Efficacy and Safety of LCZ696, a First-in-Class Angiotensin Receptor Neprilysin Inhibitor, in Asian Patients With Hypertension

A Randomized, Double-Blind, Placebo-Controlled Study

Kazuomi Kario, Ningling Sun, Fu-Tien Chiang, Opptapham Supasyndh, Sang Hong Baek, Akiko Inubushi-Molessa, Ying Zhang, Hiromi Gotou, Martin Lefkowitz, Jack Zhang

Abstract—LCZ696 (Japanese adopted name: sucabitril valsartan sodium hydrate), a first-in-class angiotensin receptor neprilysin inhibitor, concomitantly inhibits neprilysin and blocks angiotensin type 1 receptor. This randomized, double-blind, placebo-controlled study, the first in Asia for this drug, evaluated the dose-related efficacy and safety of LCZ696 in patients with hypertension using 24-hour ambulatory blood pressure (BP) monitoring. Asian patients aged ≥18 years (n=389) with hypertension were randomized to receive LCZ696 100 mg (n=100), 200 mg (n=101), 400 mg (n=96), or placebo (n=92) for 8 weeks. The primary end point was mean difference across the 3 single-dose pairwise comparisons of LCZ696 versus placebo in clinic diastolic BP after 8-week treatment. Key secondary efficacy variables included changes in clinic systolic BP and pulse pressure and changes in 24-hour, daytime, and nighttime ambulatory BPs and pulse pressure. Safety assessments included recording all adverse events and serious adverse events. A total of 362 patients completed the study. Reductions in clinic systolic BP, diastolic BP (P<0.0001), and pulse pressure (P=0.001) were significantly greater with all doses of LCZ696 than with placebo. There were also significant reductions in 24-hour, daytime, and nighttime ambulatory systolic BP, diastolic BP, and pulse pressure for all doses of LCZ696 compared with placebo (P<0.0001). LCZ696 was well tolerated, and no cases of angioedema were reported. In conclusion, LCZ696 is effective for the treatment of hypertension in Asian populations and, in general, is safe and well tolerated.


Key Words: Asia ▪ blood pressure monitoring ▪ ambulatory ▪ hypertension ▪ randomized controlled trial

Hypertension in Asian countries has a similar prevalence as Western countries; however, its onset and progression may be differentially influenced by the interaction of a higher salt consumption coupled with progressive renal impairment with age.1,2 Incidence of stroke has been reported to be higher than coronary heart disease in Asian countries, which could be attributed to lower levels of serum total cholesterol. Thus, cardiovascular outcomes are more sensitive to changes in blood pressure (BP) in these populations.3 Natriuretic peptides (NPs) have multiple biological effects, including natriuresis, vasodilatation, inhibition of the renin-angiotensin system (RAS) and the sympathetic nervous system, positive lusitropism, and inhibition of fibrosis. Levels of NPs may be decreased in some hypertensive states.4 Neprilysin degrades NPs, and inhibition of neprilysin increases NP levels.5 However, the BP reductions observed with neprilysin inhibition alone are modest.6,7 Concomitant neprilysin inhibition and RAS suppression have effects on sodium and volume excretion and BP reductions to a greater extent compared with RAS inhibitors alone.8,9 Omapatrilat, a neprilysin and angiotensin-converting enzyme inhibitor, has been shown to have significantly better systolic

Received July 16, 2013; first decision August 8, 2013; revision accepted December 10, 2013.

From the Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan (K.K.); Peking University People’s Hospital, Beijing, China (N.S.); National Taiwan University Hospital, Taipei, Taiwan (F.T.C.); Phramongkutklao Hospital, Bangkok, Thailand (O.S.); Seoul St Mary’s Hospital, The Catholic University of Korea, Seoul, Republic of Korea (S.H.B.); Novartis Pharmaceuticals Corporation, East Hanover, NJ (A.I.-M., Y.Z., M.L., J.Z.); and Novartis Pharma K.K., Tokyo, Japan (H.G.).

The study results were presented as 2 oral presentations at the 8th Asian-Pacific Congress of Hypertension, Taipei, Taiwan, November 24–27, 2011, and published in abstract form (J Hypertens. 2011;29:e17–e18). The study results were presented as 2 poster presentations at the 35th Annual Scientific Meeting of Japanese Society of Hypertension (JSH), September 22, 2012 (PB-3-077 and PB-3-078). A poster was presented at Central Haemodynamics, September 29–30, 2012. An oral presentation was delivered at Japanese Society of Nephrology, 56th Annual Meeting (Reference ID: 13A0788548).

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.113.02002/-/DC1.

Hypertension is available at http://hyper.ahajournals.org DOI: 10.1161/HYPERTENSIONAHA.113.02002
BP (SBP)—lowering effects and pulse pressure (PP)—lowering effects than ACE inhibitor alone in patients with systolic hypertension.\(^8\)\(^9\) However, the development of omapatrilat was discontinued because of an increased risk of angioedema.\(^10\)\(^11\)

LCZ696 (Japanese adopted name: sucabitril valsartan sodium hydrate) is a first-in-class angiotensin receptor neprilysin inhibitor. LCZ696 provides highly selective inhibition of neprilysin and blockade of the angiotensin (AT1) receptor.\(^12\) Ruilope et al\(^13\) had previously demonstrated significant reductions in BP with LCZ696 compared with valsartan, with no cases of angioedema reported. LCZ696 has been found to be well tolerated in patients with hypertension; however, the majority of patients in the study were white. In the present study, we evaluated the clinic BP and 24-hour ambulatory BP—lowering efficacy and safety of 3 doses of LCZ696 in Asian patients with hypertension.

### Methods

#### Study Design

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study (Figure 1). The study was conducted at 34 centers in 5 Asian countries (Japan [14], China [6], Korea [6], Taiwan [5], and Thailand [3]). The study consisted of a 4-week run-in period (period 1), 8-week double-blind treatment period (period 2), and 1-week single-blind placebo-withdrawal period (period 3). The study protocol and amendments were reviewed and approved by the independent ethics committee or institutional review board for each center. Informed consent was obtained from each patient in writing before randomization. The study was performed in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Good Clinical Practices, applicable local regulations, and ethical principles of the Declaration of Helsinki.

#### Study Participants

Asian patients aged \(\geq\) 18 years with mild-to-moderate uncomplicated essential hypertension, untreated or taking antihypertensive therapy (pretreated), were selected for the study. Untreated patients were included in the study if they had clinic diastolic BP (DBP) \(\geq\) 90 mmHg and \(<\) 110 mmHg and clinic SBP \(\geq\) 140 mmHg and \(<\) 180 mmHg at the randomization visit (visit 1; Figure 1) and the 2 preceding visits (visits 1 and 2; Figure 1). Pretreated patients were included if clinic DBP was \(\geq\) 90 mmHg and \(<\) 110 mmHg after washout (visit 2) and if clinic DBP was \(\geq\) 95 mmHg and \(<\) 110 mmHg and clinic SBP was \(\geq\) 140 mmHg and \(<\) 180 mmHg at randomization visit (visit 3). Patients were excluded if they had severe hypertension defined as clinic DBP \(\geq\) 110 mmHg or clinic SBP \(\geq\) 180 mmHg, a history of angioedema, or a secondary form of hypertension. Other main exclusion criteria included history of significant cardiovascular/cerebrovascular, hepatic, or renal diseases; previous or current diagnosis of heart failure; any significant laboratory abnormalities at visit 1 such as serum potassium \(\geq\) 5.5 or \(<\) 3.5 mEq/L, serum sodium \(\leq\) 130 mEq/L, alanine aminotransferase or aspartate aminotransferase \(\geq\) 2× the upper limit of the normal range, and serum creatinine \(>\) 1.5× the upper limit of the normal range.

#### Statistical Analysis and Sample Size

The primary analysis model for treatment comparisons was 2-way ANCOVA with treatment and region as factors and baseline clinic DBP as a covariate. The regions were specified before the unblinding of the treatment codes. To maintain an overall 2-sided significance level at 5%, the Dunnett procedure was used to adjust for multiple comparisons of the LCZ696 doses versus placebo. This analysis was vital for the assessment of the primary objective. The study was powered to detect a difference of 4.5 mmHg in clinic DBP for LCZ696 versus placebo with 389 patients. A total of 321 patients had ambulatory BP measurement (ABPM) analysis, which allowed for a power of 90% to detect a difference of 4.5 mmHg in ambulatory DBP for LCZ696 versus placebo.

#### Study Treatment

Patients were randomized (in equal ratio) to receive LCZ696 100 mg, 200 mg, 400 mg (1-week treatment with LCZ696 200 mg followed by 7-week treatment with LCZ696 400 mg), or placebo once daily orally for an 8-week double-blind period. This was followed by a 1-week single-blind placebo-withdrawal period, allowing the assessment of the effect of LCZ696 on BP after its discontinuation.

#### Study Assessments

The primary end point was mean difference across the 3 single-dose pairwise comparisons of LCZ696 versus placebo in clinic DBP after the 8-week treatment period. Secondary efficacy variables included changes in clinic SBP and PP and changes in 24-hour, daytime, and nighttime ambulatory BP and PP. Furthermore, percentage of patients achieving a successful response in BP was evaluated. Changes in clinic BP after 1-week withdrawal period from study medication (week 9) were also assessed. For ABPM, each patient’s daytime mean was the average of the hourly means between 6 AM and 10 PM, whereas the nighttime mean was the average of the hourly means between 10 PM and 6 AM.
Clinic BP determinations were made with validated automatic BP devices (Omron HEM 7080IC for Japan and equivalent Omron models [including HEM-705CP and IA-2] for other countries). Sitting and standing BP measurements were performed at trough (23- to 26-hour postmorning dose). At study entry (visit 1), BP was measured in both arms in patients. The arm with the higher DBP reading was used for the 4 measurements at visit 1 and at all subsequent visits. BP was measured using the automatic BP monitor and an appropriate size cuff. The bladder of the cuff was large enough to encircle 80% of the arm. Four sitting BP measurements were obtained with 2-minute intervals between measurements and with the cuff fully deflated between measurements. The patient was then to stand, and after standing for 2 minutes, another BP measurement was taken. The mean of the last 3 sitting BP measurements and the single standing measurement were documented.

A 24-hour ABPM was performed twice during the study (baseline and week 8) using validated automatic BP devices (Spacelabs 90207). Safety assessments consisted of collecting all adverse events (AEs) and serious AEs. Regular monitoring of clinical laboratory parameters performed at a central laboratory and regular assessments of vital signs, physical condition, and body weight were also included.

**Results**

**Patient Characteristics**

Of the 457 patients enrolled in the single-blind placebo period, 389 patients were randomized to LCZ696 100 mg (n=100), 200 mg (n=101), 400 mg (n=96), or placebo (n=92) treatment groups. A total of 362 (93.1%) patients completed the study (Figure S1 in the online-only Data Supplement for patient disposition details). Frequency of discontinuation ranged from 3% (3/96) to 7% (7/101) in the 3 LCZ696 groups, which was lower than that in the placebo group (ie, 13% [12/92]). The most common reasons for discontinuation were withdrawal of consent (n=8) and unsatisfactory therapeutic effect (n=12, mostly in the placebo group). A total of 321 patients had evaluable 24-hour BP monitoring data at the end of the study. Demographic and baseline characteristics, including clinic BP measurements and ABPMs, are summarized in Table 1. All groups were comparable at baseline. The mean age of the patients was 51.6 years (n=389), and ≈11% of the patients were aged ≥65 years. At baseline, overall mean clinic DBP and SBP were 99.9 (n=389; SD, 3.98) mm Hg and 155.0 (n=389; SD, 9.83) mm Hg, respectively. Overall mean 24-hour ambulatory DBP and SBP at baseline were 95.2 (n=321; SD, 9.02) mm Hg and 145.5 (n=321; SD, 11.28) mm Hg, respectively. Heart rate was comparable in all groups at baseline and at the end of the study; there were no appreciable changes from baseline (average change±1 bpm).

**Clinic BP and PP**

Analysis of the change in clinic DBP, SBP, and PP during the 8-week treatment period showed that LCZ696 provided significantly superior reductions from baseline than placebo (Figure 2). The least squares mean differences in change from baseline in clinic DBP were −7.84, −7.29, and −8.76 mm Hg for LCZ696 100, 200, and 400 mg, respectively, compared with placebo (all P<0.0001). Similarly, the least squares mean differences in change from baseline in clinic SBP were −11.86, −12.57, and −15.38 mm Hg for LCZ696 100, 200, and 400 mg, respectively, compared with placebo (all P<0.0001). The least squares mean differences in change from baseline in clinic PP were −4.01, −5.40, and −6.73 mm Hg for LCZ696 100, 200, and 400 mg, respectively, compared with placebo (P<0.001 for all doses). The greater reductions in clinic DBP and SBP for all LCZ696 dose groups compared with placebo were clearly seen from week 1 after the start of the treatment and remained through to the end of the double-blind treatment (week 8). LCZ696 showed numerically greater dose-dependent reductions in clinic SBP and PP for all doses, whereas for clinic DBP, the difference between LCZ696 100 and 200 mg was not observed.

---

**Table 1. Baseline and Demographic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic at Study Entry</th>
<th>Placebo (n=92)</th>
<th>LCZ696 100 mg (n=100)</th>
<th>LCZ696 200 mg (n=101)</th>
<th>LCZ696 400 mg (n=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.9 (10.65)</td>
<td>52.5 (10.03)</td>
<td>52.1 (8.82)</td>
<td>50.9 (9.81)</td>
</tr>
<tr>
<td>&lt;65 y, n (%)</td>
<td>81 (88.0)</td>
<td>88 (88.0)</td>
<td>92 (91.1)</td>
<td>87 (90.6)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male 68 (73.9)</td>
<td>60 (60.0)</td>
<td>74 (73.3)</td>
<td>73 (76.0)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>Chinese 20 (21.7)</td>
<td>21 (21.0)</td>
<td>21 (20.8)</td>
<td>19 (19.8)</td>
</tr>
<tr>
<td>Japanese</td>
<td>43 (46.7)</td>
<td>43 (43.0)</td>
<td>48 (47.5)</td>
<td>45 (46.9)</td>
</tr>
<tr>
<td>Thai</td>
<td>8 (8.7)</td>
<td>9 (9.0)</td>
<td>9 (8.9)</td>
<td>9 (9.4)</td>
</tr>
<tr>
<td>Korean</td>
<td>9 (9.8)</td>
<td>13 (13.0)</td>
<td>9 (8.9)</td>
<td>11 (11.5)</td>
</tr>
<tr>
<td>Taiwanese</td>
<td>12 (13.0)</td>
<td>14 (14.0)</td>
<td>14 (13.9)</td>
<td>12 (12.5)</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>5.0 (4.63)</td>
<td>6.7 (6.50)</td>
<td>6.3 (6.83)</td>
<td>5.3 (5.98)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.8 (3.58)</td>
<td>25.4 (3.69)</td>
<td>25.9 (3.37)</td>
<td>26.3 (3.92)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>Clinic DBP 99.8 (3.87)</td>
<td>99.9 (3.83)</td>
<td>100.1 (4.10)</td>
<td>99.9 (4.16)</td>
</tr>
<tr>
<td>Clinic SBP</td>
<td>154.6 (9.90)</td>
<td>155.7 (10.77)</td>
<td>155.7 (9.24)</td>
<td>153.9 (9.36)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75.2 (11.88)</td>
<td>74.3 (11.30)</td>
<td>74.8 (10.49)</td>
<td>75.6 (10.74)</td>
</tr>
</tbody>
</table>

Data are presented as mean (±SD) unless otherwise specified. Clinic DBP indicates mean clinic diastolic blood pressure; and clinic SBP, mean clinic systolic blood pressure.
The BP control rates (clinic DBP <90 mm Hg and clinic SBP <140 mm Hg) were significantly better for LCZ696 (47.0%, 49.0%, and 54.2% for 100, 200, and 400 mg LCZ696, respectively) than in the placebo group (15.2%; P<0.0001).

Ambulatory BP and PP
Analysis of change in 24-hour, daytime, and nighttime ambulatory BP and PP during the 8-week treatment period is represented in Figure 3A and 3B. For 24-hour, daytime, and nighttime ambulatory DBP, SBP, and PP, all the doses of LCZ696 had statistically significant greater reduction from baseline than placebo (all P<0.0001). Dose-dependent reductions in 24-hour ambulatory SBP, DBP, and PP were observed for 100, 200, and 400 mg doses.

Single-Blind Placebo Withdrawal
We also evaluated additional changes in clinic BP at week 9 after single-blind placebo withdrawal of treatment at week 8 as a secondary objective. As expected, on withdrawal, all LCZ696 dose groups showed an increase in clinic BP toward the baseline value. The mean changes in clinic DBP from week 8 to week 9 for all doses of LCZ696 were comparable. The magnitude of the increase in clinic SBP toward the baseline value was similar in the 100- and 200-mg groups (8.0 and 8.8 mm Hg, respectively) and was slightly greater in the 400-mg group (11.6 mm Hg); thus, clinic BP after a 1-week withdrawal period was similar in all 3 dosing groups. Approximately 90% of the antihypertensive effect associated with LCZ696 was removed after 1 week of...
treatment withdrawal, similar to angiotensin receptor blockers such as valsartan.13

Safety
AEs that were reported in ≥2% of the patients in any treatment group are presented in Table 2. The most commonly reported AEs were nasopharyngitis, which was similar in each treatment group, and upper respiratory tract infection, which was higher in the LCZ696 100-mg group than in the other groups. Incidence of dizziness was low (2.8%) and not dose related and even tended to be higher in the placebo group (5.4%) than in the LCZ696 groups (1%, 2%, and 3.1% for LCZ696 100, 200, and 400 mg, respectively).

There were few serious AEs reported (Table 2), which included appendicitis (1 patient in the LCZ696 200-mg arm), abnormal hepatic function (1 patient in the LCZ696 400-mg arm), and ankle fracture (1 patient in the LCZ696 400-mg arm). The patient with abnormal hepatic function was discharged with a final diagnosis of acute hepatitis, for which a causative role of study drug could not be excluded. In addition, the investigator mentioned infection and concomitant use of herbal medication as possible contributing factor. The patient recovered completely.

Overall, all doses of LCZ696 were well tolerated, and no cases of angioedema or death were reported. Incidence of AEs during the double-blind period was comparable in each treatment group and only slightly lower in the placebo group. For most laboratory parameters, there was little difference between the active treatment groups and placebo. One difference in biochemistry parameters was in uric acid values, with all doses of LCZ696 showing a decrease from baseline (−16.0, −13.1, and −19.0 μmol/L for 100, 200, and 400 mg, respectively), whereas an increase of 2.6 μmol/L was seen for placebo (see Tables S1–S6 for laboratory parameters). The mean change in body weight from baseline at end point was small and similar for all treatment groups (−0.2 to 0.7 kg). Overall, changes in aspartate transaminase were −1.1, 0.1, −1.2, and −0.6 U/L, and alanine transaminase were −2.3, −0.4, −2.8, and 0.8 U/L for LCZ696 100 mg, 200 mg, 400 mg, and placebo, respectively.

Discussion
The present study demonstrated for the first time that all 3 doses of LCZ696 significantly reduced clinic and 24-hour ambulatory BP in Asian patients with hypertension. In addition, LCZ696 significantly reduced nighttime and daytime BPs. Clinic and 24-hour ambulatory PP were also reduced significantly.

The efficacy of LCZ696 in BP lowering was first reported in patients with hypertension primarily in the Western

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>LCZ696 100 mg (n=100)</th>
<th>LCZ696 200 mg (n=101)</th>
<th>LCZ696 400 mg (n=96)</th>
<th>Placebo (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>38 (38.0)</td>
<td>38 (37.6)</td>
<td>36 (37.5)</td>
<td>30 (32.6)</td>
</tr>
<tr>
<td>Adverse events (≥2.0% in any treatment group) in the double-blind period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (6.0)</td>
<td>6 (5.9)</td>
<td>7 (7.3)</td>
<td>7 (7.6)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9 (9.0)</td>
<td>3 (3.0)</td>
<td>4 (4.2)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1.0)</td>
<td>2 (2.0)</td>
<td>3 (3.1)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>2 (2.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.0)</td>
<td>4 (4.0)</td>
<td>2 (2.1)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>2 (2.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>2 (2.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>2 (2.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0.0)</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dermal cyst</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dermatitis atopic</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>Upper respiratory tract inflammation</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Data are presented as number of patients (%). AEs indicate adverse events; and SAEs, serious adverse events.
countries.13 Here, Ruilope et al13 evaluated the same 3 doses of LCZ696 in a phase II study. Because the majority of the participants in the study were either whites (87%) or blacks (7.9%) with a small number of Asians (2.7%), the study could not make a definitive conclusion on the effect of LCZ696 on BP in Asian population. In the present study, the reduction of clinic and 24-hour ambulatory BP by LCZ696 tended to be greater in the Asian population than in the Western population reported in the previous study, particularly at lower doses. The placebo-corrected differences of ≈6 mm Hg for clinic SBP and 8 mm Hg for 24-hour ambulatory SBP were seen with LCZ696 100 mg between Asians versus Westerners; for the other doses, the placebo-corrected differences were in the range of 2 to 4 mm Hg for clinic SBP and 24-hour ambulatory SBP, respectively.14 However, antihypertensive therapy, even with inhibitors of the RAS, has been considered effective in patients with hypertension, regardless of ethnicity15; hence, our observations need further investigation. Noteworthy, the omapatrilat dose-ranging trial (20–80 mg) demonstrated dose-related reductions in BP similar to what was seen in the previous study by Ruilope et al,13 but omapatrilat was not studied in Asian patients.16 Furthermore, the dose response from Ruilope et al13 study also showed that 100 mg is minimally effective and 400 mg was the most effective dose of LCZ696.

There are several characteristics that are typical of Asian patients with hypertension.17 Notably, Asians have higher incidence of stroke compared with coronary artery disease,3,18 and the slope of the association of BP with stroke risk is steeper in Asians than in Westerners.19 In addition, Asians are genetically more likely to have a higher salt sensitivity and salt consumption than Westerners.20 Considering the recent increase in the prevalence of obesity and the related metabolic syndrome in Asia,22 the effect of salt intake would be all the more increasing in Asian patients with hypertension because obesity and metabolic syndrome are known to increase salt sensitivity.23,24 RAS inhibitor monotherapy may be less effective in Asian patients than calcium channel blockers because the BP-lowering effect of RAS inhibitors is smaller in the salt-sensitive patients with high salt intake. In fact, in our meta-analysis, RAS inhibitors were less effective to reduce 24-hour BP than calcium channel blockers in Asian patients.25

Our results indicating a potentially greater BP-lowering effect of LCZ696 in Asians than in Westerners may support that LCZ696 is particularly suitable for Asian patients with hypertension. Furthermore, the significance of neprilysin inhibition with concomitant RAS inhibition would be important in Asians because of their high salt intake and high salt sensitivity. Greater sodium excretion by increased NPs because of LCZ696 treatment may partly explain the apparently higher BP-lowering effect in Asian patients.

In addition, LCZ696 significantly reduced nighttime and daytime ambulatory BP. The degree of reduction of nighttime ambulatory BP was comparable with that of daytime ambulatory BP. Here, the reduction of nighttime ambulatory SBP by LCZ696 compared with placebo in Asians patients seemed to be greater than that reported for Westerners previously.13 Furthermore, 24-hour BP level and BP variability, such as morning BP surge,26 nondippers, and risers with higher nighttime BP, are closely associated with silent cerebrovascular diseases in Asian elderly patients with hypertension.27,28 In addition, nighttime BP level, per se, is more closely related to cardiovascular prognosis than daytime BP, particularly in medicated Asian and white patients with hypertension.29,30 It is well known that a decrease in circulating volume by a diuretic or salt restriction will reduce nighttime BP compared with daytime BP.31,32 In our previous study, a small dose of a diuretic when added to candesartan was sufficient to reduce nighttime BP in Japanese patients with hypertension who were uncontrolled on an angiotensin receptor blocker.32 Similarly, valsartan monotherapy is less effective in controlling nighttime BP in Japanese patients with hypertension.33 Thus, we hypothesize that the neprilysin inhibition delivered by LCZ696 would contribute to reducing nighttime BPs through an increased NP-mediated mechanism in Asians. Considering higher prevalence of nondippers in Asian cohorts than Western cohorts,34 LCZ696 may be suitable for preventing stroke partly through the reduction of nighttime BP in Asian patients with hypertension.

Clinic and 24-hour ambulatory PP were also significantly reduced by LCZ696 in our study. The reduction of 24-hour ambulatory PP by LCZ696 compared with placebo in the Asians seemed to be greater than that reported in the Westerners.13 In the previous study by Ruilope et al,13 the clinic and 24-hour ambulatory PP were more extensively reduced by LCZ696 compared with valsartan, suggesting that LCZ696 may be effective in preventing cardiovascular diseases related to systolic hypertension and increased vascular stiffness. In the present study, nighttime ambulatory PP was reduced by 4 to 6 mm Hg. In our Jichi Medical University ABPM Study, the nighttime PP was an independent predictor of stroke, and after adjustment for covariates, the 10-mm Hg increase in nighttime BP was associated with a 43% increase in risk of stroke in Japanese elderly patients with hypertension.35 Thus, LCZ696 may be effective in preventing age-related cardiovascular events in patients with hypertension. The main limitation of our study was the lack of an active comparator. In addition, no hard or intermediate cardiovascular end points were assessed. However, the use of 24-hour ABPM provides confirmation to the BP-lowering efficacy of LCZ696 in Asian patients with hypertension.

In conclusion, this study demonstrated that LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, was efficacious to lower BP and was well tolerated in Asian patients with hypertension.

Perspectives

This is the first study specifically designed to evaluate the effect of LCZ696 in Asian patients with hypertension. LCZ696 was effective in lowering BP across the 24-hour dosing period, including nighttime in Asian patients with hypertension, an ethnic group typically less responsive to monotherapy with RAS inhibitor compared with diuretics or calcium channel blockers. This suggests that enhancement of NPs with neprilysin inhibition is an effective approach to improve the BP-lowering effect associated with RAS inhibition in patients with a low- or less-responsive RAS (eg, salt-sensitive patients with hypertension or elderly patients with hypertension). Compared with data on Western patients, BP
Kario et al LCZ696 in Asian Patients With Hypertension

reduction by LCZ696 tended to be greater in Asian patients with hypertension, indicating that LCZ696 may be particularly suitable for the management of hypertension in Asian populations. In addition, LCZ696 was safe and well tolerated in these populations. The results support the rationale to prospectively study the effect of LCZ696 on cardiovascular events in Asian patients with hypertension.

Acknowledgments
We acknowledge Dr Keyur Brahmbhatt, Novartis Healthcare Pvt Ltd, India, for medical writing support and Dr Gregory Fyfe, CircleScience, United Kingdom, for editorial support. We also thank all the clinical investigators and study coordinators at the participating centers and all the patients who participated in the study.

Sources of Funding
The study was funded by Novartis AG, Basel.

Disclosures
K. Kario has received honoraria for participating in an advisory board for Novartis and for chairing a symposium sponsored by Novartis. A. K. Kario has received honoraria for participating in an advisory board of investigators and study coordinators at the participating centers and India, for medical writing support and Dr Gregor Fyfe, CircleScience, for Novartis and for chairing a symposium sponsored by Novartis. A.

References


---

**Novelty and Significance**

**What Is New?**
- This is the first study with primary focus on measuring effect of LCZ696 in Asian patients with hypertension.

**What Is Relevant?**
- LCZ696 was effective in lowering blood pressure across the 24-hour dosing period in Asian patients with hypertension, an ethnic group typically less responsive to therapy with a renin–angiotensin system inhibitor compared with diuretics or calcium channel blockers.

**Summary**
LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, is effective for the treatment of hypertension in Asian population and, in general, is safe and well tolerated.
Efficacy and Safety of LCZ696, a First-in-Class Angiotensin Receptor Neprilysin Inhibitor, in Asian Patients With Hypertension: A Randomized, Double-Blind, Placebo-Controlled Study
Kazuomi Kario, Ningling Sun, Fu-Tien Chiang, Ouoppatham Supasyndh, Sang Hong Baek, Akiko Inubushi-Molessa, Ying Zhang, Hiromi Gotou, Martin Lefkowitz and Jack Zhang

Hypertension, published online January 20, 2014;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2014/01/20/HYPERTENSIONAHA.113.02002

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2014/01/20/HYPERTENSIONAHA.113.02002.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
EFFICACY AND SAFETY OF LCZ696, A FIRST-IN-CLASS ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR, IN ASIAN PATIENTS WITH HYPERTENSION
A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Kazuomi Kario\textsuperscript{a,*}, Ningling Sun\textsuperscript{b}, Fu-Tien Chiang\textsuperscript{c}, Ouppatham Supasynd\textsuperscript{d}, Sang Hong Baek\textsuperscript{e}, Akiko Inubushi-Molessa\textsuperscript{f}, Ying Zhang\textsuperscript{f}, Hiromi Gotou\textsuperscript{g}, Martin Lefkowitz\textsuperscript{f}, Jack Zhang\textsuperscript{f}
\textsuperscript{a}Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan; \textsuperscript{b}Peking University People's Hospital, Beijing, China; \textsuperscript{c}National Taiwan University Hospital, Taipei, Taiwan; \textsuperscript{d}Phramongkutklao Hospital, Bangkok, Thailand; \textsuperscript{e}Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; \textsuperscript{f}Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; \textsuperscript{g}Novartis Pharma K.K., Tokyo, Japan

Short title: LCZ696 in Asian patients with hypertension

Corresponding author:
\textsuperscript{*}Kazuomi Kario, MD, PhD, FACP, FACC, 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 58-7538; fax: +81 285 44 4311; email: kkario@jichi.ac.jp
Table S1:
Laboratory parameters and treatment groups: Glucose (mmol/L)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>n</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696 100 mg (N=100)</td>
<td>99</td>
<td>5.307 (0.8214)</td>
<td>5.363 (0.7561)</td>
<td>0.056 (0.9079)</td>
</tr>
<tr>
<td>LCZ696 200 mg (N=101)</td>
<td>98</td>
<td>5.523 (0.8020)</td>
<td>5.619 (0.7347)</td>
<td>0.096 (0.7340)</td>
</tr>
<tr>
<td>LCZ696 400 mg (N=96)</td>
<td>95</td>
<td>5.374 (0.6902)</td>
<td>5.524 (0.7200)</td>
<td>0.151 (0.6371)</td>
</tr>
<tr>
<td>Placebo (N=92)</td>
<td>89</td>
<td>5.294 (0.5354)</td>
<td>5.445 (0.6000)</td>
<td>0.151 (0.5242)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)

Table S2:
Laboratory parameters and treatment groups: Cholesterol (total) (mmol/L)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>n</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696 100 mg (N=100)</td>
<td>100</td>
<td>5.067 (0.8279)</td>
<td>5.105 (0.8312)</td>
<td>0.038 (0.6280)</td>
</tr>
<tr>
<td>LCZ696 200 mg (N=101)</td>
<td>98</td>
<td>5.187 (0.8539)</td>
<td>5.157 (0.8960)</td>
<td>-0.029 (0.5911)</td>
</tr>
<tr>
<td>LCZ696 400 mg (N=96)</td>
<td>95</td>
<td>5.277 (0.8889)</td>
<td>5.367 (0.8740)</td>
<td>0.089 (0.6411)</td>
</tr>
<tr>
<td>Placebo (N=92)</td>
<td>89</td>
<td>5.223 (0.8451)</td>
<td>5.285 (0.8169)</td>
<td>0.063 (0.5923)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)
Table S3:

Laboratory parameters and treatment groups: Triglycerides (mmol/L)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>n</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696 100 mg (N=100)</td>
<td>100</td>
<td>1.657 (0.9433)</td>
<td>1.629 (1.0277)</td>
<td>-0.028 (0.7446)</td>
</tr>
<tr>
<td>LCZ696 200 mg (N=101)</td>
<td>98</td>
<td>1.814 (1.2633)</td>
<td>1.649 (1.3167)</td>
<td>-0.165 (1.1173)</td>
</tr>
<tr>
<td>LCZ696 400 mg (N=96)</td>
<td>95</td>
<td>1.590 (0.7830)</td>
<td>1.595 (0.7599)</td>
<td>0.004 (0.7129)</td>
</tr>
<tr>
<td>Placebo (N=92)</td>
<td>89</td>
<td>1.669 (0.7937)</td>
<td>1.629 (0.8201)</td>
<td>-0.041 (0.6775)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)

Table S4:

Laboratory parameters and treatment groups: Blood Urea Nitrogen (BUN) (mmol/L)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>n</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696 100 mg (N=100)</td>
<td>100</td>
<td>4.82 (1.105)</td>
<td>5.11 (1.430)</td>
<td>0.29 (1.181)</td>
</tr>
<tr>
<td>LCZ696 200 mg (N=101)</td>
<td>98</td>
<td>4.91 (1.164)</td>
<td>5.08 (1.136)</td>
<td>0.17 (1.023)</td>
</tr>
<tr>
<td>LCZ696 400 mg (N=96)</td>
<td>96</td>
<td>4.72 (1.309)</td>
<td>4.99 (1.236)</td>
<td>0.27 (1.083)</td>
</tr>
<tr>
<td>Placebo (N=92)</td>
<td>91</td>
<td>4.78 (1.303)</td>
<td>5.25 (1.277)</td>
<td>0.47 (1.403)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)
Table S5:
Laboratory parameters and treatment groups: Uric acid (µmol/L)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>n</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696 100 mg (N=100)</td>
<td>100</td>
<td>346.4 (82.64)</td>
<td>330.3 (78.82)</td>
<td>-16.0 (50.71)</td>
</tr>
<tr>
<td>LCZ696 200 mg (N=101)</td>
<td>98</td>
<td>363.8 (79.89)</td>
<td>350.7 (71.52)</td>
<td>-13.1 (39.86)</td>
</tr>
<tr>
<td>LCZ696 400 mg (N=96)</td>
<td>95</td>
<td>365.3 (76.02)</td>
<td>346.3 (73.58)</td>
<td>-19.0 (45.18)</td>
</tr>
<tr>
<td>Placebo (N=92)</td>
<td>89</td>
<td>350.8 (81.08)</td>
<td>353.4 (83.17)</td>
<td>2.6 (44.77)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)

Table S6:
Laboratory parameters and treatment groups: Creatinine (µmol/L)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>n</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696 100 mg (N=100)</td>
<td>100</td>
<td>77.1 (14.16)</td>
<td>77.7 (14.78)</td>
<td>0.7 (8.77)</td>
</tr>
<tr>
<td>LCZ696 200 mg (N=101)</td>
<td>98</td>
<td>78.0 (13.71)</td>
<td>79.1 (15.03)</td>
<td>1.0 (7.38)</td>
</tr>
<tr>
<td>LCZ696 400 mg (N=96)</td>
<td>96</td>
<td>77.2 (15.36)</td>
<td>79.5 (15.16)</td>
<td>2.3 (8.77)</td>
</tr>
<tr>
<td>Placebo (N=92)</td>
<td>91</td>
<td>79.8 (15.81)</td>
<td>81.6 (15.30)</td>
<td>1.9 (9.26)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)

Figure S1: Patient disposition
437 Patients enrolled

389 Patients assigned to treatment

100 Assigned to 100 mg LCZ696
95 Completed
  5 Discontinued
    2 Withdraw consent
    3 Unsatisfactory therapeutic effect

101 Assigned to 200 mg LCZ696
94 Completed
  7 Discontinued
    4 Withdraw consent
    1 Unsatisfactory therapeutic effect
    1 Adverse event

96 Assigned to 200 mg LCZ696
93 Completed
  3 Discontinued
    1 Withdraw consent
    1 Adverse event
    1 Administrative problems

96 Switched to 400 mg LCZ696

97 Assigned to placebo
80 Completed
  12 Discontinued
    8 Unsatisfactory therapeutic effect
    3 Adverse event
    1 Withdraw consent

68 Discontinued
  51 Abnormal test procedure results
  7 Withdrew consent
  3 Unsatisfactory therapeutic effect
  2 Lost to follow-up
  2 Adverse events
  1 Protocol deviation
  1 Patient's condition no longer requires study drug
  1 Administrative problems