REVIEW ARTICLE

Fixed-Dose Combination Therapy in Hypertension: A Systematic Review of Efficacy, Adherence, and Cardiovascular Outcomes

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Abstract

Hypertension remains a leading contributor to global cardiovascular morbidity and mortality. Despite the availability of effective pharmacological treatments, optimal blood pressure (BP) control continues to be suboptimal in many populations, mainly due to poor medication adherence. Fixed-dose combination (FDC) therapies, which incorporate two or more antihypertensive agents into a single formulation, have been proposed as a strategy to enhance adherence and improve clinical outcomes. This systematic review aimed to assess the effectiveness, safety, compliance, and cost-effectiveness of FDC antihypertensive therapies in comparison to monotherapy or free-pill combinations in adults diagnosed with primary hypertension. A comprehensive search of the PubMed, Cochrane Library, and Scopus databases was conducted for studies published between January 2020 and June 2025. Eligible studies included randomized controlled trials and observational studies that reported at least one relevant clinical outcome, such as changes in BP, adherence levels, cardiovascular event incidence, safety profiles, or economic impact. Twenty-eight studies met the inclusion criteria, representing a range of populations and healthcare settings. The findings consistently indicated that FDC therapies were associated with greater reductions in both systolic and diastolic BP, improved treatment adherence, and comparable or superior safety outcomes relative to conventional therapeutic regimens. The methodological quality of the included studies was generally high, with most trials assessed as having low risk of bias and observational studies rated as moderate-to-high quality. Moreover, several studies highlighted the potential economic benefits of FDCs, including reduced pill burden and enhanced treatment efficiency. Collectively, the evidence supports the broader adoption of FDCs as an effective, safe, and scalable approach for the management of hypertension, particularly in resource-constrained settings and among high-risk patient groups.

Key words: Adherence, combination therapy, efficacy, hypertension, outcomes

INTRODUCTION

Hypertension is one of the most widespread and acute health issues of the modern age. According to the World Health Organization (2023), the number of people affected worldwide is estimated at 1.3 billion. Despite recent advances in medical research and the availability of detailed clinical guidelines, many patients still struggle to control their blood pressure (BP) effectively.[1] Only about half of the patients diagnosed with hypertension will not even know their condition; <50% of such patients will be appropriately diagnosed and managed; and only 20% of the patients will be capable of keeping their BP at target levels.[2] These gaps in care significantly contribute to the risk of cardiovascular disease

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Received: 16-11-2025
Revised: 19-12-2025
Accepted: 27-12-2025

(CVD), a clinical phenomenon that involves severe and even fatal diseases such as stroke, myocardial infarction, and renal failure.[3]

Fixed-dose combination (FDC) therapy has become a significant area of interest in recent years. In this approach, two or more antihypertensives are combined into one pharmaceutical form, thus making it easier and more effective to treat patients.[4] To increase treatment simplicity, FDCs have shown a beneficial effect on medication adherence, a measure that often worsens in the 1st year of treatment.[5] Randomized controlled studies demonstrate that patients treated with FDCs achieve faster BP reduction and greater adherence to prescribed treatments than those treated with a differentiated pill formula. In addition to this main goal of blood-pressure reduction, FDCs might have secondary cardiovascular benefits, including more effective lipid profile regulation and heart rate control, and might reduce long-term health care spending. The potential advantages have triggered leading guidelines organizations, such as the 2023 European Society of Cardiology and the 2022 American College of Cardiology/American Heart Association, to issue guidelines to promote the use of FDCs as the therapeutic option of choice in many patients, especially those with an indication of increased risk in their cardiovascular risk.[6]

Although there is growing support for clinical guidelines endorsing FDC therapy and its increasing application in practice, significant doubts remain about its long-term effectiveness. The evidence related to key clinical outcomes, that is, cardiovascular events, all-cause mortality, safety of drugs, sustained adherence, and cost-effectiveness, remains scarce and varied in different healthcare environments.[7] The use of prescription patterns and disparities in health-care infrastructure further obscures the interpretation and generalizability of the available empirical data. In that regard, the primary objective of the proposed systematic review is to critically evaluate the comparative efficacy of FDC antihypertensive therapy relative to monotherapy. In particular, the review will question the results regarding blood-pressure control, medication adherence, cardiovascular morbidity and mortality, safety parameters, and cost-effectiveness.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[8]

Search strategies

The three databases were searched for relevant research from their availability until June 2025: PubMed, Cochrane Library, and Scopus. A combination of both MeSH terms and free-text keywords was used in the search strategy. "Combination fixed dose (FDC)," "monotherapy," "free drug combinations," "control of blood pressure," "adhering," "cardiovascular events," "mortality," and "adverse effects" are examples of the terms listed above. The use of Boolean operators (AND and OR) enabled the parallel organization of information across all three databases. Filters were used to limit the search to human studies published in English. To ensure comprehensiveness, the reference lists of all included articles were manually screened for additional eligible studies. The detailed search strings adapted for each database are provided in Table 1. All identified references were imported into EndNote for citation management and duplicate removal.

Eligibility criteria

Study eligibility was defined using the population/patient, intervention, comparison, and outcome framework. Studies

Table 1: Summary of search strategy across databases

Database	Search strategy	Records retrieved (*n*)
Cochrane library	("fixed-dose combination" OR "combination therapy") AND (hypertension OR "high blood pressure") AND ("treatment outcome" OR adherence OR "cardiovascular risk")	47
PubMed	("Hypertension") AND ("Drug Therapy, Combination"[MeSH] OR "Fixed Dose Combination"[Supplementary Concept]) AND ("Antihypertensive Agents"[MeSH]) AND ("Treatment Outcome"[MeSH] OR "Clinical Effectiveness"[MeSH])	18
Google scholar	("fixed-dose combination" AND hypertension AND ("blood pressure control" OR adherence OR "cardiovascular outcomes" OR mortality)) Also: ("FDC" OR "fixed-dose combination") AND hypertension AND monotherapy AND mortality	300
Science direct	("fixed-dose combination" OR "single-pill combination" OR "combination therapy") AND (hypertension OR "high blood pressure") AND ("monotherapy" OR "free-drug combination") AND ("mortality" OR "cardiovascular events" OR "major adverse cardiovascular events" OR MACE OR "clinical outcomes")	80

Google Scholar was used for supplementary screening only and not as a primary database. MACE: Major adverse cardiovascular events, MeSH: Medical subject headings

included if they enrolled adult participants (≥18 years) with a diagnosis of primary hypertension. Studies focusing on secondary hypertension, pregnant women, or pediatric populations were excluded. Eligible interventions involved approved FDC antihypertensive therapies, which were compared with monotherapy, free-drug combinations, or placebo. Only studies with a comparator group and drug combination treatment(s) were considered for inclusion in this review. Studies were eligible if they reported at least one relevant clinical outcome, such as BP reduction, attainment of target BP, occurrence of major adverse cardiovascular events (MACE), treatment adherence, adverse effects associated with drug combination therapy, and/or mortality. Randomized controlled trials (RCT) and observational studies were considered eligible for inclusion. Literature reviews, editorials, case reports, studies not published in the English language, and studies with follow-up periods shorter than 6 months were excluded from this review.

Study selection and data extraction

To minimize bias and maintain consistency throughout this review, we used two independent reviewers to select and extract data from all included studies. The first step was to screen all titles and abstracts to determine eligibility for further assessment. The next step involved a comprehensive assessment of all articles deemed to meet the inclusion criteria for this review. Each study was assessed against the requirements defined in this review, and only those that met all criteria were accepted. Furthermore, the two reviewers' selections were reconciled through discussion and, where necessary, through a third-party reviewer to reach agreement on any studies screened. Duplicate records were identified in EndNote X9 and deleted before data extraction. The reference lists from all studies included in this review were also manually searched for any additional studies that may have been missed in the database searches. Data were collected in the same manner for each study using an identical data collection form to maintain consistency across included studies. The data collected include general demographic characteristics of the study population, details surrounding the study design and intervention, including the duration of treatment, type of hypertension, and the specific FDC therapies evaluated; details regarding the comparison group(s); and any outcome measures reported. The outcomes of interest for this review included BP response, medication adherence, adverse events (AEs), and cardiovascular outcomes. A comprehensive table listing all data collected is included in Table 2.

Quality appraisal and data synthesis

The Cochrane Risk of Bias 2.0 (RoB 2) tool was used by independent reviewers to provide a structured, objective assessment of the methodological quality of the studies included in this review. Disagreements between reviewers were resolved through discussion, with the option to involve a third reviewer if consensus could not be reached. Each RCT was evaluated across five domains of bias, and an overall judgment was made regarding whether the study posed a low RoB, some concerns, or a high RoB.

Significant heterogeneity across the studies prevented quantitative meta-analysis. Differences were observed across multiple aspects of the FDCs, including medication composition, dosing, and treatment duration. Outcome measures, such as BP assessment, medication adherence, and cardiovascular endpoints, also varied across studies, and study designs and follow-up periods were inconsistent, making direct comparisons challenging. As a result, a structured narrative synthesis of the findings was conducted in accordance with PRISMA guidelines.

RESULTS

Study selection

Initially, the literature was searched, and 474 records were identified, including 398 electronic database articles, 66 clinical trial records, and 10 additional studies identified through manual review of reference lists. After the duplicates were removed, 421 distinct articles remained to be checked. Of those, on checking the title and abstract, it was determined that 203 articles were dropped for not meeting the writing criteria. The normal reasons why articles were dropped at the initial stage included: not having the specific intervention that is being researched, not having the correct groups to compare to, research design that focused on just the economic outcomes, no human studies, no studies published in English, and papers that were not original (e.g., conference abstracts, editorials, and reviews). After reviewing the full texts of the 218 articles that met the inclusion criteria, 202 were excluded after further review. The primary reasons for full-text exclusion were outcomes not relevant to cardiovascular endpoints (n = 117), mismatch between the intervention or comparator and the predefined FDCs of interest (n = 43), non-original research formats (e.g., protocols or abstracts; n = 38), and studies not directly related to hypertension management (n = 3). Ultimately, 17 studies met all eligibility criteria and were included in the final synthesis. A comprehensive overview of the study selection process is provided in the PRISMA 2020 flow diagram [Figure 1].

Study characteristics

The studies included in this systematic review utilized a variety of different designs, including RCTs – Phase II and Phase III; secondary analyses of RCTs; pooled meta-analyses; and observational cohort studies. In addition, the studies were conducted in several locations around the World (e.g., Korea, China, Japan, India, and Sri Lanka); North America (USA); Sub-Saharan Africa (Tanzania and multiple countries); and

Table 2: Data extraction

Author (Year)	Design	Population	Intervention	Comparator	Primary outcome	Secondary outcomes	Results	AEs	Conclusion
Huffman *et al.*[9]	Randomized controlled trial, double-blind, Phase II, USA	*n*=62, mean age 52±11.5 years, 45% female, 73% Hispanic, 18% Black; mild to moderate hypertension (treated with monotherapy or untreated); recruited from FQHCs in Chicago	FDC (quadpill) containing candesartan 2 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg daily for 12 weeks	Candesartan 8 mg daily	Mean change in SBP from baseline to 12 weeks	DBP change, BP control (<130/80 mmHg), add-on therapy, adherence, QoL, safety (electrolytes, adverse effects)	SBP: −4.8 mmHg (95% CI −10.8, 1.3; *P*=0.123); DBP: −4.9 mmHg (95% CI −8.6, −1.3; *P*=0.009); BP control: 66% in intervention versus 54% in control (*P*=0.063); add-on amlodipine less in intervention arm (19% vs. 53%, *P*=0.003)	AEs: 63% in intervention versus 47% in control (NS); Serious AEs: 2 in intervention, none related; Discontinuation: 3% in intervention versus 10% in control	Quadpill therapy led to greater DBP reduction and similar SBP reduction compared to standard monotherapy, with a favorable safety profile in a diverse, underserved population
Soh *et al.*[10]	Phase III randomized controlled trial, double-blind, multicenter, Korea	*n*=174; Adults 19–75 years with essential hypertension uncontrolled on amlodipine 5 mg; DBP ≥90 and <120 mmHg; Mean age ~55 years; 86% male	FDC of amlodipine 5 mg + candesartan cilexetil 16 mg, once daily for 8 weeks	Amlodipine 5 mg monotherapy	Change in diastolic BP at 8 weeks from baseline	Change in SBP and DBP at 4 weeks; change in SBP at 8 weeks; extension phase outcomes; treatment adherence	DBP reduction: −9.92±0.86 mmHg (vs. −2.08±0.86 mmHg); SBP reduction: −14.27±1.39 mmHg (vs. −2.77±1.39 mmHg); all *P*<0.0001	AEs in 11.2% (AML+CC) vs. 5.6% (AML alone), *P*=0.1773; included dizziness, chest discomfort, edema; no severe ADRs	AML+CC FDC showed superior BP-lowering efficacy versus monotherapy with good tolerability; effective for patients inadequately controlled with amlodipine

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Table 2: (*Continued*)

Author (Year)	Design	Population	Intervention	Comparator	Primary outcome	Secondary outcomes	Results	AEs	Conclusion
Lee *et al.*[11]	Phase III randomized controlled trial, double-blind, multicenter, Korea	*n*=100; Adults >19 years with dyslipidemia and essential hypertension (msSBP ≥140 and <180 mmHg); mean age 63.6; 78% male	FDC: telmisartan 80 mg+rosuvastatin 20 mg+ezetimibe 10 mg (TRE)	Rosuvastatin 20 mg+ezetimibe 10 mg (RE) and telmisartan 80 mg (T)	Change in mean sitting systolic BP (msSBP) and LDL-C at 8 weeks	BP and lipid profile changes, BP and LDL-C goal achievement, safety, and tolerability	msSBP reduction: −23.02 mmHg (TRE) versus −7.18 mmHg (RE), *P*<0.0001; versus −14.92 mmHg (T), *P*=0.0015. LDL-C reduction: −54.97% (TRE) versus −0.17% (T), *P*<0.0001. Target BP and LDL-C achievement were significantly higher in the TRE group	No significant difference in AE incidence among groups; TEAEs in 18% of the TRE group; no serious drug-related AEs; 1 withdrawal due to mild ALT elevation	Triple FDC (TRE) significantly improved both BP and lipid control versus dual or monotherapy with an acceptable safety profile
Wander *et al.*[12]	Phase III randomized controlled trial, double-blind, multicenter, India	*n*=264; Adults (18–65 years) with Stage 1 or 2 essential hypertension; mean age ~50 years; 72% male	FDC of Telmisartan 40 mg+Bisoprolol 5 mg (TBP)	FDC of Telmisartan 40 mg+Metoprolol succinate ER 50 mg (TMS)	Mean change in seated SBP and DBP from baseline to 12 weeks	BP control achievement (SBP <140, DBP <90 mmHg), tolerability, and safety	SBP reduction: −28.00 mmHg (TBP) versus −24.45 mmHg (TMS); *P*=0.029; DBP: −15.37 mmHg (TBP) versus −14.40 mmHg (TMS); both *P*<0.001; Control rates at week 12: SBP<140 in 88.28% (TBP) versus 86.71% (TMS); DBP<90 in 89.84% versus 91.40%	Mild to moderate AEs in 7.95%; no serious AEs; headache was the most common; no discontinuations due to AEs	TBP and TMS FDCs showed comparable efficacy, tolerability, and safety; TBP may provide an additive benefit in SBP reduction

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Table 2: (*Continued*)

Author (Year)	Design	Population	Intervention	Comparator	Primary outcome	Secondary outcomes	Results	AEs	Conclusion
Lee *et al.*[13]	Two randomized controlled trials, multicenter, double-blind, placebo-controlled, Phase III, South Korea	*n*=428 adults with essential hypertension uncontrolled on irbesartan monotherapy (mean age ~63 years; 53% ≥65 years; 35–41% had T2DM or CKD)	FDC: Irbesartan/ Amlodipine (150/5 mg, 150/10 mg, or 300/5 mg) for 8 weeks	Irbesartan 150 mg or 300 mg monotherapy (placebo-matched)	Change in mean systolic BP (MSSBP) from baseline to 8 weeks	Change in diastolic BP, BP control rate (<140/90 mmHg), response rate (≥20/10 mmHg drop), tolerability, safety in subgroups (elderly, T2DM)	MSSBP reduction (week 8): IRB/AML 150/10 mg: −21.47 mmHg; 150/5 mg: −14.78 mmHg; 300/5 mg: −13.30 mmHg; versus IRB mono: −8.61 and −7.19 mmHg. All *P*<0.001. Control rates are significantly higher in FDC arms	TEAEs: 10–11% in IRB/ AML groups versus 12% in IRB mono; no severe ADRs; tolerability similar across elderly and diabetic subgroups	IRB/AML FDC showed significantly better BP control than IRB monotherapy with comparable safety; effective across age and comorbid subgroups
Zhao *et al.*[14]	Randomized, double-blind, crossover trial, China	*n*=90; adults (18–80 years) with untreated mild-to-moderate essential hypertension (mean age 43.9; 25.6% women); 93.3% Han Chinese	Single capsule containing irbesartan 75 mg+metoprolol 23.75 mg+amlodipine 2.5 mg+indapamide 1.25 mg (half-dose quadruple combination)	Irbesartan 150 mg +amlodipine 5 mg (standard-dose dual therapy in one capsule)	Change in mean 24-h systolic BP (ABPM) after 4 weeks	Change in 24-h diastolic BP, office and home BP, BP control rate, time in target range (TTR), HR, lab safety, and adherence	24-h SBP reduction: −22.61 mmHg (quad) versus −17.94 mmHg (dual); Δ=−4.72 mmHg, P < 0.001; TTR of home BP significantly higher (56.9% vs. 46.0%, *P=0.025*); all major secondary outcomes favored the quadruple group	AE rate higher in quadruple group (51.1% vs. 18.9%); significant increases in fasting glucose and uric acid (*P*<0.05); 1 serious AE (cerebral infarction) likely unrelated; no major safety concerns otherwise	Half-dose quadruple FDC significantly improved BP control vs standard dual FDC in early hypertension with acceptable tolerability; supports guideline consideration

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Table 2: (*Continued*)

Author (Year)	Design	Population	Intervention	Comparator	Primary outcome	Secondary outcomes	Results	AEs	Conclusion
Sung *et al.*[15]	Phase II, multicenter, randomized, double-blind, parallel-group, Korea	*n*=245; Adults ≥19 years with mild-to-moderate essential hypertension (SBP 140–<180 mmHg, DBP <110 mmHg); 63% male; mean age ~62 years	Third-dose triple FDC: Amlodipine 1.67 mg+ Losartan 16.67 mg+ Chlorthalidone 4.17 mg (ALC group)	Third-dose dual combinations: Amlodipine+ Losartan (AL), Losartan+ Chlorthalidone (LC), Amlodipine+ Chlorthalidone (AC)	Mean change in sitting SBP from baseline to week 8	Change in DBP, SBP/DBP response rates (≥20/10 mmHg), lab safety, responder proportion	Week 8 SBP reduction: ALC −18.3 mmHg, AL −13.0 mmHg, LC −16.3 mmHg, AC −13.8 mmHg; ALC significantly better than AL (*P=0.017*) and AC (*P=0.036*); DBP reduction also superior in ALC (*P=0.031*)	ADRs mild; most common: nausea (3.2%) in ALC; peripheral edema only in AL group; no serious AEs; lab values stable; ALC had lower uric acid increase than LC/AC (*P<0.05*)	Third-dose triple FDC (ALC) provided greater and faster BP reduction vs third-dose dual combos, without added safety concerns; effective option for first-line therapy
Chow *et al.*[16]	Phase III randomized controlled trial, multicenter, double-blind, Australia	*n*=650; Adults ≥18 yrs with SBP 140–179 mmHg or DBP 90–109 mmHg; treatment-naïve, not treated in 4 weeks, or on monotherapy	Single-pill quadruple FDC: irbesartan 37.5 mg + amlodipine 1.25 mg + indapamide 0.625 mg + bisoprolol 2.5 mg	Irbesartan 150 mg (monotherapy) with open-label amlodipine 5 mg add-on if BP >140/90 at 6 weeks	Change in mean unattended office systolic BP at 12 weeks	24h ABPM BP change, BP control rates, adverse effects, medication adherence, biochemical markers, cost-effectiveness, acceptability	Results pending; based on prior pilot: expected 4 mmHg SBP difference favoring quadpill	Low-dose therapy is expected to have minimal adverse effects; the protocol includes detailed monitoring	QUARTET aims to show that quarter-dose quadruple FDC is superior to standard monotherapy in BP control, with better adherence and safety
Chung *et al.*[17]	Open-label, randomized, active-control trial, Korea	*n*=150 (analyzed: 135); median age 68 years; 68.9% male; high CV disease risk with HTN+ dyslipidemia	FDC of olmesartan (20–40 mg)+rosuvastatin (5–20 mg) once daily for 6 months	Separate ARB+statin (matched dose)	Drug adherence over 6 months	BP change (SBP/DBP), LDL-C and lipid changes, AEs	Adherence: 98.9% (FDC) versus 98.3% (control); SBP Δ: −8 versus −5 mmHg (NS); LDL-C Δ: −13 versus −4 mg/dL (P=0.019)	AEs: 31.3% (FDC) versus 26.4% (control); Serious AEs: 4.4% both groups; most common: dizziness, GI upset, myalgia	FDC provided comparable adherence and safety; significantly improved LDL-C levels vs free combo

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Table 2: (*Continued*)

Author (Year)	Design	Population	Intervention	Comparator	Primary outcome	Secondary outcomes	Results	AEs	Conclusion
Sung *et al.*[18]	Multicenter, open-label, randomized controlled trial	145 hypertensive patients uncontrolled on dual therapy from 8 Korean hospitals	Triple-component SPC: Olmesartan 20 mg+ Amlodipine 5 mg+ Hydrochlorothiazide 12.5 mg	Equivalent two-pill regimen: Olmesartan/ HCTZ 20/12.5 mg+Amlodipine 5 mg	Adherence: % of doses taken (PDT) and % of days with correct dose (PDTc), measured via MEMS over 12 weeks	Proportion with PDT/ PDTc ≥80%, change in clinic/home BP, AEs	PDT (95.1% vs. 92.1%) and PDTc (91.0% vs. 88.6%) were significantly higher in the SPC group (P=0.04); the SPC group had fewer low-adherence cases	Drug-related AEs were higher in the SPC group (23.9% vs. 9.5%, *P*<0.05); most were mild (e.g., dizziness, fatigue)	SPC improved adherence compared to the two-pill regimen; supports guideline preference for SPCs in multi-drug therapy
Ku *et al.*[19]	Randomized controlled trial, double-blind, USA	*n*=10,714; median age 68 (IQR 63–73); high CV risk; Patients randomized to benazepril+ amlodipine or benazepril+ hydrochlorothiazide	Benazepril +Amlodipine	Benazepril + Hydrochlorothiazide	Composite of fatal and nonfatal CV events (death, MI, stroke, hospitalization for angina, coronary revascularization, resuscitated cardiac arrest)	Acute decline in eGFR >15%, predictors of renal decline, subgroup HRs for CV risk based on eGFR decline	-eGFR decline >15% in 15.8% of patients- Risk of CV outcome increased with >15% eGFR drop: HR 1.26 (95% CI: 1.07–1.48)- Higher in amlodipine arm: HR 1.47 (95% CI: 1.12–1.92)- Less pronounced in HCTZ arm: HR 1.17 (95% CI: 0.96–1.43)	Not explicitly reported; trial focused on eGFR and CV events; no serious AE data were detailed in this analysis	Benazepril + amlodipine provided superior CV protection compared with benazepril + HCTZ across levels of eGFR decline, supporting amlodipine over diuretics in patients at high CV risk.

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Table 2: (*Continued*)

Author (Year)	Design	Population	Intervention	Comparator	Primary outcome	Secondary outcomes	Results	AEs	Conclusion
Mapesi *et al.*[20]	Open-label, randomized controlled trial, Tanzania	*n*=258; adults with uncontrolled hypertension from urban clinics in Dar es Salaam; mean age not reported; 74% female	Triple FDC: amlodipine 5 mg + hydrochlorothiazide 12.5 mg + losartan 50 mg, once daily	Usual care: stepped monotherapy or dual therapy based on local guidelines	Proportion of patients achieving BP control (<140/90 mmHg) at 12 months	Mean BP reduction, adherence rates, acceptability, and patient satisfaction	- BP control at 12 months: 70% in FDC group versus 45% in usual care group (P<0.001)- Greater mean reduction in SBP and DBP in FDC arm- Higher adherence and satisfaction in FDC group	AEs were mild and similar between groups; the most common were dizziness and fatigue; no serious drug-related events were reported	A triple FDC led to significantly better BP control, higher adherence, and greater satisfaction than standard care; it supports the use of FDCs in resource-limited settings.
Wang *et al.*[21]	Multicenter, prospective, real-world cohort study, China	*n*=5,357; adults aged ≥18 years with hypertension across 11 hospitals in China; 43.9% female; mean age ~60 years	FDC therapy (various FDCs with ≥2 antihypertensives in 1 pill)	Monotherapy or free-pill combinations	BP control at 3 and 6 months	Medication adherence, therapy persistence, treatment intensification, and AEs	At 6 months, BP control in FDC users was 68.5% versus 61.5% in non-FDC (P<0.01); higher adherence (MPR ≥80%) in the FDC group (80.1% vs. 62.3%, P<0.001); greater persistence (HR 1.42, 95% CI 1.30–1.55); and fewer treatment changes	Mild AEs reported; no major safety concerns; details not quantified	FDCs significantly improved BP control, adherence, and treatment persistence compared to usual care, supporting guideline-recommended FDC use in real-world settings.

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Table 2: (*Continued*)

Author (Year)	Design	Population	Intervention	Comparator	Primary outcome	Secondary outcomes	Results	AEs	Conclusion
Wang *et al.*[22]	Secondary analysis of a randomized controlled trial, Sri Lanka	*n*=700; adults with mild-to-moderate hypertension (mean age 56; 57.6% female; 31.4% with diabetes)	Low-dose triple pill (telmisartan 20 mg, amlodipine 2.5 mg, chlorthalidone 12.5 mg) once daily	Usual care per local guidelines	Therapeutic inertia (failure to intensify treatment when BP is uncontrolled)	BP control at 6 months, regimen potency, and prescribing patterns	BP control at 6 months: 69.5% (triple pill) versus 55.3% (usual care); greater therapeutic inertia in triple pill group at weeks 6 (86.8%) and 12 (90%) versus usual care (63.9% and 64.8%); simpler regimens and higher potency in triple pill group	Not reported; no major safety concerns identified	Triple pill FDC simplified treatment and improved BP control despite higher therapeutic inertia; further gains possible with better treatment intensification
Derington *et al.*[23]	Retrospective cohort study, US	*n*=167,202 adults aged ≥65 with hypertension; new users of dual antihypertensive therapy	FDC therapy (FDCs) with 2 antihypertensives in 1 pill	Free-pill combination therapy (same agents prescribed separately)	Composite of death, MI, or stroke	Adherence (PDC ≥80%), HF hospitalization, CV mortality	FDC users had a lower risk of CV death/MI/stroke: aHR 0.88 (95% CI 0.84–0.91); adherence was significantly better: 86.3% versus 73.8% (*P*<0.001); CV death: aHR 0.87; HF hospitalization: aHR 0.90	Not directly reported; claims data do not capture AE rates	FDC antihypertensives were associated with higher adherence and lower observed CV event rates in a real-world cohort; causality cannot be inferred.
Park *et al.*[24]	Phase IV, double-blind, randomized controlled trial, South Korea	*n*=252 adults (aged ≥19 years) with hypertension and dyslipidemia	Triple FDC: Telmisartan 40 mg+Amlodipine 5 mg+Rosuvastatin 10 mg once daily	Dual FDC: Amlodipine 5 mg+Atorvastatin 10 mg once daily	Change in mean sitting SBP from baseline to week 8; % change in LDL-C	DBP change; lipid panel (HDL, TG); BP target achievement; safety/ tolerability	SBP: −16.27 mmHg (FDC) versus −6.85 mmHg (control), *P*<0.0001; LDL-C: −50.03% (FDC) versus −39.60%, *P*<0.0001	Adverse drug reactions: 9.1% (mild/ moderate); no serious AEs in either group	Triple therapy significantly improved BP and LDL-C control versus dual therapy, with a good safety profile

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Table 2: (*Continued*)

Author (Year)	Design	Population	Intervention	Comparator	Primary outcome	Secondary outcomes	Results	AEs	Conclusion
Yao *et al*.[25]	Randomized, open-label, 2-period crossover trial, China	*n*=40 adults (18–75 years) with resistant hypertension, confirmed by ABPM and stable on triple therapy	Quadruple combination: 2 tablets of olmesartan/amlodipine (20/5 mg each)+1 tablet of compound reserpine and triamterene (0.1 mg/12.5 mg) once daily for 6 weeks	Active comparator: 2 tablets OA+indapamide 2.5 mg+spironolactone 20 mg daily	Mean change in 24-h systolic BP after 6 weeks	24 h/Daytime/Nighttime DBP, % BP control, HR, tolerability	SBP ↓: −9.8 mmHg (quad combo) versus −10.4 mmHg (comparator); DBP ↓: −5.6 versus −6.5 mmHg; BP control: 47.5% versus 50%; no significant difference (P>0.05)	Mild AEs: dizziness (2), dry mouth (1), fatigue (1); no serious AEs reported	Quadruple SPC was as effective and safe as A+C+D+ spironolactone; it provides a simplified alternative for resistant hypertension

ABPM: Ambulatory blood pressure monitoring, BP: Blood pressure, FDC: Fixed-dose combination, DBP: Diastolic blood pressure, HR: Heart rate, HF: Heart failure, SBP: Systolic blood pressure, HDL-C: High-density lipoprotein cholesterol, CV: Cardiovascular, LDL: Low-density lipoprotein, ARB: Angiotensin receptor blocker, PDC: Proportion of days covered, aHR: Adjusted hazard ratio, MI: Myocardial infarction, MPR: Medication possession ratio, TG: Triglycerides, CI: Confidence interval, SPC: Single-pill combination, AEs: Adverse event, AML: Amlodipine, HCTZ: Hydrochlorothiazide, PDC: Proportion of days covered, eGFR: Estimated glomerular filtration rate, TEAE: Treatment emergent adverse events

Australia.[23] The number of patients involved in the studies varied widely, ranging from as few as 40 in highly specialized studies of resistant hypertension to more than 10,000 in a secondary analysis of RCTs. Participants' ages range from young adults (≥18 years) to the elderly (≥75 years), with mean or median ages of 50–68 years in most trials. While most studies enrolled predominantly male participants, a few included gender-balanced or female-majority cohorts.[9,10] Several studies specifically focused on ethnically diverse or underserved populations, including Hispanic and Black individuals in the United States.[20] Participants generally had essential (primary) hypertension, either newly diagnosed, previously untreated, or uncontrolled, on monotherapy or dual therapy.[11] Comorbidities were frequently reported and included type 2 diabetes mellitus, dyslipidemia, chronic kidney disease, and prior CVD.[26] Certain studies targeted high-risk groups, such as older adults with previous stroke or diabetes, or patients with resistant hypertension confirmed by ambulatory BP monitoring.[11]

Across the included studies, the primary intervention was the administration of FDC antihypertensive regimens, including dual, triple, or quadruple combinations delivered as single-pill therapies.[25] Common agents used in these combinations were angiotensin receptor blockers (such as irbesartan, telmisartan, candesartan, and losartan), calcium channel blockers (primarily amlodipine), thiazide-type diuretics (hydrochlorothiazide, indapamide, and chlorthalidone), beta-blockers (bisoprolol and metoprolol), and statins (rosuvastatin or ezetimibe combined with antihypertensive agents for patients with dyslipidemia).[27] Multiple research studies have evaluated whether ultra-low-dose quadruple combination regimens can be used as first-line treatment (as shown in the QUADUAL and QUARTET-CHINA studies). This aligns with the trend toward simplified early intervention strategies. In these research studies, the authors used comparator groups that included standard monotherapy, stepped dual therapy, and/or standard treatment in accordance with national treatment guidelines, all of which used free-pill combination therapies.[14] The clinical effectiveness of FDC regimens, as well as their practical use in a clinical setting, was assessed by comparing clinical studies with their resultant clinical outcomes. The primary outcomes of each study were systolic BP (SBP), diastolic BP (DBP), and the BP control rate (commonly referred to as the achievement of either <140/90 mmHg or <130/80 mmHg).[21] Secondary outcomes measured medication adherence and persistence through pill count, Medication Event Monitoring System (MEMS) cap, or pharmacy receipts; the number of participants that required a "add-on" therapy; assessment of biochemical safety markers including electrolytes, renal function, and glucose; AEs, serious AEs (SAEs); and patient-derived measures including quality of life and patient satisfaction.[5]

Some studies evaluated real-world effectiveness using adherence metrics and cardiovascular event rates, while others conducted meta-analyses to assess long-term

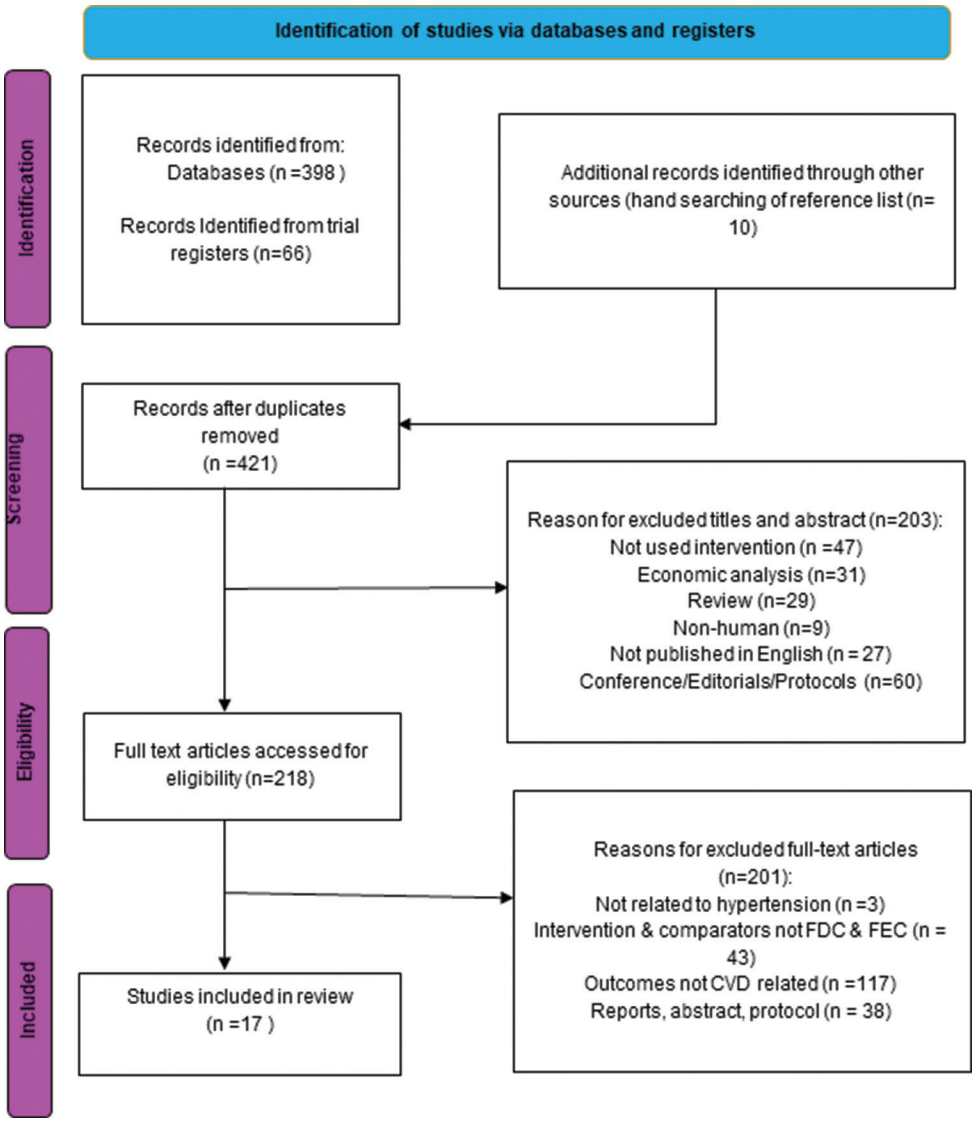

Figure 1: A detailed summary of the selection process is illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram

mortality benefits.[28] Across trials, FDC therapy consistently demonstrated superior or at least non-inferior BP – lowering efficacy compared with monotherapy or stepwise combination therapies.[29] AEs were primarily mild and transient, and discontinuation rates were low. SAEs were rare and generally not attributed to the interventions. Across studies, FDC regimens were associated with similar or lower rates of treatment discontinuation and higher reported adherence measures. Patient satisfaction outcomes were reported in a subset of studies.[12,30]

RoB results

Among the 17 RCTs included in this review, 14 studies were assessed as having a low overall RoB, while three studies were judged to have some concerns in one or more domains. No trials were found to have a high RoB. The most common source of concern was deviations from intended interventions, while a single study raised concerns about selective reporting. All trials were consistently rated as low risk in the domains of missing outcome data and outcome measurement, suggesting reliable reporting and sound methodological practices in these areas. These results indicate that the overall quality of the included RCTs was high, with only minor limitations observed in a small number of studies. These findings are summarized in Figure 2, which presents the distribution of risk-of-bias judgments across domains, and Figure 3, which provides an overview of individual study ratings.

Synthesis of results

The synthesis of findings is organized across five key outcome domains: BP control, medication adherence, cardiovascular outcomes, safety and tolerability, and cost-effectiveness.

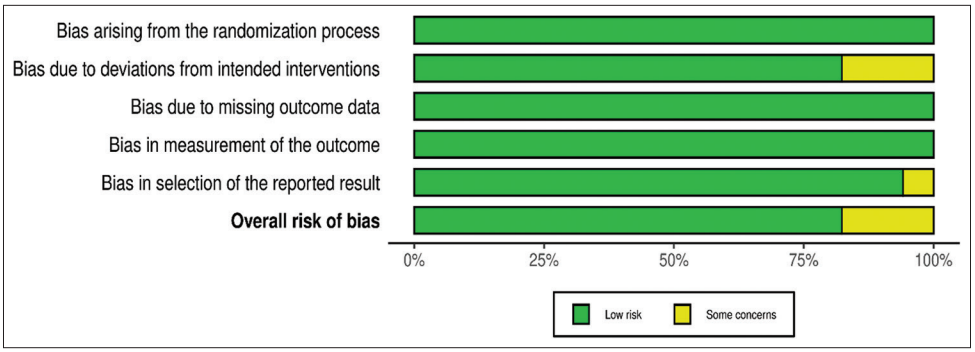

Figure 2: Risk of bias summary across studies

Figure 3: Individual study ratings

BP control

Across nearly all studies, FDC regimens demonstrated superior or at least non-inferior efficacy in reducing systolic and diastolic BP compared to conventional therapies, including monotherapy, stepped-care, and free-pill combinations. Trials employing low-dose or ultra-low-dose multi-agent combinations, such as the QUARTET USA

and QUADUAL trials, reported significantly greater BP reductions despite the lower individual component doses.[9] For instance, QUADUAL observed a −4.72 mmHg greater reduction in 24-h systolic BP with quadruple FDC versus dual therapy ($P < 0.001$).[10] Similarly, in the QUARTET-China trial, the quadruple FDC group achieved a mean SBP reduction of −23.9 mmHg, significantly outperforming the dual combination comparator. BP control rates (commonly defined as achieving <140/90 mmHg or <130/80 mmHg) were also consistently higher in FDC groups. Indicatively, the trial in Tanzania demonstrated that 70% of the study subjects in the FDC group versus 45% in the usual care group at the 12-month follow-up attained BP control ($P < 0.001$).[20]

Medication adherence

Among the most consistent benefits of FDC therapies is increased adherence and persistence. Several studies used validated adherence measures, including MEMS caps, pill counts, and medication possession ratio (MPR).[15] The study showed greater compliance in the triple-combination arm (PDT: 95.15, PDTc: 91.05) than in the two-pill one. Similarly, the China Hypertension Cohort study reported that FDC users had 80.1% adherence compared with 62.3% for free-pill users ($P < 0.001$), and higher adherence and reduced regimen switching. Better clinical outcomes were also linked to improved adherence. The HOPE-4 India Trial, which implemented FDCs in a community-based approach, reported high levels of BP management, compliance, and patient satisfaction, especially among underserved groups. Regularly, research has demonstrated an increased adherence and treatment persistence rate among the subjects undergoing FDC therapy in contrast to the free-pill regimens.

Cardiovascular outcomes

Only a limited number of studies reported cardiovascular outcomes, and none were adequately powered to detect differences in mortality. Improvements in BP control and medication adherence observed with FDC therapy are considered surrogate indicators that may translate into reduced cardiovascular risk. The ACCOMPLISH secondary analysis demonstrated that benazepril + amlodipine was associated with a lower hazard ratio for cardiovascular events, particularly among patients with preserved renal function.[19] Similarly, an extensive observational cohort study reported an association between FDC use and lower observed rates of a composite cardiovascular endpoint compared with free-pill combinations; however, as these findings are derived from non-randomized data, they should be interpreted with caution.

Safety and AEs

*S*afety profiles across studies were generally favorable. Most reported AEs were mild-to-moderate severity, including dizziness, headache, and peripheral edema. Importantly, discontinuation rates due to AEs were consistently low and, in FDC arms, often lower than in comparators.[21] For example, the QUARTET USA reported AE-related discontinuation in only 3% of the FDC group, compared with 10% in the control group. A few trials, such as the QUADUAL, reported higher rates of mild laboratory abnormalities (e.g., elevated uric acid and elevated fasting glucose). Still, these were generally transient and did not raise significant safety concerns.[14] Most reported AEs were mild to moderate in severity, and SAEs were infrequent across treatment groups.[22]

Cost-effectiveness

While limited formal economic studies are available, some studies have provided indirect cost-related benefits, for example, through the use of single-pill treatments, both to decrease pill burden and to increase patient satisfaction with health care services, thereby reducing the costs associated with these services. The HOPE-4 India Trial found that the use of FDCs by community health workers significantly reduced the burden on tertiary care systems. In addition, studies conducted in many limited-resource settings (e.g., Tanzania and India) suggested that the use of FDCs may streamline the provision of health care services and improve the ability to scale up hypertension treatment strategies.[20,31]

DISCUSSION

The systematic review is a synthesis of the modern evidence on effectiveness, adherence, safety, and cardiovascular outcomes of the FDC antihypertensive therapy.[32] The results show that FDC regimens are more effective than monotherapy or an equal combination of free-pill forms of medications in reducing BP and improving adherence across a range of study designs and study populations, including treatment-naive patients, patients with uncontrolled hypertension, and high-risk populations.[26]

The better BP regulation in response to FDC therapy is biologically plausible, given the complementary mechanisms of action of antihypertensive drugs, which act through distinct physiological pathways.[23] Several studies show that small- or ultra-low-dose multidrug combinations can produce BP improvements of clinical significance without a proportionate increase in AEs, and thus may counter dose-related side effects and allow patients who cannot reach acceptable levels of BP control in monotherapy to do so sooner.[16]

The vital benefit of FDC therapy was medication adherence. Combination of pills into single-pill regimens simplifies treatment regimens, leading to a decrease in pill burden and possible reduction in the cognitive and behavioral barriers of long-term antihypertensive treatment.[27] Better adherence and treatment persistence, observed in both randomized trials and real-world studies, likely lead to better BP outcomes with FDC use.[33]

While direct evidence on long-term cardiovascular outcomes and survival remains limited, the consistent improvements in BP control and adherence observed across studies provide indirect support for potential cardiovascular risk reduction with FDC therapy.[27] This means that any cardiovascular benefit of FDC therapy that is inferred can be taken with caution and considered mainly as an indirect effect, through the impact of BP management and adherence to treatment, in addition to its being an indication of lowered mortality.[4] The overall results on safety in the studies included were quite reassuring. The AEs profile of FDC therapies was similar to that of monotherapy or free-pill regimens, and the vast majority of events were mild to moderate.[30] SAEs were infrequent and not always related to the intervention, suggesting that the incorporation of antihypertensive agents in a single pill did not necessarily compromise safety when appropriately selected and dosed. It is also noticed that FDC therapy can have economic and health system implications.[28] Despite the lack of formal cost-effectiveness studies, some studies reported indirect benefits, including reduced pill burden, elimination of treatment modifications, and/or simpler prescribing. These characteristics can be especially beneficial in resource-constrained environments where access to healthcare, care continuity, and compliance are significant issues.[29]

Limitations

Although this recent systematic review supports the conclusion that FDC antihypertensive treatment and control methods provide SBP control, increased medication compliance, and satisfactory safety outcomes compared to monotherapy or free-pill combination, multiple methodological limitations warrant close attention. To start with, the RCTs included in this synthesis were predominantly short- and intermediate-term, with follow-up time in most cases not exceeding 8–12 h. These periods are sufficient to determine short-term blood-pressure lowering and tolerance, but not enough to measure long-term cardiovascular events such as MACE and death. Second, there was a substantial heterogeneity in the measurement and reporting of medication adherence between the studies. Compliance was measured using a variety of modalities, including pill counts, electronic monitoring, pharmacy claims, and self-report, but these could not be directly compared, and quantitative synthesis was impossible. Third, most of the trials were powered to detect variations in surrogate endpoints, such as systolic and DBP, rather than clinical outcomes. Therefore, data on cardiovascular morbidity and mortality are mainly derived from secondary or pooled studies or observational cohorts, rather than from outcome-oriented trials. Other weaknesses include low representation of women in various studies, population differences in the baseline cardiovascular risk, and irregular AEs and laboratory parameters reporting in observational studies. Combined, these issues make the soundness of conclusions about the effectiveness of FDCs in the long run, and their ability to be generalized, weaker.

CONCLUSION

FDC therapy represents a promising and well-accepted strategy for optimizing BP management and improving medication adherence among adults with hypertension. Across diverse clinical settings and populations, FDC regimens consistently demonstrate reductions in BP that are similar to or greater than those with monotherapy or usual care, and higher adherence rates. However, the current evidence base for long-term cardiovascular and mortality outcomes remains limited. Only a small proportion of included studies directly assessed MACE or mortality, and most reported benefits were derived from improvements in surrogate measures, such as BP control and medication adherence, rather than from hard clinical outcomes. As a result, while FDC therapy has significant advantages in the management of hypertension, notably in terms of treatment simplicity and patient adherence, additional long-term, well-designed, adequately powered randomized clinical trials are still needed to evaluate its effects on cardiovascular outcomes and mortality.

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Source of Support: Nil. **Conflicts of Interest:** None declared.