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Effects of linagliptin versus voglibose on treatment-related quality of life in patients with type 2 diabetes: sub-analysis of the L-STEP study

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Abstract. Treatment-related quality of life (QOL) is an important aspect of diabetes management. However, no studies have compared the influence of dipeptidyl peptidase-4 inhibitors versus alpha-glucosidase inhibitors on treatment-related QOL. This prespecified sub-analysis of the Linagliptin Study of Effects on Postprandial blood glucose (L-STEP) compared the effects of linagliptin (5 mg once daily) and voglibose (0.2 mg/meal thrice daily) on treatment-related QOL in Japanese patients with type 2 diabetes (T2DM) inadequately controlled with diet and exercise therapy. Among 366 subjects in the original study, 182 in the linagliptin group and 173 in the voglibose group were included in this analysis. The outcome of this study was change in QOL as assessed by the Diabetes Therapy-Related Quality of Life 17 (DTR-QOL17) questionnaire from baseline to week 12. Compared with baseline data, total DTR-QOL17 scores were significantly higher after 12 weeks of linagliptin and voglibose treatment. The change in the total DTR-QOL17 score and the score of one domain, burden on social activities and daily activities, was significantly greater in the linagliptin group than in the voglibose group. In addition, only linagliptin treatment was identified as a factor associated with an increased total DTR-QOL17 score. Linagliptin is superior to voglibose in terms of improving treatment-related QOL in Japanese patients with T2DM.

Key words: Dipeptidyl peptidase-4 inhibitor, Alpha-glucosidase inhibitor, Treatment-related quality of life, Type 2 diabetes mellitus

THE PREVALENCE OF TYPE 2 DIABETES MELLITUS (T2DM), which is influenced by the degree of obesity and declines in physical activity, is increasing in many countries, including Japan. The objectives of diabetes management in Japan are to maintain quality of life (QOL) and life expectancy comparable to that of healthy individuals by preventing development or progression of complications [1]. To achieve these goals, effective treatment needs to take into account many factors, including age, disease duration, glycemic control status, physical

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status, and diabetic complications. For the proper choice of treatment, consideration of treatment-related QOL is important because decreased treatment-related QOL is associated with reduction in patient motivation and adherence with treatment in patients with T2DM [2]. Reduced adherence with treatment is associated with poor glycemic control and increased risk for mortality in patients with T2DM [3].

Treatment guidelines by the American Diabetes Association and European Association for the Study of Diabetes recommend metformin as first-line therapy when lifestyle modification alone has not achieved or maintained optimal glycemic goals [4]. On the other hand, treatment guidelines by the Japan Diabetes Society recommend choosing suitable therapies in line with the pathophysiological condition of each patient such as insufficient insulin secretion or insulin resistance [5] because T2DM in East Asians are associated with more beta-cell dysfunction, less insulin resistance, and less adiposity [6]. Given this situation, various types of oral anti-hypoglycemic agents (OHAs), including alpha-glucosidase inhibitors (α-GIs) and dipeptidyl peptidase (DPP)-4 inhibitors, are chosen as first-line therapy in Japan [7].

α-GIs delay the absorption of glucose through inhibiting alpha-glucosidase activity, thus reducing postprandial blood glucose excursion [8, 9]. A meta-analysis showed that acarbose reduces the risk of cardiovascular events in patients with T2DM [10]. Supported by the evidence from clinical trials [8-10], α-GIs are frequently prescribed as first-line therapy in Japan for patients with T2DM [7]. However, the gastrointestinal adverse effects of these drugs, which include abdominal fullness and borborygmi, may be significant barriers to treatment adherence [11].

On the other hand, DPP-4 inhibitors prevent the degradation of endogenous glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, which in turn enhances glucose-dependent insulin secretion from pancreatic β cells and reduces glucagon secretion from α cells and potentially suppresses postprandial glycemic excursions [12-14]. DPP-4 inhibitors are generally safe and well tolerated without increasing body weight [15]. Indeed, sitagliptin was shown to improve QOL in a single arm-study [16]. Due to these characteristics of DPP-4 inhibitors, they are increasingly prescribed as first-line therapy in Japan [17].

We recently conducted a randomized prospective multicenter study named the Linagliptin Study of Effects on Postprandial blood glucose (L-STEP) to compare the effects of linagliptin, a DPP-4 inhibitor, and voglibose, an α-GI, on postprandial hyperglycemia and other glycemic parameters in patients with inadequately controlled T2DM despite diet and exercise therapy [18]. We found that linagliptin monotherapy had a stronger glucose-lowering effect than voglibose monotherapy in terms of reducing HbA1c and serum fasting glucose levels, but not serum glucose levels 2 hours after the start of the meal tolerance test. Here, we conducted a sub-analysis to investigate how these treatment regimens affect treatment-related QOL, a prespecified secondary endpoint, using the self-administered Diabetes Therapy-Related QOL (DTR-QOL)-17 questionnaire that has been modified from the established questionnaire DTR-QOL developed especially to assess QOL related to treatment for diabetes [19].

Material and Methods

Study design, patients, randomization, study intervention, meal tolerance tests, and laboratory data

This prespecified sub-analysis of the L-STEP study compared the effects of linagliptin and voglibose on treatment-related QOL. The study design, inclusion and exclusion criteria, study schedule, and measurements were described in detail previously [19]. Briefly, patients with inadequately controlled T2DM, who periodically visited the outpatient clinic of 44 institutions in Japan (Supplementary Table S1) despite diet and exercise therapy were asked to participate in this study. A total of 382 patients were recruited and randomly assigned to either the linagliptin group (n = 192) or the voglibose group (n = 190). Ultimately, 188 in the linagliptin group and 178 in the voglibose group were included in the intention-to-treat (ITT) analysis. After a 4-week screening period, patients in the linagliptin group took 5 mg of oral linagliptin once daily and patients in the voglibose group took 0.2 mg/meal of voglibose thrice daily. Meal tolerance tests were performed at baseline (week 0) and endpoint (week 12). The meal tolerance test consisted of a cookie test after overnight fasting [20, 21]. All adverse events were recorded during the study. Medication adherence was monitored by recording whether or not patients took medicines daily.

All patients gave written consent to participate in the study. The study was approved by the institutional review board of each participating center and was regis-

tered on the University Hospital Medical Information Network Clinical Trials Registry (study no. UMIN000008591), a non-profit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors.

Study outcomes

The DTR-QOL is a 29-item, self-administered assessment with 4 primary scales including burden on social activities and daily activities (13 items), anxiety and dissatisfaction with treatment (8 items), hypoglycemia (4 items), and satisfaction with treatment (4 items) [19]. We demonstrated that the DTR-QOL can evaluate the effect of diabetes treatment on patient QOL with high reliability and validity [19]. For this study, we created a shorter version, the DTR-QOL17, due to practical constraints. In the original study for DTR-QOL development, correlation coefficients among items were examined [19]. Based on this analysis, 13 items that had low association with other items were deleted. From the deleted 13 items, we revived one item that asked about weight gain because treatment-related weight gain likely has a major impact on QOL based on clinical experience. Thus, the shorter version of the DTR-QOL contains 17 items. The total scores and burden on social activities and daily activities, anxiety and dissatisfaction with treatment, and hypoglycemia scores had high internal consistency based on Cronbach's alpha coefficients (data not shown). The structure of the DTR-QOL17 and the original DTR-QOL are almost entirely consistent.

DTR-QOL17 included 4 primary scales, including burden on social activities and daily activities (7 items), anxiety and dissatisfaction with treatment (6 items), hypoglycemia (3 items), and satisfaction with treatment (1 item) (Table 1). The response to each question was scored using a 7-point Likert-type scale that ranges from 1 (strongly agree) to 7 (strongly disagree). The scale for item 17 was reversed, so that 7 represented the highest QOL score. Domain scores were calculated by summing the response to the items in each domain. They were then converted to a range of 0–100. Higher scores represent higher QOL. In each domain, average scores were calculated and converted to a range of 0–100. Based on the original DTR-QOL [19], we treated missing values as follows. If the number of items with missing values in the domain was less than 50% of the total number of items in that domain, the mean value excluding the missing value(s) was calculated and used for the missing value(s). If the number of items with a missing value in the domain was 50% or more of the total number of items in that domain, the domain score was not calculated. If one or more domain scores could not be calculated, the total score was not calculated. The DTR-QOL17 questionnaire was completed at baseline and at week 12. Changes in the total DTR-QOL17 score and DTR-QOL17 domain 1 to 4 scores from baseline to week 12

Table 1 DTQ-QOL questionnaire and domain structure

Domain 1: Burden on social activities and daily activities
Q1. My current diabetes treatment limits the scope of my activities.
Q2. It is difficult to find places on time for my current diabetes treatment.
Q3. My current diabetes treatment interferes with group activities and personal friendships.
Q4. With my current diabetes treatment, the restricted meal times are a burden.
Q5. When I eat out, it is difficult to manage my current diabetes treatment.
Q6. The time and effort to manage my current diabetes treatment are a burden.
Q7. I am constantly concerned about time to manage my current diabetes treatment.
Domain 2: Anxiety and dissatisfaction with treatment
Q8. I am bothered by weight gain with my current diabetes treatment.
Q12. I am worried about high blood glucose.
Q13. I am dissatisfied that my blood glucose is unstable (high and low).
Q14. I am worried that complications might worse with my current diabetes treatment.
Q15. I got anxious thinking about living while on my current diabetes treatment.
Q16. I find it unbearable to think that even if I continue my current diabetes treatment, my diabetes may not be cured.
Domain 3: Hypoglycemia
Q9. I am scared because of low blood glucose.
Q10. I am sometimes bothered by low blood glucose.
Q11. Symptoms due to low blood glucose are uncomfortable.
Domain 4: Satisfaction with treatment
Q17. With my current diabetes treatment, I am confident that I can maintain good blood glucose control.

The question numbers in the DTR-QOL 17 questionnaire are used in this table.

were one of the prespecified secondary endpoints.

Statistical analysis

Results are presented as means ± SD or medians (interquartile range) for continuous variables, or numbers (proportion) of patients for categorical variables. For all data, comparisons between the groups were assessed with Student's *t*-test or the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. Changes from baseline to week 12 were assessed with the one-sample *t*-test or Wilcoxon signed-rank test within a treatment group.

Factor analysis with promax rotation was performed on 16 items to investigate whether the structure of the DTR-QOL17 were consistent with the 3 original primary scales of DTR-QOL after excluding Q17, which was only a configuration factor in domain 4. Individual question items with factor loading >|0.4| were reported as composition factors for simplicity. The internal consistency of the total score including Q17 and domains 1 to 3 of DTR-QOL17 was assessed using Cronbach's alpha coefficients. The correlation between change in DTR-QOL17 scores and parameters were evaluated using Spearman's correlation coefficients.

All statistical tests were 2-sided with a 0.05 significance level. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Patients

Among the 366 patients in the ITT population, 11 did not complete the DTR-QOL questionnaire and were excluded from this analysis. The linagliptin group had 182 patients and the voglibose group had 173 patients. The baseline characteristics of the patients are summarized in online Supplementary Table S2. The 2 groups were well balanced at baseline, with comparable mean age, sex, and HbA1c levels except the use of statins. BMI was slightly higher in the voglibose group, and this difference was statistically significant. Consistent with the results of the original L-STEP study, the change in HbA1c levels and reduction in fasting serum glucose levels from baseline to week 12 in the linagliptin group was significantly greater than those in the voglibose group (Supplementary Table S3). There were no differences in serum glucose levels after 2 hours between the 2 groups. Subjects in the voglibose group showed a significant change in reduction of BMI than subjects in the linagliptin group (Supplementary Table S3). Over the 12-week treatment period, one patient in the voglibose group experienced hypoglycemia. There were no differences in the incidence of adverse effects including gastrointestinal symptoms between the 2 groups (data not shown). The linagliptin group had higher adherence to medication than the voglibose group (Supplementary Table S3).

Factor analysis

Factor analysis with promax rotation was performed to investigate the structure of the DTR-QOL17 without Q17 at baseline and week 12. Three factors were used in this analysis at baseline (Table 2). Factor 1 seemed to represent burden on social activities and daily activities. Factor 2 seemed to represent anxiety and dissatisfaction with treatment. Factor 3 seemed to represent hypoglycemia. Of note, Q8 could not be identified by factor 2, which is inconsistent with the original study; it was instead identified by factor 1. However, considering the meaning of Q8 in this study, it was included in domain 2. Accordingly, these data show that the structure of the DTR-QOL17 is generally but not completely consistent with that of the original DTR-QOL. Indeed, the result of the factor analysis at 12 weeks was similar to that at baseline (data not shown).

Internal consistency

Domain 1 (burden on social activities and daily activities), domain 2 (anxiety and dissatisfaction with treatment), domain 3 (hypoglycemia), and total DTR-QOL17 score showed high internal consistency, with Cronbach's alpha coefficients of 0.84, 0.96, 0.92, and 0.91 at baseline, respectively.

Change in DTR-QOL17 scores

At baseline and 12 weeks, there were no differences in total DTR-QOL17 score and domain 1–4 scores between the 2 groups (Table 3). However, the total DTR-QOL17 score and scores for each domain were significantly higher after 12 weeks of linagliptin treatment, while total DTR-QOL17 score and only the domain 2 score were significantly higher after 12 weeks of voglibose treatment. In addition, the change in total DTR-QOL17 and factor 1 scores from baseline to week 12 was significantly greater in the linagliptin group than in the voglibose group.

Regarding each question, scores for Q2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16 and 17 were significantly

Table 2 DTR-QOL17 (16 items) and factor analysis with promax rotation (n = 347)

Question number	Domain number in the original DTR-QOL	Factor 1	Factor 2	Factor 3
Q1	1	**0.73**	0.01	0.07
Q2	1	**0.94**	–0.17	0.00
Q3	1	**0.83**	–0.03	–0.01
Q4	1	**0.70**	0.05	0.08
Q5	1	**0.58**	0.21	–0.03
Q6	1	**0.69**	0.21	–0.05
Q7	1	**0.68**	0.20	–0.01
Q8	2	**0.42**	0.12	0.20
Q9	3	0.06	–0.04	**0.92**
Q10	3	0.00	0.01	**0.98**
Q11	3	–0.01	0.08	**0.88**
Q12	2	0.13	**0.40**	0.15
Q13	2	0.05	**0.51**	0.22
Q14	2	0.03	**0.76**	–0.01
Q15	2	0.04	**0.81**	–0.05
Q16	2	0.00	**0.79**	0.00

Individual question items with factor loading >|0.4| are shown in bold.

higher after 12 weeks of linagliptin treatment (Table 4). On the other hand, only scores for Q3, 5, 6, 8, 10, and 14 showed significant improvement after voglibose treatment. The change in scores for Q4, 6, and 7 from baseline to week 12 was significantly greater in the linagliptin group than in the voglibose group.

We investigated the correlation between changes in total DTR-QOL17 score and some parameters at baseline as well as the change in those parameters. Linagliptin treatment was significantly but weakly associated with an increase in total DTR-QOL17 score (Table 5), (Spearman's correlation coefficient –0.11, p = 0.034).

Discussion

While our original data suggested that linagliptin provides clinically meaningful improvement in glycemic control without any unacceptable side effects and with a low risk of hypoglycemia [18], this sub-analysis revealed the positive influence of linagliptin on treatment-related QOL, which is another important aspect of diabetes management.

Previous reports have shown that the initiation of diabetes treatment was associated with improvements in QOL as assessed by other types of patient-reported outcome evaluation [16, 22, 23]. Consistent with these findings, total DTR-QOL17 scores were significantly higher after 12 weeks of both linagliptin and voglibose treatment, suggesting that both treatments achieve better glycemic control and improved treatment-related QOL. In both groups, domain 2 scores related to anxiety and dissatisfaction with treatment improved after treatment. Both treatments positively affected domain 3 scores related to hypoglycemia. Given that patients' anxiety and dissatisfaction with treatment, and concerns about hypoglycemia were reduced by both drugs characterized by solid glucose-lowering effects, a low risk of hypoglycemia, and weight neutrality, these findings are very reasonable.

While both treatments improved treatment-related QOL, the change in total DTR-QOL17 score from baseline to week 12 was significantly higher in the linagliptin group than in the voglibose group. Generally, improvements in QOL with diabetes treatment may be affected by many factors including improved HbA1c, lower body mass index (BMI), and reduced perceived frequency of hyperglycemic or hypoglycemic episodes [23-25]. However, changes in HbA1c and BMI and frequency of hypoglycemic episodes were not associated with changes in total DTR-QOL17 score. In this study, linagliptin treatment was the only parameter related to the change in total DTR-QOL17 score. In this regard, the improved domain 1 score related to burden on social activities and daily activities in the linagliptin group was likely related to these differences because the scores of 3 items ((Q4: "With my current diabetes treatment, the restricted meal times are a burden.", Q6: "The time and effort to manage my current diabetes treatment are a burden". and Q7:"I am constantly concerned about time to manage my current diabetes treatment.") were significantly higher in the linagliptin group than in the voglibose group. It is not difficult to imagine that increased dosing frequency (once daily, twice daily, thrice daily, and 4 times daily) may place a heavier burden on social and daily activities. Furthermore, recent clinical studies have demonstrated that once daily dosing was associated with a higher rate of adherence than more frequent dosing [26-29]. In addition, taking α-GIs just before each main meal may negatively affect patient's adherence to medication and increase the burden of patients. Indeed, patients taking

Table 3 Effect of linagliptin and voglibose on DTR-QOL17 scores

Variable	Baseline (*n*)	Week 12 (*n*)	Change from baseline (*n*)	*p* value (intragroup)
Total score				
Linagliptin	70.6 (52.9, 85.3) (180)	79.4 (67.6, 90.2) (176)	6.9 (–4.9, 16.7) (176)	<0.001
Voglibose	74.0 (53.9, 88.2) (170)	76.5 (62.7, 89.2) (160)	1.0 (–8.8, 14.7) (165)	0.046
p value (intergroup)	0.42	0.35	0.035	
Domain 1 score				
Linagliptin	73.8 (54.8, 100.0) (181)	86.9 (69.0, 100.0) (178)	4.8 (–4.8, 26.2) (177)	<0.001
Voglibose	78.6 (50.0, 100.0) (171)	83.3 (64.3, 97.6) (168)	0.0 (–11.9, 14.3) (166)	0.2
p value (intergroup)	0.89	0.12	0.048	
Domain 2 score				
Linagliptin	61.1 (44.4, 77.8) (180)	66.7 (50.0, 88.9) (178)	5.6 (–8.3, 19.4) (176)	<0.001
Voglibose	61.1 (47.2, 80.6) (171)	66.7 (50.0, 86.1) (168)	2.8 (–8.3, 16.7) (166)	0.048
p value (intergroup)	0.44	0.98	0.22	
Domain 3 score				
Linagliptin	100.0 (61.1, 100.0) (180)	100.0 (83.3, 100.0) (178)	0.0 (0.0, 22.2) (176)	<0.001
Voglibose	100.0 (66.7, 100.0) (170)	100.0 (83.3, 100.0) (165)	0.0 (0.0, 11.1) (165)	0.055
p value (intergroup)	0.35	0.42	0.072	
Domain 4 score				
Linagliptin	50.0 (50.0, 66.7) (180)	66.7 (50.0, 83.3) (178)	0.0 (0.0, 16.7) (176)	<0.001
Voglibose	50.0 (50.0, 83.3) (171)	50.0 (50.0, 83.3) (168)	0.0 (0.0, 16.7) (166)	0.23
p value (intergroup)	0.23	0.51	0.13	

Data are expressed as medians (interquartile range).
Changes from baseline are shown as changes in the actual value between baseline and week 12.

linagliptin (once daily dosing) exhibited better medication adherence than patients taking voglibose (thrice daily dosing). Those points are very important when choosing OHAs; the American Diabetes Association emphasized the importance of considering patient preference in addition to efficacy, hypoglycemic risk, impact on weight, potential side effects, and cost [30].

There are several limitations to the present study. First, as this study was limited to subjects not previously taking OHAs, it is not possible to conclude that the effects of linagliptin and voglibose on treatment-related QOL can be generalized to patients already on other OHAs. These agents might differentially affect treatment-related QOL when used in combination with other drugs. Second, we did not assess the long-term effects of these agents on QOL. Third, we evaluated treatment-related QOL only using the DTR-QOL17, which we have demonstrated is a valid and reliable self-report instrument. Third, we did not collect the information about drugs other than OHAs, anti-hypertensive drugs or lipid lowering agents (Supplementary Table S2). Thus, we did not consider the influence of the frequency, number and types of drugs other than OHAs on adherence to study drugs.

In conclusion, linagliptin achieved better glycemic control with more improvement in treatment-related QOL than voglibose.

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Table 4 Effect of linagliptin and voglibose on Q1–17 scores

Question number		Linagliptin group	Voglibose group	*p* value (intragroup)
Q1	Baseline	6.0 (4.0, 7.0) (*n* = 182)	6.0 (4.0, 7.0) (*n* = 171)	0.17
	Change from baseline	0.0 (0.0, 1.0) (*n* = 175)	0.0 (0.0, 1.0) (*n* = 165)	0.31
Q2	Baseline	6.0 (4.0, 7.0) (*n* = 182)	6.0 (4.0, 7.0) (*n* = 171)	0.68
	Change from baseline	0.0 (0.0, 1.0)* (*n* = 175)	0.0 (–1.0, 1.0) (*n* = 164)	0.30
Q3	Baseline	6.0 (4.0, 7.0) (*n* = 181)	7.0 (4.0, 7.0) (*n* = 171)	0.56
	Change from baseline	0.0 (0.0, 1.0)¶ (*n* = 175)	0.0 (–1.0, 1.0)¶ (*n* = 165)	0.30
Q4	Baseline	6.0 (4.0, 7.0) (*n* = 180)	6.0 (4.0, 7.0) (*n* = 171)	0.89
	Change from baseline	0.0 (0.0, 2.0)¶ (*n* = 176)	0.0 (–1.0, 1.0) (*n* = 166)	0.045
Q5	Baseline	5.0 (4.0, 7.0) (*n* = 180)	5.0 (4.0, 7.0) (*n* = 171)	1.00
	Change from baseline	0.0 (0.0, 2.0)¶ (*n* = 176)	0.0 (–1.0, 2.0)* (*n* = 165)	0.14
Q6	Baseline	6.0 (4.0, 7.0) (*n* = 181)	6.0 (4.0, 7.0) (*n* = 171)	0.87
	Change from baseline	0.0 (0.0, 2.0)¶ (*n* = 177)	0.0 (0.0, 1.0)* (*n* = 165)	0.044
Q7	Baseline	6.0 (4.0, 7.0) (*n* = 181)	6.0 (4.0, 7.0) (*n* = 171)	1.00
	Change from baseline	0.0 (0.0, 2.0)¶ (*n* = 177)	0.0 (–1.0, 1.0) (*n* = 166)	0.027
Q8	Baseline	6.0 (4.0, 7.0) (*n* = 180)	6.0 (4.0, 7.0) (*n* = 171)	1.00
	Change from baseline	0.0 (0.0, 1.5)* (*n* = 176)	0.0 (0.0, 2.0)¶ (*n* = 166)	0.37
Q9	Baseline	7.0 (4.0, 7.0) (*n* = 180)	7.0 (5.0, 7.0) (*n* = 171)	0.42
	Change from baseline	0.0 (0.0, 1.5)¶ (*n* = 176)	0.0 (0.0, 0.0) (*n* = 166)	0.050
Q10	Baseline	7.0 (4.0, 7.0) (*n* = 180)	7.0 (5.0, 7.0) (*n* = 170)	0.39
	Change from baseline	0.0 (0.0, 1.0)¶ (*n* = 176)	0.0 (0.0, 0.0) (*n* = 165)	0.15
Q11	Baseline	7.0 (4.0, 7.0) (*n* = 180)	7.0 (5.0, 7.0) (*n* = 170)	0.34
	Change from baseline	0.0 (0.0, 1.0)¶ (*n* = 176)	0.0 (0.0, 0.0) (*n* = 165)	0.095
Q12	Baseline	4.0 (3.0, 6.0) (*n* = 179)	4.0 (3.0, 6.0) (*n* = 171)	0.31
	Change from baseline	0.0 (0.0, 1.0)* (*n* = 175)	0.0 (–1.0, 1.0) (*n* = 166)	0.078
Q13	Baseline	5.0 (4.0, 7.0) (*n* = 180)	5.0 (4.0, 7.0) (*n* = 171)	0.69
	Change from baseline	0.0 (–1.0, 1.0) (*n* = 176)	0.0 (–1.0, 1.0) (*n* = 166)	0.47
Q14	Baseline	4.0 (2.5, 6.0) (*n* = 180)	4.0 (3.0, 6.0) (*n* = 170)	0.11
	Change from baseline	0.0 (0.0, 2.0)¶ (*n* = 176)	0.0 (–1.0, 2.0)* (*n* = 165)	0.10
Q15	Baseline	4.0 (3.0, 7.0) (*n* = 180)	5.0 (4.0, 7.0) (*n* = 170)	0.22
	Change from baseline	0.0 (0.0, 1.5)¶ (*n* = 176)	0.0 (–1.0, 1.0) (*n* = 165)	0.17
Q16	Baseline	4.0 (4.0, 6.5) (*n* = 180)	4.0 (4.0, 7.0) (*n* = 170)	0.85
	Change from baseline	0.0 (0.0, 1.0)* (*n* = 176)	0.0 (–1.0, 1.0) (*n* = 166)	0.89
Q17	Baseline	4.0 (4.0, 5.0) (*n* = 180)	4.0 (4.0, 6.0) (*n* = 171)	0.23
	Change from baseline	0.0 (0.0, 1.0)¶ (*n* = 176)	0.0 (0.0, 1.0) (*n* = 166)	0.12

Data are expressed as medians (interquartile range).

Changes from baseline are shown as changes in the actual value between baseline and week 12. Changes from baseline to treatment visits were assessed with the Wilcoxon signed-rank test within a group.

* $p < 0.05$, ¶ $p < 0.01$

Table 5 Correlation between changes in total DTR-QOL score and various parameters

Characteristic	*N*	Spearman's correlation coefficient (95% confidence interval)	*p* value
Age	341	–0.04 (–0.14, 0.07)	0.48
Gender (ref = male)	341	–0.01 (–0.12, 0.10)	0.85
Change in body mass index	341	–0.02 (–0.13, 0.08)	0.69
Change in HbA1c levels	341	–0.09 (–0.19, 0.02)	0.12
Change in fasting blood glucose levels	341	–0.03 (–0.14, 0.07)	0.54
Change in 2-hour blood glucose levels	341	0.04 (–0.07, 0.14)	0.49
Medication adherence rate	336	0.07 (–0.036, 0.177)	0.19
Treatment group (ref = linagliptin)	341	–0.11 (–0.22, –0.01)	0.034

Ref: referent group

and reviewed the manuscript.

Declaration of Interests

TM has received research funds from MSD and Takeda Pharma K.K. and lecture fees from AstraZeneca K.K., Boehringer Ingelheim, Eli Lilly, Kowa Pharmaceutical Co., Mitsubishi Tanabe Pharma Co., MSD, Ono Pharmaceutical Co., Novo Nordisk Pharma Ltd., and Takeda Pharmaceutical Co. YF has received grant support from Takeda, MSD, and Nippon Eli Lilly. YF has also acted as a spokesperson for Novartis Pharma, Nippon Eli Lilly, MSD, and Sanofi Aventis. SF has received lecture fees from Ono Pharmaceutical Co., Ltd., and grant/research support from Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., MSD K.K., Astra Zeneca K.K., Eli Lilly Japan K.K., Ono Pharmaceutical Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., and Nippon Boehringer Ingelheim Co., Ltd. KT has received lecture fees from Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly Japan K.K., Takeda Pharmaceutical Co., Ltd., Sanofi K.K., Eisai Co., Ltd., Ono Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., ASKA Pharmaceutical. Co., Ltd., Mitsubishi Tanabe Pharma Factory Ltd., Shionogi & Co., Ltd., Astellas Pharma Inc., Novo Nordisk Pharma Ltd., and Kyowa Hakko Kirin Co., Ltd. HS has received grant/research support from Genzyme Japan K.K., Asahi Kasei Co., Eisai Co., Ltd., Abbott Japan Co., Ltd., Torii Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Terumo Co., Sumitomo Dainippon Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Mochida Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., MSD K.K., Novo Nordisk Pharma Ltd., Kissei Pharmaceutical Co., Ltd., and Astellas Pharma Inc. and lecture fees from Takeda Pharmaceutical Co., Ltd., Novartis Pharma K.K., Sanofi-Aventis K.K., Taisho Toyama Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., AstraZeneca K.K., Ono Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Mochida Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., MSD K.K., Novo Nordisk Pharma Ltd., Kissei Pharmaceutical Co., Ltd., and Astellas Pharma Inc. TH has received lecture fees from Sanofi K.K., Eli Lilly Japan K.K., Novo Nordisk Pharma Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Co., MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., Novartis Pharma K.K., Kissei Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd., and AstraZeneca K.K., and grant/research support from Sanofi K.K., Eli Lilly Japan K.K., Novo Nordisk Pharma Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Astellas Pharma Inc., Ono Pharmaceutical Co., Ltd., AstraZeneca K.K., Taisho Toyama Pharmaceutical Co., Ltd., Sanwakagaku and Bayer Yakuhin. MA has received lecture fees from MSD K.K. and Sanofi K.K. YO has received lecture fees from Astellas Pharma Inc., AstraZeneca K.K., MSD K.K., Ono Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Bayer Yakuhin, Ltd., Novo Nordisk Pharma Ltd., Eli Lilly Japan K.K., Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Co., Ltd., Kissei Pharmaceutical Co., Ltd., Novartis

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Supplementary Table S1

List of 44 enrolled sites.
Chimori Clinic
Fukushima Medical University
Hirose Clinic
Hotaruno Central Clinic
Irako Clinic
Ishii Hospital
Japanese Red Cross Medical Center
Juntendo Tokyo Koto Geriatric Medical Center
Juntendo University
Kaijou Bill Clinic
Kashiwa Municipal Hospital
Keiai-kai Seibu Hospital
Kenkoubunkakai Azusawa Hospital
Kochi University
Matsubara Clinic
Medical Corporation Taneda Clinic
Medical Corporation Kyoujinkai Komatsu Hospital
Misaki Naika Clinic
Nishihara Clinic
Nishimura Clinic
Otoshi Medical Clinic
Oyama East Clinic
Saitama Medical University Hospital
Sakakibara Kouseikai Shinjuku Mitsui Building Clinic
Seino Internal Medicine Clinic
Sekiminato Kinenkai Green Clinic
Sennan Nishide Hospital
Shimizu Clinic
Shiraiwa Medical Clinic
Sugawara Clinic
Takahashi Kiyohito Clinic
Takayama Hospital
Takekawa Clinic
Tanaka Clinic
Tenri Hospital
Toho University Omori Medical Center
Tokyo Metropolitan Tama Medical Center
Toyonaka-Wakabakai Hospital
University of Occupational and Environmental Health
Wakamatsu Hospital of the University of Occupational and Environmental Health
Wakayama Rosai Hospital
Yaeikai Yayoi Medical Clinic
Yokohama Ryokuen Okanoue Clinic
Yokohama Sakae Kyosai Hospital

Supplementary Table S2 Clinical characteristics of patients of the two groups

Parameters	Linagliptin group (n = 182)	Voglibose group (n = 173)	p value
Age (years)	60.9 ± 12.0	61.0 ± 11.9	0.91
Gender (males) (%)	101 (55)	92 (53)	0.67
Body mass index (Kg/m^2)	24.9 ± 4.3	25.9 ± 4.5	0.035
HbA1c (%)	7.0 ± 0.7	6.9 ± 0.6	0.39
Fasting blood glucose levels (mmol/L)	7.61 ± 1.42	7.55 ± 1.35	0.69
Anti-hypertensive drugs			
Angiotensin-converting enzyme inhibitors	2 (1)	4 (2)	0.44
Angiotensin II receptor blockers	45 (25)	37 (21)	0.53
Direct renin inhibitor	0 (0)	0 (0)	—
Calcium channel blocker	39 (21)	39 (23)	0.90
Diuretic drugs	3 (2)	4 (2)	0.72
α-adrenergic receptor antagonist	2 (1)	2 (1)	1.00
β-adrenergic receptor antagonist	4 (2)	5 (3)	0.75
Lipid-lowering agents			
Statins	58 (32)	74 (43)	0.037
Ezetimibe	7 (4)	9 (5)	0.61
Resins	0 (0)	1 (1)	0.49
Fibrates	15 (8)	9 (5)	0.29
Blood glucose level after 2 hour (mmol/L)	13.34 ± 3.43	12.92 ± 3.26	0.24

Data are number (%) of patients or mean ± SD values.

Supplementary Table S3 Comparisons of metabolic parameters and adherence between the two groups over 12 weeks-treatment period

Parameters	Linagliptin group	Voglibose group	p value
Change in BMI from baseline (Kg/m^2)	–0.07 ± 0.80 (n = 180)	–0.45 ± 0.79 (n = 168)¶	<0.001
Change in HbA1c from baseline (%)	–0.49 ± 0.49 (n = 180)¶	–0.25 ± 0.50 (n = 168)¶	<0.001
Change in fasting blood glucose levels from baseline (mmol/L)	–0.53 ± 0.96 (n = 179)¶	–0.18 ± 0.93 (n = 168)¶	<0.001
Change in blood glucose levels after 2hour from baseline (mmol/L)	–1.99 ± 2.28 (n = 179)¶	–2.04 ± 2.17 (n = 168)¶	0.84
Adherence to medication (%)	98 ± 4 (n = 182)	93 ± 11 (n = 173)	<0.001

Data are mean ± SD values or % ± SD values.
Comparisons between the groups were assessed with the Student's t-test and the Fisher's exact test for categorical variables. Changes from baseline to treatment visits were assessed with the one-sample t-test within the group* $p < 0.05$, ¶$p < 0.01$

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