**A Comparison of the effects of the DPP-4 inhibitor Sitagliptin and Sulfonylurea Glimepiride on Endothelial Function and Metabolic Parameters**

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June 6, 2013 version 10

**1． Background of the study**

Type 2 diabetes is one of the major causes of atherosclerosis and an independent risk factor of cardiovascular events1). Indeed, it has been reported that the prevalence of coronary and peripheral artery disease is 2- to 4-fold higher, and stroke risk was also 2-fold higher in overt type 2 diabetic patients2)-4). To prevent these atherosclerotic events, it is important to detect and intervene early in the development of atherosclerosis. Recently, endothelial cell dysfunction has been shown to precede endothelial thickening and atheroma development, and has been reported to be an important predictor of cardiovascular events also in type 2 diabetic patients 5), 6). Moreover, they are used for therapeutic surrogate parameters of the early phase of atherosclerosis because of their plasticity. Flow-mediated dilation of the brachial artery (FMD) reflects endothelial nitric oxide (NO) bioavailability and is widely used as a marker for early atherosclerosis7), 8). Impaired FMD is associated with type 2 diabetes independent of glucose levels and may, in part, explain the increased cardiovascular risk in this patient population9). Therefore, it is important that diabetic therapies achieve glycemic control and maintain/improve FMD to prevent the development of vascular complications. DPP-4 inhibitors are a recently approved treatment strategy for improving glycemic control and lowering hemoglobin A1c (HbA1c) in type 2 diabetics. Various additional health benefits beyond glucose control are also expected with DPP-4 inhibitor therapy, including protection from macro-vascular complications. For example, elevation of GLP-1 level resulted in improvement of endothelium-dependent vasodilatation in some rodent models 10), 11), and acute native GLP-1 infusion ameliorated endothelial and cardiac dysfunction in diabetic patients12). To date, a limited number of clinical trials have investigated the effects of commercially available DPP-4 inhibitors on endothelial function, and their results are inconsistent12) -14). Therefore, the goal of the current study was to assess whether long-term treatment with the DPP-4 inhibitor sitagliptin can improve endothelial function in patients with type 2 diabetes using a multicenter, prospective randomized parallel-group comparison study design. We provide the first direct comparison of changes in endothelial function following chronic treatment with one of two functionally distinct glucose lowering therapies, sitagliptin or glimepiride.

**2． Purpose of this study**

We investigated the efficacy of the DPP-4 inhibitor, sitagliptin on endothelial function and glycemic metabolism compared with glimepiride therapy in the design of multicenter, prospective, non-blinded, randomized parallel-group comparison study.

**3． Summary of the study drug**

3.1 Glimepiride

\* Manufacture/distributor: Sanofi-Aventis Co., Ltd.

\* Mechanism of action: a long-acting insulin secretagogue, given once or twice daily to help control the [blood glucose](http://en.wikipedia.org/wiki/Blood_sugar) level of those with [diabetes](http://en.wikipedia.org/wiki/Diabetes). It is usually started from 0.5 to 1.0 mg/day, subsequently increased as necessary.

3.2 Sitagliptin

\* Production, a sales agency: MSD Co., Ltd. and Ono pharmaceutical Co., Ltd.

\* Mechanism of action: A selective inhibitor of dipeptidyl peptidase-4 [(DPP-4)](http://en.wikipedia.org/wiki/Glucagon-like_peptide-1_agonist), given once daily to increase endogenous incretins and reduces meal-related [hyperglycemia](http://en.wikipedia.org/wiki/Hyperglycemia) by increasing [insulin](http://en.wikipedia.org/wiki/Insulin) secretion, suppressing prandial [glucagon](http://en.wikipedia.org/wiki/Glucagon) secretion.

**4． The study patients and competent criteria**

Patients who fulfill all of these criteria are eligible; (1), (2) inclusion criteria and (3) exclusion criteria.

(1) The study patients

Patients with type 2 diabetes who were treated at the Hokkaido University Hospital, or other institutions participating in this study.

(2) Inclusion criteria

(1) Age is 20 years or older at the time of consent.

(2) Inadequate HbA1c control, 6.9-8.4 % (NGSP), 6.5-8.0 % (JDS) at the agreed acquisition

(3) Patients receiving metformin or none in addition to a diet and exercise therapy.

(4) The patients who have adequate control of blood pressure and dyslipidemia.

(5) The patients who are able to understand the requirements of the study, and provide consent of their own free will.

(3) Exclusion criteria

(1) The patients who are treated with insulin therapy.

(2) The patients who are suffering serious liver damage, renal disease, or heart failure.

(3) The patients who underwent angina, myocardial infarction, cerebral infarction or arteriosclerosis obliterans.

(4) The patients who take more than four antihypertensive medications.

(5) The patients who take more than three lipid lowering medications.

(6) The patients who have a history of hypersensitivity to insulin or GLP-1 receptor agonists.

(7) A pregnant woman, nursing mother or woman who may become pregnant.

(8) In addition, the patients whom a principal investigator judged to be inadequate as subjects.

**5． Method of the study**

(1) Study design

Multicenter, prospective, non-blinded, randomized, parallel-group comparison study.

(2) Study outline

(1) Participants received an initial screening (week 0) at the Department of Cardiovascular Medicine, Hokkaido University Hospital.

(2) The medication is to be started within a month after screening. A starting dose of sitagliptin and glimepiride was 50-100 mg/day and 0.5-2.0mg/day, respectively.

(3) Glycemic control is assessed at each institution every 4-8 weeks.

(4) A final examination is carried out at the Department of Cardiovascular Medicine, Hokkaido University Hospital at 24 weeks (+/- two weeks).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| At registration | week 0 | | Every 4-8 weeks | 24 weeks |
| Written consent | Screening before randomization and administration | |  | Final examination |
| metformin and/or diet and exercise therapy | Glimepiride group | 0.5-2.0 mg | appropriate increase and decrease | appropriate increase and decrease |
| Sitagliptin group | 50-100 mg | appropriate increase and decrease | appropriate increase and decrease |
| FMD | ● |  |  | ● |
| TBI | ● |  |  | ● |
| Taskforce monitor | ● |  |  | ● |
| Blood glucose  (HbA1c, FPG) | ● |  | ● | ● |
| Biomarker measurement | ● |  |  | ● |
| Clinical laboratory examinations | ● |  |  | ● |

● are mandatory.

(3) Injection method of the study agents

A starting dose of glimepiride is 0.5-2.0 mg/day once or twice a day, and sitagliptin is started at a dose of 50-100 mg/day. The doses are to be titrated according to the judgment of physicians in charge with the goal a HbA1c below 6.9%.

(4) Concomitant medications

Patients who require the use of additional hypertension and/or dyslipidemia medications during the study period must be discontinued from the study.

(5) Method of registration and assignment

(1) Case registration

The physicians in charge complete the enrollment form and send it to the study manager.

(2) Assignment of the study agents

The study manager receives the completed enrollment form which includes data from the screening examination performed at the Hokkaido University Hospital and randomly assigns study participants to either the glimepiride group or sitagliptin group, according to computerized randomization.

(6) Study period

Each participant is treated with glimepiride or sitagliptin for 24 weeks in each institution.

(7) Correspondence after the study

After this study, each physician is required to provide the most appropriate medical care to participants.

**6． Observational and analytical analyses**

Observational and analytical testing for the following items will be performed.

(1) Patients background: Patients initial, identification cord, age, sex, type of diabetes, height, weight, BMI, abdominal circumference, contraction of a disease period, complications, presence or absence of smoking, alcohol consumption, drug medication contents

(2) Blood pressure, pulse rate

(3) Laboratory study (fasting)

Urinalysis (sugar urinary, protein urine (qualitative analysis), the urinary albumin/ creatinine ratio), blood glucose (HbA1c, fasting plasma glucose), serum insulin, proinsulin, fasting serum lipids (total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, FFA, apoprotein, RLP-C), AST, ALT, γ-GTP, uric acid, BUN, serum creatinine, Na, K, Cl, hs-CRP, NT-proBNP

Adiponectin, total PAI-1, TNF - α, SOD, urinary 8-OHdG

In addition, for biomarker measurement use, we will collect an additional 10 ml of blood at the 0 and 24 week time points. If the agreement of subjects is obtained, we will store the remaining sample and may perform additional measurements when new biomarkers are found in the future.

(4) Toe brachial index (TBI)

(5) Flow mediated dilatation (FMD) ： FMD is influenced by blood glucose level and time of measurement. Thus, we will perform fasting FMD in the morning. We prohibit caffeine, smoking, or taking any vitamin supplements before the assessment, and perform FMD assessment in a thermo-regulated room according to guidelines. Oral medicines are discontinued only on the morning of the assessment day, and taken after testing.

(6) Taskforce monitor: Using a Taskforce monitor (CNSystems, Nihon Kohden) that is noninvasive cardiac activity measuring assembly, we evaluate the cardiac output, systemic vascular resistance, the autonomic nervous function. The study day requirements are the same as (5) because we perform (5) and (6) simultaneously.

**7． Expected benefit and disadvantage (potential side effect)**

(1) The expected benefit

We may choose more appropriate medication for individuals according to insights from this study. The results of this study may also contribute to future medical progress.

(2) The expected disadvantage

The details refer to an attached document of each agent. Hypoglycemia is reported as frequent side effects for glimepiride, and hypoglycemia and constipation are reported for sitagliptin.

(1) FMD: Pain may occur by pressurizing a brachial artery with a cuff of the sphygmomanometer, but this testing is widely utilized in clinics and the pain is reported to be tolerable. However, FMD may be discontinued at the discretion of the attending doctor when pain is considered severe.

(2) Blood volumes will increase compared to standard clinical needs. These volumes are well below the suggested blood volume limits and will not affect the care of the subjects.

**8． Endpoint**

(1) Primary outcome

We will compare the change in FMD between each group before and after agent administration.

(2) Secondary endpoint

Change in the following items between the treatment groups before and after the study.

(1) Blood glucose (HbA1c, fasting plasma glucose)

(2) Evaluation of pancreatic beta cell function

(3) The change of various measurements by TBI, Taskforce monitor

(4) Various blood test values, urine test value, biomarkers

**9． Discontinuation criteria for individual subjects**

(1) Correspondence at study cancellation

Based on the following criteria it may be decided that an individual should be discontinued from the study.

(2) Discontinuation criteria

(1) When a subject withdraws consent and/or refuses to participate in the study.

(2) When we identify individuals that were enrolled but do not meetthe inclusion criteria.

(3) When we judge a patient’s condition worsens due to studytreatment.

(4) When the continuation of the study is made difficult by the exacerbation of complications.

(5) When the continuation of the study is made difficult by an adverse event.

(6) When pregnancy becomes clear.

(7) When compliance is remarkably poor.

(8) The patients who do not adhere to diet and exercise therapy.

(9) When the study is terminated.

(10) When, for others reasons, the study person in charge judges the cancellation of the study to be suitable.

**10． The handling of adverse event development**

(1) Correspondence to subjects who suffer adverse events

When an adverse event occurs, the study person in charge will administer appropriate treatment promptly and document it in a medical record and a case report. Moreover, we accurately explain the cancellation of study and treatment of adverse event to the subjects.

(2) Report of serious adverse event

Serious adverse events are defined as follows.

1) Death, or complications that may lead to death

2) Hospitalization or extension of the length of stay

3) Sequela, or fear to lead to sequela

4) Effects to congenital disease or abnormality

The study person in charge has to immediately reports all serious adverse events suspected to be related to experimental treatments during study period to the head of the hospital through the clinical studies manager.

(3) Report of the important adverse event

Not applicable.

(4) Other adverse events

About other adverse events, the study person in charge describes it in a medical record and a case report appropriately.

**11． Changes such as study enforcement plans**

When we conduct the change of a study enforcement plan and the agreement explanation document of this study or revision, we require the approval of the voluntary clinical studies screening committee beforehand.

**12． Study amendment, cancellation, interruption, the end of the study**

(1) Amendments

When we amend/revise the study protocol and/or patient consent documents, we require the approval of the Hokkaido University Hospital independence clinical studies screening committee beforehand.

(2) Early termination, interruption of the study

The study person in charge may decide early termination of the study is appropriate in any of the following cases.

(1) When the recruitment of subjects is difficult and is judged to be extremely difficult to reach the planned number of cases.

(2) When the purpose of the study is accomplished before reaching during planned number of cases or a planned period.

(3) When we judge it is difficult to change our protocols if the screening committee propose us to drastically change our protocols.

When there is a recommendation for early termination by a screening committee, the study person in charge will terminate the study. The decision to terminate early or interrupt a study is documented along with the explanation and reported immediately to the head of the hospital.

(3) The end of the study

At the end of this study, the study person in charge submits a report of this study to the head of a hospital immediately.

**13． Study duration**

After approval (March, 2011) to May 31, 2014 (a registration final day: September 30, 2013)

**14． Goal number of cases and the setting backgrounds and statistical analysis method**

(1) Goal number: 100 cases in total (50 cases in each group)

Setting backgrounds

The detailed report about the effect on FMD with the administration of sitagliptin is not found at present. According to the report of Papathanassiou K et al15) which evaluates FMD changes six months after pioglitazone or glimepiride therapy, changes in %FMD were 2.0 % (standard deviation = 2.0) in the pioglitazone group compared with 0.1 % (standard deviation = 1.0) in the glimepiride group. We hypothesize that after 6 months of treatment the effect of sitagliptin on FMD may be at least 1% (standard deviation = 2.0) change observed with pioglitazone and the effect of glimepiride will be equivalent to previous report (0.1% changes (standard deviation = 1.0)). From this assumption, it was determined that 50 patients were needed for each group to detect a significant difference with 80% power and statistical significance of 5%.

(2) Statistical analysis method

We will measure %FMD before and after treatment for all subjects and report a mean and standard deviation for each treatment group. We will compare changes in %FMD for each group using non-paired *t*-test. We will also assess the changes in the amount of %FMD using a multiple comparison testing for each change. In addition, we will determine the change in various biomarkers and β cell function for all subjects similarly and examine the association between the difference between groups and parameters in an exploratory fashion.

**15． Protective method of the consideration for the human rights of subjects and the personal information**

All people in charge of this study have to observe "Helsinki Declaration" (October, 2008 revision) and "the ethical guideline (July 31, 2008 revision, following clinical studies ethic guideline) about clinical studies".

Individual information and samples collected during this study will be assigned a unique sample number that is unrelated to the subject’s personal information. When we send information and samples to the associated organizations such as the study manager, we will use this unique identifying number to ensure that the subject’s personal information is not revealed. This numbering system will also be used when analyzing and reporting the results of the study. Information obtained from study subjects will not be used for anything other than the purposes of this study.

**16． Informed Consent**

The doctor in charge provides an informed consent document to the subjects and gives an oral explanation of the document and study and acquires a signed consent agreement with the free will of subjects.

If the protocol is amended in a way that influences the consent obtained from the subject, the doctor in charge has to give this new information to subjects immediately. At the same time, the doctor in charge has to confirm the intention of subjects, to continue their participation in this study, and obtain written consent again.

An informed consent document contains following components:

(1) Subjects are participating in this study of their own free will and don’t suffer a disadvantage because of nonparticipation. They are able to withdraw their consent to participate at any time.

(2) Significance (background), purpose, subject, method, duration of the study, planned subject number

(3) The benefit and disadvantage that are expected by participating in a study

(4) The methods about handling such as personal information, a conservation period and a material disposal.

(5) The handling about the announcement of results and a patent.

(6) The cost burden on subjects for participating in this study, a study source of funds and benefit reciprocity.

(7) Composition of research unit and consultation windows (contact information) of this study.

(8) Presence or absence of correspondence and compensation when a health hazard occurred in subjects.

**17． Correspondence and compensation to the health hazard of subjects**

In the case of a health hazard in subjects participating in the study, the doctor in charge treats appropriately. The compensation for the health hazard is carried out according to clinical studies ethic guideline. For death and severe disorder, we prepare for compensation money. For other health hazard, necessary treatment such as testing or treatment is to be provided in the medical service under health insurance of subjects.

**18． Costs burden on subjects**

The study person in charge is responsible for the costs associated with biomarker analysis and will utilize research funds from the department. Any other cost burden on subjects by participating in a study does not occur to be performed in a normal medical service under health insurance. In addition, we decide to provide 4,000 yen QUO CARD for every examination of arteriosclerosis (FMD, TBI, Taskforce monitor) enforcement for the purpose of burden on subjects’ reduction. The doctor in charge has to explain this to participants and allow subjects to decide if they wish to participate or not.

**19． The retention of records and publication of results**

The study person in charge has to save important documents (the copy of the application documents, a notice document from the head of a hospital, the consent form of various applications, reports, documents necessary to guarantee the reliability of other data or records) for three years after the completion or termination of the study. Subsequently personal information is carefully disposed. The results of the study will be presented at scientific meetings and in scientific journals.

**20． A funding source and benefit reciprocity**

This study is conducted using research funds from the department of the study person in charge. The handling of the benefit reciprocity examination is also conducted according to the rules of each institution. The study person in charge of the Hokkaido University Hospital has to report a necessary matter to the benefit reciprocity screening committee according to the rule of "benefit reciprocity management internal regulations affect clinical studies in the Hokkaido University Hospital" and should obtain the examination and approval.

**21． Study enforcement system**

This study is conducted with the following systems.

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**The study manager**

Hokkaido University Hospital internal medicine II

Person in charge: Hideaki Miyoshi

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**Case assignment enforcement organization**

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**Participating institution**

Aoki clinic, Ohtsuka eye hospital, Ohdori internal medicine clinic, Ogasawara clinic Sapporo hospital, Okamoto internal medicine clinic, Yuri Ono clinic, Clark hospital, Kurihara clinic, Hokkaido chuo rosai hospital sekison center, Hokkaido medical center, Sasaki clinic, Soen central hospital, Hokkaido social insurance hospital, Manda memorial hospital, Sapporo city general hospital, Tonan hospital, Sapporo social insurance hospital, Hokuryo clinic, NTT east japan hospital

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