Journal of Innovative and Creativity
Journal Homepage: https://joecy.org/index.php/joecy
e-mail: journaljoecy@gmail.com

Faculty of Education
University of Pahlawan Tuanku Tambusai
ISSN 2775-771X (Online)
ISSN 2962-570X **(Printed)**
6 (1) 2026, Page: 17545-17559

The Effectiveness of Single-Pill Combination (SPC) Compared to Free-Combination Therapy in Improving Long-Term Treatment Adherence in Hypertensive Patients: A Systematic Review

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Published: March, 2026

ABSTRACT

Background: Hypertension remains a global health crisis with suboptimal blood pressure control due to poor long-term treatment adherence, exacerbated by high pill burden in free-combination therapies. **Objective:** This systematic review evaluates the effectiveness of Single-Pill Combination (SPC) versus Free-Combination (FC) in improving adherence among hypertensive patients. **Methods:** Following PRISMA 2020 guidelines, we searched PubMed, Semantic Scholar, and Google Scholar (2015-2025) for RCTs and cohort studies using PICOS framework. Nine studies (3 RCTs, 6 cohorts; N>270,000 patients) were assessed via RoB 2.0 and ROBINS-I tools, with narrative synthesis. **Population/Sample:** Adult essential hypertension patients receiving combination antihypertensives. **Instruments/Data Analysis:** Risk of bias tools and structured data extraction for adherence metrics (PDC, MPR, persistence). **Results:** Eight studies showed SPC superiority (higher PDC/MPR, OR up to 3.63), linked to better BP control. **Conclusion:** SPC should be prioritized clinically to enhance adherence and outcomes, despite methodological heterogeneity.

Keywords: : Hypertension, Treatment Adherence, Single-Pill Combination, Free Combination, Pill Burden.

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INTRODUCTION

Hypertension is an urgent global public health challenge, recognized as a major and independent risk factor for cardiovascular diseases, including stroke, myocardial infarction, and kidney failure. Despite the widespread availability of clinical guidelines and antihypertensive drugs, blood pressure (BP) control rates in various regions of the world are still far from optimal. Data indicate that millions of adults fail to achieve recommended BP targets, significantly increasing the global burden of disease and healthcare costs [1], [2].

One of the biggest barriers to achieving effective BP control is long-term treatment adherence (adherence and persistence). Hypertension requires chronic therapy, and treatment regimens often involve a combination of two or more antihypertensive agents. Unfortunately, a high pill burden is inversely related to adherence rates [3]. Non-adherence is the main reason for failure to achieve BP targets and has been shown to cause significant discontinuation of long-term therapy [4].

To address compliance issues caused by pill burden, Single-Pill Combination (SPC) has been proposed as a key strategy. SPC combines two or more antihypertensive agents into a single tablet, thereby drastically simplifying the patient regimen. Theoretically, simplifying the regimen to a single pill (SPC) is expected to improve long-term treatment adherence [5]. This strategy aims to support the achievement of recommended BP control targets and mitigate treatment inertia [6], [7].

Although SPC is promising, evidence of its superiority in improving adherence remains fragmented and varies in methodological quality. Many observational studies (real-world data) reporting improved adherence are classified as having a Serious Risk of Bias due to unmeasured confounding (ROBINS-I Domain 1) [4], [8]. Additionally, available RCTs often use open-label designs (High Risk of Bias), which are susceptible to performance bias and outcome measurement bias [5], [9]. Therefore, a systematic review is needed that synthesizes evidence from RCTs and cohort studies and critically assesses the methodological quality of these studies, especially observational studies that use advanced adjustment techniques such as Propensity Score Matching (PSM) [10], [11].

This systematic review aims to comprehensively evaluate the effectiveness of Single-Pill Combination (SPC) compared to Free Combination (FC) in improving long-term treatment adherence in hypertensive patients. The secondary objective is to assess the comparison of blood pressure (BP) reduction efficacy and safety profiles between the two treatment strategies, prioritizing findings based on risk of bias assessment (RoB 2.0 and ROBINS-I).

RESEARCH METHODS

Study Design and Protocol

This systematic review was conducted to answer specific clinical questions regarding the effectiveness of Single-Pill Combination (SPC) compared to Free Combination (FC) in improving long-term hypertension treatment adherence. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Data Sources

To identify relevant studies on the effectiveness of Single-Pill Combination (SPC) compared to Free Combination (FC) in improving compliance among hypertensive patients, we conducted a systematic search of international academic databases and scientific search engines. The data sources used included PubMed/MEDLINE, Semantic Scholar, and Google Scholar.

We applied the following main keywords and Boolean operators to connect relevant Intervention, Condition, and Outcome concepts:

- (("fixed dose combination" OR "single pill combination" OR "single tablet regimen") AND ("free combination" OR "multiple pill" OR "unfixed combination")) AND (adherence OR compliance OR persistence OR adherent) AND (hypertension OR antihypertensive) AND (RCT OR "randomized controlled trial" OR cohort OR "cohort study")
- (Fixed-Dose Combination OR Single-Pill Combination OR FDC) AND (Hypertension OR Antihypertensive) AND (Adherence OR Persistence OR Compliance) AND (Free Combination OR Free Equivalent Combination).

This search was limited to studies published from 2015 to 2025, to ensure comprehensive literature coverage, covering the period from when SPCs became widely available to the most recent data. To ensure comprehensive coverage, we also searched for variations of related keywords and manually searched the reference lists of all included studies.

Selection Strategy

Studies will be included in this review if they meet the following criteria (based on the PICOS framework):

- P (Population): Adult patients (aged ≥18 years) with a diagnosis of essential hypertension.
- I (Intervention): Use of Single-Pill Combination (SPC) or Fixed-Dose Combination (FDC) antihypertensive drugs (including combinations of two or more agents).
- C (Comparison): Studies must compare SPC/FDC with Free Combination (FC) or Free-Equivalent Combination (FEC) containing equivalent antihypertensive drugs.
- O (Outcomes): Studies must report at least one relevant outcome, particularly those related to adherence or long-term treatment persistence (e.g., PDC, MPR, or discontinuation time), as well as blood pressure (BP) reduction efficacy or adverse events (AE).

- S (Study Design): Studies included are Randomized Controlled Trials (RCTs) and retrospective or prospective observational cohort studies.
- Publication Type: Peer-reviewed journal articles.
- Language: Articles published in English or Indonesian.
- Publication Date: Studies published between 2015 and 2025, to ensure coverage of historical data up to the latest evidence.

Studies will be excluded from this systematic review if they meet any of the following conditions:

- Non-Original Publication Type: Non-original works, such as editorials, commentaries, letters to the editor, opinion papers, or conference abstracts without complete data available.
- Non-Target Population: Studies that focus exclusively on specific populations in which the use of SPC/FC has a different purpose or populations that are very rare (e.g., pediatric patients, pregnant women, or patients with end-stage heart failure).
- Non-Comparative Study Design: Studies that do not involve a direct comparison between Single-Pill Combination (SPC) and equivalent Free Combination (FC).
- Non-Hypertension Drug Focus: Studies comparing SPC/FDC that exclusively focus on conditions other than hypertension (e.g., only for the prevention of dyslipidemia without antihypertensive involvement) or that do not include BP outcomes or antihypertensive adherence.
- Unacceptable Languages: Articles not published in English or Indonesian.
- Time Range: Studies published before 2015.
- Informal Reports: Community service reports, case reports, or research reports that do not have a clear research design or standardized outcome measurements.
- Data Duplication: Duplicate publications or secondary analyses that use the exact same dataset as studies already included in the review.
-

Study Selection Process

The study selection process is conducted independently by two reviewers. The first stage involves screening the titles and abstracts of all studies identified from the database search. Studies that are considered irrelevant to the PICOS (Population, Intervention, Comparator, and Outcome) criteria for hypertension or compliance will be immediately excluded at this stage. Next, potentially eligible articles will proceed to the full-text review stage. At each stage, studies that do not meet the established eligibility criteria (including Exclusion Criteria) will be excluded.

To ensure a balanced assessment and reduce the risk of selection bias, any discrepancies between two reviewers will be resolved through open discussion and consensus. If consensus cannot be reached, a third reviewer will be consulted to provide a final assessment. The final collection of studies included for data extraction and synthesis is determined collectively, guided by the predetermined eligibility criteria. This rigorous yet collaborative process is designed to maintain transparency and minimize the risk of selection bias.

Quality Assessment and Data Extraction

The methodological quality of the studies included in this review was independently assessed by two reviewers using specific instruments based on study design: the Cochrane Risk of Bias Tool (RoB 2.0) for 3 Randomized Controlled Trials (RCTs) and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) for 6 Observational Cohort Studies.

For non-randomized (cohort) studies, the ROBINS-I assessment revealed the methodological challenges typical of observational research. Of the six cohort studies, five were assessed as having a Serious Risk of bias overall, while one study, Choi et al. (2021), was assessed as having a Moderate Risk. No observational studies in this review achieved a 'Low Risk' rating across all domains.

The main issue across observational studies was Confounding Bias (Domain 1). Most studies were downgraded because they did not adequately adjust for strong potential clinical confounders, such as the clinical reasons doctors chose SPC over FC. On the other hand, studies that used strong

adjustment techniques such as Propensity Score Matching (PSM), as done by Choi et al. (2021), showed relatively stronger methodological quality, allowing for a Moderate risk rating.

In the seven ROBINS-I domains, the most common concerns were Confounding (D1), Participant Selection (D2), and Outcome Measurement (D6). Other domains, such as Intervention Classification (D3) and Outcome Reporting Selection (D7), were generally assessed as low risk.

Meanwhile, out of the three RCT studies, only one study (Wang et al., 2024) was assessed as having an overall Low Risk of bias. One study (Sung et al., 2021) was assessed as having a High Risk, mainly due to serious concerns about Bias due to Deviation from Intervention (D2), which is often associated with open-label designs. This indicates that findings should be interpreted with caution due to residual bias risks in key areas.

For data extraction, we applied a structured and consistent approach. Information collected from each study included:

- Study Identification: Title, first author, year of publication (range 2015-2025), and country of origin.
- Participants: Total sample size, age range (≥18 years), and criteria for diagnosis of essential hypertension.
- Intervention Details: Type of drug combination (SPC/FDC), dosage, and follow-up duration.
- Control Group: Comparison details, namely Free Combination or Free-Equivalent Combination (FEC) with equivalent antihypertensive drug content.
- Primary Outcomes: Measures of adherence effectiveness, such as Proportion of Days Covered (PDC), Medication Possession Ratio (MPR), or therapy persistence.
- Secondary Outcomes: Measures of blood pressure (systolic and diastolic BP) reduction efficacy and adverse events (AE) or treatment discontinuation rates.
- Quantitative Data: Mean values, standard deviations, and sample sizes for the intervention and control groups.

All data extraction was performed independently by two reviewers, and any disagreements were resolved through open discussion or consensus with a third reviewer to ensure data accuracy and completeness.

RESULTS AND DISCUSSION

Study Selection

A comprehensive search was conducted on three main databases, namely PubMed, Semantic Scholar, and Google Scholar, which collectively yielded 690 records (PubMed = 4; Semantic Scholar = 17; Google Scholar = 669). After the initial identification process, 56 duplicates were removed, leaving 634 unique records to be screened at the title and abstract stage.

At the title and abstract screening stage, 610 records were excluded for the following reasons: studies were not relevant to the research topic (n = 451), study design was not appropriate (n = 64), population was not appropriate or did not consist of primary hypertension patients (n = 50), and the intervention did not involve a combination of SPC or FC antihypertensive drugs (n = 45).

After that, 24 full-text reports were sought for retrieval. However, 5 reports could not be obtained because the full text was not available or PDF access was not possible.

A total of 19 full-text articles were retrieved and assessed for eligibility. At this stage, 10 reports were excluded, mainly because they did not assess adherence to antihypertensive treatment or did not involve a comparison between SPC and FC therapy.

Thus, a total of 9 studies met all inclusion criteria and were included in the qualitative synthesis for this systematic review. The complete flow of the study selection process is shown in the PRISMA 2020 diagram (Figure 1).

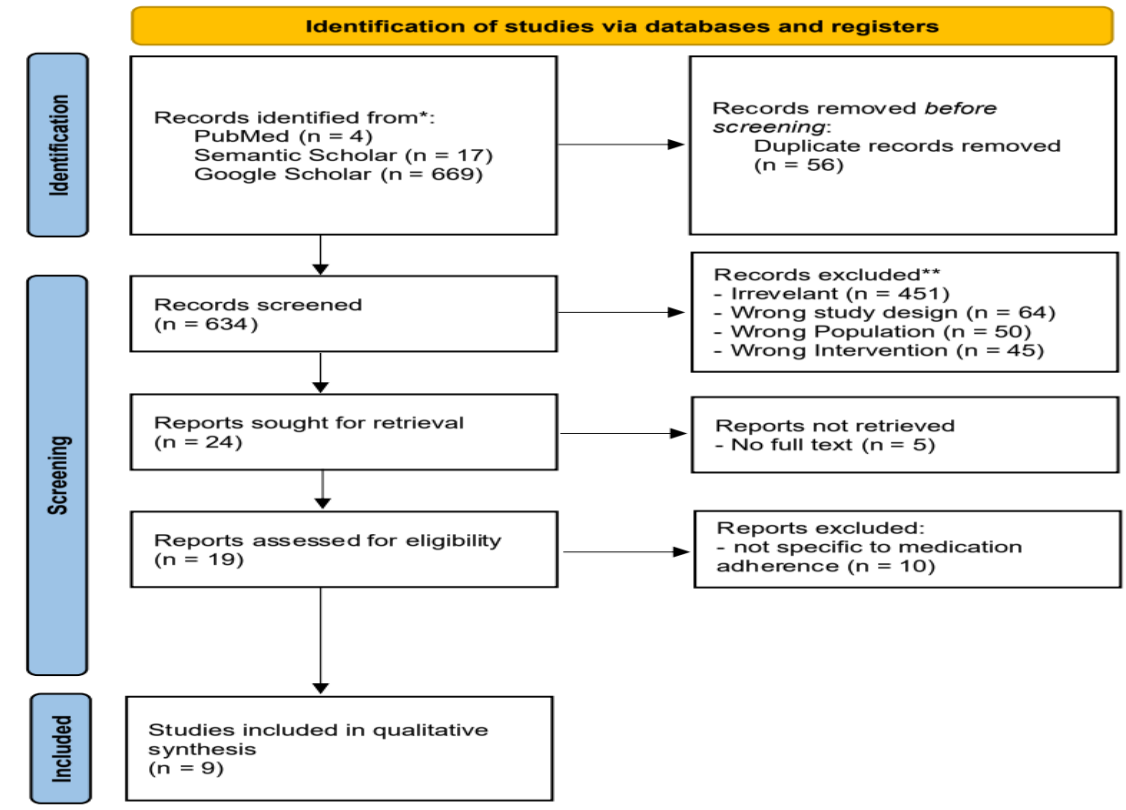


Figure 1. PRISMA flow to evaluate studies

Quality Assessment

The methodological quality of the included studies was independently assessed by two reviewers using specific instruments based on study design: the Cochrane Risk of Bias Tool (RoB 2.0) for three Randomized Controlled Trials (RCTs) and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) for six Observational Cohort Studies.

1. Cohort Study Quality Assessment (ROBINS-I)

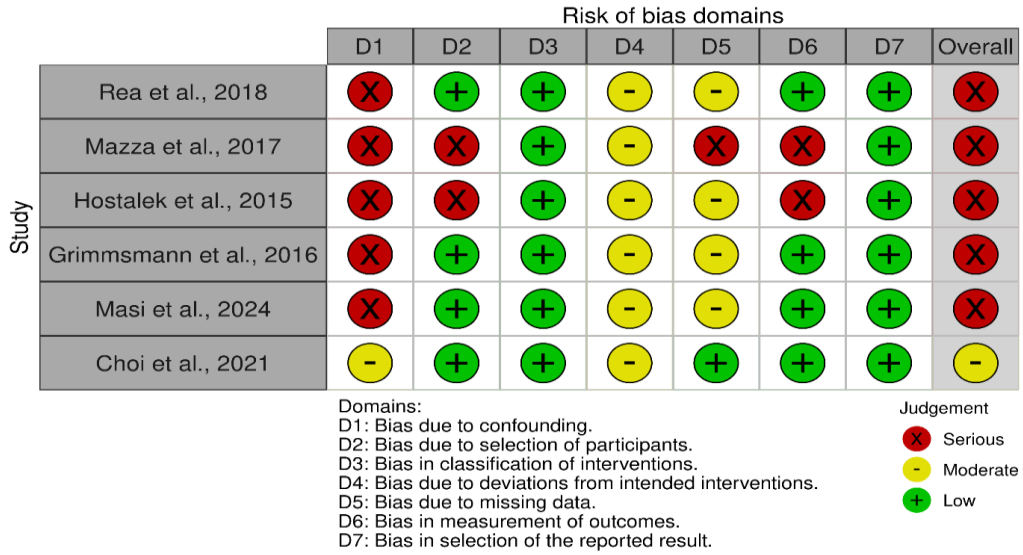


Figure 2. Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I)

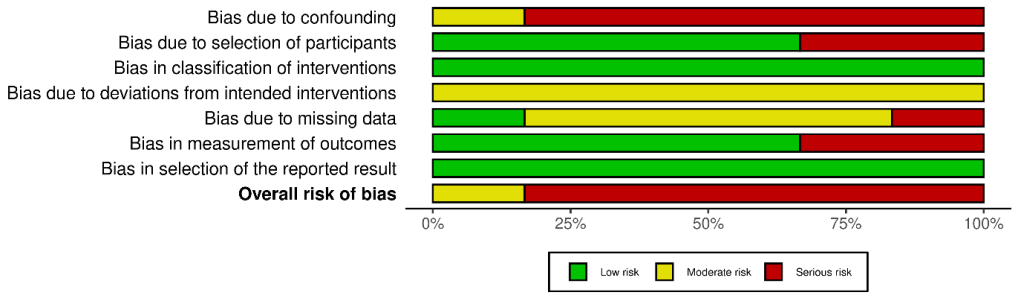


Figure 3. ROBINS-I Summary

The methodological quality of the six observational cohort studies included in this review was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) instrument. Overall, the majority of studies showed significant methodological challenges, with five of the six studies assessed as having a Serious Risk of Bias. Only one study, Choi et al. (2021), achieved an overall Moderate Risk rating. No cohort studies were categorized as having low risk across all domains, reflecting the inherent vulnerability of real-world research designs.

The main factor contributing to the decline in quality ratings was Confounding Bias (Domain 1). Five studies (Rea et al., 2018; Mazza et al., 2017; Hostalek et al., 2015; Grimmsmann et al., 2016; and Masi et al., 2024) were assessed as having serious risk in this domain because they did not adequately adjust for baseline clinical confounding factors that could influence the decision to choose between SPC and FC therapy. In contrast, the study by Choi et al. (2021) demonstrated stronger quality in this domain (moderate risk) through the use of Propensity Score Matching (PSM) techniques to minimize differences in characteristics between groups.

Additional concerns were also identified in other domains for certain studies:

- Participant Selection (D2) and Outcome Measurement (D6): The studies by Mazza et al. (2017) and Hostalek et al. (2015) were assessed as having serious risk due to potential bias in how participants were selected and how compliance outcomes were measured or reported.
- Missing Data (D5): The study by Mazza et al. (2017) was the only one that showed a serious risk related to the handling of missing data, while the other studies ranged from low to moderate risk.
- Deviation from Intervention (D4): All studies assessed consistently showed a Moderate risk in this domain, indicating potential variation in the implementation of the intervention in the field.

However, all studies showed good performance in Intervention Classification (D3) and Outcome Reporting Selection (D7), with all studies receiving a Low Risk rating in both domains. This indicates that the definition of interventions and reporting of final outcomes in these cohort studies were conducted transparently and consistently.

2. Quality Assessment of RCT Studies (RoB 2.0)

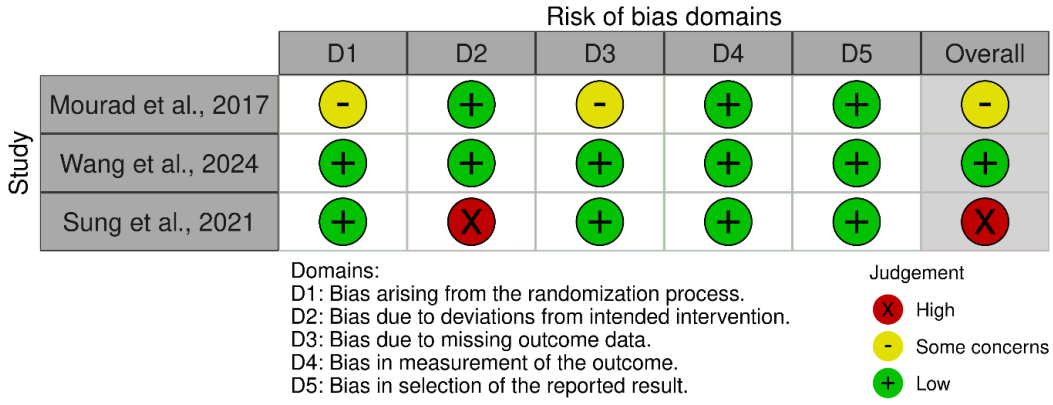


Figure 4. Risk of Bias for Randomized Controlled Trials (RCTs) Studies

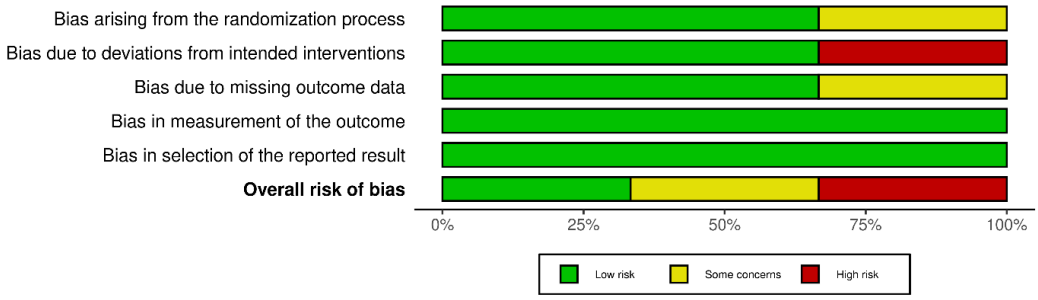


Figure 5. RoB 2.0 Summary

The methodological quality of the three Randomized Controlled Trials (RCTs) included in this review was assessed using the Cochrane Risk of Bias Tool (RoB 2.0). The assessment results showed significant variation in quality among the studies, with one study rated as having Low Overall Risk of Bias, one study rated as Some Concerns, and one study rated as High Risk.

The following are the assessment details for each study:

- Wang et al. (2024): This study was the only RCT that demonstrated excellent methodological quality with a low risk rating across all assessment domains (D1 to D5) as well as overall. This indicates that the randomization process, intervention implementation, data handling, and reporting of results were carried out to strict standards.
- Mourad et al. (2017): This study was assessed as having Some Concerns overall. The main concerns arise in Domain 1 (Bias arising from the randomization process) and Domain 3 (Bias due to missing outcome data), where there is insufficient information to ensure that the randomization process and handling of missing data did not significantly affect the final results.
- Sung et al. (2021): This study was categorized as High Risk overall. This drastic decline in rating is mainly due to Domain 2 (Bias due to deviations from intended intervention). As noted in the literature review, many RCTs in this domain use open-label designs that are prone to performance bias and deviations from the planned intervention.

In summary, the analysis per domain shows the following results:

- Outcome Measurement and Reporting Selection (D4 & D5): All studies (100%) showed low risk of bias in the domains of outcome measurement and reported outcome selection.
- Randomization Process (D1) and Missing Data (D3): The majority of studies (66.7%) were at low risk, while the rest showed some concerns.
- Deviation from Intervention (D2): This domain is the most critical area, where only 66.7% of studies had a low risk, while the remaining 33.3% were assessed as having a high risk.

Overall, despite the presence of high-quality studies such as Wang et al. (2024), the existence of studies with high risk of bias such as Sung et al. (2021) suggests that findings from this RCT group should be interpreted with caution, particularly regarding the influence of study design on patient compliance outcomes.

Characteristics and Results of Included Studies

1. Cohort Study

Table 1. Characteristics of Included Cohort Studies

No	Title	Author, Year	Country	Study Design	Population (N)	Intervention Comparison	Outcome	Adjustment Method
1.	Initial Antihypertensive Treatment Strategies	Rea, et al. (2018)	Italy (Lombardy Region, Universit	Population-based retrospective observati	125,635 hypertensive patients	SPC: Fixed-dose combination (FDC) of RAS blocker +	Method: Prescription refill (3 years). Results: SPC significantly	Adjustments were made using a high-dimension

	and Therapeutic Inertia		y of Milano-Bicocca)	onal cohort study		diuretic (93% of the population). FC: Combination of two identical agents (RAS blocker + diuretic) separately.	improved compliance and long-term therapy stability compared to FC due to the lower pill burden.	al propensity score (hdPS) algorithm and Cox regression model to balance characteristics between groups and control for bias.
2.	Fixed-Dose Triple Combination of Antihypertensive Drugs Improves Blood Pressure Control: From Clinical Trials to Clinical Practice	Mazza, et al. (2017)	Italy (Study conducted at the Hypertension Center, S. Maria della Misericordia Hospital, Rovigo, Italy)	Non-randomized interventional cohort (prospective, group comparison)	Total number of patients: 184. FDTC: 92 patients. FCT: 92 patients.	SPC (FDTC): Fixed combination of perindopril/indapamide/amlodipine in a single pill. FC: The three agents (perindopril, indapamide, amlodipine) are administered as separate drugs.	Method: Patient reports & pill counts. Results: SPC (FDTC) group compliance was higher than FC due to the ease of use of the one-pill regimen.	Multivariate statistical analysis includes ANOVA, post hoc tests, and regression to control for confounding variables in blood pressure and serum lipid parameters.
3.	Treatment of Hypertensive Patients with a Fixed-Dose Combination of Bisoprolol and Amlodipine: Results of a Cohort	Hostalek, et al. (2015)	Poland (Study conducted at 68 centers in Poland; sponsor: Merck KGaA, Germany)	Non-interventional cohort study (observational prospective cohort)	10,532 patients	FDC: Combination of bisoprolol/amlodipine in one tablet with varying doses (5/5, 10/5, 5/10 mg). FC: Bisoprolol and amlodipine are administered as two	Method: Tablet count (tablets taken/prescribed). Results: FDC > FC. FDC compliance reached 86% (excellent/good category), contributing to more effective BP	No specific statistical adjustment methods were reported; only descriptive observational analysis was used.

	Study with More Than 10,000 Patients					separate tablets.	control compared to FC.	
4.	Comparison of therapy persistence for fixed versus free combination antihypertensives: a retrospective cohort study	Grimsmann, et al. (2016)	Germany (data from AOK Mecklenburg-West Pomerania, one of Germany's health insurance providers)	Retrospective cohort study	8,032 patients with hypertension	Intervention: Diuretics, β-blockers, CCBs, and RAS blockers. SPC: Fixed combination in a single tablet. FC: Combination of the same agents but administered as separate medications.	Method: Persistence was measured via prescription refills (180/360-day interval). Results: FC > SPC in long-term therapy continuity (56.4% vs. 39.8% after 4 years).	Multivariate logistic regression was used to assess treatment continuity by adjusting for age, gender, and number of previous medications as covariates.
5.	A Retrospective Observational Real-World Analysis of the Adherence, Healthcare Resource Consumption and Costs in Patients Treated with Bisoprolol/Perindopril as Single-Pill or Free Combination	Masi, et al. (2024)	Italy (national administrative data from the Italian National Health System)	Retrospective observational study based on administrative data (cohort, real-world study)	17,961 patients	SPC: Fixed combination of perindopril (ACEI) and bisoprolol (beta-blocker) in one tablet. FC: Perindopril and bisoprolol are administered as two separate tablets.	Method: Proportion of Days Covered (PDC); compliant if PDC ≥ 80%. Results: SPC significantly improved compliance compared to FC (45.5% vs. 38.6%; $p < 0.001$). In the per-pill analysis, SPC compliance was significantly higher (76.3% vs. 38.6%).	The Propensity Score Matching (PSM) method is used to balance baseline characteristics between the SPC and FEC groups in order to minimize selection bias.
6.	Medication Adherenc	Choi, et al. (2021)	South Korea	National Retrospective	123,992 patients	SPC (FDC): Combination of ARB and	Method: Proportion of Days	Propensity Score Matching

	e and Clinical Outcome of Fixed-Dose Combination vs Free Combination of Angiotensin Receptor Blocker and Statin	(The study was conducted using the Korea National Health Insurance Service database)	Cohort Study (Observational, longitudinal, based on national administrative data)	SPC/FDC: 34,776 patients (28.1%) FC: 89,216 patients (71.9%)	statin in one fixed-dose pill. FC: ARB and statin administered separately with a flexible consumption schedule.	Covered (PDC ≥ 80%) for 540 days. Results: The FDC/SPC group showed significantly higher levels of adherence and persistence compared to FC.	(PSM) method with a 1:3 ratio to balance age, gender, and clinical characteristics between the SPC and FC groups

2. Randomized Controlled Trial (RCT) Study

Table 2. Characteristics of Included RCT Studies

No	Title	Author, Year	Country	Study Design	Number of Samples (N)	Intervention Comparison	Outcome	Risk of Bias
1.	Blood pressure-lowering efficacy and safety of perindopril/ indapamide/ amlodipine single-pill combination in patients with uncontrolled essential hypertension	Mourad, et al. (2017)	Multinational (13 countries: Argentina, Brazil, Bulgaria, Czech Republic, Hungary, Mexico, Poland, Romania, Russia, Singapore, Slovakia, Ukraine, Vietnam)	Randomized, double-blind, multicenter controlled trial (RCT)	454 patients (227 in each group)	SPC: Fixed combination of perindopril / indapamide / amlodipine in one tablet (dosage 5/1.25/5 mg or 5/1.25/10 mg). FC: The same three drugs administered separately.	Method: Ratio of capsules consumed to those that should have been taken during the study period. Results: SPC was more effective than FC in improving compliance by reducing pill burden.	There are some concerns regarding risk of bias. The study design was rigorous and compliant with GCP standards, although specific details of the randomization and blinding processes were limited.

2.	Efficacy and safety of a single- pill versus free combination of perindopril /indapamide/ amlodipine: a multicenter, randomized, double-blind study in Chinese patients with hypertension	Nedogoda, et al. (2017)	Russia and Serbia	Randomized Controlled Trial (RCT)	148 patients 75 patients: Single-Pill Combination (SPC) 73 patients: Free Combination (FC)	SPC: Single tablet combination of perindopril 5 mg, indapamide 1.25 mg, and amlodipine 5 mg. FC: Two separate pills consisting of perindopril 4 mg/indapamide 1.25 mg (1 pill) and amlodipine 5 mg (1 pill).	Method: Proportion of days of medication consumption (compliant if ≥80%). Results: SPC group compliance was significantly higher than FC (59.9% vs. 26.9%; $p < 0.001$).	Low risk of bias. The study used a double-blind, randomized design with strict control over the randomization process, blinding, and outcome measurement.
3.	Adherence to triple-component antihypertensive regimens is higher with single-pill than equivalent two-pill regimens: A randomized controlled trial	Sung, et al. (2021)	South Korea (multicenter, 8 university hospitals)	Randomized Controlled Trial (RCT), multicenter, open-label, parallel group	145 hypertensive patients (71 SPC, 74 FC); 132 fully analyzed	SPC: Triple combination single tablet (Olmesartan / amlodipine / HCTZ 20/5/12.5 mg). FC: Two separate pills consisting of dual-SPC (olmesartan/HCTZ 20/12.5 mg) and amlodipine 5 mg.	Method: Medication Event Monitoring System (MEMS) to measure PDC and PDTc. Results: SPC significantly improved compliance compared to FC (OR: 3.63; $p < 0.05$). MEMS provided a more accurate assessment of compliance than pill count.	The overall risk of bias is rated as High. This is due to the high risk of (deviation from the planned intervention. However, the study applied transparent randomization, systematic assessment of adherence variables, and blood pressure.

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3. Cohort Study

The study by Rea, et al. (2018) was a large-scale retrospective cohort study in Italy involving 125,635 hypertensive patients. Adherence was measured indirectly through prescription refill continuity over three years. The results of this study showed that the use of Single-Pill Combination (SPC), especially the combination of RAS blockers and diuretics, tended to increase patient adherence compared to Free Combination (FC) because simplifying the regimen into one tablet increased therapy stability during the follow-up period [2].

Mazza, et al. (2017) conducted a prospective cohort study in Italy involving 184 patients to compare triple combination interventions in the form of SPC and FC. Using patient reports and pill counts, this study found that compliance in the SPC group was significantly higher. The reduction in pill burden in a single tablet makes it easier for patients to follow the treatment regimen and directly improves blood pressure control and lipid parameters [7].

Research by Hostalek, et al. (2015) in Poland involved 10,532 patients in a prospective observational cohort study evaluating the combination of bisoprolol and amlodipine. Adherence was measured by tablet counting, with results showing that approximately 86% of patients in the SPC group achieved excellent adherence. This study concluded that SPC was more effective than FC in improving adherence, contributing to more effective blood pressure control in the real world [3].

In contrast, a retrospective cohort study by Grimmsmann, et al. (2016) in Germany involving 8,032 patients showed different results. By monitoring prescription refill intervals over 4 years, this study found that patients who started therapy with Free Combination (FC) actually had higher persistence (56.4%) compared to the SPC group (39.8%). These findings indicate variations in the effectiveness of SPC in certain populations or different healthcare systems [4].

Masi, et al. (2024) conducted a real-world analysis in Italy on 17,961 patients using a combination of perindopril and bisoprolol. Adherence was measured using the Proportion of Days Covered (PDC) with a threshold of ≥ 80%. The results showed that SPC was significantly more effective, with 45.5% of SPC patients achieving the compliance target compared to only 38.6% in the FC group. The use of Propensity Score Matching (PSM) in this study strengthened the validity of the comparison between the two groups [8].

A national cohort study by Choi, et al. (2021) in South Korea involved a very large number of participants, namely 123,992 patients. This study evaluated the combination of antihypertensive drugs (ARBs) and statins in the form of SPC compared to FC. Using PDC measurements over 540 days, it was found that the SPC group showed consistently higher levels of adherence and persistence compared to the FC group, confirming the long-term effectiveness of SPC [10].

B. Randomized Controlled Trial (RCT) Study

In a phase III randomized clinical trial, Mourad, et al. (2017) studied 454 patients with uncontrolled essential hypertension in 13 countries. The intervention involved a combination of three drugs (perindopril/indapamide/amlodipine). Adherence was measured by the ratio of capsules taken, and the results confirmed that the SPC formulation was more effective in improving adherence than FC because the reduced number of tablets made it easier for patients to manage their treatment consistently [12].

Nedogoda, et al. (2017) conducted a double-blind RCT in Russia and Serbia on 148 patients to compare SPC and FC of perindopril, indapamide, and amlodipine components. Adherence was defined as the proportion of days with ≥ 80% medication consumption. The results showed a statistically significant difference, with the compliance rate in the SPC group reaching 59.9%, far exceeding that of the FC group, which was only 26.9% [9].

Finally, a study by Sung, et al. (2021) in South Korea was an open-label RCT of 145 patients using the most accurate measurement method, namely the Medication Event Monitoring System (MEMS). The results of this electronic monitoring showed that adherence in the SPC group (olmesartan/amlodipine/HCTZ) was significantly superior to the equivalent two-pill regimen, with an odds ratio of 3.63. The use of MEMS provides strong evidence that SPC significantly improves patients' daily adherence behavior [5].

DISCUSSION

Findings in Several Studies

The main findings of this systematic review consistently show that the use of Single-Pill Combination (SPC) is more effective in improving treatment adherence and persistence compared to Free Combination (FC) therapy in the majority of studies analyzed. Of the nine studies included, eight reported significant advantages of SPC, while one study showed different results.

The Role of Regimen Simplification on Adherence

The main driving factor behind the effectiveness of SPC is the reduction in pill burden. RCT studies by Mourad et al. (2017) and Nedogoda et al. (2017) highlight that combining three antihypertensive agents (perindopril, indapamide, and amlodipine) into one tablet dramatically improves adherence [9], [12]. In the study by Nedogoda et al. (2017), the compliance rate in the SPC group reached 59.9%, which was much higher than that in the FC group (26.9%). This confirms that the fewer tablets a patient has to take, the less likely they are to forget or deliberately skip doses [9]. Support for this mechanism is also seen in the cohort study by Mazza et al. (2017), where administering a single-pill regimen made it easier for patients to follow treatment instructions in daily clinical practice [7].

Evidence from Real-World Studies

Data from large-scale cohort studies provide a strong picture of long-term persistence in the general population. Studies by Rea et al. (2018) in Italy (N=125,635) and Choi et al. (2021) in South Korea (N=123,992) show that SPC not only improves compliance at the outset, but also keeps patients on therapy during long follow-up periods (up to 3 years) [2], [10]. The study by Masi et al. (2024) reinforces these findings with administrative data showing that the proportion of patients achieving ideal adherence (PDC ≥ 80%) was significantly higher in the SPC group compared to the Free-Equivalent Combination (FEC) group [8]. This advantage remained evident despite the serious risk of confounding bias in these cohort studies, which was then minimized through Propensity Score Matching (PSM) techniques in the studies by Choi et al. (2021) and Masi et al. (2024) [8], [10].

Accuracy of Adherence Measurement

Variations in adherence measurement methods across studies provide important perspectives. The study by Sung et al. (2021) used highly accurate Medication Event Monitoring System (MEMS) technology, which recorded the exact time of opening the medicine bottle. The results still showed the superiority of SPC with an odds ratio of compliance of 3.63. These findings provide stronger validation than other studies that only use indirect methods such as prescription refills or pill counting [5].

Analysis of Divergent Results

The only anomaly was found in the study by Grimmsmann et al. (2016) in Germany, where the FC group actually showed a higher rate of treatment continuity (56.4%) compared to the SPC group (39.8%). This difference is likely due to specific healthcare system factors, insurance policies, or demographic characteristics of patients in the Mecklenburg-West Pomerania region who may have been more accustomed to separate drug regimens prior to the initiation of SPC [4]. This suggests that although SPC is generally superior, local contextual factors still play a role in treatment success.

Clinical Impact: Blood Pressure Control

Increased adherence in the SPC group was found to be positively correlated with clinical outcomes. The study by Hostalek et al. (2015) noted that approximately 86% of patients in the SPC group achieved excellent adherence, which directly contributed to more effective blood pressure control [3]. Similar findings were reported by Mazza et al. (2017), who observed improvements in blood pressure and lipid parameters alongside increased patient discipline in taking a single daily pill [7].

Overall, evidence from these nine studies strongly supports the recommendation to use SPC as a first-line or escalation strategy to address chronic non-compliance in hypertensive patients, thereby reducing the risk of long-term treatment failure.

Methodological Strengths

This review has significant methodological strengths because it involves a comprehensive study design, including 3 Randomized Controlled Trials (RCTs) and 6 observational cohort studies. The use of large-scale real-world data, such as in the studies by Rea et al. (2018) and Choi et al. (2021), each involving more than 100,000 participants, provides high statistical power to generalize the findings to a broad population. In addition, the application of advanced statistical adjustment techniques such as Propensity Score Matching (PSM) in several observational studies and the use of the Medication Event Monitoring System (MEMS) electronic monitoring technology in the Sung et al. (2021) study improved the accuracy of medication adherence assessment. This review also applied rigorous quality assessment procedures using the standard RoB 2.0 and ROBINS-I instruments to ensure transparency in evaluating the risk of bias across the included literature.

Limitations

Despite its strengths, this review has several limitations, particularly related to the variability in methodological quality among the included studies. The majority of cohort studies were assessed as having an overall risk of bias that was "Serious," mainly due to confounding that could not be fully controlled in real-world clinical settings. In the RCT group, the use of open-label designs in certain studies, such as Sung et al. (2021), raises concerns about bias due to deviation from the intended intervention. In addition, there was heterogeneity in the methods of measuring adherence—ranging from insurance claims data and pill counts to electronic sensors—which could complicate direct comparisons of results between studies. The presence of one study (Grimmsmann et al., 2016) showing contradictory results also indicated that local healthcare system factors may affect the effectiveness of SPC differently in different regions.

Future Research

Future research should focus on conducting high-quality RCTs with stricter blinding methods to validate findings from observational data regarding the superiority of SPC over FC. In addition to measuring compliance parameters such as Proportion of Days Covered (PDC) or Medication Possession Ratio (MPR), future studies should place greater emphasis on the long-term impact on tangible clinical outcomes (hard outcomes), such as a reduction in the risk of major cardiovascular events and mortality rates. Research evaluating the cost-effectiveness of widespread SPC implementation in various healthcare system models is also needed to provide stronger evidence for policymakers. Finally, more in-depth subgroup analyses of the influence of patient demographics and specific drug combinations on long-term adherence would be invaluable in supporting more personalized hypertension therapy strategies.

CONCLUSION

This systematic review concludes that Single-Pill Combination (SPC) is clearly more effective than Free-Combination (FC) in enhancing long-term treatment adherence and persistence among hypertensive patients. Eight out of nine analyzed studies demonstrated SPC's superiority through various indicators such as Proportion of Days Covered (PDC), Medication Possession Ratio (MPR), and therapy persistence, which correlate with improved blood pressure control and reduced risk of treatment failure. However, these findings are influenced by certain limitations, including methodological quality variations, high risk of bias in most cohort studies due to uncontrolled confounding, and heterogeneity in adherence measurement methods that complicate uniform effect size estimation. Practically, these results indicate that prioritizing SPC in clinical practice is warranted to reduce pill burden, boost patient discipline, and potentially lower healthcare costs.

Future research should prioritize high-quality randomized controlled trials with stricter blinding procedures, which measure not only adherence parameters like PDC and MPR but also long-

term clinical outcomes such as major cardiovascular events and mortality rates. Cost-effectiveness studies across diverse healthcare systems are also essential to ensure broad SPC implementation is backed by robust economic evidence. Additionally, in-depth subgroup analyses based on demographic characteristics, comorbidities, and specific drug combinations would greatly aid in developing more personalized hypertension therapy strategies. Overall, these findings affirm that optimizing SPC use represents a strategic step toward addressing chronic non-adherence in global hypertension management.

REFERENCES

[1] X. Zhao *et al.*, "Comparison of efficacies of commonly used hypertension treatment modalities: A retrospective study of 1900 participants in a hypertension clinic," *Medical Science Monitor*, vol. 26, Apr. 2020, doi: 10.12659/MSM.921211.

[2] F. Rea, G. Corrao, L. Merlino, and G. Mancia, "Initial antihypertensive treatment strategies and therapeutic inertia evidence from a large population-based cohort," *Hypertension*, vol. 72, no. 4, pp. 846–853, 2018, doi: 10.1161/HYPERTENSIONAHA.118.11308.

[3] U. Hostalek, D. Czarnecka, and E. M. W. Koch, "Treatment of Hypertensive Patients with a Fixed-Dose Combination of Bisoprolol and Amlodipine: Results of a Cohort study with More Than 10,000 Patients," *Cardiol Ther*, vol. 4, no. 2, pp. 179–190, Dec. 2015, doi: 10.1007/s40119-015-0045-z.

[4] T. Grimmsmann and W. Himmel, "Comparison of therapy persistence for fixed versus free combination antihypertensives: a retrospective cohort study," *BMJ Open*, vol. 6, p. 11650, 2016, doi: 10.1136/bmjopen-2016.

[5] J. Sung *et al.*, "Adherence to triple-component antihypertensive regimens is higher with single-pill than equivalent two-pill regimens: A randomized controlled trial," *Clin Transl Sci*, vol. 14, no. 3, pp. 1185–1192, May 2021, doi: 10.1111/cts.12979.

[6] J. G. Wang *et al.*, "Efficacy and safety of a single-pill versus free combination of perindopril/indapamide/amlodipine: a multicenter, randomized, double-blind study in Chinese patients with hypertension," *J Hypertens*, vol. 42, no. 8, pp. 1373–1381, Aug. 2024, doi: 10.1097/HJH.0000000000003741.

[7] A. Mazza *et al.*, "Fixed-Dose Triple Combination of Antihypertensive Drugs Improves Blood Pressure Control: From Clinical Trials to Clinical Practice," *Adv Ther*, vol. 34, no. 4, pp. 975–985, Apr. 2017, doi: 10.1007/s12325-017-0511-1.

[8] S. Masi, Z. Kobalava, C. Veronesi, E. Giacomini, L. Degli Esposti, and K. Tsioufis, "A Retrospective Observational Real-Word Analysis of the Adherence, Healthcare Resource Consumption and Costs in Patients Treated with Bisoprolol/Perindopril as Single-Pill or Free Combination," *Adv Ther*, vol. 41, no. 1, pp. 182–197, Jan. 2024, doi: 10.1007/s12325-023-02707-7.

[9] S. V. Nedogoda and V. J. Stojanov, "Single-Pill Combination of Perindopril/Indapamide/Amlodipine in Patients with Uncontrolled Hypertension: A Randomized Controlled Trial," *Cardiol Ther*, vol. 6, no. 1, pp. 91–104, Jun. 2017, doi: 10.1007/s40119-017-0085-7.

[10] J. M. Choi, S. H. Lee, Y. J. Jang, M. Kang, and J. H. Choi, "Medication adherence and clinical outcome of fixed-dose combination vs. Free combination of angiotensin receptor blocker and statin," *Circulation Journal*, vol. 85, no. 5, pp. 595–603, Apr. 2021, doi: 10.1253/CIRCJ.CJ-20-0966.

[11] K. Marinier, P. Macouillard, M. de Champvallins, N. Deltour, N. Poulter, and G. Mancia, "Effectiveness of two-drug therapy versus monotherapy as initial regimen in hypertension: A propensity score-matched cohort study in the UK Clinical Practice Research Datalink," *Pharmacoepidemiol Drug Saf*, vol. 28, no. 12, pp. 1572–1582, Dec. 2019, doi: 10.1002/pds.4884.

[12] J. J. Mourad, C. Amodeo, M. De Champvallins, R. Brzozowska-Villatte, and R. Asmar, "Blood pressure-lowering efficacy and safety of perindopril/indapamide/amlodipine single-pill combination in patients with uncontrolled essential hypertension: A multicenter, randomized, double-blind, controlled trial," *J Hypertens*, vol. 35, no. 7, pp. 1481–1495, Jul. 2017, doi: 10.1097/HJH.0000000000001359.