcium Channel Blockers"[Mesh] OR calcium channel blocker* OR "Beta-Blockers"[Mesh] OR beta blocker* OR nifedipine OR amlodipine OR benidipine OR azilsartan OR candesartan OR spironolactone) AND ("Chronic Kidney Disease"[Mesh] OR chronic kidney disease OR CKD OR renal insufficiency) AND (eGFR OR "Glomerular Filtration Rate"[Mesh] OR proteinuria OR albuminuria OR UACR OR UPCR OR "Cardiovascular Diseases"[Mesh])) AND (randomized controlled trial[pt] OR randomized[tiab]). Filters applied: last 10 years, English, humans, adults (≥18 years).

Eligibility criteria

Inclusion: (i) RCTs; (ii) adults with CKD (any non-dialysis stage); (iii) antihypertensive interventions vs active control/usual care; (iv) at least one endpoint on kidney function (eGFR change/slope), albumin/protein excretion (UACR/UPCR/UAE), blood pressure, or cardiovascular outcomes. *Exclusion:* observational/non-randomized studies, reviews/meta-analyses, case reports/series, non-full-text, non-English, pediatric populations, and studies published >10 years before the last search date.

Study selection

Titles/abstracts were screened and potentially eligible full texts were assessed against prespecified criteria. Screening and selection were performed by the author; uncertainties were resolved by revisiting the protocol and outcome definitions. The selection process is shown in **Figure 1**.

Outcomes and definitions

Primary outcomes were kidney endpoints: (i) eGFR slope or change (mL/min/1.73 m^2) and/or (ii) albumin/protein excretion (UACR, UPCR, or UAE). Secondary outcomes included office or ambulatory blood pressure (mmHg) and cardiovascular events (as defined by each trial). Safety outcomes included hyperkalemia, acute kidney injury, symptomatic hypotension, and treatment discontinuation. Outcome definitions and monitoring considerations were aligned with contemporary CKD guidance, particularly KDIGO 2024 [10], and with current hypertension guidelines for BP targets and drug class positioning [11],[12],[13]

Data extraction and synthesis

From each trial we extracted setting, sample size, CKD stage, interventions/comparators (dose, duration), follow-up, and outcomes with effect estimates or p-values when available. Owing to heterogeneity in populations, comparators, and follow-up duration, we conducted a **narrative synthesis** without statistical pooling, organized by drug class and outcome domain.

Risk of bias

A formal tool-based risk-of-bias or certainty assessment was not performed; potential selection, performance, and detection biases were considered qualitatively when interpreting findings.

Reporting

Figure 1 (PRISMA-style flow) summarizes study selection with the following counts: records identified (n = 2,001); after 10-year filter (n = 615); titles/abstracts

screened (n = 615); full-text assessed (n = 82); excluded with reasons (n = 76: non-randomized/observational = 57; no full-text = 4; less relevant = 15); RCTs included (n = 6). Use the "<" symbol (not HTML entities) in figure labels.

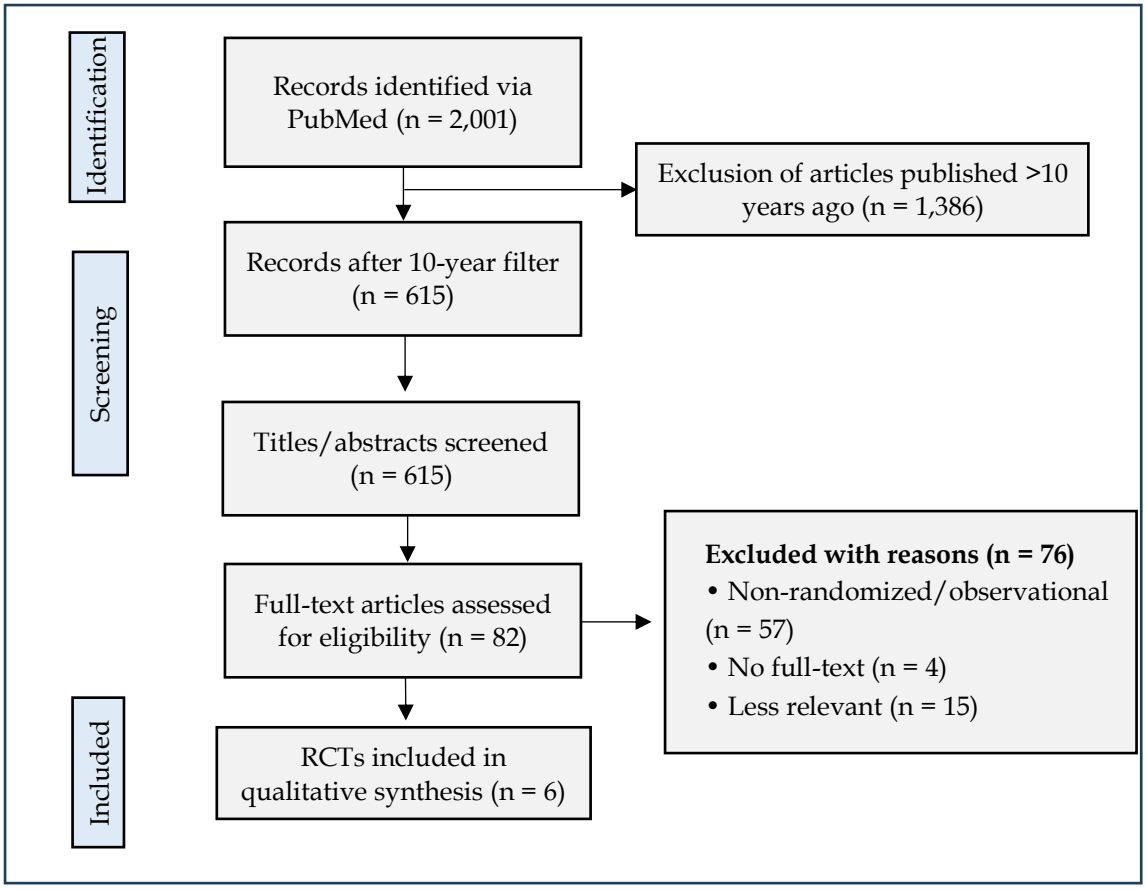

Figure 1. PRISMA-style flow diagram of study selection

3. Results and Discussion

We included six randomized controlled trials in adults with non-dialysis CKD (**Figure 1**). Across studies, sample sizes ranged from small mechanistic trials to moderate multicentre trials. Interventions covered: (i) continuation versus discontinuation of renin–angiotensin system inhibitors (RASi), (ii) head-to-head angiotensin receptor blockers (azilsartan vs candesartan), (iii) calcium channel blocker (CCB) subtypes (benidipine vs amlodipine), (iv) long-acting nifedipine GITS with or without candesartan in high-risk hypertensives with CKD subgroups, and (v) RASi plus spironolactone with or without patiromer. Primary endpoints were kidney outcomes—estimated glomerular filtration rate (eGFR) change/slope and albumin/protein excretion (UACR/UPCR/UAE)—with blood pressure (BP) and prespecified safety events (hyperkalemia, acute kidney injury, symptomatic hypotension, treatment discontinuation) as secondary outcomes.

Guideline context. Hypertension is a major cardiovascular risk factor and a cause of target-organ damage, including the kidneys; lower eGFR and albuminuria track with higher cardiovascular morbidity and mortality. Antihypertensive therapy therefore reduces cardiovascular risk and slows CKD progression [14],[9]. . Key recommendations that frame interpretation of the trial findings are summarized in **Table 1**.

Table 1. Guideline recommendations on antihypertensive therapy in CKD

Institution	Recommendations
European Society of Cardiology 2024, [10]	Lifestyle modification and BP-lowering therapy are recommended if BP ≥130/80 mmHg. The target SBP is 120–129 mmHg for patients with eGFR >30 mL/min/1.73 m², while individualized targets are advised for those with lower eGFR or kidney transplantation. SGLT2 inhibitors are recommended for patients with eGFR >20 mL/min/1.73 m². ACE inhibitors or ARBs are preferred in albuminuria.
American Heart Association 2025, [11]	In adults with CKD (eGFR <60 mL/min/1.73 m² or albuminuria ≥30 mg/g), the treatment goal is SBP <130 mmHg. ACE inhibitors or ARBs, but not both, are recommended in the presence of albuminuria to reduce cardiovascular risk and slow CKD progression.
World Health Organization 2021, [12]	Pharmacological treatment should be started within four weeks of diagnosis, or immediately if BP is severely elevated or if there is evidence of target organ damage. Patients should receive counselling, and laboratory tests and cardiovascular risk assessment should not delay treatment. Drug selection should be individualized: diuretics or CCBs for older adults or patients of African descent, beta-blockers post-myocardial infarction, and ACE inhibitors or ARBs in patients with diabetes, heart failure, or CKD.
European Society of Hypertension (2023), [13]	BP should be monitored in all CKD patients. Treatment is recommended if SBP ≥140 mmHg or

	DBP ≥90 mmHg. The general target is <140/90 mmHg, with a stricter target of <130/80 mmHg in younger, albuminuria, or high-risk patients if tolerated. ACE inhibitors or ARBs at the maximum tolerated dose are preferred in patients with albuminuria.
Kidney Disease Improving Global Outcomes (2024), [15]	ACE inhibitors or ARBs are recommended for CKD patients with albuminuria, regardless of diabetes status. Combination of ACE inhibitors, ARBs, or direct renin inhibitors should be avoided. These agents should be used at the highest tolerated dose, with monitoring of BP, creatinine, and potassium 2–4 weeks after initiation or dose adjustment. Therapy should be continued unless creatinine rises by more than 30%, symptomatic hypotension occurs, or hyperkalaemia cannot be controlled. ACE inhibitors or ARBs may still be used in patients with eGFR <30 mL/min/1.73 m² and are also indicated for hypertension or heart failure.

All guidelines emphasize tight BP control in CKD to reduce cardiovascular risk and slow disease progression, with a general target of <130/80 mmHg (institution-specific nuances apply). ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are consistently recommended as first-line therapy in albuminuric CKD, used at the highest tolerated dose and not in combination. Mechanistically, ACEIs reduce formation of angiotensin II, whereas ARBs block the angiotensin II type-1 receptor; both lower peripheral resistance and BP and provide additional renoprotection in proteinuric CKD [16].

Other antihypertensive classes are important in individualized CKD care. β-blockers reduce BP via cardiac β1-receptor blockade (some agents also vasodilate); CCBs lower BP by reducing calcium influx (dihydropyridines act predominantly on vascular smooth muscle and are preferred for hypertension; non-dihydropyridines have more cardiac effects and drug–drug interactions); thiazide diuretics improve cardiovascular outcomes but lose efficacy when eGFR <30 mL/min/1.73 m², while loop diuretics remain effective in advanced CKD. Combination diuretic therapy may be used with careful electrolyte monitoring [16].

A meta-analysis showed that RASi reduce albuminuria/proteinuria and lower BP more than other classes, whereas dual RAS blockade (ACEI + ARB) increases adverse effects (eGFR decline, hyperkalemia, hypotension). Accordingly, RASi monotherapy remains the preferred foundational strategy in CKD [17].

Table 2. The Effectiveness of Antihypertensive Use in CKD Patients

Country, Author, Year	Population	Intervention & Control	Renal Clinical Outcomes	Cardiovascular Clinical Outcomes
UK, Bhandari *et al.,* 2022 [18]	Stage 4–5 CKD, n=411	ACEI/ARB (continue vs discontinue)	No significant eGFR difference after 3 years (95% CI: -2.5 to 1.0; p=0.42).	There was no difference in cardiovascular events and mortality
Japan, Suehiro *et al.,* 2021 [19]	Hypertension + CKD, n=111	Azilsartan vs Candesartan	Azilsartan reduced proteinuria significantly at both endpoints. UPCR at the first endpoint (-3.8% vs 30.8%; p=0.0004) and the second endpoint (6.1% vs 25.8%; p=0.029).	Azilsartan lowered BP faster and more effectively
Japan, Takayama *et al.,* 2016 [7]	Hypertension + CKD, n=108	Benidipine vs Amlodipine	The use of benidipine showed a significant reduction in AI (85.7± 13.3% to 81.4± 15.2%; p=0.021) and UAE (p=0.0031).	Benidipine demonstrated a significant reduction in the augmentation index (AI), an indicator of arterial stiffness and cardiovascular risk, from 85.7± 13.3% to 81.4± 15.2% (p=0.021).

Multicentre, Mancia *et al.*, 2017 [8]	Hypertension, subgroups CKD/Diabetes Mellitus type 2	Nifedipine GITS ± Candesartan vs Placebo	No specific reports of changes in eGFR. However, blood pressure control was better in patients with eGFR <90 mL/min/1.73 m^2.	No specific reports of changes in eGFR. However, blood pressure control was better in patients with eGFR <90 mL/min/1.73 m^2.
Netherland, Gant *et al.*, 2017 [20]	Non-diabetic CKD, n=33	ARB, ARB+HCT, ACEI	Patients with high aldosterone levels (PAC) tend to have poorer kidney function, as seen in lower CrCl values, both without treatment and when using ARBs or ACE inhibitors.	Elevated aldosterone levels are also associated with higher systolic blood pressure. BP controlled with maximal therapy
Denmark, Marup *et al.*, 2022 [21]	Stage 3–4 CKD, n=140	RASi + Spironolactone ± Patiromer	Addition of patiromer reduced UACR more effectively	-

Continuation vs discontinuation of RAS inhibitors

Discontinuing RASi in advanced, progressive CKD did not produce a clinically meaningful improvement in eGFR over ~3 years; in the multicentre trial by Bhandari *et al.* [18], the between-group difference in eGFR was not significant (95% CI −2.5 to 1.0; p=0.42), and rates of major cardiovascular events, initiation of renal replacement therapy, and all-cause mortality were similar between the discontinuation and continuation groups. Blood pressure and proteinuria rose transiently during the first year after discontinuation and then improved with alternative antihypertensives, supporting individualized decision-making in advanced CKD (see **Table 2**).

ARB head-to-head (azilsartan vs candesartan)

In a short-term crossover RCT in hypertensive CKD, azilsartan 20 mg/day achieved larger and faster reductions in UPCR than candesartan 8 mg/day at both endpoints (−3.8% vs +30.8%; p=0.0004 and +6.1% vs +25.8%; p=0.029), with earlier and greater office BP lowering and a comparable safety profile [19]. These findings support the antiproteinuric potential of azilsartan in proteinuric CKD (see **Table 2**).

CCB subtype comparison (benidipine vs amlodipine)

Compared with amlodipine (L-type), benidipine (T/L-type) significantly reduced UAE (p=0.0031) and improved a vascular surrogate, lowering the augmentation index (AI 85.7 ± 13.3% → 81.4 ± 15.2%; p=0.021) in hypertensive patients with CKD [7]. These data support differential renal effects among CCB subtypes that are not solely explained by BP reduction (see **Table 2**).

DHP-CCB + ARB (nifedipine GITS ± candesartan)

In high-risk hypertensives that included CKD/T2D subgroups, nifedipine GITS with or without candesartan improved BP control—particularly when eGFR was <90 mL/min/1.73 m²—whereas kidney endpoints were inconsistently reported or not prespecified as outcomes [8]. Accordingly, firm conclusions on renoprotection for this combination remain limited (see **Table 2**).

MRA + potassium binder (spironolactone ± patiromer)

In stage 3–4 CKD, adding spironolactone on top of RASi lowered UACR, and co-administration of patiromer allowed treatment intensification with fewer potassium-related interruptions [21]. Biologically, higher aldosterone levels were associated with lower creatinine clearance and higher systolic BP despite maximal therapy, reinforcing the rationale for MRA use in selected patients [20] (see **Table 2**).

Mechanistic context and class effects

Across trials and meta-analyses, ACEIs/ARBs confer renoprotection beyond BP lowering by reducing intraglomerular pressure and albumin/protein excretion. By contrast, L-type CCBs may increase proteinuria via preferential afferent arteriolar dilation, whereas T/N-type CCBs (e.g., benidipine) tend to lower albumin/protein excretion through both hemodynamic and non-hemodynamic mechanisms (aldosterone suppression, podocyte protection) [22], [23] .

Overall synthesis

Taken together, the included trials support RAS inhibition as the foundational therapy for hypertension in albuminuric CKD, with benefits on albumin/protein excretion and eGFR trajectory that extend beyond blood-pressure lowering. To achieve guideline targets (see Table 1), dihydropyridine CCBs are appropriate add-ons for BP control, while T/N-type CCBs (e.g., benidipine) may offer additional renoprotection versus L-type agents in proteinuric disease [7],[22],[23]. For persistent albuminuria or resistant hypertension, MRA add-on can be considered, and a potassium binder

(patiromer) may expand tolerability in patients at risk for hyperkalemia [20], [21]. Consistent with trial and meta-analytic signals, dual RAS blockade (ACEI + ARB) is not recommended due to higher adverse-event rates despite short-term reductions in albuminuria [17]. Overall, therapy should be individualized to CKD stage, albuminuric status, comorbidities, and laboratory safety monitoring, aligning with contemporary guideline frameworks summarized in **Table 1**.

This review is constrained by the small number of eligible RCTs (n = 6) and heterogeneity in populations, comparators, and follow-up durations, which limits precision and generalizability of the synthesis. We conducted a narrative (non-pooled) synthesis and did not perform a formal risk-of-bias or certainty assessment, increasing the chance that unmeasured biases in individual trials could influence inferences. Several studies were short-term and emphasized surrogate endpoints (albuminuria, BP, vascular indices) rather than hard renal or cardiovascular outcomes, and most excluded dialysis populations. Our search was limited to PubMed and English-language articles, so publication and language bias cannot be excluded. These factors should be considered when applying the findings to diverse CKD populations and settings.

4. Conclusion

RAS inhibition remains the foundation of hypertension management in albuminuric CKD; use the highest tolerated dose and avoid dual RAS blockade. Add a dihydropyridine CCB to reach BP targets; T/N-type CCBs (e.g., benidipine) may provide extra renoprotection versus L-type agents. For persistent albuminuria or resistant hypertension, consider an MRA; patiromer can enable use in patients at risk for hyperkalemia. Care should be individualized by CKD stage, albuminuria, and comorbidities, with creatinine and potassium checked 2–4 weeks after initiation or dose changes. Longer, adequately powered RCTs with hard renal/cardiovascular endpoints are needed, including head-to-head T/N-type vs L-type CCBs and azilsartan vs other ARBs at equipotent doses. Trials of RASi + MRA with protocolized potassium management, plus pragmatic and cost-effectiveness studies (including background SGLT2i use), should guide individualized care.

Acknowledgements:

We would like to express our gratitude to the management of the Faculty of Pharmacy, Universitas Mahasaraswati Denpasar.

Conflicts of Interest:

The authors declare that there are no conflicts of interest associated with this research or its publication.

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