Effects of sitagliptin beyond glycemic control: focus on quality of life

Yoshiko Sakamoto[1]
Email: sakamot2@cc.saga-u.ac.jp

Jun-ichi Oyama[1*]
* Corresponding author
Email: junoyama@cc.saga-u.ac.jp

Hideo Ikeda[2]
Email: me710030@mocha.ocn.ne.jp

Shigetaka Kuroki[2]
Email: KUROKISKKUROKI@yahoo.cojp

Shigeki Gondoh[2]
Email: shigeki@kohju.jp

Taketo Iwamoto[2]
Email: i-taketo@po.saganet.ne.jp

Yasufumi Uchida[2]
Email: bc2kdebt3@i.softbank.jp

Kazuhisa Kodama[1]
Email: kodamak@cc.saga-u.ac.jp

Atsushi Hiwatashi[1]
Email: hiwatasa@cc.saga-u.ac.jp

Mitsuhiro Shimomura[1]
Email: shimomur@cc.saga-u.ac.jp

Isao Taguchi[3]
Email: taguchi@dokkyomed.ac.jp

Teruo Inoue[3]
Email: inouet@dokkyomed.ac.jp

Koichi Node[1]
Email: node@cc.saga-u.ac.jp

S-DOG [Saga Challenge Anti-Diabetes Observational Study for Sitagliptin (S-DOG)] investigators

[1] Department of Cardiovascular Medicine, Saga University, 5-1-1 Nabeshima, Saga city, Saga 849-8501, Japan

[2] Saga Medical Association, Saga, Japan

[3] Department of Cardiovascular Medicine, Dokkyo Medical University, Soka, Saitama, Japan

Abstract

Background

Recently, incretin hormones, including glucagon-like peptide-1 (GLP-1) analogue and dipeptidyl peptidase-4 (DPP-4) inhibitor, have been found to regulate glucose metabolism. The aim of this study was to elucidate the efficacy and safety of the clinical usage of DPP-4 inhibitors in Japan.

Methods

This study was designed as a prospective, open-label, multi-center trial. Patients with diabetes mellitus type 2 (T2DM) with poor glycemic profiles (HbA1c $\geq$ 6.2%) in spite of receiving a medical diet, therapeutic exercise, and/or medications were eligible for this study. The participants received 50 to 100 mg of the DPP-4 inhibitor sitagliptin once daily for 12 months.

Results

One hundred and eighty-eight subjects were enrolled. After 12 months of sitagliptin treatment, HbA1c levels decreased (7.65% $\pm$ 1.32% to 7.05% $\pm$ 1.10%, $p < 0.001$) as well as fasting plasma glucose (FPG) (145 $\pm$ 52 mg/dl to 129 $\pm$ 43 mg/dl, $p = 0.005$). The rate of glycemic control achieved (in accordance with the guidelines of the Japanese Diabetes Society) significantly increased. Blood pressure and serum levels of triglycerides and total cholesterol decreased significantly. Furthermore, the Pittsburgh Sleep Quality Index (PSQI) and Diabetes Symptomatic Scores improved significantly. Adverse events such as hypoglycemia and loss of consciousness occurred in twenty three subjects (11%).

Conclusions

These results suggest that the actions of DPP-4 inhibitors improve not only glycemic control, but also blood pressure, lipid profiles, and quality of life (QOL). Sitagliptin is a sound agent for use in the comprehensive treatment of patients with T2DM.

Keywords

DPP-4 inhibitor, Diabetes type 2, HbA1c, Blood pressure, Metabolism

Introduction

In Japan, the Ministry of Health, Labour and Welfare published a report on health and nourishment in 2007 [1] that estimated that 22.1 million people have strongly suspected diabetes mellitus (DM) (HbA1c (NGSP) $\geq$ 6.5%) or potential DM (6.0% $\leq$ HbA1c (NGSP) <

6.5%). This rate has increased 1.3 times compared to that observed in the former decade, and an upward trend continues to be maintained. Additionally, the rate of diabetic treatment has increased compared to that of 10 years ago. However, it has been reported that 36.5% of affected patients have not received diabetic treatment because conventional anti-diabetic drugs are inconvenient to use and exhibit inadequate efficacy, a short duration of activity, and side effects such as hypoglycemia, weight gain, and digestive symptoms. Therefore, these drugs are associated with problems regarding safety and tolerability. In 2006, the US Food and Drug Administration approved the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin. DPP-4 inhibitors are a new class of anti-diabetic drugs that exhibit different mechanisms of action from conventional anti-diabetic drugs.

Sitagliptin binds to DPP-4 and prevents the breakdown of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [2]. Both GLP-1 and GIP are types of incretin hormones released by the intestines that stimulate insulin secretion from β cells [3] and suppress glucagon secretion [4]. GLP-1 and GIP are rapidly broken down by DPP-4 [5]. Incretin hormones depend on the level of blood glucose to stimulate insulin. DPP-4 inhibitors are associated with a lower incidence of hypoglycemia than conventional hypoglycemic drugs.

This study is a single-arm, prospective, multi-center trial conducted to evaluate the efficacy and safety of the DPP-4 inhibitor sitagliptin in clinical use. In this trial, we particularly focused on the effects of sitagliptin on quality of life (QOL).

Methods

Study design and protocol

The Institutional Review Board of Human Research at Saga University approved this study and informed consent was obtained from all participants. Patients with T2DM (age ≥ 20 years) with poor glycemic control profiles [HbA1c ≥ 6.2%, as evaluated according to the National Glycohemoglobin Standardization Program (NGSP)] in spite of receiving a medical diet, therapeutic exercise, and/or conventional anti-diabetic medications were recruited. The exclusion criteria were treatment with insulin, a history of severe diabetic ketoacidosis or coma, severe infection, perioperative state, severe trauma, pregnancy, breast-feeding, renal dysfunction (creatinine clearance < 30 ml/min or serum creatinine: male: ≥ 1.5 mg/dl, female: ≥ 1.3 mg/dl), a history of experiencing side effects to sitagliptin or other unsuitableness. For the participants, sitagliptin was given as either a new prescription, as an additional prescription to other conventional anti-diabetic agents, or replaced other anti-diabetic drugs.

The subjects received 50 mg sitagliptin, once a day for the first 3 months. After 3 months, the dose of sitagliptin was changed to between (and including) 25 mg/day and 100 mg/day, and other oral hypoglycemic drugs were added according to the discretion of each physician. The observation period was 12 months.

Clinical measurements

After 12 months of treatment with sitagliptin, changes in HbA_{1c}, fasting plasma glucose (FPG), blood pressure, body weight (BW), body mass index (BMI), total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), triglycerides (TG), 1.5-anhydro-D-glucitol (1.5-AG), microalbuminuria, and homeostasis model assessment analyses of beta cell

function (HOMA-β) and insulin resistance (HOMA-IR) were assessed. We also assessed changes in the subjects' quality of life (QOL) using the Euro QOL (EQ)-5 Dimensions (EQ-5D), the EQ Visual Analogue Scale (EQ-VAS), the Pittsburgh Sleep Quality Index (PSQI), and the Diabetes Symptomatic Score.

The EQ-5D is a generic instrument for measuring health-related QOL that has been developed and validated in a number of European countries [6,7]. The EQ-5D describes a patient's health status according to five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels that include no problems, some problems or severe problems. This yields 243 potential combinations of health states across the five dimensions. Dolan et al. [8] measured 42 of these health states in a representative sample of the United Kingdom general population using the Time Trade-Off method [9]. Based on these evaluations, the utility scores can be deduced by means of an additive function. The utility scores may vary between −0.59 (worst health) and 1.00 (perfect health). In addition to the five dimensions, the EuroQol consists of an EQ-VAS ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) [10]. The PSQI is a self-administered questionnaire used to assess subjective sleep quality during the previous month [11]. The self-rated items of the PSQI generate seven component scores (range of subscale scores: 0 to 3) for sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. The sum of these seven component scores yields one global score of subjective sleep quality (range: 0 to 21), with higher scores representing poorer subjective sleep quality. The psychometric properties of the PSQI have been confirmed in previous studies [11,12]. We have used 5.5 points as a cut-off in the Japanese version of the PSQI global score [6]. The Diabetes Symptomatic Score is a method for assessing QOL that was originally developed for the S-DOG trial. This score is calculated as the sum of the scores, graded 1 to 5, for 10 diabetes-related symptoms (Table 1).

Table 1 Checklist of diabetes symptomatic score

	Checklist
1	Are you often thirsty?
2	Do you produce urine frequently?
3	Are you worried about urinary smell?
4	Do you feel numbness of your extremities?
5	Do you have edema in your legs?
6	Do you have cramps in your legs?
7	Are you insensitive to the pain of a small wound or burn?
8	Do you have a feeling of listlessness?
9	Do you feel lightheaded?
10	Is your vision blurry? Is your eyesight getting worse?

Diabetes Symptomatic Score is used to measure the grade of ten diabetic symptoms. Patients with a high score have worsening of diabetic symptoms.
None: 0 point, Rare: 1 point, Sometimes: 2 points, Frequent: 3 points, Always: 4 points. Maximum: 40 points.

Statistics

Values are expressed as the mean ± SD. To compare changes in the values of HbA1c, FPG, BW, BMI, BP, lipids, 1.5AG, and HOMA from baseline to after 12 weeks of treatment, we used the paired *t*-test. To compare changes in the values of the EQ-5D, EQ-VAS, PSQI, and

Diabetes Symptomatic Score, we used the Wilcoxon signed-rank test. Values of $p < 0.05$ were considered to be statistically significant.

Results

Baseline characteristics

A total of 221 patients agreed to participate in this study. Of the 221 patients, 14 were excluded due to protocol violation. Among the 207 enrolled subjects, seven were excluded due to discontinuing sitagliptin within the first 3 months, and 12 were excluded because data acquisition to evaluate the efficacy of the drug failed. Therefore, sitagliptin efficacy over 3 months was evaluated in 188 subjects as efficacy population. The safety of sitagliptin over 12 months was also evaluated in the 207 enrolled subjects as safety population (Figure 1).

Figure 1 Study Enrollment.

Table 2 shows the clinical characteristics of the study subjects prior to the start of treatment with sitagliptin. The average age of the evaluated subjects was 66.9 years, 91 subjects (48%) were male, the mean duration of diabetes was 6.9 years and the mean HbA1c level was 7.65% at baseline.

Table 2 Baseline characteristics

	Enrolled subjects (n = 207)	Evaluated subjects (n = 188)
Age (years)	66.5 ± 12.8	66.9 ± 12.6
Gender	Male: 50% (n = 103), Female: 50% (n = 104)	Male: 48% (n = 91), Female: 52% (n = 97)
BMI	25.0 ± 4.4 kg/m^2	25.0 ± 4.4 kg/m^2
Waist circumference	89.4 ± 12.8 cm	89.0 ± 12.8 cm
Obesity (BMI > 25)	51%	50%
Duration of DM (years)	6.8 ± 6.5	6.9 ± 6.6
Smoking status	Smoker: 24% Past smoker: 13% Never: 63%	Smoker: 23% Past smoker: 13% Never: 63%
Alcohol consumption	Yes: 30%	Yes: 29%,
Complications	HT: 67%, DL: 55%, HUA: 7%, Arrhythmia: 5%, CKD 43%	HT: 65%, DL: 55%, HUA: 6%, Arrhythmia: 5%, CKD 43%
Use of sitagliptin	New: 35% Added: 45%, Changed: 20%	New: 35% Added 45%, Changed 20%
Combined drugs	SU: 49%, BG: 20%, TZD: 28%, Glinide: 2%, α-GI: 7%	SU: 48%, BG: 22%, TZD: 28%, Glinide: 2%, α-GI: 7%

BMI, Body mass index; DM, diabetes mellitus; HT, hypertension; DL, dyslipidemia; HUA, hyperuricemia; CKD, chronic kidney disease; SU, sulfonylurea; BG, biguanide; TZD, thiazolidinedione; α-GI, α-glucosidase inhibitor.

Effects of sitagliptin on glycemic control

Overall, HbA1c levels decreased in all of the 188 evaluated subjects after 3 months (7.65% ± 1.32% to 7.06% ± 1.07%, $p < 0.001$) and 12 months (7.05% ± 1.10%, $p < 0.001$) of sitagliptin treatment (Figure 2a). The HbA1c decreases per subgroup are described here.

Figure 2 Serial HbA1c changes in (a) all subjects, (b) BMI-based groups, (c) age-based groups, (d) HbA1c-based groups, and (e) fasting plasma glucose. HbA1c, hemoglobin A1c; BMI, body mass index. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, vs. baseline by paired t-test.

For the 66 subjects who received sitagliptin alone, the decreases were 7.44% ± 1.31% to 6.72% ± 0.82%, $p < 0.001$ at 3 months and 6.61% ± 0.82%, $p < 0.001$ at 12 months. Eighty-five subjects received sitagliptin along with other anti-diabetic agents, HbA1c level decreases were 7.86% ± 1.25% to 7.22% ± 1.18%, $p < 0.001$, 3 months and 7.32% ± 1.20%, $p < 0.001$, 12 months. In subjects with a BMI < 25 kg/m^2 ($n = 81$) and those with a BMI ≥ 25 kg/m^2 ($n = 80$), a decrease in HbA1c levels was observed after 12 months of sitagliptin treatment: 7.59% ± 1.16% to 7.06% ± 1.12%, $p < 0.001$ and 7.68% ± 1.47% to 7.05% ± 1.03%, $p < 0.001$, respectively (Figure 2b). By age group, HbA1c levels decreased as follows: in subjects < 65 years of age ($n = 65$), 8.00% ± 1.59% to 7.29% ± 1.23%, $p < 0.001$; those 65 to 74 years of age ($n = 46$), 7.61% ± 1.11% to 7.05% ± 0.99%, $p < 0.001$; and in those ≥ 75 years of age ($n = 51$), 7.21% ± 0.87% to 6.75% ± 0.96%, $p < 0.001$ (Figure 2c).

In each subgroup of baseline HbA1c level [<6.9% ($n = 56$), 6.9% ≤ baseline HbA1c < 8.4% ($n = 89$), and 8.4% ≤ baseline HbA1c ($n = 43$)], the HbA1c levels were decreased at 3 months (−0.19%, -0.43%, and −1.45%, respectively) (Figure 2d). FPG was also decreased after 3 months ($n = 84$, 145 ± 52 to 129 ± 43 mg/dl, $p < 0.001$) and 12 months of sitagliptin treatment ($n = 65$, to 129 ± 42 mg/dl, $p = 0.005$). The rate of glycemic control achieved (in accordance with the guidelines of the Japanese Diabetes Society) significantly increased (Figure 2e).

Effects of sitagliptin on blood pressure, lipid profiles and insulin resistance

BW and BMI decreased after 3 months of sitagliptin treatment (BW: 62.1 ± 14.1 to 61.5 ± 13.8 kg, $p = 0.003$, BMI: 25.0 ± 4.5 to 24.8 ± 4.5 kg/m^2, $p = 0.006$). At 12 months, these values had returned to baseline levels (BW: 62.0 ± 13.7 kg, $p = 0.800$, BMI: 25.1 ± 4.4 kg/m^2, $p = 0.560$) (Figure 3a, b). Systolic (SBP) and diastolic blood pressure (DBP) also decreased after 3 months (SBP: 135 ± 18 to 131 ± 17 mmHg, $p < 0.001$, DBP: 75 ± 12 to 71 ±11 mmHg, $p < 0.001$) (Figure 3c, d) as did serum levels of TC and TG (TC: 201 ± 40 to 191 ± 37 mg/dl, $p < 0.001$; TG: 161 ± 171 to 136 ± 126 mg/dl, $p = 0.003$) (Figure 3e). However, there was no change in the levels of 1.5 AG, HOMA-β, and HOMA-IR observed (Figure 3f, g).

Figure 3 Serial changes of (a) body weight, (b) BMI, (c) blood pressure, (d) lipid profiles including total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol, (e) 1.5 AG, and (f) HOMA-β and –IR. M, months; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; 1.5-AG, 1.5-Anhydro-D-glucitol; HOMA-β, homeostasis model assessment analyses of beta cell function; HOMA-IR, insulin resistance. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, vs. baseline by paired t-test.

Effects of sitagliptin on QOL

PSQI scores decreased after 12 months of sitagliptin treatment (4.1 ± 2.9 to 3.4 ± 2.5 points, $p = 0.007$) in all subjects (Figure 4a). In the subgroup of subjects with a PSQI score > 5.5 points, the scores significantly decreased both at 3 months (8.0 ± 1.8 to 6.5 ± 3.0 points, $p < 0.001$) and 12 months (to 6.2 ± 3.1 points, $p < 0.001$) after sitagliptin treatment. The Diabetes Symptomatic Scores also decreased at both 3 months (5.6 ± 5.71 to 4.4 ± 4.35, $p = 0.004$) and 12 months (to 3.7 ± 3.65, $p = 0.006$) (Figure 4b). Among the 10 diabetes symptomatic questions (Table 2), scores regarding urination ($p = 0.013$) and paresthesia ($p = 0.025$) were decreased at 12 months. In contrast, the EQ-5D and EQ-VAS scores did not change significantly (Figure 4c, d).

Figure 4 Effects of sitagliptin on QOL. (a) PSQI the Pittsburgh Sleep Quality Index, **(b)** the Diabetes Symptomatic Score, **(c)** Euro QOL (EQ)-5 Dimensions (EQ-5D), and **(d)** the EQ Visual Analogue Scale (EQ-VAS). *$p < 0.05$, **$p < 0.01$, **$p < 0.001$, vs. baseline by Wilcoxon signed-rank test.

Safety

Twenty-three (11%) of the 207 enrolled subjects suffered adverse events (AEs) (Table 3). Two subjects (0.96%) experienced direct sitagliptin-related AEs causing them to discontinue sitagliptin. One subject suffered from gastrointestinal (GI) symptoms, including vomiting, stomachaches, and constipation. The other subject experienced skin eruptions.

Table 3 Adverse events

Event	Number
Death (cause unknown)	1
Worsening of vomiting, stomachache, constipation	1
Loss of consciousness	1
Hypoglycemia	1
Intestinal tuberculosis, pneumonia	1
Stool abnormality	2
Acute myocardial infarction	1
Thrombocytopenia	1
Worsening of heart failure	1
New onset of dyslipidemia	3
Bleeding or ulcer of GI tract	2
Liver dysfunction	4
Elevation of CPK	2
Fever and poor physical health	1
Skin disease including eruption	2
Total number of incidents	24 in 23 subjects

GI, gastric intestinal; CPK, creatinine phosphokinase.
Liver dysfunction is defined as elevated (> 2.5 × the upper limit of normal) alanine aminotransferase or aspartate aminotransferase.
Elevation of CPK is defined as elevated > 2 × the upper limit of normal.

Three subjects (1.15%) developed AEs that were suspected to have a causal relationship with sitagliptin. Hypoglycemia and loss of consciousness occurred in two subjects (0.96%). Pneumonia/intestinal tuberculosis and stool abnormality were recognized in one subject.

Discussion

Efficacy and safety of sitagliptin

In our study, the HbA1c and FPG levels were reduced at 3 months (HbA1c: 0.59%, FPG: 15.5 mg/dl reduction) and at 12 months (HbA1c: 0.65%, FPG: 20.2 mg/dl reduction) after treatment with sitagliptin at a dose of 25 to 100 mg/day. Our results are similar to those of previous studies reported in the US [13] and Japan [14]. Nathan et al. [15] reported that the expected percentage decrease in HbA1c levels is 1.0% to 2.0% with metformin monotherapy, 1.0% to 2.0% with sulfonylureas (SUs), 0.5% to 1.0% with glinides, 0.5% to 0.8% with α-glucosidase inhibitors (α-GI), 0.5% to 1.4% with thiazolidinediones (TZD) and 0.5% to 0.8% with DPP-4 inhibitors. Monotherapy with metformin or SU exhibits a stronger reduction of HbA1c levels than a DPP-4 inhibitor alone. However, metformin is associated with side effects such as GI symptoms and is contraindicated in patients with renal insufficiency. The major side effects of SUs are hypoglycemia and weight gain. In patients receiving treatment with SUs, the incidence of hypoglycemic episodes has been reported to be 17.6% per year [16]. Side effects appear to be more frequently seen with metformin or SUs than with sitagliptin. The most common side effects of TZD are weight gain and fluid retention along with peripheral edema and an increased risk of congestive heart failure [14,17]. In our study, body weight and BMI decreased and there was no evidence of heart failure during sitagliptin treatment. While metformin, glinides, and α-GIs are required to be taken three times daily, sitagliptin is only taken once daily. Therefore, sitagliptin should be associated with higher adherence compared to metformin, glinides, and α-GIs.

In our study, AEs after sitagliptin treatment were seen in 23 (11%) of the 207 enrolled subjects. In particular, direct sitagliptin-related AEs such as hypoglycemia and loss of consciousness were observed in only two subjects (0.96%). A previous pooled analysis [18] reported that the overall incidence of AEs was similar between sitagliptin (100 mg/day) and other diabetic-comparator agents (except for other DPP-4 inhibitors), including placebos, pioglitazone, metformin, sulfonylureas, sulfonylureas + metformin, and metformin + rosiglitazone (overall side effects: 63.0% vs. 62.8%, hypoglycemia: 3.4% vs. 10.9%). Therefore, incidence of AEs in this study, including hypoglycemia, was lower than that reported in the pooled analysis. This discrepancy appears to be related to differences in dosage. In our study, subjects received doses between 50 and 100 mg/day of sitagliptin with only 24 (11.6%) receiving the highest dose of 100 mg. In the pooled analysis, all subjects received 100 mg/day. In previous studies, sitagliptin did not increase cardiovascular risk in patients with T2DM [19] and sitagliptin reduced postprandial glucose fluctuation and stabilized blood glucose levels effectively in combination with miglitol through continuous glucose monitoring (CGM) [20]. On the other hand, vildagliptin twice a day calmed down the postprandial glucose level as compared to sitagliptin by CGM [21]. The results of this study show that sitagliptin was safe and effective in this population; however, further studies are needed to evaluate the comparison of each DPP-4 inhibitor.

Effects of DPP-4 inhibitors on blood pressure and lipid profiles

Systolic and diastolic blood pressure decreased after 3 months of treatment with sitagliptin. The active isoforms of GLP-1 include GLP-1(7–36) amide and glycine-extended GLP-1(7–37) [22]. GLP-1(7–36) exhibits vascular actions via GLP-1 receptor signaling [23]. Additionally, GLP-1(9–36), a metabolite of GLP-1 (7–36), has vasodilator effects independent of the GLP-1 receptor in a nitrous oxide/cyclic guanosine monophosphate

(cGMP)-dependent manner [23]. DPP-4 inhibitors increase the levels of GLP-1, possibly leading to vasodilatation and blood pressure reduction. In addition, Gutzwiller et al. [24] showed that a pharmacological dose of GLP-1 increases sodium excretion in the proximal renal tubule in obese and insulin-resistant men. Therefore, GLP-1-induced increases in urinary sodium excretion might also contribute to blood pressure reduction after sitagliptin treatment.

In our study, serum levels of TC and TG also decreased after 3 months of treatment with sitagliptin. Qin et al. [25] showed that GLP-1 decreases the intestinal lymph flow and reduces triglyceride absorption and apo B and apo A-IV production in rats. Vildagliptin, another DPP-4 inhibitor, has been shown to reduce the hepatic expression of genes important for cholesterol synthesis, including phosphomevalonate kinase and mevalonate decarboxylase in wild-type mice [26]. Prolonged DPP-4 inhibition modulates the expression of genes important for fatty acid oxidation, including acyl-coenzyme dehydrogenase medium chain and Acyl-CoA synthetase. In addition, DPP-4 inhibitors reduce the levels of hepatic mRNA transcripts for acetyl coenzyme A acyltransferase 1 and carnitine palmitoyltransferase 1, independent of incretin receptor actions [26]. Because these modulations depend on and/or are independent of incretin receptor actions, sitagliptin may have the ability to decrease the levels of TC and TG.

QOL and diabetes

QOL, whose evaluation is the major goal of our study, is improved after sitagliptin treatment. The sleep quality and PSQI scores decreased after 12 months of treatment with sitagliptin. Particularly, in the subgroup of poor sleepers with PSQI scores above 5.5 points, the scores were significantly reduced not only after 12 months of treatment, but also after 3 months of treatment. Sleep disorders are common in patients with diabetes. Sleep debts decrease carbohydrate tolerance and insulin resistance and increase sympathetic tone, cortisol levels, and nocturnal catecholamine levels [27,28]. Improving sleep disorders with sitagliptin therapy might improve these states, possibly preventing cardiovascular disease in patients with T2DM.

Our own QOL assessment scores for diabetes, the Diabetes Symptomatic Scores, also decreased after sitagliptin treatment. Particularly, the scores regarding urinary frequency and paresthesia of the extremities significantly decreased 12 months after sitagliptin treatment. Urinary frequency, which often appears in T2DM patients, is caused by hyperglycemia-induced polyposia and/or neurogenic bladder. We suppose that polypepsia and polyposia are improved by reductions in FPG after sitagliptin treatment, thereby decreasing the urinary frequency. Paresthesia of the extremities is characterized by striking atrophy and/or loss of myelinated and unmyelinated fibers [29]. Hyperglycemia leads to the development of macrovascular and endoneural microvascular disease in diabetic nerve tissue via several mechanisms, including the polyol pathway. We suppose that both reductions of FPG and vasodilatation, a direct action of DPP-4 inhibitors, leads to improved nerve blood flow and nerve fiber damage in patients with diabetic neuropathy.

The EQ-5D score represents an independent predictor of mortality and future cardiovascular events in patients with T2DM [30]. In our study, however, the EQ-5D scores did not change after treatment with sitagliptin. Because the EQ scores before sitagliptin treatment were as high as 0.84 points, which is close to the cut-off point for a healthy state, they might not change significantly after sitagliptin treatment.

Limitations/clinical implications

This was a preliminary, single-arm study of a small number of subjects. A large-scale, randomized study conducted over a longer period is needed in the future. However, we found that sitagliptin exerts significant effects, not only on glycemic control, but also on improving QOL, blood pressure, and lipid profiles in subjects with T2DM. Although our results showed efficacy of the drug, we could not precisely evaluate subjects' adherence to their dosing regimens. As far as we know, there is no reported data on patient adherence to DPP-4 inhibitor treatment regimes. However, adherence to a drug taken once a day is supposed to be higher than conventional drugs taken two or three times a day, which may affect efficacy. In this study, the subjects whose rates of adherence were less than 75% were to be reported as "poor adherence"; all evaluated patients had good adherence to the dosing regimen.

In this study, treatment with sitagliptin achieved adequate reductions in the levels of HbA1c and significant increases in the rate of accomplishment of glycemic control. The use of sitagliptin was shown to be safe and improved the PSQI and Diabetes Symptomatic scores.

Conclusions

The clinical use of the DPP-4 inhibitor sitagliptin has beneficial effects not only for glucose control, but also for improving blood pressure, lipid profiles, and QOL regarding sleep quality and diabetes symptoms in addition to being safe with a high rate of adherence to treatment.

Abbreviations

1.5-AG, 1.5-anhydro-D-glucitol; α-GI, α-glucosidase inhibitors; BMI, Body mass index; BW, Body weight; CGM, Continuous glucose monitoring; DPP-4, Dipeptidyl peptidase-4; EQ-5D, Euro QOL-5 dimensions; EQ-VAS, EQ-visual analogue scale; FPG, Fasting plasma glucose; GI, Gastrointestinal; GLP-1, Glucagon-like peptide-1; GIP, Glucose-dependent insulinotropic polypeptide; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; NGSP, National Glycohemoglobin Standardization Program; PSQI, Pittsburgh Sleep Quality Index; QOL, Quality of life; TC, Total cholesterol; TG, Triglycerides; T2DM, Type 2 diabetes mellitus; TZD, Thiazolidinediones; SUs, Sulfonylureas

Competing interest

The authors declare that they have no conflicts of interest.

Authors' contributions

YS, JO, MS, TI, HI, KK, AH, and KN were deeply involved in the conception and design of the study. JO was responsible for the analyses of the data. YS drafted the manuscript. All authors read and approved the final manuscript.

Authors' information

S-DOG investigators: Saga Challenge Anti-Diabetes Observational Study for Sitagliptin (S-DOG): Shigeki Gondoh, Haruda Yoshio, Minekazu Hashimoto, Hideo Ikeda, Takahiko Imamura, Taketo Iwamoto, Ryota Kaihara, Hideyuki Kamachi, Yoshiyuki Koga, Shigetaka Kuroki, Kazuo Matsunaga, Tadahiro Mizukami, Taizo Minami, Hiroshi Nakanishi, Hirofumi Naito, Masanori Nakao, Masayuki Nakayama, Shinichi Nakayama, Akira Takahashi, Norio Takeda, Otohisa Tajiri, Satoshi Tamesue, Toshifumi Uchida, Yasufumi Uchida, Tetsushi Wakiyama, Tsuneko Yamaguchi, Kenichi Yamamoto and principal investigator Koichi Node.

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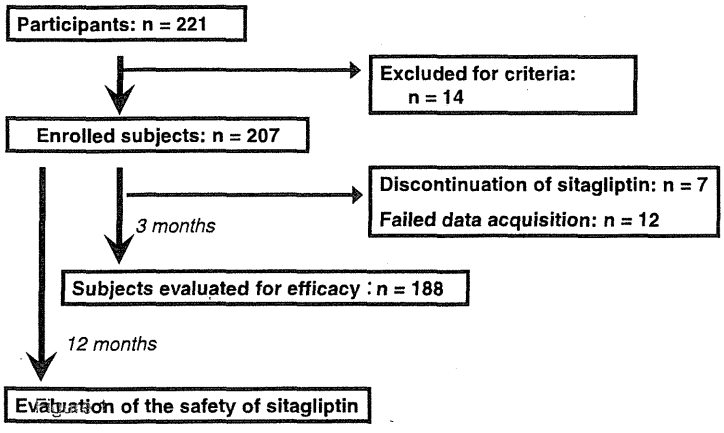
Participants: n = 221
Excluded for criteria:
n = 14
Enrolled subjects: n = 207
Discontinuation of sitagliptin: n = 7
Failed data acquisition: n = 12
3 months
Subjects evaluated for efficacy : n = 188
12 months
Evaluation of the safety of sitagliptin

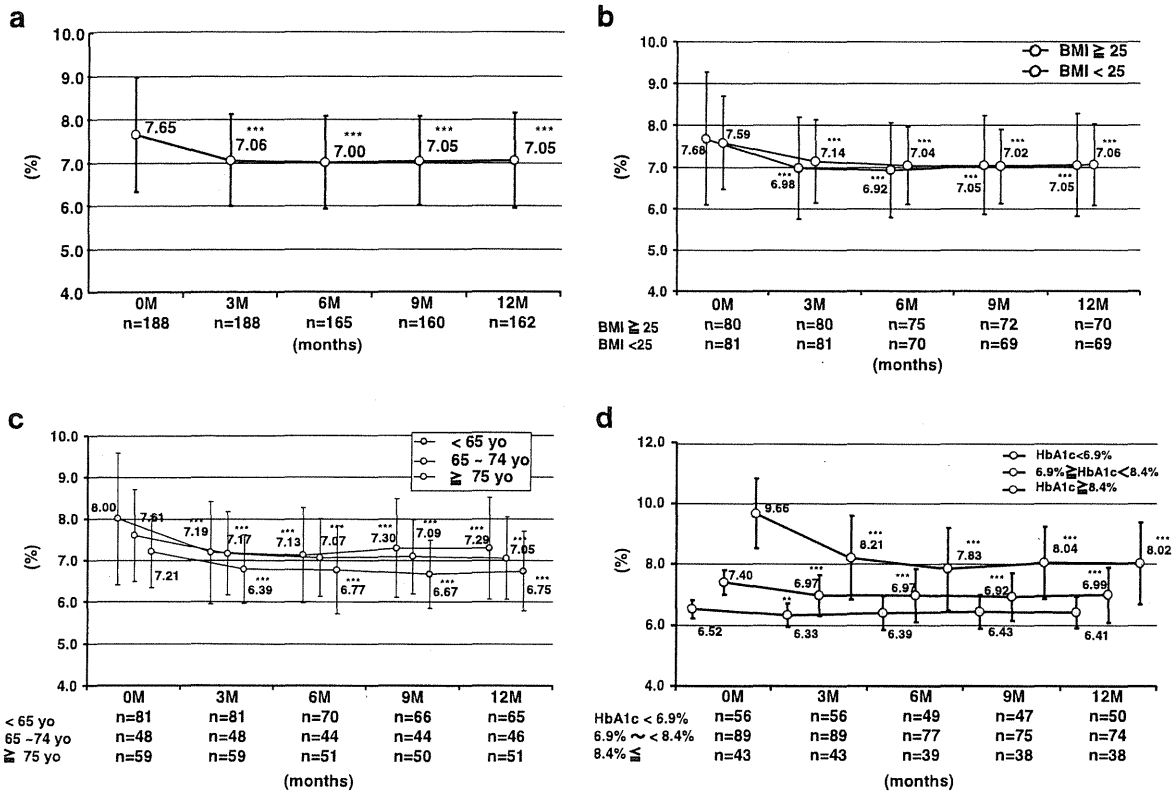
a
10.0
9.0
8.0
7.0
6.0
5.0
4.0
(%)
7.65
7.06
7.00
7.05
7.05
0M n=188
3M n=188
6M n=165
9M n=160
12M n=162
(months)
b
BMI ≧ 25
BMI < 25
7.68
7.59
6.98
7.14
6.92
7.04
7.05
7.02
7.05
7.06
0M 3M 6M 9M 12M
BMI ≧25 n=80 n=80 n=75 n=72 n=70
BMI <25 n=81 n=81 n=70 n=69 n=69
(months)
c
< 65 yo
65 ~ 74 yo
≧ 75 yo
8.00
7.61
7.21
7.19
7.17
6.39
7.13
7.07
6.77
7.30
7.09
6.67
7.29
7.05
6.75
0M 3M 6M 9M 12M
< 65 yo n=81 n=81 n=70 n=66 n=65
65 ~74 yo n=48 n=48 n=44 n=44 n=46
≧ 75 yo n=59 n=59 n=51 n=50 n=51
(months)
d
12.0
10.0
8.0
6.0
4.0
HbA1c<6.9%
6.9%≦HbA1c<8.4%
HbA1c≧8.4%
9.66
7.40
6.52
8.21
6.97
6.33
7.83
6.97
6.39
8.04
6.92
6.43
8.02
6.99
6.41
0M 3M 6M 9M 12M
HbA1c < 6.9% n=56 n=56 n=49 n=47 n=50
6.9% ~ < 8.4% n=89 n=89 n=77 n=75 n=74
8.4% ≦ n=43 n=43 n=39 n=38 n=38
(months)
e
250
200
150
100
50
0
(mg/dL)
145
129
125
132
129
0M n=84
3M n=84
6M n=62
9M n=64
12M n=65
(months)

Figure 2

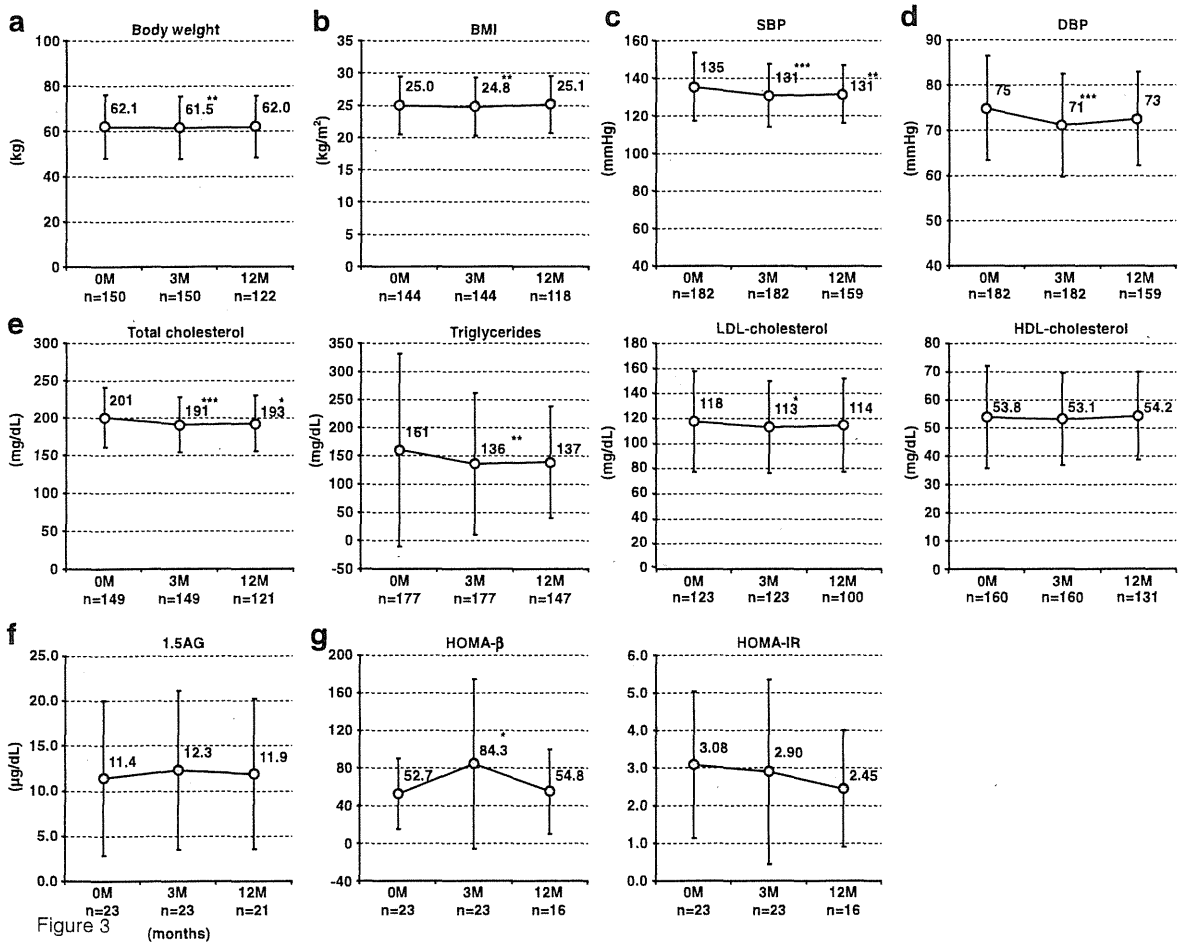
a
Body weight
(kg)
62.1
61.5**
62.0
0M n=150
3M n=150
12M n=122
b
BMI
(kg/m²)
25.0
24.8**
25.1
0M n=144
3M n=144
12M n=118
c
SBP
(mmHg)
135
131***
131**
0M n=182
3M n=182
12M n=159
d
DBP
(mmHg)
75
71***
73
0M n=182
3M n=182
12M n=159
e
Total cholesterol
(mg/dL)
201
191***
193*
0M n=149
3M n=149
12M n=121
Triglycerides
(mg/dL)
151
136**
137
0M n=177
3M n=177
12M n=147
LDL-cholesterol
(mg/dL)
118
113*
114
0M n=123
3M n=123
12M n=100
HDL-cholesterol
(mg/dL)
53.8
53.1
54.2
0M n=160
3M n=160
12M n=131
f
1.5AG
(μg/dL)
11.4
12.3
11.9
0M n=23
3M n=23
12M n=21
(months)
g
HOMA-β
52.7
84.3*
54.8
0M n=23
3M n=23
12M n=16
HOMA-IR
3.08
2.90
2.45
0M n=23
3M n=23
12M n=16

Figure 3

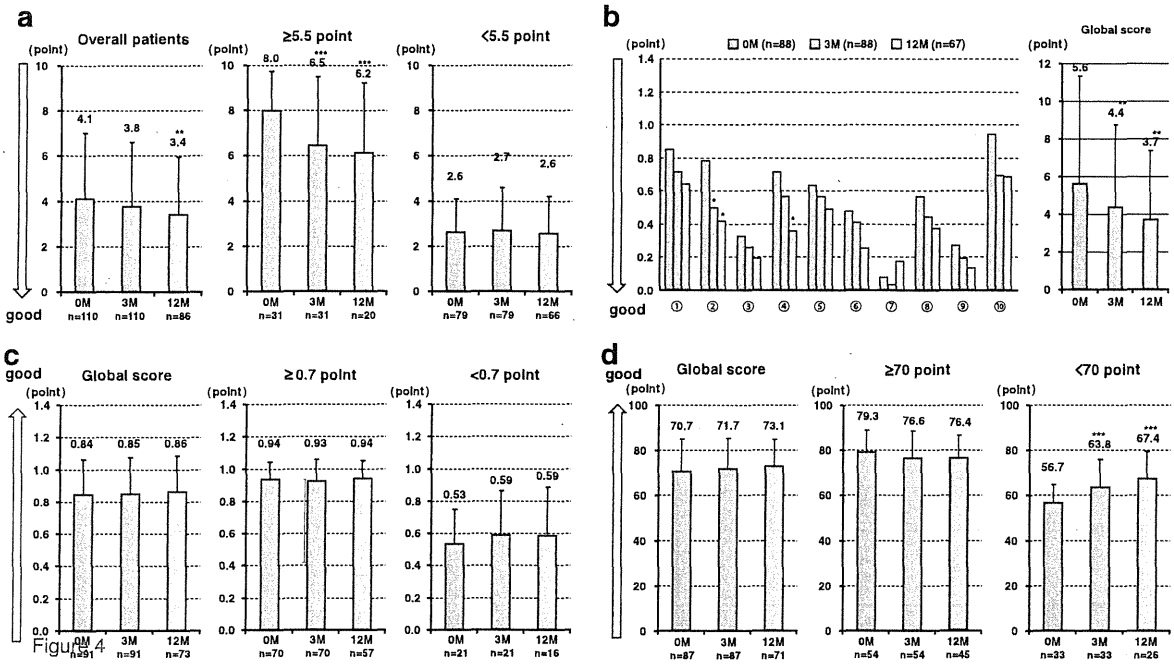
a
Overall patients
≥5.5 point
<5.5 point
(point)
good
4.1
3.8
3.4
8.0
6.5
6.2
2.6
2.7
2.6
0M n=110
3M n=110
12M n=86
0M n=31
3M n=31
12M n=20
0M n=79
3M n=79
12M n=66
b
0M (n=88)
3M (n=88)
12M (n=67)
Global score
5.6
4.4
3.7
c
Global score
≥0.7 point
<0.7 point
0.84
0.85
0.86
0.94
0.93
0.94
0.53
0.59
0.59
0M n=91
3M n=91
12M n=73
0M n=70
3M n=70
12M n=57
0M n=21
3M n=21
12M n=16
d
Global score
≥70 point
<70 point
70.7
71.7
73.1
79.3
76.6
76.4
56.7
63.8
67.4
0M n=87
3M n=87
12M n=71
0M n=54
3M n=54
12M n=45
0M n=33
3M n=33
12M n=26

Figure 4

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LATE BREAKING CLINICAL TRIAL (JCS 2013)

Effects of Pitavastatin in Japanese Patients With Chronic Heart Failure

– The Pitavastatin Heart Failure Study (PEARL Study) –

Hiroyuki Takano, MD; Hiroshi Mizuma, MD; Yoichi Kuwabara, MD; Yasunori Sato, PhD; Satoshi Shindo, MD; Norihiko Kotooka, MD; Daisuke Fujimatsu, MD; Yoshio Kobayashi, MD; Teruo Inoue, MD; Koichi Node, MD; Issei Komuro, MD
on behalf of the PEARL Study Investigators

Background: Recent clinical trials using rosuvastatin, a hydrophilic statin, did not show beneficial effects on cardiovascular events in patients with heart failure. We examined the cardioprotective effects of pitavastatin, a lipophilic statin, on Japanese patients with chronic heart failure (CHF).

Methods and Results: A total of 574 Japanese patients with CHF were randomly assigned to the pitavastatin group (n=288) or the control group (n=286). There was no significant difference between the 2 groups for the primary outcome, which was a composite of cardiac death and hospitalization for worsening HF (adjusted hazard ratio (aHR): 0.922, 95% confidence interval (CI): 0.632–1.345, P=0.672). A strongly significant statistical interaction between the effect of pitavastatin and left ventricular ejection fraction (LVEF) was found (P=0.004). In patients with LVEF ≥30%, a significant reduction in the primary outcome (aHR: 0.525, 95% CI: 0.308–0.896, P=0.018) was observed in the pitavastatin group. Pitavastatin did not show any effects on the primary outcome (aHR: 1.582, 95% CI: 0.890–2.813, P=0.118) in the subgroup of patients with LVEF <30%.

Conclusions: Pitavastatin did not reduce cardiac death or hospitalization for worsening HF in Japanese patients with CHF. (UMIN-ID: UMINC000000428). (*Circ J* 2013; **77:** 917–925)

Key Words: Heart failure; Hypercholesterolemia; Pitavastatin; Randomized controlled trial

The number of patients with heart failure (HF) has been increasing and it is becoming a major public health problem. Although there has been considerable progress in the treatment of chronic HF (CHF) with the advent of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, and aldosterone antagonists, the number of deaths from HF has been increasing steadily and further strategies are needed.

Editorial p 895

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (ie, statins) are the most widely used agents for the treatment of hypercholesterolemia. Clinical trials have shown that treatment with statins significantly reduces the incidence of cardiovascular events in patients with coronary artery disease (CAD).[1–3] In addition to their lipid-lowering action, statins have also been reported to have various pleiotropic effects, such as antiinflammatory effects, antioxidant effects, angiogenic effects, protective effects on endothelial cells, and inhibitory effects on neurohormonal activation.[4] It has been demonstrated that statins inhibit the progression of HF in animal models of nonischemic HF.[5,6] These effects of statins suggest a potential to ameliorate components of the

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Department of Molecular Cardiovascular Pharmacology, Graduate School of Pharmaceutical Sciences, Chiba University, Chiba (H.T.); Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba (H.M., Y. Kuwabara, S.S., Y. Kobayashi); Clinical Research Center, Chiba University Hospital, Chiba (Y.S.); Department of Cardiovascular Medicine, Saga University, Saga (N.K., D.F., K.N.); Department of Cardiovascular Medicine, Dokkyo Medical University, Mibu (T.I.); Department of Cardiovascular Medicine, The University of Tokyo Graduate School of Medicine, Tokyo (I.K.); and Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka (I.K.), Japan

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Mailing address: Issei Komuro, MD, Department of Cardiovascular Medicine, The University of Tokyo Graduate School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: komuro-tky@umin.ac.jp

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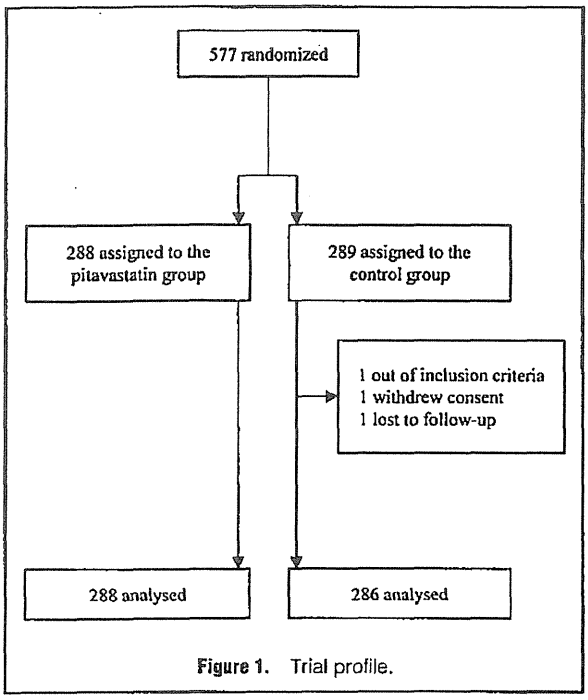

Figure 1. Trial profile.

complex pathophysiology of HF and a promising treatment for CHF in the future.

Many observational studies and retrospective analyses have suggested that treatment with statins decreases the incidence of HF in patients with CAD and reduces the mortality of patients with CHF.[7–9] Prospective trials have also confirmed the beneficial effects of statins on HF.[10–12] On the other hand, 2 recent well-controlled randomized clinical trials have shown that statin treatment has no effect on the clinical outcomes of patients with CHF.[13,14] So, it remains unclear whether treatment of patients with CHF with statins will show the same results in different studies in relation to the type of statin used, characteristics of the patients, severity of HF, and the endpoints examined.

Pitavastatin is a lipophilic statin and has longer-acting effects on decreasing low-density lipoprotein (LDL) cholesterol and increasing high-density lipoprotein (HDL) cholesterol. Pitavastatin also has high bioavailability and is minimally metabolized by the cytochrome P450 system.[15,16] The Pitavastatin Heart Failure (PEARL) study was designed to evaluate the beneficial effects of pitavastatin on the incidence of cardiac death and hospitalization for worsening HF in Japanese patients with CHF.[17]

Methods

Study Design and Patients

The rationale and design of the PEARL study (UMIN-ID: UMINC000000428) have been previously described in detail.[17] It was a multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE) trial carried out in 116 Japanese institutes. The trial was approved by each center's ethics committee and all patients provided written informed consent. Eligibility criteria for enrollment were: age 20–79 years; New York Heart Association (NYHA) functional class II or III; left ventricular ejection fraction (LVEF) as measured by echocardiography ≤45%; stable NYHA class for 2 or more weeks prior to study randomization; mild hypercholesterolemia (serum total cholesterol level ≤250 mg/dl and/or serum LDL-cholesterol level ≤170 mg/dl); written informed consent of the patient. The exclusion criteria included: receiving treatment with a statin prior to randomization; history of acute myocardial infarction within 3 months prior to the randomization; percutaneous coronary intervention (PCI), coronary artery bypass grafting, or cardiac resynchronization therapy-pacemaker or -defibrillator implantation performed within 3 months prior to the randomization; malignancy; serious renal or hepatic dysfunction; collagen disease; pregnancy or possible pregnancy; and lack of informed consent.

The eligible patients were randomly assigned to either the pitavastatin group (2 mg daily) or the control group (no statin) at the PEARL data center using a minimization method[18] with biased-coin assignment balancing on age (<50 years or ≥50 years), sex, serum total cholesterol level (<230 mg/dl or ≥230 mg/dl), LVEF (<30% or ≥30%), history of ischemic heart disease, and history of hospitalization for HF. If any patients in the control group needed further reduction of the serum total cholesterol level, lipid-lowering agents other than statins could be administered.

Study Outcomes

The primary outcome was a composite of cardiac death and hospitalization for worsening HF (hospitalization and clinical symptoms including dyspnea, shortness of breath, and peripheral edema, together with LV dysfunction by echocardiography according to AHA/ACC guidelines). For all patients, the first of these events was noted as the primary outcome. The secondary outcomes were all-cause death, cardiac death, hospitalization for worsening HF, myocardial infarction (hospitalization, chest pain, ECG-changes, and biomarkers of myocardial infarction), unstable angina (hospitalization and diagnosed by both ECG-changes corresponding with chest symptoms and coronary angiography showing >75% stenosis according to AHA/ACC guidelines), stroke (hospitalization and diagnosed by CT and/or MRI), PCI, and surgical therapy for worsening HF. Death was classified as cardiac unless a definite non-cardiovascular reason was identified. All outcomes recorded in this study were adjudicated blindly by an independent endpoint committee (**Appendix S1**) on the basis of prespecified definitions and procedures.

Statistical Analysis

The sample size calculation has been previously described in detail.[17] Our trial required 470 patients with a primary outcome occurring within 48 months to achieve 80% power to detect 43% relative reduction in the risk of the primary outcome in the pitavastatin group as compared with the control group (with a 2-sided α of 0.05) on the condition of an expected mortality rate at 24 months of 20% in the control group. Efficacy was evaluated in 2 interim analyses performed by an independent data and safety monitoring committee at the last patient registration and 1 year after the completion of enrollment. Significance was evaluated using the method of Lan and DeMets and the O'Brien-Fleming boundary (the stopping boundary, P≤0.000011 at the first interim analysis, P≤0.0089 at the second interim analysis, and P≤0.041 at the final analysis).

Comparability of baseline characteristics between the 2 groups was assessed by 2-sample t-test with equal variance or the Mann-Whitney U test for continuous variables, and Fisher's exact test for categorical variables. The analyses of the adju-

Table 1. Baseline Characteristics of the Patients

	Control (n=286)	Pitavastatin (n=288)	P-value
Age			
Age (years)	62.2±12.0	62.9±11.7	0.47
Age ≥50 years, n (%)	246 (86.0)	249 (86.5)	0.87
Female, n (%)	51 (17.8)	55 (19.1)	0.69
NYHA functional class, n (%)			0.50
II	259 (90.6)	256 (88.9)	
III	27 (9.4)	32 (11.1)	
LVEF (%)	34.0±7.7	33.9±8.9	0.88
LVEF ≥30%, no. (%)	206 (72.0)	207 (71.9)	0.96
Blood pressure (mmHg)			
Systolic	118.4±17.7	120.3±18.0	0.20
Diastolic	71.3±11.2	72.4±11.0	0.23
Heart rate (beats/min)	72.6±11.4	73.2±13.0	0.64
HF cause, n (%)			0.80
IHD	80 (28.0)	77 (26.7)	
DCM	149 (52.1)	161 (55.9)	
Hypertensive heart disease	11 (3.8)	10 (3.5)	
Valvular disease	12 (4.2)	15 (5.2)	
Others	34 (11.9)	25 (8.7)	
Medical treatment, n (%)			
Digitalis	72 (25.2)	71 (24.7)	0.86
β-blockers	204 (71.3)	212 (73.6)	0.58
Diuretic drugs	218 (76.2)	211 (73.3)	0.37
ACE inhibitors or ARBs	235 (82.2)	247 (85.8)	0.21
Calcium channel blockers	49 (17.1)	42 (14.6)	0.39
Anticoagulants	132 (46.2)	117 (40.6)	0.18
Antiplatelet agent	128 (44.8)	121 (42.0)	0.43
Medical history, n (%)			
Hospitalization for HF			0.90
At least 2 months before	131 (45.8)	127 (44.1)	
Within 2 months	47 (16.4)	50 (17.4)	
MI	73 (25.5)	71 (24.7)	0.80
CABG or PCI	56 (19.6)	60 (20.8)	0.70
Hypertension	129 (45.1)	131 (45.5)	0.92
Diabetes mellitus	79 (27.6)	78 (27.1)	0.88
Stroke	24 (8.4)	15 (5.2)	0.12
Laboratory measurements			
Total cholesterol (mg/dl)	201.2±32.6	203.2±32.2	0.45
LDL-cholesterol (mg/dl)	125.5±32.7	125.2±28.1	0.93
HDL-cholesterol (mg/dl)	50.8±15.1	50.7±14.5	0.92
hsCRP (ng/ml)			
Median	839.0	834.0	0.85
Interquartile range	394.0–2,300.0	391.0–2,535.0	

These data are the number of patients (%) or mean (SD).
NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; IHD, ischemic heart disease; DCM, dilated cardiomyopathy; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

dicated primary and secondary outcomes were conducted on data from all patients who had undergone randomization, according to the intention-to-treat principle, with the use of Kaplan-Meier estimates and Cox proportional-hazards models. Hazard ratio, 95% confidence interval (CI), and P value were calculated with the use of models adjusted for the following prespecified baseline prognostic factors: age, sex, serum total cholesterol level, LVEF, history of ischemic heart disease, and history of hospitalization for HF. Sensitivity analyses were also performed by means of unadjusted Cox models.

The consistency of the treatment effect was assessed among 19 prespecified subgroups. The effect in each subgroup was analyzed with a Cox proportional-hazards model without adjustment for covariates. The interaction between treatment and subgroup was evaluated by Cox proportional-hazards model with terms for treatment, subgroup, and their interaction.