Hypertension

ORIGINAL ARTICLE

Low-Dose TEL/AML/CHTD SPC Versus Standard-Dose TEL in Hypertension: Phase III RCT

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BACKGROUND: Although low-dose triple single-pill combination therapies show promising efficacy and safety, studies comparing them to standard-dose monotherapies remain limited. This phase III, randomized, double-blind trial evaluated the efficacy and safety of a low-dose single-pill combination of telmisartan, amlodipine, and chlorthalidone versus standard-dose telmisartan monotherapy in patients with essential hypertension.

METHODS: After a 4-week placebo run-in period, 314 eligible subjects were randomized to either receive telmisartan/amlodipine/chlorthalidone 20/2.5/6.25 mg or telmisartan 40 mg for 8 weeks. The primary efficacy end point was the change in mean sitting systolic blood pressure from baseline to week 8, with noninferiority assessed in the per-protocol set (PPS), followed by superiority testing in the full analysis set using a gatekeeping approach to control for type I error.

RESULTS: At week 8, the combination group demonstrated significant mean sitting systolic blood pressure reduction compared with monotherapy in the per-protocol set analysis (least squares mean difference, −3.8 mm Hg [95% CI: −6.7 to −0.9]; P=0.01), establishing its noninferiority. Furthermore, the superiority of the combination therapy was confirmed in the full analysis set (LS mean difference, −4.0 mm Hg [95% CI, −6.8 to −1.3]; P<0.01). Mean sitting diastolic BP, BP normalization rates, and response rates also favored the combination group at weeks 4 and 8 (all P<0.01). Subgroup analyses showed consistent efficacy across clinical strata, including age and prior antihypertensive treatment. The incidence of adverse events was comparable between groups, with no serious drug-related events reported.

CONCLUSIONS: Low-dose triple single-pill combination of telmisartan/amlodipine/chlorthalidone demonstrated superior BP-lowering efficacy with well-tolerated and comparable safety to standard-dose telmisartan monotherapy.

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Key Words: amlodipine ■ antihypertensive agents ■ blood pressure ■ chlorthalidone ■ hypertension ■ telmisartan

Hypertension remains the leading modifiable risk factor for global morbidity and mortality, affecting an estimated 1.3 billion people as of 2023.[1] According to the World Health Organization, hypertension is defined as a systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg and is responsible for 12.8% of global mortality.[2] Recent studies have reported the prevalence of hypertension to range from 11% to 48% in Asia, 46% in Africa, and 48% in the United States.[3–5] Although differences in

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NOVELTY AND RELEVANCE

What Is New?

This phase III clinical trial was the first study to evaluate the efficacy and safety of a low-dose triple single-pill combination of telmisartan/amlodipine/chlorthalidone compared with standard-dose telmisartan in essential hypertension subjects.

What Is Relevant?

The low-dose triple combination of telmisartan/amlodipine/chlorthalidone therapy effectively reduces the mean sitting systolic blood pressure, mean sitting diastolic blood pressure, and pulse pressure in patients with essential hypertension compared with standard-dose telmisartan monotherapy.

Clinical/Pathophysiological Implications?

The telmisartan/amlodipine/chlorthalidone combination offers a potential reduction in cardiovascular risk by effectively lowering blood pressure in patients with essential hypertension. It may serve as a valuable treatment option, applicable both as an initial and add-on strategy, and particularly beneficial for older adults.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE	adverse event
ARB	angiotensin receptor blocker
BP	blood pressure
DBP	diastolic blood pressure
LS	least squares
MSDBP	mean sitting diastolic blood pressure
MSSBP	mean sitting systolic blood pressure
OR	odds ratio
PPS	per-protocol set
SAS	Statistical Analysis System
SBP	systolic blood pressure
SPC	single-pill combination

treatment targets across countries may contribute to some variation, control rates also show wide disparities in population-based studies: about 30% in Europe, 51% in the United States, and 59% in South Korea, but much lower in India (≈23%) and sub-Saharan Africa (<20%).[6–10] Despite the availability of numerous antihypertensive therapies, global control remains insufficient with considerable regional variation.

According to the 2022 Korean Society of Hypertension guidelines, for patients with stage 1 hypertension (SBP, 140–159 mm Hg or DBP, 90–99 mm Hg) whose blood pressure (BP) is not adequately controlled with monotherapy, the addition of another agent is recommended, with single-pill combination (SPCs) highlighted as a strategy to improve treatment persistence.[11,12] Meanwhile, the 2024 European Society of Cardiology guidelines recommend initiating dual-combination therapy from the outset to enhance efficacy and achieve faster BP reduction, using agents with complementary mechanisms and then, based on the patient's response, increasing the number of medications in a stepwise approach.[13] Accordingly, if BP remains uncontrolled within 1 to 3 months of starting dual therapy—particularly by 3 months—treatment should be intensified by adding a third agent.[13] Consistent with these recommendations, the 2025 American College of Cardiology/American Heart Association guidelines also highlight the value of early combination therapy. Monotherapy may still be considered for patients with stage 1 hypertension (SBP, 130–139 mm Hg and DBP, 80–89 mm Hg), particularly those whose BP is close to target, but initial combination therapy is recommended for stage 2 hypertension and for selected high-risk patients with stage 1 hypertension, preferably with an SPC to improve adherence and BP control.[14]

Nevertheless, real-world treatment patterns still favor monotherapy. In a large US Claims-based cohort of newly treated adults with hypertension (2013–2021), 75% started on monotherapy, while only 25% received combination therapy (19% 2 agents; 6% ≥3 agents).[15] This persistent guideline–practice gap likely contributes to suboptimal BP control in routine care. Against this backdrop, although standard-dose combination therapy is effective, rising concerns about its side effects have fueled interest in a low-dose approach, which aims to maintain the efficacy of combined treatments while reducing adverse effects.

In addition to the pharmacological efficacy of antihypertensive agents, treatment adherence plays a critical role in indirectly improving outcomes, as poor adherence is associated with suboptimal BP control and increased cardiovascular risk.[13,16] To promote adherence and long-term persistence, major guidelines such as those from

the European Society of Cardiology, European Society of Hypertension, and the International Society of Hypertension recommend SPCs, which simplify treatment regimens and reduce pill burden.[13,17,18]

Combining these advantages, low-dose SPC can be considered a suitable initial therapy for hypertension, as it offers excellent treatment outcomes through strong efficacy, improved adherence, and favorable safety. Currently, a combination of 3 antihypertensive drugs—an ACE (angiotensin-converting enzyme) inhibitor or angiotensin receptor blocker (ARB), a calcium channel blocker, and a thiazide or thiazide-like diuretic—is considered a preferred first-line option for low-dose SPCs. Each of these drugs is known to have distinct benefits for hypertension treatment. Among these antihypertensive agents, this study combined the 3 drugs—an ARB, which is known for its high adherence and low discontinuation rates due to a favorable safety profile,[17,19,20] a calcium channel blocker, and a thiazide diuretic—into a low-dose SPC formulation. The characteristics of each drug are as follows. Within the ARB class, telmisartan has the longest half-life (24 hours) and the highest binding affinity to the angiotensin II type 1 receptor, providing potent and sustained BP control throughout the day while contributing to cardiovascular risk reduction.[21] Amlodipine, a dihydropyridine calcium channel blocker, reduces BP through arterial vasodilation, with added benefits in patients with diabetic hypertension and at high risk of stroke.[22–24] Chlorthalidone, a thiazide-like diuretic, offers sustained 24-hour BP control owing to its long half-life (22–55 hours), enabling consistent volume modulation and contributing to improved nighttime BP reduction.[25]

The efficacy and safety profiles of low-dose SPCs used for hypertension vary depending on the combination of agents, their doses, and the dosing schedule. Therefore, to guide the optimal selection of low-dose SPCs in clinical practice, robust evidence from well-designed clinical trials is essential. This phase III study is the first to evaluate the 8-week efficacy and safety of a triple low-dose SPC combining telmisartan, amlodipine, and chlorthalidone compared with standard-dose telmisartan monotherapy in patients with essential hypertension.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

This phase III, randomized, double-blind (patients and investigators), active-controlled, multicenter clinical study was conducted at 28 clinical sites across South Korea, primarily tertiary hospitals providing specialized cardiovascular care, between May and December 2024. The study was conducted in accordance with a prespecified study protocol, the synopsis of which is provided in the Supplemental Methods. The trial was registered on www.clinicaltrials.gov and approved by the Ministry of Food and Drug Safety. Ethical approval was obtained from the institutional review boards at all participating sites before study initiation. The study was conducted in compliance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonization, and applicable local regulations. All subjects provided written informed consent before any study-related procedures were performed.

Eligible participants who met all inclusion and exclusion criteria at screening entered a 4-week run-in period, during which they received a placebo once daily and were instructed to follow therapeutic lifestyle changes. After the run-in period, subjects who remained eligible at baseline were randomized in a 1:1 ratio to receive either the telmisartan/amlodipine/chlorthalidone 20/2.5/6.25 mg or telmisartan 40 mg. Stratified block randomization was performed using baseline mean sitting SBP (MSSBP; <160 mm Hg or ≥160 mm Hg) as the stratification factor. Randomization codes were generated by an independent statistician and implemented via an interactive web response system, which concealed the allocation sequence from investigators and study personnel until assignment. To maintain blinding, all treatment groups received 2 tablets once daily for 8 weeks, administered orally at the same time each day: 1 active tablet and 1 matching placebo tablet, manufactured to be indistinguishable in appearance. Follow-up visits were conducted at 4 and 8 weeks (Figure S1).

Study Population

Adults aged ≥19 years who met all eligibility criteria at both screening and randomization were included in the study. At screening, participants were required to have an MSSBP measured in the designated reference arm: ≥140 and <180 mm Hg for treatment-naïve individuals, and <180 mm Hg for those who had received antihypertensive medication within 4 weeks. The reference arm was defined as the arm with higher MSSBP, or higher mean sitting DBP (MSDBP) if MSSBP values were equal, and without any functional and anatomic abnormalities. At randomization, all participants were required to have MSSBP between ≥140 and <180 mm Hg, MSDBP <110 mm Hg, and drug adherence of ≥70% during the 4-week placebo run-in period. Participants were considered eligible if they were deemed clinically appropriate by the investigator to discontinue the prior antihypertensive medications.

Key exclusion criteria included clinically significant medical conditions or laboratory abnormalities that could confound study outcomes, subjects with an interarm discrepancy in sitting SBP ≥20 mm Hg or sitting DBP ≥10 mm Hg across 3 consecutive measurements were also excluded. Detailed inclusion and exclusion criteria are provided in Table S1.

Efficacy and Safety Outcomes

The primary efficacy end point was the change in MSSBP from baseline to week 8 between the telmisartan/amlodipine/chlorthalidone 20/2.5/6.25 mg and telmisartan 40 mg groups. Secondary end points included changes from baseline to week 4 and week 8 in MSSBP (only week 4), MSDBP, and pulse pressure (MSSBP–MSDBP). Additional secondary end points were the proportion of participants achieving target BP (<140/90

mm Hg) and BP response (defined as a reduction of ≥20 mm Hg in MSSBP or reduction of ≥10 mm Hg in MSDBP [or both] from baseline). Subgroup analyses for the primary efficacy end point were conducted based on sex, which was prespecified in the study protocol, and additional post hoc exploratory criteria. Post hoc subgroup analyses, not prespecified in the study protocol, were performed based on age (<60 years or ≥60 years), baseline MSSBP (<160 mm Hg or ≥160 mm Hg), duration of hypertension (<5 years or ≥5 years), and baseline antihypertensive treatment status (yes or no). Baseline antihypertensive treatment status was defined as yes if the patient had received medication for essential hypertension before randomization.

BP was assessed at screening, baseline, week 4, and week 8. On each BP assessment day, participants were instructed to withhold the investigational drug until completion of BP measurement and to avoid caffeine, exercise, and smoking for at least 30 minutes before measurement. After ≥5 minutes of seated rest, 3 BP readings were taken from the same arm at 2-minute intervals using the same calibrated sphygmomanometer. The mean BP was calculated using the average of the last 2 of the 3 readings from the reference arm.

Safety assessments included the incidence of treatment-emergent adverse events (AEs), AEs of special interest: defined as edema, serious AEs, adverse drug reactions (ADRs), and serious ADRs. Additional safety parameters included vital signs, physical exams, clinical laboratory tests, and 12-lead echocardiograms. All AEs were coded according to the Medical Dictionary for Regulatory Activities, version 24.1, and categorized by system organ class and preferred term.

Sample Size

The study was designed using a fixed-sequence hierarchical gatekeeping strategy, with noninferiority designated as the primary hypothesis and superiority as the secondary hypothesis, to ensure control of the family-wise type I error rate at a 2-sided significance level of 5%.

For the estimation of the treatment difference, we referred to both a prior phase 2 trial and published studies of telmisartan 40 mg, because telmisartan 40 mg was not included as a comparator in the phase 2 trial. A weighted mean for telmisartan 40 mg was calculated from several clinical trials, which yielded a mean reduction of −13.08 mm Hg at 8 weeks.[26–28] In the prior phase 2 trial, the corresponding effect was −19.55 mm Hg. The resulting difference of −6.47 mm Hg was, therefore, adopted as the expected treatment effect. Notably, across the different studies, the treatment difference was consistently within a range of −5 to −7 mm Hg, supporting the robustness of this assumption.

The noninferiority margin of 3 mm Hg was selected based on precedent from major trials of antihypertensive agents, where margins between 3 and 5 mm Hg have been commonly applied.[29,30] To ensure a conservative and clinically acceptable threshold, we applied the lower bound of this range. For the noninferiority test, a 1-sided significance level of 2.5% was applied. Although the expected treatment effect was −6.47 mm Hg, we conservatively assumed a substantially smaller between-group difference of −1 mm Hg with a pooled SD of 11.25 mm Hg for the sample size calculation. This intentionally stringent assumption was adopted to avoid any risk of overestimation and to ensure sufficient power under the most conservative scenario. Based on these assumptions, a sample size of 130 participants per group was required to achieve a statistical power of 81.4% power.

The superiority hypothesis, which was tested only on confirmation of noninferiority, was evaluated at a 2-sided significance level of 5%. Assuming a treatment difference of −6.47 mm Hg and the same SD, a sample size of 101 participants per group was estimated to provide 98.3% power.

To ensure at least 80% power for both hypotheses, the larger sample size requirement (130 participants per group) was selected. Accounting for an anticipated dropout rate of 7%, the final target sample size was set at 140 participants per group, for a total of 280 participants.

Statistical Analysis

The full analysis set (FAS) included all randomized participants who received at least 1 dose of the study drug and had at least 1 posttreatment MSSBP assessment, and the per-protocol set (PPS) included participants who completed the study without major protocol deviations. Overall efficacy was assessed in both the PPS and FAS populations, and the PPS results are primarily presented in tables, while FAS results are presented mainly through graphical formats.

The primary hypothesis of this study was to prove both noninferiority (PPS) and superiority (FAS) of low-dose telmisartan/amlodipine/chlorthalidone combination over standard-dose telmisartan monotherapy for the mean change in MSSBP from baseline to week 8. To control for multiplicity in the primary end point hypothesis, a fixed-sequence hierarchical gatekeeping strategy was applied. Noninferiority was demonstrated if the upper limit of the 95% CI for the least squares (LS) mean difference was below the prespecified margin of 3 mm Hg. Superiority was tested only if noninferiority was demonstrated.

Between-group comparisons of changes from baseline for continuous efficacy outcomes were performed using ANCOVA, with treatment group as a fixed effect and baseline values as covariates. For the primary efficacy end point, MSSBP at week 8 was analyzed using ANCOVA model, prespecified in the study protocol. In addition, a mixed model for repeated measures was performed as a post hoc sensitivity analysis to assess the robustness of the primary analysis, with visit treated as a repeated factor and baseline MSSBP, treatment group, and treatment-by-visit interaction included as covariates. For MSDBP and pulse pressure, the baseline MSSBP category was additionally included as a categorical stratification covariate in the ANCOVA model. Results were reported as LS means by treatment group, along with LS mean differences (test−control), SEs, 95% CIs, and *P* values. For categorical efficacy outcomes, logistic regression was performed with adjustment for the baseline MSSBP category. Results were summarized as odds ratios (ORs) with corresponding 95% CIs and *P* values.

Subgroup analyses of LS mean change in MSSBP were conducted using ANCOVA models, with the modeling approach determined by whether the analysis was prespecified in the study protocol. For the sex subgroup, analyses were performed as prespecified in the study protocol, using models consistent with the primary analysis and adjusting for baseline MSSBP. In contrast, post hoc subgroup analyses additionally included subgroup and treatment-by-subgroup interaction terms, and *P* values for the interaction terms were evaluated to assess potential heterogeneity of treatment effects across subgroups.

For between-group comparisons, continuous variables were analyzed using either a 2-sample *t* test or the Wilcoxon rank-sum test, depending on the normality of the data. Categorical variables were compared using the χ^2 test or Fisher exact test, as appropriate. Missing data in the FAS population were imputed using the last observation carried forward method. Analyses in the PPS and safety set populations were conducted without imputation.

All statistical analyses were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC), with a 2-sided test at a significance level of 5%.

RESULTS

Demographics and Baseline Characteristics

Among 526 subjects screened, 314 were randomized to 8 weeks of double-blind treatment, and 297 subjects completed the study, whereas 17 subjects discontinued the study (Figure 1). The primary reason for study discontinuation during the treatment period in both groups was withdrawal of consent, accounting for 59% of cases (n=10). Of the randomized subjects, 151 and 155 subjects were included in the FAS and 136 and 142 subjects in the PPS from the telmisartan/amlodipine/chlorthalidone and telmisartan groups, respectively. Subjects were excluded from PPS due to visit window violations (n=12), study discontinuation (n=4), and overall treatment compliance below 80% (n=3).

There were no statistically significant differences in demographic and baseline characteristics between the two treatment groups. In the total study population, the mean age was 59±13 years and a hypertension disease duration of 111±100 months (Table 1). The majority of participants were men (70%), and among women, 80% were postmenopausal. At baseline, 86% of all subjects had MSSBP <160 mm Hg, and 84% had received antihypertensive treatment within 4 weeks before screening.

Efficacy Outcomes

The detailed PPS data for the change from baseline in MSSBP, MSDBP, and pulse pressure at week 4 and week 8 are presented in Table 2. For the primary efficacy end point, the PPS analysis demonstrated the noninferiority of the telmisartan/amlodipine/chlorthalidone combination therapy over the telmisartan monotherapy. The LS mean difference (SE) in MSSBP reduction from baseline to week 8 in the telmisartan/amlodipine/chlorthalidone group compared with the telmisartan group was −3.8 (1.5) mm Hg with the upper bound of the 95% CI at −0.9 mm Hg (*P*=0.01), which is below the predefined noninferiority margin of 3 mm Hg (Table 2). Furthermore, the FAS analysis showed superiority of the combination therapy over monotherapy. The LS mean difference was −4.0 (1.4) mm Hg (with [95% CI, −6.8 to −1.3]; *P*<0.01), indicating a statistically significant greater reduction in MSSBP with the combination therapy (Figure 2). Similar findings were obtained in a sensitivity analysis using a mixed model for repeated measures (Figure S2). Consistent results were observed in the PPS analysis,

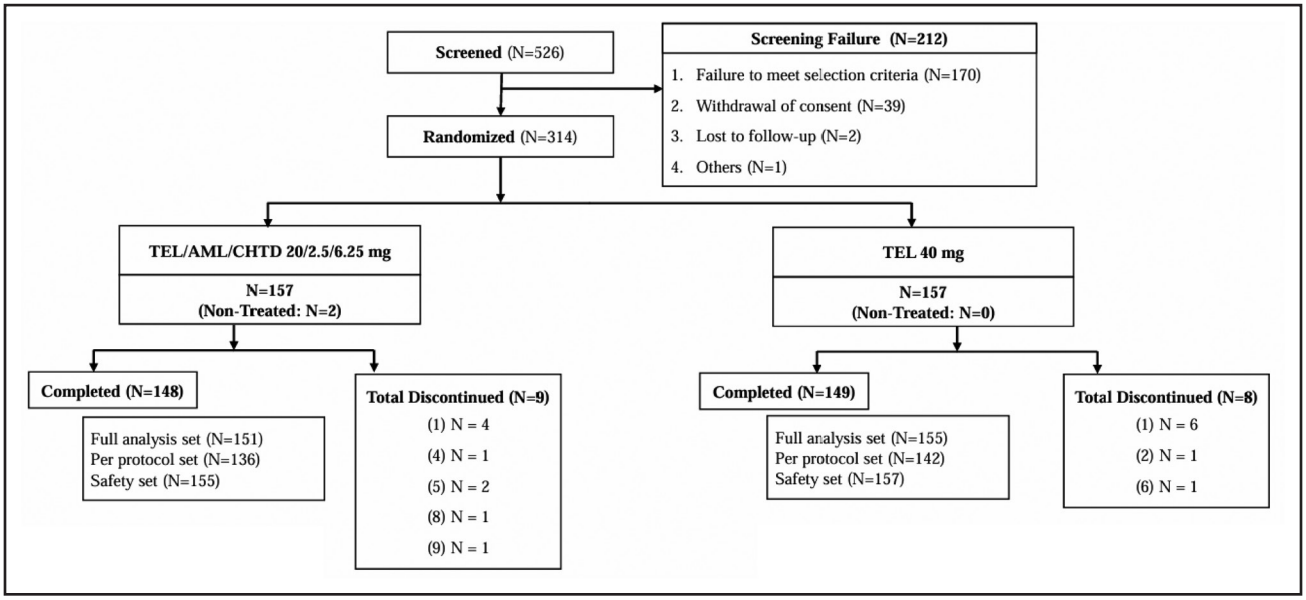

Figure 1. Subject disposition throughout the study.
Primary reasons for discontinuation included: (1) withdrawal of consent; (2) use of prohibited concurrent medication; (3) noncompliance with the investigator's instructions; (4) failure to meet selection criteria; (5) inability to continue study participation due to adverse events; (6) excessive elevation or decrease in blood pressure observed during a scheduled (visit 3) or unscheduled visit; (7) pregnancy during treatment period; (8) loss of follow-up; (9) other reasons as determined by the investigator to warrant discontinuation of the study. AML indicates amlodipine, CHTD, chlorthalidone, N, number of subjects; and TEL, telmisartan.

Table 1. Demographics and Baseline Characteristics (FAS)

Characteristic	TEL/AML/CHTD 20/2.5/6.25 mg (n=151)	TEL 40 mg (n=155)	Total (n=306)	*P* value
Mean age, y	57 (14)	60 (12)	59 (13)	0.08* (w)
Age group, n (%)				
<65 y	105 (70)	93 (60)	198 (65)	0.08* (c)
≥65 y	46 (30)	62 (40)	108 (35)	
Sex				
Male	106 (70)	109 (70)	215 (70)	0.98* (c)
Female	45 (30)	46 (30)	91 (30)	
Menopausal status,‡ n (%)				
Yes	33 (73)	40 (87)	73 (80)	0.10* (c)
No	12 (27)	6 (13)	18 (20)	
Smoking				
Smoker	29 (19)	37 (24)	66 (22)	0.55* (c)
Nonsmoker	85 (56)	79 (51)	164 (54)	
Ex-smoker	37 (25)	39 (25)	76 (25)	
Mean height, cm	166 (9)	166 (8)	166 (9)	1.00* (w)
Mean weight, kg	72 (14)	71 (12)	72 (13)	0.48* (w)
Mean BMI, kg/m^2	26 (4)	26 (3)	26 (4)	0.38* (w)
Hypertension duration, mo				
Mean (SD)	99 (95)	123 (103)	111 (100)	0.06* (w)
Baseline MSSBP, n (%)				
<160 mm Hg	129 (85)	133 (86)	262 (86)	0.93* (c)
≥160 mm Hg	22 (15)	22 (14)	44 (14)	
Antihypertensive use ≤4 wk before screening, n (%)				
Yes	127 (84)	129 (83)	256 (84)	0.84* (c)
No	24 (16)	26 (17)	50 (16)	

Duration of hypertension (months)=(date of screening−date of diagnosis of hypertension)/0.4375. AML, amlodipine; BMI, body mass index; c, χ^2 test; CHTD, chlorthalidone; f, Fisher exact test; FAS, full analysis set; MSSBP, mean sitting systolic blood pressure; n, no. of subjects; t, 2-sample *t* test; TEL, telmisartan; and w, Wilcoxon rank-sum test.

*Testing for difference between-treatment groups (t or w).

†Testing for difference between-treatment groups (c or f).

‡Denominator of percentage is the number of women in each group. Note: Denominator of percentage is the number of subjects in each group. BMI (kg/m^2)=weight (kg)/[height(cm)×0.01]2.

supporting a trend toward superiority of the combination therapy over the monotherapy.

For secondary efficacy end point (PPS), the LS mean (SE) changes for MSSBP at week 4 were −21.0 (1.0) and −15.2 (1.0) mm Hg in the combination and monotherapy groups, respectively. The LS mean difference was −5.9 (1.4) mm Hg ([95% CI, −8.6 to −3.2]; *P*<0.01). For MSDBP, the LS mean differences between telmisartan/amlodipine/chlorthalidone and telmisartan group at week 4 and week 8 were −3.4 (0.8) mm Hg ([95% CI, −5.0 to −1.8]; *P*<0.01) and −2.8 (0.8) mm Hg ([95% CI, −4.5 to −1.2]; *P*<0.01), respectively. At week 4, the telmisartan/amlodipine/chlorthalidone showed a significantly greater reduction in pulse pressure compared with telmisartan (LS mean difference [SE], −2.6 [1.0] mm Hg [95% CI, −4.6 to −0.5]; *P*=0.01). At week 8, the difference (−1.2 [1.1] mm Hg [95% CI, −3.3 to 0.9]; *P*=0.25) was not statistically significant, but numerically favored combination therapy.

The combination therapy established effective BP control and response rate compared with monotherapy (PPS; Table S2). BP control rate was higher in the telmisartan/amlodipine/chlorthalidone at both week 4 (74% versus 57%; OR, 2.20 [95% CI, 1.30–3.71; *P*<0.01]) and week 8 (70% versus 55%; OR, 1.99 [95% CI, 1.19–3.33]; *P*<0.01) compared with the telmisartan. BP response rates were 71% versus 50% at week 4 (OR, 2.52 [95% CI, 1.53, 4.16]; *P*<0.01) in the telmisartan/amlodipine/chlorthalidone and telmisartan group, respectively. At week 8, 63% of subjects in the telmisartan/amlodipine/chlorthalidone group and 47% of subjects in the telmisartan group (OR, 1.92 [95% CI, 1.19–3.10]; *P*<0.01) achieved BP response. All secondary efficacy results in FAS were consistent with PPS, and the detailed outcomes are presented in Figure S3A through S3D.

Subgroup analyses were conducted to explore treatment effects on MSSBP at week 8 across patient subgroups. In the prespecified subgroup analysis by sex, the LS mean reduction in MSSBP at week 8 was significantly greater with the low-dose telmisartan/amlodipine/chlorthalidone combination therapy than with telmisartan monotherapy in male patients (n=215; LS mean difference, −4.0 mm Hg [95% CI, −7.2 to −0.7]; *P*=0.02). In female patients (n=91), a numerically greater reduction in MSSBP was also observed with telmisartan/amlodipine/chlorthalidone compared with telmisartan monotherapy, although the difference did not reach statistical significance (LS mean difference, −3.9 mm Hg [95% CI, −9.1 to 1.2]; *P*=0.13; Table S3). In post hoc subgroup analyses based on baseline SBP, age, prior antihypertensive treatment status, and duration of hypertension, the low-dose telmisartan/amlodipine/chlorthalidone combination therapy demonstrated a consistent direction of treatment effect favoring the combination over telmisartan monotherapy in LS mean change in MSSBP at week 8 (Figure 3). Treatment-by-subgroup interaction *P* values were not statistically significant across these analyses, indicating no evidence of heterogeneity in treatment effects among the evaluated subgroups (Table S4).

Safety Outcomes

During the 8-week study period, a total of 26 subjects (8.33%) out of 312 subjects in the safety set experienced 31 treatment-emergent AEs. The incidence of treatment-emergent AEs was numerically lower in the telmisartan/amlodipine/chlorthalidone 20/2.5/6.25 mg group compared with the telmisartan 40 mg group (11 versus 20 events); however, this difference was not statistically significant (*P*=0.43). In addition, 2 (0.64%) and 3 (0.96%) subjects across both treatment groups

Table 2. Change From Baseline in MSSBP, MSDBP, and Pulse Pressure at Week 4 and Week 8 Posttreatment (PPS)

Variable	MSSBP		MSDBP		Pulse pressure	
Group	TEL/AML/CHTD 20/2.5/6.25 mg	TEL 40 mg	TEL/AML/CHTD 20/2.5/6.25 mg	TEL 40 mg	TEL/AML/CHTD 20/2.5/6.25 mg	TEL 40 mg
Baseline (n=136, n=142)						
Mean (SD)	149.3 (8.1)	150.3 (9.2)	93.0 (8.7)	92.0 (8.5)	56.3 (10.2)	58.2 (10.8)
Median (min, max)	146.7 (140.0 to 177.5)	147.5 (140.0 to 177.5)	93.0 (71.0 to 109.5)	92.0 (68.5 to 109.5)	55.5 (37.5 to 90.0)	56.5 (33.0 to 89.5)
P value*	0.66 (w)		0.28 (w)		0.15 (w)	
Week 4 (n=134, n=140)						
Mean (SD)	128.6 (10.9)	135.0 (13.2)	82.0 (9.1)	84.8 (9.1)	46.6 (10.0)	50.2 (11.2)
Median (min, max)	128.0 (101.3 to 163.3)	134.5 (98.3 to 177.5)	81.9 (63.5 to 110.7)	84.5 (62.0 to 106.0)	46.0 (26.0 to 76.3)	49.6 (24.3 to 100.0)
Change from baseline at week 4						
Mean (SD)	−20.8 (11.6)	−15.4 (12.1)	−11.0 (7.6)	−7.3 (7.1)	−9.8 (9.7)	−8.1 (9.1)
Median (min, max)	−20.6 (−49.0 to 3.0)	−15.5 (−43.7 to 15.0)	−10.6 (−28.5 to 20.5)	−6.9 (−29.5 to 8.0)	−10.1 (−37.5 to 13.0)	−8.4 (−25.5 to 17.0)
Treatment difference (ANCOVA) at week 4						
LS mean (SE)	−21.0 (1.0)	−15.2 (1.0)	−11.2 (0.7)	−7.8 (0.7)	−9.8 (1.0)	−7.3 (1.0)
LS mean difference (SE)	−5.9 (1.4)		−3.4 (0.8)		−2.6 (1.0)	
95% CI for difference	−8.6 to −3.2		−5.0 to −1.8		[−4.6 to −0.5]	
P value	<0.01†		<0.01‡		0.01‡	
Week 8 (n=136, n=142)						
Mean (SD)	130.1 (12.5)	134.5 (14.3)	82.3 (9.4)	84.5 (9.3)	47.7 (10.2)	50.0 (11.3)
Median (min, max)	129.3 (103.5 to 169.0)	133.3 (94.5 to 185.5)	81.5 (55.0 to 116.5)	84.4 (59.0 to 104.3)	47.0 (22.5 to 83.5)	48.5 (24.5 to 91.0)
Change from baseline at week 8						
Mean (SD)	−19.3 (11.7)	−15.8 (13.3)	−10.7 (7.3)	−7.6 (7.5)	−8.6 (9.6)	−8.3 (9.8)
Median (min, max)	−18.7 (−47.5 to 22.5)	−16.0 (−55.0 to 28.8)	−11.3 (−26.8 to 13.0)	−6.9 (−30.0 to 13.8)	−9.5 (−33.0 to 23.0)	−8.1 (−30.5 to 18.0)
Treatment difference (ANCOVA) at week 8						
LS mean (SE)	−19.4 (1.1)	−15.7 (1.0)	−10.1 (0.7)	−7.3 (0.7)	−7.9 (1.0)	−6.7 (1.0)
LS mean difference (SE)	−3.8 (1.5)		−2.8 (0.8)		−1.2 (1.1)	
95% CI for difference§	−6.7 to −0.9		−4.5 to −1.2		[−3.3, 0.9]	
Noninferiority (UCI<3)	Yes		…		…	
P value	0.01†		<0.01‡		0.25‡	

AML indicates amlodipine; CHTD, chlorthalidone; LS, least squares; Max, maximum; Min, minimum; MSDBP, mean sitting diastolic blood pressure; MSSBP, mean sitting systolic blood pressure; n, number of subjects; PPS, per-protocol set; t, 2-sample *t* test; TEL, telmisartan; UCI, upper limit of 95% CI; and w, Wilcoxon rank-sum test.

*Testing for difference between-treatment groups (t or w).

†Testing for difference between-treatment groups (ANCOVA model included baseline value as covariate).

‡Testing for difference between-treatment groups (ANCOVA model included baseline value and stratification factor MSSBP group [<160 mm Hg, ≥160 mm Hg] as covariate).

§Testing for difference between-treatment groups (the noninferiority and then superiority hypotheses are tested sequentially using gatekeeping).

reported 2 ADRs and 3 serious AEs, respectively, with no statistically significant differences observed between groups. No AEs of special interest, serious ADRs, ADRs leading to drug withdrawal or deaths were reported in either treatment group (Table 3).

DISCUSSION

This phase III study is the first randomized, double-blind, active-controlled study to evaluate the effect of low-dose SPC (telmisartan/amlodipine/chlorthalidone) compared with the standard-dose telmisartan monotherapy in patients with essential hypertension. The results demonstrated the noninferiority of the low-dose triple SPC and further established its superiority over standard-dose telmisartan monotherapy in reducing MSSBP at week 8. According to a meta-analysis of 48 randomized controlled trials (RCTs), each 5 mm Hg reduction in SBP is associated with a 10% decrease in cardiovascular risk, regardless of baseline BP or cardiovascular disease history.[31] In this context, the LS mean difference of −4.0 mm Hg observed in our study suggests that low-dose SPC may

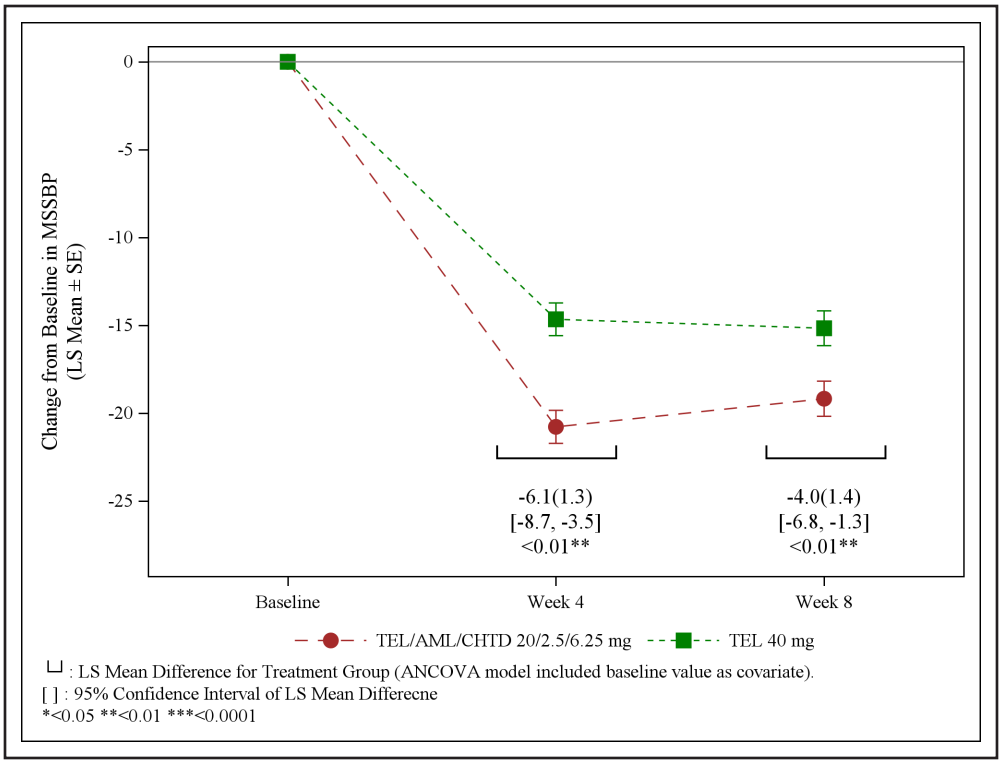

Figure 2. Change in mean sitting systolic blood pressure from baseline to week 4 and week 8 (full analysis set).
Data are presented as least squares (LS) mean differences between treatment groups at each visit, estimated using an ANCOVA model with baseline mean sitting systolic blood pressure (MSSBP) as a covariate. Values in brackets indicate 95% CIs for the LS mean differences. AML indicates amlodipine, CHTD, chlorthalidone, and TEL, telmisartan. *P<0.05; **P<0.01.

offer additional cardiovascular risk reduction beyond standard-dose monotherapy. Furthermore, the early and sustained BP reductions observed from week 4 through week 8 are also clinically meaningful, particularly in light of the 2024 European Society of Cardiology guidelines. These guidelines recommend initiating antihypertensive therapy with a low-dose combination and achieving target BP ideally within the first 3 months to ensure faster BP control with fewer side effects, thereby improving patient adherence and minimizing long-term cardiovascular risk.

The findings of the current study are also consistent with and extend previous evidence supporting this therapeutic approach. For instance, the open-label Triple Pill vs Usual Care Management for Patients with Mild-to-Moderate Hypertension (TRIUMPH) study demonstrated superior BP-lowering efficacy with low-dose telmisartan/amlodipine/chlorthalidone compared with usual care.[32] A phase II dose-finding study showed that low-dose SPC, including the half-dose telmisartan/amlodipine/chlorthalidone used in the current trial, was more effective than telmisartan (80 mg) or amlodipine (5 or 10 mg) monotherapies.[33] However, neither of these earlier studies included a direct comparison with widely used telmisartan standard-dose monotherapy. Our study fills this critical gap by providing robust, phase III evidence for the clinical superiority of the low-dose triple SPC compared with standard-dose telmisartan 40 mg.

The subgroup analyses further confirmed the robustness of the low-dose combination therapy, demonstrating consistent efficacy regardless of age or prior antihypertensive treatment status. The sustained BP reduction in both treatment-naïve and previously treated patients suggests that the low-dose triple SPC is effective as both an initial and switching therapy. Notably, the greater BP-lowering effect observed in patients aged ≥60 years underscores its potential as a particularly effective treatment option for older adults who are at elevated cardiovascular risk.

In terms of safety, no statistically significant differences in AE incidence were observed between treatment groups. Two mild ADRs were reported, 1 in each group: visual impairment and hypesthesia. Despite comprising 3 pharmacologically distinct agents, the low-dose triple SPC regimen did not result in an increased incidence of AEs, likely due to the use of each component at a low dose. These findings support that the regimen is well-tolerated and safe in patients with essential hypertension. In this study, the only prespecified AEs of special interest were edema, which is a well-established adverse effect of amlodipine. Although edema is commonly reported with amlodipine use, with incidence rates up to 17%,[34] no cases were observed in this study, possibly due to the low dose of amlodipine and the counteracting effects of telmisartan and chlorthalidone.[35,36]

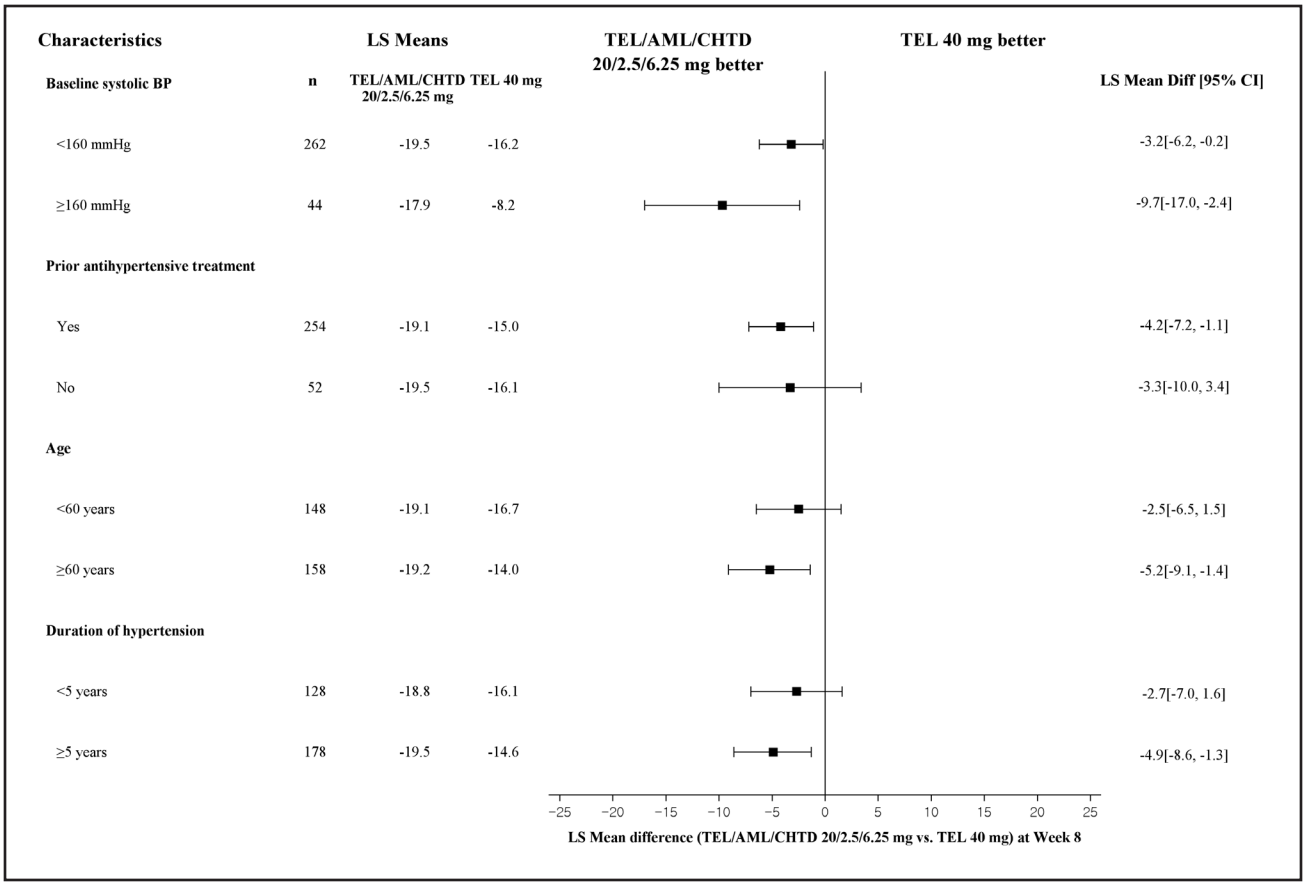

Figure 3. Subgroup analysis of least squares mean change in mean sitting systolic blood pressure (BP) at week 8 based on interaction models (full analysis set).

Forest plot depicting least squares (LS) mean changes in mean sitting systolic BP (MSSBP) at week 8 comparing telmisartan (TEL)/amlodipine (AML)/chlorthalidone (CHTD) 20/2.5/6.25 mg vs TEL 40 mg across key subgroups: baseline systolic BP (<160 vs ≥160 mm Hg), prior antihypertensive treatment (yes vs no), age (<60 vs ≥60 years), and duration of hypertension (<5 vs ≥5 years). The LS mean differences were estimated from ANCOVA models including baseline MSSBP, subgroup, treatment, and treatment-by-subgroup interaction as fixed effects. Each subgroup displays the LS mean difference with 95% CIs. Negative values favor the TEL/AML/CHTD combination. The treatment effect was consistent across most subgroups, with the largest reductions observed in patients with baseline systolic BP (SBP) ≥160 mm Hg and those aged ≥60 years. No statistically significant treatment-by-subgroup interactions were observed (Table S4). N indicates number of subjects.

This favorable safety profile, as detailed above, is particularly significant in the current therapeutic landscape. The recent approval of other novel triple-combination therapies, such as Widaplik, underscores a growing trend towards more comprehensive initial treatment strategies for hypertension. Although the pivotal Widaplik trial investigated its low-dose combination primarily as a short-term introductory phase before uptitration, our study was designed to validate the efficacy and safety of a low-dose regimen as a definitive treatment strategy in its own right. This approach allows for an assessment of the low-dose combination as a potential mainstay therapy, not just a stepping stone to higher doses.

In the context of this specific study design, our safety findings are particularly noteworthy. We found that our SPC of telmisartan, amlodipine, and chlorthalidone demonstrated a favorable safety profile, which was notably comparable to that of standard-dose monotherapy. The absence of a significant increase in AEs, despite the superior BP reduction, suggests that this particular combination is well-balanced. These results strongly support the conclusion that telmisartan/amlodipine/chlorthalidone combination is a valid and safe therapeutic strategy for managing hypertension.

The study has several limitations. First, although the 8-week duration is consistent with the design of many antihypertensive trials evaluating combination therapies, this duration does not allow the assessment of long-term clinical outcomes such as cardiovascular events. The limited duration precludes firm conclusions about the durability of BP control. Nevertheless, the present findings provide evidence for the short-term efficacy and safety of this regimen. Given the chronic nature of hypertension management, longer-term studies are warranted to fully evaluate sustained antihypertensive effects, cardiovascular outcomes and safety, given the chronic nature of hypertension management. Second, telmisartan monotherapy was selected as the

Table 3. Safety Summary

Variable	TEL/AML/CHTD 20/2.5/6.25 mg (n=155)	TEL 40 mg (n=157)	Total (n=312)	*P* value
TEAEs, n (%) [events]	11 (7.10) [11]	15 (9.55) [20]	26 (8.33) [31]	0.43 (c)*
Cough	1 (0.65) [1]	1 (0.64) [1]	2 (0.64) [2]	…
Hypesthesia	0	2 (1.27) [2]	2 (0.64) [2]	…
ADRs, n (%) [events]	1 (0.65) [1]	1 (0.64) [1]	2 (0.64) [2]	1.00 (f)*
Serious ADRs, n (%) [events]	0	0	0	NA*
SAEs, n (%) [events]	2 (1.29) [2]	1 (0.64) [1]	3 (0.96) [3]	0.62 (f)*
TEAEs leading to drug withdrawal, n (%) [events]	2 (1.29) [2]	1 (0.64) [1]	3 (0.96) [3]	0.62 (f)*

TEAEs are shown as number of participants (percentage of participants) [no. of cases]. PT terms are added only for ≥2 total events. Adverse drug reactions are displayed as the no. of subjects (percentage of subjects) [the no. of events]. ADRs indicates adverse drug reactions; AML, amlodipine; c, χ^2 test; CHTD, chlorthalidone; f, Fisher exact test; n, number of subjects; NA, not applicable; PT, preferred term; SAE, severe adverse event; TEAE, treatment-emergent adverse event; and TEL, telmisartan.

*Testing for difference between-treatment groups (c or f).

comparator because ARBs are widely prescribed as monotherapy, with telmisartan regarded as a standard agent due to its well-established tolerability and safety.[37] Supporting this, US data from 2013 to 2016 show that 40% of treated adults used a single antihypertensive class, with ACE inhibitor/ARB monotherapy most common (24%) far exceeded that of β-blockers (6%), with other classes less frequently prescribed.[38] However, given that international guidelines such as those of the AHA recommend initial dual therapy for patients with BP >140/90 mm Hg, the absence of a dual-combination comparator may limit the interpretation of the findings. Notably, in a prior phase 2 trial (reported to the Ministry of Food and Drug Safety in South Korea but not published), the low-dose triple combination of telmisartan/amlodipine/chlorthalidone demonstrated significantly greater reductions in MSSBP at 8 weeks compared with dual combinations of telmisartan/amlodipine and amlodipine/chlorthalidone, and showed numerically greater BP-lowering effects compared with telmisartan/chlorthalidone. These results provide supportive evidence that the triple combination offers additive BP-lowering benefits beyond dual therapy, while maintaining a similar safety profile. Although the lack of a dual-combination comparator remains a limitation, the phase 2 findings and the common use of monotherapy in practice support the clinical relevance of the current results. Third, only office BP was measured, and home BP or 24-hour ambulatory BP monitoring was not performed, leaving some uncertainty about whether the observed clinic BP differences reflect sustained BP control. Fourth, the use of the last observation carried forward method for imputing missing values carries a potential risk of bias. Another limitation is that all participants of this study were Korean, which calls for caution when generalizing the findings to other populations. Therefore, future multinational trials are needed to validate these results across diverse ethnic groups and ensure broader applicability.

Perspectives

Despite growing emphasis on early and effective BP control, many patients remain undertreated due to concerns regarding polypharmacy, side effects, and adherence.[39–41] The findings of this study highlight the potential of a low-dose triple SPC regimen to overcome these barriers by providing enhanced efficacy with an acceptable safety profile, regardless of age or prior antihypertensive treatment status. Given its simplicity, tolerability, and effectiveness, this fixed-dose combination may play a pivotal role in optimizing hypertension management, especially among older adults or those requiring multiple agents. Future real-world studies are warranted to evaluate long-term adherence, cardiovascular outcomes, and cost-effectiveness of this strategy in diverse clinical settings.

Conclusions

In conclusion, the present study provides robust evidence that the low-dose triple SPC of telmisartan/amlodipine/chlorthalidone demonstrates sufficient BP-lowering efficacy while maintaining a favorable safety profile. The efficacy was consistent across age groups and irrespective of prior antihypertensive treatment history, reinforcing the use of low-dose triple SPC therapy as a clinically effective and well-tolerated option, both as an initial and add-on strategy, particularly in populations including older adults.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Supplemental Methods. Study Protocol Synopsis
Tables S1–S4
Figure S1–S3

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