Effect of Niacin on Lipid and Lipoprotein Levels and Glycemic Control in Patients With Diabetes and Peripheral Arterial Disease The ADMIT Study: A Randomized Trial

Marshall B. Elam, PhD, MD
Donald B. Hunninghake, MD
Kathryn B. Davis, PhD
Rekha Garg, MD, MS
Craig Johnson, MS
Debra Egan, MSc, MPH
John B. Kostis, MD
David S. Sheps, MD
Eliot A. Brinton, MD
for the ADMIT Investigators

The Arterial Disease Multiple Intervention Trial (ADMIT) was a prospective, placebo-controlled study. ADMIT evaluated the safety and efficacy of a combination of high-density lipoprotein (HDL)–raising, antioxidant vitamin, and low-dose warfarin therapy to modify multiple atherosclerotic vascular disease risk factors in subjects with peripheral arterial disease. Niacin was selected as the intervention in ADMIT to increase HDL levels because it is effective in increasing HDL cholesterol (HDL-C), which frequently accompany diabetes, current guidelines do not recommend use of niacin in patients with diabetes because of concerns about adverse effects on glycemic control; however, this is based on limited clinical data.

Objective To determine the efficacy and safety of lipid-modifying dosages of niacin in patients with diabetes.

Design and Setting Prospective, randomized placebo-controlled clinical trial conducted in 6 clinical centers from August 1993 to December 1995.

Participants A total of 468 participants, including 125 with diabetes, who had diagnosed peripheral arterial disease.

Interventions After an active run-in period, participants were randomly assigned to receive niacin (crystalline nicotinic acid), 3000 mg/d or maximum tolerated dosage (n=64 with diabetes; n=173 without diabetes), or placebo (n=61 with diabetes; n=170 without diabetes) for up to 60 weeks (12-week active run-in and 48-week double-blind).

Main Outcome Measures Plasma lipoprotein, glucose, hemoglobin A1c (HbA1c), alanine aminotransferase, and uric acid levels; hypoglycemic drug use; compliance; and adverse events, in patients with diabetes vs without who were receiving niacin vs placebo.

Results Niacin use significantly increased HDL-C by 29% and 29% and decreased triglycerides by 23% and 28% and low-density lipoprotein cholesterol (LDL-C) by 8% and 9%, respectively, in participants with and without diabetes (P<.001 for niacin vs placebo for all). Corresponding changes in participants receiving placebo were increases of 0% and 2% in HDL-C and increases of 7% and 0% in triglycerides, and increases of 1% and 1% in LDL-C. Glucose levels were modestly increased by niacin (8.7 and 6.3 mg/dL [0.4 and 0.3 mmol/L]; P=.04 and P<.001) in participants with and without diabetes, respectively. Levels of HbA1c were unchanged from baseline to follow-up in participants with diabetes treated with niacin. In participants with diabetes treated with placebo, HbA1c decreased by 0.3% (P=.04 for difference). There were no significant differences in niacin discontinuation, niacin dosage, or hypoglycemic therapy in participants with diabetes assigned to niacin vs placebo.

Conclusions Our study suggests that lipid-modifying dosages of niacin can be safely used in patients with diabetes and that niacin therapy may be considered as an alternative to statin drugs or fibrates for patients with diabetes in whom these agents are not tolerated or fail to sufficiently correct hypertriglyceridemia or low HDL-C levels.

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EFFECT OF NIACIN ON DIABETES

cacy of niacin use in that patient population. Of 468 ADMIT participants, 125 patients with diabetes were included. This article describes the effect of niacin treatment on plasma lipoproteins and glycemic status in ADMIT participants with diabetes.

METHODS
Study Design and Organization
The design and rationale of ADMIT have been reported previously. ADMIT was a National Heart, Lung, and Blood Institute–sponsored multicenter, randomized, placebo-controlled trial designed to evaluate the feasibility of recruitment of subjects with peripheral arterial disease, and their adherence and response to 3 interventions. These interventions included niacin, antioxidant vitamins, and low-dose warfarin, or corresponding placebo treatments, administered in a $2 \times 2 \times 2$ factorial design.

Participants were enrolled at 6 clinical centers and the data were collected and analyzed by the data coordinating center (Axio Research Corp, Seattle, Wash). An independent data and safety monitoring board kept track of the progress of the trial. The protocol and consent form were approved by the institutional review board at each clinical center. Written informed consent was obtained from all participants prior to enrollment into the study.

Eligibility Criteria
This article presents information on 125 ADMIT enrollees who met study criteria for diabetes at the first study visit. Diabetes was defined as either a history of diabetes treated by diet or medication or a hemoglobin A1c ($HbA_1c$) level higher than 7% at the baseline visit. Inclusion and exclusion criteria for ADMIT have been previously presented. ADMIT participants had either a reduced ankle brachial index of less than 0.85 or a history of prior lower-extremity revascularization. Subjects were excluded from ADMIT for poorly controlled diabetes ($HbA_1c > 9.0\%$), a history of diabetic ketoacidosis or coma, renal disease, liver disease, gout, hyperuricemia, peptic ulcer disease, history of myositis, or untreated hypothyroidism. Participants with marked hypertriglyceridemia ($> 400 \text{ mg/dL}$) for whom randomization to niacin placebo would not have been appropriate, or whose low-density lipoprotein (LDL) level was not likely to be controlled by niacin and/or pravastatin (baseline LDL cholesterol [LDL-C] $> 190 \text{ mg/dL} \ (4.9 \text{ mmol/L})$) were also excluded from participation.

Run-in and Randomization
All participants underwent an active niacin run-in, during which crystalline (immediate release) niacin tablets (Niacor, Upsher-Smith, Minneapolis, Minn) were dispensed at 4-week intervals in increasing doses of 50, 250, and 500 mg twice daily.

Participants who successfully completed the active niacin run-in were then randomly assigned to receive a combination of active niacin, antioxidant vitamin cocktail, and warfarin or their respective placebo treatments. Randomization into each of the 8 possible drug combinations (of the $2 \times 2 \times 2$ factorial design) was performed independently at each clinical center using block sizes of 8, 16, or 24 selected at random. At randomization, the dosage of niacin or its placebo was increased to 750 mg twice daily with subsequent increases to 1000 mg and then 1500 mg twice daily at 6-week intervals, or until maximum tolerable dose was reached. Participants were to receive 3000 mg/d or the maximum tolerated dosage for the remainder of the 48-week double-blind treatment period.

Fasting blood glucose levels were monitored at 6-week intervals throughout the follow-up period. If the fasting blood glucose level was higher than 189 mg/dL (10.5 mmol/L), the $HbA_1c$ level was then measured, and if this was higher than 10.0%, the dosage of niacin (or its placebo) was down-titrated. Niacin down-titration was also performed if any routine $HbA_1c$ level (measured at study weeks 6, 24, and 48) was higher than 10.0%. The dosage of niacin (or its placebo) was also down-titrated in any participant whose uric acid level was higher than 595 µmol/L.

Among niacin placebo tablets, 15% contained 50 mg of active niacin. This low dose of niacin was given to cause intermittent flushing in the participants taking niacin placebo to minimize the risk of inadvertent subject unblinding. The average daily dose of niacin in the placebo group was approximately 43 mg/d at maximum, a dosage not known to have a significant effect either on lipids or on the other study parameters. Participants whose LDL-C levels remained above 130 mg/dL (3.4 mmol/L) while taking the maximum dose of niacin or placebo were provided with open-label pravastatin of 10 to 20 mg/d as needed to achieve LDL-C levels of less than 115 mg/dL (3 mmol/L). Thus, pravastatin was given in a nonrandom manner to participants in both the niacin and niacin-placebo groups. To focus on the effects of niacin monotherapy, we only report lipid results from the period prior to pravastatin therapy (first 30 weeks of the study). In contrast, the other end points are reported herein for the full 60 weeks of the study to include all available safety data.

Laboratory Methods
Lipoprotein profiles (total cholesterol, HDL-C, and total triglycerides) were measured on plasma samples, obtained after an overnight fast, using the Centers for Disease Control and Prevention’s standardized methods and calibrator standards at the Lipid Analytic Laboratory, Wake Forest University School of Medicine, Winston-Salem, NC. LDL-C was calculated as described by Friedewald et al. $HbA_1c$ level was measured by high-pressure liquid chromatography (Laboratory Corporation of America, Burlington, NC). Plasma or serum levels of glucose, uric acid, aspartate aminotransferase, and alanine aminotransferase were measured by standard autoanalyzer methods in the local clinical laboratories.

Statistical Analyses
The effect of concurrent treatment with either warfarin or antioxidant vita-
mins on the lipoprotein and glycemic response to niacin was examined by longitudinal regression analysis. There was no interaction between the effect of niacin and the other treatments on lipoproteins or glycemic control. This report therefore presents data analyzed by niacin treatment assignment only for participants both with and without diabetes. The overall study results, including results of warfarin and antioxidant treatment on the variables of interest for those interventions, will be reported elsewhere.

Descriptive statistics are reported as mean (SD) for continuous variables. Univariate comparisons were made by 2-sided t tests, χ² tests, and Fisher exact tests as appropriate. The follow-up effects of niacin treatment on plasma lipids and lipoproteins, glycemic status, and other safety parameters were each analyzed with a longitudinal regression model using generalized estimating equations with random effects to take account of the within-person correlation between visits. The baseline value of the parameter, niacin treatment assignment, diabetes, obesity, follow-up visit number, and the interaction of diabetes, niacin assignment, and obesity were included as covariates. The initial screening value or, for lipoproteins, the mean of the first 2 screening values was used as the baseline value. Follow-up visit number was modeled both as a linear term and as an indicator variable to examine nonlinear effects. Models were reduced by backward elimination to the set of variables for which P<.05. Analyses were performed and verified using STATA statistical software (release 5.0, STATA Corp, College Station, Tex).

RESULTS

Patient Characteristics

Of the 468 ADMIT participants, 125 (27%) met study criteria for diabetes (TABLE 1 and FIGURE 1). ADMIT participants with diabetes were slightly older, had higher body mass indices, higher HbA1c levels, and lower uric acid levels than those without diabetes. Participants with diabetes were more likely to be black and were less likely to be current cigarette smokers. Despite comparable ankle brachial index values, participants with diabetes were less likely to have had prior vascular procedures or symptoms of peripheral arterial disease. With the notable exception of HDL-C, which was lower among participants with diabetes, plasma lipids and lipoproteins at baseline were comparable in the 2 groups. When baseline characteristics were compared by niacin treatment assignment, participants with diabetes who were randomized to receive niacin placebo were older than those who received niacin (68 vs 66 years; P=.04). There were no other significant differences in baseline characteristics between niacin and niacin placebo groups in participants either with or without diabetes.

Effect of Niacin on Plasma Lipid and Lipoprotein Levels

During the 12-week active niacin run-in period, a small decrease in total and LDL-C and triglycerides and increased HDL-C was detected in all participants as niacin was increased from 100 mg/d to 1000 mg/d (FIGURE 2). After randomization, participants both with and without diabetes who were receiving active niacin experienced a progressive further decrease in total and LDL-C as nia-
EFFECT OF NIACIN ON DIABETES

Figure 1. Flow Diagram of Study

Only the niacin arms of the ADMIT trial are shown.

Effect of Niacin on Glycemic Status and Safety Parameters

Fasting glucose and HbA\textsubscript{1c} levels were monitored as indices of glycemic status during niacin treatment. TABLE 3 presents the glucose, HbA\textsubscript{1c}, and uric acid levels at baseline and the average of 6 postrandomization values. Niacin use resulted in a small but statistically significant increase in average glucose levels in participants both with (8.1 mg/dL [0.4 mmol/L]) and without diabetes (6.3 mg/dL [0.3 mmol/L]; \(P=0.04\) and \(P<0.001\), respectively). The effect of niacin on glucose was greater in participants with diabetes than without (\(P=0.04\)). Figure 3 depicts the course of glucose values during the niacin treatment period. In subjects randomized to receive niacin, there was a transient increase in glucose as the niacin dosage was increased to 3000 mg/d; however, plasma glucose subsequently returned to baseline with continued niacin therapy (Figure 3). Niacin use also resulted in a small but statistically significant difference in change in HbA\textsubscript{1c} levels (0.3%) in participants with diabetes treated with niacin compared with those receiving niacin placebo (\(P=0.04\); Table 3). Niacin use had no effect on HbA\textsubscript{1c} levels in participants without diabetes (\(P=0.38\)). The response of neither HbA\textsubscript{1c} nor glucose levels to niacin was significantly affected by obesity.

Niacin increased uric acid levels over baseline values (\(P\leq0.01\)) similarly in both participants with and without diabetes (interaction, \(P=0.19\); Table 3). During follow-up, uric acid levels were higher than 595 \(\mu\)mol/L (range, 613-684 \(\mu\)mol/L) for 3 of 61 participants with diabetes assigned to niacin (5%) and for 1 of 59 participants with diabetes assigned to placebo (2%). The dose was lowered for 1 participant with diabetes assigned to niacin, but none had niacin discontinued. Among participants without diabetes, 4 had the niacin dosage reduced for uric acid levels exceeding the arbitrary limit of 595 \(\mu\)mol/L and niacin was discontinued in 1 participant. One participant with diabetes assigned to niacin and 1 without diabetes assigned to placebo had niacin discontinued due to possible gout.

Mean plasma alanine aminotransferase level was not significantly changed compared with baseline values (\(P=0.09\)) nor was it higher in niacin-treated subjects compared with niacin-placebo treatment (\(P=0.08\)). Further, plasma alanine aminotransferase was not higher with niacin treatment in participants with diabetes compared with those without (interaction, \(P=0.38\)). The level of alanine aminotransferase was more than 3 times above the normal range (0-35 U/L) during follow-up for 2 participants with diabetes and 3 without, all of whom were taking niacin (\(P=0.03\)). One participant without diabetes had niacin therapy discontinued because of an elevated alanine aminotransferase level.

The effect of niacin on plasma glucose and HbA\textsubscript{1c} levels could have been modified if hypoglycemic therapy was adjusted by primary caregivers in response to receiving reports of abnormal laboratory results. We therefore examined the frequency of insulin use and average dose of insulin used at baseline and at the final follow-up visit for...
participants with diabetes randomized to niacin vs those randomized to niacin placebo. Insulin use was increased by 13% in participants with diabetes randomized to niacin vs 4% in those randomized to niacin placebo (P = .09). For patients using insulin at both first and final follow-up visits (n = 26), there was no effect of niacin use on insulin dose (P = .68). There was also no significant change in use of oral hypoglycemic agents as a result of niacin use (P = .94).

Niacin use might also have resulted in development of diabetes in patients who did not have diabetes at entry into ADMIT. Therefore, we looked for new users of insulin or oral hypoglycemic agents among ADMIT participants who did not have diabetes at the baseline visit. Among the 173 participants randomized to niacin treatment who did not have diabetes at baseline, only 1 reported use of oral hypoglycemic therapy at subsequent follow-up visits. No niacin users without diabetes reported insulin use during follow-up, nor did any participants without diabetes who were randomized to niacin placebo report subsequent use of either insulin or oral hypoglycemic therapy.

Adherence to niacin therapy was comparable in ADMIT participants with and without diabetes, with niacin discontinuation rates of 23% and 16%, respectively (P = .20). Niacin discontinuation was also comparable in participants with diabetes randomized to receive active niacin and niacin placebo (23% vs 18%, respectively; P = .46). Glucose intolerance was listed as the reason for niacin discontinuation in 4 participants with diabetes (6%) who were randomized to active niacin and in 2 participants with diabetes (3%) randomized to niacin placebo (P = .44). Other reasons for discontinuation of niacin in participants with diabetes included comorbid vascular disease, patient request, and acanthosis nigricans. The protocol specified down-titration of niacin if HbA1c level exceeded 10%. This HbA1c limit was exceeded after randomization in 18 participants with diabetes, 10 of whom were assigned to niacin and 8 assigned to placebo. The average dose of niacin at week 18 was 2553 mg in participants with diabetes, and was 2626 mg in participants without diabetes (P = .44).

**COMMENT**

Lipid-modifying therapy is recommended in both peripheral arterial disease and diabetes to reduce the risk of atherosclerotic vascular disease.\textsuperscript{13,16} Although current guidelines focus on

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**Figure 2. Effect of Niacin on Plasma Lipoproteins in Participants With and Without Diabetes**

Data are expressed as mean plasma lipoprotein levels in mg/dL. During the 12-week active niacin run-in, all participants received niacin (maximal dose, 1000 mg/d). At week 0, participants were randomly assigned in double-blind fashion to receive niacin (closed circles, maximum dose, 3000 mg/d) or its placebo (open circles). Niacin treatment resulted in significant and equal reductions in plasma triglycerides, cholesterol, low-density lipoprotein cholesterol, and equivalent increase in high-density lipoprotein cholesterol in participants with and without diabetes (P < .001). To convert total, low-density lipoprotein, and high-density lipoprotein cholesterol from mg/dL to mmol/L, multiply by 0.0259. To convert triglycerides from mg/dL to mmol/L, multiply by 0.0113.

[Diagram of lipoprotein levels during and after niacin treatment for participants with and without diabetes.]

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LDL-C as a risk factor, hypertriglyceridemia and low HDL-C are common in the dyslipidemia associated with type 2 diabetes mellitus,10,11,13 and contribute to the increased risk of arterial vascular disease in subjects with diabetes. Despite its proven ability to increase HDL and lower triglycerides, the use of niacin has been discouraged in patients with diabetes,10-13 largely due to reports of deterioration of glycemic control in subjects both with and without diabetes who were treated with niacin.3,17-19 The effect of niacin on glycemic status in patients with diabetes has, however, not previously been assessed in the setting of a randomized, placebo-controlled trial. We therefore decided to assess the safety and efficacy of niacin use in ADMIT participants with diabetes.

This report demonstrates that immediate-release niacin is equally effective in modifying lipid and lipoprotein levels in subjects with and without diabetes. We also confirmed previous observations of increased plasma glucose levels in patients both with and without diabetes and treated with lipid-modifying doses of niacin; however, the effects observed over 60 weeks of follow-up were relatively modest and did not result in significantly increased rates of niacin discontinuation or alterations in hypoglycemic therapy. It is important to note, however, that the results observed here might not reflect those obtained with other niacin formulations, and that glycemic therapy may have been modified in individual patients as a result of niacin treatment.

Previous reports of niacin-induced glucose intolerance are derived largely from uncontrolled case reports involving small numbers of subjects.17-20 Many of these earlier studies were performed on subjects without diabetes.18-20 Of studies conducted on subjects with diabetes, some,3,17 but not all,21,22 reported worsened glycemic control with niacin treatment. In addition, in these studies, glucose tolerance was examined within 2 to 8 weeks

Table 2. Effect of Niacin on Lipid and Lipoprotein Levels From Baseline to Week 18 by Treatment Group for Participants With or Without Diabetes

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<th>With Diabetes†</th>
<th>Without Diabetes‡</th>
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<tr>
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<td>Baseline Week 18 % Change P Value</td>
<td>Baseline Week 18 % Change P Value</td>
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<tr>
<td>Cholesterol, mg/dL§</td>
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<tr>
<td>Placebo 217 (32) 220 (41) 1.4 &lt;.001</td>
<td>215 (27) 217 (32) 0.9 &lt;.001</td>
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<tr>
<td>Niacin 207 (29) 198 (31) −4.3 &lt;.001</td>
<td>214 (27) 199 (31) −7.0 &lt;.001</td>
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<td>Triglycerides, mg/dL</td>
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<tr>
<td>Placebo 197 (87) 210 (132) 6.6 &lt;.001</td>
<td>166 (80) 166 (89) 0 &lt;.001</td>
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<tr>
<td>Niacin 176 (89) 136 (79) −22.7 &lt;.001</td>
<td>176 (81) 126 (64) −28.4 &lt;.001</td>
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<td>High-density lipoprotein cholesterol, mg/dL§</td>
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<tr>
<td>Placebo 39 (9) 39 (9) 0 &lt;.001</td>
<td>43 (12) 44 (9) 2.3 &lt;.001</td>
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<tr>
<td>Niacin 38 (10) 49 (14) 28.9 &lt;.001</td>
<td>41 (12) 53 (18) 29.3 &lt;.001</td>
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<tr>
<td>Low-density lipoprotein cholesterol, mg/dL§</td>
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<tr>
<td>Placebo 138 (28) 139 (34) 0.7 &lt;.001</td>
<td>140 (25) 141 (28) 0.7 &lt;.001</td>
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<tr>
<td>Niacin 133 (27) 122 (29) −8.3 &lt;.001</td>
<td>133 (24) 121 (29) −9.0 &lt;.001</td>
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</table>

*Values are expressed as mean (SD) unless otherwise indicated. Only participants for whom baseline and week 18 lipoprotein values are available are included in this table.
†There were 55 participants in the placebo group and 49 in the niacin group.
‡There were 142 participants in the placebo group and 156 in the niacin group.
§To convert to mmol/L, multiply by 0.0259.

Table 3. Effect of Niacin on Average Plasma Glucose, Hemoglobin A1c, and Uric Acid in Participants With or Without Diabetes

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<th>With Diabetes†</th>
<th>Without Diabetes‡</th>
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<tr>
<td></td>
<td>No. of Participants Baseline Follow-up† Change‡ P Value</td>
<td>No. of Participants Baseline Follow-up† Change‡ P Value</td>
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<tr>
<td>Glucose, mg/dL§</td>
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<tr>
<td>Placebo 59 165 (54) 157 (47) −8.7 .04</td>
<td>161 96 (20) 97 (13) 0.5 (1.1) ≤.001</td>
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<tr>
<td>Niacin 61 165 (63) 173 (61) 8.1</td>
<td>169 95 (13) 102 (14) 6.3 (0.7)</td>
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<tr>
<td>Hemoglobin A1c, %</td>
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<tr>
<td>Placebo 60 7.7 (1.4) 7.4 (1.2) −0.3 .05</td>
<td>164 5.3 (0.6) 5.4 (0.6) 0.1 (0.4) .38</td>
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<tr>
<td>Niacin 61 7.8 (1.5) 7.8 (1.3) 0</td>
<td>167 5.3 (0.6) 5.4 (0.7) 0.1 (0.5)</td>
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<td>Uric acid, µmol/L</td>
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<tr>
<td>Placebo 56 333 (89) 333 (71) 0 &lt;.001</td>
<td>153 380 (83) 369 (77) −12 &lt;.001</td>
<td></td>
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<tr>
<td>Niacin 58 339 (71) 386 (95) 47</td>
<td>162 375 (87) 428 (83) 53</td>
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</table>

*Values are expressed as mean (SD).
†Postrandomization values for glucose and uric acid were taken at weeks 6, 12, 18, 24, 36, and 48; hemoglobin A1c, weeks 6, 24, and 48.
‡Difference between the baseline value and the mean follow-up value.
§To convert to mmol/L, multiply by 0.0555.
following rapid institution of lipid-lowering doses of niacin (3-6 g/d). The glucose intolerance following niacin therapy in these reports may reflect short-term effects from rapid institution of lipid-lowering doses of niacin. In the present study we, in fact, observed a transient increase in plasma glucose as niacin was titrated to its maximum dose.

The only other report that includes a number of subjects comparable with our own is a retrospective study of niacin use at a Department of Veterans Affairs Medical Center. This study reported higher niacin discontinuation rates overall and higher rates of discontinuation due to poor glycemic status in patients with diabetes treated with a slow-release niacin preparation. In that study, niacin was administered without blinding or use of placebo controls. Given the current perception that niacin significantly worsens glycemic status, it is possible that physician bias may have influenced the niacin discontinuation rate. These findings may also reflect a difference between sustained release and crystalline (immediate release) niacin and/or the reliance on blood glucose rather than HbA1c level for clinical decision making.

Although the effect of niacin treatment on glycemic status overall was modest in ADMIT, our findings do not preclude the possibility that its use, particularly at doses higher than those used here, or using preparations other than crystalline niacin, may significantly adversely affect glycemic control in individual patients with diabetes. Therefore, glycemic status should be carefully monitored during niacin therapy in patients with diabetes, and the dose modified or discontinued if glycemic status clearly deteriorates. In addition, plasma insulin was not measured nor was insulin resistance formally assessed in this study. Several studies have shown decreased glucose tolerance and increased plasma insulin levels in subjects without diabetes following short-term niacin treatment. A more recent study, however, has shown minimal effect of short-term niacin treatment on insulin levels and glucose use in normal volunteers. It is also possible that the changes in glycemic indices observed here, although relatively modest, might offset some of the cardiovascular risk reduction with niacin.

Recently published guidelines for treatment of dyslipidemia in type 2 diabetes mellitus recommend aggressive lipid modification using statin drugs or fibrates. Although LDL-C is recommended as the primary target of therapy, it is recognized that hypertriglyceridemia and decreased HDL-C are highly prevalent in type 2 diabetes mellitus, and are associated with increased risk of atherosclerotic vascular disease. Niacin effectively reduces plasma triglycerides by reducing hepatic production of very LDL, and increases HDL cholesterol by up to 30%, possibly by reducing hepatic removal of apolipoprotein A-I. Niacin also reduces plasma LDL-C by 10% to 15% and normalizes LDL particle size distribution. Although the LDL-C-lowering effect of niacin is modest compared with that of statin drugs, niacin has a greater effect on HDL-C, triglycerides, and lipoprotein (a). For patients with diabetes who have hypertriglyceridemia or low HDL-C or both, gemfibrozil has been shown to be effective and does not adversely affect glycemic status; however, not all patients tolerate gemfibrozil therapy. Furthermore, in cases of extreme hypertriglyceridemia, combination therapy with gemfibrozil and niacin may be required to reduce triglycerides to acceptable levels.

There is limited information about which of the currently available lipid-modifying interventions offer the greatest benefit for patients with diabetes in terms of reduced cardiovascular morbidity and mortality. A recent post-hoc analysis of the Scandinavian Simvastatin Survival Study (4-S) indicates that participants with diabetes experienced a significant reduction in coronary heart disease events with simvastatin therapy. In the Helsinki Heart study, participants with diabetes experienced a 60% reduction in coronary heart disease events with gemfibrozil therapy. This decrease was not statistically significant, however, because of the small number of participants with diabetes in that study. Similarly, in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), participants with diabetes experienced coronary heart disease event reduction with gemfibrozil equivalent to that observed in the entire cohort. Although the effect of niacin on cardiovascular morbidity and mortality has not been demonstrated specifically in diabetes, niacin therapy has been shown to reduce vascular disease morbidity and mortality in general populations of subjects with atherosclerotic vascular disease.

Despite current recommendations against use of niacin in diabetes, the present study demonstrates that lipid-modifying doses of immediate-release niacin can be used safely in patients with stable, controlled, type 2 diabetes mellitus. Niacin therapy may be con-
considered as an alternative to statin drugs or fibrates in patients with diabetes in whom these agents are not tolerated, or in whom they fail to sufficiently correct hypertriglyceridemia or low HDL-C. Conversely, in view of the absence of an effect on glycemic status of statin drugs or fibrates, these agents should still be considered first-line therapy in diabetic dyslipidemia.

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Author Affiliations: University of Tennessee Health Science Center (Dr Elam), Memphis Veterans Affairs Medical Center (Dr Elam), Memphis, Tenn; University of Minnesota, Minneapolis (Dr Hunninghake); University of Washington (Dr Davis), Axio Research Corp (Dr Davis and Mr Johnson), Seattle, Wash; Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, MD (Dr Garg and Ms Egan); Robert Wood Johnson School of Medicine, Robert Wood Johnson University, New Brunswick, NJ (Dr Kostis); University of North Carolina, Chapel Hill (Dr Sheps); and Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC (Dr Brinton). Dr Garg is now with Eli Lilly Co; Dr Sheps is now with the University of Florida College of Medicine, Gainesville; and Dr Brinton is now with the University of Arizona College of Medicine, Tucson.

REFERENCES


