Cost-effectiveness analysis of voglibose for prevention of type 2 diabetes mellitus in Japanese patients with impaired glucose tolerance

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ABSTRACT
Aims/Introduction: The objective of this study was to estimate the cost-effectiveness of administering voglibose, in addition to standard care of diet and exercise, compared with standard care alone for high-risk Japanese patients with impaired glucose tolerance.

Materials and Methods: A Markov model was constructed to estimate the long-term prognosis of individuals with impaired glucose tolerance, in terms of expected medical costs and life expectancy. Transition probabilities were derived from the results of a clinical trial of voglibose, as well as the epidemiological information. Effectiveness was evaluated by life expectancy and only direct costs were considered. The future costs and effectiveness were discounted by 3% per year.

Results: Estimated expected lifetime costs for the voglibose administration group and the standard care group was JPY718,724 ($US7598) and JPY1,365,405 ($US14,433), respectively, with voglibose administration resulting in saving of JPY646,681 ($US6836). Estimated life expectancy was 18.672 and 18.073 years, respectively, with life expectancy prolonged by 0.599 years when voglibose was administered together with the standard care.

Conclusions: In order to prevent type 2 diabetes among Japanese patients with impaired glucose tolerance, voglibose with standard care resulted in cost-saving, as well as prolongation of life expectancy, compared with standard care alone. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00052.x, 2010)

KEY WORDS: Cost effectiveness, Diabetes mellitus, Voglibose

INTRODUCTION
The annual medical costs of diabetes are reported to be JPY1.2 trillion ($US11.8 billion, based on the currency exchange rate of $US1 = JPY94.6 on 25 May 2009, as applied hereinafter in the entire article) according to the latest official statistical data of medical costs issued by the Japanese Ministry of Health, Labour and Welfare (MHLW)1. However, actual medical costs related to diabetes might be higher, as the costs of complications that could develop in relation to diabetes might not have been included in the figure reported by the MHLW. The medical cost of diabetes, when including various complications, have been reported to reach as much as JPY5 trillion ($US52.9 billion) per year2. Meanwhile, the number of patients with diabetes in Japan is estimated to be 22.1 million, including those in whom the possibility of diabetes cannot be ruled out3, and a further increase is predicted in the future. Correspondingly, it is predicted that the medical cost of diabetes will increase and countermeasures against the cost of diabetes have also been a major issue from the perspective of national finance, because all Japanese are universally covered by the national healthcare insurance system.

It is well known that many patients with type 2 diabetes mellitus (T2DM) experience a period of impaired glucose tolerance (IGT) before developing T2DM4, and that IGT also has a larger impact as a risk factor of cardiovascular complications5,6. Therefore, it is clinically very important to control the blood glucose level in patients with IGT and to try to normalize the blood glucose level while preventing a progression to T2DM. Furthermore, an economic effect can be expected.

Through large-scale clinical studies overseas, including the Diabetes Prevention Program (DPP) and the STOP-NIDDM study, clinical efficacy for preventing the development of T2DM through management of IGT by drug treatment has been shown, while studies showing superior cost-effectiveness have been also reported7–12.

Voglibose is an alpha-glucosidase inhibitor that reduces postprandial hyperglycemia and hyperinsulinemia by inhibiting enzymes involved in the digestion and gastrointestinal tolerance.
absorption of dietary carbohydrates. In Japan, it has been marketed under the name of BASEN tablets since September 1994, and BASEN OD tablets (oral disintegration tablets) have been on the market since July 2004.

In April 2003, a multicentre, randomised, double-blind, placebo-controlled clinical trial (hereinafter referred to as the voglibose clinical trial) was carried out in a Japanese IGT population, and a significant effect of voglibose on the primary prevention of T2DM compared with the placebo was confirmed. The present cost-effectiveness analysis is based on the results of the voglibose clinical trial.

MATERIALS AND METHODS

Analytical Model
The present analysis is aimed at comparing the long-term costs, life expectancy and cost-effectiveness of the IGT population in a group using diet and exercise alone (the standard care group) versus a group using voglibose in addition to standard care (the voglibose group).

As clinical studies are usually of limited duration, it is very difficult to collect adequate data only from clinical studies in order to estimate long-term costs and life expectancy. So, it is necessary to use an economic modeling framework that simplifies the disease and the process of the treatment. In the present analysis, the long-term cost-effectiveness of voglibose was estimated using a Markov model, which consisted of five stages (normal glucose tolerance [NGT], IGT, T2DM, dialysis and death; Figure 1). Considering the large impact of dialysis on the life expectancy and long-term costs, the transition to dialysis from the onset of diabetes was taken into account.

In the standard care group, it was assumed that voglibose was not given, but individuals visited the medical institution for routine standard care. In the voglibose group, the individuals took 0.6 mg voglibose (0.2 mg BASEN tablet, three times a day) every day. We assumed that both groups visited the medical institution four times/year, and that clinical laboratory tests (blood glucose, HbA1c and urine) were carried out at the time of each visit. Furthermore, the IGT handled in this analysis should be IGT, which has a high risk of developing T2DM, which corresponds to the following patient selection criteria in the voglibose clinical trial (hereinafter referred to as a high risk IGT).

At the time of starting the observation period, a fasting plasma glucose level was <125 mg/dL, a 2-h 75 g oral glucose tolerance test (OGTT) was between 140 and 199 mg/dL, HbA1c was <6.5% (JDS) and any of the following (i) through to (iv) is met: (i) hypertension or high normal blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic); (ii) dyslipidemia (total cholesterol ≥220 mg/dL, triglyceride ≥150 mg/dL, or HDL cholesterol <40 mg/dL); (iii) obesity (a body mass index ≥25 kg/m²); and (iv) family history of diabetes (in a first- or second-degree relative).

In this analysis, the age of the IGT population was set as 56 years-of-age corresponding to the average age in the voglibose clinical trial population, and costs and life expectancy up to the age of 105 years were estimated, considering one cycle as 1 year. The analysis was carried out from the perspective of the healthcare payers, and only the direct medical costs were evaluated.

Future costs and life years were discounted by 3% per year.

Parameters

Probabilities
For probability parameters, five types of probabilities were set in the Markov model: (i) annual transition probability from IGT to T2DM; (ii) annual transition probability from IGT to NGT; (iii) annual transition probability from NGT to IGT; (iv) annual transition probability from T2DM to dialysis; and (v) annual mortality for each stage.

Annual Transition Probability From IGT to T2DM and Annual Transition Probability From IGT to NGT
The annual transition probability from IGT to T2DM and that from IGT to NGT were estimated based on the results of a modified Kaplan–Meier analysis in the voglibose clinical trial. The data for the placebo arm and the voglibose arm were used for this analysis, respectively, for the standard care and the voglibose groups of the model.

The annual transition probability was estimated exponentially based on the cumulative progression rate at 144 weeks (1008 days), which was prescribed as the study drug administration period in the voglibose clinical trial.

Annual Transition Probability From NGT to IGT
In this analysis, a transition from IGT to NGT occurs at a certain rate, but after transition to NGT, some individuals might go back to IGT again. In the voglibose clinical trial, the subsequent transition of the patients who had regressed to NGT was not traced thereafter, therefore in the present analysis, the transition probability from NGT to IGT was estimated from a literature search of studies in Japan.

Ohizumi reported from a long-term epidemiological study in Funagata city (Funagata study) that among a 980 NGT
population, 142 (14.5%) transitioned to the borderline type 5-years later, and if this is converted to the annual transition probability, it would be 3.1%.

**Transition From T2DM to Dialysis**
The transition from T2DM to dialysis was based on results from an epidemiological study of dialysis patients with type 1 diabetes in Japan, which showed that the transition probability to dialysis was 0.56% after the onset of diabetes.

**Mortality**
For the annual mortality of NGT, the average values for males and females in the national data of the abridged life table in 2008 were used.

There are several reports that mortality in the case of IGT and T2DM are higher than those with NGT. Data were used from the DECODA study, for which individuals of Asian origin were targeted for analysis in the same way as in the DECODE study, and the relative risk of death in IGT and T2DM in comparison with NGT was set as 1.35 and 3.03, respectively.

The annual mortality in dialysis patients was estimated from the cumulative survival rate in Japanese patients requiring dialysis as a result of diabetic nephropathy as reported by Maeda.

**Costs**
Three types of cost parameter were set in the Markov model: that is, annual management costs of IGT, annual medical costs of T2DM and annual medical costs of dialysis. Medical costs were converted to JPY by the past revision rate for the physicians fee point and drug price in Japan.

**Annual Management Costs of IGT**
As is the case with the setting of the voglibose clinical trial, a dosage of a 0.2 mg BASEN tablet, three times a day, was given. According to the official drug list as of May 2009, the price of a 0.2 mg BASEN tablet is JPY47.5 ($US0.5), equating to a drug price per day of JPY142.5 ($US1.5; JPY47.5 × 3 times/day).

If voglibose is to be given every day, the annual drug cost is JPY52,013 ($US550) per year (JPY142.5 × 365 days).

If patients in both groups visit the medical institution four times/year, where clinical laboratory tests (blood glucose, HbA1c and urine) are carried out at the time of each visit, annual medical costs would amount to be JPY24,110 ($US255) for the first year and JPY22,640 ($US239) for the second and following years (the fee for the initial exam comes in the first year).

**Annual Medical Costs of T2DM and Dialysis**
As diabetes is a disease that progresses in parallel with multiple complications, in order to estimate the medical costs of diabetes, it is preferable to estimate each state of progression of these complications and then sum up the total medical costs incurred by each complication. However, many data on the progression of each complication and complicated models are needed to establish these costs. Thus, in the present analysis, instead of searching onset and types of diabetic complications, annual medical costs corresponding to the morbidity period of diabetes was set. As aforementioned, the transition to dialysis from the onset of diabetes was taken into account, in view of the large impact of dialysis on life expectancy and long-term costs.

Hidaka et al. reported the medical costs by each morbidity period of diabetes based on the analysis of medical costs using the results of medical checkups and the receipts in the workplace. Thus, in the present analysis, the annual medical costs by each morbidity period reported by Hidaka et al. were used in the model.

**Annual medical cost of dialysis**
Annual medical cost of dialysis was set by JPY4,994,863 ($US52,800) on the basis of published literature.

**Base-Case Analysis and Sensitivity Analysis**
For base-case analysis, lifetime medical treatment costs and life expectancy were calculated based on a population with a mean age of 56 years.

One-way sensitivity analyses were carried out for the range between the upper and lower limits of the 95% confidence interval of results from the voglibose clinical trials, the transition probability from IGT to NGT, the transition probability from T2DM to dialysis and the relative risk of mortality associated with IGT and T2DM. No information was available for estimating the 95% confidence interval for the annual mortality rate in dialysis patients, the annual medical cost of diabetes, or the annual cost of dialysis, so those ranges were changed to 50 and 150% of the base value. The discount rate was also changed (0–6%). The influence of changes in single parameters are shown as a tornado diagram (Figure 3). Table 1 shows the parameters used in the analysis.

**RESULTS**
**Base-case Analysis**
Table 2 shows expected lifelong costs and life expectancy in the voglibose group and the standard care group.

Expected lifetime costs and life expectancy per person were JPY718,724 ($US7,589) and 18.672 years, respectively, in the voglibose group and JPY1,365,405 ($US14,433) and 18.073 years, respectively, in the standard care group. As a result, treating patients with voglibose was a dominant strategy, because expected costs of JPY646,681 ($US6,836) could be reduced and the life expectancy could be prolonged by 0.599 years with voglibose administration.

From the breakdown of costs, by preventing the development of T2DM and improving NGT by voglibose administration, the medical costs of T2DM and dialysis in the voglibose group was JPY508,717 ($US5,378), which was JPY782,641 ($US8,273) (60.6%) less than the JPY1,291,358 ($US13,651) medical costs of diabetes and dialysis in the standard care group. Through this reduction, the drug costs of JPY145,294 ($US1,536) incurred in the voglibose group were offset, and as a result, total costs in the...
The variations of the expected costs and life expectancy in the two groups in each sensitivity analysis are shown in Figure 3. The horizontal axis of this graph shows the difference of expected costs or life expectancy in the two groups, and the longer the length of the bar for the variable is, the larger the variation will be in the case of changing each parameter from low to high values. As a result of the sensitivity analyses, the expected costs were lower in the voglibose group than the standard care group, and the result that treatment with voglibose was a dominant strategy did not change.

The discount rate was the variable that had the greatest effect on expected costs and life expectancy. When the discount rate was excluded, the parameter that had the largest impact on expected costs was the annual T2DM cost, and that of the next largest impact was the transition probability from IGT to T2DM in the standard care group. The parameter that had the largest impact on life expectancy was the relative risk of mortality associated with T2DM, and that of the next largest impact...
was the transition probability from IGT to T2DM in the standard care group. The transition probability from NGT to IGT, the relative risk of mortality associated with IGT, and the IGT management cost had almost no effect on expected costs. Similarly, the rate of transition probability from NGT to IGT, the relative risk of mortality associated with IGT and the transition probability from T2DM to dialysis had almost no effect on life expectancy.

DISCUSSION

It is reported that the rate of the transition to T2DM from IGT is several times higher than that from NGT\(^{14,23-25}\). Also, IGT itself is considered to be a risk factor for coronary artery diseases and death\(^{5,17,18}\). The Evidence-based Clinical Practice Guidelines for Diabetes, 2nd Edition 2007 prepared by the Japan Diabetes Society explained that it is necessary to fully observe the clinical course of the borderline type and aggressively consider an intervention treatment for the prevention of the development of diabetes\(^{26}\).

International Diabetes Federation (IDF) announced a three-step strategy as an agreed statement on the prevention of T2DM in May 2007\(^{27}\). However, like the statement shown in Japanese clinical practice guidelines for diabetes, for the prevention of T2DM, lifestyle improvement is advocated first and if this is not sufficient, treatment by metformin as well as acarbose, an alpha-glucosidase inhibitor similar to voglibose, is recommended. Furthermore, some reports exist describing the economic benefits of the prevention of T2DM\(^{7,12}\) and the agreed statement by IDF also indicates that the prevention of T2DM is extremely superior in the cost-effectiveness analysis.

In this analysis, based on the results of the voglibose clinical trial, lifelong expected costs and life expectancy of a 56-year-old high risk IGT population were estimated, and as a result, a cost reduction of JPY646,681 ($US6836) and an extension of life expectancy by 0.599 years were predicted. Furthermore, although the sensitivity analyses were carried out on all the parameters used in the analysis, the conclusion that the voglibose group is cost-saving did not change, thus the analysis can be considered robust. Therefore, the prevention of T2DM by voglibose in the high-risk IGT population is very preferable from an economic point of view, thus it should be introduced aggressively. Furthermore, when the difference of costs in the two groups after starting intervention was calculated, it became larger over time as JPY76,961 ($US814) 10 years later, JPY412,532 ($US4361) 20 years later, JPY605,434 ($US6400) 30 years later and JPY643,786 ($US6805) 40 years later. Thus, it is considered important to increase the compliance to the treatment as much as possible, to maximize the health economic effect of intervention by voglibose.

Based on the results of this analysis, an estimation of the nationwide reduction of medical costs for introducing voglibose in the prevention of T2DM in high risk IGT population is attempted.

The IGT population in Japan is estimated by the National Health and Nutrition Survey in Japan, 2007 to be 13.2 million, which includes “those in whom the possibility of diabetes could not be ruled out”\(^{3}\). Assuming that the rate of metabolic syndrome (41.8%) according to the NCEP-ATPIII diagnostic criteria in T2DM registered in Japan Diabetes Complications...
Study (JDCS) is similar to the rate of metabolic syndrome in the IGT population,\(^{28}\) the number of people with metabolic syndrome in IGT in Japan is estimated to be 13.2 million people \(\times 41.8\% = 5.5\) million people. In the case of administering voglibose to all of the high risk IGT population, if a reduction in medical costs of JPY76,961 ($US814) and JPY412,532 ($US4361) per person could be expected in 10 and 20 years, respectively, the reduction of healthcare costs nationwide as a result of voglibose administration can be estimated to be JPY425 billion ($US4.5 billion) in 10 years and JPY2.3 trillion ($US24.1 billion) in 20 years.

Because this analysis is a simulation analysis using modeling, there are some limitations regarding the model structure and input parameter setting.

The first limitation is regarding the probability of moving backwards to IGT after transitioning from IGT to NGT. These probabilities were also targeted for investigation in the voglibose clinical trial, but an analysis is currently being carried out. Thus, in the present analysis, from the data on change of glucose tolerance over 5 years targeting cohorts of the Funagata study\(^{14}\), the transition probability from NGT to IGT was set as an annual transition probability of 3.1%. However, in the report by Ohizumi et al., those who regressed from IGT and those who did not regress were mixed in NGT, and they did not exactly match with the patients targeted for the present analysis. The transition probability from NGT to IGT is presumed to be higher in patients who moved backward from IGT than those who did not. However, in the sensitivity analysis using the upper limit of 95% confidence interval in the report by Ohizumi et al., the result that the voglibose group was cost-saving did not change. Furthermore, from Figure 3, the impact of the transition probability from NGT to IGT on the difference in expected costs and life expectancy between the two groups was very small in comparison to other parameters, so the impact of this parameter on the result is considered to be relatively small.

The second limitation is regarding the medical costs of diabetes. Not only medical costs for glycemic control, but also for the treatment of diabetic complications, such as retinopathy, nephropathy, neuropathy and macroangiopathy, account for a large proportion of the medical costs of diabetes. However, in order to estimate the treatment costs of diabetic complications, it is necessary to construct a progression model of diabetic complications, and this estimation is not easy as a result of a lack of required data in Japan. If diabetic complications progress to some extent, they become almost irreversible, and the medical costs also increase over time. That is to say, in proportion to the morbidity period, the medical costs are considered to increase. Therefore, in the present analysis, the progression of each complication was not considered, and data by Hidaka et al., which reported the medical costs by each morbidity period of diabetes\(^{21}\), were to be used. Because we obtained data regarding the transition probability from T2DM to dialysis and the annual cost of dialysis in Japan, the progression from T2DM to dialysis stage was considered in the Markov model. Furthermore, in the present analysis, only direct medical costs were estimated, because we took the payers perspective, but the longer the morbidity period of diabetes is, the larger the production loss by the treatment of diabetes or diabetic complications becomes. If we took the societal perspective and considered the production loss in this analysis, the costs of diabetes would be higher, and as a result, the amount of cost saving of voglibose would be larger. Moreover, from the results of the sensitivity analysis, it was found that the annual medical costs of T2DM was a parameter that had a relatively major impact on the expected costs in the present analysis (Figure 3a), and the medical costs of T2DM are expected to be examined in further detail.

The third limitation is concerned with the drug price of voglibose. For the drug price of voglibose, the list price of a 0.2 mg BASEN tablet (JPY47.5 ($US0.5)) as of May 2009 was used. However, under the Japanese drug price regulation of the national health insurance (NHI) system, the marketed drug prices were to be revised basically every 2 years according to the official nationwide survey data on the annually changing market delivery prices, and almost all of the drug prices for NHI reimbursement are downwardly revised. Considering such regulatory practice of drug price regulation, it can be reasonably presumed the health economic impact of voglibose will become more preferable.

It is necessary to explain why the costs of adverse effects by the voglibose group are not considered. In the voglibose clinical trial, more gastrointestinal disturbances developed in the voglibose administration group compared with the placebo group (voglibose group 40.8%, placebo group 21.2%), and most of the disturbances, such as diarrhea, flatulence and abdominal distension, could be treated by a transient discontinuation and the like. Thus, in the present analysis, the adverse reactions to voglibose were not considered in the model.

Although there are some limitations, the conclusion that voglibose administration is cost-saving in a high-risk IGT population is considered robust, and the amount of reduction is considered to be rather underestimated.

From the present analysis, it was confirmed that the prevention of T2DM by voglibose in a high-risk IGT population contributes to the prolongation of life expectancy and the reduction of costs in the IGT population and it was found to be extremely useful from the two perspectives of life prognosis and medical costs of the IGT population. In the future, it seems that it will be necessary to aggressively examine the primary prevention of T2DM by voglibose in the high-risk IGT population.

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