Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance

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Summary

Background The increased prevalence of type 2 diabetes mellitus is a major concern for health providers. We therefore assessed whether voglibose, an α-glucosidase inhibitor, could prevent the development of type 2 diabetes in high-risk Japanese individuals with impaired glucose tolerance.

Methods 1780 eligible patients on a standard diet and taking regular exercise with impaired glucose tolerance were randomly assigned to oral voglibose 0·2 mg three times a day (n=897) or placebo (n=883) in a multicentre, double-blind, parallel group trial. Treatment was continued until participants developed type 2 diabetes (primary endpoint) or normoglycaemia (secondary endpoint), or for a minimum of 3 years, subject to the findings of an interim analysis. Analysis was by full analysis set. This trial is registered with the University Hospital Medical Information Network (UMIN) clinical trials registry, number UMIN 000001109.

Findings In the interim analysis, voglibose was better than placebo (p=0·0026) in individuals treated for an average of 48·1 weeks (SD 36·3). Patients treated with voglibose had a lower risk of progression to type 2 diabetes than did those on placebo (50 of 897 *vs* 106 of 881; hazard ratio 0·595, 95% CI 0·433–0·818; p=0·0014). More people in the voglibose group achieved normoglycaemia than did those in the placebo group (599 of 897 *vs* 454 of 881; 1·539, 1·357–1·746; p<0·0001). 810 (90%) of 897 patients in the voglibose group had adverse events versus 750 (85%) of 881 in the placebo group. Serious adverse events (all one each) in the voglibose group were cholecystitis, colonic polyp, rectal neoplasm, inguinal hernia, liver dysfunction, and subarachnoid haemorrhage, and in the placebo group were cerebral infarction and cholecystitis.

Interpretation Voglibose, in addition to lifestyle modification, can reduce the development of type 2 diabetes in high-risk Japanese individuals with impaired glucose tolerance.

Funding Takeda.

Lancet 2009; 373: 1607–14

Published Online
April 22, 2009
DOI:10.1016/S0140-6736(09)60222-1

See Comment page 1579

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Introduction

Metabolic disorders with a predisposition towards impaired glucose intolerance and ultimately type 2 diabetes mellitus are a major health problem.[1,2] In 2002, the Japanese Ministry of Health, Labour and Welfare estimated that 7·4 million patients in Japan had diabetes and, more worryingly, 8·8 million people were considered to be possibly diabetic on the basis of HbA_{1c} levels that were between 5·6% and 6·1%. The number of individuals with diabetes had increased by almost 2 million since the 1997 survey.[3]

Although type 2 diabetes has a genetic basis, evidence supports a key part played by modifiable behavioural risk factors such as obesity and physical inactivity.[4] Disorders such as impaired glucose intolerance and metabolic syndrome seem to be intermediate stages between normal glucose tolerance and overt diabetes, and greatly increase the risk of type 2 diabetes and its attendant macroangiopathy.[5–7] The International Diabetes Federation Taskforce on Prevention and Epidemiology convened a consensus workshop in Lisbon, Portugal, and recommended a three-step approach—identification of those at risk, measurement of the risk, and appropriate intervention—to prevent or delay the development of type 2 diabetes.[8] At the core of this strategy is lifestyle modification—ie, dietary control and increased exercise, but the International Diabetes Federation recognises that pharmacotherapy might be needed in some individuals who cannot maintain such behavioural changes.

The European DECODE study,[5,9] a meta-analysis of 13 prospective cohort studies, some in Asian individuals,[10] reported that impaired glucose tolerance is a prognostic factor for both all-cause and cardiovascular death. Thus, impaired glucose tolerance not only increases the likelihood of developing diabetes, but also exacerbates macrovascular pathological changes. Treatment strategies designed to slow or delay the progression of impaired glucose tolerance therefore have the potential to reduce cardiovascular morbidity and mortality, and some of the burden on health-care resources. Indeed, results of large, well designed trials have suggested that intensive diet and exercise programmes,[11–13] and pharmacological intervention,[13–20] help prevent or delay the development of diabetes in high-risk individuals with impaired glucose tolerance.

Diabetes is a global problem, and its prevalence in Asia is predicted to increase substantially over the next 25 years. Studies specifically involving Asian people include the Da Qing study in China,[11] the Indian Diabetes Prevention Programme,[21] and a Japanese lifestyle intervention trial.[22] Until now, no active drug intervention trial in Japanese individuals with impaired glucose tolerance has been reported. We therefore investigated the effectiveness of voglibose, an α-glucosidase inhibitor that reduces diurnal insulin secretion,[23–25] for prevention of the development of type 2 diabetes in Japanese patients with impaired glucose tolerance.

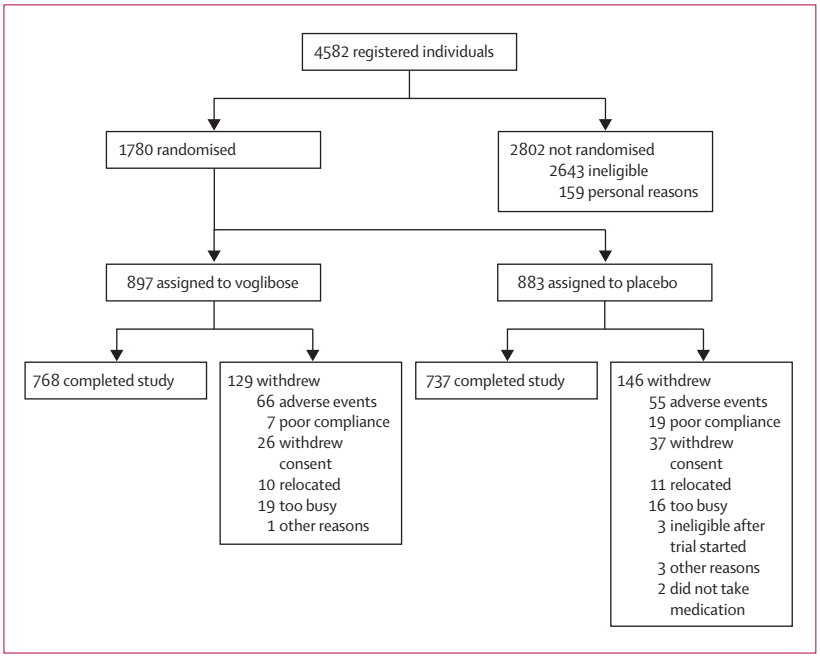

Figure 1: **Trial profile**

	Voglibose (n=897)	Placebo (n=881)
Men	541 (60%)	530 (60%)
Women	356 (40%)	351 (40%)
Age (years)	55·7 (9·08)	55·7 (9·16)
Body-mass index (kg/m²)	25·76 (3·70)	25·89 (3·82)
FPG (mmol/L)	5·80 (0·55)	5·85 (0·56)
2hPG (mmol/L)	9·107 (0·919)	9·185 (0·941)
Randomisation risk factors		
Obesity	502 (56%)	500 (57%)
Dyslipidaemia	695 (77%)	667 (76%)
Hypertension	528 (59%)	510 (58%)
Family history of diabetes mellitus*	337 (38%)	336 (38%)
2hPG (>9·4–11·0 mmol/L)	323 (36%)	345 (39%)
Number of risk factors		
≤2	340 (38%)	330 (37%)
≥3	557 (62%)	551 (63%)

Data are number (%) or mean (SD). 2hPG=2 h plasma glucose concentration during oral glucose tolerance test. FPG=fasting plasma glucose concentration.
*First-degree relatives of patients with type 1 or type 2 diabetes mellitus.

Table 1: **Baseline demographic characteristics of individuals in the voglibose and placebo groups**

Methods

Study design

This study was a multicentre, randomised, double-blind, parallel group comparison of voglibose and placebo in Japanese individuals with impaired glucose tolerance. From April, 2003, we aimed to treat people until type 2 diabetes or normoglycaemia was diagnosed, or for at least 3 years. The Independent Data Monitoring Committee planned an interim analysis to investigate whether or not to continue the study on the basis of efficacy and safety findings.

Procedure

We recruited individuals from 103 Japanese institutions, mainly through assessment of high-risk populations, and in particular from first-degree relatives of patients with type 1 or 2 diabetes. We screened 4582 men and women aged 30–70 years, with suspected impaired glucose tolerance for family history, blood pressure, body weight, body-mass index, routine blood chemistry (including lipid concentrations), fasting plasma glucose concentrations, and HbA_{1c}, and did an oral glucose (75 mg) tolerance test (OGTT) during a 4-week observation. Individuals were eligible for the trial if they had a fasting plasma glucose concentration of less than 6·9 mmol/L, a 2 h plasma glucose concentration during OGTT (2hPG) of between 7·8 mmol/L and 11·0 mmol/L, HbA_{1c} less than 6·5%, and at least one of the following risk factors for type 2 diabetes: high normal blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg) or were being treated for hypertension; dyslipidaemia (concentrations of total cholesterol ≥5·7 mmol/L, triglyceride ≥1·7 mmol/L, or HDL cholesterol <1·04 mmol/L); obesity (body-mass index ≥25 kg/m²); and a family history of diabetes (in a first-degree or second-degree relative). We excluded patients with diabetes or a disease likely to impair glucose tolerance.

All patients provided written informed consent. The trial was approved by the ethics committees of the appropriate institutional review boards, and done in compliance with Good Clinical Practice guidelines and in line with the ethical principles set out in the Declaration of Helsinki.

After 4 weeks, eligible individuals were randomly allocated to voglibose 0·2 mg or an identical-looking placebo three times a day before meals. Randomisation was done with a stratified allocation procedure designed to balance the two treatment groups in each institution with respect to the number of risk factors (≤2 or ≥3), which were hypertension or high normal blood pressure, dyslipidaemia, obesity, a family history of diabetes, and a 2hPG greater than 9·4 mmol/L (a concentration

associated with an increased risk of developing type 2 diabetes in Japan) to 11·0 mmol/L. An independent statistician computer-generated the random sequence and this was maintained securely until the study was unmasked. Allocation was concealed with sealed opaque envelopes.

4–8 weeks before the start of treatment, each person was given advice about appropriate nutrition and exercise programmes (interview, survey of lifestyle, and individualised guidance on future lifestyle habits based on intensity of daily activity categories defined by the Japanese Ministry of Health and Labour[26]) and adherence to these was assessed at each visit. The primary endpoint was the development of type 2 diabetes, which was defined as an HbA_{1c} level of at least 6·5%, and, on two separate occasions, at least one of the following: a 2hPG of at least 11·1 mmol/L, fasting plasma glucose concentration of at least 7·0 mmol/L, or random plasma glucose concentration of at least 11·1 mmol/L. The secondary endpoint was the number of people who achieved normoglycaemia (ie, 2hPG <7·8 mmol/L and a fasting plasma glucose concentration <6·1 mmol/L). Once the primary or secondary endpoint was achieved, patients discontinued their medication (those who achieved normoglycaemia are being followed up until study completion, when their responses will be analysed). Diagnosis of type 2 diabetes and normoglycaemia was made by the principal investigator in compliance with the standards of the Japan Diabetes Society.[27]

Every 12 weeks, we measured the concentrations of fasting blood glucose, HbA_{1c}, and blood lipids (triglycerides, total cholesterol, HDL cholesterol, and free fatty acids), did clinical laboratory tests (chemistry, haematology, and urinalysis), measured blood pressure and body weight, did compliance checks (returned tablet counts), and questioned patients about adverse effects. We did an OGTT every 24 weeks. All blood and urinary analytical tests were done at a central laboratory with standard methods.

Sample size, statistical analyses, and interim analysis

The planned total sample size of 864 patients was calculated on the basis of the assumptions of a 7·7% yearly progression to type 2 diabetes in the placebo group, recruitment of individuals during 2·1 years, a study duration of 4·9 years, and a 5% dropout rate. The study had a 90% power to detect a 40% reduction in the primary endpoint with a two-sided type I error of 0·05. To maintain this power the study required at least 170 individuals to progress to type 2 diabetes. However, the improvement to normoglycaemia occurred to a greater extent than anticipated, suggesting that the number of individuals progressing to type 2 diabetes would be much smaller than originally planned. Therefore, to maintain the statistical power of the trial, we amended the protocol during the recruitment phase

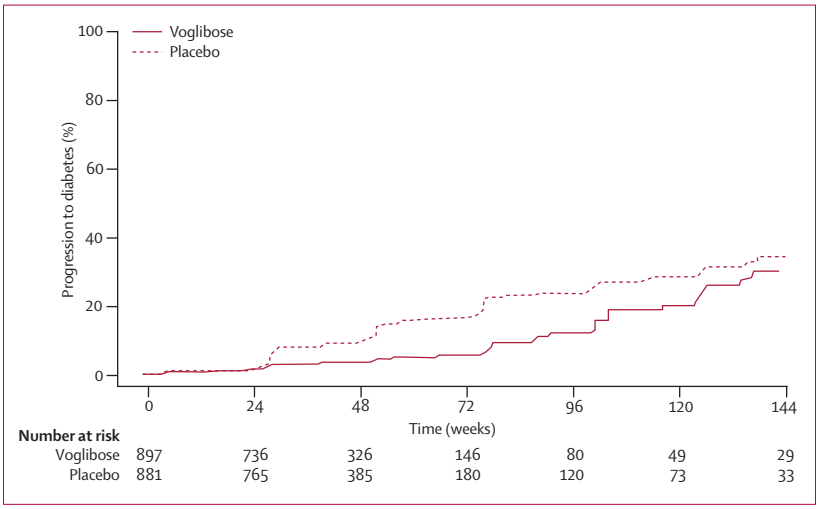

Figure 2: **Effect of voglibose and placebo on the cumulative probability of individuals developing type 2 diabetes (Kaplan–Meier method)**

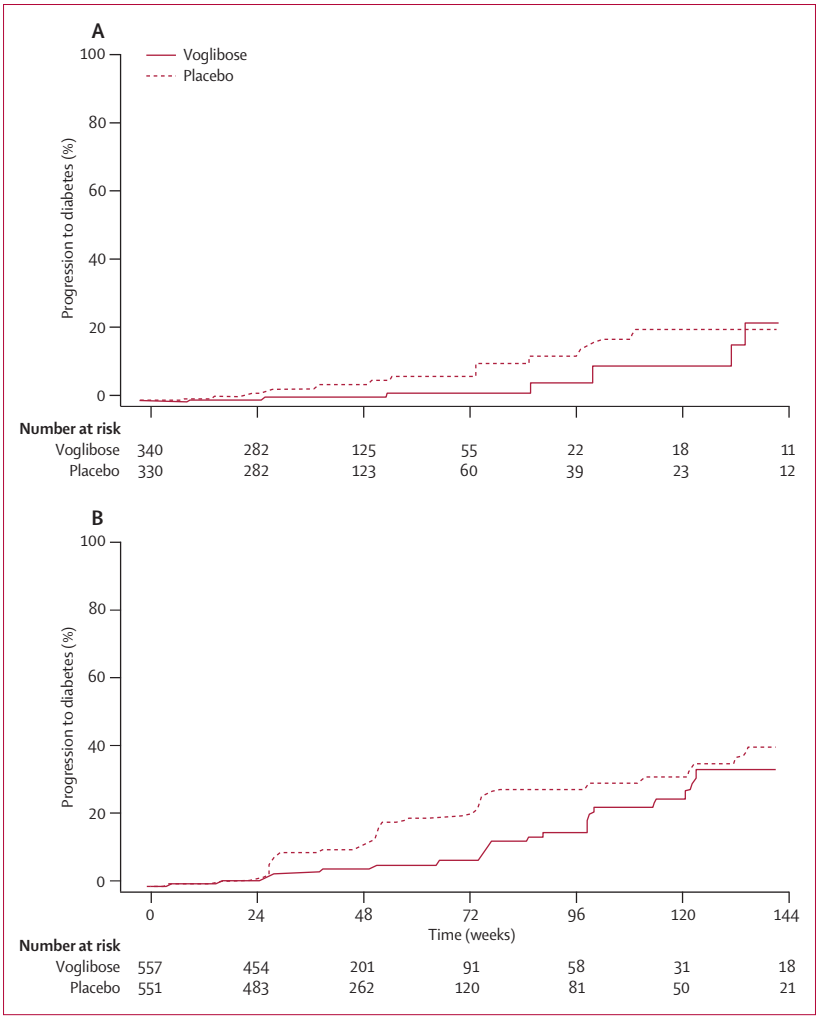

Figure 3: **Effect of voglibose and placebo on the cumulative probability of individuals developing type 2 diabetes based on the number of risk factors (Kaplan–Meier method)**
(A) At most two risk factors. (B) At least three risk factors.

	Recorded number of patients with type 2 diabetes*		Cox regression analysis	
	Voglibose	Placebo	Hazard ratio (95% CI)	p value
Hypertension†				
Present	28/528	61/510	0·554 (0·354–0·867)	0·0098
Absent	22/369	45/371	0·570 (0·342–0·950)	0·0310
Dyslipidaemia‡				
Present	41/695	82/667	0·592 (0·406–0·861)	0·0062
Absent	9/202	24/214	0·456 (0·211–0·984)	0·0453
Obesity (body-mass index ≥25 kg/m²)				
Present	35/502	65/500	0·622 (0·412–0·940)	0·0243
Absent	15/395	41/381	0·449 (0·248–0·813)	0·0082
Family history of diabetes§				
Exists	16/337	51/336	0·447 (0·255–0·785)	0·0051
None	34/560	55/545	0·686 (0·447–1·053)	0·0851
2hPG value (mmol/L)				
9·4 –11·0	34/323	69/345	0·528 (0·348–0·799)	0·0025
7·8–9·3	15/573	37/535	0·556 (0·303–1·017)	0·0568
Smoker				
Yes	14/215	40/229	0·511 (0·277–0·941)	0·0310
No	36/682	66/652	0·618 (0·412–0·929)	0·0205
Concomitant use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker				
Yes	20/279	35/300	0·770 (0·444–1·336)	0·3518
No	30/618	71/581	0·471 (0·307–0·722)	0·0006
HOMA-R				
2·50–23·39	23/329	47/325	0·601 (0·365–0·991)	0·0462
1·61–2·49	11/232	16/225	0·829 (0·382–1·800)	0·6354
0–1·60	15/334	43/330	0·405 (0·225–0·729)	0·0026
Insulinogenic index				
–3·85 to 0·39	24/337	64/341	0·439 (0·274–0·702)	0·0006
0·40 to 6·11	25/552	40/535	0·714 (0·432–1·183)	0·1909
Intensity of daily activity				
I	22/310	41/295	0·570 (0·339–0·958)	0·0340
II	23/425	53/448	0·608 (0·372–0·993)	0·0468
III–IV	5/162	12/138	0·372 (0·129–1·077)	0·0684

Data are n/N, unless otherwise indicated. 2hPG=2 h plasma glucose concentration during oral glucose tolerance test. HOMA-R=homoeostasis model assessment for insulin resistance. *Percentages not calculated because reductions in number at risk depend on treatment period. †High normal blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg) or being treated for hypertension. ‡Total cholesterol ≥5·7 mmol/L, triglyceride ≥1·7 mmol/L, or HDL cholesterol <1·04 mmol/L. §In a first-degree or second-degree relative.

Table 2: **Hazard ratio of progression to type 2 diabetes for each baseline characteristic**

and increased the total sample size to 1728. One interim analysis was planned in advance to take place when about 60% of cases of type 2 diabetes were calculated to have occurred. An independent statistician did the analysis on behalf of the Independent Data Monitoring Committee. The overall type I error (5%) was controlled with the O'Brien–Fleming α spending function method. Early discontinuation of the trial was judged appropriate if the difference in the primary endpoint was p<0·0088.

Time to event for the progression to type 2 diabetes and the improvement to normoglycaemia was analysed with the log-rank test. Treatments were compared by estimation of hazard ratios (HRs) and 95% CIs, and different levels of disease severity (≤2 or ≥3 risk factors) were assessed with a stratified log-rank test. Additionally, we used a covariate-adjusted Cox regression model with baseline variables to adjust the HR for factors that might affect the outcome. Subgroup analyses were done for each covariate included in the Cox regression model described above.

We did a modified Kaplan-Meier analysis to assess the probability of survival outcome. We used a cumulative incidence function to estimate cumulative progression rates for the progression to type 2 diabetes and improvement to normoglycaemia, taking into consideration that each event is a competitor to the other.[28] The Pepe and Mori[29] method was used to compare the groups. Two-sided student's t and χ^2 tests were used to compare differences between groups. We did final analyses on the full analysis set, which consisted of all individuals who were randomised and took at least one dose of study medication.

This trial is registered with the University Hospital Medical Information Network (UMIN) clinical trials registry, number UMIN 000001109.

Role of the funding source

This study was designed by a steering committee composed of the sponsor and an independent Japanese clinical advisory board (authors of this report). The sponsor was responsible for gathering data from all investigational centres to create the clinical database. The Independent Data Monitoring Committee did the interim analysis and the sponsor did the final analysis in conjunction with the advisory board. Interpretation of the clinical findings was undertaken by the steering committee led by the corresponding author. All authors had full access to all clinical data and the steering committee made the final decision to submit for publication.

Results

The Independent Data Monitoring Committee did an interim analysis in March, 2007, with data from 1778 individuals that had been gathered by October, 2006. The cumulative number of cases of type 2 diabetes in the interim analysis was 84 in the placebo group and 40 in the voglibose group. The HR was 0·577 (two-sided 95% CI 0·404–0·825; p=0·0026), verifying the efficacy of voglibose compared with placebo and, accordingly, the Independent Data Monitoring Committee made the decision to terminate the study early. The results discussed below include all data gathered up to the time of termination (this includes about 6 months of data in addition to that included in the interim analysis).

In the final analysis, 1780 of 4582 registered individuals fulfilled the inclusion criteria: 897 were randomly assigned to receive voglibose and 883 placebo (two participants in the placebo group did not take their medication and were excluded). Figure 1 shows the trial profile and the reasons for withdrawal. The mean duration of treatment was 48·1 weeks (SD 36·3)—

	Direction estimation	Univariable analysis		Multivariable analysis	
		Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Treatment group	Voglibose/placebo	0·564 (0·403–0·790)	0·0009	0·512 (0·360–0·727)	0·0002
Age	10-year increase	0·839 (0·708–0·995)	0·0433	0·909 (0·731–1·130)	0·3893
Sex	Men/women	1·365 (0·973–1·915)	0·0715	1·278 (0·883–1·849)	0·1936
BMI	5 kg/m² increase	1·445 (1·180–1·770)	0·0004	1·495 (1·154–1·936)	0·0023
Dyslipidaemia	Yes/no	1·305 (0·888–1·918)	0·1750	1·284 (0·868–1·899)	0·2107
Hypertension	Yes/no	0·829 (0·603–1·138)	0·2456	0·916 (0·614–1·367)	0·6665
Family history of diabetes	Yes/no	1·365 (0·994–1·875)	0·0546	1·253 (0·903–1·739)	0·1771
2hPG	0·55 mmol /L increase	1·278 (1·164–1·404)	<0·0001	1·234 (1·122–1·357)	<0·0001
Insulinogenic index	0·2 decrease	1·165 (1·103–1·230)	<0·0001	1·246 (1·176–1·319)	<0·0001
HOMA-R	1 increase	1·066 (0·999–1·148)	0·0927	1·094 (0·984–1·216)	0·0983
Smoker	Yes/no	1·648 (1·184–2·294)	0·0030	1·327 (0·931–1·893)	0·1182
Intensity of daily activity	I/III to IV	2·109 (1·231–3·614)	0·0066	1·992 (1·151–3·448)	0·0138
Intensity of daily activity	II/III to IV	1·513 (0·894–2·562)	0·1229	1·340 (0·784–2·288)	0·2842
Concomitant use of ACE inhibitor or ARB	Yes/no	0·859 (0·618–1·194)	0·3648	0·996 (0·663–1·496)	0·9834

2hPG=2 h plasma glucose concentration during oral glucose tolerance test. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. BMI=body-mass index. HOMA-R=homoeostasis model assessment for insulin resistance.

Table 3: **Simultaneous adjustment analysis by multivariables (Cox regression analysis)**

ie, 45·0 weeks (34·7) for voglibose and 51·3 weeks (37·6) for placebo. Compliance with treatment was similarly high in the two treatment groups.

Table 1 shows the baseline characteristics of the patients who were analysed; there were no differences between the voglibose and placebo groups. The cumulative number of cases that progressed to diabetes at the end of the study was 50 of 897 in the voglibose group versus 106 of 881 in the placebo group (figure 2). The HR was 0·595 (95% CI 0·433–0·818), showing that voglibose-treated individuals had a 40·5% lower risk of developing type 2 diabetes than did placebo-treated individuals (p=0·0014; figure 2). The cumulative progression rate to type 2 diabetes after 48 weeks was 9·4% (7·1–11·8) for placebo and 3·6% (2·0–5·2) for voglibose. After 96 weeks, the corresponding rates were 23·5% (18·5–28·5) and 12·1% (6·9–17·3), respectively, and after 144 weeks they were 36·2% (27·7–44·8) and 30·2% (19·5–41·0), respectively. The percentages for voglibose increased with time as an artifact of the much higher number of patients achieving normoglycaemia in this group (thus reducing the number of patients in the denominator compared with placebo). Results with a modified Kaplan–Meier analysis, taking into consideration the competing secondary endpoint of an improvement to normoglycaemia (data not shown), showed a cumulative rate of progression to type 2 diabetes after 144 weeks of 17·2% (13·8–20·6) for placebo and 8·0% (5·6–10·4) for voglibose (p<0·0001).

Figure 3 shows the results of a secondary analysis in which progression rates in individuals with different degrees of disease severity (≤2 or ≥3 risk factors) were compared. Voglibose was associated with a 39·3% risk reduction (HR 0·607, 95% CI 0·428–0·863; p=0·0053) compared with placebo in individuals with at least three

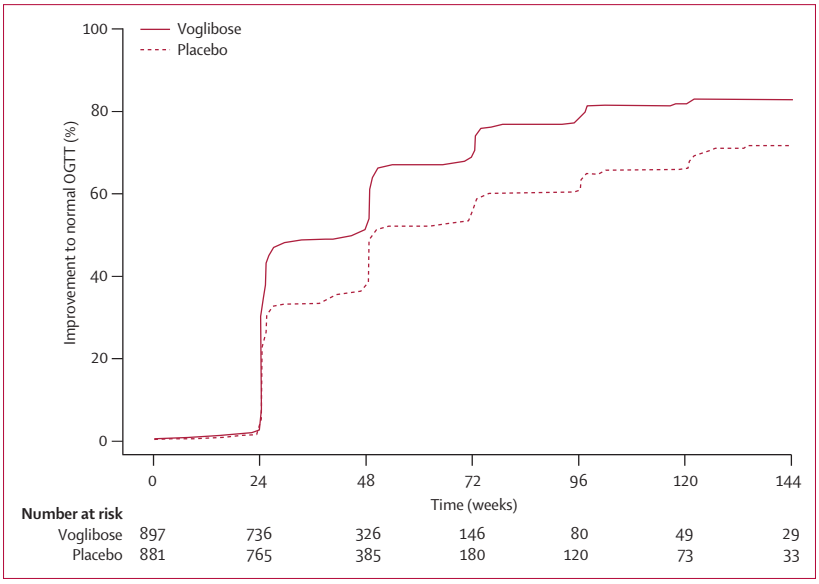

Figure 4: **Effect of voglibose and placebo on the cumulative probability of individuals achieving normoglycaemia (Kaplan–Meier method)**
OGTT=oral glucose tolerance test.

risk factors (41 *vs* 87 cases), whereas the difference was not significant in individuals with at most two risk factors (9 *vs* 19 cases, 0·544, 0·258–1·147; p=0·1098). In these patients who had a reduced rate of progression to type 2 diabetes, the duration of treatment might have been too short to identify a significant difference, despite the fact that the overall risk reduction was 45·6% compared with placebo.

Table 2 shows the lower progression to type 2 diabetes in most of the voglibose subgroups than in the placebo subgroups for the baseline characteristics (Cox regression analysis). Furthermore, the risk of an individual devel-

	Voglibose (n=897)	Placebo (n=881)	p value
All adverse events	810 (90%)	750 (85%)	0·0009
Adverse events (causality not deniable)	428 (48%)	257 (29%)	<0·0001
Serious adverse events (causality not deniable)*	5 (<1%)	2 (<1%)	0·2660
Discontinuations due to adverse events	62 (7%)	55 (6%)	0·5694
Discontinuations due to adverse events (causality not deniable)	46 (5%)	24 (3%)	0·0092
Adverse events possibly, probably, or definitely related to treatment			
Gastrointestinal symptoms:			
Flatulence	156 (17%)	63 (7%)	<0·0001
Abdominal distension	120 (13%)	49 (5%)	<0·0001
Diarrhoea	110 (13%)	45 (5%)	<0·0001
Constipation	39 (4%)	22 (2%)	0·0321
Abnormal bowel sounds	39 (4%)	11 (1%)	<0·0001
Gastrointestinal discomfort	10 (1%)	6 (<1%)	0·3328
Upper abdominal pain	4 (<1%)	4 (<1%)	0·9796
General symptoms			
Headache	2 (<1%)	3 (<1%)	0·6398
Dizziness	11 (1%)	3 (<1%)	0·0346
Eczema	2 (<1%)	2 (<1%)	0·9856
Laboratory tests†			
Increased CPK	12 (1%)	9 (1%)	0·5372
Increased ALA	30 (3%)	17 (2%)	0·0630
Increased ASA	21 (2%)	11 (1%)	0·0832
Increased GGT	14 (2%)	18 (2%)	0·4443

Data are number (%). ALA=alanine aminotransferase. ASA=aspartate aminotransferase. CPK=creatine phosphokinase. GGT=γ-glutamyltransferase. *Cerebral infarction and cholecystitis in the placebo group, and cholecystitis, colonic polyp or rectal neoplasm, inguinal hernia, liver dysfunction, and subarachnoid haemorrhage in the voglibose group. †Laboratory test analyses for individuals were done at all participating centres and activities two-fold the upper limit of normal were classified as increased. However, summary statistics of central laboratory data were calculated for each treatment group, and showed no variation in the laboratory data with a difference of one-sample *t* test between before and after administration (baseline at the time point of assessment).

Table 4: **Frequency of adverse events**

oping type 2 diabetes was reduced (HR 0·512, 95% CI 0·360–0·727; p=0·0002) in the voglibose group compared with the placebo group when adjustments were made for multivariables, including age, sex, obesity, dyslipidaemia, hypertension, family history, 2hPG, insulinogenic index, homoeostasis model assessment for insulin resistance (HOMA-R), and intensity of daily activity in a Cox regression analysis (table 3).

For the secondary endpoint of improvement to normoglycaemia, the cumulative number was 599 for voglibose and 454 for placebo, resulting in an HR of 1·539 (95% CI 1·357–1·746; p<0·0001; figure 4). The cumulative normalisation rate after 48 weeks was 45·7% (42·1–49·3) for placebo and 59·0% (55·5–62·4) for voglibose. After 96 weeks, the corresponding rates were 63·1% (58·9–67·2) and 79·6% (76·2–82·9), respectively, and after 144 weeks they were 75·0% (69·8–80·2) and 85·2% (81·6–88·8), respectively. Results with a modified Kaplan–Meier analysis (data not shown) showed a cumulative rate of normoglycaemia after 144 weeks of 67·0% (62·6–71·3) for placebo and 81·7% (78·3–85·0) for voglibose (p<0·0001).

Table 4 provides an overview of adverse events; gastrointestinal symptoms were the most common and more frequent in the voglibose group than in the placebo group. However, they were generally thought to be mild to moderate in severity. The rate of serious adverse effects was low (table 4). No deaths occurred in the placebo group versus six in the voglibose group (two accidents, and one each of suicide, possible self-intoxication with insecticide resulting in heart failure, lung cancer, and myocardial infarction); none of the deaths were thought to be related to the drug treatment.

Discussion

In our trial, even though we reinforced diet and exercise programmes, individuals remained at risk of developing diabetes. Voglibose significantly reduced the risk of individuals with impaired glucose tolerance developing type 2 diabetes and significantly increased the proportion of people who achieved normoglycaemia compared with placebo. Because of the high normalisation rate and the early termination of the trial, the average duration of treatment was about 1 year. Thus, the clinically important benefits associated with voglibose were achieved in a short time, particularly in the high-risk group (≥3 risk factors). Similarly, in terms of achieving normoglycaemia, improvement in high-risk individuals was significant. These results are encouraging and emphasise the benefits of voglibose for people at increased risk of developing type 2 diabetes, and are in line with recommendations made at the International Diabetes Federation Taskforce on Prevention and Epidemiology consensus workshop convened in Lisbon.[8] The early termination of the trial resulted in far fewer patients being treated for 3 years than was originally planned, causing concern about the long-term sustainability of the clinical benefits of voglibose that need to be verified.

One of the potential benefits of a reduction in the progression of impaired glucose tolerance to type 2 diabetes might be a reduction in cardiovascular risk. However, a 20-year follow-up from the original Da Qing Diabetes Prevention Study[30] showed that, although lifestyle changes could produce a long-lasting reduction in the incidence of type 2 diabetes, the effect on cardiovascular events was at best modest. Our trial was not statistically powered to assess such changes and the recorded rates for macrovascular events (12 [1%] of 897 in voglibose, and 18 [2%] of 881 in placebo) are a positive stimulus for future research.

In the past decade, several studies have drawn attention to the benefits of strict and individualised diet and exercise programmes in delaying the progression to type 2 diabetes. In these studies, lifestyle modification reduced the risk of type 2 diabetes by 42% over 6 years (p<0·005) in a Chinese cohort,[11] by 58% over 4 years (p<0·001) in Finnish patients,[12] and by 58% over 2·8 years in a US study.[13] Lifestyle modification thus represents a mainstay of medical care for individuals with impaired glucose

tolerance. Pharmacological approaches have also been investigated as a means of delaying the onset of type 2 diabetes and drugs such as metformin,[13] acarbose,[16] orlistat,[17] troglitazone,[18,19] and rosiglitazone[20] have all shown some ability to delay or prevent the progression of impaired glucose tolerance to type 2 diabetes. For example, in the Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM),[16,31] the α-glucosidase inhibitor acarbose reduced the risk of progression to diabetes by 25% over 3·3 years compared with placebo. This result was achieved in people with impaired glucose tolerance who were given advice on diet and exercise. Similarly, the Diabetes Prevention Program Research Group reported that metformin reduced the relative risk of people with impaired glucose tolerance developing diabetes by 31% over 2·8 years.[13] Thus, current best practice indicates a primary role for diet and exercise programmes in the management of impaired glucose tolerance, with drug treatment reserved for those unable to achieve glycaemic control, at high risk of progression to type 2 diabetes, and unable to adequately exercise.

Defects in the action or secretion of insulin, or both, are the two main abnormalities leading to the development of type 2 diabetes, and any intervention that reduces insulin resistance or protects the pancreatic β cells could help to prevent or delay the progression of the disease.[14] Results with voglibose show that it reduces diurnal insulin secretion through improvement of postprandial hyperglycaemia, and these changes should reduce the stress on overworked β cells.[23,24] In our study, 2hPG concentrations fluctuated at a lower level in the voglibose group than in the placebo group between 24 weeks and 96 weeks as indicated by lower HbA_{1c} levels during this period. Assessments beyond this timepoint are not meaningful because of the small numbers of patients.

The findings from this study are important from a Japanese perspective because treatment guidelines advocate drugs to prevent disease progression in high-risk individuals, but as yet no medication is covered by health insurance plans.[20] Voglibose significantly improved glucose tolerance, in terms of delayed disease progression and in the number of patients who achieved normoglycaemia. Thus, long-term prophylaxis with this α-glucosidase inhibitor in high-risk individuals with impaired glucose tolerance could provide a pharmacological option, along with lifestyle modification, to help reduce the burden of type 2 diabetes in Japan.

Contributors

RK was responsible for drafting the report and critical revision of important intellectual content. All authors participated in study concept, design, and supervision, and were involved in each revision of the report, and approved the final version as accurate and suitable for publication.

Study centres

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Conflicts of interest

KS and AK have received research funding, lecture fees, and travel expenses from Takeda. YI has received consultancy fees, lecture fees, travel expenses, or research funding from Astellas, Banyu, Bayer, Daiichi-Sankyo, Eli Lilly, Johnson and Johnson, Novartis, Novo Nordisk, Pfizer, Sanofi Aventis, and Takeda. NT has received research grants or lecture fees from Astellas, Banyu, Bayer, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Novo Nordisk, Ono, Sanofi-Aventis, and Takeda. KK has received research funding, consultancy fees, or lecture fees from Astellas, AstraZeneca, Banyu, Daiichi-Sankyo, Dainippon-Sumitomo, Novartis, Novo Nordisk, Sanofi-Aventis, Sanwa, and Takeda. RK has received research funding, consultancy fees, or lecture fees from Astellas, AstraZeneca, Bayer, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Sanwa, and Takeda.

Acknowledgments

This study was funded by an unrestricted research grant from Takeda. We thank the sponsor for assistance with data monitoring and gathering, and for funding editorial support that was provided by Steve Clissold; and members of the Independent Data Monitoring Committee for their invaluable assistance in collating and analysing the data.

References

1 Harris MI. Diabetes in America: epidemiology and scope of the problem. *Diabetes Care* 1998; **21** (suppl): C11–C14.
2 International Diabetes Federation. Diabetes facts and figures. http://www.idf.org (accessed April 4, 2008).
3 Japanese Health Service Bureau of Ministry of Health, Labor and Welfare. 2002 diabetes mellitus survey report. Tokyo: Japanese Health Service Bureau of Ministry of Health, Labor and Welfare, 2004.
4 Nigel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 1962; **14:** 353–62.

5 The DECODE Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 1999; **354:** 617–21.

6 Alberti KGMM. The clinical implications of impaired glucose tolerance. *Diabet Med* 1996; **13:** 927–37.

7 Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; **365:** 1415–28.

8 Alberti KGMM, Zimmet P, Shaw J. International Diabetes Federation: a consensus on type 2 diabetes prevention. *Diabet Med* 2007; **24:** 451–63.

9 DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001; **161:** 397–405.

10 Nakagami T; DECODA Study Group. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. *Diabetologia* 2004; **47:** 385–94.

11 Pan X-R, Li G-W, Hu Y-H, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997; **20:** 537–44.

12 Tuomilehto J, Lindström J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344:** 1343–50.

13 Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346:** 393–403.

14 Scheen AJ. Is there a role for α-glucosidase inhibitors in the prevention of type 2 diabetes mellitus? *Drugs* 2003; **63:** 933–51.

15 Van De Laar FA, Lucassen PL, Akkermans RP, et al. α-Glucosidase inhibitors for patients with type 2 diabetes. *Diabetes Care* 2005; **28:** 154–63.

16 Chiasson J-L, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus : the STOP-NIDDM randomised trial. *Lancet* 2002; **359:** 2072–77.

17 Heymsfield SB, Segal KR, Hauptman J, et al. Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* 2000; **160:** 1321–26.

18 Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes Care* 2002; **51:** 2796–803.

19 The Diabetes Prevention Program Research Group. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. *Diabetes* 2005; **54:** 1150–56.

20 The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006; **368:** 1096–105.

21 Ramachandran A, Snehalatha C, Mary S, et al. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006; **49:** 289–97.

22 Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. *Diabetes Res Clin Pract* 2005; **67:** 152–62.

23 Matsumoto K, Yano M, Miyake S, et al. Effects of voglibose on glycemic excursions, insulin secretion, and insulin sensitivity in non-insulin-treated NIDDM patients. *Diabetes Care* 1998; **21:** 256–60.

24 Matsumoto K, Sera Y, Abe Y, et al. Combination therapy of alpha-glucosidase inhibitor and a sulfonylurea compound prolongs the duration of good glycemic control. *Metabolism* 2002; **51:** 1548–52.

25 Fujisawa T, Ikegami H, Inoue K, et al. Effect of two α-glucosidase inhibitors, voglibose and acarbose, on postprandial hyperglycemia correlates with subjective abdominal symptoms. *Metabolism Clin Exp* 2005; **54:** 387–90.

26 Japanese Ministry of Health and Labour. Japanese nutritional requirement. http://www1.mhlw.go.jp/shingi/s9906/s0628-1_11.html (accessed May 10, 2008). Tokyo: Japanese Ministry of Health and Labour, 1999.

27 Japan Diabetes Society: Diabetes mellitus treatment guideline based on scientific ground (revised edition 2). Nankodo: Japan Diabetes Society, 2007; 257–72.

28 Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007; **26:** 2389–430.

29 Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risk failure time data. *Stat Med* 1993; **12:** 737–51.

30 Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008; **371:** 1783–89.

31 Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003; **290:** 486–94.