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| <b>GSK Medicine:</b> Lacidipine  |
| <b>Study No.:</b> 110599   |
| <b>Study Period:</b> FSFV(22-Jan-2008) ~ LSLV(31-Nov-2009)   |
| <b>Title:</b><br>Effect of lacidipine and losartan on 24 hour systolic blood pressure variability in elderly hypertensive patients, a pilot study.   |
| <b>Rationale:</b><br>Previous studies exploring the prognostic relevance of blood pressure (BP) variations have shown that alterations in 24-hour BP variability are associated with hypertensive target organ damage and with a higher rate of cardiovascular events.<br><br>The progression of atherosclerosis measured by ultrasound at the carotid artery intima-media thickness is related not only to average ambulatory BP, but also to the magnitude of BP variations. Moreover, BP variability has been linked to the presence of white matter lesion of brain, which is associated with cognitive dysfunction, geriatric syndrome, and functional impairment. So, the identification of increased BP variability by ambulatory monitoring may be one way of detecting the high-risk subject in elderly hypertensive patients. Furthermore BP variability has clinical implication because indiscriminate anti-hypertensive drug treatment, which may increase the BP fluctuation, has an adverse effect on cardiovascular outcome. So individualized therapy, based on ambulatory blood pressure, might spare the silent hypertensive-target-organ damage and clinical cardiovascular consequences governed by excessive blood pressure variability. As a result, BP variability is especially important in elderly hypertensive patients considering its clinical significance and therapeutic relevance. However, relatively few studies performed to ensure the effect of each anti-hypertensive medication in reducing BP variability. |
| <b>Indication:</b> Essential Hypertension  |
| <b>Study Investigators/Centers:</b> Cheol-Ho Kim / Seoul National University Bundang Hospital  |

**Research Methods:**Data Source:

Case Report Form

Study Design:

This is a prospective, randomized, open-label, blinded end point (PROBE), parallel group study with two treatment arms. At the end of an initial 2-week washout period, during which any eventual anti-hypertensive drug is discontinued, patients fulfilling the inclusion criteria are randomly treated with the lacidipine (4 mg) or losartan (50 mg), both given once daily at the same hour in the morning (approximately at 8 AM) for 12 weeks. If the BP goal (SBP < 140 mmHg and DBP < 90 mmHg) has not been attained after 4 week's treatment, 12.5 mg hydrochlorothiazide (HCTS) once daily can be added. Patients are checked 24-h ambulatory BP monitoring (ABPM) at the end of the washout period and after 12 weeks of active treatment. At each visit, seated cuff SBP and DBP, heart rate, use of concomitant medication and spontaneously reported adverse events are recorded. Patients are instructed not to take their trial medication on the days of clinic visits, which ensure measurement of trough blood pressures. Compliance with medication (determined by counting returned tablets) is evaluated at each visit.

Study Population:

**Inclusion Criteria**

- Elderly patients (age  $\geq$  65 years)
- who meet the criteria of essential hypertension (systolic BP  $\geq$  140 mmHg or diastolic BP  $\geq$  90 mm Hg)
- Provide written informed content

**Exclusion Criteria**

- Secondary hypertension,
- Myocardial infarction or cerebrovascular accident within the preceding 6 months
- clinically significant valvular heart disease, heart failure (Class III, IV), renal insufficiency (serum creatinine  $\geq$  2.5mg/dl), hepatic failure, uncontrolled diabetes mellitus
- Known hypersensitivity to the drugs used in the study.

**Withdrawal Criteria**

- who refuse to be enrolled during the follow up period
- subjects with a unresponsive hypertension during the medication (Mean seated SBP of  $>$  180 mmHg at any time during the study)
- subjects who would not visit the clinics more than two times subsequently at the schedule day
- subjects who showed the fatal or uncorrectable side effects during the follow up period.

any other subjects who are unsuitable for follow up due to acute illness or poor general condition after researchers

Study Exposures, Outcomes:

**Primary Endpoint(s)**

The change of **24-hour, one day systolic BP standard deviation (SD)** within subjects (the difference of SD before and after 12 weeks' treatment) in lacidipine group and losartan group

**Secondary Endpoint(s)**

- The change of **24-hour, one day diastolic BP standard deviation (SD)** within subjects (the difference of SD before and after 12 weeks' treatment) in lacidipine group and losartan group
- The difference of the changes in **office diastolic and systolic BP** after 12 weeks' treatment between lacidipine group and losartan group
- The difference of the **mean 24-hour ABPM systolic and diastolic BP** after 12 weeks' treatment between lacidipine group and losartan group
- The difference of the diastolic and systolic **BP control rates** after treatment between the 2 groups
- The difference of the **changes in 24-hour, one day BP standard deviation (SD) within subjects** between lacidipine group and losartan group
- The difference of the **variation of coefficient (CV)** of the mean values (24-hour BP SD divided by the mean multiplied by 100) between 2 groups
- The difference of the **smoothness index (SI)**, dividing the average of the 24 hourly change after treatment by the corresponding standard deviation) between 2 groups
- The difference of the **changes in pulse pressure** after treatment between the 2 groups

#### Data Analysis Methods:

- In each subject, mean  $\pm$  SD values for SBP, DBP, and HR are computed for each half hour of the recording and then averaged over the entire 24 hours, day-time (from 7:00 AM to 10:00 PM), and night-time (from 10:00 PM to 7:00 AM) and for each hourly subperiod. The SD and CV are taken, respectively, as measures of absolute and normalized short-term variability of the signals.
- Past history and demographic factors including past history, hypertension history, treatment duration and medication, previous coronary heart disease(CHD) history will be collected at baseline and analyzed to assess the possibility to be a confounding factor, and will be adjusted by statistical model if needed.
- Statistical analysis is performed on the full analysis set, based on the intent-to-treat principle. The safety population included all patients who receive at least 1 dose of study medication. Effects of treatments on the primary and secondary end points are compared using analysis of covariance (ANCOVA), which included treatment, study, and treatment-by-study interaction, with relevant baseline value as a covariate. A value of  $P < 0.05$  is taken as the level of statistical significance. Planned Interim Analysis.

#### **1) Office BP Measurement**

BP is recorded twice in both arms with a mercury sphygmomanometer in the sitting position after 15 minutes of rest. The mean of 2 consecutive readings in each arm is recorded. If there is a difference of  $>10$  mm Hg between the arms in systolic or diastolic blood pressure, the arm with the highest reading is used, otherwise the nondominant arm is used.

#### **2) Ambulatory BP Measurement (ABPM)**

ABPM are obtained using a noninvasive oscillometric system. The device is fitted to the patient by an experienced nurse. Patients are instructed not to restrict their daily activities during the monitoring periods. Before start of the monitoring period, the automatic readings are crosschecked against manually measured blood pressure by auscultation to ascertain that blood pressure monitoring is correct. The recorder is set to take readings at 30-min intervals throughout the 24-h period. Recordings are always started at the same hour in the morning and are performed throughout the 24-h period, during which patients are allowed to follow their normal daily routine after they left the laboratory. Recordings are excluded from the analysis when more than 10% of all readings or more than one reading per hour are missing or incorrect.

**Limitations:** N/A

| <b>Study Results:</b>                        |                                    |                                 |                |
|--|------------------------------------|---------------------------------|----------------|
| <b>Demographics/Baseline Characteristics</b> | <b>Comparison Group (Losartan)</b> | <b>Study Group (Lacidipine)</b> | <b>P value</b> |
| Age (yr)                                     | 68.8 (4.8)                         | 71.6 (5.7)                      | > 0.05         |
| Family History of HT                         | 4 (44.4%)                          | 3 (30.0%)                       | > 0.05         |
| Glucose (mg/dL)                              | 104.0 (14.8)                       | 99.8 (12.3)                     | > 0.05         |
| eGFR (mL/min/1.73m <sup>2</sup> )            | 69.5 (9.7)                         | 70.9 (7.2)                      | > 0.05         |
| Cholesterol (mg/dL)                          | 209.4 (39.8)                       | 201.0 (33.5)                    | > 0.05         |
| hsCRP (mg/L)                                 | 0.9 (1.3)                          | 1.5 (1.8)                       | > 0.05         |
| Clinic-SBP (mmHg)                            | 146.3 (4.7)                        | 152.2 (10.3)                    | > 0.05         |
| Clinic-DBP (mmHg)                            | 84.1 (5.6)                         | 84.2 (8.3)                      | > 0.05         |
| Clinic-HR (/min)                             | 66.8 (6.7)                         | 64.5 (6.2)                      | > 0.05         |
| 24H-SBP (mmHg)                               | 134.1 (8.9)                        | 135.1 (10.5)                    | > 0.05         |
| 24H-DBP (mmHg)                               | 82.8 (8.2)                         | 82.4 (8.6)                      | > 0.05         |
| 24H-Awake-SBP (mmHg)                         | 135.3 (8.8)                        | 136.1 (10.5)                    | > 0.05         |
| 24H-Awake-DBP (mmHg)                         | 83.8 (8.2)                         | 83.1 (9.0)                      | > 0.05         |
| 24H-Sleep-SBP (mmHg)                         | 119.3 (11.6)                       | 122.5 (15.7)                    | > 0.05         |
| 24H-Sleep-DBP (mmHg)                         | 72.0 (8.2)                         | 73.2 (9.6)                      | > 0.05         |
| SD-Day-SBP (mmHg)                            | 14.6 (3.4)                         | 13.7 (2.5)                      | > 0.05         |
| SD-Day-DBP (mmHg)                            | 9.3 (1.9)                          | 9.3 (2.0)                       | > 0.05         |
| SD-Night-SBP (mmHg)                          | 11.7 (4.7)                         | 7.3 (3.2)                       | > 0.05         |
| SD-Night-DBP (mmHg)                          | 8.6 (2.0)                          | 6.9 (2.7)                       | <b>0.034</b>   |

| <b>Primary and Secondary Outcome(s)</b> | <b>Comparison Group (Losartan)</b> | <b>Study Group (LACIDIPINE)</b> | <b>P value</b> |
|---|------------------------------------|---------------------------------|----------------|
| <b>Primary:</b>                         |                                    |                                 |                |
| Δ (SD-SBP-Day)                          | -1.3 (5.6)                         | -0.6 (3.4)                      | > 0.05         |
| Δ (SD-DBP-Day)                          | -1.0 (3.2)                         | -0.5 (2.7)                      | > 0.05         |
| Δ (SD-SBP-Night)                        | 3.3 (5.4)                          | 0.7 (5.3)                       | > 0.05         |
| Δ (SD-DBP-Night)                        | 1.0 (1.5)                          | -0.8 (3.1)                      | > 0.05         |
| <b>Secondary:</b>                       |                                    |                                 |                |
| Δ (SBP-24H)                             | 12.1 (9.4)                         | 13.7 (12.1)                     | > 0.05         |
| Δ (DBP-24H)                             | 8.0 (4.8)                          | 7.7 (6.1)                       | > 0.05         |
| Δ (SBP-Day)                             | 13.3 (9.6)                         | 14.7 (12.0)                     | > 0.05         |
| Δ (DBP-Day)                             | 9.0 (4.8)                          | 8.4 (6.3)                       | > 0.05         |
| Δ (SBP-Night)                           | 10.1 (11.3)                        | 9.4 (16.2)                      | > 0.05         |
| Δ (DBP-Night)                           | 12.1 (9.4)                         | 13.7 (12.1)                     | > 0.05         |

**Conclusion**

Although, this pilot study was not powered to identify any significant difference due to small sample size, we could not find meaningful difference in the change of blood pressure variability between lacidipine and losartan treated elderly patients.

\*\* This investigator initiated trial was terminated due to difficulty of patients' enrollment and lack of investigators' interest. Patients have been enrolled 24 out of 160 and result analyzed with 23 completed patients.