Acarbose Slows Progression of Intima-Media Thickness of the Carotid Arteries in Subjects with Impaired Glucose Tolerance R2

Markolf Hanefeld, PhD; Jean Louis Chiasson, PhD; Carsta Koehler, PhD; Elena Henkel, MD; Frank Schaper, MD; Theodora Temelkova-Kurktschiev, PhD

Background and Purpose—Impaired glucose tolerance (IGT)–a prediabetic state–is an important risk factor for atherosclerosis. Acarbose, an α-glucosidase inhibitor, was shown in the placebo-controlled prospective study to prevent noninsulin-dependent diabetes mellitus (STOP-NIDDM) trial to reduce the risk of diabetes by 36% in IGT subjects. This article reports on a placebo-controlled subgroup analysis of the STOP-NIDDM study to examine the efficacy of acarbose to slow progression of intima-media thickness (IMT) in subjects with IGT.

Methods—One hundred thirty-two IGT subjects were randomized to placebo (n=66) or acarbose (n=66) 100 mg 3 times daily; the study duration was at least 3 years, mean follow-up time 3.9 (SD 0.6) years. Carotid IMT was determined at study entry and the end of the trial. The intent-to-treat analysis included 56 subjects in the acarbose and 59 in the control group who had a baseline and endpoint measurement.

Results—A significant reduction of the progression of IMT mean was observed in the acarbose group versus placebo. After an average time of 3.9 years, IMT mean increased by 0.02 (0.07) mm in the acarbose group versus 0.05 (0.06) mm in the placebo group (P=0.027). The annual increase of IMT mean was reduced by ~50% in the acarbose group versus placebo. Multiple linear regression revealed IMT progression as significantly related to acarbose intake.

Conclusions—Acarbose slows progression of IMT in IGT subjects, a high-risk population for diabetes and atherosclerosis. This is the first placebo-controlled prospective subgroup analysis, demonstrating that counterbalancing of postprandial hyperglycemia may be vasoprotective. (Stroke. 2004;35:1073-1078.)

Key Words: acarbose ■ glucose intolerance ■ intima-media thickness ■ hyperglycemia ■ ultrasonography

Impaired glucose tolerance (IGT)–a prediabetic state–is an important risk factor for cardiovascular morbidity and mortality, stroke inclusive. Recently published studies have shown that excessive postchallenge hyperglycemia is associated with endothelial dysfunction and increase in intima-media thickness (IMT) as well as with a higher prevalence of atherosclerotic plaques of the common carotid arteries. Intima-media thickness (IMT) has been shown to be an independent predictor of coronary heart disease and stroke. It is well known that postprandial hyperglycemia initiates a cascade of proatherogenic events that exert harmful effects on the endothelium. Furthermore, IGT is already associated with the cluster of comorbidities of the metabolic syndrome. The question is therefore debated whether postprandial hyperglycemia is a risk factor in its own right or only a bystander escalating the proatherosclerotic process.

Acarbose is an α-glucosidase inhibitor that specifically reduces postprandial glucose excursion by delaying the release of glucose from disaccharides and complex carbohydrates in the upper part of the small intestine. It was already demonstrated in the study to prevent noninsulin-dependent diabetes mellitus (STOP-NIDDM) trial, a multinational placebo-controlled prospective study, that acarbose could reduce the risk of diabetes by 36% in subjects with IGT. Incidence of prespecified cardiovascular events was a secondary objective of this trial. As shown in a recent publication, the treatment with acarbose was associated with a significantly lower incidence of cardiovascular diseases and newly diagnosed hypertension. This paper reports a single-center placebo-controlled subgroup analysis of the STOP-NIDDM study looking at the progression of the IMT of the common carotids as primary objective. The question was whether acarbose could stop or delay the progression of IMT in subjects with IGT as measured ultrasonographically.

Subjects and Methods
Subjects for the STOP-NIDDM study were recruited from a high-risk population for diabetes aged 40 to 70 years with a

Received July 25, 2003; final revision received January 13, 2004; accepted January 14, 2004.
From the Centre for Clinical Studies (M.H, C.K., E.H., T.T.-K.) and Institute and Outpatient Department for Clinical Metabolic Research (F.S.), Dresden Technical University, Dresden, Germany; Research Centre-CHUM-Hotel-Dieu (J.L.C.), Montreal, Canada.
Correspondence to Prof M. Hanefeld, Zentrum für Klinische Studien GWT der Technischen Universität Dresden, Fiedlerstr. 34, 01307 Dresden, Germany. E-mail hanefeld@gwt-tud.de
© 2004 American Heart Association, Inc.
Stroke is available at http://www.strokeaha.org DOI: 10.1161/01.STR.0000125864.01546.f2
body mass index (BMI) between 25 and 40 kg/m². They were eligible if they had IGT according to World Health Organization (WHO) criteria plus a fasting plasma glucose level between 5.5 and 7.8 mmol/L. The STOP-NIDDM trial was a multinational double-blind placebo-controlled study with a total number of 1429 eligible subjects randomized to receive either 100 mg acarbose 3 times a day or placebo. This single-center substudy is based on 132 participants recruited in Dresden, Saxony, Germany. Details of design, recruitment, and methods have been published previously.¹⁷ This substudy was performed with the same treatment team through the full time of the study. The patients randomized at Dresden center did not differ from the overall STOP-NIDDM trial population. The patients remained in the study until the last randomized participant had been treated for 3 years; mean follow-up time was 3.9 (SD 0.6) years. At the end of the study a 75 g oral glucose tolerance test was performed only for those who had not developed diabetes during the trial. The protocol was approved by an Institutional Ethics committee, and written informed consent was obtained from all participants. The patients were instructed to keep a weight reduction or weight maintenance diet and to exercise regularly. Treatment of hypertension and dyslipidemia was performed according to national guidelines. In the placebo group 25 subjects were treated with statins and 12 with fibrates; in the acarbose group, 11 were treated. Both medications were equally distributed in both study arms.

Carotid B-mode Ultrasound

Ultrasonography of the distal common carotid artery (CCA) was conducted bilaterally with Acuson 128XP Computed Sonography System using a 10.5 MHz linear array transducer, as previously described.¹⁸ Briefly, we measured the IMT of the far wall of CCA, as originally described by Pignoli et al.¹⁹ We used a longitudinal 2-dimensional ultrasound image of the CCA, which is displayed as 2 bright echo-rich lines separated by a hypoechoogenic space. A careful search was performed for the IMT of the far wall of the distal CCA. When an optimal image was obtained, it was frozen in an end-diastolic phase to minimize variability during the cardiac cycle. IMT was measured twice bilaterally at 5 mm and 10 mm proximal from the dilatation of the CCA. The mean of these values presented the IMTmean of each subject. In addition, the maximal thickness (IMTmax) was determined. IMT was measured at baseline, and follow-up of all subjects recruited in Dresden who completed the study.

Laboratory Procedures

Patients were examined after an overnight fast of at least 10 hours. Aliquots of plasma were immediately frozen with liquid nitrogen and were stored at −80°C until analysis. Plasma glucose and hemoglobin A1c (HbA1c) were determined using fresh material. HbA1c was examined by high-performance liquid chromatography (HPLC) on a Diamat analyzer (BioRad Laboratories). Plasma glucose was measured by the hexokinase method (interassay CV=1.5%). After precipitation with dextran sulfate, high-density lipoprotein (HDL) cholesterol was examined in the upper layer on a Ciba Corning Express Plus analyzer (Ciba Corning Diagnostics). Triglycerides and total cholesterol were measured by enzyme colorimetric assay on a Ciba Corning Express Plus analyzer, using commercially available test kits (Boehringer). Urine was collected as fresh morning urine samples. Albuminuria was measured by nephelometry (Nephelometer BNII).

Statistical Analysis

The statistical analysis of the data were performed using SPSS 11.0 for Windows (SPSS Inc). The data are presented as mean and standard deviation. The primary variable was appointed as changes of IMT of the CCA (IMTendpoint−IMTbaseline=ΔIMT). The confirmatory analysis of the effect of the primary efficacy variable was done by use of the Mann-Whitney U test. The variable was non-normally distributed. The baseline to endpoint changes in the groups were tested by the Wilcoxon test.

Multiple linear regression analysis was used to determine the independent parameters of IMT changes. The t test calculation was applied to the anthropometrical data, glucose, lipids, and blood pressure. Smoking, sex distribution, and drug-intake were tested by χ² test. The intention-to-treat (ITT) analysis included all randomized patients who had a baseline and endpoint measurement of IMT.

Results

Ten out of the 66 patients in the acarbose and 5 out of the 66 in the placebo group terminated early; there were 2 protocol violators in the placebo group. The reasons for discontinuation are presented in Figure 1. Here we report an ITT analysis of 115 subjects who had an IMT measurement at baseline and at the last follow-up examination: 56 in the acarbose group and 59 in the placebo group. The baseline characteristics are shown in Table 1. Both groups were well-balanced for age, sex, smoking, and all major risk factors. The baseline characteristics of the premature discontinuation were not different from the findings of the ITT analysis. Furthermore, concomitant medication at baseline and during the study did not differ between the 2 groups (Table 2). The prescription of antihypertensive and lipid-lowering drugs approximately doubled during the time of the study in both groups. A final oral glucose tolerance test was performed in subjects who did not convert to diabetes during the study. Fourteen patients in the acarbose and 16 in the placebo group developed diabetes. At the end of the study, no significantly different changes were observed for the 3 lipid fractions in either groups or between the 2 groups. Also, the changes in metabolic parameters were not significantly different between the groups.

As shown in Figure 2, a significant reduction of the progression of IMTmean was observed in the acarbose versus placebo group. After a mean time of 3.9 years, IMTmean increased by 0.02 (0.07) mm in the acarbose group versus 0.05 (0.06) mm in the placebo group (P=0.027, Table 3). The annual increase of IMTmean was reduced by ~50% in the acarbose versus placebo group. There was, however, no
significant difference with respect to the progression of IMT\textsubscript{max} between the acarbose arm and controls.

The following was obtained for the change in IMT mean \((\text{IMTmean})\) in the multiple linear regression analysis when acarbose intake, sex, change of BMI, change of HDL, change of heart frequency (HF), and change of total cholesterol were included in the analysis:

\[
\begin{align*}
\text{IMTmean} & \sim 0.029 \pm 0.028 \text{ acarbose intake} \\
& \sim 0.055 \text{ IMTmean baseline} \\
& \sim 0.028 \text{ sex} \\
& \sim 0.003 \Delta \text{BMI} - 0.040 \Delta \text{HDL} + 0.007 \Delta \text{total cholesterol}.
\end{align*}
\]

The correlation coefficient of this model was 0.43. As a significant independent variable with impact on IMTmean, we found acarbose intake \((P=0.043)\). All other variables in the model were not significant.

**Discussion**

This is the first placebo-controlled intervention study testing the hypothesis that acarbose treatment of IGT is associated with significantly reduced progression of IMT. Acarbose, an \(\alpha\)-glucosidase inhibitor, delays the release of glucose from complex carbohydrates in the small intestine leading to lower postprandial glucose excursions after mixed meals.\textsuperscript{14} Previous studies have shown that IGT is associated with a significant increase in IMT even after adjustment for associated risk factors.\textsuperscript{7,8,20} In our study the treatment of IGT with acarbose was associated with a significantly diminished progression of the IMT of the common carotid arteries. The annual progression rate of IMT\textsubscript{mean} in the acarbose arm was 0.007 (0.019) mm/year versus 0.013 (0.018) mm/year \((P=0.021)\) with placebo. Thus, treatment of IGT delayed progression of IMT to rates reported in comparable healthy subjects in Japan (0.008 mm/year)\textsuperscript{21} and Germany (0.007 mm/year).\textsuperscript{22} The Asymptomatic Carotid Artery Progression Research Group found an increase of 0.006 mm/year for a nondiabetic population with coronary risk factors.\textsuperscript{23} By contrast, in patients with type 2 diabetes an average annual increase of IMT 0.02 mm/year has been reported.\textsuperscript{24,25} In our study, the patients with IGT on placebo had an annual progression rate of 0.013 mm/year, which is twice as high as in healthy subjects despite a state-of-the-art treatment of associated hypertension and dyslipidemia. This underlines that IGT is a risk factor for atherosclerosis progression.

So far, only scarce information is available from controlled randomized trials on potentials of antihypertensive agents\textsuperscript{24,25} and oral antidiabetics\textsuperscript{26,27} on regression or nonprogression of IMT in patients with diabetes. The SECURE Study\textsuperscript{24} has examined the effect of 10 mg ramipril, an angiotensin-converting enzyme–inhibitor, on IMT with 4 years follow-up. The annual progression was reduced to 0.014 versus 0.022 \((P=0.033)\) in the placebo group. In the study by Hosomi et al,\textsuperscript{25} 48 patients with type 2 diabetes treated with enalapril were compared with 50 controls, with a follow-up time of 2 years. This trial did not use placebo. When controlled for cofactors affecting IMT, enalapril reduced IMT progression by 0.01 mm/year compared with the control group. A recently published long-term follow-up examination of the Epidemiology of Diabetes Interventions and Complications (EDIC)
This substudy was not powered for multiple testing of other possible determinants of IMT changes. Thus, the question remains how correction of postprandial hyperglycemia could protect the vessel wall. Recent publications have shown that reduction of postprandial hyperglycemia could decrease oxidative stress. Postprandial hyperglycemia deteriorates flow-mediated vasodilation and impairs endothelial nitric oxide release. Furthermore, an increase in nuclear factor κB (NFκB) was observed in hyperglycemic contact lens and myopia progression (CLAMP) investigation within 2 hours after increasing plasma glucose from 5 to 10 mmol/L. NFκB is known to stimulate leukocyte adhesion, inhibit nitric oxide mediated vasodilation, and exert procoagulatory effects. Postprandial hyperglycemia is also associated with impaired removal of triglyceride-rich lipoproteins and reduction of high-density lipoprotein reverse transport capacity. Whatever the mechanisms, acarbose remains an independent risk variable of vasoprotection.

In conclusion, acarbose treatment delays progression of IMT in subjects with IGT, a state of high risk for diabetes and atherosclerosis. This is the first placebo-controlled intervention subgroup analysis demonstrating that counterbalancing of postprandial hyperglycemia may be vasoprotective. We acknowledge the limitations of our single-center subgroup analysis, namely: (1) 10 patients in the acarbose and 7 in the placebo group were unavailable for the second IMT measurement; (2) this was an add-on protocol of a single STOP-NIDDM center, the primary objective of the multinational study being prevention of diabetes; (3) this substudy was not powered for multiple testing because of the small number of participants; and (4) our study provides no definite cause and effect relationship. However, a significant effect could be seen on the primary objective of this substudy (eg, progression of IMTmean) despite these limitations, and this is of clinical relevance.

### Table 2. Comparison of Endpoint Values in the Acarbose and Placebo Group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Acarbose</th>
<th>Placebo</th>
<th>Change</th>
<th>P</th>
<th>Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.3 (4.5)</td>
<td>28.9 (2.9)</td>
<td>−0.15 (1.50)</td>
<td>NS</td>
<td>0.28 (1.69)</td>
<td>NS</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.96 (0.08)</td>
<td>0.97 (0.1)</td>
<td>0.01 (0.06)</td>
<td>NS</td>
<td>0.03 (0.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>6.15 (0.94)</td>
<td>6.17 (1.12)</td>
<td>−0.29 (0.89)</td>
<td>0.001</td>
<td>−0.17 (1.00)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fasting</td>
<td>7.52 (1.98)</td>
<td>7.34 (1.51)</td>
<td>−1.42 (1.99)</td>
<td>&lt;0.001</td>
<td>−1.32 (1.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.53 (0.71)</td>
<td>5.46 (0.69)</td>
<td>−0.40 (0.63)</td>
<td>&lt;0.001</td>
<td>−0.27 (0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.89 (1.34)</td>
<td>5.88 (1.21)</td>
<td>−0.03 (1.11)</td>
<td>NS</td>
<td>−0.04 (1.29)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.15 (1.65)</td>
<td>2.55 (2.77)</td>
<td>−0.26 (1.51)</td>
<td>NS</td>
<td>−0.11 (2.14)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.28 (0.36)</td>
<td>1.24 (0.35)</td>
<td>−0.03 (0.20)</td>
<td>NS</td>
<td>−0.04 (0.25)</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>131.6 (13.3)</td>
<td>130.7 (14.5)</td>
<td>−6.5 (15.1)</td>
<td>0.001</td>
<td>−8.6 (17.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic</td>
<td>81.7 (7.1)</td>
<td>83.3 (7.9)</td>
<td>−3.8 (9.9)</td>
<td>0.023</td>
<td>−2.8 (9.8)</td>
<td>0.032</td>
</tr>
<tr>
<td>Lipid lowering drugs (No.)</td>
<td>32 (57.1%)</td>
<td>35 (59.3%)</td>
<td>14</td>
<td>NS</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure lowering drugs (No.)</td>
<td>26 (46.4%)</td>
<td>30 (50.8%)</td>
<td>11</td>
<td>NS</td>
<td>15</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean (SD). NS indicates nonsignificant data. *Test between the groups at endpoint show no significant differences; P shows significant difference between baseline and endpoint of the study, tested by Wilcoxon test. *Includes all nondiabetic patients.

**Figure 2.** Mean intima-media thickness at study entry and end of the study in the acarbose group (closed triangle) and placebo group (closed square). *P*<0.05.
TABLE 3. Changes of IMT and IMT<sub>max</sub> Between Baseline and Endpoint of the Study (Average Time of Treatment 3.9 Years)

<table>
<thead>
<tr>
<th></th>
<th>Acarbose (A)</th>
<th>Placebo (Pl)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Endpoint</td>
<td></td>
</tr>
<tr>
<td>IMT&lt;sub&gt;max&lt;/sub&gt; (mm)*</td>
<td>0.91 (0.18)</td>
<td>0.93 (0.18)</td>
<td></td>
</tr>
<tr>
<td>ΔIMT&lt;sub&gt;max&lt;/sub&gt; (mm)†</td>
<td>0.02 (0.07)</td>
<td>0.05 (0.06)</td>
<td>0.207</td>
</tr>
<tr>
<td>ΔIMT&lt;sub&gt;max&lt;/sub&gt;/year (mm/y)†</td>
<td>0.007 (0.019)</td>
<td>0.013 (0.018)</td>
<td>0.021</td>
</tr>
<tr>
<td>IMT&lt;sub&gt;max&lt;/sub&gt; (mm)*</td>
<td>1.03 (0.24)</td>
<td>1.05 (0.23)</td>
<td>0.044</td>
</tr>
<tr>
<td>ΔIMT&lt;sub&gt;max&lt;/sub&gt; (mm)†</td>
<td>0.02 (0.08)</td>
<td>0.03 (0.08)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates nonsignificant data.

* Differences between baseline and endpoint tested by Wilcoxon test.
† Differences between the groups tested by Mann-Whitney U test.

Acknowledgments
The STOP-NIDDM trial was funded by an unrestricted research grant from Bayer AG. The sponsor provided the infrastructure and staff for data monitoring and collection, but had no role in study design, data analysis, data interpretation, or in writing this paper.

References


Acarbose Slows Progression of Intima-Media Thickness of the Carotid Arteries in Subjects with Impaired Glucose Tolerance

Markolf Hanefeld, Jean Louis Chiasson, Carsta Koehler, Elena Henkel, Frank Schaper and Theodora Temelkova-Kurktschiev

Stroke. published online April 8, 2004; Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2004/04/08/01.STR.0000125864.01546.f2.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/