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Shionogi & Co., Ltd.

Announcement of Final Results of JATOS, Japan's First Large-Scale Clinical Trial for Treatment of Hypertension in Elderly Patients

Osaka, October 19, 2006 — The final results of JATOS (The **J**Apanese **T**rial to Assess **O**ptimal **S**ystolic Blood Pressure in Elderly Hypertensive Patients), Japan's first large-scale clinical trial for the treatment of hypertension in elderly patients, were announced today at the 21st Scientific Meeting of the International Society of Hypertension (29th Annual Scientific Meeting of the Japanese Society of Hypertension) in Fukuoka, Japan.

JATOS commenced in April 2001 with the goal of answering a question that concerns healthcare professionals involved in hypertension treatment: How should hypertension in elderly patients be treated?

The results of this trial are highly evaluated not only as valuable research findings that provide much of the evidence that was lacking in guidelines for treating hypertension in older patients, but also because they come from a high-quality large-scale trial conducted primarily by the Japan Physicians Association, with backing from the Japanese Society of Hypertension and the participation of many general practitioners.

The key results of the trial are as follows:

1. The importance of blood pressure management in the treatment of elderly hypertensive patients was confirmed.
2. In addition to sufficient antihypertensive treatment, the importance of managing risk factors (brain, heart, kidneys, diabetes mellitus, smoking, lipid metabolism) was confirmed.
3. The safety of reducing systolic blood pressure (SBP) in elderly hypertensive patients to less than 140mmHg was confirmed.
4. Chronic kidney disease (CKD) was confirmed to be a risk factor of cardiovascular disease, and it was clearly demonstrated that few cases of cardiovascular disease developed in the group with improved glomerular filtration rates (GFR).
5. The incidence rate of cardiovascular disease is high in cases of metabolic syndrome, and the evidence suggested that aggressive antihypertensive treatment is particularly recommended for patients 65–75 years of age with metabolic syndrome.

Shionogi & Co., Ltd. helped compile this practical evidence, and will focus on contributing further to cardiovascular treatment in its target research areas.

- **Trial Design**

A total of 1,028 facilities nationwide participated, centered on the Japan Physicians Association, with backing from the Japanese Society of Hypertension.

The subjects of the study were elderly hypertensive patients (65–85 years old) who consistently had an SBP of 160mmHg or higher. The patients were randomly separated into Group A, which was treated to reduce SBP to less than 140mmHg, and Group B, which was treated to maintain SBP from 140mmHg to below 160mmHg. Antihypertensive treatment was conducted for two years, using efonidipine hydrochloride (Landel[®]), a long-acting dihydropyridine calcium antagonist, as the baseline drug. The trial was conducted from April 2001 to the end of 2004. There were 4,418 test subjects.

Items evaluated included the incidence rates of cardiovascular diseases, the associated mortality rates and the incidence rates of adverse events and side effects.

- **Trial Results**

Importance of Reducing Blood Pressure and Managing Risk Factors (Brain, Heart, Kidneys, Diabetes Mellitus, Smoking, Lipid Metabolism)

In a logistic regression analysis of the relationship between the cardiovascular event incidence rate and risk factors, the odds ratio of risk factors was over 2 for age and cerebrovascular disease, followed in decreasing order by kidney damage, gender, cardiac damage, diabetes mellitus, smoking and abnormal lipid metabolism. Each of these factors showed a stronger connection than a blood pressure difference of about 10mmHg. Although no significant differences were recognized between Group A and Group B, even after correcting for these risk factors, these results by no means negate the importance of lowering blood pressure. Rather, they suggest that in addition to the importance of managing blood pressure in elderly hypertensive patients, management of correctable risk factors (brain, heart, kidney, diabetes mellitus, smoking, lipid metabolism) is important as well.

Another important result was confirmation of the safety of reducing SBP to less than 140mmHg in elderly hypertensive patients.

Possibility of Different Blood Pressure Targets for “Young-Old” and “Old-Old” Patients

This study divided subject patients into the “young-old” (65 – 74 years old) and the “old-old” (75 years and older) to analyze cardiovascular event incidence rates by group and age. The incidence rate of cardiovascular disease in young-old patients tended to be lower in Group A than in Group B, but in old-old patients tended to be higher in Group A than in Group B.

These results suggest that aggressive antihypertensive treatment (SBP lower than 140mmHg) may be recommended in young-old patients. For old-old patients, particularly those with risk factors, cautious antihypertensive treatment appears advisable, but further research is necessary.

Chronic Kidney Disease (CKD) is an Independent Risk Factor of Cardiovascular Disease

In recent years, it has become clear that CKD is an independent risk factor of cardiovascular disease. In JATOS, which had more than 4,000 test subjects, the findings of a study of the relationship between estimated GFR values and the incidence rate of cardiovascular events also suggested that CKD is a risk factor of cardiovascular disease. Improvement in GFR was seen after two years of treatment using efonidipine hydrochloride as the baseline drug, and it was clear that cardiovascular disease was significantly lower in the improved group, confirming the drug's renoprotective effect.

Metabolic Syndrome and Blood Pressure Reduction in Elderly Hypertensive Patients

It was clearly demonstrated that metabolic syndrome (MS) is an independent risk factor of cardiovascular disease. In JATOS, the prevalence rate of MS was approximately 30%, and the incidence rate of cardiovascular disease was high in MS cases. In young-old patients with MS, the event incidence rate was significantly lower in Group A than in Group B. This suggests that aggressive antihypertensive treatment is recommended for young-old patients with MS.

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