



# DIABETES IS PRIMARY

TIMELY NEWS AND NOTES FOR PRIMARY CARE PROVIDERS  
from the American Diabetes Association

By Max Bingham, PhD

## FROM THE JOURNALS.....

### **Infections and Poor Glycemic Control in Diabetes**

Poor control of glucose levels in diabetes can lead to all sorts of complications, including infections. But the extent to which better glucose control can reduce infections and worse glucose control can increase infections is little understood.

A recent study by Critchley et al. (*Diabetes Care*, doi.org/gfbwnh) addresses the question, describing the infection rates in a population of just over 85,000 patients aged 40–89 years with some form of diabetes in the period 2010–2015. Summarizing infections into 18 categories, they estimate hospitalization and mortality rates according to types of infection and their outcomes. The outcomes were compared to case-control subjects who had no diabetes but were otherwise well matched.

The authors show that infection risk rose with A1C levels for numerous serious conditions, such as infections of bones and joints, endocarditis, mycosis, tuberculosis, and sepsis. They also found that poor diabetes control accounted for 15% of pneumonia infections and 16% of all infection-related deaths. Importantly, A1C levels were obtained prospectively in the study, which means that incident infection episodes should not have affected long-term A1C measures, a consistent issue in previous studies.

“Diabetes patients with the worst control were almost three times as likely to need hospital treatment for an infection compared to those with good control,” author Julia Critchley said. “This was especially high for people with type 1 diabetes and very poor control, who had about 8.5 times higher risk of needing such treatment compared to those without diabetes. Across England as a whole, we found that poor diabetes control accounted for about 20–46% of some of the most serious types of infections seen in diabetes patients.”

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<https://doi.org/10.2337/cd18-0098>

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### **CVD Mortality in Patients With and Without Diabetes**

Mortality due to cardiovascular disease (CVD) declined significantly in the United States between 1988 and 2015, with the greatest reductions seen in patients with diabetes, according to Cheng et al. (*Diabetes Care*, doi.org/cwjt). However, in 2015, adults with diabetes still had a higher risk of mortality due to a range of cardiovascular events compared to matched control subjects. In particular, heart failure and arrhythmia-related deaths did not decline in the people with diabetes.

The authors conclude that, although there has been narrowing in mortality rates due to CVD between individuals with and without diabetes, primary prevention of risk factors should continue, and improvements to monitoring and detection are still needed.

The study focused on a population of just over 677,000 individuals with or without diabetes and showed an overall positive picture of significant decreases in death due to CVD except in adults aged 20–54 years. Indeed, relative changes over a 10-year period among adults with diabetes were –33% for major CVD, –40% for ischemic heart disease, and –29% for stroke.

“Despite a significant decrease in the risk of death due to heart attack or stroke, interventions are still needed at multiple levels, including managing risk factors and improving treatment of cardiovascular diseases—particularly heart failure,” author Yiling Cheng said.

In another recent study by Rosengren et al. (*Diabetologia*, doi.org/gd8ssk), the authors compared just under 266,500 individuals with type 2 diabetes with ~1.3 million case-control subjects over a 5.6-year follow-up in Sweden and found an excess risk of hospitalization for heart failure in people with type 2 diabetes. As in the study by Cheng et al., men and women with diabetes who were <55 years of age had an elevated risk of heart failure; 7.0% of those with diabetes were hospitalized for heart failure compared to 3.8% of control subjects. After adjusting for multiple confounding variables, the authors found that younger age, poorer glycemic control, and worse renal function were all associated with excess risk of heart



failure in people with type 2 diabetes. One piece of good news was that people with diabetes who were  $\geq 75$  years of age with no albuminuria or an A1C value  $< 6.9\%$  had a risk of heart failure similar to that of individuals without diabetes.

The authors suggest that their findings might help to identify individuals with diabetes who should be targeted to prevent heart failure and underscore that “diabetes confers a near-ubiquitous but varying excess risk of heart failure in all age-groups and at all levels of glycemic control.”

## TREATMENTS + THERAPIES

### “Twincretins”: Trial Finds Reductions in A1C and Weight With New Dual Incretin

A dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist agent termed LY3298176 that is currently in development can reportedly reduce A1C and weight substantially in individuals with type 2 diabetes. A phase 2 trial by Frias et al. (*The Lancet*, doi.org/gfb3s3) investigated a range of doses of LY3298176 and compared its effects to those of the GLP-1 receptor agonist dulaglutide and placebo. The primary outcome was A1C change over 26 weeks.

The authors report that the effects of LY3298176 on change of A1C were dose dependent and showed average reductions of up to 2% depending on dose. There were also average weight reductions of up to 11.3 kg. The effects were significant compared to both dulaglutide and placebo.

At the end of the trial, 33–90% (depending on dose) of participants achieved a target A1C level  $< 7\%$ , compared to 52% in the dulaglutide group and 12% in the placebo group. A smaller number of participants also achieved an A1C  $< 5.7\%$ —a level considered by many to be nondiabetic.

A large proportion of participants experienced gastrointestinal events—up to 66% in the group who received the highest dose of LY3298176. The authors describe these incidence rates as dose-related but say that most were mild to moderate in severity. Hypoglycemia rates were low and similar across all groups, with no reports of severe hypoglycemia.

In an accompanying commentary (*The Lancet*, doi.org/gfb3s6), Michael Stumvoll and Matthias Tshöp praise the study, noting that its findings “re-emphasize that the strategy of dual or triple agonism is promising, with potential to reverse the obesity and type 2 diabetes pandemic.” However, they also urge some caution, noting that, “despite the small but significant competitive edge of this twincretin over a classic GLP-1 monoagonist, it is too early for any far-reaching clinical conclusion or recommendation.”

According to press statements (bit.ly/2CVm61R), manufacturer Lilly expects phase 3 studies to begin in early 2019 and run until the end of 2021.

### EASE Research Program: Empagliflozin Offers Benefits in Type 1 Diabetes

The sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin can improve glycemic control and reduce weight in patients with type 1 diabetes, but with an increased risk of diabetic ketoacidosis (DKA), according to Rosenstock et al. (*Diabetes Care*, doi.org/cwjv). Specifically, rates of DKA were comparable between a low 2.5-mg dose of empagliflozin and placebo but increased with higher empagliflozin doses of 10 and 25 mg, leading the authors to suggest that monitoring for ketones and considering lower doses of the SGLT2 inhibitor may be warranted. Low-dose empagliflozin still results in clinically meaningful glucose improvements, but without apparent increased risks for DKA and severe hypoglycemia.

### HARMONY Outcomes Study: Albiglutide Cuts Cardiovascular Risk in Type 2 Diabetes

The GLP-1 receptor agonist albiglutide cuts the risk of major adverse cardiovascular events in

*continued on p. 6 →*

## MARKETPLACE.....

### Closed-Loop Artificial Pancreas System Improves Glycemic Control and Reduces Hypoglycemia Risk

Progress continues on the refinement an artificial pancreas system with the publication of what has been described as the gold standard of randomized trials of such systems. The study, by Tauschmann et al. (*The Lancet*, doi.org/gfb3sw), involved 86 individuals with type 1 diabetes aged 6–65 years and compared therapy with a hybrid closed-loop system to sensor-augmented insulin pump therapy over 12 weeks in a free-living environment. The primary endpoint was time spent in a target blood glucose range of 3.9–10.0 mmol/L (70–180 mg/dL).

In the closed-loop group, time spent within the glycemic range was 65%, compared to 54% for those using pump therapy. There were modest reductions in A1C in both groups, with the closed-loop group achieving a slightly greater decrease of 0.36%. Time spent either below or above the target range was also shorter in the closed-loop group. Total insulin use and weight change did not differ between the groups. Although no hypoglycemia events occurred in either group, there were more adverse events overall with the closed-loop system than with the insulin pump.

“The use of day-and-night hybrid closed-loop insulin delivery improves glycemic control while reducing the risk of hypoglycemia in adults, adolescents, and children with

type 1 diabetes compared with conventional pump therapy or sensor-augmented pump therapy,” the authors write. “Results from our study, together with those from previous studies, support the adoption of closed-loop technology in clinical practice across all age groups.”

The closed loop system consisted of a modified Medtronic 640G insulin pump, with an Android phone enclosed in a case, the Cambridge control algorithm, and an Elite 3 glucose sensor. The system is a prototype and is not currently available commercially.

### FDA Issues Warning on the Proper Use of Insulin Pen Needles

The U.S. Food and Drug Administration has urged caution over the proper use of standard and safety pen needles, which are routinely used to inject insulin. The warnings were prompted after reports of patients failing to remove the inner needle cover on standard pen needles before attempting to inject. According to the notice (bit.ly/2DyK4ld), a number of patients developed hyperglycemia because the inner cover stopped them from receiving intended doses of insulin. Patients and caregivers are urged to check the type of needle they use and to seek advice on its proper use.

#### Treatments + Therapies, *continued from p. 5*

patients with type 2 diabetes, according to the headline outcomes of the HARMONY Outcomes study.

The positive results come at a time when the sponsor of the study, GSK, is not marketing or distributing the drug after a reworking of its strategy. Although the company committed to investing in the drug and trial after its decision, it said in a statement (bit.ly/2QgbxKJ) that it would divest the drug to a company with the right expertise and resources to realize its full potential.

According to the HARMONY Outcomes analysis by Hernandez et al. (*The Lancet*, doi.org/gfb3ss), the drug does appear to have potential. The trial involved just under 9,500 patients with type 2 diabetes who were randomly assigned to receive either once-weekly subcutaneous albiglutide (30–50 mg) or placebo over a period of 1.6 years, in addition to standard care.

The primary outcome was a composite measure of death from cardiovascular causes, myocardial infarction, and stroke in an intention-to-treat population.

This composite outcome occurred in just over 7% of patients in the albiglutide group and just over 9% of patients in the placebo group, resulting in a statistically significant risk reduction of 22% in the albiglutide group compared to placebo. In terms of secondary outcomes, the authors noted greater reductions in A1C and body weight in the albiglutide group, with few differences between groups in a range of adverse events of interest.

“We are very excited by these results, which add to the evidence that certain GLP-1 receptor agonists reduce cardiovascular events in patients with type 2 diabetes,” author Stefano Del Prato said in a statement. “This new therapeutic approach offers physicians a further means of reducing the most common and deadly complication faced by our patients with type 2 diabetes.” Author John McMurray added, “These are impressive findings, with a reduction in risk at least as large as that obtained with traditional cardiovascular drugs.”



## ADA NEWS

### New Consensus Report: Management of Hyperglycemia in Type 2 Diabetes

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recently assembled an international panel of diabetes care experts to jointly publish a new consensus report calling for a paradigm shift to patient-centered care for the treatment of type 2 diabetes. After an extensive review of the literature, with a particular focus on key cardiovascular outcomes trials reported in the past 4 years, the group developed guidance on optimizing blood glucose control, improving patient outcomes, and reducing serious complications of type 2 diabetes, including cardiovascular and chronic kidney disease.

To make the guidance as helpful for clinicians and health care providers as possible, the ADA-EASD consensus report features eight graphic figures that provide detailed health care algorithms and two tables enumerating the multiple therapy and medication options available for the care of adults with type 2 diabetes. For the first time, the report includes specific pharmacological recommendations based on a patient's profile and health history (Figure 2 in the statement). The ADA endorsed the ADA-EASD consensus report and incorporated the recommendations into its *Standards of Medical Care in Diabetes—2018* as a "Living Standards" update. More information about the Living Standards is available at [professional.diabetes.org/content-page/living-standards](http://professional.diabetes.org/content-page/living-standards). The consensus report is available online from *Diabetes Care* ([doi.org/gfdc4w](https://doi.org/gfdc4w)) and was published in the December 2018 issues of *Diabetes Care* and *Diabetologia*.

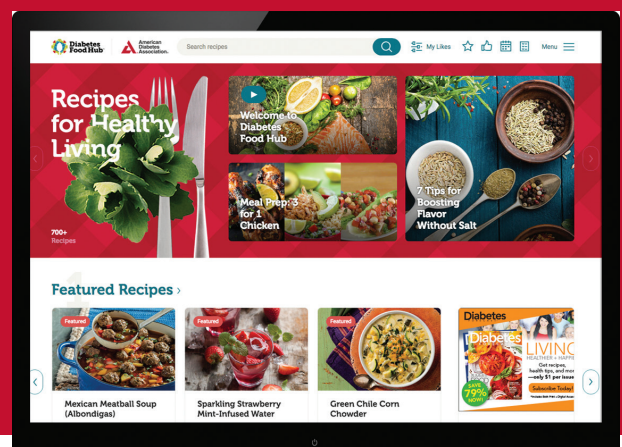
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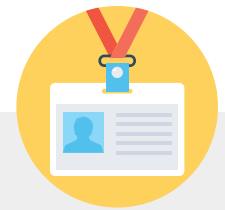
The ADA's Standards of Medical Care in Diabetes app, available for free download on iTunes and Google Play, provides complete access to the Standards of Care at your fingertips. The app also contains clinical tools, such as interactive tables and algorithms, and enables you to take notes and bookmark key sections. The app can be downloaded from [professional.diabetes.org/StandardsiOS](http://professional.diabetes.org/StandardsiOS) or [professional.diabetes.org/StandardsAndroid](http://professional.diabetes.org/StandardsAndroid).



### Diabetes Food Hub: New Resource for People With Diabetes

Diabetes Food Hub ([diabetesfoodhub.com](http://diabetesfoodhub.com)) is a cooking and recipe platform created by the ADA for people living with diabetes, their families, and their caregivers. On the platform, clinicians can find tools to help their patients manage diabetes, including a personalized, interactive meal planner that calculates nutrition facts and generates a customizable grocery list. With hundreds of ADA-approved recipes, patients can use the site to find diabetes-friendly dishes that will ease daily meal-planning challenges.





## CONFERENCE SPOTLIGHT

### **EASD 2018**

The European Association for the Study of Diabetes (EASD) held its annual meeting in Berlin, Germany, in early October 2018. Highlights included updates on novel treatment strategies for diabetes and updates from the EASD and ADA on their guidance for the management of hyperglycemia in type 2 diabetes. (See ADA News on p. 7.)

A series of outcomes were also reported from major clinical studies. We reported some of these in *Treatments and Therapies* (p. 5–6). Following are more highlights:

- Results of the CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) trial were announced, detailing that the dipeptidyl peptidase-4 inhibitor linagliptin was safe for long-term cardiovascular and renal outcomes ([bit.ly/2qv3vCt](https://bit.ly/2qv3vCt)).
- A post-hoc analysis of the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial suggests that the injectable GLP-1 receptor agonist lixisenatide may protect patients with type 2 diabetes and cardiovascular disease from developing kidney damage ([bit.ly/2P7CqE8](https://bit.ly/2P7CqE8)).
- Type 2 diabetes might be detectable a full 20 years before diagnosis, according to a Japanese study ([bit.ly/2Qgf3EV](https://bit.ly/2Qgf3EV)). If true, this finding would have significant consequences for the way diabetes is managed, allowing for novel diabetes prevention interventions.
- Household refrigerators might pose an underestimated risk to insulin quality because the actual internal temperatures in such appliances in real-world settings regularly fluctuate beyond the recommended 2–8°C (36–46°F), including below freezing point. The study used a small temperature sensor to measure temperatures in refrigerators and cooling bags used by ~400 people with diabetes. Temperature data were recorded for an average of 49 days ([bit.ly/2Qa7YFz](https://bit.ly/2Qa7YFz)). The findings are rather concerning for safe home storage of both food and insulin.

To learn more about ADA's continuing education opportunities, including Diabetes Is Primary events in your community, please visit [professional.diabetes.org/ce](https://professional.diabetes.org/ce).