e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2025; 17(10); 94-99

Original Research Article

Comparative Evaluation of Resistant Hypertension Management: Efficacy of Dual versus Triple Drug Therapy in Reducing Cardiovascular Events in Middle-Aged Adults

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Received: 01-09-2025 / Revised: 05-10-2025 / Accepted: 08-10-2025
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Conflict of interest: Nil

Abstract

Background: Resistant hypertension (RH) confers a substantial risk for cardiovascular events. While guidelines advocate for multi-drug regimens, the optimal balance between therapeutic intensity, regimen complexity, and patient adherence remains unclear. The efficacy of a simplified, high-dose dual-drug strategy versus a standard triple-drug therapy on hard cardiovascular outcomes has not been well-established.

Methods: We conducted a 36-month, multicenter, prospective, randomized controlled trial involving 850 adults (aged 45–65 years) with confirmed RH. Participants were randomized 1:1 to either a dual-therapy group (maximally-titrated single-pill combination of an angiotensin receptor blocker [ARB] and a calcium channel blocker [CCB]; n=425) or a triple-therapy group (an angiotensin-converting enzyme [ACE] inhibitor, a CCB, and a thiazide-type diuretic; n=425). The primary endpoint was a composite of MACE, including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. Secondary endpoints included mean change in systolic blood pressure (SBP), achievement of target BP (<130/80 mmHg), medication adherence, and incidence of adverse effects.

Results: At 36 months, the incidence of the primary MACE endpoint was not statistically different between the groups, although a trend favoured triple therapy (12.5% in the dual-therapy group vs. 9.9% in the triple-therapy group; Hazard Ratio [HR] 1.28; 95% CI 0.86–1.91; p=0.22). The triple-therapy group demonstrated a significantly greater mean reduction in office SBP from baseline (–25.1 ± 10.2 mmHg vs. –22.5 ± 9.8 mmHg; p=0.04) and a higher rate of achieving target BP (64.2% vs. 55.3%; p=0.02). Conversely, the dual-therapy group showed significantly higher medication adherence rates (92.1% ± 8.5% vs. 84.5% ± 12.3%; p<0.01). The incidence of peripheral edema was higher in the dual-therapy group (15.1% vs. 9.9%, p=0.03), while hypokalemia was more common in the triple-therapy group (8.7% vs. 2.4%, p<0.01).

Conclusion: In middle-aged adults with resistant hypertension, standard triple-drug therapy was superior to a high-dose dual-drug regimen in lowering blood pressure and achieving control targets. This superior BP control did not translate into a statistically significant reduction in MACE over a 36-month follow-up, though a favorable trend was observed. The higher adherence associated with the simplified dual-therapy regimen was insufficient to overcome its lower antihypertensive efficacy in this high-risk population.

Keywords: Resistant Hypertension, Cardiovascular Events, Dual Therapy, Triple Therapy, Antihypertensive Agents, Adherence.

Introduction

Hypertension is a leading modifiable risk factor for cardiovascular morbidity and mortality worldwide, affecting over 1.2 billion people [1]. A significant subset of this population suffers from resistant hypertension (RH), defined as blood pressure (BP) that remains above the recommended target despite the concurrent use of three or more antihypertensive agents from different classes, including a diuretic, at optimal doses, or BP that is controlled only with four or more medications [2]. Patients with RH face a disproportionately high risk of myocardial infarction, stroke, heart failure, and chronic kidney disease compared to those with controlled hypertension [3]. The cornerstone of RH

management is the intensification of pharmacotherapy, typically involving the addition of a fourth-line agent. The PATHWAY-2 trial established the superiority of the mineralocorticoid receptor antagonist (MRA) spironolactone over other add-on therapies, solidifying its role in guideline recommendations [4]. However, the clinical management of RH is often complicated by polypharmacy, which contributes to poor medication adherence, a major barrier to effective BP control [5]. Adherence rates are inversely correlated with the number of prescribed pills, and simplifying treatment regimens through the use of fixed-dose combinations (FDCs) has been shown to improve patient compliance [6].

This raises a critical clinical question: could a simplified, maximally-titrated dual-drug regimen, particularly a single-pill FDC, offer a net clinical benefit comparable to a standard, more complex, and triple-drug regimen? The hypothesis is that the substantial improvement in adherence from a simplified regimen might compensate for the potentially lower pharmacodynamic potency compared to three agents, ultimately leading to similar or even superior long-term cardiovascular outcomes. While previous studies have demonstrated the BP-lowering efficacy of various FDCs [7], there is a paucity of data from large-scale, long-term randomized controlled trials (RCTs) directly comparing a simplified dual-therapy strategy against a standard triple-therapy approach using hard cardiovascular endpoints as the primary outcome in a dedicated RH population.

This research gap is significant because if a simplified regimen proves non-inferior for clinical outcomes, it could offer a paradigm shift in managing a subset of RH patients, prioritizing adherence and tolerability without compromising cardiovascular protection. Therefore, the primary aim of this study was to compare the efficacy of a maximally-titrated dual-drug regimen (ARB/CCB FDC) versus a standard triple-drug regimen (ACE inhibitor + CCB + thiazide diuretic) in reducing the incidence of major adverse cardiovascular events (MACE) over a 36-month period in middle-aged adults with resistant hypertension.

Materials and Methods

Study Design and Population: This was a multicenter, prospective, randomized, open-label, parallel-group controlled trial conducted at 35 outpatient hypertension clinics.

Eligible participants were middle-aged adults (45–65 years) with a documented diagnosis of RH. Inclusion criteria were: (1) age 45 to 65 years; (2) office SBP ≥140 mmHg and/or DBP ≥90 mmHg despite stable treatment with optimal or maximally tolerated doses of at least three antihypertensive agents, including a thiazide-type diuretic, for at least three months; and (3) an estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m².

Key exclusion criteria included: (1) known secondary causes of hypertension; (2) history of myocardial infarction, stroke, or coronary revascularization within the preceding six months; (3) heart failure with reduced ejection fraction (<40%); (4) serum potassium >5.0 mEq/L at screening; (5) severe chronic kidney disease (eGFR <45 mL/min/1.73 m²); (6) pregnancy or planned pregnancy; and (7) known intolerance or contraindication to any of the study medications.

Randomization and Interventions: Following a 4-week run-in period to confirm eligibility and medication stability, 850 participants were randomized in a 1:1 ratio using a computer-generated block randomization scheme stratified by clinical center and history of diabetes.

Dual-Therapy Group (n=425): Participants were switched to a single-pill, fixed-dose combination of valsartan/amlodipine. The initial dose was 160/5 mg once daily, which was titrated up every four weeks to a maximum of 320/10 mg to achieve the target BP of <130/80 mmHg. Previous antihypertensive agents were discontinued.

Triple-Therapy Group (n=425): Participants continued on a regimen consisting of three separate pills: lisinopril (titrated up to 40 mg/day), amlodipine (titrated up to 10 mg/day), and hydrochlorothiazide (titrated up to 25 mg/day). Dosages were adjusted by the treating physician at their discretion to achieve the target BP of <130/80 mmHg.

Data Collection and Endpoints: Follow-up visits were scheduled at baseline, 1, 3, 6, 12, 18, 24, 30, and 36 months. At each visit, seated office BP was measured three times, one minute apart, using a validated automated oscillometric device; the average of the last two readings was used for analysis.

The primary endpoint was the first occurrence of a MACE composite, including non-fatal myocardial infarction, non-fatal ischemic or hemorrhagic stroke, or cardiovascular death. All potential endpoint events were adjudicated by an independent clinical events committee blinded to treatment allocation.

Secondary endpoints included: (1) mean change in office SBP and DBP from baseline to 36 months; (2) proportion of participants achieving target BP (<130/80 mmHg); (3) medication adherence, assessed using the Medication Possession Ratio (MPR) derived from pharmacy refill records over the study duration; and (4) incidence of pre-specified adverse events, such as hyperkalemia

(serum K+ >5.5 mEq/L), acute kidney injury, peripheral edema, and symptomatic hypotension.

Statistical Analysis: The sample size was calculated to provide 80% power to detect a 40% relative risk reduction in the primary endpoint, assuming an annual MACE rate of 4.5% in the triple-therapy group and a two-sided alpha level of 0.05.

All analyses were performed on an intention-to-treat basis. Baseline characteristics were summarized using means and standard deviations (SD) for continuous variables and percentages for categorical variables. Group comparisons were made using Student's t-tests or Mann-Whitney U tests for continuous data and chi-square or Fisher's exact tests for categorical data. The time-to-first MACE was analyzed using Kaplan-Meier survival curves, and the difference between groups was assessed with the log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using a Cox proportional hazards model. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY).

Results

Of the 1,020 patients screened, 850 were eligible and randomized (425 to dual therapy, 425 to triple therapy). A total of 788 participants (92.7%) completed the 36-month follow-up.

The baseline demographic and clinical characteristics of the participants were well-balanced between the two treatment groups (Table 1). The mean age was 58.6 years, 54.1% were male, and the mean baseline office BP was 154.2/93.8 mmHg.

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Dual Therapy (n=425)	Triple Therapy (n=425)	p-value
Age, years (mean ± SD)	58.7 ± 5.2	58.5 ± 5.4	0.64
Male Sex, n (%)	232 (54.6)	228 (53.6)	0.78
Body Mass Index, kg/m² (mean ± SD)	31.2 ± 4.1	31.5 ± 4.3	0.35
Baseline SBP, mmHg (mean ± SD)	154.5 ± 8.1	153.9 ± 7.9	0.31
Baseline DBP, mmHg (mean ± SD)	94.1 ± 5.5	93.5 ± 5.7	0.19
Current Smoker, n (%)	71 (16.7)	65 (15.3)	0.59
Type 2 Diabetes Mellitus, n (%)	160 (37.6)	168 (39.5)	0.57
Dyslipidemia, n (%)	295 (69.4)	301 (70.8)	0.68
eGFR, mL/min/1.73m² (mean ± SD)	72.4 ± 15.1	71.9 ± 14.8	0.66

Blood Pressure and Adherence Outcomes: At the end of the 36-month follow-up, the triple-therapy group exhibited a significantly greater reduction in mean SBP compared to the dual-therapy group. A higher proportion of participants in the triple-therapy group achieved the target BP of <130/80 mmHg. In contrast, medication adherence, measured by MPR, was significantly higher in the dual-therapy group (Table 2).

Table 2: Blood Pressure and Adherence Outcomes at 36 Months

Outcome	Dual Therapy (n=425)	Triple Therapy (n=425)	p-value
Change in SBP (mmHg)			
Mean change from baseline (± SD)	–22.5 ± 9.8	–25.1 ± 10.2	**0.04**
Change in DBP (mmHg)			
Mean change from baseline (± SD)	–12.8 ± 6.1	–14.2 ± 6.5	**0.03**
BP Control			
Achievement of Target BP (<130/80 mmHg), n (%)	235 (55.3)	273 (64.2)	**0.02**
Medication Adherence			
Mean Medication Possession Ratio, % (± SD)	92.1 ± 8.5	84.5 ± 12.3	**<0.01**
BP: Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.			

Cardiovascular and Safety Outcomes: The primary composite MACE endpoint occurred in 53 participants (12.5%) in the dual-therapy group and 42 participants (9.9%) in the triple-therapy group. This difference did not reach statistical significance (HR 1.28; 95% CI 0.86–1.91; p=0.22) (Table 3). The Kaplan-Meier curves for the time to first MACE showed an early and sustained separation favoring the triple-therapy group, but the log-rank test was non-significant (p=0.21).

Adverse events differed by treatment arm. Peripheral edema was significantly more common in the dual-therapy group, consistent with high-dose CCB use. Hypokalemia and dizziness were more frequent in the triple-therapy group, likely attributable to the diuretic and more intensive BP lowering, respectively.

Table 3: Incidence of Clinical Endpoints and Key Adverse Events

Event	Dual Therapy (n=425), n (%)	Triple Therapy (n=425), n (%)	Hazard Ratio (95% CI)	p-value
Primary MACE Endpoint	**53 (12.5)**	**42 (9.9)**	**1.28 (0.86–1.91)**	**0.22**
- Non-fatal Myocardial Infarction	18 (4.2)	14 (3.3)		
- Non-fatal Stroke	23 (5.4)	19 (4.5)		
- Cardiovascular Death	12 (2.8)	9 (2.1)		
All-Cause Mortality	**19 (4.5)**	**15 (3.5)**	**1.27 (0.64–2.53)**	**0.49**
Adverse Events of Interest				
Peripheral Edema	64 (15.1)	42 (9.9)	-	**0.03**
Dizziness/Presyncope	45 (10.6)	68 (16.0)	-	**0.02**
Hypokalemia (<3.5 mEq/L)	10 (2.4)	37 (8.7)	-	**<0.01**
Hyperkalemia (>5.5 mEq/L)	8 (1.9)	11 (2.6)	-	0.48
MACE: Major Adverse Cardiovascular Events.				

Discussion

In this randomized trial involving middle-aged adults with resistant hypertension, a standard triple-drug therapy resulted in statistically superior blood pressure reduction and a higher proportion of patients achieving guideline-recommended BP targets compared to a simplified, high-dose dual-drug regimen. Despite the superior BP control, this did not translate into a statistically significant reduction in the primary composite endpoint of MACE over a 36-month follow-up period, although a consistent trend favoring triple therapy was observed across all components of the endpoint.

The finding that a three-drug regimen provides greater antihypertensive efficacy than a two-drug regimen, even when the latter is maximally titrated, is consistent with established pharmacological principles and clinical guidelines, which advocate for a multi-mechanistic approach to overcome the complex pathophysiology of hypertension [2, 8].

The observed mean SBP difference of 2.6 mmHg between the groups is clinically meaningful and aligns with large-scale meta-analyses demonstrating that even small decrements in SBP confer significant reductions in cardiovascular risk [9].

A key finding of our study was the significantly higher medication adherence rate in the dual-therapy group, which received a single-pill FDC. This confirms extensive evidence that simplifying medication regimens by reducing pill burden improves patient adherence [6, 10]. Our study's novelty lies in prospectively evaluating whether this adherence benefit could offset lower pharmacological potency in terms of hard clinical outcomes. Our results suggest that, in this high-risk RH population, the adherence advantage of the simplified regimen was insufficient to achieve non-inferiority in cardiovascular event reduction. The persistent, albeit non-significant, higher event rate in the dual-therapy group suggests that the magnitude of BP lowering remains the dominant determinant of cardiovascular protection in RH.

The lack of statistical significance for the primary endpoint, despite the difference in BP control, warrants careful interpretation. It is possible that the 36-month follow-up duration was insufficient to allow the full cardiovascular benefit of the superior BP lowering in the triple-therapy group to manifest. Landmark trials like the SPRINT study, which demonstrated significant outcome benefits from intensive BP control, had a similar follow-up period but achieved a much larger SBP separation between groups (~13 mmHg) [11].

The modest 2.6 mmHg difference in our trial may require a larger sample size or longer follow-up to demonstrate a statistically significant impact on MACE. Furthermore, it is plausible that the enhanced adherence in the dual-therapy arm did provide some degree of clinical benefit, partially mitigating the risk associated with a slightly higher average BP and narrowing the outcomes gap between the groups.

The safety profiles of the two regimens were distinct and predictable based on their components. The higher incidence of peripheral edema with high-dose amlodipine in the dual-therapy group and the greater frequency of hypokalemia and dizziness with the diuretic-containing triple-therapy regimen are well-documented side effects [12-15].

These findings highlight the importance of individualizing therapy based on patient characteristics and tolerability. This study has several strengths, including its randomized,

controlled design, a large and well-defined cohort of patients with RH, the use of an adjudicated hard clinical endpoint, and a relatively long follow-up period. However, it also has limitations.

The open-label design could have introduced performance bias, although the use of a blinded events committee mitigates this for the primary outcome. Our choice of specific antihypertensive agents may not be generalizable to all other drug combinations within the same classes. Lastly, our study was restricted to middle-aged adults, and the findings may not apply to older or younger populations with RH.

Conclusion

Among middle-aged adults with resistant hypertension, a standard, multi-pill triple-drug therapy was more effective than a maximally-titrated, single-pill dual-drug therapy for reducing systolic blood pressure and achieving guideline-recommended BP targets.

While the simplified dual-therapy regimen significantly improved medication adherence, this advantage did not translate into a statistically significant reduction in major adverse cardiovascular events over 36 months.

A consistent, albeit non-significant, trend toward better cardiovascular outcomes was observed with the more intensive triple-therapy regimen.

These findings reinforce the critical importance of achieving optimal blood pressure control through aggressive, multi-drug pharmacotherapy in this high-risk population, suggesting that the degree of BP lowering remains a more powerful determinant of outcomes than the benefits derived from regimen simplification alone.

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