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ORIGINAL ARTICLE

Linagliptin monotherapy provides superior glycaemic control versus placebo or voglibose with comparable safety in Japanese patients with type 2 diabetes: a randomized, placebo and active comparator-controlled, double-blind study

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Aims: To evaluate the efficacy and safety of linagliptin 5 and 10 mg vs. placebo and voglibose in Japanese patients with type 2 diabetes mellitus (T2DM).

Methods: This study enrolled patients with inadequately controlled T2DM who were previously treated with one or two oral antidiabetics or were drug naïve. After a 2 to 4-week washout and placebo run-in, 561 patients were randomized (2 : 2 : 2 : 1) to double-blind treatment with linagliptin 5 or 10 mg qd, voglibose 0.2 mg tid or placebo. The primary endpoint was the change from baseline in haemoglobin A1c (HbA1c) with linagliptin vs. placebo after 12 weeks and vs. voglibose after 26 weeks.

Results: Baseline characteristics were well balanced across treatment groups (overall mean HbA1c was 8.01%). The adjusted mean (95% confidence interval) treatment differences at week 12 were −0.87% (−1.04, −0.70; $p < 0.0001$) and −0.88% (−1.05, −0.71; $p < 0.0001$) for linagliptin 5 and 10 mg vs. placebo and at week 26 were −0.32% (−0.49, −0.15; $p = 0.0003$) and −0.39% (−0.56, −0.21; $p < 0.0001$) for linagliptin 5 and 10 mg vs. voglibose. At week 12, mean HbA1c was 7.58, 7.48 and 8.34% in patients receiving linagliptin 5 mg, linagliptin 10 mg and placebo, respectively. At week 26, mean HbA1c was 7.63% with linagliptin 5 mg, 7.50% with linagliptin 10 mg and 7.91% with voglibose. Drug-related adverse event rates were comparable across treatment groups over 12 weeks (9.4% linagliptin 5 mg, 8.8% linagliptin 10 mg and 10.0% placebo) and 26 weeks (11.3% linagliptin 5 mg, 10.6% linagliptin 10 mg and 18.5% voglibose). There were no documented cases of hypoglycaemia.

Conclusions: Linagliptin showed superior glucose-lowering efficacy and comparable safety and tolerability to both placebo and voglibose in Japanese patients with T2DM.

Keywords: α-glucosidase inhibitor, DPP-4 inhibitor, glycaemic control, incretin therapy

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Introduction

An estimated 9 million Japanese individuals suffer from diabetes [1], an increase in prevalence that underlines the need for therapeutic strategies to control this disease in Japan. Deterioration of glycaemic control over time, despite treatment, is characteristic of type 2 diabetes mellitus (T2DM) [2]. In addition to the natural progression of the disease, long-term glycaemic control is often not achieved or not maintained with many oral antidiabetic drugs (OADs) because of limitations to their use, such as treatment-limiting side effects including hypoglycaemia, gastrointestinal (GI) side effects, oedema and weight gain [3], or dose restrictions in patients with declining renal function. Importantly, renal impairment may occur in a large proportion of Japanese T2DM patients, as it has been estimated that ~30% have albuminuria (a condition that often precedes renal impairment and eventually renal failure) [4] and ~44% with early-onset T2DM develop diabetic nephropathy over 30 years [5]. Therefore, new OADs are needed that are effective and safe, can be used in patients who are at risk from or already have renal disease, and show minimal propensity to elicit hypoglycaemia or weight gain.

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Dipeptidyl peptidase (DPP)-4 inhibitors are the most recently developed class of OADs. DPP-4 inhibitors have a unique mechanism of action that increases endogenous glucagon-like peptide-1 levels and consequently promotes glucose-dependent insulin secretion via pancreatic β-cells, reduces glucagon secretion via α-cells, suppresses appetite and delays gastric emptying [6]. These actions reduce hyperglycaemia with minimal risk of hypoglycaemia, no weight gain and may reduce metabolic demands on pancreatic β-cells [7,8].

Linagliptin is a new DPP-4 inhibitor with a xanthine-based structure that is primarily excreted via bile and gut [9], a route of elimination that allows it to be used without dose adjustment in patients with declining renal function [10], unlike other DPP-4 inhibitors. Owing to its favourable pharmacokinetic and pharmacodynamic properties, there are no requirements for adjustment of linagliptin dose in any patient population [11].

Early clinical studies in Caucasian patients demonstrated linagliptin to have suitable pharmacological properties for once-daily oral administration, with similar tolerability to placebo [12–14]. Similar pharmacokinetics, pharmacodynamics and tolerability with all linagliptin doses tested have also been shown in early clinical studies in Japanese individuals [15,16]. Data from Phase II studies on effects on hyperglycaemia and the biomarker of plasma DPP-4 inhibition established linagliptin 5 mg daily as the optimal therapeutic dosage as monotherapy or as add-on to metformin in Caucasian patients [13,14]. Subsequently, several large international Phase III studies, which enrolled many participants from Asian countries including Japan, demonstrated clinically meaningful improvements in glycaemic control, enhanced β-cell function and a good safety profile with linagliptin 5 mg as monotherapy or in combination with other OADs [17–20]. Based on these data, linagliptin was recently licensed for treatment of T2DM in the USA in May 2011, in Japan in July 2011 and in Europe in August 2011.

It is important to validate the therapeutic effects and optimal dose of linagliptin in dedicated studies in Japanese patients with T2DM. Equally important is to compare the efficacy and safety of linagliptin with OADs commonly used in Japanese patients with T2DM to determine if linagliptin represents a therapeutic advance for this patient population.

α-glucosidase inhibitors are OADs with a different mechanism of action to the insulin sensitizers and secretagogues [21]. These compounds inhibit absorption of dietary carbohydrate in the GI tract, which provides postprandial anti-hyperglycaemic effects without substantial hypoglycaemia or weight gain. However, the use of α-glucosidase inhibitors is often limited by GI side effects such as flatulence, abdominal distension and diarrhoea. Voglibose is an α-glucosidase inhibitor that has demonstrated anti-hyperglycaemic effects in Japanese patients when administered three-times daily with food [22,23]. Voglibose is currently widely prescribed in Japan for treatment of T2DM.

This randomized, double-blind, parallel-group Phase IIb/III trial was conducted to examine the efficacy and safety of linagliptin 5 or 10 mg once daily as monotherapy compared with placebo over 12 weeks and with voglibose 0.2 mg three-times daily over 26 weeks in a large number of Japanese patients with T2DM.

Materials and Methods

This study was conducted at 47 centres in Japan between 1 April 2008 and 14 January 2010 (ClinicalTrials.gov, number NCT00654381). The design and methodology have been reported in detail previously [24], and are summarized below. This study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice, the Declaration of Helsinki (October 1996 version) and relevant Japanese laws/regulations. All patients provided written informed consent before participation.

Study Design

Patients were randomized (2 : 2 : 2 : 1) to linagliptin 5 mg, linagliptin 10 mg, voglibose 0.6 mg or placebo following a 2-week placebo run-in (which was preceded by a 2-week washout period in patients who previously received one or two OADs). At week 12, patients receiving placebo were randomized (1 : 1) to linagliptin 5 or 10 mg. At week 26, patients receiving voglibose were randomized (1 : 1) to linagliptin 5 or 10 mg. Patients initially receiving linagliptin continued therapy at weeks 12 and 26. This was followed by an open-label extension period to evaluate the long-term safety/tolerability of linagliptin for up to 52 weeks of treatment, the results of which are to be reported in a second publication to maintain the data integrity in the randomization period.

Study Population

The study enrolled male and non-pregnant female patients with T2DM aged 20–80 years with a body mass index (BMI) $\leq$40 kg/m^{2}and inadequate glycaemic control [haemoglobin A1c (HbA1c) 7.0–10.0% in those previously untreated with OADs; HbA1c 7.0–9.0% at screening and 7.0–10% after washout in those already receiving one or two OADs for $\geq$10 weeks]. Key exclusion criteria were fasting plasma glucose (FPG) >13.3 mmol/l (>240 mg/dl) during washout or placebo run-in; myocardial infarction, stroke or transient ischaemic attack within the previous 6 months; impaired hepatic function (serum alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase levels exceeding three times the upper limit of normal); treatment with a glitazone, insulin or anti-obesity drugs within the previous 3 months or any investigational agent within the previous 2 months; and/or a history of known intolerance, allergy or hypersensitivity to voglibose or any other concomitant drugs.

Study Endpoints

The co-primary endpoints were change from baseline in HbA1c with linagliptin vs. placebo at week 12 and vs. voglibose at week 26. Secondary endpoints included the percentage of patients achieving HbA1c <6.5% or <7.0% at weeks 12 and 26, change from baseline in HbA1c over time, change from baseline in FPG at weeks 12 and 26, and change from

baseline in FPG over time. Exploratory endpoints included the following: plasma proinsulin/insulin ratio; homeostasis model assessment indices for insulin resistance (HOMA-IR) and for insulin secretion (HOMA-IS); disposition index calculated as the product of β-cell function determined from HOMA-IS and HOMA-IR; glycosylated albumin; body weight, BMI and waist circumference; plasma lipid levels; and Diabetes Treatment Satisfaction Questionnaire data. Pharmacodynamic effects were evaluated based on plasma DPP-4 inhibition. Safety and tolerability were assessed by the incidence and intensity of adverse events (AEs) throughout the study period, and clinically relevant changes or findings after physical, vital sign, 12-lead electrocardiogram and laboratory assessments. Hypoglycaemia was defined according to American Diabetes Association guidelines [25]. An independent external clinical event committee conducted blinded adjudication of any suspected cardiovascular or cerebrovascular AEs. All laboratory measurements were performed by a central laboratory (Covance Laboratories, Harrogate, UK).

Statistical Analyses

A sample size of 441 randomized patients was planned (126 patients in each of the linagliptin and voglibose groups, 63 patients in the placebo group), which assumed a 15% drop-out rate. This would provide 90% power to detect a mean difference of 0.5% [standard deviation (s.d.) of 0.9%] in change from baseline in HbA1c between linagliptin and placebo at week 12, and 90% power to detect a mean difference of 0.45% (s.d. of 1.0%) in HbA1c change from baseline at week 26 between linagliptin and voglibose, at a one-sided significance level of 0.025 in both comparisons. To control for type I error, comparisons between linagliptin group and placebo or voglibose were performed using the closed testing procedure.

Efficacy analyses at weeks 12 and 26 were performed using the full analysis set (all randomized patients who had baseline and $\geq$1 post-baseline measurement and received $\geq$1 dose of study medication). Safety analyses at weeks 12 and 26 were performed on the treated set (all randomized patients who received $\geq$1 dose of study medication).

Analysis of covariance (ANCOVA) with baseline value as covariate and treatment and previous OAD therapy as variables was used to evaluate changes in continuous efficacy endpoints. Last observation carried forward was used to impute missing data for HbA1c, FPG, glycosylated albumin, body weight, BMI and waist circumference; observed cases were used for all other efficacy endpoints. Fisher's exact test was used to evaluate changes in categorical efficacy endpoints. Descriptive statistics without imputation of data were used for safety endpoints.

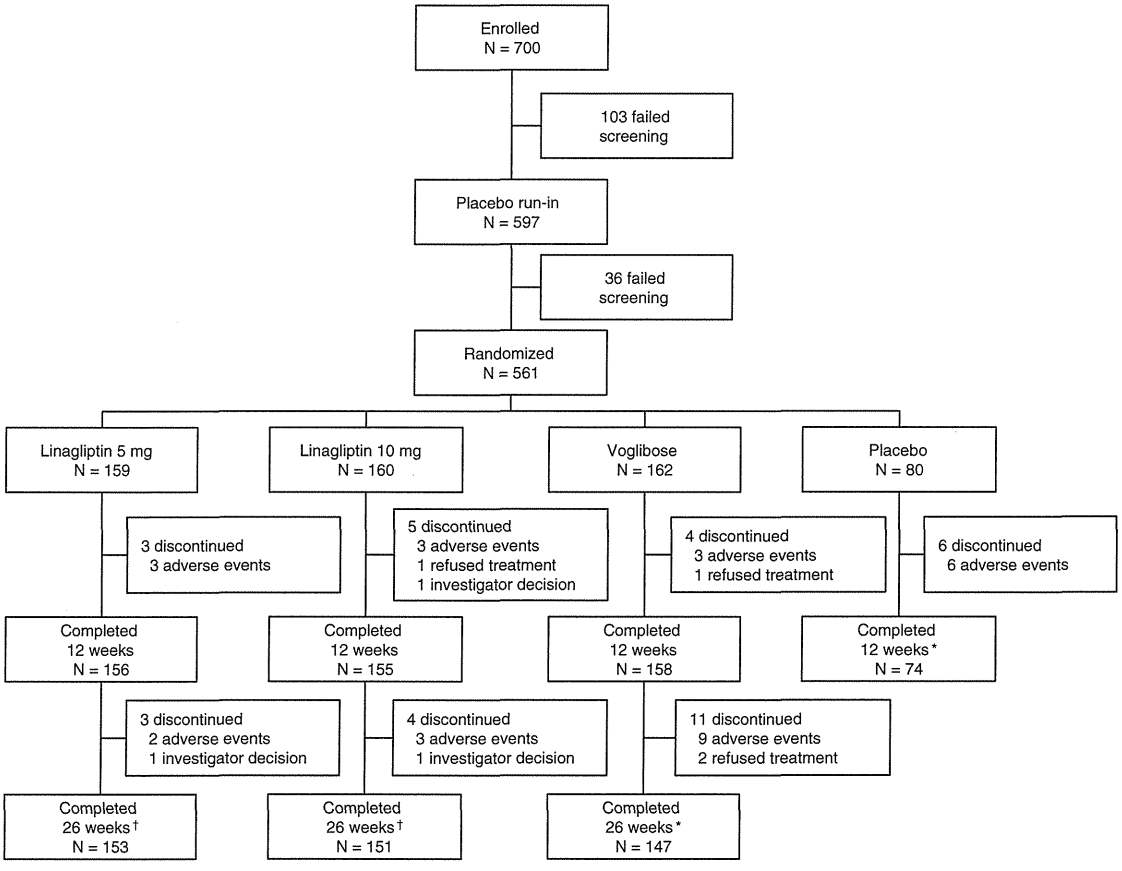

Figure 1. Patient disposition. *Patients randomized to linagliptin 5 or 10 mg for extension study. †Patients continued on linagliptin 5 or 10 mg for extension study.

Table 1. Baseline demographic and clinical characteristics by treatment group (treated set).

	Linagliptin 5 mg	Linagliptin 10 mg	Voglibose	Placebo
N	159	160	162	80
Gender, male [n (%)]	111 (69.8)	112 (70.0)	115 (71.0)	57 (71.3)
Age (years)	60.3 (9.4)	61.3 (10.0)	58.5 (9.9)	59.7 (8.9)
BMI (kg/m^2)	24.6 (4.0)	25.0 (3.8)	25.7 (4.0)	24.3 (3.4)
eGFR, MDRD (ml/min)	113.9 (24.9)	110.6 (26.5)	113.4 (25.8)	111.4 (26.3)
HbA1c (%)	8.07 (0.66)	7.98 (0.68)	8.02 (0.71)	7.95 (0.67)
FPG (mmol/l)	9.1 (1.8)	9.2 (1.9)	9.1 (1.8)	9.0 (1.7)
No. of previous OADs [n (%)]				
0	87 (54.7)	88 (55.0)	90 (55.6)	43 (53.8)
1	58 (36.5)	57 (35.6)	55 (34.0)	29 (36.3)
2	14 (8.8)	15 (9.4)	17 (10.5)	8 (10.0)
Time since diagnosis [n (%)]				
≤1 year	19 (11.9)	19 (11.9)	20 (12.3)	7 (8.8)
>1–5 years	61 (38.4)	59 (36.9)	65 (40.1)	36 (45.0)
>5 years	79 (49.7)	82 (51.3)	77 (47.5)	37 (46.3)
Concomitant disease [n (%)]				
Microvascular disease*	57 (35.8)	54 (33.8)	57 (35.2)	28 (35.0)
Macrovascular disease†	77 (48.4)	91 (56.9)	90 (55.6)	36 (45.0)
Metabolic syndrome	59 (37.1)	75 (46.9)	85 (52.5)	31 (38.8)

Data are mean (s.d.) or number (%) of patients. BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; MDRD, modification of diet in renal disease study equation; OADs, oral antidiabetic drugs.
*Including diabetic retinopathy, diabetic nephropathy and diabetic neuropathy.
†Including coronary artery disease, peripheral artery occlusive disease, cerebrovascular disease and hypertension.

Results

Patient Disposition and Characteristics

A total of 700 patients were screened; 597 entered the placebo run-in and 561 were randomized to study treatment (linagliptin 5 mg: 159; linagliptin 10 mg: 160; voglibose: 162; placebo: 80) (figure 1). More patients completed treatment with linagliptin than with placebo or voglibose (week 12: 98.1, 96.9 and 92.5% of those receiving linagliptin 5 mg, linagliptin 10 mg or placebo, respectively; week 26: 96.2, 94.4 and 90.7% of those receiving linagliptin 5 mg, linagliptin 10 mg or voglibose, respectively). The most common cause of discontinuation was AEs both at 12 and 26 weeks.

Baseline demographics and clinical characteristics were comparable across the treatment groups (Table 1). The overall mean (±s.d.) age, BMI and HbA1c were 60.0 (±9.7) years, 25.0 (±3.9) kg/m^2 and HbA1c 8.01% (±0.68%), respectively. In total, 221 (39.4%) patients had T2DM for 1–5 years and 275 (49.0%) for over 5 years, and 99 (17.6%) had some degree of renal impairment (estimated glomerular filtration rate <90 ml/min). Previously drug-naïve patients [n = 308 (54.9%)] were younger, and had slightly lower HbA1c, lower FPG and shorter disease duration than previously treated patients [n = 253 (45.1%)], but the relative proportions of these patients were similar across groups (Table S1).

Efficacy

Both doses of linagliptin elicited reductions in HbA1c that were significantly greater than the changes achieved by either placebo at week 12 or voglibose at week 26 (Tables 2 and 3). Both doses of linagliptin achieved similar treatment differences vs. placebo at week 12, and similar differences vs. voglibose at week 26 (figure 2A).

Significantly greater proportions of patients in both linagliptin groups achieved therapeutic HbA1c targets than those in the placebo or voglibose groups. At week 12, target HbA1c of <7.0% was achieved in 26.4% of patients receiving linagliptin 5 mg ($p = 0.0038$ vs. placebo), 35.7% of those receiving linagliptin 10 mg ($p < 0.0001$ vs. placebo) and 10.0% of the placebo group. At week 26, this target was achieved in 30.2, 34.4 and 22.2% of patients receiving linagliptin 5 mg, linagliptin 10 mg or voglibose, respectively ($p = 0.13$ and $p = 0.02$ vs. voglibose for linagliptin 5 and 10 mg, respectively).

Both doses of linagliptin elicited significantly greater decreases in FPG from baseline than placebo at week 12 and voglibose at week 26 (Tables 2 and 3). In parallel with the significant amelioration of hyperglycaemia, linagliptin also elicited therapeutic changes in indices of β-cell function and insulin sensitivity (Tables 2 and 3). Both the 5 and 10 mg doses produced significant reductions in the proinsulin/insulin ratio compared with placebo at week 12 and voglibose at week 26. Linagliptin 5 mg also showed a tendency to improve fasting insulin, HOMA-IR and disposition index, although these did not reach significance vs. comparators at weeks 12 and 26.

There were very small reductions in body weight, BMI and waist circumference that were similar between linagliptin and placebo, and small but significant reductions in these endpoints with voglibose over linagliptin (Tables S2 and S3). No significant changes were observed in serum levels of triglycerides or total, high-density lipoprotein (HDL) or low-density lipoprotein (LDL) cholesterol with any treatment at weeks 12 and 26, with the exception of a small but significant

Table 2. Measures of glycaemic control in the linagliptin and placebo groups at week 12 (full analysis set).

	N	Week 0 [mean (s.e.)]	Week 12 [mean (s.e.)]	Adjusted mean change from baseline [mean (s.e.)]	Difference in means [linagliptin–placebo (95% CI)]
HbA1c† (%)					
Linagliptin 5 mg	159	8.07 (0.05)	7.58 (0.08)	−0.24 (0.06)	−0.87 (−1.04, −0.70)***
Linagliptin 10 mg	157	7.98 (0.05)	7.48 (0.08)	−0.25 (0.06)	−0.88 (−1.05, −0.71)***
Placebo	80	7.95 (0.07)	8.34 (0.14)	0.63 (0.08)	
FPG† (mmol/l)					
Linagliptin 5 mg	159	9.1 (0.1)	8.2 (0.1)	−0.7 (0.1)	−1.1 (−1.4,−0.8)***
Linagliptin 10 mg	160	9.2 (0.1)	8.3 (0.1)	−0.7 (0.1)	−1.1 (−1.5,−0.8)***
Placebo	80	9.0 (0.2)	9.3 (0.2)	0.4 (0.1)	
Fasting insulin‡ (mU/l)					
Linagliptin 5 mg	28	5.36 (1.06)	4.80 (0.74)	−0.50 (0.61)	−0.27 (−2.20, 1.66)
Linagliptin 10 mg	24	5.61 (0.94)	6.41 (1.39)	0.77 (0.64)	1.00 (−0.98, 2.97)
Placebo	12	3.96 (0.38)	3.88 (0.53)	−0.23 (0.83)	
Proinsulin/insulin ratio‡					
Linagliptin 5 mg	28	0.27 (0.04)	0.24 (0.03)	−0.04 (0.02)	−0.08 (−0.14, −0.02)*
Linagliptin 10 mg	21	0.23 (0.02)	0.18 (0.02)	−0.07 (0.02)	−0.12 (−0.18, −0.06)**
Placebo	12	0.22 (0.03)	0.28 (0.04)	0.05 (0.03)	
HOMA-IR‡ (mU/l × mmol/l)					
Linagliptin 5 mg	28	2.24 (0.43)	1.83 (0.30)	−0.35 (0.23)	−0.35 (−1.07, 0.38)
Linagliptin 10 mg	24	2.34 (0.40)	2.36 (0.48)	0.07 (0.24)	0.08 (−0.66, 0.82)
Placebo	12	1.62 (0.19)	1.71 (0.31)	−0.01 (0.31)	
HOMA-IS‡ [(mU/l)/(mmol/l)]					
Linagliptin 5 mg	28	19.67 (4.76)	21.51 (4.40)	1.65 (3.10)	2.14 (−7.64, 11.92)
Linagliptin 10 mg	24	20.84 (3.67)	29.87 (7.49)	7.91 (3.24)	8.40 (−1.61, 18.42)
Placebo	12	14.75 (1.48)	13.86 (1.96)	−0.49 (4.19)	
Disposition index‡					
Linagliptin 5 mg	37	11.28 (1.11)	13.84 (1.09)	2.07 (1.06)	2.20 (−1.07, 5.47)
Linagliptin 10 mg	36	9.87 (0.92)	12.99 (1.24)	2.44 (1.03)	2.57 (−0.69, 5.82)
Placebo	16	9.43 (0.82)	10.09 (1.66)	−0.13 (1.44)	

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; HOMA-IS, homeostasis model assessment indices for insulin secretion; s.e., standard error.

*$p < 0.01$, **$p < 0.001$, ***$p < 0.0001$.

†Full analysis set, last observation carried forward analysis.

‡Full analysis set, observed cases analysis.

increase in LDL cholesterol with voglibose compared with linagliptin 5 and 10 mg at 26 weeks (Tables S2 and S3).

Both doses of linagliptin at weeks 12 and 26 (i.e. at steady state) achieved mean DPP-4 inhibition of ≥80% at trough concentrations (data not shown).

Efficacy Subgroup Analyses

Treatment differences in HbA1c reductions from baseline with linagliptin vs. placebo at week 12 tended to be greater in a pre-specified subgroup with baseline HbA1c ≥8.0% (figure 2B). In other *post hoc* analyses, treatment differences also showed significant HbA1c reductions with linagliptin 5 and 10 mg vs. placebo at week 12 and a trend towards HbA1c reductions vs. voglibose at week 26 across patient subgroups with different disease duration or different renal function (figure 3A and B). In previously drug-naïve patients, treatment differences were slightly smaller than in the overall population, although there were larger HbA1c changes from baseline with each treatment in the drug-naïve subgroup (week 12: −0.75, −0.82 and −0.16% of those receiving linagliptin 5 mg, linagliptin 10 mg or placebo, respectively; week 26: −0.69, −0.83 and −0.51% of those receiving linagliptin 5 mg, linagliptin 10 mg or voglibose, respectively).

A *post hoc* analysis in previously drug-naïve patients with baseline HbA1c <7.0% showed the target HbA1c of <6.5% was achieved at week 12 by three of four patients on linagliptin 5 mg and three of five patients on linagliptin 10 mg, whereas there were no placebo-treated patients in this subgroup; this target was achieved at week 26 in the same subgroup by four of four patients on linagliptin 5 mg, three of five patients on linagliptin 10 mg and only one of four patients on voglibose.

Safety and Tolerability

The rates of overall AEs with linagliptin 5 and 10 mg were comparable with placebo over 12 weeks (linagliptin 5 mg: 56.0%, linagliptin 10 mg: 53.1%, placebo: 56.3%) and voglibose over 26 weeks (linagliptin 5 mg: 72.3%, linagliptin 10 mg: 77.5%, voglibose: 71.6%) (Tables 4 and 5). Similar rates of drug-related AEs were also observed across treatments. No deaths occurred during the study and there were few other serious adverse events (SAEs). None of the SAEs that occurred during the study in any treatment group were deemed by the

Table 3. Measures of glycaemic control in the linagliptin and voglibose groups at week 26 (full analysis set).

	N	Week 0 [mean (s.e.)]	Week 26 [mean (s.e.)]	Adjusted mean change from baseline [mean (s.e.)]	Difference in means [linagliptin−voglibose (95% CI)]
HbA1c† (%)					
Linagliptin 5 mg	159	8.07 (0.05)	7.63 (0.09)	−0.13 (0.07)	−0.32 (−0.49, −0.15)**
Linagliptin 10 mg	157	7.98 (0.05)	7.50 (0.08)	−0.19 (0.07)	−0.39 (−0.56, −0.21)***
Voglibose	162	8.02 (0.06)	7.91 (0.10)	0.19 (0.07)	
FPG† (mmol/l)					
Linagliptin 5 mg	159	9.1 (0.1)	8.6 (0.2)	−0.3 (0.1)	−0.4 (−0.7, 0.0)
Linagliptin 10 mg	160	9.2 (0.1)	8.5 (0.1)	−0.4 (0.1)	−0.5 (−0.9, −0.2)*
Voglibose	162	9.1 (0.1)	8.9 (0.2)	0.1 (0.1)	
Fasting insulin‡ (mU/l)					
Linagliptin 5 mg	27	5.26 (1.07)	5.86 (1.25)	0.53 (0.82)	0.72 (−1.42, 2.86)
Linagliptin 10 mg	26	5.37 (0.87)	5.87 (0.91)	0.42 (0.74)	0.61 (−1.46, 2.69)
Voglibose	20	6.73 (1.41)	6.75 (2.05)	−0.19 (0.80)	
Proinsulin/insulin ratio‡					
Linagliptin 5 mg	27	0.29 (0.04)	0.23 (0.03)	−0.06 (0.02)	−0.09 (−0.14, −0.04)**
Linagliptin 10 mg	23	0.24 (0.02)	0.18 (0.02)	−0.06 (0.02)	−0.09 (−0.14, −0.04)**
Voglibose	19	0.24 (0.03)	0.26 (0.04)	0.03 (0.02)	
HOMA-IR‡ (mU/l × mmol/l)					
Linagliptin 5 mg	27	2.08 (0.41)	2.17 (0.48)	0.09 (0.32)	0.36 (−0.48, 1.19)
Linagliptin 10 mg	26	2.21 (0.36)	2.15 (0.33)	−0.06 (0.29)	0.20 (−0.61, 1.01)
Voglibose	20	2.67 (0.56)	2.36 (0.56)	−0.26 (0.31)	
HOMA-IS‡ [(mU/L)/(mmol/l)]					
Linagliptin 5 mg	27	20.58 (4.92)	25.27 (5.05)	5.58 (4.46)	0.47 (−11.18, 12.12)
Linagliptin 10 mg	26	20.24 (3.47)	27.13 (4.83)	7.86 (4.05)	2.75 (−8.55, 14.05)
Voglibose	20	29.54 (9.29)	39.15 (18.79)	5.11 (4.33)	
Disposition index‡					
Linagliptin 5 mg	34	11.63 (1.18)	13.95 (0.90)	1.39 (1.08)	−0.20 (−3.08, 2.67)
Linagliptin 10 mg	33	9.94 (0.98)	13.42 (1.25)	2.15 (1.02)	0.56 (−2.29, 3.40)
Voglibose	24	10.85 (1.22)	13.28 (1.48)	1.59 (1.14)	

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; HOMA-IS, homeostasis model assessment indices for insulin secretion; s.e., standard error.
*$p < 0.01$, **$p < 0.001$, ***$p < 0.0001$.
†Full analysis set, last observation carried forward analysis.
‡Full analysis set, observed cases analysis.

reporting investigators to be related to study drugs. While few patients discontinued because of AEs over 12 and 26 weeks of treatment, the overall drop-out was lower with linagliptin than with placebo or voglibose.

The most common types of AEs were infections/infestations, GI disorders and skin and subcutaneous tissue disorders in all treatment groups. There were no cases of hypoglycaemia with both doses of linagliptin or placebo throughout the first 12 weeks of treatment. There was one case of investigator-defined hypoglycaemia with linagliptin 10 mg and two cases with voglibose—although none of these were documented cases—during the 24-week study period. A *post hoc* analysis showed that the overall incidence of GI disorders in the combined linagliptin 5 or 10 mg group was comparable to that in the voglibose group over 26 weeks. Linagliptin 5 or 10 mg was associated with similar rates of each category of GI event compared with voglibose, except for diarrhoea, the most common GI event, which occurred in fewer linagliptin-treated than voglibose-treated patients (4.4 vs. 9.3%; $p = 0.04$). Three patients were confirmed after blinded adjudication to have experienced a cardiac or cerebrovascular event: one (0.6%) patient receiving linagliptin 5 mg and two (1.2%) receiving voglibose.

Discussion

In this 26-week study in Japanese patients with T2DM and inadequate glycaemic control, linagliptin monotherapy achieved significantly greater mean reductions in HbA1c than voglibose and had an overall safety profile similar to placebo with no documented hypoglycaemia or weight gain. In addition, a higher proportion of linagliptin-treated patients achieved evidence-based targets for glycaemic control and clinically meaningful reductions in HbA1c than those receiving voglibose or placebo.

Greater reductions in HbA1c in patients receiving linagliptin than in those receiving voglibose or placebo were seen regardless of baseline HbA1c level, renal impairment or duration of disease. As expected, reductions in HbA1c were greater in patients with higher baseline HbA1c. Effects on postprandial glucose levels were not determined in this study (because of issues of practicality); however, positive short-term effects

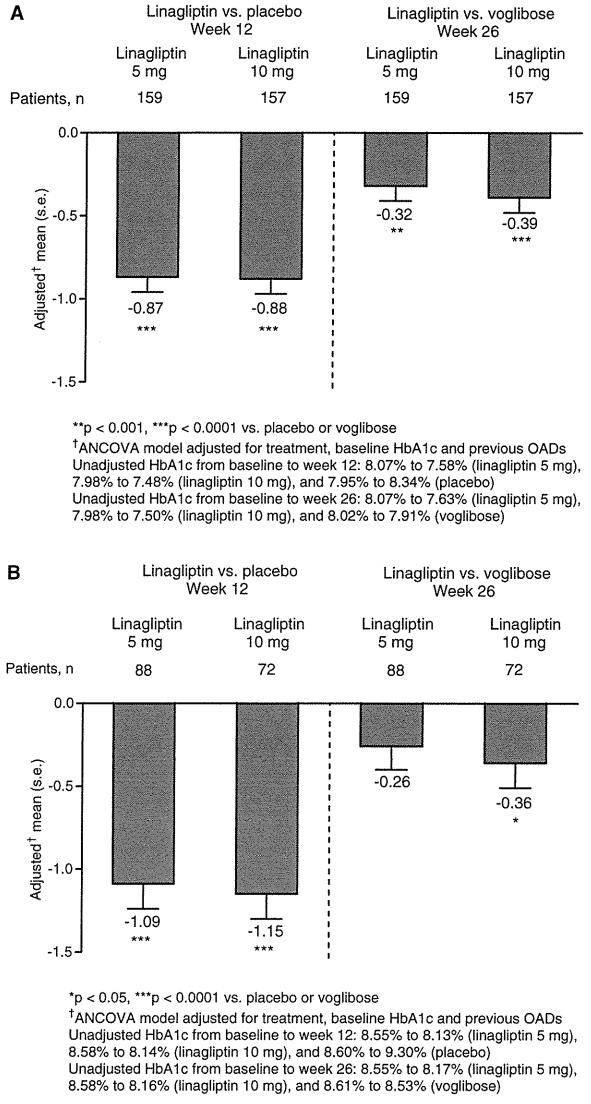

Figure 2. Differences in haemoglobin A1c (HbA1c) changes from baseline between treatments (full analysis set): (A) treatment difference in overall study population and (B) treatment difference in patients with baseline HbA1c ≥8.0%.

of linagliptin on postprandial glucose have been previously observed in an earlier Japanese Phase IIa study [16].

Very minor reductions in body weight, BMI and waist circumference occurred in all treatment groups during the study, but these were of limited clinical relevance for this generally overweight study population.

In this study, the treatment difference between linagliptin and voglibose appeared comparable to previous head-to-head studies of other DPP-4 inhibitors and voglibose in Japanese patients with T2DM [26,27], although direct comparisons between studies must always be interpreted cautiously because of potential confounding factors. In the overall study population, the absolute changes in HbA1c were smaller than those seen in the previous DPP-4 inhibitor studies; however,

Table 4. Clinical AEs in the linagliptin and placebo groups over 12 weeks (treated set).

	Linagliptin 5 mg [n (%)]	Linagliptin 10 mg [n (%)]	Placebo [n (%)]
Total number of patients	159	160	80
Number of patients having ≥1			
AE	89 (56.0)	85 (53.1)	45 (56.3)
Drug-related AE*	15 (9.4)	14 (8.8)	8 (10.0)
SAE	1 (0.6)	4 (2.5)	1 (1.3)
Drug-related SAE*	0 (0.0)	0 (0.0)	0 (0.0)
Number of patients discontinued due to			
AE	3 (1.9)	4 (2.5)	7 (8.8)
Drug-related AE	1 (0.6)	1 (0.6)	2 (2.5)
SAE	1 (0.6)	1 (0.6)	0 (0.0)
AEs of special interest (any cause)			
Hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	38 (23.9)	33 (20.6)	12 (15.0)
Metabolism and nutritional disorders	4 (2.5)	4 (2.5)	7 (8.8)
Nervous system disorders	9 (5.7)	10 (6.3)	4 (5.0)
Any GI disorders	29 (18.2)	26 (16.3)	11 (13.8)
Skin and subcutaneous tissue disorders	13 (8.2)	9 (5.6)	2 (2.5)
Musculoskeletal and connective tissue disorders	10 (6.3)	15 (9.4)	8 (10.0)
Any renal or urinary disorder	3 (1.9)	4 (2.5)	2 (2.5)
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)

AE, adverse event; GI, gastrointestinal; SAE, serious adverse event.
*Determined by the investigator to be possibly, probably or definitely drug-related.

this is likely to be a consequence of the strong washout effect in a substantial proportion (~45%) of the current study population who previously received one or two OADs (i.e. glycaemic deterioration during the treatment phase as a result of discontinuation of previous background therapies during the 4-week washout period). This interpretation is supported by the observation that in previously drug-naïve T2DM patients in this study, the absolute HbA1c changes were similar to those previously seen with other DPP-4 inhibitors, and the treatment differences, which account for effects of discontinuation of background therapies across treatment groups, confirmed similar improvements with linagliptin to those seen in the other DPP-4 studies.

Linagliptin was well tolerated in this study with an AE profile similar to placebo, which is consistent with Phase III studies in other populations [17–20]. Both linagliptin and voglibose were associated with very few cases of investigator-defined hypoglycaemia, but none were confirmed or documented by plasma measurements; this is not an unexpected finding given the mechanism of action of these agents and indicates that the anti-hyperglycaemic effects of linagliptin were not associated with any increased risk of hypoglycaemia. Linagliptin also showed GI tolerability that was generally comparable to that of voglibose, although linagliptin was associated with significantly less diarrhoea. The safety/tolerability profile of linagliptin in this Japanese study was consistent with the profiles reported for other DPP-4

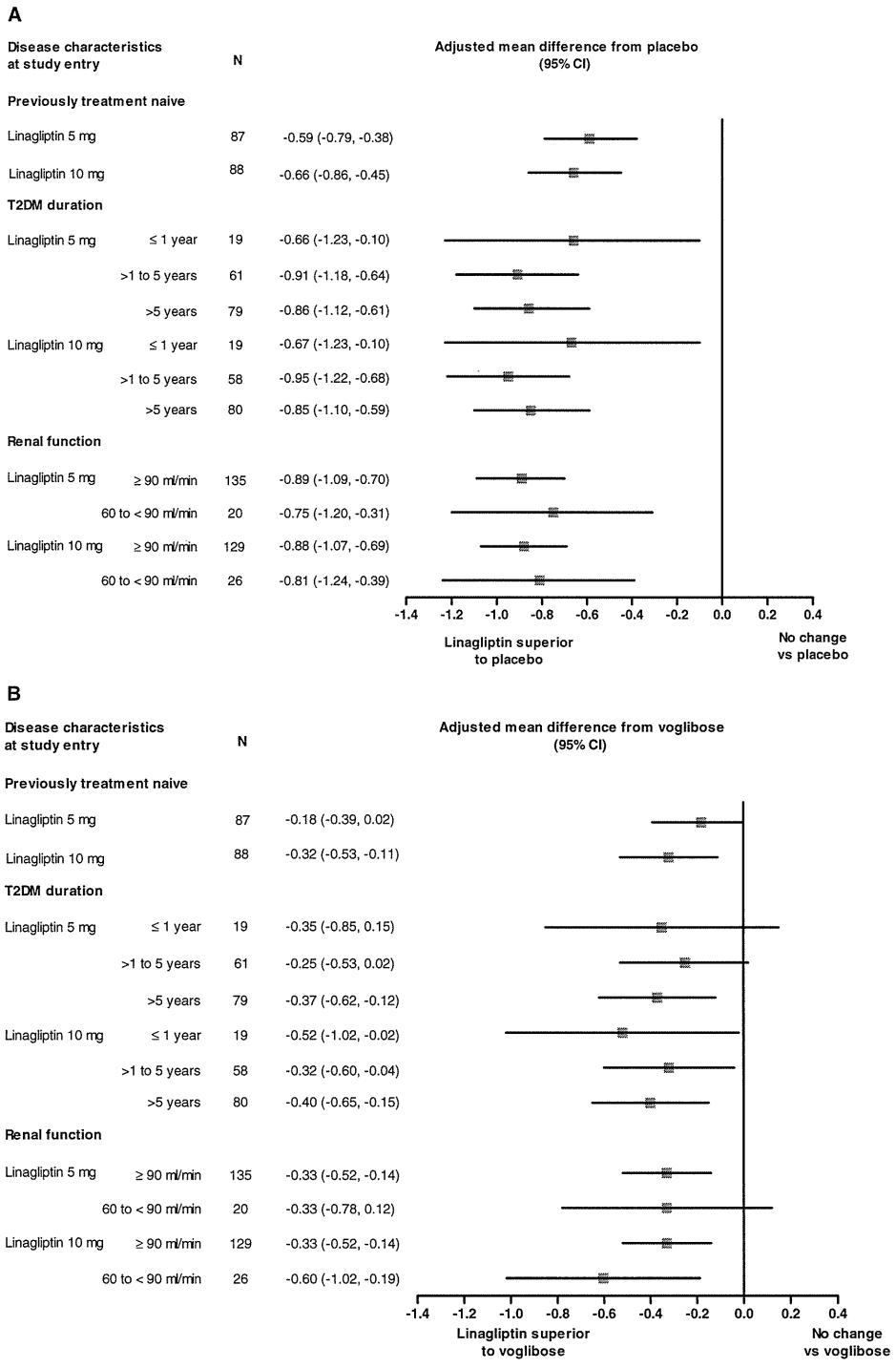

Figure 3. Subgroup analyses of haemoglobin A1c-lowering (full analysis set): (A) linagliptin vs. placebo at week 12 and (B) linagliptin vs. voglibose at week 26 (full analysis set).

inhibitors in Japanese patients, and no new safety concerns were observed [26–28].

There were no apparent differences between the two doses of linagliptin in efficacy and safety/tolerability over 12 to 26 weeks of treatment. This supports the lower 5 mg dose as the optimal therapeutic dose in Japanese patients, as this offers comparable beneficial effects but with lower drug exposure compared to the higher 10 mg dose. This is in agreement with clinical studies in other populations that also demonstrated linagliptin 5 mg was the optimal therapeutic dose [13,14].

Table 5. Clinical AEs in the linagliptin and voglibose groups over 26 weeks (treated set).

	Linagliptin 5 mg [n (%)]	Linagliptin 10 mg [n (%)]	Voglibose [n (%)]
Total number of patients	159	160	162
Number of patients having ≥1			
AE	115 (72.3)	124 (77.5)	116 (71.6)
Drug-related AE*	18 (11.3)	17 (10.6)	30 (18.5)
SAE	5 (3.1)	8 (5.0)	7 (4.3)
Drug-related SAE*	0 (0.0)	0 (0.0)	0 (0.0)
Number of patients discontinued due to			
AE	4 (2.5)	7 (4.4)	12 (7.4)
Drug-related AE	1 (0.6)	1 (0.6)	3 (1.9)
SAE	2 (1.3)	1 (0.6)	2 (1.2)
AEs of special interest (any cause)			
Hypoglycaemia†	0 (0.0)	1 (0.6)	2 (1.2)
Infections and infestations	70 (44.0)	58 (36.3)	56 (34.6)
Metabolism and nutritional disorders	7 (4.4)	12 (7.5)	14 (8.6)
Nervous system disorders	17 (10.7)	15 (9.4)	16 (9.9)
Respiratory, thoracic and mediastinal disorders	9 (5.7)	10 (6.3)	5 (3.1)
Any GI disorders	48 (30.2)	38 (23.8)	49 (30.2)
Skin and subcutaneous tissue disorders	22 (13.8)	13 (8.1)	7 (4.3)
Musculoskeletal and connective tissue disorders	19 (11.9)	24 (15.0)	14 (8.6)
Any renal or urinary disorder	6 (3.8)	7 (4.4)	3 (1.9)
Hypersensitivity	0 (0.0)	1 (0.6)‡	0 (0.0)

AE, adverse event; GI, gastrointestinal; SAE, serious adverse event.
*Determined by the investigator to be possibly, probably or definitely drug-related.
†No documented cases of hypoglycaemia as confirmed by plasma glucose measurements.
‡Hypersensitivity was worsening of pollinosis (allergy), which was reported by the investigator as due to seasonal change.

This study has certain limitations. First, the length of this study does not allow assessment of the long-term durability of glycaemic control with linagliptin. However, its 26-week duration does provide valuable information on the extended effects of DPP-4 inhibition over time compared with voglibose in Japanese patients (randomized double-blind studies comparing sitagliptin and vildagliptin vs. voglibose have reported results over 12 weeks only). To address the need for long-term data in Japanese patients, the open-label extension of this study will determine the long-term safety and durability of linagliptin's therapeutic effects after continued treatment and after switching from voglibose; in addition, another ongoing Japanese study is evaluating linagliptin vs. metformin as add-on to one other OAD (ClinicalTrials.gov, number NCT01204294). Second, as is the case with other DPP-4 inhibitors, large, adequately powered, randomized clinical trials measuring hard clinical endpoints are needed to determine if the efficacy and safety of linagliptin translate into reduced risk of diabetic complications such as vascular events. One such study is ongoing—the CAROLINA study that is taking place in many countries, including Japan, to investigate the effects of linagliptin on cardiovascular outcomes (ClinicalTrials.gov, number NCT01243424).

In conclusion, linagliptin 5 or 10 mg once daily provided superior glycaemic control compared to voglibose with a comparable safety profile in Japanese patients with T2DM. Differences in anti-hyperglycaemic effects and other parameters between the 5 and 10 mg doses of linagliptin were only minor, consistent with previous studies in patients from other racial groups, providing a rationale for a 5 mg once-daily therapeutic dose. The glucose-dependent promotion of insulin secretion by linagliptin, through stimulation and improvement in pancreatic β-cell function, may be particularly helpful for Asian patients with T2DM who are often leaner than their Western counterparts [29] and, consequently, have a pathophysiology in which defective insulin secretion is a stronger contributor to hyperglycaemia than insulin resistance [30]. This study provides support for the use of linagliptin 5 mg once daily as a new oral treatment option in Japanese patients with T2DM that can improve glycaemic control with minimal risk of hypoglycaemia, weight gain or other AEs such as GI symptoms. These effects can be achieved at a single dose strength without regard to declining renal function, which is a frequent limitation of current therapies used in diabetes management.

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Conflict of Interest

R. Kawamori has received consultancy fees from Boehringer Ingelheim and speaker fees from MSD, Novartis, Takeda, Ono, Novo Nordisk and Eli Lilly. N. Inagaki has received consultancy fees from Boehringer Ingelheim, Takeda and Novo Nordisk, speaker fees from MSD, Novartis, Novo Nordisk, Eli Lilly, Takeda and Ono, and research support from Boehringer Ingelheim, MSD, Novartis, Novo Nordisk, Eli Lilly, Takeda and Ono. E. Araki has received consultancy fees from Novo Nordisk, speaker fees from Ono, Novartis, Novo Nordisk, MSD, Eli Lilly and Takeda, and research support from Novartis. H. Watada has received consultancy fees from Boehringer Ingelheim, speaker fees from MSD, Novartis, Takeda, Novo Nordisk and Eli Lilly, and research support from MSD, Novartis, Takeda, Boehringer Ingelheim, Novo Nordisk and Eli Lilly. N. Hayashi, Y. Horie, A. Sarashina, Y. Gong, M. von Eynatten, H. J. Woerle and K. A. Dugi are employees of Boehringer Ingelheim, the study sponsor and manufacturer of linagliptin. All authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. All authors contributed to or participated in the design of the study, the analysis of data, the collection of data and the writing or revision of the manuscript. All authors saw and approved the final version of the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline demographic and clinical characteristics in previously drug-naïve or treated patients (treated set).

Table S2. Summary of lipids and other exploratory endpoints in the linagliptin and placebo groups at week 12.

Table S3. Summary of lipids and other exploratory endpoints in the linagliptin and voglibose groups at week 26.

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ORIGINAL PAPER

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Sitagliptin add-on to low dosage sulphonylureas: efficacy and safety of combination therapy on glycaemic control and insulin secretion capacity in type 2 diabetes

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SUMMARY

Aims: To assess the efficacy and safety of combination therapy with sitagliptin and low dosage sulphonylureas on glycaemic control and insulin secretion capacity in Japanese type 2 diabetes. Methods: Eighty-two subjects were sequentially recruited for the 52-week, prospective, single arm study. Sitagliptin was added on to sulphonylureas (glimepride or gliclazide) with or without metformin. The primary endpoint was a change in A1C. The secondary endpoints were changes in BMI, insulin secretion capacity, blood pressure and urinary albumin excretion, unresponsive rate, and hypoglycaemia. Insulin secretion capacity was evaluated by glucagon loading test. **Results:** Change in A1C was −0.80% (95% CI −0.90 to −0.68) ($p < 0.001$). Change in BMI, systemic and diastolic blood pressure, and urinary albumin excretion were −0.38 kg/m^2 (95% CI −0.72 to −0.04) ($p < 0.05$), −6.7/−3.6 mmHg (95% CI −10.0 to −3.4/−4.8 to −2.4) ($p < 0.001$), and −43.2 mg/gCr (95% CI −65.7 to −20.8) ($p < 0.001$) respectively. Mild hypoglycaemia was observed in three cases. The unresponsive rate was 6.1%. Glucagon loading test showed that 0-min and 6-min CPR at baseline and 52-week were not significantly changed: 0-min CPR, 1.58 ± 0.58–1.71 ± 0.73 ng/ml; 6-min CPR, 3.48 ± 1.47–3.58 ± 1.21 ng/ml. Insulin secretion capacity, CPI and SUIT index at baseline did not predict the efficacy of the combination therapy. The final dosages of glimepiride and gliclazide were 1.44 ± 0.90 mg and 34.5 ± 15.3 mg respectively. The dosage of sitagliptin was increased from 50 mg to 69.0 ± 24.5 mg in 52-week. **Conclusions:** The combination therapy with sitagliptin and low dosage sulphonylureas was safe and effective for glycaemic control. Glucagon loading test indicated that 1 year administration of sitagliptin and sulphonylureas preserved insulin secretion capacity.

What's known

- Sitagliptin is more effective for glycaemic control in Japanese patients compared with Caucasian patients.
- More than 70 cases of severe hypoglycaemia have been reported in Japanese patients treated with sulphonylureas and sitagliptin.
- A private committee to establish adequate use of incretin-based therapy recommended that the dosage of sulphonylureas should be decreased to less than 1.25 mg/day glibenclamide, 2.0 mg/day glimipiride or 40 mg/day gliclazide at the initiation of incretin-based therapy in Japan.

What's new

- The combination therapy with sitagliptin and low dosage sulphonylureas was safe and effective for glycaemic control.
- Glucagon loading test indicated that 1-year administration of sitagliptin and sulphonylureas preserved insulin secretion capacity.
- The combination therapy is weight neutral, and lowered both the blood pressure level and urinary albumin excretion.
- Because of the decrease in the dosage of sulphonylureas, hypoglycaemia seldom occurs, and there is no severe hypoglycaemia.

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Disclosures
No potential conflicts of interest relevant to this article were reported.

Introduction

Type 2 diabetes is a chronic disease usually requiring multiple antihyperglycaemic agents (AHAs) during the course of the disease. The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) algorithm for treating type 2 diabetes recommends metformin as initial monotherapy (1). However, insulin secretion capacity is genetically lower in Japanese than that it is in Caucasians. Therefore, sulphonylureas (SUs) are frequently used in Japanese type 2 diabetes, and about 60% of the patients are treated with SUs (2). However, SUs increase the likelihood of both hypoglycaemia and weight gain.

Dipeptidyl peptidase-4 (DDP-4) inhibitor is a newly developed AHA that prevents degradation of the incretin hormones, glucagon-like peptide-1 and gastric inhibitory polypeptide (3). The compound promotes glucose-dependent insulin secretion and suppresses glucagon release, and can improve both fasting and postprandial glucose levels. Four different DPP-4 inhibitors are available in Japan: sitagliptin, vildagliptin, alogliptin and linagliptin. Of these, sitagliptin is most widely used because it was the first DPP-4 inhibitor approved in Japan and both its efficacy and safety are accepted in Japanese clinical practice. Sitagliptin is more effective for glycaemic control in Japanese patients compared with Cauca-

sian patients (4,5,6). Hypoglycaemia does not occur with increased frequency when used as monotherapy or with agents that do not cause hypoglycaemia, such as metformin and thiazolidinediones, but may increase the incidence of hypoglycaemia when used with agents that cause hypoglycaemia (7). A case of severe hypoglycaemia was first reported in an aged Japanese patient when sitagliptin was combined with SUs (8). In this case, 50 mg/day sitagliptin was added to 6 mg/day glimepride. The laboratory data then showed that the plasma glucose level was 1.3 mM, and the immunoreactive insulin (IRI) level was 24.5 μU/ml. Since then, more than 70 cases of severe hypoglycaemia have been reported in patients within a week after the initiation of combination therapy with SUs and sitagliptin (9). In most of these cases, a relatively higher dosage of SUs was administered to elderly patients also having mild renal dysfunction. A private committee of diabetologists to establish adequate use of incretin-based therapy was then established. The committee recommended that the dosage of SUs should be decreased to less than 1.25 mg/day glibenclamide, 2.0 mg/day glimipiride or 40 mg/day gliclazide at the initiation of incretin-based therapy (10). As the recommendation was established in Japan, the number of severe hypoglycaemia cases has decreased remarkably.

However, the add-on effect of sitagliptin to SUs on glycaemic control when the daily dosage of SUs is reduced has not yet been determined. A reduction in the daily dosage of SUs should be helpful for many patients to prevent weight gain as well as hypoglycaemia. Although it also has not been determined whether insulin secretion capacity can be preserved by treatment with sitagliptin, SUs by themselves do not hasten the loss of beta-cell function (11) and improvement of insulin secretion capacity has been reported by vildagliptin, another DPP-4 inhibitor (12). We have conducted a prospective clinical study to determine the efficacy and safety of combination therapy with sitagliptin and lower dosage SUs on glycaemic control and insulin secretion capacity. Here, we show that sitagliptin added to a lower dosage of SUs is effective and well-tolerated for glycaemic control and that beta cell function is preserved at least for 1 year in Japanese type 2 diabetes patients.

Materials and methods

Study design

This study of add-on sitaglipitn to low dosage SUs is a prospective, 52-week, single centre, single arm, intervention study to evaluate the efficacy and safety of sitagliptin on glycaemic control in type 2 diabetes inadequately controlled with SUs. Outpatients of Takashima General Hospital were recruited consecutively for a sample size of 80 subjects who met both inclusion and exclusion criteria. Inclusion criteria were type 2 diabetes treated with SUs (glimepiride or gliclazide) ± metformin ± α-glucosidase inhibitors; aged ≥ 20 years; A1C level ≥ 6.9%; no improvement in A1C ≥ 0.5% within 3 months; and a wish to diet and exercise to improve health. The value for A1C (%) is estimated as an National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula A1C (%) = A1C (JDS) (%) + 0.4%, considering the relational expression of HbA1c (JDS) (%) measured by the previous Japanese standard substance and measurement methods and A1C (NGSP) (13). Exclusion criteria were type 1 diabetes; secondary diabetes; diabetic nephropathy stage 3–5; alcoholism; severe depression or severe psychological condition; malignancy; abnormal haemoglobinaemia; and participation in other clinical trials or studies. The study protocol was approved by the Institutional Review Board of Takashima General Hospital, and registered on the University Hospital Medical Information Network in Japan (UMIN000005498). Written informed consent was obtained from all subjects. The study began on 1 February 2010, and ended on 31 August 2011.

Procedures and intervention

The duration of the study was 52 weeks. Subjects were screened for eligibility and gave informed consent, basic demographic information, medical history and frequency of hypoglycaemia. Within a month before administration of sitagliptin, glucagon loading test was performed without any AHAs for more than 24 h to evaluate insulin secretion capacity. Type 1 diabetes was excluded by examination of autoantibodies to GAD 65 and results of glucagon loading test. At the date sitagliptin treatment was begun the dosage of glimepiride or gliclazide was decreased to equal to or less than 2.0 mg/day or 40 mg/day when the subjects had been treated with more than 2.0 mg/day of glimepiride or 40 mg/day of gliclazide, respectively. If the subjects had been treated with less than 2.0 mg/day of glimepride or 40 mg/day of gliclazide, that dosage of SUs was maintained. Metformin was continued without any changes. α-glucosidase inhibitors were discontinued. During the study, the dosage of SUs was changed depending on the frequency of hypoglycaemic episodes and glycaemic control level. Other AHAs were not added or were discontinued. The dosage of sitagliptin was started at 50 mg/day, the usual initial dosage of sitagliptin in Japan, and it was increased to 100 mg/day if the A1C level did not reach 6.9%, as

titration to 100 mg/day is acceptable. All other medications including statin and antihypertensive agents were not changed or newly prescribed during the study. If the A1C level did not reach 6.9% by treatment with 100 mg/day sitagliptin, the dosage of SUs was increased at physician discretion. Subjects visited the clinic every 4 weeks, and laboratory data including A1C, physical findings and all documented medications were collected every 4 weeks in the first 24 weeks and every 8 weeks in the last 28 weeks. On the day of the final visit, glucagon loading tests were performed under conditions that all prescribed AHAs had been withheld for 72 h.

Measurements

The primary endpoint was change in A1C in 52-week. The secondary endpoints were change in insulin secretion capacity (0-min C-peptide reactin (CPR), 6-min CPR, delta CPR) in 52-week, change in A1C in glimepiride and gliclazide subjects in 52-week, change in A1C in dosage of SUs-reduced and -unreduced subjects in 52-week, unresponsive rate in 12-week, ineffectiveness rate in 52-week, change in BMI, hypoglycaemia, change in blood pressure level, change in urinary albumin excretion and the correlation between change in A1C and insulin secretion capacity or CPR index (CPI) or the secretory unit of islet in transplantation (SUIT) index or BMI. CPI was calculated by the formula: [100 × fasting CPR (ng/ml)]/[18 × FPG (mM)] (14). SUIT index was calculated by the formula: [250 × fasting CPR (ng/ml)]/[(FPG-3.43) (mM)] (15). The day before glucagon loading test, subjects did not eat any food except water and tea without sugar after 9:00 pm. Glucagon loading test was performed in the morning, and blood glucose and C-peptide level were measured before (0 min) and 6 min after intravenous administration of 1 mg glucagon. If A1C reduction was less than 0.5% in 52-week, add-on of sitagliptin to SUs was considered to be ineffective. If A1C level in 12-week was not changed or increased, the combination therapy was judged unresponsive.

Statistical analysis

Sample size was estimated to be 64 to detect a 0.5% change in A1C in 52-week with a power 95%, alpha 0.05 two-tailed, beta 0.20, standardised effect size 0.5. To take the dropout rate of 20% into account, the aim was to include 80 subjects. Dependent samples Student's *t*-test was used to compare the means of A1C level, insulin secretion capacity, BMI and blood pressure between baseline and 52-week. Wilcoxon signed-rank test was used to compare the means of urinary albumin excretion between baseline and 52-week. Person's product-moment correlation test was used to evaluate the relationship between change in A1C and insulin secretion capacity or CPI or SUIT or BMI. p values < 0.05 were considered as statistically significant.

Results

Subjects

We screened 106 patients of whom 87 were provisionally registered. Of these, 82 were eligible and were enrolled consecutively in the study (Figure 1). Five patients declined to participate because of the visiting schedule. Average age of the subjects was 70.1 ± 8.6 years and 43.5% were female; duration of diabetes was 10.2 ± 4.7 years and A1C was 7.90 ± 0.51% (Table 1). Forty-six subjects were treated with glimepiride and 36 were treated with gliclazide. Twenty-five subjects were treated with metformin (average dose 640 ± 127 mg/day) (14

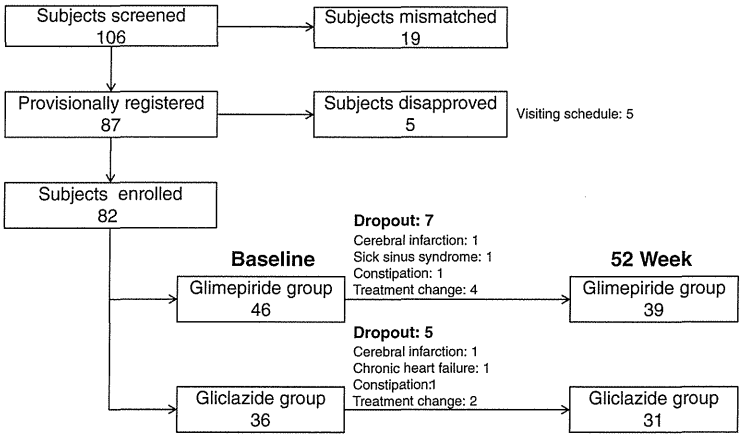

Figure 1 Progress of subjects through the study

Table 1 Background of the subjects

Subjects (*n*)	Age (years)	Female (%)	Diabetes duration (year)	A1C (%)	Nephropathy	Retinopathy	Neuropathy	Cardio vascular diseases	SU (%)	Medication Metformin (%)	αGI (%)
All 82	70.1 ± 8.6	43.5	10.2 ± 4.7	7.90 ± 0.51	36.6%	34.1%	26.8%	24.3%	100	30.4	12.2
Glimepiride 46	68.7 ± 7.5	41.3	9.9 ± 4.8	7.93 ± 0.55	34.7%	32.6%	26.1%	23.9%	56.1	17.1	7.3
Gliclazide 36	72.8 ± 10.0	42.2	10.9 ± 4.7	7.85 ± 0.49	38.9%	36.1%	27.8%	25.0%	43.9	13.4	4.9

glimepiride- and 11 gliclazide-treated subjects). α-glucosidase inhibitors were discontinued in 10 subjects (6 glimepride- and 4 gliclazide-treated subjects). There was no significant difference in the background of glimepiride and gliclizide subjects (Table 1). Twelve subjects were dropped because of hospitalisation for cerebral infarction (one glimepiride- and one gliclazide-treated subject), sick sinus syndrome (one glimepiride-treated subject), chronic heart failure (one gliclazide-treated subject), constipation by sitagliptin (one glimepiride- and one gliclazide-treated subject) or treatment changes from sitagliptin to liralgutide (four glimepiride- and two gliclazide-treated subjects) (Fig. 1). The dropout rate was 14.6% in all subjects, 15.2% in glimepiride subjects and 13.8% in gliclazide subjects (Table 2). The final number of subjects who completed the study was 70: 39 glimepiride subjects and 31 gliclazide subjects (Figure 1).

A1C findings

The A1C level in 52-week in all subjects was significantly decreased from 7.96 ± 0.53% to 7.16 ± 0.53% ($p < 0.001$). Change in A1C in 52-week was −0.80% (95% CI −0.90 to −0.68) ($p < 0.001$) (Table 2). Final dosage of sitagliptin was 69.0 ± 24.5 mg/day. In glimepiride subjects, the A1C level in 52-week was significantly decreased from 8.00 ± 0.57% to 7.19 ± 0.58% ($p < 0.001$) (Table 2). Change in A1C at 52-week from baseline was −0.81 (95% CI −0.96 to −0.62) ($p < 0.001$). The final dosages of glimepiride and sitagliptin were 1.44 ± 0.90 mg/day and 73.1 ± 25.4 mg/day respectively (Table 2). The initial and final dosages of glimepiride were significantly decreased compared with the original dosages of glimepiride ($p < 0.001$). In gliclazide subjects, A1C level in 52-week was significantly decreased from 7.92 ± 0.48% to 7.13 ± 0.49% ($p < 0.001$) (Table 2). Change in A1C at 52-week from baseline was −0.79 (95% CI −0.90 to −0.64) ($p < 0.001$). The initial dosage of gliclazide was slightly but significantly decreased from the original dosage of gliclazide ($p < 0.05$), but the final dosage of gliclazide did not differ from the original dosage. The final dosage of gliclazide and sitagliptin were 34.5 ± 15.3 mg/day and 64.6 ± 23.2 mg/day respectively (Table 2).

Differences in A1C findings in dosage of SUs-unreduced and -reduced subjects

The starting dosage of SUs was reduced to equal to or less than 2.0 mg/day glimepiride or 40 mg/day gliclazide if the two SUs were administrated at more than the suggested dosage. In addition, the dosage of SUs was reduced at physician discretion if subjects had previously experienced hypoglycaemia induced by SUs. In SU-reduced subjects, the initial dosage of glimepiride was decreased from 1.79 ± 0.97 to 1.10 ± 0.51 mg/day in 16 of the 39 glimepiride subjects and that of gliclazide was decreased from 55.0 ± 17.6 to 33.3 ± 10.3 mg/day in 12 of the 31 gliclazide subjects. The dosages for SUs-unreduced subjects of glimepiride and gliclazide were 1.15 ± 0.55 mg/day and 30.0 ± 10.3 mg/day respectively. Thus, the A1C level was almost equally decreased in SUs-unreduced and SU-reduced subjects (Table 3). The change in A1C was −0.80% (95% CI −1.02 to −0.59) ($p < 0.001$) in SUs-unreduced subjects, and −0.81% (95% CI −1.04 to −0.57) ($p < 0.001$) in SUs-reduced subjects. In glimepiride subjects, the change in A1C level was −0.88% (95% CI −1.16 to −0.59) ($p < 0.001$) in SU-unreduced subjects, and −0.70% (95% CI −0.98 to −0.42) ($p < 0.001$) in SU-reduced subjects (Table 3). In gliclazide subjects, the change in A1C was −0.71% (95% CI −1.03 to −0.39%) ($p < 0.001$) in SU-unreduced subjects, and −0.96% (95% CI −1.32 to −0.60%) ($p < 0.001$) in SU-reduced subjects (Table 3).

Hypoglycaemia

During the study no severe hypoglycaemia was documented. Mild hypoglycaemia was observed in three subjects (two glimepiride- and one gliclazide-treated subject) (Table 2). All subjects reported a sense of hunger that diminished when the dosage of glimepiride or glyclazide was reduced.

Table 2 Change in A1C and dosages of SUs and sitagliptin

Final subjects (*n*)	Dropout rate (%)	A1C level baseline	A1C level 52-week	Change in A1C (95% CI)	Original dosage of SUs (mg)	Initial dosage of SUs (mg)	Final dosage of SUs (mg)	Final dosage of sitagliptin (mg)	Hypoglycaemia (*n*)
All 70	14.6	7.96 ± 0.53	7.16 ± 0.53*	−0.80% * (−0.90, −0.68%)	–	–	–	69.0 ± 24.5	3
Glimepiride 39	13.8	8.00 ± 0.57	7.19 ± 0.58*	−0.81% * (−0.96, −0.62%)	1.75 ± 0.96	1.19 ± 0.51*	1.44 ± 0.90*	73.1 ± 25.4	2
Gliclazide 31	15.2	7.92 ± 0.48	7.13 ± 0.49*	−0.79% * (−0.90, −0.64%)	36.7 ± 18.4	30.0 ± 12.0***	34.5 ± 15.3	64.6 ± 23.2	1

*$p < 0.001$; ***$p < 0.05$.

Insulin secretion capacity

Insulin secretion capacity was measured by glucagon loading test, which was performed at baseline in the absence of any AHAs for 24 h and at 52-week in the absence of any AHAs for 72 h. At baseline, 0-min plasma glucose (PG) and CPR level were 7.6 ± 1.5 mM and 1.61 ± 0.59 ng/ml, respectively, and 6-min plasma glucose and C-peptide level were 8.7 ± 1.6 mM and 3.46 ± 1.41 ng/ml respectively (Table 4). At 52-week, 0-min PG and CPR level were 7.7 ± 1.1 mM and 1.71 ± 0.67 ng/ml, respectively, and 6-min PG and CPR level were 8.8 ± 1.1 mM and 3.45 ± 1.13 ng/ml respectively. These results indicate that insulin secretion capacity was not significantly increased, but was maintained for at least 52 weeks after 1-year administration of sitagliptin.

In the glimepiride group, 0-min PG and CPR level at baseline were 8.1 ± 1.6 mM and 1.67 ± 0.52 ng/ml, respectively, and 6-min PG and CPR level were 9.1 ± 1.6 mM and 3.48 ± 1.21 ng/ml respectively (Table 4). At 52-week, 0-min PG and CPR level were 7.9 ± 0.9 mM and 1.59 ± 0.79 ng/ml, respectively, and 6-min PG and CPR level were 8.9 ± 1.0 mg/dl and 3.12 ± 0.93 ng/ml respectively. In the gliclazide group, fasting PG and CPR level at baseline were 6.9 ± 1.3 mM and 1.61 ± 0.61 ng/ml, respectively, and 6-min PG and CPR level were 8.1 ± 1.6 mM and 3.48 ± 1.62 ng/ml respectively (Table 4). At 52-week, 0-min PG and CPR level were 7.6 ± 1.2 mM and 1.84 ± 0.70 ng/ml, respectively, and 6-min PG and CPR level were 8.7 ± 1.2 mM and 3.66 ± 1.23 ng/ml respectively. There was no statistical difference in insulin secretion capacity between the glimepiride group and the gliclazide group at baseline and 52-week. Insulin secretion capacity was preserved for 52 weeks in both the glimepiride and gliclazide groups.

CPI and SUIT index

CPI and SUIT index were evaluated as an indication of treatment outcome in all subjects and glimepiride and glilcazide subjects. If CPI or SUIT index is more than 1.2 or 50, respectively, the patient could be treated with AHAs or diet and exercise. If CPI or SUIT index is less than 0.8 or 20, respectively, patients usually require insulin therapy (14,15). CPI at baseline was 1.22 ± 0.47 in all subjects, 1.17 ± 0.45 in glimepiride subjects and 1.26 ± 0.50 in gliclizide subjects (Table 5). CPI at 52-week was 1.25 ± 0.53 in all subjects, 1.10 ± 0.40 in glimepiride subjects and 1.41 ± 0.61 in gliclizide subjects. SUIT index at baseline was 37.1 ± 18.2 in all subjects, 33.6 ± 16.9 in glimepiride subjects and 40.9 ± 19.0 in gliclizide subjects (Table 5). SUIT index at 52-week was 36.2 ± 17.7 in all subjects, 30.2 ± 11.3 in

Table 3 Change in A1C in dosage of SUs-reduced or -unreduced subjects

Un-reduced subjects(*n*)	Original and Initial dosage of SUs (mg)	Final dosage of SUs (mg)	Final dosage of sitagliptin (mg)	A1C level baseline	A1C level 52-week	Change in A1C (95% CI)
All 42			63.2 ± 22.6	7.98 ± 0.48	7.10 ± 0.55*	−0.80%* (−1.02, −0.59%)
Glimepiride 23	1.15 ± 0.55	1.36 ± 0.95	66.7 ± 24.6	8.05 ± 0.42	7.19 ± 0.60*	−0.88%* (−1.16, −0.59%)
Gliclazide 19	30.0 ± 10.3	35.0 ± 17.1	57.1 ± 18.9	7.91 ± 0.52	7.05 ± 0.53*	−0.71%* (−1.03, −0.39%)

Reduced subjects (*n*)	Original dosage of SUs(mg)	Initial dosage of SUs (mg)	Final dosage of SUs (mg)	Final dosage of sitagliptin (mg)	A1C level baseline	A1C level 52-week	Change in A1C (95% CI)
All 28				72.6 ± 25.4	7.94 ± 0.42	7.17 ± 0.56*	−0.81%* (−1.04, −0.57%)
Glimepiride 16	1.79 ± 0.97	1.10 ± 0.51*	1.53 ± 0.92*	78.6 ± 25.7	7.94 ± 0.43	7.23 ± 0.64*	−0.70%* (−0.98 −0.42%)
Gliclazide 12	55.0 ± 17.6	33.3 ± 10.3**	31.4 ± 10.7**	67.6 ± 24.6	7.93 ± 0.42	7.06 ± 0.43*	−0.96%* (−1.32, −0.60%)

*p < 0.001; **p < 0.01.

Table 4 Glucagon loading test

	Glucagon loading test							
	0-week				52-week			
	0-min		6-min		0-min		6-min	
Final subjects	PG (mm)	CPR (ng/ml)	PG (mm)	CPR (ng/ml)	PG (mm)	CPR (ng/ml)	PG (mm)	CPR (ng/ml)
All 70	7.6 ± 1.5	1.61 ± 0.59	8.7 ± 1.6	3.46 ± 1.41	7.7 ± 1.1	1.71 ± 0.67	8.8 ± 1.1	3.45 ± 1.13
Glimepiride 39	8.1 ± 1.6	1.67 ± 0.52	9.1 ± 1.6	3.48 ± 1.21	7.9 ± 0.9	1.59 ± 0.79	8.9 ± 1.0	3.12 ± 0.93
Gliclazide 31	6.9 ± 1.3	1.61 ± 0.61	8.1 ± 1.6	3.48 ± 1.62	7.6 ± 1.2	1.84 ± 0.70	8.7 ± 1.2	3.66 ± 1.23

glimepiride subjects and 42.2 ± 21.2 in gliclizide subjects. There were no significant differences in CPI and SUIT index between baseline and 52-week or among the three groups. This evidence indicates that combination therapy with any of the SUs and sitagliptin did not worsen the therapeutic selectivity in 52-week.

Correlation between efficacy of sitagliptin on glycaemic control and insulin secretion capacity, CPI, SUIT and BMI.

We then evaluated insulin secretion capacity, CPI, SUIT and BMI at baseline to predict the efficacy of combination therapy with sitagliptin and SUs on glycaemic control in all subjects. There was no correlation between 0-min C-peptide or 6-min C-peptide or delta C-peptide assessed by glucagon loading at baseline test and the efficacy of the combination therapy (Figure 2A, B, C). Other patient background, such as age and disease duration was not correlated with the efficacy of the combination therapy on glycaemic control (Data not shown). In addition, there was no relationship between CPI or SUIT index at baseline and change in A1C in 52-week (Figure 2D, E). BMI at baseline also did not correlate with the change in A1C in 52-week (Figure 2F). In the glimepiride and gliclazide groups, change in A1C in 52-week and insulin secretion capacity, CPI, SUIT index or BMI at baseline was not correlated (data not shown).

BMI, blood pressure and urinary albumin excretion changes

BMI in all subjects at baseline and 52-week were 24.1 ± 3.2 kg/m^2 and 23.7 ± 3.0 kg/m^2 respectively. Change in BMI in 52-week was −0.38 kg/m^2 (95% CI −0.72 to −0.04) ($p < 0.05$) (Table 6). BMI in glimepiride subjects at baseline and 52-week were 23.4 ± 3.0 kg/m^2 and 23.0 ± 2.5 kg/m^2 respectively. Change in BMI in 52-week was −0.43 kg/m^2 (95% CI −0.71 to −0.13) ($p < 0.01$) in glimepiride subjects. BMI in gliclazide subjects at baseline and 52-week were 24.6 ± 3.3 kg/m^2 and 24.4 ± 3.9 kg/m^2 respectively. Change in BMI in 52-week was −0.20 kg/m^2 (95% CI −0.51 to + 0.11) ($p > 0.05$).

Blood pressure at baseline was 129 ± 12.5/73.6 ± 9.6 mmHg in all subjects, 128 ± 12.1/73.2

Table 5 CPI and SUIT in the final, effective and ineffective subjects

Final subjects	CPI baseline	SUIT baseline	CPI 52-week	SUIT 52-week	Effective Subjects	CPI baseline	SUIT baseline	CPI 52-week	SUIT 52-week	Ineffective Subjects	CPI baseline	SUIT baseline	CPI 52-week	SUIT 52-week
All 70	1.22 ± 0.47	37.1 ± 18.2	1.25 ± 0.53	36.2 ± 17.7	All 58	1.23 ± 0.50	37.9 ± 19.5	1.27 ± 0.57	36.9 ± 20.0	All 12	1.12 ± 0.33	31.7 ± 9.8	1.14 ± 0.12	28.9 ± 9.4
Glimepiride 39	1.17 ± 0.45	33.6 ± 16.9	1.10 ± 0.40	30.2 ± 11.3	Glimepiride 33	1.20 ± 0.45	34.0 ± 17.3	1.12 ± 0.45	30.8 ± 12.3	Glimepiride 6	1.01 ± 0.29	31.4 ± 14.7	0.99 ± 0.13	26.9 ± 5.8
Gliclazide 31	1.26 ± 0.50	40.9 ± 19.0	1.41 ± 0.61	42.2 ± 21.2	Gliclazide 25	1.27 ± 0.53	43.0 ± 22.4	1.44 ± 0.73	44.5 ± 23.2	Gliclazide 6	1.22 ± 0.38	32.0 ± 4.8	1.28 ± 0.11	30.8 ± 12.9

± 8.5 mmHg in glimepiride subject and 132 ± 13.2/74.2 ± 11.3 mmHg gliclazide subjects. Blood pressure at 52-week was 122 ± 15.4/70.0 ± 8.8 mmHg in all subjects, 124 ± 10.4/68.9 ± 7.6 mmHg in glimepiride subjects and 124 ± 9.7/71.0 ± 10.3 mmHg in gliclazide subjects. Change in systolic and diastolic blood pressure was −6.7 mmHg (95% CI −10.0 to −3.4) ($p < 0.001$) and −3.6 mmHg (95% CI −4.8 to −2.4) ($p < 0.001$) in all subjects, respectively, −4.4 mmHg (95% CI −7.1 to −1.7) ($p < 0.05$) and −4.3 mmHg (95% CI −5.6 to −3.0 mmHg) ($p < 0.001$) in glimepiride subjects and −7.9 mmHg (95% CI −11.3 to −4.4 mmHg) ($p < 0.001$) and −3.2 mmHg (95% CI −4.7, −1.6 mmHg) ($p < 0.001$) in gliclazide subjects, respectively.

Urinary albumin excretion was decreased from 76.2 ± 95.6 to 33.0 ± 48.1 mg/gCr in all subjects: from 56.9 ± 62.0 to 23.9 ± 13.8 mg/gCr in glimepiride subjects and from 107 ± 129 to 47.4 ± 74.4 mg/gCr in gliclazide subjects. Change in urinary albumin excretion was −43.2 mg/gCr (95% CI −65.7 to −20.8) ($p < 0.001$) in all subjects, −33.0 mg/gCr (95% CI −50.5 to −15.6) ($p < 0.001$) in glimepiride subjects and −59.6 (95% CI −91.2 to −22.5) ($p < 0.01$) in gliclazide subjects respectively.

Ineffective and effective add-on treatment in 52-week

The A1C level of 12 of the 70 subjects was not improved more than 0.5% in 52-week. The ineffectiveness rate was 17.1%. A1C level at baseline and 52-week in ineffective subjects was 7.26 ± 0.43%, and 6.98 ± 0.39% respectively (Table 7). Change in A1C was −0.28% (95% CI −0.34 to −0.21) ($p < 0.001$). On the other hand, A1C level at baseline and 52-week in effective subjects was 7.51 ± 0.56% and 6.58 ± 0.45% respectively. The change in A1C was −0.93% (95% CI −1.06 to −0.81) ($p < 0.001$). The change in A1C between ineffective and effective subjects was significantly different ($p < 0.001$). Although CPI, SUIT index and 0-min CPR in ineffective subjects were relatively lower than those in effective subjects, the differences were not significant (Figure 3, Table 5). Six-minutes CPR and delta CPR evaluated by glucagon loading test also were not significantly different between the two groups of subjects (Data not shown).

Responsive and unresponsive subjects in 12-week

The combination therapy with SUs and sitagliptin was changed to liragrutide in 5 of 82 (6.1%) subjects in 12-week because of worsening in glycaemic control in 12-week. A1C level at baseline and 12-week in

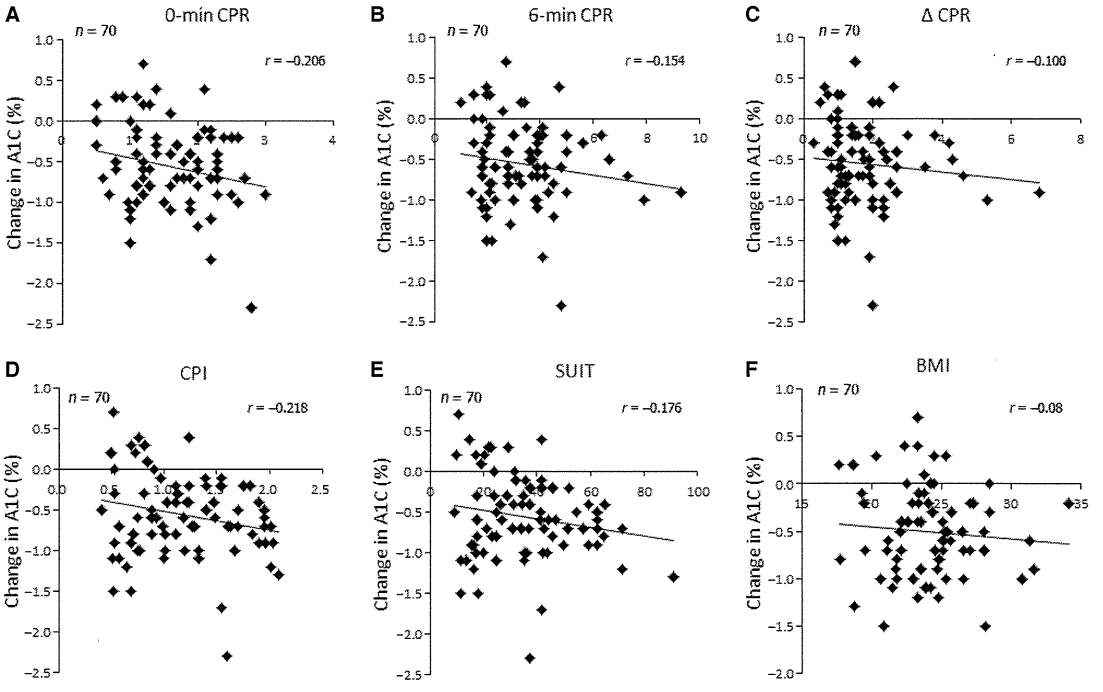

Figure 2 Relationship between change in A1C in 52-week and results of glucagon loading test, CPI, SUIT and BMI at baseline. Change in A1C in 52-week and 0-min CPR (A), 6-min CPR (B), delta CPR (C), CPI (D), SUIT index (E) and BMI (F) at baseline. CPR, C-peptide reaction; CPI, C-peptide index; SUIT, the secretory unit of islet in transplantation; BMI, body mass index

the unresponsive subjects was 7.43 ± 0.26% and 7.70 ± 0.55% respectively (Table 7). Change in A1C was + 0.27% (95% CI −0.05 to + 0.59) ($p > 0.05$). On the other hand, A1C level at baseline and 12-week in responsive subjects were 7.50 ± 0.54% and 6.66 ± 0.48% respectively. Change in A1C was −0.84% (95% CI −0.96 to −0.72) ($p < 0.001$). The change in A1C in unresponsive and responsive subjects was significantly different ($p < 0.001$). However, there was no difference between 0-min CPR and CPI at baseline in unresponsive and responsive subjects (Figure 3). SUIT index, 6-min CPR and delta-CPR at baseline also were similar in responsive and unresponsive subjects (data not shown).

Discussion

Sitagliptin was the first available DPP-4 inhibitor and is broadly administered at any step in the therapeutic algorithm in Japan. The compound is well tolerated and decreases A1C level by 1.05% compared with placebo in Japanese type 2 diabetes (4). Sitagliptin is effective for glycaemic control and is well tolerated in Caucasian type diabetes at least up to 2 years in duration (16,17). However, when combined with SUs, severe hypoglycaemia has occurred in Japanese patients with type 2 diabetes (8,9). The characteristics of these patients are aged, with mild renal dysfunction and treatment with a relatively higher dosage of SUs. In the clinical trials for combination therapy with sitagliptin and glimepiride (1–6 mg/day), such severe hypoglycaemia was never observed (5). The average dosage of glimepiride was about 2.5 mg/day in both the sitagliptin add-on group and placebo (glimepiride alone) group, and the dosage was maintained during the entire 52-week period. The average age was 61.0 years in placebo group and 60.5 years old in sitagliptin group, and subjects with moderate renal dysfunction (serum creatinine > 1.5 mg/dl in men or > 1.3 mg/dl in women) were excluded. The incidence of hypoglycaemia in 12-week was 5.6% and 0.0% in sitagliptin group and placebo group respectively. All hypoglycaemia events were considered either mild or moderate; severe hypoglycaemia was unexpected and was not observed. Japanese type 2 diabetes is characterised mainly by impaired insulin secretion, so that an insulin secretagogue is most commonly used (2). Thus, determination of the adequate dosage of SUs in combination of DPP-4 inhibitors that ensures safety and efficacy is extremely important in Japan. We find here that less than or equal to 40 mg/day of glyclazide and 2 mg/day of glimepride in combination with sitagliptin is sufficient for glycaemic control and does not cause severe hypoglycaemia.

Table 6 Changes in BMI, blood pressure and urinary albumin excretion

Final subjects	BMI Baseline (kg/m^2)	BMI 52-week (kg/m^2)	Change in BMI (kg/m^2) (95% CI)	Blood pressure Baseline (mmHg)	Blood pressure 52-week (mmHg)	Change in blood pressure Systolic/diastolic (mmHg)(95% CI)	Urinary albumin excretion Baseline (mg/gCr)	Urinary albumin excretion 52-week (mg/gCr)	Change in Urinary albumin excretion (mg/gCr)
All 70	24.1 ± 3.2	23.7 ± 3.0	−038*** (−0.72, −0.04)	129 ± 12.5/ 73.6 ± 9.6	122 ± 15.4*/ 70.0 ± 8.8*	−6.7* (−10.0, −3.4) −3.6* (−4.8, −2.4)	76.2 ± 95.6	33. 0 ± 48.1**	−43.2* (−65.7, −20.8)
Glimepiride 39	23.4 ± 3.0	23.0 ± 2.5	−0.43** (−0.71, −0.13)	128 ± 12.1/ 73.2 ± 8.5	124 ± 10.4***/ 68.9 ± 7.6**	−4.4*** (−7.1, −1.7) −4.3* (−5.6, −3.0)	56.9 ± 62.0	23. 9 ± 13.8**	−33.0* (−50.5, −15.6)
Gliclazide 31	24.6 ± 3.3	24.4 ± 3.9	−0.20 (−0.51, 0.11)	132 ± 13.2/ 74.2 ± 11.3	124 ± 9.7**/ 71.0 ± 10.3	−7.9* (−11.3, −4.4) −3.2* (−4.7. −1.6)	107 ± 129	41.4 ± 54.4***	−59.6** (−91.2, −22.5)

*p < 0.001; **p < 0.01; ***p < 0.05.

Table 7 Change in A1C in ineffective and effective subjects

Subjects	A1C Baseline	A1C 52-week	Change in A1C (95% CI)
Ineffective 12	7.26 ± 0.43	6.98 ± 0.39*	−0.28%* (−0.34, −0.21%)
Effective 58	7.51 ± 0.56	6.58 ± 0.45*	−0.93%* (−1.06, −0.81%)
Unresponsive 5	7.43 ± 0.26	7.70 ± 0.55	0.27% (−0.05, 0.59%)
Responsive 77	7.50 ± 0.54	6.66 ± 0.48*	−0.84%* (−0.96, −0.72%)

*p < 0.001.

In the present study, the A1C level in all subjects was decreased from 7.90 ± 0.53% to 7.10 ± 0.53% in 52-week. Change in A1C in 52-week was −0.80% (95% CI −0.90 to −0.68) (p < 0.001). Dosages of glimepiride and gliclazide were decreased from 1.75 ± 0.96 mg/day to 1.19 ± 0.96 mg/day and from 35.3 ± 18.4 mg/day to 30.0 ± 12.0 mg/day, respectively, at the initiation of sitagliptin. In addition, the final dosages of glimepiride and gliclazide were 1.44 ± 0.90 mg/day and 34.5 ± 15.3 mg/day, respectively, which were not significantly increased during the study. The average final dosage of sitagliptinn was 73.1 ± 25.4 mg/day in the glimepiride group and 64.6 ± 23.2 mg/day in the gliclazide group. These results show that when combined with sitagliptin, low dosages of SUs are sufficient for glycaemic control in Japanese type 2 diabetes. On the other hand, in Caucasian type 2 diabetes, change in A1C in 24-week has been found to be −0.74% (95% CI −0.90 to −0.57) by treatment with 100 mg/day sitagliptin and equivalent to 4 mg/day or more glimepiride (6). Thus, Japanese type 2 diabetes requires a lower dosage of sitagliptin and SUs for glycaemic control than Caucasian type 2 diabetes. In addition, the change in A1C in 52-week did not differ between dosages of SUs-reduced and -unreduced subjects: −0.88% (95% CI −1.16 to −0.59) in glimepiride-unreduced subjects and −0.70% (95% CI −0.98 to −0.42) in glimepiride-reduced subjects and −0.71% (95% CI −1.03 to −0.39) in gliclazide-unreduced subjects and −0.96% (95% CI −1.32 to −0.60) in gliclazide-reduced subjects. The observation that the efficacy was similar in SU-reduced and -unreduced subjects is consistent with prior observations that maximal SU efficacy is typically attained at doses that are less than the maximum prescribed dose (18). The average dosage of SUs also did not differ in both glimepiride and gliclazide subjects: the dosage of

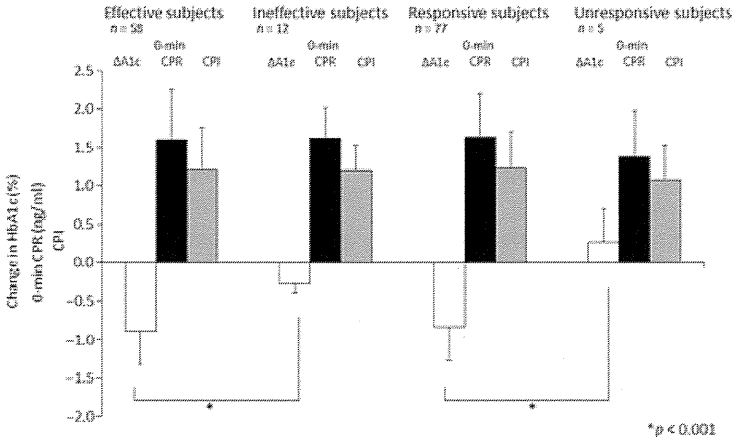

Figure 3 Differences in change in A1C in 52-week, 0-min CPR and CPI in effective and ineffective subjects in 52-week or responsive and unresponsive subjects in 12-week. CPR, C-peptide reaction; CPI, C-peptide index **p < 0.001

glimepiride was 1.53 ± 0.92 mg/day in reduced subjects and 1.36 ± 0.95 mg/day in unreduced subjects; the dosage of gliclazide was 31.4 ± 10.7 mg/day in reduced subjects and 35.0 ± 17.1 mg/day in unreduced subjects. This result indicates that the dosage of SUs can be reduced to less than 2 mg/day of glimepiride and 40 mg/day of gliclazide at initiation of combination therapy with sitagliptin.

The ineffective rate of the combination therapy with SUs and sitagliptin in 52-week was 17.1% in this study. CPI and SUIT index in ineffective subjects were relatively lower than those in effective subjects, but there was no significant difference between the two groups. About 40% of the ineffective subjects achieved a reduction of 0.5% or greater during the course of the study. Diet failure was a cause of an increase in A1C in those cases, further suggesting that sitagliptin might be effective for glycaemic control in these patients. The causes of ineffectiveness of sitagliptin in the remaining ineffective subjects remain unknown. However, the baseline A1C in the ineffective subjects was lower than that in the effective subject group (7.26% vs. 7.51%). Thus, the designation of ineffective for those subjects may simply reflect the lower baseline value and not a lack of responsiveness to sitagliptin. In addition, sulphonylurea efficacy diminishes over time, an effect called secondary failure of sulphonylureas. Thus, the failure to achieve a reduction of 0.5% at 52 weeks might also reflect a reduction in the contribution of the sulphonylurea rather than unresponsiveness to sitagliptin.

Hypoglycaemia was observed in only three cases: two in the glimepiride group and one in the gliclazide group. All patients had a sense of hunger that diminished when the dosage of the SUs was reduced. Therefore, at the beginning of therapy with sitagliptin with SUs, it is safe for patients, especially those who have had experiences of hypoglycaemia, to receive a smaller dosage of SUs.

In the present study, we examined whether or not insulin secretion capacity predicted the efficacy of the combination therapy on glycaemic control. Insulin secretion capacity evaluated by glucagon loading test did not predict the efficacy of sitagliptin, although a tendency to correlation was observed in 0-min CPR and CPI (Figure 2). There were also no differences in insulin secretion capacity, CPI and SUIT index between ineffective and effective subjects or unresponsive and responsive subjects (Figure 3). Thus, insulin secretion capacity does not predict the efficacy of combination therapy with sitagliptin and SUs. Recently, Kim et al. reported that sitagliptin responders had lower body mass index and were younger compared with non-responders in Korean type 2 diabetes (19). Nomiyama et al. reported that treatment with sitagliptin 50 mg/day for 24 weeks was especially effective in patients with higher baseline A1C, lower BMI and duration of diabetes (20). However, in our study, BMI did not correlate with the efficacy of combination therapy. Other patient background, such as age, disease duration, and gender, also did not predict the efficacy of the combination therapy in Japanese type 2 diabetes (data not shown). Thus, no suggestive marker to predict the efficacy of sitagliptin with SUs on glycaemic control has been identified.

BMI was decreased only in glimepiride subjects and not in gliclazide-treated subjects. The dosage of glimepiride was decreased from 1.75 ± 0.96 mg/day to 1.19 ± 0.51 mg/day at baseline, and was not significantly increased during the study. However, the dosage of gliclazide was not significantly decreased during the study. In the clinical trial of the combination therapy with sitagliptin and glimepiride, body weight was significantly increased by 0.50 kg in the