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Research Article

Differential effects of strict blood pressure lowering by losartan/hydrochlorothiazide combination therapy and high-dose amlodipine monotherapy on microalbuminuria: the ALPHABET study

Motoki Fukutomi, MD[a,b], Satoshi Hoshide, MD, PhD[a], Kazuo Eguchi, MD, PhD[a], Tomonori Watanabe, MD, PhD[a], Kazuyuki Shimada, MD, PhD[a], and Kazuomi Kario, MD, PhD, FACC, FACP, FAHA[a,*]

[a]*Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan; and*
[b]*Shimonoseki Municipal Tsunoshima Clinic, Yamaguchi, Japan*

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Abstract

We investigated the effects of losartan/hydrochlorothiazide (HCTZ) fixed combination therapy and high-dose amlodipine monotherapy on BP measurements and target organ protection. In this open-label multicenter trial, hypertensive patients were randomly allocated to receive losartan 50 mg or amlodipine 5 mg for 4 weeks, and the treatments were changed to combination of losartan 50 mg/HCTZ 12.5 mg or amlodipine 10 mg for a further 4 weeks. A total of 91 hypertensive patients (age 63.6 years), 47 in the losartan/HCTZ group and 44 in amlodipine group, were enrolled. After 8 weeks, the clinic BP, home BP, and 24-hour ambulatory BP were successfully controlled to the same level in both treatment groups ($P < .001$). Furthermore, both groups showed the same degree of BP reduction in the 24-hour, daytime, and nighttime ($P < .001$). B-type natriuretic peptide (BNP) also significantly decreased to the same level in both groups, whereas the reduction of urinary albumin/creatinine ratio (UACR) was greater in the losartan/HCTZ group than in the high-dose amlodipine group (–47.6% vs 2.4%, $P < .001$). Losartan/HCTZ combination and high-dose amlodipine have similar effects on clinic, home, and ambulatory BP control and BNP reduction, whereas losartan/HCTZ has superior effect on UACR reduction when compared with high-dose amlodipine. J Am Soc Hypertens 2012;6(1):73–82.

Keywords: Losartan/hydrochlorothiazide; high-dose amlodipine; home blood pressure; microalbuminuria.

Introduction

Hypertension is well recognized as the dominant risk factor for cardiovascular events.[1] To improve the cardiovascular prognosis, strict blood pressure (BP) control has been recommended in clinical practice[2]; however, despite the availability of several classes of antihypertensive agents, it is frequently difficult to achieve a target BP (<140/90 mm Hg or <130/80 mm Hg in high-risk patients[3,4]). Furthermore, most hypertensive patients usually require 2 or more antihypertensive drugs for adequate BP control throughout a 24-hour period.[5,6] Recently, to improve the compliance and adherence of patients taking 2 or more antihypertensive drugs, the availability of fixed-dose antihypertensive combinations has increased.

In many cases of clinical practice, it is difficult to achieve the target BP level with angiotensin II receptor blocker (ARB) monotherapy.[7] According to the guidelines, the additional use of diuretics in combination with the ARB is recommended for adequate BP control.[3,4,8] Recently, the fixed-dose combination of losartan and hydrochlorothiazide (HCTZ) has been reported to be effective for achieving a target BP level,[9–11] and the combination has also shown a regression of left ventricular hypertrophy (LVH)[12] and

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Conflict of interest: None reported.

*Corresponding author: Kazuomi Kario, MD, PhD, FACC, FACP, FAHA, Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, 3311-1, Yakushiji, Shimotsuke, Tochigi 329-0498, Japan. Tel: +81-285-58-7344; fax: +81-285-44-2132.

E-mail: kkario@jichi.ac.jp

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an improvement in cerebrovascular prognosis.[5] Furthermore, it was also reported that addition of diuretics on the renin-angiotensin system (RAS) inhibitor provided favorable effect for reduction of microalbuminuria.[13]

A long-acting dihydropyridine calcium channel blocker (CCB), which is commonly used in Japan, has also been recommended as a first-line antihypertensive drug. A dihydropyridine CCB, amlodipine, has a strong BP-lowering effect throughout the 24-hour period.[7] Furthermore, it has been reported that high-dose amlodipine provided target organ protection[14] and risk reduction for cardiovascular events.[15]

Considering these factors, the fixed-dose combination of losartan/HCTZ and high-dose amlodipine both seem to be useful strategies for the management of clinical hypertension; however, there have been limited studies comparing the BP-lowering and target organ protective effects between these treatments. Therefore, in this study, we investigated the changes in BP parameters, including home and ambulatory BP, and measured the target organ damage between patients on fixed-dose combination of losartan/HCTZ and high-dose amlodipine monotherapy.

Methods

Study Population

This study was a multicenter, open-label, randomized trial designed to compare the effects of losartan/HCTZ combination therapy and high-dose amlodipine monotherapy on clinic, home, and ambulatory BP. The subjects included Japanese hypertensive patients, and the entry period was April 2008 to March 2009 by 6 doctors at 4 institutions (1 primary practice, 1 hospital-based outpatient clinic, and 2 specialized university hospitals). A total of 91 outpatients (47 men and 44 women, mean age 63.6 ± 13.2 years) aged 20 years older and diagnosed as having essential hypertension were enrolled. Hypertension was defined as an average seated clinic systolic BP (SBP) of 140 mm Hg or higher or diastolic BP (DBP) of 90 mm Hg or higher on 2 or more different occasions during the run-in period (2 weeks). None of the patients had received any antihypertensive medication for at least 1 month before the start of the study. The patients were excluded if they had secondary hypertension, uncontrolled hypertension (DBP ≥120 mm Hg), uncontrolled diabetes mellitus (HbA1c ≥ 8.0%), renal insufficiency (serum creatinine ≥2 mg/dL), hyperuricemia (≥8.0 mg/dL), moderate to severe symptom of heart failure (≥ New York Heart Association class III), a history of myocardial infarction and stroke within the past 3 months, severe hepatic disease, bilateral renal artery stenosis, or allergy/hypersensitivity to drugs used in this study. Written informed consent was obtained from all subjects. The ethics committee of the internal review board of the Jichi Medical University School of Medicine, Tochigi, Japan, approved the protocol. The study protocol was registered on a clinical trial registration site (UMIN [University Hospital Medical Information Network] Clinical Trials Registry [UMIN-CTR]: #UMIN000002438) (Figure 1).

Study Design

Each patient was studied for a maximum of 10 weeks, with a run-in period of 2 weeks and a treatment period of 8 weeks. At the end of the run-in period, subjects were randomized to receive either 50 mg losartan or 5 mg amlodipine for 4 weeks. After this monotherapy period, the 50 mg of losartan was changed to a fixed-dose combination of 50 mg losartan/12.5 mg HCTZ, and the dose of amlodipine was titrated to 10 mg for a further 4 weeks. During the first 4-week treatment period, if a marked BP reduction was obtained and the physicians judged that dose titration would provide inappropriate BP reduction in these patients, or the patients rejected the dose titration because their home BPs were adequately controlled (both morning and evening systolic HBPs at least lower than 135 mm Hg), titration was stopped. The marked reduction was specifically defined as the BP (≥30 mm Hg in clinic SBP or DBP) was obtained with simultaneous achievement of the target clinic BP (<140/90 mm Hg, or <130/80 mmHg in patients with diabetes mellitus) after monotherapy for the first 4 weeks.

The clinic BP was recorded as the average of triplicate measurements taken at intervals of 15 seconds using a validated oscillometric device (HEM-5041, Omron Healthcare, Kyoto, Japan) at each visit after an initial 5 minutes of seated rest.

Home BP Monitoring

Home BP measurements were performed using the validated oscillometric device (HEM-5041, Omron Healthcare) at home according to the Japanese Society of Hypertension Guidelines for the Measurement of Hypertension.[8] After more than 60 seconds in sitting position, this self-measured HBP monitoring (HBPM) automatically makes 3 measurements taking 15-second intervals between the readings. We

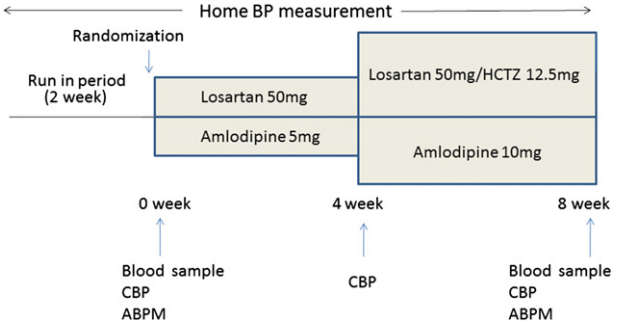

Figure 1. Study design. CBP, clinic blood pressure; ABPM, ambulatory blood pressure monitoring.