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Renal Safety of Long-Term Antihypertensive Therapy: A Systematic Review

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ABSTRACT

Background: Managing hypertension, a major risk factor for chronic kidney disease (CKD), requires long-term antihypertensive medication. However, clinical judgment and medication adherence are impacted by ongoing worries about its renal safety.

Objectives: This study aimed to systematically evaluate and compare the renal safety profiles of antihypertensive drug classes during long-term use (>6 months) in hypertensive patients.

Methods: Following the PRISMA 2020 principles, a systematic review was carried out. A thorough search of PubMed and ScienceDirect from 2015 to April 2025 was conducted ("ACEi OR ARB OR CCB OR Beta Blocker OR Diuretic AND Hypertension AND long-term use AND Renal Function"). A narrative synthesis was carried out in compliance with the Synthesis Without Meta-Analysis (SWiM) guideline due to clinical and methodological heterogeneity.

Results: A total of 7214 studies were retrieved and reviewed. Only five papers were chosen after additional analysis. In comparison to CCBs in advanced chronic kidney disease (CKD), diuretics in combination with renin-angiotensin system inhibitors (RASi) were linked to a decreased incidence of significant adverse renal events (weighted HR 0.87, 95% CI 0.77-0.97). Despite a higher frequency of reversible eGFR drop and hyperkalemia, continuous ACEi/ARB treatment before dialysis initiation significantly decreased post-dialysis mortality (aHR 0.87, 95% CI 0.83-0.92). Compared to amlodipine, ACEi alone reduced eGFR and raised serum levels of potassium and creatinine for at least a year. In patients with resistant hypertension and baseline eGFR ≥30 mL/min/1.73 m², spironolactone successfully reduced blood pressure; however, initial elevations in serum creatinine and potassium needed to be monitored. Since blood pressure was well controlled, there was no discernible difference between ARBs and CCBs regarding the risk for end-stage kidney disease (HR 0.28; CI 0.14-0.58).

Conclusion: Combining RASi with a diuretic provides superior renal protection for CKD patients compared to CCB. Post-dialysis mortality is also decreased by long-term ACEi/ARB usage. Under careful supervision, spirolactone is both safe and effective. Thus, regular use of ACEi/ARB and diuretic-RASi combination therapy is a safe and effective long-term method for maintaining renal function in hypertension.

Keywords: Antihypertensive drugs; eGFR; Long-term use; Renal safety

INTRODUCTION

Due to their long-term nature and frequent need for ongoing medical care, chronic diseases are one of the biggest problems facing the global health system. Approximately 41 million deaths occur annually, making up 74% of all causes of mortality worldwide.[1] The primary cause of chronic kidney disease (CKD) and one of the

major risk factors for cardiovascular disease is hypertension.[2] Podocytes and the glomerular basement membrane are harmed by hypertension because it raises intraglomerular pressure. This can lead to nephrosclerosis, proteinuria, and a lower glomerular filtration rate. Antihypertensive medications, such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), beta blockers (BB), and diuretics, are typically used for an extended period to treat hypertension pharmacologically.[3]

Reduced kidney function is a danger associated with the usage of medications, such as ACEi, ARB, and diuretics.[4] However, a number of studies have demonstrated that long-term use of properly administered antihypertensive medications does not always impact renal function. In fact, by managing the underlying illness, these medications can safeguard kidney function. In individuals with hypertension and chronic renal disease, ACEi and ARB can lower systolic blood pressure by roughly 20 mmHg due to their cardioprotective and renoprotective qualities. Proteinuria has also been shown to decrease in patients with diabetes and chronic renal disease, regardless of blood pressure.[5] Antihypertensive medications can reduce blood pressure for up to four years on average. According to a study by 7, there are no safety concerns when antihypertensive medications are used concurrently for up to 36 months. Furthermore, a lot of people believe that long-term drug use will undoubtedly harm the kidneys. This leads to a lack of drug compliance, which actually affects the attainment of therapeutic goals.

This begs the crucial question of whether long-term medication use in individuals with chronic illnesses inevitably poses a risk of kidney impairment or whether this therapy may have potential benefits that can be maximized. An extensive analysis of the effects of long-term antihypertensive medications on kidney function is required to address this topic, taking into consideration various elements, including the medication's mode of action, the patient's coexisting diseases, and efficient monitoring techniques. Furthermore, susceptible groups, such as the elderly, who naturally experience diminished kidney function as they age, are frequently included among individuals with chronic illnesses. The risk of developing renal disease, characterized by reduced GFR, starts at age 50.[8] Renal cortical volume decreases progressively with age, more significantly after age 50 years.[9] Through a number of mechanisms, comorbidities like diabetes mellitus, obesity, and cardiovascular disease can hasten the development of kidney disorders. For example, hyperglycemia in diabetes mellitus can increase oxidative stress and inflammation, speeding up kidney fibrosis and diabetic nephropathy.[10] Similarly, cardiovascular disease can accelerate nephron destruction due to renal hypoperfusion resulting from congestive heart failure.[11] Obesity increases glomerular pressure, causing renal hypertrophy and the progression of chronic kidney disease.[12,13]

Previous observational studies and clinical trials have examined the effects of antihypertensive medications on the kidney, mainly in the short term or in particular populations such as individuals with diabetes or cardiovascular disease. Nevertheless, the majority of research concentrated on a single medication class or a small combination, making it impossible to provide a thorough picture of the renal safety profile of all major antihypertensive classes over an extended period. Furthermore, research findings are still mixed about whether long-term use improves renal function or has protective effects, particularly in patients with chronic kidney disease. One significant gap in the literature is the absence of a systematic review that specifically compares all antihypertensive classes on long-term (>6 months) renal safety, following PRISMA recommendations. To provide evidence-based clinical recommendations on long-term antihypertensive therapy that is safe for kidney function, this systematic review will incorporate current information and assess the consistency of findings.

METHODS

Study design

The study is a systematic review designed to evaluate the impact of long-term use of antihypertensive drugs on kidney function in patients with hypertension. The review was not registered in a prospective registry. The writing was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.[14]

Eligibility criteria

Study selection was conducted based on title and abstract to exclude irrelevant studies, followed by a full-text review to ensure that studies met the inclusion criteria. Meanwhile, the entire selection process was illustrated using the PRISMA flow diagram. Studies evaluating the effects of long-term antihypertensive drugs on kidney function, including experimental and observational studies as well as articles published in the last 10 years

(2015-2025), were included. Meanwhile, studies that only discuss the acute effects of drugs on the kidneys (<6 months), animal or in vitro studies, do not explicitly report kidney function parameters (GFR, serum creatinine, BUN), are not available in English, involve a non-hypertensive population, and do not explicitly report the long-term use of antihypertensive drugs were excluded.

Information Sources

Relevant studies were identified through an extensive search of two electronic databases (PubMed and ScienceDirect) published between 2015 and 2025.

Search strategy

We conducted a systematic review of English-language articles examining the impact of long-term use of antihypertensive drugs on renal function in patients with hypertension. The search was performed using relevant keywords such as "ACEi OR ARB OR CCB OR Beta Blocker OR Diuretic AND Hypertension AND long-term use AND Renal Function".

Selection Process

Four reviewers (T.A.A, Y.L.d.C, N.B, L.P) independently screened titles/abstracts and assessed full-text articles. Discrepancies were resolved by discussion or consultation with (A.E.N and Z.I).

Data Items

Studies were grouped according to two primary dimensions: (1) antihypertensive drug class (such as ACE inhibitors, ARBs, calcium channel blockers, diuretics, and mineralocorticoid receptor antagonists), and (2) renal safety outcomes. This grouping facilitated comparative analysis within and across different therapeutic classes.

Data Extraction

After relevant studies were selected, data were extracted covering study identity (title, authors, publication year), study design, type of antihypertensive drug, medication duration, population characteristics, measured kidney function parameters, and the main outcome—the effect of long-term antihypertensive drug use on kidney function.

Synthesis Methods

A meta-analysis was not possible due to variation in study designs, demographics, and outcome measures. Consequently, results were narratively synthesized in accordance with the Synthesis Without Meta-Analysis (SWIM) standard.[15] Three complementary methods were used to conduct a narrative synthesis: (1) a tabular synthesis that presented study characteristics and outcomes in **Table I**; (2) a thematic analysis arranged by drug class effects on renal outcomes; and (3) comparative descriptions that highlighted key findings, effects, and safety on renal function. The main research question about the renal safety profiles of various antihypertensive classes was addressed by synthesizing the findings.

Study Risk of Bias Assessment

The risk of bias assessment was not performed due to the narrative nature of this synthesis, focusing on safety profiles across heterogeneous study designs.

Effect Measures

Outcomes were standardized to allow comparison across studies. The outcomes were renal safety, such as estimated glomerular filtration rate (eGFR), serum creatinine, hyperkalemia, acute kidney injury, Blood Urea Nitrogen (BUN), end-stage kidney disease (ESKD), and major adverse kidney events (MAKE).

Data Analysis

The results of eligible studies will be synthesized descriptively and presented in summary tables that describe study characteristics, type of antihypertensive drug, medication duration, and main outcomes on renal function.

RESULTS AND DISCUSSION

The PRISMA flow diagram (**Figure 1**) illustrates the process of research identification and selection. As many as 1,238 of the 8,452 items discovered through searches of the PubMed and ScienceDirect databases were eliminated as duplicates. Of the 7,214 articles that survived the title and abstract screening, 8 were fully examined. Three articles were excluded for noncompliance with the inclusion criteria: specifically, two failed to provide the medication duration, and one was published in a language other than English. Ultimately, five studies were included in the narrative analysis since they satisfied all inclusion criteria. As shown in **Table I**, study settings varied depending on clinical circumstances and geographic region. These comprised multinational trial participants, Hospital del Mar in Barcelona, Japanese patients with hypertension, and US veteran populations. When assessing the generalizability of the findings, the variety of settings was taken into account.

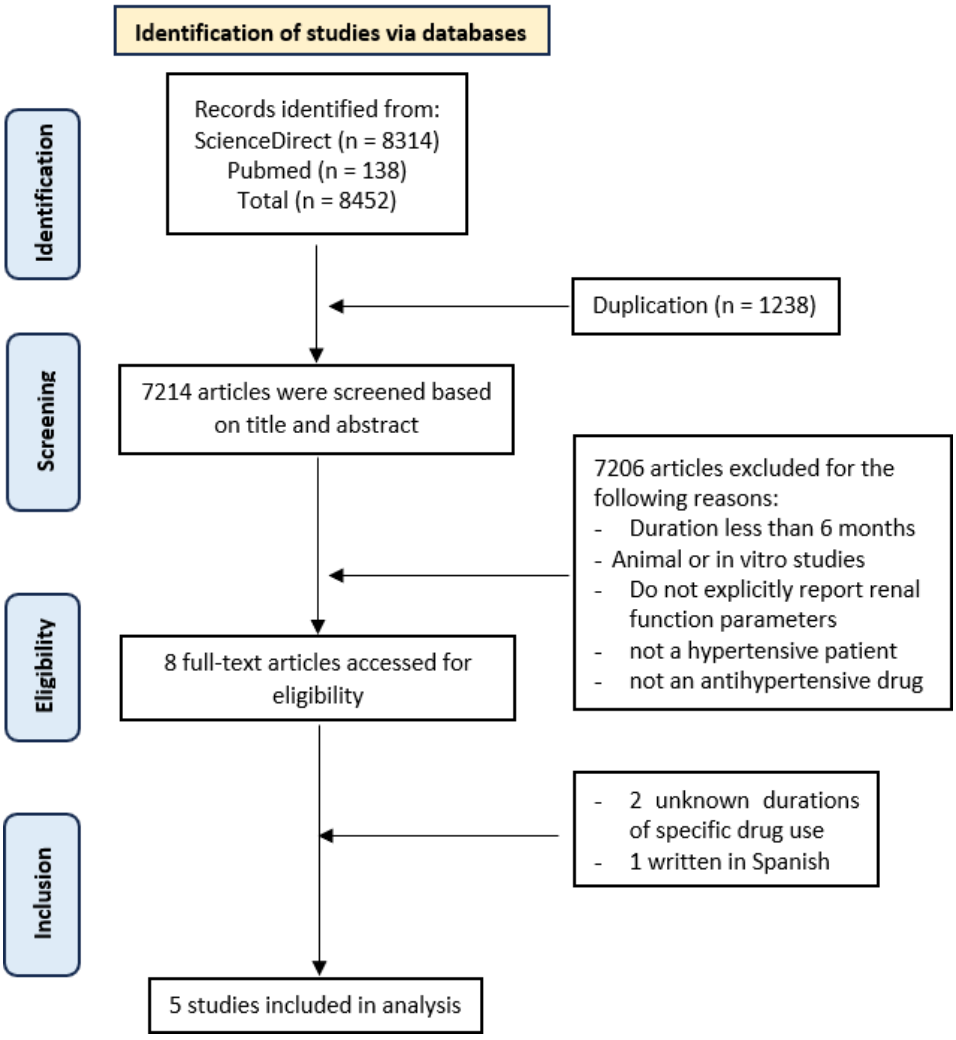

Figure 1. PRISMA diagram of the Retrieved Study

In the human body, the kidneys play a crucial role in blood filtration, fluid and electrolyte balance regulation, blood pressure regulation via the renin-angiotensin-aldosterone system, and excretion of medications and metabolic waste products.[21] In the general adult population, chronic kidney disease is a degenerative condition with no known cure and significant rates of morbidity and mortality, particularly in those with diabetes and hypertension. Both pharmaceutical treatments targeting particular kidney illnesses and chronic renal disease, as well as non-pharmacological measures (such as dietary and lifestyle modifications), can be used to preserve kidney function and improve outcomes. In addition to improving acid-base homeostasis and the gut flora, a plant-based, low-protein, low-salt diet may help lower glomerular hyperfiltration and prolong kidney function.[22]

Table I. Characteristics of long-term antihypertensive drug use studies

Author	Population	Design Study	Outcome
(Gosmanova et al., 2020)[16]	Between 2007 and 2014, 34,676 US veterans who had been exposed to ACEs or ARBs during the three-year predialysis period—and 10,690 who had not—switched to dialysis.	Retrospective cohort	eGFR, AKI, hyperkalemia
(Olsen et al., 2024)[17]	969 researchers registered and monitored 15,245 patients with hypertension.	Randomized clinical trial	End-stage kidney disease (ESKD)
(Nishida et al., 2017a)[18]	Individuals aged 20 years and above with mild to moderate hypertension who have recently used amlodipine or imidapril for at least three months between December 1, 2004, and May 31, 2012. Imidapril was used to treat 4853 patients with hypertension, while amlodipine was used to treat 22,889 patients.	Retrospective cohort	Serum Creatinine, eGFR, Serum Potassium, Serum Sodium, and Blood Urea Nitrogen (BUN)
(Galceran et al., 2020)[19]	Spironolactone was introduced to the antihypertensive regimen for 216 individuals with resistant hypertension (starting dose: 12.5–25 mg daily). Between June 2007 and March 2016, the initial 125 patients were assessed.	Retrospective and prospective cohort	eGFR, Serum Creatinine, and Kalium
(Faucon et al., 2023)[20]	5875 patients in total (mean age 71 years, 64% male, mean eGFR 26 mL/min per 1.73 m2), of whom 3165 began taking diuretics and 2710 CCBs.	A Pragmatic Clinical Trial	Mayor adverse kidney events (MAKE)

Results are reported comprehensively in **Tables II** and **III**. Key patterns emerged: (1) diuretics combined with RASi consistently showed renal protective effects; (2) Use of ACEi/ARBs was linked to lower mortality, but electrolyte monitoring was necessary; (3) spironolactone was effective, along with measurable renal parameter changes. Inconsistencies were noted in ACEi versus CCB comparisons, potentially due to differences in the populations studied.

Table II presents the long-term consequences of antihypertensive medications on renal function. The relationship between patterns of angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) use during a three-year period before dialysis and mortality following dialysis commencement in 45,266 US veterans was assessed by [16]. The results demonstrated a strong correlation between decreased postdialysis mortality and continuous or ≥75% of predialysis time use of ACEi/ARB (adjusted hazard ratio [aHR] 0.91; 95% CI 0.88–0.94). Conversely, there was no discernible benefit from sporadic or less than 50% use. Additionally, the study found that individuals with shorter durations of ACEi/ARB treatment were more likely to experience acute kidney injury (AKI) and hyperkalemia, which may influence the decision to terminate therapy. With the proviso that careful monitoring of renal function and serum potassium levels is required to prevent adverse effects, the authors concluded that sustained use of ACEi/ARB during the predialysis period may provide long-term benefits to survival after dialysis. Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi) are a class of medications that lower blood pressure and protect the kidneys by blocking the renin-angiotensin-aldosterone pathway.[5] Patients using ACEi/ARB had a lower all-cause death rate among those with acute renal failure compared to non-users (log odds ratio (OR) -0.37, 95% confidence interval (CI): −0.42–−0.32, $p < 0.01$). ACEi/ARB users had a decreased risk of recurrent adverse renal events following acute renal failure than non-users (logOR −0.25, 95% CI: −0.33–−0.18, $p < 0.01$). ACEi/ARB users had a greater risk of hyperkalemia compared to non-users (logOR 0.43, 95% CI: 0.27–0.59, $p < 0.01$). Compared to prior ACEi/ARB users who did not continue ACEi/ARB after acute renal failure, patients who continued ACEi/ARB after acute renal failure had a lower risk of dying (logOR −0.36, 95% CI: −0.4–−0.31, $p < 0.01$).[23]

Table II. Effects of Long-Term Antihypertensive Drugs on Kidney Function

Author	Group	Duration	Outcome
(Gosmanova et al., 2020)[16]	ACEi and ARB	36 months	Patients who took ACEi/ARB continuously or for longer periods of time during predialysis had a lower risk of dying after dialysis (ACEi/ARB 50%–74%: aHR 0.96 (95%CI 0.92–0.99); ACEi/ARB ≥ 75%: aHR 0.91 (95%CI 0.88–0.94); Continuous use: aHR 0.87 (95%CI 0.83–0.92). A higher risk of AKI and hyperkalemia was linked to ACEi/ARB usage <50% or stopped. Continuous or ≥75% use was linked to a lower risk of AKI and did not raise the risk of severe hyperkalemia.
(Olsen et al., 2024)[17]	Valsartan (ARB) vs Amlodipine (CCB)	50,4 months	The incidence of ESKD did not significantly differ between valsartan and amlodipine (HR=1.02; p=0.94).
(Nishida et al., 2017a)[18]	Imidapril (ACEi) vs Amlodipine (CCB)	12 months	Compared to amlodipine, imidapril produces a small reduction in renal function (eGFR declines, creatinine increases) and an increase in potassium levels after about 7–12 months of treatment.
(Galceran et al., 2020)[19]	Spironolactone (Antagonis Aldosteron)	12 months	In resistant hypertension patients with initial eGFR ≥30 mL/min/1.73 m², spironolactone significantly reduces blood pressure and is somewhat safe for the kidneys. After three months of use, potassium levels and renal function remain stable.
(Faucon et al., 2023)[20]	Diuretic vs CCB	75,6 months	2558 MAKE happened after an average follow-up of 6.3 years. Diuretic use was linked to a lower risk of MAKE (weighted hazard ratio 0.87 [95% confidence interval: 0.77-0.97]) compared to CCBs. This association held true for individual components (KRT: 0.77 [0.66-0.88], eGFR decline of more than 40%: 0.80 [0.71-0.91], and eGFR below 15 ml/min/1.73 m2: 0.84 [0.74-0.96]).

The double-blind, randomized study VALUE Trial by[17] evaluated the effect of valsartan (ARB) versus amlodipine (CCB) on the incidence of end-stage kidney disease (ESKD) in patients with hypertension and high cardiovascular risk. Of 15,245 patients followed for a mean of 4.2 years, the incidence of ESKD was not significantly different between the valsartan (0.61%) and amlodipine (0.66%) groups (HR 1.02; 95% CI 0.68–1.52; p=0.94). However, achieving a systolic blood pressure <135 mmHg was significantly associated with a reduced risk of ESKD (HR 0.28; 95% CI 0.14–0.58; p<0.001) and a reduced incidence of renal function decline (HR 0.64; 95% CI 0.50–0.83; p<0.001). These findings emphasize that achieving a lower blood pressure target is more important in kidney protection than the type of antihypertensive used.

A study by[18] evaluated and compared the effects of long-term use of imidapril, an angiotensin-converting enzyme inhibitor (ACEI), and amlodipine, a calcium channel blocker (CCB), on kidney function parameters in patients with hypertension in Japan. In this retrospective cohort study, it was found that use of imidapril for 12 months significantly increased serum creatinine and potassium levels and decreased estimated glomerular filtration rate (eGFR). In contrast, in the amlodipine group, no significant changes were found in these kidney parameters. The difference in parameter changes between the two groups also showed that imidapril had a greater impact on kidney function than amlodipine. These results are consistent with the mechanism of action of ACEI, which can decrease GFR through efferent arteriole dilation and increase the risk of hyperkalemia. Although the changes in these laboratory values were statistically significant, they remained within the normal clinical limits. Therefore, although discontinuation or dose adjustment may not be necessary, these results underscore the importance of regular monitoring of renal function and electrolyte levels in patients taking imidapril, especially in the first year of treatment. This study makes an important contribution by using data from

routine clinical practice and applying a robust study design, including propensity score matching and multivariate regression. However, it still has some limitations, such as a relatively small sample size and the unavailability of albuminuria data.

Similar studies conducted by Endo et al. (2023)[24] compared renal function and other laboratory and clinical parameters between the ACEi-treated and CCB-treated groups for 2 years. Antihypertensive treatment effectively reduced blood pressure from 222 ± 28/142 ± 21 to 2 141 ± 18/87 ± 14 mmHg in 2 weeks and eGFR was gradually restored from 33.2 ± 23.3 to 40.4 ± 22.5 mL/min/1.73 m2 in 1 year, even in patients with moderate to severe eGFR decline (<30 mL/min/1.73 m²) at hospital admission. In contrast, CCBs modestly restored eGFR during the observation period. In addition, the probability of renal survival worsened in patients who showed a decrease in eGFR (<15 mL/min/1.73 m2) or massive proteinuria (urine protein/creatinine ≥ 3.5 g/gCr) on admission. Early use of ACEi was associated with good 2-year renal survival with a probability of 0.90 [95%CI: 0.77–1.0] vs. 0.63 [95%CI: 0.34–0.92] for ACEi (+) and ACEi (-), respectively (p = 0.036), while no significant difference in renal survival was noted for CCBs. Early use of ACEi contributed to the recovery of renal function from an acute decrease in eGFR in patients with hypertensive emergency. In addition, ACEi had a greater effect on 2-year renal survival, compared to CCBs.

The study by Galceran et al. (2020)[19] evaluated the safety and efficacy of spironolactone in managing resistant hypertension (HR) in 216 patients, both retrospectively and prospectively. The addition of spironolactone (12.5–25 mg/day) resulted in significant reductions in systolic and diastolic blood pressure, as measured clinically and by 24-hour ambulatory monitoring. After 12 months, systolic blood pressure decreased by an average of 13.9 mmHg and diastolic pressure by 6.1 mmHg. In addition, there was an improvement in the circadian blood pressure pattern, with fewer patients having a “non-dipper” or “riser” pattern. However, spironolactone also caused an increase in serum creatinine levels of 0.10 mg/dL, a decrease in glomerular filtration rate (eGFR) of 5.4 ml/min/1.73 m², and an increase in serum potassium levels of 0.3 mmol/L, all of which occurred within the first 3 months and remained stable up to 12 months. A significant decrease in albuminuria was also observed, especially in patients with micro- or macroalbuminuria. Despite side effects, such as gastrointestinal intolerance, gynecomastia, or mild hyperkalemia, spironolactone was discontinued in only 9.9% of prospective patients. Overall, spironolactone was shown to be effective and relatively safe as an add-on therapy in HR with baseline renal function (eGFR) ≥30 ml/min/1.73 m². The antihypertensive effects and changes in renal parameters appeared within 3 months, and then gradually stabilized. These findings support the use of spironolactone with regular monitoring of renal function and potassium levels, especially in the early stages of treatment.

The nationwide cohort study by[20] evaluated the efficacy of diuretics compared with calcium channel blockers (CCBs) as add-on therapy in patients with chronic kidney disease (CKD) stages 3–5 who were already receiving renin-angiotensin system inhibitors (RASi). Out of the 5,875 patients analyzed, 3,165 initiated diuretic therapy, while 2,710 started CCBs. During a median follow-up of 6.3 years, diuretic therapy was significantly associated with a reduced risk of major renal events (MAKE), including the need for renal replacement therapy, a decrease in eGFR ≥40%, or eGFR <15 ml/min/1.73 m². The risk of MAKE events was lower among diuretic users (HR 0.87; CI 0.77–0.97) compared with CCB users, and this result was consistent across all MAKE components. In contrast, there were no significant differences in major cardiovascular events (MACE) or mortality between the two treatment groups. The safety of the therapy was also maintained, as the incidence of side effects, such as hyperkalemia, hypokalemia, and acute kidney injury, was similar between the two groups. Subgroup analysis showed greater renal protection benefits in elderly patients and those with high blood pressure or eGFR <30 mL/min/1.73 m². The long-term effects of monotherapy with L-, L/T-, L/N-, and L/N/T-type calcium channel blockers (CCBs) on estimated glomerular filtration rate (eGFR) and the association between treatment duration and eGFR in diabetic patients with hypertension were assessed and compared in a different retrospective cohort study. The findings demonstrated that, for all CCB types, there was no discernible correlation between treatment duration and eGFR or blood creatinine levels. Furthermore, regardless of treatment duration, there was no discernible variation in the mean change in eGFR among the five CCBs.[25] In addition, Mahfound et al. (2022)[7] stated that the use of antihypertensive drugs simultaneously for up to 36 months had no safety issues.

Table III. Comparative description of antihypertensive drugs on renal outcomes

Author	Drugs/Groups	Main results	Effects on Kidney Function	Kidney safety
(Gosmanova et al., 2020)[16]	ACEi and ARB	Lowers blood pressure significantly	Slight decrease in eGFR, increase in creatinine & potassium	Safe and beneficial if used consistently and monitored
(Olsen et al., 2024)[17]	Valsartan (ARB) vs Amlodipine (CCB)	Patients with SBP <135 mmHg had a decreased chance of ESKD, but there was no difference in ESKD.	Both drugs are equivalent; blood pressure control is more important	Both are equivalent; blood pressure <135 mmHg is more important for the kidneys.
(Nishida et al., 2017a)[18]	Imidapril (ACEi) vs Amlodipine (CCB)	Imidapril has more negative effects than CCBs	Imidapril causes eGFR to decrease, creatinine, and potassium to increase	CCBs were safer than ACEi
(Galceran et al., 2020)[19]	Spironolactone (Antagonis Aldosteron)	Lowers blood pressure significantly	Slight decrease in eGFR, increase in creatinine & potassium	Fairly safe, but electrolyte and kidney function monitoring is required.
(Faucon et al., 2023)[20]	Diuretic vs CCB (with RASi)	Compared to CCBs, diuretics lower the risk of CKD development without affecting mortality.	Diuretics can reduce the risk of Kidney Replacement Therapy and decreased eGFR.	Diuretics are safer than CCBs in advanced CKD

In summary, **Table III** shows that diuretics, especially in combination with RASi (ACEi or ARB), appear to provide better renal protection in CKD patients than CCBs, without increasing serious adverse events. Moreover, continuous and uninterrupted use of ACEi and ARB has also been shown to reduce mortality and offer long-term benefits, although it may carry potential side effects, such as decreased eGFR and hyperkalemia. While spironolactone is effective, it requires monitoring due to potential electrolyte disturbances and decreased renal function. The safest class of drugs for renal function depends on the clinical context, but in this study, diuretics in combination with RASi and stable long-term use of ACEi/ARB showed a good renal safety profile in CKD patients, with close monitoring of electrolytes and renal function.

Several factors can affect kidney function, including age, comorbidities, gender, and combinations of certain medications. As the kidney ages, structural and functional changes occur, resulting in reduced filtration capacity and functional reserve. Structurally, the number of functional glomeruli decreases due to increased nephrosclerosis, including arteriosclerosis, glomerulosclerosis, tubular atrophy, and interstitial fibrosis. In addition, the volume of the renal cortex decreases while the volume of the medulla increases until middle age, before finally decreasing after the age of 50 years, along with an increase in the number and size of renal cysts. Functionally, glomerular filtration rate (GFR) decreases by approximately 6.3 mL/min/1.73m² per decade after age 30; therefore, by 90 years, the GFR can decrease by up to 46% compared to when they were young. This finding raises concerns that older people are often misdiagnosed with CKD solely based on decreased GFR, which might be a normal aspect of aging. In addition, the aging kidney has a lower functional reserve, making it more susceptible to acute kidney injury from dehydration, nephrotoxic drugs, or infection. Decreased metabolism and protein requirements in the elderly also contribute to the decreased renal workload and the observed decrease in GFR. Clinically, dose adjustment of drugs excreted through the kidneys is important to prevent toxicity. Therefore, it is better to consider age and not only rely on the absolute GFR threshold, since many elders with low GFR maintain stable renal function without showing signs of progressive disease.[26]

Diabetic kidney disease (DKD), a chronic microvascular consequence of diabetes mellitus, is an example of a comorbidity. Renal tubular damage is a hallmark of DKD, which is the primary cause of end-stage renal disease (ESRD) globally. The main processes leading to kidney damage in diabetes include hyperglycemia, lipid buildup, oxidative stress, hypoxia, activation of the renin-angiotensin-aldosterone system (RAAS), endoplasmic

reticulum stress, inflammation, epithelial-mesenchymal transition, and programmed cell death. Reactive oxygen species (ROS) are produced more often in chronic hyperglycemia, leading to oxidative stress that damages renal tubular cells and speeds up renal fibrosis. In addition, inflammatory activation and immune cell infiltration worsen tubular dysfunction and accelerate the progression of DKD to ESRD.[10] Cardiovascular diseases (CVDs) contribute to renal impairment through complex mechanisms, including hyperuricemia, hypertension, activation of the renin-angiotensin-aldosterone system (RAAS), inflammation, and oxidative stress. Hyperuricemia can cause endothelial dysfunction and decreased nitric oxide (NO), leading to vasoconstriction, decreased renal perfusion, and increased blood pressure. In addition, high uric acid levels stimulate oxidative stress and inflammation, which contribute to renal fibrosis and the progression of chronic kidney disease (CKD). Hypertension, as a major factor in cardiovascular disease, also accelerates CKD by increasing glomerular pressure, causing hyperfiltration, which ultimately damages renal structures through proteinuria and glomerular sclerosis. Excessive activation of the RAAS further worsens the condition by increasing sodium and water retention, renal artery vasoconstriction, and interstitial fibrosis, all of which accelerate the decline in renal function. In addition, metabolic syndromes that often accompany CVD, such as insulin resistance, obesity, and dyslipidemia, also play a role in worsening glomerulosclerosis and renal tubular dysfunction. Thus, the close relationship between cardiovascular disease and CKD demands a therapeutic approach that includes blood pressure control, uric acid level reduction, RAAS inhibition, and anti-inflammatory and antioxidant strategies to prevent disease progression and reduce the risk of more severe complications.[11] Obesity contributes significantly to hypertension through multiple interacting physiological mechanisms. Accumulation of fat, especially visceral and perirenal fat, increases intra-abdominal pressure that compresses the kidneys, thereby increasing sodium reabsorption and causing fluid retention, ultimately increasing blood pressure. The kidneys play a central role in obesity-hypertension by regulating sodium balance, blood pressure, and hormonal function. In obesity, increased sodium reabsorption in the renal tubules due to activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) leads to fluid retention and increased blood pressure. In addition, accumulation of perirenal and renal sinus fat exerts direct physical stress on the kidneys, impairing pressure natriuresis and exacerbating hypertension. In response to increased blood pressure and plasma volume, the kidneys undergo glomerular hyperfiltration as a compensatory mechanism, but in the long term, this leads to glomerular damage, proteinuria, and progression of chronic kidney disease.[12,13] Glomerular cholesterol accumulation due to ABCA1 (ATP-binding cassette transporter A1) deficiency exacerbates glomerular endothelial injury and dysfunction in diabetic kidney disease (DKD). ABCA1 is a membrane protein responsible for cholesterol excretion from glomerular cells, so its deficiency can cause excessive cholesterol accumulation in glomerular endothelial cells, which contributes to inflammation, apoptosis, glomerular endothelial barrier dysfunction, and endoplasmic reticulum stress. Studies in a mouse model of type 2 diabetes with ABCA1 deficiency in glomerular endothelial cells showed increased renal damage, elevated serum creatinine, severe proteinuria, mesangial matrix expansion, podocyte fusion, and increased inflammation and renal cell death. In vitro, hyperglycemia and high cholesterol levels increase cholesterol accumulation in glomerular endothelial cells, which triggers inflammation through increased cytokines IL-6 and TNF-α, leading to more severe glomerular injury. ABCA1 deficiency also causes disruption of the endothelial glycocalyx, which is a protective layer against protein filtration, thereby increasing glomerular permeability and accelerating the progression of DKD.[27]

Sex influences kidney function through hormonal, genetic, immunological, and drug response differences. Sex hormones, such as estrogen and testosterone, play a role in regulating kidney function, and renal angiotensin-converting enzyme 2 (ACE2) activity is more strongly influenced by estradiol and the ovarian environment than by testicular hormones or the Y chromosome. In addition, women are better protected from acute kidney injury due to ischemia-reperfusion than men, and this protection is independent of the estrogen receptor, suggesting a possible role for other mechanisms, such as X chromosome effects. From an immunological perspective, there are differences in the immune response between men and women, and the type of T cells that are more dominant in the female kidney may influence the risk of cardiovascular disease and kidney injury. Furthermore, the development of hypertension also shows sex-based differences, with men tending to experience hypertension since puberty, while women only experience an increase in blood pressure after menopause, indicating a role for sex hormones in the regulation of blood pressure and kidney function. In terms of therapy, women have a 1.5 to 1.7 times higher risk of experiencing drug side effects than men, due to differences in drug absorption, distribution, metabolism, and excretion, affecting the effectiveness of renal and cardiovascular disease therapy. Therefore, understanding these differences is important for improving gender-specific prevention and treatment strategies.[28]

The use of multiple drugs is not only associated with decreased kidney function but also with accelerated kidney function decline in cardiovascular patients. Multivariate analysis showed that the number of drugs taken was significantly correlated with anemia, stage 3b or higher chronic kidney disease, and the number of cardiovascular diseases or their risk factors. Moreover, patients with multiple drugs experienced a faster decline in estimated eGFR compared to those taking fewer drugs. No single drug type was responsible for the accelerated decline in kidney function, but it is likely that the combination of several nephrotoxic drugs, such as NSAIDs and diuretics, contributed to this effect. Thus, the use of multiple drugs not only reflects the presence of multiple comorbidities but also acts as a factor that worsens kidney function.[29]

The results of this systematic review have important clinical implications in the long-term management of hypertension. Antihypertensive therapy involving a combination of diuretics and RASi (ACEi or ARB) is not only effective in lowering blood pressure, but also has been shown to provide better renal protection compared to the use of CCBs. Therefore, for patients at a high risk of CKD progression, this combination therapy can be the preferred option, with regular monitoring of renal function and electrolytes. Continuous use of ACEi/ARB is also recommended since it shows benefits for long-term mortality, but caution is necessary to avoid hyperkalemia and a significant decline in eGFR. Spironolactone can be considered an additional therapy for resistant hypertension, especially if renal function is still adequate (eGFR ≥30 mL/min/1.73 m^2). However, serum potassium levels should be closely monitored. When choosing antihypertensive medications, it is important to consider the patient's comorbidities, age, and renal function status at the time of therapy initiation to maximize therapeutic benefits and minimize the risk of renal damage.

The narrative synthesis method, while appropriate given the clinical and methodological heterogeneity, has inherent limitations. First, quantitative pooling of effect sizes was not possible, preventing precise estimation of treatment effects. Second, the small number of included studies (n=5) limits the robustness of the conclusions, particularly for drug classes represented by single studies (e.g., spironolactone). Third, variation in outcome definitions and measurement timepoints may have influenced comparability. Finally, publication bias could not be formally assessed due to the narrative approach, though the comprehensive search strategy aimed to minimize the risk.

CONCLUSION

Long-term use of antihypertensive drugs, especially diuretics in combination with RAS inhibitors (ACEi or ARB), shows better renal protection compared to CCBs in patients with chronic kidney disease (CKD), without increasing serious side effects. Consistent use of ACEi/ARB has also been shown to reduce post-dialysis mortality despite the risk of decreasing eGFR and increasing potassium levels. Meanwhile, spironolactone is effective in lowering blood pressure and is relatively safe for renal function when accompanied by strict monitoring of renal function and electrolytes. Thus, the combination of diuretics and RASi, along with a stable use of ACEi/ARB, can be considered as a safe and beneficial long-term therapy option for supporting renal function in hypertensive patients. While ACEi or ARB monotherapy is also effective in reducing the risk of postdialysis death and AKI when used consistently, regular monitoring of eGFR and potassium is necessary.

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STATEMENT OF ETHICS

This study is a systematic review and did not involve human or animal subjects; therefore, ethical approval was not required.

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