Efficacy and Safety of Sacubitril/Valsartan (LCZ696) Compared With Olmesartan in Elderly Asian Patients (≥65 Years) With Systolic Hypertension

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OBJECTIVE
Systolic hypertension is common in elderly patients and remains a challenge to treat effectively. The efficacy and safety of sacubitril/valsartan (LCZ696), a first-in-class angiotensin receptor neprilysin inhibitor, vs. olmesartan was evaluated in elderly Asian patients (≥65 years) with systolic hypertension.

METHODS
In this randomized, double-blind, 14-week study, patients initially received once-daily sacubitril/valsartan 100 mg or olmesartan 10 mg, increased to sacubitril/valsartan 200 mg or olmesartan 20 mg at week 4. At week 10, for patients with blood pressure (BP) >140/90 mm Hg, the doses were up-titrated to sacubitril/valsartan 400 mg or olmesartan 40 mg. The primary assessment was superiority of sacubitril/valsartan vs. olmesartan in reducing office mean sitting (ms) systolic BP (msSBP) from baseline at week 10. Secondary efficacy assessments included changes from baseline in ms diastolic BP (msDBP), ms pulse pressure (msPP), 24-hour mean ambulatory (ma) BP (maBP), and maPP at week 10; msBP and msPP at weeks 4 and 14.

RESULTS
Overall, 588 patients were randomized (mean age, 70.7 years; baseline msBP, 160.3/84.9 mm Hg; msPP, 75.4 mm Hg). At week 10, sacubitril/valsartan provided superior msSBP reductions vs. olmesartan (22.71 vs. 16.11 mm Hg, respectively; P < 0.001); similarly, reductions from baseline in other BP and PP assessments were significantly greater with sacubitril/valsartan. At week 14, despite more patients requiring up-titration in the olmesartan group, msBP and msPP reductions from baseline were significantly greater with sacubitril/valsartan. Both treatments were generally well-tolerated.

CONCLUSION
Sacubitril/valsartan is more effective than olmesartan in reducing BP in elderly Asian patients with systolic hypertension.

Keywords: angiotensin receptor neprilysin inhibitor; Asian; blood pressure; elderly; hypertension; pulse pressure; sacubitril/valsartan; systolic hypertension.

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Hypertension is a very common disease in the elderly (aged ≥65 years).1 More than 50% of the elderly population has hypertension,2 especially systolic hypertension, which arises primarily due to age-related changes in the arterial structure of large arteries, contributing to the large artery stiffness.3 These changes lead to loss of arterial elasticity,4 resulting in elevated systolic blood pressure (SBP) and widened pulse pressure (PP; difference between SBP and diastolic blood pressure [DBP]).

Studies have shown that elevated SBP has a stronger association with adverse cardiovascular (CV) outcomes than elevated DBP in the elderly.1,5,6 Furthermore, lowering of SBP has been shown to reduce the risk of CV events in elderly patients.7 A strong association between hypertension and CV events has been reported in Asian population.8

Olmesartan is one of the most widely prescribed angiotensin II receptor blockers (ARBs) for the treatment of systolic hypertension in elderly patients,10 including Asians.11 Despite the available antihypertensive treatments, blood pressure (BP) control is poor in Asian patients.12 In addition, SBP is considered more difficult to control than DBP, particularly in elderly patients,13,14 which further suggests the need to develop more effective treatments to target the underlying causes of systolic hypertension in this population.

BP is modulated by counter-regulatory neurohormonal interactions between natriuretic peptides, the sympathetic nervous system, and the renin–angiotensin–aldosterone system.15 Natriuretic peptide levels can be enhanced by inhibiting the enzyme neprilysin, which catalyzes the degradation of multiple vasoactive peptides in the CV system, including natriuretic peptides.16,17 Blockade of the angiotensin receptor reduces sodium and water retention and inhibits cardiac hypertrophy and remodeling (arterial stiffness).18,19 Considering the age-related changes to arteries underlying...
elevated SBP, simultaneous nephrilysin inhibition and angiotensin receptor blockade might be a promising therapeutic approach to treat patients with systolic hypertension.

Sacubitril/valsartan (LCZ696), a first-in-class angiotensin receptor nephrilysin inhibitor, has been approved recently to reduce the risk of CV death and hospitalization for heart failure (HF) in patients with chronic HF [New York Heart Association (NYHA) Class II–IV] and reduced ejection fraction,\(^\text{20}\) in view of its superior benefits over enalapril in the pivotal phase III trial, PARADIGM-HF.\(^\text{21,22}\) Sacubitril/valsartan provided significantly greater reductions in SBP and PP from baseline compared with placebo or valsartan in patients with hypertension in Caucasians\(^\text{23}\) and Asians.\(^\text{24}\)

In these studies, sacubitril/valsartan provided significantly greater reductions in SBP and PP from baseline compared with placebo or valsartan.\(^\text{23,24}\) The present study evaluated the efficacy and safety of sacubitril/valsartan compared with olmesartan in elderly Asian patients (aged ≥65 years) with systolic hypertension.

MATERIALS AND METHODS

Study design

This was a multicenter, randomized, double-blind, active-controlled, parallel-group study. The study comprised an initial washout/placebo run-in period (2–4 weeks) followed by a 14-week double-blind treatment period. In the double-blind treatment period, patients with mean sitting (ms) SBP (msSBP) between ≥150 and <180 mm Hg were eligible for randomization. In addition, they had to have an absolute difference of ≤15 mm Hg in msSBP between randomization and the immediate preceding visit. The key exclusion criteria were women of child-bearing potential, malignant or severe hypertension, history of angioedema (drug-related or otherwise), and previous or current diagnosis of HF (NYHA Class II–IV).

After washout/placebo run-in, patients were randomized to receive sacubitril/valsartan 100 mg or olmesartan 10 mg once-daily for 4 weeks followed by force-titration to sacubitril/valsartan 200 mg or olmesartan 20 mg once-daily for a further 6 weeks. At week 10, patients who reached the BP goal (defined as msSBP ≤140 mm Hg or msDBP ≤90 mm Hg) continued the same dose for the remaining 4 weeks, whereas for patients who did not reach the BP goal, doses were up-titrated to sacubitril/valsartan 400 mg or olmesartan 40 mg once-daily (Supplementary Figure 1).

This study was conducted in accordance with the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and received approval from the local Institutional Review Board. All participants provided written informed consent before participation in the study (ClinicalTrials.gov identifier: NCT01615198).

Study assessments

The primary efficacy assessment was reduction in msSBP from baseline at week 10. The secondary efficacy assessments were reduction in msDBP, msPP, 24-hour mean ambulatory (ma) SBP (maSBP), maDBP, and maPP from baseline at week 10, and msSBP, msDBP, and msPP from baseline at weeks 4 and 14. BP control (msSBP/msDBP <140/90 mm Hg) was assessed at weeks 4, 10, and 14. All office BP measurements were performed using an automated device (Omron BP monitor) in accordance with the British Hypertension Society 2004 (BHS IV) guidelines.\(^\text{25}\) Sitting and standing BP measurements were performed at screening until the end of the study at every visit. At screening, BP was measured in both the arms; the arm with the higher SBP reading was used at all subsequent visits. In a subset of patients at selected sites, hourly maBP was monitored over 24 hours using the Spacelabs 90207 device prior to administration of the first dose of the study drug and at week 10 or earlier in case of early discontinuation.

Safety assessments included monitoring of all adverse events (AEs) and serious AEs. Changes in laboratory markers (hematology, urinalysis, and blood chemistry) and vital signs were also recorded.

Statistical analysis

The sample size of 259 completed patients per group was calculated based on the primary efficacy variable, change from baseline in msSBP, and a SD of 14 mm Hg. This sample size was calculated to ensure 90% power to detect a statistical significance for the comparison between sacubitril/valsartan 200 mg and olmesartan 20 mg under the alternative hypothesis that the treatment difference would be 4 mm Hg at a 2-sided significance level of 0.05. Assuming a 10% drop-out rate, the total targeted sample size to be randomized was 576 patients.

Efficacy variables were analyzed using a 2-way analysis of covariance model with treatment and region as factors, and the baseline as a covariate. All statistical tests were performed using a 2-sided significance level of 0.05. The superiority of sacubitril/valsartan vs. olmesartan in reducing msSBP from baseline at week 10 was considered to be achieved if the test was statistically significant in favor of sacubitril/valsartan. BP control data at the study endpoint were analyzed using a logistic regression model with treatment and region as factors and baseline msSBP as a covariate. The summary statistics for postdosing hourly maSBP were also provided, which were calculated for each postdosing hour over 24 hours by determining the average of the readings recorded in the corresponding postdosing hour.

RESULTS

Patients

A total of 588 patients were randomized, of whom, 92.7% completed the study (sacubitril/valsartan group, 91.9%; olmesartan group, 93.5%). Patient disposition data are summarized in Supplementary Figure 2. The mean age of the patients was 70.7 years; 50% were male; 21.6% were aged ≥75 years; and the mean duration of hypertension was 11 years. Baseline msBP and msPP were 160.3/84.9 and 75.4 mm Hg, respectively. All baseline characteristics were broadly similar between the sacubitril/valsartan and olmesartan treatment groups (Table 1).
Office BP

Sacubitril/valsartan 200 mg provided significantly greater reductions in msSBP, msDBP, and msPP from baseline compared with olmesartan 20 mg at week 10 (P < 0.001 for all; Figure 1).

At week 4, sacubitril/valsartan 100 mg provided numerically greater but not statistically significant reductions in msSBP, msDBP, and msPP from baseline vs. olmesartan 10 mg with LSM between-treatment differences (95% confidence interval) of −1.83 mm Hg (−4.09, 0.42), −0.50 mm Hg (−1.70, 0.70), and −1.19 mm Hg (−2.83, 0.46), respectively.

An incremental reduction in msSBP was observed from week 4 (sacubitril/valsartan 100 mg) to week 10 (sacubitril/valsartan 200 mg) with a difference of −5.07 mm Hg, whereas only a small change was apparent in the olmesartan group (−0.3 mm Hg; Figure 2).

Approximately 36% (n = 105) of patients receiving sacubitril/valsartan 200 mg required dose titration to 400 mg at week 10. In comparison, 50% (n = 147) of patients receiving olmesartan 20 mg required dose titration to 40 mg. At week 14, sacubitril/valsartan treatment provided superior reductions from baseline compared with olmesartan treatment in msSBP (−22.53 mm Hg vs. −16.75 mm Hg), msDBP (−7.92 mm Hg vs. −5.97 mm Hg), and msPP (−14.65 mm Hg vs. −10.90 mm Hg). The LSM between-treatment differences (95% confidence interval) were −5.78 mm Hg (−8.31, −3.26; P < 0.001) for msSBP, −1.95 mm Hg (−3.28, −0.63; P = 0.004) for msDBP, and −3.75 mm Hg (−5.49, −2.00; P < 0.001) for msPP.

In patients whose treatment doses were up-titrated to sacubitril/valsartan 400 mg or olmesartan 40 mg from week 10 onward, a further BP reduction was observed at week 14 in both treatment groups (msSBP reduction: sacubitril/valsartan, −5.60 mm Hg; olmesartan, −3.78 mm Hg; msPP reductions: −5.71 mm Hg vs. −4.77 mm Hg).

Figure 1. Office blood pressure and pulse pressure at week 10 endpoint. *P ≤ 0.001 vs. olmesartan; error bars represent SE; endpoint represents data at week 10 or last observation carried forward; between-treatment difference presented as LSM (95% confidence interval). Abbreviations: LSM, least squares mean; msDBP, mean sitting diastolic blood pressure; msPP, mean sitting pulse pressure; msSBP, mean sitting systolic blood pressure.

Figure 2. Mean sitting systolic blood pressure at weeks 4, 10, and 14. Values represent data at weeks 4, 10, and 14 or last observation carried forward. Error bars represent SE. Abbreviations: LSM, least squares mean; msSBP, mean sitting systolic blood pressure.
group compared with the olmesartan group in patients aged between 65 to <75 years and those ≥75 years (Table 2).

Ambulatory BP measurements

A total of 154 patients in the sacubitril/valsartan group (baseline maSBP/DBP and maPP: 147.4/84.9 and 62.5 mm Hg, respectively) and 157 patients in the olmesartan group (baseline maBP and maPP: 145.7/83.5 and 62.2 mm Hg, respectively) underwent ambulatory BP monitoring (Table 1). At week 10, sacubitril/valsartan 200 mg provided significantly greater reductions in the 24-hour maSBP, maDBP, and maPP from baseline compared with olmesartan 20 mg (P < 0.001 for all; Figure 3). The mean change from baseline in hourly postdose maSBP at week 10 is shown in Figure 4. Numerically greater maSBP reductions were observed with sacubitril/valsartan at every hour throughout the 24-hour dosing period compared with olmesartan.

At week 10, the reduction from baseline in daytime (6 AM < daytime ≤ 10 PM) and nighttime (10 PM < nighttime ≤ 6 AM) maSBP, and maDBP were also significantly greater with sacubitril/valsartan vs. olmesartan. The between-treatment differences (95% confidence interval) were −4.30 mm Hg (−6.89, −1.72; P = 0.001) for daytime maSBP, −6.28 mm Hg (−8.87, −3.70; P < 0.001) for nighttime maSBP, −2.16 mm Hg (−3.65, −0.66; P = 0.005) for daytime maDBP, and −3.09 mm Hg (−4.58, −1.60; P < 0.001) for nighttime maDBP.

Safety and tolerability

AEs reported at a frequency of ≥2.0% in either treatment group are summarized in Table 3. The incidence of AEs was 47.6% in the sacubitril/valsartan group and 38.7% in the olmesartan group. The commonly reported AEs were nasopharyngitis, hyperuricemia, upper respiratory tract infection, and dizziness. Similar proportions of patients had AEs related to the study treatment in both the treatment groups (sacubitril/valsartan group, 12 [4.1%] patients; olmesartan group, 15 [5.1%] patients). There were no reports of angioedema in this study.

Seven (2.4%) patients in the sacubitril/valsartan group and 2 (0.7%) patients in the olmesartan group experienced serious AEs (Table 3). Three (1%) patients in the sacubitril/valsartan group and 2 (0.7%) patients in the olmesartan group discontinued treatment due to serious AEs. In the sacubitril/valsartan group, none of the serious AEs were related to the study drug. In the olmesartan group, an abnormal liver function test result was reported in 1 patient, and mild Henoch-Schönlein purpura nephritis was reported in another patient; both were suspected to be related to the study drug. No deaths were reported during the study.

Very few notable changes from baseline were observed in the laboratory tests. Any changes were generally small in both treatment groups for all parameters and were not considered to be clinically meaningful (Table 4). The incidence of potassium values >5.5 mmol/l was observed in 1.7% (5/295) of patients in the sacubitril/valsartan group and 0.7% (2/291) of patients in the olmesartan group. The incidence of potassium values <3.5 mmol/l was observed in 6.1% (18/295) of patients in the sacubitril/valsartan group and 4.1% (12/291) of patients in the olmesartan group. No AEs or discontinuations related to hypokalemia were reported. Sodium values <130 mmol/l were reported in 1 (0.3%) patient in each group.

DISCUSSION

Sacubitril/valsartan had previously shown superior efficacy in reducing office and ambulatory BP vs. valsartan in Caucasian patients with essential hypertension, which included 12%–17% of patients aged ≥65 years.23 This is the first study to evaluate the efficacy and safety of sacubitril/valsartan in elderly patients (≥65 years) with systolic hypertension in comparison with an ARB, olmesartan. Sacubitril/valsartan 200 mg provided superior efficacy to olmesartan 20 mg in reducing msSBP (primary objective), msDBP and msPP, as well as 24-hour maSBP, maDBP and maPP from baseline to week 10. Similarly, reductions from baseline in msSBP, msDBP, and msPP at week 14 were significantly greater in patients treated with sacubitril/valsartan 200–400 mg vs. olmesartan 20–40 mg. The 24-hour ambulatory BP results at week 10 demonstrate that reductions in maSBP with sacubitril/valsartan were consistently greater than those with olmesartan throughout the 24-hour dosing period. Such

Table 2. Office blood pressure by age subgroups at week 10 endpoint

<table>
<thead>
<tr>
<th>Age subgroup</th>
<th>Sacubitril/valsartan</th>
<th>Olmesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline value</td>
<td>Change from baseline</td>
</tr>
<tr>
<td>65 to &lt;75 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>239</td>
<td>239</td>
</tr>
<tr>
<td>msSBP</td>
<td>160.24 ± 8.30</td>
<td>−22.63 ± 13.66</td>
</tr>
<tr>
<td>msDBP</td>
<td>85.92 ± 9.40</td>
<td>−8.68 ± 7.52</td>
</tr>
<tr>
<td>≥75 years subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>msSBP</td>
<td>161.77 ± 8.91</td>
<td>−23.99 ± 16.02</td>
</tr>
<tr>
<td>msDBP</td>
<td>79.12 ± 9.40</td>
<td>−7.17 ± 8.51</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. Abbreviations: msSBP, mean sitting systolic blood pressure; msDBP, mean sitting diastolic blood pressure.
results may be of particular importance in elderly patients, in whom BP is more variable. In such patients, ambulatory BP monitoring provides a more realistic method of assessing the effects of an antihypertensive agent than office BP.

With aging, the structural and functional changes in large arteries lead to loss of arterial elasticity causing failure to effectively counteract the pressure generated by the heart during systole, contributing to the elevation of SBP. While DBP remains either normal or decreases with age, the elevation of SBP alone in elderly patients leads to the widening of PP. This increase in PP with age is a surrogate marker of arterial stiffness and is considered a strong and independent predictor of CV risk above that of SBP alone. Similar to the 24-hour assessment of SBP, ambulatory PP is more predictive of CV mortality than office PP. Natriuretic peptides have vasodilatory effects that result in reduced aortic stiffness and characteristic impedance and thereby reducing SBP and PP. In our study, we observed not only significant reductions in office PP but also in 24-hour maPP with sacubitril/valsartan compared with olmesartan. These results suggest that sacubitril/valsartan may be a suitable therapeutic option to address arterial stiffness, which is one of the underlying causes of systolic hypertension.

Fewer patients required dose up-titration in the sacubitril/valsartan group compared with the olmesartan group at week 10. Despite this, the reductions from baseline in msBP and msPP at week 14 in overall patients were significantly greater with sacubitril/valsartan than olmesartan. BP reductions with sacubitril/valsartan appear not to be influenced by advanced age (≥75 years). At week 10, sacubitril/valsartan provided similar effects on BP in patients aged between 65 and 75 years and those ≥75 years, whereas olmesartan was less effective in patients aged ≥75 years. Sacubitril/valsartan provided numerically greater BP reductions vs. olmesartan in the subgroup aged ≥75 years.

The proportion of patients achieving BP control was not demonstrated further at week 14 compared with week 10, despite a significant BP reduction observed between these 2 time points. This could be due to the short treatment duration (4 weeks) with the high dose in this more difficult to treat population. Future studies with longer duration may be needed to investigate this further.

Sacubitril/valsartan and olmesartan were generally well-tolerated in this study, with AEs comparable across the groups. There were no reports of angioedema with sacubitril/valsartan. The incidence of low-potassium levels

Table 4. Laboratory parameters

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Sacubitril/valsartan n = 296</th>
<th>Olmesartan n = 292</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8.0 mmol/l</td>
<td>1/295 (0.3)</td>
<td>0/291 (0.0)</td>
</tr>
<tr>
<td>&gt;5.5 mmol/l</td>
<td>5/295 (1.7)</td>
<td>2/291 (0.7)</td>
</tr>
<tr>
<td>&lt;3.5 mmol/l</td>
<td>18/295 (6.1)</td>
<td>12/291 (4.1)</td>
</tr>
<tr>
<td>Creatinine &gt;176.8 µmol/l</td>
<td>0/295 (0.0)</td>
<td>0/291 (0.0)</td>
</tr>
<tr>
<td>BUN &gt;14.28 mmol/l</td>
<td>0/295 (0.0)</td>
<td>0/291 (0.0)</td>
</tr>
<tr>
<td>Sodium &lt;130 mmol/l</td>
<td>1/295 (0.3)</td>
<td>1/291 (0.3)</td>
</tr>
</tbody>
</table>

Data are presented as n/m (%), where n is the number of patients with a designated value, m is the number of patients at risk for a designated value with a nonmissing value at postbaseline. Abbreviations: BUN, blood urea nitrogen.

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(<3.5 mmol/l) observed in the study was primarily observed in patients from the Philippines and was potentially attributed by site investigators to a low-potassium diet. Safety and tolerability of an antihypertensive drug are particularly important in elderly patients, as they are more likely to have renal and hepatic impairment that may affect the pharmacokinetics of the drug and suffer from orthostatic hypotension. In the elderly population, first-line treatments are diuretics and long-acting calcium channel blockers, followed by ARBs. Several studies have demonstrated that ARBs have greater efficacy and tolerability compared with other antihypertensive regimens in elderly populations; for example, in the LIFE study, a losartan-based regimen was shown to have greater beneficial effects on BP and PP vs. an atenolol-based regimen in patients aged ≥67 years compared with patients aged <67 years. In the present study, sacubitril/valsartan has shown comparable safety and tolerability, with greater efficacy, vs. olmesartan in elderly patients.

There are 2 main limitations of this study. First, PP was calculated, which is used as a surrogate marker of arterial stiffness. However, as the study was conducted over a relatively short time-frame, it is difficult to assess how the changes in PP could relate to arterial stiffness over the long term. Second, the results of this study are limited to Asian patients; therefore, these findings must be extrapolated with caution to other ethnicities.

In a recently published PARAMETER trial in elderly patients (aged ≥60 years) with systolic hypertension and stiff arteries (PP >60 mm Hg), sacubitril/valsartan has demonstrated superior efficacy over olmesartan in reducing clinic and ambulatory central aortic and brachial pressures. Overall, sacubitril/valsartan as first-in-class angiotensin receptor neprilysin inhibitor may offer an effective therapeutic approach for treating systolic hypertension and its underlying causes in the elderly population. In the PARADIGM-HF trial, sacubitril/valsartan demonstrated superior reductions in the risk of CV death, HF hospitalization, and all-cause death compared with enalapril, the benefits of which were observed across all age groups (55 years, 55–64 years, 65–74 years, and ≥75 years) in a post-hoc analysis. This demonstrates that sacubitril/valsartan provides clinical benefits to patients with hypertension and patients with HF.

In conclusion, sacubitril/valsartan may represent an effective therapeutic option in elderly Asian patients with systolic hypertension. In the present study, sacubitril/valsartan provided superior BP-lowering efficacy compared with the ARB olmesartan and was generally well-tolerated.

SUPPLEMENTARY MATERIAL

Supplementary data are available at American Journal of Hypertension online.

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DISCLOSURES

K.H. is an employee of Novartis, and as such, may be eligible for Novartis stock options. Y.Z. and J.Z. were employees of Novartis at the time of study conduct. H.R. has received research grant and honoraria from Novartis Pharma K.K. Japan. O.S. and J.W. declared no conflict of interest.

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