Original Research

Efficacy and Tolerability of Telmisartan/Amlodipine + Hydrochlorothiazide Versus Telmisartan/Amlodipine Combination Therapy for Essential Hypertension Uncontrolled With Telmisartan/Amlodipine: The Phase III, Multicenter, Randomized, Double-blind TAHYTI Study

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ABSTRACT

Purpose: This 8-week study in Korea aimed to evaluate the efficacy and tolerability of a telmisartan/amlodipine + hydrochlorothiazide (TAH)

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combination versus telmisartan/amlodipine (TA) combination in patients with essential hypertension that did not respond appropriately to 4-week treatment with TA.

Methods: All patients who met the inclusion criteria received TA (40/5 mg) during a 4-week run-in period (period 1). Patients who met the criteria for essential hypertension (mean sitting systolic blood pressure [MSSBP], ≥140 and <200 mm Hg, or ≥130 and <200 mm Hg in those with diabetes mellitus or chronic kidney disease) after period 1 were randomly assigned to receive TA 40/5 mg + hydrochlorothiazide 12.5 mg (test group) or TA only (control group). The test and control drugs were administered in each group for 2 weeks (period 2). Patients who completed period 2 underwent 6-week treatment (period 3) with a TAH and TA dose twice that in period 2. The primary end point was the change in MSSBP at week 8 of treatment. Secondary end points were the change in MSSBP at week 2 and MS diastolic BP, BP control rate, and BP response rate at weeks 2 and 8. Treatment tolerability was assessed based on adverse events (AEs), laboratory evaluations (chemistry, hematology, and urinalysis), 12-lead ECG, and physical examination including vital sign measurements.

Findings: We randomized 310 patients to the treatment groups. The mean (SD) ages of the TAH and TA groups were 62.0 (10.8) and 63.4 (10.4) years, respectively. The least squares mean change in MSSBP was significantly greater in the TAH group than in the TA group after 8 weeks (–18.7 vs –12.2 mm Hg; $P < 0.001$). Similar results were obtained on changes in MSSBP after 2 weeks and changes in sitting diastolic BP, BP control rate, and BP response rate at weeks 2 and 8 compared with the respective baseline values. The prevalences of treatment-emergent AEs (29.0% vs 16.3%; $P = 0.008$) and adverse drug reactions (20.0% vs 10.5%; $P = 0.020$) were significantly greater in the TAH group than in the TA group. Most treatment-emergent AEs were mild or moderate; none were severe. The most frequently reported AEs were dizziness and headache.

Implication: TAH triple therapy was more effective than was TA double therapy in reducing BP in these patients in Korea with essential hypertension that did not adequately respond to TA. ClinicalTrials.gov identifier: NCT02738632. (*Clin Ther*. 2018;40:50–63) © 2018 The Authors. Published by Elsevier HS Journals, Inc.

Key words: amlodipine, blood pressure control, hydrochlorothiazide, hypertension, telmisartan, triple combination.

INTRODUCTION

According to the Korean National Health and Nutrition Examination Survey (KNHANES), the prevalence of hypertension in adults aged >30 years was 27.9% (men, 32.7%; women, 23.1%) in 2015. Hypertension is closely related to cerebrovascular and cardiovascular diseases, which are the most frequent causes of death among adults; thus, the prevention and management of hypertension greatly impact public health.[1,2]

Blood pressure (BP) management and the treatment of hypertension and can significantly reduce the risk for cardiovascular disease.[3,4] It has been suggested that, in hypertensive patients, the BP-lowering effect of combination therapy is greater than that of a dose increase in monotherapy.[5,6] The use of a combination of various antihypertensive agents has been shown to have significantly positive effects on BP control and the prevention of cardiovascular events in hypertensive patients.[5,6]

According to the 8th Joint National Committee's guideline on hypertension,[7] "In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes (thiazide-type diuretic, CCB, ACEI, or ARB)."[7] The European Society of Cardiology recommends initiating a low-dose combination therapy prior to single-dose treatments of hypertension.[8] Additionally, the guideline from the British Hypertension Society and the National Clinical Guideline Center recommends 3-drug combinations of an ACEI or ARB, a calcium antagonist, and a thiazide diuretic in cases in which a 2-drug combination does not yield effective BP control.[9,10]

DM and chronic kidney disease (CKD) are important causes of cardiovascular disease owing to their associations with hypertension, and because BP control is often difficult in practice, combination therapy might be useful in patients with these conditions.

Combination therapy with an ARB and a calcium antagonist is more effective for BP control and cardiovascular disease prevention than is monotherapy.[11–13] The BP-lowering effect of thiazide-type diuretics is enhanced by combined therapy with β-blockers, ACEIs, ARBs, and dihydropyridine calcium antagonists. Studies have shown that combined therapy using an ARB and a thiazide diuretic improved compliance and markedly reduced mean BP.[14]

Combinations of telmisartan/amlodipine and telmisartan/hydrochlorothiazide have been recognized as well tolerated[11,15,16] and have been approved for use in Korea. Additionally, no drug interactions have been reported to occur when amlodipine and hydrochlorothiazide are coadministered. Therefore, it is expected that a 3-drug combination such as telmisartan/amlodipine + hydrochlorothiazide (TAH) would be well tolerated. Toxicity test results from a study in rats showed that toxicity reactions to treatment with 3-drug combinations were similar to those observed when the agents were administered individually.[15] A clinical trial conducted in Japan demonstrated that TAH was more effective and well tolerated than was a telmisartan/amlodipine (TA) combination.[17] However, the tolerability and efficacy of a 3-agent combination have not been fully tested in Korea. In the present study, we evaluated the efficacy and tolerability of TAH versus TA combination therapy in patients with essential hypertension that was not responding appropriately to TA combination therapy.

PATIENTS AND METHODS

Study Participants

At screening (visit 1), patients in Korea who were aged ≥19 years and had *uncontrolled hypertension* (defined as mean sitting systolic [MSS] BP of ≥140 and <200 mm Hg, or ≥130 and <200 mm Hg in patients with DM or *CKD* [defined as a baseline creatinine clearance of ≥30 and ≤60 mL/min] while taking antihypertensive agents, or ≥160 and <200 mm Hg off-treatment for at least 4 weeks) were eligible for the study.

Patients with any of the following criteria were excluded from the study: severe heart failure (New York Heart Association class III or IV), unstable angina, myocardial infarction, or valvular heart disease diagnosed within the previous 6 months; severe atrial fibrillation, atrial flutter, ventricular tachycardia or severe arrhythmia, or cerebral infarction occurring within the previous 6 months; severe cerebrovascular disorder with a history of cerebrovascular disease, type 1 DM, uncontrolled type 2 DM (glycosylated hemoglobin ≥9%), or moderate or malignant retinopathy occurring within the previous 6 months; serum creatinine of >2 mg/dL; a history of drug or alcohol dependence within the previous 6 months; a surgical or medical condition that may have significantly affected the pharmacokinetic properties (absorption, distribution, metabolism, or excretion) of the investigational products (IPs; telmisartan, amlodipine, or hydrochlorothiazide); severe hypersensitivity to any of the IPs; sulfonamide hypersensitivity; anuria, hypercalcemia, or low sodium/hypokalemia; Addison disease and galactose intolerance; genetic anomaly (eg, Lapp lactose dehydrogenase deficiency or glucose–galactose uptake disorder); chronic inflammatory disease requiring continuous anti-inflammatory therapy; an acute inflammatory condition that would have made it impossible to join the study in the opinion of an investigator; or a history of malignant tumor, including leukemia or lymphoma, within the previous 5 years. Patients whose first and second BP measurements varied during visit 1, who had a difference in MSSBP of ≥20 mm Hg or in MS diastolic BP (DBP) of ≥10 mm Hg, or who had an MSDBP of ≥120 mm Hg at visit 1 or 2 were also excluded from the study. In addition, patients who had been administered other IPs within 30 days prior to the present clinical study, those who took other antihypertensive or anticonvulsant drugs during the clinical trial period, and those who were pregnant/breast-feeding/possibly pregnant or not using an appropriate contraceptive method were excluded from the study.

During the 4-week (the duration of response to hypertension medication) run-in period (period 1), each patient was administered 1 tablet of TA (40/5 mg) daily. Patients with uncontrolled hypertension after 4 weeks despite TA treatment were randomly assigned to receive TAH or TA treatment (visit 2, week 0, baseline).

Study Design and Procedures

This 8-week, Phase III, multicenter, randomized, double-blind study was conducted in outpatients at 28 clinical sites in the Republic of Korea. The first patient enrollment occurred in June 2015, and the last patient completed the trial in November 2016. The study

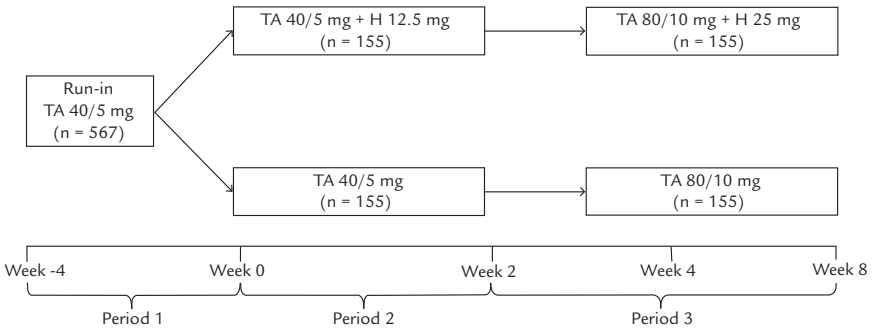

Figure 1. Study design. H = hydrochlorothiazide; TA = telmisartan/amlodipine.

protocol was approved by the institutional review board at each institution, and the study was performed in compliance with the Declaration of Helsinki, the Korean Good Clinical Practice guideline, and the standard operating procedures of Ildong Pharmaceutical Co., Ltd. (Seoul, Korea). All of the patients provided written informed consent at screening before undergoing any procedures. IPs were provided free of charge to patients. In addition, transportation reimbursements were approved by the institutional review board at each institution.

The study aimed to compare the efficacy and tolerability of TAH combination therapy with those of TA combination treatment after an 8-week treatment period in patients with high BP that did not respond adequately to 4-week treatment with TA 40/5 mg (Figure 1).

Patients who were eligible for screening by the clinician at visit 1 (week –4) were administered 1 tablet of TA 40/5 mg* once daily for 4 weeks during period 1. After period 1, at visit 2 (week 0, baseline), patients with uncontrolled hypertension despite treatment were randomly assigned to the TAH group or the TA group at a ratio of 1:1 and were administered the corresponding IP once daily for 2 weeks (period 2; TAH group, 1 tablet of TA 40/5 mg + hydrochlorothiazide 12.5 mg†; TA group, 1 tablet of TA 40/5 mg + hydrochlorothiazide-matching placebo.‡ The randomization sequence generated using computer software was used for constructing a random block of 2 or 4, stratified by the participating center. The patients were assigned to the groups using an interactive Web-response system.

Patients with uncontrolled hypertension at visit 2 were switched to a standard therapy as determined by the investigators. At visit 3 (week 2), patients returned to the clinical institution and were initiated on a double dose of IPs for 6 weeks (period 3). At visit 4 (week 4), the patients did not visit the institution, and the investigators checked patients' health status and adherence to medication by telephone contact. At visit 5 (week 8), patients who had completed the treatment completed the clinical trial, which lasted a total of 12 weeks.

To ensure double-blinding, the inactive hydrochlorothiazide placebo was manufactured in a tablet formulation with an appearance (color, shape, and size) and label identical to those of the active hydrochlorothiazide, so that no differences could be detected visually.

BP was measured by the same investigator when possible, using an electronic sphygmomanometer (HEM-7080IC; Omron Healthcare, Tokyo, Japan) supplied by the sponsor. A standardized cuff of an appropriate size was used, although the bladder was 80% longer and 40% wider than required when wrapped around the arm. This was done to ensure that the measurements were taken from arms without functional or anatomic abnormalities. After measurement of the BP using both arms at visit 1, the arm showing a higher BP value was used for subsequent measurements. However, if subsequent measurements from the same arm were not possible, the cause was recorded, and the BP was measured in the other arm. Patients were instructed to avoid caffeine intake,

*Trademark: Twynsta (Boehringer Ingelheim, Seoul, Korea).

†Trademark: Hydrochlorothiazide Towa (Towa Pharmaceutical Co, Ltd, Osaka, Japan).

‡Produced by Ildong Pharmaceutical Co, Ltd (Seoul, Korea).

exercise, and smoking for at least 30 minutes prior to each BP measurement. During the sitting BP measurement, patients sat in a chair with back support, and the arm was placed at heart level. Patients rested in a sitting position for 5 minutes or more, after which BP was measured in the upper arm. BP was measured at the same time (morning). The cuff was released completely between measurements. BP was measured 3 times at intervals of 2 minutes or more, and the MSSBP and MSDBP values were calculated.

During the clinical trial, patients whose MSSBP value was >200 mm Hg or whose MSDBP value was >120 mm Hg at any visit were withdrawn from the study. In addition, patients with signs or symptoms of hypotension, who had an MSSBP of <100 mm Hg, or an MSDBP of <60 mm Hg, at any visit during the study period were withdrawn at the investigator's discretion and treated medically by the investigator.

For standardization, the staff at the research institutes involved in this clinical study were trained in the protocol, and suggested study guidelines were provided, as was regular monitoring by PharmaCRO Inc (Seoul, Korea).

Efficacy Variables

The primary efficacy assessment variable was the least-squares (LS) mean change from baseline in SBP after 8 weeks of treatment (triple therapy vs double therapy). Secondary efficacy assessment variables were as follows: LS mean change in SBP after 2 weeks, and LS mean changes from baseline in DBP, rate of *BP control* (SBP/ DBP <140/<90 mm Hg, or <130/<80 mm Hg in patients with DM or CKD), and rate of *BP response* (reduction in SBP of >20 mm Hg or in DBP of >10 mm Hg) after 2 and 8 weeks of treatment. For missing values, the last-observation-carried-forward approach was used. In addition, subgroup analyses were performed to assess the rate of BP control after 2 and 8 weeks of treatment in patients with and without DM/CKD.

Tolerability Assessment

The tolerability assessment variables were treatment-emergent adverse events (TEAEs) after visit 2 and laboratory test results (general blood tests, serum biochemistry tests, and urinalysis), vital sign measurements (pulse and weight), and ECG. General blood testing, serum biochemistry testing, urinalysis, and vital sign measurements were performed at weeks –4, 0, 2, and 8. ECG was evaluated at visits 1 and 4 (weeks –4 and 8). The severity and causality of the AEs were evaluated based on the opinions of the study investigators.

Statistical Analysis

The sample size was calculated using 95% power at a 1-sided superiority significance level of 2.5% to detect statistical significance in between-treatment differences in mean changes from baseline in SBP, assuming a mean reduction of 5.7 mm Hg and an SD of 12.6 mm Hg.[18,19] Thus, a sample size of 254 patients who completed the study was planned for this clinical trial, assuming that 150 patients were to be randomized into each treatment group (N = 300, considering a 15% dropout rate). Efficacy analyses were carried out using a full analysis set (based on an intent-to-treat principle) and included all randomly assigned patients who took IPs at least once after randomization and had a mean SBP measured at least once before the trial ended and after IP administration. Tolerability analyses were carried out using a tolerability set that included patients who took IPs at least once after randomization and whose tolerability-related data were verified at least twice via telephone communication or clinic visits between IP intake and the end of the trial.

To compare the mean changes with triple therapy versus double therapy, an ANCOVA model was used, with treatment as a factor and baseline values as covariates. For each comparison, LS mean change (SE) and *P* value were estimated from the ANCOVA model. The BP control and response rates in each treatment group were summarized and analyzed using the Pearson χ^2 test or the Fisher exact test.

For the assessment of adverse reactions, the prevalences and percentages of patients who experienced TEAEs, ADRs, severe adverse reactions, and adverse reactions that resulted in permanent discontinuation of IPs after randomization were summarized. We also analyzed the severity of AEs and the likelihood that they were related to the IPs. For TEAEs that occurred in >1% of patients after randomization, the preferred term designated in the *Medical Dictionary for Regulatory Activities* (version 19.0) was used, and the prevalence was recorded. The frequencies of AEs by system organ class and preferred term per treatment group, as well as their severity, were recorded, as were

severe adverse reactions that necessitated permanent discontinuation of IPs.

To test differences in the frequencies of AEs likely resulting from triple or double therapy, the Pearson χ^2 test or Fisher exact test was conducted. All statistical analyses were performed using SAS software version 9.3 or higher (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patient Disposition, Demographic Characteristics, and Baseline Variables

A total of 567 patients with essential hypertension were screened; 257 were ineligible for the study. The primary reason for exclusion before randomization was the failure to satisfy all inclusion criteria or fulfillment of the exclusion criteria at visit 1 (68 [12.0%]) and visit 2 (159 [28.0%]). Of the 310 enrolled patients, 155 were randomized to receive TAH; 155, TA (Figure 2). During the double-blind treatment phase, 17 (11.0%) and 11 (7.1%) patients in the TAH and TA groups, respectively, dropped out. The most common reasons for discontinuation of TAH were the withdrawal of consent (5.2%) and AEs, protocol violation, and other factors (1.9% each). The most common reasons for discontinuation of TA were the withdrawal of consent (2.6%), AEs (1.9%), protocol violation (1.3%), and other factors (1.3%). For the efficacy analysis there were 151 and 153 patients in the TAH and TA groups, and for the tolerability evaluation, there were 155 and 153 patients in the TAH and TA groups. Four patients who did not undergo the primary efficacy evaluation in the TAH group were excluded from the efficacy analysis, and 2 patients in the TA group who were participating at multiple study sites were excluded from the efficacy analysis and tolerability evaluation.

The mean (SD) age of the randomized patients was 62.8 (10.6) years; 79% of the patients were men (76.8%, TAH group; 81.3%, TA group). The mean

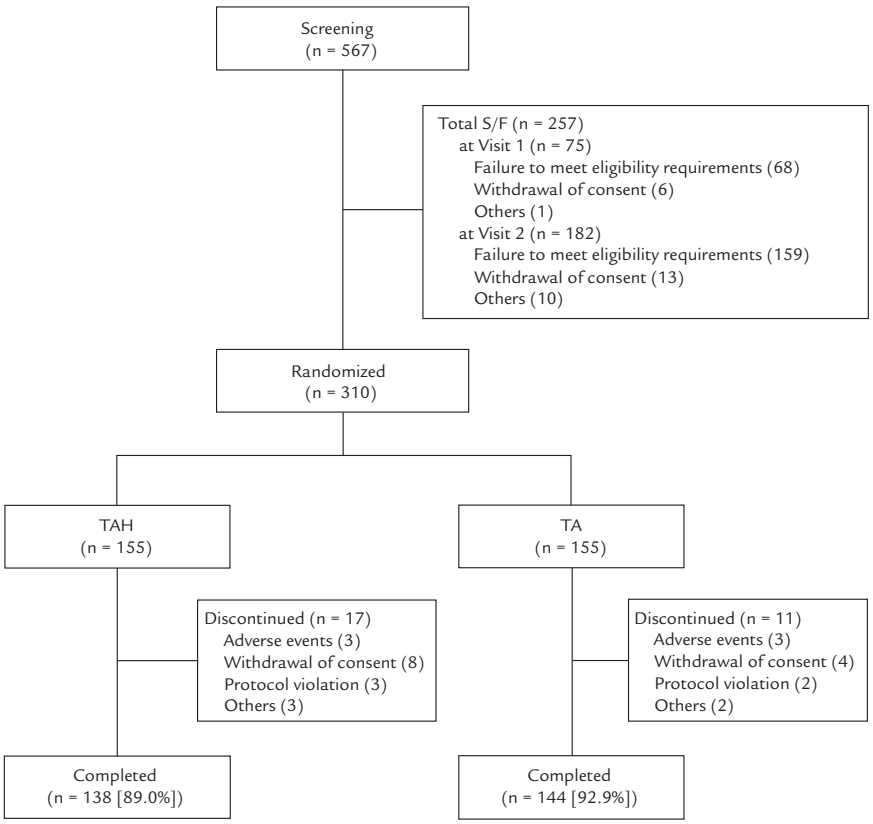

Figure 2. Patient disposition. S/F = screening failure; TA = telmisartan/amlodipine; TAH = telmisartan/amlodipine/hydrochlorothiazide.

Table I. Baseline demographic and clinical characteristics of randomized patients.

Characteristic	TAH (n = 155)	TA (n = 155)	All Patients (N = 310)	P^*
Age, mean (SD), y	62.0 (10.8)	63.4 (10.4)	62.8 (10.6)	0.187
Sex, no. (%)				0.329
Male	119 (76.8)	126 (81.3)	245 (79.0)	–
Female	36 (23.2)	29 (18.7)	65 (21.0)	–
Anthropometrics, mean (SD)				
Weight, kg	74.2 (13.4)	72 (10.9)	73.1 (12.3)	0.119
Height, cm	166.8 (7.6)	165.5 (7.8)	166.1 (7.8)	0.146
BMI, kg/m^2	26.6 (3.6)	26.3 (3.3)	26.4 (3.5)	0.426
Vital signs, mean (SD)				
Baseline sitting SBP,[†] mm Hg	153.7 (10.7)	152.6 (10.4)	153.2 (10.6)	0.357
Baseline sitting DBP,[†] mm Hg	90.1 (10.1)	88.8 (10.7)	89.5 (10.4)	0.278
Heart rate, beats/min	73.9 (10.8)	73.5 (12.5)	73.7 (11.7)	0.789
Comorbidity, no. (%)				
DM	33 (21.9)	46 (29.7)	79 (25.5)	0.090
CKD[‡]	21 (13.5)	25 (16.1)	46 (14.8)	0.523
DM or CKD[‡]	50 (32.3)	62 (40.0)	112 (36.1)	0.156

BMI = body mass index; CKD = chronic kidney disease; DBP = diastolic blood pressure; DM = diabetes mellitus; SBP = systolic blood pressure; TA = telmisartan plus amlodipine; TAH = telmisartan plus amlodipine plus hydrochlorothiazide.
*Using independent *t* test for continuous variables and Pearson χ^2 test for categorical variables.
†*Baseline BP* was defined as the mean of measurements from the randomization visit.
‡Defined as a baseline creatinine clearance rate of ≥30 and ≤60 mL/min.

body mass index was 26.4 (3.5) kg/m^2, and the mean heart rate was 73.7 (11.7) beats/min. The numbers of patients with DM and CKD were 79 (25.5%) and 46 (14.8%), respectively. The mean SBP values at baseline in the TAH and TA groups were 153.7 (10.7) and 152.6 (10.4) mm Hg; mean DBP values were 90.1 (10.1) and 88.8 (10.7) mm Hg; SBP/DBP values in both groups were therefore similar. Demographic and clinical characteristics at baseline did not differ significantly between the TAH and TA groups (Table I).

Efficacy

TAH caused a significantly greater LS mean reduction in SBP at week 8 than TA did (Figure 3). The LS mean (SE) changes in SBP were –18.7 (1.1) and –12.2 (1.1) mm Hg in the TAH and TA groups, respectively ($P < 0.001$). Treatment with TAH was associated with a significant LS mean reduction in DBP at week 8, whereas treatment with TA was not (–9.3 [0.6] vs –7.0 [0.6] mm Hg; $P = 0.013$). In both treatment groups, a BP-lowering effect was observed after 2 weeks. LS mean reductions in SBP and DBP in the TAH group were significantly less than were those in the TA group (SBP, $P < 0.001$; DBP, $P = 0.006$). MSSBP and MSDBP from weeks 2 to 8 are illustrated in Figure 4.

BP control rates were 31.8% (TAH) and 13.8% (TA) at week 2 and 52.3% (TAH) and 24.8% (TA) at week 8 (both, $P < 0.001$) (Figure 5). BP response rates were 33.8% (TAH) and 21.1% (TA) at week 2 ($P = 0.013$) and 56.3% (TAH) and 34.6% (TA) at week 8 ($P < 0.001$) (Table II).

Subanalysis of the patients after 2 and 8 weeks of treatment showed a significantly greater BP control rate among patients without DM or CKD in the TAH group than in the TA group (37.9% vs 16.5% at week 2; 62.1% vs 33.7% at week 8; both, $P < 0.001$). In the TAH group, patients without DM or CKD showed a significantly greater BP control rate after the treatments at weeks 2 and 8 than did patients with DM or CKD. However, in the TA group, patients without DM or CKD showed a significantly greater BP control rate compared with patients with DM or CKD after treatment week 8 only (33.7% vs 11.5%; $P = 0.002$) (Figure 5).

Figure 3. Least squares (LS) mean changes in sitting blood pressure after 2 and 8 weeks (W) of treatment with telmisartan/amlodipine + hydrochlorothiazide (TAH) or telmisartan/amlodipine (TA). $^{**}P < 0.001$ versus baseline; $^{\dagger}P < 0.05$ and $^{\ddagger}P < 0.001$ versus TA. DBP = diastolic blood pressure; SBP = systolic blood pressure.

Tolerability

We assessed the tolerability profiles of the treatments in 308 patients (TAH group, 155; TA group, 153) (Table III). The prevalence of TEAEs was significantly greater in the TAH group than in the TA group (29.0% vs 16.3%; $P = 0.008$). TEAEs were mild (n = 58) or moderate (n = 13), and none were severe. The most frequently reported AEs were dizziness (6.5%) and headache (2.6%). Dizziness occurred more frequently in the TAH group (11.0%) than in the TA group (2.0%) ($P = 0.001$). Serious TEAEs that occurred in the TAH group were back pain and intervertebral disc protrusion (n = 1 each). Causality relationships between these TEAEs and the treatments were assessed as "unlikely" by an investigator. One case of syncope was reported in the TA group, and the causality assessment was ruled "certain." The prevalence of ADRs was significantly greater in the TAH group than in the TA group (20.0% vs 10.5%; $P = 0.020$). There were no differences in the prevalences of TEAEs and ADRs between the 2 groups in period 2 (prior to period 3, in which the dose was double that of period 2). The prevalences of TEAEs were 9.7% and 9.8% in the TAH and TA groups, respectively, in period 2 ($P = 0.970$). The prevalences of ADRs were 5.2% and 4.6% in the TAH and TA groups in period 2 ($P = 0.811$). The prevalences of TEAEs and ADRs were significantly greater in the TAH group than in the TA group in period 3. The prevalences of TEAEs were 20.0% and 7.8% in the TAH and TA groups, respectively, in period 3 ($P = 0.002$). The prevalences of ADRs were 14.8% and 6.5% in the TAH and TA groups in period 3 ($P = 0.019$) (Table IV).

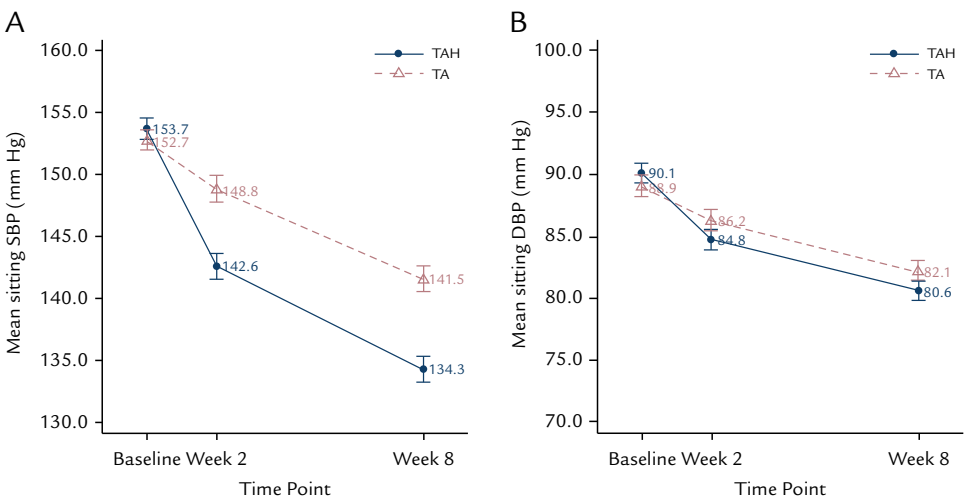

Figure 4. Mean sitting systolic blood pressure (SBP; A) and diastolic blood pressure (DBP; B) after 2 and 8 weeks of treatment with telmisartan/amlodipine + hydrochlorothiazide (TAH) or telmisartan/amlodipine (TA).

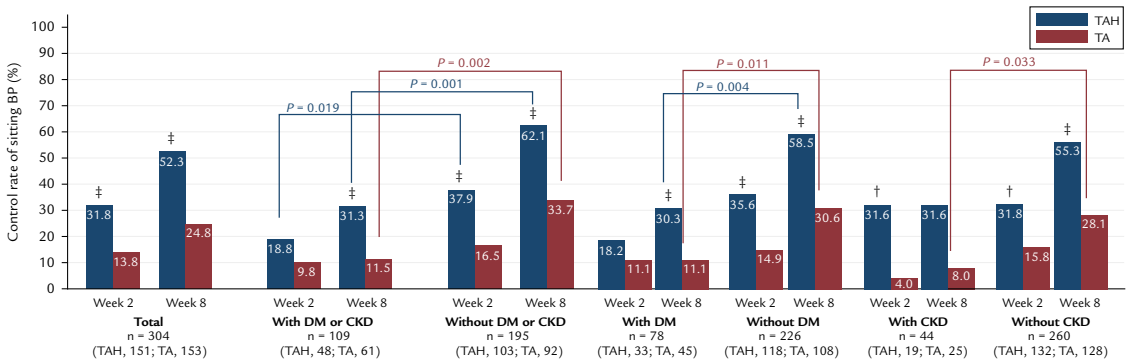

Figure 5. Rates of sitting blood pressure (BP) control (<140/<90 mm Hg [or <130/<80 mm Hg in patients with diabetes mellitus [DM] or chronic kidney disease [CKD; baseline creatinine clearance ≥30 and ≤60 mL/min]) after 2 and 8 weeks of treatment with telmisartan/amlodipine + hydrochlorothiazide (TAH) or telmisartan/amlodipine (TA). $^{\dagger}P < 0.05$ and $^{\ddagger}P < 0.001$ versus TA.

Three patients in the TAH group dropped out of the study because of dizziness (n = 2, ADRs) and intervertebral disc protrusion (n = 1, AEs). The 2 cases of dizziness were ADRs and categorized as moderate in intensity. The patients who discontinued the IPs because of dizziness were prescribed the same antihypertensive drugs they received prior to the trial and recovered. In the TA group, 3 patients dropped out of the study because of headache (mild, ADRs), syncope (moderate, ADRs), and retinal hemorrhage (moderate, ADRs). The headache and syncope continued, whereas the retinal hemorrhage improved by the end of the study. There were no significant differences in permanent discontinuation of the IPs because of ADRs or AEs between the groups.

Table II. Blood pressure response* rate. Data are given as number (%) of patients.

Visit	TAH (n = 151)	TA (n = 153)	P†
Week 2‡	51 (33.8)	32 (21.1)	0.013
Week 8	85 (56.3)	53 (34.6)	<0.001

TA = telmisartan/amlodipine; TAH = telmisartan/amlodipine/hydrochlorothiazide.
*Defined as a reduction from baseline of ≥20 mm Hg (sitting systolic blood pressure) or ≥10 mm Hg (sitting diastolic blood pressure).
†Using Pearson χ^2 test.
‡Excluding 1 patient in the TA group with a missing value.

Laboratory tests in the TAH group showed that renal function parameters such as serum creatinine, blood urea nitrogen, and blood uric acid levels increased slightly, whereas serum Na, K, and Cl levels were decreased slightly from their respective baseline values. These changes were attributed to the diuretic properties of hydrochlorothiazide. There were no significant changes in laboratory test results in the TA group (Table V).

Medication Compliance

Both groups exhibited comparable levels of medication compliance. The mean (SD) medication compliance rates were 96.5% (12.0%) and 96.9% (6.2%) in the TAH and TA groups, respectively (data not shown).

DISCUSSION

In this study, we investigated the efficacy and tolerability of TAH in patients with essential hypertension that did not respond adequately to TA. A previous systematic review and meta-analysis of 3- and 2-drug regimens for treating hypertension found that triple therapy with an ARB, a CCB, and a diuretic lowered mean (95% CI) SBP/DBP by 5.2 (4.3–6.1)/3.2 (2.6–3.7) mm Hg, yielding better results than did dual therapy with an ARB and a CCB.[20] While a direct comparison with the findings from our study is difficult, the results from the 2 studies are in agreement.

One multinational study found that 46.5% of participants with hypertension were aware of their condition, and approximately one third of those

Table III. Overview of treatment-emergent adverse events (TEAEs). Data are given as number (%) of patients.

Variable	TAH (n = 155)	TA (n = 153)	All Patients (N = 308)	P
Patients with any TEAE	45 (29.0)	25 (16.3)	70 (22.7)	0.008*
Severity				0.522†
Mild	39 (25.2)	19 (12.4)	58 (18.8)	
Moderate	7 (4.5)	6 (3.9)	13 (4.2)	
Severe	0	0	0	
Relationship to IP				0.925†
Definitely related	2 (1.3)	0	2 (0.7)	
Probably related	2 (1.3)	2 (1.3)	4 (1.3)	
Possibly related	10 (6.5)	5 (3.3)	15 (4.9)	
Probably not related	16 (10.3)	11 (7.2)	27 (8.8)	
Definitely not related	17 (11.0)	10 (6.5)	27 (8.8)	
Unknown/nonassessable	1 (0.7)	0	1 (0.3)	
Patients with serious TEAEs	2 (1.3)‡	1 (0.7)§	3 (1.0)	1.000†
Patients who withdrew because of TEAEs	3 (2.0)‖	3 (2.0)¶	6 (2.0)	1.000†
TEAEs occurring in ≥1% patients				
Dizziness	17 (11.0)	3 (2.0)	20 (6.5)	0.001*
Headache	4 (2.6)	4 (2.6)	8 (2.6)	1.000†
Nasopharyngitis	3 (2.0)	4 (2.6)	7 (2.3)	0.722†
Constipation	2 (1.3)	3 (2.0)	5 (1.6)	0.683†
Asthenia	2 (1.3)	1 (0.7)	3 (1.0)	1.000†
Edema, peripheral	2 (1.3)	1 (0.7)	3 (1.0)	1.000†
Back pain	2 (1.3)	0	2 (0.7)	0.498†
Cough	2 (1.3)	0	2 (0.7)	0.498†
Nausea	2 (1.3)	0	2 (0.7)	0.498†
Proteinuria	2 (1.3)	0	2 (0.7)	0.498†

IP = investigational product; TA = telmisartan/amlodipine; TAH = telmisartan/amlodipine/hydrochlorothiazide.

*Pearson χ^2 test.

†Fisher exact test when expected cell counts of <5 comprise 25% or more of a table.

‡Serious TEAEs that occurred in the TAH group were back pain and intervertebral disc protrusion (n = 1 each). Causality relationships between these TEAEs and the treatments were assessed as "unlikely" by an investigator.

§One serious case of syncope was reported in the TA group, and the causality assessment was assessed as "certain" by an investigator.

‖Three patients in the TAH group were withdrawn from the study because of dizziness (n = 2, ADRs) and intervertebral disc protrusion (n = 1, AEs). The 2 cases of dizziness were ADRs and categorized as moderate in intensity. The patients who discontinued the IPs because of dizziness were prescribed the same antihypertensive drugs they received prior to the trial and recovered.

¶In the TA group, 3 patients were withdrawn from the study because of headache (mild, ADRs), syncope (moderate, ADRs), and retinal hemorrhage (moderate, ADRs).

treated for hypertension achieved their target BP.[21] Clinical trials have shown that adequate BP control is possible with combinations of up to 4 antihypertensive drugs.[22–26] In the present study, the target BP (<140/<90 mm Hg) was achieved in 52.3% of the patients who received TAH and 24.8% of those who received TA. The subanalysis revealed that in patients with DM/CKD, the target BP (<130/<80 mm Hg) was more effectively achieved with TAH than with TA (31.3% vs 11.5%).

Table IV. Summary of treatment-emergent adverse events (TEAEs) in study periods 2 and 3. Data are given as number (%) of patients, [number of cases].

Variable	TAH (n = 155)	TA (n = 153)	All Patients (n = 308)	P^*
TEAEs[†]	45 (29.0), [68]	25 (16.3), [31]	70 (22.7), [99]	0.008
Period 2	15 (9.7), [24]	15 (9.8), [18]	30 (9.7), [42]	0.970
Period 3	31 (20.0), [42]	12 (7.8), [13]	43 (14.0), [55]	0.002
ADRs[‡]	31 (20.0), [46]	16 (10.5), [18]	47 (15.3), [64]	0.020
Period 2	8 (5.2), [15]	7 (4.6), [7]	15 (4.9), [22]	0.811
Period 3	23 (14.8), [30]	10 (6.5), [11]	33 (10.7), [41]	0.019

ADRs = adverse drug reactions; TA = telmisartan/amlodipine; TAH = telmisartan/amlodipine/hydrochlorothiazide.
*Pearson χ^2 test.
†Excluding 2 patients with missing data in the TAH group.
‡Excluding 1 patient with missing data in the TAH group.

With regard to tolerability, the AEs reported in this study were mild or moderate in severity. The prevalences of AEs/ADRs were greater in the TAH group than in the TA group. A clinical trial conducted in Japan comparing TAH and TA found a similar trend.[17]

In the present trial, the prevalences of dizziness were 11.0% and 2.0% in the TAH and TA groups, respectively. Although there were differences in AEs between the groups, all AEs were mild and most resolved without any treatment. In addition, there were no differences in the prevalences of TEAEs between the 2 groups in period 2. A previous forced-titration study found that the prevalence of dizziness associated with treatment was greater in patients receiving an amlodipine/valsartan/hydrochlorothiazide combination than in patients receiving an amlodipine/valsartan combination (7.7% vs 2.3%). Other similar findings have been reported as well.[25,27]

Poor medication adherence is associated with a high mortality rate and a high risk for hospitalization for specific cardiovascular diseases.[28] According to the 2011 KNHANES, the awareness, management, and control rates of hypertension among male patients with hypertension were 58.8%, 51.7%, and 36.9%, respectively. In addition, according to the 2008 KNHANES, 42% of elderly patients in Korea failed to observe medication guidelines, with the most common reason being that they "just forgot" (81.8%).[1] To improve compliance, several guidelines[29–31] recommend the use of combination medicines. Research has shown that compliance rates are greater when medications are administered as combination therapies than when they are administered as single medicaments.[29–31] The results from the present 3-period study support the clinical efficacy and tolerability of the 3-drug TAH combination, which can help in the management of hypertension by increasing compliance. At TAH doses of 80/10/25 mg and TA doses of 80/10 mg, the prevalence of dizziness was greater with TAH treatment; Clinically, there was more benefit than risk.

There were several limitations to this study. First, the duration of the study was short. We believe that 8 weeks may not have been sufficient time to observe the full benefits of the TAH combination or to determine whether its benefits decrease over a longer period. In addition, the number of patients with CKD analyzed was small. Furthermore, the study did not include patients with severely impaired kidney function (serum creatinine >2 mg/dL), who may also require combination therapies for the management of hypertension. In addition, the generalizability of the data to the global population with hypertension would be difficult because this study was limited to a population in Korea only.

CONCLUSIONS

The TAH combination was effective in lowering BP in these patients in Korea with essential hypertension that did not respond adequately to TA. Moreover, TAH

Table V. Laboratory tests results (renal function). Data are given as mean (SD).

Variables	TAH (n = 155)	TA (n = 153)	P^*
SCr, mg/dL			
Baseline	0.90 (0.2)	0.93 (0.3)	–
Week 8	0.94 (0.3)	0.92 (0.3)	<0.001
$P^\dagger$	<0.001	0.214	–
BUN, mg/dL			
Baseline	15.0 (4.5)	15.9 (5.6)	–
Week 8	16.8 (4.8)	16.4 (5.2)	0.006
$P^\dagger$	<0.001	0.102	–
Serum uric acid, mg/dL			
Baseline	5.5 (1.5)	5.5 (1.7)	–
Week 8	6.2 (1.6)	5.5 (1.5)	<0.001
$P^\dagger$	<0.001	0.757	–
Serum Na, mEq/L			
Baseline	140.8 (2.7)	140.7 (2.2)	–
Week 8	139.7 (2.6)	140.4 (2.4)	0.006
$P^\dagger$	<0.001	0.217	–
Serum K, mEq/L			
Baseline	4.3 (0.4)	4.3 (0.4)	–
Week 8	4.2 (0.4)	4.3 (0.4)	<0.001
$P^\dagger$	<0.001	0.808	–
Serum Cl, mEq/L			
Baseline	103.9 (2.7)	103.9 (2.5)	–
Week 8	102.0 (3.0)	103.9 (2.8)	<0.001
$P^\dagger$	<0.001	0.777	–

BUN = blood urea nitrogen; SCr = serum creatinine; TA = telmisartan/amlodipine; TAH = telmisartan/amlodipine/hydrochlorothiazide.
*Between-group *P*, unpaired *t* test.
†Within-group *P*, paired *t* test.

was an effective and tolerable antihypertensive drug combination with a high benefit-to-risk ratio. The findings from this study provide supporting information for clinicians for choosing a fixed-dose triple combination over a free-combination of 3 antihypertensives including an ARB, a CCB, and a diuretic.

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AUTHOR CONTRIBUTIONS

H.-S. Kim, K.C. Sung, K. Yoo, S.-W. Rha, Y.K. Ahn, A.J. Cheon, J.-Y. Jang, and T.-J. Hong designed the study. H.-S. Kim, K.C. Sung, Y.-S. Oh, D.-H. Cha, S.-J. Hong, K. Won, K. Yoo, S.-W. Rha, Y.K. Ahn, Ahn J. Cheon, J.-Y. Jang, T.-J. Hong, S.K. Cho, P.S. Ho, M.S. Hyon, C.-W. Nam, I.-H. Chae, B.-S. Yoo, J.-M. Song, J.-O. Jeong, Y.W. Yoon, B.S. Kim, Y.T. Hyun, D.-K. Cho, S.H. Kim, Y.J. Choi, and J. Ahn collected the data. H.-S. Kim and K.C. Sung interpreted the data. H.-S. Kim, K.C. Sung, and J.D.-Woon performed literature search. H.-S. Kim and K.C. Sung created the figures. K.C. Sung wrote the introduction. Y.-S. Oh, D.-H. Cha, S.-J. Hong, and K. Won wrote the methodology. H.-S. Kim wrote the

discussion. All of the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.clinthera.2017.11.006.

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SUPPLEMENTARY MATERIAL

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1-2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3-4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5-7
Participants	4a	Eligibility criteria for participants	4-5
	4b	Settings and locations where the data were collected	5-6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6

(continued)

Section/Topic	Item No	Checklist item	Reported on page No
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8-9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	9
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10-11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-12
Other information			
Registration	23	Registration number and name of trial registry	1-2

(continued)

Section/Topic	Item No	Checklist item	Reported on page No
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram