DIABETES IS PRIMARY

TIMELY NEWS AND NOTES FOR PRIMARY CARE PROVIDERS

from the American Diabetes Association

By Max Bingham, PhD

FROM THE JOURNALS

Drug Adherence in Diabetes: Old Story, New Developments

Concerns over poor medication adherence in diabetes continue with reports from numerous countries suggesting that many patients with diabetes are not adherent to their medication regimen. Good examples include reports from Saudi Arabia (doi.org/c853), Cameroon (doi.org/c854), and Ethiopia (doi.org/c855).

Although the general concept that drugs tend not to work when patients do not take them is self-evident, we continue to learn more about specific influences on drug adherence. Recently, for example, Leggett et al. (*Archives of Disease in Childhood*, doi.org/c856) revealed that adherence to metformin in children with type 1 diabetes drops by 20–25% during weekends and school holidays. Adverse effects of the medication, various clinical characteristics, and socioeconomic status did not predict adherence in the year-long study involving 90 Australian children with type 1 diabetes who received metformin or placebo via an electronic dose monitoring device that recorded when the medication was accessed.

"Clinicians should be aware of adherence issues during holidays and weekends," author Alexia Peña said in a statement (bit.ly/33qjNPc). "Targeted reminders and additional strategies are necessary to improve adherence during these less structured periods for school children and their families."

Texting and Drug Adherence

Text messaging has been shown to be a relatively inexpensive, customizable intervention to improve drug adherence. Goruntla et al. (*Journal of Pharmacy and Bioallied Sciences*, doi.org/c857) recently showed that daily text messaging on top of pharmacist-directed counseling can improve diabetes medication adherence over a period of 6 months. In their study in the economically under-developed Anantapuramu District in Andhra Pradesh, India, they found that adherence at baseline was ~80% in both treatment and placebo groups. Text messages increased adherence to ~95% at 3- and 6-month follow-up visits in the intervention group, compared to no change in adherence in the placebo group. Crucially, the authors noted that A1C, systolic blood pressure, and LDL cholesterol all decreased significantly in the treatment group.

Adherence and Accurate Measurement

One key issue relating to medication adherence is the need for accurate measurement. Patel et al. (*Diabetes Care*, doi.org/c858) report that a liquid chromatography tandem mass spectrometry (LC MS/MS) test of spot urine samples can detect adherence to 40 different diabetes-relevant therapies.

"A single urine spot sample can be used to objectively screen for nonadherence in primary care, and the technique demonstrates that nonadherence to cardiovascular therapies is high in people with [type 2 diabetes] attending primary care," the authors write. "This could be used to inform clinical decisions about treatment alteration and to improve patient outcomes."

Whether this method will catch on remains to be seen given that the cost involved in acquiring an LC MS/MS system are considerable, a fact the authors pointed out in an earlier article (doi.org/f53273). Still, they suggest that such equipment should be available in major clinical centers and quote a cost of £30 (~$36.50 USD) per sample.

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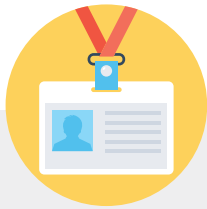

CONFERENCE SPOTLIGHT

Following is a round-up of interesting reports from recent medical conferences.

From the American Association of Clinical Endocrinologists' 29th Annual Scientific & Clinical Congress

Inpatient Diabetic Ketoacidosis Mortality Risk Is Higher on Weekends

Motlaghzadeh et al. (bit.ly/31kzWUn) report that going to a hospital on a weekend for treatment of diabetic ketoacidosis may triple a patient's mortality risk compared to seeking such treatment on a weekday.

"The difference is likely due to lower availability of medical, nursing, and other health professional staff on weekends," the authors suggest.

From the American Diabetes Association's 79th Scientific Sessions

No Major Difference in Cardiovascular Outcomes for Linagliptin Versus Glimepiride

Linagliptin (a dipeptidyl peptidase 4 inhibitor) and glimepiride (a sulfonylurea) have comparable cardiovascular (CV) risk profiles in patients with type 2 diabetes who are at high CV risk, according to results of the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) trial (bit.ly/2X1uQ0N). There were no statistically significant differences between the linagliptin and glimepiride groups in terms of a composite CV outcomes measure or a series of individual measures.

"In the context of the established cardiovascular safety profile of linagliptin versus placebo, convincingly demonstrated in the CARMELINA [Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus] trial, this comparative trial was in position to fully address the decades-long, unresolved, and highly debated cardiovascular mortality controversy for sulfonylureas," principal investigator Julio Rosenstock said. "Although we hypothesized in CAROLINA that we would potentially see differences in cardiovascular outcomes when we directly compared linagliptin and glimepiride, we saw none and are now in a position to provide a clear answer to vindicate sulfonylureas, at least glimepiride, from the old cardiovascular stigma. However, with a significantly higher risk of hypoglycemia and a modest but statistically significant weight gain with glimepiride compared with linagliptin, results from the CAROLINA trial confirm an important, clinically relevant safety advantage of linagliptin over glimepiride that should be considered in the decision-making process for selecting therapy, in addition to cost considerations."

Linagliptin Found to Be Safe Across Levels of Renal Function and Age-Groups

A deeper dive into data from the CARMELINA study has shown that linagliptin, when added to usual care of type 2 diabetes, has a long-term CV and

continued on p. 312 →

MARKETPLACE

Patients Warned About "DIY" Artificial Pancreas Setups

It's a controversial area, but a considerable community of individuals with type 1 diabetes have begun using makeshift "do-it-yourself" artificial pancreas (AP) systems. Rallying under the social media banner #wearenotwaiting, these individuals are using expertise from within their ranks to augment currently available technologies rather than waiting for commercially developed, regulated AP systems to reach the marketplace. In response, the U.S. Food and Drug Administration (FDA) has stepped in to warn patients against this effort, saying that unauthorized diabetes management devices pose safety concerns and could lead to injury. The full FDA safety communication, issued in May 2019, can be found online (bit.ly/2OrFrPr). The DIY community can be accessed via Twitter by searching #wearenotwaiting.

Use of Flash Continuous Glucose Monitoring Leads to Improved Glycemic Outcomes and Greater Treatment Satisfaction

A flash continuous glucose monitoring (FCGM) system used in combination with physician advice and carbohydrate counting by patients with type 2 diabetes can reduce A1C and may improve patients' satisfaction with their care. These conclusions, reported by Yaron et al. (*Diabetes Care*, doi.org/c86c), come from a randomized controlled trial that compared 10 weeks of use of the FreeStyle Libre FCGM system (Abbott, Alameda, Calif.) against standard care that included self-monitoring of blood glucose (SMBG).

After 10 weeks, overall patient satisfaction, as measured through questionnaires, was higher in the intervention group, although the difference fell just short of statistical significance. FCGM users also found the intervention to be more flexible than standard care with SMBG and were more likely than individuals in the standard care group to recommend their treatment to their contemporaries. The FCGM group had a change in A1C of –0.82% from baseline to 10 weeks, whereas the standard care group had a change of –0.33% over the same period.

In a poster presented in June 2019 at the American Diabetes Association's 79th Scientific Sessions in San Francisco, Calif. (poster 99-LB, bit.ly/33jBG2a), Kroeger et al. used retrospective real-world data from three studies and a meta-analysis to show how FCGM can significantly reduce A1C by as much as 0.9% in individuals with type 2 diabetes on intensive insulin therapy. Average A1C was 8.9% before initiating use of the FreeStyle Libre system and 8.0% after using the technology for 3–6 months.

TREATMENTS + THERAPIES

Canagliflozin Reduces Risk of Kidney Failure in Type 2 Diabetes

The sodium–glucose cotransporter 2 inhibitor canagliflozin can reduce the risk of a cardiovascular (CV) event or renal failure in patients with type 2 diabetes and chronic kidney disease (CKD), according to results from the CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) trial (Perkovic et al., *New England Journal of Medicine*, doi.org/c86d). These outcomes suggest that canagliflozin can be used as a new treatment approach for patients at risk of worsening CKD, making it the first new pharmacotherapeutic option for renoprotection in type 2 diabetes in the past 18 years.

First presented at the International Society of Nephrology World Congress in April 2019, the top-line results of the CREDENCE trial showed that canagliflozin reduced the risk for a composite measure of renal and CV outcomes by 30% compared to placebo over 2.5 years in patients receiving usual care for type 2 diabetes who were at high risk of CKD progression. Notably, the 4,401 trial participants were randomly assigned to receive canagliflozin or placebo on top of renin-angiotensin-aldosterone blocker therapy, which is the current approach used for CKD.

The double-blind, placebo-controlled trial enrolled patients with type 2 diabetes and CKD to receive either canagliflozin 100 mg daily or placebo. The primary end point was a composite of the occurrence of end-stage renal disease, a doubling of serum creatinine, and renal or CV death. The trial was stopped early after prespecified efficacy criteria were met. The composite primary outcome occurred in 340 patients who took placebo and 245 patients who took canagliflozin, which translated to a 30% risk reduction. Similar reductions were seen in risk for various composite and individual measures of both renal and CV outcomes.

"Canagliflozin is the first medical breakthrough in nearly 20 years proven to slow the progression of chronic kidney disease in patients with diabetes at high risk of developing kidney failure," lead author Vlado Perkovici said in a statement (prn.to/2GoZ30D). "These impressive results . . .

continued on p. 312 →

ADA NEWS

New Compendium Available on Diabetes-Related Eye Disease

Worldwide, ~35% of people with diabetes develop some form of diabetes-related retinopathy (DR), and vision-threatening DR develops in ~10% of people with diabetes. There is an urgent need to prevent and minimize this chronic complication of diabetes. For diabetes care providers, a thorough understanding of the vision-threatening aspects of DR is essential. That's why the American Diabetes Association (ADA) encouraged the development of the *Prevention and Management of Diabetes-Related Eye Disease* compendium.

This new publication provides information for primary care providers about the importance of regular screening to identify at-risk patients, prevention strategies, and novel treatment approaches. The topics were selected by Thomas W. Gardner, MD, MS, of the Kellogg Eye Center at the University of Michigan Medical School, and range from optimizing medical management for people with diabetes to advice for empowering and motivating patients by respectfully addressing their anxieties and treatments options. The compendium, which is supported by an unrestricted educational grant from Genentech, Inc., aids PCPs in their efforts to prevent, diagnose, and manage diabetes-related eye complications and thereby to improve the health and well-being of their patients.

The eye disease compendium is the third in a series published by ADA in the past year. All three compendia can be found online at professional.diabetes.org/monographs.

Expert Series Focuses on Diabetes and Heart Disease

Encourage your patients to know their risk for heart disease and learn about the connection between type 2 diabetes and heart health through the ADA's Ask the Experts Q&A series. Through this live series, part of the Know Diabetes by Heart collaboration between ADA and the American Heart Association, participants ask questions about heart health, and ADA's diabetes experts provide answers. Monthly events start at 2:00 p.m. Eastern and last for ~1 hour. Participants can access the events online or via phone. Registration is free at diabetes.org/experts4Pro, or patients can call 1-855-531-1065 at the time of the event to be directly connected.

Insulin Initiation and Titration and Insulin Intensification Self-Assessment Programs and Webcasts Available

Participants accessing the ADA's online continuing education programs on insulin will learn the most up-to-date information about initiating, titrating, and intensifying insulin therapy for people with diabetes. Content covers the characteristics of patients who are candidates for insulin therapy, dosing, potential adverse effects, advantages and disadvantages of insulin treatment, clinical practice recommendations, and individualizing the diabetes care regimen.

The two webcasts are "Beyond Basal Insulin: Intensification of Therapy" (0.5 credits) and "Insulin Initiation and Titration" (0.5 credits). The self-assessment programs include "Initiation and Titration of Insulin Therapy in People with

continued on p. 313 →

kidney safety profile across levels of renal function and age-groups. Top-line findings (bit.ly/2IgvzDa) suggest that the safety of linagliptin can be extended to older patients and to individuals with reduced renal function.

"[These data are] particularly important because [they prove] categorically the cardiovascular and kidney safety of linagliptin in those with type 2 diabetes who are at a high cardiovascular risk when some degree of kidney disease is associated," lead investigator Julio Rosenstock explained.

Oral Semaglutide Has No Added Cardiovascular Risk Compared to Placebo

Results of PIONEER 6 (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) indicate that oral semaglutide is safe in patients with type 2 diabetes with high CV risk. Conducted across 21 countries and involving >3,000 older individuals with type 2 diabetes, the trial found that, over a median follow-up of ~16 months, major adverse cardiovascular events occurred in 3.8% of individuals in the oral semaglutide group and 4.8% of those in the placebo group (hazard ratio 0.79 [95% CI 0.57–1.11], P <0.001).

There were reductions of ~50% in deaths from CV causes or from any cause in the oral semaglutide group compared to placebo. Gastrointestinal adverse events that led to discontinuation of the intervention were more common in the oral semaglutide group.

"By eliminating the barrier of an injection, oral semaglutide has the potential for widespread use in the treatment of type 2 diabetes, including in high-risk patients with cardiovascular disease and chronic kidney disease," PIONEER 6 investigator and lead author Mansoor Husain said.

Oral semaglutide is under review at the U.S. Food and Drug Administration, the European Medicines Agency, and Health Canada, PIONEER 6 investigator John Buse said.

If approved, oral semaglutide will be the first oral formulation of a glucagon-like peptide 1 (GLP-1) receptor agonist. Other drugs in the GLP-1 receptor agonist class are available in injectable formulations only.

"GLP-1 receptor agonists are arguably the most powerful class of glucose-lowering drugs in the setting of type 2 diabetes and also are associated with weight loss and evidence of cardiovascular benefit," Buse said. "We hope that the availability of an oral formulation of a GLP-1 receptor agonist will increase the range of providers and patients who will feel comfortable with prescribing and taking GLP-1s."

Treatments + Therapies, *continued from p. 310*

have significant clinical implications for preventing kidney failure and improving health for millions of people living with chronic kidney disease and type 2 diabetes."

More detailed results from the CREDENCE trial were presented in June 2019 at the American Diabetes Association's (ADA's) 79th Scientific Sessions in San Francisco, Calif., showing that canagliflozin reduced risks for renal and CV events in both primary and secondary prevention subgroups. More information on this extra analysis is available online (bit.ly/31vmzS1).

Based on the results of the CREDENCE trial, the ADA recently updated its *Standards of Medical Care in Diabetes—2019*. These updates can be found online at bit.ly/2KkmFW0 and are summarized in a press release available at bit.ly/2Xo1rLd.

In light of the CREDENCE trial outcomes, the U.S. Food and Drug Administration is considering a priority review of a supplementary new drug application for canagliflozin as a treatment for CKD in patients with type 2 diabetes (prn.to/2M4zbLE).

Results of the PIONEER 6 trial were published in the *New England Journal of Medicine* (Husain et al., doi.org/c86g).

Dulaglutide Reduces Cardiac Events in Type 2 Diabetes

The REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) trial of the GLP-1 receptor agonist dulaglutide has found that the drug reduces cardiac events in adults with type 2 diabetes. Involving nearly 10,000 participants, the REWIND trial asked whether individuals with type 2 diabetes who had additional risk factors for CV disease would benefit from the once-weekly injectable dulaglutide compared to placebo in terms of safety in reducing serious CV outcomes. Dulaglutide was found to be superior to placebo in this regard. Among recent CV outcome trials (CVOTs), REWIND is notable for including a majority of individuals without diabetes but at risk for developing it at baseline, a large study population, and a follow-up period of >5 years—reportedly the longest follow-up for any CVOT in this drug class.

"The REWIND trial was an ambitious study that conclusively assessed the effects of dulaglutide on people with type 2 diabetes both with and without prior cardiovascular disease," investigator Hertzel Gerstein said. "The reduction in cardiovascular events observed in a wide range of people with diabetes regardless of sex, baseline cardiovascular disease, age, or A1C level is compelling."

Lead investigator Matthew Riddle added, "Both health care providers and patients who are looking for ways to reduce cardiovascular risks while also lowering glucose levels, blood pressure, and weight will welcome the findings of this trial."

More information on the results of the REWIND trial are available online (bit.ly/31zjX5H). The full trial report was published in *The Lancet* (Gerstein et al., doi.org/c8sb).

Additional Reports

More information from trial reports at the 2019 Scientific Sessions is available online at bit.ly/2Yvzeqr, bit.ly/2KtPkXD, and bit.ly/2GPoAQw. All abstracts from the conference are available as an online supplement to the journal *Diabetes* (bit.ly/2yl2qLG).

ADA NEWS, *continued from p. 311*

Diabetes" (3.0 credits) and "Intensification of Basal Insulin Therapy in People with Diabetes" (3.0 credits).

Participate today at ada.healthmonix.com/allcourses/curriculum/details/4303.

Directory Connects Diabetes Care Providers With Mental Health Professionals

The ADA recommends that diabetes care providers routinely screen patients for psychosocial challenges and make referrals to mental health professionals who have experience with diabetes management and effective treatment strategies. The ADA's Mental Health Provider Directory, supported by the Leona M. and Harry B. Helmsley Charitable Trust, can help connect diabetes medical care providers with local mental health professionals who have demonstrated expertise in diabetes. Learn more at professional.diabetes.org/mhdirectory.