Mortality May Be Increased at 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]).

Decreased survival in patients achieving low HbA_{1c} levels might be related to hypoglycemia.

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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 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 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, 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). 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.

Decreased survival in patients achieving low HbA_{1c} levels might be related to hypoglycemia, a common complication of intensive blood glucose control. Postulated mechanisms include a link between the sympathomimetic or hypokalemic manifestations of hypoglycemia and the onset of cardiac arrhythmia.

Hypoglycemia might also potentiate glucose variability, contributing to increased oxidative stress and vascular inflammation and predisposing patients to atherosclerotic plaque destabilization and vascular function, Dr. Currie and his associates said.

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, said 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 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. ■

Disclosures: *The study was funded by Eli Lilly & Co. Dr. Currie has received research grants from and consulted for various pharmaceutical companies, including Eli Lilly. Four of the study coauthors are employees of Eli Lilly. Dr. Balkau and Dr. Simon have served as speakers for and been on the advisory panels of several pharmaceutical companies.*

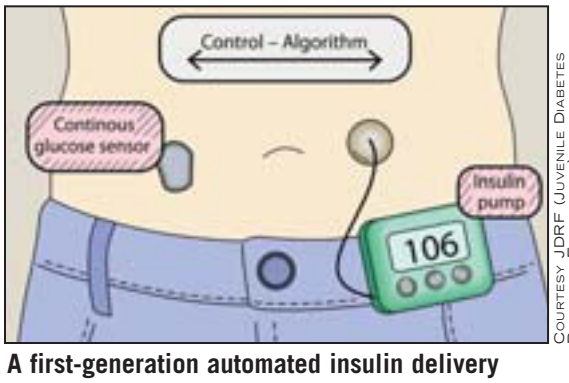
Partnerships Created to Develop Insulin Delivery Systems

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, as well as a collaboration with Becton, Dickinson and Co. to develop novel products that would work with insulin pumps to enhance insulin delivery.

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.

While the ultimate goal is to develop a fully automated "closed-loop" system to regulate blood glucose levels, the initial version of the system 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 wirelessly link the two components, enabling the device to 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)

A first-generation automated insulin delivery system would consist of an insulin pump and a continuous glucose monitor that are linked wirelessly with a computer program.

Although the patient would still need to manually instruct the pump to deliver insulin at certain times—particularly at meals—the system would improve overall control by minimizing the amount of time a patient spends out of target glucose range, which is typically more than 70% even among the most sophisticated patients with type 1 diabetes, said Aaron Kowalski, Ph.D., the JDRF's assistant vice president and director of glucose control research.

In a follow-up interview, Dr. Kowalski said that this development partnership is in addition to JDRF's ongoing annual $4-$5 million funding of academic research in closed-loop insulin delivery systems involving devices made by all of the leading pump and CGM manufacturers.

The JDRF also announced that it will provide $4.3 million over the next several years for the nonexclusive collaboration with Becton Dickinson.

Becton Dickinson will use the foundation's funds for research and development of new products aimed at delivering insulin from pumps via either infusion sets or patch-pump configurations, with the goal of minimizing pain, kinking, occlusions, and site infections. The program will also aim to speed insulin action, a JDRF statement said.

One facet will utilize Becton Dickinson microneedles, which speed subcutaneous insulin uptake at the delivery site. Microdelivery technology development will initially focus on improved glucose control. Ultimately it targets the technology of a closed-loop artificial pancreas system utilizing insulin pumps and continuous glucose sensors, with communication between the two devices. ■

More information about all of JDRF's initiatives is available at www.artificialpancreasproject.com.

Diabetes Pocket Guide and Booklet

The National Diabetes Education Program is offering a pocket guide that summarizes current recommendations for the diagnosis and management of prediabetes and diabetes, as well as a list of evidence-based treatment goals. Also offered is an evidence-based booket, Guiding Principles for Diabetes Care, that outlines the latest principles of diabetes care. It includes information on identifying and diagnosing diabetes, care and education of patients, and preventing complications.

The guide and the booklet can be downloaded from the Web site at www.yourdiabetesinfo.org. For more information, contact the NDEP by calling 888-693-6337. ■