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ORIGINAL ARTICLE

Fixed-dose combination antihypertensives in patients with chronic kidney disease: a systematic literature review

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ABSTRACT

Aim To systematically review the efficacy and safety of fixed-dose combination (FDC) antihypertensive agents in chronic kidney disease (CKD).

Methods This systematic review included studies from January 2014 to December 2023 that evaluated FDC antihypertensives in CKD. The PubMed, Embase, and the Cochrane Library databases were searched. Inclusion criteria encompassed studies written in English and published in peer-reviewed journals. Exclusion criteria, among others, were review articles, editorials, letters, and conference abstracts.

Results Six studies met inclusion criteria from 1156 identified publications. Analysed studies included randomized trials (4), cohort studies (1), and retrospective analyses (1). FDCs improved medication adherence, blood pressure control, and renal outcomes. Significant blood pressure (BP) reductions were noted with FDCs compared with free combinations. FDCs of renin-angiotensin system inhibitors and thiazide diuretics showed improved adherence, reduced major adverse cardiovascular events, and better renal function preservation. Losartan hydrochlorothiazide combination demonstrated a more significant reduction of proteinuria and urinary protein-to-creatinine ratio (UPCR), indicating potential renoprotective effects.

Conclusion While using FDC antihypertensives has shown promising results in improving patient outcomes in CKD, further large-scale, long-term randomized trials are urgently needed to confirm these findings and optimize treatment strategies.

Keywords: cardiovascular diseases, hypertension management, medication adherence, proteinuria, renoprotection

INTRODUCTION

Chronic kidney disease (CKD), according to Kidney Disease Improving Global Outcome (KDOQI) Guidelines, is defined as structural or functional abnormalities such as albuminuria more than 30 mg/g or glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² for at least three months (1). This degenerative illness causes over 1.2 million deaths annually (2), and CKD-related mortality increased by 41% between 1990 and 2017 (3). Reducing proteinuria and stabilizing GFR levels over time slows CKD progression, improving patient outcomes (4). Elevated blood pressure could be a cause or a consequence of chronic kidney disease (5). It becomes more frequent as renal function declines, affecting 60% to >90% of patients with CKD (5). Besides worsening renal function, hypertension increases the risk of major cardiovascular events (MACE) (6). Cardiovascular disease is the most common cause of death for individuals with CKD (7), and maintaining target blood pressure (BP) is crucial for better clinical outcomes (8).

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Renin-angiotensin system inhibitors (RASIs) are recommended as first-line antihypertensive agents for patients with CKD who are not receiving dialysis (9). Previous studies have shown that in individuals with CKD, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) both decrease the risk of cardiovascular events such as heart failure (9) and all-cause mortality (10). However, in the advanced stages of CKD, most of the patients need more antihypertensive medications to maintain BP control (11). According to some studies, more than 50% of patients require at least two antihypertensive medications to control their hypertension (8); in CKD stage 5, 75% of patients require ≥3 medications (12). Current guidelines recommend using 1- to 3- drug therapy with either an ACEI or ARB, a thiazide diuretic, and a calcium channel blocker (CCB) (1).

Fixed-dose combinations (FDCs), which merge two or more antihypertensive agents into a single pill, started as a promising approach to simplify treatment regimens (13). Even the use of FDCs in therapy for hypertension in the general population is well-assessed (14), very few studies have focused explicitly on CKD patients (15,16). Published review articles primarily address individual drug classes, briefly mentioning the effectiveness and safety of FDCs in CKD patients (17). The long-term impact of FDCs on CKD progression, cardiovascu-

lar risk reduction, and adherence remains unclear (11,18). Few randomized controlled trials (RCTs) examined the efficacy of different FDCs in CKD patients (19). Those studies often have short follow-up durations (20) and a small sample size (20), which limits their generalizability. Due to their complex comorbidities, renal patients are usually excluded from large hypertension trials (21). That contributes to a significant clinical evidence gap, a critical barrier to determine the optimal antihypertensive strategy for CKD patients (11), underscoring the urgent need for a systematic review of this problem.

In the Clinical Centre of the University of Sarajevo (CCUS), one of the leading clinical centres in Bosnia and Herzegovina (B&H), significant differences in antihypertensive prescribing practices for CKD patients is observed. This discrepancy is particularly evident with FDCs. To our knowledge, no studies have evaluated the prescription patterns of FDCs among CKD patients in B&H. With the absence of national clinical guidelines on antihypertensive management in CKD, many physicians may hesitate to prescribe FDCs. A probable cause is fear of potential adverse effects in patients with CKD, such as hyperkalemia and worsening renal function. With all these challenges, we wanted to provide an evidence-based study that could guide clinical decision-making and support future guideline development. This systematic review will benefit all physicians treating CKD patients, providing more precise recommendations on antihypertensive combinations. It could also offer more proven evidence to policymakers. The final results of better prescribing practice could be the reduced cardiovascular complications, delayed disease progression, and improved patient outcomes.

The aim of this study was to systematically evaluate the effects of FDCs antihypertensive therapies on key outcomes among CKD patients (blood pressure control, preservation of renal function, medication adherence, and cardiovascular risk reduction), as well as to identify optimal add-on agents for RASI-based dual therapy regimen.

MATERIAL AND METHODS:

Study design

The search approach was designed to systematically locate relevant research on the use of fixed combination antihypertensive therapies in CKD patients. It employed a comprehensive set of keywords and MeSH terms with Boolean operators (AND, OR) in PubMed, Embase, and Cochrane Library databases. The search terms “chronic kidney disease” OR “CKD” AND “fixed combination” OR “combination therapy” AND “antihypertensive” OR “blood pressure control” AND “ARB” OR “ACEI” AND “CCB”; AND “diuretics”; were used, ensuring an exhaustive search.

Inclusion criteria were randomized controlled trials, cohort studies, and observational studies with adults with CKD across various stages of the disease, written in English, and published in peer-reviewed journals from January 2014 to December 2023, where FDC therapies combine RASIs with diuretics, CCBs, or other agents. Outcomes were BP control, renal function preservation (e.g., proteinuria reduction, GFR stabilization), and cardiovascular events. These outcomes were predefined to establish the multidimensional impacts of FDC therapies. The timeframe (2014-2023) was chosen to capture recent advancements and guideline updates in FDC therapy for CKD.

Exclusion criteria were review articles, editorials, letters, and conference abstracts, studies with patients with transplanted kidneys and patients on dialysis, studies focusing solely on the pharmacokinetics or pharmacodynamics of antihypertensive agents without examining their clinical efficacy and safety in CKD patients, studies not specifically examining the outcomes of fixed combination antihypertensive therapies about blood pressure control, renal function, and cardiovascular health in CKD patients, non-English articles and studies with insufficient or unclear methodology and data.

Methods

In addition to the electronic search for articles, studies were evaluated based on their abstracts and titles. The full texts of selected articles were then carefully assessed, considering specific inclusion and exclusion criteria. The review included only articles meeting the inclusion criteria. A total of 6 articles were ultimately included for data extraction and analysis.

Quality Assessment was performed using appropriate tools, such as the Newcastle-Ottawa Scale (NOS) (22) for observational studies or the Cochrane Collaboration’s tool (23) for randomized controlled trials. The NOS is designed to assess the quality of non-randomized studies, while the Cochrane Collaboration’s tool for randomized controlled trials is widely used to assess the risk of bias in RCTs. Two reviewers performed quality assessment independently, and any discrepancies were resolved through discussion or consultation with a third reviewer if necessary.

Data were extracted from selected studies using a standardized form. Key information was systematically recorded, including study characteristics (e.g., author, publication year), types of fixed combination therapies used, patient demographics, blood pressure control outcomes, renal function measures, cardiovascular outcomes, and reported adverse events.

RESULTS

During the literature search, 1156 publications were found. Following a meticulous assessment of abstracts and titles, 121 articles were deemed relevant, and their full texts were acquired for further examination. After a thorough screening, six articles were found appropriate for review, ensuring the highest standards of research quality (Figure 1).

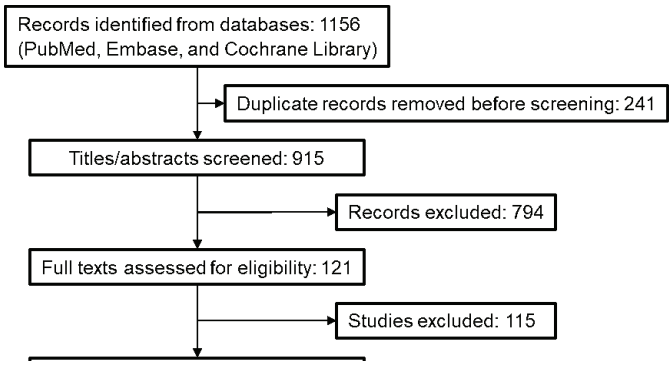

Figure 1. PRISMA flow diagram

Table 1. Characteristics and results of the studies reviewed

Studies	Design	N	Combination	Results
Okuda et al. 2018 (25)	RCT	121	Perindopril + amlodipine vs perindopril + benidipine	BP decreased significantly in both groups; among patients with diabetes, the amlodipine group had significantly decreased eGFR
Ogudu et al. 202227	RCT	129	Lisinopril-HCTZ FDC (n=64) vs separately administered lisinopril + HCTZ (n=65)	Both groups had significant reductions in MSSBP and MSDBP; adherence was higher with FDC
Rachmaini et al. 202241	Prospective cohort study	54	Candesartan-amlodipine FDC (n=27) vs candesartan-furosemide FDC (n=27)	Both groups had decreased BP; no significant differences between groups
Hayashi et al. 201526	Open-label RCT	109	Losartan-amlodipine FDC (n=36) vs losartan-enalapril FDC (n=36) vs losartan-HCTZ FDC (n = 37)	All groups had significant reductions in SBP and DBP with no significant differences between the groups; the HCTZ group had significantly increased serum uric acid and creatinine levels, significantly lower eGFR values, and significantly greater reductions in UPCR
Fujisaki et al. 201424	Open-label RCT	102	Losartan-HCTZ FDC (n=51) vs losartan (n=51)	FDC group had significantly greater reductions in UPCR and significantly higher uric acid levels; no significant differences in SBP, DBP, or eGFR between groups
Ho et al. 201834	Retrospective claims analysis	17,568	RASI-thiazide diuretic FDC (n=13,176) vs separately administered RASI + thiazide diuretic (n=4392)	FDC was associated with improved medication adherence and outcomes, including MACEs, heart failure hospitalizations and initiation of dialysis; outcomes were also improved with FDC among patients with PDC <80%

N, number of participants; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FDC, fixed-dose combination; HCTZ, hydrochlorothiazide; HR, hazard ratio; MACE, major adverse cardiovascular event; MSSBP, mean sitting systolic blood pressure; PDC, proportion of days covered; RASI, renin-angiotensin system inhibitor; RCT, randomized controlled trial; SBP, systolic blood pressure; UPCR, urinary protein-to-creatinine ratio

The PRISMA flow diagram (Figure 1) highlights the systematic process that led to the inclusion of six studies in the quantitative synthesis. It provides a transparent overview of the study selection process, ensuring the integrity and trustworthiness of our research.

Of the six studies included, four (67%) were randomized controlled trials (RCTs), one (17%) was a prospective cohort study, and one (17%) was a retrospective claims database analysis (Table 1). The number of patients included in each study ranged between 54–17,568, indicating considerable differences in the population size. FDCs evaluated included candesartan-amlodipine, candesartan-furosemide, lisinopril-hydrochlorothiazide (HCTZ), RASIs-thiazide diuretics, losartan-amlodipine, losartan-enalapril, and losartan-HCTZ.

The study outcomes showed that FDCs and separately administered combinations of antihypertensive medications worked well to lower BP with no significant differences between the different combinations. However, FDCs were associated with improvements in medication adherence and other outcomes, such as a significant reduction in major adverse cardiovascular events (MACEs), heart failure hospitalizations, and initiation of dialysis compared with separately administered combinations (Table 1). This finding provides reassurance about the potential benefits of FDCs. Additionally, a study from Japan (24) showed a higher decrease in proteinuria with losartan-HCTZ FDC vs losartan monotherapy. Group of authors from Chikushi Anti-Hypertension Trial - Benidipine and Perindopril trial (25) discovered that perindopril in combination with amlodipine resulted in a significantly decreased estimated GFR (eGFR) vs perindopril with benidipine in individuals with hypertension and diabetes. One study (26) reported that serum uric acid and creatinine levels increased considerably. They reduced eGFR and urine protein-to-creatinine ratio (UPCR) with the losartan-HCTZ FDC vs the losartan-CCB FDCs.-

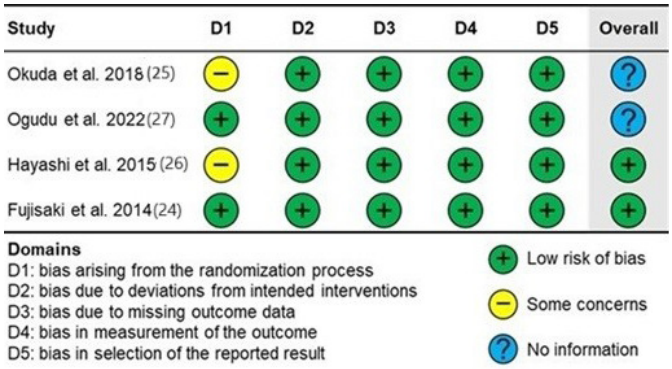

Figure 2. Quality assessment of randomized-controlled trial (RCTs) by Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) D, domain;

Quality assessment of the 4 RCTs using RoB 2 revealed that most studies had a low risk of bias across most domains (Figure 2). Some studies showed some concerns about bias in domain one from the randomization process. There was not enough information to evaluate the overall risk for the studies by Chikushi Anti-Hypertension Trial - Benidipine and Perindopril and a study made by Nigerian authors (27). Quality assessment of the NOS's two nonrandomized studies showed adequate selection, comparability, and outcome assessment (Table 2).

DISCUSSION

This systematic review assessed the clinical outcomes of FDCs in patients with CKD. It demonstrated that using FDCs prevents eGFR decline and improves blood pressure control, proteinuria, adherence, outcomes, and survival compared to free combinations of antihypertensive drugs. FDCs in CKD patients improve their overall management, potentially reducing the burden on healthcare systems.

Table 2. Quality assessment of non-randomized studies by the New Castle Ottowa Scale (NOS)

Categories and items	Rachmaini et al. 2022 (15)	Ho et al. 2018 (18)
Selection (maximum of 1 for each item)		
Representativeness of the exposed cohort	1	1
Selection of the non-exposed cohort	1	1
Ascertainment of exposure	1	1
Demonstration that outcome of interest was not present at the start of the study	1	1
Comparability (maximum of 2)		
Compare the ability of cohorts based on the design or analysis	2	2
Outcome (maximum of 1 for each item)		
Assessment of outcome	1	1
Was follow-up long enough for outcomes to occur	1	1
Adequacy of follow-up of cohorts	1	1

Medication nonadherence is a serious and one of the most common problems in patients with CKD (28). Hypertension in CKD is multifactorial (29), which means that more than one medication must be used in the treatment of hypertension (30). Besides therapy for high blood pressure, these patients also take therapy for the treatment of other sequelae of CKD (31). With the traditional monotherapy for BP, pill burden could be overwhelming (32). It could be avoided by FDCs' potential to simplify these regimens by reducing the number of pills needed (33). Significant therapeutic advantages observed in some studies with FDCs, such as decreased MACEs, heart failure hospitalizations, and the start of dialysis, likely resulted from improved adherence (34). This indicates that FDCs may help reduce the risks of non-compliance in CKD patients with hypertension.

The results of the six studies included in this review, which were selected based on their relevance and methodological rigor, were consistent with some previous research, indicating that FDCs may achieve BP control on par with separately administered combinations (35). However, combinations of monotherapies may not always be as beneficial as FDCs (36,37). Some authors reported that higher dosages of an ACEI are inferior to a combination of an ACEI with a CCB in reducing proteinuria (38). A group of authors from Japan observed that the losartan-HCTZ FDCs resulted in a more significant decrease in proteinuria vs losartan alone, suggesting possible renoprotective benefits of adding diuretics to ARBs beyond simply lowering BP (24). Additionally, the NICE-Combi research indicated that in individuals with hypertension and microalbuminuria, ARB+CCB medication provided better renal protection than ARB alone (39). This evidence supports our conclusion that FDCs are not just equivalent to monotherapies but preferable for CKD patients due to their renoprotective effects.

While these findings prove the benefits of FDCs, some challenges remain. Notably, evidence regarding the optimal add-on agent for RASI-based dual therapy is still limited (40). In our analysis, one study found that an ACEI with benidipine may prevent renal function decline in individuals with hypertension and diabetes better than an ACEI with amlodipine by avoiding decreases in eGFR (25). The combination of a RASI with a CCB has since been shown in several trials to have a renoprotective impact on individuals with CKD and hypertension (38). Other authors also found that the losartan- hydrochlorothiazide (HCTZ) HCTZ FDC was more efficient than losartan- calcium channel blocker (CCB) CCB FDCs at potentially reducing urinary protein-creatinine ratio (UPCR), which may indicate improved renal protection with HCTZ (26). A significant decrease of blood pressure was found using candesartan-amlodipine and candesartan-furosemide combinations (41). Conversely, it was demonstrated that adding a CCB to RASI therapy may not further decrease proteinuria or renal outcome; however, more BP reduction was obtained (42). Still, other studies reported no significant benefits in proteinuria or renal outcomes compared to simple RASI monotherapy or combinations of RASI with thiazide (24). The differences in antihypertensive mechanisms are likely due to sodium sensitivity, residual proteinuria, and variations in CKD stages. It is, therefore, crucial to carefully select medications to optimize renal outcomes in CKD patients (24).

The most significant limitation of the current evidence in our study is the variability in duration of the studies included. Most studies analysed were short- to medium-term, with follow-up periods ranging from 2 to 40 months. With this in mind, the sustainability of observed improvements in estimated glomerular filtration rate (eGFR) and cardiovascular outcomes is questionable (43,44). The heterogeneity in studied objectives and demographic profiles of the included complicates direct comparisons as well (45). Future studies should focus on long-term randomized controlled trials (RCTs) evaluating the sustained impact of FDCs on renal outcomes and survival in a population of patients with CKD. These studies should perform subgroup analyses with compliance monitoring and quality-of-life assessments. Also, some future research should evaluate the cost-effectiveness of FDCs in therapy. These studies are critical for optimizing treatment strategies in renal patients. It could reinforce the case for their broader adoption.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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