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Low-Dose Telmisartan/Amlodipine in Essential Hypertension: A Phase III Trial

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ABSTRACT

Low-dose single-pill combinations (SPCs) are gaining recognition as an efficient therapeutic strategy for mild hypertension. However, evidence from randomized controlled trials regarding the efficacy and safety of half-dose telmisartan/amlodipine SPCs remains limited. In this randomized, double-blind, active-controlled phase III trial, patients with essential hypertension [mean sitting systolic blood pressure (MSSBP) ≥ 140 and < 180 mmHg] were allocated to four treatment arms to receive either telmisartan/amlodipine 20/2.5 mg SPC (TEL/AML 20/2.5), or monotherapy with telmisartan 20 mg (TEL 20), amlodipine 2.5 mg (AML 2.5), or telmisartan 40 mg (TEL 40) once daily for 8 weeks. The primary endpoint was the change in MSSBP from baseline to week 8. A gatekeeping approach was used to test the superiority of TEL/AML 20/2.5 over TEL 20 and AML 2.5, followed by non-inferiority versus TEL 40. At week 8, TEL/AML 20/2.5 showed significantly greater MSSBP reductions compared with TEL 20 [least squares mean (LSM) differences: −5.79 mmHg; $p = 0.0003$] and AML 2.5 (−8.57 mmHg; $p < 0.0001$). Non-inferiority to TEL 40 was established, with an LSM difference of −3.88 mmHg (95% Confidence Interval: −6.67 to −1.09), which met the pre-specified 3 mmHg margin. The overall incidence of adverse events was 8.05%, with no statistically significant differences between groups. Overall, TEL/AML 20/2.5 SPC provided superior BP-lowering efficacy compared with TEL 20 and AML 2.5 monotherapies and was non-inferior to TEL 40. With a comparable safety profile across treatment groups, these findings suggest that TEL/AML 20/2.5 is a practical and effective option for hypertension management.

Trial Registration: ClinicalTrials.gov, NCT06052748

1 | Introduction

Hypertension affects over 1.3 billion adults worldwide [1] and is a leading modifiable risk factor for cardiovascular disease (CVD), stroke, heart failure, and premature death [2–4]. Despite being largely asymptomatic, uncontrolled hypertension substantially contributes to global morbidity and mortality, preceding up to 69% of major cardiovascular (CV) events [5, 6]. From 1990 to 2019, its global prevalence doubled, highlighting a growing public health challenge [7]. Although treatment reduces CVD risk, hypertension management remains suboptimal. Globally, only half of patients are diagnosed, 40% treated, and 20%–30% achieve adequate blood pressure (BP) control, underscoring the need for more effective and sustainable treatment strategies [7–9].

In clinical practice, most hypertension patients start on monotherapy, with additional agents being introduced only if target BP levels are not achieved [10–12]. However, emerging clinical evidence supports initiating treatment with single-pill combinations (SPCs) to improve adherence, accelerate BP control, and reduce CVD risk [13–18]. SPCs are increasingly recognized as a practical and patient-centered approach, and recent international guidelines recommend them as an initial therapy [19–21].

Angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) are key components for currently used in SPC antihypertensive therapy, due to their complementary mechanisms of action and favorable tolerability [22–24]. While standard-dose SPCs of ARBs and CCBs are common for hypertension [25–28], interest in low-dose SPCs is growing because they offer more effective and better-tolerated alternative to standard-dose monotherapy, especially for patients with mild-to-moderate hypertension or a high risk of adverse events (AEs). A meta-analysis found that low-dose combination can achieve similar BP reductions with fewer AEs, offering a more effective and better-tolerated option than standard-dose monotherapy [29].

Although the clinical implications of low-dose SPCs are actively being explored, their composition, dosage, and dosing schedules vary, making careful evaluation of their efficacy and safety essential before clinical implementation. Specifically, since most previous low-dose SPC trials have focused on triple or quadruple combinations [30–32], clinical evidence for low-dose two-drug combinations remains limited. Given this gap, we investigated the efficacy and safety of a low-dose SPC combining the widely used ARB (telmisartan 20 mg) and CCB (amlodipine 2.5 mg) in patients with mild-to-moderate hypertension, using telmisartan (20 or 40 mg) monotherapy and amlodipine (2.5 mg) monotherapy as comparators over an 8-week treatment period.

2 | Methods

2.1 | Study Design

This multicenter, randomized, double-blind, active-controlled phase III trial was conducted at 36 sites in South Korea from February 2024 to February 2025 in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), and local regulatory requirements. The study protocol was approved by the institutional review boards (IRBs) of all participating centers, and all subjects provided written informed consent. The full study protocol is provided in Supplementary Method 1. The trial was prospectively registered at ClinicalTrials.gov (NCT06052748), according to the ICMJE guidelines.

After a 4-week placebo run-in, eligible subjects were randomized in a 2:1:1:2 ratio using block randomization via an Interactive Web Response System (IWRS) to receive one of the following regimens: telmisartan/amlodipine 20/2.5 mg SPC (TEL/AML 20/2.5), telmisartan 20 mg (TEL 20), amlodipine 2.5 mg (AML 2.5), or telmisartan 40 mg (TEL 40) group. All participants received three tablets once daily for 8 weeks, consisting of active drug(s) and matching placebos, administered at the same time each day.

Efficacy was assessed at weeks 4 and 8, and safety was monitored throughout the study. TEL 40 was selected as the non-inferiority comparator because ARBs are widely prescribed for hypertension. Telmisartan, a standard monotherapy with a favorable safety profile and broad clinical acceptance, was therefore considered an appropriate and clinically relevant comparator. (Figure S1).

2.2 | Participants

Adults aged ≥ 19 years with essential hypertension were eligible, with BP at randomization of 140 mmHg ≤ mean sitting systolic blood pressure (MSSBP) < 180 mmHg. After a 4-week placebo run-in following discontinuation of any prior antihypertensive medications, subjects who met the inclusion criteria and demonstrated adequate compliance (≥ 70% during the run-in period) were randomized. Patients already receiving antihypertensive therapy could be included if, in the investigator's judgment, prior treatment could be safely withdrawn.

Key exclusion criteria included secondary hypertension, severe or unstable CV conditions, significant metabolic or renal/hepatic dysfunction, active malignancy, and hypersensitivity to study drugs. Women who were pregnant or lactating, or unwilling to use effective contraception during the study period were excluded, as were individuals with recent participation in other clinical trials.

2.3 | Study Endpoints and Measures

The primary efficacy endpoints were changes from baseline in MSSBP at week 8. Secondary efficacy endpoints included the change in MSSBP at week 4, changes in mean sitting diastolic blood pressure (MSDBP) at weeks 4 and 8, and the rates of BP control and BP response at weeks 4 and 8. BP control rate was defined as the proportion of subjects who achieved MSSBP < 140 mmHg and MSDBP < 90 mmHg in the general population, or MSSBP < 130 mmHg and MSDBP < 80 mmHg in high-risk individuals, including those with CVD, chronic kidney disease (CKD) with proteinuria or albuminuria, diabetic nephropathy, or lacunar infarction. BP response rate was defined as the proportion of subjects with a reduction of ≥ 20 mmHg in MSSBP and/or ≥ 10 mmHg in MSDBP from baseline.

Safety endpoints included treatment-emergent adverse events (TEAEs), AEs of special interest (notably peripheral edema), vital signs and laboratory parameters changes, 12-lead electrocardiograms (ECG), and physical examination findings. All AEs were coded using standardized medical dictionaries for assessment of severity, seriousness, and relationship to the investigational product.

2.4 | Sample Size Calculation

Sample size was calculated to assess both the superiority of the low-dose SPC (TEL/AML 20/2.5) over each monotherapy (TEL 20 or AML 2.5), and its non-inferiority compared to TEL 40, based on changes in MSSBP at week 8.

For the superiority comparisons, expected mean differences of −7.2 mmHg (vs. AML 2.5) and −6.8 mmHg (vs. TEL 20) were assumed, with a common standard deviation of 12.41 mmHg from prior studies [33, 34]. With 97.2% power and a 2:1 allocation ratio, the maximum required sample sizes were 75 for each monotherapy group and 150 for the SPC group. Allowing for a 7% dropout rate, 81 and 162 subjects were determined for the control and SPC groups, respectively.

For the non-inferiority comparison versus TEL 40, the margin was based on the Twynsta trial [33], where the 8-week MSSBP difference between the SPC and TEL 40 was −4.2 mmHg (upper 95% Confidence Interval (CI), −7.94 mmHg). Following FDA guidance [35] to define clinical margins below statistical ones, 50% of this value (3.97 mmHg) was considered the upper limit. Considering this and margins used in similar studies [36, 37], a conservative non-inferiority margin of 3 mmHg was adopted. Assuming a mean difference of −1 mmHg, pooled SD of 11.25 mmHg [33, 38, 39], 86.7% power, and one-sided α of 2.5%, the required sample size was 150 per group; with a 7% dropout adjustment, 162 subjects per group were planned.

In a 2:1:1:2 allocation ratio, 486 subjects were planned for enrollment; 162 in the TEL/AML 20/2.5 and TEL 40 groups, 81 in the TEL 20 and AML 2.5 groups.

2.5 | Statistical Analysis

Efficacy analyses were performed on the full analysis set (FAS), defined according to the intent-to-treat (ITT) principle as all randomized subjects who received at least one dose of study drug and had at least one post-baseline efficacy assessment. The per-protocol set (PPS), excluding subjects with major protocol deviations, was used for sensitivity analyses and as the primary analysis set for the non-inferiority comparison.

The study employed a gatekeeping procedure to control the type I error rate across co-primary endpoints as specified in the statistical analysis plan (Supplementary Method 2). Superiority of the SPC (TEL/AML 20/2.5) over each monotherapy (TEL 20, AML 2.5) was first evaluated in FAS using analysis of covariance (ANCOVA) of week-8 MSSBP change, with baseline MSSBP as a covariate. Study center was not included as a covariate in the pre-specified model. If both comparisons showed superiority, non-inferiority of the TEL/AML 20/2.5 versus TEL 40 was subsequently assessed in PPS. Non-inferiority was concluded if the upper bound of the one-sided 97.5% CI for the LSM difference (TEL/AML 20/2.5 − TEL 40) was less than the pre-specified margin of 3 mmHg.

Secondary endpoints were analyzed using ANCOVA, with baseline values as covariates. Odds ratios (ORs) with 95% CIs were estimated through logistic regression for binary endpoints such as BP control and response rates at weeks 4 and 8. These analyses were considered supportive and exploratory in nature, and therefore were not included in the formal multiplicity-controlled testing framework. Accordingly, no adjustment for multiplicity was applied to the secondary endpoints. Safety analyses were conducted on the safety set, comprising all subjects who received at least one dose of the study drug. The incidence of TEAEs, serious adverse events (SAEs), and adverse drug reactions (ADRs) was summarized by treatment group and coded using MedDRA

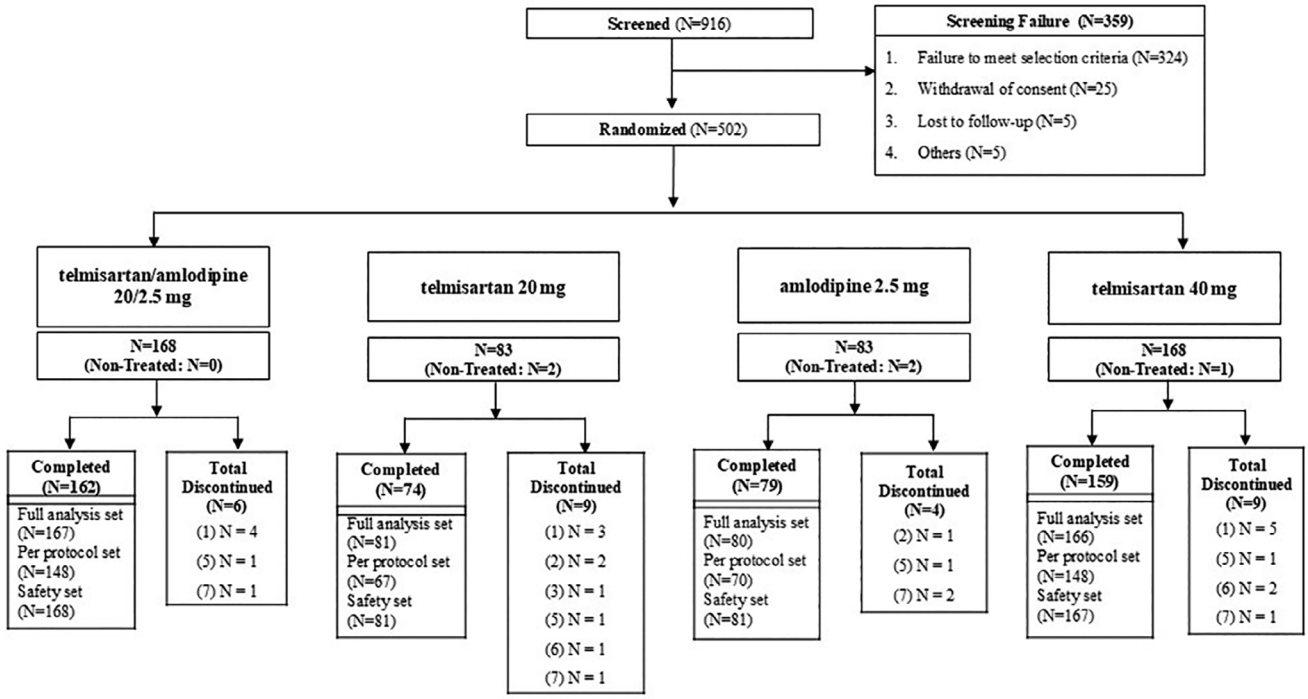

FIGURE 1 | Subject disposition throughout the study.Primary reasons for discontinuation included: (1) Withdrawal of consent; (2) Failure to meet selection criteria; (3) Use of prohibited concurrent medication; (4) Pregnancy during treatment period; (5) Inability to continue study participation due to adverse events; (6) Excessive elevation or decrease in BP observed during a scheduled (Visit 3) or unscheduled visit; (7) Loss of follow-up; (8) Other reasons as determined by the investigator to warrant discontinuation of the study.Blood pressure (BP), Number of subjects (N).

version 27.0. Clinically significant changes in laboratory parameters, vital signs, ECG, and physical examination findings were also evaluated.

Descriptive statistics were used for all variables, along with LSMs, standard errors (SEs), and 95% CIs for between-group comparisons. Within-group changes were analyzed using paired *t*-tests or Wilcoxon signed-rank tests, and between-group comparisons were performed using ANCOVA for continuous outcomes and chi-square or Fisher's exact tests for categorical outcomes. McNemar's test was used for within-group comparisons of categorical safety endpoints. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), with statistical significance defined as a two-sided p-value < 0.05.

3 | Results

3.1 | Demographics and Baseline Characteristics

After screening 916 subjects, 502 were randomized to study treatment. 474 (94.42%) completed the study and 28 (5.58%) discontinued. FAS and PPS comprised 494 and 433 subjects, respectively. PPS exclusions were due to missing MSSBP measurements at week 8 (9.72%), poor treatment compliance (< 80%) (2.63%), prohibited concomitant medication use (1.42%), and eligibility criteria violation (0.81%) (Figure 1).

In the FAS, the mean age was 57.30 ± 13.55 years; 65.59% were < 65 years and 75.91% were male. No statistically significant differences were observed across treatment groups in age or sex distribution. The mean duration of hypertension was 7.53 ± 7.41 years, with 64.17% of subjects taking antihypertensive medication at baseline. Regarding smoking status, 47.98% were non-smokers, 27.13% were former smokers, and 24.90% were current smokers. Over 70% of participants had at least one comorbidity at baseline. Metabolic disorders were most common, with hyperlipidemia observed in 35.43% of participants. Among other major conditions, CVD was present in 17.61%, CKD in 0.40%, and a history of lacunar infarction in 0.20%. There were no significant differences between treatment groups in demographic or baseline characteristics (Table 1).

3.2 | Primary Efficacy Outcomes

In the FAS, TEL/AML 20/2.5 demonstrated significantly greater reductions in MSSBP at week 8 compared with TEL 20 and AML 2.5 groups. The LSM difference ± SE was −5.79 ± 1.57 mmHg versus TEL 20 (95% CI, [−8.88, −2.70]; $p = 0.0003$) and −8.57 ± 1.45 mmHg versus AML 2.5 (95% CI, [−11.42, −5.72]; $p < 0.0001$), demonstrating the superiority of the SPC therapy (Table S1–S2).

PPS results for the comparison with TEL 40 showed an LSM difference of −3.88 ± 1.42 mmHg (95% CI, [−6.67, −1.09]), confirming non-inferiority, as the upper CI bound was below the predefined non-inferiority margin of 3 mmHg (Table S3).

Results from the PPS were generally consistent with those from the FAS, supporting the overall robustness and reliability of the efficacy findings (Figure 2A and Table S4).

TABLE 1 | Demographics and baseline characteristics (FAS).

Characteristic	TEL/AML 20/2.5 (*N* = 167)	TEL 20 (*N* = 81)	AML 2.5 (*N* = 80)	TEL 40 (*N* = 166)	Total (*N* = 494)	*p*-value[a]
Age (years)						
Mean (SD)	55.5 (14.67)	59.9 (12.37)	57.8 (12.37)	57.7 (13.34)	57.3 (13.55)	0.1526(k)
Median	56.0	63.0	58.5	59.0	59.0	
Min, Max	22, 84	31, 78	28, 80	24, 83	22, 84	
Age Group, n (%)						
< 65 years	118 (70.66)	47 (58.02)	53 (66.25)	106 (63.86)	324 (65.59)	0.2415(c)
≥ 65 years	49 (29.34)	34 (41.98)	27 (33.75)	60 (36.14)	170 (34.41)	
Sex, n (%)						
Male	124 (74.25)	65 (80.25)	60 (75.00)	126 (75.90)	375 (75.91)	0.7721(c)
Female	43 (25.75)	16 (19.75)	20 (25.00)	40 (24.10)	119 (24.09)	
Smoking Status, n (%)						
Non-smoker	86 (51.50)	30 (37.04)	35 (43.75)	86 (51.81)	237 (47.98)	0.0778(c)
Current smoker	43 (25.75)	29 (35.80)	17 (21.25)	45 (27.11)	134 (27.13)	
Former smoker	38 (22.75)	22 (27.16)	28 (35.00)	35 (21.08)	123 (24.90)	
Weight (kg)						
Mean (SD)	76.01 (16.579)	74.56 (13.800)	74.35 (16.114)	75.01 (15.545)	75.17 (15.696)	0.8312(k)
Duration of Hypertension (years)[b]						
Mean (SD)	6.762 (7.3848)	8.890 (8.0721)	6.848 (6.0427)	7.976 (7.6417)	7.533 (7.4147)	0.1011(k)
Antihypertensive Medication Use[c]						
Yes	101 (60.48)	54 (66.67)	54 (67.50)	108 (65.06)	317 (64.17)	0.6476(c)
No	66 (39.52)	27 (33.33)	26 (32.50)	58 (34.94)	177 (35.83)	

Abbreviations: Amlodipine 2.5 mg (AML 2.5), Maximum (Max), Minimum (MIN), Number of subjects (N), Standard deviation (SD), Telmisartan 20 mg (TEL 20), Telmisartan 40 mg (TEL 40), Telmisartan/Amlodipine 20/2.5 mg (TEL/AML 20/2.5).

[a]Kruskal-Wallis test(k), Chi-square test(c), Fisher's exact test(f).

[b]Duration of Hypertension (years): Calculated from the date of essential hypertension diagnosis to Visit 2 (1 year = 365.25 days).

[c]Antihypertensive Medication Use Within 4 weeks Before Visit 1.

3.3 | Secondary Efficacy Outcomes

At week 4, the TEL/AML 20/2.5 showed statistically significant reductions in MSSBP compared with all monotherapy groups (Figure 2A). In the FAS, the LSM difference ± SE was −6.51 ± 1.64 mmHg compared with the TEL 20 (95% CI: −9.75 to −3.28; $p < 0.0001$), −9.09 ± 1.62 mmHg compared with the AML 2.5 (95% CI: −12.29 to −5.90; $p < 0.0001$), and −4.51 ± 1.32 mmHg compared with the TEL 40 (95% CI: −7.10 to −1.91; $p = 0.0007$).

For MSDBP at week 4, the LSM differences were −4.14 ± 1.03 mmHg for the TEL 20 (95% CI: −6.17 to −2.10; $p < 0.0001$), −5.13 ± 1.00 mmHg for the AML 2.5 (95% CI: −7.10 to −3.16; $p < 0.0001$), and −2.27 ± 0.78 mmHg for the TEL 40 (95% CI: −3.80 to −0.74; $p = 0.0038$). At week 8, similar trends were observed, with LSM differences in MSDBP of −3.73 ± 0.95 mmHg compared with the TEL 20 (95% CI: −5.60 to −1.87; $p = 0.0001$), −5.31 ± 0.97 mmHg compared with the AML 2.5 (95% CI: −7.23 to −3.40; $p < 0.0001$), and −2.19 ± 0.82 mmHg compared with the TEL 40 (95% CI: −3.80 to −0.57; $p = 0.0080$) (Figure 2B).

For BP control rate, the TEL/AML 20/2.5 achieved 52.15% at week 4, which was statistically significantly higher than the TEL 20 at 27.50% (difference: 24.65%; 95% CI: 12.22 to 37.08; $p = 0.0003$), the AML 2.5 at 18.42% (difference: 33.73%; 95% CI: 22.12 to 45.34; $p < 0.0001$), and the TEL 40 at 40.61% (difference: 11.54%; 95% CI: 0.82 to 22.26; $p = 0.0361$). At week 8, the control rates were 52.69% for TEL/AML 20/2.5, 38.27% for TEL 20 (difference: 14.42%; 95% CI: 1.41 to 27.44; $p = 0.0330$), 22.50% for AML 2.5 (difference: 30.19%; 95% CI: 18.32 to 42.07; $p < 0.0001$), and 47.59% for TEL 40 (difference: 5.10%; 95% CI: −5.62 to 15.83; $p = 0.3516$), with statistical significance observed except for the comparison with TEL 40 at week 8 (Figure 3A).

Logistic regression analysis showed that at week 4, the TEL/AML 20/2.5 had statistically significantly higher odds of achieving BP control compared with the TEL 20 (OR: 2.87; 95% CI: 1.61 to 5.13; $p = 0.0004$), the AML 2.5 (OR: 4.83; 95% CI: 2.50 to 9.30; $p < 0.0001$), and the TEL 40 (OR: 1.59; 95% CI: 1.03 to 2.47; $p = 0.0365$). At week 8, the odds remained statistically significantly higher compared with the TEL 20 (OR: 1.80; 95% CI: 1.05 to 3.09; $p = 0.0339$) and

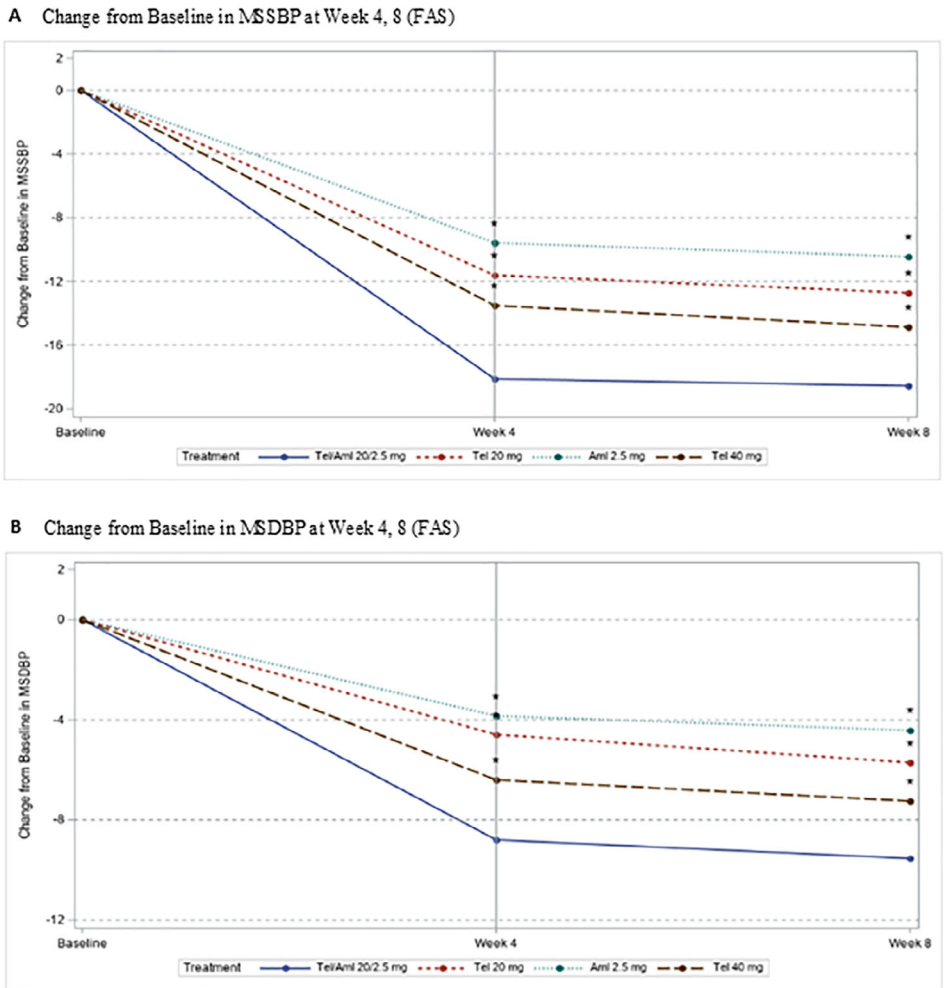

FIGURE 2 | Change from Baseline in MSSBP, MSDBP at Week 4, 8 (FAS).Amlodipine (Aml), Full analysis set (FAS), Mean systolic blood pressure (MSSBP), Mean sitting diastolic blood pressure (MSDBP), Telmisartan (Tel), Telmisartan /Amlodipine (Tel/Aml).

the AML 2.5 (OR: 3.84; 95% CI: 2.09 to 7.04; $p < 0.0001$), while no statistically significant difference was observed compared with the TEL 40 (OR: 1.23; 95% CI: 0.80 to 1.89; $p = 0.3523$) (Table S5).

For BP response rate, the TEL/AML 20/2.5 consistently showed higher rates across all time points. At week 4, the response rates were 52.15% for TEL/AML 20/2.5, 33.75% for TEL 20 (difference: 18.40%; 95% CI: 5.51 to 31.29; $p = 0.0069$), 28.95% for AML 2.5 (difference: 23.20%; 95% CI: 10.44 to 35.96; $p = 0.0008$), and 41.82% for TEL 40 (difference: 10.33%; 95% CI: −0.42 to 21.00; $p = 0.0609$). At week 8, the response rates were 61.68% for TEL/AML 20/2.5, 40.74% for TEL 20 (difference: 20.94%; 95% CI: 7.94 to 33.93; $p = 0.0019$), 35.00% for AML 2.5 (difference: 26.68%; 95% CI: 13.89 to 39.47; $p < 0.0001$), and 49.40% for TEL 40 (difference: 12.28%; 95% CI: 1.69 to 22.87; $p = 0.0242$), with statistical significance observed except for the comparison with TEL 40 at week 4 (Figure 3B).

Logistic regression analysis showed that at week 4, the TEL/AML 20/2.5 had statistically significantly higher odds of achieving a BP response compared with the TEL 20 (OR: 2.14; 95% CI: 1.23 to 3.73; $p = 0.0074$) and the AML 2.5 (OR: 2.67; 95% CI: 1.49 to 4.79; $p = 0.0009$). At week 8, the odds remained statistically significantly higher compared with the TEL 20 (OR: 2.34; 95% CI: 1.36 to 4.03; $p = 0.0021$) and the AML 2.5 (OR: 2.99; 95% CI: 1.72 to 5.21; $p = 0.0001$). When compared with TEL 40, the odds were statistically significant at week 8 (OR: 1.65; 95% CI: 1.07 to 2.55; $p = 0.0245$), while no statistically significant difference was observed at week 4 (OR: 1.52; 95% CI: 0.98 to 2.34; $p = 0.0614$) (Table S6).

No substantial differences were observed in secondary efficacy outcomes between the FAS and PPS analyses.

3.4 | Safety Outcomes

During the 8-week study period, 55 TEAEs were reported by 40/497 subjects (8.05% of the safety set), with similar incidence observed across treatment groups: 7.74% (13/168) in the TEL/AML 20/2.5, 8.64% (7/81) in the TEL 20, 7.41% (6/81) in the AML 2.5, and 8.38% (14/167) in the TEL 40, with no statistically significant differences between groups ($p = 0.9879$). Most TEAEs were mild in severity. ADRs occurred in 2.47%–2.99% of subjects across groups, all of which were mild and resolved or were resolving at the end of the study.

SAEs were reported in three subjects: two in the TEL 20 (unstable angina, cerebrovascular accident) and one in the TEL 40 (unstable angina). All SAEs were judged as unrelated or

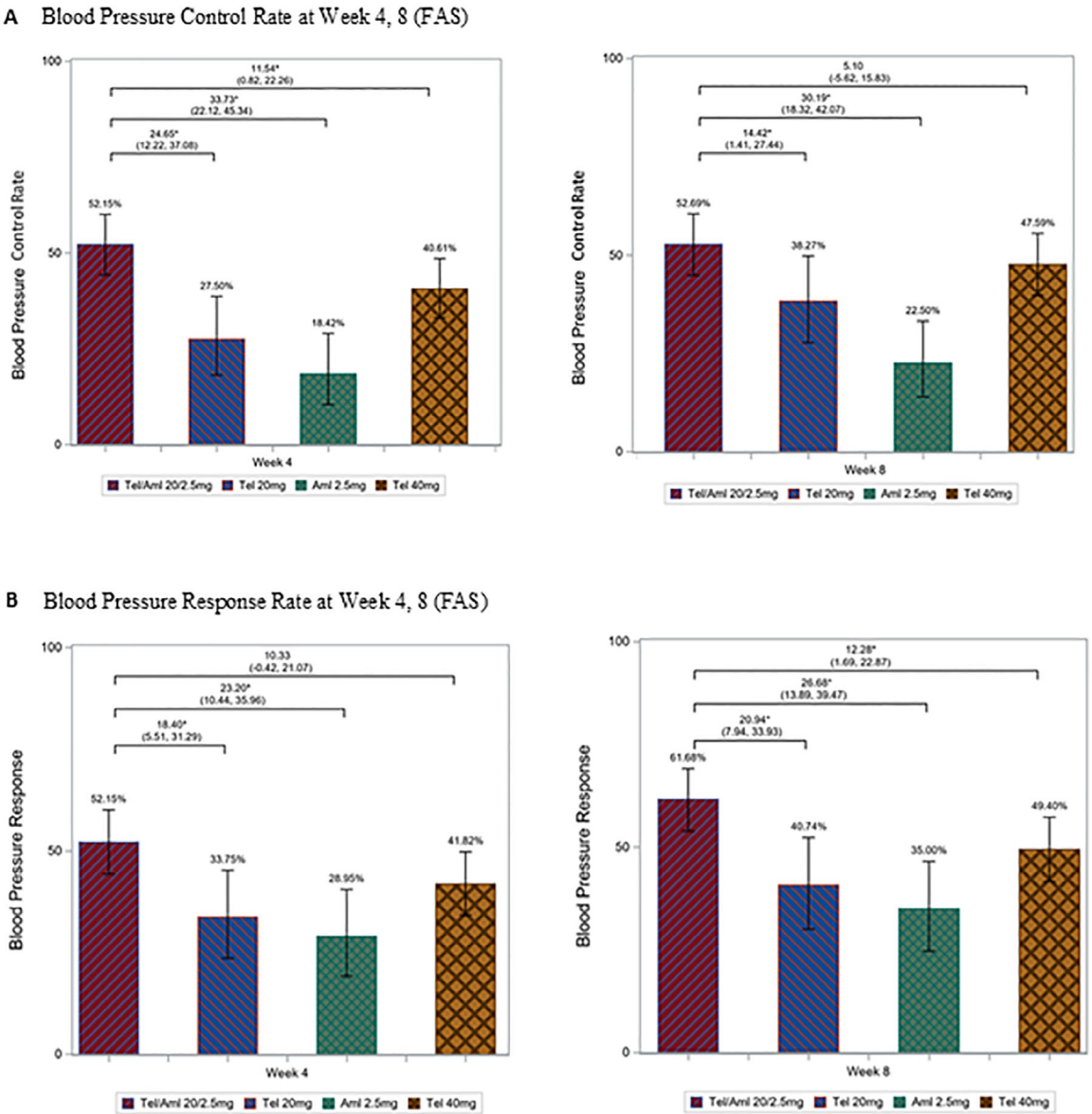

FIGURE 3 | Blood Pressure Control and Response Rates at Week 4, 8 (FAS).Panel A, Blood pressure control rates at week 4 (A) and week 8 (B) following treatment with low-dose dual combination therapy (Telmisartan/Amlodipine 20/2.5 mg) compared with monotherapy (Telmisartan 20 mg, Amlodipine 2.5 mg, and Telmisartan 40 mg).Panel B, Blood pressure response rates at week 4 (A) and week 8 (B) following treatment with low-dose dual combination therapy (Telmisartan/Amlodipine 20/2.5 mg) compared with monotherapy (Telmisartan 20 mg, Amlodipine 2.5 mg, and Telmisartan 40 mg). Between-group comparisons are presented with mean differences and 95% confidence intervals. *$p < 0.05$ versus comparator.Amlodipine (Aml), Full analysis set (FAS), Telmisartan (Tel), Telmisartan /Amlodipine (Tel/Aml).

unlikely related to the investigational product. TEAEs leading to permanent discontinuation occurred in five subjects, including four ADRs (headache, dizziness, chest discomfort, urticaria), all assessed as mild. No subjects experienced serious ADRs, adverse events of special interests (AESIs), or any TEAEs or ADRs leading to death in any treatment group. Furthermore, no TEAE occurred in more than 3% of subjects in any treatment arm (Table 2).

Clinically significant changes in laboratory tests were rare and typically mild. Notable findings included transient elevations in ALT/AST, LDL-C, and hemoglobin, with no direct causality established. No clinically meaningful abnormalities were observed in vital signs, ECGs, or physical examinations throughout the study.

4 | Discussion

In this randomized, double-blind, active-controlled trial, TEL/AML 20/2.5 produced greater BP reductions than TEL 20 or AML 2.5 monotherapy and was non-inferior to TEL 40. Importantly, the randomized design and the inclusion of multiple active comparators strengthen the clinical validity and originality of our strategy for hypertension.

The efficacy of TEL/AML 20/2.5 observed in this study was consistent with previous findings, which reported similar reductions in BP and a comparable BP control rate (52.3%) for the same low-dose regimen [34]. Although cross-trial comparisons should be interpreted cautiously due to differences in patient profiles

TABLE 2 | Safety summary (Safety Set).

Category	TEL/AML 20/2.5 (*N* = 168)	TEL 20 (*N* = 81)	AML 2.5 (*N* = 81)	TEL 40 (*N* = 167)	*p*-value[a]
Subjects with TEAE	13 (7.74) [23]	7 (8.64) [9]	6 (7.41) [7]	14 (8.38) [16]	0.9879(c)
Subjects with ADR	5 (2.98) [6]	2 (2.47) [2]	0	5 (2.99) [6]	0.5322(f)
Subjects with SAE	0	2 (2.47) [2]	0	1 (0.60) [1]	0.0874(f)
TEAEs Leading to Permanent Discontinuation	1 (0.60) [1]	2 (2.47) [2]	1 (1.23) [2]	1 (0.60) [2]	0.3716(f)
ADRs Leading to Permanent Discontinuation	1 (0.60) [1]	1 (1.23) [1]	0	1 (0.60) [2]	0.7703(f)

Notes: Denominator of percentage is the number of subjects in each group. TEAEs are displayed as number of subjects(percentage of subjects) [number of events].
Abbreviations: Adverse drug reaction (ADR), Amlodipine 2.5 mg (AML 2.5), Adverse Events of Special Interest (AESI), Number of subjects (N), Serious adverse event (SAE), Telmisartan 20 mg (TEL 20), Telmisartan 40 mg (TEL 40), Telmisartan/Amlodipine 20/2.5 mg (TEL/AML 20/2.5), Treatment emergent adverse event (TEAE).

[a]Chi-square test(c), Fisher's exact test(f).

and ethnicity, both the magnitude of BP reduction and the week 8 BP control rate achieved with TEL/AML 20/2.5 in our study (52.69%) were comparable to those reported for standard-dose combination therapies in other trials, including Park et al. [40]. (40.68%) and Neldam et al. [28]. (51.3%). Furthermore, TEL/AML 20/2.5 reduced SBP by 18.54 mmHg in this study. Although not based on a direct head-to-head comparison, this reduction falls within the 11.4–25.7 mmHg range previously reported for standard-dose dual SPCs [41], suggesting that TEL/AML 20/2.5 may be a reasonable alternative. These findings indicate that judiciously selected low-dose dual combinations can achieve clinically useful and substantial reductions without the added burden of polypharmacy or increased AE risk. Taken together, these results highlight low-dose dual SPC as a strategic option that balances efficacy and tolerability, rather than a "weaker" minimalist regimen, and as a potential first-line treatment for hypertension.

Early BP reduction has been associated with improved CV outcomes [42–44] and may also enhance patient confidence in treatment effectiveness. In this regard, the statistically significant antihypertensive effect of TEL/AML 20/2.5, observed from week 4 (the earliest assessment) and sustained through week 8, is clinically meaningful (LSM reductions in SBP/DBP: –18.12/–8.77 mmHg at week 4 and –18.54/–9.50 mmHg at week 8). Recently, Rodgers et al. [45]. reported that a low-dose triple SPC (Widaplik; telmisartan 20 mg, amlodipine 2.5 mg, and indapamide 1.25 mg) demonstrated a BP-lowering effect from the second week of administration. Despite differences in study design and drug composition, the Widaplik trial supports the efficacy of low-dose SPC therapy, and its FDA approval reflects a shift toward more comprehensive initial treatment strategies for hypertension.

TEL/AML 20/2.5 SPC therapy was generally well tolerated, without reports of SADRs, or deaths. In our study, peripheral edema, a major AE associated with CCBs, was not observed in either the TEL/AML 20/2.5 or AML 2.5 monotherapy groups. The low incidence of AEs with TEL/AML 20/2.5 likely reflects the low dose used [29, 46]. Additionally, the distinctive composition of the TEL/AML 20/2.5 SPC may also contribute to its acceptable safety profile [47–49]. In a related finding, Rogers et al. [45]. reported a significant increase in symptomatic hypotension and hyponatremia/hypokalemia in hypertensive patients receiving a triple low-dose SPC compared with those treated with a dual SPC at the same dose. Electrolyte imbalance, syncope, and falls are well-known side effects commonly associated with thiazide diuretics, especially prevalent among the elderly. As expected, these AEs were not observed in our study using TEL/AML 20/2.5 which comprise solely telmisartan and amlodipine, excluding the thiazide diuretic. These findings suggest that a TEL/AML 20/2.5 SPC may serve as a well-tolerated treatment option for patients with mild-to-moderate hypertension. It could be particularly beneficial for patients intolerant of diuretics and for elderly hypertensive patients.

Recent global hypertension guidelines, including the 2023 ESH and 2024 ESC updates, recommend initiating low-dose dual combination therapy, preferably as a SPC, and achieving BP control within 3 months to improve patient confidence and reduce CVD risk [50, 51]. Triple therapy is generally reserved for patients not controlled on dual SPCs, underscoring the importance of effective and well-tolerated two-drug combinations as the foundation of initial therapy. While triple or quadruple low-dose SPCs are widely used [32, 52, 53], studies on efficacy and safety, including comparative research based on differences in composition or dosage, remains limited. Furthermore, the 2024 ESC guidelines also note that much of the evidence supporting combination therapy is derived from observational data [51]. At this point, the findings from our pioneering study using a dual half-dose SPC align with these recommendations. Based on a randomized controlled trial design, our results provide evidence that the TEL/AML 20/2.5 SPC achieves BP reduction as early as 4 weeks and demonstrates a favorable safety profile in mild-to-moderate hypertension. These results support that TEL/AML 20/2.5 is a potential candidate as a practical and guideline-concordant treatment option.

Despite these promising results, this study has several limitations. First, reliance solely on office BP measurements represents a limitation, as home BP monitoring in future studies could mitigate white coat effects and masked hypertension effects, thereby providing a more comprehensive assessment of BP control. Second, the 8-week duration, while consistent with regulatory

guidance for antihypertensive efficacy evaluation, precludes the assessment of longer-term outcomes. Lastly, the study population was exclusively Korean, which may limit the generalizability to other racial and ethnic groups of these promising findings. Further research in more ethnically diverse populations would be valuable to confirm the efficacy and safety of this treatment across different groups.

5 | Conclusion

In conclusion, this study confirmed that SPC of TEL/AML 20/2.5 is more effective than TEL 20, AML 2.5 and comparable to TEL 40, with favorable tolerability. These results support its use as an effective and well-tolerated treatment option for essential hypertension, especially where early BP control, safety, and adherence are key priorities.

Author Contributions

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Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable local regulatory requirements. The study protocol was approved by the institutional review boards of all participating centers. The trial was prospectively registered at ClinicalTrials.gov (NCT06052748) in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines.

Consent

Written informed consent was obtained from all participants prior to enrollment.

Conflicts of Interest

The authors have declared that they have no conflicts of interest concerning the content of this article.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File 1: jch70279-sup-0001-SuppMat.docx