Acarbose Treatment and the Risk of Cardiovascular Disease and Hypertension in Patients With Impaired Glucose Tolerance
The STOP-NIDDM Trial

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CARDIOVASCULAR DISEASE (CVD) is the leading cause of death among individuals with type 2 diabetes mellitus, accounting for 40% to 50% of all deaths.1 In these patients, the mortality risk for coronary, cerebrovascular, and peripheral vascular disease is 2-fold to 10-fold higher than in the nondiabetic population.2,4 Although type 2 diabetes is frequently associated with other cardiovascular risk factors, such as dyslipidemia and hypertension,5,6 it is believed that hyperglycemia per se is an independent risk factor.6 More recently, special emphasis has been given not only to fasting but particularly to postprandial hyperglycemia as a risk factor for CVD in patients that do not have diabetes as well as those who have it.7-9

It is now believed that macrovascular disease starts before the development of diabetes.10 Several studies have now confirmed the increased risk of CVD in patients with impaired glucose tolerance (IGT) even after adjusting for classic risk factors.11-15 The moderate increase in postprandial plasma glucose levels in patients with IGT was shown to be an independent predictor for CVD. More recently, using ultrasonography to measure carotid intima-media thickness, it was shown that postchallenge
plasma glucose was a strong predictor of atherosclerosis.16-21

In the STOP-Noninsulin-Dependent Diabetes Mellitus (NIDDM) trial, we demonstrated that decreasing postprandial plasma glucose levels in patients with IGT with acarbose, an α-glucosidase inhibitor, could reduce the risk of diabetes.22 Another important objective of the study was to test whether decreasing postprandial hyperglycemia would also diminish the risk of CVD and hypertension.

METHODS

The STOP-NIDDM Trial was an international, double-blind, placebo-controlled, randomized study undertaken in hospitals in Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Israel, and Spain. Details of the study design and methods have been described elsewhere.22,23

Participants were recruited (starting in December 1995; recruitment was closed in July 1998) from a high-risk population of men and women between the ages of 40 and 70 years with a body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters, between 25 and 40. They were eligible for the study if they had IGT according to the World Health Organization criteria,24 plus a fasting plasma glucose concentration of between 100 and 140 mg/dL (5.5 and 7.8 mmol/L). Patients were excluded if they had had any cardiovascular event between the ages of 40 and 70 years with a body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters, between 25 and 40. They were eligible for the study if they had IGT according to the World Health Organization criteria,24 plus a fasting plasma glucose concentration of between 100 and 140 mg/dL (5.5 and 7.8 mmol/L). Patients were excluded if they had had any cardiovascular event before being randomized and at the end of treatment. These were read by 2 independent cardiologists who were also blinded to treatment.

The effect of acarbose on the development of new cases of hypertension was another secondary objective. Hypertension was defined as blood pressure of at least 140/90 mm Hg on 2 consecutive visits or if the family physician added antihypertensive medication between visits. Blood pressure was measured by the coordinating nurse with the patient in the sitting position and a mean of 3 measurements was used.

Plasma glucose concentration was measured in local laboratories by the glucose oxidase or hexokinase method. Plasma insulin and lipid profiles were quantitated in 2 central laboratories, one in Toronto, Ontario, the other in Dresden, Germany. Plasma insulin was measured by highly specific immunoradiometric assay with a 2-site monoclonal antibody.25 Serum triglyceride levels, total cholesterol, and high-density lipoprotein cholesterol concentrations were measured enzymatically. Low-density lipoprotein cholesterol was calculated mathematically if the triglyceride concentration was less than 400 mg/dL (4.51 mmol/L) using the Friedwald formula.26,27 Cross-

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ACARBOSE TREATMENT AND IMPAIRED GLUCOSE TOLERANCE

Sample-size calculation was based on the primary end point: the development of diabetes. It was estimated that 600 patients would be required in each treatment group for a 2-tailed \( \alpha \) of .05 and a 1−B of 90% assuming a conversion rate of 7% per year, a 36% risk reduction, and a drop-out rate of 10%.23

The cardiovascular end points and the development of hypertension were analyzed according to a modified intent-to-treat analysis excluding those who did not meet the IGT criteria (n=17) and those who did not have any valid post-randomization data (n=44). The primary variables were time to development of cardiovascular events and hypertension, for which we used survival analysis to compare the 2 treatment groups. Formal analysis was performed using the Cox proportional hazards model of the SAS software version 8.2 (SAS Inc, Cary, NC). A stratification variable was added to the Cox proportional hazards model to adjust for possible regional (ie, country) differences and homogeneity within regions and to better ensure that the assumption of proportionality was maintained in the model. The assumption of proportionality for the Cox proportional hazards models was informally assessed with a combination of log (−log [survival]) vs log (survival time) graphs to assess parallelism in the primary models. Linear hypothesis tests used the Wald \( \chi^2 \) statistic. We also tested, with the Kaplan-Meier method, the probability of survival outcome. The effect of treatment on the overall incidences of cardiovascular events and hypertension was assessed by multivariate analysis using the Cox proportional hazards model adjusting for the following baseline variables: fasting and 2-hour plasma glucose and plasma insulin concentrations; glycated hemoglobin A1c levels; total, high-density lipoprotein, and low-density lipoprotein cholesterol levels; triglyceride levels; systolic and diastolic blood pressure; heart rate; body weight; BMI; waist circumference; concomitant medications (except for hypertension); and smoking status. Specifically, these parameters were assessed individually in univariate models and, in turn, tested in a multivariate model if \( P \) was less than .25. A forward-selection process was then used, whereby parameters were kept in the multivariate model only if it was statistically significant at the 5% level. We further assessed changes over time in those same variables using a repeated-measure analysis of variance model up to 3 years after randomization. Fisher exact tests were also used for some analyses to assess actual incidences of events between various treatment groups.

RESULTS

Overall, 1429 patients were randomized to receive either acarbose (n=714) or placebo (n=715). We excluded 61 patients who did not meet the criteria for IGT (9 receiving acarbose; 8 receiving placebo) or those who had no valid postrandomization data (23 receiving acarbose; 21 receiving placebo). This left 1368 patients, 682 patients in the acarbose group and 686 patients in the placebo group (Figure 1). The mean (SD) follow-up time was 3.3 (1.2) years.

Twenty-four percent discontinued their participation prematurely, mostly during the first year (211 in the acarbose group and 130 in the placebo group). The most common reason for discontinuation was adverse gastrointestinal tract effects, such as flatulence, diarrhea, and abdominal pain. These patients, however, were followed up for outcome variables. Forty-three (3%) could not be followed up for measurements of end points. Both study patients and investigators were asked to guess the treatment assignment at the end of the study; 48% of patients receiving placebo and 79% receiving acarbose thought they were taking the active drug. Physicians guessed use of acarbose correctly in 69% and incorrectly in 31% of the cases and guessed use of placebo correctly in 64% and incorrectly in 36% of the cases.

The demographic and biochemistry data are listed in Table 1. There was no difference between the 2 treatment groups in experience of and treatment for CVD (Table 1). The baseline characteristics of the 44 patients who were excluded for lack of postrandomization data were similar to the overall study population and were similar between groups. The mean (SD) age was 55.4 (8.0) years with a BMI of 31.7 (4.2), and a waist circumference of 107.1 (12.6) cm. In this excluded group, 11.4% smoked, and 34% took cardiovascular medications.

Figure 2 shows that acarbose treatment increased the probability of re-
maining free of any cardiovascular event (P = .04 by log-rank test). Using the Cox proportional hazards model, treatment with the α-glucosidase inhibitor vs placebo was associated with a significant risk reduction of developing any cardiovascular event with a hazards ratio (HR) of 0.51 (95% confidence interval [CI], 0.28-0.95; P = .03). The assumption of proportionality was satisfied in this model with parallelism of the log (−log [survival]) vs log (survival time) graph, as well as a nonsignificant P value in the hypothesis test of linearity (Wald χ², P = .24).

Altogether, 47 patients had at least 1 cardiovascular event, 32 in the placebo-treated and 15 in the acarbose group (FIGURE 3). This gives a cumulative incidence of 4.7% in the placebo group for an annual incidence of 1.4%. Acarbose treatment was therefore associated with a relative risk reduction of 49% and an absolute risk reduction of 2.9%. Furthermore, 72% of the patients with cardiovascular events (22, placebo group; 12, acarbose) experienced a cardiovascular event during the IGT stage before they had developed diabetes (or did not develop diabetes at all during the study), while only 28% (10, placebo; 3, acarbose) experienced an event after onset of diabetes. There were 13 clinical cases of myocardial infarction, 12 occurring in the placebo group so that the difference was significant (HR, 0.09; 95% CI, 0.01-0.72; P = .02). Electrocardiographic results confirmed an additional 8 silent myocardial infarctions that were not found clinically; 1 was in the acarbose-treated group vs 7 in the placebo-treated group (P = .07, Fisher exact test). If these are included with the clinical cases of myocardial infarction, the cumulative incidence of myocardial infarctions in patients taking acarbose would have been 2 and would have been 19 for those taking placebo (P < .001, Fisher exact test). The effect of the study medication on the other individual cardiovascular events was not significant because of the small number of events, but the trend consistently favored acarbose treatment (Figure 3).

Patients who developed cardiovascular events had a larger mean waist circumference (105.5 vs 102.1 cm; P = .02) and a higher mean systolic (139.5 vs 130.9 mm Hg; P < .001) and diastolic blood pressure (86.3 vs 82.3 mm Hg; P = .004) at baseline compared with patients who did not experience cardiovascular events.

The relationship between clinical and metabolic variables at baseline and development of cardiovascular events independently of treatment allocation is shown in Table 2. Besides acarbose treatment, univariate analysis showed a significant positive correlation between fasting plasma glucose (P = .03) and triglyceride concentrations (P = .05), systolic (P < .001) and diastolic (P = .006) blood pressure, and the development of CVDs, even when those were within the normal range; the cardiovascular-related baseline medication (P = .02) was also associated with the development of cardiovascular events. On multivariate analysis, acarbose treatment (P = .02), fasting plasma glucose levels (P = .03), and systolic blood pressure (P < .001) maintained a significant relationship. For myocardial infarction, treatment allocation (P = .02), baseline fasting plasma glucose levels (P = .04), insulin (P = .02), and baseline medications (P = .04) were significant.

### Table 1. Demographic and Biochemistry Data on the Modified Intent-to-Treat Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (n = 1368)</th>
<th>Acarbose (n = 682)</th>
<th>Placebo (n = 686)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued early</td>
<td>341</td>
<td>211</td>
<td>130</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>673 (49)</td>
<td>329 (48)</td>
<td>344 (50)</td>
</tr>
<tr>
<td>Women</td>
<td>695 (51)</td>
<td>353 (52)</td>
<td>342 (50)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1334 (97)</td>
<td>664 (97)</td>
<td>670 (98)</td>
</tr>
<tr>
<td>Other</td>
<td>34 (3)</td>
<td>18 (3)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>54.5 (7.9)</td>
<td>54.3 (7.9)</td>
<td>54.6 (7.9)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>87.3 (14.7)</td>
<td>87.6 (15.3)</td>
<td>87.0 (14.1)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)*</td>
<td>30.9 (4.2)</td>
<td>31.0 (4.3)</td>
<td>30.9 (4.2)</td>
</tr>
<tr>
<td>Waist circumference, mean (SD), cm</td>
<td>102.2 (11.4)</td>
<td>102.1 (11.7)</td>
<td>102.2 (11.2)</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>178 (13.0)</td>
<td>79 (12)</td>
<td>99 (14)</td>
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<tr>
<td>Plasma glucose, mean (SD), mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>112.3 (9.3)</td>
<td>112.2 (8.9)</td>
<td>112.5 (9.6)</td>
</tr>
<tr>
<td>2-hour</td>
<td>166.7 (18.6)</td>
<td>166.7 (19.2)</td>
<td>166.6 (18.1)</td>
</tr>
<tr>
<td>Plasma insulin, mean (SD), µU/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>13.8 (7.7)</td>
<td>13.9 (8.2)</td>
<td>13.6 (7.3)</td>
</tr>
<tr>
<td>2-hour</td>
<td>83.9 (59.4)</td>
<td>84.5 (61.0)</td>
<td>83.3 (57.8)</td>
</tr>
<tr>
<td>Serum lipids, mean (SD), mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol Total cholesterol</td>
<td>219.9 (39.3)</td>
<td>222.6 (40.1)</td>
<td>217.1 (38.2)</td>
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<tr>
<td>High-density lipoprotein</td>
<td>45.6 (12.6)</td>
<td>46.1 (12.6)</td>
<td>45.2 (12.7)</td>
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<tr>
<td>Low-density lipoprotein</td>
<td>139.2 (35.0)</td>
<td>141.5 (35.1)</td>
<td>137.0 (34.8)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>183.2 (100.7)</td>
<td>183.1 (97.3)</td>
<td>183.3 (104.0)</td>
</tr>
<tr>
<td>Dyslipidemia, No. (%)†</td>
<td>789 (58)</td>
<td>395 (59)</td>
<td>394 (57)</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>131.1 (16.3)</td>
<td>131.4 (16.3)</td>
<td>130.9 (16.2)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>82.4 (9.3)</td>
<td>82.8 (9.4)</td>
<td>82.0 (9.3)</td>
</tr>
<tr>
<td>Hypertension, No. (%)‡</td>
<td>702 (51)</td>
<td>357 (52)</td>
<td>345 (50)</td>
</tr>
<tr>
<td>History of cardiovascular disease, No. (%)</td>
<td>66 (4.8)</td>
<td>34 (5.0)</td>
<td>32 (4.7)</td>
</tr>
<tr>
<td>Cardiovascular medication, No. (%)</td>
<td>284 (20.8)</td>
<td>146 (21.4)</td>
<td>138 (20.1)</td>
</tr>
</tbody>
</table>

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cantly associated with increased coronary events on univariate analysis. On multivariate analysis, while acarbose treatment remained associated with a statistically significant reduction in the risk of myocardial infarction (HR, 0.66; 95% CI, 0.49-0.89; P = .006). This gives a relative risk reduction of 34% and an absolute risk reduction of 5.3% associated with acarbose treatment. TABLE 3 shows that among the various baseline clinical and metabolic parameters, only systolic and diastolic blood pressure (HR < .001; P = .002, respectively) were positively associated with the risk of hypertension on univariate analysis. On multivariate analysis, only acarbose treatment (P = .004) and diastolic blood pressure (P < .001) remained independent factors. The assumptions of proportionality were satisfied in these Cox proportional hazards models.

The mean change from baseline to the 3 years was favorably affected by acarbose treatment for the following variables: body weight (placebo, 0.26 vs acarbose, −1.15 kg), BMI (placebo, −0.12 vs acarbose, −0.60), waist (placebo, 0.17 vs acarbose, −0.62 cm) and hip (placebo, −0.57 vs acarbose, −0.91 cm) circumference. It also significantly reduced systolic (placebo, −0.05 vs acarbose, −0.97 mm Hg) and diastolic (placebo, −1.4 vs acarbose, −2.8 mm Hg) blood pressure (FIGURE 5) as well as the 2-hour plasma glucose concentration (placebo, 0.04 vs acarbose, −0.63 mg/dL), and triglycerides (placebo, −0.04 vs acarbose, −0.18 mg/dL) over 3 years. Using a repeated measures analysis of variance, the effect of acarbose in reducing those variables over the 3-year period was significant: weight, P < .001; BMI, P < .001; waist circumference, P = .001; systolic blood pressure, P < .001; diastolic blood pressure, P = .008; 2-hour plasma glucose concentration, P < .001; and triglycerides, P = .01.

**COMMENT**

This is the first prospective intervention study testing the postprandial hyperglycemia hypothesis as a risk factor for CVD. The data show that treatment with the α-glucosidase inhibitor acarbose was associated with a significant reduction in cardiovascular events in a population with IGT characterized by moderate postprandial hyperglycemia.

Although the STOP-NIDDM trial was not initially powered to answer that question, the analysis of the data using the Cox proportional hazards and the log-rank test showed that acarbose treatment was associated with a significant reduction in cardiovascular events. The incidence of cardiovascular events in the STOP-NIDDM trial population with IGT was 1.4% per year based on the placebo-treated group. These events were ascer-
tained and confirmed by an indepen-
dent adjudicating committee blinded to
treatment. The incidence observed in the
present study was not very different from
other reports, which showed that car-
diovascular mortality in IGT populations
varied between 0.4% and 0.9% per
year.11,20-31 Since the incidence of cardio-
vascular events would be expected to be
higher than the mortality rate, our ob-
servation of 1.4% per year was not un-
expected. Thus, in the STOP-NIDDM
trial, the incidence of cardiovascular
events in the placebo group is what
would be expected; the lower-inci-
dence in the acarbose group (0.7% per
year) would suggest a treatment effect.

Overall, 84 clinical cardiovascular
events were documented throughout the
study occurring in 47 patients; 32 pa-
tients (4.7%) were in the placebo group
vs 15 (2.2%) in the acarbose group
(P=.03). Myocardial infarction by it-
self was statistically significantly more
frequent in the placebo group whether
we include the silent myocardial infarc-
tions (19 vs 2; P<.001 by Fisher exact
test) or not (12 vs 1; P=.02 by Cox pro-
portional hazards analysis; Figure 3). Al-
though the other events taken individu-
ally were not significant due to the small
numbers, they consistently favored acar-
bosé (Figure 3). Even after adjusting for
all other measured risk factors at base-
line, the acarbose treatment was still as-
associated with a significant reduction in
the risk of CVD (P=.02; Table 2). Acar-
bosé treatment was therefore associ-
ated with a relative risk reduction of 49%
for cardiovascular events and an abso-
lute risk reduction of 2.5% among IGT
patients. The number needed to treat to
prevent 1 cardiovascular event would be
40 patients with IGT over 3.3 years.

The incidence of new cases of hy-
pertension in placebo-treated patients
with IGT was 10% per year. Although
there are few data on the incidence of
hypertension among patients with IGT,
the observed incidence in the present
study is higher than expected. In The
San Antonio Heart Study, Haffner et al32
found an increased risk of hyperten-
sion only in women with IGT, for which
the hazard ratio was 1.94 with an an-
nual incidence of 1.5%. However, the
diagnostic criterion for hypertension in
that study was blood pressure of 160/90
mm Hg or higher. In the STOP-
NIDDM trial, the most recent crite-
ron for hypertension of 140/90 mm Hg

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Hazard Ratio (95% Confidence Interval)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group, acarbose vs placebo</td>
<td>0.512 (0.277-0.946)</td>
<td>.03</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>1.031 (1.014-1.049)</td>
<td>.006</td>
</tr>
<tr>
<td>Fasting</td>
<td>1.767 (1.060-2.946)</td>
<td>.03</td>
</tr>
<tr>
<td>2-hour</td>
<td>1.049 (0.791-1.392)</td>
<td>.74</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
<td>1.002 (0.998-1.007)</td>
<td>.32</td>
</tr>
<tr>
<td>Fasting</td>
<td>1.000 (0.999-1.001)</td>
<td>.65</td>
</tr>
<tr>
<td>2-hour insulin</td>
<td>1.641 (0.973-2.770)</td>
<td>.06</td>
</tr>
<tr>
<td>Glycated hemoglobin A1c,%</td>
<td>1.146 (0.850-1.545)</td>
<td>.37</td>
</tr>
<tr>
<td>Total triglycerides</td>
<td>0.382 (0.125-1.170)</td>
<td>.09</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>1.185 (0.838-1.677)</td>
<td>.34</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>1.236 (1.001-1.526)</td>
<td>.05</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.029 (1.013-1.046)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>1.045 (1.012-1.074)</td>
<td>.006</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.994 (0.962-1.028)</td>
<td>.72</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>1.001 (0.982-1.021)</td>
<td>.91</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.962 (0.894-1.035)</td>
<td>.30</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>1.022 (0.998-1.047)</td>
<td>.07</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>2.071 (1.111-3.861)</td>
<td>.02</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.804 (0.316-2.043)</td>
<td>.65</td>
</tr>
</tbody>
</table>

Table 2. Relationship Between Treatment Allocation and Other Baseline Variables on the Development of Cardiovascular Events According to the Cox Proportional Hazards Model Analysis

*For continuous variables, the hazard ratio represents the change per unit increase in the variable.
†Calculated as weight in kilograms divided by the square of height in meters.

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or higher was used. Furthermore, the San Antonio Heart Study population was much younger, being evenly distributed between the ages of 25 and 64 years. In addition, it was a population-based study while our participants were selected from a high-risk population at baseline. Acarbose significantly reduced the mean systolic and diastolic blood pressure throughout the study period (Figure 5). But, more importantly, it significantly decreased the risk of developing hypertension. Based on the recent diagnostic criteria, 193 new cases of hypertension were diagnosed during the study period; 115 (33.7% per 3.3 years) occurred in patients treated with placebo vs 78 (24% per 3.3 years) patients in the acarbose-treated group ($P = .006$). Even after adjusting for other risk factors at baseline, the acarbose treatment effect on the risk of hypertension remained significant and independent ($P = .004$, Table 3). Acarbose treatment thus resulted in a relative risk reduction of 34% for the development of hypertension and in an absolute risk reduction of 5.4%. The number needed to treat to prevent 1 case of hypertension would be 19 IGT patients for 3.3 years. Since hypertension is itself a risk factor for CVD, such an intervention would be highly cost-effective. We are not aware of any other prospective intervention studies that have looked at the prevention of hypertension in high-risk populations.

The STOP-NIDDM trial is the first prospective intervention study demonstrating that treatment with acarbose in IGT patients is associated with a lower incidence of CVD and hypertension. The intriguing question is: what is the relationship between acarbose and the reduction of postprandial hyperglycemia and the observed lower incidence of CVD and hypertension? Although the present study was not designed to answer that question, some observations from this trial can offer potential leads. Acarbose treatment was associated with a significant reduction in body weight, BMI, and waist circumference, in blood pressure, in 2-hour plasma glucose concentration, and in triglyceride levels. All of these factors have already been shown to be associated with an increased risk of CVD and hypertension. In the STOP-NIDDM trial, the patients who developed CVD had a significantly larger waist circumference (105.5 vs 102.1 cm) and higher blood pressure (139.5/86.3 vs 130.9/82.3 mm Hg) at baseline compared with those who did not. On multivariate analysis, baseline blood pressure, even within the normal range, remained a significant predictor of CVDs and hypertension (Table 2 and Table 3). Furthermore, acarbose treatment resulted in a significant decrease in blood pressure (Figure 5). Although all those factors could explain, in part, the beneficial effect of acarbose on CVD and hypertension, the effect of $\alpha$-glucosidase inhibitor treatment on those outcomes remained statistically significant and independent after adjusting for those variables (Table 2 and Table 3). However, other unknown mechanisms such as the

### Table 3. Effects of Acarbose Treatment and Baseline Clinical and Metabolic Parameters on the Incidence of Hypertension According to the Cox Proportional Hazards Model Analysis

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group, acarbose vs placebo</td>
<td>0.657 (0.487-0.886)</td>
<td>.006</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>1.195 (0.909-1.569)</td>
<td>.20</td>
</tr>
<tr>
<td>2-hour</td>
<td>1.132 (0.987-1.299)</td>
<td>.08</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
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</tr>
<tr>
<td>Fasting</td>
<td>1.002 (0.999-1.004)</td>
<td>.25</td>
</tr>
<tr>
<td>2-hour insulin</td>
<td>1.000 (0.999-1.001)</td>
<td>.12</td>
</tr>
<tr>
<td>Glycated hemoglobin A1c, %</td>
<td>0.949 (0.722-1.247)</td>
<td>.71</td>
</tr>
<tr>
<td>Serum lipids, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol Total</td>
<td>1.109 (0.957-1.285)</td>
<td>.17</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>1.096 (0.698-1.719)</td>
<td>.69</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>1.132 (0.952-1.344)</td>
<td>.16</td>
</tr>
<tr>
<td>Total triglycerides</td>
<td>1.048 (0.916-1.198)</td>
<td>.50</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>1.017 (1.008-1.026)</td>
<td>.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>1.024 (1.009-1.040)</td>
<td>.002</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>0.988 (0.971-1.007)</td>
<td>.18</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>1.007 (0.997-1.017)</td>
<td>.16</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>1.033 (1.003-1.068)</td>
<td>.07</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>1.007 (0.995-1.020)</td>
<td>.25</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.259 (0.834-1.900)</td>
<td>.27</td>
</tr>
<tr>
<td><strong>Multivariate Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group, acarbose vs placebo</td>
<td>0.610 (0.447-0.857)</td>
<td>.004</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>1.029 (1.012-1.046)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*For continuous variables, the hazard ratio represents the change per unit increase in the variable. †Calculated as weight in kilograms divided by the square of height in meters.
effects of acarbose on glucagonlike peptide 1 could be involved. 37,38

The effect of postprandial plasma glucose itself remains difficult to evaluate. The 2-hour plasma glucose concentration after 75 g of glucose is not directly affected by acarbose and, under these conditions, is not a good surrogate for the effect of the drug on postprandial plasma glucose concentration. A test meal would have been useful. However, we have already shown that acarbose could normalize postprandial plasma glucose concentration after a meal in patients with IGT. 39 In this context, Ceriello et al 40-43 have already shown that postprandial hyperglycemia concentration is associated with an increase in oxidative stress. This is true in normal individuals, in IGT patients, as well as in patients with diabetes. 44,45 It has also been shown that acarbose taken with meals can blunt this increase in oxidative stress. 33 Postprandial oxidative stress is also associated with endothelial dysfunction, which has been suggested to be involved in the development of both hypertension and CVD. 46-48 All of these observations make a reduction in oxidative stress an interesting mechanism by which acarbose could mediate, at least in part, its beneficial effect on the prevention of both CVD and hypertension. A definite cause-and-effect relationship, however, remains to be established.

We acknowledge the limitations in the interpretation of the cardiovascular data from the STOP-NIDDM trial. First, the intent-to-treat population is modified by excluding the 61 patients whose postrandomization data was unavailable because they had dropped out of the study immediately after being randomized without taking any study medications. Second, the study was powered for incidence of diabetes, not for CVD, which was an a priori secondary objective. Third, the analysis was not adjusted for multiple testing, and because of the small number of events, the possibility that the observed effect could be due to chance cannot be ignored. Fourth, premature discontinuation was higher than expected, 211 in the acarbose group vs 130 in the placebo group. However, the demographic and biochemistry data in the dropout population were identical to the overall study population. Moreover, those who had dropped out were followed up for outcome parameters and 9 patients randomized to receive placebo had a cardiovascular event compared with 4 of those randomized to receive acarbose. Fifth, 79% of patients and 69% of physicians guessed correctly about treatment assignment. Although guessing could effect the outcome, certainty was only obtained retrospectively. In fact, of the 869 patients who thought they were taking acarbose, 329 (38%) were taking placebo. It is very unlikely that it could explain a 50% difference in cardiovascular events. Nonetheless, despite all these limitations, there is a consistency in the effect of acarbose on overall cardiovascular events and on myocardial infarctions, both clinical and silent. We believe that these observations are statistically and clinically significant. They are, however, hypothesis-generating and will need to be confirmed.

In conclusion, the STOP-NIDDM trial is the first prospective intervention study showing that treatment with an α-glucosidase inhibitor in IGT patients is associated with a significant reduction in the incidence of CVD and hypertension. These observations are compatible with the hypothesis that postprandial hyperglycemia is a risk factor for CVD and provide further arguments for screening and treating patients with IGT.

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Author Contributions: Members of the publication committee had full access to all the data in this study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical expertise: Laakso.

Obtained funding: Chiasson, Josse, Gomis.

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Study supervision: Chiasson, Josse, Gomis.


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REFERENCES


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