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 more 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.11-13 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 intimomedial thickness, it was shown that postchallenge

Context The worldwide explosive increase in type 2 diabetes mellitus and its cardiovascular morbidity are becoming major health concerns.

Objective To evaluate the effect of decreasing postprandial hyperglycemia with acarbose, an \( \alpha \)-glucosidase inhibitor, on the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance (IGT).

Design, Setting, and Participants International, multicenter double-blind, placebo-controlled, randomized trial, undertaken in hospitals in Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Israel, and Spain from July 1998 through August 2001. A total of 1429 patients with IGT were randomized with 61 patients (4%) excluded because they did not have IGT or had no postrandomization data, leaving 1368 patients for a modified intent-to-treat analysis. Both men (49%) and women (51%) participated with a mean (SD) age of 54.5 (7.9) years and body mass index of 30.9 (4.2). These patients were followed up for a mean (SD) of 3.3 (1.2) years.

Intervention Patients with IGT were randomized to receive either placebo (n=715) or 100 mg of acarbose 3 times a day (n=714).

Main Outcome Measures The development of major cardiovascular events (coronary heart disease, cardiovascular death, congestive heart failure, cerebrovascular event, and peripheral vascular disease) and hypertension (\( \geq \)140/90 mm Hg).

Results Three hundred forty-one patients (24%) discontinued their participation prematurely, 211 in the acarbose-treated group and 130 in the placebo group; these patients were also followed up for outcome parameters. Decreasing postprandial hyperglycemia with acarbose was associated with a 49% relative risk reduction in the development of cardiovascular events (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.28-0.95; \( P = .03 \)) and a 2.5% absolute risk reduction. Among cardiovascular events, the major reduction was in the risk of myocardial infarction (HR, 0.09; 95% CI, 0.01-0.72; \( P = .02 \)). Acarbose was also associated with a 34% relative risk reduction in the incidence of new cases of hypertension (HR, 0.66; 95% CI, 0.49-0.89; \( P = .006 \)) and a 5.3% absolute risk reduction. Even after adjusting for major risk factors, the reduction in the risk of cardiovascular events (HR, 0.47; 95% CI, 0.24-0.90; \( P = .02 \)) and hypertension (HR, 0.62; 95% CI, 0.45-0.86; \( P = .004 \)) associated with acarbose treatment was still statistically significant.

Conclusion This study suggests that treating IGT patients with acarbose is associated with a significant reduction in the risk of cardiovascular disease and hypertension.

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Author Affiliations, Financial Disclosures, and the STOP-NIDDM Trial Research Group are listed at the end of this article.

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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 within the last 6 months.

Eligible patients were randomized to receive placebo or 100 mg of acarbose 3 times a day, taken with the first bite of each meal. Randomization was done using a computer program allocation sequence that was stratified by center.22 Randomization was done in blocks of 4 and 6 to minimize the chance that the investigators could guess the treatment assignment. Numbered drug containers were used to implement the random allocation process. Since the random code was stratified by center, the patients were randomized sequentially at each center. The random codes were concealed in 3-part container labels that were stored separately in the event that the investigator needed to know the treatment of a patient. The allocation sequence was generated by an independent statistician who was a member of the data safety and quality review committee.23 Enrollment and randomization was handled at the sites. The study was completed in August 2001 after a mean (SD) follow-up of 3.3 (1.15) years.

All patients were instructed to go on a weight-reduction or weight-maintenance diet and were encouraged to exercise regularly; these instructions were reinforced at each visit. Participants were examined every 6 months by the investigator and seen every 3 months by the coordinating nurse for pill count and distribution, documentation of adverse events, and measurement of blood pressure and fasting plasma glucose concentration. They were asked to remain in the study until the last randomized patient had been treated for 3 years. The protocol was approved by appropriate institutional review boards, and each patient signed an informed consent form.

Part of the study protocol included evaluating the effect of acarbose on the occurrence of CVD. The main outcome measure was the number of patients developing major cardiovascular events, including coronary heart disease (myocardial infarction, new angina, revascularization procedures), cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease. Myocardial infarction was defined as clinical symptoms of myocardial ischemia with elevated serum cardiac enzymes and electrocardiographic changes; at least 2 of these 3 criteria had to be present for the clinical diagnosis. The diagnosis of silent myocardial infarction was based on new Q waves and prolonged ST-segment elevation on at least 2 contiguous leads. New angina was defined as ischemic cardiac pain with diagnostic exercise electrocardiographic or stress perfusion imaging findings compatible with myocardial ischemia. Cardiovascular death was death due to congestive heart failure, myocardial infarction, cerebrovascular event, cardiovascular procedures, pulmonary embolism, or sudden death. Congestive heart failure was defined as recent onset of new or aggravation of symptoms compatible with heart failure with supportive documentation such as chest radiograph or electrocardiographic changes. Cerebrovascular events related to the presence of neurological deficits such as transient ischemic attack or stroke. Peripheral vascular disease was diagnosed based on the development of intermittent claudication with clinical vascular disease confirmed by doppler or angiography. These events were ascertained by an independent adjudicating committee of 3 cardiologists blinded to treatment. According to the protocol, all patients had undergone an electrocardiogram 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-
checked validation for various measurements was done every 4 months for all participating laboratories. The 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 α of .05 and a 1−B of 90% assuming a conversion rate of 7% per year, a 36% risk reduction, and a dropout rate of 10%. 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 postrandomization 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 χ^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-
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 signifi-

### Table 2. 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>696 (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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-hour</td>
<td>112.3 (9.3)</td>
<td>112.2 (8.9)</td>
<td>112.5 (9.6)</td>
</tr>
<tr>
<td>1-hour</td>
<td>166.7 (18.6)</td>
<td>166.7 (19.2)</td>
<td>166.6 (18.1)</td>
</tr>
<tr>
<td>2-hour</td>
<td>13.8 (7.7)</td>
<td>13.9 (8.2)</td>
<td>13.6 (7.3)</td>
</tr>
<tr>
<td>1-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</td>
<td>219.9 (39.3)</td>
<td>222.6 (40.1)</td>
<td>217.1 (38.2)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>45.6 (12.6)</td>
<td>46.1 (12.6)</td>
<td>45.2 (12.7)</td>
</tr>
<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>Dysthyemia, 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>131.1 (16.3)</td>
<td>131.4 (16.3)</td>
<td>130.9 (16.2)</td>
</tr>
<tr>
<td>Systolic</td>
<td>82.4 (9.3)</td>
<td>82.8 (9.4)</td>
<td>82.0 (9.3)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>702 (51)</td>
<td>357 (52)</td>
<td>345 (50)</td>
</tr>
<tr>
<td>Hypertension, No. (%)‡</td>
<td></td>
<td></td>
<td></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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Acarbose treatment was significantly 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, 0.61; 95% CI, 0.49-0.89; P = .006), only systolic and diastolic blood pressure (P < .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-

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**Table 3**

<table>
<thead>
<tr>
<th>Event</th>
<th>Acarbose (n = 682)</th>
<th>Placebo (n = 686)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1</td>
<td>12</td>
<td>0.09 (0.01-0.72)</td>
<td>.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>5</td>
<td>12</td>
<td>0.45 (0.16-1.28)</td>
<td>.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization Procedures</td>
<td>11</td>
<td>20</td>
<td>0.61 (0.29-1.26)</td>
<td>.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>1</td>
<td>2</td>
<td>0.55 (0.05-6.11)</td>
<td>.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive Heart Failure*</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Nervous System</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event or Stroke</td>
<td>2</td>
<td>4</td>
<td>0.56 (0.10-3.07)</td>
<td>.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>1</td>
<td>1</td>
<td>1.14 (0.07-18.30)</td>
<td>.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Cardiovascular Event</td>
<td>15</td>
<td>32</td>
<td>0.51 (0.08-0.95)</td>
<td>.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval. Asterisk indicates hazard ratio (95% CI) could not be calculated because of zero event for acarbose group.
tained and confirmed by an independent adjudicating committee blinded to treatment. The incidence observed in the present study was not very different from other reports, which showed that cardiovascular mortality in IGT populations varied between 0.4% and 0.9% per year. Since the incidence of cardiovascular events would be expected to be higher than the mortality rate, our observation of 1.4% per year was not unexpected. Thus, in the STOP-NIDDM trial, the incidence of cardiovascular events in the placebo group is what would be expected; the lower-incidence 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 patients (4.7%) were in the placebo group vs 15 (2.2%) in the acarbose group (P = .03). Myocardial infarction by itself was statistically significantly more frequent in the placebo group whether we include the silent myocardial infarctions (19 vs 2; P < .001 by Fisher exact test) or not (12 vs 1; P = .02 by Cox proportional hazards analysis; Figure 3). Although the other events taken individually were not significant due to the small numbers, they consistently favored acarbose (Figure 3). Even after adjusting for all other measured risk factors at baseline, the acarbose treatment was still associated with a significant reduction in the risk of CVD (P = .02; Table 2). Acarbose treatment was therefore associated with a relative risk reduction of 49% for cardiovascular events and an absolute 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 hypertension 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 al found an increased risk of hypertension only in women with IGT, for which the hazard ratio was 1.94 with an annual 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 criterion for hypertension of 140/90 mm Hg...
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 important, 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.33 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.9,16,34-36 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 α-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>
<td></td>
<td></td>
</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 (0.998-1.219)</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 (1.098-1.069)</td>
<td>.07</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>1.037 (1.095-1.020)</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>0.619 (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.

### Figure 5. Effects of Acarbose Treatment on Blood Pressure

- **Systolic Blood Pressure**
  - Mean Change from Baseline
  - Months After Randomization
  - P<.001

- **Diastolic Blood Pressure**
  - Mean Change from Baseline
  - Months After Randomization
  - P=.008

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effects of acarbose on glucaconlike peptide 1 could be involved.  

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.  

In this context, Ceriello et al 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. It has also been shown that acarbose taken with meals can blunt this increase in oxidative stress. Postprandial oxidative stress is also associated with endothelial dysfunction, which has been suggested to be involved in the development of both hypertension and CVD.  

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.

Study concept and design: Chiasson, Josse, Gomis, Hanefeld.

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Analysis and interpretation of data: Josse, Gomis, Karasik, Laakso.

Drafting of the manuscript: Chiasson, Josse, Hanefeld. Critical revision of the manuscript for important intellectual content: Josse, Gomis, Hanefeld, Karasik, Laakso.

Statistical expertise: Laakso.

Obtained funding: Chiasson, Josse, Gomis.

Administrative, technical, or material support: Chiasson, Hanefeld.

Study supervision: Chiasson, Josse, Gomis.


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