Efficacy of liraglutide therapy in Japanese type 2 diabetic patients insufficiently controlled with basal-supported oral therapy

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ABSTRACT

Aims/Introduction: We assessed the efficacy of liraglutide therapy in Japanese type 2 diabetic patients insufficiently controlled with basal-supported oral therapy (BOT).

Materials and Methods: We retrospectively analyzed the data of 37 patients who had postprandial hyperglycemia (≥10.0 mmol/L) with BOT (long-acting insulin plus glimepiride) with their insulin titrated enough to keep preprandial glycemia <7.2 mmol/L, and who had their treatment changed to liraglutide monotherapy, with the subsequent addition of glimepiride, when required. Those who achieved the glycemic target at all points (preprandial glycemia <7.2 mmol/L and postprandial glycemia <10.0 mmol/L) were regarded as responders and the efficacy of liraglutide therapy was assessed. We also explored the predictive clinical characteristics associated with its efficacy.

Results: Daily doses of insulin and glimepiride with BOT were 14 ± 9 units and 1.5 ± 0.9 mg, respectively. After the change to liraglutide therapy, 37% of the patients appeared to be responders to the therapy, whereas 12% had their glycemic control rather deteriorated. Efficacy of liraglutide therapy was significantly associated with baseline insulin dosage and post-breakfast glycemia with BOT. The *C*-statistic of the model was calculated to be 0.90.

Conclusions: There were responders and non-responders to liraglutide therapy in Japanese BOT failures. It is likely that baseline insulin dosage and post-breakfast glycemia with BOT are clinically useful indicators for the efficacy of liraglutide therapy. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00223.x, 2012)

KEY WORDS: Basal-supported oral therapy, Japanese, Liraglutide

INTRODUCTION

A long exposure to hyperglycemia is associated with unfavorable complications in type 2 diabetic patients[1], and its correction is now strongly recommended[1–4]. However, as type 2 diabetes mellitus is a progressive disease, the maintenance of glycemic control over a course of time is often difficult, despite the administration of increasing doses of oral hypoglycemic agents[5]. Most patients eventually require supplementary insulin therapy to target good glycemic control[3].

There are several choices for the introduction of insulin therapy in such patients. The addition of a long-acting insulin analog to oral agents, so-called basal-supported oral therapy (BOT), has been regarded as an effective option for initiating insulin therapy[6]. It can improve glycemic control with a simple regimen of titrating long-acting insulin to target fasting glucose levels and is now widely used.

However, some patients receiving BOT fail to achieve strict glycemic control. The major reason for this failure is that postprandial glycemia cannot be corrected as strictly under the therapy as fasting glycemia[7,8]. The next step to target postprandial hyperglycemia is subsequently required after overcoming fasting hyperglycemia[9]. Although it has been shown that additional prandial insulin can provide better glycemic control[10], substantial numbers of patients in clinical practice hesitate to receive this intensive insulin therapy because of the inconvenience of daily multiple injections, which would burden their lifestyle. Clinically effective regimens without frequent injections have been called for.

Recently, incretin-based therapy has been changing the management of type 2 diabetes mellitus, and now attracts increasing attention in clinical practice[11]. One recent clinical trial, Liraglutide Effect and Action in Diabetes 5 (LEAD-5)[12], showed that liraglutide, a glucagon-like peptide-1 receptor agonist, produced greater glycemic improvement in combination with oral hypoglycemic agents than long-acting insulin. These findings suggest

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that patients insufficiently controlled with BOT will possibly achieve glycemic target through changing to liraglutide therapy.

In contrast, some clinical anxieties have existed about the risk of severe hypoglycemia under liraglutide therapy with sulfonylureas in Japanese patients. Somewhat surprisingly, there were dozens of case reports of Japanese patients who were poorly controlled with sulfonylureas, but suffered severe hypoglycemia right after the addition of dipeptidyl peptidase-4 inhibitors, another type of incretin-based therapy[13]. These observations have never been reported in Caucasians, and it might be that some Japanese diabetic patients have an ethnical manifestation of potentially extreme sensitivity to incretin-based therapy with the administration of sulfonylureas. Previous studies showed the superiority of liraglutide to dipeptidyl peptidase-4 inhibitor in lowering glycemia[14]. It is now of clinical interest to determine which patients can tolerate the combination of sulfonylureas with liraglutide, and which patients are sufficiently controlled with liraglutide alone when we change treatment from BOT in Japanese diabetic patients.

On the basis of these clinical expectations and anxieties, we retrospectively carried out exploratory analyses of glycemic control after changing from BOT to liraglutide therapy in Japanese type 2 diabetic patients.

MATERIALS AND METHODS

Study Population

We retrospectively analyzed the data of 37 consecutive Japanese type 2 diabetic patients who were insufficiently controlled with BOT and thereby had their therapy changed to liraglutide monotherapy, with the subsequent addition of glimepiride when required, in 2010, right after the approval of liraglutide in Japan. The recruited patients were provided with usual and routine medical management, and the fundamentals of therapeutic procedures were not intentionally changed. The number of health professionals participating in the patients' care was not changed throughout the observed period either. Their glycemic target was set according to the recommendation of the Japan Diabetes Society[4]: fasting glycemia <7.2 mmol/L (130 mg/dL), 2-h postprandial glycemia <10.0 mmol/L (180 mg/dL) and hemoglobin A1c level <6.9%, which is equivalent to the National Glycohemoglobin Standardization Program (NGSP) value.

All the patients were treated with a long-acting insulin analog, namely, insulin glargine or insulin detemir, with a combination of glimepiride before the change to liraglutide therapy. No other hypoglycemic agents were combined. Although their long-acting insulin was titrated enough to keep preprandial glycemia below 7.2 mmol/L, their NGSP-equivalent hemoglobin A1c level still remained ≥6.9%, with postprandial glycemia ≥10.0 mmol/L. Thereafter, their medications were changed to liraglutide therapy. Liraglutide was initiated at a dose of 0.3 mg/day and was titrated to the target glycemic goal by 0.3 mg/day, up to the maximum dose of 0.9 mg/day, in accordance with the approval of the Health, Labour and Welfare Ministry in Japan. Two-week intervals were set to judge the efficacy of the current dosage and determine whether to titrate it up. A subsequent restart of glimepiride was applied to the patients whose glycemic control appeared to be insufficient with the maximum dose of liraglutide monotherapy. Its starting dose was 0.5 mg, the minimum dose of the tablet available in Japan. With the addition of glimepiride, liraglutide was decreased from 0.9 mg/day to 0.6 mg/day, on the basis of the findings in previous clinical trials, where two-thirds of the maximum dose of liraglutide in combination with glimepiride was as effective as the maximum dose[15]. Glimepiride was titrated to target glycemic goal by 0.5∼1.0 mg/day. All patients were instructed to carry out self-monitoring of blood glucose six times a day: before and 2-h after each of the three-daily meals. The follow-up data for a maximum of 12 weeks after liraglutide introduction were available.

Assessment of Glycemia

Those patients who achieved the glycemic goal at all six points (<7.2 mmol/L in the preprandial period and <10.0 mmol/L in the 2-h postprandial period) were regarded as responders to liraglutide therapy. Aside from the criteria of desirable glycemic targets, the Japan Diabetes Society also describes fasting glycemia ≥8.9 mmol/L as criteria of 'poor' glycemic control, which indicates a high risk of progressing microangiopathy and should be avoided[4]. We used these criteria for the description of undesirable hyperglycemia in the current study. Hypoglycemia was determined when glycemia was below 3.3 mmol/L, irrespective of any symptoms or any requirement of assistance from another person. The NGSP-equivalent hemoglobin A1c level was calculated by the addition of 0.4% to the measurement standardized by the Japanese Diabetes Society, in accordance with the report of the committee[16].

Statistical Analysis

Data are given as means and standard deviations (SD) for continuous variables or as percentages for dichotomous variables. Achievement of the glycemic goal was estimated by the Kaplan–Meier method. Cox proportional hazards regression model was used to determine the association of baseline characteristics with the achievement of the glycemic goal. Hazard ratios (HR) and 95% confidence intervals (CI) are reported there. The predictive impact of the model was assessed with the *C*-statistic[17]. We also used the multivariate logistic regression model to investigate the association of baseline characteristics and the satisfaction of glycemic criteria right after the introduction of liraglutide monotherapy, where odds ratios (OR) and 95% CI were reported. A P-value < 0.05 was considered statistically significant. Statistical analyses were carried out using IBM SPSS Statistics Version 19 (SPSS, Chicago, IL, USA) and R version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The baseline characteristics of the study population receiving BOT are shown in Table 1. A total of 34 patients used insulin glargine and the rest used insulin detemir. Daily doses of insulin

Table 1 | Baseline characteristics of the study population

No. recruited patients (male : female)	37 (17:20)
Age (years)	62 ± 10
Body mass index (kg/m^2)	26.0 ± 4.9
Diabetic duration (years)	16 ± 8
Dosage of insulin (units/day)	14 ± 9
Dosage of glimepiride (mg/day)	1.5 ± 0.9
NGSP-equivalent hemoglobin A1c (%)	7.7 ± 0.8
Daily profiles of blood glucose (mmol/L)	
Before breakfast	6.3 ± 0.8
2 h after breakfast	11.3 ± 3.3
Before lunch	7.2 ± 2.9
2 h after lunch	12.3 ± 3.0
Before dinner	7.8 ± 2.2
2 h after dinner	12.0 ± 2.8
Hypertension	27 (73%)
Dyslipidemia	32 (87%)
Diabetic retinopathy	11 (30%)
Diabetic nephropathy	10 (27%)
Diabetic neuropathy	24 (65%)
Cardiovascular disease	8 (22%)

Data are *n* (%) or mean ± standard deviation, except for the number of the recruited patients, which was represented as total number (the number of males : the number of females). NGSP, National Glycohemoglobin Standardization Program.

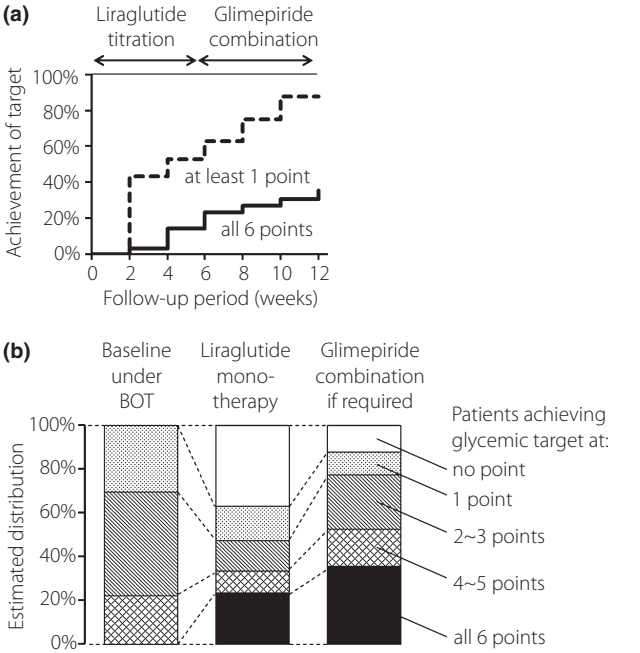

Figure 1 | (a) Kaplan–Meier estimates of achievement of targeted glycemia under liraglutide therapy at all six points (solid line) and at any one of the six points (dot line). Note that subtraction of the achievement at any one point (represented by dot line) from 100%, equivalent to the area above the dot line, represents the proportion of failures to achieve at any point. (b) The estimated distribution of the number of points where the glycemic target was achieved 6 and 12 weeks after the introduction of liraglutide compared with baseline control with basal-supported oral therapy (BOT).

and glimepiride were 14 ± 9 units and 1.5 ± 0.9 mg, respectively, with their NGSP-equivalent hemoglobin A1c level 7.7 ± 0.8%. Postprandial glycemia was insufficiently controlled, whereas fasting glycemia was as low as 6.3 ± 0.8 mmol/L. The frequency of hypoglycemia with BOT was 0.21 episodes per person per week. After the introduction of liraglutide injection, 11 patients achieved glycemic targets at all six points within 12 weeks of observation. The frequency of hypoglycemia with liraglutide monotherapy and combination therapy with glimepiride was as low as 0.04 and 0.08 episode per person per week, and there was no statistically significant difference ($P = 0.14$). No hypoglycemic event requiring assistance from another person was recorded. Three patients dropped out because of gastrointestinal side-effects.

Efficacy of Liraglutide Therapy

As shown in Figure 1, some of the patients responded to liraglutide therapy, whereas others did not at all. The glycemic target at all six points was achieved in 23% patients 6 weeks after the introduction of liraglutide monotherapy, and in 36% another 6 weeks later, with a combination of glimepiride when necessary. The dose of glimepiride at the 12th week was increased to 0.9 ± 0.4 mg/day. In contrast, 37% and 12% of the patients could not achieve the glycemic target at any one of the six points 6 and 12 weeks after the introduction of liraglutide therapy, respectively. Given the inclusion criteria of the current study, these results mean that glycemic control improved in some patients, but deteriorated in others after the change from BOT to liraglutide therapy.

These findings that a subset of patients responded to liraglutide therapy subsequently motivated us to investigate their clinical features in Cox proportional hazards regression analyses (Table 2). A stepwise multivariate model, into which the significant variables in univariate analyses were entered, showed that larger insulin doses and higher glycemia 2 h after breakfast with BOT had significant inverse associations with the achievement of the glycemic target with liraglutide therapy. Their adjusted HR in one-SD increments were 0.24 (95% CI 0.09–0.69) and 0.27 (95% CI 0.11–0.69), respectively. The predictive impact of the model assessed with the *C*-statistic was as high as 0.90. Indeed, the majority of those who used smaller doses of insulin achieved the glycemic target, whereas none of the patients with higher post-breakfast glycemia receiving larger insulin doses could achieve the glycemic target after change to liraglutide therapy (Figure 2).

Tolerance to Combination with Glimepiride

Liraglutide responders consisted of two groups: those who achieved glycemic goal with liraglutide alone and those who required additional glimepiride. It is important in clinical practice to predict who would be adequately controlled with liraglutide monotherapy and therefore should avoid combination with

Table 2 | Association of baseline variables with the efficacy of the change to liraglutide therapy

	Unadjusted HR in univariate model	Adjusted HR in multivariate model
Male (vs female)	0.73 (0.21–2.51)	
Age (in one-SD increment)	1.39 (0.73–2.65)	
Diabetic duration (in one-SD increment)	1.12 (0.55–2.29)	
Body mass index (in one-SD increment)	0.27 (0.10–0.73)*	N/I
Dosage of insulin (in one-SD increment)	0.27 (0.09–0.77)*	0.24 (0.09–0.69)*
Dosage of glimepiride (in one-SD increment)	0.20 (0.05–0.85)*	N/I
NGSP-equivalent hemoglobin A1c (in one-SD increment)	0.39 (0.15–1.01)	N/I
Daily profiles of blood glucose		
Before breakfast (in one-SD increment)	0.44 (0.21–0.93)*	N/I
2 h after breakfast (in one-SD increment)	0.27 (0.10–0.71)*	0.27 (0.11–0.69)*
Before lunch (in one-SD increment)	0.29 (0.08–1.11)	
2 h after lunch (in one-SD increment)	0.72 (0.35–1.46)	
Before dinner (in one-SD increment)	0.89 (0.46–1.74)	
2 h after dinner (in one-SD increment)	0.92 (0.44–1.93)	

Data are hazard ratios (HR) and 95% confidence intervals in Cox proportional hazards regression analyses. The dependent variable was achievement of targeted glycemia at all six points and its explanatory variables were baseline variables under BOT. Unadjusted HR was estimated in a univariate model and adjusted HR was estimated in a stepwise multivariate model, into which statistically significant variables in univariate models were entered. N/I, not included in the final multivariate model. *$P < 0.05$.

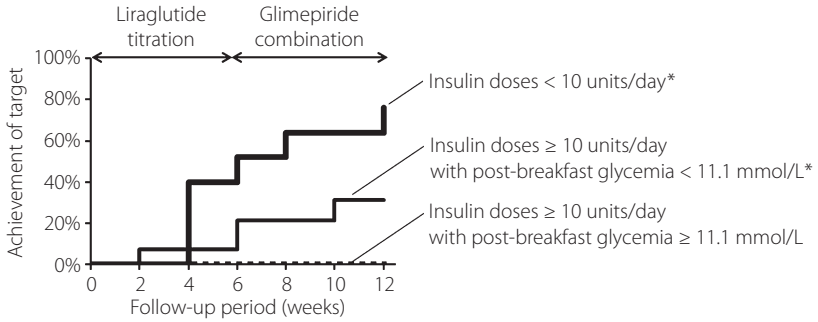

Figure 2 | Kaplan–Meier estimates of achievement of targeted glycemia at all six points with liraglutide therapy in the subgroups of basal-supported oral therapy failures. The patients were divided into three subgroups nearly equal in number on the basis of their baseline characteristics significantly associated with glycemic outcome, namely, insulin dosage and post-breakfast glycemia; the patients using less than 10 units/day of insulin (bold line, $n = 10$), those using ≥10 units/day of insulin with their post-breakfast glycemia <11.1 mmol/L (solid line, $n = 14$), and those using insulin ≥10 units/day with their post-breakfast glycemia ≥11.1 mmol/L (dot line, $n = 13$). *$P < 0.05$ vs those using insulin ≥10 units/day with their post-breakfast glycemia ≥11.1 mmol/L (log–rank test).

glimepiride, leading to further lowering glycemia, and who would be poorly controlled with liraglutide monotherapy and should have glimepiride combined from the time of liraglutide introduction. We attempted to clarify this issue by investigating the association of baseline characteristics with efficacy of liraglutide monotherapy. We carried out the investigation in the subgroup with the clinical potential to respond to liraglutide therapy, namely, those other than the patients who had post-breakfast hyperglycemia ≥11.1 mmol/L under BOT with their daily insulin doses ≥10 units, shown in Figure 2.

As a result, 42% of the patients achieved the glycemic target even with low doses of liraglutide monotherapy, with their post-prandial glycemia below 10.0 mmol/L, whereas 29% had their glycemia extremely poorly controlled, with their fasting glycemia ≥8.9 mmol/L. Stepwise multivariate logistic regression analyses showed that undesirable hyperglycemia before breakfast (≥8.9 mmol/L) with liraglutide monotherapy was associated with larger insulin doses with BOT (OR 1.22 [95% CI 1.02–1.46] in 1-unit increment), whereas well-controlled post-breakfast glycemia (<10.0 mmol/L) with liraglutide monotherapy was associated with lower post-breakfast glycemia with BOT (OR 3.82 [95% CI 1.25–11.66] in 1-mmol/L decrement). The predictive accuracy of these regression models assessed by *C*-statistic was 0.86 and 0.88, respectively.

Eventual Change of Hemoglobin A1c Levels

At the end of the follow-up period, hemoglobin A1c levels were 7.7 ± 1.4%, with no significant difference in the mean value from the baseline levels, and with little increase in the standard deviation (vs 7.7 ± 0.8%). Given that the efficacy of liraglutide therapy varied among patients, this increased standard deviation would be reasonable. Indeed, the eventual change in hemoglobin A1c levels was −0.6% ($P < 0.01$) in the responders, −0.2% ($P = 0.21$) in the non-responders without deteriorated glycemic control and +1.1% ($P = 0.08$) in the non-responders with their glycemic control rather deteriorated.

DISCUSSION

Liraglutide has been clinically available in Japan since June 2010. Its domestic clinical trials showed that liraglutide was highly effective and well-tolerated enough at doses up to 0.9 mg/day in Japanese type 2 diabetic patients[18–20]. Another clinical trial in Japan also showed that both 0.6 and 0.9 mg/day of liraglutide in combination with sulfonylureas similarly lowered fasting glycemia as early as 1 month later[21]. These domestic findings, as well as the favorable outcome of the LEAD-5 study[12], have set our expectations of glycemic improvement through changing from BOT to liraglutide therapy.

The current study, however, showed that not all BOT failures received benefits from liraglutide therapy. It is true that some indeed improved their glycemic control, but others rather experienced more severe hyperglycemia. The subsequent exploratory analyses showed that insulin dosage and post-breakfast glycemia with BOT were associated with its clinical efficacy. These two variables at baseline are easy to check in clinical practice and therefore would be useful in the predictive assessment for the potential effectiveness of liraglutide therapy.

It might be easy to understand the association of basal insulin dosages with liraglutide efficacy, because decreased β-cell function often requires increased dosages of basal insulin. Decreased β-cell function was likely accompanied by a weakened augmentation of insulin secretion, and therefore associated with the efficacy of liraglutide. It seemed reasonable that liraglutide efficacy was clinically predicted by basal insulin dosages. In contrast, the association of post-breakfast glucose levels with its efficacy might be apparently difficult to interpret. However, the variable might similarly reflect their residual β-cell function, with the following logic.

All the patients in the current study had their preprandial glucose levels sufficiently controlled with titrated insulin administration. Furthermore, the patients took sulfonylureas, which potentially augmented their insulin secretion. Even under these similar conditions, however, the increase in blood glucose levels after the load of breakfast did vary from patient to patient. It might be safely assumed that postprandial glucose elevation can be easily corrected if patients have enough residual β-cell function. Meanwhile, extremely elevated postprandial glucose levels are expected if β-cell function is substantially decreased. Taken together, a variety of post-breakfast glucose levels among patients might reflect some aspects of residual β-cell function, although their precise insulin secretory capacity was not evaluated in the current study.

We also confirmed that only a few hypoglycemic episodes were recorded in the current study population, although there were considerable anxieties about hypoglycemia under incretin-based therapy combined with sulfonylureas in Japanese diabetic patients[13]. This low frequency of hyperglycemia in the current study might be a result of the very regimens we used. In the current study, glimepiride was combined only when hyperglycemia remained with liraglutide monotherapy, which resulted in avoiding an undesired combination with glimepiride in patients who could be adequately controlled with liraglutide monotherapy. A careful titration of glimepiride from the minimum dosage recommended in Japan could also lead to an effective prevention of hypoglycemia.

One must note here, however, that an excessive priority of the avoidance of hypoglycemia could in turn lead to undesirable hyperglycemia in the management of type 2 diabetes mellitus. In fact, some patients in the current study suffered extreme hyperglycemia with liraglutide monotherapy. These patients whose glycemia would be undesirably poorly controlled with liraglutide monotherapy should have glimepiride combined from the very beginning of the change to liraglutide therapy, without fear of the risk of hypoglycemia. In contrast, those who would achieve the glycemic target with small doses of liraglutide monotherapy should avoid the combination with glimepiride, which might excessively lower their glycemia. Whether to combine glimepiride when changing from BOT to liraglutide therapy is clinically important. Our subsequent exploratory analyses showed that insulin dosage and post-breakfast glycemia could again be predictive for the necessity of its combination. Most patients with BOT might carry out self-monitoring of blood glucose in the fasting state[8], but the present findings suggest that checking post-breakfast glycemia would be informative and useful before changing to liraglutide therapy.

Gastrointestinal side-effects were observed in the current study, as in previous clinical trials[12,15,22–25]. We could not find any associations of their baseline characteristics with its occurrence (data not shown). It might be difficult to predict the likelihood of adverse events.

The current study had some limitations. First, in the current retrospective study, no unified indices of insulin secretion were available. Therefore, it remains unclear whether residual β-cell function is pathologically associated with liraglutide efficacy. In daily management of patients, however, evaluation of the clinical features that were shown to be associated with the efficacy, that is, insulin dosages and post-breakfast glucose levels, is far easier compared with the precise estimation of β-cell function. We therefore believe that the current study would offer practically useful information, rather than pathological implications.

Another limitation was the study design. The current study was retrospective, with a small sample size, and was vulnerable to various biases. Therefore, one should note that the absolute

percentage of responders to liraglutide in the current study does not reflect the true efficacy of the drug. The results could also be influenced by various non-pharmacological effects. For example, in general, initiating some new medication requires more careful management than giving continuous prescriptions, and it is no surprise that this increased intensity affects the improvement of glycemic control. In the current study, not only liraglutide therapy itself, but also the action of its initiation, which could eventually modify the patients' lifestyle, might have some influence on their glycemic control, although no data were available about the extent to which the patients' lifestyle was actually modified. These accompanying affects were expected among all the recruited patients. Notwithstanding, the current study found heterogeneous efficacy of liraglutide therapy, which was of clinical note. Furthermore, subsequent analyses showed that this heterogeneity was mostly explained by some easily evaluated clinical features, with such high *C*-statistics that even the small sample size could provide enough power. We therefore believe that the current study gave clinically important implications with respect to these risk analyses and stratification regardless of these limitations.

In conclusion, the change from BOT to liraglutide therapy provided favorable outcomes in some patients who were not well controlled with BOT. It is likely that the potential efficacy of liraglutide therapy and the necessity of combination with glimepiride can easily be predicted in clinical practice in the population by insulin dosage and post-breakfast glycemia with BOT. Future prospective studies will be required to validate the efficacy and tolerability of the change from BOT to liraglutide therapy.

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