# Lipid-Lowering Drugs Cut Diabetic Neuropathy

***If the results are confirmed, one expert says this sets the stage for earlier diagnosis and treatment.***

BY PATRICE WENDLING
*Chicago Bureau*

CHICAGO — Lipid-lowering therapy was associated with a significant reduction in the risk of developing peripheral sensory neuropathy in a large Australian observational investigation involving adults with type 2 diabetes mellitus.

Peripheral neuropathy, the most common form of nerve damage caused by diabetes, affects roughly half of those with the disease.

Animal studies have shown that both statins and fibrates may protect against nerve damage, but clinical studies have also linked their use with reversible clinical neuropathy.

The study produced no evidence that use of either statins or fibrates increased the risk of developing neuropathy or amputations, principal investigator Dr. Timothy Davis said at the annual scientific sessions of the American Diabetes Association.

He suggested that previous reports may have been coincidental, in that the individuals were developing neuropathy anyway, or that there may be a small number of patients who were sensitive to the drug.

"Statins and fibrates are relatively safe, but still have a side-effect profile that needs to be respected," he said. However, statins are typically a first-line drug because of strong evidence of their cardiovascular disease prevention benefits.

The ADA recommends statins for individuals with diabetes aged 40 years and older with a total cholesterol level greater than 135 mg/dL and no overt cardiovascular disease; for those younger than age 40 years with no overt cardiovascular disease, but at increased risk; and for any patient with diabetes and overt cardiovascular disease.

Dr. Davis and colleagues at the University of Western Australia in Fremantle used the Michigan Neuropathy Screening Instrument to determine the prevalence and incidence of peripheral neuropathy in two populations. The first was a cross-sectional sample of 1,294 patients with type 2 diabetes recruited to the Fremantle Diabetes Study between 1993 and 1996.

At admission, fibrates and statins were used by 3.5% and 6.8% of patients, respectively. Gemfibrozil was the fibrate used, and the statins in use were atorvastatin, simvastatin, and pravastatin.

Patients' mean age was 64 years, 49% were male, and 31% had peripheral neuropathy. The median diabetes duration was 4 years.

In multiple logistic regression analysis, older age, longer diabetes duration, central adiposity, increasing height, higher fasting plasma glucose levels, higher systolic blood pressure, higher urinary albumin-to-creatinine ratios, and indigenous racial background were all independently associated with prevalent peripheral neuropathy.

Fibrate use was associated with a 70% reduction in neuropathy, but the use of statins was not associated with a significant reduction in neuropathy, Dr. Davis said.

The investigators then evaluated a longitudinal subgroup of 531 people who had undergone six comprehensive annual health assessments by November 2001. Fibrate and statin use increased to 10.4% and 36.5% during the 5 years of follow-up. Gemfibrozil continued to be the primary fibrate used, although some patients had begun to use fenofibrate. Atorvastatin was the predominant statin. In all, 26% of patients had peripheral neuropathy at baseline.

In a Cox proportional analysis that controlled for a variety of confounding variables, including changes in hemoglobin $A_{1c}$ levels, fibrates and statins reduced the risk of developing neuropathy by 48% and 35%, respectively.

Analysis of the data also indicated that the beneficial effects of the lipid-lowering drugs were independent of each other and may work through different mechanisms.

"It's possible, because of the independent effect of these drugs, that combination therapy with these drugs could have an additive effect," Dr. Davis said.

During a press briefing at the meeting, Dr. Aaron I. Vinik, director of the Diabetes Research Institute at Eastern Virginia Medical School, Norfolk, said the data "may change the way clinicians look at neuropathy in the future, and may even change the way we think about treating neuropathy." The only two drugs approved in the United States for the treatment of neuropathy are for pain relief, and neither addresses the underlying pathogenic disorder of the condition, he said.

Dr. Paul Jellinger, past president of American Association of Clinical Endocrinologists, called the data intriguing, but emphasized that whereas lipid-lowering drugs may prevent the occurrence of neuropathy, they do not reverse it.

If lipid-lowering drugs are to be used for neuropathy prevention, they would have to be introduced early in the disease process, he said.

"To me, the message here is to confirm this evidence with prospective trials, and, if confirmed, to use this as an additional mandate to diagnose impaired glucose tolerance earlier and to consider applying statin or fibrate therapy independent of their lipid levels," said Dr. Jellinger, who is in private practice in Hollywood, Fla. ■

# Self-Monitoring Falls Short for Type 2 Diabetics Not On Insulin

BY PATRICE WENDLING
*Chicago Bureau*

CHICAGO — Self-monitoring of blood glucose did not significantly improve hemoglobin $A_{1c}$ levels in a trial of patients with type 2 diabetes not receiving insulin.

"Although patients with type 1 and insulin-treated type 2 diabetes benefit from self-monitoring, this trial does not provide convincing evidence of benefit in non–insulin-treated type 2 diabetes," lead researcher Dr. Andrew J. Farmer said at the annual scientific sessions of the American Diabetes Association. His team conducted the trial, known as DiGEM (Diabetes Glycaemic Education and Monitoring).

Health costs and quality of life data have yet to be presented from the three-arm, randomized, parallel group trial of 453 patients managed in U.K. general practices with diet and oral hypoglycemic agents alone.

"In the meantime, the results do not support recommendations for routine self-monitoring of blood glucose in reasonably well-controlled patients with type 2 diabetes," said Dr. Farmer, division of public health, University of Oxford (England).

The trial had an 80% power at a 5% level of significance to detect the primary outcome—a change in hemoglobin $A_{1c}$ of 0.5 percentage points—among three groups. Patients were randomized to a control group with no blood glucose monitors and 3 monthly hemoglobin $A_{1c}$ measurements; a less intensive self-monitoring group with the results interpreted by a nurse practitioner in addition to usual care; and a more intensive self-monitoring group that was given the usual care plus training in interpreting and applying the results in relation to diet, physical exercise, and medication regimens.

Patients in the more intensive group had more latitude regarding when they could test their glucose, and averaged 6-7 tests per week. Those in the less intensive group were told to use their meters before meals and averaged 5-6 tests per week, Dr. Farmer explained.

There were 152 in the control group, 150 in the less intensive self-monitoring group, and 151 in the more intensive self-monitoring group.

At admission, the average duration of diabetes was 3 years, and the mean $HbA_{1c}$ was 7.5%. Overall, 67.5%-73% of patients in each of the groups had had no prior experience with self monitoring.

At 12 months, the mean $HbA_{1c}$ value was 0.14 percentage points lower in the less intensive self-monitoring group than in the control group, and 0.17 percentage points lower in the more intensive self-monitoring group than in the control group. The differences between groups were not statistically significant.

Among secondary outcomes, there were no significant differences between groups in blood pressure control. Surprisingly, there was a significant difference between groups in change from baseline of total cholesterol, with a decrease of 0.14 mmol/L in the control group, 5.2 mmol/L in the less intensive group, and 5.4 mmol/L in the more intensive group.

**'If you give patients instructions on how to modify their oral hypoglycemia or give their physicians the opportunity to modify [it], self-monitoring of blood glucose may be very valuable in this population.'**

Hypoglycemia was reported by patients in all three arms of the trial, with the number of reports significantly higher in the self-monitoring groups than in the control group. This finding may be attributable to increased awareness of low blood glucose more than a true biochemical difference arising from the use of the monitor, Dr. Farmer said.

Over the 12 months of the trial, between one-third and one-half of patients stopped using their monitors. In all, 57 patients (13%) were lost to follow-up.

Dr. Farmer speculated that for many patients, the small day-to-day improvement in glucose results may have been obscured by the measurement variation from day to day, and may have contributed to the reason some people gave up. "It's well recognized that, in some people, when the readings don't vary—or seem uninterpretable—[there is] a loss of motivation," he said.

Interpretation of the DiGEM data will be hotly debated, in part because of the financial implications of self-monitoring on health care agencies and insurers.

The study moves the field ahead, but leaves some questions unanswered, Dr. Bernard Zinman, director of diabetes care at Mount Sinai Hospital, Toronto, said in an interview.

"This study proves definitively that self-monitoring of blood glucose does not seem to have an impact on changing an individual's lifestyle … and therefore [on improving] control," Dr. Zinman said.

But he added that the investigation didn't address the question of whether, "if you give patients instructions on how to modify their oral hypoglycemia or give their physicians the opportunity to modify [it], self-monitoring of blood glucose may be very valuable in this population." ■