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 (HR 1.46) than did combination oral agents, the investigators reported.

The study, funded by Eli Lilly & Co., utilized 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 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, Dr. Currie and his associates reported.

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.

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 adjusted risk of progression to large-vessel disease in both groups was higher for decile 1 (HR 1.54) and decile 10 (HR 1.36).

VITALS

Major Finding: Hemoglobin A_{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: The study was funded by Eli Lilly & Co. The investigators disclosed ties to numerous manufacturers of diabetes treatments, including Eli Lilly. The editorial authors reported relationships with several other pharmaceutical companies.

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 commented.

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

However, this study does have the advantage of real-world observation, noted Dr. Balkau and Dr. Simon, who are with the CESP Centre for Research in Epidemiology and Population Health in Villejuif, France (Lancet 2010 Jan. 27 [doi:10.1016/S0140-6736(09)62192-9]).

They recommended that priority 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. ■

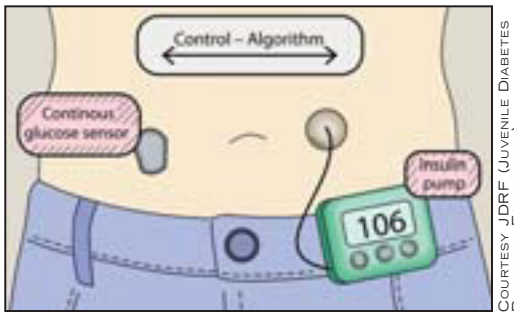
Partnership Forged to Design 'Closed-Loop' Insulin Pump

BY MIRIAM E. TUCKER

The Juvenile Diabetes Research Foundation has announced a partnership with Animas Corp. and DexCom Inc. to develop a first-generation automated system for managing type 1 diabetes.

The JDRF will provide $8 million over the next 3 years to Animas, a Johnson & Johnson company that manufactures insulin pumps. DexCom, a manufacturer of continuous glucose monitoring (CGM) devices, will supply that part of the technology for the system. The money will fund clinical trials of efficacy and safety, with the first-generation system expected to be ready for regulatory review within 4 years, Alan Lewis, Ph.D., JDRF president and CEO, said in a telephone briefing.

The ultimate goal is to develop a fully automated "closed-loop" system to regulate blood glucose levels, but the initial version would still require some input from the user and therefore would only be partially closed. It would consist of the insulin pump and the CGM—which are currently available but operate separately—with a computer program that would link the two. It would automatically increase insulin delivery upon detection of hyperglycemia and shut off delivery when hypoglycemia occurs, subsequently resuming delivery when glucose levels return to normal.



COURTESY JDRF (JUVENILE DIABETES RESEARCH FOUNDATION)

The insulin pump and glucose sensor will be linked via a computer program.

The patient would still need to manually instruct the pump to deliver insulin, but the system would improve overall control by minimizing the amount of time a patient spends out of target glucose range, said Aaron Kowalski, Ph.D., JDRF assistant vice president and director of glucose control research. ■

Childhood Plasma Glucose May Predict Adult Diabetes

BY MARY ANN MOON

Elevated fasting plasma glucose levels during childhood—even when they remain within the normoglycemic range—appear to predict prediabetes and diabetes in young adulthood, according to a new report.

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.

The investigators used data from the Bogalusa Heart Study to assess diabetes risk over a 2-decade span. The study subjects were aged 4-18 years at its 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, defined as 86-99 mg/dL, were more than twice as likely to develop prediabetes or diabetes in young adulthood as were those with lower levels of fasting plasma glucose at baseline.

Moreover, 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 comment accompanying this report, Dr. Matthew W. Gillman of Harvard Medical School, Boston, noted that the prevalence of prediabetes was 6%-7% among adult subjects whose childhood glucose exceeded 86 mg/dL, but was only 2% for those whose childhood glucose 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). ■

VITALS

Major Finding: High-normal fasting plasma glucose levels in childhood may predict prediabetes and diabetes in young adulthood.

Data Source: Data from the Bogalusa Heart Study involving 1,849 subjects who were 4-18 years at the initiation of the trial.

Disclosures: Dr. Nguyen's study was supported by the National Institute on Aging and the American Heart Association, and Dr. Gillman's involved funding from the National Institutes of Health. Both Dr. Nguyen and Dr. Gillman reported no relevant conflicts of interest.