Factors associated with the glucose-lowering efficacy of sitagliptin in Japanese patients with type 2 diabetes mellitus: Pooled analysis of Japanese clinical trials

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ABSTRACT

Aims/Introduction: To explore the factors associated with the glucose-lowering efficacy of sitagliptin treatment in Japanese patients with type 2 diabetes mellitus.

Materials and Methods: This was a post-hoc analysis of pooled data from seven sitagliptin phase II and III clinical studies carried out in Japan. All studies were double-blind, randomized, placebo-controlled, parallel-group and of 12-week duration. The analysis population consisted of 1,075 type 2 diabetes mellitus patients. In two of the trials, sitagliptin 50 mg and/or 100 mg daily were used as monotherapy; in five others, sitagliptin 50 mg daily was used as add-on treatment to ongoing pioglitazone, glimepiride, metformin, voglibose or glinides. Efficacy (reduction in hemoglobin A1c [HbA1c]) was evaluated in 12 sets of subgroups defined by demographic, glycemic, pancreatic β-cell function and insulin resistance parameters. An analysis of covariance model was used to evaluate the interaction between each parameter and efficacy.

Results: Sitagliptin consistently provided a clinically meaningful reduction in HbA1c relative to placebo across all subgroups. Within subgroups, a greater absolute HbA1c reduction was associated with higher baseline HbA1c, fasting plasma glucose and 2-h post-meal glucose. Lower β-cell function, represented by homeostatic model assessment of β-cell function and insulinogenic index, was also associated with greater HbA1c reduction. In contrast, age, sex, body mass index, duration of type 2 diabetes mellitus and insulin resistance-related parameters did not interact with HbA1c changes.

Conclusions: Sitagliptin treatment was associated with clinically meaningful improvement in glycemic control in all subgroups of Japanese patients with type 2 diabetes mellitus that were evaluated. Higher baseline glycemic status and lower baseline β-cell function were identified as factors associated with greater HbA1c reduction after sitagliptin treatment.

INTRODUCTION

The number of pharmacological options for treatment of type 2 diabetes mellitus has dramatically increased in the past two decades, and a variety of drugs with distinct mechanisms of action are approved for use in clinical practice. Although there are seven oral antihyperglycemic agent classes currently available in Japan, it is estimated that >70% of Japanese patients with type 2 diabetes who receive oral antihyperglycemic agent therapy are treated with a dipeptidyl peptidase-4 inhibitor (DPP4i), and approximately 60% receive a DPP4i as a monotherapy[1]. Given the widespread use of DPP4is in Japan, identification of interactions of clinical/demographic factors with glucose-lowering efficacy of DPP4is could improve outcomes and cost-effectiveness.

The aim of the present post-hoc analysis was to assess whether any of a selected set of baseline parameters is associated with the efficacy of the DPP4i, sitagliptin, in Japanese

patients with type 2 diabetes. To identify subgroups of patients with differential response to treatment, we calculated change from baseline in hemoglobin A1c (HbA1c) relative to placebo for subgroups of patients defined by 12 different demographic/anthropometric parameters, and assessed the interaction between these parameters and HbA1c change from baseline.

METHODS
Data sources
For the present post-hoc analysis, efficacy data from seven phase II and III sitagliptin clinical trials were pooled. A detailed description of each trial has been reported elsewhere[2–8]. Briefly, all studies were carried out in Japan, and the efficacy of sitagliptin 50 mg or 100 mg was assessed in a double-blind, randomized, placebo-controlled design with 12-week treatment duration (Table S1). Two of these studies included sitagliptin 50 mg and/or 100 mg once-daily monotherapy[2,3], and five included sitagliptin 50 mg once-daily in combination with ongoing pioglitazone 15–45 mg/day[4], glimepiride 1–6 mg/day[5], metformin 500–1,500 mg/day[6], voglibose 0.6–0.9 mg/day[7] or glinides (i.e., nateglinide 180–360 mg/day or mitiglinide 15–60 mg/day)[8]. Each of the five combination studies had a 40-week extension period in which all patients received sitagliptin; the absence of a comparator arm precluded use of data from the extension periods in the analysis reported here. All procedures carried out in the studies involving human participants were in accordance with the good clinical practice guidelines and ethical principles stated in the Declaration of Helsinki. Individual study protocol was approved by the institutional review board at each study site. Written informed consent was obtained from all individual participants in all of these studies, as described earlier[2–8].

Subgroups were defined by generally accepted clinical characteristics or designed to provide approximately equal size subgroups. Subgroups defined by clinical characteristic were baseline age (<65 years, ≥65 years), sex, body mass index (BMI; <25 kg/m^2, ≥25 kg/m^2) and duration of type 2 diabetes (<1 year, 1 to <5 years, ≥5 years). Subgroups defined by continuous variables were grouped by tertiles for glycemic parameters, otherwise they were grouped as below or at and above the median value: fasting plasma glucose (FPG; tertiles: <138 mg/dL, 138 to <165 mg/dL, ≥165 mg/dL), 2-h post-meal glucose (2h-PMG: tertiles: <209 mg/dL, 209 to <265 mg/dl, ≥265 mg/dL), HbA1c (tertiles: <7.7%, 7.7 to <8.4%, ≥8.4%), homeostatic model assessment (HOMA) of β-cell function (HOMA-β; < or ≥ median [24.4]), insulinogenic index during meal tolerance test (< or ≥ median [0.281]), fasting C-peptide (< or ≥ median [2.0 ng/mL]), HOMA of insulin resistance (HOMA-IR; < or ≥ median [2.23]) and the quantitative insulin-sensitivity check index (QUICKI; < or ≥ median [0.147]).

Statistical analysis
Patient baseline characteristics were tabulated for all patients who took at least one dose of study treatment (overall analysis population). For the efficacy analyses, patients without a baseline or at least one post-randomization efficacy measurement were excluded. In the overall analysis population ($n = 1,075$), seven patients from three studies did not have any post-randomization measurements; as a result, a total of $n = 1,068$ were included in the efficacy analysis population. Missing data were imputed using the last observation carried forward method if efficacy value(s) after randomization existed. All HbA1c values reported here were converted from Japan Diabetes Society values to National Glycohemoglobin Standardization Program values[9].

An analysis of covariance (ANCOVA) model including treatment (sitagliptin or placebo), prior other antihyperglycemic agent status (yes or no) and baseline HbA1c values as covariates (fixed effects) was used to estimate the least squares (LS) mean (95% confidence interval [CI]) change from baseline in HbA1c at week 12. Study term was used in the model as a random effect after the heterogeneity of efficacy among the seven studies was confirmed not substantial by testing the interaction of treatment effect and study ($P = 0.137$). The ANCOVA model was used to evaluate treatment effect for each parameter, and the interaction of treatment effect and subgroup category was tested for each subgroup variable. A similar model was used to evaluate changes from baseline in FPG and 2h-PMG. All testing was carried out at the significance level of 5% (two-sided).

RESULTS
Characteristics of pooled study populations
The overall analysis population included 1,075 patients. The mean HbA1c, age and BMI of the overall population at baseline were 8.2%, 59.0 years and 24.9 kg/m^2, respectively. The baseline demographic and anthropometric characteristics of the overall population were similar between the placebo and sitagliptin treatment groups (Table 1). Parameters associated with β-cell function and insulin resistance at baseline were also similar between treatment groups (Table 1). These characteristics of the pooled populations were generally consistent with those of the seven individual studies[2–8]. Although the overall pooled study population tended to be aged <65 years, male and with ≥1 year mean duration of type 2 diabetes for each subgroup category, there was a similar distribution of patients between treatment groups (Table 2).

HbA1c reduction in the efficacy analysis population
In the efficacy analysis population ($n = 1,068$ patients), the LS mean change from baseline in HbA1c (95% CI) in the sitagliptin treatment group was −0.59% (−0.69, −0.50), whereas in the placebo group, it was + 0.32% (0.22–0.41). The placebo-subtracted LS mean HbA1c reduction (95% CI) was −0.91% (−0.98, −0.84; $P < 0.001$).

HbA1c reduction by demographic parameters
To assess the association of patients' demographic characteristics at randomization with response to sitagliptin, the placebo-

Table 1 | Baseline demographic and anthropometric characteristics

Parameter	Total ($n = 1,075$)	Placebo ($n = 499$)	Sitagliptin ($n = 576$)
Age (years)	59.0 ± 9.5	58.6 ± 9.2	59.3 ± 9.7
BMI (kg/m^2)	24.9 ± 3.5	24.9 ± 3.5	24.9 ± 3.5
Duration of T2DM (years)	6.1 ± 6.0	5.8 ± 5.3	6.3 ± 6.6
HbA1c (%)	8.2 ± 0.9	8.2 ± 0.9	8.2 ± 0.9
FPG (mg/dL)	156 ± 34	158 ± 34	154 ± 35
2h-PMG (mg/dL)	241 ± 66	241 ± 67	241 ± 65
Fasting C-peptide (ng/mL)	2.1 ± 0.9	2.1 ± 0.9	2.2 ± 0.9
HOMA-β	30.4 ± 24.4	29.2 ± 21.3	31.5 ± 26.7
Insulinogenic index	0.4 ± 1.1	0.3 ± 1.5	0.4 ± 0.8
HOMA-IR	2.7 ± 1.8	2.7 ± 1.9	2.7 ± 1.8
QUICKI	0.15 ± 0.02	0.15 ± 0.02	0.15 ± 0.02

Data are expressed as the mean ± standard deviation. BMI, body mass index; FPG, fasting plasma glucose; 2h-PMG, 2-h post-meal glucose; HOMA-β, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin-sensitivity check index; T2DM, type 2 diabetes mellitus.

Table 2 | Distribution by category of patients in subgroups

Subgroup	Category	Placebo	Sitagliptin
Age (years)	<65	361 (72.3)	388 (67.4)
	≥65	138 (27.7)	188 (32.6)
Sex	Female	158 (31.7)	214 (37.2)
	Male	341 (68.3)	362 (62.8)
BMI (kg/m^2)	<25	278 (55.7)	311 (54.0)
	≥25	221 (44.3)	265 (46.0)
Duration of T2DM (years)	<1	45 (9.0)	71 (12.3)
	1 to <5	231 (46.3)	243 (42.3)
	≥5	223 (44.7)	261 (45.4)
HbA1c (%)	<7.7	151 (30.3)	188 (32.6)
	7.7 to <8.4	168 (33.7)	176 (30.6)
	≥8.4	180 (36.1)	212 (36.8)
FPG (mg/dL)	<138	141 (28.3)	211 (36.6)
	138 to <165	176 (35.3)	187 (32.5)
	≥165	182 (36.5)	178 (30.9)
2h-PMG (mg/dL)	<209	157 (34.1)	176 (32.3)
	209 to <265	147 (31.9)	188 (34.5)
	≥265	157 (34.1)	181 (33.2)
Fasting C-peptide (ng/mL)	<Median (2.0)	249 (49.9)	265 (46.0)
	≥Median	250 (50.1)	311 (54.0)
HOMA-β	<Median (24.4)	259 (51.9)	278 (48.3)
	≥Median	240 (48.1)	298 (51.7)
Insulinogenic index	<Median (0.281)	235 (51.0)	268 (49.1)
	≥Median	226 (49.0)	278 (50.9)
HOMA-IR	<Median (2.23)	245 (49.1)	292 (50.7)
	≥Median	254 (50.9)	284 (49.3)
QUICKI	<Median (0.147)	254 (50.9)	283 (49.1)
	≥Median	245 (49.1)	293 (50.9)

Data are expressed as n (%). BMI, body mass index; FPG, fasting plasma glucose; 2h-PMG, 2-h post-meal glucose; HOMA-β, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin-sensitivity check index; T2DM, type 2 diabetes mellitus.

subtracted change from baseline HbA1c in multiple subgroups of patients was analyzed. Demographic parameters did not interact with efficacy; that is, sitagliptin reduced HbA1c to a similar extent regardless of age, sex, baseline BMI and duration of type 2 diabetes (Figure 1).

HbA1c reduction by glycemic status

The patient populations with HbA1c ≥8.4, or FPG ≥165 mg/dL or 2h-PMG ≥265 mg/dL at baseline had greater placebo-subtracted reduction from baseline in HbA1c than the populations with lower levels of hyperglycemia ($P < 0.001$; Figure 1). Similarly, greater placebo-subtracted reductions from baseline in FPG and 2h-PMG were observed in patient subgroups with higher FPG and 2h-PMG (Figure S1a,b). When changes from baseline in HbA1c were calculated as the percentage of baseline value, there was a generally consistent difference among baseline HbA1c subgroups evaluated (Figure S2).

HbA1c reduction by pancreatic β-cell function and insulin resistance

With respect to the parameters associated with β-cell function, the population with an insulinogenic index less than the median (0.281) had a greater reduction from baseline in HbA1c than the population with an insulinogenic index equal to or greater than the median ($P = 0.005$; Figure 1). The population with HOMA-β less than the median also had greater reduction than that equal to or greater than the median ($P = 0.007$; Figure 1). The population with a lower fasting serum level of C-peptide had a numerically, but not statistically significant, greater reduction from baseline in HbA1c ($P = 0.162$; Figure 1). In contrast, the insulin resistance-related parameters, HOMA-IR and QUICKI scores, did not interact with efficacy ($P > 0.5$; Figure 1).

DISCUSSION

Most clinical trials of antihyperglycemic medications for treatment of type 2 diabetes are designed to include a representative

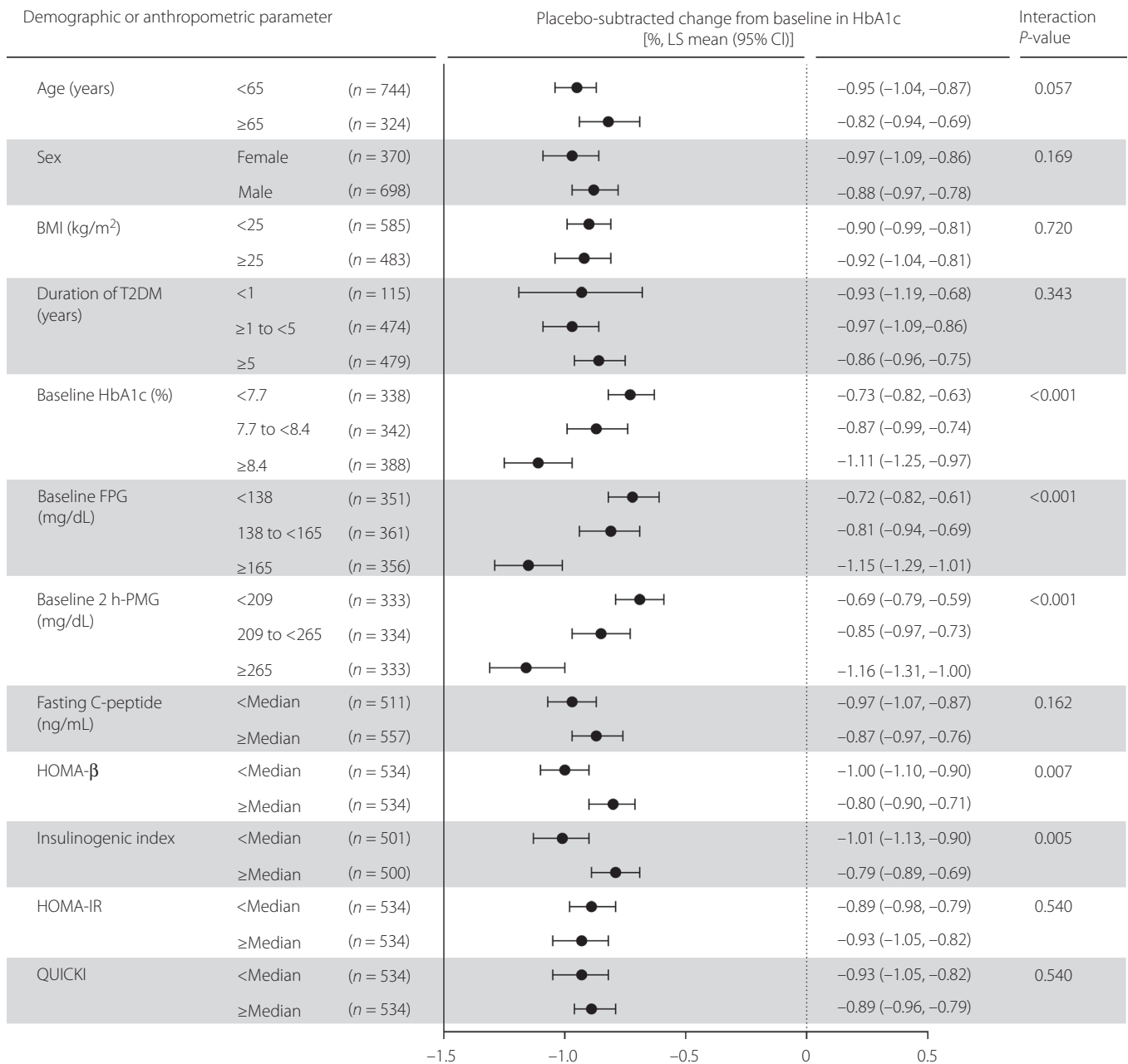| Demographic or anthropometric parameter			Placebo-subtracted change from baseline in HbA1c [%, LS mean (95% CI)]	Interaction *P*-value
Age (years)	<65	(*n* = 744)	−0.95 (−1.04, −0.87)	0.057
	≥65	(*n* = 324)	−0.82 (−0.94, −0.69)	
Sex	Female	(*n* = 370)	−0.97 (−1.09, −0.86)	0.169
	Male	(*n* = 698)	−0.88 (−0.97, −0.78)	
BMI (kg/m²)	<25	(*n* = 585)	−0.90 (−0.99, −0.81)	0.720
	≥25	(*n* = 483)	−0.92 (−1.04, −0.81)	
Duration of T2DM (years)	<1	(*n* = 115)	−0.93 (−1.19, −0.68)	0.343
	≥1 to <5	(*n* = 474)	−0.97 (−1.09,−0.86)	
	≥5	(*n* = 479)	−0.86 (−0.96, −0.75)	
Baseline HbA1c (%)	<7.7	(*n* = 338)	−0.73 (−0.82, −0.63)	<0.001
	7.7 to <8.4	(*n* = 342)	−0.87 (−0.99, −0.74)	
	≥8.4	(*n* = 388)	−1.11 (−1.25, −0.97)	
Baseline FPG (mg/dL)	<138	(*n* = 351)	−0.72 (−0.82, −0.61)	<0.001
	138 to <165	(*n* = 361)	−0.81 (−0.94, −0.69)	
	≥165	(*n* = 356)	−1.15 (−1.29, −1.01)	
Baseline 2 h-PMG (mg/dL)	<209	(*n* = 333)	−0.69 (−0.79, −0.59)	<0.001
	209 to <265	(*n* = 334)	−0.85 (−0.97, −0.73)	
	≥265	(*n* = 333)	−1.16 (−1.31, −1.00)	
Fasting C-peptide (ng/mL)	<Median	(*n* = 511)	−0.97 (−1.07, −0.87)	0.162
	≥Median	(*n* = 557)	−0.87 (−0.97, −0.76)	
HOMA-β	<Median	(*n* = 534)	−1.00 (−1.10, −0.90)	0.007
	≥Median	(*n* = 534)	−0.80 (−0.90, −0.71)	
Insulinogenic index	<Median	(*n* = 501)	−1.01 (−1.13, −0.90)	0.005
	≥Median	(*n* = 500)	−0.79 (−0.89, −0.69)	
HOMA-IR	<Median	(*n* = 534)	−0.89 (−0.98, −0.79)	0.540
	≥Median	(*n* = 534)	−0.93 (−1.05, −0.82)	
QUICKI	<Median	(*n* = 534)	−0.93 (−1.05, −0.82)	0.540
	≥Median	(*n* = 534)	−0.89 (−0.96, −0.79)	

Figure 1 | Analysis of placebo-subtracted change from baseline in HbA1c by subgroup. Data are expressed as least square (LS) mean and 95% confidence interval (95% CI). Subgroups were defined by baseline age (<65 years, ≥65 years), sex, body mass index (BMI; <25 kg/m², ≥25 kg/m²), duration of type 2 diabetes (T2DM; <1 year, 1 – <5 years, ≥5 years), HbA1c (tertiles: <7.7%, 7.7 to <8.4%, ≥8.4%), fasting plasma glucose (FPG; tertiles; <138 mg/dL, 138 to <165 mg/dL, ≥165 mg/dL), 2-h post-meal glucose (2h-PMG, tertiles; <209 mg/dL, 209 to <265 mg/dL, ≥265 mg/dL), fasting C-peptide (< or ≥ median [2.0 ng/mL]), homeostatic model assessment of β-cell function (HOMA-β; < or ≥ median [24.4]), insulinogenic index during meal tolerance test (< or ≥ median [0.281]), homeostatic model assessment of insulin resistance (HOMA-IR; < or ≥ median [2.23]) and the quantitative insulin-sensitivity check index (QUICKI; < or ≥ median [0.147]).

distribution of the patient population intended to receive treatment. The size of this somewhat heterogeneous (e.g., male/female, older/younger, lesser/greater degree of impairment of glycemic control) study population is generally based on

providing appropriate statistical power to test specific hypotheses associated with the overall study population. This usually means that the study will be underpowered to evaluate treatment effects in subgroups representing variations (e.g., sex, age,

baseline glycemic characteristics) in the overall population. One method to improve the robustness of subgroup analyses is to pool data from multiple studies, thus increasing the number of patients included in such subgroups. Here, we report the results of a post-hoc analysis of pooled data from seven Japanese clinical studies of the DPP4i sitagliptin.

In this analysis, sitagliptin treatment was associated with a clinically meaningful reduction from baseline in HbA1c in all subgroups analyzed. There was a greater improvement in glycemic control in Japanese patients with more hyperglycemia (higher HbA1c, FPG and 2h-PMG) at baseline, compared with those having lesser degrees of hyperglycemia. These findings confirm and extend previous reports that Japanese patients with type 2 diabetes and higher baseline glycemic status will experience greater absolute benefit from treatment with sitagliptin than those with lower baseline glycemic status[10–13]. They are also in agreement with analyses showing that in many studies outside Japan assessing the efficacy of a variety of antihyperglycemic agents, high baseline HbA1c correlates with greater reduction from baseline after treatment[14,15]. However, when the relative reduction in HbA1c was analyzed (i.e., placebo-subtracted change from baseline in HbA1c at week 12 / HbA1c levels at baseline), similar degrees of HbA1c reduction were observed among all baseline HbA1c subgroups. This suggests that sitagliptin provides meaningful glycemic benefit not only in a poorly controlled population, but also in better controlled populations among Japanese patients with type 2 diabetes.

Larger mean decreases in HbA1c level were also observed in the subgroups of the population with lower insulinogenic index and HOMA-β, suggesting greater potential benefit with sitagliptin treatment for Japanese patients with impaired β-cell function. A possible explanation for this may be that in such patients, β-cell dysfunction is the more dominant factor in their dysglycemia, compared to patients with relatively less impaired β-cell function for whom insulin resistance is the more dominant factor. Sitagliptin, a DPP4i, increases the active forms of the incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins at physiological concentrations enhance first-phase insulin secretion[16] through the induction of intracellular cyclic adenosine monophosphate production and subsequent activation of Epac2A/Rap1 pathway in pancreatic β-cells[17]. Thus, improvement of β-cell function by increased incretin levels may have a more favorable effect in these patients. This may also be the case for East Asian patients in general, for whom impaired insulin secretion is considered to be more relevant to hyperglycemia than is insulin resistance, when compared with Caucasian counterparts[18–21]. These observations may be related to the existence of a gain-of-function, minor allele of the GLP-1 receptor gene, rs3765467[22]. Individuals who are hetero- or homozygous for this minor allele exhibit a more than two fold increase in GLP-1-induced insulin secretion compared with individuals who are homozygous for the more common version of the gene. Consistent with the mechanism of action of DPP4is (stabilization of GLP-1 and glucose-dependent insulinotropic polypeptide GIP), type 2 diabetes patients with the minor allele have been reported to be more responsive to DPP4i treatment[23]. Furthermore, a recent meta-analysis of genome-wide association studies revealed that in the Japanese population, the frequency of the minor GLP-1 receptor allele (18%) is much greater that in European populations (0.01%)[24]. This finding can be interpreted as indicating that between 18 and 36% of Japanese individuals are homozygous or heterozygous for this gain-of-function minor allele of the GLP-1 receptor gene. The relatively high frequency of the GLP-1 receptor variant in Japanese and East Asians[23,24], and a greater frequency of the insulin secretory defect in Japanese compared with Caucasians[25–27] may help explain why DPP4is are more efficacious in Japanese and East Asians compared with Caucasians[18–21].

Only a weak interaction between HbA1c reduction and mean plasma C-peptide levels was observed. This inconsistency may result from the absence of patients with reduced fasting C-peptide levels in the analysis, due to study protocols that excluded patients with fasting C-peptide ≤0.7 ng/mL. Further studies will be required to assess the interaction between C-peptide level and sitagliptin efficacy.

Several reports suggest that the glucose-lowering efficacy of DPP4is is reduced in Japanese and East Asian patients with higher BMI[10–13,28]. A significant correlation between BMI and HbA1c reduction in Asian-dominant subgroups was also observed in a meta-analysis[18]. In contrast, no between-subgroup difference was observed in LS mean HbA1c change from baseline in subgroups associated with obesity (BMI and insulin resistance-related parameters) in the analysis reported here. This is consistent with data from a meta-analysis of placebo-controlled randomized trials[29]. Thus, the present findings suggest that sitagliptin demonstrates comparable efficacy in both the absence and presence of obesity in a Japanese population.

A strength of the present study is use of a large amount of data, from double-blind, prospective, randomized clinical trials comparing populations of placebo- and sitagliptin-treated patients who are culturally and genetically homogeneous. Limitations include the retrospective cohort analysis design and that baseline patient demographic characteristics, such as fasting C-peptide levels, age and sex distributions, differ from those of a real-world setting due to the inclusion/exclusion criteria of the individual studies.

In conclusion, the present subgroup analysis suggests that sitagliptin provides clinically meaningful improvement in glycemic control in all subgroups of Japanese patients evaluated. In addition, higher baseline glycemic status and lower baseline β-cell function are predictive factors associated with somewhat greater HbA1c reduction by sitagliptin.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Placebo-subtracted change from baseline in fasting plasma glucose (FPG [mg/dL]; (a) and 2-h post-meal glucose during meal tolerance test (2h-PMG [mg/dL]; (b) for different baseline subgroups. Data are shown as least squares mean (95% CI). **$P < 0.001$ versus placebo. [†]Mean baseline FPG (mg/dL). [‡]Mean baseline 2h-PMG (mg/dL).

Figure S2 | Relative reduction in hemoglobin A1c (HbA1c; [placebo-subtracted change from / baseline HbA1c] × 100) for different baseline HbA1c subgroups. Data are shown as least squares mean (95% confidence interval). **$P < 0.001$ versus placebo.

Table S1 | List of studies included in the analyses