Check for updates

The Journal of Clinical Hypertension

WILEY

ORIGINAL ARTICLE OPEN ACCESS

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

Hyo-Suk Ahn[1] | Jeong-Cheon Ahn[2] | Jin-Man Cho[3] | Kyung Hee Lim[4] | Seung Hwan Han[5] | Yun-Kyeong Cho[6] | Kye Hun Kim[7] | Soon Jun Hong[8] | Chan Joo Lee[9] | Jin Oh Na[10] | Ki Chul Sung[11] | KyuYoung Choi[12] | Seok-Yeon Kim[13] | Dae-Hee Kim[14] | Han Choel Lee[15] | Sang-Hyun Ihm[16] | Jong-Chan Youn[17] | Ji-Yong Choi[18] | Sang-Hyun Kim[19] | Kwang-il Kim[20] | Jung-Hoon Sung[21] | Wook Bum Pyun[22] | Woo-Shik Kim[23] | Jung Sun Cho[24] | Yonggu Lee[25] | Sung-Ho Her[26] | Eun Joo Cho[27] | Eun Mi Lee[28] | Hae-Young Lee[29] | Young Won Yoon[30] | Jang Hoon Lee[31] | Weon Kim[32] | Sang Jae Rhee[33] | Jinho Shin[34]

[1]Division of Cardiology, Department of Internal Medicine, College of Medicine, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea | [2]Department of Cardiology, Korea University Ansan Hospital, Ansan, Republic of Korea | [3]Division of Cardiology, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University, Seoul, Republic of Korea | [4]Division of Cardiology, Dong-A University Hospital, Busan, Republic of Korea | [5]Division of Cardiology, Gachon University Gil Hospital, Incheon, Republic of Korea | [6]Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Hospital, Daegu, Republic of Korea | [7]Department of Cardiovascular Medicine, Chonnam National University Medical School/Hospital, Gwangju, Republic of Korea | [8]Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea | [9]Division of Cardiology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea | [10]Cardiovascular Center, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea | [11]Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea | [12]Department of Cardiology, H-Plus Yangji Hospital, Seoul, Republic of Korea | [13]Department of Cardiology, Seoul Medical Center, Seoul, Republic of Korea | [14]Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea | [15]Division of Cardiology, Department of Internal Medicine, Medical Research Institute, Pusan National University Hospital, Busan, Republic of Korea | [16]Division of Cardiology, Department of Internal Medicine, Bucheon St Mary's Hospital and the Catholic Research Institute for Intractable Cardiovascular Disease, College of Medicine, Catholic University of Korea, Seoul, Republic of Korea | [17]Division of Cardiology, Department of Internal Medicine, College of Medicine, Catholic Research Institute For Intractable Cardiovascular Disease, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea | [18]Division of Cardiology, Daegu Catholic University Medical Center, Daegu, Republic of Korea | [19]Department of Internal Medicine and Cardiovascular Center, Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Republic of Korea | [20]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea | [21]Division of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea | [22]Division of Cardiology, Department of Internal Medicine, Ewha Womans University Medical Center, Seoul, Republic of Korea | [23]Cardiovascular Center, Department of Internal Medicine, Kyung Hee University Medical Center, Seoul, Republic of Korea | [24]Division of Cardiology, College of Medicine, Daejeon St. Mary's Hospital, The Catholic University of Korea, Daejeon, Republic of Korea | [25]Division of Cardiology, Department of Internal Medicine, Hanyang University Guri Hospital, Guri, Republic of Korea | [26]Department of Cardiology, St. Vincent's Hospital, The Catholic University of Korea, Suwon, Republic of Korea | [27]Division of Cardiology, Department of Internal Medicine, College of Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea | [28]Division of Cardiology, Department of Internal Medicine, Wonkwang University Sanbon Hospital, Gunpo, Republic of Korea | [29]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea | [30]Division of Cardiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea | [31]Department of Cardiology, Kyungpook National University Hospital, Daegu, Republic of Korea | [32]Division of Cardiovascular, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University, Seoul, Republic of Korea | [33]Division of Cardiology, Department of Internal Medicine, Wonkwang University Hospital, Iksan, Republic of Korea | [34]Division of Cardiology, Department of Internal Medicine, Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea

Correspondence: Jinho Shin (jhs2003@hanyang.ac.kr)

Received: 19 March 2026 | **Revised:** 10 April 2026 | **Accepted:** 30 April 2026

Keywords: hypertension | low-dose therapy | randomized controlled trial | single-pill combination | telmisartan/amlodipine

Hyo-Suk Ahn, Jeong-Cheon Ahn, Jinho Shin contributed equally to this work and are joint first authors

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2026 The Author(s). *The Journal of Clinical Hypertension* published by Wiley Periodicals LLC.

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.

17517176, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jch.70279 by Ewha Womans University Library, Wiley Online Library on [28/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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

17517176, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jch.70279 by Ewha Womans University Library, Wiley Online Library on [28/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

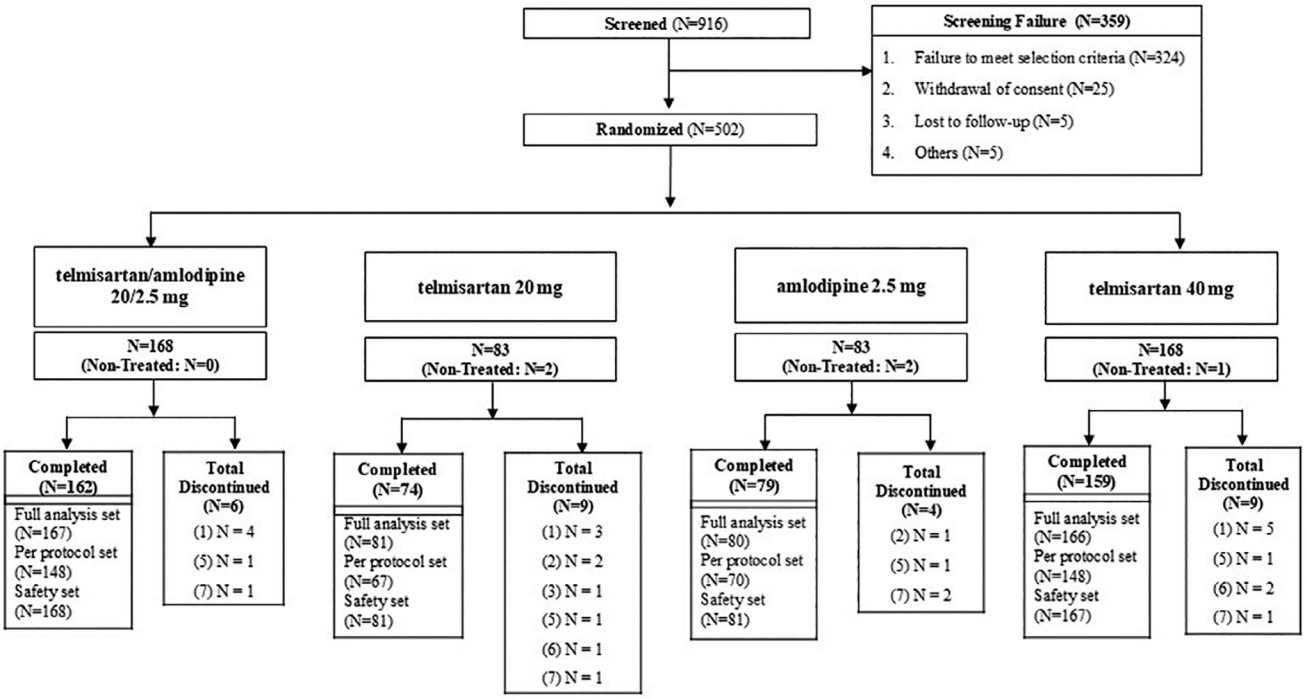


FIGURE 1 | Subject disposition throughout the study.Primary reasons for discontinuation included: (1) Withdrawal of consent; (2) Failure to meet selection criteria; (3) Use of prohibited concurrent medication; (4) Pregnancy during treatment period; (5) Inability to continue study participation due to 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).

17517176, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jch.70279 by Ewha Womans University Library, Wiley Online Library on [28/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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

17517176, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jch.70279 by Ewha Womans University Library, Wiley Online Library on [28/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

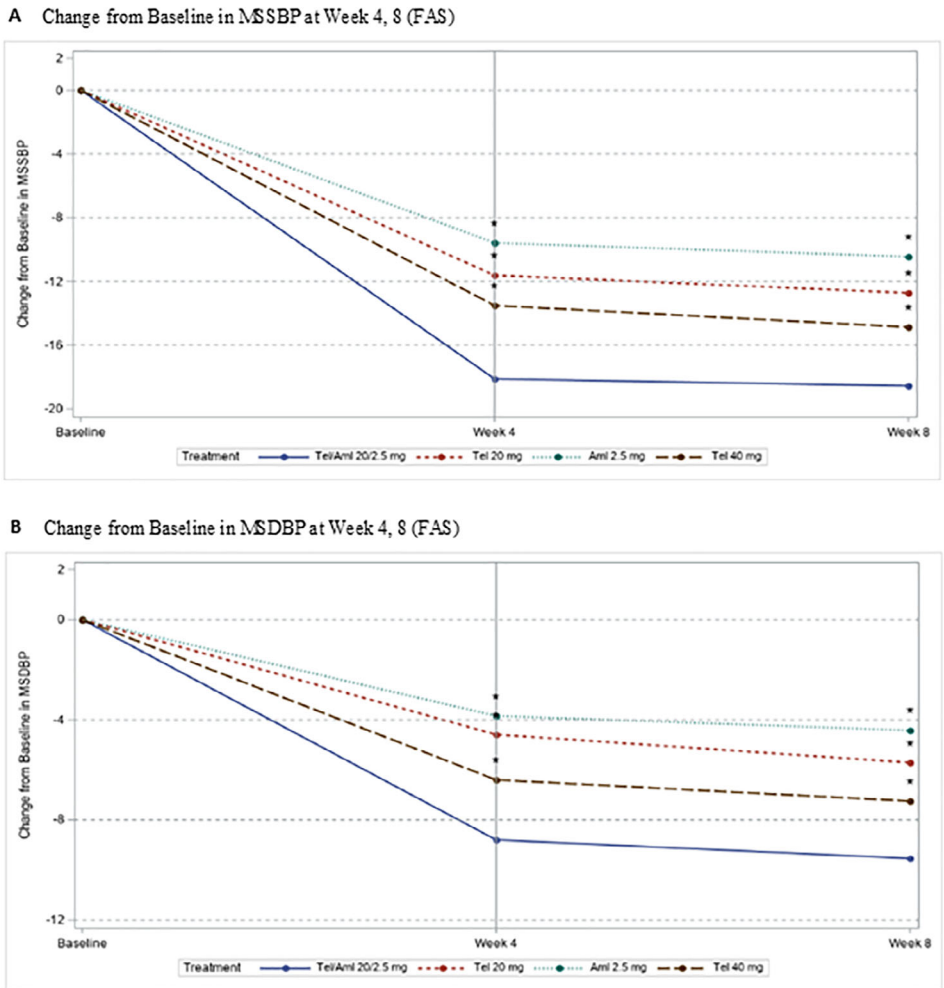


FIGURE 2 | Change from Baseline in MSSBP, MSDBP at Week 4, 8 (FAS).Amlodipine (Aml), Full analysis set (FAS), Mean systolic blood pressure (MSSBP), Mean sitting diastolic blood pressure (MSDBP), Telmisartan (Tel), Telmisartan /Amlodipine (Tel/Aml).

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

17517176, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jch.70279 by Ewha Womans University Library, Wiley Online Library on [28/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

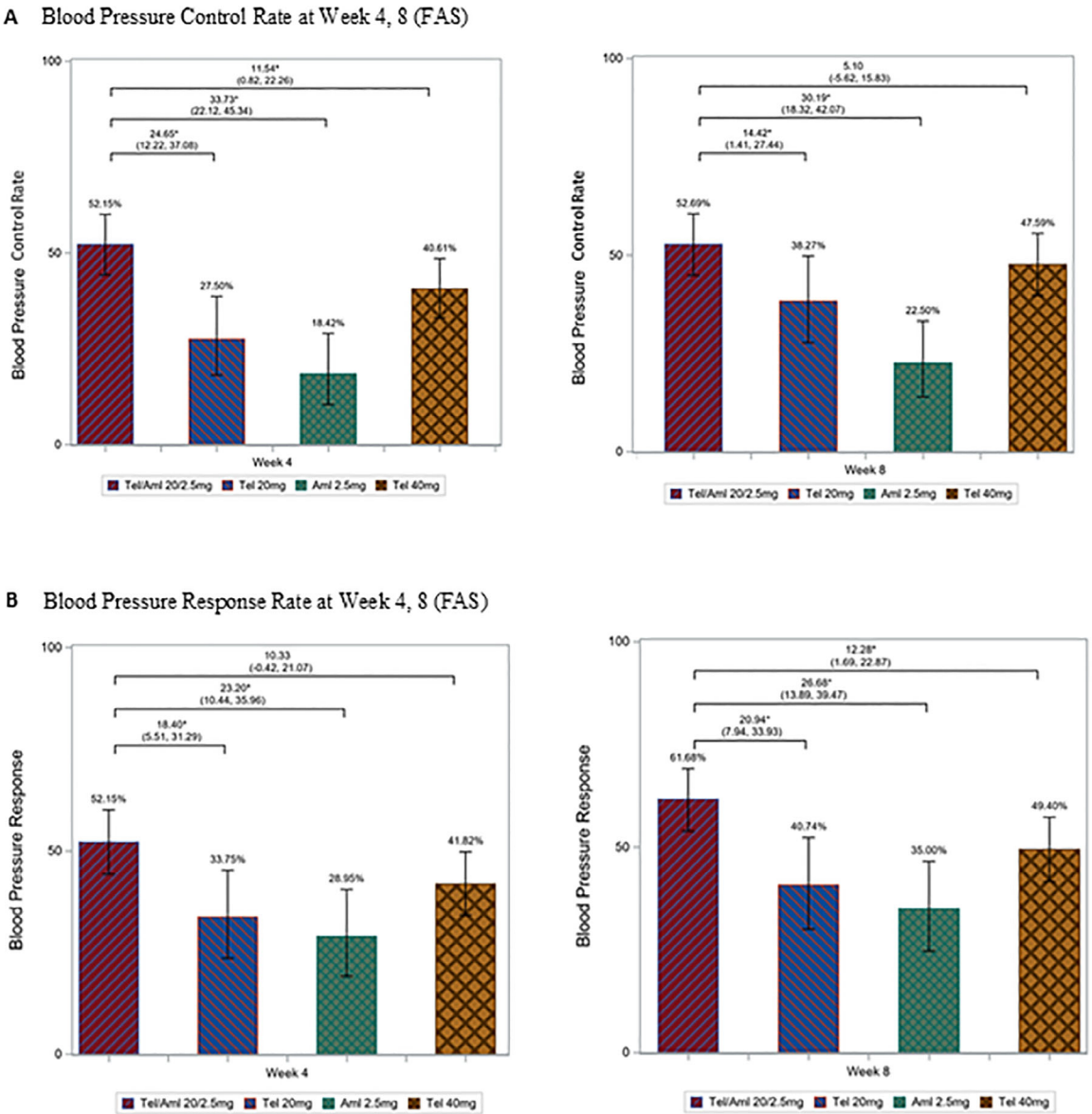


FIGURE 3 | Blood Pressure Control and Response Rates at Week 4, 8 (FAS).Panel A, Blood pressure control rates at week 4 (A) and week 8 (B) following treatment with low-dose dual combination therapy (Telmisartan/Amlodipine 20/2.5 mg) compared with monotherapy (Telmisartan 20 mg, Amlodipine 2.5 mg, and 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

17517176, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jch.70279 by Ewha Womans University Library, Wiley Online Library on [28/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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

17517176, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jch.70279 by Ewha Womans University Library, Wiley Online Library on [28/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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

Hyo-Suk Ahn: investigation, writing – original draft, writing – review & editing. **Jeong-Cheon Ahn**: investigation, writing – original draft, writing – review & editing. **Jin-Man Cho**: investigation, writing – review & editing. **Kyung Hee Lim**: investigation, writing – review & editing. **Seung Hwan Han**: investigation, writing – review & editing. **Yun-Kyeong Cho**: investigation, writing – review & editing. **Kye Hun Kim**: investigation, writing – review & editing. **Soon Jun Hong**: investigation, writing – review & editing. **Chan Joo Lee**: investigation, writing – review & editing. **Jin Oh Na**: investigation, writing – review & editing. **Ki Chul Sung**: investigation, writing – review & editing. **Kyu Young Choi**: investigation, writing – review & editing. **Seok-Yeon Kim**: investigation, writing – review & editing. **Dae-Hee Kim**: investigation, writing – review & editing. **Han Choel Lee**: investigation, writing – review & editing. **Sang-Hyun Ihm**: investigation, writing – review & editing. **Jong-Chan Youn**: investigation, writing – review & editing. **Ji-Yong Choi**: investigation, writing – review & editing. **Sang-Hyun Kim**: investigation, writing – review & editing. **Kwang-il Kim**: investigation, writing – review & editing. **Jung-Hoon Sung**: investigation, writing – review & editing. **Wook Bum Pyun**: investigation, writing – review & editing. **Woo-Shik Kim**: investigation, writing – review & editing. **Jung Sun Cho**: investigation, writing – review & editing. **Yonggu Lee**: investigation, writing – review & editing. **Sung-Ho Her**: investigation, writing – review & editing. **Eun Joo Cho**: investigation, writing – review & editing. **Eun Mi Lee**: investigation, writing – review & editing. **Hae-Young Lee**: investigation, writing – review & editing. **Young Won Yoon**: investigation, writing – review & editing. **Jang Hoon Lee**: investigation, writing – review & editing. **Weon Kim**: investigation, writing – review & editing. **Sang Jae Rhee**: investigation, writing – review & editing. **Jinho Shin**: Conceptualization, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing.

Acknowledgments

The investigators thank the participants and site staff for their contributions.

Funding

The study was funded by Yuhan Corporation, Seoul, Republic of Korea.

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.

References

1. K. T. Mills, A. Stefanescu, and J. He, "The Global Epidemiology of Hypertension," *Nature Reviews Nephrology* 16, no. 4 (2020): 223–237, https://doi.org/10.1038/s41581-019-0244-2.

2. Global Cardiovascular Risk Consortium; C. Magnussen, F. M. Ojeda, et al., "Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality," *New England Journal of Medicine* 389, no. 14 (2023): 1273–1285, https://doi.org/10.1056/NEJMoa2206916.

3. J. Lu, Y. Lu, X. Wang, et al., "Prevalence, Awareness, Treatment, and Control of Hypertension in China: Data From 1.7 Million Adults in a Population-Based Screening Study (China PEACE Million Persons Project)," *Lancett* 390, no. 10112 (2017): 2549–2558, https://doi.org/10.1016/S0140-6736(17)32478-9.

4. M. Satoh, T. Ohkubo, K. Miura, et al., "Long-Term Risk of Cardiovascular Mortality According to Age Group and Blood Pressure Categories of the Latest Guideline," *Hypertension Research* 48, no. 4 (2025): 1428–1433, https://doi.org/10.1038/s41440-025-02151-w.

5. S. Oparil, M. C. Acelajado, G. L. Bakris, et al., "Hypertension," *Nature Reviews Disease Primers* (2018): 18014, https://doi.org/10.1038/nrdp.2018.14.

6. V. L. Roger, A. S. Go, D. M. Lloyd-Jones, et al., "Heart Disease and Stroke Statistics–2012 Update: A Report From the American Heart Association," *Circulation* 125, no. 1 (2012): e2–e220, https://doi.org/10.1161/CIR.0b013e31823ac046.

7. N. C. D. Risk Factor Collaboration. Worldwide Trends in Hypertension Prevalence and Progress in Treatment and Control From 1990 to 2019: A Pooled Analysis of 1201 Population-Representative Studies With 104 Million Participants. *Lancet* 2021;398(10304):957–980, https://doi.org/10.1016/S0140-6736(21)01330-1.

8. Sprint Research Group; J. T. Wright, , J. D. Williamson, et al., "A Randomized Trial of Intensive versus Standard Blood-Pressure Control," *N Engl J Med Nov* 373, no. 22 (2015): 2103–2116, https://doi.org/10.1056/NEJMoa1511939.

9. T. Inoue, "Unawareness and Untreated Hypertension: A Public Health Problem Needs to be Solved," *Hypertension Research* 48, no. 4 (2025): 1639–1642, https://doi.org/10.1038/s41440-025-02118-x.

10. J. An, T. Luong, L. Qian, et al., "Treatment Patterns and Blood Pressure Control With Initiation of Combination versus Monotherapy Antihypertensive Regimens," *Hypertension* 77, no. 1 (2021): 103–113, https://doi.org/10.1161/HYPERTENSIONAHA.120.15462.

11. S. H. Kim, D. W. Shin, S. Kim, et al., "Prescribing Patterns of Antihypertensives for Treatment-Naive Patients in South Korea: From Korean NHISS Claim Data," *International Journal of Hypertension* 2019 (2019): 4735876, https://doi.org/10.1155/2019/4735876.

12. K. Marinier, P. Macouillard, M. de Champvallins, N. Deltour, N. Poulter, and G. Mancia, "Effectiveness of Two-Drug Therapy versus

17517176, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jch.70279 by Ewha Womans University Library, Wiley Online Library on [28/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Monotherapy as Initial Regimen in Hypertension: A Propensity Score-Matched Cohort Study in the UK Clinical Practice Research Datalink," *Pharmacoepidemiology and Drug Safety* 28, no. 12 (2019): 1572–1582, https://doi.org/10.1002/pds.4884.

13. B. M. Egan, S. E. Kjeldsen, K. Narkiewicz, R. Kreutz, and M. Burnier, "Single-Pill Combinations, Hypertension Control and Clinical Outcomes: Potential, Pitfalls and Solutions," *Blood Pressure* 31, no. 1 (2022): 164–168, https://doi.org/10.1080/08037051.2022.2095254.

14. P. Joseph, G. Roshandel, P. Gao, et al., "Fixed-Dose Combination Therapies With and Without Aspirin for Primary Prevention of Cardiovascular Disease: An Individual Participant Data Meta-Analysis," *Lancett* 398, no. 10306 (2021): 1133–1146, https://doi.org/10.1016/S0140-6736(21)01827-4.

15. G. Parati, S. Kjeldsen, A. Coca, W. C. Cushman, and J. Wang, "Adherence to Single-Pill versus Free-Equivalent Combination Therapy in Hypertension: A Systematic Review and Meta-Analysis," *Hypertension* 77, no. 2 (2021): 692–705, https://doi.org/10.1161/HYPERTENSIONAHA.120.15781.

16. G. Roshandel, M. Khoshnia, H. Poustchi, et al., "Effectiveness of Polypill for Primary and Secondary Prevention of Cardiovascular Diseases (PolyIran): A Pragmatic, Cluster-Randomised Trial," *Lancet* 394, no. 10199 (2019): 672–683, https://doi.org/10.1016/S0140-6736(19)31791-X.

17. K. Tsioufis, R. Kreutz, G. Sykara, J. van Vugt, and T. Hassan, "Impact of Single-Pill Combination Therapy on Adherence, Blood Pressure Control, and Clinical Outcomes: A Rapid Evidence Assessment of Recent Literature," *Journal of Hypertension* 38, no. 6 (2020): 1016–1028, https://doi.org/10.1097/HJH.0000000000002381.

18. S. Yusuf, P. Joseph, A. Dans, et al., "Polypill With or Without Aspirin in Persons Without Cardiovascular Disease," *New England Journal of Medicine* 384, no. 3 (2021): 216–228, https://doi.org/10.1056/NEJMoa2028220.

19. S. E. Kjeldsen, F. H. Messerli, C. E. Chiang, P. A. Meredith, and L. Liu, "Are Fixed-Dose Combination Antihypertensives Suitable as First-Line Therapy?," *Current Medical Research and Opinion* 28, no. 10 (2012): 1685–1697, https://doi.org/10.1185/03007995.2012.729505.

20. T. Unger, C. Borghi, F. Charchar, et al., "International Society of Hypertension Global Hypertension Practice Guidelines," *Hypertension* 75, no. 6 (2020): 1334–1357, https://doi.org/10.1161/HYPERTENSIONAHA.120.15026.

21. B. Williams, G. Mancia, W. Spiering, et al., "ESC/ESH Guidelines for the Management of Arterial Hypertension," *European Heart Journal* 39, no. 33 (2018): 3021–3104, https://doi.org/10.1093/eurheartj/ehy339.

22. S. S. Billecke and P. A. Marcovitz, "Long-Term Safety and Efficacy of Telmisartan/Amlodipine Single Pill Combination in the Treatment of Hypertension," *Vascular Health and Risk Management* 9 (2013): 95–104, https://doi.org/10.2147/VHRM.S40963.

23. K. C. Ferdinand and S. A. Nasser, "A Review of the Efficacy and Tolerability of Combination Amlodipine/Valsartan in Non-White Patients With Hypertension," *American Journal of Cardiovascular Drugs* 13, no. 5 (2013): 301–313, https://doi.org/10.1007/s40256-013-0033-4.

24. H. C. Kim, H. Lee, H. H. Lee, et al., "Korea Hypertension Fact Sheet 2024: Nationwide Population-Based Analysis With a Focus on Young Adults," *Clinical Hypertension* 31 (2025): e11, https://doi.org/10.5646/ch.2025.31.e11.

25. R. M. Guthrie, "Review: A Single-Pill Combination of Telmisartan Plus Amlodipine for the Treatment of Hypertension," *Postgraduate Medicine* 123, no. 6 (2011): 58–65, https://doi.org/10.3810/pgm.2011.11.2495.

26. R. M. Guthrie, B. Dahlof, K. A. Jamerson, et al., "Efficacy and Tolerability of Telmisartan plus Amlodipine in Added-Risk Hypertensive Patients," *Current Medical Research and Opinion* 27, no. 10 (2011): 1995–2008, https://doi.org/10.1185/03007995.2011.616490.

27. T. W. Littlejohn, 3rd, C. R. Majul, R. Olvera, et al., "Telmisartan Plus Amlodipine in Patients With Moderate or Severe Hypertension: Results From a Subgroup Analysis of a Randomized, Placebo-Controlled, Parallel-Group, 4×4 Factorial Study," *Postgraduate Medicine* 121, no. 2 (2009): 5–14, https://doi.org/10.3810/pgm.2009.03.1972.

28. S. Neldam, M. Lang, R. Jones, and T. Investigators, "Telmisartan and Amlodipine Single-Pill Combinations vs Amlodipine Monotherapy for Superior Blood Pressure Lowering and Improved Tolerability in Patients With Uncontrolled Hypertension: Results of the TEAMSTA-5 Study," *The Journal of Clinical Hypertension(Greenwich)* 13, no. 7 (2011): 459–466, https://doi.org/10.1111/j.1751-7176.2011.00468.x.

29. M. R. Law, N. J. Wald, J. K. Morris, and R. E. Jordan, "Value of Low Dose Combination Treatment With Blood Pressure Lowering Drugs: Analysis of 354 Randomised Trials," *BMJ : British Medical Journal* 326, no. 7404 (2003): 1427, https://doi.org/10.1136/bmj.326.7404.1427.

30. C. K. Chow, E. R. Atkins, G. S. Hillis, et al., "Initial Treatment With a Single Pill Containing Quadruple Combination of Quarter Doses of Blood Pressure Medicines versus Standard Dose Monotherapy in Patients With Hypertension (QUARTET): A Phase 3, Randomised, Double-Blind, Active-Controlled Trial," *Lancet* 398, no. 10305 (2021): 1043–1052, https://doi.org/10.1016/S0140-6736(21)01922-X.

31. S. R. Gnanenthiran, N. Wang, G. L. Di Tanna, et al., "Association of Low-Dose Triple Combination Therapy vs Usual Care With Time at Target Blood Pressure: A Secondary Analysis of the TRIUMPH Randomized Clinical Trial," *JAMA Cardiology* 7, no. 6 (2022): 645–650, https://doi.org/10.1001/jamacardio.2022.0471.

32. A. Rodgers, A. Salam, W. Cushman, et al., "Rationale for a New Low-Dose Triple Single Pill Combination for the Treatment of Hypertension," *Glob Heart* 19, no. 1 (2024): 18, https://doi.org/10.5334/gh.1283.

33. U.S. *Food and Drug Administration (FDA)* Twynsta Statistical Review(s). 2008, Accessed . https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/22401s000statr.pdf.

34. T. W. Littlejohn, 3rd, C. R. Majul, R. Olvera, et al., "Results of Treatment With telmisartan-amlodipine in Hypertensive Patients," *The Journal of Clinical hypertension (Greenwich)* 11, no. 4 (2009): 207–213, https://doi.org/10.1111/j.1751-7176.2009.00098.x.

35. U.S. Food and Drug Administration (FDA). Non-inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry 2016, Accessed August 8, 2025. https://www.fda.gov/media/78504/download.

36. A. J. Manolis, J. L. Reid, D. de Zeeuw, et al., "Angiotensin II Receptor Antagonist telmisartan in Isolated Systolic Hypertension (ARAMIS) Study: Efficacy and Safety of telmisartan 20, 40 or 80 mg versus Hydrochlorothiazide 12.5 mg or Placebo," *Journal of Hypertension* 22, no. 5 (2004): 1033–1037, https://doi.org/10.1097/00004872-200405000-00027.

37. S. Neldam, C. Edwards, and A. S. Group, "Telmisartan plus HCTZ vs. amlodipine plus HCTZ in Older Patients With Systolic Hypertension: Results From a Large Ambulatory Blood Pressure Monitoring Study," *The American Journal of Geriatric Cardiology* 15, no. 3 (2006): 151–160, https://doi.org/10.1111/j.1076-7460.2006.05219.x.

38. P. B. Akat, T. R. Bapat, M. B. Murthy, V. B. Karande, and S. R. Burute, "Comparison of the Efficacy and Tolerability of telmisartan and enalapril in Patients of Mild to Moderate Essential Hypertension," *Indian Journal of Pharmacology* 42, no. 3 (2010): 153–156, https://doi.org/10.4103/0253-7613.66838.

39. M. Kalikar, K. S. Nivangune, G. N. Dakhale, et al., "Efficacy and Tolerability of Olmesartan, Telmisartan, and Losartan in Patients of Stage I Hypertension: A Randomized, Open-Label Study," *Journal of Pharmacology and Pharmacotherapeutics* 8, no. 3 (2017): 106–111, https://doi.org/10.4103/jpp.JPP_39_17.

40. C. G. Park, T. H. Ahn, E. J. Cho, et al., "Comparison of the Efficacy and Safety of Fixed-Dose S-Amlodipine/Telmisartan and Telmisartan in Hypertensive Patients Inadequately Controlled With Telmisartan: A Randomized, Double-Blind, Multicenter Study," *Clinical Therapeutics* 38, no. 10 (2016): 2185–2194, https://doi.org/10.1016/j.clinthera.2016.09.006.

41. Lawrence Gould A, S. Unniachan and D. Wu, "Indirect Treatment Comparison Between Fixed-Dose-Combinations of amlodipine/losartan

17517176, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jch.70279 by Ewha Womans University Library, Wiley Online Library on [28/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

and amlodipine/valsartan in Blood Pressure Control," *International Journal of Clinical Practice* 68, no. 2 (2014): 163–172.

42. H. Y. Lee, J. Shin, G. H. Kim, et al., "2018Korean Society of Hypertension Guidelines for the Management of Hypertension: Part II-Diagnosis and Treatment of Hypertension," *Clinical Hypertension* 25 (2019): 20, https://doi.org/10.1186/s40885-019-0124-x.

43. P. Trenkwalder, D. Elmfeldt, A. Hofman, et al., "The Study on COgnition and Prognosis in the Elderly (SCOPE)—Major CV Events and Stroke in Subgroups of Patients," *Blood Pressure* 14, no. 1 (2005): 31–37, https://doi.org/10.1080/08037050510008823.

44. M. A. Weber, S. Julius, S. E. Kjeldsen, et al., "Blood Pressure Dependent and Independent Effects of Antihypertensive Treatment on Clinical Events in the VALUE Trial," *Lancet* 363, no. 9426 (2004): 2049–2051, https://doi.org/10.1016/S0140-6736(04)16456-8.

45. A. Rodgers, A. Salam, A. E. Schutte, et al., "Efficacy and Safety of a Novel Low-Dose Triple Single-Pill Combination of Telmisartan, Amlodipine and Indapamide, Compared With Dual Combinations for Treatment of Hypertension: A Randomised, Double-Blind, Active-Controlled, International Clinical Trial," *Lancet* 404, no. 10462 (2024): 1536–1546, https://doi.org/10.1016/S0140-6736(24)01744-6.

46. D. S. Wald, M. Law, J. K. Morris, J. P. Bestwick, and N. J. Wald, "Combination Therapy versus Monotherapy in Reducing Blood Pressure: Meta-Analysis on 11,000 Participants From 42 Trials," *American Journal of Medicine* 122, no. 3 (2009): 290–300, https://doi.org/10.1016/j.amjmed.2008.09.038.

47. R. Fogari, A. Zoppi, P. Maffioli, P. Lazzari, A. Mugellini, and G. Derosa, "Effect of telmisartan Addition to amlodipine on Ankle Edema Development in Treating Hypertensive Patients," *Expert Opinion on Pharmacotherapy* 12, no. 16 (2011): 2441–2448, https://doi.org/10.1517/14656566.2011.623698.

48. H. Makani, S. Bangalore, J. Romero, O. Wever-Pinzon, and F. H. Messerli, "Effect of Renin-Angiotensin System Blockade on Calcium Channel Blocker-Associated Peripheral Edema," *American Journal of Medicine* 124, no. 2 (2011): 128–135, https://doi.org/10.1016/j.amjmed.2010.08.007.

49. S. Neldam, D. Zhu, and H. Schumacher, "Efficacy of Telmisartan Plus Amlodipine in Nonresponders to CCB Monotherapy," *International Journal of Hypertension* 2013 (2013): 627938, https://doi.org/10.1155/2013/627938.

50. G. Mancia, R. Kreutz, M. Brunstrom, et al., "2023 ESH Guidelines for the Management of Arterial Hypertension the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)," *Journal of Hypertension* 41, no. 12 (2023): 1874–2071, https://doi.org/10.1097/HJH.0000000000003480.

51. J. W. McEvoy, C. P. McCarthy, R. M. Bruno, et al., "2024 ESC Guidelines for the Management of Elevated Blood Pressure and Hypertension," *European Heart Journal* 45, no. 38 (2024): 3912–4018, https://doi.org/10.1093/eurheartj/ehae178.

52. S. J. Hong, K. C. Sung, S. W. Lim, et al., "Low-Dose Triple Antihypertensive Combination Therapy in Patients With Hypertension: A Randomized, Double-Blind, Phase II Study," *Drug Design, Development and Therapy* 14 (2020): 5735–5746, https://doi.org/10.2147/DDDT.S286586.

53. N. Wang, P. Rueter, A. Salam, et al., "Low-Dose Combinations With 3 or 4 Blood Pressure-Lowering Medications for the Treatment of Hypertension," *JACC Advances* 4, no. 7 (2025):101883, https://doi.org/10.1016/j.jacadv.2025.101883.

Supporting Information

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

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

17517176, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jch.70279 by Ewha Womans University Library, Wiley Online Library on [28/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License