

# The STOP-NIDDM Trial

## An international study on the efficacy of an $\alpha$ -glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data

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**OBJECTIVE** — To describe the rationale and design, and to discuss the preliminary screening data, of the Study to Prevent NIDDM (STOP-NIDDM Trial), an international study on the efficacy of the  $\alpha$ -glucosidase inhibitor acarbose in preventing or delaying the development of type 2 diabetes in a population with impaired glucose tolerance (IGT).

**RESEARCH DESIGN AND METHODS** — A total of 1,418 subjects diagnosed with IGT according to the World Health Organization's criteria and having a fasting plasma glucose concentration  $\geq 5.6$  mmol/l were randomized in a double-blind fashion to receive either acarbose (100 mg t.i.d.) or placebo for a predictive median follow-up period of 3.9 years. The primary outcome is the development of type 2 diabetes diagnosed using a 75-g oral glucose tolerance test according to the new criteria. The secondary outcomes are changes in blood pressure, lipid profile, insulin sensitivity, cardiovascular events, and morphometric profile.

**RESULTS** — Screening was performed in a high-risk population. As of 1 March 1997, 4,424 subjects had been screened, and data were available for 3,919 (88.5%) subjects. Of these subjects, 1,200 (30.6%) had glucose intolerance. Of the subjects with glucose intolerance, 521 (13.3%) had previously undetected type 2 diabetes, and 679 (17.3%) had IGT. Of the IGT population, 412 (60.7%) subjects were eligible for the study. This population had the following characteristics: the mean age was 54.8 years, 52% of the subjects were female, 53% had more than one risk factor for type 2 diabetes, >90% had a family history of diabetes, 78.2% had a BMI  $\geq 27$  kg/m<sup>2</sup>, 47.5% had high blood pressure, 51.2% had dyslipidemia, and 22.8% of the women had a history of gestational diabetes.

**CONCLUSIONS** — Screening of a high-risk population yields one eligible subject per every 10 volunteers screened. This study should definitely answer the question of whether acarbose can prevent or delay the progression of IGT to type 2 diabetes mellitus.

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**Abbreviations:** ANOVA, analysis of variance; CV, coefficient of variation; DSQR, Data Safety and Quality Review Committee; ECG, electrocardiogram; FPG, fasting plasma glucose; FSIGTT, frequently sampled intravenous glucose tolerance test; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test;  $S_e$ , glucose effectiveness;  $S_i$ , insulin sensitivity index; SDI, SD index; STOP-NIDDM, Study to Prevent NIDDM; TC, total cholesterol; TG, triglyceride; ULN, upper limit of normal; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Type 2 diabetes is well recognized as a major health problem associated with increased morbidity and mortality and high health care costs (1,2). It is believed that all type 2 diabetic patients must pass through a phase of impaired glucose tolerance (IGT) before developing diabetes. IGT was first recognized as an entity in 1979 by the National Diabetes Data Group (3) and the World Health Organization (WHO) Expert Committee on Diabetes (4). Recently, the diagnostic criteria have been refined further by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (5).

The prevalence of IGT among adults varies between 3 and 10% in European populations and 11 and 20% in North American populations (6). Although IGT is not associated with diabetes-specific complications, it does increase the risk of developing type 2 diabetes and cardiovascular disease (7,8). Numerous studies have shown that the progression of IGT to type 2 diabetes can vary between 1.5 and 7.3% per year in different ethnic groups and in various regions of the world (7). Furthermore, glucose intolerance is part of a clustering of risk factors for cardiovascular disease, which includes central obesity, hypertension, high triglyceride (TG) levels, and low HDL cholesterol and has been termed syndrome X, or the metabolic syndrome (9). These disorders are all characterized by insulin resistance and hyperinsulinemia.

Insulin resistance is generally believed to be the first abnormality leading to glucose intolerance (10). However, as long as the  $\beta$ -cell can compensate by increasing insulin secretion, normal glucose tolerance is maintained. Only when the  $\beta$ -cell fails to compensate does IGT develop, resulting initially in postprandial hyperglycemia (10). Such hyperglycemia further exacerbates the insulin resistance and the  $\beta$ -cell defect, a phenomenon known as glucose toxicity (11). A large proportion of these IGT subjects eventually progress to development of type 2 diabetes (12).

With this understanding, it is hypothesized that any therapeutic intervention in

IGT subjects that could decrease insulin resistance or protect the  $\beta$ -cell, or both, could prevent or delay the progression of IGT to type 2 diabetes. Acarbose, an  $\alpha$ -glucosidase inhibitor, qualifies as a potential pharmacological agent for the prevention of type 2 diabetes. In a pilot study, we have shown in IGT subjects that acarbose, by delaying the absorption of carbohydrate by the gut, decreases the postprandial increase in plasma glucose, resulting in lower postprandial plasma insulin levels (13). This decrease in plasma insulin releases the strain on the  $\beta$ -cell and, theoretically, should protect the insulin-producing cells. We have also shown in the same subjects that 4 months of treatment with acarbose resulted in a significant decrease in insulin resistance (13). Furthermore, we have demonstrated that the long-term use of acarbose in the treatment of type 2 diabetic subjects is not associated with toxicity (14). Acarbose may therefore be a drug of choice for the long-term prevention of diabetes.

These observations provided the rationale for the Study to Prevent NIDDM (STOP-NIDDM Trial). Its primary objective is to evaluate in IGT subjects the effect of acarbose on the conversion rate of IGT to type 2 diabetes. Secondary objectives are to evaluate the effects of acarbose treatment on glucose tolerance, insulin sensitivity, hyperinsulinemia, anthropometric measurements, blood pressure, lipid profile, and the appearance and progression of cardiovascular events. In this article, we describe the study design of the STOP-NIDDM Trial and discuss the preliminary screening data.

## RESEARCH DESIGN AND METHODS

— The STOP-NIDDM Trial is an international multicenter placebo-controlled randomized study being conducted in Canada, Germany, Austria, the Nordic countries (Norway, Denmark, Sweden, and Finland), Israel, and Spain.

### Study population

Subjects were recruited from a high-risk population mainly through newspaper advertisement. Subjects enrolled in the study were all diagnosed with IGT based on the 2-h plasma glucose post-75-g glucose test according to the WHO criteria (plasma glucose  $\geq 7.8$  mmol/l [ $\geq 140$  mg/dl] and  $< 11.1$  mmol/l [ $< 200$  mg/dl]). Furthermore, they all had fasting plasma glucose (FPG)  $\geq 5.6$  but  $< 7.8$  mmol/l ( $\geq 101$  but  $< 140$  mg/dl), which has been shown to increase the risk of progression to type 2 diabetes 3.4-fold (15).

In the new diagnostic criteria for diabetes, the cutoff for FPG has been lowered to 7.0 mmol/l (126 mg/dl). As a result, subjects are considered diabetic based on an FPG measurement between 7.0 and 7.8 mmol/l (126 and 140 mg/dl). Nevertheless, the 2-h plasma glucose post-75-g glucose load remained within the original (and current) diagnostic level for IGT (7.8–11.0 mmol/l [140–199 mg/dl]). Men and women between the ages of 40 and 70 years and having a BMI between 25 and 40 kg/m<sup>2</sup> were recruited. Subjects were excluded if they had a serum creatinine level  $\geq 130$   $\mu$ mol/l ( $\geq 1.5$  mg/dl), a fasting serum TG level  $\geq 10$  mmol/l ( $\geq 886$  mg/dl), liver enzymes elevated to  $\geq 1.8$  times the upper limit of normal (ULN), or a TSH  $\geq 1.5$  times above the ULN or below the lower limit of normal ( $< 0.3$  mU/l). Subjects who had been treated within the last 3 months with systemic glucocorticoids,  $\beta$ -blockers, thiazide diuretics, and nicotinic acid were also excluded. Key exclusion criteria were based on the use of drugs that were likely to be associated with abnormal intestinal motility or altered absorption of nutrients. All subjects with a recent cardiovascular event were also excluded.

### Study design

Altogether, 1,418 subjects with IGT and an FPG concentration  $\geq 5.6$  but  $< 7.8$  mmol/l ( $\geq 101$  but  $< 140$  mg/dl) were randomized in a double-blind fashion to treatment with either placebo or acarbose, which was taken with the first bite of each meal three times a day. At entry, all subjects were given instruction in following a weight-reducing or weight-maintaining diet and were encouraged to exercise regularly. To avoid or minimize the gastrointestinal side effects of acarbose, its administration was started at 50 mg/day and titrated gradually (50 mg/day per 2 weeks) to a maximum of 100 mg t.i.d. or the maximum tolerated dosage. The subjects are examined every 3 months by the coordinating nurse and every 6 months by the investigator for a median follow-up time of 3.9 years. At the end of the treatment period, there will be a 3-month single-blind placebo washout period, after which the outcome measures will be repeated. The protocol has been approved by appropriate institutional review boards, and each subject has signed an informed consent form.

### Outcome measures

The primary outcome is the development of diabetes based on a 75-g oral glucose tol-

erance test (OGTT) (5). The OGTT is performed yearly; however, at the visits occurring every 3 months, subjects are scheduled for an OGTT if their FPG level is  $\geq 7.0$  mmol/l (126 mg/dl). If the OGTT confirms the diagnosis of type 2 diabetes, the subjects will have reached the primary end point. However, they will be kept in the study, will continue to receive the study medication in a blinded fashion, and will be monitored for the secondary end points.

Among the secondary objectives is the assessment of any improvement in glucose tolerance (i.e., reversal of IGT to normal glucose tolerance, based on the OGTT) that could result from acarbose treatment. During the OGTT, samples will also be drawn for plasma insulin measurement to evaluate the effect of the treatment on baseline insulin and its response to a glucose challenge. Before randomization, all subjects fulfilling the enrollment criteria had a second OGTT to measure basal and stimulated insulin response. The investigators are blinded to the results of this second test, which will be included, however, in the final analysis. Insulin sensitivity is measured using the frequently sampled intravenous glucose tolerance test (FSIGTT) minimal model (16) in 10% ( $n = 120$ ) of the study population, randomly selected. The insulin sensitivity index ( $S_i$ ) and glucose effectiveness ( $S_G$ ) will be quantified by application of Bergman's minimal model to an insulin-modified FSIGTT (17). The insulin and glucose data are then submitted by Diane Finegood (Burnaby, British Columbia, Canada) to the MINMOD computer system program for the determination of  $S_i$  and  $S_G$ .

Anthropometric measurements are made with the participant wearing an examining gown after having removed shoes and upper garments. A tape measure is used to measure waist circumference at the level of the iliac crest, and hip circumference at the level of the largest circumference or the greater trochanters. The waist-to-hip ratio is used as an index of upper-body versus lower-body adiposity. BMI is calculated as weight (in kilograms) divided by height (in meters) squared.

All cardiovascular events are documented and confirmed by appropriate clinical and/or laboratory data: 1) myocardial infarction: electrocardiogram (ECG) abnormalities and elevation of enzymes; 2) cerebrovascular accident: abnormal findings on neurological examination; 3) congestive heart failure: chest X-ray abnormalities. All subjects undergo a standard digital 12-lead

ECG before randomization, at the end of the study, and whenever clinically indicated. All ECGs obtained during the study are read by two independent cardiologists for cross-validation: Martin Green (Ottawa, Ontario, Canada) and Wolfgang Rafflenbeul (Hanover, Germany). Blood pressure is monitored every 3 months according to the recommendations of the Canadian Hypertension Society (18, 19). The blood pressure is measured after subjects rest for at least 5 min, and three blood pressure readings are obtained at each visit. The average of the three readings is used, and blood pressure is considered elevated if the average is >140/90 mmHg. If elevated, blood pressure is remeasured within 2 weeks, and if hypertension is confirmed, antihypertensive treatment is started. The first drug used is a calcium channel blocker. Only when calcium channel blockers are not sufficient to control blood pressure are  $\alpha$ -blockers or ACE inhibitors added, because these agents have been shown to improve insulin sensitivity (20). The  $\beta$ -blockers and thiazides are used only as a last resort because they are known to decrease insulin sensitivity.

Nutritional evaluations are performed before randomization and once a year thereafter. Evaluations are made using a 3-day dietary diary in which all food items and quantities as well as physical activities are documented for three representative days (two weekdays and one weekend day). From the beginning of the study, all subjects are given instruction on how to follow a weight-reducing diet if they are overweight or a weight-maintaining diet if they are of normal weight. The nutritional journals are used to determine any major change in the quantity or quality of the diet over the study period.

HbA<sub>1c</sub> is measured by high-performance liquid chromatography (21) at baseline, every year after randomization, and at the end of the study. Serum insulin is measured using a highly specific two-site monoclonal antibody immunoradiometric assay (22). Serum total cholesterol (TC) and TG levels are measured enzymatically (23). HDL cholesterol is measured as cholesterol after precipitation of non-HDL cholesterol using dextran sulfate-magnesium chloride (23). LDL cholesterol is then calculated for samples in which TG concentration is <4.51 mmol/l, using the following formula (24):  $LDL = [(TC - HDL) - TG] \div 2.2$ .

The lipid profile is also performed at baseline, every year, and at the end of the washout period. Plasma glucose is meas-

ured by the glucose oxidase or hexokinase method.

### Laboratories and cross-validation

One of the investigators (T.M.S. Wolever, Toronto, Ontario, Canada), is responsible for the cross-validation of data. Pooled frozen human serum or plasma samples are sent to each of the participant laboratories at 4-month intervals for glucose, insulin, and lipid analysis. For HbA<sub>1c</sub>, fresh whole blood samples are sent each time. Each sample is analyzed 10 times by each laboratory.

**Glucose.** Between- and within-laboratory means, SDs, and coefficients of variation (CVs) are calculated as measures of variability. Repeated measures two-way analysis of variance (ANOVA) will be performed, with the variables being analyte concentration and laboratory to determine whether differences between means from the different centers are significant.

For each concentration of each analyte, each laboratory's results will be displayed as the SD index (SDI), calculated as follows:  $SDI = (\text{Lab mean} - \text{Group mean}) \div \text{Group SD}$ .

An SDI >2 indicates that the laboratory result is >2 SD from the mean and is not in agreement with the group. Each laboratory's result for each concentration will be plotted on a Levey-Jennings control chart where the x-axis is the run number (throughout the study, each sample of pooled serum will be run 10 times) and the y-axis is the SDI.

A laboratory can be considered to differ consistently from the group mean if its SDI is >2 on two consecutive occasions. The group mean for the different concentrations of the affected analyte will be plotted against the laboratory mean, and if, by inspection, the relationship is linear, a regression equation will be calculated by least-squares method to allow correction of the laboratory's results to the group mean as follows:  $y = mx + b$ , where  $y$  is the group mean,  $x$  is the individual laboratory's result,  $m$  is the slope, and  $b$  is the  $y$ -intercept. If the discrepancy is not linear, a curve will be fit.

**Insulin and lipids.** For each concentration, the between- and within-laboratory means, SDs, and CVs will be presented, and repeated measures ANOVA performed, to determine whether there are significant differences between laboratories. Regression analysis will be performed for the different concentrations of each analyte, and each central laboratory will receive graphs on which are plotted its results against those of the other laboratories. In addition, a graph will be plot-

ted to show the relationship of all laboratories to the group mean (i.e., group mean on the y-axis) and regression equations will be given to adjust all results to the group mean.

**HbA<sub>1c</sub>.** Within-laboratory variation will be assessed from the difference of the duplicate samples. Between-laboratory variation will be assessed by repeated measures ANOVA and regression analysis and will be displayed as for insulin and lipids.

### Sample size estimation

Calculation of sample size was done using a two-tailed  $\alpha$  of 0.05 and  $1 - \beta$  of 90% assuming 1) a conversion rate of 7% per year, 2) a 36% risk reduction (from 27.1% in the placebo group to 17.2% in the acarbose-treated group), and 3) a 10% dropout rate. It was calculated that 600 subjects needed to be randomized per treatment group.

### Statistical analysis

The intent-to-treat analysis will be the primary analysis for this study. Only protocol-compliant subjects will be included in the secondary analysis. The primary variable for the study is time to development of diabetes. The data will be displayed using Kaplan-Meier curves for the two treatment groups. Formal analysis will be done using a Cox proportional hazards model including covariates such as treatment of any baseline variable that may influence outcome. The secondary end points will be summarized using proportions and analyzed using repeated measures ANOVA.

### Interim analysis

An O'Brien-Fleming type of boundary (25) will be used for the primary end point, that is, the time to the development of diabetes. The first analysis will be done after randomized subjects have been followed for a minimum of 1 year. Subsequent analysis will be done at ~6-month intervals for a maximum of five such analyses (including the first analysis at the 1-year follow-up). The results will be considered significant at  $P$  values of 0.00001, 0.001, 0.008, 0.023, and 0.043 for the first through final analysis, respectively.

### The Data Safety and Quality Review Committee

An independent committee, called the Data Safety and Quality Review Committee (DSQRC), has been created to review the results of data analysis at various intervals throughout the study without unblinding the investigators and the sponsor and to guarantee scientific integrity and credibility.

The DSQRC is composed of a chairperson (Charles M. Clark, Jr., Indianapolis, IN), a biostatistician (Wayne Taylor, Hamilton, Ontario, Canada), and two clinical epidemiologists (Bryan Haynes, Hamilton, Ontario, Canada, and Lothar Heinemen, Berlin, Germany). The committee will have the mandate to assess at various intervals 1) the quality of the data; 2) the efficacy of the study medication; and 3) the safety of the study medication. The DSQRC reports to the steering committee, which is composed of the principal investigator (J.-L.C.); five coinvestigators, R.G. (Spain), M.H. (Germany), R.G.J. (Canada), A.K. (Israel), and M.L. (Finland); and five representatives from our sponsor, Bayer.

**RESULTS** — Screening for the STOP-NIDDM Trial was initiated early in 1996, and final enrollment was completed on 28 February 1998. The subjects were screened from a high-risk population and were recruited mainly through newspaper advertisement. In this article, we present the screening data up to 1 March 1997. At that date, 4,424 subjects had undergone an OGTT. Data were available on 88.5% ( $n = 3,919$ ) of the subjects (Table 1). Of the overall population screened, 30.6% ( $n = 1,200$ ) had glucose intolerance. Of the latter group, 13.3% ( $n = 521$ ) had previously undetected diabetes, 17.3% ( $n = 679$ ) had IGT; of the IGT subjects, 10.5% ( $n = 412$ ) had an FPG  $\geq 5.6$  mmol/l and were eligible for the study. Reviewing the data from this study population, 7% had an FPG  $\geq 7.0$  but  $< 7.8$  mmol/l ( $\geq 126$  but  $< 140$  mg/dl) on one occasion. The new diagnostic criteria require two FPG levels  $\geq 7.0$  mmol/l to establish the diagnosis of diabetes.

The age of the population screened did not differ among various groups, but a small upward trend was observed, with increasing glucose intolerance from 52.5 years of age for those with a normal OGTT result to 54.9 years of age for those with type 2 diabetes.

At least one known risk factor for the development of diabetes was identified in  $>90\%$  of the subjects. However, the number of risk factors did not discriminate among the subjects who had diabetes, those who had IGT with an FPG level above or below 5.6 mmol/l (101 mg/dl), and those who had normal glucose tolerance. This finding is not unexpected, because recruitment of the screened population was based on risk factors. For the same reason, the family history of diabetes, which was present in

**Table 1—Characteristics of the screened population**

Characteristics	Glucose tolerance			
	Normal	Total IGT	IGT + FPG $\geq 5.6$ mmol/l	Diabetes
OGTT results (%)	69.5	17.3	10.5	13.3
Mean age (years)	52.5	54.4	54.8	54.9
Diabetes history (%)	91.0	93.0	93.0	94.0
BMI $>27$ kg/m <sup>2</sup> (%)	64.5	76.3	78.2	74.3
Hypertension history (%)	34.7	43.8	47.5	50.7
Dyslipidemia history (%)	44.2	49.8	51.2	59.3
Gestational diabetes history (% of women)	26.0	29.7	22.8	28.0

$n = 3,919$ .

$>90\%$  of the subjects screened, did not discriminate among the groups (i.e., normal versus IGT versus diabetes). Obesity defined as BMI  $>27$  kg/m<sup>2</sup> tended to be less frequent in the normal population screened (64.5%) compared with those with glucose intolerance (76.3%). Known history of high blood pressure and dyslipidemia tended to increase with worsening of glucose tolerance. The presence of hypertension was only 34.7% in those with normal glucose tolerance, compared with 43.8% in those with total IGT, 47.5% in those with IGT + FPG  $\geq 5.6$  mmol/l, and 50.7% in those with diabetes. Similarly, history of known dyslipidemia was lower in those with normal OGTT (44.2%) than in those with IGT (49.8%), IGT + FPG  $\geq 5.6$  mmol/l (51.2%), or diabetes (59.3%). Of the women,  $>27.0\%$  ( $n = 237$ ) had a history of gestational diabetes, but this prevalence did not differ between those with glucose intolerance and those with normal OGTT results.

**CONCLUSIONS** — The STOP-NIDDM Trial Research Group has invested much effort, thought, and discussion in developing the study design, deciding on the sample size, and choosing an appropriate treatment for the prevention of type 2 diabetes. The preliminary screening data confirm the feasibility of the STOP-NIDDM Trial and provide interesting information on the population under study.

The design is a straightforward randomized double-blind placebo-controlled study. Because it is a multicenter and multinational trial, it is particularly complex to coordinate, and monitoring of the various sites involved is especially difficult. Fortunately, our sponsor, Bayer, has provided the infrastructure and the qualified personnel to ensure that the study is well coor-

ordinated and that the monitoring of the various sites is adequate and timely. However, to guarantee quality and credibility of the data, randomization and analysis of the data are done by an independent group. The data are then routed to the DSQRC, which is independent of both the sponsor and the research group. The multinational character of the study also makes it difficult to have all the laboratory parameters measured in one central laboratory. For this reason, a cross-validation protocol has been elaborated to ensure reproducibility of the various assays.

In deciding on the duration of a trial in which we were monitoring subjects for the appearance of diabetes, we had to consider the expected number of events per year and the number of subjects studied; we decided to do a 3-year study, to begin after the last subject was recruited, with a predictive median follow-up of 3.9 years. According to the literature, the conversion rate of IGT to type 2 diabetes varies from 1.5 to 7.3%, with a mean of  $\sim 3$ –4% per year (7). The most consistent predicting factor for the progression to diabetes is the FPG (15). Using an FPG  $\geq 5.6$  mmol/l ( $\geq 101$  mg/dl) in the inclusion criteria increases the risk of conversion to diabetes by 3.4-fold (15). Therefore, in our IGT population, the expected conversion rate should be  $\sim 10\%$  per year. To be conservative, we have used a conversion rate of 7% in our estimation of the sample size. We have also assumed that a risk reduction of 36% would be clinically meaningful, and more important, cost-effective. Eastman et al. (26) have suggested that a 20% reduction in the risk of developing diabetes would have a cost-effectiveness of \$42,135 per quality-adjusted life years. Furthermore, the Da Qing study (27) showed that

changes in lifestyle such as diet and exercise decreased the conversion rate by ~40%. It was therefore decided that a 36% reduction in risk was realistic. Finally, we have assumed a 10% dropout rate for the 3-year study period. This rate is based on the experience of the Early Diabetes International Trial (EDIT), a 3-year multicenter study on the efficacy of acarbose, metformin, and acarbose plus metformin in preventing the deterioration of glucose tolerance (R. Holman, personal communication). With these conservative assumptions, the estimated population size required to meet the primary objective was 1,200 subjects randomized equally into each treatment for a 3-year period. To increase the power, it was decided to increase the number of subjects to 1,400 and to prolong the treatment until the last subject has been on the study medication for 3 years, which gives us a predictive median treatment period of 3.9 years.

The choice of treatment was based on our understanding of the pathophysiology of glucose intolerance and on our experience with the drug acarbose. We had already shown in IGT subjects that acarbose was effective in releasing the strain on the  $\beta$ -cell, thus theoretically protecting the  $\beta$ -cells, and in decreasing insulin resistance (13). Furthermore, we had shown in a long-term study of patients with type 2 diabetes (14) that acarbose was nontoxic and well tolerated. Thus, it appeared to have all the required characteristics of a suitable drug for the long-term prevention of type 2 diabetes.

The preliminary screening data offer some insights into the high-risk population under study. The data show that 10.5% (1 in 10) of subjects screened were eligible for the study. Even when one considers that 17.3% had IGT, this percentage is still lower than one would expect in a high-risk population. The prevalence of IGT in European and North American adult populations is already close to 10% (6). However, most of the IGT subjects are >65 years of age; the mean age of our screened population is  $52.7 \pm 0.01$  years. This finding suggests that older subjects may have been less interested in participating in the study, most likely because they believed that they were too old to benefit from such a prevention program. The younger population seemed to be more concerned about their genetic background and their immediate future health status. Our screened population contained slightly more women than men, but the sex distribution was not significantly

different from data on glucose-intolerant subjects found in the literature (6).

The known family history of diabetes did not discriminate among those with IGT, those with type 2 diabetes, and those with normal OGTT results. This outcome was not unexpected, given that family history was the most common reason for responding to our advertisement. The fact that there was less obesity among subjects with normal glucose tolerance than among those with glucose intolerance is consistent with the role of obesity in the development of IGT and diabetes (28). The increased prevalence of known history of hypertension and dyslipidemia among those with increasing glucose intolerance suggests that increasing hyperglycemia may contribute to the development of some of the risk factors for cardiovascular disease. This association has also been suggested by the San Luis Valley Diabetes Study (29). This does not rule out a direct effect of hyperglycemia, per se, as a risk factor for cardiovascular disease (30,31).

The STOP-NIDDM Trial should be completed by the year 2001. It has been carefully designed to assess the effectiveness of acarbose in preventing the conversion of IGT to diabetes. Screening from a high-risk population has confirmed the feasibility of recruitment for such a study. We believe that the results could have a major impact on the development of diabetes, and we are hopeful that they will provide evidence that specific intervention can successfully reduce the overall rate of diabetes.

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## APPENDIX

### The STOP-NIDDM Trial Research Group

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