Increased Mortality Seen With HbA_{1c} Below 7.5%

BY MIRIAM E. TUCKER

Hemoglobin A_{1c} values below 7.5% were associated with increased all-cause mortality and cardiovascular events in patients with type 2 diabetes in an analysis of nearly 48,000 patients in a U.K. general practice database.

If confirmed, the findings suggest that diabetes guidelines might need revision to include a definition of a minimum HbA_{1c} value, Dr. Craig J. Currie of Cardiff (Wales) University and his associates said (Lancet 2010 Jan. 27 [doi:10.1016/S0140-6736(09)61969-3]).

The study also showed that insulin therapy was associated with higher mortality than combination oral therapy. Unadjusted mortality rates were 16.2 deaths per 1,000 person-years of follow-up for the oral combination therapy group and 27.2/1,000 for the insulin group. After exclusion of patients with high cardiovascular risk or renal impairment, insulin-based therapy remained associated with significantly greater all-cause mortality (hazard ratio 1.46) than did combination oral agents, the investigators reported.

The study used data from November 1986 to November 2008 in the U.K. General Practice Research Database. Two cohorts of patients aged 50 years and older with type 2 diabetes were assessed: 27,965 whose treatment regimen had been intensified from oral glucose-lowering monotherapy to a combination oral regimen with a sulfonylurea plus metformin, and 20,005 on oral hypoglycemic agents alone who were initiated on insulin with or without concomitant oral agents.

All-cause mortality was the primary outcome. The secondary outcome was the occurrence of a major cardiovascular event among those who had no record of cardiovascular disease before the index date. The mean follow-up was 4.5 years in the oral medication group and 5.2 years in the insulin group.

Patients were divided by HbA_{1c} decile, with the lowest decile (1) having a median HbA_{1c} of 6.4% and the highest decile (10) at 10.5%. Mortality varied by HbA_{1c} decile in both treatment groups, with increased mortality seen in both the highest and lowest deciles. Patients in decile 4, who had a median HbA_{1c} of 7.5%, had the lowest mortality across deciles.

In the combination oral therapy group, only those in deciles 1 and 10 had significantly increased mortality, compared with patients in HbA_{1c} decile 4. However, in the insulin-treated cohort, deciles 1, 2, 3, 9, and 10 all had significantly greater mortality, compared with decile 4.

Diabetes guidelines might need revision to include a definition of a minimum HbA_{1c} value.

DR. CURRIE

Progression to large-vessel disease events occurred in 8.2% of 20,817 patients who did not have large-vessel disease at baseline in the oral medication group, and in 11.9% of 13,475 patients in the insulin group. After adjustment for covariates, the risk of progression to large-vessel disease in both groups was higher for decile 1 (HR 1.54) and decile 10 (HR 1.36).

Compared with combination oral therapy, insulin treatment also was associated with an increased likelihood of progression to a first large-vessel disease event (HR 1.31).

The data suggest that for patients on oral combination therapy, a wide HbA_{1c} range is safe with respect to all-cause mortality and large-vessel events, but a narrower range may be desirable for patients taking insulin, the investigators said.

In an editorial, Dr. Beverley Balkau and Dr. Dominique Simon noted that although this study lends support to earlier studies, epidemiologic studies cannot show causal relationships. Moreover, observational databases cannot provide the detailed information available in a randomized clinical trial, such as the actual frequency of hypoglycemia.

This study has the advantage of real-world observation, added Dr. Balkau and Dr. Simon of the CESP Centre for Research in Epidemiology and Population Health, Villejuif, France (Lancet 2010 Jan. 27 [doi:10.1016/S0140-6736(09)62192-9]).

Dr. Balkau and Dr. Simon said priority should be given to treatment with insulin sensitizers for as long as possible in patients with type 2 diabetes, because these drugs allow a low HbA_{1c} to be achieved without risk of hypoglycemia. For patients with type 2 diabetes using insulin secretagogues or insulin itself, this study provides a rationale for an HbA_{1c} threshold of 7.5%, which corresponds to the lowest threshold of death and lowest event rate for large-vessel disease, they said. ■

Disclosures: *Dr. Currie has financial ties to Eli Lilly and other drug companies. Four study coauthors are employed by Eli Lilly. Dr. Balkau and Dr. Simon have financial ties to several drug companies.*

VITALS

Major Finding: HbA_{1c} values below 7.5% were associated with increased all-cause mortality and cardiovascular events.

Data Source: A general practice database analysis of 47,970 type 2 diabetes patients with recently intensified glucose-lowering therapy.

Disclosures: Funding by Eli Lilly & Co. The investigators disclosed ties to numerous manufacturers of diabetes treatments, including Eli Lilly.

In Diabetes, Silent Cerebral Infarcts May Predict End-Stage Renal Disease

BY DENISE NAPOLI

Microvascular disease of the brain as seen on MRI is a good predictor of end-stage renal disease in diabetes and might serve as a proxy for hard-to-detect renal vessel damage.

Currently, no established method exists for assessing small vessel disease in the kidney, according to a report by Dr. Takashi Uzu of Shiga University School of Medical Science in Otsu, Japan, and colleagues.

However, "The vascular beds of the kidney and brain have similar hemodynamic properties," Dr. Uzu and colleagues wrote (J. Am. Soc. Nephrol. 2010 Jan. 28 [doi: 10.1681/ASN.2009050558]). "It is therefore possible that the presence of small artery diseases in the brain could indicate an increased risk for worsening kidney function."

The researchers looked at 608 Japanese patients aged 30-75 years with type 2 diabetes who had been hospitalized to control glucose or to examine their diabetic complications. Patients were excluded if they had a past history of cerebrovascular or cardiovascular events, including MI and heart failure.

All patients underwent MRI of the brain at baseline. A total of 177 patients were found to have had a "silent cerebral infarct" (SCI), defined as "evidence of one or more infarcts on MRI, without a history of stroke or transient ischemic attack."

Compared with the patients who showed no evidence of past SCI (431), the SCI group had longer diabetes duration (mean of 9.8 years vs. 7.6 years), were older (63.3 years vs. 57.3 years), and had higher blood pressure (the SCI patients had a systolic mean pressure of 146.8 mm Hg vs. 136.5 mm Hg in the non-SCI group; their diastolic mean was 81.6 mm Hg vs. 78.8 mm Hg).

"Over the average 7.5-year follow-up period, 58 patients (34 in the SCI group and 24 in the non-SCI group) reached the primary composite end point of ESRD or death," the authors wrote. That amounted to a hazard ratio of 2.44.

The likelihood of meeting the study's secondary end point—dialysis plus two serum creatinine values that were twice the baseline values—also was significantly greater in the SCI group compared with the non-SCI group (HR 4.79).

The frequency of patients being treated with renin-angiotensin system–blocking agents, which might lead to renal impairment as an adverse effect, was higher in the SCI group.

"However, the frequency of the primary (ESRD or death) and secondary (the composite of any dialysis and doubling of the serum [creatinine] concentration) end points did not differ" between SCI patients who were treated with RAS-blockers and those who were not, they wrote.

The findings suggest that "the presence of extrarenal microvascular diseases" might be a new predictor of renal function in type 2 diabetes patients.

The authors disclosed no conflicts of interest related to this study. ■

High Plasma Glucose Predicts Adult Diabetes

Elevated fasting plasma glucose levels during childhood—even within the normoglycemic range—appear to predict prediabetes and diabetes in young adulthood, according to a report from the Bogalusa Heart Study.

Moreover, high-normal fasting plasma glucose predicts later diabetes status independently of other traditional risk factors, said Dr. Quoc Manh Nguyen and associates at Tulane University, New Orleans.

Subjects were aged 4-18 years at study inception in 1978 and have been followed for a mean of 21 years. At the last survey, 1,723 subjects were classified as normoglycemic, 79 as prediabetic, and 47 as diabetic.

Subjects who had high-normal levels of fasting plasma glucose at baseline (86-99 mg/dL) were more than twice as likely to develop prediabetes or diabetes in young adulthood as were those with lower baseline levels.

Fasting plasma glucose level predicted later diabetes risk even after the data were controlled for other cardiometabolic risk factors, Dr. Nguyen and colleagues said (Arch. Ped. Adolesc. Med. 2010;164:124-8).

In an editorial, Dr. Matthew W. Gillman of Harvard Medical School, Boston, noted that the prevalence of prediabetes was 6%-7% among adults whose childhood glucose exceeded 86 mg/dL, but was only 2% for those whose childhood levels were lower.

Nevertheless, it would be premature to recommend using high-normal childhood glucose levels to predict later prediabetes. It would not be "sensible" to label all such children as at risk when only 7% are likely to develop the disorder, Dr. Gillman noted (Arch. Ped. Adolesc. Med. 2010;164:198-9).

The study was supported by the National Institute on Aging and the American Heart Association. Dr. Nguyen and Dr. Gillman reported no relevant conflicts of interest.

—Mary Ann Moon