Choice of Antihypertensive Combination Therapy Based on Daily Salt Intake

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Abstract: *Background:* It is unclear whether thiazide diuretics (TZs) or calcium channel blockers (CCBs) are more effective as add-on therapy to angiotensin receptor blockers (ARBs) in controlling hypertension. Because TZs are a rational choice in salt-sensitive hypertension, patients with high salt intake might preferentially benefit from ARB/TZ over ARB/CCB combination therapy. *Methods:* Hypertensive patients who failed to reach blood pressure goals despite treatment with ARBs alone were randomly assigned to receive either ARB/TZ or ARB/CCB combination therapy. Estimated daily sodium intake was calculated from spot urine values of sodium and creatinine. *Results:* Blood pressure was measured at baseline, and at 4, 8 and 12 weeks after starting combination therapy. For all study patients (n = 87), diastolic blood pressure reduction was greater in patients receiving ARB/CCB treatment. However, in the 37 patients with a baseline estimated daily salt intake greater than 10 g and baseline systolic blood pressure (SBP) ranging from 150 to 200 mm Hg, SBP was lower ($P < 0.05$) and SBP reduction was greater ($P < 0.05$) 4 weeks after starting combination therapy in those receiving ARB/TZ treatment. In the 31 patients whose estimated daily salt intake increased at 12 weeks compared with baseline, SBP at 12 weeks was lower in those receiving ARB/TZ treatment ($P < 0.05$). *Conclusions:* Estimated daily salt intake is a useful tool for guiding antihypertensive therapy and should be measured repeatedly during the therapeutic course.

Key Indexing Terms: Angiotensin receptor blockers; Thiazide diuretics; Calcium channel blockers; Combination pills; Daily salt intake.
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Recent evidence suggests that strict blood pressure control can improve cardiovascular morbidity and mortality in patients with hypertension. Angiotensin II type 1 (AT1) receptor blockers (ARBs), which act by selectively blocking the binding of angiotensin II to the AT1 receptor, are widely used in the treatment of hypertension.[1–3] To achieve strict blood pressure control, the Japanese Society of Hypertension (JSH) guidelines[4] recommend combination therapy with multiple antihypertensive agents, including rennin-angiotensin-aldosterone (RAA) system inhibitors such as angiotensin converting enzyme inhibitors (ACEIs) and ARBs. Recently, various ARB combination pills have been developed, including ARBs combined with thiazide diuretics (TZs) and calcium channel blockers (CCBs). One benefit of combination medications is increased patient compliance. However, it has yet to be determined which drug class, the TZs or the CCBs, is more efficacious as add-on therapy to ARBs in controlling hypertension.

The Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial found that cumulative 5-year composite cardiovascular events were 20% lower in high-risk hypertensive patients treated with an ACEI/CCB combination, compared with those treated with an ACEI/TZ combination. This finding may have been due to the greater antihypertensive effect of the ACEI/CCB combination relative to the ACEI/TZ combination.[5] However, it has been suggested that TZs should be more effective in salt-sensitive hypertension.[6] Because RAA system activity is accelerated in patients with the metabolic syndrome,[7] the RAS inhibitors, ARB and ACEI, are considered the agent of choice in these patients. However, the metabolic syndrome is often complicated by salt-sensitive hypertension.[8,9] Therefore, the ARB/TZ combination might be a rational therapeutic choice in patients with the metabolic syndrome and salt-sensitive hypertension.

This study was designed to test which of the combination treatment is better on a high salt diet intake to lower blood pressure, ARB/TZ or ARB/CCB.

METHODS

Study Design

This study was designed as a prospective randomized trial. Recruited were 107 hypertensive patients who did not achieve blood pressure goals, defined as systolic blood pressure (SBP) <140 mm Hg or diastolic blood pressure (DBP) <90 mm Hg, despite treatment with ARBs alone for over 4 weeks. Patients were recruited in 8 clinics belonging to the Tochigi Medical Association and in 5 hospitals in Tochigi prefecture and its surrounding areas. Patients with cardiovascular diseases, such as coronary artery disease, heart failure or cerebrovascular disease, were excluded. All patients were randomly assigned to switch from ARBs into either an ARB/TZ (80 mg valsartan/12.5 mg hydrochlorothiazide) combination pill or an ARB/CCB (80 mg valsartan/5 mg amlodipine) combination pill. Study end point was the changes in blood pressure from the baseline values to the values after switching into each combination pills during the 12 weeks' observation period. After primary analysis in overall patients, subgroup analysis based on estimated daily salt intake was proposed before the data correction (a priori analysis). The study protocol was approved by the local medical ethics committees and informed consent was obtained from all patients.

Measurements

Blood pressure and heart rate were measured at baseline and at 4, 8 and 12 weeks after starting combination therapy. After the patient rested in the seated position for 5 minutes,

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TABLE 1. Baseline characteristics

	ARB/TZ group (n = 38)	ARB/CCB group (n = 49)	*P*
Age (yr)	67 ± 13	62 ± 13	0.09
Male gender, n (%)	22 (58)	26 (53)	0.48
Heart rate/min	73 ± 11	75 ± 11	0.66
Body mass index (kg/m^2)	24 ± 3	26 ± 7	0.91
Systolic blood pressure (mm Hg)	156 ± 17	162 ± 19	0.13
Diastolic blood pressure (mm Hg)	86 ± 12	95 ± 13	0.0005
Medications			
Statins	10 (26)	14 (29)	0.63
Antidiabetic agents	7 (18)	10 (20)	0.72
Hemoglobin A1c (%)	5.6 ± 1.2	5.4 ± 0.5	0.14
Total cholesterol (mg/dL)	206 ± 44	196 ± 35	0.22
LDL cholesterol (mg/dL)	132 ± 34	118 ± 33	0.06
Triglyceride (mg/dL)	142 ± 72	143 ± 79	0.95
Na (mEq/L)	142 ± 3	141 ± 6	0.34
K (mEq/L)	4.3 ± 0.4	4.4 ± 0.5	0.28
Creatinine (mg/dL)	0.78 ± 0.24	0.76 ± 0.17	0.65
eGFR (mL·min^{-1}·1.73 m^{-2})	76 ± 18	76 ± 17	0.96
Urinary albumin (mg/g·Cr)	28 ± 32	28 ± 40	0.99
Uric acid (mg/dL)	6.0 ± 1.7	5.5 ± 1.5	0.17
Estimated daily salt intake (g)	10.6 ± 3.7	9.8 ± 3.1	0.30

ARB, angiotensin receptor blocker; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; TZ, thiazide diuretics.

blood pressure was measured twice, with an interval of at least 5 minutes between each measurement. Blood pressure was measured in the same arm at each visit using a mercury sphygmomanometer with an appropriately sized cuff and recorded to the nearest 2 mm Hg.

Height, weight, waist circumference and body mass index (BMI) were measured at baseline. The authors defined visceral fat-type obesity as a waist circumference greater than 85 cm for men and greater than 90 cm for women.

Blood and urine testing was performed at baseline and at 12 weeks. Serum creatinine levels were measured using an enzymatic method, and the estimated glomerular filtration rate (eGFR) was calculated by a formula provided by the Japanese Society of Nephrology Chronic Kidney Disease (CKD) Practice Guide: eGFR (mL·min^{-1}·1.73 m^{-2}) = 194 × (serum creatinine level [mg/dL])$^{-1.094}$ × (age [y])$^{-0.287}$. The product of this equation was multiplied by a correction factor of 0.739 for women.[10] Spot urinary albumin levels were determined using a turbidimetric immunoassay and were multiplied by the urine creatinine level (enzymatic method). The authors defined CKD as eGFR less than 60 mL·min^{-1}·1.73 m^{-2} and/or urinary albumin level greater than 30 mg/g·Cr.[11] Serum uric acid levels were determined by the uricase peroxidase method, and serum levels of sodium and potassium were measured by the electrode method. Total cholesterol and triglyceride levels were determined using enzymatic methods, HDL cholesterol was measured using the precipitation method and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula: LDL cholesterol = total cholesterol − HDL cholesterol − (triglyceride/5). LDL-cholesterol could not be calculated for those patients with a triglyceride level over 400 mg/dL. Hemoglobin (Hb) A1c was measured by high-performance liquid chromatography and values were expressed according to the National Glycohemoglobin Standardization Program.

Serum and urinary levels of sodium and potassium were measured by the electrode method. The estimated 24-hour sodium excretion was calculated from spot urine levels of sodium (mEq/L) and creatinine (mg/L) according to the following formula: estimated 24-hour sodium excretion (mEq/d) = 21.98 × ([sodium/creatinine]/10 × estimated 24-hour urinary creatinine excretion)$^{0.392}$, where the estimated 24-hour urinary creatinine excretion = −2.04 × age (y) + 14.89 × body weight (kg) + 16.14 × height (cm) − 2,244.45. The estimated 24-hour sodium excretion was converted into the estimated daily sodium intake according to the following formula: estimated daily sodium intake (g/d) = estimated 24-hour sodium excretion (mEq/d) × 0.0585.[12]

Data Analysis

Data are expressed as mean ± SD. The authors 1st assessed the normal distribution of each variable using the Kolmogorov-Smirnov test with Lilliefor's correlation. The distribution of all values was parametric; hence, changes between baseline values and values 12 weeks after treatment initiation were assessed by the paired *t* test. Serial changes in blood pressure were assessed by repeated measures analysis of variance (ANOVA). Comparisons between 2 groups were assessed by the unpaired *t* test. In subgroup analysis, a test of interaction for assessing subgroup treatment effects was performed. A *P* value <0.05 was considered statistically significant.

RESULTS

Of all patients recruited for the study, 87 had complete data sets and were thus included in the study (57 men and 30 women, aged 64 ± 13 years). Study patients were randomly assigned to receive either the ARB/TZ combination pill (38 patients including 27 men and 11 women, aged 67 ± 13 years) or the ARB/CCB combination pill (49 patients including